

## Recommendations for the use of chemoembolization in patients with hepatocellular carcinoma: Usefulness of scoring system?

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Cancer is a new prognostic staging system; it might become the reference system in Asia. Transarterial chemoembolization (TACE) is the most widely used treatment for HCC worldwide; but it showed a benefit only for intermediate stage HCC (BCLC B), and there is still no consensus concerning treatment methods and treatment strategies. In view of the highly diverse nature of HCC and practices, a scoring system designed to assist with decision making before the first TACE is performed or prior to repeating the procedure would be highly useful.

**Key words:** Hepatocellular carcinoma; Transarterial chemoembolization; Barcelona Clinic Liver Cancer; Prognostic scoring systems

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**Core tip:** Despite its widespread use in hepatocellular carcinoma, the indications for Transarterial chemoembolization are still debated. There are no rules about the treatment modalities or strategy to follow. To overcome these difficulties, a simple scoring system, including prognostic variables, designed as a decision support, would be useful. Deciding when we have to move from a loco-regional treatment to a systemic option is matter of significant interest, particularly since sorafenib now provides us with a solution.

### Abstract

Several hepatocellular carcinoma (HCC) staging systems have been established, and a variety of country-specific treatment strategies are also proposed. The barcelona - clinic liver cancer (BCLC) system is the most widely used in Europe. The Hong Kong liver

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer deaths<sup>[1]</sup>. It generally develops secondarily to chronic liver disease, mainly after a hepatitis B or C viral infection<sup>[2]</sup>. It is therefore particularly prevalent in sub-Saharan Africa and South East Asia. It is increasingly common in Europe and the United States of America<sup>[3]</sup>. Nonalcoholic steatohepatitis is a frequently reported risk factor<sup>[4,5]</sup>. HCC is a complex disease because, in addition to the characteristics of the tumour (its dimensions, the number of lesions present, vascular invasion and extrahepatic spread) and the patient's performance status, therapeutic decision-making also takes into account other parameters such as liver function, since both underlying cirrhosis and portal hypertension (PHT) complicate the treatment of HCC and limit the available curative options which are also impacted by delays in diagnosing the cancer<sup>[6]</sup>. Several HCC staging systems integrating these prognostic variables have been established as a guide to treatment practices, and a variety of country-specific treatment strategies are also proposed<sup>[7]</sup>. However, no "universally" recognised classification exists, leading to wide variations in treatment practices, particularly where patients who are not eligible for curative treatment are concerned. Several Asian countries have their own staging system<sup>[8]</sup>. In Europe and the United States, the barcelona-clinic liver cancer (BCLC) system is the most widely used and is approved by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases<sup>[9]</sup>. This staging system has demonstrated superiority over other systems and is based on randomised clinical trials. The BCLC divides HCC into four groups as a function of the number of nodules present, their size, the Child-Pugh score, the presence of PHT, performance status (PS), the presence of symptoms, vascular invasion and extrahepatic spread. It has the distinct advantage of proposing an evidence-based treatment strategy for different stages of the disease (Figure 1). Based on local clinical experience and expert opinions, the Asian guidelines recommend different treatment methods including external radiotherapy and intra-arterial hepatic chemotherapy. The Hong Kong liver Cancer (HKLC) is a new prognostic staging system established using the prognostic factors of 3856 patients most of whom presented with HBV<sup>[10]</sup>. The HKLC might become the reference system in Asia. It includes variables comparable to those in the BCLC system but also takes into account the diffuse nature of HCC. It divides HCC into 9 sub-groups and also puts forward a treatment strategy (Figure 2). We recently validated this scoring system in a European cohort consisting of 665 patients most of whom had alcoholic cirrhosis- or hepatitis C virus-related HCC; however, unlike the results published by Yau *et al.*<sup>[10]</sup>, we found that the HKLC and BCLC classifications were similar in their discriminatory ability for the prediction

