research article

CT-guided ^{125}I brachytherapy for hepatocellular carcinoma in high-risk locations after transarterial chemoembolization combined with microwave ablation: a propensity score-matched study

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Background. This study aimed to evaluate the safety and efficacy of ^{125}I brachytherapy combined with transarterial chemoembolization (TACE) and microwave ablation (MWA) for unresectable hepatocellular carcinoma (HCC) in high-risk locations.

Patients and methods. After 1:2 propensity score matching (PSM), this retrospectively study analyzed 49 patients who underwent TACE +MWA+^{125}I brachytherapy (group A) and 98 patients who only received TACE +MWA (group B). The evaluated outcomes were progression-free survival (PFS), overall survival (OS), and treatment complications. Cox proportional hazards regression analysis survival was used to compare the two groups.

Results. The patients in group A showed a longer PFS than group B (7.9 *vs.* 3.3 months, P = 0.007). No significant differences were observed in median OS between the two groups (P = 0.928). The objective response rate (ORR), disease control rate of tumors in high-risk locations, and the ORR of intrahepatic tumors were 67.3%, 93.9%, and 51.0%, respectively, in group A, and 38.8%, 79.6% and 29.6%, respectively, in group B (P < 0.001, P = 0.025 and P = 0.011, respectively). TACE-MWA-^{125}I (HR = 0.479, P < 0.001) was a significant favorable prognostic factor that affected PFS. The present of portal vein tumor thrombosis was an independent prognostic factor for PFS (HR = 1.625, P = 0.040). The Barcelona clinic liver cancer (BCLC) stage (BCLC C *vs.* B) was an independent factor affecting OS (HR = 1.941, P = 0.038). The incidence of complications was similar between the two groups, except that the incidence of abdominal pain was reduced in the group A (P = 0.007).

Conclusions. TACE-MWA-^{125}I resulted in longer PFS and better tumor control than did TACE-MWA in patients with unresectable hepatocellular carcinoma in high-risk locations.

Key words: hepatocellular carcinoma; high-risk location; transarterial chemoembolization; microwave ablation; ^{125}I brachytherapy

Introduction

Hepatocellular carcinoma (HCC) ranks the third leading cause of cancer-related death worldwide.[1,2] Up to 60% of patients with HCC are diagnosed at the intermediate to the advanced stages and potentially curative treatments are unapplicable.[3,4] Previous studies have demonstrated the benefits of combination therapies in patients with unresectable HCC.[5-8] The combined treatments of transcatheter arterial chemoembolization (TACE) and thermal ablation could induce extensive tumor necrosis and result in a significant survival benefit.[5,9-14] Prior studies of combined therapies have primarily focused on the Barcelona clinic liver cancer (BCLC) 0/A stage patients as a radical treatment.[4] For unresectable HCCs, a meta-analysis demonstrated that microwave ablation (MWA) outperformed radiofrequency ablation (RFA) in large neoplasms.[15]

Tumor location is an important factor for the procedural success of ablative techniques and TACE. For thermal ablation, firstly, tumors close to vital structures may increase the risk of bleeding and injuring of the adjacent organs.[16] Secondly, the blood flow can dissipate the heat away from the ablated lesion due to the heat sink effect.[17] Lesions adjacent to large intrahepatic vessels, hepatic capsules, or extrahepatic organs may lead to insufficient ablation. MWA exhibited better tumor control than RFA for subcapsular HCC within the Milan criteria[18] and the small single periportal HCC.[19] However, most patients with intermediate-advanced HCC require a large ablation volume and more ablation time.[12] For TACE, adjacent to organs, or previous treatment was reported to promote the formation of extrahepatic collateral arteries, leading to incomplete embolization.[20] Overall, the efficacy of combined therapies and complications related to the high-risk locations still need to be carefully considered.

Brachytherapy with iodine-125 (^{125}I) seeds implantation has been accepted as a useful method to achieve local control with low complication rates in prostate cancer, HCC, and some other solid tumors.[21-24] In previous studies, the combination of ^{125}I and RFA, as well as ^{125}I and TACE was reported to be effective for the treatment of HCC in high-risk locations.[25-28] Thus, we have conducted this retrospective study to assess the efficacy, safety, and prognostic factors of computer tomography[3] guided ^{125}I brachytherapy combined with TACE and MWA for HCC in high-risk locations. To reduce the influence of confounding bias, propensity score matching (PSM) was performed to assess survival outcomes.[29]

Patients and methods

Patients

This retrospective study was approved by the institutional review board of Sun Yat-sen University Cancer Center that waived the need for written informed consent. The data of 1577 primary HCC patients who had received TACE plus MWA as first-line therapeutic options between February 2015 to March 2021 at our center were retrospectively identified. A total of 287 patients were identified by the following eligibility criteria: (a) Diagnosed with HCC according to the Guidelines of the European Association for the Study of the Liver or American Association for the Study of Liver Diseases[3,30]; (b) BCLC stage B or C patients who were not eligible for surgical resection or liver transplantation[4]; (c) presenting with HCC in high-risk locations; (d) TACE combined with sequential MWA was performed as the first-line therapy; (e) Patients had not previously undergone liver resection or liver transplantation. Totally 106 patients were excluded based on the following exclusion criteria: (a) HCC complicated with other malignancies; (b) MWA or ^{125}I brachytherapy was not used to treat the tumors in high-risk locations; (c) Incomplete preoperative and postoperative clinical and radiographic data; (d) Child-Pugh class C or D disease and Eastern Cooperative Oncology Group (ECOG) performance status≥2 (Figure 1).

