Original Article

Transarterial Infusion Chemotherapy With and Without Embolisation in Hepatocellular Carcinoma Patients: A Systematic Review and Meta-Analysis

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Abstract

Introduction: The purpose of this meta-analysis was to compare the efficacy of transarterial chemoembolisation (TACE) and iodised oil infusion chemotherapy without embolisation (TAI) in patients with hepatocellular carcinoma. Materials and Methods: We searched for randomised controlled trials, retrospective cohort studies, and two-arm prospective studies that compared the clinical outcomes in patients who received TACE and TAI treatment. Database search was performed through 14 December 2016. Rates of survival and therapy response were compared using odds ratios (OR) with 95% confidence intervals (CI). Results: Survival rates and therapy response rates were similar between patients who received TACE and TAI treatments (pooled OR: 1.278; 95% CI , 0.783 to 2.086, *P* = 0.327; and pooled OR: 1.502; 95% CI, 0.930 to 2.426, *P* = 0.096, respectively). Conclusion: Our results suggest that treatment intensification by adding embolisation did not increase overall survival and therapy response over TAI in patients with hepatocellular carcinoma.

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Key words: Liver cancer, Liver disease, Transarterial chemoembolisation

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common type of malignant disease worldwide, with an increasing prevalence in industrialised countries.[1] Overall, the prognosis is very poor, and HCC is the second most common cause of death from cancer, with mortality closely matching incidence.[2] Curative therapies, such as liver resection, liver transplantation and percutaneous ablation (percutaneous ethanol injection and radio frequency ablation) are effective and lead to 50% 5-year survival rate.[3] However, these treatments are applicable only to patients with early-stage tumours, who make up only 30% to 40% of patients with HCC,[4] so most HCC patients are suitable for palliative care only. HCC is highly angiogenic and usually uses hepatic artery for blood supply, while the rest of the liver is predominantly supplied by the portal vein.[5] Therefore, arterial obstruction is a valid therapeutic option that can induce ischaemic tumour necrosis. Doyon et al was the first to describe the transarterial embolisation (TAE) in 1974.[6]

The process of TAE hepatic artery embolisation may be preceded by lipiodol administration, but no chemotherapeutic drugs are used. Transarterial chemoembolisation (TACE) procedure is a modification of TAE and includes injection of chemotherapeutic agents mixed with lipiodol into the hepatic artery prior to embolisation. Today, these 2 procedures are widely used to treat unresectable HCC.[3,7,8] TACE is also used for patients awaiting liver transplantation and can slow down tumour progression.[9] Despite the wide use of embolisation therapy for HCC treatment, embolisation is contraindicated in patients with severe liver dysfunction, portal vein thrombosis, and those with cancer in the very advanced stage, because of the high risk of hepatic failure and death.[10] Additionally, embolisation of the tumour-

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feeding artery may create a hypoxic and ischaemic tumour microenvironment. Ischaemia and hypoxia, in turn, may stimulate the expression of vascular endothelial growth factor, leading to neovascularisation, tumour regrowth, and progression.[11] This limitation may minimise the potential survival benefit.[12] An alternative approach designed to achieve higher therapeutic efficacy for patients in poor condition without embolisation is the hepatic arterial infusion therapy (TAI), in which an emulsion of iodised oil and anticancer agents are infused into the hepatic artery without any embolic substances.[13] Several studies comparing the rate of survival associated with TAI and TACE produced conflicting data. Maeda S et al[14] and Ikeda M et al[15] reported that the 2 therapies are comparable. Lu CD et al[16] showed that TAI was associated with improved survival compared to TACE in a subgroup of patients at high risk, while Hatanaka Y et al[17] and Takayasu et al[18] showed the opposite.

Given the unclear benefits of TACE over TAI, we performed the present meta-analysis study. The trials included in our study were randomised controlled trials (RCTs), retrospective cohort studies, and two-arm prospective studies published up until 14 December 2016, that assessed the efficacy of transarterial infusion chemotherapy with and without embolisation for patients with HCC.

