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Consensus Statement

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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Kudo et al.: Treatment of Intermediate-Stage HCC: APPLE Consensus Statement

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.

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 ≥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.

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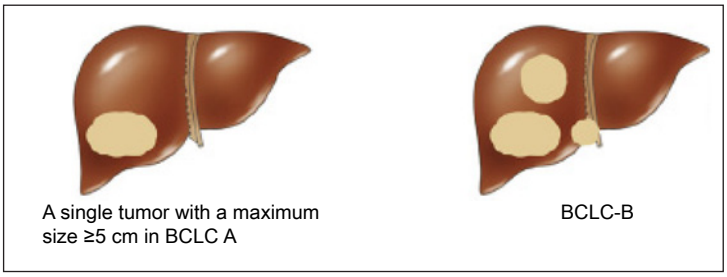

Fig. 1. Definition of intermediate-stage HCC used in this manuscript. In this APPLE consensus meeting, intermediate-stage HCC was defined as: (i) a single tumor with a maximum size of ≥5 cm in BCLC A; and (ii) BCLC B stage HCC. BCLC, Barcelona Clinic Liver Cancer.

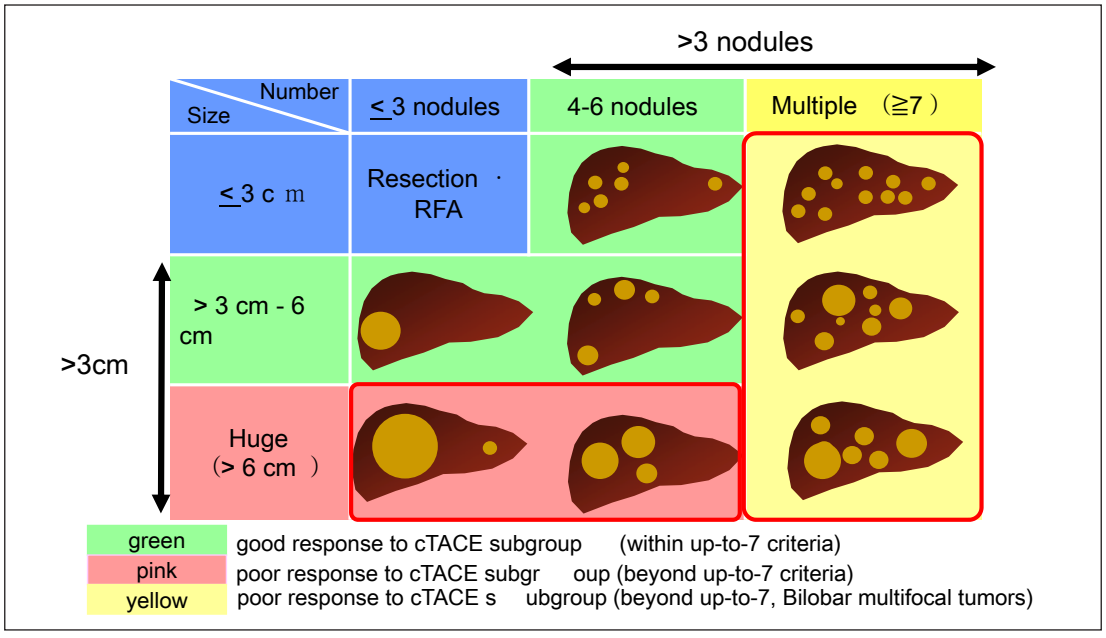

Fig. 2. Heterogeneity of intermediate-stage HCC and grade of response to TACE in each subgroup. cTACE, conventional transarterial chemoembolization.

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) lists all members of the APPLE Expert Consensus panel.

Liver Cancer 2020;9:245–260
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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 ≥ 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:

Superselective 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

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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, *n*	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 (≥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 ≥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 ≥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].

