Surveillance for hepatocellular cancer with ultrasonography vs. computed tomography – a randomised study

C. Pocha*†, E. Dieperink*†, K. A. McMaken*, A. Knott*†, P. Thuras*† & S. B. Ho‡§

*Hepatitis C Resource Center, Minneapolis VA Health Care System, Minneapolis, MN, USA.
†Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA.
‡Department of Medicine, San Diego VA Healthcare System, San Diego, CA, USA.
§Department of Medicine, University of California, San Diego, CA, USA.

Correspondence to: Dr C. Pocha, Minneapolis VAHCS System, Hepatitis C Resource Center, 1 Veterans Drive, Minneapolis, MN 55417, USA. E-mail: pocha004@umn.edu

Summary

Background
Guidelines recommend screening for hepatocellular cancer (HCC) with ultrasonography. The performance of ultrasonography varies widely. Computed tomography (CT) is less operator dependent.

Aim
To compare the performance and cost of twice-a-year ultrasonography to once-a-year triple-phase-contrast CT for HCC screening in veterans. We hypothesised that CT detects smaller HCCs at lower overall cost.

Method
One hundred and sixty-three subjects with compensated cirrhosis were randomised to biannual ultrasonography or yearly CT. Twice-a-year alpha-feto protein testing was performed in all patients. Contingency table analysis using chi-squared tests was used to determine differences in sensitivity and specificity of screening arms, survival analysis with Kaplan–Meier method to determine cumulative cancer rates. Multivariate logistic regression models were used to examine predictive factors.

Results
Hepatocellular cancer incidence rate was 6.6% per year. Nine HCCs were detected by ultrasonography and eight by CT. Sensitivity and specificity were 71.4% and 97.5%, respectively, for ultrasonography vs. 66.7% and 94.4%, respectively, for CT. Although 58.8% of screen-detected HCC were early stage (Barcelona Clinic Liver Cancer stage A), only 23.5% received potentially curative treatment despite all treatment options being available. HCC-related and overall mortality were 70.5% and 82.3%, respectively, in patients with screen-detected tumour. Overall costs were less for biannual ultrasonography than annual CT.

Conclusions
Biannual ultrasonography was marginally more sensitive and less costly for detection of early HCC compared with annual CT. Despite early detection, HCC-related mortality was high. These data support the use of biannual ultrasonography for HCC surveillance in a US patient population (NCT01350167).
INTRODUCTION

Hepatocellular cancer (HCC) is the fourth most common cancer worldwide and is one of the most common causes of cancer death with about 598 000 per year.\(^1\)\(^,\)\(^2\) Early detection of HCC is thought to reduce mortality and screening for HCC using ultrasonography and alpha-feto protein (AFP) has been recommended by professional societies for more than a decade.\(^3\)\(^,\)\(^4\) AFP was omitted from these guidelines in 2010 because of lack of sensitivity; however, it is often being used by providers in clinical practice.\(^5\) Controversy exists about how to best optimise the performance of ultrasonography for HCC screening.\(^6\) Appropriate screening intervals are still debated with intervals from 3 to 12 months recommended by practitioners.\(^7\)\(^,\)\(^8\) Ultrasonography is highly operator dependent limiting its sensitivity. Finally, much of the data using ultrasonography as a screening method come from European and Asian studies, but differences in technique and body habitus may not make these studies applicable to the US population. In practice, some providers have chosen to use triple-phase computed tomography (CT), which is thought to be more sensitive but less specific for HCC detection compared with ultrasonography.\(^9\)

Hepatocellular cancer incidence and mortality rates continue to increase, particularly among middle-aged black, Hispanic and white men.\(^10\)\(^,\)\(^11\) Similarly, the national Veterans Health Administration (VHA) Cancer Case Registry and the VHA Hepatitis C Clinical Case Registry show a rapidly increasing number of HCC.\(^12\) Recent data show a doubling in cirrhosis prevalence and a 20-fold increase in HCC prevalence from 1996 to 2006.\(^12\) With the imminent peak of HCV-related cirrhosis and the growing epidemic of patients with metabolic syndrome and non-alcoholic fatty liver disease (NAFLD) in the US, the burden of HCC is expected to increase dramatically. Currently, there are over 170 000 Veterans with chronic hepatitis C (CHC) enrolled in VHA care; many of them are obese and have multiple co-morbidities.\(^13\)\(^,\)\(^14\) To address this large patient population, a screening programme would have to consider the relative performance of different imaging tests. To date, there are no data regarding the relative sensitivity and specificity of screening tests for detection of HCC derived from a VHA population. Therefore, the purpose of this study was to obtain data on the direct comparison of the performance of twice-a-year ultrasonography and once-a-year triple-phase contrast CT in a high-risk veteran patient population. We hypothesised that once-a-year CT would perform better and cost less overall than twice-a-year ultrasonography for detection of early-stage HCC.

MATERIAL AND METHODS

The study was conducted by the Minneapolis Veterans Affairs Healthcare System (VAHCS) in accordance with Principles of Good Clinical Practice and was approved by the Minneapolis VAHCS institutional review board (ClinicalTrials.gov identifier: NCT01350167). All patients provided voluntary written informed consent prior to trial entry.

