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# Transarterial chemoembolization combined with radiofrequency ablation in the treatment of hepatocellular carcinomas larger than 5 cm

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## Abstract

**Aim:** This meta-analysis was designed to compare the effectiveness of the combination of transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) *vs.* that of TACE alone in hepatocellular carcinoma (HCC) tumors larger than 5 cm.

**Methods:** PUBMED, CNKI, and CBM were searched for all related randomized controlled trials (RCTs) up until October 22, 2018. Eleven studies were identified that compared TACE with RFA *vs.* TACE alone for HCC treatment. Tumor response rate, the proportion of patients with either complete or partial shrinkage of tumors, and survival rate were the major evaluation indices.

**Results:** Meta-analysis data revealed that TACE with RFA showed significantly better tumor response rate (risk ratio (RR) = 1.452, 95% confidence interval (CI): 1.308-1.610,  $P < 0.001$ ) and 1-year overall survival rate (RR = 1.412, 95% CI: 1.249-1.596,  $P < 0.001$ ) than that of TACE alone treatment.

**Conclusion:** The data of our study indicates that TACE combined with RFA in the treatment of HCC larger than 5 cm is an effective comprehensive interventional therapy.



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**Keywords:** Transarterial chemoembolization; radiofrequency ablation; hepatocellular carcinoma; meta-analysis

## INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common and malignant tumor in the world, with an annual incidence of over 700,000 patients worldwide<sup>[1]</sup>. As the symptoms of HCC often do not present in the early stages, most patients are in the middle and late stage at the time of diagnosis, among which only 20%-30% of patients have the chance to receive surgical resection or liver transplantation<sup>[2]</sup>. Patients with large tumors that cannot undergo surgical resection or liver transplantation are usually offered comprehensive treatment based on transarterial chemoembolization (TACE)<sup>[3,4]</sup>. However, the long-term outcome of treating HCC with TACE alone is not ideal, due to incomplete tumor necrosis<sup>[5,6]</sup>. Studies have shown that TACE combined with RFA in the treatment of HCC is more efficacious than either TACE or RFA alone<sup>[7,8]</sup>. Nevertheless, some studies have reported contradictory results<sup>[9,10]</sup>. Of note, the sample sizes of these studies are small and the observations need further validation. Additionally, it is unknown whether this combined treatment is more effective than single modality treatment for HCC tumors larger than 5 cm.

Therefore, in order to determine whether TACE plus RFA is more effective in patients with HCC than TACE alone, this current meta-analysis was performed to compare the efficacy of TACE plus RFA with TACE monotherapy. This comparison is expected to provide more convincing evidence for HCC patients having to choose between two methods. In this study, the clinical efficacy of TACE combined with RFA was compared with that of TACE alone in the treatment of HCC larger than 5 cm, to provide evidence to guide clinical practice.

## METHODS

### Search methods and quality assessment

As of October 22, 2018, randomized controlled trials (RCT) comparing the clinical efficacy of TACE with RFA *vs.* TACE alone in the treatment of HCC was performed using a computerized search on PUBMED, Chinese Journal Full-text Database (CKNI), and CBM. Search terms include “Liver Neoplasms/therapy” [Mesh], “Chemoembolization, Therapeutic” [Mesh], “TACE”, “Radiofrequency ablation”. The literature language is limited to Chinese and English.

Evaluation of literature quality (including literature data extraction and quality scoring) was carried out by the authors. According to the Jadad quality standard, the scoring method is as follows. Whether it is randomly assigned: 2 points is awarded for detailed random allocation, 1 point when it was not specifically described, and 0 point if it was not mentioned. Whether analysis was blinded, 2 points for double-blind, 1 point for blinding without detailed description, 0 point for open trial. Whether there was a detailed reason for loss of follow-up: 1 point for yes, 0 point for no. High quality research literatures are those that received 3 to 5 points; and low quality literatures are those that received 0 to 2 points.

