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CME

Surveillance for Early Diagnosis of Hepatocellular Carcinoma: Is It Effective in Intermediate/Advanced Cirrhosis?

Franco Trevisani, M.D.,[1] Valentina Santi, M.D.,[1] Annagiulia Gramenzi, M.D.,[1] Maria Anna Di Nolfo, M.D.,[2] Paolo Del Poggio, M.D.,[3] Luisa Benvegnù, M.D.,[4] Gianludovico Rapaccini, M.D.,[5] Fabio Farinati, M.D.,[6] Marco Zoli, M.D.,[1] Franco Borzio, M.D.,[7] Edoardo Giovanni Giannini, M.D.,[8] Eugenio Caturelli, M.D.,[9] and Mauro Bernardi, M.D.,[1] for the Italian Liver Cancer (ITA.LI.CA.) group

[1]*Dipartimento di Medicina Interna, Cardioangiologia, Epatologia, Alma Mater Studiorum-Università di Bologna;* [2]*Divisione di Medicina, Ospedale Bolognini, Seriate;* [3]*Divisione di Medicina, Ospedale Treviglio-Caravaggio, Treviglio;* [4]*Dipartimento di Medicina Clinica e Sperimentale, Università di Padova;* [5]*Cattedra di Medicina Interna II, Università Cattolica del Sacro Cuore di Roma;* [6]*Dipartimento di Scienze Chirurgiche e Gastroenterologiche, Università di Padova;* [7]*Dipartimento di Medicina, Unità di Gastroenterologia, Ospedale Fatebenefratelli, Milano;* [8]*Cattedra di Gastroenterologia, Dipartimento di Medicina Interna, Università di Genova; and* [9]*Unità di Gastroenterologia, Ospedale Belcolle, Viterbo; Italy*

OBJECTIVES: Surveillance of cirrhotic patients for early diagnosis of hepatocellular carcinoma (HCC), based on ultrasonography and alpha-fetoprotein (AFP) measurement, is widely used. Its effectiveness depends on liver function, which affects the feasibility of treatments and cirrhosis-related mortality. We assessed whether patients with intermediate/advanced cirrhosis benefit from surveillance.

METHODS: We selected 468 Child-Pugh class B and 140 class C patients from the ITA.LI.CA database, including 1,834 HCC patients diagnosed from January 1987 to December 2004. HCC was detected in 252 patients during surveillance (semiannual 172, annual 80 patients; *group 1*) and in 356 patients outside surveillance (*group 2*). Survival of surveyed patients was corrected for the *estimated lead time*.

RESULTS: Child-Pugh class B: cancer stage ($P < 0.001$) and treatment distribution ($P < 0.001$) were better in group 1 than in group 2. The median (95% CI) survivals were 17.1 (13.5–20.6) *versus* 12.0 (9.4–14.6) months and the survival rates at 1, 3, and 5 yr were 60.4% *versus* 49.2%, 26.1% *versus* 16.1%, and 10.7% *versus* 4.3%, respectively ($P = 0.022$). AFP, gross pathology, and treatment of HCC were independent prognostic factors. Child-Pugh class C: cancer stage ($P = 0.001$) and treatment distribution ($P = 0.021$) were better in group 1 than in group 2. Nonetheless, median survival did not differ: 7.1 (2.1–12.1) *versus* 6.0 (4.1–7.9) months ($P = 0.740$).

CONCLUSIONS: These results suggest surveillance be offered to class B patients and maintained for class A patients who migrate to the subsequent class. Surveillance becomes pointless in class C patients probably because the poor liver function adversely affects the overall mortality and HCC treatments.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common tumors worldwide, with an increasing incidence in the western world (1). The prognosis of patients with HCC has marginally improved over the last two decades, the 5-yr survival rate currently being 5% (2). This dismal result is in part due to the fact that diagnosis is frequently made at an advanced tumor stage precluding effective treatment. Therefore, most gastroenterologists routinely offer patients at risk HCC surveillance programs, based on ultrasonography (US) with or without alpha-fetoprotein (AFP) measurement (3), which can detect most tumors at a stage still eligible for treatment (for review, see (4)).

Although it has been definitely proven that surveillance increases the survival rate only in hepatitis B virus (HBV) carriers (5), several cohort studies indicate that even patients with cirrhosis, which underlies >80% of HCCs, may benefit from this practice (6–10). Consequently, both European

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and American guidelines for HCC management (11, 12) recommend offering surveillance to cirrhotic patients, provided that the following condition is met: "the patients who should undergo surveillance should be those cirrhotics who would be treated if diagnosed with HCC" (11). In this respect, it is worth noting that liver function and portal hypertension are the main limiting factors for the applicability of HCC treatments other than liver transplantation (OLT), which, however, only accounts for 10% of therapeutic options (7, 8, 10, 13). Moreover, the benefit of surveillance critically depends on the underlying cirrhosis-related survival (14).

The Child-Pugh (C-P) classification scores three liver tests and two complications of portal hypertension, and is the most widely used means of gauging the severity of cirrhosis and its prognosis in clinical practice (15). Therefore, the pertinent question that can be pragmatically posed is: which C-P class/es must a patient belong to *at the time* of HCC detection in order to benefit from surveillance? From the answer we can infer *which* patients can gainfully enter into a surveillance program and *when* they must be removed from it because they have migrated to a C-P class where the procedure is futile. This strategy may ultimately improve the unsatisfactory cost/effectiveness ratio of surveillance for HCC in unselected cirrhotic patients (7, 14, 16)

Only two studies have addressed this topic and both found that surveillance prolonged the survival of patients belonging to class A at the time of HCC diagnosis, but not that of class C subjects (6, 8). For class B, the results are less univocal: surveyed subjects had a prognostic benefit in the oriental series, while the advantage achieved in the Italian Liver Cancer (ITA.LI.CA) group series was at the borderline of statistical significance. Thus, although it is known that the occurrence of HCC halves the expected 3-yr survival rate of class B patients (7), whether they should undergo surveillance still remains undefined (11, 12). Some experts suggest offering surveillance programs to these subjects only if OLT is available (17).