Patient selection

Patients were eligible for enrolment if they were aged 18–70 years, had Child’s A cirrhosis and were potential candidates for treatment of HCC. Cirrhosis was documented histologically, or in the absence of histology, with biochemical or clinical changes consistent with cirrhosis. The Model for Endstage Liver Disease (MELD) and the Child-Turcotte-Pugh (CTP) scores were calculated for all patients. Portal hypertension was defined by the presence of any or a combination of the following characteristics: oesophageal varices, hepatic encephalopathy, ascites, thrombocytopenia if not explained otherwise; findings on imaging consistent with portal hypertension, i.e. intra-abdominal varices or splenomegaly. All patients were required to have no evidence of any liver mass by abdominal imaging within 12 months prior to enrolment. Key exclusion criteria were active malignancy other than nonmelanoma skin cancer and not being an acceptable candidate for treatment of HCC secondary to advanced medical conditions (severe cardiovascular or pulmonary disease, Child C cirrhosis). We excluded patients who were unable to receive IV contrast secondary to advanced renal insufficiency or allergy and patients with a history of a hepatic mass identified on imaging study.

Study design

A computer-generated random number list was used to allocate and randomise subjects to ultrasonography every 6 months or triple-phase contrast CT every 12 months (Figure 1). AFP was obtained in every patient for every 6 months. Ultrasonography was performed by designated technicians using a standardised protocol for scanning the liver and documenting findings. The triple-phase contrast CT was performed per institutional protocol to assure correct timing of arterial, venous and late contrast phase.

Subjects were stratified by HCV anti-viral treatment status (ever treated vs. treatment naive). Patients who no
longer received their assigned screening test (which occurred for various reasons) were still followed through regular review of their electronic medical record.

Subject evaluation
Hepatic lesions, identified by either ultrasonography or CT, were further evaluated per study protocol by an experienced hepatologist using the following criteria:

(i) Biopsy was not required for the diagnosis of HCC in the setting of a diagnostically elevated (>200 ng/mL) or rapidly rising AFP and liver lesion(s) consistent with HCC by CT showing typical features such as arterial enhancement and venous washout.

(ii) Patients with suspicious liver lesions not meeting CT diagnostic criteria and with nondiagnostic AFP elevations underwent image-guided biopsy for histological confirmation.

(iii) A standardised approach to AFP elevation was used. Patients with diagnostically elevated (>200 ng/mL) or rising AFP levels but no identifiable liver lesion on ultrasonography or CT underwent a MRI scan. If no lesion was identified on MRI, these patients were followed by CT at 6-month intervals until the AFP level returned to normal, stabilised or HCC was diagnosed. If the AFP level normalised or stabilised, the patient returned to their previous surveillance protocol.

(iv) False-positive results were defined as any new lesion detected by screening ultrasonography or screening CT; however, subsequent work up per protocol (CT, MRI and/or biopsy) did not lead to a diagnosis of HCC.

Study endpoints
The endpoint of the study was a lesion consistent with HCC histologically or by imaging criteria according to Barcelona Clinic Liver Cancer (BCLC) guidelines. Patients with HCC were staged according to BCLC staging guidelines and received standard therapy depending on the specific clinical situation.

Statistical and cost analysis
The number of HCC diagnosed by each screening protocol was identified and sensitivity and specificity were calculated. Contingency table analysis using chi-squared tests was used to determine the difference in sensitivity and specificity for each screening arm. Survival analysis of the cumulative cancer-free rate was performed according to the Kaplan–Meier method. Multivariate logistic regression models were employed to examine possible predictors of HCC.

The cost of each screening protocol to identify one potentially curable HCC using VHA and Medicare cost estimates was calculated. The VHA is a large integrated health care system in the United States and is mainly funded by Congressional appropriation. It provides care to patients mostly without charge. Therefore, costs and charges are not generally associated with specific patient

Figure 1 | Flow chart of subject enrolment. *Off protocol patients were not following their initially assigned surveillance study arm for various reasons: nonliver-related death: 6; non-adherence to the protocol: 12; withdrawal active participation in assigned screening arm 8; contrast allergy: 4; followed by transplant centre: 10; patient moved 9; others: 8.
encounters.15–17 All costs for VA out-patient care are based on data obtained from the Health Economics Resource Center and based on Medicare reimbursement rates. Medicare is the national social insurance programme for those over 65 years of age, administered by the US federal government.

RESULTS

Baseline characteristics
A total of 163 subjects were enrolled in the study between June 6, 2002 and February 8, 2011. The mean age was 59.3, 83.6% were Caucasian and 99.4% were male. The aetiology of the underlying liver disease in the study population was CHC (142/163, 87.1%), alcoholic liver disease (12/163, 7.4%), NAFLD (5/163, 3.1%), hepatitis B-related cirrhosis (HBV) (3/163, 1.8%) and primary biliary cirrhosis (1/163, 0.65%) (Table 1).

