Ultrasonographic Surveillance of Hepatocellular Carcinoma in Cirrhosis: A Randomized Trial Comparing 3- and 6-Month Periodicities

Jean-Claude Trinchet,[1,2] Cendrine Chaffaut,[3,4] Valérie Bourcier,[1,2] Françoise Degos,[5,6] Jean Henrion,[7] Hélène Fontaine,[8,9] Dominique Roulot,[2,10] Ariane Mallat,[11,12] Sophie Hillaire,[13] Paul Cales,[14] Isabelle Ollivier,[15] Jean-Pierre Vinel,[16] Philippe Mathurin,[17] Jean-Pierre Bronowicki,[18] Valérie Vilgrain,[6,19,20] Gisèle N'Kontchou,[1,2] Michel Beaugrand,[1,2] Sylvie Chevret,[3,4]
and for the Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire (GRETCH)

Detection of small hepatocellular carcinoma (HCC) eligible for curative treatment is increased by surveillance, but its optimal periodicity is still debated. Thus, this randomized trial compared two ultrasonographic (US) periodicities: 3 months versus 6 months. A multicenter randomized trial was conducted in France and Belgium (43 sites). Patients with histologically proven compensated cirrhosis were randomized into two groups: US every 6 months (Gr6M) or 3 months (Gr3M). For each focal lesion detected, diagnostic procedures were performed according to European Association for the Study of the Liver guidelines. Cumulative incidence of events was estimated, then compared using Gray's test. The prevalence of HCC ≤30 mm in diameter was the main endpoint. A sample size of 1,200 patients was required. A total of 1,278 patients were randomized (Gr3M, n = 640; Gr6M, n = 638; alcohol 39.2%, hepatitis C virus 44.1%, hepatitis B virus 12.5%). At least one focal lesion was detected in 358 patients (28%) but HCC was confirmed in only 123 (9.6%) (uninodular 58.5%, ≤30 mm in diameter 74%). Focal-lesion incidence was not different between Gr3M and Gr6M groups (2-year estimates, 20.4% versus 13.2%, $P = 0.067$) but incidence of lesions ≤10 mm was increased (41% in Gr3M versus 28% in Gr6M, $P = 0.002$). No difference in either HCC incidence ($P = 0.13$) or in prevalence of tumors ≤30 mm in diameter (79% versus 70%, $P = 0.30$) was observed between the randomized groups. *Conclusion:* US surveillance, performed every 3 months, detects more small focal lesions than US every 6 months, but does not improve detection of small HCC, probably because of limitations in recall procedures. (HEPATOLOGY 2011;54:1987-1997)

In Western countries, hepatocellular carcinoma (HCC) occurs in more than 90% of cases in patients with chronic liver diseases, most often at the cirrhosis stage. Prognosis remains very poor due to late diagnosis and the associated cirrhosis, often precluding curative treatment.[1] Currently, a major goal is to detect HCC at an early stage, when curative treatments can apply. Curable HCC is usually defined as either one tumor measuring ≤50 mm in diameter, or 2-3 tumors ≤30 mm in diameter without vascular

Abbreviations: AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; US: ultrasonography.

From the [1]AP-HP, Hôpital Jean Verdier, Service d'Hépato-gastroentérologie, Bondy, F-93140, France; [2]Université Paris 13 Paris-Nord, UFR SMBH, Bobigny, F-93000, France; [3]AP-HP, Hôpital Saint-Louis, DBIM, Paris, F-75010, France; [4]Inserm, Université Paris Diderot, UMR 717, Paris, F-75010, France; [5]AP-HP, Hôpital Beaujon, Service d'Hépatologie, Clichy, F-92110, France; [6]Université Paris 7 Denis-Diderot, Faculté de Médecine, Paris, F-75018, France; [7]Service d'Hépato-gastroentérologie, Hôpital de Jolimont, La Louvière (Haine-Saint-Paul), Belgique; [8]AP-HP, Hôpital Cochin, Service d'Hépatologie, Paris, F-75014, France; [9]Université Paris 5, Paris, F-75014, France; [10]AP-HP, Hôpital Avicenne, Unité d'Hépatologie, Bobigny, F-93000, France; [11]AP-HP, Hôpital Henri Mondor, Service d'Hépatologie, Créteil, F-94000, France; [12]Université Paris-Est Créteil, Créteil, F-94000, France; [13]Service d'Hépato-gastroentérologie, Hôpital Foch, Suresnes, France; [14]Service d'Hépato-gastroentérologie, CHU, Angers, France; [15]Service d'Hépato-gastroentérologie, CHU, Caen, France; [16]Service d'Hépato-gastroentérologie, CHU, Université de Toulouse, INSERM U858, Toulouse, France; [17]Service d'Hépato-gastroentérologie, CHU, Lille, France; [18]Service d'Hépato-gastroentérologie, CHU de Nancy, Vandœuvre, France; [19]AP-HP, Hôpital Beaujon, Service de Radiologie, Clichy, F-92110, France; and [20]INSERM CRB3, Center de Recherche Biomédicale Bichat-Beaujon, Unité 773, Paris, F-75018, France.

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extension or metastasis (Milan criteria),[1] even though these criteria can be controversial.[2] The most favorable results in terms of tumor destruction and local recurrence, by far, are observed for single tumors $\leq$30 mm in diameter, especially in patients treated by percutaneous ablation.[3] Patients with small HCC tumors are usually asymptomatic and early detection needs active surveillance. Patients with cirrhosis are the main target population as recommended by international guidelines,[1,4,5] even though surveillance is also recommended for patients with chronic liver disease without cirrhosis, such as hepatitis B virus (HBV) chronic hepatitis.[6]

