Utility of screening for hepatocellular carcinoma among cirrhotics

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Abstract

Background Screening known cirrhotics for hepatocellular cancer (HCC) has long been a contentious topic. Studies to date have failed to conclusively prove or disprove the validity of α -fetoprotein (AFP) and hepatic ultrasound as screening mechanisms for HCC among cirrhotics, particularly in the American population. It is not clear whether these screening mechanisms provide any benefit in terms of reduced morbidity and mortality.

Methods The study examined all patients with liver cirrhosis who developed HCC at the Michael E DeBakey VA Medical Center between 1999 and 2005. Those who were screened with AFP and/or imaging (either ultrasound, triphasic liver protocol CT or MRI) were compared with those patients who were not screened at all. The screened and unscreened patients were compared in terms of Barcelona Clinic Liver Cancer (BCLC) stage at the time of diagnosis.

Results Statistical analysis revealed a significant difference between the screened and unscreened groups in terms of BCLC stage at diagnosis, with the unscreened group being diagnosed at later stages than the screened group. Of the 155 patients observed, 26 were appropriately screened, and 129 were not. The BCLC stages at diagnosis for the two groups were as follows: screened patients: 34.6%, 38.5%, 7.7% and 19.2% for BCLC stages A, B, C and D, respectively; unscreened patients: 12.4%, 24.8%, 27.1% and 35.7% for BCLC stages A, B, C and D, respectively. The different trend in the two groups was found to be statistically significant, with a p value of 0.004. Furthermore, among the screened group, no particular method of screening (AFP vs imaging vs combination) was shown to be superior to another.

Conclusions Screening for HCC among cirrhotics using AFP and/or imaging every 6 months does correlate with HCC diagnosis at an earlier BCLC stage, thus portending better treatment options and improved prognosis. Therefore, screening all known cirrhotics for HCC may lead to decreased mortality.

Introduction

Worldwide, hepatocellular cancer (HCC) poses a considerable health risk; it is the fifth most common cancer in the world.¹ In the USA, according to SEER (Surveillance, Epidemiology and End Results) data, HCC affects nearly 20 000 people each year. However, this number is quickly increasing, making HCC more of a pressing concern within the American population. Both the incidence and mortality of HCC in the USA has doubled over the past 40 years, and it is expected to double again in the next 10 years.^{2,3} Furthermore, HCC typically has an extremely grave prognosis by the time it is diagnosed. In the USA, SEER data report that most patients die within 1 year of diagnosis, and 5 year survival is poor at less than 10%. If there were screening methods which could diagnose HCC sooner, many more effective therapeutic options would be available, thus improving prognosis. For example, liver transplant for stage I and II disease in an appropriately selected population yields 5 year survival rates of 70–75%.⁴

Clearly, the at risk population who would benefit the most from screening must first be accurately defined. Among those with chronic compensated cirrhosis, there is a 3–4% annual incidence of HCC.⁵ This high risk population has been studied much more extensively in Asia than in North America. In a large randomised trial conducted in China with 18 816 patients with chronic hepatitis B virus (HBV) infection or chronic hepatitis, one group was screened with α -fetoprotein (AFP) and ultrasound every 6 months while the other group was not routinely screened. Although the screened group only received 58.2% of the screening, the study found significantly improved HCC mortality in the screened group. Among those who

developed HCC, 5 year survival was 46.4% in the screened group and 0% in the unscreened group. The mortality ratio was 0.63.⁶ However, these results are not necessarily applicable to patients with cirrhosis in the USA because of the different underlying aetiology of cirrhosis in Asia compared with the USA. In the USA, alcohol and hepatitis C are responsible for the majority of liver cirrhosis cases. However, in the Asian population, HBV plays a much more significant role, with up to 80% of HCC patients positive for hepatitis B surface antigen, and approximately 40% who do not have cirrhosis.⁷ While both HBV and hepatitis C virus (HCV) carry an approximately 3–5% annual risk of HCC when associated with cirrhosis, it is known that HBV can progress to HCV in the absence of cirrhosis. Thus ongoing HBV replication is a significant risk factor for HCC, although not necessarily HBV related cirrhosis.⁵ The annual incidence of HCC arising from alcohol related HCC is slightly less at 1–4%.⁵ These differences within the cirrhotic population at risk for HCC make the question of screening likely to be different in the Asian versus the American population. Studies to date regarding HCC screening among cirrhotics have been conflicting and largely inconclusive, particularly those carried out in the American population. It is not clear whether the sensitivity and specificity of AFP and ultrasound are sufficient to lead to earlier diagnosis of HCC and decreased mortality among cirrhotics.

