Original Article

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Transarterial Y90 radioembolization versus chemoembolization for patients with hepatocellular carcinoma: A meta-analysis

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Summary **Transarterial chemoembolization (TACE) is one of the standard locoregional treatments for intermediate stage hepatocellular carcinoma (HCC). Transarterial radioembolization (TARE) using β-emitting yttrium-90 (90Y) integral to the glass matrix of the microspheres has been developed as an alternative to TACE in recent years. Thus, we conducted a meta analysis to evaluate the safety and efficacy of TARE versus TACE for unresectable HCC. We searched PubMed, EMBASE, Web of science and the Cochrane Library for clinical trials comparing TARE with TACE for unresectable HCC. Response rate, overall survival (OS), time to progression (TTP), hospitalization time days and clinical complications were analyzed and compared. Eight studies published from 2009 to 2014, with a total of 1,499 patients, were included in this meta-analysis. The pooled results showed that TARE (90Y) is significantly better in OS (HR = 0.74; 95% CI: 0.61-0.90), 3-year OS rates (RR = 1.75; 95% CI = 1.01-3.03, *p* = 0.05), TTP (HR = 0.61; 95% CI: 0.41-0.89), hospitalization time days (mean difference = −2.66; 95% CI: −4.08 - −1.24) and some complications (abdominal pain [RR = 0.30, 95% CI: 0.11-0.83, *p* = 0.02]) for patients with HCC, but did not affect tumor response (CR [RR = 1.06; 95% CI = 0.51-2.22], PR [RR = 1.24; 95% CI = 0.79-1.94], SD [RR = 1.13; 95% CI = 0.92-1.39], PD[RR = 0.75; 95% CI = 0.37-1.51], over-all tumor control [RR = 1.16; 95 % CI = 0.94-1.44]). The current meta-analysis suggests that TARE (Y90) is significantly better in OS, 3-year OS rates, TTP, hospitalization time days and some complications for patients with HCC.**

Keywords: Transarterial Y90 radioembolization, chemoembolization, hepatocellular carcinoma

1. Introduction

Hepatocellular carcinoma (HCC) is a serious cancer with high morbidity and high mortality rate (*1*). In recent years, HCC has shown a rising incidence worldwide due to increasing hepatitis C virus prevalence and other factors (*2*). Surgical resection has been considered as definitive treatment for HCC, unfortunately, most HCC patients are diagnosed at an intermediate or advanced stage in which the tumor can't be resected (*3*). Therefore, locoregional treatment for HCC patients would be actively needed and may help to achieve longer survival.

Transarterial chemoembolization (TACE) is an increasingly locoregional treatment used for HCC, it is a chemotherapeutic agent injected at the tumor site for blocking the main feeding artery of the tumor causing tumor necrosis (*4*). TACE has been recommended as the standard therapy for intermediate stage BCLC (B) (*5,6*), but it is not suitable for all unresectable HCC patients as it may cause lots of complications: postembolization syndrome, hepatic decompensation and metastasis (*7,8*).

In recent years, transarterial radioembolization (TARE) using β-emitting yttrium-90 (90Y) integrated in glass matrix or resin microspheres has been regarded as an alternative therapy to TACE for unresected HCC (*9*). The microspheres are carried out through hepatic intra-arterial injection, treating HCC from the lobar, segmental to the sub segmental. Some studies have reported good treatment results through TARE (*10-12*). Other clinical experience reports that TARE Y-90 is able to reduce tumor burden significantly for patients

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with unresectable HCC which may help to downstage tumors before surgery (*13*). However, the effect of TARE with Yttrium-90 in the treatment of unresectable liver tumors still needs to be confirmed (*14,15*). Therefore, we conducted a meta analysis based on clinical trials to evaluate the efficacy and safety of TARE versus TACE for unresectable HCC.

2. Materials and Methods

2.1. *Literature search*

We searched PubMed, EMBASE, Web of science, and the Cochrane Library for clinical trials comparing TARE (90Y) with TACE for unresectable HCC. The following searching terms were used: "chemoemboli*" or "emboli*" or "TACE" or "transcatheter" or "transarterial" for identification of TACE, "90Y" or "radioemboli*" or "Yttrium-90" or "TARE" for identification of TARE, and "(liver or hepatic or hepatocellular) and (carcinom* OR cancer OR neoplasm* OR malign* OR tumor OR tumor)" or "HCC" or "hepatoma*" for identification of HCC (*16*).

The Literature was searched limited to human studies without restricting time or language. The reference lists of all articles were also manually screened for potential studies. Abstracts and citations were screened independently by two authors, and all the agreed articles needed a second screen for full-text reports.

