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Transarterial Chemoembolization Combined with PD-1 Inhibitors and TKIs for Intermediate - to - Advanced Hepatocellular Carcinoma: Efficacy and Progress in Conversion Resection

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Abstract: ***Objective:*** *To review the mechanisms, efficacy, and progress in conversion resection of transarterial chemoembolization (TACE) combined with programmed death-1 (PD-1) inhibitors and tyrosine kinase inhibitors (TKIs) in intermediate-to-advanced hepatocellular carcinoma (HCC).* ***Methods:*** *PubMed, Embase, Cochrane Library, Web of Science, CNKI, Wanfang, and VIP were searched from inception to 2025, focusing on studies published within the past five years, using terms including "hepatocellular carcinoma," "transarterial chemoembolization," "PD-1 inhibitor," "tyrosine kinase inhibitor," "conversion therapy," and "conversion resection." Evidence was integrated narratively.* ***Results:*** *Mechanistically, ischemia and locoregional immune microenvironment remodeling induced by TACE, immune activation by PD-1 inhibitors, and the anti-angiogenic and immunomodulatory effects of TKIs together constitute a multilayered "locoregional + systemic" synergy. In terms of efficacy, the triple regimen showed higher objective response rate (ORR), prolonged progression-free survival (PFS), and overall survival (OS) than dual therapy or TACE alone in most studies. With respect to conversion resection, reported rates varied widely because of inconsistent endpoint definitions: prospective studies, which mostly used actual completion of surgery as the endpoint, generally reported higher values, whereas retrospective studies, which mostly used meeting resectability criteria or entry into the surgical pathway as the endpoint, generally reported lower values; the two are not directly comparable. The survival benefit after conversion resection was relatively consistent across studies. Predictors of successful conversion included early tumor response, magnitude of alpha-fetoprotein (AFP) decline, decreased 18F-FDG uptake, and immune microenvironment biomarkers, but most remain exploratory.* ***Conclusion:*** *TACE combined with PD-1 inhibitors and TKIs has shown the potential to convert some intermediate-to-advanced HCC into a curable state and may broaden the population eligible for curative treatment. However, current evidence is dominated by retrospective and single-arm studies, and standardized conversion resection criteria, precise patient selection, and prospective randomized validation remain to be addressed. These conclusions represent promising exploratory evidence rather than a definitive conclusion.*

Keywords: Hepatocellular carcinoma, Transarterial chemoembolization, PD-1 inhibitor, Tyrosine kinase inhibitor, Conversion therapy, Conversion resection.

1. Introduction

Hepatocellular carcinoma (HCC) is among the malignancies with the highest incidence and mortality worldwide. In China, HCC is predominantly associated with hepatitis B virus (HBV) infection, in contrast to Europe and the United States. HCC has an abundant blood supply and an insidious onset; most patients are diagnosed at an intermediate-to-advanced stage, and only about 20%-30% are eligible for curative resection. Treatment decisions rely heavily on staging: the Barcelona Clinic Liver Cancer (BCLC) system is widely used internationally, whereas the China Liver Cancer staging (CNLC) system has served as the standard for clinical staging in China since 2017 and was revised in the 2022 guidelines [1].

In recent years, the rapid development of systemic therapy (immune checkpoint inhibitors and molecular targeted agents) and locoregional therapy (TACE, hepatic arterial infusion chemotherapy has changed the treatment landscape of unresectable HCC, giving rise to "conversion therapy," i.e., the use of effective combination therapy to downstage tumors, converting unresectable disease into resectable disease and enabling curative surgery. Minimally invasive and multidisciplinary comprehensive treatment has become an important principle for intermediate-to-advanced HCC [2], and the 2022 Chinese guidelines advocate multimodal, high-intensity conversion therapy for patients with technically unresectable (CNLC stage Ia, Ib, IIa) or technically resectable but high-risk (stage IIb, IIIa) disease [1], extending the treatment goal of HCC from prolonging survival toward pursuing cure. Among conversion strategies, the triple regimen of TACE combined with PD-1 inhibitors and TKIs has attracted considerable attention: immune checkpoint inhibitors and anti-angiogenic agents act synergistically, and locoregional therapy remodels the tumor immune microenvironment; the ISMIO consensus also noted that this strategy offers a new option for patients at high risk of recurrence or with TACE refractoriness [3]. However, current evidence remains scattered; for the key endpoint of conversion resection, definitions, populations, and results are highly heterogeneous, and "conversion resection" still lacks a unified definition, making the evidence difficult to integrate. Taking conversion therapy as its thread, this review summarizes the mechanisms, efficacy, and progress in conversion resection of the triple regimen in intermediate-to-advanced HCC, and discusses controversies and future directions.

