

# Ultrasonography surveillance improves prognosis of patients with hepatocellular carcinoma

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Received October 1, 2018; Accepted April 22, 2019

DOI: 10.3892/mco.2019.1888

**Abstract.** To examine the effectiveness of ultrasonography (US) for hepatocellular carcinoma (HCC) surveillance, the prognosis of HCC patients who underwent such screening at an expert medical institution or at general clinics were analyzed, as well as those without US surveillance. From October 2006 to December 2014, 872 patients with naïve HCC were enrolled and divided into the surveillance (S)-group (n=398), who underwent follow-up examinations with US, and the non-S group (n=474). The S-group was further subdivided into patients who underwent follow-up surveillance at Ehime Prefectural Central Hospital, an expert medical institution (SE-group, n=189), and those who received surveillance at general clinics (SG-group, n=209). Prognosis and clinical characteristics were analyzed. In the non-S group, the frequency of patients without viral hepatitis (NBNC-HCC) and Tumor, Node, Metastasis stage was greater. As a result, the median survival time (MST) of the non-S group was reduced, compared with the S group (non-S group, 34.1 vs. S group, 68.2 months;  $P<0.001$ ). Tumor size was significantly different between the SE- and SG-groups (SE-group,  $2.0\pm 1.0$  vs. SG-group,  $2.5\pm 1.3$  cm;  $P<0.001$ ), whereas tumor number (SE-group:  $1.5\pm 1.1$  vs. SG-group,  $1.7\pm 1.2$ ;  $P=0.164$ ) and MST (SE-group, 72.1 vs. SG-group, 67.1 months;  $P=0.931$ ) were not significantly different. Surveillance performed at either an expert medical institution or general clinic improved the prognosis of HCC patients. Dissemination of findings demonstrating the importance of surveillance for HCC to all clinicians as well as patients with chronic liver disease

is important, and establishment of an effective surveillance strategy for NBNC-HCC is required.

## Introduction

Hepatocellular carcinoma (HCC), one of the most commonly occurring malignant tumors worldwide (1,2), often develops in patients with hepatitis C virus (HCV) or hepatitis B virus (HBV) infection (3,4), who are defined as high-risk for HCC and are recommended to undergo protocol screening for tumor development with a surveillance program. Detection of HCC at an early stage is important to improve patient prognosis, as tumor burden is an important prognostic factor along with hepatic reserve function (5-7). The progression of surgical resection (8) and/or radiofrequency ablation (RFA) (9,10) as curative treatments have improved patient prognosis when diagnosed at an earlier stage. In addition, the development of tyrosine kinase inhibitors (11-14) has contributed to a better HCC prognosis in patients who are allocated an unresectable status. Ultrasonography (US) is a popular and economical examination method that does not involve X-ray exposure, which is deemed to be suitable for HCC surveillance. Early stage HCC diagnosis is important for treatment (15), meaning that a suitable surveillance program should be evaluated.

Although the surveillance program for HCC, which primarily utilizes US, has been performed in patients with a high risk of HCC in Japan, few reports of surveillance efficacy for the improvement of prognosis have been performed. Only a limited number of studies have examined the effectiveness of HCC surveillance performed at regional hub hospitals in Japan (16). Herein, the outcomes of HCC patients with and without surveillance using with US were analyzed to elucidate its usefulness and impact for improving prognosis.

## Materials and methods

**Patients and definition of surveillance for HCC.** The records of 872 patients with naïve HCC who were examined from October 2006 to December 2014 were analyzed, following the

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**Key words:** hepatocellular carcinoma, surveillance, ultrasonography

exclusion of 170 cases without information regarding HCC surveillance. The enrolled patients were divided into those who did (S-group, n=398) and did not (non-S group, n=474) undergo surveillance. In addition, the S-group was divided into two sub-groups: i) Those who underwent surveillance at Ehime Prefectural Central Hospital (EPCH), an expert medical institution (SE-group, n=189); and ii) those who received surveillance at general clinics (SG-group, n=209; Fig. 1). Patients whose surveillance of HCC was performed only with AFP examination or whose HCC was pointed out incidentally were classified as the non-S group. The outcomes and clinical characteristics of the S- and non-S groups were compared in a retrospective manner, while those of the SE- and SG-groups were also compared as a sub-analysis.

