Comparison of the efficacy of radiofrequency ablation vs. liver resection in the treatment of hepatocellular carcinoma within Milan criteria with severe fibrosis

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Research Article

Keywords: Early hepatocellular carcinoma, Severe fibrosis, Radiofrequency ablation, Liver resection, Efficacy

Posted Date: November 30th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1103664/v1

Abstract

Background

The efficacy of RFA in the treatment of HCC with severe fibrosis is still unclear. The objective of this study is to compare the efficacy of RFA with liver resection in the treatment of HCC within Milan criteria.

Methods

The data used in the study were from the SEER database. Patients with HCC within Milan criteria were included in the study. A total of 1432 patients were included in the study; among them, 1038 patients received RFA, and 394 patients received liver resection. Propensity score matching (PSM) was used to reduce selection bias.

Results

Before PSM, the median overall survival (mOS) and median cancer-specific survival (mCSS) in the resection group were longer than the mOS and mCSS in the RFA group. However, the8re were no statistically significant differences in mOS or mCSS between the two groups (both P>0.05). After PSM, similar results were presented, and the mOS and mCSS in the resection group were similar to those in the RFA group (both P>0.05). The multivariable Cox regression analysis showed that RFA did not increase the all-cause mortality risk and cancer-specific mortality risk compared with resection before PSM. In the competing risk analysis, after excluding the potential factors that might influence the outcomes, RFA still did not increase the mortality risk compared with resection before PSM and after PSM. In the subgroup analysis. The efficacy of RFA is comparable to that of resection in patients with tumor sizes no more than 3 cm before PSM and after PSM.

Conclusion

The efficacy of RFA is similar to that of resection in the treatment of early HCC patients with severe fibrosis, especially in patients with tumor sizes no more than 3 cm.

Introduction

Liver cancer is one of the most common and fatal cancers worldwide[1]. The incidence of liver cancer is increasing every year. It is estimated that more than 100,0000 individuals will be diagnosed with liver cancer every year by 2025[2]. In USA, there are 42230 new cases of liver cancer in 2021[3]. In all patients with liver cancer, 90% of them are diagnosed with hepatocellular carcinoma (HCC)[2]. For intermediate to advanced HCC, many types of treatments have been used, such as transarterial chemoembolization (TACE) or tyrosine kinase inhibitors. However, for early HCC patients, radical treatments (liver resection and transplantation) are the first-line treatments[4]. Recently, the guidelines have recommended radiofrequency ablation (RFA) as a possible first choice for patients with a single HCC of no more than 2

cm based on several high-quality studies[4–6]. These studies have caused RFA to be more widely used in the treatment of HCC instead of being reserved for adjuvant therapy for HCC as in the past[7–10].

Liver resection is one of the most commonly used treatments for early cancer due to its high 5-year survival rate[11]. In some patients with severe fibrosis or cirrhosis, it is not suitable because liver resection can lead to liver failure after the operation[12, 13]. The most common cause of HCC is viral infection (HBV, HCV, etc.)[2]. In recent decades, an increasing number of patients with HCC have been diagnosed with nonalcoholic fatty liver disease[14]. All of these causes can lead to liver cirrhosis. Although only <3% of patients with cirrhosis develop liver cancer every year, more than 90% of patients with HCC have cirrhosis[15]. For these patients with early HCC, liver resection might not be suitable. Other treatments are necessary for these patients.

RFA has been used for the treatment of intermediate to advanced HCC combined with TACE or sorafenib and it obtained good efficacy[16–19]. However, it has been recommended as the first-line treatment of very early HCC because patients could obtain comparable survival benefits from RFA as from liver resection[4]. The mechanism of RFA killing tumor cells is heating of local tumor tissue, and the high temperature can kill tumor cells. The benefits of RFA for treatment involve its non-invasive nature in comparison to liver resection.

Whether early HCC patients with severe fibrosis or cirrhosis could obtain similar survival benefits from RFA compared with liver resection is still unclear. This study was conducted to compare its efficacy to surgery for HCC patients within the Milan criteria and with severe fibrosis or cirrhosis.

Materials And Methods

Patient selection

The data used in the study were from the Surveillance, Epidemiology, and End Results (SEER) database and were extracted by SEER*Stat software. The SEER database covers approximately 28% of the US population and collects millions of patients with different types of cancers. The study was conducted in accordance with the Declaration of Helsinki. This study was approved by the ethics committee board of the institution. The informed consent of the patient was waived by the board because the data of the patients used in the study were from the population database.

The inclusion criteria were as follows: (1) patients were diagnosed with HCC from 2004 to 2014 (ICD-O-3 histology/behavior, malignant: 8170/3-8175/3); (2) patients received RFA or liver resection; (3) the tumor stage of the patients was within the Milan criteria; and (4) the patients had severe fibrosis or cirrhosis (fibrosis scores 5-6).

