Screening for hepatocellular carcinoma in a cohort with cirrhosis mainly of alcoholic origin

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SUMMARY

Objectives — To assess the feasibility and efficiency of the screening for hepatocarcinoma in a cohort of cirrhoses mainly of alcoholic origin.

Patients and methods — 293 patients with cirrhosis, among them 186 (63.5%) from alcoholic origin, were included in a surveillance programme for hepatocarcinoma by carrying out liver ultrasonography and α-fetoprotein dosage every 6 months. Results were analyzed with a mean follow-up of 60 months. Seventeen hepatocarcinoma discovered through the surveillance programme (“screened HCC”) were compared with 40 hepatocarcinoma discovered outside the surveillance programme during the same period (“incidental HCC”).

Results — The alcoholic origin of the cirrhosis was a predictive factor of poor compliance to the surveillance programme. Among the 186 patients with alcoholic cirrhosis, 129 (69%) were lost during the surveillance programme due to lack of compliance (97 cases) or death (32 cases). By comparison, among the 65 patients with hepatitis C-related cirrhosis, 18 were lost by lack of compliance (11 cases) or death (7 cases) (P < 0.001). Moreover, sustained or relapsing alcohol abuse after inclusion in the surveillance programme were also related to the quality of the compliance. Seventeen hepatocarcinoma were discovered through the surveillance giving an annual incidence of 2% for the emergence of hepatocarcinoma. The comparison between screened (n = 17) and incidental (n = 40) hepatocarcinoma showed that screened HCC were more often asymptomatic (P < 0.01), were more often a solitary nodule less than 5 cm (P < 0.001) and underwent more often curative treatment (P = 0.02). However, the survival between screened and incidental hepatocarcinoma was not different.

Conclusions — Screening for hepatocarcinoma in patients with alcoholic cirrhosis is a difficult task due to poor compliance and early death. According to our results, a surveillance every 6 months is sufficient to detect early lesions accessible to curative treatment by surgical resection or transcutaneous ablation.

RÉSUMÉ

Dépistage du carcinome hépatocellulaire dans une cohorte de malades porteurs d’une cirrhose d’origine principalement alcoolique

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Objectifs — Évaluer la faisabilité et l’efficacité du dépistage du carcinome hépatocellulaire dans une population de malades porteurs d’une cirrhose d’origine principalement alcoolique.

Malades et méthodes — 292 malades cirrhosiques dont 186 (63.5 %) d’origine alcoolique ont été inclus dans un programme de surveillance comportant la réalisation d’une échographie du foie et d’un dosage de l’α-feto-protéine tous les 6 mois. Les résultats ont été analysés après un suivi moyen de 60 mois. Les 17 carcinomes hépatocellulaires dépistés grâce au programme de surveillance (« carcinomes hépatocellulaires dépistés ») ont été comparés avec 40 carcinomes hépatocellulaires découverts de manière occasionnelle durant la même période (« carcinomes hépatocellulaires occasionnels »).

Résultats — L’étiologie alcoolique de la cirrhose s’est révélée être un facteur prédictif de non observance au programme de surveillance. Parmi les 186 malades alcooliques, 129 (69 %) ont quitté le programme de surveillance soit par manque d’observance (97 cas), soit par décès (32 cas). Par comparaison, parmi les 65 malades porteurs d’une cirrhose liée au virus de l’hépatite C, 18 ont quitté le programme de surveillance soit par manque d’observance (11 cas), soit par décès (7 cas) (P < 0.001). La persistance ou la rechute de la consommation d’alcool après inclusion dans l’étude étaient aussi significativement corrélées avec la qualité de l’observance. Dix sept carcinomes hépatocellulaires ont été découverts grâce au programme de surveillance, ce qui correspond à une incidence annuelle de 2 %. La comparaison entre carcinomes hépatocellulaires dépistés (n = 17) et occasionnels (n = 40) a montré que les carcinomes hépatocellulaires dépistés avaient plus souvent un caractère asymptomatique (P < 0.01), correspondaient plus souvent à un nodule unique ne dépassant pas 50 mm (P < 0.001) et ont été plus souvent traités de façon curative (P = 0.02). La survie entre les carcinomes hépatocellulaires dépistés et occasionnels était similaire.