HCC detection and outcome
All patients included in the analysis had received at least one imaging study after enrolment (Tables 2–5). Two subjects did not receive an imaging study after enrolment and were excluded from this analysis. HCC incidence rate per observation year was 4.0% with an average observation time of 2.56 years (consent to last

| Demographic | Total (n = 163) | US-arm (n = 83) | CT-arm (n = 80) | P |
|-------------|----------------|----------------|----------------|---|
| Age in years, mean (s.d.) | 59.3 (5.3) | 59.2 (5.3) | 59.5 (5.3) | 0.61 |
| Race/ethnicity, n (%) | | | | 0.27 |
| Caucasian | 136 (83.6) | 73 (88.0) | 63 (78.8) | |
| African American | 14 (8.5) | 4 (4.8) | 10 (12.5) | |
| Hispanic | 3 (1.8) | 2 (2.4) | 1 (1.3) | |
| American Indian | 3 (1.8) | 2 (2.4) | 1 (1.3) | |
| Unknown | 7 (4.2) | 2 (2.4) | 5 (6.3) | |
| Male, n (%) | 162 (99.4) | 83 (100) | 79 (98.8) | 0.31 |
| Aetiology of cirrhosis, n (%) | | | | 0.89 |
| Hepatitis C | 142 (87.1) | 72 (86.7) | 70 (87.5) | |
| Hepatitis B | 3 (1.8) | 2 (2.4) | 1 (1.3) | |
| Alcoholic liver disease | 12 (7.4) | 6 (7.2) | 6 (7.5) | |
| NAFLD | 5 (3.1) | 3 (3.6) | 2 (2.5) | |
| Primary biliary cirrhosis | 1 (0.6) | 0 (0) | 1 (1.3) | |

CT, computed tomography; US, ultrasonography; NAFLD, non-alcoholic fatty liver disease.

| Variable | Total (n = 163) | US-arm (n = 83) | CT-arm (n = 80) | P |
|----------|----------------|----------------|----------------|---|
| HCC diagnosed | 17 (10.4) | 9 (10.8) | 8 (10.0) | 0.86 |
| Subjects following assigned arm | 10 (6.1) | 7 (8.4) | 3 (3.8) | |
| Subjects not following assigned arm | 7 (4.3) | 2 (2.4) | 5 (6.3) | |
| False-positive imaging | 12 (7.4) | 3 (3.6) | 9 (5.6) | 0.06 |
| False-negative imaging | 3 (1.8) | 2 (2.4) | 1 (1.2) | 0.58 |
| Additional tests ordered, n | | | | |
| US | 6 | 1 | 5 | |
| CT | 25 | 17 | 8 | |
| MRI | 21 | 9 | 12 | |
| PET | 1 | 1 | 0 | |
| AFP | 12 | 4 | 8 | |
| Liver transplanted | 6 (3.7) | 4 (4.8) | 2 (2.5) | |
| HCC in explanted liver | 1 (16.7) | 1 (25.0) | 0 (0) | |

HCC, hepatocellular cancer; AFP, alpha-feto protein; CT, computed tomography.

| Outcome, n (%) | All (n = 17) | US-arm (n = 9) | CT-arm (n = 8) | P |
|----------------|-------------|----------------|----------------|---|
| Liver biopsy to establish diagnosis | 9 (52.9) | 6 (66.7) | 3 (37.5) | 0.23 |
| Well differentiated | 4 (44.4) | 3 (50.0) | 1 (33.3) | |
| Moderately differentiated | 2 (22.2) | 2 (33.3) | 0 (0) | |
| Poorly differentiated | 2 (22.2) | 1 (11.1) | 1 (33.3) | |
| Unclassified | 1 (11.1) | 0 (0) | 1 (33.3) | |
| TNM staging | 0.96 | | | |
| I | 10 (58.8) | 5 (55.5) | 5 (62.5) | |
| II | 2 (11.8) | 1 (11.1) | 1 (12.5) | |
| III | 2 (11.8) | 1 (11.1) | 1 (12.5) | |
| IVB | 3 (17.6) | 2 (22.2) | 1 (12.5) | |
| BCLC staging | 0.93 | | | |
| Early (A1/A2) | 10 (58.8) | 5 (55.5) | 5 (62.5) | |
| Intermediate B | 2 (11.8) | 1 (11.1) | 1 (12.5) | |
| Advanced C | 5 (29.4) | 3 (33.3) | 2 (25.0) | |
| Mortality | 0.46 | | | |
| Died of HCC | 12 (70.6) | 5 (55.6) | 7 (87.5) | |
| Died of other causes | 1 (5.9) | 1 (11.1) | 0 (0) | |
| Alive | 3 (17.6) | 2 (22.2) | 1 (12.5) | |
| Unknown | 1 (5.9) | 1 (11.1) | 0 (0) | |

HCC, hepatocellular cancer; BCLC, Barcelona Clinic Liver Cancer.
Ultrasonography vs. CT for HCC surveillance

Table 4 | Cost of screening

| Costs, $ | US-arm | CT-arm |
|----------|--------|--------|
| Imaging  | 75,924 | 49,275 |
| AFP      | 2,586  | 1,722  |
| Additional workup | 5,973 | 5,307 |
| Total    | 84,483 | 56,304 |

Mean values for non-VA data were obtained from the literature.\(^{15-37}\) AFP, alpha-feto protein; HCC, hepatocellular cancer.

| Costs, $ | US-arm | CT-arm |
|----------|--------|--------|
| Imaging  | 12,069 | 18,768 |
| AFP      | 2,378  | 2,093  |
| Additional workup | 5,973 | 5,307 |
| Total    | 34,414 | 37,035 |

Mean values for non-VA data were obtained from the literature.\(^{15-37}\) AFP, alpha-feto protein; HCC, hepatocellular cancer.

\(^*\) US, $171; CT, $225; MRI, $217; AFP, $6.

\(^\dagger\) US, $185; CT, $640; MRI, $1400; AFP, $31.

