




Transcatheter Arterial Chemoembolization with Drug-Eluting Beads for the Treatment of Hepatocellular Carcinoma: Recommended Selection for Small-Caliber (<100 μm) Beads

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Abstract: Drug-eluting beads transarterial chemoembolization (DEB-TACE) is an alternative to conventional lipiodol-based TACE (cTACE) to treat hepatocellular carcinoma (HCC). With the advancement in pharmacology, small-caliber DEB-TACE (<100 μm) has been introduced since 2016. For the treatment of hepatic neoplasms or HCC, there is a tendency to use smaller beads by DEB-TACE to achieve more extensive tumor necrosis and a significant reduction in liver toxicity in comparison with that caused by cTACE. However, the indications and potential complications of small-caliber DEB-TACE remain uncertain and have not been well established, due to lack of randomized phase III clinical trials. Instead of systematic or meta-analysis review, this narrative review article describes the suggested indications and contraindications of DEB-TACE with small DEBs, benefit of super-selective embolization of the feeding arteries and the recommended selection of small-caliber DEB. This review was approved by the institutional review board (File Number: 1-105-05-158).

Keywords: chemoembolization, HCC, TACE, DEB-TACE, liver, review

Plain Language Summary

Conventional lipiodol-based TACE (cTACE) has been used to treat hepatocellular carcinoma (HCC). However, due to advancement in pharmacology, drug-eluting beads transarterial chemoembolization (DEB-TACE) using small-caliber beads (<100 μm) has been introduced to achieve more extensive tumor necrosis and a significant reduction in liver toxicity in comparison with that caused by cTACE.

Introduction

Transarterial chemoembolization (TACE) is primarily indicated in patients with hepatocellular carcinoma (HCC), chiefly in those with intermediate-stage disease but also in the early and, less frequently, advanced stages, based on the Barcelona Clinic Liver Cancer (BCLC) guidelines. Although conventional TACE (cTACE) with selective injection of lipiodol mixed with chemotherapeutic agents (doxorubicin or cisplatin) followed by vascular embolization constitutes the largest portion of transarterial treatment for HCC. The introduction of drug-eluting beads (DEBs) in the early 2000s provided an alternative to lipiodol-based regimens. Moreover, chemotherapeutic agents may be varied in different countries and institutions, cTACE has major

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drawbacks due to inter-operator variance and the lack of a universal drug delivery approach. In recent years, there has been increasing clinical evidence that DEBs have a reduced cytotoxic drug-related toxicity and liver toxicity in a sustained manner as compared with cTACE¹ with low systemic toxicity. With the advancements in drug development, different sizes of DEBs have been introduced into interventional radiology, and the size of commercially available DEBs varies considerably, ranging from 40 to 700 μm .

In the era of using DEBs larger than 100 μm , the patients had higher overall survival and lower toxicity of TACE using small (100–300 μm) DEBs in comparison with those using large (300–500 and 500–700 μm) DEBs, particularly in patients with advanced HCCs with relatively poor liver function (Child-Pugh classes B and C).^{2,3} Patients treated with smaller (<100 μm) DEBs are significantly associated with improvement with respect to the rates of treatment response, procedure-related complications and post-embolization syndrome.^{4–6} However, in comparison with cTACE, the use of such smaller (<100 μm) DEBs is associated with increased risk of hepatobiliary injuries, such as bile duct dilatation, portal vein narrowing, and hepatic failure.^{4–6}

The use of small-caliber beads (<100 μm) enables more distal embolization, greater penetration, and a higher drug concentration in the network of neoplastic vessels.^{7,8} In this narrative review, we summarize the updates on DEB-TACE and present the potential benefits of using small-caliber DEB (which is defined as beads smaller than 100 μm in this article) to treat HCC.

Mechanism of DEB-TACE and Its Pharmacokinetics

To date, at least four types of commercially available DEB have been developed (Table 1).^{9,10} These are all negatively charged and can be loaded with different chemotherapeutic agents. Doxorubicin is the most popular loaded chemotherapeutic drug used for DEB-TACE treatment of HCC. Although treatment recommendation remains controversial among the interventional radiologists, it can be basically recommended for HCC patients within or beyond the Milan criteria.^{11,12}

1. Patients within the Milan criteria: a planned dose of 50 to 75 mg of doxorubicin is loaded into one vial for each single treatment.

2. Patients beyond the Milan criteria: a planned dose of up to 150 mg of doxorubicin is loaded into two vials for each single treatment. For a huge tumor with large diameter (>8 cm) or bilobar tumors, treatment typically includes separate sessions (in intervals of 4 to 8 weeks, in the presence of complications, a longer time interval is required).

Uptake of doxorubicin onto the beads occurs between 30 minutes and 4 hours (small beads load more quickly due to surface area effects). The time required to load 99% of doxorubicin is defined as the loading time. The loading time varies for different beads, and for a given bead, different sizes can also cause different loading times.¹³ The smaller the bead size, the faster is the drug loading time.¹⁴ After loading, DEBs will be infused into tumors from the catheter or microcatheter, and doxorubicin will elute from the beads. The eluting time is the time taken to elute 75% of the total released doxorubicin. Then, doxorubicin will penetrate into tumors, and a small percentage of them will inevitably go into the systemic circulation. It is known that the plasma concentration of doxorubicin in TACE is related to the systemic toxicity. The use of DEB-TACE has been associated with a significantly lower plasma concentration of doxorubicin as compared with cTACE.¹⁵ Moreover, DEB-TACE can be used to continuously release doxorubicin, even at 2–3 weeks after embolization.¹⁶

Indications and Contraindications for DEB-TACE with Different Bead Sizes

In general, indications and contraindications for using DEB-TACE are almost the same as those for TACE.⁹ The PRECISION V study¹⁷ proposed that DEB-TACE is superior to cTACE for patients with advanced disease, poor heart function, and impaired liver function. However, with regard to TACE-related hepatic locoregional complications, DEB-TACE has been associated with a higher risk for complications than cTACE, and the latter may be a better option for patients with high baseline prothrombin value.¹⁸

