Systematic Review and Meta-Analysis

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Arsenic trioxide combined with transarterial chemoembolization for unresectable primary hepatic carcinoma

A systematic review and meta-analysis

Peng Song, PhD[a,c], Yang Hai, MD[b], Wantong Ma, MD[b], Longhe Zhao, MD[b], Xin Wang, PhD[b], Qinjian Xie, PhD[a], Yang Li, PhD[b], Zhengrong Wu, PhD[b], Yingdong Li, PhD[c], Hongyu Li, PhD[a,b,*]

Abstract

Background: Primary hepatic carcinoma (PHC) is the third commonest leading to cancer death around the world, and transarterial chemoembolization (TACE) has been proposed as the first-line therapeutic treatment for patients with unresectable PHC. This study aims to determine whether the combination of As_2O_3 and TACE is superior to alone TACE for achieving more clinical therapeutic efficacy, survival time, life quality and safety in patients with unresectable PHC.

Methods: A comprehensive literature search was conducted on the clinical controlled trials comparing therapeutic effects of As_2O_3 & TACE versus alone TACE for unresectable PHC through English databases (including PubMed, Embase, and the Cochrane Library) and Chinese databases (including China Knowledge Resource Integrated Database, Wanfang Database, Weipu Database, and Chinese Biomedical Database). The last search was in 30 August 2017. A recursive search was performed with bibliographies of relevant studies. There were no language restrictions. Primary outcomes, defined a priori, were therapeutic responses (clinical effective rate and clinical benefit rate), survival time, life quality, and adverse events of As_2O_3 & TACE compared with alone TACE expressed as relative risk (RR) with 95% confidence intervals (CI).

Results: 25 clinical controlled trials involving 1886 participants were included. We found that there were significant superiority associated with As_2O_3 & TACE compared with alone TACE in clinical benefit rate (RR: 1.24, 95% CI: 1.12–1.37), clinical effective rate (RR: 1.35, 95% CI: 1.17–1.55), 2-year survival rate (RR: 1.45, 95% CI: 1.20–1.75), and improving of KPS (RR: 1.31, 95% CI: 1.14–1.50). These associations were also observed in subgroups by intervened methods of As_2O_3 and pulmonary metastasis. Notably, the pooled relative risk of retention of sodium and water was obviously raised in patients with As_2O_3 & TACE therapy (RR: 16.616, 95% CI: 8.01 – 34.486).

Conclusion: The superiority of adjuvant As_2O_3 therapy combined with TACE in PHC individuals will outweigh alone TACE therapy, especially in PHC populations with pulmonary metastasis.

Abbreviations: ALP = acute promyelocytic leukemia, CBR = clinical benefit rate, CER = clinical effective rate, CI = confidence intervals, CR = complete response, KPS = karnofsky performance scale, PD = progressive disease, PHC = primary hepatic carcinoma, PR = partial response, RCT = randomized controlled trials, RR = relative risk, SD = stable disease, TACE = transarterial chemoembolization.

Keywords: arsenic trioxide, meta-analysis, primary hepatic carcinoma, systematic review, transarterial chemoembolization

1. Introduction

Primary hepatic carcinoma (PHC) is the third commonest leading to cancer death around the world, and being liable for about 700,000 deaths annually, based on precious statistic with an increasing incidence.[1] Furthermore, the GOLOBOCAN database demonstrates geographical differences in the incidence of PHC, with the severe disease spreading further commonly in China, southern Asia, and eastern Africa in which the popularity of the disease surpasses 20 cases per 100,000 people.[2] Therefore, PHC has a substantial influence on morbidity around the world, extraordinarily common in the developing countries, which causes both medical and economic burdens to our society.

Surgical resection and liver transplantation, supported by level IIA evidence, are considered to possess positive therapeutic effect on the patients. However, the rarely available organ and the undesirable surgical effect can impose restrictions on the cure among 90% of patients.[3] Besides, aside from the above facts, there are 80% of these patients could suffer from the tumor recurrence within 5 years after surgical resection. What's more, the tumor recurrence of disease could happen to half of these

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[a] Institute of Microbiology, School of Life Sciences, [b] School of Pharmacy, Lanzhou University, [c] Key Laboratory of Prevention and Treatment for Chronic Disease by Traditional Chinese Medicine, Gansu Province, Lanzhou, China.

[*] Correspondence: Hongyu Li, Institute of Microbiology, School of Life Sciences, Lanzhou University, Tianshui Road No. 222, Lanzhou 730000, China (e-mail: lihy@lzu.edu.cn).

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patients approximately within 2 years.[4] There are 90% of patients, as the remaining, being not suitable for surgical candidates, while interventional oncology can supply a broad extent of treatment as alternatives.[2] In recent years, transarterial chemoembolization (TACE) has been proposed as the first-line therapeutic treatment for patients with unresectable PHC, because it is capable of allowing the synergistic influence of greater local levels of chemotherapeutic agents and occlusion of the artery supplying nutrients to a tumor.[5,6] Chemotherapeutic agents commonly used in TACE include 5-fluorouracil, antibiotics (mitomycin, adriamycin, and pirarubicin), and platinum drugs (cisplatin and oxaliplatin).

Arsenic trioxide (As_2O_3) is one of the oldest drugs in the world but was progressively revived between the 1970s and 1990s, because of its striking efficacy on acute promyelocytic leukemia (APL), which represented the most malignant type of acute leukemia.[7] These paradoxical effects of As_2O_3 reflect its multiple properties, thus, it has been considered to be an effective chemotherapeutic agent for various solid tumors such as PHC.[8] Currently, As_2O_3 was only approved for palliative treatment for the patients with unresectable PHC by China Food and Drug Administration. However, recent studies have reported that the treatments of single-agent As_2O_3 were not a significant benefit for patients with PHC, but the benefit of adjuvant As_2O_3 dramatically emerged when it was combined with other therapeutic treatments such as TACE.[9,10] Moreover, in the last few years, As_2O_3 combined with TACE is used to treat PHC, as seen in the increasing number of clinical research reports. Those reports explored the potential effects of adjuvant As_2O_3 therapy in patients with PHC and revealed that As_2O_3 could induce the apoptosis of hepatic carcinoma cells by activating mitochondrial pathway of apoptosis and inhibiting the expression of proliferating cell nuclear antigen.[11]

Currently, only 2 meta-analysis reviews have been published to evaluate the benefits of As_2O_3 combined with TACE in the treatment of PHC.[12,13] However, previous reviews have been nonsystematic, have not focused on specific intervened methods or adverse events, and have not included the latest clinical trials. Additionally, there were some unknown high heterogeneity and possible publication bias in those meta-analysis reviews, which suggests the evidence on the benefits of As_2O_3 combined with TACE should also be revisited. The objective of this systematic review and meta-analysis is to evaluate broadly the available evidence that combination of As_2O_3 and TACE is superior to alone TACE for achieving more clinical therapeutic efficacy, survival time, life quality, and safety in patients with PHC.

2. Methods

2.1. Search strategy

A systematic literature search was conducted in English databases, including PubMed, Embase, and the Cochrane Library, and Chinese databases, including China Knowledge Resource Integrated Database (CNKI), Wanfang Database, Weipu Database (VIP), and Chinese Biomedical Database (CBM). The literature search was performed from inception to August 1, 2017. Randomized controlled trials (RCTs) including patients with primary hepatic carcinoma, either treated with alone TACE or combination of As_2O_3 were identified. The following search terms were used: "arsenic trioxide (or) arsenious acid (or) As_2O_3 (or) arsenic sesquioxide (or) arsenious oxide (or) arsenious anhydride (or) white arsenic (or) arsenic (III) oxide (or) arsenite (or) trisenox (or) trixenox (or) naonobin (or) arsenolite (or) arsenous," "liver cancer (or) liver neoplasms (or) hepatic carcinoma (or) hepatocellular cancer," and "transcatheter arterial chemoembolization (or) transarterial chemoembolization (or) TACE." There were no language restrictions, and abstracts of the papers identified by the initial search were evaluated by the lead reviewer for appropriateness to the study question. The bibliographies of all identified relevant studies were used to perform a recursive search of the literature.

2.2. Study selection

Articles were assessed independently by 2 investigators using predesigned eligibility forms according to the eligibility criteria, defined prospectively. Any disagreement between investigators was resolved by consensus. The inclusion criteria were as follows: clinical controlled trials were published as peer-reviewed articles; participants were diagnosed with primary hepatic carcinoma clinically; therapeutic effects of As_2O_3 & TACE and TACE were compared in the references; and main outcomes, such as therapeutic responses (categorized as clinical effective rate and clinical benefit rate according to the World Health Organization criteria), survival time, life quality, and adverse events were reported. Exclusion criteria for this meta-analysis were as follows: As_2O_3 was used in a combination with other treatment options; studies including participants with secondary hepatic carcinoma; studies including participants who were duplicated in similar studies; As_2O_3 was used by exceeding one method of administration in a study; and unsuitable publication types, such as meeting abstracts, comments, reviews, or case reports.

2.3. Data abstraction

Data extraction was completed by 2 reviewers independently, and disagreements were settled by a third reviewer. The following data were extracted from each study: the study characteristics, including first author's name, year of publication, number of patients for each group, age distribution, sex distribution, Child-Pugh classification, presence or absence of pulmonary metastasis, and protocols for each group, and the main outcomes, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), half-year survival rate, 1-year survival rate, 2-year survival rate, 3-year survival rate, improvement rate of karnofsky performance scale (KPS) scores, maintaining rate of KPS scores, and various adverse events. The corresponding authors were contacted for supplementary data which were not included in original articles.

