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ORIGINAL RESEARCH

A Novel Quadruple Conversion Therapy: Converting Initially Unresectable Hepatocellular Carcinoma to Resectable with pTAE-HAIC, Tyrosine Kinase Inhibitors, and Anti-PD-1 Antibodies

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Purpose: The aim of this study was to evaluate the potential of partial transcatheter arterial embolization (pTAE)–hepatic artery infusion chemotherapy (HAIC) in combination with tyrosine kinase inhibitors (TKIs) and anti-PD-1 antibodies for downstaging and subsequent resection in patients with initially unresectable hepatocellular carcinoma (HCC).

Methods: Patients with unresectable HCC who underwent initial treatment with a combination of pTAE, HAIC, TKIs, and an anti-PD -1 antibody were studied. The tumour response and potential for resection were assessed through imaging every month (±1 week) using RECIST v1.1.

Results: Among 17 patients (27.4%) who achieved R0 resection, the median time from quadruple therapy initiation to surgery was 89 days (range: 69–255). The cohort comprised 13 males and 4 females, with a median age of 51 years (range: 18–70). Twelve patients had BCLC stage C disease, including 11 with major vascular invasion (Vp2, Vp3, Vv2, Vv3, Vv1) and 3 with concurrent portal and hepatic venous invasion (Vp2/Vv2, Vp3/Vv2, Vp3/Vv3). Five patients had BCLC stage B HCC. The median diameter of the largest liver nodule was 11.5 cm (range: 3.9–18.8), with 10 patients presenting multiple lesions. Preoperatively, 17 patients underwent 43 cycles of pTAE-HAIC (median: 2, range: 1–5). Based on RECIST v1.1, 13 patients achieved partial response (PR), and 4 had stable disease (SD). With a median follow-up of 17.8 months (range: 12.2–38.3), the 12-month overall survival post-hepatectomy was 100%, and the median progression-free survival (PFS) was 14.5 months (range: 1.5–31.8). Tumor recurrence within 12 months occurred in 5 patients, with 4 achieving disease control after additional treatment.

Conclusion: Quadruple therapy, consisting of pTAE-HAIC combined with TKIs and anti-PD-1 antibodies, represents a feasible conversion strategy for patients with unresectable HCC to achieve successful resection and potential long-term survival.

Keywords: hepatocellular carcinoma, conversion therapy, transcatheter arterial embolization, hepatic artery infusion chemotherapy, tyrosine kinase inhibitor, anti-PD-1 antibody

Background

Worldwide, hepatocellular carcinoma (HCC) is the sixth most frequently occurring cancer and the third leading cause of cancer mortality, accounting for 90% of primary liver malignancies.[1] Despite advancements in therapeutic approaches, surgical removal continues to be the gold standard for curative treatment and provides the best potential for long-term survival.[2] However, more than 70% of individuals with HCC are diagnosed at intermediate or advanced stages, where the majority have already lost the opportunity for direct surgical intervention.[3,4] This limitation highlights the critical need

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for effective downstaging strategies to convert unresectable HCC to resectable disease. Successful conversion can not only significantly enhance the long-term outcomes of these patients but also lead to a complete pathological response (CPR) in certain patients who respond to conversion therapy, with survival outcomes comparable to those of patients initially considered to have resectable tumours.[5,6]

As far back as the 1970s, reports indicated that individuals with HCC that was initially inoperable could achieve sufficient tumour downstaging to become eligible for surgical resection.[7] As therapeutic agents and approaches for advanced HCC have progressed, treatment strategies have evolved, and multimodal, high-intensity approaches are attracting increasing attention, aiming to achieve rapid tumour shrinkage and downstaging or to augment the volume of the residual liver, ultimately providing an opportunity for curative surgical resection. Recent studies have indicated that locoregional therapy (LRT) combined with tyrosine kinase inhibitors (TKIs) and anti-programmed death-1 (PD-1) antibodies may serve as a superior conversion therapy for patients initially diagnosed with unresectable HCC while maintaining a manageable safety profile.[8] Currently, the most frequently employed LRTs in clinical practice include TACE/TAE and HAIC. The ORR rate of a quadruple therapy combining TACE, HAIC, TKIs, and anti-PD-1 antibodies is 80%, theoretically suggesting a high potential conversion rate.[9] However, no specific studies have been conducted on this topic, and this therapy is associated with considerable adverse effects, especially the potential deterioration of liver function following TACE. In TACE treatment, "complete embolization" is typically implied, but in recent years, a shift towards "partial embolization" has occurred.[10,11] Partial transcatheter arterial embolization (pTAE) can prevent liver function deterioration caused by complete embolization while slowing blood flow, thereby increasing the local concentration and retention time of HAIC drugs. Additionally, pTAE induces the release of tumour antigens, thereby enhancing the antitumour effect of TKI combined with anti-PD-1 antibody treatment. This approach may also achieve a partial remission of intrahepatic lesions, potentially leading to a more effective conversion rate.[10,11]

In this research, we assessed the potential of pTAE-HAIC in combination with TKIs and anti-PD-1 antibodies for downstaging along with resection in patients with HCC initially deemed unresectable We report a cohort of 17 patients with advanced or unresectable HCC who received pTAE-HAIC in combination with TKIs and anti-PD-1 antibodies and subsequently underwent successful R0 resection. To the best of our knowledge, this study represents the largest reported cohort of patients with unresectable HCC to achieve R0 resection after receiving this quadruple therapy approach.