### Inclusion criteria

Literature reports were eligible for inclusion if: (1) they are domestic or international publications, that compared the clinical efficacy of TACE combined with RFA *vs.* TACE alone in the treatment of intermediate and advanced staged HCC; (2) they report complete case data; (3) the results of the study include tumor response rate; (4) the maximum diameter of tumor lesions is greater than 5 cm; (5) the clinical study design is consistent with that of a RCT.

### Exclusion criteria

Literature reports were excluded if: (1) they are review articles or case reports, are of poor literature quality as evaluated by the above method, or have no proper controls; (2) they are animal studies; (3) there are

**Table 1. Main characteristics of studies concerning tumor response rate between TACE with RFA vs. TACE alone**

Ref.	Year study was conducted	Gender	Sample size	TACE		Tumor response rate	TACE + RFA		Tumor response rate
				Total	Events		Total	Events	
Dong et al. <sup>[11]</sup>	2011-2012	Both	44	22	6	0.272727273	22	11	0.5
Du et al. <sup>[12]</sup>	2015-2016	Both	80	40	14	0.35	40	23	0.575
Ge and Zhang <sup>[13]</sup>	2008-2009	Both	43	24	12	0.5	19	14	0.736842105
Kuang et al. <sup>[14]</sup>	2015-2017	Both	87	40	21	0.525	47	35	0.744680851
Li et al. <sup>[15]</sup>	2012-2013	Both	80	42	21	0.5	38	27	0.710526316
Liang <sup>[16]</sup>	2006-2008	Both	55	24	9	0.375	31	25	0.806451613
Liu et al. <sup>[17]</sup>	2011-2013	Both	128	64	10	0.15625	64	22	0.34375
Shen et al. <sup>[18]</sup>	2004-2005	Both	40	19	9	0.473684211	21	17	0.80952381
Song et al. <sup>[19]</sup>	2006-2008	Both	29	15	4	0.266666667	14	11	0.785714286
Zhang et al. <sup>[20]</sup>	2012-2014	Both	70	33	6	0.181818182	37	17	0.459459459
Yang et al. <sup>[21]</sup>	2006-2008	Both	35	11	6	0.545454545	24	16	0.666666667

duplicate reports of similar content by the same author, or if there are too few patients and unclear data; (4) the maximum diameter of tumor lesions is less than 5 cm.

### Data acquisition

The literature and extracted the data were screened independently by authors. After articles were screened by their titles and abstracts, they were filtered by reading the full text. During the screening process, the literature was selected in strict accordance with the set inclusion and exclusion criteria. After the screening was completed, the articles were read again to verify that they meet the requirements.

### Statistical methods

Statistical analysis was performed using Comprehensive Meta Analysis V2. Before the meta-analysis, the heterogeneity  $I^2$  test of each test result was performed. If the homogeneity of each test included in the study was good ( $P > 0.05$ ), the fixed effect model was used. If heterogeneity existed, the random effect model was used. A funnel chart was used to evaluate the bias risk of the inclusion test, and asymmetric funnel charts suggest that there may be publication bias.

## RESULTS

### Literature search results

Manual search of electronic databases identified a total of 1,487 studies. After checking for duplicates, there were 1,304 remaining. A large number of these studies were excluded based upon our inclusion and exclusion criteria, leaving only 11 articles to be included in the meta-analysis [Figure 1 and Table 1].

