

Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival

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Background & Aims: The current guidelines recommend the surveillance of cirrhotic patients for early diagnosis of hepatocellular carcinoma (HCC), based on liver ultrasonography repetition at either 6 or 12 month intervals, since there is no compelling

evidence of superiority of the more stringent program. This study aimed at comparing cancer stage, treatment applicability, and survival between patients on semiannual or annual surveillance.

Methods: We analyzed the clinical records of 649 HCC patients in Child-Pugh class A or B, observed in ITA.LI.CA centers. HCC was detected in 510 patients submitted to semiannual surveillance (Group 1) and in 139 submitted to annual surveillance (Group 2). In Group 1 the survival was presented as *observed* and *corrected for the lead time*.

Results: The cancer stage was less severe in Group 1 than in Group 2 ($p < 0.001$), with more single tiny (≤ 2 cm) and less advanced tumors. Treatment applicability was improved by the semiannual program ($p = 0.020$). The median *observed* survival was 45 months (95% CI 40.0–50.0) in Group 1 and 30 months (95% CI 24.0–36.0) in Group 2 ($p = 0.001$). The median *corrected* survival of Group 1 was 40.3 months (95% CI 34.9–45.7) ($p = 0.028$ with respect to the observed survival of Group 2). Age, platelet count, α -fetoprotein, Child-Pugh class, cancer stage, and hepatocellular carcinoma treatment were independent prognostic factors.

Conclusions: Semiannual surveillance increases the detection rate of very early hepatocellular carcinomas and reduces the number of advanced tumors as compared to the annual program. This translates into a greater applicability of effective treatments and into a better prognosis.

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Keywords: Hepatocellular carcinoma; Cirrhosis; Diagnosis; Surveillance interval; Cancer stage; Survival.

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The sole approach to achieve long-term survival is to detect the tumor at an early stage, suitable for curative or effective therapies, as suggested by a randomized controlled study performed in hepatitis B surface antigen (HBsAg) carriers [7] and several observational studies [2,8–10]. International guidelines for HCC management therefore recommend surveying patients at risk of HCC development with serial ultrasonographies (US) of the liver [11,12].

The ideal goal of surveillance is the detection of single tiny HCCs, which have the highest chance of being cured since the rate of microvascular invasion and satellite nodules – predictors of recurrence after radical therapy [3,13] – significantly increase when the tumor exceeds 2 cm [14]. Indeed, a size ≤ 2 cm predicts a lower recurrence and better survival after surgical [15,16] and percutaneous ablative procedures [17]. Other studies raise the threshold to 3 cm for an excellent outcome after curative treatments [18,19].

Both semiannual and annual surveillance are recommended by the American Association of the Study of the Liver Disease (AASLD) guidelines [12] since there is no clear evidence of superiority of the more stringent program concerning either cancer features [2,20] or patient survival [10,21]. However, in the studies describing survival the potential advantage offered by the semiannual program could have been marred by the presence of Child-Pugh (C-P) class C patients, in whom the surveillance becomes useless [22,23]. Lastly, a Korean study, presented as abstract, showed that the semiannual schedule improves patient survival compared with the annual one [24]. Therefore, what is the ideal interval of surveillance is still a matter of debate. This study aimed at comparing the efficiency of semiannual and annual surveillance in terms of early diagnosis of HCC and survival in C-P class A and B cirrhotic patients.

Patients and methods

Patients

We analyzed the data of the Italian Liver Cancer (ITA.LI.CA) database, currently including 2193 HCC patients seen consecutively from January 1987 to December 2006 at 10 medical institutions. The data were collected prospectively and were updated every 2 years. Antecedent versions of this database, updated at 1998 and 2004, were utilized in our previous studies describing the impact of interval surveillance on patient survival [10,21].

