Review

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Conversion therapy for initially unresectable hepatocellular carcinoma: Current status and prospects

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SUMMARY Research has shown that locoregional and/or systemic treatments can reduce the tumor stage, enabling radical surgical resection in patients with initially unresectable hepatocellular carcinoma. This is referred to as conversion therapy. Patients who undergo conversion therapy followed by curative surgery experience a significant survival benefit compared to those who receive chemotherapy alone, those who are successfully downstaged with conversion therapy but not treated with surgery, or those who are treated with upfront surgery. Several treatments have been studied as conversion therapy. However, the success rate of conversion varies greatly, ranging from 0.8% to 60%. Combined locoregional plus systemic conversion therapy has demonstrated significant clinical advantages, with a conversion rate of up to 60%, an objective remission rate of 96% for patients, and a disease control rate of up to 100%. However, patients who underwent conversion therapy experienced significantly more complications than those who underwent direct LR without conversion therapy. Conversion therapy can cause hepatotoxicity, bone marrow suppression, local adhesions, increased fragility of blood vessels and liver tissues, and hepatic edema, which can increase the difficulty of surgery. In addition, criteria need to be established to evaluate the efficacy of conversion therapy and subsequent treatment. Further clinical evidence in this area is urgently needed.

Keywords TACE, TARE, TKI, immunotherapy, clinical trial, adjuvant therapy

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and the third leading cause of cancer-related deaths worldwide. The majority of HCC cases occur in Asian countries (*1*). Treatment allocation is a critical step in managing patients with HCC due to the high heterogeneity of the disease at the clinical, pathologic, and molecular levels. Surgical resection is considered the most effective treatment for primary HCC. However, many patients may not be eligible for liver resection (LR) initially due to anatomical limitations, multifocal disease, insufficient functional hepatic reserve, extrahepatic metastases, or comorbidities (*2*). Unresectable hepatocellular carcinoma (uHCC) is defined as HCC confined to the liver but not suitable for surgical or radical treatment, according to the latest guidelines worldwide. The treatment of uHCC remains a challenge in this field.

Conversion therapy is a treatment aimed at downstaging initial uHCC to resectable HCC, providing the opportunity for subsequent curative resection (*3,4*). According to one study, patients who underwent a liver resection (LR) after tumor downstaging had a 5-year survival rate ranging from 24.9% to 57% (*5*). According to recent studies, conversion therapy has been found to increase tumor-free survival (TFS) and overall survival (OS) of patients with uHCC. However, the conversion rate from unresectable to resectable disease varies widely, ranging from 0.8% to 60% (Table 1). The surgical conversion rate with locoregional therapy alone ranges from 5.6% to 28.6%, that with systemic therapy alone ranges from 4.9% to 52%, and that with combined locoregional and systemic therapy ranges from 12% to 60%. Conversion therapy for HCC is performed in Asia with reported conversion rates ranging from 0.8% to 60% in China, 6.8% to 20% in South Korea, and 4.6% to 31.8% in Japan. In the US, locoregional or systemic therapy conversion rates ranged from 9% to 33%. Transarterial radioembolization (TARE) conversion rates

Table 1. Clinical trials on conversion therapy for initially unresectable hepatocellular carcinoma

