Review

DOI: 10.5582/bst.2026.01217

Hepatic arterial infusion chemotherapy–based triplet conversion therapy for hepatocellular carcinoma with portal vein tumor thrombus: Evidence, patient selection, and surgical endpoints

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SUMMARY: Portal vein tumor thrombus (PVTT) is a biologically aggressive and clinically heterogeneous form of hepatocellular carcinoma (HCC). Global guidelines generally classify macrovascular invasion as advanced disease and prioritize systemic therapy, whereas selected East Asian practice pathways incorporate hepatic arterial infusion chemotherapy (HAIC), radiotherapy, or resection. This review critically evaluates HAIC combined with an antiangiogenic agent and immune checkpoint inhibitor as a conversion strategy for HCC with PVTT. Randomized trials substantiate the efficacy of HAIC-based treatment in contrast to controls from the days of sorafenib but do not establish the incremental benefit of the contemporary triplet. Across prospective single-arm studies, RECIST 1.1 objective response rates ranged from approximately 36 to 77%, with higher estimates in some studies using mRECIST. Retrospective PVTT-focused comparisons also suggest longer progression-free and overall survival than with dual systemic therapy or HAIC alone, but these figures remain vulnerable to confounding by indication, heterogeneous regimens, inconsistent response criteria, and immortal-time bias related to surgery. Conversion should be defined as a prospectively documented transition from unresectable disease to an R0-resectable state with adequate liver reserve, not as radiological response alone. We propose an explicitly unvalidated multidisciplinary framework for candidate selection, reassessment, and perioperative management. Current evidence supports protocol-based use in clinical trials or experienced centers rather than routine global adoption. Randomized PVTT-stratified trials comparing the triplet to contemporary immunotherapy, with intention-to-treat reporting of resection and pathological response, are required.

Keywords: hepatectomy, downstaging, immune checkpoint inhibition, antiangiogenesis, portal hypertension

1. Introduction

Hepatocellular carcinoma (HCC) remains a leading cause of cancer mortality worldwide, and macroscopic portal-vein invasion is one of its most adverse phenotypes (*1,2*). Portal vein tumor thrombus (PVTT) is not merely a staging variable. It accelerates intrahepatic dissemination, reduces portal inflow, worsens portal hypertension, and narrows the therapeutic window by eroding hepatic reserve. The label also encompasses very different anatomical states: a segmental branch thrombus that can be removed with the involved lobe is not clinically equivalent to a tumor extending into the main trunk or contralateral portal vein.

This heterogeneity is explained by a persistent East-West divergence. The BCLC 2026, EASL 2025, AASLD, ESMO, and ASCO frameworks generally place macrovascular invasion on a systemic-therapy pathway (*3-7*). Japanese, Korean, and Chinese guidance accepts broader use of liver-directed therapy, and the 2026 Chinese PVTT guideline explicitly recommends individualized combinations of hepatic arterial infusion chemotherapy (HAIC), transarterial chemoembolization (TACE), radiotherapy, targeted agents, and immunotherapy for unresectable disease (*8-11*). Observational surgical data further suggest that selected patients with limited PVTT may outlive non-surgical comparators, although selection is profound (*12,13*).

The central question is therefore not whether a triplet can shrink tumors. It is whether adding HAIC to a modern systemic doublet creates a reproducible, oncologically meaningful conversion-to-resection opportunity, without consuming liver reserve or delaying effective systemic control. This review is organized around that question.

We performed a targeted narrative review updated through July 29, 2026. MEDLINE/PubMed, Embase, Web of Science, the Cochrane Library, ClinicalTrials.gov, WHO ICTRP-linked records, and Chinese guideline sources were searched using combinations of hepatocellular carcinoma, portal vein tumor thrombus or portal vein invasion, HAIC or hepatic arterial infusion,

FOLFOX, immune checkpoint blockade, antiangiogenic therapy, conversion, downstaging, resection, and pathological response. References listed in key trials and major guidelines were also screened. The review was not protocol-registered and did not use duplicate screening or a PRISMA selection process; it should therefore be interpreted as a critical narrative synthesis rather than an exhaustive systematic review.

We prioritized PVTT-specific randomized or prospective studies, contemporary systemic-therapy trials with macrovascular-invasion data, comparative HAIC-based cohorts, and studies reporting conversion, R0 resection, or pathological response. General unresectable-HCC studies were retained only when they provided information on the HAIC backbone, safety, mechanism, or trial design. RECIST 1.1 and mRECIST outcomes were identified and presented independently. No quantitative meta-analysis was performed because the available studies mixed single-arm and comparative designs, incompatible control regimens, different PVTT strata, and non-equivalent response criteria; a pooled estimate would therefore imply a precision and exchangeability that the evidence does not support.

2. Clinical context and biological rationale

The Japanese Vp classification is anatomically explicit: Vp1 denotes invasion distal to second-order branches, Vp2 invasion of second-order branches, Vp3 invasion of a first-order branch, and Vp4 invasion of the main trunk or a contralateral branch. Cheng type I-IV is commonly used in China and is similar but not directly interchangeable. Reporting both systems, along with the exact vessels involved, is preferable to collapsing disease into "PVTT present" (Table 1).

Resectability must be divided into technical and oncological components. Technical unresectability includes inadequate future liver remnant (FLR), inability to obtain negative margins, prohibitive portal reconstruction, or unacceptable surgical risk. Oncological unresectability includes rapidly progressive extrahepatic disease, diffuse bilobar intrahepatic dissemination, or a tumor biology indicating that major surgery would be unlikely to provide meaningful disease-free survival. Conversion therapy should document which barriers existed at the baseline and which barriers were overcome.