Materials and Methods

Search Strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance for systematic reviews of observational and diagnostic studies.[19] We searched the published literature using Medline, Cochrane, and Google Scholar databases with the following keywords combinations: transarterial chemoembolisation or TACE; transarterial infusion chemotherapy or TAI; and hepatocellular carcinoma or HCC. Additionally, we hand-searched references in relevant primary publications to identify other eligible trials. The described searches included original literature published up to 14 December 2016. For this meta-analysis, we included papers that assessed the effectiveness of TACE versus TAI in patients with primary HCC in RCTs, retrospective cohort studies, and two-arm prospective studies. We excluded Reviews, Letters, Comments, Editorials, Case reports, Proceeding, Personal communication, Expert opinions, and studies that did not report a quantitative outcome. Additionally, we excluded studies that analysed patients with extrahepatic metastases, portal vein thrombosis or portal vein obstruction.

Data Extraction

Data was extracted independently by 2 reviewers (YSF and CF). A third reviewer (RL) was consulted in case of disagreements. We extracted data on study population (number, age, and gender of subjects in each group), study design (including treatment protocols, interventions, and tumour characteristics), and the major outcomes.

Quality Assessment

We assessed the study quality using the Cochrane Risk of Bias Tool.[20] For non-randomised studies, we also assessed the quality by using Newcastle-Ottawa quality assessment scale. The quality assessment was performed by 2 independent reviewers (YSF and CF), and a third reviewer (RL) arbitrated on disagreements.

Statistical Analysis

A total of 11 studies were selected for analyses. Primary outcome measures were overall survival rates; disease-free or progression-free survival rates; and survival rates at certain follow-up time (e.g.1-year, 3-year, 5-year survival rates). Secondary outcome measure was the rate of complete or partial response to therapy. Odds ratio (OR) was used as the indicator of effect size; an OR >1 indicates higher survival rate or better response to therapy in patients treated with chemotherapy combined with embolisation compared to those without embolisation. Heterogeneity among the studies was assessed by the Cochran Q and the I^2 statistic. The Q statistic was defined as the weighted sum of the squared deviations of the estimates of all studies; $P < 0.10$ was considered statistically significant for heterogeneity. For the I^2 statistic which indicated the percentage of the observed between-study variability due to heterogeneity, the suggested ranges were as follows: no heterogeneity ($I^2 = 0\%$-25%), moderate heterogeneity ($I^2 = 25\%$-50%), large heterogeneity ($I^2 = 50\%$-75%), and extreme heterogeneity ($I^2 = 75\%$-100%). The random-effect model (DerSimonian-Laird method) was used to generate pooled estimates across studies for each outcome. A two-sided P value <0.05 was considered statistically significant.

Subgroup analysis was performed according to types of study design (i.e., randomised trial, prospective and retrospective studies). Sensitivity analysis was carried out using a leave-one-out approach. To determine whether the method of pooling the data and the choice of anticancer drug influenced the results of our study, we performed additional sensitivity analyses. First, we analysed the data from individual studies using fixed-effect model. Second, we calculated pooled OR using random-effect model and excluded studies that did not use cisplatin in the treatment regimen. Next, we excluded studies that used a combination

of cisplatin and other drugs. We conducted a leave-one-out analysis to assess if any of the studies that used only cisplatin unduly influenced the results. All statistical analyses were performed using the statistical software Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ, USA).

Results

Basic Characteristics of Included Studies

Study selection process is summarised in Figure 1. Our search yielded 219 clinical studies relevant to the topic of the present study. After reviewing the abstracts of the articles and applying exclusion/inclusion criteria, 180 of the 219 studies were excluded, and 39 were left for full-text reviewing. After full-text reviewing, 28 studies were excluded. The major reasons for study exclusion were: 1) study design did not fit our inclusion criteria (n = 23); and 2) study did not report the outcome of interest (n = 5). Figure 1 summarises the reasons for exclusion of the studies from the present analysis. Therefore, after considering inclusion and exclusion criteria, 11 articles were eligible for this review.[14-16,18,21-27]