For the purpose of this study, we selected patients fulfilling the following inclusion criteria: (1) C-P class A or B; (2) HCC diagnosis made during a regular surveillance based on liver US, with or without α -fetoprotein (AFP) determination, performed every 6 (± 1 month) or 12 month (± 1 month); (3) description of presenting cancer stage available. Accordingly, 649 patients were selected. The causes of exclusion were: C-P class C or unspecified in 472 cases, diagnosis of HCC made outside any surveillance in 816, unspecified modality of HCC diagnosis in 10, unspecified interval of surveillance in 109, and interval outside the above mentioned ranges in 137.

Patients were divided into:

- Group 1, consisting of 510 (78.6 %) patients with HCC detected during semiannual surveillance.
- Group 2, consisting of 139 (21.4 %) cases with HCC detected during yearly surveillance.

The interval was established by the referring physician of each patient, who was not necessarily one of the ITA.LI.CA clinicians since a number of patients were referred to our centers for diagnosis and/or treatment.

Etiology and diagnosis of cirrhosis

The cause of liver disease was classified as:

- hepatitis C virus (HCV), if patients were positive for serum anti-HCV antibody;

- hepatitis B virus (HBV), if patients were HBsAg + carriers;
- alcoholic, if the daily ethanol intake was more than 60 g for women and 80 g for men for more than 10 yrs, in the absence of any other known causes of liver disease;
- multifactorial, if the disease had two or more causative factors;
- other (22 cryptogenic liver diseases, 1 hereditary hemochromatosis, and 2 primary biliary cirrhosis).

Cirrhosis was histologically confirmed in 271 patients and by laparotomy or laparoscopy in 11. In the remaining patients, the diagnosis was made unequivocal by clinical evaluation, presence of nodular liver margins at US examination, endoscopic and/or US findings suggesting the presence of portal hypertension, and laboratory features.

Diagnosis and staging of HCC

The diagnosis was based on histology or cytology in 96 patients. Otherwise, diagnosis was confirmed by combining an increase (>200 ng/ml) of AFP [12,25] with typical features of the lesion in one imaging technique (dynamic computed tomography [CT] scan or magnetic resonance imaging [MRI] or contrast enhanced-US [CEUS]) or, in the absence of diagnostic AFP elevation, in at least two techniques. Cancer was staged by CT scan or MRI. All patients had a chest X-ray, while additional investigations to detect metastases were performed when extrahepatic involvement was suspected.

For the purpose of this study, HCC was staged as:

- solitary nodule ≤ 2 cm without macrovascular invasion (V0), lymph-node invasion (L0) or distant metastases (M0);
- solitary nodule of 2.1–3 cm, V0, L0, M0;
- solitary nodule of 3.1–5 cm, V0, L0, M0;
- 2–3 nodules, each ≤ 3 cm (paucifocal), V0, L0, M0;
- advanced tumor (outside the Milano criteria [26]).

Therapeutic decision

The eligibility criteria for hepatic resection, percutaneous ethanol injection (PEI), radiofrequency thermoablation (RF) or transarterial chemoembolization (TACE) have been reported in detail elsewhere [10].

Serologic testing

Liver tests, serum virological markers and AFP were determined by conventional methods, using commercial kits.

Statistical analysis

Continuous data are expressed as median $\pm$ range, and discrete variables as absolute and relative frequencies. The Mann-Whitney *U* test was used to compare continuous data, and χ^2 test or Fisher's exact test to compare discrete variables.

To identify factors significantly associated with the cancer stage, logistic regression analysis was used, only including variables available in more than 90% of patients. We tested: age, sex, etiology (HCV vs. other causes), decade of diagnosis (1987–1996 and 1997–2006), C-P class, esophageal varices (present/absent), comorbidities (cardiovascular, pulmonary, renal, gastrointestinal and hematological diseases, obesity and diabetes) (present/absent), alanine aminotransferase (ALT), platelet count, AFP (≤ 20 ng/ml, 21–200 ng/ml, >200 ng/ml) and surveillance interval. Continuous variables, if not otherwise specified, were dichotomized according to the median value. Variables associated ($p \leq 0.10$) with the cancer stage at the univariate analysis were included in a stepwise multivariate analysis to identify those providing independent information.

