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ORIGINAL RESEARCH

Adjuvant TACE Improves Prognosis After Resection in Dual-Phenotype Hepatocellular Carcinoma: A Propensity Score-Matched Study

Zijian Leng[1,*], Taifeng Zhu[1,*], Ziyue Huang[1,*], Xiaokun Chen[1,*], Yuce Lu[1], Yuehao Zhang[2], Xueshuai Wan[1], Xiaobo Yang[1], Lei Zhang[1], Haitao Zhao[1], Shunda Du[1], Zhonghai Zhao[3], Yongchang Zheng[1]

[1]Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, People's Republic of China; [2]Wannan Medical College, Wuhu, Anhui, People's Republic of China; [3]Department of General Surgery, Beijing Puren Hospital, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zhonghai Zhao, Department of General Surgery, Beijing Puren Hospital, No. 100 Chongwenmenwai Street, Dongcheng District, Beijing, 100062, People's Republic of China, Email zzh036@163.com; Yongchang Zheng, Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, 1 Shuaifuyuan, Dongcheng District, Beijing, 100730, People's Republic of China, Email zhengyongchang@pumch.cn

Background and Aims: Dual-phenotype hepatocellular carcinoma (DPHCC) is an uncommon, highly aggressive form of liver cancer defined by the concurrent expression of both hepatocellular and cholangiocytic markers. This biphenotypic nature contributes to early recurrence and significantly worse survival compared to classic HCC. The benefit of adjuvant transarterial chemoembolization (TACE) after resection for DPHCC is unclear. We aimed to evaluate whether postoperative TACE improves outcomes in patients with resected DPHCC.

Methods: We retrospectively evaluated 436 patients with confirmed DPHCC who underwent curative resection from 2013–2023 at a single center. Among them, 276 received adjuvant TACE and 160 had surgery alone. To minimize selection bias, we performed 1:2 propensity score matching, yielding a balanced cohort of 210 TACE-treated patients and 134 observation-only patients. Recurrence-free survival (RFS) and overall survival (OS) were assessed with Kaplan–Meier and Cox analyses (median follow-up 58 months).

Results: Adjuvant TACE significantly prolonged RFS and OS compared to observation. In the matched cohort, TACE reduced the hazard of recurrence by 32% (HR 0.678, P = 0.032) and the hazard of death by 47% (HR 0.533, P = 0.026). Multivariate analysis confirmed adjuvant TACE as an independent protective factor for RFS and OS. Toxicities were mostly mild (11.4% Grade 3–4; no treatment-related deaths).

Conclusion: In patients with DPHCC, the addition of adjuvant TACE after curative resection substantially lowers recurrence rates and prolongs long-term survival. These findings support incorporating TACE into postoperative management for this high-risk HCC subtype, warranting confirmation in prospective trials.

Clinical Trial Registration: This study has been registered with the Chinese Clinical Trial Registry Center (ChiCTR2500103222).

Plain Language Summary: Dual-phenotype hepatocellular carcinoma is a rare but especially aggressive form of liver cancer. Our study found that patients who received an additional targeted chemotherapy procedure delivered directly to the liver after surgery (called transarterial chemoembolization) had a much lower chance of the cancer coming back and lived longer than those who had surgery alone. These findings suggest that adding this post-surgery treatment can improve outcomes for patients with this high-risk type of liver cancer.

Keywords: dual-phenotype hepatocellular carcinoma, adjuvant transarterial chemoembolization, propensity score matching

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Introduction

Hepatocellular carcinoma (HCC) ranks as the sixth most prevalent malignancy globally and is the third leading cause of cancer-related mortality worldwide.[1] Even with curative-intent surgical resection, HCC has a high tendency to recur: roughly half of patients will experience tumor relapse within three years of surgery, and five-year recurrence rates approach 70%.[2,3] With advances in tumor biology, multiple molecular and pathological subtypes of HCC have been recognized. One such subtype is dual-phenotype hepatocellular carcinoma (DPHCC), which retains the typical histological appearance of HCC but exhibits biphenotypic differentiation: roughly 15% of the tumor cells in DPHCC simultaneously express markers of both hepatocytes (eg, HepPar-1, Glypican-3) and cholangiocytes (eg, CK19, CK7).[4] Due to this dual nature (features of both HCC and intrahepatic cholangiocarcinoma), DPHCC is highly aggressive and confers a worse prognosis than classic HCC. Notably, patients with DPHCC have significantly lower 5-year overall survival (43% vs 56%) and 5-year recurrence-free survival (28% vs 35%) compared to patients with classic HCC.[5] Among those who relapse, DPHCC patients are more likely to develop advanced-stage recurrent disease and extrahepatic metastases (both $P < 0.05$ vs pure HCC).[5] DPHCC tumors also more frequently exhibit features of high aggressiveness such as incomplete encapsulation, microvascular invasion (MVI), and poor differentiation (all $P < 0.05$).[5] Indeed, the DPHCC subtype itself has been identified as an independent risk factor for decreased postoperative survival and higher recurrence risk.[5,6] These characteristics underscore the need for individualized management strategies for DPHCC patients.

