

## TACE combined with PEI versus TACE alone in the treatment of HCC: a meta-analysis

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**Abstract** To assess the evidence for improved outcomes in hepatocellular carcinoma (HCC) with transarterial chemoembolization (TACE) plus percutaneous ethanol injection (PEI). A systematic search of MEDLINE, EMBASE, the Cochrane library, Chinese biomedicine literature database, Chinese scientific full-text database, and Chinese journal full-text database was undertaken for relevant articles. The computer search was supplemented with a manual search of reference lists for all available review articles, primary studies, and books to identify other studies not found in the computer search. The initial search identified seven randomized trials that included 623 patients. Meta-analysis results are as follows: the 6-month, 1-, 2-, and 3-year survival rates were significantly better in patients with the TACE + PEI group than TACE group; in the decline rates of the AFP level and the reduction rates of tumor size (>50%), the TACE + PEI group has better effects than TACE group; as adverse effects, TACE + PEI group has lower incidence rates than TACE group. In patients with HCC, the efficacy of TACE combined with PEI is significantly better than that of TACE alone. Although there is convincing evidence to confirm the

results mentioned, they still need to be confirmed by large sample, multicenter, randomized, controlled trials.

**Keywords** Hepatocellular carcinoma · Chemoembolization · Ethanol injection · Meta-analysis

### Introduction

*Hepatocellular carcinoma* (HCC) is one of the most common malignant tumors with an increasing incidence in the industrialized countries. It is the sixth most common neoplasm in the world, with more than half a million new cases annually [1]. According to the World Health Organization (WHO), most cases of hepatocellular carcinoma occur in Asia. East Asia particularly has a very high incidence (over 20 cases per 100,000 population). Another region of concern is sub-Saharan Africa, and particularly the western region of Africa [2].

Many risk factors can contribute to hepatocellular carcinoma occurring, mainly hepatitis B and C virus infection, cirrhosis, and aflatoxin B<sub>1</sub> ingestion. Cirrhosis is the strongest predisposing factor in hepatocellular carcinoma.

Early diagnosis of hepatocellular carcinoma is rare, and the majority of individuals present with locally advanced disease [3]. Treatments for HCC have been conventionally divided into curative treatment and palliative treatment. Curative treatments, such as resection, liver transplantation, and percutaneous ablation [4] and surgical resection is the main method, but because of lacking early symptoms most patients with liver cancer who received treatment are at the advanced stages and lose the opportunity to operation, after curative resection, recurrence is common and is the main cause of death so most patients are suitable only for receiving palliative treatments, such as radiotherapy,

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systemic chemotherapy, immunotherapy, embolization ethanol injection and so on. In many countries, transarterial chemoembolization (TACE) has been shown to improve survival, but it also has many disadvantages. Percutaneous ethanol injection (PEI) can be a curative therapy for small HCC (<3 cm). Using TACE plus PEI is either to reduce the size of larger tumors in order to subsequently apply percutaneous treatment or to combine the necrotizing effects of both procedures in order to achieve a more complete tumor necrosis [5]. Therefore, this article sets out to determine the efficacy and safety of TACE plus PEI and TACE alone for patients with HCC.

## Materials and methods

### Literature search

We searched EMBASE, PubMed, the Cochrane Library, Chinese biomedicine literature database, Chinese scientific full-text database, and Chinese journal full-text database for randomized controlled trials comparing TACE + PEI with TACE by means of the keywords “hepatocellular carcinoma” “liver cell carcinoma” “transarterial chemoembolization” “percutaneous ethanol injection” and “randomized controlled trial”. No language limitation was imposed. We hand-searched key Chinese magazines of related fields, used search engines to search related references on the Internet, and searched the references of included studies. In addition, we contacted experts to identify potentially eligible trials, published, and unpublished.

### Inclusion and exclusion

We considered all published and unpublished randomized controlled trials if they were randomized controlled trials comparing TACE + PEI with TACE; untreated patients with HCC; confirmed histologically or diagnosed HCC by means of pathologic examination of biopsy or autopsy specimens in all patients; and no evidence for extrahepatic metastases.

