Comparison of microwave ablation and radiofrequency ablation for hepatocellular carcinoma: a systematic review and meta-analysis

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ABSTRACT

Background: Microwave ablation (MWA) has several advantages over radiofrequency ablation (RFA) for the treatment of hepatocellular carcinoma (HCC). We aimed to compare the efficacy and safety of MWA with those of RFA for HCC from the perspectives of percutaneous and laparoscopic approaches.

Methods: PubMed/MEDLINE, Embase, the Cochrane library, and China Biology Medicine databases were searched. Studies comparing the efficacy and safety of MWA with those of RFA in patients with HCC were considered eligible. Complete ablation (CA), local recurrence (LR), disease-free survival (DFS), overall survival (OS), and the major complication rate were compared between MWA and RFA.

Results: Four randomized controlled trials and 10 cohort studies were included. For percutaneous ablation, no significant difference was found between MWA and RFA regarding CA, LR, DFS, OS, and the major complication rate. A subgroup analysis of tumors measuring ≥3 cm revealed no difference in CA and LR for percutaneous ablation. For laparoscopic ablation, a significantly lower LR rate and a non-significant trend toward a higher major complication rate were observed for the MWA group (odds ratio [OR] 2.16, 95% confidence interval [CI] 1.16–4.02, p = 0.01 for LR; OR 0.21, 95% CI 0.04–1.03, p = 0.05 for major complication rate). CA, DFS, and OS were similar between the two groups.

Conclusions: Percutaneous (P)-MWA had similar therapeutic effects compared with P-RFA for HCC. Patients undergoing laparoscopic MWA had a lower LR rate; however, their major complication rate appeared to be higher. The superiority of MWA over RFA remains unclear and needs to be confirmed by high-quality evidence.

Précis

The efficacy and safety of microwave and radiofrequency ablation were evaluated; however, the superiority of microwave ablation over radiofrequency ablation could not be confirmed due to lack of sufficient evidence.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide [1], and it is effectively treated with radiofrequency ablation (RFA). RFA can be as effective as surgical resection in terms of disease-free survival (DFS) and overall survival (OS) in patients with HCC [2,3]. Meanwhile, microwave ablation (MWA), a recently developed thermal ablation technique, has several advantages over RFA, including faster heating over a larger volume, less susceptibility to heat sinks and local perfusion [4].

Despite the advantages of MWA, its efficacy and safety compared with RFA are under debate. Recent meta-analyses comparing percutaneous-MWA (P-MWA) and percutaneous-RFA (P-RFA) found that the two techniques had similar efficacies [5–7]. However, these studies had several limitations. First, few randomized controlled trials (RCTs) were included, which would inevitably introduce bias [8]. Second, as a result of the improvement of MWA technology and an increase in operators’ experience, the advantages of MWA compared with RFA might be outstanding. Third, a meta-analysis comparing laparoscopic-MWA (L-MWA) and laparoscopic-RFA (L-RFA) has not been performed. For these reasons, it is necessary to evaluate the efficacy and safety of MWA compared with RFA from the perspectives of percutaneous and laparoscopic approaches.

Therefore, the purpose of this meta-analysis was to assess the efficacy and safety of MWA compared with RFA for HCC treatment. To fully assess the role of MWA, articles on laparoscopic ablation were also included. Complete ablation (CA), local recurrence (LR), DFS, OS and the major complication rate were assessed.
Materials and methods

Search strategy and inclusion criteria

A computerized literature search was conducted on PubMed, Embase, the Cochrane Library, and China Biology Medicine databases to identify articles published before May 2018. The search strategy included the following keywords: ‘carcinoma, hepatocellular’ (MeSH term) OR ‘hepatocellular carcinoma’ (text) AND ‘radiofrequency ablation’ (text) OR ‘radio-frequency therapy’ (text) OR ‘radio-frequency ablation’ (text) AND ‘microwave coagulation’ (text) OR ‘microwave ablation’ (text) OR ‘microwave therapy’ (text)).

The inclusion criteria for articles were as follows: (1) full text available in English or Chinese; (2) results that provided data on CA, LR, DFS, OS, or complications compared between MWA and RFA for HCC; and (3) RCTs or high-quality cohort studies assessed using the Newcastle-Ottawa scale (NOS) [9]. The reference lists of review articles were checked to identify additional related articles.

The exclusion criteria were as follows: (1) lack of the required data in the results, and no response after attempts to contact the author; (2) duplicate data if recent studies were included; and (3) ablative techniques combined with other locoregional therapies.

