Advances in the treatment of hepatocellular carcinoma using drug-eluting beads

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ABSTRACT

Hepatocellular carcinoma (HCC) is one of the most common types of malignant tumor. Although radical surgery and liver transplantation are possible cures for the disease, most patients are beyond the optimum stage for radical treatment at the time of diagnosis. Transarterial chemoembolization (TACE) is the first choice of treatment for advanced HCC. Owing to the widespread use of conventional TACE (cTACE), the problems with this treatment cannot be ignored. Drug-eluting beads (DEBs), a new type of embolization material, appear to overcome the problems of cTACE, and they have other advantages such as synchronous controlled continuous drug release after chemotherapy and embolization and low blood concentrations after treatment. This review summarizes the recent advances in the use of DEB-TACE to treat HCC.

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy in the world and the second leading cause of cancer-related deaths.[1] According to the Barcelona clinical liver cancer staging system and treatment strategies, patients with mid-stage HCC are treated with transcatheter chemoembolization (TACE).[2] Patients diagnosed with HCC in China are often in the middle or late stages of the disease and are past the opportunity for radical treatment such as surgery. TACE is the most commonly used method to treat patients with HCC who cannot receive radical treatment. About two-thirds of the blood flow to normal liver tissue is supplied by veins and the rest by arteries, whereas the blood supply to HCC tissue mainly comes from the arteries. TACE can provide high concentrations of chemotherapy drugs to tumor tissues while retaining the surrounding normal liver parenchyma. Embolization agents can cause tumor ischemia necrosis, which slows down the elution of chemotherapy drugs, and evidence has shown that chemoembolization can improve the survival rate of patients with HCC.[3–5] Conventional TACE (cTACE) often uses lipiodol combined with chemotherapy drugs which are typically water-soluble and have poor compatibility with lipiodol. After administration via the hepatic artery, many chemotherapy drugs enter the systemic circulation, resulting in higher drug concentrations in the blood and possible adverse consequences. Compared with traditional TACE, drug-eluting bead (DEB)-TACE continuously releases chemotherapeutic drugs at a fixed dose with good controllability,

prolonging the contact time between cancer cells and chemotherapeutic drugs and avoiding liver microcirculation injury.[6] Furthermore, DEB-TACE significantly reduces the peak plasma concentration of post-operative drugs.[7,8] Currently, commonly used DEBs that are available in China include DC Bead (Biocompatibles, UK), HepaSphere (BioSphere Medical Inc., USA), and CalliSpheres (HENGRUI MEDICAL, China). DC Bead and HepaSphere have been approved for the treatment of high malignant tumor vascularization in Europe. CalliSpheres belongs to the third class of Chinese passive implanted medical devices and is mainly used in the treatment of vascular embolization in the field of minimally invasive intervention. The three types of microspheres can effectively load doxorubicin and other drugs to treat HCC. This review covers the recent advances in DEBs for the treatment of HCC.

2. Materials and pharmacokinetics

2.1. Material characteristics

Table 1 summarizes the most commonly used drug-loading microspheres that are available on the Chinese market. DC Beads comprise a hydrogel material containing about 96% water. After loading the drug, the water in the microsphere is replaced and the bead decreases in size; the larger the bead, the more obvious is the reduction. The extent of reduction is related to the load, and larger the load, the more obvious is the decrease in microsphere size. HepaSpheres can adapt their shape to

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Table 1
Commonly used drug-eluting beads on Chinese market.