2. Materials and Methods

Chinese search terms included “hepatocellular carcinoma,” “transarterial chemoembolization,” “PD-1 inhibitor,” “tyrosine kinase inhibitor,” “conversion therapy,” and “conversion resection”; English terms additionally included “HCC,” “TACE,” “immune checkpoint inhibitor,” “TKI,” and “conversion resection.” PubMed, Embase, Cochrane Library, Web of Science, CNKI, Wanfang, and VIP were searched from database inception to 2025, with emphasis on the past five years. Included literature comprised randomized controlled trials, single-arm trials, retrospective cohort studies, systematic reviews/meta-analyses, guidelines and expert consensus statements, and mechanistic studies; non-HCC liver malignancies, duplicate publications, and articles with unavailable full text were excluded. Thirty-six relevant publications were included, and their key data were cross-checked. As a narrative review, the PRISMA process was not applied, but the screening process is described in text to maximize reproducibility.

3. Results

Mechanisms. TACE embolizes the tumor-feeding arteries and releases chemotherapeutic agents locally, causing tumor ischemia, hypoxia, and necrosis; it is a standard locoregional treatment for intermediate-stage HCC [1,4]. Its effect is not limited to local cytotoxicity: tumor necrosis releases abundant tumor-associated antigens, promoting antigen-presenting cell activation and cytotoxic T-cell infiltration, converting immunologically “cold” tumors into “hot” tumors. PD-1 inhibitors block the PD-1/programmed death-ligand 1 (PD-L1) pathway, relieving T-cell immunosuppression; TKIs (e.g., lenvatinib, sorafenib) exert dual anti-angiogenic and immunomodulatory effects, improving the immune microenvironment and reducing immunosuppressive cells. The three act in a multilayered “locoregional + systemic” synergy, creating conditions for conversion resection. In the LEN-TAP study, elevated peripheral HLA-DR^{+}CD38^{+}CD8^{+} T cells were associated with better efficacy [5]; however, this finding comes from an exploratory peripheral biomarker analysis in a single study, lacking functional and external validation, and causality has not been established.

Efficacy. Multiple studies show that the triple regimen is superior to TACE alone or dual therapy. In the prospective phase II LEN-TAP study (n=142), the ORR was significantly higher with lenvatinib + TACE + PD-1 than with TACE alone (78.9% vs. 16.9%, P<0.001) [5]; in the real-world GUIDANCE007 study (n=421), the ORR was 55.1% with triple therapy versus 34.7% with dual therapy (P<0.001) [6]; and a meta-analysis (12 studies, 2410 patients) confirmed that TACE + TKI + PD-1 prolonged OS and PFS and improved ORR compared with TACE + TKI, although the pooled effect should be regarded only as an order-of-magnitude reference given heterogeneity [7]. In the refractory population with portal vein tumor thrombus (PVTT), Li SQ et al. [8] and Chi QY et al. [9] reported ORRs of 62.1%-68.3% and median OS of 21.7-23.3 months with the triple regimen, indicating considerable response even in high-risk populations; Wang Z et al. [10], Hou G et al. [11], and Bo W et al. [12] reported consistent findings (Table 1).

