Screening Process Failures for Hepatocellular Carcinoma

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Abstract

More than 60% of patients with hepatocellular carcinoma (HCC) are diagnosed at a late stage, suggesting potential breakdowns in the HCC screening process. Understanding which steps in the screening process are not being performed is essential for designing effective interventions. To characterize HCC screening process failures, a retrospective cohort study of patients with cirrhosis diagnosed with HCC at a large urban safety-net hospital was conducted between 2005 and 2012. Screening process failures during the year before HCC diagnosis were characterized into 3 categories: absence of surveillance, failure of detection, and delayed follow-up. Univariate and multivariate analyses were performed to identify predictors of screening process failures. A total of 185 patients with cirrhosis and HCC were identified, of whom 91 (49%) were diagnosed at an early stage (Barcelona Clinic Liver Cancer system stage A). Only 16 (8.6%) patients successfully completed the screening process. Absence of surveillance was the most common screening process failure, found in 75.7% of all patients, and was associated with trends toward lower rates of early tumor detection (odds ratio, 0.51; 95% CI, 0.23–1.09) and worse overall survival (hazard ratio, 0.79; 95% CI, 0.49–1.25). Failure of detection and delayed follow-up were found in 11.4% and 2.7% of patients, respectively. (*J Natl Compr Canc Netw* 2014;12:375–382)

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See page 381 for authorship statement.

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Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide and one of the leading causes of death among patients with cirrhosis. It has an increasing incidence in the United States because of the current epidemics of nonalcoholic fatty liver disease (NAFLD) and hepatitis C virus (HCV) cases.[1] Prognosis for patients with HCC depends on tumor stage at diagnosis, with curative options only available for patients diagnosed at an early stage.[2,3] Patients with early-stage HCC achieve 5-year survival rates near 70% with resection and transplantation, whereas those with advanced HCC have a median survival of less than 1 year.[4,5]

Surveillance using ultrasound at 6-month intervals is recommended in patients with cirrhosis.[2,6,7] The goals of surveillance are to detect HCC at an early stage when it is amenable to curative therapy and to reduce all-cause mortality.[8] Effective implementation of the screening process requires surveillance (obtaining an ultrasound in patients with cirrhosis), effective detection (finding HCC when it is present at an early stage), and appropriate follow-up (obtaining a 4-phase CT or MRI in patients with an abnormal ultrasound).[9] Prior studies have suggested that HCC surveillance may be efficacious for detecting early HCC and improving survival; however, its effectiveness in clinical practice may be impacted by several factors, including low use rates and/or operator-dependency, leading to poor detection rates.[10–15] Similarly, treatment underuse and delayed treatment may mitigate any survival benefit in patients who undergo surveillance and are found at an early stage.[16,17]

Despite improvements in technology and awareness, most HCC cases in the United States continue to be diagnosed at a late stage.[18] This failure suggests potential breakdowns in the HCC screening process, including an absence of surveillance, failure of detection, or delayed follow-up. The purpose of this study was to

characterize the impact of screening process failures on tumor stage at presentation and overall survival in clinical practice among a racially diverse cohort of patients.

Methods

Study Population

A retrospective cohort study of patients with cirrhosis diagnosed with HCC at Parkland Memorial Health and Hospital System, the safety-net system for Dallas County, was conducted between January 2005 and March 2012. As a safety-net hospital, Parkland has an explicit mission to provide a significant level of care to low-income, underinsured, and vulnerable populations. Parkland is one of the few safety-net hospitals with an integrated electronic medical record for the hospital and clinics, including primary care clinics. With 11 primary care clinics in low-income neighborhoods, Parkland cares for approximately 50% of patients with HCC in Dallas County. Given this integrated structure, patients admitted to Parkland often receive their continuity care through Parkland Hospital. Similar to most hospitals nationally, Parkland does not have a systematic HCC screening program, and HCC surveillance is visit-based at the discretion of the clinic provider.

Patients were initially identified by ICD-9 codes for HCC (155.0 or 155.2), tumor conference presentation lists, and prior databases of patients who underwent surgical (resection or transplantation) or interventional (transarterial chemoembolization or local ablation) treatments for HCC. Patients were required to have had their first patient encounter at Parkland more than 1 year before HCC diagnosis so that screening process failure rates could be accurately determined.