Patients and Methods

A retrospective analysis was conducted on patients diagnosed with HCC at Chongqing University Cancer Hospital from September 1, 2021, to February 1, 2023, and treated with pTAE-HAIC plus TKI and anti-PD-1 antibody combination therapy. The diagnosis of HCC was based on both domestic and international guidelines.[3,12] Patients with unresectable HCC are primarily categorized into two types: individuals with BCLC stages B–C (advanced-stage cancer), who face a greater risk of resection failure or reduced survival than those who receive palliative treatment, or those with an insufficient remnant liver volume following hepatectomy (less than 40% in patients with cirrhosis; less than 30% in patients without cirrhosis). The exclusion criteria were as follows: (1) Child–Pugh score of Grade C; (2) Eastern Cooperative Oncology Group (ECOG)/Preservation Scale (PS) score of 3–4; (3) a history of malignant tumours other than HCC; (4) the presence of extrahepatic metastasis; (5) serious cardiac, pulmonary, or renal insufficiency; and (6) incomplete follow-up data.

The research protocol, encompassing the therapy schedule and methods for gathering data, adhered to the ethical guidelines outlined in the World Medical Association's Declaration of Helsinki and was approved by the Research Ethics Committee of Chongqing University Cancer Hospital (Approval Number: CZLS2021042-A), and written informed consent was obtained from all patients prior to undergoing pTAE-HAIC, TKI, and anti-PD-1 antibody treatment and surgery.

pTAE-HAIC Procedure

A preoperative enhanced CT scan was performed to assess all the tumour-feeding arteries. During the procedure, all extrahepatic collateral arteries were first embolized, followed by the embolization of the major intrahepatic feeding arteries. In cases where hepatic artery-to-portal vein or hepatic artery-to-hepatic vein fistulas were present, embolization

procedures should avoid the fistula site. If avoidance was not possible, appropriate embolic agents, such as particles or coils, should be used to effectively occlude the fistula. These measures should be implemented prior to embolizing the artery that supplies blood to the tumour to ensure the safety and efficacy of the treatment. The pTAE-HAIC treatment protocol and schematic are detailed in Figures 1 and 2. TAE utilized ≤10 mL of ultrafine iodized oil (purchased from Jiangsu Hengrui Medicine China Co., Ltd)., along with suitable particulate embolic materials (including embolic microspheres (purchased from Jiangsu Hengrui Medicine China Co., Ltd)., polyvinyl alcohol (PVA) particle embolic agents (purchased from Varian Medical Systems China Co., Ltd)., gelatine sponge particle embolic agents (purchased from Varian Medical Systems China Co., Ltd)., and coils (purchased from COOK Medical, USA)). Following TAE, a catheter was placed at the origin of the tumour-feeding artery for FOLFOX-HAIC (arterial infusion of oxaliplatin at a dose of 85 mg/m² for a duration of 2–3 hours; leucovorin at a dose of 400 mg/m² was administered through an arterial infusion over a period of 2 hours, whereas 5-FU at 2400 mg/m² was administered via a continuous arterial infusion for 46 hours). pTAE-HAIC treatment is administered once every 4–6 weeks.

Systemic Therapy

This study utilized different treatment regimens according to local practices and research protocols.[13,14] The TKIs used included lenvatinib[15] (administered at a fixed dose of 8 mg/day, without considering the weight of the patient), apatinib[16] (administered at 250 mg/day), and sorafenib[17] (administered at 400 mg twice daily). The following anti-PD-1 antibodies were administered intravenously: tislelizumab[18] at 200 mg every three weeks, camrelizumab[19] at 200 mg every two weeks, or sintilimab[20] at 200 mg every three weeks. All patients received regular treatments and follow-up monitoring. Specifically, comprehensive evaluations, including complete blood counts and assessments of cardiac, thyroid, adrenal, renal, and liver functions, along with oncological markers, were conducted every 2 to 3 weeks before each cycle of anti-PD-1 antibody therapy. Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), as well as chest CT, were used to assess tumour response and resectability approximately every month (±1 week). The tumour response was assessed in accordance with RECIST v1.1 and the modified RECIST (mRECIST).[21,22] The monitoring and grading of adverse events were conducted using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0.

Liver Resection Procedure

The resectability of the tumour was determined from the imaging findings according to the following criteria:[23] (1) achieving R0 resection with a sufficient remaining liver volume and function; (2) intrahepatic lesions were evaluated as a complete response (CR), partial response (PR), or stable disease (SD); (3) no serious or sustained adverse reactions were caused by any treatment; and (4) no contraindications for hepatectomy were present. Tumour resectability was discussed and approved by the multidisciplinary team (MDT) at Chongqing University Cancer Hospital, which included senior surgeons and radiologists.

Posthepatectomy liver failure (PHLF) was diagnosed and graded according to the criteria established by the International Study Group of Liver Surgery (ISGLS). PHLF is defined as an elevated international normalized ratio (INR) of prothrombin time and hyperbilirubinemia occurring on or after the fifth postoperative day.[24] Complications after surgery were categorized using the Clavien–Dindo classification system.[25] A pathological complete response (pCR) was characterized by the absence of viable residual tumour cells in haematoxylin- and eosin-stained sections of the primary tumour, tumour thrombi, and metastatic lesions that were completely resected.

Targeted immunotherapy was resumed four weeks postoperatively, with follow-up imaging and serum tumour biomarker assessments conducted every 1–2 months.

Statistical Analyses

All the statistical analyses were conducted using R software, version 3.5.3. Overall survival (OS) was calculated as the duration from the initiation of combination therapy to the patient's death. Recurrence-free survival (RFS) was determined as the interval from the date of the surgical intervention to the first occurrence of either tumour recurrence or death from any cause.

