Liver- and tumour-specific indicators predicting suboptimal survival following repeat transarterial chemoembolisation in patients with hepatocellular carcinoma

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

ABSTRACT

Introduction: This study explored liver- and tumour-specific indicators predictive of suboptimal survival outcomes following repeat transarterial chemoembolisation (TACE) in intermediate-stage hepatocellular carcinoma (HCC) patients after an initial TACE.

Methods: This study included 300 HCC patients who underwent TACE treatment. Based on whether persistent albumin–bilirubin (ALBI) grade deterioration (PABD) occurred after the initial TACE, defining as a shift in ALBI grade to a higher grade from baseline without recovery within 90 days, patients were divided into PABD and non-PABD groups. Overall survival of non-PABD and PABD groups according to subgroups stratified by baseline ALBI grade and tumour burden was compared with that of patients receiving only sorafenib or supportive care during the same period.

Results: Repeat TACE provided a survival benefit over systemic therapy or supportive care for patients in all post-TACE non-PABD or most PABD subgroups, regardless of baseline liver condition (ie, modified albumin–bilirubin [mALBI] grade and tumour burden). This benefit was absent in two subgroups among patients who developed PABD after the initial TACE, namely, (1) those with a baseline liver condition of mALBI grade 1 or 2a and tumour burden exceeding the up-to-11 criteria, and (2) those with a baseline liver condition of mALBI grade 2b, regardless of tumour burden.

Conclusion: Repeat TACE is not recommended for patients with persistent liver function deterioration after the initial TACE, particularly those exhibiting suboptimal baseline liver function or excessive tumour burden. Understanding the liver condition and tumour burden in HCC patients may assist clinicians in planning optimal treatment strategies, leading to better prognosis.

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New knowledge added by this study

- The identification of objective and specific indicators predictive of suboptimal survival outcomes following repeat transarterial chemoembolisation (TACE) would be clinically valuable.
- The survival benefit of repeat TACE was not significant in two subgroups of patients who developed persistent albumin–bilirubin (ALBI) grade deterioration after the initial TACE, namely, (1) those with a baseline liver condition of modified albumin–bilirubin (mALBI) grade 1 or 2a and tumour burden exceeding the up-to-11 criteria, and (2) those with a baseline liver condition of mALBI grade 2b, regardless of tumour burden.

Implications for clinical practice or policy

- Liver function changes after initial TACE combined with tumour burden could serve as indicators to select patients suitable for repeat TACE.
- Repeat TACE is not recommended for patients with persistent liver function deterioration and a baseline liver condition of mALBI grade 1 or 2a and tumour burden exceeding the up-to-11 criteria, or for those with a baseline liver condition of mALBI grade 2b, regardless of tumour burden.

預測肝細胞癌患者在接受重複經動脈化療栓塞後的不良生存結果之肝功能特異性及腫瘤特異性指標

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引言：本研究探討預測接受首次經動脈化療栓塞（TACE）治療的中期肝細胞癌患者在接受重複TACE後的不良生存結果之肝功能特異性及腫瘤特異性指標。

方法：本研究包括了300位接受了首次TACE治療的患者，依據首次TACE後有否發生持續性肝功能惡化將患者分為持續性肝功能惡化（PABD）組和非PABD組；首次TACE後發生持續性肝功能惡化的定義為白蛋白—膽紅素分級（ALBI分級）較基線升高，且90天內指標未恢復。我們在按基線ALBI分級和腫瘤負荷分層的亞組中，比較非PABD患者和PABD患者與同期僅接受索拉非尼或支持治療的患者的整體存活。

結果：無論基線肝臟狀況（即改良ALBI分級及腫瘤負荷）如何，對於首次TACE後全部非PABD亞組或大部分PABD亞組的患者，與系統治療或支援治療比較，重複TACE提供了生存獲益。然而，在首次TACE後出現PABD的患者中，以下兩個亞組未觀察到此獲益：（1）基線肝臟狀況為改良ALBI 1級或2a級且腫瘤負荷超過「up-to-11」標準的患者，及（2）基線肝臟狀況為改良ALBI 2b級的患者，且無論腫瘤負荷如何。

結論：對於在接受首次TACE後出現持續性肝功能惡化的患者，特別是基線肝功能不佳或腫瘤負荷過大的患者，不建議進行重複TACE治療。了解肝細胞癌患者的肝功能和腫瘤負擔可能有助醫護人員制定最佳治療策略並改善患者預後。

