Lack of Evidence That Adherence to Standard of Care Therapy Improves Survival in Subjects With Hepatocellular Carcinoma in Clinical Practice

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Currently, the BCLC classification, which links tumor stage with treatment option, is the standard system for clinical management of HCC. Thus far, this approach has been considered the standard of care worldwide. This study aimed to evaluate the survival of patients with HCC according to the BCLC Stage, surveillance, and adherence to standards of care. A 3-year prospective study enrolled 92 consecutive patients with HCC in the Gastroenterology Unit of the University of Naples "Federico II". Predictors of the likelihood of death were evaluated by the multivariate Cox model. Forty out of 92 (43%) subjects died during three years of follow up. The overall mortality rate per 100 person–years was 16.7, while the mortality rate for hepatic causes was only 14.2; it was lower in subjects under surveillance (11.4 vs. 28.2), in subjects adherent to standards of care (12.0 vs. 21.1), and in those who were in a better BCLC stage (10.6 vs. 45.8). The multivariate Cox model showed that advanced BCLC stage (HR 4.1, 95%C.I. = 1.8–9.4) was the sole independent predictor of the likelihood of mortality. In this regard, we observed lack of evidence that the adherence to the BCLC recommendations reduces the mortality of patients with HCC; and that the BCLC system cannot be accepted as a "commandment" to be invariably followed in everyday practice. Strategies to help improve adherence to international guidelines for HCC in clinical practice are required. ***J. Med. Virol. 2015.***

KEY WORDS: hepatocellular carcinoma; surveillance; standard of care; survival

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of tumor-related deaths worldwide and currently the leading cause of mortality among cirrhotic patients [El-Serag and Rudolph, 2007]. In western countries more than 80% of HCC occur in patients with cirrhosis, representing the main risk factor for this tumor [Trevisani et al., 2002]. For this reason, cirrhotic patients should undergo regular ultrasound surveillance. In fact, when the tumor is still small, early detection increases the options for therapy and the likelihood of being cured [Tanaka et al., 1990; Bruix et al., 2001; Grieco et al., 2005]. Therefore, a six-

Abbreviations: HCC, hepatocellular carcinoma; BCLC, Barcelona-Clinic Liver Cancer; AFP, alpha1-fetoprotein; AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase, AST, aspartate amino transferase; GGT, gamma-glutamil transferase; SD, Standard Deviation; HR, Hazard Ratios

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monthly surveillance for early detection of HCC in patients with cirrhosis, based on serial ultrasonographies and serum α1-fetoprotein (AFP) determination has become a standardized practice. Moreover, there is increasing evidence that this practice improves survival [Unoura et al., 1993; Wong et al., 2000; Yuen et al., 2000; Bolondi et al., 2001; Trevisani et al., 2004; Lencioni, 2010]. The success of surveillance programs and the availability of highly effective treatment options for small HCC have changed the clinical scenario described by the scientific community [Llovet et al., 2008]. Until now, early HCC diagnosis has been feasible in 30–60% of cases in developed countries and this has enabled the application of curative therapies [Llovet et al., 2003]. In this regard, it has been considered that appropriate staging systems for HCC should include four related aspects: tumor stage, degree of liver function impairment, patient's general health condition, and treatment efficacy [Raoul et al., 2010]. For this reason, numerous staging systems for the prognostic classification of HCC have been proposed [Okuda et al., 1985; Llovet et al., 1999; Clip investigation, 2000; Leung et al., 2002; Kudo et al., 2003; Sobin and Wittekind, 2007]. At present, the BCLC strategy and their update [Forner et al., 2010] are considered the standard for staging and treatment of HCC [Llovet et al., 2008; Bruix et al., 2014]. The BCLC staging system links five different stages of HCC with the appropriate therapeutic treatment options [Llovet et al., 2004] and has been endorsed by the European Association for the Study of the Liver (EASL) [Bruix et al., 2001] and the American Association for the Study of Liver Diseases (AASLD) [Bruix and Sherman, 2005]. The benefits on survival of treatment proposed strategy in each different BCLC stage (except for stage D) have already been documented in large studies, which have contributed to the diffusion and the "building" of the BCLC system itself [Llovet et al., 1999]. Thus far, this approach has been considered the standard of care worldwide. Adversely, the adherence of treatment to the current standards of care in clinical practice is much less investigated worldwide [Kim et al., 2012; Bruix et al., 2014; Graf et al., 2014].

