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Semiannual and Annual Surveillance of Cirrhotic Patients for Hepatocellular Carcinoma: Effects on Cancer Stage and Patient Survival (Italian Experience)

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OBJECTIVES: Surveillance of cirrhotic patients for early detection of hepatocellular carcinoma, based on ultrasonography and α_1-fetoprotein determination, is a recommended practice. However, it has not been proved that this procedure can improve patient survival.

METHODS: We conducted a multicenter retrospective study on 1051 consecutive patients with hepatocellular carcinoma. The criteria for eligibility were presence of underlying cirrhosis, and description of cancer stage and modalities of its diagnosis. Among 821 patients fulfilling these criteria, the tumor was detected during semiannual surveillance in 215 individuals (group 1), during annual surveillance in 155 (group 2), and as a result of symptoms or incidentally in 451 (group 3). Survival of patients under surveillance was corrected for lead time.

RESULTS: Cancer stage was similar in groups 1 and 2 and was less advanced than in group 3 ($p < 0.001$). The frequency of ablative treatments or chemoembolization was similar in groups 1 and 2 and was greater than in group 3 ($p < 0.001$). Both surveillance programs doubled the prevalence of potential candidates for liver transplantation (68.5% and 62.5%) with respect to group 3 (32.3%, $p < 0.001$). However, only 15 patients underwent transplantation. In groups 1 and 2, the 5-yr survival was equivalent and was greater than in group 3 ($p < 0.001$). By segregating patients according to severity of cirrhosis, the benefit was confined to compensated cirrhosis (adjusted relative risk of death for patients under surveillance: 0.59 [95% CI = 0.45–0.78]).

CONCLUSIONS: Semiannual and annual surveillance equally improve the survival of cirrhotic patients with hepatocellular carcinoma and greatly increase the amenability rate to liver transplantation. When access to liver transplantation is limited, this benefit is restricted to patients with a good cirrhosis-related prognosis. (Am J Gastroenterol 2002;97: 734–744. © 2002 by Am. Coll. of Gastroenterology)

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fourth most common cancer in the world, with an age-standardized incidence in the various geographic areas ranging from 3 to 80 per 100,000 persons (1). More than 80% of HCCs arise in cirrhotic patients (2), with a 1–6% annual incidence (1), suggesting that cirrhosis is the main risk factor for this tumor. In developed countries the HCC incidence and relative mortality are increasing; they are expected not only to rise further in the near future, but also to affect younger persons (3, 4).

Surveillance for early detection of HCC in cirrhotic patients, based on serial ultrasonographies (US) and serum α_1-fetoprotein (AFP) determinations, has become a common practice. Surveillance can detect small asymptomatic HCCs, but whether this can extend patient life expectancy has not been proved. Indeed, surveillance can improve survival if effective treatment for the target disease is available and if diagnosis is made while the disease is still treatable. In HCC patients, however, the mortality rate is still high for those with small tumors treated with hepatic resection and percutaneous ethanol injection (PEI), the best 5-yr survival

The authors dedicate this article to one of the authors, Professor Alighieri Mazziotti, who died in October, 2001. He was one of the pioneers who promoted liver transplantation in Italy.

* See Appendix for other members of the group.

approaching 50% (5–7). Far better results have been recently reported with orthotopic liver transplantation (OLT) (8).

Randomized controlled trials are therefore needed to investigate whether, in high risk patients, surveillance for HCC improves survival as compared with care "on demand." However, the widespread practice of surveillance of these individuals probably makes these trials unfeasible in countries where access to US is easy and cirrhotic patients may not agree to be randomized to receive no surveillance for early detection of HCC. Ethical concerns may also be raised because: 1) uncontrolled studies in both the East and the West suggest that surveillance improves survival of patients with chronic liver disease (9–13); 2) decision analysis models predict a substantial improvement of survival if semiannual surveillance is offered to patients with good cirrhosis-related life expectancy (14); and 3) several scientific authorities do recommend surveillance for HCC in patients with chronic liver disease (15–18). Based on the volume doubling time of the tumor (19), a 6-month scheduled surveillance is generally recommended, but comparisons between different surveillance programs validating this suggestion are not currently available. Moreover, the cost per year of life saved with semiannual surveillance is very high (13).

We therefore carried out a retrospective multicenter study to explore whether two different surveillance programs for HCC in cirrhotic patients can favorably influence the cancer stage at diagnosis and, above all, the survival of these patients.

MATERIALS AND METHODS

Patients

The clinical records of 1051 patients with HCC who were seen consecutively from January, 1988, to March, 1998, in six medical institutions were analyzed. Eligibility criteria were presence of underlying cirrhosis, indication of the manner of HCC diagnosis, and description of the cancer stage. All of these data were available for 821 patients (78.1%), who were enrolled in the study.

Patients were divided into three groups according to the manner of HCC diagnosis and the interval of surveillance. In group 1 (215 patients), diagnosis was made during regular surveillance, based on AFP determination and US performed every 6 months, with a tolerance of ± 1 month (semiannual surveillance). In group 2 (155 patients), diagnosis was made during regular surveillance, based on AFP determination and US performed every 12 months, with a tolerance of ± 2 months (annual surveillance). In group 3 (451 patients), diagnosis was made as a result of symptom appearance (224 patients) or incidentally, outside of any specific surveillance program or because of a diagnostic workup for other diseases (227 patients). Although this strategy probably grouped patients with different prognoses (20), it was adopted to reproduce the manner of HCC detection that is alternative to surveillance in clinical practice.

The patients receiving regular surveillance were allocated to group 1 or 2 even when presenting a symptomatic tumor at the time of diagnosis (29 and 25 patients, respectively). Patients received surveillance or care "on demand," depending on the decision of their referring physician. Namely, in each center, more than 85% of the individuals under surveillance had one of the physicians involved in the study as their referring physician, whereas all group 3 patients were referred to the Center for definite diagnosis and treatment (contemporaneous nonrandomized controls).