The exclusion criteria were as follows: (1) the tumor size of the patients could not be evaluated (code 0 or code 998 or code 999); (2) patients with fibrosis scores 0-4 or their scores were not evaluated (code 0 or

code 988 or code 999); and (3) the survival time of the patients could not be evaluated (code 0 or code 999) (Figure 1).

The Endpoints Of The Study And Their Definitions

The endpoints of the study were overall survival (OS) and cancer-specific survival (CSS). OS was defined as the interval from the diagnosis of HCC to the death of patients caused by all reasons. CSS was defined as the interval from the diagnosis to the deaths of patients caused by the tumors (reference).

Statistical analysis

All variables included in the study were categorical variables. Categorical variables were compared by the chi-square test or Fisher's precision probability test. The survival curves were plotted by Kaplan–Meier methods and compared by the log-rank test between the two groups. A Cox regression model was used to predict the variables that might influence the results in all patients. An adjusted Cox regression model was used in the subgroup analysis, and the adjusted variables were age at diagnosis, year of diagnosis, race, sex, grade of tumor, summary stage, AJCC stage, radiotherapy, chemotherapy, AFP, and marital status.

To reduce selection bias, 1:2 nearest neighbor propensity score matching (PSM) was used. All variables were included in the PSM analysis. The optimal caliper was set as 0.02. Finally, 647 patients were generated after PSM; among them, 376 patients received RFA, and 271 patients received liver resection. Patients with older age had a higher mortality risk caused by other reasons (not cancers). Thus, the competing risk was used in this study. The competing variable was the deaths caused by other reasons (not the tumor). A P value <0.05 was considered a statistically significant difference. All statistical analyses were evaluated by SPSS 26.0 and R 3.6.2.

Results

Patients

In this study, a total of 1432 patients were included based on the inclusion and exclusion criteria. Among them, 1038 patients received RFA, and 394 patients received liver resection. There were 595 patients aged more than 60 years in the RFA group and 224 patients aged more than 60 years in the liver resection group. In the RFA group, 12 patients received radiotherapy, and 304 patients received chemotherapy. In the liver resection group, 8 patients received radiotherapy, and 40 patients received chemotherapy (**Table 1**).

Survival outcomes in all patients

Before PSM, the mOS and mCSS in the RFA group were 44 months (95% CI: 39.9-48.1 months) and 55 months (95% CI: 46.3-63.7 months). In the liver resection group, the mOS and mCSS were 51 months

(95% CI: 44.9-57.1 months) and 61 months (95% CI: 52-70), respectively. There were no statistically significant differences in mOS (P=0.109) or mCSS (P=0.592) between the two groups (**Figure 2**). After PSM, similar results were presented, and there were no statistically significant differences in mOS (42 months, 95% CI: 34.9-49.1 months; vs. 57 months, 95% CI: 47.4-66.6 months; P=0.052) or mCSS (56 months, 95% CI: 46-66 months; vs. 65 months, 95% CI: 52.2-77.8 months; P=0.351) between the RFA group and the liver resection group (**Figure 3**).

Predictors for OS and CSS

In the multivariable Cox regression analysis, the results showed that RFA did not increase the all-cause mortality risk (HR: 1.172, 95% CI: 0.971-1.416; P=0.098) or the cancer-specific mortality risk (HR: 1.058, 95% CI: 0.847-1.351; P=0.569) compared with liver resection for HCC patients with the Milan criteria (**Table 2).**

In the competing risk analysis, after excluding the factor of age that might influence the outcomes, RFA still did not increase the mortality risk (HR: 1.021, 95% CI: 0.807-1.291; P=0.862) compared with liver resection in the treatment of patients with HCC within the Milan criteria before PSM. After PSM, similar results were presented (HR: 1.044, 95% CI: 0.807-1.352; P=0.742) (**Table 3**).

Subgroup analysis

Before PSM, there was no statistically significant difference in mOS (84 months, 95% CI: 57.8-110.2 months; vs. 66 months, 95% CI: 51.8-80.2 months; P=0.881) or mCSS (108 months, 95% CI: 77.8-138.2 months; vs. 75 months, 95% CI: 57.9-92.1 months; P=0.697) in the patients with a single HCC of no more than 2 cm between the RFA and liver resection treatments. In patients with a single HCC 2-3 cm, the mOS (49 months, 95% CI: 42.3-55.7 months; vs. 47 months, 95% CI: 35.5-59.5 months; P=0.835) and mCSS (56 months, 95% CI: 42.7-69.3 months; vs. 51 months, 95% CI: 40-67 months; P=0.638) in the patients with RFA were not significantly longer than those in the patients with liver resection. In the patients with a single tumor 3-5 cm, the mOS (27 months, 95% CI: 23.1-30.9 months; vs. 45 months, 95% CI: 35.2-54.8 months; P<0.001) and mCSS (31 months, 95% CI: 26.6-35.4 months; vs. 49 months, 95% CI: 36.2-61.8 months; P=0.001) in the patients with RFA were significantly shorter than those in the patients with liver resection. In the patients with 2-3 HCC no more than 3 cm, the mOS (43 months, 95% CI: 36.7-49.3 months) in the RFA group was significantly shorter than the mOS (64 months, 95% CI: 46.5-81.5 months; P=0.03) in the liver resection group. However, there was no statistically significant difference in mCSS (81 months, 95% CI: 44.2-117.8 months; vs. NA; P=0.425) between the RFA group and liver resection group (**Supplementary Figure 1**).

