Research Article

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Retreatment with TACE: The ABCR SCORE, an aid to the decision-making process

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Background & Aims: Transarterial chemoembolization (TACE) is the standard of care for intermediate stage hepatocellular carcinoma (HCC) and it is the most commonly used treatment for HCC worldwide. However, no prognostic indices, designed to select appropriate candidates for repeat conventional TACE, have been incorporated in the guidelines.

Methods: From January 2007 to April 2012, 139 consecutive HCC patients, mainly with an alcohol- or viral-induced disease, were treated with TACE. Using a regression model on the prognostic variables of our population, we determined a score designed to help for repeat TACE and we validated it in two cohorts. We also compared it to the ART score.

Results: In the multivariate analysis, four prognostic factors were associated with overall survival: BCLC and AFP (>200 ng/ml) at baseline, increase in Child-Pugh score by $\geqslant$2 from baseline, and absence of radiological response. These factors were included in a score (ABCR, ranging from −3 to +6), which correlates with survival and identifies three groups. The ABCR score was validated in two different cohorts of 178 patients and proofed to perform better than the ART score in distinguishing between patients' prognosis.

Conclusions: The ABCR score is a simple and clinically relevant index, summing four prognostic variables endorsed in HCC. An ABCR score $\geqslant$4 prior to the second TACE identifies patients with dismal prognosis who may not benefit from further TACE sessions.

Keywords: HCC; Chemoembolization; BCLC; Radiological response; ABCR score; ART score; TACE.

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, the sixth most common cancer, and the third most common cause of cancer-related deaths in the world [1,2]. This cancer generally develops secondarily to an underlying chronic liver disease, due to different aetiologies (B or C viral hepatitis, alcohol abuse, non-alcoholic steatohepatitis, genetic iron overload) [3]. There is no "universally" recognized classification, which leads to wide variations in treatment practices, particularly when patients not eligible for curative treatment are concerned. Several Asian countries have their own staging system [4]. In Europe and the USA, the Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely used, endorsed by both AASLD and EASL, and used in most recent clinical trials. The BCLC classification is an algorithm linking clinical parameters, prognosis and therapeutic options [5,6]. HCC is a complex disease: underlying cirrhosis and portal hypertension (PHT) complicate the treatment of HCC and limit the available curative options. 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 [7]. In Europe and the USA, TACE is the standard of care for intermediate (BCLC B) stage HCC (PS 0, Child-Pugh A-B, multinodular or unresectable tumors, no portal vein invasion, N0, M0), but this group includes a heterogeneous population of patients with significant variations in tumor and liver characteristics [8]. In routine practice TACE has applications beyond intermediate stage HCC. TACE can also be applied to earlier HCC (BCLC A) not suitable for surgery or radiofrequency ablation [9]. HCC progression being mainly intrahepatic rather than metastatic [10], some authors postulate that advanced HCC is not necessarily contraindicated for TACE treatment in selected cases [11,12]. Previous Asian studies and a meta-analysis of eight trials (including five retrospective studies) showed that TACE could be safely performed for selected HCC involving segmental branches of portal vein, with survival benefit compared with conservative treatment [13–16], but the recurrence rate is relatively high in

Table 1. Baseline patient and disease characteristics in both series. In Nancy cohort, oesophageal varices were assessed as absent or present: 55% of patients had oesophageal varices.

Characteristic	Initial cohort n = 139	Internal validation cohort n = 78	External validation cohort n = 100
Age, median [95% CI]	67 [65-68]	69 [63-71]	68.5 [66-71]
Sex, M/F (%)	84/16	79/21	88/12
BMI, median [95% CI]	25 [24-25]	26 [24-27]	27.5 [26-29]
Cirrhosis or advanced fibrosis (F3) %	100	100	94
Aetiology: % virus/alcohol/virus + alcohol/NASH	47/35/6/10	36/36/10/13	27/46/6/8
Diabetes %	32	24	45
Child-Pugh score: A/B %	69/31	76/24	95/4
Oesophageal varices grade 0/1/≥2%	39/23/38	44/23/33	45/55*
BCLC A/B/C %	47/34/19	32/68/0	10/81/9
Infiltrative tumours %	17	6	2
Segmental portal vein thrombosis %	15	0	9
Unifocal tumour >50 mm %	9	10	15
AFP <200 ng/ml (%)	109 (78)	50 (64%)	77 (77)
AFP ≥200 ng/ml	30 (22)	28 (36%)	23 (23)
Diagnosis based on: imaging/biopsy %	85/15	73/27	80/20
Circumstance % incidental/screening/symptoms	17/70/13	37/55/8	19/66/15
Previous treatments (surgery, RFA) %	15	17	18

BMI, body mass index; NASH, non-alcoholic steatohepatitis; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; RFA, radiofrequency ablation.
* In Nancy cohort, oesophageal varices were assessed as absent or present and therefore 55% of patients had oesophageal varices.

patients with vascular invasion [17]. In the randomized study by Lo *et al.*, 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 [18].