Definition of high-risk locations

Referring to the previous studies[31,32], The high-risk locations were defined as: (1) Type 1: less than 5 mm from the large vessels (the first- or second-grade branches of the portal veins, hepatic veins, and bile ducts); (2) Type 2: less than 5mm from the hepatic capsule or extrahepatic organs (such as heart, thoracic/abdominal wall, diaphragm, gastric, intestinal, and gall bladder). If the tumor was closed to both structures, the nearest one was chosen to define a high-risk location.

TACE MWA treatment protocol

Before TACE-MWA treatment, all patients received a standardized pretreatment evaluation including history, laboratory, and imaging. All TACE and MWA were performed by five interventional

radiologists with experience of more than 5 years. For TACE, a selective 5-F catheter (Yashiro type; Terumo Corporation) was introduced, and hepatic arterial angiography was performed to identify the tumor-feeding arteries. Then the tumor-feeding arteries were super-selective catheterized with a 2.7-F microcatheter (Renegade Hi Flo; Boston Scientific Corporation). The embolization emulsion was a mixture of 50 mg/m^2 of lobaplatin (Hainan Changan International Pharmaceutical Co., Ltd.), 10–40 mg of pirarubicin (Shenzhen Main Luck Pharmaceuticals Inc.) diluted in iodized oil (Lipoid ultra-fluid, Guerbet). MWA was performed within two weeks after TACE. MWA was performed with a commercially available system (ECO-100; ECO Microwave Electronic Institute) under CT guidance. A suitable route for puncture and ablation was designed. According to the size, number and anatomic location of the tumors, physicians chose the number of needles, the power (40–80W), and corresponding time (5–20 min) of ablation as well as the adjustable position of needles to eliminate the residual tumor. All ablations were conducted under intravenous moderate sedation and local anesthesia.

^{125}I seed implantation protocol

After MWA, CT scanning was conducted immediately to assessed the ablation area and residual tumor adjacent to high-risk sites. Then, interstitial needles were inserted into the target zone under CT guidance. The number and distribution of particles were determined by the treatment planning system (TPS) (BT-RSI, Beijing Atom and High Technique Inc.) to achieve a satisfactory dose distribution. After finishing implantation, a repeated CT scan was performed to check for complications and transmitted to TPS for dose verification. A total of 493 ^{125}I seeds (Yunke Pharmaceutical Limited Liability Company) were implanted by three radiologists with at least 5 years' experience in 49 patients with an average of 12.1 ± 15.1 seeds per patient.

Follow-up protocol and study outcomes

In both groups, patients generally underwent contrast-enhanced CT or MRI 4–6 weeks postoperatively to evaluate initial tumor response. Patients were reviewed every 3 months during the first year and every 6 months thereafter. Repeated TACE, MWA, or ^{125}I seeds implantation was performed according to the location and proportion of residual tumor. Intrahepatic tumor response was graded according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) by two radiologists independently and discrepancies of assessment results was resolved by discussions.[33] Tumor response in the high-risk sites was assessed between baseline and best response according to a modified standard: the product of maximum perpendicular diameters of the tumors in the high-risk sites were calculated and compared to the initial value.[34] The primary study endpoint was progression-free survival (PFS). The secondary endpoints included overall survival (OS), objective response rate [ORR], disease control rate (DCR) and safety. PFS was calculated from the date of the first session of MWA or MWA-^{125}I for the tumor in high-risk site to the date of tumor progression, death, or last follow-up; OS was calculated from the same treatment to the date of death due to any cause or last follow-up. The ORR was defined as the sum of complete and partial response, whereas DCR was defined as ORR plus stable disease rate. The best overall response was categorized as the final response during the treatment. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (Version 5.0).

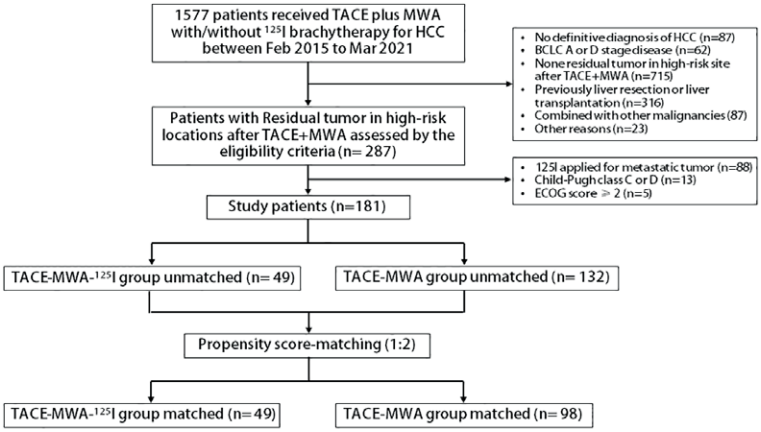

FIGURE 1. Patient flow diagram.