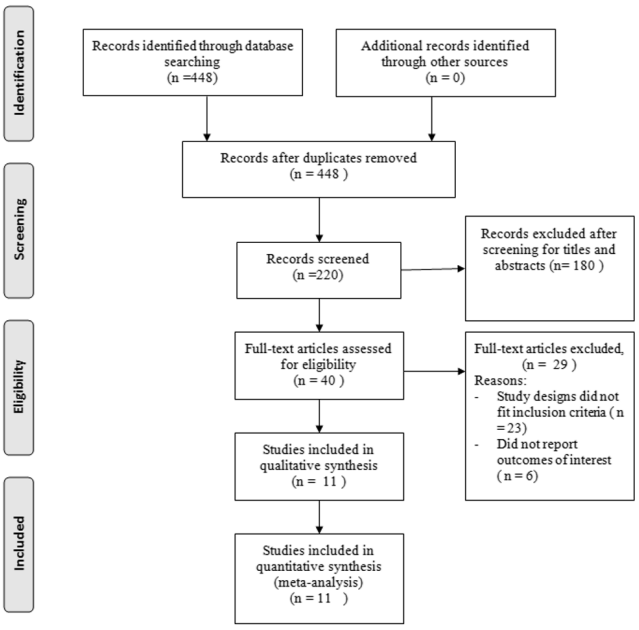

Fig. 1. Flowchart showing the selection of included studies.

Demographic and Clinical Characteristics of Included Studies

A total of 11 studies were included in the systematic review and meta-analysis. Three of the studies recruited participants from RCTs. A number of recruited participants ranged from 37 to 365, except for one prospective observational study that included 11,030 patients. In 4 studies, cisplatin was used as a single chemotherapy drug. The mean and median patients' age ranged from 41 to 74 years and the proportion of male patients ranged from 64.8% to 96.4%. Other clinical characteristics, including Child-Pugh Class, the presence of multiple tumours, type or stage of HCC, and hepatitis markers are summarised in Table 1.

The overall survival rates varied across studies, ranging from 15% to 68.1%. Nine studies reported complete or partial response to therapy that ranged from 18.9% to 80% (Table 2). Outcomes from included studies are summarised in Table 2.

Outcome Measures

We analysed 2 RCTs, 3 prospective and 4 retrospective studies to assess the effect of TACE and TAI treatments on the overall survival rate. There was no significant heterogeneity among the studies (Q = 0.2, P = 0.654, I^2 = 0% for RCTs; Q = 2.5, P = 0.288, I^2 = 19.7% for prospective studies; Q = 2.7, P = 0.433, I^2 = 0% for retrospective studies). The pooled OR was 0.884 (95% CI, 0.513 to 1.522, P = 0.859) for RCT, 1.864 (95% CI, 1.656 to 2.097, P <0.001) for prospective studies and 1.108 (95% CI, 0.802 to 1.530, P = 0.535) for retrospective studies. The overall analyses revealed that there was no significant difference in the survival rate in patients who underwent TACE or TAI treatments (pooled OR: 1.278; 95% CI, 0.783 to 2.086, P = 0.327) (Fig. 2A).

There was moderate to extreme heterogeneity among the studies in the response to treatment outcome (Q = 5.1, P = 0.077, I^2 = 61.1% for RCTs; Q = 9.0, P = 0.003, I^2 = 88.8% for prospective studies; Q = 3.3, P = 0.188, I^2 = 40.1% for retrospective studies). The overall analyses revealed that there was no significant improvement in the rate of treatment response in patients who underwent TACE versus TAI therapy regardless of the study design (pooled OR: 1.369; 95% CI, 0.627 to 2.989, P = 0.431 for RCTs; pooled OR: 1.154; 95% CI, 0.403 to 3.309, P = 0.789 for prospective studies; pooled OR: 1.864; 95% CI, 0.886 to 3.919, P = 0.101 for retrospective studies). The pooled results showed similar estimates as those stratified by study design (pooled OR: 1.502; 95% CI, 0.930 to 2.426, P = 0.096) (Fig. 2B).

Quality Assessment

The quality assessment of the studies included for this meta-analysis was performed using the Cochrane Risk of Bias Tool (Fig. 3). The majority of the included studies had performance and detection bias. In addition, selection bias was present in all the studies except the Shi et al,[27] Okusaka et al[24] and Lu et al[16] trials. For non-randomised studies, we also assessed the quality by using the Newcastle-Ottawa quality assessment scale (Table 3). All studies had low risk in the

