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REVIEW

Transarterial Chemoembolization for Hepatocellular Carcinoma: Current Role and Techniques

Toshihiro Tanaka

Department of Diagnostic and Interventional Radiology, Nara Medical University, Japan

Abstract:
In the current systemic therapy era, such as immunotherapy and molecular targeted therapy, treatment strategy of hepatocellular carcinoma is changing. Transarterial chemoembolization is more expected as a curative treatment option than before. Therefore, it is important to learn key techniques of transarterial chemoembolization procedures to achieve complete response. This article delineates the current indications for transarterial chemoembolization and several techniques used for its implementation.

Keywords:
hepatocellular carcinoma (HCC), transarterial chemoembolization (TACE), combined therapy

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Introduction

In recent years, treatment options for hepatocellular carcinoma (HCC) have evolved with the introduction of molecular targeted agents (MTAs) and immune checkpoint inhibitors (ICIs). This has led to changes in the positioning of transarterial chemoembolization (TACE). Although TACE has a priority as a treatment option in intermediate-stage HCC, its indication is limited to cases in which selective access is possible [1]. For widespread multiple diseases, systemic therapies such as atezolizumab/bevacizumab or durvalumab/tremelimumab are initially applied [2]. The role of TACE has shifted from palliative treatment to curative treatment. Cases treated by TACE are expected to have a complete response (CR) [3]. In addition, changes in liver function should be critically monitored, as deterioration of liver function caused by TACE can disrupt subsequent systemic therapies.

Looking at the reported results of TACE, there seems to be significant variation between facilities or research groups, highlighting the need for standardization of TACE techniques [4-8]. It is widely recognized that employing proper techniques in superselective TACE can yield curative outcomes [9]. In recent years, imaging techniques and devices for TACE have been improved, making it possible to perform precise TACE procedure [10, 11]. In addition, combination therapies with TACE and MTAs and/or ICIs are expected to improve therapeutic outcomes [12, 13]. In this article, we introduce the current indications of TACE and key points of the TACE technique to achieve CR that we are implementing with the intention of standardization. Moreover, we discuss future perspectives on the combination therapies of TACE with systemic therapies.

1. Indications

Current indications of TACE in guidelines

TACE stands as a crucial treatment for inoperable HCC. The Barcelona Clinic Liver Cancer (BCLC) staging system defines intermediate HCC (BCLC B stage) as presence of multifocal nodules (>3 nodules or a maximum nodule diameter of >3 cm), preserved liver function, no cancer-related symptoms, and no macrovascular invasion or extrahepatic spread. Despite discussions over the past decade about the heterogeneity of BCLC B stage, it has still been considered as an indication for TACE [14]. Japan Society of Hepatology (JSH) Guidelines recommend TACE for hypervascular HCCs with Child-Pugh class A or B, with 2-3 tumors of ≥3 cm in diameter or ≥4 tumors, which is similar to BCLC intermediate-stage [15]. Notably, the European Association for the Study of the Liver, the American Association for the

Corresponding author: Toshihiro Tanaka, totanaka@naramed-u.ac.jp
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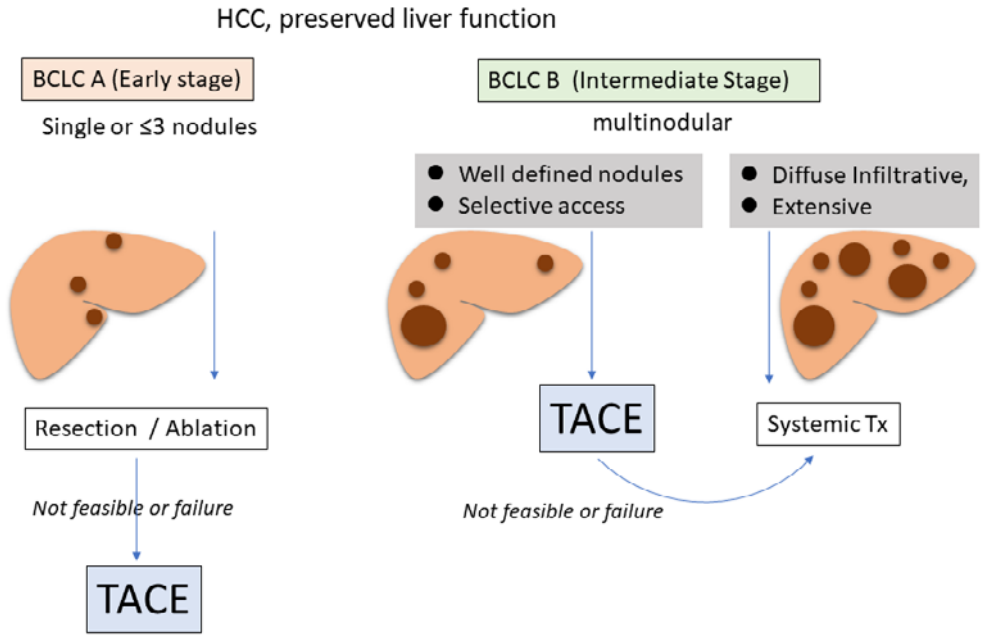

Figure 1.

Indication for TACE, adapted from the BCLC staging and treatment strategy in 2022. Transplantation description is not included. TACE is indicated for early-stage HCC when resection and ablation are not feasible and for intermediate-stage HCC with well-defined nodules that can be selectively targeted.

Study of Liver Diseases (AASLD), and the Asian Pacific Association for the Study of the Liver concur in recommending TACE as the first-line choice for BCLC B patients. However, the evolving systemic therapies, such as MTAs and ICIs, has recently introduced new complexities, prompting a reevaluation of indications and treatment strategies for this heterogeneous disease intermediate-stage HCC [16]. The updated BCLC staging system further categorizes intermediate-stage patients into subgroups, highlighting TACE as the preferred first-line choice for those without the option for liver transplantation but with preserved portal flow and feasible selective access to feeding tumor arteries. Early-stage HCC is also considered an indication for TACE if surgical resection and ablation are not feasible. Diffuse or widely spread bilobar diseases are indication of systemic therapies (**Fig. 1**) [1].

Subclassifications of intermediate-stage HCC based on tumor burden

Several subclassifications have been proposed to refine TACE indication in intermediate-stage HCC, which are mainly based on tumor burden. In the Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE) 2019, the Up-to-7 criteria, which was originally developed to guide transplantation, were recommended [17, 18]. The Up-to-7 criteria are defined as HCC with seven as the sum of the diameter of the largest tumor (in cm) and the number of tumors. Cases beyond Up-to-7 are unsuitable for TACE. However, there have been augmented by another groups. Kim et al. proposed the Up-to-11 criteria and reported a better correlation with prognosis after TACE than the Up-to-7 criteria [19]. Hu et al. proposed the Scoring Methods for Intermediate-Stage, which scores the number of tumors divided into less than 7, 7-10, and more than 10 [20]. Hung et al. also proposed the similar three-group subclassification of 7-11 criteria [21]. The above reports suggested that the population beyond Up-to-7 criteria was still heterogeneous and recommended to be further subdivided (**Fig. 2**). Previous report indicated high CR ratio of TACE in patients with high tumor burden HCC including huge tumors or beyond the Up-to-7 criteria [22].

