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ORIGINAL RESEARCH

Effect of Transarterial Chemoembolization Plus Percutaneous Ethanol Injection or Radiofrequency Ablation for Liver Tumors

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Background: The efficacy of the transarterial chemoembolization (TACE) process combined with percutaneous ethanol injection (PEI, TACE-P) or the radiofrequency ablation (RFA, TACE-R) process was found to be good when used for the treatment of patients suffering from early or intermediate hepatocellular carcinoma (eiHCC). The study was conducted to compare the efficacy and safety of the TACE-P with TACE-A processes followed during the treatment of patients with eiHCC.

Methods: A total of 241 patients suffering from eiHCC, subjected to TACE-P (147 patients) or TACE-R (94 patients) processes from January 1, 2014, to December 31, 2018, were retrospectively reviewed and included. The propensity score matching (PSM) method was used to reduce selection bias.

Results: The median overall survival (mOS) and progression-free survival (mPFS) of the TACE-P group were similar to those recorded for the TACE-R group ($P>0.05$) before using the PSM technique. Similar results were obtained post the use of the PSM technique. In the subgroup analysis after PSM, patients with single tumor (dimension: ≤5 cm), who were subjected to TACE-P-based treatment methods, exhibited worse tumor response than patients subjected to TACE-R-based methods (HR: 1.804, 95% CI: 1.083–3.005, $P=0.023$). Seven adverse events were reported. A statistically significant difference for all grades of adverse events (and grade III or IV adverse events) between the two groups (all $P>0.05$) was not reported.

Conclusion: The benefits and advantages of using the TACE-P based method was similar was those obtained using the TACE-R in patients with eiHCC, especially for patients with a single large tumor or multiple tumors.

Keywords: early or intermediate hepatocellular carcinoma, transarterial chemoembolization, percutaneous ethanol injection, radiofrequency ablation, efficacy

Introduction

Liver cancer is one of the most common and lethal cancers in the world.[1] Hepatocellular carcinoma (HCC) is the most common form of liver cancer, and it accounts for 85–90% of all cancer cases.[2] For all cases of HCC, approximately 75% of the cases are reported in Asia, and more than 50% of the cases are reported in China. HCC remains a global health challenge and is prevalent in China.[1] The guidelines for treating patients in their very early or early stages of HCC recommend liver transplantation, liver resection, or radiofrequency ablation (RFA) as the first-line treatments.[3,4] Transarterial chemoembolization (TACE) is considered as curative adjunct treatment has been used widely in the treatment of HCC.[5] For patients with intermediate-stage HCC, the first-line treatment still includes TACE.[6] However, only a small percentage of patients are eligible for liver transplantation as there is a scarcity of organs. A high 5-year

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survival rate can be achieved in patients with early-stage HCC if they are subjected to the process of liver resection.[7] Liver resection is not recommended for patients with poor liver function or suffering from severe fibrosis.[3] TACE is recommended as the first-line treatment for intermediate-stage HCC because it can improve the 2-year survival rate of patients.[8] Another important reason of TACE for patients with HCC is that it can improve the quality of life.[9] However, incomplete embolization often results in tumor recurrence, resulting in suboptimal outcomes.[10] Thus, TACE combined with other treatments might be needed.

Although for a single small HCC (≤2 cm), the survival rate of patients treated using the RFA technique is comparable to the survival rate of patients subjected to the process of liver resection.[11,12] It has recently been widely reported that patients with early or intermediate-stage HCC (eiHCC) could get more survival benefits when treated using the TACE combined with RFA (TACE-R) technique than using TACE or RFA alone.[13–16] The RFA method can be used to destroy the residual tumor cells in patients treated using the TACE technique. It also helps prevent the progression of the tumor and prolongs the survival time of patients. However, RFA is not recommended for patients with tumors in the vicinity of important organs or major vessels (as blood can absorb the heat produced during the RFA-based treatment method, resulting in the "heat–sink" effect) as it can potentially damage the organs.[17] Percutaneous ethanol injection (PEI) based treatment method is a selective RFA based method. This highly efficient method is being used for decades to treat HCC.

The PEI-based treatment method involves killing tumor cells by injecting alcohol into tumor tissues. This method exhibits good efficacy when used to treat patients with small HCC.[18] The low efficacy of the treatment method in cases of large tumors can be attributed to the fact that alcohol cannot be effectively spread throughout large tumor tissues.[18,19] Thus, residual tumor tissues are observed in these cases post treatment. Thus, the PEI-based treatment method is often combined with other treatments methods to treat HCC. Lubienski A et al presented patients with unresectable HCC who were treated following the TACE combined with PEI (TACE-P) method.[20] They reported that the survival benefits observed for these patients were more than the survival benefits observed for the patients treated with only the TACE technique. However, it has been previously reported that the survival rate recorded for patients with early-stage HCC and treated using the RFA technique was higher than the survival rate recorded for the patients treated using the PEI-based treatment method.[21,22] There are no reports which report the efficacy and safety of the TACE-R and TACE-P methods used to treat HCC.

The study was conducted to compare the efficacy and safety of the TACE-R and TACE-P methods followed to treat eiHCC.

