Alimentary Pharmacology & Therapeutics

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AP&T Alimentary Pharmacology & Therapeutics

ORIGINAL ARTICLE

Tumour Burden Score as a Predictor of Extrahepatic Progression After Transarterial Chemoembolization for Hepatocellular Carcinoma: An Observational Multicenter Study

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Received: 10 September 2025 | **Revised:** 28 December 2025 | **Accepted:** 5 January 2026

Handling Editor: Geoffrey Dusheiko

Keywords: liver cancer | locoregional treatments | metastases | prognosis | tumour burden score

ABSTRACT

Background: In patients with hepatocellular carcinoma (HCC), extrahepatic progression (EHP) has a known dismal meaning. We evaluated the incidence and risk factors of EHP in HCC patients treated with transarterial chemoembolization (TACE), and the predictive role of tumour burden.

Methods: From the ITA.LI.CA database, 890 HCC patients undergoing first-line TACE were included. Tumour burden score (TBS) was calculated and, after identification of the best cut-point value, incidence and predictors of EHP were compared between TBS-low and TBS-high groups. Independent predictors of EHP at the *first* progression episode or at any time during follow-up were identified through multivariable Cox analysis.

Results: After TACE, 7.2% of patients experienced EHP at the *first* progression episode, while the overall EHP rate during the follow-up was 26.1%. The best cut-point for TBS was 3.66. TBS-high group (> 3.66) showed a significantly higher proportion of EHP both at *first* progression (10.4% vs. 3.6%; $p < 0.001$) and overall (32.6% vs. 18.7%; $p < 0.001$) compared to the TBS-low group. Moreover, TBS-high patients had shorter progression-free survival and overall survival. TBS-high and AFP levels emerged as independent predictors of EHP at the *first* progression episode and during the follow-up, and their combined evaluation accurately stratified patients for their risk of EHP.

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; CR, complete response; CSPH, clinically significant portal hypertension; CT, computed tomography; ECOG-PS, Eastern Cooperative Oncology Group performance status; EHP, extrahepatic progression; HCC, hepatocellular carcinoma; HR, hazard ratio; HVPG, hepatic venous pressure gradient; INR, international normalised ratio; IQR, interquartile range; ITA.LI.CA, Italian Liver Cancer; MELD, Model for End Stage Liver Disease; mRECIST, modified Response Evaluation in Solid Tumours; MRI, magnetic resonance imaging; MVI, macrovascular invasion; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TACE, transarterial chemoembolization; TBS, tumour burden score.

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Conclusion: Extrahepatic dissemination is infrequent in HCC patients treated with TACE. TBS is easily calculable and helps in identifying patients at higher risk of metastasis development.

1 | Introduction

Cancers progress either through an enlargement of the primary tumoural lesion or distant spread of the tumour. Most cancers, such as pancreas, breast and lung, often develop as a systemic process from the onset, and metastatic dissemination of the disease is the cause of death in the majority of cases. By contrast, hepatocellular carcinoma (HCC) progression is unique from a biological standpoint, as in most cases it occurs locally (growth in size, development of satellites, increased vascularity of lesions, invasion of portal vein, or new intrahepatic nodules) and less frequently as a systemic disease with extrahepatic spread [1, 2]. Moreover, HCC is also characterised by the fact that it arises in patients with chronic liver disease, most often cirrhosis. Therefore, these patients display competitive causes of death related to the presence of the underlying liver disease, so that they may die because of cancer progression or liver dysfunction [3–5].

Considering the predominantly intra-hepatic progression of HCC, surgical and locoregional therapies represent the backbone of its treatment [3]. Beyond these therapeutic strategies, several tyrosine kinase inhibitors and immunotherapy-based regimens are currently approved for the systemic treatment of patients with unresectable disease [6–15]. According to the principles of therapeutic hierarchy [3, 16, 17], the best treatment in terms of survival gain should always be delivered whenever possible. Within the context of a multidisciplinary, multiparametric decision-making process, when curative treatments (transplantation, resection, ablation) are not feasible or contraindicated, and once extrahepatic spread is excluded, intra-arterial treatments are considered the correct treatment option [3]. In patients treated with transarterial chemoembolization (TACE), extrahepatic progression (EHP) is an extremely unfavourable prognostic factor; it precludes further locoregional therapy, leaving systemic treatment as the only option. Identification of patients treated with TACE who are at higher risk of EHP may allow a better tailor of treatment, possibly anticipating systemic therapy and avoiding futile TACE sessions that can increase the risk of liver dysfunction, thus jeopardising future potential treatments.

Evidence on the incidence of EHP after transarterial locoregional therapies remains limited [1], most importantly, few is known about potential risk factors and a better understanding of these aspects could guide better treatment allocation.

On these bases, we aimed to assess the pattern of HCC progression after TACE, and to evaluate the incidence and the risk factors of EHP. Considering that tumour burden is a well-known prognostic factor, and is linked to the probability of response to treatment [18, 19], we assessed the role of this variable as a risk factor for EHP occurrence after TACE.

2 | Patients and Methods

2.1 | Study Design and Data Collection

In this retrospective study, data were retrieved from the Italian Liver Cancer (ITA.LI.CA) database, a multicenter prospectively maintained registry including data of 9573 patients with HCC consecutively managed in 24 participating Institutions between January 1988 and December 2020. Patients provided written informed consent for all diagnostic and therapeutic procedures, as well as for the anonymous recording of their clinical data in the database. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of the coordinating Institution (Azienda Ospedaliero-Universitaria of Bologna, approval n. 99/2012/O/Oss).

This study included patients with HCC who received TACE as first-line treatment. Therefore, from all the patients registered in the ITA.LI.CA database ($n = 9573$), after the exclusion of patients diagnosed with HCC before January 2000 ($n = 348$), of those who have never been treated with TACE ($n = 6902$) and of those who received TACE at the time of HCC recurrence following a previous treatment ($n = 1238$), we selected 1085 patients. Among them, 23 patients were excluded due to the presence of extrahepatic disease at the time of TACE, and 172 patients because of missing data, thus leaving 890 patients for the final analysis (Figure S1).

HCC was histologically confirmed in 135/890 patients (15.2%), whereas the remaining cases were diagnosed on the basis of typical features at imaging according to the national and international guidelines available at the time of patient recruitment [20, 21].

