Systematic Review and Meta-Analysis

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Radiofrequency ablation versus microwave ablation for early stage hepatocellular carcinoma

A PRISMA-compliant systematic review and meta-analysis

Jie Han, MM, Yu-chen Fan, MD, Kai Wang, MD*

Abstract

Background: Several randomized control trials (RCTs) were conducted to compare microwave ablation (MWA) and radiofrequency ablation (RFA) in the treatment of hepatocellular carcinoma (HCC) over the years. The purpose of this study was to compare the efficacy of RFA and MWA for early stage HCC.

Methods: Studies were systematically searched on Emabse, Ovid Medline, PubMed, and Cochrane Library until March 20, 2020. Continuous variables and dichotomous variables were compared using weighted mean difference (WMD) and odds ratio (OR), respectively. For the comparison of overall survival (OS) and disease-free survival (DFS), the hazard ratio (HR) and 95% confidence interval (CI) were extracted from univariate analysis or survival plots.

Results: A total of 26 studies (5 RCTs and 21 cohorts) with 4396 patients (2393 patients in RFA and 2003 patients in MWA) were included in our study. Of these patients, 47% received treatment under general anesthesia in the MWA group and 84% in the RFA group (OR = 0.529, $P < .001$). The median ablation time was reduced in the MWA group (12 minutes) compared with RFA group (29 minutes) (WMD = –15.674, $P < .001$). In total, 17.6% patients exhibited progression during follow-up in the MWA group compared with 19.5% in the RFA group (OR = 0.877, $P = .225$). No statistically significant differences were observed between MWA and RFA groups in terms of OS and DFS (HR = 0.891 and 1.014, $P = .222$ and .852, respectively).

Conclusions: MWA exhibited similar therapeutic effects as RFA in the treatment of early stage HCC. Given the shorter ablation time, MWA can be performed under local anesthesia.

Abbreviations: CI = confidence interval, DFS = disease-free survival rate, HCC = hepatocellular carcinoma, HR = hazard ratio, LTP = long-term progression rate, MWA = microwave ablation, NCS = the Newcastle-Ottawa Quality Assessment Scale, OR = odd ratio, OS = overall survival rate, PRISMA = the preferred reporting items for systematic review and meta-analysis, RCTs = randomized control trials, RFA = radiofrequency ablation, SD = standard deviations, TACE = transarterial chemoembolization, WMD = weighted mean difference.

Keywords: frequency ablation, hepatocellular carcinoma, microwave ablation

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Ethical waived statement: Due to the study design of this meta-analysis, all the data were from the published studies, and the ethical approval could be waived in our local ethical committee.

The authors have no conflicts of interest to disclose.

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

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1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor worldwide, and its prevalence has been increasing in recent years.[1,2] The most prominent problems in the treatment of HCC are that the curative resection rate is low and the recurrence rate is high. For early HCC that meets the Milan criteria (single tumor diameter ≤5 cm; multiple tumors ≤3, and the maximum diameter ≤3 cm, no vascular invasion, no extrahepatic metastasis), liver transplantation is the first choice, but its application is severely limited at present due to donor shortage and ethical issues of living donor liver transplantation.[3] Therefore, hepatic resection remains an effective option. However, HCC patients may experience severe liver cirrhosis, and excessive liver resection may increase the risk of liver failure after hepatic surgery. Thus, <30% of liver cancer patients are suitable for surgical treatment.[4] Given the advantages of saving more liver tissue, less trauma, positive effects, and low complications, thermal ablation has become an effective treatment for liver tumor patients, of which radiofrequency ablation (RFA) and microwave ablation (MWA) are the most common.

The principle of RFA is to insert a radiofrequency electrode into the tumor, and heat the tumor tissue to >60 °C to destroy the local tumor cells. In this process, alternating current is transmitted to surrounding tissue and causes directions of the ions to change, and vibration, friction, and heat are generated, thus resulting in coagulative necrosis of tumor tissue. Currently, given the benefits of practicality, safety, reasonable cost, and minimally invasive features, RFA is widely used in the local treatment of HCC.[5] Some institutions even applied RFA to patients with early stage HCC who were suitable for surgery and have obtained good outcomes.[6,7] More recently, several studies have compared RFA and hepatectomy for small HCC.[8–10] The results showed that RFA is a minimally invasive and effective treatment with satisfying outcomes. Microwave is a type of high-frequency electromagnetic wave that converts electromagnetic wave energy into MWA energy through a microwave emitter, causing intense movement of water molecules in the tissue to heat the tumor to 60 to 100°C and resulting in cell coagulation necrosis.[11,12] In the past, MWA had been limited to small ablation ranges, long treatment times, and skin and soft tissue burns. However, recently, research on MWA has gradually developed, and the purpose is to obtain a larger area of tumor necrosis compared with RFA. Several emerging technologies in MWA have significantly improved its efficacy and safety. At present, MWA with a water-cooling cycle can obtain a larger ablation boundary and avoid the effect of tissue electrical conduction, and tissue carbonization prevents the effect of its energy diffusion. Some previous single-center studies clarified that MWA has obtained better ablation results and fewer related complications.[13,14]

Some systematically reviews and meta-analyses were performed to evaluate the efficacy of RFA and MWA in the treatment of HCC.[15–17] However, some meta-analyses included not only the primary liver cancer but also liver metastasis in their studies, which may led to a heterogeneity in the long-term outcome considering that metastasis is not representative of early stage tumors.[15] In addition, some studies enrolled patients who simultaneously underwent other treatments, such as transarterial chemoembolization (TACE), which may also be regarded as an incurable method for HCC, and resulted in decreased long-term outcomes.[15,18] Moreover, most studies compared the survival outcome with living patients in each year, which may also represent a bias in assessing the impact of treatment due to lack of the "time-to-event" data. Therefore, we designed this systematic review and meta-analysis and focused on the comparison of the efficacy between RFA and MWA for early stage HCC patients.