The following parameters were analyzed: sex, age, etiology of cirrhosis, serum AFP level, Child-Pugh class (21), gross pathology and extrahepatic extension of the tumor, portal vein and/or caval thrombosis, Okuda stage (22), potential amenability to OLT (for patients $\leq$60 yr old), HCC treatment methods, and survival.

Diagnosis of Cirrhosis

Cirrhosis was demonstrated by histology, laparoscopy, or laparatomy in 314 patients. Otherwise, the diagnosis was based on the clinical and laboratory patterns associated with endoscopic and/or US signs of portal hypertension, and/or an irregular margin of the liver at US examination.

Diagnosis of HCC

Hepatocellular carcinoma was confirmed by histology or cytology in 450 patients. In 101 cases diagnosis was made by combining a diagnostic AFP increase ($>$200 ng/ml) with typical features on imaging technique workup (US, dynamic CT, and angiography with or without lipiodol, as appropriate). In the remaining cases, the diagnosis was based on the imaging technique features and was confirmed by the follow-up and/or necropsy.

Cancer Staging and Amenability to OLT

Cancer stage was assessed with both US and CT features. When appropriate, patients also underwent angiography. The macroscopic types of HCC were classified as: solitary nodular, multinodular (paucifocal [three or fewer nodules] and multifocal [more than three nodules]), diffuse, and massive type (23).

To detect metastases, all patients underwent chest x-ray and abdominal US. Bone scintigraphy and CT scans of the chest and brain were performed in patients in whom extrahepatic involvement was suspected and in candidates for OLT.

The potential OLT feasibility was evaluated according to the "Milano criteria" proposed by Mazzaferro *et al.* (8). These criteria, excluding age, were also adopted for defining the cancer stage as "nonadvanced" or "advanced" in the whole population.

Amenability to Resection, PEI, and Transarterial Chemoembolization

Patients were considered suitable for resection according to the following criteria: 1) monofocal HCC located in the peripheral portions of the liver; 2) Child-Pugh score ≤7; 3) no evidence of portal vein infiltration/thrombosis; 4) no evidence of extrahepatic metastases; and 5) no extrahepatic contraindications to surgery. Patients were considered suitable for PEI when: 1) OLT was not offered or was refused by the patient, and surgical resection was not possible or was refused; 2) the tumor was monofocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumor was not subcapsular; 4) the Child-Pugh score was ≤10; and 5) there was no evidence of either main portal vein infiltration/thrombosis or extrahepatic metastases. Finally, transarterial chemoembolization (TACE) was offered to the patients with: 1) a paucifocal tumor not treatable with PEI or a multifocal tumor involving less than 40% of the liver volume; 2) Child-Pugh score ≤10; 3) no main portal vein infiltration/thrombosis and extrahepatic metastases; and 4) no severe associated diseases.

Survival

Survival was calculated from the time of cancer diagnosis. Data were censored at the date of death or last follow-up visit. To minimize the lead-time bias, *i.e.*, the apparent improvement in survival due to the early detection of the disease (24), we calculated the "lead time" for each group under surveillance by utilizing the formula originally proposed by Schwartz (25) for calculating tumor growth as follows:

$$t = DT \cdot 3 \cdot \log (d_1/d_0)/\log(2)$$

where t is the lead time (days), *DT* is the median tumor volume doubling time according to Sheu *et al.* (19), and d_0 and d_1 are the median tumor diameters of the groups under surveillance (group 1 or 2) and group 3, respectively. The calculated lead time was subtracted from the survival of each patient under surveillance (24, 26). If the value became negative, we attributed a survival (deceased patients) or a follow-up (living patients) of 1 day.

Laboratory Determinations

Liver tests (prothrombin activity, plasma albumin and bilirubin concentrations), tests for defining the etiology of cirrhosis and serum levels of AFP (values ≤20 ng/ml were considered normal) were determined by conventional methods. Hepatitis B virus markers were tested by radioimmunoassay or ELISA and antibody antihepatitis C virus by ELISA I (up to April 1991), II and III generation, using commercial kits. US was performed by means of high-resolution, real-time equipment with linear and/or convex-array 3.5-MHz probes.

Statistical Analysis

The distribution of variables was assessed by the Kolmogorov-Smirnov test. The results were expressed as median and range or mean ± SE, as appropriate. Contingency tables and, according to the variable distribution, one-way analysis of variance, Kruskal-Wallis, and Mann-Whitney tests were used to evaluate the statistical significance of the differences between groups. Life table estimates were calculated according to the Kaplan-Meier method, and the survival curves were compared by the log-rank test.

Logistic and Cox proportional hazards regression analyses were performed to check simultaneously for age, sex, etiology and Child-Pugh class of cirrhosis, AFP level, and surveillance in determining the cancer stage. To assess whether the surveillance was an independent predictor of patient survival, the variables that were significantly associated with survival at univariate analysis were sequentially entered in different models of Cox analysis.

Categorical variables were transformed into ordinal numbers as follows: hepatitis B virus surface antigen (HbsAg) and hepatitis C virus antibody (anti-HCV): negative/positive; alcohol abuse and surveillance: yes/no; HCC stage: nonadvanced/advanced; treatment (surgery [OLT and resection]/PEI/TACE/other and palliative treatment). A two-tailed p value < 0.05 was considered to be statistically significant.

RESULTS

Demographic, Clinical, and Laboratory Characteristics

The number of patients recruited by the participating centers ranged from 70 to 233. Every center supplied patients to all groups in different proportions (group 1, 8–52%; group 2, 5–28%; group 3, 26–85%). In each institution, the proportion of patients included in the three groups did not significantly change throughout the recruitment period.

