Ultrasound Surveillance for Hepatocellular Carcinoma of At-Risk Patients in Ramathibodi Hospital

Duangkamon Prapruttam MD*, Jitkasem Suksai MD*,
Taya Kitiyakara MD**, Sith Phongkitkarun MD*

** Department of Diagnostic and Therapeutic Radiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*
*** Division of Gastroenterology and Hepatology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*

Background: *Surveillance for hepatocellular carcinoma (HCC) is recommended for patients at risk of developing HCC. However, the pattern of surveillance in clinical practice is unclear.*
Objective: *To assess the adherence of surveillance program in the detection of HCC and to determine the prevalence of HCC in the at-risk patients who were on surveillance in Ramathibodi Hospital.*
Material and Method: *Retrospective descriptive study of at-risk patients, who were followed in the liver clinic at Ramathibodi Hospital between January 1, 2007 and December 31, 2012. Clinical data were collected from electronic medical records and radiologic data were extracted from the radiology database (PACS). The US findings of focal liver lesion were analyzed for number, size, location, and echogenicity. When focal liver lesions suggestive of HCC were detected on ultrasonography, dynamic contrast enhanced CT or MRI was used to diagnose HCC. On CT/MRI, focal lesions were considered to be HCC when hypervascularity in the arterial phase and washout in the portal venous or delayed phase was found.*
Results: *Nine hundred seven patients with risk(s) for HCC underwent ultrasound surveillance. The mean number of ultrasound examinations per patient was 4.7±2.2 scans during the course of follow-up. The mean total adherence time was 37.0±17.1 months. The median time interval between each ultrasound examination was 8.4 months (range: 1.1-63.0 months). Focal liver lesions were detected in 161 of 907 patients (17.8%). No new focal liver lesion was detected at less than 3-month interval. The majority of patients were evaluated further by MRI (n = 99; 62.3%) or by CT scan (n = 33; 20.8%). The period prevalence of HCC in patients who received US surveillance was 3.5% (32 patients in 907 patients). Most of patients with HCC were male (71.9%) and the major risk factor was chronic hepatitis B (50.0%). Twenty-one of 32 patients (65.6%) had normal serum AFP levels. Most HCC's (75.0%) were detected at 8-month interval. The cumulative percentage of HCC's detected at 6-month and 12-month surveillance intervals were 11.1% and 70.4%, respectively. The median tumor size was 22.5 mm, ranging from 12-134 mm. At the time of HCC diagnosis, eight patients (25.0%) had HCC within BCLC very early stage (by size criteria) and 19 patients (59.4%) were in BCLC early stage.*
Conclusion: *Although there were irregular surveillance intervals in our clinical practice, the overall adherence of patients to surveillance was acceptable, with the period prevalence of HCC 3.5% and the majority discovered in the early stage.*

Keywords: *Hepatocellular carcinoma (HCC), Surveillance, Ultrasonography (US)*

J Med Assoc Thai 2014; 97 (11): 1199-208
Full text. e-Journal: *http://www.jmatonline.com*

Hepatocellular carcinoma is a complex disease associated with many risk factors and cofactors. Approximately 70% to 90% of patients with HCC have an established background of chronic liver disease and cirrhosis, with major risk factors for developing cirrhosis including chronic infection with hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic liver disease, and nonalcoholic fatty liver disease (NAFLD) [1]. Patients at-risk for developing HCC should be entered into surveillance programs. The objective of surveillance is identification of an HCC at the earliest possible stage when treatment has the highest chance of cure. Early stage disease includes patients with preserved liver function (Child-Pugh A and B) with solitary HCC or up to three nodules ≤3 cm in size[2]. The early detection of HCC is critical for improving patient outcomes particularly in this era of improved surgical techniques, for resection and transplantation, and other alternative therapeutic options, such as transcatheter chemoembolization and radiofrequency ablation (RFA)[3].

Surveillance for HCC is widely practiced and is recommended for certain at-risk groups by American

Correspondence to:
Phongkitkarun S, Department of Diagnostic and Therapeutic Radiology, Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Ratchathewi, Bangkok 10400, Thailand.
Phone: 0-2201-1212, Fax: 0-2201-1247
E-mail: sith.bkk@gmail.com

Association for the Study of Liver Disease (AASLD) and European Association for the Study of the Liver (EASL) guidelines[2,4]. Ultrasonography (US) is the first line investigation for surveillance, as it has relatively low cost, non-invasive and is widely available. Ultrasound surveillance as it is currently practiced has an acceptable sensitivity of 65% to 80% and specificity of more than 90% in detecting focal liver lesions. Tumor size significantly affects the sensitivity of US in detecting HCC. Sensitivity ranges from 42% for lesions smaller than 1 cm to 95% for tumors of larger size[5].

The current guideline from the National Cancer Institute (Thailand) 2011[6] and the American Association for the Study of Liver Disease 2010 (AASLD) recommend surveillance for HCC with ultrasonography at 6-month intervals. A surveillance interval of six to 12 months has been proposed based on tumor doubling times. Nodules larger than 1 cm found on ultrasound screening of a cirrhotic liver should be investigated further with either 4-phase multidetector CT scan or dynamic contrast enhanced MRI. If the appearances are typical of HCC (i.e., hypervascular in the arterial phase with washout in the portal venous or delayed phase), the lesions should be treated as HCC.

