Epidemiology of hepatocellular carcinoma in Finistère
Prospective study from June 2002 to May 2003

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SUMMARY

Objectives — The aims of this prospective study were to evaluate the incidence of hepatocellular carcinoma (HCC) in Finistère, an administrative district of western France, and to highlight epidemiological characteristics.

Methods — From June 1st 2002 to May 31st 2003, all cases of HCC in Finistère were registered prospectively. Standardized incidence rates were calculated.

Results — One hundred and six cases of HCC were registered. Standardized incidence rates were 13.8/100000 among men and 0.8/100000 among women. Among the incident cases of HCC, 52% were discovered in patients consulting for symptoms, and 28% in patients undergoing screening. The new non-invasive diagnostic criteria of HCC were used in 60% of cases. HCC was associated with cirrhosis in 89 patients (84%). Excessive alcohol intake was the main cause of cirrhosis. In all, 27 patients (25.5%) received potentially curative treatment.

Conclusion — Incidence of HCC is high in Finistère. The proportion of patients given potentially curative treatment is still low, illustrating how difficult screening can be when alcoholic cirrhosis predominates in the target population.

Introduction

Primary liver cancer is the fifth leading cause of malignancy worldwide. An estimated 437,000 incident cases were diagnosed in 1990 [1]. The very large majority of these patients have hepatocellular carcinoma (HCC).

The annual incidence of HCC exhibits geographical variations ranging from 20 to 28 new cases per 100000 inhabitants in the Far East and certain countries in Africa to less than 5 per 100000 in males in Northern Europe, Australia and the United States [2]. An intermediary incidence is observed in Southern Europe. In France, the incidence of primary liver cancer, irrespective of the histology, was about 11/100,000 in males in 2000 with 5426 incident cases being recorded [3].

Several studies suggest that the incidence of HCC is rising, particularly in western countries [3, 4], probably in relation to the increasing incidence of cirrhosis resulting from chronic hepatitis C infection [4-6]. In France, alcohol intake remains the leading cause of cirrhosis and HCC [4-6]. Finistère, an administrative district in western France, is one of the areas where alcohol-related disease is a major health concern [7].

The aims of this study were a) to determine the incidence of HCC in Finistère during a one-year period from June 2002 to May 2003 based on prospective registration of all incident cases of HCC meeting the non-invasive diagnostic criteria of HCC defined in 2000; b) to highlight the main epidemiological features of these tumors.

Patients and methods

Study set-up

From June 1st 2000 through May 31st 2003, all cases of HCC diagnosed in Finistère were registered prospectively. All gastroenterologists, internists, surgeons and pathologists practicing in private clinics or public institutions received an information document inviting them to participate in the study. Data were collected directly by these physicians when registering incident cases of HCC or by an investigator physician who
was informed of the number of incident cases reported by the physicians participating in the study. Care was taken to achieve exhaustive data collection using recall letters or phone calls to the participating physicians. Data collection was anonymous for the patients. The following items were recorded: mode of discovery of HCC, mode of diagnosis, tumor morphology, presence or not of cirrhosis, treatment delivered. The diagnosis of HCC was based either on histological or morphological findings, considered alone or in combination with significant elevation of serum alpha-fetoprotein. In patients with cirrhosis, HCC was retained as the diagnosis in the presence of a liver tumor measuring ≥ 2 cm or more on the computed tomography (CT) scan or magnetic resonance imaging (MRI) with contrast uptake during the arterial phase or with serum alpha-fetoprotein ≥ 400 ng/mL [2].

Statistical analysis

The raw incidence of HCC was standardized using the direct world population method.

Statistical analysis was performed with Epi-Info version 6 (CDC Atlanta, GA). Discrete variables were expressed in percent of the study population and analyzed using the chi-square test. Non-discrete variables were expressed as mean ± standard deviation (m ± SD) and compared with ANOVA.

Results

During the one-year study period (June 2002-May 2003), 106 incident cases of HCC were registered in 99 males and 7 females. Mean age of this population was 66.9 ± 9.1 years (range: 42-89), 67 ± 8.7 years in males (range: 44-89) and 66.1 ± 13.9 in females (range: 42-85) — NS.

