Natural history of untreated hepatocellular carcinoma: A retrospective cohort study

Giuseppe Cabibbo, Marcello Maida, Chiara Genco, Pietro Parisi, Marco Peralta, Michela Antonucci, Giuseppe Brancatelli, Calogero Cammà, Antonio Craxì, Vito Di Marco

Giuseppe Cabibbo, Marcello Maida, Chiara Genco, Pietro Parisi, Marco Peralta, Michela Antonucci, Giuseppe Brancatelli, Calogero Cammà, Antonio Craxì, Vito Di Marco, Section of Gastroenterology, Department of Internal Medicine and Biomedical Specialist, University of Palermo, Palermo 90127, Italy

Giuseppe Cabibbo, Department of Biopathology and Biomedical Methodologies, University of Palermo, Palermo 90127, Italy

Michela Antonucci, Department of Oncology, Division of General Surgery and Oncology, University of Palermo, Palermo 90127, Italy

Giuseppe Brancatelli, Department of Radiology, DIBIMEF, University of Palermo, Palermo 90127, Italy

Author contributions: Cabibbo G and Di Marco V contributed to clinical management, study design, data analysis and writing of the study; Maida M, Genco C, Parisi P and Peralta M contributed to clinical management and data collection; Antonucci M contributed to clinical management; Cammà C and Craxì A contributed to clinical management and writing of the study; Brancatelli G contributed to diagnosis; all authors had full control over the study design, and preparation of manuscript; all authors approved the final draft manuscript.

Correspondence to: Giuseppe Cabibbo, MD, PhD, Section of Gastroenterology, Department of Internal Medicine and Biomedical Specialist, University of Palermo, Piazza delle Clinics 2, Palermo 90127, Italy. g.cab@libero.it

Telephone: +39-91-6552280 Fax: +39-91-6552156

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Abstract

AIM: To investigate the clinical course of untreated hepatocellular carcinoma (HCC) identified at any stage and to identify factors associated with mortality.

METHODS: From January 1999 to December 2010, 320 out of 825 consecutive patients with a diagnosis of HCC and not appropriate for curative or palliative treatments were followed and managed with supportive therapy. Cirrhosis was diagnosed by histological or clinical features and liver function was evaluated according to Child-Pugh score. The diagnosis of HCC was performed by Ultra-Sound guided biopsy or by multiphasic contrast-enhanced computed tomography or gadolinium-enhanced magnetic resonance imaging. Data were collected for each patient including all clinical, laboratory and imaging variables necessary for the outcome prediction staging systems considered. HCC staging was performed according Barcelona Clinic Liver Cancer (BCLC) and Cancer of the Liver Italian Program scores. Follow-up time was defined as the number of months from the diagnosis of HCC to death. Prognostic baseline variables were analyzed by multivariate Cox analysis to identify the independent predictors of survival.

RESULTS: Seventy-five per cent of patients had hepatitis C. Ascites was present in 169 patients (53%), while hepatic encephalopathy was present in 49 patients (15%). The Child-Pugh score was class A in 105 patients (33%), class B in 142 patients (44%), and class C in 73 patients (23%). One hundred patients (31%) had macroscopic vascular invasion and/or extrahepatic spread of the tumor. A single lesion > 10 cm was observed in 34 patients (11%), while multinodular HCC was present in 189 patients (59%). Thirty nine patients (12%) were BCLC early (A) stage, 55 (17%) were BCLC intermediate (B) stage, 124 (39%) were BCLC advanced (C) stage, and 102 (32%) were end-stage BCLC (D). At the time of this analysis (July 2011), 28 (9%) patients were still alive. Six (2%) patients who were lost during follow-up were censored at the last visit. The overall median survival was 6.8 mo, and the 1-year survival was 32%. The median survival of patients of BCLC stages A, B, C and D was 33, 17.4, 6.9, and 1.8 mo, respectively (P < 0.05 for comparison between stages). The median survival of Child-Pugh A, B and C classes were 9.8 mo.
Hepatocellular carcinoma (HCC) is associated with a high rate of mortality,[1] and, despite extensive application of intensive surveillance programs, considerable therapeutic progress, and technological improvement observed over the past few years, prognosis of this tumor is poor even when treatments have been considered potentially curative.[2]

