

# Combination therapy

## Meta-analysis of the effects of TACE and cryoablation on hepatocellular carcinoma

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### Abstract

**Background:** This study systematically reviews the data for transcatheter arterial chemoembolization (TACE) alone or combined TACE and cryoablation therapy of hepatocellular carcinoma, aiming to provide clinical choice references for treatment of cancer.

**Methods:** Electronic databases (PubMed, EMBASE, China National Knowledge Infrastructure, and Google Scholar) were systematically searched to include relevant studies published in English and Chinese between Jan 1, 2000, to July 31, 2017. The analysis was conducted in RevMan 5.3 based on random effects models.

**Results:** Nineteen trials (n = 1427) were included. Combined TACE and cryoablation therapy had higher survival rate (1-year survival [RR 1.37; 95%-CI 1.26, 1.49], 2-year survival [RR 1.50; 95%-CI 1.25, 1.79], 3-year survival [RR 1.67; 95%-CI 1.16, 2.40]), complete necrosis [RR 2.53; 95%-CI 2.07, 3.10] and tumor control [RR 1.57; 95%-CI 1.40, 1.75], which is more favorable for long-term efficacy of non-surgical hepatocellular carcinoma. Tumor recurrence of control group was above combination therapy [RR 0.27; 95%-CI 0.17, 0.43]. Compared with transcatheter arterial chemoembolization, effect of combination therapy occurred mainly in the survival, complete necrosis, tumor control, and recurrence. Taking combination therapy was generally more effective than taking TACE only.

**Conclusion:** Compared with TACE only used to treat cancer, combination therapy had the best effect profile in general, and it had better survival in HCC when taking an integrated approach. The prognosis of treatments based on combination therapy is modulated by cryoablation.

**Abbreviations:** CI = confidence interval, HCC = hepatocellular carcinoma, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RR = relative risk, TACE = transcatheter arterial chemoembolization.

**Keywords:** cryoablation, cryosurgery, hepatocellular carcinoma, meta-analysis, transcatheter arterial chemoembolization

### 1. Introduction

Hepatocellular carcinoma (HCC) is the most frequent tumor, the fifth most common cancer in the world, and the main cause of cancer-related mortality.<sup>[1]</sup> Almost half of the HCC cases in the world occurred in China eligible for palliative tumor treatment.<sup>[2-4]</sup> Adequate treatment can play an important role in addressing the issue of prognosis of patients. Transcatheter arterial chemoembolization (TACE) may be one of the first

choices for non-hepatectomy treatment, however, a limitation of it is that failure to address the Long-term efficacy.<sup>[5]</sup> However, this method of analysis has a number of limitations. For instance, infection, renal insufficiency, huge liver cancer (tumor burden greater than 50% of the liver) and severe hepatic dysfunction (particularly a bilirubin > 2 mg/DL).<sup>[6]</sup> Studies have compared effective in ablation and hepatectomy and found that they are essentially identical.<sup>[7]</sup> On the other hand, in spite of these recent

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YDS and HZ contributed equally to this work

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TACE is the most widely used methods for interventional treatment of liver cancer. It can be used with cryoablation to achieve best therapeutic effects, improve patient survival, and may can down the risk of recurrence.

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findings of the role of cryoablation,<sup>[6]</sup> at the same time, surveys such as that conducted by Kerkar et al have shown that the relatively low recurrence rate of this method.<sup>[8-10]</sup> To determine the effects of combining the TACE and cryoablation, several clinicians have been made to limited comparisons of differences between it and TACE only. The first step in this process was to reduce the tumor volume as much as possible by TACE. The lesions were then taken the cryoablation and were destroyed completely. The final stage of the process comprised the immune response generated by cryoablation to kill the remaining tumor cells. The benefit of this approach is that considered the advantages of TACE and cryoablation, one advantage of the combination therapy is that it avoids the problem of establishment of collateral circulation after TACE.

There has been no detailed investigation of large-scale clinical researches. Few studies have investigated TACE plus cryoablation in any systematic way. The generalizability of much published research on this issue is problematic, and much of the research up to now has been descriptive in nature. Research on the subject has been mostly restricted to limited comparisons of fewer samples in a single study. There has been no detailed investigation of the difference in long-term efficacy. To date, few of the current literature on cancer treatment pays particular attention to the subject. This study systematically reviews the data for combined therapy, aiming to provide evidence of differences in treatment outcomes. This paper analyses the impact of the efficacy of combined therapy compared with TACE alone. Our analysis combines individual patient data from randomized trials and retrospective studies. Larger sample size may have contributed to the increase in test whether the combined therapy had any advantage over single treatment. It is hoped that this research will contribute to a deeper understanding of oncotherapy.

