

## Consensus Statement

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# A Changing Paradigm for the Treatment of Intermediate-Stage Hepatocellular Carcinoma: Asia-Pacific Primary Liver Cancer Expert Consensus Statements

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## Keywords

Asia-Pacific Primary Liver Cancer Expert · Hepatocellular carcinoma · Intermediate stage · Systemic therapy · Transarterial chemoembolization

## Abstract

The Asia-Pacific Primary Liver Cancer Expert (APPLE) Consensus Statement on the treatment strategy for patients with intermediate-stage hepatocellular carcinoma (HCC) was established on August 31, 2019, in Sapporo, Hokkaido during the 10th Annual APPLE Meeting. This

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manuscript summarizes the international consensus statements developed at APPLE 2019. Transarterial chemoembolization (TACE) is the only guideline-recommended global standard of care for intermediate-stage HCC. However, not all patients benefit from TACE because intermediate-stage HCC is a heterogeneous disease in terms of tumor burden and liver function. Ten important clinical questions regarding this stage of HCC were raised, and consensus statements were generated based on high-quality evidence. In intermediate-stage HCC, preservation of liver function is as important as achieving a high objective response (OR) because the treatment goal is to prolong overall survival. Superselective conventional TACE (cTACE) is recommended as the first choice of treatment in patients eligible for effective (curative) TACE, whereas in patients who are not eligible, systemic therapy is recommended as the first choice of treatment. TACE is not indicated as the first-line therapy in TACE-unsuitable patients. Another important statement is that TACE should not be continued in patients who develop TACE failure/refractoriness in order to preserve liver function. Targeted therapy is the recommended first-line treatment for TACE-unsuitable patients. Especially, the drug, which can have higher OR rate, is preferred. Immunotherapy, transarterial radioembolization, TACE + targeted therapy or other modalities may be considered alternative options in TACE-unsuitable patients who are not candidates for targeted therapy. Better liver function, such as albumin-bilirubin grade 1, is an important factor for maximizing the therapeutic effect of systemic therapy.

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## Introduction

Transarterial chemoembolization (TACE) is the only guideline-recommended global standard of care for intermediate-stage hepatocellular carcinoma (HCC). However, not all patients benefit from TACE because intermediate-stage HCC is a very heterogeneous disease in terms of tumor burden and liver function [1–3]. Therefore, new treatment strategies for bilobar multinodular disease or large tumors are required.

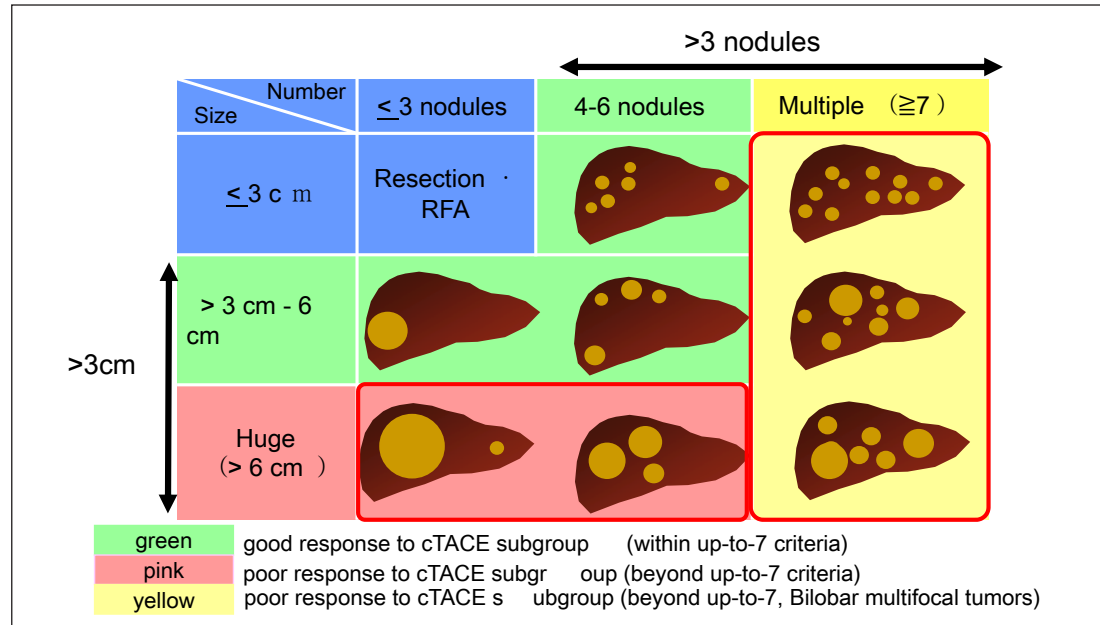
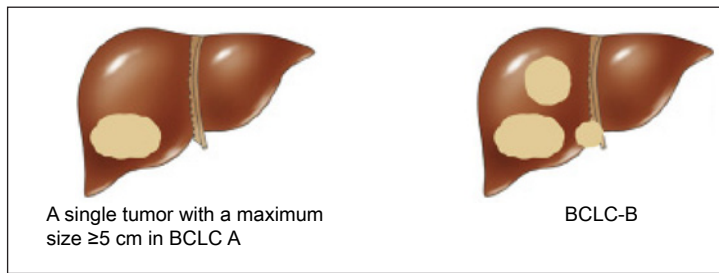
The recent approval in 2019 of ramucirumab, cabozantinib, and pembrolizumab for treatment of HCC increased the number of molecular targeted agents/immune checkpoint inhibitors available in clinical practice to 7: lenvatinib and sorafenib as first-line agents, and regorafenib, cabozantinib, ramucirumab, nivolumab, and pembrolizumab as second-line agents [4–11]. Optimal patient selection in intermediate-stage HCC is therefore crucial to maximize efficacy of treatment and overall survival (OS); however, this is not that easy in clinical practice.

