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ORIGINAL RESEARCH

Transarterial Chemoembolization Plus Radiofrequency Ablation and Iodine-125 Seed Implantation for Hepatocellular Carcinoma in High-Risk Locations: A Propensity Score-Matched Analysis

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Background & Aims: The effect of transarterial chemoembolization (TACE) plus radiofrequency ablation (RFA) (TACE-RFA) for hepatocellular carcinoma (HCC) in high-risk locations is not satisfactory. The aim of this study was to compare the clinical outcomes of TACE-RFA plus iodine-125 (^{125}I) seed implantation (TACE-RFA-^{125}I) therapy with those of TACE-RFA for unresectable HCC (≤5 cm) in high-risk locations.

Methods: From January 2010 to June 2023, the clinical data of 126 patients with unresectable HCC (≤5 cm) in high-risk locations who received TACE-RFA-^{125}I or TACE-RFA treatment were retrospectively analyzed. The clinical outcomes between the two groups were compared after propensity score matching (PSM) analysis.

Results: Forty-six pairs of patients were matched. The local progression-free survival rates at 1-, 2-, 3-, 4-, and 5-years were 100%, 82.4%, 74.8%, 63.5%, and 54% in the TACE-RFA-^{125}I group, which were significantly higher than 91.3%, 69.4%, 50.7%, 29.4%, and 26.7% in the TACE-RFA group, respectively (p = 0.004). The median progression-free survival in the TACE-RFA-^{125}I group was significantly longer than that in the TACE-RFA group (p = 0.002). The overall survival rates at 1-, 2-, 3-, 4-, and 5-years were 100%, 93.4%, 80.7%, 74.9%, and 64.7% in the TACE-RFA-^{125}I group, which were significantly higher than 97.8%, 78%, 68.6%, 51.1%, and 45.3% in the TACE-RFA group, respectively (p = 0.011). There was no occurrence of major complications or procedure-related deaths in the two groups.

Conclusion: Compared with the TACE-RFA treatment, TACE-RFA-^{125}I should be a more effective treatment strategy for patients with unresectable HCC (≤5 cm) in high-risk locations.

Keywords: radiofrequency ablation, transarterial chemoembolization, iodine-125 seed, hepatocellular carcinoma, high-risk locations

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide.[1] Radiofrequency ablation (RFA) has been accepted as an effective alternative to surgery in the management of small- to intermediate-sized (≤5 cm) HCCs.[2–4] However, for RFA of HCCs in high-risk locations (tumors close to the diaphragm, large vessels, liver capsule, gallbladder, gastrointestinal tract, or kidney), it is difficult to achieve an effective and safe ablation periphery with a 1 cm

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surgical margin beyond the tumor confinement for protecting these adjacent critical structures from heat damage, which thus often leads to a local tumor recurrence. Attempts have been made to address this issue, such as RFA combined with transarterial chemoembolization (TACE) or iodine-125 (^{125}I) seed implantation.[5,6] However, the local tumor recurrence rates and patients' long-term survival are still not satisfactory.[7,8] Thus, there is a pressing clinical need to develop a more effective treatment strategy to improve the effect of RFA on HCCs in high-risk locations.

Due to its minimal invasiveness, safety, and effectiveness, ^{125}I seed implantation is a favourable therapy for some solid malignant tumors, including HCC.[9–11] Several previous studies[5,7,12] reported that ^{125}I seed implantation could further improve the effects of TACE or RFA on HCCs. To the best of our knowledge, there was no report of the triple-combination treatment (TACE + RFA + ^{125}I seed implantation) for HCC in high-risk locations.

Percutaneous RFA and ^{125}I seed implantation procedures were usually performed under ultrasound or computed tomography (CT) guidance.[13,14] However, for HCCs in high-risk locations, ultrasound-guided percutaneous RFA or ^{125}I seed implantation is challenging for poor tumor visualization or suboptimal electrode path due to the overlapped ribs, lung, gallbladder, or gastrointestinal tract, which may result in incomplete RFA, thermal injury to the surrounding organs, or uneven distribution of ^{125}I seed in tumors. Although CT imaging usually provides a clearer visualization for such HCCs compared with ultrasound imaging, a CT-guided puncture may result in injury to the diaphragm, blood vessels, gastrointestinal tract, or gallbladder for lack of real-time dynamic imaging. So a real-time and accurate imaging guidance strategy is needed for RFA and ^{125}I seed implantation in the treatment of HCCs in high-risk locations.

In the present study, patients with HCC in high-risk locations were first treated with TACE, followed by RFA and ^{125}I seed implantation treatments (TACE-RFA-^{125}I), which were performed under ultrasound plus CT guidance, and the clinical data of these patients were retrospectively analyzed. The purpose of this study was to evaluate whether this therapy could lead to better tumor control and patients' survival compared with TACE plus RFA (TACE-RFA) for HCC in high-risk locations, and provide a more effective and safe treatment strategy in the management of this type of HCC.

Patients and Methods

Study Design and Patient Selection

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki. The study received approval from the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (Approval no.: UHCT241019). A written informed consent was waived by our ethics committee because of the retrospective nature of this study. From January 2010 to June 2023, the clinical data of 126 hCC patients who received the treatment of TACE-RFA-^{125}I or TACE-RFA in our center was retrospectively analyzed. The clinical outcomes between the two treatment groups were compared after propensity score matching (PSM) analysis. Meanwhile, a subgroup analysis according to tumor size (≤3 cm and 3–5 cm) was performed to compare the effects of these two different treatments in the two subgroups. The report of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies (Supplementary Table 1).

