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*Review Article*

# Transcatheter arterial chemoembolization in combination with stereotactic body radiation therapy in primary liver carcinoma: a systematic review and meta-analysis

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**Abstract:** Objective: Recent studies show that transcatheter arterial chemoembolization (TACE) combined with stereotactic body radiation therapy (SBRT), also referred to as Gamma Knife therapy, might have a synergistic effect on the treatment of primary liver carcinoma (PLC), however, the reports on the effects of the combined therapy appear not to be totally consistent. This meta-analysis aims to assess the effectiveness and safety of TACE combined with SBRT for PLC, compared with TACE alone. Methods: Electronic databases were searched for relevant studies, evaluating the survival benefit and the response to therapy in patients with PLC. The primary outcomes were the survival rate and the total effective rate; secondary outcomes were the tumor recurrence rate and side effects. Results: Twenty-two relevant clinical studies with a total of 2137 participants were included in this meta-analysis. TACE combined with SBRT significantly improved both the overall survival rate after 0.5 years, 1-year, 2 years, 3 years and the total effective rate (TER) respectively, compared with that of TACE alone [odds ratio (OR) 0.5 years = 5.88, 95% confidence interval (CI) 2.70-12.82, P < 0.00001], (OR 1-year = 2.91, 95% CI 2.34-3.62, P < 0.00001), (OR 2 years = 2.09, 95% CI 1.60-2.74, P < 0.00001), (OR 3 years = 2.30, 95% CI 1.23-4.32, P = 0.009) and (OR TER = 3.23, 95% CI 2.65-3.94, P < 0.00001). Sensitivity analysis also showed significant benefits of TACE combined with SBRT in terms of the overall survival rate after 0.5 years, 1-year, 2 years, 3 years and for the total effective rate. The funnel plot indicated a low publication bias. Conclusions: TACE combined with SBRT improves the overall survival rate and the response to therapy for PLC. But more RCTs are needed to provide firm evidence.

**Keywords:** Meta-analysis, primary liver carcinoma, stereotactic body radiation therapy, transcatheter arterial chemoembolization

## Introduction

Primary liver carcinoma (PLC) is the most common hepatic cancer. The increasing incidence in the past decade has made it become the sixth most common cancer worldwide and the third main cause of cancer-related death [1, 2]. It is widely known that surgical resection or liver transplantation is the first-line therapeutic choice for patients with early-stage PLC, however, only a small proportion of patients is eligible for these radical options [3-5]. Radical options are also not the only or the first strategy of therapy for patients with advanced PLC. So palliative therapies for advanced PLC such as ethanol injection, radiofrequency thermal ablation, transcatheter arterial embolization and transcatheter arterial chemoembolization (TACE) are often performed to improve quality of life for advanced PLC patients [6]. It has been proven that TACE might improve the survival of the patients with advanced PLC, and it was recommended to be the main therapy for inoperable PLC [7-9]. The technique of stereotactic body radiation therapy (SBRT), also named Gamma Knife therapy, works as follows [10]: Patients were immobilized in the stereotactic frame, the target outlines are delineated by computed tomography (CT) or Magnetic Resonance (MRI) images. Then different coplanar or non-copla-

nar fields were defined, within which a homogeneous dose of gamma rays was maintained and the amount of normal liver irradiation quantified. In the past decade, SBRT has also been shown to be highly effective in treating advanced PLC, resulting in increased response rates and survival [11, 12].

Usually, TACE is applied through a catheter in the hepatic artery, which is introduced using the Seldinger technique under local anesthesia. The rationale is that it induces embolization in the cancer-feeding arteries and increases the local concentration of chemotherapeutic drugs, resulting in tumor necrosis and tumor control [13, 14]. Complete tumor tissue necrosis, however, is generally difficult to achieve by TACE monotherapy, because of the dual and complex blood inflow supply system into the liver. The blood supply from collateral circulation or recanalization of the initially embolized artery may increase the viability of residual tumors after TACE, which thus may result in recurrence [15, 16]. It was reported that a necrosis rate of greater than 95% after TACE was only achieved in 44% of the cases reported, when HCCs were 3 cm or larger, especially in non-encapsulated tumors [17].

Recent evidence indicates that TACE, combined with SBRT may have a synergistic effect in the treatment of PLC. Honda et al reported that both the tumor response to therapy and the overall survival rate in patients treated with TACE combined with SBRT were superior to TACE alone [18]. However, there has been no consensus for the efficacy of the combined therapy.

This meta-analysis aims to assess the effectiveness and safety of TACE combined with SBRT, compared with TACE alone for patients with advanced PLC.

## Materials and methods

### *Search strategy and inclusion criteria*

Trials were identified by searching PubMed, Springer Link, the China National Knowledge Infrastructure Database (CNKI), VIP Journal Integration Platform (http://www.cqvip.com) (VIP) and WanFang data (WangFang). All searches included studies established prior to December 2015, using ("transcatheter arterial chemoembolization" or "TACE" or "chemoembolization") AND ("hepatocellular carcinoma" or "primary liver carcinoma" or "HCC") AND ("Gamma Knife" or "gamma rays"). Searches were performed for all types of publications but limited to original articles in English or Chinese. We also screened the relevant references of retrieved articles or published clinical trials.

### *Types of studies*

All published studies evaluating the effects of TACE combined with Gamma Knife versus TACE alone were included.

### *Types of participants*

The participants in the selected studies were over 18 years of age, with advanced PLC, no previous treatment for PLC, and no contraindication for neither TACE nor SBRT.

