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WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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Conventional vs drug-eluting beads transarterial chemoembolization for hepatocellular carcinoma

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Abstract

Transarterial chemoembolization (TACE) is the current standard of therapy for patients with intermediate-stage hepatocellular carcinoma (HCC) according to the Barcelona Clinic Liver Cancer classification. The concept of conventional TACE (cTACE) is the selective obstruction

of tumor-feeding artery by injection of chemotherapeutic agents, leading to ischemic necrosis of the target tumor *via* cytotoxic and ischemic effects. Drug-eluting beads (DEBs) have been imposed as novel drug-delivering agents for TACE, which allows for higher concentrations of drugs within the target tumor and lower systemic concentrations compared with cTACE. Despite the theoretical advantages of DEB-TACE, it is still controversial in clinical practice as to whether DEB-TACE is superior to cTACE in regard to overall survival and treatment response. In this review article, we summarize the clinical efficacy and safety of DEB-TACE for patients with intermediate or advanced stage HCC in comparison with cTACE.

Key words: Hepatocellular carcinoma; Drug-eluting beads transarterial chemoembolization; Transarterial chemoembolization

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Core tip: Transarterial chemoembolization (TACE) is the current standard of therapy for patients with intermediate-stage hepatocellular carcinoma. Drug-eluting beads (DEBs) have been introduced as novel drug-delivery agents for TACE, allowing for higher concentrations of drugs to the target tumor and lower systemic concentrations, compared with conventional TACE (cTACE). Despite the theoretical advantages of DEB-TACE, whether DEB-TACE shows superior efficacy to cTACE remains controversial. Reviewing the literature, we found that DEB-TACE shows similar clinical outcomes to and fewer adverse events than cTACE.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is listed as the sixth most common cancer worldwide and the third most frequent cause of cancer-related mortality^[1,2]. The majority of HCC cases occur stem from chronic liver disease and cirrhosis. Therefore, the selection of treatment modalities for HCC is determined by tumor size, multiplicity, and liver function status^[3].

Transarterial chemoembolization (TACE) has been frequently performed and has become the first-line treatment option for large or multinodular HCC with preserved liver function, no evidence of vascular invasion or extrahepatic spread, and the absence of cancer-related symptoms, which is defined as intermediate stage according to the Barcelona Clinic Liver Cancer (BCLC) classification^[4,5]. Moreover, in clinical settings, TACE is considered the standard treatment for patients with early stage HCC who are not appropriate candidates for curative therapy^[4].

The mechanism of action for conventional TACE (cTACE) is the selective obstruction of tumor-feeding arteries by injection of chemotherapeutic agents (doxorubicin or cisplatin) mixed with lipiodol^[6]. This leads to ischemic necrosis of target tumors by cytotoxic and ischemic effects. There are several drawbacks of cTACE that are associated with ineffective treatment responses in many cases: (1) the liquid motility of lipiodol to reduce the effective concentrations of chemotherapeutic agents; (2) the inability to release drugs in a controlled and sustained manner; and (3) heterogeneity in the technique and treatment schedules. To reduce these drawbacks, drug-eluting beads (DEBs) have been introduced as drug-delivering agents for TACE. After delivery of the beads to target tumors, the beads release chemotherapeutic drugs (doxorubicin or epirubicin) in a sustained fashion over a prolonged period of time^[7,8]. Figure 1 shows the mechanism of action of DEB-TACE. Treatment with DEB-TACE allows higher concentrations of drugs within the target tumor and lower systemic concentrations compared with cTACE^[9,10]. Thus, the use of DEBs can reduce drug-related adverse events such as post-embolization syndrome. As DEB-TACE is widely used interchangeably with cTACE in many hospitals globally, it is necessary to assess the current status of DEB-TACE in comparison with cTACE. Thus, this article aims to evaluate the characteristics of each modality and to compare the clinical outcomes of DEB-TACE with those for cTACE.

cTACE VS DEB-TACE: CHARACTERISTICS

cTACE

Typically, cTACE involves the infusion of chemotherapeutic drugs blended with lipiodol and embolic agents into the cancer-feeding artery^[6]. Both single chemotherapeutic agents and combination chemotherapy have been used as part of the drug regimen in TACE. However, there is no agreement on the optimal anticancer drug(s)

to be used in cTACE. Globally, the most widely used chemotherapeutic agent for TACE of HCC is doxorubicin. The dose of doxorubicin generally ranges from 30 to 75 mg/m², at a maximum of 150 mg emulsified in 5 to 20 mL of lipiodol^[11].