Within the DEB-TACE, different sizes of beads have variable levels of therapeutic efficacy and safety profiles. Currently, there is no consensus on the optimal particle size for DEB-TACE. Three types of drug-eluting beads are 100–300 μm in size after loading with doxorubicin: (1)

Table 1 Type, Sizes, and Pharmacokinetic Properties of Commercially Available Microspheres

| | DC Bead | HepaSphere | Tandem | Lifepearl |
|---------------------------------------|---|---|---|--|
| Company | BTG, London, UK | Merit Medical, South Jordan, UT, USA | CeloNova Bioscience, Inc., San Antonio, TX, USA | Terumo European Interventional systems, Leuven, Belgium |
| Component ⁸ | Polyvinyl alcohol hydrogel modified with sulfonate groups | Poly (vinyl alcohol-co-sodium acrylate) hydrogel | Hydrogel core made of sodiumpoly (methacrylate) and outer biocompatible shell of poly (bis [trifluoroethoxy] phosphazene) | Hydrogel network of poly (ethyleneglycol) and 3-sulfopropyl acrylate |
| Size (µm) | 70–150 100–300 300–500 500–700 | Dry form: 30–60 50–100 100–150 Hydrated form: 120–240 200–400 400–600 600–800 | 40, 75, 100, 250, 400, 500, 700, 900 | 100 ± 25 200 ± 50 400 ± 50 |
| Diameter distribution ⁹ | 100–300 µm become 138 ± 47 µm after loading (reduced about 20%) | 30–60 µm (dry form) become 165 ± 28 µm after loading (increased about 4 times) | 100 µm become 89 ± 15 µm after loading (reduced about 9%) | 200 µm become 151 ± 18 µm after loading (reduced about 24%) |
| Eluting time ⁹ | 197 minutes | 110 minutes | 77 minutes | 139 minutes |
| Loading time ⁹ | Within one hour | Within one hour | Within one hour | Within one hour |
| Time in Suspension (sec) ⁹ | 185 ± 11 | 172 ± 20 | 504 ± 12 | 357 ± 7 |

100–300 μm DC beads, (2) 30–60 μm Hepasphere, and (3) the 200 μm Lifepearl. It is known that 100–300 μm DC beads have a better therapeutic effect and lower complications than larger beads.² In animal models, 30–60 μm Hepasphere showed a denser distribution of microspheres, a higher tissue and equal plasma concentration of doxorubicin in comparison with the 120–240 μm Hepasphere.¹⁹ When administrated to HCC patients, TACE with 30–60 μm Hepasphere beads had an acceptable level of therapeutic efficacy with a complete response rate of 17.8%, and no 30-day mortality was encountered.²⁰ For the Lifepearl, limited studies have focused on its therapeutic efficacy and safety. The PARIS registry,²¹ which studied both 100 μm and 200 μm Lifepearl beads, showed a higher tumor response rate and lower hepatobiliary toxicity with these beads in comparison with those from cTACE.

A limited number of studies have focused on smaller-caliber DEBs. The use of the DEB-TACE with 70–150 μm DC beads and 100–300 μm DC beads was associated with greater hepatobiliary toxicity than when 100–300 μm DC beads were used alone, with no difference in tumor response.²² A retrospective study with 51 patients showed a better one-month objective response rate for 70–150 μm DC beads in comparison with 100–300 μm DC beads, without differences in overall survival or the safety profile.²³ A retrospective study with 72 HCC patients treated with idarubicin-loaded Tandem beads (75 and 100 μm) reported an objective response rate of 65%, a median time-to-treatment failure of 14.4 months, and a median overall survival time of 34.6 months.²⁴

The primary concern regarding chemoembolization with small-caliber DEBs in HCC is safety, especially in terms of pulmonary embolization, tumor rupture, and biliary damage, despite the fact that it is more effective than TACE treatments with larger beads.

Modified Response Evaluation Criteria in Solid Tumors (mRECIST) to Evaluate Treatment Response and Reasons for Tumor Viability Escape from TACE

The clinically mRECIST criteria are widely used for the assessment of tumor response after HCC treatment²⁵ and have been proven to have a strong prognostic correlation in HCC patients undergoing loco-regional treatment.²⁶ In mRECIST, the treatment response depends on intratumoral arterial enhancement rather than the whole-tumor size

measured in RECIST. It has been proven that the presence of a complete response after the initial TACE treatment is a good prognostic predictor,²⁷ because post-TACE viable tumors are prone to becoming TACE-resistant, which is probably caused by the following three mechanisms:

Sarcomatous Changes in the Viable Tumor After TACE

Sarcomatous differentiation is a poor prognostic factor for HCC patients.²⁸ It was found in 4.2% of treatment-naïve HCC patients and 20.9% of HCC patients undergoing anticancer therapy.²⁹ Of these cases, sarcomatous change was most frequently observed in patients with repeated transarterial embolization.

Presence of the Hepatocholangiocellular Phenotype

In a study involving 80 HCC nodules,³⁰ including 40 treated with TACE and 40 not treated with locoregional therapy (LRT) removed during liver transplantation, 35% of the TACE-treated nodules showed the hepatocholangiocellular phenotype, and none of the nodules had this phenotype after LRT.

Tumor Blood Supply from the Portal Vein

A study involving 12 HCCs treated with TACE showed that the portal blood supply to TACE-resistant tumors became apparent on computed tomography (CT) images in the portal venous phase,³¹ which may have been caused by arterial damage by TACE. In short, avoiding residual viable tumors in the first round of TACE treatment is critical for the treatment of unresectable HCC.