2.2. *Review strategy*

We used endnote bibliographic software to construct an electronic library of citations identified in the literature search. All the PubMed, EMBASE, Web of science and the Cochrane Library searches were performed using Endnote; duplicates were found automatically by endnote and deleted manually. All data extraction was checked and calculated twice by two independent investigators (Yafei Zhang and Hong Ji). A standardized data extraction form was used to assist the two investigators. Data extracted from the included studies were as follows: author, year of publication, and country; patients' age and sex, study design, Child-Pugh class, treatment, pretreatment MELD score, BCLC stage, overall survival (OS), time to progression (TTP), hospitalization time days, tumor response, 1, 2, 3-year OS rate, complications and laboratory adverse events. A third reviewer (Hongwei Lu) would participate if some disagreements arose. Mean and standard deviation (SD) were preferred in some data, which will be calculated from the median and range using relevant formulae if it was not reported in the article (*17*).

2.3. *Study inclusion and exclusion criteria*

Inclusion criteria: patients were diagnosised as unresectable HCC; compared TARE with TACE monotherapy; compared efficacy and/or safety between TARE (Y90) and TACE. We excluded comments, editorials, systematic reviews or studies only in abstracts from our final analysis. Besides, there was no limitation for publication language.

2.4. *Quality assessment*

The quality of nocohort studies included in this meta analysis was assessed using a modified Newcastle-Ottawa scale (*18*), which graded the quality of a study from 0 to 9 points, depending on patient selection, comparability of TARE and TACE, and exposure assessment. Articles exceeding 6 points were considered as high quality.

2.5. *Statistical analysis*

All statistical analyses were performed using Review Manage (Revman, version 5.2.0, The Cochrane Collaboration, 2012) (*19*). The hazards ratio (HR) was used to evaluate the OS and TTP. Risk ratio (RR) was applied for tumor response, 1, 2, 3-year OS rates and clinical complications. Mean difference was used to evaluate the hospitalization time days. Afterward, 95% confidence intervals (CIs) were also calculated to indicate the precision of above effect measures. Pooled estimates of HR, RR or mean difference were calculated using the fixed-effects model if no substantial heterogeneity existed, otherwise, the random-effects model was used. Defined as variation between individual studies, heterogeneity was assessed with the Q-test and the I^2 statistic. Low level of heterogeneity was defined as I^2 value $\leq$ 50 % (*20*). The publication bias was evaluated using a funnel plot (*21,22*).

3. Results

3.1. *Identification of eligible studies*

The search strategy identified 2,306 related citations, and 1,543 non-duplicate references were retrieved for titles and abstracts screening. After 1,494 studies were excluded, the remaining 49 studies were examined at length. Finally, seven case control studies (*23-29*) and one cohort study (*30*) were eligible for inclusion criteria (Figure 1). A total of 1,499 patients were included among the eight studies, with 451 patients in the TARE group and 1,048 patients in TACE group.

3.2. *Characteristics of eligible studies*

The baseline characteristics of the eight studies included in our analysis are demonstrated in Table 1. The publication years of the included studies were between 2009 and 2014. Of these included studies, six

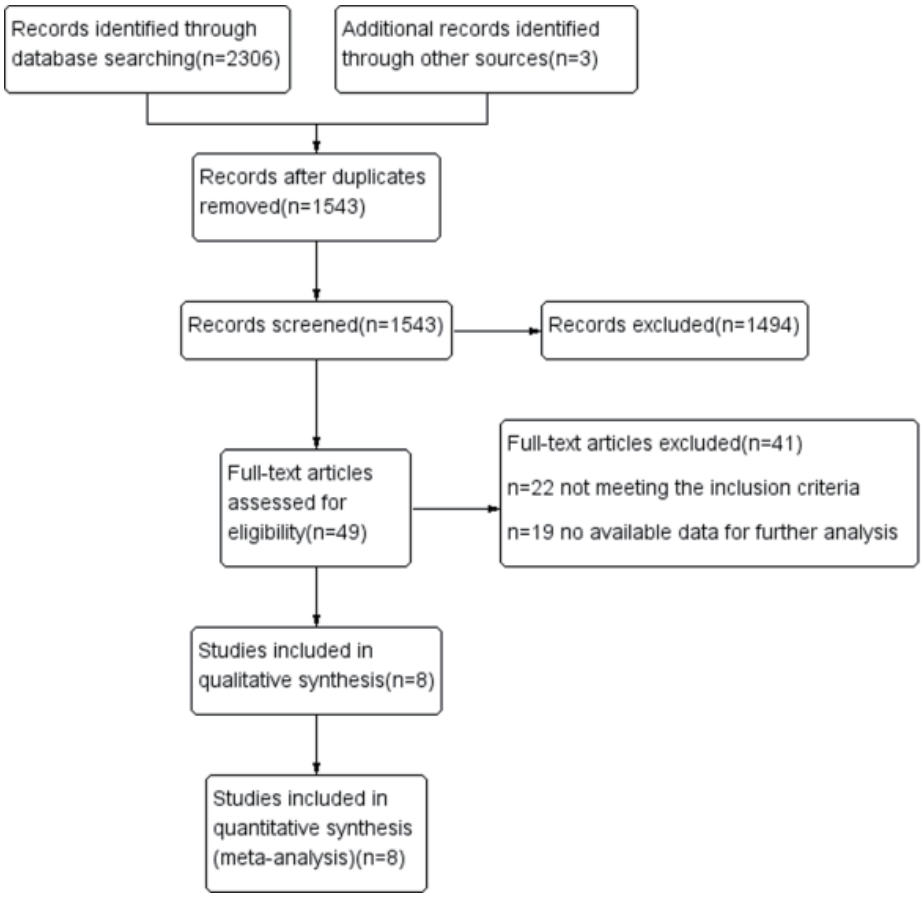

Figure 1. Flow chart of study selection.

