Randomized clinical trial

Randomized clinical trial of hepatic resection *versus* radiofrequency ablation for early-stage hepatocellular carcinoma

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Background: Hepatic resection and radiofrequency ablation (RFA) are treatment options for early-stage hepatocellular carcinoma (HCC). Whether tumour recurrence and long-term survival favour either treatment has not been established. This randomized trial aimed to test the hypothesis that RFA is superior to hepatic resection in terms of lower tumour recurrence rate and better long-term survival.

Methods: Patients with early-stage HCC (solitary tumour no larger than 5 cm; or no more than 3 tumours, each 3 cm or smaller) were randomized into hepatic resection and RFA groups. Demographic and clinical characteristics, and short- and long-term outcome measures were compared between groups. Primary and secondary outcome measures were overall tumour recurrence and survival respectively.

Results: Clinicopathological data were similar in the two groups, which each contained 109 patients. The RFA group had a shorter treatment duration, less blood loss and shorter hospital stay than the resection group. Mortality and morbidity rates were similar in the two groups. The overall tumour recurrence rate was similar in the resection and RFA groups (71·3 *versus* 81·7 per cent respectively). The 1-, 3-, 5- and 10-year overall survival rates were 94·5, 80·6, 66·5 and 47·6 per cent respectively in the resection group, compared with 95·4, 82·3, 66·4 and 41·8 per cent in the RFA group ($P = 0·531$). Corresponding disease-free survival rates were 74·1, 50·9, 41·5 and 31·9 per cent in the resection group, and 70·6, 46·6, 33·6 and 18·6 per cent in the RFA group ($P = 0·072$).

Conclusion: RFA for early-stage HCC is not superior to hepatic resection, in terms of tumour recurrence, overall survival and disease-free survival. Registration number: HKUCTR-10 (http://www.hkuctr.com).

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Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related deaths in the world and has a global incidence of more than 850 000 new cases annually[1]. Hepatic resection, radiofrequency ablation (RFA) and orthotopic liver transplantation are the main treatment options for patients with early-stage HCC[2,3].

For patients with early-stage HCC and preserved liver function, hepatic resection is widely accepted as the treatment of choice. Although the operative mortality rate of hepatic resection has been reduced to near zero[4], resection for early-stage HCC is still plagued by several major problems. These include considerable morbidity rates, need for resection of a considerable volume of non-tumorous liver if the tumour is located centrally,

and a relatively high intrahepatic recurrence rate[5]. In the past decade, local ablative therapy has evolved as an alternative to resection for early-stage HCC[6]. RFA is an efficient local hyperthermic ablative therapy that can induce homogeneous necrosis of the target tumour with an adequate margin of non-tumorous tissue[7].

Whether resection or RFA is a better treatment option for early-stage HCC has been debated extensively. Prospective non-randomized studies, RCTs and meta-analyses[8–15] have not been conclusive. Comparisons of long-term survival for these two treatment modalities for early-stage HCC are still lacking in the literature. Therefore, this single-centre RCT compared hepatic resection and RFA for patients with early-stage HCC. The primary aim was to test the hypothesis that RFA is superior to resection in terms of lower tumour recurrence risk and better long-term survival.

Methods

The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (EC 1688-01). It was registered retrospectively at the registry of the Clinical Trial Centre of the University of Hong Kong (HKUCTR-10). Informed consent was obtained after recruitment of patients with tumours that met the inclusion criteria.

Diagnosis of hepatocellular carcinoma

The diagnosis of HCC was based on the criteria used by the European Association for the Study of the Liver[2]. HCC was diagnosed when radiological imaging (spiral contrast-enhanced CT or contrast-enhanced MRI) showed typical features of HCC (contrast enhancement in the arterial phase and rapid wash-out of contrast in the venous/late phase) in patients with a raised serum α-fetoprotein (AFP) level (over 400 ng/ml). Percutaneous liver biopsy was not advocated in the authors' centre because of the risk of needle-tract metastasis.

Inclusion and exclusion criteria

Inclusion criteria were: HCC with a maximum diameter no larger than 5 cm; three or fewer tumour nodules; absence of extrahepatic metastases; absence of radiological evidence of tumour invasion of major portal or hepatic vein branches; Child–Pugh grade A or B liver function[16], with no history of hepatic encephalopathy, refractory ascites or variceal bleeding; and general condition fit for either hepatic resection or RFA.

