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Therapeutic outcomes of thermal ablation versus repeated hepatic resection for recurrent hepatocellular carcinoma by using propensity score analysis: a multicenter real-world study

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Abstract

Background The therapeutic value of thermal ablation (TA) versus repeat hepatic resection (RHR) for recurrent hepatocellular carcinoma (rHCC) after initial hepatic resection is uncertain. This study aimed to investigate the prognosis of TA and RHR.

Materials and methods In this multicenter real-world retrospective study, 473 patients were enrolled between January 2015 and August 2023, with 340 in the TA group and 133 in the RHR group. Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) were employed to reduce selection bias. Local tumor progression (LTP), recurrence-free survival (RFS), and post-recurrence survival (PRS) were compared before and after PSM and IPTW.

Results A total of 473 patients (231 aged ≥ 60 years; 393 men) were evaluated. LTP, RFS, and PRS rates did not differ significantly between groups before ($P=0.940$, $P=0.180$, and $P=0.700$) and after matching ($P=0.420$, $P=0.680$, and $P=0.810$) and weighting ($P=0.940$, $P=0.180$, and $P=0.700$). Multivariable Cox analysis identified tumor number (HR: 2.28; $P<0.001$) and PLT (HR: 0.73; $P=0.038$) as independent prognostic factors for RFS in the entire rHCC cohort. And tumor location, size, number, ascites, AST, and AFP (HR: 0.55–2.18; $P=0.004$–0.046) were independent prognostic factors for PRS. Subgroup analysis showed both TA and RHR were effective treatments for rHCC, regardless of tumor size, number, subcapsular, or perivascular lesions.

Conclusions The cumulative LTP, RFS, and PRS were not significantly different between TA and RHR for rHCC within the Milan criteria. TA may be a viable curative option for early-stage rHCC patients.

Keywords Recurrent hepatocellular carcinoma, Thermal ablation, Repeat hepatic resection, Outcomes, Propensity score matching, Inverse probability of treatment weighting

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignant liver tumor, ranking sixth among the most frequently diagnosed cancers globally and the third leading cause of cancer-related mortality in 2022 [1, 2]. Its incidence and mortality rates are continually rising, imposing an increasing burden on public health [3]. Hepatic resection remains an effective therapeutic strategy for early-stage HCC. However, owing to its histopathologic, genetic, and immunophenotypic heterogeneity, the long-term prognosis of patients following curative resection varies significantly. The 5-year recurrence rate reaches levels as high as 70% [4, 5]. Early recurrence and intrahepatic metastasis (within 2 years of resection) contribute to frequent relapses and high mortality rates in HCC [6, 7].

Currently, therapeutic approaches for recurrent HCC (rHCC) largely mirror those used for initial HCC [7]. Curative treatment modalities for early-stage rHCC [8] include repeated hepatic resection (RHR), thermal ablation (TA), and salvage liver transplantation (SLT). While SLT proves to be the most advantageous option, its utilization is limited in regions with a scarcity of liver donors, such as China. Therefore, RHR and TA are the primary first-line treatments for rHCC. The selection of the appropriate treatment is influenced by intra-abdominal adhesions, residual liver function, and the size, location, and number of recurrent tumors. Unfortunately, only 20% of patients with recurrence can benefit from repeated resection due to these factors [9]. TA has advantages over RHR in terms of lower mortality and complication rates. Some studies have suggested that TA is as effective as RHR in achieving long-term survival outcomes for rHCC [10–12]. However, other studies have indicated that TA may yield inferior outcomes compared to RHR in patients with these characteristics, such as tumor size exceeding 3 cm and alpha-fetoprotein levels above 200 mg/L [8]. Additionally, previous research found that RHR was associated with superior overall survival (OS) compared to radiofrequency ablation (RFA) [13]. Conversely, other studies have indicated that RHR was linked to prolonged recurrence-free survival but did not show a significant difference in OS compared to RFA [14]. Diverse viewpoints exist regarding the comparative effectiveness of RHR and TA in the management of rHCC.

In this study, we compared long-term survival outcomes between TA and RHR for treating rHCC within the Milan criteria. Moreover, to our knowledge, there is no comprehensive assessment of selection bias using various propensity score methods. Therefore, we adopted the propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) to reduce potential selection bias.

Materials and methods

Patients and study design

This retrospective multicenter study was approved by the institutional review board of all the participating hospitals. The necessity for written informed consent for publication was waived due to the retrospective nature of the study.

Patients who underwent hepatectomy were enrolled between January 2015 and August 2023 from two centers: Center A (The First Affiliated Hospital, Zhejiang University School of Medicine) in southern China, and Center B (Peking University Cancer Hospital) in northern China. The inclusion criteria were: (1) hepatectomy as initial curative treatment; (2) confirmation of HCC diagnosed through biopsy or pathologic histology; (3) rHCC within the Milan criteria: either a solitary tumor with a diameter < 5 cm or 2–3 tumors each with a maximum diameter < 3 cm. The exclusion criteria were: (1) clinical diagnosis of rHCC subsequent to initial resection, followed by other treatments for rHCC prior to RHR or TA; (2) occurrence of HCC recurrence within 1 month of the initial hepatic resection; (3) presence of macrovascular invasion or extrahepatic metastasis before treatments; (4) patients with a previous liver transplant or kidney-liver transplant; (5) severe hepatic and renal dysfunction or other substantial organ disorders; (6) a follow-up duration less than 6 months.

Finally, a total of 473 patients with rHCC were enrolled, with 340 in the TA group and 133 in RHR group. Details of patient participation are shown in Fig. 1.

Covariates

Baseline covariates were gathered from the electronic health record systems of both institutions. General clinical characteristics included sex, age, liver cirrhosis, etiology, and Child-Turcotte-Pugh grade. Laboratory indicators within 2 weeks included aspartate aminotransferase (AST, cut-off value: 45 U/L), alanine aminotransferase (ALT, cut-off value: 40 U/L), alkaline phosphatase (ALP, cut-off value: 160 U/L), total bilirubin (TBIL, cut-off value: 17.1 μmol/L), platelet (PLT, cut-off value: 100×10^9/L), international normalized ratio (INR, cut-off value: 1.15), alpha-fetoprotein (AFP, cut-off value: 200 ng/mL), systemic immune-inflammation index (SII, cut-off value: 119.72), neutrophil–lymphocyte ratio (NLR, cut-off value: 3.83), lymphocyte-to-monocyte ratio (LMR, cut-off value: 2.55), and prognostic nutritional index (PNI, cut-off value: 40.33). SII was calculated using the standard formula (Platelet count × Neutrophil count

