

# Clinical Efficacy and Safety of Microwave Ablation Compared to Radiofrequency Ablation in Hepatocellular Carcinoma Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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## ABSTRACT

**Background:** Ablation modalities for the treatment of hepatocellular carcinoma (HCC) including microwave ablation (MWA) and radiofrequency ablation (RFA) are clinically important due to their numerous advantages. Several trials showed inconsistent results regarding safety and efficacy, making the comparison between MWA and RFA challenging. Therefore, this study aimed to enhance the evidence on treatment modalities regarding the clinical efficacy and safety of MWA compared to RFA in HCC patients.

**Methods:** A systematic review and meta-analysis was conducted following the PRISMA guidelines. Subsequently, a literature search was carried out by PubMed, ScienceDirect, and Google Scholar for randomized controlled trials (RCTs) in HCC patients who passed through MWA compared to RFA. Quantitative analysis of pooled risk ratio with a 95% confidence interval was performed using Review Manager 5.4 software in a random-effects model or fixed-effects model forest plot.

**Results:** Based on 9 RCTs included in the analysis, there were insignificant different results in terms of complete ablation rates (CA) [RR=1.01, 95%CI (0.99 to 1.03), p=0.47] and adverse events (AE) [RR=1.15, 95%CI (0.88 to 1.50), p=0.31]. However, lower incidence of local tumor progression (LTP) [RR=0.73, 95%CI (0.54 to 0.99), p=0.04], intrahepatic de novo lesions (IDL) [RR=0.90, 95%CI (0.81 to 1.00), p=0.05], and extrahepatic metastases (EHM) [RR=0.65, 95%CI (0.44 to 0.95), p=0.03] exhibited significant differences in MWA group.

**Conclusions:** This meta-analysis provided evidence that MWA and RFA had equivalent CA rates and AE in HCC patients. However, MWA was considered superior to RFA due to a lower incidence of LTP, IDL, and EHM.

## INTRODUCTION

Liver cancer is the third most common leading cause of mortality globally in 2020, following lung and colorectal cancer. Approximately 906,000 new cases and 830,000 deaths were reported, with hepatocellular carcinoma (HCC) accounting for 75–85% [1]. Several treatment modalities are available for HCC, including surgical resection, liver transplantation, percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), microwave ablation (MWA), transarterial chemoembolization (TACE), and molecular targeted

systemic therapy [2]. Among these modalities, liver transplant remains the best curative option for early-stage HCC, but its efficiency is limited by the scarcity of available donors [3]. Concerning surgical resection, proper patient selection must be carefully considered with the result that only less than 5% meet the criteria [2].

In cases where surgical resection or liver transplantation is not feasible, thermal ablation techniques have emerged as an alternative curative treatment for HCC patients, offering advantages with minimal invasiveness [4,5]. RFA is well-known as a safe and effective thermal ablation for

treating HCC, but it is prone to heat-sink effects, particularly when the tumor is located near the main biliary tree, abdominal organs, or heart. Furthermore, MWA is a recent thermal ablation with higher temperature in a shorter time to enhance local tumor controls, given less prone to heat-sink effect, and be used in tumors adjacent to vessels [5].

The guidelines by the European Association for the Study of the Liver (EASL) reported that MWA showed promising results for local control and survival [4]. However, these results were categorized as having low evidence strength. Several studies that were recently published, including randomized controlled trials (RCTs), also showed inconsistent outcomes regarding safety and efficacy, making the comparison between MWA and RFA challenging. Therefore, this study aimed to enhance the evidence on treatment modalities using an updated systematic review and meta-analysis approach to provide the best answer regarding the clinical efficacy and safety of MWA compared to RFA in HCC patients.

## METHODS

This systematic review and meta-analysis were reported based on Preferred Reporting Items for Systematic Reviews and meta-analysis (PRISMA) guidelines [6]. Meanwhile, ethical clearance was not required for this study.

