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The Long-Term Efficacy of Radiofrequency Ablation Versus Laparoscopic Hepatectomy for Small Hepatocellular Carcinoma in East Asia: A Systematic Review and Meta-Analysis

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Abstract

Context: Hepatocellular carcinoma (HCC) is a common malignant cancer and the second leading cause of cancer-related deaths around the world. Radiofrequency ablation (RFA) and laparoscopic hepatectomy (LH) have been adopted for the treatment of HCC. The aim of the meta-analysis was to explore the long-term efficacy of RFA compared with LH for small HCC (sHCC) patients in the East Asian population.
Evidence Acquisition: We performed a systematic review and meta-analysis by the literature search on PubMed, Cochrane Library, EMBASE, Chinese Biological Medical Literature (CBM), Chinese National Knowledge Infrastructure (CNKI), and Wanfang from their inception until October 10, 2019, for comparing the long-term efficacy outcomes of RFA with LH.
Results: Fourteen retrospective studies with 1,390 subjects were included in the meta-analysis. Compared with the LH-treated group, RFA could raise the local recurrence rate under median follow-up duration and reduce disease-free survival (DFS) rates at 1 - 3 years. However, it failed to affect 5-year overall survival (OS) and DFS rates. In the subgroup analyses, different RFA approaches had significantly higher local recurrence rates than the LH group. A similar effect on OS and DFS rates within five years for single early ($\leq$ 3 cm) HCCs and on the 1- and 5-year DFS rates for nodules $\leq$ 5 cm were observed between the two groups, but RFA approaches could reduce the 3-y OS and DFS rates for single nodules $\leq$ 5 cm. The percutaneous radiofrequency ablation (PRFA) group had significantly lower 3- and 5-year OS and the 1- and 3-year DFS rates than the LH group, while no significant difference in OS and DFS rates in the laparoscopic radiofrequency ablation (LRFA) approach. The RFA approach improved the 3-year OS compared with the LH group in Japan, but reduced the 3-year OS and DFS rates within 3 years in China.
Conclusions: Our results support that LH treating sHCC had a better long-term efficacy and a lower local recurrence rate than RFA in the East Asian population. Further high-quality prospective studies are required to confirm the long-term efficacy.

Keywords: Radiofrequency Ablation, Minimally Invasive Surgery, Laparoscopic Hepatectomy, Hepatocellular Carcinomas, Meta-Analysis

1. Context

Hepatocellular carcinoma (HCC) is a common malignant cancer and the second leading cause of cancer-related deaths around the world (1, 2). It is prevalent in the Asia-Pacific Region and increasing in Western countries, which is predicted to exceed a million cases per year by 2025 worldwide (3, 4). HCC has been the third most common cause of cancer-related deaths in the Asia-Pacific Region, and almost half of the patients diagnosed worldwide are from China (5). The high prevalence of HCC in Asia Regions is related to the more prevalence of chronic virus infections (like hepatitis B or hepatitis C virus) in these regions, and acute viral hepatitis is the major cause of liver-related deaths in the Asia-Pacific Region (5, 6). Most patients with HCC were diagnosed with different degrees of liver function damage, and liver function reserve capacity is poor that may be due to combined with chronic virus hepatitis, liver cirrhosis, aflatoxin, smoking, drinking, and so on (7). Treatment options for HCC include liver transplantation, liver resection, and loco-regional therapies such as radiofrequency ablation (RFA) and chemotherapy (8). Theoretically, the ideal treatment for patients with sHCC who met the Milan criteria is still liver transplantation, but only a few patients can get this treatment limited by donor scarcity and high costs (9, 10). The treatment of liver cancer should not only completely remove the lesion but also minimize the trauma to the greatest extent. Therefore, minimally invasive surgery has been widely used in the treatment of small liver cancer, among which the efficacy of radiofrequency ablation and laparoscopic hepatectomy in the treatment of small primary liver cancer has been recognized.

RFA has recently been regarded as one of the established treatments for small hepatocellular carcinoma and is recommended as a first-line treatment for Barcelona Clinic Liver Cancer (BCLC) early-stage HCC due to its cost-effectiveness, safety, minimal invasiveness, more rapid recovery, and repeatedly operated. Previous studies showed that RFA has similar long-term efficacy with shorter hospitalization days and fewer complications compared with open resection (11-13), but it would raise local recurrence rates, especially for surface HCC, and the risk of developing severe postoperative complications and hepatic failure for some cirrhotic patients (14). Meanwhile, compared with open hepatic resection, LH therapy is characterized by reducing wounds, improving operation recovery, and shorter hospitalization, which has been adopted for the treatment of HCC, especially surface HCC (15, 16). Therefore, the clinical effects of RFA and LH treatments for sHCC have been compared in several studies and meta-analyses (11, 14, 17-23). However, the conclusions remain inconsistent that the superiority of two curative treatments has not been definitively certificated. Some studies demonstrated that LH or MIS (minimally invasive liver surgery) were associated with the highest overall survival and highest disease-free survival and lower intrahepatic recurrence that would lead to better long-term prognosis and lower local recurrence rate than RFA in patients with sHCC (19-23). Conversely, other studies have demonstrated that there are no significant differences in overall survival, disease-free survival, or intrahepatic recurrence (17, 24, 25). The discrepancies might be due to the differentials in study design, characteristics of patients, sample sizes, hepatic functional reserve at initial treatment, health care system capability, and follow-up duration. However, few studies have compared RFA and LH therapies for the treatment of primary HCC in Asia, and some studies from Chinese databases are not readily accessible limited by languages for the international readership. Thus, we performed a comprehensive meta-analysis, including English and Chinese databases, to explore the long-term efficacy of RFA compared with LH for small HCC in the East Asian population.

2. Evidence Acquisition

2.1. Search Strategy and Selection Criteria

Relevant articles were found by searching PubMed, Cochrane Library, EMBASE, Chinese Biological Medical Literature (CBM), Chinese National Knowledge Infrastructure (CNKI), and Wanfang from their inception until October 10, 2019. The search terms were used: ("laparoscopic partial hepatectomy" or "laparoscopic resection" or "laparoscopic operation") and ("radiofrequency ablation" or "radio-frequency ablation") and ("small hepatocellular carcinoma" or "small liver carcinoma" or "small hepatic carcinoma"). Besides, we manually searched potentially related articles in the reference lists of all the selected articles. Our study was reported and performed according to the preferred reporting items for the systematic review and meta-analysis (PRISMA) guidelines (26).

2.2. Inclusion and Exclusion Criteria

We identified eligible studies using the following criteria: (1) primary hepatocellular carcinoma without no recurrence or metastasis; single HCC nodule $\leq$ 5 cm in diameter or up to 3 nodules that are each $\leq$ 3 cm in diameter (27), or a single tumor $\leq$ 6.5 cm in diameter or up to 3 nodules that are each $\leq$ 4.5 cm in diameter and 8 cm in total diameter, with Child-Pugh class A/B (28); (2) radiofrequency ablation included percutaneous or laparoscopic RFA, laparoscopic hepatectomy included laparoscopic or laparoscopic-assisted or robotic-assisted liver resection; (3) study outcomes included local recurrence rate or overall survival or disease-free survival. The exclusion criteria were as follows: (1) non-primary HCC, liver distant metastases or recurrence; (2) no quantitative outcomes; (3) abstracts, case reports, editorials, or reviews.

2.3. Data Extraction and Quality Assessment

Two independent reviewers extracted the relevant data by the blind method with 89% in the Kappa coefficient, and any disagreements were resolved by the third investigator. The relative information included first author, publication year, study period, country of study, sex, age, number of patients, number of nodules, tumor size, Child-Pugh class, infection of HBV or/and HCV, and cirrhosis of patients. The long-term outcomes included local recurrence rates, survival rates. Two independent reviewers evaluated the methodological quality of included studies (87% in Kappa coefficient) based on the population selection, comparability and outcomes using 'Newcastle-Ottawa scale (NOS) for assessing the quality of non-randomized studies.