Table 1. Summary of Basic Characteristics of Studies Selected for Meta-Analysis

Study Name	Study Design	Groups	Iodised Oil Used	Embolising Agent	Number of Patients	Anticancer Agents	Mean Age (Years)	Male (%)	Child-Pugh Class	Multiple Tumours (%)	Type/Stage of HCC	Mean Follow-up Time
Shi (2016)	Retrospective	TACE	Yes	Yes	95	Epirubicin, mitomycin	Median: 56.7	87%	A: 96% B: 4%		Within the Milan criteria	44.2 months
		TAI	Yes	No	95		Median: 56.6	87%	A: 108 (86%) B: 17 (14%)			40.7 months
Nishikawa (2014)	Retrospective	TACE	Yes	Gelatin sponge	145	Epirubicin, mitomycin	72.5	64.8%	A: 69% B: 31%	≤5 tumours: 78.6%	BCLC stage B	1.8 years*
		TAI	Yes	None	81	Epirubicin, mitomycin	70.3	70.4%	A: 56.8% B: 43.2%	≤5 tumours: 71.6%		2 years*
Shi (2012)	Single-blind RCT	3-drug TACE	Yes	Gelatin sponge	122	Lobaplatin, epirubicin, and mitomycin C	≤50 y: 63.1% >50 y: 36.9%	94.3%	A: 57.4%	60%	BCLC stage B: 67.2% BCLC stage C: 32.8%	12 months
		3-drug TAI	Yes	None	121	Lobaplatin, epirubicin, and mitomycin C	≤50 y: 56.2% >50 y: 43.8%	93.4%	A: 52%	58%	BCLC stage B: 66.1% BCLC stage C: 33.9%	
		Single-drug TACE	Yes	Gelatin sponge	122	Epirubicin	≤50 y: 59% >50 y: 41%	89.3%	A: 56.6%	57%	BCLC stage B: 63.1% BCLC stage C: 36.9%	
Imai (2012)	Retrospective	TACE	Yes	Gelatin sponge	122	Miriplatin	Median: 72	65%		83.3%	Stage I: 9.3% Stage II: 46.3% Stage III: 39.5% Stage IVA: 4.9%	2.2 months*
		TAI	Yes	None	40	Miriplatin	Median: 74	75%				2.1 months*
Takayasu (2010)	Prospective	TACE	Yes	Gelatin sponge	8507	Doxorubicin, epirubicin, analog of doxorubicin, mitomycin C, cisplatin, or zinostatin stimalamer	<60 y: 22% ≥60 y: 78%	72%		57%	TNM stage I: 12% TNM stage II: 39% TNM stage III: 40% TNM stage IV: 9%	1.39 years*
		TAI	Yes	None	2523		<60 y: 24% ≥60 : 76%	73%		57%	TNM stage I: 13% TNM stage II: 34% TNM stage III: 37% TNM stage IV: 15%	0.95 years*

BCLC: Barcelona Clinic Liver Cancer; LPS: Lipiodol Cisplatin suspension; RCT: Randomised controlled trials; HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolisation; TAE: Transarterial embolisation; TAI: Transarterial infusion; TNM: Classifications of Malignant Tumours; NA: Not available

*Data presented as median.

Table 1. Summary of Basic Characteristics of Studies Selected for Meta-Analysis (Cont'd)

Study Name	Study Design	Groups	Iodised Oil Used	Embolising Agent	Number of Patients	Anticancer Agents	Mean Age (Years)	Male (%)	Child-Pugh Class	Multiple Tumours (%)	Type/Stage of HCC	Mean Follow-up Time
Kawaoka (2009)	Retrospective	TACE	Yes	Gelatin sponge	62	Cisplatin	Median: 73	70%	A: 72.1% B: 27.9% C: 27.9%	59.8%	TNM stage I: 8.4% TNM stage II: 38.3% TNM stage III: 49.5% TNM stage IV: 3.7%	13 months
		TAI	Yes	None	45							
Okusaka (2009)	Open-label RCT	TACE	Yes	Gelatin sponge	79	Zinostatin stimalamer (SMANCS)	Median: 65	77.2%		83.5%	Stage I: 2.5% Stage II: 22.8% Stage III: 35.4% Stage IVA: 39.2%	2 years
		TAI	Yes	None	82		Median: 67	85.4%		86.6%	Stage I: 4.9% Stage II: 20.7% Stage III: 30.5% Stage IVA:43.9%	
Ikeda (2004)	Prospective	TACE	Yes	Gelatin sponge	74	Cisplatin	Median: 63	81%	A: 55% B & C: 45%	65%	Okuda stage I: 70% Okuda stage II: 30%	2.8 years*
		TAI	Yes	None	94		Median: 64	66%	A: 48% B & C: 52%	56%	Okuda stage I: 60% Okuda stage II: 40%	2.5 years*
Maeda (2003)	Retrospective	LPS group	Yes	Gelatin sponge	143	Cisplatin	63.8	66.4%	A: 33.6% B: 35% C: 31.5%		TNM stage I: 12.6% TNM stage II: 31.5% TNM stage III: 27.3% TNM stage IV: 28.7%	
		LPS/TAE group	yes	None	96		62.4	78.1%	A: 49% B: 29.2% C: 21.9%		TNM stage I: 5.2% TNM stage II: 22.9% TNM stage III: 38.5% TNM stage IV: 33.3%	