Types	Preparation method	Main materials	Form	Sizes available (μm)	Specific properties
DC Bead	Inverse suspension free-radical polymerisation	PVA hydrogel modified with sulfonate groups	liquid	70–150,100–300,300–500,500–700	Spherical, Calibrated,nonabsorbable, shrinks after loading drug
HepaSphere	NA	Vinyl alcohol-sodium acrylate	solid	30-60,50–100,100–200,150-200	Calibrated, swell after loading drug, soft,deformable
CalliSpheres	Inverse suspension free-radical polymerisation	A crosslinked polymer dominated by polyvinyl alcohol(PVA)	liquid	100-300,300–500,500-700,700–900, 900-1200	Net structure, Spherical,Calibrated, nonabsorbable,shrinks after loading drug

PVA:polyvinyl alcohol.

the shape of the vascular cavity, allowing close contact with blood vessels. In contrast to DC Beads, drug-loaded HepaSpheres expand after treatment, increasing approximately 2-3.5 times in an ion contrast agent and 4 times in human plasma. CalliSpheres have good elasticity; they can be compressed to 50% of their original width to facilitate passage through a microcatheter, and afterward, are quickly restored to their original form.

DEB loading and elution of drugs mainly depend on the coulomb force of positive and negative ions. When the drug is loaded, the anion groups in the microspheres and positive ion groups in the chemotherapy drugs attract and bind to each other through the coulomb charge. In addition, HepaSpheres have a mechanical absorption mechanism, allowing them to load non-ionic drugs and other agents.[9] The drug dose that can be loaded onto a DC Bead is related to the number of sulfonate groups in the microsphere but not to its size. The smaller the microsphere, the faster is the drug-loading speed; for example, when loading 25 mg doxorubicin onto a 1 mL DC Bead, the $\geq$99% load times are 20 min (100–300 μm), 60 min (300–500 μm), 90 min (500–700 μm), and 120 min (700–900 μm). The maximum dose of Adriamycin that can be loaded onto a DC Bead is 40 mg/mL; however, after loading a bead with 37.5 mg/mL Adriamycin, the loading rate was found to decrease significantly.[10]Therefore, when loading DC Beads with doxorubicin in clinical practice, the drug should not exceed 37.5 mg/mL; otherwise, the incomplete drug load may lead to a high free-drug concentration and increase the risk of systemic adverse reactions. The elution rate of DC Beads is related to the size of the microspheres and the amount of loaded drug, i.e., the smaller the microsphere, the higher is the elution rate, and the larger the drug dose from the same-sized microspheres, the lower is the elution rate.[11] Jordan et al.[12] compared DC Beads (500–700 μm) with HepaSpheres (400–600 μm) in a study on drug loading and eluting. They found that both DC Beads and HepaSpheres effectively loaded the drug within 2 h. Notably, their study also showed that the DC Beads remained in an independent suspension state during the whole experimental process, whereas the HepaSpheres formed a cluster, which may lead to the HepaSpheres carrying an uneven drug dose and failing to pass smoothly through microcatheters. In addition, the HepaSpheres were damaged when the drug was removed. Subsequent studies by Kos et al.[9] showed that the two-step loading method can avoid the aggregation and fragmentation of microspheres and facilitate better drug elution. They compared one-step and two-step doxorubicin loading of HepaSpheres of 30-60 μm and 50–100 μm, respectively. Their research suggests that two-step loading avoids microsphere aggregation and damage; furthermore, it allowed better elution of the drug and minimized the quick-release early phase, which may substantially contribute to whole-body toxicity and side effects. Recent in vitro studies by Baere et al.[13] showed that small particle-size microspheres can complete drug loading quickly. DC Beads (100–300 μm) load over 99% of doxorubicin in 1 h, whereas HepaSpheres (30–60 μm) take only 15 min. Their study further confirmed the advantages of loading drugs into smaller microspheres. CalliSpheres, which have a reticular structure, effectively complete drug loading in 30 min.[14]