Up-to-7, Up-to-11, and 7-11 criteria are defined according to tumor burden calculation by the sum of the tumor diameter of the largest tumor and the tumor number. However, debates persist regarding the relative importance of tumor number versus size. Yamakado et al. demonstrated that tumor size of 7 cm in diameter and tumor number 4 well discriminated the prognosis of intermediated stage HCC treated by TACE [23]. Kinki Criteria set specific thresholds, which defined that the tumor number ≥ 7 and a tumor size ≥ 6 cm were unsuitable for TACE [24]. Saito et al. reported that tumor number ≥ 11 is the significant poor prognostic factor, while tumor size (≥6 cm) was not, suggesting that tumor number is a more critical factor than tumor size to predict the prognosis of intermediate-stage HCC treated by TACE [25]. **Table 1** summarizes these subclassifications.

Another factors influencing TACE outcome

It was reported that morphologic types of tumors are significantly related to the prognosis. Even in limited tumor burden cases, a nonsimple nodular type has high risk of recurrence [26]. Pathological poorly differentiated HCC,

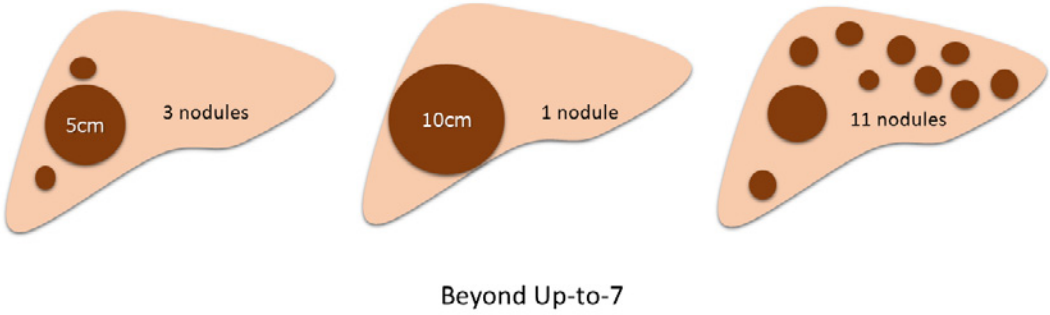

Figure 2.
Heterogeneity of the population beyond Up-to-7. Three nodules with maximum size of 5 cm in diameter. Cases with three nodules of a maximum size of 5 cm in diameter, a single nodule of 10 cm in diameter, and those with 11 nodules, each potentially requiring a different treatment strategy.

Table 1. Subclassifications of Intermediate Stage.

Criteria	Authors	Year	Country	Indication of TACE
Up-to-7	Kudo [17]	2020	Asia-Pacific	Tumor Nr + Max D ≥ 7
Up-to-11	Kim [19]	2017	Korea	Tumor Nr + Max D ≥ 11
SMIS	Hu [20]	2019	China	7–11 score + CP score
7–11	Hung [21]	2021	Taiwan	Tumor Nr + Max D ≥ 11
4/7	Yamakado [23]	2014	Japan	Tumor Nr > 4, Max D > 7
Kinki	Kudo [24]	2015	Japan	Tumor Nr ≥ 7, Max D ≥ 6
Nr 11	Saito [25]	2020	Japan	Tumor Nr ≥ 11

Nr, number; Max, maximum; D, diameter

which can be demonstrated heterogenous enhancement inside tumor on contrast-enhanced CT, has poor prognosis [25, 27]. Heterogeneity on the hepatobiliary phase (HBP) of gadoxetic acid-enhanced MRI (EOB-MRI) has surfaced as influential in TACE outcomes [28, 29]. Cases with irregular margins on HBP of EOB-MRI that indicates microvascular invasion and location of tumors near the portal vein branch also pose challenges for TACE efficacy [30, 31].

Definition of TACE failure and refractory

TACE failure/refractoriness is characterized by the following criteria: (i) residual enhancement (≥50%) of treated nodules observed on response evaluation CT/MRI images obtained 1-3 months after ≥2 consecutive TACE sessions (despite changing chemotherapeutic agent or reanalyzing the feeding artery); (ii) increased number of intrahepatic lesions from the previous TACE session observed on response evaluation CT/MRI images obtained 1-3 months after ≥ 2 consecutive TACE sessions; (iii) no decrease in tumor marker level is observed immediately after TACE, or only a minimal and transient decrease is observed after TACE, immediately followed by an increasing trend; and (iv) development of vascular invasion and/or extrahepatic spread (**Table 2**) [32]. The above criteria are often met in cases with tumor burden, including multiple tumors or those with high histological malignancy.

Table 2. Definition of TACE Failure/Refractory.

Residual enhancement (≥50%) after ≥2 consecutive TACE
Increased tumor number at 1–3 months after ≥2 consecutive TACE
No decrease in tumor marker level immediately after TACE
Development of vascular invasion and/or extrahepatic spread

2. Techniques

Importance of achieving complete response (CR)

Historically, achieving CR through TACE has been associated with prolonged overall survival of HCC patients including those in early-stage [33]. Notably, recent findings indicate that achieving CR also demonstrates a positive impact on patients with intermediate-stage HCC reported from Korea [3]. TACE is aimed at achieving a targeted survival duration of 2.5 years in BCLC criteria. In the Korean report, the 2.5-year (30-month) survival rate for those achieving CR was approximately 80%, in stark contrast to non-CR patients who exhibited a survival rate of about 30%, highlighting a significant difference. Therefore, the key lies in comprehending and refining techniques that optimize the probability of achieving CR in TACE, with enhancing overall treatment efficacy and patient outcomes. It was reported that hypoxia induced by TACE changes tumor microenvironments, triggering processes such as the stimulation of vascular endothelial growth factor (VEGF), which promotes tumor progression [34, 35]. In addition, the stress by chemotherapeu-

