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Original Article

Sequential prophylactic transarterial chemoembolization modulates recurrence dynamics and improves oncological outcomes after laparoscopic hepatectomy for high-risk hepatocellular carcinoma

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Abstract: Objectives: To evaluate whether sequential prophylactic transarterial chemoembolization (TACE) after curative-intent laparoscopic hepatectomy is associated with reduced recurrence and improved survival in patients with hepatocellular carcinoma (HCC) at high risk of postoperative recurrence. Methods: This single-center retrospective cohort study included 100 consecutive patients who underwent curative-intent laparoscopic hepatectomy between January 2021 and June 2023 and were postoperatively classified as high risk based on predefined pathological and operative criteria. Of these, 52 patients received intensive postoperative surveillance alone, whereas 48 received sequential prophylactic TACE in addition to the same surveillance schedule. Treatment allocation was non-randomized. Follow-up was censored on December 31, 2025. Recurrence-free survival (RFS) and overall survival (OS) were evaluated using Kaplan-Meier, with recurrence patterns and treatment-related safety assessed as secondary outcomes. Results: Sequential prophylactic TACE was associated with significantly improved RFS (HR 0.45, 95% CI 0.30-0.68; P<0.001) and OS (HR 0.65, 95% CI 0.45-0.94; P<0.001). The median RFS was not reached in the TACE group, whereas the RFS probability in the surveillance group declined below 50% during follow-up. Median OS was not reached in either group during the 60-month follow-up. The TACE group also had fewer early recurrences within 12 months (P = 0.012), with reductions primarily in intrahepatic recurrence. Conclusion: Sequential prophylactic TACE after laparoscopic hepatectomy was associated with a lower rate of early intrahepatic recurrence and improved RFS and OS in selected high-risk HCC patients, without a significant increase in major complications. Given the retrospective, single-center, non-randomized design, these findings should be considered exploratory and require confirmation in prospective multicenter studies.

Keywords: Hepatocellular carcinoma, laparoscopic hepatectomy, transarterial chemoembolization, prophylactic TACE, high-risk recurrence

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and a leading cause of cancer death, especially in regions where chronic hepatitis B and C virus infection are predominant and among patients with non-alcoholic fatty liver disease [1, 2]. Curative-intent interventions, such as hepatic resection, liver transplantation, and local ablation, have substantially improved outcomes in selected patients [3, 4]; long-term survival remains unsatisfactory due to high recurrence rates. Although margin-negative resection is performed, patients may still relapse more than 5 years after resection. This challenge is particularly pronounced in patients with unfavorable pathological or radiological features that confer a

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high risk of early reoccurrence, i.e., microvascular invasion, large tumor size, poor differentiation, and narrow resection margins.

Laparoscopic hepatectomy has become an increasingly preferred surgical approach for appropriately selected patients with HCC over the past decade [5, 6]. Compared with open surgery, laparoscopic hepatectomy is associated with reduced intraoperative blood loss, less postoperative pain, shorter hospital stay, and faster recovery, while maintaining comparable oncological efficacy in appropriately selected patients [7, 8]. These advantages may be particularly relevant when postoperative adjuvant treatment is considered, because more rapid recovery may allow additional therapy to be initiated earlier and tolerated more effectively. However, surgical resection alone cannot eliminate the risk of recurrence in patients with adverse pathological features, such as microvascular invasion, large tumor size, multifocal disease, poor differentiation, or a narrow resection margin. In these high-risk patients, postoperative recurrence is thought to be driven, at least in part, by occult intrahepatic micrometastases or microscopic residual tumor deposits that are not detectable on routine postoperative imaging. This provides the clinical rationale for considering prophylactic TACE after curative resection as a risk-adapted adjuvant strategy rather than as treatment for radiologically evident disease. By delivering locoregional chemotherapy and arterial embolization to the remnant liver, prophylactic TACE may suppress occult intrahepatic tumor foci and thereby reduce early recurrence. Nevertheless, its use must be balanced against potential risks, including ischemic hepatic injury, transient deterioration of liver function, post-embolization symptoms, and cumulative hepatic toxicity, particularly when repeated sessions are administered. Therefore, postoperative prophylactic TACE should be considered only in carefully selected high-risk patients with adequate hepatic functional reserve, and its potential oncological benefit must be weighed against the additional treatment-related burden.

Transarterial chemoembolization (TACE) is a cornerstone locoregional therapy for intermediate-stage HCC and is also widely used for unresectable disease or as a bridging/downstaging treatment [9-11]. Its postoperative adjuvant or prophylactic use after curative resection has been extensively investigated, but its benefit remains unsettled. Several studies have suggested that prophylactic TACE may eradicate microscopic residual disease and intrahepatic micrometastases, thereby improving recurrence-free survival in patients with high-risk features [12]. Importantly, recent meta-analyses by Huo et al. [13] and Chen et al. [14] pooled comparative studies of resection plus postoperative adjuvant TACE versus resection alone and generally suggested a favorable association with recurrence and survival outcomes, particularly in selected high-risk populations, although the magnitude of benefit varied and the underlying evidence was largely retrospective. Thus, the expected treatment effect of adjuvant TACE appears to be clinically relevant but context-dependent rather than uniform across all resected HCC patients. However, reported results have remained inconsistent, partly because of heterogeneous patient selection, variable definitions of high-risk recurrence, differences in surgical approach, and, importantly, limited differentiation between treatment schedules. In this context, single-session adjuvant TACE refers to a one-time postoperative TACE procedure, whereas sequential prophylactic TACE refers to planned repeated postoperative TACE sessions administered at predefined intervals in the absence of radiologically detectable recurrence. This distinction is clinically important, because a single postoperative session may be insufficient for biologically aggressive tumors, whereas a sequential strategy may provide more sustained control of occult intrahepatic disease, albeit at the potential cost of cumulative hepatic toxicity. This balance may be particularly relevant after laparoscopic hepatectomy, where faster postoperative recovery may facilitate additional locoregional treatment, but overtreatment could also offset the benefits of a minimally invasive approach.

Therefore, this study evaluated the association of sequential prophylactic TACE with recurrence and survival outcomes in patients with HCC at high risk of postoperative recurrence after curative-intent laparoscopic hepatectomy. We hypothesized that sequential prophylactic TACE would be associated with reduced early recurrence and more favorable survival outcomes than surveillance alone, without a significant increase in major postoperative morbidity. By focusing on a relatively homogeneous high-risk

cohort treated with a minimally invasive approach, we aimed to clarify the potential role of sequential prophylactic TACE in postoperative management.

