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Laparoscopic Hepatectomy Versus Radiofrequency Ablation for Solitary Hepatocellular Carcinoma ≤3 cm: A Retrospective Cohort Study

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Research Article

Keywords: hepatocellular carcinoma, laparoscopic hepatectomy, radiofrequency ablation, recurrence-free survival

Posted Date: November 5th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11337365/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Hepatocellular carcinoma (HCC) is commonly treated with curative-intent approaches, including laparoscopic hepatectomy (LH) and radiofrequency ablation (RFA), in patients with early-stage disease. However, the comparative effectiveness of these two treatment modalities in patients with solitary HCC measuring ≤3 cm remains unclear.

This study aimed to compare the therapeutic outcomes and recurrence patterns between LH and RFA in patients with primary solitary HCC measuring ≤3 cm.

Methods

This study is a single-center retrospective analysis conducted at Tianjin Medical University Cancer Institute & Hospital, which enrolled 383 patients with primary, solitary HCC measuring ≤ 3 cm in diameter who underwent LH and RFA. All patients were newly diagnosed and had not received prior treatment. The primary endpoints included overall survival (OS) and recurrence-free survival (RFS). Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) were performed to adjust for differences in baseline characteristics between the two treatment groups, followed by longitudinal follow-up to evaluate long-term survival and recurrence outcomes.

Results

The findings indicated that there was no statistically significant difference in OS outcomes between the two treatment modalities (P=0.25). However, LH was associated with a lower recurrence rate compared with RFA (7.7% vs. 22.9%) and longer RFS (P=0.02). This difference remained statistically significant after PSM and IPTW adjustment (P=0.0068 and P=0.02). Among patients with tumors measuring ≤2 cm, no statistically significant difference in RFS was observed in the overall cohort, after PSM, or after IPTW adjustment (P=0.074, P=0.061, and P=0.074, respectively). Among patients with tumors measuring >2 to ≤3 cm, LH was associated with improved RFS after PSM (P=0.042), whereas differences were not statistically significant in the unmatched analysis or IPTW-adjusted analysis.

Conclusion

In this retrospective cohort study of patients with solitary HCC measuring ≤3 cm, LH was associated with improved recurrence control compared with RFA, while no significant difference in OS was observed. Exploratory tumor-size subgroup analyses suggested a possible difference in RFS among patients with tumors measuring >2 to ≤3 cm, although this finding was not consistently observed across analytical approaches and the treatment-by-tumor-size interaction was not statistically significant. These findings require further validation in prospective studies.

Introduction

Liver cancer is the sixth most commonly diagnosed cancer and the third leading cause of cancer-related death worldwide, responsible for approximately 760,000 deaths annually—accounting for 7.8% of all cancer deaths. Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, accounting for approximately 80% of all liver cancer cases.[1] Advancements in diagnostic technologies, including imaging and serological screening, have led to a substantial increase in the detection rate of solitary small hepatocellular carcinomas with a diameter of ≤ 3 cm. Consequently, a growing number of patients are diagnosed at an early stage and may become eligible for curative-intent treatments.[2–5] Various therapeutic approaches are available for HCC, including open liver resection, laparoscopic hepatectomy, robotic-assisted liver resection, ablation therapy, and liver transplantation.

For small HCC, particularly solitary tumor ≤ 3 cm in diameter, laparoscopic hepatectomy and ablation therapy represent important curative-intent treatment options. Laparoscopic hepatectomy has the advantages of minimally invasive surgery, reduced surgical trauma, and faster postoperative recovery. Moreover, early-stage liver cancer patients have exhibited equivalent 5-year overall survival rates to those undergoing open surgery. [6,7] Ablation therapy is also considered a curative-intent option for selected patients with small HCC, particularly when surgical resection is not feasible or preferred. Radiofrequency ablation (RFA) is one of the most commonly used ablation techniques. In early-stage HCC patients who are candidates for surgical treatment, RFA has shown comparable or slightly inferior overall survival outcomes compared with surgical resection in previous studies, while offering advantages including lower complication rates and shorter hospital stays. [8–11]

Although previous retrospective studies have compared LH and RFA, evidence specifically focusing on patients with solitary HCC ≤ 3 cm remains limited.[12–14] Therefore, this study aimed to compare the clinical outcomes of LH and RFA in patients with solitary HCC ≤ 3 cm in diameter and to evaluate differences in survival and recurrence outcomes between these two treatment approaches.

Materials and Methods

Study Design

From 2016 to 2024, we conducted a retrospective analysis of patients with newly diagnosed, solitary HCC measuring ≤ 3 cm in diameter who were treated at our center. Patients were assigned to either the LH group or the RFA group according to their chosen treatment method. We made comparisons across groups based on perioperative clinical data and long-term oncological outcomes, including overall survival (OS) and recurrence-free survival (RFS). The inclusion criteria were as follows: (1) patients with HCC who are experiencing their first episode and have not received other treatments; (2) a solitary tumor with a diameter of ≤ 3 cm in diameter; (3) Barcelona clinical liver cancer stage 0 or A; (4) Child-Pugh class A or B; and (5) Eastern Cooperative Oncology

Group performance status (ECOG PS) 0 or 1. The exclusion criteria were as follows: (1) a history of previous liver cancer; (2) more than one tumor; (3) Tumor diameter > 3 cm; (4) Child-Pugh class C; and(5) ECOG PS ≥ 2.

Treatment Process

Treatment selection was based on routine clinical practice and individualized assessment. Patients with preserved liver function and tumors located near the liver surface were more likely to undergo LH, whereas RFA was more frequently selected for patients with deeply located tumors or those requiring extensive resection and management of multiple intrahepatic vessels. Therefore, tumor-related anatomical characteristics, including location and depth, may have influenced treatment allocation and represent potential sources of residual confounding. RFA was performed percutaneously under real-time ultrasound guidance. Each ablation point was treated for 12 minutes at a power setting of 110–180 W.

Statistical Analysis

Continuous variables are summarized as mean ± standard deviation, while categorical variables are summarized as counts (percentages). Differences in baseline characteristics between the two treatment groups were assessed using Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. The Kaplan–Meier method was used to estimate overall survival (OS) and recurrence-free survival (RFS), and the log-rank test was applied to compare survival curves. Cox proportional hazards regression analyses were performed to evaluate factors associated with OS and RFS. Both univariate and multivariate Cox regression models were constructed, with clinically relevant variables included in the multivariate analyses.

Exploratory subgroup analyses for recurrence-free survival (RFS) were performed according to clinically relevant baseline characteristics, including age (< 60 or ≥ 60 years), HBV infection status, cirrhosis status, tumor size (≤ 2 cm or > 2 to ≤ 3 cm), and AFP level (≤ 7 ng/mL or > 7 ng/mL). The interaction between treatment effect and subgroup variables was assessed using Cox proportional hazards regression models.

To reduce imbalance in measured baseline characteristics between the treatment groups, propensity scores (PSs) were estimated using logistic regression based on age, sex, HBV infection status, cirrhosis, tumor size, log-transformed AFP [log(AFP + 1)], and ALBI grade. These variables were selected based on their clinical relevance to treatment allocation and prognosis rather than statistical significance in univariable analyses. A 1:2 nearest-neighbor propensity score matching (PSM) approach was performed using the "MatchIt" package in R, with a caliper width of 0.1 standard deviations of the propensity score. Covariate balance before and after matching was assessed using the absolute standardized mean difference (SMD), with an absolute SMD < 0.1 considered indicative of adequate balance.

