Clinical Cancer Research

Adjuvant Transarterial Chemoembolization for HBV-Related Hepatocellular Carcinoma After Resection: A Randomized Controlled Study

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Abstract

Purpose: The survival of patients with hepatocellular carcinoma (HCC) recurrence after curative resection is usually poor. We sought to evaluate the safety and efficacy of adjuvant transarterial chemoembolization (TACE) in HBV-related HCC patients with an intermediate (a single tumor larger than 5 cm without microvascular invasion) or high risk (a single tumor with microvascular invasion, or two or three tumors) of recurrence.

Experimental Design: In this randomized phase 3 trial, 280 eligible patients were assigned to adjuvant TACE ($n = 140$) or no adjuvant treatment (control; $n = 140$) groups. The primary endpoint was recurrence-free survival (RFS); secondary endpoints included overall survival (OS) and safety. Multivariable Cox-proportional hazards model was used to determine the independent impact of TACE on patients' outcomes.

Results: Patients who received adjuvant TACE had a significantly longer RFS than those in the control group [56.0% vs. 42.1%, $P = 0.01$; HR, 0.68; 95% confidence interval (CI), 0.49–0.93]. Patients in the adjuvant TACE group had 7.8% higher 3-year OS rate than the control group (85.2% vs. 77.4%; $P = 0.04$; HR, 0.59; 95% CI, 0.36–0.97). The impact of adjuvant TACE on RFS and OS remained significant after controlling for other known prognostic factors (HR, 0.67; $P = 0.01$ for RFS; and HR, 0.59; $P = 0.04$ for OS). There was no grade 3 or 4 toxicity after adjuvant TACE.

Conclusions: For patients with HBV-related HCC who had an intermediate or high risk of recurrence after curative hepatectomy, our study showed adjuvant TACE significantly reduced tumor recurrence, improved RFS and OS, and the procedure was well tolerated. *Clin Cancer Res; 24(9); 2074–81. ©2018 AACR.*

Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related mortality worldwide (1). Surgical resection, tumor ablation, and liver transplantation are the three curative treatment modalities for HCC (2). Surgical resection remains the primary treatment option due to technical limitations for tumor ablation and limited donor availability for liver transplantation. However, high tumor recurrence rates after curative liver resection (60%–70% in the first 5 years of surgery) continues to be a major cause of death in HCC (3, 4). Some studies indicated that adjuvant interferon (5), sorafenib (6), immunotherapy with autologous cytokine-induced killer cells (7), systemic chemotherapy (8), heparanase inhibitor PI-88 (9), or iodine-131 (^{131}I)-labeled lipiodol (10), might decrease tumor recurrence after curative resection of HCC. However, none of these approaches have been recommended as an universally accepted adjuvant therapy by current scientific guidelines after curative surgical treatment (11–13), as there were either inconsistent study results or lack of high level evidences to support these treatments.

Our previous retrospective studies (14, 15) suggested that adjuvant transarterial chemoembolization (TACE) prolonged overall survival (OS) and reduced tumor recurrence only in patients with HCC who had an intermediate (tumor size >5 cm) or high risk of recurrence (single tumor with microvascular invasion; 2 or 3 tumors) after curative liver resection. The aim of this prospective randomized controlled trial (RCT) was to confirm this observation from our previous retrospective study.

Patients and Methods

Study design and patients

This was a randomized, open-label, controlled, phase III trial comparing TACE as adjuvant therapy for hepatitis B virus (HBV)–related HCC with an intermediate or high risk of recurrence after curative hepatectomy. Enrolled patients will be randomized to

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Disease recurrence after curative resection for hepatocellular carcinoma (HCC) patients remains the major cause for dismal outcome. Results from this large-sample prospective randomized controlled trial showed that adjuvant transarterial chemoembolization (TACE; along with adriamycin and lipiodol) can significantly reduce tumor recurrence, improve recurrence-free survival and overall survival for HBV-related HCC patients with an intermediate (a single tumor larger than 5 cm without microvascular invasion) or high risk (a single tumor with microvascular invasion, or two or three tumors) of HCC recurrence after curative liver resection. The data also suggested that adjuvant TACE decreases HCC recurrence after curative liver resection by eradicating pre-existing microscopic tumor foci that traditional imaging modalities fail to detect in the perioperative stage, and is well tolerated. The study provided strong evidence to incorporate adjuvant TACE for patients with HBV-related HCC who had an intermediate or high risk of HCC recurrence after curative liver resection.