\(^\ddagger\) HCC detected in patients following their assigned screening arm.

image date). With 17 HCC in 2.56 years, the incidence rate in the entire cohort (including patients who were followed by transplant centres or not following their initially assigned screening arm) was 6.6% per year. HCC-related mortality was 70.5%; all-cause mortality among patients with HCC was 82.3%. The overall mortality of all study patients was 14.7% (24/163).

The mean follow-up time in the CT-arm was 31 months (range 0–84) and in the ultrasonography-arm 35 months (range 0–90).

At the time of analysis, 106 subjects were actively being screened (50 followed in the CT-arm and 56 followed in the ultrasonography-arm). A total of 57 (34.9%) subjects, 30 assigned to the CT-arm and 27 to the ultrasonography-arm were no longer receiving their initially assigned screening test for the following reasons: non-adherence to the protocol (12/57); withdrawal active participation in assigned screening (5/57); contrast allergy (4/57); death (6/57); patient moved (9/57); contrast allergy (6/57). These patients were followed by periodic review of their medical records. In this group of subjects, seven additional cases of HCC were diagnosed at various tumour stages (early: 3, intermediate: 2, advanced: 2).

In the intention-to-treat analysis including all 163 study patients, a total of 17 HCC with 9/83 (10.8%) in the ultrasonography-arm and 8/80 (10.0%) in the CT-arm were found. Pearson chi-square testing was not significant. \(\chi^2(1) = 1.27, P = 0.27\). Of the total 17 HCC, 7 HCC were found in the 57 subjects who had dropped out their originally assigned screening arm with 2/27 in patients initially assigned to ultrasonography-arm and 5/30 to the CT-arm. After leaving their assigned screening arm, most patients were followed by ultrasonography ordered at the discretion of their primary medical provider; 10 patients who were evaluated for liver transplantation were followed by MRI as recommended by the assigned transplant centres.

Using per protocol analysis, we did perform Pearson chi-square testing comparing only HCC found in patients who did continue in their assigned screening arm until data analysis. There was also no statistically significant difference between the ultrasonography-arm (7/50) vs. the CT-arm (3/47); \(\chi^2(1) = 1.24, P = 0.27\).

The number of HCC diagnosed in subjects not being followed by initially assigned CT-arm seems to be proportionately greater (16.7%; 5/30) compared with those detected in subjects continued to be followed in their assigned CT-arm (6%; 3/50). However, given the small sample size in this study, any conclusions would be speculative. Of these 5/30 patients who did not follow their initially assigned CT-arm, three patients continued to be followed by ultrasonography (contrast allergy: 1; patient choice: 2) and two patients received MRI screening as recommended by the liver transplant centre.

In the intention-to-treat analysis, false-positive results were found in 7.4% (12/163) of patients requiring additional testing with three cases in the ultrasonography-arm and nine cases in the CT-arm. False-negative imaging results were obtained in two patients in the ultrasonography-arm and in one patient in the CT-arm. Additional imaging tests for work up of screen-detected liver lesions included a total of 6 liver ultrasounds (ultrasonography-arm: 1; CT-arm: 5), 25 triple-phase CT (ultrasonography-arm: 17; CT-arm: 8) and 21 MRI (ultrasonography-arm: 9; CT-arm: 12). One patient in the ultrasonography-arm received an additional PET scan as MRI and CT results were contradictory. Twelve additional AFP tests were obtained (ultrasonography-arm: 4; CT-arm: 8). Sensitivity and specificity of ultrasonography for HCC detection were 71.4% and 97.5%, respectively, with a positive predictive value (PPV) of 83.3% and a negative predictive value (NPV) of 95.1%. Sensitivity and specificity of CT for HCC detection were 66.7% and 94.4%, respectively, with a PPV of 50.0% and NPV of 97.1%.

Overall, a diagnosis of HCC was made based on imaging criteria in 8/17 subjects and in 9/17, the diagnosis was made by image-guided biopsy. The mean survival of all subjects with HCC after diagnosis was 19.9 months (range 4–73). Overall, only 4/17 (23.5%) patients
| ID | Screening arm | Age at Dx | Race* | Confirmatory test | Lesion(s) Size (mm) | AFP | MELD | CTP | Portal HTN† | Treatment choice and number‡ | Survival time in months | Cause of death§ | Cause of liver disease¶ |
|----|---------------|-----------|-------|-------------------|---------------------|-----|------|-----|-------------|----------------------------|-----------------------|----------------|-----------------|
| 1  | CT            | 53        | AA    | MRI               | 31 x 16
11 x 11           | 718      | 11    | 6               | No                | TACE (5)                         | 46                    | HCC             | HCV NR          |
| 2  | CT            | 48        | C     | Biopsy           | 24 x 17
14 x 11
61 x 39       | 8        | 8     | 5               | No                | TACE (3)                         | 28                    | HCC             | HCV NR          |
| 3  | CT            | 56        | C     | MRI, biopsy      | 8 x 15
13              | 7        | 5     | Yes             | TACE (2)                       | 46                    | Alive          | HCV NR          |
| 4  | CT            | 54        | C     | Ultrasound       | 90 x 10
1050           | 11       | 6     | Yes             | XRT (1) Sorafenib             | 8                     | HCC             | HCV NR          |
| 5  | CT            | 58        | AA    | MRI              | 24 x 24
17 x 13         | 57       | 9     | 5               | Yes               | RFA (1)                         | 15                    | HCC             | HCV NR          |
| 6  | CT            | 60        | C     | MRI              | 14 x 12
12 x 8          | 49       | 7     | 6               | Yes               | TACE (1)                         | 31                    | Other           | HCV NR          |
| 7  | CT            | 64        | C     | Biopsy           | 53 x 45
8               | 9        | 8     | Yes             | TACE (1)                       | 6                     | HCC             | HCV TN          |
| 8  | US            | 48        | C     | CT, biopsy       | 30 x 35              | 7       | 6     | 5               | None              | <1                  | HCC             | HCV SR          |
| 9  | US            | 78        | C     | CT              | 32 x 25
17 x 13         | 46       | 14    | 6               | Yes               | Hospice                         | 1                     | HCC             | HCV NR          |
| 10 | US            | 71        | C     | Ultrasound, biopsy | 61 x 52
1050           | 22       | 8     | Yes             | TACE (5)                       | 36                    | HCC             | HCV NR          |
| 11 | US            | 59        | C     | CT, biopsy       | 30 x 35
100 x 80
258           | 22       | 14    | 6               | None              | <1                  | HCC             | HCV SR          |
| 12 | US            | 54        | C     | CT, biopsy       | 10 x 12
125           | 6       | 6     | No              | TACE (1)                       | 5                     | HCC             | HCV TN          |
| 13 | US            | 59        | AA    | MRI, biopsy      | 47 x 51
145           | 13       | 6     | Yes             | Sorafenib                     | 2                     | HCC             | HCV NR          |
| 14 | US            | 66        | C     | CT, biopsy       | 48 x 46              | 145      | 13    | 6               | None              | 2                    | HCC             | HCV TN          |
| 15 | US            | 59        | C     | MRI, biopsy      | 27 x 23
3               | 6        | 5     | Yes             | RFA(1)TACE (2)               | 28                    | Alive          | HCV SR          |