Clinical effectiveness of the surveillance policy in cirrhotic patients has not been demonstrated. A randomized trial, performed in China, which included almost 20,000 patients (mainly with chronic HBV infection), found a significant survival benefit from biannual surveillance (mortality decreased by 37%), although compliance was relatively low (58.2%).[7] It is unlikely that further randomized trials that compare surveillance versus no surveillance can be performed in the future due to obvious ethical considerations. However, some data indirectly suggest that surveillance is effective in patients with cirrhosis. In the most recent studies, HCC was detected at an early stage in up to 70% of patients submitted to regular surveillance.[8] Several recent cost-effectiveness studies have concluded that surveillance is a cost-effective procedure in high-risk patients.[9,10] Additionally, a recent retrospective study found that surveillance performed between 1998 and 2004 was more effective than during the period 1991-1997, and resulted in better survival, probably due to the increased performance of curative treatments.[11]

The modalities of surveillance in cirrhotic patients are still controversial. In 2000 international guidelines recommended performing periodic ultrasonography (US) as well as a serum alpha-fetoprotein (AFP) assay, even if doubts concerning usefulness of this latter biomarker were clearly expressed.[1,4,5] US is probably the most appropriate imaging procedure, as it is noninvasive and cheap, even though its sensitivity is considered relatively low.[8] When US use is not technically valid (often due to obesity), there is no consensus on the best substitution: i.e., computed tomography (CT) scan or magnetic resonance imaging (MRI).[12] Although a serum AFP assay is routinely used, this test is considered to have a low surveillance value due to the high rates of false-positive and -negative results.[5,13] The best period of periodicity for surveillance is also controversial, ranging from every 3 months to every 12 months. In 2000, international guidelines recommended surveillance performed every 6 months on an empirical basis.[4] A recent study (not available when the trial was designed) suggests that a 12-month interval between each examination results in lower survival and HCC detection than a 6-month period.[14]

The main objective of periodic surveillance in cirrhotic patients is to detect HCC at an early stage when it is possible to offer a curative treatment option.[15] It could be postulated that shortening the interval between each surveillance assessment could result in better detection of small HCC tumors, permit more curative treatments, and, consequently, improve survival. Accordingly, this multicenter randomized trial aimed to compare a 3-month periodicity of US versus a 6-month period, which is considered the benchmark interval.

Patients and Methods

The promoter of this trial was the Assistance Publique-Hôpitaux de Paris. The trial was funded by the French Ministry of Health (PHRC 1998 and 2003) and the French Ligue de Recherche contre le Cancer. The protocol obtained approval from the Ethics Committee (CCPPRB, Aulnay-sous-Bois, France). All patients gave written informed consent to participate in the trial. The trial was performed according to Consort recommendations[16] and registered on the ClinicalTrials.gov website (http://clinicaltrials.gov/ct2/show/NCT00190385).

Selection of Patients. Patients were recruited from clinical centers belonging to a cooperative group (Supporting Appendix), which included 43 specialist liver disease centers in France and Belgium. Preinclusion assessment included the usual clinical and biological parameters; a US Doppler examination was also undertaken to check inclusion and noninclusion criteria.

Address reprint requests to: Jean-Claude Trinchet, Service d'Hépato-gastroentérologie, Hôpital Jean Verdier, 93140 Bondy, France. E-mail: jean-claude.trinchet@jvr.aphp.fr; fax: 33-1-48-02-62-02.

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Additional Supporting Information may be found in the online version of this article.

Patients with all the following criteria were selected for inclusion in the trial: (1) age older than 18 years; (2) histologically proven cirrhosis, whatever the time of biopsy; (3) cirrhosis related to either excessive alcohol consumption (80 g per day in males and 60 g per day in females for at least 10 years), chronic infection with hepatitis C virus (HCV) (serum anti-HCV antibodies-positive) or hepatitis B virus (HBV) (serum hepatitis B surface antigen (HBsAg)-positive), or hereditary hemochromatosis (liver-iron overload and C282Y homozygosity); (4) absence of previous complications of cirrhosis (particularly ascites, gastrointestinal hemorrhage or HCC); (5) patients belonging to Child-Pugh class A or B and without a focal liver lesion at inclusion; and (6) written informed consent.

Patients with at least one of the following criteria were not included in the study: (1) patients belonging to Child-Pugh class C; (2) severe uncontrolled extrahepatic disease resulting in estimated life expectancy of less than 1 year; and (3) coinfection with human immunodeficiency virus (HIV), even if controlled by an antiviral treatment.

Design. As stated in the protocol (http://clinicaltrials.gov/ct2/show/NCT00190385), this was a multicenter, stratified (according to cirrhosis etiology and center), randomized clinical trial conducted in France and Belgium (43 sites), based on a two-by-two factorial design with balanced randomization, to compare two US periodicities (3 months versus 6 months) simultaneously, and to assess the value of the serum AFP assay (no assay versus assay every 6 months). After checking selection criteria and written consents, patients were randomized into one of four groups: US and a serum AFP assay every 6 months; US every 3 months and a serum AFP assay every 6 months; US every 6 months and no serum AFP assay; and US every 3 months and no serum AFP assay.

Randomization. Randomization was computer-generated, with allocation concealed using a centralized phone procedure to the data-management center (DBIM, Saint-Louis Hospital, Paris, France).

Randomization sequence used a permuted block design with fixed block sizes of four (with trialists unaware of the block size), and a 1:1 allocation ratio. Randomization was stratified by recruitment site and by the main etiology of the cirrhosis, which distinguished three strata: excessive alcohol consumption (more than 80 g/d in men and 60 g/d in women for at least 10 years; negative serum HBsAg and HCV-antibodies; no hemochromatosis); HCV chronic infection (negative serum HBsAg and positive HCV antibodies; no hemochromatosis) whatever the alcohol consumption; and other situations: HBV chronic infection (positive serum HBsAg) or hemochromatosis.

Follow-Up. Patients were seen by physicians at regular intervals, as established by randomization for US surveillance. The usual clinical and biological data were recorded at least once a year. Regular endoscopic surveillance was performed to detect esophageal varices and other portal hypertension-related lesions. In cases of esophageal varices, preventive therapy was recommended either by beta-blockers or endoscopic ligation, according to international recommendations.[17]

All events occurring during follow-up were recorded. Their management was performed according to international recommendations. In case of death the circumstances and likely cause(s) were recorded.

