Journal of Hepatocellular Carcinoma

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ORIGINAL RESEARCH

Improved Survival in At-Risk Patients Undergoing Surveillance for Hepatocellular Carcinoma – A Nationwide Swedish Register-Based Study

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Purpose: Surveillance for hepatocellular carcinoma (HCC) is recommended in at-risk patients, but its effectiveness in Western populations has been questioned. The purpose was to evaluate the effect of surveillance in patients with HCC in a Northern European setting.

Patients and Methods: Data on patients diagnosed with HCC between 2009 and 2019 were collected from the nationwide Swedish National Registry for Tumors of the Liver and Bile Ducts (SweLiv). Patients who had undergone HCC surveillance were compared to those who had not (but had an obvious indication for surveillance, ie, liver cirrhosis or hepatic porphyria and an age of ≥50 years) regarding etiology, tumor burden, presence of extrahepatic spread, treatment and lead-time adjusted overall survival.

Results: A total of 4979 patients with index HCC were identified and information regarding surveillance was available in 4116 patients. Among these, 1078 had got their HCC diagnosis during surveillance, whereas 1647 had been diagnosed without surveillance despite a presumed indication. The most common underlying etiologies for HCC were hepatitis C (28.2%) and alcoholic liver disease (26.9%), and 94.8% had cirrhosis. The surveillance cohort more frequently met the University of California San Francisco-criteria (79% vs 53%, p <0.001), more often received a potentially curative treatment (62% vs 28%, p <0.001) and had less extrahepatic spread (7.6% vs 22.4% p <0.001). After adjustment for lead-time bias (sojourn time of 270 days), the surveillance group had a significantly longer estimated median survival time than the non-surveillance group (34 months vs 11 months, p <0.001). A multivariable cox regression analysis showed an adjusted hazard ratio of 0.59 (95% CI 0.51–0.67) in favor of surveillance.

Conclusion: Surveillance for HCC in at-risk patients is associated with diagnosis at an earlier tumor stage, treatment with curative intent and with improved lead-time adjusted overall survival. These findings encourage HCC surveillance of at-risk patients also in a Western population.

Plain Language Summary: In this research article, we aimed to evaluate whether patients who have a known risk to develop liver cancer have a better prognosis if they undergo regular screening examinations with ultrasound every sixth months. Using information from a nationwide Swedish registry, we investigated the outcome in a large group of patients who had been diagnosed with liver cancer. We compared patients who had performed regular examinations to those who had not and concluded that the screening group had less advanced disease at diagnosis, as well as a better survival.

Keywords: hepatocellular carcinoma, surveillance, survival, cirrhosis, chronic liver disease

Introduction

Hepatocellular carcinoma (HCC) is a significant global health issue. It is the sixth most common cancer form and the third most common cause of cancer-related death worldwide.[1] Geographically, the HCC occurrence and etiological panorama differs greatly with the highest incidence rates in East Asia and sub-Saharan Africa and lower incidence rates

Received: 5 May 2023
Accepted: 24 August 2023
Published: 19 September 2023

in Europe, particularly in Northern Europe.[2] However, recent reports are showing increasing incidence and mortality rates in both Europe and the USA.[2,3] It has been estimated that approximately 90% of HCC cases are associated with a known underlying etiology, most commonly liver cirrhosis.[2] The risk of HCC is elevated for all patients with liver cirrhosis, but the etiology behind cirrhosis has an impact on the risk increase, where hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are associated with a higher risk increase.[4] There is also a substantial risk of developing HCC without the presence of liver cirrhosis, such as in the case of active HBV infection and hepatic porphyrias.[4] Globally, HBV infection is the most significant underlying etiology, accounting for 33% of all HCC cases.[5] In Western Europe, however, HCV infection and alcohol-related liver disease (ALD) are the most common causes of HCC.[5] The etiological panorama is expected to shift due to the increasing use of vaccines against HBV and of direct-acting antivirals (DAAs) against HCV. In parallel, the incidence of non-alcoholic fatty liver disease (NAFLD) is increasing, especially in developed countries, and NAFLD is therefore thought to be an even more significant etiology behind HCC in the future.[6,7]

Individuals with risk factors for HCC (ie, liver cirrhosis of any cause, acute intermittent porphyria from age ≥50 years and selected cases of non-cirrhotic HBV) are recommended to attend surveillance programs with biannual abdominal ultrasonography[2,8] in order to diagnose HCC at an early stage and to increase the chance of receiving a potentially curative treatment. Prognosis is associated with the tumor stage at diagnosis, but also with liver function and health status.[4] Curative treatment for early HCC in otherwise healthy patients may provide a 5-year survival exceeding 70%,[4,9] whereas advanced disease is associated with a poor prognosis.

The recommendations on surveillance are mainly based on mathematical models, low-quality clinical trials and meta-analyses of retrospective and prospective cohort studies.[10,11] Zhang et al showed that surveillance was associated with a benefit in overall survival in a large study population with HBV infection.[12] Due to the selection of only HBV patients, the applicability of this study may be questionable in areas with a lower HBV prevalence. Furthermore, the studies that support HCC surveillance have significant methodological limitations and risk of biases, such as selection bias, lead time bias and length time bias.[4,9,13,14] Previous studies that have corrected for lead-time bias have often used the method proposed by Duffy et al. This correction depends on assumptions of the sojourn time of HCC, ie, the time during which the tumor is asymptomatic but can be detected by screening. Sojourn times ranging between 70 and 270 days have most commonly been used in earlier lead-time adjusted studies on HCC.[15–17]

The value of HCC surveillance has been questioned, especially in low endemic HBV areas, such as the United States and Europe, where other HCC etiologies are more prevalent.[14] In addition, adherence and attendance to surveillance programs may be low. In a Swedish setting, Edenvik et al showed that only 22% of HCC cases had been diagnosed through surveillance between 2005 and 2012 and that in 35% of all HCC cases, surveillance had been overlooked by physicians.[18]

Aims

The aim of this study was to evaluate the effect of surveillance for patients with HCC in a Northern European context, based on data from a nationwide Swedish liver tumor registry (SweLiv). Specifically, we wanted to determine the impact of surveillance on tumor stage at diagnosis, choice of treatment and survival. Secondly, we aimed to investigate the underlying etiologies of HCC in Sweden, and its potential impact on surveillance outcomes.

