Transarterial Chemoembolization Combined with Iodine 125 Seeds Versus Transarterial Chemoembolization Combined with Radiofrequency Ablation in the Treatment of Early and Intermediate Hepatocellular Carcinoma

chen lei
Wuhan Union Hospital https://orcid.org/0000-0003-0018-9993
Xuefeng Kan
Wuhan Union Hospital
Tao Sun
Wuhan Union Hospital
Yanqiao Ren
Wuhan Union Hospital
Yanyan Cao
Wuhan Union Hospital
Liangliang Yan
Wuhan Union Hospital
Bin Liang
Wuhan Union Hospital
Bin Xiong
Wuhan Union Hospital
Chuansheng Zheng (hqzcsxh@sina.com)
https://orcid.org/0000-0002-2435-1417

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Abstract

Background

To compare the efficacy of the combination of transarterial chemoembolization (TACE) and iodine 125 seeds implantation (TACE-Iodine 125) with the combination of TACE and radiofrequency ablation (RFA) in the treatment of patients with early and intermediate hepatocellular carcinoma (HCC).

Methods

The study included 134 patients diagnosed with early and intermediate HCC from January 1, 2014, to May 31, 2018. Among them, 47 patients were treated with TACE-Iodine 125, and 87 with TACE-RFA and the efficacy of both treatments was analyzed. To reduced selective bias, propensity score matching (PSM) was used to compare the outcomes of the treatments.

Results

In the absence of PSM, the median overall survival (OS) and progression-free survival (PFS) of the TACE-RFA group were slightly longer than those of the TACE-Iodine 125 group (OS: 42 months vs. 37 months; PFS: 18 months vs. 15 months). However, there was no significant difference in median OS, PFS, and the objective response rate (ORR) between the two groups (P>0.05). After adjusted for age, gender, liver resection, Child-Pugh class, Barcelona Clinic Liver Cancer (BCLC) stage and Alpha-fetoprotein (AFP), TACE-Iodine 125 treatment was not associated with a significant increasing in risk of death (HR: 0.725; 95%CI: 0.423,1.241, P=0.241) and recurrence (HR: 1.008; 95%CI: 0.666,1.526, P=0.969). After PSM, 47 patient pairs were generated, and there was no significant difference in median OS and PFS between the two groups.

Conclusions

The combination of TACE and iodine 125 seeds implantation may represent an effective treatment for patients with early and intermediate HCC.

Introduction

Hepatocellular carcinoma (HCC) is one of the deadliest cancers[1]. The recommended first-line treatments for patients with early HCC include surgical resection, liver transplantation, or ablation, while transarterial embolization (TACE) is the treatment of choice for patients in intermediate stages of the disease[2]. In China, the application of liver transplantation is limited due to the high cost and shortage of organs. The efficacy of radiofrequency ablation (RFA) treatment is similar to that of surgical resection when the volume of the malignant liver nodule does not exceed 3 cm[3, 4]. In the case of larger tumors, a fraction of cancer cells can still survive due to heat-sink effect[5] if the tumor is located near blood vessels, diminishing the efficacy of RFA. Therefore, combined therapy is used to treat patients with tumors larger than 3 cm. It has been reported that patients with early or intermediate HCC have better survival after the

TACE-RFA treatment than after receiving a single treatment by RFA or surgical resection[6–9]. However, the use of RFA in the treatment of HCC is problematic when the tumor is located in certain anatomic regions, such as blood vessels, diaphragm, or the heart. For these patients, radiotherapy might be a good choice. Comparison of the effects of external stereotherapy and RFA in the treatment of patients with early HCC indicated that the median overall survival (OS) was similar after both types of therapies. [10].

Recently internal radiotherapy has been used to treat several types of tumors, and was effective in the treatment of HCC[11–14]. Internal radiotherapy of HCC mainly includes the implantation of iodine 125 seeds and transarterial radioembolization. The half-life of iodine 125 is 59.6 days, ensuring tumor cell killing for a prolonged time. Iodine 125 radiates mostly X-rays and γ-rays to induce mutations and/or damage in the DNA of tumor cells, triggering their apoptosis[15]. Typically, in the treatment of HCC, the implantation of iodine 125 seeds is combined with other modalities, such as RFA or surgery[16, 17]. It has been demonstrated that at different stages of HCC, the combination of TACE with iodine 125 seeds implantation provides longer patient survival than TACE alone[18, 19]. However, the efficacy of TACE-Iodine 125 seeds implantation in early and intermediate stages of HCC is still unclear. Moreover, there are no studies focusing on the comparison of the efficacy of TACE-Iodine 125 seeds implantation with TACE-RFA in patients with early and intermediate HCC. Thus, the objective of the present study was to estimate the efficacy of TACE-Iodine 125 seeds implantation and compare it with TACE-RFA in patients with early-intermediate HCC.