2.4. Statistical Analysis

R software version 3.6.1 with the "metabin" functions in the meta-package was used for pooled data assessment. The odds ratio (OR) with a 95% confidence interval (CI) was used for estimating the long-term outcomes of RFA compared with LH groups. Engauge Digitizer 12.0 was used to extract the survival data from Kaplan-Meier curves in eligible studies, which did not provide survival rate. I2 statistic and Q test were used to detect the heterogeneity of the study. A random-effect model was applied when the $I^2 > 50\%$ and $P < 0.05$ of the Q test. Otherwise, a fixed-effect model was used. Subgroup analyses were performed based on data in patients with different lesion sizes, RFA approaches, and country of study. Sensitivity analyses were conducted by subsequently removing each study and then calculated the effect size based on the remaining studies for assessing which study markedly affected the pooled results. Funnel plot and linear regression test were used to assess publication bias among the included studies. A P value < 0.05 was considered statistically significant.

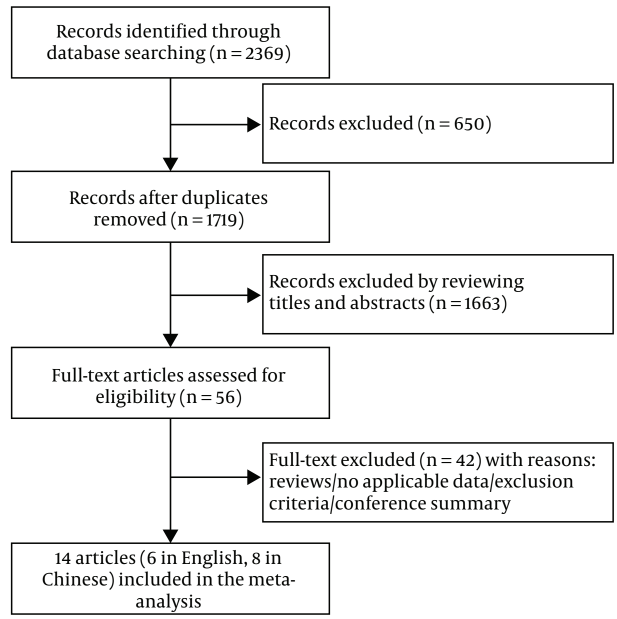

Figure 1. Flowchart for selection of the studies is shown

3. Results

3.1. Study Selection and Characteristics

We found 2,369 studies in total and screened 1,719 references after removing the duplicates. After reviewing the titles, abstracts, 56 were remained to reviewing full-texts. Finally, 14 retrospective studies in Asia with 1,390 patients (689 for RFA and 701 for LH) were included in the meta-analysis (Figure 1). All selected studies were published from 2015 to 2019, 6 studies published in English and 8 in Chinese, 3 in Japan, and 11 in China. The sample size ranged from 61 to 175, and the mean age of patients ranged from 32.7 to 74.0 years. More than half of the included studies had a long follow-up period than three years, and three studies for more than five years. The total score of quality assessment ranges from 7 to 9 (Table 1).

3.2. Local Recurrence Rate

Eight studies (14, 24, 25, 29, 30, 33-35) of 963 patients reported the postoperative local recurrence rates during median follow-up times. The meta-analysis showed that RFA approach treatment had relatively higher local recurrence rates than the LH-treatment group (OR = 2.97; 95% CI = 1.58 - 5.59; P < 0.001) (Table 2, Figure 2). Notably, significant statistical heterogeneity was observed in the analysis ($I^2 = 70\%$, $P < 0.01$), and a random-effect model was used. However, sensitivity analyses by omitting one study in each turn had no material effect on local recurrence estimates, confirmed the stability of the results (Appendix 1 in Supplementary File). No publication bias was detected by the funnel plot (Appendix 2 in Supplementary File) and linear regression test for the comparison of outcomes in the meta-analysis (P = 0.46).

3.3. Overall Survival

Ten studies (17, 24, 25, 29-32, 35-37) with 1,059 patients reported 1-year and 3-year overall survival (OS) rates, while 5-year OS rates were assessed in seven studies. Our meta-analysis showed that RFA approach treatment failed to affect 1-year (OR = 1.10; 95% CI = 0.66 - 1.84; P = 0.706), 3-year (OR = 0.79; 95% CI = 0.59 - 1.06; P = 0.117), and 5-year (OR = 0.42; 95% CI = 0.16 - 1.12; P = 0.082) OS compared with the LH-treatment group (Table 2, Figure 3). However, there was no and mild significant heterogeneity for pooling the 1-y and 3-y OS rates ($I^2 = 0\%$, $I^2 = 49\%$, respectively); thus a fix-effect model was used. Markedly, significant statistical heterogeneity was observed in the 5-year OS ($I^2 = 86\%$, $P < 0.01$), and a random-effect model was used. Then, sensitivity analyses confirmed the stability of the results, found no material effect on the pooled estimates in every study (Appendix 3 in Supplementary File). Funnel plot (Appendix 4 in Supplementary File) and linear regression test detected no publication bias for the comparison of outcomes in the meta-analysis (1-year OS: P = 0.702; 3-year OS: P = 0.824; 5 -year OS: P = 0.707, respectively).

Table 1. Baseline Characteristic of Included Studies[a]

Study	Country	Design	Period	Treat	Size	Sex (M/F)	Age	Child (A/B)	HBV/HCV Infection, %	Cirrhosis, %	Tumor Number		Tumor Size, cm	Follow-Up, mo	NOS
											1	1 - 3			
Xu et al. (29)	China	Retrospective	2012 - 2015	LH	30	25/5	52.8 ± 9.4	29/1	87.7	NA	65	0	≤ 3	28.1 (28.3, 50.5)	8
				PRFA	35	27/8	57.1 ± 12.7	32/3							
Song et al. (24)	China	Retrospective	2007 - 2013	LH	78	70/8	48.0 ± 11.1	78/0	96.2	96.2	73	83	≤ 4	31.2 (21.1, 49.5)	9
				PRFA	78	70/8	48.0 ± 9.6	76/2							
Song et al. (30)	China	Retrospective	2012 - 2014	LH	81	69/12	49.0 ± 10.7	80/1	97.1	87.4	162	13	≤ 5	39.5 (35.5, 47.0)	7
				PRFA	94	82/12	48.0 ± 11.8	88/6							
Cui et al. (31)	China	Retrospective	2013 - 2015	LH	48	21/28	53.7 ± 9.2	21/27	NA	NA	78	19	≤ 3	≥ 3 y	7
				PRFA	49	29/20	53.3 ± 9.6	21/28							
Zhou et al.(32)	China	Retrospective	2011 - 2015	LH	45	35/10	59.5 ± 10.4	31/14	NA	NA	66	21	≤ 5	≥ 3 y	7
				LRFA	42	33/9	58.3 ± 10.7	27/15							
Zheng et al.	China	Retrospective	2013 - 2013	LH	31	23/8	64.2 ± 2.2	-	NA	NA	-	-	≤ 5	≥ 5 years	7
				LRFA	31	22/9	64.2 ± 2.2	-							
Fan et al. (33)	China	Retrospective	2014 - 2016	LH	31	25/6	58.6 ± 7.2	26/5	100.0	100.0	52	17	≤ 5	≥ 5 y	8
				LRFA	38	28/10	55.7 ± 6.3	29/9							
Wu et al. (34)	China	Retrospective	2010 - 2013	LH	125	81/44	63.7 ± 9.8	107/18	86.7	56.0	166	0	≤ 3	≥ 5 y	8
				LRFA	41	28/13	65.4 ± 8.7	31/10							
Zhang et al. (35)	China	Retrospective	2012 - 2014	LH	60	34/26	32.7 ± 15.5	55/5	NA	NA	88	52	≤ 5	32.7 (5, 36)	7
				PRFA	80	45/35	35.2 ± 17.2	72/8							
Lai et al. (36)	China	Retrospective	2006 - 2011	LH	28	24/4	56.5 ± 12.6	28/0	81.9	81.9	56	5	≤ 5	≥ 3 y	9
				PRFA	33	29/4	62.8 ± 11.3	29/4							
Chong et al. (25)	China	Retrospective with PSM	2005 - 2015	LH	59	46/13	57.7 ± 10.5	59/0	88.1	88.1	112	6	≤ 3	44.7	9
				RFA	59	46/13	59.3 ± 11.0	58/1							
Harada et al. (37)	Japan	Retrospective with PSM	2008 - 2015	LH	20	9/11	74.0 ± 6.0	-	80.0	80.0	40	0	≤ 3	29.3 (0.3, 89.2)	8
				PRFA	20	11/9	73.0 ± 9.0	-							
Ito et al. (14)	Japan	Retrospective with PSM	2011 - 2013	LH	27	16/11	69 (66~72)	16/11	90.7	92.6	46	8	≤ 3	LH: 21 (2, 47); RFA: 24 (4, 44)	9
				PRFA	27	15/12	71 (68~74)	15/12							
Yamashita et al. (17)	Japan	Retrospective	2000 ~ 2016	LH	38	25/13	66.9 ± 9.1	33/5	89.0	89.0	74	26	≤ 3	LH: 37.2 (1.2, 160.8); RFA: 57.6 (2.4, 164.4)	7
				RFA	62	40/22	66.5 ± 9.5	54/8							