After PSM, there was no statistically significant difference in mOS (108 months, 95% CI: 43.1-172.9 months; vs. 66 months, 95% CI: 49.9-82.1 months; P=0.966) or mCSS (108 months, 95% CI: 34.6-181.4 months; vs. 75 months, 95% CI: 59.1-90.9 months; P=0.601) in the patients with a single HCC no more than 2 cm between the RFA and liver resection treatments. In patients with a single HCC 2-3 cm, the mOS (42 months, 95% CI: 28.5-55.5 months; vs. 39 months, 95% CI: 25.6-52.4 months; P=0.644) and mCSS (56

months, 95% CI: 26.1-85.9 months; vs. 49 months, 95% CI: 25.9-72.1 months; P=0.486) in the patients with RFA were not significantly longer than in the patients with liver resection. In the patients with a single tumor 3-5 cm, the mOS (34 months, 95% CI: 27.2-40.8 months; vs. 52 months, 95% CI: 37.7-66.3 months; P=0.033) in the patients with RFA was significantly shorter than that in the patients with liver resection. However, the mCSS (35 months, 95% CI: 25.1-44.9 months) in the patients with RFA was not significantly shorter than the mCSS (72 months, 95% CI: 39.7-104.3 months; P=0.051) in the patients with liver resection. In the patients with a 2-3 HCC no more than 3 cm, the mOS (40 months, 95% CI: 28.9-51.1 months) in the RFA group was significantly shorter than the mOS (68 months, 95% CI: 37.9-98.1 months; P=0.011) in the liver resection group. However, there was no statistically significant difference in mCSS (81 months, 95% CI: 37.3-124.7 months; vs. NA; P=0.302) between the RFA group and the liver resection group **(Supplementary Figure 2**).

Before PSM, after adjusting for age at diagnosis, sex, year of diagnosis, race, grade of tumor, summary stage, AJCC stage, radiotherapy, chemotherapy, AFP, and marital status, RFA did not increase the all-cause mortality risk (HR: 1.178, 95% CI: 0.688-2.018; P=0.551) or the cancer-specific mortality risk (HR: 1.171, 95% CI: 0.617-2.221; P=0.629) compared with liver resection in patients with a single HCC of no more than 2 cm. In patients with HCC 2-3 cm, RFA did not increase the all-cause mortality risk (HR: 0.875, 95% CI: 0.626-1.224; P=0.435) or cancer-specific risk (HR: 0.830, 95% CI: 0.562-1.228; P=0.352) compared with liver resection. However, in the patients with a single HCC 3-5 cm, RFA did increase the all-cause mortality risk (1.443, 95% CI: 1.055-1.972; P=0.022) and cancer-specific risk (1.448, 95% CI: 1.038-2.133; P=0.031) compared with liver resection. In the patients with a 2-3 HCC 2-3 cm, RFA did not increase the all-cause mortality risk (HR: 1.596, 95% CI: 0.88602.875; P=0.120) or the cancer-specific risk compared with liver resection (P=0.224) (**Table 4**).

Discussion

RFA is the most widely used local treatment for HCC[20, 21]. Previous studies have shown the efficacy of RFA in the treatment of different stages of HCC[5, 22–24]. However, few studies have focused on patients with severe fibrosis or cirrhosis. This study was conducted to explore whether HCC patients within the Milan criteria who had severe fibrosis or cirrhosis could obtain comparable survival benefits from RFA to liver resection.

The main findings of the study were that patients within the Milan criteria could obtain comparable survival benefits from RFA and liver resection. Patients with severe fibrosis or cirrhosis often have poor liver function, which might be the reason why these patients who received liver resection had more severe adverse events than RFA. The most severe adverse event is liver failure, which might be a reason for patient death after receiving liver resection.

