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Original Article

Repeat hepatic resection *versus* radiofrequency ablation for recurrent hepatocellular carcinoma: retrospective multicentre study

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Abstract

Background: The therapeutic value of repeat hepatic resection (rHR) or radiofrequency ablation (RFA) for recurrent hepatocellular carcinoma (HCC) is unknown. This study aimed to investigate the safety and efficacy of rHR or RFA.

Methods: This was a retrospective multicentre study of patients with recurrent HCC within the Milan criteria who underwent rHR or RFA at nine university hospitals in China and Italy between January 2003 and January 2018. Survival after rHR or RFA was examined in unadjusted analyses and after propensity score matching (1 : 1).

Results: Of 847 patients included, 307 and 540 underwent rHR and RFA respectively. Median overall survival was 73.5 and 67.0 months after rHR and RFA respectively (hazard ratio 1.01 (95 per cent c.i. 0.81 to 1.26)). Median recurrence-free survival was longer after rHR versus RFA (23.6 *versus* 15.2 months; hazard ratio 0.76 (95 per cent c.i. 0.65 to 0.89)). These results were confirmed after propensity score matching. RFA was associated with lower morbidity of grade 3 and above (0.6 *versus* 6.2 per cent; $P < 0.001$) and shorter hospital stay (8.0 *versus* 3.0 days, $P < 0.001$) than rHR.

Conclusion: rHR was associated with longer recurrence-free survival but not overall survival compared with RFA.

Introduction

Liver cirrhosis related to chronic hepatitis virus infection or alcohol use is the main risk factor for hepatocellular carcinoma (HCC). The treatment choice for HCC is based on tumour staging and careful evaluation of liver function and physical status[1–3]. Based on official guidelines[1–3], hepatic resection is the best treatment for patients with single HCC or tumours within Milan criteria[4]. Additional deciding factors include patient performance status, co-morbidities and preservation of liver function and remnant volume. In contrast, radiofrequency ablation (RFA) is the recommended treatment when patients have a single tumour less than 2 cm or two to three nodules of 3 cm or smaller[1–3], although patients with a single tumour 2 cm or larger and less than 5 cm are also candidates for RFA at many liver centres[5,6]. Sixty per cent of patients with early-stage HCC develop recurrent disease within 5 years after curative resection or RFA[7]. The recurrence rate is even higher for patients

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Table 1 Baseline characteristics of included patients with recurrent hepatocellular carcinoma treated with repeat hepatic resection or radiofrequency ablation (847 patients)

