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

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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.

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- 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.

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

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BACKGROUND

Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer related death among men and ninth leading cause of cancer related death among women in the United States.[1,2] Chronic hepatitis B, common in Asia, is associated with HCC even in the absence of cirrhosis because of direct oncogenic properties of the virus. In Western countries, on the other hand, cirrhosis, most commonly from chronic hepatitis C infection and alcoholic liver disease, is the predominant risk factor for the development of HCC.[3] 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 HCC diagnoses. From 1996 to 2006, the prevalence of cirrhosis among Veterans with chronic hepatitis C infection rose from 9-18.5%, and the prevalence of HCC rose from 0.07-1.3%.[4] 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.[5] While on average the 5-year survival of HCC is low (13-16.5%),[5,6] the survival of early-stage disease has risen.[5]

The rationale for screening is that imaging tests such as ultrasound can identify patients with early stage HCC[7] and there are several potentially curative treatment options for patients with early stage HCC including liver transplantation, radiofrequency ablation, and liver resection.[8] Several professional society guidelines currently recommend HCC screening using imaging studies and tumor markers, mainly in patients with chronic hepatitis B or liver cirrhosis.[8-10] 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.[11-15]

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 AND SEARCHES

We conducted a search for literature published in Medline, PsycInfo, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews from database inception to March 2013. The search strategy included terms for HCC, screening/screening, treatment modalities, and adverse effects including psychological harms of screening/screening. The detailed search strategy is provided in Appendix A. We obtained additional articles from systematic reviews, reference lists of pertinent studies, reviews, editorials, and by consulting experts. We also searched for ongoing and recently completed studies on ClinicalTrials.gov.

STUDY SELECTION

This review was commissioned by the VHA Oncology Program Office and the VHA HIV, Hepatitis and Public Health Pathogen Program. A protocol describing the review plan was posted to a publicly accessible website before the study was initiated.[16] The analytic framework and key questions which guided this review were developed in conjunction with a panel of VA and non-VA technical experts and are provided in Appendix B, Figure 1. Detailed inclusion and exclusion criteria are provided in Appendix C. We used a "best-evidence" approach to guide study design criteria depending on the question under consideration and the literature available.[17] We prioritized controlled clinical trials, then comparative observational studies, then large cohort studies. To assess the effects of screening on HCC-specific and all-cause mortality, we included clinical trials and observational studies providing primary data in adult populations. We use the term "screening" to refer to any program in which tests – including ultrasonography, computed tomography, magnetic resonance imaging, and/or alpha-fetoprotein levels – were done explicitly to look for HCC in asymptomatic patients. Studies had to include a contemporary comparison group of patients who did not undergo screening and had testing done only to evaluate symptoms. We excluded observational studies that did not account for basic confounding factors such as age, sex, and liver disease severity. Because we anticipated few clinical trials comparing screening to no screening, we also included trials comparing different frequencies of screening. We included studies of any population with chronic liver disease, with or without cirrhosis, but excluded studies of patients with prior HCC. To assess the harms of screening, we abstracted any reported adverse effects data from studies included from the above search. We also additionally searched for trials or observational studies focused on potential harms of HCC screening.

To assess the benefits and harms of treating HCC found as a result of screening, we included trials or large prospective cohort studies examining the effects of liver resection, transplant, radiofrequency ablation, transarterial chemoembolization, or sorafenib, compared to no treatment in patients with early stage HCC (defined as the equivalent of Barcelona Clinic Liver Cancer (BCLC) Stage A, or early-stage HCC by the Milan criteria).[18,19] We included studies with mixed populations of patients with early and advanced disease, but not studies including only patients with advanced disease. Because comparative effectiveness studies would not directly address the incremental effects of screening or treating screen-detected disease, we excluded studies comparing 2 or more active treatments without an untreated control group. We found

no trials and only a small number of comparative observational studies of liver resection, transplantation, and radiofrequency ablation, so we included non-comparative cohort studies of these interventions if they included consecutive patients with adequate long-term follow-up and, in the case of OLT for which several large cohorts were available, large sample size (n > 500). We prioritized systematic reviews of such studies if available.

In order to better understand the quality and content of existing recommendations guiding the practice of HCC screening, we systematically searched for HCC screening guidelines. Among published guidelines, we identified the 3 most widely disseminated guidelines representing distinct geographic areas including North America,[8] Europe,[9] and Asia.[10]

Seven investigators reviewed the titles and abstracts of citations identified from literature searches, and 2 reviewers independently assessed the selected full-text articles for inclusion based on the eligibility criteria shown in Appendix C. Disagreements were resolved through consensus.

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.