US Surveillance. Examination by Doppler US was performed every 6 months or 3 months according to randomization. For a given patient it was recommended to perform US in the same center by the same experienced operator. A standardized report was completed by each operator, mentioning the presence or not of focal liver lesions. In cases of focal lesions, echogenicity, number and diameter of nodules (classified as $\leq$10 mm, 11-20 mm, 21-30 mm, 31-50 mm, or $\geq$51 mm), and anatomic localization according to Couinaud were reported. Portal vasculature (main trunk and branches), hepatic veins, and vena cava were systematically examined.

HCC Diagnosis and Treatment. In cases of focal liver lesions a diagnostic procedure using contrast-enhanced imaging, a serum AFP assay, and/or a guided biopsy was performed according to the European Association for the Study of the Liver (EASL) guidelines, published in 2001.[4] HCC diagnosis was established in the following situations: (1) histological proof of HCC; and (2) when a focal lesion was $>$2 cm in diameter, assessed by early arterial hypervascularization, using two contrast-enhanced methods (CT-scan, MRI, arteriography), or when there was an association between serum AFP level of $>$400 ng/mL plus early arterial hypervascularization, assessed by one contrast-enhanced method. In case of an increase in serum AFP level without liver focal lesion at US, a CT scan was performed according to recommendations.[4] Subsequent modification of recommendations from the American Association for the Study of Liver Diseases (AASLD), published in 2005[1] and 2011,[5] were not taken into account in this trial.

When an HCC diagnosis was established treatment was determined using a multidisciplinary approach at each medical center, by the physicians in charge of the patient. It was recommended to perform curative

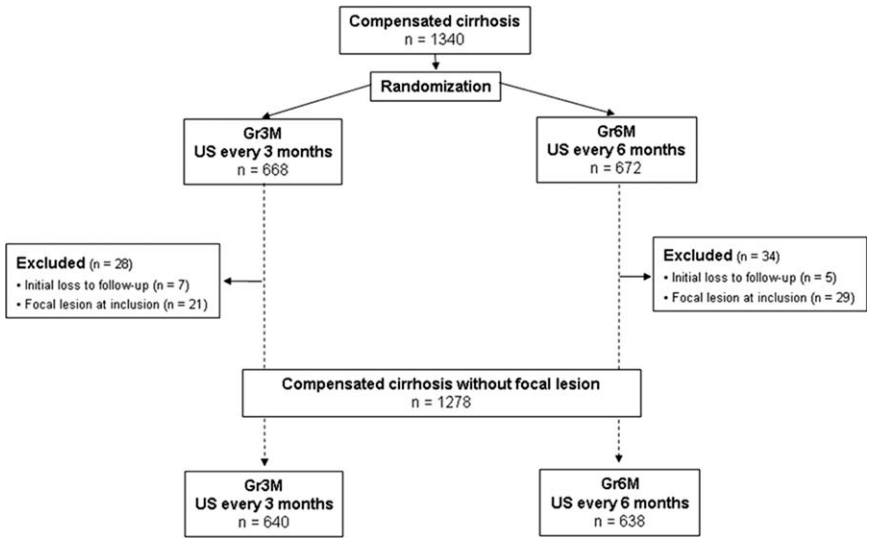

Fig. 1. Flow chart. Selection, randomization of patients, and analyses. US: ultrasonography.

treatment (percutaneous ablation, resection, or transplantation) whenever possible.

Statistical Analyses: Sample Size Computation. The main objective of the trial focused on comparing differences between the US groups using a two-step procedure. The first step was based on the expected prevalence of the primary endpoint (HCC $\leq$30 mm in diameter) being 50% in the control group. From this we calculated that we would need 158 primary endpoint events to give 95% power to detect a significant difference between randomized groups, which corresponds to a 25% increased prevalence of HCC (with a one-sided type 1 error of 5%). Based on a 5% expected yearly incidence of HCC,[18-20] within 3 years of follow-up, a sample size of at least 1,200 patients was computed to be needed. Inclusion was scheduled to continue into a second step if a significant benefit was found, on the basis of survival outcomes.

Statistical Methods. A modified intention-to-screen analysis was performed; that is, all patients were analyzed in the randomized groups, whether it applied or not, after excluding those with a focal hepatic lesion at inclusion. The date of the final analysis was set at 1 April 2008.

Comparison of the incidence of HCC tumors $\leq$30 mm in diameter in the randomized groups was based on Fisher's exact test. Cumulative-incidence curves were estimated using a competing-risk setting because of deaths that precluded the occurrence of focal lesions that included HCC. These were compared using Gray's test, whereas cause-specific Cox models, stratified according to randomization strata (cirrhosis etiology), allowed estimation of a hazard ratio (HR) with a 95% confidence interval (95% CI) as a measure of surveillance effect. Adjusted HRs were computed where the set of prognostic variables were first selected by a stepwise selection procedure in a multivariate model. Survival curves were estimated by the Kaplan-Meier method and then compared by the log-rank test.

Statistical analyses were performed using SAS 9.2 (Cary, NC) and R 2.10.1 (http://www.R-project.org) software. All tests were two-sided, with $P \leq 0.05$ denoting statistical significance.

Results

Inclusion Period. The flow chart of the trial is presented on Fig. 1. Inclusion of patients started in June 2000 in the 43 participating clinical centers (Supporting Appendix). The minimal number of patients to include in the trial (n = 1,200) was reached in May 2005, allowing us to perform comparison between rates of HCC $\leq$30 mm in diameter for each group. At the first analysis (see below), it was decided by the steering committee to stop further inclusions into the trial by March 2006. At that time, 1,340 patients were included.

Among the 1,340 randomized patients, 62 were subsequently excluded from analysis after revision of individual data due to either immediate loss to follow-up (n = 12) or to the presence of a focal liver lesion at inclusion (n = 50). The focal lesions corresponded to HCC (n = 8), intrahepatic cholangiocarcinoma (n = 1), hemangioma (n = 15), and regenerative or indeterminate nodules (n = 26). Consequently, the final analyses were performed on 1,278 patients (Fig. 1).