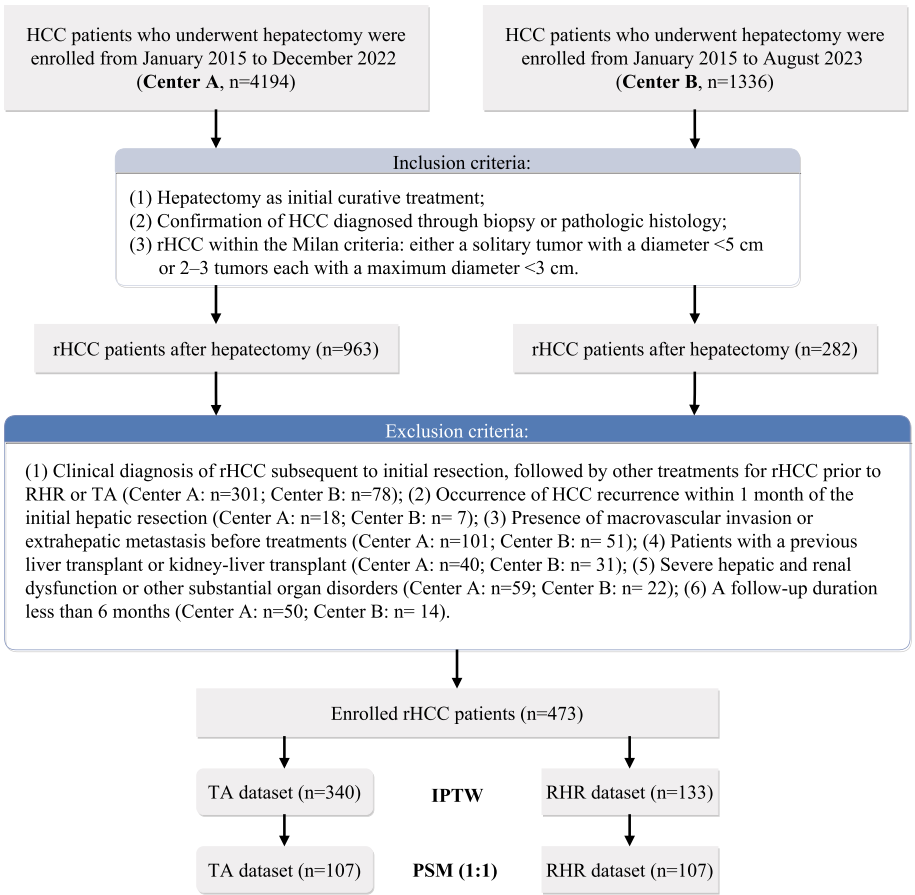

Fig. 1 Flowchart of study participants. rHCC, recurrent hepatocellular carcinoma; TA, thermal ablation; RHR, repeated hepatic resection; PSM, propensity score matching; IPTW, inverse probability of treatment weighting

/ Lymphocyte count). PNI was Albumin + 5 × Lymphocyte count. Imaging variables, including tumor location, tumor size, tumor number, portal hypertension, subcapsular lesions, and perivascular lesions, were collected from the picture archiving and communication system.

Treatment procedure and follow-up

At each institution, all patients diagnosed with intrahepatic rHCC underwent R0 liver resection, characterized by the complete removal of all macroscopically detectable tumors with histologically tumor-free margins along the parenchymal transection line.

Percutaneous ablation was performed by two radiologists with more than 10 years of experience in TA for HCC nodules under real-time ultrasound guidance, as previously reported [15]. The Cool-tip RFA system (Covidien, USA) was utilized for ablation, with an active tip of either 2 or 3 cm. Power settings ranged from 150 to 200 W, with durations of 5 to 30 min per nodule. The objective was to form an ablative margin of at least 0.5 cm in the surrounding normal tissue. Microwave ablation (MWA) was performed using the KY-2000 MWA equipment (Kangyou Medical, China), with power levels between 50 and 150 W for durations of 4 to 20 min per nodule. Postoperatively, patients underwent imaging using dynamic contrast-enhanced ultrasound, multiphase contrast-enhanced CT, or MRI after one month to assess complete ablation. Complete ablation was defined as an absence of contrast enhancement in an area equal to or larger than the ablated tumor one month post-TA.

Patients were subsequently monitored every 3 months for the first year, followed by intervals of 3 to 6 months thereafter. In case of tumor recurrence, the treatment approach was determined based on multidisciplinary discussions, including repeated ablation, transcatheter arterial chemoembolization, and systemic therapies like targeted therapy and immunotherapy. The final follow-up dates were July 15, 2023 (Center A) and January 25, 2024 (Centers B).

Outcomes

The primary study endpoint was recurrence-free survival (RFS), and the secondary endpoints were local tumor progression (LTP) and post-recurrence survival (PRS). LTP was defined as tumor recurrence along the margin of the ablation zone. RFS was defined as the duration between secondary TA or RHR and tumor progression (including LTP, intrahepatic distance recurrence, or extrahepatic metastasis) or until the last follow-up [16]. PRS was defined as the period from the first diagnosis of recurrence to death or last follow-up [17].

Statistical analysis

We utilized R software (version 4.2.2; https://www.rproject.org) for data analysis. To reduce potential confounding bias and obtains effects similar to those of randomized controlled trials, we adopted the PSM and IPTW methods [18, 19]. For PSM, we utilized the "MatchIt" package, and for IPTW, we used the "WeightIt" package. Propensity scores were estimated through multivariable logistic regression, with dependent variables including sex, age, etiology, liver cirrhosis, CTP grade, location, tumor size, tumor number, portal hypertension, ascites, subcapsular lesion, perivascular lesion, AST, ALT, ALP, TBIL, PLT, INR, AFP, SII, NLR, LMR, and PNI. PSM was conducted using a 1:1 nearest neighbor algorithm with a caliper of 0.02. To corroborate our findings, we repeated all statistical analyses following IPTW, considering the same potential confounders as those used for PSM. IPTW was conducted using weighted with inverse propensity scores and inverse of 1 minus the propensity scores. Standardized mean differences (SMD) were computed for all confounders to assess covariate balance between the TA and RHR groups. An SMD of less than 0.300 indicated satisfactory covariate balance between the two groups.

For categorical variables, comparisons between the two groups were performed using either the chi-square test or Fisher's exact test. Survival curves were generated using Kaplan–Meier analysis and compared using the log-rank test. Univariable and multivariable Cox proportional hazards regression analyses were conducted to identify clinical factors associated with RFS and PRS. All clinical variables in univariable analysis were subsequently subjected to stepwise multivariable analysis using Akaike information criterion to determine their inclusion in multivariable analysis [20]. The optimal cutoff values of the SII, NLR, LMR, and PNI were determined by maximizing the Youden index based on receiver operating characteristic (ROC) curves. The results provided P-values, hazard ratios (HR), and 95% confidence intervals (CIs). $P<0.05$ was considered statistically significant.

Results

Baseline characteristics

In this study, we enrolled 473 patients from two Chinese medical centers, with 340 in the TA group and 133 in the RHR group. Among these, 214 patients were selected for 1:1 PSM, resulting in 107 patients in each group. IPTW generated 340 and 133 patients in the two groups, respectively. The clinical baseline characteristics are presented in Table 1. In the entire cohort, there were no significant differences in sex, age, etiology, liver cirrhosis, CTP grade, location, tumor number, portal hypertension, ascites, perivascular lesions, ALP, TBIL, PLT, INR, and AFP ($P=0.084$–1.000). However, significant differences were observed in tumor size ($P<0.001$), subcapsular lesions ($P=0.003$), AST ($P=0.019$), ALT ($P=0.008$), SII ($P=0.006$), LMR ($P=0.025$) and PNI ($P<0.001$) between the TA and RHR groups. After PSM and IPTW, the baseline characteristics of the two groups were better balanced, as indicated by all SMD being less than 0.300 (Table 2).