Introduction

Hepatocellular carcinoma (HCC) imposes a substantial cancer burden worldwide; its incidence rate in 2020 was ranked seventh, whereas its mortality rate was ranked second.[1] Transarterial chemoembolisation (TACE) is commonly used as a first-line treatment for patients with intermediate-stage HCC, preserved liver function, and good performance status.[2,3]

Liver function deterioration occurs in 15.1% to 52% of patients after TACE[4-9]; among these patients, 3% to 31% experience chronic or irreversible liver function deterioration.[5-7,9] Patients with post-TACE liver function deterioration may have a suboptimal long-term prognosis.[5,8,10] Repeat TACE is indicated when residual tumour remains or when a new tumour is detected after the initial TACE.[2] Patients with tumours refractory to TACE are preferably treated with systemic therapy; switching to such therapy has demonstrated a survival benefit and better liver function preservation relative to continued TACE.[11,12]

Liver condition is crucial to the clinical outcome of repeat TACE. Patients with suboptimal liver function are more likely to experience irreversible liver function deterioration after repeat TACE, leading to suboptimal survival outcomes. Such patients also exhibit risks of reduced treatment efficacy and compromised safety during subsequent treatment with systemic therapy. In patients with HCC, liver condition is inevitably linked to tumour burden; liver function deterioration occurs more frequently in those with a high tumour burden.[5,13]

The identification of objective and specific indicators predictive of suboptimal survival outcomes following repeat TACE would be clinically valuable because such indicators could guide decisions regarding whether to pursue repeat TACE or switch to systemic therapy. We hypothesised that specific indicators based on liver condition and tumour burden, predictive of suboptimal survival outcomes following repeat TACE, could be identified. In this study, we sought to identify liver- and tumour-specific indicators predictive of suboptimal survival outcomes with repeat TACE relative to sorafenib or supportive care (SC) in patients who had received an initial TACE.

Methods

All patients presenting to our institution with unresectable HCC between January 2005 and December 2019 who met the eligibility criteria were recruited. Inclusion criteria consisted of treatment-naïve unresectable HCC confirmed by biopsy or contrast-enhanced imaging demonstrating typical enhancement features, Barcelona Clinic Liver Cancer stage B disease, and treatment with one of three options: TACE, sorafenib, or SC. Exclusion criteria were age <18 years, intrahepatic tumours with vascular invasion, extrahepatic metastases, liver function classified as albumin–bilirubin (ALBI) grade 3, or incomplete post-TACE liver function data. According to standard practice at our institution during the study period, patients with unresectable intermediate-stage HCC and no contraindication to TACE were prioritised for TACE. Patients who refused TACE were treated with sorafenib; those who declined both treatments received SC.

Liver condition indicator

Liver condition was assessed using the modified albumin–bilirubin (mALBI) grade.[14] The grade was defined by the ALBI score, which was calculated using the following equation: $\log_{10}$ (bilirubin [in μmol/L])×0.66+albumin [in g/L]×(-0.085). Patients were categorised into four grades: 1 (ALBI score ≤-2.60), 2a (ALBI score >-2.60 and ≤-2.27), 2b (ALBI score >-2.27 and ≤-1.39), and 3 (ALBI score >-1.39). Post–transarterial chemoembolisation liver condition was classified into three categories based on post-TACE ALBI grade deterioration, defined as a shift to a higher grade from baseline following

TACE, such as from grade 1 to grade 2-3, grade 2a to 2b-3, or grade 2b to 3. No ALBI grade deterioration (NABD) was regarded as the lack of a shift to a higher ALBI grade after TACE. Temporary ALBI grade deterioration (TABD) constituted ALBI grade deterioration that resolved within 90 days after TACE. Persistent ALBI grade deterioration (PABD) was defined as ALBI grade deterioration that did not resolve within 90 days after TACE. Patients in NABD and TABD groups were categorised as non-PABD group.

Tumour burden indicators

Tumour burden was assessed using the up-to-7 and up-to-11 criteria, defined as the sum of the tumour number and the largest tumour diameter in centimetres, with thresholds set at 7 and 11, respectively. Tumour burden was subclassified into four categories: within or beyond the up-to-7 or up-to-11 criteria.