TACE = transarterial chemoembolization; MWA = microwave ablation

Propensity score matching analysis

To decrease the selection bias between the two groups, propensity scores were computed by logistic regression model for each patient using the following covariates: age (y), BCLC stage (B/C), maximum tumor diameter[35], tumor number (1-2/≥3), high-risk site (Type 1/2), portal vein tumor thrombosis (PVTT) (Y/N). A 1:2 propensity score

TABLE 1. Baseline patient characteristics before and after propensity score-matched

Parameter	Total (N = 181)	Total cohort			PSM cohort		
		Group A	Group B	P value	Group A	Group B	P value
		N = 49	N = 132		N = 49	N = 98	
Sex				0.37			0.751
Male	162 (89.5%)	46 (93.9%)	116 (87.9%)		46 (93.9%)	89 (90.8%)	
Female	19 (10.5%)	3 (6.12%)	16 (12.1%)		3 (6.12%)	9 (9.18%)	
Age (y)	56.0 [47.0;64.0]	56.0 [47.0;68.0]	55.5 [48.0;62.0]	0.425	56.0 [47.0;68.0]	55.0 [48.0;62.0]	0.468
BCLC				0.041*			1
B	72 (39.8%)	13 (26.5%)	59 (44.7%)		13 (26.5%)	26 (26.5%)	
C	109 (60.2%)	36 (73.5%)	73 (55.3%)		36 (73.5%)	72 (73.5%)	
Maximum tumor diameter, median (IQR), mm	29.0 [18.0;49.0]	36.0 [22.0;53.0]	26.5 [18.0;46.0]	0.039*	36.0 [22.0;53.0]	31.0 [18.0;57.8]	0.579
Tumor number				0.927			0.66
1-2	60 (33.1%)	17 (34.7%)	43 (32.6%)		17 (34.7%)	29 (29.6%)	
≥ 3	121 (66.9%)	32 (65.3%)	89 (67.4%)		32 (65.3%)	69 (70.4%)	
PVTT				0.202			1
None	108 (59.7%)	25 (51.0%)	83 (62.9%)		25 (51.0%)	49 (50.0%)	
Yes	73 (40.3%)	24 (49.0%)	49 (37.1%)		24 (49.0%)	49 (50.0%)	
Distant metastasis				0.171			0.953
None	109 (60.2%)	25 (51.0%)	84 (63.6%)		25 (51.0%)	52 (53.1%)	
Yes	72 (39.8%)	24 (49.0%)	48 (36.4%)		24 (49.0%)	46 (46.9%)	
High risk location				0.045*			0.76
1	98 (54.2%)	33 (67.3%)	65 (49.2%)		33 (67.3%)	62 (63.3%)	
2	83 (45.8%)	16 (32.7%)	67 (50.8%)		16 (32.7%)	36 (36.7%)	
TACE sessions	2.00 [1.00;3.00]	2.00 [1.00;2.00]	2.00 [1.00;3.00]	0.442	2.00 [1.00;2.00]	1.00 [1.00;3.00]	0.464
MWA sessions	1.00 [0.00;2.00]	1.00 [0.00;2.00]	1.00 [0.00;2.00]	0.162	1.00 [0.00;2.00]	1.00 [0.00;2.00]	0.31
Cause of liver disease:				0.09			0.181
Continued							
HCV/HBV	169 (93.4%)	43 (87.8%)	126 (95.5%)		43 (87.8%)	93 (94.9%)	
Other	12 (6.6%)	6 (12.2%)	6 (4.55%)		6 (12.2%)	5 (5.10%)	
ECOG score				0.189			0.669
0	126 (69.6%)	30 (61.2%)	96 (72.7%)		30 (61.2%)	65 (66.3%)	
1	55 (30.4%)	19 (38.8%)	36 (27.3%)		19 (38.8%)	33 (33.7%)	
Child-pugh score				0.563			0.386
A	82 (45.3%)	46 (93.9%)	36 (27.3%)		46 (93.9%)	86 (87.8%)	
B	99 (54.7%)	3 (6.12%)	96 (72.7%)		3 (6.12%)	12 (12.2%)	
AFP, ng/mL				0.811			0.576
< 400	125 (69.1%)	35 (71.4%)	90 (68.2%)		35 (71.4%)	64 (65.3%)	
≥ 400	56 (30.9%)	14 (28.6%)	42 (31.8%)		14 (28.6%)	34 (34.7%)	
PT (s)	12.2 [11.5;13.1]	12.0 [11.5;12.8]	12.3 [11.6;13.1]	0.167	12.0 [11.5;12.8]	12.2 [11.5;13.1]	0.331
ALB (g/L)	40.35 [36.2;43.9]	40.8 [36.7;44.1]	40.2 [36.0;43.9]	0.329	40.8 [36.7;44.1]	40.3 [36.1;44.1]	0.518
TBIL (mg/dL)	13.55 [10.1;19.32]	12.3 [8.73;18.2]	14.6 [10.4;20.4]	0.167	12.3 [8.73;18.2]	14.6 [10.1;20.2]	0.227

AFP = alpha fetoprotein; ALB = albumin; BCLC = Barcelona Clinic Liver Cancer; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; MWA = microwave ablation; PSM = propensity score-matched; PVTT = portal vein tumor thrombosis; PT = prothrombin time; TACE = transcatheter arterial chemoembolization; TBIL = total bilirubin

SI conversion factors: To convert albumin to grams per liter, multiply by 10.0; to convert bilirubin to micromoles per liter, multiply by 17.104; and to convert a-fetoprotein to micrograms per liter, multiply by 1.0.

*p value ≤ 0.05 was considered to indicate statistical significance.