Materials and Methods

Materials and Methods

This is a retrospective study. Patients with early–intermediate-stage HCC and treated using the TACE-R and TACE-P methods were included in the study conducted in the period spanning January 2014 to December 2018. What treatments patients received is based on the multidisciplinary committee discussion. Patients were recommended to receive TACE or PEI if there were residual tumors because some studies have presented patients with HCC could get more survival benefits from TACE combined with RFA or PEI than TACE alone.[23,24] The EASL guideline also presented patients with small tumor size could get similar survival benefits from RFA compared with PEI.[3] PEI was used based on the tumor location and patients' willing. This study was conducted in accordance with the guidelines presented in the Declaration of Helsinki. This study was approved by the institutional ethical committee board. The necessity of informed consent (of the patients) was waived by the board as a retrospective study was conducted.

The inclusion criteria have been presented: the included patients were (1) were diagnosed with eiHCC (Barcelona Clinic Liver Cancer stage A or B, BCLC) by analyzing the images recorded and conducting laboratory tests (based on the guideline presented) or liver biopsy (99 patients with biopsy);[3] (2) subjected to TACE-R or TACE-P treatment methods; (3) not subjected to TACE, RFA, or PEI methods before being included into the study; (4) in good physical condition (Eastern Cooperative Oncology Group 0, ECOG); (5) exhibited good liver function (Child-Pugh A or B) (Figure 1).

The exclusion criteria have been presented: the excluded patients (1) suffered from HCC, which could not be evaluated; (2) had platelet counts $<50\times10^9$/L; (3) lost to follow up.

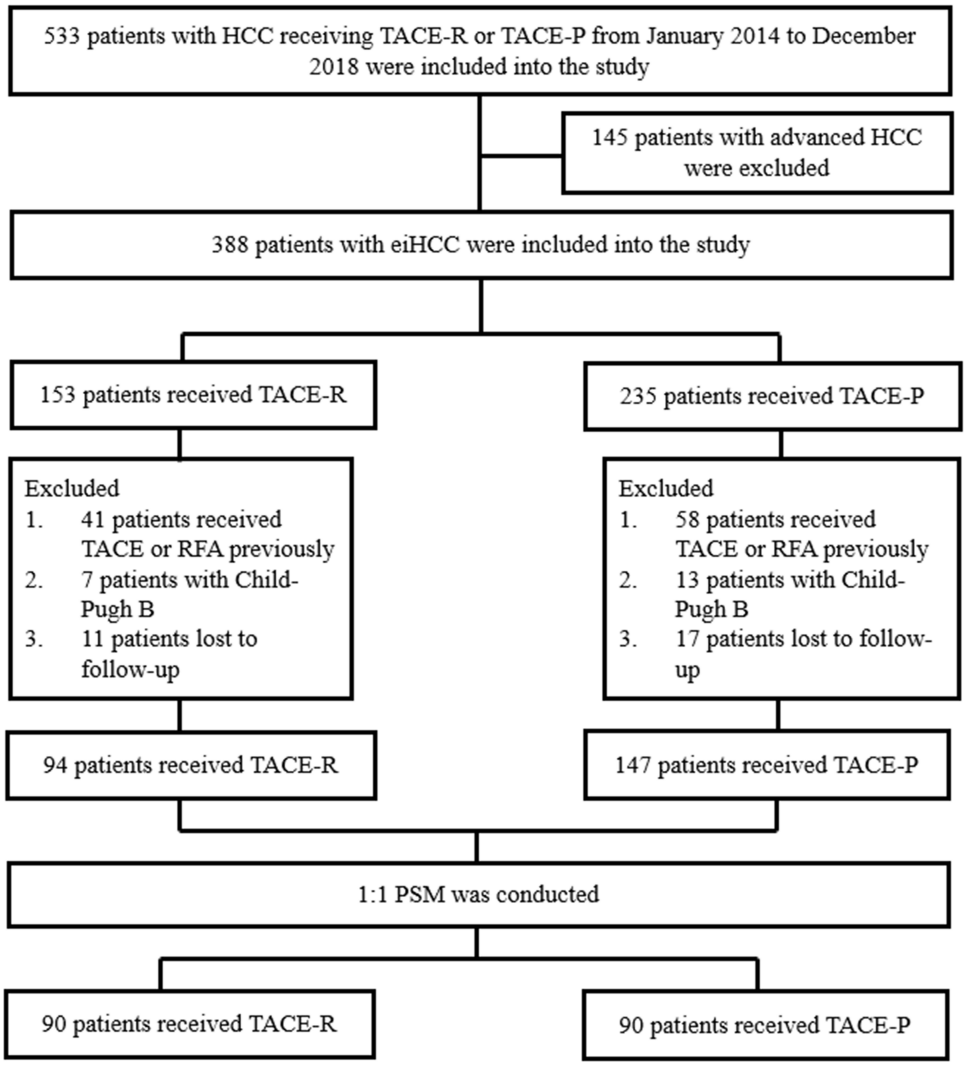

Figure 1 Flowchart presenting the process of patient selection.

TACE, RFA and PEI Procedures

All patients were subjected to the TACE-, RFA-, or PEI-based treatment methods based on the recommendations of the multidisciplinary committee. The committee recommended the most suitable treatment method for patients based on the tumor burden and the physical condition of the patients. The application of the recommended treatment method depended on the consent and of the patients and their willingness to accept the recommendation.