Table 1. Characteristics of Patients at Inclusion in the Trial According to Randomization

	US at 3 Months n = 640	US at 6 Months n = 638
Male gender	445 (69.5%)	438 (68.7%)
Age (years)	54 (47-61)	55 (48-64)
Etiology of cirrhosis		
Alcohol	252 (39.4%)	250 (39.0%)
HCV	286 (44.7%)	278 (43.6%)
HBV	82 (12.8%)	78 (12.2%)
Hemochromatosis	5 (0.8%)	15 (2.3%)
Other*	15 (2.3%)	17 (2.6%)
Body-mass index (kg/m^2)	25.9 (22.9-29.1)	26.0 (23.4-29.4)
Karnofsky index (%)	100 (95-100)	100 (90-100)
Hemoglobin (g/dL)	14.0 (12.5-15)	13.8 (12-15)
Leukocyte count ($10^3/mm^3$)	5.8 (4-7.7)	5.4 (4-7)
Platelet count ($10^3/mm^3$)	131.5 (93-179)	128 (89.5-165)
Creatinine (μm/L)	76 (65-86)	77 (68-88)
Bilirubin (μm/L)	15.0 (10-22)	15.3 (11-23)
AST (N<40 IU/L)	42 (29-68)	41 (29-72)
ALT (N<40 IU/L)	37 (23-69)	38 (24-70)
Alkaline phosphatase (N<110 IU/L)	102 (75-158)	109 (74-168)
Gamma-glutamyl-transpeptidase (N<45 IU/L)	83 (44-161)	80.5 (45-161.5)
Albumin (g/L)	41 (37-44)	40 (36-43)
Prothrombin activity (%)	81 (70-91)	79 (68-90)
Factor V (%)	80 (65-100)	82.5 (67-100)
Alpha-fetoprotein (ng/mL)	5 (3-8.3)	5 (3-8)

Data expressed as median (Q1–Q3) or N (%). US, ultrasonography. N, upper limit of normal range.
*Nonalcoholic steatohepatitis (n=15), primary biliary cirrhosis (n=2), autoimmune hepatitis (n=5), cryptogenetic cirrhosis (n=10).

Randomization. The 1,278 patients included in the final analyses were randomized into four groups: US plus an AFP assay every 6 months (n = 326), US every 3 months plus an AFP assay every 6 months (n = 328), US every 6 months but no AFP assay (n = 312), and US every 3 months but no AFP assay (n = 312). After data analyses, high rates of serum AFP assays were actually observed in the two latter groups (60.5% and 54.8%, respectively), which precluded reliable interpretation based on serum AFP assay randomization. Consequently, the steering committee decided to restrict the final analysis to US randomization only.

Accordingly, the final analysis considered only US randomization as follows: US every 3 months (n = 640, Gr3M) or US every 6 months (n = 638, Gr6M).

Baseline Characteristics of Patients. The main characteristics of patients at inclusion, according to US randomization, are reported in Table 1. Overall, patients were mainly males (69.1%), mean 55 years old, and belonged to Child-Pugh classes A, B, and C, at 87%, 12%, and 1%, respectively. The main causes of cirrhosis were excessive alcohol consumption, HCV infection, HBV infection, or hemochromatosis in 39.2%, 44.1%, 13.2%, and 1.6% of patients, respectively. Thirty-two (2.5%) patients had cirrhosis related to other etiologies, namely nonalcoholic steatohepatitis (n = 15), primary biliary cirrhosis (n = 2), autoimmune hepatitis (n = 5), and cryptogenetic cirrhosis (n = 10).

Follow-Up and Compliance with the Protocol. Mean follow-up was 47.1 months in Gr3M and 46.8 months in Gr6M (Table 2). Median time intervals between each US examination were in agreement with those scheduled for the randomization, 3 months for Gr3M and 6 months for Gr6M, with no significant time variations during the first 6 years of the trial in either group (data not shown). However, compliance was estimated as inadequate in 143 (11.9%) patients: 86 (14.6%) of Gr6M and 57 (9.4%) of Gr3M patients.

Focal Liver Lesions. Overall, a first focal lesion was observed in 358 patients (28%) during the trial: 192 in Gr3M and 166 in Gr6M patients (Table 2). The 5-year cumulated incidence was estimated as 34.1% (95% CI: 34.06-34.24). This was not significantly affected by randomization (35.5% in Gr3M compared to 32.8% in Gr6M; $P = 0.067$; Fig. 2). Similarly, the cumulative incidence of focal lesions $\leq$30 mm in diameter was not modified by 5-year estimates, at 30.1% in Gr3M versus 27.5% in Gr6M ($P = 0.06$; Fig. 2). An increased number of focal lesions $\leq$10 mm in diameter was observed in Gr3M compared to Gr6M (5-year cumulative incidence of 41% versus 28%, respectively; $P = 0.002$; Table 2, Fig. 2).

Table 3 reports the results of the prognostic analyses. Factors associated with outcome at the 5% level (alcoholic etiology of cirrhosis, age, body-mass index,

Table 2. Comparison of Outcomes According to Randomization

	US at 3 Months n = 640	US at 6 Months n = 638	*P*-value
Follow-up (months)	47 (29-65)	46 (30-66)	
Interval between US examinations (months)	3 (3-4)	6 (6-7)	
First focal lesion (number of patients)	192 (30%)	166 (26%)	0.067
Cumulative incidence			
24 months	20.4%	13.2%	
60 months	35.5%	32.8%	
Diameter of the first focal lesion (mm)	178/192	156/166	
≤10	73 (41%)	43 (28%)	
11-20	71 (40%)	78 (50%)	
21-30	23 (13%)	23 (15%)	
31-50	7 (4%)	7 (4%)	
≥51	4 (2%)	5 (3%)	
Final diagnosis of focal liver lesion	183/192	155/166	
HCC	53 (30%)	70 (45%)	
Regenerative nodule	16 (9%)	12 (8%)	
Hemangioma	15 (8%)	10 (6%)	
Cholangiocarcinoma	3 (2%)	0	
Metastasis	0	1 (1%)	
Indeterminate	96 (54%)	62 (40%)	
HCC	53 (27.6%)	70 (42.2%)	0.13
Cumulative incidence			
24 months	4.0%	2.7%	
60 months	10.0%	12.3%	
Liver decompensation	94 (14.7%)	98 (15.4%)	0.75
Transplantation	17 (2.7%)	13 (2.0%)	0.58
Death	72 (11.3%)	82 (12.1%)	0.38
Survival rate			
24 months	95.8%	93.5%	
60 months	84.9%	85.8%	
Cause of death			
Liver carcinoma	17 (23.6%)	12 (14.6%)	
Liver failure	24 (33.3%)	34 (41.5%)	
Extra-hepatic cancer	7 (9.7%)	7 (8.5%)	
Bacterial infection	5 (6.9%)	8 (9.7%)	
Other	19 (26.4%)	21 (25.6%)	