District	Conversion rate	Conversion therapy	Study design	Patients	ORR	DCR	Median PFS	Median OS
China								
Zhang *et al.* (*6*)	60.0%	Angiogenesis inhibitors+PD-1 inhibitors + HAIC (FOLFOX)	Retrospective	BCLC C	96.0%	100%	NR	NR
He *et al.* (*7*)	57.6%	PVE+TACE	Retrospective	Unresectable HCC (≥5 cm) with ipsilateral PVTT	N/A	N/A	8 months	29.4 months
Zeng *et al.* (*8*)	53%	Hepatic artery ligation+intra-arterial 131I-Hepama-1 MAb	Retrospective	Unresectable HCC	72%	N/A	N/A	N/A
Wu *et al.* (*9*)	53%	Lenvatinib+PD-1 inhibitors+TACE	Retrospective	BCLC A/B/C	77.4%	91.9%	NR	NR
Zhang *et al.* (*10*)	52.6%	TACE+PD-1 inhibitors+TKI	Prospective, multi-center	BCLC B/C	84.2%	94.7%	12 months (91.7%)	12 months (96.4%)
Zhang *et al.* (*11*)	51.0%	Lenvatinib+PD-1 inhibitor	Non-randomized, phase IV	BCLC B/C	53.1%	N/A	12 months	12 months
Qu *et al.* (*12*)	50%	Lenvatinib+TACE+toripalimab	Retrospective	BCLC B/C	76.7%	80%	NR	NR
Li *et al.* (*13*)	48.8%	HAIC (FOLFOX)+TACE	Retrospective	BCLC A/B	14.6%	92.7%	NR	NR
Liu *et al.* (*14*)	46.7%	HAIC (FOLFOX)+sintilimab+IBI305	Prospective, single-arm, phase-II	CNLC IIb/IIIa/IIIb	66.7%	N/A	N/A	N/A
Liu *et al.* (*14*)	42.4%,	Lenvatinib+PD-1 inhibitors	Prospective	Unresectable HCC	45.5%	N/A	N/A	N/A
Gan *et al.* (*15*)	40.5%	Lenvatinib+sintilimab+arterially directed therapy	Retrospective	Potentially resectable HCC	75.7%	86.5%	25 months	NR
Wu *et al.* (*16*)	38.7%	TACE+lenvatinib+PD-1 inhibitors	Retrospective	BCLC A/B/C	N/A	N/A	NR	NR
Li *et al.* (*17*)	34.0%	Lenvatinib+TACE+PD-1 inhibitors	Retrospective	BCLC A/B/C	87.2%	93.6%	NR	NR
Wang *et al.* (*18*)	33%	Sintilimab+lenvatinib	Prospective, single-arm, phase-II	BCLC B/C	35.0%	94.4%	NR	NR
Yi *et al.* (*19*)	28%	Lenvatinib+PD-1 inhibitors	Retrospective	BCLC A /B/C	50%	100%	12 months (61.6%)	12 months (95.7%)
Chen *et al.* (*20*)	25.7%	Pembrolizumab+lenvatinib+TACE	Retrospective	BCLC B /C	47.1%	70.0%	9.2 months	18.1 months
Zhu *et al.* (*21*)	23.8%	TKI+ PD-1 inhibitor	Retrospective	BCLC B /C	49.5%	79.2%	12 months (75%)	12 months (95.8%)
Zeng *et al.* (*8*)	23%	TACE+EBRT	Retrospective	Unresectable HCC	86%	N/A	N/A	N/A
Qu *et al.* (*12*)	19%	Lenvatinib+TACE	Retrospective	BCLC B/C	47.7%	57.2%	8 months	20.6 months
Luo *et al.* (*22*)	18.6%	HAIC+PD-1 inhibitor+TKI	Retrospective	BCLC B/C	57.2%	89.7%	9.7 months	N/A
Sun *et al.* (*23*)	18.3%	PD-1 inhibitor+TKI	Prospective, cohort	BCLC A /B/C	N/A	N/A	N/A	N/A
Leung *et al.* (*24*)	18%	PIAF	Prospective, Phase II	Advanced HCC	N/A	N/A	N/A	N/A
He *et al.* (*25*)	16.9%	Lenvatinib+ PD-1+HAIC (FOLFOX)	Retrospective	BCLC C	67.6%	90.1%	11.1 months	NR
Zhu *et al.* (*26*)	15.9%	PD-1 inhibitor+TKI	Retrospective	BCLC A /B/C	N/A	N/A	NR	NR
He *et al.* (*27*)	12.8%	Sorafenib+HAIC (FOLFOX)	Randomized, open-label	BCLC C	40.8%	N/A	7.03 months	13.7 months
Chiang *et al.* (*28*)	12%	TACE+SBRT+avelumab	Single-arm, phase 2 trial	Locally advanced HCC	N/A	N/A	N/A	N/A
Lau *et al.* (*3*)	11.8%	Doxorubicin or doxorubicin +TARE (yttrium-90)	Retrospective	Unresectable HCC	N/A	N/A	N/A	N/A
Li *et al.* (*29*)	11.5%	TACE+camrelizumab + TKI	Retrospective	BCLC B/C	71.3%	89.7%	10.5 months	NR
Chen *et al.* (*20*)	11.1%	Lenvatinib+TACE	Retrospective	BCLC B/C	27.8%	52.8%	5.5 months	14.1 months
Zhang *et al.* (*30*)	9.8%	TACE	Retrospective	Unresectable HCC	100%	N/A	N/A	49 months
Li *et al .*(*13*)	9.5%	c-TACE	Retrospective	BCLC A/B	2.4%	54.8%	9.2 months	13.5 months
Lau *et al .*(*3*)	5.6%	TARE (yttrium-90)	Retrospective	Unresectable HCC	N/A	N/A	N/A	N/A
Lau *et al.* (*3*)	4.7%	PIAF or PIAF+TARE (yttrium-90)	Retrospective	Unresectable HCC	N/A	N/A	N/A	N/A
Zhang *et al.* (*31*)	3.1%	Systemic+locoregional treatment	Retrospective	Unresectable HCC	76.9%	100%	12.9 months (86.9%)	11.4 months
He *et al .*(*27*)	0.8%	Sorafenib	Randomized, open-label	BCLC C	2.46%	N/A	2.6 months	7.13 months

