Review Article

Precision transarterial chemoembolization in hepatocellular carcinoma: patient selection, standardized techniques, and quantitative evaluation

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Abstract: Transarterial chemoembolization (TACE) plays a critical role in the treatment of hepatocellular carcinoma (HCC), yet variability in its performance leads to inconsistent prognostic outcomes, with objective response rates (ORRs) ranging from below 10% to over 60% for intermediate HCC. Published evidence and recommendations emphasize that TACE should be executed with precise targeting and accessibility to superselective catheterization. To enhance quality control and standardize TACE procedures, the concept of "precision TACE" is introduced by an international expert panel of International Society of

Multidisciplinary Interventional Oncology (ISMIO), emphasizing the inclusion of standardized angiography, superselective catheterization and embolization, appropriate selection of embolic agents, determination of optimal embolization endpoints, and evaluation for efficacy immediately post-TACE. Precision TACE is divided into superior precision TACE (SP-TACE) and moderate precision TACE (MP-TACE). SP-TACE aims at achieving complete response (CR) or close to CR for all treated intrahepatic lesions in one session, while minimizing damage to normal liver tissue as much as possible. For SP-TACE, ideal candidates are intermediate HCCs with moderate intrahepatic tumor burden (maximum diameters of lesions no more than 5 cm, possibly up to 7 cm, with less than 5 intrahepatic lesions) and early HCCs who are unable or unwilling to receive curative approaches. MP-TACE aims at achieving partial response (PR) or stable disease (SD) for treated intrahepatic lesions with one or repeated sessions of TACE. For MP-TACE, ideal candidates are intermediate HCCs with high intrahepatic tumor burden and locally-advanced HCCs (with vascular invasion). Besides, precision TACE combined with other therapies such as ablation, systemic therapies, and hepatic resection, is discussed. Lastly, a scoring system for quantifying the precision of TACE is proposed to evaluate its effectiveness.

Keywords: Hepatocellular carcinoma (HCC); precision; transarterial chemoembolization (TACE)

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Introduction

Transarterial chemoembolization (TACE) is one of the most commonly used locoregional therapies for unresectable hepatocellular carcinoma (HCC) (1). Two milestone randomized controlled trials (RCTs) and subsequent reports established TACE as a standard therapy for intermediate-stage HCC according to the Barcelona Clinic Liver Cancer (BCLC) staging system (2-5). TACE is also indicated for very early- or early-stage HCC where curative therapies are not feasible or have failed, as well as for locally advanced HCCs with vascular invasion but no extrahepatic spread (6,7). Although with widespread applications, the heterogeneity of TACE technique in clinical practice leads to significant variabilities in the clinical outcomes (*Figure 1*) (7,8). A systematic review including 10,108 HCC patients who treated with TACE showed significant variability in treatment efficacy across different countries and era or time of treatment. For instance, the overall survival (OS) rates were 31.1 months in Japan, 18.3 months in European/American countries, and 15.6 months in Asian-Pacific countries. The 3-year survival rates before and after 2022 were 27.8% and 43.4%, respectively (9). With inconsistent technique and efficacy evaluation, the role of TACE for HCC may be left vulnerable in an era of strengthening efficacy of increasingly effective immunotherapy-based treatments (10).

Previous studies and expert opinions have highlighted that TACE procedures are often performed with lack of standardization in techniques and periprocedural evaluation in clinical practice, which negatively impacts its efficacy for HCC (11,12). Craig *et al.* carried out a global survey to see variability in technical aspects of TACE in the treatment of HCC. A total of 1,160 responses from 62 countries were obtained, and they concluded that technical aspects of TACE for HCC vary significantly by geographical location (11). Actually, prognosis after TACE for HCC has improved during the past two decades. Such improvement was mainly based on technical refinement of TACE, including standardized angiography, superselective catheterization and embolization, selection of the appropriate embolic agents, determination of reasonable embolization endpoints, and evaluation for efficacy immediately after TACE. For example, European Association for the Study of the Liver (EASL) guideline recommends TACE should be carried out in a selective manner, and American Association for the Study of Liver Diseases (AASLD) guideline recommends TACE should be performed in a selective/segmental fashion (13,14). Previous studies also demonstrated the survival superiority of superselective TACE for the treatment of HCC (15). All these evidence and consensus highlights the necessity of implementing precision TACE. Despite the condition that operators always describe their routine TACE