Despite promising value of mRECIST in assessing treatment response of TACE, there are some limitations with inevitable major bias.^{32,33} For example, the interpretation of mRECIST relies on the observer consistency (inter- and intra-observer reproducibility). It is essentially not appropriate to use mRECIST to assess the sequential changes of arterial enhancement and diameters of the target HCC with extrahepatic metastases or HCC manifesting poor enhancement, infiltration, or high-grade portal vein invasion.²⁵ Clinically, many patients are not able to have a series of follow-up imaging studies for assessment by mRECIST, and this could lead to a bias according to the World Health Organization criteria in deciding treatment discontinuation.³²

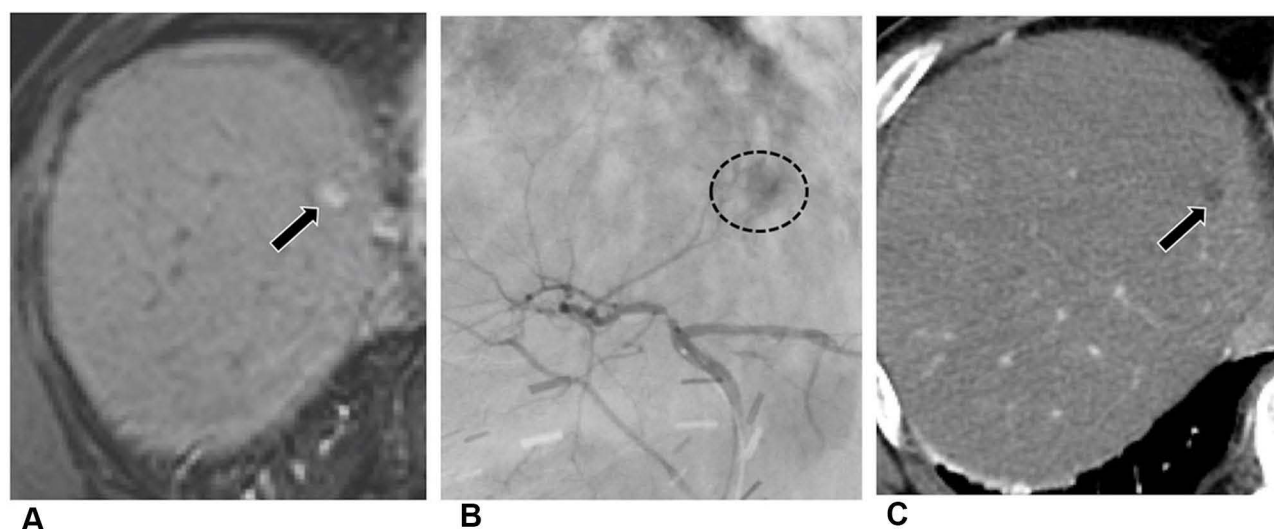


Figure 1 A small HCC supplied by small hepatic arteriole in a 62-year-old male. **(A)** Contrast-enhanced arterial-phase MR image shows a recurrent HCC in the segment 4 (black arrow). **(B)** Left hepatic angiogram demonstrates a faint hypervascular tumor in the segment 4 of liver (dotted circle) supplied by the superior branch of left hepatic artery. DEB-TACE was then performed. **(C)** Follow-up CT one month after TACE reveals no residual enhancement (black arrow). The patient was disease free without evidence of tumor recurrence to date.

Superselective Embolization of the Tumor Feeding Arteries

By definition, superselective TACE indicates management at the distal portion of the tumor-feeding subsegmental artery, in which microcatheter is engaged more distally than in selective TACE (management at the hepatic arterial branch afferent to the segment in which the tumor is located). Selective/superselective TACE has shown its therapeutic superiority compared with lobar TACE (management at the right/left hepatic artery)³⁴ in cTACE, in which 53.8% of selective/superselective TACE-treated HCC nodules reached complete necrosis in comparison with 29.8% treated with lobar TACE. In advance, ultra-selective TACE, in which a microcatheter is inserted into the tumor feeding artery, leaving a peritumoral safety margin in the liver parenchyma of at least 1 cm, has been applied with cTACE for the treatment of HCC tumors smaller than 5 cm.³⁵ For DEB-TACE, superselective TACE treatments can assure that beads will be infused into tumors without compromising normal liver parenchyma to a great extent.

Recommended Selection for Small-Caliber (<100 μ m) DEBs

The optimal bead size for HCC patients receiving DEB-TACE remains uncertain and has not been well investigated. There is no well-established indication for the selection of small-caliber DEBs in TACE treatment of HCC due to lack

of multi-center Phase II or III clinical trials. The use of commercially available small-caliber DEBs mainly depends on the experiences of interventional radiologists.

The most commonly used beads in clinical practice are the DC Bead and HepaSphere. There is a tendency to use smaller beads to achieve more extensive tumor necrosis. In the era before the launch of small-caliber DEBs, a study³ reported that 100–300 μ m doxorubicin DEBs are superior to 300–500 μ m for HCC treatment in terms of achieving a more complete imaging response at initial follow-up. Once again, a more recent study²³ demonstrated that 75–150 μ m doxorubicin DEBs are superior to 100–300 μ m ones in terms of achieving a tumor response. While differences in DEB-TACE techniques across centers still exist, based on our knowledge and experience, the recommended selection for small-caliber DEBs is as follows:

Small HCCs Supplied by Small Hepatic Arteriole

For small HCCs, 100–300 μ m DC beads have shown their therapeutic efficacy as a bridge to liver transplantation.³⁶ In theory, the smaller size beads are characterized by a greater surface area and volume that could be delivered to the tumor before stasis, which consequently induces irreversible ischemia in the liver and biliary system. Super-selective DEB-TACE with small-caliber beads (Figure 1) may spare a larger area of peritumoral hepatic parenchyma and reduce the phenomenon of hypoxic-ischemic neo-angiogenesis, but such a treatment may increase the incidence of biliary tract injury.