The etiology of cirrhosis is reported in Table 1. There was a lower proportion of anti-HCV+ individuals and a higher prevalence of patients with alcohol abuse in group 3 than in patients under surveillance.

During follow-up, a minority of the 697 patients with viral hepatitis was treated with interferon, and a higher proportion of treated individuals were found in patients under surveillance (group 1, 16 (8.3%) patients; group 2, 14 (9.9%), group 3: 13 (3.6%), $p = 0.017$). Among the 205 persons with alcoholic or mixed (alcoholic and viral) disease, four (7.7%) in group 1, three (11.6%) in group 2, and 16 (12.6%) in group 3 (p = ns) continued to drink alcohol after HCC detection.

The groups were comparable for age but not for sex; a male preponderance was greater in group 3 (Table 2). Most patients were in Child-Pugh class A (class A, 59.8%; class B, 31%; class C, 9.2%), and the class distribution was less favorable in group 3 (Table 2). In this group, a different distribution was observed in patients with an incidental or symptomatic HCC (class A, 64.5% *vs* 43.6%; class B, 26.7% *vs* 40.7%; class C, 8.8% *vs* 15.7%, $p < 0.001$).

Serum AFP was elevated in 58.1% of patients. Diagnostic

Table 1. Etiology of Cirrhosis in Patients With Hepatocellular Carcinoma

	Group 1	Group 2	Group 3	*p**
HBsAg+†	29 (13.6)	31 (20.4)	88 (20.5)	ns
Anti-HCV+‡	142 (66.6)	95 (62.5)	240 (55.9)	0.026
HBsAg+ and anti-HCV+§	21 (9.9)	15 (9.9)	36 (8.4)	ns
Alcohol	18 (8.5)	11 (7.2)	59 (13.8)	0.032
Others	3 (1.4)		6 (1.4)	ns
Unknown	2 (0.9)	3 (1.9)	22 (4.8)	0.016

The percent value is reported in parentheses.
* Assessed by the χ^2 test.
† Associated with alcohol abuse in 30 cases (group 1, four; group 2, five; group 3, 21; p = ns) and with hepatitis δ infection in six cases.
‡ Associated with alcohol abuse in 64 cases (group 1, 25; group 2, nine; Group 3, 30; p = ns).
§ Associated with alcohol abuse in 20 cases (group 1, five; group 2, six; group 3, nine; p = ns) and with hepatitis δ infection in one case.

levels (>200 ng/ml) were found in 25.3% of cases and more frequently in group 3 (Table 2).

Macroscopic Features, Cancer Stage, and Amenability to OLT

Solitary and paucifocal (fewer than three nodules) tumors were more common in patients under surveillance, whereas multifocal, diffuse, and massive cancers were more frequent in group 3 (Table 3). No differences were observed between groups 1 and 2. In group 3, the distribution of HCC types was better in patients with an incidental rather than a symptomatic HCC (solitary, 48.9% *vs* 36.6%; paucifocal, 21.1% *vs* 14.3%; multifocal, 19.4% *vs* 23.7%; diffuse, 7.5% *vs* 17.4%; massive, 3.1% *vs* 8.0%; $p = 0.018$).

Information on cancer diameter was available in 722 patients. The tumor size was not reported in 99 cases because of the cancer feature (77 diffuse HCCs) or because it was not measured (nine solitary, 13 pauci- or multifocal HCCs). In multinodular tumors, the largest nodule was considered. The median tumor size significantly increased from group 1 to group 3 (2.5 [range, 0.5–9.8] cm, 3.3 [range, 0.8–13.5] cm, and 4.0 [range, 0.7–16.0] cm, respectively, $p < 0.001$). The difference between cancer size detected by the two surveillance programs was also statistically significant ($p < 0.001$). A similar trend was found in the subgroup of solitary tumors (2.5 [range, 0.7–9.8] cm, 3.5 [range, 0.8–8.5] cm, and 4.0 [range: 1.0–10.0] cm, respectively; $p < 0.001$). The prevalence of solitary HCC ≤3 cm decreased from group 1 to group 3, and 87.8% of HCCs >5 cm were found in the latter. In group 3, the median diameter of incidental HCCs tended to be smaller than that of symptomatic tumors (4.0 *vs* 4.4 cm, $p = 0.089$).

The frequency of vein (portal and/or caval) thrombosis in group 3 was more than twice that in the other groups. Metastases were also more common in group 3, but the difference did not reach statistical significance. Among group 3 individuals, an incidental HCC was associated with a lower prevalence of vein thrombosis (12.7% *vs* 25.0%, $p = 0.003$) and metastases (1.8% *vs* 5.8%, $p = 0.045$).

The distribution of the Okuda stage did not differ between groups 1 and 2, whereas it was significantly less favorable in group 3. The prevalence of advanced cancers was similar in groups 1 and 2 and was lower than in group 3. In group 3, cancer stage was less advanced in patients with an incidental HCC, according to both Okuda (stage I, 69.9% *vs* 41.5%; stage II, 25.0 *vs* 44.2%; stage III, 6.0% *vs* 14.3%; $p < 0.001$) and Milano criteria (nonadvanced, 37.8% *vs* 24.1%, $p = 0.002$).