Currently, transarterial chemoembolization (TACE) is often employed as an adjuvant therapy after resection in HCC patients deemed high-risk, with the goal of reducing early recurrence. During the TACE procedure, angiographic imaging can reveal any occult residual or new lesions, and chemotherapy is delivered directly into the tumor bed alongside arterial embolization. By cutting off the tumor's blood supply and bathing the tumor bed in chemotherapeutic agents, TACE aims to eliminate microscopic residual disease and prevent neovascularization.[7,8] Several studies have shown that adjuvant TACE improves outcomes in high-risk HCC populations.[9,10] However, current clinical guidelines for adjuvant TACE are predominantly based on traditional clinicopathological risk factors (eg, large tumor size, vascular invasion) and do not explicitly consider molecular subtypes like DPHCC. Notably, DPHCC possesses a unique tumor microenvironment (characterized by aberrant angiogenesis and immunosuppressive features), which may result in a response to TACE that differs from that of conventional HCC. To date, there has been no systematic evaluation of adjuvant TACE efficacy specifically for DPHCC. Therefore, in this study we used a single-center real-world cohort to assess the impact of adjuvant TACE after curative resection on the outcomes of DPHCC patients, aiming to provide high-level evidence for tailored adjuvant treatment in this aggressive subtype.

Materials and Methods

Patient Selection

We retrospectively reviewed patients who underwent treatment at Peking Union Medical College Hospital between January 2013 and December 2023.

Patients were eligible for inclusion if they met all of the following criteria:

(1) underwent initial curative-intent liver resection at our center;

(2) had postoperative pathological confirmation of dual-phenotype hepatocellular carcinoma (DPHCC);

(3) were aged 18–80 years, with preserved performance status and no major organ dysfunction;

(4) had preoperative liver function classified as Child–Pugh class A or B.

Patients were excluded if they met any of the following criteria:

(1) evidence of extrahepatic spread or distant metastasis at diagnosis;

(2) receipt of any anti-cancer therapy prior to surgery;

(3) receipt of any postoperative anti-cancer treatment other than transarterial chemoembolization (TACE);

(4) a prior history of another malignancy;

(5) incomplete clinicopathological data, including missing immunohistochemical results.

The diagnosis of DPHCC was established based on standard histopathological criteria. Specifically, tumors were required to meet both of the following conditions:

(i) exhibit morphological features consistent with hepatocellular carcinoma (HCC);[11,12]

(ii) demonstrate immunohistochemical evidence of biphenotypic differentiation, defined as >15% of tumor cells co-expressing at least one cholangiocyte marker (eg, MUC1, CK7, or CK19) and at least one hepatocellular marker (eg, Arginase-1, HepPar-1, Glypican-3, or CD34) within the same lesion.[4,13,14]

Adjuvant Treatments

Approximately 4 to 6 weeks after surgery, adjuvant therapy is recommended for patients with high recurrence risks, including macrovascular invasion, MVI, multiple lesions, tumor diameter greater than 5 cm, poor differentiation, and preoperative serum alpha-fetoprotein (AFP) levels greater than 400 ng/mL. All TACE procedures were carried out under sterile conditions via a common femoral artery approach using the Seldinger technique. Based on preoperative angiography or dynamic contrast-enhanced imaging performed prior to the curative resection, which roughly identified the tumor-feeding arteries, a microcatheter was advanced under fluoroscopic guidance to super-selectively cannulate these suspected arteries. Chemotherapeutic emulsion containing 5-fluorouracil (1 g), pirarubicin hydrochloride (30 mg), and lipiodol (3–5 mL) was then infused into the target arteries, followed by embolization. An abdominal CT scan was performed approximately two weeks after TACE to evaluate lipiodol deposition and assess the necessity for a second TACE session. Patients in the observation group received no adjuvant anticancer therapy post-surgery, unless recurrence was detected during follow-up.

Outcome Measures and Follow-Up

The primary endpoints were overall survival (OS) and recurrence-free survival (RFS). OS was defined as the time from surgery to death from any cause (or to last contact if alive), and RFS as the time from surgery to the first confirmed tumor recurrence (or last follow-up if no recurrence). We also monitored adverse events (AEs) related to adjuvant therapy from the initiation of TACE through the end of follow-up, grading them according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Patients were followed regularly via clinic visits or telephone calls to document any recurrence, metastasis, or death. For patients who received adjuvant TACE, the first postoperative assessment was scheduled two weeks after the TACE procedure to evaluate lipiodol deposition, with subsequent follow-up visits every three months during the first two years post-surgery. For patients who did not receive adjuvant TACE, follow-up visits were conducted every three months during the first two years after surgery. After two years, all patients were followed up every six months. At each visit, evaluations included a physical examination, laboratory tests (complete blood count, liver and renal function tests, tumor markers), and imaging studies (chest X-ray or CT scan, plus contrast-enhanced abdominal CT or MRI). Any suspected recurrence was confirmed by appropriate imaging (and biopsy if necessary). The follow-up period extended until February 28, 2025, or until the date of death for patients who died before that point.