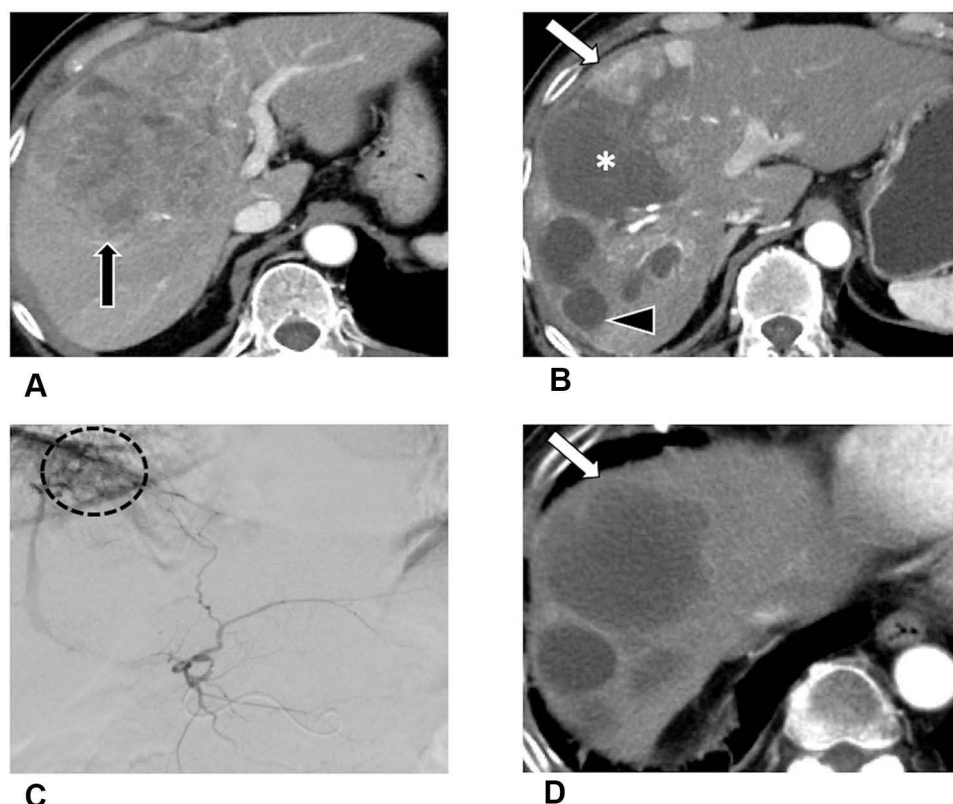


Figure 2 Repeated TACE for neovascularity of tumor-feeding arteries. An 80-year-old male with a large HCC in the segments 4/8. **(A)** A CT image in arterial phase CT shows a heterogeneous enhancing mass (black arrow). TACE with large-caliber DEBs was performed. **(B)** Follow-up CT 3 months after the 1st TACE reveals that approximately 80% of the HCC (*) is necrotic with residual enhancement (white arrow), indicative of partial response. Biloma after the 1st TACE is depicted (black arrowhead). **(C)** Left hepatic angiogram during the 2nd TACE demonstrates residual tumors (dotted circle) supplied by newly-developed feeding arteries. TACE with small-caliber DEBs was performed. **(D)** Follow-up CT 3 months after the 2nd TACE reveals necrosis of the entire tumor (white arrow) without residual enhancement.

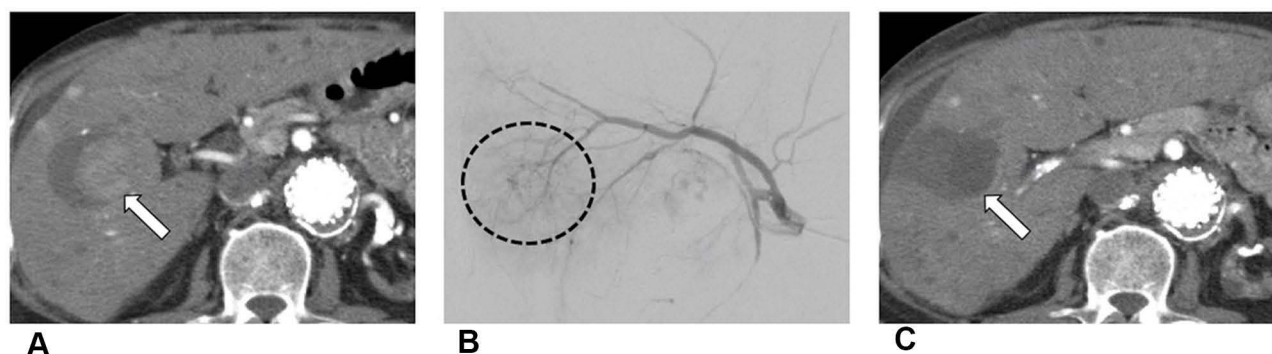


Figure 3 Another TACE treatment for residual viable tumor. A 67-year-old male with a previously treated HCC. **(A)** Follow up CT one year after the 1st TACE reveals partial necrosis of the HCC with residual enhancement (white arrow). **(B)** An angiogram during the 2nd TACE treatment reveals residual tumor with feeding arteries (dotted circle) originating from the right hepatic artery. TACE with small-caliber DEBs was then performed. **(C)** CT image three months after the 2nd DEB-TACE treatment shows no residual enhancement in the HCC (white arrow).

Repeated TACE for Neovascularity of Tumor-Feeding Arteries

Repeated TACE may deteriorate liver function³⁷ and stimulate new tumor vessel formation, which is associated with tumor recurrence after TACE. The new tumor vessels produced due to angiogenesis induced via vascular

endothelial growth factor are relatively small, very tortuous, and morphologically and functionally different from normal liver vessels. In repeated or multiple sessions of DEB-TACE, small-caliber DEBs are a better treatment option than large-caliber DEBs to treat neovascularity of tumor-feeding arteries (Figure 2).