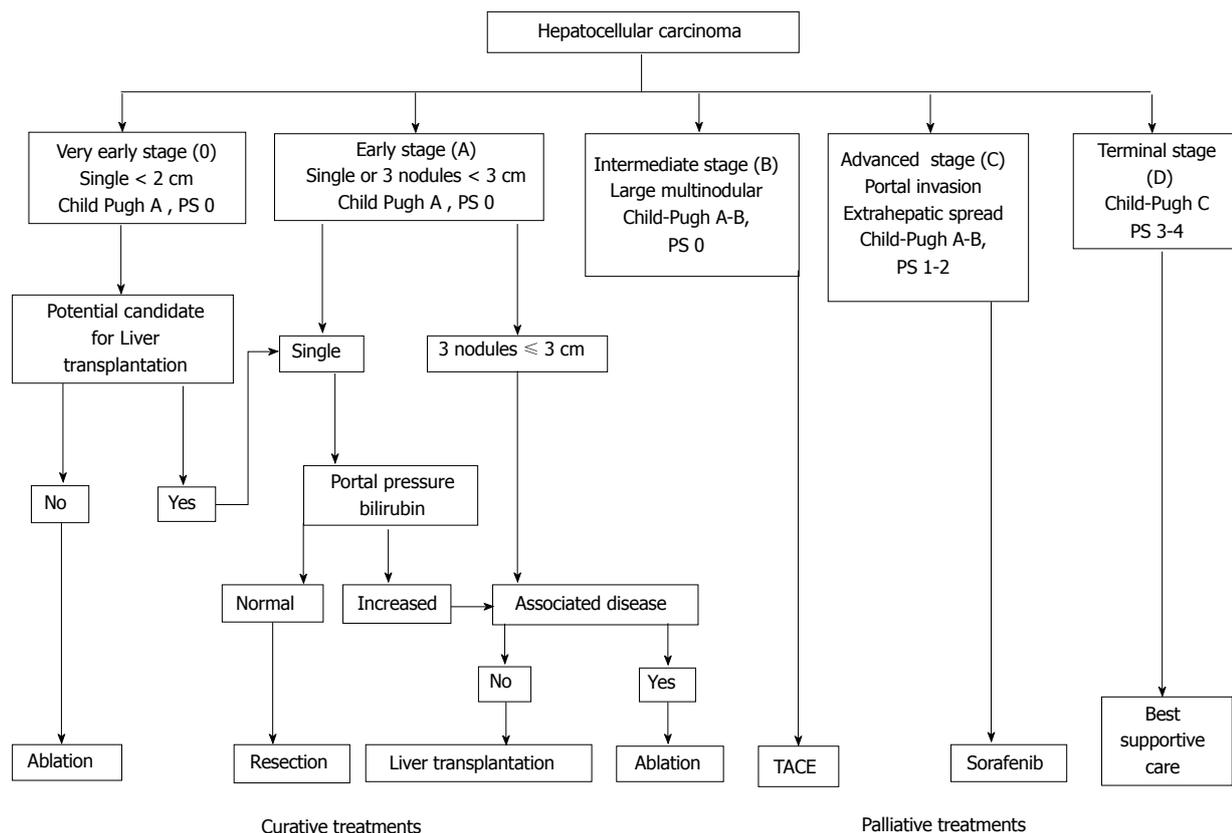
of survival<sup>[11]</sup>.

A preliminary intermediate analysis of the international Bridge study showed that transarterial chemoembolization (TACE) is the most widely used treatment for HCC worldwide, ahead of both surgical removal and systemic treatments<sup>[12]</sup>. TACE is designed to induce necrosis of the hyperarterialised tumour with the aim of achieving local tumour control whilst preserving liver function. Its use has been recommended since the publication of two positive randomised studies in 2002<sup>[13,14]</sup>. The technique has since been improved with the use of calibrated drug-eluting beads, making it possible to standardise the procedure and reduce the systemic passage of the cytotoxic substances used<sup>[15]</sup>, with comparable outcomes to those of conventional TACE in terms of tumour control (PRECISION V trial)<sup>[16]</sup>.

## RECOMMENDATIONS FOR THE USE OF CHEMOEMBOLIZATION IN PATIENTS WITH HCC

Despite its widespread use, the indications for TACE are still debated. The two reference randomised trials included 112 and 80 patients, the survival benefit was limited (4 mo)<sup>[17]</sup> and the results of the meta-analyses are contradictory. Unlike the earlier meta-analyses<sup>[17,18]</sup>, Oliveri *et al.*<sup>[19]</sup> did not find any benefit for TACE, but the analysis was criticised because it included inappropriate studies<sup>[20,21]</sup>. In Europe, TACE is recommended for intermediate stage HCC (BCLC B), but this group includes a broad spectrum of tumours (encapsulated or infiltrating, unifocal or multifocal) and patients with different degrees of liver function and consequently the survival benefit is not the same, for instance, for patients classified Child-Pugh A and B<sup>[22,23]</sup>. Careful patient selection is therefore necessary, particularly since sorafenib now provides us with a solution for cases in which chemoembolization is contraindicated or ineffective<sup>[24]</sup>. Based on evidence and experts' opinion, the general consensus is that TACE is appropriate for large nonresectable (> 50 mm) or multinodular, asymptomatic tumours without vascular invasion or extrahepatic spread and when the Child-Pugh class is A or B7<sup>[25]</sup>. In parallel, Raoul *et al.*<sup>[26]</sup> listed the cases of intermediate stage HCC in which TACE was contraindicated. The factors identified included age, comorbidities, liver function and tumour characteristics, especially diffuse HCC and tumours measuring in excess of 100 mm in diameter (Figure 3).