### *Types of intervention*

The types of intervention included in this analysis were divided into two groups. The treatment group was composed of patients accepting SBRT after TACE. The control group was composed of patients accepting merely TACE monotherapy.

### *Types of outcome measures*

The resulting outcomes were divided into two types of variables. The primary variables include the survival rate and the total effective rate of advanced PLC patients under combination therapy versus monotherapy. The secondary variables include the side effects and tumor recurrence rate. Studies have to report at least one of the above variables to be included in this analysis. The following definition was applied: The total effective rate = (CR+PR)/total participants × 100% (CR: Tumor completely subsided and no re-occurrence of new tumors for at least 4 weeks; PR: tumor size shrunk more than 50% and no re-occurrence of new tumors for at least 4 weeks; i.e. applying the WHO standards).

### *Exclusion criteria*

Studies were excluded if they: (1) did not meet the above criteria; (2) involved i.v. or p.o. or portal vein chemotherapy; (3) had metastatic or recurrent liver carcinoma; (4) involved non-con-

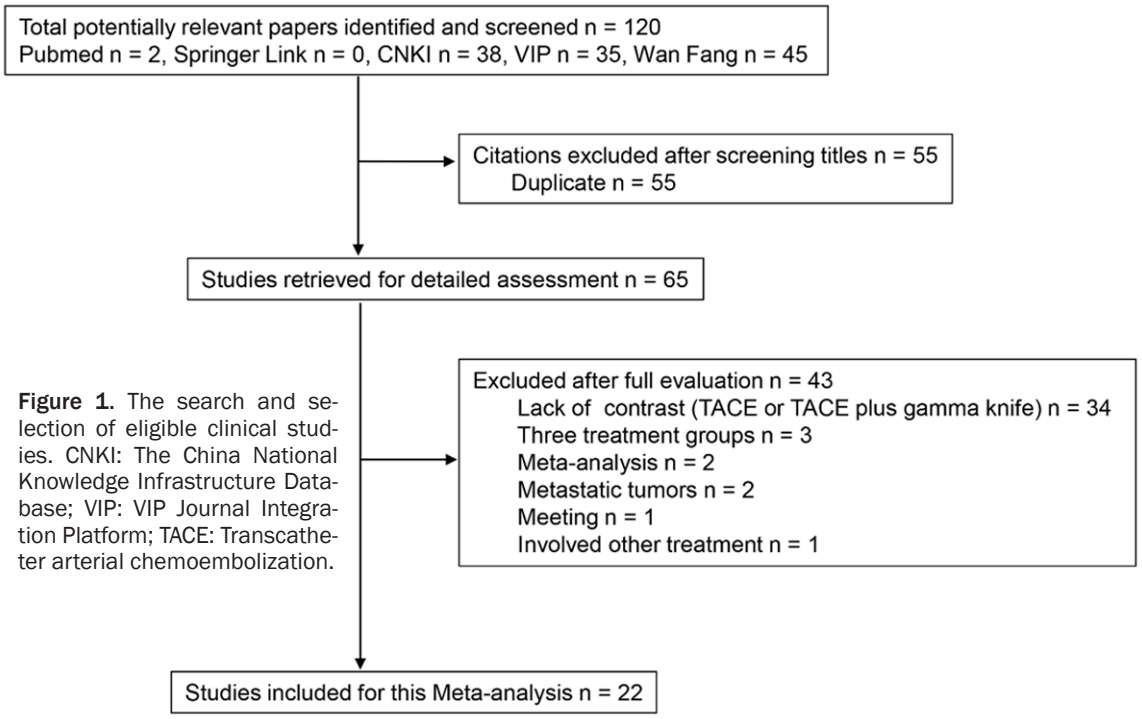


**Figure 1.** The search and selection of eligible clinical studies. CNKI: The China National Knowledge Infrastructure Database; VIP: VIP Journal Integration Platform; TACE: Transcatheter arterial chemoembolization.

trolled clinical trials; (5) involved other regional therapies or used three intervention procedures (TACE versus TACE combined SBRT versus SBRT); (6) were repeat studies or overlapping cases; (7) had no comparative data of primary or secondary variables.

*Studies and data extraction*

Two of the authors independently assessed eligibility of potential studies based on the selection criteria and the extracted data, including general information on the studies (e.g. author, year of publication, participants' characteristics and study methods), characteristics of interventions (e.g. drugs, dose and time) and outcomes with a data extraction form. The concordance rate of two reviewers was 96%. Disagreements were resolved by consensus.

*Quality assessment*

The quality of the retrieved trials was evaluated by two reviewers independently and according to the randomized method, judging allocation concealment, blinding tests, lack to follow up and reporting of dropouts in the clinical studies [19]. Disagreements were discussed and consensus was reached after discussion. It was regarded to be a high-quality trial if it reported both the randomized method in detail and the allocation concealment; a moderate-quality trial if it just reported the randomized method in detail or the allocation concealment; a low-quality trial if it neither reported randomized method in detail nor allocation concealment, and a very low-quality trial if it reported none of the items.

