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ORIGINAL RESEARCH

Comparison of Long-Term Outcomes Between Repeated Hepatic Resection and Radiofrequency Ablation in Patients with Small Recurrent Hepatocellular Carcinoma After Initial Curative Resection: A Propensity Score Matched Study

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Background: Repeat hepatic resection (re-resection) and radiofrequency ablation (RFA) are both standard treatments for small recurrent hepatocellular carcinoma (HCC) after curative resection. This study compares long-term outcomes of these treatments.

Methods: This retrospective study included patients with recurrent HCC smaller than 3 cm treated with re-resection or RFA from 2001 to 2019 in a tertiary center. Propensity score matching (PSM) minimized baseline differences. Primary outcomes were overall survival (OS) and disease-free survival (DFS). Subgroup analyses explored outcomes based on recurrence interval, hepatitis infection status, and RFA guidance method (ultrasound [US] versus computed tomography [CT]). Multivariate Cox regression identified predictors of survival and secondary recurrence.

Results: After PSM, 106 patients in the re-resection group and 106 in the RFA group were compared. OS rates at 3, 5, and 8 years for re-resection were 97.9%, 85.4%, and 75.8%, compared to 87.8%, 77.9%, and 62.8% for RFA ($p = 0.15$). DFS rates were 53.3%, 41.8%, and 26.7% for re-resection versus 43.9%, 28.1%, and 24.0% for RFA ($p = 0.15$). Subgroup analysis indicated re-resection was superior in early recurrence (<24 months) and HBV-related HCC. US-guided and CT-guided RFA showed no significant differences in OS or DFS. HCV infection and multiple tumors were independent predictors of secondary recurrence.

Conclusion: Repeat hepatic resection and RFA offer comparable survival for small recurrent HCC. Re-resection is preferred for early recurrence and HBV-related HCC. US- and CT-guided RFA are equally effective alternatives.

Keywords: hepatocellular carcinoma, outcome, radiofrequency ablation, recurrence, repeat resection

Introduction

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related mortality worldwide, with its incidence steadily rising.[1] Major risk factors for HCC include liver cirrhosis, chronic hepatitis B or C virus infection, alcohol consumption, and steatohepatitis.[2] Consequently, patients with these risk factors are recommended to undergo regular surveillance.[3] Effective surveillance facilitates the early detection of HCC, particularly in early-stage disease (Barcelona Clinic Liver Cancer [BCLC] stage 0 and A), enabling curative treatment in over 50% of patients.[4] Hepatic resection remains the cornerstone of curative treatment for resectable HCC. However, recurrence rate after resection are high, with up to 60% of patients experiencing a recurrence within five years, making recurrence the primary cause of HCC-related mortality.[5–7]

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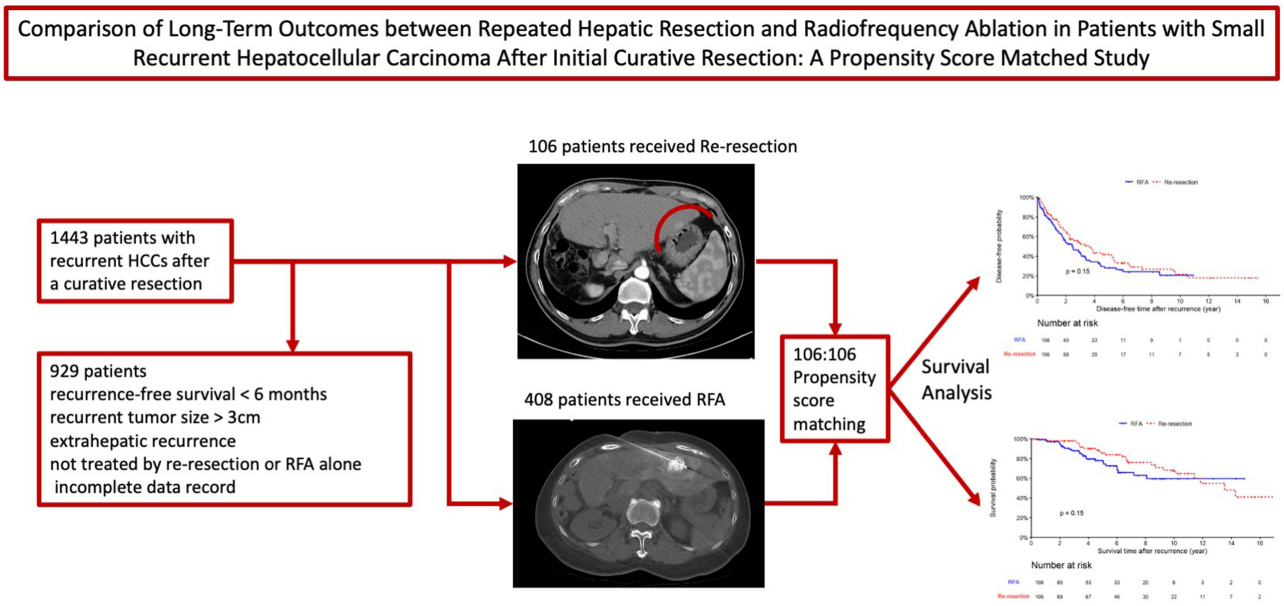
Graphical Abstract