Major advances in HCC management have occurred in recent years: (a) modern diagnostic imaging techniques can disclose "very small" HCCs ($\leq$2 cm) curable with percutaneous procedures applicable even to patients with relatively advanced cirrhosis; (b) percutaneous thermoablation, which is thought to be superior to percutaneous ethanol injection (PEI) (18, 19), has spread rapidly in specialized centers; (c) the improper "lobar" transarterial chemoembolization (TACE) has been abandoned in favor of the safer and more effective "segmental or subsegmental" procedures (11, 20); (d) the available algorithms tailoring treatment according to tumor burden, liver function, and clinical status have optimized the therapeutic strategy (21, 22). These advances, together with the reduction of cirrhosis-related mortality due to an improved management of its complications, may have enhanced the surveillance benefit, extending it beyond class A patients.

Thus, the time has come to re-evaluate surveillance for HCC in intermediate/advanced cirrhosis. The current study aims to assess whether surveillance improves the prognosis of patients belonging to C-P classes B and C at the time of HCC diagnosis as compared with their counterparts whose cancer diagnosis was made outside a periodic screening.

PATIENTS AND METHODS

Patients

The ITA.LI.CA database currently includes the data of 1,834 HCC patients seen consecutively from January 1987 to December 2004 at 10 medical institutions. The data were collected prospectively and updated every 2 yr. After data collection from any single center, the consistency of the dataset was checked by the group coordinator (F. T.). When clarification or additional information was needed, the data were resubmitted to each center before statistical evaluation. For the purpose of the study, the eligibility criteria were the description of: (a) the interval of surveillance, (b) the C-P class at the time of HCC diagnosis. According to these criteria, we retrospectively selected 608 patients: 468 class B and 140 class C cases. The causes of exclusion were: class A (1,084 patients), class unreported (59 patients), and surveillance interval unspecified (83 patients).

Patients were divided into two groups: *group 1* including 252 (41.4%) patients in whom HCC was detected during regular surveillance based on liver US and AFP performed every 6 (172 cases [68.3%]) or 12 (80 [31.7%]) months. These patients were grouped since their prognosis was unaffected by the interval (data not shown, $P = 0.531$); *group 2* including 356 (58.6%) cases in whom HCC was detected "incidentally," *i.e.*, outside any programmed surveillance or during examination for other diseases (181 patients [50.8%]), or because of symptom appearance (175 patients [49.2%]). These patients were grouped because both modalities of diagnosis reproduce an alternative to surveillance in detecting HCC in clinical practice.

Surveillance or care "on demand" was decided by the referring physician, who was a clinician of the ITA.LI.CA group in more than 80% of group 1 cases, whereas most group 2 cases were referred to our centers by their general practitioners or other institutions to confirm diagnosis or start treatment of HCC (concomitant nonrandomized controls). Owing to the absence of conclusive information on this aspect (12), the surveillance interval was decided by the referring physician based on his own opinion.

To minimize the *length bias* (23), patients under surveillance were allocated to group 1 even when US examination was brought forward due to the occurrence of symptoms (41 cases).

Etiology and Diagnosis of Cirrhosis

The cause of liver disease was classified as follows: *HBV* if patients were HBsAg +; *HCV* (hepatitis C virus) if patients were positive for serum antibody anti-HCV; *alcoholic* if the daily ethanol intake was more than 60 g for women and 80 g for men for more than 10 yr in the absence of any other

known causes of liver disease; *multietiology* if they showed a combination of two or more causative factors; *others*, including 31 cryptogenic liver diseases, two hereditary hemochromatosis, and two primary biliary cirrhosis.

Cirrhosis was confirmed by histology in 168 patients and by laparotomy/laparoscopy in 10. In the remaining cases, the diagnosis was made unequivocally by clinical (endoscopic and/or US signs of portal hypertension and a nodular margin of the liver at US examination) and laboratory features.

Diagnosis and Staging of HCC

The diagnosis was based on histology or cytology in 42 patients. Otherwise, diagnosis was made by combining a diagnostic AFP increase (>200 ng/mL) (21) with a typical feature of the lesion (arterial hypervascularity) in one imaging technique or, in the absence of diagnostic AFP, in at least two techniques.

Cancer was staged by both US (performed by means of high-resolution, real-time equipment with linear and/or convex-array 3.5 MHz probes) and CT scan (biphasic or multiphasic) or magnetic resonance and, when appropriate, by angiography. The macroscopic types of HCC were classified as: *unifocal*, *paucifocal* (≤3 nodules), *multifocal* (>3 nodules), *infiltrating* and *massive* (24). The tumor size of expanding nodules was also measured (in multinodular tumors, the largest one). All patients had a chest X-ray, while additional investigations to detect metastases were performed when extrahepatic involvement was suspected. Cancer stage was scored according to the latest versions of both the United Network for Organ Sharing (UNOS) tumor nodes metastases (TNM) system (UNOS/OPTN policy. Available at http://www.optn.org) and Cancer of the Liver Italian Program (CLIP) system (25). The Barcelona Clinic Liver Cancer system (12) was not used since many cases lacked the pertinent data, as this system was not widely used until recent years.

Therapeutic Decision

The criteria for considering patients amenable to hepatic resection, PEI, or radiofrequency thermoablation and TACE have been reported in detail elsewhere (8).

Serologic Testing

Liver tests (prothrombin activity, plasma albumin, bilirubin, and alanine aminotransferase [ALT] concentrations), serum virological markers, and plasma levels of AFP (reference range 0–20 ng/mL) were determined by conventional methods. HBV markers were tested by radioimmunoassay or enzyme-linked immunosorbent assay, anti-HCV antibody by ELISA I (up to April 1991), II, and III generation, and anti-HDV antibody by radioimmunoassay, using commercial kits.