Analysis of risk factors for RFS and PRS

The results of univariable and multivariable Cox proportional hazards regression analyses for RFS and PRS are summarized in Table 3, S1, and S2. Among all patients, multiple tumors (HR: 2.28; 95% CI: 1.69–3.07; $P<0.001$) and PLT $>100\times10^9$/L (HR: 0.73; 95% CI: 0.54–0.98; $P=0.038$) were independent prognostic factors for RFS. For PRS, tumor location in right lobe (HR: 0.55; 95% CI: 0.37–0.83; $P=0.004$), 3–5 cm in tumor size (HR: 1.95; 95% CI: 1.21–3.15; $P=0.006$), multiple tumors (HR: 1.67; 95% CI: 1.06–2.61; $P=0.026$), ascites (HR: 2.18; 95% CI: 1.15–4.14; $P=0.017$), AST >45 U/L (HR: 1.72; 95% CI: 1.02–2.90; $P=0.042$), and AFP ≥ 200 ng/mL (HR: 1.69; 95% CI: 1.01–2.84; $P=0.046$) were independent prognostic factors. Additionally, both univariable and multivariable analyses revealed that the treatment method (TA vs. RHR) was not an independent prognostic factor for RFS and PRS, regardless of whether PSM or IPTW was applied.

Analysis of LTP, RFS, and PRS

In the entire rHCC cohort, 47 out of 340 patients (13.8%) in the TA group and 16 out of 133 (12.0%) in the RHR group experienced LTP. The 1-, 3-, and 5-year cumulative LTP rates were 7.4%, 14.7%, and 17.5%, respectively, in the TA group, and 6.5%, 15.4%, and 29.5%, respectively, in the RHR group. LTP rates were not significantly different between the two groups (HR = 0.98, 95% CI = 0.55–1.73, $P=0.940$; Fig. 2a). In terms of RFS, 182 patients (53.5%) in the TA group and 70 patients (52.6%) in the RHR group experienced it. The 1-, 3-, and 5-year RFS rates were 68.8%, 45.4%, and 38.1% in the TA group,

Table 1 Baseline characteristics in the rHCC cohort

Characteristics	Overall (*N* = 473)	TA (*N* = 340)	RHR (*N* = 133)	*P*	SMD
Sex				0.786	0.042
Female	80 (16.9)	59 (17.4)	21 (15.8)		
Male	393 (83.1)	281 (82.6)	112 (84.2)		
Age (years)				0.766	0.041
< 60	242 (51.2)	172 (50.6)	70 (52.6)		
≥ 60	231 (48.8)	168 (49.4)	63 (47.4)		
Etiology				0.208	0.298
HBV	416 (87.9)	295 (86.8)	121 (91.0)		
HCV	12 (2.5)	12 (3.5)	0 (0.0)		
ALC	2 (0.4)	2 (0.6)	0 (0.0)		
PBC	0 (0.0)	0 (0.0)	0 (0.0)		
NAFLD	13 (2.7)	10 (2.9)	3 (2.3)		
Undetermined	30 (6.3)	21 (6.2)	9 (6.8)		
Liver cirrhosis				0.952	0.022
Absent	58 (12.3)	41 (12.1)	17 (12.8)		
Present	415 (87.7)	299 (87.9)	116 (87.2)		
CTP grade				0.878	0.045
A level	456 (96.4)	327 (96.2)	129 (97.0)		
B level	17 (3.6)	13 (3.8)	4 (3.0)		
Location				0.099	0.214
Left lobe	127 (26.8)	85 (25.0)	42 (31.6)		
Right lobe	330 (69.8)	246 (72.4)	84 (63.2)		
Undetermined	16 (3.4)	9 (2.6)	7 (5.3)		
Tumor size (cm)				< 0.001	0.461
< 3	415 (87.7)	314 (92.4)	101 (75.9)		
≥ 3, < 5	58 (12.3)	26 (7.6)	32 (24.1)		
Tumor number				0.644	0.060
Solitary	385 (81.4)	279 (82.1)	106 (79.7)		
Multiple	88 (18.6)	61 (17.9)	27 (20.3)		
Portal hypertension				0.469	0.088
Absent	372 (78.6)	264 (77.6)	108 (81.2)		
Present	101 (21.4)	76 (22.4)	25 (18.8)		
Ascites				0.269	0.139
Absent	436 (92.2)	310 (91.2)	126 (94.7)		
Present	37 (7.8)	30 (8.8)	7 (5.3)		
Subcapsular				0.003	0.312
No	307 (64.9)	235 (69.1)	72 (54.1)		
Yes	166 (35.1)	105 (30.9)	61 (45.9)		
Perivascular				0.638	0.063
No	394 (83.3)	281 (82.6)	113 (85.0)		
Yes	79 (16.7)	59 (17.4)	20 (15.0)		
AST (U/L)				0.019	0.243
≤ 45	407 (86.0)	301 (88.5)	106 (79.7)		
> 45	66 (14.0)	39 (11.5)	27 (20.3)		
ALT (U/L)				0.008	0.273
≤ 40	392 (82.9)	292 (85.9)	100 (75.2)		
> 40	81 (17.1)	48 (14.1)	33 (24.8)		
ALP (U/L)				1.000	0.013
≤ 160	458 (96.8)	329 (96.8)	129 (97.0)		

Table 1 (continued)

Characteristics	Overall (*N* = 473)	TA (*N* = 340)	RHR (*N* = 133)	*P*	SMD
> 160	15 (3.2)	11 (3.2)	4 (3.0)		
TBIL (μmol/L)				0.585	0.066
≤ 17.1	299 (63.2)	218 (64.1)	81 (60.9)		
> 17.1	174 (36.8)	122 (35.9)	52 (39.1)		
PLT (× 10^9/L)				0.220	0.136
≤ 100	341 (72.1)	251 (73.8)	90 (67.7)		
> 100	132 (27.9)	89 (26.2)	43 (32.3)		
INR				0.656	0.060
≤ 1.15	387 (81.8)	276 (81.2)	111 (83.5)		
> 1.15	86 (18.2)	64 (18.8)	22 (16.5)		
AFP (ng/mL)				0.605	0.068
< 200	420 (88.8)	304 (89.4)	116 (87.2)		
≥ 200	53 (11.2)	36 (10.6)	17 (12.8)		
SII				0.006	0.289
≤ 118.74	300 (63.4)	229 (67.4)	71 (53.4)		
> 118.74	173 (36.6)	111 (32.6)	62 (46.6)		
NLR				0.084	0.185
≤ 3.83	413 (87.3)	303 (89.1)	110 (82.7)		
> 3.83	60 (12.7)	37 (10.9)	23 (17.3)		
LMR				0.025	0.234
≤ 4.77	409 (86.5)	302 (88.8)	107 (80.5)		
> 4.77	64 (13.5)	38 (11.2)	26 (19.5)		
PNI				< 0.001	0.574
≤ 40.33	415 (87.7)	318 (93.5)	97 (72.9)		
> 40.33	58 (12.3)	22 (6.5)	36 (27.1)		

Unless indicated otherwise, data are the number of patients, with percentages in parentheses

SMDs indicate very small differences for values less than 0.10; 0.10–0.30, small differences; 0.30–0.50, moderate differences; and values higher than 0.50, large differences