Potential curative strategies for recurrent HCC include salvage liver transplantation, repeat hepatic resection, and RFA. Salvage liver transplantation offers the advantage of addressing both tumor recurrence and underlying liver diseases, theoretically improving outcomes.[8,9] However, the procedure carries significant surgical risk, requires long-term immunosuppression, and involves high costs. The scarcity of donor organs further limits its availability in many regions. Consequently, resection and RFA are the primary curative options for patients with small recurrent HCC.[10]

For small HCCs ≤3 cm, both repeat hepatic resection and radiofrequency ablation (RFA) are guideline-endorsed curative options.[8–10] Yet studies comparing these two modalities in the recurrent setting have produced conflicting results,[11–13] and it remains uncertain whether their equivalence holds for small tumor that recur after prior hepatectomy.[14–17] Over the past decade, some meta-analyses have compared repeat resection and RFA for recurrent HCC, yet reached conflicting conclusions. Two earlier syntheses reported no significant difference in overall survival (OS) or disease-free survival (DFS) between the modalities.[18,19] In contrast, more recent pooled analyses demonstrated a clear OS and/or DFS advantage for repeat resection, particularly beyond three years of follow-up.[16,20,21] A recent comprehensive meta-analysis of 17 studies again found no OS difference but superior recurrence control with surgery.[13]

Moreover, the challenges associated with reoperation for recurrent HCC, such as increase technical complexity, further differentiate this scenario from primary HCC and recurrent HCC treated initially with RFA. Meta-analyses indicate a 3- to 4-fold higher major morbidity with repeat resection, although 30-day mortality is low (<2%).[13,21,22] Additionally, the reduced liver volume following resection may limit the accessibility of the ultrasound (US) window for RFA, though computed tomography (CT)-guided RFA can mitigate this issue by offering better progression-free survival for lesions in challenging subdiaphragmatic or subcardiac locations.[23] These safety considerations reinforce the need for careful patient selection between treatment choices.

Despite the volume of literature, several knowledge gaps persist. Many prior studies (i) were retrospective with heterogeneous inclusion criteria, (ii) lacked adjustment for baseline imbalances, (iii) had short follow-up (<5 years), or (iv) did not distinguish between ultrasound-guided and computed tomography (CT)-guided RFA—an important technical factor for lesions located deep in the subdiaphragmatic or subcardiac dome.[19] Moreover, very few investigations have concurrently explored the impact of viral etiology (HBV vs HCV) or recurrence timing (early vs late) on long-term outcomes.

The present study aims to address these deficits. Leveraging a large single-center cohort from a high-volume institute, we compared repeat resection with RFA for first intra-hepatic recurrence ≤3 cm after curative hepatectomy. Propensity score matching (PSM) was applied to minimise selection bias. The study features (i) a longer observational window, (ii) conduct subgroup analyses by RFA guidance modality (ultrasound vs CT), and (iii) multivariable Cox modelling to identify predictors of survival and second recurrence. By integrating rigorous matching with extended follow-up, our work aims to clarify existing controversies regarding the optimal treatment for recurrent HCC, thereby contributing to evidence-based decision-making and improved management strategies for HCC patients.

Materials And Methods

Patients and Study Design

This retrospective observational study was approved by the Ethics Committee of the Institute Review Board of National Taiwan University Hospital (202409013RINC) and was conducted in accordance with the approved guidelines. Patients with recurrent HCC smaller than 3 cm who had undergone curative resection between January 2001 and December 2019 at National Taiwan University Hospital were included in the study. Curative resection was defined as an R0 resection based on pathological reports, with no residual tumors. The diagnosis of recurrent HCC was established either through biopsy-confirmation or typical dynamic imaging patterns consistent with HCC. Patients were excluded if they had a recurrence-free survival of less than 6 months, any recurrent tumor larger than 3cm, or extrahepatic recurrence. To specifically compare the outcomes of repeat hepatic resection and RFA, only patients who underwent exclusively repeat resection or exclusively RFA as treatment for recurrence were included. Patients who received any additional treatments, either prior to or following resection or RFA, as part of combination therapy, were excluded from the analysis. Data were collected from electronic medical records system, and the study follow-up was censored on December 31, 2020. The study design and patient selection process are summarized in the flow diagram shown in Figure 1.

Treatment and Follow-up

All patients included in this study had undergone curative resection for primary HCC. The efficacy of the resection was evaluated 1–2 months postoperatively using US, dynamic CT, or magnetic resonance imaging (MRI). Subsequently, patients received regular follow-ups in outpatient clinics. Follow-up protocols include physical exam, serum biochemistry testing, a-fetoprotein level measurement, liver imaging study with US, dynamic CT, or MRI every 3–6 months thereafter. Recurrence was confirmed either by typical dynamic imaging pattern or by biopsy. The decision to proceed with repeat resection or RFA for recurrent HCC was made collaboratively between the surgeon and the patient, taking into account factors such as disease status (eg, tumor location and feasibility of treatment), patient's general health, and individual preferences. Given that the study only included patients with recurrent tumors measuring no more than 3 cm, both repeat resection and RFA were viable options for most cases and both treatments adhered to the clinical guidelines for the management of HCC. Resection was performed either through traditional open surgery or minimal invasive methods, based on feasibility and the surgeon's discretion. RFA was performed percutaneously by physician under image guidance, typically using US or CT.