Liver Cancer 2020;9:245–260
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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 ≤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®, massive peritumoral necrosis was observed [64]. Overflow of lipiodol® 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

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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 live 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, biolobar 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 lenvatnib, 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

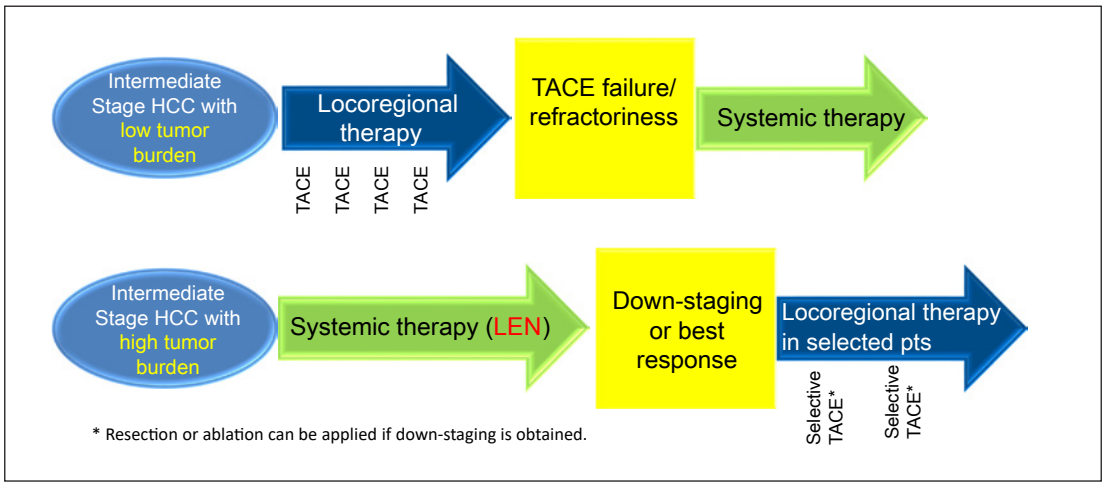

Fig. 3. Changing the treatment strategy for patients with TACE-unsuitable intermediate-stage HCC. Different from conventional sequence from TACE to systemic therapy, systemic therapy (lenvatinib) before selective TACE may be the better treatment strategy especially in patients with intermediate stage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