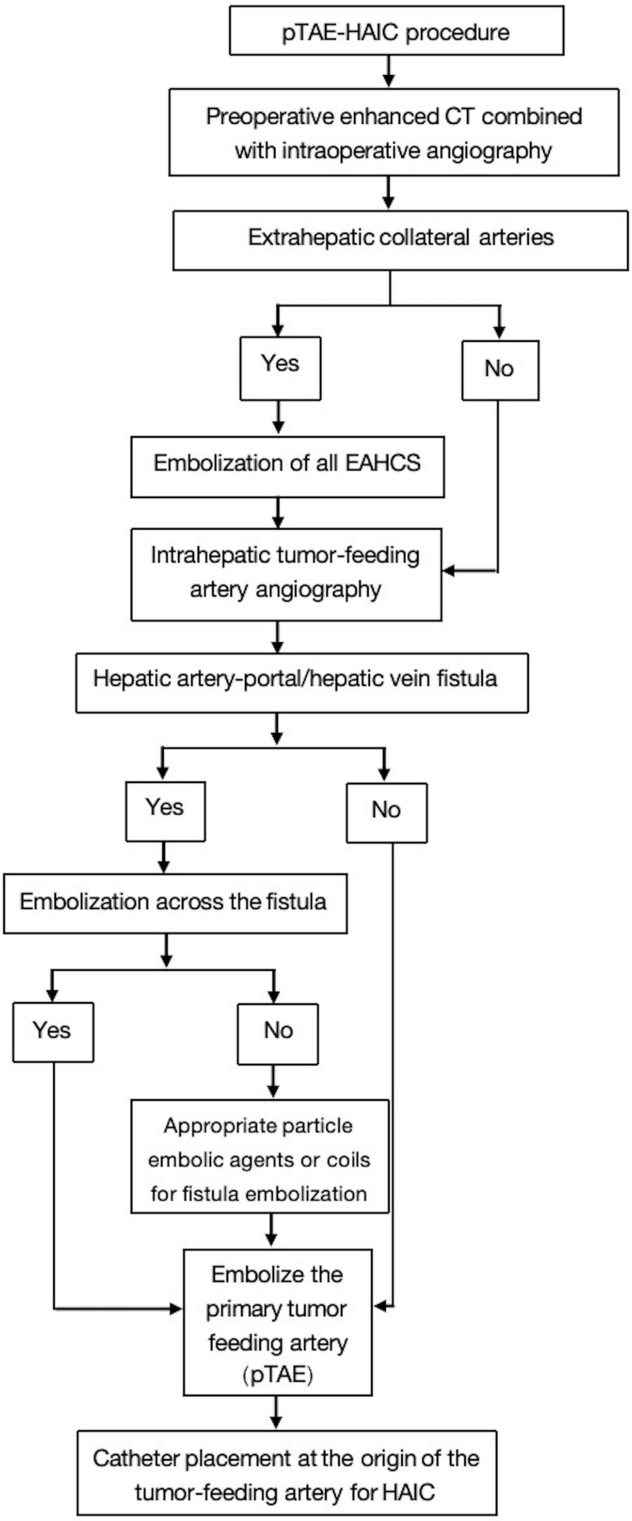

Figure 1 pTAE-HAIC treatment protocol.

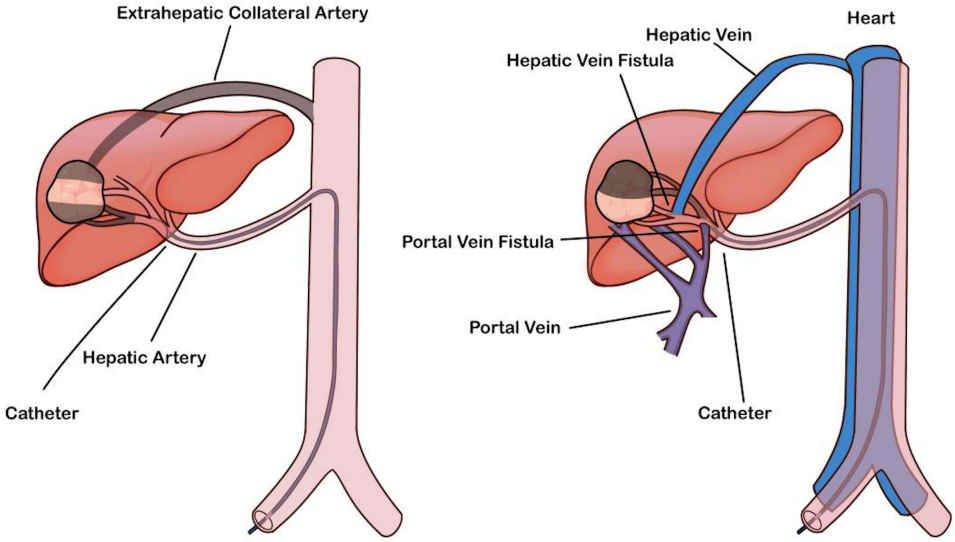

Figure 2 Schematic diagram of pTAE-HAIC, the grey areas denote the embolized vessels and tumor.

