ORIGINAL ARTICLE

Prospective Study

Hepatocellular carcinoma screening and surveillance in 2293 chronic hepatitis B patients in an endemic area

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Abstract

AIM
To determine the role of screening and surveillance of hepatocellular carcinoma (HCC) in treatment-naïve chronic hepatitis B (CHB) patients.

METHODS
We recruited 2293 CHB patients (both males and

females; aged 20-65 years). All patients were screened and underwent surveillance using abdominal ultrasonography (AUS) and serum alpha-fetoprotein (AFP) assay every 6 mo. The diagnosis, staging and treatment of HCC followed the American Association for the Study of Liver Diseases practice guidelines and the Barcelona Clinic Liver Cancer guidelines. The exclusion criteria included: decompensated cirrhosis; a history of any cancer in the last 5 years; previous antiviral treatment for CHB; concurrent infection with hepatitis C virus or human immunodeficiency virus; a Karnofsky Performance Status score < 60%; or any medical condition preventing eligibility to complete the protocol. The prevalence and incidence rates of HCC were determined; survival rates were calculated at 3-year post HCC diagnosis. The sensitivity and specificity were calculated on a per-patient basis.

RESULTS
Among 2293 treatment-naïve CHB patients, seven cases had HCC at initial screening, giving a prevalence rate of 305 per 100000 persons; 3.3% were diagnosed with liver cirrhosis, all of which were Child-Pugh class A. With a median follow-up time of 42 (range, 3-48) mo, 10 additional cases were diagnosed with HCC, resulting in an incidence rate of 143 per 100000 persons per year. This burden was as high as that reported in other studies from East Asian countries. All HCC patients were aged $\geq$ 40 years. Most were at an early stage (Stage 0, A or B); 14/17 cases were successfully treated with surgical resection or radiofrequency ablation, with a high 3-year survival rate of 90%. Hemangioma was the most common focal liver lesion in CHB patients detected by AUS; the main causes of AFP elevation at the initial screening were cirrhosis, increased alanine aminotransferase level and HCC. AUS detected 16/17 HCC cases whereas AFP levels $\geq$ 20 μg/L at diagnosis were observed in only 7/17 patients, most with a tumor size > 5 cm. For HCC screening and surveillance, AUS had a sensitivity and specificity of 94% and 82%, respectively, whereas the sensitivity and specificity of AFP at a cut-off value of $\geq$ 20 μg/L were 41% and 98%, respectively. Combined use of AUS and AFP assay did not improve effectiveness.

CONCLUSION
Implementation of active screening and surveillance using AUS to detect early-stage HCC in naïve CHB patients aged $\geq$ 40 years in an endemic area is of benefit.

Key words: Liver cancer; Ultrasonography; Alpha-fetoprotein; Early detection; Hepatitis B

Core tip: This large cohort study of 2293 patients revealed a high prevalence rate (305 per 100000 persons) and a high incidence rate (143 per 100000 persons per year) of hepatocellular carcinoma (HCC)

in treatment-naïve Thai chronic hepatitis B (CHB) patients through a screening and surveillance semi-annual ultrasonography program. Most patients were at an early stage (Stage 0, A or B) and were successfully treated, with a high 3-year survival rate of 90%. A national screening policy should thus be implemented in CHB patients residing in a developing country with a high incidence rate of HCC such as Thailand, to prevent late-stage HCC development.

INTRODUCTION
Hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC) is a major health problem in all regions of Thailand, with approximately 12000 new cases per year; most are diagnosed at an advanced stage. The mortality rate is also high with a median survival time of < 1 year[1-5]. HCC screening and HCC surveillance are defined as a one-time test and repeated tests over time for detecting HCC, respectively[6]. Abdominal ultrasonography (AUS) and serum alpha-fetoprotein (AFP) measurement are widely accepted as routine HCC screening and surveillance tests in chronic hepatitis B (CHB) patients[7]. Several previous studies have shown the benefit of HCC screening and surveillance in the detection of early-stage HCC; however, there are conflicting results regarding the efficacy of screening and surveillance concerning improvement in survival[8-10].

