Original article

Radiofrequency ablation as an alternative to hepatic resection for single small hepatocellular carcinomas

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Background: **This study aimed to investigate whether radiofrequency ablation (RFA) is an alternative to surgical resection for hepatocellular carcinoma (HCC) within the context of current guidelines.**

Methods: **This retrospective study included patients with normal portal pressure and serum bilirubin level who initially underwent liver resection or RFA for a single HCC of maximum size 3 cm. Between-group differences in cumulative rates of survival and recurrence specific for HCC were analysed in the entire cohort and in a propensity score-matched cohort.**

Results: **A total of 604 patients were enrolled, 273 in the liver resection group and 331 in the RFA group. The 5- and 10-year HCC-specific survival rates for the resection and RFA groups were 87·6 *versus* 82·1 per cent and 59·0 *versus* 61·2 per cent respectively ($P = 0·214$), whereas overall 5- and 10-year recurrence-free survival rates for the corresponding groups were 60·6 *versus* 39·4 per cent and 37·5 *versus* 25·1 per cent respectively ($P < 0·001$). In the propensity score-matched cohort (152 pairs), there were no differences in HCC-specific survival (hazard ratio (HR) 1·03 for RFA *versus* resection; $P = 0·899$), whereas recurrence-free survival again differed between the treatment groups (HR 1·75; $P < 0·001$). RFA was independently associated with poorer outcomes in terms of treatment-site recurrence-free survival (adjusted HR 1·66; $P = 0·026$), but not non-treatment-site recurrence-free survival (adjusted HR 1·15; $P = 0·354$).**

Conclusion: **Although RFA carries a higher risk of treatment-site recurrence than hepatic resection, it provides comparable overall survival in patients with a single small HCC without portal hypertension or a raised bilirubin level.**

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Introduction

The Barcelona Clinic Liver Cancer (BCLC) group has recently suggested a refinement of the decision-making strategy for patients with very early-stage hepatocellular carcinoma (HCC) in which initial radiofrequency ablation (RFA) is followed by rescue surgery in the event of failure[1]. However, whether it would be appropriate to offer RFA as a primary therapy to patients with a single small HCC, especially those with little compromised hepatic function, is still a matter of clinical debate[2]. In addition, there are barely any relevant surveys focusing specifically on patients with a solitary small HCC tumour of BCLC stage 0 or A, stringently defined, with both good physical and hepatic function.

Some authors have proposed that neither tumour multiplicity nor portal hypertension is a contraindication to surgery for HCC, even in patients with cirrhosis[3,4]. However, practice guidelines based on the BCLC classification currently recommend surgical resection only in patients with a single HCC and non-cirrhotic liver background, or cirrhosis without clinically relevant signs of portal hypertension and a normal serum bilirubin level. This is because the latter were found to be independent predictors of survival after resection for HCC in intention-to-treat analyses[5–7]. Most previous reports comparing the efficacy of RFA and resection, including randomized trials, have not excluded or even evaluated the presence of portal hypertension, and have included at least some subjects with moderate hepatic damage[8–12]. In addition, the randomized

studies[8–10] were not designed adequately in terms of liver function and tumour burden, and reported outcomes for 5 years at most.

The aim of the present study was to compare RFA as a first-line treatment with standard liver resection for very early (0) or early (specifically A1) stage HCC according to the current BCLC algorithm[13]. The outcomes, for up to 10 years after RFA *versus* surgical resection, were compared in patients with a single ablatable HCC with a 3-cm cut-off[14,15], and normal portal pressure and serum bilirubin level (absolute indication for partial hepatectomy according to BCLC guidelines[5–7]) using a propensity score matching approach and a large cohort.

Methods

The retrospective study population consisted of consecutive patients with a single asymptomatic HCC no larger than 3 cm and good health performance status, who initially underwent liver resection or RFA at a tertiary referral hospital in Korea between 2000 and 2009. Information and follow-up data on these patients were contained in the liver centre database of Asan Medical Centre. Inclusion criteria were: well preserved liver function of Child–Turcotte–Pugh class A; normal serum bilirubin level (less than 1·5 mg/dl)[16]; and no definite evidence of portal hypertension, as assessed clinically. Portal hypertension was diagnosed clinically by the presence of one or more of[11]: gastro-oesophageal varices, ascites, and splenomegaly with a platelet count lower than 100 000/mm^3. Splenomegaly was diagnosed by CT (spleen length exceeding 10 cm)[17]. Cirrhosis was diagnosed based on histological and/or radiological findings. HCC diagnoses were confirmed retrospectively using the most recent American Association for the Study of Liver Diseases criteria[6]. This study was approved by the Institutional Review Board of Asan Medical Centre.

