Chinese expert consensus on technical recommendations for the standard operation of drug-eluting beads for transvascular embolization

Guoliang Shao[1], Yinghua Zou[2], Pierleone Lucatelli[3], Diamantis I. Tsilimigras[4], Shigeo Shimise[5], Takumi Kawaguchi[5]; on behalf of the Interventional Oncology Branch of China Anti-Cancer Association

[1]Department of Intervention, Cancer Hospital of University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, China; [2]Department of Interventional Radiology and Vascular Surgery, Peking University First Hospital, Beijing, China; [3]Vascular and Interventional Radiology Unit, Sapienza University of Rome, Rome, Italy; [4]Department of Surgery, Division of Surgical Oncology, The Ohio State University, Wexner Medical Center, Columbus, OH, USA; [5]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan

Correspondence to: Guoliang Shao. Department of Intervention, Cancer Hospital of University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou 310022, China. Email: shaogl@zjcc.org.cn; Yinghua Zou. Department of Interventional Radiology and Vascular Surgery, Peking University First Hospital, Beijing 100034, China. Email: 13801105222@139.com.

Abstract: Liver cancer is among the 10 most common tumors globally. In China, liver cancer ranks 4th for prevalence and 3rd for mortality among all malignant tumors. With respect to the treatment of primary liver cancer, there are a number of therapies currently available, including surgical resection, liver transplantation, ablation, transarterial chemoembolization (TACE), systemic chemotherapy, radiation therapy, targeted drug therapy and immunotherapy. Clinical practice and research have shown that, compared with conventional TACE (cTACE), drug-eluting bead TACE (DEB-TACE) can achieve a higher response rate and longer survival time in patients with primary liver cancer. Compared with that of cTACE, DEB-TACE has more favorable basic conditions for achieving uniformity, which could facilitate the standardization of operation techniques. China is the country with the highest incidence of primary liver cancer, accounting for more than 50% of the global patients, and its etiology and epidemiology in Chinese patients differ from those in Europeans and Americans. Therefore, experts in China have drafted these technical recommendations for the standard operation of drug-eluting beads for the treatment of liver cancer on the basis of accumulated abundant clinical experience and evidence-based medical data.

Keywords: Liver cancer; drug-eluting bead; transarterial chemoembolization (TACE); expert consensus

Submitted Dec 31, 2020. Accepted for publication Apr 23, 2021.
doi: 10.21037/atm-21-1678
View this article at: http://dx.doi.org/10.21037/atm-21-1678

Introduction

Primary liver cancer is one of the most common malignant tumors, ranking 6th and 4th of all cancers for global incidence and mortality, respectively (1,2). China is a high-incidence country for primary liver cancer. According to Cancer statistics in China, 2015, among malignant tumors in the Chinese population, liver cancer ranked 4th for incidence and had the third highest fatality rate. In 2010, the China Anti-Cancer Association carried out a survey on the status quo of primary liver cancer, which showed that more than 80% of patients with primary liver cancer had already progressed to intermediate or advanced stage disease at the time of diagnosis (3). With respect to the treatment of primary liver cancer, there are a number of therapies

currently available, including surgical resection, liver transplantation, ablation, transarterial chemoembolization (TACE), systemic chemotherapy, radiation therapy, and targeted drug therapy. Immunotherapy has also recently been incorporated into the second-line clinical treatment options for patients with primary liver cancer. For patients with primary liver cancer with no indications for surgery, TACE has been recommended as the preferred therapy by Barcelona Clinic Liver Cancer (BCLC) guidelines.

TACE involves the selective or superselective insertion of a catheter into the artery supplying the tumor with blood, after which appropriate amounts of chemotherapeutic drugs and embolic agents are injected at an appropriate speed to block the target artery, thus killing tumor cells and inducing tumor tissue necrosis (4). The therapeutic mechanism of TACE in primary liver cancer mainly consists of two parts: the first involves the effect of chemotherapy, and the other involves the effect of embolization. The selection of the appropriate chemotherapeutic drug regimen and precise embolization is crucial to the prognosis of patients (5).

Since Llovet *et al.* published the results of a randomized controlled trial on TACE treatment for patients with primary liver cancer in 2002, many studies have demonstrated that this treatment can significantly improve survival of patients with liver cancer compared with conventional treatment (5-9). The therapeutic effects of TACE have been particularly noteworthy in patients with intermediate- and advanced-stage liver cancer who were not candidates for surgical resection (4,6). In recent years, various major guidelines have recommended TACE as a first-line treatment for patients with intermediate and advanced stage primary liver cancer (10,11). For instance, the BCLC guidelines recommend TACE as a first-line treatment option for patients with BCLC-B hepatocellular carcinoma (HCC). The Guidelines for the Diagnosis and Treatment of Primary Liver Cancer in China (2017 edition) adopted TACE as an alternative treatment for stage Ib to IIIb primary liver cancer; for patients with stages IIb to IIIa, TACE was also recommended as the preferred treatment (8).