The inclusion criteria of this study were as follows: (1) patients were diagnosed with HCC according to the European Association for the Study of the Liver or American Association for the Study of Liver Disease guidelines;[15,16] (2) patients with HCC in high-risk locations, which were defined as these located < 5 mm of vital structures, such as the diaphragm, large vessels, liver capsule, gallbladder, gastrointestinal tract, and kidneys;[17] (3) a solitary HCC (≤ 5.0 cm) or multiple (up to three) HCC lesions (each ≤ 3.0 cm); (4) patients were not eligible for surgical resection or liver transplantation; (5) the procedures of RFA and ^{125}I seed implantation were performed under combined ultrasound/CT guidance; (6) no vascular invasion or no extrahepatic metastasis; (7) Eastern Cooperative OncologyGroup (ECOG) performance status 0; (8) Child-Pugh class A or B; (9) blood platelet count > 40×10^9 /L. The exclusion criteria of this study were as follows: (1) before TACE-RFA-^{125}I or TACE-RFA treatment, patients received other treatments for HCC, such as stereotactic body radiotherapy, chemotherapy, and liver transplantation, et al; (2) patients were accompanied by other malignancies; (3) patients were accompanied by severe cardiac and renal dysfunction; (4) the clinical data of patients were incomplete or lost to follow-up.

TACE Procedure and Ultrasound Plus CT-Guided RFA and ^{125}I Seed Implantation

All the patients received TACE treatment before RFA and ^{125}I seed implantation procedures, and the TACE procedures were performed as described in our previous study.[18] After TACE, symptomatic treatments and protective liver function treatments were administered to address TACE-related fever, nausea, vomiting, abdominal pain, and liver dysfunction. RFA was performed 5–10 days after TACE. Before RFA treatment, laboratory examinations, such as complete blood count, liver and renal function, and prothrombin time, were performed to assess whether the patients fulfilled the RFA treatment criteria. The RFA procedures were performed with a RITA 1500 generator (RITA Medical Systems Inc., Mountain View, USA) and a 14-gauge multiple electrode (Rita Medical Systems, Mountain View, California, USA) under combined ultrasound/CT guidance, as described in our previous study.[18] The analgesia was conducted by local injection of 5 mL of 2% lidocaine and intravenous administration of 50–100 mg of a flurbiprofen axetil injection (Tide Pharmaceutical Co., Ltd., Beijing, China).

The procedures of ^{125}I seed implantation were performed within 7 days after RFA treatment. The ^{125}I seeds were implanted in the insufficient ablation tumor margin or the highly suspected zone of residual viable tumors. The number and distribution of ^{125}I seed were determined by the Treatment Planning System (TPS) (HGGR300, Hokai Medical Instruments Co., Ltd., Zhuhai, China). An interstitial needle (17-gauge, hollow needles, 15 cm long) was inserted into the site close to the tumor under ultrasound guidance, and then CT images were used to precisely guide the placement of the interstitial needle. A Mick applicator (Mick Radionuclear Instruments, Bronx, NY) was then sequentially attached to the distal end of each needle to place the ^{125}I seed (0.7 millicuries per seed) into the tumor, spaced approximately 1 cm apart along the needle track. After ^{125}I seed implantation, a CT scan was performed again to assess the ^{125}I seed position and the presence of major complications, and the images were transmitted to TPS for dose verification. Adverse events were reported using the Common Terminology Criteria for Adverse Events version 5.0.[19]

Follow-Up

Contrast-enhanced CT or contrast-enhanced magnetic resonance imaging (MRI) of the chest and liver, blood tests such as liver and kidney function, blood routine, and tumor markers were performed at each follow-up. The first follow-up was conducted 4–6 weeks after the initial treatment, and then the patients were reviewed every 3 months during the first year and every 6 months thereafter. Repeated TACE, RFA, or ^{125}I seed implantation was used to treat the recurrent or residual tumors. The follow-up of this study ended on November 30, 2023.

In the present study, local tumor progression was defined as the appearance of any viable tumor within 1 cm from the ablated margin of tumors on CT/MRI images during follow-up, and intrahepatic tumor progression was defined as the occurrence of a new tumor within the liver, except for local tumor progression. Local progression-free survival (LPFS) was defined as the time from the initial TACE to local tumor progression or death from any cause. Progression-free survival (PFS) was defined as the time from the initial TACE to local, intrahepatic, distant tumor progression, or death from any cause. Overall survival (OS) was defined as the time from the initial TACE to any cause of the patients' death. Tumor assessments were conducted by two radiologists with more than 10 years of experience (X.L. and B.L)., and reviewed by an independent radiologist (X.K).

Propensity Score Matching Analysis

A PSM analysis was conducted to reduce the potential biases that may have originated from differences in the baseline characteristics of patients in the present study. A propensity score was generated for each patient from a logistic regression model using 9 variables, including age, gender, Child-Pugh class, Barcelona Clinic Liver Cancer (BCLC) stage, tumor size, tumor number, ascites, hepatitis B virus infection, and serum α-fetoprotein level. Two pairs of matched patients (TACE-RFA-^{125}I or TACE-RFA) were obtained using a 1:1 nearest-neighbor matching algorithm with a caliper of 0.05 and without replacement. Usually a maximum standardized mean difference of 0.1 is considered acceptable.[20]

Statistical Analyses

The x^2 test and Mann–Whitney *U*-test were used for comparison of the baseline characteristics between the two groups. The LPFS, PFS, and OS between the two groups were estimated by the Kaplan-Meier method and compared by the Log rank test. The uni- and multi-variate Cox proportional hazards regression analyses were used to identify the prognostic factors associated with the LPFS, PFS, and OS. The variables with a p value ≤0.1 in the univariate analysis were entered into a multi-variate analysis. All the statistical analyses were performed using SPSS (Version 26, Chicago, Illinois, USA) or R Foundation for Statistical Computing software (Version 4.3.1, Vienna, Austria). The statistical significance was two-tailed, and a p value less than 0.05 was considered statistically significant.