Statistical Analysis

The statistical analysis was conducted after stratification of patients according to the C-P class. Continuous data are expressed as means ± standard deviations. Discrete variables are expressed as absolute and relative frequencies. The Mann-Whitney U test or the Pearson χ^2 test was used to compare continuous or discrete data, respectively.

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 Cox analysis.

As in previous studies (26), to minimize the *lead time bias* (the apparent improvement in survival due to the anticipated cancer detection by surveillance (23)), we calculated the "lead time" for surveyed patients using Schwartz's (27) formula originally proposed for calculating tumor growth:

$$t = \mathrm{DT} \times 3 \times \log(d_1/d_0)/\log(2)$$

where t is the lead time (days), DT is the median value of the tumor volume doubling time proposed by Scheu *et al*. (28), d_0 is the median tumor diameter of patients under surveillance, and d_1 is the median tumor diameter of patients outside surveillance. The calculated lead times were: 238 days for patients examined every 6 months and 121 days for those surveyed annually. These lead times were subtracted from the survival of surveyed patients. If the value became negative (48 patients), we attributed a survival (deceased patients) or a follow-up (living patients) of 1 day.

Age, sex, etiology, period of diagnosis (1987–1992, 1993–1998, and 1999–2004), comorbidity (yes/no), surveillance, ALT, AFP level (normal ≤20, elevated 21–200 and diagnostic >200 ng/mL), gross pathology, cancer size, portal vein and/or caval thrombosis, metastases, and treatment (ordered in five categories of decreasing effectiveness: OLT, hepatic resection, percutaneous ablation, TACE [± PEI], other, or palliation) were tested as predictors of survival by univariate Cox analysis. The variables significantly associated with survival at univariate analysis were tested by Cox multivariate stepwise regression analysis to identify the independent prognostic factors. The adjusted relative risks (hazard ratios) and their 95% CI were calculated for variables independently correlated with survival.

A 2-tailed P value <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS 13.0 statistical package (Chicago, IL).

Ethics

The study conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the senior staff of the participating Institutions.

RESULTS

Child-Pugh B Patients

TYPE OF HCC DETECTION. Among the 203 surveyed patients, 137 (67.5%) were on semiannual and 66 (32.5%) on annual surveillance. Among the 265 unsurveyed individuals, 147 (55.5%) had an incidental diagnosis and 118 (44.5%) a symptomatic diagnosis of HCC.

Table 1. Demographic and Clinical Characteristics of Child-Pugh B Patients

	Group 1 (Surveillance)	Group 2 (Incidental/Symptomatic HCC)	P^*
Age (yr) (N = 468)	63.8 ± 9.2	65.7 ± 10.0	0.032
Sex (M/F) (N = 468)	141/62 (69.5/30.5%)	202/63 (76.2/23.8%)	0.101
Etiology (N = 468)			<0. 001
HBV (N = 46; 9.8%)	26 (12.8%)	20 (7.5%)	
HCV (N = 221; 47.3%)	114 (56.2%)†	107 (40.5%)	
Alcohol (N = 75; 16.0%)	15 (7.4%)†	60 (22.6%)	
Multietiology (N = 96; 20.5%)	39 (19.2%)	57 (21.5%)	
Others (N = 30; 6.4%)	9 (4.4%)	21 (7.9%)	
Period of diagnosis (N = 466)			0.200
1987–1992 (N = 102; 21.8%)	40 (19.9%)	62 (23.4%)	
1993–1998 (N = 196; 42.1%)	94 (46.8%)	102 (38.5%)	
1999–2004 (N = 168; 36.1%)	67 (33.3%)	101 (38.1%)	
Comorbid illnesses (N = 370)			0.133
No (N = 195; 52.7%)	92 (57.1%)	103 (49.3%)	
Yes (N = 175; 47.3%)	69 (42.9%)	106 (50.7%)	
ALT (ULRR) (N = 451)	1.96 ± 1.50	2.22 ± 2.19	0.744
Alpha-fetoprotein (N = 428)			<0.001
≤20 ng/mL (N = 194; 45.3%)	87 (45.8%)	107 (45.0%)	
21–200 ng/mL (N = 120; 28.1%)	68 (35.8%)†	52 (21.8%)	
>200 ng/mL (N = 114; 26.6%)	35 (18.4%)‡	79 (33.2%)	

*Mann-Whitney U test or Pearson χ^2 test, as appropriate. HBV = hepatitis B virus; HCV = hepatitis C virus; ULRR = upper limit of reference range.
†$P < 0.001$, ‡$P = 0.002$ *versus* the corresponding variable of group 2.

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS (TABLE 1). The two groups were comparable for sex, period of diagnosis, comorbidity, and ALT value, but not for age, group 1 patients being younger than the counterpart. The distribution of the etiology also differed, because HCV patients were more common and alcoholic cases less frequent in group 1 than in group 2. Overall, plasma AFP was elevated (>20 ng/mL) in 54.7% of patients, reaching the diagnostic level (>200 ng/mL) in 26.6%. The prevalence of patients with an elevated AFP was similar in the two

Table 2. Characteristics and Treatment of Hepatocellular Carcinoma in Child-Pugh B Patients

