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Transcatheter Arterial Chemoembolization Plus ^{131}I-Labelled Metuximab versus Transcatheter Arterial Chemoembolization Alone in Intermediate/Advanced Stage Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

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Objective: The aim of the study was to compare transcatheter arterial chemoembolization (TACE) plus ^{131}I-labelled metuximab with TACE alone for hepatocellular carcinoma (HCC).

Materials and Methods: A comprehensive search was conducted in PubMed, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Chinese BioMedical Literature Database with published date from the earliest to February 29th, 2016. No language restrictions were applied, but only prospective randomized controlled trials (RCTs) or non-RCTs were eligible for a full-text review. The primary outcome was the overall survival (OS) and effective rate (the rate of partial atrophy or complete clearance of the tumor lesion). The odds ratios (ORs) were combined using either the fixed-effects model or random-effects model.

Results: Eight trials (3 RCTs and 5 non-RCTs) were included, involving a total of 1121 patients. Patients receiving combined therapy of TACE plus ^{131}I-labelled metuximab showed significant improvement in effective rate {OR = 4.00, (95% confidence interval [CI]: 2.40–6.66), $p < 0.001$}, 1-year OS (OR = 2.03 [95% CI: 1.55–2.67], $p < 0.001$) and 2-year OS (OR = 2.57 [95% CI: 1.41–4.66], $p = 0.002$].

Conclusion: TACE plus ^{131}I-labelled metuximab is more beneficial for treating advanced HCCs than TACE alone in terms of tumor response and OS. Large, multi-center, and blinded randomized trials are required to confirm these findings.

Keywords: *^{131}I-labelled metuximab; Hepatocellular carcinoma; Meta-analysis; Transcatheter arterial chemoembolization; Radioimmunotherapy*

INTRODUCTION

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related deaths worldwide, with increasing incidence over the past years (1). Liver transplantation and partial resection are still the curative treatments for HCC patients. Although the improvements in surgical technology has resulted in higher numbers of resectable HCC tumor, the "resectability" has remained as low as 25 to 40% (2). Thus, for advanced HCC patients staged B to C under the Barcelona Clinic Liver Cancer system, treatment options such as surgical resection, liver transplantation, and percutaneous ablation are not suggested (1, 2). Transarterial chemoembolization (TACE) is recommended as the most effective treatment in advanced HCC patients when compared with symptomatic treatment, which improves survival in both cirrhotic or non-cirrhotic patients

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(3). Although the TACE protocol has been updated several times (4), the optimal strategy, best anti-tumor agent and adjuvant treatments on TACE are still improving (5-6).

Since the 1980s, radioimmunotherapy (RIT), a combination of antigen-targeting and localized radiotherapy (RT), has attracted interest for clinical application (7). Duan et al. (8) reported that RIT with ^{131}I-labeled anti-ENG monoclonal antibody (mAb) resulted in significant suppression on HCC hyperplasia and remarkably decreased tumor volume in animal models. Fujiwara et al. (9) also revealed that RIT with ^{90}Y-labeled anti-ROBO1 mAb is a promising treatment for ROBO1-positive HCC in mice. In 2005, ^{131}I-metuximab (Licartin, Chengdu Hoist Hitech Co. Ltd., Chengdu, China; and the Fourth Military Medical University, Xi'an, China), a ^{131}I-labeled murine mAb derived from HAb18G/CD147, was approved for the clinical treatment of HCC by the China State Food and Drug Administration (Registration No. S20050039) (10). Initially, ^{131}I-metuximab monotherapy has reported to be effective in preventing the tumor recurrence after orthotopic liver transplantation (11), but conversely, He et al. (12) and Wang et al. (13) reported that ^{131}I-metuximab treatment showed no significant difference in 1-year overall survival (OS). ^{131}I-metuximab has been used as an adjuvant therapy to TACE in some of the clinical studies, however, these trials were usually small and their results were inconsistent.

Thus, we conducted this meta-analysis to evaluate the efficacy and safety of TACE plus ^{131}I-metuximab compared with TACE alone in advanced HCC patients.

MATERIALS AND METHODS

The process of the meta-analysis was carried out according to the Cochrane Collaboration recommendations (14). The analysis results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (15).

Search Strategy

A comprehensive search of the PubMed, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Chinese BioMedical Literature Database was conducted with following: "(((((transcatheter arterial chemoembolization) OR chemoembolization) OR TACE) OR TAE) AND ((131I metuximab) OR licartin)) AND (((hepatocellular carcinoma) OR HCC) OR liver tumor)". The search for clinical trials was based on Cochrane's recommendation (14). The search included literature published until February 29th, 2016 with no lower date limit. No language restrictions were applied, but only prospective randomized controlled trials (RCTs) or non-RCTs were eligible for a full-text review.

Selection

Process and Data Abstraction

Two investigators independently performed the eligibility evaluation, data extraction, and quality assessment. For the study selection, article titles and abstracts were screened first, then full-text were obtained to assess study eligibility. Each study was evaluated and classified. Any disagreement among reviewers was settled by discussion. Data extraction was independently conducted by using standardized methods, with any disagreements settled by discussion of the relevant study data and adjudicated by an experienced reviewer. Data extracted from each study were as follows: publication details (name of the first author, year of publication and country), and study characteristics (range for follow-up, hepatitis status, OS rate).