Results

Patients and Treatment

Between October 2021 and February 2023, 62 consecutive patients who received pTAE-HAIC combined with TKIs and anti-PD-1 antibodies as the first-line therapy were included in the analysis (Figure 3). Among these patients, 17 (27.4%) successfully underwent R0 resection. An additional 3 patients were deemed to have resectable tumours following the achievement of the PR of the primary lesion, thereby meeting the first and second resection criteria mentioned above. However, these three patients did not undergo liver resection—one patient experienced persistent adverse effects from anti-PD-1 antibody therapy (grade II hypothyroidism and grade II myocarditis), while the remaining two patients declined surgery.

Table 1 provides a summary of the demographics and baseline characteristics of all 62 patients who underwent quadruple conversion therapy. According to the classification by the Liver Cancer Study Group of Japan (LCSGJ),[26] none of the 13 patients with portal vein trunk and/or superior mesenteric vein invasion classified as Vp4 underwent

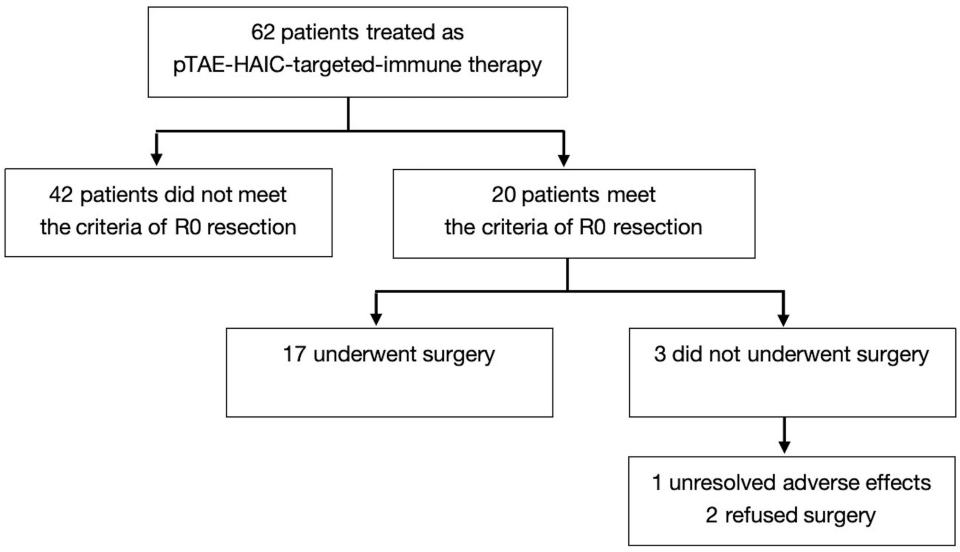

Figure 3 Patient flowchart.

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Table 1 Baseline Patient Demographics and Disease Characteristics

Characteristics	Patients Who Underwent Surgery (n = 17)	Patients Who Did Not Undergo Surgery (n=45)*	p values
Median age, years (range)	51(18–70)	55(27–72)	0.561
Sex (male/female), n (%)			0.082
Male	13(76.5)	42(93.3)	
Female	4(23.5)	3(6.7)	
ECOG performance status, n (%)			0.837
0	8(47.1)	24(53.3)	
1	9(52.9)	20(44.4)	
2	0(0)	1(2.2)	
Etiology of HCC, n (%)			0.222
HBV	14(82.4)	42(93.3)	
HCV	1(5.9)	1(2.2)	
Non-viral	2(11.8)	2(4.4)	
BCLC stage, n (%)			0.750
B	5(29.4)	11(24.4)	
C	12(70.6)	34(75.6)	
China liver cancer stage, n (%)			1.000
Ib	0(0)	1(2.2)	
IIa	1(5.9)	3(6.7)	
IIb	5(29.4)	14(31.1)	
IIIa	11(64.7)	27(60.0)	
Macrovascular invasion, n (%)			0.734
Yes	11(64.7)	27(60.0)	
No	6(35.3)	18(40.0)	
Portal vein tumor thrombus, n (%)			0.031
Vp0	9(52.9)	20(44.4)	
Vp1-2	4(23.5)	4(8.9)	
Vp3	4(23.5)	8(17.8)	
Vp4	0(0)	13(28.9)	
Hepatic vein tumor thrombus, n (%)			0.117
Vv0-1	12(70.6)	40(88.9)	
Vv2	3(17.6)	4(8.9)	
Vv3	2(11.8)	1(2.2)	
Child-Pugh class, n (%)			0.672
A	14(82.4)	40(88.9)	
B	3(17.6)	5(11.1)	
Baseline AFP, median (range), ng/mL	8449.5(3.1–200,000)	1200(1.5–146,740.8)	0.269
Baseline AFP≥400 ng/mL, n (%)			0.130
Yes	14(82.4)	28(62.2)	
No	3(17.6)	17(37.8)	
Baseline PIVKA-II, median (range), mAU/mL	8933.73(48–134,755.74)	6401.1(47.36–300,000)	0.555
Baseline PIVKA-II≥1000 mAU/mL, n (%)			0.355
Yes	14(82.4)	31(68.9)	
No	3(17.6)	14(31.1)	

Notes: *Including 3 patients who met the criteria for R0 resection but not did not undergo surgery, all were at BCLC stage C (Vp3, Vv2, ECOG 1). Portal vein tumor thrombus(PVTT) classification (Classification based on JSH typing, VP0, no PVTT; VP1, PVTT confined to portal branches distant from secondary branches; VP2, PVTT involving secondary branches of portal vein; VP3, PVTT involving primary branches of portal vein; VP4, PVTT invading main trunk of portal vein or contralateral primary branches); Hepatic vein tumor thrombus(HVTT) classification (classification based on JSH typing, Vv1, tumor thrombosis in a peripheral hepatic vein, Vv2, in a major hepatic vein, Vv3, in the inferior vena cava).