Statistical Analysis

Continuous variables were reported as medians with interquartile ranges (IQRs) and compared between groups using either the independent-samples *t*-test or the Mann–Whitney *U*-test, depending on data distribution. Categorical variables were summarized as counts and percentages and compared using the χ^2-test or Fisher's exact test (as appropriate). To mitigate selection bias between the TACE and observation groups, we performed propensity score matching (PSM). Propensity scores were estimated via multivariable logistic regression. The factors used for matching included gender, age, BMI, comorbidities, HBV, HCV, liver cirrhosis, Child-Pugh grade, AFP, CA19-9, BCLC stage, CNLC stage, TNM stage, surgical approach, intraoperative blood loss, duration of first hepatic hilum occlusion, tumor numbers, maximum tumor size, liver capsule invasion, tumor differentiation, MVI, satellite nodules, and vascular tumor thrombus. Patients were then matched in a 1:2 ratio (TACE:observation) using nearest-neighbor matching without replacement, with a caliper width of 0.1. Survival outcomes (OS and RFS) were analyzed using the Kaplan–Meier method, and differences between groups were assessed by the Log rank test. Cox proportional hazards models were used for univariate and multivariate analyses to identify prognostic factors. All analyses were conducted with R (v4.3.2) and SPSS (v29). A two-sided P value < 0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 436 DPHCC patients met the inclusion criteria, with 276 patients in the adjuvant TACE group and 160 in the observation group prior to matching. In our study cohort, 184 patients were positive for CK19, 214 for CK7, and 141 for MUC1. Table 1 presents the baseline clinicopathological characteristics of both groups before and after PSM. Prior to matching, there were significant differences between the groups: patients selected for adjuvant TACE more often had serum AFP ≥400 ng/mL, more advanced tumor stage (eg, BCLC stage B or C; TNM stage III), a higher prevalence of multiple tumors and larger tumor size, more frequent satellite nodules, and were more likely to have undergone open (as opposed to

Table 1 Baseline Characteristics of Patients in TACE and Observation Groups: Overall and PSM Cohorts

Variables (%)	Before PSM		*P-value*	After PSM		*P-value*
	TACE Group (n=276)	Observation Group (n=160)		TACE Group (n=210)	Observation Group (n=134)	
Gender			0.161			0.842
Male	229 (83.0)	124 (77.5)		169 (80.5)	109 (81.3)	
Female	47 (17.0)	36 (22.5)		41 (19.5)	25 (18.7)	
Age, years	57 [51, 64]	59 [52, 66]	0.142	58 [51, 65]	58 [52, 65]	0.484
BMI, kg/m²	24.7 [22.6, 27.0]	24.1 [22.2, 26.2]	0.117	24.7 [22.6, 26.5]	24.2 [22.7, 26.5]	0.911
Comorbidities			0.518			0.924
Positive	112 (40.6)	70 (43.8)		92 (43.8)	58 (43.3)	
Negative	164 (59.4)	90 (56.3)		118 (56.2)	76 (56.7)	
HBV infection			0.308			0.302
Positive	204 (73.9)	111 (69.4)		152 (72.4)	90 (67.2)	
Negative	72 (26.1)	49 (30.6)		58 (27.6)	44 (32.8)	
HCV infection			0.809			0.645
Positive	19 (6.9)	12 (7.5)		13 (6.2)	10 (7.5)	
Negative	257 (93.1)	148 (92.5)		197 (93.8)	124 (92.5)	
Liver cirrhosis			0.469			0.794
Positive	182 (65.9)	100 (62.5)		133 (63.3)	83 (61.9)	
Negative	94 (34.1)	60 (37.5)		77 (36.7)	51 (38.1)	
Child-Pugh grade			0.711			>0.999
A	272 (98.6)	157 (98.1)		207 (98.6)	133 (99.3)	
B	4 (1.4)	3 (1.9)		3 (1.4)	1 (0.7)	
Serum AFP			**0.002**			0.284
<400 ng/mL	200 (72.5)	137 (85.6)		164 (78.1)	111 (82.8)	
≥400 ng/mL	76 (27.5)	23 (14.4)		46 (21.9)	23 (17.2)	
Serum CA19-9			0.852			0.512
<37 U/mL	231 (83.7)	135 (84.4)		173 (82.4)	114 (85.1)	
≥37 U/mL	45 (16.3)	25 (15.6)		37 (17.6)	20 (14.9)	
BCLC stage			**0.046**			0.589
0/A	225 (81.5)	142 (88.8)		179 (85.2)	117 (87.3)	
B/C	51 (18.5)	18 (11.3)		31 (14.8)	17 (12.7)	
CNLC stage			0.059			0.610
I	225 (81.5)	142 (88.8)		179 (85.2)	117 (87.3)	
II	23 (8.3)	5 (3.1)		11 (5.2)	5 (3.7)	
III	28 (10.1)	13 (8.1)		20 (9.5)	12 (9.0)	
TNM stage			**0.006**			0.240
I	211 (76.4)	140 (87.5)		169 (80.5)	115 (85.8)	
II	51 (18.5)	15 (9.4)		36 (17.1)	14 (10.4)	
III	14 (5.1)	5 (3.1)		5 (2.4)	5 (3.7)	

(*Continued*)

Table 1 (Continued).