## 2. Methods

### 2.1. Search strategy, inclusion criteria, and data extraction

This meta-analysis was reported in line with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines.

Researchers searched Electronic databases (PubMed, EMBASE, China National Knowledge Infrastructure, and Google Scholar) in English and Chinese between Jan 1, 2000, up to July 31, 2017. Then to identify potentially eligible randomized trials and observational studies in patients with HCC that reported (or included data to derive) long-term efficacy, and evaluated the relationship of treatment with prognosis. Search terms and their combinations used in the search strategy included “Carcinoma”, “Hepatocellular”, “Cryoablation”, “Cryosurgery”, “Chemoembolization Therapeutic” and “TACE”. After the elementary screening of title or abstract, 2 independent reviewers assessed the full paper and reference lists of relevant publications for final inclusion; articles cited as references that were considered to be potentially relevant were also retrieved and assessed in full.

Five criteria had to be met for studies to be included:

1. Published papers, conference papers, and dissertations, the content of the selected papers are authentic and believable, without the question of ethics and logic;
2. They had to include unselected patients with HCC for whom treatment was primarily Interventional treatment, palliative care, or both;
3. The result of pathological diagnosis is definite;

4. The study included the main results of survival rate, metastasis rate, and recurrence rate;
5. The patient did not receive a molecular targeting drug, immunotherapy, radiotherapy, and other special treatments during the trial.

We excluded studies that

1. The data are not a reliable or higher loss to follow-up;
2. The study included fewer than 20 patients;
3. Patients received other treatments that may affect outcomes;
4. The research was financed by the manufacturers.

We excluded the conference abstracts, posters, and presentations of ongoing trials because these reports did not contain detailed efficacy data.

Two reviewers extracted treatment-related data from the study with the most detailed report; the other data were used to supplement basic information. Two reviewers used a standardized form independently to extract and summarize the following data: study information (first author, year of publication, experimental design, treatments, grouping method, experimental group, and control group, statistical processing), and patient information (sex, age, stage, survival rate, recurrent, and metastasis rate). One reviewer extracted data from the results of the studies (included text, table, figure, and picture). Another was responsible for reviewing the data and entering the database.

According to the evaluation criteria of the Cochrane Handbook, the included studies are evaluated and graded. The assessment items included:

1. Sequence generation;
2. Allocation concealment;
3. No statistical difference between the two groups;
4. Complete outcome data;
5. No selective outcome reporting;
6. Other sources of bias.

The assessment results are “yes”, “no” or “unclear”. When a project is examined a low risk can get 1 point. The total evaluation system consists of six projects.

### 2.2. Statistical analysis

We drew forest plots to show the variation of the study, estimates among all studies together with the pooled measure and appraised publication bias by Begg and Egger regression test for funnel plot asymmetry. RevMan-v5.3 software was used to perform random or fixed models to calculate the pool risk ratio or odds ratio.