The objective of the Asia-Pacific Primary Liver Cancer Expert (APPLE) Consensus Meeting was planned to suggest or to recommend the optimal treatment options for intermediate-stage HCC from a scientific standpoint; therefore, country-specific issues such as healthcare insurance or approval status were not considered.

Unlike the original Barcelona Clinic Liver Cancer (BCLC) staging system, the APPLE Consensus defined intermediate-stage HCC as follows: (i) a single tumor with a maximum size  $\geq 5$  cm in BCLC stage A or (ii) BCLC stage B because these tumor types are both good candidates for TACE in unresectable HCCs (Fig. 1).

The APPLE Consensus Statement was developed based on the principles of modern oncology to better explain the rationale and provide recommendations that can be applied internationally, albeit with the necessary adjustments to the situation in each country.

**Fig. 1.** Definition of intermediate-stage HCC used in this manuscript. In this APPLE consensus meeting, intermediate-stage HCC was defined as: (i) a single tumor with a maximum size of  $\geq 5$  cm in BCLC A; and (ii) BCLC B stage HCC. BCLC, Barcelona Clinic Liver Cancer.



**Fig. 2.** Heterogeneity of intermediate-stage HCC and grade of response to TACE in each subgroup. cTACE, conventional transarterial chemoembolization.

## Methodology

The APPLE Consensus Statements focused primarily on intermediate-stage HCC. Prior to the APPLE Consensus Meeting, several important clinical questions on the treatment of intermediate-stage HCC were raised, and published articles with high evidence related to those clinical questions were collected. Recommendations or consensus statements were then created. These clinical questions, along with consensus statements, were circulated to all panel members by email. To finalize the consensus statements, a pre-consensus meeting was held in Osaka in May 2019 in which after extensive discussion, corrections were made to the content and wording.

A final set of clinical questions and corresponding consensus statements was presented by each expert at the consensus meeting session at the APPLE Meeting held on August 31, 2019, in Sapporo. After each presentation of consensus statements and supporting literature, there was extensive discussion with the audience about the statements. Panel members addressed all questions, and additional changes were made to the wording of statements based on consensus between panel members and the attending audience/experts.

The literature supporting each statement is provided in the references section of this manuscript. Online supplementary Table 1 (for all online suppl. material, see [www.karger.com/doi/10.1159/000507370](http://www.karger.com/doi/10.1159/000507370)) lists all members of the APPLE Expert Consensus panel.

*Treatment Concept for Intermediate-Stage HCC (CQ1, 2)*

Achieving a high objective responses (OR) and preserving liver function are equally important to prolong OS with good quality of life in HCC [12]. Intermediate-stage HCC is an extremely heterogeneous disease in terms of (i) liver function, (ii) tumor size, and (iii) tumor number [13]. More precisely, liver function varies widely according to Child-Pugh class, from A5 to B9; tumor size varies from  $\geq$  a few mm to huge ( $>10$  cm); and the number of nodules varies from 2 to  $>100$ . Despite such extreme heterogeneity, TACE is the only standard of care recommended by guidelines worldwide [14–17] (Fig. 2).