Inverse probability of treatment weighting (IPTW) was performed using the same propensity score model. The inverse probability weights were calculated as 1/PS for patients undergoing LH and 1/(1 − PS) for patients undergoing RFA. Extreme weights were truncated at the 99th percentile. Weighted Kaplan–Meier analyses and weighted Cox proportional hazards models were used to evaluate survival outcomes after IPTW adjustment. Covariate balance after weighting was assessed using the absolute SMD, with an absolute SMD < 0.1 considered indicative of adequate balance.

All statistical analyses were performed using R software version 4.5.1 (http://www.rproject.org). P value < 0.05 was considered statistically significant.

Results

Baseline Characteristics

The patients' disposition is shown in Fig. 1. The baseline features are shown in the Table 1. In the overall population, the mean age was 57.73 years, males account for 70% (270/383). Most patients had HBV infection (73%, 278/383), and cirrhosis was present in 79% (301/383) of patients, and most had Child-Pugh class A (97%).

Table 1
Baseline characteristics before and after propensity score matching (PSM)

Variable	Before PSM						After PSM		
	Overall N = 383[1]	LH N = 104[1]	RFA N = 279[1]	SMD[2]	95% CI[2]	p-value[3]	Overall N = 269[1]	LH N = 97[1]	RFA N =
Age	57.73(10.23)	58.63(10.51)	57.39(10.12)	0.12	-0.10, 0.35	0.6	57.84(10.15)	57.75(9.98)	57.
Sex, cases (%)				0.20	-0.03, 0.42	0.092			
Male	270/383(70%)	80/104(77%)	190/279(68%)				203/269(75%)	75/97(77%)	128
Female	113/383(30%)	24/104(23%)	89/279(32%)				66/269(25%)	22/97(23%)	44/
LOS	4.14(2.46)	4.89(2.33)	3.85(2.45)	0.44	0.21, 0.66	< 0.001	4.15(2.39)	4.84(2.22)	3.7
HBV				0.36	0.14, 0.59	0.003			
0	105/383(27%)	17/104(16%)	88/279(32%)				51/269(19%)	16/97(16%)	35/
1	278/383(73%)	87/104(84%)	191/279(68%)				218/269(81%)	81/97(84%)	137
Cirrhosis				0.14	-0.08, 0.37	0.2			
0	82/383(21%)	18/104(17%)	64/279(23%)				47/269(17%)	18/97(19%)	29/
1	301/383(79%)	86/104(83%)	215/279(77%)				222/269(83%)	79/97(81%)	143
ALB	42.41(4.95)	43.34(4.92)	42.06(4.92)	0.26	0.04, 0.49	0.005	42.83(4.54)	43.28(5.03)	42.
TBIL	16.10(9.02)	14.98(9.41)	16.52(8.85)	-0.17	-0.39, 0.06	0.058	15.92(9.13)	14.84(9.53)	16.
DBIL	7.02(5.51)	6.84(7.75)	7.08(4.41)	-0.04	-0.26, 0.19	0.079	7.03(6.14)	6.81(7.94)	7.1
GGT	60.69(83.81)	62.61(100.67)	59.97(76.78)	0.03	-0.20, 0.25	0.7	62.15(89.75)	62.49(103.20)	61.
ChE	6,930.98(1,969.15)	7,097.71(1,846.17)	6,868.82(2,012.73)	0.12	-0.11, 0.34	0.3	6,922.52(1,946.88)	7,184.37(1,817.48)	6,7
LDH	194.05(39.96)	194.30(34.51)	193.94(41.99)	0.01	-0.23, 0.25	0.9	191.63(39.35)	194.43(33.15)	189
ALT	30.74(28.45)	32.87(40.60)	29.95(22.35)	0.09	-0.14, 0.31	0.8	32.16(31.94)	33.58(41.90)	31.
AST	32.05(24.04)	33.95(32.10)	31.35(20.27)	0.10	-0.13, 0.32	> 0.9	31.92(25.00)	33.56(32.13)	31.
PLT	148.44(63.63)	147.26(58.13)	148.89(65.68)	-0.03	-0.25, 0.20	> 0.9	145.90(60.96)	147.22(59.78)	145
AFP	267.75(1,281.05)	463.76(1,605.96)	194.69(1,131.24)	0.19	-0.03, 0.42	0.4	294.01(1,446.61)	327.33(1,497.20)	275
CA199	42.91(375.41)	23.01(27.49)	50.33(439.51)	-0.09	-0.31, 0.14	0.7	24.24(23.50)	22.53(27.98)	25.
SIZE				0.29	0.06, 0.52	0.013			
>2cm	192/383(50%)	63/104(61%)	129/279(46%)				150/269(56%)	56/97(58%)	94/
≤ 2cm	191/383(50%)	41/104(39%)	150/279(54%)				119/269(44%)	41/97(42%)	78/
NLR	2.03(1.24)	2.04(1.30)	2.02(1.22)	0.01	-0.21, 0.24	0.9	2.04(1.20)	1.99(1.23)	2.0
PLR	98.96(44.04)	92.61(39.93)	101.32(45.31)	-0.20	-0.43, 0.02	0.11	97.69(42.49)	91.29(38.37)	101
ALBI grade				-0.24	-0.47, -0.02	0.13			

Abbreviation: CI = Confidence Interval

Variable	Before PSM						After PSM		
	Overall N = 383[1]	LH N = 104[1]	RFA N = 279[1]	SMD[2]	95% CI[2]	p-value[3]	Overall N = 269[1]	LH N = 97[1]	RFA N =
1	295/383(77%)	87/104(84%)	208/279(75%)				217/269(81%)	81/97(84%)	136
2	85/383(22%)	17/104(16%)	68/279(24%)				52/269(19%)	16/97(16%)	36/
3	3/383(0.8%)	0/104(0%)	3/279(1.1%)						
[1]Mean(SD); n/N(%)									
[2]Standardized Mean Difference									
[3]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test									
Abbreviation: CI = Confidence Interval									

Before propensity score matching, baseline characteristics differed between the LH and RFA groups. After 1:2 nearest-neighbor propensity score matching, 269 patients remained in the matched cohort, including 97 patients in the LH group and 172 patients in the RFA group. The baseline characteristics between groups were substantially balanced after matching. Most covariates achieved adequate balance, with absolute standardized mean differences (SMDs) close to or below 0.1. A minor residual imbalance was observed for ALBI grade (absolute SMD = 0.11).

Perioperative Outcomes

The length of hospital stay (LOS) was compared between the LH and RFA groups as a perioperative outcome. In the overall cohort, patients undergoing LH had a significantly longer hospital stay than those undergoing RFA (4.89 vs. 3.85 days, P < 0.001). After propensity score matching, the difference remained statistically significant, with a longer LOS observed in the LH group compared with the RFA group (4.84 vs. 3.77 days, P < 0.001, Table 1).

Primary Outcomes

The median follow-up duration was 34 months (IQR, 19–48 months). During follow-up, 2 deaths (1.9%) occurred in the LH group, compared to 19 deaths (6.8%) in the RFA group. No significant difference in overall survival (OS) was observed between the two groups in the unadjusted analysis (P = 0.25, Fig. 2A).

In terms of recurrence outcomes, 8 patients (7.7%) in the LH group and 64 patients (22.9%) in the RFA group developed tumor recurrence. Patients undergoing LH showed significantly improved recurrence-free survival (RFS) compared with those undergoing RFA (P = 0.02, Fig. 2B).

After propensity score matching, 269 patients remained in the matched cohort (97 LH and 172 RFA). Baseline covariate balance was assessed using absolute standardized mean differences (SMDs), and most covariates achieved adequate balance after matching. No significant difference in OS was observed between the two groups after PSM (P = 0.39, Fig. 2C). However, LH remained associated with significantly improved RFS compared with RFA after matching (P = 0.0068, Fig. 2D).