However, no consensus exists for treatment methods, the drugs to be used, the type of beads, the number of courses to be administered, the interval to be allowed between sessions and the objectives (complete response, disease stabilization). In the randomised study by Lo *et al.*<sup>[14]</sup>, cisplatin-based TACE was performed every 2 to 3 mo until disease progression, depending on individual tolerance; the patients treated received a mean of 4.5 sessions. In

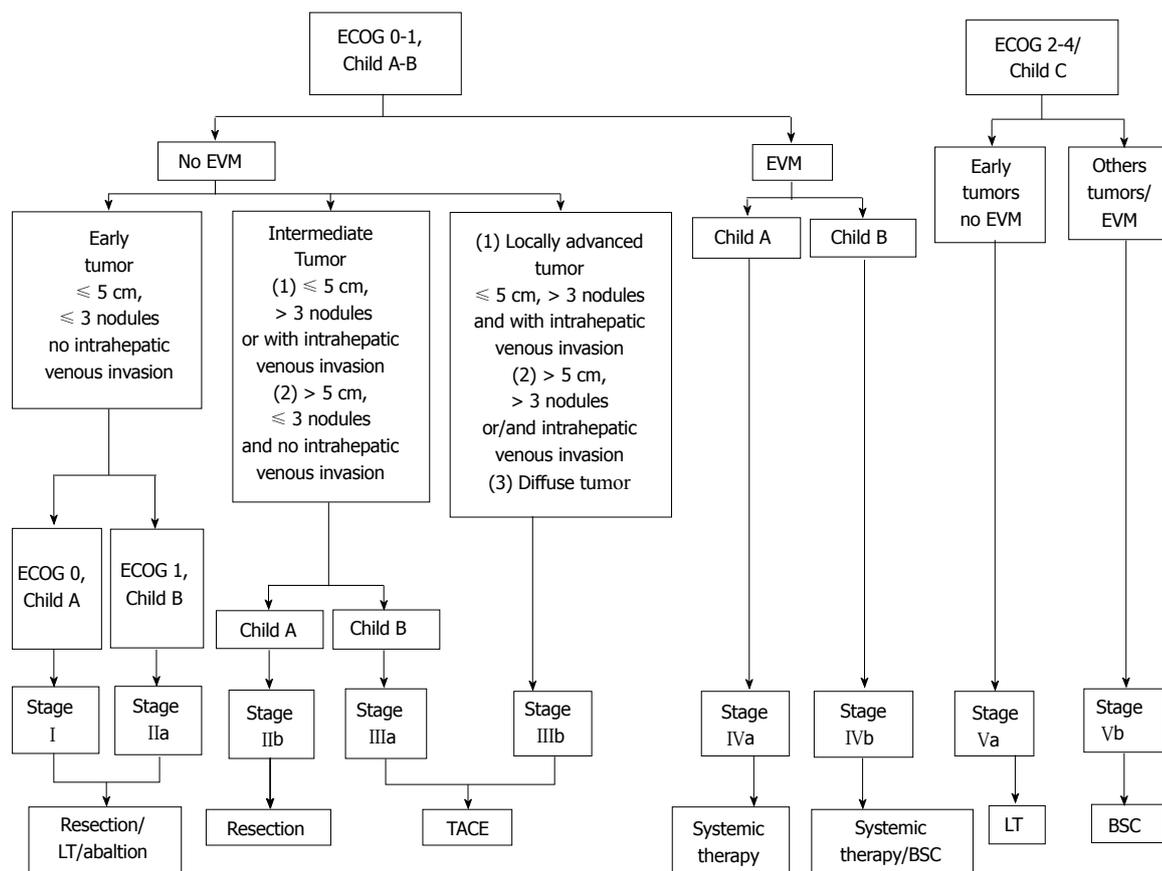


**Figure 1** Barcelona Clinic Liver Cancer staging and treatment strategy<sup>[8]</sup>. BCLC: Barcelona Clinic Liver Cancer; PS: Performance status; TACE: Transarterial chemoembolization.

the randomised study by Llovet *et al*<sup>[13]</sup>, doxorubicin-based TACE or arterial embolization alone were performed 2 and then 6 mo after the initial session, and then potentially every 6 mo thereafter until progression (vascular invasion or extrahepatic spread), depending on individual tolerance. These patients received a mean of 3.08 embolization sessions and 2.8 of TACE. There is currently no standardised treatment timescale: the sessions can be given at regular intervals or on an “as needed” basis, as a function of the radiologic response. TACE is a potentially toxic treatment and its efficacy can be outweighed by its toxicity particularly since many of the patients treated have underlying cirrhosis<sup>[27,28]</sup>. Two recently published studies (on demand or selective sequential TACE) report comparable results in terms of survival<sup>[22,23]</sup>. Antoch *et al*<sup>[22]</sup> treated 124 patients with HCC graded BCLC A (32%), B (39%) and C (29%) with 4 (± 3) selective TACE sessions, repeated every 4 wk. There was a 4.7% major complications rate, including 1 death. The 1 year survival rate was 79%, dropping to 51% at the 2 year time point. In a study by Terzi *et al*<sup>[23]</sup>, 151 patients with BCLC A (51.5%), B (40%) and C (6%) HCC were treated with on demand TACE. The complete response rate after the first TACE was 48% for the 151 patients treated; it was 57% for the 60 patients undergoing a 2<sup>nd</sup> session and 55% for the 22 patients treated a third time. The median time to progression was 8.5 mo between the first two TACE,

and 8 mo between the second and third sessions. The 1 year survival rate was 70%, dropping to 52% at the 2 year time point. There are no firm data demonstrating the superiority of one strategy over another, but performing TACE guided by the radiologic response and individual tolerance appears to be the most logical option.