TACE is not beneficial for 3 subgroups of patients with the following characteristics: (i) conditions that easily become refractory to TACE; (ii) conditions in which TACE causes deterioration of hepatic functional reserve to Child-Pugh class B; and (iii) conditions that are unlikely to respond to TACE (TACE-resistant tumor). Intermediate-stage HCC represents a broad and heterogeneous group of patients, and only a specific subset of the population will benefit from TACE [1–3]. Various systems for the subclassification of intermediate-stage HCC, along with treatment strategies for each substage, have been proposed according to tumor burden and liver function, and patient populations that highly benefit from TACE have been identified [18–21]. For subclassification of intermediate-stage HCC, up-to-7 criteria, which were originally developed for transplantation, are used globally to describe tumor burden [22]. Systemic therapy yields better progression-free survival (PFS) and OR rates (ORR) in patients with intermediate-stage HCC than in those with advanced-stage HCC who had progressed after prior treatment [5, 23, 24]. Selecting the right treatment (TACE or systemic therapy) for the right patient at the right time is important to ensure optimal long-term outcomes for those with intermediate-stage HCC.

Recently, it was revealed that combination therapy of TACE with sorafenib improves clinical outcome [25]. In addition, it should also be kept in mind that the outcome of TACE depends on tumor status and TACE techniques; some of the patients with HCCs beyond up-to-7 criteria may rarely have a good outcome by TACE [26].

**Consensus Statement 1:**

***For intermediate-stage HCC, preservation of liver function is as important as achieving a high OR because the goal of treatment is to prolong OS.***

**Consensus Statement 2-1:**

***Supers elective conventional TACE (cTACE) with curative intent is recommended as the first choice of treatment in patients who are eligible for effective TACE. Systemic therapy is recommended as the first choice of treatment in patients who are not eligible for effective TACE.***

**Consensus Statement 2-2:**

***Other modalities, including combination therapies (TACE plus systemic therapy such as sorafenib), may be considered to improve the efficacy of TACE in both TACE-suitable and -unsuitable patient populations.***

**Consensus Statement 2-3:**

***TACE alone is not indicated as the first-line therapy in TACE-unsuitable patients.***

*Correlation between Tumor Response and OS (CQ 3,4)*

## TACE

A literature-based meta-analysis indicated that OR according to mRECIST has a strong prognostic value in terms of OS [27]. According to the European Association for the Study of the Liver guideline, OR measured by mRECIST predicts OS in patients receiving loco-regional therapies, as reported in a meta-analysis [14]. A sustained response with a duration of 6 months or more is associated with better OS, whereas non-responders have a poor prognosis

**Table 1.** ALBI grade versus Child-Pugh grade/score

	ALBI grade/score	Child-Pugh grade/score
Assessment	Objective	Subjective (ascites and encephalopathy)
Confounding factor	None	Albumin and ascites
Factors, <i>n</i>	2 (Alb, Bil)	5
Frequency of data deficit	Low	High
Continuous variable	Yes	No
Easy to calculate	No (log scale)	Yes

ALBI, albumin-bilirubin.

[28, 29]. Because survival does not differ between non-responders to TACE and untreated patients, TACE is not recommended to be repeated in cases in which OR cannot be achieved by prior TACE [28]. Patients who show a complete response (CR) to initial TACE achieve significantly longer OS, suggesting the importance of achieving CR in the initial TACE procedure. Large (>5 cm) and multiple ( $\geq 4$ ) tumors are associated independently with non-CR after initial TACE [30].

In contrast, non-selective TACE cannot achieve OR and also leads to sarcomatous changes or biliary-mixed type changes, a higher malignant grade, and development of an aggressive type of cancer that does not respond to TACE [31–34].

#### Systemic Therapy

Bridging data from the SHARP and Asia-Pacific trials of sorafenib did not suggest a correlation between OS and response rate [35]. However, 4 prospective trials demonstrated that responders to systemic therapy have significantly better OS than non-responders [36–39]. These studies identified tumor response based on mRECIST as an independent prognostic factor [36–40]. Two studies showed that a landmark analysis excluded guarantee time bias; therefore, OR per mRECIST in systemic therapy is a predictive as well as a prognostic factor. The literature-based meta-analysis suggested that OR per mRECIST has a prognostic value for predicting survival benefit in patients receiving molecular targeted therapy [41].

#### **Consensus Statement 3:**

***Tumor response per mRECIST predicts longer OS in patients receiving TACE, especially initial CR, which can predict a longer survival benefit.***

#### **Consensus Statement 4:**

***Tumor response per mRECIST predicts longer OS in patients receiving systemic therapy.***

#### *Impact of Baseline Liver Function on the Outcome of Systemic Therapy (CQ5)*

Albumin-bilirubin (ALBI) grade is an alternative and more precise measure to assess liver function than Child-Pugh score (Table 1). Multivariate analysis identified ALBI grade 1 as a significant strong predictor of a high ORR, and it is associated with the lowest probability of treatment discontinuation because of adverse events (AEs) [42]. High-grade AEs were observed more frequently in patients with ALBI grade  $\geq 2$  in the sorafenib group of the SUN1120 trial [43]. Also, patients with ALBI grade 1 receiving sorafenib show significantly better OS than those with ALBI grade  $\geq 2$  [44]. In the BCLC B subgroup, patients with ALBI grade 1 treated with sorafenib show significantly better OS than those with ALBI grade 2 [45].



