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# Combining transarterial chemoembolization, radiofrequency ablation, and iodine-125 seed implantation for recurrent hepatocellular carcinoma post-hepatectomy

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**PURPOSE**

This study aimed to evaluate the efficacy and safety of transarterial chemoembolization (TACE) combined with radiofrequency ablation (RFA) and iodine-125 (125I) seed implantation (TACE-RFA-125I) for recurrent hepatocellular carcinoma (HCC) after hepatectomy.

**METHODS**

The study retrospectively analyzed patients with recurrent HCC who received TACE-RFA-125I or TACE-RFA treatment in our institution between January 2013 and January 2023. Overall survival (OS), progression-free survival (PFS), and recurrence were compared between the two groups.

**RESULTS**

A total of 187 patients were enrolled in this study, with 105 in the TACE-RFA-125I group and 82 in the TACE-RFA group. There were 67 men and 15 women in the TACE-RFA group, with an average age of 55.4 ± 10.9 years, and 93 men and 12 women in the TACE-RFA-125I group, with an average age of 55.5 ± 10.7 years. The TACE-RFA-125I group exhibited a significantly improved survival benefit compared with the TACE-RFA group (median OS: 49 months vs. 32 months, $P < 0.001$; median PFS: 24 months vs. 16 months, $P < 0.001$). The univariate and multivariate analyses revealed that TACE-RFA-125I was a protective factor for OS and PFS. A total of 32 patients in the TACE-RFA group experienced recurrence during follow-up, with local recurrence in 12 cases, intrahepatic recurrence in 10 cases, and extrahepatic metastases in 10 cases. A total of 28 patients in the TACE-RFA-125I group experienced recurrence, 6 with local recurrence, 12 with intrahepatic recurrence, and 10 with extrahepatic metastases. No procedure-related deaths occurred in this study.

**CONCLUSION**

In patients with recurrent HCC, TACE-RFA-125I demonstrates promising tumor control and acceptable safety.

**CLINICAL SIGNIFICANCE**

This study provides promising clinical guidance for patients with recurrent HCC after hepatectomy and is expected to provide beneficial strategies for the treatment of this disease.

**KEYWORDS**

Hepatocellular carcinoma, hepatectomy, radiofrequency ablation, transarterial chemoembolization, iodine-125 seeds

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Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide, and treatment options remain limited.[1] The Barcelona Clinical Liver Cancer staging system is now a widely accepted tool for the treatment allocation of patients with HCC globally.[2] For patients with early-stage HCC, hepatectomy is one of the preferred curative treatments. Nonetheless, up to 70% of patients with HCC have reported tumor recurrence within 5 years of hepatectomy, of which 61.4%–83.3% of tumors recurred within 2 years.[3] Until now, no consensus has been reached on the treatment of patients with HCC with recurrence after hepatectomy.

Previous studies have demonstrated that transarterial chemoembolization (TACE) combined with radiofrequency ablation (RFA) can cause extensive tumor necrosis and achieve significant survival benefits.[4,5] The embolization of tumor vessels reduces tumor blood supply, which can reduce the influence of the heat sink effect on RFA and increase the ablation zone. However, for the ablation of larger tumors or tumors in high-risk locations, using RFA to completely kill tumors is challenging and often results in residual tumor and damage to the surrounding normal tissues, seriously affecting the prognosis of patients.[6,7] Brachytherapy with iodine-125 (125I) seed implantation for the high-dose irradiation of focal lesions has been widely used in the treatment of HCC.[8] Studies have demonstrated that 125I seeds can increase the efficacy of RFA in the treatment of HCC.[9]

To date, there has been limited data available reporting the treatment of recurrent HCC with TACE-RFA combined with 125I seeds (TACE-RFA-125I). Hence, the purpose of this study was to evaluate the efficacy and safety of TACE-RFA-125I in the treatment of recurrent HCC and to provide a more effective treatment strategy for recurrent HCC.

**Main points**

- Transarterial chemoembolization combined with radiofrequency ablation (RFA) and iodine-125 (125I) seed implantation have a positive curative effect on hepatocellular carcinoma (HCC) after hepatectomy.
- RFA and 125I seed implantation under the dual guidance of ultrasound and computed tomography are safe and effective.
- For the long-term survival of patients with HCC, all target lesions should be controlled as much as possible.