2. Methods

This study was designed in accordance with the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines.[19]

2.1. Search strategy

This study aimed to analyze the efficacy between RFA and MWA in the treatment of HCC patients. The search strategy was designed by an experienced librarian. A systematic search was performed using Embase, Ovid Medline, PubMed, and Cochrane Central Register of Controlled Trials up to March 20, 2020, with "radiofrequency ablation," "microwave ablation," and "hepatocellular carcinoma" as keywords and Mesh terms. The gray literature and related websites and conferences were also searched on Google Scholar. Then, all studies were imported into endnote with titles and abstracts to identify duplicate studies and perform literature screening.

2.2. Inclusion and exclusion criteria

The studies comparing the efficacy of RFA and MWA in HCC patients and fulfilling the following criteria were considered for inclusion in our study: therapeutic effect assessed and presented as long-term progression rate (LTP), complete release rate, overall survival rate (OS), disease-free survival rate (DFS), or complication rate; patients included were diagnosed with HCC based on histology or clinical criteria regardless of the Child-Pugh class, tumor size, and previous or following treatments.

The following exclusion criteria were employed: liver tumor was suspected as liver metastasis and benign liver tumor; the study type was case report or <10 cases were included in the study; animal experiment; neither RFA nor MWA was chosen for ablation; outcomes were not compared between RFA, and MWA and the data could not be fully extracted; patients simultaneously received other treatments, such as TACE or liver resection. Studies should only be published in English. Reviews, comments, and other meta-analyses were screened for further inclusion.

2.3. Literature screening and data extraction

Two investigators independently screened the titles and abstracts in accordance with the inclusion and exclusion criteria. Full texts were further assessed when titles and abstracts could not determine selection. The third investigator (KW) was consulted for discussion if there were any disagreements.

Data were extracted into a standard Excel form, and the following information was recorded: the study characteristics (author name, year of publication, country, institution, recruitment period, study design, etc), patient characteristics (treatment, patient sample, age, sex, median tumor size, single tumor percentage, hepatitis B virus and hepatitis C virus infection percentage, and Child-Pugh A percentage), and outcome assessment (anesthesia status, ablation time, hospital stay, LTP, complete response, OS, DFS, and complication rate).

2.4. Quality assessment

The quality of eligible papers was independently assessed by 2 investigators. We evaluated the cohort studies according to the Newcastle-Ottawa Quality Assessment Scale (NOS), which defined studies with a score of 6 to 9 as high quality and 0 to 5 as low quality.[20] For the randomized control studies, we used the Jadad scale. Based on this scale, scores of low-quality studies ranged from 0 to 3, whereas those of high-quality studies ranged from 4 to 8.[21] Similarly, we consulted a third investigator for discussion if any disagreements existed.

2.5. Statistical analysis

The meta-analysis was performed using Stata 15.0 software (Stata Corporation, College station, TX). For the efficacy of RFA and MWA, LTP and CR were compared by using odd ratios (ORs) and 95% confidence intervals (CIs), whereas WMD was adopted for continuous outcome such as hospital stay and ablation time. If data were presented as medians and ranges instead of mean and standard deviations (SD) for the continuous variables, we converted medians and ranges into means and SD using the formula provided by Hozo et al.[22] For the outcomes of 2 treatments, the hazard ratio (HR) and 95% CI were extracted from multivariate and univariate analyses. If the HR was not described explicitly, we used Tierney method to summarize time-to-event data through survival curves.[23] A random effect model was used to calculate the overall pooled HRs with the treatment effect expressed as Peto odds with 95% CI. The Chi-squared test was used for statistical heterogeneity, and I^2 statistic was used to evaluate heterogeneity (a *P*-value with $I^2 \geq 50\%$ indicates presence of heterogeneity). For further comparison of the 1-year to 5-year survival rates, the bubble size plots were drawn in which relative sample size was proportional to bubble size.[24] A *P*-value <0.05 was considered to be statistically significant.

3. Results

3.1. Literature selection

The search strategy identified 2418 studies and 11 additional records. After deleting the duplicated studies, 1564 studies were reviewed based on abstracts and titles. In accordance with inclusion and exclusion criteria, 26 studies with 4396 patients were finally enrolled.[25–27,11,28,13,29–36,14,37–43,12,44–46] The flowchart is shown in Fig. 1.

3.2. Characteristics of included studies

The characteristics of studies included are shown in Tables 1 and 2. There were 5 RCTs, 1 prospective cohort studies and 20 retrospective cohort studies conducted in 7 countries, coving Europe, North America, Asia, Africa, and Oceania during 2002 to 2020 with recruitment years between 1997 and 2017. Among these patients, 2393 were treated with RFA, and 2003 were treated with MWA. The median age ranged from 50 to 71 years old, and 54% to 95% patients were men. In total, 40% to 92% patients undergoing ablation had single lesion with median tumor size ranging from 1.6 to 3.6 cm. The etiologies