Exclusion criteria were: tumour location unfavourable for RFA (close to hilar structures); previous treatment for HCC (transarterial chemoembolization (TACE), percutaneous ethanol injection or chemotherapy); and presence of extrahepatic metastases or evidence of tumour invasion into major portal or hepatic vein branches.

Pretreatment investigations and assessments

All patients were assessed by a multidisciplinary team of doctors. Standard investigations included: blood tests (complete blood count, liver and renal function tests, coagulation profile, serum AFP level, hepatitis B and C serology); radiological imaging (chest X-ray, spiral contrast-enhanced CT or contrasted-enhanced MRI of the abdomen, and/or dual-tracer PET); and indocyanine green retention at 15 min (ICG-R15)[17].

Study design

The study aimed to test the hypothesis that RFA is superior to hepatic resection as a treatment for early-stage HCC. Early-stage HCC was defined as a solitary tumour no larger than 5 cm in diameter; or no more than three tumours, each 3 cm or smaller in diameter. The inclusion period was from July 2002 to June 2007. Overall tumour recurrence (local recurrence or intrahepatic or extrahepatic recurrence) was set as the primary endpoint, and overall and disease-free survival rates as secondary endpoints. Double-blinding was not used because of the nature of the interventions.

Sample size

The 3-year tumour recurrence rate was used to estimate the sample size for this study. Based on a 3-year tumour recurrence rate of 60 per cent after hepatic resection[18,19] and 40 per cent after RFA[20] for early-stage HCC, it was calculated that 97 patients needed to be recruited in each arm to demonstrate a statistically significant difference between treatments with 80 per cent power at the 0·05 level of significance[21]. Allowing for a dropout rate of 10 per cent after randomization, the sample size required for this study was estimated to be at least 107 patients in each group.

Randomization

Randomization (1 : 1 ratio) was performed after informed consent had been obtained using sealed consecutively numbered envelopes. The envelopes were kept by a research assistant not involved in the treatment of the patient, and were opened only when the patient was considered suitable

for both hepatic resection and RFA after full preoperative investigations.

Hepatic resection

Tumour resection was carried out by an open approach under general anaesthesia[4]. Intraoperative ultrasonography was used routinely. The extent of resection depended on the anatomical location of the tumour. The aim of surgery was to obtain a 1-cm tumour-free margin after resection. Major hepatectomy was defined as resection of at least three Couinaud's segments, and minor hepatectomy as resection of fewer than three segments[22].

Radiofrequency ablation

RFA was performed using an internally cooled electrode (Cool-tip™ System; Radionics, Burlington, Massachusetts, USA). Depending on the tumour size, either a single or clustered electrode was used for ablation under ultrasound guidance. The electrode was effective in producing complete tumour necrosis, with ablation of a margin of non-tumorous tissue of 1 cm. The procedure was done percutaneously by an experienced interventional radiologist under local anaesthesia with intravenous sedation, if a tumour was accessible by the percutaneous route. For tumours located at the liver dome, or if there was risk of thermal injury to adjacent structures, such as diaphragm and bowel, ablation was undertaken by a laparoscopic or open approach. Subcapsular tumours were not precluded from RFA treatment[23]. Details of RFA techniques in the authors' centre have been described previously[24]. Spiral contrast-enhanced CT was performed 4 weeks after the procedure. If the scan showed incomplete ablation, repeat RFA was attempted to achieve complete tumour ablation.

Follow-up

Short-term outcomes after treatment included duration of the procedure, blood loss and need for transfusion of red blood cells or other blood products. Liver biochemistry and coagulation profile were checked on days 1, 3 and 7 after the procedure. Treatment-related complications, including severe complications (Clavien–Dindo Grade IIIa or above)[25], operative mortality and hospital stay were recorded prospectively in both groups. Operative mortality was defined as death after treatment within the same hospital admission.

No adjuvant treatment was given after the procedure. All patients were followed up regularly. Liver function (complete blood count, liver biochemistry and coagulation profile) and serum AFP level were assessed every 3 months during follow-up. Spiral contrast-enhanced CT of the thorax and abdomen was performed every 6 and 3 months after treatment respectively, to look for tumour recurrence in the first 2 years. Thereafter, spiral contrast-enhanced CT of the thorax and abdomen was undertaken every 6 months.

Patients with intrahepatic tumour recurrence were treated with further resection in the hepatic resection group or repeat ablation in the RFA group, if feasible. If further hepatic resection or repeat RFA was not feasible, TACE was offered. Patients with local tumour recurrence were regarded as having intrahepatic recurrence.