one of the two arms: treatment (adjuvant TACE) and control groups (active surveillance after surgical resection without active intervention). Patients who underwent curative liver resection for histopathologically confirmed HCC at our institution were eligible. Curative resection was defined as (5): (i) complete resection of all tumor nodules with a clear margin and the cut surface being free of cancer on histological examination; (ii) no tumor thrombus in the portal veins, hepatic veins, or bile ducts on preoperative radiological imagings; (iii) $\leq$3 tumor nodules in patients with multi-nodular HCC; (iv) absence of extrahepatic metastasis; and (v) either contrast-enhanced computer tomography (CT) or magnetic resonance imaging (MRI) carried out 4 to 6 weeks after liver resection showed no residual cancer in liver remnants.

We assessed risk of recurrence for resection based on tumor characteristics as established by the pathology report, and included only patients with an intermediate or high risk of recurrence. Patients undergoing surgical resection were defined as having a high risk of recurrence if they had a single tumor with microvascular invasion, or two or three tumors. An intermediate risk was defined as a single tumor larger than 5 cm without microvascular invasion. Patients with a single tumor of less than or equivalent to 5 cm without microvascular invasion were deemed low risk and thus not included in our study. These criteria for recurrence risk, based on the scientific literature (13), were designed specifically for this RCT study to exclude patients with a low or extremely high risk of recurrence.

Only patients who met the following inclusion criteria were enrolled in this study: (i) >18 years and $\leq$70 years of age; (ii) HBV-related HCC (HBV surface antigen [HBsAg]-positive, or had detectable HBV DNA, or had both HBV e antibody [HBeAb]- and HBcAb-positive) but negative for anti-hepatitis C virus (HCV) antibody; (iii) histopathologically confirmed HCC with an intermediate or high risk of recurrence after resection; (iv) Child-Pugh class A/B, with a serum bilirubin level $\leq$1.5 times the upper normal limit, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels $\leq$2 times the upper normal limit; (v) no major organ dysfunction; (vi) hemoglobin level $\geq$90 g/L, a white blood cell (WBC) count $\geq 4{,}000 \times 10^9$/L, and a platelet count $\geq 70 \times 10^9$/L; and (vii) written informed consent from the patients.

Patients were excluded if they met any one of the following criteria: (i) a previous history of anti-cancer treatment of HCC; (ii) a history of other malignancies; (iii) liver functional status of Child-Pugh C; (iv) any other contraindications such as active gastrointestinal bleeding, refractory ascites, coagulopathy, or severe portal hypertension; or (v) cardiac, pulmonary, cerebral, or renal dysfunction.

The study protocol was approved by the Institutional Ethics Committee of the Zhongshan Hospital, Fudan University. This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki. A detailed informed consent was obtained from each study patient. The study was registered with the U.S. NIH Clinical Trials Registry at http://clinicaltrials.gov (NCT01966133).

Randomization

When the liver function of the patient had recovered at 4 to 6 weeks after resection, patients were required to underwent screening CT or MRI confirming complete radiological response by masked independent review based on validated imaging criteria (13). Only those patients who had no residual tumors in the liver remnants were consented and randomly assigned (1:1) to either adjuvant TACE or control group. Randomization was conducted by using a computer-generated random number carried out by a research coordinator who was not involved in this study. The time interval from randomization to adjuvant TACE was within 1 week.

Procedures

The TACE procedure was carried out in the following manners. Using the Seldinger technique, an angiographic catheter was inserted through femoral artery to access hepatic artery, then common hepatic artery and superior mesentric artery angiography was applied to show the real hepatic artery anatomy and the patency of portal vein. Microcatheter was used to right and left hepatic artery and inject adriamycin (20–30 mg/m^2) and lipiodol (3–5 mL).

Post-operatively, any patients who met the antiviral therapy criteria of the Asian Pacific Association for the Study of the Liver (APASL) received either lamivudine (100 mg) daily or entecavir (0.5–1.0 mg) daily. Adefovir (10 mg) daily was added to those patients who had resistance to either lamivudine or entecavir (16).