The extent and result of using HCC surveillance in Ramathibodi Hospital, a tertiary care teaching hospital in Thailand, are unknown. The present study would address two main issues concerning ultrasound surveillance for HCC. The first was to assess the adherence of surveillance program. The second was to determine the prevalence of HCC in at-risk patients who received surveillance.

Material and Method

Study design

We conducted a descriptive study using retrospective data of at-risk patients from the liver clinic, Department of Internal Medicine, Faculty of Medicine Ramathibodi Hospital, who were followed between January 1, 2007 and December 31, 2012. The study was approved by the Ethics Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University. Informed content was waived.

Study population

The patients with HBV carrier, chronic hepatitis B virus (HBV), chronic hepatitis C virus (HCV), alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), hepatobiliary autoimmune disease, and cirrhosis of other etiologies were eligible for inclusion into the study. Patients included in the study had to be at least 18 years of age and had at least two ultrasound examinations during the six years. Patients with HCC who had undergone a previous curative resection and were undergoing surveillance during the period of study were also included. Measurements and data were obtained at the time of diagnosis of HCC.

Data collection

Patient characteristic

Data were collected from electronic medical records, included patient characteristic, laboratory tests, HCC diagnoses, and treatment. Patient characteristics included age, gender, risk for HCC, health insurance and attendance in liver clinic. Laboratory data include dates and results of serum AFP.

Radiologic data

Data were extracted from the radiology database (PACS). Radiologic data included dates, type (US, CT scan and MRI) and result of abdominal imaging. The US findings of focal liver lesion were analyzed for number, size, location (in hepatic lobes), echogenicity on the basis of the difference in echogenicity between the lesion and the surrounding liver parenchyma, as well as the background liver parenchyma.

Abdominal ultrasound examination

Abdominal ultrasonography was performed by board certified radiologist with ultrasound devices and 5.0-MHz transducers. Scans were generally performed according to the standard scanning protocol. Examinations were limited to gray-scale assessment.

Radiological diagnosis of HCCs

When focal liver lesions suggestive of HCC were detected on ultrasonography, dynamic contrast enhanced CT or MRI were ordered. On CT/MRI, a focal lesion was considered to be HCC when hypervascularity in the arterial phase and washout in the portal venous or delayed phase. If the CT/MRI findings were not characteristic or the vascular profiles were not typical, the lesions were biopsied.

Definitions of very early and early stage HCCs

Very early HCC and early HCC were classified according to the BCLC staging system by size criteria and number of tumors. Performance status

of the patients and Child-Pugh score are not included in our classification. The very early HCC was defined as single HCC <2 cm, and early stage HCC was defined as single HCC less than 5 cm or 3 HCCs <3 cm[7].

Calculation of surveillance interval

The surveillance interval was defined as the time between the ultrasound examination that first detected a new focal liver lesion and the immediately previous ultrasound surveillance with negative finding. Total adherence time was defined as time between the first and the latest ultrasound surveillance.

Statistical analysis

Statistical analyses were performed using the software STATA version 13 (StataCorp, 2013). Baseline data were descriptively summarized, and assessment of differences was completed by using the Student's t-test and Chi-squared method. All statistical significance was assess at the 0.05 level. Means, median, and standard deviations were computed for all continuous data. Categorical data were summarized by using frequencies and percentage.

Results

Baseline characteristics

Between 2007 and 2012, 907 patients with risk for HCC had received ultrasound surveillance. The mean age was 56.6±12.3 years with male predominance (54.6%).

The largest proportion of patients were chronic hepatitis B (60.9%), followed by chronic hepatitis C (15.6%), NAFLD (7.3%) and alcoholic liver cirrhosis (6.9%). The minority of the patients had other diagnosis: cryptogenic cirrhosis (2.2%) and several patients had multiple risk factors. Fourteen patients (1.5%) had a previous diagnosis of HCC and underwent surgical resection. Baseline characteristics of 907 patients were shown in Table 1.

During the surveillance, focal liver lesions were detected in 161 patients of 907 (17.8%). Most of these patients were men (n = 105; 65.2%) and had a mean age of 58.5±10.6 years. The major risk factor in patients who had focal liver lesion was chronic hepatitis B (n = 92, 57.1%), followed by chronic hepatitis C. Patients who had focal liver lesion were significantly older (58.5±10.6) than patients who did not have focal liver lesion (56.2±12.6, *p*-value = 0.031). Most of patients with NAFLD and cryptogenic cirrhosis were not found focal liver lesion (*p*-value = 0.010 and 0.041, respectively).

Surveillance interval and tumor size at detection

The focal liver lesions were detected by first ultrasound examination in 23 patients. Among the remaining 884 patients, new focal liver lesions were detected in 138 patients (15.6%) on subsequent examinations.

The mean number of ultrasound examinations per patient was 4.7±2.2 scans during the course of follow-up. The mean total adherent time was 37.0±17.1 months. The median time interval between each ultrasound examination was 8.4 months (range: 1.1-63.0 months) and the 75th percentile was 11.8 months.