Univariate analysis proved that sex ($p = 0.004$), anti-HCV status ($p = 0.023$), Child-Pugh class ($p < 0.001$), AFP ($p < 0.001$), and surveillance ($p < 0.001$) were correlated with the cancer stage assessed according to the Milano criteria. Logistic regression analysis identified female sex,

Table 2. Demographic, Clinical, and Laboratory Characteristics of Patients With Hepatocellular Carcinoma

	Group 1	Group 2	Group 3	*p*
Age (n = 821)				
Yr (mean ± SE)	63.3 ± 0.6	64.5 ± 0.6	64.8 ± 0.4	NS*
Sex (n = 821)				0.033†
Male	152 (70.7)	110 (71)	355 (78.7)	
Female	63 (29.3)	45 (29)	96 (21.3)	
Child-Pugh Class (n = 796)				0.001†
A	137 (63.7)	105 (70.9)	234 (54.0)	
B	66 (30.7)	35 (23.7)	146 (33.8)	
C	12 (5.6)	8 (5.4)	53 (12.2)	
AFP (n = 707)				<0.001†
≤20 ng/ml	78 (37.3)	53 (44.2)	165 (43.7)	
21–200 ng/ml	94 (45.0)	45 (37.5)	93 (24.6)	
>200 ng/ml	37 (17.7)	22 (18.3)	120 (31.7)	

The percent value is reported in parentheses.
* Assessed by analysis of variance.
† Assessed by χ^2 test.

Table 3. Macroscopic Features, Vascular Involvement, Presence of Metastases, and Stage of Cancer in Patients With Hepatocellular Carcinoma

	Group 1	Group 2	Group 3	*p**
HCC type (n = 821)				<0.001
Solitary	121 (56.3)	84 (54.2)	193 (42.8)	
Paucifocal (≤3 nodes)	54 (25.1)	43 (27.7)	80 (17.7)	
Multifocal (>3 nodes)	27 (12.6)	18 (11.6)	97 (21.6)	
Diffuse	13 (6.0)	6 (3.9)	56 (12.4)	
Massive		4 (2.6)	25 (5.5)	
Solitary HCC (n = 393)				<0.001
≤3 cm	91 (75.8)	35 (42.2)	71 (37.4)	
3.1–5 cm	26 (21.7)	42 (50.6)	54 (28.4)	
>5 cm	3 (2.5)	6 (7.2)	65 (34.2)	
Vascular thrombosis (n = 821)	15 (7.0)	10 (6.4)	85 (18.8)	<0.001
Metastases (n = 821)	3 (1.4)	3 (1.9)	17 (3.8)	ns
Okuda stage (n = 797)				<0.001
I	153 (71.8)	116 (76.8)	239 (55.2)	
II	57 (26.8)	30 (19.9)	150 (34.6)	
III	3 (1.4)	5 (3.3)	44 (10.2)	
Cancer stage (n = 817)†				<0.001
Nonadvanced	147 (68.7)	93 (60.4)	139 (31.0)	
Advanced	67 (31.3)	61 (39.6)	310 (69.0)	

The percent value is reported in parentheses.
* Assessed by χ^2 test.
† According to Milano criteria (8).

low AFP, and surveillance as independent protective factors for an advanced HCC. The adjusted relative risk of presenting an advanced cancer at diagnosis for patients under surveillance was 0.27 (95% CI = 0.19–0.37).

Among the 248 patients aged ≤60 yr, the amenability rate to OLT in both groups of patients under surveillance was twice that of group 3 (Fig. 1), where the OLT amenability rate was not affected by the manner of HCC diagnosis (incidental, 33.3%; symptomatic 31.6%).

Treatments

Because treatment distribution did not differ between group 1 and 2, the allocation was analyzed by combining these groups. The most common therapy was transarterial chemoembolization (TACE), followed by PEI and hepatic resection. Only 1.9% of patients underwent OLT (Table 4). Surveillance increased the proportion of patients receiving surgical or locoregional treatments, so that the prevalence of systemic chemotherapy or palliation was significantly lower than in group 3. In this group, the distribution of therapeutic options significantly differed between patients with an incidental or symptomatic tumor. Ablative procedures were indeed more frequent and palliation less common in the former (OLT, 0% *vs* 0.5%; resection, 11.2% *vs* 5.0%; PEI, 24.7% *vs* 12.7%; TACE, 25.1% *vs* 29.5%; others or palliation, 39.0% *vs* 52.3%, respectively; $p = 0.002$).

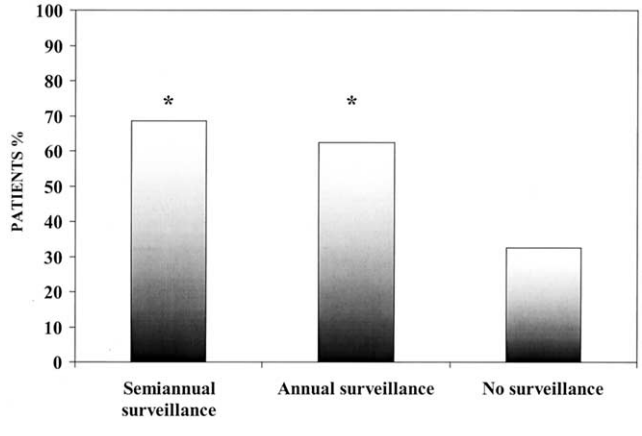

Figure 1. Prevalence of individuals fulfilling the Milano criteria for liver transplantation (8) at the time of cancer diagnosis in patients aged ≤60 yr. *$p < 0.001$ *vs* patients not under surveillance.

The stratification of patients according to the severity of cirrhosis, which crucially influences the therapeutic choice (27, 28), showed that surveillance affected treatment distribution only in Child-Pugh A and B classes, whereas most class C patients received palliation regardless of the manner of HCC diagnosis.

Survival

There were five study drop-outs in group 1, four in group 2, and nine in group 3. The actuarial 5-yr survival of group 1 and 2 patients was equivalent and significantly better than in group 3 (Fig. 2). The median survival was 36 months in group 1, 34 months in group 2 and 14 months in group 3 ($p < 0.001$). In group 3, the median survival of patients with an incidental HCC was better than in patients with a symptomatic tumor (20.0 *vs* 9.0 months, $p < 0.001$) but lower than that in group 1 and 2 ($p < 0.001$).

