Specific indicators of unsuitability for transarterial chemoembolisation in patients with intermediate-stage hepatocellular carcinoma according to thresholds of tumour burden and liver function as judged by survival benefit over sorafenib

LM Chen, Simon CH Yu *, Leung Li, Edwin P Hui, Winnie Yeo, Stephen L Chan

ABSTRACT

Introduction: This study aimed to define specific indicators of unsuitability for transarterial chemoembolisation (TACE) in patients with intermediate-stage hepatocellular carcinoma (HCC) in Hong Kong using thresholds of tumour burden and liver function, as judged by survival benefit over sorafenib.

Methods: Patients with treatment-naïve and unresectable HCC who received TACE or sorafenib from 2005 to 2019 and met the eligibility criteria were enrolled. Overall survival (OS) was compared between the TACE and sorafenib groups using the log-rank test and hazard ratios (HRs) in all subgroups classified according to baseline modified albumin–bilirubin (mALBI) grade and tumour burden, including the up-to-7, up-to-11, and N3-S5-S10 criteria.

Results: Overall survival was significantly longer in TACE subgroups than in sorafenib subgroups when stratified by mALBI grade and either the up-to-7 or the up-to-11 criteria (all P<0.05). When applying the N3-S5-S10 criteria, OS did not significantly differ between the TACE and sorafenib groups in subgroups with mALBI grade 2b and tumours with number >3 and size >5 cm but ≤10 cm, or tumours with number >3 and size >10 cm (HR=0.550 and 0.965, respectively; both P>0.05). Sensitivity analysis showed non-significant survival benefits in two additional subgroups: those with mALBI grade 2b and tumours with number ≤3 and size >10 cm, and those with mALBI grade 1 or 2a and tumours with number >3 and size >10 cm (HR=0.474 and 0.418, respectively; both P>0.05).

Conclusion: More precise criteria for TACE unsuitability are required. The combination of mALBI grade and the N3-S5-S10 criteria may better identify patients with intermediate-stage HCC who are unlikely to benefit from TACE. Validation in a larger cohort is warranted.

Hong Kong Med J 2025;31:Epub
https://doi.org/10.12809/hkmj2311239

[1,2,3] **LM Chen,** PhD
[1] **SCH Yu *,** MB, BS, MD
[4] **L Li,** MB, ChB, MD
[4] **EP Hui,** MB, ChB, MD
[4,5] **W Yeo,** MB, BS, MD
[4,5] **SL Chan,** MB, BS, MD

[1] *Department of Imaging and Interventional Radiology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China*
[2] *Department of Medical Ultrasonics, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China*
[3] *Biomedical Innovation Center, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China*
[4] *Department of Clinical Oncology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong SAR, China*
[5] *State Key Laboratory of Translational Oncology, China*

* Corresponding author: simonyu@cuhk.edu.hk

This article was published on 5 Dec 2025 at www.hkmj.org.

This version may differ from the print version.

New knowledge added by this study

- Patients regarded as unsuitable for transarterial chemoembolisation (TACE) under existing criteria may achieve better survival outcomes with TACE than those with systemic therapy.
- To determine true TACE unsuitability, more precise criteria based on clinical evidence demonstrating improved survival with alternative treatments are required. Modified albumin–bilirubin (mALBI) grade 2b and tumours with number >3 and size >5 cm, or tumours with number ≤3 and size >10 cm, as well as mALBI grade 1 or 2a and tumours with number >3 and size >10 cm, could serve as better indicators of TACE unsuitability in patients with intermediate-stage hepatocellular carcinoma.

Implications for clinical practice or policy

- Within the framework of TACE unsuitability, the use of more precise discriminatory criteria is crucial to ensure that patients are not inappropriately excluded from the potential benefits of TACE.
- The integration of mALBI grade with the N3-S5-S10 tumour burden criteria may offer a practical framework for clinicians to individualise treatment selection, optimising outcomes by identifying patients more likely to benefit from TACE versus systemic therapy.

根據對照索拉非尼治療後生存機率重新制定經動脈化療栓塞對治療中期肝細胞癌患者的不適用性指標

陳麗梅、余俊豪、李良、許斌、楊明明、陳林

引言：本研究旨在根據對照了索拉非尼治療後的生存機率分析結果，重新制定香港的經動脈化療栓塞（TACE）對治療中期肝細胞癌患者的不適用性指標。

方法：研究對象是在2005至2019年間接受TACE或索拉非尼治療且符合篩選條件的兩組患者，他們在之前從未接受過治療。方法是以對數秩檢定及風險比率比較兩組患者當中不同的基線肝功能指數（經修訂白蛋白—膽紅素分級[mALBI分級]）及腫瘤負荷（包括「up-to-7」、「up-to-11」及N3-S5-S10等標準）的亞組患者的整體存活期。

結果：在不同基線肝功能指數及腫瘤負荷（「up-to-7」及「up-to-11」標準）的所有亞組患者中，TACE組的整體存活期明顯較索拉非尼治療組長（P<0.05）。若以N3-S5-S10標準為腫瘤負荷標準作亞組分析，我們發現在以下兩個亞組中，TACE組與索拉非尼治療組的整體存活期並無明顯差異：（1）mALBI 2b級，腫瘤數量>3及腫瘤>5公分但≤10公分（風險比率=0.550；P>0.05）；（2）腫瘤數量>3及腫瘤>10公分（風險比率=0.965；P>0.05）。敏感度分析顯示在以下兩個亞組中，TACE組的整體存活期比起索拉非尼治療組沒有明顯佔優：（1）mALBI 2b級及腫瘤數量≤3和腫瘤>10公分（風險比率=0.474；P>0.05）；（2）mALBI 1級或2a級及腫瘤數量>3和腫瘤>10公分（風險比率=0.418；P>0.05）。