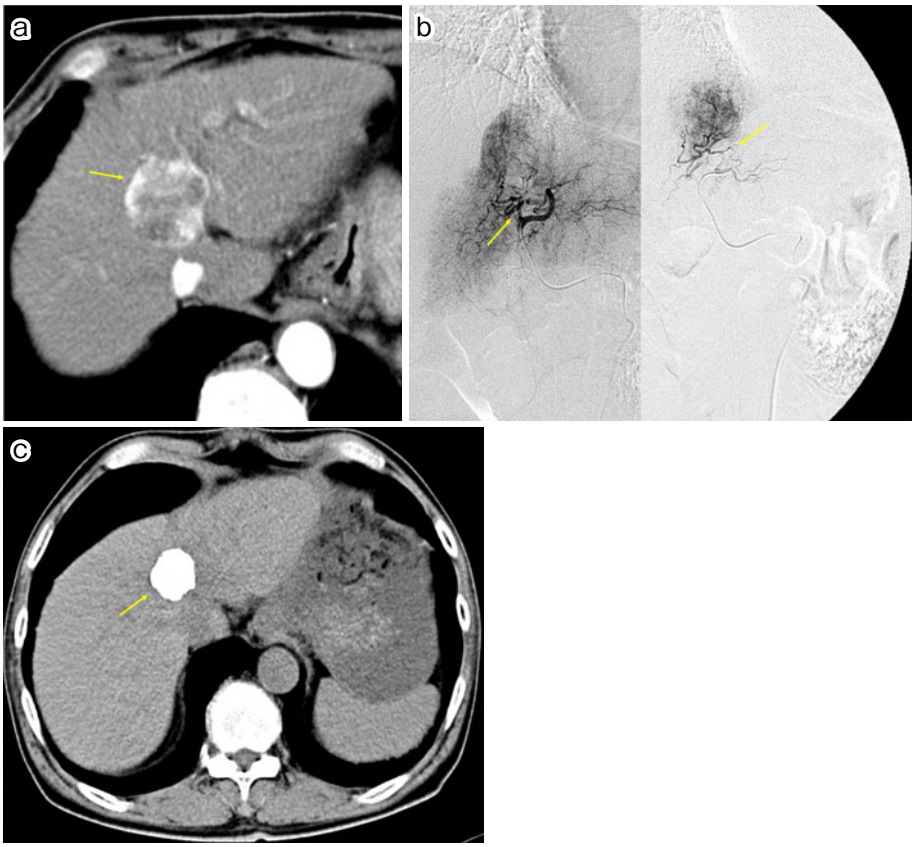

Figure 3. Superselective TACE.
a. HCC is located in the liver segment 4.
b. A microcatheter was inserted into A4 arising from the left hepatic artery and cTACE was performed.
c. CT 3 months after TACE showed well lipiodol accumulation in the tumor.

tics and hypoxia on tumor cells also changes the surviving tumor cells to "sarcomatous appearances" and "hepatocholangiocellular phenotypes"[36, 37]. Thus, the preference is to attain a CR to avoid the presence of the residual tumors following TACE.

Superselective catheterization

Superselective TACE is defined as administering TACE at the most distal part of the artery supplying the tumor (**Fig. 3**). Currently, nonselective TACE is not tolerated due to its low curative rate and adverse effects on liver function; thus, superselective TACE is demanded. Many studies have previously highlighted the potent therapeutic effects of superselective TACE [38]. Golfieri, et al. reported that selective or superselective TACE was more successful than lobar procedures in achieving complete histological necrosis in preliver transplantation patients [39]. Yamakado et al. reported that selective TACE contributes to survival in patients with HCCs [40]. Superselective TACE should be undertaken not only to achieve an antitumor effect but also to prevent damage to the liver parenchyma, thereby minimizing the deterioration of hepatic function. Superselective TACE is possible not only for single- or few-nodule cases but also for multiple lesions. In cases with relatively few tumor nodules, superselective catheterization is performed for each nodule's feeding vessel. Conversely, when multiple nodules are present within the same segment or subsegment, selective TACE is applied to the affected areas. Therefore, the number of tumor-containing segments or subsegments is critical for maximizing TACE efficacy. According to international expert opinion, achieving CR with TACE is feasible when fewer than two segments are involved [41].

Recent advancements in devices have enabled the refinement of superselective TACE procedures. For example, the development of a microcatheter with a flexible and small tip, i.e., 1.5 to 1.7 French, facilitates easier insertion into small and angulated arterial branches. This technological enhancement has further improved the precision and success of superselective TACE, offering better outcomes [11].

Alternative techniques in cases of impossible superselective catheterization

When a microcatheter cannot be successfully inserted into the tumor-feeding branches, it becomes crucial to explore alternative techniques. One approach involves embolizing the distal branches of normal liver tissue beyond the orifice of the tumor-feeding branch with a large-sized gelatin sponge. Following this temporary protection, a lipiodol emulsion is injected. An alternative protective method uses a microballoon catheter. This involves inserting a microballoon catheter

through another access route, inflating the balloon at the distal portion, and subsequently injecting a lipiodol emulsion from the proximal site of the balloon (**Fig. 4**) [42]. To execute distal protection with a single catheter, a specialized microballoon catheter with a side hole has been developed (LOGOS SWITCH; Piolax Medical Devices, Yokohama, Japan). This catheter is introduced into the targeted artery, and the balloon at the catheter tip is inflated, allowing the injection of the lipiodol emulsion through the side hole (**Fig. 5**).

TACE navigation images

TACE navigation images are typically generated through the use of hybrid angio-CT or C-arm cone-beam CT (CBCT) in the TACE procedure. These modalities allow for the acquisition of CT images, facilitating the creation of navigation images that play a crucial role in guiding TACE procedure. CT during hepatic arteriography (CTHA) is instrumental in generating high-resolution three-dimensional (3D) reconstruction images, providing valuable guidance during TACE. The process of identifying responsible branches from reconstructed vessels on workstations can be done manually by marking vessels adjacent to tumors on thin-slice multi-sectional images. The CTHA navigation image proves to be advantageous in TACE procedures by offering a clear visualization of the tumor's location and its feeding arteries. By strategically selecting the working angle, this method maximizes the visualization of tumor-feeding arteries while minimizing overlap with adjacent blood vessels or branches. This approach provides a comprehensive view of the targeted arteries, aiding in precise diagnosis and treatment planning (**Fig. 6**). The integration of novel TACE guidance software incorporates automated tumor-feeder detection (AFD). Recent reports by Miyayama et al. highlighted that AFD-assisted TACE can reduce procedural time, radiation exposure, and contrast material usage [43]. Moreover, it demonstrated improved therapeutic effects in superselective TACE. Obtaining 3D safety margin is one of the important factors to obtain curability [44]. Therefore, by using TACE navigation images, the branches supplying into adjacent to the tumor should also be embolized [45].

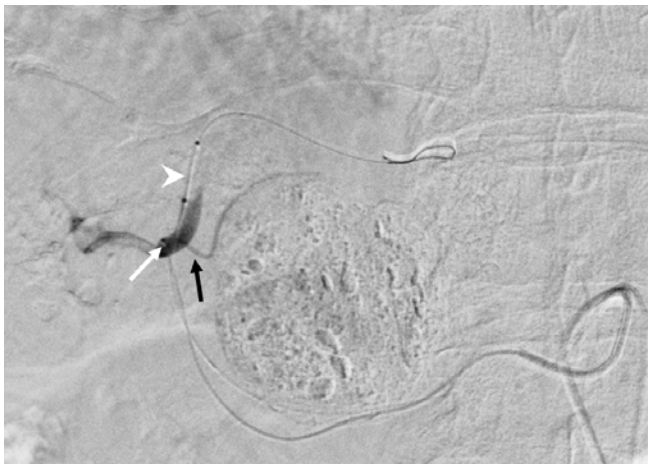

Figure 4. Distal protection technique with a microballoon catheter.
A microballoon catheter was inserted via the right femoral artery and the balloon was infiltrated at the left hepatic artery (arrowhead). A microcatheter inserted via the left femoral artery and the catheter tip was located at the proximal site of the balloon (white arrow). The targeted branch (A1) was well depicted (black arrow) and cTACE was performed.

