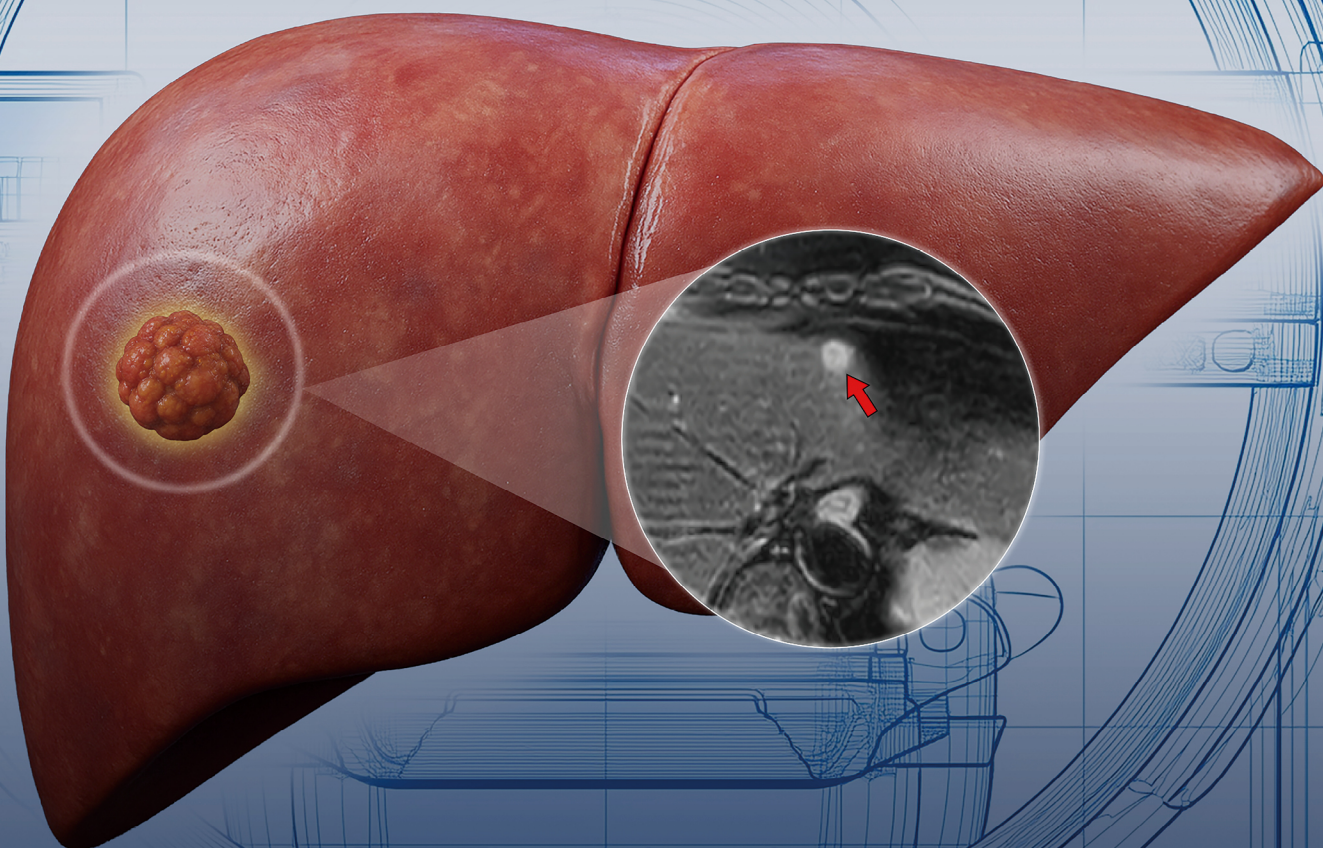


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Taiwan liver cancer association management consensus guidelines for intermediate-stage hepatocellular carcinoma

I-Cheng Lee^{1,2,*}, Hung-Wei Wang^{3,4,*}, Wei Teng^{5,6,*}, Tsung-Jung Lin^{7,*}, Chien-Hung Chen^{8,9,10}, Hsueh-Chou Lai^{3,4}, Teng-Yu Lee^{11,12}, Ching-Wei Chang^{13,14}, Chao-Hung Hung¹⁵, Chia-Yen Dai^{16,17}, Yi-Ping Hung^{2,18}, Ying-Chun Shen^{19,20,21}, Chien-Wei Su^{1,2,22}, Ming-Chih Ho^{23,24}, Wei-Chen Lee^{6,25}, Gar-Yang Chau²⁶, Chin-Tsung Ting^{27,28}, Po-Chin Liang^{29,30}, Chien-An Liu^{2,31}, Pi-Yi Chang^{32,33}, Kuan-Yang Chen⁷, Shi-Ming Lin^{5,6}, Li-Tzong Chen^{34,35}, and Yi-Hsiang Huang^{1,22,36}; TLCA Intermediate Stage HCC Working Group

¹Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital; ²School of Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei; ³Center for Digestive Medicine, Department of Internal Medicine, China Medical University Hospital; ⁴School of Medicine, China Medical University, Taichung; ⁵Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Linkou Medical Center; ⁶College of Medicine, Chang Gung University, Taoyuan; ⁷Department of Gastroenterology, Renai branch, Taipei City Hospital; ⁸Department of Internal Medicine, National Taiwan University College of Medicine; ⁹Department of Internal Medicine, National Taiwan University Hospital; ¹⁰Department of Medicine, National Taiwan University Cancer Center, Taipei; ¹¹Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taichung Veterans General Hospital; ¹²School of Medicine, Chung Shan Medical University, Taichung; ¹³Division of Gastroenterology and Hepatology, Department of Internal Medicine, MacKay Memorial Hospital, Taipei; ¹⁴Department of Medicine, MacKay Medical University, New Taipei; ¹⁵Division of Hepatogastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine; ¹⁶Hepato-Biliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University; ¹⁷School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung; ¹⁸Quality Management Center, Taipei Veterans General Hospital; ¹⁹Department of Medical Oncology, National Taiwan University Cancer Center; ²⁰Department of Oncology, National Taiwan University Hospital; ²¹Graduate Institute of Oncology, National Taiwan University College of Medicine; ²²Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei; ²³Department of Surgery, National Taiwan University Hospital Hsin-Chu Branch, Hsinchu; ²⁴Departments of Surgery, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei; ²⁵Division of Liver and Transplantation Surgery, Chang-Gung Memorial Hospital, Taoyuan; ²⁶Department of Surgery, Taipei Veterans General Hospital; ²⁷Division of Gastrointestinal Surgery, Department of Surgery, Ren-Ai Branch, Taipei City Hospital; ²⁸Department of Health and Welfare, University of Taipei; ²⁹Departments of Medical Imaging and Radiology, National Taiwan University Hospital and College of Medicine, Taipei; ³⁰Department of Medical Imaging, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu; ³¹Department of Radiology, Taipei Veterans General Hospital, Taipei; ³²Department of Medical Imaging, Taichung Veterans General Hospital; ³³Department of Post-Baccalaureate Medicine, National Chung Hsing University, Taichung; ³⁴Kaohsiung Medical University Hospital, Center for Cancer Research, Kaohsiung Medical University, Kaohsiung; ³⁵National Institute of Cancer Research, National Health Research Institutes, Tainan; ³⁶Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan

Corresponding author : Yi-Hsiang Huang

Department of Medical Research, Taipei Veterans General Hospital, 201 Shih-Pai Road, Sec. 2, Taipei 112, Taiwan
Tel: +2-28757434 ext 85201, Fax: +2-28757435, E-mail: yhhuang@vghtpe.gov.tw
<https://orcid.org/0000-0001-5241-5425>

*Lee IC, Wang HW, Teng W, and Lin TJ contribute equally in this manuscript.