Characteristic	Unweighted sample			After propensity score matching		
	rHR ($n = 307$)	RFA ($n = 540$)	SMD	rHR ($n = 227$)	RFA ($n = 227$)	SMD
Sex			0.264			0.037
Male	245 (79.8)	482 (89.3)		194 (85.5)	191 (84.1)	
Female	62 (20.2)	58 (10.7)		33 (14.5)	36 (15.9)	
Age (years)			0.102			0.046
<60	217 (70.7)	356 (65.9)		151 (66.5)	146 (64.3)	
≥60	90 (29.3)	184 (34.1)		76 (33.5)	81 (35.7)	
BMI (kg/m^2)			0.017			0.079
<18.5	17 (5.5)	32 (5.9)		14 (6.2)	10 (4.4)	
≥18.5	290 (94.5)	508 (94.1)		213 (93.8)	217 (95.6)	
Hepatitis B surface antigen			0.010			0.012
Positive	262 (85.3)	459 (85.0)		193 (85.0)	192 (84.6)	
Negative	45 (14.7)	81 (15.0)		34 (15.0)	35 (15.4)	
Hepatitis C antibody			0.102			0.065
Positive	27 (8.8)	33 (6.1)		20 (8.8)	16 (7.0)	
Negative	280 (91.2)	507 (93.9)		207 (91.2)	211 (93)	
α-Fetoprotein (ng/ml)			0.391			0.011
<200	215 (70.0)	464 (85.9)		182 (80.2)	181 (79.7)	
≥200	92 (30.0)	76 (14.1)		45 (19.8)	46 (20.3)	
Platelets (×10^9/l)			0.089			0.046
<100	53 (17.3)	112 (20.7)		43 (18.9)	39 (17.2)	
≥100	254 (82.7)	428 (79.3)		184 (81.1)	188 (82.8)	
Total bilirubin (μmol/l)			0.007			0.020
≤17.1	227 (73.9)	401 (74.3)		164 (72.2)	166 (73.1)	
>17.1	80 (26.1)	139 (25.7)		63 (27.8)	61 (26.9)	
Albumin (g/l)			0.047			0.089
<35	27 (8.8)	55 (10.2)		19 (8.4)	25 (11.0)	
≥35	280 (91.2)	485 (89.8)		208 (91.6)	202 (89.0)	
Alanine aminotransferase (U/l)			0.067			0.029
≤40	206 (67.1)	379 (70.2)		159 (70.0)	156 (68.7)	
>40	101 (32.9)	161 (29.8)		68 (30.0)	71 (31.3)	
Prothrombin time (s)			0.251			0.018
≤13	205 (66.8)	295 (54.6)		145 (63.9)	147 (64.8)	
>13	102 (33.2)	245 (45.4)		82 (36.1)	80 (35.2)	
Child–Pugh liver function			0.053			0.067
A	300 (97.7)	523 (96.9)		222 (97.8)	224 (98.7)	
B	7 (2.3)	17 (3.1)		5 (2.2)	3 (1.3)	
Liver cirrhosis			0.047			0.009
No	127 (41.4)	236 (43.7)		94 (41.4)	95 (41.9)	
Yes	180 (58.6)	304 (56.3)		133 (58.6)	132 (58.1)	
Portal hypertension			0.015			0.034
No	246 (80.1)	436 (80.7)		182 (80.2)	185 (81.5)	
Yes	61 (19.9)	104 (19.3)		45 (19.8)	42 (18.5)	
Tumour size (cm)			0.763			0.062
<3	135 (44.0)	425 (78.7)		128 (56.4)	135 (59.5)	
≥3	172 (56.0)	115 (21.3)		99 (43.6)	92 (40.5)	
Tumour number			0.022			0.010
Single	229 (74.6)	408 (75.6)		171 (75.3)	172 (75.8)	
Multiple	78 (25.4)	132 (24.4)		56 (24.7)	55 (24.2)	
Time to recurrence (months)			0.442			<0.001
≤12	80 (26.1)	253 (46.9)		71 (31.3)	71 (31.3)	
>12	227 (73.9)	287 (53.1)		156 (68.7)	156 (68.7)	

Values in parentheses are percentages. Standardized mean difference (SMD) of less than 0.1 for a given co-variable indicates a relatively small imbalance. RFA, radiofrequency ablation; rHR, repeat hepatic resection.

with intermediate or advanced HCC after hepatic resection, for whom recurrence is a major cause of death[8,9].

Curative treatment modalities for recurrent HCC include repeat hepatic resection (rHR), RFA and salvage liver transplantation. Liver transplantation is limited because of the shortage of donors, especially in Asia. Therefore, rHR and RFA are the two main curative treatments for recurrent HCC. Clinical practice guidelines from Western regions[1–3] and the Asia-Pacific region[10] do not yet state a preference or recommendation for one or the other for particular patient subgroups. Recent guidelines from South Korea[11] and India[12] and one expert consensus[13] do not recommend a specific treatment for recurrent HCC, although they do recommend that the appropriate treatment modality should 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 to identify the more appropriate treatment for recurrent HCC, particularly among those with preserved liver function and normal performance status who therefore fall within the Milan criteria. These patients often have better general health status and 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[14,15].

Table 2 Postoperative morbidity and death after repeat hepatic resection *versus* radiofrequency ablation

