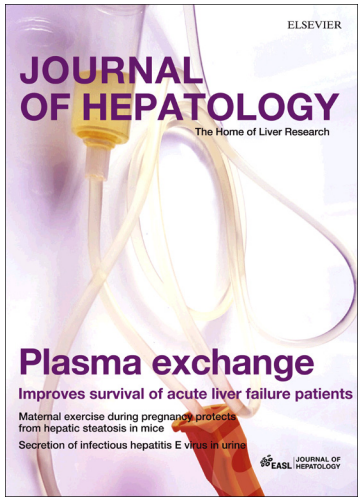
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Effectiveness of Surveillance for Hepatocellular Carcinoma in Clinical Practice: A United States cohort

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Effectiveness of Surveillance for Hepatocellular Carcinoma in Clinical Practice: A United States cohort

Short title: Effectiveness of HCC Surveillance

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Keywords: Liver cancer; Screening; Lead-time; Cirrhosis; Fatty liver

ABBREVIATIONS: Non-alcoholic fatty liver disease (NAFLD), Hepatocellular carcinoma (HCC), Veterans Administration (VA), Alpha-fetoprotein (AFP), Hepatitis C (HCV), Electronic medical records (EMR), International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), Common Procedural Terminology (CPT), Compensation and Pension Records

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Interchange (CAPRI), Computerized Patient Record System (CPRS), Hepatitis B (HBV), Outpatient Care File (OPC), Patient Treatment File (PTF)

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AUTHOR CONTRIBUTIONS: Study concept and design: Davila, El-Serag, and Mittal. Acquisition of data: Chung, Sada and Temple. Analysis and interpretation of data: Ying, Davila, El-Serag and Mittal. Drafting of manuscript: Davila, El-Serag and Mittal. Critical revision of the manuscript for important intellectual content: Davila, El-Serag, Kanwal, and Mittal. Statistical Analysis: Ying and Richardson. Study supervision: Davila.

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ABSTRACT

Background & Aims: The effectiveness of surveillance for hepatocellular carcinoma (HCC) in reducing cancer related mortality among patients with cirrhosis is largely unknown. The objective of this study was to study the effectiveness of HCC surveillance in the national Veterans Administration (VA) clinical practice.

Methods: We conducted a retrospective cohort study of patients with HCC during 2005-2010 by reviewing patients' medical records to determine receipt of HCC surveillance in the 2 years prior to HCC diagnosis. We determined association of HCC surveillance with overall mortality adjusting for age, risk factors, MELD score, co-morbidity index, AFP levels, healthcare utilization, Barcelona Clinic Liver Cancer (BCLC) stage, and treatment. We accounted for lead and length time biases.

Results: Of 887 patients with HCC, only 412 (46.5%) received any surveillance prior to HCC diagnosis. Patients who received surveillance were significantly more likely to have early stage disease HCC (BCLC stage 0/A 27.2% vs. 11.6%) and receive potentially curative (20.9% vs. 11.6%) or palliative (59.2% vs. 45.5%) treatments compared to those without HCC surveillance. Receipt of HCC surveillance was associated with 38% reduction in mortality risk (unadjusted HR 0.62, 95% CI 0.54-0.71) that declined to 20% (HR 0.80, 95% CI 0.69-0.94) after adjusting for HCC stage and treatment, compared to those without HCC surveillance.

Conclusions: Among patients with HCC, pre diagnosis HCC surveillance is associated with a significant 38% reduction in overall mortality. The reduction in mortality risk with surveillance is mediated via stage migration and receipt of HCC specific treatment.

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Lay Summary

Surveillance for liver cancer leads to earlier detection of cancer and increases chances of getting curative treatment. This ultimately leads to increased longevity in patients with liver cancer.

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INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) in the United States has increased over three folds in the past few decades [1]. Potentially curative treatments such as liver transplantation, resection and ablation are possible only among patients diagnosed with early stage disease [2]. However most patients with HCC are diagnosed at an advanced stage and receive either no treatment or only palliative treatment making HCC one of the most lethal cancer with an overall 5 year survival of approximately 15% [3].

Most clinical practice guidelines recommend surveillance for HCC in patients with cirrhosis [4-7]. The only controlled trial that evaluated efficacy of HCC surveillance using abdominal ultrasound and serum alpha-fetoprotein (AFP) was conducted in China and reported reduction in HCC related mortality by 37% in the surveillance arm [8]. The study included only patients with chronic hepatitis B (HBV) and had high risk of bias. It is unlikely a controlled trial will ever be conducted in western countries but several prospective cohort studies have shown reduced mortality with HCC surveillance [9-17].

However given the repetitive nature of HCC surveillance, need for recall for abnormal results and diagnostic evaluation, benefits seen in these studies may not translate into effectiveness in everyday real world practice. Few studies have evaluated effectiveness of HCC surveillance in clinical practice, but these studies were either small [9, 10], performed in single centers [11-15], studied population with predominantly chronic HBV [16], or used non-specific administrative data to identify surveillance [17].

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We therefore used data from the national Veteran Affairs (VA) clinical practice setting, and conducted in-depth review of electronic health records to determine effectiveness of HCC surveillance among patients diagnosed with HCC during 2005-2011. The aims of our study were to examine the effect of pre-diagnosis HCC surveillance on stage of HCC at diagnosis and to estimate the association of HCC surveillance with overall mortality while accounting for stage of HCC, extent of underlying liver disease, and lead time bias.