**Surveillance program.** EPCH is a qualified regional hub hospital, where surveillance for HCC is performed for a fixed interval (3 or 6 months) with US and  $\alpha$ -fetoprotein (AFP) in accordance with liver disease grade [chronic hepatitis (CH; n=200) or liver cirrhosis (LC; n=198)], following practical guidelines for HCC used in Japan since 2005 (17,18).

**Diagnosis of HCC.** When HCC is suspected based on US findings, contrast enhanced US (CEUS), dynamic CT, or gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (EOB-MRI) (19) was typically performed as an additional examination. HCC was diagnosed in patients based on increasing AFP expression, as well as dynamic CT (20), magnetic resonance imaging (MRI), and/or CEUS with perflubutane (Sonazoid®; Daiichi Sankyo Co., Ltd., Tokyo, Japan) (21,22) findings. Tumor, Node, Metastasis (TNM) stage was determined according to the Liver Cancer Study Group of Japan, 6th edition (23).

The study protocol was conducted in compliance with the Helsinki Declaration and was approved by the Institutional Ethics Committee of EPCH (approval no. 26-11). Values are expressed as the mean  $\pm$  standard deviation. Statistical analyses were performed using Student's t test, Welch's test, Fischer's exact test, Mann-Whitney's U test, and the Kaplan-Meier method with a log-rank test using EZR version 1.29 (24), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

Although age was not significantly different between the S- (n=398) and non-S (n=474) groups (S, 70.2 $\pm$ 9.2 vs. non-S, 70.4 $\pm$ 10.7 years;  $P = 0.689$ ), the frequency of male gender (S, 66.1% vs. non-S, 76.8%;  $P < 0.001$ ), surgical resection (S, 21.1% vs. non-S, 31.4%;  $P < 0.001$ ), NBNC-HCC (S, 14.5% vs. non-S, 36.7%;  $P < 0.001$ ), lower grade of Child-Pugh classification (B and C; S, 23.1% vs. non-S, 36.4%;  $P < 0.001$ ), and TNM stage IV (S, 1.3% vs. non-S, 29.1%;  $P < 0.001$ ) was greater, while tumor size (S, 2.3 $\pm$ 1.2 vs. non-S, 5.4 $\pm$ 3.7 cm;  $P < 0.001$ ) and tumor number (S, 1.6 $\pm$ 1.1 vs. non-S, 2.5 $\pm$ 2.0;  $P < 0.001$ ) were significantly larger in the non-S group. Furthermore, those non-S patients had higher levels of tumor markers, including AFP (S, 201.8 $\pm$ 1228.6 ng/ml vs. non-S,

