[Repeat hepatic resection versus radiofrequency ablation for recurrent hepatocellular carcinoma: a retrospective multicentre study.](https://pubmed.ncbi.nlm.nih.gov/34643677/)

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**Abstract**

**Background & Aims:**Long-term survival after repeat hepatic resection (rHR) or radiofrequency ablation (RFA) for recurrent hepatocellular carcinoma (HCC) is unknown. We investigated this in a nine-centre study in mainland China, Hong Kong and Italy.

**Methods:** Between January 01, 2003 and January 31,2018, 940 patients with recurrent HCC received rHR or RFA. All enrolled patients had recurrent HCC within the Milan criteria, they had already undergone initial resection, and they had Child-Pugh A or B liver function. Survivals after rHR or RFA were examined by unadjusted analysis, Fine-Gray test, 1:1 propensity score matching, and inverse probability of treatment weighting (IPTW).

**Results:** A total of 847 patients were enrolled. Median recurrence-free survival was significantly longer in the rHR group than in the RFA group (23.6 vs 15.2 months, hazard ratio 0.76, 95%CI 0.65-0.89), and the respective 10-year recurrence-free survival rates were 10.6% and 3.9%. Median overall survival was 73.5 months after treatment with rHR and 67.0 months after RFA (hazard ratio 1.01, 95%CI 0.81-1.26) with respective 10-year overall survival rates of 34.9% and 29.2%. These results were confirmed by Fine-Gray test, propensity score matching, and IPTW. However, patients in the RFA group experienced lower rates of perioperative mortality and morbidity and shorter hospital stays. Subgroup analysis found that patients with alpha fetoprotein ≥ 200 ng/ml showed better overall survival after rHR than RFA (HR 0.57, 95%CI 0.34-0.94).

**Conclusion:** rHR is associated with better local tumour control for patients with recurrent HCC within Milan criteria, and better overall survival in patients with alpha fetoprotein > 200 ng/ml.

**Keywords:**hepatocellular carcinoma, repeat hepaticresection, radiofrequency ablation, recurrence

**Introduction**

Liver cirrhosis related to chronic hepatitis virus infection or to alcohol useis the main risk factor of hepatocellular carcinoma (HCC). The treatment choice for HCC is based not only on tumour staging, but also on careful evaluation of liver function and physical status. Based on official guidelines,[1-3](#_ENREF_1) hepatic resection is the best treatment for patients with single HCC or tumours within Milan criteria.[4](#_ENREF_4) Additional deciding factors include patient performance status, co-morbidities, and preservation of liver function and remnant volume. Hepatic resection is also the recommended choice for treating intermediate and advanced HCC.[5](#_ENREF_5), [6](#_ENREF_6) In contrast, radiofrequency ablation (RFA) is the recommended treatment when patients have a single tumour <2 cm or 2-3 nodules ≤3 cm,[1-3](#_ENREF_1) although patients with a single tumour ≥2 cm and <5 cm are also candidates for RFA at many liver centers.[7](#_ENREF_7), [8](#_ENREF_8) However, 60% of patients with early-stage HCC suffer recurrence within five years after curative resection or RFA.[9](#_ENREF_9) The recurrence rate is even higher (74%) for intermediate and advanced HCC after hepatic resection, which is a major cause of death among such patients.[10](#_ENREF_10)

The curative treatment modalities for recurrent HCC include repeat hepatic resection (rHR), RFA, and salvage liver transplantation. Liver transplantationis limited because of the shortage of donors, especially in Asia. Therefore, rHR and RFA are the two main curative treatments for recurrent HCC. Yet clinical practice guidelines from Western regions[1-3](#_ENREF_1) and the Asia-Pacific region[11](#_ENREF_11) do not state a preference or recommendation for one or the other for particular patient subgroups. Similarly, recent guidelines from South Korea[12](#_ENREF_12) and India[13](#_ENREF_13) and one expert consensus[14](#_ENREF_14) do not recommend a specific treatment for recurrent HCC, although they do recommend that the appropriate treatment modality be chosen based on timing of recurrence, residual liver function, performance status, as well as the size, location, and number of recurrent tumours. Comparing outcomes after rHR and RFA may be helpful for identifying the more appropriate treatment for recurrent HCC, particularly among those who have preserved liver function and normal performance status and therefore fall within the Milan criteria. These patients make up a substantial proportion of those who suffer HCC recurrence and, because their general health is better than that of patients with more severe HCC, they are usually eligible for rHR or RFA.