Methods

Data Collection

Data was collected from The Swedish National Registry for Tumors of the Liver and Bile Ducts (SweLiv), which is a nationwide quality registry comprising more than 97% of all HCC cases in Sweden.[19] SweLiv is divided into four modules: an initiation form with diagnosis and staging information; an intervention form regarding treatment; a form regarding pathological anatomical diagnosis and complications 30 days after surgery; and a two-year follow-up module (since 2014).[20] Adult patients (≥18 years) diagnosed with HCC (C22.0 according to International Classification of Diseases and Related Health Problems 10th edition (ICD-10)) between January 2009 and August 2019 were included in our study. In case of multiple registrations in the same patient, only the index cancer was included for analysis.

Study Cohorts

An initial descriptive analysis was made on the whole cohort of HCC patients. Patients were then divided into two groups based on surveillance status (surveillance and non-surveillance). Next, we excluded patients without an obvious indication for HCC surveillance. Patients in the non-surveillance group were considered to have surveillance indication if they had liver cirrhosis or hepatic porphyria and an age of ≥50 years. Consequently, all subsequent outcome analyses were performed comparing the surveillance group and the non-surveillance group with a presumed indication for surveillance. No information regarding surveillance interval was recorded, nor the number of surveillance examinations. Surveillance was recorded as "Yes" or "No" and defined as "repeated investigations due to underlying hepatic-/biliary disease". The Swedish guidelines on HCC surveillance was consistent during the study period and recommended biannual radiographic examinations in all cases but for hepatic porphyria, for which an annual regimen was recommended. Patients undergoing HCC surveillance, but who had been diagnosed with HCC in-between the surveillance examinations (ie, interval cancer), was still included in the surveillance group. Alpha-fetoprotein was not recommended as an additional surveillance marker in neither the Swedish nor the European guidelines during the study period and, thus, it was not acquirable from the register.

Variables and Categories

The following variables were extracted from SweLiv: time of diagnosis, vital status (dead or alive until 2020-06-13) and date of death, diagnosis by surveillance (yes/no), underlying etiologies, presence of diabetes (any type), tumor number and sizes, performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG), presence of metastases, type of treatment received, TNM classification, presence of cirrhosis, ascites and hepatic encephalopathy, international normalized ratio (INR), total bilirubin and albumin. From these variables, we determined the Child–Turcotte–Pugh (CTP) score and fulfillment of the University of San Francisco (UCSF) criteria. We primarily used the TNM classification to determine presence of extrahepatic disease, but in cases without TNM data, variables specifically describing presence of metastases were used. Extrahepatic spread included all extrahepatic metastases, including lymph node involvement.

Underlying etiologies were reported into SweLiv by the treating physician. Etiologies comprising less than 2% of the cases were categorized as Other (see Table 1 legend for specification of etiologies), except hepatic porphyria that was

Table 1 Underlying Etiology of Hepatocellular Carcinoma. Presented as Numbers and Valid Percentages

	Total Cohort (n=2725)	Surveillance Group (n=1078)	Non-Surveillance Group (n=1647)	*p*-value
Single etiology				
HCV	591 (28.2%)	298 (32.1%)	293 (25.2%)	<0.001
ALD	563 (26.9%)	198 (21.3%)	365 (31.3%)	<0.001
NAFLD	159 (7.6%)	74 (8.0%)	85 (7.3%)	0.566
HBV	104 (5.0%)	51 (5.5%)	53 (4.5%)	0.325
PBC	88 (4.2%)	26 (2.8%)	62 (5.3%)	0.004
Porphyria	27 (1.3%)	15 (1.6%)	12 (1.0%)	0.239
Other single etiology[a]	82 (4.2%)	44 (4.7%)	38 (3.3%)	0.084
Multiple etiologies				
ALD+HCV	335 (16.0%)	158 (17.0%)	177 (15.2%)	0.260
ALD+Other etiology	77 (3.7%)	32 (3.4%)	45 (3.9%)	0.614
HBV+HCV	35 (1.7%)	18 (1.9%)	17 (1.5%)	0.396
Other combinations	33 (1.6%)	15 (1.6%)	18 (1.5%)	0.889
Unknown etiology	631 (23.2%)	149 (13.8%)	482 (29.3%)	<0.001

Notes: [a]Each comprising < 2%. Including autoimmune hepatitis, hemochromatosis, primary sclerosing cholangitis, alpha-1-antitrypsin deficiency, Budd-Chiari syndrome, Fanconi anemia, Alagille syndrome, echinococcosis, glycogen storage disease type 4, congenital portosystemic venous shunt and Wilson's disease.

Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus; ALD, alcoholic liver disease; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cholangitis.

separately presented due to its endemic presence in some Swedish regions. In the case of multiple etiologies, ALD+HCV, ALD+Other and HBV+HCV were presented as separate entities, whereas all other combined etiologies were classified as Other combinations. Presence of liver cirrhosis was recorded as "Yes" or "No" in the register. In the register manual, the reporting physician is instructed that a patient is to be considered to have liver cirrhosis if findings on liver biopsy or liver elastography shows cirrhosis, or in the presence of a combination of clinical variables supporting cirrhosis, such as portal hypertension, radiographic findings, etc.

Outcomes

The primary outcome was overall survival. The surveillance and non-surveillance groups were compared regarding survival in months from diagnosis until time of death or latest vital status (date of data extraction). Time of death (of deceased individuals) and vital status are both automatically transferred from the Swedish National Cause of Death Register to SweLiv. Secondary outcomes were tumor burden at diagnosis (low burden defined as meeting the UCSF criteria; solitary tumor ≤65 mm or ≤3 tumors of ≤45 mm each and total tumor diameter ≤80 mm), extrahepatic spread at diagnosis and receipt of curative treatment. Curative treatment was defined as receiving liver resection, liver transplantation or ablation therapy.