Methods and materials

Clinical data

This single-center retrospective cohort study consecutively included 100 patients with hepatocellular carcinoma (HCC) who underwent curative-intent laparoscopic hepatectomy at Xiangxi Autonomous Prefecture People's Hospital between January 2021 and June 2023 and who were classified as having a high risk of postoperative recurrence. In the present study, high-risk status was defined according to institutional criteria as the presence of at least one of the following adverse clinicopathological feature: tumor diameter ≥5 cm, multifocal disease, microvascular invasion, poorly or moderately differentiated histology, or a narrow surgical margin. Patients were identified after surgery based on postoperative pathological assessment and operative records, and only those meeting at least one of the predefined high-risk criteria were eligible for inclusion. Given the retrospective nature of this study, high-risk classification was determined after hepatectomy using postoperative pathological and operative information; therefore, the term "prophylactic" refers to the adjuvant intent of TACE after curative resection in patients with identified high-risk features, rather than a preoperatively planned treatment-selection strategy. After completion of patient enrollment, all study variables, including baseline clinicopathological characteristics, perioperative data, treatment information, and follow-up outcomes, were retrospectively extracted from the database and verified through review of the electronic medical records. Although the source database was maintained prospectively as part of routine clinical practice, the present study and data collection for research purposes were conducted retrospectively. Follow-up duration was not uniform for all patients but varied according to the date of surgery. For survival analyses, follow-up was calculated from the date of hepatectomy to the occurrence of the relevant endpoint or the end of observation. December 31, 2025 was used as the common administrative censoring date for the study. For recurrence-free survival, patients without documented recurrence or death by that date were censored at their last available assessment, whereas for overall survival, patients who were alive at the end of observation were censored at their last confirmed follow-up. Thus, patients undergoing surgery earlier in the enrollment period had a longer potential follow-up than those enrolled later, with follow-up extending to approximately 60 months for the earliest patients. Patients for whom clinical, imaging, or follow-up information was insufficient to reliably ascertain the study outcomes were excluded according to the predefined eligibility criteria; therefore, the final analytic cohort consisted only of patients with adequate follow-up information for assessment of the primary survival outcomes. The study protocol was approved by the Ethics Committee of Xiangxi Autonomous Prefecture People's Hospital. The requirement for informed consent was waived because of the retrospective study design. Patient confidentiality was strictly protected, and all data were anonymized and handled in accordance with institutional regulations. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

The inclusion criteria were as follows: (i) pathologically confirmed HCC; (ii) laparoscopic hepatectomy performed with curative intent and R0 resection; (iii) presence of high-risk factors for postoperative recurrence, including tumor size ≥5 cm, multifocal disease, microvascular invasion, poor or moderately poor differentiation, and a narrow surgical margin according to the institutional criteria; (iv) Child-Pugh class A liver function or carefully selected class B liver function; and (v) Eastern Cooperative Oncology Group performance status suitable for surgery. The exclusion criteria were as follows: (i) previous liver resection, liver transplantation, or transarterial chemoembolization; (ii) extrahepatic metastasis or portal vein tumor thrombus detected during surgery; (iii) conversion to open hepatectomy or non-curative (R1/R2) resection; (iv) death within 30 days after surgery; and (v) incomplete clinical, imaging, or follow-up data.

According to the postoperative treatment actually received, 52 patients were classified into the control group, who underwent laparoscopic hepatectomy followed by intensive postoperative surveillance alone, and 48 patients were classified into the observation group, who

underwent laparoscopic hepatectomy followed by sequential prophylactic transarterial chemoembolization (TACE) in addition to the same surveillance schedule. The long-term survival and recurrence outcomes were compared between the two groups.

TACE treatment

Patients in the observation group received sequential prophylactic transarterial chemoembolization (TACE) after adequate recovery from laparoscopic hepatectomy and confirmation of the absence of radiological recurrence on postoperative imaging. The initial TACE session was generally performed 4-6 weeks after surgery, provided that liver function had recovered to Child-Pugh class A or stable class B and no contraindications to arterial intervention were present. The procedure was performed via selective catheterization of the tumor-feeding hepatic arteries or the corresponding remnant liver arteries using the Seldinger technique. A chemotherapeutic emulsion consisting of epirubicin (30-50 mg) mixed with 5-10 mL of iodized oil (Lipiodol) was administered, followed by embolization with absorbable gelatin sponge particles until near stasis of arterial flow was achieved. Based on our institutional protocol and previous clinical experience with postoperative adjuvant TACE, a two-session sequential regimen was selected to achieve sustained suppression of potential occult intrahepatic micrometastases while minimizing the risk of cumulative hepatic injury associated with repeated arterial interventions. Previous studies have suggested that a single postoperative TACE session may provide insufficient duration of locoregional control in patients with high-risk pathological features; therefore, repeated treatment was considered a reasonable strategy for this selected high-risk population.

Patients in the sequential prophylactic TACE group were scheduled to receive two postoperative TACE sessions at an interval of approximately 6-8 weeks in the absence of radiological evidence of recurrence or unacceptable hepatic toxicity. In the present study, sequential prophylactic TACE was defined as a planned strategy of repeated postoperative TACE sessions administered prophylactically after curative resection, whereas single-session TACE referred to only one postoperative TACE treatment without scheduled repeat treatment. Subsequent TACE sessions were postponed or discontinued in patients who developed tumor recurrence, hepatic decompensation, or other contraindications according to institutional multidisciplinary team recommendations.

Data collection

Clinical data were retrospectively extracted from the prospectively maintained institutional database and verified against the electronic medical records using standardized electronic case report forms (eCRFs). Baseline data included demographic characteristics (age, sex, body mass index, smoking status, and alcohol consumption), comorbidities (diabetes mellitus, hypertension, cardiovascular disease, and renal disease), underlying liver disease etiology (HBV, HCV, alcohol-related, or other), the presence and histological stage of cirrhosis, and any history of prior HCC-directed treatment. Prior treatment history was specifically reviewed from medical records and included previous liver resection, liver transplantation, transarterial chemoembolization, local ablative therapy, other liver-directed therapies, and systemic antitumor treatment. In accordance with the predefined eligibility criteria, patients with a history of previous liver resection, liver transplantation, or transarterial chemoembolization were excluded from the study. Information on other prior HCC-directed treatments was also recorded to identify potential treatment-related confounding. Preoperative laboratory assessments included complete blood count, liver biochemistry (alanine aminotransferase, aspartate aminotransferase, total and direct bilirubin, albumin, γ-glutamyltransferase, and alkaline phosphatase), coagulation parameters (prothrombin time and international normalized ratio), renal function (serum creatinine and blood urea nitrogen), serum alpha-fetoprotein (AFP), and des-γ-carboxyprothrombin (DCP). Child-Pugh class, Model for End-stage Liver Disease (MELD) score, and albumin-bilirubin (ALBI) grade were calculated using standard methods. Postoperative surveillance was performed every 3 months during the first 2 years and every 6 months thereafter until recurrence, death, or the end of follow-up. At each follow-up visit, serum AFP measurement and contrast-enhanced abdominal computed tomography or magnetic resonance imaging were routinely performed, with additional chest computed tomography or other imaging studies obtained

when clinically indicated to evaluate suspected recurrence or extrahepatic metastasis. All surveillance images were independently reviewed by two experienced abdominal radiologists who were not involved in patient treatment. Discrepant findings were resolved by consensus in a multidisciplinary liver tumor meeting. Because of the retrospective study design, image reviewers were not formally blinded to treatment allocation, although radiological assessment followed standardized institutional diagnostic criteria.