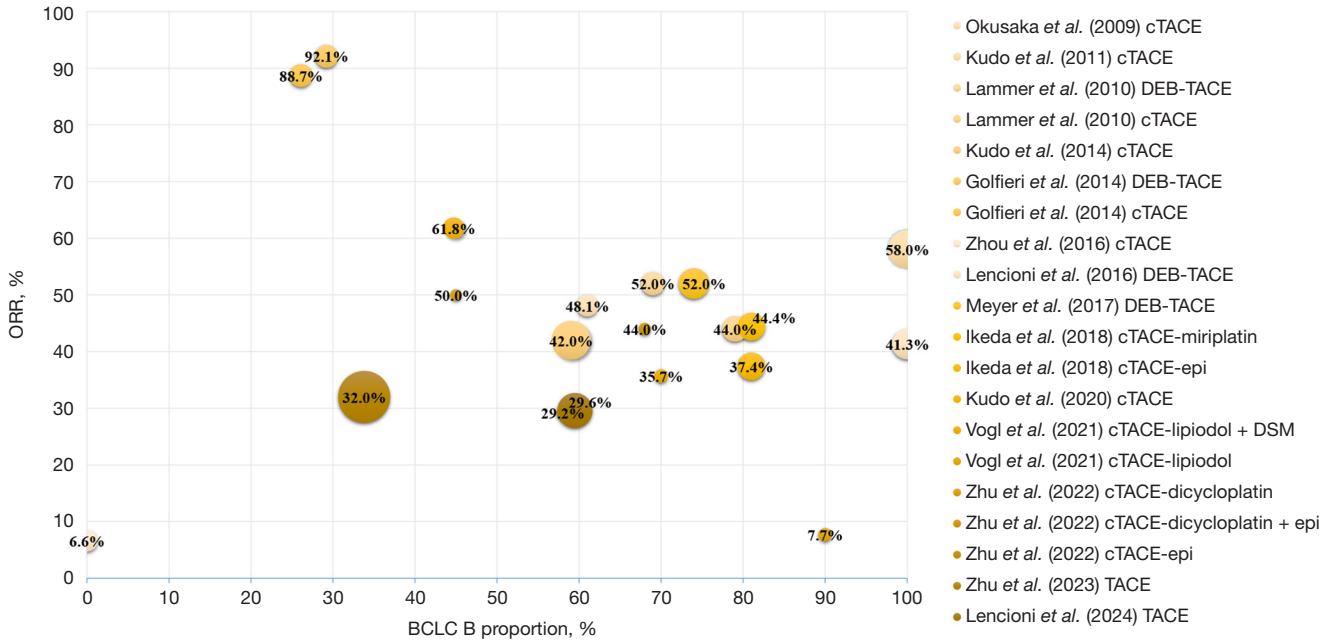

Figure 1 Reported ORR of TACE for intermediate HCC. Inconsistent ORRs have been demonstrated in these studies, ranging from less than 10% to more than 90%. BCLC, Barcelona Clinic Liver Cancer; ORR, objective response rate; cTACE, conventional transarterial chemoembolization; DEB, drug-eluting bead; TACE, transarterial chemoembolization; HCC, hepatocellular carcinoma; epi, epirubicin; DSM, degradable starch microspheres.

procedures in this way, there is still need to define and highlight standardization of TACE procedures in clinical practice.

To improve the quality control and standardization of TACE, the concept of "precision TACE" is proposed here to further standardize its clinical application for HCCs (*Table 1*). An international expert panel of International Society of Multidisciplinary Interventional Oncology (ISMIO) with experienced interventional oncologists from China (n=9), USA (n=3), Europe (n=1), Korea (n=1), and Malaysia (n=1), was convened to address this need. This diverse selection of experts reflected different practices and experiences across the East and West. After summarizing existing clinical evidence, a face-to-face expert meeting was held on June 6th, 2024, in Suzhou, China, during the annual meeting of ISMIO, to discuss definitions and establish a scoring system for precision TACE. The authors then drafted the manuscript, and after revisions the final version was edited and approved by all experts on the panel. This review aims to standardize TACE procedures, ensuring consistent and improved outcomes for HCC patients by defining and highlighting precision TACE practices.

Definition of precision TACE

The concept of precision TACE is introduced to maximize the standardization of the procedure. It involves several critical steps:

(I) Standardized angiography;
(II) Superselective catheterization and embolization;
(III) Selection of appropriate embolic agents;
(IV) Determination of reasonable embolization endpoints;
(V) Evaluation for efficacy immediately after TACE.

It is crucial to determine the appropriate TACE treatment goal based on tumor burden and patient's status. The treatment goals of TACE are divided into achieving complete response (CR), partial response (PR), and stable disease (SD) according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) (16,17). Accordingly, precision TACE is recommended to be performed according to these treatment goals, which includes superior precision TACE (SP-TACE) and moderate precision TACE (MP-TACE).

Table 1 Expert panel recommendations for precision TACE in HCC

Topics	Recommendations
SP-TACE	1. SP-TACE refers to patients with intermediate stage HCC or early-stage HCC who are unable or unwilling to receive curative treatments
	2. Based on pre-TACE imaging, standardized angiography including hepatic and extrahepatic collateral supply of HCC should be performed
	3. Microcatheter must be used to perform superselective angiography and chemoembolization for all tumor feeding arteries
	4. For conventional TACE, particles must be added following chemoembolization with lipiodol
	5. Disappearance of all tumor enhancement must be achieved, and CBCT is recommended to assist with determining embolization endpoints
MP-TACE	1. MP-TACE refers to patients with high intrahepatic tumor burden or with vascular invasion
	2. Based on pre-TACE imaging, comprehensive angiography including hepatic and extrahepatic collateral supply of HCC should be performed
	3. Superselective catheterization with microcatheters must be used
	4. For conventional TACE, particles must be added following chemoembolization with lipiodol
	5. Most of the tumor enhancement disappearance must be achieved, and CBCT is recommended to assist with determining embolization endpoints
Patient selection	1. For SP-TACE, ideal candidates are intermediate HCCs with moderate intrahepatic tumor burden (maximum diameters of lesions no more than 5 cm, possibly up to 7 cm, with less than 5 intrahepatic lesions) and early HCCs who are unable or unwilling to receive curative approaches
	2. For MP-TACE, ideal candidates are intermediate HCCs with high intrahepatic tumor burden and locally-advanced HCCs (with vascular invasion)
	3. TACE is recommended for patients with CP grade A or B
Techniques considerations	1. SMA angiography needs to be conducted at the first TACE session to clearly identify arterial anatomy and refer to the images in subsequent TACEs
	2. When the tumor cannot be identified or can be only partially identified on hepatic angiography, selective angiography for suspected extrahepatic collateral arteries should be performed to identification all potential feeding arteries of the tumor(s)
	3. Post-chemoembolization angiography should be performed to assess whether there is still tumor enhancement remained
	4. CBCT is highly recommended during procedure to detect and navigate tumor feeding arteries
Post-TACE management	1. On demand repeat TACE, which is only recommended when residual viable HCC is observed by contrast-enhanced CT/MRI, is preferred after initial TACE
	2. Currently, there is no widely-accepted consensus being established on the definitions of "TACE refractoriness"

TACE, transarterial chemoembolization; HCC, hepatocellular carcinoma; SP-TACE, superior precision transarterial chemoembolization; CBCT, cone-beam computed tomography; MP-TACE, moderate precision transarterial chemoembolization; CP, Child-Pugh; SMA, superior mesenteric artery; CT, computed tomography; MRI, magnetic resonance imaging.

SP-TACE

SP-TACE aims at achieving CR or close to CR for all treated intrahepatic lesions in one session, while minimizing damage to normal liver tissue as much as possible. Complete devascularization of the tumor and peritumoral portal vein embolization with lipiodol are recommended. The critical steps include:

(I) Patient selection: patients with intermediate stage HCC or early-stage HCC who are unable or unwilling to receive curative treatments.

(II) Angiography: perform standardized angiography, including hepatic and extrahepatic collateral supply of HCC, based on pre-TACE imaging (*Figure 2*).

