Review Article

Embolotherapy of unresectable hepatocellular carcinoma: Eastern perspective

Jian Lu[1#], Bin-Yan Zhong[2#], Hai-Dong Zhu[1], Jin-He Guo[1], Gao-Jun Teng[1]

[1]Center of Interventional Radiology & Vascular Surgery, Department of Radiology, Zhongda Hospital, Medical School, Southeast University, Nanjing 210009, China; [2]Department of Interventional Radiology, The First Affiliated Hospital of Soochow University, Suzhou 215006, China

Contributions: (I) Conception and design: All authors; (II) Administrative support: GJ Teng; (III) Provision of study materials or patients: J Lu, BY Zhong; (IV) Collection and assembly of data: J Lu, BY Zhong; (V) Data analysis and interpretation: J Lu, BY Zhong; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally as joint first authors.

Correspondence to: Gao-Jun Teng, MD. Department of Radiology, Zhongda Hospital, Southeast University, 87 Dingjiaqiao Road, Nanjing 210009, China. Email: gjteng@vip.sina.com.

Abstract: Asia suffers a particularly large prevalence of the world's hepatocellular carcinoma (HCC), accounting for nearly 72.5% of the newly diagnosed 609,596 cases and 72.4% of the 566,269 deaths. The majority of HCC patients is diagnosed at unresectable stages in Asia despite efforts to improve availability of screening. Although the Barcelona Clinic Liver Cancer (BCLC) staging algorithm is accepted worldwide, various staging systems and guidelines have been proposed in Asian regions. Embolotherapy has been endorsed by many Asian guidelines and is the most common treatment across all stages of HCC. There are considerable discrepancies of the allocation of embolotherapy for unresectable HCC in Asia. This review will focus on the indication and contraindication, technique variances, combination regimen, and when to start, repeat or stop embolotherapy for unresectable HCC with the hope to provide insights into TACE application to patients at any HCC stage.

Keywords: Hepatocellular carcinoma (HCC); transarterial chemoembolization (TACE); embolotherapy; east; advanced stage

Submitted Aug 05, 2019. Accepted for publication Nov 01, 2019.
doi: 10.21037/cco.2019.11.01
View this article at: http://dx.doi.org/10.21037/cco.2019.11.01

Introduction

Globally, hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related deaths and ranks sixth in terms of incidence (1). Asian countries account for nearly 72.5% of the newly diagnosed 609,596 cases and 72.4% of the 566,269 deaths; and half of these occur in China (2). Despite the endeavor on screening patients with liver cirrhosis, up to 85–90% of newly diagnosed HCC patients in Asia already become unresectable when diagnosed (3). Unresectable HCC is a clinically complex term and pools a heterogeneous group of patients. These patients can be either with intermediate or advanced stage; or with early stage that are theoretically feasible but fail to receive resection due to poor physical condition or subjective refusion.

Two seminal trials reported in 2002 showed transarterial chemoembolization (TACE) to be superior to best supportive care in Eastern and Western patients with unresectable HCC (4,5). According to the most widely used Barcelona Clinic Liver Cancer (BCLC) staging system, TACE is the first-line option for selected patients with intermediate-stage HCC (6). In the East, TACE has been used for nearly 30 years in unresectable HCC patients and is endorsed by almost all the Asian guidelines, including guidelines from China, Korea, Japan, Singapore (7-10). Due to constant evolution of TACE technique, differences on etiological causes, and clinicians'

preferences, embolotherapy protocols remains different in certain respects in the East versus the West. Herein, this review will present the perspective of Eastern experts on embolotherapy in the treatment of unresectable HCC.

Definition of embolotherapy

HCC is a hypervascular tumor and predominantly receives its blood supply from the hepatic artery, while the non-cancerous liver parenchyma derives a dual vascular supply from the hepatic artery and the portal vein (3,11). This vascular nature of HCC lends itself feasible to transarterial therapy. Embolotherapy for HCC was initially reported in the early 1970s, consisting of intra-arterial delivery of chemotherapeutic agents and embolic material directly leading to tumor ischemia-induced necrosis (12). In the current era, TACE has been generally accepted as an effective palliative treatment for unresectable HCC and is increasingly being bridged to downstage HCC prior to curative therapy (6,13).

In the real world, the term 'TACE' is often used synonymously and, even commonly understood as the concept of 'interventional therapy' in the public. Basically, embolotherapy can be sub-grouped into four techniques, including bland transarterial embolization (TAE), conventional transarterial chemoembolization (cTACE) using Lipiodol, TACE with drug-eluting beads (DEB-TACE), and transarterial radioembolization by injecting Yttrium-90 microspheres (TARE). However, in the real world, TAE was rarely used in most of the Eastern centers.

