Hyperthermia ablation combined with transarterial chemoembolization versus monotherapy for hepatocellular carcinoma: A systematic review and meta-analysis

Zheng Li1,2,3,4 | Qiang Li1,2,3,5 | Xiaohu Wang1,4 | Weiqiang Chen1,2,3,5 | Xiaodong Jin1,2,3,5 | Xinguo Liu1,2,3,5 | Fei Ye1,2,3,5 | Zhongying Dai1,2,3,5 | Xiaogang Zheng1,2,3,5 | Ping Li1,2,3,5 | Chao Sun1,2,3,5 | Xiongxiong Liu1,2,3,5 | Qiuning Zhang1,4 | Hongtao Luo1,4 | Ruifeng Liu1,4

1Institute of Modern Physics, Chinese Academy of Sciences, Lanzhou, China  
2Key Laboratory of Heavy Ion Radiation Biology and Medicine of Chinese Academy of Sciences, Lanzhou, China  
3Gansu Provincial Key Laboratory of Basic Research on Heavy Ion Radiation Application in Medicine, Lanzhou, China  
4Lanzhou Heavy Ion Hospital, Lanzhou, China  
5University of Chinese Academy of Sciences, Beijing, China

Correspondence:  
Qiang Li, Institute of Modern Physics, Chinese Academy of Sciences, 509 Nanchang Road, Lanzhou 730000, China.  
Email: liqiang@impcas.ac.cn

Funding information  
This work was jointly supported by the China Postdoctoral Science Foundation (Grant No. 2019M66386D), the National Key Research Program of China (Grant Nos. 2018YFC0115700 and 2018YFC0115702), the National Natural Science Foundation of China (Grant Nos. 11875299 and U1532264), the Key Deployment Project of Chinese Academy of Sciences (Grant No. KFZD-SW-222), and the West Light Foundation of Chinese Academy of Sciences (Grant No. 29Y86205).

Abstract  
Background and aims: The existing evidence has indicated that hyperthermia ablation (HA) and HA combined with transarterial chemoembolization (HATACE) are the optimal alternative to surgical resection for patients with hepatocellular carcinoma (HCC) in the COVID-19 crisis. However, the evidence for decision-making is lacking in terms of comparison between HA and HATACE. Herein, a comprehensive evaluation was performed to compare the efficacy and safety of HATACE with monotherapy.

Materials and Methods: Worldwide studies were collected to evaluate the HATACE regimen for HCC due to the practical need for global extrapolation of applicable population. Meta-analyses were performed using the RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results: Thirty-six studies involving a large sample of 5036 patients were included finally. Compared with HA alone, HATACE produced the advantage of 5-year overall survival (OS) rate (OR: 1.90; 95%CI: 1.46, 2.46; p < 0.05) without increasing toxicity (p ≥ 0.05). Compared with TACE alone, HATACE was associated with superior 5-year OS rate (OR: 3.54; 95%CI: 1.96, 6.37; p < 0.05) and significantly reduced the incidences of severe liver damage (OR: 0.32; 95%CI: 0.11, 0.96; p < 0.05) and ascites (OR: 0.42; 95%CI: 0.20, 0.88; p < 0.05). Subgroup analysis results of small (≤3 cm) HCC revealed that there were no significant differences between the HATACE group and HA monotherapy group in regard to the OS rates (p ≥ 0.05).

Conclusions: Compared with TACE alone, HATACE was more effective and safe for HCC. Compared with HA alone, HATACE was more effective for non-small-sized (>3 cm) HCC with comparable safety. However, the survival benefit
The coronavirus disease 2019 (COVID-19), an infectious disease caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared as a global pandemic by the World Health Organization (WHO) on 11 March 2020. As of 2 September 2021, there have been 218,205,951 confirmed cases of COVID-19, including 4,526,583 deaths, according to the global data reported to WHO from almost all countries and regions. The COVID-19 pandemic has tremendously altered routine medical service provision worldwide and imposed unprecedented challenges to the global healthcare systems. There exists intricate relationship among COVID-19, cancer, and its treatment. The radical transformation of cancer management caused by COVID-19 has deeply affected the patients with hepatocellular carcinoma (HCC) in the specific areas undergoing the uncontrollable COVID-19 crisis (SAUCCC). Many HCC patients without COVID-19 cannot get normal surgical resection (SR) because of the high risk of SARS-CoV-2 infection after SR in the SAUCCC. But on the other hand, giving up SR or delay in SR, a compromise strategy occurring because of the COVID-19 pandemic, has immensely increased the risk of malignant death. What is the solution for this dilemmatic predicament widespread in the SAUCCC? This dilemma could be settled easily and perfectly if there is an idealized therapy modality that only kills cancer cells without any toxicity for normal tissue. Therefore, the optimization of therapeutic safety is the realistic and feasible solution for the predicament of HCC treatment during the COVID-19 crisis.

Minimal invasiveness has become a crucial principle for HCC treatment in the SAUCCC. Namely, the weight of therapeutic safety is amplified due to SARS-CoV-2. Several meta-analyses revealed that minimally invasive hyperthermia ablation (HA) or HA combined with transarterial chemoembolization (HATACE) could be effective alternative to SR for applicable HCC patients with added benefit of lower morbidity of adverse effects and complications. Compared with SR, HA (or HATACE) is associated with lower incidence of complications, less intraoperative blood loss, shorter operative time, and shorter length of hospitalization stay, which is significant to reduce the risk of SARS-CoV-2 infection in the SAUCCC. Therefore, both HA and HATACE possess unique superiorities among multifarious therapies for applicable HCC patients in the SAUCCC. However, the evidence for decision-making is lacking in terms of comparisons between HATACE and HA monotherapy for HCC patients. Accordingly, we carried out this systematic review and meta-analysis to comprehensively compare the efficacy and safety of HATACE with HA or TACE monotherapy for treating HCC patients.

A pre-retrieval procedure was implemented to ensure that the best results of literature retrieval could be obtained, which started on 11 March 2020. A preliminary and rapid systematic review was conducted before this study to ascertain how to design this study scientifically and accurately. Systematic review and meta-analysis were identified as the preferred research method for this study due to the actual need of comprehensive and worldwide data for global extrapolation of applicable population. No ethical approval or patient consent was required for the systematic review and meta-analysis as the data originated from previously published studies.

Studies were included if they matched the following criteria based on the pilot study of systematic review and meta-analysis. (i) Participants: Patients were diagnosed with primary HCC by histopathology and imageological examination, while the patients with metastatic liver cancer were excluded. (ii) Intervention and comparison: HA modalities included radiofrequency ablation (RFA) and microwave ablation (MWA) in this article. Studies for HATACE should compare HATACE with monotherapy of HA (RFA/MWA) or TACE. (iii) Outcomes: Outcomes of evaluation were including overall survival (OS), adverse effects, and complications. The primary endpoint was OS as conventional assessment criteria, which is defined...
as the time from random assignment to the last follow-up or death. (iv) Study type: Studies with control group were included to compare HATACE with monotherapy of HA or TACE for HCC, such as randomized controlled trial (RCT), controlled clinical trial (CCT), and propensity score matching study (PSMS). Different criteria of study type were performed for general meta-analysis and sensitivity analysis due to different aims.