TABLE 2. Intrahepatic and high-risk locations tumor responses in the two groups after propensity score matching (PSM)

Tumor response	Intrahepatic Tumor			Tumor in high-risk locations		
	Group A (n = 49)	Group B (n = 98)	P value	Group A (n = 49)	Group B (n = 98)	P value
Complete response (CR)	4	6		5	9	
Partial response (PR)	21	23		28	29	
Stable disease (SD)	17	41		13	40	
Progressive disease (PD)	7	28		3	20	
Objective response rate (ORR) (%)	51.0%	29.6%	0.011†*	67.3%	38.8%	< 0.001†*
Disease control rate (DCR) (%)	85.7%	71.4%	0.055†	93.9%	79.6%	0.025†*

† Pearson χ2 test was used

* p value ≤ 0.05 was considered to indicate statistical significance.

matching was performed using the nearest-neighbor matching algorithm with an optimal caliper of 0.1 without replacement.

Statistical analysis

Categorical data are reported as counts and percentages, and continuous data are reported as medians or interquartile ranges. The Chi-square test or Fisher's exact test were used to analyze the differences in categorical variables, and the Mann-Whitney test was applied to the continuous variables. PFS and OS curves were constructed by the Kaplan-Meier (KM) method and estimated by the log-rank test. Univariate was used to analyze prognostic factors for PFS and OS using a Cox proportional hazards model. Significant univariate factors were included in the multivariate models. All tests were two-tailed and P values less than 0.05 were considered to indicate a statistically significant difference. All statistical analyses were performed by R statistical package version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

Between February 2015 to March 2021, a total of 181 HCC patients with tumors in high-risk locations were enrolled in this study. Before PSM, there were significant differences between the two groups in the BCLC stage, maximum tumor diameter, and high-risk location. In the TACE-MWA group (group B), 59 (44.7%) and 73 (55.3%) patients were classified as BCLC stage B and C, respectively. The maximum tumor diameter was significantly smaller than that in the TACE +MWA+^{125}I group (group A) (26.5 *vs.* 36.0 mm, P = 0.039). And there were more tumors in type 2 high-risk sites (50.8%) in group B. After PSM, all characteristics were balanced between the two groups. The baseline characteristics of the unweighted and weighted cohorts are outlined in Table 1. During the follow-up, patients in group A required significantly fewer sessions of TACE and MWA than that in group B (0.73 *vs.* 1.27, P = 0.048; 0.88 *vs.* 1.74, P = 0.013, respectively).

Local tumor control

In the PSM cohort, Tumor responses of the intrahepatic tumor and high-risk locations tumor are shown in Table 2. For the tumor in high-risk locations, the ORR and DCR were significantly higher in the group A (67.3% *vs.* 38.8%, P < 0.001; 93.9% *vs.* 79.6%, P = 0.025, respectively). Likewise, the ORR of intrahepatic tumors in the group A was higher than that in the TACE-MWA group (51.0% *vs.* 29.6%, P = 0.011). The DCR in the group A was slightly higher than that in the group B without a statistical difference (85.7% *vs.* 71.4%, P = 0.055)

Progression-free survival and overall survival

In the unweighted cohort, the median PFS time was 7.9 months (95CI%: 10.9–18.5 months) for patients in the group A, and 3.7 months in the group B (95CI%: 7.1–11.4 months) (P = 0.021) (Figure 2A). In the weighted cohort, the median follow-up for the study population was 16.2 months (range, 1.0–80.4 months). At the time of censoring, median