結論：在臨床實踐中，我們需要更精確的TACE不適用性標準。結合肝功能指數及以N3-S5-S10為腫瘤負荷標準的指標可能可以更精確顯示TACE對治療中期肝細胞癌患者的不適用性，值得以更大型的研究去確認。

Introduction

Hepatocellular carcinoma (HCC) is one of the leading malignancies worldwide. At diagnosis, up to 30% of patients have intermediate-stage HCC according to the Barcelona Clinic Liver Cancer system.[1] Transarterial chemoembolisation (TACE) has emerged as the first-line treatment for intermediate-stage HCC, supported by two randomised controlled trials[2,3] and a meta-analysis[4] that demonstrated superior survival outcomes compared with best supportive care or suboptimal therapies.

Because patients with intermediate-stage HCC comprise a heterogeneous group characterised by a wide range of tumour burdens and liver function, the effectiveness of TACE as first-line treatment may not be universal, particularly in subgroups with high tumour burden or suboptimal liver function. To address this issue, sub-staging of intermediate-stage HCC based on tumour burden and liver function has been proposed in several criteria, including the Bolondi,[5] Kinki,[6] and MICAN (Modified Intermediate Stage of Liver Cancer) criteria.[7] These criteria have demonstrated discriminative prognostic value in identifying subgroups of patients with intermediate-stage HCC.[7,8] Given that survival outcomes of patients treated with TACE can vary across substages of intermediate-stage HCC, it is clinically essential to identify thresholds of tumour burden and liver function that preclude the use of TACE according to survival benefit.

Sorafenib has been established as the standard of care for advanced HCC since 2007, based on the demonstration of its significant survival superiority over placebo.[9-11] Subgroup analyses of clinical trials have shown that sorafenib exerts positive therapeutic efficacy in intermediate-stage HCC, with reported overall survival (OS) ranging from 14.5 to 20.6 months,[9,12,13] which is comparable to the OS achieved with TACE. Sorafenib treatment can serve as a benchmark for evaluating the survival benefit of TACE. If TACE does not provide a significant survival benefit compared with sorafenib, it may not be appropriate to subject patients to TACE rather than systemic therapy, given that TACE is invasive and potentially harmful to the liver. Patients may benefit from systemic therapy before liver function becomes suboptimal.

It has been hypothesised that specific baseline parameters of tumour burden and liver function, at which TACE fails to show superior survival benefit compared with sorafenib, could be defined as indicators of TACE unsuitability. This study aimed to define specific indicators of TACE unsuitability at baseline in patients with intermediate-stage HCC according to thresholds of tumour burden and liver function, as judged by the survival benefit of TACE over sorafenib.

Methods

Study design

Due to the limited number of eligible participants, all available cases with complete clinical data were included. All patients with unresectable HCC who received TACE or sorafenib therapy from January 2005 to December 2019 at Prince of Wales Hospital were enrolled in the study, provided they met all eligibility criteria. Unresectability of intermediate-stage HCC was determined by a multidisciplinary team comprising a surgeon, an interventional radiologist, and an oncologist. Inclusion criteria were treatment-naïve, Barcelona Clinic Liver Cancer-B stage HCC diagnosed by biopsy or a typical vascular pattern on cross-sectional imaging; intrahepatic disease without vascular invasion; and an Eastern Cooperative Oncology Group performance status score of 0 or 1. Exclusion criteria included age under 18 years or Eastern Cooperative Oncology Group performance status score of 2 or above; prior treatment before initial TACE; receipt of hepatectomy, liver transplantation, or local therapy

after initial TACE; and any imaging evidence from computed tomography (CT), magnetic resonance imaging, or positron emission tomography/CT showing vascular invasion by tumour (including portal vein tumour thrombus) or extrahepatic metastasis (Fig 1). To identify thresholds for TACE unsuitability, OS of patients treated with TACE was compared with that of patients treated with sorafenib within subgroups defined by baseline tumour burden and liver function. Overall survival was defined as the interval between the initiation of TACE or sorafenib and death from any cause. Patients who were alive or lost to follow-up were censored.

Study participants

In total, 420 patients were enrolled in the study: 358 received TACE and 62 received sorafenib (Table 1). The TACE group included significantly more older and female patients. The median tumour size was significantly larger in the sorafenib group compared with the TACE group. No significant differences were observed between the two groups in terms of the modified albumin–bilirubin (mALBI) grade distribution or tumour multiplicity. Among patients initially treated with TACE, the median number of TACE sessions was two (range, 1-4); 124 patients received one session, 78 received two sessions, 53 received three sessions, and 103 received more than three sessions. After developing refractoriness to TACE, 60 patients subsequently received systemic agents; of these, 35 received sorafenib, eight received adriamycin, four received doxorubicin, six received lenvatinib, and seven received other agents.