Publications were excluded if they were (i) retraction by published journals; (ii) duplicate publications; (iii) clinical research without control group; and (iv) inappropriate article type including cellular or animal experiments, letters, editorials, commentaries, protocols, reviews, systematic reviews or meta-analyses.

### 2.2 Search strategy and study screening

The pre-retrieval was performed on 11 March 2020, and the comprehensive retrieval was started on 15 April 2020, following the pilot systematic review. The retrieval was updated every month during the research process in order to acquire the latest data of reports. The final retrieval time was 15 May 2021. We searched five international databases including the Cochrane Library, Web of Science, PubMed, Embase, and Scopus. We also searched other supplementary resources, such as the Google Scholar, Medical Matrix, reference lists of relevant reviews and included papers, COVID-19 Open Research Dataset Challenge (CORD-19), COVID-19 Research Database (WHO), and WHO International Clinical Trials Registry Platform. No restrictions were set for study language, publication date, and publication status. Additionally, we also communicated with some colleagues to identify the potential unpublished trials for avoiding publication bias. Studies were selected according to the inclusion and exclusion criteria through two stages: the first stage was evaluation of titles and abstracts, followed by fulltext review as the second stage.

### 2.3 Data extraction and data analysis

Data were extracted from each included article using standardized forms. Meta-analysis should not count overlapping populations in any outcome synthesis to avoid the bias of data double counting. Therefore, when multiple publications from the same institution were identified as duplicates (e.g., studies reporting the same series of patients at different phases or different perspectives), we chose the most recent updated papers with the largest sample size or longest follow-up duration for the quantitative synthesis of the meta-analyses.

The meta-analyses were performed with the RevMan version 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration) provided by the Cochrane organization. Odds ratios (ORs) and 95% confidence intervals (CIs) were used as the summary statistics for dichotomous data, which were calculated using the statistical method of Mantel–Haenszel and the analysis model of fixed-effect or random-effects according to the estimate of heterogeneity. The two-sided level of statistical significance was denoted as the two-tailed p value below the threshold of 0.05. The statistical heterogeneity (or consistency) among studies was measured with the Cochran’s Q χ² test and I² test. A p value of up to 0.10 was considered significant heterogeneity in the Cochran’s Q χ² test. An I² value of 0% indicates the optimal consistency (or no observed heterogeneity), and larger values indicate the increasing heterogeneity (or decreasing consistency). I² statistic ≤50% was considered indicative of low heterogeneity with the fixed-effect model, and >50% was considered indicative of high heterogeneity with the random-effects model.

### 2.4 Sensitivity analysis and subgroup analysis

Randomized controlled trials (RCTs) and systematic reviews of RCTs could provide the most reliable evidence about the effects of healthcare interventions. Therefore, we chose RCTs for sensitivity analysis to test the robustness of our findings from the meta-analyses. Only RCTs were included in the sensitivity analysis in order to avoid potential biases associated with case ascertainment or others from non-RCT studies. Risk ratios (RRs, instead of ORs) and 95% CIs were used as the summary statistics for dichotomous data in the sensitivity analyses of RCTs, while the others were the same as above. The risk of bias in RCTs was assessed in both table and figure formats according to the Cochrane Collaboration’s tool for randomized trials.

There is conflicting debate as to whether it is necessary to implement additional TACE of combination therapy for small (≤3 cm) HCC. Accordingly, HCC was classified into two grades according to tumor size: small-sized HCC (diameter of 3 cm or less) and non-small-sized HCC (diameter greater than 3 cm). Subgroup analysis was implemented on the basis of the size classification.