The dominant competing risk is liver failure. Portal occlusion, varices, thrombocytopenia, and a large tumor burden can make apparent antitumor activity clinically irrelevant if treatment worsens hepatic reserve. Child-Pugh class alone is insufficient; the ALBI grade, bilirubin trajectory, platelet count, ascites, variceal risk, portal collaterals, and quantitative FLR should be integrated.

HAIC is not the only liver-directed option for PVTT. External-beam radiotherapy, transarterial chemoembolization, and transarterial radioembolization are used in selected anatomical and regional settings, but their potential utility depends heavily on the extent of PVTT, liver reserve, arterial anatomy, and local expertise (*4,8-11*). This review focuses on HAIC-based triplet therapy and does not claim comparative superiority over these alternatives.

Atezolizumab plus bevacizumab and durvalumab plus tremelimumab are established immunotherapy-based first-line therapies for unresectable HCC, with camrelizumab plus rivoceranib (CARES-310 interim and final analyses; (*17*,*20*)), sintilimab plus a bevacizumab biosimilar, and nivolumab plus ipilimumab further broadening the global treatment landscape (*14-20*). These regimens were not designed as conversion programs and their eligibility criteria generally favored Child-Pugh A and ECOG 0-1 populations. Importantly, drug classes are not interchangeable: LEAP-002 did not meet its prespecified superiority boundaries for pembrolizumab plus lenvatinib *vs.* lenvatinib (*21*). Treating all 'TKI plus PD-1' combinations as a validated class is therefore scientifically unsafe.

Vp4 disease illustrates the unmet need. In the exploratory IMbrave150 analysis, median overall survival was 7.6 months with atezolizumab-bevacizumab and 5.5 months with sorafenib (HR: 0.62, 95% CI: 0.34-1.11) (*15*). This small, underpowered subgroup analysis should

Table 1. PVTT anatomy and implications for conversion planning

Category	Anatomical extent	Usual clinical implication	Conversion question
Vp1 / Cheng I	Distal segmental branches	May be technically resectable with limited hepatectomy in selected patients	Is biology favorable enough for upfront surgery or short neoadjuvant therapy?
Vp2 / Cheng I-II	Second-order portal branches	Resection possible in experienced centers if future liver remnant (FLR) and portal pressure are acceptable	Will induction therapy reduce early systemic and intrahepatic failure?
Vp3 / Cheng II	First-order right or left portal branch	Often technically complex; may require thrombectomy or en-bloc portal resection	Can PVTT regress to permit an oncologically credible R0 surgery?
Vp4 / Cheng III-IV	Main trunk and/or contralateral branch; superior mesenteric vein extension in Cheng IV	Advanced, high-risk disease; portal hypertension and hepatic decompensation are central hazards	Can treatment restore portal flow, maintain FLR, and exclude rapidly progressive systemic biology?

not be used for indirect superiority claims, but it is a clinically relevant benchmark: outcomes in main-trunk or contralateral-branch invasion remain substantially worse than in the trial population overall.

HAIC delivers chemotherapy through the hepatic artery without permanent embolization. In China, FOLFOX-HAIC is common; Japan and Korea have longer experience with cisplatin/5-fluorouracil or related regimens. Avoiding embolization can be attractive when portal inflow is compromised, although catheterization, arterial anatomy, and repeated procedures introduce distinct risks.

Randomized evidence validates the efficacy of HAIC in treating portal vein invasion. In 247 patients, sorafenib plus FOLFOX-HAIC improved median overall survival from 7.13 to 13.37 months (HR 0.35) and objective response from 2.5 to 40.8% *vs.* sorafenib alone (*22*). A randomized phase II trial restricted to Vp3/Vp4 disease reported a median overall survival of 16.3 *vs.* 6.5 months with sorafenib plus 3cir-OFF HAIC *vs.* sorafenib (HR 0.28) (*23*). FOHAIC-1 similarly favored HAIC over sorafenib in a high-risk advanced population, although it was not a PVTT-specific trial (*24*). Conversely, the randomized phase III FOLFOX-HAIC *vs.* TACE study in large HCC excluded major vascular invasion and extrahepatic spread; it provided evidence of local efficacy but cannot be cited as high-level evidence for treating PVTT (*25*).

Oxaliplatin can trigger hallmarks of immunogenic cell death, including calreticulin exposure, ATP release, and HMGB1 release, potentially increasing antigen presentation (*26*). Anti-VEGF/VEGFR treatment may transiently normalize abnormal vasculature and reduce immunosuppressive myeloid signaling, while checkpoint blockade can restore effector T-cell function (*27,28*). These concepts provide a plausible sequence from cytoreduction to immune engagement, but direct evidence from treated patients with PVTT is limited. Dose, drug identity, and timing matter: excessive vessel pruning may aggravate hypoxia or alter HAIC delivery.

PVTT itself may be immunologically distinct. Single-cell profiling has identified enrichment of immunosuppressive C5aR-positive tumor-associated macrophages in venous tumor thrombus, while other transcriptomic work describes immune-desert or immune-excluded features (*29,30*). These data strengthen the rationale for PVTT-specific translational sampling, but they do not prove that adding any particular TKI or antibody to HAIC reverses those states (Figure 1).