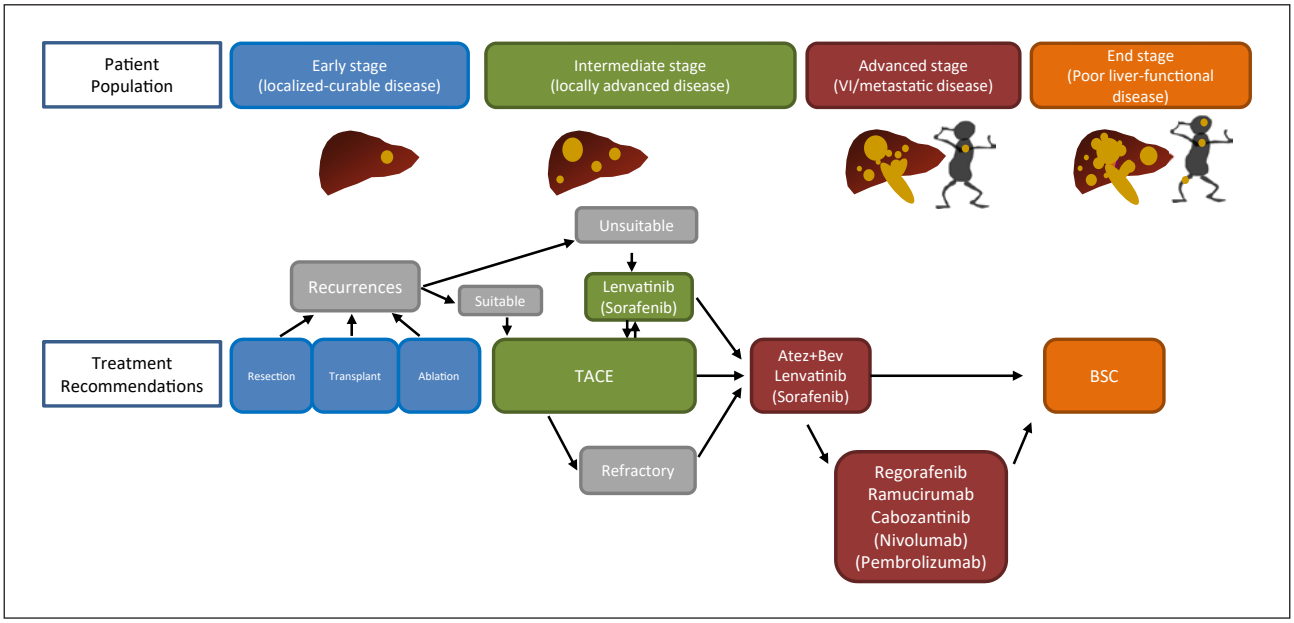

Fig. 4. A new paradigm for treatment strategy in HCC. For patients who are unsuitable to TACE, systemic therapy using agents with a high response rate followed by selective TACE would be a better treatment strategy to prolong patients' survival. TACE, transarterial chemoembolization.

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 multimolecular 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.

References

1 Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012 Mar;379(9822):1245–55.
2 Piscaglia F, Bolondi L: The intermediate hepatocellular carcinoma stage: Should treatment be expanded? Dig Liver Dis. 2010 Jul;42 Suppl 3:S258–63.
3 Bruix J, Reig M, Sherman M. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. Gastroenterology. 2016 Apr;150(4):835–53.
4 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al.; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008 Jul;359(4):378–90.
5 Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018 Mar;391(10126):1163–73.
6 Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al.; RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017 Jan;389(10064):56–66.
7 Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med. 2018 Jul;379(1):54–63.
8 Zhu AX, Park JO, Ryoo BY, Yen CJ, Poon R, Pastorelli D, et al.; REACH Trial Investigators. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2015 Jul;16(7):859–70.
9 Zhu AX, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, et al.; REACH-2 study investigators. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019 Feb;20(2):282–96.
10 El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017 Jun;389(10088):2492–502.
11 Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al.; KEYNOTE-224 investigators. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. 2018 Jul;19(7):940–52.