were conducted in USA (*24-28,30*), one in China (*23*), one in Germany combined with Egypt (*29*). All the studies were published in English. The baseline liver function of most included patients was in Child-Pugh A (*23-29*). The etiology of the included patients were reported in seven studies, and most of the patients were a result from HCV and alcohol (*23-26,28-30*). Three studies reported the BCLC stage, and more than half of the patients were in BCLC-B stage (*24-26*). The median pretreatment MELD score ranged from 7.5 to 10 (*23,25,28,29*). All the included patients were definitely diagnosed to conform to the eligibility criteria.

3.3. *Quality of the included studies*

The quality of the nocohort studies was assessed by the Newcastle-Ottawa Scale (NOS), six of the result scores were 6, and another was 7, indicating that these studies have high quality according to the criteria (Table 2).

3.4. *Overall survival (OS)*

Among the eight studies included in the meta-analysis, three studies reported the results of data on OS (947 patients) (*26,28,30*). The meta-analysis showed that the OS was significantly better in the TARE with Y90 group than in the TACE group. The pooled HR for the OS in the included studies performed using the fixed-effects was 0.74 (95% CI: 0.61-0.90; $p = 0.002$). This demonstrated a 26% reduction in the risk of death in patients treated with TARE. There was no evidence of heterogeneity among individual studies ($p = 0.20$; $I^2 = 38\%$) (Figure 2A). Furthermore, the funnel plot revealed no publication bias.

3.5. *Time to progression (TTP)*

Two of the eight studies included in the meta-analysis reported the results of data on TTP (331 patients) (*24,26*). The meta-analysis showed that the TTP was significantly better in the TARE with Y90 group than in the TACE group. The pooled HR for the TTP in the included studies performed using the fixed-effects was 0.61 (95% CI: 0.41-0.89; $p = 0.010$). This demonstrated a 39% reduction in the risk of TTP in patients treated with TARE. There was no evidence of heterogeneity among individual studies ($p = 0.74$; $I^2 = 0\%$) (Figure 2B). Furthermore, the funnel plot revealed no publication bias.

3.6. *Hospitalization time days*

Four of the eight studies included in the meta-analysis reported the results of data on hospitalization time days

Table 1. The baseline characteristics of the eight studies

Study	country	Study design	Treatment	*n*	Age	Male/female	HBV (%)	HCV (%)	Alcohol	Child-Pugh class (%) (A/B)	Pretreatment MELD score	BCLC stage (A/B/C/D)
She *et al*. (2014)	China	Case Control study	TARE (90Y)	16	55(37-73)	15/1	12 (75.0)	0	NA	15/1	7.5 (6-12)	NA
			TACE	16	62.5 (48-78)	13/3	13 (81.3)	3 (27.3)	NA	14/2	8.5 (6-12)	NA
El Fouly *et al*. (2014)	Germany + Egypt	Case Control study	TARE (90Y)	44	66.1 ± 8.9	36/8	6 (14)	8 (18)	10 (23)	37/7	9 ± 3	NA
			TACE	42	58.3 ± 6.7	38/4	1 (2)	36 (86)	NA	33/9	10 ± 2.5)	NA
Moreno-Luna *et al*. (2013)	USA	Case Control study	TARE (90Y)	61	64 (29-88)	49/12	NA	8 (13)	12 (20)	53/8	9 (6-18)	23/13/19
			TACE	55	66 (46-84)	43/12	NA	7 (13)	13 (24)	44/11	9 (6-19)	12/34/14
Salem *et al*. (2011)	USA	Case Control study	TARE (90Y)	123	66 (30-88)	87/36	13 (11)	42 (35)	20 (16)	67/54	NA	43/65/13/2
			TACE	122	61 (33-88)	102/20	12 (10)	56 (46)	21 (17)	67/53	NA	47/61/12/2
Lance *et al*. (2011)	USA	Case Control study	TARE (90Y)	38	63 (44-85)	33/5	NA	NA	NA	31/7	NA	NA
			TACE	35	61 (51-84)	28/7	NA	NA	NA	24/11	NA	NA
Kooby *et al*. (2010)	USA	Case Control study	TARE (90Y)	27	58.7 ± 10.8	23/4	NA	10 (37)	NA	13/22	10.0 ± 3.4	NA
			TACE	44	61.0 ± 9.9	36/8	NA	25 (57)	NA	14/22	10.4 ± 4.2	NA
Carr *et al*. (2010)	USA	Cohort study	TARE (90Y)	99	NA	70/29	9 (9)	30 (30)	37 (37)	NA	NA	NA
			TACE	691	NA	518/173	97 (14)	132 (19)	217 (31)	NA	NA	NA
Lewandowski *et al*. (2009)	USA	Case Control study	TARE (90Y)	43	68 (62.8-75)	38/5	2 (5)	14 (33)	9 (20)	24/19	NA	0/34/9/0
			TACE	43	65 (58.9-67.8)	36/7	6 (14)	16 (36)	10 (23)	23/18	NA	0/37/4/2

BCLC, Barcelona Clinic Liver Cancer.