### Database searching and study selection

A systematic literature search was carried out by PubMed, Google Scholar, and ScienceDirect using some keywords, which included MWA, RFA, and HCC. The review question for included studies was developed following the PICOS framework (i) Population: patients diagnosed with HCC or other liver malignancies, (ii) Intervention: MWA, (iii) Comparator: RFA, (iv) Outcomes: complete ablation rate (CA), local tumor progression (LTP) is defined by the recurrence of the tumor with the same liver segment as the previously ablated, intrahepatic de novo lesions (IDL), adverse events (AE), and extrahepatic metastases (EHM) of HCC origin, and (v) Study design: RCTs. The eligibility criteria for this study included: 1) Meet the PICOS criteria, 2) Only articles written in English, and 3) Full-text articles were available. The exclusion criteria consisted of studies in the form of a systematic review with or without meta-analysis, literature review, case report, series, non-human subjects or in vitro studies, abstract-only papers as preceding papers, conference, editorial, and author response. The literature search was carried out in October 2022 without any year restriction. All results from electronic databases were stored in Rayyan.ai to pass through the selection process [7]. Subsequently, two independent reviewers performed the selection process based on title and abstract screening, followed by full-text evaluation based on eligibility criteria. Any conflicts during article selection were discussed with all authors.

### Data extraction

Data extraction was carried out for all included studies by two independent reviewers to obtain relevant clinical outcomes, facilitating quantitative analysis. Several data were extracted from the included studies such as year of publication, country, diagnosis and criteria of HCC, number of patients, intervention, number of nodules, tumor size, and number of Child-Pugh scores. Any controversies between data extraction were discussed with other authors.

### Risk of bias assessment

The risk of bias assessment was performed using the Cochrane Risk of Bias 2 (ROB 2) tool [8]. This tool comprised several domains such as randomization sequence generation, allocation concealment, performance, detection, attrition, reporting, and other sources of bias. Each domain was graded as “low risk”, “unclear risk”, and “high risk” of bias. The risk of bias assessment was conducted by two reviewers independently and any difference in terms of grading was discussed with other authors.

### Data synthesis and analysis

The included studies were analyzed quantitatively using Review Manager (RevMan) 5.4 for meta-analysis (Cochrane Collaboration, Oxford, UK) with 95% confidence intervals (CI). The pooled risk ratio was used to calculate the dichotomous outcomes. Based on heterogeneity, the random effects model was employed when heterogeneity was high ( $I^2 \geq 50\%$ ), while fixed effects model forest plots were used at a low value ( $I^2 < 50\%$ ) [9].

### Publication bias

The publication bias was analyzed using Review Manager (RevMan) 5.4, which was visualized through a funnel plots graph. The asymmetric shape observed in the funnel plot suggested that publication bias was present, while the symmetrical shape of the funnel plot indicated the absence of publication bias.

## RESULTS

### Studies selection

A PRISMA flowchart reported all studies' selection processes, as presented in **Figure 1**. Based on databases searching from PubMed, Google Scholar, and Science Direct, a total of 4522 articles were found. This was followed by the elimination of duplication using Rayyan.ai and further screening through the review of the title and abstract to remove irrelevant topics. Subsequently, a total of 38 articles were checked for eligibility by full-text screening. Quantitative synthesis and analysis using meta-analysis were performed in 9 articles.