*Statistical analysis*

All data for this meta-analysis were analyzed using the Review Manager Software (RevMan Version 5.2, The Cochrane Collaboration; The Nordic Cochrane Center, Copenhagen, Denmark). Odds ratios (OR) with 95% confidence intervals (CI) were calculated to express therapeutic effects. For the overall effect, it was considered to be statistically significant if $P$ values < 0.05. The $I^2$ statistic and associated $P$ values were used to evaluate the heterogeneity among trials [20, 21]. Homogeneity ($I^2$-value < 25%), low heterogeneity ($I^2$-value between 25% and 50%), moderate heterogeneity ($I^2$-value between 50% and 75%) and high heterogeneity ($I^2$-value > 75%) were used to measure inconsistency across studies. Furthermore, statistically substantial heterogeneity was considered to exist in the studies included if $P$ values < 0.1, then a random-effects model

**Table 1.** Baseline characteristics of studies included in the meta-analysis

| Study | Total number | Male vs female | Combination vs TACE | KPS | Child-Pugh stage (A vs B vs C) | Aetiology (viral vs other) | Tumor size (huge vs nodule) |
|---|---|---|---|---|---|---|---|
| Li 2005 | 45 | 29 vs 16 | 15 vs 30 | ND | ND | ND | 36 vs 14 |
| Yang 2006 | 36 | 27 vs 19 | 16 vs 20 | ≥ 70 | A or B | ND | Mean: 8.8 cm |
| Jiang 2009 | 52 | 32 vs 20 | 22 vs 30 | ≥ 60 | ND | ND | Mean: 8.5 cm |
| Zhang 2010 | 72 | 42 vs 30 | 36 vs 36 | ND | ND | ND | ND |
| Ji 2010 | 120 | 90 vs 30 | 62 vs 58 | ≥ 70 | A or B | ND | 98 vs 22 |
| Liu 2011 | 62 | 55 vs 7 | 30 vs 32 | ND | 32 vs 30 vs 0 | ND | 32 vs 30 |
| Zhou 2011 | 56 | 45 vs 11 | 34 vs 22 | ≥ 70 | A or B | ND | Huge or nodule |
| Chen 2011 | 250 | 184 vs 64 | 125 vs 125 | ≥ 70 | A or B | ND | ND |
| Li 2012 | 136 | 93 vs 43 | 34 vs 102 | ≥ 70 | 39 vs 91 vs 6 | ND | 110 vs 26 |
| Kong 2012 | 120 | 76 vs 44 | 60 vs 60 | ≥ 60 | A or B | ND | 62 vs 58 |
| Zhang 2012 | 259 | 204 vs 55 | 135 vs 124 | ND | A or B | ND | 2.2-16.4 cm |
| Li 2012 | 108 | 76 vs 34 | 54 vs 54 | ≥ 60 | 88 vs 20 | ND | 97 vs 11 |
| Wang 2013 | 80 | 56 vs 24 | 40 vs 40 | ≥ 70 | A or B | ND | ND |
| Sha 2013 | 105 | 77 vs 28 | 52 vs 53 | ≥ 60 | A or B | ND | ND |
| Cao 2013 | 76 | 62 vs 14 | 38 vs 38 | ND | 65 vs 11 vs 0 | ND | 59 vs 17 |
| Sun 2014 | 62 | 43 vs 19 | 32 vs 30 | ND | 54 vs 8 vs 0 | ND | 46 vs 16 |
| Liu 2014 | 86 | 47 vs 39 | 43 vs 43 | ND | ND | 32 vs 54 | ND |
| Meng 2015 | 90 | 50 vs 40 | 45 vs 45 | ND | 78 vs 12 vs 0 | ND | 69 vs 21 |
| Luo 2015 | 74 | 42 vs 32 | 38 vs 36 | ND | 31 vs 43 vs 0 | ND | 39 vs 35 |
| Tang 2015 | 78 | 48 vs 30 | 39 vs 39 | ≥ 70 | 31 vs 47 vs 0 | 78 vs 0 | ND |
| Huang 2015 | 86 | 52 vs 34 | 43 vs 43 | ND | 60 vs 26 vs 0 | ND | ND |
| Pan 2015 | 84 | 61 vs 23 | 47 vs 37 | ≥ 70 | 54 vs 30 vs 0 | ND | Mean: 8.3 cm |

KPS: Karnofsky scores; ND: Not described; huge: Tumor diameter > 5 cm or described in paper; vs: Versus; TACE: Transcatheter arterial chemoembolizaton.

instead of the fixed-effects model was used to analyze the result. The causes were also explored, including the TNM staging and size of tumor, differences of interventions and hepatic function. Potential publication bias was assessed by symmetry of funnel plot and the visual symmetrical plot indicated that the publication bias among studies is low [22].

## Results

### *Identification and characteristics of included studies*

After the initial screening, 120 potentially relevant clinical trials of PLC were identified. Fifty-five studies were excluded after screening their titles, because they were duplication (**Figure 1**). In case of the duplicated studies, the last or the most complete data were extracted. After full assessment for eligibility by the two independent reviewers, forty-three studies were excluded: (1) thirty-four studies lacked a comparison (TACE or TACE plus SBRT); (2) three studies involved three treatment groups such as TACE versus SBRT versus TACE plus SBRT; (3) two studies were meta-analysis; (4) two studies were associated with metastatic liver carcinoma; (5) one study was a meeting article; (6) one study involved other treatments. In the end, we included 22 studies with total 2137 patients comparing the therapeutic effect of TACE combined with SBRT in the treatment of PLC with those of TACE alone for the current meta-analysis [23-44]. Among the studies included, three trials were randomized-controlled trials (RCTs) [36, 42, 43], the others were nonrandomized concurrent controlled clinical trials. All studies were performed in China. Participants were diagnosed with PLC according to investigations and/or pathology or the standards for the diagnosis and treatment of primary liver cancer (Chinese Clinical Oncology, 2011). Three studies just reported effective rate [31, 35, 43], the others reported both survival rate and effective rate.