Many small retrospective studies have compared the safety and efficacy of rHR and RFA for patients with recurrent HCC within Milan criteria, but the results have been divergent.[15](#_ENREF_15), [16](#_ENREF_16) Moreover, few studies have reported long-term survival of such patients after either treatment. In this multi-centre study, we assessed the therapeutic value of rHR compared to RFA for treating recurrent HCC within Milan criteria. To place our clinical findings in a broader context, we comprehensively analysed relevant studies from PubMed.

**PATIENTS AND METHODS**

***Study design and patients***

Data for this collaborative retrospective study were collected from patients with recurrent HCC who were treated with rHR or RFA between January 01, 2003 and January 31, 2018. Patients were seen at nine centres located in mainland China (Guangxi Medical University Cancer Hospital, Nanning; the First Affiliated Hospital of Guangxi Medical University, Nanning; the People's Hospital of Guangxi Zhuang Autonomous Region, Nanning; the Third Affiliated Hospital of Guangxi Medical University, Nanning; the First People’s Hospital of Nanning, Nanning; Peking University School of Oncology, Beijing; Tongji Hospital, Tongji Medical College, Wuhan), Hong Kong (the Chinese University of Hong Kong), and Italy (S.Orsola-Malpighi Hospital, University of Bologna, Bologna). All centres complied with ethical requirements (including informed consent) according to local practices, and research procedures were conducted in accordance with the Declaration of Helsinki (1975) and its amendments. Due to the retrospective nature of the study, formal approval of the study protocol was not required.

To be enrolled, patients had to satisfy the following criteria: (a) hepatic resection as the initial curative treatment after HCC diagnosis; (b) pathology on initial resected tissue to confirm HCC diagnosis; (c) clinical diagnosis of recurrent HCC, after initial resection, followed by either rHR or RFA as a first-line treatment; (d) recurrent HCC satisfying the Milan criteria, including a solitary nodule with a diameter of ≤5 cm or 3 or fewer nodules each ≤3 cm in diameter, and no macrovascular invasion or distant metastasis[4](#_ENREF_4); (e) preserved liver function (≤7 score); and (f) an Eastern Cooperative Oncology Group performance score of 0 to 1. Patients were were still eligible if they received other treatments for recurrent HCC in conjunction with rHR or RFA, or if they received any treatments for repeat (second) HCC recurrence after rHR or RFA. Patients were excluded if HCC reoccurred within one month of the initial hepatic resection, or if they received other treatments for recurrent HCC before rHR or RFA, such as transarterial chemoembolization, salvage liver transplantation, or targeted therapy. Patients with missing survival data were also excluded from the analysis.

***Interventions and follow-up***

All clinical and laboratory parameters were prospectively recorded and retrospectively collected from patient records. The following criteria must have been present for initial resection and rHR treatment: preserved liver function (Child-Pugh score ≤ 7 or indocyanine green 15 minutes retention rate of <10%), appropriate (30% for those without cirrhosis and ≥ 50% for those with cirrhosis) volume of residual liver tissue as determined by volumetric computed tomography and/or magnetic resonance imaging, and absence of extrahepatic metastasis.[17](#_ENREF_17), [18](#_ENREF_18) Histopathology was routinely performed postoperatively on liver tissue extracted by resection or rHR to confirm (recurrent) HCC diagnosis. RFA was chosen as treatment when the recurrent tumour(s) were located at least 1.0 cm away from the hepatic hilus (including main hepatic veins), vena cava, gallbladder, diaphragm, and adjacent gastrointestinal tract. In most cases, a personalized approach was undertaken based on multidisciplinary discussion. Contrast-enhanced ultrasonography was performed 2 to 3 days after RFA if the doctor suspected incomplete ablation. If residual tumour was present, an additional session of RFA was performed.

The first patient follow-up occurred 1 month after rHR or RFA, then once every 2 to 3 months for 2 years. After that time period, follow-ups were scheduled once every 6 months until death. Each follow-up visit included measures of liver function, [coagulation](javascript:;) [function](javascript:;), and alpha fetoprotein (AFP); [routine](javascript:;) [blood](javascript:;)  [examination](javascript:;); and computed tomography and/or magnetic resonance imaging. HCC recurrence was diagnosed using the criteria of the European Association for the Study of the Liver.[1](#_ENREF_1) Treatment regimen for repeat HCC recurrence after rHR or RFA was based on the patient’s liver function, performance score, tumour size and location, and number of nodules.[12-14](#_ENREF_12) Additional therapies were performed on patients who showed evidence of residual disease on imaging. Patients who had no residual disease received no adjuvant therapy. Patients with chronic hepatitis B received nucleos(t)ide analogue therapy. Liver failure was defined according to the 50-50 criterion on postoperative day 5.[19](#_ENREF_19)

