

The clinical safety and efficacy of conventional transcatheter arterial chemoembolization and drug-eluting beads-transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: A meta-analysis

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Summary

Transcatheter arterial chemoembolization (TACE) plays an important role in the treatment of unresectable liver cancer. We conducted this meta-analysis to compare the clinical safety and efficacy of conventional TACE (C-TACE) and drug-eluting beads (DEB)-TACE. A search for those procedures was performed using the PubMed, EMBASE, and Cochrane Library databases. A meta-analysis of patients who underwent C-TACE or DEB-TACE was conducted. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Of 334 studies, 30 were analyzed. The complete response rate, disease control rate, objective response rate, 3-year survival rate, and non-response rate were significantly higher in patients who underwent DEB-TACE than those in patients who underwent C-TACE. The 1-year survival rate, 2-year survival rate, 30-day mortality rate, complete response rate, disease control rate, complete necrosis rate, non-response rate, objective response rate, progressive disease rate, and recurrence did not differ significantly between patients who underwent C-TACE and patients who underwent DEB-TACE. Patients who undergo DEB-TACE might have a higher complete response rate, disease control rate, and 3-year survival rate than patients who undergo C-TACE. Safety did not differ significantly between C-TACE and DEB-TACE.

Keywords: TACE, DEB-TACE, liver cancer, objective response rate, survival, safety

1. Introduction

Hepatocellular carcinoma (HCC) is the 6th most common malignant tumor, and it ranks 3rd in terms

of cancer-related deaths, with an overall survival rate of 3-5% (1). Unfortunately, its incidence is still rising around the world (2). Hepatitis viral infections and alcoholism are the dominant factors that trigger HCC. Diabetes, obesity, and metabolic disorders are also associated with HCC (3). Common treatments include resection, ablation, chemoembolization, radiotherapy, and chemotherapy (4). The preferred approach, surgical resection can increase the 5-year survival rate to 60% (5). However, most patients exhibit nonspecific clinical symptoms, so when the condition is ultimately diagnosed they are unable to undergo radical surgery (6). Only 10-15% of patients with HCC are eligible for surgical resection. As a downstaging therapy, transcatheter arterial chemoembolization (TACE) has been widely used to treat unresectable HCC, and it can improve the overall survival of patients with HCC (7,8).

Released online in J-STAGE as advance publication October 14, 2019.

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In TACE, a suspension consisting of a chemotherapy drug and lipiodol is delivered via a catheter to the hepatic artery branch of the diseased liver. The released chemotherapy drug then plays an antagonistic role. Drug-eluting beads transcatheter arterial chemoembolization (DEB-TACE) has often been performed over the past decade. Its major differences compared to conventional TACE (C-TACE) are a higher adsorption capacity of the chemotherapy drug and a slower and more consistent release (9). Considering the rapid metabolism of chemotherapy drugs in C-TACE, drug use should theoretically be better in DEB-TACE. However, its therapeutic efficacy and safety are debated. Therefore, this meta-analysis was performed.

2. Methods

2.1. Search strategy

A search of the PubMed, EMBASE, and the Cochrane Library databases was conducted. The last search was conducted on July 30, 2016. Search terms were as follows: "TACE," "DEB-TACE," and "hepatocellular carcinoma." The full text of each identified article was read, and irrelevant articles were discarded. If the same subjects were referenced across multiple articles or if an article included more subjects or provided more overall information than another article, then the article was selected for meta-analysis.

2.2. Eligibility criteria

Eligible studies were randomized controlled trials (RCTs) or prospective or retrospective cohort and case-control studies published prior to June 2016 that met the following inclusion criteria: *i*) directly compared C-TACE and DEB-TACE in patients with HCC; *ii*) reported at least one of the following data: response rate and survival rate; *iii*) reported the relative odds ratio (OR) and hazard ratio (HR) or provided data for their calculation; and *iv*) articles written in English.

Case reports and abstracts or studies with insufficient data were excluded. If multiple articles included the same subjects, only the most recent and complete article was analyzed. When information was incomplete, attempts were made to contact the corresponding authors for additional data.