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METHODS

Study Population

We used data from VA administrative data files to identify a cohort of 10,695 patients who had a HCC diagnosis in VA hospitals between October 1, 2004 and September 30, 2011 based on the presence of ICD-9 CM code 155.0 (malignant neoplasm of liver) in the absence of code 155.1 (intrahepatic cholangiocarcinoma) [18]. Administrative data included the Medical SAS (MedSAS) Outpatient and Inpatient files, and the VA Vital Status File. The MedSAS files contain patient demographic data as well as diagnoses according to International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and procedures according to Common Procedural Terminology (CPT) codes. We determined date of death, if any, in the Vital Status File that uses an algorithm to select the most accurate date of death using the VA MedSAS Inpatient file, Beneficiary Identification & Records Locator System Death File, Medicare Vital Status file, and Social Security Administration death file (19). Patient EMR information were obtained by accessing the Compensation and Pension Records Interchange (CAPRI), which is a VA application that provides access to the EMR found in the Computerized Patient Record System (CPRS) at any VA facility nationwide. Based on *a priori* sample size of 1500, we selected a random computer generated sample of patients for chart review to determine the study eligibility criteria. These included that patients to have at least one inpatient or outpatient encounter at any VA facility within the 1-year prior to the date of HCC diagnosis (to ensure that patients were in regular care at the VA) and the diagnosis of HCC confirmed by either histopathology or imaging criteria according to the 2005 American Association for the Study of Liver Disease or European Association for the Study of Liver Disease guidelines [4, 6]. We reviewed the EMR of 2,719 patients with possible HCC to identify 1,500 study subjects with

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confirmed HCC. We excluded 830 patients due to insufficient evidence for HCC diagnosis in the EMR and 389 patients without recent VA healthcare utilization. These 1500 subjects formed the basis of our study cohort.

HCC Surveillance

Two hepatologists (HES, SM) manually reviewed the EMR including imaging reports, laboratory tests, and physician notes within the 2 years prior to the HCC diagnosis date to determine receipt of HCC surveillance, presence or absence of cirrhosis, and recognition of cirrhosis status by providers [20,21]. We defined HCC surveillance by receipt of at least one liver imaging test with or without AFP for surveillance purposes within 2 years prior to HCC diagnosis date. We captured surveillance imaging as receipt of liver ultrasound, CT scan, or MRI in the 2 years prior to HCC diagnosis with surveillance, liver transplantation evaluation, follow up on a known non-malignant appearing liver mass, or "cirrhosis" as the listed indications. We defined AFP surveillance as receipt of two or more AFP tests at least 6 months apart in the 2 years prior to HCC diagnosis. Among those who received surveillance, we further determined if HCC diagnosis was a result of surveillance tests or not. Patients diagnosed with HCC due to symptoms, signs or indications other than these listed in the definition of surveillance were classified as non-surveillance group. We defined confirmed cirrhosis based on liver biopsy results at any time before or at the time of diagnosis of HCC, features suggestive of cirrhosis on abdominal imaging, clinical complications of cirrhosis (ascites, hepatic encephalopathy, varices), or laboratory evidence consisting of abnormal values on two of three laboratory tests (albumin <3.0 g/L, platelets <200 000/lL, INR >1.1 between 6 months before and 4 weeks after HCC diagnosis) or an APRI (AST to platelet ratio index) score >2.0 [20]. Recognition

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of cirrhosis was defined as entry of a diagnostic code for cirrhosis or any mention of cirrhosis (or related term such as Child score) pertaining to the patient in a physician progress note on manual review of EMR [21].

Risk Factors for HCC

We defined HCV by presence of positive HCV ribonucleic acid (RNA) tests detected before or after HCC diagnosis. We defined HBV by a positive surface antigen (HBsAg) detected before or after HCC diagnosis. We captured alcohol abuse using history of more than 3 drinks a day, documentation of alcoholism or alcohol abuse in a progress notes, enrollment in a substance abuse treatment program, or history of alcoholic hepatitis. We diagnosed NAFLD based on evidence of hepatic steatosis on liver biopsy, or in the absence of liver biopsy, by the presence of metabolic syndrome in the *absence* of other causes of chronic liver disease (HCV, HBV, alcohol abuse, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, hemochromatosis or Wilson's disease). Metabolic syndrome was defined using U.S. National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines [22], except for replacing the elevated waist circumference criterion with body mass index (BMI) > 28.8 kg/m2 in both men and women [23]. Hemochromatosis, Wilson's disease, alpha-1 anti-trypsin deficiency or autoimmune hepatitis was identified by positive diagnostic laboratory tests or listed diagnoses in the problem list or progress notes. Patients having none of the above risk factors were classified as idiopathic HCC.

Patient and Tumor Characteristics

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These included demographic features, Model for End Stag Liver Disease (MELD) score, liver disease complications (ascites, encephalopathy, varices), performance status (Eastern Cooperative Oncology Group performance status 0-5), Barcelona Clinic Liver Cancer (BCLC) HCC stage (A-D) at time of diagnosis, healthcare utilization defined as at least one annual visit to the VA in each of the 3 years prior to HCC diagnosis, portal vein thrombosis or invasion, medical and mental health disorders. We defined overall mortality as death due to any cause with follow-up through October 31, 2014 using the VA vital status file [24]. HCC specific treatment was defined as receipt of liver transplantation, hepatic resection, ablation (alcohol, cryoablation or radiofrequency), trans-arterial chemoembolization (TACE) or chemotherapy received during the 12-months following HCC diagnosis captured by chart review.