Results

Study Population, Technical Success Rate, and Safety

As described in Figure 1, 126 patients with HCC in high-risk locations were enrolled in this study, including 70 patients in the TACE-RFA group and 56 patients in the TACE-RFA-^{125}I group, and 46 pairs of patients were matched after the PSM analysis. The baseline characteristics of patients between the two groups were balanced after the PSM analysis, which were shown in Table 1. All of the TACE, RFA, or ^{125}I seed implantation procedures of the 46 pairs of patients were successfully performed, and there was no occurrence of major complications or procedure-related deaths (Table 2). The median follow-up period was 43.5 months (range, 31–68 months). One representative case of TACE-RFA-125I therapy for HCC in high-risk locations is shown in Figure 2.

The Tumor Recurrence Rates Between the Two Groups After PSM

The 1-, 2-, 3-, 4-, and 5-years of local recurrence rates in the TACE-RFA-^{125}I group and TACE-RFA group were 0%, 11.1%, 16.9%, 16.9%, 20.1%, and 6.5%, 15.8%, 33.2%, 46.1%, 46.1%, respectively. The overall recurrence rates (including local, intrahepatic distant, and extrahepatic recurrences) at 1-, 2-, 3-, 4-, and 5-years were 2.1%, 24.4%, 38.5%, 53.8%, and 61.5% in the TACE-RFA-^{125}I group and 17.5%, 40%, 66.1%, 81.1%, and 90.9% in the TACE-RFA group, respectively. Both the local and overall recurrence rates in the TACE-RFA-^{125}I group were significantly lower than those in the TACE-RFA group (p = 0.037, p = 0.004).

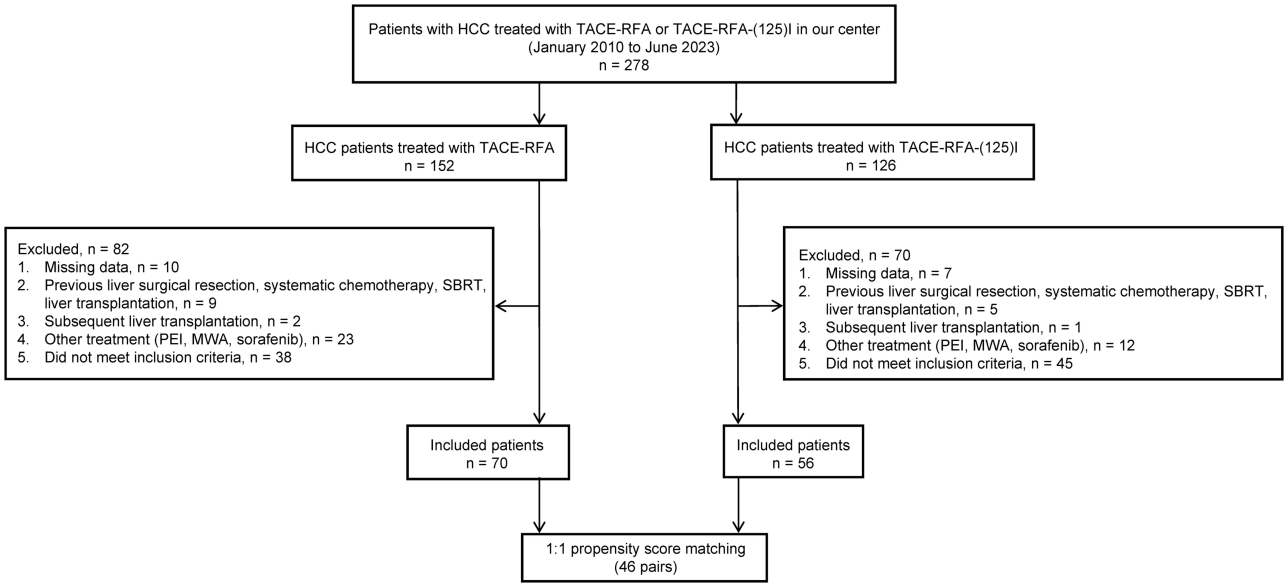

Figure 1 The flow diagram of patient selection.

Abbreviations: HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; ^{125}I, iodine-125; SBRT, stereotactic body radiation therapy; PEI, percutaneous ethanol injection; MWA, microwave ablation.

Table 1 The Patients' Baseline Characteristics Between the TACE-RFA and TACE-RFA-^{125}I Groups Before and After PSM Analysis

Variable	Before PSM (Median, IQR; No., %)		*p* value	After PSM (Median, IQR; No., %)		*p* value
	TACE-RFA (n=70)	TACE-RFA-^{125}I (n=56)		TACE-RFA (n=46)	TACE-RFA-^{125}I (n=46)	
Age (years)	61 (54–69)	59 (56–65)	0.443	61 (54–72)	59 (53–68)	0.356
Gender			0.200			0.765
Male	63 (90.0%)	46 (82.1%)		39 (84.8%)	40 (87.0%)	
Female	7 (10.0%)	10 (17.9%)		7 (15.2%)	6 (13.0%)	
Child-Pugh class			0.026*			0.216
A	45 (64.3%)	46 (82.1%)		42 (91.3%)	38 (82.6%)	
B	25 (35.7%)	10 (17.9%)		4 (8.7%)	8 (17.4%)	
BCLC stage			0.936			0.676
A	32 (45.7%)	26 (46.4%)		23 (50.0%)	21 (45.7%)	
B	38 (54.3%)	30 (53.6%)		23 (50.0%)	25 (54.3%)	
Tumor size (cm)			0.498			0.677
≤3	38 (54.3%)	27 (48.2%)		24 (52.2%)	22 (47.8%)	
3–5	32 (45.7%)	29 (51.8%)		22 (47.8%)	24 (52.2%)	
Tumor number			0.846			0.901
1	50 (71.4%)	38 (67.9%)		35 (76.1%)	35 (76.1%)	
2	11 (15.7%)	11 (19.6%)		8 (17.4%)	7 (15.2%)	
3	9 (12.9%)	7 (12.5%)		3 (6.5%)	4 (8.7%)	
Ascites			0.014*			0.503
Absent	50 (71.4%)	50 (89.3%)		40 (87.0%)	42 (91.3%)	
Mild	20 (28.6%)	6 (10.7%)		6 (13.0%)	4 (8.7%)	
HBV infection			0.302			> 0.999
No	4 (5.7%)	6 (10.7%)		4 (8.7%)	4 (8.7%)	
Yes	66 (94.3%)	50 (89.3%)		42 (91.3%)	42 (91.3%)	
AFP (μg/L)			0.151			0.832
≦400	31 (44.3%)	32 (57.1%)		27 (58.7%)	28 (60.9%)	
>400	39 (55.7%)	24 (42.9%)		19 (41.3%)	18 (39.1%)	