Preparation of lipiodol emulsification for conventional TACE (cTACE)

Creating ideal water-in-oil (W/O) emulsion could contribute to higher response rate. We need to learn about these advantage and drawbacks based on created emulsions. W/O emulsion has several advantages compared with oil-in-water (O/W): high embolic effect, high drug capacity, and longer drug release time [46]. Uniform and small droplet size has

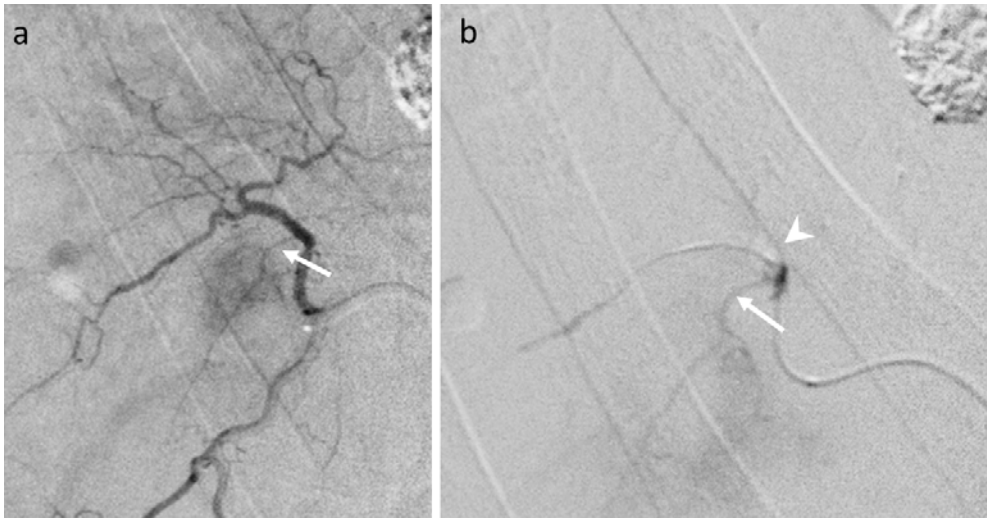

Figure 5. Distal protection technique with a microballoon catheter with a side hole.
a. HCC was supplied via a tiny branch of the right hepatic artery (arrow).
b. A microballoon catheter with a side hole was inserted and the balloon was infiltrated at the right hepatic artery (arrowhead). Targeted branch was well depicted (arrow) and cTACE was performed.

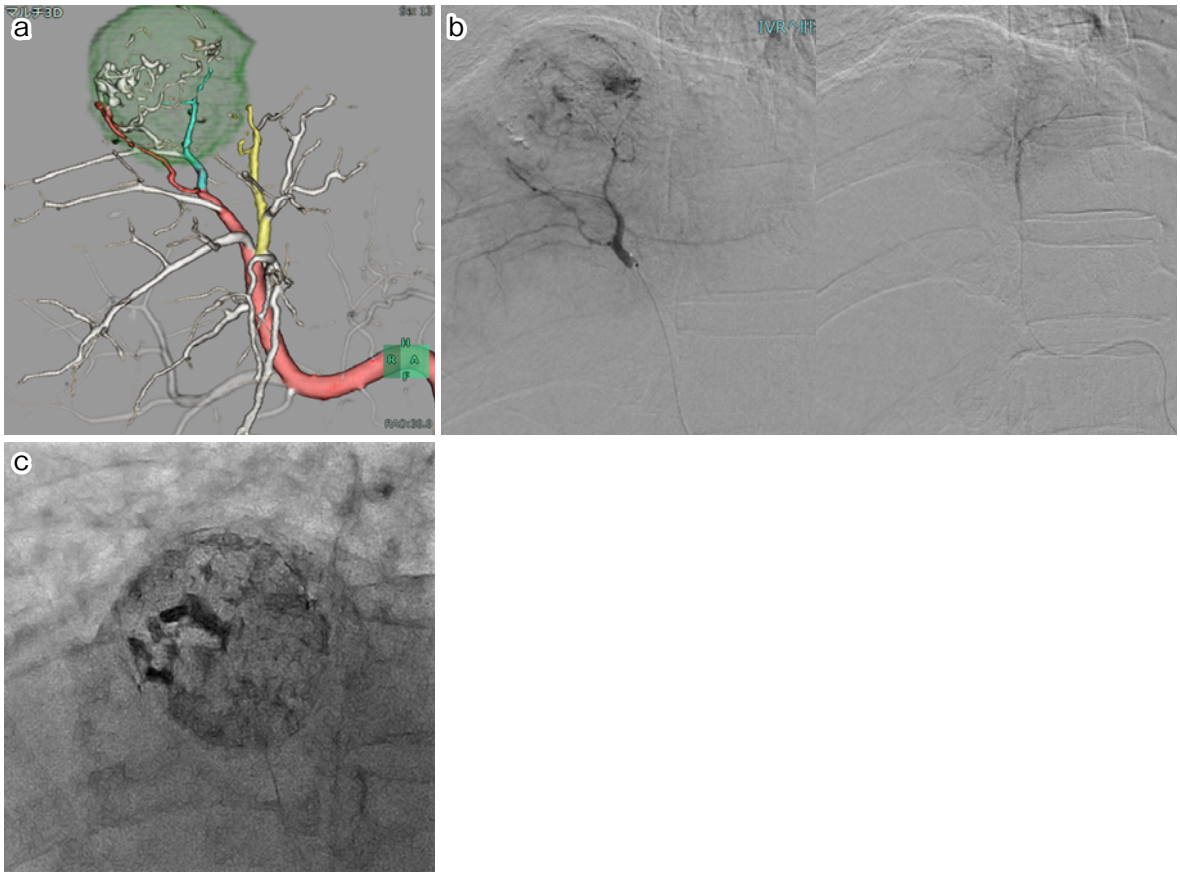

Figure 6. TACE navigation image.
a. A three-dimensional reconstruction image created from CT during hepatic arteriography (CTHA) revealed three feeding branches to the tumor. The right anterior oblique (RAO) 30° view provided the optimal working angle for clear separation of each branch.
b. A microcatheter was inserted into each branch using the same C-arm angle view and cTACE was performed.
c. Lipiodol was well accumulated in the tumor.