The validity of AFP or AUS or both for the screening and surveillance of HCC remains variable in large-scale screening programs[11-13]. The sensitivity and specificity of AFP is 40%-60% and 76%-94%, respectively[14], as compared with 71%-84% and 93%-98%, respectively, for AUS[15,16]. Currently, international liver societies including the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases recommend screening and surveillance tests in CHB patients who are at high risk of HCC development[17,18].

At present, no national policy for screening and early detection of HCC is available in Thailand, which is an endemic area for hepatitis B infection. HCC remains the number one cancer killer in the Thai population, affecting both males and females. Screening and surveillance are not accessible in most regions because of the lack of personnel and technology and its associated high costs. Moreover, the majority of CHB

patients in Thailand are unaware of the possible long-term consequences of their conditions, including the development of HCC.

In the present study, we undertook a screening and surveillance program involving treatment-naïve CHB patients using AUS and serum AFP assay to screen for early-stage HCC. The prevalence and incidence rates of HCC were determined. Patients were followed every 6 mo and survival rates were also calculated at 3-year post HCC diagnosis.

MATERIALS AND METHODS

Study population

We enrolled male and female Thai patients, aged 20-65 years, who were serologically positive for hepatitis B surface antigen (s-Ag). The exclusion criteria included: decompensated cirrhosis (Child-Pugh class C or Model for End-stage Liver Disease score > 15); a history of any cancer in the last 5 years; previous antiviral treatment for CHB; concurrent infection with hepatitis C virus infection or human immunodeficiency virus infection; a Karnofsky Performance Status score < 60%; or any medical condition preventing eligibility to complete the protocol (*e.g.*, poor renal function, a serum creatinine level > 1.5 mg/dL, or creatinine clearance < 50 mL/min. An interview questionnaire was utilized to collect the demographic data, clinical data and social determinants. All participants underwent a complete blood count, liver function tests, serum creatinine measurement, prothrombin time measurement, and human immunodeficiency virus antibody testing. Serological tests included AFP assay, quantitative measurement of hepatitis B s-Ag, electrochemiluminescence assay of hepatitis B e-antigen (COBAS 6000/e601 Roche Diagnostics, Mannheim, Germany), electrochemiluminescence assay of anti-HCV (Model e601: Cobas 600, Roche Diagnostics, United States), and alanine aminotransferase (ALT) assay using a serum chemistry auto analyzer (Model 400: COBAS Integra, Roche Diagnostics, United States) using commercial reagents (Cobas Integra ALT: Roche Diagnostics). Serum HBV DNA levels were tested using frozen samples by means of the COBAS AmpliPrep/CoBASTaqMan HBV test v2.0 (Roche Diagnostics, United States), certified at a lower detection limit of 20 IU/mL of HBV DNA. This study met the guidelines of the Helsinki Declaration and was approved by the Ethical Committee for Human Research of Chulabhorn Research Institute (Certificate No. 18/2553). Written informed consent was obtained from all patients who participated in the study.

Screening and surveillance protocol

AUS examinations were performed by experienced radiologists at the initial screening and every 6 mo thereafter to evaluate the following factors: liver size; caudate/right lobe ratio; liver parenchyma and surface; space-occupying lesions; portal vein diameter; spleen size; ascites; porto-systemic shunt; bile duct dilatation; and intraabdominal lymphadenopathy. Measurement of HBV DNA, aspartate aminotransferase, alanine aminotransferase (ALT), and AFP levels were repeated at 6-mo intervals. If the serum AFP was $\geqslant$ 20 µg/L or a focal solid liver nodule was detected on AUS, further diagnostic studies were performed including computerized tomography, magnetic resonance imaging, or biopsy of the liver lesion. Importantly, all patients were reminded by our study team to schedule follow-up examinations. Antiviral agents were given if HBV DNA levels were $\geqslant$ 2000 IU/mL, with any of the following: (1) ALT > 60 IU/mL; (2) a transient elastography (FibroScan: Echosens, Paris, France) Fibroscan score > 7.2 kPa; or (3) significant fibrosis or cirrhosis on liver biopsy.