The estimated lead time was 239 days for group 1 and 98 days for group 2. The survival corrected for the lead time was still equivalent in group 1 and 2 (median value: 28 and 31 months, respectively) and greater than in group 3 ($p < 0.001$). Therefore, the subsequent analyses were conducted

Table 4. Types of Treatments Performed in Patients With Hepatocellular Carcinoma (n = 806)

	OLT	Resection	PEI	TACE	Others/no	*p**
All patients						<0.001
Group 1 + 2	14 (3.9)	42 (11.6)	94 (26.0)	121 (33.4)	91 (25.1)	
Group 3	1 (0.2)	36 (8.2)	83 (18.7)	121 (27.3)	203 (45.7)	
Child-Pugh class A						0.001
Group 1 + 2	6 (2.5)	38 (15.8)	66 (27.5)	83 (34.6)	47 (19.6)	
Group 3		25 (11.0)	54 (23.7)	66 (28.9)	83 (36.4)	
Child-Pugh class B						0.009
Group 1 + 2	7 (7.0)	3 (3.0)	24 (24.0)	36 (36.0)	30 (30.0)	
Group 3		8 (5.5)	23 (15.8)	47 (32.1)	68 (46.6)	
Child-Pugh class C						ns
Group 1 + 2	2 (10.5)	1 (5.3)	2 (10.5)	4 (21.0)	10 (52.7)	
Group 3	2 (3.8)	1 (1.9)	6 (11.5)	13 (25.0)	30 (57.8)	

The percent value is reported in parentheses.
* Assessed by the χ^2 test.

by combining the patients under surveillance in a single group. As a whole, these patients had a median corrected survival of 30 months. Their 5-yr actuarial corrected survival was significantly better than the survival of group 3 patients (Fig. 3), even in the event of incidental HCC diagnosis ($p < 0.001$).

When the corrected survival was analyzed according to Child-Pugh class, HCC surveillance had a favorable impact in class A and B patients, but the difference was statistically significant only in the former (Fig. 3). In class A, at univariate analysis, sex ($p = 0.002$), HBsAg status ($p = 0.009$), serum AFP ($p < 0.001$), surveillance ($p < 0.001$), cancer stage ($p < 0.001$), and treatment ($p < 0.001$) were correlated with the corrected survival. The Cox model identified female sex, absence of HBsAg, low AFP level, and surveillance as independent protective factors. After stepwise adjustment for sex, HBsAg status, and AFP the relative risk of death of patients under surveillance was reduced by 41%. When cancer stage was added to the model, the protective effect of surveillance was greatly attenuated, and disappeared when treatment was also added (Table 5).

The corrected survival was also analyzed in the subgroups of patients treated with surgical resection, PEI, and TACE (Fig. 4). For those who underwent resection, the cohort under surveillance had a higher survival rate as compared with its counterpart. A similar trend was also observed in the patients who were treated with PEI and TACE, although the difference did not reach statistical significance.

Among the three groups, no difference was observed in the prevalence of patients who bled from esophageal varices (p = ns). The cause of death was reported in the clinical records of 359 (70%) of the 514 patients who died during follow-up. The death of 211 patients (58.8%) was directly attributed to the cancer progression, whereas 107 (29.8%) individuals died from liver failure, 28 (7.8%) from GI bleed-

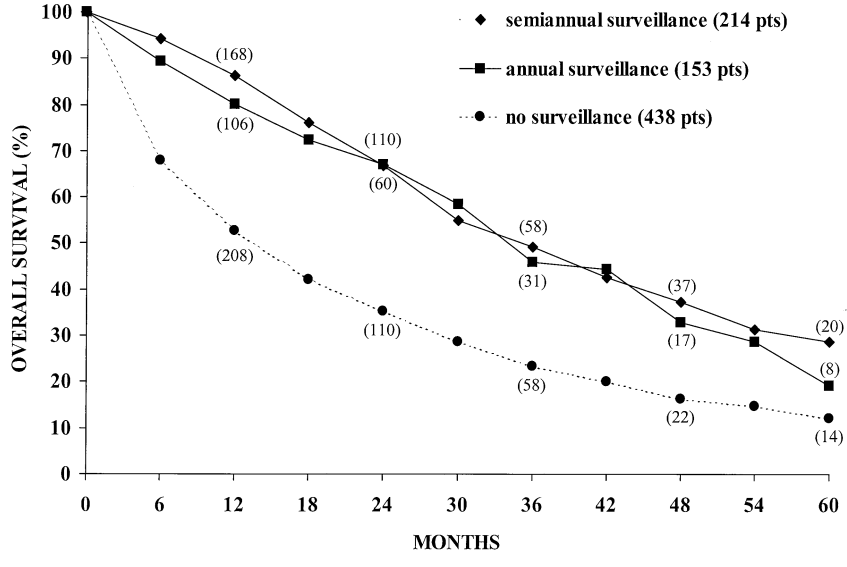

Figure 2. Actuarial survival of cirrhotic patients with hepatocellular carcinoma according to the manner of cancer diagnosis. Numbers in parentheses denote patients at risk. Patients offered semiannual and annual surveillance showed a similar survival, which was significantly better than in their counterparts not under surveillance ($p < 0.001$ for both).