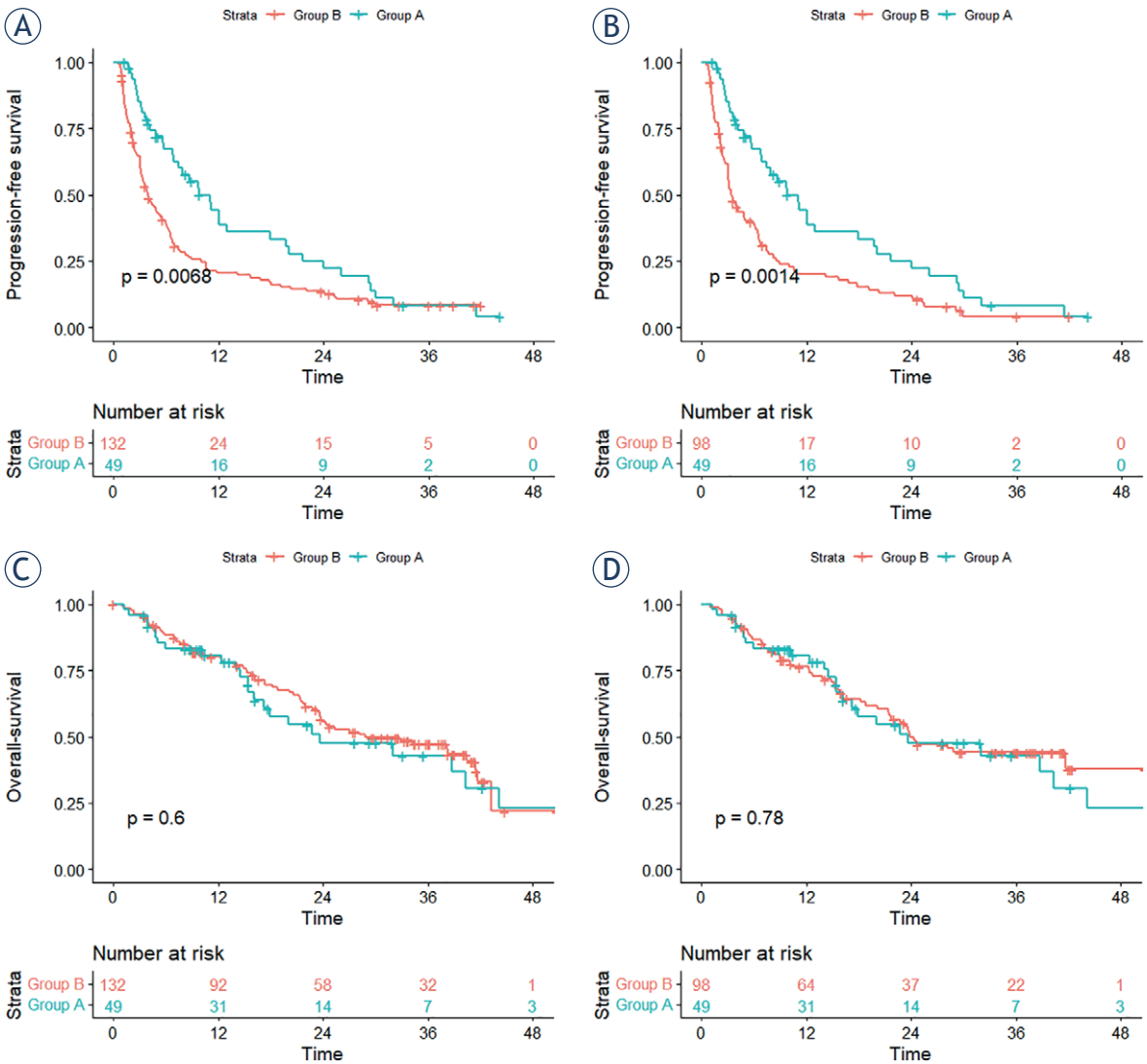

FIGURE 2. Kaplan-Meier curves comparing progression-free survival (PFS) and overall survival overall survival (OS) from different *groups.* **(A)** Cumulative PFS between the unmatched A and B groups. **(B)** Cumulative PFS between the matched A and B groups. **(C)** Cumulative OS between the unmatched A and B groups. **(D)** Cumulative OS between the matched A and B groups.

PFS was 3.3 months (95%CI: 6.1–10.5 months) for patients in the group B, and 7.9 months (95%CI: 10.9–18.5 months) in the group A with significant difference (P = 0.007) (Figure 2B). Univariable analyses revealed that treatment method, maximum tumor diameter, high-risk location, PVTT, and AFP level were significantly correlated with PFS (P < 0.1). Based on these results, the multivariate analysis including all factors of univariate analysis was performed and it identified treatment method and PVTT as independent prognostic factors for PFS (Table 3) (P < 0.05) (Figure 3A).

There was no significant difference in OS between the two groups in both unweighted and weighted cohorts (Figure 2C, 2D). As shown in Supplementary Table 1, univariate analysis results showed that sex, BCLC stage, high-risk location, PVTT, total bilirubin, and Child-pugh class were significant (P < 0.1). Because of assumed collinearity between PVTT and BCLC stage, as well as the total bilirubin and Child-pugh class, PVTT and total bilirubin were deleted from the multivariate model. Results of the multivariate analysis demonstrated that sex and BCLC stage were prognostic

TABLE 3. Multivariate analyses of predictors of progression-free survival after treatment

Risk Factor	Univariate			Multivariate		
	HR	95%CI	P value	HR	95%CI	P value
Sex						
Female	1					
Male	0.755	0.393–1.451	0.399			
Age (y)						
< 60	1					
≥ 60	1.093	0.761–1.569	0.63			
Maximum tumor diameter (mm)	1.006	1.000–1.013	0.071*	1.003	0.996-1.010	0.458
Tumor number						
1-2	1					
≥ 3	1.104	0.915–1.332	0.302			
BCLC stage						
B	1					
C	1.395	0.929–2.095	0.109			
High-risk location						
1	1					
2	0.665	0.456–0.970	0.034**	0.846	0.550-1.302	0.447
PVTT						
None						
Yes	1.615	1.124–2.319	0.010**	1.625	1.015-2.546	0.040**
Distant metastasis						
None						
Yes	1.099	0.772–1.565	0.602			
TACE sessions	1.062	0.964–1.170	0.223			
MWA sessions	1.006	0.914–1.106	0.905			
Treatment						
TACE+MWA	1					
TACE+MWA+ ^{125}I	0.527	0.357–0.778	0.002**	0.479	0.328-0.733	<0.001**
Cause of liver disease						
Other	1					
HBV/HCV	1.36	0.662–2.791	0.402			
ECOG score						
0	1					
1	1.269	0.876–1.837	0.208			
AFP						
≤ 400 ng/mL	1					
Continued						
> 400 ng/mL	1.72	1.164–2.542	0.006**	1.403	0.948-2.129	0.090
Prothrombin time (s)	0.942	0.827–1.073	0.367			
Albumin (g/L)	0.987	0.951–1.024	0.477			
Continued						
Total Bilirubin (μmol/L)	1.001	0.995–1.008	0.649			
Child-pugh class						
A	1					
B	1.216	0.654–2.263	0.536			

AFP = alpha fetoprotein; ALB = albumin; BCLC = Barcelona Clinic Liver Cancer; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; MWA = microwave ablation; PVTT = portal vein tumor thrombosis; PT = prothrombin time; TACE = transarterial chemoembolization; TBIL = total bilirubin

*P value ≤ 0.1 in uni,variate were included in multivariate analysis, **P value ≤ 0.05 was considered to indicate statistical significance in multivariate analysis