For some authors, the benefits of TACE are debatable: only two randomized controlled trials including 112 and 80 patients gave positive results, the survival benefit was limited (4 months) and meta-analysis results are conflicting [18–21]. This skepticism is maintained by the lack of homogeneity in treatment modalities (drugs to be used, the interval between courses). In the randomized study by Llovet *et al.*, doxorubicin-based TACE were performed 2 months and 6 months after the initial session, and then every 6 months until progression, depending on individual tolerance [19]. In the randomized study by Lo *et al.*, cisplatin-based TACE was performed every 2 to 3 months until disease progression, depending on individual tolerance [18]. On the other hand, antitumor efficacy of TACE can be counter-balanced by its toxicity, with immediate toxic effects due to the embolization process (haemorrhages, tumor rupture, renal insufficiency, ascites, liver failure) and with delayed toxicity related to worsening liver function [22,23]. New embolic devices (drug-eluting beads) seem to improve systemic toxicity and perhaps liver toxicity [24]. The indications and contraindications of TACE are better defined than previously; treatment algorithms for the repetition of TACE have been proposed, based on the radiological assessment, but the objectives are different according to the authors (response or stabilization) [25,26]. The contrast uptake criteria – both EASL and mRECIST – differ in terms of target lesions and calculation methods, but they are comparable and correlated with survival after TACE [27,28]. However, these criteria are not applicable for all types of HCC [29]. There are no guidelines concerning the number of TACE to be performed before switching to another treatment strategy. On the other hand, sorafenib has recently been shown to improve survival in advanced HCC (BCLC C), including BCLC B patients after TACE failure [30,31]. In view of the highly diverse nature of HCC and practices and the therapeutic options now available, a tool to help to decide whether or not to continue with TACE will be useful. There is no prognostic score designed to help for repeat TACE incorporated into the guidelines. The ART (Assessment for Retreatment with TACE) score, calculated before performing a second TACE, allowed to differentiate two groups (0–1.5 points *vs.* 2.5 points and over) with different prognosis (median overall survival of 23.7 and 6.6 months respectively) [32]. It is based on three parameters (increase of AST by >25%, increase in Child-Pugh score from baseline and tumor response). Increase (+25%) in AST was the parameter associated with the most powerful coefficient, the lowest was allocated to the radiological response. 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 suggested continuing TACE until the score changes from 0 to 1.5. This score is also applicable to subsequent courses [33]. We calculated from the prognostic variables of our population a new score and we validated it in two independent cohorts of patients mainly BCLC B treated by TACE similar to the two Austrian cohorts. We compared it to the ART score.

Patients and methods

Patients

From January 2007 to April 2012, 353 consecutive patients have been hospitalized for HCC in our Hepatology department. Diagnosis was done following EASL–AASLD criteria; if patients do not have liver cirrhosis, a biopsy was required. TACE was done in 185 of these patients (52.4%). In all cases, data (clinical, biological, radiological, follow-up, therapeutic options, response to treatment and side effects) were prospectively collected.

Patients excluded from this retrospective analysis were: patients who received TACE as a bridge for liver transplantation (12 patients) or for down-staging before resection (8 patients); patients who had another treatment associated with TACE (radiofrequency tumor ablation or other percutaneous treatments) (18 patients); patients with portal vein thrombosis involving at least one major branch; patients with extrahepatic metastases; patients with ECOG performance status >2; patients with a decompensated cirrhosis (Child-Pugh B9 and over); and patients receiving only one TACE session (8 patients). A total of 46 patients were excluded.

Patients with segmental vein thrombosis were left in the analysis because, in most centers, this is not considered as a contraindication for TACE and because this at-risk population will benefit the most from the prognostic score [13].

A second cohort of 78 patients, treated in our unit by TACE sustained during another period with the same inclusion/exclusion criteria, was analyzed as an internal validation cohort, and a third cohort of 100 patients treated in Nancy by TACE between March 2006 and July 2012 with the same inclusion/exclusion criteria was analyzed as an external validation cohort.

Treatment procedure

Senior radiologists (OB, OM, PB) performed TACE, with selective or supraselective injection of a mixture of epirubicin (50 mg) with Lipiodol (10 ml) followed by an embolization with Gelfoam fragments. Patients were hospitalized for at least 2 days for hydration, pain treatment and close monitoring. The second TACE was systematically done 6 to 8 weeks later; other TACE sessions were planned "on demand" according to radiologic and AFP assessments done every 8 weeks. Within one week before each TACE, clinical examination, biological tests (including liver enzymes), AFP serum level, Child-Pugh score and contrast-enhanced CT-scan or contrast-enhanced MRI were done in order to assess BCLC class, and tumor response. For tumor response, the 3 senior radiologists (OB, OM, PB) used EASL criteria based on bi-dimensional measurement of the enhanced viable part of the tumors; a response was defined as either a complete response (total disappearance of enhancement or retention of Lipiodol within the entire tumor volume) or a partial response (decrease by more than 50% of the viable area of the tumor). We selected all target lesions showing intratumoral arterial enhancement on contrast-enhanced CT or MRI. For infiltrative type HCC, we also take into account tumor necrosis induced by TACE. For patients with segmental vein thrombosis, arterial enhancement was considered and measurements of the extent of the malignant thrombus were also taken into account. For radiological assessment, we decided to use the EASL criteria and not the mRECIST criteria because this methodology was done in the ART paper [32]. Moreover recent studies demonstrated that both criteria could be used in HCC assessment with equivalent efficacy for treatment response [27,28].