Survival was calculated from the time of cancer diagnosis to death, with values censored at the date of the last follow-up, and was expressed as median and 95% Confidence Interval (CI). Life table estimates were calculated according to the Kaplan-Meier method, and compared by the log-rank test. To minimize the lead time bias [27], we calculated the “lead time” for semiannual surveyed patients using Schwartz's formula [28], originally proposed for calculating tumor growth:

$$t = DT \times 3 \times \log(d1/d0) / \log(2)$$

where *t* is the lead time (days), DT is the median value of the tumor volume doubling time proposed by Scheu et al. [29], *d0* is the median tumor diameter

of patients under semiannual surveillance, and $d1$ is the median tumor diameter of patients under annual surveillance.

The *calculated lead time* for patients examined every 6 months was subtracted from their survival. If the value became negative, we attributed a survival (deceased patients) or a follow-up (living patients) of 1 day. The Group 1 survival was analyzed as both *observed* and *corrected* (for the estimated lead time) survival.

To define the maximum lead time at which the semiannual program is still superior, we performed a sensitivity analysis including the “baseline model”, where the lead time (141 days) was calculated with the median value of the tumor volume DT, and additional models based on 5% incremental percentile values above the median, corresponding to progressively slower rates of tumor growth.

All the factors tested as determinants of cancer stage plus the stage and the treatment (orthotopic liver transplantation [OLT], hepatic resection, percutaneous ablation, TACE $\pm$ PEI/RF, other/palliation) were tested as predictors of survival by the log-rank test. Variables associated ($p \leq 0.10$) with the survival at the univariate analysis were tested by Cox multivariate stepwise regression analysis. The pertinent adjusted relative risks (Odds Ratio or Hazard Ratio, as appropriate) and its 95% CI were calculated. A 2-tailed p value <0.05 was considered statistically significant. Statistical analysis was performed using the SPSS 13.0 statistical package (Chicago, IL).

Ethics

The ITA.LICA database management conforms to current Italian legislation on privacy and the study conforms to the ethical guidelines of the Declaration of Helsinki. All patients provided informed consent to register their data in an anonymous way in the ITA.LICA database. The study was approved by the ethics committee of the participating Institutions.

Results

The inclusion criteria we adopted in the current study yielded an overlap of 293 cases with our first report [10] and of 414 cases with the second one [21].

The duration of surveillance was specified in 381 patients (74.7%) of Group 1 (median: 10 years, range: 0.5–42) and in 94 (67.6%) of Group 2 (9 years, 1–40).

The time elapsed between the last negative screening test(s) and the US detecting HCC was: five months in 6 patients, six months in 500 and seven months in 4 of Group 1; eleven months in 3 patients, twelve months in 136 of Group 2.

Patient characteristics, tumor stage and treatment (Table 1)

The median age of patients was 67 (range: 30–89) years, and 70.4% were male. The most common cause of liver disease was viral, with HCV infection accounting for most cases. Most patients belonged to C-P class A. About half of the patients had comorbid illnesses. An elevated AFP value was observed in 50.1% of patients, but only 14.6% of cases reached a diagnostic level (>200 ng/ml).

Solitary tumors ≤ 5 cm were diagnosed in 334 patients (52.7%): the diameter was ≤ 2 cm in 127 (20%), 2.1–3 cm in 116 (18.3%), and 3.1–5 in 91 (14.4%). Paucifocal HCCs were 93 (14.7%), and tumors outside the Milano criteria were 207 (32.6%).

Only 3.4% of patients underwent OLT and 12.2% underwent hepatic resection as the main treatment. Percutaneous ablation or TACE each accounted for about one third of cases. Finally, 20.7% of patients were considered not amenable to curative or effective treatments.

