

Treatment of solitary hepatocellular carcinoma up to 2 cm

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: In recent years, there has been considerable uncertainty about the optimal treatment option for very early hepatocellular carcinoma (HCC) with tumor size less than 2 cm. Therefore, we performed a systematic review and meta-analysis to evaluate the outcomes of the different treatments.

Methods: This study was designed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA). PubMed, EMBASE, and Cochrane library were searched for calculating the survival rates, and the “time to event” method was used to compare the outcomes of liver resection (LR) and radiofrequency ablation (RFA). All studies focusing on the treatment of solitary HCC up to 2 cm by different techniques were included in our analysis. The Hazard ratios (HR) and 95% confidence intervals (CI) derived from multivariate and univariate analysis were utilized to assess the treatment risks.

Results: We included 32 studies in our systematic review. The median 5-year overall survival (OS) and recurrence-free survival rate (RFS) for LR were 73% and 47%, respectively, and those for RFA were 73% and 43%, respectively. RFA was found to be associated with increased risk of mortality and recurrence compared to LR (HR=1.61, 95% CI: 1.35–1.92, $P < .0001$ for OS and HR=1.75, 95% CI: 1.56–1.96, $P < .0001$ for RFS).

Conclusion: Our meta-analysis demonstrated that LR is superior to RFA in the treatment of solitary HCC up to 2 cm, with reduction in mortality and recurrence risk and improved long-term outcome.

Abbreviations: AFP = α -fetoprotein, AJCC = the American Joint Committee on Cancer, BCLC = Barcelona Clinic Liver Cancer, CI = confidence intervals, HCC = hepatocellular carcinoma, HR = hazard ratio, LR = liver resection, LT = liver transplantation, OS = overall survival, RFA = radiofrequency ablation, RFS = recurrence-free survival, TACE = transarterial chemoembolization, VI = vascular invasion.

Keywords: hepatocellular carcinoma, solitary, treatment, very early

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common type of malignancy and a major cause of cancer-related deaths worldwide.^[1,2] The incidence of HCC has slightly decreased in recent years due to the surveillance programs for patients diagnosed with hepatitis virus infection and chronic liver

cirrhosis.^[3,4] Nevertheless, HCC remains the fourth common malignancy in China because of the large number of hepatitis B patients.^[3] Due to the emphasis on surveillance, more cases of early HCCs are being detected currently which means more treatment options are being adopted.^[4–6]

The relationship between tumor stage and prognosis has been analyzed for years.^[7–9] The American Joint Committee on Cancer (AJCC) cancer staging is one of the most well-known staging systems for the management of cancer patients and recently, in their 8th edition, a solitary HCC ≤ 2 cm has been regarded as T1a stage, irrespective of vascular involvement.^[8] Another reliable method is the Barcelona Clinic Liver Cancer (BCLC) system, in which a solitary HCC ≤ 2 cm, with satisfactory liver function and absence of vascular invasion or extrahepatic disease, is defined as very early stage HCC.^[7] However, for those HCC patients who are deemed “too early”, liver transplantation (LT) is not recommended as the first line treatment and there are no exceptional points in the waiting list for graft in western countries.^[8,10] Liver resection (LR) is recommended as the best choice for HCC patients with normal portal pressure.^[7] In addition, radiofrequency ablation (RFA) as one of the local treatments for HCC, is also an optional curative treatment for small HCC. However, the impact of RFA compared to that of LR remains controversial.

In our study, we systematically reviewed the survival rates in literature and used the “time to event” method to perform a

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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meta-analysis, with the aim of investigating the role of RFA in the treatment of patients with very early HCC.