Study design and statistical analyses

The ART score was calculated in our initial cohort of patients; this score was the sum of points given to three variables: increase in Child-Pugh score from baseline = 1.5 points if +1 point, 3 points if $\geqslant$2 points; AST increase >25% from baseline = 4 points if present; and absence of radiologic tumor response = 1 point.

Patient's characteristics in the estimation set and in the validation set are given (Table 1) using descriptive statistics and as median and 95% confidence interval. Overall survival (OS) was defined as the time from the second TACE until death or last follow-up. Survival curves were calculated using the Kaplan-Meier method; median OS and their 95% confidence intervals are reported. Univariate analysis of the OS time was performed on the estimation set. Log-rank test was performed to detect significant parameters in univariate analysis. Parameters with a *P* value (Log-rank) $\leqslant$0.05 in the univariate analyses were entered in the multivariate analysis.

Multivariate Cox regression analysis with stepwise selection was performed in order to detect independent predictors of survival time (entry criteria for selection into the final multivariate model was $p \leqslant 0.05$). B regression coefficients were multiplied by two and rounded to the nearest unit (1.00 unit) in order to obtain the ABCR score.

Two validation cohorts were used to validate the ABCR score. ART score was also assessed on the two validation cohorts in order to confirm results obtained in the estimation cohort.

Survival curves and histograms were used to present data. All *p* values are reported using a significance level of 0.05. All calculations were performed using SAS 9.1.3 (SAS Institute Inc., Cary, NC).

Comparison between the ABCR and the ART score in their discriminatory ability to predict survival was done using the Harrel's C index, the Linear Trend Test LT (χ^2), the Ratio Test LR (χ^2), the Akaike Information Criterion (AIC).

Results

Patients

Our cohort of 139 HCC patients treated by TACE (Table 1) between January 2007 and April 2012 were predominantly male, all had cirrhosis or advanced fibrosis (F3) and in 53% of the cases the main cause of the liver disease was a chronic viral infection (HCV in 38%, HBV in 6%, co-infection HCV-HIV in 3%, alcohol

Table 2. Univariate analysis of prognostic factors after the first TACE in our initial cohort (139 patients).

Variable	n = 139	Overall survival (months)		*p* value (Log-rank)
		Median	95% CI	
Age				
<65	57	21.3	13.2-32.4	
≥65	82	30.5	25.4-35.5	0.20
Gender				
Male	117	27.0	21.3-33.5	
Female	22	31.4	13.2-38.5	0.43
Child-Pugh stage				
A	96	31.4	25.4-35.5	
B	43	21.3	12.2-32.4	0.21
Child-Pugh increase				
Absent	92	33.5	28.4-37.5	
+1 point	31	25.4	14.5-35.5	
≥2 points	16	5.6	4.1-11.2	<0.0001
Aetiology				
Viral	65	31.4	19.2-35.5	
Other	74	26.4	18.3-34.5	0.67
BCLC stage				
A	69	37.5	33.5-65.9	
B	43	23.4	15.3-31.4	
C	27	8.1	5.1-13.2	<0.0001
AFP (ng/ml)				
<200	109	32.4	26.4-35.5	
≥200	30	8.1	5.1-12.0	<0.0001
AST increase >25%				
Absent	102	30.5	25.4-35.5	
Present	37	15.2	12.2-32.4	0.008
Diabetes				
Absent	94	25.4	16.2-31.4	
Present	45	34.5	23.4-39.6	0.32
Tumour response				
Absent	33	8.1	5.1-11.2	
Present	106	34.5	28.4-36.5	<0.0001
Oesophageal varices*				
Absent	51	34.5	19.2-41.6	
Grade 1	31	28.4	15.8-37.5	
Grade 2/3	51	23.4	12.2-31.4	0.037
Circumstance				
Incidental	24	19.2	16.2-37.5	
Screening	97	33.5	27.0-36.5	
Symptoms	18	8	4.1-14.2	<0.0001

*Six patients had no evaluation of oesophageal varices.

and viral infection in 6%). In our population, 19% of the patients were BCLC C and in most cases that was related to a segmental portal vein thrombosis. In 15% of the cases, patients had previously received a curative treatment (resection, radiofrequency). Almost half of our population was BCLC A, due to recurrence after previous curative treatment or to contraindication to resection (tumor location, past-history, Child-Pugh B cirrhosis, severe portal hypertension) or to liver transplantation (LT) (due to age or associated conditions, progression while on the waiting list, refusal). The median OS was 28 months (range: 22–34).