* AA, African American; C, Caucasian; AFP, alpha-feto protein; MELD, Model for Endstage Liver Disease; CTP, Child-Turcotte-Pugh; US, ultrasonography; CT, computed tomography.
† Portal HTN defined by the presence of oesophageal varices, ascites, hepatic encephalopathy, imaging criteria consistent with portal HTN such as splenomegaly, intra-abdominal varices.
‡ TACE, transarterial chemoembolisation therapies used: (number of treatments); XRT, radiation; RFA, radiofrequency ablation.
§ HCC, liver-related, or other (nonliver or unknown).
¶ HCV NR, anti-viral treatment nonresponder; HCV SVR, sustained virological response; HCV TN, anti-viral treatment naïve.
compared, race was a predictor of HCC; Caucasians (13/123) and African Americans (4/10) were in multi-regression analysis. When only HCC found in all races (Caucasian, African American, Hispanic, American Indian, unknown), race was not a predictor of HCC in the intention-to-treat analysis, including subjects who developed HCC in this cohort using logistic regression analysis. In the analysis of all subjects with HCC, 58.8% subjects (10/17) had early HCC (A1/A2); but only 23.5% (4/17) received potentially curative treatment; 41.1% (7/17) had intermediate stage B (two subjects) and advanced stage C cancer (five subjects). Detailed characteristics of patients with HCC are shown in Table 5. At the time of diagnosis, only two patients had a single lesion amenable to surgical resection. One subject was felt not to be an appropriate surgical candidate because of cardiovascular co-morbidities posing a high risk of perioperative morbidity and mortality (# 17 in Table 5). The second patient (# 9 in Table 5) was deferred by the surgery specialist because of portal hypertension with oesophageal varices and thrombocytopenia. He received radiofrequency ablation initially and subsequent TACE after tumour progression. Overall, portal hypertension was present in 10/17 patients. At initial diagnosis, HCC was within Milan criteria in 47% (8/17) of all patients. One subject (# 5 in Table 5) who had his HCC identified during the study underwent liver transplantation, however, died of chronic rejection a few months thereafter. Overall, three subjects received radiofrequency ablation. All subjects with intermediate HCC received one or more TACE procedures. Three subjects with advanced HCC received systemic chemotherapy with sorafenib.

An elevated baseline AFP (mean 30 ng/mL in the CT-arm – 55 ng/mL in the ultrasonography-arm) compared with normal AFP using a cut-off level of 20 ng/mL was the only significant predictor in all patients who developed HCC \( (P = 0.02; \text{OR: } 1.78; 95\% \text{CI: } 1.08–2.93). \) HCV status, HCV treatment status, age at baseline, race and number of received screening tests did not predict who developed HCC in this cohort using logistic regression analysis. In the intention-to-treat analysis, including all races (Caucasian, African American, Hispanic, American Indian, unknown), race was not a predictor of HCC in multi-regression analysis. When only HCC found in Caucasians (13/123) and African Americans (4/10) were compared, race was a predictor of HCC \( (\chi^2(1) = 4.57, P = 0.03). \) The proportion of Caucasians included in the study was significantly greater than any other race that reflects the demographics in the US Midwest region. Because there were no cases of HCC in those without HCV, odds ratios could not be calculated for HCV as a predictor. Of those with HCV, 11.8% developed HCC \( (\chi^2(1) = 3.02, P = 0.08) \) and 70.6% \( (12/17) \) were previous nonresponder to HCV anti-viral therapy. Sensitivity and specificity of AFP using cut-off level of 20 ng/mL were 70.6% and 86.3%, respectively, which confirms data reported in the literature.6–17

Barcelona Clinic Liver Cancer stage distribution was similar among cancers detected by either ultrasonography or CT and regardless if subjects were followed by study protocol or whether they were no longer receiving the allocated screening test and were followed at the discretion of their provider.