Materials And Methods

Study Cohort

The medical records of consecutive 297 patients diagnosed with HCC who received RFA or iodine − 25 seeds implantation treatment at our hospital between January 1, 2014, and May 31, 2018, were retrospectively reviewed. According to the inclusion and exclusion criteria, a total of 134 patients were included in this study (Appendix Fig. 1). Approval for this investigation was obtained from the Ethics Committee of our college Institutional Review Board. The requirement to obtain informed consent was waived by the Institutional Review Board.

The decision to perform the TACE-RFA or TACE-Iodine 125 seeds implantation was based on the multidisciplinary liver conference and patients' preference prior to the operation. Patients with early HCC were recommended to receive surgical resection, liver transplantation, or RFA. Among them, some patients were not candidates for the RFA treatment due to a suboptimal location of the tumor, and some declined the surgery because they had been treated surgically before inclusion in this study. For these patients, iodine 125 seeds were recommended as the first-line treatment. All patients with early HCC were recommended to receive the TACE treatment because of the available evidence that the efficacy of combined TACE-RFA or TACE-Iodine 125 seeds implantation therapies is better than a single treatment. Patients with intermediate HCC were recommended to undergo TACE treatment. In these cases, RFA or

iodine 125 seeds implantation acted as the adjuvant therapy because of the low tumor necrosis rate following the TACE treatment.

The inclusion criteria in this study were: (1) diagnosis of primary early-intermediate HCC by biopsy or imaging, based on European Association for the Study of the Liver (EASL) guideline and Barcelona Clinic Liver Cancer (BCLC) stage[2]; (2) no previous TACE or RFA or iodine 125 seeds implantation treatment; (3) good liver function (Child-Pugh class A or B); (4) the Eastern Cooperative Oncology Group (ECOG) score of 0; (4) the platelet count higher than 40×10^9/L; (5) absence of diffuse liver cancer; (6) no history of liver cancer rupture.

Techniques

The extent of hepatic tumor burden was assessed before the surgery by triple-phase computed tomography (CT) or magnetic resonance imaging (MRI). The liver function and patients' medical condition were determined by laboratory tests and physical examination, respectively.

Transarterial Chemoembolization

The TACE was performed by two operators who had, respectively, at least eight years and twenty years of experience in performing this type of procedures. Initially, the tip of a 5-French catheter (Cook, Bloomington, IN, USA) or 3-French microcatheter (Progreat, Terumo, Tokyo, Japan) was advanced into the tumor-feeding arteries. Then, an emulsion was prepared by mixing 1 part of lipiodol (Lipiodol Ultrafluido, Guerbet, Villepinte, France) and 2 parts of doxorubicin hydrochloride (Hisun Pharmaceutical Co. Ltd, Zhejiang, China). Depending on the liver function and the tumor size, 5–10 ml of the emulsion was injected through the catheter into the tumor-feeding arteries. Lastly, embolization with gelatin sponge seeds (300–700 μm, Cook) was performed until the stasis of arteries flow was achieved.

Iodine 125 Seeds Implantation

Iodine 125 seeds implantation was performed by three operators with seven, ten, and fifteen years of experience in interventional radiology therapy, respectively. The iodine 125 seeds were implanted into the tumors under the guide of ultrasound and CT. The iodine 125 seeds were enclosed in the NiTinol capsule (China Institute of Atomic Energy, Beijing, China). The seeds, 0.8 mm in diameter and 4.5 mm in length, were implanted at 2–3 weeks after TACE. One week before the implantation, the patients underwent a CT scan, and the obtained images were transmitted to the Treatment Planning System (TPS). The number and positions of the iodine 125 seeds were determined by TPS according to the minimum peripheral dose (mPD, 90 to 165 Gy) prescribed for each tumor. Thus, X- and γ-rays could cover the planned target volume, including the tumor and 0.5-1 cm of adjacent non-tumorous tissue. The placement of the needles (18-gauge, XinKe Pharmaceutical Ltd, Shanghai, China) was performed under CT guidance, and the seeds

were implanted into tumors at the interval of 1 to 1.5 cm through the needles. In the current study, a median of 20 seeds (range: 1–48 seeds) were implanted in each patient.