The relationship between the ultrasound surveillance interval and the number/size of HCC on among these 138 patients was shown in Table 2. No new focal liver lesion or HCC was detected in ultrasound examinations performed less than 3-month interval. HCCs were mostly detected in patients who had ultrasound surveillance at 8-month interval (six patients out of 32 HCC patients: 22.2%). The largest HCC lesion (128 mm in diameter) was detected in patient after a 32-month interval.

Focal liver lesions

Two patients of 161 patients were lost to follow-up after focal liver lesions detected. Among 159 patients, the majority of the patients were further evaluated by MRI (n = 99; 62.3%), or CT scan (n = 33; 20.7%). Twenty-seven patients (17.0%) had repeat ultrasound after a short interval. The characteristics of 159 patients with focal liver lesions

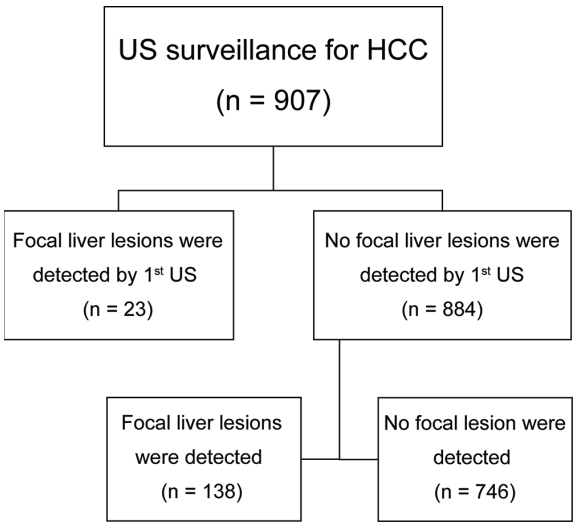

Fig. 1 Selection of patients.

Table 1. Baseline characteristic of 907 patients with chronic liver disease stratified by presence of focal liver lesion

	Overall (n = 907)	Focal liver lesion (n = 161)*	No focal liver lesion (n = 746)	*p*-value
Age (year)	56.6 (12.3)	58.5 (10.6)	56.2 (12.6)	0.031
Gender				0.003
Male	495 (54.6%)	105 (21.2)	390 (78.8)	
Female	412 (45.4%)	56 (13.6)	356 (86.4)	
AFP				<0.001
<20 ng/ml	785 (86.6%)	119 (15.2)	666 (84.8)	
≥20 ng/ml	29 (3.2%)	13 (44.8)	16 (55.2)	
No data	93 (10.2%)	29 (31.2)	64 (68.8)	
HCC risk factor				
Chronic hepatitis B	552 (60.9%)	92 (16.7)	460 (83.3)	0.287
Chronic hepatitis C	141 (15.6%)	26 (18.4)	115 (81.6)	0.816
NAFLD	66 (7.3%)	4 (6.1)	62 (93.9)	0.010
Alcoholic liver disease	63 (6.9%)	15 (23.8)	48 (76.2)	0.192
Cryptogenic cirrhosis	20 (2.2%)	7 (35.0)	13 (65.0)	0.041
Multiple risk factors	33 (3.6%)	8 (24.2)	25 (75.8)	0.320
Others disease	18 (2.0%)	4 (22.2)	14 (77.8)	0.543
HCC post resection	14 (1.5%)	5 (35.7)	9 (64.3)	0.076

AFP = alpha-fetoprotein; HCC = hepatocellular carcinoma; NAFLD = nonalcoholic fatty liver disease
Data are presented as number (%) or mean (SD)
* Twenty-three focal liver lesions were detected by first ultrasound examination

Table 2. Surveillance interval and tumor size at detection (n = 138)

Interval (months)	Total US	No. of focal lesion	HCC			Diameter (mm) as measured by US		
			No.	Detection rate of US (%)	Cumulative HCC (%)	Mean	SD	Range
≤3	58	0	0	0.0	0.0	-	-	-
4	66	4	2	3.0	7.4	26.5	19.1	13-40
5	90	4	1	1.1	11.1	14.0	-	-
6	403	14	0	0.0	11.1	-	-	-
7	512	30	3	0.6	22.2	19.0	7.2	11-25
8	391	18	6	1.5	44.4	16.0	6.2	10-25
9	266	10	0	0.0	44.4	-	-	-
10	233	7	1	0.4	48.2	65.0	-	-
11	226	11	3	1.3	59.3	20.3	9.7	12-31
12	264	5	3	1.1	70.4	27.0	19.0	8-46
13	183	8	1	0.5	74.1	52.0	-	-
14	112	7	2	1.8	81.5	24.0	4.2	21-27
15	80	5	1	1.3	85.2	24.0	-	-
16	68	1	0	0.0	85.2	-	-	-
17	48	4	1	2.1	88.9	17.0	-	-
18-31	234	7	0	0.0	88.9	-	-	-
32	8	1	1	12.5	92.6	128.0	-	-
33-35	13	0	0	0.0	92.6	-	-	-
36	3	1	1	33.3	96.3	95.0	-	-
>36	21	1	1	4.8	100.0	7.0	-	-

US = ultrasonography

Table 3. Characteristic of 159 patients with focal liver lesions stratified by further investigation