	Repeat hepatic resection ($n = 307$)		Radiofrequency ablation ($n = 540$)		*P*
Morbidity	66 (21.5)		27 (5.0)		<0.001
Major morbidity	19 (6.2)		3 (0.6)		<0.001
Death at 30 days	2 (0.7)		3 (0.6)		1.000
Complications specified	**All grades**	**Grade 3, 4 or 5**	**All grades**	**Grade 3, 4 or 5**	
Fever (>38.5°C, >3 days)	49 (16.0)	0 (0)	19 (3.5)	0 (0)	
Ascites	25 (8.1)	0 (0)	7 (1.3)	0 (0)	
Pleural effusion	16 (5.2)	7 (2.3)	1 (0.2)	0 (0)	
Liver failure	13 (4.2)	3 (1.0)	3 (0.6)	0 (0)	
Intra-abdominal haemorrhage	6 (1.9)	4 (1.3)	3 (0.6)	1 (0.2)	
Phrenic artery injury and bleeding	0 (0)	0 (0)	2 (0.4)	2 (0.4)	
Bile leakage	13 (4.2)	1 (0.3)	0 (0)	0 (0)	
Ileus	5 (1.6)	0 (0)	0 (0)	0 (0)	
Wound or puncture-site infection	12 (3.9)	2 (0.6)	0 (0)	0 (0)	
Subdiaphragmatic abscess	6 (1.9)	1 (0.3)	0 (0)	0 (0)	
Upper gastrointestinal bleeding	3 (1.0)	1 (0.3)	2 (0.4)	0 (0)	
Total complications	148	19	37	3	

Values in parentheses are percentages. These data were compared with Pearson's Chi-square test or Fisher's exact test.

Moreover, few studies have reported long-term survival after either treatment. In this multicentre study, the safety and efficacy of rHR *versus* RFA for treating recurrent HCC within Milan criteria were compared.

Methods

This was a retrospective multicentre study of patients with recurrent HCC who were treated with rHR or RFA between 1 January 2003 and 31 January 2018. The period of the initial resection was between March 2002 and November 2017. Patients were treated 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 local ethics requirements. 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. This study was conducted and reported the data according to STROBE guidelines.

To be enrolled, patients had to satisfy the following criteria: hepatic resection as initial curative treatment after HCC diagnosis; pathology on initial resected tissue to confirm HCC diagnosis; clinical diagnosis of recurrent HCC after initial resection, followed by either open R0 rHR or percutaneous RFA (margin around the tumour of at least 5 mm) as a first-line treatment; recurrent HCC satisfying the Milan criteria, including a solitary nodule with a diameter of 5 cm or less or three or fewer nodules each 3 cm or less in diameter, and no macrovascular invasion or distant metastasis[4]; preserved liver function (Child–Pugh score of 7 or less); and an Eastern Cooperative Oncology Group performance score of 0 to 1. Patients 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 recurred within 1 month of the initial hepatic resection, there was presence of extrahepatic metastasis, 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. Patients who underwent resection with a preoperative diagnosis of within-Milan recurrence, but were found to have beyond-Milan recurrence by intraoperative ultrasonography during the resection or by pathological examination after resection were excluded.

Interventions and follow-up

All clinical and laboratory parameters were collected retrospectively from patient records. For initial resection and rHR treatment, patients had to have an appropriate future remnant liver volume, defined as 30 per cent for those without cirrhosis and 50 per cent or more for those with cirrhosis, based on volumetric CT and/or MRI[16,17]. Histopathology was routinely performed postoperatively on liver tissue extracted by resection or rHR to confirm (recurrent) HCC diagnosis. Diagnosis in the RFA group was confirmed based on HCC hallmarks observed with enhanced CT and/or MRI. Percutaneous RFA was chosen as treatment when the recurrent tumour(s) were located at least 1.0 cm away from the main hepatic veins, vena cava, gallbladder, diaphragm and adjacent gastrointestinal tract. In most cases, ultrasound monitoring was used to guide intraprocedural evaluation of the ablation zone. Contrast-enhanced ultrasonography, enhanced CT and/or MRI was performed 2–3 days after RFA if the doctor suspected incomplete ablation. If residual tumour was present, an additional session of RFA was performed. In most cases, a personalized approach was undertaken based on multidisciplinary discussion to treat an inadequate ablation zone. Patients who satisfied the indications for both rHR and RFA were treated by RFA unless the patient requested rHR.