Radiofrequency Ablation

All RFA procedures utilized the guide of ultrasound and were conducted 1–2 weeks after TACE. The protocol was performed by two operators with twenty-three and thirty-two years of experience in interventional radiology, respectively. The tumor location was determined by ultrasound. Local lidocaine anesthesia was applied to relieve a patient's pain from puncture needles. Two grounding pads were attached to the patient's legs. Subsequently, the probe needles were inserted into the tumor under the guide of real-time ultrasound. After the tips of probe needles were placed in the tumor, the RFA needle with 5 hook-shaped expandable electrodes with a diameter of 3.5 cm at expansion (Rita Medical System, Mountain View, CA, USA) was extended to cover the tumor and 1 cm adjacent non-tumorous tissue. The ablation temperature was kept at 90–100 °C for 10–15 minutes. To ascertain that the ablation was complete, patients received enhanced CT scan to ensure that no residual tumor remained. Otherwise, the RFA was repeated to achieve a complete ablation.

Assessment Of Clinical Outcomes And Follow-up

The primary endpoint was overall survival (OS). The secondary endpoints were progress-free survival (PFS) and objective response rate (ORR). OS was defined as the time from the initial TACE procedure until the last follow-up or patient death. PFS was defined as the time from the first implantation of iodine 125 seeds or RFA treatment to the time of the diagnosis of tumor progression or patient death; this definition was based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST)[20]. The ORR was defined as the percentage of patients with a response rated as a complete response (CR) and partial response (PR). CR was defined as no enhancement in the arterial stage, and PR was defined as 30% off of the treated tumor with a residual arterial enhancement. Tumor progression was defined as an increase in the size of the treated tumor by 20%, interval development of new intrahepatic tumors, or metastasis based on the mRECIST assessment.

All patients underwent follow-up laboratory and imaging examination, and the end of the follow-up period was May 31, 2019. The median follow-up time was 29 months (range: 5–63 months). Patients were evaluated one month after initial treatment and then every two months by laboratory tests, contrast-enhanced CT, or contrast-enhanced MRI. The imaging results were evaluated by two radiologists and an interventional radiologist to decide whether the patient should receive a repeated treatment (TACE, RFA, or iodine 125 seeds implantation). The number of treatments for every patient was recorded.

Statistical analysis

The preoperative characteristics of patients in the two groups were recorded and compared. Continuous variables were compared by Student's t-test and Mann-Whitney U test, and categorical variables were analyzed by the Chi-square test and Fisher's exact test. OS and PFS in the two groups and subgroups were calculated by the Kaplan-Meier method. Cox proportional risk method was used to analyze the predictors for death and recurrence and adjusted for age, gender, liver resection, Child-Pugh, BCLC stage and AFP. All tests were two-tailed, and the P-value of less than 0.05 was considered statistically significant. SPSS v24.0 (IBM, Chicago, IL, USA) was used to perform all statistical analyses.

Propensity Score Matching

Propensity score matching (PSM) was applied to reduce the effect of selection bias and potential confounding effects. The following baseline characteristics of patients were included in the PSM assessment: age, gender, alanine aminotransferase (ALT), hemoglobin, platelet, lymphocyte, neutrophil, leukocyte, surgery, hepatitis B virus (HBV), alpha-fetoprotein (AFP) level, TACE number, number of tumors, tumor size level, Child-Pugh class, BCLC stage. A 1:1 ratio matching with an optimal caliper of 0.2 without replacement generated 47 pairs of patients. After the PSM, there was no significantly statistical difference of baseline characteristics (Table 1).