### 3 RESULTS

#### 3.1 Results of the systematic review and meta-analysis

Identification flow of the studies is exhibited as Figure 1 and Data S1. A total of 36 eligible studies involving a large
sample amount of 5036 patients were included finally for the systematic review and meta-analysis (Figure 1, Table 1, Data S1). All of the included studies were published in SCI journals and included in the Web of Science with good quality of reports. The main features of the included trials are detailedly presented in Table 1 and Data S1.
| Study (year) | Treatment | Nation | Study design | Research year range | Cases (n) |
|-------------|-----------|--------|--------------|---------------------|-----------|
| Chai NX 2021 | THA versus HA | America | CS | 2010–2018 | Total: 85; THA:21, HA:64 |
| Zaitoun MMA 2021 | TM versus T versus M | Egypt | RCT | 2017.1–2020.5 | Total: 265; TM:89, T:84, M:92 |
| Liu Y 2020 | TR versus T | China | PSMS | 2008.10–2016.5 | Total: 278; TR: 139, T: 139 |
| Li ZN 2020 | TM versus T | China | CS | 2015.6–2017.5 | Total: 51; TM: 23, T: 28 |
| Chu HH 2019 | TR versus T versus R | Korea | PSMS | 2000.3–2016.12 | Total: 538; TR:109, T:314, R:115 |
| Iezzi R 2019 | TR versus T | Italy | CCT | 2010.1–2017.6 | Total: 37; TR:21, T:16 |
| Liu FR 2019 | TR versus T | China | CS | 2005.1–2012.12 | Total: 404; TR:209, T:195 |
| Hirooka M 2018 | TR versus T | Japan | CS, MS | 2000.1–2015.12 | Total: 64; TR:32, T:32 |
| Smolock AR 2018 | TM versus T | America | CS | 2007–2016 | Total: 47; TM:23, T:24 |
| Wei YY 2018 | TM versus T | China | CS | 2010.9–2015.8 | Total: 81; TM:12, T:69 |
| Zhang RS 2018 | TM versus T | China | CS | 2007.3–2016.4 | Total: 150; TM:50, T:100 |
| Zheng L 2018 | TM versus T | China | CS | 2011.7–2015.4 | Total: 258; TM:92, T:166 |
| Chen QF 2017 | TM versus T | China | PSMS | 2014.6–2015.12 | Total: 144; TM:48, T:96 |
| Jiang FQ 2017 | TR versus T | China | RCT | 2012.6–2014.6 | Total: 106; TR:53, T:53 |
| Hyun D 2016 | TR versus T | Korea | CS | 2007.1–2010.12 | Total: 91; TR:37, T:54 |
| Li W 2016 | TM versus T | China | CS | 2005.12–2015.12 | Total: 84; TM:42, T:42 |
| Sheta E 2016 | THA versus T | Egypt | RCT | Unclear | Total: 50; TM:20, TR:20, T:10 |
| Song MJ 2016 | TR versus T versus R | Korea | CS | 2004.12–2010.2 | Total: 201; TR:87, T:71, R:43 |
| Tang CW 2016 | TR versus T versus R | China | CS | 2009.6–2012.6 | Total: 132; TR:40, T:43, R:49 |
| Liu HC 2014 | TR versus T | China | CCT | 2005.6–2011.6 | Total: 88, TR:45, T:43 |
| Yin X 2014 | TR versus T | China | CS | 2005.1–2011.12 | Total: 211; TR:55, T:156 |
| Yi YX 2014 | THA versus HA | China | RCT | 2008.6–2010.6 | Total: 94; THA:47, HA:47 |
| Peng ZW 2013 | TR versus R | China | RCT | 2006.10–2009.6 | Total: 189; TR:94, R:95 |
| Xu LF 2013 | TM versus T | China | CS | 2004.1–2011.12 | Total: 136; TM:56, T:80 |
| Study | Design | Year range | Cases (n) | Age (years) M/F (n) | Child–Pugh A/B/C (n) | Diameter (cm) |
|-------|--------|------------|-----------|---------------------|---------------------|--------------|
| THA: 64.2 ± 7.2; HA: 61.7 ± 8.9 | THA: 14/7; HA: 49/15 | THA: 16/5/0; HA: 49/15/0 | THA: 2.7 ± 1.0, 21 (≤3); HA: 2.2 ± 1.1, 64 (≤3) |
| TM: 52.1 ± 9.5 (48–76); T: 51.3 ± 9.5 (41–75); M: 53.8 ± 10.3 (38–72) | TM: 52/37; T: 52/32; M: 50/42 | TM: 80/9/0; T: 71/13/0; M: 78/14/0 | TM: 3.7 ± 0.8, 89 (≤3); T: 3.6 ± 0.8, 84 (≤2–4.8); M: 3.9 ± 0.9, 92 (≤3–5) |
| TR: 56 (28–78); T: 54 (25–78) | TR: 117/22; T: 112/27 | TR: 89 (A)/50 (B or C); T: 89 (A)/50 (B or C) | TR: 63 (≤3), 76 (≤5); T: 51 (≤3), 88 (≤5) |
| TM: 56 (36–69); T: 52 (34–65) | TM: 15/8; T: 19/9 | TM: 14/9/0; T: 18/10/0 | TM: 11 (≤3), 12 (≤3–5), 51 (≤3); T: 9 (≤3), 19 (≤3–5) |
| TR: 58.4 ± 10.2; T: 60.5 ± 10.6; R: 61.1 ± 10.8 | TR: 83/26; T: 224/90; R: 90/25 | TR: 93/16/0; T: 83/32/0; R: 254/60/0 | TR: 3.8 ± 0.5, 3.8 ± 0.5; R: 3.5 ± 0.4 |
| TR: 65.7 ± 6.0 (51–74); T: 63.1 ± 6.2 (48–78) | TR: 15/6; T: 12/4 | TR: 13/8/0; T: 10/6/0 | TR: 2 (≤3–5), 11 (≤3–5), 84 (≤3–5); T: 2 (≤3–5), 9 (≤3–5), 5 (≤5) |
| TR: 59.2 ± 4.0 (18–75); T: 58.7 ± 4.0 (20–75) | TR: 184/25; T: 165/30 | TR: 189/20/0; T: 180/15/0 | TR: 125 (≤3), 84 (≤3); T: 114 (≤3), 81 (≤3) |
| TR: 69.5 ± 8.9; T: 68.6 ± 8.9 | TR: 25/7; T: 28/4 | TR: 29/3/0; T: 31/1/0 | TR: 4.5 ± 2.4; T: 4.3 ± 2.6 |
| TM: 61 (44–85); T: 64 (43–76) | TM: 18/4; T: 13/3 | TM: 14/9/0; T: 14/7/3 | TM: 4.2 (≤3–5); T: 3.75 (≤3–5) |
| TM: 55 ± 11; T: 51 ± 11 | TM: 11/1; T: 59/10 | TM: 5/7/0; T: 15/47/7 | Length, TM: 13.33 ± 1.37; T: 13.21 ± 3.07; Width, TM: 9.9 ± 0.89, T: 10.20 ± 1.65 |
| TM: 22 (≤55), 28 (≥55); T: 42 (≤55), 58 (≥55) | TM: 43/7; T: 91/9 | TM: 46/4/0; T: 94/6/0 | TM: 36 (≤5), 14 (≥5); T: 73 (≤5), 27 (≥5) |
| TM: 53.3 ± 8.2; T: 54.6 ± 10.5 | TM: 79/13; T: 143/23 | Unclear | TM: 9.1 ± 2.8, 48 (≤10), 44 (≤10); T: 8.5 ± 2.5, 94 (≤10), 72 (≤10) |
| TM: 58.8 ± 9.6, 24 (≥20), 24 (≤20); T: 59.7 ± 10.5, 49 (≥20), 47 (≤20) | TM: 28/20; T: 54/42 | TM: 39/9/0; T: 84/12/0 | TM: 27.4 ± 10.9; T: 28.8 ± 12.5 |
| TR: 63 ± 7; T: 63 ± 6 | TR: 30/23; T: 31/22 | TR: 29/11/0; T: 28/20/5 | Unclear |
| TR: 57.7 ± 7.7; T: 59.5 ± 9.5 | TR: 31/6; T: 42/12 | TR: 34/3/0; T: 45/9/0 | TR: 28 (≤2), 9 (≤2–3); T: 32 (≤2), 22 (≤2–3) |
| TM: 48; T: 50 | Unclear | Unclear | Unclear |
| TR: 64.2 ± 13.48; T: 45.84 ± 15.08; R: 47.14 ± 13.27 | TR: 29/11; T: 33/10; R: 34/15 | TR: 18/22/0; T: 19/24/0; R: 22/27/0 | TR: 5.35 ± 1.10; T: 5.64 ± 1.41; R: 5.78 ± 1.35 |
| TR: 45–75; T: 44–78 | TR: 36/9; T: 34/9 | TR: 13/20/12; T: 10/23/10 | TR: 4–15; T: 5–14 |
| TR: 19 (≤50), 36 (≤50); T: 54 (≤50) | TR: 47/8; T: 138/18 | TR: 48/7/0; T: 136/20/0 | TR: 5.9 (5–8); T: 6.0 (5–8) |
| THA: 56.8 ± 5.6; HA: 55.9 ± 5.4 | THA: 37/10; HA: 34/13 | THA: 45/2/0; HA: 44/3/0 | THA: 3.45 ± 1.45, 22 (≤3), 25 (≤3); HA: 3.38 ± 1.33, 20 (≤3), 27 (≤3) |
| TR: 53.3 ± 11.0; R: 55.3 ± 13.3 | TR: 75/19; R: 71/24 | TR: 90/4/0; R: 90/5/0 | TR: 3.47 ± 1.44, 43 (≤3), 51 (≤3); R: 3.39 ± 1.35, 46 (≤3), 49 (≤3) |
| TM: 54.50 ± 12.95; T: 53.10 ± 14.80 | TM: 48/8; T: 73/7 | Unclear | TM: 9.48 ± 2.36; T: 10.16 ± 2.09 |