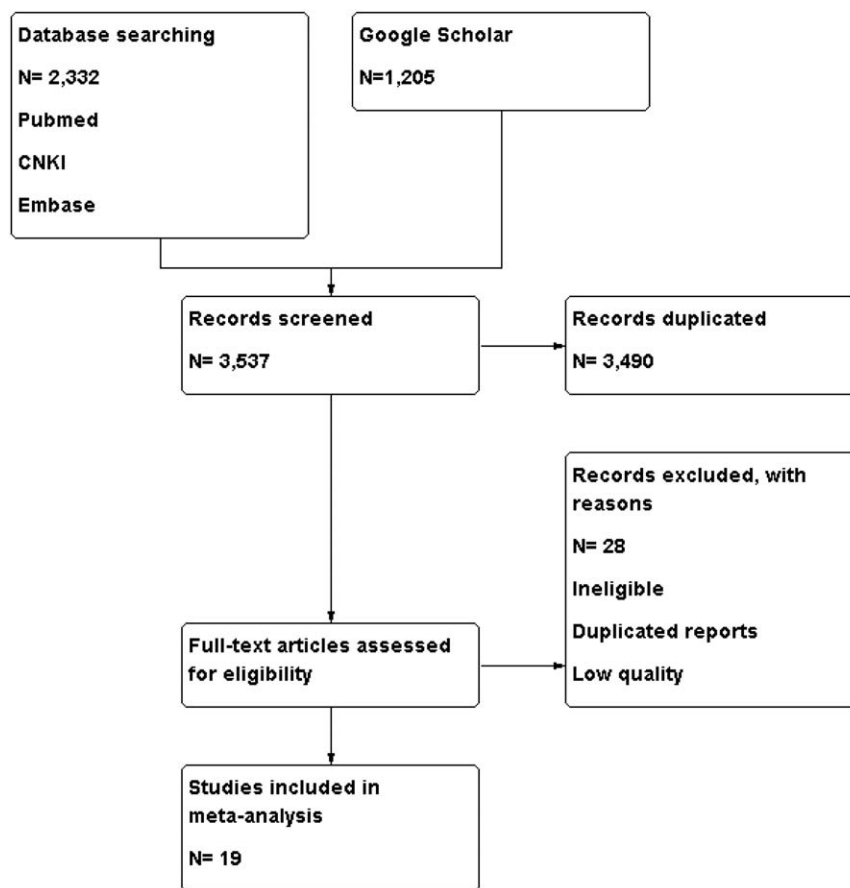
## 3. Results

### 3.1. Search results and characteristics of selected studies

Figure 1 shows a flowchart of the study selection procedure. The electronic searches yielded 3537 potentially relevant studies, of which 19 potentially eligible articles<sup>[11-29]</sup> were assessed.

A total of 1427 patients was included in this study, with 724 patients (50.74%) in the combined therapy group (combined TACE and cryoablation) and 703 patients (49.26%) in the control group (TACE alone). The 383 (26.84%) were female and 1044 males (73.16%). All literature has been published between 2002 and 2017.

One researcher collected the study data into the characteristics table (Table 1), then concluded the patient information in it.



**Figure 1.** Flow chart. A total of 3537 articles was collected by researchers, and 3490 pieces of non-conforming and repetitive articles were screened after reading the abstract. After reading the full articles, researcher removed 28 papers that incomplete data. Finally, 19 studies were selected.

### 3.2. Evaluation of the included studies

One researcher evaluated all 19 papers and aggregated the final results into the Table 2. All studies did not show any loss of outcome data or selective reporting and were not accepted company funding.

### 3.3. Survival rate and treatment effect

Import the database into the Revman 5.3, combined it and analyzed (Figs. 2 and 3), and all analysis utilized the fixed effect model.

**3.3.1. One-year survival.** A total of 1121 patients in 16 studies reported 1-year survival, 9 studies showed an RR higher than 1. The 1-year survival results showed that the patients who received the combination therapy were higher than those who received TACE only [RR 1.37; 95%-CI 1.26, 1.49;  $P < .00001$ ; Fig. 2]. Heterogeneity missed in this analysis ( $I^2 = 0\%$ ;  $\text{Chi}^2 = 12.94$ ;  $P = .65$ ).

**3.3.2. Two-year survival.** A total of 535 patients in 8 studies reported 2-year survival, a study showed an RR higher than 1. There was a key difference between the 2 groups in 2-year survival, [RR 1.50; 95%-CI 1.25, 1.79;  $P < .0001$ ; Fig. 2]; the 2-year survival rate of the HCC patients who received the combination therapy greatly improved. Heterogeneity was deficient in this analysis ( $I^2 = 0\%$ ;  $\text{Chi}^2 = 2.69$ ;  $P = .91$ ).

**3.3.3. Three-year survival.** A total of 287 patients in 3 studies reported three-year survival, 1 study showed an RR higher than 1. The 3-year survival results showed that the patients who received the combination therapy were higher than those who received TACE only [RR 1.67; 95%-CI 1.16, 2.40;  $P < .006$ ; Fig. 2]. Heterogeneity was deficient in this analysis ( $I^2 = 0\%$ ;  $\text{Chi}^2 = 1.24$ ;  $P = .54$ ).

**3.3.4. Complete necrosis.** A total of 653 patients in 7 studies reported complete necrosis, 5 studies showed an RR higher than 1. The complete necrosis results showed that the patients who received the combination therapy were higher than those who received TACE only [RR 2.53; 95%-CI 2.07, 3.10;  $P < .00001$ ; Fig. 2]. Heterogeneity was deficient in this analysis ( $I^2 = 16\%$ ;  $\text{Chi}^2 = 7.13$ ;  $P = .31$ ). After interventional therapy, the tumor tissue and the parenchyma around the organ are coagulated and necrotic, it can produce a large coagulation necrosis zone. In this region, the cancer cells can be injured. Patients with tumor necrosis have a better curative effect.

**3.3.5. Tumor control.** A total of 811 patients in 12 studies reported tumor control, 8 studies showed an RR higher than 1. The tumor control results showed that the patients who received the combination therapy were higher than those who received TACE only [RR 1.57; 95%-CI 1.40, 1.75;  $P < .00001$ ; Fig. 2].