$P < 0.05$ was considered significant

TA Thermal ablation, *RHR* Repeated hepatic resection, *SMDs* Standardized mean differences, *CTP* Child-Turcotte-Pugh, *HBV* Hepatitis B virus, *HCV* Hepatitis C virus, *ALC* Alcoholic cirrhosis, *PBC* Primary biliary cholangitis, *NAFLD* Non-alcoholic fatty liver disease, *AST* Aspartate aminotransferase, *ALT* Alanine aminotransferase, *TBIL* Total bilirubin, *PLT* Platelet, *INR* International normalized ratio, *AFP* Alpha-fetoprotein, *SII* Platelet count × neutrophil count / lymphocyte count, *NLR* Neutrophil–lymphocyte ratio, *LMR* Lymphocyte-monocyte ratio, *PNI* Albumin + 5 × lymphocyte count

compared to 69.8%, 39.8%, and 9.6% in the RHR group. The differences in RFS rates were not statistically significant (HR = 1.21, 95% CI = 0.92–1.60, $P = 0.180$; Fig. 2b). Regarding PRS, 89 patients (26.2%) in the TA group and 26 (19.5%) in the RHR group had died. The PRS rates at 1, 3, and 5 years were 92.2%, 76.5%, and 67.1% for the TA group, and 96.8%, 80.7%, and 63.6% for the RHR group. The PRS rates also showed no significant difference between the groups (HR = 0.92, 95% CI = 0.59–1.43, $P = 0.700$; Fig. 2c).

Analysis of LTP, RFS, and PRS after PSM

Kaplan–Meier curves for LTP, RFS, and PRS were evaluated by PSM. After PSM, the cumulative LTP rates were 16.8% (18/107) for the TA group and 12.1% (13/107) for the RHR group. The 1-, 3-, and 5-year cumulative LTP rates were 12.6%, 12.6% and 12.6% in the TA group and 5.9%, 16.4%, 19.2% in the RHR group, respectively (HR = 0.74, 95% CI = 0.36–1.52, $P = 0.420$; Fig. 3a). The median RFS rates for the TA (22.7 months) and RHR (22.6 months) groups were closely monitored. The RFS rates were found to be 63.6% (68/107) in the TA group and 56.1% (60/107) in the RHR group. At 1-, 3-, and 5-year, the TA group exhibited RFS rates of 56.5%, 36.9%, and 29.2%, respectively, whereas the RHR group had rates of 68.4%, 37.9%, and 16.1% (HR = 0.93, 95% CI = 0.65–1.32, $P = 0.680$; Fig. 3b). PRS rates were evaluated, revealing 28.0% (30/107) in the TA group and 23.4% (25/107) in the RHR group. The PRS rates at 1-, 3-, and 5-year for the TA group were 89.7%, 70.9%, and 67.0%, respectively, in contrast to the RHR group, which had rates of 96.1%, 77.5%, and 65.0% (HR = 0.94, 95% CI = 0.55–1.60, $P = 0.810$; Fig. 3c).

Table 2 Baseline characteristics of the rHCC cohort after PSM and IPTW

Characteristics	rHCC cohort after PSM				rHCC cohort after IPTW			
	TA (*N* = 107)	RHR (*N* = 107)	*P*	SMD	TA (*N* = 340)	RHR (*N* = 133)	*P*	SMD
Sex			1.000	< 0.001			1.000	< 0.001
Female	19 (17.8)	19 (17.8)			53.7 (15.8)	21.0 (15.8)		
Male	88 (82.2)	88 (82.2)			286.3 (84.2)	112.0 (84.2)		
Age (years)			0.412	0.131			1.000	< 0.001
< 60	52 (48.6)	59 (55.1)			179.0 (52.6)	70.0 (52.6)		
≥ 60	55 (51.4)	48 (44.9)			161.0 (47.4)	63.0 (47.4)		
Etiology			0.359	0.247			0.997	0.010
HBV	95 (88.8)	97 (90.7)			309.3 (91.0)	121.0 (91.0)		
HCV	3 (2.8)	0 (0.0)			0.0 (0.0)	0.0 (0.0)		
ALC	0 (0.0)	0 (0.0)			0.0 (0.0)	0.0 (0.0)		
PBC	0 (0.0)	0 (0.0)			0.0 (0.0)	0.0 (0.0)		
NAFLD	2 (1.9)	3 (2.8)			7.7 (2.3)	3.0 (2.3)		
Undetermined	7 (6.5)	7 (6.5)			23.0 (6.8)	9.0 (6.8)		
Liver cirrhosis			1.000	0.028			0.999	< 0.001
Absent	13 (12.1)	14 (13.1)			43.4 (12.8)	17.0 (12.8)		
Present	94 (87.9)	93 (86.9)			296.6 (87.2)	116.0 (87.2)		
CTP grade			0.373	0.163			1.000	< 0.001
A level	99 (92.5)	103 (96.3)			329.8 (97.0)	129.0 (97.0)		
B level	8 (7.5)	4 (3.7)			10.2 (3.0)	4.0 (3.0)		
Location			1.000	< 0.001			1.000	< 0.001
Left lobe	36 (33.6)	36 (33.6)			107.4 (31.6)	42.0 (31.6)		
Right lobe	65 (60.7)	65 (60.7)			214.7 (63.2)	84.0 (63.2)		
Undetermined	6 (5.6)	6 (5.6)			17.9 (5.3)	7.0 (5.3)		
Tumor size (cm)			1.000	< 0.001			1.000	< 0.001
< 3	83 (77.6)	83 (77.6)			258.2 (75.9)	101.0 (75.9)		
≥ 3, < 5	24 (22.4)	24 (22.4)			81.8 (24.1)	32.0 (24.1)		
Tumor number			1.000	0.022			1.000	< 0.001
Solitary	82 (76.6)	83 (77.6)			271.0 (79.7)	106.0 (79.7)		
Multiple	25 (23.4)	24 (22.4)			69.0 (20.3)	27.0 (20.3)		
Portal hypertension			0.067	0.276			1.000	< 0.001
Absent	78 (72.9)	90 (84.1)			276.1 (81.2)	108.0 (81.2)		
Present	29 (27.1)	17 (15.9)			63.9 (18.8)	25.0 (18.8)		
Ascites			1.000	0.042			0.999	< 0.001
Absent	102 (95.3)	101 (94.4)			322.1 (94.7)	126.0 (94.7)		
Present	5 (4.7)	6 (5.6)			17.9 (5.3)	7.0 (5.3)		
Subcapsular			0.891	0.037			1.000	< 0.001
No	54 (50.5)	52 (48.6)			184.1 (54.1)	72.0 (54.1)		
Yes	53 (49.5)	55 (51.4)			155.9 (45.9)	61.0 (45.9)		
Perivascular			0.848	0.052			1.000	< 0.001
No	90 (84.1)	92 (86.0)			288.9 (85.0)	113.0 (85.0)		
Yes	17 (15.9)	15 (14.0)			51.1 (15.0)	20.0 (15.0)		
AST (U/L)			0.575	0.102			0.999	< 0.001
≤ 45	92 (86.0)	88 (82.2)			271.0 (79.7)	106.0 (79.7)		
> 45	15 (14.0)	19 (17.8)			69.0 (20.3)	27.0 (20.3)		
ALT (U/L)			0.745	0.067			1.000	< 0.001
≤ 40	84 (78.5)	81 (75.7)			255.6 (75.2)	100.0 (75.2)		
> 40	23 (21.5)	26 (24.3)			84.4 (24.8)	33.0 (24.8)		

Table 2 (continued)