Statistical analysis

All data were collected prospectively by a research assistant in an electronic database. Statistical analysis was performed using χ^2 test with Yates' correction or Fisher's exact test to compare categorical variables, and Mann–Whitney *U* test for continuous variables. Cumulative overall and disease-free survival rates were computed by the Kaplan–Meier method, and compared by means of the log rank test. Hospital deaths were included in the overall survival analysis, but were excluded from the disease-free survival analysis.

Twelve clinicopathological variables of potential prognostic value were analysed for effects on overall and disease-free survival. Host factors included: age (less than 60 *versus* 60 or more years), sex, hepatitis B surface antigen status, hepatitis C antibody status, Child–Pugh grade[16], ICG-R15[17] (20 per cent or less *versus* over 20 per cent) and Model for End-stage Liver Disease (MELD) score[26] (10 or below *versus* more than 10). Tumour factors included: size (3 cm or smaller *versus* larger than 3 cm), number of tumours (solitary *versus* multiple) and serum AFP level (400 ng/ml or less *versus* over 400 ng/ml). Finally, the treatment arms (resection *versus* RFA) and the presence of complications were included in the analysis. Significant variables in univariable analysis with $P < 0{\cdot}100$ were selected for multivariable analysis. A multivariable Cox proportional hazards regression model was used to assess the prognostic significance of the variables in predicting overall and disease-free survival. Results of the multivariable analysis are presented as hazard ratios (HRs) with corresponding 95 per cent confidence intervals. Subgroup analyses of the influence of patient characteristics on survival were carried out for patients with very early-stage HCC (solitary tumour no larger than 2 cm) and those with solitary HCC (3–5 cm).

All statistical tests were two-sided and $P < 0{\cdot}050$ was considered statistically significant. All analyses were performed on an intention-to-treat basis. SPSS® version 18.0 (IBM, Armonk, New York, USA) was used for statistical analyses.

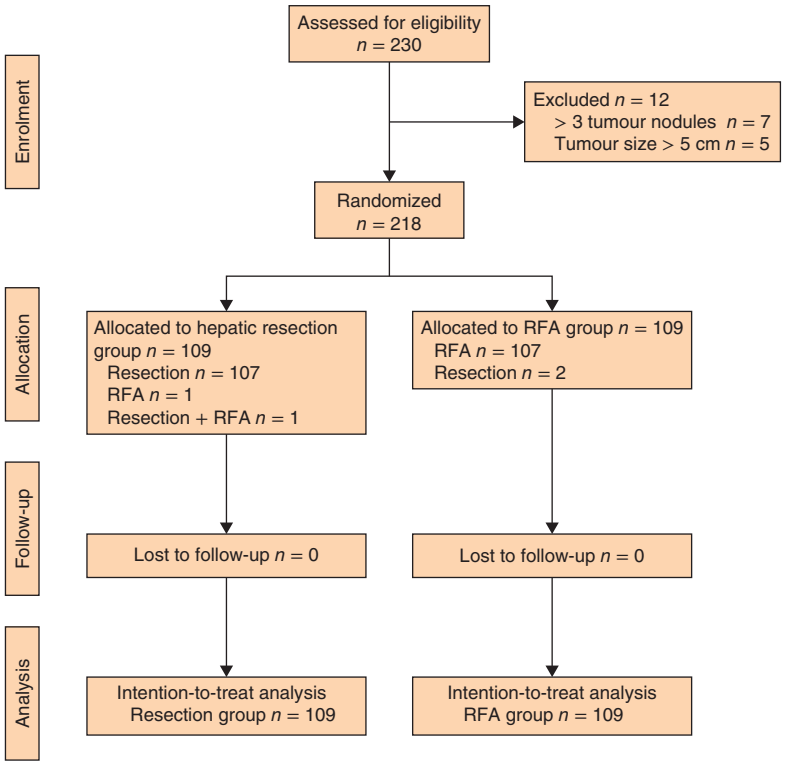

Fig. 1 CONSORT diagram for the trial. RFA, radiofrequency ablation

Results

The results of this study are reported according to the CONSORT guidelines[27]. A total of 230 patients with early-stage HCC were assessed for eligibility for the study. Seven patients with multiple tumour nodules larger than 3 cm, and five with tumours larger 5 cm were excluded. The remaining 218 patients were randomized into the hepatic resection group (109 patients) and RFA group (109). One patient in the resection group received RFA for a solitary tumour, and another underwent combined hepatic wedge resection and RFA for two tumours. Two patients underwent hepatic subsegmentectomy for a solitary tumour in the RFA group. The reason for violation of the treatment protocol was related to clinical judgement during surgery (*Fig. 1*).