Patient-reported outcomes were assessed using the validated European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). The prespecified domains analyzed in this study included global health status/quality of life, physical functioning, fatigue, and pain, which correspond to the domains reported in the Results section. Assessments were obtained at baseline before postoperative intervention and at 1, 3, and 6 months after treatment. All QLQ-C30 scores were linearly transformed to a 0-100 scale according to the EORTC scoring manual; for functional and global health status scales, higher scores indicate better status, whereas for symptom scales, higher scores indicate greater symptom burden. To summarize overall symptom severity, a composite symptom-burden score was additionally calculated from the relevant symptom-domain scores for longitudinal comparison between groups.

Sample size calculation

Given the retrospective nature of this single-center cohort study, no formal a priori sample size calculation was performed. All consecutive eligible patients treated during the predefined study period were included in order to maximize the available sample and reduce potential selection bias. Because the sample size was determined by the number of eligible patients available during the study period rather than by a prespecified statistical power calculation, no post hoc power analysis based on the observed effect size was used to infer study adequacy. A post hoc event-based assessment indicated that the observed number of recurrence events provided sufficient information to support estimation of the primary recurrence-free survival outcome; however, the study may have had limited statistical precision for smaller effect sizes, subgroup analyses, and secondary endpoints. Therefore, the present findings should be regarded as exploratory and hypothesis-generating and require confirmation in larger, prospective, multicenter studies.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics (version 25.0; IBM Corp., Armonk, NY, USA). All tests were two-sided, and a P value <0.05 was considered statistically significant unless otherwise specified. The normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed continuous variables are presented as mean ± standard deviation (SD) and were compared between groups using the independent-samples Student's t test, whereas non-normally distributed continuous variables are presented as median with interquartile range (IQR) and were compared using the Mann-Whitney U test. Categorical variables are presented as frequencies and percentages and were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate. Recurrence-free survival (RFS) and overall survival (OS) were estimated using the Kaplan-Meier method and compared between groups using the log-rank test. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models. Multivariable Cox regression analyses were used to evaluate the association between sequential prophylactic TACE and RFS or OS after adjustment for relevant clinicopathological variables. The proportional hazards assumption was assessed before interpretation of the Cox models. Early (<12 months) and late (≥12 months) recurrence, recurrence patterns, and postoperative complications were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate. Longitudinal patient-reported outcomes and liver-function parameters were analyzed using linear mixed-effects models to account for within-patient correlation arising from repeated measurements and the unbalanced follow-up data. Treatment group, follow-up time, and the group-by-time interaction were included as fixed effects, with a patient-specific random intercept. An unstructured covariance structure was specified for within-subject repeated measurements, and model parameters were estimated using restricted maximum like-

lihood (REML). Under the assumption that missing longitudinal observations were missing at random, all available measurements were included in the mixed-effects analyses without single-value imputation. Prespecified between-group comparisons at individual follow-up time points were adjusted using the Bonferroni method for multiple comparisons. RFS and OS were prespecified as the primary endpoints. Analyses of recurrence patterns, patient-reported outcomes, and longitudinal liver-function parameters were considered secondary or exploratory, with multiplicity adjustment applied where appropriate.

Results

Baseline characteristics of the study population

Baseline clinicopathological and operative characteristics were well balanced between the control and sequential prophylactic TACE groups (**Table 1**). There were no significant between-group differences in age (P = 0.526), sex distribution (P = 0.985), HBV-related etiology (P = 0.774), presence of cirrhosis (P = 0.723), or Child-Pugh class A status (P = 0.894). Tumor burden and biological features, including maximum tumor diameter (P = 0.949), multiplicity (P = 0.959), microvascular invasion (P = 0.935), and poor or moderate-poor differentiation (P = 0.986), were also comparable between the two groups. Surgical variables, including the rate of anatomical resection (P = 0.721), frequency of major hepatectomy (P = 0.985), and intraoperative blood loss (P = 0.703), likewise showed no significant between-group differences.

Kaplan-Meier estimates of recurrence-free survival (RFS) and overall survival (OS)

Kaplan-Meier analysis demonstrated a clear separation in recurrence-free survival (RFS) between the sequential prophylactic TACE group (n = 48) and the surgery-alone control group (n = 52), with the RFS probability remaining consistently higher in the sequential prophylactic TACE group throughout the 60-month follow-up period. The between-group difference was statistically significant (log-rank P<0.001), and sequential prophylactic TACE was associated with a lower hazard of recurrence (HR 0.45, 95% CI 0.30-0.68). The RFS curve of the control group declined below 50% during follow-up, whereas the median RFS was not reached in the sequential prophylactic TACE group. A similar separation was observed for overall survival (OS). Patients in the sequential prophylactic TACE group had significantly higher OS probabilities than those in the control group (log-rank P<0.001), with a lower hazard of death (HR 0.65, 95% CI 0.45-0.94). Neither group reached a median OS during the 60-month follow-up, as the estimated OS probability remained above 50% in both groups at the end of follow-up (**Figure 1**).

Perioperative and short-term postoperative outcomes

Perioperative and early postoperative outcomes were comparable between the two groups (**Table 2**). The distribution of minor versus major resections did not differ significantly between the two groups (P = 0.948), nor did operative time (P = 0.650), use of the Pringle maneuver (P = 0.932), or cumulative clamping time (P = 0.994). Intraoperative blood loss and transfusion requirements were also comparable between groups (P = 0.142 and P = 0.969, respectively). The incidence of post-hepatectomy liver failure, graded according to the criteria of the International Study Group of Liver Surgery (ISGLS), was comparable between groups (P = 0.911). Early postoperative recovery, reflected by ICU stay and total postoperative hospital stay, likewise showed no significant between-group differences (P = 0.480 and P = 0.687, respectively). Together, these findings indicate that sequential prophylactic TACE did not adversely affect perioperative safety or short-term recovery after laparoscopic hepatectomy.