**Table 2.** Interventions of included studies

| Study | Drugs and dosage of TACE | Time and dosage of Gamma Knife |
|---|---|---|
| Li 2005 | 5-fluorouracil (1000 mg), hydroxycamptothecine (20 mg~30 mg), Lipiodol (10 ml~20 ml) et al | After TACE, total 40.0~45.0 Gy |
| Yang 2006 | 5-fluorouracil (800~1200 mg), epirubicin (50~100 mg), 40% Lipiodol (10~50 ml) et al | After TACE, total 36.0~42.0 Gy |
| Jiang 2009 | 5-fluorouracil (500~100 mg), cisplatin (40~80 mg), 40% Lipiodol (5~20 ml) et al | After TACE, total 45.0~60.0 Gy |
| Zhang 2010 | Hydroxycamptothecine (10~20 mg), 5-fluorouracil (1000 mg), Lipiodol (10~20 mL) et al | After TACE, total 40.0~50.0 Gy |
| Ji 2010 | 5-fluorouracil (1000 mg), epirubicin (50~100 mg) , Lipiodol (10~15 ml) et al | After TACE, total 32.0~46.0 Gy |
| Liu 2011 | 5-fluorouracil (750~1250 mg), epirubicin (40~60 mg), 38% Lipiodol (10~20 mL) et al | After TACE, total 25.0~40.0 Gy |
| Zhou 2011 | 5-fluorouracil (1000 mg), Mitomycin (10~20 mg), Lipiodol (10~20 ml) et al | After TACE, total 45.0~52.0 Gy |
| Chen 2011 | Cisplatin, mitomycin et al, gelatin sponge, Lipiodol (10~15 ml) | After TACE, 3.5~4.5 Gy/time, 10~12 times |
| Li 2012 | 5-fluorouracil, hydroxycamptothecine (30 mg), Lipiodol (10~20 ml) et al | After TACE, 4.0~5.0 Gy/time, 10 times |
| Kong 2012 | Docetaxel (40 mg), gemcitabine (1200 mg), Lipiodol (10 mL) et al | After TACE, total 30.0~60.0 Gy |
| Zhang 2012 | 5-fluorouracil (500~1000 mg), epirubicin (30~50 mg), Lipiodol (5~20 ml) et al | After TACE, total 36.0~50.0 Gy |
| Li 2012 | Docetaxel (60 mg), gemcitabine (1200~1600 mg), Lipiodol (5~20 ml) et al | After TACE, total 38.4~44.8 Gy |
| Wang 2013 | Mitomycin, cisplatin et al, Lipiodol (10~15 ml), gelatin sponge | After TACE, 3.5~4.5 Gy/time, 10~12 times |
| Sha 2013 | 5-fluorouracil (1000 mg), pirarubicin (40~60 mg), Lipiodol (10 ml~20 ml) et al | After TACE, total 40.0~45.0 Gy |
| Cao 2013 | 5-fluorouracil, oxaliplatin, epirubicin, gelatin sponge, Lipiodol | After TACE, total 25.0~40.0 Gy |
| Sun 2014 | 5-fluorouracil, oxaliplatin, epirubicin, gelatin sponge, Lipiodol | After TACE, total 25.0~40.0 Gy |
| Liu 2014 | Pirarubicin (10~20 mg), mitomycin (10 mg), Lipiodol et al | After TACE, total 25.0~40.0 Gy |
| Meng 2015 | 5-fluorouracil (1.0 mg/m$^2$), mitomycin (10 mg/m$^2$), Lipiodol (10 ml) et al | After TACE, total 25.0~40.0 Gy |
| Luo 2015 | 5-fluorouracil, oxaliplatin, epirubicin, gelatin sponge, Lipiodol | After TACE, total 25.0~40.0 Gy |
| Tang 2015 | 5-fluorouracil (750~1000 mg), mitomycin (10~20 mg), 40% Lipiodol (5~20 mL) et al | After TACE, total 30.0~60.0 Gy |
| Huang 2015 | Pirarubicin (20 mg), carboplatin (1000 mg), gelatin sponge, gelatin sponge | After TACE, total 45.0~50.0 Gy |
| Pan 2015 | 5-fluorouracil (750~1000 mg), mitomycin (8~10 mg), 40% Lipiodol (5~20 ml) et al | After TACE, total 40.0~60.0 Gy |

TACE: Transcatheter arterial chemoembolizaton.

In **Tables 1** and **2**, the demographics, characteristics and authors of the studies are summarized. They include Karnofsky scores (KPS), Child-Pugh stage, number and size of the tumors, aetiology (virus or other) and interventions applied. The demographic data among groups were reported to be well matched in 17 of the 22 studies included [23, 29-44].

*Methodological quality of included studies*

The quality of the studies included in this meta-analysis is shown in **Table 3**. Three trials reported the randomized method in detail, the others did not [36, 42, 43]. Neither allocation concealment nor blind tests were mentioned in all of the trials. Only seven trials reported the number of losses to follow up [23, 24, 31-34, 44], however, none of the trials included reported the number of dropouts. Eleven trials were considered to be of very low quality, mentioning no characteristics of the study such as randomized method or allocation concealment [25-30, 35, 37, 38, 40, 41].

