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The risk factors for long-term survival outcome in solitary hepatocellular carcinoma up to 2 cm: Propensity score matching analysis in a population cohort with a high rate of HBV infection

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ABSTRACT

Background: The American Joint Committee on Cancer staging recently classified solitary hepatocellular carcinoma (HCC) ≤ 2 cm with or without vascular invasion as stage T1a. We aimed to discuss the risk factors of these stage T1a patients.

Methods: Patients diagnosed with solitary HCC ≤2 cm from September 2008 to June 2015 were included in our study. Due to the small number of patients undergoing a non-curable approach and liver transplantation, patients undergoing liver resection (LR) and radiofrequency ablation (RFA) were included. In the comparison between LR and RFA, 1:1 propensity score matching (PSM) was used. The overall survival (OS) and disease-free survival (DFS) were predicted, and the Cox proportional hazard model was used to find the prognostic factors, described as hazard ratio (HR) and 95% confidence interval (CI).

Results: In total, 273 HCC patients were involved in our study, of whom 192 patients underwent LR and 81 patients underwent RFA. The proportion of Child-Pugh A patients was higher in the LR group (91.7%) versus the RFA group (76.5%) (P = 0.001), and the tumour size was slightly larger in the LR group, with a median size of 1.9 cm versus 1.7 cm in the RFA group (P = 0.001). No difference was found in OS between LR and RFA. However, RFA was the only risk factor for recurrence (HR 1.578, 95% CI 1.006–2.467, P = 0.047). A total of 80 pairs were compared after PSM, and there was no significant difference in OS or DFS between LR and RFA after PSM (P = 0.5434 or P = 0.1642, respectively). Child-Pugh stage B was the only risk factor for OS in the multivariate analysis after PSM (HR 2.289, 95% CI 1.089–4.812, P = 0.029).

Conclusion: RFA was comparable with LR in treating solitary HCC up to 2 cm but with a higher risk for recurrence due to the imbalanced pre-operative covariates. When the pre-operative factors were consistent, liver function was the only prognostic factor for long-term OS.

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy in the liver, the fifth most common type of malignancy worldwide and the leading cause of cancer-related deaths globally [1,2]. Thanks to the vaccination and effective treatment for viral hepatitis, the incidence of HCC has slightly decreased in recent years [3]. Due to the high proportion of hepatitis B patients, HCC is still the fourth most common malignancy in China [4]. Despite the higher prevalence of HCC, surveillance programmes provide a better chance for a good outcome for cirrhosis patients diagnosed at an early stage of HCC, as early diagnosis is related to more optional treatment and better prognosis [5–7].

Due to the relationship between tumour stage and outcome, several staging systems are used for evaluating the HCC stage [8–10]. The American Joint Committee on Cancer (AJCC) staging system is one of the most famous staging systems for the management of cancer patients. In its 8th edition, solitary HCC ≤2 cm is regarded as stage T1a, regardless of whether the vasculature is involved [10]. However, the importance of vascular invasion (VI) in small-sized HCC is still controversial [11,12]. Another reliable method is the Barcelona Clinic Liver Cancer (BCLC) system, in which solitary HCC ≤ 2 cm, with satisfactory liver function and in the absence of vascular invasion or extrahepatic disease, is defined as very early-stage HCC [8]. However, for

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HCC patients who are deemed “too early”, liver transplantation (LT) is not recommended as a first-line treatment, and there are no exceptional points in the waiting list for grafts in Western countries [13]. Liver resection (LR) is the best choice for normal-portal-pressure HCC patients [8]. Radiofrequency ablation (RFA), as a local treatment for HCC, is also an optional curative treatment for small HCC. However, the impact of the treatment is still controversial compared to LR.

In our study, we retrospectively reviewed our single-centre data to assess the risk factors for solitary HCC up to 2 cm. Moreover, we used propensity score matching (PSM) analysis to compare the long-term outcome between LR and RFA, aiming to discuss the impact of RFA in treating very early HCC patients.