HCC was the major outcome in our study. The patients were followed until the time of HCC diagnosis and death. Patients who were lost to follow-up were censored at the time of their last visit to the clinic. HCC was diagnosed using the American Association for the Study of Liver Diseases practice guidelines and the Barcelona Clinic Liver Cancer (BCLC) guidelines were used for tumor staging[18]. All HCC patients were evaluated for hepatic resection, radiofrequency ablation, chemoembolization or systemic treatment. Additionally, cirrhosis was defined according to the following criteria: a METAVIR fibrosis score from liver biopsy equal to 4, or two consecutive AUS examinations indicating liver cirrhosis or ultrasonographic cirrhosis with a FibroScan score $\geqslant$ 10.0 kPa[19,20].

Statistical analysis

Values were expressed as medians (ranges) and frequency unless otherwise indicated. Patient survival was calculated from the time of HCC diagnosis to the time of death or last follow-up. For evaluation of the usefulness of the screening and surveillance test, the sensitivity and specificity were calculated on a per-patient basis. Patients with a mass lesion on AUS or a serum AFP level > 20 µg/dL without subsequent HCC confirmation on computed tomography or magnetic resonance imaging scans were recorded as false positive tests. All data were processed and analyzed using Stata/SE v.12 software (StataCorp LP, College Station, TX, United States).

RESULTS

CHB patient characteristics

A total of 2293 CHB patients were included in the study, of whom 1078 (47%) were males with a median age of 41.25 years and 54% were aged > 40 years. The demographic and clinical data are summarized in Table 1. HBV e-Ag negative status with an HBV DNA concentration < 2000 IU/mL was most common and noted in 52% of the patients. This

Table 1 Chronic hepatitis B Patient baseline characteristics *n* (%)	
Characteristics	**Total (*n* = 2293)**
Male sex	1078 (47.0)
Marital status (married)	1306 (57.2)
Alcohol consumption	683 (29.7)
Tobacco habit	290 (12.6)
Overweight: BMI > 25	854 (37.2)
HBV status	
Hepatitis B e-Ag positive	394 (17.0)
Hepatitis B e-Ag negative with HBV DNA < 2000 IU/mL	1184 (52.0)
Hepatitis B e-Ag negative with HBV DNA $\geq$ 2000 IU/mL	713 (31.0)
ALT > 60 IU/L	262 (11.4)
Cirrhosis	77 (3.3)

BMI: Body mass index; ALT: Alanine aminotransferase.

was followed by HBV e-Ag negative patients with an HBV DNA concentration of $\geq$ 2000 IU/mL (31%) and HBV e-Ag positive patients (17%). Elevated ALT levels were observed in 11% of the patients. At enrollment, cirrhosis was diagnosed in 77 cases (3.3%), all of which were scored as Child-Pugh class A; only eight cases had ultrasonographic evidence of portal hypertension.

With respect to protocol adherence, 203 patients withdrew from the surveillance program after completing at least one visit (8%) by our clinical cut-off date for analysis (November 1, 2015).The median number of surveillance tests per patient was 8 (range, 1-8) and 85% of patients were followed up as scheduled.

Prevalence and incidence rates and case characteristics of HCC

HCC was detected in seven cases at the first screening, giving prevalence rates of 305 per 100000 persons. With a median follow-up time of 42 (range, 3-48) mo, 10 additional cases were diagnosed with HCC, resulting in incidence rates of 143 per 100000 persons per year. The characteristics of the HCC subjects are summarized in Table 2. The median age at diagnosis was 57 (range, 40-69) years and half of the subjects also had liver cirrhosis.