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HBV, hepatitis B; HCV, hepatitis C; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II.

surgery after treatment (p = 0.031). Among the remaining 49 patients, 17 underwent surgery. Among these 17 patients, 13 were male and 4 were female, with a median age of 51 years (range: 18–70 years). Twelve patients had BCLC stage C disease, of whom one had an ECOG score of 1. Among these patients, 11 had major vascular invasion, including 4 patients classified as Vp2 and 4 as Vp3. One patient had hepatic vein invasion classified as Vv1, 3 patients were classified as Vv2, and 2 patients exhibited invasion of the inferior vena cava (IVC) and/or right atrium (RA) and were classified as Vv3. Among these patients, 3 had concurrent invasion of both the portal and hepatic venous systems, specifically, Vp2/Vv2, Vp3/Vv2, and Vp3/Vv3. Additionally, 5 patients had BCLC stage B HCC.

The median diameter of the largest hepatic nodule was 11.5 cm (range: 3.9–18.8 cm), and 10 patients had multiple liver nodules. Before surgery, the 17 patients who underwent successful surgical resection were administered 43 cycles of pTAE-HAIC (range: 1–5, median: 2). The tumour response was evaluated prior to hepatectomy via both RECIST v1.1 and mRECIST. The TKIs and anti-PD-1 antibodies administered to these 17 patients are listed in Table 2. In accordance with RECIST v1.1, 13 patients achieved a PR and 4 achieved SD. Using mRECIST, 3 patients with a CR, 12 patients with a PR, and 2 patients with SD were identified (Table 2).

Surgical and Perioperative Findings

The median time from the initiation of quadruple therapy to surgery was 89 days (range: 69–255 days). Among patients with BCLC stage C disease, all 13 patients with Vp4-grade vascular invasion failed to achieve successful conversion (P=0.031), whereas 14 of 21 patients (66.7%) with vascular invasion achieved conversion to resectable disease, including two patients who attained an R0 resection status but did not undergo surgery. The vascular invasion grades of these two patients were Vp3 and Vv2, respectively (Table 1). All participants who underwent surgery had a preoperative Child–Pugh classification of Grade A. As presented in Table 3, a total of 11 patients underwent major hepatectomy procedures (≥3 segments), with a median intraoperative blood loss volume of 300 mL (range: 100–1500 mL). The median duration of postoperative hospitalization was 13 days (range: 6–18 days). Three patients (17.6%) experienced liver failure after surgery, but their conditions improved following liver-protective treatment. Postoperative adverse events are listed in Table 4, with only two cases of grade III adverse events, both of which were peritonitis, which were resolved with antibiotic treatment.

Table 2 Characteristics of Surgical and Postoperative Features

Patient No.	Intrahepatic Tumor Size, cm	Number of Intrahepatic Tumors	BCLC Tage	CNLC Stage	Vascular Invasion	TKI Used	Anti-PD-1 Antibody Used	Tumo1 Response, by RECIST vl.1	Tumor Response, by mRECIST
1	3.9	4	B	IIB	–	Sor	Cam	SD	SD
2	18.8	1	B	IIB	–	Len	Sin	PR	PR
3	8.6	2	C	IIIA	Vp2/Vv2	Len	Sin	SD	PR
4	5.5	1	B	IIB	–	Apa	Cam	SD	PR
5	11.5	≥4	C	IIIA	Vp2	Apa	Cam	PR	CR
6	14.1	1	C	IIIA	Vp3	Sor	Cam	PR	PR
7	7.8	3	C	IIIA	Vp2	Len	Tis	PR	CR
8	15.1	1	B	IIB	–	Sor	Cam	PR	PR
9	13.0	2	B	IIA	–	Len	Sin	SD	SD
10	11	1	C	IIIA	Vp3	Len	Sin	PR	CR
11	13.8	1	C	IIIA	Vv2	Len	Tis	PR	PR
12	13.0	≥4	C	IIIA	Vv1	Len	Sin	PR	PR
13	8.8	≥4	C	IIB	–	Len	Sin	PR	PR
14	9.5	≥4	C	IIIA	Vp3/Vv2	Len	Tis	PR	PR
15	18.1	≥4	C	IIIA	Vp3/Vv3	Len	Tis	PR	PR
16	14.4	1	C	IIIA	Vp2	Len	Tis	PR	PR
17	9.5	2	C	IIIA	Vv3	Bev	Sin	PR	PR

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CNLC, Chinese Liver Cancer Stage; TKIs, tyrosine kinase inhibitors; Sor, Sorafenib; Len, lenvatinib; Apa, apatinib; Tis, Tislelizumab; Sin, sintilimab; Cam, camrelizumab; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3 Patient Characteristics Before and After Surgery

Patient No.	Days from Quadruple Therapy to Surgery	Cycles of pTAE-HAIC	pTAE-HAIC Last Time Days Before Surgery	TKI Withdrawal Days Before Surgery	Anti-PD-1 Antibody Withdrawal Days Before Surgery	Major Resection	PHLF*	Postoperative Hospital Stay, Days	pCR
1	100	2	47	9	48	Y	Y	18	N
2	69	1	69	18	35	Y	N	9	N
3	88	2	43	17	45	Y	Y	15	N
4	70	1	70	7	27	N	N	7	N
5	99	2	54	10	50	Y	N	13	N
6	134	3	64	15	51	Y	N	9	Y
7	77	2	45	13	40	N	N	16	Y
8	77	2	32	12	30	N	Y	15	N
9	81	2	48	12	49	Y	N	13	N
10	163	4	38	11	37	N	N	14	Y
11	154	4	61	14	62	Y	N	9	N
12	89	2	52	13	53	N	N	11	Y
13	78	2	40	10	41	N	N	15	Y
14	156	4	54	14	55	Y	N	6	N
15	255	5	48	12	49	Y	N	9	N
16	73	2	42	8	44	Y	N	13	Y
17	155	3	57	7	22	Y	N	11	Y