Variables (%)	Before PSM		*P-value*	After PSM		*P-value*
	TACE Group (n=276)	Observation Group (n=160)		TACE Group (n=210)	Observation Group (n=134)	
Surgical approach			**<0.001**			0.362
Open	161 (58.3)	67 (41.9)		114 (54.3)	66 (49.3)	
Laparoscopic	115 (41.7)	93 (58.1)		96 (45.7)	68 (50.7)	
Intraoperative blood loss			>0.999			>0.999
<1000 mL	271 (98.2)	158 (98.8)		207 (98.6)	132 (98.5)	
≥1000 mL	5 (1.8)	2 (1.3)		3 (1.4)	2 (1.5)	
Total duration of first hepatic hilum occlusion			0.467			0.709
<30 min	218 (79.0)	131 (81.9)		169 (80.5)	110 (82.1)	
≥30 min	58 (21.0)	29 (18.1)		41 (19.5)	24 (17.9)	
Tumor numbers			**0.043**			0.425
Single	231 (83.7)	145 (90.6)		182 (86.7)	120 (89.6)	
Multiple	45 (16.3)	15 (9.4)		28 (13.3)	14 (10.4)	
Maximum tumor size			**0.004**			0.362
<5 cm	168 (60.9)	119 (74.4)		139 (66.2)	95 (70.9)	
≥5 cm	108 (39.1)	41 (25.6)		71 (33.8)	39 (29.1)	
Liver capsule invasion			0.055			0.885
Positive	46 (16.7)	16 (10.0)		24 (11.4)	16 (11.9)	
Negative	230 (83.3)	144 (90.0)		186 (88.6)	118 (88.1)	
Tumor differentiation			0.095			0.867
Well	29 (10.5)	23 (14.4)		25 (11.9)	16 (11.9)	
Moderate	166 (60.1)	100 (62.5)		128 (61.0)	83 (61.9)	
Poor	81 (29.3)	37 (23.1)		57 (27.1)	35 (26.1)	
Microvascular invasion			0.286			0.599
M0	151 (54.7)	96 (60.0)		118 (56.2)	80 (59.7)	
M1	75 (27.2)	39 (24.4)		59 (28.1)	33 (24.6)	
M2	50 (18.1)	25 (15.6)		33 (15.7)	21 (15.7)	
Satellite nodules			**0.013**			0.577
Positive	41 (14.9)	11 (6.9)		21 (10.0)	11 (8.2)	
Negative	235 (85.1)	149 (93.1)		189 (90.0)	123 (91.8)	
Vascular tumor thrombus			0.486			0.859
Positive	28 (10.1)	13 (8.1)		20 (9.5)	12 (9.0)	
Negative	248 (89.9)	147 (91.9)		190 (90.5)	122 (91.0)	

Note: Bold values indicate significance at *P<0.05*.

Abbreviations: PSM, Propensity Score Matching; TACE, Transarterial Chemoembolization; BMI, Body Mass Index; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; AFP, Alpha-Fetoprotein; CA19-9, Carbohydrate Antigen 19–9; BCLC, Barcelona Clinic for Liver Cancer; CNLC, Chinese Liver Cancer Staging; TNM, Tumor Node Metastasis.

laparoscopic) surgery (all $P < 0.05$). These findings indicate that, initially, the TACE group had a greater tumor burden and more high-risk features than the observation group. After 1:2 PSM, we obtained a matched cohort of 210 TACE patients and 134 observation patients, achieving a well-balanced comparison. All key preoperative factors – including age, sex, comorbidities, hepatitis B/C status, presence of cirrhosis, tumor count, tumor size, histological differentiation, MVI, and macrovascular thrombosis – were comparable between the matched TACE and non-TACE groups (all post-matching $P > 0.05$). This successful matching provided a solid foundation for unbiased comparison of outcomes.

Recurrence and Survival Analysis

The median follow-up for the cohort was 57.9 months. In the propensity-matched population, patients who received adjuvant TACE had significantly better RFS and OS outcomes than those who did not. Figure 1A shows the Kaplan–