***Outcomes***

The primary measure of outcome was repeat recurrence-free survival defined as the interval from date of rHR or RFA to date of HCC recurrence or death, which ever occurred earlier. Repeat recurrence-free survival was censored on the date of the last follow-up (April 30, 2020) when the patients were still alive without repeat recurrence. Repeat recurrence was divided into early (≤12 months) and late (>12 months).[20](#_ENREF_20) The second outcome was overall survival, which was the interval from rHR or RFA to death from any cause, and it was censored on April 30, 2020 if the patients were still alive. The complications were defined using the Clavien-Dindo classification.[21](#_ENREF_21) Length of hospital stay was defined as the number of days from treatment with rHR or RFA after first HCC recurrence until discharge.

***Statistical analysis***

Categorical variables were presented as percentages. Continuous variables were divided by normal and abnormal distribution. Clinicopathological parameters were set to binary model to avoid a possible nonlinear effect, then univariable analysis was performed. Significant variables (*P* <0.05) were used to generate a multivariable Cox regression model to identify independent risk factors of repeat recurrence-free survival and overall survival. Only clinicopathological variables with likely clinical effects were included in the selection. Where appropriate, results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). The proportional hazard assumption was checked using a -ln(-ln[survival]) graph. Kaplan-Meier survival curves were plotted for the total population and separately for rHR and RFA subgroups. Median repeat recurrence-free survival and overall survival, HRs, and percentages were also calculated for each group at 1-, 3-, 5-, and 10-year follow-up. Cumulative repeat recurrence-free survival and overall survival were compared by the log-rank test.

We used time-to-event competing risk analysis to account for non-liver-related mortality and competing risk regression[22](#_ENREF_22) to calculate the subdistribution HRs of rHR vs RFA for liver-related mortality. The subdistribution HRs of liver-related mortality were calculated from rHR and RFA patients who were followed-up for the same length of time. The competing risk regression was also used to adjust for risk of all-cause mortality before HCC recurrence and after initial resection.

To reduce potential confounding of our results based on differences in baseline characteristics, patients treated with rHR were matched at a 1:1 ratio to patients treated with RFA based on propensity score (PS) matching. The PS was generated by a logistic regression that considered the following clinicopathological variables that might have influenced therapeutic choice and patient prognosis: sex, age, hepatitis B surface antigen, hepatitis C antibody positivity, body mass index, AFP, platelet count, total bilirubin, serum albumin, serum alanine aminotransferase, prothrombin time, Child-Pugh liver function, liver cirrhosis, portal hypertension, tumour size and number, and time to recurrence. Nearest-neighbour caliper matching without replacement (random order or closest distance) was used to pair rHR and RFA patients with similar PS values.[23](#_ENREF_23), [24](#_ENREF_24)

As a further sensitivity analysis, inverse probability of treatment weighting (IPTW) was applied to the PS-matched pairs. In the IPTW analysis, we applied average treatment effect on the treated weighting to estimate the average treatment effect in the treated cohort.[25](#_ENREF_25) A weight of 1 was assigned to all subjects in the rHR-treated group and PS/[1-PS] to all subjects in the RFA-treated group, so that the baseline covariates showed nearly identical distributions in the two groups.

The balance in the baseline clinical characteristics was assessed between the two groups before and after PS weighting and matching by using the standardized mean difference (SMD), with values of below 0.1 indicating good balance.[26](#_ENREF_26)

Subgroup analyses for repeat recurrence-free survival and overall survival were performed based on the independent risk factorsidentified in the multivariable analysis. Time to recurrence was defined as the interval from the initial resection to the first diagnosis of recurrence. Eastern and Western subgroup analyses were also performed to account for different characteristics of tumour and treatment modalities arising from differences in clinical guidelines.

Data were managed and analysed using SPSS 20.0 (IBM, USA) in conjunction with R version 3.4.0 (The R foundation, Vienna, Austria). Two-tailed *P* values were reported unless otherwise specified. A *P* value <0.05 was considered statistically significant.

***Comprehensive PubMed review***

We comprehensively searched the PubMed database using the following medical subject heading (MeSH) terms: (*hepatocellular carcinoma* or *liver cancer*) and (*repeat hepatectomy* or *repeat hepatic resection* or *re-hepatectomy*) and (*ablation)* and (*recurrence* or *recurrent*). Manual searching of relevant references and review articles was also performed. Studies were included in our review if they compared the efficacy of rHR to ablation for recurrent HCC and were published between January 2005 and June 2020. Studies evaluating resection or ablation to treat primary HCC or studies involving fewer than 10 patients in each group were excluded. In the case of multiple studies based on the same population, the study with the largest sample size was selected.