	Group 1 (Surveillance)	Group 2 (Incidental/ Symptomatic HCC)	P^*
Gross pathology (N = 458)			<0.001
Unifocal (N = 190; 41.5%)	104 (52.8%)†	86 (33.0%)	
Paucifocal (N = 116; 25.4%)	56 (28.4%)	60 (23.0%)	
Plurifocal (N = 83; 18.1%)	28 (14.2%)‡	55 (21.1%)	
Infiltrating (N = 45; 9.8%)	8 (4.1%)†	37 (14.2%)	
Massive (N = 24; 5.2%)	1 (0.5%)†	23 (8.8%)	
Tumor size (cm) (N = 418)	3.1 ± 1.7	5.0 ± 2.9	<0.001
Vascular invasion (N = 462)	23 (11.4%)	63 (24.1%)	0.001
Metastases (N = 460)	4 (2.0%)	8 (3.1%)	0.473
UNOS TNM cancer stage† (N = 443)			<0.001
T1 (N = 29; 6.5%)	18 (9.4%)§	11 (4.4%)	
T2 (N = 156; 35.2%)	101 (52.9%)†	55 (21.8%)	
>T2 (N = 258; 58.3%)	72 (37.7%)†	186 (73.8%)	
CLIP score (N = 421)			<0.001
0 (N = 9; 2.1%)	6 (3.2%)	3 (1.3%)	
1 (N = 135; 32.1%)	80 (43.3%)†	55 (23.3%)	
2 (N = 141; 33.5%)	67 (36.2%)	74 (31.4%)	
3 (N = 74; 17.6%)	22 (11.9%)¶	52 (22.0%)	
≥4 (N = 62; 14.7%)	10 (5.4%)†	52 (22.0%)	
Treatment (N = 462)			<0.001
Transplant (N = 12; 2.6%)	12 (6.0%)†	0	
Resection (N = 16; 3.5%)	5 (2.5%)	11 (4.2%)	
PEI or RF (N = 89; 19.3%)	53 (26.5%)†	36 (13.7%)	
TACE (± PEI) (N = 152; 33.0%)	72 (36.0%)	81 (30.9%)	
Others/palliation (N = 192; 41.6%)	58 (29.0%)†	134 (51.2%)	

*Mann-Whitney U test or Pearson χ^2 test, as appropriate. †T1: single lesion <2 cm, T2: single lesion between 2 and 5 cm or no more than 3 lesion each ≤ 3 cm. PEI = percutaneous ethanol injection; RF = radiofrequency ablation; TACE = transarterial chemoembolization.
†$P < 0.001$, ‡$P = 0.050$, §$P = 0.036$, ¶$P = 0.001$ *versus* the corresponding variable of group 2.

groups but a diagnostic level was less common in surveyed patients.

CHARACTERISTICS AND TREATMENT OF HCC (TABLE 2). Tumor features differed widely between groups. The distribution of gross pathologic types was much better in group 1, where single nodules were more frequent whereas plurifocal, infiltrating, and massive HCCs were less common than in group 2. Tumor diameter and frequency of vascular invasion were significantly lower in group 1 patients. Metastases were uncommon in both groups, so that their prevalence did not differ. As a result, the distribution of HCC stage according to both UNOS-TNM and CLIP systems was more favorable in group 1. Importantly, the prevalence of early HCCs (T1 and T2 UNOS stages) was 62.3% in group 1 and 26.2% in group 2.

The treatment distribution also differed widely. The proportion of patients treated with radical (surgical or percutaneous) procedures was higher in group 1 (35.1%) than in group 2 (17.9%), while systemic treatments (most frequently oral tamoxifen) or palliation were applied less commonly to group 1 (29.2%) than group 2 (51.2%) patients.

Survival

The median follow-up was 17 months (95% CI 14.7–19.5). Data on follow-up were lacking for four surveyed and two unsurveyed patients. Three hundred sixty-nine patients died during the follow-up. The survival adjusted for the estimated lead time of group 1 patients was higher than the observed survival of group 2 patients (median 17.1, 95% CI 13.5–20.6 months *vs* 12.0, 95% CI 9.4–14.6, $P = 0.022$). The estimated survival rates at 1, 3, and 5 yr were 60.4%, 26.1%, and 10.7% in group 1 and 49.2%, 16.1%, and 4.3% in group 2 (Fig. 1).

We also analyzed the survival after excluding the patients who underwent OLT. In the subset of nontransplanted cases, the prognosis did not differ between groups (group 1: median adjusted survival 16.0, 95% CI 12.9–19.0 months; group 2: median observed survival 12.0, 95% CI 9.4–14.6, $P = 0.253$).

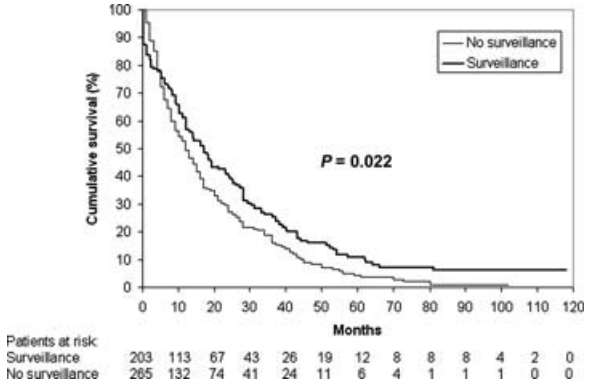

Figure 1. Survival of Child-Pugh class B patients according to the modality of cancer diagnosis. In patients under surveillance, the survival was adjusted for the estimated lead time.