### Evaluation method

The search strategy described was used to obtain titles and abstracts of randomized controlled trials that were relevant to this review. Two reviewers independently assessed the titles and abstracts of all identified trials to confirm fulfillment of inclusion criteria, with disagreements settled through consensus opinion reached using the other investigator. Data were independently extracted by two investigators and checked by the other authors. The quality of

included studies was assessed independently by two reviewers without blinding to authorship or journal. Discrepancies were resolved by discussion with the third investigator. The quality items assessed were randomization, allocation concealment, blinding (participants, investigators, outcome assessors, and data analysis), and completeness of follow-up.

### Statistical analysis

We analyzed the data using Review Manager (version 5.0) and extracted and pooled data for summary estimates. We expressed results for dichotomous outcomes as relative risk (RR) with 95% confidence intervals (CIs) and continuous outcomes as weighted mean difference (WMD) or standard mean difference (SMD). We used the  $\chi^2$  statistic to assess heterogeneity between trials and the  $I^2$  statistic to assess the extent of inconsistency. We used a fixed-effect model for calculations of summary estimates and their 95% CI unless there was significant heterogeneity, in which case results were confirmed using a random-effects statistical model. Subgroup analyses were intended to explore important clinical differences among trials that might be expected to alter the magnitude of treatment effect.

## Results

### Search results

We identified 882 potentially eligible trials and subsequently excluded 875 trials for the following reasons: 444 were not randomized; 96 were about drug therapy; 120 were review; 113 were missing test group or control group; 102 were abstracts referring exclusively to limited-stage disease or treatments other than TACE or PEI; and seven randomized controlled trials totaling 623 patients were included. Finally, the trials all reported the effective about the comparison with TACE + PEI and TACE, and the analysis of the survival rates. Similarity of comparison groups at baseline was ensured by stratified randomization based on age at entry and sex in all of the included studies.

### *The quality and characteristics of included studies*

The quality and characteristics of included studies are shown in Table 1.

### *Meta-analysis results*

**Six-month survival rates** We identified three trials (388 participants) with outcome measurement of 6-month survival rates. There is no heterogeneous among the trials

**Table 1** The quality and characteristics of included studies

Study	Country	Patients (n) (E/C)	Mean age (Years)	Child's class (A/B/C) (E/C)	Mean diameter of main tumor (cm) (E/C)	Allocated concealment	Blinding	Randomization	Incomplete data outcomes
Hongbo Li [6]	China	24/26	52	Unclear	Unclear	Adequate	Unclear	Adequate	Unclear
Xueying Li [7]	China	35/22	53	Unclear	Unclear	Adequate	Adequate	Adequate	Inadequate
Xili Zhao [8]	China	28/27	Unclear	Unclear	Unclear	Adequate	Unclear	Adequate	Adequate
Kato T [9]	Japan	24/22	63	(19/5/0)/ (17/5/0)	6.52/7.09	Unclear	Unclear	Adequate	Unclear
Zengqiang Qu [10]	China	142/170	47	(53/83/6)/ (63/107/0)	9.6/9	Unclear	Unclear	Adequate	Adequate
Bartolozzi C [11]	Italy	26/27	66	(14/12/0)/ (11/16/0)	4.84 ± 1.44/ 5.09 ± 1.36	Adequate	Unclear	Adequate	Adequate
Gerhild Becke [12]	German	27/25	64	(17/10/0)/ (22/3/0)	Unclear	Adequate	Adequate	Adequate	Adequate