# Methods

## Patients

This study retrospectively analyzed the clinical data of 253 patients with HCC recurrence after hepatectomy who were treated with TACE-RFA or TACE-RFA-125I at our center between January 2013 and January 2023. This retrospective study was approved by the Ethics Committee of Tongcheng County People's Hospital (decision no: TC-IEC-013-01-04, date: 01/01/2024), which waived the need for written informed consent.

Based on the inclusion and exclusion criteria, 187 patients were eventually included in the study. The inclusion criteria were as follows: (a) recurrent HCC diagnosed using computed tomography (CT)/magnetic resonance (MR) after hepatectomy; (b) a solitary HCC 3.0 cm in diameter, or smaller or multiple (up to three) HCCs 3.0 cm in diameter or smaller; (c) Child–Pugh A or B. The exclusion criteria were as follows: (a) prior chemoradiotherapy or other similar treatment; (b) other accompanying malignancies; (c) incomplete perioperative clinical and imaging data, or the patient was lost to follow-up.

## Transarterial chemoembolization

The TACE procedure was conducted according to the institutional standard protocol. First, a 5-F catheter (Cook, Bloomington, IN, USA) or 2.7-F microcatheter (Terumo, Japan) was inserted into the tumor-supplying arteries, and then 5–20 mL of suspension composed of lipiodol (Lipiodol Ultrafluido, Guerbet, France) and doxorubicin hydrochloride (Hisun Pharmaceutical, Zhejiang, China) was injected. Subsequently, an appropriate amount of gelatin sponge (300–700 μm, Cook) was injected to completely embolize the tumor vessels. After embolization, reexamination angiography of the feeding artery was performed to confirm the devascularization. This procedure was performed by experienced physicians.

## Radiofrequency ablation

In this study, RFA was usually administered 3–5 days after TACE. The electrode needle was inserted into the target lesion under ultrasound and CT guidance. The RITA 1500 generator (RITA Medical Systems, Mountain View, CA, USA) was then activated and ablation started. The choice of a single expandable electrode (≤2 cm) or a multi-hook probe (>2 cm) depends on tumor size. To achieve a safe ablation range of 0.5–1.0 cm, multiple overlapping ablation zones are required. 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, Beijing, China).

## Iodine-125 seed implantation

After RFA, CT scans were performed to assess possible residual tumor areas. The puncture needle was then inserted into the target area. To assess the number and total activity of the 125I seeds, a treatment planning system (TPS; HGGR300, Hokai Medical Instruments, Zhuhai, China) was used, with X-rays and γ-rays able to reach the intended target volume, including the tumors and 0.5–1 cm of the adjacent normal tissue. After implantation of the 125I seeds, CT scans were repeated to identify the location of the 125I seeds and possible complications, and dose validation was performed using TPS.

## Follow-up

Abdominal contrast-enhanced CT/MR was performed 4–6 weeks after the initial TACE. The changes in liver and kidney function, routine blood, and tumor markers were also evaluated. If the enhanced CT/MR indicated residual tumor, the TACE, RFA, or 125I seed procedures were repeated. With no residual tumor, the patient had an outpatient review every 3 months. The study was followed up until January 2024.

Tumor response was evaluated using the Modified Response Evaluation Criteria in Solid Tumors. Complete response refers to the absence of enhancement in all target lesions; partial response is classified as at least a 30% decrease in the sum of the diameters of viable tumors; progressive disease is an increase of at least 20% in the sum of the diameters of target lesions; stable disease refers to any cases that do not qualify for either partial response or progressive disease. Local and intrahepatic tumor recurrence was assessed. Local recurrence was defined as residual tumor at the lesion edge on CT/MR images during follow-up, and intrahepatic recurrence was defined as a single new lesion in the liver at a distance of more than 2.0 cm from the target lesion. Overall survival (OS) was the time from initial TACE to death or the end of follow-up. Progression-free survival (PFS) was the time from initial TACE to tumor progression, patient death, or end of follow-up. Complications were recorded and assessed using the Common Terminology Criteria for Adverse Events version 5.0. In addition, postembolization syndrome, such as fever, pain, nausea, and vomiting, was not considered a complication in itself but rather an expected outcome of embolization therapy.