**Results**

***Characteristics of the study population***

In our study, 7,178 patients with HCC who underwent curative resection were prospectively enrolled in the databases of the nine study hospitals. Among them, 847 patients (11.8%) with recurrent HCC fitting the Milan criteria were enrolled in the present retrospective study, including 307 (36.2%) patients who underwent rHR and 540 (63.8%) patients who underwent RFA (Fig. 1). In the rHR group, recurrent HCC diagnosis was confirmed by postoperative histopathological examination, whereas in the RFA group diagnosis was confirmed by using one or two imaging techniques with HCC imaging hallmarks.

Baseline demographic and clinicopathological data for the 847 patients are shown in Table 1. More patients in the rHR group were female and had shorter prothrombin time (all SMD> 0.1). Additionally, more of these patients had AFP ≥ 200 ng/ml, tumour size ≥ 3 cm, and time to recurrence > 12 months (all SMD> 0.1). PS matching generated 227 pairs without significant differences in baseline variables (Table 1), and IPTW reduced all SMDs to <0.1 (Table 1).

***Mortality, morbidity, and length of hospital stay***

In the total population, two patients in the rHR group died within 30 days of treatment because of liver failure (n=1) or intra-abdominal hemorrhage (n=1). Three patients died in the RFA group because of phrenic artery injury and bleeding during treatment (n=2) or intra-abdominal hemorrhage (n=1).No significant differences between the rHR and RFA groups were observed in 30-day mortality (0.65% vs. 0.37%, *P*=0.624) or 90-day mortality (0.65% vs. 0.56%, *P*=1.0). Most complications were grade I or II. Patients in the rHR group had a significantly higher postoperative morbidity rate (21.5%) than patients in the RFA group (5.0%). The most frequent morbidities in both groups of patients were fever and ascites (Table 2). The median length of hospital stay was significantly longer after rHR than after RFA (8.0 [range, 4.0-22.0] vs 3.0 [range, 1.0-9.0] days, *P*<0.001).

In the PS-matched pairs, the rHR and RFA groups had similar rates for 30-day mortality (0.8% vs. 0.4%, *P*=1.0) and 90-day mortality (0.8% vs. 0.8%, *P*=1.0). However, patients in the rHR group (19.0%) had significantly higher morbidity than those in the RFA group (5.48%, *P*<0.001). Also, median length of hospital stay was significantly longer after rHR than after RFA (*P*<0.001).

***Repeat recurrence-free survival***

The rHR group showed similar median follow-up period (53 months [range, 1-147]) as the RFA group (43 months [range, 0.6-142.1], *P*=0.065). During this time, 208 (67.8%) patients in the rHR group and 400 (74.1%) in the RFA group experienced repeat HCC recurrence (*P*=0.057). The rate of early recurrence (<12 months)was significantly lower in the rHR group than in the RFA group (47.6% vs. 57.3%, *P*=0.026). Median recurrence-free survival after repeat recurrence was 23.6 months in the rHR group and 15.2 months in the RFA group. The rHR group showed significantly higher rates of repeat recurrence-free survival than the RFA group at 1 year (67.4% vs. 57.3%), 3 years (37.5% vs. 28.1%), 5 years (25.5% vs. 16.0%), and 10 years (10.6% vs. 3.9%) (Fig. 2A and Fig.S1; HR 0.76, 95%CI 0.65-0.89, *P*<0.001, log-rank test).

Competing repeat HCC recurrence occurred in 16 patients (5.2%) in the rHR group and 20 (3.7%) in the RFA group. Fine-Gray testing confirmed that patients in the rHR group had significantly higher repeat recurrence-free survival rates than those in the RFA group (Fig. 2B and Fig. S1; HR 0.75, 95%CI 0.64-0.88, *P*<0.001, log-rank test). Similar findings were obtained with PS-matched patients (Fig. 2C and Fig. S1; HR 0.71, 95%CI 0.57-0.88, *P*<0.001, log-rank test) and IPTW analysis (Fig. 2D and Fig. S1; HR 0.68, 95%CI 0.57-0.83, *P*<0.001, log-rank test).