Following resection or RFA, patients continued to received regular follow-up care in outpatient clinics on a bimonthly or trimonthly basis. Each follow-up visit included physical examinations, routine blood tests to evaluate liver function and tumor markers, and abdominal imaging (US, CT, or MRI) every 3–6 months or as clinically indicated. Additional imaging studies were arranged if patients reported specific symptoms or had abnormal blood tests. Recurrence was diagnosed based on typical dynamic imaging patterns for of HCC or confirmed histopathologically in cases of atypical imaging findings.

Variables and Outcomes

Baseline patient characteristics were collected, including age, sex, hepatitis B and hepatitis C infection status, liver cirrhosis status, type of previous resection (major or minor), and blood test results (albumin and total bilirubin levels). Additionally, the recurrent-free interval prior to repeat resection or RFA, the largest tumor size, and the number of

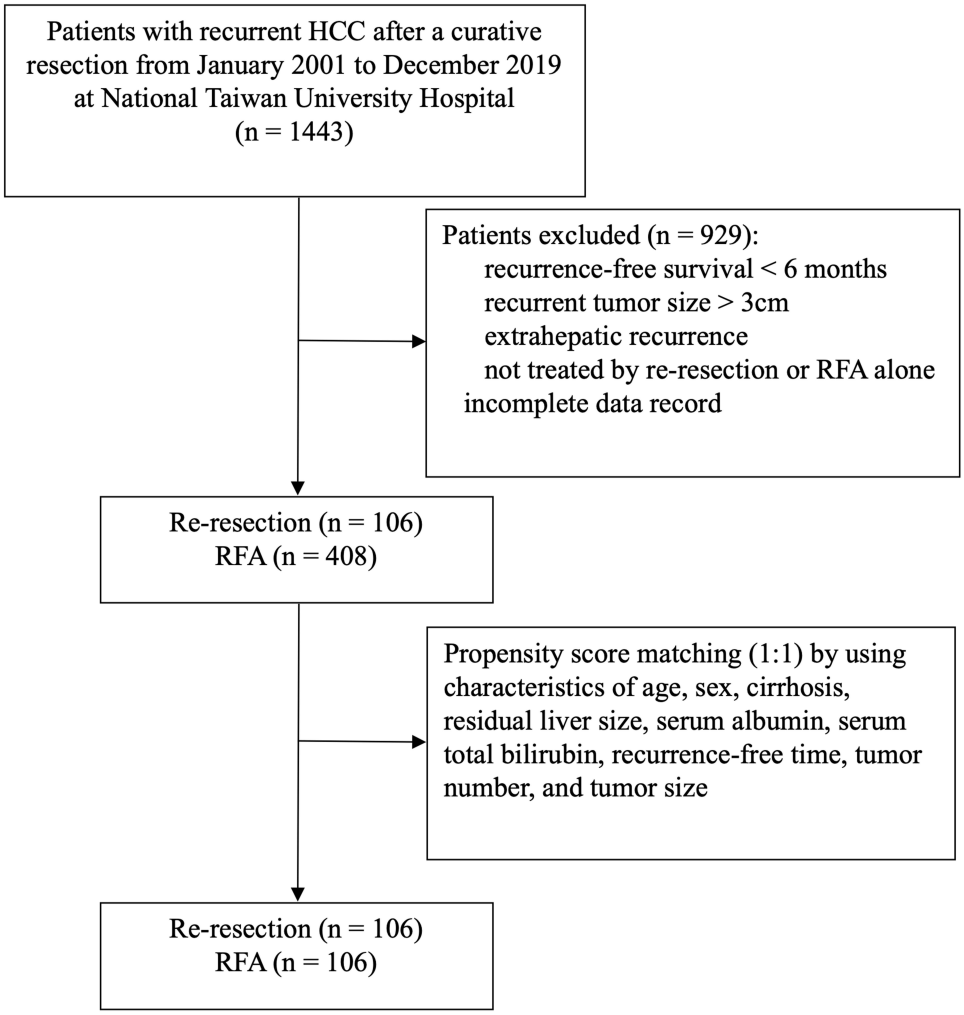


Figure 1 Study flowchart. HCC: hepatocellular carcinoma; RFA: radiofrequency ablation.

recurrent tumors were gathered. The primary outcomes evaluated were overall survival (OS) and disease-free survival (DFS) following repeat resection or RFA. Comparisons of outcomes between the Re-resection group and the RFA group were performed both before and after PSM. Subgroup analyses for OS and DFS at 3-, 5-, and 8-years intervals were conducted based on the following factors: age (>70 or <70 years), sex, hepatitis B, hepatitis C, ALBI grade (grade 1 vs 2/3), tumor number (single vs multiple), type of previous resection (major vs minor), previous DFS interval (<1 vs >1 year). Subgroup analyses were conducted to explore potential differences in outcomes across clinically relevant strata. As these analyses were exploratory in nature, no adjustment for multiple comparisons was applied. Predictors of mortality and secondary recurrence after repeat resection or RFA for the first recurrence were identified using univariate and multivariate Cox regression analysis.