advantage of the stability and high viscosity with longer retention in tumor. The worldwide consensus technique of cTACE is mixing of lipiodol and doxorubicin solution by pumping using two syringes through a three-way cock. This technique was first developed in the 1980s and has been used for more than 30 years [47]. A technical recommendation for cTACE, published in 2015, proposed several key guidelines such as (i) maintaining a drug aqueous solution volume lower than the volume of lipiodol (1:2 or 1:3 ratio), (ii) using a contrast medium for the preparation of doxorubicin aqueous solution, and (iii) ensuring a minimum of 20 pumping exchanges through the stopcock [48]. In addition, an experimental study showed that pumping speed 1 s per 1 push was one of the key factors [49]. However, this pumping technique using a three-way cock has some limitations. W/O is created only about 70% and the droplet size is various. To improve the properties of lipiodol emulsion, a pumping emulsification device with a microporous glass membrane (MicroMagic; Piolax Medical Devices) was developed [50]. Using this device, almost pure (98%) W/O emulsion with uniform droplet size can be created (**Fig. 7**). An ex vivo and in vivo studies demonstrated pharmacokinetic advantages of using device, slower release speed to systemic circulation, and higher tumor concentration of epirubicin [51, 52]. Moreover, an animal and a clinical study demonstrated higher tumor necrosis ratio and lower local recurrence ratio by using MicroMagic® compared with using three-way stopcock (**Table 3**) [52, 53].

Selection of anticancer drugs

Despite the absence of conclusive evidence about the efficacy of anticancer drugs, TACE, involving the infusion of embolic materials mixed with anticancer drugs, has become a widely adopted standard procedure. Among the commonly employed anticancer drugs, anthracycline agents such as doxorubicin and epirubicin are frequently used, along with mitomycin and cisplatin [54]. Doxorubicin and epirubicin exhibit high solubility, 100 mg of which are capable of being dissolved in 1.5 mL of water. A specific gravity adjustment is crucial in cTACE, achieved by preparing a mixture of 300 mgI/mL contrast material and saline in a 4:1 ratio, resulting in a similar specific gravity to lipiodol (1.270-1.292). This adjustment prevents the separation of the created emulsion. In Japan, cisplatin fine powder (IA-Call; Nippon Kayaku, Tokyo) is available. Results from a randomized control trial comparing the suspension of cisplatin powder and the emulsion of epirubicin solution showed no discernible differences [55]. In dissolving the cisplatin powder in a

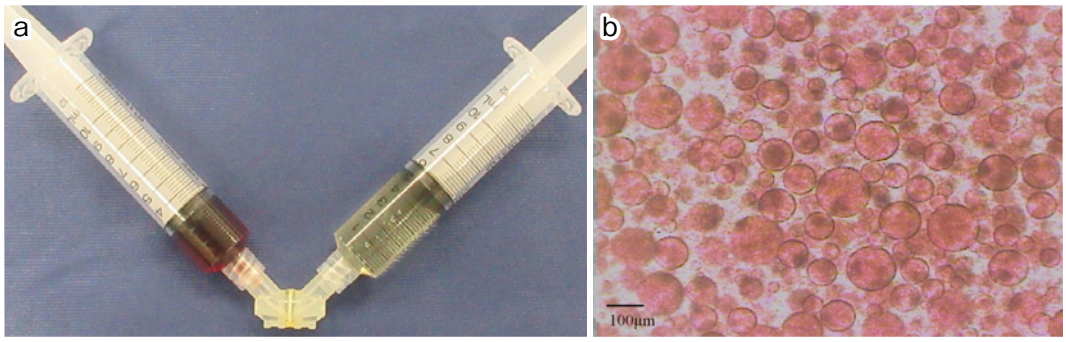

Figure 7.
a. Pumping emulsification device (MicroMagic®): This device features a disk-shaped glass membrane with 100 μm micropores, positioned between syringe adapters. The membrane surface is coated with a hydrophobic silicon layer, facilitating the dispersion of the epirubicin solution into the lipiodol in droplet form.
b. Water-in-oil emulsion created by glass membrane pumping device.

Table 3. Optimal Techniques to Form Ideal Lipiodol Emulsion.

Solvent of epirubicin	300 mgI/mL contrast material and saline in a 4:1 ratio
Epirubicin solution volume	1/2–1/3 of the lipiodol volume
Pumping exchange	20 times (push and back)
Pumping speed	1 sec/1 push
Pumping device	Glass membrane device, MicroMagic® > three-way stopcock

contrast agent, it is necessary to recognize that the dissolvability of the cisplatin powder is limited, which produce 100% O/W due to Pickering phenomenon [56]. Miriplatin (MIRIPLA®; Sumitomo Dainippon Pharma, Japan), a third-generation lipophilic platinum derivative, is also accessible in Japan. Miriplatin suspension exhibits a gradual release of an active platinum drug, ensuring a persistent antitumor effect [57]. However, there is no evidence supporting the superiority of miriplatin over epirubicin [58].

Injection techniques in cTACE

In cTACE, the administration of lipiodol emulsion necessitates a gradual injection using a small syringe, such as 1 mL syringe. The continuous injection of the emulsion can lead to early stasis attributed to its viscosity. To avoid the early stasis, alternating injections of lipiodol emulsion with lidocaine is useful. Intraarterial lidocaine is also useful for relief of pain [59]. The endpoint of the injection should be achieving the portal vein visualization. Miyayama et al. reported that there was a relationship between local recurrence and portal vein visualization. The 2-year recurrence ratios were 16% and 66% in PV visualization grade 2 (visualized segmental level) and grade 0 (no visualization), respectively [11]. Even with the application of the aforementioned techniques, such as slow and alternative injection with lidocaine, achieving an adequate volume of lipiodol may be a challenge especially in small and nonhypervascular tumor. In such cases, the utilization of "semiwedged technique" becomes valuable. This involves further advancement of the microcatheter under semiwedged conditions, allowing for forceful injection and preventing the overflow of the emulsion (**Fig. 8**). Injection of a sufficient volume of lipiodol is crucial for achieving complete tumor necrosis. The volume of lipiodol injected (in mL) should exceed the tumor's diameter (in cm); for example, it is recommended to inject more than 3 mL of lipiodol into a tumor with a diameter of 3 cm [60]. A single cTACE procedure can target nodules up-to approximately 5-6 cm in diameter because the amount of lipiodol used in a single session is 10 mL. For larger HCCs, the approach is to perform drug-eluting beads (DEB)-TACE or bland transarterial embolization (TAE) using gelatin particles or microspheres to reduce tumor blood flow followed by a staged cTACE (**Fig. 9**)[61]. The split TACE technique involving multiple cTACE session was also reported [62].