**Table 1**  
The characteristic and information of the studies.

Study	Experimental time	No. of A* (n.)	No. of B* (n.)	Male (n.)	Female (n.)	Age† (year.)	1 - year survival		2- year survival		3- year survival		Tumor recurrence		Tumor control‡		Complete necrosis	
							A	B	A	B	A	B	A	B	A	B	A	B
Bai, 2008 <sup>[11]</sup>	2005–2006	32	30	51	11	50.7	27	17	– <sup>§</sup>	–	–	–	4	14	–	–	21	8
Cao, 2012 <sup>[12]</sup>	2008–2010	40	31	63	8	57.0	30	17	–	–	–	–	–	–	–	–	20	10
Chen, 2015 <sup>[13]</sup>	2010–2012	16	16	22	10	56.7	12	8	8	5	–	–	–	–	12	7	10	3
Hou, 2013 <sup>[14]</sup>	2008–2010	22	20	34	8	52.3	–	–	–	–	–	–	–	–	19	10	–	–
Hu, 2002 <sup>[15]</sup>	1997–2001	17	19	26	10	48.2	16	8	–	–	–	–	–	–	15	11	–	–
Huang, 2011 <sup>[16]</sup>	2001–2007	56	56	100	12	55.0	42	30	38	25	23	16	–	–	45	32	11	5
Li, 2012 <sup>[17]</sup>	–	45	45	76	14	50.6	31	30	26	19	17	11	–	–	–	–	–	–
Liu, 2007 <sup>[18]</sup>	2004–2006	16	16	21	11	61.4	13	10	–	–	–	–	–	–	10	6	–	–
Liu, 2014 <sup>[19]</sup>	2010–2012	37	40	45	32	48.0	29	22	–	–	–	–	–	–	–	–	–	–
Nie, 2008 <sup>[20]</sup>	2001–2004	37	27	58	6	53.0	29	20	23	14	–	–	–	–	–	–	–	–
Qiu, 2015 <sup>[21]</sup>	2006–2010	44	41	58	27	51.0	34	21	25	15	16	6	–	–	21	19	–	–
Song, 2005 <sup>[22]</sup>	2002–2004	31	29	34	26	43.4	30	21	–	–	–	–	3	12	–	–	28	7
Wang, 2015 <sup>[23]</sup>	2012–2014	65	59	94	30	53.0	54	33	–	–	–	–	–	–	50	27	38	18
Wang, 2017 <sup>[24]</sup>	2014–2016	36	36	41	31	52.0	–	–	–	–	–	–	–	–	31	21	–	–
Ye, 2015 <sup>[25]</sup>	2009–2013	35	31	61	5	55.8	29	20	21	13	–	–	–	–	27	15	–	–
Zhang, 2004 <sup>[26]</sup>	–	60	64	98	26	51.0	50	40	–	–	–	–	–	–	41	29	–	–
Zhang, 2016 <sup>[27]</sup>	2011–2014	28	28	33	23	65.0	16	8	11	4	–	–	–	–	25	14	–	–
Zheng, 2015 <sup>[28]</sup>	2012–2014	15	15	17	13	65.26	9	7	7	4	–	–	–	–	13	8	–	–
Zhou, 2009 <sup>[29]</sup>	2005–2008	92	100	112	80	53.0	–	–	–	–	–	–	11	42	–	–	81	29

\* A = Experimental group (combined TACE and cryoablation therapy), B = Control group (TACE alone).

† Age = The average age of the patients.

‡ Tumor control =CR (complete response)+PR (partial response)(RECIST 1.1).

§ – = Not given.

Tumor control means complete response and partial response according to RECIST (Response Evaluation Criteria in Solid Tumors). Heterogeneity was deficient in this analysis ( $I^2=0\%$ ;  $\text{Chi}^2=1.83$ ;  $P=1$ ).

**3.3.6. Tumor recurrence.** A total of 314 patients in 3 studies reported tumor recurrence, 3 studies showed an RR lower than 1. The tumor recurrence survival results showed that the patients

who received the combination therapy were lower than those who received TACE only [RR 0.27; 95%-CI 0.17, 0.43;  $P<.00001$ ; Fig. 3], patients treated with combined TACE and cryoablation therapy have a lower risk of tumor recurrence. Heterogeneity was deficient in this analysis ( $I^2=0\%$ ;  $\text{Chi}^2=.09$ ;  $P=.96$ ).

### 3.4. Analysis of publication bias

Verified that we consider all possible biases, performed an Egger publication bias analysis and obtained the funnel-plot (Fig. 4 Egger publication bias plot) and Begg Test and Egger test (Fig. 5 The results of Begg Test and Egger test). Tumor recurrence was not performing funnel-plot because of less than 10 studies. Test results show that there is no obvious publication bias.