Patterns and timing of tumor recurrence

During follow-up, the proportion of patients who developed tumor recurrence was significantly lower in the sequential prophylactic TACE group than in the control group (43.8% vs. 65.4%; P = 0.030). The time to recurrence was also significantly longer in the sequential prophylactic TACE group (16.60 ± 6.74 vs. 13.08 ± 6.93 months; P = 0.012). This difference was mainly attributable to a lower rate of early (<12 months) recurrence in the sequential prophylactic TACE group (14.6% vs. 36.5%; P = 0.012), whereas late (≥12 months) recurrence rates were similar between the two groups (29.2% vs. 28.8%; P = 0.972). The distribution of the

Table 1. Baseline characteristics of the study population

	Control group (n = 52)	Observation group (n = 48)	Statistical test	*P* value
Age, years, mean ± SD	57.94 ± 10.11	56.71 ± 9.18	0.637	0.526
Male sex, n (%)	40 (76.9)	37 (77.1)	0.001	0.985
HBV-related etiology, n (%)	35 (67.3)	31 (64.6)	0.083	0.774
Cirrhosis, n (%)	30 (57.7)	26 (54.2)	0.126	0.723
Child-Pugh class A, n (%)	47 (90.4)	43 (89.6)	0.018	0.894
Maximum tumor diameter, cm, median (IQR)	5.93 ± 2.47	5.96 ± 2.37	0.064	0.949
Multiple tumors, n (%)	16 (30.8)	15 (31.3)	0.003	0.959
Microvascular invasion, n (%)	21 (40.4)	19 (39.6)	0.007	0.935
Poorly/moderately differentiated histology, n (%)	14 (26.9)	13 (27.1)	0.001	0.986
Anatomical resection, n (%)	34 (65.4)	33 (68.8)	0.128	0.721
Major hepatectomy (≥3 segments), n (%)	12 (23.1)	11 (22.9)	0.001	0.985
Intraoperative blood loss, mL, median (IQR)	252.75 ± 104.84	260.31 ± 91.93	0.382	0.703

Note: Data are presented as mean ± standard deviation (SD), median (interquartile range [IQR]), or n (%), as appropriate. For variables presented as median (IQR), the between-group difference was not estimated in this table because the comparison was performed using the non-parametric Mann-Whitney U test.

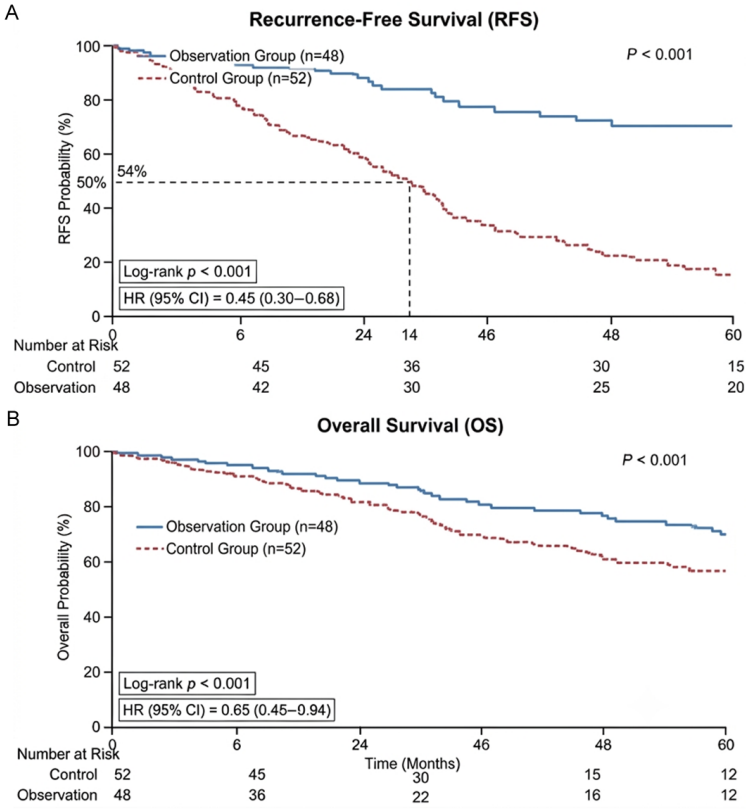

Figure 1. Kaplan-Meier estimates of recurrence-free survival (RFS) and overall survival (OS). A. RFS curves; B. OS curves.

first recurrence site also differed significantly between groups (overall P = 0.030), with intrahepatic-only recurrence occurring less frequently in the sequential prophylactic TACE group (27.1% vs. 49.0%), while the proportions of extrahepatic-only recurrence (6.3% vs. 7.7%) and combined intrahepatic and extrahepatic recurrence (10.4% vs. 9.6%) were similar. Macrovascular invasion at recurrence was numerically less frequent in the sequential prophylactic TACE group (6.3% vs. 13.5%; P = 0.230), although the difference was not statistically significant (**Table 3**).

Safety and adverse events

The overall incidence of adverse events was significantly higher in the sequential prophylactic TACE group than in the control group (38/48 [79.2%] vs. 25/52 [48.1%]; P = 0.001), and postoperative complications were also more frequent in the TACE group (32/48 [66.7%] vs. 24/52 [46.2%]; P = 0.039). In contrast, the incidence of intraoperative complications did not differ significantly between groups (6/48 [12.5%] vs. 5/52 [9.6%]; P = 0.645), including bleeding requiring transfusion, bile duct injury, and conversion to open surgery. Post-

Table 2. Perioperative and short-term postoperative outcomes

Variable	Control (n = 52)	Observation (n = 48)	Statistical test	*P* value
Type of resection, n (%)			$\chi^2 = 0.004$	0.948
Minor (≤2 segments)	30 (57.7)	28 (58.3)		
Major (≥3 segments)	22 (42.3)	20 (41.7)		
Operative time, min, mean ± SD	235.52 ± 50.68	230.79 ± 53.27	t = -0.455	0.650
Pringle maneuver used, n (%)	43 (82.7)	40 (83.3)	$\chi^2 = 0.007$	0.932
Cumulative clamping time, min	35.08 ± 9.08	35.06 ± 9.63	t = 0.008	0.994
Intraoperative blood loss, mL	329.48 ± 119.84	365.98 ± 126.55	t = 1.481	0.142
Intraoperative transfusion, n (%)	11 (21.2)	10 (20.8)	$\chi^2 = 0.002$	0.969
Post-hepatectomy liver failure, n (%)	8 (15.4)	7 (14.6)	$\chi^2 = 0.013$	0.911
Grade A	6 (11.5)	5 (10.4)		
Grade B	2 (3.8)	2 (4.2)		
Grade C	0 (0)	0 (0)		
ICU stay, days	1.44 ± 0.67	1.35 ± 0.56	t = 0.709	0.480
Postoperative hospital stay	8.81 ± 2.93	9.04 ± 2.84	t = 0.405	0.687

Note: ISGLS: International Study Group of Liver Surgery.

