Alpha-Fetoprotein Has No Prognostic Role in Small Hepatocellular Carcinoma Identified During Surveillance in Compensated Cirrhosis

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Alpha-fetoprotein is a tumor marker that has been used for surveillance and diagnosis of hepatocellular carcinoma (HCC) in patients with cirrhosis. The prognostic capability of this marker in patients with HCC has not been clearly defined. In this study our aim was to evaluate the prognostic usefulness of serum alpha-fetoprotein in patients with well-compensated cirrhosis, optimal performance status, and small HCC identified during periodic surveillance ultrasound who were treated with curative intent. Among the 3,027 patients included in the Italian Liver Cancer study group database, we selected 205 Child-Pugh class A and Eastern Cooperative Group Performance Status 0 patients with cirrhosis with a single HCC ≤3 cm of diameter diagnosed during surveillance who were treated with curative intent (hepatic resection, liver transplantation, percutaneous ethanol injection, radiofrequency thermal ablation). Patients were subdivided according to alpha-fetoprotein serum levels (i.e., normal ≤20 ng/mL; mildly elevated 21-200 ng/mL; markedly elevated >200 ng/mL). Patient survival, as assessed by the Kaplan-Meier method, was not significantly different among the three alpha-fetoprotein classes (P = 0.493). The same result was obtained in the subgroup of patients with a single HCC ≤2 cm (P = 0.714). An alpha-fetoprotein serum level of 100 ng/mL identified by receiver operating characteristic curve had inadequate accuracy (area under the curve = 0.536, 95% confidence interval = 0.465-0.606) to discriminate between survivors and deceased patients. _Conclusion_: Alpha-fetoprotein serum levels have no prognostic meaning in well-compensated cirrhosis patients with single, small HCC treated with curative intent. (HEPATOLOGY 2012;56:1371-1379)

Hepatocellular carcinoma (HCC) is the third cause of cancer death and the leading cause of mortality among patients with cirrhosis.[1] Liver cirrhosis is in fact the main risk factor for HCC, and the annual incidence of HCC in cirrhosis patients is 3%-7%.[2,3]

Detecting HCC at an early stage is the main objective of screening and surveillance programs.[3] Indeed, the utility of surveillance for HCC in patients with cirrhosis is supported by the results of a randomized trial carried out in patients with chronic hepatitis B virus (HBV) infection and several cohort studies performed in patients with cirrhosis.[4-7] Surveillance of patients at risk of HCC with liver ultrasound, with or without serum alpha-fetoprotein assessment, is recommended by European, American, and Asiatic HCC management guidelines with the aim to identify HCC at an early stage in those patients who, in the event of

cancer detection, are amenable to curative therapies able to improve their prognosis.[8-10] The American Association for the Study of Liver Diseases (AASLD) guidelines for HCC diagnosis and treatment, however, recently dropped alpha-fetoprotein assessment from the surveillance armamentarium due to poor sensitivity for early diagnosis of HCC and unacceptable specificity of this tumoral marker.[10] Nonetheless, the use of alpha-fetoprotein as a prognostic indicator when HCC is diagnosed in the most favorable setting—patients with compensated cirrhosis, optimal performance status, single, small HCC, and as such amenable to curative treatment—has not been sufficiently addressed so far.[11] In particular, some studies that evaluated the prognostic usefulness of alpha-fetoprotein in patients with HCC suggested that its prognostic role may be influenced by size and number of the HCC nodules, although contrasting results have been obtained.[11-14]

Single, small HCC in patients with compensated cirrhosis and optimal performance status are identified by the Barcelona Clinic Liver Cancer (BCLC) classification as very early (class 0) and early (class A) HCC, and at this stage patients are usually amenable to curative treatment.[15] The BCLC classification system, however, does not include alpha-fetoprotein assessment, although this serum marker has been identified by several studies as an overall independent predictor of survival.[11] However, the majority of studies that evaluated the prognostic capability of alpha-fetoprotein have included heterogeneous cohorts of patients, thus preventing an appropriate assessment of its usefulness as a prognostic tool in a well-defined subset of patients.[11,16]

In this study we evaluated the prognostic role of alpha-fetoprotein in patients with compensated cirrhosis, optimal performance status, and single, small HCC (≤3 cm) identified during surveillance and treated with curative intent. Our aim was to verify whether, in this specific setting, assessment of alpha-fetoprotein serum levels may have any prognostic relevance.

