HEPATOLOGY

The critical issue of hepatocellular carcinoma restaging: which is the best tool available?

Journal:	*Hepatology*
Manuscript ID	HEP-17-2454
Wiley - Manuscript type:	Rapid Communication
Date Submitted by the Author:	13-Dec-2017

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Keywords:	

TITLE PAGE

TITLE:

The critical issue of hepatocellular carcinoma restaging: which is the best tool available?

SHORT TITLE: RESTAGING HCC PATIENTS

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GRANT SUPPORT; None

ABBREVIATIONS

ITA.LI.CA, Italian Liver Cancer

HCC, hepatocellular carcinoma

BCLC, Barcelona Clinic Liver Cancer

CLIP, Cancer of the Liver Italian Program

HKLC, Hong Kong Liver Cancer

BSC, best supportive care

LT, liver transplantation=LT

LR, liver resection

ABL, ablation

IAT, intra-arterial therapy

SOR, Sorafenib

OTHER, other treatments

ECOG PS, Eastern Cooperative Oncology Group performance status

CPS, Child Pugh Score

ALBI, albumin-bilirubin

CR, complete response

PR, partial response

SD, stable disease

PD, progressive disease

AIC, Akaike Information Criterion

C, Concordance

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DISCLOSURES: None

WRITING ASSISTANCE: none

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ABSTRACT

Prognostic assessment in patients with hepatocellular carcinoma (HCC) remains controversial at the time of diagnosis and becomes even more complex at the time of restaging, when new variables have to be considered. The aim of the current study was to evaluate the prognostic utility of re-staging patients before proceeding with a 2nd line treatment for HCC.

The ITA.LI.CA prospective database 2008-2015 (n=3,623) was used to identify 1,196 HCC patients who had a complete restaging at the time of deciding the 2nd line therapy.

The performance of the ITA.LI.CA prognostic score at restaging was compared with that of the BCLC, HKLC, and CLIP systems. A multivariable Cox survival analysis was performed to identify baseline, restaging or dynamic variables able to improve the predictive performance of prognostic systems. At restaging, 37.5% of patients had a more advanced tumour stage, 35.3% were stable, while 27.2 % had a down-staged tumor compared with baseline. At restaging, the ITA.LI.CA scoring system demonstrated the best prognostic performance (c-index 0.707) among all systems examined. On multivariable analysis, progressive disease after the first treatment (hazard ratio [HR] 2.07, p<0.001), MELD at restaging (HR 1.06, p<0.001), and nonsurgical 2nd line treatment (HR from 2.93 with ablation to 6.30 with best supportive care) increased the discriminatory ability of the ITA.LI.CA prognostic score (c-index = 0.769). In conclusion, although the ITA.LI.CA score demonstrated the best prognostic performance at restaging, other variables should be considered to improve the prognostic assessment of patients at the time of 2nd treatment for HCC.

Keywords. Hepatocellular carcinoma; restaging; prognostic system; 2° line treatments

INTRODUCTION

Prognostic assessment in patients with hepatocellular carcinoma (HCC) is extremely complex, as it depends on several factors including tumor stage, liver functional reserve, patient general conditions, and treatment choice.[1] Although the Barcelona Clinic Liver Cancer (BCLC) classification has been endorsed by American and European guidelines for HCC management,[2,3] its prognostic performance is usually lower than that of other prognostic scores, such as the Cancer of the Liver Italian Program (CLIP).[4] Moreover, the BCLC classification is often not followed in the Eastern world, where other systems have been created, such as the Hong Kong Liver Cancer (HKLC) staging system.[5] Recently, our group proposed the Italian Liver Cancer (ITA.LI.CA) prognostic system, which had been developed in a large Italian cohort of HCC patients and validated both in an independent Italian data set as well as in a large population of patients from Taiwan.[6] Of note, the ITA.LI.CA score showed the best prognostic performance compared with other available HCC prognostic systems, and other investigators have independently confirmed its superiority.[7]

Prognostic staging can be even more complicated in HCC patients who have received a first-line treatment and are being restaged. In fact, prognostic assessment of already treated patients is more difficult than that of naïve patients for several reasons. First, radiological restaging is technically more demanding due to the need to evaluate the extension of only remnant viable tumor areas.[8] Second, dynamic variables such as the response to first-line treatment, changes of tumor and liver function from baseline, and the time elapsed from treatment could also have a prognostic role.[9,10]

To date, all available prognostic systems have been developed and validated only in treatment naïve HCC populations and the efficiency of these systems in restaging patients at the time of the 2nd therapeutic decision remain unsettled, In fact, to the best of our knowledge, no study has compared the performance of prognostic systems in this setting. The aim of the study was, therefore, to evaluate the prognostic utility of re-staging patients before proceeding with a 2nd line

treatment for HCC. In addition, we sought to define the prognostic system that performed the best in the restaging setting. Lastly, we examined whether the prognostic performance of available systems improves with the addition of other independent prognostic variables available only at the time of restaging.

METHODS

Study group

The ITA.LI.CA database includes prospectively collected data of 6,669 consecutive patients with HCC managed in 24 Italian institutions between January 1987 and March 2015. Beginning in 2008, the ITA.LI.CA database compilation changed, requiring the registration of all parameters not only at baseline (cancer diagnosis) but also at the time of each treatment. Among the 3,263 patients enrolled in the ITA.LI.CA database from January 2008, we selected 1559 (47.8%) who were evaluated and managed since HCC diagnosis by the same ITA.LI.CA centre. Because of the purpose of this study, 322 patients who received only best supportive care (BSC) since the time of HCC diagnosis were excluded. To avoid any bias in the analysis, 12 patients who underwent liver transplantation (LT) as first-line treatment for HCC were also excluded. The remaining 1,225 patients had 2nd line staging and treatment after a first non-transplant treatment. After exclusion of 29 cases who did not have complete follow-up data or were lost to follow-up, a total of 1,196 patients were finally included in the final analytic cohort.