Abbreviations: F, female; LH, laparoscopic hepatectomy; LRFA, laparoscopic radiofrequency ablation; M, male; NOS, Newcastle-Ottawa scale; PRFA, percutaneous radiofrequency ablation; PSM, propensity score matching.
[a]Values are expressed as mean ± SD.

3.4. Disease-Free Survival

Nine studies (17, 24, 25, 29, 30, 32, 35-37) of 962 patients reported 1-year and 3-year disease-free survival (DFS) rates, while 5-y disease-free survival rates were assessed in six studies. The pooled results indicated that RFA approach treatment reduced 1-year (OR = 0.63; 95% CI = 0.46 - 0.85; P = 0.002) and 3-year (OR = 0.48; 95% CI = 0.37 - 0.62; P < 0.0001) DFS rates compared with the LH-treatment group, but no significant difference was found in 5-year DFS rate (OR = 0.48; 95% CI = 0.19 - 1.26; P = 0.139) (Table 2, Figure 4). Notably, moderate or severe heterogeneity in 1-year, 3-year, and 5-year DFS rates were observed (1-year: I^2 = 51%, 3-year:

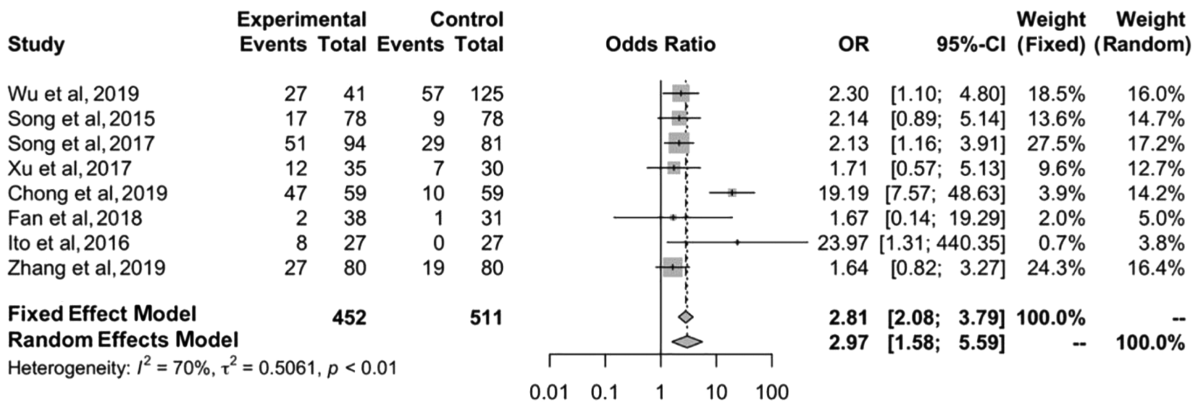

Figure 2. Forest plot of postoperative local recurrence between RFA and LH

I^2 = 57%, 5-year: I^2 = 81%, respectively) and random-effect model was used. Then, sensitivity analyses confirmed the stability of the results and did not find any study that significantly affected the pooled data (Appendix 5 in Supplementary File). No publication bias was detected by funnel plot (Appendix 6 in Supplementary File) and linear regression test for the comparison of outcomes in the meta-analysis (1-year OS: P = 0.388; 3-year OS: P = 0.427; 5-year OS: P = 0.824, respectively).

3.5. Subgroup Analysis

Eight studies were included in the subgroup analyses of the local recurrence rate under median follow-up time according to the RFA approach and country of study. The results of subgroup analyses showed that laparoscopic radiofrequency ablation (LRFA) (OR = 2.24; 95% CI = 1.11 - 4.53; P = 0.025) and percutaneous radiofrequency ablation (PRFA) (OR = 2.00; 95% CI = 1.37 - 2.92; P < 0.0001) approach treatments increased local recurrence rates compared with the LH group. Furthermore, the patients with RFA approach treatment had significantly higher local recurrence rates than the LH group both in China (OR = 2.74; 95% CI = 1.46 - 5.13; P = 0.002) and Japan (To date, only one study in Japan) (Table 2).

Moreover, thirteen studies were included in the subgroup analyses of OS and DFS rates according to the single nodule size. Our results presented that patients with RFA approach treatments showed a similar effect on OS and DFS rates at 1 to 5 years for single nodule size ≤ 3 cm (P > 0.05) as compared with the LH group. For single nodule size ≤ 5 cm, the RFA approach treatment reduced 3-year OS (OR = 0.67; 95% = CI 0.46 - 0.98; P = 0.037) and DFS (OR = 0.51; 95% CI = 0.37 - 0.70; P < 0.0001) rates compared with the LH group; however, the comparable OS and DFS rates in 1-year and 5-year were observed for two groups (P > 0.05) (Table 2).

Besides, ten studies were included in the subgroup analysis of OS and DFS rates according to RFA approach treatments. Our results indicated that for LRFA approach treatments, no significant differences were observed in 1-year, 3-year, and 5-year OS and DFS rates compared with the LH group. However, PRFA approach treatment presented lower 3-y (OR = 0.69; 95% CI = 0.49 - 0.98; P = 0.037), 5-year (OR = 0.06; 95% CI = 0.03 - 0.14; P < 0.0001) OS rates, and 1-year (OR = 0.64; 95% CI = 0.45 - 0.93; P = 0.018) and 3-year (OR = 0.48; 95% CI = 0.35 - 0.66; P < 0.0001) DFS rates than the LH group; however, no significant differences were observed in 1-year OS and 5-year DFS rates (P > 0.05) (Table 2).

Additionally, thirteen studies were included in the subgroup analysis of OS and DFS rates according to the country of the study. Our results showed that for study in Japan, RFA approach treatments improved 3-year (OR = 3.51; 95% CI = 1.17 - 10.52; P = 0.025) OS rates compared with the LH group. However, no significant differences were observed in 1-year, 5-year OS, and DFS rates between RFA and LH treatments. Comparing RFA and LH treatments in China, there were no significant differences in 1-year, 5-year OS, and 5-year DFS rates (P > 0.05); however, the RFA approach showed lower 3-year (OR = 0.69; 95% CI = 0.51 - 0.94; P = 0.019) OS and 1-3 year (1-year: OR = 0.63; 95% CI = 0.45 - 0.88; P = 0.006; 3-year: OR = 0.45; 95% CI = 0.29 - 0.72; P = 0.0007, respectively) DFS rates than the LH group (Table 2).