Patients were followed up in our clinic once every 2 to 3 months in the first postoperative year and once every 3 to 4 months thereafter. Liver function test, serum alpha fetoprotein (AFP), and hematological parameters were examined, and liver ultrasonography was performed by clinicians who were not involved in and had no access to treatment information on the patients in the study at each clinical visit. CT with contrast of the chest, abdomen and pelvis were performed once every 6 months. Bone scans or MRI were performed if clinically indicated. If tumor recurrence in the liver was suspected, CT scan or MRI with intravenous contrast would be performed. Biopsy of the lesions would be performed when necessary.

Diagnosis of tumor recurrence was based on cytologic/histologic evidence or by using the non-invasive diagnostic criteria for HCC as recommended by the European Association for the Study of the Liver (13). Intrahepatic recurrence was defined as appearance of one or more intrahepatic lesions, with a longest diameter

of at least 10 mm and typical vascular uptake patterns of intravenous contrast of HCC on dynamic imagings (i.e., hyper vascularization in arterial phase with washout in portal venous or late venous phase). Lesions larger than 10 mm that failed to show typical vascular patterns were also diagnosed as recurrences if they grew for more than 1 cm on subsequent CT scans carried out 1 to 2 months later. Extra hepatic recurrences were defined asper Response Evaluation Criteria in Solid Tumors.

All patients with recurrences were treated depending on tumor size, location, number of tumors, and liver function. In short, for localized intrahepatic tumors, liver re-resection, radiofrequency ablation (RFA), or percutaneous ethanol injection (PEI) were offered. For multiple or diffused intrahepatic recurrences, TACE was offered as the first-line treatment. External beam radiotherapy was given to lymph node or bone metastases.

Outcomes

The primary endpoint of this study was recurrence-free survival (RFS); the secondary endpoints were OS and safety of adjuvant TACE. RFS was defined as the time from date of surgery to date of the first documented disease recurrence by independent radiological assessment or liver biopsy, and or death by any cause, whichever happened first. OS was defined as the time from date of surgery to date of death regardless of the cause of death. The safety of adjuvant TACE was defined according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (17). Liver recurrence was classed as early recurrence and late recurrence using 24 months as cutoff.

Sample size

The intention-to-treat population included all randomly assigned patients irrespective of whether or not they received study treatment. Based on previous study results, the 3-year RFS rates after curative resection ranged between 20% and 48% (5). We assumed the 3-year RFS rate in the control group was 34%, and the expected 3-year RFS rate in the adjuvant TACE group was 50%. Considering a 5% loss to follow-up rate and possible post-randomization exclusion in each arm (18), and using a 5% type I error with 80% statistical power, the sample size in each group was estimated to be 140 patients.

Statistical analysis

Patients' baseline characteristics were reported as mean (± standard deviation), median (range), or percentage according to the nature of the data. Categorical variables were compared by the χ^2 test or the Fisher's exact test. Continuous variables were compared by the Student t test. This study results were based on the data with the date of the last follow-up on February 28, 2017.

The efficacy analysis was based on the intention-to treat population, which included all randomized. The Kaplan–Meier analysis was used to estimate survival function, and the log-rank test was used to evaluate the differences in survival across the different strata. A multivariable Cox proportional hazards model was used to determine adjuvant TACE's independent impact on RFS and OS, adjusting other potential confounders/other known prognostic factors. Hazard ratio (HR) and 95% confidence intervals (CI) were estimated by use of a non-parametric log-rank test, the Cox proportional hazards model.

Exploratory subgroup analyses of RFS and OS were done in patients by age group (≤60 years vs. >60 years), level of AFP (≤20 ng/mL vs. >20 ng/mL), high risk or intermediate risk of recurrence, state of HBVDNA (negative vs. positive), liver cirrhosis, and Edmondson's grade.

Treatment comparisons were done in multiple individual Cox models, separately for each factor, for subgroup analyses. Statistical analyses of the data were performed using the SAS statistical software. Two-sided P values of <0.05 were considered to be statistically significant.

Results

Demographic data

Of the 1,393 patients with HBV-related HCC who underwent curative resection between August 2011 and 2014 at our institution, 11 patients died for post-operative liver failure, 285 patients met the inclusion criteria but 5 patients declined to participate, eventually 280 patients were randomized to either the adjuvant TACE group (n = 140) or the control group (n = 140). After randomization and treatment, one patient in the adjuvant TACE group and one patient in the control group lost follow-up after the first post treatment visit. Furthermore, one patient in the adjuvant TACE group withdrew the consent to be involved in the study. Five patients in the control group received non-protocol treatments. The efficacy of adjuvant TACE was analyzed on an intention-to-treat basis (Fig. 1).