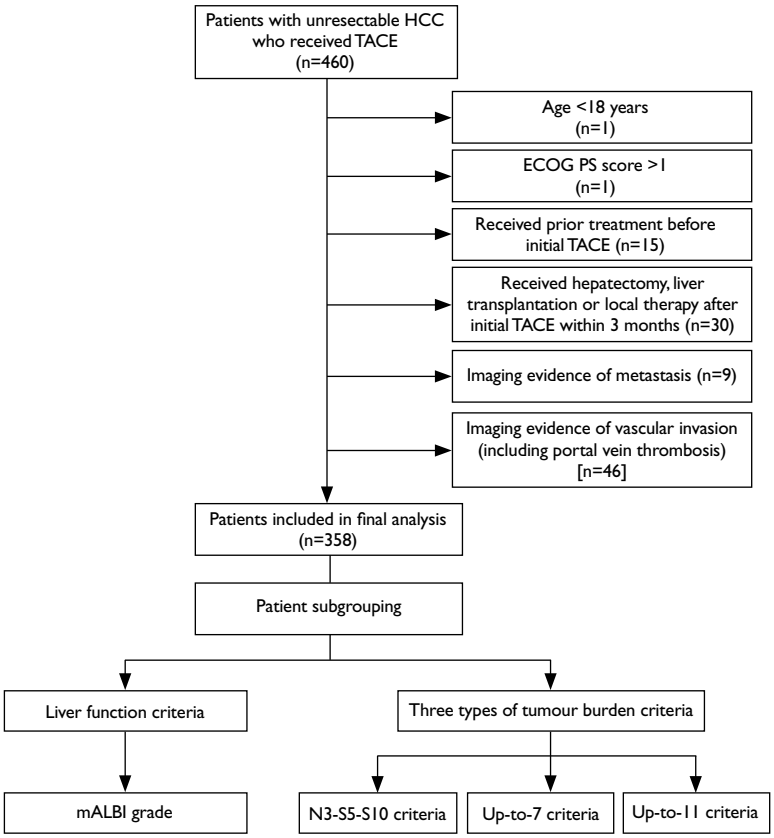

FIG 1. Study recruitment and patient subgrouping for transarterial chemoembolisation

Abbreviations: ECOG = Eastern Cooperative Oncology Group; HCC = hepatocellular carcinoma; mALBI grade = modified albumin–bilirubin grade; PS = performance status; TACE = transarterial chemoembolisation

Patient subgrouping

Patients were classified into six subgroups according to baseline tumour burden and liver function. Tumour burden was subcategorised using the up-to-7, up-to-11, and N3-S5-S10 criteria. The up-to-7 and up-to-11 criteria were derived from the sum of the maximum tumour size (in cm) and the tumour number, with cut-off values of 7 or 11, respectively. Accordingly, patients were categorised as within or beyond the up-to-7 and up-to-11 criteria. In the N3-S5-S10 system, tumour burden was subcategorised according to the combination of tumour number and maximum tumour size; three tumour nodules and 5 cm or 10 cm in size served as the respective cut-off values. This categorisation resulted in the following six subgroups: (1) tumour number ≤3, tumour size ≤5 cm; (2) tumour number ≤3, tumour size >5 cm to ≤10 cm; (3) tumour number ≤3, tumour size >10 cm; (4) tumour number >3, tumour size ≤5 cm; (5) tumour number >3, tumour size >5 cm to ≤10 cm; and (6) tumour number >3, tumour size >10 cm (Fig 1).

Liver function subgroups were classified according to the mALBI grade.[14] The mALBI grades were determined using the ALBI score, calculated as ($\log_{10}$ [bilirubin level (μmol/L)] × 0.66) + (albumin level [g/L] × −0.085). Based on three cut-off ALBI scores, grades were defined as follows: grade 1 (≤−2.60), grade 2a (>−2.60 to ≤−2.27), grade 2b (>−2.27 to ≤−1.39), and grade 3 (>−1.39). Because the sample size of patients receiving sorafenib with mALBI grade 1 or 2a was relatively small, these two subgroups were combined for analysis. Additionally, given that no patient with mALBI grade 3 received sorafenib, this subgroup was excluded from the analysis (Fig 1).

Transarterial chemoembolisation

The TACE procedures were performed using digital subtraction angiography equipment via a femoral approach under local anaesthesia.[15,16] In brief, a microcatheter was used to catheterise tumour-feeding arteries at the lobar, segmental, or subsegmental level, depending on tumour size. An emulsion of cisplatin–ethiodised oil (Platosin; Pharmachemie BV, Haarlem, the Netherlands), consisting of up to 20 mg aqueous cisplatin (20 mL)

TABLE 1. Demographics of patients (n=420)*

	TACE group (n=358)	Sorafenib group (n=62)	P value
Age, y	65.00 (56.00-72.00)	57.00 (53.75-64.00)	<0.001
Sex			0.033
Male	305 (85.2%)	59 (95.2%)	
Female	53 (14.8%)	3 (4.8%)	
mALBI grade			0.159
1+2a	179 (50.0%)	37 (59.7%)	
2b+3	179 (50.0%)	25 (40.3%)	
Tumour number			0.337
Single	102 (28.5%)	14 (22.6%)	
Multiple	256 (71.5%)	48 (77.4%)	
Tumour size, cm	7.00 (4.58-11.13)	11.55 (9.15-15.00)	<0.001
Tumour size			0.001
≤5 cm	111 (31.0%)	6 (9.7%)	
>5 cm	247 (69.0%)	56 (90.3%)	
Tumour size			<0.001
≤10 cm	257 (71.8%)	21 (33.9%)	
>10 cm	101 (28.2%)	41 (66.1%)	
Up-to-7			0.007
Within	83 (23.2%)	5 (8.1%)	
Beyond	275 (76.8%)	57 (91.9%)	
Up-to-11			<0.001
Within	224 (62.6%)	15 (24.2%)	
Beyond	134 (37.4%)	47 (75.8%)	

Abbreviations: mALBI grade = modified albumin–bilirubin grade; TACE = transarterial chemoembolisation

* Data are shown as No. (%) or median (interquartile range), unless otherwise specified

and up to 20-mL ethiodised oil mixed in a 1:1 volume ratio, was administered until flow stasis occurred or a maximum dose of 40-mL emulsion was delivered. Digital subtraction angiography, with or without non-contrast multiplanar CT, was used to confirm treatment completeness. A gelatin sponge (5-10 mL) was used to embolise the feeding arteries.