2.3. Data extraction

Once the researchers agreed on the articles to include, a flow chart was created. The relevant information was as follows: first author, date of publication, country, study design, enrollment period, type of patients, groups, number of patients, number of procedures, previous TACE, locoregional treatment, Child-Pugh stage, Barcelona Clinic Liver Cancer Center (BCLC) stage,

Okuda stage, ECOG performance status, and Milan tumor criteria.

2.4. Assessment of study quality

The quality of eligible RCTs and non-RCTs was respectively evaluated using the Cochrane Handbook for Systematic Reviews of Interventions and the Newcastle-Ottawa scale. The Cochrane Handbook for Systematic Reviews of Interventions consists of 6 items: adequacy of the generation of allocation sequence, allocation concealment, blinding, the presence of incomplete outcome data, selective outcomes, and other sources of bias. The Newcastle-Ottawa scale consists of 3 items including selection (4 points), comparability (2 points), and exposure (3 points).

2.5. Data analysis

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to compare C-TACE and DEB-TACE, and only a random-effects model was used. All tests were two-tailed, and p values of less than 0.05 were statistically significant. The I^2 statistic and Chi-square test were used to evaluate heterogeneity. When $I^2 > 50\%$ or $p < 0.10$, heterogeneity was statistically significant. All statistical analyses were performed using Stata.

3. Results

3.1. Study selection and characteristics

As shown in Figure 1, 334 studies were initially identified. After preliminary exclusion of abstracts or papers not fulfilling the search criteria, 46 potentially relevant articles were examined. Of these studies, 14 were excluded due to incomplete data. Two studies reported information on the same subjects, and two other studies were published by the same group with overlapping recruitment periods. Ultimately, 30 studies, including 5 RCTs and 25 observational studies, involving 3,195 patients (1,444 treated with DEB-TACE and 1746 with C-TACE) were included in the meta-analysis.

Eight studies were conducted in Italy, 4 studies were conducted in Germany, 4 in the US, 3 in South Korea, 3 in Spain, 2 in Australia, 2 in the UK, 1 in Belgium, 1 in Taiwan, and 1 in Saudi Arabia. Baseline data and the characteristics of studies and patients are shown in Table 1. Five studies were of high quality, one study was of moderate quality, and one study was of poor quality.

3.2. Comparison of the complete response rate

Two studies involving 167 subjects reported the complete response rate. The complete response rate was

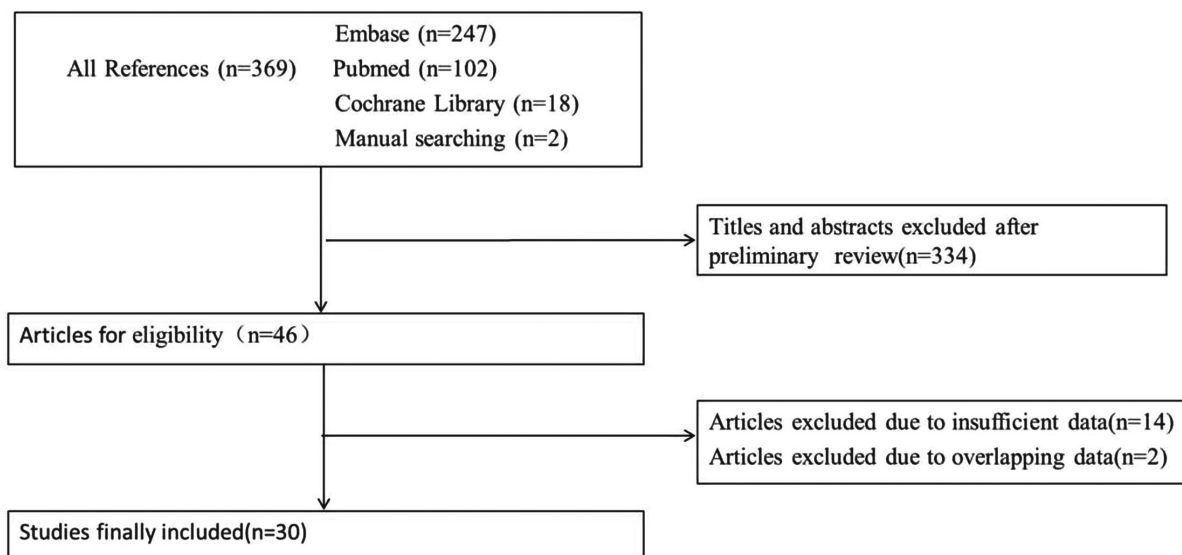


Figure 1. The search strategy used in this meta-analysis.

significantly higher in patients who underwent DEB-TACE than that in patients who underwent C-TACE (OR = 3.59, 95% CI = 1.48-8.72, $p = 0.0048$) without any significant heterogeneity ($p = 0.91$, $I^2 = 0\%$).

