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Intensity of surveillance for hepatocellular carcinoma determines survival in patients at risk in a hepatitis B-endemic area

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Summary

Background: Data are insufficient regarding the survival benefit of surveillance for hepatocellular carcinoma (HCC).

Aim: To investigate the effectiveness of HCC surveillance in a hepatitis B-endemic population.

Methods: This retrospective cohort study included 1402 consecutive patients who were newly diagnosed with HCC between 2005 and 2012 at a single tertiary hospital in Korea. The primary endpoint was overall survival. Lead-time and length-time biases were adjusted (sojourn time = 140 days) and sensitivity analyses were performed.

Results: The most common aetiology was hepatitis B (80.4%). Cirrhosis was present in 78.2%. HCC was diagnosed during regular surveillance (defined as mean interval of ultrasonography <8 months, n = 834), irregular surveillance (n = 104) or non-surveillance (n = 464). Patients in the regular surveillance group were diagnosed at earlier stages ([very] early stage, 64.4%) than the irregular surveillance (40.4%) or nonsurveillance (26.9%) groups and had more chance for curative treatments (52.4%) than the irregular surveillance (39.4%) or nonsurveillance (23.3%) groups (all $P < 0.001$). Mortality risk was significantly lower in the regular surveillance group (adjusted hazard ratio [aHR], 0.69; 95% [CI], 0.57-0.83) but not in the irregular surveillance group (aHR, 0.94; 95% CI, 0.69-1.28) compared with the nonsurveillance group after adjusting for confounding factors and lead-time. When the subjects were restricted to cirrhotic patients or Child-Pugh class A/B patients, similar results were obtained for mortality risk reduction between groups.

Conclusions: HCC surveillance was associated with longer survival owing to earlier diagnosis and curative treatment. Survival advantage was significant with regular surveillance but not with irregular surveillance.

H. Y. Kim and J. Y. Nam are the 2 authors who contributed equally to this study.
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1 | INTRODUCTION

Hepatocellular carcinoma (HCC) remains the fifth most common malignancy and is the second most common cause of cancer-related mortality worldwide.[1] Incidence of HCC has significantly increased in the last several decades.[2] HCC develops mostly in patients with risk factors, such as chronic hepatitis B or C virus (HBV or HCV) infection, liver cirrhosis or metabolic syndrome.[3] The prognosis of HCC patients depends on both tumour stage and hepatic functional reserve, and curative therapies are only available for patients diagnosed at an early stage.

Current global practice guidelines for HCC recommend surveillance in patients at risk to detect HCC at an early stage which is amenable to curative therapies and thereby to improving outcome.[4-6] However, study designs of currently available evidences on surveillance for HCC are diverse in terms of study population, follow-up interval, endpoint, surveillance programme, and adjustment for biases (eg, lead-time bias), showing a varying magnitude of survival benefit for surveillance.[7] These diversities prevent direct extrapolation of results from one population to another. For example, the results of the only controlled trial on the efficacy of HCC surveillance in patients with exclusively chronic hepatitis B cannot be directly adopted in populations with cirrhosis of other causes due to probable competing risk of non-HCC mortality and lower sensitivity of surveillance modalities with a nodular liver.[8] Moreover, uncertainties still remain in terms of the surveillance intervals (or intensity), modalities, and population- or aetiology-specific recommendations in the implementation of surveillance in practice.

In this study, we investigated the association of HCC surveillance with early tumour detection and survival improvement, and the effect of surveillance intensity on the outcome with adjustment for lead- and length-time biases in an HBV-endemic area.

2 | METHODS

2.1 | Study population

A total of 1526 consecutive patients were considered eligible; they were newly diagnosed with HCC between January 2005 and December 2012 at Seoul National University Hospital (Seoul, Korea). The diagnosis of HCC was confirmed based on the guidelines of the American Association for the Study of Liver Diseases.[6] Patients who visited our hospital at least 2 years before HCC diagnosis were candidates for this study, whereas patients without a record of surveillance receipt before HCC diagnosis were excluded. Patients were also excluded if they met any of the following criteria: age <18 years; infection with human immunodeficiency virus; other previous or current malignancies except for HCC; or severe comorbidities which could affect patients' survival, such as uncontrolled cardiac or pulmonary diseases, or chronic kidney disease requiring renal replacement therapy. After excluding 124 patients according to the exclusion criteria, 1402 patients were finally included in the study (Figure 1).

This study complied with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Seoul National University Hospital, and the requirement for informed consent from patients was waived.

2.2 | Definition of risk factors and surveillance intensities

Chronic hepatitis B was defined as the presence of serum hepatitis B surface antigen for more than 6 months. We defined chronic hepatitis C as the presence of detectable hepatitis C RNA in patients with positive antibody for HCV at the time of HCC diagnosis or before HCC diagnosis. Alcoholic liver disease was determined by medical records of patients who consumed significant amounts of alcohol (defined as alcohol intake of ≥30 g per day in men and ≥20 g per day in women).[9] Nonalcoholic fatty liver disease was diagnosed either clinically (ie, steatosis on imaging tests in the absence of other causes of chronic liver disease with or without metabolic syndrome) or histologically.[10,11] Autoimmune hepatitis,[12] primary biliary cholangitis,[13] hemochromatosis,[14] or Wilson's disease[15] was identified by using corresponding diagnostic criteria with/without liver histology. Diagnostic criteria of liver cirrhosis were defined as follows: (1) thrombocytopenia (platelet count of <100 000/mL) and image diagnosis (ultrasonography or computed tomography) of cirrhosis, including a blunted, nodular liver edge with splenomegaly (>12 cm), (2) presence of portal hypertension, such as oesophageal or gastric varices, or (3) features of decompensation such as ascites or hepatic encephalopathy.[16,17]

HCC surveillance was defined as receipt of at least 1 liver imaging study with/without alpha-fetoprotein (AFP; normal range, 0-20 ng/mL) for surveillance purposes within 2 years prior to the diagnosis of HCC. The study population was classified into 3 groups according to the surveillance intensities. Regular surveillance was defined as receipt of repeated ultrasonography with/without serum AFP with mean interval of ≤8 months for at least 2 years prior to the diagnosis of HCC, considering recently recommended surveillance interval of 4-8 months.[6] The nonsurveillance group consisted of patients who did not undergo any imaging tests within 2 years prior to diagnosis of HCC. The irregular surveillance group was a group of patients with receipt of surveillance who did not meet the abovementioned definition of regular surveillance.