In the final cohort, 201 patients underwent liver resection (LR), 481 ablation procedures (ABL), 495 intra-arterial therapy (IAT), 51 Sorafenib (SOR), and 31 other treatments (OTHER) as first-line therapy.

The institutional review boards of the participating institutions approved the study. According to Italian law, no patient approval was needed for this retrospective study. Patients gave written consent for every diagnostic and therapeutic procedure, as well as for the use of data for

medical purposes. Informed consent was obtained as usual for medical, surgical, and radiological treatments, but not specifically for patient data to be used in this retrospective study.

Clinical and treatment-related variables, such as age, sex, etiology of underlying liver disease, presence of ascites and hepatic encephalopathy, main serological parameters (total bilirubin, creatinine, prothrombin time and/or INR, α-fetoprotein, albumin, sodium), tumor radiological characteristics (number and size of lesions, vascular invasion, extra-hepatic metastases), Eastern Cooperative Oncology Group performance status (ECOG PS) and main treatment strategy were recorded. ECOG PS was prospectively assessed by clinicians of the ITA.LI.CA group. For each patient, the following composite variables were also calculated and recorded: Child-Pugh score (CPS), albumin-bilirubin (ALBI) grade, BCLC stage, HKLC stage, CLIP score, ITA.LI.CA score.[5,6,11-14] Tumor number and size, major vascular invasion and patterns of metastatic diffusion were assessed by computer tomography or magnetic resonance imaging. Specifically, vascular invasion was classified as intra- and extra-hepatic, according to the HKLC staging system criteria.[5] Intrahepatic vascular invasion was defined as the neoplastic invasion of intrahepatic branches of the portal vein, left or right portal vein, or main hepatic veins invasion. Extra-hepatic vascular invasion included main portal trunk and inferior vena cava involvement.

In considering the response to the first-line treatment, patients were classified into 4 subgroups according to mRECIST criteria:[8] complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Patients with complete response (CR) were further stratified into two subgroups: early tumor recurrence (≤2 years after fist line therapy) and late recurrence (>2 years).

Statistical analysis

Baseline characteristics were examined based on frequency distribution; continuous data were presented as median values (interquartile range) unless indicated otherwise. Univariate comparisons were assessed using Student's t test, Wilcoxon rank-sum test, or chi-squared test as

appropriate. Missing data relative to study covariates involved less than 10% of patients in a all circumstances. Thus, missing values were imputed using the maximum likelihood estimation method.[15] Overall survival was defined from the date of restaging of HCC to the date of death, last follow-up evaluation, or data censoring (31 December 2015). Kaplan—Meier survival curves were used to estimate median overall survival and 1-, 3-, 5- and 10-y overall survival in the main study group (n=1,196) and in relevant subgroups. The survival curves were also stratified according to ITA.LI.CA prognostic system quartiles, and main BCLC, HKLC, and CLIP stages. The log-rank test was used to compare differences in survival curves. To graphically describe the prognostic performance of the ITA.LI.CA score and to test its prognostic calibration at restaging, patients were divided into four subgroups corresponding to the original quartiles at the 25th, 50th, 75th percentiles of the risk score in the paper from Farinati et al.[6] Thus, quartile 1 coincided with ITA.LI.CA score ≤1, quartile 2 with score 2-3, quartile 3 with score 4-5, and quartile 4 with score >5.

To compare the prognostic performance of the ITA.LI.CA prognostic score with that of other systems the Akaike Information Criterion (AIC) was used, as well as the Concordance (C)-index and the test for trend chi-square.[16,17] The lower the AIC value, the higher the discriminatory ability of the staging system. The higher the C-index and the test for trend chi-square, the higher the discriminatory ability and monotonicity of gradients of the staging system. To assess if the ITA.LI.CA score performes better than other systems we used the likelihood ratio test.

Univariable and multivariable Cox survival analyses were performed to identify baseline, restaging or dynamic variables able to improve the performance of main prognostic staging systems (BCLC, HKLC, CLIP, and ITA.LI.CA). In all analyses, a two-tailed P-value <0.05 was considered statistically significant. All analyses were performed in JMP® 9.0.1 package (1989–2010 SAS Institute Inc.), STATA13.0 (Copyright 1985-2013 StataCorp LP), and R.app GUI 1.51 (S. Urbanek & H.-J. Bibiko, © R Foundation for Statistical Computing, 2012).

RESULTS

Characteristics of the study group

The characteristics of the population at the time of initial HCC presentation and at the time of restaging are reported in Table 1. The majority of patients (75.5%) were male, and the average age was 69 years. The main aetiological risk factors for HCC were hepatitis C (61%) followed by alcoholic consumption (34%).

The median time between the first HCC presentation and clinical-radiological restaging was 102 months. The comparison between baseline characteristics and those at the time of restaging showed a statistically significant worsening of both general conditions (e.g. ECOG PS) and liver function. In particular, a Child-Pugh class migration was noted from class A to B or C (p=0·001), with about 28% of patients being CHILD B-C at restaging versus 23% at baseline. The median MELD of 8 (8-11) remained stable, but its distributions at baseline and at restaging were different (p<0·001) due to more patients (29·5% vs. 25·3 %) having MELD >10 at restaging (p=0·014). The distributions of ALBI grades also slightly worsened (p=0·06).

Regarding tumour burden, while the size of the largest lesion was lower (2·5 vs. 3 cm, p<0·001), there was an increase in multinodular cancers (28·4% vs. 18·5%, p<0.001) and vascular invasion (11·4% vs. 4·6%, p<0·001) at the time of restaging. Furthermore, a rise in median AFP level (74 vs. 20 ng/mL, p<0·001) and metastatic disease (7·6% vs. 2·0%, p<0·001) was noted at restaging.