Overall outcomes

The median age for all the patients was 55 years (range, 20–70 years). The majority of the patients were male (82.1%) and about half of the patients (49.3%) had cirrhosis. Most patients (76.1%) were classified as having high risk of recurrence after resection. There were no significant differences in the clinicopathological characteristics between the two groups (Table 1). The median interval between resection and adjuvant TACE was 39 days (range, 27–48 days).

By the end of the last follow-up at February 2017, the median follow-up time was 44.1 months (range, 27.8–64.4 months) for all the patients. Recurrences occurred in 70 patients in the adjuvant TACE group and 85 patients in the control group (Table 2). About half of the recurrences were confined to the liver after resection (50.6% in control group, 45.7% in adjuvant TACE group). There was no difference between the two groups in the location of recurrence ($P = 0.81$). Patients who received adjuvant TACE had a significantly longer 3-year RFS than the control group (56.0% vs. 42.1%, $P = 0.01$; HR 0.68, 95% CI 0.49-0.93; Fig. 2A). The median RFS was 25.7 months longer in the adjuvant TACE group (49.5 months; 95% CI, 37.2–61.8 months) than the control group (23.8 months; 95% CI, 15.7–31.9 months). Twenty-one patients (30.0%) received potential curative treatment for recurrence in the adjuvant TACE group and 28 patients (32.9%) in the control group ($P = 0.70$). Twenty-nine patients (41.4%) received TACE for recurrence in the adjuvant TACE group and 36 patients (42.4%) in the control group ($P = 0.91$).

In the first 24 months after surgery, the cumulative early HCC recurrence rate in the TACE group was significantly lower than the control group (35.2% vs. 51.0%; $P = 0.01$). On multivariate analysis, adjuvant TACE (HR, 0.58; 95% CI, 0.40–0.84; P = 0.01), old patients (>60 years; HR, 0.59; 95% CI, 0.37–0.95; P = 0.03), tumor size (≤5 cm; HR, 0.58; 95% CI, 0.39–0.86; P = 0.01), one tumor nodule (HR, 0.57; 95% CI, 0.36–0.92; P = 0.02), and absence of microvascular invasion (HR, 0.51;

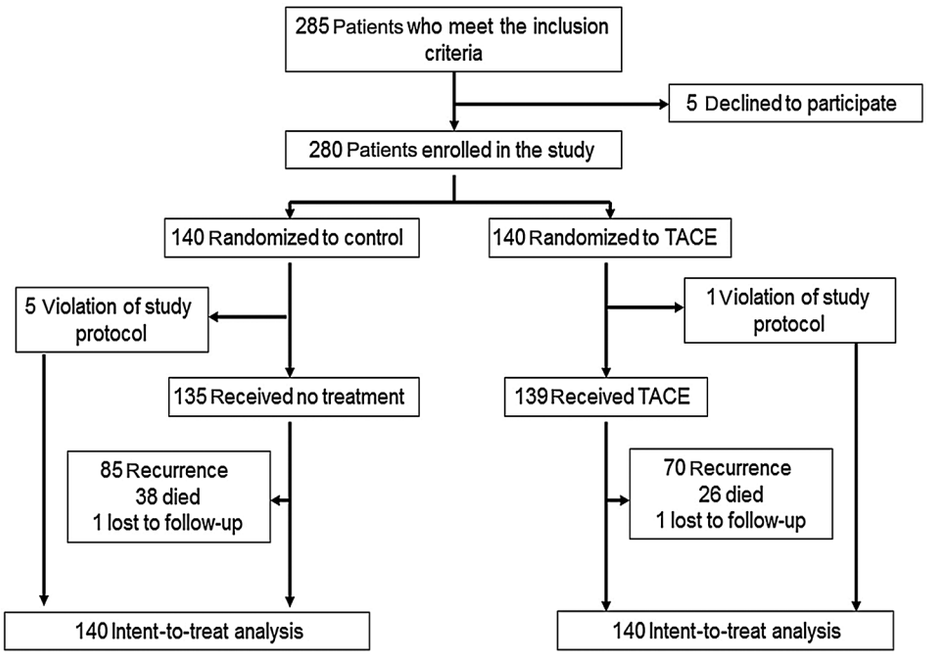

Figure 1.
Trial profile.

