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REVIEW

Navigating the complexities: challenges and opportunities in conversion therapy for advanced hepatocellular carcinoma

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Abstract

Primary liver cancer ranks as the sixth most prevalent malignant tumor and stands as the second leading cause of cancer-related mortality globally, posing a significant threat to public health. Hepatocellular carcinoma (HCC) is the most common type of liver cancer worldwide. Surgical resection remains the cornerstone treatment for achieving radical cure and prolonged survival in HCC patients. Contrary to Western countries, the majority of HCC patients in China present with hepatitis B virus infection and consequent liver cirrhosis, with most cases diagnosed at an intermediate or advanced stage. This complexity results in a poor prognosis. Recent advancements in local therapeutic techniques and the introduction of systemic therapies, including targeted and immunotherapy agents, have provided new avenues for both clinical and basic conversion therapy for advanced HCC. Integrating multi-dimensional local and systemic therapies, multi-modal sequential, and comprehensive multidisciplinary approaches into the management of HCC patients has demonstrated promising conversion success rates. This holistic management strategy involves combining multiple treatment modalities vertically and coordinating various disciplines horizontally. However, significant challenges remain, including the precise selection of patients eligible for conversion therapy, the optimal choice of conversion therapy regimens, and the accurate determination of surgical timing post-conversion therapy. Addressing these challenges is crucial for hepatobiliary surgeons. High-quality, randomized controlled trials are urgently needed to generate robust evidence for clinical practice. This review aims to synthesize the latest research developments both in China and internationally and examines key issues in the realm of HCC conversion therapy.

Keywords Hepatocellular carcinoma · Conversion therapy · Systemic therapies

Introduction

According to the latest GLOBOCAN 2022 epidemiological data, there are approximately 865,269 new cases of liver cancer globally and 367,700 in China annually, with corresponding mortality figures reaching 757,948 and 316,500, respectively; positioning it as the third leading cause of cancer death and the sixth most common cancer [1, 2]. Hepatocellular carcinoma (HCC) remains the predominant form of liver cancer worldwide, posing a significant threat to global health [3]. Barcelona Clinic Liver Cancer (BCLC) staging system recommended by EASL (European Association for the Study of the Liver) [4] and AASLD (American Association for the Study of Liver Diseases) [5] is widely applied for HCC patient assessments and therapeutic decisions on the basis of patient and tumor characteristics as well as underlying liver function. Surgical resection is the primary curative treatment for early-stage HCC, offering the best chance for long-term survival [6, 7]. However, the eligibility

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criteria for resection vary worldwide, generally more restrictively recommended in Europe and USA than Asia, by considering tumor characteristics, liver function and the availability of ablation, leading to widely different 5-year survival rates between 50 and 70% [8]. In China, approximately 70% of Chinese HCC patients are newly diagnosed at an intermediate or advanced stages (CNLC (China Liver Cancer Staging System) stage IIb, IIIa, and IIIb, covering a proportion of patients with BCLC stage B and all patients with BCLC stage C), characterized as unresectable and pertinacious with a merely low resection rate of only 15% at initial assessment of resectability [9, 10]. Furthermore, chronic hepatitis B virus (HBV) infection and consequent liver cirrhosis are the predominant causes for HCC development in China, whereas HCV infection is the major pathogenic risk factor in a diverse set of countries (e.g., Egypt, Italy, and Japan) [1]. All these factors contribute to the disease's complexity and associated poor prognosis [11, 12]. Thus, there is an urgent need for innovative strategies and multidisciplinary treatment models to enhance resection rates and postoperative outcomes. Recent years have witnessed significant advances in systemic therapies for HCC [13]. Notably, the combination of anti-angiogenic targeted drugs (AATDs) and immune checkpoint inhibitors (ICIs) has shown promise, achieving an objective response rate (ORR) of approximately 30% in advanced or unresectable HCC and extending the median overall survival (OS) to around 20 months [14, 15]. In this context, conversion therapy has emerged as a focal point in HCC research. Nevertheless, research on conversion therapy is still in its nascent stages, with ongoing debates concerning the identification of suitable patient populations, optimal therapeutic regimens, and appropriate timing for conversion surgery. This review comprehensively comments on the current first-line, second-line, and adjuvant treatment regimens for HCC based on clinical trial results, which offer opportunity to be applied in conversion therapy. Furthermore, it discusses key issues in initial unresectable HCC conversion therapy and offers five directions worthy of in-depth exploration for future research in this evolving field.

The concept and significance of conversion therapy for HCC

Conversion therapy involves transforming unresectable HCC into a resectable state, primarily aimed at reducing tumor burden to enhance the R0 resection rate and mitigate surgical risks, thereby providing superior survival benefits compared to other treatments [16]. This therapeutic approach generally encompasses two categories: (1) surgically unresectable HCC: This category includes patients whose overall condition cannot endure surgical trauma, those with intolerable liver function, or those with insufficient future liver remnant (FLR) due to the large tumor or the tumor adjacent to important ducts. At present, the main strategy for addressing FLR insufficiency is associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) to induce short-term FLR hypertrophy. Compared to traditional portal vein embolization (PVE) or ligation (PVL), ALPPS can rapidly induce FLR hypertrophy (6–16.4 days) and significantly improve the surgical resection rate to 95–100% [17]. (2) Oncologically/biologically unresectable HCC: This category pertains to cases where the tumor is technically resectable, but the expected therapeutic outcome post-resection is not superior to non-surgical treatments. The primary objective of conversion therapy is to offer unresectable HCC patients a chance at radical treatment, thereby making the surgical resection after conversion therapy bring benefits in OS and recurrence-free survival (RFS) comparable to those of naïve patients who initially received radical resection [18, 19]. A real-world study observed longer EFS (not reached vs. 12.9 months, $P < 0.001$) and similar safety profile [18]. More importantly, another conversion therapy review reported five-year survival rate after resection following tumor downstaging could be up to 57%, demonstrating good long-term results and the possibility of a cure in a proportion of patients with initially unresectable HCC [19]. Furthermore, intermediate or advanced stage patients undergoing conversion resection might gain superior survival benefits than those receiving non-surgical palliative treatment or direct surgery [20, 21]. An observational prospective study demonstrated that the patients who underwent conversion resection had longer OS than those who did not (median OS not reached vs 15.9 months [95% CI 7.0–24.7 months]; $P = 0.001$) [20]. Another prospective real-world study reported a better trend of OS ($P = 0.074$) in the conversion resection than the non-surgery population [21].