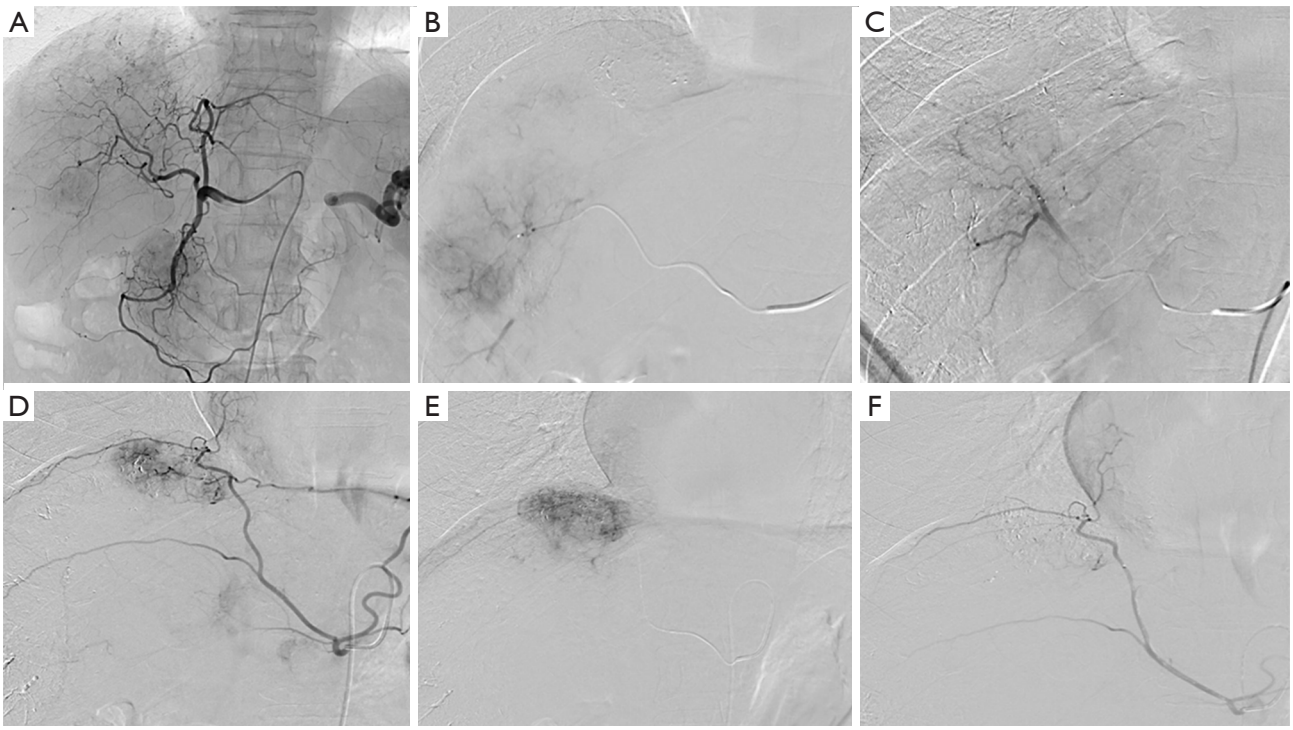

Figure 2 Angiography, superselective catheterization and embolization procedures. (A) Initial angiography of the common hepatic artery demonstrates tumor vascular supply and delineates the arterial anatomy, including potential collateral arteries. (B) Superselective catheterization of the tumor-feeding artery using a microcatheter, allowing precise delivery of embolic agents to the target lesion. (C) Post-embolization angiography of the treated tumor-feeding artery, confirming successful devascularization of the tumor with no evidence of residual enhancement. (D) Angiography of the right phrenic artery as an example of an extrahepatic collateral artery supplying the tumor, highlighting the importance of identifying and addressing collateral tumor feeders. (E) Superselective catheterization of the tumor-feeding branch of the right phrenic artery, followed by embolization to achieve complete devascularization of the tumor supplied by this collateral pathway. (F) Post-embolization angiography of the right phrenic artery confirms successful embolization, with no residual tumor enhancement observed.

(III) Superselective catheterization and embolization: use a microcatheter for superselective angiography and chemoembolization for all tumor-feeding arteries. For superselective embolization, it is not allowed to be performed on the main trunk or primary branch of the hepatic artery. Application of cone-beam computed tomography (CBCT) for target lesions detection and feeding arteries confirmation and navigation is recommended (*Figures 2,3*).

(IV) For conventional TACE (cTACE), particles must be added following chemoembolization with lipiodol (*Figure 3*).

(V) Post-embolization angiography and evaluation for efficacy: achieve disappearance of all tumor enhancement, and CBCT is recommended to assist with determining embolization endpoints (*Figure 2*).

MP-TACE

MP-TACE aims at achieving PR or SD for treated intrahepatic lesions with one or repeated sessions of TACE. Complete tumor devascularization is recommended (depending on the patient's liver function, patient's status, and portal vein patency), for cases of extensive liver involvement, fractional TACE can be performed, with additional TACE procedures considered when a residual tumor is identified. The critical steps include:

(I) Patient selection: HCCs with high intrahepatic tumor burden or with vascular invasion.

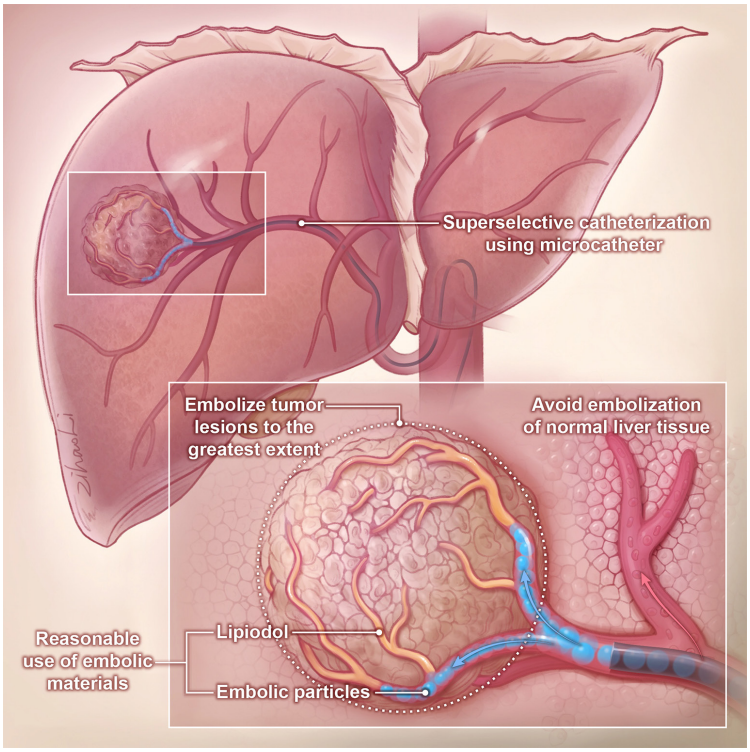

Figure 3 Superselective catheterization and embolization at every tumor-feeding artery. Superselective catheterization using a microcatheter should be performed to achieve tumor lesions embolization to the greatest extent as well as to avoid embolization of normal liver tissue as much as possible. Particles must be added following chemoembolization with lipiodol for cTACE. cTACE, conventional transarterial chemoembolization.