### Tumor response rate

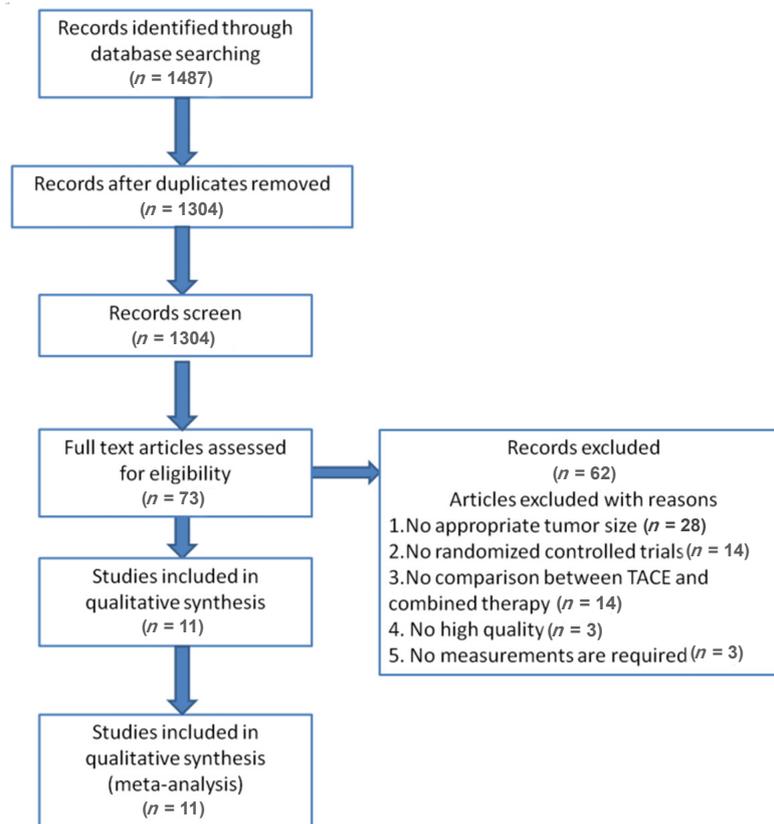
There were 11 reports with tumor response rate data comparing TACE with RFA vs. TACE alone. Tumor response rate was measured by the proportion of patients with either complete or partial shrinkage of tumors. Since the heterogeneity test had a  $P = 0.983$ , the fixed-effects model was used. The results showed that the tumor response rate of TACE with RFA in the treatment of HCC was significantly superior to TACE alone [risk ratio (RR) = 1.452, 95%CI: 1.308-1.610,  $P < 0.001$ ,  $I^2 = 0\%$ ] [Figure 2].

### Six-month survival rate

Six studies<sup>[15,16,18-21]</sup> (involving 309 participants) compared the half-year survival of the TACE with RFA group vs. the TACE alone group. The results showed that half-year survival rate was higher in the TACE with RFA group than in the TACE alone group [RR = 1.257, 95%CI = 1.128-1.401,  $P < 0.001$ ,  $I^2 = 0\%$ ] [Figure 3].

### One-year survival rate

Eight studies<sup>[14-21]</sup> (involving 524 participants) compared the 1-year survival of the TACE with RFA group vs. the TACE alone group. The results showed that 1-year survival rate was higher in the TACE with RFA group compared to the TACE alone group [RR = 1.412, 95%CI = 1.249-1.596,  $P < 0.001$ ,  $I^2 = 0\%$ ] [Figure 4].



**Figure 1.** Flow diagram of the detailed selection process of this meta-analysis. A total of 11 RCTs<sup>[11-21]</sup> [Table 1] were included in the study. There were 691 eligible patients, of whom 357 received TACE with RFA, and 334 received TACE alone. The baseline characteristics of the trials included in the meta-analysis are shown in Table 1. The quality of the included studies was assessed using the Cochrane Collaboration Tool

### **Eighteen-month survival rate**

Six studies<sup>[15,16,18-21]</sup> (involving 309 participants) compared eighteen-month survival of the TACE with RFA group vs. the TACE alone group. The results showed that eighteen-month survival rate was higher in the TACE with RFA group than in the TACE alone group [RR = 1.792, 95%CI: 1.423-2.256,  $P < 0.001$ ,  $I^2 = 0\%$ ] [Figure 5].

### **Two-year survival rate**

Three studies<sup>[14,17,20]</sup> (involving 285 participants) compared the 2-year survival rate of the TACE with RFA group vs. the TACE alone group. The results showed that 2-year survival rate was higher in the TACE with RFA group than in the TACE alone group [RR = 1.675, 95%CI: 1.233-2.275,  $P = 0.001$ ,  $I^2 = 0\%$ ] [Figure 6].