2.2. Pharmacokinetics

The efficacy and pharmacokinetics of DEBs loaded with doxorubicin

were better than those of cTACE for the treatment of a rabbit HCC model (VX-2).[8,15–17] Compared with simple arterial administration, DC Beads reduced the plasma drug concentration by 70-85%; the local drug concentration at the tumor peaked on the 3rd day and was maintained for 7–14 days.[8] CalliSpheres can deliver relatively high concentrations of doxorubicin, up to 200 μm, from the bead edge for at least 1 month.[17] A recent animal study further investigated the effectiveness of the technique, in which an average of 60 rabbits were divided into five groups (intravenous, arterial, cTACE, low-dose DEB-TACE, and high-dose DEB-TACE). The study showed that the drug plasma peak concentration (Cmax) of the TACE group was significantly lower than that of the non-TACE group; the Cmax of the low-dose DEB-TACE group was the lowest, whereas that of the cTACE group was the highest. The area under the curve showed that compared with cTACE, DEB-TACE effectively reduced the concentration of the drug in the blood. On the 7th day of the experiment, the average drug concentrations per gram of tumor in the five groups were 32 ng, 349 ng, 3282 ng, 12,189 ng, and 25,504 ng, whereas the average necrosis rates of the tumors were 21%, 24%, 87%, 71%, and 99%, respectively. DEB-TACE combined with high-dose chemotherapy drugs inactivated the tumor more effectively.[14]In clinical practice, the Cmax following DEB-TACE was found to be significantly better than the Cmax after cTACE, and DEB-TACE can reduce postoperative systemic toxicity.[7,18,19] Another serum pharmacokinetic study comparing DC beads with HepaSpheres further confirmed these results. In addition, the study found that the Cmax of epirubicin for the two types of beads peaked 5 min after treatment, and the Cmax gradually decreased and stabilized within 2 h after treatment. However, there was a more pronounced and statistically significant ($P < 0.05$) decrease in systemic exposure to epirubicin in the HepaSphere patient cohort.[20]

3. Drug delivery and distribution

In recent years, studies on the mechanisms of anti-cancer drug resistance have shown that the tumor microenvironment has a profound influence on the effect of cancer treatment. Changes in the extracellular environment, including increased interstitial fluid pressure, abnormal extracellure matrix composition, reduced pH, hypoxia, and irregular blood vessels, result in limited drug efficacy. Therefore, when selecting treatments, drugs with first-order dynamic characteristics should be considered. Although doxorubicin does not exhibit first-order kinetic characteristics, its tumor penetration is significantly improved when it is combined with lipiodol or DEBs.[21]Doxorubicin was rapidly separated from an iodinated oil suspension after cTACE operation, meaning lipiodol was not a good predictor of drug distribution in tissues. After DEB-TACE, Computer Tomography (CT) is employed to monitor the treatment coverage and predict the reaction and recurrence. However, the true locations of the microspheres are unknown and can only be inferred from indirect and temporary signs as the soluble contrast medium washes out. Interestingly, a kind of X-ray-impenetrable microsphere (DC Bead LUMI) has been developed,[22–24] which means microspheres and drugs can be used more accurately with monitoring by digital subtraction angiography and CT. Subsequently, a preclinical study found that the amount of doxorubicin in embolized livers was linearly proportional to the volume and X-ray attenuation of radiopaque DEBs

measured with CT, enabling accurate imaging-based predictions of drug dose and spatial distribution. Doxorubicin was found to be distributed within 600 μm of the microspheres.[25]

4. Progress in clinical research

4.1. Technology and treatment options

At present, there is no clear technical or therapeutic standard for TACE treatment of HCC; however, the technological advancement in DEB design may overcome these limitations. The recommendations of the European expert group on the use of DEBs with doxorubicin for the treatment of HCC are summarized as follows[26].1 For each patient, preoperative CT or magnetic resonance imaging examination and comprehensive evaluation of clinical and laboratory data should be performed.[2] Painkillers and antibiotics should be reasonably administered.[3] The recommended doxorubicin loading dose for DC Beads is 25–37.5 mg/mL. After loading, every 1 mL of DC Bead is mixed with 10–20 mL of non-ionic contrast agent, and care should be taken to ensure that the DC Beads are thoroughly suspended in the contrast agent before injection.[4] The dose of doxorubicin should depend on the degree of liver tumor load, i.e., within the standard Milan criteria range, the maximum dose of each treatment is 70 mg, whereas outside the Milan range, the maximum dose is 140 mg per treatment.[5] For patients with bilateral tumor involvement or a large tumor, the treatment can be divided into two courses with an interval of 2–4 weeks, and the interval can be extended for those without complications. Patients with both liver lobes affected or tumors that account for more than 50% of the liver tissue need experienced physicians to administer a single course of treatment.[6] Microspheres should be selected according to individual patient and tumor characteristics, with recommended sizes ranging from 100 to 300 μm.[7] If an arteriovenous shunt exists, gelatin sponge embolization should be performed first, and