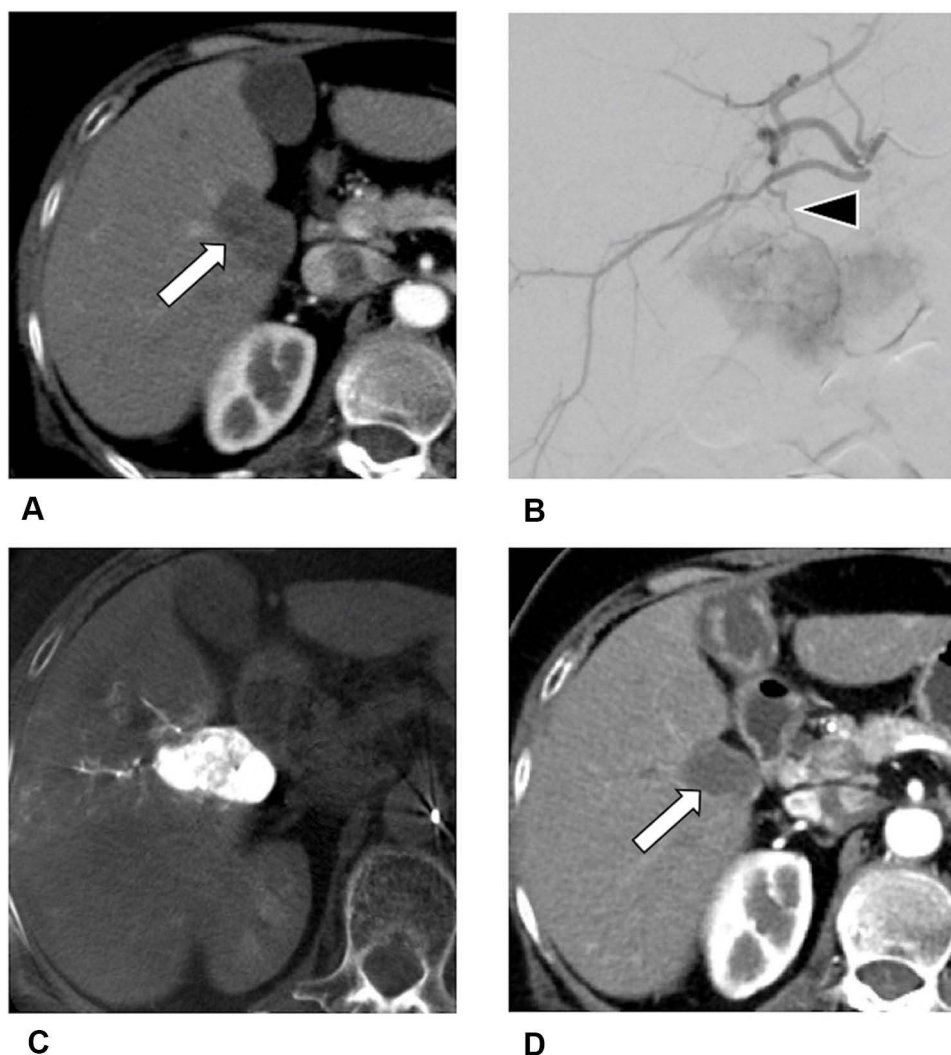


Figure 4 HCC simultaneously treated with DEB-TACE and local radiofrequency ablation (RFA). A 71-year-old male with a HCC near the hepatic hilum, which was treated with RFA. **(A)** Three months after RFA, CT shows a residual HCC (white arrow) in the right lobe of liver near hepatic hilum. **(B)** During TACE, the right hepatic angiogram reveals a hypervascular tumor supplied by a small branch of right hepatic artery (black arrowhead). **(C)** Post-TACE cone-beam CT image after small-caliber DEBs infusion shows homogeneously high attenuation of the residual HCC. **(D)** Follow-up CT one month after the TACE shows no evidence of residual enhancement (white arrow).

Another TACE Treatment for Residual Viable Tumors

It is unlikely for a single session of TACE to obtain a complete response for large HCC tumors. In order to achieve better local tumor control, switching small-caliber DEBs to another TACE treatment is recommended if the large HCC tumors are refractory to TACE (Figure 3).

Simultaneous Use of DEB-TACE and Local Radiofrequency Ablation (RFA)

The use of DEB-TACE combined with local ablative therapies has achieved excellent results for HCC treatment, with improved local tumor control and overall survival. RFA therapy has its limitations in terms of the size and number of HCCs

it can treat, and some locations in the liver might be difficult to approach with ultrasonography guidance. TACE is likely to be used as a palliative treatment, as the local recurrence rate of small HCCs after DEB-TACE treatment has been reported to be up to 45.7%.³⁸ In order to produce full necrosis or to treat local recurrences of the target HCC, the combination of DEB-TACE and RFA yields a better local tumor control and decreases tumor recurrence than each treatment alone (Figure 4).

Extrahepatic Collateral (EHC) Blood Supply to HCC

As exophytic growth of HCCs is usually located adjacently to the bare area of the liver and is treated by