Key issues in the process of conversion therapy for HCC

1.1.1.1. Accurate screening of the target population for conversion therapy

Conversion therapy aims to transition patients from unresectable to resectable and also to improve outcomes for patients whose initial resection yielded poor results. Therefore, how to accurately select the targeted population to adopt more active conversion strategies is the key. According to the CNLC staging system, which is currently the most widely utilized in China due to its alignment with local systems and practices, Chinese Experts Consensuses [22, 23] recommend that conversion therapy is suitable for three wide groups: (1) surgically unresectable CNLC Ia, Ib, and IIa patients: These patients typically exhibit intolerable liver function, insufficient residual liver volume, or tumors located near or involving major intrahepatic ducts, making

R0 resection with negative surgical margin challenging. Considering the complications or contraindications of insufficient FLR treatment, it is suggested to choose patients less than 65 years of age, with normal liver function (Child–Pugh class A, ICG-R15 < 10%), insufficient FLR volume (e.g., patients with normal liver with FLR/SLV < 40%), generally good condition and no evidence of severe liver cirrhosis, fatty liver, and portal hypertension. Conversion therapy in these cases aim to enhance liver function, increase the residual liver volume, or induce significant tumor shrinkage, facilitating R0 radical resection. (2) Surgically resectable CNLC IIb and IIIa patients without more survival benefit: These patients are classified as PVTT grade 3–4, or main hepatic vein and inferior vena cava tumor thrombus. For CNLC IIIa patients, where intrahepatic lesions are resectable but complicated by vascular invasion, the post-surgical survival time without conversion therapy ranges from 12 to 15 months [24], which is lower than that of patients receiving first-line non-surgery systemic treatment (AATDs combined with ICIs) with median OS of approximately 20 months [25]. Instead of direct resection, a multi-faceted and individualized conversion therapy approach should be employed to reduce tumor load (tumor thrombus necrosis or regression), enhance the R0 resection rate, downstage tumor and decrease surgical risk, thereby improving post-resection survival outcomes. It is encouraging that longer OS following conversion resection was observed than those who did not (median OS not reached vs 15.9 months [95% CI 7.0–24.7 months]; $P = 0.001$) [20]. (3) CNLC IIIb patients: These patients are characterized as pulmonary oligometastasis (number of tumors ≤ 5 and maximum diameter of single lesion < 3 cm) or extrahepatic lymph node metastasis. The conversion therapy strategy is to maximumly achieve metastases disappearance or complete inactivity, and downstage of the intrahepatic tumor or combined with extrahepatic metastases to resectable status.

In addition, the phenomena of pseudo-progression, a transient increase of tumor burden followed by delayed tumor shrinkage, associated with ICIs can undermine the confidence of both clinicians and patients during treatment, causing difficulties in diagnosis and comprehensive evaluation, especially a premature cessation of efficacious immunotherapeutic agents. Another phenomenon, termed hyperprogression, are under debates between polarized oncologists, with prospective studies urgently needed to confirm the underlying biology and its relation with patient outcome. Consequently, researchers are investigating predictive molecular biomarkers. Compared to serum protein biomarkers (such as alpha-fetoprotein (AFP), AFP-L3 and DCP), imaging, as well as microvascular invasion with low sensitivity and specificity, emerging biomarker of ctDNA has potentially high sensitivity and specificity. A more than 3 years' long-term follow-up study to reflect real clinical practices observed that ctDNA could detect tumors 4.6 months earlier than the imaging and precisely detect minimal residual disease (MRD) in advance [26]. ctDNA testing was demonstrated as sensitive to detect CTNNB1 (known core HCC driver gene) mutation with increased mutation detection rate of 13.5% compared to that of 8.1% in HCC tumor tissue samples, with an agreement between plasma and tissue mutational status of 91.7% (kappa value 0.53 (0.20–0.85), $P = 0.0007$) in a large proportion of CTNNB1 negative samples [27]. Another research suggested to use the noninvasive telomerase reverse transcriptase (TERT) promoter ctDNA, the independent predictor of shorter OS in unresectable HCC patients treated with combination immunotherapy, to stratify prognosis [28]. In another curative-intent hepatectomy following conversion therapy of immunotherapy plus locoregional therapy in uHCC, it was shown that ctDNA provided detectable and lasting survival benefits [29]. Other biomarkers are under investigated, such as programmed cell death ligand-1 (PD-L1) [30, 31], tumor mutational burden (TMB) [32, 33], and DNA mismatch repair deficiency (dMMR) [34]. However, the specificity of PD-L1 still remains controversial as many studies have demonstrated that patients with various solid tumors can benefit from immunotherapy regardless of PD-L1 expression status [35]. Furthermore, advanced HCC typically exhibits a low TMB, generally under 4 mutations/Mb, which limits it applied as a suitable biomarker to predict responder [36]. With the emergence of new evidence regarding ctDNA and widespread adoption of detection technologies such as NGS, more studies should be focus on refining the criteria for identifying potentially resectable patients, thereby distinguishing between subgroups that are more or less likely to benefit from conversion therapy.