Raoul *et al*<sup>[26]</sup> proposed a treatment strategy based on the radiologic response observed after two TACE (Figure 4). A partial response or a disease stabilization is considered sufficient justification to interrupt treatment, since TACE is regarded as a palliative treatment option for locally advanced disease<sup>[26]</sup>. Other authors believe that a response must be obtained before treatment can be repeated and equate stability with treatment failure<sup>[29,30]</sup>. Evaluation of response is therefore a major challenge. It is not possible to appreciate tumor response after TACE using the conventional dimension criteria Response Evaluation Criteria In Solid Tumor (RECIST); a beneficial effect is not always associated with tumor reduction and requires for its assessment the advantages of functional imaging<sup>[31]</sup>. Contrast uptake criteria - both EASL and mRECIST - provide a more accurate evaluation of response after TACE. While the EASL and mRECIST criteria differ in terms of target lesions (respectively all vs ≤ 2) and calculation methods (bidimensional vs unidimensional), they are comparable and correlated with survival. In the



**Figure 2 Hong Kong Liver Cancer prognostic classification scheme<sup>[10]</sup>.** HKLC: Hong Kong Liver Cancer; LT: Liver transplantation; OS: Overall survival; PS: Performance status; TACE: Transarterial chemoembolization; EVM: Extrahepatic vascular invasion/metastasis.

**Absolute contraindications**

Decompensated cirrhosis (Child-Pugh B ≥ 8) including:

- Jaundice
- Clinical encephalopathy
- Refractory ascites
- Hepatorenal syndrome

Extensive tumor with massive replacement of both entire lobes

Severely reduced portal vein flow (e.g., non tumor portal vein occlusion or hepatopetal blood flow)

Technical contraindications to hepatic intra-arterial treatment, e.g., untreatable arteriovenous fistula

Renal insufficiency (creatinin ≥ 2 mg/dL or creatinine clearance < 30 mL/min)

**Relative contraindications**

Tumor size ≥ 10 cm

Comorbidities involving compromised organ function:

- Active cardiovascular disease
- Active lung disease

Untreated varices at high risk of bleeding

Bile-duct occlusion or incompetent papilla due to stent or surgery

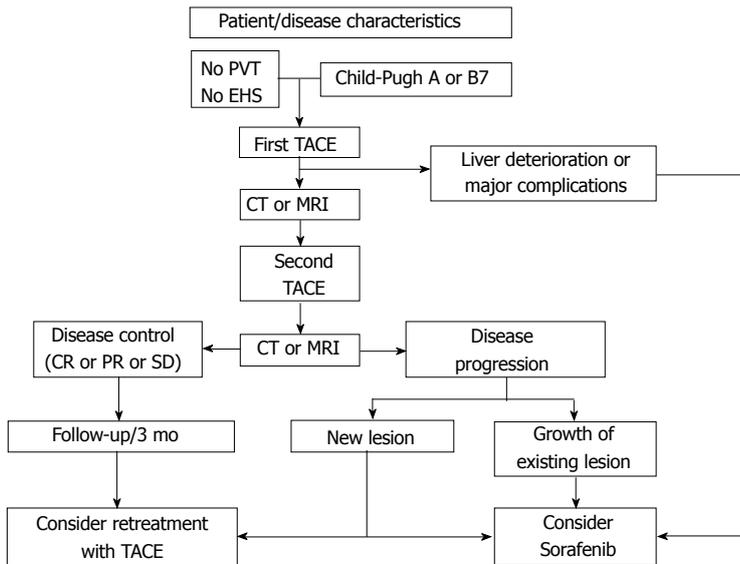
**Figure 3 Contraindications for conventional trans-arterial chemoembolisation<sup>[26]</sup>.**

studies by Gillmore *et al*<sup>[32]</sup> and Kim *et al*<sup>[33]</sup>, radiologic response according to the EASL and mRECIST criteria was found to be independent prognostic factor for survival. However, these criteria are not applicable for all types of HCC<sup>[34]</sup>.

There is no consensus concerning the rules for discontinuing treatment. It appears logical that TACE should not be pursued in cases of “obvious” tumour progression, which Bruix *et al*<sup>[29]</sup> referred to as “Untreatable progression”, *i.e.*, massive liver involvement, extrahepatic spread and vascular invasion. Other contraindications include a significant

deterioration in liver function after the first session and failure to achieve an objective response after two sessions (Figure 5). In such cases, a different treatment option will be offered if permitted by the patient’s performance status and liver function.

In routine practice, TACE has applications beyond intermediate stage HCC. It is a therapeutic option for certain patients with BCLC A HCC who are not eligible for curative treatment. In a study by Burrel *et al*<sup>[35]</sup>, median survival in selected BCLC A patients treated with microbeads was 54.2 mo vs 47.7 mo in patients with intermediate stage HCC. Some authors also