E experiment group, C control group

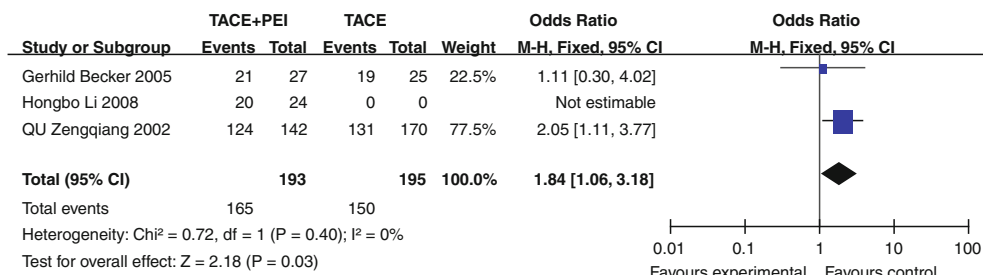
included, using fixed-effects model (RR, 1.84; 95% CI, 1.06–3.18), the results are shown in Fig. 1.

**One-year survival rates** We identified six trials (566 participants) with outcome measurement of 1-year survival rates. There is no heterogeneous among the trials included, using sing fixed-effects model (RR, 3.32; 95% CI, 2.32–4.75), the results are shown in Fig. 2.

**Two-year survival rates** We identified five trials (518 participants) with outcome measurement of 2-year survival rates. There is no heterogeneous among the trials included, using fixed-effects model (RR, 2.75; 95% CI, 1.87–4.04), the results are shown in Fig. 3.

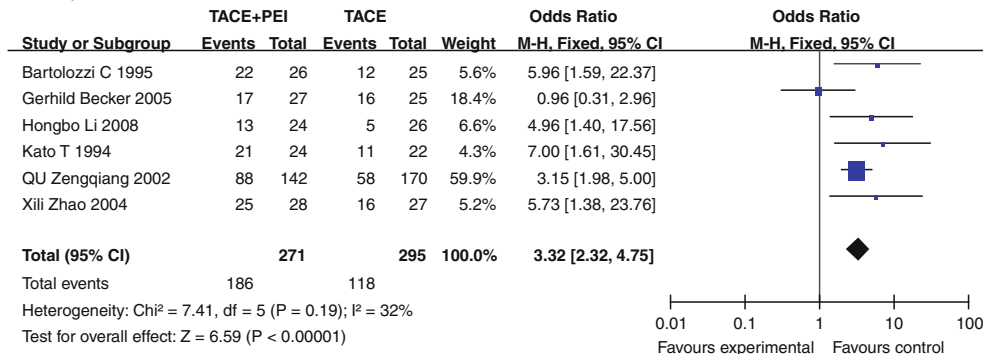
**Three-year survival rates** We identified three trials (154 participants) with outcome measurement of 3-year survival

1. 6 month survival rates



**Fig. 1** Six-month survival rates of TACE + PEI versus TACE (fixed-effects model)

2. 1 year survival rates



**Fig. 2** One-year survival rates of TACE + PEI versus TACE (fixed-effects model)

3.. 2 year survival rates

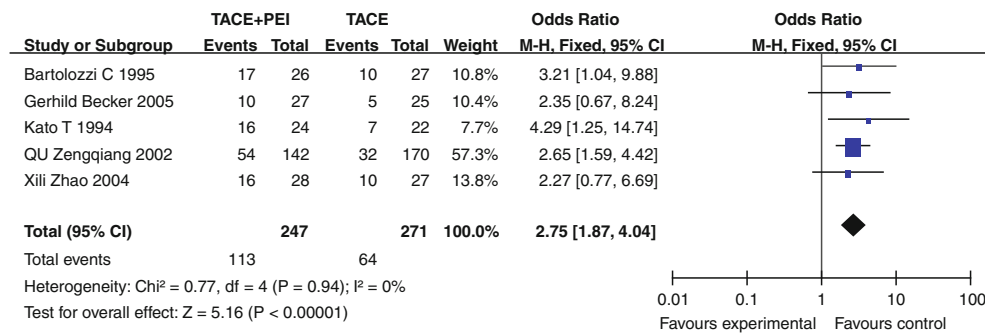


Fig. 3 Two year survival rates of TACE + PEI versus TACE (fixed-effects model)