Patients and Methods

Patients. We retrospectively analyzed the data of the Italian Liver Cancer (ITA.LI.CA) database, currently including 3,027 HCC patients consecutively seen from January 1987 to December 2008 at 11 Italian medical institutions. The data were collected prospectively and updated every 2 years. Main characteristics of the database have been previously reported.[17] Briefly, the ITA.LI.CA database includes data on patient demographics, main biochemical and hematological variables, etiology and stage of liver disease, presence of comorbidities, HCC stage and treatment, patient survival, and causes of death.[17]

For the purpose of this study, we included patients with well-compensated liver cirrhosis (Child-Pugh class A) and Eastern Cooperative Oncology Group Performance Status of 0 who were diagnosed with a single, small (i.e., ≤3 cm) HCC during periodic liver ultrasound, had no vascular invasion, no metastases, and who were treated with curative intent.[18,19]

Diagnosis, Staging, and Treatment of HCC. The diagnosis of HCC was based on histology and/or cytology in 106 (51.7%) patients. In the remainder, diagnosis was confirmed by combining an alpha-fetoprotein value >200 ng/mL with typical features in one imaging technique (dynamic computed tomography, magnetic resonance imaging, or contrast-enhanced ultrasound) or, in the absence an alpha-fetoprotein value >200 ng/mL, in at least two imaging techniques.[8] Tumor size (maximum diameter, expressed in cm) was assessed on imaging.

When available, in patients in whom the diagnosis of HCC was histologically confirmed by fine-needle aspiration biopsy, surgical specimen, or explanted liver, the tumor was graded according to the Edmondson and Steiner classification.[20] For consistency, we grouped grades I and II (well and moderately differentiated) and grades III and IV (poorly differentiated) tumors.[21]

This study included patients who were treated with curative intent alone, considering curative the surgical (orthotopic liver transplantation, hepatic resection) and percutaneous ablative (percutaneous ethanol injection [PEI] or radiofrequency thermal ablation [RFTA]) techniques.

Alpha-Fetoprotein and Survival. Alpha-fetoprotein was determined at the time of HCC diagnosis. Alpha-fetoprotein levels were classified as normal (≤20 ng/mL), mildly elevated (21-200 ng/mL), and markedly

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Table 1. Main Demographic, Biochemical, and Clinical Characteristics of the 205 Study Patients

Variable	Unit	Value
Age	years	69 (46-89)
Gender	male	135 (65.8)
ALT	n x ULN	1.8 (0.5-7.5)
Albumin	g/dL	3.9 (3.2-4.8)
Total bilirubin	mg/dL	1.0 (0.3-2.1)
Prothrombin activity	(%)	81 (61-110)
Platelet count	$\times 10^9$/L	115 (61-363)
Alpha-fetoprotein	ng/mL	14.0 (1.0-4,185)
HCC diameter	cm	2.0 (0.8-3.0)
Esophageal varices*	present	53 (32.5)

Data are shown as median value (range) or absolute frequency (%).

*Data regarding esophageal varices were available in 163 patients (79.5). ULN, upper limit of normal; ALT, alanine aminotransferase; HCC, hepatocellular carcinoma.

elevated (>200 ng/mL). Overall survival was calculated from the time of HCC diagnosis to death or to December 2008. Patients lost to follow-up (n = 22, 10.7%) were censored at the time of the last clinical examination.

Statistical Analysis. Continuous data are expressed as median value and range, and discrete variables as absolute and relative frequencies. To compare continuous variables we applied the Mann-Whitney U test and the Kruskal-Wallis test, whereas discrete variables were compared with the χ^2 test with Yates' correction and Fisher's exact test, as appropriate. Patient survival was assessed according to the Kaplan-Meier method and compared by the log-rank test. A receiver operating characteristic (ROC) curve was used to identify the alpha-fetoprotein value with the highest accuracy for discriminating between survivors and deceased patients. Moreover, the ROC curve was used to identify the cutoff prevalence-adjusted positive and negative predictive values, and positive and negative likelihood ratios for death. A 2-tailed P-value < 0.05 was considered statistically significant. Statistical analysis was performed using MedCalc statistical package (MedCalc Software, Mariakerke, Belgium).