Table 3. Patterns and timing of tumor recurrence

Variable	Control (n = 52)	Observation (n = 48)	Statistical test	*P* value
Any recurrence during follow-up, n (%)	34 (65.4)	21 (43.8)	$\chi^2 = 4.720$	0.030
Time to recurrence, months	13.08 ± 6.93	16.60 ± 6.74	t = 2.575	0.012
Early recurrence (<12 months), n (%)	19 (36.5)	7 (14.6)	$\chi^2 = 6.253$	0.012
Late recurrence (≥12 months), n (%)	15 (28.8)	14 (29.2)	$\chi^2 = 0.001$	0.972
Site of first recurrence, n (%)			$\chi^2 = 4.720$	0.030
Intrahepatic only	25 (49.0)	13 (27.1)		
Extrahepatic only	4 (7.7)	3 (6.3)		
Both intra- and extrahepatic	5 (9.6)	5 (10.4)		
Macrovascular invasion at recurrence, n (%)	7 (13.5)	3 (6.3)	$\chi^2 = 1.442$	0.230

hepatectomy liver failure, bile leakage, ascites requiring diuretics, and surgical site infection occurred at generally comparable frequencies between the two groups. According to the Clavien-Dindo classification, the proportion of patients with grade ≥III complications was similar between the sequential prophylactic TACE and control groups (7/48 [14.6%] vs. 5/52 [9.6%]; P = 0.445). Grade IIIa complications, defined as complications requiring surgical, endoscopic, or radiological intervention without general anesthesia, occurred in 4/48 (8.3%) and 2/52 (3.8%) patients, respectively. No grade IIIb complications requiring intervention under general anesthesia were recorded in either group. Grade IV complications, defined as life-threatening complications requiring ICU management, occurred in 3/48 (6.3%) patients in the sequential prophylactic TACE group and 3/52 (5.8%) patients in the control group. Serious adverse events were also comparable between the sequential prophylactic TACE and control groups (3/48 [6.3%] vs. 2/52 [3.8%]; P = 0.582) (**Table 4**). Taken together, these data indicate that although sequential prophylactic TACE increases the overall burden of mostly low-grade postoperative morbidity, it does not appear to substantially increase the risk of major or life-threatening complications.

Patient-reported outcomes: quality of life and symptom burden

During the 6-month follow-up, overall health-related quality of life improved in both groups, with more favorable changes observed in patients who received sequential prophylactic TACE. Compared with the control group, the sequential prophylactic TACE group had higher visual analogue scale scores for overall health

Table 4. Safety and adverse events

	Control (n = 52)	Observation (n = 48)	Statistical test	*P* value
Total adverse events, n (%)	25 (48.1)	38 (79.2)	$\chi^2 = 10.350$	0.001
Any intraoperative complication, n (%)	5 (9.6)	6 (12.5)	$\chi^2 = 0.212$	0.645
Bleeding requiring transfusion, n (%)	2 (3.8)	3 (6.3)		
Bile duct injury, n (%)	1 (1.9)	1 (2.1)		
Conversion to open surgery, n (%)	2 (3.8)	2 (4.2)		
Postoperative complications, n (%)	24 (46.2)	32 (66.7)	$\chi^2 = 4.262$	0.039
Post-hepatectomy liver failure (ISGLS grade A), n (%)	6 (11.5)	8 (16.7)		
Post-hepatectomy liver failure (ISGLS grade B), n (%)	2 (3.8)	3 (6.3)		
Post-hepatectomy liver failure (ISGLS grade C), n (%)	0 (0)	0 (0)		
Bile leakage, n (%)	3 (5.8)	4 (8.3)		
Ascites requiring diuretics, n (%)	9 (17.3)	12 (25.0)		
Surgical site infection, n (%)	4 (7.7)	5 (10.4)		
Clavien-Dindo classification ≥ grade III, n (%)	5 (9.6)	7 (14.6)	$\chi^2 = 0.583$	0.445
Grade IIIa (intervention not under general anesthesia)	2 (3.8)	4 (8.3)		
Grade IIIb (intervention under general anesthesia)	0(0)	0(0)		
Grade IV (life-threatening complication requiring ICU management)	3 (5.8)	3 (6.3)		
Serious adverse events (SAEs), n (%)	2 (3.8)	3 (6.3)	$\chi^2 = 0.304$	0.582

status, and higher global health status and physical functioning scores at 1, 3, and 6 months after intervention. In parallel, fatigue, pain, and composite symptom-burden scores were lower in the sequential prophylactic TACE group than in the control group at each corresponding post-intervention assessment. Importantly, all of these between-group differences at 1, 3, and 6 months remained statistically significant after Bonferroni correction for multiple comparisons (all adjusted P<0.001; **Figure 2**). These favorable differences in patient-reported quality of life and symptom burden were maintained throughout the 6-month follow-up, suggesting that the observed oncological benefits associated with sequential prophylactic TACE were not accompanied by deterioration in patient-perceived health status.

Long-term hepatic functional reserve and decompensation events

Patients in the sequential prophylactic TACE group exhibited more favorable longitudinal trajectories of Child-Pugh and MELD scores compared with the control group during follow-up (**Figure 3**). Specifically, the TACE group showed lower MELD scores and a more favorable Child-Pugh score trajectory at post-intervention assessments. Similarly, serum albumin levels increased over time, whereas serum bilirubin levels decreased in the TACE group compared with controls, indicating a more favorable longitudinal hepatic functional profile. The between-group differences at each follow-up time point remained statistically significant after Bonferroni correction for multiple comparisons (adjusted P<0.001). These findings should not be interpreted as evidence of a direct hepatoprotective effect of TACE; rather, they may reflect differences in postoperative recovery and treatment selection, because patients with better hepatic recovery and preserved liver function were more likely to receive and complete sequential TACE.

