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META-ANALYSIS

Conventional transarterial chemoembolization *vs* microsphere embolization in hepatocellular carcinoma: A meta-analysis

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Abstract

AIM: To compare conventional transarterial chemoembolization (c-TACE) with microsphere embolization in hepatocellular carcinoma (HCC).

METHODS: We searched PubMed, Medline, Embase and the Cochrane Library for trials assessing the efficacy and safety of c-TACE in comparison with those of yttrium-90 microsphere or drug-eluting bead embolization from January 2004 to December 2013. Overall survival rate (OSR), tumor response [complete response, partial response (PR), stable disease (SD), progressive disease (PD)], α-fetoprotein (AFP) response, progression rate and complications were compared and analyzed. Pooled ORs with 95%CI were calculated using either the fixed-effects model or random-effects model. All statistical analyses were conducted using the Review Manager (version 5.1.) from the Cochrane collaboration.

RESULTS: Thirteen trials were identified, including a total of 1834 patients; 1233 were treated with c-TACE, 377 underwent yttrium-90 microsphere embolization and 224 underwent drug-eluting bead embolization. The meta-analysis with either the random-effects model or fixed-effects model indicated that microsphere embolization was associated with significantly higher OSRs compared with those of c-TACE ($OR_{1\text{-year}}$ = 1.38, 95%$CI_{1\text{-year}}$: 1.05-1.82; $OR_{2\text{-year}}$ = 2.88, 95%$CI_{2\text{-year}}$: 1.18-7.05; $OR_{3\text{-year}}$ = 2.15, 95%$CI_{3\text{-year}}$: 1.18-3.91). The complete tumor response rates of patients who underwent microspheres embolization were significantly higher than those of patients treated with c-TACE (OR = 2.19, 95%CI: 1.31-3.64). The tumor progression rate after microsphere embolization was markedly lower than that after c-TACE (OR = 0.56, 95%CI: 0.39-0.81). There was no significant difference between microsphere embolization and c-TACE in PR (OR = 0.73, 95%CI: 0.47-1.15), SD (OR = 1.07, 95%CI: 0.79-1.44), PD (OR = 0.75, 95%CI: 0.33-1.68), AFP response (OR = 1.38, 95%CI: 0.64-2.94) and complications (OR = 0.68, 95%CI: 0.46-1.00).

CONCLUSION: Our analysis indicated that microsphere embolization was associated with superior survival and treatment response in comparison with c-TACE in the treatment of patients with HCC.

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Key words: Hepatocellular carcinoma; Transarterial chemoembolizaiton; Yttrium-90 microsphere; Drug-eluting bead; Meta-analysis

Core tip: Microsphere embolization has been performed more and more widely for the treatment of hepatocellular carcinoma (HCC). Whether microsphere embolization or conventional transarterial chemoembolization (c-TACE) is the better choice has been debated. In this study, we performed a meta-analysis to comprehensively compare the efficacy and safety of microspheres embolization with those of c-TACE in HCC. Our analysis indicated that microsphere embolization was associated

with superior survival and treatment response in comparison with c-TACE in patients with HCC. We hope that the comparison of these treatments could help stratify the benefits of treatment choices for patients with HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor and is the third highest cause of cancer-related death worldwide. There are more than 660000 new cases of HCC every year and it has an increasing incidence[1,2]. Although surgery (surgical resection or liver transplantation) is still considered the foremost treatment for HCC, the majority of HCC patients are diagnosed at the intermediate and advanced tumor stages with poor liver function, usually due to cirrhosis, virus infection (chronic hepatitis B or C), or alcoholic liver disease, and less than 20% of HCC patients are actually eligible for surgery[3-5].

In recent years, as a minimally invasive treatment, transarterial chemoembolization (TACE) has been widely used for the treatment of HCC patients who were not suitable candidates for surgery[6-8]. In clinical practice, conventional TACE (c-TACE) comprises intra-arterial chemotherapy using lipiodol and chemotherapeutic agents, followed by selective vascular embolization, and results in a strong cytotoxic effect combined with ischemia to inhibit tumor progression. However, according to previous clinical reports, it was clear that the long-term outcome of TACE in the treatment of HCC was not satisfactory[9-11]. In order to improve the effectiveness of TACE, microsphere embolization such as transarterial embolization (TAE) with yttrium-90 (Y90) microspheres or drug-eluting beads (DEB) has been used more often in HCC. TAE with Y90 microspheres, which is also as known as radioembolization (also called selective internal radiation therapy or SIRT) has been proved to be an effective and safe treatment for HCC. In contrast to c-TACE, SIRT is a form of brachytherapy for liver tumors in which the source of radiation has to access the network of tumoral neovessels after being injected into the hepatic arteries. In addition, TAE with DEB for the treatment of HCC has been observed to deliver higher doses of chemotherapeutic agent and to prolong contact time with the tumor. Some researchers suggested that microsphere embolization was associated with greater clinical effectiveness and fewer complications in comparison with c-TACE for the treatment of patients with HCC[12-15]. However, some other clinical studies reported conflicting results[16-19]. Hence, whether microsphere embolization or c-TACE is the better choice has been a matter of debate.

In this study, we designed a meta-analysis to comprehensively compare the efficacy and safety of microsphere embolization (Y90 microspheres or DEB) with those of c-TACE in HCC through an extensive search of the literature, which we analyzed using strict criteria. We hope that the comparison of these treatments could help stratify the benefits of treatment choices for patients with HCC.

MATERIALS AND METHODS

Search strategy

A review of studies for potential in the meta-analysis was conducted in the databases of PubMed, Medline, Embase and the Cochrane Library from January 2004 to December 2013. The study search used the following MeSH search headings: "hepatocellular carcinoma" "primary liver cancer", "yttrium-90 microsphere", "drug-eluting bead" and "transarterial chemoembolization". A limit was set on clinical studies, which had reported the data on comparing the clinical efficacy or safety of microsphere embolization (Y90 microspheres or DEB) with those of c-TACE in the treatment of HCC. There was no language restriction in this search.

Data extraction

Data extraction was independently conducted by two reviewers (Jia-yan Ni and Hong-liang Sun) using standardized methods, with any disagreements being settled by discussion of the relevant study data and adjudicated by an experienced reviewer (Lin-feng Xu). From each study, the following data were abstracted: publication details (name of the first author, year of publication and country), and study characteristics [study design, age, percentage of male, trial design, tumor size, tumor number, Child-Pugh class, Barcelona Clinic Liver Cancer (BCLC) stage, Eastern Cooperative Oncology Group (ECOG) performance status, virus infection, overall survival rate, tumor response, α-fetoprotein (AFP) response, progression rate and treatment associated complications].