### 3.5. Safety

None of the studies reported uncontrollable acute adverse reactions after the intervention.

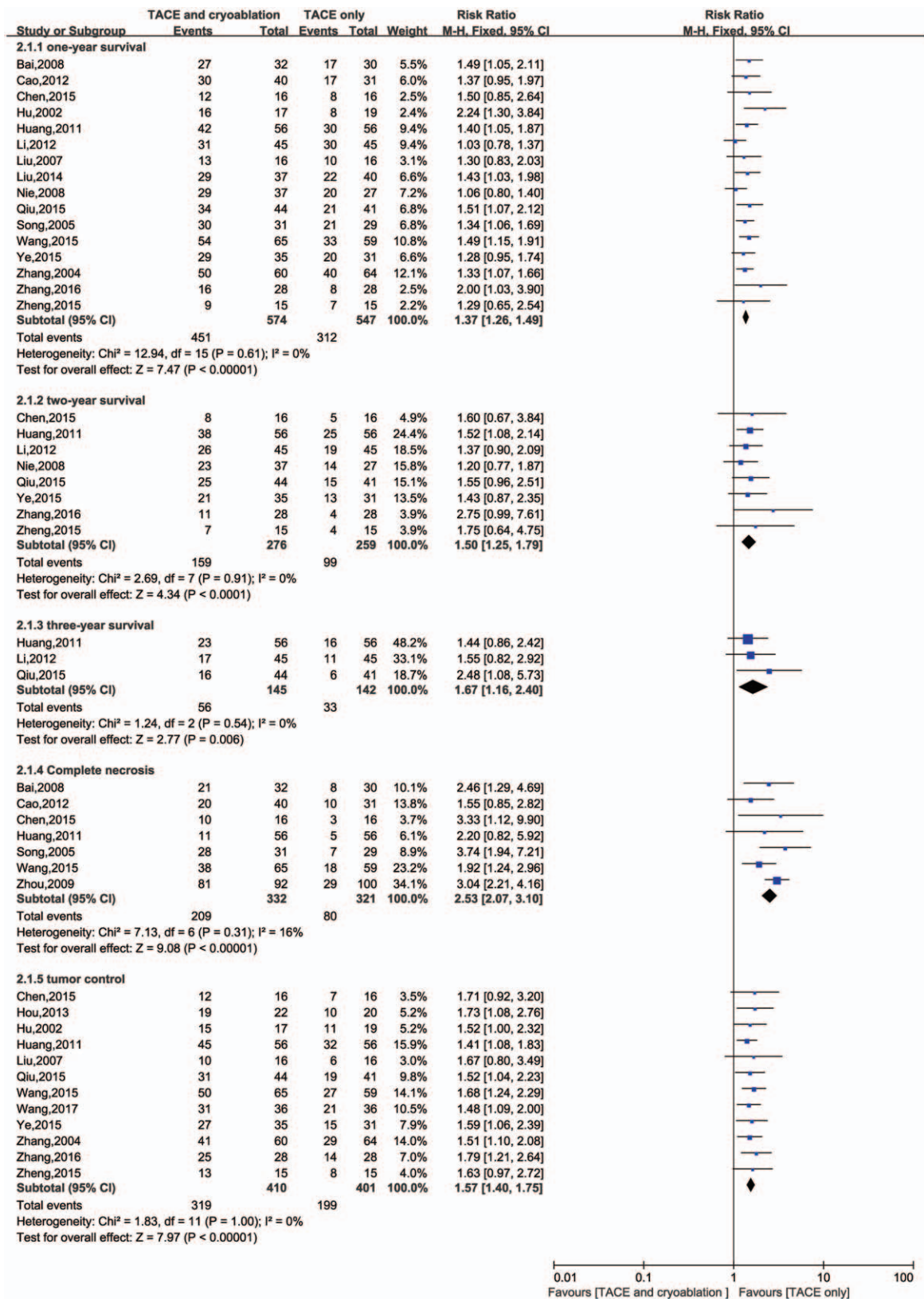
### 3.6. Treatment costs

According to the Chinese medical insurance policy, the patients undertook 3 TACE treatments for approximately 45,000 to 50,000 RMB (\$ 6513–7238). The combined treatment group included 1–2 TACE treatments and 1 microwave ablation treatment, with a total cost of roughly 44,000 to 48,000 RMB (\$ 6369–6948). The costs included treatment, consumables, and hospitalizations (excluding care costs). The cost of these 2 treatments is similar and does not increase the patient's financial burden. Two treatment options mainly consider the condition and efficacy, without having to take account of the impact of medical expenses.