Baseline demographic and clinical data are shown in *Table 1*. There was no difference between the two groups in age, sex, proportion of patients with hepatitis B and C viral infection, and concomitant medical illnesses. Liver function was mostly similar between the groups in terms of Child–Pugh classification[16], serum bilirubin level, serum alanine aminotransferase level, international normalized ratio and MELD score. However, serum albumin levels and platelet counts were lower in the RFA group than in the resection group, and ICG-R15 was worse. This might mean that patients in the RFA group had poorer liver function than those in the resection group. There was no statistical difference in tumour characteristics (size, number and serum AFP level) between the two groups. More patients in the RFA group had bilobar tumours.

Treatment

Excluding the two patients who had RFA and combined treatment, 107 patients underwent hepatectomy in the resection group. Major hepatectomy was performed in 21 patients (19·6 per cent), whereas 86 (80·4 per cent) underwent minor hepatectomy. All 21 patients who underwent major hepatectomy had Child–Pugh grade A liver function and an ICG-R15 clearance rate of less than 15 per cent. Anatomical resection was performed in 57 patients (53·3 per cent), and 50 (46·7 per cent) had a non-anatomical resection (*Table S1*, supporting information). Pathological examination of the resected specimen showed a clear margin in 105 patients (98·1 per cent) and resection margin involved by tumour in two (1·9 per cent).

In the RFA group, excluding the two patients who underwent subsegmentectomy, 107 patients had RFA by a percutaneous (45, 42·1 per cent), laparoscopic (20, 18·7 per

Table 1 Demographic and clinical data for patients in the hepatic resection and radiofrequency ablation groups

	Resection ($n = 109$)	RFA ($n = 109$)
Age (years)*	55 (31–82)	57 (23–78)
Sex ratio (M : F)	89 : 20	86 : 23
Hepatitis B viral infection	99 (90·8)	95 (87·2)
Hepatitis C viral infection	5 (4·6)	0 (0)
Concomitant medical illness	51 (46·8)	49 (45·0)
Child–Pugh grade		
A	107 (98·2)	104 (95·4)
B	2 (1·8)	5 (4·6)
Serum bilirubin (μmol/l)*	12 (2–37)	13 (4–63)
Serum albumin (g/l)*	42 (28–49)	40 (26–47)
Serum ALT (units/l)*	48 (8–314)	51 (11–463)
Platelet count ($\times 10^9$/l)*	150 (49–307)	132 (41–270)
International normalized ratio*	1·1 (0·9–1·6)	1·1 (0·9–1·5)
Preoperative ICG-R15 (%)*	11·4 (3·7–57·1)	13·6 (3·6–58)
MELD score*	7·9 (6–14)	8·39 (6–17)
Tumour size (cm)*	2·9 (1–5)	2·6 (1–5)
No. of tumour nodules		
One	99 (90·8)	90 (82·6)
Two	7 (6·4)	15 (13·8)
Three	3 (2·8)	4 (3·7)
Serum AFP level (ng/ml)*	58 (1–4880)	63·5 (2–18 070)
Distribution of tumours		
Unilobar	108 (99·1)	101 (92·7)
Bilobar	1 (0·9)	8 (7·3)

Values in parentheses are percentages unless indicated otherwise; *values are median (range). RFA, radiofrequency ablation; ALT, alanine aminotransferase; ICG-R15, indocyanine green retention rate at 15 min; MELD, Model for End-stage Liver Disease; AFP, α-fetoprotein.

Table 2 Short-term outcome measures in intention-to-treat analysis

	Resection ($n = 109$)	RFA ($n = 109$)	P‡
Duration of operation (min)*	270 (90–884)	142·5 (73–380)	< 0·001§
Operative blood loss (ml)*	400 (100–5000)	50 (0–790)	< 0·001§
Blood transfusion	5 (4·6)	0 (0)	0·070
Hospital death	1 (0·9)	0 (0)	1·000#
Postoperative complications	18 (16·5)	10 (9·2)	0·105
Pneumonia	6	1	
Pleural effusion	12	2	
Liver failure	1	0	
Renal impairment	1	1	
Subphrenic abscess	0	1	
Peptic ulcer	0	2	
Biliary fistula	0	1	
Cardiac complications	2	2	
Diaphragmatic hernia	0	1	
Wound infection	4	1	
Others	3	3	
Severe complications†	4 (3·7)	5 (4·6)	1·000#
Duration of hospital stay (days)*	7 (2–70)	4 (1–34)	< 0·001§
Readmission	5 (4·6)	1 (0·9)	0·214
3-month survival rate (%)	99·1	100	1·000