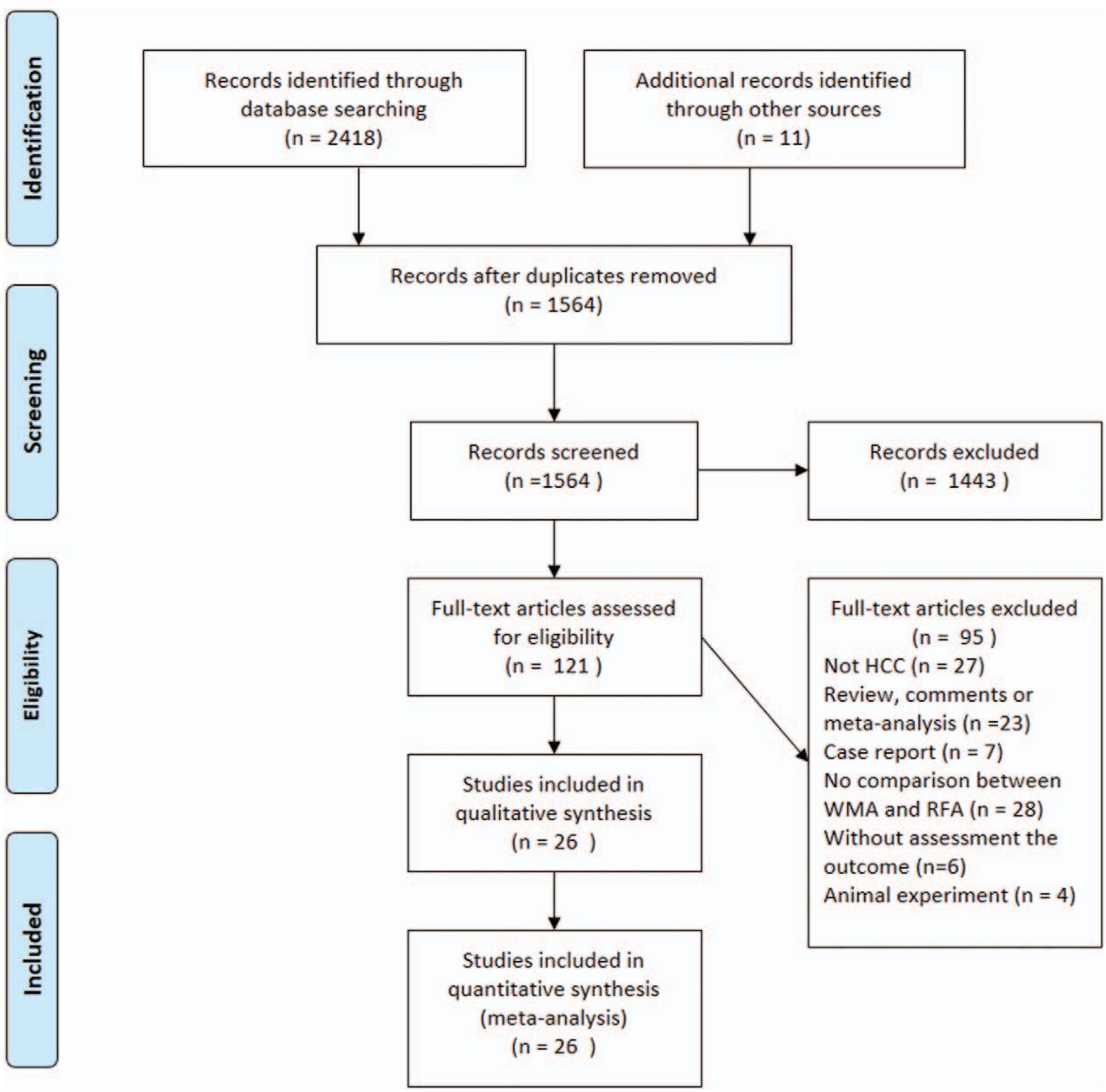

Figure 1. Flowchart of literature screening of the systematic review and meta-analysis.

Table 1

Characteristics of included cohort studies.