Statistical Analysis

The main study outcome was overall mortality following HCC diagnosis, with BCLC stage of HCC at time of diagnosis and receipt of HCC specific treatment being the main explanatory variables. To mimic intention to treat analysis we compared these outcomes between patients who received and did not receive any surveillance irrespective of compliance prior to HCC diagnosis. Kaplan-Meier analysis was used to illustrate and compare overall survival in these groups. Stepwise Cox Proportional Hazards (PH) regression was performed to determine the independent association between HCC surveillance and overall survival. Potential confounders age, race, risk factors, non-hepatic Deyo index, MELD score, AFP levels and healthcare utilization that were significantly *(P*<0.1) associated with mortality in univariate Cox PH analyses were used as input variables. The model was constructed in a forward step-wise fashion and variables with *P*<0.05 in multivariable analyses were retained in the final models.

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We hypothesized that any effect of surveillance on mortality will be mediated or explained by changes in HCC stage at the time of diagnosis and/or receipt of HCC specific treatment. Therefore we examined changes in the parameter estimate of surveillance in the full model before and after adding these two potential explanatory variables. Hazard ratios (HR) and their 95% confidence intervals (CI) were calculated. PH assumptions were fulfilled in all models.

We conducted two sensitivity analyses to test the robustness of the findings to the definitions of the exposure and the cohort at risk. First, we defined receipt of HCC surveillance using a more stringent definition as regular (receipt of imaging based surveillance every 6-12 months after cirrhosis recognition), irregular (received surveillance that did not meet definition of regular surveillance) or no surveillance. Second, we limited the analysis to a cohort of patients with cirrhosis Child Pugh class A and B only.

To adjust for lead-time bias we applied a parametric model proposed by Duffy [25], assuming an exponential distribution of the sojourn time. Sojourn time is the period in which the tumor is asymptomatic but detectable by screening, and it indicates the upper limit of time by which diagnosis is advanced by screening (lead time). The lead-time was corrected by subtracting E(s) from the observed survival time [26]. Lastly, to adjust for length time bias in which tumors diagnosed early in the surveillance program differ in their biology and/or prognosis from those diagnosed later on, we performed the analysis after excluding patients in whom HCC was diagnosed within 1 year of cirrhosis recognition. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

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RESULTS

Patient characteristics

We confirmed presence of cirrhosis in 1201 (80.7%), 887 of whom had cirrhosis recognized by their providers prior to HCC diagnosis and thus were candidate to receive HCC surveillance; these patients formed our study analysis cohort. The mean age at the time of HCC diagnosis was 62.5 years (standard deviation=8.9) and the vast majority were men (99.8%). The greatest proportions of patients were white non-Hispanic (58.4%), followed by blacks (25.4%) and Hispanics (13.7%). HCV testing was performed in 96.1%, HBV testing in 89.5% and liver biopsy in 52.4% of patients in the study cohort. The main HCC risk factors were HCV (72.7%), alcoholic liver disease (84.3%), NAFLD (5.4%) and HBV (5.1%).

Association between HCC surveillance and HCC outcomes

Patients with and without HCC surveillance are compared in Table 1. A total of 475 (53.5%) received HCC surveillance in the 2 years prior to HCC diagnosis; 92 (22.3%) with imaging only and 320 (77.7%) with both AFP and liver imaging. Only 23.1% of patients with NAFLD related HCC received surveillance prior to HCC diagnosis compared to 51.8% for those with HCV and 47.4% with alcohol related HCC. Among those who received any HCC surveillance, 362 (87.9%) were diagnosed with HCC as a result of surveillance, whereas the rest were diagnosed by either symptoms (43, 10.4%) or were detected incidentally (7, 1.7%).

Patients who received HCC surveillance were significantly more likely to have early stage (BCLC stage 0/A) and less likely to have BCLC stage C or D at time of HCC diagnosis compared to those who did not receive any surveillance prior to HCC diagnosis. A significantly

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greater proportion of patients in surveillance received potentially curative treatment than those without prior surveillance (transplantation – 3.6% vs. 3.8%, resection – 7.0% vs. 2.9%, and ablation 10.2% vs. 4.4%, respectively). Similarly, the proportion of patients receiving any palliative treatment (59.2% vs. 45.5%, P<0.01) was higher in patients with versus those without HCC surveillance.

HCC surveillance was associated with reduced risk of overall mortality in unadjusted as well as adjusted analyses (Table 2). There was a significant 38% reduction in mortality risk among those who received HCC surveillance compared to those without HCC surveillance (HR-0.62, 95% CI-0.55-0.70). In multivariate analysis that adjusted for demographic and clinical features, survival benefit associated with receipt of HCC surveillance was attenuated but remained significant with a 32% reduction in mortality risk (HR-0.68, 95% CI 0.59-0.79). After adjusting for BCLC stage at diagnosis and HCC treatment as possible explanatory variables of surveillance effect, mortality risk was considerably reduced (HR-0.80, 95% CI -0.69-0.94) with HCC surveillance. As expected, AFP> 100 ng/ml, non-hepatic Deyo index ≥1, MELD score > 10 and receipt of no treatment were associated with increased mortality risk.