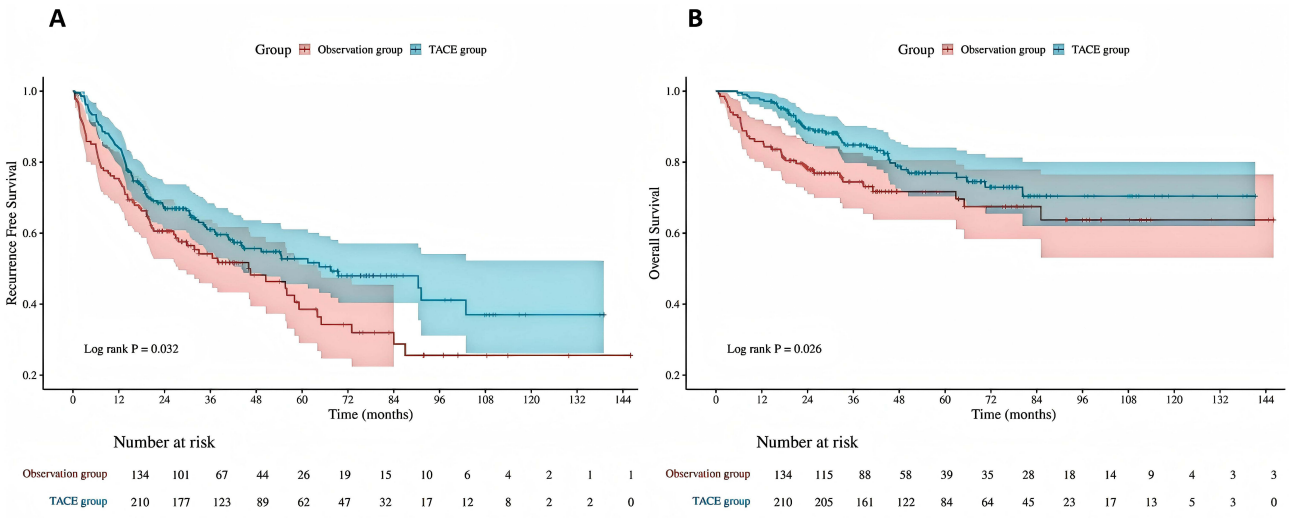

Figure 1 Adjuvant transarterial chemoembolization (TACE) improves recurrence-free and overall survival in patients with dual-phenotype hepatocellular carcinoma (DPHCC) following curative resection. (**A**) Kaplan–Meier curves of recurrence-free survival (RFS) for patients receiving postoperative adjuvant TACE (n = 210) versus observation only (n = 134) in the propensity score–matched cohort. (**B**) Kaplan–Meier curves of overall survival (OS) comparing the TACE and observation groups. In both panels, shaded areas represent 95% confidence intervals. Tick marks indicate censored observations. The numbers below each plot show the number of patients at risk at each time point.

Meier curves for RFS: the TACE group maintained a higher recurrence-free proportion of patients over time compared to the observation group. The separation of the RFS curves became evident by about 24 months post-surgery and widened through approximately 50–100 months. Figure 1B illustrates OS curves: the adjuvant TACE group also exhibited a clear survival advantage. Over the follow-up period, patients who received TACE had a consistently lower cumulative risk of death than those who did not.

Across the full cohort, the vast majority of recurrences were confined to the liver in both study arms. Among patients who experienced recurrence, 83.1% had intrahepatic-only relapse (84.0% in the TACE group vs 81.9% in the observation group), and there was no significant difference between the groups in terms of intrahepatic vs extrahepatic recurrence patterns (Supplementary Table 1; P > 0.05). We further analyzed the sites of intrahepatic recurrence in both the TACE and observation groups. After matching, recurrence at the original tumor bed was observed in 44 (55.7%) patients in the TACE group and 35 (59.3%) in the observation group, while new intrahepatic lesions occurred in 35 (44.3%) patients in the TACE group and 24 (40.7%) in the observation group. The difference in the distribution of recurrence sites between the two groups was not statistically significant (Supplementary Table 2; P > 0.05).

Prognostic Factor Analysis

We next examined which factors influenced postoperative outcomes in DPHCC. Table 2 summarizes the univariate Cox regression results for RFS. The following were significantly associated with shorter RFS in univariate analysis: elevated preoperative CA19-9 (≥37 U/mL; HR 1.620, 95% CI 1.12–2.35; P = 0.011), large tumor size (maximum diameter ≥5 cm; HR 1.550, 95% CI 1.13–2.12; P = 0.006), presence of satellite nodules (HR 1.849, 95% CI 1.14–3.00; P = 0.013), and omission of adjuvant TACE (ie, being in the observation group; HR for TACE vs none = 0.715; 95% CI 0.53–0.97; P = 0.032). In the multivariate Cox model (Table 2), three of these factors remained independent predictors of worse RFS: CA19-9 ≥37 U/mL (HR 1.608, 95% CI 1.10–2.35; P = 0.014), tumor size ≥5 cm (HR 1.504, 95% CI 1.10–2.06; P = 0.012), and presence of satellite nodules (HR 1.929, 95% CI 1.17–3.17; P = 0.010). Notably, receiving adjuvant TACE was independently associated with significantly better RFS (HR for TACE vs observation = 0.678; 95% CI 0.50–0.93; P = 0.014), reinforcing that adjuvant TACE provides a protective effect against recurrence even after adjusting for other variables. In summary, high tumor burden and aggressive tumor features (eg, large size, satellite lesions) were linked to higher recurrence risk, whereas adjuvant TACE substantially reduced the likelihood of post-operative recurrence.

Table 2 Univariate and Multivariate Analysis of Prognostic Factors for RFS in DPHCC Patients

