Surveillance for hepatocellular carcinoma : compliance and results according to the aetiology of cirrhosis in a cohort of 141 patients

J. Henrion[1], E. Libon[2], S. De Maeght[1], M. Schapira[1], J.M. Ghilain[1], J.M. Maisin[1], F.R. Heller[1]

(1) Département de Médecine Interne, Service de Gastroentérologie ; (2) Département de Radiologie.

Abstract

Surveillance for early detection of hepatocarcinoma (HCC) in patients with cirrhosis is widely accepted. In a cohort of 141 patients with cirrhosis collected during the year 1995, we conducted a surveillance program by performing liver ultrasonography and blood alpha-foetoprotein measurement every 6 months. The median follow-up was 34 months. This study addressed to two questions : the compliance to the surveillance schedule according to the aetiology of cirrhosis and the results in terms of emergence of HCC and outcome.

Aetiology of cirrhosis was alcohol-induced in 86 (61%), HCV-related in 30 (21%) and from other origins in 25 (18%). Compliance to the program schedule was good in patients with HCV-related cirrhosis (29/30 - 97%) and patients with cirrhosis of «other origins» (20/25 - 80%) but was poor in patients with alcoholic cirrhosis (45/86 - 52%). The lack of compliance was significantly linked to the failure to achieve alcohol abstinence.

During follow-up, 6 HCC lesions were observed in 6 male patients with median age of 68 years. All 6 HCC were single nodule, less than 4 cm and accessible to percutaneous acetic acid injection. Nevertheless, the outcome was disappointing, four patients dying 3-15 months later (median : 8 months), two of them with extensive HCC. One of the two patients still alive developed extensive HCC, 36 months after percutaneous acetic acid injection. (Acta gastroenterol. belg., **2000**, 63, **5-9**).

Introduction

Surveillance for early detection of hepatocellular carcinoma (HCC) in patients with liver cirrhosis has become widely accepted practice by hepatologists. The rationale for HCC surveillance has been recently reviewed (1). We previously reported in the Acta the change in our attitude according to new therapeutic options in this field (2). Since, several studies have demonstrated the efficacy of regular screening by alpha-foetoprotein (α-FP) dosage and liver ultrasonography (US) for the early detection of small and asymptomatic HCC. However some important questions remain controversial. First, the benefits for the patients in terms of survival are a matter of debate (3). Moreover, to our knowledge, the compliance to the surveillance strategy, particularly according to the aetiology of cirrhosis, has not been evaluated. Several published studies do not even mention their drop-outs (46). A possible explanation is that many of these studies come from Japan or European countries with a high rate of hepatitis C virus (HCV) infection and with a low prevalence of alcoholic cirrhosis (4,5,7,8). In our country, where alcohol abuse remains the main cause of cirrhosis, it can be suspected that compliance and results will be quite different. The aim of this study was to assess the compliance to the surveillance schedule and the results according to the aetiology of cirrhosis.

Patients and methods

Patients

During the year 1995, all patients with cirrhosis free of HCC (n = 141), seen at the outpatient clinic of one of us (J.H.) were proposed to enter a surveillance program of HCC detection. They received full information about the annual risk of HCC emergence on cirrhosis, the possibility to detect HCC at an early asymptomatic stage, and the possibility to destroy small HCC nodules by percutaneous acetic acid injection (PAI) when surgical resection appears too risky. Diagnosis of cirrhosis was confirmed by liver histology in 109 patients and was evident on clinical, radiological and endoscopic basis in 32. Aetiologies of cirrhosis were divided in 3 groups, alcohol (alc), hepatitis C virus (HCV), and others according to historical, clinical, biochemical and histological data.

Methods

The surveillance strategy consisted in blood α-FP determination and liver US performed at 6-month-interval. US was almost exclusively performed by the same experienced radiologist (E.L.). If blood α-FP was between 20-200 ng/ml or if a doubtful lesion less than 15 mm was observed at US, the surveillance strategy was reinforced and scheduled every 3 months according to the increased risk of emergence of HCC in these patients (6,7,9).

Pertinent clinical, laboratory and imaging data were prospectively collected. Information about patients lost for follow up was sought by consulting their individual hospital chart and contacting their general practitioner by phone.

When HCC was highly suspected at US, additional diagnosis procedures were performed such as CT-scan and magnetic resonance. Histological confirmation by percutaneous biopsy was not attempted when the lesion

Corresponding author : J. Henrion, AD : Service de Gastroentérologie, Hôpital de Jolimont, B-7100 Haine-Saint-Paul, Belgium.

appeared highly suspect of HCC after the imaging work-up for the following reasons : 1/ the additional burden for already very medicalized patients ; 2/ the difficulty to differentiate benign regenerative macronodules from well differentiated HCC on histology ; 3/ the high probability that suspect nodules, not observed on prior US examinations, were HCC or regenerative macronodules with potential risk of malignant degeneration ; 4/ the good tolerance and low rate of dangerous side effects of PAI allowing treatment without complete assurance of malignancy.