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Clavien–Dindo grade IIIa or above. RFA, radiofrequency ablation. ‡χ^2 test with Yates' correction, except §Mann–Whitney U test and #Fisher's exact test.

cent) or open (42, 39·3 per cent) approach. Judging from CT images 1 month after treatment, complete ablation was achieved in 101 patients (94·4 per cent). The remaining six (5·6 per cent) received a second session of RFA and complete tumour ablation was achieved.

Short-term outcomes

Compared with the hepatic resection group, the RFA group had a shorter procedure duration and less operative blood loss (*Table 2*). This was mainly because a minimally invasive approach (percutaneous or laparoscopic) was used in most patients in the RFA group (65, 60·7 per cent). One patient in the resection group died from severe sepsis and multiple organ failure 4 weeks after extended left hepatectomy for three tumours (1 measuring 3 cm and 2 of 2 cm each), contributing to a hospital mortality rate of 0·9 per cent in this group. There was no hospital death in the RFA group. The postoperative complication rate was not statistically different between the resection and RFA groups (16·5 and 9·2 per cent respectively). The proportion of patients with severe complications was similar in the two groups. Median hospital stay was shorter in the RFA group. Readmission and 3-month survival rates were similar in the two groups.

Long-term outcome

With a median follow-up of 93 months (7·7 years), 31 patients (28·7 per cent) in the resection group and 20 (18·3 per cent) in the RFA group remained recurrence-free (*Table 3*). Seventy-seven patients (71·3 per cent) in the resection group and 89 (81·7 per cent) in the RFA group developed tumour recurrence. Although the difference was not statistically significant ($P = 0·092$), there was a tendency towards higher recurrence rates after RFA. Rates of early (2 years or less) and late (after 2 years) tumour recurrence were similar in the resection and RFA groups. The majority of patients in both groups developed intrahepatic recurrence. The rate of local recurrence at the treatment site was 3·7 per cent (4 of 108) in the resection group and 4·6 per cent (5 of 109) in the RFA group. A higher proportion of patients underwent hepatic resection for recurrence in the

Table 3 Tumour recurrence pattern and treatment in hepatic resection and radiofrequency ablation groups

	Resection† (*n* = 108)	RFA (*n* = 109)	*P*‡
Recurrence pattern			0·092
None	31 (28·7)	20 (18·3)	
Margin	4 (3·7)	5 (4·6)	
Intrahepatic	45 (41·7)	56 (51·4)	
Extrahepatic recurrence	5 (4·6)	1 (0·9)	
Both intrahepatic and extrahepatic	27 (25·0)	32 (29·4)	
Early recurrence (≤ 2 years)	40 (37·0)	47 (43·1)	0·334§
Late recurrence (> 2 years)	37 (34·3)	42 (38·5)	0·568§
Treatment for recurrence			0·033
Hepatic resection	21 (27)	10 (11)	
RFA	16 (21)	27 (30)	
TACE	18 (23)	30 (33)	
Liver transplantation	0 (0)	3 (3)	
No active treatment	22 (29)	19 (21)	

Values in parentheses are percentages. †Excluding one patient who died in hospital. RFA, radiofrequency ablation; TACE, transarterial chemoembolization. ‡χ^2 test with Yates' correction, except §Fisher's exact test.

resection group than in the RFA group. More patients in the RFA group received further ablation, TACE or salvage transplantation to treat recurrence.

The 1-, 3-, 5- and 10-year overall survival rates were 94·5, 80·6, 66·5 and 47·6 per cent respectively in the resection group, and 95·4, 82·3, 66·4 and 41·8 per cent in the RFA group. Median overall survival was 118·8 and 93·5 months respectively. There was no significant difference in overall survival rate between the two groups ($P = 0·531$) (*Fig. 2a*).

The 1-, 3-, 5- and 10-year disease-free survival rates in the resection group were 74·1, 50·9, 41·5 and 31·9 per cent respectively. Corresponding rates in the RFA group were 70·6, 46·6, 33·6 and 18·6 per cent. Median disease-free survival was 39·5 and 23·7 months. There was no significant difference between the two groups ($P = 0·072$) (*Fig. 2b*). Nonetheless, there was a tendency towards poorer disease-free survival in the RFA group 2 years after treatment.

