Screening for hepatocellular carcinoma: survival benefit and cost-effectiveness

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Background: The prognosis for patients with hepatocellular carcinoma (HCC) is poor by the time they present with symptoms. This review examines the usefulness of screening programs from the perspectives of survival benefit and of cost-effectiveness.

Materials and methods: Articles were searched through Medline for screening, HCC, treatment and cost-effectiveness.

Results: Both ultrasonography and α-fetoprotein testing have a low sensitivity for detecting HCC, although a combination of the two investigations can increase sensitivity. They remain the main screening methods because they are convenient, non-invasive and easily assessable. Though earlier studies fail to show improvement in patient management and survival by screening, more recent studies demonstrate that screening can increase the chance of curative treatment and, more importantly, improve survival even after the adjustment of lead-time bias. This is probably due to the improvement in medical treatment and technology. The cost per tumor detected for a region is inversely proportional to the tumor incidence of that region.

Conclusions: In countries with a low prevalence of HCC, screening for HCC is not cost-effective. But in countries with a high prevalence of HCC, especially when screening is directed at older patients with a high risk of HCC, screening programs for HCC become much more cost-effective.

Key words: α-fetoprotein, cost-effectiveness, hepatocellular carcinoma, survival, ultrasonography

Introduction

Hepatocellular carcinoma (HCC) ranks as the fourth most common cancer in the world and is responsible for nearly a quarter of a million deaths annually [1, 2]. The age-specific incidence is estimated to be around 3 and 80 per 100,000 people in North America and China, respectively [3]. A recent study shows that the incidence of HCC is rising and that age-specific incidence has shifted towards younger people in the United States over the past two decades [4]. The survival of patients is extremely poor by the time they present with symptoms related to the tumor [5]. The median survival for patients with symptomatic HCC is around 3–4 weeks [6]. One of the main issues concerning HCC is whether screening for HCC can improve patient survival.

According to the World Health Organization (WHO), there are 10 criteria for cost-effective screening programs [7]: (i) the condition should be an important health problem; (ii) accepted treatments are available; (iii) facilities for diagnosis and treatment are available; (iv) the condition can be recognizable in the latent/early stage; (v) suitable tests for screening are available; (vi) the screening tests are acceptable to the population; (vii) the natural history of the condition is well understood; (viii) agreed policy on whom to treat is available; (ix) the cost of diagnosis and treatment should be economically balanced with the whole medical expenditure; and (x) case-finding should be continued. Screening for HCC basically fulfils nearly all the above criteria, with the exception of cost-effectiveness, which is still under debate.

This review will address the following three main issues concerning screening programs for HCC. The first is to determine the specificity and sensitivity of the screening tests, and the interval of surveillance. The second is whether screening for HCC has any impact on patient management and survival. If the answer to this is positive, the final issue is whether screening for HCC is cost-effective.

Screening methods: ultrasonography and α-fetoprotein

The two most common tests used for screening are ultrasonography of the liver and serum α-fetoprotein (AFP). Ultrasonography can detect lesions as small as 1 cm inside the liver; however, it is often difficult to distinguish HCC from other conditions, e.g. hemangioma and regeneration nodules in patients with cirrhosis. According to one study from North America involving 538 subjects, the sensitivity and specificity for ultrasonography are 71.4% and 93.8%, respectively [8]. The positive and negative predictive values are 15.1% and 98.4%, respectively. However, the false positive rate is as high as 82.5%. The sensitivity according to our own previous...
study involving 306 subjects is comparable, at 81% [9]. Using ultrasonography as the sole test for screening of HCC may miss tumors in >20% of the patients. It will also frequently lead to a false alarm. Finally, the sensitivity of ultrasonography is largely dependent on the competence of the ultrasonographists.

AFP testing is commonly used as a screening test for HCC because it can be performed easily in hospital laboratories. One of the problems with AFP is in defining the cut-off level for the diagnosis of HCC. Defining >500 ng/ml as a diagnostic level for HCC is unsatisfactory because many patients with early HCC have the AFP levels well under 500 ng/ml [10, 11]. Furthermore, patients with chronic hepatitis B or C with reactivation sometimes have AFP levels >500 ng/ml.