Statistics

Continuous data are presented as means or medians with interquartile ranges. Mann–Whitney U or Kruskal–Wallis tests were used to compare continuous variables and the χ^2-test was used for categorical variables. For all analyses, a two-sided p-value <0.05 was considered statistically significant if not stated otherwise. The surveillance and non-surveillance groups were compared regarding tumor burden, receipt of curative treatment and extrahepatic spread using multivariable logistic regression analyses presented as adjusted odd ratios (aOR) with age, sex, etiology, PS and presence of diabetes as independent variables. Only statistically significant variables from the univariate analyses were included in the final analysis. Etiologies were grouped as ALD, viral hepatitis, and other single and multiple etiologies for these analyses.

Kaplan–Meier curves and log rank tests were used to compare survival between the surveillance and non-surveillance groups. Multivariable Cox proportional hazard regression analyses were performed including the following variables: surveillance status, age, sex, etiology, PS and presence of diabetes. Only statistically significant variables from the univariate analyses were included in the final analysis. Results were presented as adjusted hazard ratios (aHR). Subgroup analyses were carried out for patients with cirrhosis, with an additional adjustment for CTP class. Further subgroup analyses were performed comparing the survival for patients with a PS of ECOG 0.

Survival time for patients in the surveillance group were adjusted for lead-time bias according to the model proposed by Duffy et al, and an exponential distribution of the mean sojourn time ($1/\lambda$) was assumed.[21] Thus, the expected additional follow-up time in surveillance patients who had died at time t was $E(s)=\frac{1-e^{-\lambda t}-\lambda t e^{-\lambda t}}{\lambda(1-e^{-\lambda t})}$ and $E(s)=\frac{1-e^{-\lambda t}}{\lambda}$ in surveillance patients known to be alive at time t, respectively. Lead-time was then corrected by subtracting E(s) from the survival time of the patients in the surveillance group. Based on earlier studies, the longer estimated sojourn time (270 days) was used to reduce risk of overestimation of survival in the surveillance group.[2,22] Sensitivity analyses using sojourn times of 730 and 1460 days were also performed. To further account for lead-time bias, we also performed a multivariable Cox regression analysis comparing difference in survival after the first 36 months of follow-up, according to the findings by Cucchetti et al.[22]

All statistical analyses were performed using IBM® SPSS® version 27.

Ethics

The study was approved by the Swedish Ethical Review Authority (reference number: 2020-00410). No informed consent procedure is required for participation in Swedish quality registers, but patients are given the possibility to deny participation (opt-out) in SweLiv, and all data was acquired from an anonymized data file. The study was conducted in agreement with the Declaration of Helsinki.

Results

A total of 5874 cases were initially identified in SweLiv but after exclusion of non-eligible cases and duplicates, 4979 patients remained. Patient characteristics and the underlying etiologies for this original cohort is presented in Supplementary Tables S1 and S2.

Surveillance status was reported in 4116 patients and, of those, 1078 (26.2%) had undergone HCC surveillance and were included in the surveillance group. Among the non-surveilled patients, 1647 had characteristics that would have motivated HCC surveillance and this cohort constituted the non-surveillance group. All subsequent analyses were performed using these two cohorts (total n=2725), unless stated otherwise. See Figure 1 for a schematic presentation of the inclusion process.

For the combined surveillance/non-surveillance cohort (n=2725), the median age of HCC diagnosis was 67 years (range 22–93) and 78.1% of the patients were males. Liver cirrhosis was reported in 89.1% of the patients in the surveillance group, and 99.6% of patients in the non-surveillance group. Detailed patient characteristics are presented in Table 2. The median follow-up time was 16 months (range 0–129). The minimum follow-up time of 0 months was reported for 5 (0.46%) patients in the surveillance group and 136 (8.3%) patients in the non-surveillance group, respectively. Kaplan–Meier analysis for the combined cohort showed an estimated median survival time of 20 months (95% CI 18.26–21.74) and 3- and 5-year survival rates of 36.6% (standard error (SE) 0.010) and 26.2% (SE 0.010), respectively.

Outcomes

Survival

At follow-up, 1810 patients had died, of whom 526 (49.0%) were in the surveillance group and 1284 (78.1%) in the non-surveillance group. After lead-time adjustment (sojourn time 270 days), the estimated median survival was 34 months (95% CI 28.25–39.75) in the surveillance group and 11 months (95% CI 9.72–12.28) in the non-surveillance group (log rank test p <0.001), Figure 2). Corresponding 3- and 5-year survival was 48.4% and 37.8% in the surveillance group vs 26.0% and 16.2% in the non-surveillance group.

In a multivariable Cox regression analysis, surveillance was associated with a significantly lower mortality with an aHR of 0.59 (95% CI 0.51–0.67), as presented in Table 3. Sensitivity analyses using sojourn times of 730 and 1460 days, yielded an aHR of 0.72 (95% CI 0.63–0.82) and 0.87 (95% CI 0.76–0.99), respectively, thus still statistically significant findings. When comparing only patients with a PS of ECOG 0 (surveillance n = 492, non-surveillance n = 379), mortality was still lower in the surveillance group with an aHR of 0.65 (95% CI 0.53–0.81).

Subgroup Cox regression analysis on patients with cirrhosis, with additional adjustment of CTP class, also showed a beneficial survival for the surveillance group with an aHR of 0.56 (95% CI 0.48–0.65). In cirrhotic individuals with a PS of ECOG 0 (surveillance n = 426, non-surveillance n = 376), with additional adjustment of CTP class, results were similar with an aHR of 0.61 (95% CI 0.48–0.78).

Furthermore, when analyzing patients who had survived for ≥36 months after HCC diagnosis (surveillance n = 302, non-surveillance n = 298), the surveillance group showed a better survival outcome with an aHR of 0.47 (95% CI 0.32–0.68), as seen in Figure 3. For the subgroup with only cirrhotic individuals, with additional adjustment for CTP class, the aHR was 0.55 (95% CI 0.36–0.85).