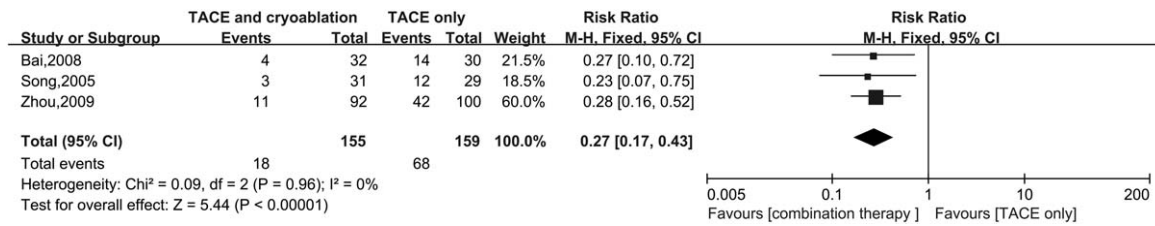
**Table 2**  
The methodological quality of included studies.

Study	A	B	C	D	E	F	Total
Bai, 2008			✓	✓	✓	✓	4
Cao, 2012			✓	✓	✓	✓	4
Chen, 2015			✓	✓	✓	✓	4
Hou, 2013	✓		✓	✓	✓	✓	5
Hu, 2002			✓	✓	✓	✓	4
Huang, 2011			✓	✓	✓	✓	4
Li, 2012	✓		✓	✓	✓	✓	5
Liu, 2007			✓	✓	✓	✓	4
Liu, 2014	✓		✓	✓	✓	✓	5
Nie, 2008			✓	✓	✓	✓	4
Qiu, 2015			✓	✓	✓	✓	4
Song, 2005	✓		✓	✓	✓	✓	5
Wang, 2015			✓	✓	✓	✓	4
Wang, 2017			✓	✓	✓	✓	5
Ye, 2015			✓	✓	✓	✓	4
Zhang, 2004			✓	✓	✓	✓	5
Zhang, 2016			✓	✓	✓	✓	4
Zheng, 2015	✓		✓	✓	✓	✓	5
Zhou, 2009			✓	✓	✓	✓	4

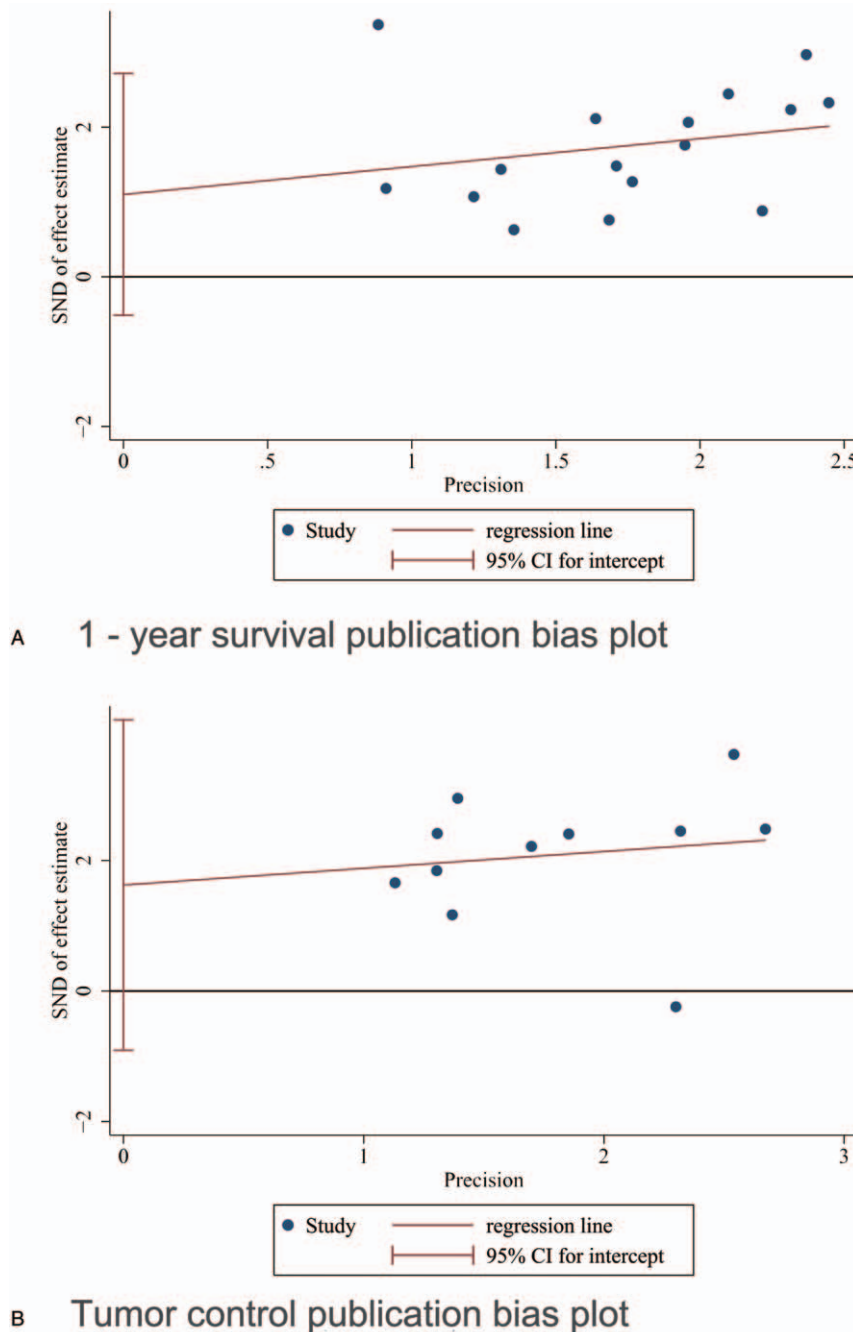
✓ = low risk; A = sequence generation; B = allocation concealment; C = no statistical difference between the 2 groups; D = complete outcome data; E = no selective outcome reporting; F = other sources of bias.