Univariate and multivariate analysis of prognostic factors in our population

On univariate analysis (Table 2), seven variables demonstrated a significant impact on OS, at baseline: BCLC, AFP (⩾200 ng/ml), portal hypertension (oesophageal varices), and initial presentation of the disease; and before the second TACE: tumor response, worsening in Child-Pugh score and AST increase (⩾25%) between baseline and evaluation.

These seven parameters of predictive value were entered in the multivariate analysis. After a stepwise removal of variables, four remained significant predictors of OS (Table 3): BCLC and AFP at baseline, Child-Pugh increase by 2 points or more, and radiological response. Variation of AST was not significantly associated with prognosis in our population, nor worsening by 1 point of the Child-Pugh score. The calculated B values (regression coefficients) were multiplied by 2 and rounded in order to determine a new score. This score, called ABCR (standing for alpha-fetoprotein, BCLC, Child-Pugh and Response), ranges from −3 to +6. The score was then calculated for the 133 patients for whom we had the four parameters. We observed a linear decrease in median OS (Fig. 1) when ABCR scores increased; for example patients with an ABCR score of −3 (n = 54) had a median OS of 37.5 months [95% CI, 34.5–38.5], an ABCR score of 0 (n = 15) had a median OS of 25.4 months [95% CI, 11.1–31.4], an ABCR score of 3 (n = 12) a median OS of 12.2 months [95% CI, 9.1–15.2] and an ABCR score ranging from 4 to 6 (n = 16) had a median OS <5.1 months. Using a threshold of 2, we were able to define two groups of patients with significantly different OS (p <0.0001), with a median OS of 35 months [95% CI, 28–37] for ABCR score ⩽2 (n = 105), and a median OS of 6 months [95% CI, 5–10] for ABCR score >2 (n = 28) (Fig. 2A). More interestingly using two different thresholds, ⩽0 and ⩾4, we were able to

Table 3. Multivariate analysis of prognostic factors of survival after the first TACE in our population.

Variable	Overall survival			Score*	p value (Cox)
	Hazard ratio	95% CI	B		
AFP (ng/ml)					
<200	1	-	-	0	-
≥200	2.04	1.22-3.41	0.71	1	0.007
BCLC					
A	1	-	-	0	-
B	2.60	1.49-4.54	0.95	2	0.0008
C	3.73	1.76-7.89	1.32	3	0.0006
Child-Pugh increase					
Absent	1	-	-	0	-
+1 point	0.92	0.52-1.66	-0.08	0	0.79
≥2 points	3.03	1.62-5.65	1.11	2	0.0005
Tumour response					
Absent	1	-	-	0	-
Present	0.28	0.15-0.53	-1.26	-3	<0.0001

BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein.