Table 1. Clinicopathological characteristics in control and adjuvant TACE group

Clinicopathological factors	Control ($n = 140$)	Adjuvant TACE ($n = 140$)	*P*
Gender			0.06
Male	109	121	
Female	31	19	
Age (y; mean ± sd)	52.6 ± 10.3	54.2 ± 9.7	0.16
Alpha fetoprotein			0.81
≤20 ng/mL	51	53	
>20 ng/mL	89	87	
Tumor size (cm)			0.45
≤5	61	56	
>5	79	84	
Tumor capsule			0.30
Complete	101	93	
Incomplete	39	47	
Number of tumor nodules			0.33
1	109	102	
2 or 3	31	38	
Microvascular invasion			0.27
Yes	87	78	
No	53	62	
Edmondson's grade			0.90
I-II	80	81	
III-IV	60	59	
HBVDNA			0.91
Positive	69	70	
Negative	71	70	
HBeAg			0.16
Positive	39	29	
Negative	101	111	
Cirrhosis			0.47
S1-3	74	68	
S4	66	72	
Surgical approach			0.74
Sectionectomy	45	39	
Segmentectomy	77	82	
Hemihepatectomy	18	19	
Risk			0.48
Intermediate risk	31	36	
High risk	109	104	

Abbreviation: TACE, transarterial chemoembolization.

95% CI, 0.33–0.78; $P = 0.01$) were significantly associated with a low risk of early HCC recurrence.

At the time of this analysis, 26 patients had died in the adjuvant TACE group, and 38 in the control group. Patients in the adjuvant TACE group had a significantly better 3-year survival rate than those in the control group (85.2% vs. 77.4%, $P = 0.04$; HR, 0.59; 95% CI, 0.36–0.97; Fig. 2B). The median survival had not been reached in either of the two groups.

Adjuvant TACE provided a clinical benefit in all exploratory subgroup analyses, despite some patients having characteristics associated with poor prognosis, including age ≤60 years, high level of AFP, presence of high risk of recurrence, HBVDNA positive, liver cirrhosis, and Edmondson's grade 3–4 (Fig. 3).

TACE efficacy after controlling for known risk features

Among the potential prognostic factors that included age, sex, level of AFP, tumor size, number of tumor nodules, tumor encapsulation, microvascular invasion, Edmondson's grade, HBVDNA load, HBeAg positivity, degree of cirrhosis, the type of surgery, and the risk of recurrence after resection, significant factors that were associated with improved RFS after adjuvant TACE were old patients (>60 years; HR, 0.66; 95% CI, 0.44–0.98; $P = 0.04$), low AFP level (HR, 0.66; 95% CI, 0.48–0.92; $P = 0.01$), and absence of microvascular invasion (HR, 0.69; 95% CI,

Table 2. Location of recurrent hepatocellular carcinoma

	Control (n=140)	Adjuvant TACE (n=140)	*P*
No. of recurrence	85	70	
Location of recurrence			0.81
Intrahepatic	43 (50.6%)	32 (45.7%)	
Extrahepatic	10 (11.8%)	10 (14.3%)	
Both intrahepatic and extrahepatic	32 (37.6%)	28 (40.0%)	
Single lesion of recurrent hepatocellular carcinoma	25 (29.4%)	20 (28.6%)	0.91