2. Materials and methods

The protocol was approved by the Ethics Committee of the Second People's Hospital of Lanzhou City. This study was designed according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines.^[11]

2.1. Search strategy and study selection

A systematic review with meta-analysis was undertaken to evaluate and assess the outcome of very early HCC patients with different treatments. We systematically searched the PubMed, EMBASE Medline, and Cochrane Central Register of Controlled Trials (CENTRAL) up to September 25, 2019. Moreover, Google Scholar was used for finding additional related grey literature. The search strategy that we used was as follows: medical subject heading (MeSH) major topic "hepatocellular carcinoma" AND "solitary", "very early", "2cm", AND "liver resection", "hepatic resection", "hepatectomy"(MeSH), "liver transplantation"(MeSH), "transarterial chemoembolization", "radiofrequency ablation", "percutaneous ethanol injection", "microwave ablation", "stereotactic body radiation therapy", "sorafenib". A systematic literature search was performed independently by 2 investigators. There was no language restriction. After completing the search, the records were imported into Endnote (Clarivate Analytic, version X6) for screening the titles and abstracts.

2.2. Inclusion and exclusion criteria

Studies focusing on solitary HCC up to 2 cm were included in our analysis. Survival results were collected either from Kaplan–Meier Curves or from the description of the results. Case reports and conference abstracts were excluded. Review articles were searched for relevant references. If the results of different studies came from the same center, only 1 study was included.

2.3. Literature screening, data extraction, and quality assessment

Two investigators independently screened the titles and abstracts for inclusion in the study. If the inclusion criteria were not clearly satisfied after going through the abstract, the full-text was further analyzed. Any disagreement regarding a study selection was solved by discussing with a third investigator.

The general study information and demographic data were recorded, including author details, publication year, recruitment period, country, study design, total sample size, and median tumor size. The primary outcomes of overall survival rate (OS), recurrence-free survival rate (RFS), recurrence rate, and VI rate were collected if available. Two authors together assessed the risk of bias in different studies. The Newcastle–Ottawa Scale was used to assess the quality of the cohort studies or case-control studies.

2.4. Statistical analysis

For comparing the impact of LR and RFA, the outcomes analyzed were "time to achieve 5-year OS" or "time to achieve 5-year RFS". We derived the hazard ratios (HR) and 95% confidence intervals (CI) from multivariate and univariate analyses. If the

HR was not described explicitly, we summarized the time-to-event data through survival curves based on the Tierney's method.^[12] Fixed effect model was used for calculation of the overall pooled HRs, involving calculation of the observed events minus the expected events and variance of each endpoint in each trial, with the treatment effect expressed as Petos odds with 95% CI. The χ^2 test was used for statistical heterogeneity, and I^2 statistic was used to evaluate heterogeneity (P value with $I^2 \geq 50\%$ indicating presence of heterogeneity). For the studies included in the systematic review, 1-, 3-, and 5-year OS and RFS were summarized using bubble size plots, where sample size was proportional to the bubble size.^[13] The meta-analysis and bubble plot construction were performed using Stata 15.0 software (Stata Corporation, College station, TX, USA). A P value $< .05$ was considered statistically significant for all analyses.

3. Results

3.1. Literature selection

Our search strategy yielded a total of 1456 studies. After screening the abstracts and titles, we were left with 32 articles in our systematic review,^[10,14–43] involving 10,517 patients with solitary HCC up to 2 cm who were treated with different treatment strategies. The screening procedure used for the articles is shown in the flowchart in Figure 1.