### Statistical analysis

For the statistical analyses, SPSS software (version 24.0; IBM, Armonk, NY, USA) was used. Discrete variables were represented by numbers with percentages, and a chi-square test was used to compare the differences. Continuous variables were presented as mean ± standard deviation, and the Student's t-test was used to compare the difference. OS and PFS were evaluated using the Kaplan–Meier method. The 95% confidence interval (CI) was calculated for median OS, median PFS, and hazard ratio. Multivariate Cox proportional hazards regression analysis was used to analyze the potential prognostic factors affecting OS and PFS. The statistical significance was two-tailed, and a $P$ value <0.05 was considered statistically significant.

## Results

### Study population

Between January 2013 and January 2023, a total of 187 patients with recurrent HCC were enrolled in this study (Figure 1). There were 67 men and 15 women in the TACE-RFA group, with an average age of 55.4 ± 10.9 years, and 93 men and 12 women in the TACE-RFA-125I group, with an average age of 55.5 ± 10.7 years, with no significant difference between the two groups. In the TACE-RFA-125I group, a total of 2,188 seeds were implanted, an average of 20.8 ± 9.6 per patient. Detailed baseline data of the two groups of patients are presented in Table 1. The median follow-up time was 20 months (range, 15–59 months) in the TACE-RFA group and 30 months in the TACE-RFA-125I group (range, 17–85 months). By January 2024, 30 and 40 patients in the two groups had died, respectively.

### Recurrence

A total of 32 patients in the TACE-RFA group experienced recurrence during follow-up, with local recurrence in 12 cases, intrahepatic recurrence in 10 cases, and extrahepatic metastases in 10 cases. A total of 28 patients in the TACE-RFA-125I group experienced recurrence, with 6 cases of local recurrence, 12 of intrahepatic recurrence, and 10 of extrahepatic metastases.

### Overall survival

The median OS was 32 months (95% CI, 29.3–34.7) in the TACE-RFA group and 49 months (95% CI, 43.6–54.4) in the TACE-RFA-125I group ($P$ < 0.001) (Figure 2). Univariate analyses indicated that tumor number and treatment method correlated with OS ($P$ < 0.2) (Table 2). These factors were included in the multivariate analysis, which revealed that treatment method was an independent prognostic factor affecting patients' OS (Table 3).

### Progression-free survival

The median PFS in the TACE-RFA group was 16 months (95% CI, 13.9–18.1), which was significantly lower than that in the TACE-RFA-125I group (24 months, 95% CI, 20.9–27.1, $P$ < 0.001) (Figure 3). Univariate analyses revealed that Child–Pugh score, albumin, platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, α-Fetoprotein level, and treatment method were related to patients' PFS ($P$ < 0.2) (Table 2), and further multivariate analyses demonstrated that albumin and treatment method were independent prognostic factors affecting patients' PFS (Table 4).

### Complications

No procedure-related deaths occurred in this study. Post-embolization syndrome, such as pain, fever, nausea, and vomiting, was common in both groups, and symptoms improved or disappeared substantially after symptomatic treatment. Pneumothorax occurred in three patients in the TACE-RFA group and four patients in the TACE-RFA-125I group; all cases were mild with no discomfort. No migration of seeds from the liver to other organs was observed during follow-up.

## Discussion

The synergy between radiation therapy and thermal ablation is reported to have "reciprocal zones of efficacy".[10] Hyperther-

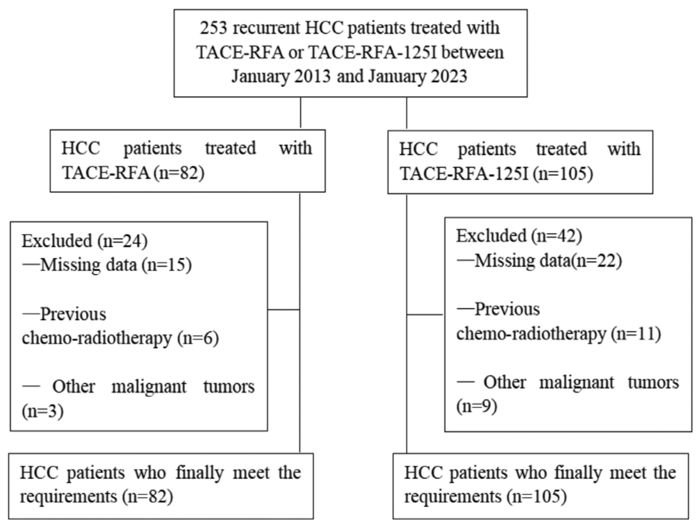


**Figure 1.** Flowchart of the screening procedure for patients with recurrent hepatocellular cancer. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; 125I, iodine-125.