12 Kudo M, Matsui O, Izumi N, Kadoya M, Okusaka T, Miyayama S, et al.; Liver Cancer Study Group of Japan. Transarterial chemoembolization failure/refractoriness: JSH-LCSGJ criteria 2014 update. Oncology. 2014;87 Suppl 1:22–31.
13 Kudo M. Heterogeneity and Subclassification of Barcelona Clinic Liver Cancer Stage B. Liver Cancer. 2016 Apr; 5(2):91–6.
14 Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul JL, et al.; European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. Management of hepatocellular carcinoma. J Hepatol. 2018 Jul;69(1):182–236.
15 Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018 Aug;68(2):723–50.
16 Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017 Jul;11(4):317–70.
17 Korean Liver Cancer Association KL, National Cancer Center NC; Korean Liver Cancer Association; National Cancer Center. 2018 Korean Liver Cancer Association-National Cancer Center Korea Practice Guidelines for the Management of Hepatocellular Carcinoma. Gut Liver. 2019 May;13(3):227–99.
18 Bolondi L, Burroughs A, Dufour JF, Galle PR, Mazzaferro V, Piscaglia F, et al. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis. 2012 Nov;32(4):348–59.
19 Kudo M, Arizumi T, Ueshima K, Sakurai T, Kitano M, Nishida N. Subclassification of BCLC B Stage Hepatocellular Carcinoma and Treatment Strategies: Proposal of Modified Bolondi's Subclassification (Kinki Criteria). Dig Dis. 2015 Oct;33(6):751–8.
20 Kudo M. Extremely High Objective Response Rate of Lenvatinib: Its Clinical Relevance and Changing the Treatment Paradigm in Hepatocellular Carcinoma. Liver Cancer. 2018 Sep;7(3):215–24.
21 Yamakado K, Hirota S. Sub-classification of intermediate-stage (Barcelona Clinic Liver Cancer stage-B) hepatocellular carcinomas. World J Gastroenterol. 2015 Oct;21(37):10604–8.
22 Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al.; Metroticket Investigator Study Group. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol. 2009 Jan;10(1):35–43.
23 Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol. 2012 Oct;57(4):821–9.
24 Yamashita T, Kudo M, Ikeda K, Izumi N, Tateishi R, Ikeda M, et al. REFLECT-a phase 3 trial comparing efficacy and safety of lenvatinib to sorafenib for the treatment of unresectable hepatocellular carcinoma: an analysis of Japanese subset. J Gastroenterol. 2020 Jan;55(1):113–22.
25 Kudo M, Ueshima K, Ikeda M, Torimura T, Tanabe N, Aikata H, et al.; TACTICS study group. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. Gut. 2019, Epub ahead of print.
26 Miyayama S, Yamashiro M, Hashimoto M, Hashimoto N, Ikuno M, Okumura K, et al. Identification of small hepatocellular carcinoma and tumor-feeding branches with cone-beam CT guidance technology during transcatheter arterial chemoembolization. J Vasc Interv Radiol. 2013 Apr;24(4):501–8.
27 Vincenzi B, Di Maio M, Silletta M, D'Onofrio L, Spoto C, Piccirillo MC, et al. Prognostic Relevance of Objective Response According to EASL Criteria and mRECIST Criteria in Hepatocellular Carcinoma Patients Treated with Loco-Regional Therapies: A Literature-Based Meta-Analysis. PLoS One. 2015 Jul; 10(7):e0133488.
28 Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, et al.; Barcelona Liver Cancer Group. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002 May;359(9319):1734–9.
29 Zhang Y, Zhang M, Chen M, Mei J, Xu L, Guo R, et al. Association of Sustained Response Duration With Survival After Conventional Transarterial Chemoembolization in Patients With Hepatocellular Carcinoma. JAMA Netw Open. 2018 Oct;1(6):e183213.
30 Kim BK, Kim SU, Kim KA, Chung YE, Kim MJ, Park MS, et al. Complete response at first chemoembolization is still the most robust predictor for favorable outcome in hepatocellular carcinoma. J Hepatol. 2015 Jun;62(6):1304–10.
31 Kojiro M, Sugihara S, Kakizoe S, Nakashima O, Kiyomatsu K. Hepatocellular carcinoma with sarcomatous change: a special reference to the relationship with anticancer therapy. Cancer Chemother Pharmacol. 1989; 23(Suppl):S4–8.
32 Zen C, Zen Y, Mitry RR, Corbeil D, Karbanová J, O'Grady J, et al. Mixed phenotype hepatocellular carcinoma after transarterial chemoembolization and liver transplantation. Liver Transpl. 2011 Aug;17(8):943–54.
33 Wang B, Xu H, Gao ZQ, Ning HF, Sun YQ, Cao GW. Increased expression of vascular endothelial growth factor in hepatocellular carcinoma after transcatheter arterial chemoembolization. Acta Radiol. 2008 Jun;49(5): 523–9.
34 Miyayama S, Matsui O, Zen Y, Yamashiro M, Hattori Y, Orito N, et al. Portal blood supply to locally progressed hepatocellular carcinoma after transcatheter arterial chemoembolization: Observation on CT during arterial portography. Hepatol Res. 2011 Sep;41(9):853–66.
35 Huang L, Sanctis YD, Shan M. Weak Correlation of Overall Survival (OS) and Response Rate (RR) by RECIST in Advanced Hepatocellular Carcinoma (HCC). ILCA 2017 abstract #P-056.