The compliance to the surveillance program was rated as follows : *failure* : 1/ lack of any follow-up ; 2/ interrupted surveillance after a period of compliance. *Success* : 3/ irregular but sustained surveillance ; 4/ regular surveillance.

When HCC was detected, the patient was informed about therapeutic options. Surgical resection was considered in first intention, but PAI was recommended if surgery was estimated cliffficult or risky to perform. Acetic acid at 50% dilution was used according to Ohnishi *et al.* (10). Three sessions were scheduled at 2-week-interval during a brief hospitalization. The destruction of the lesion was controlled by Doppler-US and by CT-scan with contrast injection. Additional injections were performed if the destruction seemed incomplete.

The compliance to the surveillance program and the results were checked on July 1998 after a median follow-up of 34 months. The statistical differences between the 3 groups of cirrhosis (Alc, HCV, others) were assessed by the Chi-square and the Student's t tests.

Results

Demographic findings. One hundred and fifty four patients with cirrhosis were seen at the outpatient liver clinic during the year 1995. Among them, 13 had HCC (Alc 4, HCV 7, others 2) and were not included in the surveillance program. The cause of cirrhosis in the 141 included patients was alcohol abuse in 61% (n = 86, among them, 4 positive for HCV antibodies and 2 for HBS Ag), HCV infection in 21% (n = 30, among them 1 with past alcoholism and 1 positive for HBs Ag) and from other origins in 18% (n = 25, among them 9 HBV-related, 4 genetic haemochromatosis, 3 primary biliary cirrhosis, 3 autoimmune hepatitis, 4 drug-induced cirrhosis, 2 cryptogenic). The demographic findings at inclusion and the mortality rate of these 141 patients on July 1st 1998 are reported in Table 1. Alcoholic patients were younger, more often male, had poorer liver function and higher rate of mortality (28%). These data were significantly different by comparison with the 2 other groups. Patients with HCV-related cirrhosis had significantly higher blood level of α-FP at inclusion. Information about survival was collected on all patients except 1 alcoholic patient who had moved.

Compliance to the surveillance program. Compliance to the surveillance program is reported in Table 2. Compliance was appropriate (rate 3+4) in 97% and 80% of patients with cirrhosis due to HCV infection or other causes, respectively. Even, for the only patient with HCV-related cirrhosis lost to follow-up at the outpatient liver clinic, the survey was regularly performed by the general practitioner. On the opposite,

Table 1. — **Demographic findings according to the aetiology of cirrhosis (N = 141)**

	Alcohol n = 86	HCV n = 30	Others n = 25
Median age (Range)	50 *, ** (20 - 84)	64 (45 - 77)	59 (18 - 75)
Sex ratio (M / F)	61 / 25 *, **	15 / 15	13 / 12
Mean alpha-FP (ng/ml) (± SD)	4.7 (± 2.9) *	17.4 (± 34)	4.6 (± 2.8)
Child Pugh : A / B / C	51 / 24 / 11 *, **	27 / 3 / 0	20 / 5 / 0
Child Pugh : mean value	6.9 *, **	5.3	5.7
Mortality rate on 1 /7/98	24 (28%) *, ** n = 85	4 (13%)	2 (8%)

* : difference significant between alcohol and HCV ; ** : difference significant between alcohol and others.

Table 2. — **Compliance to the surveillance schedule according to the aetiology of cirrhosis**

	Quality of surveillance					
	Failure			**Success**		
	1	2	Total (%)	3	4	Total (%)
Alcohol (n = 86)	20	21	41 (48%)	11	34	45 (52%)
HCV (n = 30)	1	0	1 (3%)	5	24	29 (97%)
Others (n = 25)	1	4	5 (20%)	4	16	20 (80%)
	T O T A L		**47 (33%)**			**94 (66%)**

only 52% of alcoholic patients were compliant to the surveillance program. As expected, ongoing alcohol abuse was significantly related to failure of compliance : alcohol abstinence was achieved in 28% (11/39, lack of information for 2 patients) in non-compliant patients compared to 60% (27/45) in compliant patients ($p < 0.05$).

Main events during follow-up. Median follow-up for the 94 patients compliant to the surveillance program was 34 months (range 3-42). Main events registered during this period are reported in Figure 1. Twelve patients (Alc 9, HCV 1, others 2) died free of HCC and without undergoing orthotopic liver transplantation (OLT) from liver failure (n = 6), extrahepatic cancer (n = 3) or sepsis (n = 3). Three (Alc 2, HCV 1) underwent OLT, two of them dying 16 and 19 months later from severe recurrence of HCV infection in one case and extrahepatic cancer in another one. Primary hepatocarcinoma emerged in 6 patients (Alc 3, HCV 3) in a median follow up of 17 months (range 3-33), giving an annual incidence of 2.4%. On July 1st, 1998, 73 patients with cirrhosis but free of HCC remained on the surveillance program.