Standard demographic and clinicopathological data, such as age, sex, comorbidities, aetiology of the underlying liver disease, main serological parameters (albumin, bilirubin, international normalised ratio [INR], creatinine, platelet count, alpha-fetoprotein [AFP]), presence of ascites and hepatic encephalopathy, clinically significant portal hypertension (CSPH), and Eastern Cooperative Oncology Group performance status (ECOG-PS) were considered and analysed. AFP level was studied as an ordinal variable, categorised into three clinically meaningful groups as previously validated [22]: ≤100 ng/mL, 101–1000 ng/mL, and >1000 ng/mL. The presence of CSPH was based on unequivocal signs (presence of splenomegaly, varices, ascites) and platelet count $<100 \times 10^9$/L [23]. Liver function was assessed using the Child-Pugh classification, the albumin-bilirubin (ALBI) grade and the Model for End Stage Liver Disease (MELD) score. Tumour radiological characteristics (location and size of the largest liver lesion, number of nodules, presence of macrovascular invasion [MVI]) were assessed with contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), and the ITA.LI.CA [16, 17, 24] and the

Barcelona Clinic Liver Cancer (BCLC) [25] staging systems were used to stage patients.

In this study, tumour burden was assessed using the tumour burden score (TBS), originally proposed as a prognostic tool for colorectal cancer liver metastases [26, 27] but which has been found to be also able to stratify the prognosis of patients with HCC [28, 29]. TBS was calculated by applying the Pythagorean formula: $TBS = \sqrt{}$ [(maximum tumour diameter)^2 + (number of tumours)^2] on pre-treatment imaging. Treatment efficacy was evaluated with abdomen contrast-enhanced CT or MRI performed 1 month after the procedure, and the response was graded using the modified Response Evaluation Criteria in Solid Tumour (mRECIST) criteria as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) [30]. For each patient, complete information regarding the progression of the disease (defined either as the appearance of a new lesion or as the progression of a pre-existing neoplastic lesion), including the sequence of treatments performed, is registered in the ITA.LI.CA database. In case of EHP, the location of metastasis is also recorded. Tumour progression was divided into *intrahepatic* and *extrahepatic*, and when both were present, progression was classified as extrahepatic. Moreover, both EHP at the time of first progression after TACE and EHP at any time during follow-up were considered.

2.2 | Study Outcomes

The primary outcome of the study was the time-to-EHP, defined as the time elapsed between TACE and EHP detection. This outcome was also divided as time-to-EHP at the *first* episode of progression and time-to-EHP at any time during follow-up after TACE. Other outcomes of interest were: rate of HCC progression, rate of EHP, progression-free survival (PFS), and overall survival (OS). Patients alive at the end of follow-up who did not experience EHP or patients who died without exhibiting EHP on their last imaging scan were censored as non-extrahepatic progressors. PFS was defined as the time between TACE and progression (intrahepatic and/or extrahepatic) or death, whichever occurred first. OS was calculated from the date of TACE to the date of death from any cause. The study follow-up ended on December 31st 2020, and patients alive and without progression at this date were censored in PFS and OS analyses.

2.3 | Statistical Analysis

Categorical variables are reported as absolute and relative frequency (percentage), while continuous data as median and interquartile range (IQR). Differences between groups were evaluated using chi-square test and Fischer's exact test for categorical variables, and Mann–Whitney test for continuous variables, as appropriate.

Time-to-event curves were estimated with the Kaplan–Meier method and compared with the log-rank test. TBS linearity assumption, in predicting EHP after TACE, was tested using fractional polynomials and restricted cubic splines. Subsequently, the best cut-point for TBS was defined as the one that minimised the *p*-value for the hazard ratio (HR) in the univariable Cox model. Univariate and multivariate Cox regression analyses were performed to evaluate factors associated with EHP, using cause-specific hazards and censuring patients who died without EHP. In the multivariate model, only variables significantly or borderline ($p \leq 0.10$) associated with the outcome at the univariate analyses were included. Results of Cox analyses are presented as hazard ratio (HR) and 95% confidence interval (95% CI). Radiologic response to first TACE according to mRECIST was added as a predictive variable in the model for identification of predictors of EHP at any time during follow-up.

IBM SPSS Statistics (Version 25.0. Armonk, NY, IBM Corp.) and GraphPad Prism version 8.3.1 (GraphPad Software) were used for statistical analyses. Statistical significance was set at $p < 0.05$.

3 | Results

3.1 | Timing and Pattern of HCC Progression After TACE

Baseline characteristics of the study cohort are described in Table 1. The median TBS in the entire cohort was 3.9 (IQR 2.9–5.1). Preliminary univariable Cox regression analysis demonstrated an exponential association between TBS and the risk of EHP after TACE (Figure S2A). The best cut-point of TBS was identified in the value of 3.66 (Figure S2B,C). Accordingly, the study population was divided into two groups: patients with TBS ≤ 3.66 (TBS-low group) vs. patients with TBS > 3.66 (TBS-high group). At the time of TACE, the TBS-low group included 418 patients (47.0%), while the TBS-high group included the remaining 472 patients (53.0%).

During a median follow-up of 28.6 months (IQR 14.0–50.0), HCC progression was diagnosed in 678 patients (76.2%). The median PFS was 10.0 months (95% CI 9.0–11.0) for the entire cohort. The median PFS was 11.0 months (95% CI 0.6–12.4) in the TBS-low group and 8.3 months (95% CI 6.9–9.6) in the TBS-high group ($p = 0.001$) (Figure 1).

Table 2 reports the pattern of progression. Overall, the first episode of progression after TACE occurred as *intra-hepatic* progression in 614 patients (69.0%) and as EHP in 64 (7.2%). The time-to-progression was 6.3 months (95% CI 5.3–7.2) in patients with *intra-hepatic* progression and 13.0 months (95% CI 8.1–17.9) in those with EHP ($p = 0.04$). EHP at the *first* episode of progression was generally uncommon, but much more frequent in the TBS-high group (10.4%) than in the TBS-low group (3.6%) ($p < 0.001$), so that the cumulative hazard of *first* EHP was significantly higher in the former group ($p < 0.001$) (Figure 2A).

During the entire follow-up, EHP occurred in 232 patients (26.1%) with a median time of 26.0 months (IQR, 15.0–39.1) after TACE. Namely, 78 patients (18.7%) in the TBS-low group and 154 patients (32.6%) in the TBS-high group developed EHP ($p < 0.001$), with a cumulative hazard of EHP significantly higher in the TBS-high group ($p < 0.001$) (Figure 2B). Sites of EHP, both at the time of the first progression and at any time of the follow-up, are shown in Table 2.