Propensity Score Matching

To minimize background differences in covariates and ensure comparability between the two study groups, PSM was conducted using the *MatchIt* package in *R* software. Propensity scores were calculated through a multivariable logistic regression model that included the following covariates: age at recurrence, sex, presence of cirrhosis, major resection status, recurrence-free interval, tumor number, tumor size, serum albumin levels, and serum total bilirubin levels. A 1:1 nearest-neighbor matching approach was applied, utilizing a logit distance measure to match participants in the two

groups. The balance between groups after matching was evaluated using standardized mean differences, with a standardized mean difference of less than 0.10 considered indicative of adequate balance (Supplement 1).

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR), depending on their distribution. Categorical variables were expressed as frequencies and percentages. Survival outcomes were estimated using the Kaplan-Meier method. Univariate analyses were performed to compare continuous variables, categorical variables, and survival outcomes between the two groups. Statistical tests were chosen based on the data type and distribution; the Student's *t*-test, Mann–Whitney *U*-test, Wilcoxon rank-sum test, Chi-square test, Fisher's exact test, and Log rank test were employed as appropriate. Variables with a p-value ≤ 0.1 in univariate analysis were included in the multivariate analysis. Multivariate analysis was conducted using the Cox proportional hazards regression model to estimate the adjusted effects of risk and prognostic factors on survival outcomes. Statistical significance was defined as a two-sided p-value ≤ 0.05. All statistical analyses were performed using R software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

The baseline characteristics of patients in the RFA and Re-resection groups, before and after PSM, was are summarized in Table 1. In the unmatched cohort, significant differences were observed between the RFA group (n = 408) and Re-resection group (n = 106). Patients in the RFA group were older (mean age: 65.7 vs 61.4 years, $p < 0.01$), and had lower median serum albumin levels (4.3 vs 4.4 g/dL, $p = 0.02$). Conversely, the Re-resection group had a higher proportion of single recurrent tumor (87.7 vs 77.0%, $p = 0.01$) and larger recurrent tumor size (2.1 vs 1.8 cm, $p < 0.01$). No significant differences were noted between the groups in terms of hepatitis B or C infection rates, ALBI grade, liver cirrhosis, and other clinical factors. After PSM, baseline characteristics, including age, sex, hepatitis status, liver function, and tumor characteristics, were well-balanced between the RFA and Re-resection groups, ensuring comparability for subsequent outcome analysis. Detailed demographic data before and after matching were presented in Table 1.

Table 1 Comparison of the Baseline Characteristics Between the RFA and Re-Resection Groups Before and After Matching

Characteristic	Unmatched Cohort			Propensity Score Matched Cohort		
	RFA (n=408)	Re-Resection (n=106)	*p* value	RFA (n=106)	Re-Resection (n=106)	*p* value
Age at recur, year, mean ± sd	65.7 (11.1)	61.4 (11.5)	< 0.01 (1)	61.4 (10.9)	61.4 (11.5)	0.97 (1)
Sex, male, n (%)	301 (73.8%)	84 (79.2%)	0.25 (2)	83 (78.3%)	84 (79.2%)	0.87 (2)
Hepatitis B infection, n (%)	262 (64.2%)	74 (69.8%)	0.28 (2)	69 (65.1%)	74 (69.8%)	0.46 (2)
Hepatitis C infection, n (%)	113 (27.7%)	32 (30.2%)	0.61 (2)	31 (29.2%)	32 (30.2%)	0.88 (2)
Albumin, g/dL, median (iqr)	4.3 (4.1, 4.6)	4.4 (4.2, 4.7)	0.02 (5)	4.4 (4.1, 4.7)	4.4 (4.2, 4.7)	0.82 (5)
T-bilirubin, mg/dL, median (iqr)	0.8 (0.6, 1.1)	0.8 (0.7, 1.2)	0.06 (5)	0.9 (0.7, 1.2)	0.8 (0.7, 1.2)	0.79 (5)
ALBI grade 1, n (%)	330 (80.9%)	88 (83.0%)	0.62 (2)	90 (84.9%)	88 (83.0%)	0.71 (2)
Liver cirrhosis, n, (%)	207 (50.7%)	43 (40.6%)	0.06 (2)	46 (43.4%)	43 (40.6%)	0.68 (2)
Post major resection, n, (%)	113 (27.7%)	22 (20.8%)	0.15 (2)	21 (19.8%)	22 (20.8%)	0.86 (2)
Recurrence-free time (month)	25.0 (13.2, 50.0)	27.7 (12.7, 49.3)	0.83 (4)	26.8 (14.9, 50.9)	27.7 (12.7, 49.3)	0.79 (5)
Single recurrent tumor, n, (%)	314 (77.0%)	93 (87.7%)	0.01 (2)	87 (82.1%)	93 (87.7%)	0.25 (2)
Tumor Size, cm, mean (sd)	1.8 (0.6)	2.1 (0.6)	< 0.01 (1)	2.1 (0.6)	2.1 (0.6)	0.95 (5)

Notes: 1. Linear Model ANOVA; 2. Pearson's Chi-squared test; 3. Trend test for ordinal variables; 4. Chi-squared test for given probabilities; 5. Kruskal–Wallis rank sum test.
Abbreviation: RFA, radiofrequency ablation.