2.2.2.2. Selection of conversion therapy regimens

With the introduction of ICI, its role as a key stone in unresectable and advanced HCC is becoming increasingly significant, with the newly established first-line treatment standard of atezolizumab (anti-PD-L1) combined with bevacizumab, and durvalumb (anti-PD-L1) combined with tremelimumab (anti-CTLA4) instead of sorafenib and lenvatinib. Many phase II/III promising results [37] from either ICIs alone or in combination with tremelimumab (anti-CTLA4) instead of sorafenib and lenvatinib. Is, AATDs, and locoregional treatments like transarterial chemoembolization (TACE), stereotactic body radiation therapy (SBRT), and hepatic arterial infusion chemotherapy (HAIC) have demonstrated remarkable efficacy, especially higher ORR (up to 96%) and longer OS (up to 41.6 months), which offered new hope to unrescetable HCC patients to possibly apply these promising PD-1 antagonists in conversion therapy. In addition, the first positive phase III trial (EMERALD-1) reported a significant improvement in combination therapy

(ICI + AATD + locoregional approach) progression-free survival (PFS) of 15.0 months in the first-line setting of unresectable HCC [38]. Notably, these registrational trials generally enroll patients with well-preserved liver function and attentions are needed to pay on tailoring treatments to patient-specific factors, such as insufficient FLR and liver impairment for conversion therapy. To achieve tumor downstaging, reduce tumor load, or increase residual liver volume within a short timeframe, and ultimately facilitate radical resection, it is imperative to employ aggressive conversion strategies. These strategies often involve the intensive combination of multiple treatment modalities for patients with potentially resectable HCC. Currently, conversion therapy can be categorized into three main approaches: local treatment, systemic treatment, and a combination of both. Local conversion therapies include TACE [39, 40], HAIC [41–43], transarterial radioembolization (with yttrium-90 microspheres (Y90) [44] and other agents such as holmium-166 and rhenium-188), and radiotherapy [45, 46]. Notably, holmium-166-based TARE have more advantages over Y90 [47]. First, 166Ho allows for post-procedural imaging because it emits both beta particles and gamma radiation (which is not emitted by Y90, making its imaging very challenging); second, 166Ho is capable of more precisely calculated radiation dose with improved dosimetry. Systemic therapies encompass targeted therapy, immunotherapy, and chemotherapy. Due to incomplete tumor necrosis and/or liver function impairment caused by repeated local treatments, the overall success rate of purely local therapies remains limited. However, advancements in AATDs and ICIs have significantly enhanced the efficacy of targeted therapy and immunotherapy for HCC [43, 48]. Despite this progress, the ORR for standalone targeted and immune therapies is still limited to approximately 20–30% [49, 50]. Consequently, numerous conversion strategies have been devised, yet selecting the optimal regimen among these options presents a complex challenge (Table 1).

In our view, the selection of a systemic treatment plan for conversion therapy should primarily be based on ORR and the remission profile, which includes factors such as tumor progression rate, time to remission, duration of remission, and depth of remission. A higher ORR and conversion resection rate indicate a greater potential for conversion therapy to translate into survival benefits. Additionally, the incidence of adverse events associated with conversion therapy must be considered, as a lower incidence will enhance surgical safety. Atezolizumab-based combinations reported ≥ 3 grade treatment-related adverse events (TRAEs) in 14–83.3% of HCC patients [14, 51]. Camrelizumab combinations reported ≥ 3 grade TRAEs in 24–74.3% of HCC patients across various trials [15, 64, 65].

A recently published study performed a series of meta-analyses to systematically evaluate various treatment strategies for conversion therapy in HCC [66]. This meta-analysis included 24 studies that met the inclusion criteria: 4 studies in the chemotherapy group, 7 in the TACE group, 8 in the molecular therapy group, and 7 in the combined local-systemic therapy group. The quality of 19 studies was deemed acceptable according to the IHEQA checklist, while 5 studies were rated medium to high quality based on the MINORS tool. The primary outcome of this meta-analysis was the conversion rate, with secondary outcomes including the ORR and the incidence of grade 3 treatment-related adverse events (TRAEs). The findings indicated that the conversion rates for chemotherapy, TACE, and molecular therapy were similar and relatively low. In contrast, the conversion rates for combined local-systemic therapy were significantly higher. Subgroup analysis revealed no significant differences in conversion rates among different monotherapy strategies, but combination therapy exhibited a substantially higher conversion rate compared to monotherapy. This enhanced conversion potential of combination therapy likely results from the synergistic anti-tumor mechanisms of the various treatments employed. Notably, the combination of AATDs with ICIs and local therapy yielded the highest conversion rate (33%) among all strategies examined. Similar to the trend observed in conversion rates, combination therapy demonstrated a superior ORR compared to monotherapy, with the highest ORR (73%) achieved by the combination of AATDs, ICIs, and local therapy. In terms of safety, the chemotherapy group experienced the highest incidence of significant side effects (grade ≥ 3 AEs), affecting approximately 70% of patients, which is higher than 34% (TACE), 30% (molecular therapy), and 40% (combined local and systemic treatment), respectively. The safety profiles of the TACE, molecular therapy, and local-systemic combined therapy groups were comparable and acceptable. Although combination therapy carried a slightly increased safety risk compared to monotherapy, the increase was not statistically significant. Within combination therapies, the safety of AATDs combined with ICIs was equivalent to that of AATDs combined with local therapy. Therefore, the study concludes that local-systemic combination therapy currently appears to be the most effective conversion therapy for HCC. It offers not only acceptable safety but also superior ORR and conversion potential.