Analysis of prognostic factors

In univariable analysis, seven of 12 evaluated factors had a significant prognostic influence on overall survival (*Table S2*, supporting information). Old age, hepatitis B viral infection, hepatitis C viral infection, preoperative ICG-R15 exceeding 20 per cent, preoperative MELD score over 10, post-treatment complications and multiple tumour nodules were associated with worse overall survival. In multivariable analysis, only preoperative ICG-R15 exceeding 20 per cent (HR 1·03, 95 per cent c.i. 1·01 to 1·05; $P = 0·001$), hepatitis C viral infection (HR 2·94, 1·63 to 5·30; $P < 0·001$), post-treatment complications (HR 1·80, 1·12 to 2·90; $P = 0·015$) and multiple tumour nodules (HR 1·76, 1·12 to 2·77; $P = 0·015$) were independent poor prognostic factors for overall survival.

Concerning disease-free survival, in univariable analysis, old age, hepatitis C infection, preoperative ICG-R15 exceeding 20 per cent, tumour size larger than 3 cm, multiple tumour nodules and RFA were associated with worse outcome (*Table S3*, supporting information). In multivariable analysis, only preoperative ICG-R15 exceeding 20 per cent (HR 1·02, 1·00 to 1·04; $P = 0·030$), tumour size larger than 3 cm (HR 1·22, 1·06 to 1·40; $P = 0·005$) and multiple tumour nodules (HR 1·80, 1·19 to 2·73; $P = 0·005$) were independent predictors of poor disease-free survival.

Subgroup analysis: patients with very early hepatocellular carcinoma

There were 29 patients in the resection group and 26 in the RFA group with very early HCC (solitary tumour no larger than 2 cm) (*Table S4*, supporting information). These two groups were similar in age, proportion of patients with viral hepatitis, liver function and tumour factors. The RFA group had more women and lower platelet counts than the resection group. In terms of short-term clinical outcomes, the RFA group had shorter treatment duration (median 115 *versus* 220 min), less blood loss (median 50 *versus* 250 ml) and a shorter hospital stay (median 4 *versus* 7 days), compared with the resection group.

The 1-, 3-, 5- and 10-year overall survival rates were 100, 93, 76 and 52 per cent respectively in the resection group, compared with 100, 89, 69 and 59 per cent in the RFA group ($P = 0·950$) (*Fig. 2c*).

The 1-, 3-, 5- and 10-year disease-free survival rates were 83, 66, 52 and 35 per cent respectively in the resection group, and 77, 62, 46 and 39 per cent in the RFA group ($P = 0·896$) (*Fig. 2d*).

Subgroup analysis: patients with solitary hepatocellular carcinoma

There were 49 patients with solitary HCC (3–5 cm) in the resection group and 32 in the RFA group (*Table S5*, supporting information). These two groups were similar in terms of demographic characteristics and tumour status, except that patients in the resection group had a significantly higher serum albumin level and better clotting profile. The RFA group had a shorter duration of treatment (median 130 *versus* 250 min) and less blood loss (median 60 *versus* 500 ml).