Conventional TACE (cTACE) is routinely used in clinical practice. cTACE is delivered by mixing iodinated oil with chemotherapeutic drugs (such as doxorubicin) at a certain ratio to form an iodinated oil emulsion. Embolic particles (such as polyvinyl alcohol) or gelatin sponge can also be added to strengthen vascular embolism. The emulsion is then injected into the tumor blood vessels in a selective or superselective manner via a catheter (12). However, in its clinical application, cTACE has several shortcomings. First, a unified technical standard for the selection of chemotherapeutic drug regimens, embolic materials and operating methods has not been formed, and significant variations in technical details exist among treating physicians. Second, it is challenging to fully mix the lipiodol and chemotherapeutic drugs used in the emulsion in cTACE and to achieve sufficient stability. Furthermore, the chemotherapeutic drugs and lipiodol can quickly separate, causing the drugs to stay in the tumor only for a short time. Third, lipiodol cannot be deposited into some special tumors, such as metastatic liver cancer and cTACE resistant; thus, continuous embolization and chemotherapy fail to be delivered which limits the efficacy of this approach significantly (6,13,14). Indeed, adequate local concentration of chemotherapeutic drugs within lesions and the continuous treatment with chemotherapeutic drugs are closely associated with killing tumor cells.

Clinical practice has indicated that long-term deposition of lipiodol and continuous high-concentration release of chemotherapeutic drugs into the lesion are the key factors in achieving treatment efficacy (6). As such, new treatment is needed to solve the defect of lipiodol, and the drug-eluting microspheres have emerged with the development of medicine and biotechnology. The mechanism of drug-eluting microsphere drug includes absorption of positive and negative ions, which enables the slow and continuous release of chemotherapeutic drugs into the lesion as well as occlusion of tumor blood vessels by the microspheres. In 2004, British BTG plc developed and launched DC Bead, the world's first drug-eluting bead onto which doxorubicin and irinotecan can be loaded, which then quickly obtained approval from various European and American organizations for application in the treatment of primary and secondary liver cancer (15-18). In the years that followed, several drug-eluting microspheres were launched successively, including HepaSphere (19), CalliSpheres (20) and TANDEM (21). Drug-eluting microspheres come in a variety of sizes. Currently, the most commonly used particle sizes are 70–150, 100–300 and 300–500 μm. Microspheres of different particle sizes can be applied to tumors with different sizes and varying degrees of blood supply. Furthermore, drug-eluting microspheres have unique advantages in terms of drug loading, and can load and release a therapeutic dose of chemotherapeutic drugs in a continuous and slow manner. Currently, the commonly used drug-eluting microspheres on the market can be loaded with 50–75 mg of doxorubicin or 100 mg of irinotecan per bottle. The limit for epirucibinc for single session is

150 mg. The concentration of drug delivered to the tumor tissue by drug-eluting microspheres can reach 11.5 times that delivered via transarterial drug perfusion (22), with a sustained chemotherapy drug release time of 36 days. Furthermore, many studies have shown that the effective drug concentration can be detected at a distance of 600 μm from the microspheres (18,23-26). After being loaded with chemotherapeutic drugs, a drug-eluting microsphere may undergo certain changes in its diameter. DC Beads and CalliSpheres microspheres shrink to a certain degree after drug loading, whereas HepaSphere microspheres, as a swelling-type drug-loaded bead, can expand up to four times their original volume.

More than 10 years of clinical experience have been accumulated in the use of drug-eluting bead TACE (DEB-TACE) since 2004. In 2016, Facciorusso *et al.* summarized the published literature over the previous decade and reported that DEB-TACE can achieve a better complete response (CR) rate and longer survival time than cTACE in patients with primary liver cancer. In addition, the authors mentioned that DEB-TACE and is superior to cTACE in the aspects of hepatic injury and chemotherapeutic side effects (27). The results of a meta-analysis conducted by Zou *et al.* arrived at the same conclusions (4,28-32). However, analyses of survival time with these two treatments have produced inconsistent results. For instance, another study by Arabi *et al.* showed no difference between cTACE and DEB-TACE with respect to the survival time of patients with liver cancer (33). In 2018, DEB-TACE is considered important treatment for HCC like TACE and SIRT in the EASL Clinical Practice Guidelines (34). Despite some inconsistencies, there is no doubt that DEB-TACE, as a new type of chemotherapy and embolization technology, has become increasingly valued by clinicians for the treatment of intermediate- and advanced-stage liver cancer. In 2015, drug-eluting microspheres obtained approval in China and started to be used clinically, and to date, we have already accumulated experience using them to treat more than 50,000 patients.

Compared with that of cTACE, DEB-TACE has more favorable basic conditions for achieving uniformity, which could facilitate the standardization of operation techniques. In 2012, the European Guidelines for DEB-TACE Operation were published, and in 2018, the Expert Consensus on DEB-TACE Operation in Taiwan was published (35). China is the country with the highest incidence of primary liver cancer, accounting for more than 50% of the global patients, and its etiology and epidemiology in Chinese patients differ from those in Europeans and Americans. Therefore, it is of great significance to formulate an expert consensus and guidelines for DEB-TACE in patients with primary liver cancer in China. After soliciting opinions from tumor interventional therapy experts in China, and taking into account treatment data from more than 5,000 patients (36-39), we finally formed this China Experts Consensus on the Technical Recommendations for Standard Operation of DEB-TACE through repeated discussions, with the aim of standardizing DEB-TACE operation techniques to benefit a wider range of patients. The levels of evidence and recommendations have been evaluated by the U.S. Preventive Services Task Force (Tables S1,S2).

Indications for DEB-TACE

(I) The indications for DEB-TACE are the same as those for cTACE. We may refer to the Chinese Clinical Practice Guidelines for Transarterial Chemoembolization (40).

(II) DEB-TACE may also be used as a salvage treatment for patients with cTACE-resistant hepatocellular carcinoma (41).