Ethics. The ITA.LI.CA database management conforms to the past and current Italian legislation on the 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 demographic, biochemical, and clinical characteristics of the 205 study patients are reported in Table 1. The main cause of liver cirrhosis was chronic infection with hepatitis viruses (n = 180, 87.8%). The Child-Pugh score was 5 in 151 patients (73.7%), and the maximum diameter of the HCC nodule was ≤2 cm in 122 patients (59.5%). Serum alpha-fetoprotein levels were within the normal range (≤20 ng/mL) in 116 patients (56.6%), mildly elevated (21-200 ng/mL) in 71 patients (34.6%), and markedly elevated (>200 ng/mL) in 18 patients (8.8%). Seven patients (3.4%) had an extremely high (>400 ng/mL) serum alpha-fetoprotein level. Treatment of HCC was liver transplantation in three patients (1.5%), hepatic resection in 53 patients (25.8%), RFTA and PEI in 66 (32.2%) and 83 (40.5%) patients, respectively. Median duration of follow-up was 3.7 years, and median time to death was 48 months. Figure 1 shows the log-transformed serum alpha-fetoprotein levels in the 205 patients subdivided according to status (survivors and deceased).

Among the 180 patients with viral etiology of liver disease, 154 patients (85.6%) had chronic hepatitis C virus (HCV) infection (including four patients with chronic HCV-HBV coinfection), and 26 patients (14.4%) had chronic HBV infection alone. All in all, 47 patients had been treated with interferon-based antiviral therapy before HCC diagnosis (41 HCV-positive alone, 4 HBV-positive alone, and 2 with HCV-HBV coinfection). Among HBV patients, seven were being treated with nucleos(t)ide analogs at the time of HCC diagnosis. We subdivided viral patients into two groups—those with current and past antiviral therapy (n = 50) versus those who received no antiviral therapy at all (n = 104)—and evaluated alpha-fetoprotein levels in these two groups. The median alpha-fetoprotein level was 19.5 ng/mL (range, 2.0-4,185 ng/mL) and 16.0 ng/mL (range, 1.0-1,600 ng/mL), respectively (P = 0.874).
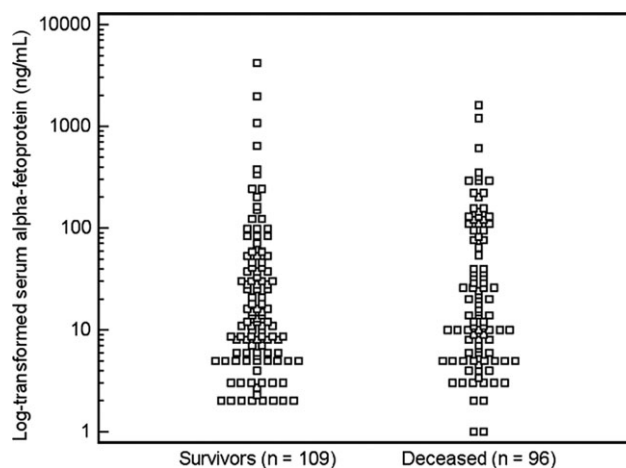

Fig. 1. Plot of log-transformed serum alpha-fetoprotein levels of all study patients (n = 205) subdivided according to status (survivors and deceased).

