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Prognosis of Untreated Hepatocellular Carcinoma

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The prognosis of untreated patients with hepatocellular carcinoma (HCC) is heterogeneous, and survival data were mainly obtained from control arms of randomized studies. Clinical practice data on this topic are urgently needed, so as to help plan studies and counsel patients. We assessed the prognosis of 600 untreated patients with HCC managed by the Italian Liver Cancer Group. Prognosis was evaluated by subdividing patients according to the Barcelona Clinic Liver Cancer (BCLC) classification. We also assessed the main demographic, clinical, and oncological determinants of survival in the subgroup of patients with advanced HCC (BCLC C). Advanced (BCLC C: n = 138; 23.0%) and end-stage HCC (BCLC D; n = 210; 35.0%) represented the majority of patients. Overall median survival was 9 months, and the principal cause of death was tumor progression (n = 279; 46.5%). Patients' median survival progressively and significantly decreased as BCLC stage worsened (BCLC 0: 38 months; BCLC A: 25 months; BCLC B: 10 months; BCLC C: 7 months; BCLC D: 6 months; $P < 0.0001$). Female gender (hazard ratio [HR] = 0.55; 95% confidence interval [CI] = 0.33-0.90; $P = 0.018$), ascites (HR = 1.81; 95% CI = 1.21-2.71; $P = 0.004$), and multinodular (>3) HCC (HR = 1.79; 95% CI = 1.21-2.63; $P = 0.003$) were independent predictors of survival in patients with advanced HCC (BCLC C). *Conclusion:* BCLC adequately predicts the prognosis of untreated HCC patients. In untreated patients with advanced HCC, female gender, clinical decompensation of cirrhosis, and multinodular tumor are independent prognostic predictors and should be taken into account for patient stratification in future therapeutic studies. (HEPATOLOGY 2015;61:184-190)

Hepatocellular carcinoma (HCC) is a highly malignant tumor with an incidence/mortality ratio close to 1.0.[1,2] HCC surveillance programs are associated with improved patient survival as a result of an increased proportion of patients diagnosed with early-stage disease—and therefore more likely to be amenable to curative treatments.[3-5] However, the uptake of screening and surveillance programs in clinical practice remains poor, with the 1-year survival rate less than 50% for patients diagnosed with HCC in the general population, a figure mainly resulting from large tumoral burden at diagnosis in most patients and therefore low likelihood of candidacy to curative treatments.[6-9] Indeed, less than 30% of patients diagnosed with HCC in the United States received any treatment in the largest published series reporting this figure, and, although this finding may be related to diagnoses at an advance stage, even the treatment rate for patients with early HCC was likewise disappointingly low.[10,11]

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; HR, hazard ratio; ITA.LI.CA, Italian Liver Cancer; PS, performance status; SOR, sorafenib; TAM, tamoxifen..

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Survival figures in untreated patients with HCC derived from everyday clinical practice are useful for evaluating the natural history of disease, patient counseling, and to provide a solid background for planning therapeutic studies. In fact, although the prognosis of patients with untreated HCC is generally grim, studies on this topic showed quite heterogenous results and this heterogeneity was also observed in more-recent studies that considered cases enrolled in the control arms of therapeutic trials, thus evaluating patients with well-defined—and often rigorous—inclusion criteria.[12-15] Indeed, a recent meta-analysis of studies that included patients enrolled in the control arm of randomized studies emphasized the presence of wide survival-rate ranges in patients with untreated HCC, even within the same Barcelona Clinic Liver Cancer (BCLC) stage.[2,16] This meta-analysis did not explicitly evaluate the prognostic predictors in patients with advanced HCC (BCLC C) because of the impossibility to abstract specific data in older studies, and its results—as the authors themselves commented—may hardly be generalizable to different patient populations owing to the above-mentioned limitations. Only a recent, single-center study specifically evaluated the prognosis of untreated HCC patients according to the BCLC classification and found, in a smaller series, that BCLC has prognostic usefulness also in this group of patients, although it did not explicitly address more in detail the prognostic determinants.[17]