Inclusion and exclusion criteria

Clinical studies were required to fulfil the following inclusion criteria: (1) study design: the trials had to have comparative data on clinical efficacy or safety of microsphere embolization with Y90 microspheres or DEB and c-TACE in the treatment of HCC; (2) clear documented indications for microspheres embolization and c-TACE; (3) treatment design: microsphere embolization with Y90 microspheres or DEB *vs* c-TACE; (4) characteristics of patients: trials were required to have relatively integrated basic characteristics of enrolled patients, such as age, percentage of males, trial design, tumor size, tumor number, Child-Pugh class, BCLC stage, ECOG performance status, virus infection, overall survival rate, tumor response rate, AFP response rate, tumor progression rate and

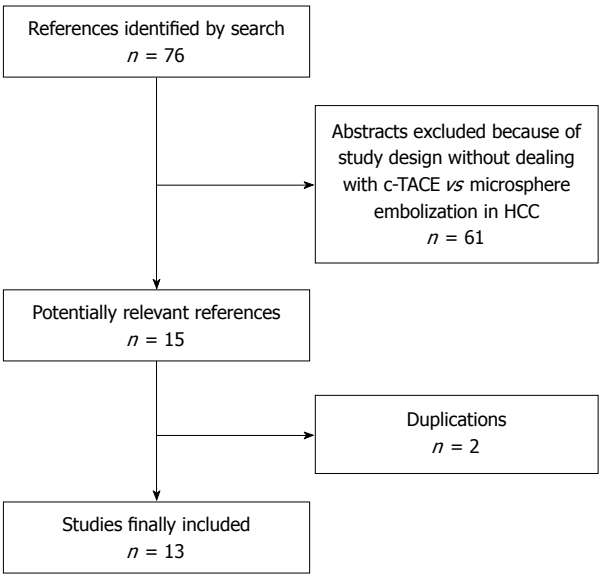


Figure 1 Flow chart of search strategy for study inclusion. c-TACE: Conventional transarterial chemoembolization; HCC: Hepatocellular carcinoma.

treatment-associated complications; (5) year of publication: from January 2004 to December 2013; and (6) each trial had to report at least one of the following results: overall survival rate at 1, 2 or 3 years, tumor response, AFP response, tumor progression rate or treatment associated complications.

Reviews without original data, expert opinions, abstracts, editorials, letters, case reports and studies lacking control groups were excluded from the analysis.

Statistical analysis

All statistical analyses were performed using Review Manager (version 5.1.) from the Cochrane collaboration. Pooled ORs with 95%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 significant.

RESULTS

Trial selection

This study examined a total of 76 potentially relevant studies. Based on the inclusion criteria, 13 clinical trials comparing the efficacy and safety of microsphere embolization (Y90 microspheres or DEB) with those of c-TACE for HCC were included[12-24]. The flow chart of the search strategy is shown in Figure 1. The studies included a total of 1834 patients, and 1233 were treated with c-TACE, 377 with Y90 microsphere embolization and 224 with drug-eluting bead embolization. The basic characteristics of the included studies and the overall survival rate, tumor response (complete response, partial response, stable disease and progressive disease), AFP response and progression rate are summarized in Tables 1 and 2.

Overall survival rate

There were 7, 3, and 3 studies that reported comparative data for 1-, 2- and 3-year overall survival rate, respectively. Based on the results of tests for heterogeneity between trials ($\chi^2_{1\text{-year}} = 9.91$, $P_{1\text{-year}} = 0.13$, $I^2_{1\text{-year}} = 39\%$; $\chi^2_{2\text{-year}} = 4.81$, $P_{2\text{-year}} = 0.09$, $I^2_{2\text{-year}}$: 58%; $\chi^2_{3\text{-year}} = 1.76$, $P_{3\text{-year}} = 0.41$, $I^2_{3\text{-year}} = 0\%$), either the random-effects model or fixed-effects model was used to pool the results in the analysis of overall survival rate. Our study indicated that the 1-, 2- and 3-year overall survival rates of patients who underwent microsphere embolization were significantly higher than those of patients treated with c-TACE (Y90 or DEB *vs* c-TACE: $OR_{1\text{-year}} = 1.38$, 95%$CI_{1\text{-year}}$: 1.05-1.82, $P_{1\text{-year}} = 0.02$; $OR_{2\text{-year}} = 2.88$, 95%$CI_{2\text{-year}}$: 1.18-7.05, $P_{2\text{-year}} = 0.02$; $OR_{3\text{-year}} = 2.15$, 95%$CI_{3\text{-year}}$: 1.18-3.91, $P_{3\text{-year}} = 0.01$) (Figure 2).

Tumor response

Complete response: Ten studies reported comparative data for tumor complete response rate. Based on the results of tests for heterogeneity between trials ($\chi^2 = 15.06$, $P = 0.09$, $I^2 = 40\%$), the random-effects model was used to pool the results. Our meta-analysis indicated that microsphere embolization was associated with significantly higher tumor complete response rate in comparison with c-TACE for treatment of HCC (Y90 or DEB *vs* c-TACE; OR = 2.19, 95%CI: 1.31-3.64, $P = 0.003$) (Figure 3A).

Partial response: Seven studies reported comparative data for partial response rate. Based on the results of tests for heterogeneity between trials ($\chi^2 = 11.17$, $P = 0.08$, $I^2 = 46\%$), the random-effects model was used to pool the results. Our study indicated that there was no significant difference between microsphere embolization and c-TACE in tumor partial response rate for treatment of HCC (Y90 or DEB *vs* c-TACE, OR = 0.73, 95%CI: 0.47-1.15, $P = 0.17$) (Figure 3B).

Stable disease: Six studies reported comparative data for rates of stable disease. Based on the results of tests for heterogeneity between trials ($\chi^2 = 8.92$, $P = 0.11$, $I^2 = 44\%$), the fixed-effects model was used to pool the results in the analysis. Our study indicated that there was no significant difference in rates of stable disease between microsphere embolization and c-TACE for treatment of HCC (Y90 or DEB *vs* c-TACE, OR = 1.07, 95%CI: 0.79-1.44, $P = 0.67$) (Figure 3C).