Author	Publish year	Country	Recruitment year	Study type	NCS	Method	Sample	Age	Male, %	Single lesion, %	HBV, %	HCV, %	Child A, %	Median tumor size
Du, S. et al	2020	China	2014–2016	Retrospective cohort	9	MWA	218	NG	173 (79)	177 (81)	190 (87)	28 (13)	200 (92)	NG
						RFA	234	NG	192 (82)	202 (86)	213 (91)	32 (14)	216 (92)	NG
Loriaud, A. et al	2018	Switzerland	2007–2015	Retrospective cohort	8	MWA	40	69 (61–75)	37 (93)	NG	NG	7 (18)	NG	2.3
						RFA	40	66 (61–75)	33 (83)	NG	NG	15 (38)	NG	2.1
Liu, W. et al	2018	China	2002–2017	Retrospective cohort	9	MWA	126	54 (45–60)	114 (90)	99 (79)	113 (90)	5 (4)	NG	2.3
						RFA	436	56 (46–65)	391 (90)	400 (92)	388 (89)	15 (3)	NG	2.3
Xu, Y. et al	2017	China	2007–2012	Retrospective cohort	7	MWA	301	54 ± 11	235 (78)	NG	250 (83)	11 (4)	278 (92)	1.7
						RFA	159	54 ± 11	132 (83)	NG	128 (81)	8 (5)	140 (88)	1.7
Santambrogio, R et al	2017	Italy	2009–2015	Retrospective cohort	7	MWA	60	70 (66–76)	43 (72)	35 (58)	9 (15)	40 (67)	60 (100)	2.2
						RFA	94	71 (65–76)	69 (73)	63 (67)	16 (17)	53 (56)	94 (100)	1.9
Lee, K.F. et al	2017	China	2009–2011	Retrospective cohort	7	MWA	26	63 (49–79)	19 (73)	24 (92)	21 (81)	NG	23 (88)	NG
						RFA	47	58 (43–77)	40 (85)	42 (89)	39 (83)	NG	42 (89)	NG
Potretzke, T. A. et al	2016	USA	2011–2013	Retrospective cohort	6	MWA	99	61 (44–82)	81 (82)	NG	4 (4)	56 (57)	NG	2.2
						RFA	55	62 (23–88)	40 (73)	NG	4 (7)	28 (51)	NG	2.4
Vogl, T.J. et al	2015	Egypt	2008–2010	Retrospective cohort	7	MWA	28	57 (40–64)	23 (82)	22 (79)	NG	NG	NG	3.2
						RFA	25	60 (45–68)	19 (76)	20 (80)	NG	NG	NG	3.6
Chinnaratha, A. et al	2015	Australia	2006–2012	Retrospective cohort	5	MWA	25	57 (40–64)	NG	NG	NG	NG	NG	NG
						RFA	101	60 (45–68)	NG	NG	NG	NG	NG	NG
Cillo, U. et al	2014	Italy	2009–2010	Prospective cohort	9	MWA	42	64 (47–81)	35 (83)	22 (52)	2 (5)	28 (67)	NG	2.5
						RFA	100	63 (34–81)	83 (83)	54 (54)	28 (28)	39 (39)	NG	3
Zhang, L. et al	2013	China	2006	Retrospective cohort	7	MWA	77	54 (26–76)	67 (87)	56 (73)	71 (92)	NG	77 (100)	NG
						RFA	78	54 (30–80)	64 (82)	63 (81)	75 (96)	NG	78 (100)	NG
Ding, J. et al	2013	China	2006–2010	Retrospective cohort	7	MWA	113	59 (30–86)	85 (75)	NG	78 (69)	25 (22)	75 (66)	2.6
						RFA	85	58 (40–77)	68 (80)	NG	62 (73)	15 (18)	49 (58)	2.4
Qian, G.J. et al	2012	China	2009–2010	Retrospective cohort	6	MWA	22	52 (43–75)	20 (91)	NG	NG	NG	NG	2.1
						RFA	20	56 (43–76)	19 (95)	NG	NG	NG	NG	2
Simo, A. et al	2011	USA	2006–2008	Retrospective cohort	6	MWA	13	60 (49–72)	7 (54)	10 (77)	1 (8)	8 (62)	7 (54)	NG
						RFA	22	58 (45–79)	19 (86)	17 (77)	2 (9)	14 (64)	12 (55)	NG
Kuang, M. et al	2011	China	1997–2008	Retrospective cohort	5	MWA	19	NG	NG	NG	NG	NG	NG	NG
						RFA	31	NG	NG	NG	NG	NG	NG	NG
Yin, X. et al	2009	China	1997–2007	Retrospective cohort	5	MWA	49	NG	NG	NG	NG	NG	NG	NG
						RFA	59	NG	NG	NG	NG	NG	NG	NG
Sakaguchi, H. et al	2009	Japan	1994–2005	Retrospective cohort	7	MWA	142	66 ± 9	107 (75)	NG	NG	NG	85 (60)	NG
						RFA	249	65 ± 8	169 (68)	NG	NG	NG	147 (59)	NG
Ohmoto, K. et al	2009	Japan	2002–2006	Retrospective cohort	7	MWA	49	64 (38–75)	41 (84)	NG	3 (6)	29 (59)	31 (63)	1.7
						RFA	34	67 (44–78)	25 (74)	NG	3 (9)	43 (126)	20 (59)	1.6
Lu, M.D. et al	2005	China	1997–2002	Retrospective cohort	8	MWA	49	50 (24–74)	44 (90)	36 (73)	39 (80)	NG	NG	2.5
						RFA	53	55 (20–74)	43 (81)	21 (40)	49 (92)	NG	NG	2.6
Xu, H.X. et al	2004	China	1997–2001	Retrospective cohort	5	MWA	54	NG	NG	NG	NG	NG	NG	2.5
						RFA	43	NG	NG	NG	NG	NG	NG	2.6
Shibata, T. et al	2002	Japan	1999–2000	Retrospective cohort	5	MWA	36	63 (52–74)	24 (67)	NG	4 (11)	32 (89)	19 (53)	2.3
						RFA	36	64 (44–83)	26 (72)	NG	1 (3)	34 (94)	21 (58)	2.2

HBV = hepatitis B virus infection; HCV = hepatitis C virus infection; MWA = microwave ablation; NCS = the Newcastle-Ottawa Quality Assessment Scale; NG = not given; RFA = radiofrequency ablation.

vary, and the prevalence of hepatitis B virus infection ranged from 1% to 96% in studies conducted in different countries. The majority of patients (75%) had a satisfying liver function, and 87% patients were suspected with liver cirrhosis.

3.3. Quality assessment of included studies

We used the NOS assessment to evaluate the quality of the cohort studies (Table 1). A total of 16 studies scored ≥7 were defined as high quality, and the remaining 5 were defined as low quality. The Jadad scale was used to evaluate the quality of the 5 RCTs.

Table 2

Characteristics of included RCT trials.

Author	Publish year	Country	Recruitment year	Jadad scale	Method	Sample	Age	Male, %	Single lesion, %	HBV, %	HCV, %	Child A, %	Median tumor size
Chong, C.N. et al	2020	China	2011–2017	7	MWA	47	63 (50–80)	30 (64)	43 (91)	38 (81)	NG	39 (83)	3.1
					RFA	46	65 (42–85)	38 (83)	39 (85)	34 (74)	NG	40 (87)	2.8
Kamal, A. et al	2019	Egypt	2017	5	MWA	28	NG	NG	24 (86)	NG	NG	22 (79)	NG
					RFA	28	NG	NG	22 (79)	NG	NG	22 (79)	NG
Vietti V.N. et al	2018	Switzerland	2011–2015	8	MWA	71	68 (60–72)	59 (83)	44 (62)	1 (1)	22 (31)	57 (80)	1.8
					RFA	73	65 (59–73)	62 (85)	46 (63)	4 (5)	28 (38)	53 (73)	1.8
Yu, J. et al	2017	China	2008–2015	4	MWA	203	NG	NG	NG	NG	NG	NG	NG
					RFA	200	NG	NG	NG	NG	NG	NG	NG
Abdelaziz, A. et al	2014	Egypt	2009–2014	3	MWA	66	57±7	48 (73)	57 (86)	NG	NG	25 (38)	3
					RFA	45	54±5	31 (69)	39 (87)	NG	NG	24 (53)	2.9

HBV = hepatitis B virus infection; HCV = hepatitis C virus infection; MWA = microwave ablation; NG = not given; RFA = radiofrequency ablation.