Study design

At our institution, it was standard practice for patients initially treated with TACE to receive repeat TACE if residual or recurrent intrahepatic tumours were present, until a contraindication to TACE occurred. Contraindications included an Eastern Cooperative Oncology Group performance status score >2 or a Child-Pugh score >7, regardless of liver condition changes following the initial TACE. Assuming that patients with PABD after the initial TACE have a higher risk of further liver damage and worse survival outcomes if subjected to repeat TACE, such patients were targeted in this study. The overall survival (OS) of patients with or without PABD after the initial TACE was compared with the OS of patients receiving only sorafenib or SC during the same period. Among patients with or without post-TACE PABD, we identified subgroups with baseline mALBI grade and tumour burden who showed no survival benefit over sorafenib or SC; these patients were considered unsuitable for repeat TACE. Overall survival was calculated from the date of TACE or sorafenib initiation to the date of death from any cause. For patients who received SC, OS was calculated from the date of HCC diagnosis to the date of death from any cause. Censoring was applied to patients who were lost to follow-up, underwent subsequent liver resection, or were last known to be alive.

Transarterial chemoembolisation

The TACE procedure was performed under local anaesthesia and guided by digital subtraction angiography. An emulsion consisting of aqueous cisplatin (Platosin; Pharmachemie BV, Haarlem, the Netherlands) and ethiodised oil in a 1:1 volume ratio was delivered transarterially into the tumour vasculature until flow stagnation occurred or a maximum dose of 40 mL emulsion was reached. Tumour-feeding arteries were subsequently embolised using 5 to 10 mL of gelatin sponge. The completeness of the procedure was verified using digital subtraction angiography, with or without non-contrast multiplanar computed tomography (CT).

Systemic therapy

Oral sorafenib was administered twice daily at a standard dose of 400 mg. Dose adjustments or drug discontinuation were performed at the discretion of the oncologist based on patient tolerance.

Statistical analysis

Categorical variables are presented as numbers (percentages) and continuous variables are presented as medians (interquartile ranges). The Chi squared test was used to compare categorical data. The Mann-Whitney *U* test or Kruskal–Wallis test was performed for comparisons of continuous data. Differences in OS between subgroups were analysed using the log-rank test and hazard ratios (HRs) with 95% confidence intervals (CIs). Interaction terms were included to evaluate whether the survival benefit of the post-TACE PABD or non-PABD group over the sorafenib or SC group varied across subgroups. P values <0.05 were considered statistically significant. Data analysis was performed using SPSS (Windows version 25.0; IBM Corp, Armonk [NY], United States).

Results

Study participants

In total, 300 treatment-naïve patients with HCC received TACE. The median age was 65 years (interquartile range, 56-72); the cohort included 255 men and 45 women. After the first TACE, 235 of 300 patients experienced ALBI deterioration: 154 exhibited TABD and 81 displayed PABD. The demographics of patients with NABD, TABD, and PABD are listed in Table 1. The OS was similar for patients with NABD and TABD (22.40 vs 23.83 months), indicating that TABD did not adversely affect treatment outcomes. Therefore, patients with NABD and TABD were combined into the non-PABD group. The demographics of patients in non-PABD group and PABD group were compared to sorafenib group and SC group, as listed in Table 2. Patients in non-PABD group and PABD group had significantly better OS than those in sorafenib and SC group (23.13, 8.03, 5.11, and 2.57 months, respectively).

TABLE 1. Demographics of patients with different albumin–bilirubin deterioration statuses after the initial transarterial chemoembolisation*

