Clinical practice of transarterial chemoembolization for hepatocellular carcinoma: consensus statement from an international expert panel of International Society of Multidisciplinary Interventional Oncology (ISMIO)

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Importance: Transarterial chemoembolization (TACE) has been associated with a wide range of practice variations for hepatocellular carcinoma (HCC) between the East and the West. This considerable ambiguity may lead to the heterogeneous quality in treatment and have a negative impact on the role of TACE in the overall multidisciplinary HCC treatment system.

Objective: It may be a good start to establish a guideline worldwide to have this consensus from experts who represent east and west, although it does not cover all aspects of TACE.

Evidence Review: An international expert panel on TACE is convened to cluster the expert's opinions and summary a standard consensus. This panel committee consist of leading physicians in TACE on HCC from USA, France, Japan, Singapore, Korea, China, and so on. The first-round face-to-face consensus meeting was held during in Nanjing, China in October 2019. The second-round conference for revision of the consensus was held during the Annual Meeting of Chinese College of Interventionalists in August 2020 by a hybrid format of a Webinar and roundtable meeting. After several on-line revisions, the final manuscript was approved by all members of the panel in June 2021.

Findings: The consensus statements were organized into the following categories: patients' selection, performing the procedure, TACE outcomes, repeat TACE, TACE failure/refractory, and TACE-based combination treatments.

Conclusions and Relevance for Reviews: More and more evidences have showed the better outcomes with strategy of combined TACE with other local therapies such as ablations. The most-recently

developing strategy of combined TACE with PD-1/PD-L1 plus tyrosine kinase inhibitor (TKI) agents has shined a light to the HCC patients, especially to those with high risk of tumor recurrence after treatment or TACE failure/refractory.

Introduction

Liver cancer is the sixth most diagnosed cancer and the third leading cause of cancer-related death worldwide in 2020 (1). Asia accounts for nearly 72.5% of the newly diagnosed cases and 72.4% of the deaths. In addition, a rising trend of incidence has been observed in most countries of Europe, the Americas, and Oceania over recent decades (2). Hepatocellular carcinoma (HCC) typically represents nearly 85% of all liver cancer cases. The prognosis of HCC remains dismal with the maximum 5-year survival estimated at 18% and thus poses a heavy health burden globally (2). As a pillar technique of interventional radiology, transarterial chemoembolization (TACE) plays a fundamental component in the management of HCC.

TACE has been associated with a wide range of practice pattern variations for HCC between the East and the West, and there is even considerable variability among the physicians practicing within the same institution (3-6). This considerable ambiguity may lead to the heterogeneous quality in treatment and have a negative impact on the role of TACE in the overall multidisciplinary HCC treatment system.

Therefore, to optimize the TACE practice and improve the care of HCC patients, an international expert panel on TACE was convened to cluster the expert's opinions to provide a standard consensus. This panel committee consisted of leading physicians in TACE on HCC from the USA, France, Japan, Singapore, Korea, and China. The first-round face-to-face consensus meeting was held during in Nanjing, China in October 2019 and the panel decided to write a global expert consensus statement on TACE practice. The second-round conference for revision of the consensus was held during the Annual Meeting of the Chinese College of Interventionalists (CCI 2020) in August 2020 by a hybrid format of a webinar and roundtable meeting. After several subsequent on-line revisions, the final manuscript was approved by all members of the panel in February 2021. The consensus statements were organized into the following categories: patients' selection, procedural technique, TACE outcomes, repeat TACE and TACE failure/refractory, and TACE-based combination treatments (*Table 1*). We present the following article in accordance with the RIGHT reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-260/rc).

Patient selection

According to recommendations from the Barcelona Clinic Liver Cancer (BCLC) staging system, intermediate stage HCC is the main indication for TACE. However, a global survey entitled the "HCC BRIDGE Study" showed that TACE was the most frequently used first-line treatment across all BCLC stages (BCLC A–D) in North America, Europe, China, and South Korea; with 51% of HCC patients from China and 35% from other Asian regions receiving TACE as the initial treatment for HCC (7). Even after first resection or ablation with relapse or high-risk patients, TACE was still the most frequently used therapy (48–72%) in those HCC population in Asian regions, which seemed higher than that in the West (31–43%) (7).