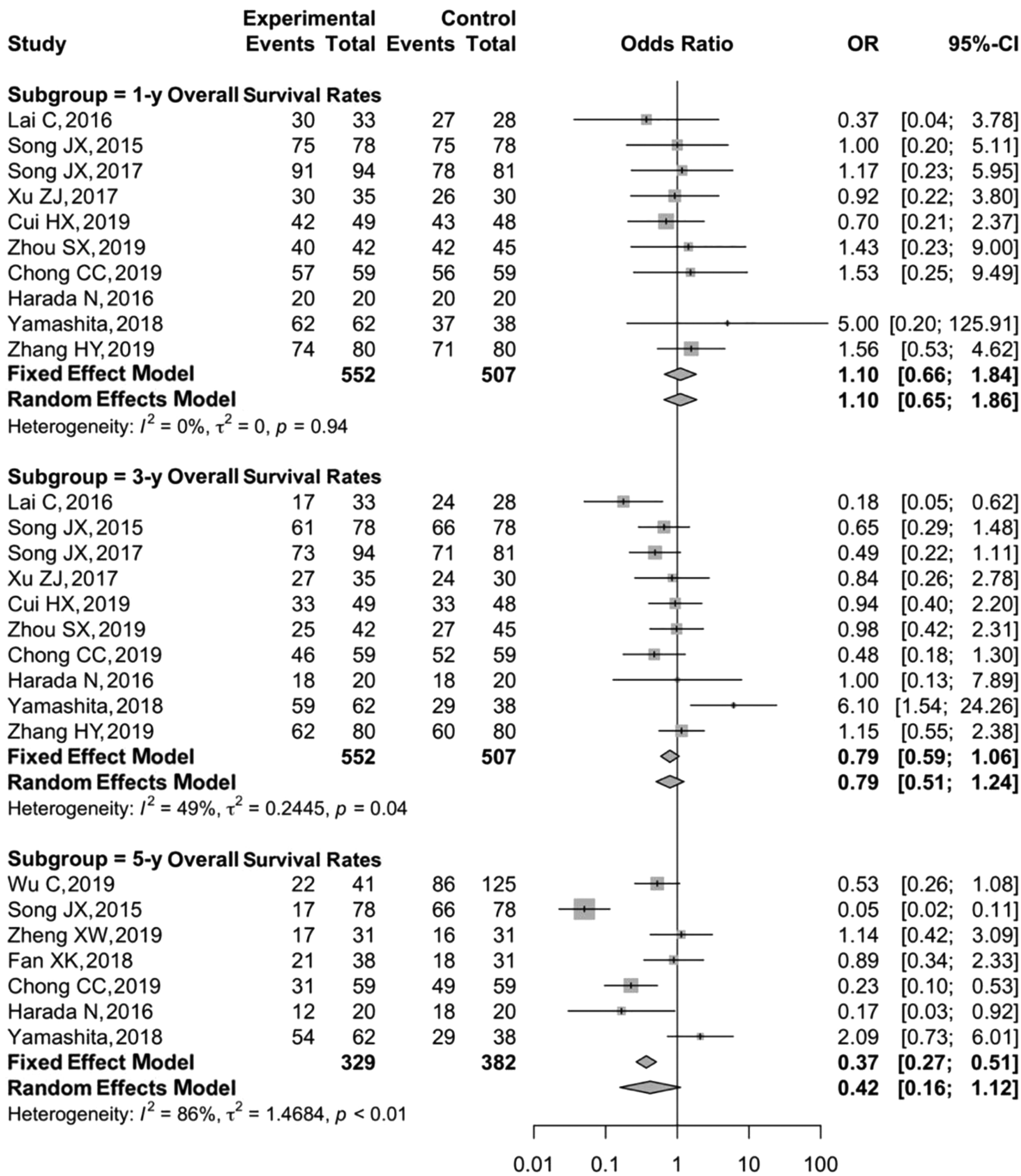

Figure 3. Forest plot of 1-y, 3-y and 5-y overall survival rates between RFA and LH

4. Discussion

Previous studies have shown that the LH approach had a lower incidence of postoperative ascites and liver failure compared with the open approach and no significant differences with the oncological results (38, 39). Laparoscopic hepatectomy (LH) has been a feasible option to open surgery and extended the indications to patients with severe cirrhosis and HCCs, mainly for tumors located in the

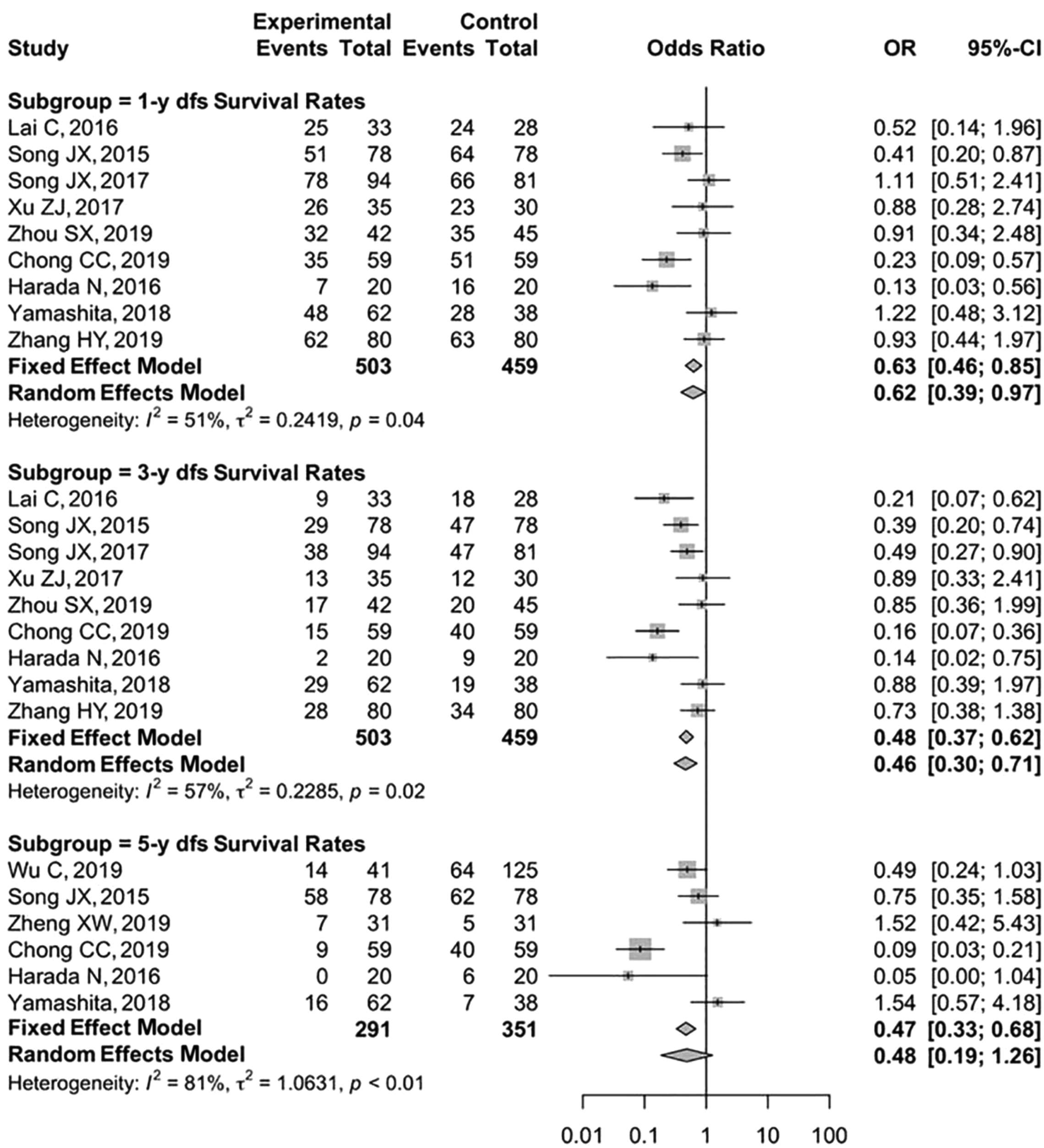

Figure 4. Forest plot of 1-y, 3-y, and 5-y disease-free survival rates between RFA and LH