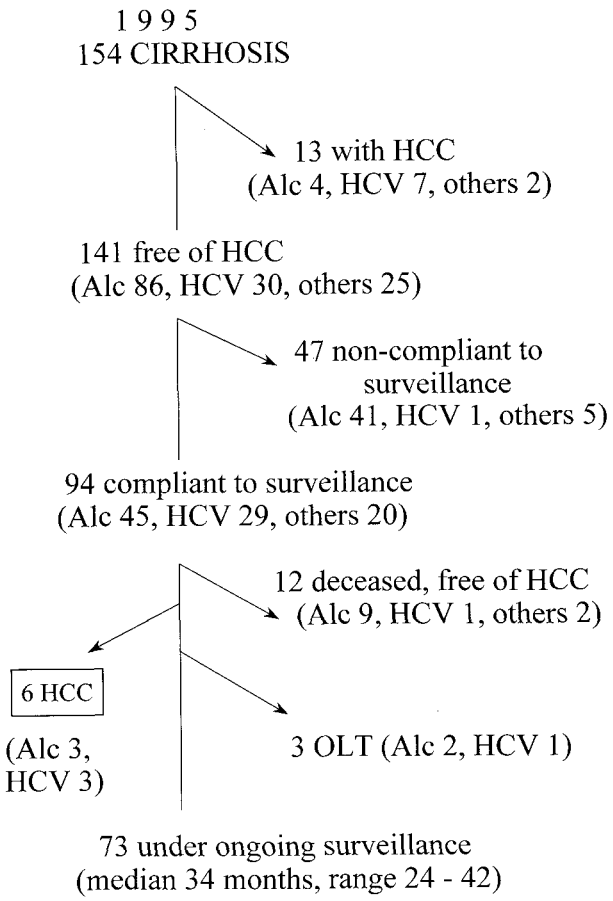

Fig. 1. — Main Hepatic events during the 34-month-follow-up of 141 patients with cirrhosis.

HCC features and outcome. The main features of patients with emergence of HCC are reported in Table 3. All 6 patients were men with a median age of 68 years (range 50-80). Alcohol abuse was the cause of cirrhosis in 3 (one of them positive for HCV antibodies) and HCV infection in 3 others. At the time of HCC diagnosis, the Child-Pugh score was A in 4 patients and B in 2, but 4 of these patients had been earlier in stage C (Table 3). The 3 patients with alcohol-related cirrhosis were abstinent at the time of HCC diagnosis and the 3 patients with HCV related cirrhosis had been previously treated by Interferon, one of them (case 1) with a sustained biochemical response. In 3 cases (cases 2, 3, 4), HCC was revealed only by liver US, in 1 case (case 5) concomitantly by liver US and blood α-FP determination and in 2 cases (cases 1, 6) was first suggested by elevation of α-FP. In case 1, when α-FP was found at 310 ng/ml, liver US was negative, but a lesion was revealed by CT scan. In case 6, when α-FP was at 945 ng/ml, liver US performed in another center was reported as negative, but the same imaging technique revealed a 25-mm size lesion when performed by an experienced operator (EL). In all cases, the HCC lesion was a single nodule less than 4 cm, without apparent vascular invasion. Okuda score was : I in 2 cases, II in 2 cases and III in 2 cases (Table 3). All patients were treated by PAI. Surgical resection was considered as too risky because of poor general condition in 4 cases and poor liver function in 2. Outcome was disappointing. Four patients died after 3-15 months (median : 8 months) from extensive HCC in 2 cases, liver failure in one case and sudden unexplained death in one case. Two patients were alive on July 1st, 1998. HCC seemed to be under control in one case at 6 months but was extensive and metastatic at 36 months in the other.

Discussion

In Belgium, alcohol remains the main cause of cirrhosis. This contrasts with Japan or Italy where numerous studies on surveillance for HCC come from. In these latter countries, cirrhosis is mainly of viral origin with HCV playing the major role (4,7,8), and the prevalence of alcoholic cirrhosis is low, averaging 5-10% (4,5,7,8) which probably explains why the compliance seems not to be a concern. In the present study, the surveillance strategy was indeed fully accepted by patients with HCV-related cirrhosis (97%) but was poorly followed by patients with alcoholic cirrhosis (52%), particularly when abstinence from alcohol was not achieved. We are aware of only one study addressing a similar cohort of cirrhosis with a similar surveillance strategy (11). In this French cohort of 118 patients, alcohol abuse was the cause of cirrhosis in 69%. The drop-out rate appeared very low (3.5%) during a median 36-month period of follow-up, but patients were included at the condition that the follow-up appeared feasible. Thus, only 64% of the patients with cirrhosis were judged suitable (11).