Postprocedure monitoring included blood tests for liver function and tumour markers within 2 days, at 2 weeks, and then every 1 to 3 months, as well as CT imaging every 3 months. Systemic therapy was administered to patients with well-preserved liver function who developed TACE refractoriness, as indicated by continuous elevation of tumour markers and CT evidence of tumour progression.

Systemic therapy

According to the customary protocol at Prince of Wales Hospital, The Chinese University of Hong Kong during the study period, patients with unresectable intermediate-stage HCC and no contraindications to TACE were prioritised for TACE treatment. Patients who declined TACE were treated with sorafenib; as a result, some patients in the sorafenib group had smaller tumours or fewer tumour nodules. Sorafenib was administered orally at a prescribed dose of 400 mg twice daily. In the event of intolerable side-effects or serious adverse events, oncologists could adjust the treatment by reducing the dose or discontinuing the drug.

Statistical analysis

Categorical variables were presented as numbers (percentages), while continuous variables were summarised as median (interquartile range), median (95% confidence interval [95% CI]), or depending on the results of normality testing. The Chi squared test was used to compare categorical data, and the Mann-Whitney *U* test was performed for continuous data. Kaplan-Meier curves and Cox proportional hazards models were used to compare OS values among subgroups. The log-rank test and hazard ratio (HR) were utilised to assess survival differences between subgroups. A sensitivity analysis of survival outcomes was conducted, excluding participants who received systemic therapy after TACE. A P value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS (Windows version 25.0; IBM Corp, Armonk [NY], United States).

Results

Comparison of overall survival between transarterial chemoembolisation and sorafenib

The median OS of all patients who received TACE was significantly longer than that of patients who received sorafenib (19.37 [16.89-21.85] months vs 5.12 [4.37-5.84] months, P<0.001; Fig 2a). When stratified by mALBI grade, patients with mALBI grade 1 or 2a had significantly longer median OS in the TACE group compared with the sorafenib group (23.83 [18.53-29.13] months vs 6.60 [3.61-9.59] months, P<0.001; Fig 2b). Similarly, patients with mALBI grade 2b had significantly longer median OS in the TACE group than in the sorafenib group (16.20 [11.91-20.49] months vs 4.39 [3.44-5.35] months, P<0.001; Fig 2c).

Overall survival by modified albumin–bilirubin grade and tumour burden in sorafenib-treated patients

The median OS of patients treated with sorafenib, stratified by mALBI grade and tumour burden, is summarised in Table 2. As the sorafenib subgroups with tumour number ≤3 had a relatively small sample size (n=8) according to the N3-S5-S10 criteria, these patients were not further subdivided