Progressive disease: Seven studies reported comparative data for rates of progressive disease. Based on the results of tests for heterogeneity between trials ($\chi^2 =$

Table 1 Baseline characteristics of included trials

Ref.	Country	Design	Treatment	No. pts	Age (yr)	Sex (M/F)	Tumor size (cm)	Tumor number (single/multiple)	Child-Pugh class (A/B/C)	Virus infection (HBV/HCV)	BCLC stage (A/B/C/D)	ECOG status (0/1/2)
Moreno-Luna *et al*[16] (2013)	United States	Clinical study	TARE-90Y	61	64 (29-88)	49/12	5.0 (3.3-8.4)	13/48	53/8/0	0/8	12/34/15/0	51/7/1
			TACE	55	66 (46-84)	43/12	5.0 (3.2-8.5)	20/35	44/11/0	0/7	23/13/19/0	40/15/0
Nicolini *et al*[21] (2013)	Italy	Clinical study	DEB-TACE	22	57.2 ± 6.5	19/3	1.8 (0.7-4.5)	8/14	NA	8/10	14/8/0/0	NA
			TACE	16	55.6 ± 6.5	15/1	2.2 (1-10)	8/8	NA	3/12	7/9/0/0	NA
Song *et al*[12] (2012)	South Korea	Cohort study	DEB-TACE	60	61.7 ± 9.8	42/18	4.2 ± 2.8	26/34	56/4/0	44/8	27/33/0/0	NA
			TACE	69	59.0 ± 11.2	48/21	5.0 ± 3.1	31/38	62/6/0	46/8	28/41/0/0	NA
Salem *et al*[17] (2011)	United States	Clinical study	TARE-90Y	123	66 (30-88)	87/36	4.5 (3.1-6.6)	55/68	67/54/2	13/42	43/65/13/2	NA
			TACE	122	61 (33-88)	102/20	3.6 (2.6-5.7)	57/65	67/53/2	12/56	47/61/12/2	NA
van Malenstein *et al*[13] (2011)	Belgium	RCT	DEB-TACE	16	67.3 ± 9.8	14/2	NA	4/12	14/2/0	4/4	2/9/5/0	9/7/0
			TACE	14	56.6 ± 13.4	11/3	NA	1/13	14/0/0	4/0	1/10/3/0	10/2/2
Carr *et al*[19] (2010)	United States	Cohort study	TARE-90Y	99	NA	70/29	NA	NA	NA	9/30	NA	NA
			TACE	691	NA	518/173	NA	NA	NA	97/132	NA	NA
Malagari *et al*[22] (2010)	Greece	RCT	DEB-TACE	41	70.7 ± 6.9	31/10	8.3 ± 2.7	12/29	23/18/0	NA	NA	26/15/0
			TACE	43	70.0 ± 7.9	34/9	8.1 ± 2.8	15/28	26/17/0	NA	NA	28/15/0
Dhanasekaran *et al*[14] (2010)	United States	Clinical study	DEB-TACE	45	59.9 ± 11.4	35/10	5.5 ± 4.3	21/24	22/11/12	5/20	NA	NA
			TACE	26	58.9 ± 13.3	19/7	7.4 ± 4.9	10/16	11/11/4	3/11	NA	NA
Nicolini *et al*[20] (2010)	Italy	Clinical study	DEB-TACE	8	57.0 ± 3.8	8/0	3.0 ± 0.9	7/1	5/3/0	0/3	NA	NA
			TAE	8	56 5 ± 2.0	7/1	3.4 ± 0.2	5/3	6/2/0	2/4	NA	NA
Scartozzi *et al*[23] (2010)	Italy	Clinical study	DEB-TACE	32	68 (41-79)	29/3	NA	NA	14/18/0	NA	NA	NA
			TACE	50	74 (42-89)	36/14	NA	NA	26/24/0	NA	NA	NA
Kooby *et al*[18] (2010)	United States	Cohort study	TARE-90Y	27	58.7 ± 10.8	23/4	7.4 ± 3.2	12/15	13/14/0	0/10	NA	NA
			TACE	44	61.0 ± 9.9	36/8	7.4 ± 5.1	25/19	22/22/0	0/25	NA	NA
Lewandowski *et al*[15] (2009)	United States	Clinical study	TARE-90Y	43	68 (44-88)	38/5	NA	20/23	24/19/0	NA	0/34/9/0	NA
			TACE	43	65 (36-89)	36/7	NA	23/10	23/18/2	NA	0/37/4/2	NA
Ahmad *et al*[24] (2005)	United States	Clinical study	TARE-90Y	24	61 (40-82)	20/4	NA	NA	NA	5/19	NA	NA
			TACE	52	57 (19-80)	46/6	NA	NA	NA	19/28	NA	NA

RCT: Randomized Controlled trial; TRAE: Transarterial radioembolization; 90Y: Yttrium-90; DEB: Drug-eluting bead; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NA: Not applicable; BCLC: Barcelona Clinic Liver Cancer; ECOG: Eastern Cooperative Oncology Group.

20.42, $P = 0.002$, $I^2 = 71\%$), the random-effects model was used to pool the results. Our study indicated that there was no significant difference in rates of progressive disease between microsphere embolization and c-TACE for treatment of HCC (Y90 or DEB *vs* c-TACE: OR = 0.75, 95%CI: 0.33-1.68, $P = 0.48$) (Figure 3D).

AFP response

Five studies reported comparative data for AFP response rate. Based on the results of tests for heterogeneity between trials ($\chi^2 = 13.06$, $P = 0.01$, $I^2 = 69\%$), the random-effects model was used to pool the results. Our study indicated that there was no significant difference in AFP response rate between microsphere embolization and c-TACE for treatment of HCC (Y90 or DEB *vs* c-TACE; OR = 1.38, 95%CI: 0.64-2.94, $P = 0.41$) (Figure 4).

Progression rate

Five studies reported comparative data for overall tumor progression rate. Based on the results of tests for heterogeneity between trials ($\chi^2 = 3.52$, $P = 0.48$, $I^2 = 0\%$), the fixed-

Table 2 Prognosis of patients reported in included trials *n* (%)