Previous studies focused on the comparison of RFA with liver resection in the treatment of very early or early HCC but did not take fibrosis into account. Some studies have presented comparable results of RFA compared with liver resection[6, 8, 9]. However, only patients with a single HCC less than 2 cm are

recommended to receive RFA as the first-line treatment by the guidelines because of the small sample size in some studies[4]. In the current study, a large sample of patients (1432 patients) with severe fibrosis was included, and PSM was used to reduce the selection bias. The results indicate that patients within the Milan criteria could obtain survival benefits from RFA compared with liver resection. The OS in the current study was slightly shorter than that in previous studies because most of the studies included patients with tumor sizes no more than 3 cm[7, 25]. Another study included patients within the Milan criteria and compared the efficacy of these patients with RFA with patients with liver resection. The mOS of the patients with RAF and liver resection were more than 48 months and 60 months, respectively, which were longer than the mOS generated in the current study[25]. This might be the reason why they included 61.7% patients with cirrhosis (65.2% patients with cirrhosis in the liver resection group, 58.2% patients with cirrhosis in the RFA group), but in the current study, all patients included had severe fibrosis or cirrhosis. Multivariable Cox regression was conducted because the sample was so large that univariable Cox regression could not be conducted. After excluding potential factors that might influence the comparison results, RFA did not increase all-cause mortality risk or cancer-specific mortality risk compared with liver resection. In this study, more than 57% of patients were older than 60 years. The older they were, the more likely they were to die from non-cancer reasons. Thus, noncancer-specific death was considered a competing risk factor. After excluding this potential factor that might influence the outcomes of the patients, RFA still did not increase the mortality risk compared with liver resection. These results mean that patients achieved comparable survival benefits from RFA and liver resection.

There are many factors that affect the survival prognosis of patients with early HCC. The guidelines recommend that patients receive the most suitable treatments based on the tumor size, tumor number, liver function, and physical condition[4]. Previous studies have shown that patients with small tumor and single tumor might obtain more survival benefits than larger tumor or multiple tumors[26–30]. Thus, patients with different tumor sizes and tumor numbers were assigned to subgroup analysis. After excluding relevant factors, similar results were found, where patients with 1-3 tumors no more than 3 cm achieved comparable survival from RFA and liver resection. The results of this study showed that RFA might be more suitable for early HCC patients with tumor sizes no more than 3 cm.

There are some limitations existing in the study. First, selection bias is present because the study was a retrospective study, although PSM was used. Second, the liver function and physical condition of the patients were considered in this study, which might influence the results. However, the study included a large sample, and the results of this study could provide new evidence for future studies. We hope future prospective studies could include these factors to compare RFA with liver resection.

Conclusions

The results of this study showed that patients within the Milan criteria could obtain comparable survival with RFA and liver resection. For patients with a tumor size no more than 3 cm, RFA might be more suitable.

Declarations

Ethics approval and consent to participate: The study was approved by the Ethics Committee board of Tongji Medical College, Huazhong University of Science and Technology. The requirement of informed consent was waived by the board of Tongji Medical College, Huazhong University of Science and Technology because the study utilized the SEER database.

Guidelines for Methods: This study was carried out in compliance with the Helsinki Declaration.

Consent for publication: All authors approve it for publication.

Data Availability: The data used in the study can be available from SEER database (https://seer.cancer.gov/data/) (accession umbers: 12577-Nov2019).

Competing interests: All authors declared that there were no conflicts of interest existing.

Funding: This study was supported by National Natural Science Foundation of China (No. 81873919 and No. 81801810).

Authors' contributions: Conception and design: CS Zheng and LM Liu; Administrative support: CS Zheng; Data collection: L Chen, LC Zhu and DQ Xiang; Data analysis: L Chen, YQ Ren, LC Zhu, and B Sun; Manuscript writing: L Chen, DQ Xiang, T Sun, LC Zhu, LX Wu and WH Zhang; Manuscript reviewed: CS Zheng and YM Liu; Final approval of manuscript: All authors.

Acknowledgments: We acknowledge the SEER database for providing the data used in the study.

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Tables

Table 1 Baseline characteristics of patients before PSM and after PSM

	Before matching			After matching		
Characteristics	RFA (N=1038)	Liver resection (N=394)	P value	RFA (N=376)	Liver resection (N=271)	P value
Age at diagnosis (years)			0.618			0.661
30-44	18 (1.7)	10 (2.5)		6 (1.6)	7 (2.6)	
45-59	425 (40.9)	160 (40.6)		156 (41.5)	109 (40.2)	
≥60	595 (57.3)	224 (56.9)		214 (56.9)	155 (57.2)	
Year of diagnosis			0.057			0.793
2004-2007	169 (16.3)	76 (19.3)		65 (17.3)	52 (19.2)	
2008-2011	370 (35.6)	156 (39.6)		141 (37.5)	102 (37.6)	
2012-2014	499 (48.1)	162 (41.1)		170 (45.2)	117 (43.2)	
Race			<0.001			0.992
White	702 (67.6)	223 (56.6)		237 (63.0)	172 (63.5)	
Black	115 (11.1)	62 (15.7)		44 (11.7)	31 (11.4)	
Other	221 (21.3)	109 (27.7)		95 (25.3)	68 (25.1)	
Gender			0.756			0.741
Male	775 (74.7)	298 (75.6)		298 (79.3)	211 (77.9)	
Female	263 (25.3)	96 (24.4)		78 (20.7)	60 (22.1)	
Grade of tumor *			<0.001			0.112
Grade I	148 (14.3)	71 (18.0)		102 (27.1)	69 (25.5)	
Grade II	170 (16.4)	211 (53.6)		159 (42.3)	131 (48.3)	
Grade III	37 (3.6)	68 (17.3)		36 (9.6)	32 (11.8)	
Grade Iv	0 (0.0)	5 (1.3)		0 (0.0)	0 (0.0)	
Unknown	683 (65.8)	39 (9.9)		79 (21.0)	39 (14.4)	
Summary stage			0.021			0.492
Localized	873 (84.1)	351 (89.1)		322 (85.6)	238 (87.8)	
Regional	165 (15.9)	43 (10.9)		54 (14.4)	33 (12.2)	
AJCC stage			0.123			0.678