Most measured baseline covariates were reasonably balanced after IPTW weighting, although minor residual imbalance remained for some covariates (Supplementary Table S1). No significant difference in OS was observed between the two treatment groups (P = 0.25, Fig. 2E). In contrast, IPTW-adjusted analysis demonstrated that LH was associated with significantly improved RFS compared with RFA (P = 0.02, Fig. 2F).

In multivariable Cox regression analysis, LH was associated with a lower hazard of recurrence than RFA (HR = 0.33, 95% CI 0.15–0.75, P = 0.008; Table 2).

Primary Outcomes in Subgroups

Exploratory subgroup analyses were performed to assess the consistency of the association between treatment modality and RFS across clinically relevant subgroups, including age, HBV infection status, cirrhosis, tumor size, and AFP level. No significant interactions were observed between treatment modality and any of the evaluated subgroup variables (all P for interaction > 0.05). The detailed subgroup results are presented in Fig. 3.

Subgroup analysis based on tumor size

We subsequently analyzed patients according to tumor size, including tumors measuring ≤ 2 cm and > 2 to ≤ 3 cm in diameter. Baseline characteristics before and after propensity score matching are presented in Tables 3 and 4. After 1:2 propensity score matching, 103 patients with tumors ≤ 2 cm remained in the matched cohort, including 37 patients in the LH group and 66 patients in the RFA group. Most measured baseline covariates showed improved balance after PSM, and covariate balance after IPTW adjustment is presented in Supplementary Tables S2 and S3.

Table 3
Baseline characteristics before and after PSM in patients with tumors measuring ≤ 2 cm

Variable	Before PSM						After PSM		
	Overall N = 191[1]	LH N = 41[1]	RFA N = 150[1]	SMD[2]	95% CI[2]	p-value[3]	Overall N = 103[1]	LH N = 37[1]	RFA N =
Age	57.28(10.36)	56.71(12.43)	57.43(9.76)	-0.07	-0.41, 0.28	0.5	56.25(10.91)	56.65(11.95)	56.(
Sex, cases (%)				0.43	0.08, 0.77	0.023			
Male	120/191(63%)	32/41(78%)	88/150(59%)				84/103(82%)	28/37(76%)	56/
Female	71/191(37%)	9/41(22%)	62/150(41%)				19/103(18%)	9/37(24%)	10/
HBV				0.29	-0.06, 0.64	0.12			
0	56/191(29%)	8/41(20%)	48/150(32%)				18/103(17%)	7/37(19%)	11/
1	135/191(71%)	33/41(80%)	102/150(68%)				85/103(83%)	30/37(81%)	55/
Cirrhosis				0.31	-0.04, 0.66	0.10			
0	41/191(21%)	5/41(12%)	36/150(24%)				14/103(14%)	5/37(14%)	9/6
1	150/191(79%)	36/41(88%)	114/150(76%)				89/103(86%)	32/37(86%)	57/
ALB	42.35(5.18)	43.63(4.99)	42.00(5.19)	0.32	-0.02, 0.67	0.026	42.94(4.86)	43.35(5.18)	42.1
TBIL	16.39(9.05)	14.30(6.05)	16.96(9.65)	-0.33	-0.68, 0.01	0.3	15.23(7.40)	14.52(6.04)	15.(
DBIL	6.96(4.45)	6.08(2.94)	7.20(4.76)	-0.29	-0.63, 0.06	0.3	6.54(3.30)	6.24(3.01)	6.7
GGT	50.63(68.18)	60.15(117.69)	48.03(46.67)	0.14	-0.21, 0.48	0.9	59.85(85.36)	63.38(123.60)	57.8
ChE	6,925.98(1,932.60)	6,992.76(1,749.79)	6,907.73(1,984.73)	0.05	-0.30, 0.39	> 0.9	7,008.85(1,957.35)	7,042.62(1,811.63)	6,98
LDH	194.43(39.85)	200.42(32.40)	192.62(41.78)	0.21	-0.15, 0.57	0.2	196.02(33.59)	203.41(32.41)	191
ALT	27.74(17.11)	28.76(17.04)	27.46(17.17)	0.08	-0.27, 0.42	0.7	31.01(18.38)	28.59(16.13)	32.3
AST	30.53(20.46)	34.14(32.42)	29.55(15.72)	0.18	-0.16, 0.53	0.3	32.58(23.64)	35.48(33.73)	30.(
PLT	148.31(66.10)	158.95(63.10)	145.40(66.81)	0.21	-0.14, 0.56	0.2	152.12(69.73)	153.27(62.89)	151
AFP	97.44(331.79)	159.30(365.35)	80.53(321.25)	0.23	-0.12, 0.58	0.030	110.47(386.63)	135.55(351.69)	96.4
CA199	59.78(531.12)	16.76(13.23)	71.54(599.18)	-0.13	-0.48, 0.22	0.2	20.57(17.92)	17.40(13.75)	22.3
NLR	1.99(1.14)	1.78(0.70)	2.04(1.23)	-0.27	-0.61, 0.08	0.4	1.94(1.08)	1.81(0.72)	2.0
PLR	99.00(42.75)	93.12(36.13)	100.60(44.36)	-0.19	-0.53, 0.16	0.4	98.42(44.88)	91.25(37.44)	102
ALBI grade				-0.24	-0.58, 0.11	0.5			
1	146/191(76%)	34/41(83%)	112/150(75%)				83/103(81%)	30/37(81%)	53/
2	42/191(22%)	7/41(17%)	35/150(23%)				19/103(18%)	7/37(19%)	12/
3	3/191(1.6%)	0/41(0%)	3/150(2.0%)				1/103(1.0%)	0/37(0%)	1/6

[1]Mean(SD); n/N(%)

[2]Standardized Mean Difference

Abbreviation: CI = Confidence Interval

Variable	Before PSM						After PSM		
	Overall N = 191[1]	LH N = 41[1]	RFA N = 150[1]	SMD[2]	95% CI[2]	p-value[3]	Overall N = 103[1]	LH N = 37[1]	RFA N =

[3]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Abbreviation: CI = Confidence Interval

Table 4
Baseline characteristics before and after PSM in patients with tumors measuring > 2 to ≤ 3 cm

