



Combined percutaneous radiofrequency ablation and ethanol injection versus hepatic resection for 2.1–5.0 cm solitary hepatocellular carcinoma: a retrospective comparative multicentre study

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Abstract

Objectives To compare combined percutaneous radiofrequency ablation and ethanol injection (RFA-PEI) with hepatic resection (HR) in the treatment of resectable solitary hepatocellular carcinoma (HCC) with 2.1–5.0 cm diameter.

Methods From June 2009 to December 2015, 271 patients whom underwent RFA-PEI ($n = 141$) or HR ($n = 130$) in three centres were enrolled. The overall survival (OS) and recurrence-free survival (RFS) between groups were compared with Kaplan–Meier method and log-rank tests. Complications, hospital stay and cost were assessed.

Results The OS rates at 1, 3 and 5 years were 93.5%, 72.7%, 58.6% in RFA-PEI group and 82.3%, 57.5%, 51.8% in HR group ($p = 0.021$). The corresponding 1-, 3- and 5-year RFS rates were 65.8%, 41.3%, 34.3% in RFA-PEI group and 50.5%, 33.8%, 28.4% in HR group ($p = 0.038$). For patients with 2.1–3.0 cm tumours, the 1-, 3- and 5-year OS after RFA-PEI and HR were 98.0%, 82.3%, 74.2% and 89.4%, 65.1%, 61.9%, respectively ($p = 0.024$). The corresponding RFS were 79.6%, 54.7%, 45.1% in RFA-PEI group, and 57.6%, 43.9%, 31.7% in HR group, respectively ($p = 0.020$). RFA-PEI was superior to HR in major complication rates, length of hospital stay and cost (all $p < 0.001$).

Conclusion RFA-PEI had a survival benefit over HR in the treatment of solitary HCCs, especially for those with 2.1–3.0 cm in diameter.

Key Points

- RFA-PEI provided superior survival to HR in solitary HCC with 2.1–5.0 cm in diameter.
- RFA-PEI is superior to HR in complications, length of hospital stay and cost.
- RFA-PEI might be an alternative treatment for solitary HCC within 5.0 cm in diameter.

Keywords Ablation techniques · Ethanol · Hepatectomy · Carcinoma, hepatocellular · Comparative study

Shuling Chen and Zhenwei Peng contributed equally to this work.

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Abbreviations

BCLC	Barcelona clinic liver cancer
CECT	Contrast-enhanced computed tomography
CEUS	Contrast-enhanced ultrasound
ECOG	Eastern cooperative oncology group
HCC	Hepatocellular carcinoma
HR	Hepatic resection
LTP	Local tumour progression
MWA	Microwave ablation
OS	Overall survival
PEI	Percutaneous ethanol injection
RCT	Randomized controlled trial
RFA	Radiofrequency ablation
RFS	Recurrence-free survival
TACE	Transarterial chemoembolization

Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related mortality worldwide [1]. For small, solitary tumours without macrovascular invasion or extrahepatic metastasis, hepatic resection (HR), liver transplantation or percutaneous ablation is recommended as the initial curative treatment modality according to the international guidelines [2, 3]. The shortage of donors limits the widespread use of liver transplantation [4]. For solitary HCCs no larger than 2 cm in diameter, the latest Barcelona Clinic Liver Cancer (BCLC) system has considered ablation as a non-inferior and more cost-effective option to HR and liver transplantation [5]. For solitary tumours larger than 2.0 cm in diameter, HR has been considered the first-choice treatment, reserving liver transplantation for patients with recurrence of cancer after treatment, and those with microvascular invasion or satellites detected by pathological analysis [5]. Percutaneous ablation is usually considered to be a second-choice treatment for unresectable tumours owing to impaired liver function and associated diseases [5]. However, for solitary resectable tumours measuring 2.1–5.0 cm in diameter, there has been no randomized controlled trial (RCT) or large-scale cohort study comparing the efficacy of HR with ablation. Because HR inevitably accompanies invasiveness, micro-invasive treatment such as ablation might hold great promise as an alternative strategy with comparable or even superior efficacy to HR.