(II) Angiography: perform comprehensive angiography, including hepatic and extrahepatic collateral supply of HCC, based on pre-TACE imaging.
(III) Superselective catheterization: use a microcatheters and avoid embolization on the main trunk of the hepatic artery.
(IV) For cTACE, particles must be added following chemoembolization with lipiodol.
(V) Post-embolization angiography and evaluation for efficacy: achieve most of the tumor enhancement disappearance, and CBCT is recommended to assist with determining embolization endpoints.

Comparison between SP-TACE and MP-TACE

SP-TACE and MP-TACE differ in their treatment goals, patient selection, and procedural techniques.

- Treatment goals: SP-TACE aims for CR or near-CR for all targeted lesions in a single session, prioritizing complete devascularization while minimizing damage to normal liver tissue. MP-TACE seeks PR or SD, often requiring multiple sessions to manage extensive or advanced disease.
- Patient selection: SP-TACE is suited for intermediate-stage or early-stage HCC patients with limited tumor burden who are ineligible for curative treatments. MP-TACE is recommended for patients with high intrahepatic tumor burden, vascular invasion, or locally advanced disease.
- Procedural techniques: SP-TACE employs superselective catheterization, CBCT guidance, and lipiodol-based embolization with strict endpoint control to eliminate all tumor enhancement. MP-TACE uses comprehensive angiography and staged embolization, emphasizing maximal tumor devascularization while allowing flexibility for repeat TACE in extensive disease.

These differences highlight the tailored application of precision TACE strategies based on clinical scenarios and therapeutic goals.

Patient selection

Ideal candidates for SP-TACE are intermediate HCCs with moderate intrahepatic tumor burden (maximum diameters of lesions no more than 5 cm, possibly up to 7 cm, with less than 5 intrahepatic lesions) and early HCCs who are unable or unwilling to receive curative approaches (15,18,19). A previous study reported by Yamakado *et al.* demonstrated that for patients with maximum tumor diameter ≤7 cm and less than 6 lesions, OS of patients who received selective/superselective TACE was significantly better compared to those received non-selective TACE (P=0.0034) (15). Golfieri *et al.* found that tumor involvement more than 50% of the liver volume is associated with a poor prognosis (18). Experts from the INSPIRE consensus recommended that superselective TACE should be recommended for patients with less than five lesions and a maximum number of two (and possibly up to four) segments involved (19). Most SP-TACE for these kinds of patients just needs to be performed in a single session, and the CR rate range from 42% to 91% (18,20,21).

For MP-TACE, the ideal candidates are intermediate HCCs with high intrahepatic tumor burden and locally-advanced HCCs (with vascular invasion) (22,23). MP-TACE is usually performed with repeated sessions to achieve treatment goal (24).

Another aspect of patient selection for TACE is assessing liver function, as HCCs occur primarily in patients with cirrhosis, which negatively affects prognosis (25). Assessment of liver function before TACE acts as an important role in the management of HCC as TACE have potential to damage liver function (25). Currently, the most widely applied liver function assessment tool in clinical practice is Child-Pugh (CP) grade and it is adopted by most HCC treatment guidelines. According to the BCLC staging system and AASLD and EASL clinical practice guidelines, TACE is recommended for HCCs with "preserved liver function", whereas there is no clear consensus on what is considered preserved liver function (1,13,14). In China, TACE is recommended for patients with CP grade A or B (26). Published evidence demonstrated that TACE can be effectively and safely performed for patients with CP A or B, with CP B score of 7 preferred compared to CP B score of 8–9 (27).

Techniques for precision TACE

The critical techniques for precision TACE include:

(I) Standardized angiography: perform digital subtraction angiography (DSA) by placing the catheter in the common or proper hepatic artery and conduct superior mesenteric artery (SMA) angiography at the first TACE session.
(II) Superselective catheterization and embolization: position the catheter as distal as possible and close to the tumor.
(III) Selection of appropriate embolic materials: in cTACE, use lipiodol and particle embolic agents. In drug-eluting bead (DEB)-TACE, use anthracycline agents loaded on microspheres.
(IV) Determination of reasonable embolization endpoints: for cTACE, achieve complete stasis of blood flow. For DEB-TACE, achieve stasis or near stasis with an injection speed of 1 mL/min.

Standardized angiography

DSA is performed by placing the catheter in the common or proper hepatic artery. SMA angiography needs to be conducted at the first TACE session so that physicians can clearly identify arterial anatomy and refer to the images in subsequent TACEs. For patients with severe liver cirrhosis and/or portal vein occlusion, indirect portal vein angiography through the SMA or splenic artery is recommended to assess the patency and hepatic blood flow of the portal vein (28). The imaging collection should include arterial phase, parenchymal phase and venous phase. The angiographic findings are carefully analyzed to determine tumor location, size, number and arterial supply.

When the tumor cannot be identified or can be only partially identified on hepatic angiography, selective angiography for suspected extrahepatic collateral arteries, such as SMA, renal artery, left gastric artery, inferior phrenic artery, intercostal artery, internal thoracic artery, should be performed to identify all tumor feeding arteries. Post-chemoembolization angiography should be performed to assess whether there is still tumor enhancement remained.

Compared to DSA, CBCT has shown superiority in the detection of tumor-feeding arteries, with superior accuracy (96.9% *vs.* 75.4%), sensitivity (96.9% *vs.* 77.2%), and specificity (97.0% *vs.* 73.0%) (29). Besides, combined DSA with CBCT can identify more tumor feeding arteries compared with DSA alone (30). With three-dimensional (3D) reconstructed technology, CBCT has high accuracy on navigating tumor feeding arteries, as vascular recognition and navigation software programs have been developed and

applied successfully. With these programs, feeding arteries can be automatically displayed by targeting the position of the lesion(s), demonstrating the vascular pathway from catheter tip to the target lesion(s) (31-33). Miyayama *et al.* reported that intraprocedural CBCT monitoring of embolized areas reduces the local tumor recurrence, with the 1-, 2-, and 3-year local recurrence rates in the DSA + CBCT and DSA groups were 22.3% and 33.3%, 26.8% and 41.3%, and 30.6% and 48%, respectively (P=0.0217) (34). Similarly, Cornelis *et al.* reported that adding CBCT during TACE procedure achieved improved local tumor response without increasing the dose exposure, with a higher rate of CR observed for DSA + CBCT group versus DSA group (68.4% *vs.* 36%, P=0.03) (35).

