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Effectiveness of Hepatocellular Carcinoma Surveillance and an Optimal Surveillance Interval: Nationwide Cohort of Korea

Heejin Bae[1*], Sang Ah Lee[2*], Jong Won Choi[3], Shin Hye Hwang[4], Sumi Park[5], and Mi-Suk Park[1]

[1]Department of Radiology and Research Institute of Radiological Science, Yonsei University College of Medicine, Seoul;
[2]Big Data Strategy Department, National Health Insurance Service, Wonju;
Departments of [3]Internal Medicine and [5]Radiology, National Health Insurance Service Ilsan Hospital, Goyang;
[4]Department of Radiology, Yongin Severance Hospital, Yongin, Korea.

Purpose: To assess associations between surveillance intervals in a national hepatocellular carcinoma (HCC) surveillance program and receiving curative treatment and mortality using nationwide cohort data for Korea.

Materials and Methods: Using the National Health Insurance Service Database of Korea, we retrospectively identified 3201852 patients, the target population of the national HCC surveillance program, between 2008 and 2017. After exclusion, a total of 64674 HCC patients were divided based on surveillance intervals: never screened, ≤6 months (6M), 7–12 months (1Y), 13–24 months (2Y), and 25–36 months (3Y). Associations for surveillance interval with the chance to receive curative therapy and all-cause mortality were analyzed.

Results: The 6M group (51.9%) received curative therapy more often than the other groups (1Y, 48.3%; 2Y, 43.8%; 3Y, 41.3%; never screened, 34.5%). Odds ratio for receiving curative therapy among the other surveillance interval groups (1Y, 0.87; 2Y, 0.76; 3Y, 0.77; never screened, 0.57; $p<0.001$) were significantly lower than that of the 6M group. The hazard ratios (HRs) of all-cause mortality were 1.07, 1.14, and 1.37 for 2Y, 3Y, and never screened groups. The HR for the 1Y group (0.96; $p=0.092$) was not significantly different, and it was lower (0.91; $p<0.001$) than that of the 6M group after adjustment for lead-time bias. Curative therapy was associated with survival benefits (HR, 0.26; $p<0.001$).

Conclusion: HCC surveillance, especially at a surveillance interval of 6 months, increases the chance to receive curative therapy.

Key Words: Hepatocellular carcinoma, surveillance, mortality

INTRODUCTION

Primary liver cancer, including hepatocellular carcinoma (HCC, 75–85% of cases), intrahepatic cholangiocarcinoma (10–15% of cases), and other rare types, is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer-related mortality worldwide, as of 2018.[1,2] Although the age-standardized rate (ASR) of liver cancer has decreased continuously annually since 1999, liver cancer is still the sixth most common cancer in Korea, with a crude rate of 30.1/100000 and ASR of 17.0/100000, which are relatively high, compared with rates seen in other countries.[3] Moreover, liver cancer is the second most common

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Co-corresponding authors: Mi-Suk Park, MD, PhD, Department of Radiology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Tel: 82-2-2228-7400, Fax: 82-2-393-3035, E-mail: RADPMS@yuhs.ac and
Sumi Park, MD, Department of Radiology, National Health Insurance Service Ilsan Hospital, 100 Ilsan-ro, Ilsandong-gu, Goyang 10444, Korea.
Tel: 82-31-900-0837, Fax: 82-31-900-0343, E-mail: smp0304@nhimc.or.kr

*Heejin Bae and Sang Ah Lee contributed equally to this work.
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cause of cancer-related mortality in Korea.[4] The mortality rate for liver cancer is highest among individuals in their forties and fifties, the most economically active working-age population, which makes the economic burden of liver cancer highest among all cancers.[4,5]

Curative treatments for HCC, including hepatic resection, liver transplantation, and local ablative therapies, are recommended for early stage HCC and Barcelona Clinic Liver Cancer stage A HCC, with a reported median 5-year survival rate of 50% to 70% after curative treatments.[6-8] Specifically, the 5-year disease-free survival rate is reportedly 23% to 56.3% after hepatic resection and 74% after liver transplantation.[6-8] However, most patients with HCC are diagnosed at advanced stages, and curative treatments are occasionally unavailable based on tumor size, tumor location, and liver function.[6,7,9-11] Therefore, early detection of HCC through cancer surveillance is crucial to implementing curative treatment and improving patient survival. As HCC almost exclusively develops in patients with well-known risk factors such as chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection, liver cirrhosis, alcohol intake, and metabolic disease, HCC surveillance can be effective.[12,13]

South Korea launched the National Cancer Screening Program for liver cancer in 2003. HCC surveillance is recommended in high-risk individuals by several clinical practice guidelines; however, surveillance methods, including imaging modality and surveillance intervals, vary among the guidelines.[14-16] In Korea, the National HCC surveillance program conducts serum alpha-fetoprotein tests and ultrasonography for high-risk people older than 40 years who had liver cirrhosis, tested positive for HBV antigen or anti-HCV antibody, or had chronic HBV or HCV liver disease. The surveillance interval has remained at 6 months, except during 2012–2015, when the surveillance interval changed from 6 months to 1 year in Korea. To date, several studies have been conducted to evaluate the effectiveness of the surveillance program, and most of them have covered data from a single institution.[17-20] In this study, we analyzed associations between surveillance intervals and the rates of receiving curative treatment and mortality to evaluate the effectiveness of the national HCC surveillance program using nationwide cohort data.