(Continues)
### Table 1 (Continued)

| Study (year) | Treatment | Nation | Study design | Research year range | Cases (n) |
|--------------|-----------|--------|--------------|---------------------|----------|
| Kim JW 2012  | TR versus R | Korea | CS | 2001.6–2008.9 | Total: 314; TR: 83, R: 231 |
| Peng ZW 2012 | TR versus R | China | RCT | 2002.1–2006.12 | Total: 139; TR: 69, R: 70 |
| Kim JH 2011  | TR versus R | Korea | CS | 2000.3–2010.4 | Total: 123; TR: 57, R: 66 |
| Liu C 2011   | TR versus T | China | CCT | 2004.5–2006.12 | Total: 34; TR: 16, T: 18 |
| Morimoto M 2010| TR versus R | Japan | RCT | 2005.8–2009.4 | Total: 37; TR: 19, R: 18 |
| Shibata T 2009| TR versus R | Japan | RCT | 2003.7–2007.12 | Total: 89; TR: 46, R: 43 |
| Yang W 2009  | TR versus T versus R | China | CS | 2000.7–2007.1 | Total: 103; TR: 31, T: 35, R: 37 |
| Yamagishi K 2008 | TR versus T | Japan | CS | 1995.1–2004.12 | Total: 201; TR: 115, T: 86 |
| Yang P 2008  | TR versus T versus R | China | RCT | 2004.2–2006.7 | Total: 47; TR: 24, T: 11, R: 12 |
| Wang YB 2007 | TR versus T | China | CCT | 2003.10–2004.12 | Total: 87; TR: 43, T: 40 |
| Aikata H 2006 | TR versus R | Japan | RCT | Unclear | Total: 44; TR: 21, R: 23 |
| Shen SQ 2005 | TR versus R | China | CCT | 2001.9–2004.6 | Total: 34; TR: 18, R: 16 |

Abbreviations: CCT, controlled clinical trial, prospective; CS, case–control study, or retrospective cohort study; F, female; HA: hyperthermia ablation, RFA or MWA; M, male; M: microwave ablation, MWA; MS, multicenter study; PSMS, propensity score matching study; R: radiofrequency ablation, RFA; RCT, randomized controlled trial; T: transarterial chemoembolization, TACE; THA: HA combined with TACE, HATACE; TM: TACE combined with MWA; TR: TACE combined with RFA.

*Median.

^Range.

^Average.

^Number of people.

The meta-analyses results showed that compared with HA alone, HATACE was associated with a significant improvement in the OS rate at 1 year (OR = 2.17, 95% CI = 1.48–3.20, p < 0.0001), 2 years (OR = 1.83, 95% CI = 1.36–2.46, p < 0.0001), 3 years (OR = 1.77, 95% CI = 1.42–2.20, p < 0.00001), 4 years (OR = 1.67, 95% CI = 1.29–2.15, p < 0.0001), and 5 years (OR = 1.89, 95% CI = 1.48–2.41, p < 0.0001; Figure 2). No significant differences were found between the HATACE group and HA alone group with respect to the incidences of severe liver damage (OR = 0.41, 95% CI = 0.18–0.98, p = 0.04) and ascites (OR = 0.54, 95% CI = 0.30–0.98, p = 0.04). No significant differences were observed between HATACE group and TACE alone group with respect to the incidences of abdominal infection, abdominal pain, bleeding, pleural effusion, fever, and nausea and vomiting (Table 2).

### 3.2 Results of the sensitivity analysis with RCTs

The sensitivity analysis of RCTs was performed to test the robustness of our findings derived from the meta-analyses above. A total of 10 RCTs^40,52,55,60,61,64,67,68,71,73^ were identified from the 36 included studies,^39–74^ which contained 6 studies^60,61,64,67,68,73^ of HATACE versus HA monotherapy, 2 studies^52,55^ of HATACE versus TACE monotherapy, and 2 studies^52,55^ of HATACE versus RFA monotherapy.
TABLE 1

| Study (year) | Treatment | Nation | Design | Cases (n) | Age (years) | Child–Pugh A/B/C | Diameter (cm) |
|-------------|-----------|--------|--------|-----------|-------------|-----------------|---------------|
| Aikata H 2006 | TR versus R | Japan | Unclear | 44 | TR: 21/12; R: 23/11 | TR: 59.1 ± 11.4<sup>c</sup>; T: 57.6 ± 11.8<sup>c</sup>; R: 57.9 ± 10.5<sup>c</sup> | TR: 67.2 ± 8.9<sup>c</sup> (45–83)<sup>b</sup>; R: 69.8 ± 8.0<sup>c</sup> (44–87)<sup>b</sup> |
| Shibata T 2009 | TR versus R | Japan | RCT | 89 | TR: 45/12; R: 51/15 | TR: 57.9 ± 10.5<sup>c</sup> | TR: 67.2 ± 8.9<sup>c</sup> (45–83)<sup>b</sup>; R: 69.8 ± 8.0<sup>c</sup> (44–87)<sup>b</sup> |
| Morimoto M 2010 | TR versus R | Japan | RCT | 37 | TR: 49/8/0; R: 67/16/0 | TR: 57.8 ± 10.5<sup>c</sup> | TR: 67.2 ± 8.9<sup>c</sup> (45–83)<sup>b</sup>; R: 69.8 ± 8.0<sup>c</sup> (44–87)<sup>b</sup> |
| Liu C 2011 | TM versus T | China | CCT | 34 | TR: 69/14; R: 82/10 | TR: 57.9 ± 10.5<sup>c</sup> | TR: 67.2 ± 8.9<sup>c</sup> (45–83)<sup>b</sup>; R: 69.8 ± 8.0<sup>c</sup> (44–87)<sup>b</sup> |
| Kim JW 2012 | TR versus R | Korea | CS | 314 | TR: 83/1; R: 231/2 | TR: 59.7 ± 10.4<sup>c</sup>; R: 58.0 ± 10.1<sup>c</sup> | TR: 59.7 ± 10.4<sup>c</sup>; R: 58.0 ± 10.1<sup>c</sup> |
| Peng ZW 2012 | TR versus R | China | RCT | 139 | TR: 69/14; R: 182/49 | TR: 57.9 ± 10.5<sup>c</sup> | TR: 59.7 ± 10.4<sup>c</sup>; R: 58.0 ± 10.1<sup>c</sup> |
| Yang W 2009 | TR versus T versus R | China | CS | 103 | 2000.7–2007.1 | TR: 69/14; R: 182/49 | TR: 57.9 ± 10.5<sup>c</sup> | TR: 59.7 ± 10.4<sup>c</sup>; R: 58.0 ± 10.1<sup>c</sup> |
| Shibata T 2009 | TR versus R | Japan | RCT | 89 | 2003.7–2007.12 | TR: 69/14; R: 182/49 | TR: 57.9 ± 10.5<sup>c</sup> | TR: 59.7 ± 10.4<sup>c</sup>; R: 58.0 ± 10.1<sup>c</sup> |
| Morimoto M 2010 | TR versus R | Japan | RCT | 37 | 2005.8–2009.4 | TR: 69/14; R: 182/49 | TR: 57.9 ± 10.5<sup>c</sup> | TR: 59.7 ± 10.4<sup>c</sup>; R: 58.0 ± 10.1<sup>c</sup> |
| Liu C 2011 | TM versus T | China | CCT | 34 | 2004.5–2006.12 | TR: 69/14; R: 82/10 | TR: 57.9 ± 10.5<sup>c</sup> | TR: 59.7 ± 10.4<sup>c</sup>; R: 58.0 ± 10.1<sup>c</sup> |
| Kim JH 2011 | TR versus R | Korea | CS | 123 | 2000.3–2010.4 | TR: 69/14; R: 82/10 | TR: 57.9 ± 10.5<sup>c</sup> | TR: 59.7 ± 10.4<sup>c</sup>; R: 58.0 ± 10.1<sup>c</sup> |
| Peng ZW 2012 | TR versus R | China | RCT | 139 | 2002.1–2006.12 | TR: 69/14; R: 82/10 | TR: 57.9 ± 10.5<sup>c</sup> | TR: 59.7 ± 10.4<sup>c</sup>; R: 58.0 ± 10.1<sup>c</sup> |