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Intermediate-stage hepatocellular carcinoma (HCC) encompasses a diverse patient population that requires individualized treatment strategies and a multidisciplinary approach. Recent advancements in systemic therapy have expanded the therapeutic options for intermediate-stage HCC, allowing for combination strategies such as systemic therapy with transarterial chemoembolization (TACE) and upfront systemic therapy for individuals deemed unsuitable for TACE. Additionally, the ongoing development of treatment modalities for intermediate-stage HCC has improved the potential for curative conversion and tumor downstaging. Nevertheless, consensus on the optimal management of intermediate-stage HCC remains limited. Thus, the primary aim of this study was to develop a set of consensus guidelines for the management of intermediate-stage HCC. To address this gap, the Taiwan Liver Cancer Association (TLCA) established a working group to develop a multidisciplinary strategy for managing intermediate-stage HCC. Here, we present eight consensus statements formulated by this expert panel, which outline criteria for TACE unsuitability, treatment recommendations based on TACE eligibility, and considerations for various modalities, including conventional TACE, drug-eluting bead TACE, and transarterial radioembolization, as well as the appropriate timing for initiating systemic therapy to enable curative conversion and downstaging. These statements provide specific, evidence-based recommendations for clinicians, addressing treatment pathways based on TACE eligibility and other key considerations for intermediate-stage HCC management. The development of this consensus guideline is intended to aid clinicians in selecting the most appropriate treatment pathway for intermediate-stage HCC, support personalized treatment planning, and ultimately enhance the feasibility of achieving curative conversion. ([Clin Mol Hepatol 2025;31:1213-1232](#))

Keywords: Hepatocellular carcinoma; Intermediate stage; Transarterial chemoembolization; Systemic therapy; Immunotherapy

INTRODUCTION

Intermediate-stage hepatocellular carcinoma (HCC) encompasses a heterogeneous patient population, necessitating tailored treatment strategies and a multidisciplinary approach.¹ Recent advances in systemic therapy have contributed to improved outcomes through combination approaches, such as systemic therapy with transarterial chemoembolization (TACE) or upfront systemic therapy in individuals deemed unsuitable for TACE.² Additionally, evolving therapeutic options have increased the potential for curative outcomes and tumor downstaging in intermediate-stage HCC.^{3,4}

In recent years, several consensus guidelines for HCC management have been proposed.^{1,5-7} However, with the continued emergence of clinical trial and real-world data, a unified consensus on optimal treatment strategies for intermediate-stage HCC remains an unmet need. For example,

recent evidence from the 2024 EMERALD-1 and LEAP-012 trials supports combining immunotherapy with TACE to improve progression-free survival (PFS) following locoregional treatment.^{8,9}

In response to these developments, the Taiwan Liver Cancer Association (TLCA) convened a multidisciplinary working group to establish updated treatment guidelines for intermediate-stage HCC. Here, we present eight consensus statements from this expert panel, addressing criteria for TACE unsuitability, treatment recommendations based on TACE eligibility, and considerations among various treatment modalities, including conventional TACE, drug-eluting bead TACE (DEB-TACE), and transarterial radioembolization (TARE), as well as guidance on when to initiate systemic therapy to enable potential curative conversion and tumor downstaging.

Abbreviations:

BCLC, Barcelona Clinic Liver Cancer; CR, complete response; cTACE, conventional transarterial chemoembolization; DCR, disease control rate; HCC, hepatocellular carcinoma; HR, hazard ratio; IRF, independent review facility; LEN, lenvatinib; LRT, locoregional therapy; mRECIST, modified RECIST; NR, not reported; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PFS, progression-free survival; PSM, propensity score matching; RECIST, response evaluation criteria in solid tumors; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TLCA, Taiwan Liver Cancer Association; TTDP, time to disease progression

METHODS

Expert panel

The intermediate-stage HCC working group panel consisted of 24 experts, including 14 hepatologists, four hepatobiliary surgeons, three medical oncologists, and three interventional radiologists, nominated from among the experts and committee members of the TLCA. Four members were assigned to conduct detailed literature reviews prior to discussion. The expert panel convened on three occasions since July 2024.

Definition of intermediate-stage HCC

The definition of intermediate-stage HCC varies between the APPLE consensus and the Barcelona Clinic Liver Cancer (BCLC) staging system. Following a formal vote, the TLCA panel adopted the BCLC stage B classification to define intermediate-stage HCC for this consensus guideline.⁶

Evidence level

The methodological framework for this guideline was based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, an internationally endorsed method for rating the quality of evidence in systematic reviews.¹⁰ Incorporating GRADE allowed for comprehensive appraisal of the supporting evidence, ensuring

methodological rigor in the development of each recommendation. The quality of evidence underlying each statement was systematically evaluated using GRADE criteria (Table 1). All statements were independently reviewed for appropriateness and clarity by members of the drafting committee. Final consensus recommendations were formulated based on a thorough synthesis of evidence from systematic reviews.

Consensus statements

Statement 1: Intermediate-stage (BCLC B) HCC is a heterogeneous group, and treatment should be tailored based on tumor burden and liver reserve (agreement 100%)

Intermediate-stage HCC represents a highly heterogeneous disease, encompassing a broad range of tumor burdens and liver function statuses.¹¹ Survival outcomes in previous randomized controlled trials evaluating TACE have varied substantially, ranging from 14 to 37 months, likely due to significant differences in patient characteristics across studies.² Liver functional reserve and tumor burden are critical determinants incorporated into various subclassification systems and prognostic models designed to predict outcomes following TACE.¹² These models typically include baseline liver function assessments, such as the Child–Pugh score or ALBI grade, tumor burden criteria like tumor size, number, up-to-7 and up-to-11 criteria, and tumor markers including AFP.^{13–17}

Although TACE has historically been the standard treat-

Table 1. Representations of quality of evidence and strength of recommendations

Category	Grade	Description
Quality of evidence		
High quality	A	We are confident that the true effect approximates the effect estimates
Moderate quality	B	Moderate confidence in the effect estimates. The true effect is approximately close to the effect estimate, but it may be substantially different
Low quality	C	Confidence in the estimated effect is limited. The true effect may be substantially different from the effect estimate
Very low quality	D	Effect estimates are largely unreliable. The true effect is likely to be substantially different from the effect estimate
Strength of recommendation		
Strong recommendation for using intervention	1	-
Weak recommendation for using intervention	2	-

ment for intermediate-stage HCC, it is not universally beneficial. Alternative strategies, such as upfront systemic therapies, have been proposed for individuals either unsuitable for or unlikely to respond to TACE.^{1,18,19} Conversely, curative-intent options, including surgical resection, local ablation, or liver transplantation (LT) under extended criteria, may be feasible for select individuals with intermediate-stage HCC and limited tumor burden.^{20,21} Accordingly, effective management of intermediate-stage HCC demands tailored therapeutic strategies and a multidisciplinary approach, with treatment selection individualized based on tumor burden and liver reserve to optimize outcomes and improve survival.

Statement 2: TACE is widely used for treating unresectable intermediate-stage HCC. However, not all patients are suitable for TACE, particularly those with a tumor burden exceeding the up-to-11 criteria or with unfavorable radiological patterns (agreement 100%, evidence B)

Achieving radiologic responses while preserving liver function following TACE is critical for prolonging overall survival (OS) in individuals with HCC. Therefore, identifying those unlikely to respond to TACE or at high risk of hepatic function deterioration is essential to avoid unnecessary TACE in individuals who are poor responders.

Definitions of high tumor burden differ across various subclassification systems and prognostic models.^{12,22,23} The up-to-7 criteria are frequently applied to define high tumor burden in intermediate-stage HCC, as demonstrated in models such as Bolondi's subclassifications,²⁴ the Kinki criteria,²⁵ and the STATE score.¹⁶ However, up-to-7 was originally developed for early-stage HCC candidates under evaluation for LT.^{22,26} and may not accurately stratify tumor burden in intermediate-stage HCC. Recent studies indicate that the up-to-11 criteria outperform up-to-7 in predicting survival outcomes after TACE.¹⁴ In Taiwan, the 7–11 criteria have been introduced to classify intermediate-stage HCC into low, intermediate, and high tumor burden groups.^{14,15} The 7–11 criteria effectively predict radiologic response and OS in intermediate-stage HCC,²⁷ with cure conversion rates after immunotherapy decreasing as tumor burden increases.³ Moreover, individuals exceeding the up-to-11 threshold experience a significantly elevated risk of hepatic function deterioration following TACE.^{27,28} Therefore, a tu-

mor burden exceeding the up-to-11 criteria is strongly discouraged for TACE due to the low likelihood of radiologic response and the high risk of hepatic function deterioration, whereas an intermediate tumor burden (between up-to-7 and up-to-11) is regarded as relatively unsuitable for TACE.

