

Reviewing « six and twelve »

it is very interesting manuscript , but i have few questions to the authors: 1- p 17 BCLC classification "BCLC stage A was defined as patients having tumor > 2 cm...." i think it is a mistake the correct is lesion < 2cm ,so please correct 2- You have 145 (45%) of the patients BCLC stage A why this patients do TACE ?? no other curative lines line RFA can be offered?? this need clarification as BCLC A can do curative therapy according to guidelines 3- Why you separate Marceillie cohort from the whole cohort i think this added too much tables and nearly the same findings

Scientific Quality:

Grade B (Very good)

Language Quality:

Grade A (Priority publishing)

Conclusion:

Minor revision

Dear Professors, we are grateful for the opportunity to revise our paper entitled " The "six-and-twelve score" for outcome prediction of unresectable HCC treated with TACE. In-depth analysis from a multicenter French cohort." We appreciate the reviewer's insightful comments

Response 1

Current Barcelona Clinic Liver Cancer (BCLC) staging considers single tumor >2 cm as stage A[1], whereas previous BCLC stage considers single tumor ≤ 5 cm or no more than 3 tumors with maximum diameter ≤ 3 cm as stage A[2].

Patients with very early-stage (BCLC 0) hepatocellular carcinoma (HCC) have a solitary lesion ≤ 2 cm[1].

No tumor was classified at the very early stage of HCC in this multicenter French cohort. We have mentioned it in the main text ([page 17](#))

Response 2

We thank the reviewer for this relevant comment. Obviously, early stage hepatocellular carcinoma (HCC) patients (BCLC stage A) must be referred to a curative treatment: surgical resection, ablation or even transplantation. However, this population was not suitable for a curative treatment after discussion during our multidisciplinary tumor board. We provide details regarding the characteristics of these patients with an early stage HCC ([table 1](#)). These patients were slightly older than those with intermediate stage HCC. These were mainly cirrhotic patients (n=139) with portal hypertension (median serum level Platelets: 106 [82-153] $10^9 / l$). More than half of the patients had esophageal varices, and liver function was not optimal in most cases (stratification according to ALBI grade was grade 2 or 3 in 81% of cases) ([table 1](#)). Regarding the tumor status, fifty-nine patients presented with multinodular HCC (2 or 3 nodules), and twenty patients had (single) tumor size greater than 5 cm. Moreover, twenty-two patients have received a previous treatment by resection or ablation. Causes of transarterial chemoembolization (TACE) also included unfeasible ablation due tumor location. Thus, we have applied the concept of "treatment stage

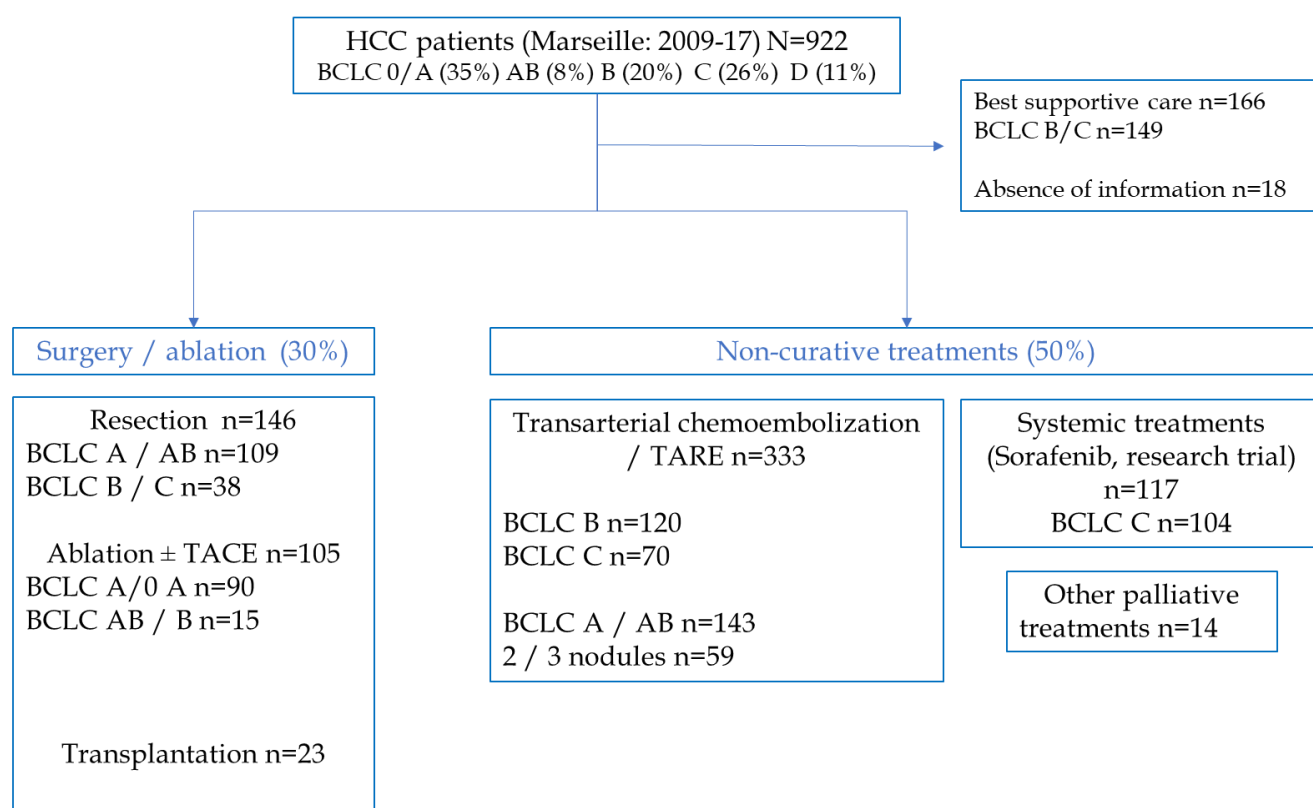
migration” [1, 3] (indicated on [page 4](#)); TACE was performed to patients at an earlier stage (BCLC-A) who are not considered for surgery or ablation. Of course, TACE is not a curative treatment, but it is sometimes possible to achieve complete necrosis[4, 5] and longtime survival[3], especially when it involves HCC of limited size[6] without increased alfa-fetoprotein (AFP) serum level[5]. We mentioned it on [page 6](#). Since the majority of patients come from our cohort, we provide details regarding the overall management of patients in our institution in recent years ([figure 1](#)). The flowchart show that a curative treatment is proposed for most patients with early-stage HCC.