### **Incidence of fever**

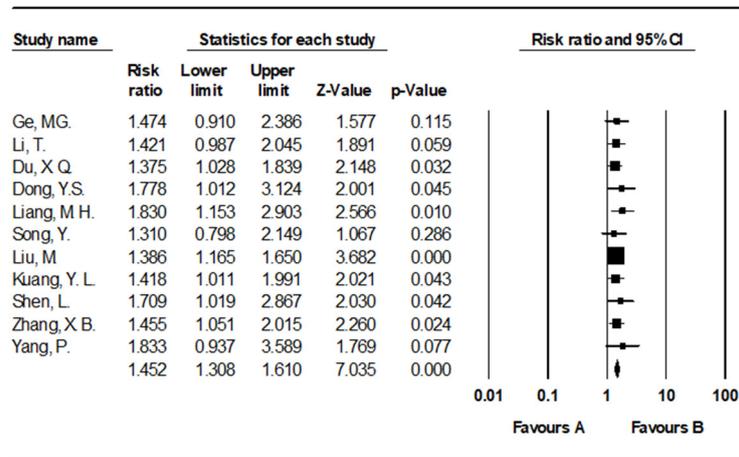
Three studies<sup>[11,12,20]</sup> (involving 194 participants) compared the incidence of fever of the TACE with RFA group vs. the TACE alone group, and showed that there was no significant difference between the two groups [RR = 1.177, 95%CI: 0.904-1.532,  $P = 0.227$ ,  $I^2 = 0\%$ ] [Figure 7].

### **Publication bias assessment**

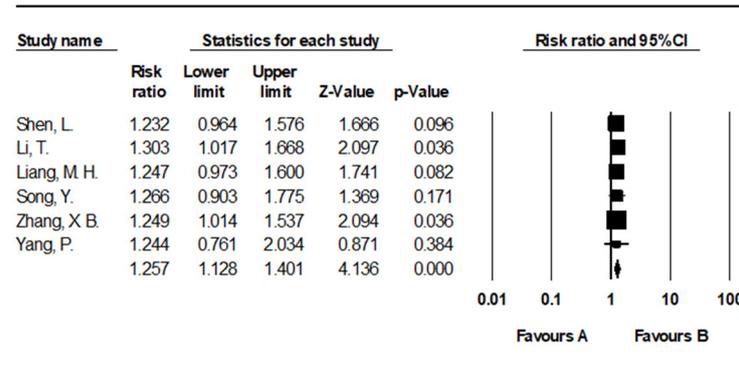
Based on statistical analysis, the meta-analysis of TACE with RFA vs. TACE alone obtained better symmetry of the funnel plot<sup>[22]</sup> and can be assessed without significant publication bias in the study literature [Figure 8].

## **DISCUSSION**

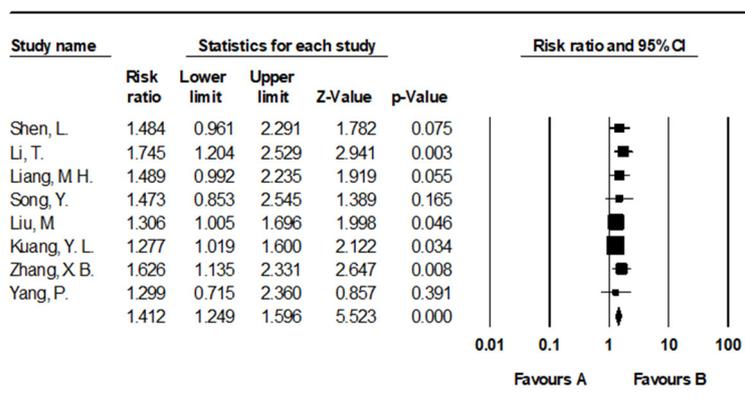
Compared to treatment with TACE alone, this study showed that TACE combined with RFA showed significantly better outcomes on tumor response rate [RR = 1.452, 95%CI: 1.308-1.610,  $P < 0.001$ ], six-month