Tumor Burden

Adequate tumor characteristics for assessment of the UCSF-criteria were available in 2531 patients (92.9%) – 1046 (97.0%) in the surveillance group and 1485 (90.2%) in the non-surveillance group. Overall, 1606 (63.5%) patients met the UCSF-criteria – 821 (78.5%) in the surveillance group vs 785 (52.9%) in the non-surveillance group (p <0.001), as presented in Figure 4. In a multivariable logistic regression analysis, surveillance was associated with an increased odds of meeting the UCSF-criteria, aOR 2.73 (95% CI 2.15–3.47).

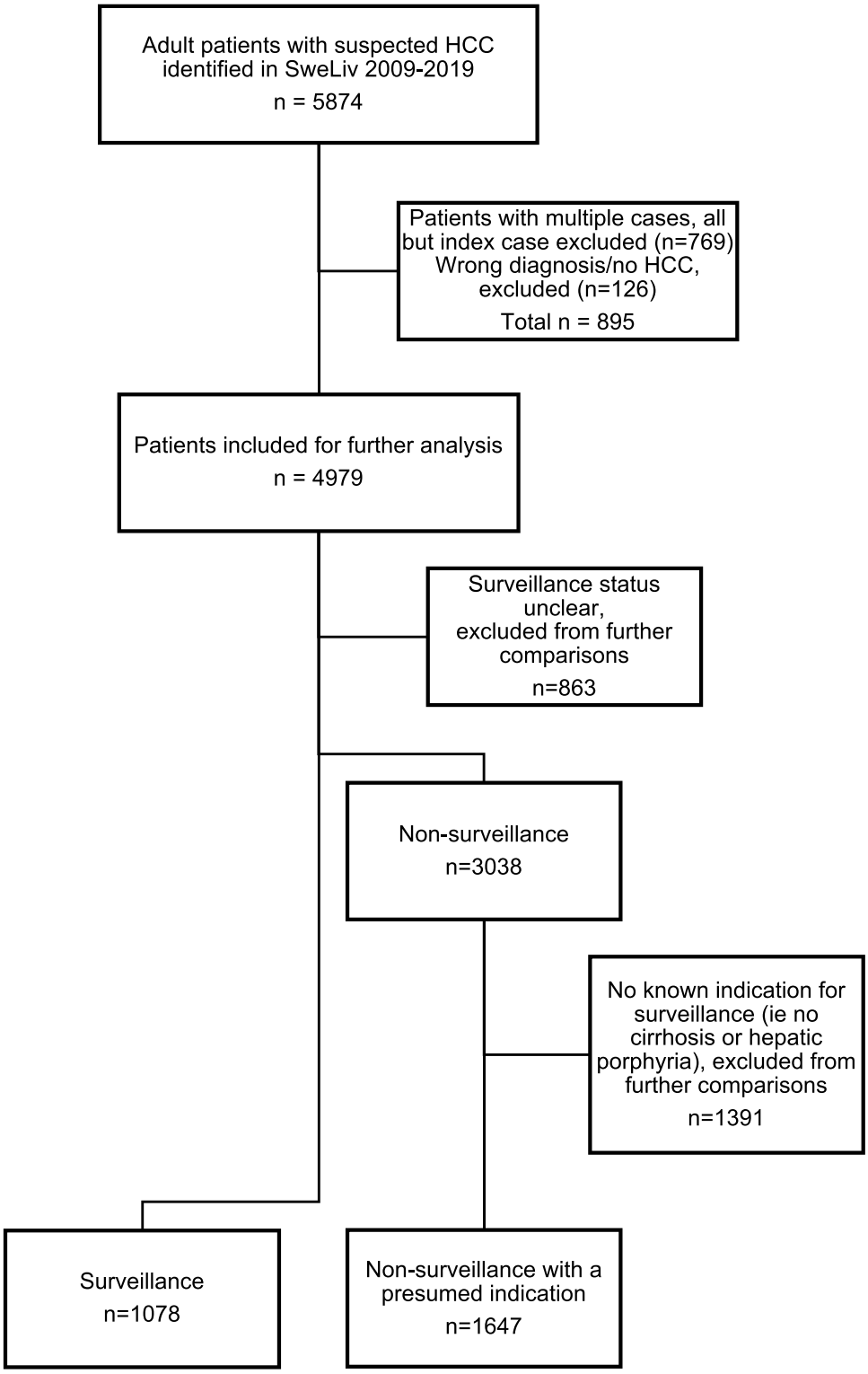

Figure 1 Inclusion flow chart.
Abbreviation: HCC, hepatocellular carcinoma.

Extrahepatic Spread

Extrahepatic spread at diagnosis, either as lymph node involvement or distant metastases, was found in 433 patients (16.4%). The occurrence was significantly lower in the surveillance group compared to the non-surveillance group, 80 (7.6%) vs 353 (22.4%) ($p < 0.001$), as presented in Figure 4. A multivariable logistic regression analysis showed