TACE Procedure

After local anesthesia, the Seldinger technique was used to introduce a 5F catheter into the Femoral artery. Following this, the catheter was introduced to the celiac artery. Celiac angiography was performed to relocate the tumor. A 5F catheter or 3F microcatheter was positioned into the feeding artery of the tumor. Subsequently, an emulsion containing lipiodol (10–20 mL) and epirubicin (5–20 mg), and absorbable gelatin sponge particles (350–560 μm) were injected into the tumor.

RFA Procedure

RFA was conducted within two weeks after TACE (3–14 days). RFA was performed following local anesthesia (performed by interventional radiologists with more than 10 years of experience in the field). All RFA sessions were performed using a RITA 1500 generator (RITA Medical Systems, Mountain View, CA, USA). The CT or ultrasound

technique was used for the effective execution of the procedure. A single extendable electrode was used when the tumor diameter was ≤2 cm. When the diameter of the tumor was >2 cm, a multi-electrode was used. Multiple overlapping ablations were needed to accomplish a safe margin with 0.5–1.0 cm around the tumor.

PEI Procedure

PEI was conducted within two weeks after TACE (2–12 days). PEI was performed by interventional radiologists with more than 10 years of experience in the relevant field. Following local anesthesia, two 21-gauge Chiba PEI needles were inserted percutaneously into the tumor under ultrasound conditions. An appropriate amount of absolute ethanol was then slowly injected into the tumor until the tumor area appeared hyperechoic. The mean injection of alcohol was 4.3±2.1 mL (2.0–6.9 mL).

The primary endpoint of the study was overall survival (OS). The secondary endpoints of the study were progression-free survival (PFS) and Objective Response Rate (ORR). OS was defined as the time interval between the execution of the initial TACE-based treatment process and the patient's death. PFS was defined as the time interval between the execution of the initial TACE-based treatment method and tumor progression (or patient's death). ORR was defined as the proportion of patients exhibiting complete response (CR) and partial response (PR) (with respect to all patients). The tumor response was evaluated based on the mRECIST criteria.[25]

Follow-Up

The conditions of all the patients included in the study were followed up every 4–6 weeks (after they were subjected to the initial RFA- or PEI-based methods). Subsequently, the interval was increased to 8–12 weeks. The patients were asked to undergo tests and get the images of the tumor recorded before every follow up session. The tumor response was evaluated by one radiologist (with more than seven years of experience in the field) and one interventionalist (with more than thirteen years of experience in the field) based on the mRECIST criteria. If the presence of a residual tumor or the progression of a tumor was observed, another round of TACE, RFA, or PEI was recommended. The study was terminated on December 2021.

Statistical Analysis

All statistical analyses were conducted using SPSS 26.0 (IBM Corp, Armonk, NY, USA). The continuous variables were presented as mean ± standard deviation (SD), and the results between the two groups were compared by conducting Student's *t* or Mann–Whitney *U*-tests. The categorical variables were compared by conducting the Chi-square or Fisher's tests. Survival outcomes for the two groups were compared by conducting the Log rank test, and the survival curves were plotted following the Kaplan–Meier method. The Cox regression analysis method was used to predict the potential variables which might influence the survival outcomes. The variables with P values less than 0.05 (in the univariable regression analysis) were used to conduct the multivariable regression analysis.

We used the propensity score matching (PSM) method to reduce the potential selection bias. The nearest-neighbor method (PSM model) was applied using an optimal caliper of 0.1 and a matching ratio of 1:1. All variables were included in PSM analysis. Following the conduction of the PSM method, 90 pairs of patients were identified, and the baseline characteristics of the patients in the two groups were balanced. $P<0.05$ was considered statistically significant.

Results

Patients

From January 2014 to December 2018, a total of 241 patients who met the inclusion criteria were included in the study. Among them, 147 patients were subjected to TACE-P-based treatment methods, and 94 patients were subjected to TACE-R-based treatment methods. The TACE-P group consisted of 119 male and 28 female participants, and the TACE-R group consisted of 80 male and 14 female participants. The mean age of the patients in the TACE-P group was 58.0±9.6, and that of the patients in the TACE-R group was 57.1±10.4. The median PEIs of the patients belonging to the TACE-P group was 1 (range: 1–6). The median RFAs of the patients belonging to the TACE-R group was 1 (range: 1–7) (Table 1).

Table 1 Baseline Characteristics of Patients Subjected to TACE-R- or TACE-P-Based Treatment Methods (Before and After Conducting PSM)

Characteristic	Before Matching			After Matching		
	TACE-P (N=147)	TACE-R (N=94)	P value	TACE-P (N=90)	TACE-R (N=90)	P value
Age	58.0±9.6	57.1±10.4	0.478	58±9.1	56.7±10.4	0.353
ALT	38.7±30.1	38.4±24.6	0.931	40.4±28.9	38.6±24.7	0.654
AST	40.3±24.9	40.0±25.6	0.931	41.1±23	40.1±26	0.796
Platelet	129.4±59.5	136.5±68.6	0.392	136.4±65.5	138.4±69.1	0.841
Leukocyte	4.8±1.9	4.6±1.6	0.345	4.7±1.7	4.7±1.6	0.855
Lymphocyte	1.6±3.1	1.4±0.5	0.468	1.5±2.1	1.4±2.1	0.736
Gender			0.407			0.380
Male	119	80		80	76	
Female	28	14		10	14	
HBV			0.705			0.324
Yes	105	65		67	61	
No	42	29		23	29	
Cirrhosis			0.156			0.527
Yes	108	61		62	58	
No	39	33		28	32	
Ascites			0.237			0.494
Yes	16	6		3	6	
No	131	88		87	84	
TACE session			0.007			0.320
1	8	15		7	11	
≥2	139	79		83	79	
Tumor size			0.030			0.116
≤5 cm	102	77		64	73	
>5 cm	45	17		26	17	
Tumor number			0.063			0.369
1	68	55		46	52	
≥2	79	39		44	38	
AFP level			0.616			0.606
≤ 200	110	73		66	69	
>200	37	21		24	21	

(*Continued*)

Table 1 (Continued).