**Figure 2.** Tumor response rate of comparison TACE with RFA vs. TACE alone



**Figure 3.** Six-month survival rate of TACE with RFA vs. TACE alone



**Figure 4.** One-year survival rate of TACE with RFA vs. TACE alone

survival rate [RR = 1.257, 95%CI: 1.128-1.401,  $P < 0.001$ ], 1-year overall survival rate [RR = 1.412, 95%CI: 1.249-1.596,  $P < 0.001$ ], eighteen-month survival rate [RR = 1.792, 95%CI: 1.423-2.256,  $P < 0.001$ ], and 2-year overall survival rate [RR = 1.675, 95%CI: 1.233-2.275,  $P = 0.001$ ]. To our knowledge this study is the first meta-analysis to disclose the efficacy of TACE combined with RFA for HCC tumors larger than 5 cm, compared with TACE alone. The publication bias of this study was evaluated using the symmetry level of the funnel plot<sup>[22]</sup>. In the analysis of the tumor response rate and survival rate, the symmetry of the shape of the

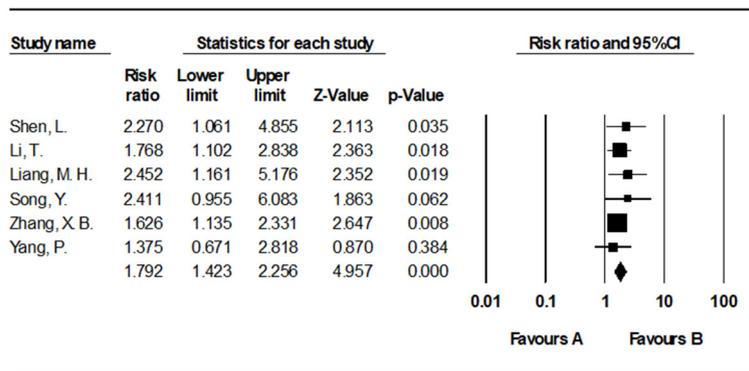


Figure 5. Eighteen-month survival rate of TACE with RFA vs. TACE alone

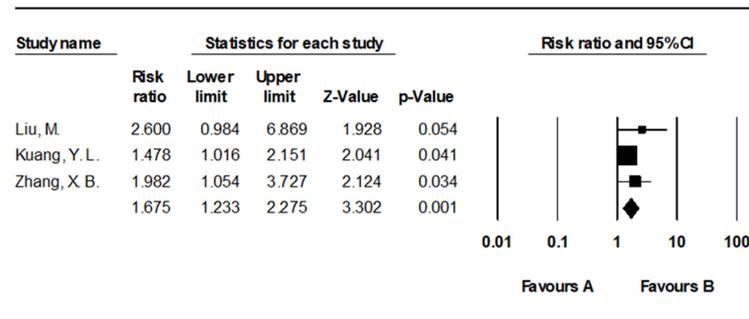


Figure 6. Two-year survival rate of TACE with RFA vs. TACE alone

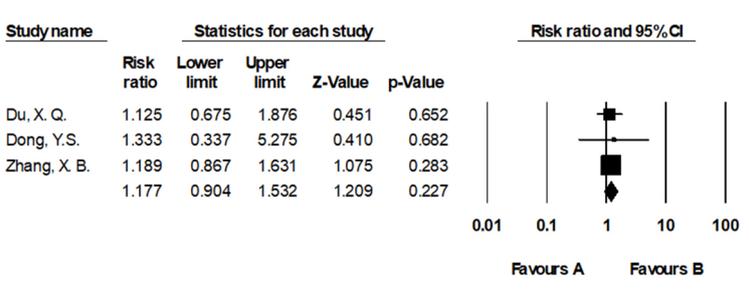
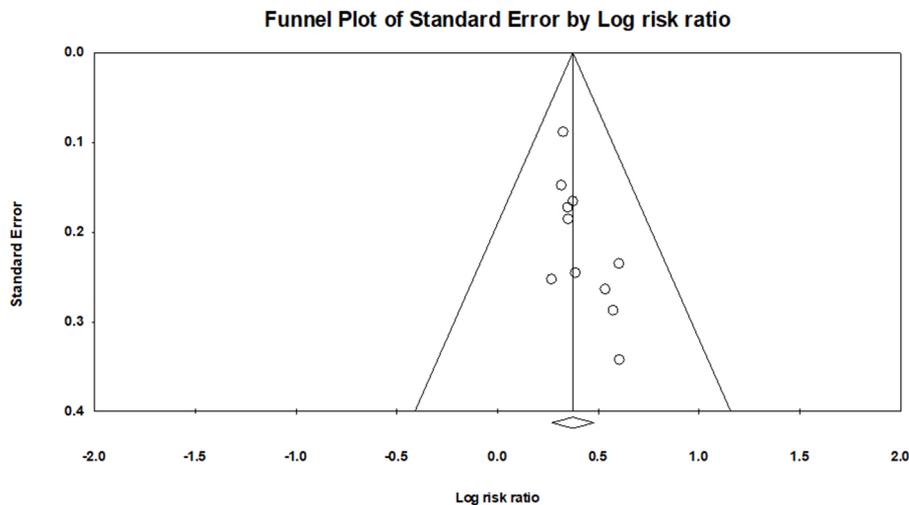


Figure 7. Incidence of fever in the TACE with RFA group vs. TACE alone group

funnel plots indicates that there is no significant bias in this meta-analysis. The overall quality of the studies included in this meta-analysis was evaluated to be of high quality, which gives confidence to our results.

HCC is a serious global health problem and the third most common cause of cancer death. Most patients with HCC are diagnosed with intermediate or advanced stage, with baseline liver dysfunction, intrahepatic metastasis or excessive load, and are not suitable for surgical resection. The established local treatment options include TACE, RFA, ethanol injection, and microwave coagulation; however, it is still unclear which method is the most efficacious<sup>[23-25]</sup>. In the 2018 NCCN Clinical Practice Guidelines for Malignancies, TACE is recommended as a first-line palliative treatment for unresectable HCC. However, the tumor response rate and survival rate of patients treated with TACE alone are not ideal. Therefore, the treatment of TACE combined with other local treatment options such as RFA for comprehensive treatment is gradually being adopted.