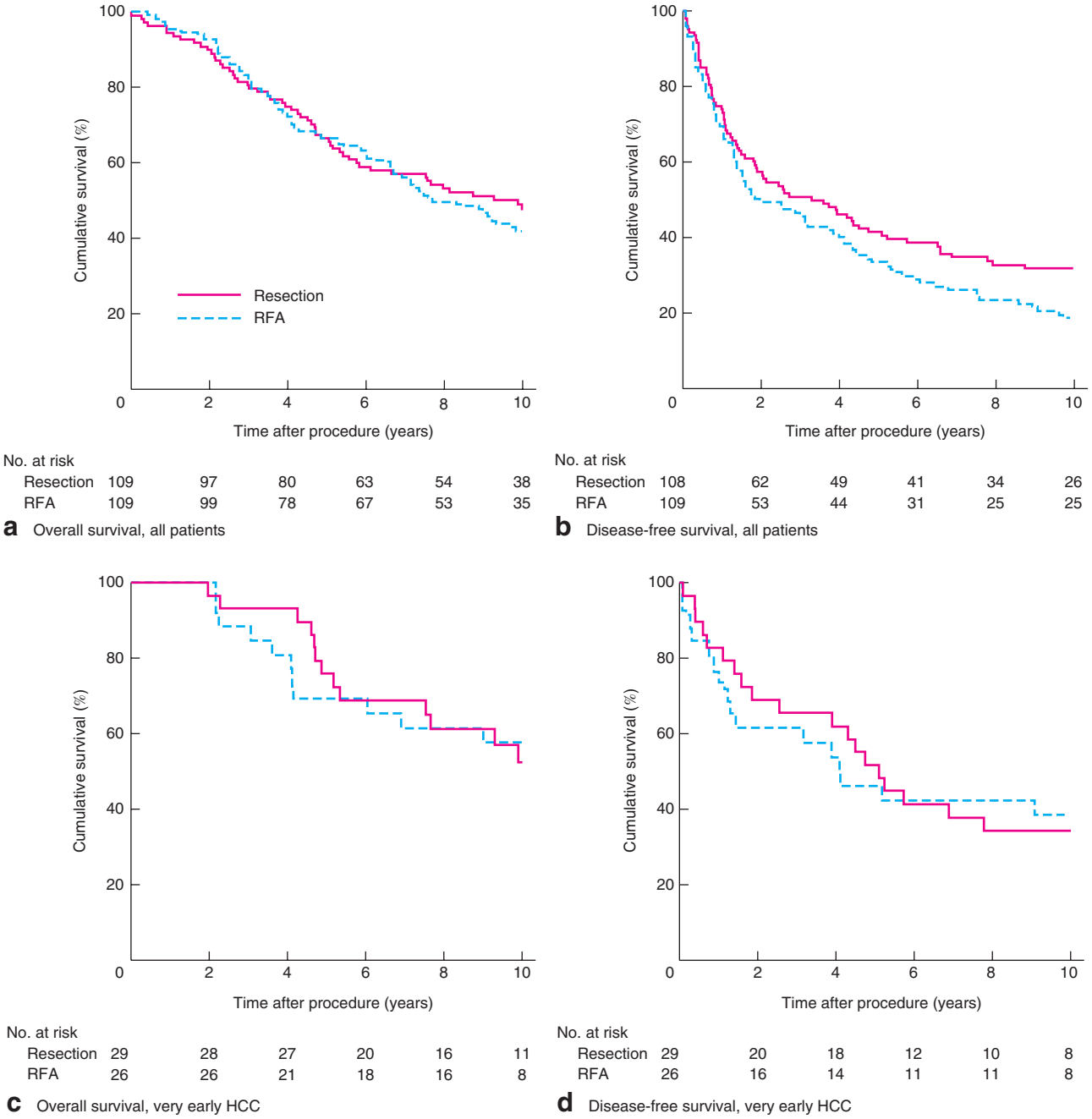

Fig. 2 **a** Overall and **b** disease-free survival rates in the hepatic resection and radiofrequency ablation (RFA) groups by intention-to-treat analysis. **c** Overall and **d** disease-free survival rates among patients with very early hepatocellular carcinoma (HCC) in the resection and RFA groups. **a** $P = 0{\cdot}531$, **b** $P = 0{\cdot}072$, **c** $P = 0{\cdot}950$, **d** $P = 0{\cdot}896$ (log rank test)

The 1-, 3-, 5- and 10-year overall survival rates were 88, 79, 71 and 57 per cent respectively in the resection group, and 88, 71, 68 and 42 per cent in the RFA group ($P = 0{\cdot}349$). Corresponding disease-free survival rates were 71, 50, 42 and 37 in the resection group, and 59, 44, 31 and 9 per cent in the RFA group ($P = 0{\cdot}075$).

Discussion

This RCT has shown that RFA is not superior to hepatic resection for treatment of early-stage HCC, in terms of tumour recurrence, or 10-year overall and disease-free survival.

Hepatic resection is regarded as the standard treatment of choice for early-stage HCC with preserved liver function. Anatomical hepatectomy with curative intent has the advantage of eradicating potential tumour cells along the portal venous tributaries[28]. However, it may not be applicable to all patients because of compromised function of the background cirrhotic liver[29].

Theoretically, RFA may have several advantages over hepatic resection. It carries low morbidity and mortality rates compared with hepatic resection. It also allows better preservation of liver function, as little non-tumorous liver is destroyed. Surgical stress and immune suppression are less in RFA than in resection. Finally, as it is a minimally invasive procedure, RFA may be associated with better quality of life.