Pretreatment investigations

Clinicians explained the therapeutic options to all patients. An appropriate method (surgical resection or RFA) was selected for each patient, with informed consent for the procedure being obtained, taking into account the patient's preference and the cost, as well as the medical evidence[18]. Before treatment all patients underwent dynamic liver CT and/or MRI, chest CT and bone scan. Routine laboratory parameters including α-fetoprotein (AFP) were measured using standard analytical procedures, and serum markers of hepatitis were assayed, including hepatitis B surface antigen and antihepatitis C virus (HCV). Endoscopic examination for oesophageal and gastric varices was undertaken in patients with cirrhosis.

Resection and radiofrequency ablation protocols

Surgical resection was performed under general anaesthesia, and anatomical liver resection was generally carried out with a resection margin of at least 1 cm. Decisions concerning the extent of liver resection were based on tumour location and underlying liver status.

All RFA procedures were performed percutaneously under ultrasonographic guidance with local anaesthesia at the entry site of radiofrequency electrodes and conscious sedation, as described previously[19,20]. CT-guided RFA was carried out in patients with a poor ultrasonographic window. The ablation was performed by one of three radiologists. The radiologists performed the procedures with a single electrode, multiple overlapping insertions of a single electrode, or a cluster electrode consisting of three parallel electrodes, depending on the size of the tumour. A 2- or 3-cm active tip with a 17-G internally cooled electrode (ValleyLab, Burlington, Massachusetts, USA) or a 17-G internally cooled wet electrode system (RF Medical, Seoul, Korea) was used. Radiofrequency current was emitted generally for 12 min by a 200-W generator set to deliver maximum power using the automatic impedance control method. Ablation was repeated until complete ablation of the tumour and margins of at least 0·5–1·0 cm in the normal liver parenchyma had been achieved. When complete ablation of an index tumour was not evident at immediate follow-up CT on the same day as the RFA session, additional RFA was performed on the same or next day.

Follow-up monitoring

The short-term effectiveness of surgical resection or RFA was evaluated after 1 month by dynamic liver CT or MRI. Thereafter, patients routinely underwent clinical examinations, liver function tests with AFP assays, and dynamic liver CT covering most of the chest field, at 2–3-month intervals during the first 2 years, and then at 3–6-month intervals until recurrence. Recurrent lesions were treated locoregionally or surgically according to established guidelines for managing primary tumours, taking into account patient condition and hepatic function.

Definition of clinical endpoints

Patient survival was defined as the interval between the date of treatment and time of death caused by HCC *per se* and associated complications (HCC-specific survival). Recurrence-free survival was defined as the interval

between date of treatment and first relapse, or death related to HCC. Loss to follow-up or death from other causes was censored. Tumour recurrence was defined as the appearance of new lesion(s) with typical radiological features of HCC[5]. Treatment-site recurrence (recurrence at the ablation or resection site) was defined by the reappearance of viable tumour within or directly adjacent to the ablated or resected site, where the largest diameter was in direct contact with the treated site[21]. Non-treatment-site recurrence included distant intrahepatic recurrence and extrahepatic recurrence. Early recurrence was defined as tumour recurrence within 2 years of treatment[22].

Statistical analysis

Baseline characteristics were compared by χ^2 test and Student's *t* test for categorical and continuous variables respectively. The Kaplan–Meier method and log rank test were used to compare survival and recurrence outcomes in the two treatment groups. Predictive factors for postprocedure endpoints were identified by multivariable analysis using a Cox proportional hazards model, which was fitted with the backward selection approach after univariable analysis.

To reduce the impact of potential confounding effects, rigorous adjustment was made for significant differences in baseline characteristics by means of the propensity score-based matching method. The variables used to derive propensity scores were age, sex, body mass index (BMI), cause of liver disease, liver cirrhosis, levels of aspartate aminotransferase, alanine aminotransferase (ALT), albumin, bilirubin, creatinine and AFP, platelet count, prothrombin time and tumour size. Propensity scores were matched for patients undergoing resection and RFA based on a difference of ±0·05 in propensity scores. After propensity score estimation, the matched cohorts were compared using paired *t* test or the Wilcoxon signed-rank test for continuous variables, as appropriate, and McNemar's test or the marginal homogeneity test for categorical variables. Differences in HCC-specific and recurrence-free survival between the two groups were compared using Cox regression models, with robust standard errors that accounted for the clustering of matched pairs[23]. $P < 0{\cdot}050$ was considered statistically significant. All statistical analyses were performed with SAS® software 9.3 (SAS Institute, Cary, North Carolina, USA).

Results

The database contained a total 1097 consecutive patients with a single HCC of 3 cm or less, of whom 337 had undergone liver resection and 760 RFA between 2000 and 2009. Sixty-four patients in the resection group and 429 in the RFA group were excluded based on the inclusion and exclusion criteria. This left 273 patients in the liver resection group and 331 in the RFA group (*Fig. S1*, supporting information). The demographic characteristics of the study patients are shown in *Table 1*. Of the 604 patients, 465 (77·0 per cent) were men, 468 (77·5 per cent) were hepatitis B virus (HBV)-positive and 352 (58·3 per cent) had liver cirrhosis, with no significant differences between the treatment groups. Propensity score matching for the entire cohort generated 152 matched pairs. There were no significant differences between treatment groups in the propensity-matched cohort (*Table 1*).