	Overall (n = 159)	Follow-up (n = 27)	Further investigation		*p*-value for FU vs. further investigation	*p*-value for CT vs. MRI
			CT (n = 33)	MRI (n = 99)		
Age (year)	58.4 (10.6)	56.6 (12.7)	59.5 (10.5)	58.5 (10.0)	0.342	0.603
Gender					0.552	0.172
Male	104 (65.4)	19 (18.3)	18 (17.3)	67 (64.4)		
Female	55 (34.6)	8 (14.5)	15 (27.3)	32 (58.2)		
Health insurance					0.184	0.506
Comptroller general department	76 (47.8)	12 (15.8)	14 (18.4)	50 (65.8)		
National health care security office	27 (17.0)	2 (7.4)	9 (33.3)	16 (59.3)		
Social security office	11 (6.8)	1 (9.1)	3 (27.3)	7 (63.6)		
Private	45 (28.3)	12 (26.7)	7 (15.5)	26 (57.8)		
AFP					0.460	0.483
<20 ng/ml	117 (73.6)	23 (19.7)	22 (18.8)	72 (61.5)		
≥20 ng/ml	13 (8.2)	1 (7.7)	4 (30.8)	8 (61.5)		
No data	29 (18.2)					
No. of focal liver lesions					0.786	0.722
Solitary	121 (76.1)	20 (16.5)	26 (21.5)	75 (62.0)		
Multiple	38 (23.9)	7 (18.4)	7 (18.4)	24 (63.2)		
Size of focal liver lesion					0.697	0.019
<1 cm	48 (30.2)	9 (18.7)	7 (14.6)	32 (66.7)		
≥1 cm	111 (69.8)	18 (16.2)	26 (23.4)	67 (60.4)		
Background liver parenchyma					0.246	0.169
Normal	9 (5.7)	1 (11.1)	0 (0.0)	8 (88.9)		
Fatty liver	14 (8.8)	5 (35.7)	1 (7.1)	8 (57.1)		
Parenchymatous disease	27 (16.9)	5 (18.5)	4 (14.8)	18 (66.7)		
Cirrhosis	109 (68.6)	16 (14.7)	28 (25.7)	65 (59.6)		

Data are presented as number (%) or mean (SD)

stratified by further investigation methods are shown in Table 3.

The final radiologic diagnosis of all 159 focal liver lesions is shown in Table 4. Seventy-one lesions were hyperechoic, 50 lesions were hypoechoic, and 38 lesions were mixed echoic. HCCs were found in 32 patients (20.1%). Of these, nine were hyperechoic, 10 were hypoechoic, and 13 were mixed echoic. The largest subgroup of focal liver lesions (n = 39, 24.5%) detected during surveillance ultrasound were considered to be pseudolesions, and were not present in the further CT scan or MRI. Twenty nodules (12.6%) remained indeterminate but stable over the course of follow-up. At the end of follow-up, two patients were confirmed as metastatic lung cancer and one patient was confirmed as adenocarcinoma (possibly cholangiocarcinoma or metastasis).

Among 39 patients who had focal liver lesion smaller than 1 cm and underwent further investigation (CT or MRI), three patients (7.7%) had diagnosis of HCC by typical imaging findings on MRI, 14 patients (35.9%) had pseudolesions. Twenty-two patients (56.4%) had benign lesions. These three HCC patients subsequently received curative treatment with surgical resection or RFA.

Among 111 patients who had focal lesion larger than 1 cm in diameter, most of the patients underwent further investigation (83.8%) and 29 patients were diagnosed of HCC. Eighteen patients (16.2%) were kept under follow-up US examination. Among these patients, five patients (27.8%) still had undetermined nature of the lesion on follow-up US examination. The follow-up US examinations suggested abnormal fat accumulation in four patients and hepatic hemangiomas in two patients. The focal liver lesions were not detected in the subsequent follow-up US in seven patients.

Hepatocellular carcinoma

The period prevalence of HCC in patients who received US surveillance was 3.5% (32 patients in 907 patients). Five HCC patients (15.6%) were

Table 4. Final radiological diagnosis of focal liver lesions (n = 159)

Diagnosis	Total (n = 159)
HCC	32 (20.1)
Benign lesion	
Cirrhotic nodule	31 (19.5)
Hemangioma	16 (10.1)
Abnormal fat accumulation	9 (5.7)
Cyst	3 (1.9)
Calcified granuloma	2 (1.3)
FNH/adenoma	2 (1.3)
Other benign lesion	2 (1.3)
Other malignant lesion	
Adenocarcinoma	1 (0.6)
Metastatic lung cancer	2 (1.3)
Indeterminate	20 (12.6)
No lesion	39 (24.5)

FNH = focal nodular hyperplasia
Data are presented as number (%)