Radiologic pattern is also an important criterion for assessing TACE unsuitability.¹ Radiologic features of HCC can be classified into encapsulated nodular type, simple nodular type with extranodular growth, confluent multinodular type, and infiltrative type.²⁹ A study from Taiwan reported that encapsulated nodular HCC had the highest objective response rate (ORR) after TACE (58%), followed by the extranodular type (45.8%), confluent multinodular type (29%), and infiltrative type (19.5%).³⁰ Both tumor burden and radiologic morphology were significantly associated with ORR and OS. These findings suggest that confluent multinodular and infiltrative HCC demonstrate markedly poorer ORR and OS following TACE and should be considered key factors in identifying TACE-unsuitable individuals. A combined approach, integrating tumor burden thresholds, radiologic features, and prognostic models such as the ALBI-TAE score developed in a Taiwanese cohort,¹⁴ can enhance the identification of patients who are less likely to benefit from TACE.

Statement 3: For intermediate-stage HCC that is unsuitable for TACE, systemic therapy should be initiated as the first-line treatment (agreement 95%, evidence C)

Based on multiple treatment guidelines, systemic therapy is recommended for individuals who are unsuitable or ineligible for effective TACE.^{1,6,7,29,31} Repeated TACE in individuals who have become refractory to treatment often leads to hepatic function deterioration and consequently poor prognosis.³² Subgroup analyses from four previous phase III clinical trials indicate that systemic therapy can be effective in individuals with BCLC stage B disease. In the REFLECT trial,³³ lenvatinib demonstrated similar OS (hazard ratio [HR]: 0.91, 95% confidence interval [CI]: 0.65–1.28; 18.5 vs. 17.3 months) but superior PFS compared to sorafenib (HR: 0.70, 95% CI: 0.50–0.99; 9.1 vs. 5.5 months). Japanese subset analyses³⁴ revealed a higher ORR with lenvatinib than with sorafenib (OR: 10.2, 95% CI: 2.99–35.0; 61.3% vs. 11.8%). In the IMbrave150 trial,³⁵ patients treated with

atezolizumab plus bevacizumab demonstrated a trend of better OS (HR: 0.64, 95% CI: 0.31–1.31; 25.8 vs. 18.1 months), PFS (HR: 0.66, 95% CI: 0.38–1.15; 12.6 vs. 8.6 months), and ORR (OR: 2.33, 95% CI: 0.79–6.91; 44% vs. 25%) than those with sorafenib. In the HIMALAYA trial, patients receiving the combination of tremelimumab and durvalumab exhibited a trend towards improved OS (HR, 0.87; 95% CI: 0.57–1.33),³⁶ with 4-year update data indicating a hazard ratio of 0.81 (95% CI: 0.55–1.19) compared to those treated with sorafenib.³⁷ Similarly, the CheckMate 9DW trial³⁸ reported trends of enhanced OS with the administration of nivolumab plus ipilimumab. In summary, individuals with intermediate-stage HCC derived substantial benefits from systemic therapy across these trials, with superior tumor responses and survival outcomes compared to historical outcomes with TACE alone.

Lenvatinib administered prior to TACE may offer greater survival benefits for TACE-unsuitable individuals, such as those with bilobar multifocal nodules, compared to TACE alone.³⁹ A proof-of-concept study reported that pretreatment with lenvatinib followed by TACE in individuals beyond the up-to-7 criteria with Child–Pugh A liver function resulted in favorable outcomes.¹⁸ Lenvatinib was associated with significantly longer PFS than that with TACE alone (16.0 vs. 3.0 months; HR: 0.19; 95% CI: 0.10–0.35; $P<0.001$). Improved OS was also observed (37.9 vs. 21.3 months; HR: 0.48; 95% CI: 0.16–0.79; $P<0.01$), demonstrating a clear advantage. Two real-world Japanese studies further indicated that lenvatinib followed by selective TACE improved TACE efficacy and prolonged outcomes. One study of 208 intermediate-stage HCC individuals receiving early lenvatinib or TACE alone⁴⁰ showed, via Cox modeling adjusted by Inverse Probability Weighting (IPW), that lenvatinib significantly improved OS in those beyond up-to-7 (HR: 0.230; 95% CI: 0.059–0.904; $P=0.035$). Another prospective study in 31 individuals with BCLC-B2 suggested lenvatinib offered OS of 17.0 months (95% CI: 15.3–19.2) and PFS of 10.4 months (95% CI: 6.6–13.8), with a comparable safety profile.⁴¹ Additionally, atezolizumab plus bevacizumab showed promising efficacy in uHCC beyond up-to-7,⁴² with 6-month PFS of 63.2% and mPFS of 8.0 months, and favorable ORR/disease control rate (DCR) per response evaluation criteria in solid tumors (RECIST) and modified RECIST (mRECIST) (17.7%/84.7% and 42.5%/86.2%, respectively). A recent real-world study comparing

21 patients receiving atezolizumab plus bevacizumab and 28 patients receiving lenvatinib for BCLC stage B HCC exceeding the up-to-7 criteria showed no significant differences in OS (19.8 vs. 22.2 months, $P=0.763$), PFS (10.2 vs. 7.2 months, $P=0.343$), ORR, or DCR between the atezolizumab–bevacizumab and lenvatinib groups.⁴³ Another study comparing 177 TACE-unsuitable patients treated with atezolizumab plus bevacizumab and 181 patients treated with lenvatinib as first-line systemic therapy for BCLC stage B HCC demonstrated a significantly longer PFS in the atezolizumab–bevacizumab group after propensity score matching (10.2 vs. 6.9 months, $P=0.020$).⁴⁴ Among the subgroup of patients with tumors exceeding the up-to-7 criteria, the median PFS was also significantly longer in the atezolizumab–bevacizumab group compared to the lenvatinib group (10.5 vs. 6.3 months, $P=0.044$). These findings suggest that both therapeutic options are feasible, but atezolizumab–bevacizumab might be more suitable for this patient population; however, further large-scale prospective studies are needed to validate these results. In one retrospective real-world study,⁴⁵ TACE combined with lenvatinib and tislelizumab significantly improved PFS (8.5 vs. 4.4 months) and OS (31.5 vs. 18.5 months; all $P<0.001$) compared to TACE alone in individuals beyond the up-to-11 criteria, with acceptable safety. Therefore, systemic therapy may be appropriate for managing intermediate-stage HCC beyond the up-to-11 criteria.

Statement 4: To improve outcomes (PFS) in intermediate-stage HCC, systemic therapy combined with TACE can be used in TACE-eligible cases (agreement 100%, evidence B)

In the context of intermediate-stage HCC with high tumor burden, emerging evidence supports the use of systemic therapies, including tyrosine kinase inhibitors (TKIs) or immunotherapies, in combination with TACE as a promising approach over TACE alone.