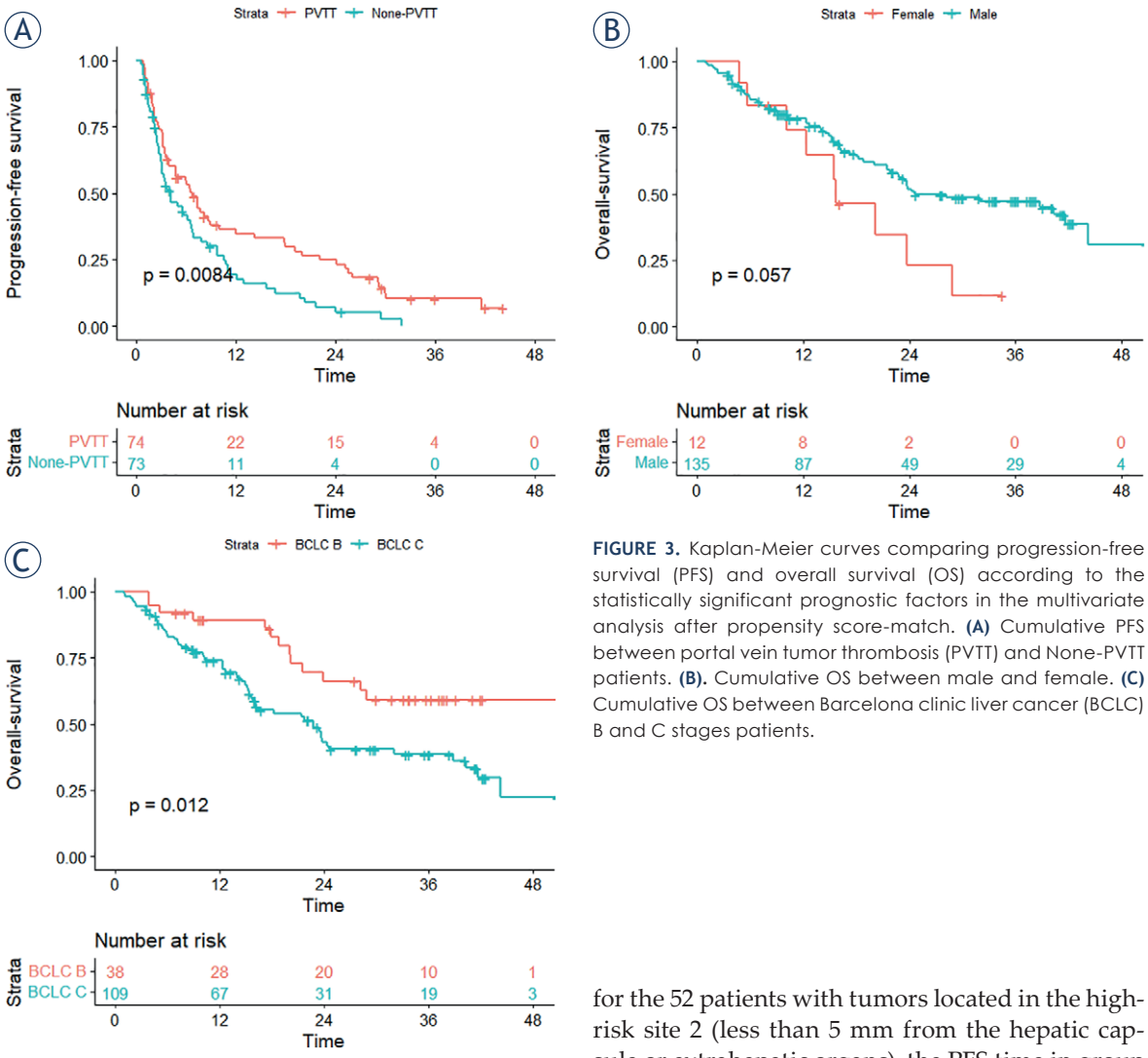

FIGURE 3. Kaplan-Meier curves comparing progression-free survival (PFS) and overall survival (OS) according to the statistically significant prognostic factors in the multivariate analysis after propensity score-match. **(A)** Cumulative PFS between portal vein tumor thrombosis (PVTT) and None-PVTT patients. **(B).** Cumulative OS between male and female. **(C)** Cumulative OS between Barcelona clinic liver cancer (BCLC) B and C stages patients.

factors for OS (P < 0.05). However, no significant difference was detected between male and female groups (P = 0.057). KM analysis showed significant difference between the BCLC B/C groups (P = 0.012) (Figure 3B, 3C).

Subgroup analyses

The patients without PVTT tended to get a better PFS in group B (P < 0.05) (Figure 4A). No significant difference was detected in group A between PVTT and non-PVTT patients (Figure 4B). Moreover, we observed significant differences between the two groups concerning PFS in both PVTT and non-PVTT patients (Figure 4C, 4D). For the 95 patients with tumors located in the high-risk site 1 (less than 5 mm from the large vessels or bile ducts), the mean PFS time was 11.4 months (95%CI: 7.9–14.9 months) in group A and 7.1 months (95%CI: 4.6–9.5 months) in group B (P < 0.01) (Figure 4e). Similarly, for the 52 patients with tumors located in the high-risk site 2 (less than 5 mm from the hepatic capsule or extrahepatic organs), the PFS time in group A was longer than that in group B (20.3 *vs.* 10.1 months, P = 0.02) (Figure 4F).