Note: *Classified according to the International Study Group of Liver Surgery.
Abbreviations: pTAE-HAIC, partial transarterial embolization-hepatic artery infusion chemotherapy; PHLF, post-hepatectomy liver failure; TKIs, tyrosine kinase inhibitors; pCR, pathological complete response.

Seven patients (41%) achieved pCR across all surgical specimens. In Patient 11, the resected middle hepatic vein tumour thrombus achieved pCR, while a few viable tumour cells were still present in the intrahepatic lesions, resulting in a downstaging of the BCLC classification from Stage C to Stage A. Additionally, in Patient 15, the intrahepatic tumour achieved pCR, but a few viable tumour cells were still observed in the right anterior branch of the PVTT.

Follow-Up

All patients continued receiving systemic therapy and regular follow-up after surgery. Among the 17 patients, with a median observation period of 17.8 months (range: 12.2–38.3 months), the 12-month OS rate after hepatectomy was 100%, and the median postoperative PFS was 14.5 months (range: 1.5–31.8 months). Five patients experienced tumour recurrence within 12 months, with only one patient experiencing continued progression, and the remaining four patients achieved disease control following treatment. Patients 3 and 6 developed pulmonary metastasis; after changing the systemic treatment regimen, Patient 3 achieved a stable disease, with no new tumours detected at the last follow-up, whereas Patient 6 subsequently developed new hepatic, bone, and lymph node metastases. Patient 5 experienced recurrence at the hepatic surgical site and underwent repeat partial hepatectomy, with no recurrence observed at the last follow-up. Patients 9 and 11 developed intrahepatic metastasis postoperatively, which was well controlled with interventional therapy, with no recurrence noted at the final follow-up.

Treatment Safety

The adverse events are detailed in Table 4. Among the grade 3 adverse events, two cases (11.8%) of peritoneal infection were observed, both of which improved with antibiotic treatment, leading to discharge. The most common grade 1–2 adverse events included hypoalbuminaemia (9 patients, 52.9%), pleural effusion (7 patients, 41.2%), and hypokalaemia (6 patients, 35.3%).

Table 4 Postoperative Adverse Events

Adverse Event	Grade 1–2, n (%)	Grade ≧3, n (%)
Hypothyroidism	1(5.9)	–
Hypertension	1(5.9)	–
Hypokalemia	6(35.3)	–
Hypoalbuminemia	9(52.9)	–
Hyperbilirubinemia	3(17.6)	–
Thrombocytopenia	2(11.8)	–
Anemia	1(5.9)	–
Gastric ulcer	1(5.9)	–
Hand–foot skin reaction	3(17.6)	–
Fever	2(11.8)	–
Abdominal pain	5(29.4)	–
Diarrhoea	1(5.9)	–
Hydrothorax	7(41.2)	–
Neoascites	5(29.4)	–
Peritonitis	–	2(11.8)
Gastritis	2(11.8)	–
Pneumonia	3(17.6)	–
PVT	2(11.8)	–
DVT	1(5.9)	–

Abbreviations: PVT, portal vein thrombosis; DVT, Deep venous thrombosis.

Discussion

In this study, 62 patients with HCC that was initially inoperable received conversion therapy, and 27.4% (17/62) achieved R0 resection. Quadruple therapy consisting of pTAE-HAIC combined with TKIs and anti-PD-1 antibodies represents a feasible conversion strategy for patients with unresectable HCC to achieve successful resection and potential long-term survival.

The quadruple combination therapy, which includes pTAE-HAIC, TKIs, and anti-PD-1 antibodies, has a high objective response rate (ORR), with significant short-term tumour reduction observed in our study (Figure 4a–d). One of the most critical factors for achieving successful conversion is the ORR. Quick effectiveness reduces the duration of exposure to conversion therapy, thus lowering the risk of negative side effects. A more rapid ORR indicates a greater likelihood of shrinking the tumour size and downgrading the stage, which is undoubtedly more favourable for subsequent surgical resection.[14]

Why do we consider and recommend pTAE rather than TACE in combination therapy? Typically, TACE refers to complete chemoembolization of all lesions within the liver, aiming to maximize the CR rate. The latest studies have shown that the combination of TACE-HAIC with targeted and immune therapies can provide better efficacy for patients with intermediate and advanced HCC along with PVTT.[9,27] In these studies, TACE utilized epirubicin, whereas HAIC employed oxaliplatin, leucovorin, and fluorouracil. However, the combined use of multiple chemotherapeutic agents can exacerbate liver damage. This damage is further compounded by the liver function impairment attributable to complete