Including and Excluding Criteria

Publications with the following criteria were accepted: 1) unresectable or advanced HCC diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI); 2) prospective RCTs or non-RCTs; 3) published trials that included a treatment group receiving TACE plus ^{131}I-metuximab and a control group receiving TACE alone; and 4) reported survival rate or tumor response rate on at least 1-year follow-up, with clearly described criteria for tumor response. Abstracts, letters, case reports, and studies without control groups were excluded. The most recent and/or largest publication among multiple publications from treatment centers was included.

Data Extraction

Data extraction was performed using a standardized form, collecting information on the study design, baseline characteristics, treatments and outcomes. End-points were considered as survival, tumor response, and adverse events. Survival data were collected either from the Table reported in the trials or derived from the survival curves. Tumor response was evaluated by the change in tumor size on abdominal CT and MRI before and after treatment. Tumor response rates were recorded according to the modified

Response Evaluation Criteria in Solid Tumors (RECIST) guidelines for HCC (16). Complete response (CR) is defined as complete clearance of the lesion after treatment; partial response (PR) is defined as ≥ 30% decrease in the diameters of target lesions; progressive disease (PD) is ≥ 20% increase in the summed diameters of target lesions, taking the smallest summed value recorded since treatment as reference; stable disease is the summed value between PD and PR. The effective rate was the sum of CR and PR.

Quality Assessment

The risk of bias in RCTs was assessed based on Cochrane recommendations, considering random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting. Each category was assessed as low, unclear or high risk of bias and summarized in a Table with a plus, question mark or minus, respectively (17).

For non-RCTs, we utilized the Newcastle-Ottawa Scale for risk of bias assessment (18). This scale assesses risk of bias in three domains: 1) selection of the study groups (including representativeness of exposed cohort, selection of non-exposed, ascertainment of exposure, outcome not present at start); 2) comparability of groups; and 3) determination of exposure and outcome (including assessment of outcome, adequate follow-up length, adequacy of follow-up). A study was rated 0–9 stars based on these criteria. Studies with scores > 7 were considered as having a low risk of bias, scores of 4–6 as having a moderate risk of bias, and scores < 4 as having a high risk of bias. We assessed that follow-up was adequate if the median or mean follow-up was in excess of 2-year.

Publication bias was evaluated by funnel plots and Egger's regression (14).

Statistical Analyses

The primary outcome was the OS and effective rate (the rate of partial atrophy or complete clearance of the tumor lesion). Pooled odds ratios (ORs) with 95% confidence interval (CI) were calculated using either the fixed-effects model or random-effects model. For each meta-analysis, the χ^2 and I^2 statistics were first calculated to assess the heterogeneity of the included studies. $p < 0.1$ and $I^2 > 50\%$ were considered significant. For $p < 0.1$ and $I^2 > 50\%$, the random-effects model was used; otherwise, data were assessed using the fixed-effects model. The risk of publication bias in this study was assessed by visual inspection of the symmetry of the funnel plot. The significance of the pooled ORs was assessed by the Z-test. $p < 0.05$ was considered statistically significant. All statistical analyses were performed using the Stata 12.0 (Stata Corporation, College Station, TX, USA).

RESULTS

Description of the Studies

We searched a total of 193 studies, and 8 remaining studies were excluded. The full-texts were carefully evaluated. They were published from 2007 to 2015, and all had investigated TACE plus ^{131}I-metuximab therapy (11-13, 19-23). Totally 1121 patients were included in these studies. All the patients suffered from intermediate-advanced HCC not suitable for surgical methods. Among those, 546 patients underwent TACE plus ^{131}I-metuximab therapy, as compared with 575 patients who received TACE alone. There were: 3 RCTs (11, 22, 23), and 5 non-RCTs (12, 13, 19-21) (Fig. 1). The number of patients in each control ranged from 46 to 341. All the studies described the mean age of their patients; 7 studies (11-13, 19-21, 23) described severity of liver disease by Child-Pugh score. The anticancer drugs used were cyclosporin A (11), cisplatin (22), fluorouracil (12, 13, 22), mitomycin-C (13), and adriamycin (12, 22, 23), and