Lipiodol is a key element in TACE due to its distinctive combination of features as a drug-carrying, tumor-seeking, and embolizing agent^[12]. Even though the principle is not concretely comprehended, it seems to be absorbed by a pump in the cancer cell wall and transported to the intracellular space. Then, upon hypoxia within cancer cells, this pump is disabled, such that lipiodol is retained within the cell. Lipiodol is confined to tumors when injected *via* the hepatic artery, and it is generally trapped in HCC for months, even up to a year, whereas it is washed out from non-tumor portions of the liver within 4 wk.

Several embolic agents, such as gelfoam, polyvinyl alcohol (PVA) particles, and tris-acryl gelatin microspheres, have been used over the past three decades in chemoembolization^[12]. Among these embolic agents, gelfoam has recently emerged the most commonly used substance worldwide. The intended aim of embolization is as follows: To assist lipiodol to be sustained selectively in the tumor, to inhibit chemotherapeutic agent washout from HCC, and to cause ischemic necrosis.

A significant problem of cTACE is the great inhomogeneity of the technique and treatment schedules used in clinical centers worldwide. Two randomized controlled trials on cTACE used quite different technical approaches. Furthermore, some HCCs do not show lipiodol uptake which may result in lower effectiveness of the treatment^[13].

DEB-TACE

The most commonly used DEB, DC Beads (BTG, United Kingdom) are nonbiodegradable PVA microspheres, loaded with calibrated doxorubicin. They can release doxorubicin in a controlled and maintained mode^[14]. Through an ion-exchange mechanism, DC Beads actively sequester oppositely charged drugs. In initial *in vitro* studies, doxorubicin could be efficiently loaded into the DC beads up to 45 mg/mL, regardless of the size of beads^[15]. Currently, a loading of 37.5 mg doxorubicin/mL beads is recommended, in consideration of a practical therapeutic dose and optimum handling characteristics. According to an animal pharmacokinetic study comparing two sizes of doxorubicin-eluting beads (100-300 μ m and 700-900 μ m) loaded with same amount of doxorubicin, treatment with the smaller beads (100-300 μ m) elicited higher doxorubicin plasma levels^[16]. This finding was caused by the increased surface area of the smaller beads, leading to a profuse release of doxorubicin.

In DEB-TACE, the extent of the liver cancer burden should be considered in planning the dose of doxorubicin. As a general rule, for patients within the Milan criteria (defined as single tumor \leq 5 cm, or multiple tumors of up to three and $<$ 3 cm each), a planned dose should be up to 75 mg doxorubicin loaded into one vial, including

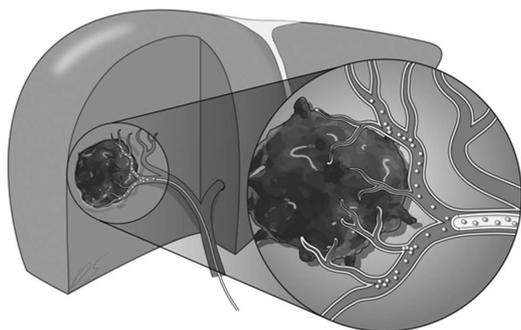


Figure 1 Action mechanism of drug-eluting bead-transarterial chemoembolization in hepatocellular carcinoma. Sustained release of chemotherapeutic agents from microbeads of uniform size, which embolize supplying vessels more distally, enables local concentration of cytotoxic agents to be higher within tumor.