Characteristics	rHCC cohort after PSM				rHCC cohort after IPTW			
	TA (*N* = 107)	RHR (*N* = 107)	*P*	SMD	TA (*N* = 340)	RHR (*N* = 133)	*P*	SMD
ALP (U/L)			1.000	0.062			0.999	< 0.001
≤ 160	104 (97.2)	105 (98.1)			329.8 (97.0)	129.0 (97.0)		
> 160	3 (2.8)	2 (1.9)			10.2 (3.0)	4.0 (3.0)		
TBIL (μmol/L)			1.000	< 0.001			1.000	< 0.001
≤ 17.1	66 (61.7)	66 (61.7)			207.1 (60.9)	81.0 (60.9)		
> 17.1	41 (38.3)	41 (38.3)			132.9 (39.1)	52.0 (39.1)		
PLT (× 10^9/L)			1.000	< 0.001			1.000	< 0.001
≤ 100	82 (76.6)	82 (76.6)			230.1 (67.7)	90.0 (67.7)		
> 100	25 (23.4)	25 (23.4)			109.9 (32.3)	43.0 (32.3)		
INR			0.350	0.154			1.000	< 0.001
≤ 1.15	87 (81.3)	93 (86.9)			283.8 (83.5)	111.0 (83.5)		
> 1.15	20 (18.7)	14 (13.1)			56.2 (16.5)	22.0 (16.5)		
AFP (ng/mL)			0.839	0.055			1.000	< 0.001
< 200	94 (87.9)	92 (86.0)			296.5 (87.2)	116.0 (87.2)		
≥ 200	13 (12.1)	15 (14.0)			43.5 (12.8)	17.0 (12.8)		
SII			0.065	0.274			1.000	< 0.001
≤ 118.74	75 (70.1)	61 (57.0)			181.5 (53.4)	71.0 (53.4)		
> 118.74	32 (29.9)	46 (43.0)			158.5 (46.6)	62.0 (46.6)		
NLR			0.460	0.127			1.000	< 0.001
≤ 3.83	92 (86.0)	87 (81.3)			281.2 (82.7)	110.0 (82.7)		
> 3.83	15 (14.0)	20 (18.7)			58.8 (17.3)	23.0 (17.3)		
LMR			0.863	0.047			1.000	< 0.001
≤ 4.77	87 (81.3)	85 (79.4)			273.5 (80.5)	107.0 (80.5)		
> 4.77	20 (18.7)	22 (20.6)			66.5 (19.5)	26.0 (19.5)		
PNI			1.000	0.025			1.000	< 0.001
≤ 40.33	90 (84.1)	89 (83.2)			248.0 (72.9)	97.0 (72.9)		
> 40.33	17 (15.9)	18 (16.8)			92.0 (27.1)	36.0 (27.1)		

Unless indicated otherwise, data are the number of patients, with percentages in parentheses

SMDs indicate very small differences for values less than 0.10; 0.10–0.30, small differences; 0.30–0.50, moderate differences; and values higher than 0.50, large differences

$P < 0.05$ was considered significant

PSM Propensity score matching, *IPTW* Inverse probability of treatment weighting, *TA* Thermal ablation, *RHR* Repeated hepatic resection, *SMDs* Standardized mean differences, *CTP* Child-Turcotte-Pugh, *HBV* Hepatitis B virus, *HCV* Hepatitis C virus, *ALC* Alcoholic cirrhosis, *PBC* Primary biliary cholangitis, *NAFLD* non-alcoholic fatty liver disease, *AST* Aspartate aminotransferase, *ALT* Alanine aminotransferase, *TBIL* Total bilirubin, *PLT* Platelet, *INR* International normalized ratio, *AFP* Alpha-fetoprotein, *SII* Platelet count × neutrophil count / lymphocyte count, *NLR* Neutrophil–lymphocyte ratio, *LMR* Lymphocyte-monocyte ratio, *PNI* Albumin + 5 × lymphocyte count

Analysis of LTP, RFS, and PRS after IPTW

To validate findings of PSM, Kaplan–Meier curves for LTP, RFS, and PRS were also evaluated using IPTW. The cumulative LTP rates post-IPTW were 17.5% (59.5/340.0) in the TA group and 16.0% (12.0/133.0) in the RHR group. Specifically, the 1-, 3-, and 5-year LTP rates for the TA group were 7.7%, 19.5%, and 26.7%, respectively, compared to 6.5%, 15.4%, and 29.5% in the RHR group (HR = 0.73, 95% CI = 0.34–1.58, $P = 0.940$; Fig. 3d). In terms of RFS, the TA group had a median RFS of 19.2 months, while the RHR group's median RFS was 24.1 months. The RFS rates were observed to be 61.0% (207.5/340.0) in the TA group and 52.6% (70.0/133.0) in the RHR group. The 1-, 3-, and 5-year RFS rates were 59.5%, 35.7%, and 31.3% for the TA group, compared to 69.8%, 39.8%, and 9.6% for the RHR group (HR = 0.89, 95% CI = 0.61–1.29, $P = 0.180$; Fig. 3e). Evaluating PRS, the TA group had 31.7% (107.7/340.0) of patients, while the RHR group had 19.5% (26.0/133) who died. The 1-, 3-, and 5-year PRS rates were 83.7%, 68.2%, and 64.8% for the TA group, and 96.8%, 80.7%, and 63.6% for the RHR group (HR = 0.63, 95% CI = 0.35–1.14, $P = 0.700$; Fig. 3f).

Subgroup analysis

Tumor size, tumor number, subcapsular lesions, and perivascular lesions not only affect the difficulty of