Data expressed as median (Q1–Q3) or number (%). US, ultrasonography.

platelet count, serum AST and ALT, and prothrombin activity) were introduced into a multivariate model. Only two variables were selected by the multivariate model, age and prothrombin activity. Adjusted HR of the focal lesion, stratified according to cirrhosis etiology, was estimated at 0.77 (95% CI: 0.62-0.96) in the Gr6M group compared to the Gr3M group ($P = 0.02$).

Overall, after the diagnostic procedures, most focal liver lesions detected during surveillance remained indeterminate (44.1%) or were considered regenerative (benign) nodules (8%) at the end of the trial (Table 2). A precise diagnosis was established in 152 patients (42.5%): HCC (n = 123), intrahepatic cholangiocarcinoma (n = 3), metastasis (n = 1), and hemangioma (n = 25) (Table 2). At the end of follow-up, only 19% of nodules ≤10 mm in diameter were confirmed as HCC, without a significant difference between the two groups (16 [22%] versus 6 [14%] for the Gr3M and Gr6M groups, respectively).

Hepatocellular Carcinoma. HCC was diagnosed in 123 patients (9.6%) during the trial: 53 in Gr3M and 70 in Gr6M (Table 2). The prevalence of HCC ≤30 mm in diameter was estimated at 79% (95% CI: 69-90%) in Gr3M and 70% in Gr6M (95% CI: 59-81%) ($P = 0.30$). The 5-year cumulative incidence of HCC was 11.9% (95% CI: 11.85-11.97), and was 10.0% in Gr3M versus 12.3% in Gr6M ($P = 0.13$) (Fig. 3). Similarly, there was no difference in the cumulative incidence of HCC ≤30 mm in diameter between the Gr3M and Gr6M groups (7.8% versus 9.1%, $P = 0.48$; Fig. 3). Additionally, no differences in the cumulative incidences of HCC ≤20 mm in diameter were observed between the two groups (Fig. 3).

The characteristics of HCC at diagnosis are reported in Table 4. Most tumors were uninodular (58.5%) and ≤30 mm in diameter (74%). In accordance with these results, portal obstruction and serum AFP levels >200 ng/mL at diagnosis were only observed in a small subset of patients (11.4% and 3.3%, respectively).

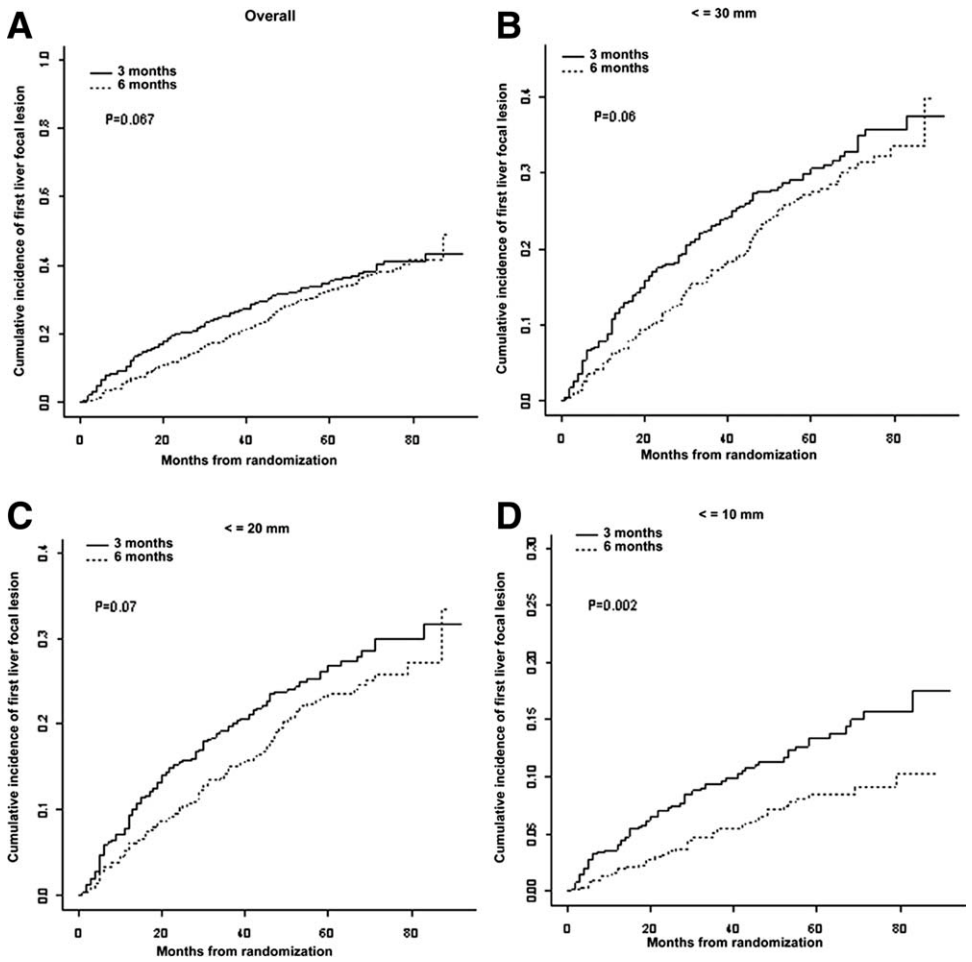

Fig. 2. Cumulative incidence of the first nodule according to randomization: (A) Overall ($P = 0.067$), (B) Nodule $\leq$30 mm in diameter ($P = 0.06$), (C) Nodule $\leq$20 mm in diameter ($P = 0.07$), (D) Nodule $\leq$10 mm in diameter ($P = 0.002$).