2. Materials and methods

This study was approved by the Ethics Committee and in accordance with the ethical guidelines of the Declaration of Helsinki. This study was conducted and reported based on STROCSS guidelines [14]. This retrospective study was registered in the Research Registry (UIN researchregistry2862).

2.1. Study design

We retrospectively analysed 4725 patients with newly diagnosed HCC from September 2008 to June 2015. All the patients who were first diagnosed with solitary HCC up to 2 cm were assessed. Patients suspected to have distant metastasis, lymph node metastasis or adjacent organ invasion were excluded. Patients with liver function at Child-Pugh stage C or incomplete clinical data were excluded from our present study. Due to the study design and the low numbers of patients undergoing transarterial chemoembolization (TACE), chemotherapy, radiotherapy and LT, we only included patients undergoing LR or RFA.

2.2. Diagnosis and treatment for HCC patients

HCC diagnosis was based on the Guidelines of Diagnosis and Treatment of HCC of China as previously reported [15,16]. Briefly, the diagnosis was based on two types of clinical imaging (ultrasound, enhanced CT or MRI), and a high serum level of α-fetoprotein (AFP) was also helpful for confirmation. All the images were evaluated, and the VI in imaging was assessed by two experienced radiologists independently. The pretreatment clinical data were collected when the patients were first diagnosed with HCC in our centre, including the aetiological history, laboratory blood examination, and imaging tumour characteristics. The indication for LR and RFA was reported in the previous study [17,18]. Generally, the selection of LR and RFA was determined mainly by the location of the tumour and the resident liver volume if LR was undergone, and both LR and RFA are regarded as curative approaches for treating HCCs in our centre. Platelets less than 100 000/μL was not regarded as a contraindication for LR unless the patients had a recent history of upper gastrointestinal bleeding due to portal hypertension.

2.3. AJCC cancer staging

All the patients were classified according to the 8th edition of the AJCC cancer staging guidelines [9,19]. In this latest version, for HCC, a solitary tumour ≤ 2 cm with/without VI is categorized into T1a. If the tumour is involved in the major branch of the portal vein or hepatic vein or with direct invasion of adjacent organs, it is categorized into T4. If the lymph nodes are assessed pre-operatively as having metastasis, they are categorized into N1. M1 is assigned if there is distant metastasis upon the first diagnosis of HCC. In our study, we only included HCC patients at stage T1a.

2.4. Follow-up and treatment

All the patients were followed up until December 2017. The follow-up data were routinely collected in the outpatient clinic. Blood tests, including liver function and serum AFP, and ultrasound were performed every three months after treatment. The OS was defined as the time from first treatment to the date of the last follow-up. DFS was defined as the time from the date of curative treatment until recurrence or death (by any cause).

2.5. Statistical analysis

All the demographic and clinical data were retrospectively collected in the database, and all the patients were prospectively followed up. Categorical variables are expressed as counts, and continuous variables are described as median and interquartile range (IQR). In the comparison between the LR and RFA groups, the chi-square test was used for categorical variables, and the Mann-Whitney *U* test was used for continuous variables. To adjust the balance of variables in patients treated with LR and RFA, logistic regression was undertaken to calculate the propensity score using pre-operative imbalanced characteristics as covariables. The nearest available neighbour matching within a calliper of 0.10 was used for 1:1 PSM. Survival outcomes were analysed by the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazard model to acquire the prognostic factors for survival (both OS and DFS), which are described as hazard ratio (HR) and 95% confidence interval (CI). In multivariable analyses, we used forward stepwise selection containing covariates with $p < 0.05$ in univariate regression. All the statistical analyses were performed with Stata version 15 (StataCorp, College Station, TX). A P value < 0.05 was considered to be statistically significant for all the analyses.