In a sensitivity analysis, we defined HCC surveillance as regular (receipt of imaging based surveillance every 6-12 months after recognition of cirrhosis), irregular (receipt of surveillance but did not meet definition of regular) or none, and excluded patients in whom HCC was diagnosed within 6 months of cirrhosis recognition date. In unadjusted analysis, mortality risk was reduced by 33% (HR-0.67, 95% CI -0.55-0.80) among those with regular or irregular surveillance as compared to no surveillance. After adjusting for age, comorbidity, AFP levels,

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underlying etiology and MELD scores, overall mortality was 30% lower in patients who received regular HCC surveillance compared to those without any surveillance (HR-0.70, 95% CI-0.58-0.86) (Table 3). The reduced risk of mortality associated with surveillance in this sensitivity analysis was attenuated and became statistically insignificant after adjusting for HCC stage and receipt of HCC treatment (HR-0.88, 95% CI- 0.72-1.08). Limiting the analysis to patients with Child A and B only did not change the direction or magnitude of the association between HCC surveillance and mortality risk (Table 3). There were no significant differences between regular vs irregular surveillance as evidence by the considerable overlap in the bounds of 95% CI of the risk estimates for each of these levels.

HCC surveillance was associated with significant reduced risk of death as compared to no surveillance after adjustment for possible lead time bias (Figure 1). For all three lead time assumptions, mortality remained significantly lower in surveillance group compared to no surveillance (Table 4). We varied the presumed lead point and an found inflection point where effect of surveillance is almost lost at sojourn time of 220 days; the associated lead time was 151 days and tumor doubling time 143 days (data not shown). Re-analysis after excluding patients diagnosed with HCC within 12 months of the date of cirrhosis recognition (to adjust for possible length time bias), the reduction in risk of mortality was slightly stronger among patients with HCC diagnosed > 12 months after cirrhosis recognition (unadjusted HR-0.59, 95% CI-0.48-0.73) as compared to overall cohort. In both analyses, adjusting for stage and treatment of HCC as possible explanatory variables removed the significance of the association between HCC surveillance and mortality risk reduction suggesting that the benefit of surveillance was mediated through early stage and increased HCC treatment (Tables 4 and 5).

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DISCUSSION

In a large national cohort of US veterans with HCC with underlying cirrhosis, we found that HCC surveillance was associated with 38% reduction in overall mortality risk. The observed benefit was mediated by stage migration and receipt of HCC treatment and persisted after adjusting for lead and length time bias. In the absence of a randomized trial addressing this important question, this study provides further evidence to support guidelines that recommend HCC surveillance in patients with cirrhosis.

A recent systematic review on role of HCC surveillance highlighted that most published observational studies on HCC surveillance were single centered, had selection bias, used stage migration as end point, and suffered from lead and length time bias [27]. For this study we used a patient sample from a national multicenter cohort and therefore the results represent benefits of surveillance program implemented in a major health care system. We adjusted for various demographic and clinical factors, including a validated co-morbidity score and severity of underlying liver disease but the effect of HCC surveillance remained significant. Patients who seek medical care regularly are more likely to be offered surveillance on a routine basis. Therefore to control for this possible healthy volunteer bias we adjusted for regular health care utilization; this adjustment also did not affect the observed association. Lastly, most differences in survival between those who received surveillance and patients who did not were accounted for by adjusting for stage and treatment – providing support to the causal link between HCC surveillance and improved outcomes. Collectively, our findings show that prior HCC surveillance in this large representative sample of patients with HCC was associated with an

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early stage at diagnosis, higher rates of curative treatments, and reduction in overall mortality - the ultimate goal of a surveillance program.

Lead-time likely explains some of the observed benefit in our analysis. However, reduced risk of mortality persisted after adjusting for lead-time bias. Furthermore, we have recently shown that among untreated HCC lead-time adds a modest one to two months to the observed overall survival compared to stage matched cases that did not receive any HCC surveillance (Khalaf N, unpublished data). We also hypothesized, and our analytic technique has demonstrated, that any improvement in survival would be mediated by detection of early stage tumor and subsequent application of curative therapy. This observation argues against lead time bias as the main reason for differences in survival.

Length time bias refers to when slow growing tumors are more likely to be detected by surveillance than faster growing tumors. For example, in prostate cancer where 5-year survival of stage I-III cancer is almost 100%, earlier stage diagnosis as a result of surveillance offers no true survival benefit [28]. However studies have shown that even small HCC can grow and are associated with markedly shortened survival [29]. Surveillance, Epidemiology, and End Results (SEER) registry analysis shows that 1-year and 5-year survival for localized HCC is 67% and 28% respectively [30]. Our results showed that survival benefit of HCC surveillance was not limited to potentially slower growing tumors (HCC diagnosed > 12 months after cirrhosis recognition). Further approximately 82% patients succumbed to their HCC within three years of diagnosis, suggesting that length time bias might not play a major role in explaining the beneficial effects of HCC surveillance.