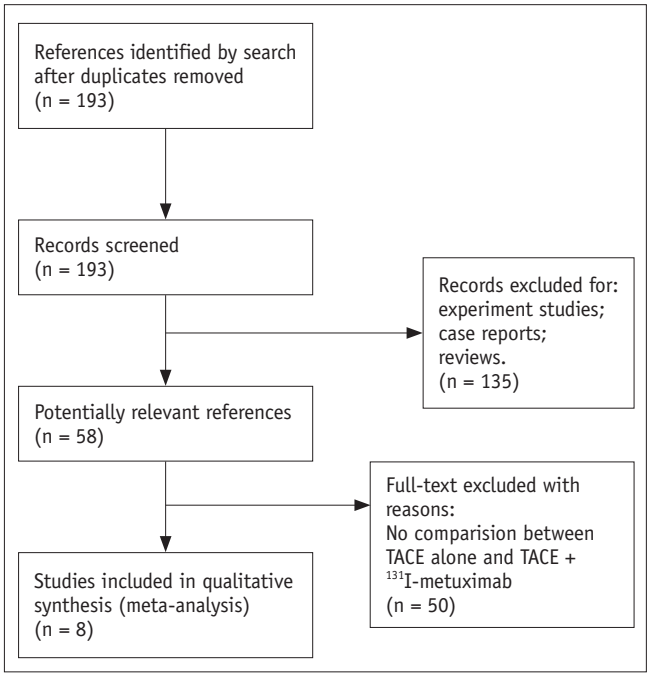

Fig. 1. Identification of eligible studies from databases. TACE = transcatheter arterial chemoembolization

Table 1. Characteristics of Studies Included in Meta-Analysis

Study (Year)	Design	Arms	Country of Origin	Study Period	No. of Patients.	Sex (Male)	Age (Mean ± SD, Years)	Child-Pugh Class (A/B/C)	Tumor Size (Mean ± SD, cm)	AFP (Mean ± SD, μg/L)	Dosage of ^{131}I-Metuximab	1-Year Survival	2-Year Survival
Xu et al. 2007 (11)	RCT	Experiment	China	2004	30	27	44.9 ± 7.77	14/13/3	22 > 5 cm	22 > 20 μg/L	15.4 MBq/Kg	86.7%	NA
		Control			30	27	45.07 ± 8.57	16/16/2	21 > 5 cm	22 > 20 μg/L		63.3%	NA
Wang et al. 2009 (13)	Control trail	Experiment	China	2005–2006	21	17	50 ± 14	7/14/0	NA	NA	27.75 MBq/Kg (tumor > 8 cm,37MBq/Kg)	61.9%	47.6%
		Control			25	20	51 ± 15	11/14/0	NA	NA		64.0%	16.0%
Wu et al. 2010 (19)	Control trail	Experiment	China	2008–2009	110	76	48	76/34/0	31 > 5 cm	54 > 200 μg/L	27.75 MBq /Kg	791%	22.7%
		Control			132	103	52	86/46/0	NA	NA		68.2%	15.9%
Guo et al. 2011 (22)	RCT	Experiment	China	2008–2009	31	20	49.1 ± 4.9	NA	NA	NA	30 MBq/Kg	NA	NA
		Control			31	18	47.6 ± 3.8	NA	NA	NA		NA	NA
Wu et al. 2012 (20)	Control trail	Experiment	China	2009–2010	68	54	51	54/14/0	NA	35 > 200 μg/L	27.75 MBq/Kg	80.9%	52.9%
		Control			70	56	46	57/13/0	NA	33 > 200 μg/L		72.9%	38.6%
He et al. 2013 (12)	Control trail	Experiment	China	2009–2011	95	83	50.2	91/4/0	80 > 5 cm	NA	27.75 MBq/Kg	60.0%	46.3%
		Control			90	76	51.4	82/8/0	81 > 5 cm	NA		34.4%	15.6%
Li et al. 2013 (23)	RCT	Experiment	China	2009–2010	24	20	62.42 ± 13.7	13/7/4	6.60 ± 0.87 cm	NA	27.75 MBq/Kg	45.8%	NA
		Control			23	19	57.48 ± 10.69	16/6/1	6.51 ± 0.88 cm	NA		30.4%	NA
Ma et al. 2015 (21)	Control trail	Experiment	China	2007–2009	167	141	52.19 ± 11.828	146/21/0	NA	581.55 ± 342.18 μg/L	27.75 MBq/Kg	79.6%	NA
		Control			174	172	51.32 ± 12.887	152/22/0	NA	539.32 ± 301.90 μg/L		65.5%	NA

AFP = alpha fetoprotein, NA = not applicable, RCT = randomized controlled trial

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epirubicin (19, 20). Usually, lipiodol was mixed with the drugs at a uniform dosage or a dosage calculated according to tumor size before the procedure. The dosage of lipiodol ranged from 2 to 20 mL. ^{131}I-metuximab injections were performed through the femoral artery using the Seldinger technique with local anesthesia. Patients in the test group underwent ^{131}I-metuximab therapy immediately after TACE. At each injection, ^{131}I-metuximab ranging from 15.4–37 MBq/kg was administered and the intra-arterial injection usually lasted 1–2 minutes. These characteristics were listed in Table 1.

Quality Assessment

The quality assessment of RCTs was performed using the Cochrane Collaboration's tool. Only one trial reported the blinding procedure (11). Moreover, the tumor feature was hardly comparable, introducing an unclear risk of selection bias. Risk of attrition bias was not presented across studies. The overall risk of all types of bias in the RCTs was generally low to unclear (Fig. 2).

Non-randomized controlled trials were assessed by the Newcastle-Ottawa Quality Assessment Scale and studies included in this review were all 6 stars or above (Table 2).