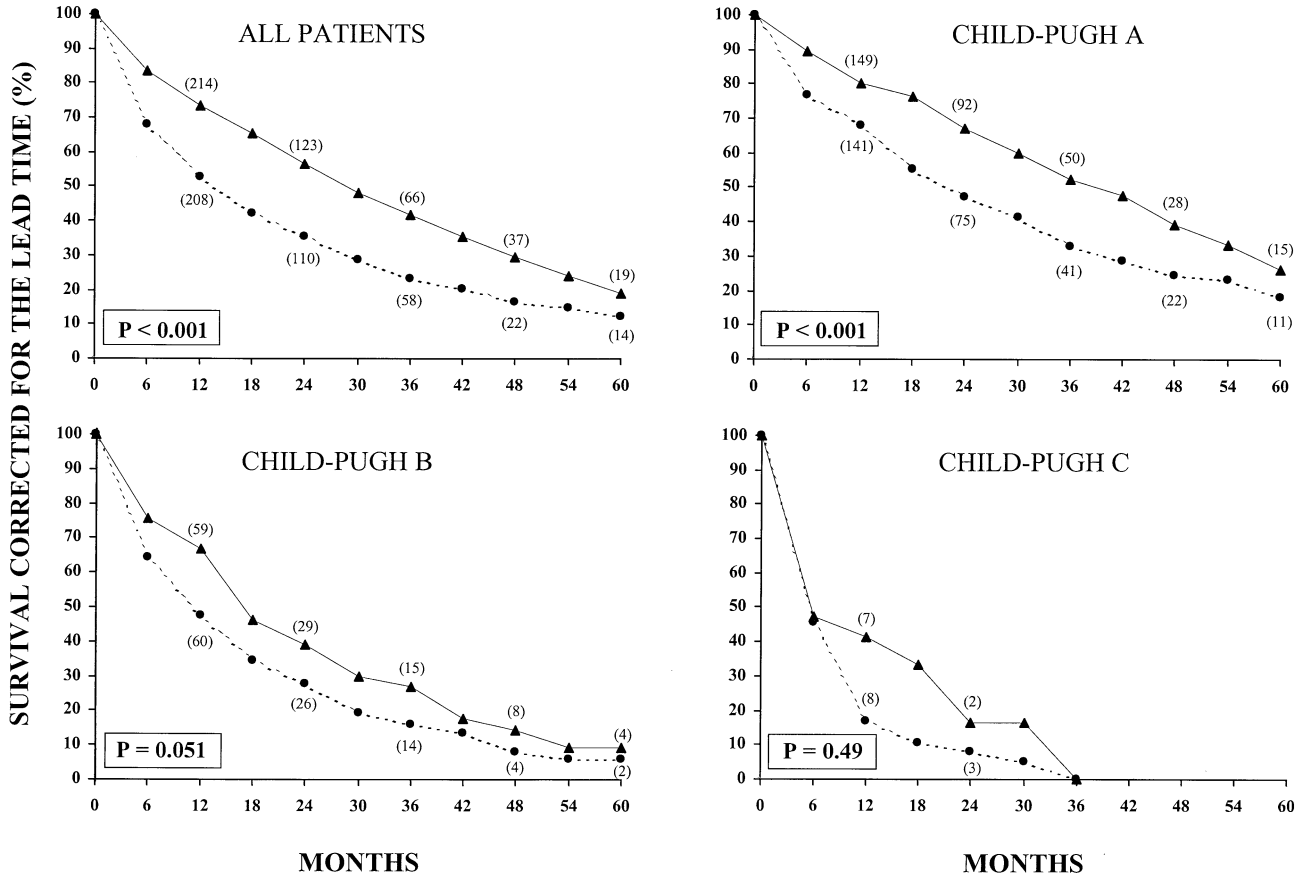

Figure 3. Survival corrected for the lead time according to the modality of cancer diagnosis in the whole population and in each Child-Pugh class. Numbers in parentheses denote patients at risk. Individuals under semiannual and annual surveillance were combined, as their corrected survivals were equivalent. Filled triangles and connecting solid lines indicate patients under surveillance; filled circles and connecting broken lines indicate patients not under surveillance.

ing, and 13 (3.6%) from other causes. The distribution of these events did not significantly differ between patients with HCC detected during or outside surveillance (cancer progression, 57.6% *vs* 59.9%, liver failure, 31.8% *vs* 28.1%, GI bleeding, 6.2% *vs* 9.0%; and other causes, 4.4% *vs* 3.0%, respectively; p = ns). Among the 250 class A patients who died, the cause of death was reported in 172 (68.8%); these patients did not significantly differ between those under or not under surveillance (cancer progression, 61.5% *vs* 69.2%; liver failure, 21.8% *vs* 17.0%; GI bleeding, 10.3% *vs* 8.5%; and other causes, 6.4% *vs* 5.3%, p = ns).

Table 5. Relative Risk of Death at 5 Years for Patients Under Surveillance Belonging to Child-Pugh Class A

Cox Analysis	Relative Risk	95% CI
Sequentially adjusted for		
Sex, HBsAg status, and AFP	0.59	0.45–0.78
Above variables + cancer stage*	0.74	0.56–0.99
Above variables + treatment	0.79	0.59–1.06

Patients not under surveillance served as a reference group.
* According to the Milano criteria (8).

DISCUSSION

This study confirmed that most tumors (approximately 80%) detected by regular surveillance were single small or paucifocal, so that the risk of diagnosing HCC at an advanced stage was reduced by approximately 70%. Interestingly, the semiannual and annual programs were equally valid in this respect. As expected, the tumor size was smaller in individuals under semiannual surveillance but the difference was rather small (<1 cm) because of the slow growth rate of minute HCCs (25). These results confirm those of a recent prospective study describing the impact of a semiannual and annual surveillance on HCC gross pathology (29).