The comparison of Groups 1 and 2 showed the following differences (Table 1):

- (1) The proportion of patients recruited in the second decade was higher in Group 1.

- (2) The cancer stage was more favorable in Group 1, where single nodules ≤ 2 cm were almost 5-fold more frequent than in Group 2, whereas no differences were found for both 2.1–3 cm solitary nodules and paucifocal HCCs. Moreover, Group 1 patients were less frequently diagnosed with HCCs of 3.1–5 cm and with an advanced tumor. The median HCC diameter was significantly lower in Group 1.
- (3) Curative and effective therapies were more frequent in Group 1 so that the proportion of patients judged eligible only for palliation or other treatments was lower.

Factors associated with a tumor beyond the very early stage were surveillance interval, sex, etiology, ALT, AFP, and C-P class (Table 2). Multivariate analysis proved that annual surveillance, low ALT, and an AFP >200 ng/ml independently increased the risk of missing very early HCCs.

Survival

Data on follow-up were available in 508 (99.6%) patients of Group 1 and in all Group 2 patients. The mean follow-up after HCC diagnosis was 38.6 ± 32.8 months, and 522 (80.4%) patients died during the follow-up.

The median *observed* survival was higher in Group 1 than in Group 2 (45.0 [95% CI 40.0–50.0] vs. 30.0 [95% CI 24.0–36.0] months, $p = 0.001$). The estimated survival rates at 1, 3, and 5 years were 85.4 % vs. 80.6 %, 57.2 % vs. 40.1 %, and 37.5 % vs. 21.1 %, respectively (Fig. 1).

Using the median value (117 days) of tumor volume DT proposed by Scheu et al. [29], the *calculated lead time* was 141 days. The median survival of Group 1 *corrected* for this lead time was 40.3 (95% CI 34.9–45.7) months, and the *corrected* survival rate at 1, 3, and 5 years were 78.5%, 54.1%, and 34.3%. These figures were significantly higher than those regarding the observed survival of Group 2 ($p = 0.028$) (Fig. 2). Sensitivity analysis showed that Group 1 had a significantly better survival than Group 2 ($p = 0.048$) up to an adjustment for a lead time of 177 days (5.9 months), corresponding to the 70° percentile (147 days) of the tumor volume DT series reported by Scheu et al. [29].

Age, surveillance interval, platelet count, AFP, C-P class, esophageal varices, cancer stage and HCC treatment were associated with survival (Table 3). After stepwise adjustment for age, platelet count, AFP, C-P class and esophageal varices, the Cox model showed an increased risk of death of patients under annual surveillance (Hazard Ratio 1.39 [95% CI 1.05–1.82]). The protective effect of semiannual surveillance disappeared when cancer stage was added to the model. Therefore, the final model retained as risk factors of death: younger age, low platelet count, elevated AFP, C-P class B, cancer stage (solitary tumor >3 cm or advanced) and all treatments other than OLT (Table 3).

Discussion

Numerous studies indicate that regular surveillance of patients at risk of HCC increases the chance of detecting curable – or efficiently treatable – tumors, improving the patient prognosis [2,7–10]. Hence, surveillance is gaining growing consent among hepatologists [30] and is recommended by the guidelines for HCC management [11,12]. However, what the ideal interval of surveillance is remains unsettled. The identification of the best

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Table 1. Demographic and clinical characteristics of patients and treatment of hepatocellular carcinoma.