Superselective catheterization and embolization

Superselective catheterization is crucial for precision TACE. EASL and AASLD highlight that TACE should be carried out in a selective/segmental manner (over lobar treatment) (13,14). The radial artery approach has emerged as an alternative to the femoral artery approach for performing TACE, offering distinct advantages in select patient populations. This technique is particularly beneficial for patients with severe obesity or limited femoral artery access due to prior interventions or anatomical variations. Integrating the radial artery approach into clinical practice guidelines for TACE could expand its use in appropriately selected patients, further enhancing procedural safety and patient outcomes. When performing TACE, the catheter should be position as distal as possible and close to the tumor, which could maximize the anti-tumoral effect and minimize the collateral damages of the surrounding liver parenchyma. CBCT can also be used to navigate feeding vessels with the help of 3D reconstructed images overlaid onto fluoroscopic images (36).

Generally, catheterization of segmental, subsegmental, and more distal hepatic arterial branches is required (37,38). In cases of a tumor supplied by multiple feeders or multiple tumors, superselective TACE should be performed for each feeder. The main tumor feeder should be embolized last. If the tumor is partially supplied by an extrahepatic artery, the feeding branch from the extrahepatic artery should be embolized first (39). The distal tumor-feeder should then be embolized first, and the proximal tumor-feeder should be embolized last to avoid inadvertently occluding the distal tumor-feeders with overflowing embolic agents. When it fails to superselectively catheterize to the feeding artery, non-selective and aggressive TACE should be avoided. The expert panel agrees and recommends that for SP-TACE, it is not allowed to perform chemoembolization on the main trunk or primary branch of the hepatic artery. Also, for MP-TACE, it is not allowed to perform chemoembolization on the main trunk of the hepatic artery.

While superselective catheterization is critical for optimizing the efficacy and safety of TACE, certain anatomical variations or technical challenges may render it infeasible. Common issues include tortuous or stenotic arteries, and unfavorable vascular anatomy caused by prior treatments or cirrhosis-induced changes. In such scenarios, alternative strategies can be employed, mainly include advanced imaging techniques, alternative access routes, and adjunctive therapies. For advanced imaging techniques, CBCT with 3D reconstruction and automated tumor-feeder detection software can assist in navigating complex vascular anatomy and identifying collateral feeders. For alternative access routes, employing alternative arterial access, such as the radial artery, may improve catheter maneuverability. For adjunctive therapies, combining TACE with systemic or ablative therapies can compensate for suboptimal embolization in anatomically challenging cases.

Selection of appropriate embolic materials

In cTACE procedures, lipiodol is the most commonly used embolic agent. The volume ratio of the lipiodol and water solution is usually 2:1. The lipiodol and water solution and chemotherapy drugs should then be mixed together, forming a “water in oil” emulsion to improve the stability of the solution (40). The amount of lipiodol used mainly depends on the size, number, and vascularity of the tumor but should not exceed 20 mL per procedure (26,41). A particle embolic agent, such as gelfoam, polyvinyl alcohol (PVA) particles, or acrylic microspheres, must be administered after cTACE to increase embolization efficacy and tumor necrosis (42,43).

In DEB-TACE procedures, anthracycline agents are commonly loaded on microspheres. The recommended maximum dose of doxorubicin or epirubicin that can be safely administered to an adult patient in a single session is 150 mg (44,45). The selection of DEB size and dose mainly depends on the tumor size, vascularity, and treatment goals. Generally, DEBs of 100–300 μm are preferred. For hypervascular tumors and those with significant arteriovenous shunts, additional 300–500 μm DEBs can be considered. In general, for tumors with a diameter <3 cm,

Table 2 Preferred embolic agents based on tumor size, stage, and patient profile

Tumor size/stage	Patient profile	Preferred embolic agent	Rationale
Small tumors (<3 cm)	Preserved liver function, early-stage HCC	Lipiodol + microspheres (40–120 μm) or lipiodol + gelatin sponge particles (150–350 μm)	Allows precise embolization of microvessels feeding the tumor; minimizes non-target embolization
Medium tumors (3–5 cm)	Intermediate-stage HCC, preserved liver function	Lipiodol + microspheres (40–300 μm) or lipiodol + particles or DEBs (40–300 μm)	Allows precise embolization of microvessels feeding the tumor; minimizes non-target embolization; DEBs provide sustained drug release
Large tumors (>5–10 cm)	Hypovascular, intermediate or locally advanced HCC	Lipiodol + microspheres (40–120/100–300 μm) + gelatin sponge particles (150–350 μm) or DEBs (40–70/100–300/300–500 μm)	Larger particles reduce vascularity effectively; DEBs improve local drug retention in large tumor volumes
	High tumor burden, hypervascularity, intermediate or locally advanced HCC	Lipiodol + microspheres (100–300/300–500 μm) + gelatin sponge particles (350–560 μm) or DEBs (100–300/300–500 μm)	
Large tumors (>10 cm)	High tumor burden, intermediate or locally advanced HCC	Lipiodol + microspheres (100–300/300–500/500–700 μm) + gelatin sponge particles (350–560 μm) or DEBs (100–300/300–500 μm) + larger particles (350–560 μm)	Larger particles reduce vascularity effectively; DEBs improve local drug retention in large tumor volumes
Tumors with vascular invasion	Portal vein invasion, advanced HCC	If no arterioportal/arteriovenous fistula observed or arterioportal/arteriovenous fistula observed while tip of the catheter exceeded the fistula achieved, choice of embolic agents is similar to it mentioned above. If arterioportal/arteriovenous fistula observed and tip of the catheter is unable to exceeded the fistula, larger microspheres or particles should be used	Balances efficacy with safety by minimizing risk of non-target embolization in compromised vasculature
Refractory tumors	Poor response to previous precision TACE(s)	DEBs loaded with alternative chemotherapeutics (e.g., irinotecan) or smaller microspheres (40–70/40–120/100–300 μm)	Optimizes penetration in tumors resistant to standard chemoembolization

HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; DEB, drug-eluting bead.