Several studies have shown that radiofrequency ablation (RFA) may provide similar survival rates but less invasiveness compared to HR for patients with solitary HCC no larger than 5.0 cm in diameter [6–8]. Since local tumour control of RFA was reported to be less efficient than HR, it has been suggested to combine other therapies with RFA to improve the local efficacy. Among them, the combination of RFA with

percutaneous ethanol injection (PEI) (RFA-PEI) with a multi-pronged needle has been reported, through which a complete ablation rate of 94% could be achieved after one session of treatment in patients with tumours measuring 3.0–7.0 cm in diameter [9]. This strategy was compared with RFA alone for HCC larger than 3 cm in diameter in an RCT, and higher complete ablation rate, better survival outcomes and comparable safety were achieved [10, 11]. To the best of our knowledge, no study has directly compared RFA-PEI with HR for solitary HCCs up to 5.0 cm so far. Thus, we retrospectively compared the efficacy of RFA-PEI with HR in the treatment of solitary resectable HCC with diameter 2.1–5.0 cm.

Materials and methods

Study design

This is a retrospective multicentre study on prospectively collected data in the First Affiliated Hospital of Sun Yat-sen University, Cancer Center of Sun Yat-sen University and the Affiliated Eastern Hepatobiliary Surgery Hospital of the Second Military Medical University. The study was approved by the ethics committee of each centre.

Patients presented with a first-time diagnosis of HCC in each centre from June 2009 to December 2015 were considered potential candidates for this study. HCC was diagnosed according to the most current clinical guidelines at the time of treatment [12, 13]; for example, two dynamic contrast-enhanced imaging modalities showing typical features of HCC, or one imaging study together with elevated serum alpha fetoprotein (AFP) level over 400 ng/dL, or a cytologic/histologic confirmation of HCC. The maximal diameter of the tumour was measured on cross-sectional imaging of computed tomography (CT) or magnetic resonance imaging (MRI). The histological diagnosis was confirmed by biopsy in 4 (2.8%) patients in the RFA-PEI group and by resected specimen for all patients in the HR group. Patients who met the following criteria were included in the study: (1) age between 18 and 75 years; (2) solitary tumour with 2.1–5.0 cm in diameter; (3) tumour defined resectable after evaluation of the feasibility of removing the lesion while leaving an adequate remaining liver remnant by our surgery team; (4) lesions visible on ultrasound with an acceptable and safe path for electrode insertion; (5) Child–Pugh A liver function; (6) no any other previous treatment; (7) an Eastern Cooperative Oncology Group (ECOG) performance status of 0.

The exclusion criteria were as follows: (1) underwent liver transplantation; (2) radiological evidence of vascular invasion or extrahepatic metastases; (3) severe coagulopathy (prothrombin activity < 40% or a platelet count < 40,000/mm³); (4) evidence of hepatic decompensation; (5) an American

Society of Anesthesiologists score of 3 or more; (5) history of any other concurrent malignancies; (6) complicated with severe comorbidities; (7) allergic to ethanol; (8) fitted with a pacemaker.

Our multidisciplinary team including surgeons, interventional oncologists and radiologists recommended both the RFA-PEI and HR as a curative treatment choice for HCC measuring 2.1–5.0 cm in diameter, according to the previous experience [9, 14, 15]. The final choice of treatment was decided by patients, after being informed of the advantages and disadvantages of both treatments in detail by the attending physicians. Reasons for choosing RFA-PEI instead of HR included psychological resistance to invasive treatment and refusal of general anaesthesia. Informed consent was obtained from all patients before treatment.

RFA-PEI procedure

At each centre, RFA-PEI was performed percutaneously by the interventional radiologists with at least 10 years of experience in RFA according to the methods described in previous studies [9, 10]. The whole procedure was under the real-time guidance of ultrasound. For PEI, an 18-gauge needle (Hakko Co., Ltd, Japan) was used. RFA was performed by using a commercially available Cool-tip™ RFA system (Valleylab, Boulder, CO, USA) or an RF 2000 system (Radio-Therapeutics Mountain View, CA). First, the radiofrequency needle was inserted into the low-centre of the target tumour. Then, the 18-gauge needle was placed immediately adjacent to the radiofrequency needle in another access path. The ethanol was slowly injected in an injection–rotation–injection manner. The mean volume of ethanol used was 10.2 ± 2.0 mL (range, 5–30 mL). RFA was performed 3–5 min after PEI. Multiple overlapping techniques were conducted as appropriate [16]. The detailed procedures are described in the [Supplementary Material](#).