We compared the 1-year, 2-year survival, and the effective

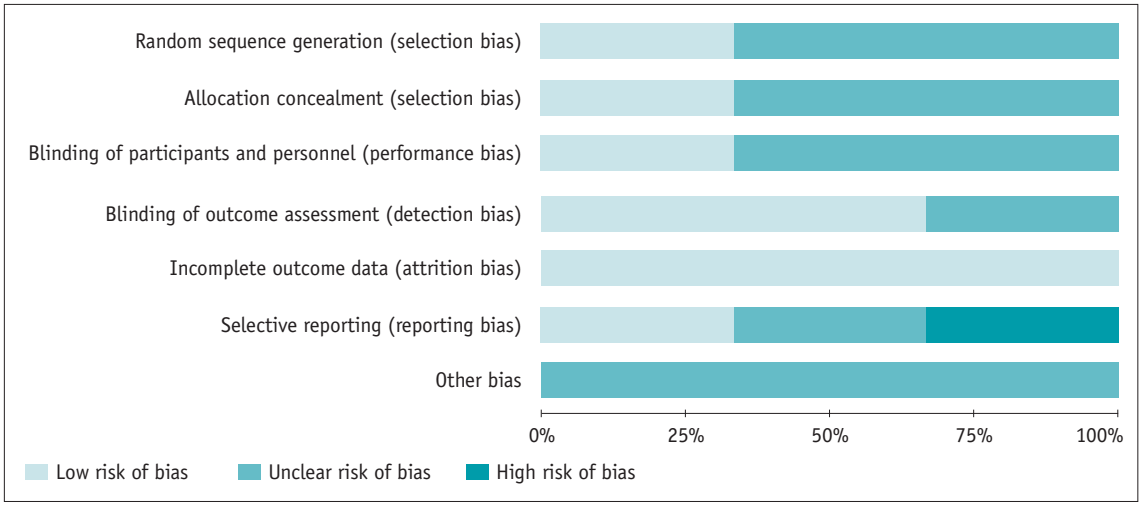

Fig. 2. Assessment of risk of bias in this meta-analysis. Risk of bias graph of individual risk of bias items presented as percentages across all included trails. Risk of bias for 3 RCTs are: Xu et al. (11), low risk; Guo et al. (22), unclear risk; Li et al. (23), unclear risk. Adapted from Xu J et al. *Hepatology* 2007;45:269-276, with permission of Wiley (11). Adapted from Guo XD et al. *China J Mod Med* 2011;21:1206-1208, with permission of China Academic Journal Electronic Publishing House (22). Adapted from Li Z et al. *Zhonghua Gan Zang Bing Za Zhi* 2013;21:728-733, with permission of Chinese Medical Association (23).

Table 2. Newcastle-Ottawa Scale for Risk of Bias Assessment of Studies Included in Meta-Analysis

Study (Year)	Selection				Comparability	Outcome			Overall
	Representativeness of Exposed Cohort	Selection of Non Exposed	Ascertainment of Exposure	Outcome Not Present at Start		Assessment of Outcome	Adequate Follow-Up Length	Adequacy of Follow-Up	
Wang et al. 2009 (13)	*		*	*	**		*		6
Wu et al. 2010 (19)	*	*	*	*	**		*	*	8
Wu et al. 2012 (20)	*	*	*	*	**	*	*	*	9
He et al. 2013 (12)	*	*	*	*	**		*		7
Ma et al. 2015 (21)	*	*	*	*	**		*		7

*represents one star, **represents two stars.

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rate (CR + PR, according to the RECIST).

Survival Rates

One-Year Survival

In meta-analysis of these controlled trials, there were 7 studies; 2 RCTs (11, 23) and 5 non-RCTs (12, 13, 19-21). Subgroup analysis was performed depending on study design. The results of tests for heterogeneity between trials were $p = 0.618$, $I^2 = 0\%$. Data showed that TACE plus ^{131}I-labelled metuximab (515 patients) was associated with a higher one-year survival rate, as compared with TACE alone (544 patients) (OR: 2.03, 95% CI: 1.55–2.67; $p < 0.001$), while the total survival benefit of ^{131}I-labelled metuximab therapy was significant (Fig. 3).

Two-Year Survival

Data for two-year survival rate were reported in 4 studies (12, 13, 19, 20) of no RCT. The result of tests for heterogeneity between trials was $p = 0.074$, $I^2 = 56.8\%$, so the random-effects model was used. TACE plus ^{131}I-labelled metuximab (294 patients) had a higher two-year survival rate, as compared with TACE alone (317 patients) (OR: 2.57, 95% CI: 1.41–4.66; $p = 0.002$). TACE Plus ^{131}I-labelled metuximab significantly improved the two-year survival, as compared with monotherapy (Fig. 4).

Sources of heterogeneity were explored by subgroup analysis. Subgroup analysis was conducted by the patients' liver functions. As expected, low heterogeneity was detected among the 3 studies (13, 19, 20) in the same group ($p = 0.345$, $I^2 = 6.0\%$) (Supplementary Fig. 1 in the online-only Data Supplement), suggestive of highest contribution of the liver function to study heterogeneity.