microspheres should be used after angiography confirms the absence of a shunt; then, the larger microspheres should be selected.[8] As far as possible, a microcatheter should be used, attention should be given to the super-selection of target and abnormal blood vessels, and reflux should be avoided.[9] A 1-mL injection of contrast-agent-microsphere suspension should be administered every minute until a near-stagnation state is observed in the blood supply artery of the tumor. If the endpoint of near-stagnation is not reached after injection, another course of repeated treatment should be arranged.[10] The modified Response Evaluation Criteria in Solid Tumors (mRECIST) should be used to evaluate tumor status every 2–4 weeks after surgery. Patients with partial response (PR), stable disease (SD), and progressive disease with no contraindications should be treated again after 4–8 weeks, and patients with complete response (CR) should be followed up every 2–3 months. Treatment should be discontinued if the patient's disease progresses, the target objective response is not achieved after at least two DEB-TACE treatments, the disease worsens, or sustained hepatic decompensation occurs. These recommendations will undoubtedly make an outstanding contribution to the standardization of TACE therapy for HCC; however, they need to be verified and supplemented by a substantial number of clinical studies.

4.2. Survival and tumor response

Raoul et al. investigated the 2008–2009 studies on TACE therapy for HCC, almost all of which were cTACE, including 41 prospective studies, 48 retrospective studies, and 3 meta-analyses. The overall survival time was 3.4–31 months (median 14 months), and the 1-year survival rate was 0-92% (median 61.5%). A retrospective study showed that overall survival was 8.5–48 months (median 16.5 months), and the 1-year survival rate was 0-100% (median 62.5%).[27] A 2012 Japanese study of 4966 patients with HCC treated with cTACE showed that the median survival was 3.3 years (about 40 months), and the 1-, 2-, 3-, 4-, and 5-year survival rates

Table 2
Survival of HCC treated with DEB-TACE versus cTACE.