It should also be pointed out that the Chinese cohorts mainly included HCC patients with single tumor (> 50%)[7, 8], classified as BCLC A in the most recent BCLC staging.

Table 1

	BCLC A (N=145)	BCLC B (N=179)	P
Age (years)- Median [IQR]	69 [62-76]	68 [62-73]	0.0580
Tumor Size (mm) - Median [IQR]	28 [25-35]	40 [30-55]	<0.0001
ALBI grade (GD)- N (%)			0.5233
GD1	28 (19%)	36 (20%)	
GD2	100 (69%)	129 (72%)	
GD3	17 (12%)	14 (8%)	
Platelets count, 10 ⁹ /L- Median [IQR]	106 [82-153]		
esophageal varices (OV) (available data for 138 patients)	BCLC A (N=138)		
OV - N (%)			
0	63 (46%)		
GD 1	26 (19%)		
GD 2-3	49 (35%)		

Figure 1: flowchart of HCC patients from Marseille (staging and treatment strategy)



HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; BCLC stage AB: single tumor >5 cm; TACE, transarterial chemoembolization; TARE, transarterial radioembolization

Question 3:

We thank the reviewer for his comments. We wanted to compare the “six-and-twelve” model with other models, different from those tested in the Chinese cohorts. Our Chinese colleagues focused on models designed especially for chemoembolization, such as the Hepatoma Arterial-embolization Prognostic (HAP) score and its different versions. However, we have shown that other models can be used as a decision-making aid before TACE[9, 10]. Some data were not available in the cohort from Nancy, such as serum alkaline phosphatase level required for computing the Model to Estimate Survival for HCC (MESH) score (table 2). We have therefore also studied

the cohort coming from Marseille. It appeared relevant to assess the prognostic value of the “six-and-twelve” model and to compare it to the MESH score and other models such as the Cancer of the Liver Italian Program (CLIP) score, or the up-to-seven criteria used in the subclassifications of intermediate-stage HCC. The CLIP and the MESH scores provided better prognostic information in previous studies[11, 12] compared with other systems. It is also noteworthy that we get the same kind of result, which enhances the whole results. In striving for simplification, we removed the table 6. In the same time, the main text has been revised (page 6).

Table 2: the MESH score

Prognostic factors	Scores	
	0	1
Tumor burden	Within Milan criteria	Beyond Milan criteria
Vascular invasion or metastasis	Absent	Present,
Child-Pugh class	5	≥6
Performance status	0-1	≥2
Serum alpha-fetoprotein level	<20 ng/ml	≥20 ng/ml
Serum alkaline phosphatase level	<200 IU/L	≥ 200 IU/L

References:

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