***Overall survival***

In the entire study population, the rHR group was observed for a median duration of 54 months (range, 1-178); the RFA group, for a median of 49.3 months (range, 1-156) (*P* = 0.002). During that time, 128 (41.7%) rHR-treated patients and 208 (38.5%) RFA-treated patients died. The rHR and RFA groups showed similar overall survival rates at 1 year (92.1% vs. 92.1%), 3 years (67.4% vs. 71.3%), and 5 years (56.4% vs. 53.1%), but not at 10 years (34.9% vs. 29.2%) (Fig. 3A and Fig. S2; HR 1.01, 95%CI 0.81-1.26, *P*=0.955, log-rank test). These findings were supported by Fine-Gray testing (Fig. 3B and Fig. S2; HR1.04, 95%CI 0.83-1.30, *P*=0.781, log-rank test), PS matching (Fig. 3C and Fig. S2; HR1.06, 95%CI 0.79-1.41, *P*=0.694, log-rank test), and IPTW analysis (Fig. 3D and Fig. S2; HR 0.93, 95%CI 0.71-1.19, *P*=0.533, log-rank test). Median survival time was 73.5 months in the rHR group and 67.0 months in the RFA group. However, when overall survival was calculated from the initial hepatectomy, the rHR group showed slightly higher overall survival rate than the RFA group (Fig. S3; HR 0.799, 95%CI 0.64-0.99, *P*=0.046, log-rank test). Non-liver-related mortality occurred in 7 patients (2.3%) in the rHR group and 15 (2.8%) in the RFA group.

***Subgroup analysis of the entire study population***

To compare in greater detail the efficacy of rHR and RFA for treating recurrent HCC within Milan criteria, we performed subgroup analyses based on age, AFP level, serum albumin, tumour size and number, and time to recurrence. rHR was associated with better repeat recurrence-free survival in patients regardless of stratification by age, AFP or tumor size; and in patients with serum albumin levels ≥ 35 g/L, single tumour, or whose time to recurrence was longer than 12 months (Fig.4). However, the two treatments were associated with similar rates when serum albumin levels were < 35 g/L (HR 1.01, 95%CI 0.53-1.92), the patient had multiple tumours (HR 0.96, 95%CI 0.68-1.33), or the time to recurrence was ≤ 12 months (HR 0.79, 95% CI 0.60-1.04).

Overall survival subgroup analyses were also performed on data from patients who experienced a repeat recurrence after rHR or RFA treatment and the consequential re-treatment. Overall survival was similar between the two treatment groups regardless of the stratification variable, except in the case of AFP, where patients with AFP ≥ 200 ng/ml showed better survival after rHR than RFA (HR 0.57, 95%CI 0.34-0.94) (Fig. 5).

Subgroup analysis based on Eastern (n=809) and Western (n=38) cohorts showed that in both cohorts, rHR was associated with significantly higher repeat recurrence-free survival, while the two treatments were associated with comparable overall survival (Fig. S4).

***Patterns of repeat recurrence and treatments***

Though more patients in the RFA group experienced repeat HCC recurrence than in the rHR group, the rates of intra- and extrahepatic recurrence were similar between the two groups before PS matching (*P*=0.930) and after matching (*P*=0.618) (Table S1). In contrast, more patients in the RFA group experienced early repeat recurrence (57.3% vs. 47.1%; *P*=0.021). A majority of patients in the rHR group (84.1%) and RFA (85.7%) received positive treatment for repeat recurrent HCC (*P*=0.595). The remaining patients received best supportive care or no treatment. The treatment modalities for repeat recurrent HCC are detailed in Table S2. After repeat HCC recurrence, significantly more patients in the RFA group received one or more subsequent curative treatment modalities, including rHR, RFA, percutaneous ethanol injection, or orthotopic liver transplantation (55.3% vs. 39.4%, *P*<0.001) (Table S2).

***Uni- and multivariable analysis***

Among all patients, univariate (Table S3) and multivariable analyses for repeat recurrence-free survival time were performed. Independent predictors of repeat HCC recurrence included age < 60 yr, AFP ≥ 200 ng/ml, albumin <35 g/L, multiple tumours, time to recurrence ≤ 12 months, and RFA (Table S4). Next we analysed overall survival (Table S5). The following prognostic factors increased risk of mortality in the total population: AFP ≥ 200 ng/ml, albumin <35 g/L, tumour size ≥ 3 cm, time to recurrence ≤ 12 months, repeat recurrence, and no treatment for repeat recurrent HCC (Table S6).

Similar results were obtained for PS-matched pairs of patients.