Incidence data

Incidence curves for the period June 2002-May 2003 are presented by gender and age in figure 1. The incidence of HCC was higher among men aged over 50 years and reached a peak in the 65-74 age range. Among women, HCC was exceptional before the age of 50 years and no peak could be identified. The overall incidence figures for HCC in Finistère are presented in table I.

Clinical and morphological data

Diagnostic circumstances

HCC was discovered in 55 patients (52%) who consulted for symptoms, in 30 (28%) who underwent a screening test, and fortuitously in 21 (20%) who were undergoing investigations for a co-morbid affection or who presented perturbed liver tests without known liver disease. In the patients who presented symptoms revealing the disease, the main clinical signs were ascites (40%), weight loss (26%), pain (18%), jaundice (6%), digestive tract bleeding (5%) and hepatomegaly (5%).

Positive diagnosis of HCC

Diagnosis was histologically proven in 42 patients (40%). Serum alpha-fetoprotein level was known for 102 patients (96%) and was normal in 24 (23%). Alpha-fetoprotein was significantly elevated, ≥ 400 ng/mL, in 39 patients (37%). Elevated alpha-fetoprotein (≥ 400 ng/mL) was associated with several hepatic tumors measuring ≥2 cm in 30 patients (28%) with cirrhosis.

For 34 patients (32%), the diagnosis was established on the basis of clinical and morphological findings. These patients had cirrhosis and presented liver nodules with contrast uptake during the arterial time of CT or MRI explorations. Half of these 34 patients, had an elevated serum alpha-fetoprotein level measured at 10 to 400 ng/mL.

Cirrhosis

Cirrhosis was noted in 89 patients (84%), 86 males and 3 females. The diagnosis of cirrhosis was based on histological criteria for 29%, and on the association of clinical, biological and morphological findings for 71%. Cirrhosis was known in 36 patients whose HCC was discovered at an organized screening examination. The causes of cirrhosis are noted in table II. Child-Puch staging was: grade A in 30%, grade B in 43%, and grade C in 27%. Among the 63 patients who had an upper endoscopic exploration, 29% did not present esophageal varices, 27% grade 1 esophageal varices, 25% grade 2, and 19 grade 3. For 46%, HCC was the inaugural manifestation of the liver disease, while for 54% cirrhosis was known at the time of diagnosis of HCC. Among these latter patients, mean time from diagnosis of cirrhosis to diagnosis of HCC was 54.7 ± 54.2 months (range: 11-276 months). Complications had been noted before discovery of HCC in 56% of patients whose cirrhosis was known before the diagnosis of HCC: ascites (48%), digestive bleeding and ascites (33%), digestive bleeding alone (15%), hepatic encephalopathy (4%).

HCC without cirrhosis

HCC was not associated with cirrhosis in 14 patients (13%). The absence of cirrhosis was proven histologically by the
pathological examination of the extratumoral hepatic parenchyma. Two of these patients had chronic viral hepatitis B (METAVIR histological scores A2F1 and A1F3). One patient had genetic hemochromatosis. Two patients had large-cell dysplasia, two presented steatosis without fibrosis, and three presented mild to moderate fibrosis of non-tumor parenchyma. The diagnosis of HCC on a healthy liver was retained for four patients (4%) whose extra-tumor hepatic parenchyma was free of fibrosis, steatosis, or iron overload and who had no risk factor for chronic hepatitis. Two of these patients presented the characteristic features of fibrolamellar HCC.

The presence or not of cirrhosis could not be established for 3 patients (3% of the study population) who did not present any clinical, biological or morphological manifestation of cirrhosis and for whom there was no pathology data.

The main findings comparing HCC patients with and without cirrhosis are presented in table III. In HCC patients without cirrhosis, male predominance was less marked, single tumors were more frequent, as was ascites, and chronic alcoholism, but with significant differences. Tumor size was greater in this group but did not reach statistical significance (P = 0.06).

**Morphological characteristics**

Liver size was normal in 46% of patients, with hypertrophy in 49% and atrophy in 5%. There was one nodule in 44% of patients, several in 43% and diffuse lesions in 13%. For the nodular forms, mean tumor size was 5.63 ± 2.59 cm (range: 1-16 cm). The presence or not of portal vein thrombosis was known for 95 patients and was present in 34 (35.8%).