Note: *p value <0.05 was considered to indicate statistical significance.
Abbreviations: TACE, transarterial chemoembolization; RFA, radiofrequency ablation; PSM, propensity score matching; IQR, interquartile range; No., Number; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; AFP, α-fetoprotein.

The Local Progression-Free Survival Between the Two Groups After PSM Analysis

The 1-, 2-, 3-, 4-, and 5-years LPFS rates in the TACE-RFA-^{125}I group were 100%, 82.4%, 74.8%, 63.5%, and 54%, respectively, which were significantly higher than those of 91.3%, 69.4%, 50.7%, 29.4%, and 26.7% in the TACE-RFA group, respectively (p = 0.004; Figure 3A). The uni- and multi-variate analyses demonstrated that the TACE-RFA-^{125}I treatment, tumor size ≤ 3 cm, a solitary HCC, and BCLC stage A were the protective factors for patients' LPFS (Table 3).

The Progression-Free Survival Between the Two Groups After PSM Analysis

The 1-, 2-, 3-, 4-, and 5-years PFS rates in the TACE-RFA-^{125}I group were 97.8%, 69.3%, 53.7%, 38.2%, and 31.8%, respectively, which were significantly higher than those of 84.8%, 54.3%, 29.3%, 16.3%, and 7.2% in the TACE-RFA group, respectively.The median PFS was 42.0 months in the TACE-RFA-^{125}I group, and 29.0 months in the TACE-RFA-^{125}I group (p = 0.002; Figure 3B). The uni- and multi-variate analyses indicated that the TACE-RFA-^{125}I treatment, tumor size ≤3 cm, a solitary HCC, BCLC stage A, and absence of ascites were the protective factors for patients' PFS (Table 4).

The Overall Survival Between the Two Groups After PSM Analysis

At the end of follow-up, 28.3% (13/46) patients in the TACE-RFA-^{125}I group and 56.5% (26/46) patients in the TACE-RFA group died. The 1-, 2-, 3-, 4-, and 5-years OS rates were 100%, 93.4%, 80.7%, 74.9%, and 64.7% in the TACE-RFA-^{125}I group, respectively, which were significantly higher than those of 97.8%, 78%, 68.6%, 51.1%, and 45.3%

Table 2 Adverse Events Related to TACE, RFA and ^{125}I Seeds Implantation After PSM Analysis

Adverse events	TACE-RFA (n=46)	TACE-RFA-^{125}I (n=46)	*p* value
Fever (>38.0°C)			
Total	15 (32.6%)	17 (37.0%)	0.741
Grade 1	14 (30.4%)	16 (34.8%)	
Grade 2	1 (2.2%)	0 (0.0%)	
Grade 3	0 (0.0%)	1 (2.2%)	
Nausea/Vomiting			
Total	19 (41.3%)	17 (37.0%)	0.744
Grade 1	18 (39.1%)	15 (32.6%)	
Grade 2	1 (2.2%)	2 (4.4%)	
Pleural effusion			0.999
Grade 1	1 (2.2%)	0 (0.0%)	
Abdominal pain			
Total	25 (54.3%)	27 (58.7%)	0.789
Grade 1	22 (47.8%)	25 (54.4%)	
Grade 2	3 (6.5%)	2 (4.4%)	
Ascites			
Total	2 (4.3%)	2 (4.3%)	0.999
Grade 1	2 (4.4%)	1 (2.2%)	
Grade 2	0 (0.0%)	1 (2.2%)	
Leukopenia			
Total	0 (0.0%)	4 (8.7%)	0.117
Grade 1	0 (0.0%)	3 (6.5%)	
Grade 2	0 (0.0%)	1 (2.2%)	

Abbreviations: TACE, transarterial chemoembolization; RFA, radiofrequency ablation.

in the TACE-RFA group, respectively (p = 0.011; Figure 3C). The uni- and multi-variate analyses showed that the TACE-RFA-^{125}I treatment, tumor size ≤3 cm, a solitary HCC, BCLC stage A, and Child-Pugh class A were the protective factors for patients' OS (Table 5).