Discussion

In this study, sequential prophylactic TACE following laparoscopic hepatectomy was associated with significant and sustained improvements in recurrence-free survival (RFS) and overall survival (OS) among patients with hepatocellular carcinoma at high risk of postoperative recurrence, without a significant increase in major perioperative complications. Multivariable analyses further demonstrated that sequential prophylactic TACE remained independently associated with improved RFS and OS after adjustment for adverse clinicopathological features, including microvascular invasion. In addition, sequential prophylactic TACE was associated with a lower incidence of early recurrence and altered patterns of disease

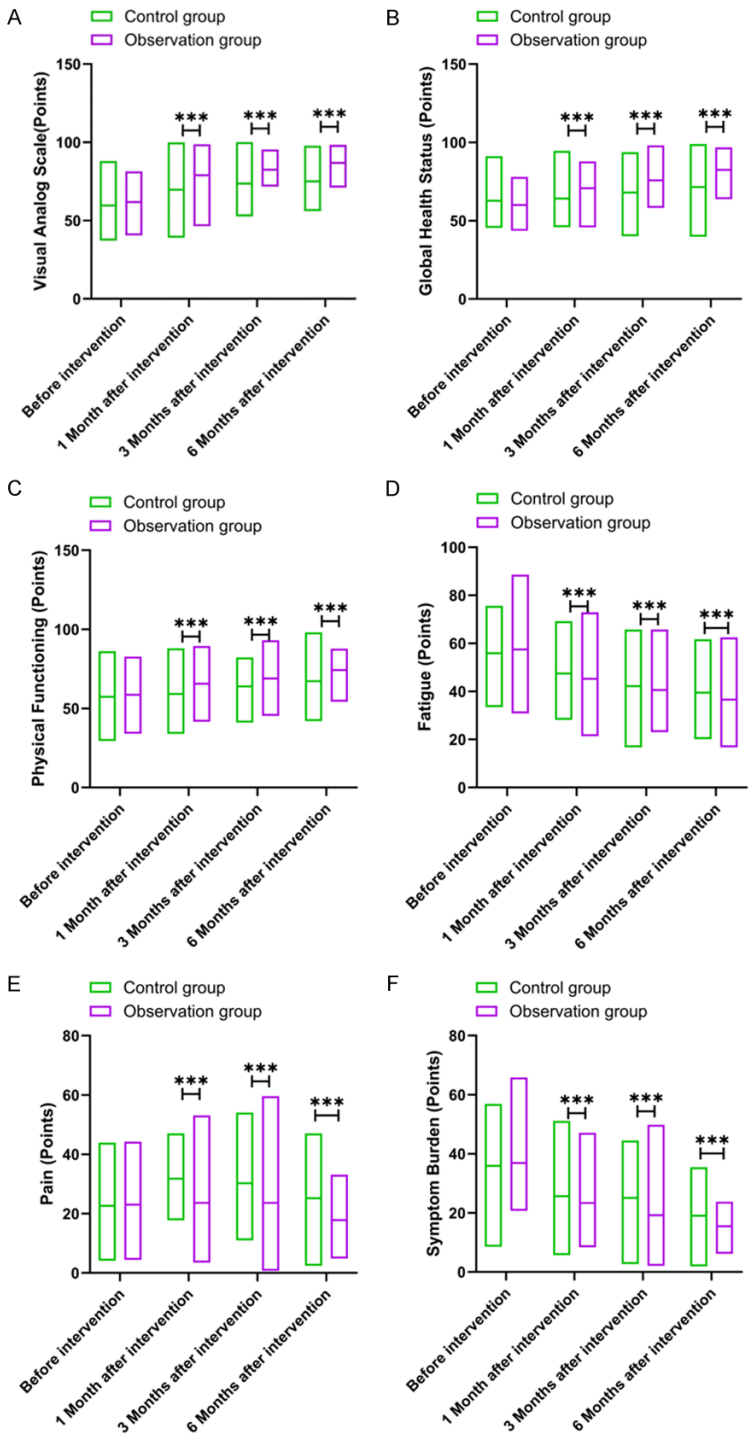

Figure 2. Patient-reported outcomes: quality of life and symptom burden. A. Visual analog scale (VAS) score. B. Global health status score. C. Physical functioning score. D. Fatigue score. E. Pain score. F. Composite symptom-burden score. Asterisks indicate between-group comparisons between the observation and control groups at the corresponding follow-up time points, rather than comparisons with baseline. *P* values were derived from linear mixed-effects models, with Bonferroni correction for multiple comparisons between groups at each follow-up time point. ***P<0.001 after Bonferroni adjustment.

relapse. Patients receiving sequential prophylactic TACE also exhibited more favorable patient-reported quality-of-life outcomes and longitudinal hepatic functional reserve profiles; however, these findings should be interpreted cautiously, as they may partly reflect differences in postoperative recovery, recurrence status, and treatment selection rather than direct effects of TACE itself. Collectively, these findings suggest that sequential prophylactic TACE may represent a promising postoperative adjunct to curative-intent laparoscopic hepatectomy in carefully selected patients with HCC at high risk of recurrence. Given the retrospective, single-center, and non-randomized design of this study, these observations should be considered exploratory and require validation in prospective multicenter studies.

We found that sequential prophylactic TACE was associated with a substantial reduction in recurrence and mortality, primarily driven by a decrease in early post-hepatectomy recurrence, which represents a major determinant of poor prognosis in patients with high-risk HCC. The role of postoperative adjuvant TACE after hepatic resection has been investigated in multiple heterogeneous studies, partly due to differences in patient selection, inclusion of both open and minimally invasive surgical approaches, and variations in risk stratification criteria [15, 16]. Although some individual studies have suggested a reduction in early intrahepatic recurrence, many have failed to demonstrate a consistent survival advantage, and the