3. Clinical evidence for HAIC-based triplet therapy

Prospective single-arm studies have provided evidence of variable but clinically relevant antitumor activity, but they have not quantified the incremental effect of HAIC. Lenvatinib, toripalimab, and FOLFOX-HAIC were reported to result in a RECIST 1.1 ORR of 63.9% and a median PFS of 10.4 months in 36 patients with high-risk advanced HCC (*31*). The TRIPLET phase II study of camrelizumab, apatinib, and FOLFOX-HAIC enrolled 35 BCLC C patients and reported a confirmed

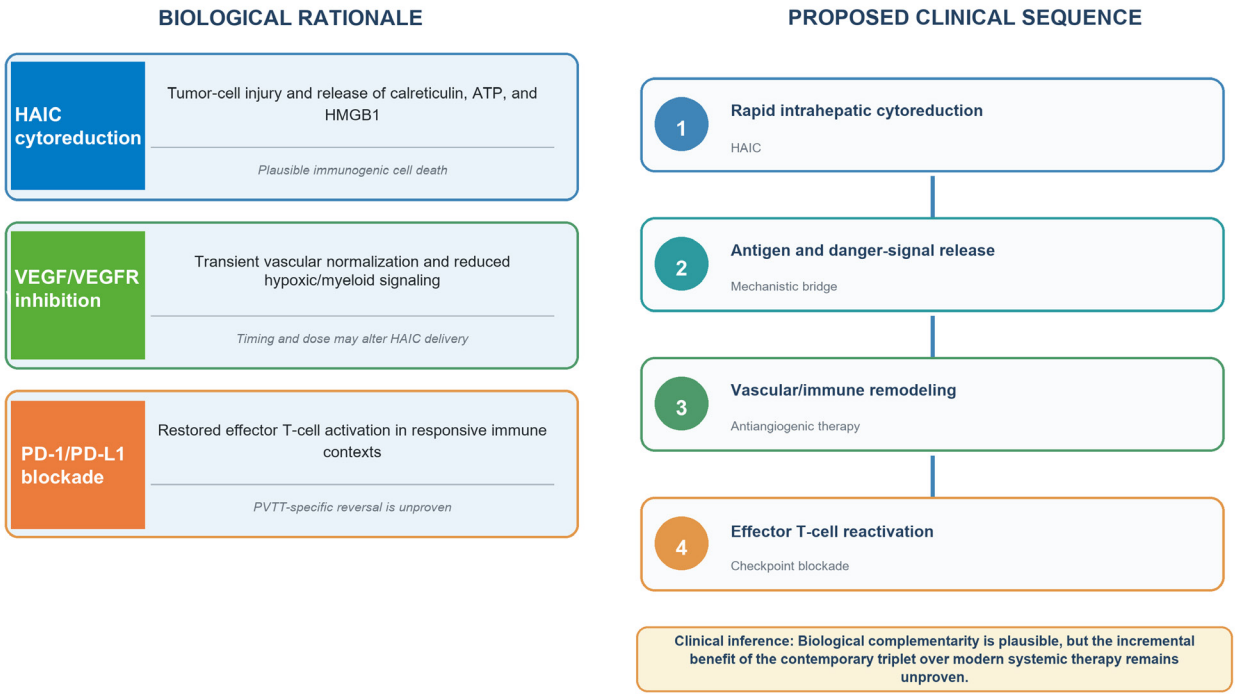

Figure 1. The biological and clinical logic of HAIC-based triplet therapy. This figure separates the mechanistic rationale from clinical inference. HAIC-induced cytoreduction, VEGF/VEGFR inhibition, and checkpoint blockade may be biologically complementary, but the incremental clinical benefit of the contemporary triplet over modern systemic therapy has not been established.

RECIST ORR of 77.1% and a median PFS of 10.38 months (*32*). Cal Era used raltitrexed-oxaliplatin HAIC with camrelizumab-lenvatinib in 39 evaluable patients, resulting in an ORR of 66.7% and a median PFS and OS of 13.8 and 21.2 months, respectively, but grade 3–4 treatment-related events occurred in 79.5% of the patients (*33*).

Not all prospective signals are uniformly strong. Double-IA-001, a small phase II study of FOLFOX-HAIC, camrelizumab, and sorafenib, did not meet its prespecified first-stage activity requirement; the median OS was 8.87 months and grade 3 or higher treatment-related events occurred in 76% of patients (*34*). Negative or modest studies are important because they counter publication-driven assumptions that any triplet is synergistic (Table 2).

PVTT-specific comparative evidence expanded substantially between 2024 and 2026. In a four-center study including 411 patients with PVTT, camrelizumab plus rivoceranib with or without HAIC was compared. After propensity score matching, the triplet regimen achieved significantly longer median OS (18.7 *vs*. 11.0 months) and PFS (10.0 *vs*. 5.6 months); however, the ORR remained identical in both groups (42.2%). These findings suggest that the observed survival advantage was driven primarily by improved disease control and delayed progression rather than greater tumor shrinkage (*35*). This distinction underscores that radiographic response, survival outcomes, and conversion to resectability represent related but non-interchangeable endpoints. Therefore, while the study supports a beneficial effect of HAIC on disease control and time-to-event outcomes, it does not provide evidence that HAIC enhanced conversion eligibility or increased the likelihood of R0 resection through additional cytoreduction.

In a multicenter high-risk cohort defined by Vp4 and/or tumor diameter of at least 10 cm, FOLFOX-HAIC plus heterogeneous TKIs and PD-1 inhibitors was compared to TKI-PD-1 therapy. After matching 194 pairs, median OS was 24.6 *vs.* 11.9 months, PFS was 10.0 *vs.* 7.7 months, and ORR was 57.7% *vs.* 28.9%; grade 3–4 events were also higher (59.2% *vs.* 47.4%) (*36*). Only one-third of the original cohort had Vp4, so the result cannot be assumed to represent all main-trunk PVTT.