**Figure 8.** Meta-analysis of funnel plots of tumor response rate

Based on our meta-analysis, combination therapy of TACE with RFA is an effective method for HCC treatment. HCC is mainly supplied by the hepatic artery. Even when the hepatic artery blood flow is blocked by TACE, the thermal coagulation effect of RFA is not affected. Thus, it increases the area of necrosis induced by RFA. Additionally, the effects of expanded ablation zones and anticancer agents on liver cancer cells during treatment may reduce the chance of tumor recurrence<sup>[26]</sup>.

This meta-analysis has some limitations. Firstly, the complications and adverse reactions of combination therapy cannot be assessed fully due to the lack of original research data. Therefore, future studies can further evaluate these indicators. Secondly, the sample size of this current meta-analysis is limited; large-scale randomized controlled trials of long-term follow-up are needed to validate this result.

In conclusion, our study suggests that TACE combined with RFA is superior to TACE alone in the treatment of HCC larger than 5 cm. Patients in the combined treatment group showed significantly increased tumor response rate and survival rates compared with those treated with TACE alone. This article provided clinical and systematic evidence for the improved treatment of HCC larger than 5 cm.

## DECLARATIONS

### Authors' contributions

Design of the work: Yang Y, Long Y, Zhang WL

Acquisition, analysis of data: Yang Y, Lv ZM, Yan M

Wrote this paper: Yang Y, Zhang HX, Long Y, Zhang WL

Revised the manuscripts: All authors

### Availability of data and materials

All data did by the authors listed in this paper.

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### Conflicts of interest

All authors declared that there are no conflicts of interest.

## Ethical approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Copyright

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