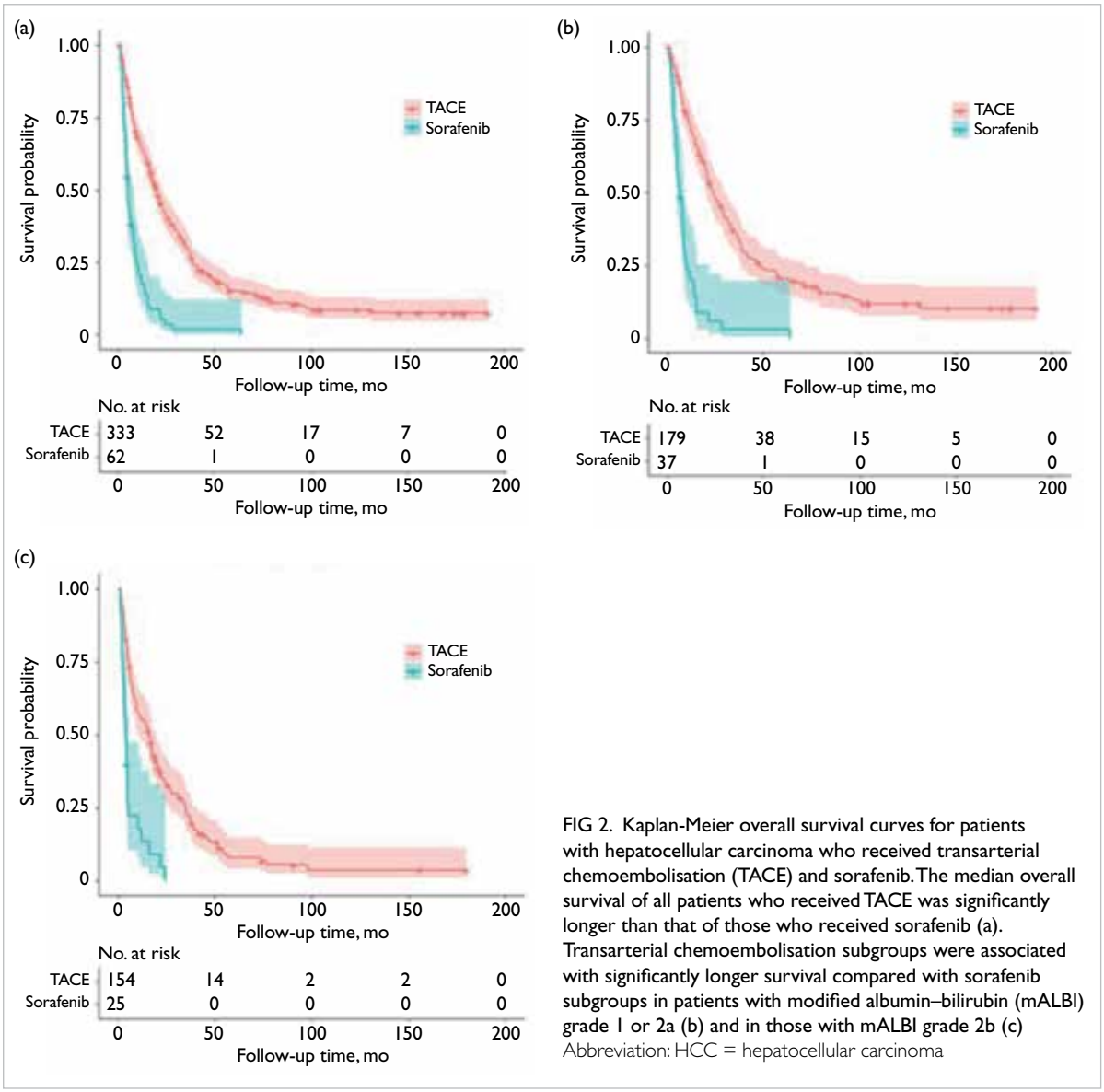

FIG 2. Kaplan-Meier overall survival curves for patients with hepatocellular carcinoma who received transarterial chemoembolisation (TACE) and sorafenib. The median overall survival of all patients who received TACE was significantly longer than that of those who received sorafenib (a). Transarterial chemoembolisation subgroups were associated with significantly longer survival compared with sorafenib subgroups in patients with modified albumin–bilirubin (mALBI) grade 1 or 2a (b) and in those with mALBI grade 2b (c)
Abbreviation: HCC = hepatocellular carcinoma

based on tumour size. Instead, they were combined into a single subgroup with tumour number ≤3 to increase the sample size for comparison with the TACE group. Consequently, OS in the combined sorafenib subgroup (tumour number ≤3, any tumour size) was used for comparison with OS in the three tumour-size TACE subgroups of tumour number ≤3 (Table 2).

The distribution of sample sizes was uneven across the sorafenib subgroups with tumour number >3 based on the N3-S5-S10 criteria, which may have introduced bias in the survival outcomes, such as a lower tumour burden being associated with worse OS. To avoid underestimation of OS in any tumour-size subgroup when comparing with the TACE subgroups, the longest OS among the subgroups with tumour number >3 was utilised as the OS value for all these subgroups in the analysis, irrespective of tumour size (Table 2). As no patients with mALBI grade 2 were present in the tumour burden subgroup defined as within up-to-7, the OS of patients with tumour burden beyond up-to-7 (Table 2) who were treated with sorafenib was used as the control.

Overall survival in modified albumin–bilirubin grade 1 or 2a: transarterial chemoembolisation versus sorafenib

Table 3 presents the median OS of patients treated with TACE or sorafenib, stratified by mALBI grade 1 or 2a and tumour burden. Across all subgroups defined by various tumour burden criteria, patients who received TACE achieved significantly longer OS than those who received sorafenib (all P<0.05), with HRs favouring TACE (ranging from 0.130 to 0.331). Sensitivity analysis showed that survival was not significantly different between TACE and

sorafenib in the subgroup with tumour number >3 and tumour size >10 cm (HR=0.418 [95% CI=0.147-1.171]; P=0.097).

Overall survival in modified albumin–bilirubin grade 2b: transarterial chemoembolisation versus sorafenib

In subgroups with mALBI grade 2b, defined by either the up-to-7 or up-to-11 criteria, patients who received TACE exhibited significantly longer median OS than those who received sorafenib across all subgroups (all P<0.05; Table 4). However, when using the N3-S5-S10 criteria, TACE resulted in a significantly longer median OS than sorafenib only in the subgroups with tumour number ≤3 (any tumour size) and in the subgroup with tumour number >3 and tumour size ≤5 cm (both P<0.05; Table 4). In the subgroups with tumour number >3 and tumour size >5 cm to ≤10 cm, and those with tumour number >3 and tumour size >10 cm, although TACE subgroups demonstrated longer median OS than sorafenib subgroups (6.07 vs 3.74 months and 7.73 vs 3.74 months, respectively), the differences were not statistically significant (Table 4). Sensitivity analysis showed that survival was also not significantly different between TACE and sorafenib in the additional subgroup with tumour number ≤3 and tumour size >10 cm (HR=0.474 [95% CI=0.185-1.261]; P=0.120).

Due to the small sample size, it was difficult to demonstrate a clear survival benefit of TACE over sorafenib; thus, the risk of overestimating the survival benefit of TACE, due to potential bias from more advanced disease in the sorafenib group, was likely minimised. For example, given the limited number of patients in the subgroups with tumour number >3 and tumour size >5 cm to ≤10 cm and those with tumour number >3 and tumour size >10 cm, these two subgroups were combined into one subgroup (tumour number >3 and tumour size >5 cm). In this combined subgroup, TACE (n=38) still yielded no significant survival benefit over sorafenib

TABLE 2. Overall survival of patients receiving sorafenib (n=62)*

Tumour burden	mALBI grade 1 or 2a		mALBI grade 2b	
	No.	OS, mo	No.	OS, mo
N3-S5-S10 criteria				
N≤3, any tumour size	8	8.88 (2.34-15.41)	6	4.52 (3.12-5.92)
N>3, ≤5 cm	6	5.17 (1.02-9.33)	0	N/A
N>3, >5 to ≤10 cm	7	8.16 (4.16-12.17)	5	2.96 (1.63-4.29)
N>3, >10 cm	16	5.11 (3.32-6.89)	14	3.74 (1.65-5.83)
Up-to-7 criteria				
Within up-to-7	5	5.17 (3.91-6.43)	0	N/A
Beyond up-to-7	32	6.60 (3.85-9.35)	25	4.39 (3.44-5.35)
Up-to-11 criteria				
Within up-to-11	12	5.76 (1.14-10.37)	3	4.52 (1.03-8.01)
Beyond up-to-11	25	6.60 (2.62-10.58)	22	4.10 (2.68-5.52)
OS for all patients	37	6.60 (3.61-9.59)	25	4.39 (3.44-5.35)