Variable	Before PSM						After PSM		
	Overall N = 192[1]	LH N = 63[1]	RFA N = 129[1]	SMD[2]	95% CI[2]	p-value[3]	Overall N = 154[1]	LH N = 59[1]	RFA N =
Age	58.18(10.11)	59.89(8.94)	57.34(10.57)	0.26	-0.04, 0.56	0.3	58.56(9.46)	59.08(8.59)	58.
Sex, cases (%)				0.07	-0.23, 0.37	0.7			
Male	150/192(78%)	48/63(76%)	102/129(79%)				118/154(77%)	44/59(75%)	74/
Female	42/192(22%)	15/63(24%)	27/129(21%)				36/154(23%)	15/59(25%)	21/
HBV				0.41	0.10, 0.71	0.013			
0	49/192(26%)	9/63(14%)	40/129(31%)				27/154(18%)	9/59(15%)	18/
1	143/192(74%)	54/63(86%)	89/129(69%)				127/154(82%)	50/59(85%)	77/
Cirrhosis				0.03	-0.28, 0.33	0.9			
0	41/192(21%)	13/63(21%)	28/129(22%)				30/154(19%)	11/59(19%)	19/
1	151/192(79%)	50/63(79%)	101/129(78%)				124/154(81%)	48/59(81%)	76/
ALB	42.47(4.71)	43.16(4.91)	42.14(4.60)	0.22	-0.09, 0.52	0.052	42.95(4.52)	43.13(4.92)	42.
TBIL	15.80(9.00)	15.41(11.10)	15.99(7.81)	-0.06	-0.36, 0.24	0.11	15.30(7.60)	14.32(6.96)	15.
DBIL	7.07(6.41)	7.34(9.67)	6.94(3.99)	0.05	-0.25, 0.36	0.13	6.49(3.60)	6.24(3.53)	6.6
GGT	70.69(96.03)	64.21(88.84)	73.85(99.53)	-0.10	-0.40, 0.20	0.4	63.45(86.46)	66.78(91.23)	61.
ChE	6,935.95(2,009.90)	7,166.02(1,917.00)	6,823.59(2,051.63)	0.17	-0.13, 0.48	0.2	7,093.69(1,960.22)	7,117.68(1,942.57)	7,0
LDH	193.66(40.20)	190.00(35.58)	195.50(42.38)	-0.14	-0.47, 0.19	0.3	192.95(38.37)	192.52(35.57)	193
ALT	33.73(36.20)	35.54(50.33)	32.84(26.94)	0.07	-0.23, 0.37	0.8	33.36(37.85)	36.15(51.93)	31.
AST	33.57(27.11)	33.83(32.14)	33.44(24.42)	0.01	-0.29, 0.31	0.4	31.30(24.10)	34.63(33.03)	29.
PLT	148.53(60.72)	139.65(53.81)	152.86(63.58)	-0.23	-0.53, 0.08	0.2	147.28(59.56)	139.24(55.43)	152
AFP	437.18(1,764.88)	661.90(2,024.19)	327.44(1,620.56)	0.18	-0.12, 0.49	0.6	478.89(1,910.78)	611.79(1,983.77)	396
CA199	26.12(26.03)	27.09(33.16)	25.66(21.85)	0.05	-0.25, 0.35	0.8	24.62(25.55)	27.90(34.10)	22.
NLR	2.07(1.34)	2.21(1.56)	2.00(1.22)	0.15	-0.15, 0.45	0.6	2.10(1.23)	2.24(1.60)	2.0
PLR	98.92(45.40)	92.28(42.50)	102.16(46.56)	-0.22	-0.53, 0.08	0.14	98.70(41.47)	92.87(43.65)	102
ALBI grade				-0.24	-0.54, 0.06	0.13			
1	149/192(78%)	53/63(84%)	96/129(74%)				126/154(82%)	50/59(85%)	76/
2	43/192(22%)	10/63(16%)	33/129(26%)				28/154(18%)	9/59(15%)	19/

[1]Mean(SD); n/N(%)

[2]Standardized Mean Difference

Abbreviation: CI = Confidence Interval

Variable	Before PSM						After PSM		
	Overall N = 192[1]	LH N = 63[1]	RFA N = 129[1]	SMD[2]	95% CI[2]	p-value[3]	Overall N = 154[1]	LH N = 59[1]	RFA N =
[3]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test									
Abbreviation: CI = Confidence Interval									

Among patients with tumors measuring ≤ 2 cm, no statistically significant difference in OS was observed between LH and RFA in the overall cohort, after PSM, or after IPTW adjustment (P = 0.28, P = 0.25, and P = 0.28, respectively; Fig. 4A, C, E). Similarly, no statistically significant difference in RFS was observed before matching, after PSM, or after IPTW adjustment (P = 0.074, P = 0.061, and P = 0.074, respectively; Fig. 4B, D, F).

Among patients with tumors > 2 to ≤ 3 cm, 192 patients were included in the overall cohort, comprising 63 patients in the LH group and 129 patients in the RFA group. After 1:2 propensity score matching, 154 patients remained in the matched cohort, including 59 patients in the LH group and 95 patients in the RFA group. No statistically significant difference in OS was observed between LH and RFA before matching, after PSM, or after IPTW adjustment (P = 0.38, P = 0.49, and P = 0.38, respectively; Fig. 5A, C, E). For RFS, no statistically significant difference was observed before matching (P = 0.084, Fig. 5B), whereas a statistically significant difference was observed after PSM (P = 0.042, Fig. 5D). After IPTW adjustment, the difference was not statistically significant (P = 0.084, Fig. 5F).

Discussion

In this retrospective single-center cohort study of patients with solitary HCC measuring ≤ 3 cm, no statistically significant difference in overall survival (OS) was observed between LH and RFA. In contrast, LH was associated with longer recurrence-free survival (RFS) in the overall cohort, and this association remained statistically significant after propensity score matching (PSM) and inverse probability of treatment weighting (IPTW). The difference between the two treatment approaches was therefore more evident for recurrence control than for OS.

The absence of a significant difference in OS should be interpreted cautiously. Only 21 deaths occurred during follow-up, which may have limited the statistical power to detect differences in OS. In addition, subsequent treatments after recurrence may have influenced long-term survival outcomes. However, detailed information on salvage treatment, including the number of patients treated, treatment modalities, and time to treatment, was not systematically analyzed in the present study. Therefore, the contribution of subsequent treatment to the observed similarity in OS remains uncertain.

In the overall cohort, the recurrence rate was lower in the LH group than in the RFA group, and the Kaplan–Meier analysis showed significantly longer RFS with LH. This finding remained consistent after PSM and IPTW adjustment. Multivariable Cox regression analysis also showed that treatment modality was independently associated with RFS; compared with RFA, LH was associated with a lower risk of recurrence (HR = 0.33, 95% CI: 0.15–0.75, P = 0.008). These findings suggest an association between LH and improved recurrence control in this cohort.

Previous studies have compared LH and RFA in patients with small HCC, but evidence specifically focusing on solitary tumors measuring ≤ 3 cm remains limited. Previous studies have reported heterogeneous findings regarding the comparative effectiveness of LH and RFA. A previous retrospective study based on the SEER database revealed that, for small hepatocellular carcinoma, OS and disease-specific survival (DSS) were significantly higher in the LH group than in the RFA group at 1, 3, and 5 years, regardless of PSM status. [15] A systematic review and meta-analysis of propensity score-matched studies demonstrated that, compared with RFA for small hepatocellular carcinoma, LH showed no significant difference in one-year OS, but significantly higher three-year OS. LH also yielded significantly better one-year and three-year disease-free survival (DFS) than the RFA group and lower rates of local and intrahepatic distant recurrence postoperatively. [12] Furthermore, a multicenter retrospective study of elderly patients with solitary hepatocellular carcinoma revealed that open and laparoscopic hepatectomy resulted in significantly higher five-year OS and DFS rates compared to RFA. This finding was validated by PSM. [16] Several retrospective studies have suggested potential advantages of LH, particularly regarding recurrence-related outcomes. [17–21] Meanwhile, other studies have come to the same conclusion as we have: LH and RFA treatments yield similar OS rates, but LH has been shown to have superior RFS rates and lower recurrence rates than RFA. [22–25] However, some early studies reported no significant difference in OS and RFS between surgery and RFA. [26,27] The SURF trial demonstrated that surgery was not significantly more effective than RFA. The SURF trial's patient population primarily consisted of patients with hepatitis C-related hepatocellular carcinoma, whereas this study focused on patients with hepatitis B-related hepatocellular carcinoma. Additionally, the authors noted that more than half of the patients in the trial had tumors with a maximum diameter of 2 cm or less. [28] Such differences should be considered when comparing results across studies.