(Level of evidence: III; pagrade of recommendation: A).

(III) DEB-TACE may be more effective than cTACE in patients with Child-Pugh B, ECOG 1, bilobar disease, and recurrent disease (42).

(IV) Patients who have liver-only or liver-dominant metastatic disease and tumor load does not exceed 60% may be considered irinotecan-loaded drug-eluting beads (DEBIRI) (43).

Contraindications to DEB-TACE

Relative contraindications: (I) for patients with ≥70% of the tumor in the whole liver whose liver function is graded as Child-Pugh class A–B, then fractional embolization may be considered. (II) For patients with peripheral blood leukocytes $<3.0\times10^9$/L and platelets $<50\times10^9$/L due to hypersplenism, partial splenic arterial embolism should be performed first, followed by DEB-TACE. (III) According to Cheng's Classification (Table S3), for patients with type II or higher portal vein tumor thrombosis whose liver function is graded as Child-Pugh class A–B, if there is collateral circulation in the portal vein, then DEB-TACE should be performed. (IV) Patients with hepatic arterioportal fistula should undergo correction by embolism before treatment with DEB-TACE.

(Level of evidence: II-1; grade of recommendation: A).

Absolute contraindications: (I) severe liver dysfunction (Child-Pugh class C liver function), including severe jaundice, hepatic encephalopathy, refractory ascites, or hepatorenal syndrome; (II) uncorrectable severe coagulation hypofunction; (III) complete embolism of the main portal vein by cancer embolus, with little collateral angiogenesis, for which the portal vein stent cannot improve the main portal vein's blood flow to the liver; (IV) complicated with active hepatitis or severe infection which cannot be treated synchronously; (V) diffuse tumor or widespread metastasis, with an expected survival duration of <3 months; (VI) Eastern Cooperative Oncology Group (ECOG) score >2 points, cachexia, or multiple organ failure; (VII) renal dysfunction, with creatinine >176.8 μmol/L or creatinine clearance rate <30 mL/min; (VIII) a significant and uncorrectable reduction in peripheral white blood cells and platelets caused by chemotherapeutic drugs or other drugs, with white blood cells $<3.0\times10^9$/L, and platelets $<50\times10^9$/L; (IX) severe hypersensitivity to iodinated contrast agent; (X) hepatic artery-hepatic venous fistula that cannot be corrected by embolization.

(Level of evidence: II-1; grade of recommendation: A).

Pre-procedural patient preparation

(I) Preprocedural imaging: should be assessed number, size, and location of liver lesions, imaging should be either a contrast-enhanced multiphasic CT or contrast-enhanced MRI examinations should include plain scanning in the arterial and venous phases and for what concern MRI hepatobiliary late phase.

(Level of evidence: I; grade of recommendation: A).

(II) Laboratory examinations and clinical assessments: routine bloods, hepatic and renal function, electrolyte, coagulation function, hepatitis virus index, tumor marker and Performance Status (PS) score, Child-Pugh classification (Table S4), and BCLC classification (Table S5), with reference to the *Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China* (2017 edition) (8).

(III) Perioperative medication: In general, antibiotics are not used before surgery. However, for patients undergoing bilioenteric anastomosis, who have a history of Endoscopic Retrograde Cholangiopancreatography (ERCP), sfinterotomy, intrahepatic bile duct stones, Transjugular Intrahepatic Portosystemic Shunt (TIPS), diabetes mellitus, HIV+, antibiotic therapy may be used during the perioperative period. Acid suppression, anti-emesis, and other treatments should be given 1 hour before the operation.

(Level of evidence: III; grade of recommendation: B).

Drug loading

In this consensus, we have collected the drug loading processes of three types of microspheres currently available in China, as detailed in Appendix 1.

Recommendations on the selection of particle size for drug-eluting microspheres

See *Table 1*.

The use of drug-eluting microspheres

Recommendations on the dosage and loading drugs of microspheres

(I) For tumors meeting the Milan standards for liver cancer (i.e., diameter of a single tumor ≤5 cm; with <3 multiple tumors and a maximum diameter ≤3 cm), 1 bottle (2×2 mL) of microspheres is recommended, and for tumors exceeding the Milan standards, up to 2 bottles (2×2 mL) of microspheres are recommended. For patients with primary liver cancer, doxorubicin is recommended as the loading drug.

(II) For patients with metastatic liver cancer (e.g., colorectal cancer metastasis), the loading of 100 mg irinotecan is recommended.

In cases in which the tumor lesion still has a visible blood supply after the injection of drug-eluting microspheres, then other blank microspheres or gelatin sponge particles can be injected to strengthen embolism.

Recommendations on microcatheter selection

To ensure smooth operation, Different size of microsphere need appropriate microcatheter. Please refer to the Table S6.

Recommended injection speed

After the catheter has been placed, an injection speed of 1 mL/min is recommended. With respect to large tumors with abundant blood vessels, a slightly faster (2–3 mL/min)

Table 1 Recommendations on the selection of particle size for drug-eluting microspheres

Particle size of microsphere	Patient group selection
70–150 μm	<5 cm (tumor size), 70–150 μm is recommended
	>5 cm (tumor size), insufficient blood supply without arteriovenous fistula
	Metastatic liver cancer
	(Level of evidence: II-2; grade of recommendation: A)
100–300 μm	>5 cm, with sufficient blood supply, 100–300 μm is recommended
	(Level of evidence: II-1; grade of recommendation: A)
300–500 μm	>7 cm, 300–500 μm is recommended for primary liver cancer with abundant blood supply
	(Level of evidence: II-2; grade of recommendation: B)

initial injection speed can be used, depending on blood flow conditions, and then slowed down. Before the injection of drugs, surgeon should ensure that microspheres are suspended properly, and the entire process of microsphere injection should be performed under X-ray monitoring.