Treatment Outcomes and Survival Analysis

The OS rates were compared between the Re-resection and RFA groups in patients with recurrent HCC. In the unmatched cohort, the 3-, 5-, and 8-year OS rates for the Re-resection group were 97.9%, 85.4%, and 75.8%, respectively, compared to 92.2%, 85.1%, and 73.9% in the RFA group ($p = 0.89$). After PSM, the Re-resection group showed slightly higher OS rates at 3, 5, and 8 years (97.9%, 85.4%, and 75.8%) compared to the RFA group (87.8%, 77.9%, and 62.8%; $p = 0.15$, Supplement 2). DFS rates were also analyzed. In the unmatched cohort, the 3-, 5-, and 8-year DFS rates were 53.3%, 41.8%, and 26.7% for the Re-resection group, compared to 43.5%, 30.5%, and 25.0% for the RFA group ($p = 0.13$). In the matched cohort, the Re-resection group showed DFS rates of 53.3%, 41.8%, and 26.7% at 3, 5, and 8 years, respectively, while the RFA group had rates of 43.9%, 28.1%, and 24.0%. Again, this difference was not statistically significant ($p = 0.15$, Table 2). No significant differences in OS or DFS outcomes were observed between the two groups, either before or after matching, regardless of the imaging guidance used (Figures 2 and 3).

Subgroup Analysis

In the subgroup analysis of OS (Supplement 2), Re-resection generally exhibited higher survival rates compared to RFA, although the differences were not statistically significant in most subgroups. Notably, in patients with a recurrence interval of less than 24 months, Re-resection was associated with significantly better survival rates compared to RFA (3-year OS rate: 97.6% vs 79.9%, $p = 0.022$). Other subgroups, including those defined by age, sex, HBV or HCV infection status, ALBI grade, tumor number, and prior resection type, did not demonstrate significant differences in OS between

Table 2 Comparison of Disease-Free Survival (DFS) Rates in Selective Subgroup Patients Who Underwent Repeat Liver Resection (rHR) and Radiofrequency Ablation (RFA) in the Matched Cohort

Subgroup	*n*	3-year DFS (%)		5-year DFS (%)		8-year DFS (%)		*P value*
		RFA	rHR	RFA	rHR	RFA	rHR	
All cohort	212	43.9	53.3	28.1	41.8	24.0	26.7	0.154
Age								
>70	44	41.8	45.3	34.8	32.4	NA	NA	0.830
<70	168	44.4	55.7	26.3	44.5	21.7	24.7	0.137
Sex								
Man	167	40.5	55.4	25.7	44.4	22.1	28.4	0.058
Woman	45	55.0	45.1	35.0	32.2	29.2	21.5	0.679
HBV								
Yes	143	43.2	61.9	23.6	51.8	21.2	37.9	0.015*
No	69	44.8	32.4	40.3	18.5	NA	NA	0.182
HCV								
Yes	63	29.8	39.5	18.6	31.6	NA	NA	0.239
No	149	49.1	58.9	31.6	45.6	29.2	33.6	0.391
ALBI								
Grade 1	178	44.0	56.3	29.7	45.4	25.0	31.2	0.089
Grade 2/3	34	40.7	38.4	13.6	25.6	NA	NA	0.990
Tumor number								
Single	180	46.0	55.4	33.5	41.6	28.3	28.6	0.347
Multiple	32	34.4	38.5	6.9	38.5	6.9	14.4	0.268
Previous resection								
Major	43	43.7	76.7	43.7	54.2	43.7	40.7	0.775
Minor	169	43.8	47.8	24.9	39.0	20.3	23.9	0.201
Recurrence time								
<24 months	95	36.0	43.1	26.2	32.3	21.8	20.9	0.480
>24 months	117	50.0	60.9	29.0	49.3	24.9	31.1	0.172

Note: *: $p < 0.05$.