In addition, Ogasawara et al. [46] reported that the prognosis after introducing sorafenib according to the median value of ALBI grade 2, and patients with the better subgrade showed similar prognosis to that of ALBI grade 1. Subsequently, Hiraoka et al. [47] reported modified ALBI (mALBI) grade, which has 2 subgrades divided by the cut-off value of ICG-R15 30% (ALBI score:  $-2.27$ ). The mALBI grade has been reported to have good predictive potential for survival of patients treated with lenvatinib [48, 49]. They described that good therapeutic results with lenvatinib can be expected in patients with mALBI grade 1 and 2a, and that good ALBI score ( $-2.56$ ), which was similar to the cut-off value of ALBI grade 1, was desirable hepatic function at introducing first molecular targeted agents [50].

Subgroup analysis of the REFLECT study revealed that time to the development of Child-Pugh B liver function in both the lenvatinib and sorafenib groups was slower in patients with ALBI grade 1 liver function than in patients with ALBI grade 2 liver function [51].

Several studies suggest that repeated TACE procedures impair liver function. Thus, an early switch or initial use of systemic therapy may be important to maintain liver function and avoid dose reduction/interruption because of AEs; this should improve the overall outcome, including ORR and OS.

**Consensus Statement 5:**

***Better liver function such as ALBI grade 1 and mALBI grade 2a is an important factor for maximizing the effect of systemic therapy.***

*Selective and Non-Selective TACE Procedures (CQ 6,7)*

Selective TACE procedures include selective TACE and superselective TACE, and selective TACE is generally defined as TACE at the segmental hepatic artery and superselective TACE is defined as TACE at the distal portion of the subsegmental hepatic artery.

Superselective TACE (curative TACE) results in significantly better OS than non-superselective TACE (non-curative TACE) [52–55]. After the first TACE procedure, the proportion of patients showing deterioration of liver function is higher in patients exceeding the up-to-7 criteria than in those within the up-to-7 criteria and, in many cases, liver function does not recover to the baseline level [56]. In patients exceeding the up-to-7 criteria, non-selective TACE worsens liver function [57, 58].

HCC cells are mostly fed by the hepatic artery; however, areas of extracapsular invasion, well-differentiated HCC, and satellite nodules are also fed by portal venous flow via the sinusoidal pathway after TACE; therefore, complete tumor necrosis cannot be achieved when only arterial flow is embolized [59]. TACE induces hypoxic and chemotherapeutic stress on HCC cells, and the surviving hypoxic tumors frequently change to sarcomatous or mixed hepatocholangiocellular phenotypes; in addition, it induces vascular endothelial growth factor, which further promotes tumor progression [31, 32, 34]. Moreover, when the artery is impaired, tumor cells can be fed by the collateral arteries, and infrequently by the portal vein [60]. It is speculated that these factors underlie the development of TACE refractoriness. In patients with local tumor progression after initial TACE, the frequency of intrahepatic distant recurrence is significantly high as compared with those with no local tumor progression ( $p = 0.0004$ ) [61]. Centrally, if a local cure is achieved through initial TACE, this leads to a better prognosis, and the method can be referred to as curative TACE [62].

Pathological examination after non-selective cTACE in HCC  $\leq 2$  cm showed that in 9 out of 14 (64.3%) lesions, tumors mainly persisted in areas of extracapsular invasion and in satellite nodules, which lack capsule formation [31]. In 10 of 12 (83%) tumors (mean tumor size: 4.3 cm) with marked portal vein opacification that regurgitated iodized oil (lipiodol®) through the peribiliary plexus after superselective cTACE, necrosis developed not only in the main tumor but also in satellite nodules, in areas of extracapsular invasion, and in the

surrounding liver parenchyma [63]. The tumor necrosis rate was 75.1% for selective/superselective cTACE and 52.8% for non-selective cTACE, suggesting that tumor necrosis was achieved over a significantly wider range with selective/superselective cTACE ( $p = 0.002$ ; complete necrosis rate: 53.8 vs. 29.8%,  $p = 0.013$ ) [63]. Moreover, resected specimens showed complete necrosis in 6/9 (66.7%) lesions (mean tumor size: 3.1 cm) after superselective cTACE. In case there was marked visualization of the portal vein in the surrounding area of embolized area after injection of lipiodol<sup>®</sup>, massive peritumoral necrosis was observed [64]. Overflow of lipiodol<sup>®</sup> into the portal vein within the area of embolization allows simultaneous embolization of the artery and the portal vein, which necrotizes the surrounding liver parenchyma (including the tumor) in a process called medical segmentectomy [62].

