

Doxorubicin-eluting beads vs conventional TACE for hepatocellular carcinoma: a Meta-analysis

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Abstract: Objective To conduct a Meta-analysis for assessing the therapeutic efficacy and safety of doxorubicin-eluting bead transcatheter arterial chemoembolization (DEB-TACE) vs conventional TACE (C-TACE) in the treatment of hepatocellular carcinoma (HCC). **Methods** The relevant studies on DEB-TACE and C-TACE for HCC were searched from PubMed, Web of Science and CKIN databases. The tumor responds and adverse events in the selected studies were analyzed with RevMan5.0 statistical software. Moreover, publication bias was assessed by a funnel plot. **Results** Thirteen studies with 1 325 HCC patients were finally included in this analysis. The tumor response to DEB-TACE was better than that to C-TACE (OR: 2.28; 95%CI [1.75, 2.96]; $P<0.001$). The risk of adverse events in DEB-TACE group was also lower than that in C-TACE group (RR: 0.56; 95% CI [0.32, 0.97]; $P=0.04$). **Conclusion** Compared with C-TACE, DEB-TACE is more effective and has lower risk of adverse events in the treatment of HCC.

Keywords: hepatocellular carcinoma; drug-eluting bead transarterial chemoembolization; Meta-analysis; therapeutic efficacy

Introduction

Hepatocellular carcinoma (HCC) has become the 6th most common tumors worldwide with approximately 600 000 new cases increasing per year and is the 3rd leading cause of cancer-related death worldwide^[1-2]. Although liver transplantation and surgical resection are treatment options with high survival rates, about 70% of patients have lost the chance of surgery and transplantation at the time of diagnosis, and their median survival is only a few months^[3-5]. Using transcatheter arterial chemoembolization (TACE) can isolate tumor cells, thereby blocking the tumor blood supply. Nowadays, TACE is widely used in the patients who has lost the last chance for curative treatments as first-line treatment of advanced HCC^[6]. However, there are also some severe post-TACE complications, such as acute liver or renal failure, upper gastrointestinal bleeding, ascites

and hepatosplenic abscesses, etc^[7].

The doxorubicin-eluting bead (DEB), a novel drug delivery embolization system, has been introduced into TACE. DEB-TACE uses microspheres as embolic agents, which will deliver higher concentration of chemotherapeutic agent and prolong the time of drug-tumor contact^[8-9]. Some clinical trails have proved that DEB-TACE can reduce systemic doxorubicin concentration and improve tumor concentration^[10-13].

Compared with conventional TACE (C-TACE), DEB-TACE is a preferred treatment strategy for patients with advanced HCC. However, some Meta-analysis published in recent years showed that there is no significant difference in the outcomes between C-TACE and DEB-TACE. Whether DEB-TACE or C-TACE is a better choice for patients with advanced HCC is still controversial. Herein we perform a Meta-analysis to address this dilemma.

1 Methods

1.1 Study search and inclusion criteria

We used the keywords of "advanced HCC", "DEB-TACE", "efficacy" and "adverse" to search for the relevant studies from PubMed, Web of Science and CKIN databases (from 2000-01 to 2016-12). Inclusion criteria:

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(1) all the patients were diagnosed with advanced liver cancers by clinical diagnosis or pathology, and they lost the chance of surgery or refused operation; (2) using the method of random assignment or according to the wishes of patients to divide these patients into C-TACE group and DEB-TACE group; (3) providing a case control or cohort study on the original data; (4) objective response rate (ORR), overall survival (OS) and adverse events (AE) are available^[14]. Exclusion criteria: (1) raw data are not suitable for computational analysis; (2) conference summary, case report, current affairs, review and other Meta-analysis; (3) study of repeated or similar data^[15].

1.2 Data extraction and quality assessment

The clinical data, including patients' characteristics, study characteristics and outcomes, were extracted by two researchers independently. Disagreements were solved by discussion or the 3rd investigator. The quality of randomized controlled trials (RCT) was evaluated by Jadad scale^[16]. There are 4 items in this scale, namely randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 point) and distribution (0-2 points).

1.3 Statistical analysis

RevMan5.0 statistical software provided by Cochrane collaboration network was used for Meta-analysis. Odds ratio (OR) and 95% confidence intervals (95%CI) are used to evaluate tumor respond, while risk ratio (RR) is used to analyze the rates of AE and OS. Both fixed-effect model (FEM) and random-effect model (REM) are established. P value <0.05 or $I^2 > 50\%$ suggests that there is heterogeneity among those studies. In case of heterogeneity, we preferred to perform the REM for Meta-analysis. Publication bias was assessed with a funnel plot.

2 Results

2.1 Study search

A total of 1 080 potential studies were searched from PubMed, Web of Science and CKIN databases. According to inclusion and exclusion criteria, only 13 relevant studies with 1 325 patients are included in this analysis (Fig.1).