TACE is often chosen as a bridge therapy prior to liver transplantation (LT) when the anticipated waiting time for receiving an organ is longer than 6 months, and has been associated with a decrease in the dropout rate for patients waiting for LT. Patients with BCLC-A stage HCC who are not candidates for surgical resection or ablation can also benefit from the treatment of TACE for its effective tumor response and clinical outcome (8,9). TACE has also been combined with portal vein embolization prior to resection to increase the rate of future liver remnant hypertrophy and to obtain a high rate of complete tumor necrosis (10).

BCLC-B stage represents a wide group of patients with a variety of tumor burdens and liver functions. Indications of TACE for BCLC-B stage are mainly patient populations with massive or multinodular tumors but without

Table 1 Summary of recommendations for TACE in HCC

Categories	Consensus statements
No. 1 Patient selection	TACE is indicated for those patients who belong to BCLC-B, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2, Child-Pugh A and B. For BCLC-A patients, TACE is recommended if surgical resection or ablation is impractical or refused by patient. For BCLC-C patients with liver dominant lesions, including those with macrovascular invasion, TACE is recommended as an option if the Child-Pugh < C and PS are tolerant
No. 2 Tumor targeting	Selective or super-selective vessel catheterization should be achieved as much as technically feasible to target the tumor, and three-dimension CTA images with Angio-CT system or cone-beam CT is recommended for TACE
No. 3 Chemotherapy regimen of cTACE	Doxorubicin is the fundamental chemotherapeutic agent for TACE, either in combination with cisplatin, mitomycin-C, or other drugs. Dosage of ethiodized oil administered should be tumor-based volume
No. 4 Chemotherapeutic drugs for DEB-TACE	At present, various cytotoxic agents alone or in combination with other drugs are used for DEB-TACE while doxorubicin is the most widely used chemotherapeutic agent. However, there is no clinical evidence to suggest any superiority of doxorubicin-DEB-TACE over epirubicin-DEB-TACE over for HCC
No. 5 TACE endpoint	The endpoint of TACE is defined as a "tree in winter" appearance in case of non-selective TACE. Filling in the peritumoral portal veins around the tumor must be attempted in cTACE while reflux of embolic materials must be avoided in DEB-TACE
No. 6 Conventional *vs.* DEB-TACE	At present, none of the RCTs have showed significant OS differences between DEB-TACE and cTACE. DEB-TACE has less systemic toxicity, but more bile duct injury. Nevertheless, there are some specific clinical settings to choose DEB-TACE or cTACE in the real-world practice, including huge tumors or bilobar tumors, hypovascular tumors, or HCC with PVTT
No. 7 Repeat TACE, TACE failure/refractory	TACE should be performed according to the "on demand" approach and not on schedule. The concepts of "TACE failure/refractoriness" have been introduced although high-level evidence is still lacking
No. 8 The combination of TACE and local therapy	The combination of TACE with thermal ablative techniques may result in better outcomes than ablation or TACE monotherapy in selected populations of early- or intermediate-HCC. For patients with macrovascular invasion, TACE plus radiotherapy may be an alternative choice to systemic therapies.
No. 9 Combined TACE with systemic therapy	TACE plus systemic therapy with an appropriate protocol may improve the therapeutic outcomes in the treatment of unresectable HCC

BCLC, Barcelona Clinic Liver Cancer; CTA, computed tomography angiography; DEB, drug-eluting bead; HCC, hepatocellular carcinoma; OS, overall survival; PVTT, portal vein tumor thrombosis; RCT, randomized controlled trial; TACE, transarterial chemoembolization; cTACE, conventional TACE.

macrovascular invasion or extrahepatic metastasis (5,6). TACE can function as a downstaging treatment in patients with BCLC-B stage to meet the threshold of surgical resection, and/or LT (11).