Cost analysis

The total cost for detection of one HCC including subsequent work up for false-positive tests with either ultrasonography or CT was calculated using cost data from the Minneapolis VAHCS as well as non-VHA cost from the literature (Table 4).6, 15–17 The cost to detect one HCC with ultrasonography ranges from $12 069 in the VHA system to $17 041 in non-VHA care setting. If CT is used as the preferred screening tool, the cost estimates range from $18 768 for patients in VHA care to $57 383 in non-VHA care.

DISCUSSION

Our study is the first prospective randomised study comparing two different HCC screening procedures – twice-a-year (biannual) ultrasonography vs. once-a-year (annual) triphasic CT; both arms combined with biannual AFP – in a US patient population. In addition, the study provides valuable information with regard to efficacy of HCC screening in a general clinic population of VHA patients with cirrhosis. The data suggest that biannual ultrasonography is comparable to annual CT in detecting early-stage HCC, with lower costs.

The validity of ultrasonography as screening tools among cirrhotics, particularly in the US population, has still not been proven conclusively to result in decreased HCC mortality. Because of data indicating less sensitivity of ultrasonography, some clinicians have advocated CT or magnetic resonance imaging for HCC screening programmes.6 In an effort to optimised cost-effectiveness, the length of screening intervals is still being debated. An earlier Italian study showed that semi-annual and annual surveillance with ultrasonography equally improved survival in cirrhotic patients with HCC.8 A more recent study from Trinchet et al. could not provide evidence that shorter screening intervals of 3 months detected more small HCC (<3 cm), but led to increased cost of recall procedures.7 One earlier randomised trial
as well as several cross-sectional, longitudinal cohort and population-based studies documented potential benefits of screening for HCC with ultrasonography such as diagnosis at an earlier stage and prolonged survival; with some studies correcting for length and lead time biases.\textsuperscript{21–27} However, results need to be applied with caution to the US population as studies conducted in Europe or Asia have included up to 25% of non-cirrhotic subjects\textsuperscript{18} or did not report the prevalence of cirrhosis altogether.\textsuperscript{20}

We found that the overall HCC incidence rate per year was 6.6%, which was expected in patients with primarily (87%) HCV-related cirrhosis, although appears somewhat low given the older age and almost exclusively male study cohort. Of those with screen-detected HCC, 58.8% (10/17) had early-stage HCC; but only 23.5% (4/17) received potentially curative treatment. Only one patient in the screen-detected HCC group underwent liver transplantation; others had medical or psycho-social co-morbid conditions interfering with transplant eligibility. Stravitz et al. found in a retrospective cohort study that HCC screening is effective if the option of liver transplantation is considered; however, in patients with low eligibility for liver transplantation, HCC screening is less effective.\textsuperscript{28}

None of our patients was considered an appropriate candidate for surgical resection because of cirrhosis with portal hypertension and/or medical co-morbidities. In Asia, about 40% of patients with screen-detected HCC are candidates for surgical resection because of cancers arising in noncirrhotic livers; in the United States, only approximately 5% are considered appropriate surgical candidates.\textsuperscript{19} Potential false-positive imaging results place screened individuals at risk of increased morbidity and mortality from unnecessary diagnostic and therapeutic interventions, including biopsies, developing radiation-related malignancies and renal toxicity. In our trial, false-positive results occurred in 7.4% (12/163) of patients requiring additional testing including CT, MRI and PET scans; no additional biopsies were performed.

Among our patients diagnosed with HCC, HCC-related mortality was 70.5% and all-cause mortality was 82.3%, suggesting that the majority of patients died of their cancer despite all treatment options including liver transplantation were available and considered at the time of HCC detection and during follow-up care. The overall mortality in our study population was 14.7%; subsequently, HCC represents a major cause of death in this population.

In the United States, ultrasonography is widely available, relatively inexpensive and easily performed. Its use is limited by body habitus, inability to image entire liver because of limited depth penetration, and insensitivity in detecting small lesions and distinguishing HCC from regenerative nodules in the cirrhotic liver. In prior studies, the overall sensitivity for HCC detection of ultrasonography ranges from 40% to 81% with a specificity of 80–100%. Overall, the sensitivity and specificity of triple-phase CT ranges from 85% to 90% and 80% to 96% respectively.\textsuperscript{6} Despite higher sensitivity and specificity, CT was not been found cost-effective for routine HCC surveillance.\textsuperscript{6} Many studies of the sensitivity and specificity of imaging modalities for HCC detection were derived from relatively small numbers of highly selected patients who were candidates for liver transplantation, with comparisons of preoperative imaging and HCC detected in the liver explants.\textsuperscript{6} Singal et al. performed a meta-analysis of prospective studies using surveillance ultrasound for detection of early-stage HCC in patients with cirrhosis. The meta-analysis included 19 studies, all of which were performed in Europe or Japan. They found an overall sensitivity of 63% for early HCC detection. Studies with ultrasound surveillance intervals of <6 months had a pooled sensitivity of 70.1% (95% CI: 55.6–84.6), whereas studies with surveillance intervals between 6 and 12 months had a pooled sensitivity of 50.1% (95% CI: 40.0–59.2).\textsuperscript{29} The authors concluded that the results of the meta-analysis may not be generalisable to other ethnic and geographical populations as all of the included studies were conducted in experienced liver centres in Europe and Asia where many ultrasounds are performed and the performance of ultrasound may be worse in an American cohort in which obesity can further limit its sensitivity.\textsuperscript{29}

When using CT for HCC screening, providers need to consider other potential risks related to the test, especially the potentially increased risk of developing radiation-related malignancies and renal toxicity. A recent study estimated that, in the United States, about 29 000 future cancers could be related to diagnostic scans performed in 2007 with 14 000 cancers caused by scans of the abdomen/pelvis alone.\textsuperscript{30} The risk of radiation of multiple triple-phasic CT for HCC screening has to be weighed against the benefit of detecting early-stage cancer.