Two authors (A.S. and A.Y.) adjudicated HCC cases to confirm they met diagnostic criteria, based on American Association for the Study of Liver Disease (AASLD) guidelines.[19] For tumors larger than 1 cm, diagnosis was made based on a typical vascular pattern on dynamic imaging (arterial enhancement and delayed washout) or histology. Patients without imaging were excluded given that tumor characteristics could not be determined. Patients with Child-Pugh C cirrhosis and those with poor performance status were also excluded, because surveillance is not recommended in these patients. This study was approved by the Institutional Review Board at UT Southwestern Medical Center.

Data Collection

Patient demographics, clinical history, laboratory data, and imaging results were obtained through review of computerized and paper medical records. Two investigators (A.S. and A.Y.) independently extracted information using standardized forms, with a third investigator (J.M.) available to resolve discrepancies. Age, gender, race/ethnicity, and lifetime alcohol and smoking history were recorded, with active alcohol abuse defined as drinking more than 40 g/d. Dates of cirrhosis diagnosis, HCC surveillance testing, and HCC diagnosis were abstracted. Date of first medical encounter and number of primary care and hepatology clinic visits were documented. Data regarding liver disease included underlying origin and the presence of decompensation (ascites or encephalopathy). Patients were classified according to the cause of liver disease, including HCV, hepatitis B virus, alcohol-related liver disease, NAFLD, and other. Laboratory data of interest included platelet count; creatinine, aspartate aminotransferase, alanine aminotransferase, bilirubin, α-fetoprotein, and albumin levels; and international normalized ratio. Tumor characteristics were determined by imaging studies (4-phase CT or MRI)interpreted by radiologists at UT Southwestern Medical Center, and the Barcelona Clinic Liver Cancer (BCLC) system was used for tumor staging.

Statistical Analysis

Patients were assigned to 1 of 2 groups based on HCC stage at diagnosis. Early-stage patients were defined as those with BCLC stage A HCC, characterized by well-preserved liver function (Child-Pugh A–B cirrhosis), good performance status, and limited tumor burden (1 tumor <5 cm or 2–3 tumors, each <3 cm in maximum diameter, without gross vascular invasion or distant metastases). Patients with BCLC stage B HCC (more extensive intrahepatic disease) or stage C HCC (vascular invasion and/or distant metastases) were categorized as having advanced HCC. This cutoff was chosen because curative options are available for patients with BCLC stage A HCC, whereas only palliative options exist for those

with more advanced tumors. Patients with BCLC stage D HCC were excluded because surveillance is not recommended in patients with Child-Pugh C cirrhosis or those with poor performance status.

The authors classified breakdowns in care during the year before HCC diagnosis into 1 of 3 mutually exclusive categories: absence of surveillance, failure of detection, or delayed follow-up. *Absence of surveillance* was defined as lack of ultrasound performed for surveillance purposes within the 12-month period before HCC diagnosis. A 1-year period was chosen based on HCC surveillance guidelines during the study period.[19] Imaging was determined to be for surveillance purposes through chart review of imaging reports and clinical notes. *Failure of detection* was defined as when a suspicious lesion was not seen on surveillance ultrasound within the year prior to HCC diagnosis. *Delayed follow-up* was defined as lack of cross-sectional imaging within 3 months of a positive surveillance ultrasound. A cutoff of 3 months was chosen based on tumor doubling time.[20,21]

Fisher exact and Mann-Whitney rank-sum tests were performed to identify factors associated with tumor stage at presentation and screening process failures. Patient sociodemographic and clinical characteristics were assessed, including age, gender, race/ethnicity, language, alcohol abuse, insurance status, cause of liver disease, platelet count, bilirubin, Child-Pugh class, and presence of hepatic decompensation (ascites and/or hepatic encephalopathy). Multivariate logistic regression was performed using factors significant on univariate analysis, with statistical significance being defined as a *P* value less than .05 for both univariate and multivariate analyses. Overall survival after HCC diagnosis was determined using Kaplan-Meier analysis, and Cox regression analysis was used to assess potential factors associated with survival. All data analysis was performed using Stata 11 (StataCorp, College Station, TX).

Results

Patient Characteristics

Between January 2005 and March 2012, 457 patients with cirrhosis were diagnosed with HCC. A total of 188 patients who had less than 1 year of care at Parkland before HCC diagnosis were excluded, and 84 patients with Child-Pugh C cirrhosis and/or poor functional status were also excluded, given that HCC surveillance is not of benefit for these patients. Table 1 shows baseline characteristics of the remaining 185 patients.