Variables	RFS					
	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P-value*	HR	95% CI	*P-value*
Gender (Male vs Female)	1.534	1.00–2.35	**0.049**			
Age (≥60 vs <60)	1.029	0.76–1.40	0.857			
HBV infection (Positive vs Negative)	1.022	0.73–1.43	0.900			
HCV infection (Positive vs Negative)	1.152	0.65–2.03	0.624			
Liver cirrhosis (Positive vs Negative)	1.148	0.83–1.58	0.399			
Child-Pugh grade (B vs A)	1.406	0.35–5.67	0.633			
Serum AFP (≥400 ng/mL vs <400 ng/mL)	1.001	0.69–1.45	0.994			
Serum CA19-9 (≥37 U/mL vs <37 U/mL)	1.620	1.12–2.35	**0.011**	1.608	1.10–2.35	**0.014**
BCLC stage (B/C vs 0/A)	1.323	0.89–1.97	0.166			
CNLC stage (III vs I/II)	1.240	0.99–1.55	0.057			
TNM stage (III vs I/II)	1.214	0.90–1.65	0.212			
Intraoperative blood loss (≥1000 mL vs <1000 mL)	1.606	0.60–4.34	0.350			
Total duration of first hepatic hilum occlusion (≥30 min vs <30 min)	1.120	0.75–1.68	0.584			
Tumor number (Multiple vs Single)	1.126	0.73–1.73	0.587			
Maximum tumor size (≥5 cm vs <5 cm)	1.550	1.13–2.12	**0.006**	1.504	1.10–2.06	**0.012**
Liver capsule invasion (Positive vs Negative)	1.232	0.80–1.89	0.338			
Tumor differentiation (Poor vs Well/ Moderate)	1.184	0.92–1.52	0.190			
Microvascular invasion (M2 vs M0/ M1)	1.374	1.14–1.66	**0.001**			
Satellite nodules (Positive vs Negative)	1.849	1.14–3.00	**0.013**	1.929	1.17–3.17	**0.010**
Vascular tumor thrombus (Positive vs Negative)	1.671	1.08–2.60	**0.023**			
Postoperative adjuvant TACE (Positive vs Negative)	0.715	0.53–0.97	**0.032**	0.678	0.50–0.93	**0.014**

Note: Bold values indicate significance at P <0.05.

Abbreviations: RFS, Recurrence Free Survival; HR, Hazard Ratio; 95% CI, 95% Confidence Interval; DPHCC, Dual-phenotype Hepatocellular Carcinoma.

We performed a similar analysis for overall survival. On univariate analysis (Table 3), the following factors were significantly associated with worse OS: AFP ≥400 ng/mL (HR 1.870; P = 0.009), CA19-9 ≥37 U/mL (HR 2.046; P = 0.005), advanced tumor stage by BCLC (stage B or C vs A; HR 1.734; P = 0.041), advanced stage by CNLC (stage III vs I/II; HR 1.452; P = 0.011), advanced pathological stage by TNM (stage III vs I/II; HR 1.611; P = 0.019), largest tumor diameter ≥5 cm (HR 2.235; P < 0.001), poor tumor differentiation (HR 1.743; P = 0.004), presence of microvascular invasion (HR 1.581; P < 0.001), and presence of macrovascular tumor thrombus (HR 2.259; P = 0.005). In the multivariate Cox analysis (Table 3), three factors emerged as independent predictors of decreased OS: CA19-9 ≥37 U/mL (HR 1.820, 95% CI 1.08–3.08; P = 0.025), tumor size ≥5 cm (HR 2.030, 95% CI 1.29–3.20; P = 0.002), and not receiving adjuvant TACE (observation group; HR for TACE vs none = 0.533, 95% CI 0.34–0.84; P = 0.006). In other words, absence of adjuvant TACE was independently associated with significantly worse overall survival, whereas the administration of adjuvant TACE conferred a substantial survival benefit (roughly cutting the hazard of death in half). Collectively, these results underscore the critical role of adjuvant TACE in improving long-term outcomes for high-risk DPHCC patients, while reaffirming that large tumor burden and aggressive tumor biology (eg, elevated CA19-9, large tumor size) adversely impact prognosis.

Safety

Treatment-related adverse events (AEs) in the adjuvant TACE group are summarized in Supplementary Table 3. The most common AEs were transient elevations in liver enzymes ("transaminitis", observed in 131 patients), postoperative nausea/vomiting (110 patients), and leukocytopenia (89 patients). Most AEs were mild (Grade 1–2). A total of 24 patients (11.4%) experienced Grade 3–4 AEs, primarily marked elevations in liver transaminases or bone marrow suppression; all of these were managed conservatively. Notably, there were no treatment-related deaths in the adjuvant TACE group.

Table 3 Univariate and Multivariate Analysis of Prognostic Factors for OS in DPHCC Patients

Variables	OS					
	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P-value*	HR	95% CI	*P-value*
Gender (Male vs Female)	1.394	0.75–2.58	0.290			
Age (≥60 vs <60)	0.958	0.61–1.50	0.853			
HBV infection (Positive vs Negative)	0.759	0.48–1.21	0.246			
HCV infection (Positive vs Negative)	0.356	0.62–2.95	0.442			
Liver cirrhosis (Positive vs Negative)	0.868	0.55–1.37	0.542			
Child-Pugh grade (B vs A)	3.234	0.79–13.20	0.102			
Serum AFP (≥400 ng/mL vs <400 ng/mL)	1.870	1.17–3.00	**0.009**			
Serum CA19-9 (≥37 U/mL vs <37 U/mL)	2.046	1.24–3.38	**0.005**	1.820	1.08–3.08	**0.025**
BCLC stage (B/C vs 0/A)	1.734	1.02–2.94	**0.041**			
CNLC stage (III vs I/II)	1.452	1.09–1.94	**0.011**			
TNM stage (III vs I/II)	1.611	1.08–2.40	**0.019**			
Intraoperative blood loss (≥1000 mL vs <1000 mL)	1.534	0.38–6.27	0.551			
Total duration of first hepatic hilum occlusion (≥30 min vs <30 min)	1.102	0.60–2.01	0.752			
Tumor number (Multiple vs Single)	1.472	0.82–2.63	0.192			
Maximum tumor size (≥5 cm vs <5 cm)	2.235	1.43–3.49	**<0.001**	2.030	1.29–3.20	**0.002**
Liver capsule invasion (Positive vs Negative)	1.470	0.82–2.63	0.193			
Tumor differentiation (Poor vs Well/ Moderate)	1.743	1.20–2.54	**0.004**			
Microvascular invasion (M2 vs M0/ M1)	1.581	1.21–2.07	**<0.001**			
Satellite nodules (Positive vs Negative)	0.971	0.42–2.24	0.945			
Vascular tumor thrombus (Positive vs Negative)	2.259	1.28–3.97	**0.005**			
Postoperative adjuvant TACE (Positive vs Negative)	0.607	0.39–0.95	**0.028**	0.533	0.34–0.84	**0.006**