***Literature review***

A total of 21 eligible studies, involving 1209 patients who underwent rHR and 1781 patients who underwent RFA, satisfied the literature review inclusion criteria (Table S7).[20](#_ENREF_20), [27-46](#_ENREF_27) Most patients in the included studies were from southeast Asia, the region with the highest prevalence of HCC. Fourteen studies[20](#_ENREF_20), [27-30](#_ENREF_27), [32](#_ENREF_32), [35-39](#_ENREF_35), [41](#_ENREF_41), [42](#_ENREF_42), [46](#_ENREF_46) reported the rate of perioperative mortality, while 12 studies[20](#_ENREF_20), [27-30](#_ENREF_27), [35-39](#_ENREF_35), [41](#_ENREF_41), [42](#_ENREF_42) reported morbidity. The median perioperative mortality was 0% (range, 0-2.6%) after rHR and 0% (0-2.2%) after RFA; the corresponding rates of morbidity were 17.0% (5.5-36%) and 2.8% (0-13%). The two groups showed similar median overall survival at 1, 3, and 5 years (Fig. 6). However, patients in the rHR group had higher repeat recurrence-free survival at1year (76.2% vs. 69.5% ), 3 years (48.1% vs. 37.8%), and 5 years (36.2% vs. 29.6%) (Fig. 6). Nearly none of the included studies reported 10-year repeat recurrence-free survival or overall survival, and only a handful reported length of hospital stay.

**Discussion**

Our findings revealed that rHR treatment led to significantly higher repeat recurrence-free survival and 10-year overall survival in patients with recurrent HCC within Milan criteria. These findings were confirmed by Fine-Gray test, PS matching, IPTW, and subgroup analyses. However, RFA was safer and required shorter hospital stays. Nevertheless, rates of 30-and 90-day mortality were less than 1% in both treatment groups. These findings were consistent with our literature review. We also found that patients in the RFA group had slightly higher rates of repeat recurrence. However, the rate of available treatment options to patients was similar in the two groups. In addition, patients in the RFA group had significantly higher rates of early repeat recurrence and shorter median repeat recurrence-free survival time, and significantly more of them subsequently received curative treatment modalities, especially repeat RFA.

The results of the present study are consistent with retrospective studies[27](#_ENREF_27), [30](#_ENREF_30), [35](#_ENREF_35), [41](#_ENREF_41) and a randomized controlled trial[20](#_ENREF_20) that reported that the two treatment groups showed similar short-term overall survival. At the same time, some of our results differ from those of similarly conducted studies[20](#_ENREF_20), [27-46](#_ENREF_27) and are inconsistent with official guidelines.[1](#_ENREF_1), [2](#_ENREF_2), [12](#_ENREF_12), [13](#_ENREF_13), [47](#_ENREF_47), [48](#_ENREF_48) First, patients in the RFA group had a significantly higher rate of early repeat recurrence, which translates into lower median repeat recurrence-free survival. However, the two groups had similar short-term overall survival rates, mainly because significantly more patients in the RFA group received one or more subsequent curative treatment modalities. Second, the rate of patients who did not experience repeat recurrence or were lost to follow-up was higher in the rRH group (32.2%) than in the RFA group (25.9%) may translate into a higher 10-year overall survival rate. Therefore, we conclude that rHR is superior to RFA for patients with recurrent HCC within Milan criteria, as demonstrated by significantly higher repeat recurrence-free survival and long-term overall survival. This mirrors findings in patients with untreated primary HCC.

Our subgroup analyses found that rHR did not significantly improve repeat recurrence-free survival relative to RFA in patients with reports of serum albumin < 35 g/L, multiple tumours, or time to recurrence < 12 months. Low serum albumin usually implies moderate to severe cirrhosis.[49](#_ENREF_49) For such patients, surgery is not the obvious choice due to the high risk of liver failure and tumour recurrence.[50](#_ENREF_50) HCC recurrence with multinodular tumours is always accompanied by occult intrahepatic recurrence, which is difficult to diagnose before resection.[14](#_ENREF_14) These occult intrahepatic recurrences could develop into repeat recurrent HCC. RFA is a local treatment that targets the macroscopic disease, which means occult intrahepatic recurrences miss timely treatment. Time to recurrence < 12 months may indicate greater aggressiveness of the initial tumour, which influences risk of recurrence.[51](#_ENREF_51) Therefore, for patients with serum albumin < 35 g/L, multiple tumours, or time to recurrence < 12 months, RFA may be the superior option for safety reasons, although the two treatments are associated with similar rates of repeat recurrence-free survival and overall survival.

Our subgroup analyses found that, compared to RFA-treated patients, rHR was associated with significantly better overall survival when AFP ≥ 200 ng/ml. This is consistent with the results from the only randomized controlled trial in our literature review.[20](#_ENREF_20) The level of AFP is commonly used to estimate the severity of tumor burden and as a prognostic factor for the response to different treatments.[52](#_ENREF_52), [53](#_ENREF_53) This may reflect that rHR may especially suited to those with severe tumor burden.