The diagnosis of HCC was histologically confirmed in 14 patients. Interestingly, one case (patient no. 15) was diagnosed with a combined hepatocholangiocarcinoma subtype. Of the 17 patients who developed HCC, seven tumors were classified as very early stage (BCLC stage 0) and nine were classified as early stage (BCLC stage A), and only one patient had an intermediate stage tumor (BCLC stage B). Altogether, HCC were resected in 12 cases and two cases underwent radiofrequency ablation. Two out of 12 resectable patients received preoperative transarterial chemoembolization (TACE) because they had large tumors. Furthermore, three cases (patient no. 8, 10 and 15) were inoperable because of excessive portal hypertension, and radio-

frequency ablation was not performed because of a difficult tumor location. No patient was sent for liver transplant in this study.

During follow-up, three of the 17 patients died. One patient died from sepsis and two patients died from HCC. All patient tumors were inoperable at the initial presentation. The 1- and 3-year survival rates were 100% and 90%, respectively. The median survival time was not reached.

Sensitivity and specificity of AFP measurement in the detection of HCC

AFP levels $\geq$ 20 μg/L at diagnosis were observed in seven of 17 HCC patients, most with a tumor size > 5 cm. The reasons for elevation of the AFP level at initial screening ($\geq$ 20 μg/L) are detailed in Table 3. AFP elevation was caused by pregnancy in two women. In 10 patients, the increased AFP level was accompanied by a transient increase in ALT levels. After treatment with antiviral medication, ALT and AFP levels returned to normal. The remaining 10 cirrhotic patients had a single episode of transient AFP elevation of undetermined cause. The per-patient sensitivity and specificity of AFP in the detection of HCC was 41% and 98%, respectively (Table 4).

Sensitivity and specificity of AUS in the detection of HCC

AUS could detect 16 out of 17 HCC cases with a median tumor size of 2.5 (range, 1.2-7.8) cm. In 2293 subjects, the initial AUS revealed a focal solid liver nodule in 96 patients (4%). Hemangioma was the most common focal hepatic lesion (Table 5). The per-patient sensitivity and specificity of AUS in the detection of HCC in CHB patients was 94% and 82%, respectively. Using AUS in combination with AFP did not increase the sensitivity or specificity (Table 4).

DISCUSSION

A requirement for HCC screening is presently not a national policy in Thailand. The majority of CHB patients are not offered antiviral therapy, leading to very high mortality from associated conditions including HCC. According to studies by Vatanasapt *et al*[21], hospital-based 5-year survival rates of HCC cases were only 8.5% in males and 8.3% in females. The present study confirmed that the HCC burden was a major health problem in Thailand, with an urgent need to implement an HCC screening and surveillance program. The prevalence and incidence rates of HCC in our study were as high as those reported in previous studies from other East Asian countries[22].

In our study, we found that screening and surveillance for HCC using AUS and serum AFP testing every 6 mo led to tumor detection at an operable and early stage in 80% of cases; this resulted in patients having a higher chance of receiving curative treatment.

Table 2 Hepatocellular carcinoma patient characteristics

Patient No.	Age (yr)	Sex	Time from entry to diagnosis (mo)	Tumor No.	Size (cm)	Cirrhosis	BCLC stage	AFP at diagnosis (μg/L)	Treatment
1	50	M	At entry	1	6.5	Y	A	391	Segmental resection
2	63	M	At entry	2	6.4	N	B	8419	TACE then segmental resection
3	54	M	At entry	1	4.5	Y	A	4	Hepatectomy
4	57	M	At entry	1	7.8	Y	A	25	TACE, PVE then hepatectomy
5	44	M	At entry	1	1.7	N	0	4	Segmental resection
6	51	M	At entry	1	6.5	N	A	24	Hepatectomy
7	45	F	At entry	1	4.5	N	A	55	Hepatectomy
8	45	F	6	1	1.4	Y	0	5	TACE
9	62	F	6	2	1.3	Y	0	13	RFA
10	61	M	6	1	4.7	Y	A	22	TACE
11	57	F	12	2	4.0	N	A	15	Segmental resection
12	66	M	24	1	1.7	Y	0	3	Segmental resection
13	40	F	24	1	1.4	N	0	< 1	Segmental resection
14	69	F	30	1	1.4	N	0	2	Segmental resection
15	61	F	39	1	2.2	Y	A	3020	SBRT, TACE
16	64	M	39	1	1.7	Y	0	8.2	RFA
17	48	M	45	1	2.6	N	A	2.5	Segmental resection