Abbreviations: BCLC, Barcelona Clinic Liver Cancer staging system; CCRT, concurrent chemoradiotherapy; CNLC, Chinese Liver Cancer staging system; c-TACE, conventional lipiodol-based chemoembolization; DCR, disease control rate; EBRT, external beam radiotherapy; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; LR, liver resection; LT, liver transplantation; N/A, not available; NR, not reached; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival; PIAF, cisplatin/interferon alpha-2b/doxorubicin/5-fluorouracil; PVE, portal vein embolization; PVTT, portal vein tumour thrombus; RT, radiotherapy; SBRT, stereotactic body radiotherapy; TACE, transcatheter arterial chemoembolization; TARE, transarterial radioembolization; TKI, tyrosine kinase inhibitor.

Table 1. Clinical trials on conversion therapy for initially unresectable hepatocellular carcinoma

District	Conversion rate	Conversion therapy	Study design	Patients	ORR	DCR	Median PFS	Median OS
Japan								
Kudo *et al*. (*32*)	31.8%	Atezolizumab+bevacizumab	Retrospective	BCLC A/B	36.4%	81.8%	NR	NR
Kudo *et al*. (*33*)	28.7%	Atezolizumab+bevacizumab	Retrospective	BCLC B	N/A	N/A	N/A	N/A
Takeyama *et al*. (*34*)	12.5%	Sorafenib	Retrospective	Advanced HCC	N/A	N/A	NR	NR
Shimose *et al*. (*35*)	10.9%	Atezolizumab+bevacizumab	Retrospective	BCLC B/C	32.0%	84.0%	NR	NR
Tomonari *et al*. (*36*)	5.3%	Atezolizumab+bevacizumab	Retrospective	BCLC B/C	20.4%	79.6%	12.6 months	40.3 months
Tomonari *et al*. (*36*)	4.6%	Lenvatinib	Retrospective	BCLC B/C	26.7%	89.3%	12.6 months	40.3 months
South Korea								
Byun *et al*. (*37*)	20% (≥ 72 Gy), 12%(< 72 Gy)	RT (≥72 Gy or <72 Gy) +HAIC (fluorouracil)	Retrospective	BCLC C	N/A	N/A	N/A	104 months
Lee *et al*. (*38*)	16.9 %	CCRT+HAIC (FOLFOX)	Retrospective	Advanced HCC	N/A	N/A	N/A	23 months
Lee *et al*. (*39*)	12.8%	TACE+CCRT or TACE+RT	Retrospective	BCLC B/C	68.0%	N/A	24.9 months (LR), 30.6 months (LT)	166 months (LR), 62.5 months (LT)
Yoon *et al*. (*40*)	11.1%	TACE+RT	Randomized	BCLC C	N/A	N/A	7.75 months	13.75 months
Lee *et al*. (*41*)	6.8%	CCRT	Retrospective	Unresectable HCC	83.3%	N/A	N/A	N/A
USA								
Kaseb *et al*. (*42*)	33%	Modified PIAF	Retrospective	Unresectable HCC with no hepatitis or cirrhosis	36%	N/A	N/A	21.3 months
Meric *et al*. (*43*)	16%	HAI	Retrospective	Unresectable HCC	N/A	N/A	NR	NR
Labgaa *et al*. (*44*)	9%	TARE (yttrium-90)	Retrospective	BCLC A/B/C	N/A	N/A	N/A	47 months
Spain								
Inarrairaegui *et al*. (*45*)	28.6%	TARE (yttrium-90)	Retrospective	BCLC A/B	N/A	N/A	N/A	NR
Italy								
Tabone *et al*. (*46*)	20%	TARE (yttrium-90) (454 or 248 or 138 Gy)	Retrospective	BCLC C	N/A	N/A	N/A	54, 30 and 11 months

Abbreviations: BCLC, Barcelona Clinic Liver Cancer staging system; CCRT, concurrent chemoradiotherapy; CNLC, Chinese Liver Cancer staging system; c-TACE, conventional lipiodol-based chemoembolization; DCR, disease control rate; EBRT, external beam radiotherapy; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; LR, liver resection; LT, liver transplantation; N/A, not available; NR, not reached; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival; PIAF, cisplatin/interferon alpha-2b/doxorubicin/5-fluorouracil; PVE, portal vein embolization; PVTT, portal vein tumour thrombus; RT, radiotherapy; SBRT, stereotactic body radiotherapy; TACE, transcatheter arterial chemoembolization; TARE, transarterial radioembolization; TKI, tyrosine kinase inhibitor.

were reported to be 20% in Spain and 28.6% in Italy. The variation in conversion rates is primarily related to the choice of the conversion therapy regimen and the patient's disease stage, systemic status, and response to treatment. However, there is controversy regarding the timing of conversion therapy, the new challenges faced in surgery after conversion therapy, and the establishment of endpoints for clinical studies. This paper has analyzed and summarized the current status of clinical trials on conversion therapy in patients with unresectable HCC, and it discusses the prospects for the development of conversion therapy based on the results of relevant research.