It was reported that miriplatin suspension more frequently caused local recurrence after TACE than epirubicin and mitomycin emulsion [63]. Miriplatin is often stagnant in a proximal portion of tumor-feeding arteries due to a dilatant fluid behavior of the suspension of hydrophobic particles in oil. The characteristics of miriplatin, such as very slow release of active platinum (5.9% at 28 days after incubation) and less damage to the artery, might also cause frequent local tumor recurrence [57, 63]. Warming technique is reported to reduce the viscosity to 22 cP at 40℃, which is much low than that of epirubicin-lipiodol emulsion of 120 cP at room temperature [64].

Efficacy of balloon-occluded TACE (B-TACE) was reported. B-TACE could perform forceful injection to infuse more volume of lipiodol and may also enhance treatment success, due to its ability to redistribute flow toward lower resistance vascular territories [65]. Superiority of B-TACE using cisplatin/lipiodol over cTACE in achieving higher CR ratios and longer PFS in medium size HCC (>3 cm) was re-

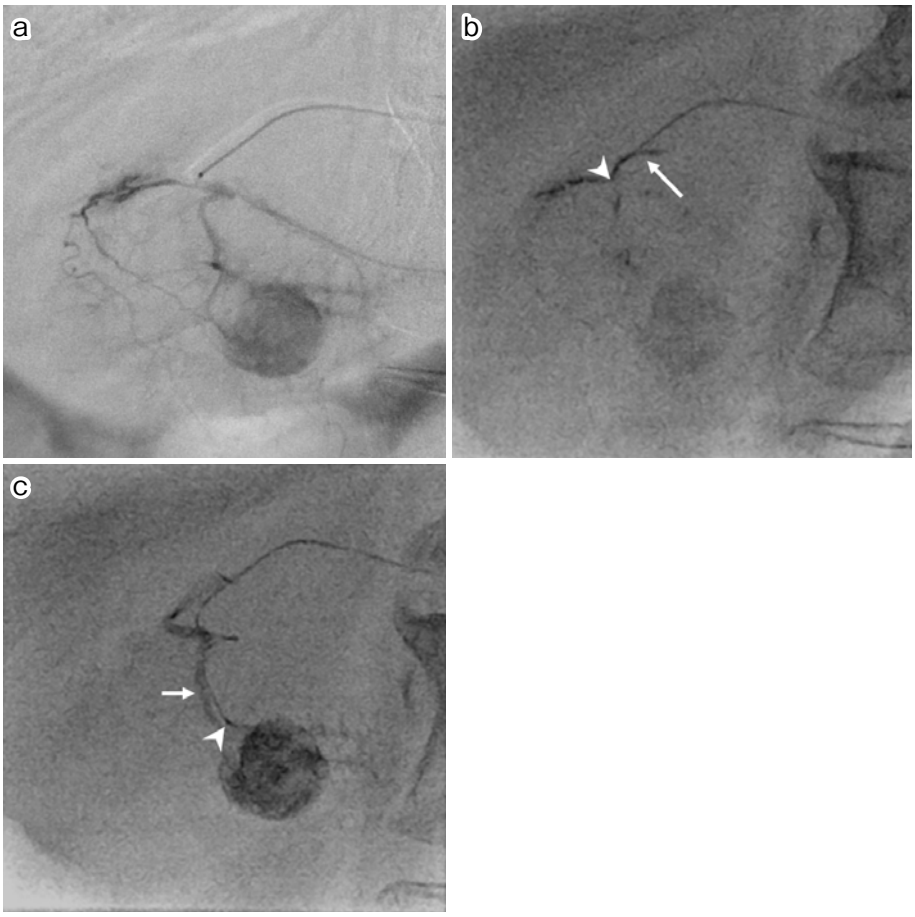

Figure 8. Semiwedged technique.
a. HCC located in segment 2 of the liver supplied by a branch of A2.
b. Lipiodol emulsion was injected from the tumor-feeding branch (arrowhead). Overflow to the proximal site was observed during injection (arrow).
c. The microcatheter was advanced further, and lipiodol emulsion was injected under semiwedged conditions to allow for forceful injection while preventing overflow. Subsequently, the portal vein was visualized.

ported [66]. However, in small lesions (<3 cm), cTACE demonstrated higher CR rate than B-TACE [67]. B-TACE seem to employ a similar concept with the "semiwedged technique," which aimed at achieving a forceful injection of lipiodol emulsion into the targeted tumor. However, there are differences in the positioning of the catheter tip; B-TACE is typically performed at a more proximal site, potentially resulting in a wider embolization area. Therefore, B-TACE requires careful monitoring to avoid liver function deterioration and bile duct injury (**Fig. 10**).

Preparation of drug-eluting microspheres

DC beads (Boston Scientific, Marlborough MA, USA) are most frequently used in DEB-TACE in Japan, composed of polyvinyl alcohol (PVA) with an augmented sulfo group (SO3-) to establish a negative charge. This design facilitates the absorption of positively charged drugs, such as anthracycline-based anticancer agents, through ion exchange. As similar products, TANDEM (Varian) and LifePearl (Terumo) are available outside Japan. HepaSphere (Merit Medical, South Jordan, Utah) is a unique product that is a hydrophilic copolymer with the property of expansion by the absorption of water and expands approximately four times larger than original sizes in the dry stage.

For DC beads with sizes of 100-300 μm, it takes 30 min for the impregnation of 90% of doxorubicin and 60 min for 98% impregnation. The loading speeds are similar among the products, but microspheres' size is a factor of the loading speeds [68]. Using a vortex mixer during the impregnation process can enhance drug loading speed [69]. However, it should be recognized that shaking for over 30 s could cause the beads to fracture (**Fig. 11a**). Moreover, 37-50 mg of doxorubicin can be loaded on 1 mL microspheres' volume [68].

Injection techniques in DEB-TACE

Dilution and slow injection are the key techniques of microsphere injection to prevent early stasis. Despite the small size of microspheres, there is a tendency for them to aggregate, leading to unforeseen early stasis. To counter this, the microspheres are mixed with a contrast material diluted 10-30 times in volume [70]. In addition, the diffusion of micro-