Table 2. Main Demographic, Biochemical, and Clinical Characteristics of the 205 Study Patients Subdivided According to Serum Alpha-Fetoprotein Levels

| Variable | Unit | Serum Alpha-Fetoprotein Level | | | P-value |
		0-20 (n = 116)	21-200 (n = 71)	>200 (n = 18)	
Age	years	69 (47-89)	69 (46-84)	69 (58-84)	0.953
Gender	male	87 (75.0)	39 (54.9)	9 (50.0)	0.007
ALT	n x ULN	1.5 (0.4-6.6)	2.0 (0.3-7.5)	1.8 (0.9-5.0)	0.011
Child-Pugh	score 5	84 (72.4)	52 (73.2)	15 (83.3)	0.616
HCC diameter	cm	2.0 (0.8-3.0)	2.0 (0.8-3.0)	2.4 (1.0-3.0)	0.163
HCC treatment	Resection	32 (27.6)	15 (21.1)	6 (33.3)	
	OLT	0 (0)	2 (2.8)	1 (5.6)	
	PEI	49 (42.2)	29 (40.9)	5 (27.8)	
	RFTA	35 (30.2)	25 (35.2)	6 (33.3)	0.444
Deceased	n	52 (44.8)	34 (47.9)	10 (55.6)	0.681
Cause of death	HCC progression	28 (53.8)	16 (47.1)	5 (50.0)	
	Liver failure	10 (19.2)	8 (23.5)	2 (20.0)	
	Bleeding	5 (9.6)	3 (8.8)	1 (10.0)	
	Sepsis	2 (3.8)	1 (2.9)	1 (10.0)	
	Other	5 (9.6)	5 (14.7)	1 (10.0)	
	Not available	2 (3.8)	1 (2.9)	0 (0)	0.825

Data are shown as median value (range) or absolute frequency (%).

ALT, alanine aminotransferase; ULN, upper limit of normal; HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation; PEI, percutaneous ethanol injection; RFTA, radiofrequency thermal ablation.

Table 2 shows the main demographic and clinical characteristics of the patients subdivided according to alpha-fetoprotein levels ($\leq$20 ng/mL; 21-200 ng/mL; >200 ng/mL). Among the parameters evaluated, female gender ($P = 0.007$) and greater increase in alanine aminotransferase ($P = 0.011$) were significantly more common in patients with mildly (21-200 ng/mL) or markedly elevated (>200 ng/mL) alpha-fetoprotein levels. HCC diameter and degree of liver failure were not significantly different among the three alpha-fetoprotein classes. Modality of HCC treatment (surgical versus ablation, $P = 0.444$) and causes of death were similar among the three groups. Edmondson grading was available only in a minority of patients in all classes (27% in patients with alpha-fetoprotein $\leq$20 ng/mL; 17% in patients with alpha-fetoprotein 21-200 ng/mL; 11% in patients with alpha-fetoprotein >200 ng/mL). Despite this limitation, patients with well and moderately differentiated HCCs tended to be more frequently observed in the group with normal ($\leq$20 ng/mL) or mildly elevated (21-200 ng/mL) alpha-fetoprotein levels ($P = 0.056$).

During the follow-up, 96 patients (46.8%) died and the proportion of deceased patients was similar in the three alpha-fetoprotein classes ($\leq$20 ng/mL; 21-200 ng/mL; >200 ng/mL). Similarly, the causes of death were not different across the three alpha-fetoprotein classes. Figure 2 shows the actuarial survival curves of these patients. There was no statistically significant difference among the three alpha-fetoprotein classes ($\chi^2 = 1.4162$, $P = 0.493$). The analysis was repeated in

the subgroup of 122 patients with a nodule $\leq$2 cm (Fig. 3A) and in the subgroup of 83 patients with a nodule 2-3 cm (Fig. 3B): again, no significant survival difference was observed among the three alpha-fetoprotein classes (HCC $\leq$2 cm: $\chi^2 = 0.6744$, $P = 0.714$; HCC 2-3 cm: $\chi^2 = 2.0926$, $P = 0.351$). We also compared survival between patients with normal ($\leq$20 ng/mL) and elevated (>20 ng/mL) alpha-fetoprotein (Fig. 4A), and between patients with an alpha-fetoprotein above or below 200 ng/mL (Fig. 4B). Even with these cutoffs, no statistically significant differences
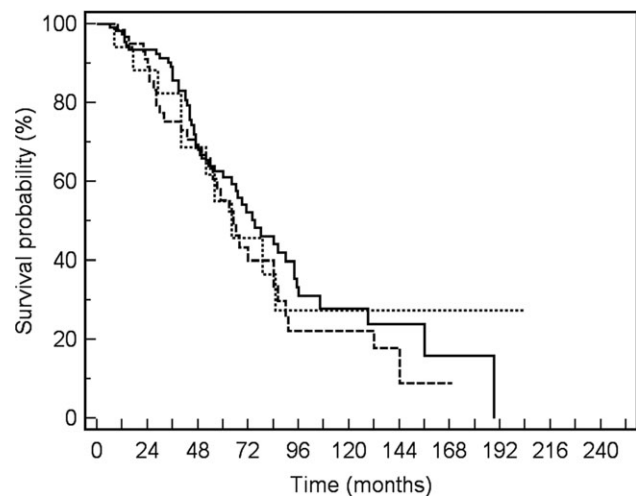