peripheral portion of the anterolateral liver segments and easily accessible lesions (40-43). However, due to the difficulty in controlling bleeding and limited visualization, LH is considered to be technically challenging for lesions located in the posterior or superior region of the liver (43, 44). Meanwhile, RFA has been widely used for HCC as a commonly used minimally invasive technique, which had an effective treatment for BCLC stage 0 HCCs with a similar prognostic effect at a lower cost and a lower complication rate than open resection (14). Besides, advantages of RFA also included less invasiveness, reduced operative-related complications morbidity, shorter hospitalization and more rapid postoperative recovery that might interact with the socioeconomic and psychological status of patients, enhancing the life quality of these patients (4, 36). Additionally, RFA can be repeated subsequently and acts as an effective supplementary therapy without causing much damage to the cirrhotic liver. However, few studies in the Asian region have compared the long-term efficacy of RFA versus LH in patients with sHCC, and it remains highly controversial.

We primarily performed the comprehensive meta-analysis to explore the long-term efficacy of RFA compared with LH therapy for sHCC in the East Asian population. Our meta-analysis revealed that there were no significant differences in OS rates within five years and DFS rates at 5-years between RFA and LH groups. However, RFA approach treatment decreased the DFS rates within 3 years that LH group presented significantly better DFS rates. Meantime, the RFA approach raised the local recurrence rate during median follow-up times compared with the LH group. Considering long-term efficacy, LH was found to be superior to RFA in terms of treating patients with sHCC. Previous studies had suggested that LH had better survival outcomes compared with RFA (11, 22, 23, 45), which was consistent with our results, and it might have the advantage of oncological outcomes for the recurrent patients with sHCC (23, 45). However, Casaccia et al. (11) only found there was a significantly higher OS in LH therapy and no significant differences for DFS between LH and RFA therapies; Chong et al. (25) only demonstrated that MIS was significantly related to better DFS rates, but there was no significant difference in OS rates. Previous studies showed that patients with sHCC had recurrence usually, and multiple treatment strategies for the recurrence would cause a slow, gradual influence on the overall survival of patients (46). Meanwhile, local recurrence is a major tumor-related problem of RFA due to it is a poor prognostic factor. In our study, local recurrence rates were found to be more frequent in patients with sHCC treated with the RFA approach, which was consistent with previous studies (36) that might be due to the worse long-term prognosis. Subgroup analysis results also presented the consistent conclusion that RFA treatment raised the local recurrence rates during median follow-up duration compared with the LH-treated group. Local recurrence following RFA may be attributed to various risk factors, including insufficient radiofrequency ablation or malignant cells spread under ablation, incomplete necrosis, technically infeasibility due to the dangerous location of tumors or the microscopic tumor foci, heat sink effect, tumor venous invasion (47). Owing to these drawbacks, the long-term survival outcomes of RFA are inferior to LH. However, underlying molecular mechanisms responsible for the higher recurrence rate and lower survival outcome with RFA remain to be determined.

Previous studies reported that several factors would influent the OS and DFS, involving tumor size, number of tumor nodules, child class, alpha-fetoprotein (AFP) levels, and treatment modality (11). Our subgroup analyses according to single nodules size presented that RFA and LH treatments had a similar effect on OS and DFS rates within five years in patients with single nodules size $\leq$ 3 cm that might be explained by the fact that vascular invasion is less frequent in smaller tumors (48). Therefore, RFA treatments might be a reliable choice for those patients according to the RFA approach's advantages, which is consistent with previous studies and National Comprehensive Cancer Network (NCCN) guidelines (15, 19, 21). As for a single nodule size $\leq$ 5 cm, it showed comparable OS and DFS rates in 1- and 5-year for RFA and LH groups; however, the LH-treated group had significantly higher 3-year OS and DFS rates. The lower 3-year DFS and OS of RFA may be due to the following reasons: first, patients who underwent RFA were not eligible for the surgery because of the inadequate liver functional reserve, extensive tumor burden, or poor health conditions that would independently lead to lower 3-year survival. Second, LH allows better pathological evaluation and in-depth intraoperative exploration, which is not possible with RFA. Third, patients under RFA are more likely to have local recurrence due to incomplete ablation of the lesion or heat sink effect (49).

We found that LRFA- and LH-treated groups had similar effects on OS and DFS rates within 5 years, but the results should be cautioned for only one study compared to the outcomes with 1 - 3 years between these groups and included in each subgroup analyses. However, PRFA approach treatment reduced OS rates at 3 - 5 years and DFS rates within 3 years compared with the LH group. Previous studies have also proven that LRFA treatment was superior to the PRFA in tumors that are difficult or impossible to be treated in such a way or in severe liver disease (50) that might be due to that the use of laparoscopic approaches increased the probability of tumor detection by complete abdominal exploration and intraoperative ultrasound assessments, and it could perform the precise treatment by place electrodes at accurate tumor locations or tumors that invading adjacent organs or inaccessible areas by percutaneously (47).

Our subgroup analysis, according to the country of the study, indicated that RFA approach improved the 3-year OS rate compared with the LH group in Japan, which was contrary to the results of studies in China. Yamashita et al applied "multimodal" RFA combining various approaches for sHCC, such as laparoscopy and thoracoscopy, which gained the better outcomes of OS and DFS and enabled easy access to HCC and led to good ablation effects, resulting in good oncological outcomes or effects (17), they applied "multimodal" RFA combining various approaches such as laparoscopy and thoracoscopy, which gained the better outcomes of OS and DFS and enabled easy access to HCC and led to good ablation effects. New prospective studies are still needed to explore the duration of follow-up to assess the long-term efficacy of RFA and LH for sHCC.

Nonetheless, there are several limitations to the present study. First, all studies included in the meta-analysis were retrospective studies and conducted only in China and Japan because few studies had been performed in Asia, which might cause selection bias or unpredictable confounding bias. Thus, potential bias might affect the pooled data, and the clinical evidence of the study was relatively low. Second, characteristics for HBV/HCV infection and cirrhosis were not fully reported, which were the major factors that induce HCC in Asians. Third, the heterogeneity of several results was moderate or severity and could not be avoided in the present study; however, subgroup and sensitivity analyses were performed that might be associated with the different approaches and systems of RFA therapy, sample sizes, the time interval of recurrence, the severity of comorbidities, and treatment modality. The number of samples in total or in subgroup analyses was limited (8 included studies were less than 100 subjects), which weakened the power of statistical and affected the reliability of evidence. Fourth, there was variation in the palliative methods used during the 3-years follow-up among the studies, including chemotherapy, traditional Chinese medicine, and others that might have affected the clinical outcomes.

5. Conclusions

The meta-analysis confirmed the long-term efficacy of LH treatment for patients with sHCC compared with RFA in the East Asian population. However, further high-quality prospective studies are required to confirm the long-term efficacy.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Footnotes

Authors' Contribution: Study concept and design: Qiong Yu, Xueqi Fu, and Bai Ji. Analysis and interpretation of data: Xiaozheng Lu and Zhijun Li. Drafting of the manuscript: Xiaozheng Lu and Zishuai Wang. Critical revision of the manuscript for important intellectual content: Yahui Liu Xueqi Fu and Bai Ji. Statistical analysis: Zhijun Li and Qiong Yu.