3. Result

3.1. Characteristics and survival analysis in patients treated with LR and RFA

In the study period, 412 patients were first diagnosed with solitary HCC up to 2 cm, of whom 19 patients having a Child-Pugh C liver function, 11 patients lacking clinical data, 34 patients suspected to have metastasis or adjacent organ invasion, and 75 patients undergoing other therapy were excluded from our study. Finally, 273 patients diagnosed with T1a stage undergoing LR or RFA were included in our study, including 192 patients undergoing LR and 81 patients undergoing RFA.

The characteristics of T1a HCC patients undergoing LR and RFA are described in Table 1. The median total bilirubin was slightly higher in the RFA group than in the LR group (P = 0.033), while the albumin was higher in the LR group than in the RFA group (P = 0.020). The proportion of Child-Pugh A patients was higher in the LR group (91.7%) versus the RFA group (76.5%) (P = 0.001). In addition, the tumour size was slightly larger in the LR group, with a median size of 1.9 cm versus 1.7 cm in the RFA group (P = 0.001). In the LR group, there were 101 patients (52.3%) undergoing anatomical LR, while 81 patients (42.7%) underwent non-anatomical LR.

The OS and DFS are summarized in Fig. 1. The median follow-up time was 27 months, and the 5-year OS rates for LR and RFA were 79.32% and 68.84%, respectively. There was no significant difference between LR and RFA (P = 0.1891, Fig. 1A). The 1-, 3- and 5-year DFS rates were higher in the LR group versus the RFA group (84.45%, 67.08% and 59.65% versus 68.80%, 56.95% and 50.43%, respectively, P = 0.0438, Fig. 1B). Within the LR group, there were no significant between the in anatomical LR and non-anatomical LR subgroups in terms of OS (P = 0.4016), while anatomical LR provided a slightly higher DFS than non-anatomical LR, though without a significant difference (P = 0.0742) (Supplement Fig. 1).

Table 1
Comparison of characteristics in solitary HCC up to 2 cm treating with liver resection and radiofrequency ablation.

	LR (n = 192)	RFA (n = 81)	P value
Age, year[a]	52 (42–60)	52 (45–62)	0.926
BMI[a]	22.5 (20.2–25.7)	23.0 (21.5–25.0)	0.392
Sex, male, %	158 (82.3)	65 (80.2)	0.690
HBV infection history, %	177 (92.2)	75 (92.6)	0.909
Drinking alcohol hobby, %	73 (38.0)	30 (37.0)	0.878
Platelets, 100 000/μL[a]	109 (83–153)	107 (62–148)	0.789
Total bilirubin, umol/L[a]	14 [11–18]	16 [12–26]	0.033
Albumin, g/L[a]	42 (39–47)	40 (35–42)	0.020
AST, U/L[a]	34 (27–53)	36 (27–61)	0.588
ALT, U/L[a]	41 (27–70)	38 (25–56)	0.109
PT, seconds[a]	12 [11–13]	12 [11–13]	0.390
Child-Pugh stage A, %	176 (91.7)	62 (76.5)	0.001
AFP, ng/ml[a]	11 (4–349)	33 (6–348)	0.104
Tumor size, cm[a]	1.9 (1.5–2.0)	1.7 (1.5–2.0)	0.001
Vascular invasion, %	9 (4.7)	5 (6.2)	0.611

Abbreviation: HBV = hepatitis B virus; BMI = Body mass index; AFP = α-Fetoprotein; AST = aspartic aminotransferase; ALT = alanine aminotransferase; PT = prothrombin time; LR = liver resection; RFA = radiofrequency ablation.
[a] Statistical description using median and interquartile.

In the univariate analysis, Child-Pugh stage B and AFP ≥400 ng/ml were the significant risk factors for OS (P = 0.019 and P = 0.032, Table 2). After combining the covariates in univariate analysis, Child-Pugh stage B (HR 2.401, 95% CI 1.204–4.786, P = 0.013) and AFP ≥400 ng/ml (HR 2.092, 95% CI 1.123–3.895, P = 0.020) were still the risk factors for OS in the multivariate analysis. However, in terms of DFS, in both the univariate and multivariate analyses, RFA was the only risk factor for recurrence (HR 1.578, 95% CI 1.006–2.467, P = 0.047, Table 2).