Variable	Group 1	Group 2	<i>p</i> [*]
Median age (yr) (<i>n</i> = 648)	67.0 (30.0–89.0)	68.0 (46.0–88.0)	0.219
Sex (M/F) (<i>n</i> = 649)	358/152 (70.2/29.8%)	99/40 (71.2/28.8%)	0.835
Etiology (<i>n</i> = 648)			0.110
HBV (<i>n</i> = 59; 9.1 %)	40 (7.9 %)	19 (13.7%)	
HCV (<i>n</i> = 410; 63.3 %)	331 (65.0%)	79 (56.8%)	
Alcohol (<i>n</i> = 51; 7.9 %)	39 (7.7%)	12 (8.6%)	
Multietiology (<i>n</i> = 103; 15.9 %)	77 (15.1%)	26 (18.7%)	
Others (<i>n</i> = 25; 3.9 %)	22 (4.3%)	3 (2.2%)	
Period of diagnosis (<i>n</i> = 648)			0.010
1987–1996 (<i>n</i> = 180; 27.8%)	129 (25.3%)	51 (36.7%)	
1997–2006 (<i>n</i> = 468; 72.25%)	380 (74.7%)	88 (63.3%)	
Comorbid illnesses (<i>n</i> = 606)			0.369
No (<i>n</i> = 311; 51.3%)	251 (52.3%)	60 (47.6%)	
Yes (<i>n</i> = 295; 48.7%)	229 (47.7%)	66 (52.4%)	
Median ALT (ULRR) (<i>n</i> = 633)	1.79 (0.25–13.60)	1.50 (0.42–9.13)	0.062
Alpha-fetoprotein (<i>n</i> = 631)			0.188
≤20 ng/ml (<i>n</i> = 315; 49.8%)	250 (50.3%)	65 (48.5%)	
21–200 ng/ml (<i>n</i> = 224; 35.5%)	181 (36.4%)	43 (32.1%)	
>200 ng/ml (<i>n</i> = 92; 14.6%)	66 (13.3%)	26 (19.4%)	
Child-Pugh class (<i>n</i> = 649)			0.829
A (<i>n</i> = 477; 73.5%)	37 (7.37%)	101 (72.7%)	
B (<i>n</i> = 172; 26.5%)	134 (26.3%)	38 (27.3%)	
Cancer stage (<i>n</i> = 634)			<0.001
Solitary ≤2 cm, V0, N0, M0 (<i>n</i> = 127; 20.0%)	120 (24.1%) ^a	7 (5.1%)	
Solitary 2.1–3 cm, V0, N0, M0 (<i>n</i> = 116; 18.3%)	94 (18.9%)	22 (16.1%)	
Solitary 3.1–5 cm, V0, N0, M0 (<i>n</i> = 91; 14.4%)	61 (12.3%) ^b	30 (21.9%)	
2–3 nodules, ≤3 cm, V0, N0, M0 (<i>n</i> = 93; 14.7%)	73 (14.7%)	20 (14.6%)	
Outside Milano criteria (<i>n</i> = 207; 32.6%) ^{**}	149 (30.0%) ^c	58 (42.3%)	
Median tumor size (cm) (<i>n</i> = 622)	2.5 (0.2–18)	3.3 (0.8–11)	<0.001
Treatments (<i>n</i> = 641)			0.020
Transplantation (<i>n</i> = 22; 3.4%)	18 (3.6%)	4 (3.0%)	
Resection (<i>n</i> = 78; 12.2%)	59 (11.7%) ^a	19 (14.1%)	
Percutaneous ablation (<i>n</i> = 200; 31.2%)	164 (32.4%) ^d	36 (26.7%)	
TACE (± percutaneous ablation) (<i>n</i> = 208; 32.4%)	173 (34.2%) ^e	35 (25.9%)	
Others/palliation (<i>n</i> = 133; 20.7%)	92 (18.2%) ^f	41 (30.4%)	

ALT = alanine aminotransferase; HBV = hepatitis B virus; HCV = hepatitis C virus; TACE = transarterial chemoembolization; ULRR = upper limit of reference range; V0 = no vascular invasion; N0 = no lymph-node invasion; M0 = no metastases.

^{*} Mann–Whitney U test, χ^2 test or Fisher's exact test, as appropriate.