MATERIALS AND METHODS

Database

The National Health Insurance Service (NHIS) system is a health insurance program that covers the entire Korean population. In this study, the NHIS-National Health Information Database (NHIS-NHID) (NHIS-2020-1-539) was used to retrieve demographic and medical information of people who were eligible for inclusion in the national HCC surveillance program. This database contained not only demographic and socioeconomic data, but also healthcare information, including medical history, diagnoses, and prescription data. Additionally, we accessed the National Liver Cancer Surveillance Program database, which included laboratory and ultrasonography results. Furthermore, annual reports on the cause of death statistics issued by the Microdata Integrated Service of Statistics Korea were used to analyze all-cause mortality and its association with surveillance intervals.

Study population

The Institutional Review Board of National Health Insurance Service Ilsan Hospital approved this study (NHIMC 2020-06-008). The target population of the national HCC surveillance included high-risk people aged ≥40 years who had liver cirrhosis, tested positive for HBV antigen or anti-HCV antibody, or had chronic HBV or HCV liver disease. The International Classification of Diseases-10 codes (ICD-10) was used to identify patients who were diagnosed with HCC (ICD-10 code C22.0). Additionally, the NHIS Service code V193, which is applied to patients with pathological or radiological diagnosis of cancer who visited the hospital and underwent medical expense deduction, was used to select patients who visited health care institutions for HCC treatment.

A flow diagram of patient selection is shown in Fig. 1. Between January 2008 and December 2017, 3201852 patients were included in the national HCC surveillance program's target population. Among them, 68448 patients visited the hospital for treatment of newly diagnosed HCC (both ICD-10 code C22.0 and NHIS code V193) between January 2011 and December 2018 and were retrospectively registered in this study. After excluding patients whose income or residential status were unidentifiable (n=3774), 64674 patients were included in the final study population, and the following demographic and medical information were evaluated: age, sex, income status, residential area, disability in the year of HCC diagnosis, liver cirrhosis, alcohol-related liver disease, HBV, HCV, and Charlson Comorbidity Index (CCI). For CCI, patient comorbidities detected during the 2 years prior to the diagnosis of HCC were analyzed.[21]

Surveillance intervals and curative therapy

We defined the date of HCC diagnosis (the date of the first visit to the medical institution with C22.0+V193 codes) as the index date and calculated surveillance intervals using the difference between the index date and the last surveillance date. Accordingly, surveillance intervals were classified into five groups: never screened, ≤6 months (6M), 7–12 months (1Y), 13–24 months (2Y), and 25–36 months (3Y).

In this study, we considered that curative therapy was administered when patients underwent hepatic resection, liver transplantation, or local ablative therapies, including percutaneous ethanol injection, radiofrequency ablation, cryoablation, and microwave ablation, within 1 year after the diagnosis of HCC.[7,22]

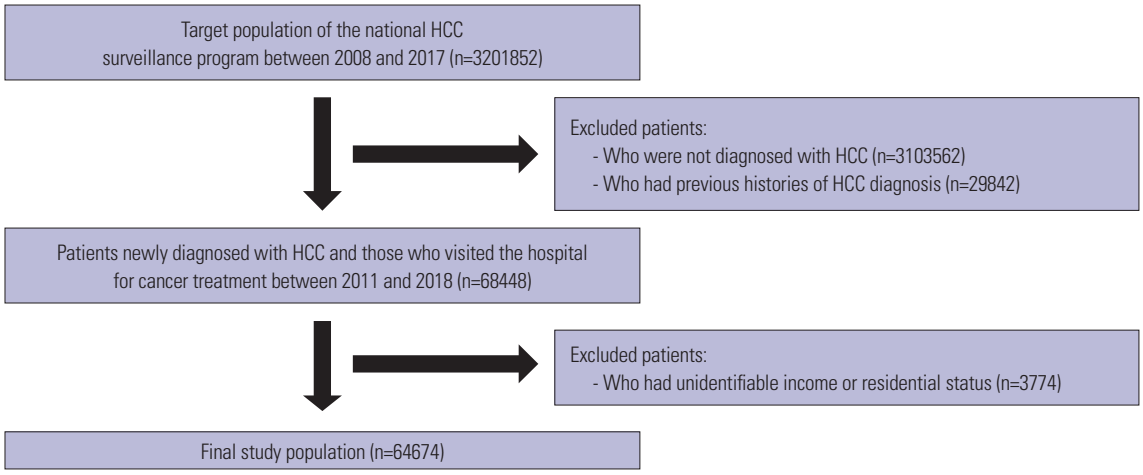

Fig. 1. Flow diagram of patient selection. HCC, hepatocellular carcinoma.