Table 1: Efficacy of TACE combined with PD-1 inhibitors and TKIs versus control regimens

Study (Year)	Design	N	Regimen (vs. control)	ORR	Survival	Ref
Zhang X (2026, LEN-TAP)	Prospective phase II	142	Lenvatinib + TACE + PD-1 vs. TACE alone	78.9% vs. 16.9% (P<0.001)	-	[5]
Ye L (2026, GUIDANCE007)	Retrospective, multicenter, real-world	421	TACE + lenvatinib + PD-1 vs. TACE + lenvatinib	55.1% vs. 34.7% (P<0.001)	-	[6]
He Y (2025)	Meta-analysis (12 studies)	2410	TACE + TKI + PD-1 vs. TACE + TKI	Improved	OS and PFS prolonged	[7]
Li SQ (2023)	Multicenter retrospective (PVTT)	-	TACE + lenvatinib + PD-1	62.1%-68.3%	Median OS 21.7-23.3 mo	[8]
Chi QY (2025)	Multicenter real-world (PVTT)	-	Lenvatinib + anti-PD-1 + locoregional	62.1%-68.3%	Median OS 21.7-23.3 mo	[9]
Wang Z (2025)	Real-world (BCLC B/C)	-	TACE + TKI + ICI	Consistent	Consistent	[10]
Hou G (2024)	Neoadjuvant triple therapy (PVTT type I/II)	-	Triple therapy	Consistent	Consistent	[11]
Bo W (2025)	Neoadjuvant triple therapy (centrally located)	-	Triple therapy	Consistent	Consistent	[12]

Note: ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; PVTT, portal vein tumor thrombus. Dashes indicate that the corresponding value was not specified in the source data cited in this review. Data are drawn from the studies cited in the Results section; pooled estimates should be interpreted as order-of-magnitude references only, given study heterogeneity.

Conversion resection. Conversion resection is the most central value of this strategy, but definitions vary significantly across studies, constituting a core obstacle to evidence synthesis: some prospective studies use “actual completion of resection” as the endpoint, whereas some retrospective studies use “meeting resection criteria / being referred to surgery.” As the two reflect different clinical events, their values are not directly comparable and are presented separately below.

For actual completion of resection, the salvage resection rate in LEN-TAP was 59.2% with the triple regimen versus 18.3% with TACE alone (P<0.001) [5]; the PLATIC study reported 77.2%, the highest to date [13]; and SILENSES reported 56% [14]. For meeting resection criteria or referral to surgery, the real-world GUIDANCE001 and GUIDANCE007 studies reported approximately 35%-36% [6,15]. A meta-analysis (44 studies, 5065 patients) reported a pooled conversion resection rate of approximately 29% for triple therapy, higher than dual therapy (8%-15%) and TACE alone (6%-9%) [16], while another reported approximately 23%-30% [17]; however, because the underlying studies are inconsistent in endpoint definition, the pooled values have limited clinical interpretability and serve only as an order-of-magnitude reference (Table 2).

Regarding resection quality and postoperative survival, Zhang W et al. [18] reported an R0 rate of 85.7% and a pathological complete response (pCR) rate of 38.1% among converted

patients; Wu JY et al. [19], Lin KY et al. [20], and SILENSES [14] reported 2-year OS rates of 79.9%-87.3% and median recurrence-free survival (RFS) of 25.4-40.0 months among resected patients; and Li X et al. [21] reported a significantly lower incidence of microvascular invasion (MVI) after conversion surgery than after direct surgery (3.1% vs. 50.4%, P<0.001). Arita J et al. [22] similarly reviewed the indications and outcomes of conversion surgery. Of note, the survival difference between converted and non-converted patients may partly reflect a selection effect—those able to undergo surgery have better baseline status and tumor biology—and should therefore not be directly interpreted as a causal benefit of conversion therapy (Table 3).