2 mL of DC beads in each single treatment. Meanwhile, for patients beyond the Milan criteria, each treatment should involve a dose up to 150 mg loaded into two vials of DC beads^[17]. Generally, the recommended size of beads is 100-300 μm for standard DEB-TACE procedures. This choice is based on the fact that small particles can be transported inside the tumor or in nearness to the tumor margin, and thus they are ideal for drug delivery or accurate embolization.

cTACE VS DEB-TACE: OVERALL EFFICACY AND SAFETY IN INTERMEDIATE AND ADVANCED STAGE HCC

The survival benefit of cTACE has been the issue of a finite number of randomized controlled trials (RCTs) that have provided controversial results^[18]. Among seven RCTs^[19-25] all published between 1988 and 2002, only two trials showed favorable results in respect of overall survival^[19,20]. However, a systematic review based on these seven RCTs showed that cTACE has been found to improve 2-year survival (OR = 0.53; 95%CI: 0.32-0.89; $P = 0.017$) of patients with unresectable HCC, compared with best supportive care^[26]. Subsequent sensitivity analysis in this study showed a significant survival benefit for chemoembolization with cisplatin or doxorubicin by analyzing 323 patients in four studies (OR = 0.42; 95%CI: 0.20-0.88), but not for embolization alone by assessing 215 patients in three studies (OR = 0.59; 95%CI: 0.29-1.20)^[26]. In a current Cochrane review, the evidence based survival benefits of cTACE was challenged^[27]. This meta-analysis involved RCTs published after 2002 and showed no solid evidence to support TACE or transarterial embolization (TAE) compared with conservative management, in patients with unresectable HCC. However, some experts have doubted such conclusions, because this review involved RCTs with inappropriate selection of patients and control arms, which likely biased the results of the analysis.

Primarily, DEB-TACE has been introduced to enhance the ability of drug-delivery to target tumor while reducing systemic toxicity and to provide a standardized embolic effect. The role of doxorubicin in embolic microspheres was evaluated in a randomized, cancer-size adjusted trial assessing DEB-TACE vs TAE with similar characteristics (BeadBlock-TAE)^[28]. Although no survival benefit was reported in the study, the value of doxorubicin was favorable in the setting of TACE with microspheres, because DEB-TACE showed higher local response, less recurrence at 12 mo, and a longer time-to-progression than BeadBloc-TAE. Another trial assessed the rate of tumor necrosis after chemoembolization with epirubicin-loaded beads vs TAE with unloaded microspheres (Embosphere particles), which was pathologically proved in explanted livers of HCC patients undergoing liver transplantation: Epirubicin-loaded beads TACE showed complete necrosis in 77% of lesions, while TAE showed complete necrosis in only 27% of lesions ($P = 0.043$)^[29]. A recently reported prospective clinical trial of DEB-TACE in a large Korean HCC population showed an overall 6-mo survival rate was 97.4%, although more than half of patients had early stage HCC (BCLC-A, $n = 77$, 50.7%)^[30]. Varela *et al.*^[7] firstly reported that systemic concentrations of doxorubicin were significantly lower in patients treated with DEB-TACE than patients treated with cTACE. This result was verified by Poon *et al.*^[14], who performed DEB-TACE with possibly the highest dose of doxorubicin (150 mg). Both studies showed that none of treated patients exhibited doxorubicin-related systemic toxicity (alopecia, bone marrow suppression, or dyspnea)^[7,14].

Despite the aforementioned theoretical advantages of DEB-TACE, previous studies comparing DEB-TACE with cTACE in HCC of intermediate stage have shown rather conflicting results. Recently reported meta-analysis showed that the two modalities represent comparable results, suggesting an absence of difference in tumor response between DEB-TACE and cTACE^[31]. On the contrary, three other meta-analyses, assessing the efficacy of DEB-TACE vs cTACE in HCC patients, showed different results^[32-34]. Huang *et al.*^[32] (seven studies, $n = 700$) and Xie *et al.*^[33] (six studies, $n = 652$) demonstrated that significantly better objective tumor response was found for DEB-TACE than for cTACE. In another meta-analysis of nine studies (866 patients) conducted in 2016, DEB-TACE presented significantly higher complete response rate and better overall survival, although similar objective tumor responses compared with cTACE. Regarding adverse events in these meta-analyses^[32-34], overall and severe adverse events were similar or slightly lower in patients receiving DEB-TACE than patients receiving cTACE. Tables 1 and 2 summarize the clinical outcomes and adverse events of the studies that were included in these meta-analyses comparing DEB-TACE and cTACE.