2.4. Assessment of risk of bias

Risk of bias assessment was performed independently by 2 investigators, with disagreements resolved by discussion. Risk of bias was assessed as described in the Cochrane Collaboration's tool by recording the method used to generate the randomization schedule and conceal allocation; whether blinding was implemented for participants, staff, and outcome assessment; what proportion of subjects completed follow-up; and whether there was evidence of selective reporting of outcomes.[14]

2.5. Data synthesis and statistical analysis

The clinical benefit rate (CBR) was defined as the percentage of CR, PR, and SD patients, and the clinical effective rate (CER) was

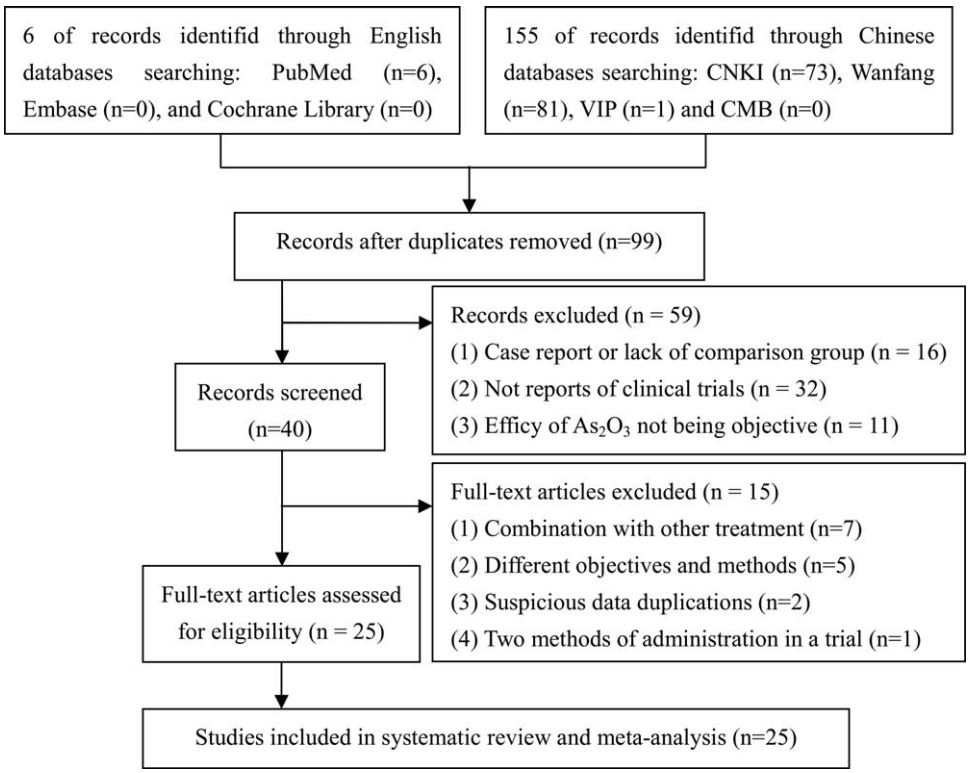

Figure 1. Flow diagram of assessment of studies identified in the systematic review.

defined as the percentage of CR and PR patients. Data of risk ratios (RR) were pooled using a random effects model to give a more conservative estimate of the effect of As_2O_3 & TACE therapy on the subsequent occurrence of CER and CBR, allowing for any heterogeneity. Heterogeneity between studies was assessed using both the I^2 statistic with a cut off of ≥50% and the chi-squared test with a P value <.10 used to define a significant degree of heterogeneity.[15] Where the degree of statistical heterogeneity was greater than this between trial results, possible explanations were investigated using subgroup analyses according to intervened methods of As_2O_3 (intravenous drip, arterial chemoembolization with other drugs in TACE group, arterial perfusion, and arterial chemoembolization without other drugs) and presence or absence of pulmonary metastasis. The survival rates for the different time, the improvement and maintaining rates of KPS scores, and various adverse events were presented as RR with 95% confidence interval (CI) by using the fixed-effects model (Mantel–Haenszel method). We compared individual relative risks between these analyses using the Cochran Q statistic. Publication bias was tested with funnel plots regression, and Egger test[16] and Harbord modified test[17] were used to measure funnel plot asymmetry. However, the publication bias would not be formally assessed if a small number of studies (<10) were included in the analyses of outcome measures.[18] These were exploratory analyses only and may explain some of the observed variability, but the results should be interpreted with caution. All statistical analyses were performed using the Review Manager version 5.3.4 (RevMan for Windows WIN7, the Nordic Cochrane Centre, Copenhagen, Denmark) and StataSE version 12.0 (Stata Corporation, College Station, TX). All analyses were based on previous published studies; thus, no ethical approval and consent from patients are required.

3. Results

3.1. Search result

The search of literature initially identified 161 potentially relevant references. The references included 6 English articles and 155 Chinese articles. Sixty-two studies were excluded as duplicates in different databases. Following the examination of titles and abstracts, 40 studies were selected for further full-text evaluation. Of the remaining records, 25 RCTs fulfilled the criteria for inclusion in a quantitative synthesis (meta-analysis).[10,19–42] Details of study selection are presented in Fig. 1.

3.2. Description of the included studies

Of the remaining 25 articles we identified, 3 studies were written in English and 22 studies were written in Chinese. All included studies were published in China between 2003 and 2017. Descriptive data for the studies included in our analysis were summarized in Table 1. A total of 1886 patients were enrolled, comprising 940 patients from the experimental group and 946 patients from the control group. The total male/female ratio was 1476/410, and the age range was 21 to 82 years. All included trials used similar inclusion criteria for each group. The TACE therapy was implemented with a standard protocol in each study, including the following steps: the Seldinger method was adopted for the puncture of the femoral artery; a catheter was inserted, then digital subtraction arteriography-guided celiac arteriography was performed; a 3F microcatheter was used to infuse chemotherapeutic agents, and gelatin sponge particles into each target vessel. In the experimental group, the intervened methods of As_2O_3 were respectively implemented by intravenous drip, arterial chemoembolization with other drugs in TACE group, arterial perfusion, and arterial chemoembolization without other

Table 1

Baseline characteristics of the included studies.

No	Study (reference)	Year (language)	Samples(n)		Sex (male/female)		Age		Child-Pugh classification		Pulmonary metastasis	Protocol (per course)		Number of course
			E	C	E	C	E	C	E	C		E	C	
1	Wang XD (37)	2013 (Chinese)	34	33	55/12		31–77		B34	B33	No	As_2O_3(10 mg/d,iv,14 days)+TACE	TACE(Epi-ADM 30 mg+^{125}I 18 g+IO 5–15 mL, 28 days)	4
2	Zhuang XL (39)	2006 (Chinese)	62	56	44/18	36/20	26–76	24–79	A28,B32,C2	A25,B28,C3	No	As_2O_3(20 mg/d,ap,7 days)+TACE	TACE(DDP 50 mg+MMC 10 mg+Epi-ADM 50 mg+IO 10–30 mL, 30 days)	2
3	Zhang XB (35)	2011 (Chinese)	30	30	24/6	25/5	28–72	31–68	A3,B23,C4	A4,B23,C3	No	As_2O_3(20 mg,ac)+TACE	TACE(CBP 300 mg+MMC 10 mg+IO 5–20 mL,35 days)	2
4	Zhou ZT (42)	2007 (Chinese)	41	45	35/6	40/5	27–75	23–74	A35,B6	A37,B8	No	As_2O_3(20 mg,ac)+TACE	TACE(5-FU 750 mg+CAP 300 mg+THP 60 mg +IO 3–5 mL,28–56 days)	NA
5	Meng YL (26)	2012 (Chinese)	30	30	22/8	19/11	36–77	23–78	NA	NA	Yes	As_2O_3(10 mg/d,iv,14 days)+TACE	TACE (ADM 20–30 mg+CBP 100–300 mg+IO 3–5 mL,30 days)	3–4
6	Cui SZ (31)	2006 (Chinese)	26	29	21/5	25/4	39–65	37–67	A19,B7	A22,B7	No	As_2O_3(20 mg/d,ap,7 days)+TACE	TACE(MMC 6 mg/m^2+Epi-ADM 40 mg/m^2+CBP 30 mg/m^2+IO 10–30 mL,28 days)	2
7	Zheng S (29)	2013 (Chinese)	30	34	22/8	22/12	38–72	29–76	NA	NA	Yes	As_2O_3(10 mg/d,iv,14 days)+TACE	TACE(ADM 20–30 mg+CBP 100–300 mg+IO 6–20 mL,28 days)	3–4
8	Qi XJ (38)	2003 (Chinese)	34	30	28/6	24/6	32–68	36–72	A28,B4,C2	A22,B4,C4	No	As_2O_3(2 mL/cm/week,ap,4 weeks)+ TACE	TACE(5-FU 1 g+MMC 10 mg+Epi-ADM 60 mg +IO 1 mL/cm,28–35 days)	3
9	Liu XD (36)	2006 (Chinese)	27	25	24/3	23/2	35–71	34–72	A/B	A/B	No	As_2O_3(20 mg+IO 5–20 mL,ac, 15 days)	TACE(MMC10 mg+DDP 60 mg+Epi-ADM NA +IO 5–20 mL,15 days)	1
10	Yan TH (32)	2013 (Chinese)	30	32	26/4	26/6	29–72	31–74	A25,B5	A26,B6	No	As_2O_3(20 mg,ac)+TACE	TACE(5-FU 0.75–1.0 g+IL-ll2 million U+DDP 40–50 mg+Epi-ADM 40–50 mg+IO 5–15 mL,28–56 days)	1–3
11	Zha GH(22)	2010 (Chinese)	16	15	27/4		27–82		NA	NA	No	As_2O_3(7–8 mg/m^2/d,iv,14 days) +TACE	TACE(5-FU750 mg/m^2+DDP 60 mg/m^2+THP20 mg/m^2+IO,28 days)	3
12	Xie YR (41)	2007 (Chinese)	33	32	25/8	23/9	21–70	21–70	NA	NA	No	As_2O_3(20 mg,ac)+TACE	TACE(HCPT 20 mg/ADM 60 mg+DDP 60 mg+IO 5–20 mL,28–42 days)	2–3
13	Hu Q (27)	2014 (Chinese)	28	25	21/7	17/8	31–80	28–70	NA	NA	No	As_2O_3(10–20 mg,ac)+TACE	TACE(5-FU1.5 g+Epi-ADM 50 mg+OXA 150 mg +IO 10–20 mL,30 days)	2–6
14	Meng YL (40)	2015 (Chinese)	30	30	27/3	26/4	36–76	36–72	A/B	A/B	No	As_2O_3(10 mg/d,iv,14days)+TACE	TACE(ADM 20–30 mg+OXA 100 mg+IO 3–15 mL,35 days)	NA
15	Xiang W (33)	2014 (Chinese)	27	28	22/5	25/3	60.2±10.50	58.76±10.78	A24,B3	A24,B4	No	As_2O_3(15 mg+IO <30 mL,ac, 30–60 days)	TACE(THP20 mg+MMC10 mg+IO <30 mL,30–60 days)	2
16	Xing R (28)	2012 (Chinese)	23	25	18/5	23/2	55.43±10.49	54.84±8.24	A17,B6	A21,B4	No	As_2O_3(20 mg,ac)+TACE	TACE(Epi-ADM 40 mg+IO)	1–5
17	Qian LK (25)	2014 (Chinese)	40	40	32/8	35/5	33–81	31–68	A/B	A/B	No	As_2O_3(20 mg,ac)+TACE	TACE(LBP40 mg+Epi-ADM 40 mg+IO)	2–3
18	Huang LJ (24)	2011 (Chinese)	15	15	13/2	11/4	57.80±9.76	57.80±12.38	A/B	A/B	No	As_2O_3(10 mg/d,iv,14 days)+TACE	TACE(5-FU 500–750 mg+THP 20–40 mg+IO 1.5 mL/cm,28–35days)	4
19	Wang SM (30)	2012 (Chinese)	30	30	26/4	25/5	54.72±10.77	57.04±9.46	A/B	A/B	No	As_2O_3(20 mg,ac)+TACE	TACE(CBP300 mg+MMC10 mg+IO 5–20 mL,30days)	2
20	Qiu CK (20)	2015 (Chinese)	78	78	48/30	51/27	22–74	23–76	NA	NA	No	As_2O_3(20 mg,ac)+TACE	TACE(LBP50 mg+MMC10 mg+Epi-ADM40 mg/m^2+IO10 mL,28–42 days)	3–4
21	Nian DF (21)	2015 (Chinese)	75	81	96/60		45–76		A76,B65,C15		No	As_2O_3(15–30 mg,ac)	TACE(5-FU 250–750 mg+MMC 5–10 mg+ADM 10–40 mg+IO 5–20 mL,28–42 days)	No
22	Yang BJ (19)	2015 (Chinese)	40	40	21/19	22/18	59.1±2.03	61.50±1.80	NA	NA	No	As_2O_3(10 mg/d,iv,14 days)+TACE	TACE(DDP 20–40 mg/m^2+DOX 20–40 mg/m^2+IO,14 days)	2
23	Bing L (10)	2015 (English)	70	69	58/12	62/7	36 (<55) 34 (≥55)	31 (<55) 38 (≥55)	A42,B28	A40,B29	Yes	As_2O_3(10 mg/d,iv,21 days)+TACE	TACE(As_2O_3 20 mg+IO 20 mL,35 days)	NA
24	Hui W (34)	2015 (English)	61	64	51/10	55/9	33–70	31–70	A52,B9	A54,B10	No	As_2O_3(10 mg/d,iv,14 days)+TACE (2 course) +MWA/125I (2 course)	TACE(OXA 100 mg+Epi-ADM 30–50 mg+IO 2–10 mL, 21 days, 2 course)+MWA/^{125}I (2 course)	4
25	Hu HT (23)	2017 (English)	30	30	22/8	19/11	51.7±9.2	52.4±12.3	A30	A30	Yes	As_2O_3(10 mg/d,iv,14 days)+TACE	TACE(CBP 90–120 mg+ADM 30–50 mg+IO 6–20 mL, 21 days)	4