36 Meyer T, Palmer DH, Cheng AL, Hocke J, Loembe AB, Yen CJ. mRECIST to predict survival in advanced hepatocellular carcinoma: Analysis of two randomised phase II trials comparing nintedanib vs sorafenib. Liver Int. 2017 Jul;37(7):1047–55.
37 Lencioni R, Montal R, Torres F, Park JW, Decaens T, Raoul JL, et al. Objective response by mRECIST as a predictor and potential surrogate end-point of overall survival in advanced HCC. J Hepatol. 2017 Jun;66(6):1166–72.
38 Kudo M, Ueshima K, Yokosuka O, Ogasawara S, Obi S, Izumi N, et al.; SILIUS study group. Sorafenib plus low-dose cisplatin and fluorouracil hepatic arterial infusion chemotherapy versus sorafenib alone in patients with advanced hepatocellular carcinoma (SILIUS): a randomised, open label, phase 3 trial. Lancet Gastroenterol Hepatol. 2018 Jun;3(6):424–32.
39 Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Cheng AL, et al. Analysis of survival and objective responses in patients with hepatocellular carcinoma in a phase 3 study of lenvatinib (REFLECT). J Clin Oncol. 2019;37:186.
40 Kudo M, Ueshima K, Chiba Y, Ogasawara S, Obi S, Izumi N, et al. Objective Response by mRECIST Is an Independent Prognostic Factor for Overall Survival in Hepatocellular Carcinoma Treated with Sorafenib in the SILIUS Trial. Liver Cancer. 2019 Nov;8(6):505–19.
41 Kudo M, Chiba Y, Meyer T, Lencioni R, Llovet JM. Association of objective response by mRECIST with better overall survival (OS) in patients with advanced hepatocellular carcinoma (HCC) treated with systemic therapies: A systematic review and meta-analysis of randomized controlled trials. J Clin Oncol. 2020;38:586.
42 Ueshima K, Nishida N, Hagiwara S, Aoki T, Minami T, Chishina H, et al. Impact of Baseline ALBI Grade on the Outcomes of Hepatocellular Carcinoma Patients Treated with Lenvatinib: A Multicenter Study. Cancers (Basel). 2019 Jul;11(7):11.
43 Abdel-Rahman O. Impact of baseline characteristics on outcomes of advanced HCC patients treated with sorafenib: a secondary analysis of a phase III study. J Cancer Res Clin Oncol. 2018 May;144(5):901–8.
44 Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol. 2015 Feb;33(6):550–8.
45 Hiraoka A, Kumada T, Kudo M, Hirooka M, Koizumi Y, Hiasa Y, et al.; Real-life Practice Experts for HCC (RELPEC) Study Group and HCC 48 Group (hepatocellular carcinoma experts from 48 clinics). Hepatic Function during Repeated TACE Procedures and Prognosis after Introducing Sorafenib in Patients with Unresectable Hepatocellular Carcinoma: multicenter Analysis. Dig Dis. 2017;35(6):602–10.
46 Ogasawara S, Chiba T, Ooka Y, Suzuki E, Kanogawa N, Saito T, et al. Liver function assessment according to the Albumin-Bilirubin (ALBI) grade in sorafenib-treated patients with advanced hepatocellular carcinoma. Invest New Drugs. 2015 Dec;33(6):1257–62.
47 Hiraoka A, Michitaka K, Kumada T, Izumi N, Kadoya M, Kokudo N, et al. Validation and Potential of Albumin-Bilirubin Grade and Prognostication in a Nationwide Survey of 46,681 Hepatocellular Carcinoma Patients in Japan: The Need for a More Detailed Evaluation of Hepatic Function. Liver Cancer. 2017 Nov;6(4):325–36.
48 Hiraoka A, Kumada T, Kariyama K, Takaguchi K, Atsukawa M, Itobayashi E, et al.; Real-life Practice Experts for HCC (RELPEC) Study Group, HCC 48 Group (hepatocellular carcinoma experts from 48 clinics in Japan). Clinical features of lenvatinib for unresectable hepatocellular carcinoma in real-world conditions: multicenter analysis. Cancer Med. 2019 Jan;8(1):137–46.
49 Hiraoka A, Kumada T, Atsukawa M, Hirooka M, Tsuji K, Ishikawa T, et al.; Real-life Practice Experts for HCC (RELPEC) Study Group, HCC 48 Group (hepatocellular carcinoma experts from 48 clinics in Japan). Prognostic factor of lenvatinib for unresectable hepatocellular carcinoma in real-world conditions-Multicenter analysis. Cancer Med. 2019 Jul;8(8):3719–28.
50 Hiraoka A, Kumada T, Atsukawa M, Hirooka M, Tsuji K, Ishikawa T, et al.; Real-life Practice Experts for HCC (RELPEC) Study Group; HCC 48 Group (hepatocellular carcinoma experts from 48 clinics in Japan). Important Clinical Factors in Sequential Therapy Including Lenvatinib against Unresectable Hepatocellular Carcinoma. Oncology. 2019;97(5):277–85.
51 Okusaka T, Ikeda K, Kudo M, Finn RS, Qin S, Han KH, et al: Safety and efficacy of lenvatinib by starting dose (8 mg or 12 mg) based on body weight in patients with unresectable hepatocellular carcinoma in REFLECT. J Clin Oncol 2019;37(suppl 4):316.
52 Yamakado K, Miyayama S, Hirota S, Mizunuma K, Nakamura K, Inaba Y, et al. Hepatic arterial embolization for unresectable hepatocellular carcinomas: do technical factors affect prognosis? Jpn J Radiol. 2012 Aug;30(7):560–6.
53 Cammà C, Schepis F, Orlando A, Albanese M, Shahied L, Trevisani F, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. Radiology. 2002 Jul;224(1):47–54.
54 Yip WM, Hung HG, Lok KH, Li KF, Li KK, Szeto ML. Outcome of inoperable hepatocellular carcinoma patients receiving transarterial chemoembolisation: a real-life retrospective analysis in a Hong Kong regional hospital. Hong Kong Med J. 2009 Oct;15(5):339–45.
55 Kothary N, Weintraub JL, Susman J, Rundback JH. Transarterial chemoembolization for primary hepatocellular carcinoma in patients at high risk. J Vasc Interv Radiol. 2007 Dec;18(12):1517–26.
56 Cheng AL, Raoul JL, Lee HC. Acute and chronic deterioration in liver function after transarterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC): the final analysis of OPTIMIS. ILCA, 12th Annual Conference, Abstract #P-34.