Curative treatments for early-stage tumors include liver transplantation, resection and percutaneous ablation. Transarterial chemoembolization (TACE) and sorafenib can improve survival for patients with intermediate and advanced tumors, respectively.[3]

Although in two large-scale studies,[4,5] sorafenib has been shown to improve survival in unresectable HCC patients with well-preserved liver function, response rates remain poor. Moreover, recent studies showed that tolerability was moderate and that most patients need reduction or interruption of treatment[6-8]. So, there is a need for further properly designed randomized controlled trials (RCTs) to assess the survival benefits of second-line systemic therapies. The design of such trials would require an accurate estimation of the survival of patients with untreated disease, preferably with stratification according to known prognostic factor. In addition, as soon as the results of such trials are available, patients and their physicians will become aware of the natural history of the untreated disease will be better able to decide whether or not to accept other palliative treatments.

The natural course of unresectable HCC has recently been evaluated in a meta-analysis[9] which analyzed the survival rates of the placebo and untreated arms of several RCTs on HCC patients, showing that the 1- and 2-year survival is extremely heterogeneous.

For ethical reasons it is not possible to evaluate the natural history of early HCC in RCTs. However a milestone paper[10] published in 1989 showed that 1- and 2-year overall survival (OS) of asymptomatic patients with HCC and cirrhosis was 96% and 50%, respectively.

To provide updated survival data on untreated HCC in Italy, we analyzed the clinical data of a cohort of HCC patients followed in our Liver Unit.

**MATERIALS AND METHODS**

**Patients**

From January 1999 to December 2010, 825 consecutive patients with cirrhosis and a new diagnosis of HCC were observed at our Liver Unit. Cirrhosis was diagnosed by histological or clinical features and the liver function was evaluated according to Child-Pugh score. The diagnosis of HCC was performed by ultrasound guided biopsy or by multiphasic contrast-enhanced computed tomography or gadolinium-enhanced magnetic resonance imaging. Performance status (PS) was scored according to the Eastern Cooperative Oncology Group (ECOG)[11]

All patients were evaluated according to European Association for the Study of the Liver criteria[12] up to 2005, and to American Association for the Study of Liver Diseases criteria[13] from January 2006. HCC staging and the choice of treatment were performed according to the Barcelona Clinic Liver Cancer (BCLC) schedule[14].

Patients with early tumors (BCLC A) were considered for curative therapies [resection, orthotopic liver transplantation (OLT), or radiofrequency thermal ablation (RFTA)]. TACE was performed in patients at intermediate stage (BCLC B) according to BCLC and in early-stage (BCLC A) patients for whom percutaneous RFTA was not feasible because of tumor location (proximity to gall-bladder, biliary tree, or blood vessel) or in whom surgery could not be performed because of comorbidities[15-19]. Combined treatments were used when indicated to achieve a better radical cure[20]. Starting July 2008, patients with advanced HCC and patients with an intermediate HCC who were not eligible for or failed loco-ablative therapies were treated with sorafenib.

The current study analyzed the natural course of patients with HCC at any stage who were untreated for any cause. Follow-up was censored on July 31, 2011. The main causes for non-treatment were the presence of severe co-morbidities or impaired PS[14], advanced age,
refusal of treatment, diffuse or massive tumor with or without macro-vascular invasion or extra-hepatic spread before the advent of sorafenib, poor residual liver function (Child-Pugh > B8) precluding OLT.

Outcome
The primary outcome measure in this analysis was survival. Follow-up time was defined as the number of months from the diagnosis of HCC to death. All subjects were followed as outpatients or inpatients at our Liver Unit and clinical data were collected by telephone follow-up when clinical worsening did not allow the patient to present for medical controls.