Sorafenib has demonstrated efficacy in intermediate-stage HCC across multiple large-scale real-world studies. For example, the GIDEON trial reported significantly longer median OS in individuals with BCLC-B disease treated with sorafenib compared to those with BCLC-C, suggesting benefit in earlier-stage disease.⁴⁶ Additionally, combining sorafenib with TACE has been shown to improve outcomes in individuals with high tumor burden, where TACE alone

may be insufficient (SOFIA trial: OS 20.6 vs. 8.4 months; INSIGHT trial: OS 19.6 vs. 13.6 months).^{47,48} The TACTICS trial, a randomized multicenter study, compared TACE plus sorafenib to TACE alone in unresectable HCC. Among 156 participants, 80 received combination therapy, and 76 underwent TACE alone. Median OS was 36.2 months in the combination group vs. 30.8 months in the TACE-alone group, though the difference was not statistically significant (HR: 0.861; $P=0.40$). However, TACE-specific PFS significantly improved with combination therapy, particularly among individuals with tumor burdens beyond the up-to-7 criteria.^{49,50}

The TACTICS-L trial demonstrated the significant efficacy of combining lenvatinib with TACE in treating individuals with unresectable intermediate-stage HCC. The trial reported a high ORR of 79.0% at 4 weeks following the first TACE session. The best response ORR reached 88.7%, with a complete response (CR) rate of 67.7%. Median PFS was 28.0 months, indicating favorable long-term disease control. However, median OS was not reached during follow-up, suggesting a potential for extended survival benefit.⁵¹ An additional analysis compared lenvatinib-TACE (LEN-TACE) with TACE alone, using inverse probability weighting to adjust for baseline characteristics. Results indicated that LEN-TACE was more effective, particularly for individuals classified as “up-to-7 OUT.” This group demonstrated improved PFS (HR: 0.49) and OS (HR: 0.41) compared to the “up-to-7 IN” group, which also showed benefit with LEN-TACE but to a lesser degree (PFS HR: 0.70; OS HR: 0.89). The study concluded that “up-to-7 OUT” individuals are unsuitable for TACE monotherapy and that LEN-TACE offers a significantly superior treatment strategy for both groups.⁵²

In one retrospective cohort study, Zhou et al.⁵³ demonstrated that combining TACE with lenvatinib (TACE-Lenv) significantly improved outcomes in individuals with intermediate-stage HCC. Median OS was 28 months in the TACE-Lenv group vs. 12 months for TACE alone ($P=0.017$). PFS was 8.2 months with TACE-Lenv compared to 3.7 months with TACE alone using mRECIST ($P=0.018$), and 8.9 vs. 3.7 months using RECIST v1.1 ($P=0.003$). Notably, subgroups with larger tumors (114 to 162 mm) experienced significant survival benefits ($P<0.05$).⁵³

One retrospective study demonstrates that combining TACE with atezolizumab and bevacizumab (TACE+Atez/

Bev) significantly improves outcomes in intermediate-stage HCC. After applying the PSM, the median OS was not reached for TACE+Atez/Bev vs. 21.4 months for TACE alone ($P=0.008$), and median PFS was 21.7 vs. 9.7 months ($P=0.009$). The combination also showed superior ORR (66.7% vs. 38.1%, $P=0.009$) and DCR (92.9% vs. 57.1%, $P<0.001$). The survival benefit (both PFS and OS) of combining TACE with atezolizumab and bevacizumab was significantly higher than that of TACE alone, especially when the tumor burden exceeds the up-to-7 criteria.⁵⁴

Recently, two phase 3 studies investigating intermediate-stage HCC reported positive outcomes. The EMERALD-1 Phase 3 study met its primary endpoint, demonstrating a statistically significant improvement in PFS among individuals with unresectable HCC eligible for embolization. Median PFS was 15.0 months in the group receiving durvalumab, bevacizumab, and TACE, compared to 8.2 months in the placebo plus TACE group (HR: 0.77, $P=0.032$). Most participants had intermediate-stage HCC, with some presenting with portal vein invasion (Vp1 or Vp2). The PFS benefit was consistent across subgroups, including baseline tumor burden within or beyond the up-to-7 criteria, and the safety profile was manageable. This regimen may represent a new standard of care regardless of tumor burden.⁸

The LEAP-012 Phase 3 trial demonstrated that lenvatinib, pembrolizumab, and TACE significantly improved outcomes in intermediate-stage HCC. Median PFS was 14.6 months vs. 10.0 months in the placebo group (HR: 0.66; $P=0.0002$), and ORR was higher (46.8% vs. 33.3%; $P=0.0005$). While OS data remain immature, early results suggest a favorable trend. Subgroup analysis showed consistent PFS benefit, with notable OS improvement in individuals with tumor burden scores between 6 and 12.⁹ Furthermore, several Phase III clinical trials are currently underway to evaluate the efficacy of on-demand TACE combined with immune checkpoint inhibitors (with or without anti-vascular endothelial growth factor [VEGF] agents) compared to on-demand TACE alone in individuals with intermediate-stage HCC. These include TACE-3 (NCT04268888), CheckMate 74W (NCT04340193), TALENTACE (NCT047126430),⁵⁵ and EMERALD-3 (NCT05301842). TACE is hypothesized to release neoantigens and act as an immune modulator, thereby enhancing the efficacy of systemic therapies through synergistic mechanisms. When combined with immune checkpoint inhibitors and anti-VEGF or TKIs agents, on-

demand TACE or partial embolization may improve tumor response rates, especially in individuals with high tumor burden.⁵⁶

Systemic therapies, including TKIs and immunotherapies (e.g., sorafenib, lenvatinib, durvalumab–bevacizumab, lenvatinib–pembrolizumab), when combined with TACE, have significantly improved survival in individuals with intermediate-stage HCC, particularly those with higher tumor burdens. These regimens are now favored over TACE alone. Growing evidence supports the integration of systemic therapy with TACE, which has been shown to enhance PFS in appropriate candidates. As a result, combination therapy is increasingly regarded as a promising treatment approach for intermediate-stage HCC. A comparison of systemic therapy studies involving individuals with intermediate-stage HCC eligible for TACE is provided in Table 2.

It should be noted that none of the current trials to date have demonstrated a statistically significant improvement in OS compared to TACE alone. For example, although the TACTICS trial showed prolonged TACE-specific PFS, it failed to demonstrate a survival benefit. Similarly, the LEAP-012 and EMERALD-1 trials have thus far reported immature or neutral OS results. Nevertheless, in the setting of curative conversion, achieving a higher ORR may increase the likelihood of successful downstaging or conversion to curative therapies, which could potentially translate into improved OS outcomes in selected patients. Based on this, our committee reached a consensus to support the use of combination strategies primarily aimed at improving PFS and ORR. Otherwise, this approach should currently be considered investigational or selectively applied, pending confirmation from ongoing or future trials with mature OS data.

Statement 5: For TACE-refractory intermediate-stage HCC (failed by at least two TACE sessions), immunotherapy is recommended as the first-line treatment, with lenvatinib or sorafenib as alternatives (agreement 100%, evidence B)

TACE is frequently overused in individuals with intermediate-stage HCC, which can lead to deterioration in liver function.^{28,57,58} TACE failure or refractoriness in liver cancer management is defined by a poor tumor response or continued disease progression despite multiple TACE sessions. Insufficient tumor response refers to cases where

over 50% of the lesion remains viable in two or more sessions, indicating limited therapeutic effect. Disease progression is characterized by two or more instances of tumor growth, evidenced by an increased number of tumors relative to pre-treatment imaging. Both scenarios indicate the need to transition from TACE to systemic therapy to ensure more effective management strategies are pursued for individuals with liver cancer.^{1,6,7,29,59,60}

A study by Ogasawara et al.³² demonstrated that switching to sorafenib in TACE-refractory intermediate-stage HCC significantly improved survival outcomes. Median OS was 25.4 months for the sorafenib group, compared to 11.5 months for individuals continuing TACE ($P=0.003$). Additionally, the median time to disease progression (TTDP) was 22.3 months with sorafenib vs. 7.7 months with continued TACE ($P=0.001$).³² Similarly, Arizumi et al.⁶¹ evaluated 497 individuals with HCC treated with TACE and identified 56 as refractory. The sorafenib-treated group demonstrated a significantly longer OS (24.7 months) compared to the TACE group (13.6 months, $P=0.002$). A recent real-world study compared 163 patients who continued with TACE and 108 patients who shifted to sorafenib treatment after confirmation of refractoriness to TACE therapy. In the sorafenib group, the median TTDP was 23.4 months, and the median OS was 25.3 months. In contrast, the TACE group had a median TTDP of 11.6 months and a median OS of 14.2 months ($P=0.0001$).⁶² These findings underscore the importance of early assessment of TACE efficacy and prompt transition to sorafenib when warranted. Sorafenib remains a viable systemic option for improving survival in intermediate-stage HCC following TACE failure.⁶¹ A multicenter cohort study further showed that lenvatinib significantly prolonged PFS compared to both sorafenib and TACE, with median PFS of 5.8, 3.2, and 2.4 months, respectively ($P<0.001$), indicating superior efficacy.⁶³

The encouraging outcomes of recent first-line systemic therapies, including IMbrave150,^{35,64} HIMALAYA,³⁷ and CheckMate 9DW,³⁸ in most individuals with advanced-stage HCC also suggest potential benefit in intermediate-stages, such as BCLC stage B, where some may be refractory to TACE. Recent immunotherapies have improved OS and recurrence-free survival (RFS) compared to TKIs. The IMbrave150 exploratory analysis shows that atezolizumab combined with bevacizumab enhances OS and PFS compared to sorafenib in unresectable BCLC stage B HCC.