Catheter positioning

Prior to each embolization, angiography of the hepatic should be performed to demonstrate liver arterial anatomy and feeding arteries to the tumor, as well as to check for obvious portal or venous shunts.

(I) Radiography should be used to confirm the nourishing blood vessels of the tumor before embolism. Cases of arteriovenous fistula should first be corrected through embolization for any blood vessels that cannot be avoided (such as the gastroduodenal artery), protective embolization can be performed with spring coils.

(Level of evidence: II-2; grade of recommendation: B).

(II) For lesions with multiple tumor-feeding blood vessels, superselective embolization should be performed on all tumor-feeding blood vessels for which it is possible. For lesions that cannot be treated with superselective embolization, embolization should be performed as close to complete embolization as possible, and important blood vessel branches such as the gallbladder artery should be avoided.

Selection of endpoint for embolization

After DEB-TACE has been performed, there are two endpoints for embolization.

(I) Complete embolization the blood flow in tumor-feeding vessels is observed to be completely stagnated.

(II) Approximate embolization: contrast agent retention which is cleared after 2–5 cardiac cycles.

These embolization endpoints should be confirmed by angiography again in 5 minutes later. Whether further embolization is needed should be considered based on the staining results of the tumor.

(Level of evidence: II-2; grade of recommendation: B).

Currently, the selection of complete embolization or approximate embolization needs to be determined on a case-by-case. Complete embolization is recommended as the endpoint if the microcatheter can be superselectively into the tumor-feeding artery, whereas approximate embolization is recommended, because we must reduce the complications which induced by completed embolization.

Postoperative follow-up and evaluation

Postoperative follow-up

Enhanced CT or MRI reexamination should be performed 4–6 weeks after DEB-TACE treatment, with enhanced MRI being the preferred examination method. If no remaining viable tissue are found during the imaging reexamination, follow-up imaging reexamination should be conducted every 3 months thereafter.

(Level of evidence: I; grade of recommendation level: A).

Efficacy evaluation

Reference to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) is recommended for

evaluation of the therapeutic effect on lesions. Tumor response is evaluated as follows, CR: CT or MRI shows no enhancement in any of the target lesions; partial response (PR): the total diameter of the target lesions in contrast-enhanced images in the arterial phase is reduced by ≥30%; progressive disease (PD): the total diameter of the target lesions in contrast-enhanced images in the arterial phase is increased by ≥20% or new lesions are found; stable disease (SD): the total diameter of the target lesions in contrast-enhanced images in the arterial phase is between decreased by <30% and increased by <20%. For patients who fail to reach CR but meet the treatment requirements in terms of liver function, blood test results, and other conditions with no contraindications, DEB-TACE treatment may be repeated. Clinical efficacy may be evaluated according to short-term efficacy and long-term efficacy. The evaluation index for short-term efficacy is time to progression, and the evaluation index for long-term efficacy is overall survival. Neutrophil-to-lymphocyte ratios (NLR) and platelet-to-lymphocyte ratios (PLR) maybe be good marker to predict the prognosis of DEB-TACE in HCC. The article proved that high baseline NLR and PLR were predictive of poorer tumor response and shorter PFS (44).

Treatment of postoperative complications

The postoperative complications of DEB-TACE are basically similar to those of cTACE and are described below.

(I) Post-embolization syndrome, which mainly manifests as fever, nausea, vomiting, oppressive liver pain, abdominal distension, anorexia, and other symptoms, can be treated with oxygen inhalation, anti-emesis, analgesia, acid suppression, fasting, intravenous hydration, liver protection therapy, and other therapies (4,8,17,32).

(Level of evidence: III; grade of recommendation: B).

(II) The incidence rate of bile duct injury and ectopic hepatic embolic necrosis is higher after DEB-TACE than after cTACE. Therefore, superselection must be performed properly during the operation, and the best endpoint of embolization should be chosen. In cases of increased bilirubin, supportive therapy, such as liver protection and jaundice treatments, should be actively administered.

(III) Liver abscess and biloma: patients with liver abscesses after surgery should be administrated with antibiotics or treated with percutaneous drainage; percutaneous drainage can also be used to treat cases of large biloma (45-47). For high-risk patients (such as those with a history of biliary surgery, antibiotics should be used prophylactically).

(Level of evidence: III; grade of recommendation: B).

(IV) For patients with ectopic embolism, the following precautions should be taken: (i) microspheres with a particle size appropriate to the tumor size and blood supply conditions should be selected. (ii) Superselection of tumor-feeding arteries should be performed in a proper manner to prevent the microspheres from entering into normal liver tissues. (iii) The speed of the microsphere injection should be controlled by 1 mL/min (48).

(Level of evidence: III; grade of recommendation: B).