All-cause mortality

Both NHIS data and the causes of death statistics provided by the Microdata Integrated Service of Statistics Korea were used to identify the deaths of study patients and to calculate all-cause mortality from the date of HCC diagnosis to the date of death or the end of 2018, whichever occurred first. Meanwhile, early diagnosis of cancer due to cancer surveillance can lead to an overestimation of prognosis and survival.[23] To address lead-time bias, the Schwartz formula[24] based on tumor volume doubling time and tumor diameter can be used. However, these necessary data were unavailable from the NHIS-NHID and national liver cancer surveillance program database that were used in this study. Therefore, we applied two different lead times (157 and 174 days) estimated by previous studies to adjust for lead-time bias.[24,25]

Statistical analyses

The chi-square test was conducted to compare rates of receiving curative therapy and all-cause mortality between the different demographic and medical conditions. Odds ratios (ORs) computed by logistic regression were used to investigate the associations between the surveillance intervals and curative therapy. Additionally, Cox proportional hazards regression was performed to investigate the association between surveillance intervals and all-cause mortality. After univariable analyses of various demographic and clinical factors associated with curative treatments for HCC and all-cause mortality, multivariable analyses were performed using both logistic regression and Cox regression. All statistical analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, NC, USA). A p value less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics

Between January 2011 and December 2018, 64674 patients [sex: male, 49966 (77.3%); female, 14708 (22.7%); mean age: male, 60.9±10.0; female, 65.6±10.9] were diagnosed with HCC. The patient characteristics of the study cohort are summarized in Table 1. Among these patients, 63.4% (40983) of the patients had liver cirrhosis, and 53.8% (34823) and 11.1% (7203) had HBV and HCV infections, respectively. Patients underwent national HCC surveillance for ≤6 months (15587), 7–12 months (6569), 13–24 months (7383), and 25–36 months (3853) before the diagnosis of HCC. Patients who never underwent surveillance or received surveillance more than 36 months prior to the diagnosis were classified as never screened (31282).

Association between HCC surveillance and curative therapy

In total, 41.6% (26885) of HCC patients received curative therapy. Patients in the 6M group (51.9%) received curative therapy more often than those in the other surveillance interval groups (1Y, 48.3%; 2Y, 43.8%; 3Y, 41.3%; and, never screened, 34.5%) (Table 2). As shown in Table 2, univariable analysis demonstrated a significant association between curative therapy and surveillance interval [1Y group: OR, 0.87; 95% confidence interval (CI), 0.82–0.92; 2Y group: OR, 0.72; 95% CI, 0.68–0.76; 3Y group: OR, 0.65; 95% CI, 0.61–0.70; never screened: OR, 0.49; 95% CI 0.47–0.51; p<0.001]. Likewise, age greater than 60 years, income status, living in rural areas, disability, liver cirrhosis, alcoholic liver disease, hepatitis infection, and CCI were significantly associated with curative therapy in univariable analysis.

After adjusting for covariates, surveillance interval was still found to be significantly associated with curative therapy. The adjusted OR for receiving curative therapy decreased as surveillance interval increased (Table 2). Compared to the 6M group, the adjusted ORs were 0.87 for the 1Y group (95% CI, 0.82–0.93; p<0.001), 0.76 for the 2Y group (95% CI, 0.72–0.81; p<0.001), 0.77 for the 3Y group (95% CI, 0.71–0.83; p<0.001), and 0.57 for the never screened group (95% CI, 0.54–0.59; p<0.001) (Table 2). Cirrhotic patients were more likely to receive curative therapy than non-cirrhotic patients (OR, 1.11; 95% CI, 1.07–1.15; p<0.001). Hepatitis infection was also independently associated with a

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greater likelihood of receiving curative therapy (hepatitis B: OR, 1.88; 95% CI, 1.81–1.96; hepatitis C: OR, 1.54; 95% CI, 1.46–1.64; co-infection: OR, 1.97; 95% CI, 1.80–2.15; p<0.001). The ORs of receiving curative therapy were 1.07 (95% CI, 1.02–1.13; p=0.007) for CCI 1, 0.67 (95% CI, 0.64–0.70; p<0.001) for CCI ≥2, 0.92 (95% CI, 0.87–0.98; p=0.004) for the 60–69 year age, 0.55 (95% CI, 0.52–0.59; p<0.001) for the ≥70 year age, and 1.13 (95% CI, 1.08–1.19; p<0.001) for disability. Compared to patients with low income, those with middle-high (OR, 1.20; 95% CI, 1.14–1.26; p<0.001) and high incomes (OR, 1.43; 95% CI, 1.36–1.50; p<0.001) were more likely to receive curative treatment, whereas those with medical aid (OR, 0.68; 95% CI, 0.63–0.73; p<0.001) were less likely to receive curative treatment (Table 2).