57 Arizumi T, Minami T, Chishina H, Kono M, Takita M, Yada N, et al. Time to Transcatheter Arterial Chemoembolization Refractoriness in Patients with Hepatocellular Carcinoma in Kinki Criteria Stages B1 and B2. Dig Dis. 2017;35(6):589–97.
58 Yasui Y, Tsuchiya K, Kurosaki M, Takeguchi T, Takeguchi Y, Okada M, et al. Up-to-seven criteria as a useful predictor for tumor downstaging to within Milan criteria and Child-Pugh grade deterioration after initial conventional transarterial chemoembolization. Hepatol Res. 2018 May;48(6):442–50.
59 Kuroda C, Sakurai M, Monden M, Marukawa T, Hosoki T, Tokunaga K, et al. Limitation of transcatheter arterial chemoembolization using iodized oil for small hepatocellular carcinoma. A study in resected cases. Cancer. 1991 Jan;67(1):81–6.
60 Miyayama S, Yamashiro M, Sugimori N, Ikeda R, Okimura K, Sakuragawa N. Outcomes of Patients with Hepatocellular Carcinoma Treated with Conventional Transarterial Chemoembolization Using Guidance Software. J Vasc Interv Radiol. 2019 Jan;30(1):10–8.
61 Matsuo N, Uchida H, Nishimine K, Soda S, Oshima M, Nakano H, et al. Segmental transcatheter hepatic artery chemoembolization with iodized oil for hepatocellular carcinoma: antitumor effect and influence on normal tissue. J Vasc Interv Radiol. 1993 Jul-Aug;4(4):543–9.
62 Matsui O, Kadoya M, Yoshikawa J, Gabata T, Arai K, Demachi H, et al. Small hepatocellular carcinoma: treatment with subsegmental transcatheter arterial embolization. Radiology. 1993 Jul;188(1):79–83.
63 Golfieri R, Cappelli A, Cucchetti A, Piscaglia F, Carpenzano M, Peri E, et al. Efficacy of selective transarterial chemoembolization in inducing tumor necrosis in small (<5 cm) hepatocellular carcinomas. Hepatology. 2011 May;53(5):1580–9.
64 Golfieri R, Renzulli M, Mosconi C, Forlani L, Giampalma E, Piscaglia F, et al.; Bologna Liver Oncology Group (BLOG). Hepatocellular carcinoma responding to superselective transarterial chemoembolization: an issue of nodule dimension? J Vasc Interv Radiol. 2013 Apr;24(4):509–17.
65 Peck-Radosavljevic M, Kudo M, Raoul JL, Lee HC, Decaens T, Heo J, et al: Outcomes of patients (pts) with hepatocellular carcinoma (HCC) treated with transarterial chemoembolization (TACE): Global OPTIMIS final analysis. J Clin Oncol. 2018;36:4018.
66 Ogasawara S, Chiba T, Ooka Y, Kanogawa N, Motoyama T, Suzuki E, et al. Efficacy of sorafenib in intermediate-stage hepatocellular carcinoma patients refractory to transarterial chemoembolization. Oncology. 2014; 87(6):330–41.
67 Arizumi T, Ueshima K, Chishina H, Kono M, Takita M, Kitai S, et al. Validation of the criteria of transcatheter arterial chemoembolization failure or refractoriness in patients with advanced hepatocellular carcinoma proposed by the LCSGJ. Oncology. 2014;87(Suppl 1):32–6.