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The observed reduced mortality risk related to surveillance was relatively modest compared to previous published studies [11-12, 14, 31-33]. There are several possible reasons for this finding. Some of the HCC surveillance captured in our study was programmatic (i.e. repeated at regular interval) and some was opportunistic. Some patients in our study had HCC diagnosed on their first surveillance imaging; they were included in the surveillance category. These factors probably tempered the observed benefit of HCC surveillance. Nonetheless, our study reflects the effectiveness of HCC surveillance in a real life clinical setting including a diverse group of patients managed in nonspecialized centers throughout the US.

The main liver societies practice guidelines recommend surveillance for HCC in high-risk individuals [5-8]; however others and we have observed that the penetration of these recommendations is still low [33, 34]. In this study, the proportion of HCC patients receiving surveillance prior to diagnosis increased during more recent years but overall less than half of HCC patients received any surveillance prior to HCC diagnosis. These proportions were markedly low among patients with NAFLD related HCC, probably because it is a less recognized risk factor for HCC [35].

Curative treatment options for HCC are applicable only for patients diagnosed with early stage disease. In our study patients diagnosed with HCC under surveillance were 2 times more likely to receive potentially curative treatments compared to no surveillance. However, most patients with HCC were diagnosed at an advanced stage of disease when survival is poor (5-year survival

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<5%) [3]. Given the available evidence in favor of surveillance, failure to provide surveillance may result in great harm while waiting for controlled trials that may not be forthcoming.

In our study approximately 12% of patients had surveillance failure i.e. received HCC surveillance at least once but HCC diagnosis was prompted by symptoms or was incidental. A previous study has shown that the most common reason for surveillance failure is non-compliance [36]. In the only controlled trial on HCC surveillance, adherence to surveillance was only 60% [8]. Thus our study highlights the benefit of surveillance given minimum surveillance failures as well as availability of HCC specific treatments.

Our study had several limitations. The study population was predominantly male, which may limit generalizability of results to women. Some patients may have received care including HCC surveillance outside VA that we could not capture. Our prior research has shown that this percentage is low and unlikely to impact major findings [17]. Lastly, we did not examine the overall benefits, costs and harms of surveillance in the at risk group, and therefore cannot comment on the cost effectiveness of the surveillance program.

In summary, we found that HCC surveillance was associated with lower tumor stage at diagnosis, and higher rates of curative treatment culminating in a significant reduction in the risk of overall mortality. There is need to increase penetration of surveillance recommendations and with more precise risk stratification that will augment the benefit of HCC surveillance program.

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Table 1. Characteristics of the study cohort of 1162 patients with HCC and cirrhosis stratified by receipt of surveillance tests within the 2 years prior to HCC diagnosis

Variable		**No Surveillance n=475 (53.5%)**	**Surveillance n=412 (46.5%)**	***P* value**
Age (years)				
	≤ 55	90 (18.9%)	82 (19.9%)	<0.01
	56-60	140 (29.5%)	150 (36.4%)	
	61-65	109 (22.9%)	115 (27.9%)	
	66-70	44 (9.3%)	40 (9.7%)	
	71+	92 (19.4%)	25 (6.1%)	
Race				
	White	274 (57.7%)	262 (63.6%)	0.11
	Black	125 (26.3%)	80 (19.4%)	
	Hispanic	67 (14.1%)	61 (14.8%)	
	Others	9 (1.9%)	9 (2.2%)	
Gender				
	Male	474 (99.8%)	412 (100%)	1.00
Non-hepatic Deyo Index				<0.01
	0	194 (40.8%)	174 (42.2%)	
	1	169 (35.6%)	174 (42.2%)	
	2+	112 (23.6%)	64 (15.5%)	
Child Pugh Class				
	A	161 (33.9%)	168 (40.8%)	0.0334
	B	209 (44%)	182 (44.2%)	
	C	83 (17.5%)	48 (11.7%)	
	unknown	22 (4.6%)	14 (3.4%)	
MELD Score				
	<10	135 (28.4%)	156 (37.9%)	<0.01
	10-19.9	256 (53.9%)	218 (52.9%)	
	20+	38 (8%)	12 (2.9%)	
	unknown	46 (9.7%)	26 (6.3%)	
HBV		22 (4.6%)	19 (4.6%)	0.99
HCV		333 (70.1%)	358 (86.9%)	<0.01
Alcohol		412 (86.7%)	372 (90.3%)	<0.01
NAFLD		21 (4.4%)	6 (1.5%)	0.01
Annual visit*	Yes	298 (62.7%)	283 (68.7%)	0.06
BCLC Stage				
	0/A	55 (11.6%)	112 (27.2%)	<0.01
	B	105 (22.1%)	94 (22.8%)	
	C	168 (35.4%)	109 (26.5%)	
	D	115 (24.2%)	62 (15%)	
	M	32 (6.7%)	35 (8.5%)	
Mode of HCC Diagnosis				
	Diagnostic	425 (89.5%)	43 (10.4%)	<0.01
	Incidental	50 (10.5%)	7 (1.7%)	
	Surveillance	-	362 (87.9%)	
HCC Treatment				<0.01
	Transplantation	18 (3.8%)	15 (3.6%)	
	Resection	14 (2.9%)	29 (7.0%)	
	Ablation	21 (4.4%)	42 (10.2%)	
	Palliative	216 (45.5%)	244 (59.2%)	
	None	206 (43.4%)	82 (19.9%)	

