Early Detection of Hepatocellular Carcinoma Increases the Chance of Treatment: Hong Kong Experience

Man-Fung Yuen,1 Chi-Chung Cheng,1 I. J. Auder,2 Shui-Kam Lam,1 Clara Gaik-Cheng Ooi,3 and Ching-Lung Lai1

The prognosis for patients with hepatocellular carcinoma (HCC) is poor because of the low chance of curative treatment. To increase the chance of intervention and to improve survival, early detection of subclinical HCC (SCHCC) by α-fetoprotein (AFP) and/or ultrasonography (USG) screening is implemented in many countries. Three hundred sixty Chinese patients with HCC diagnosed between January 1995 and December 1997 were recruited. They were categorized into two groups: 142 patients (group 1) had SCHCC diagnosed by screening (AFP and/or USG), and 164 patients (group 2) presented with symptomatic HCC. The tumor size was significantly smaller in group 1 compared with that of group 2 (3.5 cm vs. 8.1 cm; P < .0001). A significantly higher proportion of patients had bilobar involvement, multifocal HCC, diffuse-type HCC, portal vein infiltration, and distant metastasis in group 2 when compared with group 1. Operability and feasibility of treatment by transcatheter intra-arterial chemoembolization (TACE) in group 1 patients (26.8% and 45.1%, respectively) were significantly better than in group 2 patients (7.9% and 32.3%, P < .0001 and P = .03, respectively). The cumulative survival rate was significantly higher in group 1 than in group 2 (P < .0001). For those who had surgical resection and those who had TACE, group 1 patients had a higher cumulative survival rate compared with that of group 2 patients (P = .04 and P = .0003, respectively). Screening for HCC by AFP and/or USG can identify tumors at an early stage, resulting in a higher chance of receiving treatment. Whether it can improve survival requires a further prospective, randomized study. (Hepatology 2000; 31:330-335.)

Hepatocellular carcinoma (HCC) is one of the major health problems throughout the world. The annual incidence is estimated as 530,000 cases globally.1 A recent study shows that the incidence of HCC is rising in the United States over the past 2 decades, with age-specific incidence shifting toward younger persons.2 The problem is even more overwhelming in regions where the incidence of chronic viral hepatitis B and/or C is of high prevalence. The prognosis for patients with HCC is still dismal. At present, surgical resection and liver transplantation are the only forms of curative treatment available. However, the chance of curative treatment is often limited by several features of the HCC. HCCs are usually large in size before they give rise to symptoms. Bilobar or multifocal tumors are common. The incidence of associated cirrhosis is also high, being over 80% in most series.3,5 The efficacy for other modalities of treatment, e.g., transcatheter intra-arterial chemoembolization (TACE), also depends on the above factors.6 To increase the chance of intervention and, more importantly, to improve survival, early detection of subclinical HCC (SCHCC) by α-fetoprotein (AFP) and/or ultrasonography (USG) screening is implemented in many countries. Though studies of Asian populations show encouraging results,7,9 these are not substantiated in European studies.10,11 The impact on survival and the cost-effectiveness of screening programs are still controversial.

There are 10 criteria for cost-effective screening programs as suggested by the World Health Organization12: 1) The condition should be an important health problem; 2) an accepted treatment for diagnosed patients should be available; 3) facilities for diagnosis and treatment should be available; 4) the condition should be recognizable in the latent/early symptomatic stage; 5) suitable tests for screening should be available; 6) the tests available should be acceptable to the population to be tested; 7) the natural history of the condition should be adequately understood; 8) an agreed policy on whom to treat should be established; 9) the cost of diagnosis and treatment should be economically balanced with the whole medical expenditure; and 10) case-finding should be continued. Screening programs for HCC fulfill 9 of these criteria, though the cost-effectiveness proposed in the ninth criteria is still subject to debate.4,5,13,14 The aim of this study was to examine whether SCHCC detected by screening methods can achieve any significant clinical and survival benefits.

Patients and Methods

Patients. All patients with HCC diagnosed between January 1995 and December 1997 in the University Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong, were recruited into this study. The diagnosis of HCC was based on AFP levels and imaging techniques including USG, computerized tomography (CT), hepatic angiography (HAG), and/or liver biopsy. The diagnostic criteria for HCC was either a confirmative liver biopsy or elevated AFP (>20 ng/mL) together with neovascularization and arterio-venous shunting in HAG and/or characteristic lipiodal up-
take in CT. They were categorized into two groups: group 1 included patients with SCHCC diagnosed by screening (see below). Group 2 was patients who presented with symptomatic HCC.

