Clinical course of sub-centimeter-sized nodules detected during surveillance for hepatocellular carcinoma

Yang Won Min, Geum-Youn Gwak, Min Woo Lee, Moon Seok Choi, Joon Hyoek Lee, Kwang Cheol Koh, Seung Woon Paik, Byung Chul Yoo

RESULTS: During 667 person-years of follow-up, HCC developed in 33 patients. The calculated HCC development rate was 4.9% per year. The cumulative one-, two-, three- and five-year HCC development rates were 5.6%, 10.6%, 14.1% and 20.4%, respectively. Upon baseline comparison, the HCC group was older (54.4 ± 8.3 years vs 48.9 ± 9.4 years; \( P = 0.003 \)) and had lower albumin levels (3.56 ± 0.58 g/dL vs 3.84 ± 0.55 g/dL; \( P = 0.012 \)) and higher baseline alpha-fetoprotein (AFP) levels (8.5 ng/mL vs 5.4 ng/mL; \( P = 0.035 \)) compared to the non-HCC group. Nodule pattern and initial radiologic diagnosis also differed between the two groups. Multivariate analysis revealed that age [\( P = 0.012 \), odds ratio (OR) =1.075, 95% confidence interval (CI) =1.016-1.137], sex (\( P = 0.009 \), OR = 3.969, 95% CI: 1.403-11.226), and baseline AFP level (\( P = 0.024 \), OR = 1.039, 95% CI: 1.005-1.073) were independent risk factors for developing HCC.

CONCLUSION: The overall risk of HCC development in patients with SCSNs is similar to that in liver cirrhosis patients. Patients with these risk factors need to be closely monitored during follow-up.

© 2012 Baishideng. All rights reserved.

Key words: Chronic liver disease; Hepatocellular carcinoma; Risk factor; Sub-centimeter-sized nodule

Peer reviewer: Philip Abraham, Professor, Hinduja National Hospital and Medical Research Centre, Veer Savarkar Marg, Mahim, Mumbai 400016, India

Min YW, Gwak GY, Lee MW, Choi MS, Lee JH, Koh KC, Paik SW, Yoo BC. Clinical course of sub-centimeter-sized nodules detected during surveillance for hepatocellular carcinoma. World J Gastroenterol 2012; 18(21): 2654-2660 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i21/2654.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i21.2654
INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death in the world, and the ninth leading cause of cancer deaths in the United States[1-7]. The number of deaths per year from HCC is virtually identical to the incidence throughout the world, underscoring the high fatality rate of this aggressive disease[8]. The sole approach to achieve long-term survival is to detect the tumor at an early stage, when effective therapy can be applied[9]. Accordingly, the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases recommend performing screening for HCC in patients at risk, who would be treated if diagnosed with this condition[10-12]. Under these guidelines, imaging criteria for the diagnosis of HCC are established for lesions 1 cm or larger in patients at risk, but owing to a high false-positive rate, a wait-and-see policy is recommended for nodules smaller than 1 cm in diameter[11,12]. However, the possibility remains high that minute hepatic nodules detected during surveillance may become malignant over time[13,14]. In addition, a delay in the start of treatment of early-stage HCC may be associated with a poorer patient survival[15]. Nevertheless, clinicians have limited data on the clinical course of sub-centimeter-sized nodules (SCSNs) detected during surveillance.

A variety of important risk factors for the development of HCC have been identified. These include chronic hepatitis B and C virus infection and cirrhosis due to almost any cause[16-22]. Almost 80% of cases are due to underlying chronic hepatitis B and C virus infection[17]. Since patients with chronic hepatitis B who may not have fully developed cirrhosis or have regressed cirrhosis as well as patients with cirrhosis are at increased risk of developing HCC, an updated the American Association for the Study of Liver Diseases guidelines recommended surveillance in patients with chronic hepatitis B[23].

The purpose of our study was to evaluate the outcome of SCSNs detected during HCC surveillance in patients at risk and to determine the risk factors for development of those nodules into HCC.