Among randomized controlled trials reported until recently, the largest trial is the PRECISION V phase-2 trial assessing DEB-TACE vs cTACE in 212 patients with mostly HCC of intermediate stage^[10]. The primary

Table 1 Clinical outcomes from studies comparing drug-eluting bead-transarterial chemoembolization and conventional transarterial chemoembolization in patients with intermediate-stage hepatocellular carcinoma

Ref.	Study design	Arm	BCLC stage <i>n</i> (A/B/C)	Clinical outcomes in intermediate-stage (BCLC-B) (DEB-TACE/cTACE)					
				OS rate	<i>P</i> value	TTP	<i>P</i> value	Response rate	<i>P</i> value
Lammer <i>et al</i> ^[10]	RCT	DEB-TACE cTACE	24/69/0 29/79/0	NR		NR		OR 52.4%/34.7% ² DC 63.5%/44.4% ²	0.038 0.026
Wiggermann <i>et al</i> ^[46]	Retrospective	DEB-TACE cTACE	1/17/3 4/15/2	70%/55% (1-yr survival rate)	0.01	NR		OR 22.7%/22.7% ³ DC 90.9%/68.2% ³	0.066
Song <i>et al</i> ^[9]	Retrospective	DEB-TACE cTACE	27/33/0 28/41/0	DEB > cTACE (log-rank test)	0.020	DEB > cTACE (log-rank test)	0.038	OR 75.6%/34.1% ⁴	< 0.001
Golfieri <i>et al</i> ^[35]	RCT	DEB-TACE cTACE	41/26/22 41/23/24	NR		NR		CR 19.2%/26.1% ⁵ CR 42.1%/22.2% ⁶	0.734 0.295

¹In this study, subgroup analysis according to BCLC stage was not performed. However, majority of patients was BCLC-B (DEB-TACE, 81%; cTACE, 71%); ²The 6-mo tumor response rate, according to the European Association for the Study of the Liver response criteria; ³The average 8-mo tumor response rate, according to the EASL response criteria; ⁴The 3-mo tumor response rate, according to the mRECIST; ⁵The 1-mo; ⁶The 6-mo tumor response rate, according to the EASL criteria and mRECIST. RCT: Randomized controlled trial; OS: Overall survival; TTP: Time to progression; NR: Not reported; OR: Objective response; DC: Disease control; CR: Complete response; mRECIST: Modified Response Evaluation Criteria in Solid Tumors; BCLC: Barcelona Clinic Liver Cancer; TACE: Transarterial chemoembolization; DEB: Drug-eluting bead.

Table 2 The incidence of adverse events from studies comparing drug-eluting bead-transarterial chemoembolization and conventional transarterial chemoembolization in patients with unresectable hepatocellular carcinoma

Adverse event	Lammer <i>et al</i> ^[10]	Wiggermann <i>et al</i> ^[46]	Song <i>et al</i> ^[9]	Golfieri <i>et al</i> ^[35]
Nausea	Post-embolization syndrome	Post-embolization syndrome	Post-embolization syndrome	2.2%/3.4%, <i>P</i> = 0.682
Pain	24.7%/25.9%	21.7%/16.3%, <i>P</i> = 0.52	22.2%/20.6%, <i>P</i> = 0.850	24.7%/71.6%, <i>P</i> = 0.01
Fever				7.9%/11.4%, <i>P</i> = 0.457
Fatigue				0%/4.5%, <i>P</i> = 0.059
Marrow suppression	5.4%/5.6%	NR	NR	NR
Cholecystitis	NR	NR	4.7%/3.3%, <i>P</i> = 0.692	2.2%/1.1%, <i>P</i> = 0.999
Abscess	NR	²	NR	1.1%/1.1%, <i>P</i> = 0.999
Alopecia	1.1%/20.4%	NR	NR	NR
Liver function worsening	Significant reduction in DEB ¹	NR	AST, 36%/52%, <i>P</i> = 0.259 ALT, 31%/20%, <i>P</i> = 0.280	1.1%/5.7% ³ , <i>P</i> = 0.118
Hematoma	NR	NR	NR	1.1%/3.4%, <i>P</i> = 0.368
Infection	NR	NR	NR	0%/1.1%, <i>P</i> = 0.497