Results

Patients

From the total of 297 patients treated with RFA or iodine 125 seeds implantation, 134 patients met the inclusion criteria. Among them, 87 received TACE-RFA treatment, and 47 patients received TACE-iodine 125 seeds implantation treatment. The baseline preoperative characteristics of the patients are listed in Table 1. Mean age of all patients was 57.5 years (range: 32–80 years); it averaged 57.4 years (range: 32–77 years) in the TACE-RFA group and 57.9 years (range: 33–80 years) in the TACE-Iodine 125 seeds implantation group. In all patients, the operation was successfully performed. In the TACE-RFA group, 81 patients received one RFA treatment, and 6 patients received two treatments. In TACE-iodine 125 seeds implantation group, 30 patients received one iodine 125 seeds implantation treatment, 12 patients received two treatments, 2 patients received three treatments, and 3 patients received four treatments.

Overall Survival And Progression Free Survival

Analysis of data before PSM has shown that 44 (50.6%) patients had died in the TACE-RFA group and 22 (46.8%) patients had died in the TACE-iodine 125 seeds implantation group. The median OS in the TACE-RFA group was 42 months (95%CI: 35.4, 48.6 months), which was slightly longer than in the TACE-Iodine 125 seeds implantation group (37 months, 95%CI: 29.8, 44.2 months). There was no significant difference in median OS between the two groups (P = 0.551) (Fig. 1A). The median PFS in the TACE-RFA and TACE-iodine 125 seeds implantation groups was 18 months (95%CI: 14.7, 21.3 months) and 15

months (95%CI: 10.5, 19.5 months), respectively. There was no significant difference in median PFS between the two groups (P = 0.526) (Fig. 1B). The ORR was comparable with both types of treatment (71.3% in the TACE-RFA group, 74.5% in the TACE-Iodine 125 seeds implantation group, P = 0.692).

When adjusted for age, gender, liver resection, Child-Pugh class, BCLC stage and AFP, level, the results of cox regression analysis of all patients before PSM determined that TACE-Iodine 125 treatment was not associated with increased mortality (HR:0.725; 95%CI: 0.423,1.241, P = 0.241) and recurrence (HR:1.008; 95%CI: 0.666,1.526, P = 0.375) (Table 2, Table 3).

After the PSM protocol, 47 patient pairs were identified. The median OS in the TACE-RFA group was 41 months (95%CI: 27.1, 54.9 months), which was slightly longer than in the TACE-Iodine 125 seeds implantation group (37 months, 95%CI: 29.8, 44.2 months); this difference did not reach statistical significance (P = 0.535) (Fig. 2A). No significant difference of median PFS was present between the two groups (TACE-RFA: 17 months, 95%CI: 13, 21 months, and TACE-Iodine 125 seeds implantation: 15 months, 95%CI: 14.7, 21.3 months; P = 0.848) (Fig. 2B). The ORR did not differ significantly (P = 0.264) between the TACE-RFA group (66.7%, 30 of 47 pairs) and the TACE-Iodine 125-seeds implantation group (74.5%, 35 of 47 pairs). The cox regression analysis of all patients showed that TACE-Iodine 125 treatment was not associated with increased mortality (HR:0.860; 95%CI: 0.477,1.552, P = 0.618) and recurrence (HR:1.319; 95%CI: 0.826,2.099, P = 0.243) (Table 4).

Complications

There were no procedure-related mortalities and no iodine 125 particle migration from the tumor to the lung, heart, or other organs. One patient died for liver failure 2 days after receiving the third treatment with iodine 125 seeds implantation. After PSM, leucopenia, increased ALT, and fever were significantly worse in the TACE-iodine 125 seeds implantation group than in the TACE-RFA group. Fever, liver pain, nausea, and fatigue typically occurred from 1 to 7 days postoperatively and were relieved in 1–2 weeks after receiving treatment for the symptoms (Table 5).

Discussion

In our institution, surgery and RFA are recommended as the first-line treatment for patients with early stages of HCC, and TACE is recommended as the first-line treatment for patients with intermediate stages of HCC. The combination of TACE and RFA was deemed appropriate for patients with early HCC since previous studies had demonstrated better outcomes in patients receiving combined therapies than in those subjected to a single treatment[21, 22]. Iodine 125 seeds implantation was used as a treatment option for patients who were not candidates for RFA or surgery or patients willing to receive the treatment due to its low cost and risk. At present, it is well-established that the combination of TACE and iodine 125 seeds implantation is more effective in the treatment of HCC than TACE alone. However, whether iodine 125 is more beneficial than RFA remain unknown. Thus, the purpose of this study was to determine

whether TACE-Iodine 125 seeds implantation is a feasible treatment option for patients unfit or unwilling to undergo TACE-RFA.