Abbreviations: mALBI grade = modified albumin–bilirubin grade; N = tumour number; N/A = not available; OS = overall survival

* Data are shown as No. (%) or median (95% confidence interval), unless otherwise specified

TABLE 3. Overall survival of patients with liver function classified as modified albumin–bilirubin grade 1 or 2a

Tumour burden	TACE group		Sorafenib group		Hazard ratio (95% CI)	P value
	No.	OS, mo (median [95% CI])	No.	OS, mo (median [95% CI])		
N≤3, ≤5 cm	20	29.07 (25.71-32.43)	8*	8.88 (2.34-15.41)	0.139 (0.051-0.384)	<0.001
N≤3, >5 cm to ≤10 cm	55	20.30 (13.40-27.20)	8*	8.88 (2.34-15.41)	0.316 (0.143-0.700)	0.003
N≤3, >10 cm	27	24.17 (11.83-36.50)	8*	8.88 (2.34-15.41)	0.295 (0.120-0.726)	0.005
N>3, ≤5 cm	38	31.70 (25.88-37.53)	7†	8.16 (4.16-12.17)	0.136 (0.049-0.379)	<0.001
N>3, >5 cm to ≤10 cm	17	20.97 (14.21-27.72)	7	8.16 (4.16-12.17)	0.137 (0.038-0.489)	<0.001
N>3, >10 cm	22	16.17 (9.41-22.93)	7†	8.16 (4.16-12.17)	0.265 (0.097-0.727)	0.006
Within up-to-7	38	33.93 (23.64-44.23)	5	5.17 (3.91-6.43)	0.130 (0.043-0.392)	<0.001
Beyond up-to-7	141	20.97 (17.75-21.19)	32	6.60 (3.85-9.35)	0.265 (0.174-0.403)	<0.001
Within up-to-11	116	28.17 (22.40-33.94)	12	5.76 (1.14-10.37)	0.153 (0.076-0.304)	<0.001
Beyond up-to-11	63	19.37 (14.50-24.24)	25	6.60 (2.62-10.58)	0.331 (0.199-0.552)	<0.001

Abbreviations: 95% CI = confidence interval; N = tumour number; OS = overall survival; TACE = transarterial chemoembolisation

* The OS of patients with N≤3 and any tumour size who were treated with sorafenib was used as the control group because the sample size was small in these subgroups

† The longest OS among sorafenib subgroups with tumour number >3 was used as the control to avoid underestimating the OS in this subgroup

TABLE 4. Overall survival of patients with liver function classified as modified albumin–bilirubin grade 2b

Tumour burden	TACE group		Sorafenib group		Hazard ratio (95% CI)	P value
	No.	OS, mo [median (95% CI)]	No.	OS, mo [median (95% CI)]		
N≤3, ≤5 cm	20	35.33 (26.42-44.25)	6*	4.52 (3.12-5.92)	0.086 (0.021-0.356)	<0.001
N≤3, >5 cm to ≤10 cm	38	19.63 (14.30-24.97)	6*	4.52 (3.12-5.92)	0.157 (0.056-0.437)	<0.001
N≤3, >10 cm	33	10.77 (7.81-13.73)	6*	4.52 (3.12-5.92)	0.345 (0.134-0.883)	0.020
N>3, ≤5 cm	25	22.03 (12.39-31.68)	6*	4.52 (3.12-5.92)	0.138 (0.047-0.406)	<0.001
N>3, >5 cm to ≤10 cm	29	6.07 (3.84-8.29)	14†	3.74 (1.65-5.83)	0.550 (0.273-1.108)	0.090
N>3, >10 cm	9	7.73 (0-16.21)	14	3.74 (1.65-5.83)	0.965 (0.395-2.357)	0.937
Within up-to-7	38	33.57 (21.84-45.29)	25‡	4.39 (3.44-5.35)	0.122 (0.061-0.244)	<0.001
Beyond up-to-7	116	10.27 (6.09-14.45)	25	4.39 (3.44-5.35)	0.365 (0.230-0.581)	<0.001
Within up-to-11	95	21.90 (17.50-26.30)	3	4.52 (1.03-8.01)	0.112 (0.032-0.388)	<0.001
Beyond up-to-11	59	9.43 (7.19-11.68)	22	4.10 (2.68-5.52)	0.489 (0.290-0.824)	0.006

Abbreviations: 95% CI = 95% confidence interval; N = tumour number; OS = overall survival; TACE = transarterial chemoembolisation

* The OS of patients with N≤3 and any tumour size who were treated with sorafenib was used as the control group because the sample size was small in these subgroups

† The longest OS among the sorafenib subgroups with N>3 was used as the control to avoid underestimating the OS in this subgroup

‡ The OS of patients with tumour burden beyond up-to-7 who were treated with sorafenib was used as the control group because the sample size was zero in the subgroup within up-to-7

(n=14), with OS values of 6.07 months (4.10-8.03) and 3.74 months (1.71-5.78), respectively (HR=0.586 [95% CI=0.325-1.054]; P=0.071).