The TACE related chemotherapeutic agents are summarized in brackets (5-FU = fluorouracil, ADM = adriamycin, Epi-ADM = epirubicin, DOX = doxorubicin, CBP = carboplatin, HCPT = hydroxycamptothecin, THP = theprubicin, DDP = cisplatin, MMC = mitomycin, CAP = chloromycetin, OXA = oxaliplatin, LBP = lobaplatin).

ac = arterial chemoembolization, ap = arterial perfusion, As_2O_3 = arsenic trioxide, C = control group for TACE alone, E = experimental group for As_2O_3 and TACE, iv = intravenous drip, NA = not applicable, TACE = transarterial chemoembolization.

Table 2

Quality assessment of the studies included in the meta-analysis.

Included studies	A	B	C	D	E	F	G
Wang, XD 2013	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear
Zhuang, XL 2006	Yes	Unclear	Unclear	Unclear	Yes	Yes	Unclear
Zhang, XB 2011	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear
Zhou, ZT 2007	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear
Meng, YL 2012	Yes	Unclear	Unclear	Unclear	Yes	Yes	Unclear
Cui, SZ 2006	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear
Zheng, S 2013	Yes	Unclear	Unclear	Unclear	Yes	Yes	Unclear
Qi, XJ 2003	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear
Liu, XD 2006	Yes	Unclear	Unclear	Unclear	Yes	Yes	Unclear
Yan, TH 2013	Unclear	No	Unclear	Unclear	Yes	Yes	Unclear
Zha, GH2010	Unclear	No	Unclear	Unclear	Yes	Yes	Unclear
Xie, YR2007	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear
Hu, Q 2014	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear
Meng, YL 2015	Yes	Unclear	Unclear	Unclear	Yes	Yes	Unclear
Xiang, W 2014	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear
Xing, R 2012	Yes	Unclear	Unclear	Unclear	Yes	No	Unclear
Qian, LK 2014	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear
Huang, LJ 2011	Yes	yes	Unclear	Unclear	Yes	No	Unclear
Wang, SM 2012	Yes	Unclear	Unclear	Unclear	Yes	Yes	Unclear
Qiu, CK 2015	Yes	Unclear	Unclear	Unclear	Yes	Yes	Unclear
Nian, DF 2015	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear
Yang, BJ 2015	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear
Bing, L 2015	Yes	No	Yes	Unclear	Yes	Yes	Yes
Hui, W 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hu, HT 2017	Yes	Yes	No	Unclear	Yes	Yes	Yes

A = random sequence generation (selection bias), B = allocation concealment (selection bias), C = blinding of participants and personnel (performance bias), D = blinding of outcome assessment (detection bias), E = incomplete outcome data, F = selective reporting (reporting bias), G = other biases.

drugs. Only in the 4 trials, all patients were diagnosed PHC with pulmonary metastasis and intervened by the intravenous drip of As_2O_3. We also performed a subgroup analysis of some outcome measure basing on intervened methods of As_2O_3 and presence or absence of pulmonary metastasis, if the heterogeneity was significant.

3.3. Quality assessment of the included studies

We used the Cochrane Collaboration's tool to evaluate the quality of the included studies and found that 25 studies were randomized. The results of the quality assessment can be seen in Table 2. A major problem we found was that, although the participants were randomized into 2 groups in each trial, most of the trials did not present the details of sequence generation (10 RCTs),[19,25,27,31,33,35,37,38,41,42] allocation concealment (19 RCTs),[19–21,25–31,33,35–42] and blinding methods (22 RCTs).[19–22,24–33,35–42] Therefore, the corresponding risks of bias could not be excluded. Furthermore, as a result of inadequate information was given, the judgment for "other sources of bias" also was "unclear" for most included trials (22 RCTs).[19–22,24–33,35–42]

3.4. Quantitative analyses

3.4.1. Clinical benefit rate. The clinical benefit rate (CBR) was reported in 23 studies. The pooled CBR was significantly higher in the As_2O_3 & TACE group compared with the TACE group (RR: 1.24, 95% CI: 1.12–1.37, $Z = 4.13$, $P = .000$). Notably, the significant heterogeneity was detected among the studies ($P = .000$, $I^2 = 71.1\%$). In the subgroup analysis according to intervened methods of As_2O_3, statistically significant differences of CBR were obtained from intravenous drip group (RR: 1.65, 95% CI: 1.21–2.26, $Z = 3.12$, $P = .002$) and arterial chemoembolization with other drugs in TACE group (RR: 1.17, 95% CI: 1.09–1.26, $Z = 4.19$, $P = .000$), however, no statistically significant differences of CBR were obtained from arterial perfusion group (RR: 1.07, 95% CI: 0.94–1.22, $Z = 0.97$, $P = .330$) and arterial chemoembolization without other drugs group (RR: 1.22, 95% CI: 0.98–1.52, $Z = 1.77$, $P = .077$) (Fig. 2). Heterogeneity between studies for each subgroup indicated that the reason of significant heterogeneity for all studies is the high heterogeneity for intravenous drip group ($P = .000$, $I^2 = 90.2\%$), and the heterogeneity for other groups were not detected ($P > .1$, $I^2 = 0.0\%$). Furthermore, in order to explore the reason of high heterogeneity for intravenous drip group, we distinguished 2 subgroups based on presence or absence of pulmonary metastasis in intravenous drip group with the high heterogeneity. Similar positive results were obtained from both the absence of pulmonary metastasis group (RR: 1.15, 95% CI: 1.06–1.25, $Z = 3.22$, $P = .001$) with no heterogeneity between studies ($P = .919$, $I^2 = 0.0\%$) and presence of pulmonary metastasis group (RR: 4.55, 95% CI: 2.69–7.68, $Z = 5.65$, $P = .000$) with no heterogeneity between studies ($P = .191$, $I^2 = 36.8\%$) (Fig. 3).

3.4.2. Clinical effective rate. The clinical effective rate (CER) was reported in 24 studies. The pooled CER was significantly higher in the As_2O_3 & TACE group compared with the TACE group (RR: 1.35, 95% CI: 1.17–1.55, $Z = 4.23$, $P = .000$). Notably, the significant heterogeneity was detected among the studies ($P = .029$, $I^2 = 38.6\%$). In the subgroup analysis according to intervened methods of As_2O_3, statistically significant differences of CER were obtained from intravenous drip group (RR: 1.64, 95% CI: 1.18–2.29, $Z = 2.91$, $P = .004$) and arterial chemoembolization with other drugs in TACE group (RR:

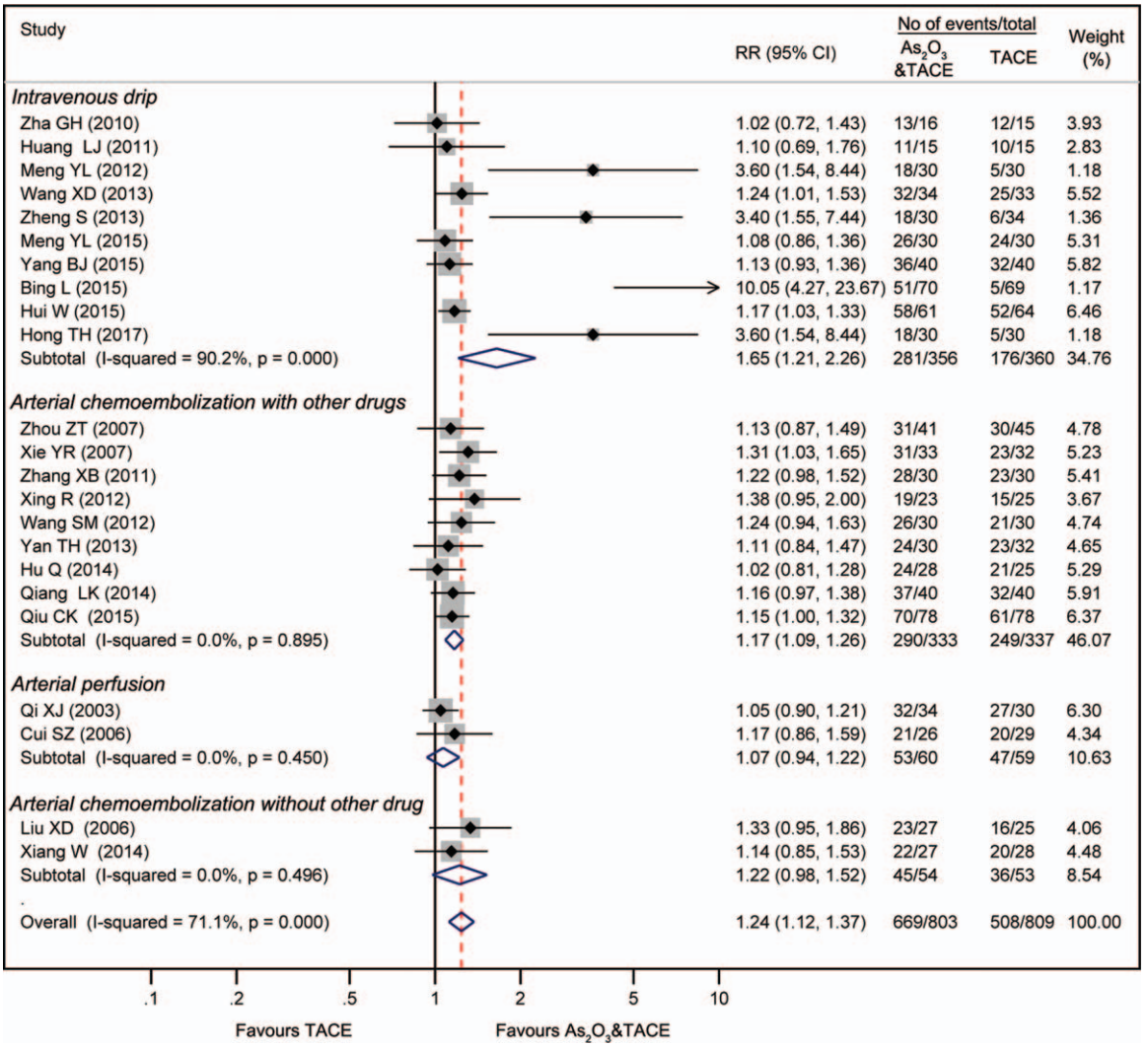

Figure 2. Forest plot of subgroup analysis by intervened methods of As_2O_3: clinical benefit rate of As_2O_3 & TACE and alone TACE in treating PHC. PHC = primary hepatic carcinoma, TACE = transarterial chemoembolization.

1.39, 95% CI: 1.18–1.65, $Z = 3.87$, $P = .000$), however, no statistically significant differences of CBR were obtained from arterial perfusion group (RR: 1.20, 95% CI: 0.80–1.79, $Z = 0.90$, $P = .370$) and arterial chemoembolization without other drugs group (RR: 1.22, 95% CI: 0.91–1.65, $Z = 1.32$, $P = .187$) (Fig. 4). Heterogeneity between studies for each subgroup indicated that the reason of significant heterogeneity for all studies is the high heterogeneity for intravenous drip group ($P = .034$, $I^2 = 50.2\%$) and arterial perfusion group ($P = .074$, $I^2 = 61.6\%$), however, the heterogeneity for arterial chemoembolization with other drugs in TACE group ($P = .556$, $I^2 = 0.0\%$) and arterial chemoembolization without other drugs group ($P = .308$, $I^2 = 3.8\%$) was not significant. Furthermore, in order to explore the reason of high heterogeneity for intravenous drip group, we distinguished 2 subgroups based on presence or absence of pulmonary metastasis in intravenous drip group with the high heterogeneity. Similar positive results were obtained from both the absence of pulmonary metastasis group (RR: 1.40, 95% CI: 1.18–1.65, $Z = 3.92$, $P = .000$) with no heterogeneity between studies ($P = .835$, $I^2 = 0.0\%$) and presence of pulmonary metastasis group (RR: 15.73, 95% CI: 3.83–64.60, $Z = 3.82$, $P = .000$) with no heterogeneity between studies ($P = .993$, $I^2 = 0.0\%$) (Fig. 5). The high heterogeneity for arterial perfusion group may be due to different ratio of patients for Child-Pugh Classification or different TACE drugs or different sample number. Due to including only 3 studies for arterial perfusion group, the reason of high heterogeneity cannot be explored.

3.4.3. Survival rate. The half-year survival rates were reported in 6 studies. The relative risk of half-year survival rates from As_2O_3 & TACE group compared with the TACE group was 1.08 (95% CI: 1.02–1.14, $Z = 2.54$, $P = .011$), with no heterogeneity between studies ($I^2 = 0\%$, $P = .825$). A total of 13 studies reported the 1-year survival rates, and the quantitative synthesis was conducted. A higher pooled result was obtained from the As_2O_3 & TACE group compared with the TACE group (RR: 1.36, 95% CI: 1.23–1.50, $Z = 6.21$, $P = .000$), and no evidence of heterogeneity was identified ($I^2 = 1.1\%$, $P = .435$). There were 6 studies providing data on 2-year survival rates, and the relative risk of 2-year survival rates was obtained from the As_2O_3 & TACE group compared with the TACE group (RR: 1.45, 95% CI: 1.20–1.75, $Z = 3.85$, $P = .000$), and no evidence of heterogeneity was identified ($I^2 = 0.0\%$, $P = .588$). Similar relative risk of 3-year survival rates (RR: 1.38, 95% CI: 1.06–1.79, $Z = 2.38$, $P = .017$)

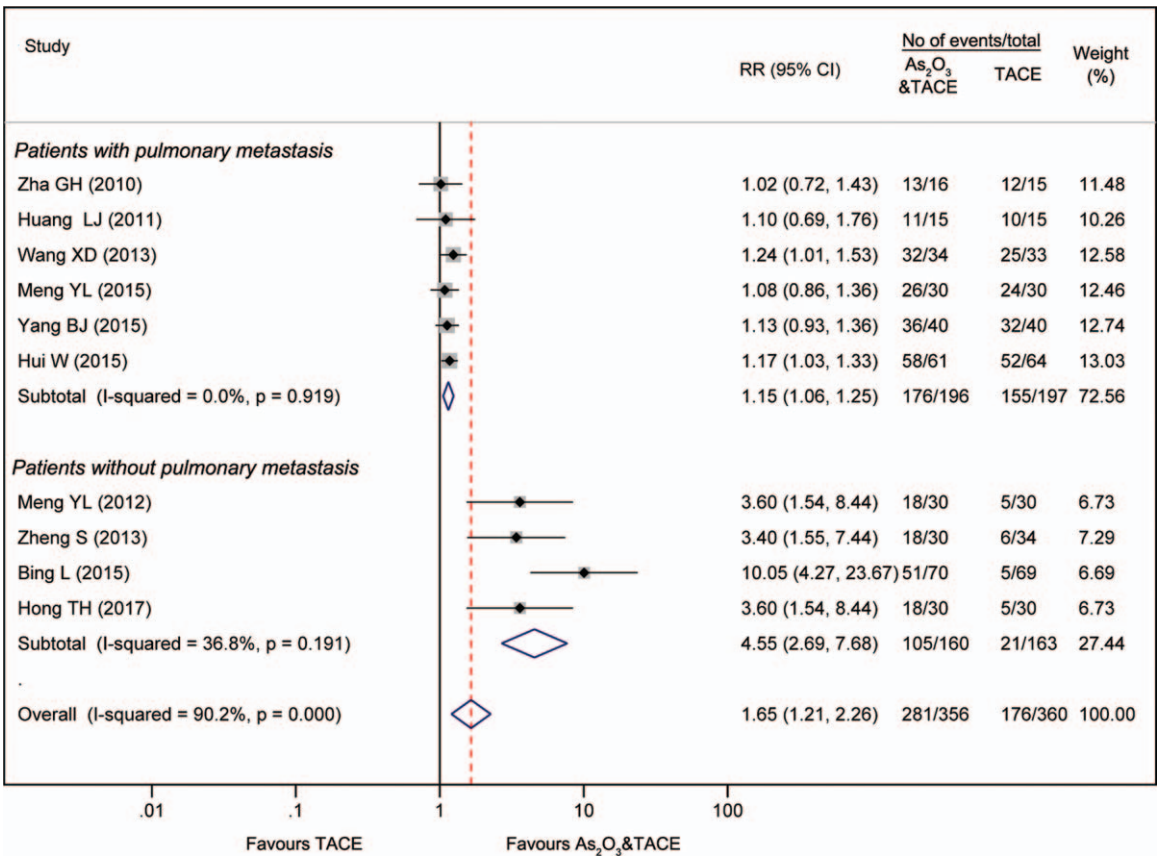

Figure 3. Forest plot of subgroup analysis by patients with or without pulmonary metastasis: clinical benefit rate of intravenous drip As_2O_3 & TACE and alone TACE in treating PHC. PHC = primary hepatic carcinoma, TACE = transarterial chemoembolization.

was obtained from only 3 studies with no heterogeneity (I^2 = 8.8%, P = .334) (Fig. 6).

3.4.4. Life quality. The karnofsky performance score (KPS) was used to evaluate life quality for included patients. A total of 12 studies reported KPS, and the meta-synthesis was conducted using the fixed-effects model. The results for the superior of As_2O_3 & TACE therapy were obtained from both the patients with improvement of KPS scores (RR: 1.31, 95% CI: 1.14–1.50, Z = 3.90, P = .000) with no heterogeneity between studies (P = .552, I^2 = 0.0%) and the patients with maintaining of KPS scores (RR: 1.00, 95% CI: 0.83–1.22, Z = 0.05, P = .963) with no heterogeneity between studies (P = .285, I^2 = 16.2%). Notably, the relative risk of improvement of KPS scores in 2 studies with pulmonary metastasis[26,29] was significantly higher than in other studies without pulmonary metastasis (Fig. 7).

3.4.5. Adverse events. There were 18 studies that clearly described adverse reactions in the As_2O_3 & TACE group and the TACE group. The most common adverse events in the treatment of PHC were leukopenia, thrombopenia, myelosuppression, liver dysfunction, nausea, febrile reactions, ache, and retention of sodium and water. However, some adverse events from these studies were selected reported by quantitative results. We conducted meta-synthesis for these some adverse events according to quantitative synthesis with existing data, and the results were shown in Table 3. Notably, the relative risk of leukopenia was obtained from the As_2O_3 & TACE group compared with the TACE group (RR: 1.44, 95% CI: 1.03–2.02), and the significant difference of retention of sodium and water was obtained from the As_2O_3 & TACE group compared with the TACE group (RR: 16.616, 95% CI: 8.01–34.486). There was no obvious difference in occurrence rate of other adverse events between 2 groups in each study, and no severe syndrome or treatment-related death was reported by all included studies (Table 3).