	NABD group (n=65)	TABD group (n=154)	PABD group (n=81)	P value (NABD vs TABD)	P value (NABD vs PABD)	P value (TABD vs PABD)
Characteristics						
Age, y [median (IQR)]	61 (56-72)	65 (56-72)	66 (57-71)	0.664	0.466	0.758
Sex				0.292	0.207	0.680
Male	52 (80.0%)	132 (85.7%)	71 (87.7%)			
Female	13 (20.0%)	22 (14.3%)	10 (12.3%)			
Up-to-7 criteria				0.040	0.021	0.521
Within	22 (33.8%)	32 (20.8%)	14 (17.3%)			
Beyond	43 (66.2%)	122 (79.2%)	67 (82.7%)			
Up-to-11 criteria				0.045	0.027	0.099
Within	50 (76.9%)	97 (63.0%)	42 (51.9%)			
Beyond	15 (23.1%)	57 (37.0%)	39 (48.1%)			
mALBI grade (1 or 2a/2b)				<0.001	<0.001	0.785
1 or 2a	9 (13.8%)	98 (63.6%)	53 (65.4%)			
2b	56 (86.2%)	56 (36.4%)	28 (34.6%)			
mALBI grade and up-to-7 criteria				<0.001	<0.001	0.868
1 or 2a, within 7	3 (4.6%)	20 (13.0%)	8 (9.9%)			
1 or 2a, beyond 7	6 (9.2%)	78 (50.6%)	45 (55.6%)			
2b, within 7	19 (29.2%)	12 (7.8%)	6 (7.4%)			
2b, beyond 7	37 (56.9%)	44 (28.6%)	22 (27.2%)			
mALBI grade and up-to-11 criteria				<0.001	<0.001	<0.001
1 or 2a, within 11	8 (12.3%)	70 (45.5%)	25 (30.9%)			
1 or 2a, beyond 11	1 (1.5%)	28 (18.2%)	28 (34.6%)			
2b, within 7	42 (64.6%)	27 (17.5%)	17 (21.0%)			
2b, beyond 11	14 (21.5%)	29 (18.8%)	11 (13.6%)			
Median OS, mo (95% CI)	22.40 (16.37-28.43)	23.83 (18.96-28.71)	8.03 (3.97-12.10)	0.591	0.001	<0.001

Abbreviations: 95% CI = 95% confidence interval; IQR = interquartile range; mALBI grade = modified albumin-bilirubin grade; NABD = no albumin–bilirubin grade deterioration; OS = overall survival; PABD = persistent albumin–bilirubin grade deterioration; TABD = temporary albumin–bilirubin grade deterioration

* Data are shown as No. (%), unless otherwise specified

Overall survival

Patients with post–transarterial chemoembolisation persistent albumin–bilirubin grade deterioration versus sorafenib in subgroups

Online supplementary Figure 1 illustrates the median OS of patients with post-TACE PABD relative to patients treated with sorafenib. Patients receiving TACE who developed post-TACE PABD had significantly longer median OS than those receiving sorafenib in subgroups within and beyond the up-to-7 criteria (19.63 vs 5.17 months; P=0.019 and 7.63 vs 5.11 months; P=0.030, respectively).

A significantly longer median OS was observed in patients receiving TACE who developed post-TACE PABD relative to those receiving sorafenib in the subgroup within the up-to-11 criteria (10.20 vs 5.37 months; P=0.016). However, this difference was not significant in the subgroup beyond the up-to-11 criteria (8.00 vs 4.94 months; P=0.083). Similarly, OS was significantly improved in the post-TACE PABD group relative to the sorafenib group within the mALBI grade 1 or 2a subgroup (11.50 vs 6.60 months; P=0.001). However, no significant difference was observed in the mALBI grade 2b subgroup (3.47 vs 4.39 months; P=0.517) [online supplementary Fig 1].

Based on stratification according to mALBI grade and the up-to-7 criteria, patients receiving TACE who developed post-TACE PABD had significantly longer median OS relative to those receiving sorafenib in the subgroup with mALBI grade 1 or 2a and within the up-to-7 criteria (29.57

TABLE 2. Demographics of patients with different albumin–bilirubin deterioration statuses after the initial transarterial chemoembolisation relative to those receiving sorafenib or supportive care*