We further examined outcomes according to tumor size. Among patients with tumors measuring ≤ 2 cm, no statistically significant difference in RFS was observed between LH and RFA before matching, after PSM, or after IPTW adjustment. Among patients with tumors > 2 to ≤ 3 cm, a statistically significant difference in RFS was observed after PSM, but this difference was not maintained after IPTW adjustment. In addition, the treatment-by-tumor-size interaction was not statistically significant (P for interaction = 0.541). These findings suggest that patients with tumors measuring 2–3 cm may represent a population in whom LH could provide greater recurrence-control benefit; however, the absence of a significant interaction indicates that this observation requires further validation. Therefore, the observed difference after PSM in the > 2 to ≤ 3 cm subgroup should be considered exploratory and interpreted cautiously. Similar conclusions have been reached by some studies. Wang et al.'s findings indicate that, for tumors ≤ 2 cm in diameter, there was no significant difference in overall survival (OS) and disease-specific survival (DSS) between LH and RFA. For tumors larger than 2 cm, however, the LH group demonstrated significantly superior OS and DSS compared to the RFA group. [15] Similarly, Song et al. found no significant difference in RFS between the LH and RFA groups for tumors ≤

2 cm in diameter. However, the LH group demonstrated superior RFS outcomes for tumors > 2 cm in diameter. [25] Lee et al. also concluded that, for tumors measuring ≤ 3 cm in diameter, the surgical group demonstrated significantly superior RFS compared to the RFA group. However, no significant difference in RFS was observed between the two groups for tumors measuring ≤ 2 cm in diameter. [29] Meanwhile, the SURF trial concluded that a tumor diameter greater than 2–2.5 cm is a risk factor for local recurrence and poor overall survival following ablation therapy. [28]

Exploratory subgroup analyses were performed to assess the consistency of the association between treatment modality and RFS across clinically relevant subgroups, including age, HBV infection status, cirrhosis, tumor size, and AFP level. Although the association between LH and improved RFS was statistically significant in some individual subgroups, none of the treatment-by-subgroup interactions was statistically significant. Therefore, the available data do not demonstrate significant heterogeneity of the treatment association across these clinical characteristics. Given the exploratory nature of these analyses and the relatively small sample sizes of some subgroups, these findings should be interpreted cautiously.

This study has several limitations. First, the single-center retrospective design is subject to selection bias and residual confounding. Although PSM and IPTW were used to reduce imbalance in measured baseline covariates, important anatomical characteristics that may have influenced treatment selection, particularly tumor location and depth, were not incorporated into the propensity score model. Therefore, residual confounding by indication cannot be excluded. Second, a minor residual imbalance remained after PSM for ALBI grade (absolute SMD = 0.11). In addition, although IPTW improved the distribution of many measured covariates, some weighted SMDs remained above 0.1, indicating that complete covariate balance was not achieved for all variables. Third, the study collected limited perioperative outcome data. Only length of hospital stay was evaluated whereas operative time, intraoperative blood loss, postoperative complications, and other measures of treatment-related morbidity were not systematically analyzed. Therefore, a comprehensive comparison of the risk-benefit profiles of LH and RFA cannot be made. Fourth, only 21 deaths occurred during follow-up, limiting the statistical power of the OS analysis. The duration of follow-up may also have been insufficient to detect potential long-term differences in survival. Finally, the subgroup analyses were exploratory, and several subgroups had relatively small sample sizes, which may have resulted in imprecise estimates and limited statistical power. Further prospective, multicenter studies are warranted to validate these observations.

In summary, in this retrospective cohort of patients with solitary HCC measuring ≤ 3 cm, LH was associated with improved recurrence control compared with RFA, while no significant difference in OS was observed. In exploratory tumor-size subgroup analyses, the association between LH and improved RFS appeared more evident among patients with tumors measuring 2–3 cm, whereas no statistically significant difference was detected among patients with tumors ≤ 2 cm. However, the absence of a significant treatment-by-tumor-size interaction indicates that these findings should be interpreted as hypothesis-generating and require further validation.

Declarations

Disclosures

Statement of Ethics This study was conducted in accordance with the Declaration of Helsinki (2013 revision). Ethical approval was granted by the Ethics Committee of Tianjin Medical University Cancer Institute & Hospital, and the requirement for informed consent was waived.

Conflict of Interest Statement Zezheng Xu, Haijing Zheng, Dongyang Li, Lu Yang, Zhaolong Pan, Xu Bao, Guangtao Li, Lu Chen, Chen Liu, Xiaomeng Liu, Ping Chen, Feng Fang, Huikai Li, Yunlong Cui, Qiang Wu, Tianqiang Song, Qiang Li, and Wei Zhang have no conflicts of interest or financial ties to disclose.

Data Availability The original data in this research can be obtained by contacting the corresponding author.

Funding

(1) Tianjin Medical University Cancer Hospital, Precision Treatment Technology Construction Project for Cancer Surgery, ZLWKJZZL14. (2) Zhongguancun Precision Medicine Foundation, Medical and Health Public Welfare - Cancer Medical Research Special Project, ZGC-YXKY-ZL004.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63. 10.3322/caac.21834.
2. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004;130(7):417–22. 10.1007/s00432-004-0552-0.
3. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68(2):723–50. 10.1002/hep.29913.
4. Vogel A, Chan SL, Dawson LA, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2025;36(5):491–506. 10.1016/j.annonc.2025.02.006.
5. Omata M, Cheng AL, Kokudo N, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017;11(4):317–70. 10.1007/s12072-017-9799-9.
6. Jiang Htao, Cao Jyu. Impact of Laparoscopic Versus Open Hepatectomy on Perioperative Clinical Outcomes of Patients with Primary Hepatic Carcinoma. Chin Med Sci J. 2015;30(2):80–3. 10.1016/s1001-9294(15)30016-x.
7. Zhu P, Liao W, Zhang WG, et al. A Prospective Study Using Propensity Score Matching to Compare Long-term Survival Outcomes After Robotic-assisted, Laparoscopic, or Open Liver Resection for Patients With BCLC Stage 0-A Hepatocellular Carcinoma. Ann Surg. 2023;277(1):e103.

10.1097/SLA.0000000000005380.