BCLC: Barcelona Clinic Liver Cancer; LPS: Lipiodol Cisplatin suspension; RCT: Randomised controlled trials; HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolisation; TAE: Transarterial embolisation; TAI: Transarterial infusion; TNM: Classifications of Malignant Tumours; NA: Not available

*Data presented as median.

Table 1. Summary of Basic Characteristics of Studies Selected for Meta-Analysis (Cont'd)

Study Name	Study Design	Groups	Iodised Oil Used	Embolising Agent	Number of Patients	Anticancer Agents	Mean Age (Years)	Male (%)	Child-Pugh Class	Multiple Tumours (%)	Type/Stage of HCC	Mean Follow-up Time
Sumie (2003)	Prospective	TACE	Yes	Only lipiodol	21	Epirubicin	Median: 67	76%	A: 61.9% B: 38.1% C: 0%		TNM stage II – III: 42.9% TNM stage IV: 57.1%	
		TAI	No	None	16	Cisplatin	Median: 66.5	75%	A: 43.8% B: 56.3% C: 0%		TNM stage II – III: 37.5% TNM stage IV: 62.5%	
Lu (1994)	RCT	TACE	Yes	Gelatin sponge	24	Cisplatin, adriamycin, mitomycin	41.4	95.8%	A: 16.7% B: 54.2% C: 29.2%			
		TAI	Yes	None	28		46.3	96.4%	A: 10.7% B: 64.3% C: 25%			

BCLC: Barcelona Clinic Liver Cancer; LPS: Lipiodol Cisplatin suspension; RCT: Randomised controlled trials; HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolisation; TAE: Transarterial embolisation; TAI: Transarterial infusion; TNM: Classifications of Malignant Tumours; NA: Not available

*Data presented as median.

Table 2. Summary of Outcomes for Each Individual Study

Study Name	Groups	No. of Patients	Overall Survival	Complete or Partial Response to Therapy
Shi (2016)	TACE	95	62%	NA
	TAI	95	59%	NA
Nishikawa (2014)	TACE	145	32.7%	80%
	TAI	81	26%	66.7%
Shi (2012)	3-drug TACE	122	NA	45.9%
	3-drug TAI	121	NA	29.7%
	Single-drug TACE	122	NA	18.9%
Imai (2012)	TACE	122	NA	58%
	TAI	40	NA	33%
Takayasu (2010)	TACE	8507	25%	NA
	TAI	2523	15%	NA
Kawaoka (2009)	TACE	62	24%	NA
	TAI	45	16%	NA
Okusaka (2009)	TACE	79	48.2%	46.8%
	TAI	82	49.6%	32.9%
Ikeda (2004)	TACE	74	25%	73%
	TAI	94	18.3%	51%
Maeda (2003)	TACE	143	29.6%	57.4%
	TAI	96	24.2%	62.5%
Sumie (2003)	TACE	21	28.6%	23.8%
	TAI	16	37.4%	56.3%
Lu (1994)	TACE	24	60%	54.2%
	TAI	28	68.1%	71.4%

NA: Not available; TACE: Transarterial chemoembolisation; TAI: Transarterial infusion