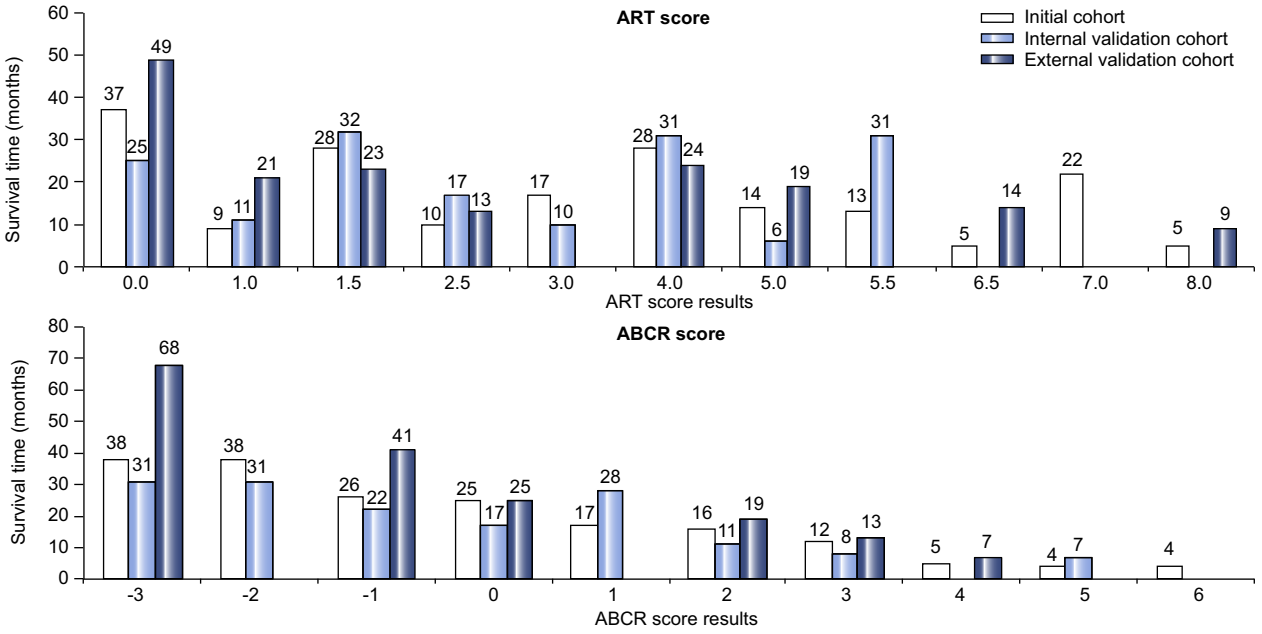
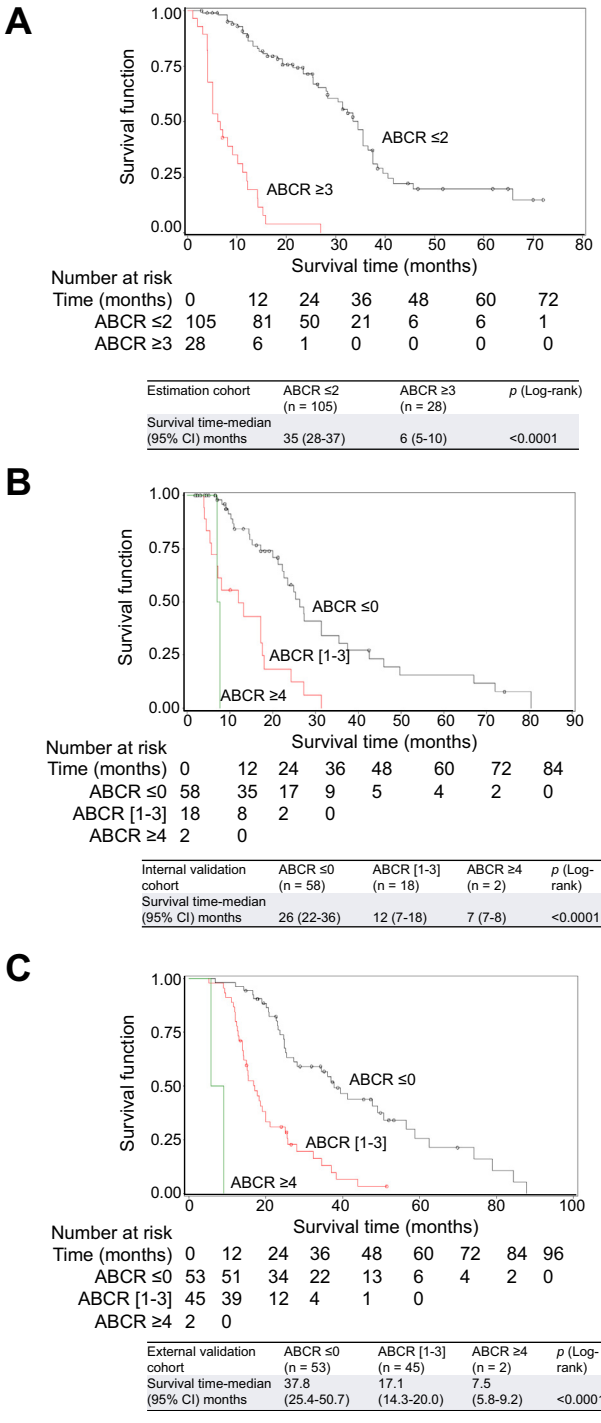


Fig. 1. Histograms of evolution of median overall survival following ART and ABCR scores in our estimation cohort, internal validation cohort, and external validation cohort.

enhance the prognostic value and to define three groups of patients with significantly different OS (p <0.0001). Median OS of the three groups were respectively 34.5 months [31.4–37.6] for ABCR score ⩽0, 13.2 months [9.1–15.8] for ABCR score 1–3, and 4.6 months [4.1–5.1] for ABCR score ⩾4.



Estimation cohort	ABCR ≤2 (n = 105)	ABCR ≥3 (n = 28)	p (Log-rank)
Survival time-median (95% CI) months	35 (28-37)	6 (5-10)	<0.0001

Internal validation cohort	ABCR ≤0 (n = 58)	ABCR [1-3] (n = 18)	ABCR ≥4 (n = 2)	p (Log-rank)
Survival time-median (95% CI) months	26 (22-36)	12 (7-18)	7 (7-8)	<0.0001

External validation cohort	ABCR ≤0 (n = 53)	ABCR [1-3] (n = 45)	ABCR ≥4 (n = 2)	p (Log-rank)
Survival time-median (95% CI) months	37.8 (25.4-50.7)	17.1 (14.3-20.0)	7.5 (5.8-9.2)	<0.0001

Fig. 2. Overall survival in our cohorts of patients treated by TACE determined just before the second session. (A) Initial cohort according to ABCR score with a cut off value of 2, (B) internal validation cohort according to ABCR score with a cut off value of ⩽0 *vs.* [1–3] *vs.* ⩾4, (C) external cohort according to ABCR score with a cut off value of ⩽0 *vs.* [1–3] *vs.* ⩾4. (This figure appears in colour on the web.)