MATERIALS AND METHODS

Patients

This retrospective study was conducted according to the principles of the Declaration of Helsinki. The study involved patients with liver cirrhosis of any etiology or chronic liver disease including chronic hepatitis B and C virus infection, without a prior history of HCC in whom a SCSN was detected during HCC surveillance with ultrasonography (US) or computed tomography (CT) of the liver at Samsung Medical Center, Seoul, South Korea between January 1, 2005 and April 30, 2005 (n = 198). At inclusion, two patients had other types of cancer, and one patient was 12 mo of follow-up; (2) subjects who were lost to follow-up and diagnosed with HCC at an outside hospital; and (3) any history of cancer. Thus, a total of 56 patients were excluded from the study. Forty patients had less than 12 mo of follow-up, seven patients were excluded because HCC was diagnosed at the time of inclusion in the study, and three patients were lost to follow-up. Additionally, three patients had hepatic nodules 1 cm or larger in size at inclusion, two patients had other types of cancer, and the etiology of liver disease in one patient was unclear.

Data collection

The following clinical and laboratory information was collected from each patient: age, sex, etiology of liver disease, presence of liver cirrhosis, the Child-Pugh classification, aspartate aminotransferase (AST), alanine aminotransferase (ALT), prothrombin time (PT), serum total bilirubin, platelet count, serum albumin, and baseline and follow-up AFP levels.

Image interpretation

The initial radiologic diagnosis of SCSNs was based on the results of US or CT during surveillance. In addition, all radiologic images were reviewed by one radiologist who had 11 years of experience in liver imaging interpretation. He did not participate in the initial patient selection and was blinded to the final diagnoses and clinical information such as AFP levels. Each detected lesion was evaluated for the number, location, and echogenicity/attenuation of nodules. Lesions were categorized as follows: (1) hypoechoic/low-attenuation; (2) hyperechoic/high-attenuation; and (3) mixed echoic/attenuation (Figure 1). All lesions were included in one of these three categories.

The diagnosis of HCC was based either on biopsy or the clinical criteria of the Korean Liver Cancer Study Group and the National Cancer Center, South Korea[18]. Briefly, the diagnosis of HCC was made when the AFP level was ≥400 ng/mL and at least one of the dynamic enhancement CT or MRI showed a vascular pattern typical of HCC in patients at risk including patients with HBV or HCV infection, or liver cirrhosis. If the AFP level was <400 ng/mL, at least two of the dynamic enhancement CT, MRI or transarterial angiography must show vascular patterns typical of HCC in order to make a diagnosis of HCC.

Statistical analysis

Statistical analyses were conducted using PASW Statistics.
A total of 142 patients were included in this study. Their characteristics are summarized in Table 1. Eighty-four patients (59.2%) were male and the mean age was 50.2 ± 9.4 (SD) years. The etiology of liver disease was hepatitis B virus infection in 126 patients (88.7%), hepatitis C virus infection in 9 (6.3%), and alcoholic liver disease in 7 (5.0%). One hundred and eleven patients (78.2%) had cirrhotic liver. Ninety-eight patients (88.3%) were Child-Pugh class A, 10 (9.0%) were class B, and 3 (2.7%) were class C. A total of 33 patients had at least one SCSN: 23 patients were detected by US and 10 were detected by CT. There was one SCSN in 26 patients (18.3%), two SCSNs in 26 patients (18.3%), two SCSNs in 7 (5.0%), three in 3 (2.1%), four in 1 (0.7%), and more than four in 105 (73.9%). The SCSNs were hypoechoic/low-attenuation in 77 patients (54.3%), hyperechoic/high-attenuation in 31 (21.8%), and mixed echoic/attenuation in 34 (23.9%). Initial radiologic diagnosis of the hepatic nodules was regenerative nodule (RN)/dysplastic nodule (DN) in 119 patients (83.8%), hemangioma in 17 (12.0%), indeterminate nodule in 5 (3.5%), and arterioporal shunt in 1 (0.7%).

Continuous variables were compared parametrically using Student’s t-test or non-parametrically using the Mann-Whitney U-test. Categorical variables were compared using the $\chi^2$-test or Fisher’s exact test as appropriate. Multiple logistic regression analysis was performed on variables that were different between the non-HCC and HCC groups in the univariate analysis ($P < 0.100$), in order to identify variables independently associated with the development of HCC. HCC development rates were calculated using the Kaplan-Meier method. A two-sided $P$ value < 0.05 was considered statistically significant.