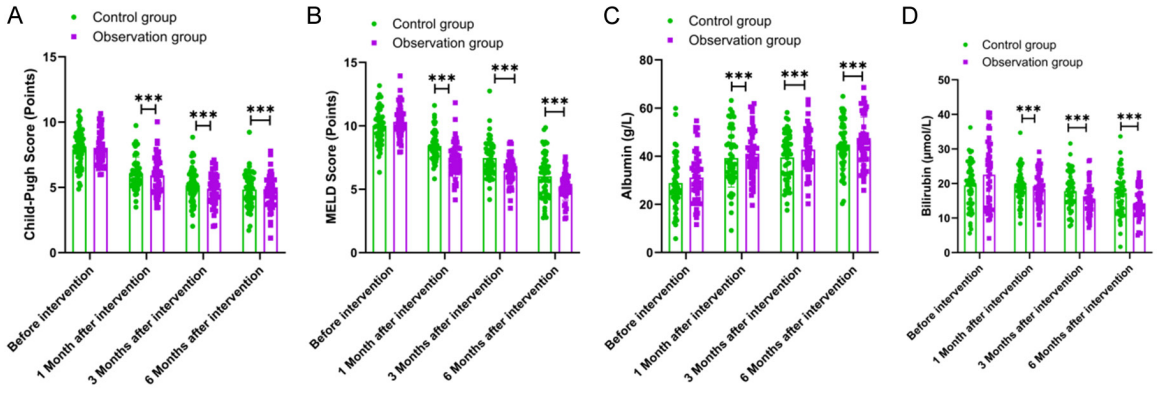

Figure 3. Long-term hepatic functional reserve. A. Child-Pugh score. B. Model for End-Stage Liver Disease (MELD) score. C. Serum albumin level (g/L). D. Serum bilirubin level (μmol/L). Asterisks indicate between-group comparisons between the observation and control groups at the corresponding follow-up time points, rather than comparisons with baseline. Between-group *P* values at each follow-up time point were derived from linear mixed-effects models and adjusted for multiple comparisons using the Bonferroni correction. ***Adjusted P<0.001.

routine application of postoperative TACE remains controversial [17]. Compared with previous meta-analyses reporting more modest associations between postoperative adjuvant TACE and recurrence-free survival (typically HR approximately 0.65-0.75), the larger effect size observed in our study requires cautious interpretation. Several factors may contribute to this difference. First, our cohort consisted exclusively of carefully selected patients with high-risk HCC after laparoscopic hepatectomy, who were more likely to harbor occult intrahepatic micrometastatic disease and therefore potentially derive greater benefit from postoperative locoregional control. Second, unlike many previous studies evaluating single-session postoperative TACE, our study investigated a sequential prophylactic strategy involving planned repeated treatments, which may provide more sustained suppression of residual intrahepatic disease. Third, the minimally invasive surgical approach may have facilitated postoperative recovery and improved tolerance of additional locoregional therapy. Nevertheless, the observed magnitude of association should be interpreted cautiously because the retrospective, single-center, and non-randomized design of this study may introduce residual confounding and treatment-selection bias. From a biological perspective, early recurrence after hepatectomy is considered to arise partly from the growth of residual intrahepatic micrometastases or tumor cells disseminated through the portal venous system. By delivering chemotherapy and arterial embolization to the remnant liver, TACE may suppress susceptible microscopic tumor deposits before they become clinically detectable. These findings suggest that postoperative adjuvant interventions may be most relevant for patients with a genuine risk of early intrahepatic recurrence, while emphasizing that the observed association should not be extrapolated to lower-risk populations. Prospective randomized studies are warranted to validate the magnitude of benefit and further define the role of sequential prophylactic TACE in postoperative HCC management.

Sequential prophylactic TACE was not associated with adverse effects on operative parameters, early postoperative recovery, or the incidence of major complications, despite an increased overall frequency of low-grade postoperative events. Concerns regarding cumulative hepatic injury have historically limited the application of postoperative adjuvant TACE, particularly when administered after hepatectomy or in patients with marginal hepatic functional reserve [18]. In our study, operative time, intraoperative blood loss, transfusion requirements, use of the Pringle maneuver, and conversion rates were comparable between groups. Furthermore, sequential prophylactic TACE was not associated with an increased incidence of post-hepatectomy liver failure according to the ISGLS criteria or Clavien-Dindo grade ≥ III complications. These findings are consistent with recent clinical series suggesting that postoperative TACE can be safely performed during the early period after hepatectomy when patients are appropriately selected and standardized

treatment protocols are applied. From a mechanistic perspective, the favorable safety profile observed in our cohort may reflect several factors, including the parenchymal-preserving advantage of laparoscopic hepatectomy, careful patient selection, and advances in embolic materials and treatment dosing strategies. Clinically, these findings suggest that safety concerns alone should not preclude the use of sequential prophylactic TACE in appropriately selected patients with adequate hepatic reserve. However, clinicians should remain aware that repeated locoregional treatment may increase the burden of minor adverse events and contribute to additional healthcare resource utilization.

The recurrence patterns observed in our study suggest that sequential prophylactic TACE may not only delay recurrence but also modify the distribution and characteristics of disease relapse. The reduction in early recurrence and the lower proportion of intrahepatic-only failures, accompanied by a relative increase in distant intrahepatic and extrahepatic recurrence patterns, collectively support the hypothesis that TACE primarily exerts its effect through improved control of microscopic residual disease within the remnant liver. Previous studies have indicated that residual microscopic tumor deposits at the resection margin and within high-risk vascular territories represent important sources of early intrahepatic recurrence [19, 20]. By targeting the arterial blood supply of the remnant liver, adjuvant chemoembolization may suppress susceptible microscopic disease reservoirs, thereby shifting residual recurrence risk toward mechanisms such as systemic dissemination or de novo carcinogenesis [21, 22]. Consistent with this interpretation, our study observed a lower intrahepatic tumor burden at recurrence in the sequential prophylactic TACE group, suggesting a potential reduction in intrahepatic tumor seeding. These findings have important translational implications. Although prophylactic TACE may be effective in controlling occult intrahepatic micrometastatic disease, it is unlikely to prevent all patterns of recurrence, particularly extrahepatic relapse driven by systemic tumor dissemination. Therefore, future clinical strategies may consider rational combinations of sequential TACE with systemic therapies to address both intrahepatic and systemic recurrence risks. In addition, clinicians should remain vigilant for extrahepatic recurrence in patients with aggressive tumor biology despite effective locoregional control.

The association between sequential prophylactic TACE and improved survival outcomes remained significant after adjustment for microvascular invasion and other clinicopathological characteristics, suggesting that the observed association was not solely attributable to differences in baseline tumor biology. Microvascular invasion is a well-established adverse prognostic factor in hepatocellular carcinoma and has consistently been associated with an increased risk of early recurrence and poorer long-term survival [23, 24]. In our multivariable Cox regression analyses, microvascular invasion remained independently associated with higher risks of both recurrence and mortality, whereas sequential prophylactic TACE remained independently associated with improved recurrence-free survival and overall survival after adjustment for this aggressive pathological feature. These findings suggest that sequential prophylactic TACE may provide additional postoperative disease control even in patients with biologically aggressive tumors. From a mechanistic perspective, microvascular invasion reflects the presence of microscopic tumor cell clusters within small intrahepatic vessels, particularly branches of the portal venous system, and is considered an important route of intrahepatic tumor dissemination. In contrast, TACE predominantly acts through selective delivery of chemotherapy and embolization of the arterial supply to the remnant liver. Thus, although postoperative TACE may suppress residual arterialized microscopic tumor deposits and occult intrahepatic micrometastases, it is unlikely to completely overcome the recurrence risk associated with vascular invasion and tumor dissemination. The persistence of microvascular invasion as an independent adverse prognostic factor despite sequential prophylactic TACE therefore underscores the importance of refined postoperative risk stratification and supports further investigation of multimodal strategies integrating locoregional and systemic therapies for patients at the highest risk of recurrence.