Table 2. Newcastle-Ottawa Scale (NOS) for assessing the quality of nocohort studies

Author	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	main factor: Child-Pugh Class	secondary factor: Aetiology	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	Total quality score
She *et al*. (2014)	*	*		*	*	*		*	*	7
El Fouly *et al*. (2014)	*	*		*	*	*		*	*	7
Moreno-Luna *et al*. (2013)	*	*		*	*	*		*	*	7
Salem *et al*. (2011)	*	*		*	*	*		*	*	7
Lance *et al*. (2011)	*	*		*	*			*	*	6
Kooby *et al*. (2010)	*	*		*	*	*		*	*	7
Lewandowski *et al*. (2009)	*	*		*	*	*		*	*	7

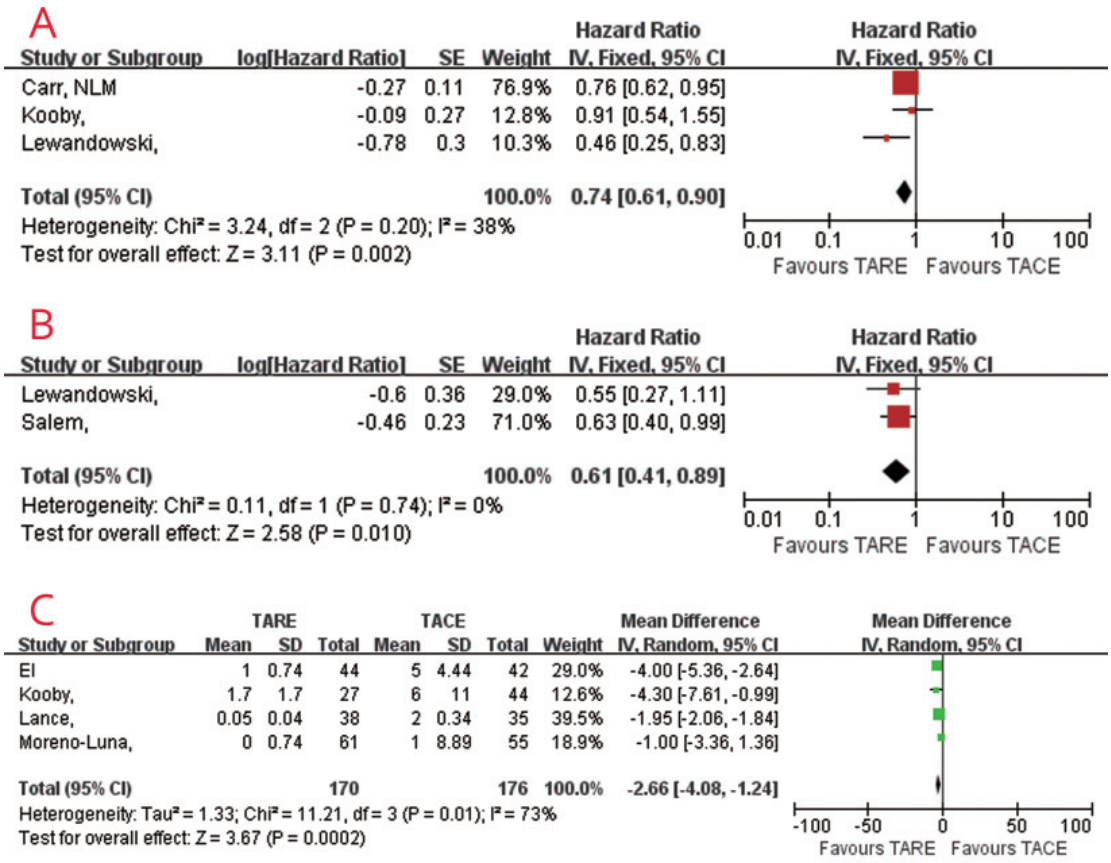

Figure 2. Forest plots of overall survival (OS) (A); time to progression (TTP) (B); hospitalization time days (C) in HCC patients that received TARE or TACE.

(346 patients) (*25,27-29*). The meta-analysis showed that the hospitalization time days was significantly shorter in the TARE with Y90 group than in the TACE group. The pooled mean difference for the hospitalization time days in the included studies performed using the random-effects was −2.66 (95% CI: −4.08 - −1.24; $p = 0.0002$). The heterogeneity among individual studies was ($p = 0.01$; $I^2 = 73\%$) (Figure 2C). Furthermore, the funnel plot revealed no publication bias.

3.7. *Tumor response*

The tumor response (involves CR [complete response], PR [partial response], SD [stable disease], PD [progressive disease], over-all tumor control [CR + PR + stable disease]) was reported in five case control studies (*23,25,26,28,29*) and one cohort study (*30*) (1,181 patients) (Table 3).