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Method of Surveillance				
	Imaging +AFP	-	320 (77.7%)	
	Imaging Only	-	92 (22.3%)	

HBV- Hepatitis B virus; HCV – Hepatitis C virus; NAFLD – Non-alcoholic fatty liver disease; BCLC staging – Barcelona Clinic Liver Cancer staging; AFP-Alpha-fetoprotein

*At least one annual visit to the VA in each of the 3 years prior to HCC diagnosis

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Table 2. Multivariate Cox PH analysis of association of HCC surveillance prior to HCC diagnosis with risk of mortality following HCC diagnosis

Variable	n (%)	Adjusted HR (95% CI)*	Adjusted HR (95% CI)[#]
HCC surveillance			
Yes	412 (53.6)	0.68 (0.59-0.79)	0.80 (0.69-0.94)
No	475 (46.4)	Ref	Ref
Age (years)			
56-60	290 (32.7)	0.87 (0.72-1.06)	0.94 (0.77-1.15)
61-65	224 (25.3)	0.94 (0.76-1.16)	0.99 (0.80-1.22)
66-70	84 (9.5)	0.69 (0.51-0.93)	0.70 (0.51-0.95)
71+	117 (13.2)	1.11 (0.84-1.47)	1.09 (0.82-1.44)
≤55	172 (19.4)	Ref	Ref
AFP (ng/ml)			
10-100	287 (32.4)	1.30 (1.08-1.57)	1.13 (0.94-1.37)
100-1000	178 (20.1)	1.78 (1.45-2.20)	1.32 (1.07-1.63)
1000+	146 (16.5)	3.92 (3.13-4.91)	3.33 (2.65-4.19)
Missing	32 (3.6)	1.00 (0.67-1.51)	0.77 (0.52-1.16)
0-10	244 (27.5)	Ref	Ref
Non-hepatic Deyo index			
1	343 (38.7)	1.20 (1.02-1.41)	1.21 (1.03-1.42)
2+	176 (19.8)	1.30 (1.06-1.59)	1.21 (0.99-1.48)
0	368 (41.5)	Ref	Ref
Annual visit[**]			
Present	581 (65.5)	1.00 (0.85-1.17)	1.08 (0.92-1.26)
Absent	306 (34.5)	Ref	Ref
Alcohol abuse			
Present	784 (88.4)	1.34 (1.05-1.69)	1.15 (0.90-1.47)
Absent	103 (11.6)	Ref	Ref
HCV			
Positive	691 (77.9)	1.17 (0.95-1.44)	1.35 (1.09-1.66)
Negative	196 (22.1)	Ref	Ref
HBV			
Positive	41 (4.6)	0.86 (0.62-1.21)	0.75 (0.53-1.05)
Negative	846 (95.4)	Ref	Ref
MELD score			
10-19.9	474 (53.4)	1.70 (1.45-1.99)	1.42 (1.21-1.68)
20+	50 (5.6)	3.01 (2.18-4.15)	1.69 (1.19-2.41)
unknown	72 (8.1)	1.14 (0.86-1.51)	0.99 (0.73-1.34)
< 10	291 (32.8)	Ref	Ref
BCLC stage			
B	199 (22.4)		1.19 (0.95-1.50)
C	277 (31.2)		1.76 (1.41-2.19)
D	177 (20)		3.30 (2.55-4.27)
M	67 (7.6)		1.08 (0.78-1.51)
0/A	167 (18.8)		Ref
HCC Treatment			
Curative	139 (15.7)		0.15 (0.12-0.20)
Palliative	460 (51.9)		0.48 (0.41-0.57)
None	288 (32.5)		Ref

*Adjusted for surveillance status, age, AFP, non-hepatic Deyo index, HCV, HBV, alcohol abuse, MELD score

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#Adjusted for surveillance status, age, AFP, non-hepatic Deyo index, HCV, MELD score, BCLC stage and treatment

** At least one annual visit to the VA in each of the 3 years prior to HCC diagnosis

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Table 3. Survival in patients diagnosed with HCC in association with pre-diagnosis HCC surveillance with sensitivity analysis.

Variable	n	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR# (95% CI)
Defining HCC surveillance using a stricter definitions as per AASLD recommendations	556			
Regular surveillance	278	0.67 (0.55-0.80)	0.70 (0.58-0.86)	0.88 (0.72-1.08)
Irregular	57	0.70 (0.52-0.95)	0.69 (0.50-0.95)	0.76 (0.55-1.06)
No surveillance	221	Ref	Ref	Ref
Restricting cohort to Child A/B only	720			
HCC surveillance				
Yes	350	0.61 (0.52-0.71)	0.65 (0.55-0.76)	0.72 (0.60-0.85)
No	370	Ref	Ref	Ref

*Adjusted for surveillance status, age, AFP, non-hepatic Deyo index, HCV, HBV, alcohol abuse, MELD score
#Adjusted for surveillance status, age, AFP, non-hepatic Deyo index, HCV, MELD score, BCLC stage and treatment

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Table 4. Survival in patients diagnosed with HCC in association with pre-diagnosis HCC surveillance with adjustment for possible lead time.