4. 3 year survival rates

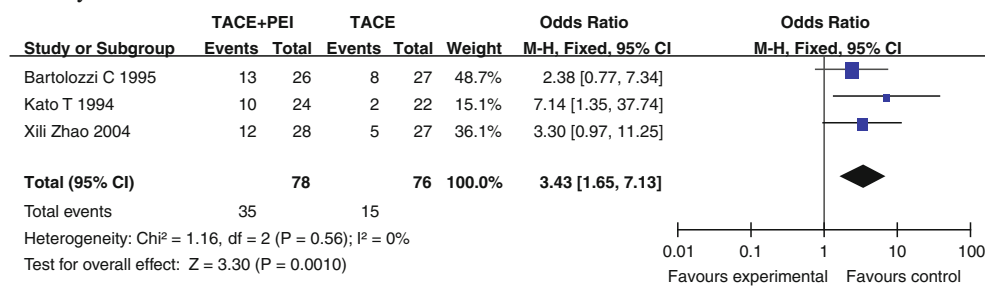


Fig. 4 Three-year survival rates of TACE + PEI versus TACE (fixed-effects model)

5. The decline rates of the AFP level

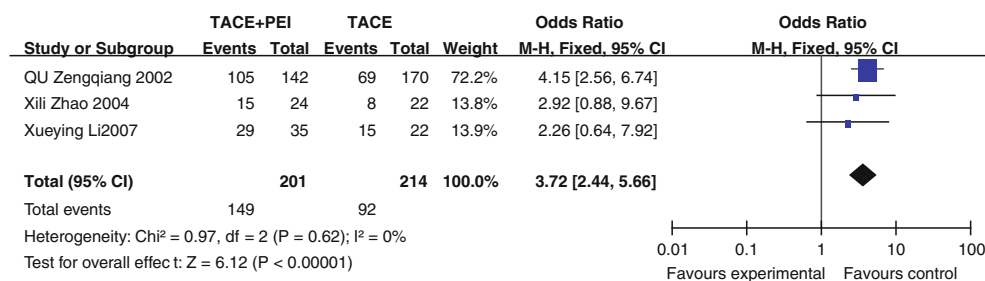


Fig. 5 The decline rates of the AFP level of TACE + PEI versus TACE (fixed-effects model)

rates. There is no heterogeneous among the trials included, using fixed-effects model (RR, 3.43; 95% CI, 1.65–7.13), the results are shown in Fig. 4.

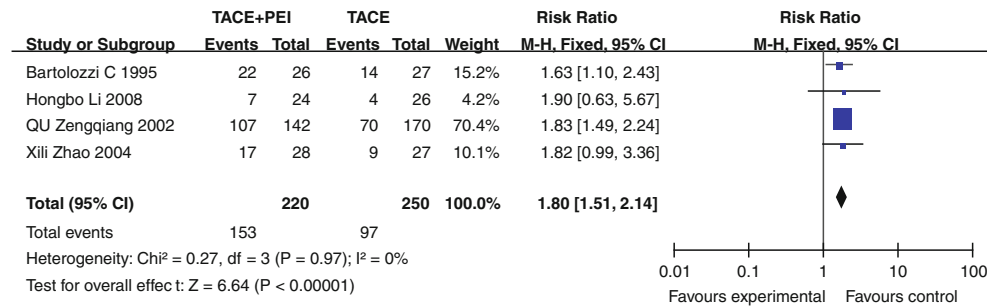
*The decline rates of the AFP level* We identified three trials (415 participants) with outcome measurement of the decline rates of the AFP level. There is no heterogeneous among the trials included, using fixed-effects model (RR, 3.72; 95% CI, 2.44–5.66), the results are shown in Fig. 5.

*The reduction rates of tumor size (>50%)* We identified four trials (470 participants) with outcome measurement of

the reduction rates of tumor size (>50%). There is no heterogeneous among the trials included, using fixed-effects model (RR, 1.80; 95% CI, 1.51–2.14), the results are shown in Fig. 6.