	Non-PABD group (n=219)	PABD group (n=81)	Sorafenib group (n=62)	SC group (n=89)
Characteristics				
Age, y [median (IQR)]	65 (56-72)†	66 (57-71)†	57 (54-64)	61 (54-71)
Sex				
Male	184 (84.0%)†	71 (87.7%)	59 (95.2%)	77 (86.5%)
Female	35 (16.0%)†	10 (12.3%)	3 (4.8%)	12 (13.5%)
Up-to-7 criteria				
Within	54 (24.7%)†	14 (17.3%)	5 (8.1%)	16 (18.0%)
Beyond	165 (75.3%)†	67 (82.7%)	57 (91.9%)	73 (82.0%)
Up-to-11 criteria				
Within	147 (67.1%)†‡	42 (51.9%)†	15 (24.2%)	36 (40.4%)
Beyond	72 (32.9%)†‡	39 (48.1%)†	47 (75.8%)	53 (59.6%)
mALBI grade				
1 or 2a	107 (48.9%)†‡	53 (65.4%)†‡	19 (30.6%)	15 (16.9%)
2b	112 (51.1%)†‡	28 (34.6%)†‡	43 (69.4%)	74 (83.1%)
mALBI grade and up-to-7 criteria				
1 or 2a, within 7	23 (10.5%)†‡	8 (9.9%)‡	5 (8.1%)	3 (3.4%)
1 or 2a, beyond 7	84 (38.4%)†‡	45 (55.6%)‡	32 (51.6%)	30 (33.7%)
2b, within 7	31 (14.2%)†‡	6 (7.4%)‡	0	10 (11.2%)
2b, beyond 7	81 (37.0%)†‡	22 (27.2%)‡	25 (40.3%)	46 (51.7%)
mALBI grade and up-to-11 criteria				
1 or 2a, within 11	78 (35.6%)†‡	25 (30.9%)†‡	12 (19.4%)	11 (12.4%)
1 or 2a, beyond 11	29 (13.2%)†‡	28 (34.6%)†‡	25 (40.3%)	22 (24.7%)
2b, within 7	69 (31.5%)†‡	17 (21.0%)†‡	3 (4.8%)	25 (28.1%)
2b, beyond 11	43 (19.6%)†‡	11 (13.6%)†‡	22 (35.5%)	31 (34.8%)
Median OS, mo (95% CI)	23.13 (19.24-27.03)†‡	8.03 (3.97-12.10)†‡	5.11 (4.37-5.84)	2.57 (2.05-3.09)

Abbreviations: 95% CI = 95% confidence interval; IQR = interquartile range; mALBI grade = modified albumin–bilirubin grade; OS = overall survival; PABD = persistent albumin–bilirubin grade deterioration; SC = supportive care

* Data are shown as No. (%), unless otherwise specified

† P<0.05 compared with sorafenib group

‡ P<0.05 compared with SC group

vs 5.17 months; P=0.003) and the subgroup with mALBI grade 1 or 2a and beyond the up-to-7 criteria (10.57 vs 6.60 months; P=0.020). However, OS was not significantly improved in the subgroup with mALBI grade 2b and within the up-to-7 criteria (6.40 vs 4.39 months; P=0.071) or in the subgroup with mALBI grade 2b and beyond the up-to-7 criteria (3.07 vs 4.39 months; P=0.891). The interaction between treatment effects in subgroups stratified according to mALBI grade and the up-to-7 criteria had a 5% level of significance, with a tendency of a significant interaction that warrants further studies (P=0.058) [online supplementary Fig 1].

Based on stratification according to mALBI grade and the up-to-11 criteria, patients receiving TACE who developed post-TACE PABD had significantly longer median OS relative to those receiving sorafenib in the subgroup with mALBI grade 1 or 2a and within the up-to-11 criteria (13.37 vs 5.76 months; P=0.004). However, OS was not significantly improved in the subgroup with mALBI grade 1 or 2a and beyond the up-to-11 criteria (11.50 vs 6.60 months; P=0.061), the subgroup with mALBI grade 2b and within the up-to-11 criteria (5.07 vs 4.52 months; P=0.313), or the subgroup with mALBI grade 2b and beyond the up-to-11 criteria (3.07 vs 4.10 months; P=0.316). The interaction between treatment effects in subgroups stratified according to mALBI grade and the up-to-11 criteria had a 5% level of significance, with a tendency of a significant interaction that warrants further studies (P=0.071) [online supplementary Fig 1].

Patients with post–transarterial chemoembolisation persistent albumin–bilirubin grade deterioration versus supportive care in subgroups

The median OS of patients who developed post-TACE PABD relative to those receiving SC is shown in online supplementary Figure 2. Patients receiving TACE who developed post-TACE PABD had significantly longer median OS compared with those receiving SC in the subgroup with mALBI grade 1 or 2a and within the up-to-7 criteria (29.57 vs 15.38 months; P=0.036) and the subgroup with mALBI grade 1 or 2a and beyond the up-to-7 criteria (10.57 vs 3.32 months; P<0.001). However, no significant improvement in OS was observed in the subgroup with mALBI grade 2b and within the up-to-7 criteria (6.40 vs 5.40 months; P=0.266) or in the subgroup with mALBI grade 2b and beyond the up-to-7 criteria (3.07 vs 2.18 months; P=0.051).