3.3. Comparison of the disease control rate

Nine studies involving 909 subjects reported the disease control rate (19,21,25,26,30,32,35,36,38). Of those studies, 2 were published by the same group. Ultimately, eight studies involving 869 patients were analyzed. The disease control rate was significantly higher in patients who underwent DEB-TACE than that in patients who underwent C-TACE (OR = 2.17, 95% CI = 1.22-3.87, $p = 0.0082$), and statistical heterogeneity was evident ($p = 0.08$, $I^2 = 44.8\%$).

3.4. Comparison of the objective response rate

The overall response rate (ORR) was reported in 13 studies (12,17,19,21,25,26,30-32,34,35,36,38). Due to the high heterogeneity found among the included studies ($\chi^2 = 6.67$, d.f. = 10, $I^2 = 71\%$; $p = 0.011$), the DerSimonian and Laird test for the random-effects models was used. The objective response rate was significantly higher in patients who underwent DEB-TACE than that in patients who underwent C-TACE (OR = 2.05, 95% CI = 1.17-3.55, $p = 0.011$), and statistical heterogeneity was evident ($p = 0.0001$, $I^2 = 71\%$). Subgroup analyses of RCTs and observational studies confirmed the non-significant OR in favor of DEB-TACE (OR = 1.27, 95% CI = 0.78-2.07 and OR = 2.40, 95% CI = 1.17-4.90, respectively) and detected, as expected, a high heterogeneity among the observational studies (Figure 2). The high heterogeneity may be caused by response assessment, namely, the timing of the response assessment, the response criteria, and the study design and quality.

3.5. Comparison of the survival rate

Fourteen studies involving 1,645 patients estimated the overall survival (OS) and compared the two groups using log-rank tests (13,16,17,19,21,23,24,26,28,31,34,35,38). As described in Table 2, the two groups had a similar 1-year survival rate (SR) that tended to be higher, albeit not significantly so, in patients who underwent DEB-TACE (OR 1.51, 95% CI 0.48-1.21, $p = 0.08$) (Figure 3). With treatment, survival was prolonged and the OR tended to decrease, albeit not significantly so, thus indicating better long-term outcomes in patients who underwent DEB-TACE (2-year SR: OR 1.32, 95% CI 0.74-2.36, $p = 0.34$; 3-year SR: OR 1.92, 95% CI = 1.00-3.68, $p = 0.049$). The meta-analysis of plotted HRs revealed no significant differences in the 1-year survival rate and 2-year survival rate. The 3-year survival rate was significantly higher in patients who underwent DEB-TACE than that in patients who underwent C-TACE (OR = 1.92, 95% CI = 1.00-3.67, $p = 0.049$), and statistical heterogeneity was evident ($p = 0.043$, $I^2 = 51.7\%$).

4. Discussion

This meta-analysis included a large number of studies on the efficacy and safety of TACE and DEB-TACE. A total of 30 studies (5 RCTs and 25 observational studies) involving 2,920 patients were analyzed. The DEBs, from 150 to 650 nm in size, were loaded with doxorubicin in all of the studies. The C-TACE arms widely differed with regard to the drugs used (Table 1). The current study indicated that patients who underwent DEB-TACE might have a higher complete response rate and disease control rate than patients who underwent C-TACE. In addition, meta-analysis indicated that the 1-year survival rate and 2-year survival rate did not differ significantly between