¹The mean maximum ALT elevation in the DEB-TACE group was 50% less than in the cTACE group (95%CI: 39%-65%; *P* < 0.001) and 41% less with regard to AST (95%CI: 46%-76%; *P* ≤ 0.001); ²Major complications was defined hospitalization > 24 h, greater therapy and unplanned added costs in treatment, permanent persisting sequelae and death of the patient. DEB-TACE vs cTACE, 13.0% (*n* = 6, including 2 liver abscesses) vs 2.3% (*n* = 1), *P* = 0.06; ³Increase in Child-Pugh score of ≥ 2 points. DEB-TACE: Drug-eluting bead-transarterial chemoembolization; cTACE: Conventional transarterial chemoembolization; ALT: Alanine aminotransferase; AST: Aspartate transaminase; NR: Not reported.

efficacy endpoint (response at 6 mo, *P* = 0.11) and primary safety endpoint (incidence of severe adverse events within 30 d, *P* = 0.86) were comparable in both two groups. After performing a post hoc comparison, the DEB-TACE group indicated a significant decrease in chemotherapeutic agent-related systemic and liver toxicity compared to the cTACE group. Furthermore, in subgroup analysis, the objective response rate and disease control rate were significantly better (*P* = 0.038 and *P* = 0.026, respectively) with DEB-TACE than with cTACE in 67% of patients with more advanced disease (Child-Pugh B, bilobular or recurrent disease, ECOG 1). Another RCT for evaluating the potential effect of DEB-TACE on overall survival, compared to cTACE using epirubicin, showed no statistical differences between both modalities in terms of survival, treatment response, or adverse episodes^[35]. However, it should be considered that the maximally used dose of doxorubicin/epirubicin was limited to only 75 mg for both procedures in this trial.

Furthermore, the trial mainly recruited patients with low tumor burden (46% of patients with early HCC, only 20% patients with bilobar disease). Thus, this restricted one of the significant advantages of DEB-TACE, which is the ability to use higher doxorubicin doses without rising drug-related systemic toxicity in patients with larger tumor burden as mentioned in the PRECISION V study. This trial indicated that DEB-TACE did not show better clinical outcomes, compared with cTACE in patients with relatively well preserved liver function and low tumor burden. A retrospective study by Song *et al*^[9] reported that overall survival and treatment responses for DEB-TACE were significantly better than those for cTACE. Performing subgroup analysis in accordance with BCLC stage, treatment efficacy was shown in intermediate stage HCC (BCLC B) but not in early stage HCC (BCLC A). Regarding adverse events, there was no statistically significant difference between DEB-TACE and cTACE. On the contrary, a recently published retrospective study

showed that overall survival, time to progression, and disease control rate were not significantly different between DEB-TACE and cTACE groups, even when subgrouped by BCLC stage^[36]. However, the incidence of adverse events was significantly lower, particularly in HCC larger than 5 cm in BCLC-B patients receiving DEB-TACE^[36]. Considering the results from these studies, there is still controversy regarding clinical outcomes. However, it seems that DEB-TACE shows at least similar efficacy and less adverse events than cTACE. DEB-TACE might be favorable to cTACE for large HCC especially in patients with decreased liver function, even though there is lack of evidence that DEB-TACE is superior to cTACE in term of efficacy.

For advanced HCC (BCLC C), the role of chemoembolization has not been fully established. In accordance with the BCLC staging system, it recommends systemic treatment or palliative therapy to patients with advanced stage. In a small retrospective study comparing cTACE and sorafenib in patients with advanced HCC, overall survival in the cTACE group was higher than the sorafenib group (9.2 mo vs 7.4 mo, $P = 0.377$)^[37]. Recently, two studies on DEB-TACE for patients with advanced HCC were reported: Kalva *et al.*^[38] conducted a retrospective trial recruiting 80 patients with advanced HCC treated with DEB-TACE. This study reported median progression free survival of 5.1 mo (95%CI: 4.1-7.7) and overall survival of 13.3 mo (95%CI: 10.1-18.6). Subgroup analysis showed that median survival was better in patients with ECOG performance status (PS) ≤ 1 than ECOG PS > 1 (17.7 mo vs 5.6 mo, $P = 0.025$, respectively). Another retrospective study by Prajapati *et al.*^[39] reported median survival of 13.5 mo (range, 8.2-18.7 mo) without severe adverse episodes. Subgroup analyses showed that the median survival of Child-Pugh class A patients was 17.8 mo (range, 9.0-26.7 mo). In comparison with median survivals of 10.7 mo and 6.5 mo for sorafenib in the SHARP and Asia-Pacific trials^[40,41], it appears that cTACE as well as DEB-TACE shows better or at least comparable efficacy in patients with advanced stage HCC, Child-Pugh class A and good performance status.