Summary and outlook

With the standardization of operation techniques, the clinical application of DEB-TACE is expected to increase and further improve the efficacy of interventional therapies for liver tumors. In the meantime, the drug-loading range of microspheres is expected to be further expanded to enable the loading of immune drugs, targeted drugs, radioactive substances, and other drugs. Moreover, the research and development of luminous microspheres will increase the accuracy of microsphere embolization, thus reducing the risks of ectopic embolism and complications, and further improving the efficacy of DEB-TACE for patients with liver cancer. As we know, the treatment of liver cancer is a comprehensive treatment. In any studies, DEB-TACE combined with radiofrequency ablation or sorafenib get better effect compared with DEB-TACE alone in liver cancer (49,50). In the future, DEB-TACE combined other treatment like SIRT, immunotherapy will get better overall response rate and overall survival in HCC. It need more studies to prove.

Acknowledgments

The authors appreciate the academic support from AME Liver Cancer Collaborative Group. Ming Chao, MD, The Second Affiliated Hospital of Zhejiang University of Medicine; Xiaohua Guo, MD, Jinhua Municipal Center Hospital; Jiaping Zheng, MD, Cancer Hospital Chinese Academy of Medical Sciences; Liwen Guo, MD, Cancer Hospital Chinese Academy of Medical Sciences; Wenqiang Yu, MD, Zhejiang Provincial People's Hospital; Xia Wu,

MD, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University; Wenhao Hu, PhD, The First Affiliated Hospital of Wenzhou Medical University; Zhongwei Zhao, MD, Lishui Municipal Center Hospital; Diamantis I. Tsilimigras, MD, The Ohio State University; the above authors provided suggestions for revision during the writing process. Manager Zhiyong Shi, MD, The Medical Affairs Department of Boston Scientific provided assistance in the medical information collection process.
Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-21-1678). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424. Erratum in: CA Cancer J Clin 2020;70:313.
2. Park JW, Chen M, Colombo M, et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. Liver Int 2015;35:2155-66.
3. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115-32.
4. Gaba RC, Lokken RP, Hickey RM, et al. Quality improvement guidelines for transarterial chemoembolization and embolization of hepatic malignancy. J Vasc Interv Radiol 2017;28:1210-23.e3.
5. Raoul JL, Forner A, Bolondi L, et al. Updated use of TACE for hepatocellular carcinoma treatment: how and when to use it based on clinical evidence. Cancer Treat Rev 2019;72:28-36.
6. Rammohan A, Sathyanesan J, Ramaswami S, et al. Embolization of liver tumors: past, present and future. World J Radiol 2012;4:405-12.
7. Ministry of Health of the People's Republic of China. Guidelines for the diagnosis and treatment of primary liver cancer (2011 edition). Chin Clin Oncol 2011;16:929-46.
8. National Health and Family Planning Commission of the People's Republic of China. Guidelines for diagnosis and treatment of primary liver cancer in china (2017 edition). Chinese Journal of Digestive Surgery 2017;16:635-47.
9. Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359:1734-9.
10. Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005;42:1208-36.
11. Omata M, Lesmana LA, Tateishi R, et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. Hepatol Int 2010;4:439-74.
12. Shi M, Lu LG, Fang WQ, et al. Roles played by chemolipiodolization and embolization in chemoembolization for hepatocellular carcinoma: single-blind, randomized trial. J Natl Cancer Inst 2013;105:59-68.
13. Varela M, Real MI, Burrel M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol 2007;46:474-81.
14. Poon RT, Tso WK, Pang RW, et al. A phase I/II trial of chemoembolization for hepatocellular carcinoma using a novel intra-arterial drug-eluting bead. Clin Gastroenterol Hepatol 2007;5:1100-8.
15. Takayasu K, Arii S, Ikai I, et al. Overall survival after transarterial lipiodol infusion chemotherapy with or without embolization for unresectable hepatocellular carcinoma: propensity score analysis. AJR Am J Roentgenol 2010;194:830-7.
16. Liu X, Wang Z, Chen Z, et al. Efficacy and safety of transcatheter arterial chemoembolization and transcatheter arterial chemotherapy infusion in hepatocellular carcinoma: a systematic review and meta-analysis. Oncol