Advanced HCC, with vascular invasion or extrahepatic metastasis, is typically considered a contraindication for TACE according to the BCLC staging system (4). However, a meta-analysis demonstrated that only 1% of patients developed liver failure and 18% acquired post-embolization complications after TACE, and the median overall survival (OS) was 11 months for patients with segmental portal vein tumor thrombosis (PVTT) and 5 months for those with main PVTT (12). For patients with limited extrahepatic metastasis with liver-dominant disease, who are most likely to die from intrahepatic disease, TACE may still play a role in controlling the intrahepatic tumors (13). For selected Child-Pugh C patients within Milan criteria, TACE is also performed in Asia (14). With the accumulation of clinical evidence, more and more experts are advocating to expand the indications of TACE for selected patients with advanced stage in the BCLC treatment algorithm.

Consensus No. 1

TACE is indicated for those patients who belong to BCLC-B, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2, Child-Pugh A and B. For BCLC-A patients, TACE is recommended if surgical

resection or ablation is impractical or refused by patient. For BCLC-C patients with liver dominant lesions, including those with macrovascular invasion, TACE is recommended as an option if the Child-Pugh < C and PS are tolerant.

Procedural technique

Tumor targeting

Adequate visualization of all tumor-feeding feeding arteries should be obtained during the procedure, including vessels' origin, variant anatomy, and ectopic or collateral blood supply. Computed tomography (CT) during arteriography and advanced imaging technique with cone-beam CT/3D rotational angiography, Angio-CT system, or other software guidance are advocated to best delineate the vascular anatomy and/or tumor supply/evaluation for additional tumor supply/assessment completeness of embolization (15). Regarding catheter position for embolization, catheterization within selective or super-selective tumor feeding arteries should be always achieved as much as possible (16).

Consensus No. 2
Selective or super-selective vessel catheterization should be achieved as much as technically feasible to target the tumor, and three-dimension computed tomography angiography (CTA) images with Angio-CT system or cone-beam CT is recommended for TACE.

Chemotherapy regimen of conventional TACE (cTACE)

Chemotherapy regimen selection varies from center to center, whether in the East or in the West. Doxorubicin is the most common single chemotherapeutic drug, while the most common combination regimens is doxorubicin and cisplatin (17). In addition, mitomycin C, hydroxycamptothecin, fluorouracil, arsenic trioxide, and raltitrexed serve as the alternative agents. However, the scenarios and indications for such alternatives have yet to be determined. The dosage of chemotherapeutic drug used could be body surface area-based, liver function-based, weight-based, or even empiric. Currently used dose ranges as follows: doxorubicin, 10–100 mg; epirubicin, 5–120 mg; cisplatin, 10–100 mg; miriplatin, 20–140 mg; mitomycin, 2–30 mg, and idarubicin, 10–20 mg (17). The ethiodized oil and chemotherapeutic drugs should be mixed into an emulsion and configured as a "water-in-oil" emulsifier

to improve its stability. The volume ratio of ethiodized oil to drug aqueous solution is usually 2:1. Doxorubicin-ethiodized oil emulsions prepared with nonionic contrast medium would be safer and more stable compared to be prepared with ionic contrast medium (18). The volume of ethiodized oil injected is generally determined by the size and vascularity of the tumor, with common usage of 5–15 mL, with increased risk of complication above 20 mL (5).

Particulate embolic agents (e.g., standardized gelatin sponge particles, microspheres, polyvinyl alcohol particles) should be used following embolization with ethiodized oil chemoembolic emulsion. The size of embolic materials should be based on the tumor size, blood supply, and therapeutic aim. Gelatin sponge particles measuring ~500 mm and blank microspheres measuring 100–300 mm have been widely used (19). All tumor-feeding arteries should be embolized to achieve devascularization of the tumor.