Indication and contraindication

There are controversies between the East and the West regarding the indication of embolotherapy for HCC. Although the BCLC has been served as the backbone system to guide treatment decision of HCC, many Eastern experts consider the indication of BCLC for TACE relatively stringent and conservative. Asian guidelines recommend TACE not only in the group of intermediate stage, but also in selected patients at advanced stage and even early stage (7-10,14). Among the Eastern guidelines, the guidelines from China and Korea provide the broadest indications for TACE, almost throughout all the stages of HCC (7,8).

Tumor size/number, liver function, and performance status are the main considerations as for indication of TACE. In the East, cTACE for HCC is commonly indicated in three main settings under the basic precondition of Eastern Cooperative Oncology Group (ECOG) score of 0–2 and Child-Pugh A or B.

(I) Early stage: (i) patients with resectable HCC lesions who cannot or refuse to receive surgical resection (e.g., older age, severe cirrhosis) or local ablation is not feasible (8); (ii) prior to surgical resection or liver transplantation as a bridge therapy, particularly if the waiting time is likely to be longer than 6 months (7,15);

(II) Intermediate stage: asymptomatic patients with multinodular lesions but without macrovascular invasion or extrahepatic metastasis (8,9);

(III) Advanced stage: (i) with lobar or segmental portal vein thrombosis; (ii) with the main portal vein embolus that is not completely occlusive or is completely occlusive but compensatory collateral circulation formed between the hepatic artery and portal vein (7,8).

cTACE is also considered in some particular conditions, such as bleeding due to rupture of the liver tumor, hepatic artery-portal venous static shunt or arteriovenous fistula, and detection of residual lesions or tumor recurrence after resection (8).

Indication criteria for DEB-TACE are similar to that of cTACE. Besides the indications it shares with cTACE, DEB-TACE may be considered as a substitute when the tumor was refractory to cTACE. The potential indications for TARE include patients with intermediate stage who are inferior candidates for cTACE, patients with segmental or sub-segmental portal vein invasion, and patients with progressive disease after cTACE (7,10).

cTACE has various absolute contraindications and are listed as follows: (I) severe liver dysfunction (Child-Pugh class C); (II) uncorrectable bleeding disorder severe coagulation dysfunction that impossible to be corrected; (III) completely embolized main portal vein with few collateral blood vessels formed; (IV) active HBV infection or active infections that complicate the condition and not likely to be treated simultaneously; (V) wide distant metastasis with an estimated survival less than 3 months; (VI) cachexia or multiple organ failure; (VII) liver burden accounting for ≥70% of the entire liver (staged embolization with small amounts of iodized oil emulsion can be considered if liver function is normal); (VIII) significant reductions in peripheral blood leukocytes and platelets, white blood cell (WBC) count $<3.0\times10^9$/L due to toxicity of chemotherapy, and platelets $<50\times10^9$/L; (IX) renal dysfunction (creatinine

>2 mg/dL or creatinine clearance rate <30 mL/min); and (X) previous shock related to contrast media (7-10).

Absolute contraindications for DEB-TACE are similar to cTACE while TAE is be relatively safe in patients with leucopenia without the use of chemotherapeutic drugs. The excessive hepatopulmonary shunting and technically inevitable gastrointestinal deposition based on 99mTCMMA scan are absolutely contraindicated only in 90Y-radioembolization (7-10).

Embolotherapy is relatively contraindicated in (I) large tumor burden >70% of the volume of the whole liver (fractional embolotherapy could be considered for Child-Pugh class A or B) (8); (II) significant reductions in peripheral blood leukocytes and platelets, WBC count $<3.0\times10^9$/L due to hypersplenism (splenic artery embolization could be considered to improve the leucopenia prior to embolotherapy) (8); and (III) limited extrahepatic metastasis with the bulk of disease within the liver (if the clinician concludes that the patient is most likely to die from liver disease, TACE may still take a role in controlling the intrahepatic tumor) (16).

TAE

Bland transarterial embolization without the use of tumoricidal agents destined to cause ischemia-induced effects on tumor. The most common used embolization materials include ethiodized oil, gelatin sponge particles, cyanoacrylate glue, polyvinyl alcohol (PVA), and calibrated microspheres as small as 40 μm in diameter (3,8,11). The dosage of lipiodol is usually 5–20 mL, adjusted by the tumor burden, with a limited dose of 30 mL (8). All tumor-feeding arteries should be embolized to achieve devascularization of the tumor. The endpoint of the procedure is defined as the presence of flow stasis of tumor supplying artery under the fluoroscopic monitoring.