In this study, CA was defined as no enhancement in ablated areas after ablation. LR was defined as any new lesion inside or adjacent to the ablated zone. DFS was defined as the length of time from the start of ablation to the date of death or the last follow-up. According to the Clavien-Dindo Classification [10], complications of grade 3 or higher were defined as major complications.

The quality of the included studies was assessed independently by two authors (T.WC, D.QW) according to the Cochrane Collaboration’s tool [11] for RCTs and the NOS for cohort studies.

Statistical analyses

Reviewer Manager 5.3 (Cochrane Informatics) was used for pooling data. Data of CA, LR, DFS, OS and the major complication rate were analyzed and presented as odds ratios (ORs) and 95% confidence intervals (CIs). Heterogeneity was assessed by means of Cochrane’s Chi-square test, with a value of >50% suggestive of significant heterogeneity. A fixed-effects model was used if heterogeneity was significant; otherwise, the random-effects model was used. A p values <.05 was considered statistically significant.

Results

Literature search and characteristics of included studies

Figure 1 shows the search strategy used in this meta-analysis. Initially, we identified 450 potentially relevant studies. After a preliminary review, 418 papers were excluded because they were considered irrelevant studies, case reports, animal studies, comment letters, or reviews. Among 32 potentially relevant papers, we excluded five studies in which patients were treated with embolization combined with MWA or RFA [12–16] and another seven because of insufficient data [17–23]. Six studies were excluded because of duplicate data [24–29]. For studies with duplicate data, reports with the lower number of patients and incomplete data were excluded. Finally, four RCTs [30–33] and 10 cohort studies [25,34–42] with 1816 patients were included. All four RCTs focused on percutaneous ablation. Among the 10 cohort studies, four [35,38,40,41] compared L-MWA and L-RFA.

The main characteristics of the included studies are reported in Table 1. The recruitment period ranged from...
1997 to 2015. The baseline background characteristics of patients, including age, Child-Pugh class, tumor size, and tumor location, were comparable. The 10 cohort studies were assigned 8–9 points upon NOS evaluation. The RCTs had a high risk of performance bias because blinding of physicians was difficult as different devices were used during the therapy. Initial follow-up was performed with computed tomography or magnetic resonance imaging, the data of which were objective. Therefore, detection bias in the outcome evaluation was low. Details on the quality assessment are presented in Table S1 and Figure S1.

Complete ablation rate

As shown in Figure 2, no significant difference in the CA rate was found between the P-RFA and P-MWA groups (OR 0.85, 95% CI 0.41–1.79, p = .67 in RCTs; OR 0.8, 95% CI 0.47–1.38 p = .43 in cohort studies). No evidence of heterogeneity was found in these studies (I²=0%). There was also no significant difference in the CA rate between the L-RFA and L-MWA groups (OR 0.78, 95% CI 0.26–2.36, p = .66).

Local recurrence rate

Three RCTs with 424 individuals and 10 cohort studies with 1522 individuals reported the LR rate. Heterogeneity was found among the RCTs (I²=65%), and the random-effects model yielded an OR of 1.47 for the RCTs (95% CI 0.45–4.84, p = .52). No significant difference in the LR rate was found in the meta-analysis of cohort studies using percutaneous ablation (OR 0.95, 95% CI 0.66–1.36, p = 0.77, I²=24%). However, a significantly lower LR rate was found in patients treated with L-MWA (OR 2.21, 95% CI 1.19–4.07, p = .01, I²=0%) (Figure 3).

Disease-free survival and overall survival

DFS at three years was reported by four cohort studies of percutaneous ablation with 915 patients and two cohort studies of laparoscopic ablation with 106 patients. A low grade of heterogeneity was found for these studies (I²=47%; I²=0%, respectively); hence, the fixed-effects model was used. No significant difference in the LR rate was found (OR 0.97 95% CI 0.71–1.32, p = .83 for percutaneous ablation; OR 0.75, 95% CI 0.32–1.76, p = .50 for laparoscopic ablation) (Figure 4).

As shown in Figure 5, OS at three years was available for two RCTs with 197 patients and seven cohort studies with 1225 patients. There was no significant difference in OS rate between the two treatment groups (OR 0.68, 95% CI 0.34–1.37, p = .28, I²=0% in RCTs; OR 1.15, 95% CI 0.70–1.90, p = 0.58, I²=60% in cohort studies of percutaneous ablation; OR 1.94, 95% CI 0.82–4.60, p = 0.13, I²=53% in cohort studies of laparoscopic ablation).