Table 2 Patient Characteristics for Included Patients

	Total Cohort (n=2725)	Surveillance Group (n=1078)	Non-Surveillance Group (n=1647)	*p*-value
Median age at diagnosis (IQR)	67 (13)	65 (13)	68 (13)	<0.001
Gender				0.034
Male	2127 (78.1%)	819 (76.0%)	1308 (79.4%)	
Female	598 (21.9%)	259 (24.0%)	339 (20.6%)	
Liver cirrhosis				<0.001
Yes	2584 (94.8%)	944 (87.6%)	1640 (99.6%)	
No	122 (4.5%)	116 (10.8%)	6 (0.4%)	
Unknown	19 (0.7%)	18 (1.7%)	1 (0.1%)	
CTP class[a]				<0.001
CTP A	1105 (42.8%)	536 (56.8%)	569 (34.7%)	
CTP B	627 (24.3%)	202 (21.4%)	425 (25.9%)	
CTP C	199 (7.7%)	42 (4.4%)	157 (9.6%)	
Median tumor size in mm[b] (IQR)	35 (37)	28 (20)	45 (40)	<0.001
Unknown	653 (25.3%)	164 (17.4%)	489 (29.8%)	
ECOG				<0.001
0	871 (32.0%)	492 (45.6%)	379 (23.0%)	
1	656 (24.1%)	282 (26.2%)	374 (22.7%)	
2	407 (14.9%)	99 (9.2%)	308 (18.7%)	
3	204 (7.5%)	29 (2.7%)	175 (10.6%)	
4	37 (1.4%)	5 (0.5%)	32 (1.9%)	
Unknown	550 (20.2%)	171 (15.9%)	379 (23.0%)	
Diabetes mellitus[c]				<0.001
Yes	905 (33.2%)	308 (28.6%)	597 (36.2%)	
No	1766 (64.8%)	748 (69.4%)	1018 (61.8%)	
Unknown	54 (2.0%)	22 (2.0%)	32 (1.9%)	
Ascites				<0.001
None	1765 (64.8%)	829 (76.9%)	936 (56.8%)	
Mild	356 (13.1%)	123 (11.4%)	233 (14.1%)	
Moderate-Severe	353 (13.0%)	59 (5.5%)	294 (17.9%)	
Unknown	251 (9.2%)	67 (6.2%)	184 (11.2%)	
Hepatic encephalopathy				<0.001
None	2241 (82.2%)	976 (90.5%)	1265 (76.8%)	
Grade I–II	89 (3.3%)	23 (2.1%)	66 (4.0%)	
Grade III–IV	23 (0.8%)	4 (0.4%)	19 (1.2%)	
Unknown	372 (13.7%)	75 (7.0%)	297 (18%)	

Notes: [a]Percentage for cirrhotic patients only. [b]Largest tumor in case of multiple lesions. [c]Any type.
Abbreviations: IQR, interquartile range; CTP, Child-Turcotte-Pugh; ECOG, Eastern Cooperative Oncology Group.

a significantly lower likelihood of extrahepatic spread in the surveillance group (aOR 0.37 (95% CI 0.26–0.52)) compared to the non-surveillance group.

Curative Treatment

Information regarding treatment choice was available in 2721 (99.9%) of the patients. Of these, 1136 patients (41.7%) had undergone a potentially curative treatment. There was a significantly higher proportion of patients receiving curative treatment in the surveillance group (669 patients, 62.2%), compared to the non-surveillance group (467 patients, 28.4%) ($p < 0.001$), as seen in Figure 4. In a multivariable logistic regression analysis, surveillance was associated with an increased odds of receiving curative treatment, with an aOR 2.97 (95% CI 2.38–3.71) compared to no surveillance.

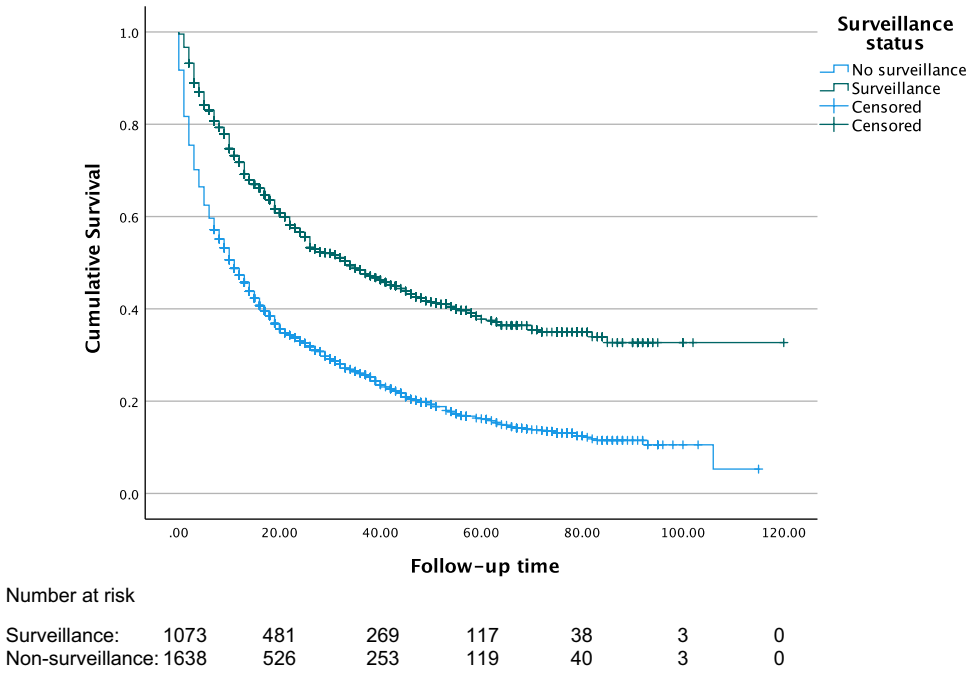

Figure 2 Kaplan–Meier curve showing estimated lead-time adjusted survival. Non-surveillance group including only patients with a presumed surveillance indication.

Etiology

An underlying etiology of HCC was reported in 2094 (76.8%) of the patients included in the surveillance comparisons (n=2725). For patients with known etiology, 23.0% had multiple underlying etiologies of HCC registered. In patients

Table 3 Multivariable Cox Regression Analyses for Overall Mortality, Corrected for Lead-Time Bias with a Sojourn Time of 270 Days

Variables	Adjusted Hazard Ratio (95% CI) Multivariable Analysis	*p*-value
Surveillance status		
Non-surveillance	Ref	
Surveillance	0.59 (0.51–0.67)	<0.001
Age	1.024 (1.016–1.032)	<0.001
Sex		
Male	Ref	
Female	0.95 (0.81–1.11)	0.52
Performance status		
ECOG 0	Ref	
ECOG 1	1.47 (1.26–1.71)	<0.001
ECOG 2	2.41 (2.02–2.88)	<0.001
ECOG 3	3.81 (3.07–4.73)	<0.001
ECOG 4	11.4 (7.50–17.4)	<0.001
Diabetes	0.92 (0.80–1.05)	0.223
Etiology		
Viral	Ref	
ALD	1.07 (0.91–1.26)	0.398
Other single	1.039 (0.85–1.26)	0.705
Other multiple	1.23 (1.04–1.47)	0.017

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ALD, alcoholic liver disease.

