Outcomes Of Microwave vs Radiofrequency Ablation for Hepatocellular Carcinoma: A Systematic Review and Meta-analysis

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Abstract

BACKGROUND

Studies to date comparing outcomes of microwave ablation (MWA) with radiofrequency ablation (RFA) on patients with hepatocellular carcinoma have yielded conflicting results, with no clear superiority of one technique over the other. The aim of this systematic review and meta-analysis is to compare the efficacy and safety of MWA with RFA.

AIM

To perform a systematic review and meta-analysis comparing the efficacy and safety of MWA with RFA

METHODS

A systematic literature search was performed using Ovid MEDLINE, EMBASE, PubMed, Cochrane Central and Cochrane systematic review databases and Web of Science. Abstracts and full manuscripts were screened for inclusion utilizing predefined inclusion and exclusion criteria comparing outcome(s) of MWA and RFA. A random-effects model was used for each outcome. Meta-regression analysis was performed to adjust for the difference in follow-up period between the studies. Primary outcome measures included complete ablation (CA) rates, local recurrence (LRR), survival (local recurrence free [LRFS], overall [OS]) and adverse event rates.

RESULTS
A total of 42 published studies (34 cohort and 8 randomised controlled trials [RCT]) with 6719 patients fulfilled the selection criteria. There was no significant difference in tumour size between treatment groups. CA rates between MWA and RFA groups were similar in prospective cohort studies (OR 0.95, 95%CI 0.28-3.23) and RCTs (OR 1.18, 95%CI 0.64-2.18), however retrospective studies reported higher rates with MWA (OR = 1.29, 95%CI = 1.06-1.57). Retrospective cohort studies reported higher OS (OR = 1.54, 95%CI = 1.15-2.05) and lower LRR (OR 0.67, CI 0.51-0.87). No difference in terms of LRFS or 30D mortality was observed between both arms. MWA had an increased rate of adverse respiratory events when compared to RFA (OR 1.99, CI 1.07-3.71, P = 0.03).

CONCLUSION
MWA achieves similar CA rates and as good or better longer-term outcomes in relation to LRR and OS compared to RFA. Apart from an increased rate of respiratory events post procedure, MWA is as safe as RFA.

INTRODUCTION
Hepatocellular carcinoma (HCC) now ranks worldwide as the seventh most common cancer and the second leading cause of cancer mortality[1-3] and is rapidly increasing in incidence in several developed regions including North America, Europe, and Australasia[4-6]. Furthermore, an increasing proportion of HCC patients are being diagnosed at an early stage and are eligible for curative therapy[7-8] including local ablation which is considered standard of care for those not suitable for surgery[9-11].

Of the common modalities used to ablate HCC, radiofrequency ablation (RFA) is the most strongly recommended[12]. This is based on evidence from randomised controlled trials (RCTs)[13-16] and three meta-analyses[17-19] showing RFA provides better local disease control and overall survival outcomes than percutaneous ethanol injection, particularly among non-surgical candidates[20]. Recently, microwave ablation (MWA) has become a popular ablative technique because of its reduction in heat-sink effect, ability to produce wider and more predictable ablation volumes that result in high complete ablation rates, and the ability to simultaneously treat multiple and/or larger lesions more effectively and over a shorter procedural time[12].
Studies to date comparing outcomes of MWA with RFA have yielded conflicting results, with no clear superiority of one technique over the other\cite{22-24}. A Cochrane review reported that there were insufficient data to recommend RFA over other thermal ablation techniques in the management of HCC\cite{25}, with the authors emphasising that only a single small RCTs comparing MWA with RFA, with a total of 72 patients, had been performed\cite{23}. Subsequently, a further 6 RCT’s have been performed with the latest meta-analysis only including 5 RCTs and 21 cohort studies\cite{26}. In this context, additional evidence particularly from a comprehensive meta-analysis that incorporate all RCTs and data from large real-world observational cohort studies would provide clinicians with a better understanding of whether the comparative overall efficacy and safety of MWA over RFA supports the current preferential use of MWA for the treatment of early-stage HCC.

This study is a contemporary systematic review and meta-analysis of RCTs and cohort studies to determine whether MWA is equivalent to or more effective than RFA in relation to the primary treatment endpoints of complete ablation (CA), local recurrence rate (LRR), local recurrence free survival (LRFS), overall survival (OS), and safety including adverse events.