Table 2. Studies of systemic therapy in patients with intermediate-stage HCC who were eligible for TACE

Study	Design	Intervention and patient number	Treatment response (%)	mPFS (mo)	mOS (mo)	Tumor burden (beyond up-to-7): subgroup analysis
TACTICS ⁵⁰	Phase 3	TACE plus sorafenib (n=80) vs. TACE (n=76)	ORR: 71.3 vs. 61.8	22.8 vs. 13.5 (HR: 0.661, <i>P</i> =0.02)	36.2 vs. 30.8 (HR: 0.861, <i>P</i> =0.40)	Not significant for PFS & OS
TACTICS-L ⁵¹	Phase 2	TACE plus lenvatinib (n=62)	ORR: 88.7 CR: 67.7	28	Not reached	Not significant for PFS & OS
Zhou et al. ⁵³	Retrospective	TACE plus lenvatinib (n=32) vs. TACE (n=32) (PSM)	ORR: 94 vs. 47 DCR: 97 vs. 62	8.2 vs. 3.7 (<i>P</i> =0.018)	28.0 vs. 12.0 (<i>P</i> =0.017)	Significant for PFS & OS
LEN-TACE ¹⁸	Retrospective	LEN-TACE (n=30) vs. TACE (n=60) (PSM)	ORR: 73.3 vs. 33.3	16 vs. 3 (HR: 0.19, <i>P</i> <0.001)	37.9 vs. 21.3 (HR: 0.48, <i>P</i> <0.01)	Significant for PFS & OS
Zheng et al. ⁵⁴	Retrospective	TACE plus atezolizumab/ bevacizumab (n=42) vs. TACE (n=42) (PSM)	ORR: 66.7 vs. 38.1	21.7 vs. 9.7 (<i>P</i> =0.009)	Not reached vs. 21.4 (<i>P</i> =0.008)	Significant for PFS & OS
EMERALD-1 ⁸	Phase 3	1:1:1 randomization (n=616) to 1. TACE, then durvalumab+bevacizumab 2. TACE, then durvalumab 3. TACE, then placebo	ORR: 43.6 vs. 41.0 vs. 29.6	15 vs. 10 vs. 8.2 (1 vs. 3, HR: 0.77, <i>P</i> =0.032; 1 vs. 3, HR: 0.94, <i>P</i> =0.638)	NR	Not significant for PFS & OS
LEAP-012 ⁹	Phase 3	1:1 randomization (n=480) to 1. Lenvatinib plus pembrolizumab plus TACE 2. Placebo plus TACE	RECIST ORR: 46.8 vs. 33.3 mRECIST ORR: 71.3 vs. 49.8	14.6 vs. 10.0 (HR: 0.66, <i>P</i> =0.0002)	Both not reached (HR: 0.80, <i>P</i> =0.0867)	Significant for PFS & OS

CR, complete response; DCR, disease control rate; HCC, hepatocellular carcinoma; HR, hazard ratio; LEN, lenvatinib; mRECIST, modified RECIST; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PSM, propensity score matching; RECIST, response evaluation criteria in solid tumors; TACE, transarterial chemoembolization.

Notably, 43% of patients in the atezolizumab–bevacizumab arm had received prior TACE treatment. The combination yielded HRs of 0.63 (OS) and 0.64 (PFS), with ORRs of 43–50%, outperforming sorafenib's 26–30%. These findings support its use as a preferred therapy for systemic treatment-naïve individuals ineligible for or progressing after locoregional therapies.⁶⁵ A comparison table of systemic therapy trials in intermediate-stage HCC refractory to TACE is presented in Table 3.

Phase 3 trials for intermediate-stage HCC often include individuals unresponsive to multiple TACE sessions. However, the current evidence base for immunotherapy in TACE-refractory BCLC stage B patients remains limited. Most of the available data on immunotherapy in this setting are derived from exploratory analyses of major phase III trials, which may be underpowered to draw definitive conclusions for the post-TACE-refractory population. Administering systemic therapy prior to TACE has shown promise by promoting vascular normalization, suppressing hypoxia-inducible factor-1, and upregulating VEGF, PDGF, and angiopoietin-2. These mechanisms enhance the delivery of lipiodol mixed with anticancer drugs, improving tumor targeting.^{66,67} Although current evidence supporting the use of immunotherapy in TACE-refractory HCC remains limited, it is wide-

ly accepted that systemic therapy should be initiated in such cases, with immunotherapy currently preferred over TKIs as the first-line systemic treatment. Based on this rationale, our committee reached a unified agreement to recommend systemic therapy as the first-line treatment for TACE-refractory intermediate-stage HCC, supported by subgroup analyses of phase 3 trials and expert consensus. Nonetheless, dedicated prospective studies are warranted to confirm the survival benefit of immunotherapy in this specific patient population.

Statement 6: Y90 TARE may serve as an alternative therapy to TACE (agreement 100%, evidence B)

Yttrium-90 (⁹⁰Y) selective internal radiation therapy is a treatment method whereby radiation is delivered to liver tumors through the hepatic artery.⁶⁸ Yttrium-90 microspheres are typically infused into the hepatic artery to localize radiation delivery to liver tumors, thereby maintaining radiation exposure to healthy liver tissue within a safe threshold to minimize damage. Unlike conventional transarterial chemoembolization (cTACE), the primary therapeutic effect arises from the radiotherapeutic action rather than ischemic or chemotherapeutic mechanisms due to embolization.

A prior phase II randomized controlled trial enrolled 72

Table 3. Studies of systemic therapy in patients with intermediate-stage HCC who were refractory to TACE

Study	Design	Intervention and patient number	Treatment response (%)	mPFS (mo)	mOS (mo)
Ogasawara et al. ³²	Retrospective	Sorafenib-group, n=20 TACE-group, n=36	RECIST: DCR: 80 vs. 25 mRECIST: DCR: 80 vs. 25	mTTDP: 22.3 vs. 7.7 (<i>P</i> =0.001)	25.4 vs. 11.5 (<i>P</i> =0.003)
Ashour et al. ⁶²	Retrospective	Sorafenib-group, n=108 TACE-group, n=163	NR	mTTDP: 23.4 vs. 11.6 (<i>P</i> =0.0001)	25.3 vs. 14.2 (<i>P</i> =0.0001)
Arizumi et al. ⁶¹	Retrospective	Sorafenib-group, n=32 TACE-group, n=24	NR	NR	24.7 vs. 13.6 (<i>P</i> =0.002)
Shimose et al. ⁶³	Retrospective	Lenvatinib-group, n=45 Sorafenib-group, n=53 TACE-group, n=73	ORR: 42.2 vs. 1.9 vs. 6.8 DCR: 88.9 vs. 56.6 vs. 19	mPFS: 5.8 vs. 3.2 vs. 2.8 (<i>P</i> <0.001)	NR
IMbrave 150 ⁶⁴	Phase 3 (exploratory analysis)	Atezolizumab+bevacizumab, n=49 Sorafenib, n=24	RECIST: ORR: 43 vs. 26 mRECIST: ORR: 50 vs. 30	IRF RECIST 1.1 mPFS: 12.6 vs. 8.6 Investigator-assessed RECIST 1.1 mPFS: 10.0 vs. 4.2	25.8 vs. 21.9