Predictors of successful conversion. Factors associated with successful conversion include: (1) early tumor response—Li X et al. [23] found a higher conversion rate in early responders than in non-responders (44.1% vs. 7.7%, P=0.001), with early response the only independent factor (OR=10.296, 95% CI 2.076-51.063), although the small number of events and wide confidence interval limit stability; (2) magnitude of AFP decline—Zhao W et al. [24] found a higher proportion of >90% AFP decline in the surgical group and lower conversion success with baseline AFP >1000 μg/L; (3) imaging metabolic indicators—a decline in 18F-FDG uptake may predict successful conversion, particularly in PVTT [24]; and (4) immune microenvironment biomarkers—elevated peripheral HLA-DR$^+$CD38$^+$CD8$^+$ T cells and tumor CD8$^+$ T-cell enrichment were associated with response [5,18]. Most of these remain exploratory and lack prospective validation (Table 4).

Table 2: Summary of conversion resection rates for TACE combined with PD-1 inhibitors and TKIs

Study (Year)	Design	N	Regimen	Conversion resection rate	Endpoint definition category
Zhang X (2026, LEN-TAP) [5]	Prospective phase II	142	Lenvatinib + TACE + PD-1 vs. TACE	59.2% vs. 18.3%	Actual completion of surgery
Qiu J (2026, PLATIC) [13]	Prospective phase II, single-arm	57	Sintilimab + lenvatinib + TACE-HAIC	77.2%	Actual completion of surgery
Lu S (2026, SILENSES) [14]	Prospective phase II	120	Sintilimab + lenvatinib	56.0%	Actual completion of surgery
Qu WF (2022) [35]	Real-world	51	Toripalimab + lenvatinib + TACE vs. dual	50.0% vs. 19.0%	Actual completion of surgery
Ye L (2026, GUIDANCE007) [6]	Retrospective, multicenter	421	TACE + lenvatinib ± PD-1	35.5% vs. 15.7%	Meeting resection criteria / referral
Yang DL (2025, GUIDANCE001) [15]	Retrospective, multicenter	802	TACE ± ICI + TKI	36.4% vs. 23.5%	Meeting resection criteria / referral
Chen S (2022) [36]	Retrospective (PD-L1+)	142	Pembrolizumab + lenvatinib + TACE vs. dual	25.7% vs. 11.1%	Meeting resection criteria / referral
Zeng Y (2026) [16]	Meta-analysis	5065 (44 studies)	TACE + TKI + ICI (pooled)	~29%	Mixed (pooled)
Hu L (2025) [17]	Meta-analysis	3497 (36 studies)	ICI + TKI + TACE/HAIC	~23%-30%	Mixed (pooled)

Note: definitions of "conversion resection" differ across studies; "actual completion of surgery" and "meeting resection criteria / referral" do not reflect the same clinical event, so values in this table are not directly comparable; pooled meta-analytic values derive from studies with inconsistent definitions and serve only as an order-of-magnitude reference.

Table 3: Survival benefit after conversion resection

Study (Year)	N	Survival outcome
Lin KY (2023) [20]	83 (salvage resection)	mRFS 25.4 mo; 2-year OS rate 87.3%
Wu JY (2024) [19]	144 (91 resected vs. 53 non-resected)	2-year OS rate 79.9% vs. 39.6% (P=0.007)
Yu H (2025) [27]	64	Triple group PFS HR 0.450, OS HR 0.437 (vs. dual)
Li X (2024) [21]	32 conversion surgery vs. 419 direct surgery	EFS HR 0.231; MVI 3.1% vs. 50.4%
Zhang W (2023) [18]	56 (prospective)	Conversion rate 55.4%; R0 85.7%; pCR 38.1%
Lu S (2026, SILENSES) [14]	120 (prospective)	Conversion rate 56%; mOS 36.0 mo; 5-year OS rate 73.9% in resected patients

Note: the survival difference between converted and non-converted patients may partly reflect selection effects and time bias, and should not be directly interpreted as a causal benefit of conversion therapy.