**MATERIALS AND METHODS**

**Literature search**

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines\cite{27} was followed and the “Assessment of Multiple Systematic Reviews” (AMSTAR) measurement tool\cite{28} was used to perform this study. A systematic electronic search was conducted independently by two authors in the Ovid MEDLINE, EMBASE, PubMed, Cochrane library databases and Web of Science was performed from the inception of each until the first week of October 2021 inclusive of the database of articles that were accepted but not yet published, as well as the clinicaltrials.gov website to identify relevant articles for our review (Supplementary Table 1-5). The search strategy used the search terms “radiofrequency ablation”, “microwave ablation” and “hepatocellular carcinoma” both as exploded medical subject headings (MeSH) where possible, and as text words. In addition, reference lists of relevant articles including recent reviews, and systematic reviews related to locoregional therapy of hepatocellular carcinoma were searched. Studies were
limited to cohort studies and randomized controlled trials using appropriate hedges for each database. A search for unpublished literature was also performed.

**Eligibility criteria**

Studies were included using the following criteria: 1) Age ≥ 18 years; 2) Diagnosis of HCC by American Association for the Study of Liver Disease (AASLD) imaging criteria or histopathology; 3) HCC of any size; and 4) No evidence of macrovascular invasion or extrahepatic spread. Studies were excluded based on the following criteria: 1) Case series; 2) Studies from the same group that contain overlapping patient populations; 3) Treatment with any other modality in conjunction with local ablation therapy with microwave ablation or radiofrequency ablation; 4) Non-HCC liver cancer; and 5) Studies where treatment was given as a bridge to liver transplantation.

**Study outcomes**

The primary outcomes of this study were CA, LRR, LRFS, OS and safety including adverse events and complications. CA was defined in studies as the absence of residual HCC on follow up imaging post-ablation. LRR was defined in studies as the development of HCC lesions within the same liver segment as the treated tumour on imaging after a complete ablation. LRFS was defined as the proportion of patients alive at various timepoints in the absence of any evidence of local recurrence of HCC after treatment. Included studies had to have reported at least one of the primary endpoints as part of an RCT or observational cohort study.

**Selection process**

The initial literature search was performed independently by two reviewers (MT and JL) to identify relevant articles based on the above inclusion and exclusion criteria. Where a difference of opinion occurred on the inclusion of studies for the review, consensus agreement was obtained via formal discussion between the two reviewers.

**Data collection and bias assessment**

Included RCTs were assessed for methodological quality and were classified as being of low, high, or unclear risk of bias according to the Jadad scale. Included
cohort studies were quality assessed using the Newcastle Ottawa Scale (NOS)[31] where a value of 7 or higher qualified the study as high-quality. Data were extracted from the selected studies independently using a data extraction form to collect data on the following: 1) Study details (First author, publication year, journal, country, study design, interventions used, intervention group size); 2) Baseline participant characteristics (Age, sex, and cirrhosis status); 3) Tumour characteristics (Tumour stage and staging system, largest nodule size, nodule number, alfa-fetoprotein level, mean-tumour size); 4) Intervention details and 5) Outcome measures: (complete ablation, local recurrence rate, overall and local recurrence free survival, adverse events, 30-D mortality).

**Statistical analysis**
A random-effects model using the method of DerSimonian and Laird was used for each outcome. Meta-regression analysis was performed to adjust for the difference in follow-up period between the studies. Analysis was also performed individually for RCTs, prospective and retrospective cohort studies. Heterogeneity was assessed using the F statistic with results of 30-60% (moderate), and >50% (high) levels of heterogeneity[32]. Outcomes were reported using a pooled odds ratio (OR) and hazard ratio (HR) with 95% confidence intervals (CI). We assessed publication bias using the Egger’s regression model only if there were greater than ten studies. All analyses were performed with Comprehensive Meta-analysis (version 3.0), Biostat, Englewood, NJ (2014). The statistical methods of this study were reviewed by academic statistician Guy Eslick from Clued Ptd Ltd.