TABLE 1 | Baseline patient characteristics.

Variable	Overall ($n=890$)	TBS-low group ($n=418$)	TBS-high group ($n=472$)	p
Males, *n* (%)	699 (78.5)	317 (75.8)	382 (80.9)	0.07
Age, median (IQR)	69 (61–76)	69 (60–76)	69 (61–76)	0.51
BMI, median (IQR)	25.3 (23.2–28.7)	25.4 (23.4–28.3)	25.1 (23.1–29.1)	0.82
Aetiology				
Viral	486 (54.6)	236 (56.5)	250 (53.0)	0.53
Not viral	319 (35.8)	142 (34.0)	177 (37.5)	
Viral + other	85 (9.6)	40 (9.6)	45 (9.5)	
Surveillance, *n* (%)	561 (63.0)	314 (75.1)	247 (52.3)	<0.001
Biopsy for diagnosis, *n* (%)	135 (15.2)	29 (6.9)	106 (22.5)	<0.001
ECOG 0, *n* (%)	716 (80.4)	339 (81.1)	377 (79.9)	0.67
CSPH, *n* (%)[a]	586 (65.8)	292 (69.9)	294 (62.3)	0.02
Ascites, *n* (%)	124 (14.6)	58 (14.7)	66 (14.5)	0.98
Hepatic encephalopathy, *n* (%)	38 (4.3)	20 (4.8)	18 (3.8)	0.55
HCC number	2 (1–3)	1 (1–2)	2 (1–3)	<0.001
HCC size (cm)	3.0 (2.2–4-4)	2.2 (1.7–3.0)	4.3 (3.3–5.2)	<0.001
TBS	3.9 (2.9–5.1)	2.8 (2.2–3.3)	5.1 (4.3–6.1)	<0.001
Intrahepatic MVI, *n* (%)	18 (2.0)	3 (0.7)	15 (3.2)	0.01
Albumin (g/L), median (IQR)	3.6 (3.2–4.0)	3.7 (3.2–4.0)	3.6 (3.2–4.0)	0.04
Bilirubin (mg/dL), median (IQR)	1.10 (0.70–1.60)	1.10 (0.70–1.70)	1.00 (0.72–1.58)	0.21
ALBI grade				
1	140 (16.9)	76 (19.8)	64 (14.4)	0.050
2	537 (64.8)	233 (60.7)	304 (68.3)	
3	152 (18.3)	75 (19.5)	77 (17.3)	
INR, median (IQR)	1.17 (1.07–1.30)	1.18 (1.07–1.30)	1.16 (1.08–1.29)	0.60
Platelets count, median (IQR)	99 (70–143)	93 (66–136)	102 (74–155)	0.01
Creatinine (mg/dL), median (IQR)	0.90 (0.70–1.00)	0.90 (0.70–1.00)	0.90 (0.70–1.00)	0.44
MELD, median (IQR)	9 (8–12)	9 (8–12)	9 (8–11)	0.32
Child-Pugh, *n* (%)				
A	602 (67.6)	280 (67.0)	322 (68.2)	0.83
B	273 (30.7)	130 (31.1)	143 (30.3)	
C	15 (1.7)	8 (1.9)	7 (1.5)	
AFP (ng/mL), median (IQR)	11.0 (4.5–61.5)	8.0 (4.0–44.3)	14.0 (5.0–87.0)	0.0001
AFP (ng/mL), *n* (%)				
≤100	715 (80.3)	351 (84.0)	364 (77.1)	0.003
101–1000	121 (13.6)	53 (12.7)	68 (14.4)	
>1000	54 (6.1)	14 (3.3)	40 (8.5)	
ITA.LI.CA tumour stage				

(Continues)

TABLE 1 | (Continued)

Variable	Overall ($n=890$)	TBS-low group ($n=418$)	TBS-high group ($n=472$)	p
0	68 (7.6)	—	—	—
A	484 (54.4)			
B1	170 (19.1)			
B2	125 (14.0)			
B3	43 (4.8)			
Radiologic response (mRECIST)				
CR	336 (37.8)	187 (44.7)	149 (31.6)	<0.001
PR	302 (33.9)	141 (33.7)	161 (34.1)	
SD	119 (13.4)	45 (10.8)	74 (15.7)	
PD	133 (14.9)	45 (10.8)	88 (18.6)	

Abbreviations: ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; BMI, body mass index; CSPH, clinically significant portal hypertension; CR, complete response; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; INR, international normalized ratio; MVI, macrovascular invasion; MELD, Model for End-stage Liver Disease; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PD, progressive disease; PR, partial response; SD, stable disease; TBS, tumor burden score.
[a]CSPH diagnosis was based on the presence of unequivocal signs of portal hypertension (splenomegaly, ascites, varices) and platelet count $<100\times10^9$/L.

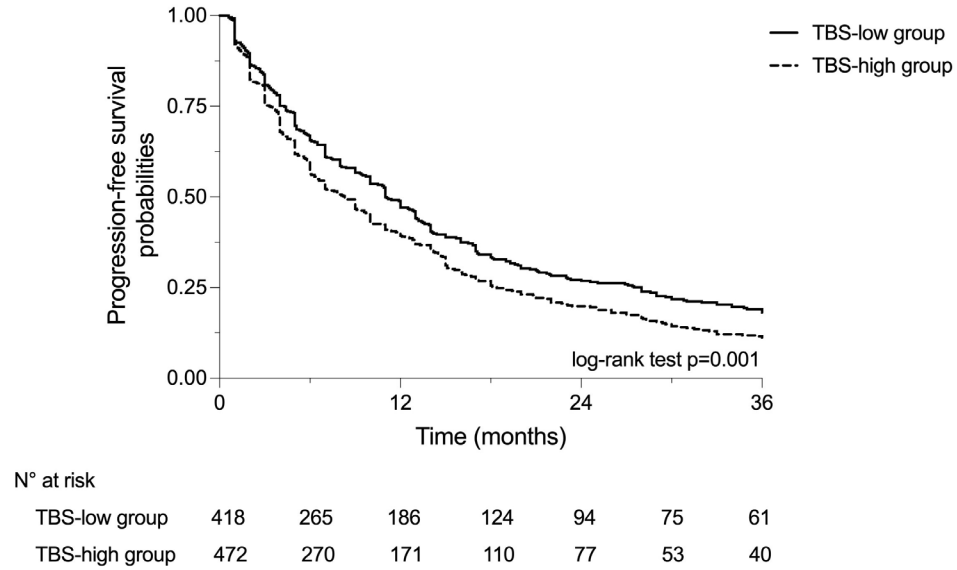

FIGURE 1 | Progression-free survival probabilities among patients of TBS-low and TBS-high groups treated with first-line TACE ($p=0.001$). TBS, tumour burden score.