2.3 | Clinical and tumour characteristics

Demographic and clinical characteristics were collected at the time of HCC diagnosis, including age, sex, body mass index, performance status according to the Eastern Cooperative Oncology Group (ECOG), diabetes mellitus, hypertension, aetiology of chronic liver disease, presence of cirrhosis, laboratory findings, Child-Pugh class, model for end-stage liver disease (MELD) score, the duration of practice providers' clinical experience (<10 years vs ≥10 years), and socioeconomic status of each patient reflected by type of medical insurance. At the time of HCC diagnosis, liver cirrhosis complications such as oesophageal and gastric varices, ascites, and hepatic encephalopathy were evaluated. Liver dynamic computed

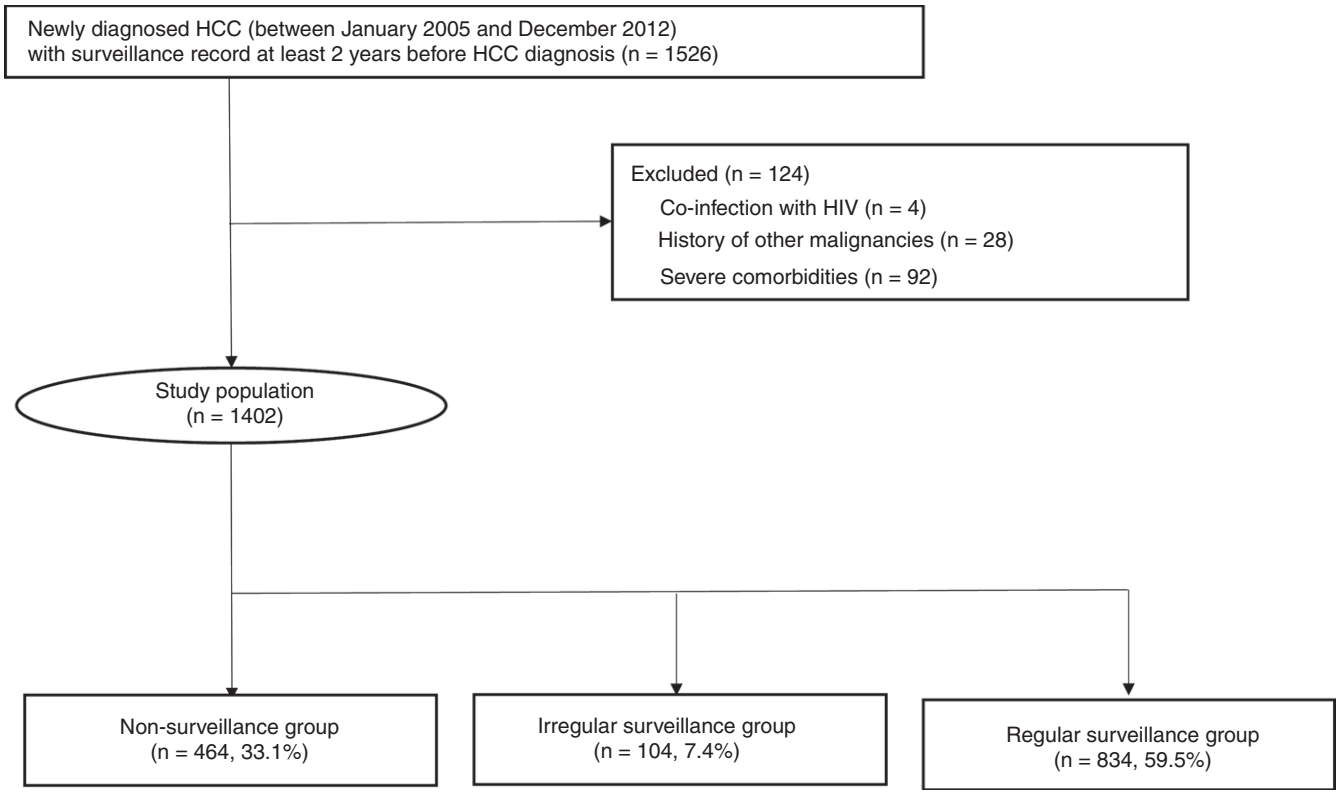


FIGURE 1 CONSORT diagram. A total of 1584 HCC patients were identified of whom 182 did not meet inclusion criteria. The final study group consisted of 1402 patients. Among 1402 patients, 834 (59.5%) underwent regular surveillance, 104 (7.4%) underwent irregular surveillance, and 464 (33.1%) underwent nonsurveillance

tomography or magnetic resonance imaging, which was performed to evaluate an abnormal ultrasonography finding, was reviewed by 2 independent radiologists (J.M.L. and D.H.L.) with >10 years of experience to assess tumour type (nodular, diffuse/infiltrative or massive) and multiplicity, the presence of portal vein thrombosis (PVT), vessel invasion, regional lymph node metastasis and distant metastasis.[18,19]

2.4 | Endpoints

The primary endpoint was overall survival (OS), which was measured from the date of HCC diagnosis to death from any cause. Survival data of the enrolled patients were obtained from national statistical data provided by the Korean Ministry of Government Administration and Home Affairs. Data cut-off date was 17 April 2017. The secondary endpoints were initial HCC stage and treatment modalities. HCC stage was evaluated according to both the American Joint Committee on Cancer[20] and Barcelona Clinic Liver Cancer (BCLC) staging systems.[21] The curative therapies for HCC were defined as liver transplantation within-Milan criteria, surgical resection, radiofrequency ablation or percutaneous ethanol injection.