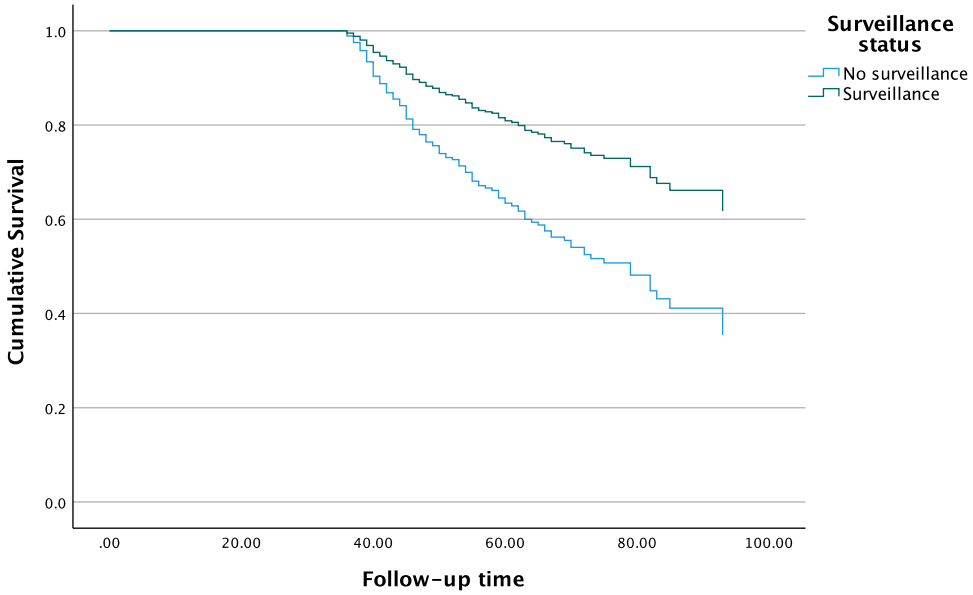

Figure 3 Survival curve from multivariable Cox regression analysis in patients with a follow-up time of ≥ 36 months. Non-surveillance group including only patients with a presumed surveillance indication. Adjusted for age, sex, performance status, etiology and presence of diabetes. Lead-time adjusted with a sojourn time of 270 days.

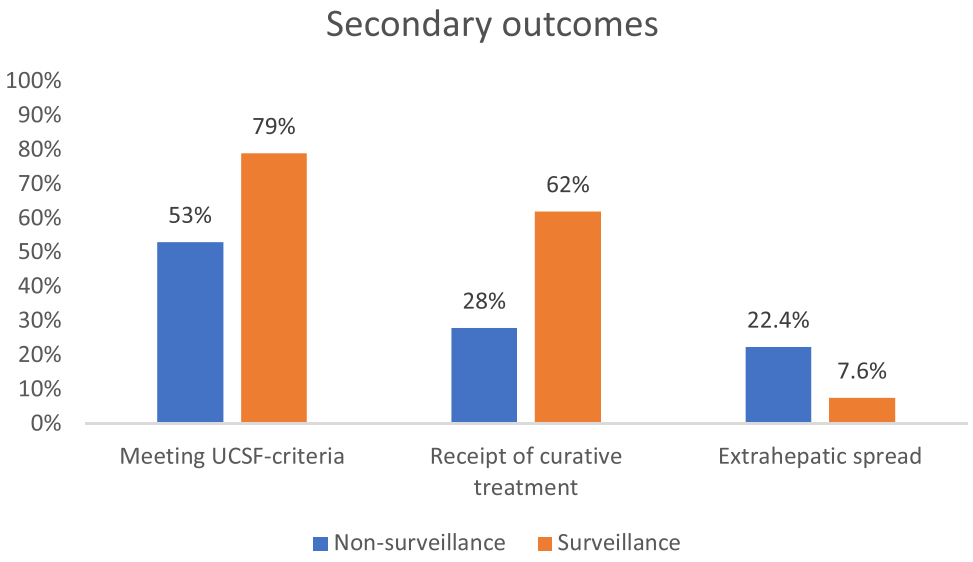

Figure 4 Comparisons between surveillance groups for meeting the UCSF-criteria, receiving curative treatment and presence of extrahepatic spread. Non-surveillance group including only those with a presumed surveillance indication.
Abbreviation: UCSF, University of California San Francisco.

with a single reported etiology, HCV (28.2%), ALD (26.9%) and NAFLD (7,6%) were the most prevalent diagnoses, whereas ALD+HCV (16.0%) was the most prevalent combination in patients with multiple etiologies. Details are presented in Table 1.

Survival and Etiology

Porphyria was the etiology with the longest estimated median survival time (66 months, 95% CI N/A), whereas primary biliary cholangitis (PBC) patients showed the shortest estimated median survival time (7 months, 95% CI 4.53–9.48). The PBC patients did also have the highest median age and the highest mean ECOG-score. Among the two dominating

Table 4 Estimated Median Survival Time in Months for Specific Etiology of Hepatocellular Cancer. Only Patients with Known Etiologies Included