Overall, 74.8% of patients with HCC were within the Milan criteria, and curative treatments were performed in 61% (Table 4). Only five patients had HCC $\leq$10 mm in diameter at diagnosis (Table 4).

Predictive factors for the occurrence of HCC were the alcoholic and HCV etiologies of cirrhosis, age, platelet count, serum bilirubin, AST, ALT, alkaline phosphatase, gamma-glutamyl-transpeptidase, albumin, prothrombin activity, and serum AFP (Table 5). When considered jointly in a multivariate model, three variables remained associated with the outcome: age, platelet count, and serum bilirubin. Adjusted HR, stratified according to the etiology of cirrhosis, in the Gr6M versus Gr3M groups, was estimated at 1.18 (95% CI: 0.82-1.72; $P = 0.37$).

Survival. Overall, 154 patients (12%) died during the trial: 72 (11.3%) in the Gr3M group and 82 (12.1%) in the Gr6M group (Table 2). No evidence of difference in survival between the randomized groups was observed regarding 5-year estimated survival at 84.9% versus 85.8% for the Gr3M and Gr6M groups, respectively ($P = 0.38$; Fig. 4). The main causes of deaths were HCC or cholangiocarcinoma (18.8%), liver failure (37.6%), extrahepatic cancer (8.9%), and severe bacterial infection (8.2%).

Discussion

The main goal of our trial was to compare the effectiveness of US surveillance according to the time interval between two examinations: 3 months versus 6 months. A second goal was to assess the importance of serum AFP in this surveillance.[13] The latter part of this study was rapidly abandoned, as serum AFP assays were inadequately prescribed in more than half of the patients within the nonsurveillance group. Therefore, the steering committee considered such a high rate as an intolerable deviation to the protocol, and this precluded any reliable analysis.

Conversely, the compliance of patients toward US surveillance was generally adequate, as shown in Table 2, and the observed periodicities of US examinations

Table 3. Predictive Factors for the Occurrence of a First Focal Lesion

	Univariate Analysis			Multivariate Analysis		
	Absence of Focal Lesion n = 920	First Focal Llesion n = 358	*P*-value	Hazard Ratio	95% Confidence Interval	*P*-value
Etiology of cirrhosis						
Alcohol	380 (41.3%)	122 (34.1%)	0.02			
HCV	396 (43.0%)	168 (46.9%)	0.21			
HBV	108 (11.7%)	52 (14.5%)	0.19			
Male gender	630 (68.5%)	253 (70.7%)	0.30			
Age (years)	54 (46-62)	56 (49-64)	0.0005	1.016	1.005-1.027	0.004
Body mass index (kg/m^2)	25.8 (22.8-29.1)	26.9 (24-29.7)	0.006			
Karnofsky index (%)	100 (90-100)	100 (90-100)	0.82			
Platelet count (n/mm^3)	135 (94-178)	117 (83-164)	0.0002			
Creatinine (μmol/L)	76 (66-87)	77 (67-88)	0.97			
Bilirubin (μmol/L)	15 (10-22)	16 (11-23)	0.06			
AST (N <40 IU/L)	41 (29-67)	47 (31-80)	0.008			
ALT (N <40 IU/L)	36 (23-66)	45 (25-81)	0.003			
Alkaline phosphatase (N <110 IU/L)	106 (74-167.5)	104 (77-171)	0.77			
Gamma-glutamytrans- peptidase (N <45 IU/L)	81 (44-160)	84.6 (47-175)	0.33			
Albumin (g/L)	40 (37-44)	40 (36-43)	0.09			
Prothrombin activity (%)	80 (69-92)	78 (69-8)	0.04	0.985	0.978-0.993	<0.0001
Factor V (%)	82 (66-100)	78 (65-98)	0.47			
Alpha-fetoprotein (ng/mL)	5 (3-8)	6 (3.7-8.7)	0.06			

Data expressed as median (Q1–Q3) or N (%).

were close to those scheduled. This allowed us to conclude that, in our population of cirrhotic patients, US surveillance performed every 3 months did not improve either the rate of detection of small HCCs eligible for curative treatment or the overall survival rates compared to patients undergoing US surveillance every 6 months. When the trial was designed in 1998-2000, HCC below 30 mm in diameter was widely considered an adequate limit for small HCC and therefore was chosen as the main criterion for the trial. It is currently recognized that 20 mm in diameter is a more reliable limit for small HCC,[5] but again the incidence of such nodules was not increased in the 3-month group (Fig. 3).

A further result from our trial was that US surveillance every 3 months increased the cumulative incidence of detected focal lesions, although not significantly, thereby increasing the cost of recall procedures. At 2 years, focal lesions were detected in more than 20% of the 3-month group versus ≈13% of the 6-month group; most lesions proved nonmalignant during the follow-up. Moreover, this increase was mainly related to a significantly higher number of lesions ≤10 mm in diameter (Table 2, Fig. 2). Such nodules represented 41% of focal lesions in the 3-month group versus 28% in the 6-month group. Interestingly, the number of detected nodules sized ≤20 mm in diameter was similar between the two groups: 81% in the 3-month group versus 78% in the 6-month group (Table 2). This suggests that performing US at shorter intervals than 6 months allowed us to only detect a higher rate of very small nodules (≤10 mm in diameter), for which recall policies according to current guidelines usually fail to achieve a definite diagnosis and are considered not indicated.[5] This might be expected owing to the lead-time bias that incurs in the shorter interval.