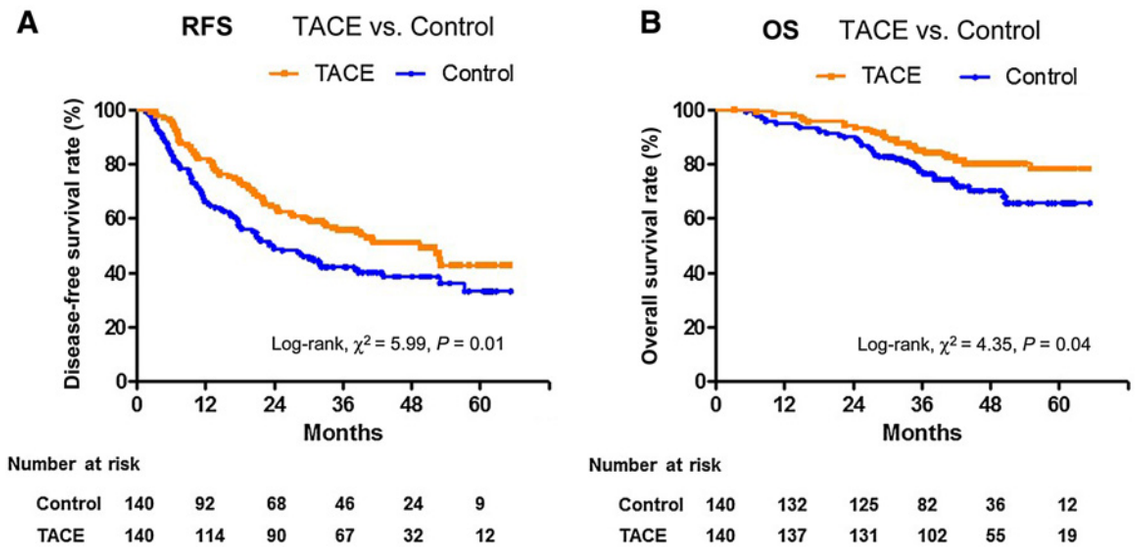

Figure 2.
Kaplan–Meier estimates of RFS (**A**), or OS (**B**) for patients between adjuvant TACE and control group.

0.49–0.95; $P = 0.02$; Supplementary Table S1). Negative HBeAg (HR, 0.71; 95% CI, 0.50–1.01; $P = 0.05$), and an intermediate risk recurrence after resection (HR, 0.70; 95% CI, 0.47–1.04; $P = 0.07$) were associated with marginally better RFS rates. On the other hand, there was no association between advanced patient age (>60 years) and OS (HR, 0.88; 95% CI, 0.49–1.57; $P = 0.67$). Microvascular invasion and HBVDNA load were the significant prognostic factor of OS (HR, 0.59; 95% CI, 0.35–1.00; $P = 0.049$; and HR, 0.51; 95% CI, 0.31–0.86; $P = 0.01$, respectively; Supplementary Table S1). Tumor size of less than or equivalent to 5 cm was associated with marginally better OS rates (HR, 0.62; 95% CI, 0.37–1.05; $P = 0.07$).

The forward stepwise Cox-proportional hazard model, which included all the prognostic factors with $P < 0.10$ on univariable analysis, was used to evaluate the impact of adjuvant TACE on patients' prognoses (Table 3). After controlling for the influences of age, AFP, microvascular invasion, HBeAg status, and risk of recurrence after resection, adjuvant TACE was associated with a 33% risk-reduction for tumor recurrence (HR, 0.67; 95% CI, 0.49–0.97; $P = 0.01$). For OS, after adjusting for the confounding