Screening Strategy. All patients who were chronic carriers of hepatitis B and/or hepatitis C had AFP levels and liver function biochemistry measured every 3 to 6 months of follow-up in the Hepatitis Clinic of Queen Mary Hospital irrespective of the age of the patients. The screening program also included patients with Child's B and Child's C because of the availability of transplantation in this center. Patients with elevated AFP levels (defined as >20 ng/mL) were called back for further investigations after a 2- to 4-week interval. In the absence of an elevated alanine transaminase level suggestive of hepatitis exacerbation and/or if the AFP level was either rising or persistently elevated, USG and CT were arranged for the patients for the detection of HCC. A proportion of patients (25.4%) had regular USG screening performed on their own.

Etiology of HCC. Viral hepatitis B infection and hepatitis C infection were diagnosed by testing for serum hepatitis B surface antigen (HBsAg) (enzyme-linked immunosorbent assay; Abbott Laboratories, Chicago, IL) and hepatitis C virus antibodies (anti-HCV) (microparticle enzyme immunoassay; Abbott Laboratories), respectively. For patients with positive HBsAg, serum hepatitis B e antigen (HBeAg) and antibody to HBeAg were tested by enzyme-linked immunosorbent assay (Abbott Laboratories). The history of alcohol intake and the presence of cirrhosis diagnosed by imaging techniques and/or the presence of cirrhosis-related complications, i.e., esophageal varix, ascites, and encephalopathy before or at the time of diagnosis of HCC, were noted.

Operability and Other Modalities of Treatment. All patients were assessed for surgical resection once the HCCs were diagnosed. The assessment would be based on lobar involvement and liver functional status. The lobar involvement was delineated by a combination of USG, CT, and HAG. For those patients who were deemed resectable by the above imaging techniques, liver functional reserve was assessed by the indocyanine green clearance test. Patients were considered not suitable for resection by the following criteria: 1) bilobar involvement; 2) evidence of main portal vein infiltration/thrombosis; 3) evidence of extrahepatic metastases from chest x-ray and/or CT of the abdomen; 4) poor liver biochemistry suggestive of severe cirrhosis as defined by a bilirubin level >50 µmol/L (normal <30 µmol/L), a serum albumin of <25 g/L, and prolongation of prothrombin time to 5 seconds over that of the control; 6) Child's C cirrhosis; 7) poor liver function reserve as indicated by the indocyanine green clearance retention of >10% at 15 minutes; and 8) poor cardiac and respiratory performance status. If the patients were not suitable for operation, TACE would be the second choice of treatment offered to the patients, unless the main portal vein was thrombosed, the liver function was too poor (bilirubin >50 µmol/L or prothrombin time more than 5 seconds above the control), or there was severe arterio-venous shunting or extrahepatic metastases.

Statistical Analysis. The time of survival was measured from the time of the diagnosis of HCC to the time of death or until the time of writing. The data were analyzed by the Mann-Whitney test for the continuous ordinal data, the χ² test with Yates' correction and the Fisher exact test for the association between two qualitative variables, and the Kaplan-Meier method for the calculation of the survival and the postresection recurrence of HCC of two groups of patients. The standard error was calculated based on the binomial model for the response proportion. P < .05 was considered statistically significant.

RESULTS

Demographic Data and Liver Function. A total of 306 patients with HCC were diagnosed during the study period. The number of patients attending the Hepatitis clinic of the Queen Mary Hospital who were screened varied slightly through the 3-year period of the study. The average number was estimated to be 2,000 patients at any one time. One hundred forty-two asymptomatic patients were diagnosed to have SCHCC under the screening program (group 1), and 164 patients presented with symptomatic HCC (group 2). For group 1 at the time of diagnosis of HCC, all 142 patients had AFP levels performed, 124 (87.3%) had USG, 121 (85.2%) had CT, 112 (78.9%) had HAG, and 65 (45.8%) had liver biopsies. In group 2 at the time of diagnosis, all 164 patients had AFP levels, 129 (78.7%) had USG, 99 (60.4%) had CT, 87 (53%) had HAG, and 35 (21.3%) had liver biopsies. The median age was 61 years (range, 22-90 years), and the male:female ratio was 249:57 (approximately 4:1). The underlying causes of the HCC were as follows: 243 (79.4%) patients were positive for HBsAg (31.9% HBeAg-positive and 68.1% hepatitis B e antigen antibody-positive); 15 (4.9%) were positive for anti-HCV; 4 (1.3%) were positive for both HBsAg and anti-HCV; 17 (5.6%) had a history of significant alcoholic intake and were negative for HBsAg and anti-HCV; and 27 (8.8%) had no known etiology. Two hundred thirty-four (76.5%) patients had evidence of cirrhosis: 108 (35.3%) patients and 126 (41.2%) patients had the cirrhosis diagnosed before and at the time of the diagnosis, respectively.