3.2. Characteristics of the included studies

The characteristics of the included studies are shown in Table 1, and the OS and RFS rates published in different studies are listed in Table 2. Three multicenter and 31 single-center retrospective case series were included. However, there were no randomized clinical trials. All papers were written in English. Two studies reported by Kim et al (2016) and Kim et al (2014) were reported from the same center, therefore, only the transarterial chemoembolization (TACE) group study by Kim et al was included in our analysis.^[19,24] The publication years ranged from 1993 to 2019, and the patients were recruited from 1981 to 2014. There were 27 studies involving 4938 patients who reportedly underwent LR and 18 studies involving 3531 patients who underwent RFA in this period. Only 1 study coming from the Surveillance, Epidemiology, and End Results database reported the OS for LT. Figure 2 shows the bubble plots for 1-, 3-, 5-year OS (drawn in red bubble) and RFS (drawn in blue bubble) for different treatments; the bubble sizes stands for the patient sample sizes of different studies. The 5-year OS rate ranged from 40% to 91.5% (median 73%) for LR, 40% to 86% (median 73%) for RFA, and 31.3% to 63.1% (median 56%) for TACE. The 5-year RFS rate ranged from 23% to 76% (median 47%) for LR and 13% to 71% (median 43%) for the RFA group.

3.3. Survival comparison between LR and RFA

A total of 10 studies compared of the survival outcomes of LR and RFA.^[16–19,28,30,31,33,42,43] Among them, 9 articles contained OS rates (Fig. 3) and 9 articles contained RFS rates (Fig. 4). For comparison of the OS of the 2 treatment methods, a total of 2556 patients were analyzed and 1984 patients lived more than 5 years. There was no clear evidence of statistical heterogeneity between trials ($I^2=23.1\%$, $P=.238$). Patients treated with RFA were observed to have a higher mortality than those treated with LR (HR=1.61, 95%:1.35–1.92, $P<.0001$).