I	700 (67.4)	259 (65.7)		245 (65.2)	178 (65.7)	
II	330 (31.8)	127 (32.2)		127 (33.8)	88 (32.5)	
IIIA	8 (0.8)	8 (2.0)		4 (1.1)	5 (1.8)	
Radiotherapy			0.314			0.914
Yes	12 (1.2)	8 (2.0)		4 (1.1)	4 (1.5)	
No	1026 (98.8)	386 (98.0)		372 (98.9)	267 (98.5)	
Chemotherapy			<0.001			0.163
Yes	304 (29.3)	40 (10.2)		71 (18.9)	39 (14.4)	
No	734 (70.7)	354 (89.8)		305 (81.1)	232 (85.6)	
Tumor size			<0.001			0.961
1-2 cm	320 (30.8)	78 (19.8)		89 (23.7)	66 (24.4)	
2-3 cm	444 (42.8)	146 (37.1)		157 (41.8)	114 (42.1)	
3-5 cm	274 (26.4)	170 (43.1)		130 (34.6)	91 (33.6)	
Tumor number			0.073			0.642
1	888 (85.5)	352 (89.3)		320 (85.1)	235 (86.7)	
2-3	150 (14.5)	42 (10.7)		56 (14.9)	36 (13.3)	
AFP			0.259			0.689
Positive	656 (63.2)	237 (60.2)		234 (62.2)	168 (62.0)	
Negative	285 (27.5)	109 (27.7)		105 (27.9)	71 (26.2)	
Unknown	97 (9.3)	48 (12.2)		37 (9.8)	32 (11.8)	
Marital status			0.521			0.622
Married	564 (54.3)	227 (57.6)		221 (58.8)	153 (56.5)	
Single	440 (42.4)	156 (39.6)		150 (39.9)	112 (41.3)	
Unknown	34 (3.3)	11 (2.8)		5 (1.3)	6 (2.2)	

Table 2 Multivariate regression for OS and CSS before PSM

	OS		CSS	
	HR (95%CI)	P value	HR (95%CI)	P value
Treatments				
Liver resection	Ref		Ref	
RFA	1.172 (0.971-1.416)	0.098	1.070 (0.847-1.351)	0.569
Gender				
Male	Ref		Ref	
Female	0.899 (0.759-1.064)	0.217	0.901 (0.731-1.110)	0.901
Age at diagnosis				
30-44	Ref		Ref	
45-59	1.580 (0.880-2.838)	0.125	1.431 (0.724-2.828)	0.302
≥60	1.991 (1.110-3.572)	0.021	1.821 (0.923-3.593)	0.084
Year of diagnosis				
2004-2007	Ref		Ref	
2008-2011	0.759 (0.632-0.911)	0.003	0.742 (0.590-0.932)	0.010
2012-2014	0.569 (0.466-0.695)	<0.001	0.465 (0.363-0.596)	<0.001
Race				
White	Ref		Ref	
Black	1.087 (0.883-1.338)	0.431	1.096 (0.851-1.411)	0.477
Other	0.576 (0.476-0.697)	<0.001	0.556 (0.440-0.702)	<0.001
Grade of tumor				
Grade I	Ref		Ref	
Grade II	1.063 (0.842-1.343)	0.607	1.067 (0.792-1.437)	0.670
Grade III	1.434 (1.047-1.964)	0.025	1.661 (1.128-2.445)	0.010
Grade Iv	1.873 (0.672-5.216)	0.230	2.050 (0.718-5.852)	0.180
Unknown	1.309 (1.057-1.619)	0.013	1.491 (1.137-1.955)	0.004
Summary stage				
Localized	Ref		Ref	
Regional	1.269 (1.018-1.583)	0.034	1.332 (1.025-1.731)	0.032