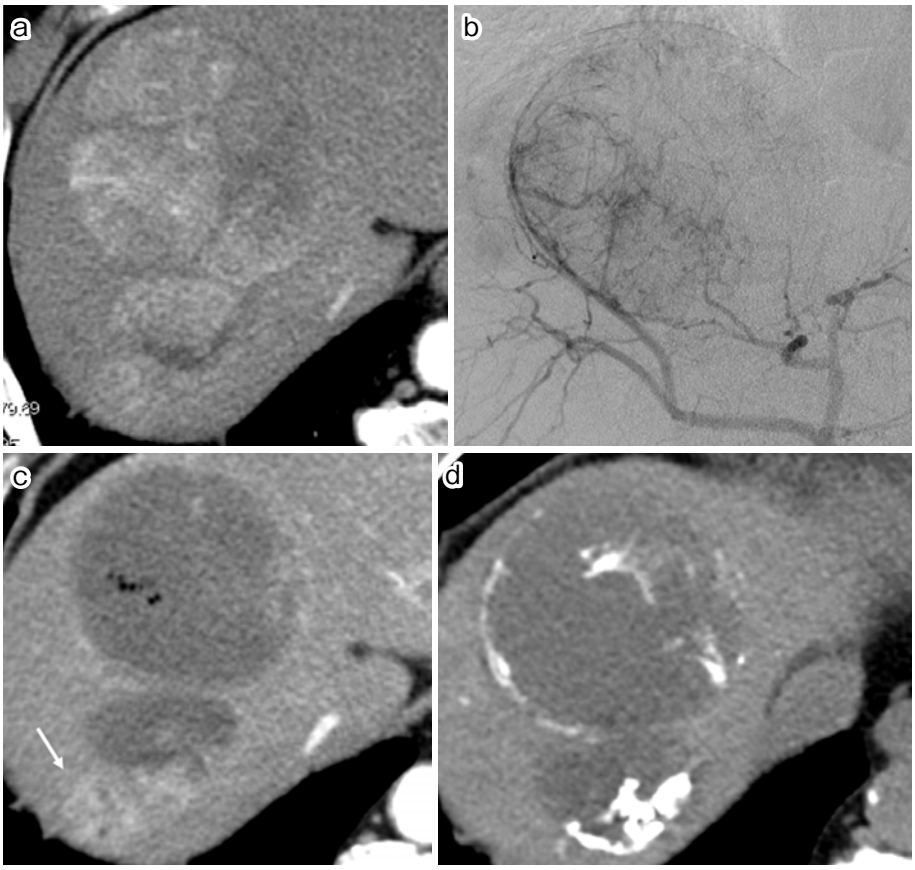

Figure 9. Bland TAE followed by cTACE for huge HCC (beyond Up-to-11).
a. Huge HCC 11 cm in diameter (three nodules) located in the liver right lobe.
b. Bland TAE was performed using microspheres (Embosphere®) 100 to 300 μm in size.
c. Contrast-enhanced CT at 3 weeks after the bland TAE showed large part of the tumor became necrosis, but in the dorsal side residual tumor presented (arrow).
d. cTACE was performed for the residual viable tumor. The noncontrast-enhanced CT showed that the lipiodol accumulation was obtained and complete response was achieved.

spheres in the syringe is crucial and can be facilitated by regularly shaking the syringe and adjusting the density of the mixed contrast material. Epirubicin-loaded DC bead has a density almost equivalent to that of a 180 mgI/mL contrast material. Consequently, we employ a dilution contrast by mixing 300 mgI/mL contrast with saline in a ratio of 3:2. This technique is vital for maintaining the diffusion of microspheres in the syringe, thereby preventing their aggregation (**Fig. 11b**). Vascular lake more frequently occurs in DEB-TACE, which achieved better tumor response [71]. In a case with vascular lake appeared during microsphere injection, the corresponding branch of the vascular lake should be embolized using large-sized microspheres or gelatin particles.

Selection of cTACE or DEB-TACE

There is a difference in mechanism between cTACE and DEB-TACE. Lipiodol and the emulsion of anticancer drugs are liquid with a viscosity of around 150 cP, and it is known that they reach not only the inside of the tumor but also the surrounding sinusoids and portal vein when injected into the tumor's nutrient blood vessels, which can necrotize the peritumoral area including capsular invasion through a portal venous flow block around the tumor [72]. However, beads, although their behavior differs between hard DC beads® and easily deformable Hepaspheres®, are solid particles with a certain particle size and have a limited embolization reach, remaining inside the tumor's arteries [73]. A recent randomized controlled trial demonstrated that curability is higher in selective cTACE than in selective DEB-TACE. The CR rate at 3 months after TACE was 75.2% in cTACE versus 27.6% in DEB-TACE [74]. DEB-TACE is preferable for patients with poor liver function, advanced age, or poor performance status [75]. The postembolization syndrome, as well as elevated AST and ALT levels, is notably milder with DEB-TACE [76]. There are also reports on the safety of DEB-TACE in cases of poor performance status [77]. However, the occurrence of biloma or AP shunt is more common with DEB-TACE [78, 79].

TACE combined with systemic therapy

In recent times, the strategy of combining TACE with molecular targeted drugs has attracted significant attention. Notably, the TACTICS trial highlighted that adding sorafenib to TACE led to better PFS than TACE alone [80]. The later TACTICS-L trial showed that combining lenvatinib

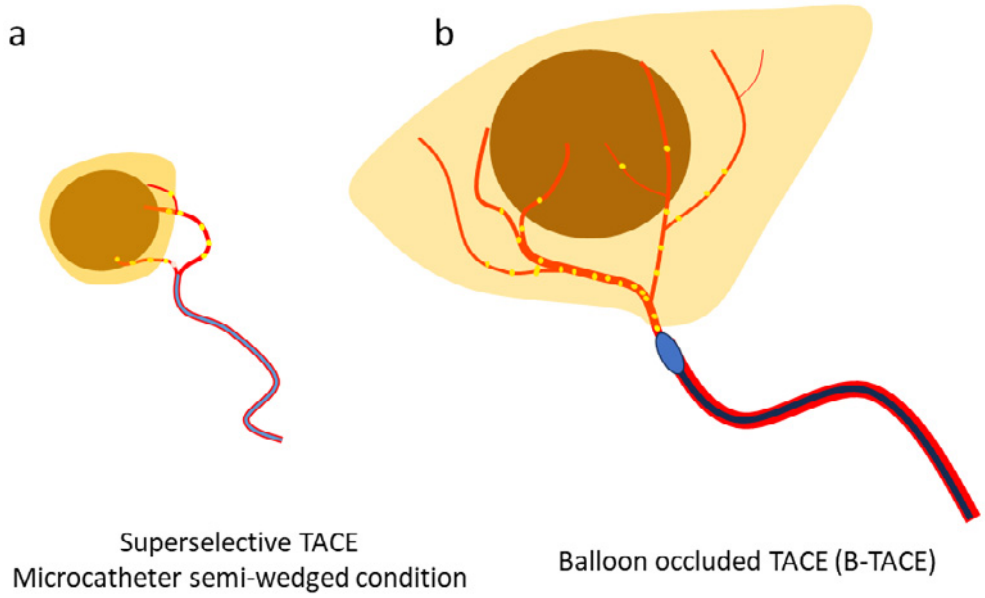

Figure 10. Schemas of superselective TACE with "semiwedged technique" and balloon-occluded TACE (B-TACE).
a. Superselective TACE with "semiwedged technique": A microcatheter is placed at the periphery of the tumor-feeding artery, allowing for controlled injection of lipiodol emulsion under semi-wedged conditions. This technique ensures adequate distribution of lipiodol emulsion within the tumor and its peritumoral surroundings.
b. B-TACE: A microballoon catheter is positioned at the segmental level, enabling injection of lipiodol emulsion under balloon-inflated conditions. This method facilitates forceful injection of lipiodol emulsion, although attention must be paid to potential liver parenchymal damage depending on tumor location and catheter position.