For CR, the pooled RR between TARE and TACE group was 1.92 (95% CI = 0.68-5.41; $I^2 = 0\%$) for case control study and 0.57 (95% CI = 0.18-1.80) for cohort study. The pooled RR of all six studies was (RR = 1.06; 95% CI = 0.51-2.22; $I^2 = 11\%$), and suggested that there was no statistical difference between groups (Table 3). Furthermore, the funnel plot revealed no publication bias.

For PR, the meta analysis of case control studies suggested that the patients in the TARE group had a significantly better response than those in the TACE group (RR = 1.44; 95% CI = 1.02-2.04; $I^2 = 34\%$), but the pooled RR of the cohort study favored the TACE group (RR = 0.70; 95% CI = 0.54-0.90), meta analysis of all available studies suggested that there was no statistical difference between groups (RR = 1.24; 95% CI = 0.79-1.94; $I^2 = 76\%$) (Table 3). Furthermore, the funnel plot revealed no publication bias.

For SD, the meta-analysis in the subgroup of case control studies (RR = 1.05; 95% CI = 0.79-1.40; $I^2 = 0\%$) and subgroup of cohort study (RR = 1.23; 95% CI = 0.92-1.64) suggested the patients that underwent the TARE therapy tended to have a better response to treatment than those underwent TACE treatment, though the estimates failed to achieve statistical significance. Meta analysis of all available studies suggested that there was no statistical difference between groups (RR = 1.13; 95% CI = 0.92-1.39; $I^2 = 0\%$) (Table 3). Furthermore, the funnel plot revealed no publication bias.

For PD, the meta-analysis of case control studies suggested that there was no statistical difference between groups (RR = 0.62; 95% CI = 0.37-1.04; $I^2 = 29\%$), but the pooled RR of the cohort study suggested that the patients in the TARE group had a significantly

Table 3. Tumor response compaired between the two treatments

Tumor response	Study or Subgroup	Patients (TARE/TACE)	Weight	Heterogeneity	Risk ratio (95% CI)
CR	case control study	191/200	36.40%	$p = 0.57$; $I^2 = 0\%$	1.92 (0.68-5.41)
	cohort study	99/691	63.60%	Not applicable	0.57 (0.18-1.80)
	Total	290/891	100%	$p = 0.34$; $I^2 = 11\%$	1.06 (0.51-2.22)
PR	case control study	191/200	75.30%	$p = 0.20$; $I^2 = 34\%$	1.44 (1.02-2.04)
	cohort study	99/691	24.70%	Not applicable	0.70 (0.54-0.90)
	Total	290/891	100%	$p = 0.0009$; $I^2 = 76\%$	1.24 (0.79-1.94)
SD	case control study	191/200	54.70%	$p = 0.93$; $I^2 = 0\%$	1.05 (0.79-1.40)
	cohort study	99/691	45.30%	Not applicable	1.23 (0.92-1.64)
	Total	290/891	100%	$p = 0.93$; $I^2 = 0\%$	1.13 (0.92-1.39)
PD	case control study	191/200	77.40%	$p = 0.23$; $I^2 = 29\%$	0.62 (0.37-1.04)
	cohort study	99/691	22.60%	Not applicable	2.14 (1.41-3.25)
	Total	290/891	100%	$p = 0.0007$; $I^2 = 77\%$	0.75 (0.37-1.51)
over-all	case control study	191/200	77.20%	$p = 0.73$; $I^2 = 0\%$	1.27 (1.14-1.42)
tumor control	cohort study	99/691	22.80%	Not applicable	0.86 (0.77-0.96)
	Total	290/891		$p = 0.0001$; $I^2 = 80\%$	1.16 (0.94-1.44)

Data were pooled with random-effect models. Complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) and over-all tumor control in HCC patients that received TARE or TACE.