The present study, which included 600 untreated patients with HCC managed by the Italian Liver Cancer (ITA.LI.CA) centers before the advent of sorafenib (SOR) for the treatment of advanced HCC, aimed to assess the survival of untreated patients in various BCLC stages in real-life clinical practice, focusing on the main prognostic determinants in patients with advanced HCC (BCLC C).[18,19]

Patients and Methods

Patients. The ITA.LI.CA database currently contains data of 5,136 HCC patients consecutively diagnosed with HCC from 1987 to 2012 at 21 Italian medical institutions in Italy. These data were collected prospectively and updated every 2 years with information on the follow-up of the patients. After data entry by any single center, the consistency of the data set was checked by the group coordinator and, when clarification or additional information was needed, it was resubmitted to each center before statistical evaluation.[20] For the purpose of this study, we included all patients who received no anticancer treatment, but best supportive care, and who were enrolled between 1988 and 2008 (n = 600), the year when SOR became commercially available in our country. Among these patients, we included those who received tamoxifen (TAM; n = 161; 26.8%) because of the demonstrated lack of any effect of this drug on survival of HCC patients.[21-24] The causes for treatment withdrawal were various and related to the presence of comorbidities preventing any therapeutic approach, advanced age, advanced tumor stage, poor residual liver function in patients not candidates for liver transplantation, and refusal of treatment by patients.

Methods. Liver tests and tests for identifying the etiology of liver disease were determined by conventional methods using commercially available assays. Presence of cirrhosis was assessed by the physician in charge of the patient according to histological or unequivocal clinical and instrumental evidence, and liver function was evaluated using the Child-Pugh classification.[25] The diagnosis of HCC was made by ultrasound-guided biopsy or by characteristic, contrast-enhanced, radiological imaging results according to the guidelines published at the time of patients' inclusion. Cancer size and stage were assessed by radiological imaging and performance status (PS) scored according to the Eastern Cooperative Oncology Group.[26] Patients were classified according to the BCLC classification in very early (BCLC 0), early (BCLC A), intermediate (BCLC B), advanced (BCLC C), and end-stage HCC (BCLC D).[2] Survival was defined as the time—expressed in months—elapsed from the date of HCC diagnosis and the date of death or the last follow-up information.

Statistical Analysis. Continuous data are shown as median value and 95% confidence interval (CI) for the median, and discrete variables as absolute and relative frequencies. Comparison of continuous data was carried out using Mann-Whitney's U test and

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Table 1. Main Characteristics of the 600 Patients With Untreated HCC

Variable	Unit	Value
Age	Years	68 (50-83)
Gender	Male	444 (74.0)
Viral etiology	Yes	434 (72.3)
Period of HCC diagnosis	≥2000	293 (48.8)
ALT	n × ULN	1.5 (0.6-5.0)
Albumin	g/dL	3.2 (2.3-4.3)
Bilirubin	mg/dL	1.6 (0.6-8.8)
Platelet count	n × 10^9/L	107 (39-264)
AFP	ng/mL	48 (3-34,393)
AFP ≤10 ng/mL	Yes	152 (25.3)
BCLC stages	0 (very early)	12 (2.0)
	A (early)	101 (16.8)
	B (intermediate)	139 (23.2)
	C (advanced)	138 (23.0)
	D (end-stage)	210 (35.0)

Data are shown as median and 95% CI, and absolute value and percentage. ALT data were available in 595 patients, platelet count in 595 (99.1%), and AFP level in 574 (95.7%).