Effective Rate (CR + PR)

Three studies (12, 22, 23) compared the effective rate, with 394 patients included. Two RCTs (22, 23), subgroup analysis was made according to the study design. They all followed the RECIST after treatment. Heterogeneity between trials was not significant $p = 0.903$, $I^2 = 0\%$. Effective rate (CR + PR) for the ^{131}I-labelled metuximab therapy was higher than TACE alone (OR: 4.00, 95% CI: 2.40–6.66; $p < 0.001$) (Fig. 5).

Side Effect

In ^{131}I-metuximab group, no serious adverse events or

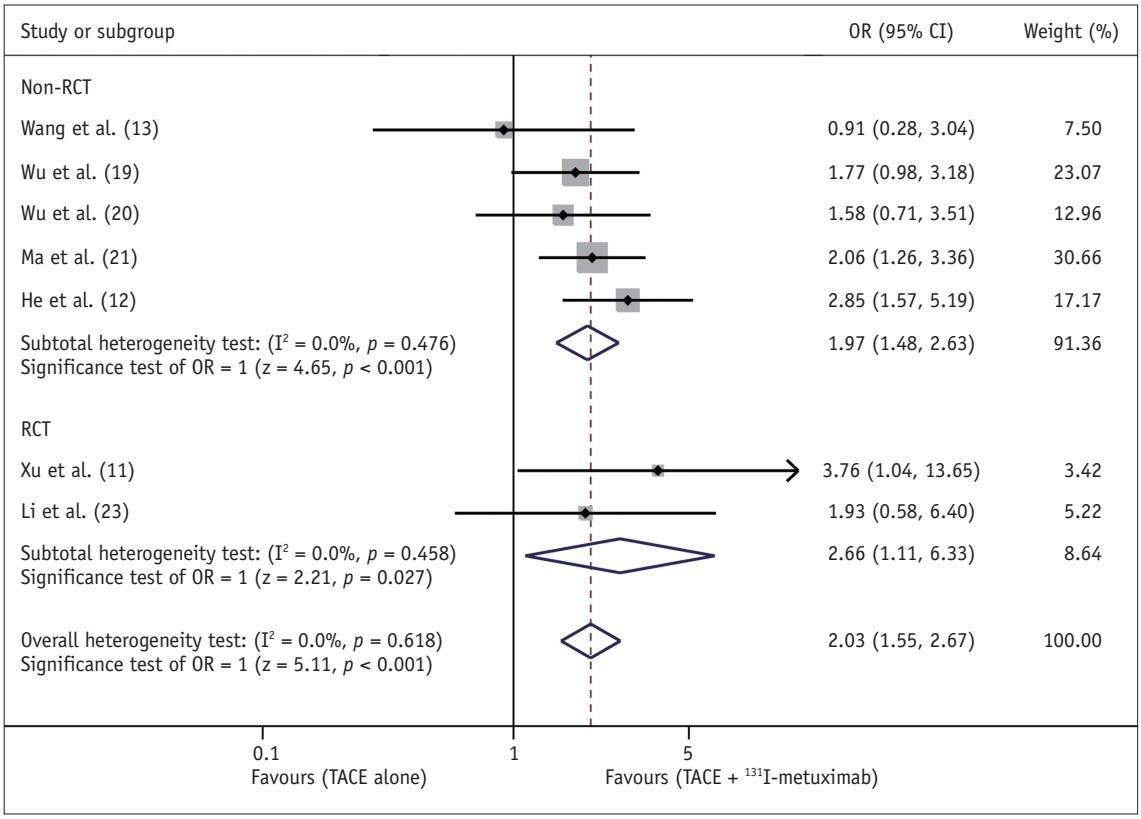

Fig. 3. Meta-analysis of trials. Comparison of combined therapy with TACE alone for HCC in terms of one-year survival rate. CI = confidence interval, HCC = hepatocellular carcinoma, OR = odds ratio, RCT = randomized controlled trial, TACE = transcatheter arterial chemoembolization

treatment-related deaths were reported. The most common adverse effects were the postembolization syndrome including fever, mild nausea and mild abdominal pain, and were usually self-limited (Table 3).

Assessment of Publication Bias

In our study, the Egger regression test and Begg funnel plot was used for the risk of publication bias. The high symmetry level of the funnel plots suggested no obvious publication bias in the trials included in our study (Fig. 6A-C). Further confirmation of no publication bias was by use