2.5 | Statistical analysis

Basic characteristics were presented as either mean ± standard deviation for continuous variables or number of subjects with percentage for categorical variables. One-way analysis of variance and Student's *t* test were applied to compare the means between groups. Distribution of categorical variables was compared using the chi-square and Fisher's exact test. Survival times were estimated with Kaplan-Meier analysis and compared between groups by using log-rank test. Possible covariates for OS were identified by univariate Cox proportional-hazards regression analysis, and factors that showed a significant difference ($P < 0.05$) in univariate analyses were included in multivariate analyses. The proportional-hazards assumption was checked via a log minus log graph. In addition, we assessed effects of surveillance on the treatment modalities and HCC stages. Adjustment for lead-time bias was done using the methods of Duffy et al[22] and Schwartz et al,[23] and sensitivity analysis was conducted under various conditions. To calculate lead-time, we assumed average sojourn times of 70 and 140 days (Duffy's method) and tumour doubling time of 60, 90 and 120 days (Schwartz's method), with reference to previous studies.[24,25] In Schwartz's method, median values of tumour diameter in the nonsurveillance group (7.0 cm) and surveillance group (2.1 cm) were determined on the basis of the collected data at the time of HCC diagnosis. Lead-time bias was corrected by subtracting estimated lead-time from the observed survival time in the surveillance group. Furthermore, the risk of case fatality was estimated with adjustment for length-time bias of surveillance according to Duffy's method. In sensitivity analyses, the effect of HCC surveillance was assessed in (1) patients with cirrhosis at the time of HCC diagnosis, and (2) patients with Child-Pugh class A/B. Statistical analysis was performed by SPSS version 23.0 (IBM Co.,

Armonk, NY) and SAS 9.4 (SAS Institute, Cary, NC). A 2-sided $P < 0.05$ was considered significant.

3 | RESULTS

3.1 | Patient characteristics at the time of HCC diagnosis

Mean age of the 1402 patients was 57.9 ± 9.7 years, and 78.9% were male. Median follow-up duration was 57.0 months (interquartile range, 15.0-104.6). HBV was the most common aetiology of HCC (80.4%) followed by HCV (n = 131, 9.3%). Three patients eradicated their HCV with interferon-based treatment before the diagnosis of HCC, and they were also deemed to have HCV-related HCC. Liver cirrhosis was present in 1097 patients (78.2%) at the time of HCC diagnosis: 816 patients (74.4%) were Child-Pugh class A, 228 (20.8%) were class B, and 53 (4.8%) were class C (Table 1).

Among the 1402 patients, 834 (59.5%) underwent regular surveillance, 104 (7.4%) underwent irregular surveillance, and 464 (33.1%) underwent nonsurveillance (Figure 1). In patients of surveillance groups (ie, both regular surveillance and irregular surveillance groups; n = 938), 904 (96.4%) patients were diagnosed with HCC as a result of surveillance; the remaining 29 (3.1%) were diagnosed by symptoms of HCC, and only 5 (0.5%) were diagnosed incidentally. In the nonsurveillance group (n = 464), 191 (41.1%) were diagnosed incidentally and 273 (58.8%) patients were diagnosed with HCC due to symptoms. Duration of clinical experience of practice providers (<10 years: regular vs nonsurveillance, irregular vs nonsurveillance, and regular vs irregular surveillance; all $P > 0.05$) and types of National Health Insurance Service which reflected the socioeconomic status of each patient (the lowest income patients: regular vs nonsurveillance, irregular vs nonsurveillance, and regular vs irregular surveillance; all $P > 0.05$) were not different among 3 groups (Table 1).

3.2 | Tumour stages according to surveillance intensity

When HCC was staged according to the BCLC staging system, HCC was diagnosed at earlier stages (stage 0 or A) in the regular surveillance group (64.4%) than in either the irregular surveillance (40.5%) or nonsurveillance group (26.9%) (both $P < 0.001$) and in the irregular surveillance group than in the nonsurveillance group ($P < 0.001$). Also on the basis of on TNM staging system, stage I or II tumours were significantly more frequent in the regular surveillance group (90.0%) than in either irregular surveillance (74.1%) or nonsurveillance group (44.7%) (both $P < 0.001$) and also more frequent in the irregular surveillance group than in the nonsurveillance group ($P < 0.001$). Diffuse/infiltrative or massive tumours were diagnosed frequently in the order of nonsurveillance, irregular surveillance, and regular surveillance, in each case showing a significant difference. The patients diagnosed with HCC due to symptoms were also frequent in the order of nonsurveillance, irregular surveillance, and regular surveillance with significant differences. A significantly greater proportion in the regular surveillance group underwent potentially curative therapies than in the irregular surveillance or nonsurveillance group. Curative therapies, such as within-Milan liver transplantation, surgical resection, radiofrequency ablation, or percutaneous ethanol injection, were more frequently performed as an initial HCC treatment modality in the regular surveillance (52.4%) and irregular surveillance (39.4%) groups than in the nonsurveillance (23.3%) group ($P < 0.001$ for regular vs nonsurveillance, irregular vs nonsurveillance, and regular vs irregular surveillance). In subgroup analyses, the performance status was better in the regular surveillance group than in either the irregular surveillance or nonsurveillance group (regular vs nonsurveillance, irregular vs nonsurveillance, and regular vs irregular surveillance; all $P < 0.001$). Compared with the regular surveillance group, Child-Pugh class (A and noncirrhosis: regular vs nonsurveillance, irregular vs nonsurveillance, and regular vs irregular surveillance; all $P < 0.001$) and MELD scores (score <10: regular vs nonsurveillance, irregular vs nonsurveillance, and regular vs irregular surveillance; all $P < 0.001$) also tended to be worse in the irregular surveillance or nonsurveillance group (Table 1).