The demographic data and other basal parameters for group 1 and group 2 are listed in Table 1. The prevalence of cirrhosis in group 1 and group 2 was 85.2% and 68.9%, respectively. The duration of follow-up was shorter in the group 2 patients. Compared with group 2, group 1 patients had a higher proportion of cirrhosis, and lower albumin levels and platelet counts. Group 2 patients had higher levels of bilirubin, aspartate transaminase, alkaline phosphatase and glutamyl transpeptidase when compared with those of group 1 patients.

Features of HCC. The characteristics of the HCC in the two groups as assessed by US, CT, and/or HAG are listed in Table 2. The tumor size of the index HCC (the largest one if more than one focus of HCC was present) was significantly smaller in group 1 compared with that of group 2 (P < .0001). Group 1 had a higher proportion of patients with small HCCs of less than 3 cm and 5 cm compared with those of group 2 (P < .0001). A significantly higher proportion of patients had

| Table 1. The Demographic Data and Other Basal Parameters of the 306 Patients With HCC |
|---------------------------------|-----------------|-----------------|--------|
| Number of patients             | 142             | 164             |       |
| Median age in years at diagnosis (range) | 61 (26-83) | 61.5 (22-90) | NS    |
| Sex ratio (M:F)                | 119:23          | 130:34          | NS    |
| Median follow-up in months (range) | 10.5 (1-47) | 4 (0.5-36) | <.0001 |
| Number of patients with cirrhosis (%) | 121 (85.2) | 113 (68.9%) | .0013 |
| Liver function tests (median)  |                 |                 |       |
| Albumin (g/L)                  | 35              | 37              | .0173 |
| Globulin (g/L)                 | 37              | 37              | NS    |
| Bilirubin (µmol/L)             | 18              | 30              | .0001 |
| Alanine transaminase (U/L)     | 48.5            | 61              | NS    |
| Aspartate transaminase (U/L)   | 62              | 111             | <.0001 |
| Alkaline phosphatase (U/L)     | 117.5           | 167             | <.0001 |
| Glutamyl transpeptidase (U/L)  | 74.5            | 169             | <.0001 |
| Prothrombin time (sec)         | 12.4            | 12.45           | NS    |
| Median platelet count (>10^9/L)| 90              | 152             | <.0001 |
bilibiliary involvement, multifocal HCC, diffuse-type HCC, portal vein infiltration, and metastasis in group 2 when compared with group 1. The median AFP level was significantly lower in group 1 patients ($P = 0.0001$).

**Sensitivity of AFP and USG.** Seventy-nine of the total 306 patients (25.8%) had normal AFP at the time of diagnosis. The sensitivity of AFP alone and USG alone for the detection of HCC was 74.2% and 81.9%, respectively.

**Treatment of HCC.** For group 1, 38 (26.8%) patients underwent curative resection. The rate of operability was significantly higher compared with group 2 (13 patients [7.9%]; $P < 0.0001$). There was a trend for a lower cumulative rate of postresection tumor recurrence in group 1 patients when compared with group 2 patients (Fig. 1; $P = 0.066$). For patients with postresection recurrence, the median time of recurrence-free interval was longer in group 1 than in group 2 (11.5 months [3-26 months] vs. 5 months [1-14 months]), though this did not reach statistical significance ($P = 0.0698$).

A total of 117 patients (64 in group 1 and 53 in group 2) received TACE treatment. A significantly higher proportion of patients in group 1 received TACE treatment compared with those in group 2 (45.1% vs. 32.3%; $P = 0.03$).