Our previous study reported real-world data from 26 consecutive cases of unresectable HCC conversion therapy conducted at our center [67]. Out of 1,904 HCC patients identified, 1,672 received anti-HCC treatment, with 328 patients deemed initially resectable. Of the remaining 1344 unresectable HCC patients, 311 underwent locoregional treatment, 224 received systemic therapy, and 809 received a combination of systemic and locoregional therapy. Post-treatment, one patient from the systemic group and 25 patients from the combination group achieved resectable

Table 1 Clinical studies on combined immunotherapy and targeted therapy for hepatocellular carcinoma

References	Trial name/identifier	Combination protocol	Control group	Phase of trial	Line of therapy	Results
[51]	IMbrave150	Atezolizumab + Bevacizumab	Sorafenib	Phase III	First-line	mPFS: 6.9 months vs 4.3 months mOS: 19.2 months vs 13.4 months
[52]	ORIENT-32	Sintilimab + Bevacizumab	Sorafenib	Phase III	First-line	mPFS: 4.6 months vs 2.8 months mOS: NR vs 10.4 months
[53]	SHR-1210-III-310	Camrelizumab + Apatinib	Sorafenib	Phase III	First-line	mPFS: 5.6 months vs 3.7 months mOS:22.1 months vs 15.2 months
[54]	Leap-002	Pembrolizumab + Lenvatinib	Sorafenib	Phase III	First-line	mPFS: 8.2 months vs 8.0 months mOS:21.2 months vs 19.0 months
[55]	COSMIC-312	Atezolizumab + Cabozantinib	Sorafenib	Phase III	First-line	mPFS: 6.8 months vs 4.2 months mOS:15.4 months vs 15.5 months
[56]	NCT04052152 KEEP-G04	Sintilimab + Anlotinib	None (single arm)	Phase II	First-line	ORR: 35.0%(RECIST v1.1) ORR: 55.0%(mRECIST) mPFS: 12.2 months
[57]	NCT03347292	Regorafenib + Pembrolizumab	None (single arm)	Phase Ib	First-line	120 mg regorafenib group, ORR: 31%, DCR: 88% 80 mg regorafenib group, ORR: 18%, DCR: 91%
[58]	ALTER-H003	Anlotinib + Toripalimab	None (single arm)	Phase II	First-line	ORR: 32.3% (mRECIST) DCR: 77.4% (mRECIST) mPFS: 11.0 months mOS: 18.2 months
[59]	NCT04444167	AK104(anti-PD-1/CTLA4 bispecific antibodies, BsAbs) + Lenvatinib	None (single arm)	Phase II	First-line	Cohort A (AK104 6 mg/kg Q2W) vs Cohort B (AK104 15 mg/kg Q3W) ORR: 35.5% vs 35.7% mPFS:8.61 months vs 9.82 months mOS: 27.1 months vs NR
[60]	IMMUNIB	Nivolumab + Lenvatinib	None (single arm)	Phase II	First-line	ORR: 28% mPFS: 7.06 months mOS: 27.1 months
[61]	NCT04542837	KN046(anti-PD-L1/CTLA4 bispecific antibodies, BsAbs) + Lenvatinib	None (single arm)	Phase II	First-line	ORR: 51.9% (RECIST v1.1) DCR: 86.5% (RECIST v1.1) mPFS: 9.3 months mOS: NR
[62]	NCT03289533	Avelumab + Axitinib	None (single arm)	Phase Ib	First-line	ORR: 13.6% (RECIST v1.1) / 31.8% (mRECIST) DCR: 68.2% (RECIST v1.1) / 68.2% (mRECIST)
[63]	RESCUE	Camrelizumab + Apatinib	None (single arm)	Phase II	Second-line	mPFS: 5.5 months mOS: 21.8 months

NA not available, *NR* not reached

status. The conversion therapy demonstrated a high ORR, with 42.3% under Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and 76.9% under modified RECIST (mRECIST) criteria. The disease control rate (DCR) reached 100%, and 23 patients proceeded to curative hepatectomy. The incidence of major postoperative morbidity was comparable between the groups ($P = 0.76$). Pathological complete response (pCR) was observed in 39.1% of patients. During the conversion treatment, grade 3 or higher TRAEs were reported in 50% of patients. The median follow-up duration was 12.9 months (range 3.9–40.6) from the initial diagnosis and 11.4 months (range 0.9–26.9) from the time of resection. Disease recurrence was observed in three patients following conversion surgery. These findings align with previous studies, indicating that a combination of locoregional and systemic modalities is relatively safe and effective for conversion therapy in unresectable HCC. While short-term outcomes are promising, long-term follow-up with a larger patient cohort is necessary to comprehensively evaluate the efficacy of this approach.

Numerous studies have explored HCC conversion therapy, yet high-level evidence from evidence-based medicine to identify the optimal treatment remains lacking (Table 2). With the development of comprehensive treatment, in-depth exploration of conversion strategies for the triple combination comprising targeted therapy, immunotherapy and locoregional therapy is gradually increasing and the triple combination therapy may become a new trend of conversion approach. One prospective study demonstrated synergistic effect and manageable safety of the triple combination therapy (TACE + lenvatinib + camrelizumab) as conversion therapy for uHCC, which brought a high ORR of 76.4%, encouraging conversion resection rate of 54.5% and high R0 resection rate of 96.6% [68]. This synergistic effect could be explained from the following three perspectives [69], (1) The localized hypoxia induced by locoregional therapy (such as TACE) in tumors recruits hypoxia-inducible factor-1α to regulate hypoxia-responsive genes to trigger VEGF expression, and then the addition of VEGF inhibitor may improve local tumor control by inhibiting hypoxia-induced angiogenesis following TACE. (2) Locoregional therapy reduces tumor load, mediates tumor antigens releasing, activate antigen-specific $CD4^+$ and $CD8^+$ T cells, induce inflammatory cytokines (such as IL-1β), upregulate PD-L1/PD-1 expression in the circulation and eventually enhance immune response. (3) Systemic therapy aims at modulating the immune function of the body, improving tumor microenvironment and blocking tumor immunosuppression. Combination with VEGF inhibitor could further overcome tumor immunosuppression through inducing vascular normalization and thus synergy ICI effect.

The next challenge lies in determining which types of combinational treatments and their corresponding sequences of administration can provide the best therapeutic effect with minimal toxicity. This clinical question was studied and proven by IDEAL (Idea, Development, Exploration, Assessment, Long-term study) phase 1 study [70] and the multidisciplinary team (MDT) found that LEN-TAP conversion therapy achieved both specific goals of safety and preliminary efficacy, with treatment sequence of first lenvatinib (the initial dose was 12 mg QD for patients with body weight ≥ 60 kg and 8 mg QD for patients with body weight < 60 kg), then TACE performed 2 weeks after the initiation of lenvatinib and finally 200 mg Q3W of camrelizumab given intravenously 2 weeks after TACE procedure.