DEBs <300 μm in size are preferred (depending on tumor vascularity); for tumors with a diameter >5 cm, DEBs 100–300 μm in size can be used for initial chemoembolization, followed by DEBs 300–500 μm in size for additional chemoembolization (46-48). *Table 2* summarizes preferred embolic agents based on tumor size, stage, and patient profile.

Commonly used chemotherapeutic agents in TACE include anthracyclines, platinum-based compounds, mitomycin C, 5-fluorouracil, irinotecan, and hydroxycamptothecin. The selection and dosage of these agents should consider various factors, including tumor burden, patient body surface area, hepatic and renal function, performance status, prior treatment history, and coexisting medical conditions. For monotherapy, an anthracycline (e.g., doxorubicin) or platinum agent (e.g., cisplatin) is generally recommended. In cases requiring combination chemotherapy, two or more agents can be selected to achieve enhanced therapeutic effects.

Determination of reasonable embolization endpoints

The embolization endpoints should be based on treatment goal, tumor and patient's status. Also, the embolization endpoints vary depending on cTACE or DEB-TACE.

In cTACE procedures, lipiodol can be delivered to the portal vein and deposited into the tumor, and additional particle embolic agents should be injected to achieve complete stasis of blood flow. For selective segmental

chemoembolization, the endpoint should be adjusted until the feeding arteries resemble "trees in winter", i.e., small tumor-feeding arteries should be embolized while the patency of segmental/lobar arteries should be preserved to facilitate subsequent TACE procedures (49). Angiography should be performed 5 minutes after complete stasis to confirm the endpoint (50).

For DEB-TACE procedures, an injection speed of 1 mL/min is recommended. Using this speed ensures that the microspheres remain uniformly suspended and prevents reflux. The chemoembolization endpoint can be graded as "stasis" or "near stasis", i.e., DEBs and contrast agent are slowly washed out within 2 to 5 heartbeats (48). Angiography should be performed 5 minutes after stasis to confirm the efficacy of the procedure. If tumor enhancement still exists, further chemoembolization should be considered to achieve stasis or near stasis.

Post-TACE managements

Evaluation for efficacy immediately after TACE

During cTACE, CBCT can be used to monitor lipiodol deposition and distribution, thus allowing physicians to avoid incomplete embolization and evaluate for nontarget embolization due to blind spots on DSA. Research has shown that CBCT is almost equivalent to conventional CT for monitoring incomplete lipiodol deposition after TACE. The degree of lipiodol deposition is considered one of the predictive factors for CR. If lipiodol deposition does not entirely cover the tumor, potential collateral arteries need to be identified and thoroughly embolized (34,51). Hence, the endpoint of cTACE can be determined by monitoring the distribution and deposition of lipiodol using CBCT; this can improve both the efficacy and safety of the cTACE procedure (34,51).

In TACE procedures using DEB-TACE, the nonvisualization of the drug-eluting microspheres limits the ability of CBCT to monitor their distribution. In this case, contrast-enhanced CBCT is recommended. Notably, visualization of drug-eluting microspheres can be seen on CBCT if using LC Lumi beads. Parenchymal blood volume (PBV) perfusion using CBCT technique provides both quantitative and qualitative analyses and can be used for efficacy evaluation both for cTACE and DEB-TACE (52,53).

Recent studies underscore the critical role of nutritional status as a prognostic factor in patients undergoing TACE for HCC (54-56). Several indicators such as the prognostic nutritional index and body composition measurements have been associated with worse OS and a higher incidence of complications after TACE (54,55). Integrating nutritional assessment into pre-treatment and follow-up evaluations may enhance patient stratification and contribute to improved clinical outcomes.

Follow-up and repeat TACE assessment

Post-TACE imaging follow-up, regularly performed 4–8 weeks after TACE, needs to be performed with contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Currently, there is weak evidence and recommendation on whether CT or MRI is better to the other for post-TACE imaging follow-up. Both contrast-enhanced CT and MRI are widely used for post-TACE follow-up, each offering distinct advantages and limitations in detecting residual tumors. CT is more accessible and cost-effective, with shorter scanning times and broader availability. It provides excellent visualization of vascular structures, making it suitable for assessing arterial phase enhancement. However, its sensitivity for detecting small residual tumors is lower compared to MRI, particularly in patients with cirrhotic livers or complex tumor anatomy. MRI offers superior soft tissue contrast and sensitivity, especially with hepatocyte-specific contrast agents, making it more effective in identifying small residual lesions or areas of incomplete necrosis. In addition, it is less affected by beam-hardening artifacts caused by lipiodol deposition. However, compared to contrast-enhanced CT, limitations of MRI include higher cost, longer imaging times, and reduced availability in some clinical settings. Briefly, CT is preferred for rapid evaluation and in settings with limited MRI access. MRI is recommended when detailed assessment of residual tumor tissue or differentiation between viable and necrotic tissue is required, especially in challenging cases.

Apart from mRECIST, Response Evaluation Criteria in Cancer of the Liver (RECICL) has also been reported to be an alternative as treatment response evaluation tool after TACE (57). Both mRECIST and RECICL are with distinct strengths and limitations. mRECIST focuses on changes in arterial phase enhancement, making it effective for detecting viable tumor tissue after locoregional therapies like TACE. It is simple, widely recognized, and standardized in clinical trials and practice. However, mRECIST may underestimate residual disease in patients with atypical enhancement patterns or lesions with extensive necrosis, particularly in cases with cirrhosis or complex tumor anatomy. RECICL

Table 3 Scoring system of precision TACE

Items	Score
Incomplete tumor enhancement without finding other potential feeding arteries	1
Residual tumor enhancement after post-embolization angiography	1
Failure to embolize all feeding arteries	1
Failure to perform superselective catheterization and embolization	1
Failure to add particles after lipiodol-based chemoembolization for cTACE	1

TACE, transarterial chemoembolization; cTACE, conventional transarterial chemoembolization.

offers a more detailed assessment by incorporating findings from additional imaging modalities and broader evaluation criteria, such as viable tumor volume and tumor marker levels. This makes it more sensitive for detecting residual or progressive disease. However, RECICL is more complex and less universally adopted, requiring additional training and resources, which may limit its use in routine clinical practice.