Patients more frequently received radical therapies to treat the first HCC (i.e. LR 16·8 %, and ABL 35%) compared with the disease at restaging, which was treated with IAT, SOR or BSC in 73% of patients (p<0·001). The patient distributions for each HCC prognostic system are shown in Supplementary Table 1. Of note, there was an increase in the proportion of patients who had advanced stages of disease at restaging. For instance, the proportion of patients who had an ITA.LI.CA score of 5 doubled (from 6·2% to 11·6%), while the proportion of patients with an ITA.LI.CA score ≥ 9 increased from 0·8 to 4·9%. In contrast, the proportion of patients with score 1

at restaging decreased from 18·4% to 13·1%, and that of patients with a score 2 from 22·2% to 15·7%.

Given the general trend toward a progression of cancer staging from baseline to restaging, we sought to better understand how patients migrated using the ITA.LI.CA system.

Table 2 demonstrates patient migration according to the ITA.LI.CA tumour staging and functional score. As shown in the supplementary Tables 2-3, tumor staging included main tumor variables (size and number of nodules, macroscopic vascular invasion, and metastases), while functional score included main patient- and liver function- variables (i.e. ECOG PST and Child Pugh score).

At restaging, 37·5% of patients had a worse tumour stage (26% with an up-grade of 1 or 2 stages), 35·3% maintained the same stage and 27·2 % were down staged. Considering the functional stage, there was no migration for 49·1% of patients, while liver function worsened in 40% of cases.

Prognostic performance of different systems

The median follow up time was 34·5 months (31·4 - 35·5). Overall survival at 1-, 3-, 5- and 10- years was 81%, 56%, 41% and 29%, respectively, with a median survival of 42 months (37·6-46·7) (Supplementary Figure 1). To examine which staging system had the best prognostic power, each system was applied to the cohort both at the time of the first HCC diagnosis and at restaging (Supplementary Figures 2-3, Figure 1). The ITA.LI.CA prognostic system had the lowest AIC value among patients (4908·583) and the highest C- index (0·707) at restaging, indicating the best discriminatory ability and monotonicity of gradients (Table 3). The discriminatory ability of ITA.LI.CA system is shown by the best separation of survival curves associated with different prognostic subgroups (Figure 1). There was good calibration of the ITA.LI.CA score at restaging, with the observed and predicted survival curves largely overlapping (Supplementary Figure 4).

Improving the prognostic performance of the ITA.LI.CA prognostic score at restaging

Univariable survival analyses were performed including all clinical variables collected both at the time of HCC diagnosis and at restaging (Supplementary Table 4). The dynamic trend of some relevant variables were also analysed (stated as Δ), showing that not only the final value (at restaging) but also any change in a number of variables during the follow-up period for some parameters had an impact on survival. To test whether these variables and their changes significantly associated with survival improved the prognostic performance of ITA.LI.CA score at restaging, they were included in the multivariate analysis. The final model is shown in Table 4. While no dynamic variable retained an independent prognostic significance, MELD at restaging (HR 1·06, p<0·001), PD after the first treatment (HR 2·07, p<0·001) and nonsurgical treatment after restaging (HR from 2·93 with ABL to 6·30 with BSC) maintained their prognostic independence from the ITA.LI.CA score at restaging. The inclusion of these variables improved the C-index of the ITA.LI.CA prognostic score system (0·707 vs. ITA.LI.CA + additional variables, 0·769).

DISCUSSION

Over the last 20 years, a static and simplistic vision of HCC clinical management has prevailed in international guidelines.[2,3] According to this view, prognostic assessment has been performed using systems/scores based on variables available at the time of diagnosis. In routine clinical practice, these time-independent algorithms are sequentially applied to the patients during the follow-up, considering that most HCC patients have a complex disease history characterized by multiple consecutive treatments, requiring on-going reassessment and restaging. With this in mind, we sought to analyse the prognostic relevance of restaging. Specifically, we explored: 1) whether, how much and how frequently HCC patients change their initial stage after the first-line treatment; 2) whether the performance of the most utilized staging systems changes at restaging after the first-line treatment. Indeed, we demonstrated that the performance of each prognostic system changed compared with the baseline (Table 3). This was largely due to the fact that the oncologic composition of the population modifies over the follow-up with only 35% maintaining a stable disease, while the remainder were down-staged by treatment (about one third) or had a disease progression (Table 2). To date, the concept of down-staging in HCC patients has been exclusively adopted in potential candidates for LT.[18,19] The current study demonstrated that the concept of down-staging can be applied to all HCC patients and is a factor that affects the performance of prognostic system.

Of note, at baseline the prognostic performance of the various systems had a discriminatory power worse than reported in previous studies.[6] The reason may be related to a selection bias. Indeed, according to the design of the study, patients undergoing LT or BSC as initial therapy were excluded, as well as those with early death after the first-line therapy were also excluded, lacking the restaging at the time of the second treatment.

This study also showed that the ITA.LI.CA score[6] had the best prognostic discriminatory power both at the time of initial HCC diagnosis and after primary HCC treatment at the time of

restaging. The difference in predictive ability between ITA.LI.CA and BCLC system (the more utilized in Western countries) is clear comparing Figure 1 with Supplementary Figure 2.

We also found that other variables when included in the ITA.LI.CA staging system could improve the accuracy of this staging system at the time of restaging. For example, deterioration of liver function (i.e. MELD score at restaging) was an independent prognostic factor of prognosis at restaging. This finding is consistent with a recent ITA.LI.CA study from Cabibbo et al.[20] that examined on radically treated HCV-HCC patients. Another relevant variable to be considered at restaging after first-line therapies included progressive disease.[21,22] In turn, these factors were probably surrogate markers of biologically more aggressive tumors. In addition, surgery as second-line therapy was another independent prognostic factor at restaging. Collectively, these data confirm the results of other experiences evaluating prognostic factors in recurrent HCC.[23,24]

In conclusion, patients restaged before receiving a second-line treatment for HCC were not accurately staged using traditional prognostic tools. Among them, the ITA.LI.CA score demonstrated the best discriminatory power in predicting survival both at the time of HCC diagnosis and at restaging. Additional variables, such as MELD score at restaging, response to first-line therapy, and non-surgical therapy as second-line therapy, improved prognostic ability when considered in conjunction with the ITA.LI.CA score.