The analysis of the pattern of progression according to ITA.LI.CA tumour stage, ITA.LI.CA integrated prognostic score and BCLC (Tables 3A, 3B and 3C) further demonstrates that the greater the tumour burden, the higher the percentage of patients experiencing EHP at the first episode of progression after TACE.

Overall, an *early* HCC progression (defined as ≤6 months after TACE) occurred in 319 patients (35.8%) (Table S1), and it was significantly more common in the TBS-high group than in the TBS-low group (40.0% vs. 31.1%, respectively; $p=0.006$). Moreover, among the 96 patients (10.8%) with an early EHP, this event was more frequent in patients with high TBS compared to patients with low TBS (13.8% vs. 7.4%, respectively; $p=0.002$). However, the majority of these patients experienced an *intra-hepatic* progression before EHP, and only 16 patients (1.8%) had EHP as the initial episode of progression, with this event significantly more frequent in the TBS-high group than in the TBS-low group (3.0% vs. 0.5%, respectively; $p=0.005$).

3.2 | Treatment After the First Progression

Treatment modalities at the time of first progression after TACE are shown in Table S2. In most patients, intra-arterial treatments were repeated at the time of progression, without significant differences between TBS-low and TBS-high groups (48.5% vs. 55.3%, respectively; $p=0.09$). In patients with *intra-hepatic* progression, 146 patients (50.0%) in the TBS-low group and 200

TABLE 2 | Patterns of progression after TACE as first-line therapy for patients with HCC.

Progression patterns	Overall $n=890$	TBS-low group $n=418$	TBS-high group $n=472$	p
Progression, *n* (%)	678 (76.2)	307 (73.4)	371 (78.6)	0.08
First progression type, *n* (%)				
Intrahepatic	614 (69.0)	292 (69.9)	322 (68.2)	0.61
Extrahepatic	64 (7.2)	15 (3.6)	49 (10.4)	<0.001
Extrahepatic progression, *n* (%)				
At first progression	64 (7.2)	15 (3.6)	49 (10.4)	<0.001
At any time during follow-up	232 (26.1)	78 (18.7)	154 (32.6)	<0.001
Sites of extrahepatic progression at first progression[a]				
Lymph nodes/peritoneum	30 (3.4)	8 (1.9)	22 (4.7)	0.99
Lung	32 (3.6)	9 (2.1)	22 (4.7)	
Bone	10 (1.1)	2 (0.5)	8 (1.7)	
Adrenal glands	6 (0.7)	1 (0.2)	5 (1.1)	
CNS	0 (0.0)	0 (0.0)	1 (0.2)	
Other	1 (0.1)	0 (0.0)	1 (0.2)	
Sites of extrahepatic progression at any time during follow-up[a]				
Lymph nodes/peritoneum	97 (10.9)	35 (8.4)	62 (13.1)	0.99
Lung	116 (13.0)	40 (9.6)	76 (16.1)	
Bone	50 (5.5)	19 (4.5)	31 (6.6)	
Adrenal glands	23 (2.6)	9 (2.2)	13 (2.8)	
CNS	3 (0.3)	1 (0.2)	2 (0.4)	
Other	6 (0.7)	2 (0.5)	4 (0.8)	

Note: Difference between groups were evaluated using chi-square test and Fischer's exact test for categorical variables, and Mann–Whitney test for continuous variables, as appropriate.
Abbreviations: CNS, central nervous system; TACE, transarterial chemoembolization; TBS, tumour burden score.
[a]Patients may exhibit > 1 localization of metastatic progression.

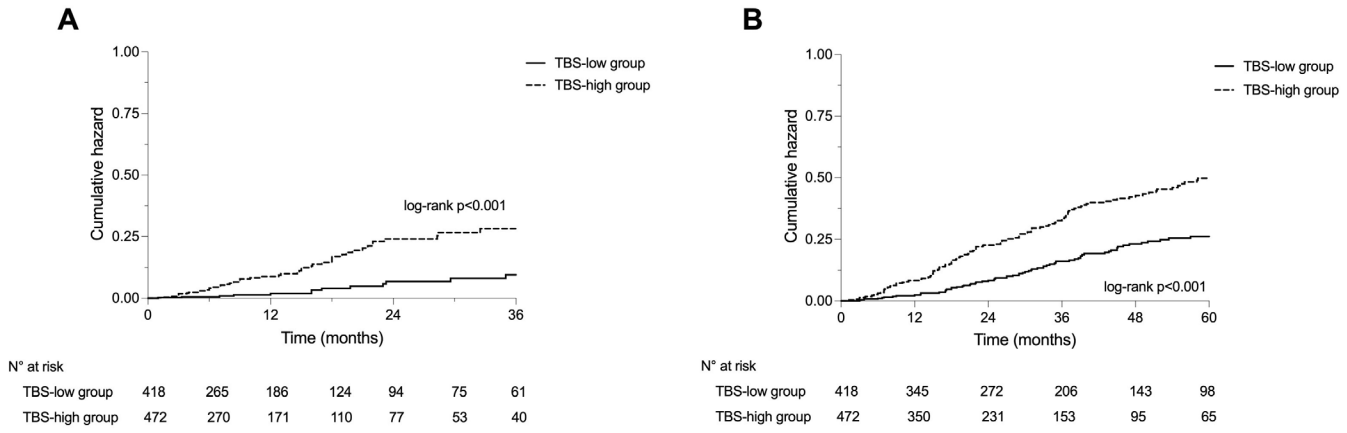

FIGURE 2 | Cumulative hazard of EHP after TACE. (A) Cumulative hazard of *first* EHP among patients of TBS-low and TBS-high groups treated with first-line IAT. (B) Cumulative hazard of overall EHP (at any time during follow-up) among patients of TBS-low and TBS-high groups undergoing first-line TACE. EHP, extrahepatic progression; IAT, intra-arterial therapies; TBS, tumour burden score.