## RESULTS

A total of 142 patients were included in this study. Their characteristics are summarized in Table 1. Eighty-four patients (59.2%) were male and the mean age was 50.2 ± 9.4 (SD) years. The etiology of liver disease was hepatitis B virus infection in 126 patients (88.7%), hepatitis C virus infection in 9 (6.3%), and alcoholic liver disease in 7 (5.0%). One hundred and eleven patients (78.2%) had cirrhotic liver. Ninety-eight patients (88.3%) were Child-Pugh class A, 10 (9.0%) were class B, and 3 (2.7%) were class C. A total of 33 patients had at least one SCSN: 23 patients were detected by US and 10 were detected by CT. There was one SCSN in 26 patients (18.3%), two SCSNs in 26 patients (18.3%), two SCSNs in 7 (5.0%), three in 3 (2.1%), four in 1 (0.7%), and more than four in 105 (73.9%). The SCSNs were hypoechoic/low-attenuation in 77 patients (54.3%), hyperechoic/high-attenuation in 31 (21.8%), and mixed echoic/attenuation in 34 (23.9%). Initial radiologic diagnosis of the hepatic nodules was regenerative nodule (RN)/dysplastic nodule (DN) in 119 patients (83.8%), hemangioma in 17 (12.0%), indeterminate nodule in 5 (3.5%), and arterioporal shunt in 1 (0.7%).

During 667 person-years of follow-up (mean, 28.5 ± 20.0 mo), HCC developed in 33 patients (23.2%). The mean durations of follow-up were 32.6 ± 19.5 and 64.3 ± 17.6 in the HCC and non-HCC groups, respectively. The mean time to diagnosis of HCC after detection of SCSNs was 33.1 ± 18.9 mo. Except for one biopsy-proven case, most of the HCC cases were diagnosed according to the clinical criteria of the Korean Liver Cancer Study Group and the National Cancer Center, South Korea,[1] which were not same as the international guidelines[10,11] at that time. However, when retrospectively reevaluated, all diagnoses of HCC were satisfied with the updated American Association for the Study of Liver Diseases guidelines.[12] Following diagnosis, twelve patients (36.4%) underwent radiofrequency ablation, 13 (39.4%) underwent transarterial chemoembolization, 5 (15.2%) underwent surgical resection, 1 (3.0%) underwent liver transplantation, and 2 (6.0%) did not receive any treatment.

The calculated HCC development rate was 4.9% per year. The cumulative one-, two-, three- and five-year HCC development rates were 5.6%, 10.6%, 14.1% and 20.4%, respectively.

**Clinical features and initial radiologic results of patients in the HCC and non-HCC groups**

Patients diagnosed with HCC were older (54.4 ± 8.3 years vs 48.9 ± 9.4 years; $P = 0.003$) and had lower albumin levels (3.56 ± 0.58 g/dL vs 3.84 ± 0.55 g/dL; $P = 0.012$) and elevated baseline AFP levels (8.5 (range: 3.2-211.6) ng/mL vs 5.4 (range: 1.0-55.9) ng/mL; $P = 0.035$) compared to patients with non-HCC nodules. In terms of nodule pattern, patients diagnosed with HCC had more hypoechoic/low-attenuation nodules and less hyperechoic/high-attenuation nodules than patients with non-HCC nodules [23 (69.7%) vs 54 (49.5%) and 1 (3.0%) vs 30 (27.5%), respectively, $P = 0.011$]. In the initial radiologic diagnosis of hepatic nodules, RN/DN accounted for 31 (93.9%) in patients diagnosed with HCC, while RN/DN and hemangioma accounted for 88 (80.7%) and 17 (15.6%), respectively, in patients with non-HCC nodules ($P = 0.036$). There were no significant differences in...
Table 1  Baseline characteristics of high-risk patients who had sub-centimeter-sized nodules (n = 142)