A major limitation of TACE is a high rate of cancer recurrence. In two RCTs, a sustained response lasting for 3 to 6 mo was reported in only 28% to 35% of patients treated with cTACE^[19,20]. Recently, several trials made an attempt to analyze the potential benefit of combined strategies with chemoembolization and other treatment options for overcoming this limitation. Several RCTs have sought to determine the benefit of an addition of sorafenib to cTACE or DEB-TACE in patients with more advanced HCC. The rationale for this concept is grounded in the demonstration that TACE causes hypoxia and induce angiogenesis by activating angiogenic factors and that the use of sorafenib could decrease angiogenesis. However, these RCTs have not proved definite improvement of clinical outcomes in combination therapy of sorafenib and chemoembolization, compared with chemoembolization alone^[42,43]. Recently, trials have been conducted on combination of TACE with other

molecular target agents, such as brivanib, sunitinib, and thalidomide. It is hoped that these ongoing trials will contribute to the determination of optimal combinations.

CONTROVERSIAL ISSUES ON cTACE VS DEB-TACE

Apart from the overall comparison of clinical outcomes between conventional and DEB-TACE, it is still controversial as to whether DEB-TACE is superior to cTACE in large HCC (≥ 5 cm), which frequently suffers from incomplete response or recurrence after cTACE^[44]. Considering that liver damage given by DEB-TACE is less than that by cTACE, it might be assumed that DEB-TACE offers more therapeutic advantages over cTACE in large HCC. However, regarding response to procedures, complete response rates at 1 and 6 mo were lower in HCC larger than 5 cm, compared with HCC less than 2 cm or 2-5 cm in size^[30]. Moreover, in a Korean retrospective study, there was no significant difference in survival between cTACE and DEB-TACE in HCC larger than 5 cm (36.3 mo vs 33.4 mo, $P = 0.702$)^[36]. Therefore, the notion that a big tumor is more appropriate for DEB-TACE than for cTACE is not currently accepted. Paradoxically, small HCC (less than 2 cm) is sometimes difficult to achieve complete response to both cTACE and DEB-TACE, because the tumor vascularity is fine. In particular, unlike lipiodol in cTACE, the diameter of microspheres in DEB-TACE is still too wide to block peripheral hepatic arteries. Accordingly, the outcomes of small HCC (< 2 cm) treated with DEB-TACE, compared to cTACE are controversial. Indeed, the time to progression after DEB-TACE was shorter than after cTACE in HCC < 2 cm (10.3 mo vs 13.8 mo, $P = 0.023$), although there was no difference in overall survival between the two modalities^[36]. Lastly, repeated sessions of a procedure could be another distinguishing advantage or disadvantage between cTACE and DEB-TACE. The severity of hepatic arterial damage has been compared between cTACE and DEB-TACE in a retrospective study. After a single session of cTACE or DEB-TACE, the incidence of hepatic arterial damage was significantly higher for DEB-TACE group than cTACE, with doxorubicin dose being a possible risk factor for such damage^[45].

CONCLUSION

In comparison with cTACE, DEB-TACE facilitates higher concentrations of drugs within the target tumor and lower systemic concentrations. Despite the theoretical advantages of DEB-TACE, it is still controversial in several clinical studies as to whether DEB-TACE is superior to cTACE in terms of efficacy. However, it seems that DEB-TACE shows at least similar clinical outcomes and less adverse events than cTACE. In order to gain better results for these treatment modalities, selecting proper candidate patients for DEB-TACE or cTACE is needed. Moreover, further well-defined studies are required to identify combination strategies and to develop better

treatment approaches for patients with advanced HCC.

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