2.2 Study characteristics

As shown in table 1, all studies were comparing DEB-TACE with C-TACE or another. The main characteristics of the included 13 studies were presented. There are 5 RCT and 8 non-randomized controlled

trials (NRCT). RCT was evaluated by Jadad scale according to relevant criteria. Patients were rated as child-pugh A/B and BCLC A/B/C. The ORR was defined as complete response and partial response.

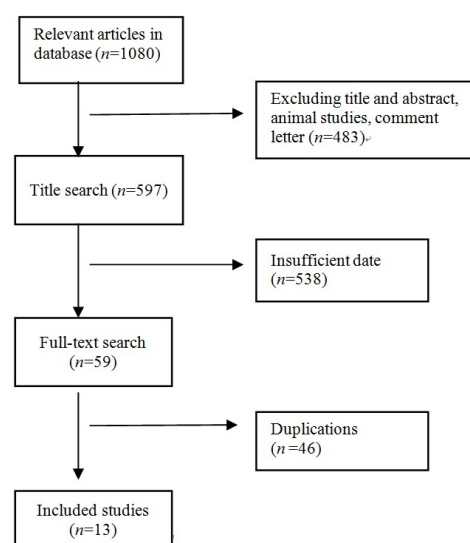


Fig.1 Process of study search

2.3 ORR

The tumor response rate (ORR) was reported in 10 studies (988 patients). The results suggested that compared with C-TACE, DEB-TACE for patients with advanced HCC achieved a higher ORR (OR: 2.28, 95%CI [1.75, 2.96], $P < 0.0001$) (Fig.2). Moreover, the analysis of heterogeneity showed that $\text{Chi}^2 = 14.35$, $\text{df} = 9$ ($P = 0.11$), $I^2 = 37\%$, therefore a FEM was established. Subgroup analysis was used to divide the included studies into RCT and NRCT. The OR of NRCT and RCT was 2.57 [1.73, 3.81] and 2.09 [1.07, 4.09], respectively, without significant differences (Fig.3-4). The funnel plot revealed that there was no significant publication bias (Fig.5).

2.4 AE

Only 10 studies reported the rate of AE. RDM was established to perform Meta analysis for the heterogeneity was high ($\text{Chi}^2 = 40.26$, $\text{df} = 9$, $I^2 = 78\%$) (Fig.6). The pooled results showed that there were significant differences between DEB-TACE group and C-TACE group (RR=0.56, 95%CI [0.32, 0.97], $P = 0.04$), which indicated that DEB-TACE was safer than C-TACE.

2.5 OS

The analysis on the included studies in which the OS rates were reported showed that DEB-TACE for advance HCC significantly improved 1-year and 2-year

Tab.1 Characteristics of 13 included studies

Studies	Design	Treatment	Sample size	Median age	Child-Pugh (A/B)	BCLC(A/B/C)
Golfieri R, et al ^[17]	NRCT	DEB-TACE	89	68.9±8.0	75/14	41/26/22
		C-TACE	88	68.3±8.0	77/11	41/23/24
Yoo J J, et al ^[18]	NRCT	DEB-TACE	51	67	-	-
		C-TACE	25	67	-	-
Chen H S, et al ^[19]	NRCT	DEB-TACE	21	65±10	16/5	-
		C-TACE	20	60±8	17/3	-
Malagari K, et al ^[20]	RCT	DEB-TACE	41	70.4±7.4	23/18	26/15/0
		C-TACE	43	70.4±7.4	26/17	28/15/0
Wiggermann P, et al ^[21]	NRCT	DEB-TACE	22	70.32±7.06	22/0	4/15/3
		C-TACE	22	67.72±9.0	22/0	2/17/3
Liu Y S, et al ^[22]	NRCT	DEB-TACE	64	66.2±9.6	-	6/58/0
		C-TACE	41	66.7±9.8	-	1/40/0
Lencioni R, et al ^[23]	RCT	DEB-TACE	93	67.3±9.1	77/16	24/69/0
		C-TACE	108	67.4±8.8	89/19	29/79/0
Dhanasekaran R, et al ^[24]	NRCT	DEB-TACE	45	59.96±11.45	-	22/11/12
		C-TACE	26	58.96±13.30	-	11/11/4
Sacco R, et al ^[25]	RCT	DEB-TACE	33	71.3±7.2	29/4	22/11/0
		C-TACE	34	68.7±8.1	25/9	22/12/0
Song M J, et al ^[26]	NRCT	DEB-TACE	60	61.7±9.8	56/4	27/33/0
		C-TACE	69	62.3±11.2	63/6	28/41/0
Recchia F, et al ^[27]	NRCT	DEB-TACE	35	72	13/22	-
		C-TACE	60	70	28/32	-
Ferrer Puchol M D, et al ^[28]	RCT	DEB-TACE	47	68.48±0.54	-	-
		C-TACE	25	69.26±11.80	-	-
Mabed M, et al ^[29]	RCT	DEB-TACE	50	52	34/16	-
		C-TACE	50	51	35/15	-