Patients receiving TACE who developed post-TACE PABD also had significantly longer median OS relative to those receiving SC in the subgroup with mALBI grade 1 or 2a and within the up-to-11 criteria (13.37 vs 4.29 months; P=0.035) and the subgroup with mALBI grade 1 or 2a and beyond the up-to-11 criteria (11.50 vs 3.32 months; P=0.001). However, no significant improvement in OS was observed in the subgroup with mALBI grade 2b and within the up-to-11 criteria (5.07 vs 2.57 months; P=0.084) or in the subgroup with mALBI grade 2b and beyond the up-to-11 criteria (3.07 vs 2.08 months; P=0.269) [online supplementary Fig 2].

Patients with post–transarterial chemoembolisation non-persistent albumin–bilirubin grade deterioration versus sorafenib or supportive care in subgroups

Significantly longer median OS was observed among patients in the non-PABD group after TACE relative to those receiving sorafenib (all P<0.001) [online supplementary Fig 3] or SC in all subgroups (all P<0.001, except for the subgroup with mALBI grade 1 or 2a and within the up-to-7 criteria, which displayed a P value of 0.012) [online supplementary Fig 4] stratified according to various criteria.

Discussion

Principal findings

This study demonstrated that repeat TACE provided a survival benefit over systemic therapy or SC for patients who developed TABD or PABD after the first TACE, regardless of baseline liver condition (according to ALBI grade, tumour burden, or liver function). However, this benefit was absent in the following two subgroups among patients who developed PABD after the first TACE: (1) those with a baseline liver condition of mALBI grade 1 or 2a and tumour burden exceeding the up-to-11 criteria, and (2) those with a baseline liver condition of mALBI grade 2b, regardless of tumour burden. These two subgroups could serve as specific indicators to guide the decision against prescribing repeat TACE for individual patients, based on their baseline liver condition, tumour burden, and occurrence of PABD after the initial TACE. In such cases, the treatment outcomes of repeat TACE are unlikely to differ from those of sorafenib or SC. Notably, there was a 5% level of significance, with a tendency of a significant interaction that warrants further studies.

Current knowledge of previous studies

Liver function deterioration after TACE is associated with worsened long-term survival.[5,8,10] Patients with no increase in Child-Pugh score 1 month after TACE had significantly better survival rates than those with an increased Child-Pugh score at the same time point (84.5% vs 44.4%, 43.75% vs 18.5%, and 8.3% vs 0% for 1-year, 2-year, and 3-year survivals, respectively).[8] The extent of liver function deterioration after TACE also impacts survival outcomes. The median OS was significantly longer in patients with ALBI grade migration to grade 2 than in patients with migration to grade 3 during both the acute phase (30.9 months vs 8.9 months; P<0.001) and the chronic phase (30.9 months vs 5.7 months; P<0.001).[5] Higher tumour burden is linked to liver function deterioration and worse survival outcomes after TACE.[15-17] Based on the 7-11 criteria, patients with high tumour burden experienced significantly higher rates of liver function deterioration (24.4% vs 14.9% or 14.4%) and shorter median survival (11.9 vs 22.3 or 33.1 months) relative to those with low or intermediate tumour burden.[17] Currently, there are no reports in the literature concerning studies that identified liver- and tumour-specific indicators to predict survival benefits of repeat TACE.

Implications for clinical practice

Repeat TACE can damage liver function and worsen long-term survival. If a patient's liver function is irreversibly and severely impaired by repeat TACE, the opportunity to switch to systemic therapy may be missed. To maximise survival benefits, the decision to repeat TACE, discontinue TACE, or transition to systemic therapy should be carefully considered and individualised. Two scoring systems have been developed to guide retreatment strategies,[18,19] but universal validation of their predictive value is needed. Studies have shown that these systems are ineffective in terms of supporting decision-making for sequential treatment.[20,21]