Despite the better survival rates following rHR treatment, patients treated with RFA experienced significantly lower postoperative morbidity rates and spent less time in the hospital, which may translate into lower medical cost and higher quality of life. However, the higher rate of repeat recurrence after RFA and subsequent treatments may negatively impact medical cost in the long-term. Analysing the cost-effectiveness for either treatment should be investigated in future studies.

Our multivariable analysis revealed that young age, elevated AFP level, low albumin level, multiple or large hepatic metastases, short disease-free interval, repeat recurrence, and no treatment for repeat recurrent HCC were independent risk factors of repeat recurrence-free survival or overall survival. This is consistent with the findings of other studies,[15](#_ENREF_15), [20](#_ENREF_20) but suggests that management of recurrent HCC is challenging. These risk factors, tumour location, as well as the positive findings of our subgroup analyses should be considered when choosing appropriate treatments for patients with recurrent HCC. This is especially important given the few cases in which rHR and RFA are equally suitable for the patient. Nonetheless, recent advances in treatment modalities have rendered recurrent HCC a treatable disease and the possibility of long-term survival has improved. This was confirmed in our study by median survival of 73.5 months in the rHR group and 67.0 months in the RFA group.

There is no consensus on whether hepatic resection or RFA is the better treatment for patients with untreated primary HCC within Milan criteria. Both produce similar rates of overall survival and recurrence-free survival according to randomized trials[7](#_ENREF_7), [54](#_ENREF_54) and Western clinical guidelines.[1](#_ENREF_1), [2](#_ENREF_2) However, hepatic resection emerged as superior in meta-analyses of large studies[55](#_ENREF_55), [56](#_ENREF_56), and this modality is indeed recommended in Chinese clinical guidelines[47](#_ENREF_47), [48](#_ENREF_48). Nevertheless, rHR for recurrent HCC is limited in clinical practice because it leaves small volumes of residual liver parenchyma and this poses a problem in cases of repeat HCC recurrence.[12-14](#_ENREF_12) On the contrary, RFA is extensively performed because the procedure is minimally invasive.[12-14](#_ENREF_12)

Despite its strengths, this large, multicenter study has limitations. First, it was a retrospective analysis, so we did not have data for certain variables that may influence choice of rHR or RFA (e.g. tumour location or comorbidity) or subsequent survival. Nevertheless, the reliability of our findings is suggested by PS matching and IPTW. We also took into acount non-liver-related mortality. Second, one or more additional subsequent treatments are typically administered for repeat recurrent HCC, which may influence overall survival, yet we were unable to suggest the patients receiving similar treatments. Combination treatments may give better oncological outcomes.[1-3](#_ENREF_1)

Even with these limitations, the findings from our large retrospective study suggest that rHR is associated with better local tumour control. Moreover, rHR is associated with better overall survival than RFA in patients with AFP > 200 ng/ml. These findings could be incorporated into further treatment guidelines.

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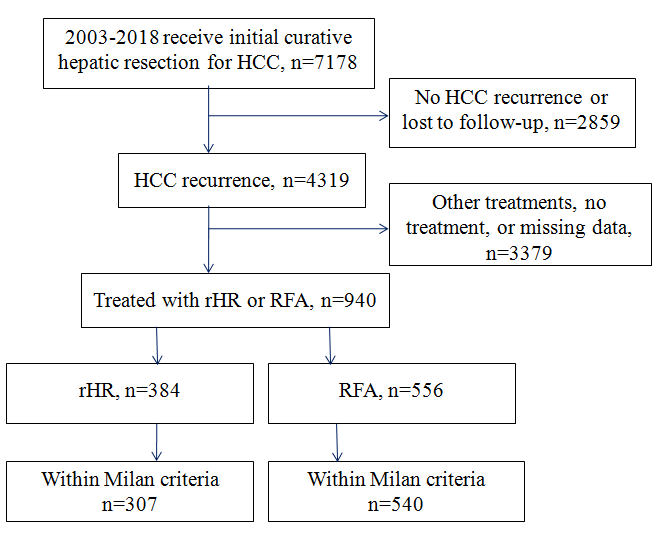
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**Figure legends**

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**Figure 1.** Patient selection process from international multicentre study. HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; rHR, repeat hepatic resection.