AJCC stage				
I	Ref		Ref	
II	1.183 (0.996-1.406)	0.056	1.256 (1.018-1.548)	0.033
IIIA	1.255 (0.649-2.429)	0.500	1.227 (0.601-2.503)	0.574
Radiotherapy		0.006		<0.001
No	Ref		Ref	
Yes	0.481 (0.286-0.810)		0.390 (0.221-0.686)	
Chemotherapy				
No	Ref		Ref	
Yes	1.143 (0.963-1.357)	0.125	1.131 (0.917-1.395)	0.251
Tumor size				
1-2 cm	Ref		Ref	
2-3 cm	1.281 (1.066-1.541)	0.008	1.180 (1.160-1.890)	0.002
3-5 cm	1.909 (1.557-2.341)	<0.001	2.270 (1.762-2.923)	<0.001
Tumor number				
1	Ref	Ref	Ref	
2-3	1.098 (0.890-1.355)	0.382	0.550 (0.300-0.010)	0.054
AFP				
Positive	Ref	Ref	Ref	
Negative	0.782 (0.662-0.923)	0.004	0.740 (0.601-0.912)	0.005
Unknown	0.813 (0.638-1.036)	0.095	0.788 (0.583-1.064)	0.120
Marital status				
Married	Ref	Ref	Ref	
Single	1.215 (1.051-1.404)	0.008	1.227 (1.024-1.470)	0.027
Unknown	0.931 (0.632-1.372)	0.719	0.939 (0.586-1.505	0.795

Table 3 Competing multivariate regression analysis for patients before PSM and after PSM

	Before PSM		After PSM	
	HR (95%CI)	P value	HR (95%CI)	P value
Treatments				
Liver resection	Ref		Ref	
RFA	1.021 (0.807-1.291)	0.862	1.044 (0.807-1.352)	0.742
Gender				
Male	Ref		Ref	
Female	0.976 (0.791-1.210)	0.826	1.016 (0.716-1.441)	0.928
Age at diagnosis				
30-44	Ref		Ref	
45-59	1.276 (0.654-2.487)	0.475	1.019 (0.403-2.578)	0.967
≥60	1.644 (0.847-3.189)	0.141	1.418 (0.573-3.508)	0.450
Year of diagnosis				
2004-2007	Ref		Ref	
2008-2011	0.765 (0.612-0.956)	0.019	0.932 (0.664-1.308)	0.683
2012-2014	0.535 (0.422-0.679)	<0.001	0.505 (0.349-0.731)	<0.001
Race				
White	Ref		Ref	
Black	1.162 (0.902-1.498)	0.246	1.151 (0.768-1.724)	0.496
Other	0.640(0.506-0.809)	<0.001	0.608(0.429-0.863)	0.005
Grade of tumor				
Grade I	Ref		Ref	
Grade II	1.040 (0.774-1.396)	0.795	0.921 (0.649-1.307)	0.645
Grade III	1.503 (1.019-2.216)	0.040	1.517 (0.941-2.447)	0.087
Grade Iv	2.432 (0.845-7.005)	0.099	NA	NA
Unknown	1.353 (1.028-1.781)	0.031	1.559 (1.061-2.292)	0.024
Summary stage				
Localized	Ref		Ref	
Regional	1.267 (0.970-1.656)	0.082	1.775 (1.226-2.569)	0.002

AJCC stage				
I	Ref		Ref	
II	1.271 (1.034-1.564)	0.023	1.372 (1.015-1.854)	0.040
IIIA	1.566 (0.757-3.238)	0.227	3.178 (1.542-6.554)	0.002
Radiotherapy		<0.001		<0.001
Yes	Ref		Ref	
No	3.305 (1.938-5.638)		3.311 (1.902-5.766)	
Chemotherapy		0.451		0.313
No	Ref		Ref	
Yes	0.922 (0.748-1.138)		1.180 (0.855-1.629)	
Tumor size				
1-2 cm	Ref		Ref	
2-3 cm	1.395 (1.102-1.766)	0.006	1.702 (1.179-2.457)	0.005
3-5 cm	1.901 (1.484-2.436)	<0.001	1.707 (1.178-2.475)	0.005
Tumor number				
1	Ref		Ref	
2-3	0.102 (0.056-0.183)	<0.001	0.107 (0.048-0.240)	<0.001
AFP				
Positive	Ref		Ref	
Negative	0.824 (0.675-1.007)	0.058	0.705 (0.514-0.966)	0.030
Unknown	0.850 (0.642-1.128)	0.260	0.623 (0.393-0.988)	0.044
Marital status				
Married	Ref		Ref	
Single	1.196 (0.995-1.438)	0.057	1.056 (0.803-1.389)	0.695
Unknown	0.939 (0.599-1.472)	0.784	0.307 (0.109-0.864)	0.025

Table 4 Adjusted Cox regression analysis for OS and CSS in subgroup analysis. Adjusted for age at diagnosis, gender, year of diagnosis, race, grade of tumor, summary stage, AJCC stage, radiotherapy, chemotherapy, AFP, marital status