Therefore, close cooperation among MDTs is crucial, and personalized treatment plans should be tailored to the specific clinical conditions of each patient.

The primary goal of conversion therapy is to provide patients with the opportunity for radical treatment, thereby extending tumor-free survival and OS. A pertinent question arises: for patients who respond significantly to systemic treatment, is surgical resection still necessary? In the IMbrave150 [14] and CARES-310 [15] studies, OS following targeted combined immunotherapy reached approximately 20 months. However, in real-world clinical settings, the OS benefit after direct surgical resection for some patients with stage CNLC IIIA may only be 15–18 months [24]. This raises a critical question in the practice of HCC conversion therapy: Do patients who exhibit a considerable therapeutic response to systemic treatment still require surgery? The decision hinges on achieving an optimal balance between OS and quality of life. Currently, most studies on conversion therapy focus on short-term benefits such as surgical resection rates and postoperative recurrence rates as primary endpoints, with fewer studies emphasizing long-term survival. Additionally, in patients undergoing conversion therapy, robust systemic treatments have been shown to lead to pCR in HCC. However, there is no conclusive evidence supporting the long-term survival of HCC patients who achieve pCR without subsequent surgical intervention. Without the surgical removal of all primary and metastatic lesions, confirming whether a patient has achieved pCR remains challenging.

It remains uncertain whether surgical intervention is necessary for patients who achieve imaging remission following treatment. Current studies indicate that most cases in remission experience progression within 1.0–1.5 years, even with continued pharmacotherapy [84]. Drawing from the experience of liver metastasis in colorectal cancer, more than 50% of lesions that disappear (imaging complete remission) post-chemotherapy recur during follow-up [85]. Thus, while surgical resection is anticipated to extend tumor-free survival and OS, the actual benefit for patients in remission requires validation through prospective randomized controlled trials. A recent retrospective study aimed to determine the

Table 2 Evidence from studies of systemic therapy + topical therapy in conversion therapy

References	Trial name/identifier	Combination protocol	Sample size	Results
[71]	NCT04042805	Sintilimab + Lenvatinib	36(6 + 30)	ORR: 36.1% (RECIST v1.1) DCR: 94.4% conversion surgery resection rate: 30.6% (11/36) mEFS: NR mOS: NR
[72]	NCT04997850	Lenvatinib + TACE + PD-1 inhibitors (Sintilimab/Camrelizumab)	71 (combination) vs 71 (TACE)	ORR: 78.9% vs 16.9% (mRECIST) conversion surgery resection rate: 50.7% vs 15.5% mPFS: 531 ± 81.2 days vs 224 ± 33.3 days 1-year OS rate: 93.3% vs 64.3%
[73]	ChiCTR2000033692	Hepatic portal vein ligation (PVL) + Apatinib + Camrelizumab	14	ORR: 40% (evaluable in 10 cases) DCR: 100% (evaluable in 10 cases) Among 10 evaluable participants, 7 met the criteria for surgery, 5 underwent secondary hepatectomy, 1 declined surgery, and 1 was awaiting surgery. The median interval between primary and secondary surgeries was 138.8 days
[74]	ChiCTR2100050410	TACE + Camrelizumab + Lenvatinib	55	ORR: 72.0% conversion surgery resection rate: 55.3% pCR: 23.1% MPR: 69.2%
[75]	ChiCTR2000039508	HAIC + Camrelizumab + TKI	87	ORR: 35.6% (31/87) (RECIST v1.1) ORR: 71.3%(62/87) (mRECIST) DCR: 87.4%(76/87) (RECIST v1.1) DCR: 89.7%(78/87) (mRECIST) conversion surgery resection rate: 11.5% (10 cases) R0 resection rate: 100% pCR: 20% MPR: 40%
[76]	NCT05029973	HAIC + Sintilimab + IBI305	30	ORR: 66.7%(20/30) conversion surgery resection rate: 46.7% (14/30) R0 resection rate: 100% pCR:52.6%
[77]	START-FIT	Sequential after transarterial chemoembolization and stereotactic radiotherapyAvelumab	33	18 (55%) patients were deemed amenable to curative treatment: conversion surgery resection rate:12%(4/33) CR %: 42%(14/33)
[21]		Toripalimab + Lenvatinib + TACE vs Lenvatinib + TACE	51	ORR: 76.7% vs 47.6% DCR: 90.0% vs 57.1% OS/EFS: NR Conversion resection rate: 50.0% vs 19.0%
[78]		Lenvatinib + Sintilimab + TACE	98(37vs 61)	potentially resectable population (PRP): ORR: 67.6%(RECIST v1.1) ORR: 75.7%(mRECIST) conversion rate: 40.5%(15/37) pCR: 20%(3/15) non-potentially resectable population (NPRP): ORR: 22.9%(RECIST v1.1) ORR: 31.1%(mRECIST) mPFS: 25 months vs 13 months mOS: NR vs 21 months
[79]		HAIC + TKIs + anti-PD-1 antibodies	67	pCR: 34.3%(23/67) mRFS: 19.3 months mOS: 28.7 months

Table 2 (continued)