More anatomically focused data are informative but remain retrospective. In Vp4 disease, HAIC-lenvatinib-tislelizumab was associated with a median OS of 23.2 *vs.* 6.9 months and a tumor ORR of 77.1% *vs.* 42.9% compared to HAIC alone after matching 35 patients per group (*37*). A 2026 single-arm Vp4 cohort of 35 patients reported an mRECIST ORR of 60%, a median OS of 313 days, and grade 3–4 events in 45.7% (*38*). Another 2026 weighted comparison of 97 Vp4 patients found that adding a PD-1 blockade to HAIC-TKI improved the adjusted median OS from 10.1 to 14.6 months (HR 0.47) and PFS from 5.5 to 7.3 months (HR 0.48) (*39*). These estimates are hypothesis-generating, not practice-defining.

The large TACE-HAIC study by Yuan *et al*. is often cited as triplet evidence, but the intervention combines embolization, infusion chemotherapy, a targeted agent, and immunotherapy; it should not be pooled conceptually with HAIC-only triplets (*40*). Similarly, examination of the extrahepatic-metastasis cohort by Guan *et al*. suggests that intrahepatic control may still matter when distant disease is present, but residual confounding and liver-dominant selection limit causal interpretation (*41*) (Table 2).

By study, ORR, conversion, resection, pathological response, and grade 3–4 toxicity are therefore summarized descriptively in Table 2. The ranges should not be interpreted as pooled effects: patient selection, the extent of PVTT, drug combinations, response criteria, adverse-event attribution, and denominators differ materially across studies.

Conversion endpoints are especially susceptible to inflation. In a study by Luo *et al*., pCR was achieved in 7 of 27 patients who underwent resection (25.9%) but in only 7 of all 145 treated patients (4.8%) (*42*). In a study by Liu *et al*., a radiological complete response, and not a pathological complete response, was achieved in 22.2% (*43*). In a 19-patient prospective conversion study, 14 were considered eligible for resection, nine underwent R0 resection, and pCR was achieved in two: The conversion and R0 resection rates were 73.7% (14/19) and 47.4% (9/19), respectively; pCR was 22.2% (2/9) among resected patients and 10.5% (2/19) in the intention-to-treat population (*44*). High-quality reviews must report all denominators.

Comparing patients who underwent surgery to those who did not is also biased: surgery is only possible after a period of survival and favorable response. Conventional Kaplan-Meier analyses from treatment initiation create guarantee-time bias, also known as immortal time bias. Landmark analysis, time-dependent exposure modeling, or target-trial methods are required. The CHANCE2416 publication is a protocol for a retrospective target-trial emulation and has not reported hypothesized survival figures as results (*45*).

4. Conversion criteria, patient selection, and safety

The optimal candidate is not defined by PVTT alone. As a pragmatic and explicitly unvalidated MDT framework, consideration may be given to patients with an ECOG performance status of 0–1, Child-Pugh A or carefully selected B7 liver function, ALBI grade 1 or favorable grade 2, adequate marrow and renal function, controlled HBV, no uncontrolled ascites or encephalopathy, and manageable portal hypertension. Disease should be liver-dominant and the barrier to R0 resection should be anatomically resolvable. Vp1/Vp2 disease may already be directly resectable in selected patients; Vp3/

Table 2. Evidence from randomized HAIC backbones, prospective triplets, comparative cohorts, and conversion studies. RECIST 1.1 and mRECIST are retained as reported and are not combined; no pooled effect is presented because designs, comparators, populations, and denominators are heterogeneous

Study	Design; Population	Treatment	Key outcomes	Main limitation
He *et al*. (*22*)	randomized, *n* = 247; HCC with portal-vein invasion	Sorafenib + FOLFOX-HAIC *vs.* sorafenib	OS 13.37 *vs.* 7.13 mos; HR 0.35; RECIST ORR 40.8% *vs.* 2.5%	Outdated systemic comparator
Zheng *et al*. (*23*)	randomized phase II, *n* = 64; Vp3/Vp4, treatment-naive	Sorafenib + 3cir-OFF HAIC *vs.* sorafenib	OS 16.3 *vs.* 6.5 mos; HR 0.28; ORR 41% *vs.* 3%	Small study; port-catheter regimen
Lai *et al*. (*31*)	phase II, *n* = 36; High-risk advanced HCC; mixed high-risk criteria	Lenvatinib + toripalimab + FOLFOX-HAIC	RECIST ORR 63.9%; PFS 10.4 mos; extended OS 17.9 mos	Single center; no control
TRIPLET (*32*)	phase II, *n* = 35; BCLC C HCC	Camrelizumab + apatinib + FOLFOX-HAIC	RECIST ORR 77.1%; PFS 10.38 mos	Small, single arm; not PVTT-specific
Cal Era (*33*)	phase II, *n* = 39; BCLC B/C HCC	Camrelizumab + lenvatinib + RALOX-HAIC	ORR 66.7%; PFS 13.8 mos; OS 21.2 mos; grade 3-4 TRAE 79.5%	Non-FOLFOX HAIC; exploratory biomarkers
Double-IA-001 (*34*)	phase II, *n* = 25; BCLC C HCC	Camrelizumab + sorafenib + FOLFOX-HAIC	ORR 44%; PFS 4.87 mos; OS 8.87 mos; primary endpoint not met	Small; modest activity; high toxicity
Luo *et al*. (*42*)	Single-center retrospective, *n* = 145 uHCC	Single-arm HAIC + ICI + TKI	mRECIST ORR 57.2%; PFS 9.7 mos	Resection 27/145 (18.6%); pCR 7/27 (25.9%) among resected, 7/145 (4.8%) ITT
Liu *et al*. (*43*)	Retrospective, *n* = 27; 70.4% PVTT; heavily pretreated	Single-arm HAIC + anti-PD-1 + TKI	ORR 63%; radiological CR 22.2%; PFS 10.6 mos	No pathological proof for the reported CR; grade ≥ 3 AE 55.6%
Li *et al*. (*35*)	Multicenter retrospective PVTT, *n* = 411; PSM 83 pairs	HAIC + camrelizumab + rivoceranib *vs.* systemic doublet	Matched OS 18.7 *vs.* 11.0 mos; PFS 10.0 *vs.* 5.6 mos; ORR 42.2% in both arms	DCR 94.0% *vs.* 78.3%; grade 3–4 TRAE 70.5% *vs.* 62.2%
Zuo *et al*. (*36*)	Multicenter high-risk HCC, *n* = 466; PSM 194 pairs	HAIC + TKI + PD-1 *vs.* TKI + PD-1	Matched OS 24.6 *vs.* 11.9 mos; PFS 10.0 *vs.* 7.7 mos; ORR 57.7% *vs.* 28.9%	Resection/ablation 16.5% *vs.* 9.2%; only 33.3% had Vp4 before matching
Tang *et al*. (*37*)	Multicenter Vp4, *n* = 155; PSM 35 pairs	HAIC + lenvatinib + tislelizumab *vs*. HAIC	OS 23.2 *vs.* 6.9 mos; PFS 6.6 *vs*. 2.4 mos; tumor ORR 77.1% *vs.* 42.9%	Hepatectomy 15.8% *vs.* 0.9%; small matched sample
Wang *et al*. (*38*)	Retrospective Vp4, *n* = 35	Single-arm HAIC + TKI + PD-1	mRECIST ORR 60%; OS 313 days; PFS 204 days	Grade 3-4 AE 45.7%; 97.1% HBV; no control
Liu *et al*. (*39*)	Retrospective Vp4, *n* = 97; sIPTW	HAIC + TKI + PD-1 *vs.* HAIC + TKI	Adjusted OS 14.6 *vs.* 10.1 mos (HR 0.47); PFS 7.3 *vs.* 5.5 mos (HR 0.48)	Single center; potential cohort overlap; RECIST 1.1
Yalikun *et al*. (*44*)	Prospective single arm, *n* = 19 uHCC; no extrahepatic spread	HAIC + camrelizumab + apatinib	RECIST ORR 47.4%; mRECIST ORR 89.5%; survival immature	Resectable 14/19 (73.7%); R0 9/19 (47.4%); pCR 2/9 (22.2%) resected and 2/19 (10.5%) ITT; grade ≥ 3 TRAE 73.7%