Res 2018;26:231-9.
17. Sommer CM, Pallwein-Prettner L, Vollherbst DF, et al. Transarterial embolization (TAE) as add-on to percutaneous radiofrequency ablation (RFA) for the treatment of renal tumors: review of the literature, overview of state-of-the-art embolization materials and further perspective of advanced image-guided tumor ablation. Eur J Radiol 2017;86:143-62.
18. Fuchs K, Duran R, Denys A, et al. Drug-eluting embolic microspheres for local drug delivery - state of the art. J Control Release 2017;262:127-38.
19. Kennoki N, Saguchi T, Sano T, et al. Long-term histopathologic follow-up of a spherical embolic agent; observation of the transvascular migration of HepaSphereTM. BJR Case Rep 2019;5:20180066.
20. Liu Y, Huang W, He M, et al. Efficacy and safety of CalliSpheres® drug-eluting beads transarterial chemoembolization in Barcelona Clinic Liver Cancer stage C patients. Oncol Res 2019;27:565-73.
21. Guiu B, Colombat S, Piron L, et al. Transarterial Chemoembolization of Hepatocellular Carcinoma with Idarubicin-Loaded Tandem Drug-Eluting Embolics. Cancers (Basel) 2019;11:987.
22. Hong K, Khwaja A, Liapi E, et al. New intra-arterial drug delivery system for the treatment of liver cancer: preclinical assessment in a rabbit model of liver cancer. Clin Cancer Res 2006;12:2563-7.
23. Sakr OS, Berndt S, Carpentier G, et al. Arming embolic beads with anti-VEGF antibodies and controlling their release using LbL technology. J Control Release 2016;224:199-207.
24. Fuchs K, Bize PE, Denys A, et al. Sunitinib-eluting beads for chemoembolization: methods for in vitro evaluation of drug release. Int J Pharm 2015;482:68-74.
25. Denys A, Czuczman P, Grey D, et al. Vandetanib-eluting radiopaque beads: in vivo pharmacokinetics, safety and toxicity evaluation following swine liver embolization. Theranostics 2017;7:2164-76.
26. Forster RE, Tang Y, Bowyer C, et al. Development of a combination drug-eluting bead: towards enhanced efficacy for locoregional tumour therapies. Anticancer Drugs 2012;23:355-69.
27. Facciorusso A, Di Maso M, Muscatiello N. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma: a meta-analysis. Dig Liver Dis 2016;48:571-7.
28. Vogl TJ, Lammer J, Lencioni R, et al. Liver, gastrointestinal, and cardiac toxicity in intermediate hepatocellular carcinoma treated with PRECISION TACE with drug-eluting beads: results from the PRECISION V randomized trial. AJR Am J Roentgenol 2011;197:W562-70.
29. Burrel M, Reig M, Forner A, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. J Hepatol 2012;56:1330-5.
30. Malagari K, Pomoni M, Moschouris H, et al. Chemoembolization with doxorubicin-eluting beads for unresectable hepatocellular carcinoma: five-year survival analysis. Cardiovasc Intervent Radiol 2012;35:1119-28.
31. Liu YS, Lin CY, Chuang MT, et al. Five-year outcome of conventional and drug-eluting transcatheter arterial chemoembolization in patients with hepatocellular carcinoma. BMC Gastroenterol 2018;18:124.
32. Aliberti C, Carandina R, Lonardi S, et al. Transarterial chemoembolization with small drug-eluting beads in patients with hepatocellular carcinoma: experience from a cohort of 421 patients at an Italian center. J Vasc Interv Radiol 2017;28:1495-502.
33. Arabi M, BenMousa A, Bzeizi K, et al. Doxorubicin-loaded drug-eluting beads versus conventional transarterial chemoembolization for nonresectable hepatocellular carcinoma. Saudi J Gastroenterol 2015;21:175-80.Erratum in: Saudi J Gastroenterol 2015;21:264.
34. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236. Erratum in: J Hepatol 2019;70:817.
35. Chang PY, Huang CC, Hung CH, et al. Multidisciplinary Taiwan Consensus Recommendations for the use of DEBDOX-TACE in hepatocellular carcinoma treatment. Liver Cancer. 2018;7:312-22. Erratum in: Liver Cancer 2019;8:68.
36. Shao G, Liu R, Ding W, et al. Efficacy and safety of raltitrexed-based transarterial chemoembolization for colorectal cancer liver metastases. Anticancer Drugs 2018;29:1021-5.
37. Sun J, Zhou G, Zhang Y, et al. Comprehensive analysis of common safety profiles and their predictive factors in 520 records of liver cancer patients treated by drug-eluting beads transarterial chemoembolization. Medicine (Baltimore) 2018;97:e11131.
38. Sun J, Zhou G, Xie X, et al. Efficacy and safety of drug-eluting beads transarterial chemoembolization by CalliSpheres® in 275 hepatocellular carcinoma patients: results from the Chinese CalliSpheres® Transarterial

Chemoembolization in Liver Cancer (CTILC) study. Oncol Res 2020;28:75-94.
39. Zhang X, Zhou J, Zhu DD, et al. CalliSpheres® drug-eluting beads (DEB) transarterial chemoembolization (TACE) is equally efficient and safe in liver cancer patients with different times of previous conventional TACE treatments: a result from CTILC study. Clin Transl Oncol 2019;21:167-77.
40. Chinese College of Interventionalists. Guidelines for clinical practice of transarterial chemoembolization (TACE) for hepatocellular carcinoma in China. Chinese Journal of Interventional Radiology 2019;7:178-84.
41. Li H, Wu F, Duan M, et al. Drug-eluting bead transarterial chemoembolization (TACE) vs conventional TACE in treating hepatocellular carcinoma patients with multiple conventional TACE treatments history: a comparison of efficacy and safety. Medicine (Baltimore) 2019;98:e15314.
42. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol 2010;33:41-52.
43. Lencioni R, Aliberti C, de Baere T, et al. Transarterial treatment of colorectal cancer liver metastases with irinotecan-loaded drug-eluting beads: technical recommendations. J Vasc Interv Radiol 2014;25:365-9.
44. Schobert IT, Savic LJ, Chapiro J, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as predictors of tumor response in hepatocellular carcinoma after DEB-TACE. Eur Radiol 2020;30:5663-73.
45. Luo PF, Fu L, Chen XM, et al. Formation of biloma after interventional treatment for liver cancer and its clinical significance. Chinese Journal of Radiology 2000;11:757-60.
46. Shi HB, Gu JP, He X, et al. Percutaneous intraarterial therapy of peripheral pseudoaneurysm. Chinese Journal of Radiology 2005;39:929-31.
47. Collaborative Group of Interventional Group of Chinese Society of Radiology. Expert consensus on standardized technical operation for transcatheter arterial chemoembolization of primary hepatocellular carcinoma. Chinese Journal of Radiology 2011;45:908-12.
48. Shi CS, Yang Q, Shi ZJ, et al. Two cases of lipiodol ectopic cerebral embolism after TACE treatment of liver cancer. Chinese Journal of Interventional Radiology 2016;4:243-5.
49. Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. J Hepatol 2016;64:1090-8.
50. Zhang Y, Zhang MW, Fan XX, et al. Drug-eluting beads transarterial chemoembolization sequentially combined with radiofrequency ablation in the treatment of untreated and recurrent hepatocellular carcinoma. World J Gastrointest Surg 2020;12:355-68.