8. A multicenter, non-randomized, controlled trial to evaluate the efficacy of surgery versus radiofrequency ablation for small hepatocellular carcinoma (SURF-Cohort Trial): Analysis of overall survival. | Journal of Clinical Oncology. Accessed November 26, 2025. https://ascopubs.org/doi/10.1200/JCO.2022.40.16_suppl.4095
9. Takayama T, Hasegawa K, Izumi N, et al. Surgery versus Radiofrequency Ablation for Small Hepatocellular Carcinoma: A Randomized Controlled Trial (SURF Trial). Liver Cancer. 2022;11(3):209–18. 10.1159/000521665.
10. Zhong JH, Xing BC, Zhang WG, et al. Repeat hepatic resection versus radiofrequency ablation for recurrent hepatocellular carcinoma: retrospective multicentre study. Br J Surg. 2021;109(1):71–8. 10.1093/bjs/znab340.
11. Zhuang BW, Li W, Wang W, et al. Treatment effect of radiofrequency ablation versus liver transplantation and surgical resection for hepatocellular carcinoma within Milan criteria: a population-based study. Eur Radiol. 2021;31(7):5379–89. 10.1007/s00330-020-07551-9.
12. Chen W, Lin X, Wu Z, Pan W, Ke Q, Chen Y. Laparoscopic liver resection is superior to radiofrequency ablation for small hepatocellular carcinoma: a systematic review and meta-analysis of propensity score-matched studies. Hepatol Int. 2024;18(3):998–1010. 10.1007/s12072-024-10645-x.
13. Shin SW, Ahn KS, Kim SW, Kim TS, Kim YH, Kang KJ. Liver Resection Versus Local Ablation Therapies for Hepatocellular Carcinoma Within the Milan Criteria: A Systematic Review and Meta-analysis. Ann Surg. 2021;273(4):656. 10.1097/SLA.0000000000004350.
14. Shaaban Abdelgalil M, Amer BE, Yasen N, et al. Efficacy and safety of laparoscopic liver resection versus radiofrequency ablation in patients with early and small hepatocellular carcinoma: an updated meta-analysis and meta-regression of observational studies. World J Surg Oncol. 2024;22:47. 10.1186/s12957-023-03292-3.
15. Wang X, Chai X, Tang R, Xu Y, Chen Q. Comparison of laparoscopic hepatectomy and radiofrequency ablation for small hepatocellular carcinoma patients: a SEER population-based propensity score matching study. Updates Surg. 2024;76(8):2755–66. 10.1007/s13304-024-02016-w.
16. Delvecchio A, Conticchio M, Casella A, et al. Open, laparoscopic liver resection and percutaneous thermal ablation in elderly patients with hepatocellular carcinoma: outcomes and therapeutic strategy. Surg Endosc. 2024;38(11):6700–10. 10.1007/s00464-024-11269-w.
17. Lei ZL, Tan ZL, Luo YH, et al. Comparison of the efficacy of laparoscopic hepatectomy and radiofrequency ablation for small hepatocellular carcinoma: A retrospective study. World J Gastroenterol. 2025;31(45):111540. 10.3748/wjg.v31.i45.111540.
18. Hu L, Lin J, Wang A, Shi X, Qiao Y. Comparison of liver resection and radiofrequency ablation in long-term survival among patients with early-stage hepatocellular carcinoma: a meta-analysis of randomized trials and high-quality propensity score-matched studies. World J Surg Oncol. 2024;22(1):56. 10.1186/s12957-024-03330-8.
19. Liu PH, Hsu CY, Hsia CY, et al. Surgical Resection Versus Radiofrequency Ablation for Single Hepatocellular Carcinoma ≤ 2 cm in a Propensity Score Model. Ann Surg. 2016;263(3):538–45. 10.1097/SLA.0000000000001178.
20. Jin S, Tan S, Peng W, Jiang Y, Luo C. Radiofrequency ablation versus laparoscopic hepatectomy for treatment of hepatocellular carcinoma: a systematic review and meta-analysis. World J Surg Oncol. 2020;18(1):199. 10.1186/s12957-020-01966-w.
21. Cheung TT, Chan ACY, Chok KSH, Lo CM. Laparoscopic liver resection versus percutaneous radiofrequency ablation in patients with hepatocellular carcinoma and liver cirrhosis: a case-matched study. Lancet. 2017;390:S39. 10.1016/S0140-6736(17)33177-X.
22. Liu F, Tan L, Luo L, Pan J. jiang. Comparison of laparoscopic hepatectomy and percutaneous radiofrequency ablation for the treatment of small hepatocellular carcinoma: a meta-analysis. *BMC Surg*. 2024;24:83. 10.1186/s12893-024-02376-5
23. Lee DH, Kim JW, Lee JM, et al. Laparoscopic Liver Resection versus Percutaneous Radiofrequency Ablation for Small Single Nodular Hepatocellular Carcinoma: Comparison of Treatment Outcomes. Liver Cancer. 2021;10(1):25–37. 10.1159/000510909.
24. Xu L, Lin Z, Chen D, Huang Z, Huang X, Che X. Laparoscopic liver resection versus radiofrequency ablation for hepatocellular carcinoma within Milan criteria: a meta-analysis and systematic review. Front Oncol. 2024;14:1442499. 10.3389/fonc.2024.1442499.
25. Song J, Wang Y, Ma K, et al. Laparoscopic hepatectomy versus radiofrequency ablation for minimally invasive treatment of single, small hepatocellular carcinomas. Surg Endosc. 2016;30(10):4249–57. 10.1007/s00464-015-4737-1.
26. Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg. 2006;243(3):321–8. 10.1097/01.sla.0000201480.65519.b8.
27. Feng K, Yan J, Li X, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol. 2012;57(4):794–802. 10.1016/j.jhep.2012.05.007.
28. Kawaguchi Y, Hasegawa K, Kashiwabara K, et al. Surgery Versus Ablation for Hepatocellular Carcinoma: A Randomized Controlled Trial (SURF-RCT Trial) and a Nonrandomized Prospective Observational Trial (SURF-Cohort Trial). J Clin Oncol. 2025;43(23):2628–38. 10.1200/JCO-24-02030.
29. Lee J, Jin YJ, Shin SK, et al. Surgery versus radiofrequency ablation in patients with Child- Pugh class-A/single small (≤ 3 cm) hepatocellular carcinoma. Clin Mol Hepatol. 2022;28(2):207–18. 10.3350/cmh.2021.0294.

Table 2

Table 2 is available in the Supplementary Files section.

Figures

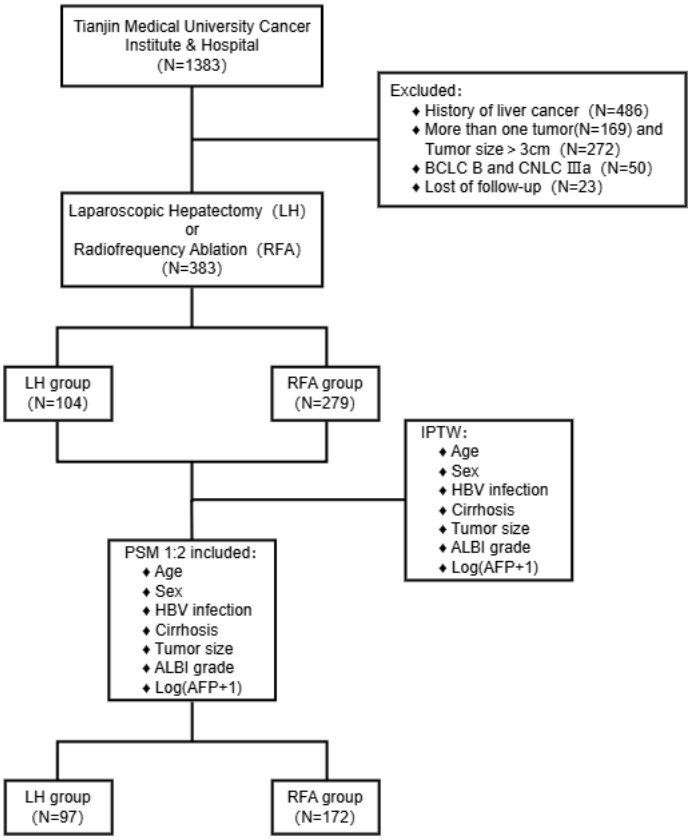


Figure 1

Flowchart of patient selection. BCLC, Barcelona Clinic Liver Cancer; CNLC, China liver cancer; HBV, hepatitis B virus; ALB, albumin; PSM, propensity score matching; IPTW, inverse probability of treatment weighting.