Compared to performing repeat TACE at regular intervals, "on demand" repeat TACE, which is only recommended when residual viable HCC is observed by contrast-enhanced CT/MRI, is preferred after initial TACE. With the aim to avoid ineffective repeat TACE, the concept of "TACE refractoriness" has been introduced by several societies around the world. Currently, there is no widely-accepted consensus being established on the definitions of "TACE refractoriness" (58). In 2021, the Chinese College of Interventionalists (CCI) introduced the CCI definition and consensus statement on "TACE refractoriness", which is as follows: After three or more consecutive standardized and precision TACE sessions, the target tumor(s) was still in a progressive disease state (according to mRECIST criteria seen on contrast enhanced CT/MRI at 1–3 months after the latest TACE) compared with that before the first TACE session (59). Repeated TACE should be terminated after occurrence of TACE refractoriness and other treatments such as systematic therapy (molecular targeted agent and immune checkpoint inhibitor), other locoregional therapy (hepatic artery infusion chemotherapy, selective internal radiation therapy, ablation therapy), and combination therapies should be considered (59,60).

The scoring system of precision TACE

To evaluate the precision TACE quantitatively, a scoring system for precision TACE is proposed (*Table 3*). The scoring system categorizes precision TACE into high (score 0), moderate (score 1–2), or low (score >2) quality, guiding clinical decisions:

- ❖ High quality (score 0): indicates optimal procedure; follow standard post-TACE imaging and surveillance protocols.
- ❖ Moderate quality (score 1–2): suggests areas for improvement; repeat TACE may be necessary for residual disease.
- ❖ Low quality (score >2): highlights significant procedural issues; consider immediate re-evaluation of feeding arteries or alternative treatments.

The proposed precision TACE scoring system focuses on evaluating procedural quality and technical performance during TACE, whereas existing models such as the six-and-twelve score, ALBI-TAE model, and FAIL-T model are designed to predict patient prognosis post-TACE. These existing models primarily integrate clinical, biochemical, and radiological parameters to estimate survival or tumor response, while this scoring system provides a real-time assessment of the technical precision achieved during the procedure.

Here is an example on how this scoring system would be used in clinical practice, linking score ranges to specific treatment decisions and outcomes. A patient undergoing cTACE receives a score of 2 due to residual tumor enhancement on post-embolization angiography and incomplete embolization of feeding arteries. The clinician reviews the CBCT images, identifies potential collateral feeders, and performs a follow-up repeat TACE session to improve tumor devascularization. This iterative approach ensures comprehensive treatment and highlights the practical value of the scoring system. A decision tree to guide clinicians through patient selection and procedural decision of precision TACE is presented in *Table 4*.

To validate accuracy of the scoring system in real-

Table 4 Decision tree of precision TACE

Step	Criteria/decision point	Action
Step 1: liver function assessment	1. Preserved liver function (e.g., Child-Pugh A/B)	Proceed to tumor burden evaluation
	2. Impaired liver function	Consider supportive care
Step 2: tumor burden	1. <5 lesions, each ≤7 cm	Proceed with SP-TACE
	2. Extensive tumor burden or vascular invasion	Proceed with MP-TACE
Step 3: angiography and procedure	1. SP-TACE: superselective catheterization of tumor-feeding arteries, use of CBCT for guidance and endpoint determination	Achieve complete tumor devascularization
	2. MP-TACE: comprehensive angiography and selective catheterization/embolization, fractional TACE as needed	Focus on maximal tumor devascularization with potential for repeat sessions
Step 4: post-TACE outcome evaluation	1. SP-TACE: complete devascularization confirmed by post-embolization CBCT	Proceed with surveillance
	2. MP-TACE: most tumor enhancement disappearance confirmed by post-embolization CBCT	Plan repeat TACE or integrate adjunctive therapies

TACE, transarterial chemoembolization; SP-TACE, superior precision transarterial chemoembolization; MP-TACE, moderate precision transarterial chemoembolization; CBCT, cone-beam computed tomography.

world clinical practice, a summary of preliminary data on the topic was presented. As for now, 1,022 patients have been enrolled across 8 centers, with the final sample size still to be determined. The primary outcome of the study was objective response rate (ORR) after the first TACE, with secondary outcomes included OS and progression-free survival (PFS). Of the 1,022 patients enrolled, 746 (73.0%) patients met the precision TACE criteria, while 276 (27.0%) patients did not. Preliminary results indicated that the precision TACE criteria effectively stratify patients according to their response to treatment. Specifically, the ORR after the first TACE for patients who met the precision TACE criteria was 76.0%, significantly higher compared to 64.1% in the non-precision group (P<0.001). The median OS for the precision TACE group was 39.5 months [95% confidence interval (CI): 34.0–45.0], compared to 27.7 months (95% CI: 22.2–33.1) in the non-precision group (P<0.001), and the median PFS was 15.6 months (95% CI: 14.3–16.9) in the precision group, versus 10.8 months (95% CI: 9.0–12.6) in the non-precision group (P<0.001). These findings underscore the clinical significance of precision TACE in achieving improved short-term outcomes, while also providing patients with better opportunities for subsequent treatment and potentially leading to improved long-term outcomes. Continued analysis with extended follow-up will further validate these results, making them more reliable and helping to optimize patient management in the future.

Controlling operator experience and geographical variability in the scoring system development

The introduction of precision TACE concept and development of the precision TACE scoring system accounted for operator experience and geographical variability to ensure its applicability across diverse clinical settings. This was achieved through the following approaches. First, the concept and scoring system was developed in collaboration with a multidisciplinary panel of interventional radiologists from high-volume centers across different regions. This ensured that the criteria reflect universally applicable standards while accommodating variations in practice. Second, each element of the concept and scoring system was based on evidence from peer-reviewed studies and expert consensus, ensuring its relevance regardless of operator expertise or regional practice differences. Third, the concept and scoring system was preliminarily validated using multicenter retrospective data, capturing variability in operator skill levels and institutional protocols. This validation step demonstrated its consistency and practicality in different geographical contexts. Forth, to mitigate the impact of operator experience, the scoring system encourages the use of advanced imaging technologies, such as CBCT, which reduces reliance on individual expertise by providing objective procedural guidance. By addressing these factors, the scoring system supports reproducible, high-quality

TACE procedures across diverse clinical environments.

Combined TACE with other therapies

TACE combined with ablation

The combination of precision TACE and ablation represents a valuable therapeutic strategy for HCC, particularly in complex cases where single-modality treatment is insufficient. This approach is especially relevant in two clinical scenarios: patients with multiple lesions and those with large tumors (>5 cm).