Conclusions — Le dépistage du carcinome hépatocellulaire sur cirrhose chez les malades porteurs d’une cirrhose alcoolique est difficile en raison principalement du manque d’observance et de la mortalité précoce. Dans cette étude, une périodicité de 6 mois a été satisfaisante pour le dépistage de lésions précoces accessibles à un traitement curatif par résection chirurgicale ou ablation par voie percutanée.
Surveillance programs designed to identify hepatocellular carcinoma in an early stage is now a common practice in western countries even where the incidence is lower [1, 2]. In France for example, screening for hepatocellular carcinoma among French general practitioners in general hospitals is practiced in the hospital setting [2], despite the lack of proven efficacy in terms of patient survival [3] or early detection of lesions [4]. The difficulty in screening for hepatocellular carcinoma in western countries could stem from the large proportion of patients with alcoholic cirrhosis. It is noteworthy that most of the screening reports concerning hepatocellular carcinoma in cirrhosis patients have been conducted in patients with viral cirrhosis. In these different studies, including those conducted among the Caucasian population in Europe [5-10] and the United States [11], the proportion of patients with alcoholic cirrhosis has never exceeded 21%. To our knowledge, only two studies have been devoted to patients with cirrhosis mainly of alcoholic origin. Both of these studies reported disappointing results with poor patient compliance to the surveillance program [12] or few tumors discovered early [13]. In the study conducted in France [13], the prevalence of cirrhosis of alcoholic origin was 69% and while 14 cases of hepatocellular carcinoma were discovered, only 6 involved a solitary nodule measuring less than 5 cm without portal vein thrombosis. In light of these disappointing results, a national screening program (CHC 2000) was initiated in France comparing two monitoring intervals, 3 months versus 6 months [14]. In the present study, we report our experience with hepatocellular carcinoma surveillance among a cohort of patients with cirrhosis mainly of alcoholic origin. We focused on how aspects of patient compliance to the surveillance program as a function of the etiology of cirrhosis and efficiency of the surveillance program in terms of early detection at a stage allowing potentially curative treatment.

Patients and methods

From January 1995 to December 1998, patients with cirrhosis without hepatocellular carcinoma attending the hepatology clinic at our three hospital centers (Jolimont, Nivelles, Lobbes) were informed of the risk of hepatocellular carcinoma and invited to participate in a surveillance program. These patients were also informed that curative treatment was available in the event of the discovery of a small solitary hepatocellular carcinoma. Histological proof of cirrhosis was not required for inclusion if the following three conditions were met: 1) obvious potential etiology such as alcohol abuse or viral infection, 2) presence of ascitis and/or esophageal varices, 3) evocative aspect at the liver imaging. At inclusion, the cause of cirrhosis was identified as alcoholic, hepatitis C virus (HCV)-related, or other.

The surveillance program included abdominal ultrasound and alpha-fetoprotein assay every six months. Most of the ultrasound explorations were performed by one experienced operator (EL). When serum alpha-fetoprotein was in the 20-200 ng/mL range or when ultrasound revealed a doubtful lesion measuring less than 15 mm, the patient was also scheduled for a complete imaging work-up every 3 months. A reminder was not sent to patients who did not attend scheduled visits in order to preserve a confident relationship with the general practitioners in the region.

A 4-point scale was used to assess patient compliance to the surveillance program [12]: 1 = patient not seen again after a first visit; 2 = patient who abandoned the program after initially attending scheduled visits; 3 = patient who attended visits irregularly; 4 = patient who attended all scheduled visits. Patients scored 1 and 2 were considered to be “non-compliant” and patients scored 3 and 4 were considered to be “compliant”. The etiology of cirrhosis and the persistence of alcohol abuse were considered to be factors affecting the quality of compliance. Follow-up was considered to be too short to assign patients who died less than one year after inclusion to the “compliant” or “non-compliant” category. These patients were not included in the analysis of compliance.