Ref.	Treatment	No. pts	1-yr OSR	2-yr OSR	3-yr OSR	CR	PR	SD	PD	AFP response	Progression rate[1]
Moreno-Luna *et al*[16]	TARE-90Y	61	NA	18 (30)	13 (21)	7 (12)	22 (39)	22 (39)	5 (9)	14 (23)	NA
(2013)	TACE	55	NA	13 (24)	9 (16)	2 (4)	22 (47)	16 (34)	7 (15)	18 (33)	NA
Nicolini *et al*[21]	DEB-TACE	22	NA	NA	16 (73.9)	14 (37)	NA	NA	NA	NA	NA
(2010)	TACE	16	NA	NA	9 (58.7)	7 (28)	NA	NA	NA	NA	NA
Song *et al*[12] (2012)	DEB-TACE	60	53 (88)	NA	NA	33 (55)	16 (26)	9 (15)	2 (3)	46 (77)	30 (50)
	TACE	69	46 (67)	NA	NA	16 (23)	18 (26)	21 (30)	14 (20)	31 (45)	48 (69)
Salem *et al*[17] (2011)	TARE-90Y	123	92 (75)	NA	NA	NA	NA	NA	NA	40 (32)	42 (34)
	TACE	122	92 (75)	NA	NA	NA	NA	NA	NA	37 (30)	54 (44)
van Malenstein *et al*[13]	DEB-TACE	16	NA	NA	NA	NA	NA	NA	NA	8 (89)	3 (23)
(2011)	TACE	14	NA	NA	NA	NA	NA	NA	NA	4 (67)	1 (8)
Carr *et al*[19] (2010)	TARE-90Y	99	50 (50)	NA	NA	3 (3)	38 (38)	35 (35)	23 (23)	NA	NA
	TACE	691	301 (43)	NA	NA	37 (5)	390 (55)	199 (29)	75 (11)	NA	NA
Malagari *et al*[22]	DEB-TACE	41	35 (85)	NA	NA	11 (27)	NA	NA	NA	NA	5 (12)
(2010)	TACE	43	37 (86)	NA	NA	6 (14)	NA	NA	NA	NA	9 (21)
Dhanasekaran *et al*[14]	DEB-TACE	45	26 (58)	21 (48)	NA	NA	NA	NA	NA	NA	NA
(2010)	TACE	26	8 (31)	3 (12)	NA	NA	NA	NA	NA	NA	NA
Nicolini *et al*[20] (2013)	DEB-TACE	8	NA	NA	NA	5 (63)	1 (12)	NA	2 (25)	NA	NA
	TACE	8	NA	NA	NA	0 (0)	5 (63)	NA	3 (37)	NA	NA
Scartozzi *et al*[23] (2010)	DEB-TACE	58	NA	NA	NA	14 (24)	32 (39)	16 (19)	19 (22)	NA	NA
	TACE	85	NA	NA	NA	17 (20)	19 (33)	7 (12)	18 (31)	NA	NA
Kooby *et al*[18] (2010)	TARE-90Y	27	4 (16)	NA	NA	0 (0)	3 (11)	11 (41)	9 (33)	5 (24)	NA
	TACE	44	9 (20)	NA	NA	1 (2)	2 (4)	16 (36)	16 (36)	11 (26)	NA
Lewandowski *et al*[15]	TARE-90Y	43	33 (77)	25 (59)	19 (45)	20 (47)	17 (39)	6 (14)	0 (0)	NA	6 (15)
(2009)	TACE	43	31 (73)	12 (28)	8 (19)	6 (17)	19 (54)	9 (26)	1 (3)	NA	11 (32)
Ahmad *et al*[24] (2005)	TARE-90Y	24	NA	NA	NA	22 (92)	NA	NA	NA	NA	NA
	TACE	52	NA	NA	NA	39 (75)	NA	NA	NA	NA	NA

[1]Total data of the relative study. NA: Not applicable; pts: Patients; OSR: Overall survival rate; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; AFP: Alpha fetal protein.

effects model was used to pool the results. Our study indicated that microsphere embolization was associated with significantly lower tumor progression rate compared with c-TACE for treatment of HCC (Y90 or DEB *vs* c-TACE: OR = 0.56, 95%CI: 0.39-0.81, $P = 0.002$) (Figure 5).

Safety

Seven studies reported comparative data for treatment-associated complications. Based on the results of tests for heterogeneity between trials ($\chi^2 = 5.34$, $P = 0.50$, $I^2 = 0\%$), the fixed-effects model was used to pool the results. Our study indicated there was no significant difference in complication rates between microsphere embolization and c-TACE for treatment of HCC (Y90 or DEB *vs* c-TACE; OR = 0.68, 95%CI: 0.46-1.00, $P = 0.05$) (Figure 6).

Assessment of publication bias

In this study, the risk of publication bias was assessed by visual inspection of symmetry of the funnel plot. The fixed-effects model was used to pool the results in the analysis of 1- and 3-year overall survival rate, stable disease, tumor progression rate and safety. The results of our meta-analysis revealed that the symmetry level of the funnel plots was high.