2. Conversion therapy improves the prognosis for patients with uHCC

2.1. Conversion therapy for uHCC *vs*. systemic therapy alone

Conversion therapy has been found to result in better patient outcomes and longer survival rates compared to systemic therapy for uHCC. Patients receiving transarterial chemoembolization (TACE) plus radiotherapy (RT) conversion therapy had a significantly higher 12-week progression-free survival (PFS) rate (86.7% *vs*. 34.3%, $p < 0.001$), longer median time to progression at 24 weeks (31.0 *vs*. 11.7 weeks, $p < 0.001$), and longer OS (55.0 *vs*. 43.0 weeks, $p = 0.04$) than those receiving sorafenib alone (*40*). A study found that patients who underwent conversion therapy had a significantly longer median OS of 1208 days (range: 1064 to not reach) compared to those who received chemotherapy alone with a median OS of 569 days (range: 466 to 704, $p < 0.01$) (*36*).

In classic clinical trials of systemic therapies for uHCC, such as SHARP (*52*), RELECT (*51*), CheckMate 040 (*47*), CheckMate-040 cohort 4 (*47*), IMbrave150 (*48,49*), HIMALAYA (*50*), REACH-2 (*53*), CELESTIAL (*54*), and RESORSE (*55*), results indicated the achievement of an objective response rate (ORR) ranging from 2% to 29.8%, a disease control rate (DCR) of 43–75.5%, a median PFS of 2.8–7.4 months, and a median OS of 8.5–19.2 months. As shown in Table 1, patients who underwent conversion therapy had an ORR ranging from 2.4% to 96%, a DCR ranging from 52.8% to 100%, a median PFS ranging from 2.6 to 25 months, and a median OS ranging from 7.13 to 166 months. Further comparative studies with conventional systemic therapy need to be conducted to more directly demonstrate the prognostic role of translational therapy for patients with advanced hepatocellular carcinoma.

2.2. Surgery after conversion therapy downstaging *vs*. no surgery after successful downstaging

Surgical resection can optimize the prognosis for patients with uHCC who have undergone successful conversion therapy. The OS rates at 1, 2, and 5 years postoperatively were 90%, 58%, and 42%, respectively, for patients who underwent conversion therapy (*56*). Patients with advanced HCC that was initially unresectable had a good long-term survival after undergoing concurrent chemoradiotherapy (CCRT) followed by hepatic arterial infusion chemotherapy (HAIC) conversion therapy in the curative resection group compared to the non-surgery group (49.6% *vs*. 9.8% at 5 years; $p < 0.001$) (*38*). Compared to patients whose cancer was successfully downstaged without surgery, patients who underwent conversion therapy and then received radical treatment had a significantly longer median survival. The surgery group had 2-, 4-, and 5-year survival rates of 93%, 47%, and 26%, respectively, which were significantly better than the 2-, 4-, and 5-year survival rates of 74%, 18%, and 10% in the group that refused surgery ($p = 0.019$) (*30*). In addition, patients with HCC and major vessel invasion (MVI) who underwent surgery had a significantly better median OS of 58 months compared to 30 months in the group that refused surgery ($p = 0.024$) (*30*). In patients with Barcelona Clinic Liver Cancer (BCLC) stage C advanced HCC who received liver-directed simultaneous radiotherapy, those who underwent surgery had a significantly longer median OS (104 months *vs*. 11 months, $p < 0.001$) (*37*).

Studies have reported that patients with uHCC treated with TACE alone have a median survival ranging from 19 to 38 months (*57-61*). When conversion therapy with TACE is conducted, however, the median survival can be extended to 49 months (30). Nevertheless, a study found no statistically significant difference in disease-free survival (DFS) and OS between patients who underwent surgery after conversion therapy and nonsurgical patients in whom clinical complete remission (cCR) was achieved after conversion therapy (*62*).

A comparison of surgical resection following conversion therapy and liver transplantation (LT) revealed no significant differences in median OS (166.0 months *vs*. 62.5 months, $p > 0.050$), median PFS (24. 9 months *vs*. 30.6 months, $p > 0.050$), median DFS (161.3 months *vs*. 45.1 months, $p > 0.050$), and the median intra-hepatic non-recurrence interval (96.9 months *vs*. 39.9 months, $p > 0.050$) (*39*). Several large clinical series conducted in Europe, the US, and Asia have shown that the 5-year survival rate after radiofrequency ablation (RFA) for HCC (≤ 3 cm) ranges from 33% to 55%, which is comparable to that in an LR series (*63-66*). Moreover, a recent study found no significant difference in treatment choice between conversion therapy followed by ablation and LR (recurrence-free survival (RFS), 274 days [157-not reached (NR)] in the ablation group *vs*. RFS, not available (N/A) days [447-NR] in the LR group; $p = 0.09$) (*36*).