Hepatic computed tomography with contrast injection was performed when tomographic ultrasound identified a doubtful lesion. Magnetic resonance imaging was performed as needed. The diagnosis of hepatocellular carcinoma was retained without histological proof when imaging confirmed the development of a hypervascularized lesion measuring more than 15 mm. Histological proof of hepatocellular carcinoma was not sought in all cases due to: 1) the high probability (> 90%) of diagnosis in the event of a new hypervascularized nodule identified in a cirrhotic liver and measuring more than 15 mm, 2) the risk of false negative cytology or histology, 3) the low morbidity of transcatheter treatment which is warranted even when formal proof of the cancerous nature of the lesion is lacking. This approach is currently widely accepted as good clinical practice [15, 16].

Pertinent clinical, biological, and radiological data were collected prospectively on an individual chart. Results were analyzed up through July 1, 2001, giving an average follow-up of 60 months (range: 30-78). The CLIP score (Cancer of the Liver Italian Program) [17] was determined. Theoretical indications for curative treatment were assessed using the Barcelona Clinical Liver Cancer (BCLC) criteria: an early tumor designated as a solitary nodule measuring ≤ 5 cm or 3 nodules measuring ≤ 3 cm [18].

In the second part of the study, hepatocellular carcinomas discovered during the surveillance program (screened hepatocellular carcinoma, n = 17) were compared with hepatocellular carcinomas discovered incidentally outside the surveillance program (incidental hepatocellular carcinomas, n = 40). The two groups were compared for oncological stage (CLIP stage), theoretical indications for curative treatment (BCLC stage) and treatments actually given.

The chi-square test and Student’s t test were applied as appropriate.

Results

Patient data

Two hundred ninety-three patients with cirrhosis (190 men, 103 women, mean age 55 years) were included during the 4-year period from January 1995 through December 1998. Liver biopsy had confirmed the diagnosis of cirrhosis in 220 patients (75%). Cirrhosis was alcohol-related in 186 patients (63.5%), HCV-related in 65 patients (22%) and related to another cause in 42 patients (14.5%). Among the patients with alcohol-related cirrhosis, 6.7% (12/178 tests) were HBsAg positive. Among the patients with HCV-related cirrhosis, daily alcohol consumption was greater than 40 g in 5 (7.6%). Among the patients with cirrhosis related to another cause, 14 had hepatitis B virus-related cirrhosis, 10 had hemochromatosis (9 genetic, 1 secondary), 8 had autoimmune liver disease, and 3 had drug-related cirrhosis. Cryptogenic cirrhosis was diagnosed in 7 patients. Patient data (age, gender, Child Pugh score, alpha-fetoprotein level at inclusion) are given in table I according to cause of cirrhosis. In general, patients with alcohol-related cirrhosis were younger, were more often male, and had a higher Child Pugh score.

Compliance to the surveillance program

Patient compliance to the surveillance program as of July 1, 2001 is indicated in figure 1 for 293 patients.

Sixteen patients (14 alcohol, 1 HCV, 1 other) died shortly after inclusion (mean survival 5.5 months, range: 2-10 months) and were excluded from the analysis of factors influencing compliance. Analysis of the quality of compliance (table II) was thus performed on 277 patients with cirrhosis due to alcohol consumption (n = 172, 62%), HCV infection (n = 64, 23%), or another cause (n = 41, 15%). Among these 277 cirrhosis...
Among the patients with alcoholic cirrhosis, interruption of alcohol consumption after entering the surveillance program was significantly correlated with better compliance. Complete abstinence from alcohol was observed in 73.5% (36/49) of the score 4 patients compared with 23% (6/26) of the score 3 patients (P < 0.001).

Overall, at the end of the 60-month period, 129 of the 186 patients with alcoholic cirrhosis (69%) initially enrolled in the surveillance program had left due to non-compliance (n = 97) or death (n = 32, early for 14 or during the surveillance period for 18). As 6 patients underwent liver transplantation and 7 developed hepatocellular carcinoma, only 44 patients with alcoholic cirrhosis (24% of the initial cohort) were still in the program on July 1, 2001 (figure 1). By comparison, 18 of the 65 patients (28%) with HCV-related cirrhosis initially enrolled had left the program due to non-compliance (n = 11) or death (n = 7) (P < 0.001), so 37 (57%) were still in the surveillance program on July 1, 2001 (P < 0.001) (figure 1).