**RESULTS**

1. **Study selection and characteristics of included studies**

As shown in Figure 1, the search strategy utilised for this meta-analysis identified 2758 studies initially. After removing duplicates and excluding studies based on our inclusion and exclusion criteria, 170 studies were assessed for eligibility from which a total of 42 studies, eight RCTs[22, 23, 33-38] and 34 cohort studies[33, 39-71] were finally included in the meta-analysis. The main characteristics of included studies are reported in Table 1. The sample size of included studies (eight RCTs and 34 cohort studies) ranged from 42 to 879 with males forming the majority. In total, we examined a cohort of 6719 patients A total of twenty-four studies were conducted in
Asia, nine in Europe, five in Egypt, two in the United States, and one each in Australia and Turkey. Study follow up duration ranged from three months to 126 mo and was performed through the utilisation of computed tomography or magnetic resonance imaging. Across all studies, the mean age reported was 61 years. Most studies recruited patients with Child-Pugh (C-P) stage A and B liver disease with only one RCT and nine cohort studies recruiting C-P stage C patients. Notably, all 42 studies were comparable with regards to clinical and tumoral parameters. Maximum nodule sized ranged from 9mm to 55mm in RCTs and 8mm to 60mm in cohort studies. In total, 6 RCTs and 18 cohort studies reported mean tumour size. There was no significant difference in tumour size treated with MWA compared to RFA in both RCTs (OR 1.13, 95%CI 0.88-1.46) and cohort studies (OR 0.96, 95%CI 0.77-1.20) (Supplementary Figure 1). Furthermore, there was no significant difference in mean tumour size amongst RCTs (OR 0.05, 95%CI -0.07-0.18; $P = 0.395$) and cohort studies (OR -0.01, 95%CI -0.09-0.07; $P = 0.777$) (Supplementary Figure 2).

The total number of lesions treated per study with MWA and RFA ranged from 15-1090 and 20-562 respectively.

**Quality assessment**

Seven of the eight RCTs assessed were deemed to be high quality studies with one study[^23] deemed to be of low quality (Supplementary Table 6). All RCTs were determined to be at high risk of performance bias as it was not practical to blind the administrator to the procedure. However, four RCTs[^23, 34, 37, 38] were able to blind the outcome of assessment. Potential for selection and detection bias was identified in four RCTs[^22, 35, 36, 72]. Of the 34 cohort studies identified, 30 scored a value of 7 or higher, meeting the definition of a high-quality study (Supplementary Table 7).

**Complete ablation**

In total, 7 RCTs[^22, 23, 34-37, 72] and 24 cohort studies[^39, 42-46, 48-51, 54, 55, 60-71] reported data on complete ablation post treatment. No significant difference in the CA rate was found between the MWA and RFA groups in the prospective cohort studies (OR 0.95, 95%CI 0.28-3.23; $P = 0.82$)[^41, 46, 49, 59, 71] and RCTs (OR 1.18, 95%CI 0.64-2.18; $P = 0.60$)[^22, 23, 34-37, 72]. However, retrospective cohort studies reported higher CA rates with MWA compared to RFA (OR = 1.29, 95%CI = 1.06-1.57; $P = 0.01$) (Figure 2a) [^59].
No evidence of heterogeneity was found in these studies ($P = 0.99$). Funnel plot analysis concluded that publication bias was unlikely (Figure 2b).

**Overall survival**
A total of 5 RCTs$^{22, 34, 35, 38, 72}$ and 17 cohort studies$^{33, 41, 43, 47, 51, 52, 54, 57, 59-63, 66, 68, 70, 71}$ reported data on overall survival (OS) post-ablation (Table 2). Heterogeneity was identified in the results reported at 3- and 4-years by retrospective cohort studies (Table 2)$^{33, 43, 51, 53, 54, 57, 66, 68, 70}$. In studies that categorised data into OS into specific years, no statistically significant difference in OS was noted between MWA and RFA groups. Meta-analysis of four retrospective studies, that did not specify the follow up period$^{52, 54, 59, 63}$, reported significantly higher OS in patients treated with MWA. No potential bias was identified during visual assessment and Egger’s test of funnel plot.

Individual study overall survival rates were plotted on a dot graph for both MWA and RFA treated subjects (Figure 3) with median OS rates according to year of follow up post treatment shown in Table 3. Of note, MWA was associated with improved median OS at 3- and 4-years of follow up but this difference was lost at 5-years.