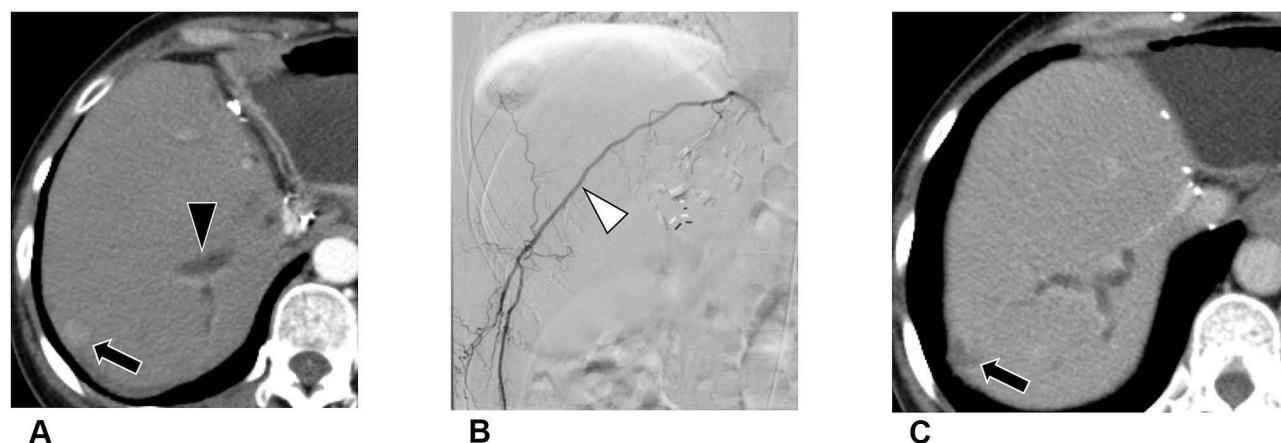


Figure 5 Extrahepatic collateral blood supply to HCC. A 46-year-old female with history of HBV-related HCC in the left lobe was treated with wedge resection. **(A)** Three years after the surgery, CT shows a recurrent HCC (black arrow) in the subcapsular region of segment 7 of liver. Focal dilatation of intrahepatic bile duct (black arrowhead) is depicted, which may be due to postoperative change. **(B)** During TACE, the right 12th lumbar angiogram (white arrowhead) reveals a hypervascular tumor in the right lobe of liver. Subsequently, TACE was performed with small-caliber DEBs. **(C)** Sixth month after DEB-TACE, the follow-up CT shows no residual enhancement of the entire HCC (black arrow).

LRT,³⁹ they may recruit the EHC blood supply. Most studies focusing on using TACE through EHC arteries have been limited to cTACE,⁴⁰ and a retrospective study with 42 HCC patients treated with 30–60 μ m Hepasphere beads through EHC arteries showed that DEB-TACE has a potential therapeutic effect on HCC tumors with an EHC blood supply, with a comparable safety level to cTACE.⁴¹ Small-caliber DEBs can be super-selectively delivered to more distal branches of these EHC arteries, preventing non-target embolization of non-liver organs (Figure 5).

Patients with Poor Liver Function (Child–Pugh Score 8–9)

DEB-TACE has been associated with a significant reduction in liver toxicity in comparison with that caused by cTACE.¹⁷ Moreover, DEB-TACE with small-caliber DEBs potentially benefits HCC patients with poor liver function due to superselective embolization of a more focused liver area. Small-caliber DEBs can be delivered more distally by sparing non-tumoral cirrhotic liver parenchyma as much as possible to decrease liver toxicity (Figure 6).

HCC with Relatively Low or Small Vascularity

When an HCC features a low contrast medium enhancement on a dynamic CT or MRI in the arterial and portal venous phases, it is defined as HCC with relatively low or small vascularity (Figure 6).⁴² To date, few studies have

focused on the TACE treatment of HCC with relatively low or small vascularity.

A single-center series enrolled 98 patients with atypical HCC (including relatively low or small vascularity and well-differentiated HCC) proposed decreased efficacy of TACE in these patients.⁴³ Another single-institution retrospective study showed that DEB-TACE had better therapeutic efficacy and equivalent safety to cTACE.⁴⁴ HCC with relatively low or small vascularity indicates less tumoral blood supply, and in this circumstance, small-caliber DEB can penetrate into tumor through small-sized tumor-feeding arteries, lead to better saturation of target tumors.

Contraindications of Small-Caliber DEBs

Portal vein thrombosis (PVT) with and without intrahepatic shunt are poor prognostic factors for HCC patients. Due to the high risk of developing hepatic failure, treatment with TACE is sometimes contraindicated. There is still uncertainty about the lower limitation of effective bead size, because the presence of PVT and intrahepatic shunts with smaller DEBs increases the risk of disease progression and complications (Figure 7).

Follow-Up Imaging with mRECIST in HCC Patients Treated with cTACE and DEB-TACE

Follow-up imaging is essential for evaluating the treatment response and determining whether further therapy is required. The recommendation of the mRECIST criteria,^{25,45,46} based