Vp4 disease has a greater need for local control but less physiological margin for error. These categories should not be interpreted as a validated selection rule (Table 2).

Extrahepatic disease is not an absolute biological prohibition, but it changes the endpoint. Limited, controllable metastases may permit a consolidated strategy in exceptional cases; widespread or rapidly progressing metastases make major hepatectomy difficult to justify. The benefit reported in an extrahepatic-metastasis cohort should be viewed as evidence that liver control matters, not proof that surgery is curative in disseminated disease (*41*) (Figure 2 and Table 3).

Reassessment after approximately two HAIC cycles, often 6–8 weeks, is a pragmatic practice-based approach rather than a prospectively validated universal interval. RECIST 1.1 and mRECIST should be reported separately because size reduction and loss of arterial enhancement measure different effects. Operability requires more than response: R0 resection must be anatomically feasible; FLR and liver function must be adequate; portal inflow and outflow must be reconstructable; and extrahepatic disease must be absent or controllable. Stability at one reassessment may help exclude rapidly progressive biology, although excessive delay risks cumulative toxicity or regrowth.

Radiological CR is not pathological CR. Residual viable cells may persist in a non-enhancing mass or thrombus, and immune-related patterns can complicate imaging. Observational data and recent meta-analyses have yet to demonstrate that non-surgical observation after complete response is equivalent to resection (*46*). Pathology should report the viable tumor percentage separately for the hepatic lesion and PVTT, margin status, microvascular invasion, nodal disease, and treatment effect.

Triplet therapy combines non-overlapping and overlapping toxicities. FOLFOX-HAIC causes marrow suppression, transaminase elevation, nausea, abdominal pain, and cumulative oxaliplatin neuropathy; catheter complications include dissection, thrombosis, infection, and extrahepatic perfusion. Antiangiogenic agents cause hypertension, proteinuria, bleeding, thrombosis, and impaired wound healing, whereas immune checkpoint inhibitors may cause hepatitis, colitis, pneumonitis, endocrinopathy, myocarditis, or other immune toxicities. Across contemporary studies, grade 3 or higher event rates ranged from approximately 46 to 80%, but the definitions, regimens, populations, and follow-up differed (*33,35,36,38,44*). These rates should therefore be presented by study rather than pooled as a single safety estimate.

Before administering therapy that includes bevacizumab, clinically significant varices and other manifestations of portal hypertension should be assessed and managed according to current portal-hypertension guidance (*47*). Perioperative interruption must be