The implantation of iodine 125 seeds has been used in the treatment of HCC, and its therapeutic efficacy was encouraging. The advantage of this procedure in the treatment of tumors is that it rarely damages the surrounding normal tissue given its limited radiation distance. A study comparing the efficacy of RFA alone and the combination of RFA and iodine 125 seeds implantation in the treatment of early HCC has demonstrated that the RFA-Iodine 125 group had longer survival than the group treated with RFA alone[16]. Additional studies have compared the effects of TACE-Iodine 125 seeds implantation with those of TACE alone in the treatment of HCC based on BCLC stage or tumor size; the results indicated better outcomes in patients treated with the combination therapy[18, 23, 24].

The current study did not identify differences in OS and PFS between the two groups. The ORR was similar in the TACE-RFA group and the TACE-Iodine 125 seeds implantation group. Previous studies implied that BCLC stage, AFP level, and Child-Pugh class, among others, might influence the outcomes in HCC patients treated with various therapies. Here, the patients receiving TACE-RFA and TACE-Iodine 125 seeds implantation were compared based on liver resection, BCLC stage, AFP level and Child-Pugh class. The results indicated that TACE-Iodine 125 treatment won't increase mortality and recurrence compared with TACE-RFA treatment. To reduce the impact of selective bias on the comparison of the therapeutic efficacy of the two treatments, PSM was performed. The matching factors used for PSM included tumor burden, liver function, physical capacity, and risk factors of HCC. After PSM, there was no significant difference in OS, PFS, and ORR between the two groups.

Concerns regarding the possibility of damaging organs surrounding the tumor by X-ray and γ-ray and bleeding resulting from the insertion of needles into a vascularized organ have limited the use of implantation of iodine 125 seeds in HCC treatment. However, in this study, only two patients suffered from hepatic hemorrhage in the TACE-iodine 125 group, migration of particles to other organs was not observed. However, postoperative fever, increased ALT, and leucopenia were more frequent in patients treated with TACE-Iodine 125 than in the TACE-RFA group. The symptoms were relieved by symptomatic treatment. Thus, TACE-Iodine 125 seeds implantation treatment appears as safe as the TACE-RFA treatment.

Although this study provided encouraging results on the TACE-Iodine 125 seeds implantation treatment in patients with early and intermediate HCC as compared with the TACE-RFA treatment, some limitations have to be acknowledged. First, despite the implementation of PSM, an inherent selection bias might be present due to the retrospective character of the study. Second, the follow-up time was not long, which might have lead to an underestimation of OS and PFS. However, the obtained results are encouraging and document the feasibility and efficacy of a novel selective treatment for patients with early and intermediate HCC.

Conclusion

The combined treatment with TACE and implantation of iodine 125 seeds may be an alternative and safe therapy for patients with early and intermediate HCC who cannot undergo RFA or surgery.

Abbreviations

TACE
Transarterial chemoembolization
RFA
Radiofrequency ablation
HCC
Hepatocellular carcinoma
PSM
Propensity score matching
OS
Overall survival
PFS
Progress-free survival
ORR
Objective response rate
EASL
European Association for the Study of the Liver
BCLC
Barcelona Clinic Liver Cancer
ECOG
Eastern Cooperative Oncology Group
mRECIST
modified Response Evaluation Criteria in Solid Tumors
CR
Complete response
PR
Partial response
ALT
Alanine aminotransferase
AST
Aspartate aminotransferase
HBV
Hepatitis B virus
AFP
Alpha-fetoprotein
CT

Computed Tomography
MRI
Magnetic Resonance

Declarations

Ethics approval and consent to participate: Approval for this investigation was obtained from the Ethics Committee of our college Institutional Review Board. The requirement to obtain informed consent was waived by the Institutional Review Board.

Available of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions:

ZCS, CL and KXF analyzed and interpreted the patient data. CL, KXF and ST performed the data collection. XB, LB and ZCS performed the operations. CL, RYQ, CYY and YLL writ the manuscript. All authors read and approved the final manuscript.