Characteristic	Before Matching			After Matching		
	TACE-P (N=147)	TACE-R (N=94)	P value	TACE-P (N=90)	TACE-R (N=90)	P value
BCLC stage			0.061			0.350
A	84	65		55	61	
B	63	29		35	29	
Child-Pugh			0.632			>0.999
A	125	82		80	80	
B	22	12		10	10	
Surgery pre-TACE			0.240			0.773
Yes	7	8		6	7	
No	140	86		84	83	

Abbreviations: PSM, propensity score matching; TACE-P, transarterial chemoembolization plus percutaneous ethanol injection; TACE-R, transarterial chemoembolization plus radiofrequency ablation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B; AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer.

Survival Outcomes and Tumor Response

The median OS (mOS) and median PFS (mPFS) recorded for the TACE-P group (before using the propensity score matching (PSM) technique) were 46 months (95% CI: 40.9–51.1 months) and 21 months (95% CI: 17.0–25.0 months), respectively. For the TACE-R group, the mOS and mPFS were 49 months (95% CI: 40.1–57.9 months) and 22 months (95% CI: 16.3–27.7 months), respectively. A significant statistical difference for mOS and mPFS (P=0.195 and P=0.295, respectively) between the two groups was not observed (Supplementary Figure 1). A significant statistical difference for mOS (49 months, 95% CI: 44.1–53.9 months; vs 51 months, 95% CI: 43.3–58.7 months; P=0.184) and mPFS (21 months, 95% CI: 16.8–25.2 months; vs 23 months, 95% CI: 17.1–28.9 months, P=0.226) between the TACE-P and TACE-R groups (post the execution of the PSM method) was not observed (Figure 2).

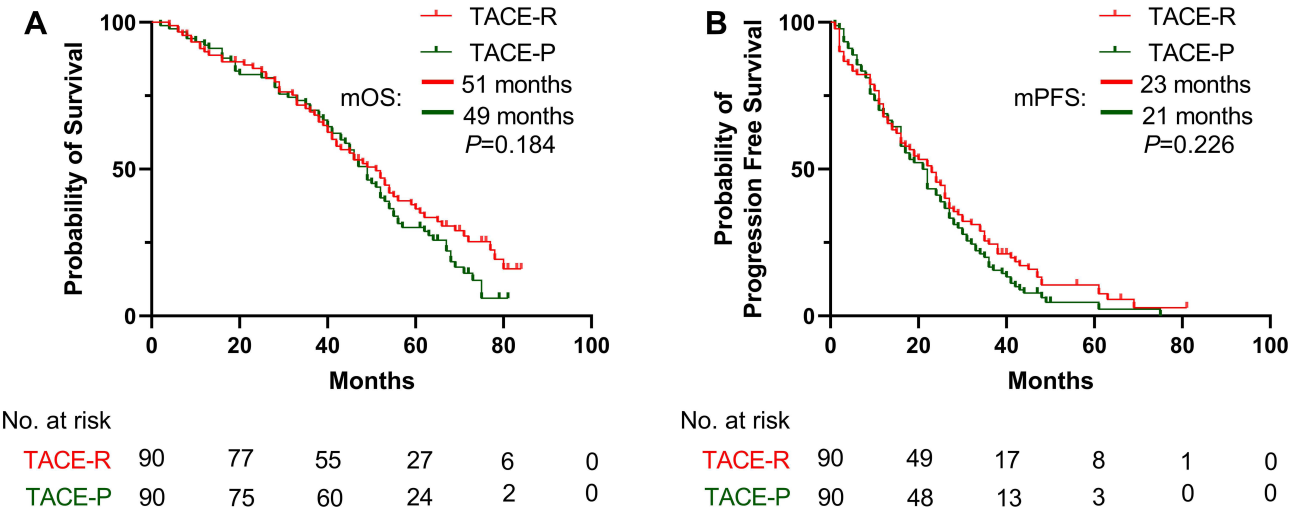

Figure 2 Kaplan–Meier curves for OS and PFS (after PSM). (**A**) Kaplan–Meier curves for OS; (**B**) Kaplan–Meier curves for PFS.

The ORR at 6 months (recorded before using the PSM method) recorded following the treatment of the patients belonging to the TACE-P group was 68% (100/147). The value was found to be 71.3% (67/94) for the TACE-R group. A significant statistical difference for ORR between the two groups (P=0.594) was not observed. A statistical difference for ORR (between the TACE-P (67.8%, 61/90) and TACE-R groups) was also not observed post PSM (71.1%, 64/90, P=0.627) (Table 2).