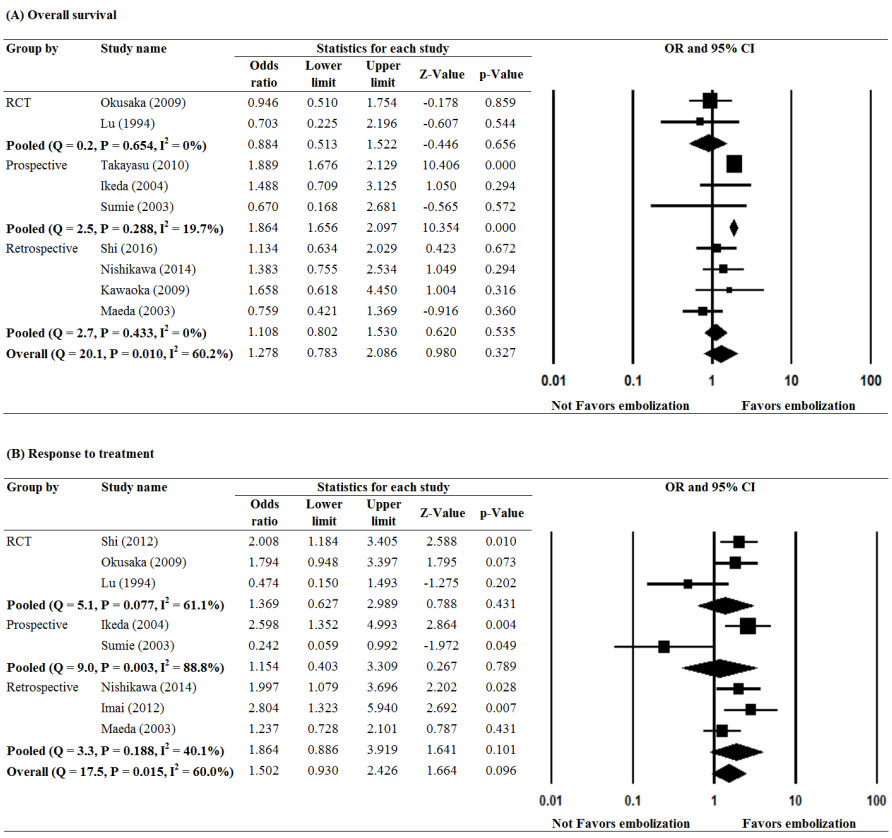

Fig. 2. Forest plot comparing treatment effect of transarterial lipiodol infusion chemotherapy with embolisation on (A) overall survival and (B) response to treatment.

Table 3. Quality Ratings for Included Non-Randomised Studies on the Basis of Newcastle-Ottawa Quality Assessment Scale

	Selection				Comparability	Outcome			
	Representative of Exposed Cohort	Selections of Non-Exposed Cohort	Assessment of Exposure	Absence of Outcome at Start of Study	Control for Age/Gender or Clinical Characteristics	Assessment of Outcome	Follow-up Period >1 Year	Adequacy of Follow-up	Total Score
Shi (2016)	1	1	1	1	2	1	1	1	9
Nishikawa (2014)	1	1	1	1	2	1	1	1	9
Imai (2012)	1	1	1	1	1	1	1	1	8
Takayasu (2010)	1	1	1	1	2	1	1	1	9
Kawaoka (2009)	1	1	1	1	2	1	1	1	9
Ikeda (2004)	1	1	1	1	2	1	1	1	9
Maeda (2003)	1	1	1	1	0	1	1	1	7
Sumie (2003)	1	1	1	1	0	1	1	1	7