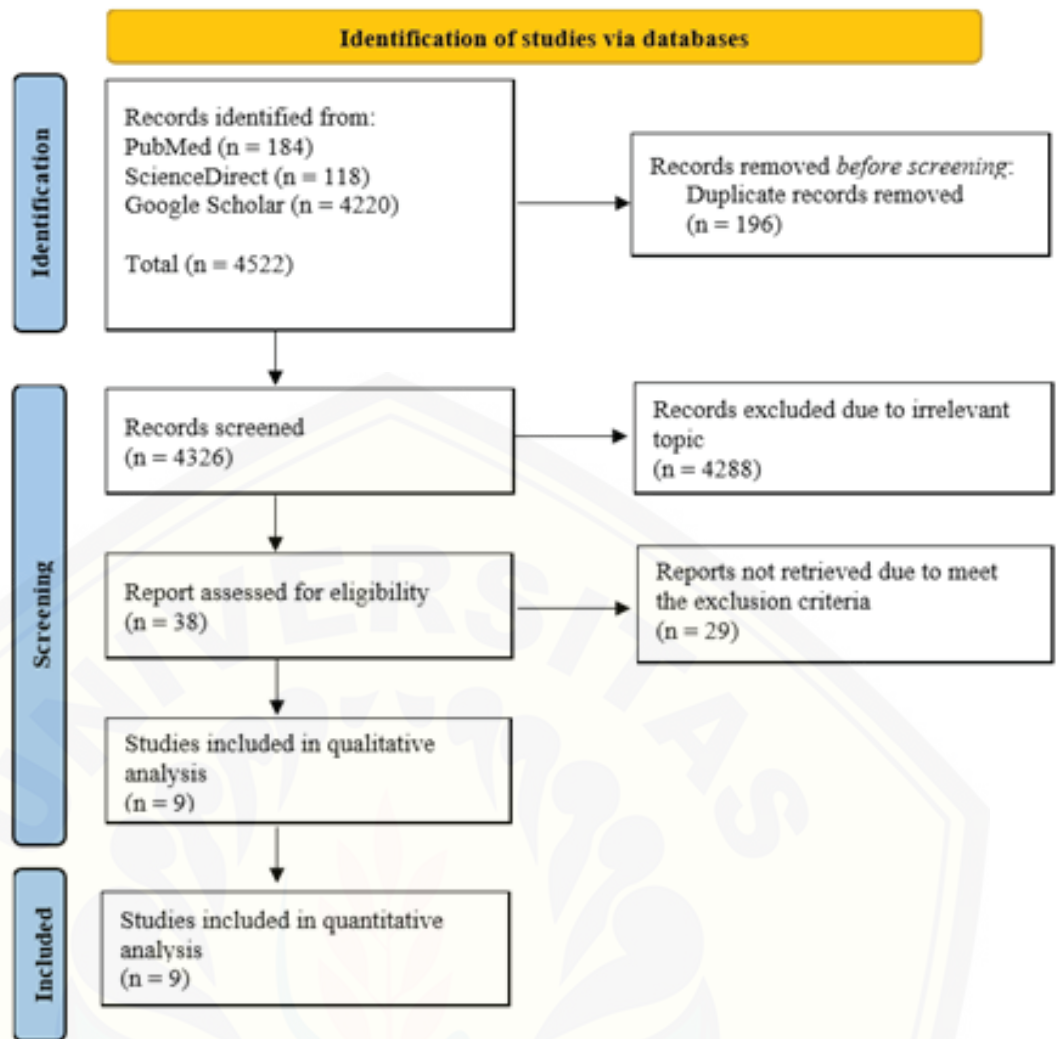


Figure 1. PRISMA flow diagram

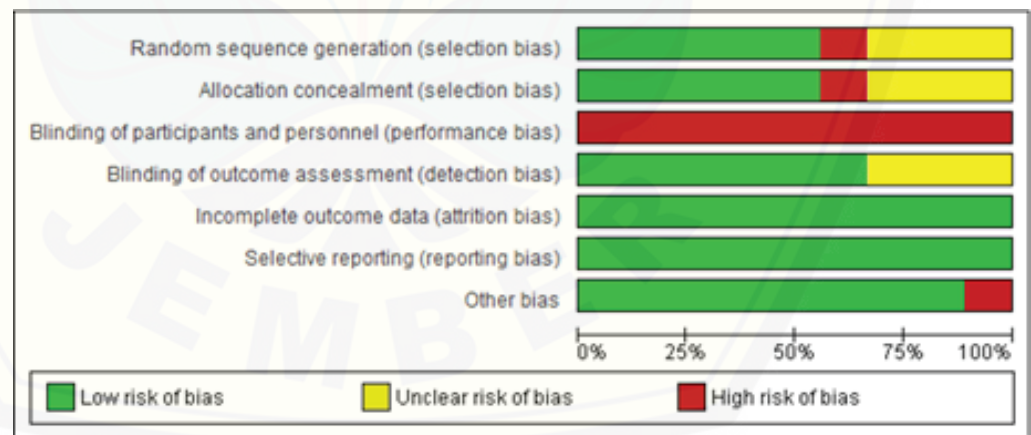


Figure 2. Risk of bias assessment based on RoB 2 tools

**Study characteristics and risk of bias**

Table 1 summarized all included RCTs with the sample size varied between each study ranging from 40 to 403 samples. Several nodules were reported between 20 to 265 in MWA groups and 20 to 251 in RFA groups. The included studies were conducted in several countries, including 1 study in Japan, Italy, Hongkong, and Spain, 2 studies were reported in China

and Egypt, and as well as 1 multi-country study involving France and Switzerland. The risk of bias assessment was conducted using the Cochrane RoB 2. The blinding of participants and personnel domain was judged as a high risk of bias. This led to an elevated overall risk of bias in included studies, as shown in Figure 2.



**Table 1.** Characteristics of included studies

Study, year (Country)	HCC Criteria and Diagnosis	Number of patients (Male)	Mean/Median Age	Intervention		Number of Nodules (≤3/>3 cm)	Mean/Median Size of Nodules	Child-Pugh A/B/C
				MWA	RFA			
Shibata et al., 2002 (Japan) <sup>[10]</sup>	Solitary HCC nodule smaller than 4 cm in diameter or those with two or three nodules less than or equal to 3 cm in diameter was confirmed in all patients with ultrasonographically (US) guided needle biopsy	MWA: 36 (24) RFA: 36 (26)	MWA: 62.5 (52–74) RFA: 63.6 (44–83)	Microwave electrode 1.6 mm in diameter and 25 cm in length connected to 2450 MHz microwave generator	15-gauge needle electrode with 8 or 10 hook-shaped expandable electrode tines connected to a 460-kHz radiofrequency generator	MWA: 46 (43/3) RFA: 48 (45/3)	MWA: 2.2 (0.9–3.4) RFA: 2.3 (1–3.7)	MWA: 19/17/- RFA: 21/15/-