**Local recurrence rate**
Overall, six RCTs$^{22, 23, 36, 38, 72}$ and 26 cohort studies$^{39-41, 43, 44, 46, 47, 49, 51-58, 60, 61, 63-70}$ reported data regarding local recurrence rate (LRR) following ablation (Table 2). One RCT$^{42}$ reported lower 5-year LRR when patients were treated with MWA (OR 0.52, CI 0.30-0.91; $P = 0.023$). Heterogeneity was identified in the results reported at 1-, 2- and 3-yrs by retrospective cohort studies while meta-analysis of 2 retrospective cohort studies$^{53, 57}$ reported a higher 4-yr LRR in patients treated with MWA (OR $2.14$, CI $1.12-4.07$, $P = 0.021$) (Table 2). However, meta-analysis of 20 retrospective cohort studies that reported LRR over an unspecified period$^{39-41, 43, 44, 46, 52-54, 56-58, 60, 63, 65-70}$ concluded that LRR was significantly lower in patients treated with MWA (OR $0.67$, CI $0.51-0.87$, $P = 0.002$). Three cohort studies reported LRR according to tumour size $\leq3$cm$^{43, 52, 54}$ with no statistically significant differences were identified between the MWA and RFA groups (OR $0.86$, CI $0.45-1.64$, $p=0.64$). No potential bias was identified during visual assessment and Egger’s test of funnel plot.
Hazard ratios (HR) for OS and LRR
In total, four RCTs[22, 34, 38, 72] and 18 cohort studies[39, 41, 43-45, 51-53, 57-61, 64, 66, 68, 70] reported HR data regarding overall survival (Table 4). No statistically significant differences were noted in OS between both arms. However, there was a trend towards better overall survival rates in patients treated with MWA in both RCT (P = 0.08) and prospective cohort studies (P = 0.08) over an unspecified period (Table 4). Five retrospective cohort studies reported HR data regarding LRR[39, 53, 58, 61, 64]. No statistically significant differences were noted in LRR between both arms. No potential bias was identified during visual assessment and Egger’s test of funnel plot.

Local recurrence free survival
One RCT[35] reported that there was no statistically significant difference between MWA and RFA group with regards to 1-year LRFS (OR 1.175, CI 0.178-7.737, P = 0.93). One cohort study[63] reported that there was no statistically significant difference between MWA and RFA group with regards to LRFS (OR 0.53, CI 0.148-1.86).

Safety
In total, 3 RCTs[34, 35, 38] and 14 cohort studies[33, 39, 47, 48, 51, 58, 60, 62-64, 67-70] reported data regarding 30-day mortality (Figure 4). No statistically significant differences were identified between the MWA and RFA group in both RCTs (OR 1.00, CI 0.19-5.14, P = 1.0) and cohort studies (OR 0.67, CI 0.27-1.68, P = 0.39). There was no heterogeneity identified between studies. A sensitivity analysis excluding studies that reported 0 deaths in both arms was performed (Figure 4), but results remained consistent with the main analysis (OR 0.61, CI 0.25-1.51, P = 0.29). No potential bias was identified during visual assessment and Egger’s test of funnel plot.

In regard to morbidity, 5 RCTs[23, 35, 36, 38, 72] and 20 cohort studies[33, 39, 43, 44, 47-49, 51, 52, 54, 57, 58, 60, 61, 63-66, 68, 70] reported data on adverse events (Table 5). There were no statistically significant differences in rates of liver related morbidity, post-procedural bleeding and infections, local events, and bile duct injury when comparing the two interventions. MWA had a statistically significant increased rate of adverse
respiratory events when compared to RFA (OR 1.99, CI 1.07-3.71, \( P = 0.03 \)). No potential bias was identified during visual assessment and Egger’s test of funnel plot.

**DISCUSSION**

Local thermal ablation is the standard of care for patients with unresectable early-stage HCC. MWA is increasingly preferred to RFA because of its ability to produce wider and more predictable ablation volumes over a shorter procedural time\(^{17,19,22}\). Moreover, MWA has theoretical advantages including minimising heat-sink effect that limits the use of RFA to lesions with proximity to adjacent structures. To our knowledge, our study is the most detailed systematic review and meta-analysis to date having identified 42 studies including eight RCT’s and 34 cohort studies involving a total of 6719 subjects, that compared the outcomes of the two treatment modalities. Our main findings were that MWA achieves similar complete ablation rates compared with RFA, as well as lower local recurrence rates and similar overall survival. However, adverse events associated with MWA appear higher particularly in relation to procedural-related respiratory events.

In our study, we found MWA achieved similar or better complete ablation rates than RFA depending on the study design. Notably CA rates were similar between the two modalities among RCT’s as previously reported\(^{73,74}\) as well as among prospective cohort studies. However, higher CA rates were associated with MWA among retrospective cohort studies that is likely due to multiple factors including patient selection, tumour size and the technique used, notwithstanding the fact that nearly 3-fold more cohort studies were captured in our study compared to other smaller meta-analyses of this type\(^{40,73,75}\). These findings align with pre-clinical data that MWA results in higher infra-tumour temperature and greater ablation range\(^{76}\), that should in theory lead to faster ablation times and high rates of CA\(^{77}\).