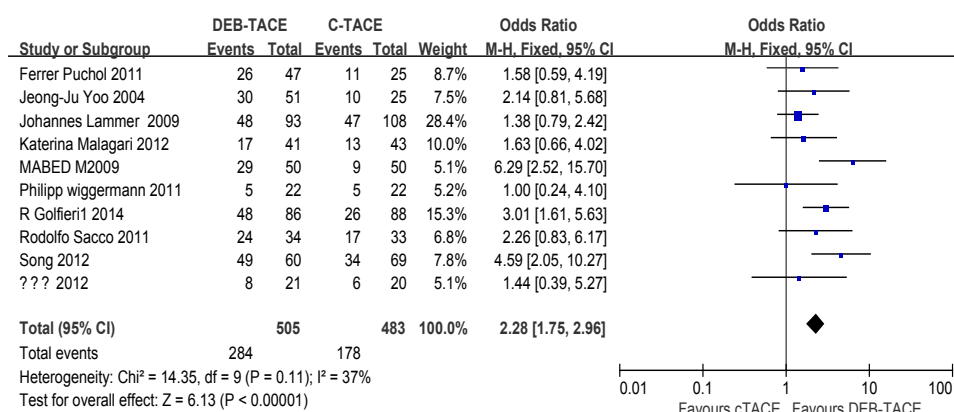


Fig.2 Forest plot depicting ORR reported in the included studies

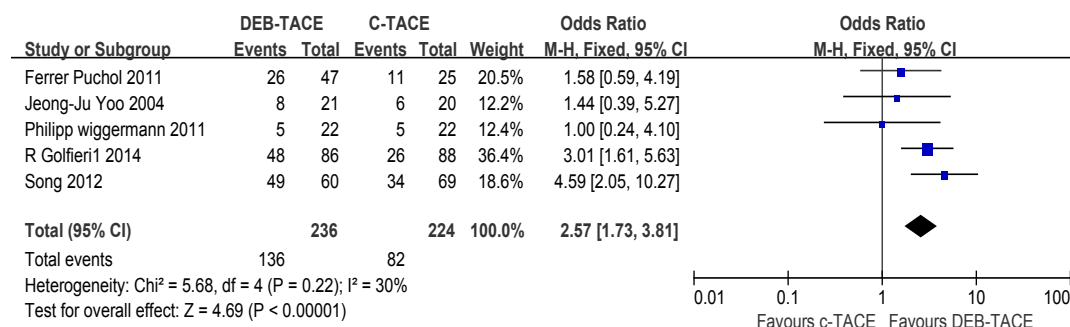


Fig.3 Forest plot depicting ORR reported in NRCT

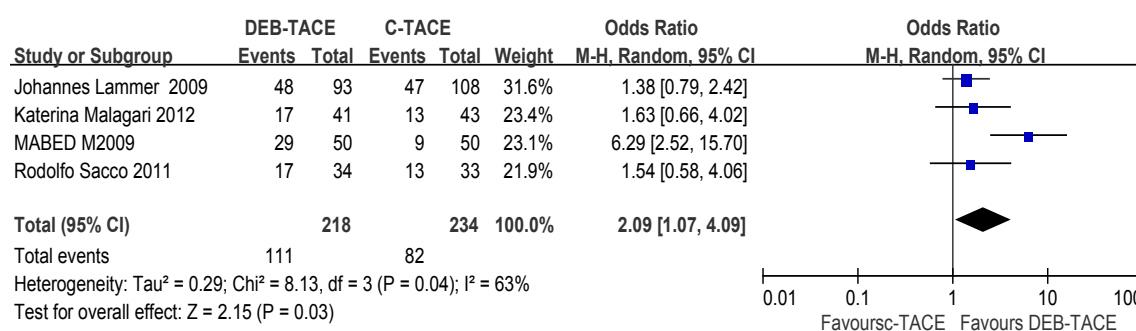


Fig.4 Forest plot depicting ORR reported in RCT

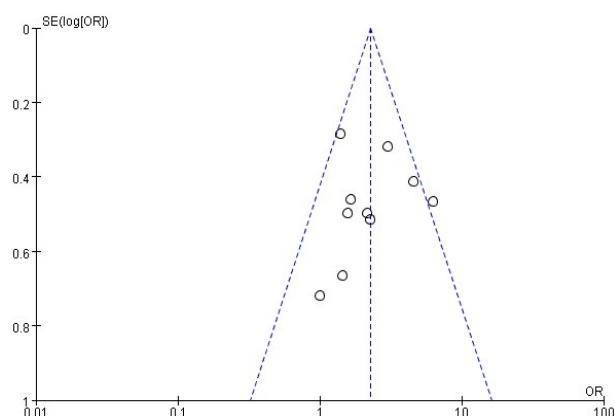


Fig.5 Funnel plot depicting the publication bias in the included studies

OS rates, respectively ($RR=1.12$, 95%CI [1.05, 1.19], $Z=3.60$, $P=0.000\ 03$; $RR=1.21$, 95%CI [1.02, 1.45], $Z=2.18$, $P=0.03$).