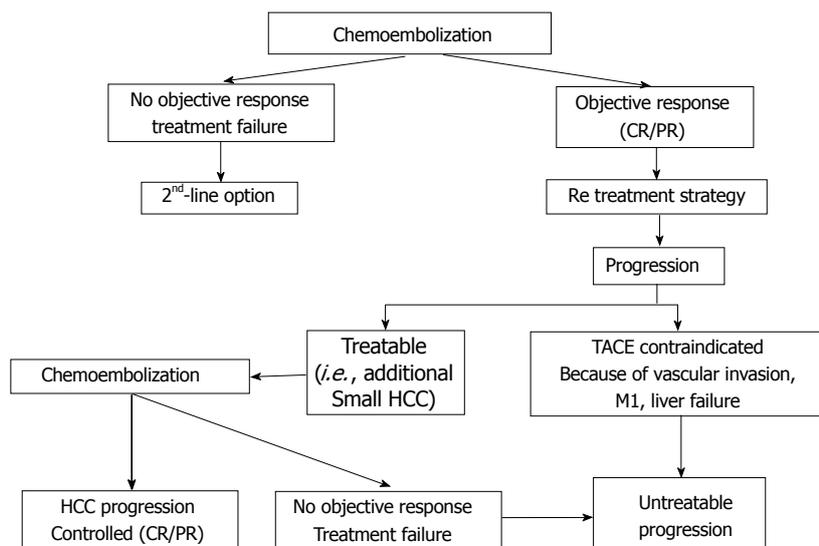
**Figure 4 Proposed treatment algorithm for the repetition of conventional transarterial chemoembolization in patients with intermediate-stage hepatocellular carcinoma.** Response defined according to modified RECIST criteria. CR: Complete response; CT: Computed tomography; cTACE: Conventional TACE; EHS: Extrahepatic spread; HCC: Hepatocellular carcinoma; MRI: Magnetic resonance imaging; PD: Progressive disease; PR: Partial response; PVT: Portal vein thrombosis; RECIST: Response Evaluation Criteria In Solid Tumours; SD: Stable disease; TACE: Transarterial chemoembolization.

consider that TACE can be used to treat advanced HCC, since progression to metastatic disease is rare<sup>[36]</sup>. In the randomised study by Lo *et al*<sup>[14]</sup>, about 20% of the patients treated with TACE presented with segmental portal vein thrombosis but no significant difference in survival was detected amongst these patients whether they were treated with TACE or not. In both the Asian Pacific Association for the Study of the Liver (APASL) guidelines and HKLC scoring system, TACE is a possible treatment option for patients with HCC and limited portal vein thrombosis<sup>[8,10]</sup> (Figure 6). A number of Asian studies and a meta-analysis of eight trials (including five retrospective studies) have shown a survival benefit vs untreated control arms, on condition that the portal vein thrombosis is limited<sup>[37-40]</sup>. However, it is not possible to validate the use of TACE in this indication on the basis of these results. In addition to the risks related to embolization, the recurrence rate is relatively high in patients with vascular invasion; segmental portal vein thrombosis was the independent prognostic factor with the greatest impact on survival in a Japanese cohort of 8510 patients treated with TACE<sup>[41]</sup>. A combination of sorafenib and TACE has therefore become a viable treatment option for patients with locally advanced HCC. A retrospective study conducted in Austria found comparable survival results with sorafenib and TACE in patients with locally advanced HCC and vascular invasion (BCLC C)<sup>[42]</sup>. However, there are no studies providing a definitive response for such patients at the present time. The sorafenib-TACE combination has been explored in two recently published meta-analyses, each including six studies. However, there are large variations in the designs of the studies included (randomised and retrospective cohorts), the populations enrolled (intermediate and advanced HCC) and the treatment methods<sup>[43,44]</sup>. Zhao *et al*<sup>[45]</sup> suggest using the sorafenib-TACE combination in certain BCLC C patients as a function of a score calculated from four independent prognostic variables: vascular invasion,

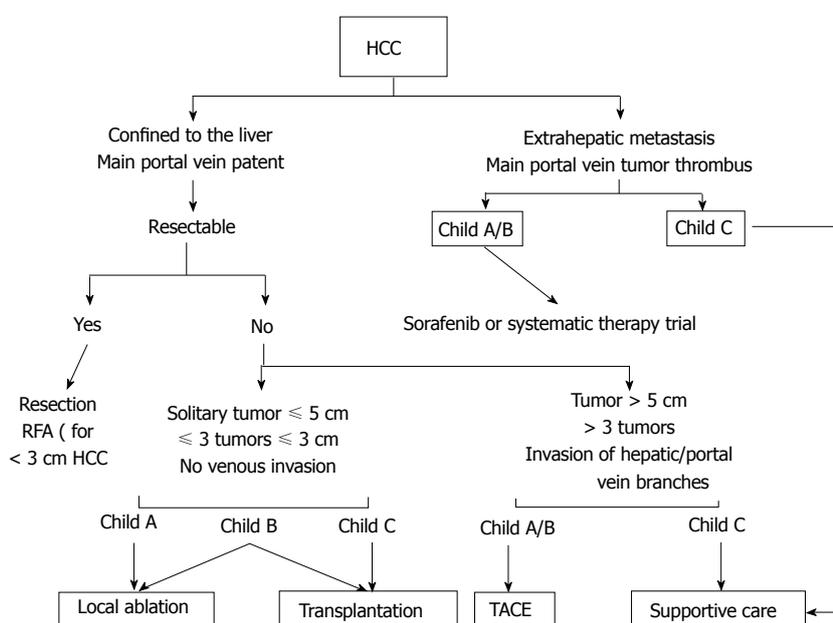
Child-Pugh class A or B, number of nodules 1-2 or  $\geq 3$ , and ECOG (Eastern Cooperative Oncology Group) PS 0 or  $\geq 1$ . These results have yet to be confirmed and validated in a prospective study before they can be more widely applied.