3.2. Propensity score matching analysis

Because an imbalance existed in the comparison between the LR group and RFA group, we used the PSM to adjust the pre-operative covariates (Child-Pugh stage, total bilirubin, albumin, and tumour size) and calculated the propensity score. The comparison of the characteristics of PSM between the two treatments is described in Table 3. There were a total of 80 pairs (160 patients) involved after PSM, and no significant difference was found in pre-operative variables.

There was no significant difference in OS or DFS between LR and RFA after PSM (P = 0.5434 or P = 0.1642, respectively, Fig. 2). Child-Pugh stage B was the only risk factor for OS in the multivariate analysis after PSM (HR 2.289, 95% CI 1.089–4.812, P = 0.029, Table 4), while no significant variables were found in association with DFS after PSM (Table 4).

3.3. Subgroup analysis

In all 273 patients, there was no significant difference in OS between LR and RFA in the macrovascular invasion–positive patients (P = 0.0575) or in the macrovascular invasion–negative patients (P = 0.0652) (Supplement Fig. 2). The patients undergoing LR had a better DFS than RFA in macrovascular invasion–negative patients (P = 0.0111). No significant difference was found in OS between the two treatments in the subgroup with Child-Pugh stage A (P = 0.0512) or with Child-Pugh stage B (P = 0.0856). The patients undergoing LR had a better DFS than RFA among Child-Pugh stage A patients (P = 0.0140). Moreover, no significant difference was found in OS or DFS between the two treatments in terms of AFP, albumin or platelets (all P > 0.05).

In the 160 patients after PSM, no significant difference was found in OS or DFS between the two treatments in the macrovascular invasion–positive patients (P = 0.1838 and P = 0.0509) or macrovascular invasion–positive patients (P = 0.0575 and P = 0.0784) (Supplement Fig. 3). Moreover, no significant difference was found in OS between the two treatments in the subgroup with Child-Pugh stage A (P = 0.0642) or Child-Pugh stage B (P = 0.0593). The patients undergoing LR had a better DFS than RFA among Child-Pugh stage A patients (P = 0.0186).

4. Discussion

This is a retrospective study using single-centre data to assess the risk factors for solitary HCC up to 2 cm, and in our results, patients undergoing RFA had a higher recurrence rate compared to LR when pre-operative imbalanced covariates were present. We demonstrated that liver function always had a crucial role in predicting the OS rate both before and after PSM when comparing LR and RFA. When the pre-operative indicators were fully matched, patients treated with RFA had the same DFS rate as LR. However, for patients without macrovascular invasion or Child-Pugh stage A liver function, RFA might be associated with a higher recurrence rate compared to LR.

The debate between RFA and LR still exists due to the lack of randomized controlled trials focussing on very early-stage patients. In the BCLC guidelines, patients diagnosed with solitary HCC ≤2 cm with normal portal pressure should be treated with LR [8]. However, in HCC patients with cirrhotic liver disease, portal hypertension is quite common, and it may be the main contraindication for LR due to post-operative hepatic decompensation [20]. In such cases, RFA would be an optional treatment for those patients. In addition, as a local and less invasive treatment, it is usually considered a bridging therapy for LT. A