Furthermore, AFP has long been a confounding factor in the question of HCC screening. While highly

elevated AFP (>400 ng/ml) has high specificity for detecting HCC, lower indeterminate ranges may be indicative of either hepatitis flare and liver regeneration or HCC.⁸ Also, approximately 10–20% of HCCs do not overexpress AFP, resulting in a sensitivity of only 0–64% for AFP values >400 ng/ml.⁵

Routine liver ultrasound as a screening measure is also controversial because it is fraught with so much variability between observers. However, it is, nonetheless, the least expensive and invasive of the radiographic techniques. Sensitivity ranges from 11% to 99%, and specificity from 95% to 100%.⁵

Methods

Using the computerised database of the Michael E DeBakey VA Medical Center, all patients between 1999 and 2005 who met the following two criteria were studied: (1) those who had HCC and (2) those with known cirrhosis from either chronic hepatitis B or C, or from heavy alcohol use. All subjects were over 18 years of age, and their diagnosis of HCC had to postdate the diagnosis of cirrhosis. Patient data were kept entirely confidential, accessible only to those investigators actively involved in the study, and the protocol was approved by the Institutional Review Board of Baylor College of Medicine as well as the VA Research and Development Committee. The diagnosis of HCC was defined as either a pathological diagnosis based on biopsy data or a clinical diagnosis according to the American Association for the Study of Liver Diseases (AASLD) guidelines (see figure 1). Namely, those patients with known cirrhosis who have liver

Figure 1 American Association for the Study of Liver Diseases (AASLD) guidelines for the diagnosis of hepatocellular cancer (HCC).⁹ AFP, α -fetoprotein.

masses 1–2 cm in size and a typical vascular pattern for HCC on two dynamic imaging studies (eg, triphase CT scan and MRI) are considered to have HCC. Also, those cirrhotics with liver lesions >2 cm, a typical vascular pattern on one dynamic imaging study or AFP >200 are also clinically diagnosed with HCC.⁹ This method is particularly practical because HCC is notoriously difficult to diagnose by biopsy, with as high as a 10–20% false negative rate on biopsy for lesions greater than 2 cm, and there is a potential risk for tumour seeding when needle biopsy is performed.^{10 11} In addition, patients with cirrhosis may have a coagulopathy that increases the risk of bleeding following a biopsy procedure.

Patients were considered to have viral hepatitis if they had a serological diagnosis of hepatitis B and/or C, as indicated by hepatitis B surface antigen or anti-HCV antibody positive for more than 6 months, intermittent or persistent elevation of transaminases, and serum HBV DNA >100 000, or detectable HCV RNA. For the diagnosis of alcoholic liver cirrhosis, patients were required to have a history of heavy drinking (defined in this study as drinking alcohol at least 4 days of the week for more than 5 years). Finally, all patients had cirrhosis, proven by biopsy, or by typical findings on radiology and physical examination.

The following subjects were excluded: (1) those with active primary cancer other than HCC, (2) those who were pregnant during the time of the testing in question and (3) those with non-seminomatous germ cell tumours, as the latter two conditions could give false positive rises in the AFP level.

A total of 205 charts were reviewed; 155 patients met all of the inclusion criteria and were included in the final analysis. Several pieces of information were obtained from each patient's chart, including demographic data, laboratory and radiology data to classify their cirrhosis, AFP values, etc. A full list of the parameters recorded for each patient is included in table 1.

Then, based on these data, patients were initially divided into two groups: screened and unscreened. Those in the screened group met one or both of the following criteria: (1) screening AFP checked 6–12 months before the diagnosis of HCC, in the absence of patient signs or symptoms; and/or (2) imaging study of the liver (ultrasound, CT or MRI) performed 6–12 months before suspicion of HCC. The interval of at least 6 months was chosen because most recommendations for screening cirrhotics suggest biannual testing for optimal early cancer detection. Furthermore, if AFP was only checked because there was an abnormal mass on imaging, or because the patient exhibited symptoms concerning for HCC (eg, weight loss or jaundice), then those patients were included in the unscreened group because the testing served more as a diagnostic aid rather than a screening tool. In the event that an AFP >20 was not

Table 1 Data obtained for each patient

Name
Last 4 digits of social security number
Date of death
Biopsy histopathology
Age
Race
Gender
Drinking history
Viral hepatitis serology
WHO performance status
Bilirubin
Albumin
International normalised ratio
Ascites
Encephalopathy
Child–Pugh cirrhosis class
Number, size of liver nodules per imaging
Barcelona Clinic Liver Cancer stage
α -Fetoprotein values and dates
Ultrasound, CT or MRI data

followed-up appropriately with imaging and biopsy if warranted (this occurred in rare cases because of other pressing comorbidities which posed a greater threat at the time), the case was also included in the unscreened group because the appropriate screening guidelines were not followed. The selection of 20 for the AFP cut-off was chosen based on AASLD guidelines.⁹ Similarly, in the case of imaging, ultrasound, conventional CT scan, triphase CT or MRI had to have been done without the preceding suspicion of HCC in order to be considered a screening test. However, it should be stated that even if the imaging study was performed for an entirely different reason other than HCC screening (eg, to workup another suspected cause of illness), it would still be counted in the screening group even though it was not intended as a screening test.