Four patients (3 in group 1 and 1 in group 2) received percutaneous ethanol injection. Thirty-seven and 97 patients were treated conservatively in group 1 and group 2, respectively.

**Survival.** The median survival of all 306 patients was 11 months. The median survival of various subsets of patients in group 1 and group 2 are shown in Table 3. The cumulative actuarial survival rate was significantly higher in group 1 than in group 2 (Fig. 2; $P < 0.0001$). By stratifying according to the Child-Pugh score, patients in group 1 with Child’s A and Child’s B had a higher cumulative survival rate than those in group 2 (Fig. 3; $P = 0.0001$ and $P = 0.0072$, respectively). However, there was no difference in the cumulative survival rate of Child’s C patients between the two groups (Fig. 3).

For those who had surgical resection and those who had TACE, group 1 patients had a higher cumulative survival rate compared with that of group 2 patients (Fig. 4; $P = 0.04$ and $P = 0.003$, respectively).

**Cost-Effectiveness of Screening Program.** Over the 3-year period, 2,000 chronic hepatitis B and hepatitis C carriers were screened, with 142 cases detected, of which 102 were treatable by surgery or TACE. The proportion of cases detected by screening was thus 142 of 2,000 (0.071). The standard error of this estimate was 0.0057. Taking the 95% CI for the true value as (proportion of cases + 2 × SE), the number of patients needed to be screened to detect one HCC was 14 (95% CI: 12-17). The corresponding number of patients needed to be screened for detecting one HCC that was treatable was 20 (95% CI: 16-24). The cost for performing one AFP testing is estimated (in U.S. dollars) to be around $25, and one USG is approximately $100. Because each patient was screened twice a year, the annual cost of screening to detect one HCC would be $1,167 (95% CI: 1,000-1,417). The annual cost of screening to detect one HCC that was treatable was $20 × (125 × 2)/3 = $1,167 (95% CI: 1,333-2,000).

**DISCUSSION**

At present, it is difficult to conduct a prospective, randomized trial on screening programs for HCC because of the ethical issue. In areas in which facilities are easily available for performing AFP and USG, chronic hepatitis B and hepatitis C carriers may not acquiesce in being randomized to receive no screening for early HCC. Nearly 80% of the patients in the present study were HBsAg-positive. This incidence is similar to those of other studies. Validation of the usefulness of screening programs in HCC is of paramount importance in areas such as Southeast Asia, where 10% to 20% of the population have chronic hepatitis B infection.

**Table 3. The Median Survival of Different Subsets of 306 Patients With HCC**

| Group          | Number of patients | Median survival (mo) |
|----------------|--------------------|----------------------|
| All patients   | 142                | 22                   |
| Child’s A      | 47                 | 19                   |
| Child’s B      | 12                 | 3                    |
| Child’s C      | 2                  | NS                   |
| Patients with surgical resection | 32 | 11 |
| Patients with TACE | 26 | 11 |

*Median survival cannot be calculated, because only 3 of 13 patients were dead at the time of writing, i.e., 20 months of follow-up.*
Our study attempts to define the usefulness of screening programs for HCC by retrospectively comparing the outcome of SCHCC detected by screening (group 1) and of symptomatic HCC (group 2).

The shorter median duration of follow-up in group 2 (4 months) compared with group 1 (10.5 months) is related to the shorter survival time in the former group (Table 1). Not surprisingly, bilirubin, aminotransferases, and ductal enzymes were more deranged in group 2 as a result of the larger size of the tumors exerting a space-occupying effect. However, group 1 had a higher proportion of patients with cirrhosis compared with group 2 (85.2% vs. 68.9%; P = .0013). Furthermore, group 1 patients had lower albumin levels and platelet count when compared with group 2 patients. The patients in our screening program had a higher proportion of cirrhosis that was more severe than those who presented with symptomatic HCC. It has been suggested that screening programs may be more beneficial to patients with cirrhosis. According to Izzo et al., 98.5% of patients with HCC had either cirrhosis or chronic active hepatitis.