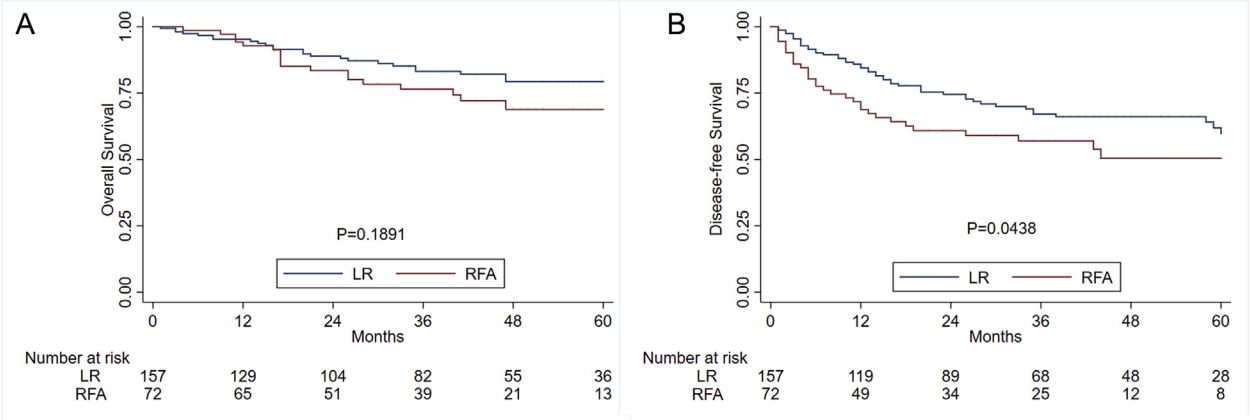

Fig. 1. The comparison of overall survival curves (A) and disease-free survival curves (B) between LR and RFA before propensity score matching analysis.

Table 2
Univariate and multivariate Cox regression analysis for overall survival and disease-free survival in solitary HCC up to 2 cm treating with liver resection and radiofrequency ablation.

	Overall Survival			Disease-free Survival		
	HR	95% CI	P value	HR	95% CI	P value
Univariate analysis						
Treatment, RFA vs LR	1.494	0.815–2.741	0.194	1.578	1.006–2.476	0.047
Age, ≥55 vs < 55 years	1.046	0.574–1.906	0.882	1.138	0.734–1.763	0.565
BMI	1.029	0.896–1.182	0.680	1.059	0.962–1.166	0.242
Sex, male vs female	0.698	0.344–1.417	0.320	0.834	0.488–1.426	0.508
HBV infection history, yes vs no	1.324	0.319–5.484	0.698	0.652	0.313–1.356	0.253
Drinking alcohol hobby, yes vs no	1.171	0.635–2.160	0.612	1.393	0.893–2.172	0.143
Platelets, $\geq 10^5$ vs < 10^5/uL	1.227	0.666–2.263	0.511	1.341	0.852–2.109	0.205
Total bilirubin, ≥28 vs < 28 μmol/L	2.058	0.986–4.295	0.055	1.294	0.799–2.391	0.411
Albumin, ≥40 vs < 40 g/L	0.952	0.516–1.756	0.874	1.204	0.754–1.923	0.437
AST, ≥50 vs < 50 U/L	1.196	0.735–1.947	0.471	0.785	0.506–1.219	0.281
ALT, ≥40 vs < 40 U/L	1.382	0.754–2.534	0.295	0.866	0.555–1.353	0.528
Child-Pugh stage, B vs A	2.276	1.146–4.521	0.019	1.534	0.874–2.691	0.136
AFP, ≥400 vs < 400 ng/ml	1.967	1.060–3.652	0.032	1.288	0.786–2.110	0.315
Tumor size	0.932	0.388–2.240	0.876	1.015	0.521–1.977	0.965
Vascular invasion, yes vs no	2.286	0.705–7.405	0.168	0.996	0.314–3.158	0.994
Multivariate analysis						
Child-Pugh stage, B vs A	2.401	1.204–4.786	0.013	–	–	–
AFP, ≥400 vs < 400 ng/ml	2.092	1.123–3.895	0.020	–	–	–
Treatment, RFA vs LR	–	–	–	1.578	1.006–2.476	0.047

Abbreviation: HBV = hepatitis B virus; BMI = Body mass index; AFP = α-Fetoprotein; AST = aspartic aminotransferase; ALT = alanine aminotransferase; LR = liver resection; RFA = radiofrequency ablation; HR = hazard ratio; CI = confidence interval; PSM = propensity score matching.
†statistical description using median and interquartile.