	OS		CSS	
Characteristics	**HR (95%CI)**	**P value**	**HR (95%CI)**	**P value**
Single tumor size ≤2 cm				
Liver resection	Ref		Ref	
RFA	1.178 (0.688-2.018)	0.551	1.171 (0.617-2.221)	0.629
Single tumor size 2-3 cm				
Liver resection	Ref		Ref	
RFA	0.875 (0.626-1.224)	0.435	0.830 (0.562-1.228)	0.352
Single tumor size 3-5 cm				
Liver resection	Ref		Ref	
RFA	1.443 (1.055-1.972)	0.022	1.448 (1.038-2.133)	0.031
2-3 tumors ≤3 cm				
Liver resection	Ref		Ref	
RFA	1.596 (0.886-2.875)	0.120	NA	0.224

Figures

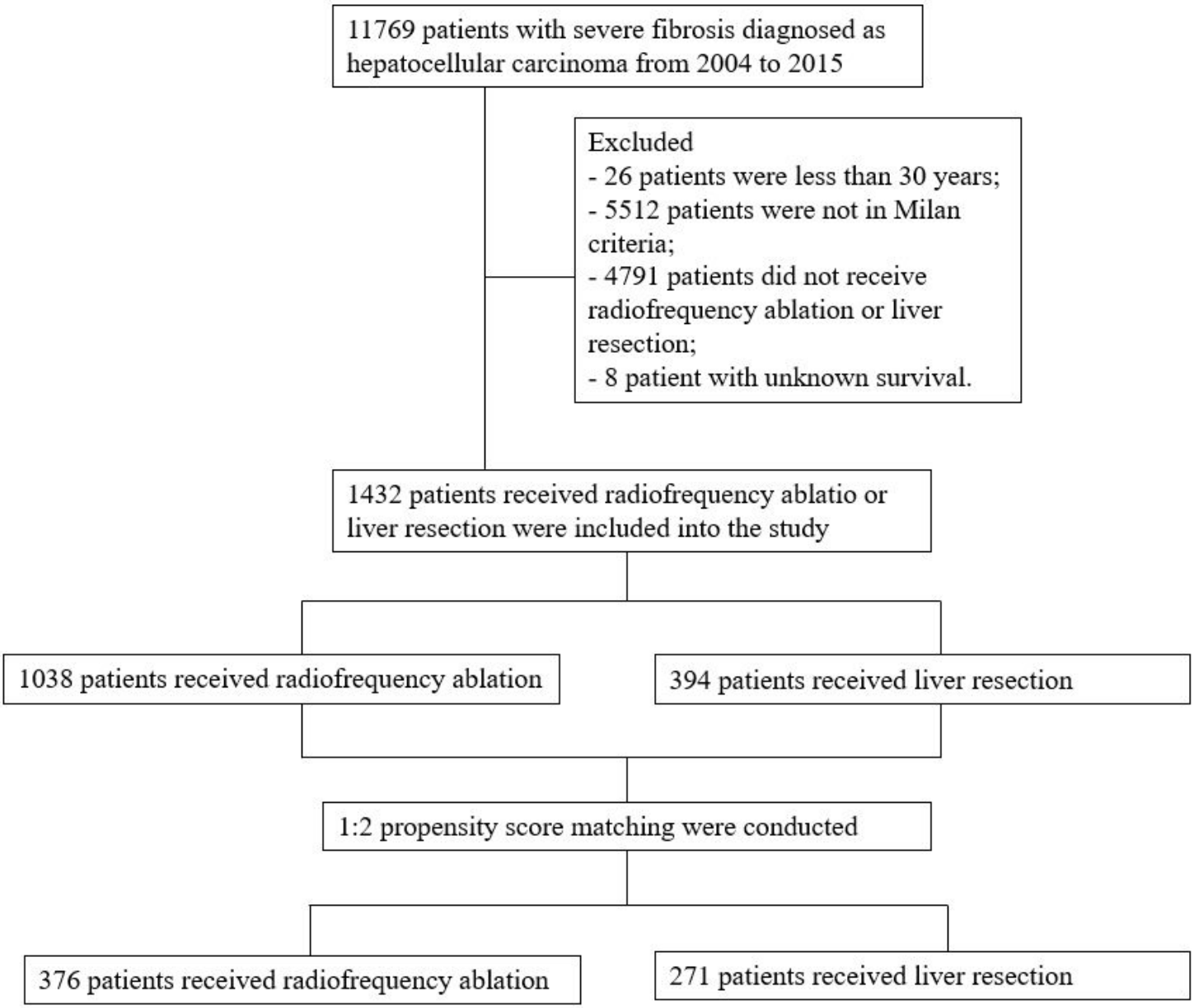

Figure 1

Flowchart for patient selection.