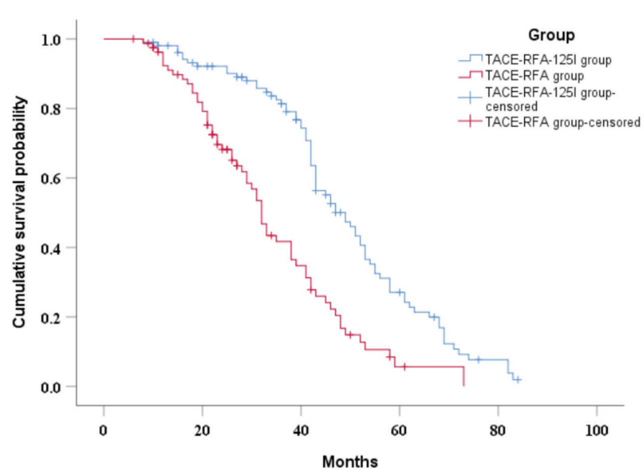


**Figure 2.** Kaplan–Meier curve of overall survival in patients with hepatocellular cancer. TACE, transarterial chemoembolization; RFA, radiofrequency ablation; 125I, iodine-125.

mia leads to increased vasodilation and vascular permeability around the tumor, increasing oxygenation in the area and further improving the efficacy of radiotherapy. Furthermore, ablation and radiotherapy lead to tumor necrosis, which stimulates the body's immunity and enhances the anti-tumor effect.[11] Additionally, the application of TACE in this study embolized tumor blood vessels and reduced the influence of the heat sink effect.[4] The deposition of lipiodol in tumors can also be used as a marker, and it is more conducive to RFA and seed treatment, especially for HCC in high-risk locations, reducing the risk of surgery and improving the curative effect. Hence, TACE-RFA-125I seeds could theoretically significantly enhance the therapeutic efficacy of HCC.

**Table 1.** Baseline characteristics

| Characteristics | TACE-RFA-125I group (n = 105) (No, %; mean ± SD) | TACE-RFA group (n = 82) (No, %; mean ± SD) | *P* value |
|---|---|---|---|
| **Age (years)** | 55.5 ± 10.7 | 55.4 ± 10.9 | 0.971 |
| **Gender** | | | |
| Male | 93 (88.6%) | 67 (81.7%) | 0.185 |
| Female | 12 (11.4%) | 15 (18.3%) | |
| **Child–Pugh score** | | | |
| A | 82 (78.1%) | 67 (81.7%) | 0.542 |
| B | 23 (21.9%) | 15 (18.3%) | |
| **Hepatitis** | | | |
| Hepatitis B | 86 (81.9%) | 71 (86.6%) | 0.387 |
| Other | 19 (18.1%) | 11 (13.4%) | |
| **Albumin (g/L)** | 37.9 ± 5.8 | 36.6 ± 5.1 | 0.117 |
| **PT(s)** | 13.8 ± 2.1 | 13.6 ± 1.2 | 0.894 |
| **TB (μmol/L)** | 22.4 ± 12.5 | 20.6 ± 11.3 | 0.169 |
| **AST (μmol/L)** | 40.3 ± 29.2 | 41.5 ± 30.2 | 0.471 |
| **ALT (μmol/L)** | 41.3 ± 30.2 | 41.8 ± 30.1 | 0.214 |
| **PLR** | 122.8 ± 97.7 | 137.1 ± 75.1 | 0.276 |
| **NLR** | 3.3 ± 3.5 | 3.2 ± 2.4 | 0.866 |
| **Tumor size (cm)** | 2.5 ± 0.8 | 2.3 ± 0.6 | 0.092 |
| **Tumor number** | | | |
| 1 | 85 (81.0%) | 65 (79.3%) | 0.774 |
| 2–3 | 20 (19.0%) | 17 (20.7%) | |
| **α-Fetoprotein level** | | | |
| >400 ng/mL | 45 (42.9%) | 32 (39.0%) | 0.597 |
| ≤400 ng/mL | 60 (57.1%) | 50 (61.0%) | |

TACE, transarterial chemoembolization; RFA, radiofrequency ablation; 125I, iodine-125; SD, standard deviation; PT, prothrombin time; TB, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