Complications

Adverse events for both treatment groups were listed in Table 4. During follow-up, there were no treatment-related deaths in either group and all of these patients were relieved after symptomatic treatment. The most common complication after treatment was abdominal pain in both groups and it was more frequent in the group B (P = 0.007). A slightly higher puncture hemorrhage rate was found in the group B (8.2%), without a significant difference (P = 0.274). One patient developed liver abscess after MWA in the group B. No displacement of ^{125}I seeds or radiation-induced liver disease was noted. All of these patients recovered with conservative treatment during the hospital stay.

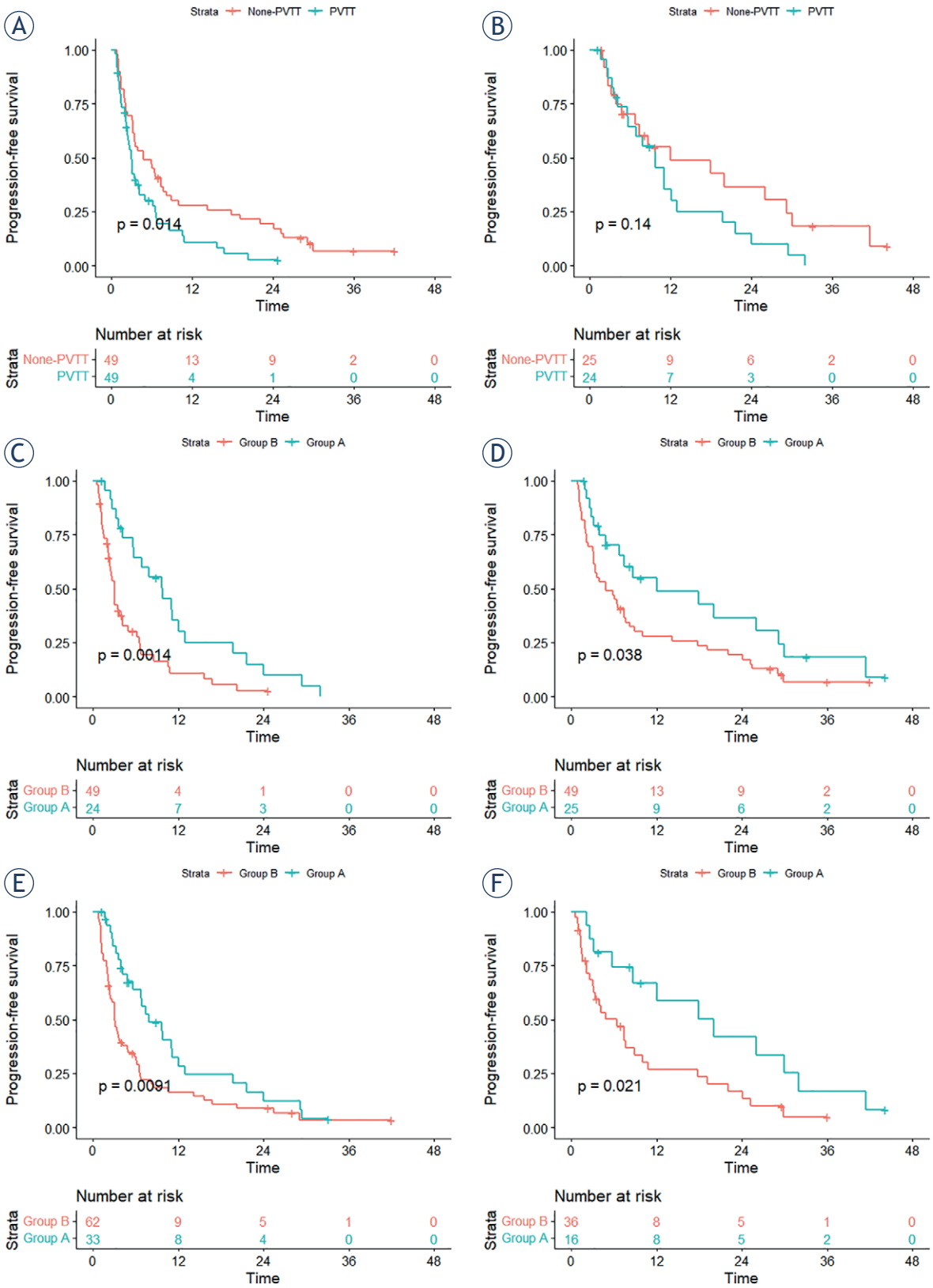

FIGURE 4. Subgroup analyses revealed by Kaplan-Meier curves comparing progression-free survival (PFS). **(A)** Comparison of the PFS between portal vein tumor thrombosis (PVTT) and None-PVTT patients in group B. **(B)** Comparison of the PFS between PVTT and None-PVTT patients in group A. **(C)** Comparison of the PFS between group A and B in patients with PVTT. **(D)** Comparison of the PFS between group A and B in none-PVTT patients. **(E)** Comparison of the PFS between group A and B in high-risk location 1. **(F)** Comparison of the PFS between group A and B in high-risk location 2.

TABLE 4. Complications related to the procedure

Adverse events	Group A (N = 49)	AE Grade			Group B (N = 98)	AE Grade			P value
		1	2	3-4		1	2	3-4	
Fever	3	3	0	0	3	9	10	0	0.608‡
Nausea	5	3	2	0	5	9	11	0	0.852†
Diarrhea	3	2	1	0	3	5	5	0	1‡
Pain required treatment	13	10	3	0	13	39	42	0	0.007†*
Liver abscess	0	0	0	0	0	1	1	0	1‡
Puncture hemorrhage	1	1	0	0	1	5	8	0	0.274‡
Displacement of seeds	0	0	0	0	0	-	-	-	-
RILD	0	0	0	0	0	-	-	-	-

AE = adverse effects; RILD = radiation-induced liver disease
† Pearson $\chi 2$ test was used; ‡ Continuity correction was used
*p value ≤ 0.05 was considered to indicate statistical significance.