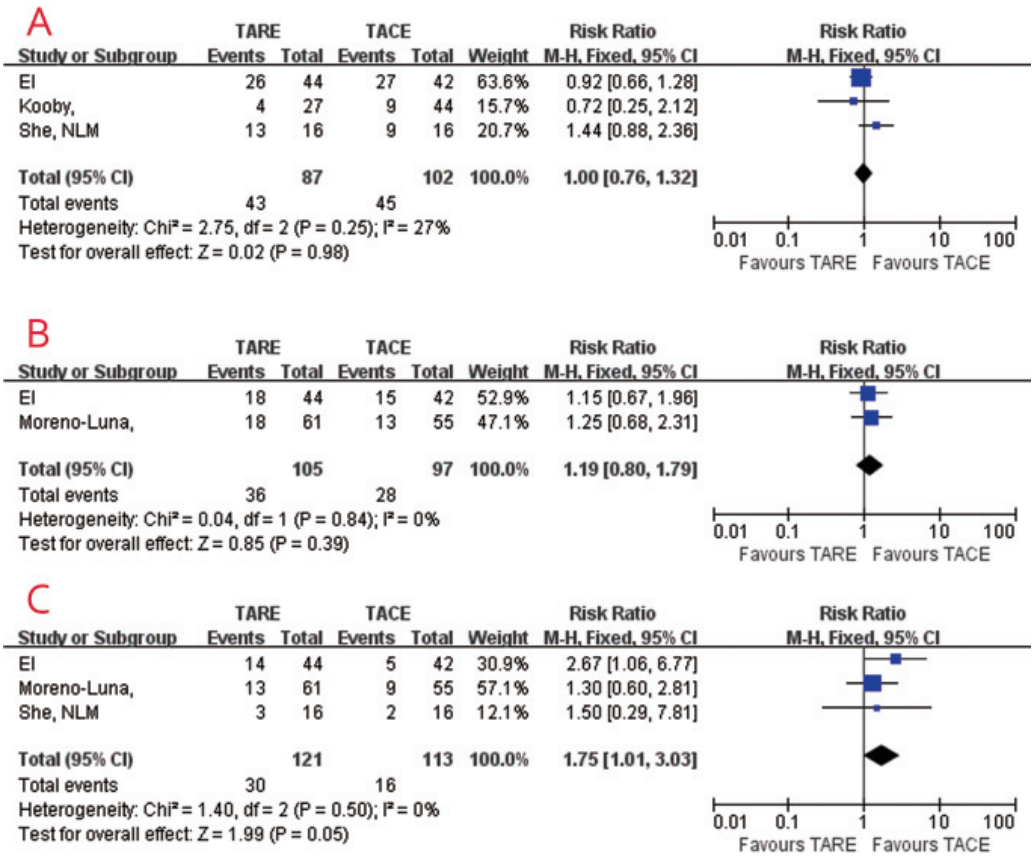

Figure 3. Forest plots of 1-year (A), 2-year (B) and 3-year (C) OS rates in HCC patients that received TARE or TACE.

better response than those in the TACE group (RR = 2.14; 95% CI = 1.41-3.25), meta analysis of all available studies suggested that there was no statistical difference between groups (RR = 0.75; 95% CI = 0.37-1.51; $I^2 = 77\%$) (Table 3). Furthermore, the funnel plot revealed no publication bias.

For over-all tumor control, the meta analysis of case control studies suggested that the patients in the TARE group had a significantly better response than those in the TACE group (RR = 1.27; 95% CI = 1.14-1.42; $I^2 = 0\%$), but the pooled RR of the cohort study favored the TACE group (RR = 0.86; 95% CI = 0.77-0.96), meta analysis of all available studies suggested that there was no statistical difference between groups (RR = 1.16; 95% CI = 0.94-1.44; $I^2 = 80\%$) (Table 3). Furthermore, the funnel plot revealed no publication bias.

