ORIGINAL ARTICLE

Prospective screening increases the detection of potentially curable hepatocellular carcinoma: results in 8900 high-risk patients

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Abstract

Objectives: Historically, only 10% of patients with hepatocellular carcinoma (HCC) are diagnosed with early-stage, potentially curable disease. In this study, chronic hepatitis virus-infected patients were prospectively screened to determine: (i) the proportion of patients diagnosed with potentially curable HCC, and (ii) survival following curative therapy.

Methods: The study included 8900 chronic hepatitis virus-infected patients enrolled in a prospective screening programme, of whom 1335 (15.0%) were infected with hepatitis B virus (HBV), 7120 (80.0%) with hepatitis C virus (HCV), and 445 (5.0%) with both HBV and HCV. Screening was conducted every 6 months and included serum alpha-fetoprotein (AFP) measurement and ultrasonography. Curative treatments included liver transplantation, resection, radiofrequency ablation and/or ethanol injection.

Results: Hepatocellular carcinoma was diagnosed in 765 (8.6%) patients. Of 1602 patients with cirrhosis, 758 (47.3%) developed HCC. Curative treatment was possible in 523 (68.4%) of the 765 HCC patients. Two- and 5-year rates of overall survival in the curative treatment group were 65% and 28%, respectively, compared with 10% and 0% in the advanced disease group ($P < 0.001$).

Conclusions: Prospective screening of patients at high risk for the development of HCC increases the proportion of patients diagnosed with potentially curable disease. This may result in an increase in the number of longterm survivors. Screening strategies should focus on patients with chronic HBV or HCV infection who have progressed to cirrhosis because more than 40% of these patients will develop HCC.

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Introduction

Worldwide, hepatocellular carcinoma (HCC) remains the fifth most common malignancy, following lung, breast, colorectal and stomach carcinomas.¹ Over 600 000 new cases were anticipated in 2007.² Despite the large number of new cases annually, there remains a dearth of effective therapies for HCC and only patients in the earliest stages of disease are eligible for curative therapies such as transplantation, resection and tumour ablation.^{3–8} Early-stage HCC accounts for only 10–30% of

patients at presentation.⁹ Typically, HCC is asymptomatic in the early stages.

The vast majority of instances of HCC will arise in patients chronically infected with hepatitis B virus (HBV) or hepatitis C virus (HCV).^{2,10} Prior population-based studies have not indicated any survival advantage to patients diagnosed during the screening process, although this is controversial.^{11–14} Similarly, the cost-effectiveness of screening populations in which HBV and HCV infections are not endemic is not clear.^{15,16} Ostensibly, the goal of screening for HCC is to detect early-stage disease and thus to allow more patients to be treated with curative intent.

The present group instituted a prospective screening programme of patients with chronic HBV or HCV infection according

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to the hypothesis that the screening of this population would result in early detection of HCC and that more HCC patients would be eligible for curative therapy.

This paper updates a previously published report from the study institution.¹⁷

Materials and methods

Enrolment

Patients from the Campania region of Italy were enrolled into the study. All patients were diagnosed serologically with chronic HBV and/or HCV. Patients without chronic viral hepatitis were excluded from the study. Enrolled patients were already undergoing regular medical examinations for management of their chronic viral hepatitis. A total of 8900 patients voluntarily enrolled in this screening programme. The enrolment period extended from 1993 to 2003 and the follow-up reported here was documented to December 2008.

Each patient was required to have had a liver biopsy within a year prior to enrolment or at the time of enrolment. This biopsy was utilized to establish the underlying severity of hepatitis virus-induced liver injury in each patient. The institutional clinical and ethical review board at the G. Pascale National Cancer Institute, Naples, Italy approved this study and all of its components.

Screening

The screening programme consisted of transabdominal ultrasonography and serum alpha-fetoprotein (AFP) measurement at the time of enrolment. These two diagnostic tests were repeated at 6-month intervals for the duration of the study. Further diagnostic investigation was instituted in patients in whom an AFP value of >10 ng/ml was recorded or tumour was detected on ultrasonography. Patients in whom either or both of these findings emerged during screening underwent computed tomography or magnetic resonance imaging of the abdomen. The imaging modality was selected at the discretion of the clinician. When cross-sectional imaging resulted in findings suspicious for HCC, the diagnosis was confirmed with percutaneous fine needle aspiration biopsy. Equivocal fine needle aspiration results were confirmed with core needle biopsy.