*Results of meta-analysis*

*0.5-year survival:* Most studies, except for three trials [31, 35, 43], confirmed combination therapy could improve survival rate compared with monotherapy. Five studies (492 patients) assessed the rate of 0.5-year survival with meta-analysis (OR = 5.88, 95% CI 2.70-12.82, P < 0.00001), suggesting that combination therapy improved 0.5-year survival in comparison with monotherapy. Heterogeneity between trials was not significant (P = 0.45, $I^2$ = 0%) (**Figure 2**).

*1-year survival:* Nineteen studies (1835 patients) reported the 1-year survival rate. The 1-year survival was statistically significant in favor of combination therapy over monotherapy according to the pooled result (OR = 2.91, 95% CI 2.34-3.62, P < 0.00001). There was no statistical heterogeneity among the studies (P = 0.92, $I^2$ = 0%) (**Figure 3**).

*2-year survival:* Nine studies (941 patients) reported the 2-year survival rate. The 2-year survival supported a favorable outcome for the combination therapy over the monotherapy according to the pooled result (OR = 2.09, 95% CI 1.60-2.74, P < 0.00001) and no statistical heterogeneity among studies was found (P = 0.92, $I^2$ = 0%) (**Figure 4**).

*3-year survival:* Four studies (531 patients) reported the 3-year survival rate. The 3-year

**Table 3.** Quality assessment of included studies

| Study | Design | Method | Allocation concealment | Blinding | Loss to follow up (Combination vs TACE) | Number of dropouts | Quality |
|---|---|---|---|---|---|---|---|
| Li 2005 | NRCCT | ND | ND | Not used | 1 vs 2 | ND | Low |
| Yang 2006 | NRCCT | ND | ND | Not used | 0 vs 0 | 0 | Low |
| Jiang 2009 | NRCCT | ND | ND | Not used | ND | ND | Very low |
| Zhang 2010 | NRCCT | ND | ND | Not used | ND | ND | Very low |
| Ji 2010 | NRCCT | ND | ND | Not used | ND | ND | Very low |
| Liu 2011 | NRCCT | ND | ND | Not used | ND | ND | Very low |
| Zhou 2011 | NRCCT | ND | ND | Not used | ND | ND | Very low |
| Chen 2011 | NRCCT | ND | ND | Not used | ND | ND | Very low |
| Li 2012 | NRCCT | WP | ND | Not used | 0 vs 0 | ND | Low |
| Kong 2012 | NRCCT | ND | ND | Not used | 3 vs 3 | ND | Low |
| Zhang 2012 | NRCCT | ND | ND | Not used | 0 vs 0 | 0 | Low |
| Li 2012 | NRCCT | ND | ND | Not used | 0 vs 0 | 0 | Low |
| Wang 2013 | NRCCT | ND | ND | Not used | ND | ND | Very low |
| Sha 2013 | RCT | DL | ND | Not used | ND | ND | Moderate |
| Cao 2013 | NRCCT | ND | ND | Not used | ND | ND | Very low |
| Sun 2014 | NRCCT | ND | ND | Not used | ND | ND | Very low |
| Liu 2014 | NRCCT | WP | ND | Not used | ND | ND | Very low |
| Meng 2015 | NRCCT | ND | ND | Not used | ND | ND | Very low |
| Luo 2015 | NRCCT | ND | ND | Not used | ND | ND | Very low |
| Tang 2015 | RCT | RN | ND | Not used | ND | ND | Moderate |
| Huang 2015 | RCT | ND | ND | Not used | ND | ND | Moderate |
| Pan 2015 | NRCCT | ND | ND | Not used | Total: 9 | ND | Low |

ND: Not described; WP: Will of patients; NRCCT: Nonrandomized concurrent controlled clinical trial; DL: Drawing of lost; RN: Random number; RCT: Randomized controlled trial; TACE: Transcatheter arterial chemoembolizaton.

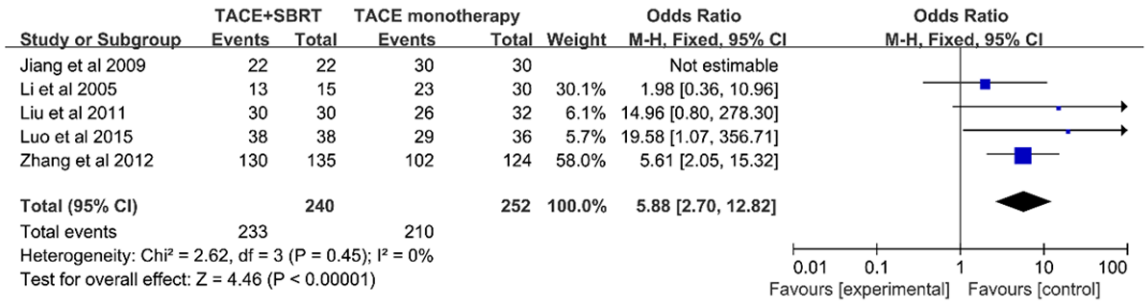


**Figure 2.** Meta-analysis of the 0.5-year survival rate in 5 studies comparing TACE plus SBRT with TACE monotherapy for primary liver carcinoma. CI: Confidence interval; M-H: Mantel-Haenszel's method; Fixed: Fixed-effects model; SBRT: Stereotactic body radiation; TACE: Transcatheter arterial chemoembolization.

survival showed the combination therapy to be superior to that of monotherapy with statistical significance (OR = 2.30, 95% CI 1.23-4.32, P = 0.009), but there was potential heterogeneity among studies (P = 0.08, $I^2$ = 56%) (**Figure 5**).