Most of the detected focal lesions were followed according to the EASL recommendations[4] but, even when malignant, their earlier detection did not lead to earlier diagnosis or treatment. It is currently admitted that, for very small nodules, the sensitivity and specificity of elevated serum AFP is low,[5,13] that contrast-enhanced imaging only demonstrates a typical HCC pattern in a minority of cases,[21,22] and that a US-guided biopsy provides a high rate of false-negative results.[1,23] Therefore, in many cases the putative lesions are kept under imaging surveillance for several months, which precludes the potential benefit of early detection. It is noteworthy that, in our trial, a very low rate of HCCs were diagnosed that were ≤10 mm in diameter (4%, Table 4) in contrast to the high number of nodules detected below this size (Table 2). Interestingly, at the end of the trial, and despite a long follow-up, about 45% of the detected nodules either disappeared or were considered to be of indeterminate nature (Table 2).

Our conclusions apply only to those conditions in which the US surveillance was tested in our study:

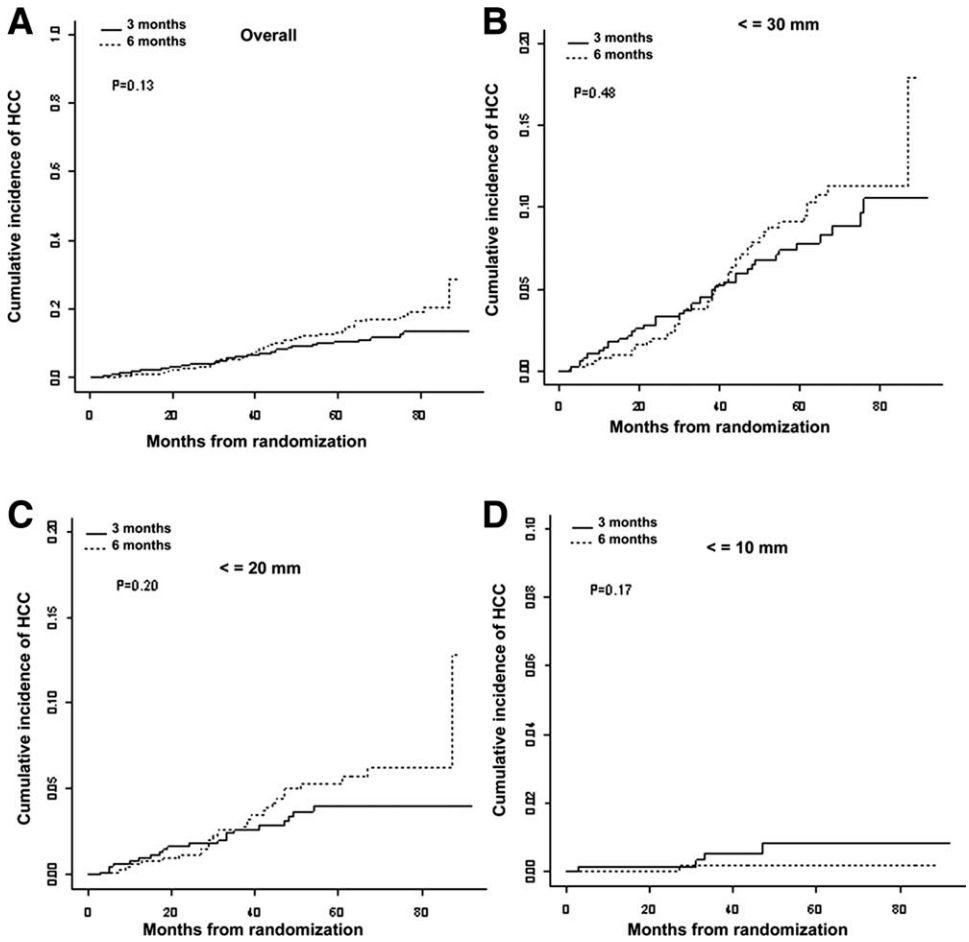

Fig. 3. Cumulative incidence of HCC according to randomization: (A) Overall ($P = 0.13$), (B) Largest HCC nodule $\leq$30 mm in diameter ($P = 0.48$), (C) Largest HCC nodule $\leq$20 mm in diameter ($P = 0.20$), (D) Largest HCC nodule $\leq$10 mm in diameter ($P = 0.17$).

inclusion of French and Belgian patients with cirrhosis caused mostly by HCV or alcohol, and application of the guidelines of the first Barcelona conference endorsed by EASL.[4] Although other international guidelines have been proposed that allow noninvasive diagnosis of HCC by radiological means, for nodules between 10 and 20 mm in diameter[1,5] it is likely that application of these new guidelines would not have modified the results of our trial, as only a minority of nodules between 10 and 20 mm diameter exhibited a typical vascular pattern using two different imaging techniques.[21] Conversely, the cause of the underlying liver disease could have influenced the results. The data from our double multivariate analysis of predictive factors (Tables 3, 5) show that more focal lesions were discovered in patients with alcoholic cirrhosis in contrast to a higher rate of HCC in patients with HCV cirrhosis. This suggests that "false lesions" could be more common in patients with alcoholic liver disease. Our data do not allow the likely explanation that irregular steatosis sparing of some cirrhotic nodules can be seen by contrast imaging with hypoechoic.[24] It is likely that the significance of a small nodule (particularly those $\leq$10 mm in diameter) is not similar according to the cause of cirrhosis. This allows us to speculate that, in countries where HCV etiology of cirrhosis is predominant, such as Japan, results could have been different with a lower rate of "false positive" lesions.

The fact that focal lesions that were not eventually characterized as HCC were more numerous in the 3-month group, although not significantly, is clearly a disadvantage, as it enhances the rate of recall procedures, which leads to increased costs, increased stress for patients, and a lassitude that could lead to demotivation for surveillance.