Based on these results, 4 studies were defined as high quality and 1 study was defined as low quality.

3.4. Comparison of the operative characteristics between MWA and RFA

Two studies discussed the anesthesia approach adopted when patients received MWA or RFA.[25,43] In total, 47% patients of the MWA group received general anesthesia compared with 84% patients in the RFA group (OR = 0.529, 95% CI = 0.419–0.667, I^2 = 85.8%, P < .001). Two studies assessed ablation time.[26,29] The median ablation time was shorter in the MWA group (12 minutes) compared with the RFA group (29 minutes) (WMD = –15.674, 95% CI = –17.187 to –14.161, I^2 = 6.5%, P < .001).

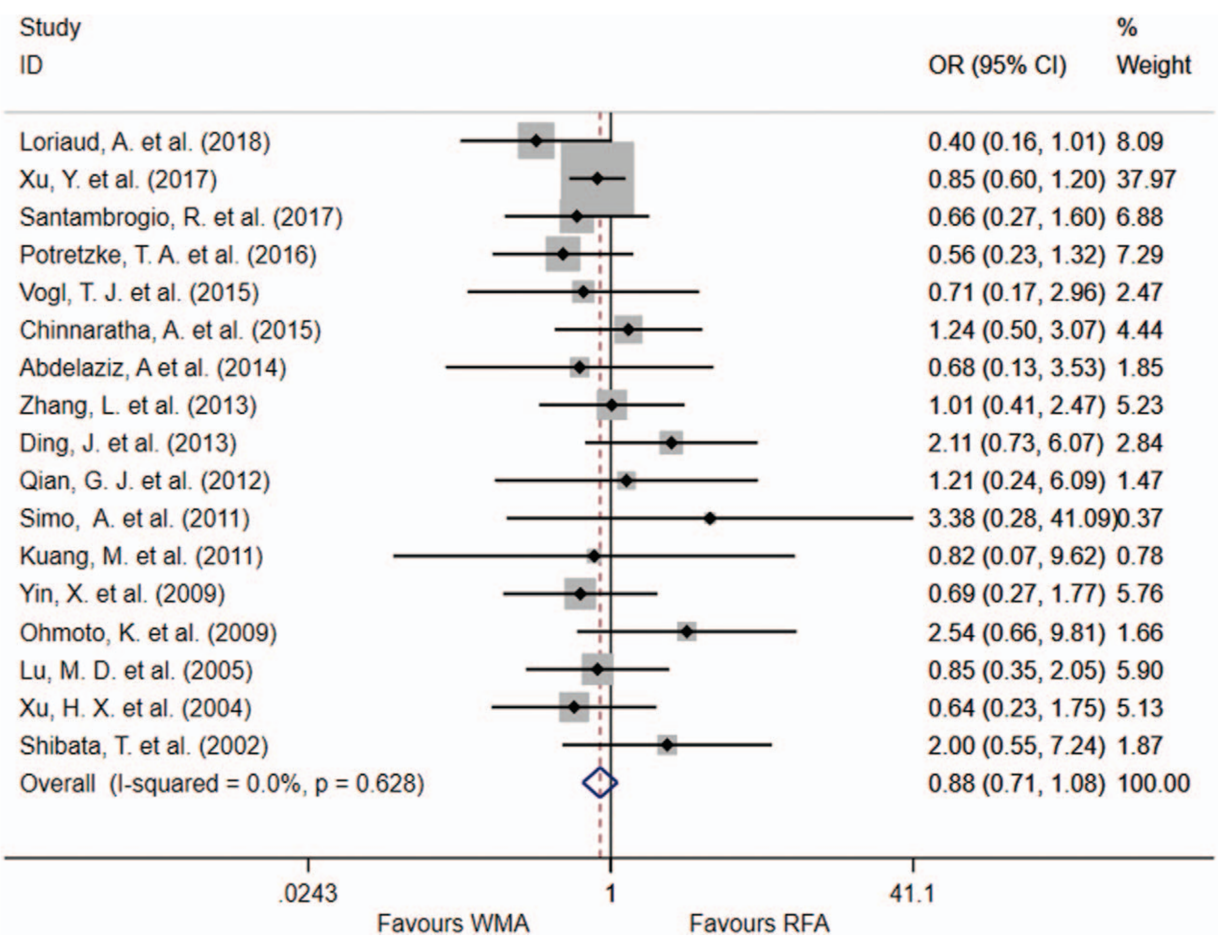

Figure 2. The comparison of long-term progression rates between RFA and MWA treatments for early stage HCC patients. HCC = hepatocellular carcinoma; MWA = microwave ablation; RFA = radiofrequency ablation.