*Total effective rate*

All studies (2137 patients) reported the total effective rate. The combination therapy showed a significant benefit compared with monotherapy according to the result of this meta-analysis (OR = 3.23, 95% CI 2.65-3.94, P < 0.00001) and no statistical heterogeneity among studies was found (P = 0.99, $I^2$ = 0%) (**Figure 6**).

*Sensitivity analysis*

In order to avoid potential bias of the studies included, a sensitivity analysis with a fixed-

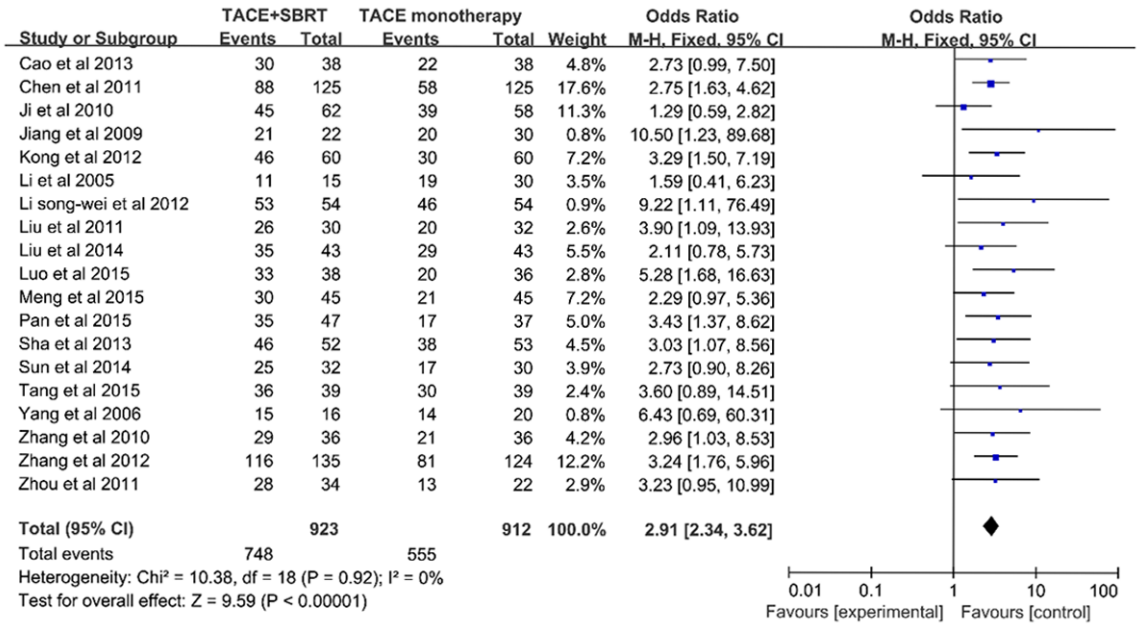


**Figure 3.** Meta-analysis of the 1-year survival rate in 19 studies comparing TACE plus SBRT with TACE monotherapy for primary liver carcinoma. CI: Confidence interval; M-H: Mantel-Haenszel's method; Fixed: Fixed-effects model; SBRT: Stereotactic body radiation; TACE: Transcatheter arterial chemoembolization.

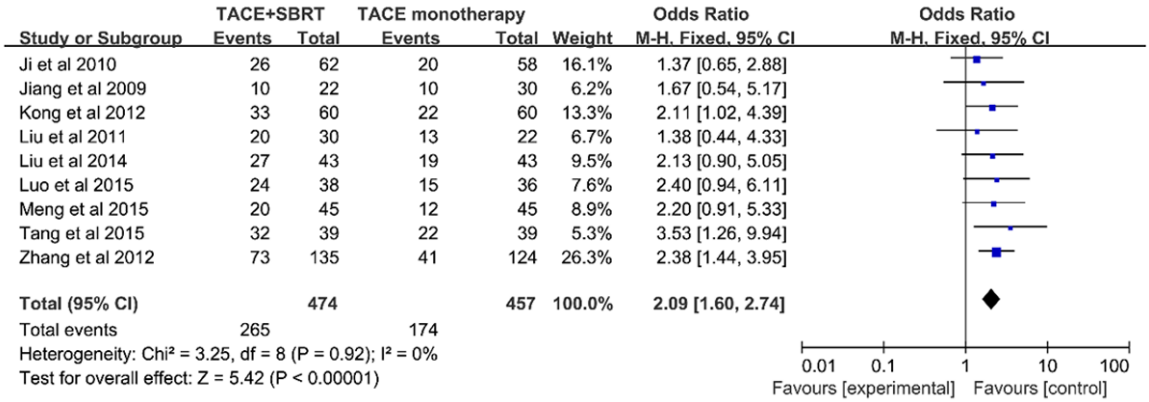


**Figure 4.** Meta-analysis of the 2-year survival rate in 9 studies comparing TACE plus SBRT with TACE monotherapy for primary liver carcinoma. CI: Confidence interval; M-H: Mantel-Haenszel's method; Fixed: Fixed-effects model; SBRT: Stereotactic body radiation; TACE: Transcatheter arterial chemoembolization.