Study	Type	Number DEB-TACE vs cTACE	CP DEB-TACE vs cTACE	BCLC DEB-TACE vs cTACE	OS DEB-TACE vs cTACE	Survival rate DEB-TACE vs cTACE
Dhanasekaran et al.[30] 2010	R	45 vs 26	22/11/12 vs 11/11/4	NA	median OS:610 vs 284 d (p = 0.03)	0.5/1/2/y:72%/67%/40% vs 58%/46%/19% (p = 0.031)
Sacco et al.[43] 2011	RCT	33 vs 34	29/4 vs 25/9 (A/B)	22/11 vs 22/12 (A/B)	NA	2 y: 86.8% vs 83.6% (p = 0.96)
Song et al.[40] 2012	R	60 vs 69	26/34 vs 31/38 (A/B)	27/33 vs 28/41 (A/B)	mean OS:26.4 vs 27.2 m	6/12/18 m:93%/88%/88% vs 80%/67%/61% (p = 0.005)
Recchia et al.[41] 2012	P	35 vs 70	NA	NA	mean OS:18.4 vs 11.4 m (p > 0.05)	NA
Golfieri et al.[31] 2014	RCT	89 vs 88	75/14 vs 77/11 (A/B)	41/26/22 vs41/23/24 (A/B/C)	median OS:29 vs 28 m	1 y:86.2% vs 83.5% 2 y:56.8% vs 55.4% (p = 0.949)
Facciorusso et al.[32] 2015	R	145 vs 104	129/16 vs 93/11 (A/B)	5/53/81/6 vs 2/39/63/0 (0/A/B/C)	median OS:32 vs 39 m (p = 0.10)	NA
Kucukay et al.[42] 2015	R	53 vs 73	NA	NA	mean OS:37.4 vs 39.0 m (p = 0.888)	1 y:95.9% vs 84.9% 2 y:92.3% vs 74.6% (p = 0.543)
Kloeckner et al.[33] 2015	R	76 vs174	51/22/3 vs 103/64/7 (A/B/C)	8/34/30/4 vs 30/59/77/8 (A/B/C/D)	median OS:369 vs 409 d (p = 0.76)	NA
Arabi et al.[44] 2016	R	35 vs 19	NA	NA	NA	2 y:58% vs 60% (p = 0.96)
Lee et al.[34] 2017	R	106 vs 144	85/21 vs 95/49 (A/B)	20/77/9 vs 49/73/22 (A/B/C)	mean OS:46.6 vs 44.9 m (p = 0.660)	NA
Massani et al.[35] 2017	R	28 vs 54	24/4 vs 45/9 (A/B)	3/4/21 vs 10/27/17 (A/B/C)	median OS:22.7 vs 21.8 m (p = 0.708)	NA
Liu et al.[36] 2018	R	72 vs 201	69/3 vs 194/7 (A/B)	16/56 vs 71/128 (A/B + C)	median OS:37 vs 37 m (p = 0.091)	NA
Xiang et al.[37] 2019	R	36 vs 37	30/6 vs 30/7 (A/B)	9/17/10 vs 13/18/6 (A/B/C)	median OS:26.3 vs 23.9 m (p = 0.106)	NA
Karalli A et al.[38] 2019	R	110 vs 69	71/36 vs 48/21 (A/B)	1/34/66/4/1 vs 1/20/31/15/0 (0/A/B/C/D)	median OS:17.1 vs 19.1 m (p > 0.05)	NA
Zhao C et al.[39] 2019	R	42 vs 47	25/16/1 vs 38/8/1 (A/B/C)	5/9/22/6 vs 9/11/17/10 (A/B/C/D)	mean OS:15.0 vs 13.1 m (p = 0.976)	NA

DEB-TACE:Drug-eluting beads transarterial chemoembolization; cTACE:Conventional transarterial chemoembolization; CP:Child-Pugh; BCLC:Barcelona clinic liver cancer; P:Prospective; R:Retrospective; RCT:Randomized controlled trial; OS:Overall survival; m:month; d:day.

were 87%, 70%, 55%, 42%, and 34%, respectively.[5]In the same year, two studies on the treatment of HCC by DEB-TACE showed that the median survival was 48.6 months,[28] and the 1-, 2-, 3-, 4-, and 5-year survival rates were 93.6%, 83.8%, 62.0%, 41.04%, and 22.5%,[29] respectively.

Table 2 summarizes the comparative studies on survival after DEB-TACE and cTACE. The studies reported that the median survival times[30–38] of DEB-TACE and cTACE were 12.3–37 and 9.4–39 months and the mean survival times[29,34,39–42] were 15.0–44.6 and 11.4–44.9 months, respectively. The 1- and 2-year survival rates after treatment with DEB-TACE were 67–95.9% and 40–92.3%, respectively, and the 1- and 2-year survival rates after treatment with cTACE were 46–84.9% and 19–83.6%, respectively.[30,31,40,42–44]

Table 3 summarizes the HCC tumor response to DEB-TACE treatment. Table 3 excludes studies with unclear follow-ups and studies that did not calculate the overall tumor response. From 2007 to 2019, mRECIST was used to evaluate the tumor response rate after 1 month of DEB-TACE treatment. Objective response (OR) was the sum of CR and PR. Disease control(DC) was the sum of CR,PR and SD. According to these reports, the rates of CR, OR, and DC were 6.7–59.8%, 52–100%, and 76.7–100%, respectively.[6,31,37,40,43,45–51]