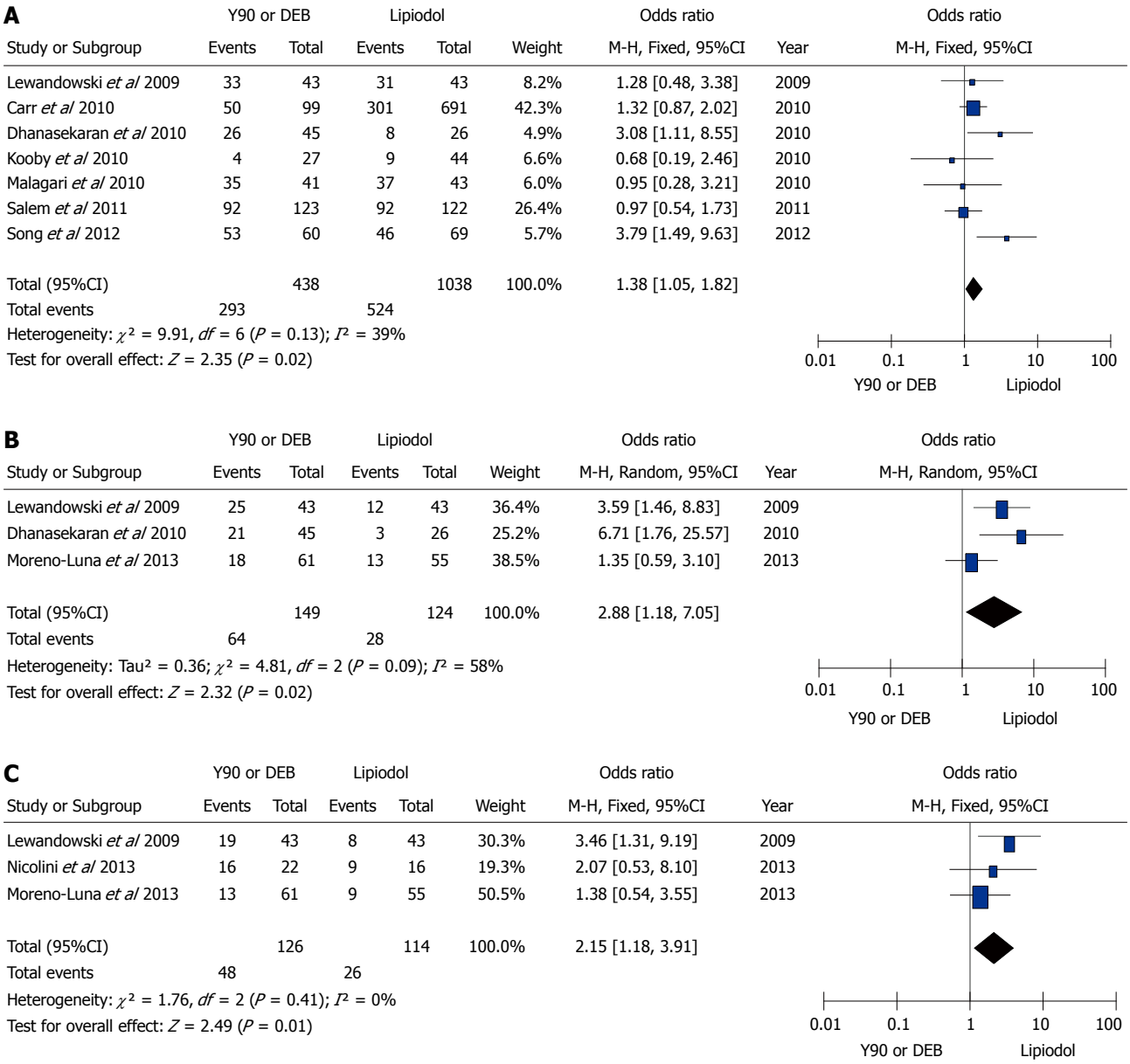


Figure 2 Microsphere embolization (90Y or DEB) *vs* conventional transarterial chemoembolization for treatment of patients with hepatocellular carcinoma in terms of overall survival rates. A: Meta-analysis of 1-year results; B: Meta-analysis of 2-year results; C: Meta-analysis of 3-year results. M-H: Mantel-Haenszel.

It suggested that there was no obvious publication bias in the trials included in this study (Figure 7).

DISCUSSION

TACE is a palliative therapy which has been widely accepted as the treatment of choice for HCC patients who were not candidates for surgical resection. However, the incomplete tumor necrosis after TACE makes the long-term outcome unsatisfactory. Some researchers suggested that microsphere embolization with Y90 microspheres or DEB was associated with better clinical efficacy than c-TACE for treatment of patients with HCC[12-15]. However, some other clinical studies had reported conflicting results[16-19]. Meta-analysis combines data from all eligible studies, and has the advantages of reducing random error, obtaining more precise estimates and defining the effect of clinical interventions more precisely. It may be the appropriate method for resolving such conflicts. In this study, we searched formally published studies to comprehensively compare the efficacy and safety of microsphere embolization with those of c-TACE for treatment of patients with HCC. A total of 13 studies and 1834 HCC patients were identified and statistically analyzed. Overall survival rate, complete response, partial response, stable disease, progressive disease, AFP response, progression rate and complications were compared and analyzed. The analyzed data of our study indicated that microsphere embolization (Y90 or DEB) was a better treatment choice in comparison with c-TACE, in terms of overall survival and complete tumor response. Additionally, we found that there was no significant difference between those two treatments in complication rates.

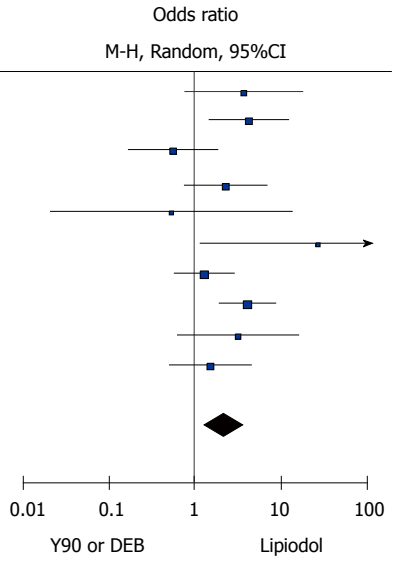
Our study indicated that the patients who underwent

A

Study or Subgroup	Y90 or DEB Events	Y90 or DEB Total	Lipiodol Events	Lipiodol Total	Weight	Odds ratio M-H, Random, 95%CI	Year
Ahmad *et al* 2005	22	24	39	52	7.5%	3.67 [0.76, 17.76]	2005
Lewandowski *et al* 2009	20	43	6	35	12.4%	4.20 [1.45, 12.18]	2009
Carr *et al* 2010	3	99	37	691	10.9%	0.55 [0.17, 1.83]	2010
Malagari *et al* 2010	11	41	6	43	11.9%	2.26 [0.75, 6.83]	2010
Kooby *et al* 2010	0	27	1	44	2.3%	0.53 [0.02, 13.41]	2010
Nicolini *et al* 2010	5	8	0	8	2.4%	26.71 [1.14, 624.23]	2010
Scartozzi *et al* 2010	14	58	17	85	16.3%	1.27 [0.57, 2.84]	2010
Song *et al* 2012	33	60	16	69	17.0%	4.05 [1.90, 8.62]	2012
Moreno-Luna *et al* 2013	7	57	2	47	7.2%	3.15 [0.62, 15.95]	2013
Nicolini *et al* 2013	14	38	7	25	12.1%	1.50 [0.50, 4.48]	2013
Total (95%CI)		455		1099	100.0%	2.19 [1.31, 3.64]	
Total events	129		131				

Heterogeneity: Tau² = 0.25; χ^2 = 15.06, *df* = 9 (*P* = 0.09); I^2 = 40%

Test for overall effect: *Z* = 3.01 (*P* = 0.003)

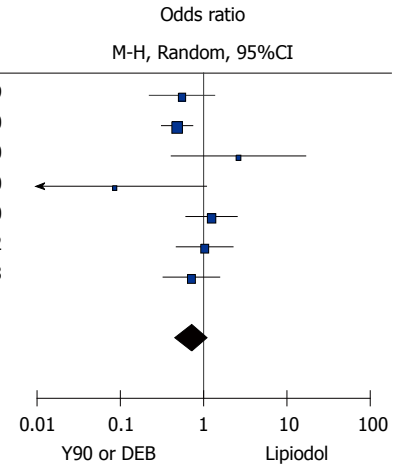


B

Study or Subgroup	Y90 or DEB Events	Y90 or DEB Total	Lipiodol Events	Lipiodol Total	Weight	Odds ratio M-H, Random, 95%CI	Year
Lewandowski *et al* 2009	17	43	19	35	14.3%	0.55 [0.22, 1.36]	2009
Carr *et al* 2010	38	99	390	691	26.1%	0.48 [0.31, 0.74]	2010
Kooby *et al* 2010	3	27	2	44	4.9%	2.63 [0.41, 16.83]	2010
Nicolini *et al* 2010	1	8	5	8	2.8%	0.09 [0.01, 1.08]	2010
Scartozzi *et al* 2010	32	82	19	56	18.4%	1.25 [0.61, 2.53]	2010
Song *et al* 2012	16	60	18	69	16.7%	1.03 [0.47, 2.26]	2012
Moreno-Luna *et al* 2013	22	57	22	47	16.7%	0.71 [0.33, 1.56]	2013
Total (95%CI)		376		950	100.0%	0.73 [0.47, 1.15]	
Total events	129		475				