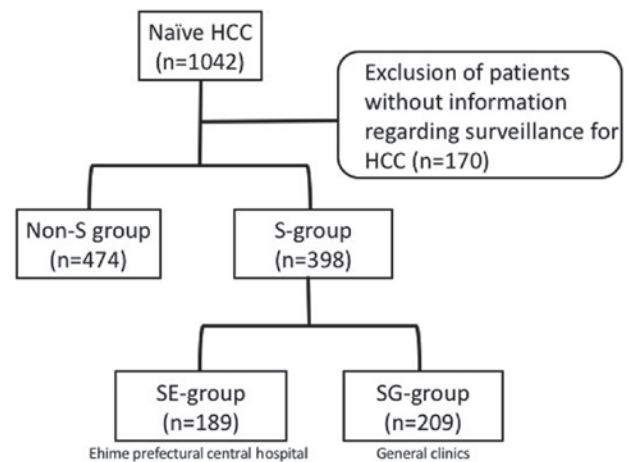


Figure 1. Patients with naïve HCC enrolled in the present study. In total, 872 patients with naïve HCC were enrolled, who were examined from October 2006 to December 2014, following the exclusion of cases without information regarding surveillance findings. They were divided into those who did (S-group, n=398) and did not (non-S group, n=474) undergo surveillance. The S-group was further subdivided into patients who underwent surveillance at Ehime Prefectural Central Hospital (SE-group, n=189) and general clinics (SG-group, n=209). HCC, hepatocellular carcinoma; S-group, surveillance group; non-S, non-surveillance group; SE-group, follow-up surveillance at Ehime Prefectural Central Hospital; SG-group, follow-up surveillance at general clinics.

15,123.4 $\pm$ 77,037.9 ng/ml;  $P < 0.001$ ), fucosylated-AFP (AFP-L3; S, 9.2 $\pm$ 17.0% vs. non-S, 19.9 $\pm$ 25.8%;  $P < 0.001$ ), des- $\gamma$ -carboxy prothrombin (DCP; S, 757.2 $\pm$ 4918.0 mAU/ml vs. non-S, 17,472.5 $\pm$ 46,451.4 mAU/ml;  $P < 0.001$ ; Table I). In addition, the overall survival rate (OSR) after 1 (S, 91.6% vs. non-S, 71.8%), 3 (S, 75.3% vs. non-S, 47.8%) and 5 years (S, 55.2% vs. non-S, 34.7%) was significantly higher in the S group, compared with the non-S group, as was median survival time (MST; S, 68.2 vs. non-S, 34.1 months;  $P < 0.001$ ; Fig. 2).

Sub-analyses were also performed for comparison of patient characteristics and prognosis. The S-group was divided into those who underwent surveillance at EPCH, an expert medical institution (SE-group, n=189), and at a general clinic (SG-group, n=209). It was determined that average age was older (SG-group, 71.4 $\pm$ 8.8 vs. SE-group, 68.8 $\pm$ 9.5 years), tumor size was larger (SG-group, 2.5 $\pm$ 1.3 vs. SE-group, 2.0 $\pm$ 1.0 cm), and frequency of TNM stage II and III (SG-group, 71.8 vs. SE-group, 52.9%) was greater in the SG-group (all  $P < 0.001$ ; Table II). Although there were significant differences in tumor size and frequency of TNM stage II and III, tumor number was not significantly different (SE-group, 1.5 $\pm$ 1.1 vs. SG-group, 1.7 $\pm$ 1.2;  $P = 0.164$ ). As a result, the 1-, 3- and 5-year OSR (SG-group, 92.4, 76.0 and 55.8% vs. SE-group, 90.8, 74.5 and 54.6%, respectively) and MST (SG-group, 67.1 vs. SE-group, 72.1 months) were not significantly different between the SG- and SE-groups ( $P = 0.931$ ; Fig. 3).

## Discussion

Surveillance for HCC in high-risk patients, such as those with viral hepatitis or LC has been expected to improved patient prognosis due to earlier tumor detection. There are a number of reasons why a surveillance program improves prognosis,

Table I. Comparison for the characteristics of S- and non-S group.