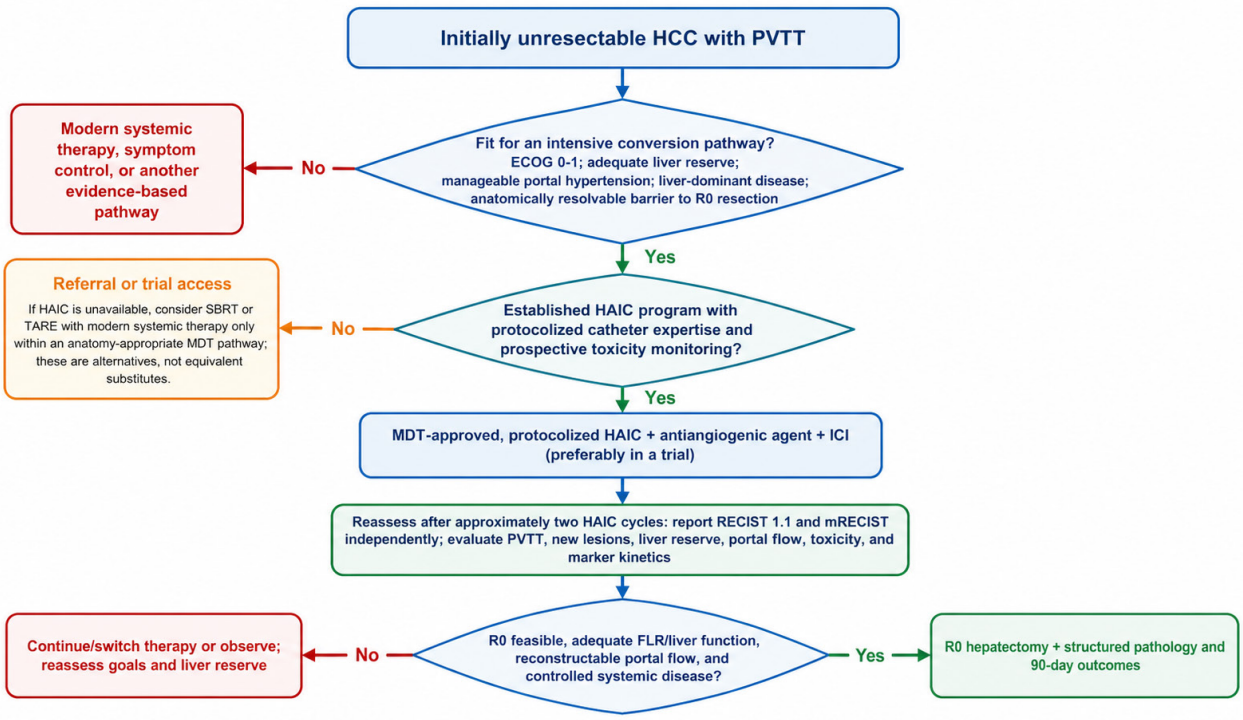

Figure 2. Multidisciplinary selection and reassessment pathway. This unvalidated framework distinguishes centers with an established HAIC program from settings in which referral, structured training, SBRT, or TARE may be considered. Alternative locoregional modalities are not presented as equivalent substitutes for HAIC. RECIST 1.1 and mRECIST should be reported independently. This class-level pathway does not imply interchangeability among HAIC backbones, antiangiogenic agents, or ICIs; any regimen should be protocol-specified and evidence-informed. *Abbreviations*: MDT, multidisciplinary team; FLR, future liver remnant; SBRT, stereotactic body radiotherapy; TARE, transarterial radioembolization.

Table 3. Practical selection, reassessment, and perioperative checklist

Domain	Before treatment	At each reassessment	Before surgery
Tumor anatomy	Triphasic CT or MRI; PVTT extent; arterial anatomy; liver volumetry	RECIST 1.1 and mRECIST separately; PVTT regression; new lesions	R0 plan; portal reconstruction; FLR and inflow/outflow; exclude progression
Liver reserve	Child-Pugh, ALBI, bilirubin, INR, platelets, ascites, ICG where used	Trend rather than a single value; treatment-related injury	No unresolved hepatitis or decompensation; adequate FLR (context-specific)
Portal hypertension	Endoscopy when anti-VEGF therapy is planned; collaterals, spleen, platelets	Bleeding, ascites, portal-flow changes	Variceal control; operative bleeding strategy
Systemic biology	Chest imaging; bone/brain imaging if symptomatic; AFP and DCP	Marker kinetics; extrahepatic response; tempo of disease	No uncontrolled systemic progression
Treatment safety	Neuropathy, marrow, renal function, cardiovascular and immune history	Cumulative oxaliplatin toxicity; hypertension/proteinuria; immune hepatitis; catheter events	Agent-specific washout; normalized coagulation and marrow; steroid plan if prior irAE
Patient-centered factors	Goals, uncertainty, procedure burden, costs and access	Quality of life and preference at each decision point	Informed trade-off between surgery, continued therapy, and observation
Program capability	Trained interventional oncology team; catheter and rescue protocols; MDT review; referral pathway if unavailable	Procedure-level quality assurance; catheter complications; center-level outcome registry	Experienced hepatobiliary surgery, anesthesia, portal reconstruction, pathology, and 90-day outcome capture

individualized to drug half-life, bleeding and wound-healing risks, immune toxicity, and surgical urgency. A longer interval is generally required for bevacizumab than for oral TKIs, but a universal window cannot be inferred from the HAIC-triplet literature; it should be governed by current product information and institutional protocols. Surgery should be deferred after clinically significant immune hepatitis until toxicity has resolved and immunosuppression has been appropriately tapered. In Vp4 disease with complete main-trunk occlusion, uncontrolled or recent variceal bleeding, or worsening liver reserve, antiangiogenic therapy and repeated HAIC catheterization should be deferred or avoided until portal-hypertension risk is stabilized and an MDT judges the residual risk acceptable.

HBV status and HBV DNA should be assessed before treatment, antiviral therapy should be optimized when indicated, and reactivation surveillance should continue during and after anticancer therapy (*49*). Nutritional status, sarcopenia, and patient-reported outcomes also deserve systematic attention because repeated HAIC procedures impose travel, hospitalization, and financial burdens not discernable from conventional adverse-event tables.

5. Evidence gaps and future directions

Most modern HAIC-triplet data originate from HBV-predominant Chinese cohorts treated at high-volume centers. Whether those data can be generalized to HCV, alcohol-, or metabolic-dysfunction-associated HCC is uncertain. Arterial techniques, inpatient infrastructure, drug availability, and surgical thresholds differ between regions. The Japanese and Korean experience also involves regimens that are not identical to Chinese FOLFOX-HAIC (*8-10*).