Heterogeneity: Tau² = 0.15; χ^2 = 11.17, *df* = 6 (*P* = 0.08); I^2 = 46%

Test for overall effect: *Z* = 1.36 (*P* = 0.17)

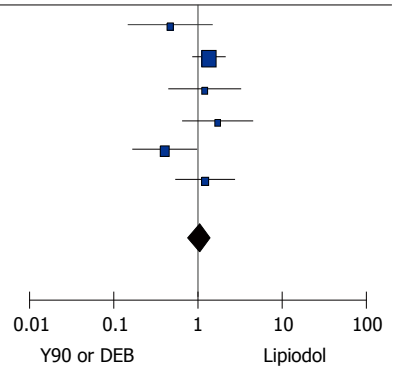


C

Study or Subgroup	Y90 or DEB Events	Y90 or DEB Total	Lipiodol Events	Lipiodol Total	Weight	Odds ratio M-H, Fixed, 95%CI	Year
Lewandowski *et al* 2009	6	43	9	35	10.4%	0.47 [0.15, 1.48]	2009
Carr *et al* 2010	35	99	199	691	39.3%	1.35 [0.87, 2.11]	2010
Kooby *et al* 2010	11	27	16	44	8.8%	1.20 [0.45, 3.22]	2010
Scartozzi *et al* 2010	16	84	7	58	8.2%	1.71 [0.66, 4.48]	2010
Song *et al* 2012	9	60	21	69	20.2%	0.40 [0.17, 0.97]	2012
Moreno-Luna *et al* 2013	22	57	16	47	13.1%	1.22 [0.54, 2.72]	2013
Total (95%CI)		370		944	100.0%	1.07 [0.79, 1.44]	
Total events	99		268				

Heterogeneity: χ^2 = 8.92, *df* = 5 (*P* = 0.11); I^2 = 44%

Test for overall effect: *Z* = 0.42 (*P* = 0.67)



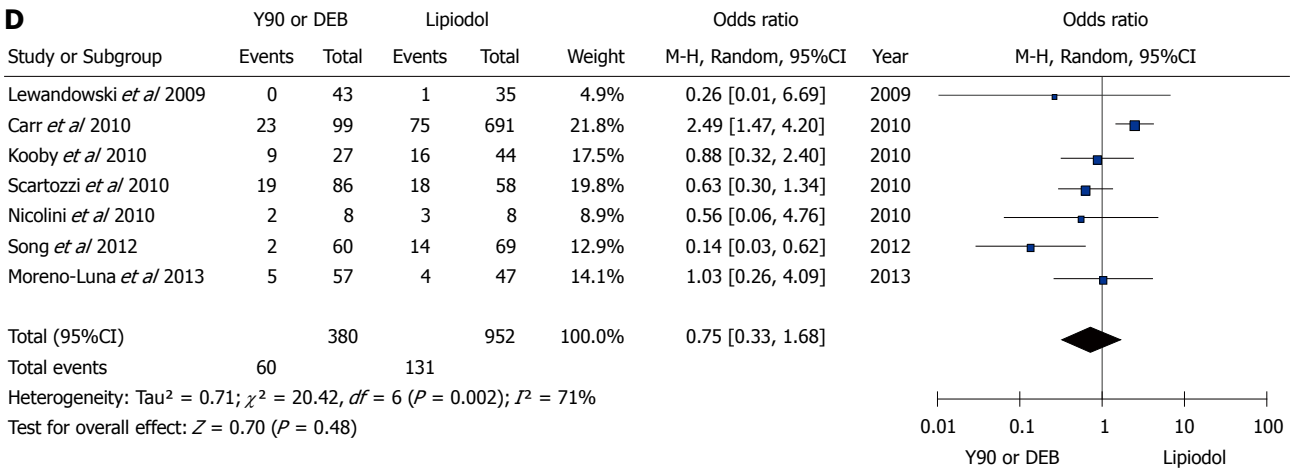


Figure 3 Microspheres embolization (90Y or DEB) *vs* conventional transarterial chemoembolization for treatment of patients with hepatocellular carcinoma in terms of tumor response. A: Meta-analysis of complete response results; B: Meta-analysis of partial response results; C: Meta-analysis of stable disease results; D: Meta-analysis of progressive disease results.

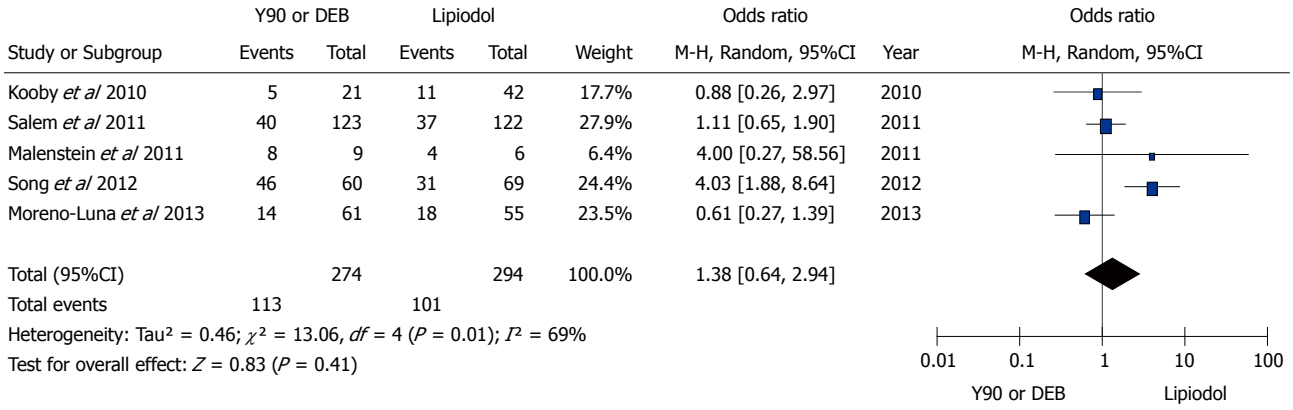


Figure 4 Microsphere embolization (90Y or DEB) *vs* compare conventional transarterial chemoembolization for treatment of patients with hepatocellular carcinoma in term of α-fetoprotein response.