Qian et al., 2012 (China) <sup>[11]</sup>	Small HCC is defined single nodule with less than 3 cm diameter diagnosed according to the non-invasive diagnostic criteria	MWA: 22 (20) RFA: 20 (19)	MWA: 52 ± 12 RFA: 56 ± 11	14-gauge cooled-shaft antenna connected to a 2450 MHz generator with and maximum power output of 100 W	17-gauge internally cooled needle electrode and two dispersive pads connected to RF generator with a maximum power output of 200 W	MWA: 22 (NR/NR) RFA: 20 (NR/NR)	MWA: 2.1 ± 0.4 RFA: 2.0 ± 0.5	NR
Di Vece et al., 2014 (Italy) <sup>[12]</sup>	Single liver tumor measuring ≥2 cm to <7 cm in diameter	MWA: 20 (16) RFA: 20 (13)	MWA: 63 (52–92) RFA: 59 (47–83)	Performed using AMICA MWA System consisting of a generator with a frequency of 2,450 MHz and a maximum power output of 110 W.	Performed using a generator with a maximum output power of 200 W and a 17G internally cooled needle electrode with a 3-cm exposed tip	MWA: 20 (NR/NR) RFA: 20 (NR/NR)	MWA: 3.6 (2.2–6.9) RFA: 3.2 (2.3–6.4)	NR
Abdelaziz et al., 2014 (Egypt) <sup>[13]</sup>	All patients with HCC with 3 or fewer focal lesions (the largest not exceeding 5 cm in size) who were diagnosed and managed according to the EASL guidelines	MWA: 66 (48) RFA: 45 (31)	MWA: 53.6 ± 5 RFA: 56.8 ± 7.2	AMICA® GEM machine operated at a frequency of 2,450 MHz through 14 gauge (150 and 200 mm) cooled shift electrodes	18 gauge (200 mm) internally Cool tip electrodes (Radionics®) connected to a 500-KHz radiofrequency generator	MWA: 76 (55/21) RFA: 52 (32/20)	MWA: 2.9 ± 0.97 RFA: 2.95 ± 1.03	MWA: 25/41/- RFA: 24/21/-
Yu et al., 2017 (China) <sup>[14]</sup>	Early-stage HCC with tumor size ≤5 cm in diameter and tumor number ≤3	MWA: 203 (NR) RFA: 200 (NR)	NR	Cooled-shaft microwave system	Cooled-shaft radiofrequency system	MWA: 265 (190/75) RFA: 251 (174/77)	MWA: 2.7 ± 1 RFA: 2.6 ± 1	NR