Table 1. Characteristics of the included studies

Study (Ref.)	Arm	Drug	Sample size	Study period	Design	Region	Previous TACE ^a	CP (A/B/C)	BCLC (0/A/B/C/)	Okuda (I/II/III)
Alsina 2011 (10)	C-TACE	Cisplatin Adryamicin Mytomycin-C	74	1996-2010	R	USA	NA	NA	NA	NA
Arabi 2015 (11)	DEB-TACE	LC Beads	28	2006-4014	R	Saudi Arabia	NA	NA	NA	NA
	C-TACE	Cisplatin	19				0	17/2/0	NA	NA
Bloom 2012 (12)	DEB-TACE	Doxorubicin	35	2008-2011	R	Australia	4	24/11/0	NA	NA
	C-TACE	NA	15				NA	NA	NA	NA
Burrell 2014 (13)	DEB-TACE	NA	15	2006-2011	R	NA	NA	NA	NA	NA
	C-TACE	NA	80				NA	NA	NA	NA
Castelli 2013 (14)	DEB-TACE	NA	26	NA	NA	Italy	NA	NA	NA	NA
	C-TACE	NA	60				NA	NA	NA	NA
Cuomo 2011 (15)	DEB-TACE	NA	28	2007-2010	R	Italy	NA	NA	NA	NA
	C-TACE	Doxorubicin	45				NA	NA	NA	NA
Dhanasekaran 2010 (16)	DEB-TACE	Doxorubicin	68	1998-2008	R	USA	NA	NA	NA	NA
	C-TACE	Doxorubicin Cisplatin Mitomycin	26				11/11/4	NA	11/10/5	
Facciorusso 2016 (17)	DEB-TACE	Doxorubicin	45	2007-2011	R	Italy	NA	22/11/12	NA	17/13/15
	C-TACE	Doxorubicin	104				NA	93/11/0	2/39/63/0	NA
Farris 2010 (18)	DEB-TACE	Doxorubicin	145	NA	R	NA	NA	129/16/0	5/53/81/6	NA
	C-TACE	NA	13				NA	NA	NA	NA
Ferrer Puchol 2011 (19)	DEB-TACE	NA	13	2000-2009	R	Spain	NA	NA	NA	NA
	C-TACE	Adriamycin	25				NA	NA	NA	NA
Frenette 2012 (20)	DEB-TACE	Adriamycin	47	2005-2010	R	USA	NA	NA	NA	NA
	C-TACE	NA	148				83/52/13	12/62/71/3	NA	NA
Golfieri 2014 (21)	DEB-TACE	NA	127	2008-2010	RCT	Italy	NA	72/50/5	7/46/65/9	NA
	C-TACE	Epirubicin	88				NA	77/11/0	0/41/23/24	NA
Gorodetski 2015 (22)	DEB-TACE	Doxorubicin	89	2000-2013	R	USA	NA	75/14/0	0/41/26/22	NA
	C-TACE	NA	95				NA	NA	NA	NA
Kloekner 2015 (23)	DEB-TACE	NA	38	2002-2013	R	Germany	NA	NA	NA	NA
	C-TACE	Mitomycin-C	174				NA	103/64/7	30/59/77/8	NA
Kumar 2013 (24)	DEB-TACE	NA	76	2002-2011	R	UK	NA	51/22/3	8/34/30/4	NA
	C-TACE	NA	38				NA	NA	NA	NA
Lammer 2010 (25)	DEB-TACE	NA	81	2005-2007	RCT	Austria	NA	NA	NA	NA