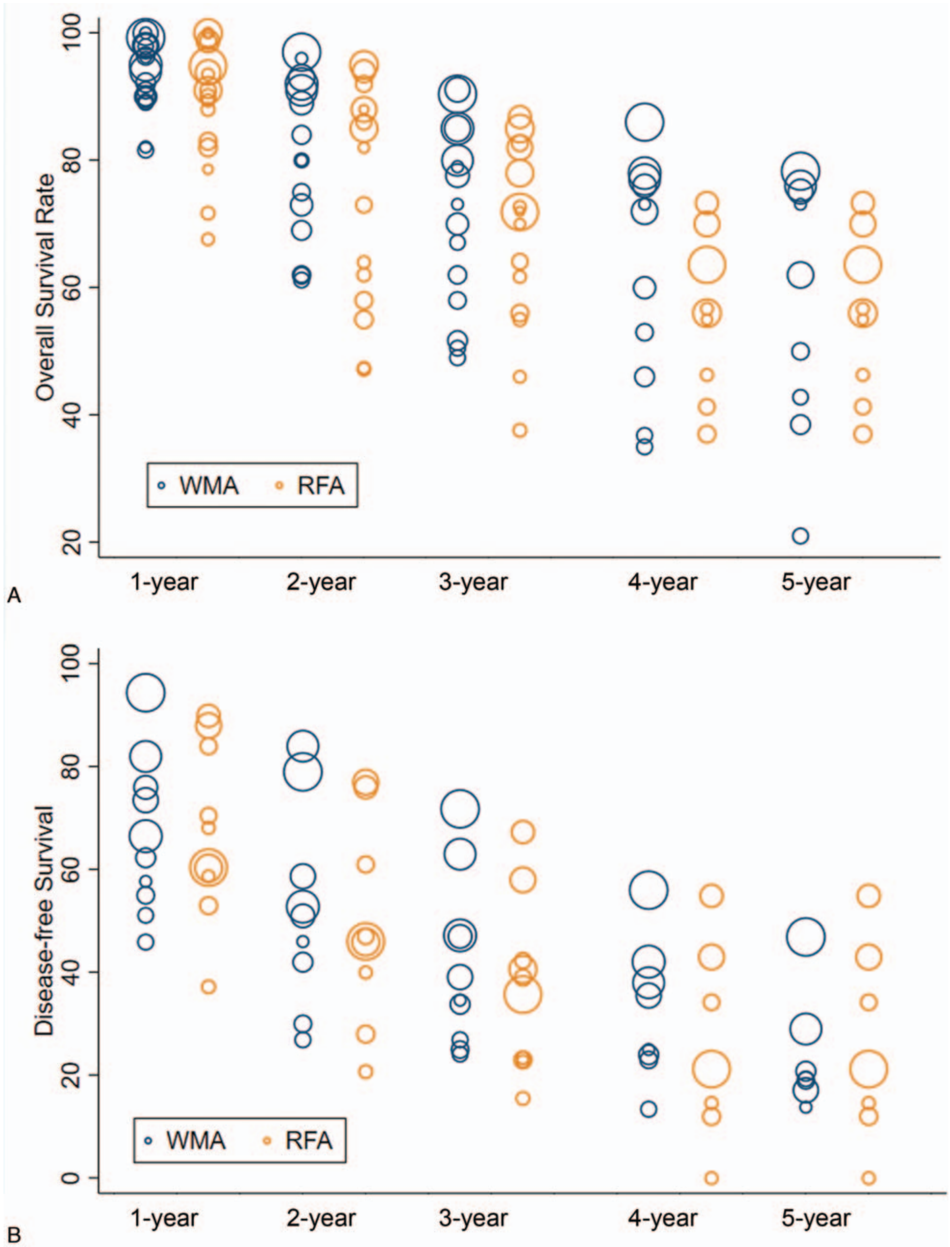

Figure 3. Bubble plots show the 1-year to 5-year overall survival (A) and disease-free survival (B) in RFA and MWA patients. MWA = microwave ablation; RFA = radiofrequency ablation.

3.5. Comparison of long-term outcome between MWA and RFA

The comparison of LTR was summarized in Fig. 2. In total, 17.6% patients experienced disease progression in the follow-up in the MWA group (243/1100), compared with 19.5% patients in the RFA group (228/980) (OR = 0.877, 95% CI = 0.710–1.084, I^2 = 0%, P = .225).

The survival rate was plotted and compared in Fig. 3. The median 1-year, 2-year, 3-year, 4-year, and 5-year OS were 93.3%, 80.2%, 71.3%, 63.0%, and 57.4%, respectively, in the MWA group compared with 89.5%, 74.4%, 68.1%, 58.0%, and 55.5%, respectively, in RFA group. Similarly, the median 1-year, 2-year, 3-year, 4-year, and 5-year OS were 66.4%, 52.3%, 41.3%, 32.1%, and 23.7%, respectively, in the MWA group compared with 67.0%, 49.0%, 36.8%, 33.5%, and 25.7%, respectively, in the RFA group.

The comparisons of pooled HR in OS are shown in Fig. 4. No statistically significant differences in OS were noted between the MWA and RFA groups; however, a slightly better trend was observed in the MWA group (HR = 0.891, 95% CI = 0.740–1.072, I^2 = 52.2%, P = .222). Statistical heterogeneity existing across the studies was assessed by subgroup analysis according to different study types. Similarly, no significant differences in OS were noted between the MWA group and the RFA group in cohort studies (HR = 0.904, 95% CI = 0.730–1.118, I^2 = 60%, P = .350) and RCTs (HR = 0.754, 95% CI = 0.538–1.032, I^2 = 0%, P = .076).

The summarized pooled DFS is shown in Fig. 5, and no significant difference was observed in DFS between the MWA