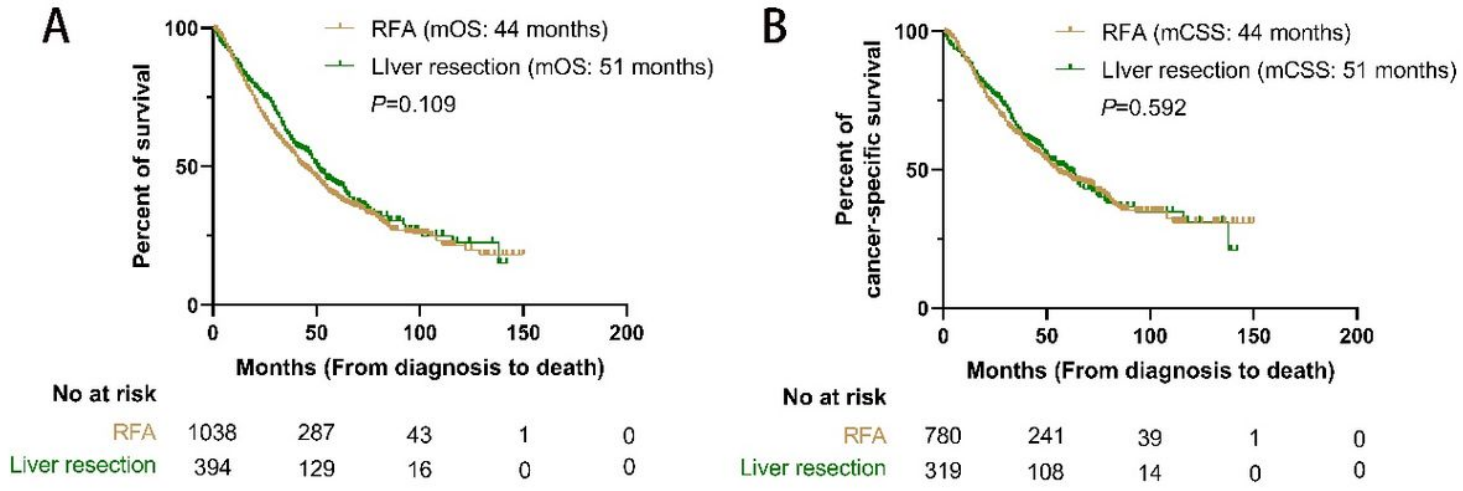

Figure 2

Kaplan-Meier curves for OS and CSS before PSM. (A) Kaplan-Meier curve for OS; (B) Kaplan-Meier curve for CSS.

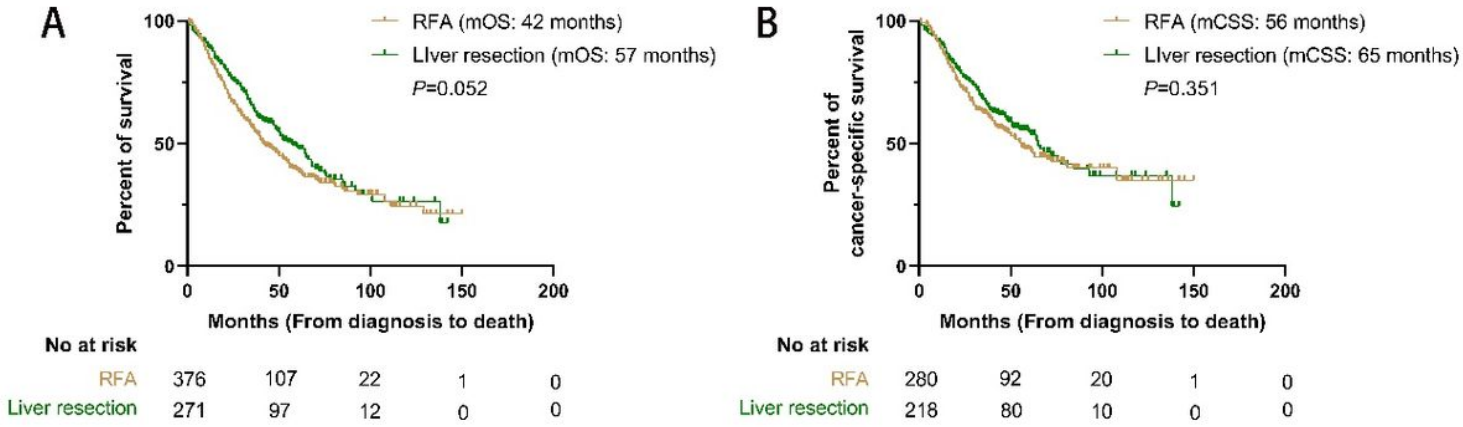

Figure 3

Kaplan-Meier curves for OS and CSS after PSM. (A) Kaplan-Meier curve for OS; (B) Kaplan-Meier curve for CSS.

Supplementary Files

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