3.3 | Overall survival with/without adjustment for lead-time

In Kaplan-Meier survival analysis, the regular surveillance group showed significantly longer OS than did the irregular surveillance or nonsurveillance group (regular vs irregular surveillance, $P = 0.028$; regular vs nonsurveillance, $P < 0.001$). The OS of the irregular surveillance group was also significantly longer than that of the nonsurveillance group ($P < 0.001$, Figure 2). This statistically significant difference remained consistent after adjusting the lead-time. After adjustment for lead-time with sojourn time either 70 or 140 days, median OS of the regular surveillance group was significantly longer than that of irregular surveillance (at sojourn time = 70 days, $P = 0.029$; at sojourn time = 140 days, $P = 0.029$) or nonsurveillance group (at sojourn time = 70 days, $P < 0.001$; at sojourn time = 140 days, $P < 0.001$). After Schwartz's method was applied,[23] median OS of the regular surveillance group was also significantly longer than that of nonsurveillance but not that of irregular surveillance, when changing the doubling time of HCC to 60 days (regular vs irregular surveillance, $P = 0.506$; regular vs nonsurveillance, $P < 0.001$), 90 days (regular vs irregular surveillance, $P = 0.457$; regular vs nonsurveillance, $P < 0.001$), and 120 days (regular vs irregular surveillance, $P = 0.457$; regular vs nonsurveillance, $P < 0.001$) (Table 2). Based on lead-time calibrations with 2 sojourn times (70 or 140 days) or 3 tumour doubling times (60, 90 or 120 days), 1-year, 2-year and 5-year survival rates were higher in the regular surveillance group than in the irregular surveillance or nonsurveillance group and were also higher in the irregular surveillance than nonsurveillance group. Collectively, the estimated 5-year survival rates with adjustment for lead-time were significantly higher in the regular surveillance group (64.3-66.8%) than in the

TABLE 1 Patient and tumour characteristics at the time of HCC diagnosis

	Total (N = 1402)		Nonsurveillance (N = 464, 33.1%)		Irregular surveillance (N = 104, 7.4%)		Regular surveillance (N = 834, 59.5%)		*P* value (regular vs none)	*P* value (irregular vs none)	*P* value (regular vs irregular)	*P* value (regular vs irregular vs none)
Age	57.9 ± 9.7		57.0 ± 10.5		57.6 ± 9.3		58.4 ± 9.2		0.016	0.613	0.385	0.04
BMI	23.0 ± 3.3		23.0 ± 3.4		23.0 ± 3.4		23.4 ± 3.2		<0.001	0.035	0.266	<0.001
Gender												
Male	1106	78.9%	382	82.3%	79	76.0%	645	77.3%	0.034	0.133	0.752	0.08
Cirrhosis[a]												
Yes	1096	78.2%	289	62.3%	90	86.5%	717	86.0%	<0.001	0.001	0.051	<0.001
DM												
Yes	250	17.9%	78	17.0%	17	16.5%	155	18.6%	0.470	0.905	0.603	0.71
HTN												
Yes	248	17.8%	86	18.8%	15	14.6%	147	17.7%	0.615	0.301	0.429	0.59
Mode												
Diagnostic	302	21.5%	273	58.8%	7	6.7%	22	2.6%	<0.001	<0.001	0.039	<0.001
Incidental	196	14.0%	191	41.1%	2	1.9%	3	0.4%				
Surveillance	904	64.5%	–	–	95	91.4%	809	97.0%				
Ascites												
Yes	120	8.7%	31	6.8%	16	15.5%	73	8.8%	0.211	0.004	0.028	0.02
SBP												
Yes	19	1.4%	4	0.9%	2	1.9%	13	1.6%	0.299	0.351	0.789	0.52
VB												
Yes	77	5.5%	21	4.6%	8	7.7%	48	5.8%	0.370	0.200	0.439	0.41
HE												
Yes	31	2.2%	2	0.4%	5	4.8%	24	2.9%	0.003	<0.001	0.289	<0.001
Rupture												
Yes	34	2.4%	22	4.8%	3	2.9%	9	1.1%	<0.001	0.402	0.124	<0.001
Aetiology												
HBV	1127	80.4%	335	72.2%	96	92.3%	696	83.5%	<0.001	<0.001	<0.001	<0.001
HBV+HCV	5	0.4%	1	0.2%	1	1.0%	3	0.4%				
HCV	131	9.3%	34	7.3%	5	4.8%	92	11.0%				
Others	139	9.9%	94	20.3%	2	1.9%	43	5.2%				
ECOG[b]												
0	996	71.3%	300	64.9%	65	62.5%	631	75.9%	<0.001	0.002	<0.001	<0.001
1	248	17.8%	66	14.3%	28	26.9%	154	18.5%				
2	104	7.4%	66	14.3%	9	8.7%	29	3.5%				
3	42	3.0%	26	5.6%	0	0%	16	1.9%				
4	7	0.5%	%4	0.9%	2	1.9%	1	0.1%				
Child-Pugh												
Cirrhosis (–)	306	21.8%	175	37.7%	14	13.5%	117	14.0%	<0.001	0.030	0.087	<0.001
A	816	58.2%	180	38.8%	72	69.2%	564	67.6%				
B	228	16.3%	88	19.0%	12	11.5%	128	15.3%				
C	52	3.7%	21	4.5%	6	5.8%	25	3.0%				
MELD												
<10	852	60.8%	300	66.1%	58	63.7%	494	63.5%	0.495	0.912	0.911	<0.001
10-19	434	31.0%	140	30.8%	30	33.0%	264	34.0%				
≥20	37	2.6%	14	3.0%	3	3.3%	20	2.6%				

(Continues)

TABLE 1 (Continued)