HCC surveillance	Median survival months	Unadjusted HR (95% CI)	Adjusted *HR (95% CI)	Adjusted # HR (95% CI)
Lead time= 70 days				
Yes	16.8	0.67 (0.58-0.77)	0.75 (0.65-0.87)	0.92 (0.79-1.07)
No	9.9	Ref	Ref	(Ref)
Lead time= 100 days				
Yes	15.9	0.69 (0.60-0.79)	0.77 (0.67-0.90)	0.96 (0.82-1.11)
No	9.9	Ref	Ref	(Ref)
Lead time= 140 days				
Yes	14.9	0.70 (0.61-0.80)	0.79 (0.68-0.92)	0.97 (0.83-1.14)
No	9.9	Ref	Ref	(Ref)

*Adjusted for surveillance status, age, AFP, non-hepatic Deyo index, HCV, HBV, alcohol abuse, MELD score
#Adjusted for surveillance status, age, AFP, non-hepatic Deyo index, HCV, MELD score, BCLC stage and treatment

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Table 5. Survival in patients diagnosed with HCC in association with pre-diagnosis HCC surveillance with adjustment for possible length time.

Variable	n	Unadjusted HR (95% CI)	Adjusted *HR (95% CI)	Adjusted *# HR (95% CI)
Excluding HCC diagnosed within 6 months of cirrhosis recognition				
HCC surveillance				
Regular	278	0.67 (0.55-0.80)	0.70 (0.58-0.86)	0.88 (0.72-1.08)
Irregular	57	0.70 (0.52-0.95)	0.69 (0.50-0.95)	0.76 (0.55-1.06)
No	221	Ref	Ref	(Ref)
Excluding HCC diagnosed within 12 months of cirrhosis recognition				
HCC surveillance				
Regular	236	0.59 (0.48-0.73)	0.61 (0.49-0.76)	0.80 (0.63-1.02)
Irregular	57	0.64 (0.47-0.87)	0.63 (0.45-0.87)	0.71 (0.51-1.00)
No	172	Ref	Ref	(Ref)

*Adjusted for surveillance status, age, AFP, non-hepatic Deyo index, HCV, HBV, alcohol abuse, MELD score
#Adjusted for surveillance status, age, AFP, non-hepatic Deyo index, HCV, MELD score, BCLC stage and treatment