Open hepatic resection

Open HR was performed under general anaesthesia by surgeons with 10–40 years of experience. Intraoperative US was routinely used to assist in operative evaluation including tumour burden, liver remnant and the possibility of a negative resection margin. The type of hepatectomy was defined according to the current guideline [17]. Anatomic resection was defined as the complete removal of at least one Couinaud segment containing the tumour and the corresponding hepatic territory. Other types of resection, such as wedge resection or tumour enucleation, were classified as non-anatomic resection. The surgical approach was chosen on the basis of hepatic functional reserve, tumour location and preference of the operator. Generally, anatomic resection was performed if the patient's liver functional reserve permitted.

Treatment assessment and follow-up

In the RFA-PEI group, contrast-enhanced ultrasound (CEUS) was performed the following morning after treatment to evaluate the technical success. An additional RFA-PEI was given if residual viable tumour was found. If enhanced areas were still observed in CEUS after the additional RFA-PEI, the treatment was considered a failure and the patients were referred to other therapies [18]. In the HR group, resection margins and status (R0 or R1 resection) were evaluated according to the absence of microscopic tumour invasion at the resection margin [19].

In both groups, contrast-enhanced dynamic CT (CECT) and CEUS were conducted 4 weeks after the treatment for evaluation of technique efficacy [20]. Thereafter, the patients were followed up once every 3 months for the first 2 years, once every 6 months from 2 to 5 years and then once every 12 months after 5 years. At each follow-up visit, CEUS and blood tests including liver function tests and serum AFP level assay were performed. CECT was performed every 6 months. Chest radiography, CT of the chest, MRI and bone scan were performed when clinically indicated.

When local tumour progression (LTP) (defined as the appearance of tumour enhancement around the ablation or resection margins) [20], intrahepatic distant recurrence or extrahepatic recurrence was detected during the follow-up, corresponding treatments were given according to the tumour characteristics, patients' liver function and requests, etc.

Complications were reported using the Dino–Clavien classifications [21]. Major complications were defined as clinical events leading to additional therapeutic interventions or prolonged hospitalisation [22]. Hospital costs were estimated with the frequency and unit cost of drugs, procedures, inpatient and outpatient visits, laboratory testing and imaging examination which included the direct costs for RFA-PEI or HR and also the costs for re-treatments after failure of these treatments. All the costs were converted to US dollars in 2016.

Overall survival (OS) was defined as the time interval from the date of diagnosis to the date of death from any cause or to the date of the last follow-up visit. Recurrence-free survival (RFS) was defined as the time interval between the date of diagnosis and the date of recurrence or last follow-up. This study was censored on 30 June 2016.

Statistical analysis

Continuous variables are presented as means \pm SD and categorical variables as numbers and percentages. Differences between the two groups were compared with the *t* test for continuous variables and χ^2 test for categorical variables. Survival curves were generated by the Kaplan–Meier method and compared by the log-rank test. Subgroup analyses were performed according to the

tumour size. The prognostic relevance of potential survival predictors was analysed by univariate and multivariate Cox proportional hazard regression models. Statistical significance was considered as a two-sided p value of less than 0.05. The above statistical analysis was performed with SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

From June 2009 to December 2015, 3448 consecutive patients received a first-time diagnosis of HCC in our three centres. On the basis of the inclusion and exclusion criteria, 3177 patients were excluded because of tumour size greater than 2.1 cm or greater than 5.0 cm ($n = 1122$), tumour number greater than 1 ($n = 1031$), Child–Pugh B or C liver function ($n = 300$), ECOG score greater than 0 ($n = 154$), vascular invasion or extrahepatic tumour ($n = 570$). Finally, 271 patients (219 men, 52 women; mean age, 59.0 years; range, 20–75 years) with solitary HCC (2.1–5.0 cm) who had undergone percutaneous RFA-PEI ($n = 141$) or open HR ($n = 130$) as their initial therapies in these three centres (Fig. 1) were enrolled in this study. In the RFA-PEI group, there were 77 patients with tumours measuring 2.1–3.0 cm in diameter and 64 with tumours measuring 3.1–5.0 cm in diameter. In the HR group, there were 70 patients with tumours measuring 2.1–3.0 cm in diameter and 60 with tumours measuring 3.1–5.0 cm in diameter. Baseline characteristics of the study population are summarised in Table 1. No significant difference in demographic data was detected between the RFA-PEI and HR groups.

Technical success of RFA-PEI and open hepatic resection

In the RFA-PEI group, technical success was achieved in all the patients, including 137 after a single treatment session, and 4 after two sessions of RFA-PEI. In the HR group, 79 patients had anatomic resection and 51 patients had non-anatomic resection. Among the patients with anatomic resection, 59 patients had resection of one liver segment and 20 patients had resection of more than one segment. R0 resection was achieved in all the patients in the HR group. Table S1 summarises the operative data and perioperative outcomes for patients in the HR group.