For centers without an established HAIC program, triplet adoption should not precede a formal implementation pathway: referral or proctorship from a high-volume center, protocol-based catheter training, standardized FOLFOX preparation and dose modification, prospective catheter- and liver-toxicity surveillance, hepatobiliary surgical participation, and independent radiology review. Where that infrastructure is unavailable, anatomy-appropriate stereotactic body radiotherapy (SBRT) or transarterial radioembolization (TARE) may be paired with contemporary systemic therapy as part of an experienced MDT or clinical trial (*4,5,8-11*). These modalities should be viewed as alternative locoregional strategies, not interchangeable substitutes for HAIC, because direct comparative conversion data are lacking. Institutional registries should include all treated patients, including those who deteriorate before the first response scan, to prevent survivorship-biased internal impressions.

No biomarker currently indicates which patients to select for HAIC-based triple therapy. AFP and des-gamma-carboxy prothrombin kinetics are useful adjuncts but cannot replace imaging. Baseline ALBI, the neutrophil-to-lymphocyte ratio, tumor size, and tumor number are repeatedly associated with outcome, and yet they may be prognostic rather than predictive. Small exploratory studies have proposed CCL28/BTC or IL-2/CXCL13/CCL19 signatures (*31,33*); these require assay standardization and validation in treatment-interaction analyses.

The most promising research direction is longitudinal

multi-compartment profiling. Paired primary tumor and PVTT tissue can resolve the myeloid, stromal, and hypoxic programs highlighted by single-cell and spatial studies (*29,30,48*). Serial circulating tumor DNA may help identify molecular residual disease after radiological response or resection, while radiomics and digital pathology may quantify thrombus viability and treatment effect. Models should be established and judged by calibration and clinical utility, not only discrimination.

A decisive trial should enroll cohorts with untreated HCC and prospectively stratified Vp3 and Vp4 disease, Child-Pugh A, and clearly defined B7, and extrahepatic spread should be separately stratified. The control must be a contemporary immunotherapy regimen, not sorafenib. The experimental arm should specify one HAIC regimen, one antiangiogenic agent, one ICI, a catheter technique, dose-modification rules, a response review, and surgical criteria. A registered randomized phase II study, NCT04947826, compares HAIC plus HLX10 and HLX04 to HAIC plus a placebo in major PVTT; its registration is evidence of an appropriate design, not evidence of efficacy (*50*).

Overall survival should remain the primary endpoint, with blinded central review of RECIST 1.1 and mRECIST reported simultaneously but independently; hepatic, PVTT, and extrahepatic responses should also be described separately. Future conversion trials should prespecify the full intention-to-treat population as the mandatory denominator for conversion, R0 resection, major pathological response, and pCR. Surgical-cohort percentages may be reported only as secondary conditional estimates and must never replace intention-to-treat rates. Ninety-day mortality, major morbidity, patient-reported quality of life, time to hepatic decompensation, and grade 3–5 toxicity should be key secondary endpoints. Surgery should be analyzed as a time-dependent exposure with a prespecified landmark sensitivity analysis.

Randomization alone will not solve every question. Embedded translational studies should examine whether HAIC changes antigenicity, T-cell clonality, myeloid states, or ctDNA clearance and whether those changes interact with treatment. Health-economic and implementation analyses are essential because repeated arterial procedures, specialized catheter skills, and costly systemic therapy may worsen inequity in access. Trial reports should include center volume, operator experience, catheter technique, admission burden, and cross-over to SBRT or TARE so that geographic transferability can be judged.

A review-length synthesis should also contrast HAIC with other liver-directed strategies rather than treating HAIC as the sole local platform. In a randomized trial of 90 patients with liver-confined HCC and macroscopic vascular invasion, TACE plus external-beam radiotherapy improved PFS and OS *vs.* sorafenib and enabled curative resection in five patients (*51*). NRG/RTOG 1112 subsequently showed that SBRT followed by sorafenib produced a clinically meaningful, although not statistically significant, improvement in

Table 4. Competing locoregional strategies in HCC with PVTT: evidence signal, selection logic, and limitations

Strategy	Evidence signal	Most plausible selection context	Conversion relevance	Key limitation
HAIC + antiangiogenic agent + ICI	High ORR in small prospective cohorts; favorable retrospective comparisons (*31-39*)	Liver-dominant, high-burden disease; preserved liver reserve; experienced HAIC/MDT program	Potential cytoreduction and PVTT regression; few ITT R0 and pathological endpoints	No randomized comparison to a contemporary ICI regimen
TACE + external-beam RT	Randomized benefit versus sorafenib in liver-confined macroscopic vascular invasion (*51*)	Preserved unilateral portal flow, Child-Pugh A, liver-confined disease	Five of 45 patients underwent curative resection in the randomized trial	Single-center, sorafenib-era comparator; embolic ischemia risk
SBRT + systemic therapy	Phase III RTOG 1112 showed clinically meaningful but non-significant OS improvement (*52*)	Focal or anatomically targetable PVTT; adequate uninvolved liver; radiotherapy expertise	May eliminate vascular invasion and preserve arterial options	Not a PVTT-specific conversion trial; liver-dose constraints
TARE (yttrium-90)	PVTT-focused meta-analysis suggests activity, but SARAH/SIRveNIB did not improve ITT OS (*54-56*)	Liver-dominant disease, favorable shunt/dosimetry, preserved liver reserve, expert center	Potential lobar control without macroembolization	Selection and dosimetry heavily influence outcomes; limited resection data
Selective TACE	Systematic-review signal in selected PVTT populations (*53*)	Peripheral PVTT with preserved portal flow and superselective access	May facilitate local control in combination programs	Main-trunk occlusion and poor reserve increase hepatic failure risk