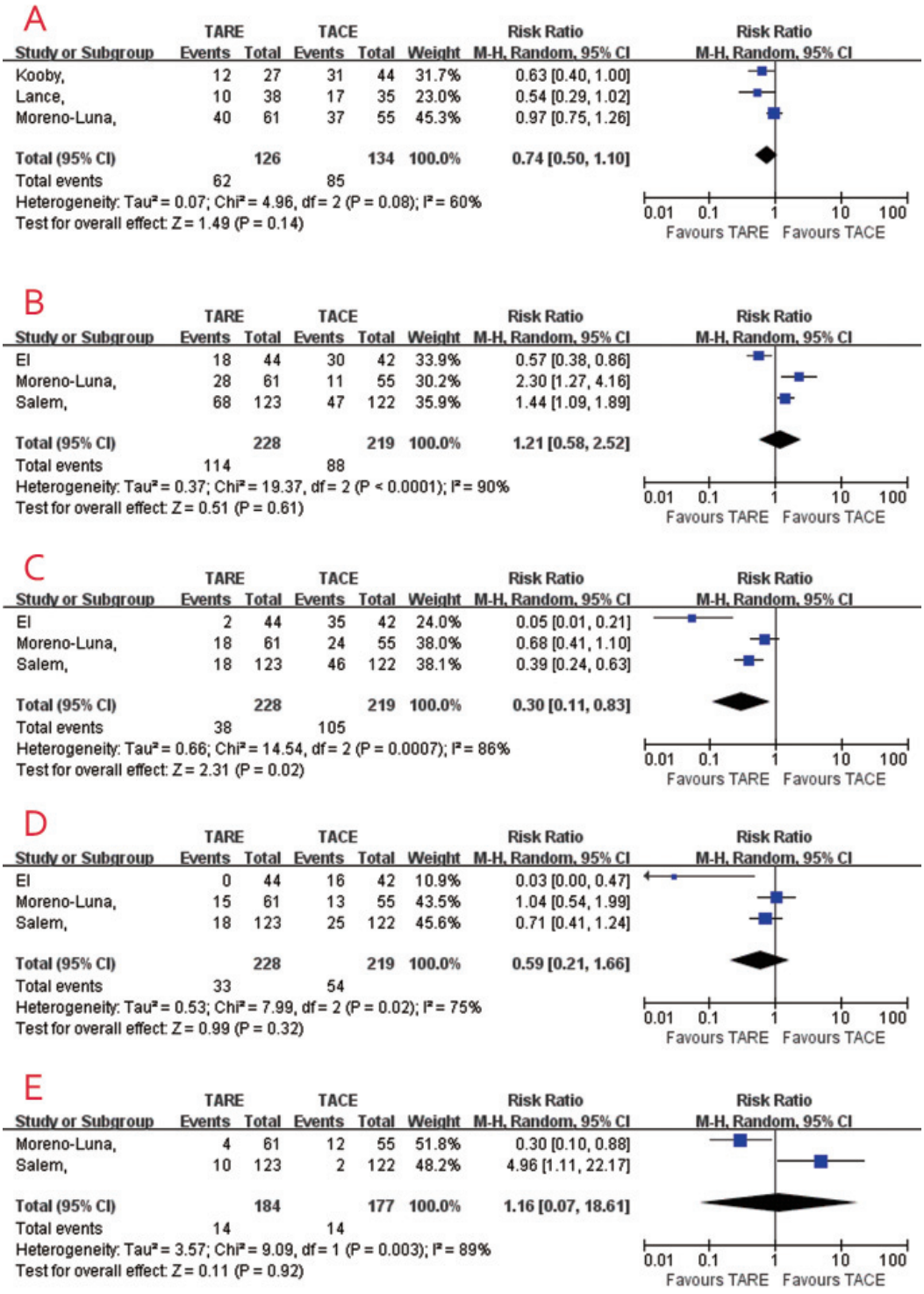

Figure 4. Forest plots of any complications (A), fatigue syndrome (B), lower abdominal pain (C), nausea/vomiting (D) and fever (E) in HCC patients that received TARE or TACE.

3.8. *1-year, 2-year, and 3-year OS rates*

A fixed-effect model was used to analyze the 1-year (p = 0.25, I^2 = 27%), 2-year (p = 0.84, I^2 = 0%) and 3-year (p = 0.50, I^2 = 0%) OS rates since there was no significant heterogeneity among these studies. Three studies reported 1-year OS rates (*23,28,29*) and two studies reported 2-year OS rates (*25,29*). The meta analysis showed that there was no statistical difference between groups on both 1-year (RR = 1.00, 95% CI 0.76-1.32, p = 0.98) (Figure 3A) and 2-year (RR = 1.19, 95% CI: 0.80-1.79, p = 0.39) (Figure 3B) OS rates. However, the pooled RR of three studies (*23,25,29*) suggested that the patients in the TARE group had a significantly higher 3-year OS rate than those in the TACE group (RR = 1.75; 95% CI = 1.01-3.03, p = 0.05) (Figure 3C). Furthermore, the funnel plot revealed no publication bias.

3.9. *Clinical complications*

We found that the TARE treatment lead to lower abdominal pain (*24,25,29*) (RR = 0.30, 95% CI: 0.11-0.83, p = 0.02) (Figure 4C) than TACE. However, the meta analysis showed that there was no statistical difference between groups on any complications (*25,27,28*) (RR = 0.74, 95% CI: 0.50-1.10, p = 0.14) (Figure 4A), fatigue syndrome (*24,25,29*) (RR = 1.21, 95% CI: 0.58-2.52, p = 0.61) (Figure 4B), nausea/vomiting (*24,25,29*) (RR = 0.59, 95% CI: 0.21-1.66, p = 0.32) (Figure 4D) or fever (*24,25*) (RR = 1.16, 95% CI: 0.07-18.61, p = 0.92) (Figure 4E). A random-effect model was used to analyze all the clinical complications for I^2 > 50% significant heterogeneity existed (Figure 4). Furthermore, the funnel plot revealed no publication bias.

4. Discussion

As modest benefit locoregional therapeutic modalities for HCC, the use of TACE had been demonstrated by two landmark trials (*31,32*), which stated that TACE was the standard therapy for intermediate HCCs. TARE with Yttrium-90, however, shows low toxicity and may provide therapeutic benefits for patients with unresectable HCC (*33*). A randomized controlled trial showed a benefit progression free survival of TARE (Y90) in patient with liver metastasis to colorectal tumors, after which, TARE (Y90) has been approved by the FDA (*34*). Presently, the safety and effectiveness of TARE (Y90) in advanced HCCs especially associated with portal vein thrombosis have been partly affirmed by many studies (*11,35-37*). Therefore, it is necessary to compare the efficacy and safety of TARE with Y90 in patients with intermediate or advanced stage HCCs.

To the best of our knowledge, this meta analysis is the first and most comprehensive to compare the efficacy and safety of TARE with Y90 in patients with an intermediate or advanced stage of HCC with TACE. Seven case control studies and one cohort study were identified and statistically analyzed in the present meta analysis, which included 451 and 1,048 patients with unresectable HCC who were treated with TARE (Y90) and TACE, respectively. With a relatively high level of evidence, the meta analysis showed that HCC patients treated with TARE (Y90) had significantly higher OS, TTP, 3-year OS rates, shorter hospitalization time days, better clinical complications and laboratory AEs than those treated with TACE. The TARE (Y90) therapy in the case control studies subgroup may also improve the PR and over-all tumor control treatment, while the total pooled estimates failed to achieve statistical significance.