	C-TACE	Doxorubicin	108				89/19/0	0/29/79/0	74/19/0	
Liu 2015 (26)	DEB-TACE	Doxorubicin	93	2010-2011	R	Taiwan, R.O.C.	NA	77/16/0	0/24/69/0	80/28/0
	C-TACE	Doxorubicin	105				NA	NA	0/7/98/0	NA
Malenstein 2011 (27)	DEB-TACE	Doxorubicin	53	2006-2009	RCT	Belgium	NA	NA	0/53/0/0	NA
	C-TACE	Doxorubicin	14				NA	14/0/0	1/10/3	NA
Megías Vericat 2015 (28)	DEB-TACE	Doxorubicin	16	2008-2009	R	Spain	NA	14/2/2	2/9/5	NA
	C-TACE	Cisplatin	30				NA	19/11/0	NA	NA
Monier 2014 (29)	DEB-TACE	Doxorubicin	30	NA	RCT	NA	NA	14/16/0	NA	NA
	C-TACE	Doxorubicin	67				NA	NA	NA	NA
Nicolini 2010 (30)	DEB-TACE	Doxorubicin	63	2003-2007	R	Italy	NA	NA	NA	NA
	C-TACE	Embosphere particles	8				NA	6/2/0	NA	NA
Nicolini 2013 (31)	DEB-TACE	Epirubicin	8	2005-2011	R	Italy	NA	5/3/0	NA	NA
	C-TACE	Epirubicin	16				NA	NA	7/9/0/0	NA
Park 2010 (32)	DEB-TACE	Doxorubicin	22	2008-2010	R	South Korea	NA	NA	14/8/0/0	NA
	C-TACE	NA	52				NA	NA	NA	NA
Recchia 2012 (33)	DEB-TACE	NA	20	2008-2010	P	Italy	NA	NA	NA	NA
	C-TACE	Lipiodol	70				NA	NA	NA	24/14/0
Sacco 2011 (34)	DEB-TACE	Doxorubicin	35	2006-2009	RCT	Italy	NA	NA	NA	46/21/0
	C-TACE	Doxorubicin	34				NA	25/9/0	0/22/12/0	NA
Song 2012 (35)	DEB-TACE	Doxorubicin	33	2008-2011	R	Korea	NA	29/4/0	0/22/11/0	NA
	C-TACE	Doxorubicin	69				NA	63/6/0	0/28/41/0	NA
Song 2011 (36)	DEB-TACE	Doxorubicin	60	2008-2010	R	Korea	NA	56/4/0	0/27/33/0	NA
	C-TACE	Cisplatin Doxorubicin Epirubicin	20				NA	16/4/0	0/7/6/7	NA
Vogl 2011 (37)	DEB-TACE	Doxorubicin	20	2005-2007	RCT	Germany	NA	18/2/0	0/6/10/4	NA
	C-TACE	Doxorubicin	108				NA	89/19/0	29/81/0	104/6/0
Wiggermann 2011 (38)	DEB-TACE	Doxorubicin	93	2003-2008	R	Germany	NA	77/16/0	26/76/0	88/14/0
	C-TACE	Cisplatin	22				NA	22/0/0	4/15/2	NA
Zwaka 2011 (39)	DEB-TACE	Epirubicin	22	2010-2011	R	Germany	NA	22/0/0	1/17/3	NA
	C-TACE	NA	19				NA	NA	NA	NA
	DEB-TACE	NA	15				NA	NA	NA	NA