| Baseline characteristics | Number of patients |
|-------------------------|--------------------|
| Age (yr)                | 50.2 ± 9.4         |
| Male                    | 84 (59.2)          |
| Hepatitis B infection   | 126 (88.7)         |
| Hepatitis C infection   | 9 (6.3)            |
| Alcohol liver cirrhosis | 7 (5.0)            |
| Liver cirrhosis         | 111 (78.2)         |
| Child-Pugh A            | 98 (88.3)          |
| Child-Pugh B            | 10 (9.0)           |
| Child-Pugh C            | 3 (2.7)            |
| AST (UI/L)              | 47.9 ± 26.8        |
| ALT (UI/L)              | 53.2 ± 42.5        |
| PT (INR)                | 1.19 ± 0.17        |
| Bilirubin (mg/dL)       | 1.24 ± 0.97        |
| Platelets (10^12/L)     | 125.3 ± 60.3       |
| Albumin (g/dL)          | 3.77 ± 0.56        |
| Baseline AFP (ng/mL, range) | 5.7 (1.0-211.6) |
| Number of nodules       |                   |
| One                     | 26 (18.3)          |
| Two                     | 7 (5.0)            |
| Three                   | 3 (2.1)            |
| Four                    | 1 (0.7)            |
| Over four               | 105 (73.9)         |
| Nodule pattern          |                   |
| Hypoechoic/low-attenuation | 77 (54.3)     |
| Hyperechoic/high-attenuation | 31 (21.8) |
| Mixed                   | 34 (23.9)          |
| Initial radiologic diagnosis |         |
| RN/DN                   | 119 (83.8)         |
| Hemangioma              | 17 (12.0)          |
| Indeterminate nodule    | 5 (3.5)            |
| Arterioporal shunt     | 1 (0.7)            |

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; PT: Prothrombin time; AFP: Alpha-fetoprotein; RN: Regenerative nodule; DN: Dysplastic nodule; INR: International normalized ratio. Data are shown as the mean ± SD, median (range) or n (%) of patients.

Table 2  Risk factors for the development of hepato-cellular carcinoma from sub-centimeter-sized nodules

| Variables                          | Diagnosis              | P value | OR  | 95% CI       |
|------------------------------------|------------------------|---------|-----|--------------|
|                                   | HCC (n = 33)           |         |     |              |
| Age (yr)                           | 54.4 ± 8.3             | 0.003   |     |              |
| Male                               | 24 (72.4)              | 0.070   |     |              |
| Hepatitis B infection              | 27 (81.8)              | 0.364   |     |              |
| Hepatitis C infection              | 3 (9.1)                |         |     |              |
| Alcohol liver cirrhosis            | 3 (9.1)                |         |     |              |
| Liver cirrhosis                    | 29 (87.9)              | 0.123   |     |              |
| AST (UI/L)                         | 49.3 ± 20.4            | 0.736   |     |              |
| ALT (UI/L)                         | 50.9 ± 36.5            | 0.722   |     |              |
| PT (INR)                           | 1.23 ± 0.17            | 0.088   |     |              |
| Bilirubin (mg/dL)                  | 1.27 ± 0.78            | 0.831   |     |              |
| Platelets (10^12/L)                | 110.1 ± 53.9           | 0.099   |     |              |
|Albumin (g/dL)                      | 3.56 ± 0.58            | 0.012   |     |              |
| Number of nodules                  | 0.390                  |         |     |              |
| One                                | 4 (12.1)               | 22 (20.0)| |              |
| Two                                | 1 (0.0)                | 6 (5.5) |     |              |
| Three                              | 0 (0.0)                | 3 (2.8) |     |              |
| Four                               | 0 (0.0)                | 1 (0.9) |     |              |
| Over four                          | 28 (84.8)              | 77 (70.6)| |              |
| Nodule pattern                     | 0.111                  |         |     |              |
| Hypoechoic/low-attenuation         | 23 (69.7)              | 54 (49.5)| |              |
| Hyperechoic/high-attenuation       | 1 (0.0)                | 30 (27.5)| |              |
| Mixed                              | 9 (27.3)               | 25 (22.9)| |              |
| Initial radiologic diagnosis       | 0.036                  |         |     |              |
| RN/DN                              | 31 (93.9)              | 88 (80.7)| |              |
| Hemangioma                         | 0 (0.0)                | 17 (15.6)| |              |
| Indeterminate nodule               | 2 (6.1)                | 3 (2.8) |     |              |
| Arterioporal shunt                 | 0 (0.0)                | 1 (0.9) |     |              |
| Baseline AFP (ng/mL, range)        | 8.5 (3.2-211.6)        | 5.4 (1.0-55.9)| | 0.035 |

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; PT: Prothrombin time; AFP: Alpha-fetoprotein; RN: Regenerative nodule; DN: Dysplastic nodule; INR: International normalized ratio; HCC: Hepatocellular carcinoma. Data are shown as the mean ± SD, median (range) or n (%) of patients.