^{**} 24 patients with a solitary HCCs >5 cm, 73 patients with >3 nodules, 50 patients with 2–3 nodules of which at least one >3 cm, 60 patients in whom the excluding criteria was the presence of vascular invasion and/or metastases.

^a *p* < 0.0001.

^b *p* = 0.007.

^c *p* = 0.009.

^d *p* = 0.057.

^e *p* = 0.014.

^f *p* = 0.018 vs. Group 2.

interval would optimize the cost-effectiveness of this procedure which is suboptimal [9,31,32]. Based on the estimated HCC volume DT [29], the European guidelines [11] advocated a 6-month interval, while the subsequent AASLD guidelines [12] leaves the choice between 6 and 12 months to the referral physician, since the superiority of the more stringent program is debated [10,21,24], and a 3-monthly program does not provide any advantage with respect to a semiannual schedule and increases costs due to false positive results [33].

Nowadays, the identification of nodules ≤2 cm is considered the ideal goal of surveillance [13] due to their excellent prognosis after radical treatments [15–17]. The present study shows that the semiannual surveillance increases the detection rate of single HCC ≤3 cm, quintuplicating those ≤2 cm as compared with the yearly program. The importance of the interval length was confirmed by the multivariate analysis which attributed to the yearly

surveillance a 6-fold higher risk of missing HCCs ≤2 cm. In addition, the semiannual program halved the prevalence of solitary HCCs >3 cm and remarkably reduced the prevalence of not efficiently treatable tumors.

The prevalence of tiny tumors in our semiannually surveyed patients is however relatively low. This is probably due to the fact that our data reflect what occurs in the “real word” clinical practice which leads to rather different results from those achievable with an ideal management. In particular, our patients frequently underwent US at their regional non-specialized hospitals, where the chance to detect tiny HCCs with this highly operator-dependent technique is lower than in specialized institutions [34,35]. Our study, therefore, depicts a scenario generated by the “minimal” rather than the “best” results achievable with US surveillance.

The semiannual program, however, could have been favored by a “recruitment bias” due to the increased proportion of cases

Table 2. Independent risk factors for the detection of a HCC beyond the very early stage (i.e. solitary nodule >2 cm or multinodular tumor with/without vascular invasion and/or metastases).

Variable	Univariate analysis <i>p</i>	Multivariate analysis Odds ratio (95% CI)
Sex	0.024	–
Median ALT	0.023	–
>1.72 (ULRR)		1
≤1.72 (ULRR)		1.55 (1.02–2.37)
Alpha-fetoprotein	0.091	–
<20 ng/ml		1
21–200 ng/ml		0.91 (0.59–1.41)
>200 ng/ml		2.58 (1.17–5.69)
Surveillance	<0.001	–
Semiannual		1
Annual		5.99 (2.57–13.98)
Etiology	0.048	–
HCV		–
Other causes		–
Child-Pugh class	0.086	–
A		–
B		–

ALT = alanine aminotransferase; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; ULRR = upper limit of reference range.

on the more stringent program enrolled in the second decade (likely due to the publication of the 2001 European guidelines). They could have benefited from the improved sensitivity of the latest generation US devices more than their counterpart. However, the recruitment bias cannot be considered important since the period of diagnosis did not affect the detection rate of very early HCCs and an *ad hoc* analysis showed that the semiannual program produced a favorable stage migration in both decades (1987–1996: $p = 0.003$; 1997–2006: $p = 0.001$, data not reported).