Table 3 Prognostic factor analysis for RFS and PRS in the entire rHCC cohort

Characteristics	RFS				PRS			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex (Female vs. Male)	1.19 (0.85–1.67)	0.303	1.28 (0.91–1.80)	0.153	1.06 (0.65–1.73)	0.821		
Age (< 60 vs. ≥ 60)	1.08 (0.84–1.38)	0.543			0.94 (0.65–1.35)	0.721		
Etiology (HBV vs. HCV)	0.63 (0.26–1.52)	0.299			0.85 (0.27–2.67)	0.776		
Etiology (HBV vs. NAFLD)	0.82 (0.36–1.85)	0.633			0.59 (0.14–2.37)	0.454		
Etiology (HBV vs. Undetermined)	1.23 (0.76–1.99)	0.401			0.48 (0.18–1.31)	0.152		
Liver cirrhosis (Absent vs. Present)	1.26 (0.85–1.87)	0.245			1.01 (0.58–1.73)	0.981		
CTP grade (A level vs. B level)	1.00 (0.44–2.24)	0.992			3.35 (1.63–6.88)	0.001	2.05 (0.88–4.80)	0.097
Location (Left lobe vs. Right lobe)	0.87 (0.66–1.15)	0.322			0.52 (0.36–0.77)	0.001	0.55 (0.37–0.83)	0.004
Location (Left lobe vs. Undetermined)	1.56 (0.82–2.94)	0.174			1.05 (0.45–2.47)	0.906	0.87 (0.34–2.24)	0.776
Tumor size (< 3 cm vs. ≥ 3, < 5 cm)	1.51 (1.06–2.15)	0.023	1.34 (0.93–1.93)	0.114	2.24 (1.42–3.55)	0.001	1.95 (1.21–3.15)	0.006
Tumor number (Solitary vs. Multiple)	2.24 (1.68–3.00)	<0.001	2.28 (1.69–3.07)	< 0.001	2.13 (1.42–3.20)	<0.001	1.67 (1.06–2.61)	0.026
Portal hypertension (Absent vs. Present)	1.03 (0.76–1.39)	0.855			1.17 (0.76–1.80)	0.479		
Ascites (Absent vs. Present)	0.71 (0.41–1.22)	0.213			2.00 (1.14–3.49)	0.015	2.18 (1.15–4.14)	0.017
Subcapsular (Absent vs. Present)	1.07 (0.83–1.39)	0.594			1.05 (0.72–1.54)	0.787		
Perivascular (Absent vs. Present)	0.93 (0.66–1.32)	0.687			1.04 (0.63–1.70)	0.882		
AST (≤ 45 U/L vs. > 45 U/L)	1.43 (1.00–2.06)	0.051			1.68 (1.02–2.74)	0.040	1.72 (1.02–2.90)	0.042
ALT (≤ 40 U/L vs. > 40 U/L)	1.07 (0.76–1.50)	0.689			1.06 (0.64–1.75)	0.819		
ALP (≤ 160 U/L vs. > 160 U/L)	0.89 (0.46–1.73)	0.725			0.73 (0.23–2.29)	0.585	0.39 (0.12–1.34)	0.135
TBIL (≤ 17.1 μmol/L vs. > 17.1 μmol/L)	0.92 (0.71–1.20)	0.536			1.36 (0.94–1.97)	0.104		
PLT (≤ 100 × 10^9/L vs. > 100 × 10^9/L)	0.80 (0.59–1.07)	0.129	0.73 (0.54–0.98)	0.038	1.27 (0.85–1.91)	0.244	1.40 (0.91–2.14)	0.122
INR (≤ 1.15 vs. > 1.15)	0.90 (0.64–1.26)	0.539			1.40 (0.90–2.19)	0.135		
AFP (< 200 ng/mL vs. ≥ 200 ng/mL)	1.40 (0.97–2.04)	0.073			1.76 (1.07–2.92)	0.027	1.69 (1.01–2.84)	0.046
SII (≤ 118.74 vs. > 118.74)	0.93 (0.72–1.21)	0.606			1.40 (0.96–2.04)	0.080		
NLR (≤ 3.83 vs. > 3.83)	1.49 (1.05–2.13)	0.026	1.33 (0.92–1.92)	0.128	1.74 (1.07–2.82)	0.024	1.60 (0.96–2.64)	0.069
LMR (≤ 4.77 vs. > 4.77)	1.04 (0.72–1.50)	0.847			1.41 (0.87–2.29)	0.162		
PNI (≤ 40.33 vs. > 40.33)	0.78 (0.50–1.20)	0.259			0.74 (0.36–1.52)	0.409		
Treatment (TA vs. RHR)	1.21 (0.92–1.60)	0.181			0.92 (0.59–1.43)	0.705		

Data in parentheses are 95% CIs

P < 0.05 was considered significant

TA Thermal ablation, *RHR* Repeated hepatic resection, *RFS* Recurrence-free survival, *PRS* Post-recurrence survival, *CTP* Child-Turcotte-Pugh, *HBV* Hepatitis B virus, *HCV* Hepatitis C virus, *NAFLD* Non-alcoholic fatty liver disease, *AST* Aspartate aminotransferase, *ALT* Alanine aminotransferase, *TBIL* Total bilirubin, *PLT* Platelet, *INR* International normalized ratio, *AFP* Alpha-fetoprotein, *SII* Platelet count × neutrophil count / lymphocyte count, *NLR* Neutrophil–lymphocyte ratio, *LMR* Lymphocyte-monocyte ratio, *PNI* Albumin + 5 × lymphocyte count

surgical resection or ablation but also determine the prognosis of patients. Therefore, this subgroup analysis was stratified based on these factors to observe their influence on LTP, RFS, and PRS in both groups (Fig. 4 and S1-2). After PSM, no statistically significant differences in RFS were observed for the subgroups with tumor sizes < 3 cm ($P = 0.940$) or ≥ 3 cm ($P = 0.380$) and solitary tumor ($P = 0.630$) or multiple tumors ($P = 0.110$) (Fig. 4b). Similarly, no statistically significant differences were found for the subgroups after IPTW ($P = 0.320$ and $P = 0.120$; $P = 0.890$ and $P = 0.630$; Fig. 4c). RFS did not show statistically significant differences between the subgroups without and with perivascular lesions after PSM ($P = 0.780$ and $P = 0.055$, respectively) and IPTW ($P = 0.052$ and $P = 0.130$, respectively; Fig. 4b and c) There were no statistically significant differences in RFS for the subgroups without and with subcapsular lesions after PSM ($P = 0.100$ and $P = 0.220$, respectively; Fig. 4b). However, a statistically significant difference in RFS was observed for the subcapsular subgroup after IPTW ($P = 0.008$; Fig. 4c).

Figures S1 and S2 display the analyses of tumor size, tumor number, subcapsular, and perivascular subgroups for LTP and PRS, revealing no statistically significant differences between the two groups.

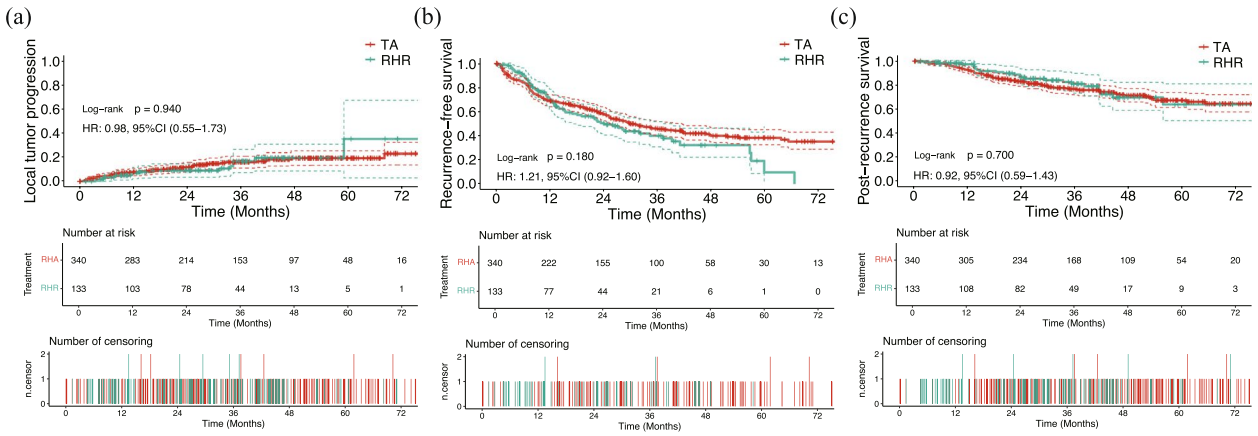

Fig. 2 Kaplan-Meier analysis of LTP (**a**), RFS (**b**), and PRS (**c**) in patients who underwent TA and RHR in the entire rHCC cohort. TA, thermal ablation; RHR, repeated hepatic resection; rHCC, recurrent hepatocellular carcinoma; LTP, local tumor progression; RFS, recurrence-free survival; PRS, post-recurrence survival