Currently, the efficacy of DEB-TACE for the treatment of HCC is widely recognized; however, there are differing opinions on whether the efficacy of DEB-TACE is better than that of cTACE. Three randomized controlled trials provided different results. Lammer et al. concluded that DEB-TACE significantly ($P = 0.038$) improved the OR rate of Child-Pugh B, ECOG1 score, bilobar disease, and patients with recurrent disease.[52] However, two subsequent randomized controlled trials found no significant difference between the two treatments.[31,43] In addition, three meta-analyzes published in the same year produced contrasting findings. According to the meta-analyses by Facciorusso et al., DEB-TACE showed no significant advantages for the 1-, 2- and 3-year survival rates.[53] However, a meta-analyses by Zou et al. indicated that DEB-TACE prolonged survival and improved survival rate,[54] and one by Chen et al. showed that DEB-TACE improved the 1-, 2- and 3-year survival rates.[55]

According to prospective and retrospective studies, DEB-TACE shows better short-term efficacy for treating HCC than cTACE. A prospective study conducted in Germany in 2011 showed there was a higher rate of DC with DEB-TACE than with cTACE for HCC, but unfortunately, the difference was not statistically significant. It is worth noting that the average tumor diameter in their study was larger, with average tumor diameters of patients receiving cTACE and DEB-TACE of 6.98 cm and 7.44 cm, respectively, and they were evaluated 8 months after treatment.[56] In a prospective study in South Korea, also in 2011, DEB-TACE performed better than cTACE, and the tumor response was assessed about 1 month after treatment. The OR rate of the patients receiving DEB-TACE and cTACE were 85% and 30%, respectively ($P = 0.001$), whereas the average tumor diameters were 6.3 cm and 6.2 cm, respectively. DEB-TACE significantly improved the OR rate compared with cTACE, especially when the tumor was larger than 5 cm. Although DEB-TACE performed better, the study was limited by the small sample size.[45] The following year, Song et al.[40] from South Korea conducted another retrospective study with a larger sample size, in which 60 and 69 patients were treated with DEB-TACE and cTACE, respectively, and the efficacy was evaluated at 1 month. The results showed that, after receiving DEB-TACE and cTACE, the CR, OR, and DC rates were 55.0%, 81.6%, and 96.6% and 23.1%, 51.4%, and 79.8%, respectively ($P <$ 0.001). Later studies also showed that the short-term efficacy of DEB-TACE was better than that of cTACE.[37,57] In addition, two recent studies showed that using DEB-TACE was more effective for the treatment of large HCC tumors, further confirming the previous findings.[39,58]

Further studies discovered that the efficacy of DEB-TACE in the treatment of HCC was related to tumor size. Grosso et al. found that tumor response at 1 month was correlated with tumor size, and the mean tumor size (3.9 cm) of CR was smaller than that of PR (5.1 cm).[59] Subsequently, Lee et al.[50] found tumor size to be an independent predictor of CR, and the CR rates of tumors with diameters of less than 2 cm were significantly higher than that of larger tumors. The evaluation criteria of European Association for the Study of the Liver and mRECIST for CR are the same, namely, the disappearance of arterial enhancement in all target lesions, so they were included in the discussion. According to the studies reported to date, the CR rates 1 month after DEB-TACE treatment tend to decrease as the mean sum of tumor diameters increases: 30% (2.3 cm),[47]

Table 3
Summary of tumor response to the treatment of HCC by DEB-TACE.