patients (62.1%) in the TBS-high group repeated an intra-arterial treatment ($p=0.003$). Interestingly, 254/614 patients with *intra-hepatic* progression (41.4%) were managed with curative treatments: compared to patients with high TBS at baseline, a significantly higher proportion of patients in the TBS-low group received liver transplant (12.7% vs. 6.8%; $p=0.02$) while no statistically significant differences were observed between the two groups for liver resection (6.2% in the TBS-low group vs. 5.9% in

TABLE 3A | Incidence and pattern of extrahepatic progression by ITA.LI.CA tumour staging.[a]

	Patients treated with TACE ($n = 890$) mOS = 43.3 months (95% CI 39.2–47.6)									
Tumour staging	**ITA.LI.CA tumour stage 0, $n = 68$**		**ITA.LI.CA tumour stage A, $n = 484$**		**ITA.LI.CA tumour stage B1, $n = 170$**		**ITA.LI.CA tumour stage B2, $n = 125$**		**ITA.LI.CA tumour stage B3, $n = 43$**	
Diameter (cm)	≤2		≤3	2–5	≤5	>5	>5	≤5	>5	Any
N° of nodules	1		2–3	1	2–3	1	2–3	>3	>3	Any
Vascular invasion	No		No	No	No	No	No	No	No	Intrahep
Median OS	mOS = 63.5 months (95% CI 46.5–80.5)		mOS = 50.2 months (95% CI 42.9–57.5)		mOS = 34.8 months (95% CI 27.4–42.3)		mOS = 29.0 months (95% CI 21.0–37.0)		mOS = 18.0 months (95% CI 10.3–25.7)	
Pattern of progression (first progression)	Progressed: $n = 49$ (72.1%) • Intrahepatic: $n = 47$ (95.9%) • Extrahepatic: $n = 2$ (4.1%)		Progressed: $n = 355$ (73.3%) • Intrahepatic: $n = 331$ (93.2%) • Extrahepatic: $n = 24$ (6.8%)		Progressed: $n = 129$ (75.9%) • Intrahepatic: $n = 113$ (87.6%) • Extrahepatic: $n = 16$ (12.4%)		Progressed: $n = 107$ (85.6%) • Intrahepatic: $n = 93$ (86.9%) • Extrahepatic: $n = 14$ (13.1%)		Progressed: $n = 38$ (88.4%) • Intrahepatic: $n = 30$ (78.9%) • Extrahepatic: $n = 8$ (21.1%)	
Outcome	Alive, $n = 27$ (55.1%)	Dead, $n = 22$ (44.9%)	Alive, $n = 171$ (48.2%)	Dead, $n = 184$ (51.8%)	Alive, $n = 47$ (36.4%)	Dead, $n = 82$ (63.4%)	Alive, $n = 33$ (30.8%)	Dead, $n = 74$ (69.2%)	Alive, $n = 7$ (18.4%)	Dead, $n = 31$ (81.6%)

Abbreviations: CI, confidence interval; ITA.LI.CA, Italian Liver Cancer; mOS, median overall survival; TACE, transarterial chemoembolization.
[a]ITA.LI.CA tumour staging, considering only tumour morphological characteristics and not accounting for the functional score (Child-Pugh class and ECOG performance status) [16].

TABLE 3B | Incidence and pattern of extrahepatic progression by ITA.LI.CA prognostic score.[a]

Prognostic score	Patients treated with TACE, *n* = 890, mOS = 43.3 months (95% CI 39.2–47.6)				
	ITA.LI.CA Score 0–1 (low risk) *n* = 365		ITA.LI.CA Score 2–3 (intermediate risk) *n* = 427		ITA.LI.CA Score 4+ (high risk) *n* = 98
Median OS	mOS = 59.7 months (95% CI 52.9–69.0)		mOS = 35.0 months (95% CI 29.0–39.1)		mOS = 20.1 months (95% CI 15.0–30.0)
Pattern of progression (first progression)	Progressed: *n* = 275 (75.3%) • Intrahepatic: *n* = 259 (94.2%) • Extrahepatic: *n* = 16 (5.8%)		Progressed: *n* = 327 (76.6%) • Intrahepatic: *n* = 293 (89.6%) • Extrahepatic: *n* = 34 (10.4%)		Progressed: *n* = 76 (77.6%) • Intrahepatic: *n* = 62 (81.6%) • Extrahepatic: *n* = 14 (18.4%)
Outcome	Alive, *n* = 148 (53.8%)	Dead, *n* = 127 (46.2%)	Alive, *n* = 109 (33.3%)	Dead, *n* = 218 (66.7%)	Alive *n* = 28 (36.8%) Dead *n* = 48 (63.2%)

Abbreviations: CI, confidence interval; ITA.LI.CA, Italian Liver Cancer; mOS, median overall survival; TACE, transarterial chemoembolization.
[a]ITA.LI.CA tumour staging, considering tumour morphological characteristics, Child-Pugh class, ECOG performance status and AFP [24].

TABLE 3C | Incidence and pattern of extrahepatic progression by BCLC staging system.[a]

BCLC Stage	Patients treated with TACE, *n* = 890, mOS = 43.3 months (95% CI 39.2–47.6)					
	BCLC A, *n* = 337		BCLC B, *n* = 384		BCLC C, *n* = 169	
Median OS	mOS = 62.5 months (95% CI 52.0–73.0)		mOS = 36.1 months (95% CI 32.0–40.0)		mOS = 31.0 months (95% CI 21.0–38.8)	
Pattern of progression (first progression)	Progressed: *n* = 256 (76.0%) • Intrahepatic: *n* = 242 (94.5%) • Extrahepatic: *n* = 14 (5.5%)		Progressed: *n* = 300 (78.1%) • Intrahepatic: *n* = 269 (89.6%) • Extrahepatic: *n* = 31 (10.3%)		Progressed: *n* = 122 (72.2%) • Intrahepatic: *n* = 103 (84.4%) • Extrahepatic: *n* = 19 (15.6%)	
Outcome	Alive, *n* = 138 (53.9%)	Dead, *n* = 118 (46.1%)	Alive, *n* = 110 (36.7%)	Dead, *n* = 190 (63.3%)	Alive, *n* = 37 (30.3%)	Dead, *n* = 85 (69.7%)

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; mOS, median overall survival; TACE, transarterial chemoembolization.
[a]BCLC staging according to the 2022 updated classification [25].

the TBS-high group; $p = 0.99$) and ablation (29.1% in the TBS-low group vs. 22.7% in the TBS-high group; $p = 0.08$).