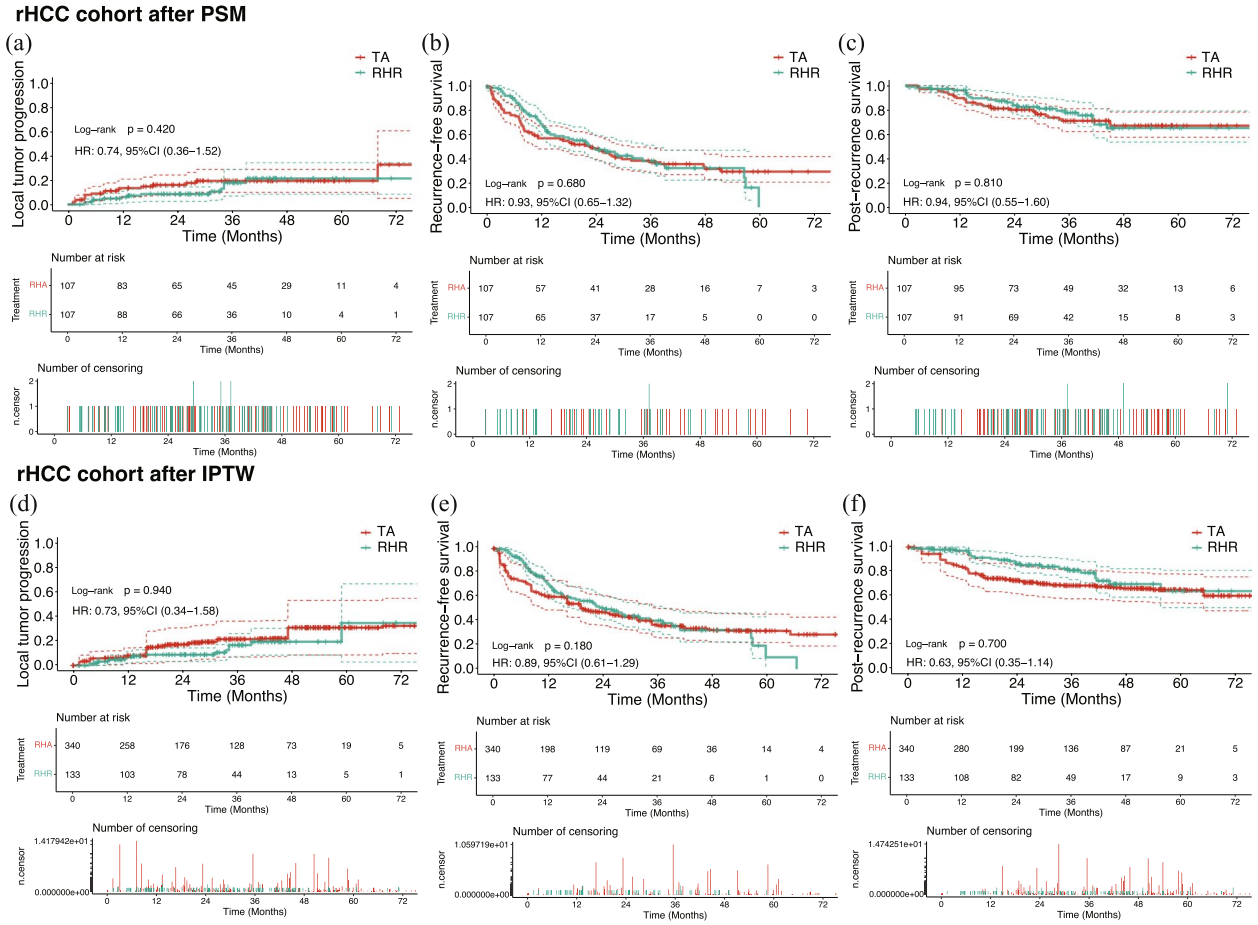

Fig. 3 Kaplan-Meier analysis of LTP (**a**, **d**), RFS (**b**, **e**), and PRS (**c**, **f**) in patients who underwent TA and RHR after PSM and IPTW. TA, thermal ablation; RHR, repeated hepatic resection; rHCC, recurrent hepatocellular carcinoma; LTP, local tumor progression; RFS, recurrence-free survival; PRS, post-recurrence survival; PSM, propensity score matching; IPTW, inverse probability of treatment weighting

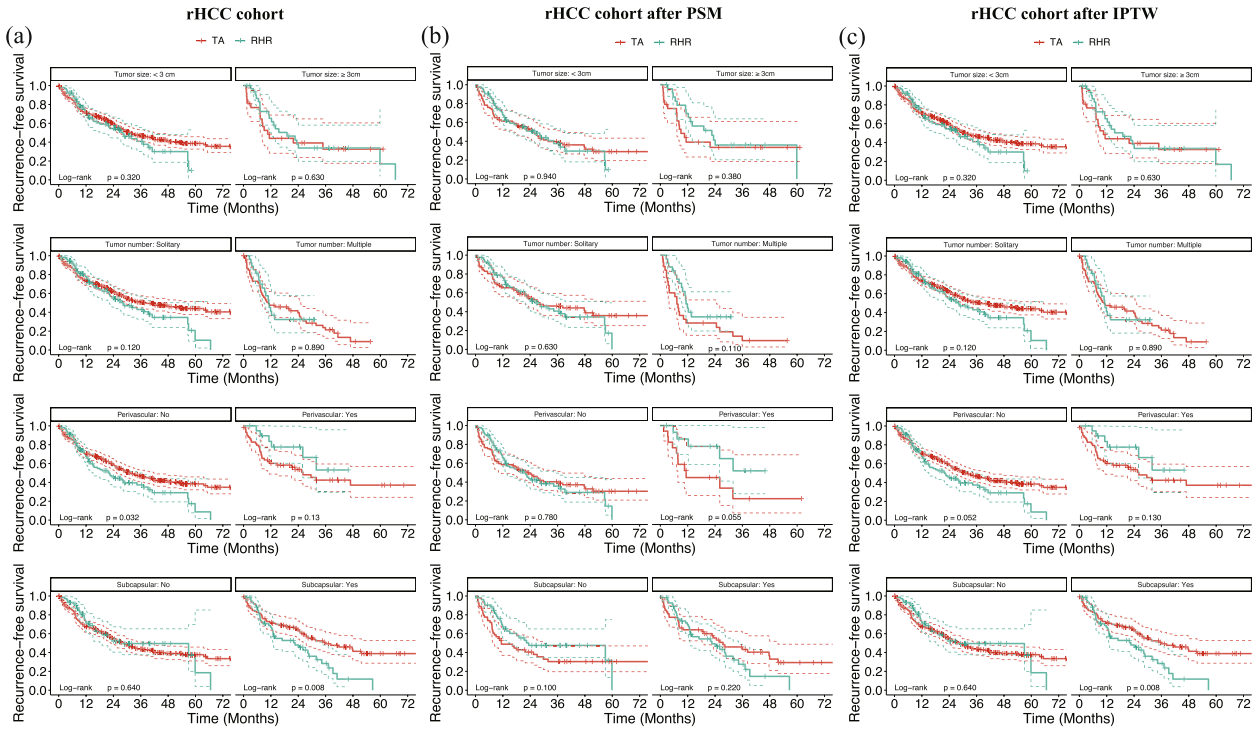

Fig. 4 Subgroup analyses for RFS between TA and RHR groups in the patients with rHCC. **a** Subgroup analyses of the entire rHCC cohort by tumor size, number, perivascular lesions, and subcapsular lesions. **b** Subgroup analyses of the rHCC cohort after PSM by tumor size, number, perivascular lesions, and subcapsular lesions. **c** Subgroup analyses of the rHCC cohort after IPTW by tumor size, number, perivascular lesions, and subcapsular lesions. TA, thermal ablation; RHR, repeated hepatic resection; rHCC, recurrent hepatocellular carcinoma; RFS, recurrence-free survival; PSM, propensity score matching; IPTW, inverse probability of treatment weighting