Predictors for OS and PFS

The results obtained from univariable regression analysis revealed that AST (HR: 1.012, 95% CI: 1.005–1.018, P<0.001), gender (HR: 1.442, 95% CI: 1.001–2.077, P=0.049), ascites (HR: 0.622, 95% CI: 0.390–0.991, P=0.046), tumor size (HR: 1.857, 95% CI: 1.339–2.574, P<0.001), tumor number (HR: 1.967, 95% CI: 1.463–2.646, P<0.001), AFP level (HR: 2.073, 95% CI: 1.499–2.847, P<0.001), BCLC stage (HR: 2.172, 95% CI: 1.610–2.930, P<0.001), and Child-Pugh (HR: 2.192, 95% CI: 1.488–3.230, P<0.001) were independent predictors for OS. The results from multivariable regression analysis revealed that following the exclusion of the potential variables which might influence the outcomes, tumor size (HR: 1.677, 95% CI: 1.166–2.411, P=0.005), AFP level (HR: 1.639, 95% CI: 1.163–2.309, P=0.005), and Child-Pugh (HR: 1.895, 95% CI: 1.205–2.979, P=0.006) were the independent predictors for OS (Table 3).

For PFS, the results from univariable regression analysis revealed that ALT (HR: 1.005, 95% CI: 1.000–1.010, P=0.030), AST (HR: 1.011, 95% CI: 1.005–1.017, P<0.001), tumor size (HR: 1.857, 95% CI: 1.376–2.506, P<0.001), tumor number (HR: 1724, 95% CI: 1.324–2.244, P<0.001), AFP level (HR: 1.885, 95% CI: 1.389–2.556, P<0.001), BCLC stage (HR: 1.976, 95% CI: 1.507–2.590, P<0.001), and Child-Pugh (HR: 1.850, 95% CI: 1.277–2.681, P=0.001) were the independent predictors. The results from multivariable regression analysis revealed that following the exclusion of the potential variables which might influence the outcomes, the variables tumor size (HR: 1.631, 95% CI: 1.181–2.252, P=0.003), AFP level (HR:1.640, 95% CI: 0.728–1.818, P=0.003), BCLC stage (HR: 1.609, 95% CI: 1.003–2.582, P=0.048), and Child-Pugh (HR: 1.763, 95% CI: 1.141–2.726, P=0.011) were the independent predictors of PFS (Table 4).

Subgroup Analysis Before and After PSM

The TACE-P method did not increase the all-cause mortality risk (HR: 1.152, 95% CI: 0.783–1.696, P=0.472) and PFS risk (HR: 1.162, 95% CI: 0.825–1.637, P=0.389) in patients with BCLC A. The risks were assessed prior to conducting PSM. The risks recorded in this case were not higher than the risks recorded under conditions of TACE-R. The TACE-P method did not increase the all-cause mortality risk (HR: 1.041, 95% CI: 0.639–1.695, P=0.873) and PFS risk (HR: 0.904, 95% CI: 0.577–1.415, P=0.658) in patients with BCLC B. The risks recorded in this case were not higher than the risks recorded under conditions of TACE-R. The TACE-P method did not increase the all-cause mortality risk (HR: 1.284, 95% CI: 0.769–2.144, P=0.339) and PFS risk (HR: 1.436, 95% CI: 0.908–2.270, P=0.122) in patients with single tumors (≤5 cm). The risks recorded in this case were not higher than the risks recorded under conditions of TACE-R. The

Table 2 Analysis of Tumor Response Six Months After Patients Were Subjected to TACE-R-Based or TACE-P-Based Treatment Methods (Before and After PSM)

	Before PSM			After PSM		
Tumor Response	**TACE-P (N/%)**	**TACE-R (N/%)**	**P value**	**TACE-P (N/%)**	**TACE-R (N/%)**	**P value**
Complete response	41 (27.9)	40 (42.6)	0.019	25 (27.8)	38 (42.2)	0.042
Partial response	59 (40.1)	27 (28.7)	0.071	36 (40.0)	26 (28.9)	0.117
Stable disease	24 (16.3)	11 (11.7)	0.320	13 (14.4)	11 (12.2)	0.661
Progression disease	23 (15.7)	16 (17.0)	0.777	16 (17.8)	15 (16.7)	0.844
Objective response rate	100 (68)	67 (71.3)	0.594	61 (67.8)	64 (71.1)	0.627

Abbreviations: PSM, propensity score matching; TACE-P, transarterial chemoembolization plus percutaneous ethanol injection; TACE-R, transarterial chemoembolization plus radiofrequency ablation.

Table 3 Univariable and Multivariable Regression Analysis for OS (Before PSM)

Characteristic	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age	0.998 (0.983,1.014)	0.824		
ALT	1.004 (0.998,1.009)	0.187		
AST	1.012 (1.005,1.018)	<0.001	1.007 (0.999,1.014)	0.072
Platelet	0.999 (0.997,1.001)	0.474		
Leukocyte	1.038 (0.948,1.138)	0.417		
Lymphocyte	0.999 (0.942,1.058)	0.964		
Gender		0.049		0.351
Male	Ref		Ref	
Female	1.442 (1.001,2.077)		1.199 (0.819,1.755)	
HBV		0.747		
Yes	Ref			
No	1.053 (0.770,1.441)			
Cirrhosis		0.151		
Yes	Ref			
No	1.260 (0.919,1.729)			
Ascites		0.046		0.571
Yes	Ref		Ref	
No	0.622 (0.390,0.991)		0.863 (0.519,1.436)	
TACE session		0.346		
1	Ref			
≥2	0.800 (0.503,1.273)			
Tumor size		<0.001		0.005
≤5 cm	Ref		Ref	
>5 cm	1.857 (1.339,2.574)		1.677 (1.166,2.411)	
Tumor number		<0.001		0.167
1	Ref		Ref	
≥2	1.967 (1.463,2.646)		1.423 (0.863,2.348)	
AFP level		<0.001		0.005
≤ 200	Ref		Ref	
>200	2.073 (1.499,2.847)		1.639 (1.163,2.309)	
BCLC stage		<0.001		0.135
A	Ref		Ref	

(*Continued*)

Table 3 (Continued).