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Ethical Approval: N/A

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References

1. Zhu ZX, Huang JW, Liao MH, Zeng Y. Treatment strategy for hepatocellular carcinoma in China: Radiofrequency ablation versus liver resection. *Jpn J Clin Oncol*. 2016;**46**(12):1075–80. doi: 10.1093/jjco/hyw134. [PubMed: 27677661].
2. Crocetti L. Radiofrequency ablation versus resection for small hepatocellular carcinoma: Are randomized controlled trials still needed? *Radiology*. 2018;**287**(2):473–5. doi: 10.1148/radiol.2018172822. [PubMed: 29668405].
3. Zhu GQ, Sun M, Liao WT, Yu WH, Zhou SL, Zhou ZJ, et al. Comparative efficacy and safety between ablative therapies or surgery for small hepatocellular carcinoma: A network meta-analysis. *Expert Rev Gastroenterol Hepatol*. 2018;**12**(9):935–45. doi: 10.1080/17474124.2018.1503531. [PubMed: 30025486].
4. Li L, Zhang J, Liu X, Li X, Jiao B, Kang T. Clinical outcomes of radiofrequency ablation and surgical resection for small hepatocellular carcinoma: A meta-analysis. *J Gastroenterol Hepatol*. 2012;**27**(1):51–8. doi: 10.1111/j.1440-1746.2011.06947.x. [PubMed: 22004366].
5. Jafri W, Kamran M. Hepatocellular carcinoma in Asia: A challenging situation. *Euroasian J Hepatogastroenterol*. 2019;**9**(1):27–33. doi: 10.5005/jp-journals-10018-1292. [PubMed: 31988864]. [PubMed Central: PMC6969322].
6. Sarin SK, Kumar M, Eslam M, George J, Al Mahtab M, Akbar SMF, et al. Liver diseases in the Asia-Pacific region: a Lancet Gastroenterology & Hepatology Commission. *Lancet Gastroenterol Hepatol*. 2020;**5**(2):167–228. doi: 10.1016/S2468-1253(19)30342-5. [PubMed: 31852635]. [PubMed Central: PMC7164809].
7. Jiang B, Yan XF, Zhang JH. Meta-analysis of laparoscopic versus open liver resection for hepatocellular carcinoma. *Hepatol Res*. 2018;**48**(8):635–63. doi: 10.1111/hepr.13061. [PubMed: 29330919].
8. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: A 2017 update. *Hepatol Int*. 2017;**11**(4):317–70. doi: 10.1007/s12072-017-9799-9. [PubMed: 28620797]. [PubMed Central: PMC5491694].
9. Okabe H, Yoshizumi T, Yamashita YI, Imai K, Hayashi H, Nakagawa S, et al. Histological architectural classification determines recurrence pattern and prognosis after curative hepatectomy in patients with hepatocellular carcinoma. *PLoS One*. 2018;**13**(9). e0203856. doi: 10.1371/journal.pone.0203856. [PubMed: 30216361]. [PubMed Central: PMC6138409].
10. Zamora-Valdes D, Taner T, Nagorney DM. Surgical treatment of hepatocellular carcinoma. *Cancer Control*. 2017;**24**(3):1.0732748177293E+15.

doi: 10.1177/1073274817729258. [PubMed: 28975836]. [PubMed Central: PMC5937244].