The purposes of this study were to provide an epidemiological, diagnostic, and therapeutic description of patients with HCC in a single referral center of Southern Italy and to evaluate the survival of patients with HCC, according to surveillance programs and adherence to current approved standard schedules of treatment.

MATERIALS AND METHODS

Patients

From January 2009 to December 2010, 92 consecutive adult patients with a new diagnosis of HCC were recruited at the Gastrointestinal Unit of the University of Naples "Federico II". All of the patients were diagnosed with HCC and an available description of the tumor stage was accepted in the study, without any exclusion. The 92 enrolled patients were evaluated according to the modality of cancer diagnosis (surveillance yes/not) and type of treatment (standards of care yes/not). Patients were divided into two groups according to the modality of diagnosis: the first group including patients diagnosed with HCC during a regular surveillance, and the second group including patients with a diagnosis of incidental HCC from a specific surveillance program, as a result of symptom appearance, or because of a diagnostic workup for other diseases.

Demographic characteristics and clinical parameters at baseline, including age, sex, BMI, etiology of cirrhosis, presence of portal hypertension, Child-Pugh class [Pugh et al., 1973], gross pathology, and extrahepatic diffusion of HCC, portal vein thrombosis, and biochemistry parameters were recorded.

All patients underwent a periodic follow up including clinical, laboratorial, and imaging evaluation (ultrasonography–CT-RMN) performed at intervals of 4–24 weeks in relation to HCC stage and clinical needs of a single patient.

The study was performed in accordance with the principles of the Declaration of Helsinki and its appendices. Approval was obtained from the Institutional Review Board and Ethics Committee and a written informed consent was obtained from all enrolled patients.

Diagnosis of Cirrhosis and HCC

Cirrhosis was documented by histology in 43 patients. Otherwise, the diagnosis was based on clinical and lab tests associated with endoscopic and/or ultrasonographic signs of portal hypertension.

The diagnosis of HCC was performed according to international guidelines of the AASLD [Bruix and Sherman, 2005] by imaging technique workup (dynamic CT, contrast-enhanced ultrasonography, dynamic MRI), showing arterial vascularization characteristics at least in two imaging modalities, thereafter combining the diagnostic AFP increase (>200 ng/ml). HCC diagnosis was confirmed by histology with an ultrasonography-guided biopsy in only 17 patients.

What is more, 75 patients were diagnosed with HCC during the ultrasonographic follow up with frequency range between 6–12 months, while in the remaining 17 patients the diagnosis was completely occasional.

HCC Staging

Tumor stage was assessed with both ultrasonography and CT features, according to BCLC staging system. Macroscopic types of HCC were classified as: solitary nodular (<2 cm, between 2 and 3 cm, >3 cm), multifocal, and diffuse [Trevisani et al., 1993]. Bone

scintigraphy and total body CT were performed in all patients to investigate extrahepatic involvement.

Amenability to the Best Treatment Option

Treatment options were evaluated according to the BCLC staging system in most of the patients. Liver transplantation was evaluated according to the "Milano criteria" proposed by Mazzaferro et al [Mazzaferro et al., 1996]. Patients were defined suitable for resection according to the following criteria: solitary nodule, Child-Pugh A, no evidence of portal vein infiltration or thrombosis, no evidence of extrahepatic metastases, no general contraindications to surgery. Patients were defined suitable for local ablation (radiofrequency ablation, laser thermal ablation, percutaneous ethanol injection, cryoablation) according to the following criteria: solitary nodule or paucifocal with each node <3 cm, Child-Pugh A–B, no evidence of extrahepatic metastases, no general contraindication to the specific technique. Patients were candidates for transcatheter arterial chemoembolization according to the following criteria: paucifocal HCC not treatable with local ablation or multifocal HCC, involving less than 40% of the liver volume; Child-Pugh A–B, no portal vein infiltration or thrombosis, no extrahepatic metastases, no severe associated diseases, no general contraindications to transcatheter arterial chemoembolization. Systemic therapy with Sorafenib was indicated according to the following criteria: advanced HCC with or without extrahepatic metastases or portal vein infiltration/thrombosis, Child-Pugh A–B, adequate hematologic, hepatic and renal function, no severe associated diseases, no general contraindications to Sorafenib.