Treatment outcomes and survival analysis

The median follow-up duration was 63.9 months (range, 11–84 months) in the RFA-PEI group and 61.8 months (range, 12–84 months) in the HR group, respectively.

During follow-up, recurrence occurred in 87 patients after RFA-PEI (8 LTP and 79 of distant recurrence) and 96 patients after HR (1 LTP, 95 distant recurrence and 1 extrahepatic recurrence with distant recurrence) (Table 2). For the whole population, LTP rate was higher in the RFA-PEI group than in the HR group (9 vs 1, $p = 0.046$). However, LTP rate was comparable between RFA-PEI and HR in both the subgroups of 2.1–3.0 cm ($p = 0.686$) and 3.1–5.0 cm ($p = 0.225$) tumours. The intrahepatic distant recurrence rate was significantly higher in the HR group than in the RFA-PEI group in the subgroup of 2.1–3.0 cm tumours ($p = 0.023$) but was comparable between RFA and HR in the subgroup of 3.1–5.0 cm tumours ($p = 0.999$). The modalities used to treat recurrent HCC are summarised in Table 3. At the time of censoring, a total of 54 patients in the RFA-PEI group and

Fig. 1 Flow diagram of study treatments. HCC hepatocellular carcinoma, RFA-PEI combined radiofrequency ablation and percutaneous ethanol injection, HR hepatic resection

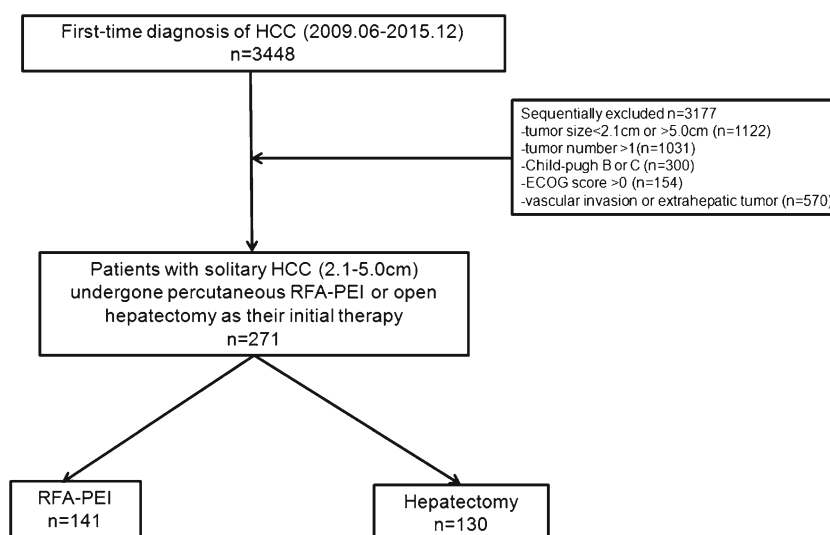


Table 1 Baseline characteristics of the study patients

	RFA-PEI (<i>n</i> = 141)	HR (<i>n</i> = 130)	<i>p</i> value
Sex(M/F)	114/27	105/25	0.880
Age (years)*	59.0 ± 7.5	59.0 ± 8.2	0.892
Associated comorbidities, <i>n</i> (%)			
Cardiac dysfunction	9 (7.8)	7 (4.0)	0.999
History of stroke	2 (2.9)	2 (1.0)	0.999
Chronic pulmonary disease	8 (9.8)	6 (7.1)	0.813
Hypertension	37 (26.5)	32 (15.2)	0.896
Diabetes	37 (17.6)	35 (15.2)	0.897
HBsAg (+/-)	113/28	104/26	0.881
HCV (+/-)	9/132	7/123	0.819
Portal hypertension (yes/no)	51/90	45/95	0.530
ALT (U/L)*	32.6 ± 8.3	31.9 ± 8.5	0.935
ALB (g/L)*	36.4 ± 2.0	36.5 ± 2.0	0.867
Total bilirubin (μmol/L)*	11.2 ± 5.1	11.0 ± 5.2	0.890
GGT (U/L)*	84.6 ± 35.2	84.5 ± 36.3	0.787
Platelet count (× 10 ⁹ /L)*	122.0 ± 31.0	123.0 ± 31.4	0.898
AFP (ng/ml)			
≤ 400	85	80	
> 400	56	50	
Tumour size (cm)			
2.1–3.0	77	70	0.810
3.1–5.0	64	60	

Except where indicated, data values represent the number of patients

RFA radiofrequency ablation, PEI percutaneous ethanol injection, HR hepatic resection, HBsAg hepatitis B surface antigen, HCV hepatitis C virus, ALT alanine aminotransferase, ALB albumin, GGT γ-glutamyl transpeptidase, AFP alpha fetoprotein

*Data are means ± standard deviations

67 patients in the HR group died, and causes of death are reported in Table S2.