2 studies<sup>40,71</sup> of HATACE versus HA (or TACE) monotherapy. Assessment list of methodological quality of all RCTs is summarized in Table 3. The risk of bias in each RCT was further assessed with figures by the RevMan software according to the Cochrane Collaboration’s tool for randomized trials.<sup>38</sup> Details of the analysis and correction for risk of bias assessment are presented in the Data SI. Based on the comprehensive analysis of risk of bias in RCTs,<sup>40,52,55,60,61,64,67,68,71,73</sup> we had a high degree of confidence in getting reliable results from the sensitivity analysis (Figure 3 and Figure 4).

The sensitivity analysis for HATACE versus HA was completed with a total of eight RCTs.<sup>40,60,61,64,67,68,71,73</sup> The meta-analyses results demonstrated that HATACE significantly improved the OS rate over HA alone at 1 year (RR = 1.10, 95% CI = 1.03–1.17, p = 0.003), 2 years (RR = 1.19, 95% CI = 1.09–1.31, p = 0.0002), 3 years (RR = 1.22, 95% CI = 1.10–1.35, p < 0.0001), 4 years (RR = 1.20, 95% CI = 1.01–1.43, p = 0.04), and 5 years (RR = 1.35, 95% CI = 1.11–1.64, p = 0.003; Figure 5). There were no significant differences between the HATACE group and HA alone group with respect to the incidences of severe liver damage (RR = 2.98, 95% CI = 0.48–18.71, p = 0.24), ascites (RR = 1.30, 95% CI = 0.49–3.40, p = 0.60), abdominal infection (RR = 1.01, 95% CI = 0.21–4.95, p = 0.99), abdominal pain (RR = 1.04, 95% CI = 0.89–1.21, p = 0.62), bleeding (RR = 1.49, 95% CI = 0.43–5.19, p = 0.53), pleural effusion (RR = 0.99, 95% CI = 0.33–2.99, p = 0.99), fever (RR = 1.16, 95% CI = 0.88–1.52, p = 0.29), and nausea and vomiting (RR = 1.59, 95% CI = 0.80–3.17, p = 0.19; Table 4). The findings of HATACE versus HA were identified as reliable and stable on the basis of the results of sensitivity meta-analyses with RCTs (Figure 5 and Table 4).

The sensitivity analysis for HATACE versus TACE was completed with a total of four RCTs.<sup>40,52,55,71</sup> We could not finish the sensitivity meta-analysis of RCTs because of the limited studies and insufficient data, so qualitative synthetic evaluation was carried out for the sensitivity analysis of HATACE versus TACE. The
synthetic results of the four RCTs revealed that compared with TACE alone, HATACE was associated with significant improvement in the efficacy and significant reduction in the incidences of adverse reaction and complication, which is in conformity with the meta-analyses results of HATACE versus TACE above.

3.3 Results of the subgroup analysis for small HCC

The subgroup analyses results for small HCC demonstrated that there were no significant differences between the HATACE group and HA alone group with respect to the OS rates at 1, 2, 3, 4, and 5 years (p ≥ 0.05; Table 5).

4 DISCUSSION

The statistics showed that liver cancer was the third leading cause of cancer death worldwide in 2020, with about 906,000 new cases and 830,000 deaths annually. In addition, there were approximately half cases and deaths of the total number worldwide distributed in China. There is some debate that compared with the monotherapy of HA (or TACE) for treating HCC, whether HATACE could improve the efficacy meanwhile without increasing (or even reducing) toxicity and complications. This question should be definitively answered by the comprehensive systematic review and meta-analysis results.

The synergistic effects of combined HA and TACE may overcome their own limitations and improve the therapeutic outcomes. The results of meta-analyses demonstrated that the oncologic outcomes of HATACE were markedly superior to those of HA or TACE alone: (i) Compared with HA monotherapy, HATACE could significantly improve the OS rates of 1, 2, 3, 4, and 5 years, what is more, without increasing the incidences of adverse effects and complications. The robustness of the results was tested by the meta-analysis of RCTs, and the results of sensitivity meta-analysis confirmed that all of the measurement outcomes are reliable evidence. Therefore, the results of HATACE versus HA manifested that adjuvant TACE is necessary and complementary in the HA-based integrated therapy. (ii) Compared with TACE monotherapy, HATACE could significantly improve the OS rates without increasing the incidences of abdominal infection, abdominal pain, bleeding, pleural effusion, fever, and nausea and vomiting; more importantly, HATACE was associated with significant reduction in the incidences of severe liver damage and ascites. These findings are in conformity with the sensitivity analysis results of qualitative synthetic evaluation with the data of RCTs. Therefore, the results of HATACE versus TACE manifested that HA plays a significant synergistic role in HATACE; most important of all, HA is confirmed to be effective in reducing the toxicity of TACE and protecting liver function to some extent.

There are two sides as coins in the relation between TACE and HCC patients’ systemic function status (including immunity). (i) Although systemic chemotherapy leads to immunosuppression, minimally invasive TACE controls it to a minimum via its substantively limited dose and focally delivered administration; (ii) TACE is beneficial to improve patient’s holistic status (including immunity) because cancerous damage to the body (including immunosuppression caused by cancer) is ameliorated after reducing the cancer quantity; and (iii) The synthetical risk–benefit result of TACE, depending on the balance of the two aspects above, is superior to majority of the therapies for HCC, especially when the synergistic advantages were unlocked with HA combination. It is also in line with the meta-analysis results that HATACE was associated with significant improvement in the OS rates and significant reduction in the incidences of severe liver damage and ascites.

HATACE has a broad clinical applications for different stages of HCC based on the studies for systematic review, including early or very early stage (Barcelona Clinic Liver Cancer [BCLC] stage 0 & A), intermediate stage (BCLC stage B), and advanced stage (BCLC stage C & D). However, conflicting conclusions exist among some different studies in regard to the survival benefit from HATACE compared with HA monotherapy for small (<3 cm) HCC. To explore the potential different benefits associated with the different size classification of HCC, subgroup analyses were carried out for small HCC to compare HATACE with HA alone. The results revealed that the survival benefit of additional TACE is very limited without statistical significance for the patients with small HCC. Therefore, HATACE is more effective and befitting for non-small-sized (>3 cm) HCC than HA monotherapy.