^aNumber (percentage) of patients who had already undergone TACE before enrollment in the study. C-TACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting beads-TACE; R, retrospective; RCT, randomized controlled trial; P, prospective; CP, Child–Pugh; BCLC, Barcelona Clinic Liver Cancer; Okuda, Okuda stage; NA, not assessed.

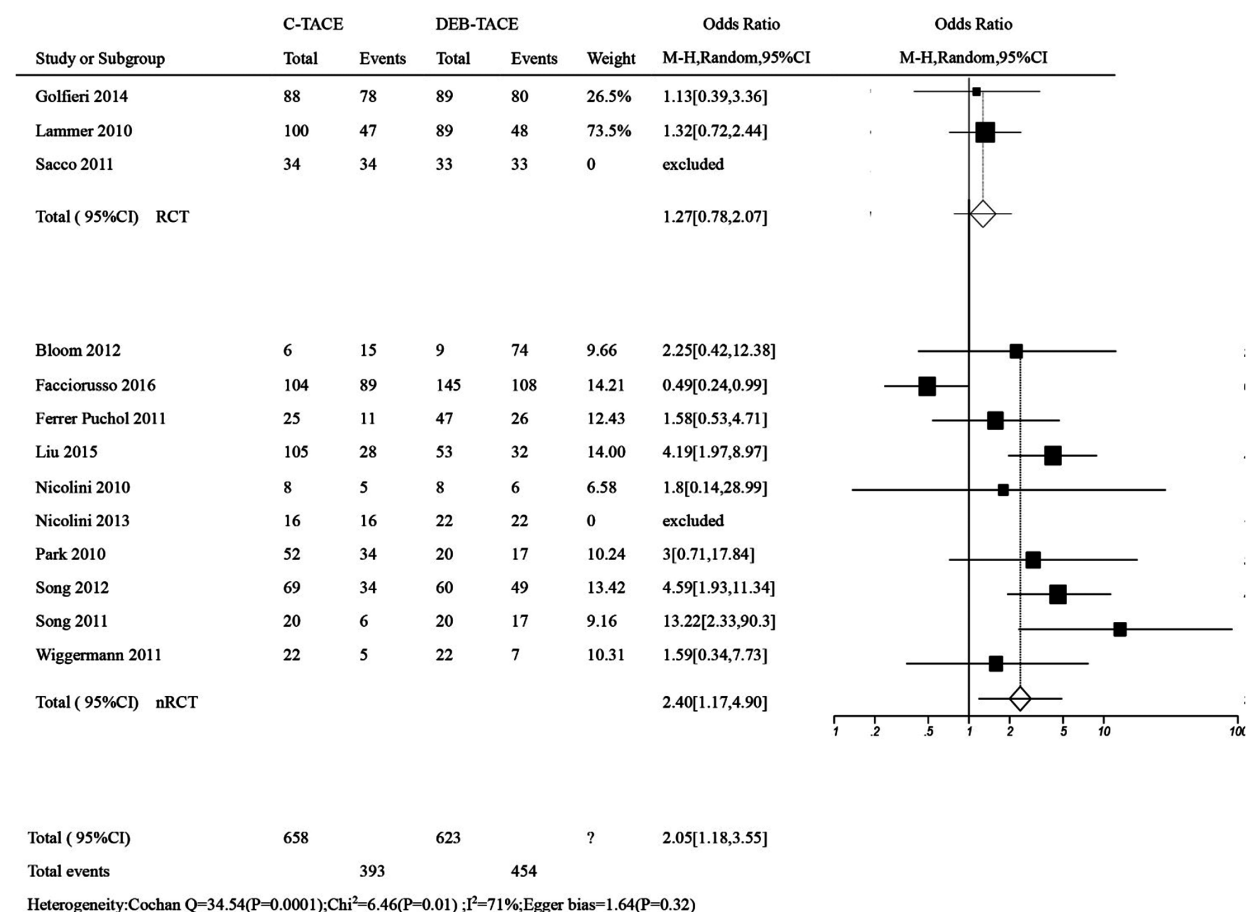


Figure 2. Forest plot comparing objective response rate for DEB-TACE to that for C-TACE. A random effect DerSimonian Laird model showed a summary odds ratio significantly higher after DEB-TACE than that in c-TACE. Subgroup analyses of the RCTs and observational studies confirmed the non-significant OR in favor of DEB-TACE and detected statistical heterogeneity. DEB-TACE, drug-eluting bead transarterial chemoembolization; C-TACE, conventional transarterial chemoembolization; RCT, randomized controlled trial; nRCT, non-randomized controlled trial.

Table 2. Odds ratios and heterogeneity of 1-year, 2-year, and 3-year survival rates

Estimate survival rate	No. of studies	No. of patients	OR (95% CI)	p value	Heterogeneity I ²	p
1-year SR	14	1604	1.51 (0.95-2.41)	0.08	73.0%	< 0.0001
2-year SR	13	1422	1.32 (0.74-2.36)	0.34	73.6%	< 0.0001
3-year SR	8	840	1.92 (1.00-3.68)	0.049	51.7%	= 0.04

SR, survival rate; OR, odds ratio; CI, confidence interval.

patients who underwent C-TACE or DEB-TACE. However, the 3-year survival rate was significantly higher in patients who underwent DEB-TACE than that in patients who underwent C-TACE. This finding probably suggests that DEB-TACE results in a better OS than TACE. However, this finding is not consistent with the conclusions of a systematic review recently published in this field (17), perhaps because the current meta-analysis analyzed more studies. However, long-term follow-up needs to be conducted and more standard randomized studies need to be assembled to assess the survival benefit of DEB-TACE. The complete response rate, disease control rate, full necrosis rate, non-response

rate, objective response rate, progressive disease rate, and recurrence did not differ significantly between patients who underwent C-TACE and patients who underwent DEB-TACE.