3.5. Publication bias

We respectively performed the funnel plots of CER, CBR, 1-year survival rates, and improving KPS (Fig. 8), which suggested the possible presence of publication bias due to visually asymmetry. Furthermore, the Egger test and Harbord modified test also suggested significant asymmetry of funnel plots for CBR, CER and improving KPS ($P < .05$), however, the publication bias of 1-year survival rates was not identified using Egger test and Harbord modified test ($P > .05$). Using a "trim" method to make an adjusted estimation of Egger test and Harbord modified test, we found that the publication biases of CBR, CER, and improving KPS were not identified after removing the studies with pulmonary metastasis ($P > .05$) (Table 4).

4. Discussion

4.1. Principal findings

This systematic review and meta-analysis suggest that As_2O_3 & TACE therapy achieves better therapeutic results compared with alone TACE on both short-term effects (CBR and CER) and long-

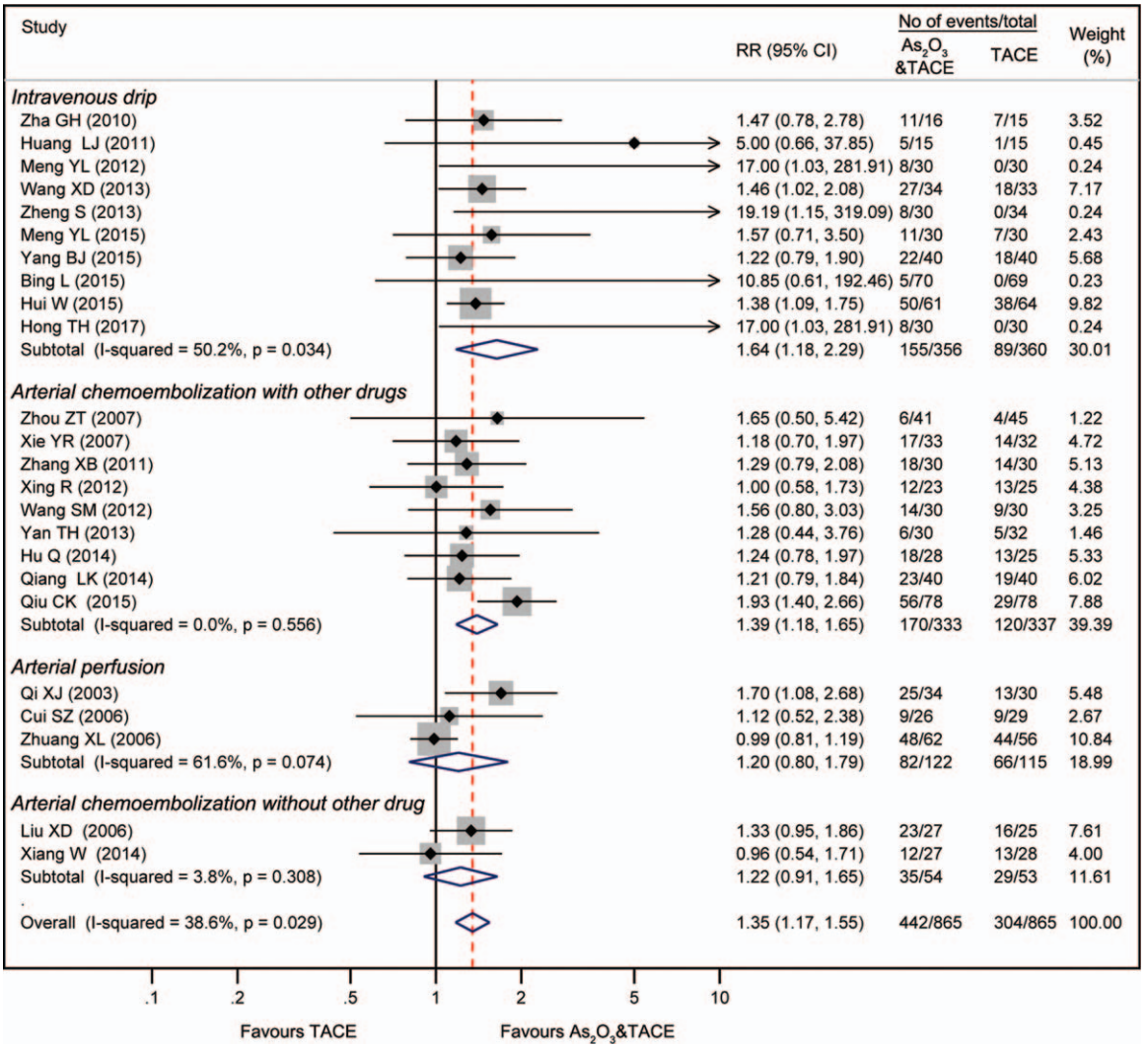

Figure 4. Forest plot of subgroup analysis by intervened methods of As_2O_3: the clinical effective rate of As_2O_3 & TACE and alone TACE in treating PHC. PHC = primary hepatic carcinoma, TACE = transarterial chemoembolization.

term effects (survival rates and life quality). In PHC patients without pulmonary metastasis, the adjuvant As_2O_3 therapy using intravenous drip or arterial chemoembolization with other drugs achieved more effective results for short-term effect than alone TACE, with no difference between 2 administration methods of As_2O_3, however, the other 2 methods using arterial perfusion or arterial chemoembolization without other drugs was not superior to alone TACE. Notably, the intravenous drip of As_2O_3 & TACE was extremely significant superior to alone TACE for short-term effect and long-term effect in PHC patients with pulmonary metastasis. Those observations were robust through different subgroup analyses we performed. Moreover, we found that the relative risk of leucopenia and retention of sodium and water was obviously raised in patients with As_2O_3 & TACE therapy. However, those adverse events were relieved with symptomatic treatments in the included studies, which proved the safety of As_2O_3 for a long-term use.

4.2. Strengths and limitations of study

A contemporaneous and exhaustive search strategy was included in this study, which permitted us to pool data from 1886 subjects in our initial and basic analysis. We also made a contact with all authors in included studies and some excluded studies, so that we were able to acquire some data from the last point of follow-up, and made certain that we had not missed the potentially eligible trials, or embraced data from the exactly same study at 2 different points of follow-up. Furthermore, strengths of this study include accurate and comprehensive quantitative analysis, administering to exploring the reasons of high heterogeneity, and publication bias. Finally, the better administration approach of adjuvant As_2O_3 and the most effective patient for using As_2O_3 & TACE therapy were identified from the included studies.

Despite our efforts to provide an accurate and comprehensive analysis, limitations of our meta-analysis need to be addressed. First, all included studies were conducted in China, because As_2O_3 was only approved for palliative treatment for the patients with unresectable PHC by China Food and Drug Administration. Although we found the authors of included studies came from different cities and provinces of China, the results may still not be generalizable to a wider population all over the world, which may have produced a potential bias of publication. Second, most studies included in this systematic review had a low-moderate methodological quality. Most of the included studies did not

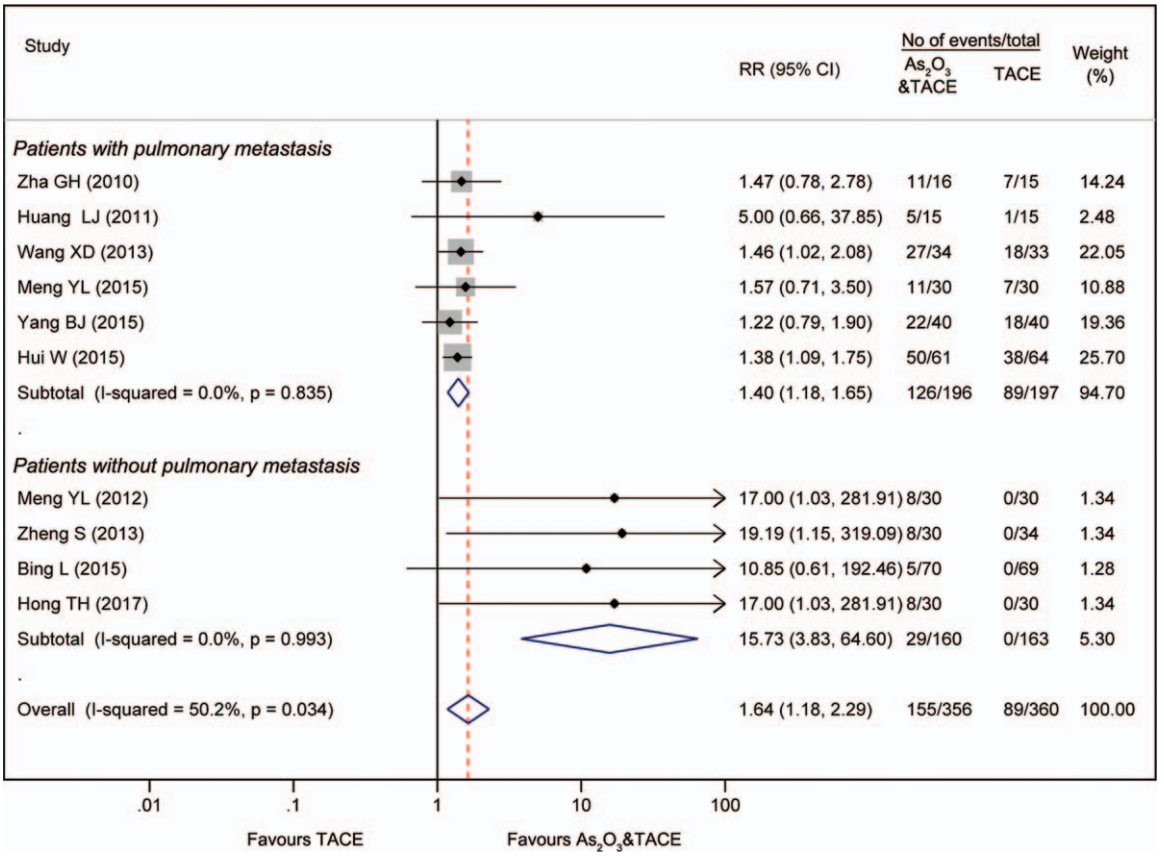

Figure 5. Forest plot of subgroup analysis by patients with or without pulmonary metastasis: the clinical effective rate of intravenous drip As_2O_3 & TACE and alone TACE in treating PHC. PHC = primary hepatic carcinoma, TACE = transarterial chemoembolization.

describe how the random allocation sequence was generated and how the blinding of outcome assessment was performed, which implied that the corresponding risks of bias could not be ruled out. All studies included in this paper used an "A + B versus B" design in which patients were randomized to receive either As_2O_3 & TACE therapy or alone TACE, and there was no rigorous control for the placebo effect. Third, none of the included studies were formally registered with the WHO International Clinical Trials Registry Platform. Therefore, the protocols were not available to confirm that the studies were free of selective reporting. Finally, individual adverse events data were not reported comprehensively and quantitatively by many of the trials we identified, and the sample size in some included studies was small. Thus, we were not able to definitely assess the balance of benefits and harms if As_2O_3 combined with TACE was to be adopted in the general PHC population. Therefore, the results and conclusions in this study should be interpreted with caution due to those limitations of this study and characteristics of the published literature identified, and it will be necessary to carry out high-quality, multicenter studies with large sample sizes that are regularly reported to provide for evidence-based medicine in the future.