### Development of hepatocellular carcinoma

Hepatocellular carcinoma was identified in 17 patients (13 men, 4 women, mean age 62 years, age range: 48-80 years) who had complied with the screening program. These patients had alcoholic cirrhosis (n = 7, including one HBsAg positive patient), HCV-related cirrhosis (n = 7), or cirrhosis related to another cause (n = 3: 1 HBV, 1 autoimmune hepatitis, 1 cryptogenic hepatitis). These 17 cases of hepatocellular carcinoma were identified 9 to 76 months after inclusion in the surveillance program (mean 36 months). A solitary nodule was identified in 16 patients (measuring less than 3 cm in diameter in 13 patients and 3-4 cm in 3). Three lesions measuring less than 3 cm were identified in one patient. Vascular invasion was not present. Curative treatment was attempted in 14 patients, surgical resection in 3 and percutaneous acetic acid injection in 11 (followed by liver transplantation proposed for 5). The 3 other patients were given symptomatic care due to contraindications for more radical treatment. On July 1, 2001, nine of the 17 patients with identified hepatocellular carcinoma were living (mean survival 22.3 months, range: 1-42). The incidence of hepatocellular carcinoma on an intent-to-monitor basis was 5.8% for the entire cohort (n = 293) giving an annual incidence of 2%. The "real" incidence, calculated among the compliant population (n = 158), was 10.7%, giving an annual incidence of 2.5%.

### Hepatocellular carcinoma discovered during the surveillance program (n = 17) versus hepatocellular carcinoma discovered incidentally (n = 40)

During the study period, hepatocellular carcinoma was discovered in 40 patients (25 men, 15 women, mean age 67 years) in an incidental manner, outside the surveillance program. These 40 patients had alcoholic cirrhosis (n = 12), HCV-related cirrhosis (n = 18), and cirrhosis related to another cause (n = 10: 4 hepatitis B, 1 genetic hemochromatosis, 1 autoimmune hepatitis, 4 cryptogenic hepaticis). The tumor was identified at ultrasonography in 39 of these patients and was revealed by elevated alpha-fetoprotein (1281 ng/ml) in one. Twenty-three of these patients (57.5%) were asymptomatic, hepatocellular carcinoma being discovered during the initial or follow-up work-up for cirrhosis. Twenty patients were given symptomatic treatment due to tumor extension or severe degradation of liver function. On July 1, 2001, 8/40 patients were living (mean survival 32.8 months, range: 6-67). Death (n = 32)

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**Table I. – Demographic data according to aetiology of cirrhosis in the series of 293 patients.**

<table>
<thead>
<tr>
<th>A/B/C</th>
<th>Alcohol N = 186</th>
<th>N = 65</th>
<th>Other N = 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>52.3</td>
<td>63.3</td>
<td>56.3</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>(17-84)</td>
<td>(27-84)</td>
<td>(17-82)</td>
</tr>
<tr>
<td>A/B/C</td>
<td>89/68/29</td>
<td>54/11/0</td>
<td>37/5/0</td>
</tr>
<tr>
<td>Mean Score</td>
<td>7.2</td>
<td>5.6</td>
<td>5.7</td>
</tr>
<tr>
<td>Median (range)</td>
<td>(1.3-64)</td>
<td>(1.7-244)</td>
<td>(0.8-12)</td>
</tr>
</tbody>
</table>

- **Fig. 1** – Screening status on 1/7/2001: mean follow-up: 60 months; CHC: hepatocarcinoma.
had occurred 13.1 months (range: 1-52) after diagnosis due to end-stage hepatocellular carcinoma (n = 25), liver failure (n = 5), or another cause (n = 2).

Comparing these 40 cases of incidentally discovered hepatocellular carcinoma with the 17 cases of hepatocellular carcinoma identified by the surveillance program revealed a higher incidence of the following features among the “screened” cases: asymptomatic patients (P < 0.01), solitary nodule < 5 cm (P < 0.001), CLIP score = 1 (P = 0.05), accessibility to curative treatment (P = 0.02) (table III).

Despite these differences, the survival curves were not significantly different according to mode of discovery (figure 2).