Cite this article as: Shao G, Zou Y, Lucatelli P, Tsilimigras DI, Shimise S, Kawaguchi T; on behalf of the Interventional Oncology Branch of China Anti-Cancer Association. Chinese expert consensus on technical recommendations for the standard operation of drug-eluting beads for transvascular embolization. Ann Transl Med 2021;9(8):714. doi: 10.21037/atm-21-1678

Appendix 1

Drug loading process of three microspheres launched in China

Preparation steps of DC Bead dug-loaded microspheres

Step 1

Load 50 mg chemotherapy: Use a 5 mL syringe to pump 2 mL of sterile water for injection, then dilute and transfer 5 bottles of chemotherapeutic drug (doxorubicin, epirubicin or pirarubicin) one by one, to reach a concentration of 25 mg/mL after dilution.

Load 75 mg chemotherapy: Use a 5 mL syringe to pump 3 mL of sterile water for injection, and then dilute and transfer 8 bottles of chemotherapeutic drug (doxorubicin, epirubicin or pirarubicin) one by one, to reach a concentration of 25 mg/mL after dilution.

Step 2

Use a 30 mL or 20 mL syringe to pump out the drug-loaded microspheres, and then stand still for 1 minute in a vertical position. Replace to filtering needle, and push the supernatant off (the storage solution of microspheres contains ions, which would affect the drug-loading efficiency).

Step 3

Using a tee joint to mix 2 mL (50 mg) or 3 mL (75 mg) chemotherapy drug into a 30 mL syringe containing microspheres and mix them gently.

Step 4

Shake the syringe gently every 10–15 min.

Step 5

- After loading drug for 45–60 minutes, use a filtering needle to push the supernatant from the syringe;
- Use a 20 mL syringe to draw 15–20 mL non-ionic contrast medium, mix it with the bead diluent via a tee joint, and then shake the mixture gently for several times;
- If the microspheres float up, add sterilized water for injection 1 mL per time;
- If the microspheres sink down, add the contrast medium 1 mL per time;
- Make the microspheres suspended evenly.

For contrast mediums of different brands with different densities (such as 320 or 350 mgI/mL), the use volume of microspheres, sterilized water for injection and non-ionic contrast mediums needs to be adjusted for the first time of use. Generally, after the initial adjustment, the use volume for each preparation could be determined.

Preparation steps of CalliSpheres

Material preparation: 1 20 mL syringe, 2 10 mL syringes, 1 1 mL luer lock syringe, 1 tee joint, 1 bottle of CalliSpheres drug-loadable microspheres, appropriate amount of water for injection or 5% glucose solution, chemotherapeutic drug (specific dosage and type of which are depending on clinical needs) and contrast agent.

Step 1

Open the microsphere bottle cap, insert a syringe needle, balance the pressure in the bottle, and gently shake the penicillin bottle to make the microspheres distributed evenly.

Tilt the penicillin bottle and withdraw the microspheres and saline with a 20 mL syringe.

Place the microsphere-containing syringe upright for 1–2 min until the microspheres have settled completely, and push out the supernatant as far as possible

Step 2

The type and dosage of chemotherapeutic drugs depend on clinical needs.

The higher the concentration of chemotherapeutic drug, the faster the loading speed, therefore, it is recommended that the preparation of the chemotherapeutic drug with a concentration of not less than 20 mg/mL could only use water for injection or 5% glucose solution.

Step 3

Use a tee joint to connect the microsphere-loaded syringe (20 mL) and the syringe containing chemotherapeutic drug (10 mL).

Ensure steady tee link and pay attention to the flow direction.

Push the syringe containing chemotherapeutic drug (10 mL) while pulling the microsphere-loaded syringe (20 mL).

Mix microspheres and chemotherapeutic drug into one syringe (20 mL).

Cap the syringe containing microspheres and chemotherapeutic drug, stand it still, and shake it every 5 minutes. After loading for 15 minutes in total, it could be seen that a large amount of chemotherapeutic drug would load into microspheres.

http://dx.doi.org/10.21037/atm-21-1678

Step 4

After the microspheres have been loaded with the chemotherapeutic drugs, add high-contrast contrast medium (such as iodophorol 350) immediately, with no need to wait until the TACE operation.

Measure the liquid amount of the chemotherapeutic drug containing microspheres, add the non-ionic contrast medium at a ratio of 1:1–1:2 and mix them evenly, and then stand the mixture still for 5 minutes before using.

Step 5

Use a tee joint to connect a 1 mL luer lock syringe with a syringe containing microspheres + chemotherapeutic drug + contrast medium (20 mL). Make sure to connect firmly, and shake the microspheres in the large syringe (20 mL) before injecting microspheres into the 1 mL syringe.

Use a small syringe to connect the catheter, shake the microspheres in the 1 mL syringe, and inject through adopting pulse injection method injecting at an injection speed of 1 mL/min.