The median age of patients was 56 years (range, 33–81), and more than 80% were men. The population was racially diverse, with 40% African Americans, 22% non-Hispanic whites, and 30% Hispanic whites. Nearly 49% of patients were uninsured (but received medical care through a Dallas County subsidy plan), and another 46% had Medicare or Medicaid. The most common causes of cirrhosis were HCV (73%), alcohol-induced liver disease (11%), and NAFLD (7%). The median Child-Pugh score at diagnosis was 6 (range, 5–9), with 51% of patients having Child-Pugh A cirrhosis. Patients had been followed at Parkland for a median of 4.7 years (range, 1.0–11.7) before HCC diagnosis; 17% had been followed for 1 to 2 years, 13% for 2 to 3 years, and 70% for more than 3 years.

Tumor Stage at Presentation

Early-stage tumors were diagnosed in 91 patients (49%), whereas 20 (11%) presented with BCLC stage B tumors and 74 (40%) with BCLC stage C tumors. Patient characteristics according to tumor stage are shown in Table 1. Patients with early-stage tumors had similar age, gender, and race as those with more advanced tumors. Both groups included a similar proportion of patients with underlying viral liver disease; however, patients with BCLC stage A tumors were significantly more likely to have Child-Pugh A disease (63% vs 39%; P=.002) than those with more advanced tumors. Patients with early-stage tumors were significantly less likely to present with abdominal pain or weight loss (43% vs 76%; P<.001). As expected, patients with early-stage tumors had significantly better survival than those with more advanced tumors (hazard ratio [HR], 4.19; 95% CI, 2.79–6.30).

Absence of Surveillance

Absence of surveillance represented the most common screening process failure in both patients with early-stage tumors (Figure 1) and those with advanced HCC (Figure 2). Overall, 42 (21.2%) patients had a surveillance ultrasound in the year before HCC diagnosis and 140 (78.8%) had an absence of surveillance. Three patients were excluded from this analysis because they were followed up with cross-sectional imaging for nonspecific liver lesions

Table 1 Patient Characteristics

Patient Characteristics	Early-Stage HCC (n=91)	Advanced-Stage HCC (n=94)	*P* Value
Age, y (range)	56.0 (41.5–81.5)	57.1 (33.7–75.8)	.28
Sex (% male)	74 (81.3%)	80 (85.1%)	.56
Race			.91
White	21 (23.0%)	20 (21.3%)	
Black	36 (39.6%)	39 (41.5%)	
Hispanic	27 (29.7%)	28 (29.8%)	
Origin			.90
Hepatitis C	66 (72.5%)	70 (74.5%)	
Hepatitis B	9 (7.3%)	6 (6.4%)	
Alcohol	9 (11.2%)	12 (12.8%)	
NAFLD	7 (6.7%)	6 (6.4%)	
Insurance status			.64
Medicare	23 (25.3%)	21 (22.3%)	
Medicaid	17 (18.7%)	23 (24.5%)	
Private Insurance	8 (8.8%)	2 (2.1%)	
None	39 (42.9%)	37 (39.4%)	
Primary language (% English)	74 (82.2%)	77 (81.9%)	1.0
Alcohol (% active)	25 (27.5%)	29 (30.9%)	.63
Presence of ascites	23 (25.3%)	30 (31.9%)	.33
Presence of hepatic encephalopathy	4 (4.4%)	37 (6.4%)	.75
Platelet count x 1000/mm^3 (range)	121 (17–518)	139 (30–484)	.05
Bilirubin, mg/dL (range)	1.0 (0.2–7.4)	1.3 (0.3–22.4)	.02
Albumin, g/dL (range)	3.4 (2.2–4.5)	3.1 (1.8–4.5)	.01
INR	1.2 (0.9–1.7)	1.2 (0.9–3.3)	.01
AFP, ng/mL (range)	26 (1–101,997)	328 (2–680,789)	<.001
Symptomatic presentation	39 (42.9%)	71 (75.5%)	<.001
Receipt of hepatology care before HCC diagnosis	24 (26.4%)	20 (21.3%)	.49
Presence of known cirrhosis	48 (53.3%)	49 (53.3%)	1.0
Child-Pugh score (range)	6 (5–9)	7 (5–9)	<.001
Child-Pugh classification			.002
A	57 (62.6%)	37 (39.4%)	
B	34 (37.4%)	57 (60.6%)	
Surveillance in prior year	24 (26.4%)	18 (19.1%)	.29

All data are expressed as median (range) unless otherwise specified
Abbreviations: AFP, α-fetoprotein; HCC, hepatocellular carcinoma; INR, international normalized ratio; NAFLD, nonalcoholic fatty liver disease.