Trevisani and his colleagues in Italy conducted a case–control study of 170 HCC patients and 170 matched patients with chronic liver disease [12]. It was found that the higher the AFP level chosen as cut-off value, the higher the specificity and the lower the sensitivity. An AFP level of 16 ng/ml was calculated to have the best discriminating power after balancing sensitivity and specificity. An AFP level of 20 ng/ml (the upper normal range) was chosen as the cut-off level in the study since the specificity and sensitivity are very near to those for 16 ng/ml. Using an AFP level of 20 ng/ml as cut-off, specificity and sensitivity are 60% and 90.6%, respectively. The positive and negative predictive values are 25% and 97.7%, respectively, assuming 5% to be the prevalence of HCC in the study population. For patients without hepatitis B or C infection, the positive predictive value becomes 100%.

According to another study involving 290 Chinese patients with chronic hepatitis B infection, among 44 patients with AFP levels of >20 ng/ml, only six (14%) had HCC [13]. The remaining 18 (41%) and 20 (45%) patients had AFP elevation due to hepatitis B exacerbation and unknown causes, respectively. Therefore, even when an AFP of just above the upper limit of normal is used as a cut-off level, a substantial proportion of HCC will still be missed with a sensitivity of only 60%, while the positive predictive value (14–25%) is still, surprisingly, very low. It has been documented that ultrasonography screening is superior to AFP for the detection of HCC [14, 15]. According to Bolondi et al., elevation of AFP level, even to >200 ng/ml, during surveillance does not increase the detection rate of HCC in the absence of nodules visible with ultrasonography [16]. Some clinicians regard AFP to be of no use for screening, and only useful for the confirmation of nodules detected by imaging [17]. However, according to a study conducted in Italy by Tremolda et al., although the sensitivity of combining ultrasonography and AFP is 100% [18], the combination of AFP and ultrasonography as screening tools is not generally used in many countries due to the following reasons: (i) the sensitivity of ultrasonography in detecting minute HCCs (<3 cm) is high, and the diagnostic efficiency of ultrasonography equipment continues to improve; (ii) >80% of new solid nodules detected by ultrasonography are malignant [16, 19]; (iii) the sensitivity and positive predictive value of AFP are very low for minute HCCs; and (iv) additional AFP testing increases direct and indirect costs of screening through expensive additional diagnostic interventions, which may also lead to unwarranted patient anxiety [12, 20]. Only randomized controlled trials comparing the use of ultrasonography alone or in combination with AFP to survey patients with chronic liver disease can resolve the issue.

Another practical issue in screening for HCC is deciding the optimal interval of surveillance. The interval between screening should not be too short since the screening procedures would fail to identify tumors at a very early stage, e.g. <1 cm in size for ultrasonography. On the other hand, the surveillance interval should not be too long, thus allowing tumors to grow to an extent precluding curative treatment. The optimal surveillance interval is obviously related to tumor growth rate. Surgical resection and other modalities of treatment (e.g. radiofrequency ablation, percutaneous alcohol injection) are best in patients with tumors <3 cm in size. According to a study in Chinese patients with HCC, the most rapidly growing HCCs take ∼4.6 months to grow to 3 cm [21]. Therefore, theoretically the optimal interval between screening is around 4–6 months. However, according to a large population study conducted by McMahon et al., a screening program with 61–79% of the screened population having annual AFP surveillance is still effective [22]. Another study conducted by Trevisani et al. shows that there are no differences in terms of the feasibility of treatment and survival between patients who have semi-annual and annual surveillance [23]. Mathematical analysis of tumor growth by Kang et al. also shows that annual surveillance is the most cost-effective strategy [24]. Therefore, the relatively minor advantage in terms of earlier cancer detection by a semi-annual screening has to be balanced with the marked reduction of direct and indirect costs offered by annual surveillance. Once again, randomized controlled trials to compare the cost-effectiveness of semi-annual and annual screening are the only way of resolving the issue.