Group 1 patients had a significantly smaller tumor size compared with group 2 patients (3.5 cm vs. 8.1 cm; P < .0001). This finding confirms the fact that HCC patients only become symptomatic when the diameter is above 8 cm. In addition, a higher proportion of group 1 patients had tumors of less than 3 cm and 5 cm (P < .0001 for both measurements). Group 2 patients had a higher median AFP level and higher proportions of other adverse features of HCC including bilobar involvement, multifocal HCC, diffuse HCC, portal vein infiltration, and distant metastasis (Table 2). Patients with HCCs diagnosed by a screening program were
at an earlier stage of the disease in spite of their more severe concomitant cirrhosis. This led to better treatment options.

Patients with SCHCC diagnosed by a screening program had a better chance of receiving curative or palliative therapy. This finding confirms the findings of previous studies. The proportions of patients receiving curative resection and TACE were higher in group 1 when compared with group 2 (P < .0001 and P = .03, respectively). Although it is known that the postresection recurrence rate is quite high for HCC, there were trends indicating that the cumulative rate of postresection recurrence was lower and the median recurrence-free interval was longer in group 1 patients (Fig. 1; P = .066 and P = .0698, respectively). The number of operated patients in the current study (n = 51) may not be large enough for statistical significance to be shown. This study demonstrated the phenomenon of stage migration in which the group in the screening program had an earlier stage of disease, which could increase the chance of likelihood of receiving treatment. This may confer a decrease in disease-specific mortality.

The estimated annual cost needed for screening 2,000 chronic hepatitis B and hepatitis C carriers to detect one HCC was $1,167 and to detect one HCC which was treatable was $1,667 (U.S. dollars). Considering the poor prognosis of HCC, our screening program was very cost-effective. The reason for this cost-effectiveness is most likely related to the high risk of development of HCC in chronic hepatitis B and C infections. In a study of 22,707 civil servants from Taiwan, the relative risk for the development of HCC in chronic hepatitis B carriers compared with noncarriers was between 103 to 390 times. The cost-effectiveness of a screening program can probably be further increased by limiting the screening to patients over the age of 40, because the majority of HCC develops over the age of 40.

The most important aspect for any screening program is whether it can improve survival of the patients. This aspect can only be studied in a prospective, randomized control study. However, as mentioned before, such studies would be almost impossible to conduct in areas where there is a very high prevalence rate of hepatitis B infection because of the ethical implications and possible patient noncompliance. In this study, the cumulative survival rate was significantly higher in group 1 compared with group 2 (Fig. 2). Group 1 patients who underwent resection and TACE also had a higher cumulative survival rate. Though group 2 had a smaller number of patients with cirrhosis and the degree of cirrhosis was less severe, the more advanced HCC in these patients decreased the chance of receiving treatment and the survival time. The one subgroup that did not show a difference was the patients with Child's C cirrhosis. Patients with Child's C cirrhosis probably died rapidly of poor liver reserve resulting from the advanced cirrhosis, so that the survival was not significantly affected by the early detection of any superimposed HCC.

There are two problems concerning the interpretation of the better outcome of group 1 when compared with group 2. First, because the patients in group 1 were identified with tumors at an earlier stage with smaller size than those in group 2, the better survival might be the result of lead-time bias, i.e., bias introduced by earlier diagnosis. The second problem is the length bias resulting from differences in intrinsic growth rates of tumors. Screening would tend to identify slower-growing tumors. Thus, patients in group 1 were more likely to have slower-growing tumors. Rapidly growing tumors might present with symptoms in between screening procedure, and thus were included in the symptomatic group (group 2) of patients. A partial solution to the problem of lead-time bias may be dealt with mathematically. The median doubling time of HCC in Asians has been estimated to be 117 days, or approximately 4 months. In our study, the median diameter of the HCC in group 1 and group 2 was 3.5 cm and 8.1 cm, respectively. The median "lead-time" of group 1 over group 2 at the time of diagnosis could be roughly estimated as the ratio of 8.1 to 3.5 divided by 2 and multiplied by 4-month doubling time, i.e., 4.5 months. But the median survival of group 1 and group 2 was 22 months and 5 months, respectively (Table 3). The prolongation of the median survival by 17 months was unlikely to be solely the result of lead-time bias. The higher chance of receiving treatment because of detection of disease at an earlier stage (i.e., stage migration) probably played an important role in prolonging survival.

CONCLUSION

Screening for HCC in chronic hepatitis B and hepatitis C carriers by AFP and/or USG can identify tumors at an early stage, resulting in a higher chance of receiving treatment. Whether screening programs can also improve survival can only be studied in prospective, randomized studies.

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