Fig. 2. Kaplan-Meier survival curves of the 205 study patients subdivided according to their alpha-fetoprotein serum levels at the diagnosis of hepatocellular carcinoma (solid line, $\leq$20 ng/mL; dashed line, 21-200 ng/mL; dotted line >200 ng/mL).
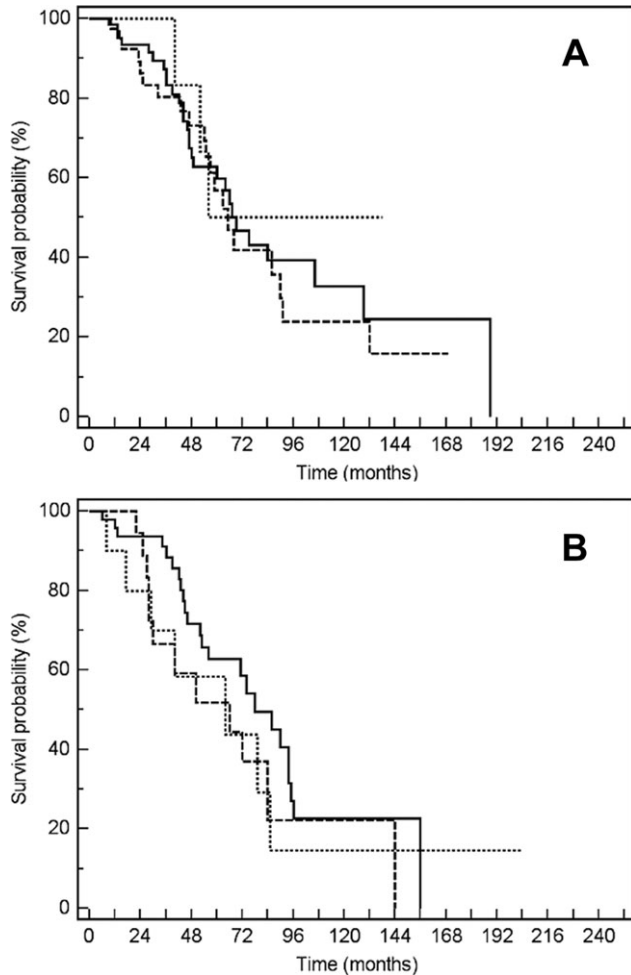
Fig. 3. Kaplan-Meier survival curves of the 122 study patients with HCC ≤2 cm (A) and of the 83 study patients with HCC between 2 and 3 cm (B), subdivided according to their alpha-fetoprotein serum levels (solid line, ≤20 ng/mL; dashed line, 21-200 ng/mL; dotted line >200 ng/mL).

were observed. Lastly, we evaluated treatment and survival of the seven patients with extremely high alpha-fetoprotein levels (>400 ng/mL): three (42.9%) had a tumor ≤2 cm, four underwent hepatic resection, and three percutaneous ablation. Four patients died after a median of 56 months (range, 17-79 months) and three were alive after a median of 60 months (range, 6-100 months). Taking into account the caveat such an analysis may bear, due to the very small sample size, there was no survival difference between patients with alpha-fetoprotein above and below 400 ng/mL ($\chi^2 = 0.137$, $P = 0.712$).