Abbreviation: ULN, upper limit of normal.

comparison of discrete variable using Fisher's exact test or the chi-square (χ^2) test with Yates' correction, as appropriate. Cumulative overall survival was estimated by Kaplan-Meier's method, and statistical comparison of survival distribution was analyzed by the log-rank test. Associations with a P value ≤0.1 at univariate analysis were entered into a Cox's step-wise multivariate regression analysis, where the cutoff for continuous variable (i.e., diameter of the largest nodule and number of HCC nodules) was the median value of the series; for age, the commonly accepted definition of elderly (>65 years) was used. A two-tailed P value <0.05 was considered statistically significant. Statistical analysis was performed using the MedCalc statistical package (MedCalc Software; Mariakerke, Belgium).

Ethics. The ITA.LI.CA database management conforms to the past and current Italian legislation on privacy, and the present study conforms to the ethical guidelines of the Declaration of Helsinki. Approval for the study was obtained by the institutional review board of the participating centers.

Results

The main characteristics of the 600 untreated patients are shown in Table 1. Data regarding alanine aminotransferase (ALT) levels and platelet count were available in 595 patients (99.1%), and alpha-fetoprotein (AFP) serum levels were available in 574 patients (95.7%). Median age was >65 years, and patients were prevalently male (74.0%). As expected in our country, the predominant etiology of liver disease was viral (72.3%). Among the 434 patients with viral liver disease, 326 (75.1%) had hepatitis C virus (HCV) infection alone, 68 (15.7%) had hepatitis B virus (HBV) infection alone, 32 (7.4%) had both HBV and HCV infection, and 8 (1.8%) had HBV and hepatitis D virus infection. The relative prevalence of patients increased with increasing BCLC stage severity, so that the majority of patients (n = 348; 58.0%) were in the advanced (BCLC C: n = 138; 23.0%) and end-stage (BCLC D: n = 210; 35.0%) stages.

Overall Survival. The overall median survival in the whole cohort of 600 patients was 9.0 months (95% CI: 7.9-10.2), and the 6-month, 1-, 3-, and 5-year survival rates were 56.6%, 36.9%, 12.7%, and 9.1%, respectively. At the time of analysis, 38 patients (6.3%) were still alive and 72 (12.0%) were lost to follow-up.

Causes of death were HCC progression in 279 patients (46.5%), liver failure in 97 (16.2%), gastrointestinal bleeding in 25 (4.2%), infection in 4 (0.7%), various causes in 17 (2.8%), whereas in 68 the causes of death were not known (11.3%).

Survival According to BCLC Stages. Overall survival progressively and significantly decreased with worsening BCLC stages (Fig. 1). Median survival was, in fact, 38 months in BCLC stage 0, 25 months in stage A, 10 months in stage B, 7 months in stage C, and 6 months in stage D ($P < 0.0001$). Survival was significantly different in all the contiguous BCLC stages (stage A vs. B: $P < 0.0001$; stage B vs. C: $P = 0.008$; stage C vs. D: $P = 0.04$), except for stage 0 vs. A ($P = 0.142$), likely owing to the very small number of patients with very early HCC (n = 12; 2.0%). The same results were obtained when a sensitivity analysis was performed to evaluate whether the use of TAM

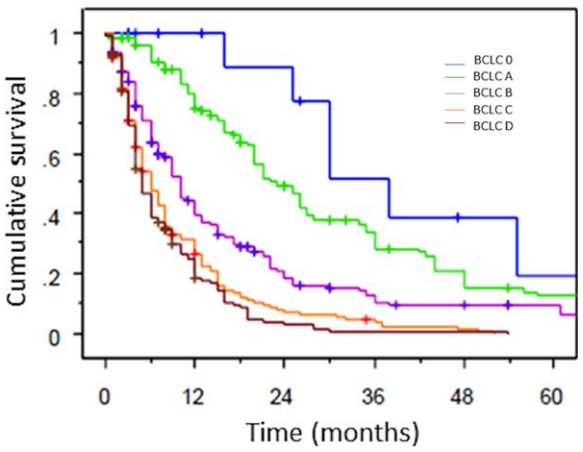

Fig. 1. Kaplan-Meier's curve showing the survival of the 600 patients with untreated HCC subdivided according to the BCLC stages (BCLC 0, blue line; BCLC A, green line; BCLC B, purple line; BCLC C, orange line; BCLC D, red line).