4.3. Comparison with other studies

Recent studies demonstrated that the surgical resection for PHC has a positive effect on a minority of patients;[43] however, the majority patients with untreated nonsurgical PHC die from tumor progression (63.2%) and liver failure (31.1%) in a brief period time relatively. Meanwhile, the survival rate, on average, was 3 months, as well as 7.8% for survival rates for 1- year.[3,44] It is much harder for PHC patients to put up with the systemic chemotherapy for their hepatic function can easily get impaired as a consequence of the underlying cirrhosis, and such condition is often accompanied by hypersplenism and peripheral cytopenia.[45] TACE is an alternative approach to intra-arterial chemoinfusion that relies on embolization, and take an apparent effect on allowing the synergistic influence of increased local levels of chemotherapeutic agents and occlusion of the artery which supplies nutrients for a tumor.[46] Lo et al[47] made an assessment for the similar cohort of PHC patients. The study, based on analysis, demonstrated that the survival rates of 1-year for TACE are 57% versus 32% respectively in the regulated team that received symptomatic therapy, and 2-year survival rates of 31% versus 11%, respectively. Therefore, TACE has been discovered to own the clinical therapeutic effect to a significant degree, and at the same time, its therapeutic effect can reduce systemic toxicity across hepatic malignancies, compared with systemic chemotherapy.[48]

TACE is also being combined with systemic therapies, such as sorafenib.[2,3] Sorafenib is currently approved as the only systemic therapy for PHC by American Food and Drug Administration, and inhibits angiogenesis by targeting the vascular endothelial growth factor receptor 2 (VEGFR2) and platelet-derived growth factor receptor (PDGFR) pathway.[49]

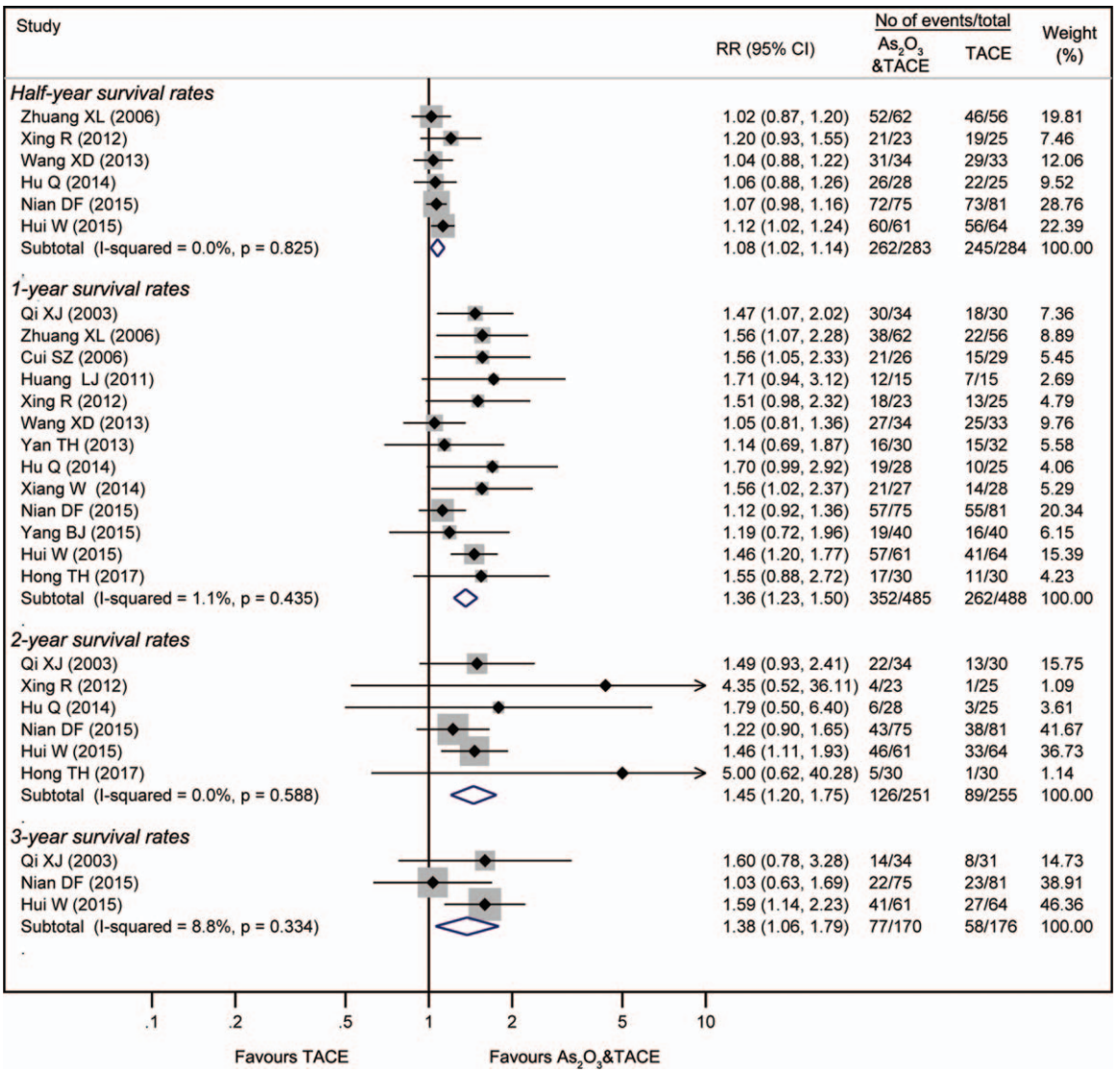

Figure 6. Forest plot on survival rates of As_2O_3 & TACE and alone TACE in treating PHC. PHC = primary hepatic carcinoma, TACE = transarterial chemoembolization.

The exploratory phase II trial of 307 patients randomized tested the efficacy of TACE plus sorafenib in patients with intermediate stage HCC, and demonstrated the CERs for patients in the sorafenib and placebo groups with post-baseline scans were respectively 56% and 41%, and the CBRs were 89% and 76%, respectively.[50] However, our meta-analysis suggests that CER for As_2O_3 & TACE group of 51% versus 35% in alone TACE group, and CBR of 83% and 63%, respectively. Although these data suggested that TACE combined with systemic therapies either sorafenib or As_2O_3 significantly improved similar clinical efficacy in advanced HCC patients, the price of sorafenib is much higher than that of As_2O_3.

A large number of studies in vivo and in vitro have shown As_2O_3 has a strong antitumor activity for hepatic carcinoma in recent years. The possible mechanisms for antitumor effects of As_2O_3 were as follows: induction of tumor cell apoptosis was achieved by regulating expression of apoptotic-related proteins [51]; inhibition of tumor cell proliferation was achieved by regulating expression of cycle related proteins[52]; reduction of tumor angiogenesis was achieved by inhibiting of the vascular endothelial growth factor receptor (VEGFR).[53] However, 2 clinical phase II trial of As_2O_3 therapy in PHC patient demonstrated 1-year survival rate of 30%, CER of 7%, CBR of 76%, and improvement of life quality of 22.5%, which revealed that single-agent As_2O_3 had a less clinically therapeutic effect than alone TACE for PHC patient.[8,54]

Two recent meta-analysis reviews of As_2O_3 combined with TACE studies had suggested this strategy achieved better therapeutic results compared with alone TACE in the treatment of PHC. One of the meta-analysis reviews only reported that As_2O_3 combined with TACE had significant effects in improving CER, decreasing alpha-fetoprotein, increasing 1-year survival rate, and improving life quality of PHC patients, and with some unknown high heterogeneity and possible publication bias.[12] Another meta-analysis review further supported the superiority of As_2O_3 & TACE therapy on increasing CER, CBR, and 1-year