Table 1. Patient Characteristics of the Study Cohort (n=64674)

Parameter	Value (%)
Age (yr)	
40–49	7453 (11.5)
50–59	21310 (33.0)
60–69	19591 (30.3)
≥70	16320 (25.2)
Sex	
Male	49966 (77.3)
Female	14708 (22.7)
Income status	
Medical aid	4398 (6.8)
Low	11280 (17.4)
Middle-low	11777 (18.2)
Middle-high	15227 (23.5)
High	21992 (34.0)
Residential area	
Capital area	24272 (37.5)
Metropolitan area	16562 (25.6)
Rural area	23840 (36.9)
Disability	
None	54942 (85.0)
Disabled	9732 (15.0)
Liver cirrhosis	
No	23691 (36.6)
Yes	40983 (63.4)
Alcoholic liver disease	
No	56660 (87.6)
Yes	8014 (12.4)
Hepatitis	
None	20308 (31.4)
Hepatitis B	34823 (53.8)
Hepatitis C	7203 (11.1)
Co-infection	2340 (3.6)
CCI	
0	14178 (21.9)
1	11478 (17.8)
≥2	39018 (60.3)
Surveillance interval	
≤6 months	15587 (24.1)
7–12 months	6569 (10.2)
13–24 months	7383 (11.4)
25–36 months	3853 (6.0)
Never screened	31282 (48.4)

Co-infection, hepatitis B and C infection; CCI, Charlson Comorbidity Index.

Association between HCC surveillance and all-cause mortality

In total, 43.7% (28279) of the patients died during the follow-up period. The cumulative mortalities of the 6M, 1Y, 2Y, 3Y, and never screened groups were 36.0%, 33.3%, 37.3%, 43.2%, and 51.4%, respectively (Table 3). Contrary to the rate of receiving curative therapy, the association between surveillance interval and all-cause mortality was not straightforward and varied. The hazard ratios (HR) for the 2Y group (adjusted HR, 1.07; 95% CI, 1.03–1.12; p=0.003), 3Y group (adjusted HR, 1.14; 95% CI, 1.08–1.21; p<0.001), and never screened groups (adjusted HR, 1.37; 95% CI, 1.33–1.42; p<0.001) were significantly greater than those of the 6M group (Table 3, Fig. 2). However, the HR of the 1Y group (adjusted HR, 0.96; 95% CI, 0.91–1.01; p=0.092) was not significantly different from that of the 6M group (Table 3). Even after adjusting for lead-time bias, the 1Y group surveillance interval was significantly associated with a lower risk of all-cause mortality than the 6M group surveillance interval (HRs with 157 days and 174 days of lead time, 0.91; p<0.001) (Table 4, Fig. 2). After correction of lead-time bias, the survival benefit of the 2Y group was not significantly different from that of the 6M group (HRs with 157 days and 174 days of lead time, 1.01; p=0.557 and p=0.721).

Patients who received potentially curative therapy were more likely to have survival benefits (adjusted HR, 0.26; 95% CI, 0.25–0.26; p<0.001) than those who did not receive curative therapy (Table 3, Fig. 3). The cumulative mortality of the patients who received curative therapy was 21.1%, whereas that of patients who did not receive curative therapy was 59.8%. A significant survival benefit was noted for patients with liver cirrhosis (adjusted HR, 0.96; 95% CI, 0.93–0.98; p<0.001) and those with hepatitis infection (hepatitis B: adjusted HR, 0.74; 95% CI, 0.72–0.76; hepatitis C: adjusted HR, 0.81; 95% CI, 0.78–0.84; co-infection: adjusted HR, 0.73; 95% CI, 0.68–0.78; all p<0.001) (Table 3). Significant associations with a survival benefit were also observed in the 50–59 years age (adjusted HR, 0.95; 95% CI, 0.91–0.99; p=0.018), 60–69 years age (adjusted HR, 0.92; 95% CI, 0.89–0.96; p<0.001), female (adjusted HR, 0.79; 95% CI, 0.77–0.81; p<0.001), middle-high income (adjusted HR, 0.94; 95% CI, 0.91–0.98; p=0.001), and high income (adjusted HR, 0.83; 95% CI, 0.80–0.86; p<0.001) (Table 3). On the other hand, an increased risk of mortality was associated with ages ≥70 (adjusted HR, 1.29; 95% CI, 1.23–1.34; p <0.001), living in metropolitan areas (adjusted HR, 1.24; 95% CI, 1.20–1.27; p<0.001), living in ru-

ral areas (adjusted HR, 1.21; 95% CI, 1.18–1.24; $p<0.001$), disability (adjusted HR, 1.04; 95% CI, 1.00–1.07; $p=0.027$), and CCI ≥2 (adjusted HR, 1.23; 95% CI, 1.19–1.27; $p<0.001$) (Table 3).