11. Casaccia M, Santori G, Bottino G, Diviacco P, Andorno E. Laparoscopic resection vs laparoscopic radiofrequency ablation for the treatment of small hepatocellular carcinomas: A single-center analysis. *World J Gastroenterol*. 2017;**23**(4):653–60. doi: 10.3748/wjg.v23.i4.653. [PubMed: 28216972]. [PubMed Central: PMC5292339].
12. Vitali GC, Laurent A, Terraz S, Majno P, Buchs NC, Rubbia-Brandt L, et al. Minimally invasive surgery versus percutaneous radio frequency ablation for the treatment of single small (</=3 cm) hepatocellular carcinoma: A case-control study. *Surg Endosc*. 2016;**30**(6):2301–7. doi: 10.1007/s00464-015-4295-6. [PubMed: 26534770].
13. Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. *Gastroenterology*. 2016;**150**(4):835–53. doi: 10.1053/j.gastro.2015.12.041. [PubMed: 26795574].
14. Ito T, Tanaka S, Iwai S, Takemura S, Hagihara A, Uchida-Kobayashi S, et al. Outcomes of laparoscopic hepatic resection versus percutaneous radiofrequency ablation for hepatocellular carcinoma located at the liver surface: A case-control study with propensity score matching. *Hepatol Res*. 2016;**46**(6):565–74. doi: 10.1111/hepr.12592. [PubMed: 26386248].
15. Benson AB, 3rd, D'Angelica MI, Abbott DE, Abrams TA, Alberts SR, Saenz DA, et al. NCCN guidelines insights: Hepatobiliary cancers, version 1.2017. *J Natl Compr Canc Netw*. 2017;**15**(5):563–73. doi: 10.6004/jnccn.2017.0059. [PubMed: 28476736]. [PubMed Central: PMC5557008].
16. Llovet JM, Bruix J. Novel advancements in the management of hepatocellular carcinoma in 2008. *J Hepatol*. 2008;**48 Suppl 1**:S20–37. doi: 10.1016/j.jhep.2008.01.022. [PubMed: 18304676].
17. Yamashita YI, Imai K, Kaida T, Yamao T, Tsukamoto M, Nakagawa S, et al. Multimodal radiofrequency ablation versus laparoscopic hepatic resection for the treatment of primary hepatocellular carcinoma within Milan criteria in severely cirrhotic patients: Long-term favorable outcomes over 10 years. *Surg Endosc*. 2019;**33**(1):46–51. doi: 10.1007/s00464-018-6264-3. [PubMed: 29872945].
18. Yazici P, Akyuz M, Yigitbas H, Dural C, Okoh A, Aydin N, et al. A comparison of perioperative outcomes in elderly patients with malignant liver tumors undergoing laparoscopic liver resection versus radiofrequency ablation. *Surg Endosc*. 2017;**31**(3):1269–74. doi: 10.1007/s00464-016-5105-5. [PubMed: 27444839].
19. Si MB, Yan PJ, Hao XY, Du ZY, Tian HW, Yang J, et al. Efficacy and safety of radiofrequency ablation versus minimally invasive liver surgery for small hepatocellular carcinoma: A systematic review and meta-analysis. *Surg Endosc*. 2019;**33**(8):2419–29. doi: 10.1007/s00464-019-06784-0. [PubMed: 30989373].
20. Li X, Wu YS, Chen D, Lin H. Laparoscopic hepatectomy versus radiofrequency ablation for hepatocellular carcinoma: A systematic review and meta-analysis. *Cancer Manag Res*. 2019;**11**:5711–24. doi: 10.2147/CMAR.S189777. [PubMed: 31417314]. [PubMed Central: PMC6600087].
21. Casaccia M, Santori G, Bottino G, Diviacco P, Negri AD, Moraglia E, et al. The procedure outcome of laparoscopic resection for 'small' hepatocellular carcinoma is comparable to vlaparoscopic radiofrequency ablation. *J Minim Access Surg*. 2015;**11**(4):231–5. doi: 10.4103/0972-9941.144093. [PubMed: 26622111]. [PubMed Central: PMC4640020].
22. Cheung TT, Chan ACY, Chok KSH, Lo CM. Laparoscopic liver resection versus percutaneous radiofrequency ablation in patients with hepatocellular carcinoma and liver cirrhosis: A case-matched study. *Lancet*. 2017;**390**. doi: 10.1016/s0140-6736(17)33177-x.
23. Lin MX, Peng ZW, Chen SL, Dai ZH, Wei GY, Kuang M. Laparoscopic surgery versus radiofrequency ablation for the treatment of recurrent hepatocellular carcinoma: a propensity score matching study. *Hepatol Int*. 2017;**11**(1):67. doi: 10.1007/s12072-016-9783-9.
24. Song J, Wang Y, Ma K, Zheng S, Bie P, Xia F, et al. Laparoscopic hepatectomy versus radiofrequency ablation for minimally invasive treatment of single, small hepatocellular carcinomas. *Surg Endosc*. 2015;**30**(10):4249–57. doi: 10.1007/s00464-015-4737-1. [PubMed: 26715020].
25. Chong CC, Lee KF, Chu CM, Chan AW, Yu SC, Lai PB. Laparoscopic hepatectomy (with or without robotic assistance) versus radiofrequency ablation as a minimally invasive treatment for very early-stage or early-stage hepatocellular carcinoma. *Dig Surg*. 2020;**37**(1):65–71. doi: 10.1159/000497112. [PubMed: 30917378].
26. Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ*. 2009;**339**:b2535. doi: 10.1136/bmj.b2535. [PubMed: 19622551]. [PubMed Central: PMC2714657].
27. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996;**334**(11):693–9. doi: 10.1056/NEJM199603143341104. [PubMed: 8594428].
28. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: Expansion of the tumor size limits does not adversely impact survival. *Hepatology*. 2001;**33**(6):1394–403. doi: 10.1053/jhep.2001.24563. [PubMed: 11391528].
29. Xu ZJ, Xu GL, Ma JL, Jia WD, Ge YS, Pan TT. [Ultrasound guided percutaneous radiofrequency ablation versus laparoscopic hepatectomy for small primary liver cancer]. *Chin J Gen Surg*. 2017;**26**:18–24. Chinese.
30. Song JX, Chen J, Li JW. [Clinical analysis of laparoscopic hepatectomy and radiofrequency ablation in the treatment of early hepatocellular carcinoma]. *J Hepatobiliary Surg*. 2017;**25**:349–53. Chinese.
31. Cui HX, Wang Y, Gao Y, Ren JP. [Ultrasound-guided radipfrequency ablation combined with anhydrous ethanol injection versus laparoscopic hepatectomy for small hepatocellular carcinoma]. *J Chin Pract Diagn Ther*. 2019;**33**:700–3. Chinese.
32. Zhou SX, Chen YJ, Yin XB, Ying FM, Feng XF. [The comparison of efficacy between laparoscopic radiofrequency ablation and laparoscopic hepatectomy in the treatment of small hepatic carcinoma]. *J Laparosc Surg*. 2019;**24**(4):258–62. Chinese.
33. Fan XK, Shi LJ, Guo L. [Comparison of laparoscopic-guided radiofrequency ablation and laparoscopic hepatectomy for the treatment of hepatocellular carcinoma]. *J Clin Exp Med*. 2018;**17**(14):1540–4. Chinese.
34. Wu CB, Cao H, Yu H, Wei FL, Wan P. [Effect of laparoscopic hepatectomy and laparoscopic radiofrequency ablation on small hepatocellular carcinoma]. *Jiangxi Med J*. 2019;**54**(4):348–51. Chinese.
35. Zhang HY, Zhuang ZB, Lin CD, Su ZY, Wang T. [Efficacy and prognosis comparison of percutaneous radiofrequency ablation and laparoscopic hepatectomy in treatment of small hepatocellular carcinoma]. *Chin J of Gen Surg*. 2019;**28**(1):24–30. Chinese.
36. Lai C, Jin RA, Liang X, Cai XJ. Comparison of laparoscopic hepatectomy, percutaneous radiofrequency ablation and open hepatectomy in the treatment of small hepatocellular carcinoma. *J Zhejiang Univ Sci B*. 2016;**17**(3):236–46. doi: 10.1631/jzus.B1500322. [PubMed: 26984844]. [PubMed Central: PMC4794515].
37. Harada N, Maeda T, Yoshizumi T, Ikeda T, Kayashima H, Ikegami T, et al. Laparoscopic liver resection is a feasible treatment for patients with hepatocellular carcinoma and portal hypertension. *Anticancer Res*. 2016;**36**(7):3489–97. [PubMed: 27354613].
38. Jiang S, Wang Z, Ou M, Pang Q, Fan D, Cui P. Laparoscopic versus open hepatectomy in short- and long-term outcomes of the hepatocellular carcinoma patients with cirrhosis: A systematic review and meta-analysis. *J Laparoendosc Adv Surg Tech A*. 2019;**29**(5):643–54. doi: 10.1089/lap.2018.0588. [PubMed: 30702362].
39. Deng ZC, Jiang WZ, Tang XD, Liu SH, Qin L, Qian HX. Laparoscopic hepatectomy versus open hepatectomy for hepatocellular carcinoma in 157 patients: A case controlled study with propensity score matching at two Chinese centres. *Int J Surg*. 2018;**56**:203–7. doi: 10.1016/j.ijsu.2018.06.026. [PubMed: 29935365].
40. Buell JF, Thomas MT, Rudich S, Marvin M, Nagubandi R, Ravin-

dra KV, et al. Experience with more than 500 minimally invasive hepatic procedures. *Ann Surg*. 2008;**248**(3):475–86. doi: 10.1097/SLA.0b013e318185e647. [PubMed: 18791368].
41. Dagher I, Belli G, Fantini C, Laurent A, Tayar C, Lainas P, et al. Laparoscopic hepatectomy for hepatocellular carcinoma: A European experience. *J Am Coll Surg*. 2010;**211**(1):16–23. doi: 10.1016/j.jamcollsurg.2010.03.012. [PubMed: 20610244].
42. Zhang W, Wang X, Wang Y, Zhao X, Duan W, Wang Q, et al. Effective viral suppression is necessary to reduce hepatocellular carcinoma development in cirrhotic patients with chronic hepatitis B: Results of a 10-year follow up. *Medicine (Baltimore)*. 2017;**96**(44). e8454. doi: 10.1097/MD.0000000000008454. [PubMed: 29095292]. [PubMed Central: PMC5682811].
43. Hikspoors J, Peeters M, Kruepunga N, Mekonen HK, Mommen GMC, Kohler SE, et al. Human liver segments: Role of cryptic liver lobes and vascular physiology in the development of liver veins and left-right asymmetry. *Sci Rep*. 2017;**7**(1):17109. doi: 10.1038/s41598-017-16840-1. [PubMed: 29214994]. [PubMed Central: PMC5719430].
44. Tian ZQ, Su XF, Lin ZY, Wu MC, Wei LX, He J. Meta-analysis of laparoscopic versus open liver resection for colorectal liver metastases. *Oncotarget*. 2016;**7**(51):84544–55. doi: 10.18632/oncotarget.13026. [PubMed: 27811369]. [PubMed Central: PMC5356680].
45. Mariani NM, Santambrogio R, Barabino M, Scifo G, Giovenzana MOE. Laparoscopic liver resection vs radiofrequency ablation in cirrhotic patients with hepatocellular carcinoma: towards the 'gold standard'. *Surg Endosc*. 2017;**31**(2):912–6. doi: 10.1007/s00464-016-5054-z. [PubMed: 27357926].
46. Wang Y, Luo Q, Li Y, Deng S, Wei S, Li X. Radiofrequency ablation versus hepatic resection for small hepatocellular carcinomas: A meta-analysis of randomized and nonrandomized controlled trials. *PLoS One*. 2014;**9**(1). e84484. doi: 10.1371/journal.pone.0084484. [PubMed: 24404166]. [PubMed Central: PMC3880302].
47. Weis S, Franke A, Mossner J, Jakobsen JC, Schoppmeyer K. Radiofrequency (thermal) ablation versus no intervention or other interventions for hepatocellular carcinoma. *Cochrane Database Syst Rev*. 2013;(12). CD003046. doi: 10.1002/14651858.CD003046.pub3. [PubMed: 24357457].
48. Adachi E, Maeda T, Kajiyama K, Kinukawa N, Matsumata T, Sugimachi K, et al. Factors correlated with portal venous invasion by hepatocellular carcinoma: Univariate and multivariate analyses of 232 resected cases without preoperative treatments. *Cancer*. 1996;**77**(10):2022–31. doi: 10.1002/(SICI)1097-0142(19960515)77:10<2022::AID-CNCR9>3.0.CO;2-S. [PubMed: 8640665].
49. Kong J, Kong L, Kong J, Ke S, Gao J, Ding X, et al. After insufficient radiofrequency ablation, tumor-associated endothelial cells exhibit enhanced angiogenesis and promote invasiveness of residual hepatocellular carcinoma. *J Transl Med*. 2012;**10**:230. doi: 10.1186/1479-5876-10-230. [PubMed: 23171368]. [PubMed Central: PMC3543343].
50. Podnos YD, Henry G, Ortiz JA, Ji P, Cooke J, Cao S, et al. Laparoscopic ultrasound with radiofrequency ablation in cirrhotic patients with hepatocellular carcinoma: Technique and technical considerations. *Am Surg*. 2001;**67**(12):1181–4. [PubMed: 11768826].