Verna et al. indicated that all non-essential studies were halted when the COVID-19 pandemic started, and COVID-19 should become the preferred research subject during this unprecedented pandemic for rescuing patients in disaster. Mancilla-Galindo et al. presented a novel idea of mild hyperthermia (thermotherapy) as a potential therapy for patients with mild-to-moderate COVID-19 to prevent disease progression. Hyperthermia
FIGURE 2  Meta-analysis of OS in HATACE group compared with HA alone. CI, confidence interval; HA, hyperthermia ablation; HATACE, HA combined with TACE; M–H, Mantel–Haenszel; OS, overall survival; TACE, transarterial chemoembolization
| Outcome                  | Included studies                                      | HATACE | Monotherapy | Heterogeneity | Results of meta-analysis |
|-------------------------|------------------------------------------------------|--------|-------------|--------------|--------------------------|
|                         |                                                      | n      | N           | I²           | p            | OR (95% CI)       | p          |
| Severe liver damage     | 7, 40, 43, 63, 65, 68, 74                           | 4      | 471         | 3            | 633          | 0%              | 0.89       | 1.36 (0.46, 4.03) | 0.58       |
| Ascites                 | 3, 40, 61, 64                                        | 9      | 210         | 7            | 212          | 0%              | 0.97       | 1.31 (0.48, 3.60) | 0.60       |
| Abdominal infection     | 3, 40, 61, 64                                        | 2      | 210         | 2            | 212          | 0%              | 0.63       | 1.01 (0.20, 5.05) | 0.99       |
| Abdominal pain          | 5, 40, 60, 61, 64, 67                               | 151    | 318         | 147          | 322          | 25%              | 0.26       | 1.09 (0.78, 1.53) | 0.62       |
| Bleeding                | 1, 40, 43, 45, 46, 48–51, 53, 54, 56, 58, 62, 66, 69 | 11     | 597         | 11           | 817          | 0%              | 0.89       | 1.38 (0.64, 2.98) | 0.41       |
| Pleural effusion        | 4, 40, 61, 67, 74                                     | 7      | 178         | 7            | 176          | 0%              | 0.89       | 0.97 (0.33, 2.84) | 0.96       |
| Fever                   | 4, 40, 60, 61, 64                                    | 79     | 299         | 69           | 304          | 13%              | 0.33       | 1.23 (0.84, 1.82) | 0.29       |
| Nausea and vomiting     | 4, 40, 60, 61, 64                                    | 85     | 299         | 53           | 304          | 73%              | 0.01       | 1.97 (0.77, 5.08) | 0.16       |

Abbreviations: CI, confidence interval; HA, hyperthermia ablation; M–H, Mantel–Haenszel; OS, overall survival; TACE, transarterial chemoembolization.
therapy (including HA) could improve the immunity of cancer patients,23–33,83,84 which should be given adequate attention to for the anticancer treatment in the context of COVID-19 crisis.8–14,26 The need of minimal invasion has already become a crucial consideration for therapeutic decision-making in the SAUCCC.8–14 Accordingly, HA and HATACE possess unique superiorities among multifarious therapies for appropriate HCC patients in the SAUCCC,17–20,22,33,85–88 which is fully exhibited in the Data S1.

COVID-19 throughout the world has caused unprecedented social turmoil on a global level, triggering...
a comprehensive transformation of global healthcare systems.⁴⁻⁷,⁸⁹⁻⁹⁷ There exists dilemmatic predicament in regard to SR for HCC patients in the SAUCCC, which has been mentioned in the introduction section. So far, the minimally invasive HA and HATACE were identified as the optimal alternative to SR for applicable HCC patients in the SAUCCC.⁸⁻¹⁴,¹⁷⁻²¹ The data of several meta-analyses¹⁷⁻²¹ have already demonstrated that HA (or HATACE) offers comparable oncologic outcomes for applicable HCC patients as compared with SR and with added safety benefit of lower morbidity. (i) The specific safety advantages of HA (HATACE), such as lower incidence of complications, less intraoperative blood loss, and shorter operative time, are beneficial to reduce the risk of SARS-CoV-2 infection by preserving patients in a relatively good holistic state.⁸⁻¹⁴,¹⁷⁻²¹ (ii) The shorter hospitalization duration, one verified superiority of HA (HATACE) compared with SR,¹⁷⁻²¹ is significant not only to minimize the risk of nosocomial cross-infection of SARS-CoV-2 by reducing the exposure frequency and total duration of SARS-CoV-2, but also to increase the turnover rate of hospitalization. In the summer of 2021, SARS-CoV-2 Delta Variant surge has caused a new wave of epidemic peak in America and some other countries.⁴,⁹⁸ As a matter of fact, hospital beds and other medical resources have become more and more shortage due to the severely escalating COVID-19 epidemics, causing the increasing death of both patients with COVID-19 and without COVID-19.⁵,⁹⁷,⁹⁸ Therefore, it is necessary and urgent to accelerate the turnover rate of hospitalization for improving the capacity of medical service and alleviating the widespread shortage of healthcare resource in the context of the unprecedented COVID-19 crisis.⁹⁹⁻¹⁰¹

To our knowledge, this article is the first systematic review and meta-analysis to evaluate HATACE for HCC, regarding ablation modalities including both RFA and MWA. Additionally, it addresses not only the largest sample size of 5036 patients from 36 included studies in this subject,³⁹⁻⁷⁴,¹⁰² but also a total of 10 RCTs for sensitivity analyses. Therefore, the present study could provide more comprehensive and reliable evidence for decision-makings than other congeneric research.¹⁰² However, there are some limitations in our study indeed. The robustness of the HATACE versus HA results was demonstrated by the sensitivity meta-analysis of RCTs with adequate qualification, but the sensitivity meta-analysis of RCTs for HATACE versus TACE was not implemented finally because of the insufficient studies and data. So the evidential strength grade of HATACE versus TACE should be judged to be lower than that of HATACE versus HA. Nevertheless, it is very circumscribed and impractical to investigate the adverse reactions of therapies only relying on RCTs in this topic. Non-RCT clinical studies are necessary and important for assessing the safety; therefore, the adverse reactions evaluation of HATACE, which is a key consideration for clinical decision-making during the COVID-19 pandemic, is relatively independent on the test strategy of meta-analysis with RCTs. Hence, the conclusions on the safety of HATACE, including that HA significantly reduces the toxicity of TACE and preserves the liver function to some extent, could be considered adequately reliable.

In this study, we have demonstrated that HATACE for HCC is superior to TACE monotherapy with respect to either efficacy or safety. HATACE is more effective than HA monotherapy with comparable safety for non-small-sized (>3 cm) HCC. Compared with HATACE, HA monotherapy could provide comparable survival benefit for the patients with small (≤3 cm) HCC. Namely, adjuvant TACE is not necessary for HA therapy in treating small HCC. Although there are some deficiencies as discussed in limitations above, this research could provide a comprehensive reference for clinical decision-making on the base of the 36 included studies and the adequately large sample size of 5036 patients. In addition, we should pay more attention to HA and HATACE due to their superiorities in the SAUCCC.
FIGURE 5  Sensitivity analysis of OS for HATAE group compared with HA group. CI, confidence interval; HA, hyperthermia ablation; HATAE, HA combined with TACE; M–H, Mantel–Haenszel; OS, overall survival; TACE, transarterial chemoembolization
ACKNOWLEDGMENTS
We thank all authors for their contributions to this study.