In the entire resection group, 250 patients (91·6 per cent) underwent anatomical resection: four segments were resected in 17 patients, three in 14 patients, two in 113 and one in 106; only 23 patients (8·4 per cent) underwent non-anatomical wedge resection. Pathological examination of the resected specimens revealed that 20 patients (7·3 per cent) had microscopic vascular invasion, 33 (12·1 per cent) had capsular invasion and nine (3·3 per cent) had satellite nodules. In the entire RFA group, complete ablation was achieved in 322 patients (97·3 per cent) after the first RFA session, whereas nine patients (2·7 per cent) required two treatment sessions to obtain complete ablation.

Outcomes in the entire cohort

The median follow-up times after resection and RFA were 61 (i.q.r. 40–82) and 66 (52–88) months respectively. In the entire cohort, the 5- and 10-year HCC-specific survival rates were 87·6 and 59·0 per cent respectively for the resection group with a median survival of 61 months, and 82·1 and 61·2 per cent respectively for the RFA group with a median survival of 66 months ($P = 0{\cdot}214$) (*Fig. 1a*).

During the observation period, tumours recurred in 115 patients (42·1 per cent) treated by resection and 198 (59·8 per cent) treated by RFA ($P < 0{\cdot}001$). Treatment-site recurrence as first event was detected in five patients (1·8 per cent) in the resection group and 52 (15·7 per cent) in the RFA group ($P < 0{\cdot}001$), whereas non-treatment-site recurrence including extrahepatic recurrence as first event was observed in 110 (40·3 per cent) and 146 patients (44·1 per cent) respectively ($P = 0{\cdot}345$). Eight of 15 patients with recurrent HCC at extrahepatic sites had simultaneous intrahepatic recurrence distant from the treated area, and there was no difference in terms of extrahepatic relapse between the resection and RFA groups (2·2 and 2·7 per cent respectively; $P = 0{\cdot}682$).

Median overall recurrence-free survival was shorter in the RFA group (36 months; 39·4 per cent at 5 years and 25·1 per cent at 10 years) than in the resection group

Table 1 Baseline characteristics according to treatment group in the entire cohort and in the propensity score-matched cohort

	Entire cohort				Propensity score-matched cohort			
	RFA ($n = 331$)	Resection ($n = 273$)	P‡	SMD	RFA ($n = 152$)	Resection ($n = 152$)	P#	SMD
Age (years)*	57·3(10·3)	54·4(8·5)	< 0·001§	0·311	55·4(10·0)	55·4(8·3)	0·965**	0·005
Sex ratio (M : F)	260 : 71	205 : 68	0·315	0·082	121 : 31	119 : 33	0·786	0·032
BMI < 23 kg/m^2	120 (36·3)	97 (35·5)	0·854	0·015	50 (32·9)	48 (31·6)	0·806	0·028
Aetiology of liver disease			0·052	0·202			0·911	0·051
HBV	246 (74·3)	222 (81·3)			126 (82·9)	123 (80·9)		
HCV	40 (12·1)	18 (6·6)			10 (6·6)	11 (7·2)		
Other	45 (13·6)	33 (12·1)			16 (10·5)	18 (11·8)		
Liver cirrhosis	189 (57·1)	163 (59·7)	0·518	0·053	83 (54·6)	89 (58·6)	0·453	0·080
AST (units/l)†	36 (29–48)	33 (27–43)	0·002¶	0·252	32 (26–40)	32 (26–42)	0·915††	0·041
ALT (units/l)†	35 (25–49)	33 (22–47)	0·127¶	0·128	33 (24–46)	31 (21–43)	0·603††	0·014
Albumin (g/dl)†	3·8 (3·6–4·1)	3·8 (3·6–4·1)	0·119¶	0·129	3·9 (3·7–4·2)	3·9 (3·6–4·2)	0·695††	0·012
Bilirubin (mg/dl)†	0·9 (0·7–1·0)	0·9 (0·7–1·0)	0·753¶	0·026	0·9 (0·7–1·1)	0·9 (0·7–1·1)	0·947††	0·037
Platelet count (× 10^3/μl)†	142 (115–177)	156 (128–190)	< 0·001¶	0·268	152 (122–186)	147 (124–175)	0·283††	0·099
Creatinine (mg/dl)†	0·9 (0·8–1·0)	0·9 (0·8–1·0)	0·008¶	0·209	0·9 (0·8–1·0)	0·9 (0·8–1·0)	0·678††	0·018
Prothrombin time (INR)†	1·06 (1·02–1·11)	1·05 (1·01–1·11)	0·294¶	0·085	1·05 (1·01–1·10)	1·05 (1·00–1·11)	0·269††	0·126
Serum AFP ≥ 20 ng/ml	123 (37·2)	153 (56·0)	< 0·001	0·386	75 (49·3)	76 (50·0)	0·904	0·013
Tumour diameter (cm)†	1·8 (1·5–2·3)	2·4 (2·0–2·8)	< 0·001¶	0·697	2·0 (1·6–2·5)	2·0 (1·5–2·5)	0·807††	0·026
< 2	181 (54·7)	64 (23·4)			66 (43·4)	54 (35·5)		
≥ 2, < 3	150 (45·3)	209 (76·6)			86 (56·6)	98 (64·5)		