Table 3. Variables Associated With Survival in Child-Pugh B Patients

	Univariate Analysis *P*	Multivariate Analysis	
		Hazard Ratio (95% CI)	*P*
Age	0.001		
Sex	0.243		
Etiology	0.742		
Period of diagnosis	0.339		
Comorbidity	0.393		
Surveillance	0.026		
ALT	0.994		
AFP	<0.001		0.005
≤20 ng/mL		1	
21–200 ng/mL		1.09 (0.82–1.44)*	
>200 ng/mL		1.62 (1.20–2.18)*	
Gross pathologic types	<0.001		<0.001
Unifocal		1	
Paucifocal		1.14 (0.85–1.52)*	
Plurifocal		1.78 (1.29–2.51)*	
Infiltrating or massive		3.46 (2.10–5.70)*	
Cancer diameter	<0.001		
Vascular invasion	<0.001		
Metastases	0.919		
Treatment	<0.001		<0.001
Transplant		1	
Resection		4.10 (1.42–11.81)*	
PEI or RF		4.69 (1.81–12.09)*	
TACE (± PEI)		4.94 (1.96–12.45)*	
Others/palliation		7.57 (3.00–19.11)*	

**Versus* the most favorable condition (AFP ≤20 ng/mL, unifocal HCC and liver transplant, respectively).

Predictors of survival at univariate analysis were age, surveillance, AFP, gross pathology, cancer size, vascular invasion, and treatment (Table 3). Multivariate analysis proved that AFP, gross pathology, and treatment were independent prognostic factors.

Child-Pugh C Patients

TYPE OF HCC DETECTION. Among the 49 surveyed patients, 35 (71.4%) were on semiannual and 14 (28.6%) on annual surveillance, while 34 (37.4%) out of 91 unsurveyed individuals had an incidental and 57 (62.6%) a symptomatic diagnosis of tumor.

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS (TABLE 4). Patients under or outside surveillance did not differ for age, sex, etiology of liver disease, period of diagnosis, comorbidity, or ALT value. Instead, AFP levels were different. Overall, AFP level was elevated (>20 ng/mL) in 58% of patients and diagnostic (>200 ng/mL) in 39.7%. The distribution of AFP categories was better in group 1, so that diagnostic levels were less common in this group.

CHARACTERISTICS AND TREATMENT OF HCC (TABLE 5). All tumor features but metastases differed between groups. Group 1 was more likely to have unifocal

Table 4. Demographic and Clinical Characteristics of Child-Pugh C Patients

	Group 1 (Surveillance)	Group 2 (Incidental/Symptomatic HCC)	P^*
Age (yr) (N = 139)	61.6 ± 10.6	60.4 ± 10.8	0.453
Sex (M/F) (N = 140)	40/9 (81.6/18.4%)	72/19 (79.1/20.9%)	0.723
Etiology (N = 140)			0. 354
HBV (N = 17; 12.1%)	7 (14.3%)	10 (11.0%)	
HCV (N = 62; 44.3%)	26 (53.1%)	36 (39.6%)	
Alcohol (N = 24; 17.1%)	5 (10.2%)	19 (20.8%)	
Multietiology (N = 32; 22.9%)	10 (20.4%)	22 (24.2%)	
Others (N = 5; 3.6%)	1 (2.0%)	4 (4.4%)	
Period of diagnosis (N = 140)			0.515
1987–1992 (N = 26; 18.6%)	7 (14.3%)	19 (20.9%)	
1993–1998 (N = 56; 40.0%)	19 (38.8%)	37 (40.6%)	
1999–2004 (N = 58; 41.4%)	23 (46.9%)	35 (38.5%)	
Comorbid illnesses (N = 115)			0.906
No (N = 65; 56.5%)	24 (55.8%)	41(56.9%)	
Yes (N = 50; 43.5%)	19 (44.2%)	31 (43.1%)	
ALT (ULRR) (N = 136)	2.00 ± 1.16	2.33 ± 2.06	0.958
Alpha fetoprotein (N = 131)			0.015
≤20 ng/mL (N = 45; 42.0%)	24 (51.1%)	31 (36.9%)	
21–200 ng/mL (N = 24; 18.3%)	12 (25.5%)	12 (14.3%)	
>200 ng/mL (N = 52; 39.7%)	11 (23.4%)†	41 (48.8%)	

*Mann-Whitney U test or Pearson χ^2 test, as appropriate. HBV = hepatitis B virus; HCV = hepatitis C virus; ULRR = upper limit of reference range.
†$P = 0.008$ *versus* the corresponding variable of group 2.

and paucifocal HCCs than group 2. Also, cancer diameter was smaller and vascular invasion less frequent than in group 2. The prevalence of early HCCs (T1 and T2 UNOS stages) decreased from 55.3% in group 1 to 25.9% in group 2. CLIP score distribution also significantly benefited from surveillance.

Although not as much as in class B, treatment application also differed. Group 1 patients underwent percutaneous procedures and TACE more frequently than their counterparts, so that 55% of group 1 and 81% of group 2 cases were not considered eligible for effective therapies and underwent other approaches or palliation.

Table 5. Characteristics and Treatment of Hepatocellular Carcinoma in Child-Pugh C Patients

	Group 1 (Surveillance)	Group 2 (Incidental/Symptomatic HCC)	P^*
Gross pathology (N = 139)			0.007
Unifocal (N = 42; 30.2%)	20 (40.7%)†	22 (24.4%)	
Paucifocal (N = 32; 23.0%)	16 (32.7%)†	16 (17.8%)	
Plurifocal (N = 36; 25.9%)	9 (18.4%)	27 (30.0%)	
Infiltrating (N = 23; 16.5%)	4 (8.2%)	19 (21.1%)	
Massive (N = 6; 4.3%)	0	6 (6.7%)	
Tumor size (cm) (N = 115)	3.0 ± 1.5	4.3 ± 2.6	0.009
Vascular invasion (N = 140)	6 (10.2%)	26 (28.6%)	0.013
Metastases (N = 139)	3 (6.1%)	3 (3.3%)	0.440
UNOS TNM cancer stage§§ (N = 132)			0.002
T1 (N = 5; 3.8%)	4 (8.5%)§	1 (1.2%)	
T2 (N = 43; 32.6%)	22 (46.8%)‡	21 (24.7%)	
>T2 (N = 34; 63.6%)	21 (44.7%)¶	63 (74.1%)	
CLIP score (N = 130)			0.001
0 (N = 0)	0	0	
1 (N = 0)	0	0	
2 (N = 30; 23.1%)	17 (36.2%)¶¶	13 (15.7%)	
3 (N = 43; 33.1%)	19 (40.4%)	24 (28.9%)	
≥4 (N = 57; 43.8%)	11 (23.4%)**	46 (55.4%)	
Treatment (N = 135)			0.021
Transplant (N = 6; 4.4%)	3 (6.4%)	3 (3.4%)	
Resection (N = 1; 0.7%)	0	1 (1.1%)	
PEI or RF (N = 11; 8.2%)	7 (14.9%)§	4 (4.5%)	
TACE (± PEI) (N = 20; 14.8%)	11 (23.4%)††	9 (10.2%)	
Others/palliation (N = 97; 71.9%)	26 (55.3%)¶	71 (80.8%)	