Table 2. Subgroup Analyses Based on RFA Approach, Country and Single Nodule Size Between RFA Versus LH

Subgroup	Categories	Study	Patients	Statistical Method	Effect Estimate (95% CI)	I^2, %	P Value
Postoperative local recurrence							
Total		8	963	OR (M-H, random)	2.97 (1.58 - 5.59)	70.0	< 0.001
RFA approach	LRFA	2	235	OR (M-H, fixed)	2.24 (1.11 - 4.53)	0.0	0.025
	PRFA	5	610	OR (M-H, fixed)	2.00 (1.37 - 2.92)	0.0	< 0.0001
	Mixed	1	118	OR (M-H, fixed)	19.19 (7.57 - 48.63)	-	< 0.0001
Country	China	7	909	OR (M-H, random)	2.74 (1.46 - 5.13)	71.0	0.002
	Japan	1	54	OR (M-H, fixed)	23.97 (1.31 - 440.35)	-	0.032
Overall survival							
Total	1-y	10	1059	OR (M-H, fixed)	1.10 (0.66 - 1.84)	0.0	0.706
	3-y	10	1059	OR (M-H, fixed)	0.79 (0.59 - 1.06)	49.0	0.117
	5-y	7	711	OR (M-H, random)	0.42 (0.16 - 1.12)	86.0	0.082
Single nodule, cm							
≤ 5	1-y	5	639	OR (M-H, fixed)	1.17 (0.59 - 2.30)	0.0	0.653
	3-y	5	639	OR (M-H, fixed)	0.67 (0.46 - 0.98)	48.0	0.037
	5-y	3	287	OR (M-H, random)	0.37 (0.05 - 2.88)	93.0	0.339
≤ 3	1-y	5	420	OR (M-H, fixed)	1.02 (0.47 - 2.23)	0.0	0.954
	3-y	5	420	OR (M-H, fixed)	1.04 (0.49 - 2.45)	55.0	0.874
	5-y	4	424	OR (M-H, random)	0.48 (0.18 - 1.32)	75.0	0.155
RFA approach							
LRFA	1-y	1	87	OR (M-H, Fixed)	1.43 (0.23 - 9.0)	-	0.704
	3-y	1	87	OR (M-H, fixed)	0.98 (0.42 - 2.31)	-	0.964
	5-y	3	297	OR (M-H, fixed)	0.74 (0.45 - 1.22)	0.0	0.236
PRFA	1-y	7	754	OR (M-H, fixed)	0.98 (0.55 - 1.74)	0.0	0.952
	3-y	7	754	OR (M-H, fixed)	0.69 (0.49 - 0.98)	23.0	0.037
	5-y	2	198	OR (M-H, fixed)	0.06 (0.03-0.14)	34.0	< 0.0001
Mixed	1-y	2	218	OR (M-H, fixed)	2.09 (0.44 - 9.95)	0.0	0.354
	3-y	2	218	OR (M-H, random)	1.63 (0.13 - 19.86)	88.0	0.702
	5-y	2	218	OR (M-H, random)	0.67 (0.08 - 5.96)	90.0	0.722
Country							
China	1-y	8	919	OR (M-H, fixed)	1.05 (0.62 - 1.77)	0.0	0.850
	3-y	8	919	OR (M-H, fixed)	0.69 (0.51 - 0.94)	21.0	0.019
	5-y	5	571	OR (M-H, random)	0.35 (0.12 - 1.06)	88.0	0.064
Japan	1-y	2	140	OR (M-H, fixed)	5.00 (0.20 - 125.91)	-	-
	3-y	2	140	OR (M-H, fixed)	3.51 (1.17 - 10.52)	51.0	0.025
	5-y	2	140	OR (M-H, random)	0.65 (0.05 - 7.81)	84.0	0.733

Disease-free survival							
Total	1-y	9	962	OR (M-H, fixed)	0.63 (0.46 - 0.85)	51.0	0.002
	3-y	9	962	OR (M-H, fixed)	0.48 (0.37 - 0.62)	57.0	< 0.0001
	5-y	6	642	OR (M-H, random)	0.48 (0.19 - 1.26)	81.0	0.139
Single nodule, cm							
≤ 5	1-y	5	639	OR (M-H, fixed)	0.74 (0.51 - 1.08)	5.0	0.116
	3-y	5	639	OR (M-H, fixed)	0.51 (0.37 - 0.70)	32.0	< 0.0001
	5-y	2	218	OR (M-H, fixed)	0.90 (0.47 - 1.71)	0.0	0.744
≤ 3	1-y	4	323	OR (M-H, random)	0.45 (0.16 - 1.24)	72.0	0.121
	3-y	4	323	OR (M-H, random)	0.39 (0.14 - 1.09)	76.0	0.074
	5-y	4	424	OR (M-H, random)	0.30 (0.07 - 1.26)	85.0	0.101
RFA approach							
LRFA	1-y	1	87	OR (M-H, fixed)	0.91 (0.34 - 2.48)	-	0.86
	3-y	1	87	OR (M-H, fixed)	0.85 (0.36 - 1.99)	-	0.708
	5-y	2	228	OR (M-H, fixed)	0.65 (0.35 - 1.22)	55.0	0.183
PRFA	1-y	6	657	OR (M-H, fixed)	0.64 (0.45 - 0.93)	45.0	0.018
	3-y	6	657	OR (M-H, fixed)	0.48 (0.35 - 0.66)	36.0	< 0.0001
	5-y	2	198	OR (M-H, random)	0.30 (0.02-3.70)	67.0	0.345
Mixed	1-y	2	218	OR (M-H, random)	0.53 (0.10 - 2.73)	84.0	0.446
	3-y	2	218	OR (M-H, random)	0.38 (0.07 - 1.98)	88.0	0.249
	5-y	2	218	OR (M-H, random)	0.36 (0.02 - 6.12)	94.0	0.479
Country							
China	1-y	7	822	OR (M-H, fixed)	0.63 (0.45 - 0.88)	40.0	0.006
	3-y	7	822	OR (M-H, random)	0.45 (0.29 - 0.72)	59.0	0.0007
	5-y	4	502	OR (M-H, random)	0.45 (0.15 - 1.35)	84.0	0.154
Japan	1-y	2	140	OR (M-H, random)	0.43 (0.05 - 3.78)	84.0	0.450
	3-y	2	140	OR (M-H, random)	0.40 (0.07 - 2.47)	74.0	0.326
	5-y	2	140	OR (M-H, random)	0.38 (0.01 - 11.18)	79.0	0.576

Abbreviations: LRFA, laparoscopic; M-H, Mantel-Haenszel method; OR, odds ratio; PRFA, percutaneous.