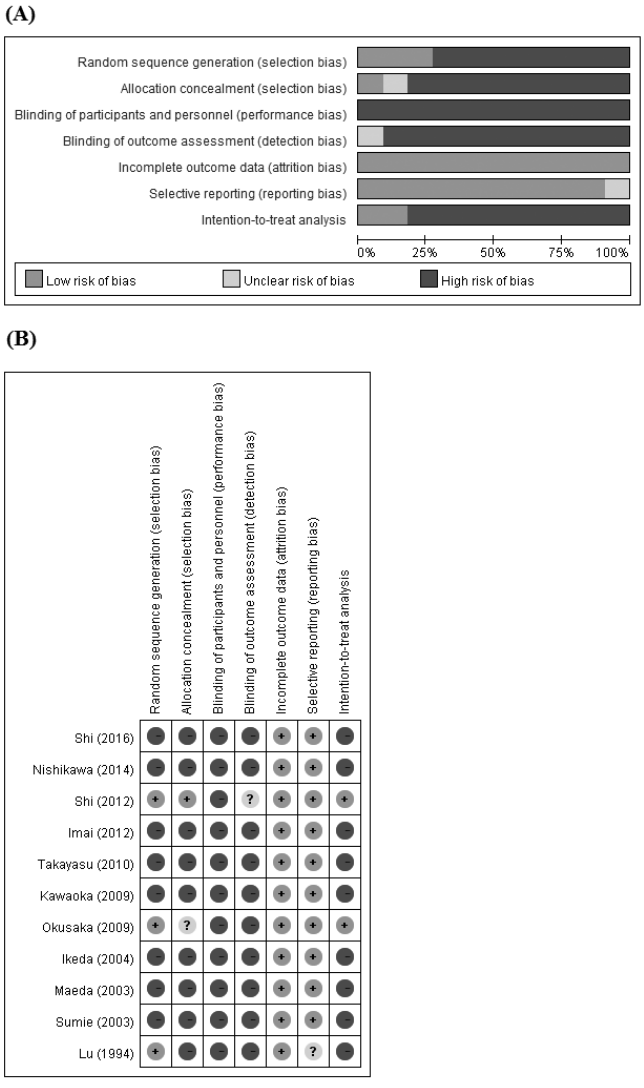

Fig. 3. Quality assessments results.

selection of study population, exposure ascertainment, and outcome measurement and follow-ups. Only 2 studies[14,22] did not perform statistical analyses taking into account demographic or clinical characteristics.

Sensitivity Analyses

Sensitivity analyses were performed using the leave-one-out approach. The sensitivity analysis was not performed for the overall survival outcome since only 2 studies were analysed. The Lu et al[16] trial had a significant impact on the response to treatment outcome. The removal of this study from the analyses led to a significant increase in the OR level (pooled OR: 1.918; 95% CI, 1.277 to 2.882, $P = 0.002$) (Fig. 4).

We analysed if the choice of anticancer drugs used for the treatment had any impact on the pooled results. Exclusion of studies using non-cisplatin chemotherapeutic agents did not have a significant treatment effect on the overall survival rate for patients treated with the combination treatment regimen (pooled OR: 0.995; 95% CI, 0.682 to 1.452, $P = 0.981$). Similar results were obtained when we excluded studies using either non-cisplatin agents or cisplatin combined with other drugs (pooled OR: 1.125; 95% CI = 0.675 to 1.875, $P = 0.651$). Leave-one-out sensitivity analyses were also performed for studies that used cisplatin as a single therapeutic agent. Sensitivity analyses results are summarised in Table 4.

Discussion

TACE is an established treatment modality that was shown to improve survival in HCC patients in 2 RCTs[28, 29] and 3 meta-analyses of randomised trials.[4,30,31] TACE, however, is not recommended for patients with poor liver function and advanced stage of cancer. To prevent post-therapeutic

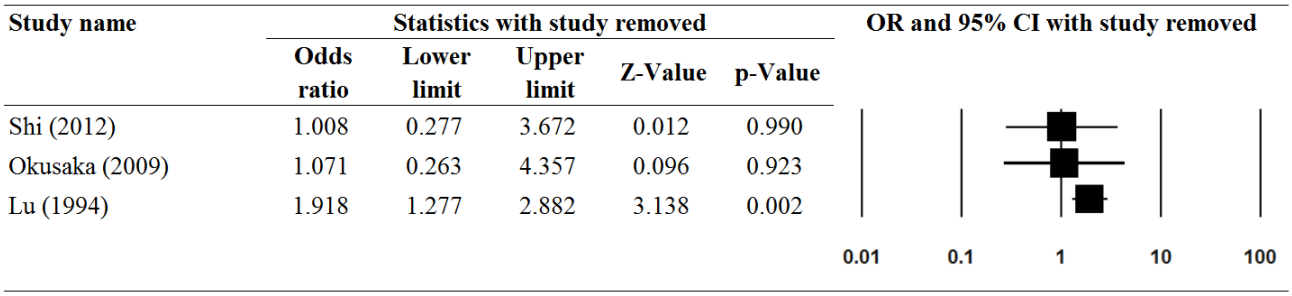

Fig. 4. Sensitivity analysis using leave-one-out approach on the treatment effect of transarterial lipiodol infusion chemotherapy with embolisation on response to treatment in RCTs.