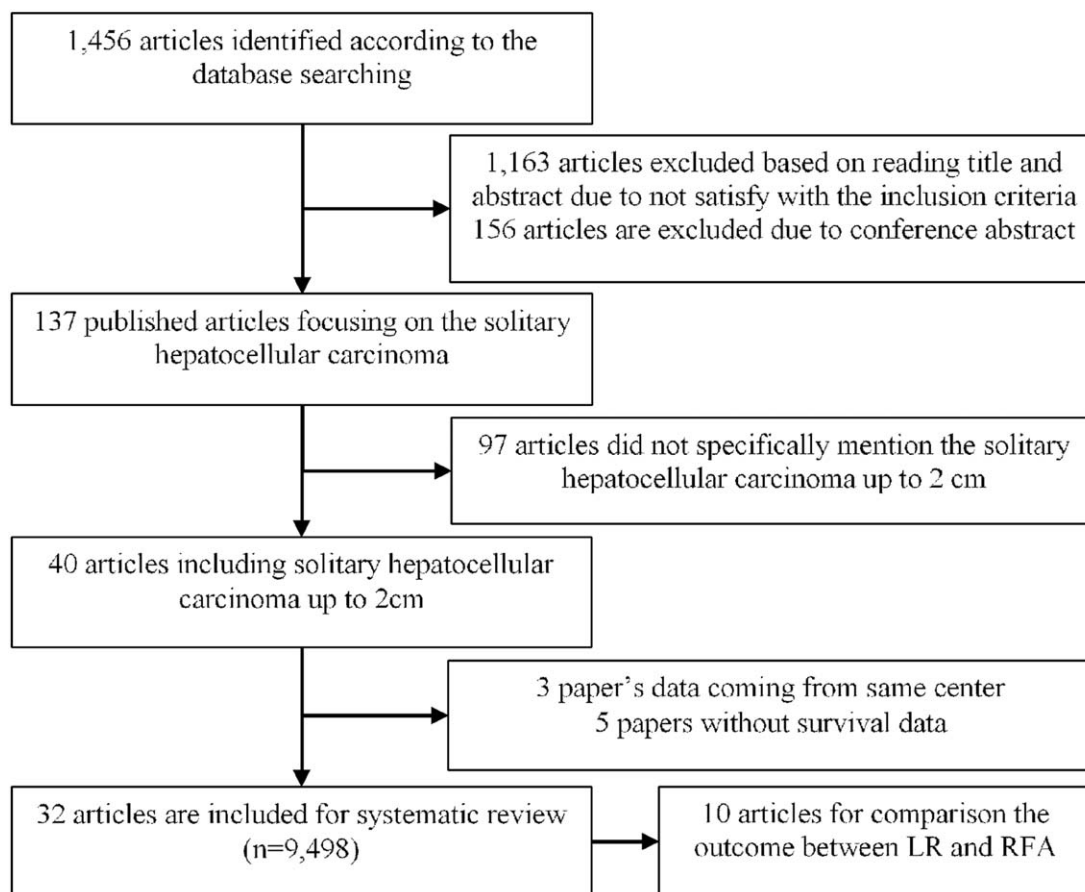


Figure 1. The flow diagram of study selection in our systematic review.

For analyzing the RFS, a total of 2409 patients were included and 1077 patients lived for more than 5 years without any recurrence. There was also no significant heterogeneity between trials ($I^2 = 8.3\%$, $P = .366$). The combined results demonstrated a significant increase in RFS associated with the use of LR for treatment of solitary HCC up to 2 cm ($HR = 1.75$, $95\% CI = 1.56-1.96$, $P < .0001$), which represents a 1.75-fold increase in the risk of recurrence if RFA is used for treatment.

4. Discussion

In our meta-analysis, we used the “time to event” method by utilizing the HRs available in various studies to compare the outcomes of LR and RFA in patients with very early HCC. Our findings revealed that treatment with RFA may have a higher risk of recurrence and mortality compared to LR.

The classification and treatment strategies for “very early HCC” patients have been controversial for many years. It has been the general opinion that these patients have a good outcome and therefore, LT should not be considered as the first-line treatment. Consequently, in some centers, these patients are not considered in the LT waiting list because they may deprive the advanced HCC patients. Additionally, these patients have different treatment options to choose from, and in some centers, even if non-curative treatment was adopted, the patients had a favorable outcome. Nevertheless, curative treatment has still been the major approach in treating very early HCC patients.

However, a Korean study recently demonstrated that there was no significant difference in the overall survival rate between RFA and TACE for very early stage HCC, although RFA was associated with a better tumor response and delayed tumor progression.^[24] Nevertheless, TACE is not considered the first-line treatment for small HCCs unless the patients are unable to tolerate surgery due to suboptimal liver function, anesthesia factors, advanced age, or other personal conditions.

With respect to curative treatment, the choice between RFA and LR is still debatable due to the absence of randomized controlled trials focusing on very early stage HCC patients. According to the BCLC guidelines, patients diagnosed with solitary HCC ≤ 2 cm with normal portal pressure should be treated by LR.^[7] However, the majority of HCC patients have a background of cirrhotic liver disease, and portal hypertension is quite common, which is the chief contraindication for LR due to the risk of post-operative hepatic decompensation.^[44] Therefore, RFA could be a possible treatment option in such patients. As a local and less-invasive treatment, it is usually considered as a bridging therapy for LT. A few studies have demonstrated that the RFS is better in patients who have undergone LR than in those who have undergone RFA.^[18,19,30] Similarly, Wang et al demonstrated that the LR group of patients had a better overall survival than the RFA group.^[30] In contrast, 4 other studies found no significant difference in OS and RFS on comparing the 2 treatments.^[16,17,28,31,33] In our study, we did not find any significant difference between RFA and LR in terms of overall