Statistical analysis

The screened and unscreened groups were then compared with each other in terms of Barcelona Clinic Liver Cancer (BCLC) stage at diagnosis, using the t test and the χ^2 test. Next, those in the screened group were further subdivided into those who were screened by AFP only, imaging only, or both AFP and imaging. These three groups were compared with each other to determine differences in stage at diagnosis when using different screening modalities. Finally, in order to prove that the screened and unscreened groups were not only different from each other, but had opposing trends, we ran the Mantel–Haenszel χ^2 test on the two groups. All statistical analyses were performed using SPSS for windows (V.12.0) and Statistical Analysis Software.

Results

Of the 155 patients included in the study with cirrhosis and HCC, only 26 (17%) were screened, leaving 129 patients who were not appropriately screened. The screened and unscreened groups were compared in terms of several baseline characteristics such as age, race, gender, hepatitis serology, drinking history and Child–Pugh cirrhosis class. In all respects, the two groups were found to have no significant differences, as shown in table 2. However, the groups were found to be significantly different from each other in terms of BCLC stage at diagnosis. As figure 2 shows, it is clear that there are more patients in stages A and B in the screened group; conversely, there are more patients in stages C and D in the unscreened group. The different trend in the two groups was found to be statistically significant ($p=0.004$). A Mantel–Haenszel χ^2 test was performed on the two groups, which proved that there was a general trend for the screened subjects to be diagnosed at earlier stages and the unscreened group to be diagnosed at later stages ($p=0.0014$).

The screened group was divided into three subgroups: those screened with AFP only, those screened with imaging only and those screened with AFP and imaging. There was no significant difference among the three subgroups in terms of BCLC stage at diagnosis

($p=0.25$), indicating that no single screening method is superior to another in diagnosing HCC earlier. Thus any type of screening (AFP, imaging or a combination of both) is potentially effective at diagnosing HCC at an earlier stage within the cirrhotic population. The number needed to screen in order to diagnose HCC at stage A or B rather than C or D is 3 (95% CI 2 to 6).

Discussion

High risk patients who were screened for HCC clearly were diagnosed at an earlier BCLC stage (stage A or B) compared with those patients who were not screened. Earlier BCLC stage at diagnosis allows for more treatment options and better prognosis, as shown in figure 3. When HCC is diagnosed in the early stage, it is amenable to resection, liver transplant or locoregional ablative therapies. The AASLD recommends using the BCLC staging system because it essentially combines the tumour extent and the patient's liver function impairment in order to classify the patient as a certain stage. Then, this stage dictates which treatment options, if any, are most appropriate for this particular patient, and it also offers an idea of the patient's prognosis.¹² Among those in the unscreened group, the majority of patients were diagnosed at stage C or D, leaving little, if any, meaningful treatment options.

However, it should be noted that there may have been selection bias in this group of patients. The screened group contained 38.5% Child's class A patients while the unscreened group had only 17.2%. Conversely, there were 19.2% Child's class C patients in the screened group compared with 33.6% in the unscreened group. Physicians may have been more likely to aggressively screen healthier patients with high functionality, leading to some bias in the selection of the groups. However, it should also be pointed out that the BCLC only screens cirrhotics for HCC if they are candidates for treatment. Thus, Child's class C cirrhotics are generally not screened because they are usually offered only symptomatic treatment according to the BCLC schema. Thus it may be appropriate that the majority of the screened patients had Child–Pugh class A cirrhosis.

It should also be pointed out that in any screening study, certain biases inevitably come into play. Namely, lead time bias is a confounding factor. Although these patients may have been diagnosed at an earlier BCLC stage, this study does not prove that this earlier diagnosis actually leads to prolonged survival or higher rate of cure. Also, there may be some length time bias in which the slower growing cases of HCC are caught on screening more often because they are present for a longer period of time and are more indolent in their growth. Finally, in this particular study, gender bias may have played a role. In the entire group of 155 patients, there was only one female patient as most of the veterans were males. From this study, it is unclear whether females would benefit from HCC screening.