	Total Cohort, Known Etiologies, n=2094 (95% CI)	Surveillance Group, n=929 (95% CI)	Non-Surveillance Group, n=1165 (95% CI)	*p*-value
Single etiology				
HCV	24 (18.1–29.8)	46 (34.3–57.7)	11 (8.26–13.7)	<0.001
ALD	17 (14.4–19.6)	26 (18.2–33.8)	11 (7.92–14.1)	<0.001
NAFLD	23 (8.95–37.1)	35 (18.0–52.0)	16 (6.72–25.3)	0.065
HBV	41 (17.3–64.7)	N/A[a]	16 (8.11–23.9)	<0.001
PBC	7 (4.53–9.48)	8 (6.40–9.50)	7 (3.58–10.4)	0.134
Porphyria	66 (N/A)	58 (10.3–105.7)	N/A[a]	0.723
Other single etiology[b]	16 (6.44–25.1)	23 (11.3–34.7)	10 (4.27–15.7)	0.142
Multiple etiologies				
ALD+HCV	18 (14.9–21.1)	42 (25.6–58.4)	11 (6.95–15.1)	<0.001
ALD+Other etiology	16 (9.69–22.3)	32 (6.05–58.0)	11 (5.89–16.1)	0.009
HBV+HCV	25 (3.07–46.9)	26 (2.65–49.3)	9 (3.82–14.1)	0.057
Other combinations	20 (N/A)	N/A[a]	11 (0.61–21.4)	0.165

Notes: [a]Median survival not reached. [b]Each comprising < 2%. Including autoimmune hepatitis, hemochromatosis, primary sclerosing cholangitis, alpha-1-antitrypsin deficiency, Budd-Chiari syndrome, Fanconi anemia, Alagille syndrome, echinococcosis, glycogen storage disease type 4, congenital portosystemic venous shunt and Wilson's disease.

Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus; ALD, alcoholic liver disease; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cholangitis.

etiologies, HCV and ALD, surveillance was associated with a significantly longer survival. Median survival times (lead-time adjusted) for the different etiologies are presented in Table 4.

Discussion

In this nationwide Swedish register-based study, HCC surveillance was associated with a markedly better lead-time adjusted survival, as well as higher odds of low tumor burden at diagnosis, curative treatment, and absence of extrahepatic tumor spread. Survival remained significantly improved also after adjusting for important confounders and using sojourn times of up to 1460 days. Neither did the underlying etiology seem to have a significant impact on the benefit of HCC surveillance, although the low patient numbers for some of the etiologies makes these subgroup analyses uncertain.

Receiving potentially curative treatment is vital for long time survival in HCC and, in turn, low tumor burden and absence of extrahepatic spread are important factors to make this a viable option. HCC surveillance has repeatedly been shown to increase the likelihood of diagnosis at an earlier stage, without presence of metastasis and vascular invasion.[10,11,17,23–25] In our study, surveillance was associated with considerably higher odds of receiving potentially curative treatment and this could explain the better survival seen in the surveillance group.

In our study, the survival time of the surveillance group was lead-time adjusted with an assumed sojourn time of 270 days. A variety of sojourn times have been used in earlier studies, commonly ranging between 70 and 270 days.[15,16,22,26] In our material, survival times were significantly longer for the surveillance group, even when using sojourn times of up to 1460 days. The impact of lead-time bias seems to be affected by the follow-up time. In a large national Italian cohort study, Cucchetti et al concluded that the impact of lead-time bias in the context of HCC surveillance mainly was significant during the first three years of follow-up after HCC diagnosis.[22] In our study, the survival benefit remained significant also when analyzing only patients with follow-up times exceeding 36 months. These findings imply that our findings were not only related to a lead-time bias.

Several further measures were taken to increase the comparability between the surveillance and non-surveillance groups and to minimize potential biases. Firstly, patients in the non-surveillance group who did not have a clear indication for surveillance were excluded from the final analyses. This was made to decrease the risk of comparing patients that would never have been subjected to HCC surveillance. Secondly, differences in baseline characteristics

between the groups were accounted for in multivariable Cox regression and logistic regression analyses. Additionally, we performed subgroup Cox regression analyses limited to patients with cirrhosis and patients with a PS of ECOG 0, respectively. Still, after applying these measures, outcomes were significantly better for the surveillance group.

Adherence to surveillance programs may be challenging in some cases. One could hypothesize that there may be groups of patients that are less prone to attend to surveillance programs and are less likely to seek medical attention upon symptoms, eg, in the case of alcohol or substance abuse, and they may therefore present with more advanced tumors. This could possibly contribute to the higher tumor burden observed in the non-surveillance group in our study. However, this might also warrant the use of HCC surveillance since it at least increases the chance of timely investigations in patients who show less attention to serious symptoms. Nevertheless, the potential benefit of surveillance in these patients needs to be weighed against the risk of missed appointments and an inadequate use of health care resources.

Our results are in concordance with several previous studies.[10,11,15,16,26,27] In a recently published meta-analysis by Singal et al,[23] 42 studies from various geographical settings were identified. They showed that surveillance was associated with a better overall survival with a pooled HR of 0.64 (95% CI 0.59–0.69). The twelve studies using lead-time adjustment also showed an improved survival with surveillance, with a pooled HR of 0.67 (95% CI 0.61–0.72), thus, somewhat higher than the aHR of 0.59 shown in our study. In an earlier meta-analysis by Singal et al,[11] 36 studies were identified, of which six had used lead-time adjusted survival data. They showed a pooled 3-year survival of 51% for the surveillance groups vs 28% for the non-surveillance group. In the six lead-time adjusted studies, the pooled 3-year survival rate was 39.7% for the surveillance group vs 29.1% for the non-surveillance group. In our study, the 3-year survival was higher (48.4%) in the surveillance group compared to the previous lead-time-adjusted studies, whereas that of the non-surveillance group was similar. Comparisons between earlier lead-time adjusted studies are, however, complex since assumptions regarding lead-time adjustment (assumed sojourn time or doubling time of HCC), choice of statistical methods (Duffy's or Schwartz's formula[21,28]), and adjustment for confounding factors have been highly diverse. Comparing 3- and 5-year survival rates or hazard ratios between different studies, should therefore be made cautiously. Nonetheless, one needs to acknowledge the high level of consistency between studies on the favorable outcomes for patients included in HCC surveillance.