Laboratory Determinations

Liver tests (prothrombin activity, plasma albumin, bilirubin concentration), complete blood count, renal tests (creatinine and blood urea), ferritin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamiltransferase (GGT), alkaline phosphatase, tests to define the etiology of cirrhosis and serum levels of AFP (values <20 ng/ml were considered as normal) were determined at the time of diagnosis. All the biochemical parameters were performed at the laboratories of the Department of Biochemistry and Virology of the University of Naples "Federico II", using commercial methodology.

Statistical Analysis

Baseline characteristics were expressed as median and range for continuous and not normally distributed data, as mean and standard deviation (SD) for normally distributed data, and as a percentage for categorical data; the differences between the groups were evaluated, respectively, with the Wilcoxon ranks sum test, the Student's *t*-test, and the χ^2 test. The probability value <0.05 was considered statistically significant. Patient survival was calculated from the time of tumor diagnosis to death, or in case of survival, to the date of the last follow up with values censored at the date of the last follow up. Mortality rate (MR) was expressed per 100 person-years and 95% confidence interval (CI) was computed considering the Poisson distribution. Survival function was estimated using the Kaplan–Meier method and log-rank test was used to compare the survival distribution between groups. The univariate and multivariate Cox proportional hazard models were used to examine risk factors for hepatic mortality causes. The variables included in the survival analysis were: modality of diagnosis, adherence to standards of care, stage of the disease; age, and gender were considered as confounding variables. An interaction term between adherence to standards of care and stage of the disease was evaluated. Results were given as hazard ratios (HR) and a 95% confidence interval. The proportional assumption was checked using the Schoenfeld residuals. All the analyses were performed using STATA, version 11 (Stata Corporation LP, College Station, TX).

RESULTS

Demographic, Clinical, and Laboratory Characteristics

Baseline demographics, clinical and laboratory characteristics of patients are summarized in Table I. HCV infection accounted for the majority (78.4%) of cases. Two-third of patients were in Child-Pugh class A (66.3%). Serum AFP was elevated in 51.1% of the patients. Diagnostic levels (>200 ng/ml) were found in 25.0% of the cases.

Macroscopic Features, HCC Stage, and Modality of Diagnosis

The main characteristics of the tumor are summarized in Table II. Solitary nodule, multifocal and diffuse pattern were detected in 38.0%, 28.3% and 33.7% of cases, respectively. Information on the cancer diameter (the largest nodule) was available in all cases: the median tumor size was 2.7 cm (range, 1–21 cm). Portal vein thrombosis was observed in 20 patients (21.7%); in 15 of them the diagnosis was performed before the evidence of HCC and successfully treated with low molecular weight heparin. Metastases were present in 12.0% of cases. The HCC stage was evaluated according to BCLC staging system. Therefore, 55.4% of patients were included in early and very-early stage, 29.3% in intermediate stage, 6.6% in advanced stage, and 8.7% in terminal stage. According to the modality of diagnosis, the tumor was incidentally detected during surveillance in 75 patients, and/or for symptoms in 17 patients. The main features of the two groups are summarized in Table III.

Treatments

With regard to the treatment, 84% of patients performed at least one type of procedure, while only

TABLE I. Demographic, Clinical, and Laboratory Characteristics of Patients Population With HCC (n = 92)

Patients' characteristics	N (%)
Age, Yr	
median (range)	67 (45–81)
Sex	
Male	68 (73.9%)
Female	24 (26.1%)
BMI	
median (range)	26 (19–34)
Child-Pugh Class	
A	61 (66.3%)
B	23 (25.0%)
C	8 (8.7%)
Etiology of cirrhosis	
HBsAg +	8 (8.8%)
HCV-Ab +	73 (78.4%)
HBsAg + and HCV-Ab +	2 (2.2%)
HBsAg+ and HDV-Ab	4 (4.8%)
Alcohol	2 (2.2%)
Others	3 (3.6%)
AFP, ng/ml	
<20	45 (48.9%)
20–200	24 (26.1%)
>200	23 (25.0%)
Platelets, n/mm^3	
mean ± SD	118.9 ± 63.3
Prothrombin activity, %	
mean ± SD	79.0 ± 16.0
Plasma albumin, g/dl	
mean ± SD	3.7 ± 0.6
Bilirubin concentration, mg/dl	
mean ± SD	2.13 ± 4.1