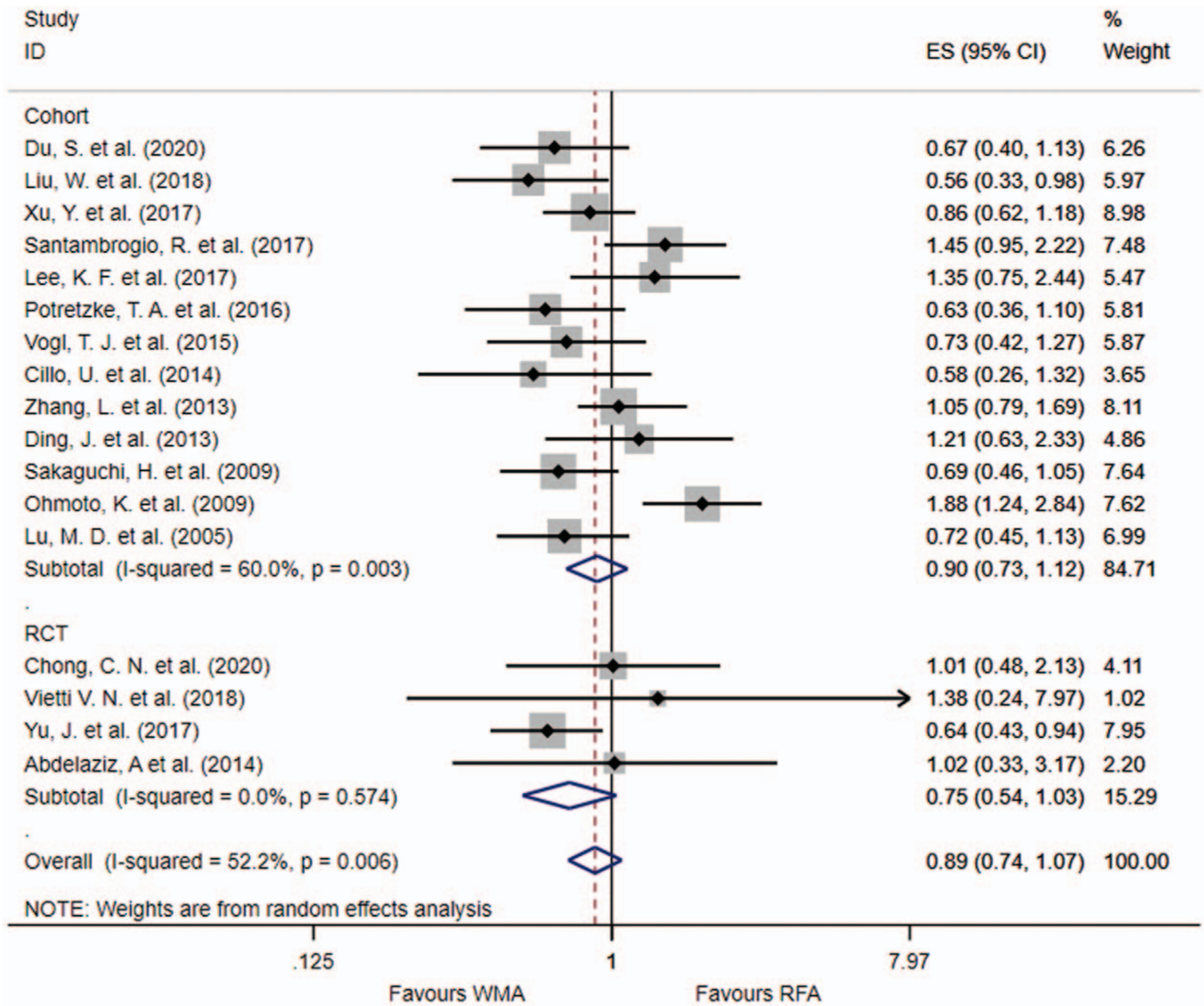

Figure 4. The comparison of overall survival between RFA and MWA treatments. MWA=microwave ablation; RFA=radiofrequency ablation.

and RFA groups in all studies (HR=1.014, 95% CI=0.873–1.179, I^2=48.4%, P=.852), cohorts (HR=1.990, 95% CI=0.811–1.209, I^2=58.5%, P=.924), and RCTs (HR=1.109, 95% CI=0.936–1.313, I^2=0%, P=.232).

4. Discussion

Our systematic review and meta-analysis included 26 studies with 4396 patients to compare the efficacy of RFA and MWA in the treatment of early stage HCC. We extracted the HRs from each survival plot provided information was available and attempted to show the differences in the 2 approaches based on "time-to-event" data. Given the shorter ablation time, we suggest that it is safe to receive MWA under local anesthesia. Although no significant difference in long-term outcome was noted between the 2 treatments, a slight increase in OS was observed in the MWA group.

RFA was introduced into clinical application in the 1990s and has gradually become an indispensable treatment for small liver cancer, especially for recurrent and deep-seated liver tumors.[47,48] Huang et al[49] compared the long-term efficacy of RFA and surgical resection for 833 HCC patients with a diameter ≤2 cm, and the results showed the same long-term efficacy for the 2 treatments. Of note, RFA still exhibits some limitations in the treatment of liver cancer, and the most important limitation is the heat sink effect, in which the lower temperature is not sufficient to inactivate tumor cells and may cause incomplete ablation.[50] Lehmann et al[51] used in vitro experiments to confirm that a minimum vascular flow of 1 mL/min could cause an obvious heat sink effect during the RFA of isolated liver. A single-center retrospective study by Lin et al[52] found that the heat sink effect caused by blood vessels was an important factor of the recurrence of liver malignant tumors after RFA. MWA emerged after RFA as a new therapy for local thermal ablation of liver cancer. Unlike RFA, MWA generates heat by polar molecules and charged ions in the human body under the action of an external high-frequency microwave electric field.[42,43,45,46] This technique is less dependent on tissue heat conduction ability and has certain advantages compared with RFA, such as increased infra-tumor temperature, shorter ablation time, and greater ablation range, thus being less affected by the vascular heat sink effect.[53,54] Thus, MWA may provide a shorter ablation time. In addition, the number of the needles might be another reason why WMA provided a shorter ablation time. Theoretically, multipolar needles could provide a larger ablation range than monopolar needles and result in a shorter