AFP: Alpha-fetoprotein; BCLC: Barcelona Clinic Liver Cancer; TACE: Transarterial chemoembolization; PVE: Portal vein embolization; RFA: Radiofrequency ablation; SBRT: Stereotactic body radiation therapy.

Table 3 Cause of alpha-fetoprotein elevation at the initial screening and the number of subjects

Cause	No. of subjects
Hepatocellular carcinoma	5
Cirrhosis	10
Increased ALT levels	10
Pregnancy	2

ALT: Alanine aminotransferase.

Table 4 Performance of screening and surveillance tests for hepatocellular carcinoma

Test	Sensitivity (%)	Specificity (%)
AFP	7/17 (41)	2247/2276 (98)
Ultrasound	16/17 (94)	1879/2276 (82)
Ultrasound and AFP	16/17 (94)	1872/2276 (82)

AFP: Alpha-fetoprotein.

Table 5 Diagnosis of focal liver nodules at initial screening using abdominal ultrasonography

Diagnosis	*n* (%)
HCC	7 (8)
Hemangioma	49 (51)
Calcified granuloma	8 (8)
Liver cyst	8 (8)
Regenerate nodule	3 (3)
Arteriovenous shunt	6 (6)
Normal liver parenchyma	15 (19)

HCC: Hepatocellular carcinoma.

Our results were better than those of the previous large screening study conducted by Zhang *et al*[9], in which 18816 participants were randomly allocated to a screening or control group; the proportion of small HCC was higher at 45.3% *vs* 0%, with resection rates in the screening group of 46.5% *vs* 7.5%. Mortality was also reduced by 37%. Our studies showed that resection was possible in 80% of the screened HCC cases, while a tumor size of < 5 cm was found in 70%. Despite a large tumor size in some patients in this study, there were also other alternative treatment modalities such as TACE or portal vein embolization which could convert initially unresectable HCC to a resectable tumor[23]. However, there is no established preoperative adjuvant strategy to improve prognosis in HCC patients[24]. Cirrhosis is another important factor determining operability because it indicates poor hepatic reserve. The heterogeneous proportion of cirrhosis in screened populations in several studies seemed to affect the treatment modality[10,25]. Liver transplantation is the only potentially curative method for both chronic liver disease and HCC. Nevertheless, low availability of liver transplantation facilities in many parts of the world and scarcity of donor organs, with long and unpredictable waiting times, are the main obstacles to the long-term survival of most HCC patients. None of the HCC patients in our study received liver transplantation.

There are conflicting results regarding the benefit and efficacy of screening for improved survival. A randomized controlled study conducted in Qidong, China[8] resulted in an earlier diagnosis of liver cancer, but no reduction in mortality. Mok *et al*[10] studied HCC patients with a tumor size of < 5 cm detected using ultrasonography; serum AFP levels revealed no benefit of early detection. In contrast, according to our findings the 3-year survival rate of HCC patients was 90%. This rate was as high as the rate in stage 0 and

stage A HCC based on BCLC staging[26].

