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. 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. 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.

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. Among the Eastern guidelines, the guidelines from China and Korea provide the broadest indications for TACE, almost throughout all the stages of HCC.

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:

(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; (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;

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

(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.

TACE 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.

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.

cTACE has various absolute contraindications and are listed as follows: (I) severe liver dysfunction; (II) uncorrectable bleeding disorder; (III) completely embolized main portal vein with few collateral blood vessels formed; (IV) active HBV infection; (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; (VIII) significant reductions in peripheral blood leukocytes and platelets, white blood cell (WBC) count <3.0×10^9/L due to toxicity of chemotherapy, and platelets <50×10^9/L; (IX) renal dysfunction.
>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 <3.0×10^9/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).

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 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).
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 addition, toxicity was lower in the glass group. 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 125I 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 125I 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 destined 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.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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