Major complication rate

Four RCTs with 550 patients and eight cohort studies with 1213 patients reported major complications with details. No perioperative deaths related to the therapy were reported. As shown in Figure 6, no significant difference in the major complication rate was found between the RCTs and cohort studies of percutaneous ablation (OR 0.63, 95% CI 0.22–1.76, p = .28, I²=0%).

### Table 1. Characteristics of the included studies.

| Reference          | Country | Type   | Arm    | NP | Age (years) | NL | Size, mean (range or SD, mm) | CPC (A/B/C) |
|--------------------|---------|--------|--------|----|-------------|----|-----------------------------|-------------|
| Shibata T 2002[31] | Japan   | RCT    | P-RFA  | 36 | 63.6 (44–83)| 48 | 23 (10–37)                 | 21/15/0     |
| Tian WS 2014[32]   | China   | RCT    | P-RFA  | 36 | 62.5 (52–74)| 46 | 22 (9–34)                  | 19/17/0     |
| Abdelaziz A 2014[33]| Egypt  | RCT    | P-RFA  | 45 | 56.8 (7.3) | 52 | 29.5 (10.3)               | 24/21/0     |
| Vietti Violi N 2018[30] | Switzerland | RCT    | P-RFA  | 73 | 65 (59–73) | 104| 18 (7.1)                | 53/20/0     |
| Lu MD 2005[34]     | China   | cohort | P-RFA  | 71 | 68 (60–72) | 98 | 18 (6.5)                 | 57/14/0     |
| Ohmoto K 2009[46]  | Japan   | cohort | P-RFA  | 49 | 50.1 (13.7)| 98 | 25 (12)                 | 19/17/0     |
| Simo KA 2011[35]   | USA     | cohort | L-RFA  | 22 | 58 (8.64) | 27 | 25.3 (12–44)             | 12/7/3      |
| Zhang L 2013[36]   | China   | cohort | L-RFA  | 74 | 54 (10.5) | 97 | NR                        | 78/0/0      |
| Ding J 2013[37]    | China   | cohort | L-RFA  | 77 | 54 (9.5)  | 105| 77/0/0                   | 49/36/0     |
| Cillo U 2014[38]   | Italy   | cohort | L-RFA  | 85 | 58.64 (8.5)| 98 | 23.8 (8.1)               | 49/36/0     |
| Vogl TJ 2015[39]   | Germany | cohort | L-RFA  | 28 | 64 (34–80)| 131| 19.3 (9.8)               | 75/38/0     |
| Lee KF 2017[40]    | China   | cohort | L-MWA  | 28 | 64 (47–80)| 32 | 21.5 (9.8)               | 74/0/0      |
| Santambrogio R 2017[41] | Italy    | cohort | L-RFA  | 26 | 52 (43–77)| 37 | 16 (7–20)                | 20/11/3     |
| Xu Y 2017[42]      | China   | cohort | P-RFA  | 159| 54 (11)  | 17 (3) | 140/19/0               | 278/23/0     |

NP: number of patients; NL: number of nodules; CPC: Child-Pugh classification; P-MWA: percutaneous microwave ablation; P-RFA: percutaneous radiofrequency ablation; L-MWA: laparoscopic microwave ablation; L-RFA: laparoscopic radiofrequency ablation; NR: no report.
\[ p = 0.38, \quad \hat{I}^2 = 0\% \]; OR 0.97, 95% CI 0.41–2.25, \( p = 0.93, \hat{I}^2 = 0\% \), respectively. For cohort studies of laparoscopic ablation, the OR was 0.21 (95% CI 0.04–1.03, \( p = 0.05, \hat{I}^2 = 0\% \)). The major complication rate was higher after L-MWA without reaching the significance threshold.

**Subgroup analysis**

Subgroup analysis of tumors \( \geq 3\,\text{cm} \) revealed no difference in CA and LR rates between P-RFA and P-MWA (OR 1.09, 95% CI 0.30–3.93, \( p = 0.90, \hat{I}^2 = 0\% \); OR 0.85, 95% CI 0.35–2.10, \( p = 0.73, \hat{I}^2 = 0\% \), respectively) (Figure S2).