Discussion

Our study aims to compare the effectiveness and safety outcome of TACE-MWA-^{125}I with that of TACE-MWA in patients with tumors in high-risk locations. As far as we know, this is the first study addressing this topic. A 1:2 PSM was performed to adjust for a variety of covariates and potential confounders between the two groups.

A peri-hepatic-vein location was a risk factor for the regional recurrence and a peri-portal-vein location was a potential high-risk factor for incomplete RFA in small HCCs.[36] Based on that, the results of our study demonstrated that treatment of high-risk sites contributes to the local tumor control and PFS. The initial intrahepatic tumor DCR and ORR of 85.7% and 51.0%, respectively, in the group A, are slightly higher than the published outcomes of Peng *et al.*, who demonstrated that patients with advanced recurrent HCC treated with TACE-RFA combined with sorafenib received DCR and ORR of 84% and 40.6%, respectively.[7] The PFS yielded higher PFS than the previously TACE-MWA outcomes of Zhang *et al.* (median PFS 4.2 months).[37] The results of the group B in our study were slightly lower than the results presented by Zhang *et al.* which may in part be due to the more advanced stage of HCC (BCLC C) patients included in our study. Considering the theoretical advantages of MWA in the controlling of high-risk site tumors, these results indicated the strengths of TACE-MWA-^{125}I in the local tumor control. As a low-dose rate brachytherapy, X-rays and γ-rays emit from the ^{125}I seeds could suppress the proliferation and induce apoptosis in tumor cells.[38,39] Numerous studies have demonstrated the value of brachytherapy in the locoregional therapies.[21-24] Furthermore, the synergy between brachytherapy and TACE-MWA might further increase the therapeutic effect.[40] The tumors neighboring large vessels, hepatic capsule, or extrahepatic organs, may increase the risk of sublethal temperatures and reversible injury due to the heat sink effect or the limited margin of ablation. But the increased vasodilation and vascular permeability due to the hyperthermia would improve the oxygenation in the high-risk tumors. The cytotoxicity of ^{125}I seeds radiation is primarily oxygen dependent, which might explain the synergy and survival advantages.[39]

The previous studies for the high-risk location related to the thermal ablation have mainly focused on the RFA in the small HCCs. The studies by Kang *et al.* suggested that neither perivascular nor subcapsular was a statistically significant risk factor for the OS outcomes.[41,42] Since the ^{125}I seeds implantation was only targeted at high-risk sites and extrahepatic metastasis occurred in 47.6% (n = 70) patients, there was no significant improvement in OS in our study. Interestingly, previous studies indicated that low dose irradiation could lead to an increase in CD8$^+$T cells and promote antitumor immunity.[43,44] These findings suggest that further combination of systemic therapies such as immunotherapy and targeted therapy may yield better survival benefit.

From the Cox proportional hazards regression, we found that the presence of PVTT was an independent prognostic factor for PFS (P = 0.04). In the

subgroup analysis, we were delighted to find that the difference in PFS between the PVTT and non-PVTT patients in the group B was not detected in the group A, and the group A achieved better PFS in both PVTT and non-PVTT patients. ^{125}I seeds implanted around the portal vein might play a role in the treatment of PVTT. Results from previous studies have indicated the effectiveness of ^{125}I seeds implantation for PVTT which might account for the survival advantages.[45,46] Besides, the TACE-MWA-^{125}I therapy achieved superior PFS in both high-risk location 1 and 2 patients, suggesting its potential broad applicability.

In terms of safety, there were no treatment-related deaths. Most adverse events were considered mild or moderate and easily managed. Our results showed that the combination with ^{125}I did not increase the risk of complications, and the incidence of abdominal pain and Puncture hemorrhage was decreased during the follow-up period ($P < 0.01$, $P = 0.274$). This might be due to the ^{125}I seeds implantation providing a sufficiently safe distance from the ablation boundary to the high-risk location, which could reduce the difficulty and risk of ablation. No brachytherapy-related complications such as displacement of seeds and radiation-induced liver disease were detected during follow-up. In addition, as a less invasive treatment, the utility of stereotactic body radiation therapy (SBRT) for the treatment of HCC in high-risk site compensates for the limitations of thermal ablation and the clinical effectiveness of SBRT plus TACE and AMW is worth further investigation.[47]

Nevertheless, there were several limitations in our study. Firstly, the present study was an observational, retrospective, single-center study with inherent limitations. Secondly, the classification of high-risk locations was more meticulous and comprehensive in previous studies.[36,41,42] Considering the complex anatomical structure of inter- to advance-stage HCC included in this study, the classification stratified by peri-hepatic-vein, peri-portal-vein and subcapsular was hard to apply. We can only make a relatively rough classification by referring to the studies by Teratani *et al.* and Lin *et al.*[31,32] Further comparison based on a more comprehensive classification might reveal more valuable information. Third, the gender distribution in this study was unbalanced (Female 12/147), suggesting the impact of sex on OS might be amplified in the multivariate analysis. larger prospective randomized clinical trials are still needed.

Conclusions

TACE-MWA-^{125}I resulted in longer PFS and better tumor control than did TACE-MWA in patients with unresectable hepatocellular carcinoma in high-risk locations.

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