Table 3
Comparison of characteristics in solitary HCC up to 2 cm treating with liver resection and radiofrequency ablation after propensity matching.

	After matching		
	LR (n = 80)	RFA (n = 80)	P value
Age, year[a]	56 (41–62)	52 (44–62)	0.635
BMI[a]	22.3 (20.2–24.2)	23.0 (21.5–25.0)	0.144
Sex, male, %	66 (82.5)	64 (80.0)	0.685
HBV infection history, %	74 (92.5)	74 (92.5)	1.000
Drinking alcohol hobby, %	36 (45.0)	29 (36.3)	0.260
Platelets, 100 000/μL[a]	109 (71–156)	107 (60–148)	0.750
Total bilirubin, umol/L[a]	14 [11–18]	16 [12–23]	0.096
Albumin, g/L[a]	40 (38–43)	40 (35–43)	0.936
AST, U/L[a]	36 (28–58)	36 (27–61)	0.874
ALT, U/L[a]	41 (27–72)	38 (25–56)	0.268
PT, seconds[a]	12 [11–13]	12 [11–13]	0.823
Child-Pugh stage A, %	66 (82.5)	62 (77.5)	0.429
AFP, ng/ml[a]	17 (3–378)	34 (6–348)	0.934
Tumor size, cm[a]	1.8 (1.5–2.0)	1.7 (1.5–2.0)	0.206
Vascular invasion, %	8 (10.0)	5 (6.2)	0.385

Abbreviation: HBV = hepatitis B virus; BMI = Body mass index; AFP = α-Fetoprotein; AST = aspartic aminotransferase; ALT = alanine aminotransferase; PT = prothrombin time; LR = liver resection; RFA = radiofrequency ablation.
[a] Statistical description using median and interquartile.

few studies demonstrated that the DFS was better in the LR group than in the RFA group [21–23], and Wang et al. also demonstrated that LR achieved a better OS than RFA [23]. However, in another four studies, there was no significant difference between treatment groups in OS or DFS [24–28]. It is worth mentioning that the main reason for the occurrence of HCC in our country is HBV infection, and thus, the percentage of HBV patients in our study was more than 90%, which might not be generalizable to Western countries. However, until now, there have been no reports comparing LR and RFA in patients with solitary HCC ≤2 cm in Western countries. Future studies need to be undertaken to understand the outcome of T1a tumours in different pathogenetic situations. In our study, the OS rate was comparable between the two treatments. However, T1a stage HCC patients treated with RFA had a worse DFS compared to LR patients, but with a higher percentage of Child-Pugh stage A patients and a slightly smaller tumour size. To balance the covariates existing when we compared to the two treatments, we used the PSM method to decrease the intergroup bias. After PSM and when the intergroup covariates were balanced, there was no significant difference in the DFS rate.

Liver function was another crucial role affecting the outcome of HCC patients. According to the most recent BCLC classification guidelines, end-stage liver function includes both Child-Pugh stages B and C, which means that patients without Child-Pugh A liver function should be treated with the best supportive care to improve the quality of human life rather than to cure the disease itself. Additionally, some experts have stated that patients undergoing LT combined with HCC and Child-Pugh C liver function had worse short-term and long-term outcomes. However, for patients diagnosed with Child-Pugh B liver function, there was still a contradiction in treatments recommended. In the previous BCLC classification guidelines, patients with Child-Pugh B liver function could be treated like Child-Pugh A liver function patients [8,29]. Moreover, some studies showed that Child-Pugh classification might not be the best index to assess the patients' outcome since the "five indexes" have their own weight in the determination of treatment [30,31]. For example, ascites was usually thought to be an absolute contraindication for liver resection, while slight ALB decreases were not. In our study, we demonstrate that the patients with Child-Pugh B liver function had a worse survival outcome than those with Child-Pugh A liver function, but they lived more than 3 months, which the BCLC classification predicts. Thus, patients in Child-Pugh stage B are still a topic worthy of discussing.