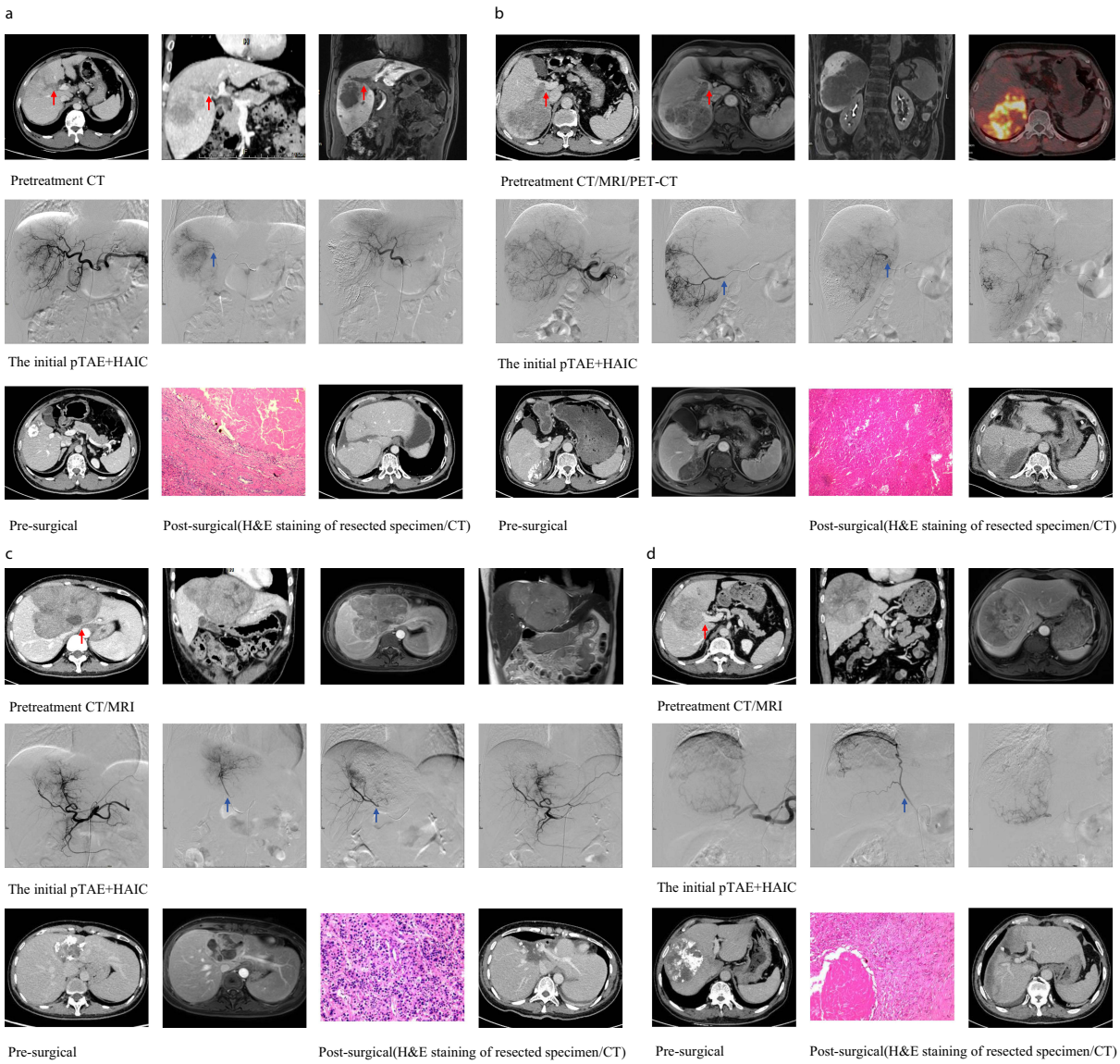

Figure 4 Four representative cases.

Notes: Patient 7 (**a**) was diagnosed with multiple HCC tumours in the right hepatic segment, with invasion into the right anterior branch of the portal vein (indicated by the red arrow). The tumour stage was classified as BCLC stage C. The patient was administered 8 mg of lenvatinib daily and 200 mg of tislelizumab every 3 weeks combined with two cycles of pTAE-HAIC (as shown via angiography, only one main tumour-feeding artery was embolized, with the blue arrow indicating its location). The catheter was inserted and positioned within the right hepatic artery to facilitate HAIC. Following quadruple therapy, the tumours exhibited substantial shrinkage, and the primary tumours and portal vein tumour thrombosis showed no arterial enhancement on a contrast-enhanced CT scan. Curative liver resection was performed, and the patient transitioned from planned hemiliver resection to segmental resection following conversion therapy. The surgically removed specimen displayed a pCR upon H&E staining. Patient 10 (**b**) was identified with an isolated HCC tumour located in the right hepatic segment, with invasion into the right branch of the portal vein (indicated by the red arrow). The tumour was classified as BCLC stage C. The patient was administered 8 mg of lenvatinib daily and 200 mg of sintilimab every 3 weeks combined with four cycles of pTAE-HAIC (as shown by angiography, only two main tumour-feeding arteries were embolized, with the blue arrow indicating its location). The microcatheter was inserted and positioned within the right hepatic artery to facilitate HAIC. Following quadruple therapy, the tumour displayed substantial shrinkage, and the primary tumour and PVTT did not exhibit arterial enhancement on a contrast-enhanced CT scan and MRI. Curative liver resection was performed, and the patient transitioned from planned hemiliver resection to segmental resection following conversion therapy. The surgically removed specimen displayed a pCR upon H&E staining. Patient 11 (**c**) was found to have an isolated HCC tumour that invaded the middle hepatic vein (indicated by the red arrow). The tumour was classified as BCLC stage C and the patient had an insufficient remnant liver volume following hepatectomy. The patient was administered 8 mg of lenvatinib daily and 200 mg of tislelizumab every 3 weeks combined with four cycles of pTAE-HAIC (as shown via angiography, only two main tumour-feeding arteries were embolized, with the blue arrow indicating its location). The microcatheter was inserted and positioned within the proper hepatic artery to facilitate HAIC. Following quadruple therapy, the tumours displayed substantial shrinkage, and presurgery CT and MRI scans indicated the disappearance of the tumour thrombus in the middle hepatic vein, suggesting downstaging from BCLC stage C to stage B; moreover, the remnant liver volume increased significantly. Curative liver resection was performed. Patient 16 (**d**) was identified with a solitary HCC tumour located in the right hepatic segment, which invaded both the right anterior and posterior branches of the portal vein (indicated by the red arrow). The tumour was categorized as BCLC stage C. The patient was administered 8 mg of lenvatinib daily and 200 mg of tislelizumab every 3 weeks combined with four cycles of pTAE-HAIC (as shown by angiography, the lateral hepatic branch blood supply was embolized, with the right inferior phrenic artery, with the blue arrow indicating its location). The microcatheter was inserted and positioned within the proper hepatic artery to facilitate HAIC. All extrahepatic collateral arteries should be embolized first, as in this patient. Following successful quadruple therapy, curative liver resection was performed.