Our study also shows the limitations of the current surveillance policy. At diagnosis, a significant proportion of patients had an infiltrative tumor (10%), more than three nodules (9%), or vascular involvement (11%), and less than 75% had a well-limited nodule $\leq$30 mm in diameter. In addition, about 25% had a

Table 4. Characteristics of Hepatocellular Carcinoma (HCC) According to Randomization

	US at 3 Months n = 640	US at 6 Months n = 638	*P*-value
Number of patients with HCC	53	70	0.11
Type of tumor			0.28
Uninodular	31 (58.5%)	41 (58.6%)	
2 or 3 nodules	15 (28.3%)	12 (17.1%)	
>3 nodules	4 (7.5%)	7 (10.0%)	
Infiltrative	3 (5.7%)	10 (14.3%)	
Diameter of the largest nodule (mm)			0.13
≤10	4 (7.5%)	1 (1.4%)	
11-20	16 (30.2%)	28 (40.0%)	
21-30	22 (41.5%)	20 (28.6%)	
31-50	6 (11.3%)	7 (10.0%)	
≥51	5 (9.4%)	14 (20.0%)	
Portal obstruction (even partial)	3 (5.6%)	11 (15.7%)	0.09
Milan criteria			0.40
Within criteria	42 (79.2%)	50 (71.4%)	
One nodule ≤50 mm	29 (54.7%)	40 (57.1%)	
2 or 3 nodules ≤30 mm	13 (24.5%)	10 (14.3%)	
Beyond criteria	11 (20.8%)	20 (28.6%)	
Alpha-fetoprotein			
Median (Q1–Q3) (ng/mL)	9 (4.5-21)	7 (5-59)	0.44
Mean ± SD (ng/mL)	23.2 ± 37.3	1403 ± 7324	
Number of patients ≥200 ng/mL	0	4 (6%)	0.13
Treatment			0.10
Transplantation	10 (18.9%)	3 (4.3%)	
Resection	3 (5.7%)	8 (9.7%)	
Percutaneous ablation	20 (37.7%)	31 (44.3%)	
Arterial chemoembolization	9 (17.0%)	9 (12.3%)	
Supportive care	5 (9.4%)	12 (17.1%)	
Missing data	6 (11.3%)	6 (8.6%)	

Data expressed as N (%). US, ultrasonography.

Table 5. Predictive Factors for the Occurrence of Hepatocellular Carcinoma

	Univariate Analysis			Multivariate Analysis		
	No HCC n = 1155	HCC n = 123	*P*-value	Hazard Ratio	95% Confidence Interval	*P*-value
Etiology of cirrhosis						
Alcohol	468 (40.5%)	34 (27.6%)	0.006			
HCV	499 (43.2%)	65 (52.8%)	0.045			
HBV	141 (12.2%)	19 (15.4%)	0.32			
Male gender	785 (68.7%)	89 (72.4%)	0.29			
Age (years)	54 (47-62)	60 (53-67)	<0.0001	1.048	1.028-1.068	<0.0001
Body mass index (kg/m^2)	26 (23-29.4)	26.7 (24.4-29.4)	0.08			
Karnofsky index (%)	100 (90-100)	100 (90-100)	0.35			
Platelet count (n/mm^3)	132 (93-176)	107 (81.5-155.5)	0.0003	0.995	0.992-0.998	0.0044
Creatinine (μmol/L)	76 (65.5-87)	78 (69-87)	0.69			
Bilirubin (μmol/L)	15 (10.5-22)	18 (12-28)	0.003	1.031	1.021-1.040	<0.0001
AST (N <40 UI/L)	40 (29-67)	58 (37-92.5)	<0.0001			
ALT (N <40 UI/L)	36 (23-67)	55 (28.5-89.5)	0.0002			
Alkaline phosphatase (N <110 UI/L)	104 (74-166)	121 (88-174)	0.04			
Gamma-glutamyl-transpeptidase (N <45 UI/L)	81 (44-159)	93 (52-189)	0.003			
Albumin (g/L)	40 (37-44)	39 (35-41)	<0.0001			
Prothrombin activity (%)	80 (70-91)	76 (65-86)	0.003			
Factor V (%)	81 (67-100)	78 (62-100)	0.58			
Alpha-fetoprotein (ng/mL)	5 (3-8)	7 (4-10)	0.004			
Portal hypertension*	559 (48.6%)	70 (57.9%)	0.06			

Data expressed as median (Q1–Q3) or N (%).

*Esophageal and/or gastric varices.

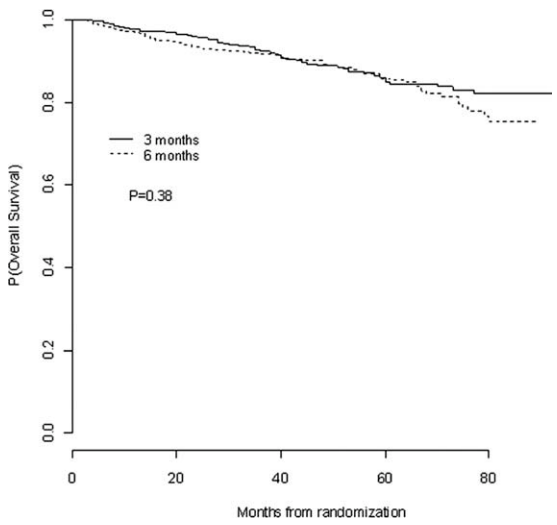

Fig. 4. Overall survival according to randomization ($P = 0.38$).

tumor burden beyond the Milan criteria. This emphasizes the high prevalence of multicentric hepatocarcinogenesis, but also the need for improving diagnostic procedures and surveillance methods. Moreover, knowing the main predictive factors for HCC in patients with cirrhosis, such as age, gender, body-mass index, platelet count, and basal serum AFP level, as well as the etiology of cirrhosis,[25] it is tempting to interpret the significance of a newly seen echographic nodule according to these easily recordable criteria. Therefore, we need to refine the current probabilistic approach, which, up to now, has relied mainly on radiological means and remains poorly sensitive to small nodules.

In conclusion, US surveillance performed every 3 months in patients with cirrhosis, mainly caused by HCV or alcohol abuse, fails to improve the detection rate of HCCs $\leq$30 mm in diameter that are eligible for curative treatment, although it detects more focal lesions than US performed every 6 months. This negative result is probably linked to the limitations of the recommended diagnostic procedures for small focal lesions in current practice.

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