Department of Veterans Affairs
Health Services Research & Development Service | Evidence-based Synthesis Program

QUERI

Screening for Hepatocellular Cancer in Chronic Liver Disease: A Systematic Review

January 2014

Prepared for:
Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service
Washington, DC 20420

Prepared by:
Evidence-based Synthesis Program (ESP) Center
Portland VA Medical Center
Portland, OR
Devan Kansagara, M.D., M.C.R., Director

Investigators:
Principal Investigators:
Devan Kansagara, M.D., M.C.R.
Janice H. Jou, M.D., M.H.S.

Co-Investigators
Joel Papak, M.D.
Amirala S. Pasha, D.O., M.S.
Maya O'Neil, Ph.D.
Michele Freeman, M.P.H.
Rose Relevo, MLIS, M.S.
Ana Quinones, Ph.D.
Makalapua Motu'apuaka, B.S.

VA HEALTH CARE Defining EXCELLENCE in the 21st Century

PREFACE

Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of QUERI Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

Recommended citation: Kansagara D, Papak J, Pasha AS, O'Neil M, Freeman M, Relevo R, Quinones A, Motu'apuaka M, Jou JH. Screening for hepatocellular cancer in chronic liver disease: a systematic review. VA-ESP Project #05-225; 2013.

This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at the Portland VA Medical Center, funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

EXECUTIVE SUMMARY

BACKGROUND

In the Veterans Health Administration (VHA), there has been a marked increase in the prevalence of cirrhosis from chronic hepatitis C infection with a corresponding increase in the number of hepatocellular cancer (HCC) diagnoses. From 1996 to 2006, the prevalence of cirrhosis among Veterans with chronic hepatitis C infection rose from 9 to 18.5%, and the prevalence of HCC rose from 0.07 to 1.3%. In the general population, the incidence of HCC rose between 1992 and 2005 from 3.1/100,000 to 5.1/100,000, with localized tumors accounting for most of the increase. While, on average, the 5-year survival of HCC is low (13 to 16.5%), the survival of early-stage disease has risen.

The rationale for screening is that imaging tests such as ultrasound can identify patients with early stage HCC and there are several potentially curative treatment options for patients with early stage HCC including liver transplantation, radiofrequency ablation, and liver resection. Several professional society guidelines currently recommend HCC screening using imaging studies and tumor markers mainly in patients with chronic hepatitis B or liver cirrhosis. However, recommendations for HCC screening remain controversial in part because of concerns over the quality and paucity of existing evidence, and because there have been concerns raised about overdiagnosis and patient harms in other cancer screening programs.

We conducted a systematic review of the published literature to better understand the incremental benefits and harms of routine HCC screening in patients with chronic liver disease compared to clinical or incidental diagnosis. We looked for direct evidence of the health outcome effects of screening. We also looked for indirect evidence of the effects of screening by evaluating studies examining the health outcome benefits and harms of treating early-stage HCC which, because the intent and result of routine screening is detection of early-stage disease, is a proxy for screen-detected disease.

METHODS

Data sources: Medline, PsycInfo, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews to March 2013; clinical trial registries; reference lists; and technical advisors.

Study Selection: We examined controlled clinical trials and observational studies comparing screening to no screening, and controlled clinical trials comparing different screening intervals. We also examined controlled clinical trials and observational studies comparing one of the following active treatments to conservative treatment in patients with early-stage HCC: transarterial chemoembolization (TACE), partial hepatic resection, orthotopic liver transplant (OLT), radiofrequency ablation (RFA), and sorafenib. Because of the dearth of studies for all treatments other than TACE comparing active to conservative treatments, we evaluated noncomparative observational studies for evidence on harms and long-term survival. The population of interest was patients with chronic liver disease with or without cirrhosis.

Data Extraction and Quality Assessment: From each study, we abstracted study design, objectives, setting, population characteristics (including sex, age, race/ethnicity, liver disease etiology and severity), subject eligibility and exclusion criteria, number of subjects, years of enrollment, mode and frequency of screening, adjusted and unadjusted mortality, and adverse events. A second author checked each entry for accuracy. Studies were dual-reviewed for quality using standard criteria.

Data Synthesis: We did not perform meta-analyses of screening or treatment interventions because of the dearth of trial data and the clinical heterogeneity among the small number of trials. Rather, we qualitatively synthesized the results of trials and observational studies.

RESULTS

Of 11,321 citations, 264 were reviewed at the full-text level. Thirty-five studies contained primary data relevant to the efficacy of HCC screening or treatment of early-stage HCC and met our inclusion criteria. We also examined 2 systematic reviews of treatment modalities.