Table 4: Predictors of successful conversion and treatment response

Category	Predictor	Finding	Evidence	Ref
Early tumor response	Objective response at early assessment	Conversion rate 44.1% in early responders vs. 7.7% in non-responders (P=0.001); early response the only independent factor (OR=10.296, 95% CI 2.076-51.063)	Limited stability (few events, wide CI)	[23]
AFP dynamics	Magnitude of AFP decline	Higher proportion of >90% AFP decline in the surgical group; lower conversion success with baseline AFP >1000 ug/L	Exploratory	[24]
Imaging metabolic markers	18F-FDG uptake decline	Uptake decline may predict successful conversion, particularly in PVTT	Exploratory	[24]
Immune microenvironment	Peripheral HLA-DR+CD38+CD8+ T cells	Elevated levels associated with better efficacy	Single-study exploratory, no functional or external validation	[5]
Immune microenvironment	Tumor CD8+ T-cell enrichment	Associated with response	Exploratory	[18]

Note: AFP, alpha-fetoprotein; 18F-FDG, fluorine-18 fluorodeoxyglucose; PVTT, portal vein tumor thrombus; OR, odds ratio; CI, confidence interval. All predictors are exploratory and have not been prospectively validated.

Safety. The adverse event profile of the triple regimen resembles that of dual therapy and monotherapy, mainly comprising hepatic dysfunction, hypertension, fatigue, decreased appetite, fever, rash, and immune-related adverse events (irAEs), mostly grade 1-2. In GUIDANCE007, grade 3-4 adverse events were similar between the triple and dual groups (35.6% vs. 36.4%, P=0.885), though irAEs were more common [6]; GUIDANCE001 reported a higher incidence of serious adverse events with triple therapy than with TACE alone (35.6% vs. 27.0%, P=0.009) [15]; and in LEN-TAP,

grade 3 treatment-related adverse events were more frequent with triple therapy (60.6% vs. 21.1%, P<0.001), without grade 4 or higher toxicity [5]. Surgical safety after conversion was generally acceptable, with a perioperative complication rate of 48.2% and a major complication rate of 16.9% [20]. Repeated ineffective TACE may aggravate hepatic injury; accordingly, the Chinese College of Interventionalists (CCI) proposed a definition and consensus on "TACE refractoriness" [25,26]. In the era of combination therapy, timely combination with or switching to systemic therapy or conversion surgery is important to preserve hepatic function.

Patient selection and treatment strategies. Not all patients with unresectable HCC are suitable for conversion therapy. Patients with intermediate-to-advanced disease (BCLC stage B/C and corresponding CNLC stages) appear to benefit more clearly than early-stage patients [15], and those with lower tumor burden, better hepatic function (Child-Pugh class A, ALBI grade 1), and tolerance of combination therapy are more likely to convert successfully [27]. Regarding resectability, the 2022 Chinese guidelines advocate conversion therapy based on CNLC staging [1,2]; the 2026 Chinese guidelines for HCC with PVTT recommend resection as the first choice for resectable Cheng type I/II PVTT and, for unresectable cases, locoregional therapy combined with targeted and immune therapy [28] (building on a prior Chinese multidisciplinary consensus [29]); the 2026 Chinese clinical practice guideline on transarterial interventional therapy gives recommendations on the choice between HAIC and TACE and the timing of combination systemic therapy [30]; and a 2023 Japanese expert consensus proposed oncological resectability criteria (resectable, borderline resectable 1 and 2) [31]. The treatment paradigm for intermediate-stage HCC is shifting from "TACE first" toward "systemic therapy upfront, pursuing conversion" [32], and the controversies surrounding perioperative combination therapy have also been reviewed [33]. Biomarker exploration is ongoing: dynamic AFP changes, early imaging response, and decreased 18F-FDG uptake, as well as $CD8^+$ T-cell infiltration and PD-L1 expression, may predict efficacy, but most remain exploratory and lack prospective validation. No unified standard exists for treatment sequencing, duration, or surgical timing; most studies recommend assessment after 2-4 cycles and timely surgery for those with sufficient depth of response. For patients unsuitable for surgery or with severe underlying liver disease, combination therapy may serve as a downstaging modality for bridging to liver transplantation, but the risk of acute rejection associated with pretransplant immunotherapy (23.1% vs. 5% for ICI exposure, P=0.002) [34] warrants attention.