CONFLICT OF INTEREST
The authors declare no conflict of interest. The authors alone are responsible for the content and writing of the article.

ETHICAL DECLARATION
No ethical approval was required for the systematic review and meta-analysis as all data originated from previously published studies.

DATA AVAILABILITY STATEMENT
The authors confirm that they included a citation for available data in References section. The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID
Zheng Li https://orcid.org/0000-0002-8837-0318
Qiang Li https://orcid.org/0000-0003-0096-7679

REFERENCES
1. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-273. doi:10.1038/s41586-020-2012-7
2. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origin and receptor binding. Lancet. 2020;395(10224):565-574. doi:10.1016/s0140-6736(20)30251-8
3. WHO time-line COVID-19. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/event-as-they-happen
4. WHO Coronavirus Disease (COVID-19) Dashboard. https://covid19.who.int/
5. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382(10):929-936. doi:10.1056/NEJMoa2001191
6. Rosenbaum L. The untold toll — the pandemic's effects on patients without Covid-19. N Engl J Med. 2020;382(24):2368-2371. doi:10.1056/NEJMs2009984
7. Tuech JJ, Gangloff A, Di Fiore F, Benyoucef A, Michel P, Schwarz L. The day after tomorrow: how should we address health system organization to treat Cancer patients after the peak of the COVID-19 epidemic? Oncology. 2020;98(12):827-835. doi:10.1159/000509650
8. Zhang H, Wang L, Chen Y, et al. Outcomes of novel coronavirus disease 2019 (COVID-19) infection in 107 patients with cancer from Wuhan, China. Cancer. 2020;126(17):4023-4031. doi:10.1002/cncr.33042

9. Zhang L, Zhu F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol. 2020;31(7):894-901. doi:10.1016/j.annonc.2020.03.296

10. Yarza R, Bover M, Paredes D, et al. SARS-CoV-2 infection in cancer patients undergoing active treatment: analysis of clinical features and predictive factors for severe respiratory failure and death. Eur J Cancer. 2020;135:242-250. doi:10.1016/j.ejca.2020.06.001

11. Tian J, Yuan X, Xiao J, et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncol. 2020;21(7):893-903. doi:10.1016/s1470-2045(20)30309-0

12. Yang K, Sheng Y, Huang C, et al. Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective, cohort study. Lancet Oncol. 2020;21(7):904-913. doi:10.1016/s1470-2045(20)30310-7

13. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335-337. doi:10.1016/s1470-2045(20)30096-6

14. Tang LV, Hu Y. Poor clinical outcomes for patients with cancer during the COVID-19 pandemic. Lancet Oncol. 2020;21(7):862-864. doi:10.1016/s1470-2045(20)30311-9

15. Garg PK, Kaul P, Choudhary D, et al. Discordance of COVID-19 guidelines for patients with cancer: a systematic review. J Surg Oncol. 2020;122(4):579-593. doi:10.1002/jso.26110

16. Huillard O, Goldwasser F. Cancer treatment during the coronavirus disease 2019 pandemic: do not postpone but decide wisely. Eur J Cancer. 2020;135:51. doi:10.1016/j.ejca.2020.05.024

17. Yang G, Xiong Y, Sun JJ, et al. The efficacy of microwave ablation versus liver resection in the treatment of hepatocellular carcinoma and liver metastases: a systematic review and meta-analysis. Int J Surg. 2020;77:85-93. doi:10.1016/j.ijsu.2020.03.006

18. Gui CH, Baey S, D’Cruz RT, Shetel VG. Trans-arterial chemoembolization + radiofrequency ablation versus surgical resection in hepatocellular carcinoma – A meta-analysis. Eur J Surg Oncol. 2020;46(5):763-771. doi:10.1016/j.ejso.2020.01.004

19. Wang WD, Zhang LH, Ni JY, et al. Radiofrequency ablation combined with transcatheter arterial chemoembolization therapy versus surgical resection for hepatocellular carcinoma within the milan criteria: a meta-analysis. Korean J Radiol. 2018;19(4):613-622. doi:10.3348/kjr.2018.19.4.613

20. Jia JB, Zhang D, Ludwig JM, Kim HS. Radiofrequency ablation versus resection for hepatocellular carcinoma in patients with Child-Pugh A liver cirrhosis: a meta-analysis. Clin Radiol. 2017;72(12):1066-1075. doi:10.1016/j.crad.2017.07.024

21. Zhang M, Ma H, Zhang J, He L, Ye X, Li X. Comparison of microwave ablation and hepatic resection for hepatocellular carcinoma: a meta-analysis. Onco Targets Ther. 2017;10:4829-4839. doi:10.2147/ott.S141968

22. Yu J, Liang P. Status and advancement of microwave ablation in China. Int J Hyperthermia. 2017;33(3):278-287. doi:10.1080/02656736.2016.1243261

23. Costa ACD, Sodergren M, Jayant K, et al. Radiofrequency combined with immunomodulation for hepatocellular carcinoma: state of the art and innovations. World J Gastroenterol. 2020;26(17):2040-2048. doi:10.3748/wjg.v26.i17.2040

24. Waitz R, Solomon SB. Can local radiofrequency ablation of tumors generate systemic immunity against metastatic disease? Radiology. 2009;251(1):1-2. doi:10.1148/radiol.2511082215

25. Leuchte K, Staib E, Thelen M, et al. Microwave ablation enhances tumor-specific immune response in patients with hepatocellular carcinoma. Cancer Immunol Immunother. 2021;70(4):893-907. doi:10.1007/s00262-020-02734-1

26. Mancilla-Galindo J, Galindo-Sevilla N. Exploring the rationale for thermotherapy in COVID-19. Int J Hyperthermia. 2021;38(1):202-212. doi:10.1080/02656736.2021.1883127

27. Frey B, Weiss EM, Rubner Y, et al. Old and new facts about hyperthermia-induced modulations of the immune system. Int J Hyperthermia. 2012;28(6):528-542. doi:10.3109/02656736.2012.677933

28. Mazmishvili K, Jayant K, Janikashvili N, et al. Study to evaluate the immunomodulatory effects of radiofrequency ablation compared to surgical resection for liver cancer. J Cancer. 2018;9(17):3187-3195. doi:10.7150/jca.25084

29. Li G, Staveley-O’Carroll KF, Kimchi ET. Potential of radiofrequency ablation in combination with immunotherapy in the treatment of hepatocellular carcinoma. J Clin Trials. 2016;6(2):257. doi:10.4172/2167-0870.1000257

30. Qi X, Yang M, Ma L, et al. Synergizing sunitinib and radiofrequency ablation to treat hepatocellular cancer by triggering the antitumor immune response. J Immunother Cancer. 2020;8(2):e001038. doi:10.1136/jitc-2020-001038

31. Wust P, Hildebrandt B, Sreenivasa G, et al. Hyperthermia in combined treatment of cancer. Lancet Oncol. 2002;3(8):487-497. doi:10.1016/s1470-2045(02)00818-5

32. Hamamoto S, Okuma T, Yamamoto A, et al. Radiofrequency ablation and immunostimulant OK-432: combination therapy enhances systemic antitumor immunity for treatment of VX2 lung tumors in rabbits. Radiology. 2013;267(2):405-413. doi:10.1148/radiol.13120249.