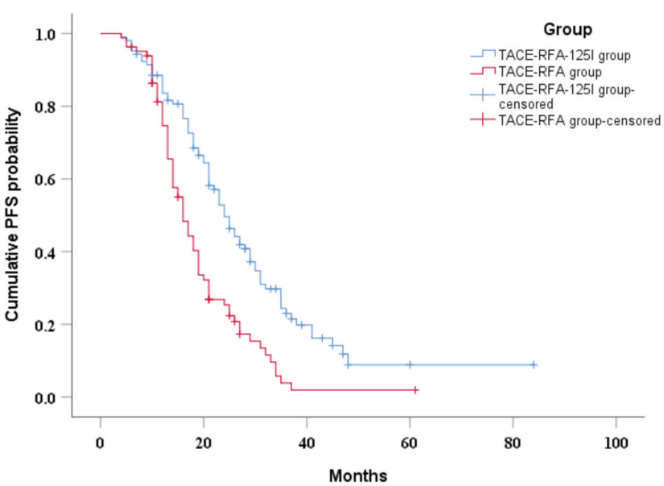


**Figure 3.** Kaplan–Meier curve of progression-free survival in patients with hepatocellular cancer. TACE, transarterial chemoembolization; RFA, radiofrequency ablation; 125I, iodine-125.

In our study, the efficacy of TACE-RFA-125I in the treatment of recurrent HCC was enhanced, primarily because the OS and PFS of patients were significantly improved compared with those of the TACE-RFA group. Liu et al.[12] reported that for recurrent HCC, the median OS and PFS of patients treated with TACE alone were 24 months and 10 months, respectively, which is significantly lower than the median OS and PFS of patients in our study. Zheng et al.[13] compared the efficacy of TACE-RFA with that of repeat hepatectomy for recurrent HCC, demonstrating that the two groups of patients had similar OS and PFS. However, the efficacy of TACE-RFA-125I in this study was significantly superior to the results achieved by Zheng et al.[13] This indicates that, as described by the theoretical advantages, the combination of the three treatment modalities produces a certain synergistic therapeutic effect, which can significantly improve the therapeutic effect on patients with recurrent HCC.

Brachytherapy with 125I has been reported to be effective in local tumor control.[14] Chen et al.[11] revealed that RFA combined with 125I seed implantation significantly improved cumulative recurrence in patients with small HCC compared with RFA alone. Similarly, the results of this study demonstrated that the number of patients with local recurrence in the TACE-RFA-125I group was lower than that in the TACE-RFA group. The effective control of intrahepatic lesions is beneficial to the overall prognosis of patients. In the present study, the patients in the TACE-RFA-125I group had improved OS compared with the TACE-RFA group. Therefore, controlling all target lesions as much as possible is essential for the prognosis of patients with recurrent HCC.

Efficacy and safety are equally crucial for the treatment of recurrent HCC. In this study, there were no operation-related deaths or massive bleeding after puncture in the two groups of patients, and there were no significant fluctuations in the postoperative electrocardiogram monitoring of blood pressure and heart rate. To minimize treatment complications, the choice of puncture path and image-guidance tool is vital. Lin et al.[15] per-