As far as patients with EHP were considered, in both groups the majority of patients were managed with systemic therapies (40.0% in the TBS-low group vs. 51.0% in the TBS-high group; $p = 0.56$) and best supportive care (33.3% in the TBS-low group vs. 38.8% in the TBS-high group; $p = 0.77$).

3.3 | Predictors of Extrahepatic Progression After TACE

Variables associated with EHP after TACE are shown in Table 4. Independent predictors of EHP at *first* progression episode were high TBS (HR = 3.62, 95% CI 1.94–6.77) and AFP levels (HR = 5.34, 95% CI 2.71–10.53, for AFP > 1000 ng/mL).

High TBS (HR = 2.24, 95% CI 1.65–3.05) and baseline AFP levels (HR = 3.31, 95% CI 2.22–4.94 for AFP > 1000 ng/mL) remained independent predictors of EHP at any time during follow-up. In addition, mixed aetiology (viral + other) remained independently associated with the risk of EHP during the follow-up (HR = 1.56, 95% CI 1.06–2.31, compared to patients with viral aetiology only). Up-to-seven criteria showed a potential prognostic role in the univariate analysis (HR = 0.52, 95% CI 0.30–0.91 and HR = 0.51, 95% CI 0.38–0.68), but this was not confirmed in the multivariate analysis.

When radiologic response after the first TACE was added to the model, this variable remained independently associated with the risk of EHP during follow-up, together with TBS, AFP levels, and viral + other aetiology (compared to CR: HR = 1.39, 95% CI 0.98–1.96 for PR; HR = 1.97, 95% CI 1.30–2.99 for SD; and HR = 3.66, 95% CI 2.53–5.31 for PD) (Table S3).

The combination of the independent risk factors available pre-TACE (TBS and AFP levels) accurately stratified the risk of first and overall EHP (Figure 3). Patients were divided into three groups according to the presence of 0, 1, or 2 risk factors (TBS-high and AFP > 1000 ng/mL). The 3-year EHP rate at the first progression episode was 7.8% in patients without pre-operative risk factors, 25.6% in those with only one risk factor, and 68.7% in those with both risk factors. Similar results were obtained considering the risk of EHP at any time during follow-up.

3.4 | Overall Survival

Median OS after TACE for the entire cohort was 43.4 months (95% CI 39.2–47.6). The OS of patients in the TBS-low group (59.4 months, 95% CI 47.8–71.0) was significantly longer than that of patients with higher TBS (33.0 months, 95% CI 29.3–36.7; $p < 0.001$) (Figure 4). The 1-, 3-, and 5-year survival rates were 93.1%, 70.1%, and 48.3% in the TBS-low group and 83.5%, 46.6%, and 30.6% in the TBS-high group. HCC progression was the cause of death in 235/890 patients (26.4%), and this cause of mortality was significantly more frequent in the TBS-high group than in the TBS-low group (33.5% vs. 18.4%, respectively; $p < 0.001$).

Patients with EHP as the *first* episode of progression showed a statistically significant lower OS (16.1 months, 95% CI 13.4–18.8) compared to patients with *intra-hepatic* progression at first progression (48.3 months, 95% CI 42.5–54.0; $p < 0.001$). Univariate and multivariate OS analyses are presented in Table S4. Independent predictors were TBS-high (HR = 1.87, 95% CI 1.53–2.29, $p < 0.001$), AFP > 1000 ng/mL (HR = 2.28, 95% CI 1.62–3.21, $p < 0.001$), and ECOG ≥ 1 (HR = 1.64, 95% CI 1.31–2.06, $p < 0.001$).

4 | Discussion

Despite therapeutic advancements, HCC is still characterised by poor prognosis, mainly because many patients are diagnosed in the advanced stage when curative treatments are no longer feasible [31]. For patients with unresectable HCC, the landscape of systemic therapies is rapidly evolving, and a significant expansion of treatment possibilities has occurred in recent years [6–13]. Currently, immunotherapy-based regimes (atezolizumab + bevacizumab, durvalumab + tremelimumab) have been shown to extend survival in patients with advanced disease compared to tyrosine-kinase inhibitors (i.e., sorafenib) [12, 13]. However, according to the principles of therapeutic hierarchy, if surgical options are contraindicated and whenever extrahepatic disease is excluded, intra-arterial locoregional therapies should be considered [3, 17, 32]. Despite its application declining, TACE is a treatment still widely used worldwide [33]. Before switching to systemic treatment, an attempt to control the disease with an intra-arterial locoregional approach is reasonable, considering that HCC has a predominant locoregional progression [1]. Indeed, the development of metastases is rather infrequent in unselected patients with HCC, ranging from 14% to 37% [2, 34–38]. In our large cohort of patients treated with TACE, EHP was observed in 26.1% of patients during the follow-up and, notably, EHP as a *first* episode of progression after TACE was a relatively rare event (7.2% of patients). These results lend support to the concept of HCC progression being predominantly local (intrahepatic) in patients treated with locoregional therapies.

Tumour burden (number and size of lesions) has a very relevant impact on the choice of treatment and on the patient's prognosis [39]. Since in patients managed with TACE the probability to respond to treatment and the consequent prognosis are linked to the tumour burden [18], we postulated that this variable may be helpful in predicting EHP after TACE. TBS is a simple concept proposed by Sasaki et al. [26, 27], which is defined as the distance from the origin on a Cartesian plane that incorporates two variables: maximum tumour size and number of liver lesions [26, 27]. The TBS was originally developed and validated to predict the risk of liver metastases in patients with colorectal cancer undergoing liver resection [27], but it can be applied to other liver malignancies such as HCC. Indeed, TBS demonstrated a good prognostic performance in an unselected population of patients with HCC managed with different curative and palliative treatments [28]. In this study, we demonstrated that high TBS is associated with a higher probability of developing EHP after TACE, both at first progression and at any time during follow-up, thereby overcoming the up-to-seven criteria as a prognostic factor. Moreover, high TBS was associated with a higher risk of early (≤ 6 months) intra- and extrahepatic progression.

TABLE 4 | Multivariable regression models to predict extrahepatic progression at *first progression* and at any time during the follow-up in HCC patients treated with first-line TACE.