Study, year (Country)	HCC Criteria and Diagnosis	Number of patients (Male)	Mean/Median Age	Intervention		Number of Nodules (≤3/>3 cm)	Mean/Median Size of Nodules	Child-Pugh A/B/C
				MWA	RFA			
Violi et al., 2018 (France and Switzerland) <sup>[15]</sup>	Patients with chronic liver disease and HCC lesions of 4 cm or smaller. HCC diagnosed by cross-sectional imaging or biopsy according to EASL or AASLD guidelines	MWA: 71 (59) RFA: 73 (62)	MWA: 68 (60–72) RFA: 65 (59–73)	15-gauge liquid-cooled antenna and a 2.45 GHz generator with a power of 140 W were used	A 200 W generator in the impedance control mode and a clustered internally cooled electrode	MWA: 98 (NR/NR) RFA: 104 (NR/NR)	MWA: 1.8 ± 0.65 RFA: 1.8 ± 0.71	MWA: 57/14/- RFA: 53/20/-
Kamal et al., 2019 (Egypt) <sup>[16]</sup>	Patients with definite HCC on top of liver cirrhosis related to HCV whose HCC lesions are 3 or less with no lesion more than 5 cm	MWA: 28 (21) RFA: 28 (22)	55 (42–80)	14 gauge 200 mm disposable MWA probe (AMICA probe MW) and a 2.45 GHz generator (AMICA GEN® AGN-H-1.2)	(Angiodynamics RITA model® 1,500×) generator and RITA StarBurst XL needle were used complying with the manufacturer's instructions	MWA: 34 (NR/NR) RFA: 34 (NR/NR)	MWA: 3.25±0.92 RFA: 3.28±0.91	MWA: 22/6/- RFA: 22/6/-
Chong et al., 2020 (Hong Kong) <sup>[17]</sup>	HCC is diagnosed based on histology or the typical imaging appearance and raised alpha-fetal protein (AFP) with tumor size ≤5 cm in diameter and tumor number ≤3	MWA: 47 (30) RFA: 46 (38)	MWA: 63.0 (50–80) RFA: 64.5 (42–85)	Percutaneous microwave needle with various power and duration settings depending on tumor size	Cool-tip RFA needles of various sizes	MWA: NR RFA: NR	MWA: 3.1 (2–4.5) RFA: 2.8 (2–5.5)	MWA: 39/7/1 RFA: 40/6/-
Radosevic et al., 2022 (Spain) <sup>[18]</sup>	HCC or other liver malignancies suitable for ablation are assessed by cross-sectional imaging or biopsy (according to BCLC classification 1 or ESMO guidelines). Tumor number at presentation ≤ 3 and the largest tumor diameter between 1.5 and 4 cm	MWA: 39 (22) RFA: 38 (29)	MWA: 75 (46–93) RFA: 67 (48–84)	2.45 GHz MW ablation generator with a maximum output of 140 W and a cooled mini-choked 14-gauge antenna	A single 14-gauge, 3 cm long internally cooled electrode with two electrically isolated expandable and conducted with a 200 W generator	MWA: 47 (NR/NR) RFA: 50 (NR/NR)	MWA: 2.5 (1.5–4.0) RFA: 2.4 (1.5–4.0)	MWA: 28/2/ NR RFA: 21/6/ NR