DISCUSSION

Through this current study of nationwide cohort data, we analyzed the effectiveness of HCC surveillance and demonstrated

Table 2. Univariable and Multivariable Analyses of Variables Associated with Curative Therapy for Hepatocellular Carcinoma (HCC)

Variables	Patients* (%)	Univariable analysis		Multivariable analysis	
		OR (95% CI)	*p* value	OR (95% CI)	*p* value
Total	26885/64674 (41.6)				
Surveillance interval					
≤6 months	8095/15587 (51.9)	1.00		1.00	
7–12 months	3176/6569 (48.3)	0.87 (0.82–0.92)	<0.001	0.87 (0.82–0.93)	<0.001
13–24 months	3236/7383 (43.8)	0.72 (0.68–0.76)	<0.001	0.76 (0.72–0.81)	<0.001
25–36 months	1591/3853 (41.3)	0.65 (0.61–0.70)	<0.001	0.77 (0.71–0.83)	<0.001
Never screened	10787/31282 (34.5)	0.49 (0.47–0.51)	<0.001	0.57 (0.54–0.59)	<0.001
Age (yr)					
40–49	3574/7453 (48.0)	1.00		1.00	
50–59	9974/21310 (46.8)	0.96 (0.91–1.01)	0.087	0.98 (0.93–1.04)	0.513
60–69	8598/19591 (43.9)	0.85 (0.81–0.90)	<0.001	0.92 (0.87–0.98)	0.004
≥70	4739/16320 (29.0)	0.44 (0.42–0.47)	<0.001	0.55 (0.52–0.59)	<0.001
Sex					
Male	20881/49966 (41.8)	1.00		1.00	
Female	6004/14708 (40.8)	0.96 (0.93–1.00)	0.036	1.02 (0.98–1.06)	0.336
Income status					
Medical aid	1271/4398 (28.9)	0.63 (0.58–0.68)	<0.001	0.68 (0.63–0.73)	<0.001
Low	4424/11280 (39.2)	1.00		1.00	
Middle-low	4750/11777 (40.3)	1.05 (0.99–1.10)	0.084	1.03 (0.97–1.09)	0.321
Middle-high	6571/15227 (43.2)	1.18 (1.12–1.24)	<0.001	1.20 (1.14–1.26)	<0.001
High	9869/21992 (44.9)	1.26 (1.21–1.32)	<0.001	1.43 (1.36–1.50)	<0.001
Residential area					
Capital area	10274/24272 (42.3)	1.00		1.00	
Metropolitan area	6952/16562 (42.0)	0.99 (0.95–1.03)	0.477	0.96 (0.93–1.01)	0.090
Rural area	9659/23840 (40.5)	0.93 (0.90–0.96)	<0.001	0.99 (0.95–1.03)	0.584
Disability					
None	23015/54942 (41.9)	1.00		1.00	
Disabled	3870/9732 (39.8)	0.92 (0.88–0.96)	<0.001	1.13 (1.08–1.19)	<0.001
Liver cirrhosis					
No	9091/23691 (38.4)	1.00		1.00	
Yes	17794/40983 (43.4)	1.23 (1.19–1.27)	<0.001	1.11 (1.07–1.15)	<0.001
Alcoholic liver disease					
No	23949/56660 (42.3)	1.00		1.00	
Yes	2936/8014 (36.6)	0.79 (0.75–0.83)	<0.001	0.98 (0.93–1.03)	0.345
Hepatitis					
None	5656/20308 (27.9)	1.00		1.00	
Hepatitis B	17412/34823 (50.0)	2.59 (2.50–2.69)	<0.001	1.88 (1.81–1.96)	<0.001
Hepatitis C	2695/7203 (37.4)	1.55 (1.46–1.64)	<0.001	1.54 (1.46–1.64)	<0.001
Co-infection	1122/2340 (47.9)	2.39 (2.19–2.60)	<0.001	1.97 (1.80–2.15)	<0.001
CCI					
0	7251/14178 (51.1)	1.00		1.00	
1	5829/11478 (50.8)	0.99 (0.94–1.04)	<0.001	1.07 (1.02–1.13)	0.007
≥2	13805/39018 (35.4)	0.52 (0.50–0.54)	<0.001	0.67 (0.64–0.70)	<0.001

OR, odds ratio; CI, confidence interval; Co-infection, hepatitis B and C infection; CCI, Charlson Comorbidity Index.
*Data are presented as n_1/n (%), where n_1 refers to the number of patients who received curative therapy and n refers to the total number of patients in each subcategory.