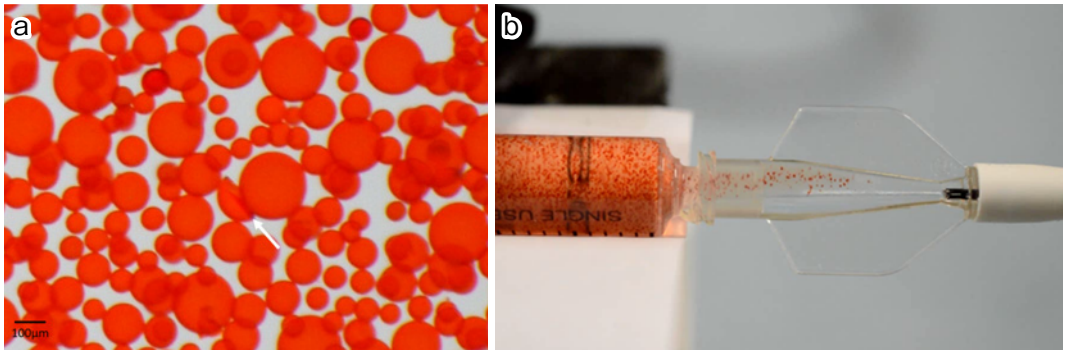

Figure 11. Preparation and injection techniques of drug-eluting beads (DEB)-TACE.
a Epirubicin-loaded DC bead (100–300 μm) prepared by shacking on vortex mixer for 30 s. A fractured bead is observed (arrow).
b Epirubicin-loaded DC beads (100–300 μm), mixed with diluted contrast material (180 mgI/mL), are injected through a microcatheter. The microspheres are dispersed within the syringe and the hub of the microcatheter.

with TACE resulted in a CR rate of 53.2% post-TACE and long PFS [81]. This CR rate surpassed the 28% observed in the TACE plus sorafenib group from the TACTICS trial, highlighting the potent synergistic effect when TACE is combined with lenvatinib. In addition, a high CR rate of 59.1% was observed in patients beyond the Up-to-7 criteria and 63.0% in cases with nonsingle nodules, such as multinodular, infiltrative, or diffuse tumors. Administering lenvatinib prior to TACE may normalize the tumor-feeding vessels, potentially enhancing drug distribution within the tumors. This effect can be achieved with a short-term administration of lenvatinib for 4 days, as confirmed by clinical and animal studies [82-85]. Lenvatinib helps prevent the surge in VEGF—a protein that promotes angiogenesis—typically triggered by TACE [86]. These results suggest that combining TACE with lenvatinib (LEN-TACE) could expand its indications to include cases of high tumor burden, such as beyond Up-to-7 criteria and those with nonsingle nodular

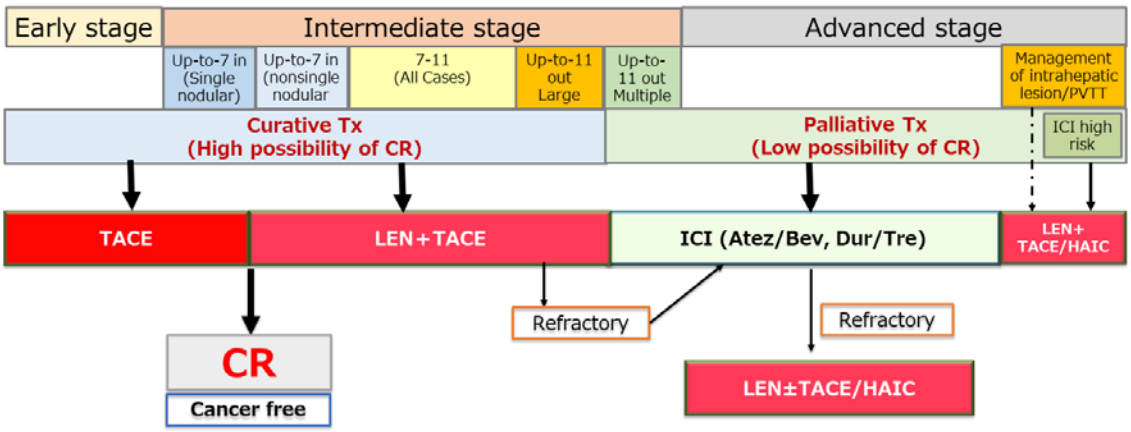

Figure 12. Treatment strategy of intermediate- and advanced-stage HCC.
LEN-TACE can be applied to most intermediate-stage and a portion of advanced-stage HCC with the goal of achieving CR.
Large, large tumor; Multi, multiple tumors; PVTT, portal vein thrombus; ICI, immune checkpoint inhibitor; Atez/Bev, atezolizumab/bevacizumab; Dur/Tre, durvalumab/tremelimumab

type HCC. The LAUNCH study provided further evidence, showing that the combination of TACE and lenvatinib led to significantly longer survival and slower disease progression than lenvatinib alone in patients with advanced-stage HCC [87]. Although the current first-line therapies for advanced-stage HCC are atezolizumab/bevacizumab or durvalumab/tremelimumab, locoregional therapy such as LEN-TACE also shows promise for treating advanced HCC. Hepatic arterial infusion chemotherapy (HAIC) has shown enhanced effects when combined with lenvatinib (LEN-HAIC). The LEOPARD study demonstrated a high response ratio and longer PFS and OS [88]. These results support the use of LEN-TACE for most intermediate-stage HCC, except in cases with more than 11 multiple nodules, and also for a subset of advanced-stage cases, as well as LEN-HAIC (**Fig. 12**).

Combination of TACE and immunotherapy is also promising [89]. TACE could influence microenvironments of tumors [90-92]. Several clinical trials are currently ongoing to evaluate this combined therapy. For example, the EMERALD-1 trial showed improved PFS with a combination of TACE, durvalumab, and bevacizumab than TACE alone [93]. Ongoing trials such as LEAP-012 and TALENTACE, which are testing combinations of lenvatinib with pembrolizumab and atezolizumab with bevacizumab, respectively, alongside TACE, are in phase III [94,95]. These outcomes could potentially change recommended treatment strategies in future guidelines. Expanding the indications for TACE by combining it with ICIs and MTAs is a promising prospect.

Conclusion

In subclassifying intermediate-stage HCC, several criteria have been proposed, such as Up-to-7, Up-to-11, 7-11, and Nr-11 criteria, which could be viable for determining the suitability of TACE. It is crucial to tailor treatment plans to the specific tumor burden and malignancy potential of each case. Achieving CR is critical; thus, choosing between cTACE and DEB-TACE and mastering appropriate techniques are essential. Advances in imaging technologies and the development of new devices are set to standardize and enhance the precision and effectiveness of TACE. The development of combination strategies that integrate TACE with ICIs and MTAs is promising. These combinations are expected to expand the indications for TACE and improve the overall prognosis for HCC patients.

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