Criticism against the current advice on HCC surveillance in guidelines has mainly focused on the low number of high-quality prospective randomized controlled trials (RCTs), and that the few conducted prospective studies have been performed with weak study designs and questionable applicability. However, many authors claim it practically impossible to conduct high-quality RCTs today, given the number of studies indicating a beneficial outcome of surveillance.[10,29] In 2011, Poustchi et al investigated whether patients with cirrhosis would consent to participate in an RCT in which they would randomize patients to receive surveillance or not.[30] More than 90% of these patients answered that they would decline participation in such a study, and the authors concluded that it would not be feasible to conduct future RCTs for this purpose. Thus, to evaluate the current recommendations on HCC surveillance, other types of study designs are needed. There could also be value in studying alternative surveillance regimens, such as the role of annual MRI examinations.[31–33]

There have also been studies unable to show a beneficial effect on survival from surveillance programs. Moon et al performed a matched case–control study within the US Veterans Affairs health care system, where they compared the association between HCC-related mortality and receipt of HCC screening/abdominal ultrasound examinations.[34] Their results showed that cirrhotic patients who died from HCC had undergone HCC screening examinations to a similar extent as the cirrhotic non-HCC controls, concluding that HCC screening was not associated with a decreased HCC mortality. However, during the 4-year study period, the 238 patients in the case group had performed only 492 ultrasound examinations, of which 284 of these were defined as actual HCC screening. This translates to one ultrasound every second year per patient and an actual HCC screening about once every fourth year, thus far from biannual screening. A potentially beneficial effect of biannual HCC surveillance may therefore not be excluded despite these findings.

The distribution of the underlying etiologies in our study differed somewhat from earlier global international studies. According to a WHO publication, the most common etiologies in Western Europe have been HCV, ALD and HBV.[35] As predicted in earlier publications,[6,7,23] our study showed an increasing frequency of NAFLD, which was the third most

common single etiology, slightly more common than HBV. HBV was, however, more prevalent than NAFLD overall, as it was more frequently seen in combination with other etiologies. HCV and ALD were the most common etiologies also in our material. Considering the introduction of new DAAs against HCV, the proportion of patients with HCV developing liver cirrhosis will likely decrease substantially, and consequently leading to a lower incidence of HCV-related HCC. Future efforts in preventing HCC should therefore be focused on identifying patients with ALD and NAFLD, and offer suitable measures to avoid future liver cirrhosis in these cases.

In this material, PBC showed the shortest survival times. However, this patient group did also have both the highest median age and ECOG-score which could act as confounding factors and have a negative impact on the survival times. Thus, it cannot be concluded that PBC in itself is to be considered a high-risk etiology. Porphyria, on the other hand, was the etiology with the longest survival times. Notably, this etiology does not per se involve a serious underlying liver condition which could explain the better outcome seen in this population. Earlier studies have shown that female sex might be associated with a favorable prognosis in HCC.[36] In our study, there was a female dominance in the surveillance group, but no sex difference was shown in overall survival. The slight female overweight in the surveillance group may have been too small to make an impact on overall survival.

We acknowledge that our study has several limitations. Its register-based design bears risk of bias and, although we adjusted for several possible confounders, there may still be important differences between the surveillance and non-surveillance groups. Lead time-bias may still have affected the survival analyses, despite statistical methods of correction, and length time-bias could not be correctly adjusted for due to insufficient register information. Surveillance status is registered dichotomously in SweLiv, and surveillance intervals were not specified. However, advice on HCC surveillance were consistent during the study-period (biannual for cirrhosis and HBV, and annual for hepatic porphyria). For patients with inconsistent surveillance intervals, the interval would likely have been longer than recommended, and thus rather diluting the potential benefits and attenuating survival. Moreover, almost a quarter of the patients had no data regarding the underlying etiology registered, mainly in the non-surveillance group, which may have weakened the reliability of the etiological presentation. It is likely that some of these patients did in fact have an undiagnosed liver disease, since this has been described to hold true for about 90% of HCC cases.[5] It is also possible that some etiologies, such as NAFLD, are more likely to be overlooked and underreported compared to, for example, viral hepatitis that is more straight-forward to diagnose and, in some contexts, also screened for.

Since RCTs are difficult to conduct today, we believe that our study does contribute to the evaluation of HCC surveillance. The strength of our study is that it is based on a large national cohort, comprising of nearly all cases of HCC in Sweden during a recent ten-year period. Further, it was conducted in a geographical area with low HBV incidence, which mirrors a Western European setting. Since much of the evidence hitherto has been based on studies from areas with higher HBV incidence, which is a high-risk etiology,[2] studies on HCC surveillance in a Western context has been encouraged. Moreover, survival was lead time-adjusted and sensitivity analyses showed preserved surveillance benefits, which increase the robustness of the results.

Conclusion

In this nationwide Swedish register-based study, HCC surveillance was associated with diagnosis at an earlier tumor stage, a higher degree of treatment with curative intent and with improved survival. Our results should therefore encourage a continued use of HCC surveillance for at-risk patients also in Western populations.

Abbreviations

HCC, hepatocellular carcinoma; SweLiv, Swedish National Registry for Tumors of the Liver and Bile Ducts; HBV, hepatitis B virus; HCV, hepatitis C virus; ALD, alcohol-related liver disease; DAAs, direct-acting antivirals; NAFLD, non-alcoholic fatty liver disease; ICD-10, International Classification of Diseases and Related Health Problems 10th edition; PS, performance status; ECOG, Eastern Cooperative Oncology Group; INR, international normalized ratio; CTP, Child–Turcotte–Pugh; UCSF, University of San Francisco; aOR, adjusted odd ratio; aHR, adjusted hazard ratio; PBC, primary biliary cholangitis; RCT, randomized controlled trials.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics

The study was approved by the Swedish Ethical Review Authority (reference number: 2020-00410).

Acknowledgments

We would like to thank and acknowledge all members of SweLiv for their commitment, as well as Björn Tavelin and Ove Björ for their accommodating statistical support.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Funded by research grants from the Region of Västerbotten.

Disclosure

The authors report no conflicts of interest in this work.

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