33. Dromi SA, Walsh MP, Herby S, et al. Radiofrequency ablation induces antigen-presenting cell infiltration and amplification of weak tumor-induced immunity. Radiology. 2009;251(1):58-66. doi:10.1148/radiol.2511072175

34. Lan T, Chang L, Rahmathullah MN, Wu L, Yuan YF. Comparative efficacy of interventional therapies for early-stage hepatocellular carcinoma: a PRISMA-compliant systematic review and network meta-analysis. Medicine. 2016;95(15):e3185. doi:10.1097/md.0000000000033185

35. Xu Z, Xie H, Zhou L, Chen X, Zheng S. The combination strategy of transarterial chemoembolization and radiofrequency ablation or microwave ablation against hepatocellular carcinoma. Anal Cell Pathol. 2019;2019:1-7. doi:10.1155/2019/8619096

36. Liu PH, Lee YH, Hsu CY, et al. Survival advantage of radiofrequency ablation over transarterial chemoembolization for patients with hepatocellular carcinoma and good performance status within the Milan criteria. Ann Surg Oncol. 2014;21(12):3835-3843. doi:10.1245/s10434-014-3831-2

37. Cui R, Wang XH, Ma C, et al. Comparison of microwave ablation and transarterial chemoembolization for single-nodule hepatocellular carcinoma smaller than 5cm: a propensity score
50. Zheng L, Li HL, Guo CY, Luo SX. Comparison of the efficacy and prognostic factors of transarterial chemoembolization plus microwave ablation versus transarterial chemoembolization alone in patients with a large solitary or multinodular hepatocellular carcinomas. *Korean J Radiol*. 2018;19(2):237-246. doi:10.3348/kjr.2018.19.2.237

51. Chen QF, Jia ZY, Yang ZQ, Fan WL, Shi HB. Transarterial chemoembolization monotherapy versus combined transarterial chemoembolization-microwave ablation therapy for hepatocellular carcinoma tumors ≤5 cm: a propensity analysis at a single center. *Cardiovasc Intervent Radiol*. 2017;40(11):1748-1755. doi:10.1007/s00270-017-1736-8

52. Jiang FQ, Lu W, Yang C, et al. Curative effect of transcatheter arterial chemoembolization combined with radiofrequency ablation in treating hepatic cell carcinoma and its effect on serum markers. *Cancer Biomark*. 2017;20(1):17-22. doi:10.3233/cbm-160508

53. Hyun D, Cho SK, Shin SW, et al. Early stage hepatocellular carcinomas not feasible for ultrasound-guided radiofrequency ablation: comparison of transarterial chemoembolization alone and combined therapy with transarterial chemoembolization and radiofrequency ablation. *Cardiovasc Intervent Radiol*. 2016;39(3):417-425. doi:10.1007/s00270-015-1194-0

54. Li W, Man W, Guo H, Yang P. Clinical study of transcatheter arterial chemoembolization combined with microwave ablation in the treatment of advanced hepatocellular carcinoma. *J Cancer Res Ther*. 2016;12(7):C217-C220. doi:10.4103/0973-1482.200598

55. Sheta E, El-Kalla F, El-Gharib M, et al. Comparison of single-session transarterial chemoembolization combined with microwave ablation or radiofrequency ablation in the treatment of hepatocellular carcinoma: a randomized-controlled study. *Eur J Gastroenterol Hepatol*. 2016;28(10):1198-1203. doi:10.1097/MEG.0000000000000688

56. Song MJ, Bae SH, Lee JS, et al. Combination transarterial chemoembolization and radiofrequency ablation therapy for early hepatocellular carcinoma. *Korean J Intern Med*. 2016;31(2):242-252. doi:10.3904/kjim.2015.112

57. Tang C, Shen J, Feng W, et al. Combination therapy of radiofrequency ablation and transarterial chemoembolization for unresectable hepatocellular carcinoma: a retrospective study. *Medicine (Baltimore)*. 2016;95(20):e3754. doi:10.1097/md.0000000000003754

58. Liu HC, Shan EB, Zhou L, et al. Combination of percutaneous radiofrequency ablation with transarterial chemoembolization for hepatocellular carcinoma: observation of clinical effects. *Chin J Cancer Res*. 2014;26(4):471-477. doi:10.3978/j.issn.1000-9604.2014.08.18

59. Yin X, Zhang L, Wang YH, et al. Transcatheter arterial chemoembolization combined with radiofrequency ablation delays tumor progression and prolongs overall survival in patients with intermediate (BCLC B) hepatocellular carcinoma. *BMC Cancer*. 2014;14:849. doi:10.1186/1471-2407-14-849

60. Yi Y, Zhang Y, Wei Q, et al. Radiofrequency ablation or microwave ablation combined with transcatheter arterial chemoembolization in treatment of hepatocellular carcinoma by comparing with radiofrequency ablation alone. *Chin J Cancer Res*. 2014;26(1):112-118. doi:10.3978/j.issn.1000-9604.2014.02.09

61. Peng ZW, Zhang YJ, Chen MS, et al. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective
hepatocellular carcinoma: a systemic review and meta-analysis.

Int J Hyperthermia. 2020;37(1):624-633. doi:10.1080/02656736.2020.1774667

98. Afaghi P, Lapolla MA, Ghandi K. Percutaneous microwave ablation applications for liver tumors: recommendations for COVID-19 patients. Heliyon. 2021;7(3):e06454. doi:10.1016/j.heliyon.2021.e06454

99. Ng SSW, Ning MS, Lee P, McMahon RA, Siva S, Chuong MD. Single-fraction stereotactic body radiation therapy: a paradigm during the coronavirus disease 2019 (COVID-19) pandemic and beyond? Adv Radiat Oncol. 2020;5(4):761-773. doi:10.1016/j.adro.2020.06.011

100. Kidane B, Spicer J, Kim JO, et al. SABR-BRIDGE: Stereotactic ABlative Radiotherapy Before Resection to Avoid Delay for Early-Stage LunG Cancer or OligomEts During the COVID-19 Pandemic. Front Oncol. 2020;10: 580189 doi:10.3389/fonc.2020.580189

101. Ni JY, Liu SS, Xu LF, Sun HL, Chen YT. Transarterial chemoembolization combined with percutaneous radiofrequency ablation versus TACE and PRFA monotherapy in the treatment for hepatocellular carcinoma: a meta-analysis. J Cancer Res Clin Oncol. 2013;139(4):653-659. doi:10.1007/s00432-012-1369-x

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

How to cite this article: Li Z, Li Q, Wang X, et al. Hyperthermia ablation combined with transarterial chemoembolization versus monotherapy for hepatocellular carcinoma: a systematic review and meta-analysis. Cancer Med. 2021;10:8432-8450. doi:10.1002/cam4.4350