Although cTACE still plays a predominant role in the family of embolotherapy, the advantage of TACE over TAE and the benefit of intraarterial chemotherapy have not been clearly described (17). Up to now, there is no randomized controlled trial to compare the treatment outcome between TAE and TACE, partially because of the divergences in the embolization materials and different techniques (18). Therefore, some experts in the Eastern centers favor the use of TAE because they believe that when super selective embolization is achieved using dedicated particles, excellent tumor response can be obtained (17). And even in TACE, the trigger of tumor cell death related to the ischemia is mainly provided by the embolization. Besides, the use of chemotherapeutic drugs may act as a double-edged sword to concurrently kill the tumor and worsen liver function, particularly in the Eastern population with a high portion of cirrhosis (17).

cTACE

cTACE, also known as Lipiodol TACE, has been adopted as the most frequent nonsurgical therapy for unresectable HCC, which involves intra-hepatic administration of a water-in-oil emulsion of a chemotherapeutic agent cocktail mixed with ethiodized oil (3,11). As an imageable-drug carrier and a micro-embolic agent, Lipiodol is absorbed by the tumor cell membrane and maintained in the intracellular space (18). The synergistic effect caused by the microvascular embolization and chemotherapeutic agent delivery helps to increase the local concentration of chemotherapeutic agent to the tumor. Moreover, Lipiodol retention within the target tumor on the post-procedure CT images is a significant indicator for tumor response and overall survival (OS) (19).

The volume of ethiodized oil injected is generally determined by the volume and vascularity of the tumor, with a common usage of 5–20 mL but 30 mL top (8). In the East, chemotherapy regimen selection varies from center to center. Doxorubicin or epirubicin is the most common single chemotherapeutic drug, while the most common combination regimens are cisplatin, doxorubicin, and mitomycin C. In addition, hydroxycamptothecin, fluorouracil, arsenic trioxide, and raltitrexed serve as the alternative choices (8). However, the scenarios and indications for such alternatives remained to be determined. The dosage of chemotherapeutic drug used could be liver function-based, weight-based, or even empiric. Currently used dose ranges were reported as follows: doxorubicin, 10–100 mg; epirubicin, 5–120 mg; cisplatin, 10–100 mg; miriplatin, 20–140 mg; and mitomycin, 2–30 mg (20). Granular embolization agents (e.g., standardized gelatin sponge particles, microspheres, polyvinyl alcohol particles) should be used after embolization with Lipiodol emulsion. All tumor-feeding arteries should be embolized to achieve devascularization of the tumor. The endpoint of the procedure is defined as the presence of flow stasis of the tumor supplying artery under fluoroscopic monitoring.

Data from the global HCC BRIDGE study demonstrated that TACE was the most frequently used first treatment across all stages in North America, Europe,

China and South Korea; 51% of Chinese HCC patients and 35% from other Asian regions receive TACE firstly (21). Even after first resection or ablation, TACE was still the most frequently (48–72%) second treatment for HCC in Asian regions, which seemed higher than that in the West (31–43%) (21).

Patients with early-stage HCC who are not candidates for surgical resection or ablation can benefit from the treatment of cTACE for its tumor response and clinical outcome (22,23). In a recent study, 54 patients were treated with the combination of TACE and portal vein embolization prior to resection (24). Subsequently, 72% of patients successfully underwent resection, with prolonged survival in those undergoing resection alone (24). TACE is also associated with a decrease of dropout rate in patients waiting for liver transplantation, which was reported to be 3–13% (25-27).

Advanced HCC with vascular invasion or extrahepatic metastasis has been historically considered a contraindication for TACE according to the recommendation of BCLC staging system (6). A meta-analysis demonstrated that only 1% of patients developed liver failure and 18% acquired post-embolization complications after TACE. Median OS was 11 months for segmental PVTT and 5 months for main PVTT (28). Another meta-analysis from China demonstrated that even for HCC patients with extrahepatic spread, TACE can be safely performed and may improve OS than conservation management in patients with preserved liver function (29). More recently, a large-scale systematic review summarized the efficacy of cTACE in a total of 10,108 HCC patients from 101 studies. Of note, 45 studies enrolled patients with vascular invasion (mostly portal vein invasion) and 25 included a minority of patients in Child Pugh class C. The median OS after cTACE was 18.1 months in the West and 15.6 months in the Asia-Pacific region (P=0.363). With the accumulation of clinical evidence, the Eastern experts advocate to expand the indication of TACE for selected patients with advanced stage in BCLC treatment algorithm. However, solid evidence from prospective controlled studies is still required to evaluate this strategy.

DEB-TACE

Due to inconsistent drug delivery and retention that may potentially limit the prognosis of cTACE, DEB-TACE was introduced as an alternative approach for unresectable hepatic tumors (4,5,30). Drug-eluting beads are non-resorbable embolic microspheres that can be loaded with cytotoxic agents. Compared to cTACE, DEB-TACE provides sustained release of chemotherapy and decreases plasma concentration of chemotherapeutic drugs, according to several *in vitro* and *in vivo* studies (31-33). Doxorubicin, which is the major chemotherapeutic agent, can be loaded up to 37.5 mg per mL of microspheres within 30 minutes to 2 hours. One *in vitro* study stated that only 30% of the doxorubicin was released from the drug-eluting beads and was detected 1.2 mm away from the occluded arteries in explanted HCC livers (34).