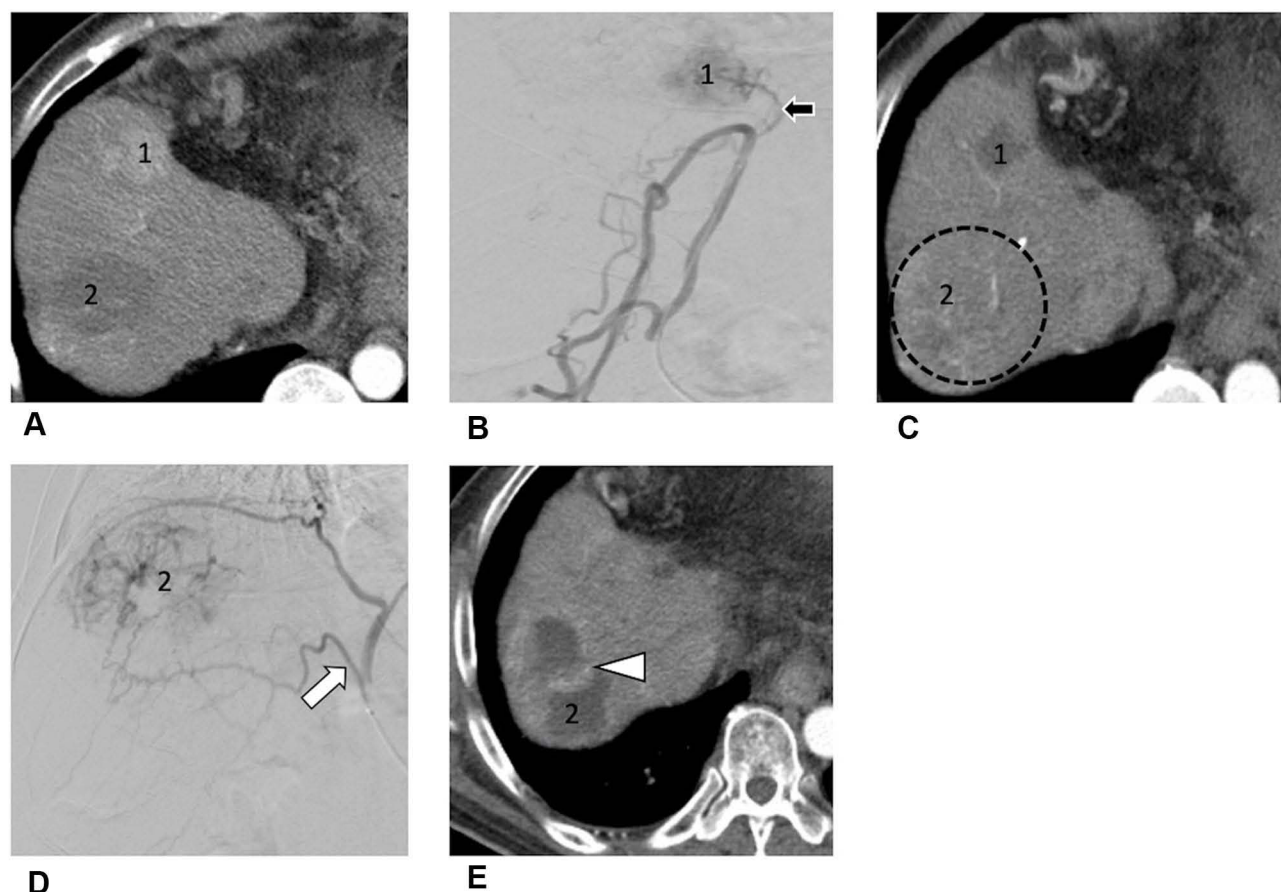


Figure 6 A 60-year-old HBV carrier had HCC in the left lobe which was treated with extended left lobectomy. He has poor liver function (Child-Pugh score 8–9) and HCC with relatively small or low vascularity. **(A)** CT image in arterial-phase shows two recurrent HCCs (tumor 1 and 2). The tumor 1 featured early arterial enhancement, and tumor 2 was not hypervascular suggestive of a HCC with relatively small or low vascularity. **(B)** An angiogram during the 1st TACE reveals a hypervascular tumor (tumor 1) which is supplied by the right colic artery (black arrow, a branch of superior mesenteric artery). TACE with small-caliber DEBs of right colic artery was performed. **(C)** Three months after the 1st TACE, follow-up CT shows no evidence of residual enhancement of the tumor 1 lesion. However, the tumor 2 lesion features progression of tumor size with mild increase of the tumor vascularity (dotted circle). **(D)** An angiogram during the 2nd TACE shows that the tumor 2 is supplied by right inferior phrenic artery (white arrow) with low vascularity. TACE of right inferior phrenic artery was performed with small-caliber DEBs. **(E)** Three months after the 2nd TACE, CT image shows marked cystic change of the tumor 2 with residual band-like enhancement (white arrowhead) suggesting partial response. The tumors were downgraded and the patient subsequently received liver transplantation.

on the one- or two-dimensional measurement of the enhanced portions of target tumors, has been advocated for the assessment of HCC after TACE treatment. In this criteria, if a target HCC that is solid at baseline becomes entirely necrotic and features no arterial enhancement after TACE, the treated HCC is classified as having complete response. Gillmore et al⁴⁷ reported that the overall response measured based on the mRECIST within the first 3-month interval after TACE is independently related to survival.

The CT images of HCC of cTACE could be different from those after DEB-TACE (Table 2). After cTACE treatment, HCC tumors may feature a highly attenuated lipiodol deposition on unenhanced CT images, the distribution and pattern of retained lipiodol may be used to predict the therapeutic response. A triphasic contrast-enhanced CT is required to assess residual tumors that may be located near

the retained lipiodol area. Retained lipiodol after cTACE may cause beam hardening artifacts and obscuration of residual tumors on CT images. Unlike cTACE, residual tumors on CT images in the arterial phase are more clearly delineated after DEB-TACE because of necrotic changes. Perilesional hyperenhancement after cTACE or DEB-TACE may be present and should not be misinterpreted as residual tumor, because this finding does not show portal venous washout and is typically circumferential rather than nodular.

MRI is superior to CT due to the absence of beam hardening artifacts and the better distinction of residual tumors.⁴⁸ It also provides both anatomical and functional information about HCC tumors treated with TACE. The appearance of treated lesions can be variable in terms of signal intensity on T1-weighted and T2-weighted (T2W) images due to the presence of hemorrhage, cystic necrosis, and inflammation.⁴⁹