Values in parentheses are percentages unless indicated otherwise; values are *mean(s.d.) and †median (i.q.r.). RFA, radiofrequency ablation; SMD, standardized mean difference; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; AFP, α-fetoprotein. ‡χ^2 test, except §Student's t test and ¶Mann–Whitney U test; #McNemar's test or the marginal homogeneity test, except **paired t test and ††Wilcoxon signed rank test.

(44 months; 60·6 per cent at 5 years and 37·5 per cent at 10 years) ($P < 0·001$) (*Fig. 1b*). Closer analysis of the data showed that 5- and 10-year treatment-site recurrence-free survival rates were 86·6 *versus* 70·4 per cent and 58·3 *versus* 50·7 per cent respectively in the resection and RFA groups ($P < 0·001$) (*Fig. S2a*, supporting information). Five- and 10-year non-treatment-site recurrence-free survival rates were 61·6 *versus* 51·1 per cent and 38·1 *versus* 35·5 per cent respectively ($P = 0·009$) (*Fig. S2b*, supporting information).

Of the total of 57 treatment-site recurrences as first events, 39 (68 per cent) occurred within 2 years of the treatment date. The five recurrent tumours in the resection group were treated by RFA in one patient and transarterial chemoembolization in the other four. Of the 52 patients in the RFA group with a recurrence, 27 (52 per cent) were managed effectively with repeat RFA, six (12 per cent) by resection with curative intent, one (2 per cent) with percutaneous ethanol injection, 16 (31 per cent) with transarterial chemoembolization, and two (4 per cent) with best supportive care because of old age (1) and haematological malignancy (1).

Outcome predictors in the entire cohort

Predictive factors included in the univariable and multivariable analyses were: treatment group, age, sex, BMI, cause of liver disease, liver cirrhosis, serum ALT, albumin, bilirubin, creatinine and AFP levels, platelet count, prothrombin time and tumour size (*Table 2*; *Table S1*, supporting information). In univariable and multivariable Cox analyses, type of treatment did not influence HCC-specific survival, with an unadjusted hazard ratio HR of 1·24 (95 per cent c.i. 0·88 to 1·76; $P = 0·216$) and adjusted HR of 1·15 (0·81 to 1·64; $P = 0·423$). In multivariable Cox analysis, age (adjusted HR 1·03, 95 per cent c.i. 1·02 to 1·05; $P < 0·001$), serum albumin level (adjusted HR 0·59, 0·39 to 0·88; $P = 0·010$) and prothrombin time (adjusted HR 12·43, 2·52 to 61·29; $P = 0·002$) were independently associated with HCC-specific survival.

However, treatment regimen was associated with overall recurrence-free survival, which was poorer in the RFA group than in the resection group: unadjusted HR 1·84 (1·47 to 2·31; $P < 0·001$) and adjusted HR 1·77 (1·41 to 2·23; $P < 0·001$) (*Table 2*; *Table S1*, supporting information). Liver cirrhosis (adjusted HR 1·27; 1·00 to 1·60; $P = 0·047$), serum albumin level (adjusted HR 0·60, 0·47 to 0·77; $P < 0·001$) and platelet count (adjusted HR 0·94, 0·92 to 0·96; $P = 0·029$) were identified by multivariable Cox analysis as independent predictors of overall recurrence-free survival (*Table S1*, supporting information).