Treatment

Once the diagnosis of HCC was established, the treatment modality was selected at the discretion of the clinician and patient based on the stage of malignant disease and the severity of the underlying chronic liver injury. Potentially curable lesions were treated with surgical resection, hepatic transplantation or tumour ablation. During the first 3 years of the enrolment period, ablation therapy included percutaneous ethanol injection or percutaneous radiofrequency ablation (RFA). After the initial 3 years, RFA alone was utilized as tumour ablation therapy. In patients treated with palliative intent, four potential modalities were considered: tran-

Table 1 Proportions of 8900 patients enrolled in a prospective screening trial for hepatocellular carcinoma with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, and severity of viral-induced liver injury

Hepatitis type	Patients, n (%)
HBV infection	1335 (15.0%)
HCV infection	7120 (80.0%)
HBV + HCV infection	445 (5.0%)
Hepatic parenchyma	
Chronic active hepatitis: mild	5073 (57.0%)
Chronic active hepatitis: severe	2225 (25.0%)
Cirrhosis	1602 (18.0%)

sarterial bland embolization; transarterial chemoembolization; systemic chemotherapy, and best supportive care.

Statistical analysis

Chi-squared or Fisher's exact tests were performed, as appropriate, to assess the associations between treatment groups and subgroups, as well as number of tumours, local recurrence and presence of lesions at follow-up. Patient characteristics were tabulated and the Kruskal–Wallis test was used to determine group differences based on age, tumour size and preoperative AFP. The Kaplan–Meier method was used to estimate the distribution of overall survival (OS) and the log-rank test was used to compare survival between groups. Estimated median OS and disease-free survival rates are reported with 95% confidence intervals (CIs). A *P*-value of < 0.05 was considered to indicate statistical significance. All analyses were performed using the Statistics Toolbox of MATLAB R2007a (MathWorks, Inc., Natick, MA, USA).

Results

Patient demographics

The mean $\pm$ standard deviation (SD) age across the entire cohort of patients ($n = 8900$) in the screening population was 58.8 ± 7.7 years. The majority of patients were men ($n = 6079$, 68.3%). Incidences of hepatitis virus infection and severity of parenchymal injury in the study population are depicted in Table 1. At the time of enrolment in the study, HCV was present in 80.0% of the screening population and 1602 (18.0%) patients had cirrhosis.

The screening programme resulted in the detection of 765 cases of HCC. The rate of false positive findings in the current screening strategy was 7.4%.

The demographics of the screening programme population are outlined in Table 2. Nearly all cases of HCC ($n = 758$, 99.1%) occurred in patients with biopsy-proven cirrhosis (Child–Pugh class A 29.2%, class B 52.1%, class C 18.7%) at the time of enrolment in the screening programme. The other seven cases of HCC developed in non-cirrhotic patients with severe chronic active hepatitis.

Table 2 Characteristics of 765 patients diagnosed with hepatocellular carcinoma (HCC) among a screening population of 8900 patients with chronic hepatitis B or C virus infection

Patients, <i>n</i> (%)	765 (8.6%)
Age, years, mean $\pm$ SD (range)	60.0 $\pm$ 9.8 (28–80)
HCC, initial screen, <i>n</i> (%)	122 (15.9%)
HCC, follow-up screen, <i>n</i> (%)	642 (83.9%)
Tumour size, cm, mean $\pm$ SD (range)	3.6 $\pm$ 1.8 (1.2–15.0)
Tumours, <i>n</i> , mean $\pm$ SD (range)	2.0 $\pm$ 1.5 (1–6)
AFP, ng/ml, mean $\pm$ SD (range)	91 $\pm$ 1840 (0.8–30 288)

SD, standard deviation; AFP, serum alpha fetoprotein.

Treatment

Over two-thirds of patients with HCC (*n* = 523, 68.4%) were treated with curative intent. Table 3 details the Child–Pugh classification of severity of cirrhosis in each treatment group. Hepatic resection was initially utilized in 225 (43.0%) patients, over half of whom were classified as having Child–Pugh class A disease. Patients with Child–Pugh class B or C disease were medically optimized and subsequently subjected to no more than single segment resection or non-anatomic wedge resection at the discretion of the treating surgeon. Radiofrequency ablation and/or percutaneous ethanol injection were the primary therapies in 271 (51.8%) patients, 76.3% of whom were classified as having Child–Pugh class B or C disease. Orthotopic liver transplantation was the initial therapy in 27 (5.2%) patients, 88.9% of whom had Child–Pugh class B or C disease. An analysis of the different groups of patients (stratified according to Child–Pugh class) shows that hepatic resection was the preferred treatment in Child–Pugh class A patients ($P < 0.001$), RFA was most frequently adopted in patients of Child–Pugh class B status ($P < 0.001$) and liver transplantation was the preferred treatment in patients of Child–Pugh class C status ($P < 0.001$).