In our study, we included the patients with vascular invasion in imaging, which was regarded as stage T1a, which means may have the same outcome compared to those without VI according to AJCC 8th edition [9]. Generally, the proportion of microvascular invasion will increase according to the tumour size, and the rate of VI varied from 14.4% to 28.8% in previous studies [11,32]. However, the impact of VI is still controversial. Yamashita et al. conducted a study to assess the effect of VI in very early-stage cohorts and found that the DFS in the positive-VI group was significantly worse than that in the negative-VI group [11]. However, another multicentre study with 155 patients with

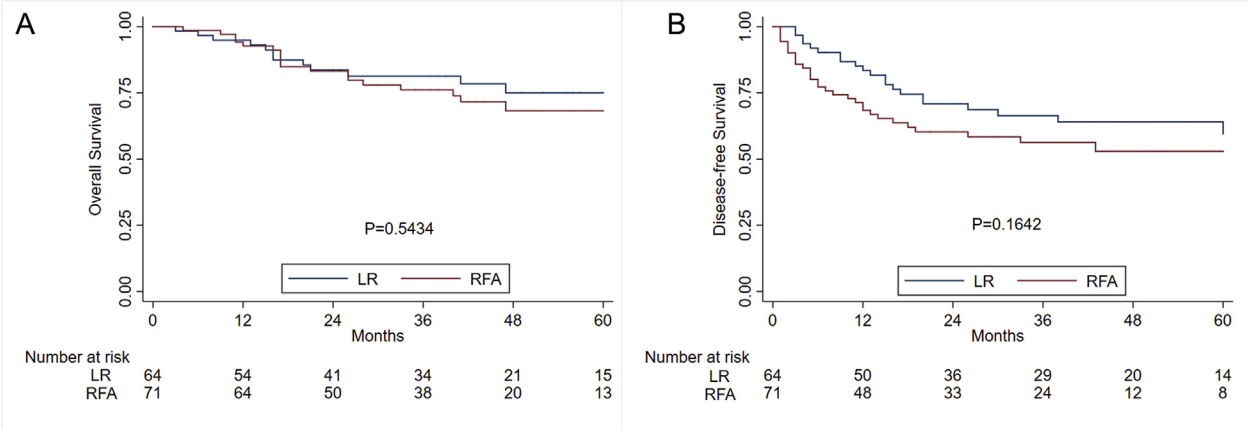

Fig. 2. The comparison of overall survival curves (A) and disease-free survival curves (B) between LR and RFA after propensity matching analysis.

solitary HCC less than 2 cm showed that VI would not be considered a risk factor for the OS rate [12]. In our study, we assessed vascular invasion on imaging and found that VI was not a risk factor for OS. However, we found that RFA still increased the risk of recurrence in the VI-negative group before PSM, which could be related to the larger margin in the LR group and the resulting decrease in the rate of local recurrence. Nevertheless, studies focussing on the impact of VI either in imaging or in a histological report on very early HCCs are still insufficient, and larger cohort studies need to be done to verify the staging.

There are some limitations to our study. For the intention-to-treat study, there were not many patients who underwent LT, so we cannot compare their outcomes with outcomes after other curative treatments. The bias inherent to a retrospective, single-centre study and selection bias could not be avoided completely, even though the PSM method was used to avoid intergroup bias.

5. Conclusion

RFA is comparable with LR in treating solitary HCC up to 2 cm but with a higher risk for recurrence due to the imbalanced pre-operative covariates. When the pre-operative factors were consistent, liver function was the only prognostic factor for long-term OS.

Ethical approval

This study was approved by the West China Hospital Ethics Committee (2019/22), and in accordance with the ethical guidelines of the Declaration of Helsinki.

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Author contribution

Conception and design: Guoliang Wang, Wei Zhang, Li Jiang, Lunan Yan, Jiayin Yang.