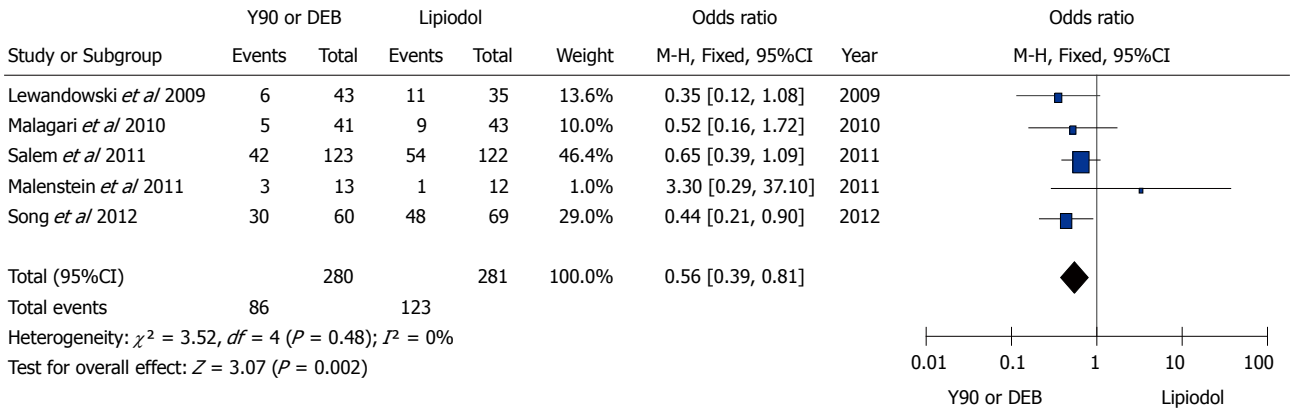


Figure 5 Microsphere embolization (90Y or DEB) *vs* conventional transarterial chemoembolization for treatment of patients with hepatocellular carcinoma in terms of tumor progression rate.

microsphere embolization had significantly higher 1-, 2-, and 3-year overall survival rates and complete tumor response rate than those treated with c-TACE. In clinical practice, microsphere embolization and TACE are mechanistically quite different, though both treatments are delivered through the hepatic artery. C-TACE comprises intra-arterial chemotherapy using lipiodol and chemotherapeutic agents, followed by selective vascular embolization, which causes arterial occlusion and chemotherapeutic effects, resulting in a strong cytotoxic effect combined with ischemia, thus inhibiting the progression of the tumor[25,26]. Although the short-term effectiveness

Study or Subgroup	Y90 or DEB Events	Y90 or DEB Total	Lipiodol Events	Lipiodol Total	Weight	Odds ratio M-H, Fixed, 95%CI	Year	Odds ratio M-H, Fixed, 95%CI
Nicolini *et al* 2010	3	8	2	8	2.0%	1.80 [0.21, 15.41]	2010	
Kooby *et al* 2010	12	27	31	44	21.1%	0.34 [0.12, 0.91]	2010	
Malagari *et al* 2010	33	41	35	43	10.7%	0.94 [0.32, 2.80]	2010	
Dhanasekaran *et al* 2010	3	45	2	26	3.8%	0.86 [0.13, 5.50]	2010	
Malenstein *et al* 2011	4	16	8	14	10.3%	0.25 [0.05, 1.18]	2011	
Song *et al* 2012	24	60	34	69	30.5%	0.69 [0.34, 1.38]	2012	
Moreno-Luna *et al* 2013	40	61	37	55	21.6%	0.93 [0.43, 2.01]	2013	
Total (95%CI)		258		259	100.0%	0.68 [0.46, 1.00]		
Total events	119		149					

Heterogeneity: $\chi^2 = 5.34$, $df = 6$ ($P = 0.50$); $I^2 = 0\%$

Test for overall effect: $Z = 1.98$ ($P = 0.05$)

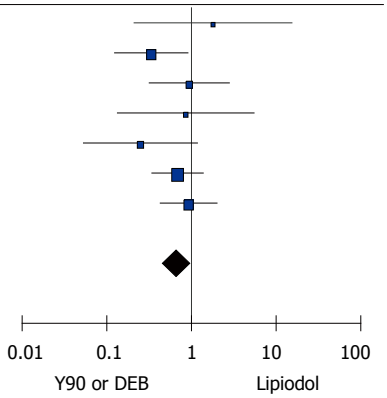


Figure 6 Microsphere embolization (90Y or DEB) *vs* conventional transarterial chemoembolization for treatment of patients with hepatocellular carcinoma in terms of complications.