2.3. Conversion therapy plus surgery *vs*. upfront surgery

Patients with locally advanced HCC who received

conversion therapy followed by LR had a better prognosis than those who received upfront surgery alone. A retrospective study reported that patients who received preoperative Y90-SIRT conversion therapy had a significantly better 5-year OS rate (69.0% *vs*. 47.5%, $p = 0.048$) and a significantly better 5-year RFS rate (53.5% *vs*. 27.0%, $p = 0.047$) than those who underwent upfront resection (*67*). Additional studies, particularly prospective ones, need to be conducted to verify this.

3. Strategies for conversion therapy

3.1. Locoregional therapy

The conversion rate for TACE alone is 9.5% to 10%, and the objective remission rate (ORR) for conventional TACE is low (2.4%) (*13,30,68*).Patients with HCC who undergo TACE conversion therapy have a median OS of up to 49 months (*13,30,68*). In the US, the conversion rate for previously uHCC conversion therapy with HAI alone was 16% (*43*).Conversion rates with TARE (yttrium-90) alone range from 5.6% to 28.6% (*3,44-46*). In addition, studies have shown that increasing the dosage of TARE can enhance patient survival rates. Patients with HCC who undergo TARE conversion therapy have a median OS time of up to 54 months (*46*).

Locoregional combination therapies, such as HAIC (FOLFOX: folinic acid, fluorouracil, and oxaliplatin) plus TACE (*13*), portal vein embolization (PVE) plus TACE (*7*), TACE plus external beam radiotherapy (EBRT) (*8*), RT plus HAIC (fluorouracil) (*37*), and TACE plus RT (*40*), are mainly performed in Asia and have a conversion rate ranging from 11.1% to 57.6%. A trial of RT plus HAIC (fluorouracil) revealed that the group receiving a radiation dose ≥ 72 Gy had a higher conversion rate in advanced BCLC-C HCC compared to the intensity-modulated radiotherapy (IMRT) radiation dose < 72 Gy group (20% *vs*. 12%, $p = 0.03$) (*37*). Moreover, the group receiving a radiation dose ≥ 72 Gy had a significantly higher localized 1-year failure-free survival (LFFS) (95% *vs*. 79%, $p < 0.001$) and median OS (21 months *vs*. 13 months, $p = 0.002$) (*37*).

3.2. Systemic therapy

The development of tyrosine kinase inhibitors (TKI) and immune checkpoint inhibitors (ICI) has significantly improved the survival prognosis for patients diagnosed with HCC. Treatment with cisplatin, interferon α-2b, doxorubicin, and 5-fluorouracil (PIAF) resulted in a conversion rate of 18% for patients with initially unresectable HCC (*24*). The conversion rate increased to 33% with the use of modified PIAF, which also resulted in an ORR of 36% and a median OS of 21.3 months (*42*). In comparison, sorafenib had conversion rates ranging from 0.8% to 12.5% (*27,34*), while lenvatinib had a conversion rate of 4.6% (*36*). In Japan, the conversion rates for a combination of anti PD-L1 antibodies and a vascular endothelial growth factor inhibitor ranged from 5.3% to 31.8%. Post-conversion treatments included LR, ablation, and superselective TACE, and the median OS reached 40.3 months (*32,33,35,36*). Compared to TKI monotherapy, the combination of TKI and PD-1 has a higher conversion rate. Studies have reported a conversion rate ranging from 15.9% to 51%, with a median OS of up to 12 months (*19,21,32,69,70*).

Moreover, patients diagnosed with unresectable primary HCC and severe vascular infiltration who received anti-PD-1 antibodies in combination with TKI conversion therapy had 70% (7/10) partial remission (PR) and 30% (3/10) complete remission (CR) prior to surgery. These findings demonstrate the effectiveness of anti-PD-1 antibodies in combination with TKI conversion therapy for patients with unresectable primary HCC and severe vascular infiltration, resulting in an increased long-term oncologic benefit. The 12-month RFS rate for these patients was 75% (*71*).

3.3. Combined locoregional and systemic therapy

The heterogeneity of HCC in terms of tumor number, size, and liver function can preclude some patients from being treated with TACE. Patients with good liver function and a high tumor burden who are not eligible for TACE may benefit from preoperative systemic therapy followed by TACE (*72*). Clinical trials have shown that combining TACE with TKIs for intermediate and advanced HCC can result in prolonged OS and improved PFS compared to TACE alone (*73-75*). Moreover, combination therapy with TACE and lenvatinib has resulted in conversion rates of 11.1-19%, with a median PFS of up to 8 months and median OS of up to 20.6 months (*12,20*). The use of TACE, TKIs, and ICIs has been found to increase residual liver volume in patients with intermediate to advanced HCC, thereby enhancing the safety of conversion resection (*76*). A meta-analysis of 18 studies found that the conversion rate of triple therapy (TACE+TKIs+ICIs) was 42%, which was higher than that of TACE alone (10%) and TACE combined with other therapies (19%) (*77*). The tumor response to triple therapy was superior to that of TACE alone or dual therapy (*77*).