References	Trial name/identifier	Combination protocol	Sample size	Results
[80]	LTHAIC	Lenvatinib + Toripalimab + Hepatic artery infusion chemotherapy	33	ORR: 63.9%(RECIST v1.1) ORR: 66.7%(mRECIST) CR%: 13.9% mPFS: 10.5 months mOS: NR mDOR: 12.1 months Conversion resection rate: 24.2%(8/33) pCR: 3.0%(1/33)
[81]	ChiCTR2100043462	TACE + Donafenil + Camrelizumab	16	Conversion resection rate: 80.0%(12/15) R0 resection rate: 100% MPR: 50.0%(6/12) ORR: 81.3%, DCR: 93.8%(mRECIST) mEFS: 9.0 months
[82]	NCT05213221	Enafolimab + Lenvatinib + TACE	36	ORR: 36.1%(RECIST v1.1) ORR: 80.6%(mRECIST) DCR: 77.8%(RECIST v1.1) DCR: 83.3%(mRECIST) Conversion resection rate: 30.5%(11/36)
[83]	DoHAICs study	Donafenil + HAIC + Sintilimab	24	ORR: 78.3%(mRECIST,CR 13.0%;PR 65.2%) Conversion resection rate: 65.2%(15/23), pCR: 30.0%(3/10) MPR: 50.0%(5/10) mPFS: 10.2 months

necessity and prognostic value of salvage hepatectomy for patients with unresectable HCC who achieved clinical complete response (cCR) after conversion therapy [86]. The findings revealed no significant differences in disease-free survival (DFS) and OS between the surgical and non-surgical groups (HR = 1.547, 95% CI 0.512–4.669, $P = 0.439$; HR = 1.024, 95% CI 0.168–6.242, $P = 0.979$, respectively), illustrating that salvage hepatectomy might not be essential for unresectable HCC patients with cCR, particularly those at high risk for surgical complications [86]. Similar results of possibly unnecessity of salvage hepatectomy for patients with cCR were also observed in a larger retrospective study of 1880 uHCC patients, and the study team observed that watch-and-wait (W-W) strategy (NCCN guideline recommendation with certain restrictions) yielded comparable OS and PFS rates to salvage surgery (SR) in patients with cCR after conversion therapy [87]. Another recent retrospective study found both OS and PFS were significantly better in the SR group in patients who were assessed as partial responses (PR) than those in the non-SR group [88]. Therefore, salvage surgery is preferred to unresectable HCC patients with partial response after conversion therapy, while for those achieving complete response, a watch-and-wait strategy may be a viable alternative [86–88]. Notably, radiologic complete response (rCR) subsequent optimal management remains unclear. First, rCR or cCR achievement does not unequivocally guarantee that pathological CR (pCR) has been reached (such as only 41.3% of patients with rCR were confirmed as pCR in study [87]), unless verified through surgical resection. Even pCR cannot be equivalent to absolute CR. Second, rCR might also develop to in situ recurrence. Third, the study [87] observed a better PFS in the SR group than in the W-W group (46.5 vs 14.4%, $P = 0.002$), suggesting that patients may still benefit from the resection of residual lesions.

This discussion illuminates the complexities surrounding the necessity of salvage hepatectomy, but it also raises the critical issue of establishing a unified standard for cCR. In our previous study [89], we addressed this clinical question and proposed the following criteria for defining cCR in HCC: (1) imaging complete response: All tumors must achieve complete response according to mRECIST guidelines; (2) biochemical complete response: Baseline positive serum tumor markers must return to the normal range; (3) exclusion of distant metastasis: This must be confirmed by computed tomography (CT) and positron emission tomography-CT (PET-CT) examinations; 4) Stability over time: The aforementioned conditions must remain stable for a specified period. The three aforementioned studies [86–88] have emphasized the necessity for prospective trials with long-term follow-up to thoroughly evaluate this treatment option. A significant phase III study (TALENTop), currently underway in multiple centers in China (NCT04649489), aims to compare the benefits of surgical resection in patients with objective remission or stable disease over time. The outcomes of this study are eagerly anticipated.

There is ongoing debate among researchers regarding the optimal timing for sequential surgical resection after successful conversion therapy. Some experts advocate for immediate surgical resection once the patient is deemed surgically resectable. They argue that prolonged conversion therapy could lead to irreversible liver function impairment, thereby compromising the safety of the operation and patient tolerance. Simultaneously, there is a risk of tumor progression during conversion therapy, potentially resulting in the loss of surgical opportunities. This approach mirrors the management of liver metastasis from colorectal cancer, where surgery is recommended as soon as the lesion becomes resectable. Conversely, another perspective suggests maintaining the conversion regimen to maximize its therapeutic effect. Studies have demonstrated that the survival benefit for HCC patients post-conversion resection correlates with the degree of pathological remission, with longer DFS observed in patients achieving pCR.

The Chinese Experts Consensus recommended that choosing the optimal operation time should be deliberated in light of both efficacy and safety considerations and the surgery can be performed when (1) tumors reach objective remission (partial response/complete response) or at least maintain stable disease for 3–4 months before-surgical resection; and (2) adverse events (if occurred during TKIs or ICIs conversion therapy) return to grade I or normal [22]. Different conversion therapies may consider different timing of resection because of different drug half-life, administration frequency and presence/absence of AE, etc. For small molecular TKIs, literatures reported that continues use did not increase postoperative complications. For AATDs, 4–6 weeks is suggested to guarantee the safety of hepatectomy to minimize its anti-angiogenic effect which leads to increased bleeding risk and reduced wound healing capacity. For ICIs, it is notably to pay a careful attention on evaluating immune hepatitis not only through conventional markers of AST/ALT, but also liver aspiration biopsy, which can observe inflammatory, lymphocyte infiltration and hepatocyte necrosis. For TACE, 4–6 weeks between the last round of TACE and surgery are suggested with very limited/no significant effect on the perioperative complication rate, mortality rate, etc. Overall, the timing recommendation is based on the premise that early surgery might not fully leverage the therapeutic benefits of conversion therapy and might bring an increased surgery risk or even surgical death (immune hepatitis case after ICIs), whereas delaying surgery might risk secondary drug resistance and tumor progression. Current research on the optimal timing of sequential surgical resection following successful conversion remains limited. Therefore, further studies are required to balance the postoperative survival benefits of deeper remission against the risks of tumor progression and resection safety.