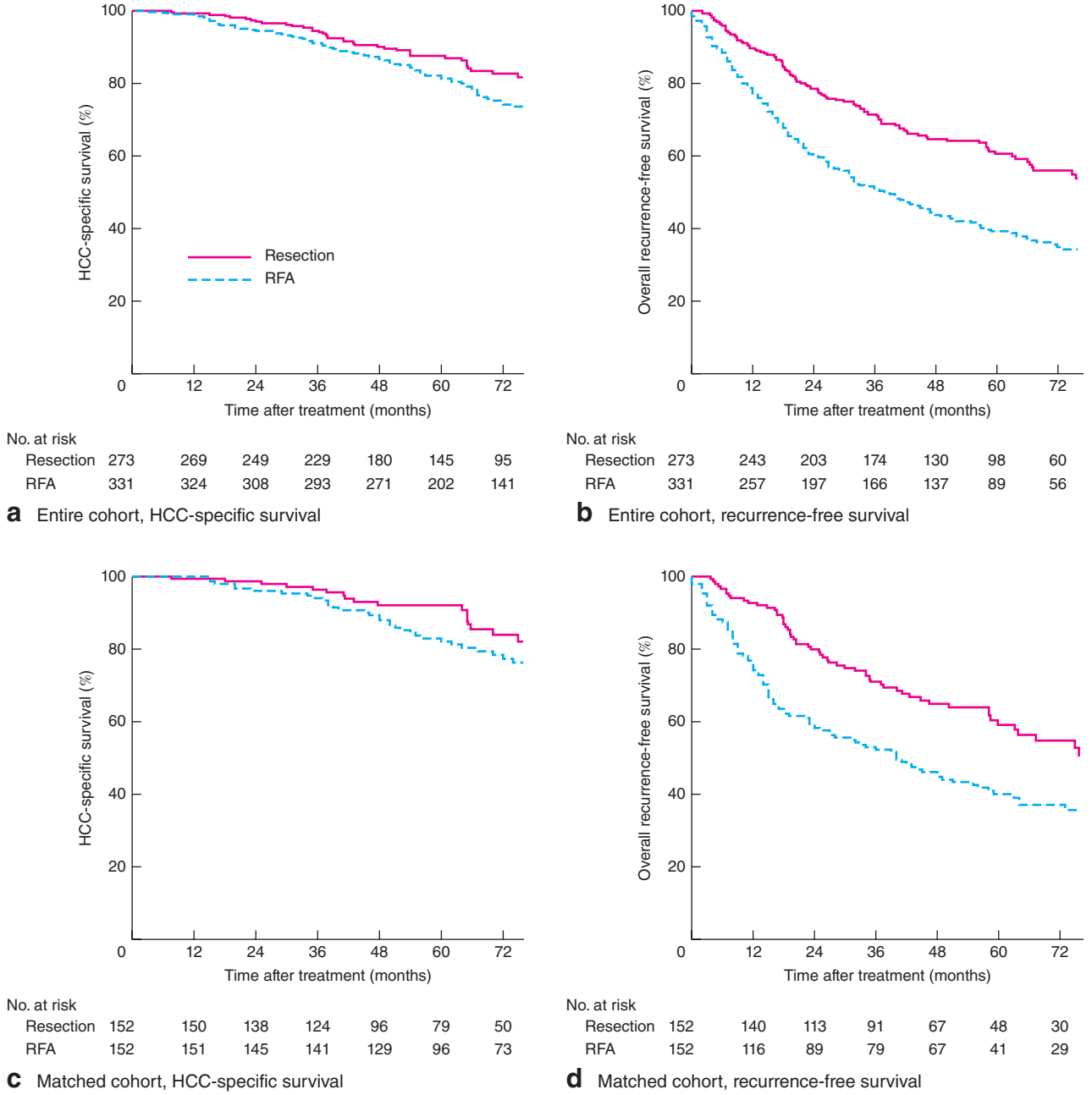


Fig. 1 Kaplan–Meier estimates of **a**,**c** hepatocellar carcinoma (HCC)-specific survival and **b**,**d** overall recurrence-free survival according to treatment group in **a**,**b** the entire cohort and **c**,**d** the propensity score-matched cohort. RFA, radiofrequency ablation. **a** $P = 0{\cdot}214$, **b** $P < 0{\cdot}001$, **c** $P = 0{\cdot}899$, **d** $P < 0{\cdot}001$ (log rank test)

Further analysis of predictive factors for recurrence-free survival as a function of the type of relapse showed that RFA treatment was independently associated with poorer outcomes in terms of treatment-site recurrence-free survival (adjusted HR 1·81, 1·31 to 2·51; $P < 0{\cdot}001$), but this was not the case for non-treatment-site recurrence-free survival (adjusted HR 1·24, 0·97 to 1·57; $P = 0{\cdot}084$) (*Table S2*, supporting information). Tumour size was not related to either treatment-site (unadjusted HR 1·20, 0·94 to 1·53; $P = 0{\cdot}148$) or non-treatment-site (unadjusted HR 0·98, 0·81 to 1·18; $P = 0{\cdot}805$) recurrence-free survival (*Table S2*, supporting information).

Table 2 Predictions of time-dependent endpoints in the radiofrequency ablation group *versus* resection group according to method of analysis

	Hazard ratio	*P*
Overall recurrence-free survival		
Crude*	1·84 (1·47, 2·31)	< 0·001
Adjusted†	1·77 (1·41, 2·23)	< 0·001
Propensity-matched‡	1·75 (1·28, 2·40)	< 0·001
HCC-specific survival		
Crude*	1·24 (0·88, 1·76)	0·216
Adjusted†	1·15 (0·81, 1·64)	0·423
Propensity-matched‡	1·03 (0·63, 1·68)	0·899

Values in parentheses are 95 per cent c.i. HCC, hepatocellular carcinoma. *Cox proportional hazards models; †Cox proportional hazards models with backwards elimination; ‡Cox regression.