Characteristic	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
B	2.172 (1.610,2.930)		1.474 (0.887,2.450)	
Child-Pugh		<0.001		0.006
A	Ref		Ref	
B	2.192 (1.488,3.230)		1.895 (1.205,2.979)	
Surgery pre-TACE		0.994		
Yes	Ref			
No	0.998 (0.556,1.792)			
Treatment		0.201		
TACE-R	Ref			
TACE-P	1.217 (0.901,1.643)			

Abbreviations: PSM, propensity score matching; TACE-P, transarterial chemoembolization plus percutaneous ethanol injection; TACE-R, transarterial chemoembolization plus radiofrequency ablation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B; AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer.

all-cause mortality risk (HR: 1.080, 95% CI: 0.433–2.689, *P*=0.869) and PFS risk (HR: 0.898, 95% CI: 0.399–2.024, *P*=0.796) recorded for the patients with a single tumor (>5 cm) and subjected to the TACE-P-based treatment method were not higher than those recorded for patients subjected to the TACE-R-based treatment methods. In patients with multiple tumors and subjected to conditions of TACE-P, the all-cause mortality risk (HR: 0.774, 95% CI: 0.509–1.177, *P*=0.232) and PFS risk (HR: 0.691, 95% CI: 0.468–1.019, *P*=0.062) were not higher than those recorded under conditions of TACE-R (Supplementary Figure 2).

The all-cause mortality risk (HR: 1.316, 95% CI: 0.853–2.031, *P*=0.215) and PFS risk (HR: 1.328, 95% CI: 0.905–1.947, *P*=0.147) recorded for patients with BCLC A and subjected to conditions of TACE-P (following the conduction of the PSM methods) were not higher than those recorded for the patients subjected to conditions of TACE-R. The all-cause mortality risk (HR: 0.969, 95% CI: 0.562–1.671, *P*=0.910) and PFS risk (HR: 0.888, 95% CI: 0.538–1.467, *P*=0.644) recorded for patients with BCLC B and subjected to conditions of TACE-P were not higher than those recorded for the patients subjected to conditions of TACE-R. The all-cause mortality risk (HR: 1.624, 95% CI: 0.919–2.871, *P*=0.095) in patients with a single tumor (≤5 cm) and subjected to conditions of TACE-P was not higher than that recorded for patients subjected to conditions of TACE-R. However, the PFS risk (HR: 1.804, 95% CI: 1.083–3.005, *P*=0.023) in patients with tumor size no more than 5 cm and subjected to conditions of TACE-P were higher than that recorded for the patients subjected to conditions of TACE-R. In patients with a single tumor larger than 5 cm (in length) and subjected to conditions of TACE-P, the all-cause mortality risk (HR: 0.839, 95% CI: 0.314–2.243, *P*=0.727) and PFS risk (HR: 0.687, 95% CI: 0.284–1.663, *P*=0.406) were not higher than those recorded for the patients subjected to conditions of TACE-R. In patients with multiple tumors and subjected to TACE-P-based treatment methods, the all-cause mortality risk (HR: 0.845, 95% CI: 0.525–1.361, *P*=0.489) and PFS risk (HR: 0.753, 95% CI: 0.484–1.172, *P*=0.209) were not higher than those recorded for the patients subjected to conditions of TACE-R (Figure 3).

Evaluation of Adverse Events

The adverse events observed in patients treated using TACE-P- or TACE-R-based methods were evaluated before conducting PSM. For all grades of adverse events, a significant statistical difference for abdominal pain (*P*=0.460), fever (*P*=0.624), nausea (*P*=0.362), vomit (*P*=0.233), fatigue (*P*=972), poor appetite (*P*=0.253), and bleeding (*P*>0.999) was not observed between the two groups. For grade III or IV adverse events, a significant statistical difference for

Table 4 Univariable and Multivariable Regression Analysis for PFS (Before PSM)

Characteristic	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age	0.994 (0.980,1.008)	0.388		
ALT	1.005 (1.000,1.010)	0.030	1.005 (0.997,1.012)	0.206
AST	1.011 (1.005,1.017)	<0.001	1.003 (0.993,1.012)	0.578
Platelet	1.000 (0.998,1.002)	0.773		
Leukocyte	1.017 (0.933,1.108)	0.699		
Lymphocyte	1.006 (0.947,1.069)	0.845		
Gender		0.187		
Male	Ref			
Female	1.257 (0.895,1.766)			
HBV		0.898		
Yes	Ref			
No	1.019 (0.767,1.353)			
Cirrhosis		0.167		
Yes	Ref			
No	1.223 (0.919,1.627)			
Ascites		0.273		
Yes	Ref			
No	0.773 (0.487,1.225)			
TACE session		0.791		
1	Ref			
≥2	0.939 (0.592,1.490)			
Tumor size		<0.001		0.003
≤5 cm	Ref		Ref	
>5 cm	1.857 (1.376,2.506)		1.631 (1.181,2.252)	
Tumor number		<0.001		0.549
1	Ref		Ref	
≥2	1.724 (1.324,2.244)		1.150 (0.728,1.818)	
AFP level		<0.001		0.003
≤200	Ref		Ref	
>200	1.885 (1.389,2.556)		1.640 (1.182,2.275)	
BCLC stage		<0.001		0.048
A	Ref		Ref	

(*Continued*)

Table 4 (Continued).