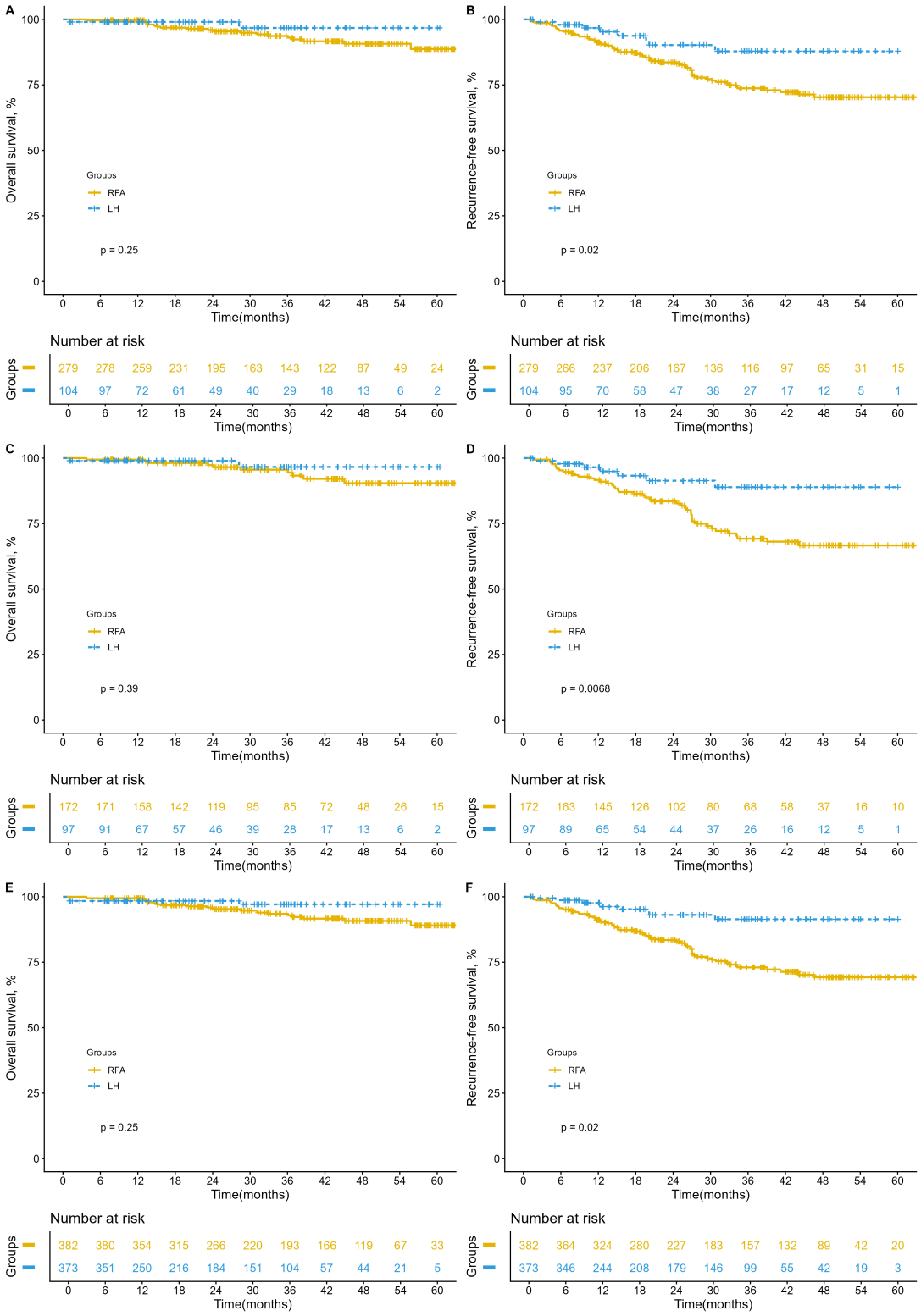


Figure 2

Kaplan–Meier curves of overall survival (OS) and recurrence-free survival (RFS) according to treatment group. OS (A) and RFS (B) of patients in the RFA group (N = 279) or the LH group (N = 104) before PSM. OS (C) and RFS (D) for the RFA group (N = 172) and the LH group (N = 97) after PSM. OS (E) and RFS (F) after IPTW weighting of the original cohort.

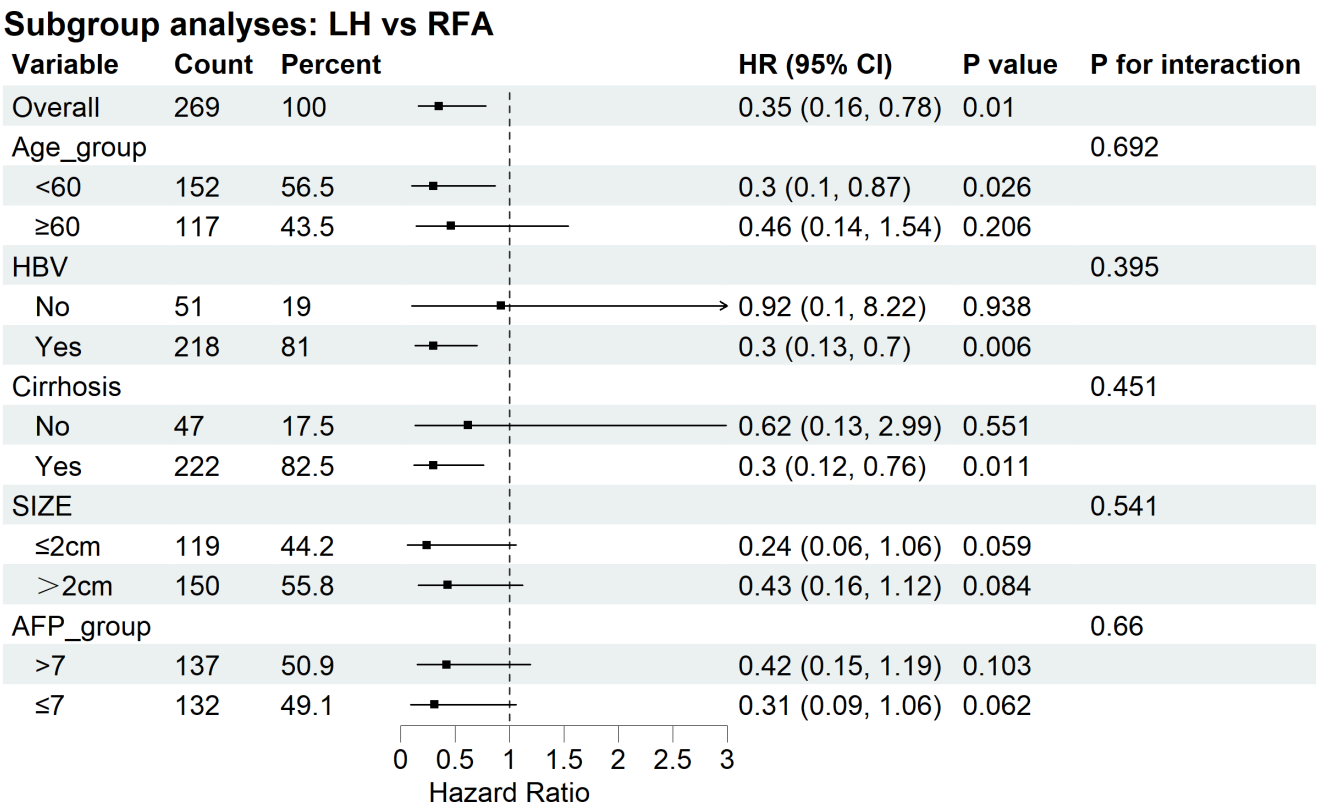


Figure 3

Forest plot of exploratory subgroup analyses for recurrence-free survival (RFS).