Validation of the ABCR score

In order to validate this score, we collected data among a second cohort of patients treated by TACE in our institution obtained during another period. This second cohort comprised 78 patients (Table 1), and characteristics of these patients were close to those of the Austrian cohorts (mainly BCLC B patients, BCLC A patients not suitable for curative option and no BCLC C patients). Using the ABCR score, prognosis gradually decreased with increasing score (Fig. 1); with a cut-off value set at 0 (⩽0) and 4 (⩾4), median OS of the three groups were 26 months [95% CI: 22–36] for ABCR score ⩽0, 12 months [95% CI: 7–18] for ABCR score 1–3, and 7 months [95% CI: 7–8] for ABCR score ⩾4 (p <0.0001) (Fig. 2B). Using two different thresholds, ⩽0 and ⩾4, we were able to define three groups of patients with significantly different OS.

In order to externally validate this score, we used the same inclusion and exclusion criteria and collected data about a third cohort of patients treated by TACE in Nancy University hospital between March 2006 and July 2012. This third cohort included 100 patients (Table 1). Characteristics of these patients were slightly different compared to our initial cohort, quite similar to the Austrian cohorts with more alcoholic patients, less BCLC A patients and a majority of BCLC B patients. Again, using the ABCR score, prognosis gradually decreased with increasing score (Fig. 1) and with a cut-off value set at 2 (⩽2 *vs.* >2), median OS of the two groups were respectively 27.4 months [95% CI: 23.7–37.1] (n = 84) and 12.8 months [95% CI: 9.6–15.4] (n = 16) (p <0.0001). With a cut-off value set at 0 (⩽0) and 4 (⩾4), median OS of the three groups were respectively 37.8 months [95% CI: 25.4–50.7] for ABCR score ⩽0, 17.1 months [95% CI: 14.3–20.0] for ABCR score 1–3, and 7.5 months [95% CI: 5.8–9.2] for ABCR score ⩾4 (p <0.0001) (Fig. 2C). Using two different thresholds, ⩽0 and ⩾4, we were able to define three groups of patients with significantly different OS.

ART score assessment in the three cohorts

Initial cohort. One week before the second TACE, 32 patients had a worsening in the Child-Pugh score by 1 point, 16 patients by 2 points or more, and 33 had no tumor response. 34 patients had an increase in AST by >25% from baseline. Those having an increase by >25% in AST had an underlying viral disease (24 out of 34) more frequently than those with stable AST (50 out of 105) (p <0.0001). They had more frequently a Child-Pugh A cirrhosis (22 out of 34) and a radiologic response was observed in a majority of them (19 out of 34). Less than half of patients having an increase by >25% in AST had vascular invasion (10 out of 26). The ART score was: 0 in 67 patients (48%), 1 in 11 patients (8%), 1.5 in 18 patients (13%), 2.5 in three patients (2%), 4 in 18 patients (13%) and >4 in 22 patients (16%). Overall, 43 patients (31%) had a score ⩾2.5 points and the remainder, 96 patients, a score from 0 to 1.5. These two groups differed (Table 4) by initial AFP values, Child-Pugh score, BCLC, and presence of an infiltrative tumor or a segmental portal vein thrombosis. Median OS was statistically different (p <0.0001): 34 months [95% CI, 28–38] in the low-score group and 13 months [95% CI, 10–16] in the high-score group. However, there was no clear progression between the score and the median OS decrease in our population (Fig. 1) with median OS of 37 months [95% CI, 31–42] in score 0 (n = 67),

Table 4. Baseline patients and disease characteristics in initial cohort following ART score 0–1.5 and ⩾2.5.

Patient characteristics	ART 0-1.5 n = 96	ART ≥2.5 n = 43	*p* value
Age, median [95% CI]	67.5 [65-68]	65 [61-70]	0.49
Sex M/F (%)	85	81	0.62
BMI (median) [95% CI]	25 [24-26]	25 [22-27]	0.60
Aetiology: % virus/alcohol/virus + alcohol/NASH	42/32/6/14	56/40/2/2	0.90
Diabetes %	31	35	0.39
Child-Pugh class A/B %	76/24	53/47	0.01
Oesophageal varices grade 0/1/≥2 %	47/23/30	28/21/51	0.19
BCLC A/B/C %	60/30/10	21/37/42	<0.0001
Infiltrative tumour %	8	35	<0.0001
Segmental portal vein thrombosis %	7	28	<0.0001
Unifocal tumour >50 mm, %	8	12	0.54
AFP <200 ng/ml (%)	80 (83)	29 (67)	0.045
AFP ≥200 ng/ml	16 (17)	14 (33)	0.045
Diagnosis based on: imaging/biopsy %	85/15	93/7	0.10
Circumstance % incidental/screening/symptoms	71/19/10	67/14/19	0.20
Previous treatment (surgery/RF) %	13	21	0.21
Tumour response: yes/no %	89/11	49/51	<0.0001
Median overall survival [95% CI]	34 [28-38]	13 [10-16]	<0.0001

BMI, body mass index; NASH, non-alcoholic steatohepatitis; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; RFA, radiofrequency ablation.