Characteristic	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
B	1.976 (1.507,2.590)		1.609 (1.003,2.582)	
Child-Pugh		0.001		0.011
A	Ref		Ref	
B	1.850 (1.277,2.681)		1.763 (1.141,2.726)	
Surgery pre-TACE		0.197		
Yes	Ref			
No	0.708 (0.419,1.197)			
Treatment		0.307		
TACE-R	Ref			
TACE-P	1.151 (0.879,1.507)			

Abbreviations: PSM, propensity score matching; TACE-P, transarterial chemoembolization plus percutaneous ethanol injection; TACE-R, transarterial chemoembolization plus radiofrequency ablation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B; AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer.

abdominal pain (P=0.921), fever (P>0.999), nausea (P=0.967), vomit (P>0.999), fatigue (P>0.999), poor appetite (P>0.999), and bleeding (P>0.999) was not observed between the two groups (Table 5).

Discussion

TACE is the first-line treatment for patients with intermediate-stage HCC.[3] It has been recently reported that patients in their early stages of TACE-based treatment could potentially benefit from the method,[26,27] resulting in an improved survival rate. However, complete embolism could only be observed in approximately 20% of the patients with HCC who were subjected to conditions of TACE.[28] This can potentially result in tumor progression and poor prognosis. PEI- and RFA- based treatment methods, as adjuvant treatment methods, have been used to treat patients with HCC who were subjected to conditions of TACE. It has been previously reported that the survival benefits observed in patients treated using the TACE-P- or TACE-R-based treatment methods were better than the survival benefits observed in patients treated following only the TACE treatment method.[24] Previous study has presented the cost of PEI is less than RFA in the treatment.[29] However, whether the efficacy of the TACE-P method is comparable with that of the TACE-R method used to treat patients with eiHCC is unknown. Hence, this study was conducted to compare the efficacy and safety achieved using the TACE-P method with those achieved using the TACE-R method.

The primary finding is that the mOS and mPFS recorded for patients with eiHCC subjected to conditions of TACE-P were comparable to the mOS and mPFS recorded for patients treated using the TACE-R method. The results reported herein agree well with previously reported results. Zhang YJ et al conducted a study to determine the long-term outcomes of using the TACE-R method for treating patients with early-stage HCC.[30] They reported that the mOS of the patients belonging to the TACE-R group was 62 months and the median recurrence-free survival (mRFS) was 46 months. The mOS and mRFS reported in their study were longer than those obtained by us. It is possible that only 69.1% of the patients considered in the current study were suffering from early-stage HCC. Liu FR et al conducted a study that included 404 patients with BCLC stage B1 who were subjected to TACE-R and TACE methods.[31] The efficacy of the methods was compared for the two groups. The results showed that the mOS and mPFS of the patients belonging to the TACE-R group were 33.1 months and 20 months, respectively, which are shorter than the mOS and mPFS reported herein. This can be potentially attributed to the fact that all patients included in the study were suffering from intermediate-stage HCC, but only 30.9% of the patients considered