Of those patients treated with palliative intent (*n* = 242), 196 (81.0%) were able to receive some type of therapy (transarterial chemoembolization, transarterial bland embolization or systemic chemotherapy). Nearly all of the 46 patients provided with best supportive care (*n* = 43, 93.5%) were considered to have Child–Pugh class B or C disease.

Overall survival of HCC patients

In the 765 patients with HCC, 5-year OS was 18% and 10-year OS was 2%. Patients treated with curative intent demonstrated a significantly improved OS outcome (5-year OS was 28% in patients treated with curative intent and 0% in patients treated with palliative intent; $P = 0.00001$). Ten-year OS in patients treated with curative intent was 4%. In patients diagnosed with cirrhosis at enrolment and subsequently diagnosed with HCC (*n* = 758, 99.1%), a significant survival advantage emerged for patients with Child–Pugh class A cirrhosis compared with patients with class B or C disease (5-year OS was 25% in class A patients, 15% in class

B patients and 12% in class C patients; $P = 0.00001$), regardless of the type of potentially curative treatment.

The number of hepatic tumours present at diagnosis of HCC also had an impact on OS. Patients with a solitary tumour had a 5-year OS rate of 33%, whereas patients with two or three hepatic tumours at diagnosis achieved 5-year OS of 20% ($P = 0.001$). A total of 122 (15.9%) cases of HCC were detected at the initial screening visit. The majority (62.3%, *n* = 76) of patients in whom HCC was detected at the initial screening had multiple tumours. There were no 5-year survivors among patients in whom more than three malignant hepatic tumours (41.8%, *n* = 51) or extra-hepatic disease were present at diagnosis ($P = 0.0001$, compared with patients with solitary tumours).

A comparison of patients stratified according to inciting viral aetiology showed that HBV patients with HCC achieved better OS than HCV patients with HCC (5-year OS was 21% in patients with HBV infection and 15% in patients with HCV infection; $P = 0.006$).

However, this survival advantage for HBV-infected patients was not evident when HCC patients who underwent curative treatment were evaluated (5-year OS in patients treated with curative intent was 24% in HBV-infected patients and 25% in HCV-infected patients; $P = 0.83$).

Discussion

The rationale for providing a screening programme is to offer to a target population (at high risk for the development of a certain disease) the possibility of early-stage diagnosis of asymptomatic disease that is amenable to effective therapies. Clearly, the goal of such a strategy is to increase the proportion of patients treated with curative intent and to reduce disease-specific mortality. The benefits of screening programmes must be calculated according to the prevalence and socioeconomic impact of the disease in the target population, and the economic impact of the screening strategy. Screening for HCC has been shown to be feasible, but few studies have demonstrated either community benefit or survival benefit when screening is employed.^{11–15} Studies that evaluate entire community populations regardless of risk level are likely to comprise too large a patient pool to impact on HCC outcomes economically, no matter how inexpensive the screening tools. This would be especially true in Western countries, in which endemic rates of HBV and HCV infection, albeit that they are rising, refer to only a small fraction of the population.

In the case of HCC, cost-effectiveness studies have demonstrated that an incidence of $\geq 1.5\%$ per year would justify a surveillance policy in patients with cirrhosis.¹⁸ Clear evidence is still lacking in the case of patients without cirrhosis. As a result of these concerns of economic and survival benefit, knowledge of the appropriate population to enrol in a screening programme for HCC remains elusive. In the present study, in order to maximize efforts to improve HCC outcomes, the study population purposefully included for screening only those patients with chronic active

Table 3 Child–Pugh class in 523 patients with hepatocellular carcinoma treated with curative intent

Treatment type	Class A, n (%)	Class B, n (%)	Class C, n (%)
Hepatic resection	121 (53.8%)	101 (44.9%)	3 (1.3%)
RFA or PEI	65 (24.0%)	135 (49.8%)	71 (26.2%)
Transplantation	3 (11.1%)	9 (33.3%)	15 (55.6%)

RFA, radiofrequency ablation; PEI, percutaneous ethanol injection.

HBV or HCV infections because these were considered to represent those at the highest risk. The results derived from the entire cohort of patients suggest that screening all patients with chronic, active viral hepatitis still casts too wide a net to provide a cost-effective programme because only 8% of high-risk patients develop HCC. Recent research has demonstrated that HCC can develop in patients without cirrhosis who are affected by chronic active HCV infection and bridging fibrosis (Metavir score of F3).¹⁹ This finding and the use of transient elastography may offer the possibility of stratifying different subsets of patients at risk for HCC development and provide a rationale for the proposal of targeted screening programmes in high-risk patients without cirrhosis with chronic HCV infection in order to increase the rate of HCC diagnosis in this population. There is also evidence in the literature to support the use of screening in patients affected by chronic active HBV infection, mainly in Asian populations.²⁰ Nevertheless, the results of the current study do not seem to justify the unselected screening of this class of patients in southern Italy. Improvement in the rate of early diagnosis could be achieved by selective screening of patients with chronic active HBV infection who have a relatively higher risk for HCC, such as those with alcohol problems, concomitant HCV infection or a family history of HCC. Unfortunately, clear evidence in the field is still lacking.