After several years' exploration and application, a prospective randomized study, PRECISION V study, was carried out in European countries and published in 2010 (33). This study compared treatment efficacy and safety between DEB-TACE using DC-Beads (Biocompatibles, Farnham, Surrey, UK) and cTACE for the treatment of cirrhotic patients with HCC. The primary efficacy endpoint was the 6-month tumor response rate and the primary safety endpoint was the incidence of treatment-related serious adverse events (SAEs) occurring within 30 days post procedure. The results showed that the rates of complete response, objective response, and disease control in the DEB-TACE group was higher than those in the cTACE group (27% *vs.* 22%, 52% *vs.* 44%, and 63% *vs.* 52%, respectively). Nevertheless, none of these comparisons achieved statistical significance (P=0.11). DEB-TACE was associated with improved tolerability, with a significant reduction in serious liver toxicity (P<0.001) and a significantly lower rate of doxorubicin-related side effects (P=0.0001).

After that, the PRECISION ITALIA STUDY GROUP phase III trial was reported in 2014 (35). This trial was carried out in Italy and planned to enroll 214 patients to compare efficacy and safety between DEB-TACE with DC-Beads and cTACE for HCC. Nevertheless, the trial was stopped due to futility after 177 patients were enrolled, since no significant difference on tumor response was observed.

Song and colleagues carried out and released a retrospective study in Korea in 2012 (36). They compared 3-month tumor control and treatment-related adverse events between HCC treated with DEB-TACE and cTACE. The results showed that tumor response was significantly higher in the DEB-TACE (DC-Beads) group than that in the cTACE group (P<0.001) The rate of complete response, partial response, stable disease, and progressed disease were 55%, 26.6%, 15%, and 3.4% in the DEB-TACE group and

23.1%, 26.3%, 30.4%, and 20.2% in the cTACE group, respectively. No statistical difference was observed in liver toxicity between these two groups (P>0.05).

Since the inconsistency of the results from several powerful studies, there is still no recommendation for choosing DEB-TACE or cTACE for the treatment of HCC. The main advantage of cTACE when compared to DEB-TACE is that lipiodol is a radiopaque embolic agent that is retained by the tumors. Thus, it offers the ability to track tumor response and tumor coverage both intra- and post-procedurally. Such unique characteristic has prompted the development of radiopaque drug-eluting beads, LUMI. Notably, an updated meta-analysis including 1,449 patients from four RCTs and eight retrospective studies demonstrated that non-superiority was observed in DEB-TACE over cTACE in terms of tumor response and survival (37). At present, DEB-TACE is primarily indicated in patients who are ineligible for achieve curative treatment including surgery, liver transplantation, or local ablation, which is similar to cTACE (38,39).

TARE

TARE is performed by injecting Yttrium-90 microspheres into the hepatic artery feeding tumors. Currently, two kinds of yttrium-90 microspheres, resin microspheres (SIR-Spheres; Sirtex Medical, Sydney, N.S.W., Australia) and glass microspheres (TheraSpheres; MDS Nordion, Ottawa, Ont., Canada), are available for hepatic tumors (40). TARE was first explored for treating HCC with PVTT. Biederman and colleagues performed a retrospective study comparing efficacy and safety between resin and glass microspheres (41). The reported median OS for resin and glass groups were 3.7 and 9.4 months (P<0.001), respectively. In addition, toxicity was lower in the glass group. In 2017, an open-label randomized controlled phase III trial, SARAH trial, which was carried out in France was reported (42). The study focused treatment efficacy and safety between TARE and sorafenib for HCC with PVTT. The results showed that the median OS was 8.0 and 9.9 months (P=0.18) in the TARE group and sorafenib group, respectively. In 2018, another similar trial, SIRveNIB trial, carried out in the Asia-Pacific region, was published (43). The median OS were 8.8 and 10.0 months (P=0.36) for TARE group and sorafenib group, respectively. Both of these two trials gave negative survival benefit for locally advanced HCC treated with TARE or sorafenib. Nevertheless, the improved toxicity profile of TARE may inform treatment choice in select patients.

TARE is also regarded as a bridge to liver transplantation for HCC with PVTT since it can prolong time to progression for those on the liver transplantation waiting list (44). With regret, TARE has not been approved for clinical application in some eastern countries such as mainland China and Japan, even though it has been clinically employed in some other Asian countries.

When to start, repeat or stop TACE

So far, several models or prognostic scores such as the Selection for TrAnsarterial chemoembolization TrEatment (STATE), the hepatoma arterial-embolization prognostic (HAP), and the "six-and-twelve" scores, have been developed to select ideal HCC patients who will benefit from the first TACE treatment (45-47). Among them, the "six-and-twelve" score, which was established based on a multicenter retrospective study in China, was introduced recently (47). The score divided patients with BCLC A/B into three strata with the sum of tumor size and number ≤6, >6 but ≤12, and >12, which had significantly different median OS. This model has potential to be simply applied in clinical practice with high accuracy. In addition, the Assessment for Retreatment with TACE (ART) and the ABCR (α-fetoprotein, Barcelona Clinic Liver Cancer, Child-Pugh, and Response) scores were developed to assess whether patients would benefit from second TACE or not (48,49).