Snowberger et al. showed in a retrospective cohort study that MRI is the most sensitive test for detecting HCC; however, to date, MRI is not endorsed for screening purposes.\textsuperscript{31} Recently, Seitz et al. evaluated the diag-
nostic role of contrast-enhanced ultrasonography and MRI for the evaluation of liver lesions (DEGUM Multi-center Trial: CEUS vs. MRI) and found that both diagnostic tools are extremely reliable for the diagnosis and differentiation of liver lesions with a sensitivity of 81.8% and specificity of 63.0% for MRI.32 Contrast-enhanced ultrasonography is not generally available in the United States.

Improved technologies are more expensive and will influence current and future strategies such as the use of Eovist with MRI, a contrast agent that is taken up by hepatocytes. Ideally, all these newer techniques would require randomised controlled trials to demonstrate usefulness related to HCC screening and to accurately assess cost-effectiveness.

Biannual AFP testing added little to overall HCC detection. One patient in this study was identified by increasing AFP level, although initial imaging was negative. Prior studies have indicated that AFP has a lower sensitivity (40–50%) and specificity (63–94%) for HCC detection,6 and a meta-analysis of ultrasound surveillance studies found no benefit from the addition of AFP.18 However, the cost of AFP is low and AFP levels appear to identify patients with an increased risk for HCC. A recent single-centre US study of 442 cirrhotic patients reported a sensitivity of 58.1% and specificity of 91% in patients who received consistent surveillance, and a sensitivity and specificity of 65.9% and 90.5% for AFP > 20 ng/mL respectively. The combination of tests increased the sensitivity to 90.2% with a small decrease in specificity to 83%.33 These data indicate the importance of studies in real-world community settings.

Our study has several limitations, including long enrolment period, relatively small sample size, predominance of Caucasian race and performance of the study in an all-male veteran population, making generalisability to other US populations difficult. However, the study was designed to obtain baseline and initial test performance estimates to help design further trials in the US population as, to our knowledge, no prospective US study using either ultrasonography or CT exists to date. Although 35% of enrolled patients continued not to be followed in their initially assigned screening arm, comprehensive data could be obtained on all but eight patients (8/163, 5.0%), due to exclusive use of an electronic medical record and performance of the study at a single site. Other studies have reported dropout rates of nearly 50% in screened groups and have not reported data in control groups.20 Despite these limitations, our randomised prospective study confirms results of other observational cohort studies that screening can detect HCC at an earlier, potential curative stage; however, treatment options and subsequent outcomes are limited by other factors in this patient population, despite careful selection of patients.

We found that ultrasonography and CT screening strategies have similar costs in the VHA setting. However, using non-VHA cost estimates, screening with CT is significantly more expensive. Given lack of increased sensitivity in detecting HCC – including increased false-positive results, increased risk/benefit ratio especially related to cumulative radiation exposure and higher cost – we conclude that CT should not be used as screening tool for a population at risk for HCC. Due to the small number of subjects in this study, we could not demonstrate a mortality benefit with either screening modality.

Our data indicate that biannual ultrasound is marginally more effective with less overall costs than annual CT in a VHA patient population with cirrhosis. The overall efficacy of HCC surveillance in a cirrhotic population in the United States has yet to be demonstrated, and further research is needed. Currently, surveillance programmes must recognise the limitations in HCC surveillance tests and treatment efficacy in specific patient populations. Continued improvements in screening technologies, such as the use of contrast-enhanced ultrasonography,34 which is not generally available in the United States, along with improved HCC treatments may provide further incremental improvements in the cost/effectiveness equation. These factors emphasise the need for continued cost and effectiveness studies of specific HCC surveillance tests in real-world clinical populations.

AUTHORSHIP
Guarantor of the article: Christine Pocha.

Author contributions: Eric Dieperink contributed to the development of research protocol, performed the research and helped substantially to draft the manuscript. Astrid Knott helped with data collection and analysis as well as manuscript preparation. Kelly McMaken acted as study coordinator and helped to draft the manuscript. Paul Thuras performed all statistical analyses. Samuel B. Ho developed the initial protocol and was involved in all steps of the research. All authors approved the final version of the article, including the authorship list.

ACKNOWLEDGEMENTS
Declaration of personal interests: None.
C. Pocha et al.

Declaration of funding interests: The study was supported in part by the Department of Veterans Affairs Hepatitis C Resource Centers and the Research Service of the Minneapolis VA Health Care System.