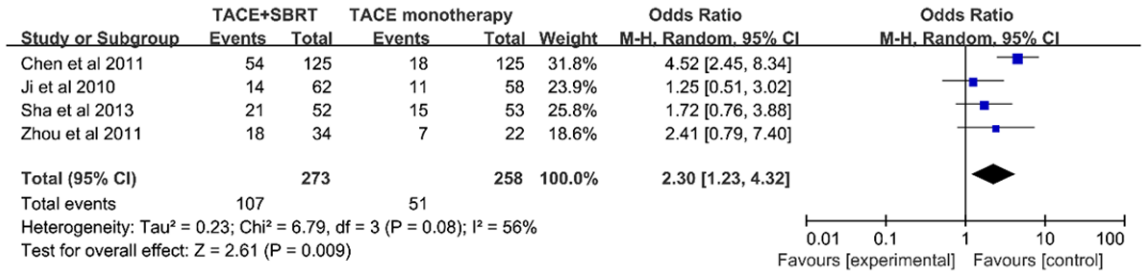


**Figure 5.** Meta-analysis of the 3-year survival rate in 4 studies comparing TACE plus SBRT with TACE monotherapy for primary liver carcinoma. CI: Confidence interval; M-H: Mantel-Haenszel's method; Random: Random-effects model; SBRT: Stereotactic body radiation; TACE: Transcatheter arterial chemoembolization.

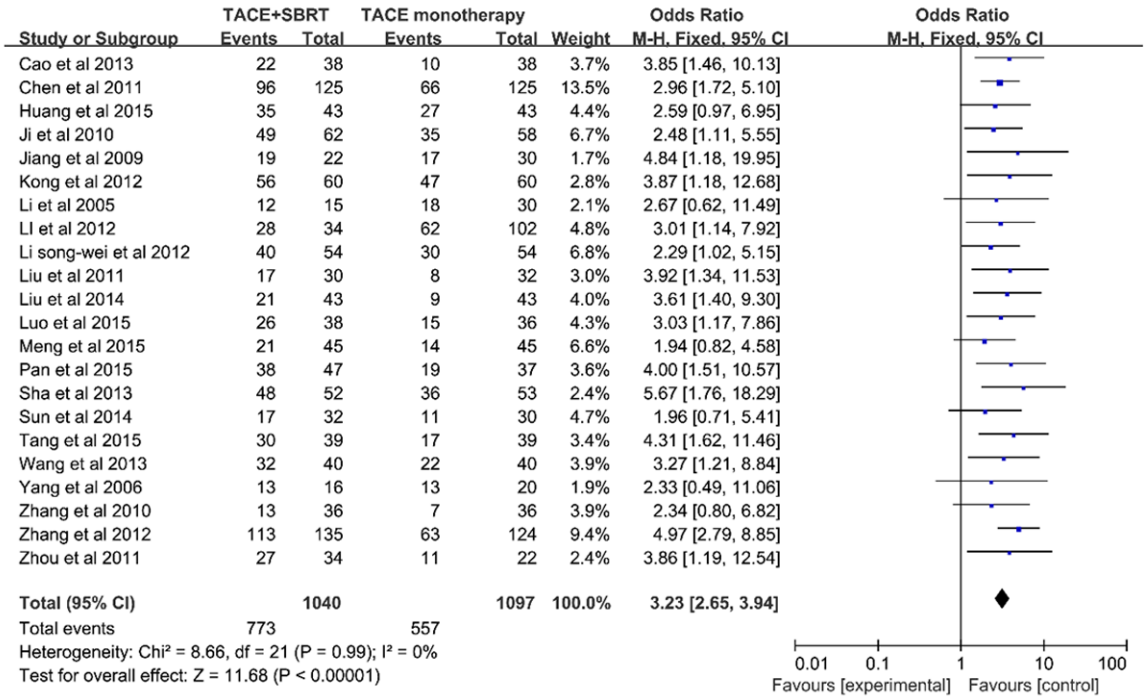


**Figure 6.** Meta-analysis of tumor response to therapy in 22 studies comparing TACE plus SBRT with TACE monotherapy for primary liver carcinoma. CI: Confidence interval; M-H: Mantel-Haenszel's method; Fixed: Fixed-effects model; SBRT: Stereotactic body radiation; TACE: Transcatheter arterial chemoembolization.

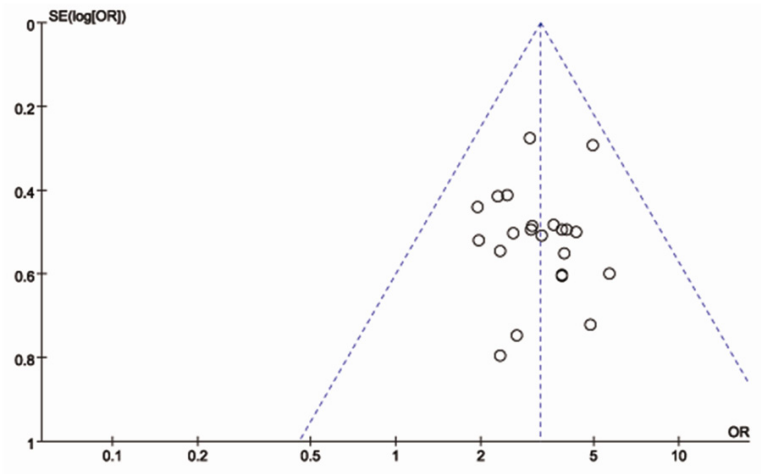


**Figure 7.** Funnel plot of publication bias among studies.

effects model and a random-effects model was performed to assess the therapeutic effects. Analysis on TACE combined with SBRT versus TACE showed that the combination therapy significantly improved the overall survival rates determined after 0.5 years, 1-year, 2 years, 3 years and with the total effective rate of P < 0.00001, P < 0.00001, P < 0.00001, P = 0.009 and P < 0.00001 respectively, with no statistical heterogeneity (P = 0.45, P = 0.92, P = 0.92 and P = 0.99, respectively) beyond that of the overall survival rate after 3 years (P = 0.08 < 0.1), compared with that of the monotherapy.