Discussion

This study illustrates the difficulty encountered when attempting to conduct a surveillance program among patients with alcoholic cirrhosis. After five years (mean follow-up) only 44 patients among the 186 with alcoholic cirrhosis (24%) initially enrolled continued to participate in the surveillance program. This proportion is to be compared with the 57% (37/65) compliance observed in the cohort of patients with HCV-related cirrhosis (figure 1). The principal cause of this low percentage was the poor compliance of the patients with alcoholic cirrhosis. More than half of the alcoholic cirrhosis cohort (56.4%) abandoned the surveillance program compared with 17.2% of the HCV-related cirrhosis cohort and 26.8% of the cohort of patients with cirrhosis related to another cause. Persistent alcohol abuse after enrollment in the program was also a factor influencing compliance. Nearly three-quarters (73.5%) of the alcoholic patients who scrupulously attended the screening visits totally abstained from alcohol after enrollment; this percentage was only 23% among those whose abstention was only partial (P < 0.001).

The question of patient compliance was rarely addressed in the literature and often completely overlooked [6, 7, 19]. This is probably because most of the published studies have been conducted in patients with cirrhosis secondary to viral infection who generally do not have any problem complying with surveillance programs. In a recent Italian report on 313 patients with cirrhosis where more than 80% of the patients had virus infection-related cirrhosis, only 24 (7.7%) failed to complete the 51-month follow-up [9]. There is no reason however to exclude alcoholic patients from surveillance programs. The annual incidence of hepatocellular carcinoma observed in compliant patients with alcoholic cirrhosis was not different from that in compliant patients with cirrhosis related to HCV infection or another cause (10 cases of hepatocellular carcinoma among 85 patients, incidence 12%). It would undoubtedly be useful to define selection criteria for alcoholic patients taking into account the ability to comply and prognosis. Likewise, studies devoted to cost effectiveness should take into consideration the “waste”

Table III – Screened and incidental hepatocarcinoma: clinical, carcinologic and therapeutic comparisons.

<table>
<thead>
<tr>
<th></th>
<th>Screened HCC</th>
<th>Incidental HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range)</td>
<td>62 (48-80)</td>
<td>67 (36-83)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>13/4</td>
<td>25/15</td>
</tr>
<tr>
<td>Alcohol/HCV/Other</td>
<td>7/7/3</td>
<td>12/18/10</td>
</tr>
<tr>
<td>Child Pugh (at diagnosis)</td>
<td>A/B/C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11/4/2</td>
<td>27/8/5</td>
</tr>
<tr>
<td>Mean</td>
<td>6.3</td>
<td>6.4</td>
</tr>
<tr>
<td>Asymptomatic HCC</td>
<td>17 (100%)</td>
<td>23 (57.5%)</td>
</tr>
<tr>
<td>Solitary nodule &lt; 5 cm</td>
<td>16 (94%)</td>
<td>10 (25%)</td>
</tr>
<tr>
<td>CLIP Score ≤ 1</td>
<td>13 (76.5%)</td>
<td>19 (47.5%)</td>
</tr>
<tr>
<td>Theoretical therapeutic accessibility</td>
<td>17 (100%)</td>
<td>14 (35%)</td>
</tr>
<tr>
<td>Therapeutic abstention</td>
<td>3 (18%)</td>
<td>20 (50%)</td>
</tr>
</tbody>
</table>

HCC: hepatocellular carcinoma.

Table II – Compliance scores according to the etiology of cirrhosis.

<table>
<thead>
<tr>
<th>CAUSE OF CIRRHOSIS</th>
<th>NON COMPLIANCE</th>
<th>COMPLIANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Score 1</td>
<td>Score 2</td>
</tr>
<tr>
<td>Alcohol n = 172</td>
<td>41</td>
<td>56</td>
</tr>
<tr>
<td>HCV n = 64</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Others n = 41</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

(1) Score 1: total non-compliance; score 2: discontinuation after initial participation; score 3: irregular compliance; score 4: regular compliance. Quality of compliance was analyzed in 277 patients in the initial cohort (n = 293), excluding 16 patients who died less than one year after inclusion.