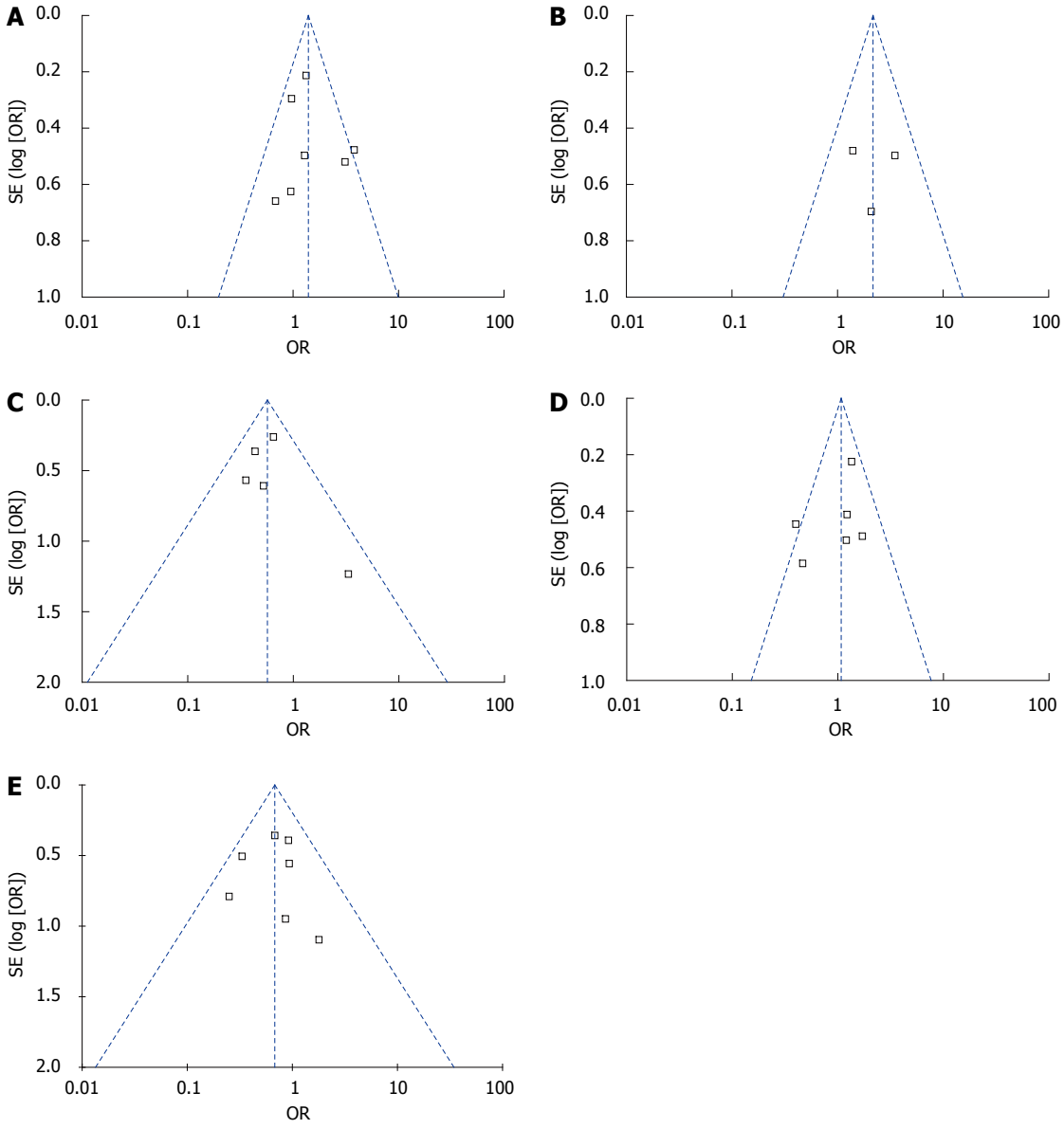


Figure 7 Funnel plots in this study. A: Funnel plot of 1-year overall survival rate; B: Funnel plot of 3-year recurrence-free survival rate; C: Funnel plot of tumor progression rate; D: Funnel plot of stable disease; E: Funnel plot of complications.

of c-TACE is obvious in the treatment of HCC, the long-term outcome is still unsatisfactory[27-29], because the micro-environmental hypoxia of tumor tissue caused by arterial occlusion results in overexpression of hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF)[30,31]. Overexpression of HIF-1α always results in increased angiogenesis, tumor progression, invasion, metastasis and poor prognosis of patients[32-34]. VEGF promotes the proliferation of vessel endothelial cells, inhibits the apoptosis of vessel endothelial cells, and stimulates the formation of blood vessels, thus promoting tumor progression[35-37]. In addition, TACE induces pain and post-embolization syndrome, and often requires anti-inflammatories, narcotics, and larger number of treatment hospitalizations[38].

Y90 is a pure beta emitter and decays to stable zirconium-90 with a physical half-life of 64.1 h, making it an ideal transarterial liver-directed agent. In comparison with c-TACE, microsphere embolization using Y90 involves injecting radioactive particles into the selected liver artery without causing arterial occlusion[38]. Hence, there is no hypoxia initiated gene overexpression or post-embolization syndrome, and fatigue can easily be managed in outpatients settings. DEB have been used to bind, deliver and elute chemotherapeutic drugs in the tumor area during TACE. Unlike conventional TACE, which is the most commonly used therapy, DEB-TACE is based on calibrated microspheres made of non-degradable polymers that produce permanent vascular embolization[39-41]. In addition, DEB-TACE introduces a higher drug concentration and longer contact time within the tumor than c-TACE, while maintaining a lower systemic concentration[12,13]. Thus, DEB-TACE can significantly improve the clinical efficacy and reduce the drug related adverse events in comparison with c-TACE.

Both microsphere embolization and c-TACE are minimally invasive and target-selective treatments, guided by imaging devices. There was no treatment-related death observed in the included trials. Our study showed that the patients undergoing microsphere embolization had similar adverse effects as those who received c-TACE. There was no significant difference in safety between microsphere embolization and c-TACE in the treatment of patients with HCC. The most commonly observed adverse effects of both procedures were fatigue, abdominal pain, nausea, fever, vomiting, hepatic abscess and bleeding puncture site[42-45]. However, all the mentioned adverse effects can be ameliorated after relatively symptomatic treatment.

To the best of our knowledge, there is no other meta-analysis which comprehensively compares the clinical efficacy and safety of microsphere embolization with those of c-TACE in the treatment of patients with HCC. In this study, overall survival rate, tumor response, AFP response, progression rate and complications were compared and analyzed. The risk of publication bias in the included studies was assessed by visual inspection of symmetry level of funnel plot. The data of our study revealed that the level of symmetry of the funnel plot and was judged to be high. It suggested that there was no significant publication bias in the included trials in this study.

The potential limitations of our meta-analysis may be mentioned. Firstly, the etiological factors of HCC (alcoholic hepatic disease, autoimmune liver disease, virus hepatitis, *etc*) were not well considered in the included trials. Secondly, there was a limited number of available randomized controlled trials (RCTs) comparing the efficacy and safety of microsphere embolization and c-TACE for HCC in the last decade. 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 are insufficient[46]. In the future, more RCTs should be enrolled to provide further evidence.

In conclusion, our analysis showed that microsphere embolization with Y90 or DEB was associated with superior survival and treatment response in comparison with c-TACE in the treatment of patients with HCC.

COMMENTS

Background

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors. Microsphere embolization has been used more widely for the treatment of HCC. Some researchers suggested that microsphere embolization was associated with greater clinical efficacy in comparison with conventional transarterial chemoembolization (c-TACE) in HCC. Some other studies had reported conflicting results. Hence, whether microsphere embolization or c-TACE is the better treatment choice has been debated. However, there was no meta-analysis on that issue.

Research frontiers

Over the past decade, several clinical trials were designed to compare the effectiveness of microsphere embolization with that of c-TACE in the treatment of HCC. However, there was no consistent conclusion on that issue. In the current study, the authors designed a meta-analysis to comprehensively compare the efficacy and safety of microsphere embolization compared with c-TACE in patients with HCC.

Innovations and breakthroughs

Based on the data of this meta-analysis, microsphere embolization was associated with significantly higher overall survival and complete tumor response in comparison with c-TACE. Additionally, there was no significant difference between these two kinds of treatments in terms of adverse effects. Hence, the study indicated that microsphere embolization is superior to c-TACE in the treatment of patients with HCC.

Applications

The analysis showed that the clinical effectiveness of microsphere embolization was much better than that of c-TACE for treatment of HCC. The comparison of these treatments could help stratify the benefits of treatment choices for patients with HCC.

Terminology

Conventional TACE is one of the most widely performed treatments for unresectable HCC, which is a type of interventional radiology. Yttrium-90 is a pure beta emitter and decays to stable zirconium-90 with a physical half-life of 64.1 hours. Drug-eluting beads are a kind of calibrated microsphere made of non-degradable polymers that produce permanent vascular embolization. In recent years, both c-TACE and microsphere (Y90 or DEB) embolization have been used for the treatment of HCC.

Peer review

This is a well-performed meta-analysis of currently available studies to compare

comprehensively the efficacy and safety of microsphere (Y90 or DEB) embolization with those of c-TACE in HCC. The comparison of these treatments could help stratify the benefits of treatment choices for patients with HCC.

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