Table 2 Baseline characteristics of screened and unscreened patients

Patient characteristic	Screened	Unscreened	p Value
Patients (N)	26	129	0.0001
Age (years)	62.8	60.9	0.364
Race (%)			
Black	26.9	31.0	0.146
Hawaiian	3.8	0.0	
Hispanic	11.5	15.5	
White	57.7	53.5	
Gender (% male)	100	99.2	0.652
Hepatitis (%)			
B	3.8	6.2	0.566
C	3.8	11.6	
B and C	65.4	57.4	
None	19.2	21.7	
Unknown	7.7	3.1	
Drinking (%)			
None or quit >5 years ago	46.2	37.2	0.731
Current heavy	53.8	51.9	
Occasional	0	10.9	
Both alcoholic and hepatic cirrhosis (%)	16	40	
Cirrhosis (Child's) (%)			
Class A	38.5	17.2	0.086
Class B	42.3	49.2	
Class C	19.2	33.6	

BCLC stage by screening status

Figure 2 Barcelona Clinic Liver Cancer (BCLC) stage at diagnosis.

Figure 3 Barcelona Clinic Liver Cancer staging system.⁴ CLT, cadaveric liver transplantation; HCC, hepatocellular cancer; LDLT, living donor liver transplantation; PEI, percutaneous ethanol injection; PST and PS, performance status; RF, radio frequency ablation.

If it is known that screening will not affect the outcome of a person's disease, then the cost, time and overall stress to the healthcare system likely is not warranted. Thus some recommendations suggest not screening Child's class C cirrhotics as they will generally not be candidates for curative therapy. However, all cirrhotics were included in this study regardless of Child's class. As an initial data gathering and hypothesis generating study, we felt that it was appropriate to include all cirrhotics in order to better understand the differences between the groups.

Another issue to consider in this study is the unfortunately low number of patients who were screened. Of 155 patients included in the study, only 17% were screened. This was due to many factors, including the lack of strong evidence to support biannual screening within the American cirrhotic population, as well as the difficulty in follow-up of many of the patients.

Generally speaking, those with liver cirrhosis tend to have multiple other medical and social problems, making regular healthcare a difficult goal to attain. Although the US veteran population in this study has the unique advantage of full medical coverage and no concerns about co-pays, many patients in the study were noted to miss their regularly scheduled appointments. Many never sought medical attention until they were so decompensated that they were beyond the point of treatment. This would likely also be a problem in the implementation of biannual screening for cirrhotics in America. However, with the appropriate outreach and education programmes, screening for HCC among cirrhotics could very well prove to be a beneficial policy.

While these findings are highly suggestive that HCC screening with AFP and imaging may be a useful tool for American cirrhotics, more studies are necessary in

this field. For example, although the AASLD guidelines for HCC diagnosis are widely accepted and clinically reasonable, some centres would not resort to such a complicated and limited resource as liver transplant unless the patient had an established tissue diagnosis. This raises the question of cost and risk. Will the diagnosis of HCC based on history and imaging alone be enough to warrant treatment for HCC, including liver transplant? If not, then screening all cirrhotic patients would require biopsies in many more cases, increasing the cost and risk of screening. Furthermore, this study did not look at the cost effectiveness of HCC screening, which is an important component of any screening proposal. Another study has shown that the estimated cost for each quality adjusted life year gained through HCC surveillance is between US\$35 000 and US\$45 000.^{13,14} This is considered to be acceptable, as a screening intervention which costs US\$50 000/year of life gained is considered cost effective.⁹ Finally, these data do not prove that screening will affect survival. A randomised, prospective study in the American population carried out over a number of years looking at the overall survival of cirrhotics who are screened and unscreened would be very enlightening. Such a study would be able to compare survival, cancer detection and stage at detection. For now, we believe that the present study lends weight to the idea of screening cirrhotics routinely with AFP and ultrasound.

What is already known on this topic

- Incidence of hepatocellular carcinoma (HCC) is increasing rapidly in the USA.
- Early detection is critical in order to offer curative therapy.
- It is unclear whether screening cirrhotics in the US population leads to diagnosis of HCC at an earlier stage.

What this study adds

- Routine screening with α -fetoprotein (AFP) and hepatic ultrasound in this study group did, in fact, lead to diagnosis of HCC at an earlier stage compared with unscreened patients.
- Neither AFP measurement nor hepatic ultrasound is superior as a screening method.
- Cirrhotic patients at high risk of developing HCC likely do benefit from routine screening with AFP and/or hepatic ultrasound.

How might it impact on clinical practice in the foreseeable future

- US physicians should routinely screen known cirrhotic patients for HCC with AFP or hepatic ultrasound every 6 months.
- Ideally, HCC will be more commonly detected at earlier stages, thus allowing for improved treatment modalities and hopefully increased cure rate.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Ethics approval The study was approved by the Institutional Review Board of Baylor College of Medicine as well as the VA Research and Development Committee.

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