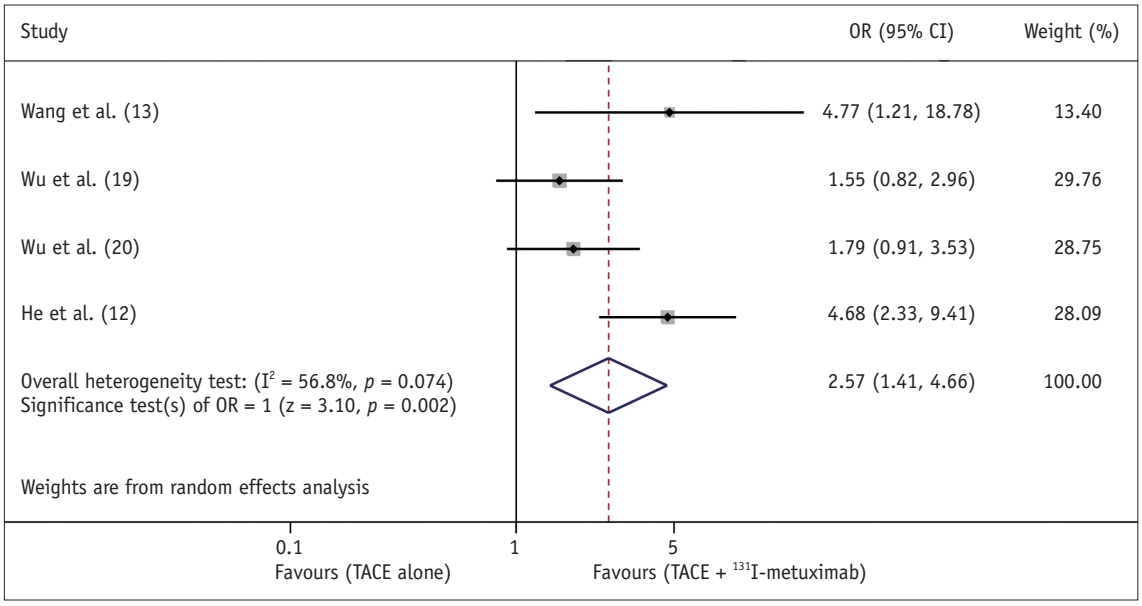

Fig. 4. Meta-analysis of trials. Comparison of combined therapy with TACE alone for HCC in terms of two-year survival rate. CI = confidence interval, HCC = hepatocellular carcinoma, OR = odds ratio, TACE = transcatheter arterial chemoembolization

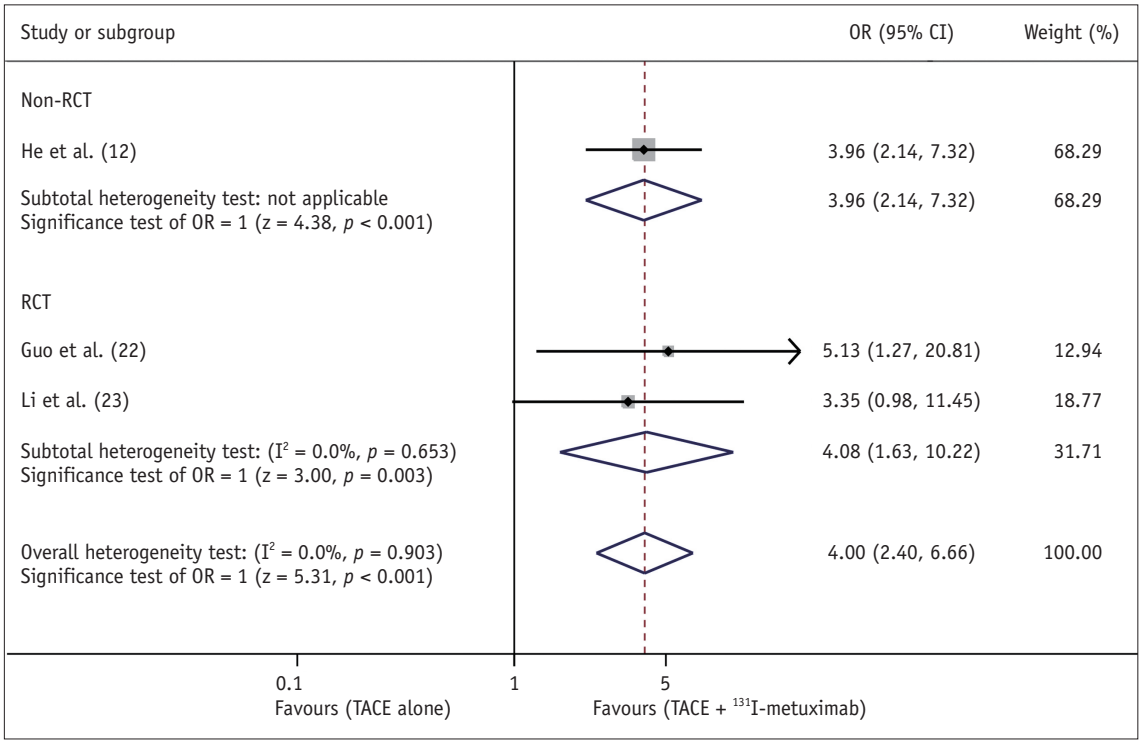

Fig. 5. Meta-analysis of trials. Comparison of combined therapy with TACE alone for HCC in terms of effective rates. CI = confidence interval, HCC = hepatocellular carcinoma, OR = odds ratio, RCT = randomized controlled trial, TACE = transcatheter arterial chemoembolization

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Table 3. Adverse Events in Studies Reported

Study (Year)	Arms	Patients, n	Fever, %	Nausea/Vomiting, %	Pain/Abdominal Distension, %
Wu et al.	Experiment	110	60.9	52.7	49.1
2010 (19)	Control	132	58.3	50.7	59.9
Wu et al.	Experiment	68	44.1	33.8	63.2
2012 (20)	Control	70	47.1	37.1	65.7
He et al.	Experiment	95	94.7	77.8	97.9
2013 (12)	Control	90	31.1	21.1	17.8
Ma et al.	Experiment	167	77.8	58.6	68.3
2015 (21)	Control	174	79.8	51.1	70.7