As TACE could damage liver function, it is critical to screen out those patients who can barely benefit from TACE treatment and thus should stop TACE and switch to other approaches. Therefore, TACE "failure/refractoriness" was developed by the Japan Society of Hepatology (JSH) and the Expert Panel Opinion on Interventions in Hepatocellular Carcinoma (EPOIHCC) (16,50). Patients who meet TACE "failure/refractoriness" criteria should stop further TACE procedure and should receive other treatments such as systemic therapy.

Combination therapy

TACE with systemic agents

TACE is recommended by BCLC staging system as first-line treatment for intermediate HCC (51). Nevertheless, it is hard to achieve curative outcome in clinical practice and usually needs to be repeated several times, which may damage liver function and affect

treatment outcome. One major reason why curative outcome is difficult to achieve for TACE is that it induces ischemic or hypoxic changes, which lead to an increase in vascular endothelial growth factor (VEGF) expression in the residual surviving cancerous tissue as well as in the serum (52). Such increase in angiogenesis may promote tumor growth and is associated with poor treatment outcome of TACE (53). Based on this, being a potent multikinase inhibitor that targets VEGF receptor, sorafenib has potential to act as a synergistic action when combining with TACE for HCC. Nevertheless, three major RCTs including Post-TACE trial, SPACE trial, and TACE-2 trial, demonstrated negative efficacy results regarding TACE combined with sorafenib *vs.* TACE alone for unresectable HCC (54-56). Interestingly, subgroup analysis demonstrated that in the SPACE trial, Asian patients who received sorafenib had longer median time to progression when compared to those received placebo (24.0 *vs.* 16.1 months), while the difference is moderate between Non-Asian patients (25.0 *vs.* 24.0 months). Sorafenib treatment duration between these two cohorts was different, with 30 weeks in Asian cohort and 21 weeks in non-Asian cohort, respectively. Duration of sorafenib treatment may be an important factor for prognosis for HCC treated with TACE combined with sorafenib (55). Apart from the study design, the diversity of the patients' responses to the combination therapy and lack of prognostic sorafenib-related biomarkers may answer the negative outcomes of these trials. One retrospective study conducted in China identified that early onset of hypertension and sorafenib-related dermatologic AEs (≥grade 2) are early biomarkers for the clinical prognosis of HCC treated with TACE combined with sorafenib (57).

Notably, the TACTICS trial that carried out in Japan demonstrated positive treatment efficacy on TACE combined with sorafenib compared to TACE alone for unresectable HCC, with primary endpoint of progression free survival significantly longer in the combination group (25.2 *vs.* 13.5 months; P=0.006) (58). The median duration of sorafenib administration was long at 38.7 months. TACE combined with other systemic agents such as with brivanib (the BRISK-TA trial) and with orantinib (the ORIENTAL trial) also showed negative treatment benefit (59,60).

TACE with local ablation

Local ablation mainly including radiofrequency ablation (RFA) and microwave ablation (MWA) is regarded as an alternative curative approach when surgical resection or liver transplantation is unable to be performed (61,62). RFA and MWA mainly target on small HCC, but the efficacy is limited in larger HCC. The combination of TACE with RFA or MWA has potential to improve efficacy in patients with unresectable HCC. A previous study identified that TACE could block hepatic arterial blood flow and attenuate the cooling effect of tumor blood flow. This effect is important to treat tumors with larger size, which is not suitable to receive RFA monotherapy (63).

An RCT carried out in China compared treatment efficacy for solitary recurrent HCC lesions up to 5 cm in diameter between RFA combined with TACE and RFA monotherapy (64). The results showed significantly higher OS rates and recurrence-free survival rates for the combination group when compared to those in the monotherapy group. Several retrospective studies demonstrated that TACE combined with RFA had better tumor control and longer OS than TACE monotherapy for HCC especially at intermediate stage (65,66). Similar results were also elaborated by several retrospective studies when concerning TACE combined with MWA *versus* TACE monotherapy (67-69). With regret, no RCT has been reported on comparing efficacy between TACE combined with RFA or MWA and TACE monotherapy.

TACE with portal vein revascularization

Portal vein revascularization by endovascular stent placement could theoretically recover portal vein blood flow and improve liver parenchymal perfusion, improve liver function, decrease portal hypertensive complications (variceal hemorrhage and ascites), and therefore improve prognosis (70). By adding TACE with portal vein revascularization, intrahepatic lesions could be treated in addition to portal vein blood flow recovery. A previous study carried out in Japan identified that TACE following portal vein stenting achieved a satisfactory survival outcome for HCC with main portal vein tumor thrombosis, with mean OS of 13.7 months (71). To prolong stent patency caused by tumor infiltration, brachytherapy with ^{125}I seed implantation with portal vein stent was developed, and the majority of studies were carried out in China (72-75). In addition, an irradiation stent system was developed in China (76). It is comprised of an inner self-expanding conventional stent and an outer four-array-seeds loaded stent, giving the advantage of better radiation dose distribution comparing to traditional portal vein stenting with ^{125}I seed implantation. The single arm prospective

trial of this irradiation stent system combined with TACE for HCC with PVTT demonstrated satisfactory safety and efficacy, with a median OS of 12.5 months (76).