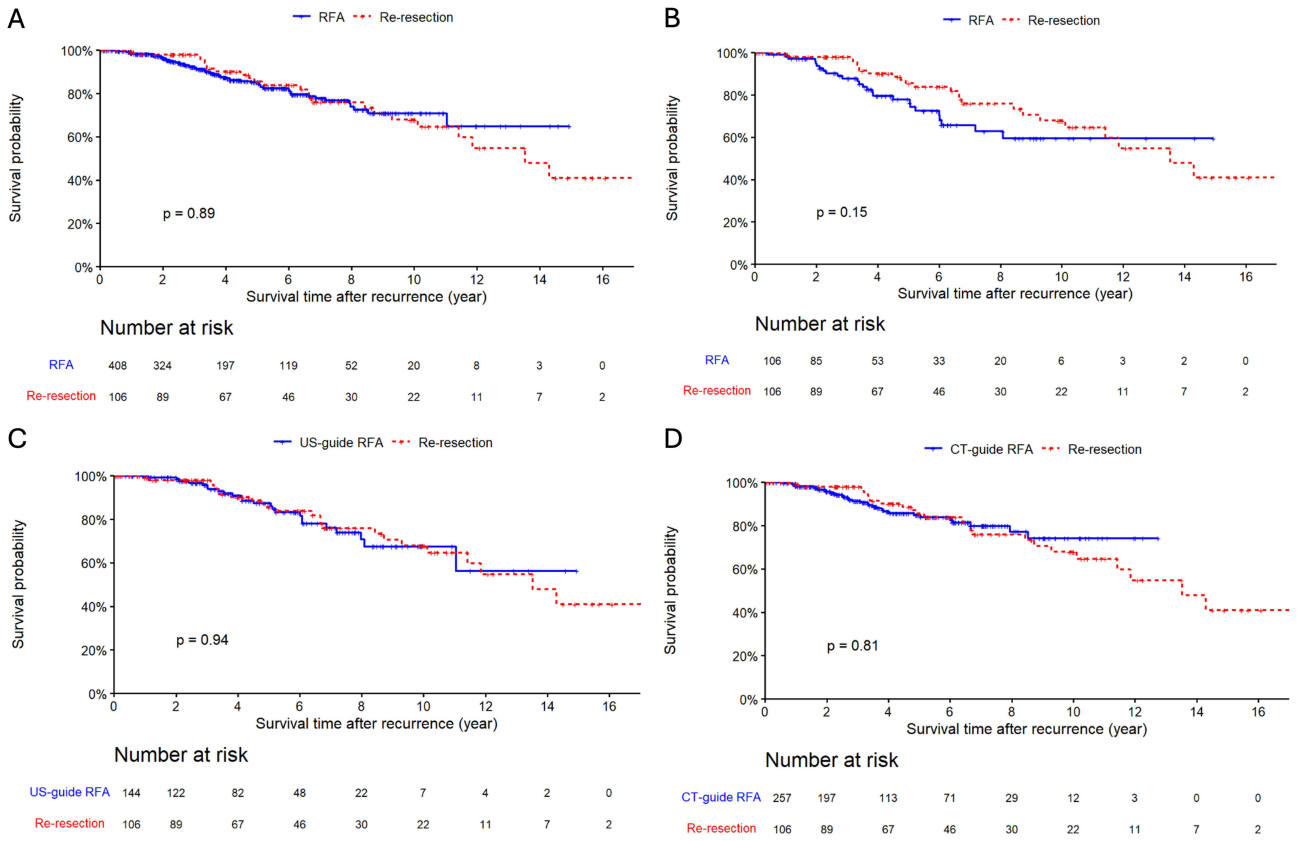


Figure 2 Comparison of long-term overall survival rates between repeat liver resection and radiofrequency ablation (RFA) in patients with recurrent HCC. (**A**) Unmatched cohort. (**B**) Propensity score matched cohort. There were no significant differences in survival outcomes before or after propensity score matching. There are also no significant differences in survival outcomes whether ultrasound (US) or computed tomography (CT) was used as guiding instruments for RFA (**C** and **D**).

the two treatments. For DFS (Table 2), Re-resection also tended to show higher survival rates across most subgroups, but these differences were generally not statistically significant. However, among patients with HBV infection, Re-resection provided significantly better DFS compared to RFA (5-year DFS rate: 51.8% vs 23.6%, $p = 0.015$). No significant differences in DFS were observed in other subgroups, including those defined by age, sex, HCV infection status, ALBI grade, tumor number, prior resection type, and recurrence interval.

Predictors of Death After Recurrence

Univariate analysis (Supplement 3) identified several factors as potential predictors of death following recurrence in patients who underwent curative liver resection for HCC. Age at recurrence (hazard ratio [HR]: 1.032, 95% confidence interval [CI]: 1.004–1.061, $p = 0.023$) and HCV infection (HR: 1.836, 95% CI: 1.046–3.223, $p = 0.034$) were associated with increased risk of death, while HBV infection appeared protective (HR: 0.553, 95% CI: 0.314–0.973, $p = 0.040$). However, in the multivariate analysis, none of these factors remained statistically significant. Specifically, the HR for age at recurrence was 1.025 (95% CI: 0.996–1.055, $p = 0.097$), and for HCV infection, it was 1.320 (95% CI: 0.638–2.733, $p = 0.454$). Repeat hepatic resection as a treatment modality did not show a significant survival benefit (HR: 0.664, 95% CI: 0.377–1.168, $p = 0.156$). Consequently, no significant predictor of death after recurrence were identified in the multivariate analysis.

Predictors of Secondary Recurrence After Recurrence

Univariate analysis (Table 3) identified HCV infection (HR: 1.637, 95% CI: 1.130–2.373, $p = 0.009$) and multiple tumors at recurrence (HR: 1.742, 95% CI: 1.134–2.681, $p = 0.011$) as significant predictors of secondary recurrence after curative treatment for the first HCC recurrence. These factors remained significant in the multivariate analysis. HCV