The first patient follow-up occurred 1 month after rHR or RFA, then once every 2–3 months for 2 years. Thereafter, follow-up visits were scheduled every 6 months. Each follow-up visit included

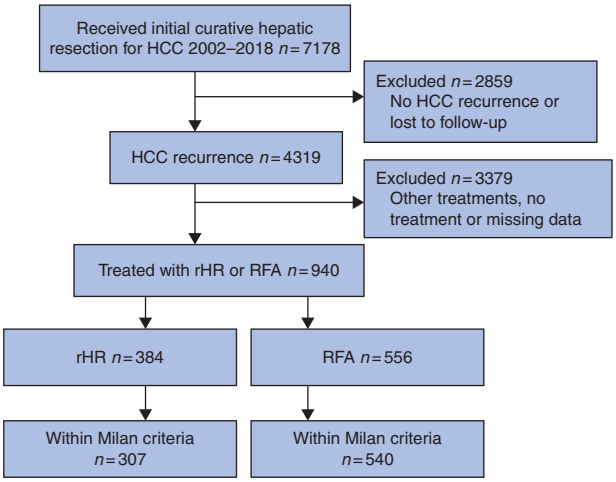

Fig. 1 Patient-selection process

HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; rHR, repeat hepatic resection.

measures of liver function, coagulation function and α-fetoprotein (AFP), routine blood examination, enhanced CT and/or MRI. HCC recurrence was diagnosed using the criteria of the European Association for the Study of the Liver[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[11–13]. 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 or hepatitis B virus-related liver cirrhosis received nucleos(t)ide analogue therapy. Patients with hepatitis C virus-related chronic hepatitis or liver cirrhosis received direct-acting antiviral therapy. Liver failure was defined according to the 50–50 criteria on postoperative day 5[18].

Outcomes

The main outcome was overall survival, defined as the interval from rHR or RFA to death from any cause or last follow-up. Data were censored on 30 April 2020 if patients were still alive. Repeat recurrence-free survival (rRFS) was defined as the interval from date of rHR or RFA to date of HCC recurrence or death, which ever occurred earlier, or last follow-up if recurrence did not occur. Data for rRFS were censored on the date of the last follow-up (30 April 2020) if patients were still alive without repeat recurrence. Repeat recurrence was classified as early (12 months or less) or late (more than 12 months)[19]. Complications were defined using the Clavien–Dindo classification[20]. 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 numbers and corresponding percentages. Continuous variables were analysed differently depending on whether they showed a normal or skewed distribution. Clinicopathological parameters were analysed using a binary model to avoid a possible non-linear effect, then univariable analysis was performed. Significant variables ($P < 0.050$) were used to generate a multivariable Cox regression model to identify independent risk factors of rRFS 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 per cent confidence intervals. The proportional hazard assumption was checked using a-ln(-ln[survival]) graph. Kaplan–Meier survival curves were plotted for rHR and RFA groups. Median rRFS and overall survival, HRs and percentages were also calculated for each group at 1-, 3-, and 5-year follow-up. Cumulative rRFS and overall survival were compared using the log rank test.

Time-to-event competing risk analysis to account for non-liver-related death and competing risk regression[21] to calculate the subdistribution HRs of rHR *versus* RFA for liver-related death were used. The subdistribution HRs of liver-related death was calculated from rHR and RFA patients who were followed for the same length of time. The competing risk regression for rRFS was also used to adjust for risk of all-cause death before HCC recurrence and after initial resection.

To reduce potential confounding of the results based on differences in baseline characteristics, patients treated with rHR were matched at a 1:1 ratio with 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, BMI, 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 calliper matching without replacement (random order or closest distance) was used to pair rHR and RFA patients with similar PS values[22,23].

The balance in baseline characteristics between the two groups was assessed before and after PS weighting and matching by using the standardized mean difference (SMD), with values of below 0.1 indicating good balance[24]. Time to recurrence was defined as the interval from rHR to the second diagnosis of recurrence. Data were managed and analysed using SPSS®, version 20.0 (IBM, Armonk, New York, USA) in conjunction with R® version 3.4.0 (The R Foundation, Vienna, Austria). Two-tailed *P* values were reported unless otherwise specified. $P < 0.050$ was considered statistically significant.