The ROC curve showed that alpha-fetoprotein had inadequate accuracy to discriminate survivors and deceased patients (area under the ROC curve = 0.536, 95% confidence interval [CI] = 0.465-0.606). A ROC curve-identified alpha-fetoprotein cutoff of 100 ng/mL had good specificity (88%, 95% CI = 81%-94%) but

unacceptably low sensitivity (23%, 95% CI = 15%-33%) for discriminating survivors and deceased patients (Fig. 5). Prevalence-adjusted positive and negative predictive values for death of this cutoff were 63.6% and 56.5%, respectively, whereas positive and negative likelihood ratios were 1.96 and 0.86, respectively. Moreover, there was no significant survival difference between patients with an alpha-fetoprotein below or above this cutoff ($\chi^2 = 0.8301$; $P = 0.367$).

Lastly, we also evaluated the predictors of death in this very homogenous population of cirrhosis patients with HCC and found that the type of curative treatment (hepatic surgery, median survival 86 months versus ablative treatment, median survival 64 months, $P = 0.019$) was the only predictor of survival, whereas there was no significant survival difference associated with gender, age below 65 years, etiology of liver disease (viral versus nonviral), presence of esophageal
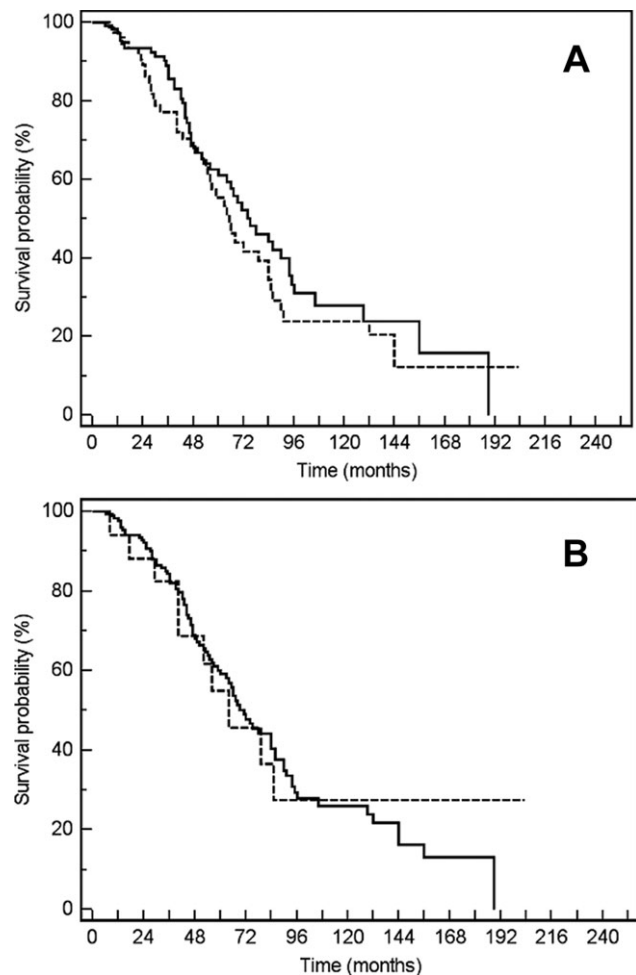

Fig. 4. Kaplan-Meier survival curves of the 205 study patients subdivided according to their alpha-fetoprotein serum levels at the diagnosis of hepatocellular carcinoma (A.: solid line, ≤20 ng/mL; dashed line, >20 ng/mL; B: solid line, ≤200 ng/mL; dashed line, >200 ng/mL).
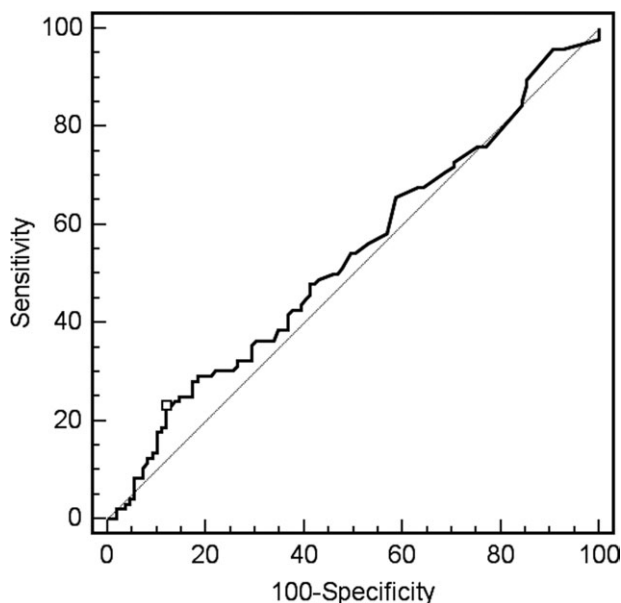
Fig. 5. ROC curve showing the overall accuracy of alpha-fetoprotein serum levels for discriminating between survivors and deceased patients. The empty dot identifies the best cutoff value (i.e., 100 ng/mL) of serum alpha-fetoprotein.