(n=2) or other abdominal pathology (n=1). Among those who underwent surveillance ultrasound, 24 had BCLC stage A tumors and 18 had more-advanced HCC. Patients who had a surveillance ultrasound showed a trend toward higher rates of early-stage HCC at diagnosis (57.1% vs 47.1%), but this finding did not reach statistical significance (*P*=.29). The association between HCC surveillance and early-stage detection was stronger after adjusting for Child-Pugh class and symptomatic presentation (adjusted odds ratio [AOR], 1.98; 95% CI, 0.92–4.31; *P*=.08). Similarly, HCC surveillance was associated with a trend toward improved overall survival compared with no HCC surveillance (HR, 0.79; 95% CI, 0.49–1.25; *P*=.31) (Figure 3).

Patients who had undergone surveillance ultrasound were of similar age and race as those without

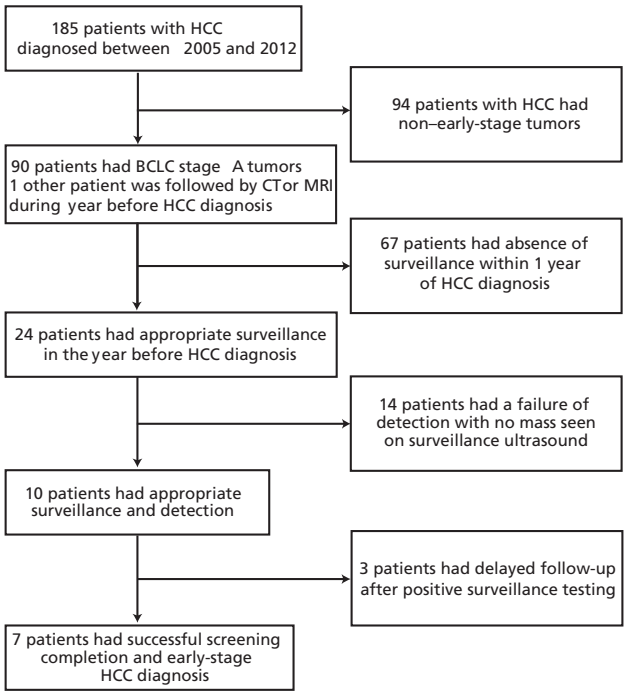

Figure 1 Hepatocellular carcinoma (HCC) screening process failures among patients with early-stage tumors. Abbreviation: BCLC, Barcelona Clinic Liver Cancer.

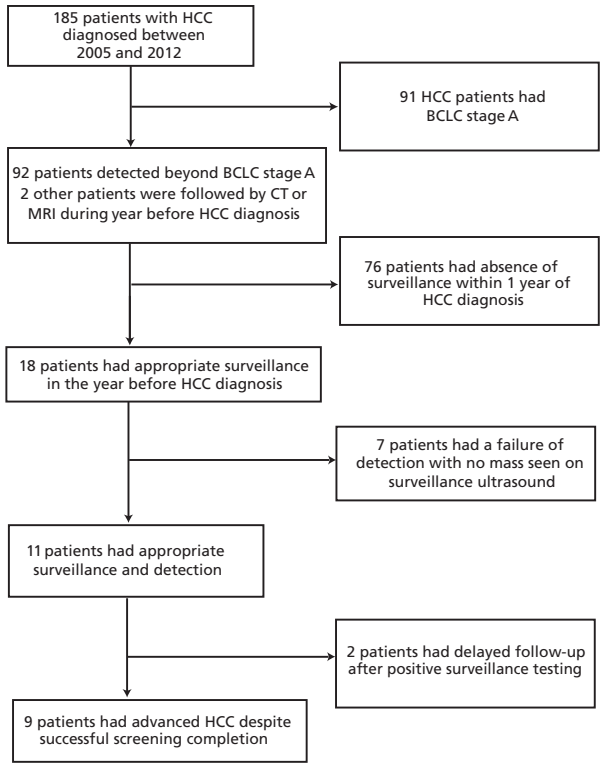

Figure 2 Hepatocellular carcinoma (HCC) screening process failures among patients with advance- stage tumors. Abbreviation: BCLC, Barcelona Clinic Liver Cancer.