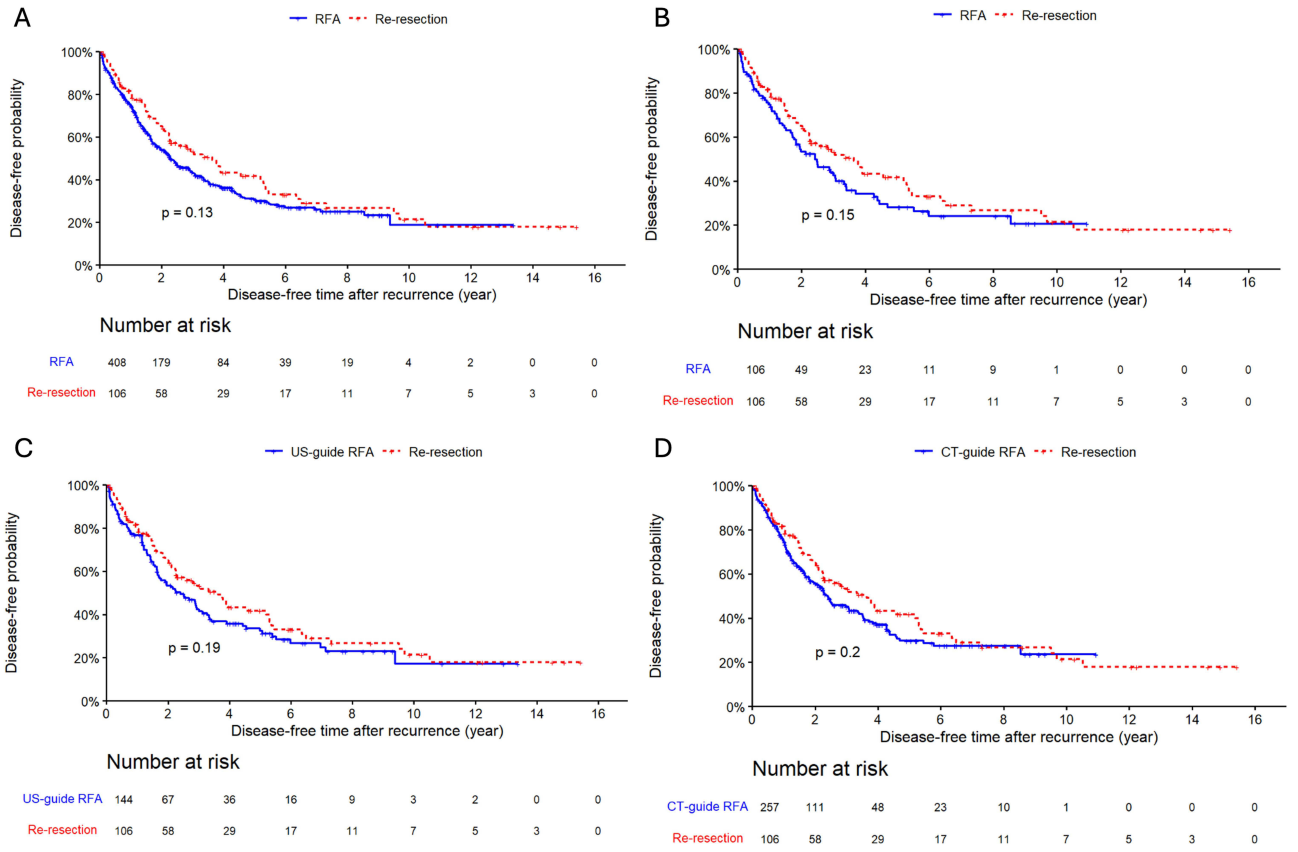


Figure 3 Comparison of long-term disease-free survival rates between repeat liver resection and radiofrequency ablation (RFA) in patients with recurrent HCC. (**A**) Unmatched cohort. (**B**) Propensity score matched cohort. There are also no significant differences in survival outcomes whether ultrasound (US) or computed tomography (CT) was used as guiding instruments for RFA (**C** and **D**).

infection was associated with an increased risk of secondary recurrence (HR: 1.624, 95% CI: 1.121–2.353, $p = 0.01$), as was the presence of multiple tumors at recurrences (HR: 1.724, 95% CI: 1.122–2.653, $p = 0.013$). Other factors, including repeat resection as a treatment modality, age, sex, cirrhosis, HBV infection, and high ALBI grade, were not significant predictors in either univariate or multivariate analysis.

Table 3 Univariate and Multivariate Cox Regression Analyses of Predictors for Secondary Recurrence After Patients Underwent Curative Liver Resection for Their First HCC Recurrence

Characteristic	Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Re-resection as treatment	0.778 (0.551–1.100)	0.155		
Age (year)	0.997 (0.982–1.012)	0.724		
Male sex	0.984 (0.655–1.480)	0.939		
Cirrhosis	1.156 (0.816–1.636)	0.415		
HBV (HBsAg+)	0.760 (0.526–1.096)	0.142		
HCV (anti-HCV+)	1.637 (1.130–2.373)	0.009	1.624 (1.121–2.353)	0.010
Previous major resection	0.715 (0.448–1.141)	0.160		
Multiple recurrence	1.742 (1.134–2.681)	0.011	1.724 (1.122–2.653)	0.013
High ALBI grade (2 or 3)	1.393 (0.894–2.171)	0.143		

Discussion

This study demonstrated that for patients who had undergone curative resection of primary HCC and presented with recurrent HCC smaller than 3 cm, there were no significant differences in OS and DFS between the Re-resection and RFA groups. These findings are consistent with a randomized controlled trial that reported similar DFS outcomes between surgery and RFA for small primary HCC.[24] Additionally, retrospective studies have shown no differences in prognosis between surgical resection and percutaneous US-guided RFA for recurrent HCC after curative treatment.[25] To address potential confounding factors, PSM was employed to balance baseline characteristics between the two groups. Prior to matching, the RFA group included older patients, smaller tumor sizes, lower albumin levels, and a higher prevalence of multiple lesions. After matching, the groups were well-balanced, and the comparable outcomes observed between Re-resection and RFA align with findings from previous studies.[11,15]