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Authors' information: CL, MD[1,2], KXF, MD[1,2], ST, MD[1,2], RYQ, MD[1,2], CYY, MD[1,2], YLL, MD[1,2], LB, MD, PhD[1,2], XB, MD, PhD[1,2], ZCS, MD, PhD[1,2]

[1] From the department of Radiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, China;

[2] From Hubei Province Key Laboratory of Molecular Imaging, Wuhan, 430022, China.

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Tables

Table 1: The baseline characteristics of patients before and after PSM

Characteristics	TACE-Iodine 125 group	TACE-RFA group before PSM	P^a value	TACE-RFA group after PSM	P^b value
Age (Years)	57.9±10.1	57.4±9	0.752	56.9±8.7	0.593
ALT (U/L)	38.6±20.7	46.8±39	0.181	43.6±26.9	0.317
Hemoglobin (g/L)	123.1±20.4	128.3±22.6	0.195	128±24.4	0.293
Platelet ($\times 10^9$/L)	119.6±61.1	133.5±69.5	0.251	144.3±73.4	0.08
Lymphocyte($\times 10^9$/L)	1.2±0.6	1.3±0.6	0.564	1.2±0.6	0.996
Neutrophil ($\times 10^9$/L)	3.1±2.3	3.1±1.8	0.953	3.1±1.7	0.994
Leukocyte ($\times 10^9$/L)	5.1±2.9	5.1±2.4	0.945	5±2.3	0.981
Liver resection (Yes/No)	9/38	13/74	0.53	7/40	0.583
Gender (male/female)	37/10	75/12	0.264	39/8	0.600
HBV+/-	29/18	66/21	0.085	32/15	0.517
AFP (>200ug/L)	9/38	18/69	0.832	12/35	0.458
TACE number (≥2)	41/6	61/26	0.027	37/10	0.272
Tumor number (≥2)	28/19	31/56	0.008	24/23	0.407
Tumor size (>3cm)	28/19	45/42	0.384	34/13	0.192
CHILD (B/A)	14/33	18/69	0.239	11/36	0.484
BCLC (B/A)	29/18	35/52	0.021	35/12	0.184

P^a: Comparison of baseline characteristics of patients between TACE-RFA and TACE-Iodine 125 group before PSM.

P^b: Comparison of baseline characteristics of patients between TACE-RFA and TACE-Iodine 125 group after PSM.

Abbreviations: HBV, Hepatitis B Virus; +, Positive, -, Other, ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; AFP, Alpha Fetoprotein; BCLC, Barcelona Clinic Liver Cancer.

Table 2: Associations between TACE-Iodine 125 treatment and mortality in patients with early-intermediate HCC before PSM

Characteristics	HR (95%CI)	P value	Adjusted HR (95%CI)	P value
Overall				
TACE-RFA	Reference		Reference	
TACE-Iodine 125	0.856 (0.511,1.436)	0.556	0.725 (0.423,1.241)	0.241
Liver resection				
TACE-RFA	Reference		Reference	
TACE-Iodine 125	0.547 (0.170,1.753)	0.310	0.416 (0.107,1.617)	0.205
Child-Pugh A				
TACE-RFA	Reference		Reference	
TACE-Iodine 125	0.879 (0.491,1.573)	0.663	0.815 (0.449,1.481)	0.502
Child-Pugh B				
TACE-RFA	Reference		Reference	
TACE-Iodine 125	0.908 (0.286,2.886)	0.870	0.486 (0.123,1.915)	0.302
BCLC A				
TACE-RFA	Reference		Reference	
TACE-Iodine 125	0.617 (0.232,1.639)	0.332	0.331 (0.106,1.036)	0.057
BCLC B				
TACE-RFA	Reference		Reference	
TACE-Iodine	0.859 (0.460,1.603)	0.633	0.837 (0.437,1.603)	0.591

Abbreviations: TACE, Transarterial chemoembolization; RFA, Radiofrequency ablation; BCLC, Barcelona Clinic Liver Cancer.