surveillance; however, they were significantly more likely to be female (35% vs 18%; *P*=.03), were significantly less likely to be active alcohol drinkers (15% vs 33%; *P*=.03), and had similar rates of active tobacco use. Patients were equally likely to have Child-Pugh A disease, but those who received surveillance were significantly more likely to have overt hepatic decompensation with ascites (46% vs 24%; *P*=.006). Patients who underwent surveillance ultrasound were more likely to have underlying viral liver disease (92% vs 79%; *P*=.05) and higher rates of recognized cirrhosis (77% vs 47%; *P*=.001). On multivariate analysis, patients who had received surveillance were more likely to have viral liver disease AOR, 4.25; 95% CI, 1.11–16.3), recognized cirrhosis (AOR, 2.97; 95% CI, 1.26–7.01), and hepatic decompensation with ascites (AOR, 2.86; 95% CI, 1.26–6.47), and to be female (AOR, 2.73; 95% CI, 1.03–7.24), and less likely to be active alcohol abusers (AOR, 0.29; 95% CI, 0.11–0.78) (Table 2).

Failure of Detection and Delayed Follow-up

Among the 42 patients who had a surveillance ultrasound in the year before HCC diagnosis, only 21 (50.0%) had a hepatic mass suggestive of HCC and 21 had failure of detection. As anticipated, failure of detection was more common among patients with early-stage HCC than among those with more advanced tumors (58.3% vs 38.9%), but rates of detection were disappointingly low in both groups (Figures 1 and 2). Patients with failure of detection had ascites in 55.0% of cases, compared with only 36.8% of patients in whom ultrasound was able to detect HCC. Patients with failure of detection also had a trend toward higher body mass index (BMI) than those in whom ultrasound was able to detect HCC (median BMI, 29.0 vs 26.4 kg/m^2). However, no statistically significant associations were found between failure of detection and BMI (*P*=.25), Child-Pugh class (*P*=.57), or presence of ascites (*P*=.21), potentially related to limited statistical power. On univariate analysis, failure of detection was significantly associated with diameter of the largest HCC lesion (*P*=.006). The median diameter of the largest lesion was 2.0 cm among patients with failure of detection, compared with 4.0 cm in those for whom HCC was detected on surveillance ultrasound.

Among the 21 patients who had a mass detected on surveillance ultrasound, 16 had follow-up cross-

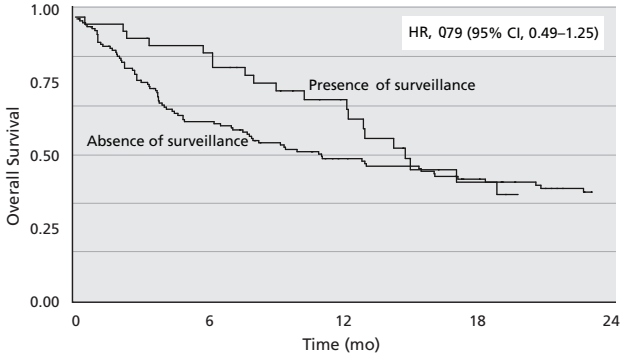

Figure 3 Survival according to hepatocellular carcinoma surveillance status.
Abbreviation: HR, hazard ratio.

sectional imaging within 3 months and 5 (26.3%) had delayed follow-up. Rates of early tumor detection were similar among patients with timely and delayed follow-up (43.8% vs 60.0%, respectively; *P*=.64). Predictors of delayed follow-up were not studied, given the small number of patients.

Discussion

Surveillance is a complex process in clinical practice, with multiple potential steps that are prone to failure. Screening process failures are common and potentially lead to late-stage tumor detection. This was highlighted in the present study, in which fewer than 1 in 10 patients successfully completed the screening process. An absence of surveillance was the most common HCC screening process failure and was associated with trend toward more-advanced tumor stage and worse survival. However, failure of detection and delayed follow-up were also prevalent among those who underwent surveillance ultrasound.