*Mann-Whitney U test or Pearson χ^2 test, as appropriate. §§T1: single lesion <2 cm, T2: single lesion between 2 and 5 cm or no more than 3 lesion each ≤ 3 cm. PEI = percutaneous ethanol injection; RF = radiofrequency ablation; TACE = transarterial chemoembolization.
†$P = 0.040$, §$P = 0.050$, ‡$P = 0.008$, ¶$P = 0.002$, ¶¶$P = 0.005$, **$P = 0.001$, ††$P = 0.043$ *versus* the corresponding variable of group 2.

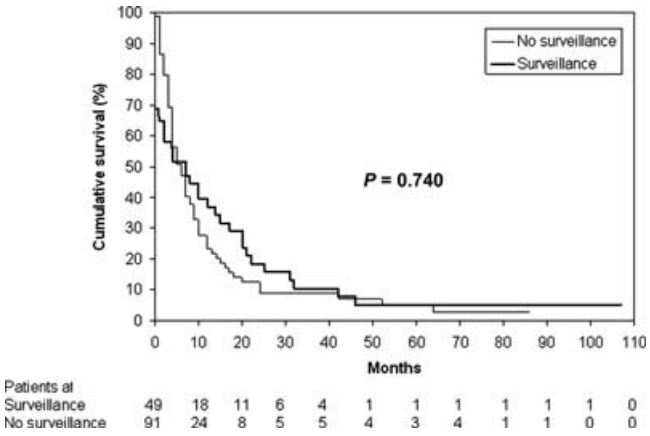

Figure 2. Survival of Child-Pugh class C patients according to the modality of cancer diagnosis. In patients under surveillance, the survival was adjusted for the estimated lead time.

Survival

The median follow-up was 7 months (95% CI 5.2–8.8). Data on follow-up were lacking for one patient under and two outside surveillance. One hundred eighteen patients died. The survival adjusted for the estimated lead time of group 1 patients did not differ with respect to the observed survival of group 2 patients (median 7.1, 95% CI 2.1–12.1 *vs* 6.0, 95% CI 4.1–7.9 months, $P = 0.740$). The survival rates at 1, 3, and 5 yr were 39.5%, 10.5%, and 5.3% in group 1, and 23.2%, 8.9%, and 5.3% in group 2 (Fig. 2).

Table 6. Variables Associated With Survival in Child-Pugh C Patients

	Univariate Analysis *P*	Multivariate Analysis	
		Hazard Ratio (95% CI)	*P*
Age	0.979		
Sex	0.358		
Etiology	0.594		
Period of diagnosis	0.009		0.031
1999–2004		1	
1993–1998		1.49 (0.87–2.55)*	
1987–1992		2.29 (1.23–4.25)*	
Comorbidity	0.194		
Surveillance	0.740		
ALT	0.046		
AFP	<0.001		
Gross pathologic type	<0.001		
Cancer diameter	0.003		
Vascular invasion	<0.001	1.92 (1.08–3.39)	0.025
Metastases	0.013	4.37 (1.28–14.6)	0.018
Treatment	0.031		0.003
Transplant		1	
Resection		25.57 (2.17–301.20)*	
PEI or RF		1.61 (0.31–8.36)*	
TACE (± PEI)		5.07 (1.10–23.37)*	
Others/palliation		6.22 (1.46–26.40)*	

* *Versus* the most favorable condition (period 1999–2004 and liver transplant, respectively).

Univariate analysis proved that the period of diagnosis, ALT, AFP, gross pathology, cancer size, vascular invasion, metastases, and treatment were predictors of survival. Multivariate analysis showed that the period of diagnosis, vascular invasion, metastases, and treatment were independent prognostic factors (Table 6).

DISCUSSION

Several observational studies suggest that cirrhotic patients are an appropriate target population for surveillance for early detection of HCC (6–10). However, in terms of patient survival, the performance of surveillance critically depends on the severity of the underlying cirrhosis, which not only affects the applicability and outcome of HCC treatments but also the cumulative mortality rate (14). Therefore, periodic screening should only be applied in patients in whom the advantage of detecting treatable tumors is not overcome by inadequate liver function.

Most studies on surveillance excluded C-P class C patients, and only two addressed the relation between liver function and outcome of surveillance, both documenting a greater life expectancy of surveyed patients in class A at the time of HCC discovery, but not in class C (6, 8). Class B patients still represent a "gray zone": only the Hong Kong study showed a significant advantage for surveyed patients. However, this result is not conclusive because: (a) the surveillance adopted (3-monthly AFP determination) does not conform to that recommended by the international guidelines; (b) the number of class B cases was fairly low; (c) surveyed patients were only compared with symptomatic subjects, while in most countries many HCCs may be found in a subclinical stage even outside surveillance programs due to easy access to US (7, 8); (d) the symptomatic patients were included in the unsurveyed group regardless of type of diagnosis, thus maximizing the length bias (23); (e) survival was not adjusted for the lead time.