Table 3  Multivariate analysis of risk factors for the development of hepatocellular carcinoma from sub-centimeter-sized hepatic nodules

| Variables                          | P value | OR  | 95% CI       |
|------------------------------------|---------|-----|--------------|
| Age (yr)                           | 0.012   | 1.073| 1.006-1.137  |
| Male                               | 0.009   | 3.969| 1.403-11.226 |
| PT (INR)                           | 0.877   | 0.698| 0.007-66.718 |
| Platelets (10^12/L)                | 0.917   | 0.999| 0.090-1.009  |
| Albumin (g/dL)                     | 0.478   | 0.624| 0.169-2.298  |
| Nodule pattern                     | 0.081   |     |              |
| Nodule pattern (1)                 | 1.000   | 0.812| 0.233-2.827  |
| Nodule pattern (2)                 | 0.054   | 0.075| 0.006-1.026  |
| Baseline AFP (ng/mL)               | 0.024   | 1.039| 1.005-1.073  |

1 Between hypoechoic/low-attenuation and mixed echoic/attenuation, 2 between hyperechoic/high-attenuation and mixed echoic/attenuation. OR: Odds ratio; CI: Confidence interval; PT: Prothrombin time; AFP: Alpha-fetoprotein; INR: International normalized ratio. Data are shown as the mean ± SD, median (range) or n (%) of patients.

DISCUSSION

The purpose of our study was to evaluate the outcome of SCSNs detected during surveillance in patients at risk and to determine risk factors for developing HCC from those nodules. The current practice guidelines recommend follow-up of SCSNs every few months in order to detect growth suggestive of malignant transformation. However, early diagnosis of HCC has a significant impact on survival because it enables the timely implementation of effective treatment strategies, including hepatic resection, loco-regional ablative therapy, and liver transplantation. In addition, even in cases of HCC that are...
Min YW et al. Sub-centimeter-sized hepatic nodules
detected early and can be treated with radiofrequency ablation, a delay (more than five weeks) in treatment may be associated with poorer patient survival\cite{18,21,25-33}. Therefore, in the present study, we focused on the SCSNs, which have not been investigated so far, even though occasionally encountered in practice, and identified clinical risk factors for the development of HCC from SCSNs.

Several studies have reported an HCC yearly incidence in HBV or HCV infection, which is between 2%-8% per year depending on the study population\cite{12,18,21,25-33}. In the present study, the annual HCC incidence from SCSNs was 4.9% per year, which is similar to above-mentioned HCC incidences of 2%-8%/year in chronic HBV or HCV infection. Thus, although the detection of SCSNs during surveillance is not infrequent and their management could be a major clinical challenge, it seems that the HCC incidence does not increase significantly in patients with SCSNs compared to patients without SCSNs.