For patients who meet the following criteria after conversion therapy, surgical resection can be considered: (1) tumor response: According to the mRECIST standard, the tumor should achieve partial response or complete response, or maintain stable disease for 3–4 months, indicating that surgery may offer additional benefits. (2) Surgical resectability: The tumor should be amenable to R0 resection, which includes achieving a wide surgical margin, and ensuring the inactivation and retraction of any vascular cancer thrombus. (3) Liver function: Post-R0 resection, adequate liver function must be maintained. The remaining liver volume should be at least 40% of the standard liver volume. 4) Liver function scores: the Child–Pugh score should be ≤ 7, and the indocyanine green retention rate at 15 min should be $\leq 20\%$. The Eastern Cooperative Oncology Group performance status (ECOG-PS) score should be 0 to 1. 5) Absence of extrahepatic disease: There should be no extrahepatic lesions or other surgical contraindications, such as significant damage to vital organs caused by systemic treatment.

(4) Formulating adjuvant therapy post-conversion resection

Postoperative adjuvant therapy aims to prevent tumor recurrence following radical treatment, thereby reducing recurrence and/or metastasis and extending OS in patients. The recurrence rate of HCC can reach up to 70% within five years post-surgery, due to the presence of microscopic spreading foci or multicentric occurrence prior to surgery [7]. Key risk factors for high recurrence rates include multiple tumors, tumor size greater than 5 cm, poor differentiation (Edmondson grade III-IV), microvascular or macrovascular invasion, lymph node metastasis, narrow surgical margins (≤ 1 cm), and persistent abnormalities in tumor markers such as AFP and des-gamma-carboxy prothrombin (DCP). The main challenge in HCC management is that tumor recurrence and metastasis significantly impact long-term survival with no effective adjuvant therapy to prevent recurrence post-surgery. This is particularly true for patients who have undergone neoadjuvant or conversion therapy prior to surgery, as there is limited high-level evidence-based medicine supporting the use of adjuvant therapy after achieving R0 resection.

A prospective phase III randomized controlled trial, the STORM study, indicated that sorafenib did not extend recurrence-free survival (RFS) or OS in HCC patients who underwent radical resection or ablation [90]. However, the majority of patients in the STORM study were early-stage HCC patients without high recurrence risk factors, which may account for the lack of positive outcomes. The first international multicenter phase III clinical trial to report positive result in HCC adjuvant setting was IMbrave050, which assessed the efficacy and safety of atezolizumab plus

bevacizumab as early postoperative adjuvant therapy for HCC patients with high-risk recurrence factors. The first interim analysis result showed a statistically significant improvement in independent review facility (IRF) assessed RFS in the treatment group compared to active surveillance (HR: 0.72 [adjusted 95% CI 0·53–0·98]; $P = 0·012$) with a median follow-up of 17.4 months [91]. Unfortunately, initial RFS benefit was not sustained over time (median follow-up, 35.1 months) with the updated RFS HR from the second IA analysis of 0.90 (95% CI 0.72, 1.12) [92]. Though no new safety concerns were observed and post hoc analyses showed pronounced recurrence delay with atezolizumab + bevacizumab within the first 12 months after curative-intent resection in some patients, the benefit-risk profile did not support atezolizumab + bevacizumab as an adjuvant therapy for all patients with high-risk HCC. These results inform future ways to improve patient outcomes. IMbrave050 considered high-risk factors but the actual risk of recurrence was insufficient, such as very similar baseline characteristics with failed STORM study of prior resection (87.7% and 81%), longest diameter of largest tumor (5.3 cm and 3.5 cm), single tumor (90.8% and 91%), tumor numbers of 2 (6.8% and 8%), and tumor numbers of 3 or more (6.8% and 8%) [90, 92]. Furthermore, the selection criteria for surgical and ablation populations were not uniform across countries (e.g., Europe/USA generally took recommendations from BCLC guidance [93] and enrolled prior resection patients of BCLC 0 or A stage than those in China with later stages up to BCLC B or even C recommended by China guidance [94]), which also affected treatment outcomes [8]. Other phase III studies in adjuvant setting are currently underway, such as toripalimab (JUPITER-04), durvalumab combined with bevacizumab (EMERALD-2), and pembrolizumab (KEYNOTE-937). In future, restriction of BCLC stages, unweighted risk factors, modeling of relapse prediction and dynamic MRD detection through ctDNA, etc. should be taken into account comprehensively for both clinical trials design and patient management in real-world practice.

The Chinese Expert Consensus recommended that AATDs combined with ICIs should be continued for 6 to 12 months following conversion resection, starting one month after surgery [22]. For postoperative adjuvant therapy, the following principles should be emphasized: (1) effectiveness and safety: Ensure the chosen regimen remains effective and has an acceptable safety profile. (2) Original conversion regimen: Continue with the original conversion therapy regimen. (3) Patient tolerance: Take into account the patient's tolerance to the treatment. (4) Individualized treatment: Tailor the treatment plan based on the postoperative pathological condition of each patient. In summary, the use of AATDs and ICIs, either alone or in combination, is anticipated to enhance the prognosis for HCC patients with high-risk recurrence factors. However, further high-quality, evidence-based clinical research is essential to validate these findings and optimize treatment strategies.

(5) Formulating subsequent or second-line treatment plans for patients with conversion failure

Currently, FDA has approved TKIs, such as regorafenib [95], cabozantinib [96], and ramucirumab [97], and ICIs like pembrolizumab [98, 99], nivolumab [100], and nivolumab plus ipilimumab [101] as second-line standard treatments for treating advanced HCC. It is to note that these registrational pivotal trials were studied in patients who received sorafenib as first-line treatment. As atezolizumab plus bevacizumab was approved by FDA as the first-line therapy in advanced HCC in 2020, optimal subsequent second-line regimen following Atezol + Bev were well studied these years. Mayo Clinic Study in this patient setting found that there was no statistically significant difference in OS between AATDs and ICIs and worse liver functions may impact the therapeutic benefit and tolerability of subsequent second-line therapy [102].