Table 2. Characteristics of the 138 Patients With Advanced HCC (BCLC C)

Variable	Unit	Value
Age	Years	68 (48-82)
Gender	Male	113 (81.9)
Viral etiology	Yes	101 (73.2)
Period of HCC diagnosis	≥2000	61 (44.2)
ALT	n × ULN	1.5 (1.0-4.5)
Albumin	g/dL	3.4 (2.6-4.3)
Bilirubin	mg/dL	1.4 (0.6-3.2)
Platelet count	n × 10^9/L	114 (45-255)
PS	≥1	102 (73.9)
Child-Pugh class	A	69 (50.0)
	B	69 (50.0)
Ascites	Yes	45 (32.6)
HE	Yes	4 (2.9)
AFP	ng/mL	80 (4-42,800)
AFP ≤10 ng/mL	Yes	25 (18.1)
Diameter of the largest nodule	cm	4.4 (1.9-12.5)
No. of nodules	n	3 (1-5)
Macroscopic vascular invasion	Yes	91 (65.9)
Extrahepatic spread	Yes	6 (4.3)
TAM treatment	Yes	47 (34.0)

Data are shown as median and 95% CI, and absolute value and percentage. ALT data were available in 134 patients, platelet count in 135, and AFP level in 133.

Abbreviation: ULN, upper limit of normal.

might have influenced survival in both the whole cohort and the various BCLC stages. This subanalysis positively confirmed that survival progressively decreased with increasing BCLC stages in both patients who received TAM (median survival: BCLC A = 23 months, BCLC B = 13 months, BCLC C = 7 months, and BCLC D = 5 months; $P < 0.0001$) and those who received best supportive care alone (median survival: BCLC A = 25 months, BCLC B = 10 months, BCLC C = 7 months, and BCLC D = 6 months; $P < 0.0001$). Furthermore, no statistically significant survival difference was observed in the various BCLC stages between TAM-treated and untreated patients. Because of the presence of an extremely small number of TAM-treated patients in BCLC stage 0 (n = 2), these patients were not included in these subanalyses.

Determinants of Survival in Untreated Patients With Advanced HCC (BCLC C). Table 2 shows the main demographic and clinical characteristics of the 138 patients with advanced HCC (BCLC C). Median survival of this group of patients was identical when patients were subdivided according to etiology of liver disease (nonviral vs. viral: 7 vs. 7 months; $P = 0.888$), AFP levels (≤10 vs. >10 ng/mL: 7 vs. 7 months, $P = 0.779$), and treatment with TAM (TAM-treated vs. untreated: 7 vs. 7 months, $P = 0.337$). Moreover, the observed differences did not reach statistical significance when patients were divided according to age (≤65 vs. >65 years: 5 vs. 8 months; $P = 0.130$), period of HCC diagnosis (<2000 vs. ≥2000: 5 vs. 9 months; $P = 0.159$), PS (0 vs. ≥1: 7 vs. 8 months; $P = 0.236$), degree of liver dysfunction (Child-Pugh A vs. B: 8 vs. 5 months; $P = 0.306$), hepatic encephalopathy (HE; absent vs. present: 7 vs. 9 months; $P = 0.455$), diameter of the largest nodule (≤4.4 vs. >4.4 cm: 8 vs. 6 months; $P = 0.725$), portal vein thrombosis (absent vs. present: 10 vs. 6 months; $P = 0.201$), and extrahepatic spread (absent vs. present: 7 vs. 6 months; $P = 0.556$). Instead, a longer survival was significantly associated with female gender (female vs. male: 16 vs. 6 months; $P = 0.0001$; Fig. 2A), absence of ascites (absent vs. present: 8 vs. 5 months; $P = 0.0336$; Fig. 2B), and fewer HCC nodules (≤3 vs. >3 nodules: 9 vs. 6 months; $P = 0.0118$; Fig. 2C). In multivariate analysis, gender ($P = 0.018$), ascites ($P = 0.004$), and nodule number ($P = 0.003$) were independent predictors of survival (Table 3).