DCR, disease control rate; HCC, hepatocellular carcinoma; IRF, independent review facility; mRECIST, modified RECIST; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumors; TACE, transarterial chemoembolization; TTDP, time to disease progression.

patients with unresectable HCC, of whom 61 (84.7%) were classified as stage B according to the BCLC system.⁶⁹ Interim analysis showed that among the 38 patients treated with TARE, the median TTP was 17.1 months, whereas for the 34 patients treated with DEB-TACE, the median TTP was 9.5 months (intention-to-treat [ITT] group HR, 0.36; 95% CI: 0.18–0.70; $P=0.002$). Median OS for the TARE and DEB-TACE groups was 30.2 months and 15.6 months, respectively (ITT group HR, 0.48; 95% CI: 0.28–0.82; $P=0.006$). These statistically significant differences led to early termination of the clinical trial.

The meta-analysis compared TACE and TARE, with OS as the primary endpoint and TTP as the secondary endpoint.⁷⁰ Seventeen studies encompassing 2,465 patients were included, with the majority diagnosed with BCLC stage B disease, accounting for 42.8% of the total cohort. The results indicated no significant differences in OS between the two treatment modalities. Among the three studies that analyzed TTP, a significantly longer TTP was observed in the TARE group than in the TACE group (mean TTP of 17.5 months vs. 9.8 months; mean TTP difference of 4.8 months, 95% CI: 1.3–8.3 months).

Two TARE studies were conducted in Taiwan, both employing single-arm designs. One involved the RESIN registry, in which 83 of 107 participants had HCC, and 51 (61.5%) had BCLC stage B disease.⁷¹ The ORR among participants with HCC was 55.41%, with an OS of 24.07 months; eight individuals were successfully downstaged (DS) or downsized and proceeded to other therapies. The second study, conducted by Kaohsiung Chang Gung Memorial Hospital, enrolled 32 individuals with unresectable HCC.⁷² Only three experienced portal vein invasion, and the median follow-up was 18 months. OS rates at 3, 6, and 12 months were 94%, 87%, and 59%, respectively. The PFS rates were 78%, 64%, and 60%, respectively. In terms of tumor response, seven individuals (21.9%) achieved CR, 14 (43.7%) partial response (PR), four (12.5%) stable disease (SD), and seven (21.9%) progressive disease (PD); 11 individuals (34.4%) were successfully DS.

Therefore, comprehensive evaluation is required when selecting between TACE and TARE.⁷³ Relevant factors include the individual's socioeconomic status, behavioral patterns, comorbidities, hepatic function, liver volume targeted, tumor stage, presence of vascular invasion, and extent of lung shunting. Additional considerations involve the

treating physician's expertise and whether the procedure is covered by the individual's health insurance. Ultimately, the decision should be shared between the physician and the individual and tailored to the individual's clinical context.

The combination of TARE and immunotherapy represents a novel therapeutic strategy currently under investigation. A recent phase I/IIa trial evaluating Yttrium-90 radioembolization in combination with durvalumab for patients with locally advanced, unresectable HCC reported an 18-month OS rate of 58.3%, a median PFS of 6.9 months, a CR rate of 29.2%, and an ORR of 83.3%. Grade 3 treatment-related adverse events occurred in 8.7% of patients.⁷⁴ These findings suggest that the combination of TARE and immune checkpoint inhibitors demonstrates a favorable safety profile and promising antitumor activity, warranting further evaluation in large-scale, controlled trials.

Statement 7: The efficacy of DEB-TACE is comparable to that of cTACE, but the adverse reactions associated with cTACE can be alleviated (agreement 100%, evidence B)

HCC TACE is recommended as a primary treatment option for intermediate-stage HCC in current clinical guidelines.^{5,75,76} In cTACE, lipiodol and chemotherapeutic agents such as cisplatin or doxorubicin are administered via the hepatic artery, followed by gelatin sponge particles to embolize the tumor's blood supply. DEB-TACE uses microspheres as both drug carriers and embolic agents to enable continuous release of cytotoxic agents, resulting in permanent vascular occlusion.⁷⁷ Currently, three types of DEBs are available: (1) 100–300 μm DC Bead, (2) 30–60 μm HepaSphere, and (3) 200 μm LifePearl.⁷⁸ Although smaller DEBs (<100 μm) may theoretically achieve more complete embolization, no head-to-head studies have directly compared DEB size. Therefore, safety concerns, such as pulmonary embolization, tumor rupture, and biliary injury, must be considered when using smaller particles.

A Turkish single-center study on DEB-TACE enrolled 133 individuals with unresectable HCC, 58 (48%) of whom were at intermediate-stage B.⁷⁹ The treatment responses were as follows: CR in 20 individuals (17%), PR in 36 (32%), SD in 24 (21%), and PD in 35 (30%). The median follow-up period was 14 months (range, 1–77 months), and the median PFS and OS were 4 and 11 months, respectively. These findings suggest that DEB-TACE is an effective treatment

strategy for unresectable HCC, including individuals with intermediate-stage B disease.

In a Chinese prospective study of 120 individuals with HCC,⁸⁰ 68 underwent cTACE (of whom 24, or 35.3%, had BCLC stage B), and 52 underwent DEB-TACE (24, or 56.2%, had BCLC stage B). The DEB-TACE group achieved a higher CR rate (30.8%) compared with that of the cTACE group (7.4%). In terms of survival, the DEB-TACE group had a longer median PFS of 15 months (95% CI: 12–18 months) compared with 11 months (95% CI: 10–12 months) in the cTACE group. Median OS was also longer in the DEB-TACE group, at 25 months (95% CI: 22–28 months) compared with 21 months (95% CI: 18–24 months) in the cTACE group. Multivariate analysis confirmed DEB-TACE as an independent predictor of CR.

However, a meta-analysis compared OS, adverse events, and response rates between individuals who received cTACE and DEB-TACE, incorporating a total of six randomized controlled trials.⁸¹ The meta-analysis identified no significant differences in treatment outcomes or major complications between the two groups.

A systematic review evaluated the safety and efficacy of cTACE and DEB-TACE using a comprehensive database search and a rigorous screening process.⁸² A total of 10 studies were included, comprising two randomized controlled trials, one meta-analysis, and seven observational studies. In total, 5,288 treatment-naïve individuals with unresectable HCC were analyzed. The findings indicated comparable safety between the two modalities, but suggested superior efficacy for DEB-TACE when patients were carefully selected. However, the study did not specify the proportion of individuals with BCLC stage B disease.

Statement 8: For curative conversion of intermediate-stage HCC, liver-directed therapy, systemic therapy, or combined therapy followed by curative therapy should be considered to achieve a cancer-free and drug-free state (agreement 100%, evidence B)

TACE represents the standard therapy for most individuals with treatment-naïve intermediate-stage HCC, and whenever feasible, curative treatments should be prioritized over palliative treatments as they provide the best outcomes.⁸³ As intermediate-stage HCC is potentially curable except in cases with an extremely high tumor burden, such as bilobar multifocal disease >10 or disease exceed-

ing the up-to-11 criteria,²⁷ the therapeutic goal is to achieve clinical or pathological CR and a drug-free status.