Statistical analysis
Data collected for each patient included all clinical, laboratory and imaging variables necessary for the outcome prediction staging systems considered. Patients were also stratified according to Child-Pugh, BCLC and Italian (Cancer of the Liver Italian Program) classifications. Continuous variables were expressed as mean ± SD. The Kaplan-Meier estimator was applied to survival. Differences in the survival rate were assessed by log-rank testing. Variables listed in Table 1 were analyzed using univariate analysis. All variables with a \( P \)-value less than 0.05 by univariate analysis were subjected to multivariate analysis. The multivariate analysis was performed by the Cox proportional hazard model. All statistical analyses were performed with the Statistical Analysis System (SAS) version 8.1 (SAS Institute, Inc., Cary, NC, United States).

RESULTS

Patient features at baseline
The study population consisted of 320 patients with HCC secondary to cirrhosis of various etiologies. The demographical, clinical and tumor staging features of the 320 patients are given in Table 1. Chronic hepatitis C virus infection was the dominant etiology (75%).

At presentation, the Child-Pugh score was class A in 105 patients (33%), class B in 142 patients (44%), and class C in 73 patients (23%). Ascites was present in 169 patients (53%), while hepatic encephalopathy was present in 49 patients (15%).

Regarding the features of HCC, 100 patients (31%) had macroscopic vascular invasion and/or extra-hepatic spread of the tumour. A single lesion > 10 cm was observed in 34 patients (11%), while multinodular HCC was present in patients 189 (59%). Thirty nine patients (12%) were BCLC early (A) stage, 55 (17%) were BCLC intermediate (B) stage, 124 (39%) were BCLC advanced (C) stage, and 102 (32%) were end-stage BCLC (D).

At the time of this analysis (July 2011), 28 (9%) patients were still alive. Six (2%) patients who were lost during follow-up were censored at their last visit.

Survival
The median OS was 6.8 mo (95%CI: 5.8-7.7), corresponding to 33% of the patients being alive at 1 year. The 1-year survival according to BCLC class was 100%,
patients according to the stage of the tumor and liver disease, such as the BCLC classification which stratifies patients according to the stage of the tumor as well as the development of clinically based staging systems. The median survival of Child-Pugh A, B and C classes were 9.8 mo (range 6.4-13), 6.1 mo (range 4.9-7.3), and 3.7 mo (range 1.5-6), respectively (P < 0.05 for comparison between stages).

By univariate analysis, the variables significantly associated to an increased likelihood of mortality were ECOG PS, presence of ascites, low level of albumin, elevated level of bilirubin, international normalized ratio (INR) and Log-[α fetoprotein (AFP)]. Cox regression analysis showed that PS [hazard ratio (HR) 2.875, 95% CI: 2.547-3.245, P < 0.0001], INR (HR 1.811, 95% CI: 1.328-2.469, P = 0.0001), and Log-AFP (HR 1.078, 95% CI: 1.018-1.142, P = 0.009) were independent risk factors for mortality (Table 3).

### DISCUSSION

HCC secondary to cirrhosis is a complex and heterogeneous disease with wide variations during its clinical course. In this context, the management of cirrhotic patients with neoplasm is a major clinical issue.

A better knowledge of the natural history of the tumor as well as the development of clinically based staging systems, such as the BCLC classification which stratifies patients according to the stage of the tumor and liver disease, has meant that life expectancies can be confidently predicted, and the appropriate treatment can be chosen according to stage.

This study shows that in patients with untreated HCC, survival can be predicted from information collected by the physician as part of the initial assessment. In fact, the identified prognostic factors (PS, INR and AFP) are easily measured. Decreased PS has been previously found to have prognostic value in patients with HCC. In our cohort, advanced liver diseases, assessed by high INR was associated with improvement in survival, while elevated serum AFP reflects the degree of cellular differentiation and thus the spread of the tumor. Moreover, our study confirms that the BCLC staging classification sensitively identifies HCC patients with a good or unfavorable prognosis.