Table 1**The characteristics of the studies involved in the systematic review.**

Study	Publish year	Country	Enrollment period	Total	Median size
Arii et al	2000	LCSGJ	1988–1996	2576	NG
Asahara et al	1998	Japan	1986–1994	40	NG
Hung et al	2011	China	2002–2007	115	NG
Imai et al	2013	Japan	2000–2011	89	NG
Inoue et al	2004	Japan	1982–1991	68	NG
Kim	2016	Korea	2000–2009	245	NG
Kim et al	2014	Korea	2005–2007	287	1.6
Kutlu et al	2017	SEER	2004–2013	351	1.5
Lee et al	2011	Korea	2000–2008	58	NG
Liu et al	2016	China	2004–2013	262	NG
Livraghi et al	2008	Italy	1995–2006	218	NG
Miraglia et al	2007	Italy	NG	69	NG
Oh et al	2017	Korea	2007–2012	368	NG
Peng et al	2012	China	2003–2008	145	NG
Pompili et al	2015	Italy	1988–2011	244	1.95
Roayaie et al.	2013	USA	1990–2009	132	1.6
Sapisochin et al	2013	Spain	1991–2007	22	NG
Sasaki et al	2015	Japan	1994–2012	233	1.6
Sawada et al	2011	Japan	2000–2008	46	NG
Shindoh et al	2013	USA	1981–2011	155	1.8
Song et al	2016	China	2007–2013	73	NG
Takayama et al	2010	LCSGJ	2002–2003	2550	NG
Takuma et al	2013	Japan	2000–2010	111	NG
Torii et al	1993	Japan	1981–1991	32	NG
Wang et al	2012	China	2002–2009	143	NG
Xu et al	2017	China	2007–2012	460	NG
Yamamoto et al	2002	Japan	1985–1994	125	NG
Yamashita et al	2012	Japan	1994–2010	149	1.7
Zhang et al	2014	China	2002–2010	70	NG
Zhou et al	2014	China	2003–2008	52	1.7
Chu et al	2019	Korea	2000–2013	1208	1.7
Kim et al	2019	Korea	2004–2014	154	1.6

LCSGJ=the Liver Cancer Study Group of Japan, SEER=the Surveillance, Epidemiology, and End Results database.

Table 2**The overall survival and recurrence-free survival rate in solitary HCC less than 2cm.**

Study	Publish year	Sample size	treatment	Overall survival, %			Recurrence-free survival, %		
				1-y	3-y	5-y	1-y	3-y	5-y
Kim et al	2019	52	LR	94	77	40	86	51	23
		102	RFA	96	83	51	82	38	13
Chu et al	2019	631	LR	98	92	89	92	70	60
		577	RFA	98	90	80	90	53	41
Kutlu et al	2017	131	LR	94	70	56	–	–	–
		89	RFA	91	62	40	–	–	–
		131	LT	94	84	80	–	–	–
Xu et al	2017	159	RFA	98.7	86.8	73.3	89.9	67.3	54.9
		301	MWA	99.3	90.4	78.3	94.4	71.8	46.9
Oh et al	2017	368	RFA	98	90	83	–	–	–
Liu et al	2016	109	LR	98	97	81	91	64	49
		128	RFA	98	88	76	72	38	24
Song et al	2016	33	La LR	–	–	–	92	65	60
		40	RFA	–	–	–	71	55	40
Kim et al [†]	2016	64	LR	99	95	91	91	81	71
		181	RFA	98	92	86	80	53	41
Sasaki et al	2015	233	LR	–	–	–	88.5	58.8	44.9
Pompili et al	2015	136	RFA	87.7	77.1	62.3	79.6	52.3	42.6
		108	PEI	88	70	44	84	38	15
Zhang et al	2014	70	LR	100	89.6	84	87.1	75.4	70.5
Kim W et al [†]	2014	122	TACE	93.4	75.4	63.1	–	–	–
Zhou et al	2014	21	LR	95.2	85.7	81	90.5	81	76.2

(continued)

Table 2
(continued).