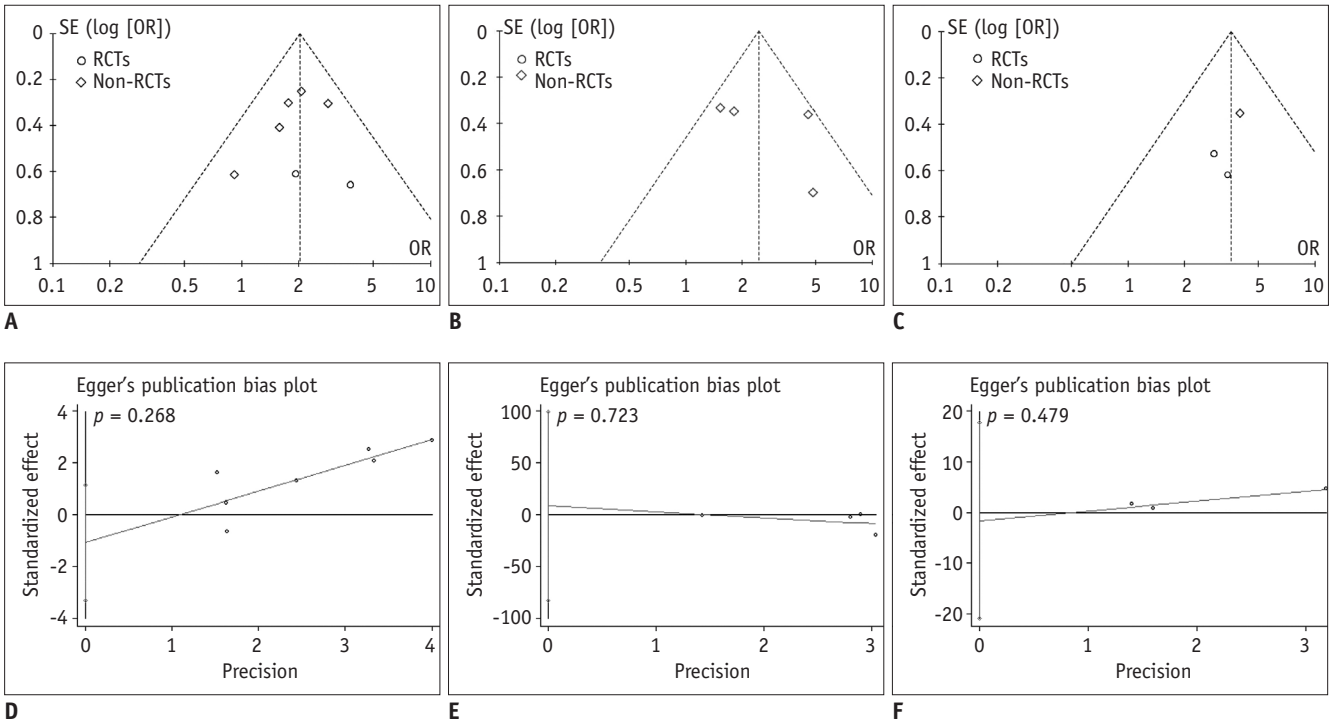

Fig. 6. Begg's and Egger's test for one-year, two-survival and effective rates show no evidence of publication bias.
A. Funnel plot of one-year survival. **B.** Funnel plot of two-year survival. **C.** Funnel plot of effective rates. **D.** Egger's test of one-year survival. **E.** Egger's test two-year survival. **F.** Egger's test of effective rates. OR = odds ratio, RCT = randomized controlled trial

of Egger regression test $p \geq 0.268$ (Fig. 6D-F).

DISCUSSION

This meta-analysis provides evidence that TACE plus ^{131}I-labelled metuximab significantly improved 1- and 2-year survival, as well as tumor CR and PR in patients with HCC compared with TACE alone. In regard to adverse events, TACE plus ^{131}I-metuximab had similar incidences of nausea and/or vomiting, and fever, as compared with TACE alone. Slight or no differences were seen between study types, or embolization type.

Transarterial chemoembolization, as a palliative treatment for HCC, has become one of the most common interventional therapies; however, it still has some limitations, and the outcomes are poor (24, 25). RT for HCC has traditionally not been used because older techniques fail to adequately localize the radiation to the tumor. However, recent improvements in RT have allowed increased intra-tumor radiation and decreased radiation to the adjacent normal liver and organs, thereby reducing the rate of adverse events (26).

A phase 1/2 trials demonstrated that ^{131}I-labelled metuximab can accumulate in HCC lesions and is safe and effective in the treatment of HCC (11). The target antigen for ^{131}I-metuximab, HAb18G/CD147, a member of the CD147 family, is highly expressed on HCC cells. The binding rate of HAb18 to human 7721 hepatoma cells, determined by

flow cytometry, is up to 99.6% (27-29). The mechanism by which ^{131}I-metuximab may benefit patients with HCC has been investigated both *in vitro* and *in vivo*, as well as in clinical trials (29, 30). Injection of ^{131}I-metuximab into HCC cells inhibits oncogenesis and metastasis within and outside the liver, blocking and destroying cells carrying HAb18G/CD147 and inhibiting HCC metastasis (31).