*Publication bias*

The visual symmetrical plot indicated that the publication bias among studies is low (**Figure 7**).

*Tumor recurrence and side effects*

Only one study reported the tumor recurrence rate [34], which was not enough to perform a meta-analysis because the number of included trials was too small. In addition, sixteen studies described adverse effects after treatment [23-25, 27, 28, 30-36, 39, 40, 42, 44], but that was not applicable to perform a meta-analysis with no unified standard in these studies. The main

adverse effects were gastrointestinal reactions (nausea/vomiting), liver function damage and hematologic toxicity (leukopenia).

## Discussion

This meta-analysis aimed to assess the effectivity and safety of TACE combined with SBRT in treating PLC on survival and response to therapy. According to this meta-analysis, there was a statistically significant effect on the overall survival rate after 0.5 years, 1-year, 2 years, 3 years and the total effective rate between the two therapeutic schemes. It suggests that TACE combined with SBRT is superior to TACE alone for patients with PLC, with significant survival benefit and high responsiveness to therapies. The sensitivity analysis of this current evidence also demonstrated the same trend for TACE combined with SBRT.

It is recognized that TACE is effective for PLC [45-47]. Additionally, SBRT is also appropriate for PLC [48, 49]. Hence, TACE combined with SBRT can be more effective for PLC and may contribute to the improved outcomes due to the following effects: (1) TACE can block the hepatic arterial flow [6], resulting in decreasing the tumor size, which in turn contributes to the increase in the effective radiological doses of the tumor targets without injuring normal liver tissue excessively [8, 50]; (2) Chemotherapy drugs left in the tumors after TACE may interact with the gamma rays such as to improve the sensitivity of cancer cells to the gamma rays [32, 37]; (3) Lipiodol deposited in the tumor by TACE increased the visibility of target [10]; (4) Gamma rays may improve the effects of anticancer drugs on cancer cells [32]; (5) Gamma rays can be effective in remedying the limitations of TACE, such as incomplete necrosis, due to dual blood supply around the tumor, multiple collateral circulation and recanalization [36, 51, 52].

The sensitivity analysis showed that the studies which reported the 3-year survival rate showed potential heterogeneity ($P = 0.08$, $I^2 = 56\%$). The imbalance among these studies may be one cause, because not all the characteristics of patients were well matched: Different doses of drugs and gamma rays, different tumor stage and tumor numbers, selection bias, performance biases, publication biases and limited RCTs may be other reasons. It was difficult to explore the origin of heterogeneity based on the limited number of enrolled patients. Moreover, there was also one clinical control study reporting no statistical difference in the 3-year survival rate between the combination therapy and TACE monotherapy for PLC patients [36]. In this study the following specific characteristics were published: (1) The probability of the side effects, such as nausea/vomiting, liver function damage and leukopenia, was increased after application of the combination therapy; (2) Patients were treated by chemotherapy medications, however, without the most popular drug combinations being used (e.g. doxorubicin, cisplatin, epirubicin and mitomycin). Both of these characteristics can affect the long term outcome. Hence, some higher quality RCTs are required to confirm the superiority of the combination therapy.

Moreover, a tumor recurrence analysis was not performed in this meta-analysis due to lack of sufficient data. Only one non-randomized concurrent controlled clinical trial reported that the combined therapy did decrease 1-year recurrence of tumor in comparison of monotherapy with statistically significance [34]. For side effects after treatment, meta-analysis was not performed due to inconsistencies in the definition within the studies included. Although sixteen studies were integrated to report the adverse effects (e.g. nausea/vomiting, liver function damage and leukopenia), only four studies described the criteria for them [24, 27, 30, 44]. Some studies reported that there was no statistical significance between the two groups [23, 24, 28, 35, 39, 40, 42, 44], and the side effects did not affect further treatment and prognosis after supportive treatment such as liver-protecting drugs and drugs for leucopenia. However, it has also been reported that repeated TACE may result in progressive damage of hepatic function [53, 54]. Chen et al also concluded that a combination of treatment may improve the incident of side effects with statistical significance, compared with monotherapy [30, 36]. The potential reasons for this controversy may be different drugs, dosage and time of interventions used (**Table 2**). Firstly, different chemotherapeutic drugs may produce different effect for therapy. Lau et al reported that there was no consensus on a golden standard in the therapy of TACE [55]. Ramsey et al reported that doxorubicin, cisplatin and mitomycin C

were recommended as the preferred drug combinations [56]. However, all of the included studies described different drug combinations respectively, such as epirubicin/doxorubicin, mitomycin, and 5-fluorouracil with epirubicin being the most popularly drug combination applied. Secondly, although SBRT was implemented after TACE in the studies included, the time and dosage of the SBRT may also play an important role in the side effects of the treatment and the prognosis [50, 57]. Therefore, well-designed RCTs should be conducted to assess the risk of combination treatment over monotherapy.

In conclusions, this meta-analysis indicates that TACE combined with SBRT improves the overall survival rates and response to therapy compared to TACE alone, but the trend needed to be further confirmed by higher quality RCTs.

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## Disclosure of conflict of interest

None.

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