Study	Publish year	Sample size	treatment	Overall survival, %			Recurrence-free survival, %		
				1-y	3-y	5-y	1-y	3-y	5-y
Shindoh et al	2013	31	RFA	93.5	90.3	80.6	90.3	83.9	71
Roayaie et al	2013	155	LR	90.1	81.7	73.9	—	—	—
Sapisochin et al	2013	132	LR	—	—	—	80	44	31
Takuma et al	2013	22	LR	85	63	60	—	—	—
		52	LR	98	96	89	94	72	52
		59	TACE + RFA	100	83	58	93	54	24
Imai et al	2013	38	LR	100	90	90	93	55	42
		51	RFA	94	82	82	73	45	30
Yamashita et al	2012	149	LR	98	90	81	94	80	64
Peng et al	2012	74	LR	90.5	70.9	62.1	75.6	56.1	51.3
		71	RFA	98.5	87.7	71.9	76.4	65.2	59.8
Lee et al	2011	58	LR	95	82.5	—	78	71.5	—
Sawada et al	2011	46	LR	100	92.6	72.8	86	43	31
Hung et al	2011	50	LR	100	91.1	84.6	90	59.5	45.2
		65	RFA	98.3	86.5	77.8	81.1	42.6	25.2
Takayama et al	2010	1235	LR	98	—	—	91	—	—
		1315	RFA	99	—	—	84	—	—
Livraghi et al	2008	218	RFA	95	76	55	66	26	20
Miraglia et al	2007	69	TACE	87	79	—	—	—	—
Inoue et al	2004	68	LR	—	—	62.7	—	—	—
Yamamoto et al	2002	125	LR	—	—	68	—	—	—
Arii et al	2000	1318	LR	96	87.6	71.5	—	—	—
		767	PEI	96	81	54	—	—	—
		491	TACE	96	69.9	31.3	—	—	—
Asahara et al	1998	40	LR	—	86.6	53.3	—	—	—
Torii et al	1993	32	LR	—	66	59	—	—	—

*The multi-center data were involved into the bubble plots chart, while not into the meta-analysis.

†Those 2 articles are from the same centers, ONLY the TACE group was kept in the KIM. J. W.s article.

La LR=laparoscopic liver resection, LR=liver resection, LT=liver transplantation, MWA=microwave ablation, PEI=percutaneous ethanol injection, RFA=radiofrequency ablation, TACE=transarterial chemoembolization.

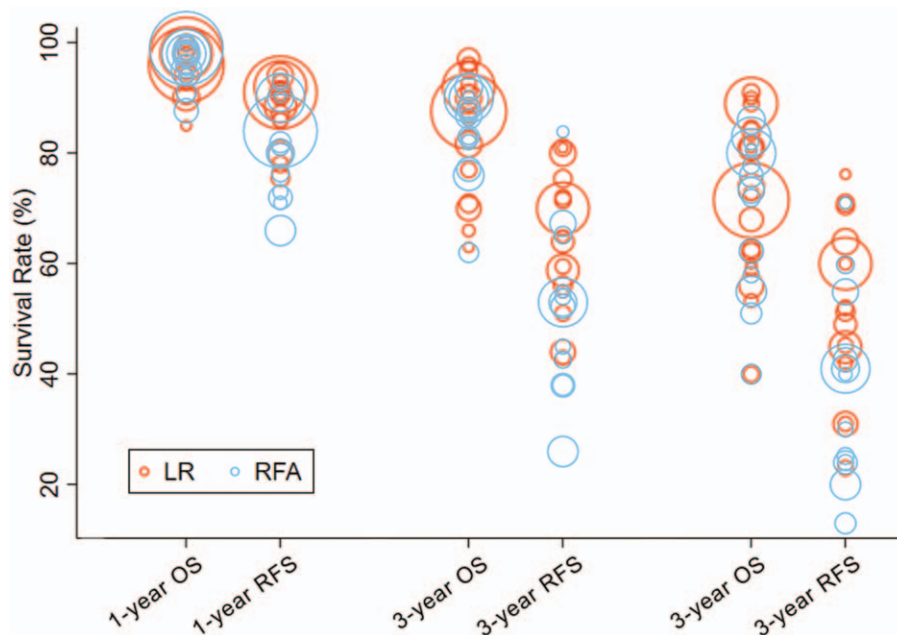


Figure 2. The bubble plot of 1-,3-,5-year overall and recurrence-free survival in different treatment from systematic review in patients diagnosing as solitary HCC up to 2 cm. Bubble size indicates relative cohort size (LR=red bubble, RFA=blue bubble).