Outcomes in the matched cohort

In the propensity score-matched cohort (152 pairs), there was no significant difference in median HCC-specific survival between the two treatment groups (61 months for the resection group *versus* 69 months for the RFA group; HR 1·03, 95 per cent c.i. 0·63 to 1·68, $P = 0·899$) (*Fig. 1c* and *Table 2*). Tumour progression occurred in 64 patients (42·1 per cent) in the resection group and 94 (61·8 per cent) in the RFA group. Recurrence-free survival was poorer in the RFA group, with a median of 39 months compared with 42 months in the resection group (HR 1·75, 1·28 to 2·40; $P < 0·001$) (*Fig. 1d* and *Table 2*).

Unlike the treatment-site recurrence-free survival rate (HR 1·66, 1·06 to 2·58; $P = 0·026$) (*Fig. S2c*), the non-treatment-site recurrence-free survival rate did not differ between the two groups (HR 1·15, 0·85 to 1·56; $P = 0·354$) (*Fig. S2d*).

Using a cut-off time for early-phase recurrence of 2 years, the RFA group had a higher early overall recurrence rate than the resection group (HR 2·41, 1·54 to 3·75; $P < 0·001$) (*Fig. 2a*), whereas late overall recurrence rates were similar (HR 1·09, 0·68 to 1·76; $P = 0·720$) (*Fig. 2b*).

Outcomes according to Barcelona Clinic Liver Cancer stage

According to the BCLC system, tumours in 245 patients (181 in the RFA group and 64 in the resection group) were classified as BCLC stage 0 (very early stage) with lesion diameters smaller than 2 cm, and the remaining 359 as BCLC stage A1 (early stage). Subgroup analysis revealed no between-group differences in 5- and 10-year HCC-specific survival rates for BCLC stage 0 (91 *versus* 85·9 per cent and 66 *versus* 66·4 per cent respectively for resection *versus* RFA groups; $P = 0·416$) (*Fig. 3a*). Similar results for 5- and 10-year HCC-specific survival were noted in patients with BCLC stage A1 (86·7 *versus* 77·4 per cent and 56·7 *versus* 55·4 per cent for resection *versus* RFA groups; $P = 0·110$) (*Fig. 3b*).

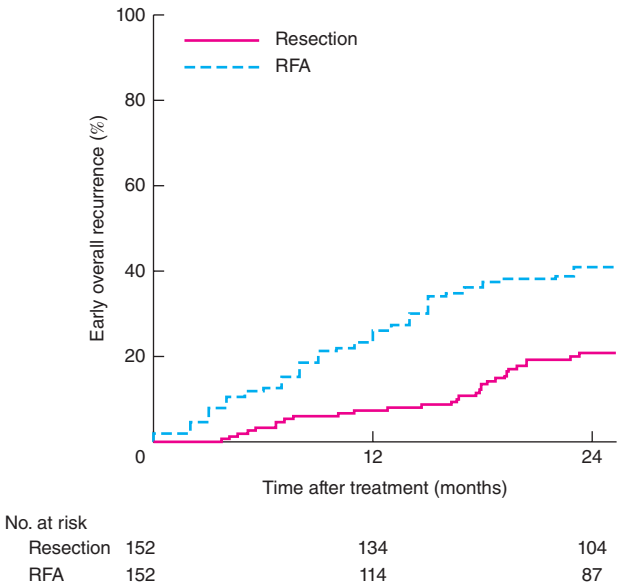
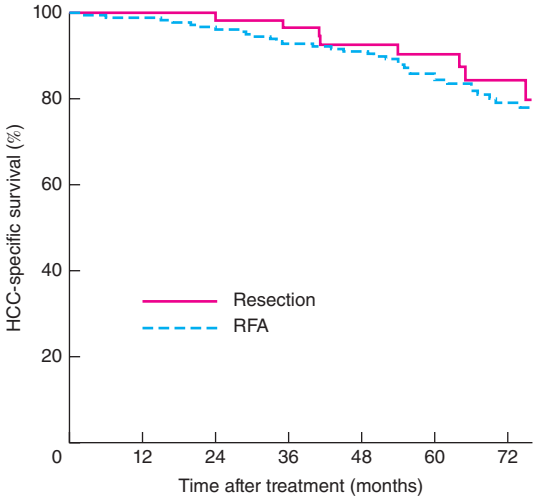