Table 5. Characteristic of 32 patients with radiological diagnosis of HCC

Factors	Mean (SD) or number (%)
Age (year)	60.0 (9.6)
Gender	
Male	23 (71.9)
Female	9 (28.1)
Risk factor	
Chronic hepatitis B	16 (50.0)
Chronic hepatitis C	8 (25.0)
Multiple risk factor	2 (6.3)
Cryptogenic cirrhosis	2 (6.3)
Alcoholic liver disease	1 (3.1)
NAFLD	1 (3.1)
HCC post resection	2 (6.3)
Serum AFP	
<20 ng/ml	21 (65.6)
≥20 ng/ml	6 (18.8)
No data	5 (15.6)
Size of the largest lesion (mm)	22.5 (12-134)
No. of nodules	
1 nodule	22 (68.7)
2-3 nodules	8 (25.0)
>3 nodules	2 (6.3)
BCLC	
Very early stage (1 HCC, <2 cm)	8 (25.0)
Early HCC (1 HCC or 3 HCC <3 cm)	19 (59.4)
Intermediate to advance stage	5 (15.6)
Treatment	
Surgical resection	9 (28.1)
RFA	9 (28.1)
TOCE	12 (37.5)
Loss follow-up	2 (6.3)

BCLC = Barcelona Clinic Liver Cancer; RFA = radiofrequency ablation; TOCE = transarterial oily chemoembolization
Data are presented as number (%) or mean (SD)

detected by first ultrasound examination. HCC detection was found in twenty-seven (84.4%) patients in subsequent examinations after an interval of 3.3 to 45.6 months (median = 10.6).

The characteristics of 32 patients with radiological diagnosis of HCC during the course of the study were shown in the Table 5. Twenty-one of 32 patients (65.6%) had normal level of serum AFP. The median tumor size was 22.5 mm, ranging from 12 to 134 mm. Eight patients (25.0%) had HCC size compatible with very early stage HCC and 19 patients (59.4%) had size compatible with early HCC. However, five patients (15.6%) had HCC size compatible with intermediate to advance stage.

Nine HCC patients underwent surgical resection, seven patients underwent RFA only, two patients underwent RFA followed by TOCE and 12 patients received TOCE. The remaining two patients were lost to follow-up after diagnosis of HCC.

Among 12 patients who received TOCE, eight patients had small tumor size and were suitable for curative treatment. The various reasons as to why they underwent TOCE included poor physical condition for surgery (three patients), unresectable tumor at the caudate lobe (one patient), unsafe location of the tumor to perform RFA (three patients), and one patient was a candidate for liver transplantation.

Exceptional cases

Among the 907 patients studied, HCC was first detected not on ultrasonography but on CT in one patient and on MRI in two patients (0.3%). CT and MRI were used in surveillance instead of ultrasonography in one patient (0.1%) because the immediately previous ultrasonography had negative findings despite an elevated serum AFP. In the remaining two patients (0.2%), CT/MRI was ordered because of coarse and nodular liver parenchyma. The interval between the previous ultrasonography and the CT/MRI was 12 to 75 days. Among these three patients, two patients had tumor size of 12 and 16 mm and one patient had multiple HCCs with tumor thrombus within right portal vein.

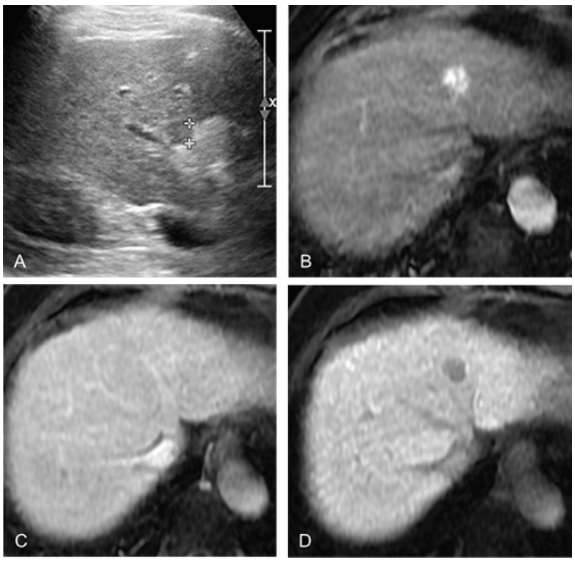

Fig. 2 A 78-year-old woman known case of cryptogenic cirrhosis with serum AFP level of 5.4 ng/ml was sent to surveillance for HCC. The US of the liver (A) showed a background cirrhotic liver with a 7-mm hypoechoic hepatic nodule at the hepatic segment IV. MRI of the liver revealed rapid arterial enhancement (B), isointense on venous phase (C) and no hepatocyte-specific agent uptake (D). These image findings were typical for early HCC and the patients were treated by radiofrequency ablation.

Discussion

To be useful, any surveillance program must be implemented well. Unfortunately, there is little data on HCC surveillance program performance in Thailand. We found that implementation of HCC surveillance guidelines was acceptable in our clinical practice because 75% of the surveillance intervals were within one year and 50% were between six and 12 months. However, in some cases there were irregular surveillance intervals. Several factors may contribute to this observation, including the compliance of patients toward ultrasound surveillance and the difficulty in scheduling follow-up ultrasound.

According to a recent meta-analysis by Singal et al[8], which included 13 studies, surveillance with ultrasound detected the majority of HCC before they presented clinically, with a pooled sensitivity of 94% and pooled specificity of 94%. Sensitivity and specificity of ultrasound in our study were approximately 76.2% and 20.1%, respectively.