varices (datum available in 163 patients), and size of HCC (≤2 or 2-3 cm).

Discussion

The usefulness of serum alpha-fetoprotein as a surveillance and diagnostic test for HCC has been dramatically challenged by the impressive technical improvement of abdominal ultrasound and contrast medium-enhanced diagnostic imaging that have led to great accuracy in the early identification and noninvasive characterization of small HCCs.[22] In fact, it has repeatedly been shown that serum alpha-fetoprotein levels tend to be nonspecifically altered in patients affected by chronic liver disease, and that diagnostic levels of this tumor marker are seldom observed in patients with small HCCs.[23-27] This evidence has led the providers of the updated AASLD guidelines for the diagnosis and management of HCC to drop alpha-fetoprotein from the surveillance armamentarium for HCC in patients with cirrhosis, although this decision was debated.[10,28,29]

However, alpha-fetoprotein may have a prognostic meaning in patients with HCC, and is included in prognostic classifications such as the Cancer of the Liver Italian Program score, although also in this setting the results of various studies have provided inconsistent findings.[11-14,30,31] Recently, Tandon and Garcia-Tsao[11] performed a comprehensive, systematic review of prognostic indicators in HCC and identified

alpha-fetoprotein as one of the most robust prognostic indexes, although they observed that the appropriate cutoff level and group of patients in which this serum marker may be helpful remain to be established. Thus, we deemed it of interest to evaluate whether alpha-fetoprotein might be a prognostic indicator in patients who might benefit most from the application of curative treatment, and therefore where prognostication should be of utmost importance.

In this study we demonstrated that alpha-fetoprotein has no prognostic relevance in patients with well-compensated cirrhosis, optimal performance status, and a single, small HCC (i.e., ≤3 cm) identified during surveillance and treated with curative intent. The poor prognostic performance of alpha-fetoprotein we observed in this particular setting may be due to several reasons. First, alpha-fetoprotein levels were within the normal range in more than half of the population, and reached markedly elevated levels (i.e., >200 ng/mL) in less than 10% of the patients. These findings are strikingly in keeping with previous features (i.e., 11.1%) observed in a population of 153 patients with small (<2 cm) HCC seen in our geographical area.[32] Even when patients were more broadly subdivided according to normal or elevated alpha-fetoprotein levels (i.e., above or below 20 ng/mL) no survival difference surfaced between the two groups. Furthermore, in order to avoid limitations related to the use of pre-test fixed cutoffs of a continuous variable, we also performed an analysis using an *ad hoc* alpha-fetoprotein cutoff identified by ROC curve. However, even this analysis showed that alpha-fetoprotein had negligible prognostic accuracy (area under the ROC curve = 0.536, 95% CI = 0.465-0.606), and the ROC curve-identified alpha-fetoprotein cutoff (i.e., 100 ng/mL) had largely inadequate sensitivity (23%, 95% CI = 15%-33%). Second, as previously reported by others,[33,34] we too observed that increased alpha-fetoprotein levels were associated with female gender and greater hepatic cytolytic activity, although they had no association with clinical and tumoral characteristics, and were not influenced by current and past antiviral therapy. In this regard, it has to be emphasized that some of its determinants such as degree of liver failure and HCC size varied within a narrow range as per study inclusion criteria. These findings confirm that the prognostic role of alpha-fetoprotein reported in other studies may be due to the heterogeneous liver- and tumor-related characteristics, and different modalities of HCC treatment in the studied populations.[11,16] In fact, it seems that the predictive ability of alpha-fetoprotein is highly dependent on tumor size