These data may help better predict prognosis of both patients undergoing the first treatment of HCC and those in need of restaging thereafter. Moreover the importance of selecting patients carefully is getting stronger as new 2nd line therapies for HCC will be soon developed. Therefore using a more accurate prognostic score to predict the clinical response could allow customise the therapeutic options to the patient's clinical features.

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ACKNOWLEDGEMENTS

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Dipartimento di Scienze Mediche e Chirurgiche, Alma Mater Studiorum - Università di Bologna: Maurizio Biselli, Laura Bucci, Paolo Caraceni, Alessandro Cucchetti, Marco Domenicali, Lucia Napoli, Francesca Garuti, Annagiulia Gramenzi, Alessandro Granito, Donatella Magalotti, Giulia Negrini, Fabio Piscaglia, Matteo Ravaioli, Carla Serra, Francesco Tovoli, Federico Ravaioli, Giovanni Marasco; *Dipartimento di Scienze Chirurgiche e Gastroenterologiche, Università di Padova:* Giulia Peserico, Filippo Pelizzaro, Paola Todesca, Caterina Pozzan; *Dipartimento di Medicina Interna, Unità di Gastroenterologia, IRCCS-Azienda Ospedaliera Universitaria San Martino-IST, Università di Genova:* Matteo Brunacci, Alessandro Moscatelli, Gaia Pellegatta, Vincenzo Savarino; *Unità Operativa di Chirurgia, Policlinico S. Marco, Zingonia:* Paolo Del Poggio, Stefano Olmi; *Unità di Medicina Interna e Gastroenterologia, Complesso Integrato Columbus, Università Cattolica di Roma, Roma:* Nicoletta de Matthaeis; *Unità Operativa di Medicina, Azienda Ospedaliera Bolognini, Seriate, Italia:* Claudia Balsamo, Elena Vavassori; *Unità Operativa di Gastroenterologia, Ospedale Belcolle, Viterbo:* Paola Roselli, Valentina Lauria, Giorgio Pelecca; *Unità Operativa di Medicina Protetta, Ospedale Belcolle, Viterbo:* Serena Dell'Isola, Anna Maria Ialungo, Elena Rastrelli; *Dipartimento Biomedico di Medicina Interna e Specialistica, Unità di Gastroenterologia, Università di Palermo:* Calogero Cammà, Marcello Maida, Andrea Costantino; *Dipartimento Biomedico di Medicina Interna e Specialistica, Unità di Medicina Interna 2, Azienda Ospedaliera Ospedali Riuniti Villa Sofia-Cervello, Palermo:* Andrea Affronti - Emanuele Orlando - Maria Rosa Barcellona.; *Ospedale Regionale di Bolzano, Unità di Gastroenterologia, Bolzano: Andrea Mega; Unità di Medicina Interna e Gastroenterologia, Policlinico Gemelli, Università Cattolica di Roma, Roma:* Emanuele Rinninella; *Unità Operativa Gastroenterologia e Malattie del Ricambio, Azienda Ospedaliero-Universitaria Pisana, Pisa:* Valeria Mismas; *Dipartimento di Medicina Interna; Ospedale per gli Infermi di Faenza, Faenza:* Anna Chiara Dall'Aglio, Vittoria Bevilacqua, Andrea Casadei Gardini, Giorgio Ercolani, Erica Fiorini, Arianna Lanzi, Federica Mirici Cappa ; *Unità di Malattie Infettive ed Epatologia, Azienda Ospedaliero-Universitaria di Parma*: Elisabetta Biasini, Gabriele Misaale; *Department of Clinical Medicine and Surgery, Unit of Gastroenterology and Hepatology, University of Naples, "Federico II", Naples, Napoli:* Maria Guarino, Anna Vitiello; *Clinica di Gastroenterologia, Università Politecnica delle Marche, Ancona:* Alessio Ortolani ed Alba Kostandini; *Unità di Gastroenterologia, Ospedale Sacro Cuore Don Calabria, Negrar:* Maria Chiaramonte, Fabiana Marchetti, Matteo Valerio; *Dipartimento di Medicina Diagnostica e Prevenzione, Azienda ospedaliero-universitaria di Bologna, Unità Operativa di Radiologia:* Alberta Cappelli, Rita Golfieri, Cristina Mosconi, Matteo Renzulli; *Dipartimento di Medicina Clinica e Chirurgia, Unità di Epato-Gastroenterologia, Università di Napoli "Federico II", Napoli:* Piero Coccoli, Marco Sanduzzi Zamparelli; *Medicina Interna ed Epatologia, Dipartimento di Medicina Sperimentale e Clinica – Università di Firenze, Firenze* **:** Andrea Lorenzo Inghilesi e Sami Aburas.

TABLES

Table 1. Patient characteristics at baseline and at restaging.