Consensus No. 3
Doxorubicin is the fundamental chemotherapeutic agent for TACE, either in combination with cisplatin, mitomycin-C, or other drugs. Dosage of ethiodized oil administered should be tumor-based volume.

Chemotherapeutic drugs for drug-eluting bead (DEB)-TACE

DEB-TACE releases chemotherapeutic drugs in a controlled and sustained manner. By now, the most widely used cytotoxic agent for DEB-TACE is doxorubicin; however, other anthracycline drugs such as epirubicin or idarubicin that can be loaded into drug-eluting microspheres (20). The value of doxorubicin-DEB-TACE in the setting of enhancing the local drug concentration was investigated in a randomized trial testing DEB-TACE *vs.* bland embolization. Better outcomes, including local response, local recurrences, and time to progression was achieved in patients treated with DEB-TACE than bland embolization alone (21). On the other hand, another randomized controlled trial (RCT) demonstrated that there were no significant differences in the tumor response and survival between the DEB-TACE and bland embolization groups (22).

Epirubicin, an epimer of doxorubicin which was commonly considered having less myelosuppression and cardiac toxicities than doxorubicin, has also been used in clinical trials of HCC patients treated with DEB-TACE and

compared to bland-transarterial embolization (TAE) (23). Seventy-seven percent of lesions treated with epirubicin-DEB-TACE achieved complete necrosis, whereas only 27.2% of lesions in the bland-TACE group showed such responses (P=0.043) (23). At present, no study exists that compared the clinical benefits between epirubicin-DEB-TACE with doxorubicin-DEB-TACE in patients with HCC. To that end, further studies involving epirubicin-DEB-TACE for HCC patients should be cautiously designed because there were limiting data from the pre-clinical study that testing the pharmacokinetic and safety of epirubicin-beads in hepatic arterial embolization.

Consensus No. 4

At present, various cytotoxic agents alone or in combination with other drugs are used for DEB-TACE while doxorubicin is the most widely used chemotherapeutic agent. However, there is no clinical evidence to suggest any superiority of doxorubicin-DEB-TACE over epirubicin-DEB-TACE over for HCC.

TACE endpoint

The endpoint of TACE is defined at angiography as the presence of flow stasis of the tumor feeding arteries under fluoroscopic monitoring. Complete stasis is visualized as a static contrast column for at least 5 heartbeats. For cTACE, the optimal complete embolization is featured by the appearance of the lipiodol filling of in periphery portal veins around the tumor (24). For DEB-TACE, injection must be stopped once stasis is observed in the tumor feeding arteries to avoid reflux of embolic materials (25).

Consensus No. 5

The endpoint of TACE is defined as a "tree in winter" appearance in case of non-selective TACE. Filling in the peritumoral portal veins around the tumor must be attempted in cTACE while reflux of embolic materials must be avoided in DEB-TACE.

TACE outcomes

In 2002, the Asian RCT reported that patients with unresectable HCC who in the cTACE cohort had a 57%, 31%, and 26% survival rate at 1, 2 and 3 years compared to a 32%, 11%, and 3%, respectively (P=0.002) survival rate in patients who received symptomatic therapy (26). Similarly, a European cohort demonstrated that the survival rate at 1 and 2 years with cTACE was 82% and 63% which was significantly higher than the symptomatic therapy which had a 63% and 27% at 1 and 2 years (P=0.025) (27). An Asian prospective study enrolled 99 patients with unresectable HCC from Japan and Korea. The 2-year survival rate achieved 75.0% (95% CI, 65.2–82.8%). The median OS was 3.1 years. And the response rate was 73% using modified Response Evaluation Criteria in Solid Tumors (mRECIST) (28).