There have been a few studies of sub-centimeter-sized HCC\cite{16,34,35}. Park et al\cite{34} reported that small (5-10 mm) arterially enhancing nodules at the hepatic arterial phase of CT in surveillance for HCC have a 29.5% probability of developing into HCC over a mean 35.7 mo of follow-up on a per-person basis. They also identified the presence of HCC treatment history, a larger size of small (5-10 mm) arterially enhancing nodules, presence of coexistent HCC, and absence of coexistent typical arteriportal shunts as independent risk factors for future development of HCC. In our study, SCSNs had a 23.2% probability of developing into HCC over a mean of 28.5 mo of follow-up. The unique feature of the present study that differentiates it from that of Park et al\cite{34} is that our study population had no prior HCC history and included 77 (54.3%) patients who had hypoechoic/low-attenuation SCSNs. In addition, patients diagnosed with HCC had more hypoechoic/low-attenuation SCSNs than patients with non-HCC nodules (69.7% vs 49.5%; \( P = 0.011 \); Table 2), although the difference was not significant in the multivariate analysis (\( P = 0.081 \)). This could be due to hemangiomas, which are mainly hypoechoic/high-attenuation and benign, because 17 patients with a hemangioma were included only in the non-HCC group (Table 2). Therefore, we selected patients who had RN/DN and performed a subgroup analysis. The proportion of patients with hypoechoic/low-attenuation SCSNs did not differ between the two groups (70.0% vs 56.5%, \( P = 0.134 \)). According to our results, non-enhancing minute hepatic nodules also might have considerable malignant potential and should receive as much attention as enhancing nodules.

A study by Forner et al\cite{36} evaluated the accuracy of contrast-enhanced US and dynamic MRI for the diagnosis of nodules 20 mm or smaller detected during US surveillance. The study included 89 patients with cirrhosis, of whom 13 patients (14.6%) had a SCSN. Among those with SCSNs, 2 (15.4%) were ultimately diagnosed with HCC. Significant differences were found in age, nodule size, and the presence of a halo between patients diagnosed with HCC and patients with non-HCC nodule in all subjects, although multivariate analysis was not performed. In our study, old age, male sex, and high baseline AFP levels were associated with an increased risk of developing HCC from SCSNs detected during surveillance. Among these variables, male sex was the strongest risk factor (\( P = 0.009 \), OR = 3.969, 95% CI: 1.403-11.226). Elevated baseline AFP levels may be affected by undiscovered HCC. Therefore, we excluded subjects who were diagnosed with HCC at the time of inclusion in the study. Additionally, we investigated the change in AFP levels and calculated the AFP ratio as the last AFP level divided by the baseline AFP level. The AFP ratios were also significantly elevated in the HCC group compared to the non-HCC group (1.0 (range: 0.2-74.3) vs 0.7 (range: 0.0-4.7); \( P = 0.040 \)), even though baseline AFP levels were elevated. Thus, elevated AFP level at baseline could be considered a risk factor for developing HCC, and an increased AFP ratio during follow-up should be considered a critical warning sign for HCC development.

The present study had some limitations. First, the retrospective design likely introduced selection bias. Second, there was a lack of histological confirmation for the benign lesions, which were defined on the basis of radiologic images. However, it is unlikely that HCCs were incorrectly categorized as benign because our follow-up period was sufficiently long. Furthermore, pathological confirmation of these lesions would not be practical in clinical settings. Last, our assessments regarding the number, location, nodule pattern, and size of SCSNs had an element of subjectivity due to the small nodule sizes and sometimes ill-defined margins. To overcome this limitation, all radiologic images were reviewed by an experienced radiologist who was blinded to the final diagnoses.

In conclusion, the overall risk of HCC development in patients with SCSNs is similar to that in liver cirrhosis patients. However, since old age, male sex, and high baseline AFP level are associated with an increased risk of developing HCC from SCSNs, patients with these risk factors need to be closely monitored during follow-up.

**COMMENTS**

**Background**

During hepatocellular carcinoma (HCC) surveillance, the detection of sub-centimeter-sized nodules (SCSNs) is not infrequent and their management is a major clinical challenge. Owing to a high false-positive rate, a wait-and-see policy is recommended for those nodules. However, the possibility remains high that small nodules detected during surveillance may become malignant over time and a delay in the start of treatment of even early-stage HCC may be associated with a poorer patient survival.

**Research frontiers**

Clinicians have limited data on the clinical course of SCSNs in clinical settings. Last, our assessments regarding the number, location, nodule pattern, and size of SCSNs had an element of subjectivity due to the small nodule sizes and sometimes ill-defined margins. To overcome this limitation, all radiologic images were reviewed by an experienced radiologist who was blinded to the final diagnoses.

In conclusion, the overall risk of HCC development in patients with SCSNs is similar to that in liver cirrhosis patients. However, since old age, male sex, and high baseline AFP level are associated with an increased risk of developing HCC from SCSNs, patients with these risk factors need to be closely monitored during follow-up.