Collection and assembly of clinical data: Li Jiang, Jian Yang, Lunan Yan, Jiayin Yang.

Data analysis and interpretation: Guoliang Wang, Wei Zhang and

Table 4
Univariate and multivariate Cox regression analysis for overall survival and disease-free survival in solitary HCC up to 2 cm treating with liver resection and radiofrequency ablation after propensity matching.

	Overall Survival			Disease-free Survival		
	HR	95% CI	P value	HR	95% CI	P value
Univariate analysis						
Treatment, RFA vs LR	1.252	0.603–2.601	0.547	1.478	0.846–2.584	0.170
Age, ≥55 vs < 55 years	1.243	0.607–2.550	0.552	0.934	0.539–1.618	0.808
BMI	0.994	0.817–1.208	0.949	1.005	0.890–1.136	0.927
Sex, male vs female	0.520	0.238–1.136	0.101	0.912	0.468–1.778	0.787
HBV infection history, yes vs no	0.847	0.201–3.567	0.821	0.897	0.322–2.495	0.834
Drinking alcohol hobby, yes vs no	0.923	0.439–1.942	0.834	1.330	0.765–2.310	0.312
Platelets, $\geq 10^5$ vs $< 10^5$/uL	1.154	0.560–2.378	0.697	1.058	0.610–1.837	0.841
Total bilirubin, ≥28 vs < 28 μmol/L	1.939	0.887–4.236	0.097	1.138	0.584–2.220	0.704
Albumin, ≥40 vs < 40 g/L	1.196	0.584–2.454	0.624	1.468	0.840–2.565	0.178
AST, ≥50 vs < 50 U/L	1.423	0.794–2.549	0.236	0.984	0.568–1.706	0.954
ALT, ≥40 vs < 40 U/L	1.821	0.877–3.783	0.108	0.934	0.539–1.618	0.808
Child-Pugh stage, B vs A	2.289	1.089–4.812	0.029	1.492	0.806–2.761	0.203
AFP, ≥400 vs < 400 ng/ml	1.733	0.811–3.704	0.156	1.478	0.809–2.700	0.204
Tumor size	0.985	0.364–2.663	0.976	1.343	0.584–3.092	0.487
Vascular invasion, yes vs no	1.932	0.585–6.383	0.280	0.871	0.271–2.798	0.817
Multivariate analysis						
Child-Pugh stage, B vs A	2.289	1.089–4.812	0.029	–	–	–

Abbreviation: HBV = hepatitis B virus; BMI = Body mass index; AFP = α-Fetoprotein; AST = aspartic aminotransferase; ALT = alanine aminotransferase; LR = liver resection; RFA = radiofrequency ablation; HR = hazard ratio; CI = confidence interval; PSM = propensity score matching.
†statistical description using median and interquartile.

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Manuscript writing: Guoliang Wang and Wei Zhang.

Final approval of manuscript: all authors.

Conflicts of interest

No conflict of interests existed in this study.

Research registration number

1. Name of the registry:
Research Registry.
2. Unique Identifying number or registration ID: researchregistry2862.
3. Hyperlink to the registration (must be publicly accessible): https://www.researchregistry.com.

Guarantor

Jiayin Yang.

Provenance and peer review

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Data statement

The research protocols used in this research were approved by the ethics committee of the West China Hospital of Sichuan University, Chengdu, Sichuan Province, China [IRB Protocol #2019–22].

CRediT authorship contribution statement

Guoliang Wang: Conceptualization, Data curation, Formal analysis, Software, Writing - original draft, Writing - review & editing. **Wei Zhang:** Conceptualization, Data curation, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. **Yifei Tan:** Formal analysis, Methodology. **Li Jiang:** Conceptualization, Data curation, Funding acquisition. **Jiayin Yang:** Conceptualization, Data curation, Funding acquisition, Investigation, Project administration, Resources, Supervision. **Lunan Yan:** Conceptualization, Data curation.

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Appendix A. Supplementary data

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