**Comparison of characteristic clinical and morphological features depending on discovery mode**

We compared characteristic clinical and morphological features of patients whose HCC was discovered at a screening examination versus those of patients whose HCC was diagnosed following clinical manifestations or fortuitously (table IV). One third of the screened tumors were single, measuring ≤ 3 cm. More of the screened tumors were potentially curable (P < 0.0001), and fewer associated with portal thrombosis (P < 0.005). Potentially curative treatment was proposed more often (P < 0.05) when the diagnosis was fortuitous or made after onset of clinical manifestations.

### Table I

Incidence of hepatocellular carcinoma per 100,000 inhabitants in Finistère from June 2002 to May 2003.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Raw incidence</th>
<th>Standardized incidence based on the world population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>23.7</td>
<td>13.8</td>
</tr>
<tr>
<td>Female</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>14.8</td>
<td>17.2</td>
</tr>
</tbody>
</table>

The raw annual incidence is the number of new cases of hepatocellular carcinoma registered during a one-year period divided by the mean number of inhabitants during the same period. The reference populations used for Finistère were provided by the official French Statistics Institute (INSEE).

Standardized incidence was based on the direct standardization method which applies the age-specific rates observed in the study population to the corresponding age-specific world population to determine the overall incidence which would have been observed in this reference population.

### Table II


<table>
<thead>
<tr>
<th>Cause</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>68 (76.4)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>4 (4.5)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>4 (4.5)</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Alcohol and hepatitis C</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td>Alcohol and hemochromatosis</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Other (metabolic, cryptogenetic)</td>
<td>6 (6.8)</td>
</tr>
</tbody>
</table>

### Treatments

In all, 27 patients (25.5%) were given potentially curative treatment for HCC, by liver transplantation (N = 1), surgical resection (N = 11), surgical ablation (N = 11). Liver transplantation was proposed for four patients. Two declined transplantation and were treated by radiofrequency ablation. One patient developed a cardiovascular condition (coronary artery disease) incompatible with transplantation and was treated by radiofrequency ablation. There was one liver transplantation. Thirteen patients (12.3%) underwent intraarterial chemoembolization, including two who later had second-intention local tumor destruction. Therapeutic ablation was retained in 37 patients (34.9%).

### Discussion

This population-based study collected epidemiological data concerning incident cases of hepatocellular carcinoma (HCC) observed over a one year period in Finistère in western France. Despite the prospective nature of this study, data collection was probability not absolutely complete. Nevertheless, we cross checked information provided by healthcare institutions, pathology laboratories, and medical and surgical specialists, so the number of incident cases of HCC registered is most likely very close to the real figure. In addition, it must be noted that data was collected over a short period of one year so that any extrapolation must be made prudently.

Among men, the incidence observed between June 1st, 2002 and May 31st, 2003 was higher than reported elsewhere in France, and in other geographical areas in recent reports [3, 4, 8, 9]. In the literature, the incidence of HCC is usually reported within the overall figure for primary liver cancer, which includes various histological types including cholangiocarcinoma. In France in 2000, the standardized incidence of primary liver cancer was 11/100,000 inhabitants for males and 1.5/100,000 for females [3]. The incidence we recorded for women was very close to that noted in earlier reports in the literature [3, 4].

Several recent studies have demonstrated an increase in the incidence of HCC in western countries [4]. In France, the annual incidence of primary liver cancer, standardized for the world-wide population, increased from 1980 to 2000 from 4.4 to 11/100,000 in males, and from 0.8 to 1.5/100,000 in females [3]. The same trend was noted in the United States.
In western countries, HCC occurs, for the very large majority of patients, in a context of cirrhosis and one of the reasons for the increasing incidence of HCC is better management of the other complications of cirrhosis. HCC is becoming the leading cause of mortality in this category of patients [4].

In accordance with the Barcelona criteria set forward in 2001 [2], it is possible to establish the diagnosis of HCC in patients with cirrhosis on the basis of imaging criteria (CT, MRI) or in combination with the serum alpha-fetoprotein level [2].

Table III. – Characteristic features of patients with and without cirrhosis who developed hepatocellular carcinoma newly diagnosed from 2002 to 2003 in Finistère.