Overall, we found very low strength evidence examining the effects of screening for HCC on mortality among patients with chronic liver disease. Two trials and 16 observational studies compared the effects of screening to no screening. Three trials comparing HCC treatment to no treatment included patients with early-stage HCC, and 12 observational studies provided data about the effects of treatment of early-stage HCC.

Effects of screening on mortality: RCTs

Two trials, both conducted in China, compared the effects of screening to no screening on mortality among participants mainly with hepatitis B. One trial used a cluster-randomized design to assign factories, business, and schools to screening or no screening groups. Screening group participants (n = 9,757) were offered serum AFP testing and ultrasonography every 6 months. The primary outcome of HCC mortality occurred less frequently in the screening group (83.2/100,000 person-years vs 131.5/100,000 person-years; rate ratio 0.63, 95% CI 0.41 – 0.98). However, this trial, carried a high-risk of bias because of several serious methodological limitations that threaten the validity of the results. The second trial used patient-level randomization stratified by township to assign hepatitis B patients to the screening intervention (n = 3,712), which consisted of serial AFP tests followed by ultrasound for high AFP values, or the usual care group (n = 1,869). HCC mortality was similar in both groups (1,138/100,000 person-years vs 1114/100,000 person-years, p = 0.86), as was all-cause mortality (1,843/100,000 person-years vs 1,788/100,000 person-years, p = NS). This trial carried an unclear risk of bias because of poor reporting of randomization and allocation concealment techniques.

Two additional trials compared different ultrasound screening intervals. One unclear risk of bias trial found no survival advantage comparing 4-month to 12-month ultrasound screening intervals in patients with serologic evidence of hepatitis B or C. A trial with low risk-of-bias compared 3-month to 6-month ultrasound screening intervals in 1,278 patients with cirrhosis from alcohol use and/or viral hepatitis and found similar all-cause mortality rates in both groups.

Effects of screening on mortality: observational studies

Sixteen observational studies, which mainly included patients with HBV, HCV, and/or alcoholic liver disease, showed that screening detects patients with earlier stage disease, more of whom undergo potentially curative therapy. Median survival ranged among studies from 12-56 months in the screening group, and from 3-37 months in the non-screening group. Three-year survival ranged from 22-67% in the screening group, and from 15-51% in the non-screening group. However, it is impossible to say whether the longer survival in screen-detected patients is a true effect of screening or, rather, reflects lead- and length-time biases inherent to all observational studies, and selection biases which were common in many of the studies.

Harms of screening

None of the included studies reported harms of screening, but the direct physical harms of HCC screening using ultrasound and/or AFP – which were the most commonly studied screening modalities – are likely to be minimal. However, most patients with positive screening ultrasound and/or AFP undergo further confirmatory testing. In most of the studies, confirmatory testing was done with CT and, less commonly, with MRI or liver biopsy, though very few studies reported rates of actual testing used for diagnosis. One meta-analysis of 8 studies found the risk of needle track seeding from liver biopsy done for work-up of HCC to be 2.7%. One recent systematic review of the diagnostic accuracy of imaging for HCC screening and diagnosis found very few studies reporting harms data: one study found that contrast-enhanced CT was associated with adverse events in 13-15% of patients, while another found mild-moderate adverse events in 25% of patients receiving gadoxetic acid-enhanced MRI. We found no studies evaluating the psychologic harms of screening.

Effects of treating screen-detected HCC

No studies specifically enrolled patients with screen-detected HCC, so we examined studies of patients with early-stage HCC as a way of approximating screen-detected disease. Overall, there is little evidence from which to draw conclusions about the net benefits of actively treating early-stage HCC compared to conservative treatment. Low-strength evidence from one trial found TACE decreased mortality in patients with hepatitis B, while low-strength evidence from 2 trials found TACE increased mortality in patients with alcoholic cirrhosis. Observational studies show that patients selected for treatment with OLT, resection, or RFA had good long-term survival (27-75%), which was substantially higher than patients not selected for such therapy (0-30%), but it is unclear whether such effects reflect a true effect of treatment or reflect confounding by indication. Serious harms occurred in 1.8-20% of patients, depending on the intervention.

Conclusions

There is very low strength evidence from which to draw conclusions about the effects of HCC screening on mortality in high-risk patients with chronic liver disease. Screening tests can identify early stage HCC and patients who are selected for surgical treatment often have good long-term survival, but some treatments may be associated with substantial harms. Trials examining the balance of benefits and harms of HCC screening in patients with chronic liver disease should be considered. The table below summarizes the findings and strength of evidence.