(2) P < 0.001 for difference in quality of compliance between alcohol-related cirrhosis and cirrhosis related to HCV infection or another cause.

Fig. 2 – Survival curves of screened and incidental hepatocarcinoma; CHC: hepatocarcinoma.

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resulting from early abandon and early mortality among alcoholic patients [20].

Another objective of the present study was to ascertain the efficacy of screening in terms of identifying hepatocellular carcinoma early, when curative treatment has a reasonable chance of success as determined by current criteria: solitary tumor measuring ≤ 5 cm, no more than 3 tumors measuring ≤ 3 cm without vascular invasion [18]. All 17 hepatocellular carcinomas identified during the present surveillance program met these criteria since 16 were solitary nodules measuring less than 5 cm and 1 involved 3 nodules measuring less than 3 cm without portal thrombosis. In 13 patients (76%), the solitary nodule measured less than 3 cm, an important criteria for the efficacy for percutaneous ablation using ethanol or acetic acid injections or thermal or radiofrequency treatments known to be less effective if the nodule measures more than 3 cm [21]. In the studies conducted in western countries, the efficacy of tomographic ultrasound screening programs has varied between 21 and 79% for small-sized tumors (< 3 cm) identified at the stage of a solitary nodule [8-10, 16, 22]. The difference between these studies is undoubtedly related to the quality of the ultrasound examination [22]. In our program, three-quarters of the patients (224/293) were followed by the same experienced radiologist (EL). In the study reported by Pateron et al. [13], the lower rate of detection of solitary nodules measuring less than 3 cm (21%, 3 of 14 detected hepatocellular carcinomas) was probably related to the lower performance of the ultrasound equipment available at that time and diversity of the operators. It is noteworthy that the recommendations for the national study currently under way in France (CHC 2000, designed to compare 3-month versus 6-month screening intervals), propose that the same experienced radiologist perform the tomographic ultrasound examinations [14].

We also searched for differences between the 17 patients with hepatocellular carcinoma identified within the framework of the surveillance program and 40 patients with hepatocellular carcinoma discovered “incidentally” outside the surveillance program. Earlier detection—in terms of symptoms, radiographic stage, or theoretical or real therapeutic options—was the rule in the “screened” patients. Unfortunately, prognosis—in terms of survival—was not improved. There is little data in the literature useful for pertinent comparison. To our knowledge, only 3 studies conducted among Caucasian patients have compared the oncological stage and prognosis between screened hepatocellular carcinoma and incidentally-discovered hepatocellular carcinoma [9-11] and these 3 studies provide very conflicting data. In the study reported by Chalasani et al. [11] in the United States, radiographic stage and patient survival were not different between the two groups (5 screening and 22 incidental diagnoses), but the inclusion criteria defined a very special type of patient with severe cirrhosis on a waiting list for liver transplantation. In the Italian study reported by Trevisani et al. [10], hepatocellular carcinomas were discovered earlier within the framework of the surveillance program and more often in patients eligible for curative treatment. In that study, survival was significantly longer for the Child-Pugh class A and B patients despite the fact that a solitary nodule measuring less than 3 cm were only identified in 42% of the patients (95/215 diagnoses of hepatocellular carcinoma) screened every 6 months. The most rigorous study to date is certainly the Italian work reported by Bolondi et al. [9]. In that study, 61 patients with hepatocellular carcinoma identified during a surveillance program were compared with 104 whose hepatocellular carcinoma was an incidental discovery during the same period. The screened tumors were discovered at an earlier radiographic stage in patients who were more often eligible for curative treatment, although the differences did not reach statistical significance. Conversely, survival was significantly better among patients whose hepatocellular carcinoma was discovered during the systematic surveillance program. The absence of a control group is a common drawback of all these studies, a methodological problem which is inevitable since it would be unethical to follow without treatment patients with small-sized tumors. Knowledge of the natural history of small-sized hepatocellular carcinoma is thus insufficient but larger studies using more recent high-performance ultrasound equipment or other imaging methods should provide new insight and be helpful in determining whether regular screening can improve the prognosis of hepatocellular carcinoma developing in patients with cirrhosis.

REFERENCES