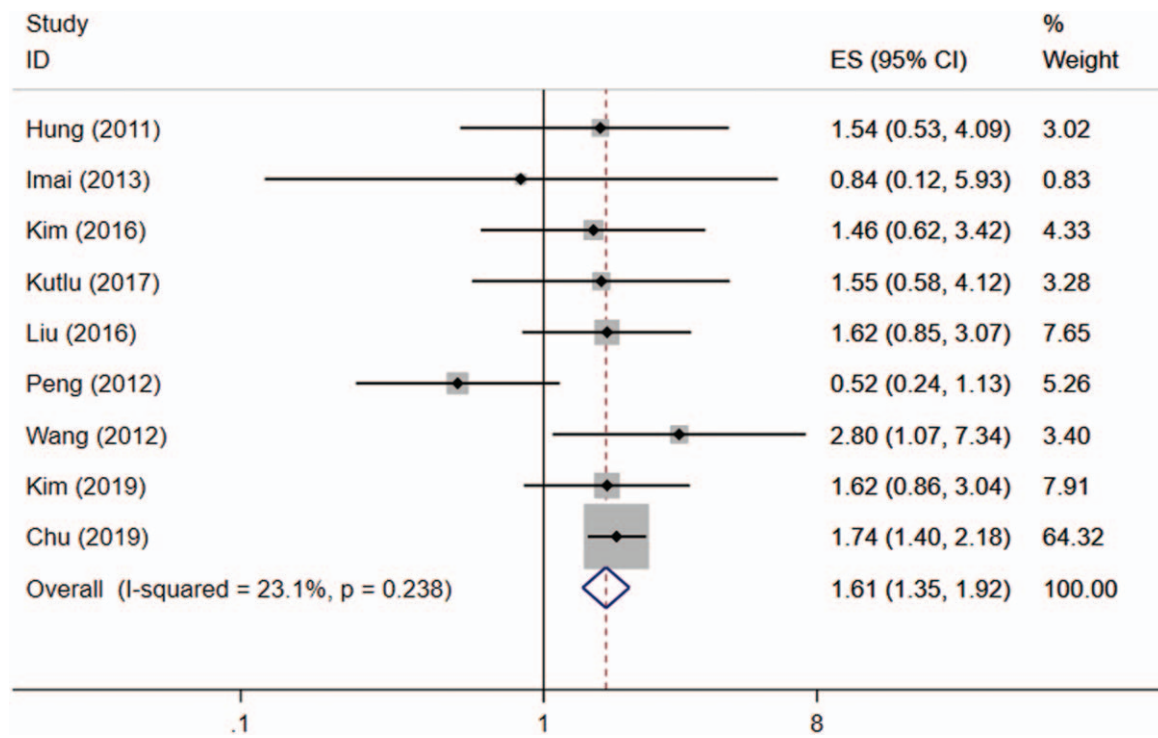


Figure 3. The forest plots of studies included comparing the overall survival rate between RFA and LR.