Comparison of variables between the first HCC presentation and at restaging				
		At the time of 1st HCC presentation	**At restaging**	**P value**
Variables		**Number (%) Median(IQR)**	**Number (%) Median(IQR)**	
Gender	Female	293 (24.50)		
	Male	903 (75.5)		
Age (years)	Median	69 (62-75)		
Aetiology				
	Alcohol	407 (34)		
	HBsAg	161 (13.5)		
	anti-HCV	727 (61)		
Time from the 1st to 2nd clinical exam (months)	Median	10.2 (5-21)		
ECOG PS	0	987 (82.5)	729 (61.0)	<0.001
	1	172 (14.4)	353 (29.5)	
	2	31 (2.6)	83 (6.9)	
	> 2	6 (0.5)	31 (2.6)	
MELD	Median	9 (8-11)	9 (8-11)	<0.001
	> 10	303 (25.3)	352 (29.4)	0.014
Child Pugh class	A	922 (77)	865 (72.3)	<0.001
	B	267 (22.5)	306 (25.6)	
	C	7(0.5)	25 (2.1)	
ALBI grades	1	268 (22.4)	224 (18.7)	0.006
	2	880 (73.6)	896 (74.9)	
	3	48 (4)	76 (6.4)	
Diameter of the largest lesion (cm)	Median	3 (2-4.1)	2.5 (1.8-3.79)	<0.001
Nodular pattern	Single lesion	682 (57)	578 (48.3)	<0.001
	Up to 3 lesions	293 (24.5)	279 (23.3)	
	> 3 lesions	221 (18.5)	339 (28.4)	
Vascular invasion (VI)	Intrahepatic	32 (2.6)	72 (6)	<0.001
	Extrahepatic	25 (2.0)	65 (5.4)	
AFP (ng/ml)	Median	20 (6-442)	74 (8- 606)	<0.001
Metastatic disease	yes	24 (2.0)	91 (7.6)	<0.001
Treatment administration	LT	-	41 (3.4)	<0.001
	LR	201 (16.8)	37 (3.1)	
	ABL	418 (35)	164 (13.7)	
	IAT	495 (41.4)	446 (37.3)	
	SOR	51 (4.3)	253 (21.2)	
	Other	31 (2.5)	79 (6.6)	
	BSC	-	176 (14.7)	
Response to the 1st treatment	Late recurrence	239 (20)		
	Early recurrence	382 (32)		
	PR	358 (30)		
	SD	84 (7)		
	PD	133 (11)		

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; MELD, Model for End Stage Liver disease; ALBI= albumin-bilirubin; AFP, alpha-fetoprotein; LT, liver transplantation; LR, liver resection; IAT, Intra Arterial Treatment; SOR, Sorafenib; BSC, Best Supportive Care; PR, Partial Response; SD, Stable Disease,; PD, Progressive Disease

Table 2. Stage Migration within ITA.LI.CA tumour staging and functional score

ITA.LI.CA tumour staging migration	**Number of points migrated**	**Number (%) Median (IQR)**
Down-staging	-5	3 (0.2)
	-4	8 (0.7)
	-3	26 (2.2)
	-2	74 (6.2)
	-1	214 (17.9)
	total	325(27.2)
Stable disease	0	**422 (35.3)**
Up-staging	1	191 (16)
	2	120 (10)
	3	82 (6.8)
	4	36 (3)
	5	20 (1.7)
	total	449 (37.5)
ITA.LI.CA functional score migration		
Down-staging	-3	2 (0.2)
	-2	10 (0.8)
	-1	118 (9.9)
	total	130(10.9)
Stable disease	0	588 (49.1)
Up-staging	1	361 (30.2)
	2	92 (7.7)
	3	14 (1.2)
	4	10 (0.8)
	5	1 (0.1)
	total	478 (40)

Abbreviations: ITA.LI.CA, Italian Liver Cancer

Table 3. Prognostic ability of different prognostic systems at baseline and at restaging.

Prognostic System	AIC	C-index	χ^2 test	lr test, p value
ITA.LI.CA at restaging	**4908.583**	**0.7071**	**213.08**	-
HKLC at restaging	4922.160	0.6900	267.25	23.80, <0.001
CLIP at restaging	4960.322	0.6788	168.48	68.05, <0.001
BCLC at restaging	4976.321	0.6659	113.72	86.07, <0.001
HKLC baseline	5054.732	0.6213	116.94	156.37, <0.001
ITA.LI.CA baseline	5071.975	0.6092	89.27	171.58, <0.001
BCLC baseline	5079.535	0.6049	52.48	189.35, <0.001
CLIP baseline	5076.824	0.5839	49.60	184.55, <0.001

In each column have been reported the Akaike Information Criterion (AIC) as first value, the C-index as second value, and the test for trend chi-square as third value. The lower the AIC value, the higher the discriminatory ability of the prognostic system. The higher the c-index and the test for trend chi-square, the higher the discriminatory ability and monotonicity of gradients of the prognostic system.

In addition, in each column the ITA.LI.CA score was compared with other systems by using the likelihood ratio test.

Abbreviations: AIC, Akaike Information Criterion; C, concordance; χ^2, chi square**;** lr, likelihood ratio; ITA.LI.CA, Italian Liver Cancer; HKLC, Hong Kong Liver Cancer; CLIP, Cancer Liver Italian Program; BCLC, Barcelona Clinic Liver Cancer.

Table 4. Variables improving the prognostic performance of the ITA.LI.CA score at restaging: multivariable survival analysis.

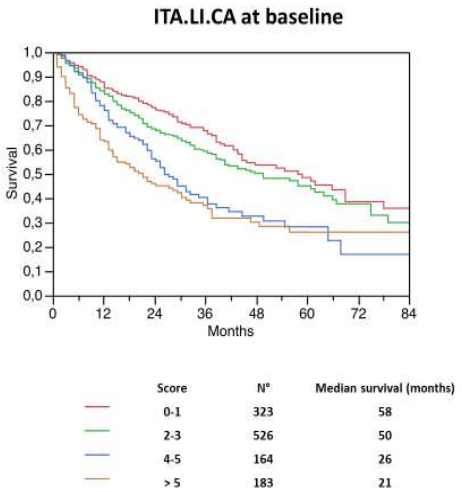
Variables		HR	95% CI	lr χ^2	p Value
MELD	Restaging	1.06	1.03 – 1.08	18.46	**<0.001**
Response to first treatment	Late recurrence	---		40.48	
	PR	0.94	0.68 – 1.28		0.682
	Early recurrence	1.18	0.86 – 1.60		0.296
	SD	1.12	0.71 – 1.76		0.620
	PD	2.07	1.43 – 3.01		**<0.001**
Treatment after restaging	LT	---		54.03	
	LR	2.10	0.85 – 5.45		0.110
	ABL	2.93	1.47 – 6.68		0.001
	IAT	3.66	1.90 – 8.20		**<0.001**
	SOR	5.57	2.87 – 12.52		**<0.001**
	Other	5.70	2.78 – 13.29		**<0.001**
	BSC	6.30	3.17 – 14.36		**<0.001**
ITA.LI.CA score	Restaging	1.18	1.13 – 1.23	57.52	**<0.001**