Although, the median survival for early stage observed in our study was good (33 mo), data on survival rates of early HCC patients confirm, even in absence of data from RCT, the effectiveness of any current treatment for this cancer.

Clearly, the impact of sorafenib for patients with advanced HCC and with intermediate HCC who were unfit or failed to respond to ablative therapies, is a landmark in the treatment of liver cancer. However, given the high rate of therapy discontinuation for adverse events or radiological progression, data on survival of untreated intermediate/advanced stage patients could give useful information in the design of RCTs on second-line treatment with new agents after failure of sorafenib therapy.

### Table 2 Summary of follow-up in 320 untreated hepatocellular carcinoma patients (%)

| Outcome                                      | Patients (n = 320) |
|----------------------------------------------|-------------------|
| Death                                        | 292 (91)          |
| Overall survival                             |                   |
| Median (95%CI) (mo)                          | 6.8 (5.8-7.7)     |
| 1-yr survival rate                           | 32                |
| 2-yr survival rate                           | 13                |
| BCLC A (early stage) survival                |                   |
| Median (95%CI) (mo)                          | 33 (20-46)        |
| 1-yr survival rate                           | 100               |
| 2-yr survival rate                           | 57                |
| 3-yr survival rate                           | 41                |
| BCLC B (intermediate stage) survival         |                   |
| Median (95%CI) (mo)                          | 17.4 (14.8-20)    |
| 1-yr survival rate                           | 79                |
| 2-yr survival rate                           | 22                |
| 3-yr survival rate                           | 5                 |
| BCLC C (advanced stage) survival             |                   |
| Median (95%CI) (mo)                          | 6.9 (6.3-7.3)     |
| 1-yr survival rate                           | 12                |
| BCLC D (end-stage) survival                  |                   |
| Median (95%CI) (mo)                          | 1.8 (1.2-2.4)     |
| 1-yr survival rate                           | 0                 |

BCLC: Barcelona Clinic Liver Cancer classification.

### Table 3 Multivariate Cox-regression models for predicting over all survival in 320 patients with hepatocellular carcinoma patients in cirrhosis

| Variable                      | HR     | 95%CI     | P value |
|-------------------------------|--------|-----------|---------|
| Performance status            | 2.875  | 2.547-3.245 | <0.0001 |
| INR                           | 1.811  | 1.328-2.469 | 0.0001  |
| Log-AFP                       | 1.078  | 1.018-1.142 | 0.009   |

1 Eastern Cooperative Oncology Group-Performance Status. HR: Hazard ratio; INR: International Normalized Ratio; AFP: α fetoprotein.
In our cohort, HCC patients in BCLC D stage at baseline have a 1-year survival of less than 5%. Given this poor life expectancy, BCLC suggests only symptomatic treatment. The study had some bias. Firstly, it was conducted retrospectively although, because the only defined endpoint was survival, it is unlikely that the results were affected. Another weakness is the lack of data on molecular factors, such as gene expression profiling, which can have some impact on patient outcome.25,26

The treatment of HCC has changed dramatically. Years ago, there were no safe or reliable therapies for patients diagnosed with this cancer and their prognosis was uniformly grim. Now, all stages of the disease may receive effective therapy and current research will expand the existing benefits. However, the current therapeutic approach still needs significant improvement. Furthermore, the therapeutic options for patients with advanced HCC have limited impact and thus, development of new agents and strategies for this group of patients is of major importance.

In untreated HCC patients, the available evidence is sufficient to conclude that poor PS, high INR values and high AFP levels are associated with worse prognosis. BCLC staging classification sensitively identifies HCC untreated patients with a good or unfavorable prognosis. Patients at BCLC end-stage should only receive symptomatic treatment.

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