MWA, microwave ablation; RFA, radiofrequency ablation, HCC; hepatocellular carcinoma; EASL, European Association for the Study of the Liver; AASLD, American Association for the Study of Liver Diseases; HCV, hepatitis C virus; NR, not reported

### Outcomes: complete ablation (CA) rates

A total of 9 studies were reported on complete ablation rates with 635/655 and 601/625 events in MWA and RFA groups, respectively. The results showed that the pooled estimates did not show statistically significant

[pooled RR = 1.01, 95%CI (0.99 to 1.03), p=0.47], with low heterogeneity between studies observed (I<sup>2</sup>=0%), as shown in **Figure 3**.

**Outcomes: local tumor progression (LTP)**

A total of 7 studies were reported on LTP with 63/576 and 83/547 events in MWA and RFA groups, respectively. This quantitative analysis showed statistically significant differences, where LTP was lower in MWA groups [pooled RR = 0.73, 95%CI (0.54 to 0.99), p=0.04], and there was a mild heterogeneity (I2=45%), as presented in Figure 4.

**Outcomes: intrahepatic de novo lesions (IDL)**

A total of 4 studies were reported on IDL with 239/451 and 257/422 events in MWA and RFA groups, respectively. This quantitative analysis showed that IDL was statistically significantly lower in MWA groups [pooled RR = 0.90, 95%CI (0.81 to 1.00), p=0.05]. Furthermore, the heterogeneity was low between groups (I2=17%), as shown in Figure 5.

**Outcomes: extrahepatic metastases (EHM)**

EHM, which was conducted by only two studies, showed a statistically significant difference. The results indicated that MWA groups were lower with 38/363 events compared to RFA with 56/355 events [pooled RR = 0.65, 95%CI (0.44 to 0.95), p=0.03], exhibiting low heterogeneity (I2=0%), as shown in Figure 6.

**Outcomes: adverse events (AE)**

A total of 8 studies were reported on AE with 72/547 and 62/529 events in MWA and RFA groups, respectively. The results showed a significant difference between the groups [pooled RR = 1.15, 95%CI (0.88 to 1.50), p=0.31], and mild heterogeneity in the analysis was observed (I2=44%), as presented in Figure 7.

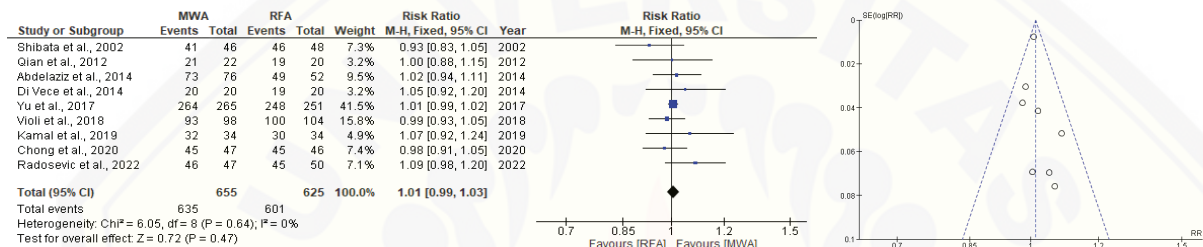


Figure 3. Forest plots and funnel plots in terms of complete ablation (CA) rates

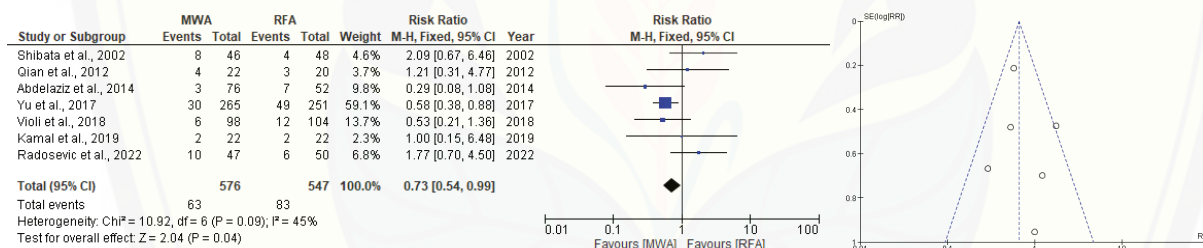


Figure 4. Forest plots and funnel plots in terms of local tumor progression (LTP)