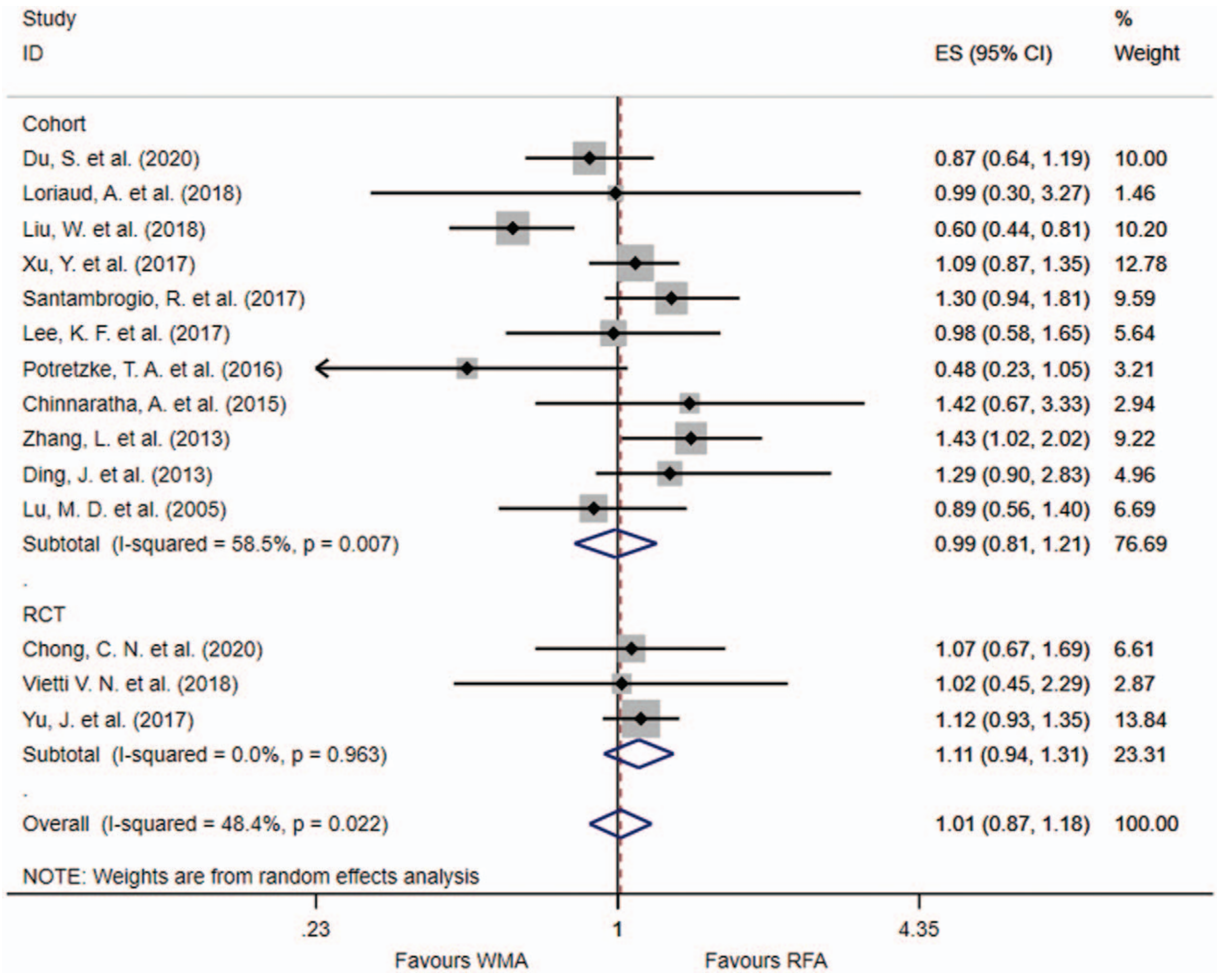

Figure 5. The comparison of disease-free survival between RFA and MWA treatments. MWA=microwave ablation; RFA=radiofrequency ablation.

ablation time.[26] However, due to the small number of samples that compare the efficacy of multipolar needles among studies, further investigations are still needed to compare different ablations using different needles. In our meta-analysis, we found that the proportion of patients under local anesthesia was greater in the WMA group compared with the RFA group. The reason for and the effect of the difference remained unclear. One reason might be related to the notion that HCC patients might easily suffer from local anesthesia in a shorter ablation time; thus, WMA performed under local anesthesia is more tolerable and safe. Similarly, more prospective studies are needed to further assess the safety of different anesthesia approaches.

In recent years, the efficacy of MWA and RFA have been compared in numerous studies, and most studies have shown that MWA has comparable safety and long-term efficacy for liver tumors with a diameter $\leq$4 cm.[11,38] In this meta-analysis, OS and DFS presented the outcomes of 2 ablation approaches, and comparisons were performed using the "time-to-event" method. In addition, the advantageous principle determines that MWA is more suitable for larger tumors and tumors adjacent to blood vessels than RFA. One study reported that MWA could achieve a comparable therapeutic effect to surgical resection for liver cancer $\leq$3 cm in diameter compared with surgical resection.[55] Although MWA is effective in treating HCC, it also has some shortcomings. The long diameter of MWA is much larger than the transverse diameter. To obtain a sufficient transverse diameter during the treatment, the long diameter often exceeds the tumor boundary and unnecessarily damages too much normal liver tissue, especially in patients with severe cirrhosis or those undergoing liver resection, and increases the risk of liver dysfunction post treatment. On the other hand, the method easily causes adverse effects to adjacent important tissue and organs, and the effects are exacerbated during the ablation of tumors in certain dangerous locations.[56] Additionally, changes in tissue characteristics during ablation affect the stability of the microwave field, making the shape of the ablation difficult to predict.[57] In tumor ablation, multiple ablation overlaps may cause omissions, incomplete ablation, or increase the risk of local progression. Therefore, new technology needs to be developed to improve the controllability of the ablation range and obtain a more regular spherical ablation volume.

Some limitations in our meta-analysis should be noted. First, we only included the studies published in English, which might cause a selection bias. Second, although a subgroup analysis was performed based on study types, only 5 RCTs were enrolled, and the majority of the studies included retrospective data. Third, we tried to select the studies only on early stage HCC, but the median tumor size of different countries ranged from 1.6 to 3.6 cm, which might affect the long-term survival outcomes. Meta-regression and individual patient meta-analysis are needed in the future to assess the intergroup heterogeneity and evaluate the risks for patients treated with ablation.

5. Conclusions

MWA has similar efficacy compared with RFA for early stage HCC patients. Given its shorter ablation time, MWA could be performed under local anesthesia. More RCTs are needed to evaluate the cost and ablation time associated with long-term therapeutic outcome.

Author contributions

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