13% of patients did not perform any treatment (refusal by five patients and inability to perform effective treatment in seven cases for their end-stage disease). Most treatments performed in this population consisted of loco-regional treatments (62 patients, 67.8%) because over 75% of patients was included in stage A or B according to BCLC. Surgical resection and liver transplantation were performed in 8.7% of cases. Similarly, treatment with sorafenib was rarely performed (7.6% of cases), related to the small number of patients suitable for this therapy according to current guidelines.

Concerning the modality of treatment, 67 patients were treated with standards of care according to the BCLC stage, while 25 were treated with non-standardized procedures. The main features of the two groups of patients in relation to adherence to standards of care are summarized in Table IV. The causes of non adherence to the standards of care were due to:

- refusal of proposed treatment by eight patients,
- inability to perform the appropriate and standardized treatment for the presence of severe comorbidities or

TABLE II. Macroscopic Features, Vascular Involvement, Presence of Metastases, and Stage of HCC

Tumor characteristics	N (%)
HCC type	
solitary<2–cm	8 (8.7)
solitary 2–3 cm	19 (20.6)
solitary> 3 cm	8 (8.7)
multifocal	26 (28.3)
diffuse	31 (33.7)
Tumor size, cm	
median (range)	2.7 (1–21)
Presence of vascular thrombosis	20 (21.7)
Metastases	11 (12.0)
BCLC stage	
A	51 (55.4)
B	27 (29.3)
C	6 (6.6)
D	8 (8.7)

TABLE III. Baseline Characteristics of Patients According to the Modality of Diagnosis

	Surveillance (n = 75)	No surveillance (n = 17)	*P*
Age, Yr			
median (range)	67 (45–80)	70 (56–81)	ns
Sex			
Male	55 (73.3%)	13 (76.5%)	ns
Female	20 (26.7%)	4 (23.5%)	
Child-Pugh Class			
A	55 (73.3%)	6 (35.3%)	
B	17 (22.7%)	6 (35.3%)	0.001
C	3 (4.0%)	5 (30.4%)	
HCC type			
solitary	30 (40%)	5 (29.4%)	
multifocal	20 (26.7%)	6 (35.3%)	ns
diffuse	25 (33.3%)	6 (35.3%)	
Tumor size, cm			
median (range)	2.6 (1–7)	3.5 (1–21)	0.003
Presence of vascular thrombosis	17 (10.6%)	3 (35%)	ns
Metastases	5 (6.7%)	6 (35.3%)	0.001
BCLC stage			
A	45 (60%)	6 (35.3%)	
B	22 (29.4%)	5 (29.4%)	0.053
C	4 (5.3%)	2 (11.8%)	
D	4 (5.3%)	4 (23.3%)	

for tumor morphology that preclude standards of care treatment in 17 cases (for example, a solitary subglissonian or exophytic nodule <3 cm, where loco-regional treatment was not practicable).

Survival

During the 3 years of follow up, 40/92 patients (43.5%) died. Among them, 6/40 (15.0%) died for extra-hepatic causes. The overall mortality rate per 100 person–years was 16.7, while the mortality rate for hepatic causes was only 14.2 per 100 person–years. It was lower in subjects under surveillance (11.4 vs. 28.2, $P = 0.014$); in subjects adherent to standards of care (12.0 vs. 21.1, $P = 0.118$); and in those in non-advanced BCLC stage (10.6 vs. 45.8, $P < 0.0001$) (Table V). The six subjects who died for non-hepatic causes were considered censored in the further analysis. At the univariate analysis, the crude Hazard Ratios (HR) related to the likelihood of death were HCC diagnosis in subjects not in surveillance (crude HR 2.59; 95%CI: 1.26–5.32) and

TABLE IV. Baseline Characteristics of Patients According to Adherence to Standards of Care