The main result of our study is the demonstration that the semiannual surveillance provides a prognostic advantage over

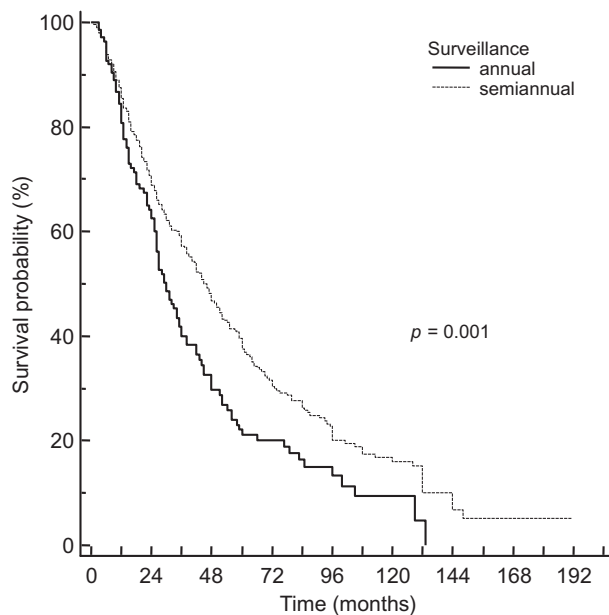


Fig. 1. Observed survival of patients under semiannual or annual surveillance. The semiannual surveillance significantly increased the survival with respect to yearly program.

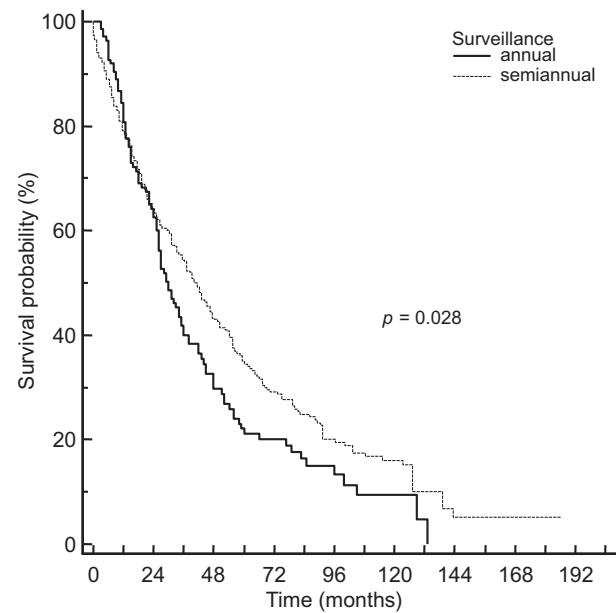


Fig. 2. Corrected survival of patients under semiannual surveillance vs. observed survival of patients under annual surveillance. The semiannual program significantly increased the survival with respect to yearly program, even after the adjustment for the calculated lead time.

the annual program. Notably, the interval was removed from the independent prognostic factors when cancer stage was added to the Cox model, indicating that surveillance interacts with prognosis through its effect on HCC stage [10,22].

Nonetheless, our study has several limitations caused by its retrospective nature. The first one is generated by the “lead time bias”, we took care to minimize by “adjusting” the survival of 6-monthly surveyed patients for the calculated lead time. We found that the semiannual program provided better survival considering tumor volume DTs up to 147 days (giving a lead time of 5.9 months). Since this cut-off may include as many as 70% of HCCs [29], it is conceivable that most patients take advantage to be assigned to the semiannual surveillance. However, it should be pointed out that the superiority of the more stringent program decreases in parallel with the increase of the percentage of indolent, slowly growing tumors.

Another limitation may derive from the “selection bias” determined by the subjective choice of the interval. Doctors tend to shorten the interval in patients considered at very high risk of HCC as, for instance, those with an elevated baseline AFP [2]. This custom, although consistent with the results of cost-effectiveness analyses [36], is not supported by any evidence that the speed of tumor growth is proportional to the risk [11]. In any case, such a habit could have increased the number of higher risk patients submitted to a semiannual surveillance, but this does not favor the program.