Patient characteristics	S-group (n=398)	Non-S group (n=474)	P-value
Age (years)	70.2±9.2	70.4±10.7	0.689
Gender (male:female)	263:135	364:110	<0.001
Etiology (HCV:HBV:HBV+HCV:NBNC)	310:25:5:58	250:46:4:174	<0.001
Number of HCV patients obtained SVR	8	7	1.000
Number of HBV patients treated with NA	18	0	<0.001
Maximum tumor diameter (cm)	2.3±1.2	5.4±3.7	<0.001
Tumor number	1.6±1.1	2.5±2.0	<0.001
AFP (ng/ml)	201.8±1228.6	15,123.4±77,037.9	<0.001
AFP-L3 (%)	9.2±17.0	19.9±25.8	<0.001
DCP (mAU/ml)	757.2±4918.0	17,472.5±46,451.4	<0.001
Child-Pugh classification (A:B:C)	306:78:14	301:123:50	<0.001
TNM classification of LCSGJ 6th (I:II:III:IV)	143:183:67:5	42:172:122:138	<0.001
JIS score (0:1:2:3:4:5)	115:161:91:27:3:1	26:139:119:113:54:23	<0.001
Treatment (resection:RFA:PEIT:others)	84:246:2:66	149:64:1:260	<0.001
MST (months)	68.2	34.1	<0.001

HCV, hepatitis C virus; HBV, hepatitis B virus; NBNC, negative for both HCV and HCV; SVR, sustained virological response; NA, nucleotide analogue; AFP,  $\alpha$ -fetoprotein; AFP-L3, fucosylated AFP; DCP, des- $\gamma$ -carboxy prothrombin; TNM, tumor node metastasis stage; LCSGJ 6th, Liver Cancer Study Group of Japan 6th edition; JIS, Japan Integrated Staging Score; RFA, radiofrequency ablation; PEIT, percutaneous ethanol injection therapy; MST, median survival time.

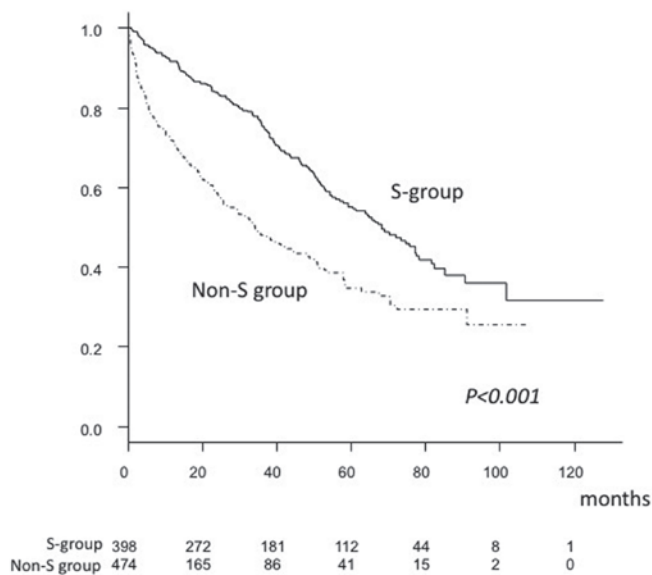


Figure 2. Overall survival of patients in the S- and non-S groups. The overall survival rate after 1, 3, and 5 years, as well as median survival time of the S-group were higher than that of the non-S group ( $P<0.001$ ). group, surveillance group; non-S, non-surveillance group.

including advancements in imaging modalities such as CEUS (21,22,25) and EOB-MRI (19), allowing the rapid detection and diagnosis of smaller HCC. In addition, the development of therapeutic modalities and assistance methods with low invasiveness, such as RFA (10,26), virtual US (VUS) (27), and artificial effusion in RFA (28) have bettered small HCC treatment. Surveillance for smaller HCC detection in high-risk

patients is important to increase the likelihood of successful curative treatment, thus obtaining a better prognosis.

