Research Article

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Effectiveness of surveillance for hepatocellular carcinoma in clinical practice: A United States cohort

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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, model for end-stage liver disease (MELD) score, comorbidity index, alpha-fetoprotein 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 hazard ratios (HR) 0.62, 95% confidence intervals (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.

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.

Keywords: Liver cancer; Screening; Lead-time; Cirrhosis; Fatty liver.
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Abbreviations: NAFLD, non-alcoholic fatty liver disease; HCC, hepatocellular carcinoma; VA, Veterans Administration; AFP, alpha-fetoprotein; HCV, hepatitis C; EMR, electronic medical records; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; CPT, common procedural terminology; CAPRI, Compensation and Pension Records Interchange; CPRS, computerized patient record system; HBV, hepatitis B; OPC, outpatient care file; PTF, patient treatment file.

Introduction

The incidence of hepatocellular carcinoma (HCC) in the United States has increased over threefold 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 a 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].

We therefore used data from the national Veteran Administration (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.

Materials and 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 the 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 and records locator system death file, Medicare vital status file, and social security administration death file [19]. Patient electronic medical record (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 2719 patients with possible HCC to identify 1500 study subjects with 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/μl, INR >1.1 between 6 months before and 4 weeks after HCC diagnosis) or an APRI (aspartate aminotransferase to platelet ratio index) score >2.0 [20]. Recognition of cirrhosis was defined as entry of a diagnostic code for cirrhosis or any mention of cirrhosis (or related term such as Child-Pugh score) pertaining to the patient in a physician progress note on manual review of EMR [21].

Risk factors for HCC

We defined hepatitis C virus (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 three 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 non-alcoholic fatty liver disease (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 >28.8 kg/m^2 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

These included demographic features, model for end-stage 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 hazard (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 stepwise fashion and variables with p <0.05 in multivariable analyses were retained in the final models.

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).

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