Results

Characteristics of the study population

Of 847 (11.8 per cent) patients with recurrent HCC fitting the Milan criteria, 307 (36.2 per cent) and 540 (63.8 per cent) patients underwent rHR and RFA respectively (*Fig. 1*). To check incomplete ablation 27, four and five patients underwent contrast-enhanced ultrasonography, enhanced CT and MRI 2–3 days after RFA, respectively. Baseline demographic and clinicopathological data are shown in *Table 1*. Patients in the rHR group were more often female, had shorter prothrombin time, more often had AFP of 200 ng/ml or above, tumour size 3 cm or greater, and time to recurrence more than 12 months (all SMD greater than 0.1). PS matching generated 227 pairs without significant differences in baseline variables (*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 (1 patient) or intra-abdominal haemorrhage (1 patient). Three patients died in the RFA group because of phrenic artery injury and bleeding during treatment (2 patients) or intra-abdominal haemorrhage (1 patient). No differences in 30-day mortality rates between the rHR and RFA groups were observed. Patients in the rHR group had a

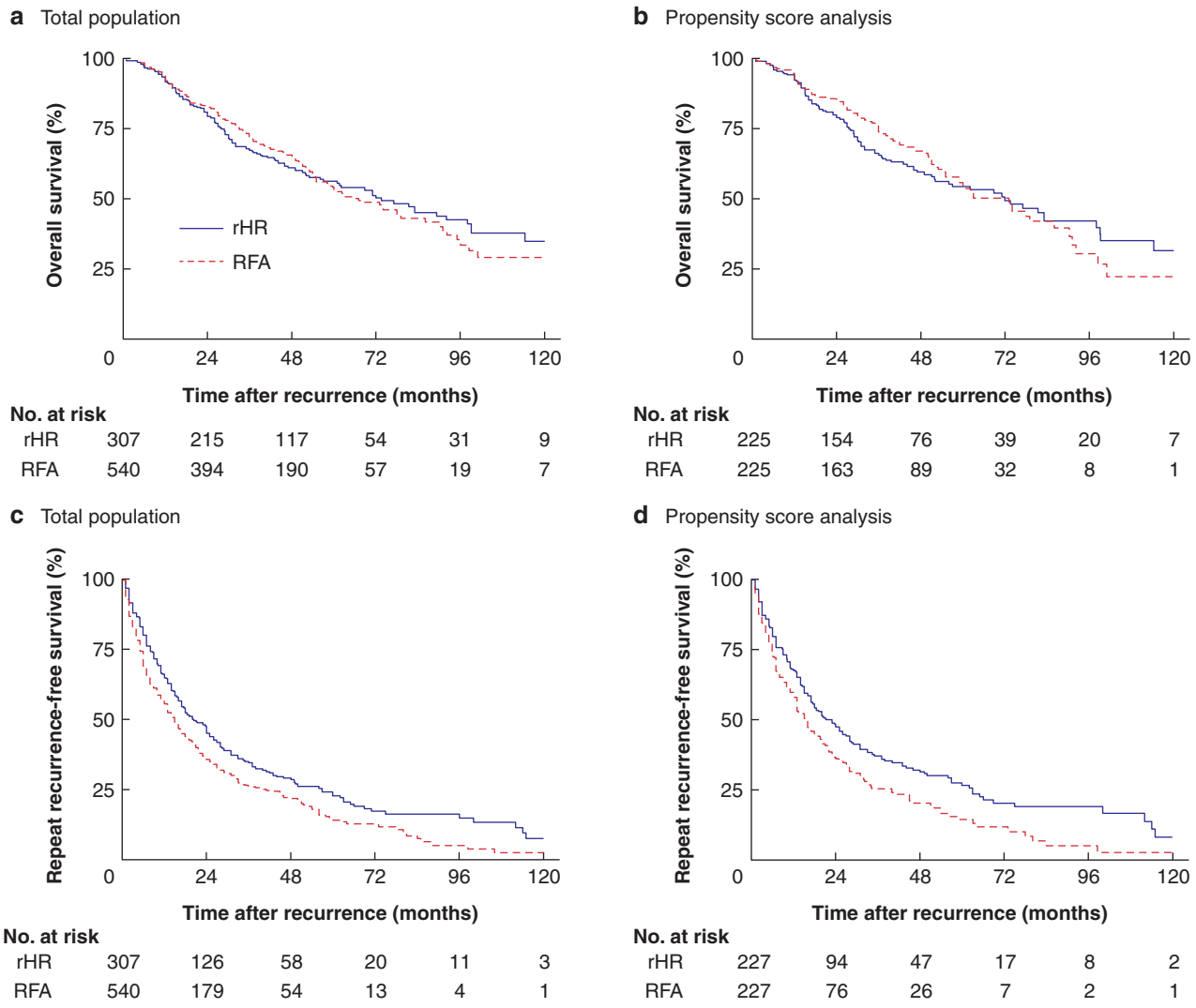

Fig. 2 Cumulative overall and recurrence-free survival of patients with recurrent hepatocellular carcinoma within Milan criteria after repeat hepatic resection or radiofrequency ablation