Discussion

RHR may be the optimal first-line treatment for rHCC within the Milan criteria. However, it is only feasible in a small proportion of patients, particularly those with smaller tumor size, solitary tumors, and better residual liver function [21]. Aggressive local treatments may improve the prognosis of patients with intrahepatic rHCC after surgery and should therefore be attempted. In this study, we analyzed long-term survival outcomes of TA and RHR in 473 rHCC patients within the Milan criteria, revealing no statistically significant difference in 1-, 3-, and 5-year LTP, RFS, and PRS through PSM and IPTW analyses. Subgroup analysis also showed no significant differences in LTP, RFS, and PRS between the two treatments among patients with tumors smaller or larger than 3 cm, solitary or multiple, with or without subcapsular, and with or without perivascular involvement after PSM. However, a significant difference in RFS was observed among patients with subcapsular lesions after IPTW.

Using both PSM and IPTW, we reduced the SMD for all potential confounding factors to less than 0.300, effectively adjusting for these factors. PSM is regarded as more robust and less biased compared to other propensity score methods [22]. However, a notable disadvantage of PSM is the reduction in sample size, especially in datasets with highly imbalanced groups. To address this limitation, our study also employed IPTW, which helps maintain a larger sample size while still effectively controlling for confounding factors. By using PSM and IPTW, we ensured a comprehensive adjustment for confounding factors, leveraging the strengths of both methods to enhance the reliability of our findings. Therefore, the results of our study, which balanced patient demographics, liver function reserves, and tumor characteristics between the RHR and TA groups, provide important data for clinical decision-making in rHCC after initial hepatic resection.

In this study, LTP was observed in 13.3% (63 out of 473) of patients with rHCC: 13.8% (47 out of 340) in the TA group and 12.0% (16 out of 133) in the RHR group. These results align with previously reported LTP rates of 8.4–14.8% [23–25]. The cumulative LTP rates showed no significant difference between the TA and RHR groups ($P = 0.420$–0.940), both before and after applying PSM and IPTW. This lack of significant difference can be attributed to the relatively small tumor size and complete thermal ablation in our study. Additionally,

the median RFS was nearly the same between the TA and RHR groups, both before and after PSM. Although there was a tendency toward a longer RFS in RHR group, this difference remained statistically insignificant after applying IPTW. This tendency aligns with the findings of Zhong et al. [14], where RFS for rHCC was significantly longer in the RHR group compared to the RFA group, with a statistically significant difference. This discrepancy can be explained by the different methods used to reduce confounding factors or the smaller sample size in our study. Similarly, the RHR group had a longer PRS compared to the TA group before and after applying PSM and IPTW, but this difference was not statistically significant. This finding is consistent with previous studies [10, 12, 14, 26].

We analyzed prognostic variables with rHCC and found that long-term RFS and PRS results were associated with ascites, tumor number, size, location, AST, PLT, AFP, and NLR. Liver function damage emerged as a significant indicator of poor prognosis. Ascites and elevated transaminase levels, representing liver damage, suggest high tumor invasiveness and poor liver function, leading to a worse prognosis [7]. A recent meta-analysis confirmed that PLT count is a prognostic marker in HCC, particularly with a PLT count cutoff of $< 100 \times 10^9$/L [27]. Liu et al. [28] further demonstrated that intra-platelet 5-HT might affect progression and prognosis of HCC by regulating Yes-associated protein expression. Tang et al. [29] identified that tumors located in the left lobe were linked to OS and RFS after hepatectomy for HCC. Additionally, previous studies have reported that systemic inflammation biomarkers can evaluate HCC prognosis, finding that higher NLR levels and lower LMR levels were associated with worse survival outcomes [30, 31]. Therefore, our prognostic analysis is consistent with previous reports and confirms that the underlying biological features of HCC are the main determinants of survival.

In this study, we compared two groups of patients with rHCC: those who underwent TA and those who underwent RHR. The subgroup analysis was based on tumor size, tumor number, subcapsular lesions, and perivascular lesions. Of the tumors, 35.1% (166/473) were located subcapsularly, and 16.7% (79/473) were close to large central vessels. Our study demonstrated that both TA and RHR are effective treatments for early-stage rHCC (within the Milan criteria) in terms of LTP, RFS, and PRS, regardless of whether the tumors were larger (3–5 cm), multiple (≤3), subcapsular or perivascular. Liu et al. [32] indicated that MWA showed comparable LTP, OS, and disease-free survival to surgical resection for subcapsular HCC meeting the Milan criteria. Lee et al. [33] compared long-term outcomes between surgical resection and RFA as first-line treatments, finding both to be viable options for perivascular small HCC (≤3 cm). However, few studies have reported on the long-term prognosis of subcapsular or perivascular rHCC treated with TA and RHR. Our results provide additional evidence in this area.

Our study had several limitations. Firstly, we used a multicenter retrospective approach. In the future, we will employ large-sample, prospective randomized controlled trials to validate these results. Secondly, despite performing PSM and IPTW to enhance intergroup comparison, there were still unavoidable and unidentified confounding factors and selection bias.

In conclusion, the cumulative LTP, RFS, and PRS were not significantly different between TA and RHR for rHCC patients within the Milan criteria. TA showed comparable therapeutic outcomes to RHR for rHCC within the Milan criteria, and may be a viable curative option for early-stage rHCC patients.

Abbreviations

AFP	Alpha-fetoprotein
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CI	Confidence intervals
HR	Hazard ratios
INR	International normalized ratio
IPTW	Inverse probability of treatment weighting
LMR	Lymphocyte-to-monocyte ratio
LTP	Local tumor progression
MWA	Microwave ablation
PNI	Prognostic nutritional index
PRS	Post-recurrence survival
PSM	Propensity score matching
RFA	Radiofrequency ablation
RFS	Recurrence-free survival
rHCC	Recurrent hepatocellular carcinoma
RHR	Repeat hepatic resection
SII	Systemic immune-inflammation index
SMD	Standardized mean differences
TA	Thermal ablation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13660-9.

Supplementary Material 1.

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None.

Authors' contributions

Study concept and design: Ke Zhang, Wenbo Wang, Wei Yang, and Tianan Jiang; Acquisition of data: Ke Zhang, Wenbo Wang, and Lei Mu; Analysis and interpretation of data: Ke Zhang and Wenbo Wang; Drafting of the manuscript: Ke Zhang and Wenbo Wang; Critical revision of the manuscript: All authors; Statistical analysis: Ke Zhang and Wenbo Wang; Study supervision: All authors.

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Data availability
Due to patient privacy considerations, data related to patients cannot be made publicly accessible. However, interested parties can request access to the data from the corresponding author through a reasonable inquiry process, subject to approval by the Institutional Review Board of all enrolled centers.

Declarations

Ethics approval and consent to participate
This study was approved by Ethics Committee of The First Affiliated Hospital, Zhejiang University School of Medicine and Peking University Cancer Hospital.

Consent for publication
Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Competing interests
The authors declare no competing interests.

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