TACE rarely achieves a complete radiologic response after a single session, and most patients need repeated TACE procedures. However, the overall response rate decreases with additional TACE sessions compared with the response to initial TACE [64, 65]. In addition, repeated TACE can increase morbidity and mortality through TACE-induced risks such as deterioration of liver function.

**Consensus Statement 6:**

***Non-selective TACE is associated with a higher risk of irreversible liver parenchymal injury.***

**Consensus Statement 7:**

***Effective (curative) TACE is a procedure performed with the objective of achieving CR by using superselective cTACE.***

*When to Stop TACE and Start Systemic Therapy (CQ 8,9)*

**TACE Failure/Refractoriness**

TACE is used commonly to treat unresectable HCC, although there is no global consensus on its indications or the definition of TACE failure.

Retrospective studies have suggested that repeated TACE after TACE refractoriness/failure is not beneficial and can affect eligibility for subsequent systemic therapy due to deterioration of liver function [66, 67]. OPTIMIS, an international, prospective, non-interventional study, showed that patients who switched to sorafenib at the time of TACE refractoriness had a longer OS [65]. Furthermore, even at the time of TACE refractoriness, 20–30% of patients are Child-Pugh B or C, and systemic therapy is no longer indicated [66–68]. Therefore, in the era of multi-molecular targeted agents and immune checkpoint inhibitors, continuing TACE until development of TACE refractoriness ultimately leads to the deterioration of liver function, which in turn leads to loss of an opportunity to switch to systemic therapy [20]. All approved molecular targeted agents and immune checkpoint inhibitors are indicated only for patients with Child-Pugh A liver function [69].

**TACE-Unsuitable**

The largest therapeutic effect of cTACE is observed in encapsulated simple nodular type HCCs. In contrast, a high frequency of vascular invasion and a poor therapeutic effect of cTACE are observed in confluent multinodular type, massive type, infiltrative type, and simple nodular type HCCs with extranodular growth, all of which lack capsule formation [70, 71]. Similar to these types, the efficacy of TACE is also low in poorly differentiated and undifferentiated HCCs, due to resistance to TACE [72].

TACE induces hypoxic and chemotherapeutic stress in HCC, and the surviving hypoxic tumors frequently change to sarcomatous or mixed hepatocholangiocellular phenotypes (20 and 35%, respectively), which are more aggressive and often TACE-resistant [31, 32]. Generally, small intrahepatic tumors that develop frequently are likely to be intrahepatic

disseminated nodules. In these cases, even superselective TACE is often followed by the appearance of new recurrent lesions outside the embolized area; therefore, repeated TACE is required. This repeated TACE causes damage to the hepatic artery and deterioration of liver function, which worsen the prognosis of patients. Moreover, disseminated lesions (satellite nodules) usually have no capsule and show marked resistance to TACE [59].

A number of reports, such as the global observational study OPTIMIS and 2 other studies, indicate that repeated TACE procedures lead to a deterioration of liver function in up-to 7 criteria out patients [56, 57, 73–75]. In terms of liver function, ALBI grade 2 especially mALBI grade 2b is a poor prognostic factor for OS after TACE [73, 75].

**Consensus Statement 8:**

***To preserve liver function, TACE should not be continued if patients show TACE failure/refractoriness.***

**Consensus Statement 9:**

***TACE-unsuitability is defined as each one of the following 3 clinical conditions that prevent a survival benefit from TACE or conditions that TACE is even harmful:***

***(i) Unlikely to respond to TACE:***

***Confluent multinodular type, massive or infiltrative type, simple nodular type with extranodular growth, poorly differentiated type, intrahepatic multiple disseminated nodules, or sarcomatous changes after TACE***

***(ii) Likely to develop TACE failure/refractoriness:***

***Up-to-7 criteria out nodules***

***(iii) Likely to become Child-Pugh B or C after TACE:***

***Up-to-7 criteria out nodules (especially, bilobar multifocal HCC)***

***mALBI grade 2b***

***Treatment Recommendations for TACE-Unsuitable Patients (CQ10)***

Lenvatinib is the only first-line agent to demonstrate an OS benefit over TACE in TACE-naïve patients with up-to-7 criteria out tumor burden although this is a retrospective propensity score matched study [76]. Lenvatinib is associated with significantly better PFS (16.0 months) and ORR (73.3%) than TACE alone (PFS 3.0 months, ORR 33.3%). In addition, the ALBI score in the TACE group worsens over time compared with that in the lenvatinib group. At the end of treatment, a worse ALBI score was not recovered in the TACE treated group, whereas it was recovered to the baseline level in the lenvatinib treated group. Lenvatinib extends the OS significantly than TACE (37.9 vs. 21.3 m) [76, 77]. Lenvatinib treatment also shows favorable results in TACE-resistant tumors such as poorly differentiated, confluent multinodular type, or infiltrated type HCCs [78–80].