Overall survival was calculated for the **a** total population ($P = 0.955$) or **b** propensity score matching ($P = 0.694$), repeat recurrence-free survival was calculated for the **c** total population ($P < 0.001$) or **d** propensity score matching ($P < 0.001$; all log-rank test). The sample sizes of overall and repeat recurrence-free survival after propensity score matching were different because one more variable (time to recurrence) had been included in overall survival. rHR, repeat hepatic resection; RFA, radiofrequency ablation.

higher postoperative morbidity rate (21.5 per cent) than patients in the RFA group (5.0 per cent, $P < 0.001$). Most complications were grade I or II. The most frequent complications in both groups of patients were fever and ascites (*Table 2*). In addition, RFA was associated with lower morbidity of grade 3 and above (0.6 *versus* 6.2 per cent; $P < 0.001$) than rHR. Median hospital stay was longer after rHR *versus* RFA (8.0 (range, 4.0–22.0) *versus* 3.0 (range, 1.0–9.0) days, $P < 0.001$).

In the PS-matched pairs, the rHR and RFA groups had similar rates of 30-day mortality (0.9 *versus* 0.4 per cent, $P = 1.000$) and 90-day mortality (0.9 *versus* 0.9 per cent, $P = 1.000$). rHR was associated with higher morbidity compared with RFA (19.0 *versus* 5.3 per cent, $P < 0.001$). Median length of stay was longer after rHR than after RFA ($P < 0.001$).

Overall survival

Median follow-up was 54 (range 1–178) months and 49.3 (range 1–156) months ($P = 0.002$) after rHR and RFA respectively. During follow-up, 128 (41.7 per cent) and 208 (38.5 per cent) patients died in the rHR and RFA groups respectively. Median overall survival was 73.5 months in the rHR group and 67.0 months in the RFA group (*Fig. 2a*; HR 1.01 (95 per cent c.i. 0.81 to 1.26); $P = 0.955$). There was no difference in overall survival at 1 year (92.1 *versus* 92.1 per cent), 3 years (67.4 *versus* 71.3 per cent) and 5 years (56.4 *versus* 53.1 per cent). These findings were supported by PS matching (*Fig. 2b*; HR 1.06 (95 per cent c.i. 0.79 to 1.41); $P = 0.694$). Non-liver-related death occurred in seven patients (2.3 per cent) in the rHR group and 15 patients (2.8 per cent) in the RFA group. Fine-Gray testing led to similar findings (HR 1.04 (95 per cent c.i. 0.83 to 1.30); $P = 0.781$) (*Fig. S1a*).

Repeat recurrence-free survival

After rHR and RFA, 208 (67.8 per cent) and 400 (74.1 per cent) patients developed repeat HCC recurrence respectively ($P = 0.057$). Early recurrence (less than 12 months) was less frequent after rHR than after RFA (47.6 *versus* 57.3 per cent,

$P = 0.026$). Median recurrence-free survival after rHR or RFA was 23.6 *versus* 15.2 months. rRFS was longer after rHR than after RFA (*Fig. 2c*; HR 0.76 (95 per cent c.i. 0.65 to 0.89); $P < 0.001$). Recurrence-free survival rates after rHR and RFA respectively were 67.4 *versus* 57.3 per cent at 1 year, 37.5 *versus* 28.1 per cent at 3 years, and 25.5 *versus* 16.0 per cent at 5 years. Similar findings were observed in PS-matched patients (*Fig. 2d*; HR 0.71 (95 per cent c.i. 0.57 to 0.88); $P < 0.001$).

Competing repeat HCC recurrence occurred in 16 patients (5.2 per cent) in the rHR group and 20 patients (3.7 per cent) in the RFA group. Fine-Gray testing confirmed that patients in the rHR group had longer rRFS rates than those in the RFA group (HR 0.75 (95 per cent c.i. 0.64 to 0.88); $P < 0.001$) (*Fig. S1b*).