Hepashere preparation method

Adopt the preparation method of loading one bottle of hepasphere with 50 mg epirubicin (thp) (four times method)

Step 1: medicine preparation: 30 mL syringe, 18 g (No. 12) needle ×2, 0.9% normal saline; thp ×5 bottles;

Step 2: start to prepare about 20–30 minutes before surgery;

Step 3: draw 20 mL normal saline with a 30 mL syringe, add it into thp (5 bottles, 4 mL per bottle), and dissolve them fully;

Step 4: draw the dissolved thp solution of 20 mL in total and inject 10 mL of it into a hepasphere bottle;

Step 5: sway the microsphere bottle gently, but do not shake it vigorously, then wait for 10 minutes (during which the microsphere bottle could be inverted for many times), to make the microsphere fully mix with thp solution;

Step 6: replace to 18 g needle, and use the syringe containing the remaining 10 mL thp solution to draw the solution (10 mL) in the microsphere bottle, thus to obtain a 20 mL suspension;

Step 7: remove the needle, cover syringe cap, and cover with a sterile sheet if possible;

Step 8: wait 30–60 minutes so that the hepasphere could fully absorb drug, and gently shake the syringe every 10 minutes during this period of time;

Step 9: transfer to the operating table via a tee joint;

Step 10: stand it still for about 10 minutes, to enable the microspheres to settle, drain the upper layer of liquid as much as possible, and then draw 20 mL of non-ionic contrast medium, and mix thoroughly for use;

Step 11: The preparation has been completed.

http://dx.doi.org/10.21037/atm-21-1678

Table S1 U.S. Preventive Services Task Force grading method, which could be used to evaluate the quality of evidence for treatment or screening

Level of evidence	Description
Evidence level I	Evidence obtained from at least one well-designed randomized controlled clinical trial
Evidence level II-1	Evidence obtained from well-designed non-randomized controlled trials
Evidence level II-2	Evidence obtained from well-designed cohort or case-control studies (preferably multi-center studies)
Evidence level II-3	Evidence obtained from multiple time series studies with or without intervention. Significantly different results concluded in non-controlled trials are sometimes considered as evidence of this level
Evidence level III	Authoritative opinions from clinical experience, descriptive researches or expert committee reports.

Table S2 Recommendation evaluation by the U.S. Preventive Services Task Force

Recommendation grading	Description
Grade A recommendation	There are good scientific evidences suggesting that the benefits of such medical practice substantially outweigh its potential risks
	Clinicians should discuss the medical practice with applicable patients
Grade B recommendation	There are at least acceptable evidences suggesting that the benefits of such medical practice outweigh its potential risks.
	Clinicians should discuss such medical practice with applicable patients
Grade C recommendation	There are at least acceptable scientific evidences suggesting that such medical practice could provide benefits, but its benefits are very close to the risks
	Clinicians could not make general recommendations, and are not required to provide such medical practice unless there are certain individual considerations
Grade D recommendation	There are at least acceptable scientific evidences suggesting that the potential risks of such medical practice outweigh its potential benefits
	Clinicians should not routinely perform such medical practice on asymptomatic patients
Grade I recommendation	Such medical practice lacks scientific evidence, or its evidences are of low quality or conflict with each other, such as the inability to measure and evaluate risks
	Clinicians should help patients understand the uncertainty of such medical practice

Table S3 Cheng's classification of portal vein tumor thrombus

Typing	Description
I_0	Tumor thrombus under the microscope
I	Tumor thrombus invades the portal vein branch of liver lobe or hepatic segments
II	Tumor thrombus invades the left and right branches of portal vein
III	Tumor thrombus invades to main portal vein
IV	Tumor thrombus invades to the superior mesenteric vein

http://dx.doi.org/10.21037/atm-21-1678

Table S4 Child-Pugh grading

Clinical biochemical indicators	Score 1	Score 2	Score 3
Hepatic encephalopathy (grade)	None	1–2	3–4
Ascites	None	Mild	Moderate and severe
Bilirubin (μmol/L)	<34	34–51	>51
Albumin (g/L)	>35	28–35	<28
Increased prothrombin time (second)	<4	4–6	>6

Table S5 BCLC staging classification

BCLC staging	Behavioral status	Tumor status	Liver function status
0 (the earliest stage)	0	Single tumor ≤2 cm	Normal bilirubin, without portal hypertension
A (early stage)			
A1	0	Single tumor ≤5 cm	Normal bilirubin, without portal hypertension
A2	0	Single tumor ≤5 cm	Normal bilirubin, with portal hypertension
A3	0	Single tumor ≤5 cm	Abnormal bilirubin, with portal hypertension
A4	0	3 tumors ≤3 cm	Child-Pugh A-B
B (middle stage)	0	Multiple or single tumor >5 cm	Child-Pugh A-B
C (advanced stage)	1–2 points	Vascular invasion or metastasis	Child-Pugh A-B
D (end stage)	3–4 points	Any tumor	Child-Pugh C

BCLC, Barcelona Clinic Liver Cancer.

Table S6 Catheter and microsphere matching

Calibration range	Matching catheter
DC Bead M1 70–150 μm	1.8–2.0 Fr
DC Bead 100–300 μm	2.2–2.4 Fr
DC Bead 300–500 μm	2.4–2.7 Fr
DC Bead 500–700 μm	≥2.7 Fr

http://dx.doi.org/10.21037/atm-21-1678