LT enables the removal of both visible and microscopic tumor lesions, along with the diseased liver. For individuals beyond the Milan criteria, growing evidence over the last two decades supports expanding transplant criteria,^{84–88} while another strategy uses locoregional or systemic therapies to downstage the disease into Milan eligibility. The potential of TARE to induce tumor downstaging, thereby enabling previously ineligible patients to meet transplantation criteria, garnered substantial interest within the medical community. A recent prospective multiregional study based on the UNOS-DS criteria⁸⁹ reported a high probability of initial downstaging with a low risk of subsequent progression (post-LT HCC recurrence rate, 7.9%) and comparable efficacy between TACE and yttrium-90 radioembolization (89% vs. 86%) as initial downstaging modalities. A retrospective study showed that approximately 39% of patients were successfully DS at 6 months, and 23% of these patients ultimately underwent curative treatment, primarily LT or resection, after Y-90 radioembolization.⁹⁰ Patients who achieved DS had a significantly longer OS (51 vs. 10 months, $P<0.001$) and PFS (47 vs. 11 months, $P<0.001$) than those without DS. Surgery after DS further improved the survival, with a median OS of 71 months. In a large 11-year study of 413 patients,⁹¹ with more than half of the patients (51.8%) beyond the up-to-7 criteria treated by yttrium-90 radioembolization, notably, 70 (17%) patients were DS to curative therapy (either resection or LT), and these individuals achieved dramatically prolonged survival (79.7 months), underscoring the potential of adequate radiation dosing and tumor control to improve long-term outcomes. Another study⁹² enrolled 214 patients treated with yttrium-90 radioembolization; 30% were successfully DS and listed for LT and 23% ultimately underwent transplantation. Patients receiving LT had a 5-year OS rate of 61%, with better outcomes observed in those with a lower tumor burden.

For more advanced HCC, combining TACE with local percutaneous thermal ablation may improve survival and limit disease progression. In individuals DS with TACE, local ablation may improve long-term outcomes. One retrospective study found that OS and DFS were similar between individuals undergoing radiofrequency ablation (RFA) for TACE-DS HCC and those who initially met the Milan criteria ($P=0.74$ and $P=0.39$, respectively) after propensity

score matching.⁹³ No significant differences were found in the OS and RFS rates ($P=0.981$ and $P=0.586$) between the groups following microwave ablation.⁹⁴ Embolization may contribute to downstaging by shrinking tumors or eliminating satellite lesions, thus enabling transplantation with a curative intent.

External beam radiation therapy (EBRT) has also emerged as an option in select cases. In a meta-analysis, stereotactic body radiotherapy (SBRT) demonstrated comparable OS (HR: 0.83, $P=0.44$) and significantly superior local control (HR: 0.25, $P=0.006$) compared to TACE, without significant toxicity in patients with HCC.⁹⁵ In patients on the LT waitlist, SBRT has been shown to be safe, achieving significantly higher tumor control rates and reducing the risk of waitlist dropout.⁹⁶ SBRT is also an effective treatment option for patients with inoperable HCC who experience an incomplete response following TACE.⁹⁷ In one study, individuals received SBRT as bridging therapy before LT, with 64% initially outside the Milan criteria; the 5-year post-transplant survival rate was 75%.⁹⁸ The phase 2 TRENDY trial, which compared SBRT with TACE in patients with initially unresectable HCC eligible for definitive or downstaging therapy, found no significant difference in median time to progression between the two groups.⁹⁹ However, SBRT showed a trend toward improved local control compared to TACE. These findings suggest that EBRT may offer advantages in local tumor control and PFS for patients with unresectable HCC, supporting its potential use as an alternative to conventional bridging or downstaging therapies. Collectively, numerous studies have demonstrated that locoregional therapy (LRT) can downstage intermediate-stage HCC initially beyond the Milan criteria but is limited to liver-only disease without vascular invasion, achieving eligibility for transplant in >80% of cases and yielding post-LT oncologic outcomes comparable to those within the criteria at baseline.

Upfront systemic therapy, followed by LRT, has emerged as a novel treatment strategy for intermediate-stage HCC. Use of VEGF inhibitors reduces microvascular density, tumor interstitial pressure, and vascular permeability while normalizing tumor vasculature, thereby enhancing drug delivery and improving the therapeutic effect of subsequent selective TACE.⁶⁷ With advancements in systemic therapy, the conversion resection rate has increased to 15.9–30.6%.^{100–102} LEN-TACE sequential therapy was developed through

proof-of-concept studies demonstrating significant OS prolongation in patients with intermediate-stage HCC beyond the up-to-7 criteria.^{18,103} Moreover, five of 30 individuals (17%) receiving LEN-TACE sequential therapy achieved cancer-free and drug-free status, suggesting the potential for cure in selected patients. Another strategy is atezolizumab/bevacizumab curative (ABC) conversion,³ in which curative modalities such as resection, RFA, or curative TACE are employed after significant tumor regression (ORR per RECIST v1.1: 44%), achieving a cancer-free, drug-free status in 20–30% of 110 individuals. For patients with small confluent multinodular or PET-positive HCC, ABC-LEN-TACE sandwich therapy, consisting of atezolizumab/bevacizumab induction, LEN-TACE, and subsequent atezolizumab/bevacizumab, may offer a promising approach to achieve cancer-free and drug-free status and a potential cure for this subgroup.¹⁰⁴

Other real-world data have also demonstrated that combining local and systemic therapies is a promising approach for improving tumor response and increasing surgical conversion rates through complementary mechanisms of action. One retrospective study showed that an upfront lenvatinib strategy followed by RFA to achieve deep response was associated with better OS (21.3 vs. 17.1 months) and PFS (12.5 vs. 5.5 months) than those with lenvatinib monotherapy in individuals with intermediate-stage HCC beyond the up-to-7 criteria.¹⁰⁵ Another study enrolled 70 individuals, including 22 with intermediate-stage disease, and evaluated salvage surgery outcomes after conversion therapy using triple therapy (TACE plus lenvatinib and anti-programmed death-1 antibodies) in individuals initially diagnosed with uHCC.¹⁰⁶ Pathological CR and major pathological response were observed in 29 (41.4%) and 59 (84.3%) individuals, respectively. The 2-year OS and RFS rates following surgery were 94.4% and 54.4%, respectively. The phase 2 START-FIT trial investigated the efficacy of sequential TACE and SBRT followed by avelumab in patients with locally advanced, unresectable HCC.¹⁰⁷ Among the 33 patients enrolled, 18 (55%) were considered amenable to curative treatment, 4 (12%) underwent curative therapy, while 14 (42%) achieved a radiological CR and were managed with close surveillance. The finding highlights the potential of sequential TACE–SBRT combined with immunotherapy as a curative conversion strategy in selected patients with advanced HCC.

Table 4. Summary of the consensus statements

No.	Consensus statement	Agreement	Evidence
1	Intermediate-stage (BCLC B) hepatocellular carcinoma (HCC) is a heterogeneous group and treatment should be tailored based on tumor burden and liver reserve.	100%	
2	Transarterial chemoembolization (TACE) is widely used for treating unresectable intermediate-stage HCC. However, not all patients are suitable for TACE, particularly those with a tumor burden exceeding the up-to-11 criteria or with unfavorable radiological patterns.	100%	B
3	For intermediate-stage HCC that is unsuitable for TACE, systemic therapy should be initiated as the first-line treatment.	95%	C
4	To improve outcomes (progression-free survival) in intermediate-stage HCC, systemic therapy combined with TACE can be used in TACE-eligible cases.	100%	B
5	For TACE-refractory intermediate-stage HCC (failed by at least two TACE sessions), immunotherapy is recommended as the first-line treatment, with lenvatinib or sorafenib as alternatives.	100%	B
6	Y90 radioembolization (TARE) may serve as an alternative therapy to TACE.	100%	B
7	The efficacy of drug-eluting bead TACE is comparable to that of conventional TACE, but the adverse reactions associated with TACE can be alleviated.	100%	B
8	For curative conversion of intermediate-stage HCC, liver-directed therapy, systemic therapy, or combined therapy followed by curative therapy should be considered to achieve a cancer-free and drug-free state.	100%	B

BCLC, Barcelona Clinic Liver Cancer; TARE, transarterial radioembolization.