For patients experiencing conversion failure, such as treatment-resistant, tumor progression, insufficient FLR growth, and the deterioration of basic liver disease, the formulation of subsequent or a second-line treatment plan should be individualized based on their specific clinical circumstances (underlying liver disease, prior treatments, progression pattern (intrahepatic/extrahepatic increase in tumor size, new intrahepatic lesion, and new extrahepatic lesion) and patients' willingness): (1) conversion failure with tumor progression: (a) intrahepatic increase in tumor size while stable extrahepatic lesion: TACE or HAIC is recommended [22]. (b) New lesions while stable lesions of all the others: RFA can be selected to treat this new lesion. (c) Both intrahepatic and extrahepatic progression: active combination systemic therapy is suggested with different MOAs, such as TKIs, ICIs, and systemic chemotherapy. (2) Intolerance to further conversion therapy: If the patient's organ function cannot endure additional conversion therapy, the second-line regimen should consider a "downgrading" approach. For instance, if the first-line treatment consisted of local therapy combined with AATDs and ICIs, the second-line treatment might shift to an AATDs and ICIs combination regimen or monotherapy with fewer adverse effects. (3) Deterioration of underlying liver disease: Active symptomatic and supportive therapy can be the option. (4) Patients' willingness and monitoring compliance: as HCC evolution process is in deep complexed, close follow-up (shorten to 4–6 weeks if possible) is also helpful for clinical decision.

(6) Other issues worthy of extensive and in-depth exploration

Several issues remain unresolved, warranting further investigation and discussion: (1) discrepancy between imaging and pathological complete response to immunotherapy: A comprehensive post hoc analysis of the IMbrave150 study by comparing with comparable patients from an international multicenter real-world study who underwent resection after atezo-bev treatment (PR or SD per imaging assessment), observed a remarkable discrepancy between radiologic and pathological findings and demonstrated that current imaging techniques were insufficient to fully detect pCR cases as around half of the durable PR tumors and even some SD tumors appeared to be ghost tumors (radiologically persistent tumors without viable cancer cells) [103]. Furthermore, prospective high-level evidence is urgently needed to explain the scientific question whether it is necessary to perform hepatectomy for unresectable HCC patients who achieved cCR following conversion therapy as one retrospective study has observed no prognostic value and doubted its necessity, particularly in those at high risk for surgical complications [86]. Thus, how does cCR determined by imaging and clinical indicators compare to pCR? How to address the controversy over whether or not to perform surgery in patients who were converted to cCR? Establishing standardized criteria for determining cCR in HCC and verifying it in prospective trials are crucial. 2) Drug management and surgical safety: How can drugs be managed to ensure the safety of operations, and what criteria should be used to choose the mode of operation? (3) Suitability of conversion therapy for patients with vascular tumor thrombus: Are patients with tumor thrombus in the vena cava or main portal vein suitable candidates for conversion therapy? The TALENTop study aimed to address this question and clarify conversion response and prognostic factors in HCC patients with macrovascular invasion and without extrahepatic metastasis treated with Atezo/bev [104]. The study enrolled a total of 201 patients (all patients with MVI at baseline and 95% with PVTT) and showed high response rate (18.9% of ORR and 71.6% of DCR), high conversion rate (36.3%), as well as manageable safety profile (Grades ≥ 3 TRAEs:12.9%; most common TRAEs: fever (13.4%) and proteinuria (10.9%)) in the HCC patients with MVI, indicating that conversion strategy in this population holds promise. (4) Simple, practical, and reliable biomarkers to early detect recurrence and predict clinical outcome: The evolution of HCC is deeply complex and non-invasive biomarkers with new technologies are needed to be explored to support medical decision. Qiu et al. [105] developed a simplified point system (0, 2 for low/high TBS, 0, 1 for low/high AFP and 0,1 for ALBI grade 1/2), named TAA score (tumor burden score (**T**BS)-**A**FP-albumin-bilirubin (**A**LBI), which was independently associated with HCC patient survival after resection. Yang et al. [106] developed the *TORNADO* technology to detect MRD based on ctDNA methylation and mutations and offered superior predictive power for recurrence in early-stage HCC patients compared to traditional biomarkers, like AFP and DCP. Yang et al. [107] constructed a nomogram based on systemic immune inflammation index and prognostic nutrition index and proved its better recurrence prediction than BCLC and AJCC8th. Lin et al. [108] selected $a \geq 80\%$ decrease in AFP level as a surrogate marker to observe RFS in uHCC patients who underwent salvage hepatectomy following conversion therapy with TKI and ICIs. It was revealed that AFP responders had significantly better postoperative RFS compared to non-responders ($P < 0.001$). Chuma et al. [109] explored predictive ability of serum CXCL9 and LAG-3 levels in uHCC treated with atezolizumab plus bevacizumab and demonstrated that they were both independent positive predictive factors. Shirane et al. [110] dynamically monitored peripheral T cell status and observed that high CD8 + central memory T (TCM) cells at baseline could predict longer PFS was independently, indicating its potential as a surrogate biomarker during ICIs treatment in HCC patients. (5) Multidisciplinary team model: The complexity of HCC, especially uHCC with goal of curative-intent resection, requires collective decision-making to finally achieve alignment on personalized conversion therapy plan through effective communication and collaboration among MDT members from targeted population definition, appropriate conversion strategy selection, resection timing determination and follow-up, etc.[111]. Good MDT is not just applied for conversion therapy process but also the full-cycle management in HCC. Currently, the limited evidence available cannot fully address all these five questions mentioned above. Further clarification requires well-designed clinical trials with larger sample sizes and extended follow-up periods.

Summary and prospect

At the time of diagnosis, more than two-thirds of HCC patients in China present at intermediate or advanced stages. Conversion therapy offers the potential for radical cure in these patients, thereby improving OS. Recent advancements in systemic therapies, such as AATDs and ICIs, have provided powerful tools for conversion therapy. However, conversion therapy remains in an exploratory phase, with numerous unresolved issues requiring thorough investigation. We anticipate the results of ongoing clinical trials and future studies to provide valuable insights, ultimately extending the OS of HCC patients worldwide.

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Author contribution All authors made a significant contributions to the reported work, including in the conception, study design, experimental implementation, execution and/or interpretation; participated in

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Declarations

Conflict of interest The authors declare no competing interests.

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