The selection of treatment is influenced by patient-specific factors. Previous studies have shown that older age, lower albumin levels, and more extensive liver resection are associated with an increased risk of post-hepatectomy liver failure.[26,27] In such cases, RFA may be the preferred treatment option. However, the efficacy of RFA diminishes as tumor size increases,[28] underscoring the need to adjust for these factors, as demonstrated in this study. Tumor location is another critical consideration. For example, laparoscopic surgery has been shown to yield better outcomes than RFA for single small subcapsular HCCs,[29] while other studies reported no survival difference between Re-resection and RFA for subcapsular location.[30] For lesions near the diaphragmatic dome or perivascular regions, the optimal treatment remains uncertain, and further research is needed to clarify the comparative efficacy of repeat resection and RFA in these challenging locations.

In our study, the 5-year and 8-year OS rates reached 85.4% and 75.8% for the Re-resection and 77.9% and 62.8% for the RFA group, respectively. While these OS outcomes are favorable, the 5-year and 8-year DFS rates were considerably lower at 41.8% and 26.7% for the Re-resection group and 28.1% and 24.0% for the RFA group. Nevertheless, these results surpass those reported in previous studies and systematic reviews[15–17] and are consistent with prior findings from our institution. These data underscore the importance of curative therapies, such as resection and RFA, in managing recurrent HCC after initial curative resection. Multivariate analysis identified HCV-related HCC and multiple recurrences as factors associated with poorer DFS. Recent multi-center data by Wang et al (2023) likewise underscore the prognostic weight of early post-hepatectomy recurrence, further supporting the clinical relevance of our results.[31]

In subgroup analysis, repeat resection conferred a survival benefit for patients with early recurrence (< 24 months) and for those with HBV-related HCC after their first curative resection—an association that has been seldom examined and has not been consistently demonstrated in earlier studies. Early recurrence is often associated with aggressive tumor behavior,[32] suggesting that repeat resection may be the preferred option in these cases. Additionally, repeat resection provided better DFS in patients with HBV-related HCC, which may reflect the higher likelihood of non-cirrhotic liver status in HBV-related HCC compared to HCV-related HCC, enabling more patients to undergo liver resection. Although HCV-related HCC was an independent prognostic factor in the multivariate analysis, advancements in treatment, such as direct-acting antiviral agents, may improve outcomes for these patients in the future.[33] In the multivariate model, HBV infection was not an independent predictor, which may be attributed to reduced power following subgrouping and the effect being mediated or confounded by other covariates, including liver function status and tumor number. Multiple recurrences were another independent prognostic factor, highlighting the importance of targeted tumor eradications and potential role of adjuvant therapy.

This study has several limitations, First, it is a single-center retrospective study, which limits the generalizability. Larger, multicenter studies are needed to validate our findings. Second, we did not stratify patients by open versus laparoscopic surgery or compare the outcomes of US- versus CT-guided RFA. Third, most of patients were followed up in surgical outpatient clinics, which may have introduced referral bias. Fourth, the subgroup comparisons were exploratory in nature and not adjusted for multiple testing. Due to limited sample sizes in certain subgroups, these analyses may lack sufficient statistical power and should therefore be interpreted with caution. However, we employed PSM to minimized baseline differences between the two groups. Additionally, the large sample size and long follow-up period represent significant strengths of this study.

In conclusion, there is no significant survival difference between repeat hepatic resection and RFA for patients with recurrent HCC smaller than 3 cm after curative resection. Treatment selection should consider patient age, liver function,

tumor size, and number. Repeat hepatic resection is recommended for patients with early recurrence or HBV-related HCC due to its survival benefits. HCV-related HCC and multiple recurrences, as independent risk factors for poorer DFS, highlight the importance of antiviral therapies and tailored strategies for managing recurrent HCC.

Highlights

- Re-resection and RFA provide similar survival outcomes for small recurrent HCC.
- Re-resection is preferred for early recurrence and HBV-related HCC.
- Both US- and CT-guided RFA for recurrent small HCCs are effective alternatives.

List of All Abbreviations

HCC, Hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; RFA, radiofrequency ablation; US, Ultrasound; CT, Computed tomography; PSM, Propensity score matching; MRI, Magnetic resonance imaging; OS, Overall survival; DFS, Disease-free survival; SD, Standard deviation; IQR, Interquartile range; HR, Hazard ratio; CI, Confidence interval.

Data Sharing Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

Ethics Approval

Written informed consent was waived for this retrospective study. All clinical information, laboratory data, and images were collected under routine workup. This study followed the Health Insurance Portability and Accountability Act guidelines and the Declaration of Helsinki of 1975, as revised in 2008. Institutional Review Board of National Taiwan University Hospital approval was obtained (NTUH-202409013RINC).

Consent to Publication

All authors were aware of and agreed to the submission and that they had all contributed to the work described sufficiently to be named as authors.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; Chih-Yang Hsiao took part in drafting; Chih-Horng Wu revised, reviewed and gave final approval of the version to be published; Rey-Heng Hu and Po-Chin Liang have agreed on the journal to which the article has been submitted and agreed to be accountable for all aspects of the work.

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Disclosure

All author declared no conflict of interest.

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