Most patients who develop TABD are able to spontaneously recover their baseline liver function. In this study, similar median OS was observed among patients with TABD and NABD (23.83 vs 22.40

months). Transarterial chemoembolisation provided a statistically significant survival benefit for patients within the non-PABD group, regardless of tumour burden, relative to those receiving sorafenib or SC. This finding suggests that TABD has minimal impact on survival benefit or long-term prognosis after TACE, and repeat TACE remains feasible in these patients with reversed or reversible liver function. Based on the present findings, repeat TACE is not recommended for patients with PABD and a baseline liver condition of mALBI grade 2b, regardless of tumour burden, because survival outcomes in this subgroup are unlikely to be superior to those achieved with sorafenib or SC. For the same reason, repeat TACE is not recommended for patients with PABD, a baseline liver condition of mALBI grade 1 or 2a, and tumour burden beyond the up-to-11 criteria. Systemic therapy is preferred for this subgroup, considering that its effectiveness is likely maximised in patients with better liver function (eg, those with ALBI grade 1 or mALBI grade 2a, as stated in an expert consensus).[22]

Limitations

We acknowledge that sorafenib is no longer first-line systemic therapy for HCC. Regimens such as lenvatinib[23] or atezolizumab-bevacizumab[24] have been associated with significantly better OS relative to sorafenib. We recognise that the use of sorafenib as a control was a limitation of this study. However, no alternative was available because a sufficiently large database with long-term clinical outcomes for newer systemic therapies was not accessible for the local population. The primary objective of this study was not to evaluate the role of sorafenib compared with TACE, but to use sorafenib as a control to identify specific liver and tumour indicators predictive of suboptimal survival outcomes after repeat chemoembolisation. These indicators are intended to serve as contraindications for repeat TACE in patients with the corresponding liver and tumour conditions. The use of a systemic drug with lower OS benefit, such as sorafenib, as a control might lead to overestimation of the value of repeat TACE and, consequently, to the identification of indicators under worse liver and tumour conditions. However, this observation does not compromise the validity of these indicators as criteria for contraindicating repeat TACE.

Other limitations of the study include the relatively small sample size in patient groups receiving sorafenib or SC. Patient numbers were further reduced in some subgroups after stratification according to liver function and tumour burden, which could introduce bias in survival comparisons. Serum alpha-fetoprotein (AFP) levels and tumour response after TACE were not analysed in this study. Considering that elevated AFP levels have been associated with ALBI deterioration, AFP may be partially represented in the baseline ALBI grade. The median time to Child-Pugh deterioration was significantly longer in patients who responded to the initial TACE than in those who were refractory to the initial TACE (55.9 vs 19.6 months).[25] Most patients (22/27, 81.5%) ineligible for repeat TACE due to hepatic decompensation exhibited tumour progression at the time of TACE discontinuation.[26] Target lesion progression has been associated with no survival improvement and an increased risk of liver dysfunction after repeat TACE.[27] Based on findings in the above studies, poor tumour response may eventually lead to liver function deterioration. Although tumour response was not analysed in this study, it is reasonable to assume that tumour response varies according to treatment effectiveness. Given that treatment effectiveness is assumed to remain consistent under the same treatment protocol within a single centre, it may be argued that the overall effect of tumour response in individual patients was reflected in liver function deterioration.

Conclusion

This study found that repeat TACE is not recommended for patients with persistent liver function deterioration after the initial TACE, particularly those exhibiting suboptimal baseline liver function or excessive tumour burden. Understanding the liver condition and tumour burden in HCC patients may assist clinicians in planning optimal treatment strategies and improving patient prognosis.

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.

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Ethics approval

This research was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research

Ethics Committee, Hong Kong (Ref No.: 2020.672). The research was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation, Good Clinical Practice. The requirement for written informed patient consent was waived by the Committee due to the retrospective nature of the research.

Supplementary material

The supplementary material was provided by the authors, and some information may not have been peer reviewed. Accepted supplementary material will be published as submitted by the authors, without any editing or formatting. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by the Hong Kong Academy of Medicine and the Hong Kong Medical Association. The Hong Kong Academy of Medicine and the Hong Kong Medical Association disclaim all liability and responsibility arising from any reliance placed on the content. To view the file, please visit the journal online (https://doi.org/10.12809/hkmj2311208).