Not surprisingly, most focal liver lesions in the present study were found in older and male patients. On the other hand, a lower frequency of focal liver lesions were detected in the patients with NAFLD and cryptogenic cirrhosis. It is unclear whether this is due to an actual lower incidence rate (as compared to viral hepatitis) or due to the difficulty of detecting focal liver lesion by ultrasound in a background of fatty liver and severe cirrhosis.

The optimal interval for ultrasound surveillance is unclear at present. The current guideline from AASLD recommends surveillance of cirrhotic patients with ultrasound every six to 12 months. In the meta-analysis by Singal et al[8], their meta-regression analysis demonstrated a significantly higher sensitivity for early HCC with ultrasound every six months than with annual surveillance. The meta-analysis study suggested that surveillance with ultrasound every six months was currently the best interval for detecting early HCC among patients with cirrhosis[8]. The retrospective cohort study from Japan also concluded that ultrasound surveillance at 6-month interval was appropriate in general for the detection of HCC at a size smaller than 30 mm[9]. Another multicenter randomized trial in France and Belgium[10] compared two ultrasonography performed at three months versus six months in 1,278 patients. The study reported that ultrasound surveillance, performed every three months, detected more small focal lesions (≤10 mm) than US every six months. In our practice, the median surveillance interval was 8.4 months, which was within the optimal interval. The mean size of detected HCC was below 20 mm.

It was unclear what the effects of performing surveillance at 12 months rather than six months would be from this study. The cumulative percentage of detected HCC patients was 11.1% and 70.4% at 6-month and 12-month surveillance interval, respectively. This observation implied that the diagnosis of HCC in 16 patients (59.3%) were delayed because their ultrasound examinations were performed after six to 12 months interval, rather than <6 months. However, the shorter surveillance interval did not seem to provide further advantage in terms of lesion size (median size of 13 mm at <6-month interval and 12 mm at ≥6-month interval (p-value = 0.89). Therefore, it remains unclear whether reducing the surveillance to a strict 6-month interval would be more benefit than 12-month interval as the median size was already small in both situations.

HCC can be diagnosed radiologically without the need for biopsy if typical imaging features were present. Although the AASLD recommended a contrast-enhanced study for diagnosis of HCC, there is no recommendation regarding the decision to use

CT or MRI to evaluate the focal liver lesion. According to a systemic review of Colli et al[9], MRI was more sensitive than CT in diagnosing HCC (81% vs. 68%). In our institute, MRI was the most frequently used investigation, and this was seen across differences in gender, health insurance, attending physician, serum AFP level, background liver parenchyma, number, and size of focal liver lesions. One reason for this may be because of the new hepatocyte-specific contrast used at our institution since 2008. Since then, MRI became more popular than CT scan for the evaluation of focal liver lesions (increasing from 33.3% to 57.9%).

For lesions smaller than 1 cm, AASLD recommend close follow-up at 3-month intervals using the technique that first documented the presence of the nodule. No detailed investigation is required, because most of these will be cirrhotic nodules rather than HCC. In the present study, however, most of the detected focal liver lesions that were smaller than 1 cm were not followed according to this recommendation. The majority of patients (39/48 patients) underwent CT or MRI rather than sonographic follow-up and most had diagnosis of benign lesion. This may have been due to the influence of the interdepartmental conference and the belief in the superior accuracy of modern (hepatocyte-specific contrast enhanced) MRI. For lesions larger than 1 cm in diameter, either MRI or CT scan should be performed. Unexpectedly, 18 patients (16.2%) in this group were kept under follow-up with US examination rather than having cross-sectional imaging and five patients still had lesions of undetermined nature on follow-up US, all of which may have precluded them from the potential benefit of early HCC detection. The reasons why they had not proceeded with CT or MRI was not clear.

In the present study, serum AFP level was normal in more than half of HCC patients (65.63%). Our findings may indicate that AFP is suboptimal for screening and ultrasound may be more helpful for early detection of HCC. Although AFP has been known as an HCC-specific tumor marker, the usefulness of AFP in HCC surveillance has been questioned. Reasons for the suboptimal performance of AFP as a serological test in the surveillance mode are (1) fluctuating levels of AFP in patients with cirrhosis might reflect either flares of HBV/HCV infection, exacerbation of underlying liver disease or HCC development and (2) only a small proportion of tumors at an early stage (10-20%) present with abnormal AFP serum levels, a fact that has been recently correlated with a molecular subclass of aggressive HCCs. By using the usual cut-off point of 20 ng/mL, sensitivities and specificities for detecting all stage of HCC were 41% to 65% and 80% to 94%, respectively[11]. A recent retrospective study in Thailand[12] reported the detection rate of 59.5% when AFP level of 20 ng/mL was used as the trigger point. The study concluded that the physician should not depend upon AFP to make the decision for further investigation. In fact, the latest AASLD guideline has excluded AFP as part of the screening process of HCC as it is not cost-effective.