The observation that patients receiving sequential prophylactic TACE reported better health-related quality of life and a lower symptom burden should be interpreted with caution. Alth-

ough the addition of an invasive locoregional treatment might intuitively be expected to increase treatment-related burden, previous studies have reported heterogeneous trajectories of quality of life after TACE. Evidence regarding post-TACE quality of life remains mixed, with physical functioning and symptom scores often deteriorating initially before gradually recovering [25, 26]. However, most of these studies were conducted in palliative or downstaging settings rather than in the adjuvant setting following curative-intent resection. In our cohort, patients receiving sequential prophylactic TACE had higher global health status and physical functioning scores, together with lower fatigue and pain scores, from 1 month after surgery, and these differences persisted through 6 months of follow-up. Nevertheless, these findings should not be interpreted as definitive evidence that prophylactic TACE directly improves postoperative quality of life. Given the retrospective and non-randomized study design, residual confounding cannot be excluded. In particular, differences in recurrence status, timing of recurrence, and disease burden at the time of quality-of-life assessment may have influenced patient-reported outcomes. Patients with delayed or absent recurrence may naturally experience better physical functioning, fewer symptoms, and greater psychological well-being than those with earlier disease relapse. Accordingly, the observed differences in quality of life may, at least in part, reflect improved disease control and delayed recurrence rather than a direct effect of TACE itself. The minimally invasive nature of laparoscopic hepatectomy, careful patient selection, and standardized timing and dosing of postoperative TACE may also have helped limit the additional treatment burden. However, these observations remain exploratory. Prospective studies incorporating longitudinal quality-of-life assessments and appropriate adjustment for recurrence status and other time-varying clinical factors are warranted to clarify the independent association between prophylactic TACE and patient-reported outcomes.

An unexpected finding of our study was that sequential prophylactic TACE was associated with more favorable longitudinal profiles of Child-Pugh and MELD scores. This observation should be interpreted with caution and should not be taken as evidence that TACE directly improves hepatic function. From a biological perspective, TACE may impose additional hepatic stress through arterial embolization and exposure to chemotherapeutic agents, and deterioration in liver function may occur in some patients rather than improvement. Several alternative explanations should therefore be considered. First, because treatment allocation was not randomized, patients selected for sequential prophylactic TACE may have had better postoperative recovery, greater hepatic functional reserve, or more favorable clinical conditions that enabled them to undergo and complete the planned TACE sessions, thereby introducing potential treatment-selection bias. Second, the observed differences may partly reflect the natural course of postoperative recovery, during which transient surgical stress gradually resolves and hepatic function returns toward the preoperative or early postoperative baseline. Third, Child-Pugh scores are determined by several clinical and biochemical variables, including serum albumin, bilirubin, ascites, and hepatic encephalopathy, all of which may fluctuate during follow-up and do not necessarily reflect structural or intrinsic recovery of hepatic function. Similarly, longitudinal changes in MELD scores may be influenced by postoperative clinical status and other time-varying factors. Accordingly, the association between sequential prophylactic TACE and more favorable hepatic functional reserve profiles should be regarded as exploratory and hypothesis-generating rather than as evidence of a hepatoprotective effect. Prospective studies incorporating standardized longitudinal assessments of hepatic function, objective measures of hepatic functional reserve, and appropriate adjustment for baseline postoperative status and other time-varying clinical factors are warranted to clarify the independent relationship between prophylactic TACE and hepatic function after hepatectomy.

Several limitations of this study should be acknowledged when interpreting the findings. First, although our cohort detected differences in the major clinical endpoints, the sample size remained limited, and all patients were treated at a specialized center with extensive experience in both laparoscopic hepatectomy and TACE. Therefore, the generalizability of our findings to centers with different technical expertise, treatment protocols, or patient populations requires further validation. Second, despite the use of multivariable adjustment, the

retrospective and non-randomized design of this study cannot completely eliminate the possibility of residual confounding. Unmeasured differences in tumor biology, underlying hepatic function, postoperative management strategies, or other clinical factors may have influenced treatment allocation and outcomes. Third, although the timing, number of TACE sessions, and selection of chemotherapeutic and embolic agents were standardized within our institution, variations in these treatment parameters across different practice settings may affect both the efficacy and safety profiles of sequential prophylactic TACE. Fourth, patient-reported outcome assessments were limited to a 6-month follow-up period. Although oncological outcomes were evaluated for up to 60 months, late differences in functional recovery or quality-of-life trajectories cannot be completely excluded. Finally, this study did not directly compare sequential prophylactic TACE with emerging postoperative systemic therapies or combination treatment strategies. Therefore, the precise role of sequential prophylactic TACE within the rapidly evolving postoperative management landscape of HCC remains to be further defined.

In conclusion, our findings suggest that sequential prophylactic TACE after laparoscopic hepatectomy is associated with improved recurrence-free and overall survival in carefully selected patients with HCC at high risk of postoperative recurrence. This association appears to be driven, at least in part, by a reduction in early intrahepatic recurrence and was associated adverse clinicopathological characteristics, including microvascular invasion. Sequential prophylactic TACE was not associated with an increased incidence of major perioperative complications, although a higher frequency of low-grade adverse events was observed. More favorable longitudinal profiles of hepatic functional reserve and patient-reported quality of life were also observed; however, these findings should be considered exploratory and should not be interpreted as evidence of direct hepatoprotective or quality-of-life benefits of TACE. The observed changes in recurrence patterns, including fewer marginal and high-burden intrahepatic recurrences, further suggest a potential role of sequential prophylactic TACE in controlling occult residual intrahepatic disease. Nevertheless, given the retrospective, single-center, and non-randomized design of this study, these findings do not establish a definitive indication for routine postoperative TACE. Large-scale, prospective, multicenter, and preferably randomized studies incorporating molecular and imaging biomarkers are warranted to validate these findings, refine patient selection, optimize treatment timing and procedural strategies, and clarify the role of sequential prophylactic TACE, alone or in combination with systemic therapies, in the evolving postoperative management of high-risk HCC.

Disclosure of conflict of interest

None.

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