**Innovations and breakthroughs**

This is the first report to evaluate the outcome of SCSNs detected during surveillance in patients with cirrhosis or chronic liver disease and to determine...
risk factors for developing HCC from those nodules. Therefore, the study could provide valuable information to clinicians managing patients with chronic liver disease.

Applications
The study results suggest that patients with risk factors such as old age, male sex and high baseline alpha-fetoprotein need to be closely monitored during follow-up.

Peer review
This study is very informative for clinicians because the detection of SCSNs during surveillance is frequently encountered in practice setting. In addition, their results have scientific relevance for understanding the epidemiology of the disease.

REFERENCES

1 Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74-108
2 Altukruse SF, McClynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 2009; 27: 1485-1491
3 Bosch FX, Ribes J, Díaz M, Cléries R. Primary liver cancer: worldwide incidence and trends. Gastroenterology 2004; 127: S5-S16
4 Stroffolini T, Andreone P, Andriulli A, Ascione A, Craxi A, Chiaravalloti M, Galante D, Manghisi OG, Mazzanti R, Medaglia C, Pilleri G, Rapaccini GL, Simonetti RG, Taliani G, Tosti ME, Villa E, Gassabarin G. Characteristics of hepatocellular carcinoma in Italy. J Hepatol 1998; 29: 944-952
5 El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999; 340: 745-750
6 Deuffic S, Poynard T, Buffat L, Valleron AJ. Trends in primary liver cancer. Lancet 1998; 351: 214-215
7 Taylor-Robinson SD, Foster GR, Arora S, Hargreaves S, Tho-
8 Parkin DM. Global cancer statistics in the year 2000. Lancet Oncol 2001; 2: 533-543
9 Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 2010; 30: 61-74
10 Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodès J. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001; 35: 421-430
11 Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005; 42: 1208-1236
12 Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-1022
13 Fracanzani AL, Burdick L, Borzio M, Roncalli M, Bonelli N, Borzio F, Maraschi A, Fiorelli G, Fargion S. Contrast-enhanced Doppler ultrasonography in the diagnosis of hepatocellular carcinoma and premalignant lesions in patients with cirrhosis. Hepatology 2001; 34: 1109-1112
14 Takayama T, Makucuchi M, Hirohashi S, Sakamoto M, Okazaki N, Takayasu K, Kosuge T, Motoo Y, Yamazaki S, Hasegawa H. Malignant transformation of adenomatous hyperplasia to hepatocellular carcinoma. Lancet 1990; 336: 1150-1153
15 Chen WT, Fernandes ML, Lin CC, Lin SM. Delay in treatment of early-stage hepatocellular carcinoma using radiofrequency ablation may impact survival of cirrhotic patients in a surveillance program. J Surg Oncol 2011; 103: 133-139
16 Davila JA, Morgan RO, Shaib Y, McClynn KA, El-Serag HB. Hepatitis C infection and the increasing incidence of hepatocellular carcinoma: a population-based study. Gastroenterology 2004; 127: 1372-1380
17 Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006; 45: 529-538
18 Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22 707 men in Taiwan. Lancet 1981; 2: 1129-1133
19 Tsukuma H, Hiyama T, Tanaka S, Nakao M, Yabuuchi T, Kitamura T, Nakanishi K, Fujimoto I, Inoue A, Yamazaki H. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. N Engl J Med 1993; 328: 1797-1801
20 Yu MW, Chen CJ. Hepatitis B and C viruses in the development of hepatocellular carcinoma. Crit Rev Oncol Hematol 1994; 17: 71-91
21 Sherman M, Peletkian KM, Lee C. Screening for hepatocellular carcinoma in chronic carriers of hepatitis B virus: incidence and prevalence of hepatocellular carcinoma in a North American urban population. Hepatology 1995; 22: 432-438
22 Chen JD, Yang HL, Illoje UH, You SL, Lu SN, Wang LY, Su J, Sun CA, Liao YF, Chen CJ. Carriers of inactive hepatitis B virus are still at risk for hepatocellular carcinoma and liver-related death. Gastroenterology 2010; 138: 1747-1754
23 Gonzalez SA, Keeffe EB. Diagnosis of hepatocellular carcinoma: role of tumor markers and liver biopsy. Clin Liver Dis 2011: 15: 297-306, vii-x
24 Ishikawa M, Yogita S, Miyake H, Fukuda Y, Harada M, Wada D, Tashiro S. Differential diagnosis of small hepatocellular carcinoma and borderline lesions and therapeutic strategy. Hepatogastroenterology 2002; 49: 1591-1596
25 Sakuma K, Saitoh N, Kasai M, Itsukawa H, Yoshino I, Yamaguchi M, Nobutomo K, Yamumi M, Tsuda F, Komazawa T. Relative risks of death due to liver disease among Japanese male adults having various statuses for hepatitis B s and e antigen/antibody in serum: a prospective study. Hepatology 1988; 8: 1642-1646
26 McMahon BJ, Alberts SR, Wainwright RB, Bulkow L, Lainer AP. Hepatitis B-related sequelae. Prospective study in 1400 hepatitis B surface antigen-positive Alaska native counterfeiters. Arch Intern Med 1990; 150: 1051-1054
27 Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, Nevens F, Solinas A, Mura D, Brouwer JT, Thomas H, Njapoum C, Casarin C, Bonetti P, Fuschi P, Basho J, Tocco A, Bhalla A, Galassi E, Novembre F, Schahin SW, Rea Al K. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997; 112: 463-472
28 Degos F, Christidis C, Ganne-Carrie N, Farmachidi JP, Degott C, Guettier C, Trinchet JC, Beaugrand M, Chevet S, Hepatitis C virus related cirrhosis: time to occurrence of hepatocellular carcinoma and death. Gut 2008; 57: 131-136
29 Villeneuve JP, Desrochers M, Infante-Rivard C, Willems B, Raymond G, Bourcier M, Côté J, Richer G. A long-term follow-up study of asymptomatic hepatitis B surface antigen-positive carriers in Montreal. Gastroenterology 1994; 106: 1000-1005
30 Manno M, Cannâ, Scheper S, Bassi F, Gelmini R, Giannini F, Misseri F, Grottola A, Ferretti I, Vecchi C, De Palma M, Villa E. Natural history of chronic HBV carriers in northern Italy: morbidity and mortality after 30 years. Gastroenterology 2004; 127: 756-763
31 Hu S, Chien RN, Yeh CT, Sheen IS, Chiu HY, Chu CM, Liaw YF. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. Gastroenterology 2002; 125: 1522-1527
32 de Franchis R, Mucci G, Vecchi M, Tatarrella M, Colombo M, Del Ninno E, Rumi MG, Donato MF, Ronchi G. The natural history of asymptomatic hepatitis B surface antigen carriers.