Conclusions

The Eastern experiences have demonstrated that patients with unresectable HCC can benefit from the treatment of embolotherapy. Nevertheless, embolotherapy for unresectable HCC is destinated to be a challenging area because of the diversities of techniques and the heterogeneity of disease. The geographic differences in tumor etiology (Hepatitis B for Asia *vs.* C in the west with Obesity/NASH coming in as a major cause) and medical resources make it tough to reach a universally accepted guideline in the field of embolotherapy for unresectable HCC. Meanwhile, it is feasible and important to convene interventional radiologists from the East and the West to construct a joint consensus on a standard embolotherapy technique and treatment allocation for the purpose of order to improving patient outcome.

Acknowledgments

We thank Dr. Chu-Hui Zeng from Canada for her polishing this paper.

Footnote

Conflicts of Interest: 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.
2. International Agency for Research on Cancer. Liver Source: Globocan 2018. Available online: https://www.iarc.fr (accessed March 2019).
3. Gaba RC, Lokken RP, Hickey RM, et al. Quality improvement guidelines for transarterial chemoembolization and embolization of hepatic malignancy. J Vasc Interv Radiol 2017;28:1210-1223.e3.
4. Llovet JM, Real MI, Montana 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.
5. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164-71.
6. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. Easl clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
7. Korean Liver Cancer Study Group (KLCSG); National Cancer Center, Korea (NCC). 2014 Korean liver cancer study group-national cancer center Korea practice guideline for the management of hepatocellular carcinoma. Korean J Radiol 2015;16:465-522.
8. Zhou J, Sun HC, Wang Z, et al. Guidelines for diagnosis and treatment of primary liver cancer in china (2017 edition). Liver Cancer 2018;7:235-60.
9. Kokudo N, Hasegawa K, Akahane M, et al. Evidence-based clinical practice guidelines for hepatocellular carcinoma: The japan society of hepatology 2013 update (3rd JSH-HCC guidelines). Hepatol Res 2015. doi: 10.1111/hepr.12464.
10. Chow PK, Choo SP, Ng DC, et al. National cancer centre singapore consensus guidelines for hepatocellular carcinoma. Liver Cancer 2016;5:97-106.
11. Gaba RC, Lewandowski RJ, Hickey R, et al. Transcatheter therapy for hepatic malignancy: Standardization of terminology and reporting criteria. J Vasc Interv Radiol 2016;27:457-73.
12. Tadavarthy SM, Knight L, Ovitt TW, et al. Therapeutic transcatheter arterial embolization. Radiology 1974;112:13-6.
13. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American association for the study of liver diseases. Hepatology 2018;68:723-50.
14. Yau T, Tang VY, Yao TJ, et al. Development of Hong Kong liver cancer staging system with treatment stratification for patients with hepatocellular carcinoma. Gastroenterology 2014;146:1691-700.e3.
15. Graziadei IW, Sandmueller H, Waldenberger P, et al.

Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. Liver Transpl 2003;9:557-63.
16. Cheng AL, Amarapurkar D, Chao Y, et al. Re-evaluating transarterial chemoembolization for the treatment of hepatocellular carcinoma: Consensus recommendations and review by an international expert panel. Liver Int 2014;34:174-83.
17. Mauri G, Varano GM, Orsi F. TAE for HCC: When the old way is better than the new ones!!! Cardiovasc Intervent Radiol 2016;39:799-800.
18. Pesapane F, Nezami N, Patella F, et al. New concepts in embolotherapy of HCC. Med Oncol 2017;34:58.
19. 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.
20. Lencioni R, de Baere T, Soulen MC, et al. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: A systematic review of efficacy and safety data. Hepatology 2016;64:106-16.
21. 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.
22. Bargellini I, Sacco R, Bozzi E, et al. Transarterial chemoembolization in very early and early-stage hepatocellular carcinoma patients excluded from curative treatment: A prospective cohort study. Eur J Radiol 2012;81:1173-8.
23. Golfieri R, Cappelli A, Cucchetti A, et al. Efficacy of selective transarterial chemoembolization in inducing tumor necrosis in small (<5 cm) hepatocellular carcinomas. Hepatology 2011;53:1580-9.
24. Ronot M, Cauchy F, Gregoli B, et al. Sequential transarterial chemoembolization and portal vein embolization before resection is a valid oncological strategy for unilobar hepatocellular carcinoma regardless of the tumor burden. HPB (Oxford) 2016;18:684-90.
25. De Luna W, Sze DY, Ahmed A, et al. Transarterial chemoinfusion for hepatocellular carcinoma as downstaging therapy and a bridge toward liver transplantation. Am J Transplant 2009;9:1158-68.
26. Alba E, Valls C, Dominguez J, et al. Transcatheter arterial chemoembolization in patients with hepatocellular carcinoma on the waiting list for orthotopic liver transplantation. AJR Am J Roentgenol 2008;190:1341-8.
27. Millonig G, Graziadei IW, Freund MC, et al. Response to preoperative chemoembolization correlates with outcome after liver transplantation in patients with hepatocellular carcinoma. Liver Transpl 2007;13:272-9.
28. Silva JP, Berger NG, Tsai S, et al. Transarterial chemoembolization in hepatocellular carcinoma with portal vein tumor thrombosis: A systematic review and meta-analysis. HPB (Oxford) 2017;19:659-66.
29. Zhao Y, Cai G, Zhou L, et al. Transarterial chemoembolization in hepatocellular carcinoma with vascular invasion or extrahepatic metastasis: A systematic review. Asia Pac J Clin Oncol 2013;9:357-64.
30. Gaba RC, Baumgarten S, Omene BO, et al. Ethiodized oil uptake does not predict doxorubicin drug delivery after chemoembolization in vx2 liver tumors. J Vasc Interv Radiol 2012;23:265-73.
31. Lewis AL, Taylor RR, Hall B, et al. Pharmacokinetic and safety study of doxorubicin-eluting beads in a porcine model of hepatic arterial embolization. J Vasc Interv Radiol 2006;17:1335-43.
32. 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.
33. 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.
34. de Baere T, Plotkin S, Yu R, et al. An in vitro evaluation of four types of drug-eluting microspheres loaded with doxorubicin. J Vasc Interv Radiol 2016;27:1425-31.
35. Golfieri R, Giampalma E, Renzulli M, et al. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer 2014;111:255-64.
36. Song MJ, Chun HJ, Song DS, et al. Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. J Hepatol 2012;57:1244-50.
37. 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.
38. Chang PY, Huang CC, Hung CH, et al. Multidisciplinary Taiwan consensus recommendations for the use of debdoxtace in hepatocellular carcinoma treatment. Liver cancer 2018;7:312-22.
39. Lencioni R, de Baere T, Burrel M, et al. Transcatheter

treatment of hepatocellular carcinoma with doxorubicin-loaded dc bead (debdox): Technical recommendations. Cardiovasc Intervent Radiol 2012;35:980-5.
40. Kennedy A, Nag S, Salem R, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: A consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys 2007;68:13-23.
41. Biederman DM, Titano JJ, Tabori NE, et al. Outcomes of radioembolization in the treatment of hepatocellular carcinoma with portal vein invasion: Resin versus glass microspheres. J Vasc Interv Radiol 2016;27:812-21.e2.
42. Vilgrain V, Pereira H, Assenat E, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (sarah): An open-label randomised controlled phase 3 trial. Lancet Oncol 2017;18:1624-36.
43. Chow PKH, Gandhi M, Tan SB, et al. SIRveNIB: Selective internal radiation therapy versus sorafenib in asia-pacific patients with hepatocellular carcinoma. J Clin Oncol 2018;36:1913-21.
44. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using yttrium-90 microspheres: A comprehensive report of long-term outcomes. Gastroenterology 2010;138:52-64.
45. Hucke F, Pinter M, Graziadei I, et al. How to state suitability and start transarterial chemoembolization in patients with intermediate stage hepatocellular carcinoma. J Hepatol 2014;61:1287-96.
46. Kadalayil L, Benini R, Pallan L, et al. A simple prognostic scoring system for patients receiving transarterial embolisation for hepatocellular cancer. Ann Oncol 2013;24:2565-70.
47. Wang Q, Xia D, Bai W, et al. Development of a prognostic score for recommended TACE candidates with hepatocellular carcinoma: A multicentre observational study. J Hepatol 2019;70:893-903.
48. Sieghart W, Hucke F, Pinter M, et al. The art of decision making: Retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma. Hepatology 2013;57:2261-73.
49. Adhoute X, Penaranda G, Naude S, et al. Retreatment with tace: The abcr score, an aid to the decision-making process. J Hepatol 2015;62:855-62.
50. Kudo M, Matsui O, Izumi N, et al. Jsh consensus-based clinical practice guidelines for the management of hepatocellular carcinoma: 2014 update by the liver cancer study group of japan. Liver Cancer 2014;3:458-68.
51. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301-14.
52. Wang B, Xu H, Gao ZQ, et al. Increased expression of vascular endothelial growth factor in hepatocellular carcinoma after transcatheter arterial chemoembolization. Acta Radiol 2008;49:523-9.
53. Kaseb AO, Hassan MM, Lin E, et al. V-clip: Integrating plasma vascular endothelial growth factor into a new scoring system to stratify patients with advanced hepatocellular carcinoma for clinical trials. Cancer 2011;117:2478-88.
54. Kudo M, Imanaka K, Chida N, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer 2011;47:2117-27.
55. 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.
56. Meyer T, Fox R, Ma YT, et al. Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): A randomised placebo-controlled, double-blind, phase 3 trial. Lancet Gastroenterol Hepatol 2017;2:565-75.
57. Zhong BY, Ni CF, Chen L, et al. Early sorafenib-related biomarkers for combination treatment with transarterial chemoembolization and sorafenib in patients with hepatocellular carcinoma. Radiology 2017;284:583-92.
58. Kudo M. Proposal of primary endpoints for TACE combination trials with systemic therapy: Lessons learned from 5 negative trials and the positive tactics trial. Liver Cancer 2018;7:225-34.
59. Kudo M, Han G, Finn RS, et al. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: A randomized phase III trial. Hepatology 2014;60:1697-707.
60. Kudo M, Cheng AL, Park JW, et al. Orantinib versus placebo combined with transcatheter arterial chemoembolisation in patients with unresectable hepatocellular carcinoma (oriental): A randomised, double-blind, placebo-controlled, multicentre, phase 3 study. Lancet Gastroenterol Hepatol 2018;3:37-46.
61. Lau WY, Lai EC. The current role of radiofrequency ablation in the management of hepatocellular carcinoma: A systematic review. Ann Surg 2009;249:20-5.
62. Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and