68 Peck-Radosavljevic M, Lee HC, Kudo M, Nakajima K, Bayh I, Cheng AL, et al. Practice patterns and outcomes of transarterial chemoembolization in patients with hepatocellular carcinoma who were either ineligible or eligible for transarterial chemoembolization at inclusion: Global OPTIMIS exploratory analysis. EASL, April 10-14, 2019, Vienna, Austria, Abstr #FRI-494.
69 Llovet JM, Montal R, Sia D, Finn RS. Molecular therapies and precision medicine for hepatocellular carcinoma. Nat Rev Clin Oncol. 2018 Oct;15(10):599–616.
70 Kanai T, Hirohashi S, Upton MP, Noguchi M, Kishi K, Makuuchi M, et al. Pathology of small hepatocellular carcinoma. A proposal for a new gross classification. Cancer. 1987 Aug;60(4):810–9.
71 Hashimoto T, Nakamura H, Hori S, Tomoda K, Nakanishi K, Murakami T, et al. Hepatocellular carcinoma: efficacy of transcatheter oily chemoembolization in relation to macroscopic and microscopic patterns of tumor growth among 100 patients with partial hepatectomy. Cardiovasc Intervent Radiol. 1995 Mar-Apr;18(2):82–6.
72 Yamashita Y, Matsukawa T, Arakawa A, Hatanaka Y, Urata J, Takahashi M. US-guided liver biopsy: predicting the effect of interventional treatment of hepatocellular carcinoma. Radiology. 1995 Sep;196(3):799–804.
73 Kimura H, Ohkawa K, Miyazaki M, Sakakibara M, Imanaka K, Tamura T, et al. Subclassification of patients with intermediate-stage (Barcelona Clinic Liver Cancer stage-B) hepatocellular carcinoma using the up-to-seven criteria and serum tumor markers. Hepatol Int. 2017 Jan;11(1):105–14.
74 Eso Y, Takai A, Takahashi K, Ueda Y, Taura K, Marusawa H, et al. Combination of Mac-2 Binding Protein Glycosylation Isomer and Up-To-Seven Criteria as a Useful Predictor for Child-Pugh Grade Deterioration after Transarterial Chemoembolization for Hepatocellular Carcinoma. Cancers (Basel). 2019 Mar;11(3):11.
75 Izumoto H, Hiraoka A, Ishimaru Y, Murakami T, Kitahata S, Ueki H, et al. Validation of Newly Proposed Time to Transarterial Chemoembolization Progression in Intermediate-Stage Hepatocellular Carcinoma Cases. Oncology. 2017;93 Suppl 1:120–6.
76 Kudo M, Ueshima K, Chan S, Minami T, Chishina H, Aoki T, et al. Lenvatinib as an Initial Treatment in Patients with Intermediate-Stage Hepatocellular Carcinoma Beyond Up-To-Seven Criteria and Child-Pugh A Liver Function: A Proof-Of-Concept Study. Cancers (Basel). 2019 Jul;11(8):11.
77 Kudo M. A New Treatment Option for Intermediate-Stage Hepatocellular Carcinoma with High Tumor Burden: Initial Lenvatinib Therapy with Subsequent Selective TACE. Liver Cancer. 2019 Oct;8(5):299–311.
78 Kudo M, Ueshima K, Aikata H. Association Between Tumor Response by mRECIST and Overall Survival in Patients With Poorly Differentiated HCC in REFLECT Study. 10th Asia-Pacific Primary Liver Cancer Expert (APPLE 2019) Meeting.
79 Kawamura Y, Kobayashi M, Shindoh J, Kobayashi Y, Kasuya K, Sano T, et al. 18F-Fluorodeoxyglucose Uptake in Hepatocellular Carcinoma as a Useful Predictor of an Extremely Rapid Response to Lenvatinib. Liver Cancer. 2020 Jan;9(1):84–92.