	Total (N = 1402)		Nonsurveillance (N = 464, 33.1%)		Irregular surveillance (N = 104, 7.4%)		Regular surveillance (N = 834, 59.5%)		*P* value (regular vs none)	*P* value (irregular vs none)	*P* value (regular vs irregular)	*P* value (regular vs irregular vs none)
AFP[c]												
Quartile 1	351	25.2%	77	16.8%	20	19.4%	254	30.5%	<0.001	<0.001	0.023	<0.001
Quartile 2	345	24.8%	81	17.7%	38	36.9%	226	27.2%				
Quartile 3	348	25.0%	93	20.3%	25	24.3%	230	27.6%				
Quartile 4	348	25.0%	206	45.1%	20	19.4%	122	14.7%				
Type												
Nodular	1200	85.6%	307	66.2%	93	89.4%	800	95.9%	<0.001	<0.001	0.002	<0.001
Diffuse	201	14.3%	157	33.8%	11	10.6%	33	4.0%				
Others	1	0.1%	0	0%	0	0%	1	0.1%				
Size												
mm	43.6 ± 39.6		76.0 ± 46.9		44.5 ± 37.7		27.1 ± 21.6		<0.001	<0.001	<0.001	<0.001
PVT												
Yes	263	18.8%	185	39.9%	16	15.4%	62	7.4%	<0.001	<0.001	0.006	<0.001
Metastasis												
Yes	72	5.1%	62	13.4%	3	2.9%	7	0.8%	<0.001	0.002	0.055	<0.001
LN												
Yes	60	4.3%	48	10.3%	4	3.9%	8	1.0%	<0.001	0.038	0.014	<0.001
TNM												
I	788	56.3%	138	29.8%	55	52.9%	595	71.3%	<0.001	<0.001	<0.001	<0.001
II	247	17.6%	69	14.9%	22	21.2%	156	18.7%				
IIIA, IIIB	247	17.6%	160	34.6%	19	18.3%	68	8.2%				
IIIC, IVA, IVB	119	8.5%	96	20.7%	8	7.7%	15	1.8%				
BCLC												
0	231	16.5%	20	4.3%	14	13.5%	197	23.6%	<0.001	0.005	<0.001	<0.001
A	473	33.7%	105	22.6%	28	27.0%	340	40.8%				
B	114	8.1%	62	13.3%	11	10.6%	41	4.9%				
C	498	35.5%	232	50%	44	42.3%	222	26.6%				
D	86	6.1%	45	9.7%	7	6.7%	34	4.1%				
Treatment												
Curative	586	41.8%	108	23.3%	41	39.4%	437	52.4%	<0.001	0.002	0.036	<0.001
Uncurative	786	56.1%	336	72.4%	61	58.7%	389	46.6%				
Unknown	30	2.1%	20	4.3%	2	1.9%	8	1.0%				
Clinicians' experience												
≥10 y	738	52.6%	254	54.7%	59	56.7%	425	51.0%	0.202	0.744	0.298	0.292
<10 y	664	47.4%	210	45.3%	45	43.3%	409	49.0%				
Insurance type												
Medicaid	55	3.9%	16	3.4%	5	4.8%	34	4.1%	0.653	0.563	0.611	0.761

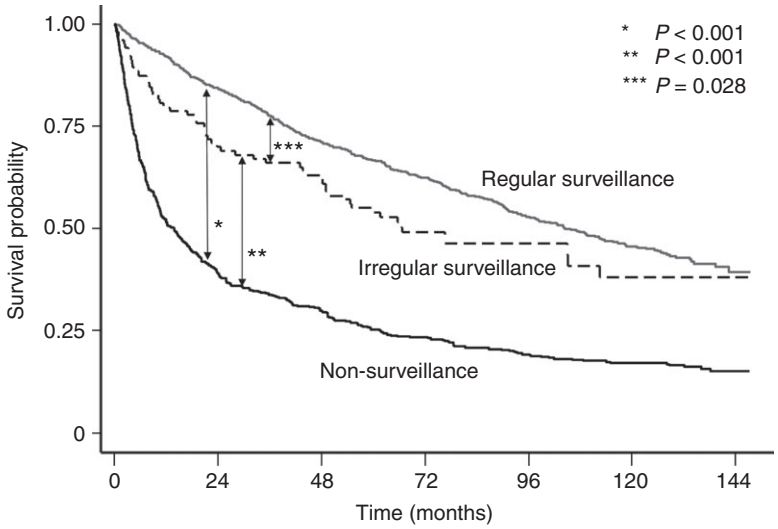
Data are expressed as n (%) or mean ± standard deviation.

BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; SBP, spontaneous bacterial peritonitis; VB, Variceal bleeding; HE, hepatic encephalopathy; ECOG, eastern cooperative oncology group; AFP, alpha-fetoprotein; MELD, model for end-stage liver disease; CTP, Child-Turcotte-Pugh, PVT, portal vein thrombosis; LN, lymph node metastasis.

[a]Liver cirrhosis was diagnosed by the presence of histological and radiological evidence.

[b]The ECOG performance status assesses on a scale ranging from 0 (fully active) to 5 (dead).

[c]Interquartile range, 6.0-422 (ng/mL).