In the OPTIMIS study, only 9% of patients received sorafenib after developing TACE refractoriness; indeed, in clinical practice, sorafenib is rarely used in TACE-unsuitable patients who easily develop TACE-refractoriness. In TACE-unsuitable patients, there is no solid evidence that sorafenib has a benefit over TACE [65]. Similarly, hepatic arterial infusion chemotherapy plus sorafenib does not show a greater benefit than sorafenib alone in patients with bilobar multiple tumors; therefore, hepatic arterial infusion chemotherapy is not indicated for this population [38, 81]. Transarterial radioembolization using Y90 (TARE) does not offer a greater benefit than sorafenib alone in those with intrahepatic multiple tumors; therefore, TARE may not be indicated routinely for patients with bilobar multiple intrahepatic tumors [82, 83].

The TACTICS trial showed the benefit of sorafenib followed by TACE as a treatment option to improve the clinical outcome of patients with intermediate-stage HCC [25]. Pretreatment with systemic therapy (both sorafenib and lenvatinib) improves the clinical outcome of TACE [5] presumably by promoting vascular normalization and improving the



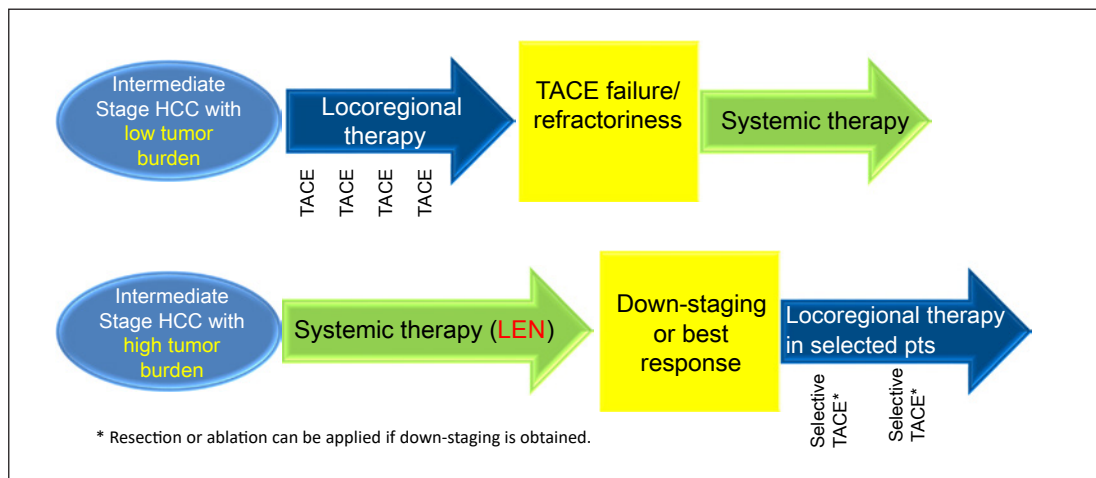
**Table 2.** Clinical questions and consensus statements