<table>
<thead>
<tr>
<th>Characteristic feature</th>
<th>With cirrhosis N = 89 (%)</th>
<th>Without cirrhosis N = 14 (%)</th>
<th>p (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>86 (96.6)</td>
<td>10 (71.4)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
<td>67.3 (47-89)</td>
<td>64.85 (42-85)</td>
<td>NS</td>
</tr>
<tr>
<td>Unique nodule ≤ 3</td>
<td>34 (38.2)</td>
<td>11 (78.6)</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>nodule</td>
<td>57 (64)</td>
<td>12 (85.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Tumor size ≤ 30 mm</td>
<td>18 (20.2)</td>
<td>2 (14.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Presence of ascites</td>
<td>47 (52.8)</td>
<td>0</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Presence of portal thrombosis</td>
<td>30/80 (37.5)</td>
<td>3/12 (25)</td>
<td>NS</td>
</tr>
<tr>
<td>Chronic alcoholism(b)</td>
<td>73/82 (89)</td>
<td>2 (16.7)</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Proposition given potentially curative treatment (surgery or tumor destruction)</td>
<td>20 (22.5)</td>
<td>7 (50)</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

(a) Chi-square test; NS: non significant; (b) alcohol intake greater than 40 g/d for more than 10 years.

Table IV. – Characteristic features of patients with hepatocellular carcinoma by mode of tumor discovery.

<table>
<thead>
<tr>
<th>Characteristic feature</th>
<th>Mode of tumor discovery</th>
<th>p (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screening test N = 30 (%)</td>
<td>Other N = 76 (%)</td>
</tr>
<tr>
<td>Male gender</td>
<td>30 (100)</td>
<td>69 (90.8)</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
<td>65.1 (47-85)</td>
<td>67.6 (42-89)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>29 (96.7)</td>
<td>60 (78.9)</td>
</tr>
<tr>
<td>Alcohol-related cirrhosis</td>
<td>19/29 (65.5)</td>
<td>49/60 (81.7)</td>
</tr>
<tr>
<td>Child Pugh class A</td>
<td>14/29 (48.3)</td>
<td>13/60 (21.7)</td>
</tr>
<tr>
<td>Unique nodule ≤ 3 cm</td>
<td>15 (50)</td>
<td>5 (6.6)</td>
</tr>
<tr>
<td>Tumor size ≤ 3 cm</td>
<td>4/30 (14.3)</td>
<td>30/67 (44.8)</td>
</tr>
<tr>
<td>Proposition given potentially curative treatment (surgery or tumor destruction)</td>
<td>11 (36.7)</td>
<td>14 (18.4)</td>
</tr>
</tbody>
</table>

(a) Chi-square test; NS: non significant.

In our study, only 40% of the diagnoses of HCC were proven histologically, less than in the earlier reports of surveys conducted before 1996 in two other French administrative districts (67.2% for Côte-de-Or and 50% for Calvados) [5, 6]. In our study, HCC was diagnosed late, after the tumor had produced clinical manifestations, in two-thirds of patients. Only 28% of HCC diagnoses were established by screening tests, which is a proportion higher than reported by Even et al. (4%) in Calvados [6]. Among the tumors identified by screening tests, one third were unique foci measuring ≤ 3 cm in patients without
portals who were thus eligible for potentially curative treatment. For this type of tumor, the diagnostic yield of ultrasound explorations performed every six months has varied from 21% to 79% [14, 15]. There could be several explanations for the small percentage of potentially curable tumors detected by screening tests observed in the present study. First of all, the time interval between screening tests was unknown and we had no information on the quality of patient compliance to screening schedules. As clearly illustrated in our study, Henrion et al. [14] pointed out how difficult it is to screen for HCC in patients with alcoholic cirrhosis. These authors reported a follow-up cohort and found that only 24% of patients with alcoholic cirrhosis scheduled for a screening program were followed five years versus 57% of those with viral cirrhosis. It is also known that variable quality of the ultrasound examination can in part account for differences between studies. Henrion et al. [14] and Bolondi et al. [15] reported good screening results in studies where the majority of patients were followed by the same experienced radiologists. Data on the ultrasound protocols used for patients in our study were not available.