Singal *et al* (29), reported that the combination of US and AFP maximizes the sensitivity for HCC detection at an early stage, compared to surveillance with US or AFP alone (combination, US alone, AFP alone sensitivity: 90, 44 and 66%, respectively; specificity: 83, 92 and 91%, respectively) (29). In a randomized control trial (RCT), it was demonstrated that biannual screening for HCC with US and AFP in HBV patients reduced mortality by 37%, as compared to the control group that did not undergo screening (30). In addition, surveillance with US and AFP in patients with LC significantly improved survival as compared to patients with incidentally detected HCC (15). On the other hand, in another report, biannual AFP screening in HBV patients did not result in an overall reduction in mortality (31). Thus, it is thought that surveillance with both US and AFP is most effective. Costentin *et al* (32) reported that compliance with HCC surveillance guidelines (fewer than 7 months between image evaluations) lead to early diagnosis, allocation of curative treatment, and a longer adjusted OS of patients with compensated HCV- or HBV-associated cirrhosis and a diagnosis of HCC (32). In the present study, average tumor size of the SG-group was larger than that of the SE-group ( $P<0.001$ ). This result may have depended on an easier access system to CEUS, CT or MRI in the SE-group. However, the frequency of curative treatments (resection, RFA and PEIT) did not show a significant difference between the groups, and prognosis was similar. Surveillance with US and AFP improves the prognosis of patients with chronic liver disease. The clinical usefulness of AFP-L3 and DCP other than AFP as tumor markers for HCC surveillance should be examined in additional future studies. Lead-time bias should be taken into

Table II. Characteristics of SE- and SG-groups.

Patient characteristics	SE-group (n=189)	SG-group (n=209)	P-value
Age (years)	68.8±9.5	71.4±8.8	<0.001
Gender (male:female)	120:69	143:66	0.301
Etiology (HCV:HBV:HBV&HCV:NBNC)	141:12:2:34	168:13:3:25	0.204
Number of HCV patients obtained SVR	6	2	0.145
Number of HBV patients treated with NA	11	7	0.073
Maximum tumor diameter (cm)	2.0±1.0	2.5±1.3	<0.001
Tumor number	1.5±1.1	1.7±1.2	0.164
AFP (ng/ml)	169.0±929.5	231.3±1447.5	0.614
AFP-L3 (%)	7.4±13.4	10.7±19.6	0.055
DCP (mAU/ml)	369.5±1812.9	1107.0±6549.6	0.130
Child-Pugh classification (A:B:C)	140:42:7	166:36:7	0.218
TNM classification of LCSGJ 6th (I:II:III:IV)	88:77:23:1	55:106:44:4	<0.001
JIS score (0:1:2:3:4:5)	68:72:39:8:1:1	47:89:52:19:2:0	0.003
Treatment (resection:RFA:PEIT:others)	34:125:1:29	50:121:1:37	0.540
MST (months)	72.1	67.1	0.931

HCV, hepatitis C virus; HBV, hepatitis B virus; NBNC, negative for both HCV and HCV; SVR, sustained virological response; NA, nucleotide analogue; AFP,  $\alpha$ -fetoprotein; AFP-L3, fucosylated AFP; DCP, des- $\gamma$ -carboxy prothrombin; TNM, tumor node metastasis stage; LCSGJ 6th, Liver Cancer Study Group of Japan 6th edition; JIS, Japan Integrated Staging Score; RFA, radiofrequency ablation; PEIT, percutaneous ethanol injection therapy; MST, median survival time; SE-group, follow-up surveillance at Ehime Prefectural Central Hospital; SG-group, follow-up surveillance at general clinics.