REFERENCES
1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74–108.
2. Kew MC. Hepatocellular cancer. A century of progress. Clin Liver Dis 2000; 4: 257–68.
3. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020–2.
4. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma: Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001; 35: 421–30.
5. Tyson GL, Duan Z, Kramer JR, Davila JA, Richardson PA, El-Serag HB. Level of alpha-fetoprotein predicts mortality among patients with hepatitis C-related hepatocellular carcinoma. Clin Gastroenterol Hepatol 2011; 9: 989–94.
6. Andersson KL, Salomon JA, Goldie SJ, Chung RT. Cost effectiveness of alternative surveillance strategies for hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol 2008; 6: 1418–24.
7. Trinchet JC, Chaffaut C, Bourcier V, et al. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: a randomized trial comparing 3- and 6-month periodicities. Hepatology 2011; 54: 1987–97.
8. Trevisani F, De Notarissi S, Rapaccini G, et al. Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). Am J Gastroenterol 2002; 97: 734–44.
9. Colli A, Fraquelli M, Casazza G, et al. Accuracy of ultrasonography, spiral CT, magnetic resonance, and alphafetoprotein in diagnosing hepatocellular carcinoma: a systematic review. Am J Gastroenterol 2006; 101: 513–23.
10. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 2009; 27: 1485–91.
11. Center for Disease Control and Prevention. Hepatocellular carcinoma - United States 2001-2006. MMWR Morb Mortal Wkly Rep 2010; 59: 517–20.
12. Davila JA, Henderson L, Kramer JR, et al. Utilization of surveillance for hepatocellular carcinoma among hepatitis C virus-infected Veterans in the United States. Ann Intern Med 2011; 154: 85–93.
13. Dominitz JA, Boyko EJ, Koepsell TD, et al. Elevated prevalence of hepatitis C infection in users of United States veterans medical centers. Hepatology 2005; 41: 88–96.
14. Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol 2011; 9: 509–516 e1.
15. Phibbs CS, Bhandari A, Yu W, Barnett PG. Estimating the costs of VA ambulatory care. Med Care Res Rev 2003; 60(Suppl. 3): 54S–73S.
16. HERC. B6. How do VA costs compare to the cost of non-VA providers? Available at: http://www.herc.research.va.gov/resources/faq_b6.asp. Accessed March 7, 2013.
17. HERC. B7. Comparison of VA and Medicare costs. Available at: http://www.herc.research.va.gov/resources/faq_b07.asp. Accessed March 7, 2013.
18. Ren FY, Piao XX, Jin AL. Efficacy of ultrasonography and alpha-fetoprotein on early detection of hepatocellular carcinoma. World J Gastroenterol 2006; 12: 4656–9.
19. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999; 30: 1434–40.
20. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004; 130: 417–22.
21. Chen JC, Parkin DM, Chen QG, et al. Screening for liver cancer: results of a randomised controlled trial in Qidong, China. J Med Screen 2003; 10: 204–9.
22. Colombo M, de Franchis R, Del Ninno E, et al. Hepatocellular carcinoma in Italian patients with cirrhosis. N Engl J Med 1991; 325: 675–80.
23. Fasani P, Sangiovanni A, De Fazio C, et al. High prevalence of multinodular hepatocellular carcinoma in patients with cirrhosis attributable to multiple risk factors. Hepatology 1999; 29: 1704–7.
24. Pateron D, Ganne N, Trinchet JC, et al. Prospective study of screening for hepatocellular carcinoma in Caucasian patients with cirrhosis. J Hepatol 1994; 20: 65–71.
25. McMahon BJ, Bulkow L, Harpster A, et al. Screening for hepatocellular carcinoma in Alaska natives infected with chronic hepatitis B: a 16-year population-based study. Hepatology 2000; 32: 842–6.
26. Farinati F, Gianini S. Surveillance for hepatocellular carcinoma in cirrhosis: is it cost-effective? Eur J Cancer Prev 2001; 10: 111–5.
27. Caturelli E, Bartolucci F, Biasini E, et al. Diagnosis of liver nodules observed in chronic liver disease patients during ultrasound screening for early detection of hepatocellular carcinoma. Am J Gastroenterol 2002; 97: 397–405.
28. Stravitz RT, Heuman DM, Chand N, et al. Surveillance for hepatocellular carcinoma in patients with cirrhosis improves outcome. Am J Med 2008; 121: 119–26.
29. Singal A, Volk ML, Waljee A, et al. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther 2009; 30: 37–47.
30. Berrington de Gonzalez A, Mahesh M, Kim KP, et al. Projected cancer risks from computed tomographic scans performed in the United States in 2007. Arch Intern Med 2009; 169: 2071–7.
31. Snowberger N, Chinnakotla S, Lepe RM, et al. Alpha fetoprotein, ultrasound, computerized tomography and magnetic resonance imaging for detection of hepatocellular carcinoma in patients with advanced cirrhosis. Aliment Pharmacol Ther 2007; 26: 1187–94.
32. Seitz K, Bernatik T, Strobel D, et al. Contrast-enhanced ultrasound (CEUS) for the characterization of focal liver lesions in clinical practice (DEGUM Multicenter Trial): CEUS vs. MRI – a prospective comparison in 269 patients. Ultraschall Med 2010; 31: 492–9.
33. Singal AG, Conjeevaram HS, Volk ML, et al. Effectiveness of hepatocellular carcinoma surveillance in patients with cirrhosis. Cancer Epidemiol Biomarkers Prev 2012; 21: 793–9.
34. Kudo M, Hatanaka K, Kumada T, Toyoda H, Tada T. Double-contrast ultrasound: a novel surveillance tool for hepatocellular carcinoma. Am J Gastroenterol 2011; 106: 368–70.