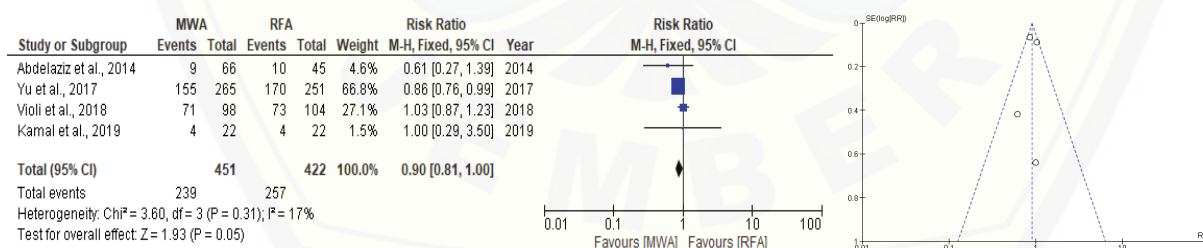


Figure 5. Forest plots and funnel plots in terms of intrahepatic de novo lesions (IDL)

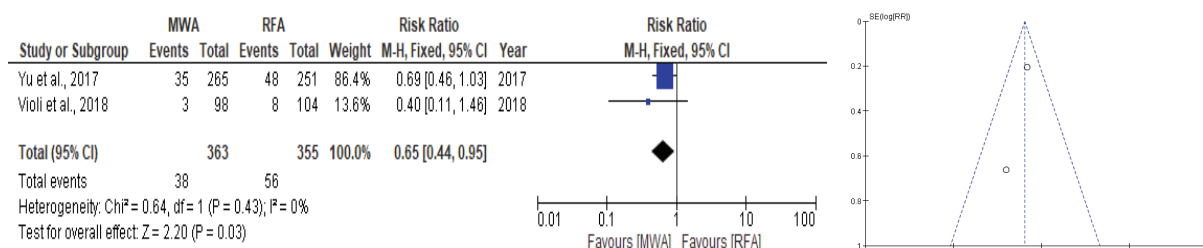


Figure 6. Forest plots and funnel plots in terms of extrahepatic metastases (EHM)



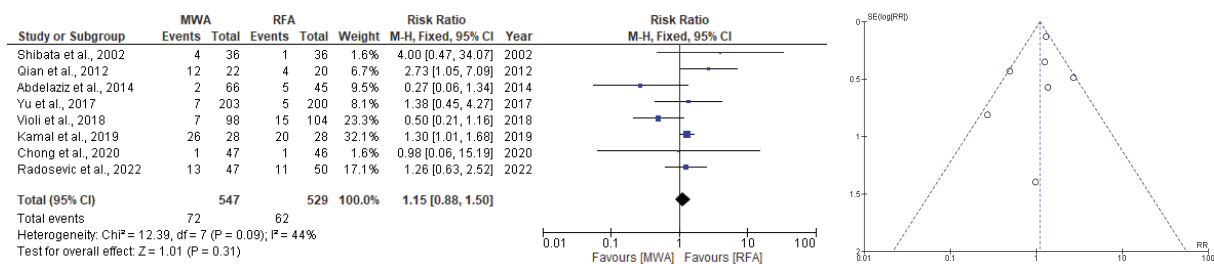


Figure 7. Forest plots and funnel plots in terms of adverse events (AE)

## DISCUSSION

A meta-analysis of 9 RCTs involving 998 HCC patients was conducted to enhance the evidence regarding the clinical efficacy and safety of MWA compared to RFA. Ablation therapy including MWA and RFA had been selected as the best modality for the early and very early stages of HCC when the resection was infeasible and the liver donor transplantation was not suitable. Although several studies regarding efficacy and safety between MWA and RFA had been published, inconsistent results were found, contributing to ongoing debates.