On the other hand, the nonstatistically significant benefit reported by the first ITA.LI.CA study (8) may no longer be representative of the current potential of surveillance in class B patients due to the improved management of both HCC and cirrhosis. Finally, the updated ITA.LI.CA database, having almost doubled its sample size, yielded more robust results.

The present study showed that surveillance significantly improves the prognosis of class B patients diagnosed with HCC. Since an intervention is judged effective if it prolongs survival by at least 100 days (29), the moderate prognostic gain (5.1 months) we observed can also be considered clinically acceptable. Conceivably, it depended on the earlier diagnosis improving the presenting cancer stage (stage migration) and treatment applicability: radical procedures indeed doubled (35% *vs* 18%) whereas the number of patients considered untreatable almost halved (29% *vs* 51%) with respect to the control group. The removal of surveillance from the independent prognostic factors by multivariate analysis further testifies that the benefit was mediated by its effect on HCC features and treatment.

A noticeable finding of our study is that, although a few patients underwent OLT, the availability of this treatment was crucial to achieve a better survival rate by surveillance, thus corroborating the opinion of experts (17). This requirement could dampen the practical utility of surveillance because most HCC patients are not eligible for OLT due to their age or to extrahepatic comorbidity, and some countries cannot offer this treatment. However, OLT might be not so essential a condition if the referral to medical centers of unsurveyed patients is very late, as in the Hong Kong study, which reports, in symptomatic cases, a much larger median cancer diameter (8.1 cm) than in our unsurveyed cases (6).

Class C is itself an indication to consider patients for OLT and periodic screening for HCC is strongly recommended in individuals on the OLT waiting list to identify small tumors that may be treated (to prevent their progression beyond listing criteria) and to give them greater priority (12). Thus, the dilemma concerning the utility of surveillance for class C patients only refers to those who cannot be enlisted for OLT. Our study mimics a setting virtually without OLT and indicates that surveillance is not worthwhile in these cases since the better presenting tumor stage and the higher amenability to treatments of surveyed individuals did not translate into a longer survival. This apparent paradox may have two explanations: first, although the applicability rate of all radical therapies was doubled by surveillance, it remained low (22%); second, the poor liver function likely worsened the treatment results and increased the cirrhosis-related mortality. Interestingly, the prognosis of class C patients improved over time and was less influenced by the HCC characteristics than in class B, suggesting that recent advances in the management of cirrhosis complications have a maximal impact in the setting where the cirrhosis-related mortality maximally competes with the cancer-related death.

Another finding that merits comment is the few OLT performed in our patient population, despite the fact that more than one third of HCCs were detected at a stage compatible with this treatment. An "underutilization" of OLT has already been reported by a prospective Italian survey started in 1985 (10) and by a population-based study analyzing the Surveillance Epidemiology and End Results (SEER)-Medicare data collected from 1991 to 1999 (13). Several reasons may account for this phenomenon: (a) the age of many HCC patients crosses the threshold for OLT; (b) extrahepatic comorbidities are common and many of them preclude OLT; (c) before the availability of the Milano criteria ensuring good results with OLT (30), surgeons were reluctant to transplant these patients; (d) the delisting rate of HCC patients was very high before the recent proposal to give them priority (31).

Our cohort study has several limitations and cannot replace a randomized trial, which is the only way to establish the effectiveness of surveillance once and for all. However, such a trial is not feasible in Italy because it would be jeopardized by the appropriateness of a control arm where unscheduled examinations are so frequent (in our series 55.5% of HCCs were detected incidentally). Moreover, management of the control arm in contrast with the prevailing opinion of the gastroenterologist community (3) and guidelines (11, 12) may be considered unethical in a country where access to US is easy. Therefore, we compared the surveyed cases with nonrandomized concomitant controls, thus exposing our study to the effect of some biases.

The arbitrary allocation of patients to surveillance introduces a *selection bias*, making it possible for prognostic factors to be unequally distributed among groups. Class B surveyed patients were indeed younger, more likely to be infected by HCV, and less likely to be alcoholics. At least in part, these differences were due to a greater propensity of the referring physicians to regularly survey younger and virally infected patients. However, it is unlikely that this accounts for the different survival of the two groups, because etiology did not influence prognosis, while the adverse impact of age disclosed by univariate analysis was overwhelmed when the result was adjusted for the most powerful prognostic determinants such as the tumoral features and treatment (Table 3). It should be also outlined that the difference in age between groups, although statistically significant, was small (2 yr) and probably clinically not relevant. Instead, a larger gap could have more markedly affected the result of surveillance, because the benefit of this practice decreases in patients aged 70 yr or more. In these patients, in contrast with unselected cirrhotic patients (8), the benefit was restricted to the first 3 yr after HCC discovery (26). This may worsen the cost-effectiveness of surveillance, which cannot be yet considered satisfying in unselected patients (7).

AFP levels and HCC features (which were instead independent prognostic factors) also differed, but the better profile observed in surveyed cases reflects the expected "stage migration" phenomenon produced by the earlier tumor diagnosis (12).

As in previous studies (8, 26), we tried to minimize the *length bias* by allocating to the surveillance group the surveyed patients whose examinations were brought forward because of a symptomatic tumor. We also took care to reduce the unavoidable *lead time bias* by presenting data of a long follow-up and adjusting the survival of surveyed cases for this bias.

Another limitation might derive from the *intercenter heterogeneity* of HCC management. Our database was generated by three primary referral hospitals and seven centers operating as both primary and tertiary referral institutions. The longstanding scientific links between ITA.LI.CA members and the availability of national guidelines for HCC management (21) may have limited the problem to some extent. Nonetheless, a certain degree of heterogeneity concerning patient characteristics and physician skill in HCC diagnosis and management mirrors what happens in clinical practice, providing results more representative of what can be achieved in everyday practice than findings from "ideal" settings (32, 33). This representativeness is particularly important for HCC, a disease where a large gap still separates the results provided

by state-of-the-art management from those achieved in everyday practice, where many patients are "undertreated" or "overtreated" (13).