Number at risk

Non-surveillance	464	178	137	107	88	78	9
Irregular surveillance	104	72	63	38	23	10	3
Regular surveillance	834	702	592	409	285	203	21

FIGURE 2 Overall survival according to surveillance intensity in all enrolled patients. In Kaplan-Meier survival analysis, the regular surveillance group showed significantly longer overall survival than did the irregular surveillance or nonsurveillance group (regular vs irregular surveillance, $P = 0.028$; regular vs nonsurveillance, $P < 0.001$). The overall survival of the irregular surveillance group was also significantly longer than that of the nonsurveillance group ($P < 0.001$)

TABLE 2 Kaplan-Meier survival probability after adjustment for a lead-time

		Uncorrected for lead-time bias		Corrected for lead-time bias (Sojourn time = 70 days)		Corrected for lead-time bias (Sojourn time = 140 days)	
	N	Median	95% CI	Median	95% CI	Median	95% CI
Overall	1402 (100.0%)	65.6	57.5-73.6	63.5	55.8-71.2	62.1	54.4-69.7
HCC surveillance							
Nonsurveillance	464 (33.1%)	13.9	10.7-17.1	13.9	10.7-17.1	13.9	10.7-17.1
Surveillance	938 (66.9%)	104.0	93.9-114.2	101.7	91.6-111.9	99.4	89.3-109.6
Receipt of HCC surveillance							
None	464 (33.1%)	13.9	10.7-17.1	13.9	10.7-17.1	13.9	10.7-17.1
Irregular	104 (7.4%)	66.7	23.2-110.1	64.4	20.9-107.8	62.1	18.7-105.4
Regular	834 (59.5%)	104.5	92.3-116.7	102.2	90.0-114.4	99.9	87.7-112.1

	Corrected for lead-time bias (Doubling time = 60 days)			Corrected for lead-time bias (Doubling time = 90 days)			Corrected for lead-time bias (Doubling time = 120 days)		
	N	Median	95% CI	N	Median	95% CI	N	Median	95% CI
Overall	1339	65.0	57.1-73.0	1305	63.7	55.9-71.5	1276	63.3	55.3-71.3
HCC surveillance									
Nonsurveillance	464	13.9	10.7-17.1	464	13.9	10.7-17.1	464	13.9	10.7-17.1
Surveillance	875	102.3	89.4-115.2	841	105.0	91.8-118.2	812	106.7	97.6-115.8
Receipt of HCC surveillance									
None	464	13.9	10.7-17.1	464	13.9	10.7-17.1	464	13.9	10.7-17.1
Irregular	87	102.1	60.1-144.2	84	97.0	45.9-148.1	81	105.0	
Regular	788	102.8	89.2-116.4	757	106.0	92.2-119.9	731	107.5	100.3-114.7

Data are expressed as n (%) or median with minimum and maximum. Regular follow-up was defined as mean interval of ultrasonography being less than 8 months.
CI, confidence interval.

irregular surveillance group (59.3%-61.3%) and nonsurveillance group (25.3%) (Table S1). Subanalyses for cirrhotic patients or patients with Child-Pugh class A/B also showed significantly longer OS for the regular surveillance group than either irregular surveillance or nonsurveillance group (all $P < 0.05$) (Figure S1 and Figure 2).

TABLE 3 Mortality risk reduction according to surveillance regularity compared with the no-surveillance group after the adjustment for lead-time and length-time

		Regular surveillance			Irregular surveillance			Regular surveillance			Irregular surveillance		
10-year mortality		**RR**	**95% CI**	***P* value**	**RR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
No correction		0.58	0.53-0.63	<0.001	0.63	0.52-0.77	<0.001	0.33	0.29-0.38	<0.001	0.43	0.32-0.58	<0.001
Lead-time correction	70[a]	0.58	0.54-0.64	<0.001	0.63	0.52-0.77	<0.001	0.34	0.30-0.40	<0.001	0.44	0.33-0.60	<0.001
	140[a]	0.59	0.54-0.64	<0.001	0.63	0.52-0.77	<0.001	0.35	0.31-0.41	<0.001	0.46	0.34-0.62	<0.001
Lead- and length-time correction	70[a]	0.62	0.59-0.77		0.65	0.63-0.72		0.38	0.35-0.53		—	—	—
	140[a]	0.62	0.59-0.77		0.65	0.63-0.72		0.38	0.35-0.54		—	—	—
5-year mortality		**RR**	**95% CI**	***P* value**	**RR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
No correction		0.44	0.39-0.50	<0.001	0.59	0.47-0.75	<0.001	0.26	0.22-0.30	<0.001	0.39	0.28-0.53	<0.001
Lead-time correction	70[a]	0.45	0.40-0.50	<0.001	0.59	0.47-0.75	<0.001	0.27	0.23-0.32	<0.001	0.40	0.29-0.56	<0.001
	140[a]	0.47	0.42-0.52	<0.001	0.59	0.47-0.75	<0.001	0.29	0.24-0.34	<0.001	0.41	0.30-0.57	<0.001
Lead- and length-time correction	70[a]	0.49	0.46-0.61		0.61	0.59-0.67		0.32	0.30-0.41		0.42	0.31-0.44	
	140[a]	0.50	0.47-0.62		0.62	0.61-0.69		0.33	0.31-0.43		0.43	0.32-0.46	

Regular follow-up was defined as mean interval of ultrasonography being less than 8 months.
RR, relative risk; HR, hazard ratio; CI, confidence interval.
[a]Sojourn time (day).

3.4 | Survival probability in association with adjustment for possible lead- and length-time

In correction of length-time bias, hazard ratios (HRs) were calculated by dividing the period of 10 years and 5 years, because it could not be adjusted for each patient.[22] The 5-year mortalities of the regular surveillance and irregular surveillance groups decreased significantly, compared to that of the nonsurveillance group without lead-time bias correction (HR, 0.26; 95% CI, 0.22-0.30). When lead-time was calibrated under assumption of sojourn time of 70 or 140 days, the 5-year mortalities were reduced in the regular surveillance group (sojourn time = 70 days: HR, 0.27; 95% CI, 0.23-0.32; sojourn time = 140 days: HR, 0.29; 95% CI, 0.24-0.34) or in the irregular surveillance group (sojourn time of 70 days: HR, 0.40; 95% CI, 0.29-0.56; sojourn time of 140 days, HR, 0.41; 95% CI, 0.30-0.57) (all $P < 0.001$). When the length-time bias was also corrected, 5-year mortality risk in the regular surveillance group was slightly increased yet still significantly lower compared with the results with only lead-time correction (sojourn time = 70 days: HR, 0.32; 95% CI, 0.30-0.41; sojourn time = 140 days: HR, 0.33; 95% CI, 0.31-0.43). In the irregular surveillance group, 5-year mortality risk was also slightly increased but the effectiveness of surveillance was still maintained (sojourn time = 70 days: HR, 0.42; 95% CI, 0.31-0.44; sojourn time = 140 days: HR, 0.43; 95% CI, 0.32-0.46) (Table 3).