The cumulative OS rates at 1, 3 and 5 years were 93.5%, 72.7% and 58.6% in the RFA-PEI group and 82.3%, 57.5% and 51.8% in the HR group, respectively ($p = 0.021$, Fig. 2a). Correspondingly, the 1-, 3- and 5-year RFS rates were 65.8%, 41.3% and 34.3% in the RFA-PEI group and 50.5%, 33.8% and 28.4% in the HR group, respectively ($p = 0.038$, Fig. 2b).

On subgroup analysis, for patients with tumours measuring 2.1–3.0 cm in diameter, the 1-, 3- and 5-year OS rates after

RFA-PEI ($n = 77$) and HR ($n = 70$) were 98.0%, 82.3%, 74.2% and 89.4%, 65.1%, 61.9%, respectively ($p = 0.024$, Fig. 3a). The corresponding RFS rates were 79.6%, 54.7% and 45.1% in the RFA-PEI group and 57.6%, 43.9% and 31.7% in the HR group, respectively ($p = 0.020$, Fig. 3b). For patients with tumours measuring 3.1–5.0 cm in diameter, the 1-, 3- and 5-year OS rates after RFA-PEI ($n = 64$) and HR ($n = 60$) were 86.4%, 65.1%, 55.4% and 88.9%, 64.5%, 49.6%, respectively ($p = 0.125$, Fig. S1a). The corresponding RFS rates were 53.5%, 29.4% and 24.0% in the RFA-PEI

Table 2 Recurrence after treatment

Variable	2.1–3.0 cm			3.1–5.0 cm		
	RFA-PEI (<i>n</i> = 77)	HR (<i>n</i> = 70)	<i>p</i> value	RFA-PEI (<i>n</i> = 64)	HR (<i>n</i> = 60)	<i>p</i> value
Local recurrence	3	0	0.686	6	1	0.225
Distant recurrence	25	46	0.023	52	48	0.999
Distant recurrence + extrahepatic recurrence	0	0	–	1	1	0.999

Except where indicated, data values represent the number of patients

RFA radiofrequency ablation, PEI percutaneous ethanol injection, HR hepatic resection

Table 3 Treatment for recurrence

Variable	2.1–3.0 cm			3.1–5.0 cm		
	RFA-PEI (<i>n</i> = 77)	HR (<i>n</i> = 70)	<i>p</i> value	RFA-PEI (<i>n</i> = 64)	HR (<i>n</i> = 60)	<i>p</i> value
RFA or RFA-PEI	20	22	0.613	29	21	0.625
HR	1	0	0.709	1	1	0.999
TACE	5	24	0.001	27	26	0.874
TACE + sorafenib	0	1	0.999	1	1	0.999
Conservative treatment	0	0	–	1	1	0.999

Except where indicated, data values represent the number of patients with recurrent tumours whom underwent certain additional treatments for recurrence

RFA radiofrequency ablation, PEI percutaneous ethanol injection, HR hepatic resection

group and 42.2%, 26.6% and 21.9% in the HR group, respectively ($p = 0.715$, Fig. S1b).

Univariate analysis showed that AFP ($p = 0.045$), tumour size ($p = 0.033$) and treatment type ($p = 0.021$) were significantly associated with OS, while tumour size ($p = 0.030$) and treatment type ($p = 0.025$) were associated with RFS. Multivariate analysis demonstrated that treatment type was the only independent predictor of OS (hazard ratio (HR) = 1.523, 95% CI, 1.063–2.182; $p = 0.022$) and RFS (HR = 1.357, 95% CI, 1.014–1.815; $p = 0.040$) (Table S3).