	EHP at first progression				EHP at any time during follow-up			
	Univariable		Multivariable		Univariable		Multivariable	
Variable	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Sex								
Male	1	—	—	—	1	—	—	—
Female	0.95 (0.52–1.71)	0.85			0.91 (0.66–1.25)	0.56		
Age (per 10-year increase)	0.97 (0.78–1.21)	0.8	—	—	1.09 (0.97–1.23)	0.17	—	—
Surveillance								
No	1	—	—	—	1	—	—	—
Yes	0.79 (0.46–1.37)	0.4			0.81 (0.61–1.07)	0.13		
Aetiology								
Viral	1	—	—	—	1	—	1	—
Not viral	1.22 (0.72–2.08)	0.47			1.18 (0.89–1.57)	0.25	1.09 (0.83–1.43)	0.55
Viral+other	1.78 (0.79–4.04)	0.17			1.67 (1.11–2.50)	0.01	1.56 (1.06–2.31)	0.06
Platelet	1.11 (0.93–1.33)	0.24	—	—	1.03 (0.93–1.14)	0.56	—	—
CSPH								
No	1	—	—	—	1	—	—	—
Yes	0.82 (0.49–1.39)	0.46			0.91 (0.69–1.19)	0.48		
Ascites								
No	1	—	—	—	1	—	—	—
Yes	1.35 (0.67–2.73)	0.4			1.02 (0.68–1.54)	0.92		
Hepatic encephalopathy								
No	1	—	—	—	1	—	—	—
Yes	0.65 (0.16–2.67)	0.55			0.83 (0.44–1.57)	0.57		
TBS								
Low	1	—	1	—	1	—	1	—
High	3.67 (2.05–6.55)	< 0.001	3.62 (1.94–6.77)	< 0.001	2.47 (1.88–3.25)	< 0.001	2.24 (1.65–3.05)	< 0.001
Up to Seven								
Out	1	0.02	1	0.77	1	—	1	0.63
In	0.52 (0.30–0.91)		0.91 (0.48–1.73)		0.51 (0.38–0.68)	< 0.001	0.92 (0.66–1.28)	

(Continues)

TABLE 4 | (Continued)

	EHP at first progression				EHP at any time during follow-up			
	Univariable		Multivariable		Univariable		Multivariable	
Variable	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Intrahepatic MVI								
No	1	—	1	—	1	—	1	—
Yes	3.32 (0.80–13.68)	0.09	1.31 (0.30–5.72)	0.72	2.76 (1.23–6.23)	0.01	1.51 (0.65–3.46)	0.33
AFP (ng/mL)								
≤100	1	—	1	—	1	—	1	—
101–1000	2.04 (1.02–4.09)	0.04	1.83 (0.85–3.95)	0.12	2.31 (1.65–3.23)	<0.001	2.17 (1.53–3.07)	<0.001
>1000	6.59 (3.58–12.14)	<0.001	5.34 (2.71–10.53)	<0.001	3.86 (2.61–5.72)	<0.001	3.31 (2.22–4.94)	<0.001
MELD	1.05 (0.99–1.11)	0.09	1.04 (0.98–1.09)	0.2	1.02 (0.99–1.06)	0.22	—	—
Child-Pugh								
A	1	—	—	—	1	—	—	—
B-C	1.05 (0.58–1.87)	0.88			1.04 (0.77–1.41)	0.78		
ALBI grade								
1	1	—	—	—	1	—	—	—
2	1.06 (0.53–2.12)	0.87			1.11 (0.77–1.60)	0.58		
3	0.84 (0.33–2.13)	0.71			1.04 (0.65–1.69)	0.86		

Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin grade; CR, complete response; CRPH, clinically relevant portal hypertension; MELD, model for end-stage liver disease; mRECIST, modified Radiologic Evaluation Criteria in Solid Tumour; MVI, macrovascular invasion; PD, progressive disease; PR, partial response; SD, stable disease; TBS, tumour burden score.

The analysis by ITA.LI.CA. tumour stage confirmed the association between higher tumour burden and EHP; in fact, over 10% of patients in stage B1, B2 and B3 had a probability of EHP > 10% at the time of the first progression, rising to 20% when considering only patients in stage B3. These results were confirmed by stratifying patients according to the ITA.LI.CA prognostic score and the BCLC staging system.

The higher risk of EHP for patients with high tumour burden undergoing TACE may be explained by the activation of neoangiogenesis following treatment [40]. Indeed, incomplete TACE increases tumour hypoxia, leading to the up-regulation of hypoxia-inducible factor-1-α (HIF-1α) that, in turn, up-regulates the expression of Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor (FGF), or Platelet-Derived Growth Factor (PDGF) and increases tumour angiogenesis [40–44]. Therefore, one may speculate that performing TACE in patients with high tumour burden might induce a spike in intra-tumoural concentration of VEGF, FGF, and PDGF, which boost the progression of the tumour and the development of metastases.

EHP is an extremely unfavourable prognostic factor for HCC patients, indicating a peculiar aggressiveness of the tumour and precluding both curative and locoregional palliative treatments. Therefore, the knowledge of risk factors of EHP may help clinicians in the initial choice of treatment. In this study, we demonstrated that tumour burden is a key variable that has to be considered in the evaluation of the risk of progression after TACE. Moreover, when associated with AFP levels, this variable is able to accurately discriminate patients according to their risk of EHP, both at the first time of progression and at any time during follow-up.