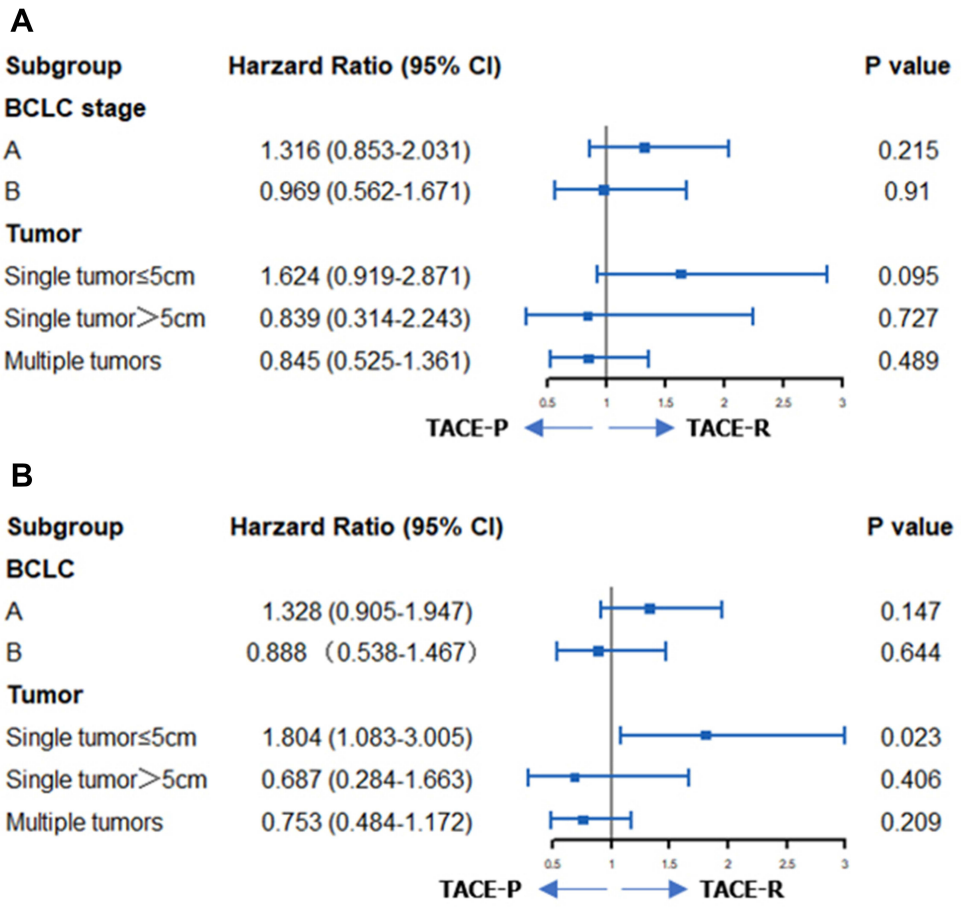

Figure 3 Forest plots for subgroup analysis (after PSM). (**A**) Forest plot for OS; (**B**) Forest plot for PFS.

by us were suffering from intermediate-stage HCC because the BCLC stage was a strong prognostic factor. This has been previously reported. Kirikoshi H et al compared the efficacy of the TACE combined with ablation (RFA/PEI) and TACE-alone methods and found that the mOS for the patients belonging to the TACE combined with ablation group was 46.6 months, which is similar to the mOS recorded by us.[32] The previously reported results can potentially help validate the results

Table 5 Analysis of Adverse Events (Before PSM)

Adverse Events	All Grades			III or IV Grades		
	TACE-P (N)	TACE-R (N)	P value	TACE-P (N)	TACE-R (N)	P value
Abdominal pain	93	55	0.460	21	13	0.921
Fever	45	26	0.624	3	2	>0.999
Nausea	57	31	0.362	8	5	0.967
Vomit	18	7	0.233	1	0	>0.999
Fatigue	31	20	0.972	4	3	>0.999
Poor appetite	101	71	0.253	1	0	>0.999
Bleeding	6	4	>0.999	0	0	>0.999

Abbreviations: PSM, propensity score matching; TACE-P, transarterial chemoembolization plus percutaneous ethanol injection; TACE-R, transarterial chemoembolization plus radiofrequency ablation.

obtained by us. The univariable and multivariable regression methods were used to reduce other factors which might influence the results. The results revealed that the all-cause mortality risk and PFS risk recorded for the case of TACE-P were not higher than those recorded for the case of TACE-R. This reveals that comparable survival benefits can be obtained by patients subjected to conditions of TACE-P or TACE-P.

It has been previously reported that tumor burden influences the survival and tumor response of patients with HCC.[33,34] Hence, BCLC stage A or stage B patients with a single tumor of length ≤5 cm, a single tumor of length >5 cm, or multiple tumors were included for subgroup analysis. The results revealed that the PFS risk in patients subjected to TACE-P-based treatment methods was higher than that in patients subjected to TACE-R-based treatment methods (the results were obtained when patients with a single tumor no more than 5 cm in length (following PSM) were studied). In cases of small tumors, complete ablation under condition of RFA might be achieved using a multipolar ablation needle. However, it might be difficult to diffuse ethanol throughout all tumor tissues. This can result in incomplete ablation for PEI, and the residual tumor may be obtained. Tumor progression and poor prognosis are observed under these conditions. This might the reason why patients with small tumors could get more survival benefits from TACE-R than TACE-P.

The major adverse events observed in patients subjected to conditions of TACE-P or TACE-R have been reported herein. The results revealed that significant statistical difference (between the TACE-P and TACE-R groups) was not observed for any of the grades of adverse events (or for the cases of severe adverse events). This revealed that TACE-P-based treatment methods could beas safe as TACE-R used to treat patients with eiHCC. This method was safer than the TACE-R-based method.

There are several limitations of using the treatment methods proposed herein. Firstly, a retrospective study was conducted. Although the PSM method was used for analysis, the potential selection bias could be excluded. Secondly, the sample size considered is not large. Third, the study did not include the comparison of quality of life, the data of microvascular invasion and the cost in patients with TACE-P or TACE-R. We hope that perspective studies with more patients will be conducted and evaluate the quality of life for patients receive TACE-P or TACE-R in the future to validate the results presented herein.

Conclusions

Similar survival benefits might be obtained by patients with eiHCC (except for small tumor) using the TACE-P-based and TACE-R-based methods. TACE-P might be a good selective treatment method for TACE-R for patients with eiHCC.

Data Deposition and Data Sharing

The data used in the study were available from the correspondence author on reasonable request.

Research Ethics and Consent

This study was approved by ethics committee of Union Hospital of Huazhong University of Science and Technology. Written informed consent was waived by this institution because the study is a retrospective study. All the data used in the study were uploaded to offline database. The data can be available by the researchers and the patients and their families upon reasonable request.

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Disclosure

All authors declared that there were no competing interests existing.

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