Discussion

Results of subgroup analysis

Subgroup analysis in this study revealed that, within the limitations of the data, TACE probably did not confer a statistically significant survival benefit over sorafenib for patients with mALBI grade 2b and a high tumour burden (number >3 and size >5 cm, or number ≤3 and size >10 cm), or for patients with mALBI grade 1 or 2a and tumour burden of number >3 and size >10 cm. In contrast, TACE did provide a survival benefit when the beyond up-to-7 or beyond up-to-11 criteria were applied. These findings suggest that the use of more precise criteria to define tumour burden and liver function could help identify specific subgroups unsuitable for TACE. Such criteria highlight the threshold at which TACE no longer provides a survival advantage over sorafenib, thereby indicating TACE unsuitability. These indicators would be valuable in guiding the clinical management of intermediate-stage HCC. The small sample size in the sorafenib group may have limited the statistical power to detect a survival benefit of TACE in subgroups with tumour number >3 and size >5 cm. Given that the overall results showed a consistent trend favouring TACE, validation through further studies with larger sample sizes is warranted.

Sorafenib as a control

In recent years, systemic therapy for HCC has undergone rapid development, leading to the emergence of new drugs after sorafenib. The combination of certain agents has shown significant improvements in survival compared with sorafenib alone. The IMbrave150 study demonstrated that treatment with atezolizumab plus bevacizumab resulted in a significantly longer median OS than sorafenib alone (19.2 vs 13.4 months).[17] Similarly, both sintilimab plus a bevacizumab biosimilar[18] and tremelimumab plus durvalumab[19] provided significant survival benefits over sorafenib in patients with unresectable HCC. Nevertheless, sorafenib remains the first-line standard treatment and the most effective single agent for advanced HCC. It serves as a benchmark for newer single-agent therapies such as lenvatinib, nivolumab, and durvalumab, which have shown statistical non-inferiority in survival compared with sorafenib.[19-21] Therefore, the use of sorafenib as the control arm versus TACE in this study is reasonable. With the rapid advancement of systemic agents, novel treatment strategies—such as switching to systemic therapy[22] or initiating systemic therapy upfront

followed by curative conversion[23]—have been advocated for patients with intermediate-stage HCC who may not benefit from TACE or repeated TACE. In such cases, it is important to define specific indicators of TACE unsuitability among patients with intermediate-stage HCC, in whom systemic therapy may potentially improve survival.

Deficiencies of conventional criteria of unsuitability for transarterial chemoembolisation

The concept of TACE unsuitability has emerged in conjunction with the development and availability of systemic therapies.[24] In patients with intermediate-stage HCC, TACE unsuitability has been defined as the presence of mALBI grade 2b and tumour burden beyond the up-to-7 criteria.[25,26] This definition was based on worse survival in patients with mALBI grade 2b and the beyond up-to-7 criteria relative to patients displaying better liver function and lower tumour burden, without addressing the potential survival benefit of TACE over alternative treatment options in this subgroup. However, this definition has two key limitations. First, it lacks clinical evidence demonstrating greater survival benefit from other alternative treatments when TACE is withheld. Second, there remains controversy regarding the optimal criteria for defining high tumour burden. If the beyond up-to-7 criteria is used as the criterion for TACE unsuitability, the majority of patients with intermediate-stage HCC would be considered unsuitable, which is both unrealistic and unsupported. In the present study, 79% of patients had high tumour burden beyond up-to-7, comparable to the 70% reported by Hung et al.[27]

Limitations of conventional sub-staging systems

The sub-staging system using the up-to-11 criteria has shown better discriminatory power than the up-to-7 criteria for predicting survival after TACE.[28,29] Nonetheless, in this study, neither the up-to-7 nor the up-to-11 criteria were able to identify TACE unsuitability. The findings indicated that both the patient subgroup with mALBI grade 2b and tumour burden beyond the up-to-7 criteria, as well as the subgroup with mALBI grade 2b and tumour burden beyond the up-to-11 criteria, still derived survival benefits from TACE compared with sorafenib, indicating that these subgroups should not be considered TACE unsuitable. The lack of discriminatory power may be attributed to the persistently high heterogeneity among patients classified as having high tumour burden under to these two criteria. Worse survival after TACE in these subgroups, compared with patients displaying better liver function and lower tumour burden, does not justify entirely abandoning TACE in these patients.

We propose using the N3-S5-S10 criteria to define tumour burden, as these criteria allow for more specific subgrouping and enable the identification of TACE unsuitability with greater precision, thereby reducing the likelihood of denying patients a potentially beneficial treatment (TACE). Our findings demonstrate that the proposed criteria can identify TACE unsuitability precisely in specific subgroups where the up-to-7 or up-to-11 criteria fail to distinguish survival differences. Based on these findings, we recommend that physicians assess intermediate-stage HCC using both the mALBI grade and the N3-S5-S10 criteria—a more rigorous framework—to determine TACE unsuitability. To our knowledge, this is the first study to demonstrate the survival benefit of TACE over sorafenib in patients with intermediate-stage HCC stratified by both liver function and tumour burden, as well as to identify TACE unsuitability within these subgroups.

Limitations

This study provided a larger sample size than previous studies comparing survival benefits between TACE and sorafenib. However, several limitations should be noted. First, the retrospective design of this study inevitably introduced patient selection bias between the TACE and sorafenib groups. Although there were significant differences in age, sex, and tumour size between the groups, such disparities in overall patient demographics might not have critically affected the validity of the survival comparisons, given that these were based on subgroup analyses. Second, the sample size was exceedingly small in some sorafenib subgroups with low tumour burden. The substantial disparity in patient numbers may have contributed to non-significant differences in OS between subgroups. We attempted to mitigate this limitation by combining subgroups with very small sample sizes. Third, some patients in the TACE group received systemic therapy after disease progression. Consequently, survival in the TACE group may have been overestimated as it reflected outcomes of TACE with or without systemic therapy, rather than TACE alone. Nonetheless, 'TACE followed by systemic therapy' represents standard clinical practice aimed at achieving the greatest patient benefit, and isolating a TACE-alone group for analysis would not be realistic. Notably, 'TACE followed by systemic therapy' accurately reflects real-world treatment practice and does not conflict with the study's primary objective, which was to define specific indicators of TACE unsuitability at baseline rather than at the point when TACE becomes unsuitable. Finally, no power calculation was performed in the statistical analysis.