Discussion

An accurate assessment of the prognosis of untreated HCC patients is essential to evaluate the natural history of disease and identify predictive factors that may assist in planning therapeutic trials, thus allowing an appropriate stratification for confounding factors. Our knowledge on this topic is mainly based on the results of a systematic review and a meta-analysis that have shown a marked heterogeneity of prognosis in patients with untreated HCC or in those who received placebo in randomized studies.[16,27] However, the majority of studies evaluated in the meta-analysis included small series of patients, and meta-analytical evaluation was also difficult because of studies' heterogeneity and lack of individual data.[16] Moreover, survival data derived from the control arms of therapeutic trials, although providing well-defined figures, are not automatically applicable to clinical practice because of inherent strict inclusion criteria that may select patients not fully representative of the entire population observed in everyday clinical practice. Therefore, survival data obtained in adequately sized cohorts of patients managed in clinical practice are needed to provide real-life data regarding the prognosis of untreated HCC and help physicians evaluate the applicability of clinical studies results and therefore adequately counsel their patients.

To the best of our knowledge, this is the largest study assessing the prognosis of untreated patients with HCC, and the size of our cohort allowed us to evaluate more in detail the prognosis of patients subdivided according to the BCLC classification, especially

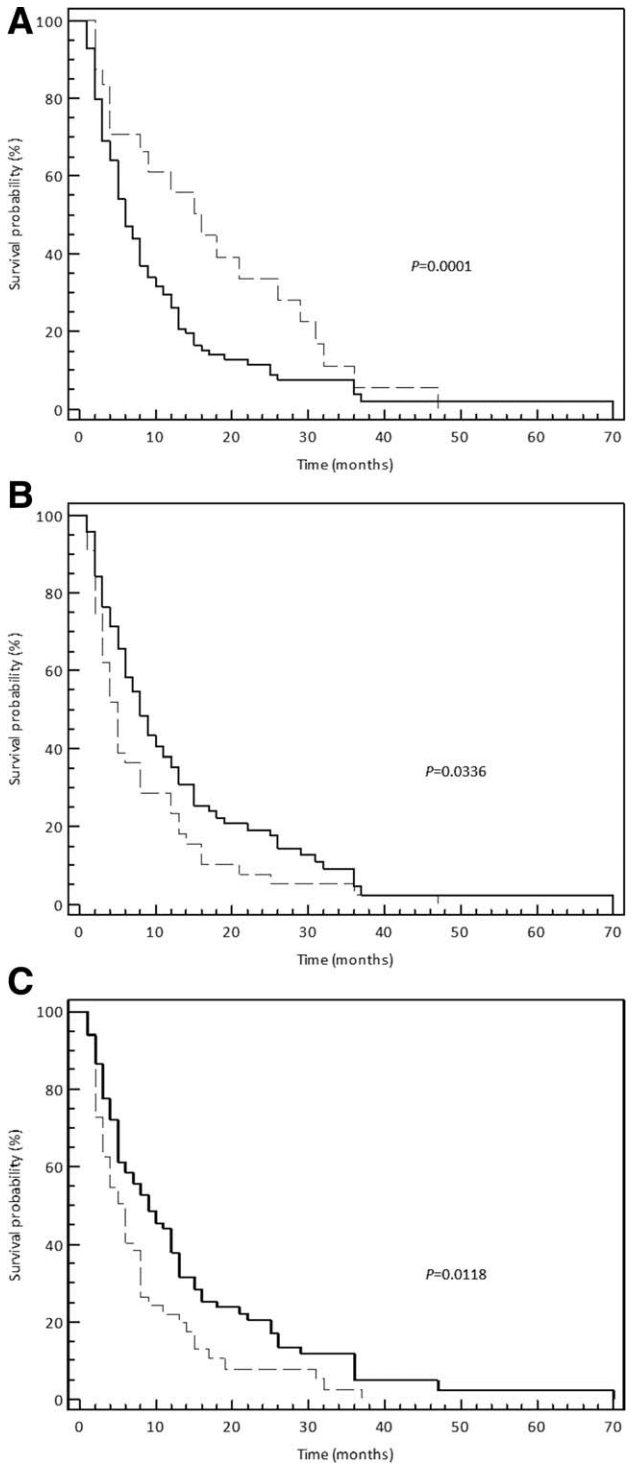

Fig. 2. Kaplan-Meier's survival curves of patients with advanced HCC (BCLC stage C) subdivided according to gender (A: solid line, male; dashed line, female), ascites (B: solid line, absent; dashed line, present), and number of HCC nodules (C: solid line, ≤3 nodules; dashed line, >3 nodules).

in patients with advanced HCC stages, for whom new effective treatments are urgently needed and eagerly searched. We observed that median survival progressively decreased with increasing severity of BCLC stages, confirming that both liver function and HCC burden are relevant in determining the outcome of these patients and therefore supporting, in a large series, the prognostic usefulness of BCLC classification also in untreated patients.