### USEFULNESS OF SCORING SYSTEM?

We do not have any guidelines concerning the number of TACE to be performed before switching to another treatment strategy. It is evident that, in view of the highly diverse nature of HCC and practices and the numerous therapeutic options now available, a scoring system designed to assist with decision making before the first TACE is performed or prior to repeating the procedure would be highly useful. Several prognostic indices designed to help practitioners select appropriate candidates for an initial or repeat conventional TACE have been put forward in the past but none has been formally enshrined in the guidelines since they are difficult to implement or insufficiently discriminatory and are limited to conventional TACE<sup>[46,47]</sup>. The potentially useful staging systems published recently include: the hepatoma arterial-embolization prognostic (HAP) score published by Kadalayil *et al*<sup>[48]</sup> in 2013 which was also designed as an aid to selecting appropriate candidates for TACE. In this system, patients are awarded 1 point for each of the following four variables if present: albumin < 36 g/L, bilirubin > 17 mcml/L, AFP > 400 ng/mL and tumour > 7 cm. The patients were then divided into four median survival groups on the basis of their HAP scores: HAP A (0 points) 27.6 mo, HAP B (1 point) 18.35 mo, HAP C (2 points) 9.0 mo and HAP D (> 2 points) 3.6 mo. This scoring system was developed using the prognostic variables generated by a cohort of 114 BCLC A (35%), B (31%), C (31%) and D (4%) patients included over a period of more than 10 years. It was validated in 167 patients considered to be comparable, but more of whom presented with segmental portal vein



**Figure 5** Diagram to define untreatable tumor progression<sup>[29]</sup>. CR: Complete response; PR: Partial response; HCC: Hepatocellular carcinoma.



**Figure 6** APASL guideline on the treatment algorithm for hepatocellular carcinoma<sup>[8]</sup>. RFA: Radiofrequency ablation; HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization.

thrombosis (28% vs 6%, respectively). These authors suggest that a strategy other than TACE is more appropriate for C and D score patients.

The assessment for retreatment with TACE (ART) score published by Sieghart *et al*<sup>[30]</sup> in 2013 is calculated before performing a second TACE. It is based on three parameters (increase of ASAT by > 25%, increase in Child-Pugh score from baseline and tumor response). Increase (+ 25%) in ASAT was the parameter associated with the most powerful coefficient (4 points), the lowest was allocated to the radiological response (1 point)<sup>[30]</sup>. Patients are divided into two groups on the basis of the resulting scores (0-1.5 drop in score or drop of 2.5 points and over) with a different prognosis: 23.7 vs 6.6 mo. This system was developed using a regression model in a cohort of 107 patients enrolled over 10 years, most of whom presented with alcoholic cirrhosis and were BCLC B HCC. The authors suggest continuing TACE

until the score changes from 0 to 1.5. This score is also applicable to subsequent courses<sup>[49]</sup>.

We performed a retrospective analysis of the HAP score in a cohort of 153 Child- Pugh A (91%) or B (9%) cirrhotic patients with BCLC A (17%) (not suitable for curative treatment), BCLC B (69%) and BCLC C (14%) (owing to segmental portal vein thrombosis) HCC<sup>[50]</sup>. These patients underwent a mean of 2.75 conventional TACE sessions. The response rate (EASL criteria) was 61%. Mean follow-up was 19 mo<sup>[17-23]</sup>. The HAP score divided the patients into three groups each with a different survival time (Table 1); median survival was the same for the HAP A and HAP B groups (31 mo). The patients in the HAP C and HAP D groups were considered to be poorer candidates for TACE and had a median survival of 22 mo and 18 mo, respectively, which is higher than the figures reported for the Kadalayil *et al*<sup>[48]</sup> cohort (9.0 mo and 3.6 mo, respectively). It should be noted that the risk of death

**Table 1 Overall survival in a cohort of 153 patients treated by TACE using the HAP score with a cut-off value of: 0 (HAP A) vs 1 (HAP B) vs 2 (HAP C) vs > 2 (HAP D)**

HAP	HAP A (n = 46)	HAP B (n = 43)	HAP C (n = 49)	HAP D (n = 15)
Median-survival, mo (95%CI)	31 (25-37)	31 (20-51)	22 (17-25)	18 (6-32)
P value	0.0454			

HAP: Hepatoma arterial-embolization prognostic; TACE: Transarterial chemoembolization.

in the HAP B and HAP D groups was not significantly different from that in the HAP A reference group [HR = 0.88 (0.52-1.50), *P* = 0.640; HR = 1.56 (0.81-2.99), *P* = 0.1820, respectively]. Only the patients in the HAP C group were at significantly higher risk of death vs the HAP A reference group [HR = 1.69 (1.02-2.80); *P* = 0.0436]. In total, the ability of the score to identify good candidates for TACE appears limited, since each variable is allocated the same number of points (1 point), for example, albumin < 36 g/L and AFP > 400 ng/mL; and only HCC exceeding 70 mm are taken into account although the success of TACE is partially dependent on the size of the tumour (generally less than 50 mm) and the number of lesions present<sup>[51]</sup>.