Complications and hospital costs

There was no treatment-related mortality in our study population. Major complications were observed in 3 of the 141 (2.1%) in the RFA-PEI group and 33 of the 130 patients (25.4%) in the HR group ($p < 0.001$) (Table 4). Pain and fever were the two most common minor complications. All the minor complications were also more common in the HR group than in the RFA-PEI group (all $p < 0.05$). The hospital stay was significantly shorter in the RFA-PEI group compared with that in the HR group (5 vs 11 days, $p < 0.001$). The hospital cost was \$3456.70 ± 940.98 for the RFA-PEI group and \$6516.50 ± 965.70 for the HR group ($p < 0.001$).

Discussion

Our multicentre study showed that RFA-PEI achieved better long-term survival outcomes, fewer major complications, shorter hospital stay and lower cost than HR for patients with solitary HCCs measuring 2.1–5.0 cm in diameter.

For local tumour control, no significant difference in LTP rate was observed between the RFA-PEI and HR groups in either the subgroup of 2.1–3.0 cm tumours or 3.1–5.0 cm tumours. Considering the inferior local efficacy of RFA to HR, the local efficacy of RFA-PEI relative to HR was improved, which might be explained by the increased ablation zone resulting from the following factors. First, ethanol could

destruct the vessels within or around the tumours to reduce the heat-sink effect of RFA. Second, ethanol could diffuse into the tumour area not reached by radiofrequency power. Third, thermal conduction could be improved by the lower extent of carbonization of tissue around electrode with ethanol [23, 24].

RFA-PEI presented a lower distant recurrence rate than HR in the subgroup of 2.1–3.0 cm tumours but a comparable rate to HR in the subgroup of larger (3.1–5.0 cm) tumours. It is reasonable to assume that in the subgroup of smaller (2.1–3.0 cm) tumours, RFA-PEI and HR could both achieve sufficient safety margin to ensure complete ablation and resection. It is also conceivable that the activating effect of RFA on the immune system might to some extent inhibit the intrahepatic distant metastasis (true recurrence) [25, 26]. Conversely, HR may suppress the immune system without the potential to prevent distant recurrence. Moreover, blood loss and blood transfusion, which are more likely to be required in HR than in RFA-PEI, can promote tumour recurrence [27, 28]. We believe that these are potential reasons to explain why more distant recurrence occurred after HR when compared to RFA-PEI for 2.1–3.0 cm HCCs. However, in the subgroup of 3.1–5.0 cm tumours, RFA-PEI may have not consistently produced sufficient safety margin because of the larger tumour size. Hazard from potentially inadequate safety margin in the RFA-PEI group may have outweighed the positive immunological effect of RFA-PEI on suppressing tumour recurrence. Thus, for 3.1–5.0 cm HCCs, no significant difference in the distant recurrence was observed between these two groups.

In our study, RFA-PEI achieved better OS and RFS compared to HR in patients with HCCs measuring 2.1–5.0 cm in diameter. More specifically, subgroup analyses revealed that the improved OS and RFS for RFA-PEI compared to HR was for 2.1–3.0 cm tumours, but not for 3.1–5.0 cm tumours. There might be several underlying reasons. First, a safety margin was reported to be one of the most important factors affecting recurrence after RFA and HR [29–31]. The enlarged ablation zone with wider safety margin by RFA-PEI can lead to a good local tumour control with full ablation of target tumour and effective clearance of micrometastases and