Although highly debated, screening is a widespread practice in France [16]. Efficacy in terms of patient survival remains to be demonstrated. Prospective studies including a large number of patients are being conducted to determine whether a regular surveillance program among patients with cirrhosis can improve the prognosis of HCC. While waiting for the results of these studies, it would appear reasonable to propose screening to selected patients with cirrhosis, i.e. a target population presenting demonstrated risk factors of HCC (male gender, age over 50 years, viral or alcoholic cirrhosis, low prothrombin level, low platelet count, large-cell dysplasia) [16-18] and whose general status is compatible with potentially curative treatment.

In the population identified in this study, 84% of the patients with HCC had cirrhosis. This rate is comparable to earlier population-based studies in western countries where HCC is found in about 90% of patients with cirrhosis [4-6, 9, 16, 17]. The main cause of cirrhosis in our study was alcohol intake, noted in two-thirds of the patients and in agreement with earlier nationwide studies [5, 6, 16, 17]. It has been demonstrated that the presence of cirrhosis is a major risk factor for the development of HCC [2, 18] and several studies have demonstrated that high-level alcohol intake is associated with greater risk of HCC [18-20]. The situation is different in other western countries, particularly in Italy and Spain where HCC in cirrhosis is mainly associated with hepatitis C and to a lesser extent hepatitis B (60-70% of patients) [4, 9, 21]. In our study, HCC revealed the cirrhosis in 46% of patients with cirrhosis. This is comparable to the rate observed by Even et al. (49%) [6]. These data clearly demonstrate that cirrhosis is not diagnosed at an early stage when surveillance could be instituted before the development of HCC.

Fourteen patients (13.2%) developed HCC without cirrhosis. The percentage of HCC tumors which develop on cirrhosis-free livers has varied geographically. European series have reported rates from 5% to 22% [6, 22, 23]. The main etiological factors known to be associated with the development of HCC on a cirrhosis-free liver are hepatitis B and hepatitis C, both viruses playing a direct role in the hepatic carcinogenic process independently of cirrhosis [23]. The carcinogenic effect of iron overload and genetic hemochromatosis has been recently discussed [22, 24, 25]. Other genetic factors have been suggested, such as estrogen- and androgen-related malignant transformation of an adenoma [23] or exposure to certain chemical compounds such as aflatoxin or nitrosamines. Several studies have recently demonstrated that diabetes and obesity, risk factors for non-alcoholic steatohepatitis, can be causal factors for the development of HCC without cirrhosis [26, 27].

One quarter of our patients were given potentially curative treatment, by liver transplantation, surgical resection, radiofrequency ablation or alcohol injection. In the study from Calvados, potentially curative treatment was delivered for only 8% of patients, all by surgical resection [6]. This difference results in part from the fact that liver transplantation and local destruction techniques, particularly radiofrequency ablation, were not readily available at the time of the earlier study [6]. It also results from the large proportion of tumors detected by screening tests in cirrhosis patients in the present study. Considering only tumors discovered at a screening test, the rate of potentially curative treatment was only 36.7%. In their studies, Henrion et al. [14] and Bolondi et al. [15] reported corresponding rates of 82.3% and 68.9% respectively. The main explanation for this discordance is that a large number of positive screening tests in our population involved advanced-stage HCC, for reasons mentioned above.

In conclusion, our study demonstrated a high incidence of HCC in Finistère during the period of June 2002 through May 2003. The incidence observed in males was higher than recorded elsewhere in France. More than 80% of patients who developed HCC had cirrhosis, mainly caused by alcohol consumption. These data are probably the consequence of improved management practices for complications of cirrhosis, particularly ascites and digestive tract bleeding. Our study suggests that the new non-invasive diagnostic criteria for HCC, as defined at the Barcelona conference, should be used for tumor registries because tumor biopsy was necessary for diagnosis in less than half of our patients. We also observed that the diagnosis of HCC was established late in a large number of patients. Although evidence demonstrating the beneficial effect of HCC screening in terms of patient survival is not yet available, it would be advisable to improve the quality of HCC screening in patients with alcoholic cirrhosis who have difficulty complying with surveillance protocols. Targeted screening should be the goal. A significant number of cases of cirrhosis were discovered at the diagnosis of HCC, highlighting the importance of early diagnosis of cirrhosis.

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REFERENCES