Table. Summary of the evidence on screening for hepatocellular carcinoma in patients with chronic liver disease, and treatment in patients with early-stage hepatocellular carcinoma

	Outcome	For each study design: N studies: N studies by liver disease etiology; N=combined number of participants	Findings	Strength of Evidence*	Comments
Effects of screening					
Screening vs no screening	Mortality	2 RCT: 2 HBV; N=19200 16 NRCS: 1 HBV; 3 HCV; 7 HBV/HCV; 5 HBV/HCV/EtOH; N =11340	One high risk of bias trial of US, RR of death due to HCC, 0.63 (95% CI, 0.41-0.98) One unclear risk of bias trial of AFP, Incidence rate all-cause mortality/100 person-years: 1.83 vs 1.79, *P* = NS	Very low	Numerous methodologic issues in the trials including allocation concealment, outcome assessment, analytic problems, and selective outcome reporting, limit conclusions. Methodologic issues in the observational studies including selection bias, as well as lead- and length-time bias similarly limit conclusions. Studies consistently found HCC diagnosed with screening was earlier stage, but impact on overall mortality unclear. Applicability to hepatitis C and alcoholic liver disease populations limited.
	Harms: needle track seeding	1 Meta-analysis of 8 NCS; N=1340 1 NCS; N=3391	Overall risk of seeding: 2.7% (95% CI, 1.8-4.0%)	Low	Range of seeding 0 to 5.8%, most recent study not in meta-analysis found risk of .12%. Applicability to current practice may be limited as liver biopsy not often used in diagnosis of HCC.
	Harms: other	No studies	--	No evidence	
Shorter intervals vs longer intervals	Mortality	2 RCT: 1 HCV/EtOH, 1 HBV/HCV; N=2022	Shorter screening intervals (3-4 months) offered no advantage over longer intervals (6-12 months)	Moderate	One trial had unclear risk of bias. No evidence comparing 6- to 12-month intervals.
	Harms	NA	NA		

	Outcome	For each study design: N studies: N studies by liver disease etiology; N=combined number of participants	Findings	Strength of Evidence*	Comments
Effects of treatment of screen-detected or early-stage HCC compared to no treatment					
TACE	Mortality	3 RCT: 1 HBV, 2 EtOH; N=217 3 NRCS: 1 HBV, HCV; 1 HBV, EtOH; 1 HBV, HCV, EtOH; N=795	No difference in 2 trials of EtOH patients. RR of death, 0.49 (95% CI, 0.29-0.81) in one trial of HBV patients.	Low (EtOH) Low (HBV)	Evidence base is limited by poor methods reporting in 2 trials and small sample size. Directness of evidence to screen-detected disease also limited.
	Harms	3 RCT: 1 HBV; 2 EtOH; N=217	Serious complications in 8 to 20% patients	Low	Serious complications included GI hemorrhage, treatment-related death, renal failure, and thrombosis. Studies included patients with both early and late-stage disease and applicability to those with early-stage disease is unclear.
RFA	Mortality	4 NRCS: 1 HBV, HCV; 1 HBV, EtOH; 2 HBV, HCV, EtOH; N=965 2 NCS: 2 HBV/HCV; N=339	5-year survival 27-55% vs 0-30%	Very low	All non-randomized studies in which confounding by indication limits conclusions about impact on mortality
	Harms	1 NRCS: 1 HBV, HCV, EtOH; N=170 2 NCS: 2 HBV/HCV; N=1249	Serious complications in 1.8-9.9%; needle-track seeding in 3.2%	Low	Complications included peritoneal bleeding, hemothorax, and portal vein thrombosis. Information comes from one large cohort study focused only on needle-track seeding, and 2 small cohort studies.
OLT	Mortality	1 NRCS: 1 HBV, HCV; N=278 3 NCS: 2 HBV/HCV, 1 NR; N=12,304	4-5 year survival, 53-73% vs 0-30%	Very low	All non-randomized studies in which confounding by indication limits conclusions about impact on mortality
	Harms	0	--	No evidence	Poor reporting of harms in studies.
Resection	Mortality	3 NRCS: 1 HBV, HCV; 1 HBV, EtOH; 1 NR; N=952	5-year survival, 33-75% vs 0-8.3% HR for death, 0.45 (95% CI, 0.34-0.59)	Low	No direct evidence examining mortality. Data from one large, well-conducted observational study which did account for some important confounding factors, but was not able to control for patient comorbidities.
	Harms: perioperative mortality	1 systematic review of 23 studies N=3366	Perioperative mortality 4%	Low	Data up through 2004; applicability to current practice unclear.
Sorafenib	Mortality	0	--	No evidence	No studies in patients with early-stage disease.
	Harms	0	--		

Abbreviations: EtOH = ethanol; HBV = hepatitis B virus; HCV = hepatitis C virus; NCS = non-comparative study; NR = not reported; NRCS = non-randomized comparative study; NS = not specified; RCT = randomized controlled trial; RR = relative risk

* GRADE classification: high = further research is very unlikely to change our confidence on the estimate of effect; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.