Patterns of repeat recurrence and treatments

Although more patients in the RFA group experienced repeat HCC recurrence than those in the rHR group, the distribution of intra- and extrahepatic recurrence was not different between the two groups before PS matching ($P = 0.930$) and after matching ($P = 0.618$) (*Table S1*). The majority of patients in the rHR group (84.1 per cent) and RFA group (85.7 per cent) received treatments for repeat recurrent HCC ($P = 0.595$). The remaining patients received best supportive care. Treatment modalities for repeat recurrent HCC are listed in *Table S2*. After repeat HCC recurrence, 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 *versus* 39.4 per cent, $P < 0.001$) (*Table S2*).

Univariable and multivariable analysis

Univariable and multivariable analyses for rRFS are shown in *Tables S3* and *S4*, respectively. Independent predictors of repeat HCC recurrence included age less than 60 years, AFP 200 ng/ml or higher, albumin less than 35 g/l, multiple tumours, time to recurrence 12 months or less, and RFA. Factors independently influencing overall survival (*Table S5*) included AFP 200 ng/ml or greater, albumin less than 35 g/l, tumour size 3 cm or larger, time to recurrence 12 months or less, repeat recurrence, and no treatment for repeat recurrent HCC (*Table S6*). Similar results were obtained for PS-matched pairs of patients.

Discussion

Resection and RFA for recurrent HCC within Milan criteria led to comparable overall survival. Resection was associated with increased postoperative morbidity, longer hospital stay and longer recurrence-free survival. The postoperative mortality rate was low in both groups. These findings can be incorporated into future revisions of treatment guidelines.

Some of the results in the present study are discordant with earlier reported studies[19,25–29]. Patients in the RFA group had a higher rate of early repeat recurrence and lower median rRFS. This did not translate into shorter overall survival, possibly because more patients in the RFA group received one or more subsequent curative treatments, in particular subsequent RFA. The higher rate of early repeat recurrence after RFA may reflect the incompleteness of percutaneous ablation, despite adequate monitoring with ultrasonography, enhanced CT or MRI and aiming for a margin of at least 5 mm around the tumour[30–32]. Lachenmayer and colleagues[33] observed that 14.9 per cent of patients had insufficient margins after stereotactic navigation during percutaneous CT-guided microwave ablation. Therefore, incomplete ablation is an important issue of early repeat recurrence. This mirrors findings in patients with untreated primary HCC.

Multivariable analysis revealed that young age, elevated AFP level, low albumin level, multiple or larger hepatic metastases, short disease-free interval, repeat recurrence and no treatment for repeat recurrent HCC were independent risk factors of rRFS or overall survival. This is consistent with the findings of other studies[14,19], but suggests that management of recurrent HCC is challenging. These risk factors and tumour location should be considered when choosing appropriate treatments for patients with recurrent HCC. This is especially important for patients in which both resection and RFA are suitable. Nonetheless, recent advances in treatment modalities have rendered recurrent HCC a treatable disease and the possibility of long-term survival has improved. This was reflected by the long median survival in the present study.

Limitations of this study included the retrospective design and long time span. Even with PS matching it is impossible to adjust completely for selection bias. Additional subsequent treatments were typically administered for repeat recurrent HCC, and were likely to influence overall survival. In this study it was impossible to further unravel the role of specific liver-directed treatments. No details on the specific site of intrahepatic re-recurrence was available. A higher intrahepatic re-recurrent rate after RFA than after resection (37.8 *versus* 21.7 per cent) has been published previously[19].

Both resection and RFA are valuable options to treat recurrent HCC. For individual decision making a higher chance of recurrence-free survival for resection must be weighed against favourable short-term outcomes of RFA. Both procedures are continuously improved. Learning curves for minimally invasive liver surgery have become insightful[34] and it is likely that the proportion of primary HCC resections performed with a minimally invasive technique will increase further. rHR can be performed with a minimally invasive technique[35] and its use will increase if the proportion of primary HCC resections increases. This may decrease postoperative morbidity and impact survival, as complications have been associated with decreased survival[36]. Thermal ablation procedures, including RFA and microwave ablation (MWA), also improve. The devices are being developed to produce ablation zones more reliably. Navigation and ablation confirmation software are also being developed. This may lower the rate of inaccurate ablations and therefore increase recurrence-free survival.

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Supplementary material

Supplementary material is available at *BJS* online.

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