Study	Type	DEB-TACE (Numbers)	CP A/B/C (Numbers)	BCLC 0/A/B/C (Numbers)	Mean tumor size (Sum/Max)	Criteria	Follow-up (Time&number)	Tumor Response Rates		
								CR	OR	DC
Poon et al.[18] 2007	P	35	35/0/0	NA	10.0cm/NA		1 m(35)	6.7%	70.0%	76.7%
Grosso et al.[58] 2008	P	50	46/4/0	NA	4.25cm/NA	EASL	1 m(50)	48.0%	84.0%	100.0%
							6 m(31)	51.0%	76.8%	76.8%
Lammer et al.[52] 2009	RCT	93	77/16/0	0/24/69/0	8.89cm/NA	EASL	6 m(93)	26.9%	51.6%	63.4%
Wiggermann et al.[55] 2011	P	22	22/0/0	NA	7.44cm/NA	EASL	8 m(22)	13.6%	22.7%	90.1%
Sacco et al.[43] 2011	RCT	33	29/4/0	0/22/11/0	4.47cm/NA	mRECIST	1 m(33)	51.5%	100.0%	100.0%
Song et al.[40] 2011	P	20	18/2/0	0/6/10/4	6.30cm/NA	mRECIST	1 m(20)	35.0%	85.0%	100.0%
Song et al.[45] 2012	R	60	26/34/0	0/27/33/0	NA/4.20 cm	mRECIST	1 m(60)	55.0%	81.6%	96.6%
Malagari et al.[29] 2012	P	45	25/20/0	0/7/38/0	8.30cm/NA	mRECIST	1 m(45)	17.8%	68.9%	88.9%
Padia et al.[59] 2013	R	61	47/14/0	0/25/15/21	NA/NA	EASL	1 m(61)	50.8%	65.6%	86.9%
Boulin et al.[46] 2013	P	21	16/5/0	0/20/1/0	NA/4.60 cm	mRECIST	1 m(21)	28.0%	52.0%	95.0%
							2 m(21)	28.0%	52.0%	95.0%
Golfieri et al.[31] 2014	RCT	89	75/14/0	0/41/26/22	NA/3.10 cm	mRECIST	1 m(89)	43.8%	89.9%	93.3%
Bishay et al.[47] 2014	P	20	13/7/0	0/16/4/0	2.30cm/NA	mRECIST	1 m(20)	30.0%	65.0%	95.0%
Manini et al.[35] 2015	P	55	38/17/0	0/55/0/0	NA/NA	mRECIST	1 m(55)	53.0%	84.0%	93.0%
Yu et al.[49] 2016	R	60	NA	NA	NA/2.30 cm	mRECIST	1 m(60)	40.0%	73.3%	88.3%
Lee M et al.[50] 2017	P	152	143/9/0	11/77/26/38	5.50cm/NA	mRECIST	1 m(152)	40.1%	91.4%	98.0%
Lee YK et a.[34] 2017	P	106	85/21/0	0/20/77/9	3.40cm/NA	mRECIST	1 m(106)	59.4%	78.3%	96.2%
Sandow et al.[51] 2018	R	93	52/36/5	NA	NA/3.5 cm	mRECIST	1 m(93)	32.0%	76.0%	100.0%
Wu et al.[57] 2018	R	24	10/14/0	0/0/13/11	7.25cm/NA	mRECIST	3 m(24)	25.0%	83.3%	91.6%
							6 m(24)	20.8%	62.5%	83.3%
Xiang et al.[37] 2019	R	36	30/6/0	0/9/17/10	NA/5.5 cm	mRECIST	1 m(25)	16.0%	68.0%	96.0%
							3 m(15)	20.0%	100.0%	100.0%
							6 m(9)	33.3%	100.0%	100.0%
Zhang X et al.[56] 2019	P	66	59/7/0	25/23/18	NA/5.4 cm	mRECIST	1–3 m(66)	37.9%	81.8%	92.4%

18*:17 patients+1 lost to follow-up; mRECIST; modified Response Evaluation Criteria in Solid Tumors; EASL:European Association for Study of Liver; CR:complete response; OR:Objective response was the sum of complete response and partial response; DC:Disease control was the sum of complete response, partial response and stable disease.