9 months [95% CI, 7–14] in score 1 (n = 11), 28 months [95% CI, 25–40] in score 1.5 (n = 18), 10 months [95% CI, 5–27] in score 2.5 (n = 3), 28 months [95% CI, 7–36] in score 4 (n = 18) and 12 months in score >4 (n = 22).

Internal cohort. In this second cohort, there was no significant correlation between median OS and ART score (Fig. 1). Median OS were not statistically different ($p = 0.9955$) between patients with an ART score 0–1.5, 23 months [95% CI, 18–27], and those with an ART score ⩾2.5, 17 months [95% CI, 8–31].

When we compare the performance of these two scores using the 4 tests in this internal cohort, ABCR was superior to the ART score in its ability to predict survival. The discriminatory ability of ABCR (LT χ^2) was 9.2229 ($p = 0.0024$) *vs.* 1.6867 ($p = 0.1940$); the homogeneity likelihood of ABCR (LR χ^2) was 31.3227 ($p < 0.0001$) *vs.* 0.0813 ($p = 0.7755$), with a lower value of AIC (ABCR 292.959 *vs.* 324.200). Previous results were confirmed by a higher C-index value for the ABCR with 0.689 [0.607–0.777] *vs.* 0.608 [0.480–0.703]. By contrast, in multivariate analysis, ABCR score was identified as independent predictors of OS (HR 1.53 [1.31–1.77]; $p < 0.0001$ *vs.* HR 0.96 [0.82–1.13], $p = 0.6394$ for the ART score).

External cohort. In this third cohort, median OS for patients with an ART score 0–1.5 was higher than median OS in patients with ART score ⩾2.5: 27.4 months [95% CI, 24.7–37.8] *vs.* 15.5 months [95% CI, 13.0–23.7] respectively ($p = 0.001$). However, as in our two cohorts, there was no clear progression between the score and the median OS decrease in the Nancy HCC population (Fig. 1). In this cohort, 21 patients had an increase in AST by >25% from baseline. These patients had mostly a Child-Pugh A cirrhosis (20 out of 21), no vascular invasion (20 out of 21), a radiologic response was observed in eight of them.

Follow up of patients and scores in the initial cohort

126 patients were alive after two TACE, 45% were BCLC A, 45% BCLC B and 10% BCLC C, with segmental portal vein thrombosis in 10%. Patients were treated on average by 4 sessions of TACE. The median time to radiologic progression was 6 months [5.5–8]. The median follow-up was 21.8 months [17.3–26.4]. ART score differentiated two groups with significant difference survival; however increase in the score was not correlated with prognosis. Again, the ABCR score differentiated three groups with different survival and increase in the score was better correlated with prognosis than the ART score (linear correlation coefficient $R^2 = 0.94$ *vs.* 0.21 (ART) $p < 0.001$).

Overall 43/139 patients had received sorafenib after progression. The mean OS was 21.3 months *vs.* 21.7 months for the 96 patients not receiving sorafenib. In the sorafenib group, 58% (25/43) had a radiological response and 39.5% were BCLC C *vs.* 69% (66/96) and 10% (10/96) respectively for those not receiving sorafenib. As expected, sorafenib appeared to increase OS in those with poor response to TACE.

Discussion

The ABCR score determined just before the planned second session of TACE allows an excellent differentiation between patients with good median OS and those with dismal prognosis if they continue TACE. According to Kudo *et al.*, the ART score could only be used in a minority of patients in Japan since the interval between two sessions exceeded three months, and treated tumors being smaller [34]. In 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. In our series, the ART score was not of major value; using

a cut-off value of 1.5 (0–1.5 *vs.* ⩾2.5), there was a statistically significant difference between these two groups but there was no clear relationship between score and survival. In all our cohorts, patients with an ART score of 4, i.e. an increase in AST >25%, had a better OS than patients with an ART score of 1, i.e. not showing a radiologic response, as expected since radiological response is correlated with post-TACE survival times. By contrast, evolution of the ABCR score was closely associated with evolution in survival. These results were confirmed in our external cohort assessed independently by three investigators (JPB, SB, and CB). This gives reliability and reproducibility to the ABCR score.