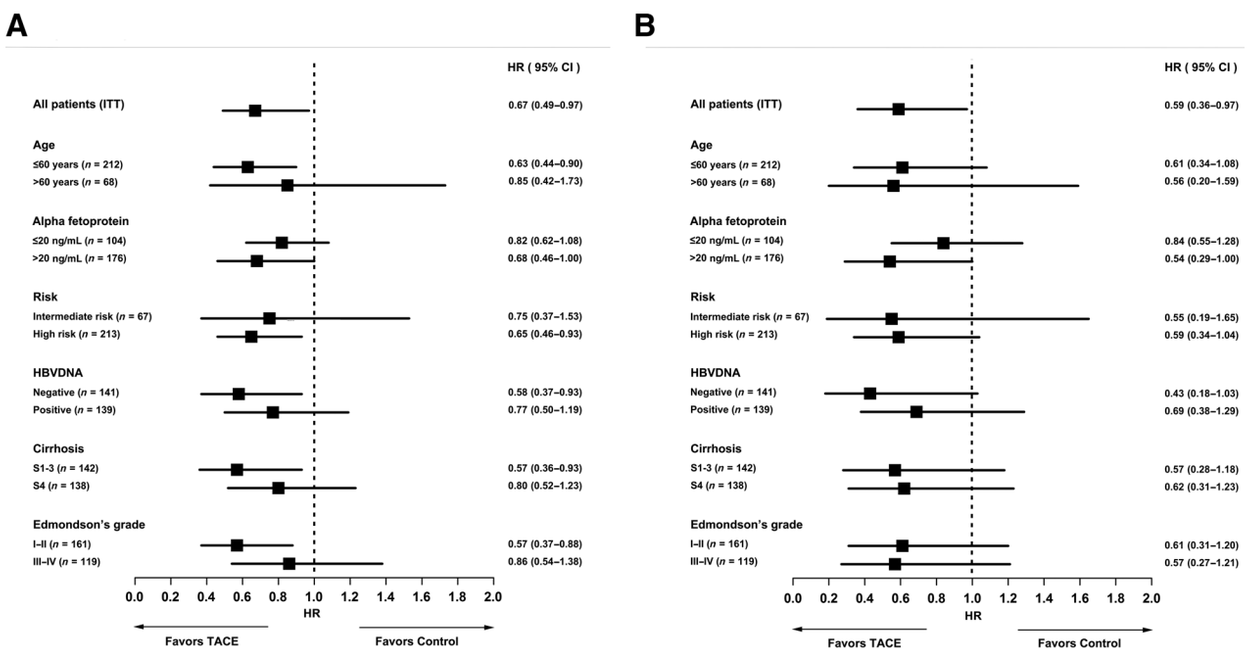

Figure 3.
Subgroup analyses for RFS (**A**), or OS (**B**) by Cox regression based on independent assessment.

Table 3. Multivariable analysis of influencing factors for RFS and OS

Independent factors	Significance	HR	95% CI for HR Lower–Upper
Recurrence-free survival[a]			
Treatment	0.01	0.67	0.49–0.92
Alpha fetoprotein	0.01	0.65	0.47–0.92
Age	0.04	0.66	0.44–0.97
Overall survival[b]			
Treatment	0.03	0.57	0.35–0.95
HBVDNA	0.02	0.55	0.33–0.92
Microvascular invasion	0.02	0.51	0.30–0.88

[a]Multivariate forward stepwise Cox regression analysis showed that microvascular invasion, HBeAg status, and risk of recurrence after resection were not the independent risk factors for postoperative tumor recurrence.
[b]Multivariate forward stepwise Cox regression analysis showed that tumor size was not the independent risk factor for postoperative survival.

factors, including tumor size, microvascular invasion, and HBVDNA load, the risk reduction associated with adjuvant TACE remained significant with an HR of 0.59; 95% CI (0.36–0.97), and $P = 0.04$.

Toxicity of adjuvant TACE

The toxicity data for patients who received adjuvant TACE are summarized in Supplementary Table S2. Overall, the adjuvant TACE was well tolerated. The most significant toxicities associated with adjuvant TACE were nausea/vomiting (48.6%) and transient hepatic toxicity (elevation of ALT/AST up to 41.4%, elevation of bilirubin up to 31.4%, and elevation of γ-glutamyltranspeptidase up to 18.6%). According to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (17), no grade 3 or 4 adverse events occurred (Supplementary Table S2).

Discussion

The high HCC recurrence rate (up to 75% at 5 years after curative resection) continues to be a significant clinical problem and is associated with patients' poor survival outcomes (19). A variety of adjuvant therapies, including systemic chemotherapy (8), α-interferon (5), targeted therapy (6), vaccination, and immunotherapy (7) have been reported with limited success. Although the SHARP and ORIENTAL trials have shown promising effectiveness with sorafenib in treatment of advanced HCC, the STORM study failed to show any effectiveness in the adjuvant setting for patients after surgical resection or who had complete radiological response to ablation (20).

Previous prospective/retrospective studies have shown that TACE may improve survival outcomes in patients with unresectable HCC (21). On the other hand, many retrospective studies on adjuvant TACE showed conflicting results on patients' postoperative prognoses (22). Our retrospective studies suggested that TACE might be only beneficial to patients with an intermediate (tumor size >5cm) or high risk of HCC recurrence (single tumor with microvascular invasion; 2 or 3 tumors) after resection (14, 15). In this RCT, HCC patients with an intermediate or high risk of HCC recurrence who underwent curative resection had significantly better RFS rates when they were treated with TACE (TACE group) than those received no additional therapy (control group), with a 33% risk reduction in disease recurrence. More importantly, patients who received adjuvant TACE had 7.8% increase in the 3-year OS rate than those in the control group. These results were consistent with the findings reported in retrospective studies with smaller sample size (23–27). This study is the first phase III randomized trial with adequate statistical power to show the independent impact of adjuvant TACE after curative liver resection by controlling the commonly known prognostic factors.