The ultimate objective of surveillance for lethal diseases is to reduce the mortality of the target population. This aspect can be properly investigated by prospective, randomized, controlled studies. However, in the case of surveillance for HCC, such studies are almost impossible to conduct in areas where the easy access to diagnostic procedures raises ethical concerns and makes patient compliance very unlikely. The best we can do to gain insight into this topic is careful scrutiny of information coming from retrospective

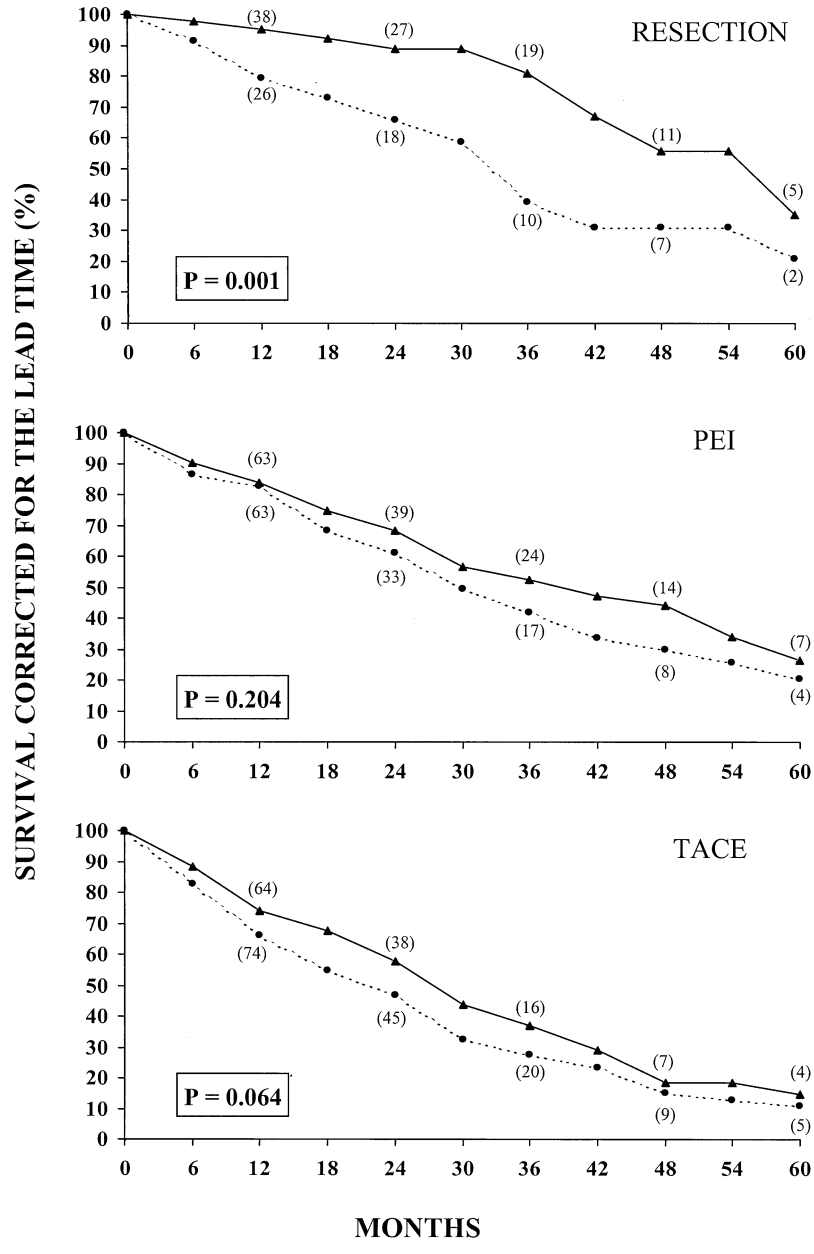

Figure 4. Survival corrected for the lead time according to the type of treatments. Numbers in parentheses denote patients at risk. Individuals under semiannual and annual surveillance were combined, as their corrected survivals were equivalent. Filled triangles and connecting solid lines indicate patients under surveillance; filled circles and connecting broken lines indicate patients not under surveillance.

investigations. Two important findings emerged from our study: 1) patients under surveillance had a better survival than their counterparts, and 2) the benefit of semiannual and annual surveillance in this respect was equivalent. The first result is in line with what was reported by a study carried out in Asian patients with chronic viral liver disease, showing a better prognosis for HCCs detected by surveillance as compared with large (median size 8.1 cm) symptomatic tumors (11). Interestingly, we confirmed the benefit of surveillance even though our control patients had much smaller tumors and a 3-fold higher survival than that reported in the Hong Kong series. This was due to the fact that half of our control patients had an incidental tumor, supporting the assumption that many of them had undergone periodic examinations, although outside a regular surveillance program. In Italy this practice is indeed facilitated by the widespread use of laboratory and ultrasonographic check-ups, which are frequently performed even in asymptomatic individuals. Consequently, most patients with chronic liver disease are aware of their condition and, if they are kept out of a scheduled surveillance program, they nevertheless wish to repeat examinations quite frequently. The combined use of AFP

monitoring and US, which is more sensitive in detecting early HCC (11, 30), was probably crucial for early cancer diagnosis, as less than 45% of HCC detected during surveillance led to an increase in AFP.

The demonstration that semiannual and annual surveillance have an equivalent effect on survival is a novel finding; it implies that, although multivariate analysis confirmed that prognosis greatly depends on cancer stage (10), the advantage in tumor size obtained with the semiannual program is not crucial for determining life expectancy. This is an important finding at a time in which economic resources are limited and results are considered essential to justify expenditure in clinical practice.

Because of the retrospective nature of our study, however, some biases may have affected the results. First, the better survival of patients with HCC detected during surveillance could be simply ascribed to the lead time bias. We attempted to minimize this pitfall by presenting a rather long follow-up and correcting the time of HCC diagnosis for lead time bias (24, 26) in patients under surveillance. After this adjustment the survival was still better in these patients, suggesting that the benefit of early diagnosis was not virtual. However, this adaptation, based on a literature-derived tumor growth rate and the median size of HCC in our groups, might not be sufficient because of the propensity of surveillance to detect slowly progressive rather than aggressive tumors at the subclinical stage (length bias). To minimize the length bias, which is unavoidable in a retrospective study, we maintained in their original group those patients under surveillance who presented with an aggressive tumor responsible for symptoms and an anticipated examination.