3.5 | Survival analysis according to HCC surveillance intensity with sensitivity analysis

In unadjusted Cox proportional-hazards analysis, mortality risk of the regular surveillance group was reduced significantly for each lead-time correction compared with that of the nonsurveillance group (no correction of lead-time: HR, 0.34; 95% CI, 0.29-0.39; correction with sojourn time = 70 days: HR, 0.35; 95% CI, 0.30-0.40; correction with sojourn time = 140 days: HR, 0.36; 95% CI, 0.31-0.41). Mortality risk of the irregular surveillance group was also reduced significantly under each assumption for lead-time correction compared with the nonsurveillance group (no lead-time correction: HR, 0.44; 95% CI, 0.34-0.59; sojourn time = 70 days: HR, 0.46; 95% CI, 0.35-0.61; sojourn time = 140 days: HR, 0.48; 95% CI, 0.36-0.63) (unadjusted model in Table 4). After adjustment for age, sex, aetiology, AFP, tumour size, PVT, MELD score, ECOG, Child-Pugh class, and possible lead-time bias, mortality risk reduction of the regular surveillance group remained significant compared with the nonsurveillance group under the following conditions for lead-time correction: no lead-time correction: HR, 0.63 (95% CI, 0.52-0.75); sojourn time = 70 days: HR, 0.66 (95% CI, 0.55-0.79); and sojourn time = 140 days: HR, 0.69 (95% CI, 0.57-0.83). However, after adjustment for the abovementioned factors, mortality risk of the irregular surveillance group was not reduced significantly compared with the nonsurveillance group (model 1 in Table 4). When tumour stage was additionally calibrated, only the regular surveillance group, but not irregular surveillance group, showed significant mortality risk reduction (model 2 in Table 4). Additionally, subanalyses in cirrhotic patients or Child-Pugh class A/B patients demonstrated similar reduction in mortality risk between surveillance groups (Table 4).

4 | DISCUSSION

This study showed that regular surveillance for HCC in at-risk patients was associated with a significant reduction in mortality risk, providing diagnosis at earlier stages and receipt of curative treatments. These observed benefits were maintained after adjustment for lead- and length-time biases. On the contrary, although HCC

TABLE 4 Survival analysis according to HCC surveillance type with sensitivity analysis

	Unadjusted model		Model 1		Model 2		Model 3	
	Unadjusted HR	95% CI	Adjusted HR	95% CI	Adjusted HR	95% CI	Adjusted HR	95% CI
Overall patients								
No correction for lead-time								
Regular	0.34	0.29-0.39	0.63	0.52-0.75	0.68	0.57-0.82	0.69	0.58-0.84
Irregular	0.44	0.34-0.59	0.82	0.60-1.11	0.81	0.60-1.10	0.84	0.62-1.14
None	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Sojourn time = 70 days								
Regular	0.35	0.30-0.40	0.66	0.55-0.79	0.72	0.60-0.87	0.74	0.61-0.89
Irregular	0.46	0.35-0.61	0.89	0.65-1.21	0.89	0.66-1.21	0.93	0.68-1.26
None	Reference		1 (Reference)		1 (Reference)		1 (Reference)	
Sojourn time = 140 days								
Regular	0.36	0.31-0.41	0.69	0.57-0.83	0.76	0.63-0.91	0.77	0.64-0.93
Irregular	0.48	0.36-0.63	0.94	0.69-1.28	0.96	0.70-1.30	1.00	0.73-1.36
None	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Patients with cirrhosis								
No correction for lead-time								
Regular	0.31	0.27-0.37	0.60	0.48-0.74	0.62	0.50-0.76	0.63	0.50-0.79
Irregular	0.42	0.31-0.56	0.78	0.56-1.09	0.75	0.54-1.05	0.77	0.55-1.08
None	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Sojourn time = 70 days								
Regular	0.33	0.28-0.38	0.64	0.52-0.79	0.67	0.54-0.83	0.68	0.55-0.86
Irregular	0.44	0.32-0.59	0.87	0.62-1.22	0.84	0.60-1.18	0.88	0.63-1.23
None	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Sojourn time = 140 days								
Regular	0.34	0.29-0.40	0.68	0.54-0.84	0.71	0.57-0.88	0.73	0.58-0.91
Irregular	0.45	0.33-0.62	0.94	0.67-1.32	0.92	0.66-1.29	0.96	0.68-1.35
None	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Patients with CTP A/B								
No correction for lead-time								
Regular	0.34	0.30-0.40	0.64	0.53-0.77	0.68	0.57-0.82	0.70	0.58-0.84
Irregular	0.43	0.32-0.58	0.81	0.59-1.11	0.79	0.57-1.09	0.82	0.60-1.13
None	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Sojourn time = 70 days								
Regular	0.35	0.31-0.41	0.67	0.56-0.81	0.72	0.60-0.87	0.74	0.61-0.90
Irregular	0.45	0.33-0.60	0.88	0.64-1.21	0.86	0.63-1.19	0.90	0.65-1.25
None	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Sojourn time = 140 days								
Regular	0.37	0.32-0.42	0.70	0.58-0.84	0.76	0.63-0.91	0.77	0.64-0.94
Irregular	0.46	0.34-0.62	0.93	0.68-1.29	0.93	0.67-1.28	0.97	0.70-1.34
None	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	

Regular follow-up was defined as mean interval of ultrasonography being less than 8 months.

HR, hazard ratio; CI, confidence interval; AFP, alpha-fetoprotein; PVT, portal vein thorombosis; MELD, model for end-stage liver disease; ECOG, Eastern Cooperative Oncology Group; CTP, Child-Turcotte-Pugh.