Clinical question	Consensus statement
CQ.1 What is the treatment concept for intermediate-stage HCC?	For intermediate-stage HCC, preservation of liver function is as important as achieving a high OR because the goal of treatment is to prolong OS.
CQ.2 Is TACE the only one first-line standard of care in intermediate-stage HCC?	1) Superselective cTACE with curative intent is recommended as the first choice of treatment in patients who are eligible for effective TACE. Systemic therapy is recommended as the first choice of treatment in patients who are not eligible for effective TACE. 2) Other modalities, including combination therapies (TACE plus systemic therapy such as sorafenib), may be considered to improve efficacy of TACE both in TACE-suitable or -unsuitable patient populations. 3) TACE alone is not indicated as the first-line therapy in TACE-unsuitable patients.
CQ.3 Does tumor response to TACE contribute to the survival benefit in HCC?	Tumor response per mRECIST predicts longer OS in patients receiving TACE, especially initial CR, which can predict a longer survival benefit.
CQ.4 Does tumor response to systemic therapy contribute to the survival benefit in HCC?	Tumor response per mRECIST predicts longer OS in patients receiving systemic therapy.
CQ.5 How does baseline liver function affect the outcome of systemic therapy?	Better liver function such as ALBI grade 1 and mALBI grade 2a is an important factor for maximizing the effect of systemic therapy.
CQ.6 Does non-selective TACE worsen the liver function?	Non-selective TACE is associated with a higher risk of irreversible liver parenchymal injury.
CQ.7 What is effective (curative) TACE?	Effective (curative) TACE is a procedure performed with the objective of achieving CR by using superselective cTACE.
CQ.8 Should TACE be continued until being classified as TACE failure/refractoriness?	To preserve liver function, TACE should not be continued if patients show TACE failure/refractoriness.
CQ.9 What is TACE-unsuitable?	TACE-unsuitability is defined as each one of the following 3 clinical conditions that prevent a survival benefit from TACE or conditions that TACE is even harmful: (i) Unlikely to respond to TACE: Confluent multinodular type, massive or infiltrative type, simple nodular type with extranodular growth, poorly differentiated type, intrahepatic multiple disseminated nodules, or sarcomatous changes after TACE (ii) Likely to develop TACE failure/refractoriness: up-to-7 criteria out (iii) Likely to become Child-Pugh B or C after TACE: up-to-7 criteria out (especially, biobar multifocal HCC), mALBI grade 2b
CQ.10 Which treatment is recommended for TACE-unsuitable patients?	Targeted therapy is recommended as the first choice in the first-line treatment with subsequent selective locoregional therapy for TACE-unsuitable patients. Especially, the drug that can have higher objective response such as lenvatinib, is preferred. Immunotherapy, TARE, TACE plus sorafenib, or other modalities may be considered alternative options for TACE-unsuitable patients who are not candidates for targeted therapy.

OR, objective response; TACE, transarterial chemoembolization; cTACE, conventional TACE; HCC, hepatocellular carcinoma; CR, complete response; ALBI, albumin-bilirubin; mALBI, modified ALBI.

distribution of lipiodol mixed with anticancer drugs [84–87]. Since OS benefit has not yet been proved with TACTICS trial, panelists decided that lenvatinib is the preferred agent for TACE-unsuitable patients based on the high response rate, survival benefit over TACE, and possibility of conversion to resection or ablation therapy as of 2020.

Second-line treatment options include sorafenib, regorafenib, cabozantinib, ramucirumab, nivolumab, pembrolizumab, or superselective TACE depending on the patient's tumor



**Fig. 3.** Changing the treatment strategy for patients with TACE-unsuitable intermediate-stage HCC. Different from conventional sequence from TACE to systemic therapy, systemic therapy (lenvatinib) before selective TACE may be the better treatment strategy especially in patients with intermediate stage HCC with high tumor burden. TACE, transarterial chemoembolization.

condition. Although the APPLE Consensus is a general statement, it should be kept in mind that TACE unsuitable HCC is not always contraindicated for TACE monotherapy and some “up-to-7 criteria out” tumors may also be indicated for superselective cTACE when tumors are localized in limited segments.

Immunotherapy (nivolumab or pembrolizumab) failed to achieve the primary endpoint of OS in Phase III trials [88, 89]; however, because a clinical benefit was observed, panels indicated that immunotherapy should be considered an alternative treatment in TACE-unsuitable patients who are not candidates for molecular targeted therapy. Atezolizumab plus bevacizumab resulted in better OS, PFS, and ORR than sorafenib alone in patients with advanced HCC [90]. Thus, panels suggested that this combination is worth considering in patients with intermediate-stage HCC, despite the lack of ORR data in patients with intermediate-stage HCC in the Phase III IMbrave trial.