In a systematic review, including a total of 10,108 patients treated with cTACE, the OS was 70.3% at 1 year, 51.8% at 2 years, 40.4% at 3 years, and 32.4% at 5 years. Median OS was 19.4 months (17). These data further confirmed the efficacy of cTACE from historical RCTs and meta-analyses. Unfortunately, in such a high heterogeneity population, the outcomes of subgroup survival analysis based on BCLC stage, Child-Pugh class, PS, etc., were not stratified due to insufficient data.

cTACE vs. DEB-TACE

Since DEB-TACE first became commercially available in 2006, multiple clinical trials have been conducted to confirm its theoretical superiority in efficacy over cTACE. In 2010, the randomized phase II PRECISION V study first reported the results comparing DEB-TACE with cTACE for patients with unresectable HCC (29). The disease control rates in the DEB-TACE group failed to reach a statistical significance when compared to those in the cTACE group (63.4% vs. 51.9%, P=0.11). Notably, in a post-hoc analysis, 67% of patients with more advanced disease (Child-Pugh B, ECOG 1, bilobar or recurrent disease) had a significant increase in objective response and disease control (P=0.038 and P=0.026, respectively) in the DEB-TACE group compared with the cTACE group. Furthermore, DC Beads reduced the rate of serious liver toxicity (P<0.001) and doxorubicin-related side effects (P=0.0001) (29). On the other hand, increase in liver parenchyma damage has been reported for DEB-TACE vs. cTACE, namely in patient with the lower degree of cirrhosis (30).

A subsequent multicenter RCT reported the survival and safety comparison between the doxorubicin-loaded DEB-TACE and cTACE in patients with unresectable HCC. The 1- and 2-year survival rates were 86.2% and 56.8% after DEB-TACE and 83.5% and 55.4% after cTACE (P=0.949) and the only distinct advantage of DEB-TACE was its lower rate of post-procedural abdominal pain (71.6%

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in the cTACE group *vs.* 24.7% in the DEB-TACE group, P=0.001) (31).

Interestingly, an updated meta-analysis including 1,449 patients from four RCTs and eight retrospective studies demonstrated that non-superiority was observed in DEB-TACE when compared with cTACE in terms of tumor response and survival (32). Recently, a multi-center RCT demonstrated that cTACE appeared to have greater efficacy for local tumor control as compared to DEB-TACE (complete response rate at 3 months: 75.2% in cTACE group *vs.* 27.6% in DEB-TACE group, P<0.0001) (33). It should be indicated that 74.3% and 73.5%, respectively patients in cTACE and DEB-TACE group in this study had small tumor burden of ≤30 mm (33).

Consensus No. 6

At present, none of the RCTs have shown significant OS differences between DEB-TACE and cTACE. DEB-TACE has less systemic toxicity, but more bile duct injury. Nevertheless, there are some specific clinical settings to choose DEB-TACE or cTACE in the real-world practice, including huge tumors or bilobar tumors, hypovascular tumors, or HCC with PVTT.

Repeat TACE, TACE failure/refractory

The purpose of TACE for patients with HCC is to locally control or shrink the tumor. Several previous studies demonstrated that the repetition of cTACE maximizes tumor response as well as prolongs OS (34). Repeated TACE could be associated with liver damage and increased side effects. Therefore, a delicate balance between the necessity of repeat TACE and treatment benefit should be considered. Two major modes of therapy, classified as "scheduled" or "on-demand" modes, are now applied in clinical practice, with the latter one more widely accepted. For the "scheduled" approach, TACE is performed and repeated at fixed intervals even if intrahepatic tumors respond favorably. However, this approach may result in impaired liver function as a result of unnecessary repeated procedures. For the "on-demand" approach, repeat TACE is performed only upon the demonstration of a viable tumor (non-complete response) or local and/or distant intrahepatic recurrences for patients with preserved liver function. For the "on-demand" approach, TACE should also be repeated if partial response/stable disease has been achieved from the previous TACE, which is paradoxical to the palliative nature of TACE. In addition, based on a previous study, at least two

TACE sessions to a particular tumor, should be performed before assessing general tumor response, since 47% patients who did not respond to the first TACE ultimately achieved complete response or partial response, and the OS did not differ significantly between patients who achieved response in the first and second session (35). Notably, a qualitative definition rather than a quantitative definition is applied in "on-demand" mode when assessing tumor response. Several predictive models such as ART (Assessment for Retreatment with TACE) score and ABCR (α-fetoprotein, BCLC, Child-Pugh, and response) score have been established to assess and determine the survival benefit of repeat TACE during the past years (36). Nevertheless, none of them has been widely applied in clinical practice.