Model 1, multivariate analysis adjusted with age, sex, aetiology, AFP, tumour size, PVT, MELD score, CTP class, and ECOG; Model 2, multivariate analysis adjusted with age, sex, aetiology, AFP, PVT, MELD score, CTP class, Treatment modality, ECOG, and T stage; Model 3, multivariate analysis adjusted with age, sex, aetiology, AFP, PVT, MELD score, CTP class, Treatment modality, ECOG, and TNM stage.

diagnosis was more frequently made at earlier stages in the irregular surveillance than nonsurveillance group, the irregular surveillance group failed to show significant survival benefit compared with the nonsurveillance group.

The surveillance strategy is required to be established as a specific population-based approach to which homogeneity is maintained, because surveillance of patients with risk factors is influenced by a variety of factors in practice. Liver cirrhosis is a generally accepted indication for surveillance regarding its high association with HCC. Increased HCC risk in patients with chronic hepatitis C or alcoholic liver diseases is almost entirely restricted to those with cirrhosis, because HCC occurs mostly after developing advanced liver fibrosis and cirrhosis in those circumstances.[26-28] Until recently, large-scale observational cohort studies on HCC surveillance were conducted in the HCV-prevalent areas (ie, the United States and Europe) and only included patients with cirrhosis.[29,30] More than 20% of HBV-related HCC, however, occurs through the direct carcinogenic effect of HBV without liver cirrhosis.[31-33] For example, approximately 40% of patients who received curative treatment for HCC did not have underlying liver cirrhosis in an HBV-endemic region.[34,35] In addition, HCC in HBV-endemic areas is diagnosed earlier by a decade compared with HCV-prevalent Western areas.[36] Collectively, effective surveillance strategies for HBV-endemic populations might be different from those for populations with other aetiologies, considering the characteristics of HBV-related HCC in terms of carcinogenesis and epidemiological aspects.[37,38] Our study, including noncirrhotic HCC patients (21.8%), showed that surveillance for HCC was essential to detect HCC at earlier stages and also improved prognosis in an HBV-endemic area. Recently, Korean National Liver Cancer Surveillance Program started to provide surveillance tests including ultrasonography at 6-month intervals for patients at high risk for developing HCC, such as patients older than 40 years who have chronic hepatitis B, C, or underlying liver cirrhosis. Thus, we hope that the proportion of regular surveillance will increase, and consequently, the survival of HCC patients can be improved.

The surveillance programme in our study was based on semiannual ultrasonography and serum AFP measurement, which is most widely accepted at present. In some studies, there is no difference between follow-up interval of less than 6 months and annual surveillance.[39] However, in several studies, surveillance with follow-up intervals of ≤6 months showed better prognosis than annual surveillance.[40-42] Since surveillance with <3-month intervals did not further improve prognosis compared with 6-month intervals,[43] international practice guidelines recommend surveillance in 6-month intervals, considering the tumour doubling time.[5,6] Furthermore, although the survival benefit of HCC surveillance was proved in previous studies including a randomised study in an HBV-infected population,[44] real-world effectiveness according to surveillance intensity (ie, regularity) has not been fully investigated. Thus, we categorised the study population into 3 groups according to surveillance intensity. The regular surveillance group was defined as having a mean interval of surveillance of <8 months for at least 2 years prior to diagnosis, which was in concordance with international practice guidelines.[6] Compared with nonsurveillance, the irregular surveillance group failed to prove a better prognosis after adjustment in multivariate analysis and sensitivity analysis; only the regular surveillance group showed better prognosis than the nonsurveillance group. The results showed that regular surveillance (mean interval of <8 months) was more effective in improving prognosis than irregular surveillance (ie, surveillance with longer intervals) in both unadjusted and adjusted analyses, where significant reduction in mortality risk was only achieved with regular surveillance (ie, by 26% at sojourn time of 70 days and 23% at sojourn time of 140 days) and not with irregular surveillance. Adherence to surveillance with intervals of <8 months in at-risk patients needs to be emphasised to improve the outcome by better implementation of existing surveillance programmes.

Rigorous adjustments or corrections were made for lead- and length-time biases using both Duffy's and Schwartz's methods.[22,23] Because lead-time bias depends on doubling time of HCC, mortality risk reduction owing to surveillance disappeared with more than 90 days of tumour doubling time in previous studies.[24,45] In the present study, surveillance groups showed significant reduction in mortality risk compared with nonsurveillance under the assumptions of all 3 tumour doubling times (60, 90 or 120 days). However, only regular surveillance provided significant survival benefit in the entire study population with adjustment for lead-time bias (assumed sojourn time = 70 or 140 days) in the multivariate analysis. Likewise, similar beneficial effect in subgroups with cirrhosis or Child-Pugh class A/B underscores the importance of regular surveillance.

There were several limitations in the present study. First, this study was a single tertiary centre-based retrospective study, where there might have been a greater utilisation of surveillance than in primary care settings, potentially causing intervention bias.[46] Second, liver cirrhosis was diagnosed clinically in most cases, whereas histological diagnosis was made in only a minority of the study subjects. Thus, potential selection bias might have occurred because of possible underestimation of the proportion of cirrhotic patients. Lastly, although this study demonstrated the importance of surveillance intensity with adjustment for lead-time and length-time biases unlike previous studies,[44,47] a specific surveillance programme for noncirrhotic patients, particularly in HBV-infected populations, cannot be directly suggested on the basis of our results.

In conclusion, HCC surveillance was associated with longer survival owing to tumour detection at earlier stages and increased chance of receiving curative treatment in an HBV-endemic area. Survival advantage was significant in patients who underwent regular surveillance but not irregular surveillance compared with those who did not undergo surveillance. It is necessary to enhance implementation of HCC surveillance with better risk stratification for the at-risk population in practice to improve their outcome.

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