**Figure 2.** Forest plot 1. The results of 1-year survival (RR 1.37- 95%, 1.26 to 1.49,  $P < .00001$ ), 2-year survival (RR, 1.50- 95%, 1.25 to 1.79  $P < .0001$ ), 3-year survival (RR, 1.67 95%, 1.16 to 2.40,  $P < .006$ ), complete necrosis (RR, 2.53: 95%, 2.07 to 3.10,  $P < .00001$ ) and tumor control (RR, 1.57:95%1.40 to 1.75,  $P < .00001$ ) have statistical significance, the rhombus is entirely on the right.



**Figure 3.** Forest plot 2. The tumor recurrence survival results showed that the patients who received the combination therapy were lower than those who received TACE only [RR 0.27; 95%-CI 0.17, 0.43;  $P < .00001$ ], patients treated with combined TACE and cryoablation therapy have a lower risk of tumor recurrence. Heterogeneity was deficient in this analysis ( $I^2 = 0\%$ ;  $Chi^2 = .09$ ;  $P = .96$ ).



**Figure 4.** Eggers publication bias plot.

**Begg's Test**

adj. Kendall's Score (P-Q) = **8**  
 Std. Dev. of Score = **22.21**  
 Number of Studies = **16**  
 z = **0.36**  
 Pr > |z| = **0.719**  
 z = **0.32** (continuity corrected)  
 Pr > |z| = **0.753** (continuity corrected)

**Egger's test**

Std_Eff	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
slope	.373233	.4175638	0.89	0.387	-.5223523	1.268818
bias	1.100811	.7534943	1.46	0.166	-.5152734	2.716896

**A The results of 1-year survival' test**

The result of Begg's test (rank correlation method) did not show any significant statistical bias (P>|z|=0.719). Linear regression analysis (Egger's test) of the funnel plot did not identify any significant graphic or statistical bias (t=1.46,P>|t|=0.166).

**Begg's Test**

adj. Kendall's Score (P-Q) = **15**  
 Std. Dev. of Score = **12.85**  
 Number of Studies = **11**  
 z = **1.17**  
 Pr > |z| = **0.243**  
 z = **1.09** (continuity corrected)  
 Pr > |z| = **0.276** (continuity corrected)

**Egger's test**

Std_Eff	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
slope	.2570265	.5939786	0.43	0.675	-1.086646	1.600699
bias	1.622529	1.119462	1.45	0.181	-.9098708	4.154929

**B The results of Tumor control' test**

The result of Begg's test (rank correlation method) did not show any significant statistical bias (P>|z|=0.243). Linear regression analysis (Egger's test) of the funnel plot did not identify any significant graphic or statistical bias (P>|t|=0.181).

Figure 5. The results of Begg test and Egger test.

**4. Discussion**

In our investigation, the effects of the combination treatment group and TACE alone on survival and tumor recurrence were evaluated in HCC. As mentioned in the literature review, the results suggest that the long-term effect of the combined treatment group was better than that of the TACE group alone.