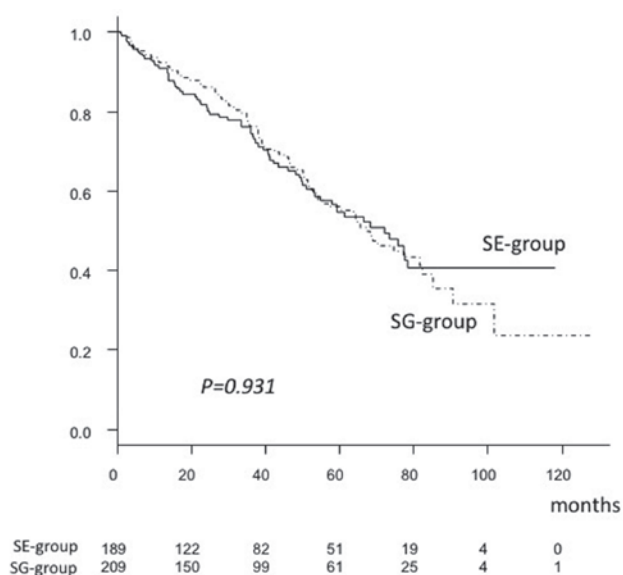


Figure 3. Overall survival of patients in the SE- and SG-groups. The overall survival rate after 1, 3, and 5 years, and median survival time were not significantly different between the groups ( $P=0.931$ ).

consideration for this type of investigation. Toyoda *et al* (33) reported that the surveillance group exhibited a significantly better survival than the non-surveillance group after adjusting for lead-time bias (MST: Surveillance vs. non-surveillance group, 7.18 vs. 5.65 years;  $P<0.0001$ ). Further study is required to confirm the influence of lead-time bias to survival.

In the present cohort, the frequency of NBNC-HCC was greater in the non-S group, compared with the S-group.

Along with an increasing aging population in Japan, the frequency of patients without HCV or HBV (NBNC-HCC) has increased (34-36), thus establishment of a method for identifying affected patients without viral hepatitis or alcohol abuse is becoming increasingly important. Recently, non-alcoholic steatohepatitis (NASH) has been recognized to increase the risk for development of HCC; therefore, patients with NASH must be enrolled in a HCC screening program (37). Nevertheless, many patients with diabetes mellitus (DM), who often also have NASH, are receiving regular medical check-ups at local clinics. To control DM, it may be possible to focus high-risk patients, who require HCC surveillance with US, from those with DM. It has been proposed that age and fibrosis-4 index (38,39) are factors that indicate individuals at high risk for HCC among DM patients without alcohol abuse (alcohol intake:  $>60$  g/day) (37). Additional investigations to form a surveillance strategy for detection of HCC at an earlier stage in patients without viral hepatitis or alcohol abuse are required.

US is easily introduced due to its lower cost relative to other radiological modalities, such as enhanced CT and EOB-MRI (40). Furthermore, examinations may be repeatedly performed, although some issues remain. The accuracy of US findings for HCC surveillance is strongly dependent on the quality of the equipment and expertise of the performing operator (41), thus special training is warranted for ultrasonographers. Although tumor diameter and TNM stage in the SG-group of the present study were greater compared with the SE-group, tumor number and OSR were not significantly different between those groups. It was speculated that the reason why repeated surveillance screening for HCC using the combination of US and AFP was effective, was because of the increased chance for detection of

smaller sized and fewer tumors, resulting in the possibility to be treated with a curative method.

The present study has certain limitations. First, the present study was retrospective. Second, the quality of US examination of each institution could not be exactly compared. Additional analyses with a prospective study or RCT, if possible, are required. However, physicians and their patients should be notified of the importance of surveillance for HCC with a combination of US and AFP for high-risk patients with viral hepatitis and/or alcohol abuse. In addition, management of high-risk patients without viral hepatitis or alcohol abuse is necessary. It was concluded that repeated surveillance with US and AFP leads to diagnosis of HCC at an earlier stage, and improved prognosis of affected patients compared with patients who did not undergo surveillance.

### Acknowledgements

Not applicable.

### Funding

No funding was received.

### Availability of data and materials

The datasets of this study are not publicly available, but are available from the corresponding author on reasonable request.

### Authors' contributions

AH and HY conceived the present study, analyzed the data and wrote the manuscript. YH, BM, AM and MH conceived, reviewed and edited the manuscript of the current study. TM, HI, HU, MO, TA, TO, RI, YS, KMo, HM, ET, MK, TN and KMi acquired the data.

### Ethics approval and consent to participate

The study protocol was conducted in compliance with the Helsinki Declaration and was approved by the Institutional Ethics Committee of EPCH (approval no. 26-11).

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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