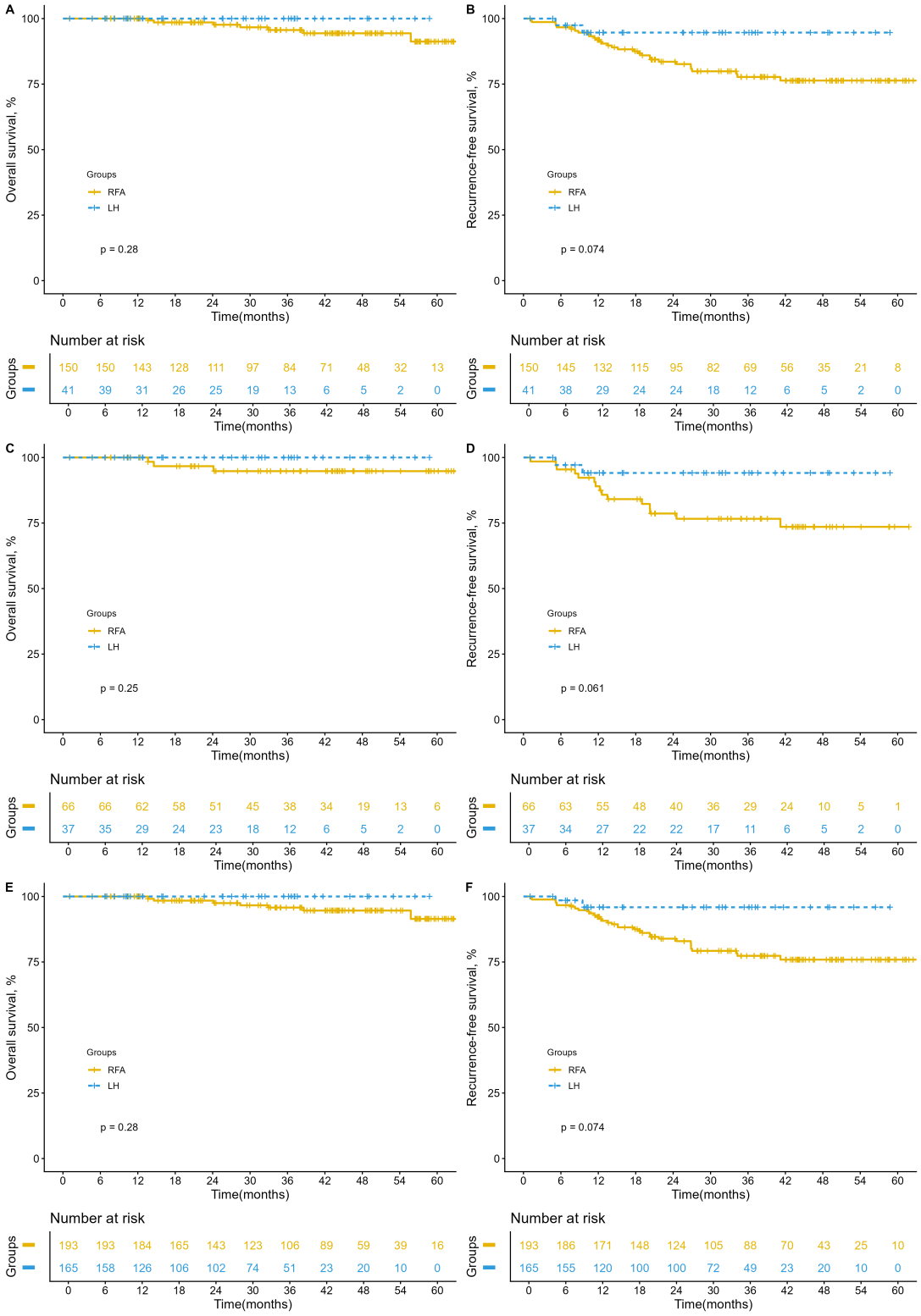


Figure 4

Kaplan–Meier curves of overall survival (OS) and recurrence-free survival (RFS) in patients with tumors measuring ≤2 cm. OS (A) and RFS (B) of patients in the RFA group (N = 150) or the LH group (N = 41) before PSM. OS (C) and RFS (D) for the RFA group (N = 66) and the LH group (N = 37) after PSM. OS (E) and RFS (F) after IPTW of the patients with tumors measuring ≤2 cm.

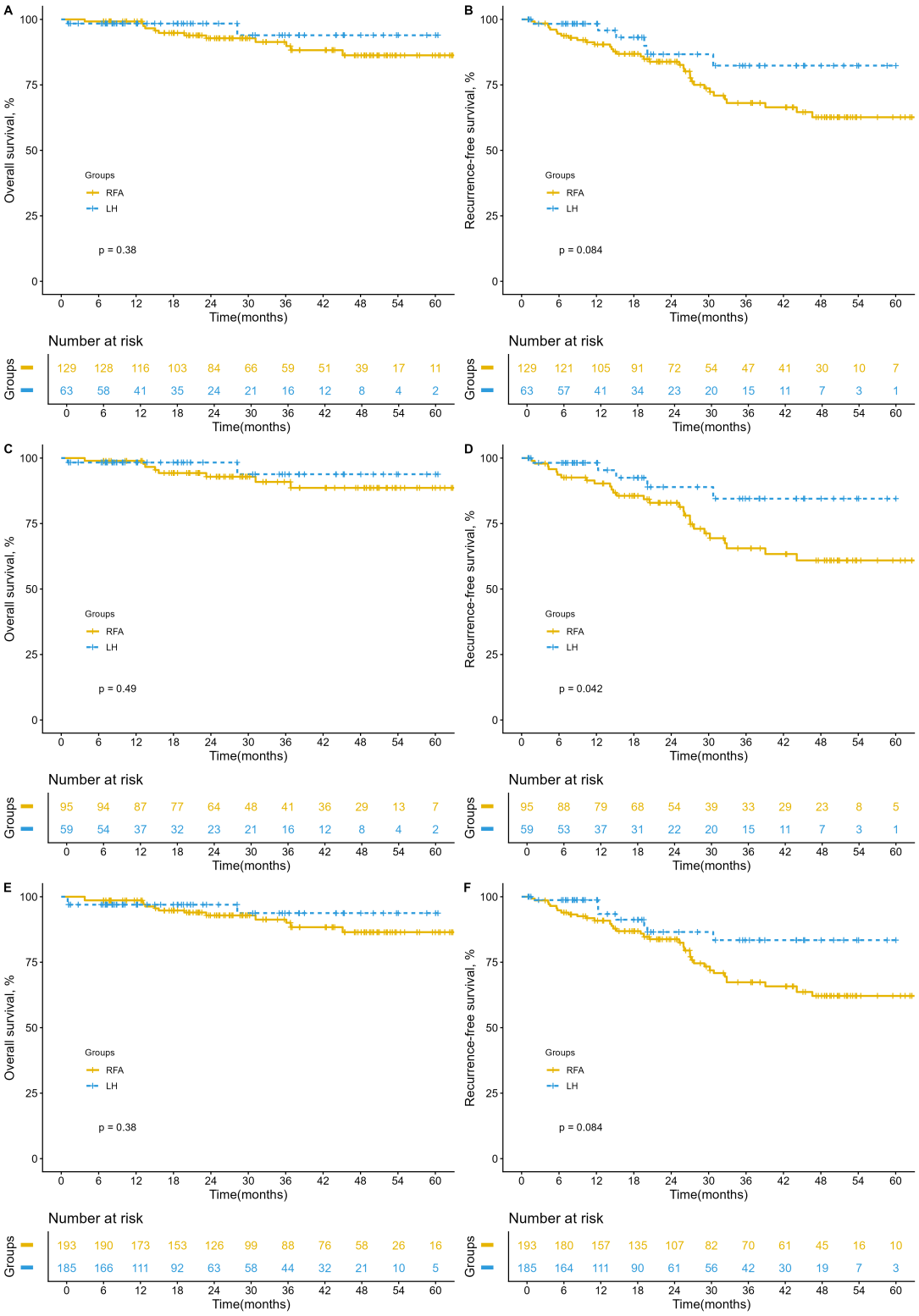


Figure 5

Kaplan–Meier curves of overall survival (OS) and recurrence-free survival (RFS) in patients with tumors measuring >2 to ≤3 cm. OS (A) and RFS (B) of patients in the RFA group (N = 129) or the LH group (N = 63) before PSM. OS (C) and RFS (D) for the RFA group (N = 95) and the LH group (N = 59) after PSM. OS (E) and RFS (F) after IPTW of the patients with tumors measuring >2 to ≤3 cm.

Supplementary Files

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