Compliance to the surveillance program could not represent the only factor explaining the different results

Table 3. — **Main characteristics of the six patients with hepatocarcinoma emergence**

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	Male	Male	Male	Male	Male	Male
Age (years)	79	62	72	50	80	65
Aetiology of cirrhosis	HCV	HCV	HCV	Alcohol	Alcohol	Alcohol (+ HCV)
Year of cirrhosis diagnosis	1995	1987	1995	1994	1990	1985
Child-Pugh stage (points)						
– at cirrhosis diagnosis	C(11)	A(5)	A(5)	C(12)	C(10)	C(12)
– at HCC diagnosis	B(9)	A(6)	A(5)	A(5)	A(6)	B(8)
α-FP level (ng/ml)						
– start of surveillance	5.1	38.5	17.8	6.2	2.8	17.2
– most elevated value before HCC diagnosis	18.1	48.1	17.8	8.7	18.9	17.2
– at HCC diagnosis	310	40.9	42.3	6.4	153	945
HCC size at diagnosis (mm)	35	20	25	20	35	25
Okuda score (points)	III (3)	II (1)	I (0)	I (0)	II (1)	III (3)
Outcome	Death at 3M Liver failure	Death at 15M Extensive HCC	Alive at 36M Extensive HCC	Alive at 6M No extension	Death at 3M Sudden death	Death at 13M Extensive HCC

between patients with alcohol or HCV-related cirrhosis. Indeed, emergence of HCC seems to be more frequent when cirrhosis is related to HCV infection. In this study, from the initial cohort of 154 patients, alcohol abuse was the cause of cirrhosis in 61% of the 141 patients free of HCC but in only 30% of the 13 patients when HCC was present on the first screening. Moreover, the annual incidence of HCC was 3.9% in the 29 compliant patients with HCV infection and 2.5% (not significant) in the 45 compliant patients with alcoholic cirrhosis. Large studies from Japan (4,12) and two recent surveys from France (13,14) have shown that the yearly incidence of HCC could reach 5% in patients with HCV-related cirrhosis. Finally, several recent studies have clearly shown that the risk of HCC was highly linked to HCV infection even in countries where alcohol remained the main cause of cirrhosis (15 - 17). These results do not necessarily indicate that patients with HCV-related cirrhosis are more prone to develop HCC, as patients with alcoholic cirrhosis are younger, have poorer liver function and bear a greater risk to die before developing HCC.

As far as these preliminary results authorize any conclusion, the surveillance program was well efficient from an oncologic point of view. Indeed, all lesions were discovered at the early stage of a single nodule, less than 4 cm wide, without apparent vascular invasion, and all seemed curable by PAI. This contrasts with the results of the above quoted study (11) which addressed to a similar cirrhotic population with the same surveillance design. In this French study, the surveillance program was disappointing in terms of early HCC recognition. Fourteen lesions were discovered (annual incidence : 5.4%) but only 6 were solitary nodules less than 4 cm. The only explanation for this discrepancy might rely on the experience of the US operator. It seems us pivotal that HCC detection by US was performed by the same experienced US operator.

Nevertheless, even if the ability to discover small lesions was encouraging, the results were disappointing in terms of benefits for the patients in this study. Four died after a short median follow-up of 8 months after the first PAI procedure. It must be noted that none of these 6 patients could have been safely proposed to surgical resection.

In conclusion, even if these preliminary results have to be interpreted cautiously, they indicate that surveillance for HCC is a complex process that could be of low benefit for patients in countries where alcohol remains the main cause of cirrhosis. The failure is not only related to the low compliance from patients with alcoholic cirrhosis but also depends on the poor general condition of cirrhotic patients who develop HCC and on the lack of a very effective treatment when a HCC nodule is discovered. Surgical resection and percutaneous ethanol or acetic acid injection have proven their ability to completely destroy HCC nodules less than 5 cm, but long-term survival rates are disappointing because of liver failure and high rate of recurrence more often in another liver segment due to multicentric carcinogenesis (18-20). Moreover, only a small percentage of patients with HCC on cirrhosis are suitable for surgery (5,7,11). Liver transplantation gives the best results for small HCC on cirrhosis, but its feasibility is limited by organ shortage and long delay before transplantation (21). To our opinion, surveillance for HCC should be restricted at the present time to cirrhotic patients with a good life expectancy according to liver function and associated medical conditions and, in case of alcoholic cirrhosis, to patients with a reasonable chance to achieve abstinence.

Addendum : Since this study was submitted, two more patients of this cohort developed HCC. In both, the lesion was a solitary nodule less than 3 cm. One patient was treated by surgical resection and the other by PAI.

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