TACE is the standard of care for BCLC B patients and for BCLC A patients who recurred or could not benefit from curative options [7]. However, there is no real consensus on the frequency of TACE and on the interval between two TACEs. For some authors, TACE must be repeated every 4 to 8 weeks, while for others TACEs are only given on demand [35,36]. An algorithm has been proposed based on tolerance of the first TACE and on the efficacy of the first round of two sessions [25]. The ART score has been designed in order to determine the median OS expected for patients in line to receive their second session. This score has been based on two cohorts (training and validation) of Austrian patients [32]. The authors have distinguished two groups of patients, one good prognostic group (score 0–1.5) with a median OS of 23.7 months, justifying continued TACE, and a second group (score of 2.5 or higher) with a poorer survival of 6.6 months for whom TACE can be discontinued and systemic treatment proposed. This score was composed of three parameters linked with treatment efficacy (tumor response) and tolerance (increase from baseline by 25% of AST or by 1 or 2 points of Child-Pugh score). Increase of AST value (+25%) from baseline had the highest importance (4 points) in this score and the positivity of this parameter alone can lead the patient in the poor prognostic group. The Austrian population was composed of only one-third of viral liver disease and most of the patients had alcoholic liver disease. In cases of underlying viral liver disease, fluctuations in ALT/AST values are not infrequent. In our population, an increase by more than 25% of AST was more frequently observed in patients with viral disease than in those with other causes of liver disease, which can explain why an ART score of 4 was not associated with a poor OS in our 2 cohorts. Moreover, in our initial cohort of patients, this parameter was of prognostic value only in the univariate analysis, and disappeared in the multivariate analysis. In view of these results, the ART score calculated before the 2nd and 3rd TACE cannot be used to guide the treatment decision for all patients, particularly those whose ART score is evaluated to be 1 and 4, poorly distributed.

In routine practice TACE has applications beyond intermediate stage HCC. For example, in our initial cohort, many patients were BCLC A, and had, after their first TACE, a correct OS, as observed in some other recent series [7]; by contrast some patients had more advanced tumors. Therefore, we determined from our population another score more convenient for these patients with more frequent viral diseases. The ABCR score associates two parameters observed at baseline and usually linked with OS (BCLC and AFP level) and two treatment-related parameters, one associated with efficacy (tumor response) and the other with toxicity (increase by more than 1 point in the Child-Pugh score). We have to notice that two parameters are common to the two scores: tumor response and worsening in Child-Pugh score. When we compare the performance of these two scores, ABCR was superior to the ART score in its ability to predict survival: in the ABCR score, the highest scores are associated with tumor response (−3 points) or BCLC C at baseline (+3 points). The main interest of this score is the fact that, in our population there was a clear parallel evolution of median OS with the score. This was confirmed in the two validation cohorts. Moreover, using two different thresholds, ⩽0 and ⩾4, we were able to define three groups of patients with significantly different OS that can be used for further studies in order to evaluate the benefit of sorafenib alone or in combination with TACE in patients with an ABCR score between 1 and 3. However, our cohorts included only a limited subgroup of BCLC C HCC (infiltrative HCC with distant thrombosis that showed arterial enhancement on CT or MRI). Therefore our results could not be generalized to all patients with BCLC C HCC treated by TACE.

Conclusions

TACE is the most widely used treatment for HCC, but its efficacy has principally been shown in a selected population of patients. Determining, after a first TACE, of the patients who will not benefit from continuing TACE or who have poor prognosis is very important in order to avoid potentially toxic treatment and to propose another therapeutic option. The current classification system does not take into account the histological criteria or biomarkers correlated with survival. A score that combines different prognostic markers could be a useful aid to select appropriate candidates for repeated TACE. The ART score is not well correlated with survival for all patients with HCC undergoing TACE. By contrast we have defined in our population another score based on BCLC, AFP level at baseline and tumor response, and worsening of Child-Pugh status. This score, the ABCR score, was confirmed in two validation cohorts (internal and external) and was clearly correlated with median OS. It is important that these scores should be tested in different populations and validated in prospective trials.

Conflict of interest

Adhoute Xavier: Board member (Bayer).
Penaranda Guillaume: grant from Bayer.
Raoul Jean-Luc: Board member (Bayer, BMS, Daichi).
Bronowicki Jean-Pierre: Board member (Merck-Schering Plough, Janssen, Roche, BMS, Boehringer-Ingelheim, Gilead, Novartis, GSK, Bayer), speaker (Merck-Schering Plough, Janssen, Roche, BMS, Boehringer-Ingelheim, Gilead, Novartis, GSK, Bayer).
Bourliere Marc: Board member (Merck-Schering Plough, Giléad, Janssen, Vertex, Boehringer-Ingelheim, BMS, Roche, Abbvie, GSK), speaker (Merck-Schering Plough – Giléad, Janssen, Vertex, Boehringer-Ingelheim, BMS, Roche, Abbvie, Novartis, GSK).
All other authors have no conflict of interest.

Authors' contributions

XA, MB, JPB, SN, HP, PC, JLR are MD in charge of the patients.
OB, OM, PB, CB are radiologists who make TACE.
BP is the liver surgeon involved in patients treatments.
GLF and GP collected and revised the data, and proceeded to statistical analysis.
XA, JLR, GP, and MB wrote the manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2014.11.014.

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