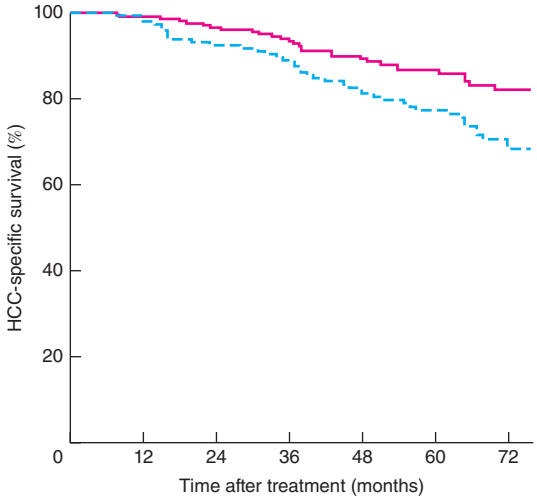
Fig. 2 Kaplan–Meier estimates of **a** early and **b** late overall recurrence according to treatment group in the propensity score-matched cohort. RFA, radiofrequency ablation. **a** $P < 0·001$, **b** $P = 0·720$ (log rank test)



No. at risk

Resection	64	63	58	56	44	34	21
RFA	181	178	174	166	156	115	77

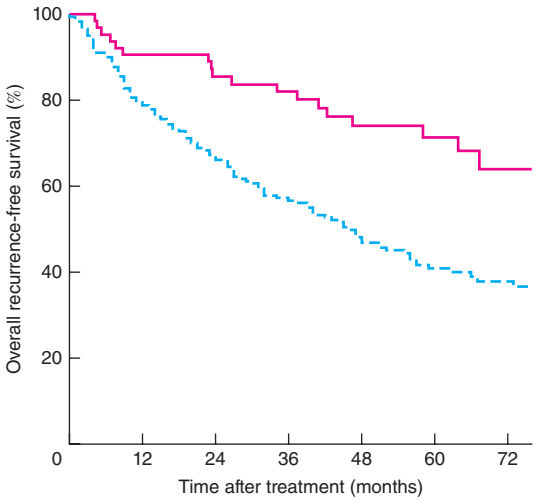
a BCLC stage 0, HCC-specific survival



No. at risk

Resection	209	205	191	173	136	111	74
RFA	150	146	134	127	115	87	64

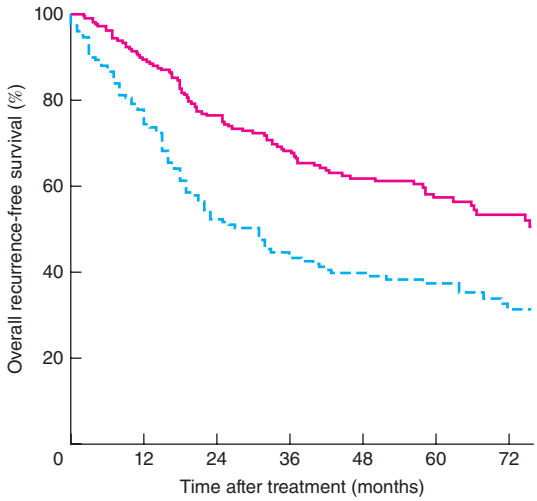
b BCLC stage A1, HCC-specific survival



No. at risk

Resection	64	58	49	47	34	26	14
RFA	181	143	121	102	82	52	31

c BCLC stage 0, recurrence-free survival



No. at risk

Resection	209	185	154	127	96	72	46
RFA	150	114	76	64	55	37	25

d BCLC stage A1, recurrence-free survival

Fig. 3 Kaplan–Meier estimates of **a**,**b** hepatocellular carcinoma (HCC)-specific survival and **c**,**d** overall recurrence-free survival according to treatment group in Barcelona Clinic Liver Cancer (BCLC) **a**,**c** stage 0 and **b**,**d** stage A1 in the entire cohort. RFA, radiofrequency ablation. **a** $P = 0{\cdot}416$, **b** $P = 0{\cdot}110$, **c** $P < 0{\cdot}001$, **d** $P < 0{\cdot}001$ (log rank test)

Among patients with BCLC stage 0 disease, 5- and 10-year overall recurrence-free survival rates in the resection and RFA groups were 71 *versus* 41·0 per cent and 42 *versus* 25·0 per cent respectively ($P < 0{\cdot}001$) (*Fig. 3c*). Corresponding values for patients with BCLC stage A1 tumours were 57·3 *versus* 37·4 per cent and 33·7 *versus* 24·5 per cent respectively ($P < 0{\cdot}001$) (*Fig. 3d*). The same effects were noted in multivariable analyses: adjusted HR 2·28 (95 per cent c.i. 1·44 to 3·62; $P < 0{\cdot}001$) for BCLC stage 0 and 1·68 (1·25 to 2·25; $P = 0{\cdot}001$) for BCLC stage A1.

Discussion

In this propensity-matched study with 10-year follow-up, RFA yielded survival outcomes comparable to those of standard surgery in patients with a single HCC of ablatable size (3 cm or less),with a normal bilirubin level and without portal hypertension. These are current, well established indications for hepatic resection[5–7]. However, RFA had a considerable disadvantage over surgical resection in terms of treatment-site recurrence, mainly in the early phase after treatment, although other types of recurrence were similar in the two treatment groups. These outcomes were found by both the Cox regression and matching approaches.