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Table 3. Univariable and Multivariable Analyses of Variables Associated with All-Cause Mortality

Variables	Patients* (%)	Univariable analysis		Multivariable analysis	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value
Total	28279/64674 (43.7)				
Surveillance interval					
≤6 months	5608/15587 (36.0)	1.00		1.00	
7–12 months	2185/6569 (33.3)	1.01 (0.96–1.06)	0.825	0.96 (0.91–1.01)	0.092
13–24 months	2751/7383 (37.3)	1.18 (1.13–1.24)	<0.001	1.07 (1.03–1.12)	0.003
25–36 months	1666/3853 (43.2)	1.35 (1.28–1.43)	<0.001	1.14 (1.08–1.21)	<0.001
Never screened	16069/31282 (51.4)	1.69 (1.64–1.75)	<0.001	1.37 (1.33–1.42)	<0.001
Curative therapy					
No	22595/37789 (59.8)	1.00		1.00	
Yes	5684/26885 (21.1)	0.22 (0.22–0.23)	<0.001	0.26 (0.25–0.26)	<0.001
Age (yr)					
40–49	2976/7453 (39.9)	1.00		1.00	
50–59	8443/21310 (39.6)	0.99 (0.95–1.03)	0.493	0.95 (0.91–0.99)	0.018
60–69	7752/19591 (39.6)	1.03 (0.99–1.07)	0.216	0.92 (0.89–0.96)	<0.001
≥70	9108/16320 (55.8)	1.74 (1.67–1.81)	<0.001	1.29 (1.23–1.34)	<0.001
Sex					
Male	22389/49966 (44.8)	1.00		1.00	
Female	5890/14708 (40.0)	0.85 (0.82–0.87)	<0.001	0.79 (0.77–0.81)	<0.001
Income status					
Medical aid	2493/4398 (56.7)	1.22 (1.16–1.28)	<0.001	0.99 (0.94–1.04)	0.657
Low	5039/11280 (44.7)	1.00		1.00	
Middle-low	5236/11777 (44.5)	0.98 (0.94–1.02)	0.299	0.99 (0.96–1.03)	0.706
Middle-high	6465/15227 (42.5)	0.92 (0.88–0.95)	<0.001	0.94 (0.91–0.98)	0.001
High	9046/21992 (41.1)	0.85 (0.82–0.88)	<0.001	0.83 (0.80–0.86)	<0.001
Residential area					
Capital area	9741/24272 (40.1)	1.00		1.00	
Metropolitan area	7453/16562 (45.0)	1.18 (1.15–1.22)	<0.001	1.24 (1.20–1.27)	<0.001
Rural area	11085/23840 (46.5)	1.24 (1.21–1.28)	<0.001	1.21 (1.18–1.24)	<0.001
Disability					
None	23570/54942 (42.9)	1.00		1.00	
Disabled	4709/9732 (48.4)	1.16 (1.12–1.19)	<0.001	1.04 (1.00–1.07)	0.027
Liver cirrhosis					
No	10793/23691 (45.6)	1.00		1.00	
Yes	17486/40983 (42.7)	0.86 (0.84–0.88)	<0.001	0.96 (0.93–0.98)	<0.001
Alcoholic liver disease					
No	24188/56660 (42.7)	1.00		1.00	
Yes	4091/8014 (51.1)	1.23 (1.19–1.27)	<0.001	1.00 (0.97–1.04)	0.996
Hepatitis					
None	11444/20308 (56.4)	1.00		1.00	
Hepatitis B	12428/34823 (35.7)	0.49 (0.48–0.51)	<0.001	0.74 (0.72–0.76)	<0.001
Hepatitis C	3495/7203 (48.5)	0.73 (0.70–0.76)	<0.001	0.81 (0.78–0.84)	<0.001
Co-infection	912/2340 (39.0)	0.54 (0.51–0.58)	<0.001	0.73 (0.68–0.78)	<0.001
CCI					
0	4738/14178 (33.4)	1.00		1.00	
1	4157/11478 (36.2)	1.08 (1.04–1.13)	<0.001	1.03 (0.99–1.07)	0.193
≥2	19384/39018 (49.7)	1.70 (1.64–1.75)	<0.001	1.23 (1.19–1.27)	<0.001

HR, hazard ratio; CI, confidence interval; Co-infection, hepatitis B and C infection; CCI, Charlson Comorbidity Index.
*Data are presented as n_1/n (%), where n_1 refers to the number of deaths and n refers to the total number of patients in each subcategory.