Conclusion

More precise criteria for TACE unsuitability are required. The combination of mALBI grade and N3-S5-S10 criteria may serve as a better indicator of TACE unsuitability than the beyond up-to-7 or beyond up-to-11 criteria for patients with intermediate-stage HCC. TACE likely offers no survival benefit compared with sorafenib beyond these thresholds. However, validation in a larger cohort is warranted.

Author contributions

Concept or design: SCH Yu.
Acquisition of data: LM Chen, L Li, EP Hui, W Yeo, SL Chan.
Analysis or interpretation of data: LM Chen, SCH Yu.
Drafting of the manuscript: LM Chen, SCH Yu.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This research was funded by the Vascular and Interventional Radiology Foundation, Hong Kong. The funding body was not involved in the design of the study, collection of data, analysis/interpretation of data, or writing of the manuscript.

Ethics approval

This research was approved by The Chinese University of Hong Kong–New Territories East Cluster Ethics Committee, Hong Kong (Ref No.: 2020.672). It was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation–Good Clinical Practice guidelines. The requirement for written informed patient consent was waived by the Committee due to the retrospective nature of the research.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49.
2. Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359:1734-9.
3. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164-71.
4. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology Feb 2003;37:429-42.
5. Bolondi L, Burroughs A, Dufour JF, et al. Heterogeneity of patients with intermediate (BCLC B) hepatocellular carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis 2012;32:348-59.
6. 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;33:751-8.
7. Hiraoka A, Kumada T, Nouso K, et al. Proposed new sub-grouping for intermediate-stage hepatocellular carcinoma using albumin–bilirubin grade. Oncology 2016;91:153-61.
8. Arizumi T, Ueshima K, Iwanishi M, et al. Validation of Kinki criteria, a modified substaging system, in patients with intermediate stage hepatocellular carcinoma. Dig Dis 2016;34:671-8.
9. Bruix J, Raoul JL, Sherman M, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol 2012;57:821-9.
10. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34.
11. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
12. Iavarone M, Cabibbo G, Piscaglia F, et al. Field-practice study of sorafenib therapy for hepatocellular carcinoma: a prospective multicenter study in Italy. Hepatology 2011;54:2055-63.
13. Marrero JA, Kudo M, Venook AP, et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: the GIDEON study. J Hepatol 2016;65:1140-7.
14. Hiraoka A, Michitaka K, Kumada T, 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;6:325-36.
15. Yu SC, Hui JW, Hui EP, et al. Unresectable hepatocellular carcinoma: randomized controlled trial of transarterial ethanol ablation versus transcatheter arterial chemoembolization. Radiology 2014;270:607-20.
16. Yu SC, Hui JW, Li L, et al. Comparison of chemoembolization, radioembolization, and transarterial ethanol ablation for huge hepatocellular carcinoma (≥10 cm) in tumour response and long-term survival outcome. Cardiovasc Intervent Radiol 2022;45:172-81.
17. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol 2022;76:862-73.
18. Ren Z, Xu J, Bai Y, et al. Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, phase 2-3 study. Lancet Oncol 2021;22:977-90.
19. Abou-Alfa GK, Chan SL, Kudo M, et al. Phase 3 randomized, open-label, multicenter study of tremelimumab (T) and durvalumab (D) as first-line therapy in patients (pts) with unresectable hepatocellular carcinoma (uHCC): HIMALAYA. J Clin Oncol 2022;40(4_suppl):379.

20. Yau T, Park JW, Finn RS, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2022;23:77-90.
21. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-73.
22. Ogasawara S, Ooka Y, Koroki K, et al. Switching to systemic therapy after locoregional treatment failure: definition and best timing. Clin Mol Hepatol 2020;26:155-62.
23. Kudo M. A novel treatment strategy for patients with intermediate-stage HCC who are not suitable for TACE: upfront systemic therapy followed by curative conversion. Liver Cancer 2021;10:539-44.
24. Kudo M. Extremely high objective response rate of lenvatinib: its clinical relevance and changing the treatment paradigm in hepatocellular carcinoma. Liver Cancer 2018;7:215-24.
25. Kudo M, Han KH, Ye SL, et al. A changing paradigm for the treatment of intermediate-stage hepatocellular carcinoma: Asia-Pacific Primary Liver Cancer Expert Consensus Statements. Liver Cancer 2020;9:245-60.
26. Kudo M, Kawamura Y, Hasegawa K, et al. Management of hepatocellular carcinoma in Japan: JSH Consensus Statements and Recommendations 2021 update. Liver Cancer 2021;10:181-223.
27. Hung YW, Lee IC, Chi CT, et al. Redefining tumor burden in patients with intermediate-stage hepatocellular carcinoma: the seven-eleven criteria. Liver Cancer 2021;10:629-40.
28. Kim JH, Shim JH, Lee HC, et al. New intermediate-stage subclassification for patients with hepatocellular carcinoma treated with transarterial chemoembolization. Liver Int 2017;37:1861-8.
29. Lee IC, Hung YW, Liu CA, et al. A new ALBI-based model to predict survival after transarterial chemoembolization for BCLC stage B hepatocellular carcinoma. Liver Int 2019;39:1704-12.