**Discussion**

Thermal ablative therapies have become important alternative treatments for HCC. In our study, there were no significant differences in CA, LR, DFS, OS and the major complication rate between P-MWA and P-RFA. A significantly lower LR rate and a non-significant trend toward a higher rate of major complications were found in the L-MWA group compared with the L-RFA group.

MWA and RFA are commonly used for the treatment of HCC. They differ in their mechanism of action: RFA uses electric current, whereas MWA uses electromagnetic energy. However, the principle underlying these two treatment methods is similar, in that high temperatures are induced in localized areas to coagulate tissue. MWA has several advantages over RFA. The heat-sink effect, a phenomenon that occurs when thermal energy is dispersed from the target lesion due to blood flow in the adjacent vessels, is an important disadvantage of RFA. Consequently, the shape and size of the ablation zone in RFA may be unpredictable, and such limitations can lead to an inadequate ablation zone. For MWA, the time needed for ablation is less than that required for RFA. Moreover, MWA can deliver higher temperatures in the ablation zone. These two features of MWA lead to a more predictable ablation zone. Several studies [29,43,44] have found that MWA produced significantly larger zones than RFA. Therefore, the apparent superiority of MWA over RFA has made it an alternative method to RFA, and it may potentially be a more powerful technique than RFA.

In our study, CA, LR, DFS, OS and the major complication rate between P-MWA and P-RFA were not significantly different. In subgroups with a tumor size \( \geq 3\,\text{cm} \), no difference...
Figure 3. Forest plot of local recurrence rate after ablation.

Figure 4. Forest plot of disease-free survival rate after ablation.
was detected in CA and LR rates between P-MWA and P-RFA. Similar results were reported previously [5,45]. Although MWA has been shown to have certain theoretical advantages over RFA, these advantages have not been confirmed in clinical practice. There may be several reasons for the reportedly conflicting results. First, microwave devices in some clinical trials have not been perfect. Different types of available MWA machines may have varying efficacies, which could lead to a failure of MWA to achieve the expected results. Second, the tumors involved in the research articles were often smaller than 3 cm or the number of patients included was small; consequently, the advantages of MWA failed to be demonstrated.

To fully assess the role of MWA, we included articles on laparoscopic as well as percutaneous ablation. Laparoscopic approaches for the ablation of HCC are viable in a proportion of patients who are unsuitable for hepatic resection or percutaneous ablation. A laparoscopic approach provides access to tumors that are located underneath the liver capsule, adjacent vessels, gallbladder, or diaphragm and that may be difficult to reach. Our study revealed a lower incidence of LR in the L-MWA group. This result may be interpreted as evidence of the superiority of MWA over RFA, which was mentioned above. However, RCTs comparing L-MWA and L-RFA have not been conducted. Selection bias and heterogeneity of the device used must be taken into consideration. Consequently, robust data are needed to demonstrate this result.

The major complication rate of MWA and RFA remains controversial. A recent meta-analysis found that the major complication rate of MWA was higher than that of RFA, although the results did not reach statistical significance. Similar results were observed in our study. Given the fact that MWA is less affected by the heat-sink effect, MWA can produce more uniform and larger tumor necrosis. However, these characteristics, in turn, are associated with a theoretically increased risk of damaging neighboring organs, especially vascular and biliary structures [46]. A larger ablation area might account for a higher complication rate [36,47]. However, according to previously published data, the incidence of vascular and biliary complications caused by MWA and RFA appeared to be similar and infrequently reported [48–50]. It should be noted that the majority of clinical studies are retrospective. This raises the possibility of under- and misreporting of clinical complications. Insufficient clinical data make it difficult to compare the incidence of vascular and biliary complications between the two groups. Therefore, high-quality evidence is needed to compare the complication rates of MWA and RFA.

This study had some limitations. First, many included studies were conducted over different time periods and with different ablation devices. The evolving ablation technology and the increase in the experience of operators affected the results. Second, most of the studies involved HCC with nodules less than 3 cm in size, and it was difficult to compare MWA with RFA according to tumor location. Therefore, the
advantages of MWA in terms of generating larger ablation areas and avoiding the heat-sink effect were difficult to demonstrate. Third, the small number of included articles were limited in their significance. Additional evidence is needed to confirm our findings.

In conclusion, our study showed that P-MWA had similar therapeutic effects compared with P-RFA for HCC. Patients undergoing L-MWA had a lower LR rate but appeared to have a higher rate of major complications. The superiority of MWA over RFA still needs to be confirmed by high-quality research.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Figure 6. Forest plot of major complication rate after ablation.
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