A clinical study showed that combination therapy with sorafenib and HAIC (FOLFOX) resulted in a conversion rate of 12.8% (*27*). Treating patients with unresectable advanced HCC using HAIC locoregional therapy following CCRT not only reduced the tumor stage but also significantly increased the future remnant liver volume (FRLV) from 47.5% to 69.9% before surgery, which further improved the curative resection of HCC (*38*).

Another study found that the conversion rate of TACE combined with CCRT or combined RT was 12.8% (*39*). LR accounted for 8.9% and LT accounted for 3.9%

(*39*). The study in question revealed that patients who underwent LR had a median PFS of 24.9 months, whereas those who underwent LT had a median PFS of 30.6 months. LR patients had a median OS of 166 months, while LT patients had a median OS of 62.5 months. The combination of CCRT with HAIC (FOLFOX) resulted in a conversion rate of 16.9% (*39*), whereas the combination of TACE plus SBRT plus anti PD-L1 antibodies resulted in a conversion rate of 12% (*28*).

The conversion rate of triple therapy TACE/HAIC plus TKI plus anti-PD-1 antibodies ranged from 11.5% to 53% (*9,12,15-17,20,22,25,29*). A point worth noting is that the difference in conversion rates may be related to the patients' disease status. Specifically, the treatment group with the higher conversion rate included patients with BCLC stage A initially unresectable HCC. The combination of TACE, TKI, and anti-PD-1 antibodies resulted in a 55% rate of pathological complete remission (pCR) and an 83% rate of major pathological remission (MPR) (*9*). A study found that patients with uHCC who received HAIC in combination with TKI and anti-PD-1 antibody conversion therapy had a significant survival benefit after surgery (*78*). The median RFS was 19.3 months, and the median OS was 28.7 months. The study in question noted a significant reduction in tumor size, with a median decrease of 4.7 cm. Moreover, pCR was achieved in 23 out of 67 patients (34.3%), indicating a favorable pathological response.

A meta-analysis of 24 studies was performed to determine the conversion rates and ORR of different therapies. Results indicated that locoregional plus systemic combination therapy had the highest conversion rate at 25%, followed by TACE at 13%, chemotherapy at 12%, and systemic therapy at 10% (*56*). Locoregional plus systemic combination therapy had the highest ORR at 60%, while chemotherapy had the lowest at 19% (*56*). The other therapies had an ORR ranging from 30% to 32% (*56*). Locoregional-systemic combination therapies have a lower incidence of adverse reactions, and particularly grade ≥ 3 adverse events (AEs). The incidence of adverse reactions was 67% with chemotherapy, 34% with TACE, 30% with systemic therapies, and 40% with locoregional-systemic combination therapies (*56*). Subgroup analyses have confirmed the benefits of locoregional-systemic triple combination therapies. Combination therapy with TACE, TKIs, and ICIs resulted in a significant therapeutic advantage. The therapy resulted in a conversion rate of 33%, an ORR of 73%, and a rate of grade ≥ 3 AEs of 31% (*56*).

A point worth noting is that triple combination therapy with an anti-PD-1 antibody (sintilimab) plus an anti-PD-1 antibody analog (IBI305) plus HAIC resulted in a conversion rate of 46.7% and an ORR of 66.7% (*14*). Likewise, triple combination therapy with an angiogenesis inhibitor plus anti-PD-1 antibody plus HAIC (FOLFOX) resulted in significant clinical benefits, with a conversion rate of 60%, an ORR of 96%, and a DCR of 100% (*6*). The results suggest that locoregional-systemic combination therapies have optimal conversion rates and clinical remission benefits.

Kudo suggested that subsequent immunotherapy should follow locoregional therapy since the release of cancer antigens and cancer antigen-specific immune responses will further enhance the efficacy of systemic therapy (*33*). Combining locoregional therapy with ICIs preserves T-cell effector function. Locoregional therapy activates the innate immune system and generates durable and widespread T-cell immunity through tumor antigen release and danger signal production, driving the anti-tumor immune response (*79*). Studies have noted an increased PD-1 and PD-L1 expression in HCC after TACE (*80*). Moreover, TACE resulted in elevated levels of circulating GPC3-specific cytotoxic T lymphocytes (CTL), IL-6 (*81*), CD4+ T cells, a higher CD4+/CD8+ T cell ratio, and elevated NK cells while reducing CD8+ Treg cells (*82*). Combining TACE with immunotherapy has the potential to enhance tumor response.