Note: Bold values indicate significance at P <0.05.
Abbreviation: OS, Overall Survival.

Discussion

DPHCC is a unique and highly aggressive variant of HCC defined by the concurrent expression of hepatocellular and cholangiocytic markers (most notably cytokeratin 19 (CK19) and CK7). In terms of clinicopathological characteristics, DPHCC tumors are frequently associated with microvascular invasion, poor differentiation, and a strong propensity for both intrahepatic and extrahepatic metastasis.[4,5,15] Consistent with these features, previous studies have reported that patients with DPHCC have significantly worse recurrence-free and overall survival after curative resection compared to those with classical HCC.[5] This disparity in outcomes is thought to stem from the tumor's highly malignant dual biology (HCC and cholangiocarcinoma features) and its tendency for early recurrence.[6,16–18]

The aggressive behavior of DPHCC is largely attributed to its biphenotypic nature. One hallmark of DPHCC is CK19 positivity, which is associated with stem cell–like properties in cancer cells. CK19-expressing liver tumors have been shown to exhibit enhanced proliferative and metastatic potential, greater chemoresistance, and a higher likelihood of vascular invasion.[19–21] Notably, microvascular invasion is especially common in DPHCC and is closely linked to early postoperative recurrence and poor survival.[6] In addition, multifocal disease, poor differentiation, and an early dissemination tendency further heighten the risk of relapse and reduce long-term survival in DPHCC patients.[5,22,23] In our study, we confirmed the prognostic impact of these pathological factors on patient outcomes. Multivariate Cox analysis demonstrated that large tumor size (≥5 cm), elevated CA19-9, and the presence of satellite nodules were independent adverse predictors of RFS, underscoring how tumor burden and invasive characteristics jointly determine the risk of post-surgery recurrence. Although variables such as AFP ≥400 ng/mL, MVI, and macrovascular thrombus were only significant in univariate analyses, these factors are well-established predictors of recurrence and metastasis in HCC and remain clinically important. All of these features are manifestations of tumor aggressiveness and should be considered in postoperative risk stratification for DPHCC.

Adjuvant TACE appears to improve outcomes in DPHCC through multiple mechanisms. First, by selectively embolizing the hepatic arterial supply to the tumor bed, TACE effectively disrupts the microvascular channels that could allow residual cancer cells to disseminate after surgery. This "vascular pathway blockade" helps to prevent early spread of micrometastases. Second, TACE provides a sustained local cytotoxic effect: the use of lipiodol-based chemotherapy emulsions or drug-eluting beads ensures prolonged, high-concentration exposure of any residual tumor tissue to chemotherapeutic agents (such as anthracyclines), thereby eradicating microscopic disease and delaying recurrence.[24] Third, TACE has important immunomodulatory effects on the tumor microenvironment. For example, Pinato et al reported that TACE treatment significantly reduces the proportion of PD-1–expressing CD8+ T cells in peripheral blood, thereby attenuating immunosuppressive signaling and potentially reversing tumor resistance to immune checkpoint inhibitors.[25] TACE has also been shown to decrease levels of circulating regulatory T cells (Tregs). In a study by Ren et al, among 33 HCC patients treated with TACE using gelatin sponge particles, the peripheral Treg fraction declined from 11.7% before treatment to 7.6% at 3–5 weeks post-TACE.[26] Overall, the immunologic profile following TACE is characterized by an increased $CD4^{+/CD8+}$ T cell ratio, expansion of Th17 cells, and a marked reduction in Tregs, changes that are indicative of a more favorable anti-tumor immune status.[25,27]

Current Chinese clinical practice guidelines and consensus statements recommend postoperative TACE for patients with high-risk HCC features, in order to reduce recurrence and prolong survival.[28–30] Our study provides the first direct clinical evidence of benefit from adjuvant TACE in the specific setting of DPHCC. In a PSM-adjusted real-world cohort of DPHCC patients, we found that adjuvant TACE significantly improved both RFS and OS, and this protective effect remained robust in multivariate analysis (adjusted HR ≈0.68 for RFS and 0.53 for OS). These findings support the inclusion of TACE as a key component of postoperative therapy for DPHCC, an HCC subtype for which no standardized adjuvant strategy has previously been established. Notably, our results align with a recent large-scale retrospective analysis which reported that adjuvant TACE was an independent protective factor against recurrence and mortality in patients with CK19-positive HCC (including DPHCC).[31] Numerous other studies have also consistently shown that adjuvant TACE can improve post-resection outcomes in various high-risk HCC populations.[32–37] Although some guidelines have questioned the broad applicability of adjuvant TACE[38,39] – arguing that its efficacy may depend on factors such as tumor stage, postoperative residual disease status, and tumor biology – our findings (derived after rigorous PSM to control for confounding) reinforce the significant clinical value of adjuvant TACE in the context of DPHCC.