According to many international guidelines and reports[17,18,27], AUS is the most appropriate tool for screening and surveillance. In the current study, AUS could detect almost all HCC lesions with a sensitivity and specificity of 94% and 82%, respectively, and more efficiently than using serum AFP level. Increased AFP levels were observed in only half of the HCC patients, most of whom had a tumor size of > 5 cm. This was supported by a report demonstrating that increased AFP levels might be indicative of severe liver injury[28], and AFP can be increased by many other factors. AFP levels may be elevated in patients without HCC, especially during exacerbation of the hepatitis. Another study using AFP for HCC detection achieved the same diagnostic accuracy as in our study[14]. Thus, serum AFP alone is not an ideal marker for the screening of HCC. The combined use of AFP and ultrasonography is also not recommended because of increased false positive rates that lead to increased costs.

Based on cost-effectiveness data, several guidelines recommend that the HCC screening in patients with chronic HBV begins when they are cirrhotic, or for non-cirrhotic patients at the age of 40 and 50 years for Asian males and females, respectively; this is because many CHB infection patients in Asian countries develop early onset HCC at a younger age[29]. The strength of our study is the fact that we also screened a large number of CHB infection patients aged < 40 years (half of the participants). However, none of the younger patients developed early onset HCC as of the last follow-up. Thus, our data support a low incidence of HCC in the younger age group who may further require the use of other clinical or laboratory predictors to determine the risk of early-onset HCC.

Patient adherence can play an important role in cancer screening and surveillance. Wong *et al*[30] reported an association between HCC screening adherence and greater access to curative treatment. In our study, the adherence rate was very high during the 42 mo of follow-up. Our strategic methods included short public service messages, reminder phone calls and letters, appointments at the most convenient time for the patient, and home visits. After implementing this strategy, the adherence rate improved from 52% to 99.9% in later visits (unpublished data). Lastly, the present data support our previous economic evaluation and budget impact analysis[31]. Semi-annual AUS was a cost-effective option for HCC screening and surveillance in CHB patients aged 40-50 years, at a willingness-to-pay threshold of 160000 Thai Baht per quality adjusted life years.

Our study is the first large cohort study to report the high prevalence and incidence rates of HCC in CHB patients in Thailand through a screening and surveillance program involving AUS. AUS examination was more sensitive than serum AFP testing for early-stage HCC detection. Serum AFP did not provide any benefit for HCC screening and surveillance. The active AUS screening program led to a high 3-year survival benefit in our CHB population who developed HCC. It is suggested that a screening and surveillance program be implemented in CHB patients aged ≥ 40 years, at a national policy level, to improve HCC detection at a potentially operable and curable stage.

ACKNOWLEDGMENTS

COMMENTS

Background

Hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC) is a major health problem in all regions of Thailand. Abdominal ultrasonography (AUS) and serum alpha-fetoprotein (AFP) measurement are widely accepted as routine HCC screening and surveillance tests in chronic hepatitis B (CHB) patients to detect early-stage HCC; however, there are conflicting results regarding survival improvement. At present, no national policy for screening and early detection of HCC is currently available in Thailand. The study was designed to evaluate a screening and surveillance program for naïve CHB patients using AUS and serum AFP for early-stage HCC detection and its potential to improve survival after HCC diagnosis.

Research frontiers

This study confirmed the high prevalence and incidence rates of HCC in Thailand. Semi-annual examination using AUS can detect early stage HCC; this led to a high 3-year survival benefit. Serum AFP did not add benefit for HCC screening and surveillance.

Innovations and breakthroughs

The current study suggests the benefit of AUS as an early-stage HCC screening and surveillance tool in treatment-naïve CHB patients aged ≥ 40 years.

Applications

This study provides additional evidence supporting the role of HCC screening and surveillance using AUS. The results should change the way the policy makers in developing countries, in particular Thailand, perceive and deal with CHB cases; they hopefully will lead to the implementation of an effective screening and surveillance program regarding HCC in CHB patients residing in an endemic area.

Peer-review

This is an excellent work with very useful clinical information on the value of AUS screening of HBV-infected patients for early detection of HCC in Thailand.

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