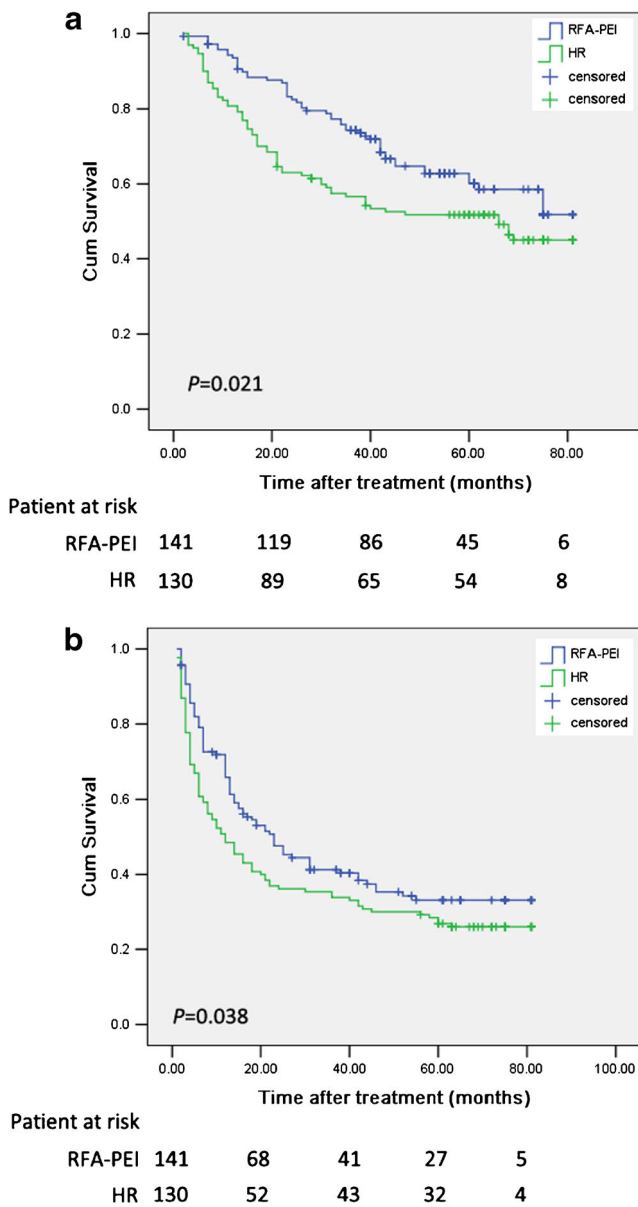


Fig. 2 Cumulative survival curves for patients with 2.1–5.0 cm solitary hepatocellular carcinomas after combined radiofrequency ablation and ethanol injection (RFA-PEI) and hepatic resection (HR). Curves for overall survival (a) and recurrence-free survival (b) are shown

microvascular invasion around the tumour. Thus, in our study, RFA-PEI achieved comparable LTP rates to HR, which suggested that RFA-PEI can obtain enough ablative margin at most cases, at least not inferior to that of HR. Second, in the case of complete ablation and resection, the intrahepatic distant recurrence may have contributed to the difference of RFS between the groups. The higher intrahepatic distant recurrence rate in the HR group in the subgroup of 2.1–3.0 cm tumours might contribute to a poorer RFS of patients after HR. However, in the subgroup of 3.1–5.0 cm tumours, the RFS rate was not significantly different with comparable intrahepatic distant recurrence between the groups. Third,

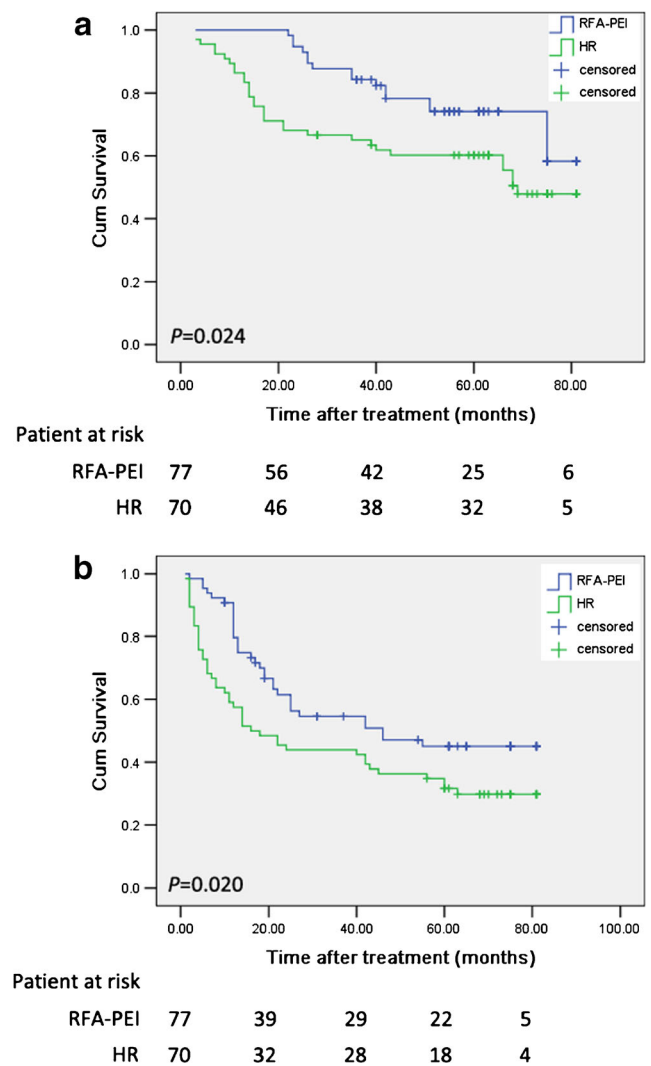


Fig. 3 Cumulative survival curves for patients with 2.1–3.0 cm solitary hepatocellular carcinomas after combined radiofrequency ablation and ethanol injection (RFA-PEI) and hepatic resection (HR). Curves for overall survival (a) and recurrence-free survival (b) are shown