In the present study, a subset analysis of patients who had cirrhosis at the time of enrolment determined that screening was beneficial in terms of detection. Surveillance of only these patients with cirrhosis identified nearly all cases of HCC (99.1% in this study) in the screening programme. As 68.4% of cirrhosis patients with HCC were eligible for curative therapies at the time of detection, screening increased the pool of patients able to benefit from intervention and may potentially result in improved longterm disease-free and overall survival rates. Although the screening of properly selected patients may reduce rates of cancer-related death, its ultimate impact on longterm survival is difficult to ascertain because of the significant rate of cirrhosis-related death over time.

The false positive rate reported in the current study (7.4%) is relatively low compared with those cited in other reports in the literature.²¹ Nevertheless, the use of AFP values in the surveillance setting has been questioned. Measurement of AFP proved to add only 6–8% of detected cases compared with the use of ultrasonography alone,²² which is not enough to counterbalance the high false positive rate associated with the use of AFP levels in screening.^{22,23} In fact, only a small proportion of patients with early-stage

HCC (10–20%) present with an increase in serum AFP.²⁴ In addition, fluctuating levels of serum AFP can reflect the exacerbation of underlying liver disease or flares in viral infection, rather than HCC development.²⁵ For these reasons, the use of AFP as a serological test in the surveillance setting has not been recommended in the European Association for the Study of the Liver and European Organization for Research and Treatment of Cancer (EASL–EORTC) Clinical Practice Guidelines.²⁶ Several alternative markers such as des-gamma carboxyprothrombin or AFP-L3 have been studied, but have failed to show any superiority over AFP.^{27,28} Currently, there is still a need for reliable serological markers to be used in the surveillance setting as those available have failed to offer substantial advantages over simple ultrasound surveillance and probably carry an unjustified increase in the costs of screening programmes.^{22,23} The current study was designed in the early 1990s, when the role of AFP was probably overestimated.

This update of this prospective study reveals that this screening programme was able to detect HCC that was treatable with curative intent in 68.4% of the patients diagnosed and adds value to the mid-term follow-up previously reported.¹⁷ However, HCC remains difficult to treat with the armamentarium of therapeutics currently available (5-year OS in HCC patients treated with curative intent in the present study was 28%). Clearly, the biology of the disease is not impacted by early detection. The survival outcomes reported in the present study are in line with those reported in historical series^{29–33} and should be analysed in a manner that takes into account the high percentage of patients presenting with multiple tumours in the setting of advanced cirrhosis (Child–Pugh class B or C disease). Underlying hepatic parenchymal disease is likely to have contributed to the poor rate of OS in patients treated with curative intent. Ostensibly, the main benefit of screening may refer to the ability to detect more patients with early-stage HCC who are eligible for resection, ablation or transplantation.

The disappointing results in patients treated with curative intent mitigate the benefits of the improved rate of early detection in the screening programme. Because liver transplantation treats both HCC and underlying chronic liver disease, it should be considered the optimal treatment for hepatitis virus-induced cirrhosis in patients diagnosed with early-stage HCC in a prospective screening programme.³⁴ It may be that OS would improve in a population similar to that studied here if the use of liver transplantation was more extensive, both as a first-line treatment and as a secondary option after initial resective therapy.^{35,36} Unfortu-

nately, the paucity of donor organs continues to limit the potential positive impact of this approach.

Previous research indicates that in a general population only 10–30% of patients presenting with HCC are eligible for curative therapy.^{9,33} On the assumption that only 10% of early-stage disease is detected in an unscreened population, the fact that 68% of the HCC patients detected in the present study population were found to have potentially curable disease implies that the screening programme enabled as many as 446 more patients to receive potentially curative treatments than would have done in an unscreened population of the same size. If the detection rate of potentially curable lesions in an unscreened population is 30%, the 68% detection rate afforded by the present programme reflects the identification of an additional 294 patients.

The update of follow-up reported here supports proposals for the instigation of screening strategies in patients with chronic active hepatitis in the setting of underlying cirrhosis. Screening broader populations in Western nations is unlikely to increase the detection rate of potentially curable HCC and may be cost-prohibitive.

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Conflicts of interest

None declared.

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