As patients with higher tumour burden may be more easily refractory to TACE, in these cases an early shift to systemic therapies has been advocated [45]. Moreover, considering that a high tumour burden is associated with an increased probability of EHP, in these patients the early use of systemic agents could be reasonable, also considering the efficacy in terms of response rate and survival of the immunotherapy-based regimens [11–13]. In patients with high tumour burden and other

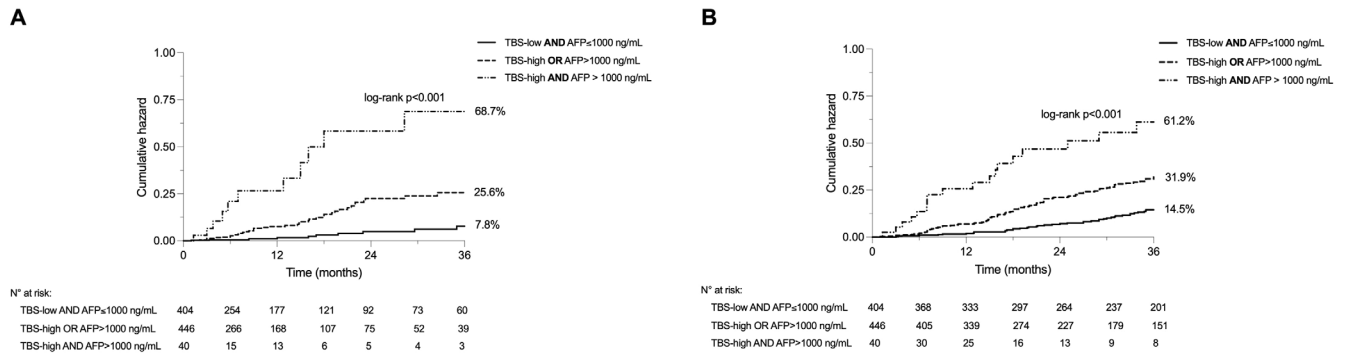

FIGURE 3 | Risk of extrahepatic progression according to TBS and alpha-fetoprotein levels at the time of TACE. (A) Rates of EHP at the first progression episode. (B) Rates of EHP at any time during follow-up. EHP, extrahepatic progression' TBS, tumour burden score; TACE, transarterial chemoembolization.

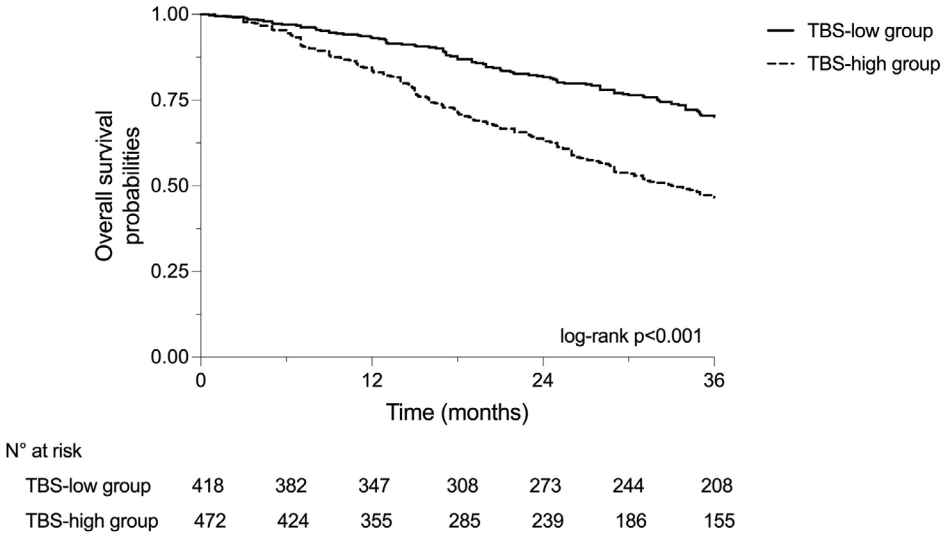

FIGURE 4 | Overall survival probabilities between TBS-low and TBS-high groups of patients treated with first-line TACE. TBS, tumour burden score; TACE, transarterial chemoembolization.

risk factors of EHP (e.g., high pre-treatment AFP levels), clinicians may ponder the opportunity to prefer systemic therapy instead of intra-arterial treatments or to combine these treatments [46, 47]. These considerations regarding patients at high risk of progression following TACE and the opportunity of starting systemic therapy early probably will have to be questioned following the results of randomised controlled trials that evaluated the combination of TACE with immunotherapy and bevacizumab (EMERALD-1) demonstrating a benefit in terms of progression-free survival [48].

Our study has some limitations. First, its retrospective and observational nature may have introduced unintended biases in the analyses. Even though we were unable to use a homogeneous imaging follow-up for patients after treatment (due to the multicenter, real-life, observational nature of the database), this study offers insight into the pattern of progression of HCC in a real-life setting. Second, the selection of patient population probably does play a role in the findings because the pattern of progression that we described may be specific to patients managed with TACE. Third, histologic information such as tumour grade that could have an impact on the risk of both intra- and extra-hepatic progression was not used in this study mainly because the majority of patients had an HCC diagnosed using non-invasive criteria, as ordinarily it occurs in clinical practice.

In conclusion, our study demonstrates that 74% of HCC patients died without developing EHP following TACE, since the pattern of progression in HCC is most commonly intra-hepatic. In this regard, TBS is an easy-to-calculate score that is associated with the risk of developing EHP, and it can help clinicians identify patients at higher risk of metastatic progression, especially when evaluated in combination with AFP levels. This may help tailor treatment, assessing whether the patient may benefit from up-front systemic treatment, an earlier shift to this therapeutic option, or a combined treatment.

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Marco Ferronato, Nicola Reggidori, Maria Ricci, Francesco Santopaolo, Lucia Cerrito, Nicoletta de Matthaeis, Antonio Gasbarrini, Gabriele Missale, Elisabetta Biasini, Andrea Olivani, Maria Guarino, Mario Capasso, Valentina Cossiga, Ester Marina Cela, Antonio Facciorusso, Camilla Graziosi, Valentina Lauria, Giorgio Pelecca, Fabrizio Chegai, Armando Raso, Pierluigi Aloisio, Serena Dell'Isola, Irene Cacciola, Maria Stella Franzè, Roberto Filomia, Concetta Pitrone, Giovanni Raimondo, Marco Arru, Elton Dajti, Alberto Porro, Filippo Oliveri, Gabriele Ricco, Veronica Romagnoli, Alessandro Inno, Fabiana Marchetti, Leonardo Natola, Leonardo De Marco, Aldo Filice, Andrea Dalbeni, Pietro Coccoli, Alba Rocco, Alberta Cappelli, Cristina Mosconi, Matteo Renzulli, Luca Marzi, Pietro Guerra, Silvia Cagnin.

Funding

This study was funded by the University of Padova.

Conflicts of Interest

Edoardo G. Giannini; AstraZeneca, Eisai, Roche: speaking and teaching. Ipsen: consulting. Franco Trevisani: AbbVie, Astra Zeneca, Gilead, MSD, Roche: research grants; EISAI, Roche: advisory board, consulting.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** apt70534-sup-0001-Supinfo.docx.