Increasingly, there is recognition that DPHCC, as a distinct molecular-pathological subtype of HCC, warrants dedicated management approaches. Accurate identification of DPHCC relies on integrated pathological assessment (morphology plus immunophenotyping for markers like CK19 and CK7), and new research is exploring noninvasive methods (such as radiomics and MRI features) to predict CK19 expression preoperatively.[33,40] Our results further support incorporating TACE into the standard postoperative management of DPHCC, especially for patients presenting with high-risk features (eg, large tumor size, multifocal tumors, presence of MVI, or poor differentiation). In the future, personalized adjuvant treatment pathways for DPHCC could involve multimodal strategies—combining locoregional therapy like TACE with systemic therapies (targeted agents or immunotherapies). With validation in large multicenter prospective trials, such combination approaches may achieve even greater improvements in long-term survival for DPHCC patients.

Our study has several limitations. First, as a retrospective analysis from a single center, it is subject to selection biases and the influence of unmeasured confounding factors. We used propensity score matching to improve the comparability of our groups, but unknown confounders might still have affected the outcomes. Second, although our cohort is relatively large given the rarity of DPHCC, the sample size still constrained certain analyses – we had limited power for detailed subgroup explorations and could not evaluate certain dynamic prognostic markers (for example, post-treatment tumor marker trends) in our models. Looking forward, larger prospective studies (ideally multi-center) are necessary to validate the survival benefits of adjuvant TACE in DPHCC and to determine which subsets of patients derive the greatest benefit.

Moreover, further research into the molecular basis of DPHCC is warranted. A deeper understanding of the genetic and phenotypic drivers of this subtype could unveil novel biomarkers for risk stratification and potential therapeutic targets. In the long run, integrating local therapeutic strategies like TACE with systemic treatments (eg, molecular

targeted agents or immunotherapy) – guided by biomarker-driven patient selection – may offer the best chance to improve the long-term outcomes and quality of life for patients with DPHCC.

In summary, our study demonstrates that in patients with DPHCC, the use of adjuvant TACE after curative resection significantly lowers recurrence risk and improves long-term survival. Considering the extremely aggressive behavior and poor prognosis of DPHCC, integrating adjuvant TACE into routine postoperative management for these patients appears to be a logical, evidence-backed approach. Continued research aimed at refining individualized treatment strategies is warranted to achieve even better long-term outcomes for patients with DPHCC.

Conclusions

In conclusion, our propensity score–matched retrospective analysis of a single-center cohort indicates that adjuvant TACE after curative resection significantly improves prognosis in patients with dual-phenotype HCC. Compared to surgery alone, postoperative TACE was associated with markedly longer recurrence-free and overall survival, with the risk of recurrence and death reduced by approximately 32% and 47%, respectively. Adjuvant TACE remained an independent protective factor for both RFS and OS on multivariate analysis. Importantly, this treatment was generally well tolerated in our cohort, with manageable adverse events and no treatment-related mortality observed. Given the highly aggressive nature of DPHCC, these findings underscore the potential value of incorporating adjuvant TACE into postoperative management for this high-risk HCC subtype. Nevertheless, prospective multi-center studies are warranted to confirm our results and to further optimize patient selection and timing of adjuvant TACE in DPHCC.

Abbreviations

HCC, Hepatocellular carcinoma; DPHCC, Dual-phenotype hepatocellular carcinoma; TACE, transarterial chemoembolization; RFS, Recurrence-free survival; OS, Overall survival; CK19, Cytokeratin 19; CK7, Cytokeratin 7; MVI, Microvascular invasion; MUC1, Mucin 1; CD34, cluster of differentiation 34; CT, Computed tomography; MRI, Magnetic resonance imaging.

Data Sharing Statement

Clinical data: De-identified individual participant data underlying this study will be available upon reasonable request. Data access will be provided to qualified researchers who submit a scientifically valid proposal and obtain approval from the Ethics Committee of Peking Union Medical College Hospital. Requests should be directed to the corresponding author, Yongchang Zheng, at zhengyongchang@pumch.cn. Access requests will be reviewed by the study steering committee.

Ethics Approval and Informed Consent

This retrospective study was performed according to the ethical guidelines of the 1975 Declaration of Helsinki. This study, titled "The Impact of Postoperative Adjuvant Transarterial Chemoembolization on the Prognosis of Patients with Dual-Phenotype Hepatocellular Carcinoma: A Retrospective Single-Center Real-World Cohort Study", was granted approval by the Ethics Committee of PUMCH (No.I-25PJ1026).

Consent for Publication

The authors confirm that all individuals whose identifiable information (including but not limited to images, videos, audio recordings, or clinical details) is included in this manuscript have given their explicit written consent for publication. The individuals providing consent have been shown the contents of the manuscript as it will appear in the journal and have agreed to its publication. Copies of the signed consent forms are retained by the corresponding author and are available for review by the journal's editorial office upon request, in accordance with the journal's editorial policies.

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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 report no conflicts of interest in this work.

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