4. Discussion

Taking conversion resection as its central thread, this review integrates evidence on the mechanisms, efficacy, and conversion outcomes of the triple regimen in intermediate-to-advanced HCC: mechanistically, locoregional therapy-induced immune microenvironment remodeling, PD-1 inhibitor-mediated immune activation, and the anti-angiogenic and immunomodulatory effects of TKIs act in multilayered synergy; in terms of efficacy and conversion, the triple regimen appears generally superior to dual therapy or monotherapy, with prospective studies reporting actual completion of conversion resection in approximately 50%-70% and considerable survival benefit among resected patients; and the available evidence is highly heterogeneous, with the absence of a unified definition of conversion resection and the predominance of retrospective and single-arm studies constituting the greatest obstacle to evidence synthesis. These observations are based mainly on observational data and therefore have limited power for causal inference. The overall direction is consistent with previous meta-analyses (the triple regimen generally superior in response and survival); however, conversion resection rates differ markedly, largely because of inconsistent endpoint definitions—studies using actual completion of surgery report higher values, whereas those using meeting resection criteria or referral report lower values, the two reflecting different clinical events and thus not directly comparable; the divergence may also arise from study design and selection bias and from differences in treatment composition, and these explanations are inferences requiring verification. Nevertheless, for patients with intermediate-to-advanced disease, particularly those with poor-prognosis features such as PVTT, the triple conversion strategy still offers a realistic possibility of achieving curative surgery.

Given the source characteristics of the cited evidence, the main biases warrant noting: single-arm studies lack concurrent controls, so efficacy and conversion rates are susceptible to population selection and assessor subjectivity; retrospective studies generally have selection bias; and, importantly, survivor bias and immortal time bias—during the interval from initiating conversion therapy to completing surgery, patients must first "survive and remain progression-free" to enter the surgical group, and this period itself confers a survival advantage, so the conclusion that "converted patients survive longer than non-converted patients" may be exaggerated and should be corrected by landmark analysis or by treating conversion as a time-dependent covariate; publication bias may also overrepresent positive results.

The strength of this review lies in integrating multidimensional evidence along the thread of conversion resection and highlighting the heterogeneity in its definition. However, as a narrative review it did not adopt rigorous systematic screening, so literature selection may be subjective; included studies are predominantly retrospective or single-arm, generally with selection bias, survivor bias, and confounding; the studies are highly heterogeneous in stage, hepatic function, regimen, and endpoint definition; follow-up durations vary, and long-term data remain immature; and the predictive biomarkers are mostly exploratory and lack prospective validation. Future research should prioritize rigorously designed multicenter randomized controlled trials with conversion resection rate as the primary endpoint, establish a unified definition of conversion resection and oncological resectability criteria, and advance biomarker-driven patient stratification; given that whether patients achieving complete response still require surgery remains controversial, whether "successful conversion (reaching a resectable state)" rather than "actual completion of resection" should serve as the primary endpoint also merits discussion. Such trials face practical difficulties—ethical issues when converted patients decline surgery, sample-size

requirements given low conversion rates, and the difficulty of blinding—that require consideration at the design stage.

5. Conclusion

TACE combined with PD-1 inhibitors and TKIs is among the most promising strategies for conversion therapy in intermediate-to-advanced HCC, showing relatively consistent exploratory signals of improving response, promoting conversion resection, and improving survival, and may broaden the population eligible for curative treatment. However, current evidence is dominated by retrospective and single-arm studies, and the lack of a unified definition of conversion resection, the absence of patient selection criteria, and insufficient prospective validation remain key bottlenecks. Given that the survival advantage of converted patients in observational studies may partly reflect selection effects and time bias, these conclusions should be regarded as promising exploratory evidence rather than a definitive conclusion.

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