For patients with multiple lesions, precision TACE and ablation can be complementary. TACE effectively targets lesions located in high-risk or anatomically challenging areas, while ablation focuses on accessible lesions, achieving comprehensive tumor control. Studies have demonstrated that this combination significantly improves local control rates compared to TACE or ablation alone, particularly in intermediate-stage HCC (61). For large tumors (>5 cm), TACE is used to reduce tumor vascularity and size, creating favorable conditions for subsequent ablation. Ablation can then precisely target residual viable tumor tissue, minimizing the risk of recurrence. This combination has shown to improve treatment efficacy while sparing adjacent liver parenchyma (62).

Optimal patient selection and timing of these treatments are critical to maximizing outcomes. Factors such as lesion size, location, and liver function should guide the choice and sequence of therapy. The integration of precision TACE and ablation into treatment protocols highlights the importance of a tailored, multidisciplinary approach for managing complex HCC cases.

TACE combined with systemic therapies

The combination of TACE with systemic therapies has shown potential in improving outcomes for HCC (10). Tyrosine kinase inhibitors (TKIs), such as sorafenib and lenvatinib, are commonly combined with TACE. While early trials, including Post-TACE, SPACE, and TACE-2, reported negative results, the optimized design of the TACTICS trial demonstrated a significant improvement in PFS with sorafenib and TACE (63). However, no OS benefit was observed. The LAUNCH trial, using lenvatinib and TACE, was the first phase 3 study to show a significant OS benefit (64). One of the key reasons for the success of the LAUNCH trial was the performance of precision TACE with high quality.

In the era of immunotherapy, it has further expanded the potential of TACE combinations. Retrospective studies, such as CHANCE001 and CHANCE2201, demonstrated improved outcomes with TACE combined with programmed death 1/programmed cell death-ligand 1 [PD-(L)1] inhibitors and TKIs compared to monotherapy (65,66). The EMERALD-1 trial, combining TACE with durvalumab and bevacizumab, was the first phase 3 trial to report a significant PFS benefit compared to TACE monotherapy for intermediate HCC, though OS data remain inconclusive (67). Recently, the LEAP-012 trial, combining TACE with pembrolizumab and lenvatinib, also demonstrated a significant PFS benefit compared to TACE monotherapy for intermediate HCC (68). These findings align with retrospective studies but highlight challenges such as the lack of real-world applicability of specified TACE regimens. Ongoing trials are exploring various combinations of TACE with systemic therapies, aiming to optimize efficacy and establish standards. This evolving paradigm underscores the importance of multidisciplinary approaches in improving HCC outcomes. Also, performance of precision TACE in RCTs on this topic is the key to achieve success of the trials.

TACE combined with hepatic resection (prior to hepatic resection)

TACE can serve as a valuable neoadjuvant strategy in patients with HCC undergoing hepatic resection, particularly in cirrhotic patients or those with borderline resectable tumors. By inducing necrosis and reducing tumor size and vascularity, TACE facilitates a clearer demarcation of tumor margins, which is critical for achieving R0 resection. This is especially beneficial in cases of large or multifocal tumors where complete surgical excision might otherwise be challenging.

Several studies have reported that preoperative TACE can improve resectability and reduce intraoperative blood loss by minimizing the tumor's vascular supply (69,70). Additionally, this approach may help identify patients who would benefit most from surgery by excluding those with poor tumor biology or rapid progression. However, patient selection remains crucial, as TACE can compromise liver function in cirrhotic patients if not carefully planned. Future research should focus on optimizing the timing and patient criteria for preoperative TACE to maximize its benefits in multidisciplinary HCC management.

TACE combined with hepatic arterial infusion chemotherapy (HAIC)

The combination of TACE and HAIC has gained attention as a promising strategy for improving outcomes in HCC, particularly in patients with advanced or TACE-refractory disease. TACE achieves tumor devascularization and induces ischemic necrosis, while HAIC provides sustained delivery of high concentrations of chemotherapeutic agents directly to the tumor via the hepatic artery, maximizing local efficacy while minimizing systemic toxicity. This combination is especially effective for large or infiltrative tumors and cases with vascular invasion, where TACE alone may be insufficient (71).

However, the optimal integration of TACE and HAIC—such as sequencing, chemotherapeutic regimens, and timing—remains under investigation. Commonly used agents in HAIC include cisplatin and 5-fluorouracil, with regimens tailored to tumor characteristics and patient tolerance. While promising, this approach is associated with increased procedural complexity and higher costs, necessitating careful patient selection. Future research should focus on RCTs to standardize protocols and validate the survival benefits of TACE-HAIC combinations, particularly in diverse clinical settings.

Limitations and future directions

The ISMIO expert panel emphasizes the need for standardization and introduces the concept of "precision TACE", while existing evidence to support on this concept is not enough. In addition, the proposed scoring system may lack sufficient clinical validation or empirical evidence to support the superiority of this scoring system in improving outcomes of TACE. The scoring system is an interesting approach to quantifying precision in TACE, but it would benefit from stronger clinical data or case studies demonstrating its direct impact on patient outcomes. The rationale for assigning points to certain procedural elements (such as failure to embolize all feeding arteries or incomplete tumor enhancement) needs to be better justified. The clinical significance of each point in the scoring system should be elaborated upon to ensure its practicality in clinical settings. To further validate the concept of precision TACE and its scoring system, several key research directions should be prioritized. First, large-scale multicenter retrospective/prospective studies are encouraged to be conducted to evaluate the reproducibility and reliability of the precision TACE and its scoring system across different institutions and operators. These studies should assess its impact on procedural quality, tumor response, and long-term clinical outcomes. Second, it is interesting to investigate how the precision TACE scoring system can complement existing prognostic models, such as the six-and-twelve score or ALBI-TAE model, to create a comprehensive framework that combines procedural quality with survival predictions. Third, researches should focus on exploring the role of emerging technologies, such as artificial intelligence-driven imaging analysis and real-time navigation systems, in enhancing precision TACE planning, execution, and scoring. Last but not least, in the era of immunotherapy, designing clinical trials to evaluate the efficacy of precision TACE in combination with systemic therapies, focusing on optimizing treatment sequencing and patient selection, is warranted.

Conclusions

The implementation of precision TACE is crucial for quality control in TACE procedures for HCC. Precision TACE should focus on key aspects of standardized angiography, superselective catheterization and embolization, selection of the appropriate embolic agents, determination of reasonable embolization endpoints, and evaluation for efficacy immediately after TACE. The quality of precision TACE should be evaluated quantificationally using the proposed scoring system. All physicians should strictly adhere to the steps of precision TACE to ensure improved outcomes for HCC patients.

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Footnote

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