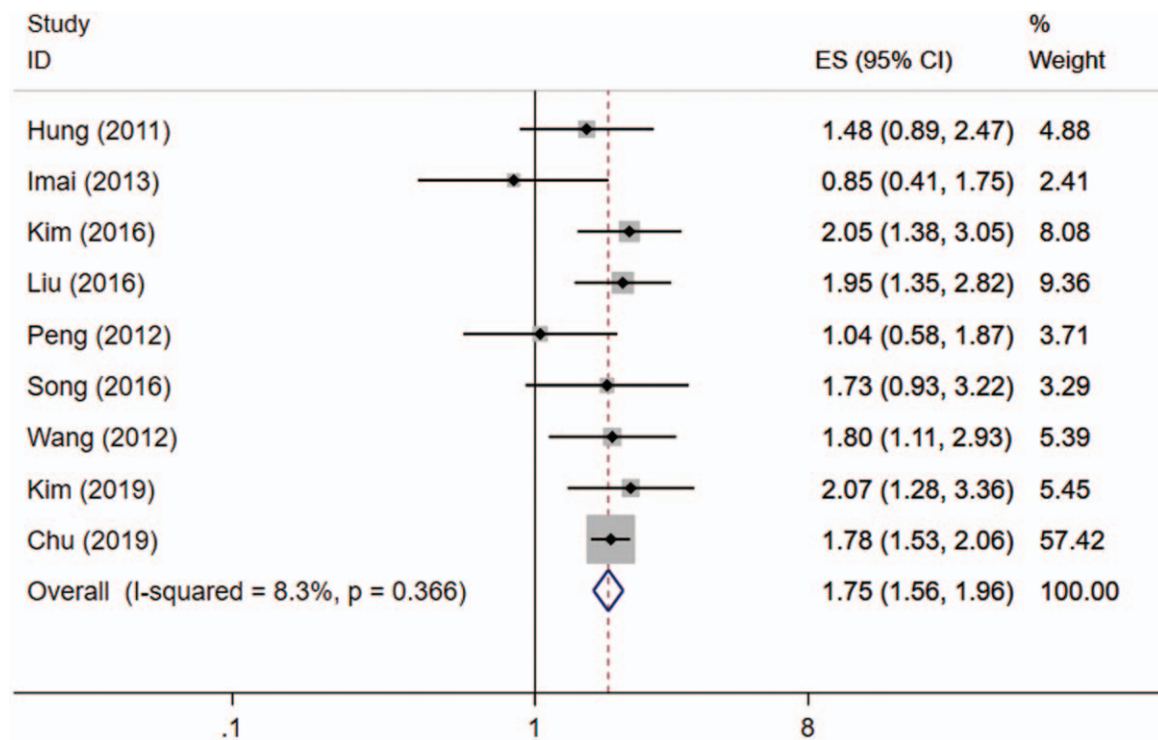


Figure 4. The forest plots of studies included comparing the recurrence-free survival rate between RFA and LR.

survival and recurrence-free survival rate in patients with very early HCC. Consequently, a meta-analysis was needed to explore the outcome in these patients. Some previous meta-analyses have analyzed the different treatment options focusing on tumors < 3

cm, or only comparing the 1-, 3-, 5-year survival rates.^[45–47] However, in survival analysis, patients censored in the study period should be considered as factors. Therefore, we used the “time to event” method utilizing the HRs obtained from

literature to compare the outcomes of T1a stage patients. In our meta-analysis, patients who underwent LR had a better OS and RFS compared to patients who underwent RFA. This might be because anatomical resection may reduce the incidence of intrahepatic recurrence as reported by some studies.^[30] Moreover, in our study, we used bubble plots, with sample size as bubble size to indicate the 1-, 3-, 5-year survival rates for different treatments and therefore, the intuitive changes between survival rate, study samples, and treatment could be seen.

Our study does have some limitations. For the meta-analysis, even though we used the “time to event” method to decrease the influence of censoring in the survival analysis, the lack of randomized controlled studies still affected the results and the quality of current evidence remains low. Moreover, even though there was no significant difference in heterogeneity between studies, the variations in therapy techniques are unavoidable in different studies.

In conclusion, our meta-analysis revealed that LR is superior to RFA in the treatment of solitary HCC up to 2 cm, and is associated with decreased mortality and recurrence risk with improved long-term outcome.

Author contributions

FHY and ZWQ designed the study; FHY, ZCG, YJZ, MWH performed the research and collected the data; FHY and ZWQ analyzed and interpreted the data; FHY wrote the first draft of the manuscript; All authors edited the manuscript and approved the final draft.

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