Abbreviations: HR, hazard ratio; CI, confidence interval; lr χ^2, likelihood ratio chi square; MELD= Model for End Stage Liver disease, ALBI= albumin-bilirubin, LT, liver transplantation; LR, liver resection; IAT, Intra Arterial Treatment; SOR, Sorafenib; BSC, Best Supportive Care; PR, Partial Response; SD, Stable Disease,; PD, Progressive Disease;

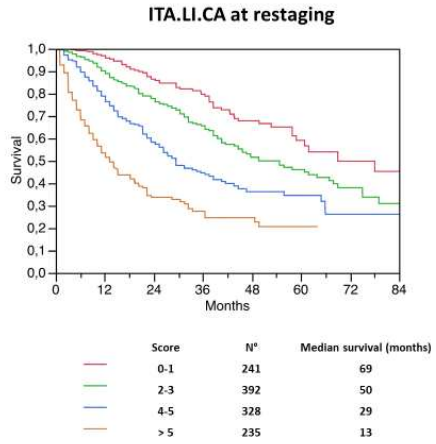
LEGEND OF FIGURES

Figure 1. Survival curves according to ITA.LI.CA score quartiles at baseline (A), and at restaging (B).

A



B



Supplementary Table 1. Distribution of patients according to stages of different scoring systems.

Classification of patients according to different staging systems		At the time of 1st HCC staging	At restaging	P Value
Scoring System	Stages /points	Number (%)	Number (%)	
BCLC CLASSIFICATION	0	115 (9.6)	117 (9.8)	0.001
	A	573 (47.9)	414 (34.6)	
	B	246 (20.6)	110 (9.2)	
	C	254 (21.2)	516 (43.1)	
	D	8 (0.7)	39 (3.3)	
CLIP SCORE	0	406 (33.9)	297 (24.8)	<0.001
	1	473(39.5)	454 (38)	
	2	228 (19.1)	288 (24.1)	
	3	74 (6.2)	120 (10)	
	4	14 (1.2)	31 (2.6)	
	>5	1 (0.1)	6 (0.5)	
HKLC STAGING	I	560 (46.8)	414 (34.6)	<0.001
	II a	279 (23.3)	291 (24.3)	
	II b	168 (14.1)	169 (14.1)	
	III a	40 (3.3)	54 (4.5)	
	III b	76 (6.4)	58 (4.9)	
	IV a	29 (2.4)	75 (6.3)	
	IV b	12 (1)	30 (2.5)	
	V a	17 (1.4)	31 (2.6)	
	V b	15 (1.3)	74 (6.2)	
ITA.LI.CA SCORE	0	103 (8.6)	84 (7.0)	<0.001
	1	220 (18.4)	157 (13.1)	
	2	266 (22.2)	188 (15.7)	
	3	260 (21.7)	204 (17.1)	
	4	164 (13.7)	189 (15.8)	
	5	74 (6.2)	139 (11.6)	
	6	52 (4.4)	80 (6.7)	
	7	38 (3.2)	63 (5.3)	
	8	10 (0.8)	34 (2.8)	
	≥9	9 (0.8)	58 (4.9)	

Abbreviations: ITA.LI.CA, Italian Liver Cancer; HKLC, Hong Kong Liver Cancer; CLIP, Cancer Liver Italian Program; BCLC, Barcelona Clinic Liver Cancer.

Supplementary Table 2. The ITA.LI.CA tumor staging. [6]

Stages / **Variables**	**0**	**A**		**B1**		**B2**		**B3**		**C**
Diameter of the largest nodule (cm)	≤ 2	≤ 3	2-5	3-5	> 5	> 5	≤ 5	> 5	Any	Any
N° nodules	1	2-3	1	2-3	1	2-3	> 3	> 3	Any	Any
Vascular invasion or metastases	no	no	no	no	no	no	No	no	Intrahep.	Extrahep.

Abbreviations: ITA.LI.CA, Italian Liver Cancer; Intrahep., intra-hepatic vascular invasion, no metastases; Extrahep., extra-hepatic vascular invasion (main portal or caval veins trunk) or metastases.

Supplementary Table 3. The ITA.LI.CA prognostic system. [6]

Variabies		Points
ITA.LI.CA Tumor Staging		
	0	***0***
	A	**1**
	B1	**2**
	B2	**3**
	B3	**4**
	C	**5**
ITA.LI.CA Functional Score		
CPS score	5	**0**
	6	**1**
	7	**1**
	8	**2**
	9	**2**
	10-15	**3**
ECOG PST	0	**0**
	1	**1**
	2	**1**
	3-4	**3**
AFP (ng/ml)		
	≤ 10	**0**
	> 10	**2**

Abbreviations: ITA.LI.CA, Italian Liver Cancer; AFP, alpha-fetoprotein; CPS, Child-Pugh score; ECOG= Eastern Cooperative Oncology Group , PST, performance status