According to Kudo *et al.*<sup>[52]</sup>, the ART score is only applicable to a minority of patients in Japan, since the interval between two sessions exceeds 3 mo; the treated tumours being smaller as a result of a best screening in the country. In the patients treated twice consecutively (only 9.6% of the population), the ART score did not highlight a significant difference in survival between the two groups. As our TACE method was similar to that of the Viennese team, we carried out a retrospective analysis of ART scores before the second TACE in a total of 321 French patients with viral and/or alcoholic HCC enrolled in two cohorts in Marseilles and one in Nancy<sup>[53]</sup>. In order to create a population similar to that of Sieghart *et al.*<sup>[30]</sup>, we selected patients who had undergone at least two successive conventional TACEs without any other treatments, excluding patients undergoing pre-transplant TACE or presenting with severe cirrhosis (Child-Pugh ≥ 9). Our patients included BCLC B HCC, BCLC A HCC who were not eligible for curative treatment and unlike the study by Sieghart *et al.*<sup>[30]</sup>, cases of BCLC C HCC with sectoral portal vein thrombosis, as these patients were treated with TACE in routine practice before the advent of sorafenib (Table 2). Radiologic response was assessed using the EASL scoring system.

Our findings differed from those of Kudo *et al.*<sup>[52]</sup> since, in our three cohorts, the ART score clearly divided the patients into two groups with different median survival times for an aggravation of 0-1.5 vs ≥ 2.5. However, changes in the score were not correlated with the prognosis in these three cohorts. Median survival was lower in patients with an ART score of 1,

**Table 2 Baseline patients and disease characteristics in three sets (%)**

Characteristics	Cohort 1 (n = 139)	Cohort 2 (n = 82)	Cohort 3 (n = 100)
Age, median, yr (95%CI)	67 (65-68)	63 (60-69)	68.5 (66-71)
Sex, M/F	84/16	90/10	88/12
Cirrhosis or advanced fibrosis (F3)	100	100	94
Aetiology:	47/35/6/10	49/29/9/7	27/46/6/8
Virus/alcohol/virus + alcohol/ NASH			
Child-Pugh score: A/B	69/31	75/25	95/5
BCLC A/B/C	47/34/19	34/46/20	10/81/9
Infiltrative tumours	17	22	2
Segmental portal vein thrombosis	15	19.5	9
AFP < 200 ng/mL	78	60	77
AFP ≥ 200 ng/mL	22	40	23
Diagnosis based on: Imaging/ biopsy	85/15	77/23	80/20
Incidental/screening/symptoms	17/70/13	31/53/16	19/66/15
Previous treatments (surgery, RFA)	15	15	18

NASH: Non-alcoholic steatohepatitis; BCLC: Barcelona Clinic Liver Cancer; AFP: α-fetoprotein; RFA: Radiofrequency ablation.

*i.e.*, not showing a radiologic response, vs those with an ART score of 4, *i.e.*, an increase in AST > 25% (Tables 3-5). Fifty-six percent (56%), 23% and 38% of the patients with an ART score of 4 in each of the cohorts, respectively, showed a radiologic response. Unlike the results reported by Sieghart *et al.*<sup>[30]</sup>, an increase in AST > 25% was not an independent prognostic factor in the Marseilles cohorts. We analysed and compared the patients showing a partial and complete radiologic response in the ART 0-1.5 and ART ≥ 2.5 groups (in cohorts 1 and 2) (Table 6). The median survival times were similar, but the patients were offered a different treatment strategy as per the approach recommended by Sieghart *et al.*<sup>[30]</sup>.

We assessed the ART score before the 3<sup>rd</sup> TACE in 126 cirrhotic patients with virally induced (57%) or alcohol-induced HCC (33%); these patients were BCLC A (45%), BCLC B (45%) and C (10%), and had undergone an average of 4 TACE<sup>[54]</sup>. The score also distinguished two groups with a significantly different median survival time, but changes in the score were not correlated with prognosis. Once again, median survival was lower in the patients with an ART score of less than 1 than those whose score was evaluated at 4 (Table 7).

In view of these results, the ART score calculated before the 2nd and 3rd TACE cannot be used to define the treatment strategy for all patients, particularly those whose ART score is evaluated to be 1 and 4, poorly distributed. A prospective study is required to further explore and establish the prognostic value of this score.

## CONCLUSION

TACE is the most widely used treatment for HCC

**Table 3 Overall survival in the first cohort of patients using the ART score calculated before the second transarterial chemoembolisation with a cut-off value of: 0-1.5 vs ≥ 2.5**

ART (n = 139)	ART [0] (n = 67)	ART [1] (n = 11)	ART [1.5] (n = 18)	ART [2.5] (n = 3)	ART [3] (n = 2)	ART [4] (n = 16)	ART [5] (n = 5)	ART [5.5] (n = 5)	ART [6.5] (n = 3)	ART [7] (n = 2)	ART [8] (n = 7)
Median-survival, mo (95%CI)	37 (31-42)	9 (7-14)	28 (25-40)	10 (5-27)	17 (12-21)	28 (7-36)	14 (12-16)	13 (6-15)	5 (3-5)	22 (8-36)	5 (4-11)
P value ART (0, 1.5) vs ART ≥ 2.5	34 (28-38) < 0.0001										

TACE: Transarterial chemoembolization; ART: Assessment for retreatment with TACE.