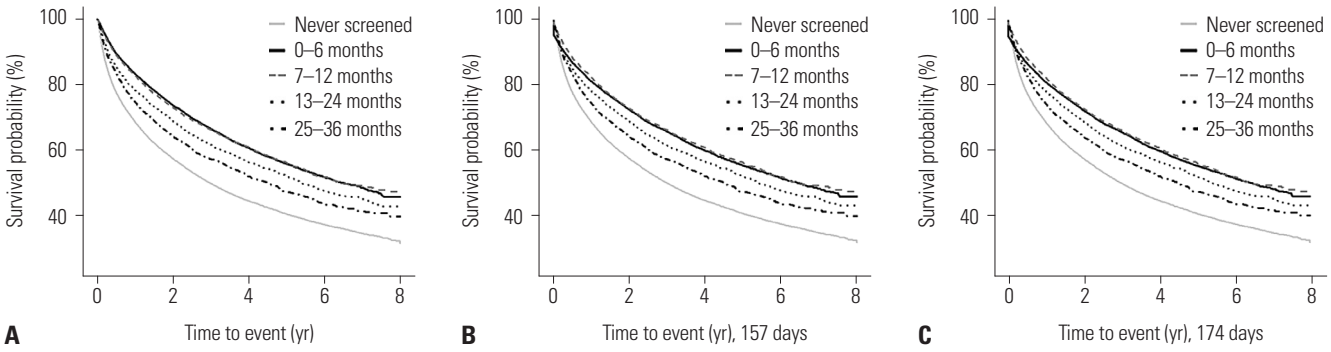

Fig. 2. Kaplan-Meier (KM) survival curves of patients with hepatocellular carcinoma (HCC) stratified according to HCC surveillance intervals. (A) The KM survival curve without adjustment for lead-time bias demonstrated that longer surveillance intervals were associated with decreased overall survival, although the ≤6 months and the 7–12 months groups showed no significant difference. (B and C) After adjusting for bias with 157 days (B) and 174 days (C) of lead times, the survival benefit of the 7–12 months group became significantly higher than that of ≤6 months group. The difference between the ≤6 months and the 13–24 months groups became statistically insignificant.

Table 4. Association between Surveillance Intervals and All-Cause Mortality after Adjusting for Lead-Time Bias

Lead-time	157 days		174 days	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Surveillance interval				
≤6 months	1.00		1.00	
7–12 months	0.91 (0.87–0.96)	<0.001	0.91 (0.86–0.95)	<0.001
13–24 months	1.01 (0.97–1.06)	0.557	1.01 (0.96–1.06)	0.721
25–36 months	1.08 (1.02–1.14)	0.008	1.07 (1.01–1.13)	0.014
Never screened	1.28 (1.24–1.32)	<0.001	1.27 (1.23–1.31)	<0.001

HR, hazard ratio; CI, confidence interval.

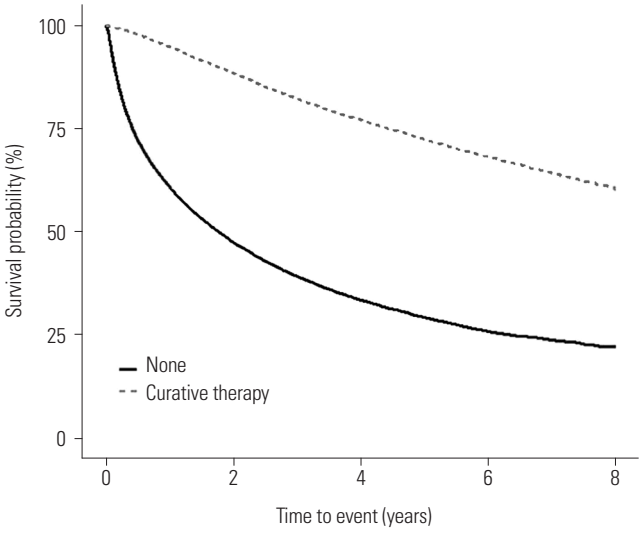

Fig. 3. Kaplan-Meier (KM) survival curve of patients with hepatocellular carcinoma (HCC) depending on curative therapy. The receipt of curative therapy was significantly associated with decreased overall survival among patients with HCC. Patients who did not receive curative therapy within 1 year from the diagnosis of HCC exhibited significantly lower overall survival than those who received curative therapy.

that a longer surveillance interval was significantly associated with a decreased likelihood of receiving curative therapy. HCC surveillance programs have been proven to prolong the survival of patients with HCC by detecting HCC and increasing the application of curative therapies.[22,26-32] One of the most important factors determining the effectiveness of a surveillance program is the selection of an optimal surveillance interval. In this study, a linear association was observed between surveillance interval and curative therapy, the most effective surveillance interval being 6 months. Similar to our study, Santi, et al.[33] compared semiannual and annual surveillance and reported that semiannual surveillance was superior to annual surveillance in terms of early detection of HCC. In addition, Wu, et al.[22] demonstrated that shorter surveillance intervals were associated with the probability of receiving curative therapy, although both 6-month and 12-month surveillance intervals showed a comparable chance of receiving curative therapy. However, reducing the surveillance interval to 3 months increased the detection of nonmalignant lesions and eventually led to a higher number of unnecessary procedures.[34] Therefore, in accordance with our study, a surveillance interval of 6 months is considered to be effective in detecting HCC patients who may be candidates for curative therapy.