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**Figure 2.** Cumulative recurrence-free survival of patients with recurrent hepatocellular carcinoma within Milan criteria after repeat hepatic resection (rHR) or radiofrequency ablation (RFA) treatment. Repeat recurrence-free survival was calculated for the (A) total population or for subpopulations subjected to (B) Fine-Gray testing, (C) propensity score matching, or (D) inverse probability of treatment weighting (IPTW).

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**Figure 3.** Cumulative overall survival of patients with recurrent hepatocellular carcinoma within Milan criteria after repeat HR (rHR) or radiofrequency ablation (RFA) treatment. Overall survival was calculated in (A) total population or the included population by (B) Fine-Gray’s test, (C) propensity 1:1 matching, (D) the inverse probability of treatment weighting (IPTW).

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**Figure 4.** Subgroup analysis for recurrence-free survival. Hazard ratios were derived from a multivariable-adjusted Cox proportional-hazards regression with robust variance estimation. Abbreviations: rHR, repeat hepatic resection; RFA, radiofrequency ablation; AFP, alpha fetoprotein.

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**Figure 5.** Subgroup analysis for overall survival. Hazard ratios were derived from a multivariable-adjusted Cox proportional-hazards regression with robust variance estimation. Re-recurrence refers to recurrence of hepatocellular carcinoma after rHR and RFA treatment. Abbreviations: rHR, repeat hepatic resection; RFA, radiofrequency ablation; AFP, alpha fetoprotein.

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**Figure 6.** Bubble plots of (A) recurrence-free survival and (B) overall survival of recurrent HCC patients at 1, 3, and 5 years after repeat hepatic resection(rHR) or radiofrequency ablation (RFA). Bubble size is proportional to the sample size in the study.

**Figure legends for supplementary figures**

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**Figure S1.** Effect of repeat hepatic resection on risk of hepatocellular carcinoma recurrence.

aHazard ratios were derived from a univariable Cox proportional-hazards regression with robust variance estimation.

bA multivariable-adjusted Cox proportional-hazards regression with robust variance estimation further accounted for the following prognostic covariates: sex, age, body mass index, hepatitis B surface antigen, alpha fetoprotein, platelet count, total bilirubin, albumin, aminotransferase, prothrombin time, Child-Pugh liver function score, liver cirrhosis, portal hypertension, tumour size, tumour number, and time to recurrence.

cHazard ratios were derived from a univariable competing risk regression.

dA multivariable-adjusted competing risk regression further accounted for the following prognostic covariates: gender, age, body mass index, hepatitis B surface antigen, alpha fetoprotein, platelet count, total bilirubin, albumin, aminotransferase, prothrombin time, Child-Pugh liver function score, liver cirrhosis, portal hypertension, tumour size, tumour number, and time to recurrence.

eA Cox proportionalhazard regression with robust variance estimation after 1:1 propensity score matching.

fA Cox proportionalhazard regression with robust variance estimation adjusted for inverse probabilityof treatment weighting.

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**Figure S2.** Effect of repeat hepatic resection on risk of mortality.

aHazard ratios were derived from a univariable Cox proportional-hazards regression with robust variance estimation;

bA multivariable-adjusted Cox proportionalhazard regression with robust variance estimation further accounted for the following prognostic covariates: gender, age, body mass index, hepatitis B surface antigen, alpha fetoprotein, platelet count, total bilirubin, albumin, aminotransferase, prothrombin time, Child-Pugh liver function score, liver cirrhosis, portal hypertension, tumor size, tumor number, treatment for re-recurrent hepatocellular carcinoma, time to recurrence, and re-recurrence;

cHazard ratios were derived from a univariablecompeting risk regression;

dA multivariable-adjusted competing risk regression further accounted for the following prognostic covariates: gender, age, body mass index, hepatitis B surface antigen, alpha fetoprotein, platelet count, total bilirubin, albumin, aminotransferase, prothrombin time, Child-Pugh liver function score, liver cirrhosis, portal hypertension, tumor size, tumor number, treatment for re-recurrent hepatocellular carcinoma, time to recurrence, and re-recurrence;

eA Cox proportional-hazards regression with robust variance estimation after 1:1 propensityscore-matched design;

fA Cox proportional-hazards regression with robust variance estimation adjusted for inverse probabilityof treatment weighting.

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**Figure S3.** Cumulative overall survival from the initial hepatectomy of patients with recurrent hepatocellular carcinoma within Milan criteria.

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**Figure S4.** Subgroup analysis based on Eastern and Western cohorts. Repeat recurrence-free survival and overall survival were calculated from patients with recurrent hepatocellular carcinoma treated with repeat hepatic resection (rHR) or radiofrequency ablation (RFA).