There are two patterns of HCC recurrence after curative liver resection: the early-phase ($\leq$2 years) and the late-phase (>2 years). These two patterns of tumor recurrence differ in their biological behavior, clinical courses, and prognoses. The early-phase recurrence occurring in liver remnants usually originates from intrahepatic metastasis of the primary tumor, whereas the late-phase recurrence represents de novo lesions in the liver remnant (28). We hypothesized that adjuvant TACE would improve the prognosis in patients with an intermediate or high risk of HCC recurrence by treating any pre-existing microscopic tumor foci or occult intrahepatic multifocality that traditional imaging modalities fail to detect in the perioperative stage (29). And the treatment effect of lipiodol embolization is related to the unique rich microcirculation of visible/invisible early micro tumor nodules that results in retention of lipiodol to cause tumor necrosis or inhibition. The observed TACE benefit in preventing early recurrence rate within 2 years after surgery in this study is consistent with our speculation. In addition, of the 14 patients in the adjuvant TACE group who were found to have lipiodol concentration foci during TACE treatment, 10 patients did not have any tumor recurrence detected in the follow-up period; 3 patients were diagnosed to have recurrence on CT/MRI scan $\geq$1 year after adjuvant TACE, and another patient was diagnosed to have recurrence 6 months after adjuvant TACE on MRI scan. These data also supported the impact of adjuvant TACE in improving prognosis of HCC patients with an intermediate or high risk of HCC recurrence.

Sub-analyses were done on the basis of various factors associated with the prognosis of patients with HCC after resection, including age, AFP level, risk of HCC recurrence after resection, HBVDNA status, liver cirrhosis, and Edmondson's grade. Although not statistically significant, the HRs of these analyses were less than one, suggesting that adjuvant TACE provided benefit to all the subpopulations analyses, including those patients who normally fareworse. However, one should note that there were wide 95% CI ranges for patients with an intermediate risk of HCC recurrence, and for patients greater than 60 years of age, which might be attributed to a low number of patients in each subset ($n = 67$ for intermediate risk of HCC recurrence, and $n = 68$ for >60 years of age).

Adjuvant TACE can accelerate deterioration of liver function, suppress host immunity against tumor progression and affect regeneration of hepatocytes (30). These may have adverse effects on long-term survival of patients after curative resection of HCC. In our study, to minimize these adverse effects, only one cycle of TACE was given, and the dosages of the drugs chosen were purposely lower than that used in conventional treatment. As a consequence, the adverse effects in the adjuvant TACE group were relatively mild and the treatment was well-tolerated by the patients. Vomiting, upper abdominal pain, and transient hepatic toxicity were the most commonly encountered adverse effects, with no serious side effects occurring in our patients. None of the patients dropped out of the study because of adverse side effects of adjuvant TACE.

There are limitations of this study. First, this study came from a single institution, further confirmatory study is needed before

recommending it as a routine treatment. Second, all the patients in this study had HBV-related HCC. Whether the results of this study can be extrapolated to other etiological factors of HCC is unknown.

In conclusion, this prospective RCT with good statistical power supported the use of adjuvant TACE after curative HCC resection. The treatment significantly reduced tumor recurrence, improved RFS and OS rates for HCC patients with an intermediate or high risk of HCC recurrence after curative liver resection. The treatment was well tolerated with no grade 3 or 4 toxicities.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: Z. Ren, Y. Chen, Z. Tang, J. Fan, J. Wang, J. Zhou
Development of methodology: J. Wang, J. Zhou
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Z. Wang, Z. Ren, Y. Chen, J. Hu, G. Yang, X. Yang, A. Huang, X. Zhang, S. Zhou, H. Sun, Y. Wang, X. Xu, J. Fan, J. Zhou
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Z. Wang, J. Hu, L. Yu, H. Sun, W. Lau, J. Fan, J. Wang, J. Zhou
Writing, review, and/or revision of the manuscript: Z. Wang, Z. Ren, J. Hu, W. Lau, J. Wang, J. Zhou
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Y. Chen, A. Huang, H. Sun, N. Ge, Z. Tang, J. Wang, J. Zhou
Study supervision: J. Zhou

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