**Table 4 Overall survival in the second cohort of patients using the ART score calculated before the second TACE with a cut-off value of: 0-1.5 vs ≥ 2.5**

ART (n = 82)	ART [0] (n = 39)	ART [1] (n = 14)	ART [1.5] (n = 5)	ART [2.5] (n = 1)	ART [3] (n = 3)	ART [4] (n = 5)	ART [5] (n = 10)	ART [5.5] (n = 1)	ART [8] (n = 4)
Median-survival, mo (95%CI)	27 (22-38)	11 (7-18)	15 (11-50)	N/A	10 (3-31)	31 (8-31)	8 (7-12)	N/A	8 (4-23)
P value ART (0, 1.5) vs ART ≥ 2.5	22 (15-27) 0.07 10 (8-23)								

TACE: Transarterial chemoembolization; ART: Assessment for retreatment with TACE.

**Table 5 Overall survival in the third cohort of patients using the ART score calculated before the second TACE with a cut-off value of: 0-1.5 vs ≥ 2.5**

ART (n = 100)	ART [0] (n = 38)	ART [1] (n = 30)	ART [1.5] (n = 3)	ART [2.5] (n = 8)	ART [4] (n = 10)	ART [5] (n = 8)	ART [6.5] (n = 2)	ART [8] (n = 1)
Median-survival, mo (95%CI)	49 (36-63)	21 (17-26)	23 (21-23)	13 (6-15)	24 (19-35)	19 (9-20)	14 (13-15)	9 (-)
P value ART (0, 1.5) vs ART ≥ 2.5	27.4 (24.7-37.8) 0.0001 15.5 (13.0-23.7)							

TACE: Transarterial chemoembolization; ART: Assessment for retreatment with TACE.

**Table 6 Overall survival of patients using the ART score calculated before the third TACE with a cut-off value of: 0-1.5 vs ≥ 2.5**

ART (n = 126)	ART [0] (n = 73)	ART [1] (n = 12)	ART [1.5] (n = 6)	ART [2.5] (n = 4)	ART [4] (n = 21)	ART [5] (n = 2)	ART [6.5] (n = 4)	ART [7] (n = 2)	ART [8] (n = 2)
Median-survival, mo (95%CI)	35 (30-37)	12 (10-18)	34 (27-38)	13 (8-24)	28 (19-41)	21 (9-32)	8 (5-9)	28 (25-31)	6 (4-8)
P value ART (0, 1.5) vs ART ≥ 2.5	31 (27-36) 0.004 21 (13-28)								

TACE: Transarterial chemoembolization; ART: Assessment for retreatment with TACE.

but its efficacy has mainly been demonstrated in a selected population of patients with intermediate stage HCC, *i.e.*, with large (> 50 mm) or multinodular nonoperable tumours, without vascular invasion or extrahepatic spread and a Child-Pugh class of A or B7. Other "good" indications probably exist, including some forms of limited HCC which are not eligible for curative treatment (radiofrequency ablation or surgery), and

even some cases of advanced HCC in combination with other treatments, but this can only be confirmed by randomised studies. While there is still no consensus concerning treatment methods, including the use of DC beads vs conventional TACE, the indications and contraindications of TACE and the strategy to be employed are better defined than previously, as are the rules for discontinuation-for example, the

**Table 7** Characteristics, median survival, comparative study of patients (first and second cohorts) with an objective radiologic response in both ART 'groups before the second TACE (%)

Patients with radiologic response	ART (0-1.5) (n = 113)	ART ≥ 2.5 (n = 28)	P value
AFP < 200 ng/mL	81	82	1.00
AFP ≥ 200 ng/mL	19	18	
Child-Pugh A/B	77/23	61/39	0.05
BCLC A/B/C	55/41/4	50/42/8	0.14
Median TACE sessions (95%CI)	3 (3-4)	2 (1-5)	0.17
Median-survival, mo (95%CI)	33 (27-38)	28 (13-35)	0.04
Median follow-up, mo (95%CI)	25 (22-29)	21 (13-31)	0.42

BCLC: Barcelona Clinic Liver Cancer; TACE: Transarterial chemoembolization.

“untreatable progression” defined by Bruix *et al.*<sup>[29]</sup>. The classification systems do not as yet take into account the histological criteria or biomarkers correlated with survival nor do they integrate all the patients whose profiles differ depending on their geographical location. Consequently, a score that combines different prognostic markers could be a useful aid when deciding to perform a first or repeat TACE and also help standardise current strategies, especially since new treatment options are now available (biotherapies, radioembolization in clinical trials). However, none of the recently published scores (ART, HAP) replaces the rigorous selection of patients on the basis of their liver function, underlying conditions, tumour characteristics and EASL or m RECIST radiologic response correlated with post-TACE survival times.

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