Supplementary Table 4. Univariable survival analysis

Variables		**HR**	**95% CI**	**p Value**
Age	Baseline	1.00	0.99 - 1.01	0.550
	Restaging	1.00	0.99 - 1.00	0.778
Gender	Female	0.81	0.65 - 1.00	**0.055**
Aetiology	HCV	0.97	0.80 - 1.15	0.725
	HBV	1.4	0.89 - 1.45	0.297
	Alcohol	0.99	0.82 - 1.19	0.927
ECOG PS Baseline	0	---		
	1	1.58	1.26 - 1.98	**<0.001**
	2	1.84	1.17 – 2.89	**0.008**
	>2	2.77	1.14 – 6.70	0.024
ECOG PS Restaging	0	---		
	1	1.68	1.39 – 2.04	**<0.001**
	2	3.70	2.74 - 4.99	**<0.001**
	>2	4.23	2.65 – 6.76	**<0.001**
Child Pugh Baseline	A	---		
	B	1.42	1.16 - 1.74	**0.001**
	C	2.94	1.31 - 6.59	**0.009**
Child Pugh Restaging	A	---		
	B	1.74	1.44 - 2.11	**<0.001**
	C	4.39	2.75 - 6.99	**<0.001**
ALBI grade Baseline	1	---		
	2	1.17	0.94 - 1.44	0.149
	3	1.62	1.04 - 2.53	**0.031**
ALBI grade Restaging	1	---		
	2	1.50	1.17- 1.92	**0.001**
	3	2.86	1.95 - 4.19	**<0.001**
MELD	Baseline	1.06	1.03 - 1.09	**<0.001**
	Restaging	1.11	1.08 – 1.13	**<0.001**
Largest diameter (cm)	Baseline	1.11	1.07 – 1.14	**<0.001**
	Restaging	1,12	1.09 – 1.14	**<0.001**
Nodular pattern Baseline	Single	---		

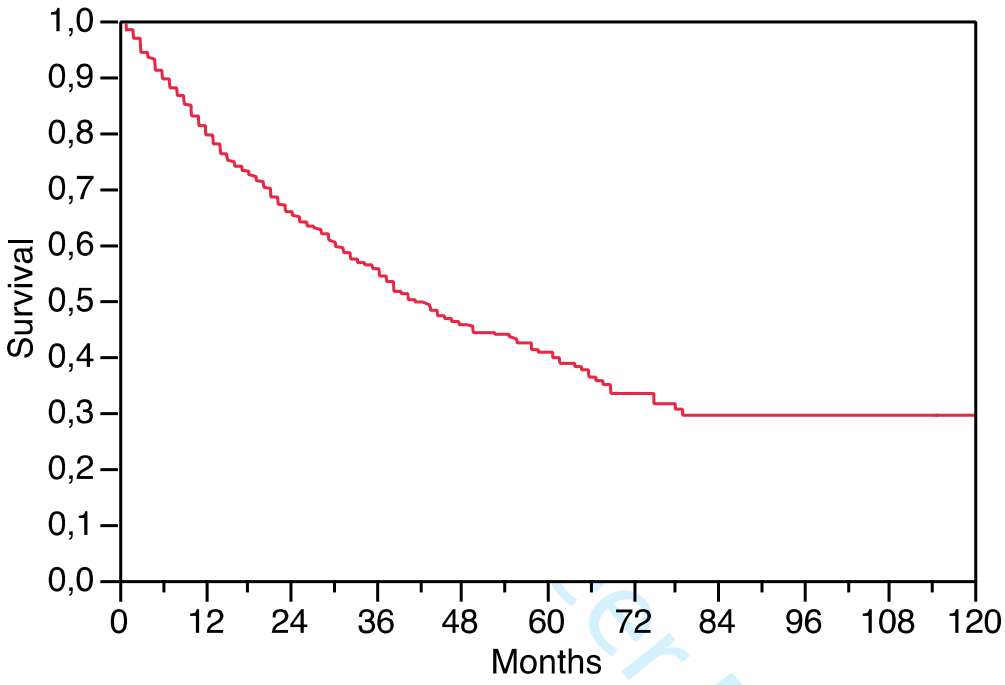
	Up to 3 lesions	1.18	0.95 – 1.46	0.131
	> 3 lesions	1.81	1.46 – 2.24	**<0.001**
Nodular pattern Restaging	Single	---		
	Up to 3 lesions	1.21	0.96 – 1.53	0.103
	> 3 lesions	2.54	2.08 – 3.11	**<0.001**
VI Baseline	No VI	---		
	Intra hepatic VI	1.88	1.15 – 3.05	**0.011**
	Extra hepatic VI	2.40	1.47 – 3.89	**<0.001**
VI Re Staging	No VI	---		
	Intra hepatic VI	2.53	1.83 – 3.49	**<0.001**
	Extra hepatic VI	3.10	2.24 – 4.28	**<0.001**
Metastatic disease	Baseline	4.13	2.53 – 6.72	**<0.001**
	Restaging	3.17	2.41 – 4.16	**<0.001**
Log e AFP	Baseline	1.22	1.11 – 1.33	**<0.001**
	Restaging	1.33	1.21 – 1.46	**<0.001**
Treatment Baseline	LR	---		
	ABL	0.77	0.59 – 1.00	0.059
	IAT	0.99	0.77 – 1.27	0.947
	SOR	2.71	1.81 – 4.06	**<0.001**
	Other	1.58	0.92 – 2.70	0.091
Response to first treatment	Late recurrence	---		
	PR	1.15	0.86 – 1.51	0.332
	Early recurrence	1.22	0.93 – 1.61	0.134
	SD	1.90	1.28 – 2.79	**0.001**
	PD	3.88	2.86 – 5.28	**<0.001**
Treatments after Restaging	LT	---		
	LR	1.85	0.74 – 4.62	0.185
	ABL	2.50	1.18 – 5.24	**0.016**
	IAT	3.30	1.60 – 6.76	**0.001**
	SOR	7.13	3.46 – 14.71	**<0.001**
	Other	11.31	5.33 – 23.99	**<0.001**
	BSC	10.80	5.17 – 22.40	**<0.001**
Δ ITA.LI.CA tumor staging		1.53	1.28 – 1.83	**<0.001**