Note: The table is a clinical-reasoning comparison, not a network-derived treatment ranking. *Abbreviations*: ICI, immune checkpoint inhibitor; ITT, intention-to-treat; MDT, multidisciplinary team; OS, overall survival; RT, radiotherapy; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

Table 5. Minimum endpoint and denominator framework for PVTT conversion studies

Domain	Required definition	Denominator and time origin	Minimum report
Whole-tumor response	RECIST 1.1, independently reviewed when feasible (*59*)	All treated patients; baseline to prespecified scan times	CR, PR, SD, PD; confirmed/unconfirmed ORR; missing scans counted explicitly
Viable-tumor response	mRECIST reported separately, not merged with RECIST 1.1 (*60*)	All treated patients and response-evaluable subset	Enhancing viable diameter; discordance with RECIST 1.1
PVTT response	Predefined change in Vp/Cheng extent, enhancement, portal flow, and surgical clearance	All patients with baseline PVTT; fixed imaging schedule	PVTT CR/PR definition, recanalization, differentiation from bland thrombus
Conversion eligibility	Prospectively specified technical and oncological resectability at MDT review	All patients starting conversion therapy	Date, reason, and criteria for resectability; reasons for non-conversion
Resection and margin	Surgery attempted, completed hepatectomy, R0/R1/R2, thrombectomy or en-bloc resection	ITT and underwent surgery as denominators, both stated	ITT resection and R0 rates; 90-day morbidity/mortality
Pathological response	Viable tumor percentage in liver lesion and PVTT separately; MPR and pCR thresholds prespecified	ITT and underwent resection as denominators, both stated	pCR/MPR in each denominator; margins, nodes, microvascular invasion
Liver reserve and safety	Child-Pugh components, ALBI, portal-hypertension events, CTCAE grade (*61*)	Baseline and each cycle; safety population defined	Decompensation, bilirubin/albumin trajectory, grade 3–5 events, catheter complications
Survival and surgery effect	OS/PFS from treatment start; surgery as time-dependent exposure or landmark analysis (*62,63*)	All treated patients; time zero aligned with eligibility and assignment	ITT Kaplan-Meier; adjusted time-dependent/landmark estimate; loss to follow-up

Abbreviations: CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; ITT, intention-to-treat; MDT, multidisciplinary team; MPR, major pathological response; ORR, objective response rate; OS, overall survival; pCR, pathological complete response; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

OS over sorafenib alone in locally advanced HCC (*52*). Systematic reviews have substantiated the effectiveness of carefully selected TACE and TARE approaches in PVTT (*53,54*), but the negative results of the SARAH and SIRveNIB phase III trials with regard to OS caution against extrapolating a favorable single-center TARE series to unselected advanced HCC (*55,56*). Broader meta-analytic and network comparisons are useful for generating hypotheses but remain limited by era effects, treatment heterogeneity, and indirectness (*57,58*). Table 4 therefore presents selection logic rather than a treatment ranking.

Response and conversion reporting also require a common measurement architecture. RECIST 1.1 should quantify the whole tumor burden, whereas mRECIST should independently quantify enhancing viable HCC; neither framework alone adequately describes PVTT regression, recanalization, or surgical clearance (*59,60*). Baseline and longitudinal liver reserve should be reported with Child-Pugh components and an objective score such as ALBI because radiological response without preserved hepatic function cannot produce a safe conversion (*61*). Table 5 specifies the minimum denominators, time origins, and endpoint definitions needed to compare future studies.

For observational conversion cohorts, eligibility, treatment assignment, the start of follow-up, and surgical status must be aligned. A target-trial protocol should be specified before analysis (*62*), and surgery should be modeled as a time-dependent exposure or evaluated with a prespecified landmark analysis to prevent immortal time bias (*63*). These methods do not remove unmeasured confounding, but they make the causal question and principal assumptions auditable.

6. Conclusion

HAIC-based triple therapy is one of the most active conversion strategies under investigation for HCC with PVTT. The rationale is compelling and early response, survival, and resection signals are clinically meaningful. And yet the evidence has an important asymmetry: randomized trials have established the value of HAIC in contrast to controls from the days of sorafenib, whereas the modern triplet is mainly substantiated by small prospective cohorts and retrospective comparisons in a limited geographic setting. Its superiority to contemporary ICI-based systemic therapy has not been established.

The appropriate current position is neither dismissal nor routine universal adoption. In experienced multidisciplinary centers, carefully selected patients with preserved liver function, liver-dominant high-burden disease, and anatomically actionable PVTT

may reasonably be placed on a protocolized conversion pathway, preferably as part of a trial. Centers that lack HAIC capability should prioritize referral, structured training, or anatomy-appropriate alternative locoregional strategies such as SBRT or TARE rather than informal replication. Every claim of success should preserve the intention-to-treat denominator, report RECIST 1.1 and mRECIST independently, distinguish radiological from pathological response, and demonstrate that technically feasible surgery is also oncologically worthwhile.

Funding: This work was supported by the National Natural Science Foundation of China (82372810); the Key Research and Development Program of Yunnan Province (202403AC100023); Kunming Medical University's Project to Create a First-class Team in the Discipline (2024XKTDYS04); Yunnan Province's Support Program for Personnel to Develop the Province: Special Project for Young Talent (2025 Zhitian Shi); the Yunnan Provincial Health Commission's Medical Personnel Development Program (H-2024056); and the Joint Special Project of the Science and Technology Department of Yunnan Province and Kunming Medical University (202601AY070001-191).

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

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Received July 12, 2026; Revised August 22, 2026; Accepted August 25, 2026.

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Released online in J-STAGE as advance publication August 28, 2026.