We also found a relationship between interval and treatment, with a greater use of curative procedures and TACE in 6-monthly surveyed patients. It could have been expected that the shift of the 3–5 cm solitary tumors toward those ≤2 cm translates into an even greater utilization of ablative treatments than what we observed. Several factors may justify this finding: (1) many HCCs detected during yearly surveillance had a size compatible with ablation (median diameter: 3.3 cm); (2) in clinical practice the

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Table 3. Variables associated with the mortality. Note that in Group 1 patients the survival was corrected for the lead time bias (see Methods).

	Univariate analysis <i>p</i>	Multivariate analysis Hazard ratio (95% CI)
Median age	0.099	
>67 yr		1
≤67 yr		1.27 (1.01–1.60)
Surveillance	0.028	-
Semiannual		
Annual		
Median platelet count	0.005	
≥101,000/μl		1
<101,000/μl		1.32 (1.04–1.66)
Alpha-fetoprotein	<0.001	
≤20 ng/ml		1
21–200 ng/ml		1.32 (1.03–1.70)
>200 ng/ml		1.77 (1.27–2.46)
Child-Pugh class	<0.001	
A		1
B		1.62 (1.27–2.07)
Esophageal varices	<0.001	-
No		
Yes		
Cancer stage	<0.001	
T ≤2 cm, V0, N0, M0		1
2 cm <T ≤3 cm, V0, N0, M0		1.35 (0.90–2.01)
3 cm <T ≤5 cm, V0, N0, M0		1.57 (1.04–2.38)
2–3 nodules, ≤3 cm, V0, N0, M0		1.38 (0.91–2.11)
Outside Milano criteria		2.61 (1.84–3.71)
Treatments	<0.001	
Transplantation		1
Resection		5.07 (1.89–13.58)
Percutaneous ablation		5.04 (1.98–12.78)
TACE (± percutaneous ablation)		7.41 (2.96–18.56)
Others/palliation		16.91 (6.64–43.08)

TACE = transarterial chemoembolization; ULRR = upper limit of reference range; T = tumor size; V0 = no vascular invasion; N0 = no lymph-node invasion; M0 = no metastases.

therapeutic decision takes into account not only the size but also the location of the nodule, the clotting profile, the local expertise and resources; (3) an over-utilization of TACE occurred before the current guidelines, providing a stage-tailored guidance for treatment, were issued [37].

Moreover, few patients received liver transplantation or resection. This result likely has several causes: (1) our recruitment started in 1987, and until 1996 (year of publication of the Milano criteria) there was a reluctance to transplant HCC patients, due to the poor results achieved in the absence of criteria able to select patients with a low risk of recurrence; (2) before the recent implementation of a HCC priority policy, the transplantation applicability was limited by a high delisting rate because of tumor progression; (3), some of our centers likely tended to prefer locoregional ablative treatments instead of resection.

An over-time improvement in survival has been recently reported in a cohort of cirrhotic patients prospectively surveyed over fifteen years, due to the improved prognosis of treatable HCCs [2]. In this light, the already cited recruitment bias may have favored our patients submitted to semiannual surveillance. However, the finding that survival was independent of the recruitment period (Table 3) refutes this hypothesis.

Lastly, our study testifies once again that AFP is a poor surveillance test being normal in half of cases at the HCC diagnosis, whereas its elevation has a robust adverse prognostic meaning,

suggesting that this oncomarker should be incorporated in the prognostic systems [38].

In conclusion, a 6-monthly surveillance of cirrhotic patients belonging to C-P class A or B increases the detection rate of HCCs with the best chance of being cured, and reduces the number of advanced cancers with respect to an annual program. This improves the patient prognosis even when the lead time bias is taken into account. Our results support those of computer-based Markov model [32] and meta-analytic [39] studies, indicating that semiannual US is the best way of surveying cirrhotic patients. Nonetheless, prospective studies, which can avoid both the confounding factors affecting retrospective analyses and the theoretical assumptions of mathematical models, are needed to definitely confirm the superiority of the semiannual over the annual surveillance.

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Conflicts of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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