and treatment strategy, being more apparent in patients with advanced HCC and in those treated with palliative intention, and less evident in patients with small tumors and in those who underwent curative treatment.[11-14,30,35] Indeed, in studies where patients with advanced liver disease and/or advanced HCC were excluded from the analyses, the prognostic role of alpha-fetoprotein was dramatically diluted.[12,30] These considerations are also supported by the evidence that in our series there was no "therapeutic disparity," and that mortality and causes of death were evenly distributed across patients with normal, mildly, and markedly elevated alpha-fetoprotein levels, likely ruling out the presence of other possible prognostic confounding factors.

Some studies have shown that the rate of rise of serum alpha-fetoprotein levels may have prognostic meaning in HCC patients awaiting liver transplantation, yet these studies did not identify static alpha-fetoprotein levels as a predictor of survival or HCC recurrence after liver transplantation.[36-38] As serial alpha-fetoprotein determinations were not available in our patients, we were not able to assess the possible prognostic role of dynamic alpha-fetoprotein determinations in the clinical setting of this study.

In this study we selected the 3-cm cutoff to define small HCC, as several studies have shown an excellent outcome after curative treatment in these patients, and this threshold is also accepted for curative treatment by the Asian Pacific Association for the Study of the Liver.[9,39,40] However, we also performed the same analyses in patients with an HCC ≤2 cm, as other studies have shown that the prevalence of the two main negative prognostic factors, microvascular invasion and satellite nodules, tends to increase in lesions above this threshold.[41-43] We confirmed, also in this group of HCC classified "very early" (stage 0) by the BCLC system, that serum alpha-fetoprotein had no prognostic role, thus confuting the hypothesis that adding this tumor marker to the BCLC classification might increase its prognostic yield for patients with very early (stage 0) and early (stage A) HCCs.[11,16]

Noteworthy, in our cohort the 5-year survival rate was ≈60% in both patients with alpha-fetoprotein serum levels below and above 200 ng/mL. This result is in keeping with those previously obtained in similar patient populations treated with RFTA and hepatic resection, and compares favorably with the results of liver transplantation.[44-46] Therefore, the survival figures obtained in this and previous studies carried out in similar patient populations question the appropriateness of liver transplantation to cure solitary tumors

up to 3 cm in well-compensated cirrhosis patients, especially when the "transplant benefit" and the worldwide organ shortage are taken into consideration.[46,47]

This study undoubtedly has some limitations. In the current version of the ITA.LI.CA database, data regarding tumor recurrence after treatment are not available, and therefore in this study the influence of alpha-fetoprotein levels on some important composite endpoints such as recurrence plus death could not be assessed. Furthermore, as expected in our country, hepatitis virus infection was the cause of cirrhosis in most cases, and therefore it remains to be established whether these results can be generalized to HCC patients with other etiologies.[48,49] Lastly, although the ITA.LI.CA database includes more than 3,000 HCC patients, the selection criteria for this study were very strict, and therefore the study population was limited to 205 patients. A *post-hoc* analysis shows that this sample size had a statistical power of 22% to detect a difference between the observed 5-year survival rates of patients with alpha-fetoprotein below (61%) and above (55%) 20 ng/mL. With such survival rates, a sample size of 2,118 patients with compensated cirrhosis and single, small HCC treated with curative intent, derived from a population of more than 30,000 patients with HCC, would have been needed to achieve a power of 80%. All in all, we feel that even these figures, if framed in the context of clinical practice, confirm the bland prognostic potential of alpha-fetoprotein in the subset of patients we selected.

In conclusion, we found that serum alpha-fetoprotein has no prognostic role in compensated cirrhosis patients with a single, small HCC diagnosed during surveillance and treated with curative intent. These findings emphasize the futility of serum alpha-fetoprotein determination in a clinical setting where surveillance for HCC may provide its maximal benefit in terms of amenability to curative treatment and patients survival. New, more accurate markers are therefore needed to improve our current ability to predict the outcome of patients diagnosed with early HCC.

Appendix

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