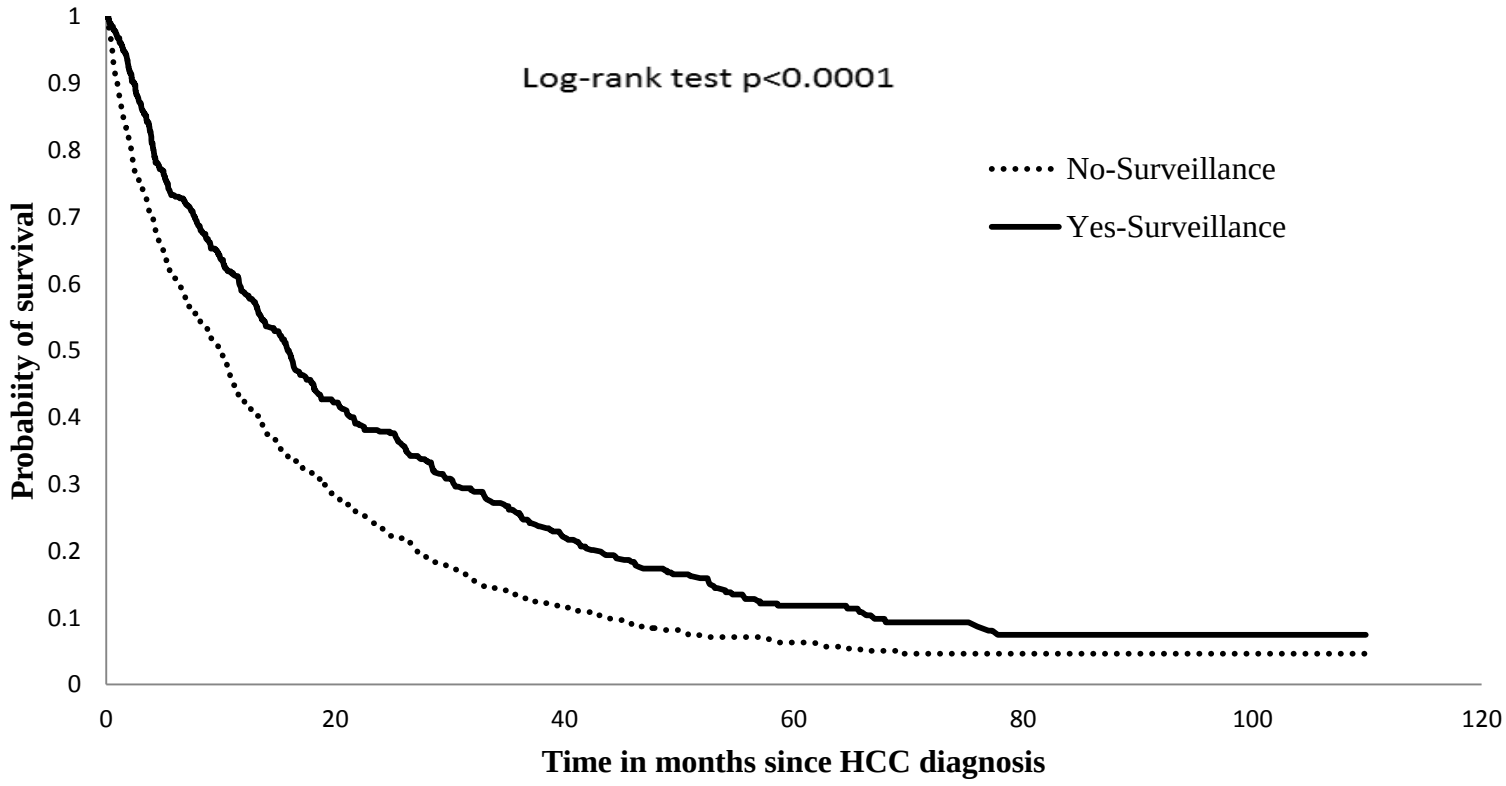
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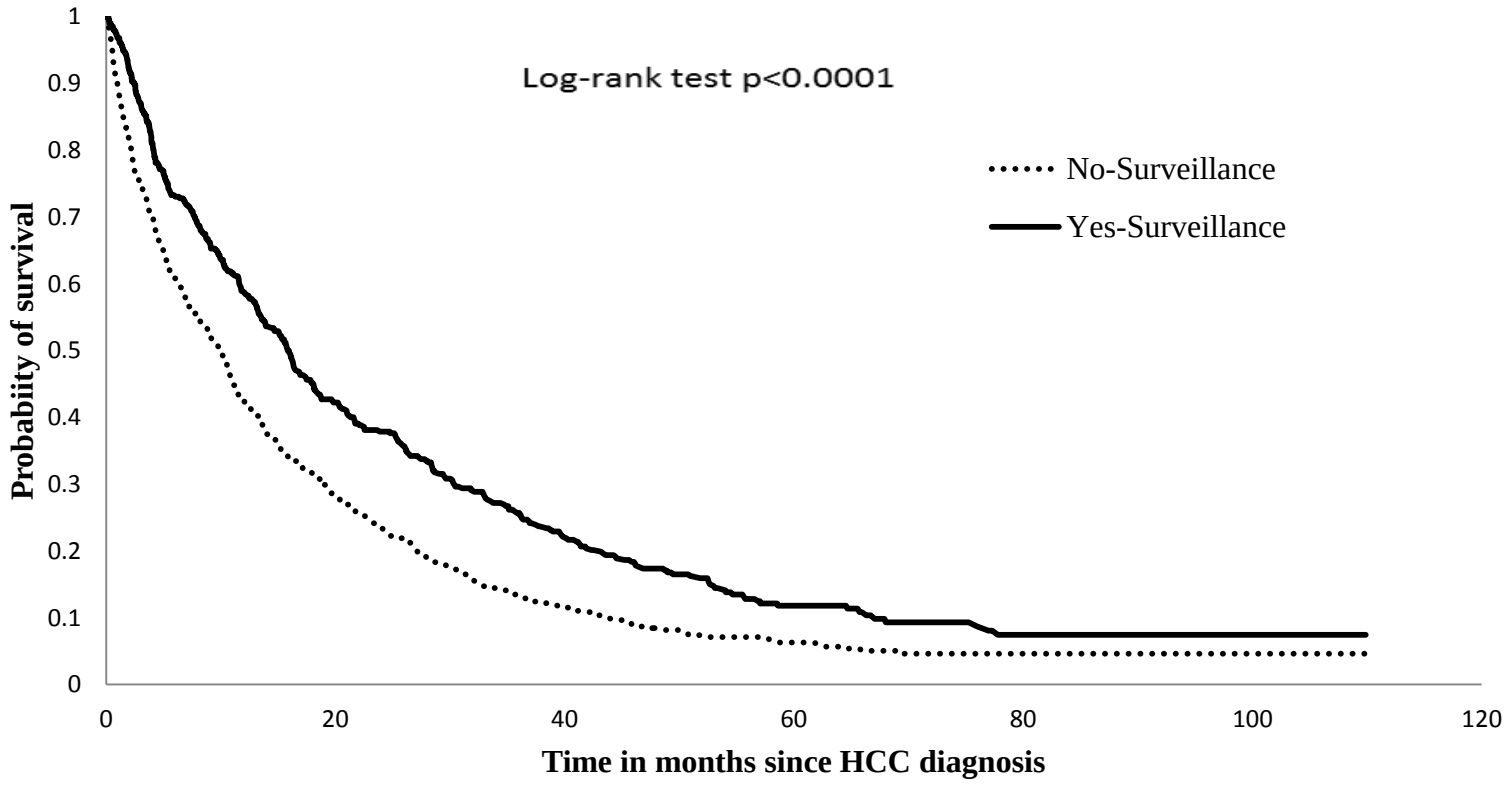
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Figure Legend

Figure 1. Kaplan Meier showing survival probability in months following HCC diagnosis stratified by surveillance category after adjustment for a presumed lead time of 100 days. Patients were censored for death due to any reason or lost to follow up.

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Log-rank test p<0.0001
No-Surveillance
Yes-Surveillance
Probabiity of survival
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
80
100
120
Time in months since HCC diagnosis


Log-rank test p<0.0001
No-Surveillance
Yes-Surveillance
Probabiity of survival
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
80
100
120
Time in months since HCC diagnosis