[17] Notably, the survival of the ITA.LI.CA patients diagnosed with BCLC C HCC (7.0 months) was exactly overlapping with the survival of both the BCLC C placebo-treated patients in the SOR registration trial (7.0 months) and the BCLC C untreated patients included in the single-center Italian study carried out in clinical practice (6.9 months).[17,28] It was instead shorter than that of patients treated with SOR in the Italian field-practice multicentre study.[29] In our view, these findings provide further robust data supporting, although indirectly, the validity of SOR therapy in clinical practice.

Assessing the prognosis of patients with more-advanced HCC, a group where curative options are not feasible and where the benefit of palliative treatment is not as straightforward as they may appear in clinical trials, is of utmost importance.[30] Indeed, such information may represent the benchmark for field-practice cohort studies reporting on treatment results in these patients. Overall, we observed that the prognosis of patients with advanced HCC (BCLC C) was positively influenced by female gender, whereas the presence of ascites and HCC multinodularity negatively influenced patients' survival. Indeed, the presence of ascites marks a clear landmark that defines prognosis in patients with cirrhosis, and therefore it is not surprising that it represents an independent prognostic factor also in patients with advanced HCC, independently of Child-Pugh class.[31] A large tumoral burden is also an unsurprising prognostic predictor, even in a rather homogeneous subgroup of patients such as those with advanced HCC, and both the presence of ascites and large tumor burden (i.e., Okuda stage >1) were also identified as predictors of survival in a recent meta-analysis, although such a meta-analytic evaluation did not assess patients with intermediate and advanced HCC separately.[16] Last, female gender is a well-known positive prognostic factor in patients with HCC—both treated and untreated—although a previous study failed to find a significant association between gender and survival in patients with

Table 3. Results of Multivariate Analysis of Predictors of Survival in Patients With Advanced HCC (BCLC C)

Variable	HR	95% CI	*P* Value
Female gender	0.55	0.33-0.90	0.018
Presence of ascites	1.81	1.21-2.71	0.004
No. of nodules >3	1.79	1.21-2.63	0.003

advanced and end-stage HCC.[16,32,33] Overall, we feel that the predictive factors identified in this study, that is, gender, ascites, and multinodularity (>3 lesions) should be taken into account so as to refine patient stratification in future trials exploring new treatments for patients with advanced HCC.