In addition, we identified MWA utilisation was overall associated with similar rates of local recurrence to RFA among RCTs and prospective cohort studies. However lower recurrence rates with MWA were reported among retrospective cohort studies, although results were inconsistent with two retrospective cohort studies reporting lower rates of local recurrence with RFA at the four year mark while one
RCT reported lower rates of LRR with MWA at the five year mark\cite{22, 53, 54}. Moreover, because this was an analysis of LRR data without a specific timeframe, caution should be exercised as the follow up for individual studies varied. Potential reasons for discordance in results include the fact that different generators were among studies as well as variation in the reporting outcomes with some studies reporting cumulative LRR. Notably, previous meta-analyses evaluating MWA and LRR have also drawn different conclusions, with two reports concluding that MWA resulted in significantly lower LRR\cite{73, 78}, while a more recent study found no difference between both interventions\cite{74}. These data combined with ours point to the fact that LRRs following MWA of HCC are at least as good as that following RFA.

An important finding from our study was the identification that MWA appears to lead to better overall survival particularly among retrospective cohort studies. However, because this was mainly among studies with no specified follow up period, we were unable to determine the timeframe to which the improvement in overall survival applies to. Still, median OS rates tend to favour MWA particularly within the first few years post ablation. Previous meta-analyses found that up until the 5 year mark, there was no difference between OS rates\cite{24, 40, 73, 74, 78}. Except for Huo and colleagues\cite{75}, these meta-analysis did not look at yearly OS. Long-term overall survival could be affected by interventional factors such as frequency, duration, and power of the ablative machines used. Furthermore, patient factors such as age, pre-existing liver disease and severity, and socio-economic status could all contribute to OS. As we were unable to account for all these potentially confounding factors, it raises the question whether our results can be applied to the clinical setting with certainty.

In relation to adverse events, previous meta-analyses have concluded that there was no difference in complication rates between both interventions \cite{24, 73, 74}. In our study, we identified a statistically significant increased rate of adverse respiratory events (i.e. pleural effusion and pneumothorax) associated with MWA in 14 studies but no significant differences in local and/or liver related complications. This novel finding could influence the current perception that MWA has a similar safety profile to that of RFA despite the larger ablation zone. One possible explanation of the presence of
pleural effusions could be due to thermal injury to the diaphragm resulting in an inflammatory response and/or diaphragmatic microperforation(s) resulting in leakage of fluid from the peritoneal cavity to the pleural space. Similarly, the increased rates of pneumothorax could reflect inadvertent pleural puncture with subsequent air leakage into the pleural space. Ultimately, this novel safety finding adds a layer of complexity when making the decision to choose between MWA or RFA for ablating HCC.

The strengths of our study include it being the most comprehensive study on this topic to date, to our knowledge. We examined a large cohort of 6719 patients that enabled us to identify outliers and provide results with a smaller margin of error. In addition, data were categorised based on follow up period, allowing us to identify if the difference between our primary outcomes for each individual year was statistically significant. Finally, an analysis of tumour size was performed ruling out a potential confounding factor. Nevertheless, our findings should be interpreted with caution in view of certain limitations. Firstly, only studies published in English were included, which could lead to selection bias. Secondly, we did not explore the influence of generators and antennas used to perform the procedures which could present as a confounding factor. Furthermore, although we had a significant number of RCTs, the majority of studies were of retrospective cohort studies that are susceptible to both selection bias and information bias due to the difficulty in achieving accurate record keeping and recounts of events, as well as complete data retrieval. Conference abstracts were included in our study which allows for a more comprehensive look at the subject-matter but potentially at the cost of preliminary results. Also, a significant number of studies included were conducted by a single centre, and hence subject to patient selection bias. Moreover, eligibility criteria for inclusion of patients were not standardized among studies.

CONCLUSION
In conclusion, our results suggest that compared to RFA, MWA achieves similar complete ablation rates and as good or better longer-term outcomes in relation to local recurrence and overall survival. Our analysis of tumour size suggests that it is unlikely to affect our conclusion. Apart from an increased likelihood of respiratory events post procedure, MWA is as safe as RFA. Current guidelines recommend RFA
to bridge transplantation or in early HCC \cite{10, 79}. Our novel results suggest that all guidelines should consider these ablative techniques as being interchangeable as standard of care.
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