The Subgroup Analyses by Tumor Size After PSM

In the subgroup analysis of patients with tumor size ≤3 cm, the 1-, 2-, 3-, 4-, and 5-years LPFS, PFS, and OS rates in the TACE-RFA-^{125}I group (LPFS rates: 100%, 92.9%, 89.1%, 85.3%, and 72.5%; PFS rates: 100%, 85.7%, 74.7%, 53.1%, and 44.2%; OS rates: 100%, 100%, 96.3%, 92.4%, and 79.8%, respectively) were all significantly better than those in the TACE-RFA group (LPFS rates: 100%, 80%, 69.4%, 44.9%, and 44.9%; PFS rates: 93.3%, 70%, 45.2%, 25.1%, and 11.2%; OS rates: 96.7%, 93.3%, 89.9%, 75%, and 66.5%, respectively) (p = 0.005, p = 0.005, p = 0.040, Figure 4A-C). Meanwhile, the median PFS in the TACE-RFA-^{125}I group was significantly longer than that in the TACE-RFA group (50.0 months vs 34.0 months, p = 0.005, Figure 4B).

As described in Figure 4D-F, in the subgroup analysis of patients with tumor size >3 cm and ≤5 cm, the 1-, 2-, and 3-years LPFS and OS rates in the TACE-RFA-^{125}I group (LPFS rates: 100%, 82.6%, and 49.1%; OS rates: 100%, 82.6%, and 48.7%, respectively) were significantly higher than those in the TACE-RFA group (LPFS rates: 75%, 48.6%, and 13.9%; OS rates: 93.8%, 48.1%, and 24.8%, respectively) (p = 0.034, p = 0.011, respectively). The 1-, 2-years PFS rates in the TACE-RFA-^{125}I group (PFS rates: 94.4%, 42.4%, respectively) were also significantly higher than those in the TACE-RFA group (PFS rates: 56.3%, 25%, respectively) (p = 0.011). In addition, the median LPFS, PFS, and OS in the TACE-RFA-^{125}I group were significantly longer than that of in the TACE-RFA group (median LPFS: 36.0 months vs 23.0 months, p = 0.034; median PFS: 23.0 months vs 17.0 months, p = 0.011; median OS: 36.0 months vs 23.0 months, p = 0.011).

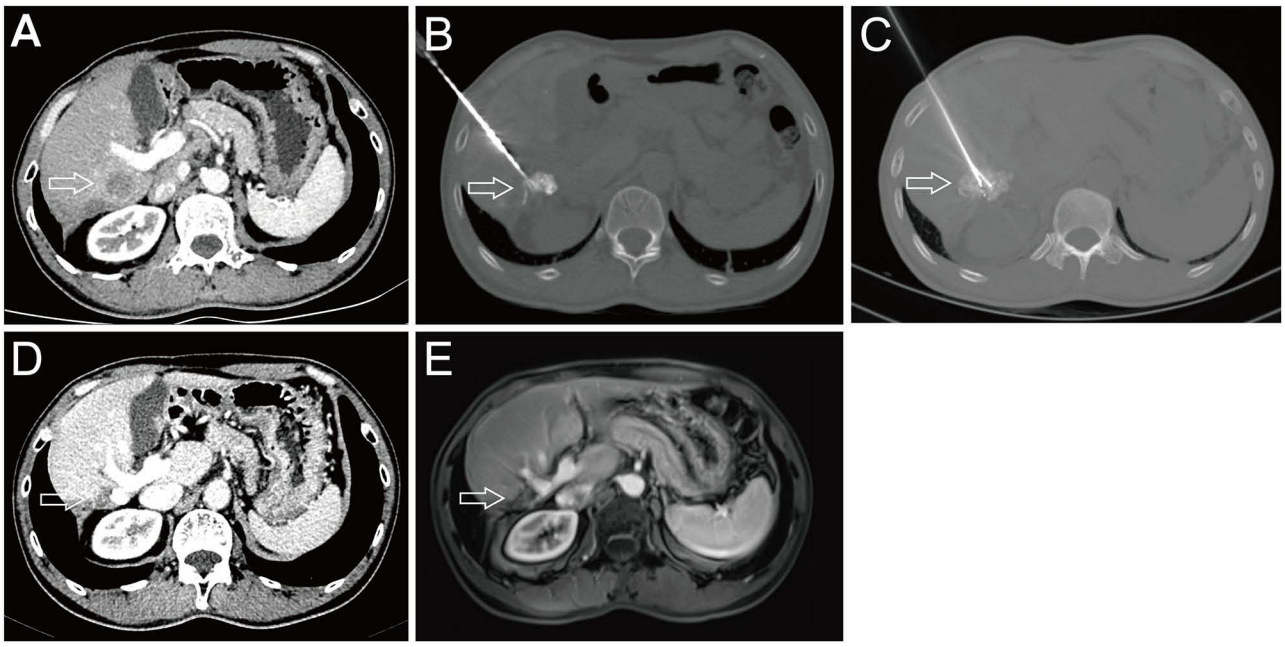

Figure 2 A 58-year-old male patient with an unresectable HCC in high-risk locations received the TACE-RFA-^{125}I treatment. **(A)** A contrast-enhanced CT scan showed a 3 cm HCC (white arrow) near the right branch of the portal vein and the right kidney. **(B)** The RFA treatment for HCC (white arrow) was performed after the TACE. **(C)** The ^{125}I seed implantation for HCC (white arrow) was performed after the RFA treatment. (**D-E**) The follow-up at seven years after TACE-RFA-^{125}I treatment with contrast-enhanced CT and MRI showed a significant shrinkage of tumor size (white arrow), and there was no enhancement of the tumor. Meanwhile, the AFP value decreased from the initial 2800 μg/L to 2.7 μg/L in the last follow-up. The treatment effect of HCC in this patient was a complete response according to the modified Response Evaluation Criteria in Solid Tumors.

Abbreviations: HCC, hepatocellular carcinoma; TACE-RFA-^{125}I, transarterial chemoembolization (TACE) plus radiofrequency ablation (RFA) and iodine-125 seed implantation.