*Side effects* In both groups, there was no obvious treatment-related complication occurred. After TACE treatment or TACE plus PEI treatment, most patients showed symptoms of a mild postembolization syndrome: fever, mild nausea and wild abdominal pain, but all were self-limited postembolization syndrome. And these side effects were transient and disappeared within a short time.

## 6. The reduction rates of tumor size (&gt;50%)



**Fig. 6** The reduction rates of tumor size (>50%) of TACE + PEI versus TACE (fixed-effects model)

## Discussion

TACE has become one of the most common forms of interventional therapy. But because of the periphery of the massive hepatocellular carcinoma more portal blood supply, simple TACE treatment is not to achieve complete necrosis of the main tumors, and the recurrence rate post-TACE is still high, the long-term survival is unsatisfactory. It is a challenge to postpone disease progression and prolong survival of inoperable HCC [13]. It is well known that improving the overall therapeutic effects of HCC depends on the combined therapies. PEI is the seminal technique, it is also widely used and is an effective means of treating HCC, and its advantages and limitations were widely reported. It is inexpensive, safe, and easy to perform and has few adverse effects. But the effectiveness of PEI has been limited to small HCC lesions, the tumor less than 3 cm in diameter [14]. In lesions larger than 3 cm in diameter, it is difficult to inject ethanol throughout the entire tumor. Compared with TACE, the combination of TACE and PEI can get more complete necrosis rates of tumor and prolong overall survival [15]. Therefore, the combination of TACE and PEI should be a better treatment option for inoperable HCCs than TACE alone. Adding PEI after TACE has been expected to obtain adequate control of this tumor and to alter the texture of the tumor parenchyma, so that a large volume of ethanol can be administered to penetrate entire tumor lesions resulting in a complete necrosis [12].

The aim of the meta-analysis was to review the available evidence to estimate the effectiveness and safety of TACE plus PEI. This meta-analysis of data from the including studies have shown the 6-month, 1-, 2-, and 3-year survival rates: the decline rates of the AFP level and the reduction rates of tumor size (>50%) and the side effects. There are some limitations to this meta-analysis. Because the trials we found were of generally poor methodological quality, so it might not allow for a reliable conclusion. Of these including studies, few studies [7, 12] were mentioned

double blinding, which can produce high performance bias and measuring bias. Another potential limitation is that not all studies were mentioned allocation concealment, two studies [9, 10] were not mentioned. This might bring selective bias in these trials, because it was possible for those responsible for recruiting the participant to alter their assignment if allocation was concealed. Some included [6–8] trials were not mentioned the Child's class and the mean diameter of main tumor, these will influence the results of the meta-analysis. And most studies were come from China, so publication bias may have occurred.

The including studies were not inadequate, so we suggest that the outcome measurements should include multiple end-points in the future trails: 1. Future research should clearly show the detailed methods of how to implement blinding; 2. The enroll patients should be included in the analysis of the outcomes using an intention-to-treat analysis to determine the overall cost-utility of a treatment; 3. Quality of life would be an important additional outcome, so the quality of life should be administered at regular time intervals so that quality-adjusted life year and cost-utility analysis can be performed; 4. Future study should pay attention to the impact of geographic differences. Therefore, we still need more high quality, multicenter, randomized, well-designed randomised clinical trials from other countries and regions.

In conclusion, the combination of TACE and PEI compared with TACE alone improved the 6-month, 1-, 2-, and 3-year survival rates of patients and showed a clearly better outcome with respect to tumor size, AFP level. Side effects were mild in the TACE + PEI group. But because the most including studies were Chinese, the bias in the surgical approach, the difference in the doses of the ethanol injection and the number of injections. So further prospective, randomized trials investigating the more outcomes of combined TACE and PEI versus TACE alone in a large number of patients are warranted.

**Conflict of interest statement** The authors made no disclosures.

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