**Table 2.** Univariate analysis of prognostic factors for overall survival and progression-free survival

| Variables | OS | | PFS | |
|---|---|---|---|---|
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| **Age (years)** | 1.005 (0.988, 1.023) | 0.553 | 1.005 (0.989, 1.021) | 0.530 |
| **Gender** | | | | |
| Male | 1 | | 1 | 0.788 |
| Female | 1.081 (0.663, 1.763) | 0.754 | 1.066 (0.670, 1.695) | |
| **Child–Pugh score** | | | | |
| A | 1 | | | 0.151 |
| B | 0.808 (0.532, 1.225) | 0.315 | 0.744 (0.497, 1.114) | |
| **Hepatitis** | | | | |
| Hepatitis B | 1 | | 1 | 0.653 |
| Other | 0.897 (0.581, 1.387) | 0.626 | 1.102 (0.721, 1.685) | |
| **Albumin (g/L)** | 0.991 (0.962, 1.021) | 0.547 | 0.978 (0.951, 1.007) | 0.131 |
| **PT (s)** | 0.950 (0.852, 1.058) | 0.350 | 0.949 (0.866, 1.041) | 0.270 |
| **TB (μmol/L)** | 1.004 (0.991, 1.016) | 0.562 | 1.003 (0.990, 1.016) | 0.663 |
| **AST (μmol/L)** | 1.124 (0.837, 1.273) | 0.212 | 1.137 (0.875, 1.179) | 0.392 |
| **ALT (μmol/L)** | 1.221 (0.925, 1.287) | 0.372 | 1.026 (0.931, 1.126) | 0.835 |
| **PLR** | 1.001 (0.999, 1.003) | 0.205 | 1.001 (0.999, 1.003) | 0.186 |
| **NLR** | 1.031 (0.977, 1.088) | 0.266 | 1.046 (0.991, 1.103) | 0.101 |
| **Tumor size** | 0.933 (0.727, 1.199) | 0.589 | 0.967 (0.748, 1.250) | 0.799 |
| **Tumor number** | | | | |
| 1 | 1 | | 1 | 0.925 |
| 2–3 | 1.373 (0.926, 2.036) | 0.115 | 0.983 (0.683, 1.413) | |
| **α-Fetoprotein level** | | | | |
| <400 ng/mL | 1 | | 1 | 0.065 |
| ≥400 ng/mL | 1.018 (0.931, 1.181) | 0.256 | 1.365 (0.980, 1.901) | |
| **Treatment method** | | | | |
| TACE-RFA | 1 | | 1 | <0.001 |
| TACE-RFA-125I | 0.411 (0.288, 0.586) | <0.001 | 0.493 (0.354, 0.687) | |

OS, overall survival; PFS, progression-free survival; HR, Hazard ratio; CI, confidence interval; PT, prothrombin time; TB, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; 125I, iodine-125.

**Table 3.** Multivariate analysis of prognostic factors for overall survival

| Variables | HR (95% CI) | *P* value |
|---|---|---|
| **Tumor number** | | |
| 1 | | |
| 2–3 | 1.443 (0.973, 2.138) | 0.068 |
| **Treatment method** | | |
| TACE-RFA | 1 | <0.001 |
| TACE-RFA-125I | 0.404 (0.284, 0.576) | |

HR, Hazard ratio; CI, confidence interval; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; 125I, iodine-125.

formed RFA-125I seed therapy for HCC under MR guidance, but this procedure lasted a relatively long time and required magnetic compatible puncture equipment, which greatly limited its clinical application. Chen et al.[16] applied CT-guided seed implantation and ablation therapy, but CT alone required the repeated adjustment of the needle tip position, and the researchers were unable to observe the puncture path in real time. In our study, to improve the curative effect and reduce operation risk, all patients were first treated with TACE, and lipiodol played a role in further clarifying tumor location. In addition, we applied RFA-125I seed implantation under the guidance of ultrasound and CT, achieving a safe and positive therapeutic effect.

The main limitations of this study are its single-center and retrospective design. Therefore, prospective multicenter studies are necessary to verify our results. Recall bias is a potential limitation, possibly affecting the adverse effects assessment. In addition, the present study did not analyze the impact of follow-up treatment on outcomes or the incidence and severity of adverse events.

In conclusion, for recurrent HCC, TACE-RFA-125I seed therapy may be a promising treatment option. Moreover, ultrasound and CT-guided puncture are safe and reliable. The efficacy of this combination therapy still requires further validation in multicenter prospective studies.

**Table 4.** Multivariate analysis of prognostic factors for progression-free survival

| Variables | HR (95% CI) | *P* value |
|---|---|---|
| **Child–Pugh score** | | |
| A | 1 | 0.088 |
| B | 1.102 (0.921, 1.271) | |
| **Albumin** | 0.583 (0.409, 0.832) | 0.003 |
| **PLR** | 1.000 (0.998, 1.002) | 0.782 |
| **NLR** | 1.020 (0.958, 1.087) | 0.529 |
| **α-Fetoprotein level** | | |
| <400 ng/mL | 1 | 0.377 |
| ≥400 ng/mL | 1.026 (0.924, 1.172) | |
| **Treatment method** | | |
| TACE-RFA | 1 | 0.003 |
| TACE-RFA-125I | 0.583 (0.409, 0.832) | |

HR, Hazard ratio; CI, confidence interval; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; 125I, iodine-125.

### Footnotes

### Conflict of interest disclosure

The authors declared no conflicts of interest.

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