Δ diameter		1.06	1.02 – 1.09	**0.001**
Δ number		1.05	1.02 – 1.08	**<0.001**
Δ AFP		1.06	0.98 – 1.15	0.129
Δ ITA.LI.CA functional score		1.37	1.24 – 1.50	**<0.001**
Δ MELD		1.11	1.07 – 1.14	**<0.001**
Δ ALBI		1.23	1.05 – 1.44	0.010
CHILD migration *		1.81	1.39 – 2.36	**<0.001**
Follow up > 1 year		0.85	0.71 – 1.01	0.077

Abbreviations: HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MELD, Model for End Stage Liver disease; ALBI= albumin-bilirubin; VI, vascular invasion; AFP, alpha-fetoprotein; LT, liver transplantation; LR, liver resection; IAT, Intra Arterial Treatment; SOR, Sorafenib; BSC, Best Supportive Care; PR, Partial Response; SD, Stable Disease,; PD, Progressive Disease; Δ, difference between the value of the variable at restaging and that at baseline-

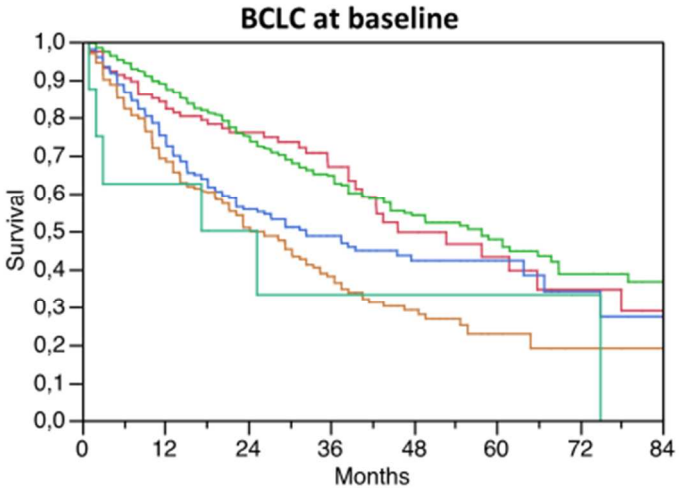
* from Child A to B or C.

Supplementary Figure 1. Survival Curve after restaging.



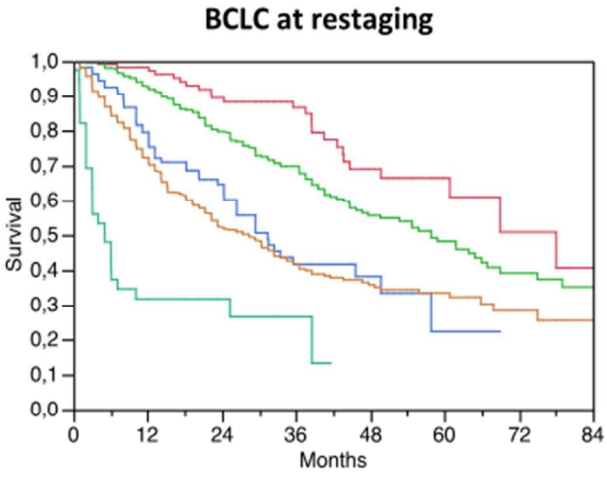
Supplementary Figure 2. Survival curves according to BCLC staging system at baseline (A), and at restaging (B).

A



Stages	N°	Median survival (months)
0	115	46
A	573	58
B	246	32
C	254	34
D	8	21

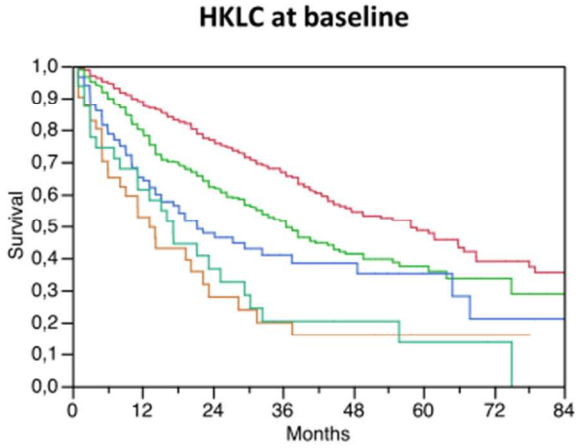
B



Stages	N°	Median survival (months)
0	117	78
A	414	58
B	110	31
C	516	28
D	39	5

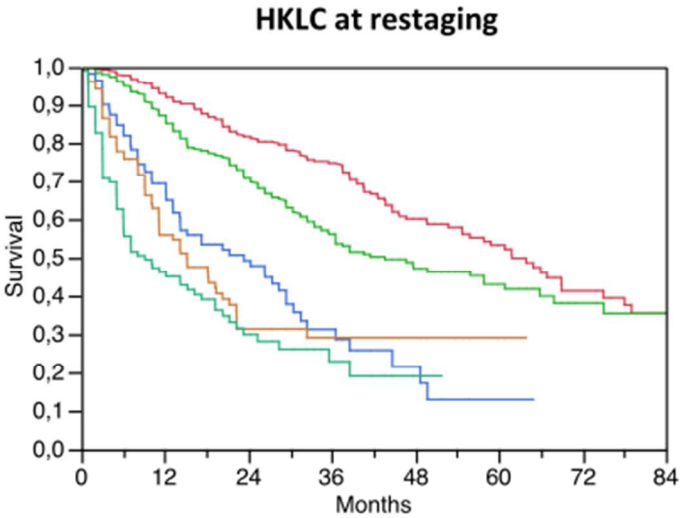
Supplementary Figure 3. Survival curves according to HKLC staging system at baseline (A), and at restaging (B).

A



Stages	N°	Median survival (months)
I	560	58
II	447	37
III	116	21
IV	41	13
V	32	17

B



Stages	N°	Median survival (months)
I	414	62
II	460	44
III	112	23
IV	105	15
V	105	9

Supplementary figure 4. Calibration of ITA.LI.CA score quartiles at restaging.