This study has some limitations. First, as expected, the number of patients with very early HCC was small, and this prevented a statistically sound comparison of their survival with that of patients with early HCC, although we feel that the difference observed in median survival (i.e., 38 vs. 25 months) is nevertheless clinically meaningful. Second, because the actual reason for the absence of treatment in our patients with very early and early HCC—as in the whole cohort—were not explicitly recorded, we do not know whether survival of these patients was heavily affected by non-liver-related factors, such as older age and comorbidities. However, we feel this hypothesis quite unlikely, given the observed median survival times in these two groups of patients and by the finding that the principal cause of death was tumor progression. Third, a proportion of patients included in this study received TAM. We nevertheless decided to include these patients, given that several randomized studies and a meta-analysis definitely demonstrated the lack of any effect of TAM on survival of HCC patients, and also a sensitivity analysis carried out in this study confirmed this lack of efficacy in the whole cohort and across BCLC stages. Noteworthy, in BCLC C stage patients, the median survival of TAM-treated patients (i.e., 7 months) overlapped with the survival of the placebo arm enrolled in the SOR registration trial.[18,21] Last, patients were accrued over a long period of time, during which the management of cirrhosis may have improved. Nonetheless, the overall survival in the whole series of 600 patients was not significantly different when they were subdivided according to period of diagnosis (before and after 2000), suggesting that this factor had limited influence on the survival of a population where early HCCs are a minority and the median overall survival is <1 year. This assumption is robustly supported by the overlapping survivals of our BCLC C patients and untreated patients recruited by other centers over the current century.[17,28]

In conclusion, this study provided the survival figures of patients with untreated HCC that are likely to be expected in everyday clinical practice, offering a benchmark for the available and future field-practice studies on HCC treatment. Moreover, it confirmed, in a large series, the validity of the BCLC staging system in predicting the prognosis, even in untreated patients. Last, given that female gender, ascites, and multinodular HCC appeared to be independent prognostic factors in the subgroup of patients with advanced HCC, stratification for these factors may be recommended in new randomized trials focused on the treatment of this group of patients.

Appendix

Other members of the ITA.LI.CA group are: Dipartimento di Scienze Mediche e Chirurgiche, Alma Mater Studiorum–Università di Bologna: Mauro Bernardi, Luigi Bolondi, Maurizio Biselli, Paolo Caraceni, Alessandro Cucchetti, Marco Domenicali, Francesca Garuti, Annagiulia Gramenzi, Barbara Lenzi, Donatella Magalotti, Fabio Piscaglia, and Carla Serra; Dipartimento di Scienze Chirurgiche e Gastroenterologiche, Università di Padova: Anna Giacomin, Veronica Vanin, Caterina Pozzan, and Gemma Maddalo; Unità Operativa di Chirurgia, Policlinico S. Marco, Zingonia: Paolo Del Poggio and Stefano Olmi; Unità Operativa di Medicina, Azienda Ospedaliera Bolognini, Seriate, Italia: Claudia Balsamo, Maria Anna Di Nolfo, and Elena Vavassori; Dipartimento di Medicina Clinica e Sperimentale, Università di Padova: Alfredo Alberti and Angelo Gatta; Dipartimento di Malattie Apparato Digerente e Medicina Interna, Azienda ospedaliero-universitaria di Bologna, Unità Operativa di Radiologia: Alberta Capelli, Rita Golfieri and Matteo Renzulli; Unità di Medicina Interna e Gastroenterologia, Complesso Integrato Columbus, Università Cattolica di Roma, Roma: Giulia Bosco; Unità Operativa di Gastroenterologia, Ospedale Belcolle, Viterbo: Paola Roselli; Unità Operativa di Medicina Protetta, Ospedale Belcolle, Viterbo: Serena Dell'Isola and Anna Maria Ialungo; Dipartimento di Medicina Interna, Unità di Gastroenterologia, Università di Genova: Vincenzo Savarino, Domenico Risso, and Giorgio Sammito.

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