A recent retrospective cohort study by Sarkar et al[13] among hepatitis B-infected Asian-Americans identified 51 patients (6.19%) with HCC in 824 at-risk patients received screening for HCC. Most of the patients were male (78%) and 82% were ≥50 years of age, 61% were cirrhotic and 35% had early stage disease at the time of HCC diagnosis. In the present study, surveillance of 907 patients with chronic liver disease identified 32 HCCs before clinical symptom became evident in these patients. The period prevalence of HCC is 3.5%. Similar to the retrospective cohort study mentioned prior, the majority of HCC patients in our study were male with a mean age of 50.0±9.6 years. Most of our HCC patients (27 patients; 84.4%) had solitary HCC or up to three nodule ≤3 cm in size. Such cases would be suitable for receiving curative treatments such as transplantation, surgical resection, or radiofrequency ablation although the actual treatment would depend on the state of the preserved liver function. Among the 27 patients who had a tumor size of very early/early stage HCC, 18 patients had curative treatments while eight patients underwent TOCE. The explanation for receiving palliative treatment in these early (according to size) HCC patients were poor physical condition for surgery (three patients), unresectable tumor at the caudate lobe (one patient), unsafe location of the tumor for performing RFA (three patients). One patient became a candidate for liver transplantation.

The overall detection rate of focal liver lesions and HCC in the present study was 17.8% and 3.5% respectively. This low rate of detection, which is more likely to be the result of the broad criteria for screening given in the guidelines, also determines the cost-effectiveness of the surveillance program. It may be possible to improve this detection rate in the future, and thus improve the cost-effectiveness of surveillance, by using new risk scores for hepatitis B as proposed by many authors[14,15], to select more at-risk patients. However, this important aspect will need to be confirmed in future studies.

The main limitation of the present study was the retrospective design and that detailed clinical information about the patient and calculation of the patients' liver function could not be assessed. This study may had a selection bias in that only patients in the liver clinic participating the surveillance program were included. Patients with liver disease treated outside this designated clinic, for example in specific consultant gastroenterologists or hepatologists clinics, were not included. Future studies are needed to evaluate the cost effectiveness and impact of surveillance on patient's survival.

Conclusion

Although there were irregular surveillance intervals in our clinical practice, the adherence to surveillance was acceptable with a period prevalence of HCC 3.5%. The majority of HCC's were discovered in the early stage with a median size of 22.5 mm.

What is already known on this topic?

The current guideline from the National Cancer Institute (Thailand) 2011 and the American Association for the Study of Liver Disease 2010 (AASLD) recommend surveillance for HCC with ultrasonography at 6-month intervals. Unfortunately, there is little data on HCC surveillance program performance in Thailand. In addition, the prevalence of HCC detection according to this surveillance program is not known.

What this study adds?

This study revealed the practice of HCC surveillance program of at-risk patients in tertiary hospital. Implementation of HCC surveillance guidelines was acceptable in our clinical practice. Seventy-five percent of the surveillance intervals were within one year and 50% were between six and 12 months. However, in some cases there were irregular surveillance intervals. The overall detection rate of focal liver lesions and HCC in this study was 17.8% and 3.5% respectively. Importantly, the majority of HCC's were discovered in the early stage with a median size of 22.5 mm.

Potential conflicts of interest

None.

References

1. Sanyal AJ, Yoon SK, Lencioni R. The etiology of hepatocellular carcinoma and consequences for treatment. Oncologist 2010; 15 (Suppl 4): 14-22.
2. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-2.
3. Bennett GL, Krinsky GA, Abitbol RJ, Kim SY, Theise ND, Teperman LW. Sonographic detection of hepatocellular carcinoma and dysplastic nodules in cirrhosis: correlation of pretransplantation sonography and liver explant pathology in 200 patients. AJR Am J Roentgenol 2002; 179: 75-80.
4. European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012; 56: 908-43.
5. Andreana L, Isgro G, Pleguezuelo M, Germani G, Burroughs AK. Surveillance and diagnosis of hepatocellular carcinoma in patients with cirrhosis. World J Hepatol 2009; 1: 48-61.
6. National Cancer Institute Thailand. Screening, diagnosis and treatment of liver and bile duct cancer. Bangkok: National Cancer Institute Thailand; 2011.
7. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999; 19: 329-38.
8. Singal A, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, et al. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther 2009; 30: 37-47.
9. Sato T, Tateishi R, Yoshida H, Ohki T, Masuzaki R, Imamura J, et al. Ultrasound surveillance for early detection of hepatocellular carcinoma among patients with chronic hepatitis C. Hepatol Int 2009; 3: 544-50.
10. Trinchet JC, Chaffaut C, Bourcier V, Degos F, Henrion J, Fontaine H, et al. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: a randomized trial comparing 3- and 6-month periodicities. Hepatology 2011; 54: 1987-97.
11. van Meer S, de Man RA, Siersema PD, van Erpecum KJ. Surveillance for hepatocellular carcinoma in chronic liver disease: evidence and controversies. World J Gastroenterol 2013; 19: 6744-56.
12. Chamadol N, Somsap K, Laopaiboon V, Sukeepaisarnjaroen W. Sonographic findings of hepatocellular carcinoma detected in ultrasound

surveillance of cirrhotic patients. J Med Assoc Thai 2013; 96: 829-38.
13. Sarkar M, Stewart S, Yu A, Chen MS, Nguyen TT, Khalili M. Hepatocellular carcinoma screening practices and impact on survival among hepatitis B-infected Asian Americans. J Viral Hepat 2012; 19: 594-600.
14. Wong VW, Chan SL, Mo F, Chan TC, Loong HH, Wong GL, et al. Clinical scoring system to predict hepatocellular carcinoma in chronic hepatitis B carriers. J Clin Oncol 2010; 28: 1660-5.
15. Yang HI, Yuen MF, Chan HL, Han KH, Chen PJ, Kim DY, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. Lancet Oncol 2011; 12: 568-74.