Min YW et al. Sub-centimeter-sized hepatic nodules

WJG | www.wjgnet.com

2659 | June 7, 2012 | Volume 18 | Issue 21 |
Min YW et al. Sub-centimeter-sized hepatic nodules

Ann Intern Med 1993; 118: 191-194

33. Sánchez-Tapias JM, Costa J, Mas A, Bruguera M, Rodés J. Influence of hepatitis B virus genotype on the long-term outcome of chronic hepatitis B in western patients. Gastroenterology 2002; 123: 1848-1856

34. Park MJ, Kim YS, Lee WJ, Lim HK, Rhim H, Lee J. Outcomes of follow-up CT for small (5-10-mm) arterially enhancing nodules in the liver and risk factors for developing hepatocellular carcinoma in a surveillance population. Eur Radiol 2010; 20: 2397-2404

35. Kim JE, Kim SH, Lee SJ, Rhim H. Hypervascular hepatocellular carcinoma 1 cm or smaller in patients with chronic liver disease: characterization with gadoxetic acid-enhanced MRI that includes diffusion-weighted imaging. AJR Am J Roentgenol 2011; 196: W758-W765

36. Forner A, Vilana R, Ayuso C, Bianchi L, Solé M, Ayuso JR, Boix L, Sala M, Varela M, Llovet JM, Brú C, Bruix J. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: Prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. Hepatology 2008; 47: 97-104

S- Editor Gou SX  L- Editor O’Neill M  E- Editor Xiong L