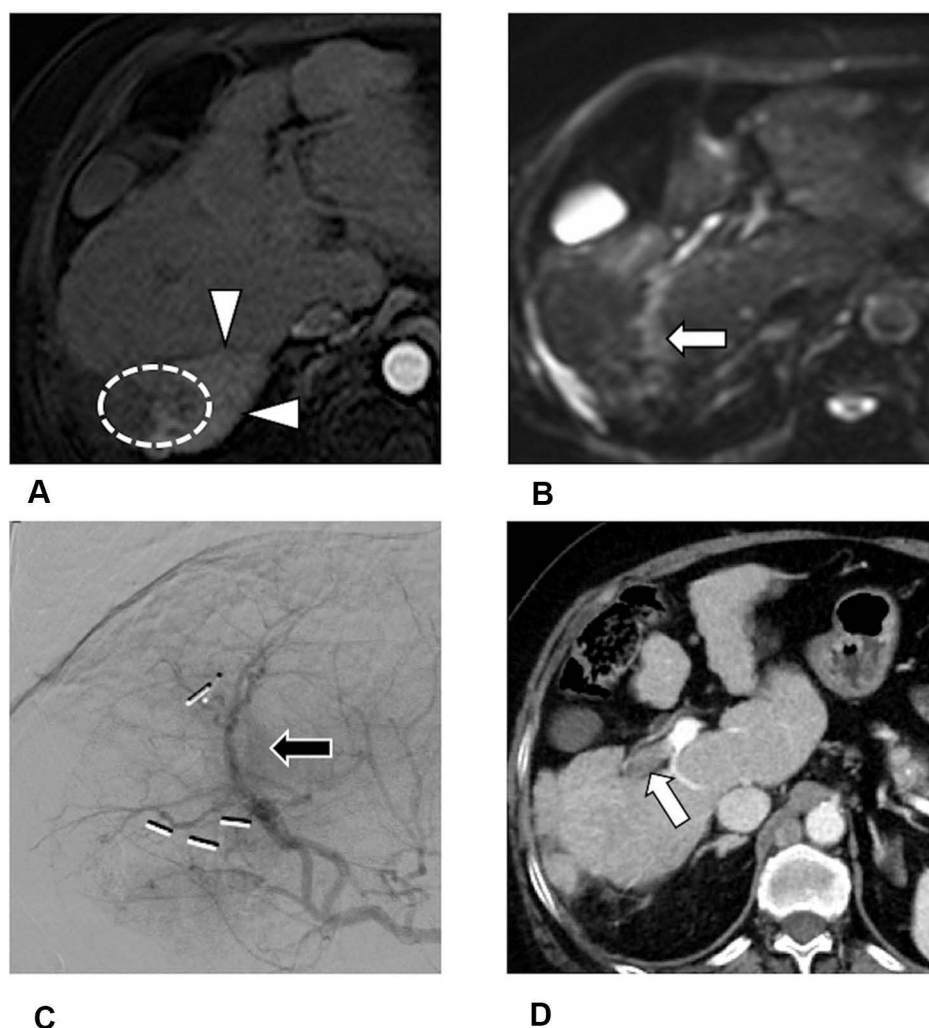


Figure 7 Contraindication of TACE with small-sized DEB: HCC with arterio-portal shunt and portal vein tumor thrombosis. A 69-year-old female with HCC in the segment 7 of liver was treated by stereotactic body radiation therapy. **(A)** Arterial-phase MR image shows a HCC (dotted line) with transient difference of the hepatic attenuation around the tumor (white arrowheads) probably due to arterio-portal shunt. **(B)** Diffusion-weighted MR image shows evidence of tumor thrombosis in the distal portion of right portal vein (white arrow). **(C)** During TACE, the right hepatic angiogram reveals early draining vein (black arrow) near the HCC. TACE with small-caliber DEBs was performed. **(D)** Follow-up CT 3 months after the TACE shows progression of the tumor thrombosis in the central portion of right portal vein (white arrowhead).

Residual tumors typically feature mild to moderate hyperintensity on T2W images.⁵⁰ The necrotic cells in treated HCC tumors are associated with increased cell membrane permeability, mobility of water molecules, and ADC values.⁵¹ Both diffusion-weighted images and contrast-enhanced MRI may show early changes associated with the therapeutic response.⁵²

Conclusion and Future Perspectives

DEB-TACE is effective and safe for the treatment of HCC, and interventions with small-caliber DEBs (<100 μ m) is recommended, especially in the following situations: 1) Small HCC supplied by small hepatic arterioles; 2) Repeated TACE for neovascular tumor-feeding arteries; 3) Repeated TACE for residual viable tumors; 4) Combined use of DEB-

TACE with local radiofrequency ablation; 5) Extrahepatic collateral blood supply to HCC tumors; 6) Patients with poor liver function (Child–Pugh score of 8–9); and 7) HCC with low or small vascularity. In comparison with DEB-TACE using larger-caliber beads, TACE treatment with small-caliber DEBs (<100 μ m) may theoretically offer more complete embolization of the tumor with a better local tumor response and a lower recurrence rate. TACE treatment with small-caliber DEBs (<100 μ m) is indicated for super-selective embolization of feeding arteries in order to prevent major complications. It is necessary to conduct clinical trials to overcome the potential limitation of TACE with small-caliber DEBs (<100 μ m). Prospective multicenter studies with a larger number of HCC patients, different bead sizes, and

Table 2 Evaluation of Tumor Responses on CT and MR Imaging of HCC Treated with DEB-TACE and cTACE Based on mRECIST Criteria

| | DEB-TACE | cTACE |
|--------------------------|---|--|
| mRECIST on CT after TACE | | |
| Complete response (CR) | Entire cystic low-density of the tumor; no arterial-enhancing part | Homogeneous high-density of lipiodol retention, no arterial-enhancing part. |
| Partial response (PR) | (1) > 70% of tumor features cystic low-density (2) Residual peripheral arterial-enhancing part, with early wash-out | Inhomogeneous high-density of retained lipiodol with residual arterial-enhancing part. Lipiodol defect may indicate residual tumor despite absence of arterial enhancement or early wash-out Dense retained lipiodol may affect early identification of viable tumor |
| mRECIST on MR after TACE | | |
| Complete response (CR) | T1-weighted image: Homogeneous low signal intensity of entire tumor | T1-weighted images: Homogeneous low signal intensity of entire tumor |
| | T2-weighted image: High signal intensity of entire tumor suggesting total necrosis | T2-weighted image: (1) Homogeneously high signal intensity of entire tumor; or (2) Heterogeneous signal intensity due to tumor necrosis |
| | Dynamic study: No arterial-enhancement or early wash-out | Dynamic study: No arterial-enhancement or early wash-out |
| Partial response (PR) | T1-weighted image: Low signal intensity of entire tumor, and viable tumors are indistinguishable in this sequence | T1-weighted image: Low signal intensity of whole tumor, and viable tumors are indistinguishable in this sequence |
| | T2-weighted image: Viable tumor may feature hypointense to necrotic part | T2-weighted image: Viable tumor may feature hypointense to necrotic part |
| | Dynamic study: 70% of tumor features low signal intensity on precontrast images Residual tumor features enhancement in arterial phase with early wash-out | Dynamic study: 70% of tumor features low signal intensity on precontrast images Residual tumor features enhancement in arterial phase with early wash-out |

Abbreviations: DEB-TACE, drug-eluting beads transarterial chemoembolization; cTACE, conventional lipiodol-based transarterial chemoembolization; mRECIST, modified response evaluation criteria in solid tumor.

longer follow-up periods are required to validate the clinical efficacy of DEB-TACE treatment for HCC.

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Disclosure

All the authors report no conflicts of interest in this work.

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