การเฝ้าระวังโรคมะเร็งตับด้วยการตรวจอัลตราซาวด์ในผู้ป่วยกลุ่มเสี่ยงที่คลินิกโรคตับ

ดวงกมล ประพฤติธรรม, จิตต์เกษม สุขใส, ทยา กิตติยากร, สิทธิ์ พงษ์กิจการุณ

ภูมิหลัง: *การตรวจพบมะเร็งตับในระยะเริ่มแรกมีผลต่อการรักษาและอัตราการอยู่รอดของผู้ป่วย แนวทางการตรวจคัดกรองและวินิจฉัยโรคมะเร็งตับ พ.ศ. 2554 จัดทำโดยสถาบันมะเร็งแห่งชาติ แนะนำให้เฝ้าระวังด้วยการตรวจอัลตราซาวด์ทุก 6 เดือนในผู้ป่วยกลุ่มเสี่ยงต่อการเกิดโรคมะเร็งตับ*

วัตถุประสงค์: *เพื่อศึกษาแบบแผนการปฏิบัติตามโปรแกรมการเฝ้าระวังโรคมะเร็งตับด้วยการตรวจอัลตราซาวด์และหาความชุกของโรคมะเร็งตับในผู้ป่วยกลุ่มเสี่ยง*

วัสดุและวิธีการ: *ทำการศึกษาย้อนหลังของภาพรังสีวิทยาที่ทำในผู้ป่วยกลุ่มเสี่ยงที่เข้ารับการดูแลที่คลินิกโรคตับ หน่วยตรวจผู้ป่วยนอกอายุรกรรม ตั้งแต่เดือนมกราคม พ.ศ. 2550 ถึง ธันวาคม พ.ศ. 2555*

ผลการศึกษา: *ผู้ป่วยกลุ่มเสี่ยงต่อการเกิดโรคมะเร็งตับ 907 ราย ได้รับการตรวจเฝ้าระวังโรคมะเร็งตับด้วยภาพอัลตราซาวด์ มีระยะเวลาเฝ้าระวังทั้งหมดเฉลี่ย 37±17.1 เดือน โดยผู้ป่วยแต่ละรายจะได้รับการตรวจอัลตราซาวด์เฉลี่ย 4.7±2.2 ครั้ง ระยะห่างระหว่างการตรวจอัลตราซาวด์แต่ละครั้งมีค่ามัธยฐานเท่ากับ 8.4 เดือน (1.1 ถึง 63 เดือน) ทั้งนี้พบก้อนผิดปกติจากการตรวจอัลตราซาวด์ในผู้ป่วย 161 ราย (ร้อยละ 17.8) ผู้ป่วยส่วนใหญ่ที่พบก้อนในตับได้รับการตรวจเพิ่มเติมด้วยเครื่องตรวจคลื่นแม่เหล็กไฟฟ้า (ร้อยละ 62.3) หรือเครื่องเอกซเรย์คอมพิวเตอร์ (ร้อยละ 20.8) พบโรคมะเร็งตับทั้งสิ้น 32 ราย คิดเป็นความชุกของโรคมะเร็งตับในผู้ป่วยกลุ่มเสี่ยงในระยะเวลาที่ทำการศึกษาเท่ากับร้อยละ 3.5 ส่วนใหญ่เป็นเพศชาย และปัจจัยเสี่ยงที่พบบ่อยที่สุดคือ ไวรัสตับอักเสบชนิดบี (ร้อยละ 50) โดยมีระดับซีรัม alpha-fetoprotein อยู่ในระดับปกติร้อยละ 65.6 ก้อนมะเร็งส่วนใหญ่ถูกพบจากการตรวจเฝ้าระวังที่ระยะห่างทุก 8 เดือน เมื่อตรวจเฝ้าระวังทุก 6 เดือน และ 12 เดือน จะตรวจพบจำนวนผู้ป่วยมะเร็งตับสะสมร้อยละ 11.1 และ 70.4 ตามลำดับ ก้อนมะเร็งตับส่วนใหญ่จัดอยู่ในระยะเริ่มแรก มีค่ามัธยฐานของขนาดก้อนเท่ากับ 2.3 เซนติเมตร*

สรุป: *ผู้ป่วยกลุ่มเสี่ยงที่คลินิกโรคตับ แม้จะได้รับการเฝ้าระวังโรคมะเร็งตับด้วยการตรวจอัลตราซาวด์ไม่สม่ำเสมอ แต่พบว่าได้รับการตรวจตามเกณฑ์ โดยมีค่าเฉลี่ยทุก ๆ 8 เดือน จากการเฝ้าระวังพบความชุกของโรคมะเร็งตับร้อยละ 3.5 ซึ่งก้อนมะเร็งตับส่วนใหญ่ที่ตรวจพบ จัดเป็นมะเร็งตับระยะเริ่มแรก*