partial hepatectomy for small hepatocellular carcinoma. Ann Surg 2006;243:321-8.
63. Buscarini L, Buscarini E, Di Stasi M, et al. Percutaneous radiofrequency thermal ablation combined with transcatheter arterial embolization in the treatment of large hepatocellular carcinoma. Ultraschall Med1999;20:47-53.
64. Peng ZW, Zhang YJ, Liang HH, et al. Recurrent hepatocellular carcinoma treated with sequential transcatheter arterial chemoembolization and RF ablation versus RF ablation alone: A prospective randomized trial. Radiology 2012;262:689-700.
65. Yin X, Zhang L, Wang YH, et al. Transcatheter arterial chemoembolization combined with radiofrequency ablation delays tumor progression and prolongs overall survival in patients with intermediate (BCLC B) hepatocellular carcinoma. BMC Cancer 2014;14:849.
66. Azuma S, Asahina Y, Nishimura-Sakurai Y, et al. Efficacy of additional radiofrequency ablation after transcatheter arterial chemoembolization for intermediate hepatocellular carcinoma. Hepatol Res 2016;46:312-9.
67. Xu LF, Sun HL, Chen YT, et al. Large primary hepatocellular carcinoma: Transarterial chemoembolization monotherapy versus combined transarterial chemoembolization-percutaneous microwave coagulation therapy. J Gastroenterol Hepatol 2013;28:456-63.
68. Liu C, Liang P, Liu F, et al. MWA combined with TACE as a combined therapy for unresectable large-sized hepatocellular carcinoma. Int J Hyperthermia 2011;27:654-62.
69. Li W, Man W, Guo H, et al. Clinical study of transcatheter arterial chemoembolization combined with microwave ablation in the treatment of advanced hepatocellular carcinoma. J Cancer Res Ther 2016;12:C217-C220.
70. Chan SL, Chong CC, Chan AW, et al. Management of hepatocellular carcinoma with portal vein tumor thrombosis: Review and update at 2016. World J Gastroenterol 2016;22:7289-300.
71. Yamakado K, Tanaka N, Nakatsuka A, et al. Clinical efficacy of portal vein stent placement in patients with hepatocellular carcinoma invading the main portal vein. J Hepatol 1999;30:660-8.
72. Lin J, Jiang H, Yang W, et al. Predictive factors of benefit from iodine-125 brachytherapy for hepatocellular carcinoma with portal vein tumor thrombosis. Brachytherapy 2019;18:233-9.
73. Sun H, Zhang M, Liu R, et al. Endovascular implantation of (125)i seed combined with transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma. Future Oncol 2018;14:1165-76.
74. Luo J, Yan Z, Liu Q, et al. Endovascular placement of iodine-125 seed strand and stent combined with chemoembolization for treatment of hepatocellular carcinoma with tumor thrombus in main portal vein. J Vasc Interv Radiol 2011;22:479-89.
75. Zhang ZH, Zhang W, Gu JY, et al. Treatment of hepatocellular carcinoma with tumor thrombus with the use of iodine-125 seed strand implantation and transarterial chemoembolization: A propensity-score analysis. J Vasc Interv Radiol 2018;29:1085-93.
76. Lu J, Guo JH, Zhu HD, et al. Safety and efficacy of irradiation stent placement for malignant portal vein thrombus combined with transarterial chemoembolization for hepatocellular carcinoma: A single-center experience. J Vasc Interv Radiol 2017;28:786-794.e3.

Cite this article as: Lu J, Zhong BY, Zhu HD, Guo JH, Teng GJ. Embolotherapy of unresectable hepatocellular carcinoma: Eastern perspective. Chin Clin Oncol 2019;8(6):60. doi: 10.21037/cco.2019.11.01