Safety did not differ significantly between C-TACE and DEB-TACE. Many clinical research studies suggest that tumor eradication cannot readily be achieved with TACE and that HCC can only be controlled by palliative treatment. Therefore, a low adverse reaction rate and a high tumor response rate in DEB-TACE therapy will be advantageous to patients needing to undergo radical surgery in the short term. Because this population of patients is in the early stage of disease, DEB-TACE can

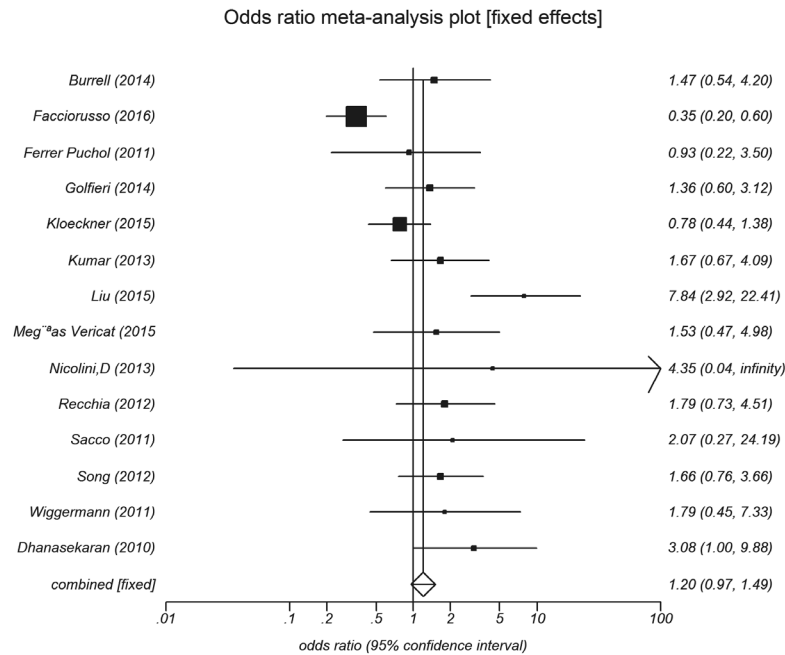


Figure 3. Forest plot of hazard ratios for patient 1-year survival rate after DEB-TACE and C-TACE. A fixed effect Mantel-Haenszel model yielded a summary odds ratio not significantly in favor of DEB-TACE with a low heterogeneity. DEB-TACE, drug-eluting bead transarterial chemoembolization; C-TACE, conventional transarterial chemoembolization; RCT, randomized controlled trial; nRCT, non-randomized controlled trial.

be an efficient and safe way to control the tumor, down-regulate the tumor stage, and protect liver function to the greatest extent. In theory, therefore, DEB-TACE will lay a better foundation for radical surgery and possibly prolong long-term survival.

This meta-analysis provides relatively comprehensive evidence of the benefits of DEB-TACE compared to C-TACE for the treatment of primary liver cancer, but there are still some limitations to this study. First, the evaluation criteria for tumor response in the included literature were not entirely consistent, and mRECIST and EASL standards assess tumor response differently, which may lead to different interpretations. Second, treatment with conventional technology has matured, but many of the RCT designs lacked conventional standardization of evaluation metrics, and this was especially true for C-TACE involving conventional technology and chemotherapy drugs for embolism.

In conclusion, this meta-analysis has shown that patients who underwent DEB-TACE might have a higher complete response rate, disease control rate, and 3-year survival rate than patients who underwent C-TACE. Safety did not differ significant between C-TACE and DEB-TACE. Therefore, DEB-TACE may be a better choice for patients with primary HCC than liver transplantation, liver resection, or partial ablation in the short term.

Acknowledgements

This work was supported by the National Natural

Science Foundation (grant no. 81702622), Key Projects of the Liaoning Natural Science Foundation (2018010153-301), and the Guiding Projects of the Liaoning Natural Science Foundation (20170540981).

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(Received June 24, 2019; Revised August 21, 2019; Accepted September 26, 2019)