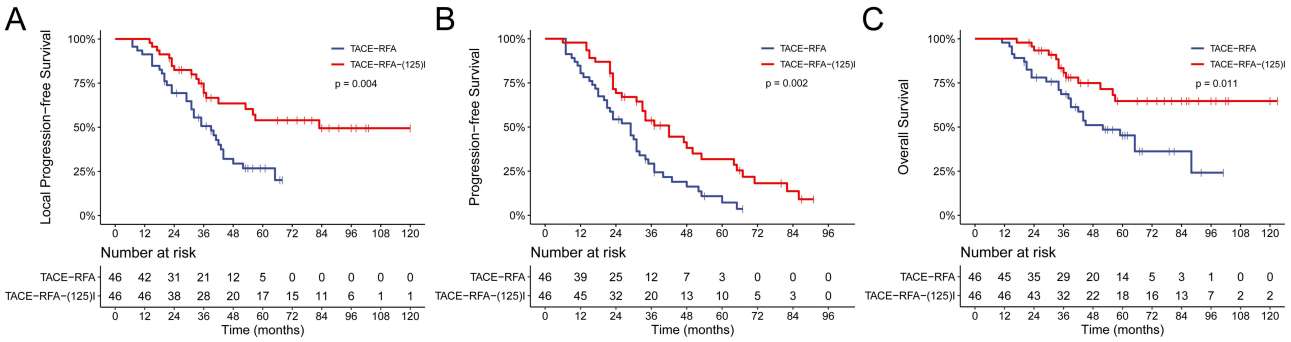

Figure 3 The Kaplan-Meier curves of LPFS, PFS, and OS for patients with HCC in high-risk locations who received TACE-RFA or TACE-RFA-^{125}I treatment after PSM. **(A)** The LPFS rates at 1-, 2-, 3-, 4-, and 5-years in the TACE-RFA-^{125}I group were significantly higher than those in the TACE-RFA group (p = 0.004). **(B)** The PFS rates at 1-, 2-, 3-, 4-, and 5-years in the TACE-RFA-^{125}I group were significantly higher than those in the TACE-RFA group, and the median PFS in the TACE-RFA-^{125}I group was also significantly longer than that of the TACE-RFA group (42.0 months vs 29.0 months, p = 0.002). **(C)** The OS rates at 1-, 2-, 3-, 4-, and 5-years were significantly higher than those in the TACE-RFA group (p = 0.011).

Abbreviations: LPFS, local progression-free survival; PFS, progression-free survival; OS, overall survival; HCC, hepatocellular carcinoma; TACE-RFA, transarterial chemoembolization combined with radiofrequency ablation; TACE-RFA-^{125}I, transarterial chemoembolization plus radiofrequency ablation and iodine-125 seed implantation; PSM, propensity score matching.

Discussion

In recent years, the application of ^{125}I seed implantation in the treatment of some malignant solid tumors extended the indication of brachytherapy, and the therapeutic effectiveness was proven to be preferable, such as in HCC.[7,21] The results of our study showed that, for patients with HCC ≤ 5 cm in high-risk locations, the tumor control and patients' survival in the TACE-RFA-^{125}I group were significantly better than those in the TACE-RFA group. Meanwhile, the results of our study showed that the treatment method of TACE-RFA-^{125}I was an independent protective factor for tumor

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Table 3 The Uni- and Multi-Variate Analyses of LPFS Between the TACE-RFA and TACE-RFA-^{125}I Groups After PSM Analysis

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (years)	0.99 (0.97–1.02)	0.710		
Treatment method				
TACE-RFA-^{125}I	Ref		Ref	
TACE-RFA	2.32 (1.30–4.16)	0.005*	3.35 (1.79–6.26)	<0.001
Gender				
Female	Ref			
Male	2.17 (0.78–6.03)	0.138		
HBV infection				
No	Ref			
Yes	0.87 (0.37–2.05)	0.752		
Tumor size (cm)				
≤3	Ref		Ref	
3–5	6.27 (3.24–12.14)	<0.001*	2.56 (1.14–5.73)	0.022
Tumor number				
1	Ref		Ref	
2–3	2.66 (1.48–4.80)	0.001*	2.84 (1.49–5.43)	0.002
BCLC stage				
A	Ref		Ref	
B	6.84 (3.50–13.36)	<0.001*	3.80 (1.69–8.53)	0.001
AFP (μg/L)				
≤400	Ref			
>400	0.80 (0.45–1.43)	0.445		
Ascites				
Absent	Ref			
Mild	1.50 (0.64–3.54)	0.349		
Child-Pugh class				
A	Ref		Ref	
B	3.83 (1.77–8.33)	<0.001*	2.85 (1.15–7.07)	0.024

Note: *p value ≤0.1 in univariate analysis were included in multivariate analysis.
Abbreviations: LPFS, local progression-free survival; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; Ref, reference; HBV, hepatitis B virus; BCLC, Barcelona Clinic Liver Cancer; AFP, α-fetoprotein.

control and patients' survival outcomes. These outcomes supported the hypothesis that adding ^{125}I seed implantation therapy on the basis of TACE-RFA can further improve the effect of TACE-RFA on unresectable HCC (≤ 5 cm) in high-risk locations.

For unresectable HCC ≤ 5 cm, TACE-RFA or TACE in combination with microwave ablation (TACE-MWA) was a favourable treatment. A previous study[22] reported the OS rates at 1-, 2-, 3-, and 4-years after TACE-RFA for patients with HCCs < 3 cm were 100%, 100%, 84.8%, and 72.7%, respectively, and the recurrence-free survival rates at 1-, 2-, 3-, and 4-years were 71.3%, 59.9%, 48.8%, and 36.6%, respectively. Meanwhile, a randomized controlled trial[23] reported that 93 patients with HCC ranging from 3 to 5cm received TACE-MWA treatment, the recurrence rate at 1 year was 22.47%, and the median OS was 24 months. Compared with these studies, our study focused on HCCs in high-risk locations, the treatment effects of which are usually inferior to those of HCCs in non-high-risk locations under the same treatment. However, in the present study, the results of our study were comparable or superior to those of studies, which indicated TACE-RFA-^{125}I was an excellent treatment strategy for patients with unresectable HCC (≤ 5 cm) in high-risk locations.