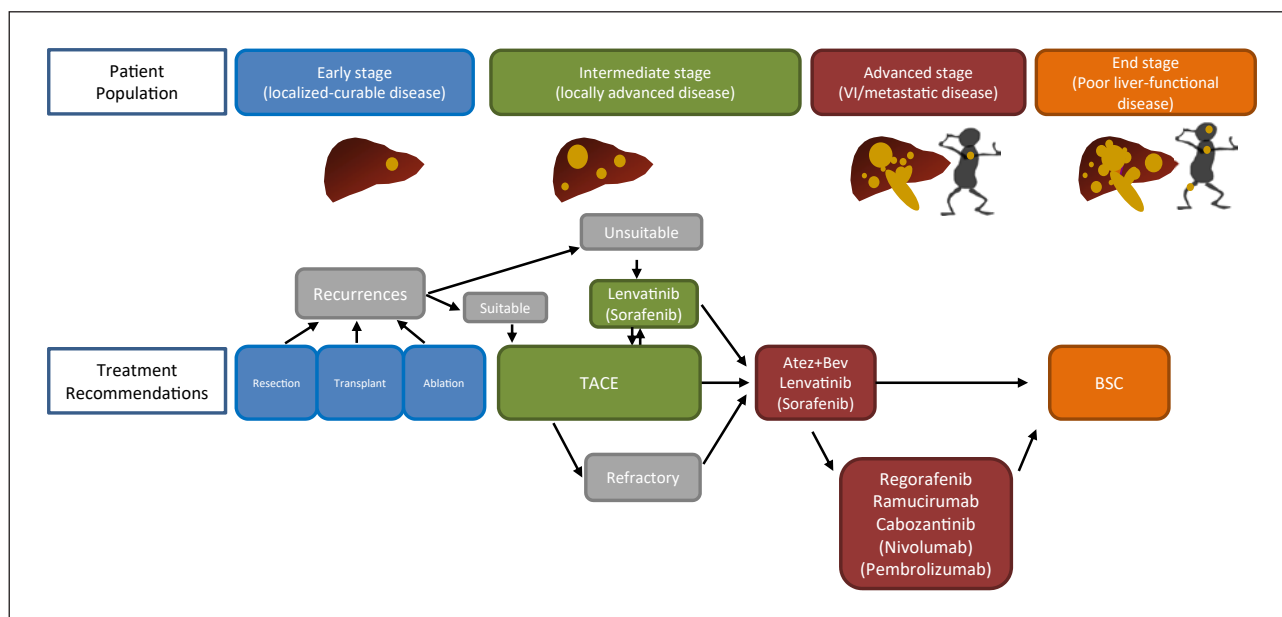
#### **Consensus Statement 10:**

**Targeted therapy is recommended as the first choice in the first-line treatment with subsequent selective locoregional therapy for TACE-unsuitable patients. Especially, the drug that can have higher OR such as lenvatinib, is preferred. Immunotherapy, TARE, TACE plus sorafenib or other modalities may be considered alternative options for TACE-unsuitable patients who are not candidates for targeted therapy.**

#### *Summary of APPLE Expert Consensus*

The clinical questions and consensus statements are summarized in Table 2. Although TACE represents the standard of care for intermediate-stage HCC, intermediate-stage HCC constitutes a very heterogeneous patient population that is characterized by marked differences in tumor burden and liver function. Real-world experience indicates that loco-regional therapy is overused in most patients outside clinical practice guidelines, which frequently leads to the deterioration of liver function and thereby to exclusion of patients from systemic therapy and/or clinical trials.

Because of its high anti-tumor effect of lenvatinib on massive, confluent multinodular, infiltrative, poorly differentiated and simple nodular with extranodular growth tumor types,



**Fig. 4.** A new paradigm for treatment strategy in HCC. For patients who are unsuitable to TACE, systemic therapy using agents with a high response rate followed by selective TACE would be a better treatment strategy to prolong patients' survival. TACE, transarterial chemoembolization.

LEN-TACE sequential therapy is a rational and effective treatment strategy for patients who do not benefit from TACE alone and are susceptible to deterioration of hepatic functional reserve (Fig. 3). Other systemic therapies, such as combination immunotherapy of atezolizumab plus bevacizumab, may play a role in intermediate stage HCC in the near future, since ORR by atezolizumab plus bevacizumab is as high as 62% in intermediate stage HCC in phase 1b study (Arm A) [91]. Sorafenib in combination with TACE is a choice of treatment in intermediate-stage HCC as shown in TACTICS trial [25]. This trial is still ongoing; therefore, this combination will be more important and persuasive when survival benefit is shown in the near future.

Current advances in the development of new anticancer agents will lead to a paradigm shift or even paradigm change in the treatment of HCC, and systemic therapy may become the first choice of treatment, followed by curative/selective TACE for treatment of intermediate-stage HCC with a high tumor burden (Fig. 3, 4).

The concept of TACE refractoriness was proposed initially in Japan in 2011 and then spread worldwide [12, 92]. However, this concept is becoming outdated in an era of multi-molecular targeted agents because and immunotherapy a more important concept – “TACE-unsuitable” – is being proposed and established by the APPLE Expert Panel and APPLE Association (Fig. 4).

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### Statement of Ethics

Not applicable.

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## Author Contributions

M.K. conceived, wrote, and approved the final manuscript. K.-H.H., S.-L.Y., J.Z., Y.-H.H., S.-M.L., C.-K.W., M.I., S.L.C., S.P.C., S.M., and A.L.C. conceived, contributed, reviewed, gave critical comments and approved the final manuscript.

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