The current study found that the 1/2/3 year-survival of TACE combined cryoablation was better than TACE only but recurrence risk was lower. We also investigated the necrosis effect of the therapy method on necrosis outcomes. As we hypothesized, the combined therapy of TACE and cryoablation resulted in better complete necrosis and local control rates relative to the control group.

This project is the first comprehensive investigation of cryoablation and TACE for HCC. The study was conducted in the form of meta-analysis, with data being gathered via published studies. It is now understood that TACE plays an important role in the non-operative treatment of advanced HCC.<sup>[30,10]</sup> Drugs were administered by blood vessels to tumor necrosis and blocking the blood supply to the tumor. This method has a number of advantages over traditional chemotherapy, like slighter liver function damage and fewer associated complications.<sup>[31]</sup> However, the collateral circulation establishment and recurrence risk of TACE remains a major challenge.<sup>[32–34]</sup> Unlike TACE, cryoablation is a method that destroyed tumor cells and supply vessels in the tumor tissues by temperature changes.<sup>[35–36]</sup> Another significant aspect of cryoablation is it also stimulates the immune system to kill cancer cell.<sup>[37–38]</sup> Among the 1427 HCC patients, combination treatment use was associated with a significantly lower risk of cancer mortality at 1/2/3 year. Lower recurrence rate in the combined group in this study corroborates these earlier findings. The reason for this result is not clear, but it may have something to do with specific substances released by cryoablation in tumors. In the study of Cao et al, patients had positive changes of CD4+ and CD8+ after cryoablation, but those receiving TACE did not change significantly. However, cryoablation also has a number of serious drawbacks. The effect of cryoablation on large tumors is not satisfactory.<sup>[39]</sup> In addition, the tumor's abundant blood supply and external blood vessels also weakened the efficacy of it. The analysis showed that combined TACE and cryoablation therapy can get a better prognosis for HCC patients.

Based on the previous clinical research of TACE, this study performed an innovative analysis of the therapeutic efficacy and survival of TACE plus cryoablation or TACE alone. Research on the subject has been mostly restricted to limited comparisons of small-scale surveys. This project is the first comprehensive investigation of cryoablation and TACE for HCC. The study was conducted in the form of meta-analysis, with data being gathered via published studies. To date, known methods for advanced HCC have various different disadvantages, and the combination therapy is necessary. TACE could stop the blood supply of the tumor and decreased the volume of the tumor. Pre-TACE can expand the frozen area, the ice hockey of lesions with hepatocellular carcinoma formed faster and larger, and frozen necrosis were more noticeable.<sup>[40–41]</sup> The results of recurrence study indicated that combination therapy may be effective in reducing the risk of recurrence. Possible causes include

1. Cryoablation completely killed residual tumor cells and thoroughly treats the tumor to lose its risk of recurrence.
2. Cryoablation activates the body's immune system.

Activated immune cells and factors kill residual tumor cells and destroy the recurrent lesions before they are discovered, so that patients need not have to worry about the threat of tumor recurrence. During ablation, a preoperative TACE treatment could reduce the risks of bleeding. Theoretically, TACE before cryoablation is an effective modality for HCC patients who are not candidates for hepatectomy.<sup>[42]</sup>

Despite these promising results, questions remain. All 19 studies that meet the inclusion criteria were made by Chinese researchers. These results may be somewhat limited by the lack of worldwide comparisons. These data must be interpreted with caution because the number of patients involved is not large enough. With a small sample size, caution must be applied, as the

findings might not be typical. This is an important issue for future research. Our researchers searched the published studies as much as possible and utilized a variety of retrieval methods, but still, some of the research may not be gathered. The current study does not get follow-up data of more than 3 years, and could not compare it. These results, therefore, need to be interpreted with caution. A long-term, multinomial trial may be needed to arrive at a more definitive answer. We will pay very close attention to this issue and update the analysis results when appropriate. Another problem with this approach is that it fails to take viral hepatitis into account. Since the included studies were all conducted in China, and the Chinese HCC patients have a high proportion of viral hepatitis, the application of antiviral drugs during treatment should be noted. It was found that the hepatitis virus is reactivated by chemotherapy drugs in related research, which not only affects the liver function and the prognosis but also caused liver failure. For patients with a history of hepatitis, some measures should be taken to prevent reactivation of the virus. However, we failed to find relevant descriptions in the included studies, so we failed to analyze the problems in this aspect, which is also a great deficiency and regret. We will continue to focus on relevant research and update it.

## 5. Conclusion

In summary, the combined treatment of TACE and cryoablation for HCC patients may have better long-term efficacy, included better survival and lower recurrence risk.

## Author contributions

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