Table 4 The Uni- and Multi-Variate Analyses of PFS Between the TACE-RFA and TACE-RFA-^{125}I Groups After PSM Analysis

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (years)	1.01 (0.98–1.03)	0.656		
Treatment method				
TACE-RFA-^{125}I	Ref		Ref	
TACE-RFA	2.07 (1.28–3.34)	0.003*	2.96 (1.75–5.01)	<0.001
Gender				
Female	Ref		Ref	
Male	2.07 (0.98–4.36)	0.057*	1.25 (0.56–2.77)	0.583
HBV infection				
No	Ref			
Yes	1.70 (0.72–4.03)	0.230		
Tumor size (cm)				
≤3	Ref		Ref	
3–5	5.34 (2.89–9.89)	<0.001*	2.67 (1.25–5.68)	0.011
Tumor number				
1	Ref		Ref	
2–3	2.39 (1.38–4.16)	0.002*	3.98 (2.06–7.71)	<0.001
BCLC stage				
A	Ref		Ref	
B	7.44 (3.83–14.43)	<0.001*	5.90 (2.57–13.55)	<0.001
AFP (μg/L)				
≤400	Ref			
>400	0.74 (0.46–1.20)	0.228		
Ascites				
Absent	Ref		Ref	
Mild	3.72 (1.79–7.74)	<0.001*	2.93 (1.34–6.42)	0.007
Child-Pugh class				
A	Ref		Ref	
B	1.96 (0.95–4.02)	0.067*	1.08 (0.46–2.53)	0.862

Note: *p value ≤0.1 in univariate analysis were included in multivariate analysis.
Abbreviations: PFS, progression-free survival; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; Ref, reference; HBV, hepatitis B virus; BCLC, Barcelona Clinic Liver Cancer; AFP, α-fetoprotein.

The possible potential mechanisms of TACE-RFA-^{125}I for HCC are as follows: (1) the tumor-killing effect of hyperthermia and radiotherapy complement each other. The tumor cells in the S phase of the cell cycle are less sensitive to radiotherapy, but respond relatively better to hyperthermia. Meanwhile, the sensitivity of anoxic tumor cells to radiotherapy is lower, but that to hyperthermia is relatively stable;[24,25] (2) radiofrequency hyperthermia could increase the vasodilation and vascular permeability in the treated peritumoral area, which could increase the oxygen supply of this area, and subsequently improve the treatment effect of radiotherapy on HCC;[26,27] (3) the RFA treatment could trigger the systemic anti-tumor immune response, and subsequently enhance the anti-tumor effect of radiotherapy;[28] (4) TACE treatment could embolize the tumor blood vessels and reduce the influence of heat-sink effect;[29,30] (5) the deposition of lipiodol in the tumor after TACE treatment can be used as a marker, which helps to achieve a precise RFA and iodine-125 seed implantation treatment. Based on these potential mechanisms, the triple combination treatment (TACE-RFA-^{125}I) strategy was used for unresectable HCC in high-risk locations in the present study.

MWA of HCC is becoming increasingly popular as MWA allows for a larger ablation zone in a relatively short time. However, for MWA of HCC in high-risk locations, this feature may cause thermal injury to the adjacent important structures of HCC, such as the biliary and gastrointestinal tracts. Compared to MWA, RFA has the characteristic of a slower heating

Table 5 The Uni- and Multi-Variate Analyses of OS Between the TACE-RFA and TACE-RFA-^{125}I Groups After PSM Analysis

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (years)	0.98 (0.95–1.02)	0.315		
Treatment method				
TACE-RFA-^{125}I	Ref		Ref	
TACE-RFA	2.34 (1.20–4.56)	0.013*	4.60 (2.11–10.00)	<0.001
Gender				
Female	Ref			
Male	2.47 (0.76–8.06)	0.133		
HBV infection				
No	Ref			
Yes	1.21 (0.43–3.43)	0.713		
Tumor size (cm)				
≤3	Ref		Ref	
3–5	11.76 (5.07–27.26)	<0.001*	7.46 (2.68–20.74)	<0.001
Tumor number				
1	Ref		Ref	
2–3	2.66 (1.38–5.14)	0.004*	3.44 (1.66–7.11)	<0.001
BCLC stage				
A	Ref		Ref	
B	8.38 (3.71–18.90)	<0.001*	3.40 (1.30–8.89)	0.013
AFP (μg/L)				
≤400	Ref			
>400	1.23 (0.65–2.33)	0.532		
Ascites				
Absent	Ref			
Mild	1.13 (0.40–3.20)	0.819		
Child-Pugh class				
A	Ref		Ref	
B	6.79 (2.83–16.30)	<0.001*	5.84 (2.00–17.00)	0.001

Note: *p value ≤0.1 in univariate analysis were included in multivariate analysis.
Abbreviations: OS, overall survival; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; Ref, reference; HBV, hepatitis B virus; BCLC, Barcelona Clinic Liver Cancer; AFP, α-fetoprotein.

rate, and thus it may reduce the risk of thermal damage to the surrounding tissues of ablated tumors. Therefore, in the present study, we used RFA instead of MWA for HCC. In addition, in this study, RFA and ^{125}I seed implantation were performed under ultrasound plus CT guidance. The advantages of co-guidance with ultrasound and CT are real-time, fast, and precise. Meanwhile, compared with CT guidance alone, it can reduce X-ray radiation to patients. We believed these were the main reasons for the absence of major complications and procedure-related deaths in our study.