A selection bias may derive from the subjective nature of the decision to start surveillance by the referring physician. Indeed, almost all individuals under surveillance were followed-up by our institutions, whereas their counterparts were referred to our centers after cancer detection. However, among patients not under surveillance, the incidental diagnosis improved both cancer stage and survival, indicating that subclinical HCCs have a better prognosis than symptomatic tumors regardless of the manner of diagnosis. Nonetheless, the fact that patients under surveillance had the best prognosis suggests that a systematic effort to achieve an early diagnosis optimizes the benefit.

Patients under surveillance were more frequently offered effective treatments. This result has been anticipated by others (11, 12) and can be attributed to the better cancer stage. Patients not under surveillance were in fact taken into care by our centers soon after HCC diagnosis, and the yearly proportion of individuals under and outside of surveillance remained steady throughout the study in each center. Thus, the two groups were offered the same therapeutic opportunities.

Other factors might have contributed in generating a different prognosis for patients both under and outside surveillance, such as a different rate of ongoing alcohol abuse, GI bleeding, and antiviral treatment. The prevalence of the first two factors did not differ between the groups, whereas a greater proportion of patients under surveillance was treated with interferon. Given that only 4.8% of all patients were treated, it is unlikely that this difference was crucial in determining the worse prognosis of the group outside surveillance. The similar rates of different causes of death among the three groups are also reassuring in this respect.

The importance of cancer stage in influencing the therapeutic decision is also supported by the finding that in the control group, incidental lesions were more frequently judged to be amenable to effective treatments than symptomatic tumors. Moreover, it should be remembered that when surveillance failed to improve cancer stage, the proportion of treated patients did not differ between patients with HCC detected either with or without this procedure (13). As expected, the distribution of treatments in class C patients was not affected by the type of HCC diagnosis. Although the low sample size could affect this result, it is conceivable that the poor liver function, ruling out any possibility of effective treatment, was the main cause.

In agreement with a previous investigation (11), surveillance conferred a better prognosis to patients treated with surgical resection. Trends toward a better prognosis for those treated with PEI and TACE were also observed, but the difference did not reach statistical significance. This discrepancy with respect to the Hong Kong experience (11) may be due to the use of survival corrected for the lead time instead of actuarial survival.

Patients under surveillance showed a less advanced Child-Pugh class, which is an independent predictor of mortality (31, 32). This "stage migration" phenomenon has already been reported (11) and likely depends on the different cancer stage. Nonetheless, to overcome any confounding effect by the unequal distribution of Child-Pugh classes, we assessed the impact of surveillance in each class. Interestingly, the benefit of surveillance was limited to well compensated patients, in whom the estimated death risk was reduced by 41%. As expected (7, 11, 28, 32), this benefit was due to the ability of surveillance to detect HCC at an early stage, which, in turn, increases the proportion of patients amenable to effective treatments. In fact, the benefit disappeared when cancer stage and treatment were added to the Cox model (Table 5). Therefore, it can be concluded that surveillance and tumor stage are strictly related and that the impact on survival of the latter is prevalent.

Another point that needs to be commented on is that, although the surveillance improved the survival of class A patients, this benefit was not associated with a significant decrease in the prevalence of death attributed to the cancer progression. Such a result may have been generated by the fact that the cause of death was determined in 70% of patients. Alternatively, assuming that the surveillance affects the HCC-related mortality, it can be inferred that HCC plays a role in the decline of liver function and in the development of GI bleeding even in patients without clear evidence of tumor progression.

Hepatocellular carcinoma occurrence abates life expectancy even in patients with advanced cirrhosis (13). Therefore, the failure of surveillance in these patients needs to be explained. First, a poor liver function precludes the feasibility of treatment. Second, decompensated patients are more susceptible to the adverse and potentially lethal effects of treatments able to cure or control cancer. This may explain why, despite the fact that surveillance increased the number of treated patients in class A and B equally, survival improved only in class A. Third, the lack of benefit was also due to the low access rate to OLT, which offers excellent survival for patients with nonadvanced HCC, regardless of the Child-Pugh class at transplantation (8). Both semiannual and annual surveillance doubled the percentage of HCCs treatable with OLT as compared with the control cohort (Fig. 1). However, only 15 of 121 potential candidates underwent OLT, as a result of both organ shortage and the reluctance of surgeons to perform transplantations in patients with HCC because of the poor results previously obtained in patients with large tumors. This allowed us to confirm the results of a decision analysis study indicating that, when OLT availability is limited, the success of surveillance for HCC critically depends on the underlying cirrhosis-related life expectancy (14). The surveillance strategy should thus be tailored according to local resources, bearing in mind that in centers without an OLT program or when the demand greatly exceeds donor organ availability, surveillance can be beneficial only for patients with a good cirrhosis-related prognosis.

In conclusion, this study showed that in patients with cirrhosis: 1) HCCs detected during semiannual or annual surveillance, based on US and AFP determination, have a better prognosis than those detected outside surveillance; 2) the two surveillance programs are equally valid in terms of patient survival; 3) if access to OLT is limited, the benefit remains confined to patients with a good cirrhosis-related prognosis at the time of cancer diagnosis; and 4) two thirds of HCCs detected during surveillance fulfill the criteria heralding excellent disease-free survival after OLT.

However, as biases cannot be fully removed from a retrospective study, these results should be confirmed by prospective randomized trials. Nevertheless, because they provide support to the recommendation to regularly examine cirrhotic patients (15–18), it seems advisable to conduct trials comparing the cost-effectiveness of semiannual to annual surveillance for HCC, rather than surveillance to care "on demand."

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APPENDIX

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