Table 3: Associations between TACE-Iodine 125 treatment and recurrence in patients with early-intermediate HCC before PSM

Characteristics	HR (95%CI)	P value	Adjusted HR (95%CI)	P value
Overall				
TACE-RFA	Reference		Reference	
TACE-Iodine 125	1.134 (0.763,1.685)	0.535	1.008 (0.666,1.526)	0.969
Liver resection				
TACE-RFA	Reference		Reference	
TACE-Iodine 125	0.586 (0.228,1.503)	0.266	0.575 (0.169,1.952)	0.375
Child-Pugh A				
TACE-RFA	Reference		Reference	
TACE-Iodine 125	1.182 (0.749,1.865)	0.472	1.044 (0.647,1.686)	0.859
Child-Pugh B				
TACE-RFA	Reference		Reference	
TACE-Iodine 125	1.172 (0.503,2.773)	0.713	0.926 (0.336,2.556)	0.882
BCLC A				
TACE-RFA	Reference		Reference	
TACE-Iodine 125	0.834 (0.429,1.620)	0.592	0.546 (0.239,1.249)	0.152
BCLC B				
TACE-RFA	Reference		Reference	
TACE-Iodine	1.274 (0.762,2.129)	0.356	1.315 (0.786,2.201)	0.297

Abbreviations: TACE, Transarterial chemoembolization; RFA, Radiofrequency ablation; BCLC, Barcelona Clinic Liver Cancer

Table 4: Associations between TACE-Iodine 125 treatment and mortality and recurrence in patients with early-intermediate HCC after PSM

Characteristics	Mortality		Recurrence	
	Adjusted HR (95%CI)	P value	Adjusted HR (95%CI)	P value
Overall				
TACE-RFA	Reference		Reference	
TACE-Iodine 125	0.860 (0.477,1.552)	0.618	1.319 (0.829,2.099)	0.243
Liver resection				
TACE-RFA	Reference		Reference	
TACE-Iodine 125	1.448 (0.225,9.325)	0.697	0.2.462 (0.493,12.280)	0.272
Child-Pugh A				
TACE-RFA	Reference		Reference	
TACE-Iodine 125	0.808 (0.339,1.925)	0.808	0.905 (0.474,1.730)	0.764
Child-Pugh B				
TACE-RFA	Reference		Reference	
TACE-Iodine 125	3.954 (0.228,68.617)	0.345	3.649 (0.298,44.640)	0.311
BCLC A				
TACE-RFA	Reference		Reference	
TACE-Iodine 125	1.296 (0.268,6.257)	0.748	0.828 (0.264,2.593)	0.746
BCLC B				
TACE-RFA	Reference		Reference	
TACE-Iodine	0.791 (0.337,1.855)	0.589	0.958 (0.497,1.848)	0.898

Abbreviations: TACE, Transarterial chemoembolization; RFA, Radiofrequency ablation; BCLC, Barcelona Clinic Liver Cancer

Table 5: Adverse events of patients with TACE-Iodine 125 or TACE-RFA treatments after PSM

Adverse events	Grade I and II			Grade III and IV		
	TACE-RFA	TACE-Iodine 125	P value	TACE-RFA	TACE-Iodine 125	P value
Fatigue	13	17	0.376	2	1	>0.99
Nausea	10	12	0.626	0	1	>0.99
Fever	3	10	**0.036**	0	0	>0.99
Leucopenia	1	8	**0.030**	0	0	>0.99
Liver pain	28	31	0.522	2	3	>0.99
Hepatic hemorrhage	4	2	0.677	1	0	>0.99
Increased ALT	8	17	**0.036**	3	7	0.181
Pneumothorax	2	5	0.435	0	0	>0.99

Abbreviations: TACE, Transarterial chemoembolization; RFA, Radiofrequency ablation;