Our study had limitations. This is a single center and retrospective study. Although a PSM analysis was performed to reduce the potential selection bias, it could not be completely avoided. So a prospective multi-center randomized controlled trial is necessary to confirmed the results of this study.

Conclusions

Compared with TACE-RFA treatment, TACE-RFA-^{125}I should be a more effective therapy for patients with unresectable HCC (≤5 cm) in high-risk locations. TACE-RFA-^{125}I under ultrasound plus CT guidance is an excellent and safe treatment strategy for this type of unresectable HCC, and is worth of clinical promotion and application.

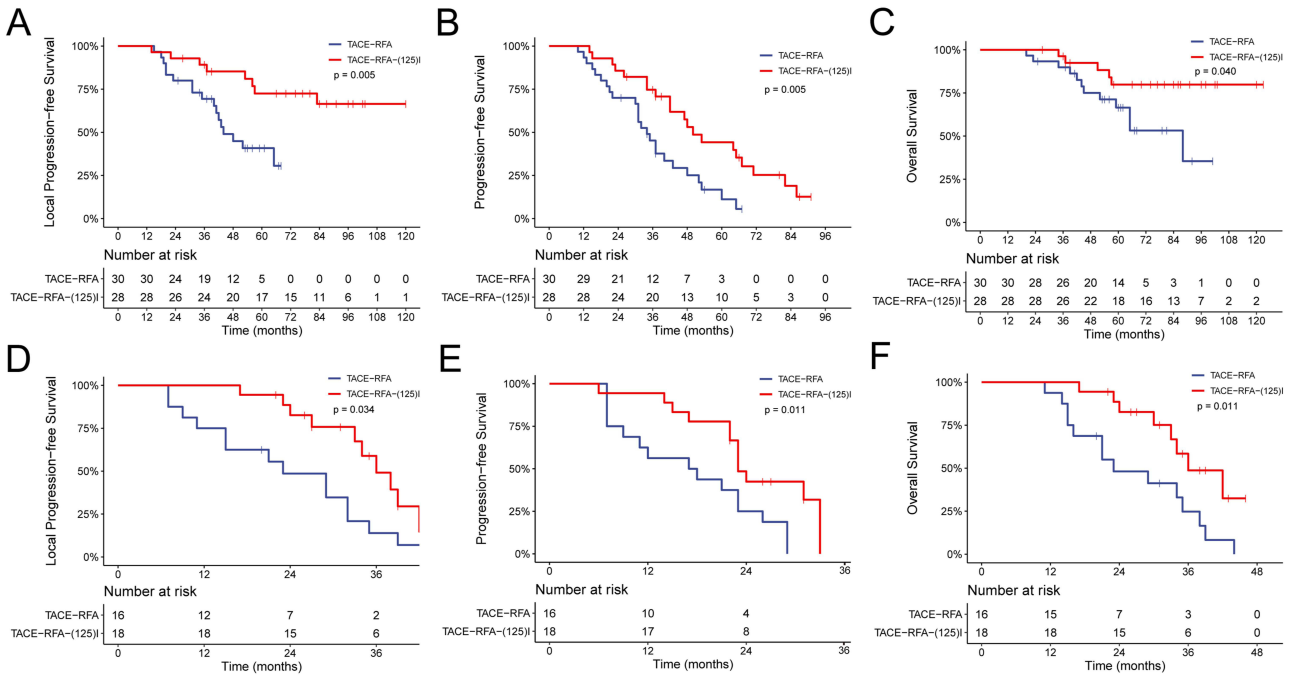

Figure 4 The Kaplan-Meier curves of subgroup analyses for patients with tumor size ≤3 cm and 3–5 cm after PSM. For HCCs sized ≤3 cm, the 1-, 2-, 3-, 4-, and 5-years LPFS, PFS, and OS rates in the TACE-RFA-^{125}I group were significantly higher than those in the TACE-RFA group (p = 0.005, p = 0.005, p = 0.040, respectively) (**A-C**), and the median PFS in the TACE-RFA-^{125}I group was also significantly longer than that of the TACE-RFA group (**B**). For HCCs sized >3 and ≤5 cm, the 1-, 2-, and 3-years LPFS and OS rates in the TACE-RFA-^{125}I group were significantly higher than those of in the TACE-RFA group (p = 0.034, p = 0.011, respectively) (**D, F**), the 1-, 2-years PFS rates in the TACE-RFA-^{125}I group were significantly higher than those of in the TACE-RFA group (p = 0.011) (**E**), and the median LPFS, PFS, and OS in the TACE-RFA-^{125}I group were also significantly longer than those of in the TACE-RFA group (**D-F**).

Abbreviations: PSM, propensity score matching; HCC, hepatocellular carcinoma; LPFS, local progression-free survival; PFS, progression-free survival; OS, overall survival; TACE-RFA, transarterial chemoembolization combined with radiofrequency ablation; TACE-RFA-^{125}I, transarterial chemoembolization plus radiofrequency ablation and iodine-125 seed implantation.

Abbreviations

TACE, transarterial chemoembolization; RFA, radiofrequency ablation; HCC, hepatocellular carcinoma; LPFS, local progression-free survival; PFS, progression-free survival; OS, overall survival; PSM, propensity score matching.

Ethical Approval

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki. The study received approval from the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (Approval no.: UHCT241019). A written informed consent was waived by our ethics committee because of the retrospective nature of this study. All patients' data was handled with strict confidentiality and anonymity. All patients' data was handled with strict confidentiality and anonymity. The data used in this study was anonymized and securely encrypted to protect patients' privacy.

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Disclosure

The authors declare no competing interest in this work.

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