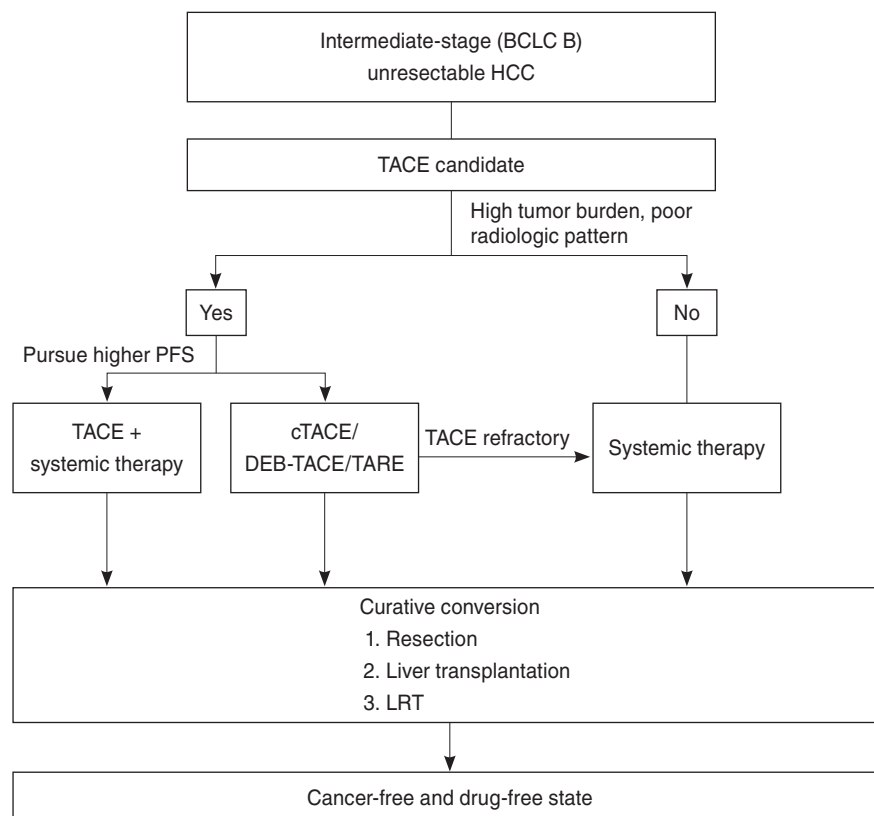


Figure 1. Overall treatment recommendation algorithm for intermediate-stage HCC. BCLC, Barcelona Clinic Liver Cancer; DEB-TACE, drug-eluting bead TACE; HCC, hepatocellular carcinoma; LRT, locoregional therapy; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

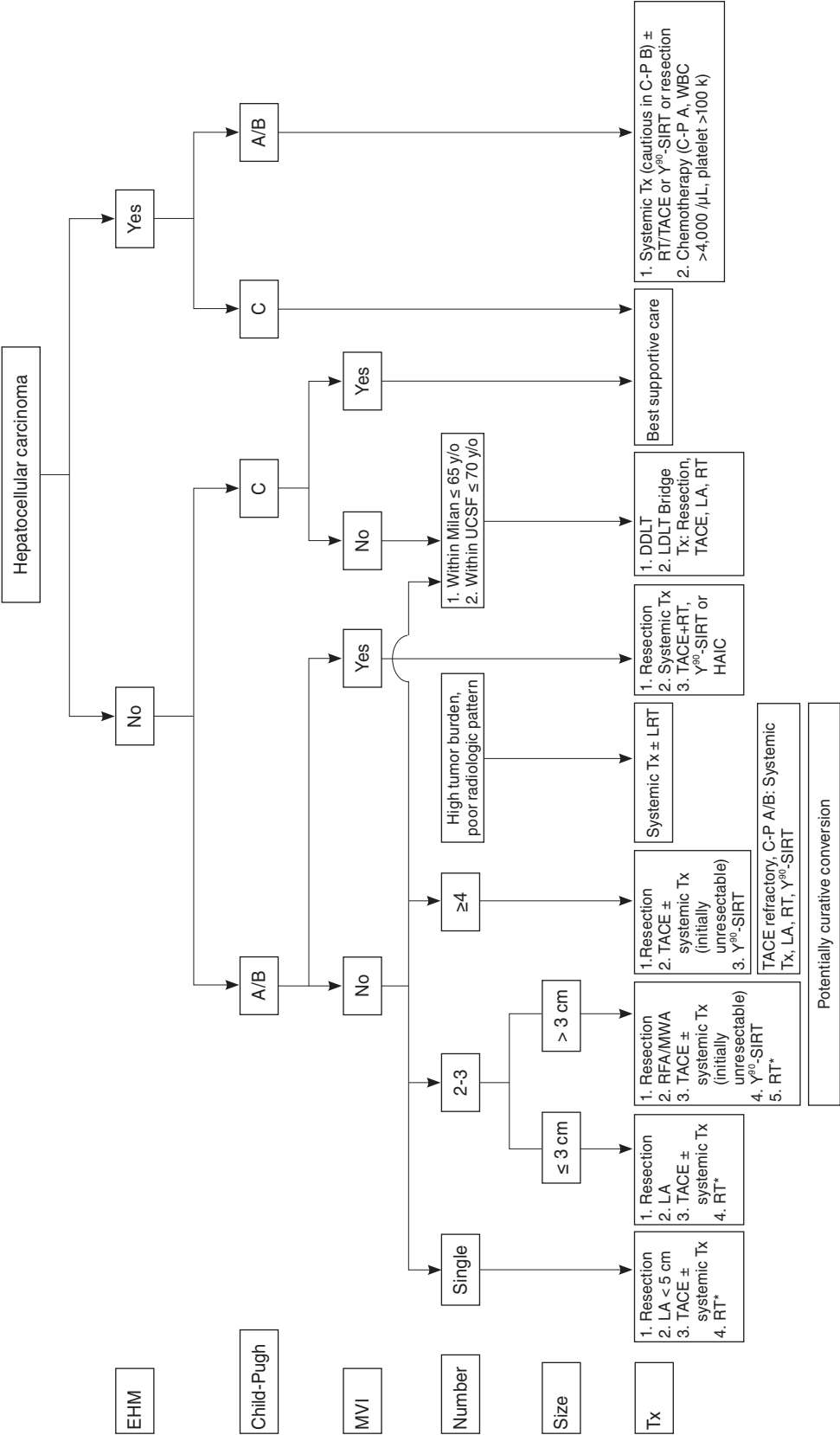


Figure 2. Updated TLCA HCC treatment algorithm encompassing all disease stages. C-P, Child-Pugh; DDLT, deceased donor liver transplantation; EHM, extrahepatic metastasis; HAIC, hepatic arterial infusion chemotherapy; LA, local ablation; LDLT, living donor liver transplantation; MVI, macrovascular invasion; MWA, microwave ablation; RFA, radiofrequency ablation; RT, radiotherapy; TACE, transarterial chemoembolization; UCSF, University of California, San Francisco; WBC, white blood cells; SIRT, selective internal radiation therapy.

CONCLUSION

In summary, we present the TLCA guidelines for the management of intermediate-stage HCC, outlining criteria for TACE unsuitability, treatment recommendations for both eligible and ineligible individuals, and comparisons among treatment modalities including cTACE, DEB-TACE, and TARE. A summary of the consensus statements is shown in Table 4. Additionally, the guidelines incorporate key considerations related to curative conversion and downstaging. The comprehensive treatment algorithm for intermediate-stage HCC is depicted in Figure 1, while an updated TLCA treatment algorithm covering all disease stages is shown in Figure 2. By refining these consensus recommendations, we aim to optimize treatment decision-making and support personalized therapeutic strategies, ultimately advancing the adoption of curative conversion therapy in intermediate-stage HCC.

Authors' contribution

I-Cheng Lee, Wei Teng, Hung-Wei Wang, and Tsung-Jung Lin drafted the manuscript. Yi-Hsiang Huang was responsible for study concept, design, supervision, and manuscript revision. Other authors contributed to the literature review, discussion, and consensus voting.

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Conflicts of Interest

The authors have no conflicts to disclose.

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