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. Cheung TT, Kwok PC, Chan S, et al. Hong Kong consensus statements for the management of unresectable hepatocellular carcinoma. Liver Cancer 2018;7:40-54.
3. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
4. Min YW, Kim J, Kim S, et al. Risk factors and a predictive model for acute hepatic failure after transcatheter arterial chemoembolization in patients with hepatocellular carcinoma. Liver Int 2013;33:197-202.
5. Chi CT, Lee IC, Lee RC, et al. Effect of transarterial chemoembolization on ALBI grade in intermediate-stage hepatocellular carcinoma: criteria for unsuitable cases selection. Cancers (Basel) 2021;13:4325.
6. Hiraoka A, Kumada T, Kudo M, et al. Hepatic function during repeated TACE procedures and prognosis after introducing sorafenib in patients with unresectable hepatocellular carcinoma: multicenter analysis. Dig Dis 2017;35:602-10.
7. Miksad RA, Ogasawara S, Xia F, Fellous M, Piscaglia F. Liver function changes after transarterial chemoembolization in US hepatocellular carcinoma patients: the LiverT study. BMC Cancer 2019;19:795.
8. Kohla MA, Abu Zeid MI, Al-Warraky M, Taha H, Gish RG. Predictors of hepatic decompensation after TACE for hepatocellular carcinoma. BMJ Open Gastroenterol 2015;2:e000032.
9. Park KH, Kim JH, Choe WH, et al. Risk factors for liver function deterioration after transarterial chemoembolization refractoriness in Child-Pugh class A hepatocellular carcinoma patients. Korean J Gastroenterol 2020;75:147-56.
10. Sun Z, Li G, Ai X, et al. Hepatic and biliary damage after transarterial chemoembolization for malignant hepatic tumors: incidence, diagnosis, treatment, outcome and mechanism. Crit Rev Oncol Hematol 2011;79:164-74.
11. 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.
12. Piscaglia F, Ogasawara S. Patient selection for transarterial chemoembolization in hepatocellular carcinoma: importance of benefit/risk assessment. Liver Cancer 2018;7:104-19.
13. Yasui Y, Tsuchiya K, Kurosaki M, et al. Up-to-seven criteria as a useful predictor for tumor downstaging to within Milan criteria and Child-Pugh grade deterioration after initial conventional transarterial chemoembolization. Hepatol Res 2018;48:442-50.
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. Khisti R, Patidar Y, Garg L, Mukund A, Thomas SS, Sarin SK. Correlation of baseline portal pressure (hepatic venous pressure gradient) and indocyanine green clearance test with post–transarterial chemoembolization acute hepatic failure. J Clin Exp Hepatol 2019;9:447-52.
16. Siriwardana RC, Niriella MA, Dassanayake AS, et al. Factors affecting post-embolization fever and liver failure after trans-arterial chemo-embolization in a cohort without background infective hepatitis—a prospective analysis. BMC Gastroenterol 2015;15:96.
17. 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.
18. Sieghart W, Hucke F, Pinter M, et al. The ART of decision making: retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma. Hepatology 2013;57:2261-73.
19. Adhoute X, Penaranda G, Naude S, et al. Retreatment with TACE: the ABCR SCORE, an aid to the decision-making process. J Hepatol 2015;62:855-62.
20. Arizumi T, Ueshima K, Iwanishi M, et al. Evaluation of ART scores for repeated transarterial chemoembolization in Japanese patients with hepatocellular carcinoma. Oncology 2015;89 Suppl 2:4-10.
21. Kloeckner R, Pitton MB, Dueber C, et al. Validation of clinical scoring systems ART and ABCR after transarterial chemoembolization of hepatocellular carcinoma. J Vasc Interv Radiol 2017;28:94-102.
22. 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.
23. 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.
24. 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.
25. Maesaka K, Sakamori R, Yamada R, et al. Initial treatment response to transarterial chemoembolization as a predictive factor for Child-Pugh class deterioration prior to refractoriness in hepatocellular carcinoma. Hepatol Res 2020;50:1275-83.
26. Labeur TA, Takkenberg RB, Klümpen HJ, van

Delden OM. Reason of discontinuation after transarterial chemoembolization influences survival in patients with hepatocellular carcinoma. Cardiovasc Intervent Radiol 2019;42:230-8.

27. Zhang YF, Guo RP, Ouyang HY, et al. Target lesion response predicts survival of patients with hepatocellular carcinoma retreated with transarterial chemoembolization. Liver Int 2016;36:1516-24.