**Effect of screening on patient management and survival**

To prove conclusively whether screening programs are effective in improving patient management, prospective randomized trials comparing the outcome of HCC patients with and without screening are required. However, there are some ethical and practical obstacles to the performance of such trials. It may not be deemed ethically justifiable to recruit patients into a study arm with no screening procedure for HCC. Also, in actual practice, a substantial number of patients randomized to have no screening procedures will probably have the screening done on their own initiatives because of the easy availability of such procedures. To date, there is only one prospective study on screening for HCC [25]. The majority of the data come from non-randomized clinical trials. Some trials are designed to compare the outcome of patients who undergo screening with historical controls who did not have screening. The major problem with this type of trial is that the outcome of patients would be affected by the improvement and advances in medical treatment with time. This does not make comparison of patient outcome with historical controls ideal. Other trials try to address the efficacy of screening by comparing the outcome of patients who undergo screening with patients who present with symptomatic HCC. These trials are beset by two problems: lead-time bias is introduced by the earlier diagnosis of
HCC using screening; and length bias is introduced because screening procedures tend to identify slower growing tumors, the more rapidly growing tumors being more likely to present with symptoms between screening procedures.

According to an early longitudinal study involving 447 Italian patients with cirrhosis, patients presenting with HCC paradoxically had a higher rate of resection compared with patients with HCC diagnosed by screening (44.8% and 13.8%, respectively; $P = 0.027$) [26]. For those undergoing resection ($n = 12$), 1-year survival was 67% and the recurrence rate was 60%. The authors concluded that a screening program does not increase the detection of potentially curable tumors. A subsequent study from the same group found that screening was particularly inadequate for early detection of multinodular HCC [27].

Similarly, another study involving 118 French patients showed that screening programs cannot effectively identify potentially resectable HCC [20]. However, these findings are not confirmed by other studies from the same time period [28–32]. In the sole prospective, randomized, controlled study from Shanghai, involving >17800 hepatitis B patients [25], patients with screening for HCC had a higher proportion of tumors diagnosed at the subclinical stage and undergoing surgical resection compared with the control group [76.3% and 0% ($P <0.01$), and 70.6% and 0% ($P <0.05$), respectively; both $P <0.01$]. None of the patients with HCC in the control group survived past 1 year of follow-up, whereas the first- and second-year survival rates were 88.1% and 77.5%, respectively ($P <0.01$), for patients with HCC diagnosed using screening. These positive findings are indeed confirmed by more recent studies in the last 5 years. Unfortunately, the more recent studies all suffer from the problems associated with non-randomized trials as outlined above.

A population-based study involving 1487 Alaskan patients with hepatitis B has been published [22]. By using AFP testing as a screening tool, 100 patients were found to have elevated AFP, of which 32 had HCC. The cumulative survival was significantly better for patients who had the HCC diagnosed by screening compared with the historical controls. The improvement in survival was still significant when a 2-year period was added to the control analysis to correct for lead-time bias. The authors concluded that screening with half-annual AFP could significantly prolong survival for patients when compared with historical controls.

Another study conducted in Hong Kong involving 306 patients compared the outcome between 142 patients with HCC diagnosed using screening procedures and 164 patients presenting with symptomatic HCC for the same time period [9]. Patients with HCC diagnosed by screening had a better liver reserve compared with patients with symptomatic HCC. More importantly, compared with patients with symptomatic HCC, patients with HCC diagnosed by screening had a lower median AFP level (825.5 compared with 111 ng/ml, respectively), smaller median tumor size (8.1 compared with 3.5 cm, respectively), and lesser chance of bilobar involvement, diffuse HCC, portal vein thrombosis and metastasis. These findings indicate that screening can identify tumors at an earlier stage (stage migration). Furthermore, the favorable parameters led to a higher chance of receiving treatment in patients with HCC diagnosed by screening compared with patients presenting with symptomatic HCC [surgical resection: 26.8% versus 7.9%, respectively ($P <0.0001$); and transcatheter arterial chemoembolization (TACE): 45.1% versus 32.3%, respectively ($P = 0.03$)]. There was also a significant improvement in cumulative survival for patients with HCC diagnosed by screening, even after a theoretical adjustment for lead-time bias.

Farinati et al., in a study of 280 Italian patients, showed that patients with HCC diagnosed by screening had an earlier tumor staging compared with unscreened patients, resulting in a mean gain in survival of 16 months, even after 10 months was added to the survival for the unscreened patients [33].