Lastly, the objective of surveillance is to reduce the *disease-specific* mortality, which was not assessed in our study, as it was difficult to obtain accurate information on the cause of death for many patients who died outside ITA.LI.CA institutions. However, because information on cause of death is more subjective than the death event (particularly in the case of HCC on cirrhosis), it is debatable whether primary outcome should use total mortality, which avoids any subjective interpretation, rather than reason of death (34). In any case, the description of the overall mortality may have underestimated the benefit of periodic screening on the HCC-specific mortality, further corroborating the suggestion to offer surveillance to class B individuals.

In conclusion, our study shows that, in the Italian healthcare system, surveillance for early diagnosis of HCC increases the survival of cirrhotic patients belonging to B class when diagnosed with cancer, and suggests making surveillance more targeted, offering periodic screening to those without conditions precluding OLT when cancer is detected. Instead, for class C patients, who should be enlisted for OLT before HCC development whenever possible, surveillance should be reserved to those awaiting surgery (12). For the remainder surveillance becomes pointless, probably because their poor liver function has too great an impact on total mortality and feasibility/results of the other HCC treatments.

Our observational study suffers from systematic limitations and cannot replace a randomized trial. Nevertheless, trials cannot make cohort studies unnecessary (33) and, when they are not feasible, observational studies become the main means of analyzing the question.

APPENDIX

Other members of the ITA.LI.CA group: *Dipartimento di Medicina Interna, Cardioangiologia, Epatologia, Alma Mater Studiorum-Università di Bologna*: Pietro Andreone, M.D., Maurizio Biselli, M.D., Eleonora Bracci, M.D., Paolo Caraceni, M.D., Maria Chiara Cantarini, M.D., Rachele Casadio, M.D., Carmela Cursaro, M.D., Giulia Magini, M.D., Antonio Di Micoli, M.D., Marco Domenicali, M.D., Silvia Li Bassi, M.D., Donatella Magalotti, M.D., Federica Mirici Cappa, M.D., Andrea Zambruni, M.D.; *Divisione di Medicina, Ospedale Bolognini, Seriate*: Claudia Balsamo, M.D., Maria Di Marco, M.D., Elena Valvassori, M.D.; *Divisione di Medicina, Ospedale Treviglio-Caravaggio, Treviglio*: Lodovico Gilardoni, M.D., Mario Mattiello, M.D.; *Dipartimento di Medicina Clinica e Sperimentale, Clinica Medica V, Università di Padova*: Alfredo Alberti, M.D., Angelo Gatta, M.D., Maurizio Gios, M.D.; *Cattedra di Medicina Interna II, Università Cattolica del Sacro Cuore di Roma*: Marco Covino, M.D., Giovanni Gasbarrini, M.D.; *Cattedra di Malattie dell'Apparato Digerente, Università di Padova*: Anna Baldan, M.D., Dario Marino, M.D., Adriana Sergio, M.D.; *Dipartimento di Medicina, Unità di Gastroenterologia, Ospedale Fatebenefratelli, Milano*: Mariella Molaro, M.D., Maurizio Sala, M.D.; *Unità di Gastroenterologia, Ospedale Belcolle, Viterbo*: Giorgia Ghiottoni, M.D., Paola Rosselli, M.D.; *Dipartimento di Discipline Chirurgiche, Rianimatorie e dei Trapianti, Alma Mater Studiorum-Università di Bologna*: Gian Luca Grazi, M.D., Bruno Nardo, M.D., Matteo Ravaioli, M.D., Antonio Daniele Pinna, M.D.; *Dipartimento di Scienze Radiologiche ed Istocitopatologiche, Alma Mater Studiorum-Università di Bologna*: Cristina Rossi, M.D.; *Dipartimento di Radiologia, Policlinico S. Orsola-Malpighi, Bologna*: Emanuela Giampalma, M.D., Rita Golfieri, M.D.

STUDY HIGHLIGHTS

What Is Current Knowledge

- Surveillance of cirrhotic patients for early diagnosis of hepatocellular carcinoma (HCC) is recommended by international guidelines.
- Surveillance appears to be effective in those with well-compensated cirrhosis.
- There is no evidence that surveillance offers a benefit to patients with intermediate/advanced cirrhosis.

What Is New Here

- In intermediate cirrhosis, surveillance increases the detectability rate of early HCC and the applicability of curative or effective treatments.
- Surveillance improves the prognosis of these patients, provided that liver transplantation is available.
- Instead, surveillance does not ameliorate the prognosis of patients with advanced cirrhosis.

Reprint requests and correspondence: Franco Trevisani, M.D., Dipartimento di Medicina Interna, Cardioangiologia, Epatologia, Semeiotica Medica, via Albertoni, 15, 40138 Bologna, Italy.
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CONFLICT OF INTEREST

Guarantor of the article: Prof. Franco Trevisani, M.D.
Specific author contributions: F. Trevisani: Study planning and conducting, drafting manuscript. V. Santi: Study planning and conducting, drafting manuscript. A. Gramenzi: Drafting manuscript. M. A. Di Nolfo: Study planning and conducting, manuscript review. P. Del Poggio: Study planning and conducting, manuscript review. L. Benvegnù: Study planning and conducting, manuscript review. G. Rapaccini: Study planning and conducting, manuscript review. F. Farinati: Study planning and conducting, manuscript review. M. Zoli: Study planning and conducting, manuscript review. F. Borzio: Study planning and conducting, manuscript review. E.G. Giannini: Study planning and conducting, manuscript review. E. Caturelli: Study planning and conducting, manuscript review. M. Bernardi: Manuscript review. Other members of the ITA.LI.CA group (see Appendix): Study conducting. The authors have approved the final draft submitted.
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