Liver Cancer 2020;9:245–260
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80 Kawamura Y, Kobayashi M, Shindo J, Kobayashi Y, Kasuya K, Sano T, et al. Pretreatment heterogeneous enhancement pattern of hepatocellular carcinoma may be a useful new predictor of early response to lenvatinib and overall prognosis. Liver Cancer. 2020, Epub ahead of print.
81 Ogasawara S, Ueshima K, Ikeda M, Yasui Y, Terashima T, Yamashita T, et al. Sorafenib versus hepatic arterial infusion chemotherapy in patients with advanced hepatocellular carcinoma: A Japanese multi-center large cohort study. J Clin Oncol. 2019;37:323.
82 Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, et al.; SARAH Trial Group. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol. 2017 Dec;18(12):1624–36.
83 Chow PK, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, et al.; Asia-Pacific Hepatocellular Carcinoma Trials Group. SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. J Clin Oncol. 2018 Jul;36(19):1913–21.
84 Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science. 2005 Jan;307(5706):58–62.
85 Kano MR, Komuta Y, Iwata C, Oka M, Shirai YT, Morishita Y, et al. Comparison of the effects of the kinase inhibitors imatinib, sorafenib, and transforming growth factor-beta receptor inhibitor on extravasation of nanoparticles from neovasculature. Cancer Sci. 2009 Jan;100(1):173–80.
86 Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. Nature. 2000 Sep;407(6801):249–57.
87 Tohyama O, Matsui J, Kodama K, Hata-Sugi N, Kimura T, Okamoto K, et al. Antitumor activity of lenvatinib (e7080): an angiogenesis inhibitor that targets multiple receptor tyrosine kinases in preclinical human thyroid cancer models. J Thyroid Res. 2014;2014:638747.
88 Yau T, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, et al. CheckMate 459: A randomized, multi-center phase 3 study of nivolumab vs sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma. ESMO 2019; Abstr #6572, Barcelona.
89 Finn RS, Ryoo BY, Merle P, Kudo M, Bouattour M, Lim HY, et al.; KEYNOTE-240 investigators. Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial. J Clin Oncol. 2020 Jan;38(3):193–202.
90 Cheng AL, Qin S, Ikeda M, Galle PR, Ducreux M, Zhu AX, et al. IMbrave150: Efficacy and safety results from a ph III study evaluating atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (Sor) as first treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). Ann Oncol. 2019;30(suppl 9):LBA3.
91 Lee KH, Ryoo BY, Hsu CH, Numata K, Stein S, Verret W, et al. Phase Ib study results: Subgroup efficacy analysis of Atezolizumab + Bevacizumab in patients with previously untreated, unresectable hepatocellular carcinoma. ILCA, 13th Annual Conference, September 20-22, Chicago, Abstr # O-32.
92 Kudo M, Izumi N, Kokudo N, Matsui O, Sakamoto M, Nakashima O, et al.; HCC Expert Panel of Japan Society of Hepatology. Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. Dig Dis. 2011;29(3):339–64.