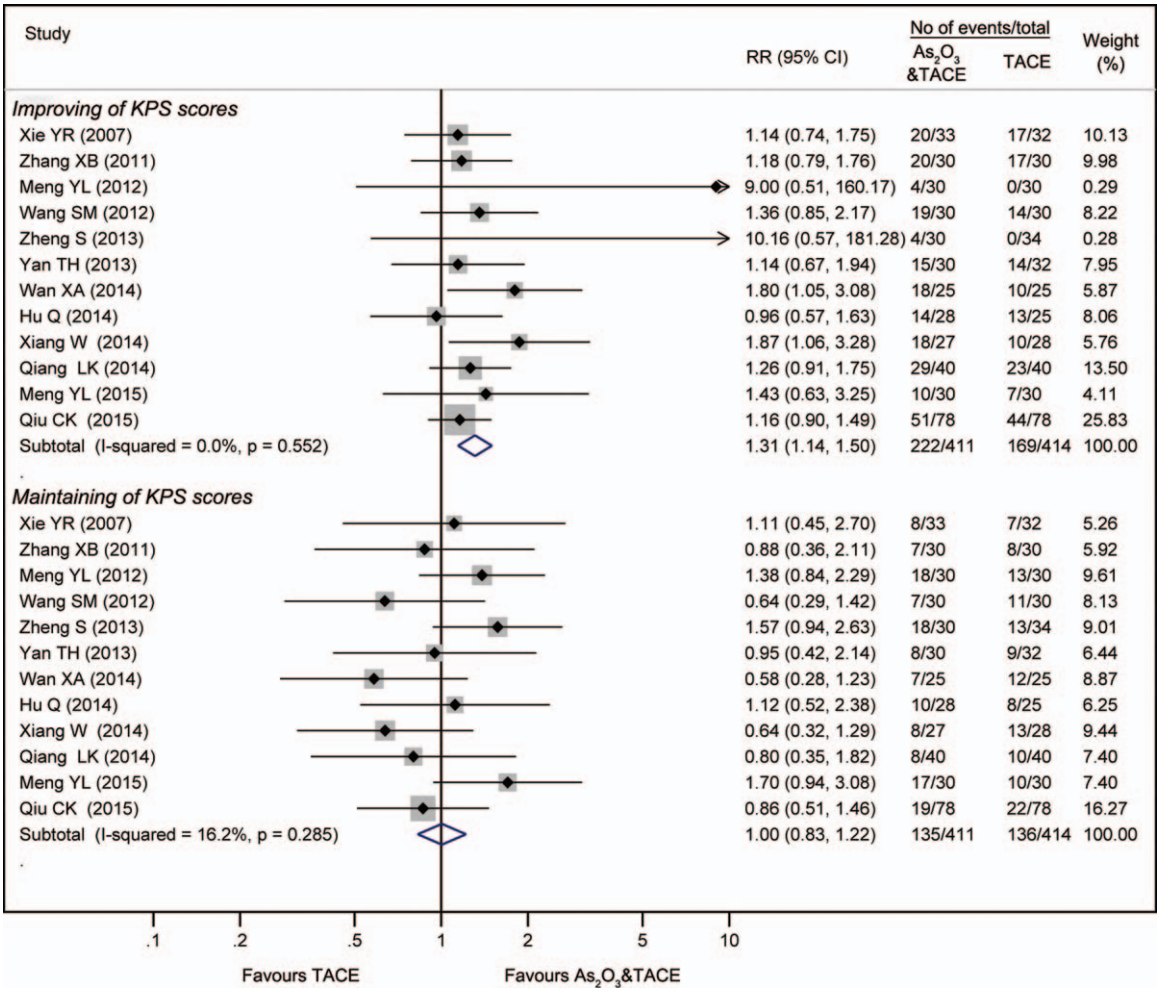

Figure 7. Forest plot on KPS scores of As_2O_3 & TACE and alone TACE in treating PHC. PHC = primary hepatic carcinoma, TACE = transarterial chemoembolization.

Table 3

Meta-analysis for adverse events of As_2O_3 & TACE group compared with TACE group.

Study (reference)	Number of study	Number of events/total		Risk ratio M-H, fixed (95% CI)	Test for overall effect	Test for heterogeneity
		As_2O_3 & TACE	TACE			
Leukopenia[37,42,32,22,33,28,25,24,34]	9	66/287	47/297	1.441 (1.030, 2.016)	Z=2.13, P=.033	P=.650 I^2=0.0%
Thrombopenia[37,42,31,32,33,28,24]	7	43/162	37/174	1.254 (0.840, 1.872)	Z=1.11 P=.269	P=.348 I^2=10.6%
Myelosuppression[41,30,20,21,19]	5	86/170	90/261	0.921 (0.795, 1.067)	Z=1.09 P=.274	P=.710 I^2=0.0%
Liver dysfunction[41,25,24,20,21,34]	6	138/298	137/310	1.054 (0.851, 1.305)	Z=0.48 P=.629	P=.092 I^2=47.2%
Nausea[37,32,41,28,24,30,20,34]	8	114/304	113/309	1.308 (0.868, 1.241)	Z=0.41 P=.685	P=.946 I^2=0.0%
Febrile reactions[32,41,30,20,19]	5	100/211	96/212	1.032 (0.872, 1.223)	Z=0.37 P=.713	P=.976 I^2=0.0%
Ache[41,28,30,20,21,19]	6	115/244	129/286	0.912 (0.795, 1.067)	Z=1.09 P=.274	P=.710 I^2=0.0%
Retention of sodium and water[23,26,29,31,34]	5	108/177	5/187	16.616 (8.006, 34.486)	Z=7.54 P=.000	P=.600 I^2=0.0%

As_2O_3 = arsenic trioxide, CI = confidence intervals, M-H = Mantel-Haenszel, TACE = transarterial chemoembolization.

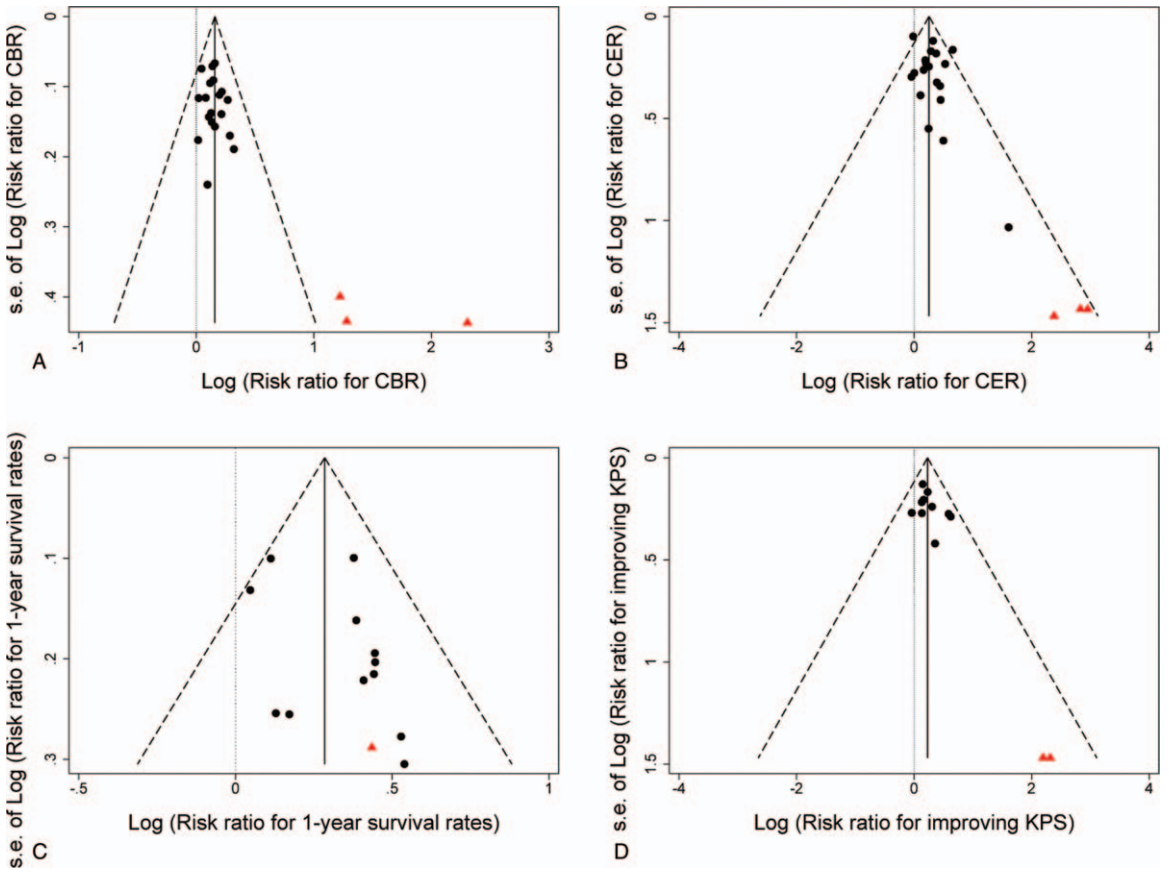

Figure 8. Funnel plot analysis to detect publication bias CBR (A), CER (B), 1-year survival rates (C), and improving KPS (D). Each black circle represents an individual study of patients without pulmonary metastasis; each red triangle represents an individual study of patients with pulmonary metastasis. CBR = clinical benefit rate, CER = clinical effective rate, KPS = karnofsky performance scale.

Table 4

An estimates of publication bias by "trim" method.

Estimates of publication bias	Number of study	Egger test	Harbord modified test
Clinical benefit rate			
All included studies [10,19,20,22–38,40–42]	23	*P* = .000	*P* = .001
Studies without pulmonary metastasis [19,20,22,24,25,27,28,30–38,40–42]	19	*P* = .365	*P* = .571
Clinical effective rate			
All included studies [10,19,20,22–42]	24	*P* = .003	*P* = .004
Studies without pulmonary metastasis [19,20,22,24,25,27,28,30–42]	20	*P* = .171	*P* = .309
1-year survival rates			
All included studies [19,21,23,24,27,28,31–34,37–39]	13	*P* = .123	*P* = .295
Studies without pulmonary metastasis [19,21,24,27,28,31–34,37–39]	12	*P* = .165	*P* = .311
Improving KPS			
All included studies [20,25–27,29,30,32,33,35,40,41]	11	*P* = .012	*P* = .018
Studies without pulmonary metastasis [20,25,27,30,32,33,35,40,41]	9	*P* = .239	*P* = .455

KPS = karnofsky performance scale.

survival rate, however, As_2O_3 & TACE therapy was not superior to alone TACE for improving life quality. Although subgroup analysis was performed in that review, the heterogeneity of each subgroup was still obvious, and without no explanation.[13] In addition, compared with our meta-analysis, the included studies were not exhaustive and in-depth analysis, especially crude and qualitative conclusion of adverse events.

5. Conclusions

These data provide moderate and appropriate quality and evidence that As_2O_3 & TACE therapy achieves better therapeutic results compared with alone TACE on both short-term effect and long-term effect, and both intravenous drip and arterial chemoembolization with other drugs were good adjuvant options for clinical therapy of PHC. Especially, the intravenous drip of As_2O_3 & TACE was extremely significant superior to alone TACE for clinical effect in PHC patients with pulmonary metastasis. As the exactly limited trials operated in Chinese PHC population succeeded to demonstrate a significant profit of As_2O_3 & TACE therapy, these data should not be applied to the exact populations outside of China. Considering that any programmes on account of such the interference will concern about healthy topics and themes. There are of greater confidence in the estimate of influence and more precious information on the benefit of As_2O_3 & TACE therapy before such a tactic can be recommended as a method of treating unresectable PHC. It appears that the advantages of adjuvant As_2O_3 therapy combined with TACE in PHC individuals will outweigh alone TACE therapy, especially in PHC populations with pulmonary metastasis. Nevertheless, there are urgent requirements for the consequences from more researches in various geographical populations to amplify the evidence foundation. On the other hand, there are some multicenter randomized controlled clinical study in progress in China, countries that wish to apply Western medicine combined with Chinese medicine to treat PHC should think about properly randomized designs to implement so as to improve our related knowledge.

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Author contributions

Peng Song, Peng Chen, and Hongyu Li contributed to conception and design. All authors were involved in analysis and interpretation of the data. Peng Song and Yang Hai contributed to systematic literature search and study selection. Longhe Zhao and Wantong Ma contributed to data extraction and risk of bias assessment. Peng Song and Qinjian Xie designed and conducted the statistical analysis. Peng Song and Xin Wang drafted the manuscript. All authors approved the final version.