3 Discussion

Although the optimal method to treat liver cancer is radical resection, but the postoperative 5-year-survival rate is only 25% to 50%, and only 18% of the patients has operation indications^[30-32]. TACE is one of the most frequently used treatment options for unresectable HCC. Herein we used Meta-analysis to assess the safety and

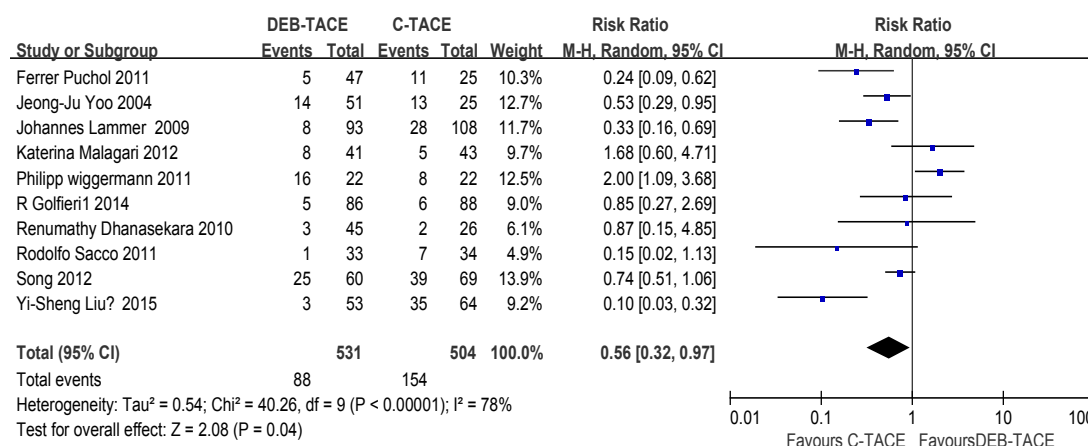


Fig.6 Forest plot depicting AE reported in the included studies

therapeutic efficacy of DEB-TACE and C-TACE in patients with HCC. A total of 13 clinical studies including 1 325 patients were included. The analysis results suggested that compared with C-TACE, DEB-TACE for patients with advanced HCC achieved a higher ORR and a lower AE. Moreover, the OS rate was higher in DEB-TACE group as compared with C-TACE group. C-TACE is considered as first-line treatment for patients with advance HCC, while DEB-TACE is a novel drug delivery system using microspheres as embolic agents. Unlike C-TACE, DEB-TACE can sequester doxorubicin hydrochloride from solution and release it sustainedly.

Despite our results showed that the HCC patients benefited more from DEB-TACE than C-TACE, there are some limitations in our study. Firstly, the small sample size of the included studies affected the reliability of the results. Secondly, the clinical trials included in this study have small sample size. Over-estimation of the treatment effect is more likely in smaller trials compared with larger trials^[33]. Thirdly, patients vary greatly in the clinical characteristics, including disease statues, gender and ethnicity. In conclusion, this Meta-analysis on DEB-TACE vs C-TACE for HCC shows that DEB-TACE has a high efficacy and safety.

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生物力学与材料

阿霉素洗脱微球 TACE 对比传统 TACE 治疗肝癌的 Meta 分析

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【摘要】目的:采用 Meta 分析方法评价和比较阿霉素洗脱微球 TACE (DEB-TACE) 与传统 TACE (C-TACE) 治疗肝癌的有效性和安全性。**方法:**从 PubMed、Web of Science 和 CKIN 数据库检索 DEB-TACE 和 C-TACE 治疗肝癌的文献。分别采用 RevMan5.0 软件分析肿瘤反应和不良事件, 漏斗图分析出版偏倚。**结果:**共有 13 个研究 1 325 例肝癌患者纳入分析。DEB-TACE 组的肿瘤反应率优于 C-TACE 组 (OR: 2.28; 95%CI [1.75, 2.96]; $P < 0.0010$)。DEB-TACE 组的不良事件风险低于 C-TACE 组 (RR: 0.56; 95%CI [0.32, 0.97]; $P = 0.04$)。**结论:**和 C-TACE 对比, DEB-TACE 治疗肝癌更有效、不良事件风险更低。**【关键词】**肝癌; 药物洗脱微球 TACE; Meta 分析; 疗效

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