We considered hepatic resection, liver transplantation, and local ablative therapies performed within 1 year after the diagnosis of HCC as curative therapies. These curative therapies led to a significantly lower risk (adjusted HR, 0.26) of overall mortality, with a 38.7% reduction in the mortality rate in this study. This result was concordant with previous studies that reported 5-year survival rates of 23–80% after surgical interventions[7,8,35,36] and 40–50% after local ablative therapies.[36] Especially, the detection of small HCCs is important because tumor size, particularly less than 3 cm, is closely related to complete ablation of a tumor and, ultimately, a lower rate of local tumor recurrence.[37,38]

Notably, the 6M group and 1Y group showed comparable all-cause mortalities in our study, although the former received curative therapies more often than the latter, which was significantly associated with survival benefits. After adjusting for lead-time bias, the HR for the 1Y group was significantly lower than that for the 6M group. Adjustment of lead-time bias also made the difference between the 6M group and 2Y group insig-

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nificant. This discrepancy might be due to various prognostic factors that can affect morbidity and mortality after curative therapies. Other than tumor size, another major prognostic factor is a patient's liver function, which is known to influence treatment decisions and to be associated with late tumor recurrence after resection and all-cause mortality.[39-41] Compared to patients with normal liver function who can achieve a 5-year survival rate of 70%, those with portal hypertension show a lower 5-year survival rate of 50%, which can be even lower in patients with impaired liver function.[36] Liver cirrhosis, particularly decompensated liver cirrhosis, is associated with increased resection-related complications, postoperative liver failure, and mortality.[7,13,36,42] In Korea, the national HCC surveillance program does not exclude patients with severely impaired liver function, namely Child–Pugh class C, when designating the target population. The severity of liver function in the target population of the national HCC surveillance program is an important prognostic factor and may lead to results of all-cause mortality that are different from those of the chance to receive curative therapies in this study. Therefore, even though HCC surveillance with a 6-month surveillance interval can lead to higher rates of curative therapies, clinical factors, especially liver function, should be considered when evaluating prognosis and patient survival after treatment.

Unlike most previous observational studies, our study used a nationwide cohort, avoided selection bias, and tried to adjust for lead-time bias. Furthermore, through comprehensive health care information, various demographic and clinical factors, such as underlying liver disease and patient comorbidity, were investigated to correct possible confounding factors that might disturb the effect of HCC surveillance. Nevertheless, some limitations exist in this study. First, calculation of surveillance interval based on all surveillance results for the patients was not possible, because following the surveillance interval strictly is often difficult in the real world and the actual time interval between surveillance exams can vary. Moreover, we could not identify patients who personally underwent cancer screening at their own expense. Instead, we used the last surveillance date and the date of HCC diagnosis to define the surveillance interval. Second, pathological results and imaging data were not obtainable to confirm the diagnosis of HCC. Future studies may include histopathological and imaging data of HCC to analyze all-cause mortality or liver-specific mortality because HCC prognosis can differ according to histopathologic variants. Although we tried to correct for lead-time bias, HCC surveillance might still detect indolent tumors, which would cause lead-time bias. Forth, since we followed up the patients and evaluated whether they were diagnosed with HCC or not until the end of 2018, patients with less than 3 years of follow-up may be included in the final study population, and inclusion of these patients may cause misclassification bias. Finally, since not all the necessary data were accessible, we could not evaluate accurate stages of HCC and consider liver function while evaluating all-cause mortality.

In conclusion, HCC surveillance, especially at a surveillance interval of 6 months, is independently associated with an increased chance of receiving curative therapy.

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AUTHOR CONTRIBUTIONS

Conceptualization: Mi-Suk Park and Sumi Park. Data curation: Heejin Bae and Sang Ah Lee. Formal analysis: Sang Ah Lee. Funding acquisition: Sumi Park. Investigation: Heejin Bae and Mi-Suk Park. Methodology: Sang Ah Lee. Project administration: Sumi Park and Jong Won Choi. Resources: Sang Ah Lee and Shin Hye Hwang. Software: Heejin Bae and Sang Ah Lee. Supervision: Sumi Park and Mi-Suk Park. Validation: Sumi Park and Mi-Suk Park. Visualization: Heejin Bae. Writing—original draft: Heejin Bae. Writing—review & editing: Sang Ah Lee, Sumi Park, and Mi-Suk Park. Approval of final manuscript: all authors.

ORCID iDs

Heejin Bae https://orcid.org/0000-0002-1227-8646
Sang Ah Lee https://orcid.org/0000-0001-5415-0141
Jong Won Choi https://orcid.org/0000-0001-9546-7313
Shin Hye Hwang https://orcid.org/0000-0003-2367-0413
Sumi Park https://orcid.org/0000-0002-8130-0368
Mi-Suk Park https://orcid.org/0000-0001-5817-2444

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