	Standard of care (n = 67)	No standard of care (n = 25)	*P*
Age, Yr			
median (range)	68 (45–80)	67 (54–81)	ns
Sex			
Male	49 (73.1%)	19 (76.0%)	ns
Female	18 (26.9%)	6 (24.0%)	
Child-Pugh Class			
A	49 (73.1%)	12 (48.0%)	
B	16 (23.9%)	7 (28.0%)	0.004
C	2 (3.0%)	6 (24.0%)	
HCC type			
solitary	31 (46.2%)	4 (16.0%)	
multifocal	18 (26.9%)	8 (32.0%)	0.019
diffuse	18 (26.9%)	13 (52.0%)	
Tumor size, cm			
median (range)	2.7 (1–7)	3.5 (1.6–21)	0.03
Presence of vascular thrombosis	14 (20.9%)	6 (24.0%)	ns
Metastases	6 (8.9%)	5 (20.0%)	ns
BCLC stage			
A	41 (61.3%)	10 (40.0%)	
B	18 (26.9%)	9 (36.0%)	ns
C	4 (5.9%)	2 (8.0%)	
D	4 (5.9%)	4 (16.0%)	

TABLE V. Mortality Rate for Hepatic Causes (MR Per 100 Person-Years), According to the Modality of Diagnosis, the Adherence to Standards of Care and the Adherence to Standards of Care by Cancer Stage

	p–y	deaths	MR	95% C.I.
Total (hepatic causes)	240	34	14.2	(10.1–19.8)
Modality of diagnosis:				
Surveillance	201	23	11.4	(7.6–17.2)
No surveillance	39	11	28.2	(15.6–50.9)
Adherence to standards of care:				
Yes	183	22	12.0	(7.9–18.3)
No	57	12	21.1	(12.0–37.1)
BCLC stage:				
A	144	11	7.6	(4.2–13.8)
B	72	12	16.7	(9.4–29.3)
C	10	5	50.0	(20.8–120.1)
D	14	6	42.9	(19.3–95.4)

advanced BCLC stage (crude HR 5.21; 95%CI: 2.49–10.92). The lack of adherence to the standards of care (crude HR 1.83; 95%CI: 0.90–3.71) was not associated with survival (Table VI and Fig. 1), as well as age (crude HR 1.02; 95%CI: 0.97–1.06) and gender (crude HR 1.5; 95%CI: 0.7–3.1). No interaction between adherence to standards of care and BCLC stage was detected. After adjusting to the effect of each variable considered by the multivariate Cox model, the sole predictor of mortality was the advanced BCLC stage (adj. HR 4.07; 95%CI: 1.76–9.41) (Table VI).

DISCUSSION

The main result of our study is the observation of the lack of association between adherence to the BCLC therapeutic recommendations and the reduction of the mortality of patients with HCC.

This study is a single-center, 3 year-prospective observational study of 92 consecutive patients with HCC referred to a University Center in Southern Italy from 2009 to 2010. It provides information on the main features and clinical outcome of patients diagnosed with HCC performed in a geographical area neglected by previous studies who considered alone [Santi et al., 2012] or mainly [Stroffolini et al., 2011] patients referred to centers of Northern–Central Italy. At first, we found that the characteristics of this HCC population were similar to those observed by the ITA.LI.CA (Italian Liver Cancer) group (years 2002–2008) in a very large case series for age, male/female ratio, Child-Pugh class, AFP levels, tumor size, and tumor features, [Santi et al., 2012]. With reference to the etiology, it is interesting to note that these results confirm the progressive decrease in the proportion of patients with HBV-related HCCs among patients with liver cancer. In this series 8.8% of patients with active HBV infection was observed, and this percentage is even lower than that reported in Italy by Santi [Santi et al., 2012] and Stroffolini [Stroffolini et al., 2011] who observed a percentage of 10.6% and 13.3%, respectively. Differently, HCV infection remains the main etiological factor of HCC in Southern Italy with a percentage of 78.4%, representing more than two-thirds of cases observed, a figure higher than that observed in different Italian series in the last decade [Santi et al., 2012; Stroffolini et al., 2011; Cabibbo et al., 2012; Trinchet et al., 2007; Giovannucci et al., 2010; El-Serag et al., 2006]. In the present investigation, the cases related to alcoholic etiology and NAFLD-associated cirrhosis were likely low (2.2% and 3.6%, respectively).

The principal reasons for these findings may be related to the higher prevalence of HCV infection in all age groups and less alcohol consumption in the population of Southern Italy as compared to northern Italians.