In the study conducted by Trevisani et al., described above, 821 Italian patients with HCC of known staging (370 diagnosed by screening and 451 presenting with symptoms) were recruited. It demonstrated again that screening identified tumors at an earlier stage and increased the chance of ablative treatment and transplantation [23], even though half of the unscreened patients had the HCC detected incidentally and in a subclinical stage. Screening also improved the 5-year survival of the patients. In another study involving 91 Asians in Hawaii, asymptomatic patients with HCC diagnosed by screening had a better survival compared with patients who presented with symptoms [34]. A more recent large population study of 1827 patients conducted by Caturelli et al. also shows that ultrasonography screening can detect HCC at an early stage [19].

The differences in the results of the initial and more recent studies may be partly related to the continued improvement in medical treatment. They may also be due to the differences in the study populations, with different causative agents for HCC. The current available data seem to indicate that implementing screening programs improves the outcome for patients in terms of increasing the chance of successful treatment and, very importantly, prolonging survival. However, according to our previous study and the study by Trevisani et al. [9, 23], screening does not improve the survival of patients with a poor liver reserve, since treatment of HCC is unsatisfactory and there is a high cirrhosis-related mortality. The only viable option for these patients is liver transplantation. Therefore, unless liver transplantation can be offered, patients with poor liver function should be excluded from screening programs. As a good general rule, only patients who can undergo effective treatment for early HCC should be included in any surveillance program.

### Cost-effectiveness of screening

Whether screening can be implemented in particular countries depends ultimately on the decision of the health care providers after analyzing the cost-effectiveness of the screening programs. According to our study in Hong Kong [9], the annual costs of detecting one HCC and one treatable HCC are (US)$1167 and $1667, respectively. However, according to a study conducted by Sarasin et al. in Switzerland [35], the cost-effectiveness ratios are in the range of $48 000–$284 000 for each additional life-year gained, a much higher figure than in our study. For patients with a predicted cirrhosis-related survival rate >80% at 5 years, screening could increase life expectancy by 3–9 months, depending on
the age of the patients, the cancer incidence (1.5–6% per year) and the survival rate after surgery (40–60% at 3 years). The cost-effectiveness ratios then become $26000–$55000 for each additional life-year gained. According to a study by Bolondi et al., in which 61 out of 313 Italian patients with HCC were identified by screening, the median survival (30 months) was significantly better than that of 104 unscreened patients with HCC (15 months; \( P = 0.02 \)), although all the HCCs of the unscreened patients were detected incidentally [16]. The cost for screening each treatable HCC is US$17934 and the cost per year of life saved is US$112993. The authors conclude that it is not cost-effective to screen for HCC, although they concede that the cost-effectiveness of screening for HCC may depend on the prevalence of disease and the resources of the particular country. Since the cost per tumor detected is inversely proportional to the tumor incidence [24], screening is more cost-effective in regions where HCC is common, e.g. southeast Asia and Africa, where the prevalence of hepatitis B infection is high. Bruix and Llovet comment that the effect of a screening program may be different if done on a community basis rather than a hospital basis [36]. For screening performed on a community basis, the risk of HCC is expected to be low, but the liver function of the patients should be better, allowing for more curative treatment. Community-based screening will increase the chance of curative treatment but cost-effectiveness will be altered. Finally, cost-effectiveness may be improved by restricting the screening programs to older patients. The median age for the development of HCC in Asian patients with chronic hepatitis B is 55–60 years [37, 38]. The issue of cost-effectiveness should be calculated depending on the local prevalence of HCC and the chance of receiving treatment in different age groups in order to identify the group of patients with the highest benefits and lowest cost.

Conclusions

The sensitivities of both ultrasonography and AFP to detect early HCC are not satisfactory. Despite their limitations, studies using one or both screening methods show that screening can detect HCC at an earlier stage, increase the chance of receiving curative treatment, and improve survival. In countries where HCC is of low prevalence, screening for HCC may not be cost-effective. The cost-effectiveness should increase for countries with a high prevalence of HCC, especially if the screening is limited to well defined groups of patients, such as patients with chronic hepatitis B and C over the age of 40–50 years. In areas with low HCC prevalence, selected patient groups should also be screened. These should include patients with cirrhosis of the liver due to hepatitis B or C, alcohol, or genetic hemochromatosis. Screening of high-risk groups for early HCC should be an important health consideration worldwide.

References