Conceptualization: Peng Song, Hongyu Li.
Data curation: Peng Song, Yang Hai, Wantong Ma, Longhe Zhao, Hongyu Li.
Software: Peng Song, Wantong Ma, Longhe Zhao, Yingdong Li.
Writing – original draft: Peng Song, Xin Wang.
Writing – review and editing: Peng Song, Xin Wang, Hongyu Li.
Formal analysis: Yang Hai, Wantong Ma, Longhe Zhao, Qinjian Xie, Yang Li, Zhengrong Wu, Yingdong Li, Hongyu Li.
Investigation: Yang Hai, Hongyu Li.
Methodology: Wantong Ma, Longhe Zhao, Qinjian Xie, Yang Li, Zhengrong Wu, Yingdong Li, Hongyu Li.
Visualization: Xin Wang.
Project administration: Hongyu Li.
Supervision: Hongyu Li.

References

[1] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
[2] Habib A, Desai K, Hickey R, et al. Transarterial approaches to primary and secondary hepatic malignancies. Nat Rev Clin Oncol 2015;12:481–9.
[3] Bruix J, Sherman M. American Association for the Study of Liver DManagement of hepatocellular carcinoma: an update. Hepatology 2011;53:1020–2.
[4] Gluer AM, Cocco N, Laurence JM, et al. Systematic review of actual 10-year survival following resection for hepatocellular carcinoma. HPB (Oxford) 2012;14:285–90.
[5] Sacco R, Tapete G, Simonetti N, et al. Transarterial chemoembolization for the treatment of hepatocellular carcinoma: a review. J Hepatocell Carcinoma 2017;4:105–10.
[6] Schwartz M, Roayaie S, Konstadoulakis M. Strategies for the management of hepatocellular carcinoma. Nat Clin Pract Oncol 2007;4:424–32.
[7] Alimoghaddam K. A review of arsenic trioxide and acute promyelocytic leukemia. Int J Hematol Oncol Stem Cell Res 2014;8:44–54.
[8] Lin CC, Hsu C, Hsu CH, et al. Arsenic trioxide in patients with hepatocellular carcinoma: a phase II trial. Invest New Drugs 2007;25: 77–84.
[9] Subbarayan PR, Ardalan B. In the war against solid tumors arsenic trioxide needs partners. J Gastrointest Cancer 2014;45: 363–71.
[10] Liu B, Huang JW, Li Y, et al. Arsenic trioxide transarterial chemoembolization with and without additional intravenous administration of arsenic trioxide in unresectable hepatocellular carcinoma with lung metastasis: a single-blind, randomized trial. J Cancer Res Clin Oncol 2015;141:1103–8.
[11] Chen SJ, Zhou GB, Zhang XW, et al. From an old remedy to a magic bullet: molecular mechanisms underlying the therapeutic effects of arsenic in fighting leukemia. Blood 2011;117:6425–37.
[12] He L, Xu Q, Chen L, et al. A meta-analysis of arsenic trioxide combined with transcatheter arterial chemoembolization for treatment of primary hepatic carcinoma. Evid Based Complement Alternat Med 2016;2016: 3428370.
[13] Lv XH, Wang CH, Xie Y. Arsenic trioxide combined with transarterial chemoembolization for primary liver cancer: a meta-analysis. J Gastroenterol Hepatol 2017;32:1540–7.
[14] Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[15] Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[16] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[17] Harbord RM, Didelez V, Palmer TM, et al. Severity of bias of a simple estimator of the causal odds ratio in Mendelian randomization studies. Stat Med 2013;32:1246–58.
[18] Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.
[19] Ying BJ, Li M. Inhibition effect of arsenic trioxide on liver cancer growth and metastasis. China Pharma 2015;24:109–11.
[20] CK Q, RJ T, ZF W, et al. Study on the clinical effects of arsenic trioxide in the treatment of advanced primary liver cancer by interventional ways. Med Innovat China 2015;12:35–8.
[21] Nian DF, Yan AF, Hou LY, et al. Clinical application of transcatheter arterial chemoembolization combined with arsenic trioxide in the treatment of primary liver cancer. Chin Imagi J Integ Tradit West Med 2015;13:211–3.

[22] Kui GH, Long J, Mei LH, et al. Clinical study of arsenic trioxide combined with TACE in the treatment of middle or advanced hepatocellular carcinoma. Jiangxi Med J 2010;45:534–6.
[23] Hu HT, Yao QJ, Meng YL, et al. Arsenic trioxide intravenous infusion combined with transcatheter arterial chemoembolization for the treatment of hepatocellular carcinoma with pulmonary metastasis: long-term outcome analysis. J Gastroenterol Hepatol 2017;32:295–300.
[24] Huang LJ. The Effects of TCM-based Arsenic Trioxide on VEGF and Clinical Efficacy Evaluation after Transcatheter Arterial Chemoembolization in HCC [Master]. Guangzhou University of Chinese Medicine, Guangzhou, China:2011.
[25] Qian LK. Clinical Observation on Arsenic Trioxide Combined with Transcatheter Arterial Chemoembolization in Treatment of Patients With Primary Liver Cancer [Master]. China Medical University, Shengyang, China:2014.
[26] Meng YL, Hu HT, Li HL, et al. [The clinical therapeutic effects of arsenic trioxide combined with transcatheter arterial chemoembolization in treating primary liver cancer with pulmonary metastases]. Zhonghua Nei Ke Za Zhi 2012;51:971–4.
[27] Hu Q, Wei YM, Guan R, et al. Clinical effect of transcatheter arterial chemoembolization combined with arsenic trioxide in the treatment of primary liver cancer. Modern Oncol 2014;22:2679–81.
[28] Xing R. Randomized Controlled Study of Lipiodol-Arsenic Trioxide Emulsion in the Treatment of Primary Hepatic Carcinoma [Master]. China Medical University, Shengyang, China:2012.
[29] S Z, L L. Clinical observation on arsenic trioxide combined with transcatheter arterial chemoembolization in treatment of patients with primary liver cancer and lung metastasis. Chin J Liver Dis 2013;5:27–30.
[30] Wang SM. Oleum of Brcuea Javanica and As2O3 Used in TACE to Treat PHC: A Clinical Study [Master]. Shandong University of Traditional Chinese Medicine, Jinan, China:2012.
[31] Cui SZ, Wu YB, Wang JK, et al. Clinical research of arsenic trioxide continous regional hepatic arterial infusion in the treatment of primary hepatic carcinoma. J Mod Clin Med Bioeng 2006;12:433–6.
[32] Yan TH, Xu WD, Gu WL, et al. Clinical observation of arsenic trioxide combined with transcatheter arterial chemoembolization treatment of advanced primary liver cancer. Chin J Clin Oncol Rehabil 2013;20:1377–80.
[33] Xian W. The Clinical Efficacy of Lipiodol-Arsenic Trioxide Emulsion in the Treatment of Primary Hepatic Carcinomavia TACE [Master]. Wenzhou Medical University, Wenzhou, China:2014.
[34] Wang H, Liu Y, Wang X, et al. Randomized clinical control study of locoregional therapy combined with arsenic trioxide for the treatment of hepatocellular carcinoma. Cancer 2015;121:2917–25.
[35] Zhang XB, Xie JG, Tang ZM, et al. Clinical study of arsenic trioxide in the treatment of primary hepatic carcinoma by interventional ways. J Diagn Imag Interven Radiol 2011;20:58–60.
[36] Liu XD, Wu WJ, Li HT, et al. The intervention-therapeutic effect of lipiodol-arsenic trioxide emulsion for primary hepatic carcinoma. J Intervent Radiol 2006;15:716–8.
[37] X.D.W. , G.W.C. , H.F.N. , et al. The recent therapeutic efficacy of arsenic trioxide by intravenous drip infusion during TACE perioperative combined with 125I paricle for the treatment of hepatocelluar carcinoma. J Med Imagi 2013;23:799–802.
[38] Qi XJ, Zhao HD, Gao WB, et al. Combined pereutancous arsenic trioxide injection with transcatheter arterial chemoembolization for primary liver cancer. J Chin Oncol 2003;9:147–9.
[39] Zhuang XL, Wu XQ, Wu WY. Efficacy of hepatic artery infusion of arsenic trioxide in treatment of hepatocellular carcinoma. Chin J Cancer Prev Treat 2006;13:1106–7.
[40] Yanli M, Hailiang L, Chenyang G, et al. Arsenic trioxide combined with TACE for the treatment of multiple nodular or diffuse HCC: a clinical study. J Intervent Radiol 2015;24:680–3.
[41] Y.R.X. , Y.F.Z. , X.L.Y. Efficacy of hepatic artery infusion of arsenic trioxide in treatment of middle-late hepatocarcinoma. Zhejiang Clin Med J 2007;9:1161–2.
[42] Zhou ZT, Lin XJ, Cui BK, et al. Clinical study of arsenic trioxide-containing regimen in the treatment of middle or advanced hepatocellular carcinoma by TACE. Chin J Cancer Prev Treat 2007;14:1094–6.
[43] Chan DL, Alzahrani NA, Morris DL, et al. Systematic review of efficacy and outcomes of salvage liver transplantation after primary hepatic resection for hepatocellular carcinoma. J Gastroenterol Hepatol 2014;29:31–41.
[44] Yeung YP, Lo CM, Liu CL, et al. Natural history of untreated nonsurgical hepatocellular carcinoma. Am J Gastroenterol 2005;100:1995–2004.
[45] Le Grazie M, Biagini MR, Tarocchi M, et al. Chemotherapy for hepatocellular carcinoma: the present and the future. World J Hepatol 2017;9:907–20.
[46] Wang N, Lv YZ, Xu AH, et al. Application of lobaplatin in trans-catheter arterial chemoembolization for primary hepatic carcinoma. Asian Pac J Cancer Prev 2014;15:647–50.
[47] Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164–71.
[48] Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359:1734–9.
[49] Bruix J, Raoul JL, Sherman M, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol 2012;57:821–9.
[50] Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: the SPACE trial. J Hepatol 2016;64:1090–8.
[51] Jiang L, Wang L, Chen L, et al. As2O3 induces apoptosis in human hepatocellular carcinoma HepG2 cells through a ROS-mediated mitochondrial pathway and activation of caspases. Int J Clin Exp Med 2015;8:2190–6.
[52] Zhang X, Jia S, Yang S, et al. Arsenic trioxide induces G2/M arrest in hepatocellular carcinoma cells by increasing the tumor suppressor PTEN expression. J Cell Biochem 2012;113:3528–35.
[53] Woo SH, Park MJ, An S, et al. Diarsenic and tetraarsenic oxide inhibit cell cycle progression and bFGF- and VEGF-induced proliferation of human endothelial cells. J Cell Biochem 2005;95:120–30.
[54] Qu FL, Hao XZ, Qin SK, et al. [Multicenter phase II clinical trial of arsenic trioxide injection in the treatment of primary hepatocarcinoma]. Zhonghua Zhong Liu Za Zhi 2011;33:697–701.