To ensure that patients receive continuous benefit from repeated TACE and in an attempt to avoid ineffective repeat treatments, several organizations, including the Japan Society of Hepatology (JSH), the European Association for the Study of the Liver (EASL), and the International Association for the Study of the Liver, introduced the concept of "TACE failure/refractoriness" (37). Among them, the updated version by the JSH-Liver Cancer Study Group of Japan (LCSGJ) in 2014 was most widely introduced in clinical trials, of which TACE failure/refractoriness was defined by intra-hepatic progression or vascular/extra-hepatic invasion after one or two TACE sessions (38). Mainly based on the results of the OPTIMIS trial, the concept suggests switching to systemic agent monotherapy if "TACE failure/refractoriness" occurs (39). By contrast, several studies demonstrated that repeat TACE especially TACE combination therapy can also achieve survival benefit (34,40). In addition, the rationality of "TACE failure/refractoriness" concept needs further discussion. Further studies with high-level evidence are warranted to demonstrate subsequent treatment after failure of TACE.

Consensus No. 7

TACE should be performed according to the "on demand" approach and not on schedule. The concepts of "TACE failure/refractoriness" have been introduced although high-level evidence is still lacking.

The combination of TACE and local therapy

TACE combined with thermal ablation

For patients with early-stage HCC, further TACE use might improve the survival outcome of thermal ablation

such as radiofrequency ablation (RFA) and microwave ablation (MWA). A RCT demonstrated that RFA plus TACE could decrease the rate of recurrence compared to RFA alone for early-stage HCC with characteristics of a solitary nodule no more than 7 cm in diameter or multiple (three or fewer) lesions with each diameter no more than 3 cm (35.11% *vs.* 54.74%). Patients in the TACE-RFA group had better OS and recurrence-free survival (RFS) than those in the RFA group (P=0.002; P=0.009) (41). Chu *et al.* reported a propensity-score analysis comparing the OS of patients with single medium-sized (3.1–5.0 cm) HCCs who underwent first-line treatment with TACE, RFA, or a combination of the two therapies (42). The 10-year OS rates were significantly different among the three groups (the poor cohort, 40.1% with combined therapy, 25.5% with TACE alone, and 19.5% with RFA alone; the matched cohort, 41.8%, 28.4%, and 11.9%, respectively; P=0.022). In the treatment of recurrent early-stage HCC, TACE-RFA combined therapy also showed better efficacy than RFA monotherapy. The 1-, 3-, and 5-year RFS rates in a RCT were 80%, 45%, and 40% for the combined group and 64%, 18%, and 18% for the control group (P=0.005) (43). Recently, a meta-analysis, including eight retrospective studies and one RCT, compared the efficacy and survival outcome between TACE plus RFA and surgical resection in patients with early-stage HCC. The combined therapy showed similar OS, disease-free survival, intrahepatic distant recurrence rate and distant metastasis rate to the resection therapy, but showed a higher local tumor progression rate [objective response rate (ORR) 2.48, 95% CI, 1.05–5.86, P=0.04] (44). Patients treated with MWA of HCC after downstaging with TACE obtain similar OS and RFS to those initially met Milan criteria (45).

TACE combined with radiotherapy (RT)

In the past decade, an increasing number of studies have indicated the therapeutic benefit of TACE combined with RT for HCC. A recent RCT showed that first-line treatment with TACE plus RT provides longer OS (55.0 *vs.* 43.0 weeks; P=0.04) and time to disease progression (31.0 *vs.* 11.7 weeks; P<0.001) than sorafenib for HCC patients with macroscopic vascular invasion (46).