4. Challenges of conversion therapy

4.1. Adverse reactions to conversion therapy

Preservation of liver function is crucial for sequential surgery following initial unresectable HCC conversion therapy. The Asia-Pacific Expert Consensus Statement on Primary Liver Cancer (APPLE) emphasizes that for intermediate stage HCC, maintaining liver function is as equally important as achieving a high rate of surgical resection, with the ultimate aim of treatment being to prolong OS (*83*). Maintaining the Child-Pugh score during conversion therapy is beneficial to the prognosis for patients with advanced HCC, and even in those with adequate hepatic function reserve (*84-86*). However, hepatic impairment after conversion therapy is often more severe than anticipated, and a single Child-Pugh score may not fully reflect hepatic reserve function.

Chemotherapeutic agents used in conversion therapy can have various effects on liver physiology, including steatosis and hepatic sinusoidal vascular changes such as sinusoidal obstruction syndrome (SOS) or nodular regenerative hyperplasia (NRH) (*87*). TKIs can cause hepatotoxicity in 23% to 40% of patients, which can manifest as hepatocellular injury, hepatocellular steatosis, or cholestasis (*88*). Over a 10-year period, 38 of 432 (8.8%) patients treated with ICIs experienced liver injury, which was primarily hepatocellular or cholestatic (*89,90*). A point worth noting is that the common terminology criteria for adverse events (CTCAE) classification may overestimate the severity of checkpoint inhibitor-induced liver injury. Therefore, attention should be paid to toxic adverse reactions that may occur during conversion therapy. Moreover, preventing and treating post-hepatectomy liver failure (PHLF) is crucial.

Conversion therapy has been associated with systemic adverse reactions. Studies have reported that 50% of patients experienced grade 3 or higher treatment-related adverse events (TRAE) during conversion therapy (*31*). A study of PIAF conversion therapy for advanced unresectable HCC found that patients had a median OS of only 8.9 months, AEs including myelosuppression and mucositis were reported, and there were two treatment-related deaths due to neutropenic sepsis (*24*). Patients in the surgery group who did not receive conversion therapy experienced significantly fewer complications of any grade compared to the triple conversion therapy group (51.2% *vs*. 82.9%, $p = 0.002$). In addition, the incidence of grade 3/4 complications was significantly lower in patients who did not receive conversion therapy compared to those who did (4.9% *vs*. 26.8%, $p = 0.013$) (*91*).

4.2. Criteria for evaluating the effectiveness of conversion therapy

Currently, there are no universally accepted criteria for evaluating the effectiveness of conversion therapy. Several studies have adopted the following criteria to classify patients as having resectable HCC after conversion therapy: (1) Adequate residual liver volume and function are needed to achieve an R0 resection., (2) The intrahepatic lesion must be assessed as partially responsive or stable for at least 2 months, (3) Systemic therapy should not cause any serious or persistent adverse effects, and (4) LR should not be contraindicated (*26*). Zhang *et al*. defined the criteria for successful conversion as follows: for a Child-Pugh score of less than 7.2, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 1 or less, the absence of extrahepatic lesions, and a preserved liver with structurally intact vasculature and adequate FLR (*71*).

4.3. Treatment subsequent to conversion therapy

Thorough evaluation of the timing of resection after conversion therapy for HCC is crucial. Prior to surgery, safety needs to be assessed. Perioperatively, treatment with lenvatinib or bevacizumab should be discontinued due to its antiangiogenic action, which can result in complications such as delayed healing and bleeding. Lenvatinib has a plasma clearance time of 28–35 hours (*92*). According to one study, the drug should be discontinued for at least 1 week prior to surgery or ablation (*93*). Bevacizumab, in contrast, should be discontinued for at least 4–6 weeks before LR and 3 weeks before ablation or radical TACE (*94*). Strictly adhering to the dosing instructions for preoperative discontinuation is important in order to minimize the effects on surgery. If a patient experiences severe adverse drug reactions during targeted therapy or immunotherapy, surgery should only be performed after he or she has fully recovered.

Curative treatment options include LR, LT, and ablation therapy . Studies have confirmed that both LR and ablation therapy have favorable long-term outcomes, with no significant difference in post-treatment complications or RFS (*33*). Some studies have suggested that surgery should be performed after successful downstaging through continued treatment with TKIs and/or anti-PD-1 antibodies to stabilize lesions, an interval that is typically 1–2 months. In instances of less difficult resection, LR is recommended after downstaging to meet surgical resectability criteria to minimize complications (*91*). In instances of more difficult resection and poor tumor behavior, surgery is recommended only after achieving maximum remission depth and maintaining stability for 3–4 months to improve the partial response rate (*91*).