Whether resection or RFA is a better treatment for early-stage HCC has been debated previously. Until now, four RCTs[8–10,13] have been published with contradictory results. RFA was shown to be associated with survival rates similar to those of hepatic resection in two trials[8,10], whereas it was inferior to resection in terms of patient survival and tumour recurrence in the other two[9,13]. A meta-analysis[11] of randomized trials found that resection was associated with better overall and disease-free survival than RFA. However, resection resulted in more treatment-related complications and longer hospital stay than RFA. A drawback of these studies[8–10,13] is the highly variable and relatively short median follow-up period, the varying degree of protocol violation and the number of patients lost to follow-up.

The present study compared data on 10-year actual survival and tumour recurrence for resection *versus* RFA in patients with early-stage HCC. The protocol violation rate was less than 2 per cent in each arm. Moreover, no patients were lost to follow-up. RFA was not found to be superior to resection in terms of tumour recurrence rate and 10-year overall survival. The favourable overall 10-year survival rates in both groups can be attributed to a fairly aggressive approach to the detection and treatment of tumour recurrence. In fact, the majority of patients with recurrence had intrahepatic recurrences alone, which were treated with further resection, RFA, TACE or salvage liver transplantation.

In the present study, there was a tendency towards a difference in disease-free survival curves, favouring the hepatic resection group 2 years after treatment. The fact that this did not reach significance may be due to the relatively small patient numbers. Late tumour recurrence after curative treatment for HCC may be related to multicentric development of new tumour associated with the underlying cirrhotic liver[30].

A shortcoming of previous randomized studies[8–10,13] was the percutaneous approach to RFA. Although RFA by a percutaneous approach is the least invasive procedure, it may not eradicate the disease effectively if the tumour has a subcapsular location, is in close proximity to the biliary system, or near major vessels or intestine. This may result in more local recurrences after percutaneous RFA, resulting in worse survival[31]. The authors' centre adopted a laparoscopic or open approach to RFA for tumours in difficult anatomical locations. Multiple ablations in different directions were then carried out under ultrasound guidance to ensure complete ablation. This could explain the relatively high complete ablation rate here. RFA was associated with a shorter treatment duration, less intraoperative blood loss and shorter hospital stay than resection.

Treatment arm (resection or RFA) was not identified as a prognostic factor in multivariable analysis for either overall or disease-free survival. In contrast, poor dynamic liver function, as measured by ICG clearance, and multiple tumour nodules were independently associated with poor overall and disease-free survival. This signifies the importance of selection of patients with early-stage HCC for either resection or RFA. To ensure a favourable survival outcome, patients with solitary small HCC and preserved liver function can be effectively treated by resection or RFA. For patients with multiple tumours or marginal liver function, resection or RFA should be considered cautiously, and adjuvant therapy might have a role after the treatment procedure.

A retrospective study[32] using a propensity score model on 237 patients with very early-stage HCC showed that resection resulted in better overall and disease-free survival rates than RFA. Similar results were reported in a recent systemic review[33]. The present study also provided a long-term survival analysis of patients with very early-stage HCC. Although patient numbers were relatively small, 10-year overall and disease-free survival rates were comparable in the resection and RFA groups.

There are several limitations to this study. It was designed as a superiority study but failed to refute the null hypothesis. It might be underpowered to allow detection of any difference between the resection and RFA groups. A non-inferiority study design with a larger sample size might help overcome this shortcoming. It is unusual for a clinical trial to be reported longer than 5 years after the end of enrolment. Although this has allowed long-term follow-up and the associated outcome analyses, generalization of the present results to current clinical practice could be questioned, given evolving developments in the management of patients with early HCC. Since completion of the present study, contrast MRI has become the preferred

diagnostic imaging method for HCC, rather than CT. Microwave ablation is currently superior to RFA in treating HCC[34]. Moreover, hepatic resection using a laparoscopic approach has gained much attention in recent years and now plays a more important role in treatment of early-stage HCC[35]. This study can be criticized for not adopting the double-blind technique in delivering the treatment to patients. Finally, quality of life was not assessed in this trial.

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Supporting information

Additional supporting information may be found online in the supporting information tab for this article.

Editor's comments

This randomized trial aimed to provide evidence that radiofrequency ablation (RFA) is superior to hepatic resection for early-stage hepatocellular carcinoma (HCC) in terms of recurrence rates and long-term survival. The trial did not show that RFA is superior in treating early-stage HCC. However, a subgroup analysis concerning very early-stage HCC (single tumour, no larger than 2 cm) suggests that RFA is just as good in terms of overall and disease-free survival with a shorter length of hospital stay. As RFA can frequently be done percutaneously, it would seem appropriate to use RFA as the first treatment option instead of surgery in very early HCC.

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