Figures

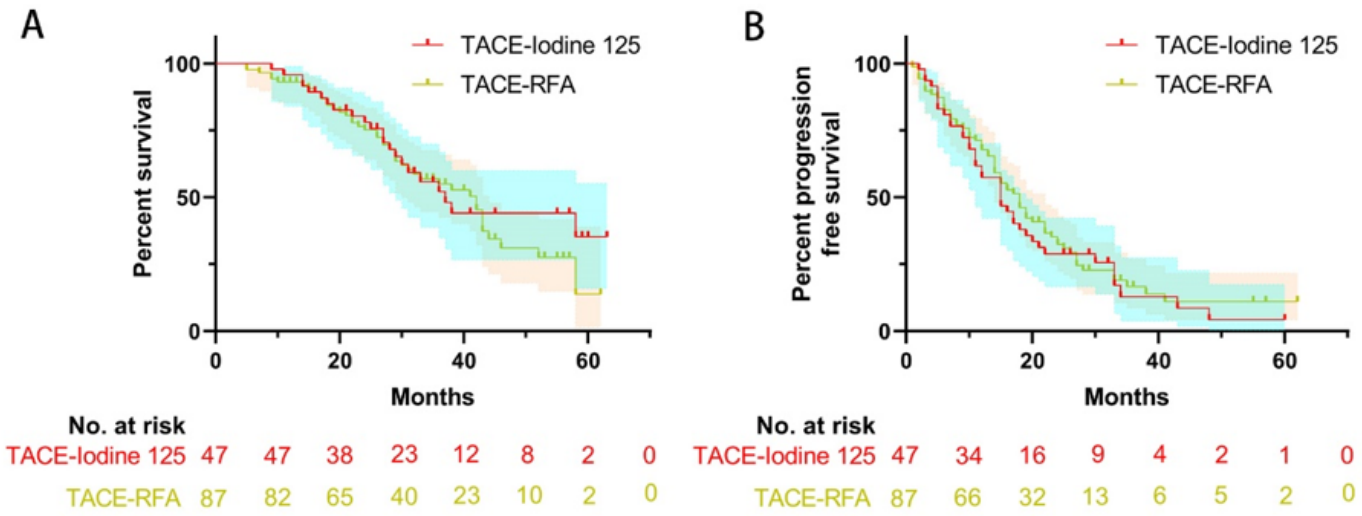

Figure 1

Kaplan-Meier curve of overall survival (A) and progression free survival (B) of patients before PSM, the shaded area indicates the 95% Confidence Interval

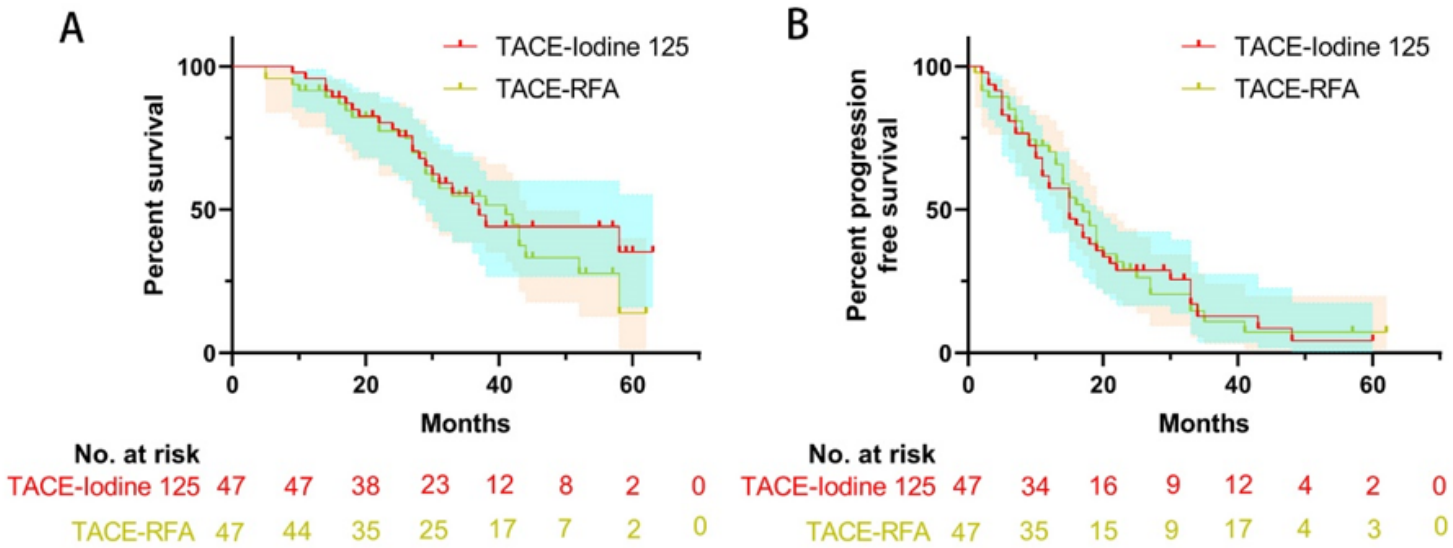

Figure 2

Kaplan-Meier curve of overall survival (A) and progression free survival (B) of patients after PSM, the shaded area indicates the 95% Confidence Interval

Supplementary Files

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- AppendixsInformation.docx