Table 4. Sensitivity Analysis for Treatment Effect of Transarterial Lipiodol Infusion Chemotherapy with Embolisation on Overall Survival

	No. of Studies	Statistics with Studies Removed		
		OR	(5% CI)	*P* Value
Fixed-effect model	9	1.706	(1.531, 1.901)	<0.001
Excluding studies with drugs without cisplatin*	5	0.995	(0.682, 1.452)	0.981
Excluding studies with cisplatin combined with other drugs*	3	1.125	(0.675, 1.875)	0.651
Studies with chemotherapy with cisplatin only*†				
Excluding Kawaoka (2009)	2	1.022	(0.531, 1.967)	0.948
Excluding Ikeda (2004)	2	1.011	(0.483, 2.112)	0.978
Excluding Maeda (2003)	2	1.547	(0.855, 2.800)	0.149

*Random-effect model was performed.
†Sensitivity analysis using leave-one-out approach was performed.

hepatic failure and prolong survival in these patients, infusion therapy of an emulsion of iodised oil and an anticancer agent without gelatin sponge particles was developed. A number of studies were conducted in order to compare the clinical outcomes between TACE and TAI in HCC patients. Specifically, Okusaka et al[24] compared the clinical outcomes for HCC patients treated with TACE using zinostatin stimalamer and those treated with TAI using zinostatin stimalamer in RCT. This study reported that embolisation did not improve survival over TAI with zinostatin stimalamer. Another study reported that TACE using cisplatin suspended in lipiodol had a higher treatment efficacy than TAI using cisplatin suspended in lipiodol.[15] However, TACE did not significantly improve the survival of patients with HCC in the retrospective comparative analysis.[15] Therefore, these comparative studies produced inconsistent data regarding the superiority of either TAI or TACE in the treatment of HCC.

In this systematic review, we evaluated all published RCTs, retrospective cohort studies, and two-arm prospective studies that compared the clinical outcomes in patients who received TAI and TACE treatments in order to provide a more comprehensive understanding of the available data. Our analyses showed no significant difference in the overall survival and treatment response between patients who received TACE or TAI therapy. To further determine if any of the therapies would lead to a better outcome, subgroup analyses of treatment response outcome were performed and results were similar to those from pooled analysis. We did observe that TACE treatment was associated with significant improvement of survival in prospective cohort studies, but not in RCT or retrospective cohort studies. The most common side effects included fever and anaemia. Other uncommon side effects were renal failure,[27] hepatic failure,[16,21] upper gastrointestinal bleeding [16,21,23] and liver abscess.[21,22] Overall, the analysed studies did not report severe adverse events associated with the interventions, except for 3 cases of treatment-related mortality reported in the embolisation group.[15,27]

Numerous anticancer agents have been used to treat HCC, including epirubicin hydrochloride, mitomycin C, doxorubicin hydrochloride (ADM), cisplatin and zinostatin stimalamer. In our study, the sensitivity analyses showed that different choices of chemotherapy agents or their combinations did not affect the overall findings. With our growing understanding of the underlying molecular mechanism of HCC initiation and progression and the emergence of targeted therapeutics, treatments for advanced liver cancer will almost certainly be evolving in the coming years.

The results of this meta-analysis are subject to several limitations. First, differences in the baseline severity of illness in the population may lead to treatment group

assignment bias. Furthermore, selection criteria used to identify the candidates for TACE and TAI procedures vary dramatically between clinical centres. Second, variations in the chemoembolisation procedures (gelatin sponge size, for example) and their duration are also likely to influence the outcomes. In the study by Sumie et al,[23] gelatin sponge was not used for embolisation, and the only occlusive agent used in the TACE group was Lipiodol. The study by Mabed et al[32] used intravenous doxorubicin and did not use Lipiodol, and therefore was excluded from our analysis. Our study did not address several confounding factors, such as severity of the underlying liver disease, and number and size of the tumour lesions, which could also affect the accuracy of the results. We did, however, exclude patients with portal vein metastasis and/or thrombosis from our analysis (subgroup type-2 in Lu CD et al[16] study). Due to the nature of the disease and treatment, the included studies could not be performed blinded; therefore, the results may be skewed by detection and performance bias as well. Additionally, sample sizes of individual studies differed significantly. In the Takayasu et al study,[18] the sample size was much larger compared to other studies analysed. This difference in the sample size can significantly distort our analysis and lead to high risk of bias, especially in prospective cohort subgroup. To overcome the described limitations, future prospective studies with well balanced patients' groups are warranted.

Our meta-analysis demonstrated that HCC patients in the TAI and TACE groups had a similar prognosis, with neither treatment being favoured with a statistically significant increase in treatment response or overall survival over the other. Further studies with better controlled trials and well balanced patient groups are warranted. However, per our current results, both TACE and TAI can be equally valid therapeutic options for treating HCC.

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