The survival of this cohort of 92 patients at 1, 2, and, 3 years was 88%, 73.9%, and 58%, respectively. These data were comparable with those reported by Grieco [Grieco et al., 2005] that identified a 1- and 3-year survival of 92% and 46%, and with those reported by Santi [Santi et al., 2012] that identified a 1- and 3-year survival of 78.7% and 50.4% in patients observed between 2002 and 2008. Thus this center, either by surveillance or adherence to standards of

TABLE VI. Characteristics Associated With the Risk of Death for Hepatic Causes in 92 HCC Cases–Crude and Adjusted Hazards Ratios (HR) Derived by Univariate and Multivariate Cox Model

Characteristic	Crude HR (95% CI)	Adjusted HR (95% CI)
Age (one year increments)	1.02 (0.97–1.06)	—
Female gender	1.49 (0.73–3.06)	—
Lack of adherence to standards of care	1.83 (0.90–3.71)	1.29 (0.62–2.71)
Lack of surveillance	2.59 (1.26–5.32)	1.48 (0.66–3.36)
BCLC stage 3–4	5.21 (2.49–10.92)	4.07 (1.76–9.41)

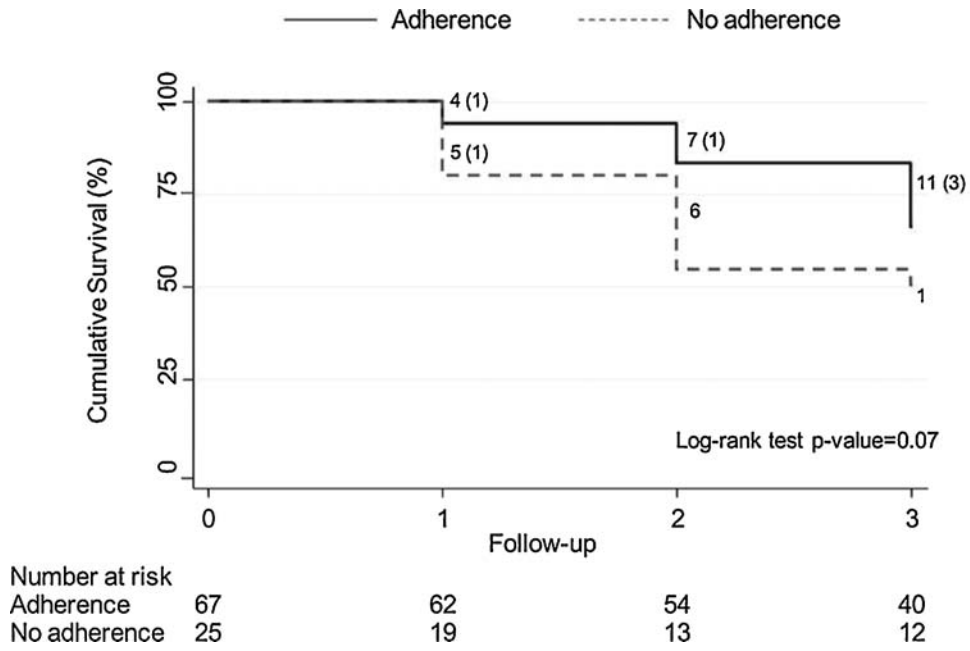

Fig 1. Survival curves by adherence to standards of care. In the graph are displayed the number of deaths for hepatic cause and not hepatic cause in brackets.

care, showed a similar survival rate of a nationwide survey and confirmed the exceptional therapeutic performance of the center. It is well established that a periodic surveillance for early detection of HCC in cirrhotic patients improves survival [Unoura et al., 1993; Wong et al., 2000; Yuen et al., 2000; Bolondi et al., 2001; Trevisani et al., 2004; Lencioni et al., 2010; Cucchetti et al., 2012; Santi et al., 2012; Sarkar et al., 2012]. Throughout this experience, the 3-year mortality rate was 28 per 100 person–years in patients with occasional diagnosis, while 11.4 ($P = 0.014$) for patients in surveillance. Therefore, this study confirms the importance of surveillance in patients at risk of developing liver cancer to diagnose the infection early and reduce mortality.