LR after conversion therapy can be challenging due to the adverse reactions it causes, such as bone marrow suppression, decreased platelet function and count, increased fragility of blood vessels and liver tissue, localized adhesions, and hepatic edema. Compared to patients who underwent direct surgery, those in the triple conversion therapy group (HAIC/TACE+anti-PD-1 antibody+TKI) for LR conversion lost more blood during surgery (600 mL *vs*. 400 mL, $p = 0.015$), had a longer operating time (270 min *vs*. 240 min, $p = 0.02$), a higher transfusion rate, and a longer duration of hospitalization (11 days *vs*. 8 days, $p < 0.001$) (*91*).

Adjuvant therapy should be considered after conversion therapy. Repeated liver treatments may create a hypoxic microenvironment, which can make the remaining tumor more aggressive and resistant. Postoperative recurrence was noted in 42.9% (21/49) of patients who underwent salvage LR, 66.7% (14/21) of which was intrahepatic recurrence (*3*). A point worth noting is that studies have noted the significance of postoperative antiviral therapy in patients with HBV-related HCC (*95,96*). Patients with uHCC who underwent FOLFOX-HAIC conversion therapy and who received adjuvant therapy had a significantly longer median RFS compared to those who did not receive adjuvant therapy (19.2 months *vs*. 10.8 months, $p = 0.028$). The best RFS after adjuvant therapy was observed in patients with uHCC who were younger than 60 years of age, had large vessel invasion, and who were positive for hepatitis B surface antigen (*97*).

5. Future perspectives

Sixty-seven percent of HCC patients are in Asia. The majority of HCC patients are initially diagnosed with BCLC stages B or C. Most patients are not eligible for radical surgery, and the median survival time is only 23–33 months (*98,99*). For patients with initially unresectable HCC, surgery can only be undergone f

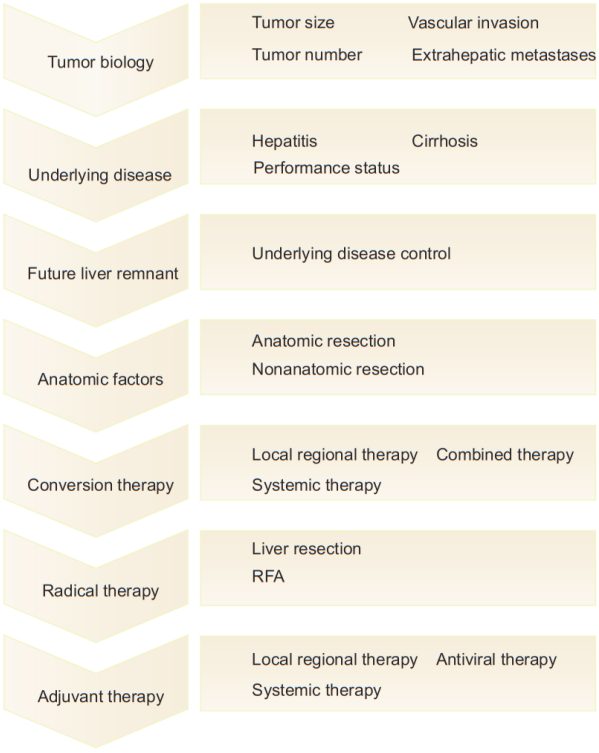

Figure 1. Conversion therapy paradigm for initial unresectable hepatocellular carcinoma. Abbreviation: RFA, radiofrequency ablation.

the tumor is shrunk or downstaged. Figure 1 shows a reference paradigm for administering conversion therapy for initially uHCC. With further development, conversion therapy could potentially yield prognostic outcomes similar to those of early HCC resection. Pathological examination can determine the tumor's sensitivity to transformative therapy and guide postoperative adjuvant therapy, potentially leading to long-term survival.

Most studies on conversion therapy focus on short-term outcomes, primarily assessing the conversion rate and ORR. Few studies have included long-term survival as a primary endpoint. In order to determine the significance of conversion surgery, the long-term outcomes of patients who underwent conversion surgery due to a positive tumor response to systemic therapy need to be compared to those who did not undergo conversion surgery despite a positive tumor response. Several clinical studies have found that a triple conversion regimen with locoregional and systemic therapy has a high conversion rate and results in significant survival benefits compared to other conversion strategies. The difficulty of LR increases after conversion therapy, and ensuring the safety of surgery requires comprehensive preoperative evaluation, appropriate selection of the procedure, and precise intraoperative technique. Emphasis should be placed on the prevention and treatment of PHLF, as well as postoperative adjuvant therapy and long-term follow-up. Due to the heterogeneity of study centers, conversion therapy protocols, and evaluation criteria, however, there is currently no unified approach to conversion therapy. Therefore, further optimization of conversion therapy would require a large prospective multicenter clinical study.

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