A previous study[12] of patients with very early- or early-stage HCC employed propensity score matching without considering portal pressure and bilirubin levels. A recent meta-analysis[24] found similar survival outcomes in the subgroup of patients with a single HCC of 2 cm or less, indicating that RFA may be an alternative to surgical resection. Results for a subgroup of patients with very early-stage HCC clearly support the present observations in terms of both survival and recurrence outcomes[12,24]. More recently, a multicentre study[11] of patients with cirrhosis and a single HCC of 3 cm or less also reported comparable survival in the resected and ablated groups. Interestingly, the authors found no significant difference in the cumulative probability of overall recurrence between the two treatment groups in spite of a higher local progression rate in the RFA group, which is not consistent with the present findings. However, their findings were based on data from a cohort with cirrhosis that included predominantly HCV-infected patients, unlike the present population from an HBV-endemic area. A considerable number of their patients had portal hypertension and/or bilirubin levels exceeding normal levels before undergoing one or other procedure, which probably accounts for their somewhat poorer long-term outcomes.

The current BCLC staging system recommends surgical resection for single HCCs in patients with well preserved liver function, defined as a normal bilirubin level with either a hepatic venous pressure gradient no greater than 10 mmHg or a platelet count of 100 000/mm^3 or more[17]. Although contradictory results have been obtained in individual studies and meta-analyses, including the present selected group with very good prognosis, many authors, especially surgeons, still advocate liver resection as first choice over RFA[25]. The present observations indicate that, if the tumour is visible radiologically, RFA deserves to be considered as a suitable alternative for treating single small HCCs in patients with (near) normal liver function. In fact, the BCLC group[1] recently proposed a refinement of the decision-making strategy, especially for patients with very early-stage HCC who were not potential candidates for liver transplantation, in which RFA was considered the primary option, and surgery was limited to patients in whom RFA was not feasible or had failed. A Markov model analysis also yielded this hierarchical strategy for the management of BCLC 0 tumours[26].

However, the present findings underline the fact that closer surveillance for recurrent HCC is essential following RFA, and should be programmed into clinical practice for at least a few years after this treatment. In line with previous investigations[11,16], treatment-site recurrence was more troublesome following RFA than after surgery, mainly during the first 2 years after treatment. This was true even in patients with tumours smaller than 2 cm, which can be cured by inserting a single electrode[2,27], and contrasted with non-treatment-site recurrence, which was reported previously to be correlated with host and initial tumour factors[28]. This finding has been explained conventionally by the presence of tumour factors such as microscopic satellites and emboli in portal branches not included in the ablation zone, which could be dealt with by anatomical resection[29]; or the heat-sink effect adjacent to vessels[30]. These explanations are supported by the present finding that 68 per cent of locally recurrent tumours presented as early recurrences within the second year after RFA. These are known to be due to dissemination of the primary tumour, unlike later recurrences which involve *de novo* tumours[22]. Moreover, microscopic examination of the resected specimens showed that 7·3 per cent were associated with vascular invasion and 3·3 per cent with satellite nodules (no relevant data were available from the RFA group). In this study, with a 3-cm cut-off, treatment-site recurrence did not depend on pretreatment tumour size. In this respect, achieving a sufficient safety margin during treatment appears to be essential, regardless of the target size, when selecting RFA as the initial therapy instead of hepatic resection for relatively small single HCCs.

It is of great importance to treat HCC recurrence rapidly and optimally to prolong survival. Indeed, about two-thirds of the present patients who experienced relapse after RFA were managed by surgical or percutaneous modalities and survived for long periods. As a result, in spite of its vulnerability to relapse, the RFA group had postprocedure survival outcomes comparable to those after tumour resection in multivariable adjusted models. Similar unmatched results for recurrence and survival have also been reported in previous studies[12,16]. At this point, the authors believe that the higher risk of treatment-site recurrence is not a critical obstacle to accepting the reliability of primary RFA for managing solitary small HCCs.

Although the aim of this study was to minimize potential confounders by using the propensity score-matching method, the study design retained the inherent drawback of imperfect randomness, especially owing to hidden bias from latent unobservable variables that could not be controlled for statistically[31]. Another consideration is that data regarding the feasibility of the other therapeutic options were not available in the present retrospectively enrolled groups, although feasibility has not been shown to be associated with prognosis after each treatment.

Disclosure

The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article:

Fig. S1 Patient selection criteria in the pooled and matched sets (Word document)

Fig. S2 Kaplan–Meier estimates of treatment-site and non-treatment-site recurrence-free survival according to treatment group in the entire cohort and the propensity score-matched cohort (Word document)

Table S1 Univariable and multivariable Cox proportional hazards analyses of variables related to clinical endpoints in the entire cohort (Word document)

Table S2 Univariable and multivariable Cox proportional hazards analyses of recurrence-free survival in the entire cohort (Word document)