59.4% (3.4 cm),[34] 48.0% (4.25 cm),[59] 51.5% (4.47 cm),[43] 40.1% (5.5 cm),[50] 35% (6.3 cm),[45] 17.8% (8.3 cm),[6] and 6.7% (10 cm).[18] However, further research is needed to confirm this.

4.3. Safety

DEB-TACE is a safe and reliable treatment for HCC. Common adverse reactions after TACE treatment are post-embolism syndrome, i.e., abdominal pain, fever, nausea, vomiting, and less common complications are liver abscess, tumor rupture, bile duct injury, cholecystitis, upper gastrointestinal bleeding, pleural effusion, pulmonary embolism, splenic infarction, and spinal cord embolism. Three current randomized controlled trials do not support the superiority of DEB-TACE with regards to the incidence of complications; however, the severity of complications after DEB-TACE treatment was less than that after cTACE.[31,43,52] A retrospective study comparing the safety of microspheres of different sizes found that smaller microspheres (100–300 μm) led to fewer complications and were better tolerated than larger microspheres (300–500 μm), with statistically significant differences.[60] The results of a 2017 study of 421 patients in Italy showed that no patients died within 1 month after DEB-TACE treatment, and no bleeding events or pulmonary complications occurred; however, all patients developed post-embolism syndrome. The incidence of complications after embolization in grades 1–2 and 3–4 was 72.9% and 27.1%, respectively. All 421 patients had laboratory evidence of elevated bilirubin and aminotransferase levels; only 1 (0.2%) patient had a serious increase in bilirubin levels, whereas 25 (5.9%) patients showed seriously increased aminotransferase levels.[61] The incidence of hepatic artery injury after DEB-TACE treatment was higher than that after cTACE.[62] After conventional treatment of hepatic artery injury associated with toxicity caused by chemotherapy arteritis, histological results showed hepatic artery intimal fibrosis and chronic inflammation with arteritis outside the catheter tip; thus, the drug was the main reason for the damage.[63] DEB-TACE leads to a greater incidence of arterial damage than conventional treatment perhaps because drug-carrying microspheres release a larger dose of chemotherapy drugs, and the slow-release effect prolongs the drug-activation time. Nevertheless, further studies are needed to explore these ideas.

The most recent noteworthy finding is the vascular lake phenomenon (VLP), which is a local accumulation of contrast agent abnormalities during DEB-TACE that are similar to exudation within the tumor. Previously, the VLP phenomenon was considered to be a complication of DEB-TACE, but this view has changed in recent years. In Seki et al.'s[64] study, tumor response rates in the VLP and non-VLP groups were 91.4% and 54.0%, respectively (P < 0.0001). A prospective study later suggested that VLP could be a predictor of improved tumor response,[65] and VLP was more likely to occur when the tumor size was greater than 3 cm. Although it is unclear what causes VLP, Seki et al.[64] believe HCC tumors form a heterogeneous vascular system of fragile capillaries; then, with microsphere embolism and physiological saline injection, pressure increases in the tumor leading to the destruction of the fragile capillaries and the appearance of VLP. Further exploration of the causes of VLP is necessary as this may help us to better manage HCC.

5. Summary and outlook

DEB-TACE treatment for HCC is safe and effective and, in combination with high-dose chemotherapy drugs, can efficiently inactivate the tumor. Although there is controversy over whether DEB-TACE is more efficacious than cTACE, a large number of studies have shown that DEB-TACE is more efficacious in the short term and for patients with larger lesions, and the efficacy of DEB-TACE is related to the tumor size. In short, the smaller the lesion, the better is the therapeutic effect; however, further studies are needed. The sustained release properties of drug-eluting microspheres can significantly reduce the postoperative drug concentration in the blood, and small-particle microspheres are more advantageous for loading and eluting drugs and can reduce postoperative

complications. In future, studies on factors affecting treatment efficacy, the further exploration of VLP, research and development of DC Bead LUMI, and the gradual standardization of drug-eluting bead use will aid in the further understanding and management of HCC.

Declaration of competing interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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