Our meta analysis showed that the OS was significantly better in the TARE with Y90 group than in the TACE group (HR = 0.74; 95% CI: 0.61-0.90) (Figure 2A). This demonstrated a 26% reduction in the risk of death in patients treated with TARE. Furthermore, the meta analysis showed that there was no statistical difference between groups on both 1-year (RR = 1.00, 95% CI: 0.76-1.32, p = 0.98) (Figure 3A) and 2-year (RR = 1.19, 95% CI 0.80-1.79, p = 0.39) (Figure 3B) OS rates, however, the pooled RR of three studies suggested that the patients in the TARE group had significantly higher 3-year OS rate than those in the TACE group (RR = 1.75; 95% CI = 1.01-3.03, p = 0.05) (Figure 3C), suggesting that the effects of TARE (Y90) were gradually enhanced as time went by. While due to less patients included in our analysis, more studies with patients from different races are needed to further confirm this conclusion.

TTP is one of the most important indexes in treating intermediate stage HCC (*26,38*). El Fouly (*29*) reported that the TTP in TARE (Y90) patients (13.3 months) is much longer than in TACE patients (6.8 months), while the difference was not significant. In another study, TTP was significantly longer in a TARE (Y90) group than TACE (*24*). Our meta-analysis showed that the TTP was significantly better in the TARE with Y90 group than in the TACE group (HR = 0.61; 95% CI: 0.41-0.89), demonstrating a 39% reduction in the risk of TTP in patients treated with TARE (Figure 2B).

Furthermore, the meta-analysis showed that the hospitalization time days were significantly shorter in the TARE with Y90 group than in the TACE group (mean difference = −2.66; 95% CI: −4.08 - −1.24) (Figure 2C). This may be explained by the fact that most patients were accompanied by re-hospitalization to receive consecutive cycles of TACE (29).

Recently, radiological response rate was assessed according to modified RECIST (*5,39-41*). In El Fouly's study (*29*), objective response during a median time of 6 months reached disease control in 75% of TARE (Y90) patients *vs*. 50% in the TACE cohort, which reflects the higher capability of TARE (Y90) to induce tumor necrosis and ablation in vascular HCCs *(4*). For the outcome of tumor response, we used subgroup analysis to pool data from case control studies and cohort studies separately according to the study design. For CR, PR, SD, PD and over-all tumor control, meta-analysis of all available studies suggested that there was no statistical difference between groups, though the subgroup of case control studies favored the TARE for PR and over-all tumor control (Table 3). For all the six available studies, five were case control studies, only one was a cohort study, although the cohort studies can reflect the ‘‘real-world" and further support the conclusion, cohort data are of course inclined to bias because of patient selection. Thus, physicians should carefully interpret the results when applying them in clinical practice.

Lastly, we found that the TARE treatment lead to lower abdominal pain (RR = 0.30, 95% CI: 0.11-0.83, p = 0.02) than TACE, TARE (Y90) injects radioactive particles into a selected liver artery without causing

arterial occlusion (*42*). So, there is no overexpression of hypoxia-inducible factor 1a and vascular endothelial growth factor, which is clinically manifested as pain (*29*). However, the meta-analysis showed that there was no statistical difference between groups on any complications (RR = 0.74, 95% CI: 0.50-1.10, $p = 0.14$) (Figure 4A), fatigue syndrome (RR = 1.21, 95% CI: 0.58-2.52, $p = 0.61$), nausea or vomiting (RR = 0.59, 95% CI: 0.21-1.66, $p = 0.32$) and fever (RR = 1.16, 95% CI: 0.07-18.61, $p = 0.92$) (Figure 4). The heterogeneity of meta-analysis in clinical complications is significant. This may be due to variety in treatment schedule and complication designing criteria in the original studies. As the number of included studies is insufficient, we are unable to carry out subgroup analysis or meta-regression to explore the source of heterogeneity. The most frequient clinical complication in TARE (Y90) patients is post-embolization fatigue syndrome. While our analysis result showed that there was no statistical difference between the two groups.

There are several potential limitations in this meta-analysis. First, among the eight included studies, only one was a cohort study and the remaining seven were case control studies. While case control data are of course inclined to bias because of investigator selection. Thus, physicians should carefully interpret our results when applying them in clinical practice. Second, the characteristics of population and study designs vary considerably between the included trials, which may lead to heterogeneity and affect the results. Third, the majority of patients involved were from the USA, which limits universality of the conclusion. Hence, the results of updated clinical trials are eagerly awaited. Furthermore, because of the limited number of studies regarding the interest outcomes, caution should be taken when interpreting the results.

In conclusion, the current meta-analysis suggests that TARE (Y90) is significantly better in OS, 3-year OS rates, TTP, hospitalization time days and some complications for patients with HCC. The use of TARE (Y90) for HCC patients is promising. However, further multi-center, well-designed RCTs are needed to improve the treatment benefits for HCC patients.

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