prior studies including meta-analyses have shown poorer survival outcomes for non-anatomic resections, compared to anatomic resections for HCC patients after hepatectomy [32–34]. In our study, a relatively high proportion of non-anatomical resection (51/130, 39.2%) might be one of the reasons for better survival outcomes of the RFA-PEI group than the HR group. Fourth, RFA-PEI has the advantage over HR in causing less damage to liver function, which enables patients to endure repeated curative treatments in the case of relapse after RFA-PEI. And the interventions for recurrence might have a significant influence in the prognosis. Fifth, RFA-PEI has the advantage over HR in terms of micro-invasiveness with much fewer major complications and shorter hospital stay, which boosted the patients’ recovery and might therefore have improved their prognosis.

Table 4 Complications after treatment

Variable	RFA-PEI (<i>n</i> = 141)	HR (<i>n</i> = 130)	<i>p</i> value
Major complication	3	33	< .001
Hepatic failure			.032
Grade 3a	0	4	.162
Grade 4a	0	3	.268
Postoperative haemorrhage			.048
Grade 2	1	6	.129
Grade 3b	0	2	.432
Ascites			
Grade 3a	1	8	.048
Lung infection			
Grade 2	0	3	.268
Pleural effusion			
Grade 3a	1	7	.079
Minor complication	24	88	< .001
Pain			.001
Grade 1	11	32	.001
Fever (temperature > 38.5 °C)			< .001
Grade 1	10	30	.002
Grade 2	0	4	.162
Ascites			
Grade 1	1	12	.006
Pleural effusion			
Grade 1	2	10	.004
Hospital stay*	5 (3–10)	11 (10–17)	< .001

Except where indicated, data values represent the number of patients

RFA radiofrequency ablation, PEI percutaneous ethanol injection, HR hepatic resection

*Data are the days of hospital stay. Numbers in parentheses are ranges

Our study revealed that RFA-PEI was safe with a low incidence of major complications (2.1%), which was similar to those reported previously (0–4.6%) [9, 10]. Moreover, RFA-PEI resulted in much fewer major complications and shorter hospital stay than those of HR. The average cost in the HR group was approximately 1.9 times higher than that in the RFA-PEI group, and RFA-PEI might be more emotionally acceptable for some patients because RFA-PEI was performed with local anaesthesia while HR with general anaesthesia. Therefore, RFA-PEI was superior to HR in terms of being less invasive, more cost-effective and in facilitating patients' fast recovery, which make RFA-PEI clinically preferable in the era of micro-invasive treatment.

Recently, combined RFA with traditional or drug-eluting beads TACE (RFA-TACE) has shown favourable efficacy for HCC [35–38]. Compared to RFA-TACE, RFA-PEI can be performed in the same session with lower cost, less effort and fewer adverse effects. Besides, microwave ablation (MWA), an increasingly popular technique, is able to create larger ablation zones and to overcome the heat-sink effect more effectively than RFA [39, 40]. Compared to MWA, RFA-PEI might be more suitable to treat tumours adjacent to

critical structures such as the subcapsular region and areas near large vessels or the gallbladder [9, 10]. However, since no study has been performed to compare RFA-PEI with RFA-TACE or MWA so far, this warrants future studies.

This multicentre retrospective study is the first investigation comparing RFA-PEI with HR in the treatment of solitary HCCs with diameter of 2.1–5.0 cm in the largest study population ever reported; however, there are limitations to our study. First, it is a retrospective study with all its inherent defects. Non-randomization regarding choices of treatment inevitably introduced selection bias. Second, our study was based on a cohort of mono-ethnic Chinese patients with hepatitis B viral infection as the predominant aetiology of HCC, and the results must be validated in other areas with different demographics and underlying causes of liver disease.

In conclusion, RFA-PEI is superior to HR in terms of long-term survival for patients with solitary HCCs with 2.1–3.0 cm in diameter whereas it provides comparable survival outcomes to HR for patients with HCCs with 3.1–5.0 cm in diameter. However, the results need to be validated in RCTs with a large sample size.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Ming Kuang.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors (Bin Li) has significant statistical expertise.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional review board approval was obtained.

Methodology

- retrospective
- observational
- multicentre study

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