embolization. According to previous reports, the incidence of liver damage in the combination therapy group was markedly higher than that in the TACE-alone control group (68.3% vs 47.6%).[27] Poorer liver function may not only affect subsequent treatments but also lead to liver failure, ultimately shortening the survival period. Therefore, when using the quadruple combination therapy, we do not recommend the use of multiple chemotherapeutic agents during TACE but instead advocate simple TAE. In recent years, the role of TACE in combination therapies has also undergone significant transformation, gradually shifting from "complete embolization" to "partial embolization". Our centre has been exploring the combination of pTAE and HAIC with targeted therapy and immunotherapy for quite some time, and this approach has been widely applied in clinical practice. We have also developed a procedural diagram and schematic diagram for pTAE-HAIC (Figures 1 and 2). Additionally, adverse reactions following successful surgical resection after conversion are controllable.

In the quadruple combination therapy, pTAE plays a crucial synergistic role. pTAE effectively reduces the tumour burden while preventing liver function deterioration and postembolization syndrome associated with complete embolization. Since the HAIC catheter is typically placed within the hepatic artery, pTAE requires the embolization of all extrahepatic collateral arteries involved in the tumour blood supply; simultaneously, embolizing the major intrahepatic feeding arteries slows blood flow and increases the local drug concentration and exposure time, thereby increasing the efficacy of HAIC chemotherapy.[28] Additionally, pTAE induces tumour cell death, leading to the release of antigens and modification of the tumour microenvironment, which enhance the immune response.[10,11] Finally, when used in conjunction with TKIs, these agents can counteract the angiogenic activity induced by hypoxia following embolization.[29] Overall, the multifaceted benefits of pTAE contribute to a more effective and well-tolerated therapeutic regimen in the quadruple combination therapy.

Notably, none of the 13 patients with portal vein trunk/superior mesenteric vein invasion classified as Vp4 underwent surgery after treatment (P=0.031). Previous research has shown that although surgical resection may provide a more favourable prognosis for HCC patients who have PVTT than nonsurgical therapies, including TACE/HAIC or sorafenib,[30] subgroup analyses have revealed that if the neoplastic thrombus has spread to the main trunk of the portal vein (Vp4), the prognosis following combined liver resection and thrombectomy does not seem to be superior to that of nonsurgical treatments.[30,31] Moreover, Vp4 independently predicts a poor prognosis for HCC patients, and treatment outcomes for patients with PVTT Vp4 are generally suboptimal, whether through interventional therapy, targeted therapy, or a combination of targeted and immune therapy, with a limited survival benefit.[32] Therefore, the conversion rate for Vp4 patients is likely to be the lowest, and the timing for surgery after conversion may need to be more cautious. Whether achieving a CR (complete response) in the main trunk of the PVTT according to mRECIST is the optimal surgical timing remains to be determined. This question warrants further investigation.

This study has several limitations that warrant discussion. First, the postoperative follow-up duration was relatively short, precluding a comprehensive understanding of the long-term outcomes. Second, the combination of TKIs and anti-PD-1 antibodies used in this study was not uniform. Treatment decisions can evolve over time with the emergence of new clinical guidelines and research findings. Third, this analysis was conducted retrospectively at a single centre, which introduces the potential for selection bias. Well-designed prospective randomized controlled trials are needed in the future to further confirm these findings.

In summary, the findings reveal that the novel quadruple conversion therapy strategy, which combines pTAE-HAIC with TKIs and anti-PD-1 antibodies, is feasible for treating initially unresectable HCC, subsequent liver resection is both effective and safe, demonstrating potential long-term survival benefits after successful conversion therapy. Nevertheless, large-scale prospective studies will be required to confirm the observed therapeutic advantages.

Data Sharing Statement

All data used during the study are available from the corresponding author RongZhong Huang, Rong Zhou upon reasonable request.

Ethics Statement

The research protocol, encompassing the therapy schedule and methods for gathering data, adhered to the ethical guidelines outlined in the World Medical Association's Declaration of Helsinki and was approved by the Research Ethics Committee of Chongqing University Cancer Hospital (Approval Number: CZLS2021042-A), and written informed consent was obtained from all patients prior to undergoing pTAE-HAIC, TKI, and anti-PD-1 antibody treatment and surgery.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no conflicts of interest.

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