In fact, patients with an occasional diagnosis showed advanced liver disease more frequently (Child C: 30.4% vs. 4.0%), and more regularly advanced HCC stage (BCLC C–D: 35.1% vs. 10.6%) with a tumor size greater than in patients in surveillance (3.5 cm vs. 2.6 cm). Moreover, this study confirms that a large percentage (40%) of tumors detected by regular surveillance were solitary in comparison with that observed (29.4%) in the non-surveillance group. In this study 75/92 (81.5%) patients were under surveillance, and this was due to the fact that this center is a tertiary referral center; while it is possible that in a different clinical setting, surveillance could not have the same implementation. Furthermore, patients under surveillance were more frequently offered curative treatments. This results has been reported by others [Fasani et al., 1999; Wong et al., 2000; Bruix et al., 2001; Trevisani et al., 2002] and can be attributed to the better tumor stage and to the less advanced Child-Pugh class, which is an independent predictor of mortality [Wong et al., 2000].

Adversely, the adherence of treatment to the current standards of care in clinical practice is much less investigated worldwide [Kim et al., 2012; Bruix et al., 2014; Graf et al., 2014]. At present, the BCLC strategy and their update [Forner et al., 2010] are considered the standard for staging and treatment of HCC [Bruix et al., 2014].

The benefits on survival of treatment proposed strategy in each different BCLC stage (except for stage D) have already been documented in large studies, which have contributed to the diffusion and the "building" of the BCLC system itself [Llovet et al., 1999].

During this study, 74% of patients adhered perfectly to the current standard of care [Bruix and Sherman, 2005]; this is different from other studies showing that the treatment procedures did not exactly match the BCLC paradigm in clinical practice, especially in the Asian population [D'Avola et al., 2011; Bolondi et al., 2012; Kim et al., 2012; Borzio et al., 2013; Radu et al., 2013; Trovato et al., 2013]. The characteristics of patients lacking standards of care in this population were: more advanced liver disease (24.0% vs. 3.0%), a diffusive or multifocal HCC (84% vs. 53.8%), and a greater diameter of the main nodule (3.5 cm vs 2.7 cm). Nonetheless, the multivariate analysis of the factors related to mortality indicates that the only independent factor of survival is the BCLC tumor stage. This also suggests that the lack of evidence that adherence to standards of care does not modify survival could be linked to different factors. First, the study limitations such as

the small number of patients recruited and, probably, the different characteristics of the series of patients in comparison to the patients of the BCLC building era (1999).

On the other hand, increasing evidence from the literature put forward that the BCLC staging system can be imperfect in selecting the best treatment option for the different stages of HCC, especially for the intermediate stage [D'Avola et al., 2011; Bolondi et al., 2012; Kim et al., 2012; Borzio et al., 2013; Radu et al., 2013; Trovato et al., 2013; Bruix et al., 2014; Graf et al., 2014]. This problem is prevalently due to the wide range of the morphological characteristics of HCC in the intermediate stage, which should not be treated with a unique type of therapy. Currently, a lot of effort is being made to improve the criteria for therapeutic indications. All of these conditions can explain the limited influence of adherence to standards of care on survival and suggest that the BCLC stratification system has to be refined and adapted to the characteristics of current HCC patients who are older, presenting more Child-Pugh A class cirrhosis and a mounting proportion of tumors unrelated to virus infection [Stroffolini et al., 2011].

Finally, during this 3-year prospective study we have observed that: (i) in Southern Italy the causes of HCC are still largely linked to the HCV infection; (ii) the percentage of patients with NAFLD-related HCC is almost half of that observed in other series of different geographical origins; (iii) the overall survival of patients referred to this center is similar to that observed at national and international levels; (iv) the lack of evidence regarding the adherence to the BCLC therapeutic recommendations reduces the mortality of patients with HCC; and (iv) the BCLC system cannot be accepted as a "commandment" to be invariably followed in everyday practice, and that refinements are urgently needed; it is important to individualize the subclasses of patients in each stage (particularly the intermediate one) and give treatments that are different and more appropriate than the current standards of care. The difficulties in applying the algorithms in routine clinical practice and the high prevalence of older patients with relevant comorbidities may account for these findings. Strategies to help improve adherence to international guidelines for HCC in clinical practice are required.

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