Recently, a propensity score-matching study revealed that TACE plus brachytherapy with iodine-125 implantation significantly improved local control and survival in patients with 3–5 cm HCC (47). A meta-analysis demonstrated that HCC patients receiving combined therapy of TACE plus iodine-125 implantation obtained higher 1- and 2-year OS (P<0.001) than TACE monotherapy (48).

Consensus No. 8

The combination of TACE with thermal ablative techniques may result in better outcomes than ablation or TACE monotherapy in selected populations of early or intermediate HCC. For patients with macrovascular invasion, TACE plus RT may be an alternative choice to systemic therapies.

Combined TACE with systemic therapy

As a potent multikinase inhibitor that targets vascular endothelial growth factor (VEGF) receptors, sorafenib has been expected to induce a synergistic action when combining with TACE for HCC.

Unfortunately, in the past decade, series of multi-center RCTs including the post-TACE trial (49), the SPACE trial (50), the TACE-2 trial (51), and the STAH trial (52) failed to demonstrate the expected synergistic results regarding TACE combined with sorafenib *vs.* TACE alone for unresectable HCC. TACE combined with other molecular targeted agent such as with brivanib (the BRISK-TA trial) and with orantinib (the ORIENTAL trial) also showed negative treatment benefit (53,54).

More recently, the TACTICS trial demonstrated positive treatment efficacy for TACE when combined with sorafenib compared to TACE alone for unresectable HCC. The primary endpoint of progression-free survival was significantly longer in the combination group. Different from the previously mentioned trials above, sorafenib was earlier administered pre-treatment with TACE. Time to untreated progression (TTUP) was proposed as a new primary endpoint in TACE combination trials with systemic therapy (55). The ideal candidates or prognostic biomarkers of TACE combined with molecular targeted agents for HCC is still uncertain.

Following the recent successes of targeting immune checkpoints in various malignancies, the immunotherapy era for HCC treatment has begun. The CheckMate-040 trial with Nivolumab, KEYNOTE-224 trial with Pembrolizumab, and IMBRAVE 150 trial with atezolizumab plus bevacizumab in advanced HCC has shown promising outcomes (56-58). Several phase I or II trial have been underway to evaluate the safety and efficacy of TACE plus nivolumab (NCT03143270, NCT03572582,

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NCT04268888). Similarly, the safety and efficacy of TACE plus pembrolizumab is also being studied in a phase I/II trial (NCT03397654). There are some phase III RCTs in TACE-based combination investigation in patients with HCC, such as LEAP-012 trial (NCT04246177) using lenvatinib plus pembrolizumab *vs.* placebo in combination with TACE, CheckMate 74W trial (NCT04340193) using nivolumab and ipilimumab plus TACE, and EMERALD study (NCT03778957) using durvalumab and bevacizumab plus TACE. These ongoing studies deserve further evaluation and may open a new chapter of TACE combined with systemic therapies.

Consensus No. 9

TACE plus systemic therapy with an appropriate protocol may improve the therapeutic outcomes in the treatment of unresectable HCC.

Perspective

Although the use of TACE has over 40 years of history, none of an international consensus or guideline document on TACE technique has been published so far. Obviously, the heterogeneity of TACE technique exists extensively among the different regions, medical sites, and even colleagues within the same interventional radiologist team. Therefore, it may be a good start to establish a guideline worldwide to have this consensus from experts who represent East and West, although it does not cover all aspects of TACE. The present international consensus statement compromises the opinions between East and West experts who are from Northern America, Europe, and Asia-Pacific areas.

More and more evidences have shown the better outcomes with a strategy of combined TACE with other local therapies such as ablations. The most-recently developing strategy of combined TACE with PD-1/PD-L1 plus tyrosine kinase inhibitor (TKI) agents has shined a light to the HCC patients, especially to those with high risk of tumor recurrence after treatment or TACE failure/refractory.

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Footnote

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