Thus, the improvement of survival and tumor response rates for combination treatments compared with TACE alone is due to the following reasons: a potential synergistic effect of the combination of ^{131}I-metuximab and TACE in the treatment of HCC. First, TACE can reduce blood flow to the HCC, and may enhance the efficacy of ^{131}I-metuximab due to its arterial embolization effect and prolonged retention of ^{131}I-metuximab in the tumor. Second, the anticancer drug in the tumor may have a radio-sensitizing effect on ^{131}I-metuximab, and can kill cancer cells after TACE for its continuous radiation. These mechanisms may explain the ability of combination therapy to enhance survival, as compared with conventional TACE alone, especially in patients with advanced HCC (19, 20).

For studies included in our meta-analysis, 3 articles (13, 20, 23) reported that the 1-year survival rate in combination therapy group shows no significantly difference compared with TACE alone. An RCT (11) reported that the survival rate increased by 20.6% in the combination group, as compared with those in the TACE alone group, indicating that ^{131}I-metuximab is a promising drug for advanced HCC patients excluded by surgical methods. These different conclusions may be derived from different baselines of characteristics included in these studies i.e., age, tumor size, alpha fetoprotein levels or the techniques of TACE.

No previous meta-analysis reported on the efficacy of TACE combined with ^{131}I-labelled metuximab, or other RIT. One meta-analysis (31) reported that survival could be prolonged with adjuvant iodine-131 lipiodol in patients with resected HCC, as compared with surgery alone. Huo and Eslick (32) also reported that TACE plus RT was more therapeutically beneficial than TACE alone for treating HCC, and should be recommended for suitable patients with unresectable HCC.

All the studies used ^{131}I-metuximab after TACE, and the general process of using ^{131}I-metuximab was similar in these included studies: Lugol's liquid was administered before and after treatment to block thyroid uptake of ^{131}I; following confirmation of a negative response to a subcutaneous injection of metuximab, the appropriate dose of ^{131}I-metuximab was administered through the femoral artery into the proper hepatic artery using the Seldinger technique with local anesthesia.

One study showed that patients in the test group obviously suffered more frequent adverse events than those in the control group (12) (Table 3). Only two studies showed the comparative data of clinical and laboratory toxicities observed during the trial, serum aminotransferase level (alanine aminotransferase or aspartate transaminase) or total bilirubin, leukocyte count, indicative of no statistical significance of the combination subgroup as compared with TACE alone (11, 20). None of these studies reported a significant difference in major complications between the combination group and TACE alone.

To our knowledge, there is no multi-center, large sample size published study on ^{131}I-metuximab, and this meta-analysis is the first to compare the efficiency and safety of TACE plus ^{131}I-metuximab. This study may have several possible limitations: first, both RCTs and non-RCTs were included, which may have introduced selection bias and heterogeneity in outcomes reported. However, no evidence of high level of heterogeneity was found in each subgroups. In fact, a considerable number of patients enrolled in the included trials were in Child-Pugh class A, while two studies (11, 23) included even Child-Pugh C patients. Meanwhile, the heterogeneity for the analysis of 2-year survival rate was high (p = 0.074, I^2 = 56.8%). Sources of heterogeneity were explored by means of subgroup analysis, the percentage of patients in Child-Pugh class A reported by He et al. (12) was 93.5%, which was much higher than the other 3 trials (< 80%) (13, 19, 20). Subgroup analysis conducted by the patients' liver functions indicated that the heterogeneity decreased and become more acceptable (Supplementary Fig. 1 in the online-only Data Supplement), suggestive of the role of liver function to study heterogeneity. The meta-analysis by stratifying the outcomes according to the characteristics of the tumor or the liver function was not possible due to the lack of data. Second, only two studies showed the specific data of the adverse effect; third, no article shows 3-year survival rate and the etiological factors of HCC (alcoholic hepatic disease, autoimmune liver disease, virus hepatitis, etc.) were not well considered in the included trials. Besides, only 3 RCTs were included. Although a meta-analysis has traditionally been applied and is best confined to RCTs, meta-analytical techniques using non-RCTs might be a valid method in clinical settings in which either the number or the sample size of the RCTs

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is insufficient (33). In the future, more RCTs should be enrolled to provide further evidence.

Thus, multimodal therapies have more survival benefit than TACE therapy alone. HCC patients with countable nodules often have more treatment choices, better treatment efficacy, and longer lifespan than those with countless nodules. TACE plus ^{131}I-metuximab had an extensive range of therapeutic function, especially for advanced liver cancer with wide metastasis and multiple lesions. The combination of ^{131}I-metuximab and TACE may greatly improve the treatment efficacy in these patients and extend their poor life expectancy.

In conclusion, the treatment of TACE plus ^{131}I-metuximab (Licartin) could offer a more effective treatment for intermediate or advanced, especially unresectable HCC patients than TACE alone.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3348/kjr.2016.17.6.882.

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