This up-to-date meta-analysis showed that there was no statistically significant difference in terms of CA rates between MWA and RFA. Meanwhile, the latest meta-analysis by Dou et al. [19] including 7 RCTs and 26 cohort studies reported that CA rates of MWA were higher than RFA. This study confirmed the previous meta-analysis by Spiliotis et al. [21], which included 4 RCTs and 11 observational studies. According to a previous report by Facciorusso et al. [20] on 7 RCTs, MWA and RFA exhibited similar rates of complete tumor ablation. The theoretical advantages of MWA regarding higher temperature and faster heating, larger ablation volume, and less heat-sink effect than RFA were associated with other indicators compared to CA rates.

This study showed the advantages of MWA over RFA regarding the reduction of LTP, IDL, and EHM. The lower incidence of LTP after MWA treatment was in line with three previous meta-analyses by Glassberg et al. [22], Spiliotis et al. [21], and Dou et al. [19], but in contrast with Facciorusso et al. [20]. The study by Lin et al. [23] involving 564 hepatic malignant tumors showed that the heat-sink effect due to RFA treatment was an important factor affecting the recurrence of hepatic malignant tumors. Furthermore, this analysis suggested that LTP was considered a more reliable indicator for treatment efficacy than CA rates. Intrahepatic de novo lesions also referred to as distant intrahepatic tumor progression or intrahepatic metastases are beneficial to MWA treatment. This result was contradictory to Spiliotis et al. [21], where extrahepatic new tumors were discovered for distant recurrence analysis. A meta-analysis conducted by Facciorusso et al. [20] on only 2 RCTs for de novo lesion outcomes stated

that the advantage might be related to the necrosis of microsatellites in association with the wider area of necrosis due to MWA treatment. Similarly, Radosevic et al. [18] highlighted that MWA created larger ablation zones than RFA.

Glassberg et al. [22] showed insignificant results in terms of EHM with 1 RCT and 1 cohort study that were analyzed. Although this study obtained lower incidences of EHM in MWA treatment, the result should be interpreted with caution due to the inclusion of only 2 RCTs in the analysis. Yu et al. [14] reported EHM for 1-year, 3-year, and 5-year were 1.6%, 5.9%, and 13.2% for MWA compared to 2.2%, 11.2%, and 19.3% for RFA.

The achievement of a larger ablation zone through MWA led to concerns about more complications, including liver injury and potential impact on organs, particularly vascular and biliary structures [24]. However, these results aligned with the meta-analysis by Tan et al. [25], Spiliotis et al. [21], and Dou et al. [19], which refuted the significant difference between MWA and RFA treatment regarding adverse events. These studies also reported that the highest incidence of adverse events was pain at the site of intervention about 42.9% in both MWA and RFA treatment [16]. The meta-analysis suggested that both the ablative therapies were safe with a low incidence of adverse events.

The systematic review and meta-analysis were carried out using the latest literature search, focusing on clinically relevant outcomes, and yielding results with low heterogeneity. The meta-analysis involving only RCTs might help to empower the answer regarding the inconsistent results. However, the limitations of this study consisted of the inclusion of articles on different follow-up times for the outcomes. Different types of MWA and RFA machine treatments that were used also affected the outcomes. The intervention and evaluation procedures depended on the operators, contributing to variations in experiences and capabilities between the included studies. Consequently, further RCTs with larger sample sizes and various outcomes were urgently needed to provide high-quality evidence and enhance the robustness of the current systematic review and meta-analysis.

## CONCLUSIONS

This meta-analysis provided valuable evidence indicating that MWA and RFA exhibited equivalent CA rates and AE in HCC patients. However, MWA was considered superior to RFA due to a lower incidence of LTP, IDL, and EHM.

## DECLARATIONS

### Competing interest

The authors declare no competing interest in this study.

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