The high rate of surveillance underuse in this study is striking, although consistent with a recent meta-analysis that reported a pooled surveillance rate of 18% among studies conducted in the United States.[22] In clinical practice, surveillance underuse could be related to several factors, including lack of provider orders, patient noncompliance, and/or limited radiologic capacity, although prior studies have suggested that lack of provider orders may be the most common intermediary.[15,23–25]

Underrecognition of liver disease and cirrhosis may contribute to underuse of surveillance. In one study, nearly 40% of patients presented with HCC without having previously recognized liver disease and/or cirrhosis.[24] Surveillance underuse may be particularly problematic for safety-net hospital systems given the high number of patients in need of surveillance relative to the limited available resources and increased patient-level barriers to cancer screening, such as underinsurance, transportation issues, and language barriers. No association was found with insurance status and surveillance underuse, although this may relate to Parkland's sliding fee scale program, which provides a subsidy for medical care such as HCC surveillance. Further studies are needed to better characterize determinants of surveillance underuse, in hopes of designing interventions to increase surveillance rates.

Although absence of surveillance was the most common screening process failure, failure of detection was present in 50% patients who underwent surveillance, highlighting the suboptimal sensitivity of current surveillance tools. In a secondary analysis of the Hepatitis C Long-term Treatment Against Cirrhosis (HALT-C) trial, failure of detection was the most common reason for late-stage tumor detection, being present in 70% of cases beyond the Milan criteria.[14] Similarly, an effectiveness study from the University of Michigan showed that ultrasound only had a sensitivity of 32% for early-stage tumors.[13]

Table 2 Predictors of Hepatocellular Carcinoma Surveillance

	Univariate Analysis		Multivariate Analysis	
Variable	**OR**	**95% CI**	**AOR**	**95% CI**
Viral origin of cirrhosis	3.23	0.93–11.2	4.25	1.11–16.3
Presence of known cirrhosis	3.78	1.68–8.53	2.97	1.26–7.01
Presence of ascites	2.72	1.30–5.67	2.86	1.26–6.47
Female gender	2.48	1.07–5.74	2.73	1.03–7.24
Active alcohol abuse	0.37	0.15–0.95	0.29	0.11–0.78

Abbreviation: AOR, adjusted odds ratio; OR, odds ratio.

These data are in stark contrast to data from Europe, which suggest that ultrasound can detect most tumors at an early stage.[26] The variable effectiveness of ultrasound may be related to its operator-dependent nature. Furthermore, the ability of ultrasound to accurately visualize the liver in patients with morbid obesity or a very nodular liver may be impaired.[27] Although a difference in detection rates according to BMI, Child-Pugh class, or presence of ascites was not seen in the present study, this may have been related to limited statistical power for subgroup analyses. Clearly, better surveillance tools, including more accurate biomarkers and/or cost-effective advanced imaging with lower radiation risk, are necessary to help improve the sensitivity of finding tumors at an early stage.

The authors recently found that delays in follow-up may occur in one-third of patients with cirrhosis who have positive surveillance tests (unpublished data). However, delayed follow-up was found in fewer than 10% of patients in this study. Furthermore, the authors did not find any impact of delayed follow-up on tumor stage and/or survival. Rates of delayed follow-up may increase with higher surveillance rates and a larger burden of positive surveillance tests. Therefore, careful process evaluation will be crucial after implementation of interventions to increase surveillance rates.

This study has several limitations. It was performed in a single, large, safety-net hospital, and therefore the findings may not be generalizable to other practice settings. Given its retrospective nature, this study was also limited by possible unmeasured confounders and missing data. Although some patients may have received surveillance at outside institutions, the authors believe this is unlikely given that Parkland, as the safety-net health system for Dallas County, is the only option for most indigent patients. To minimize this bias, patients with less than 1 year of care at Parkland before HCC diagnosis were excluded. Overall, the authors believe the limitations of this study are outweighed by its strengths, including its well-characterized cohort and its racially and socioeconomically diverse population.

These data provide insight into the prevalence and significance of screening process failures in clinical practice. Screening process failures are common, with fewer than 1 in 10 patients successfully completing the screening process. Although an absence of surveillance was the most common HCC screening process failure, failure of detection and delayed follow-up were also prevalent. These screening process failures seem to contribute to more-advanced tumor stage at diagnosis and worse overall survival. Interventions are needed to target multiple steps in the HCC screening process, including use of surveillance , effective detection, and timely follow-up of positive surveillance tests.

Authorship Statement

Amit Singal was involved in study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, and study supervision. Amit Singal is the guarantor of the article.

Jorge Marrero was involved in interpretation of data and critical revision of the manuscript for important intellectual content.

Adam Yopp was involved in acquisition of data, interpretation of data, and critical revision of the manuscript for important intellectual content.

All authors approved the final version of the manuscript.

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