Two reviewers independently assessed the quality of each trial using a tool developed by the Cochrane Collaboration.[20] Disagreements were resolved through discussion. Each study was given an overall summary assessment of low, high, or unclear risk of bias. We graded the strength of evidence for outcomes using published criteria which consider the consistency, coherence, and applicability of a body of evidence, as well as the internal validity of individual studies.[21]

Though there is no widely accepted standard for quality assessment of observational studies, we adapted existing assessment tools.[22,23] For the observational screening studies, we additionally adapted causal inference criteria[24] relevant to this review and specifically assessed: 1) methods for ascertaining screening status, and 2) use of an inception cohort. We do not report an overall summary assessment for observational studies because there are no validated criteria for doing so.

We assessed the quality of published guidelines using the AGREE framework.[25]

DATA SYNTHESIS AND ANALYSIS

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

We reviewed 11,321 titles and abstracts, including 10,996 from the electronic search and an additional 325 from reviewing reference lists and performing manual searches for recently published and unpublished or ongoing studies (Appendix B, Figure 2). After applying inclusion/exclusion criteria at the abstract level, 264 full-text articles were reviewed. Thirty-five primary studies contained primary data relevant to the efficacy of HCC screening or treatment of early-stage HCC and met our inclusion criteria. We also included 2 systematic reviews of providing evidence on harms of treatment modalities.[26,27]

EFFECTS OF SCREENING ON MORTALITY

Two trials and 16 observational studies provided very low strength evidence from which to draw conclusions about the mortality effects of HCC screening compared to no screening. The trials had substantial methodologic flaws that threaten their internal validity, and their applicability was limited to the hepatitis B population. The 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. 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.

Effects of screening on mortality: Randomized controlled trials

Two trials, both conducted in China, compared the effects of screening to no screening on mortality among participants mainly with hepatitis B (Appendix D, Table 1).[28,29] 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 control group (n = 9,443) was not made aware of the study or actively followed. Information on HCC development and mortality was based on physician reporting and a cancer registry, though there were no details reported about registry development. 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).

The trial, however, carries a high risk of bias because of several serious methodological limitations (Appendix D, Table 2). One major concern is whether the baseline groups had the same risk of HCC. There is no information about randomization technique or allocation concealment, and very little information about the baseline characteristics of the 2 groups. In cluster-randomized trials, in which patients are assigned to treatments based on where they live or work, it is important to know whether the underlying populations are similar in socioeconomic status, the incidence of other diseases, and overall mortality. Another concern is that weak methods used to ascertain the outcome measure – death from HCC – could have introduced bias. Outcome ascertainment depended on physician report, but there was no systematic effort described to ensure complete and equal outcome reporting nor was there any information about the cancer registry or about the proportion of patients for whom survival data was available. If deaths were under-reported in the control group, results could have been biased towards the

null. On the other hand, if outcome adjudicators were not blinded, more control group deaths could have been misclassified as HCC-related, especially because the symptoms that define stage III HCC (cachexia, jaundice, ascites) overlap substantially with symptoms of end-stage liver disease and there was no data provided about liver disease severity in either group. Selective reporting and analysis of favorable outcomes was another concern. Though the authors report that vital status was available for all patients, overall mortality was not reported, and there was no statistical adjustment for the effects of clustering. Finally, the study is less applicable to the US wherein cirrhosis, most often from hepatitis C, is the most common risk factor for HCC, and there is probably limited applicability for these results to contemporary practice, in which the threshold for imaging for symptoms may be lower and the number of patients with incidentally-discovered HCC on imaging is higher.

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).[29] Cancer diagnoses were available in a population-based cancer registry which used active case finding techniques, and mortality was ascertained through the cancer registry and a population-based vital status registry. Cancer staging using the same Chinese staging system was done by personnel blinded to intervention status. Only 28.8% of screening-group participants completed all scheduled testing, but all participants completed at least one screening test. There were fewer Stage III HCC in the screening group (19.8 vs 41.0%, p = NR). 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.[30,31] One found no survival advantage comparing 4-month to 12-month ultrasound screening intervals in patients with serologic evidence of hepatitis B or C.[30] About one-third of patients in both groups had liver cirrhosis. Systematic ultrasound exams were performed by trained hepatologists and all patients with new nodules ≥ 1 cm were referred for further follow-up. More patients in the 4-month interval group had new liver nodules (11.9 vs 7.8%, p = 0.049), but the 3-year cumulative incidence of HCC was similar in both groups (11.7 vs 9.7%, p = 0.198). Although screening every 4 months identified more patients with ≤ 2 cm HCC (70.8 vs 20.0%, p = 0.006) and more patients with HCC in the 4-month interval group underwent resection or radiofrequency ablation treatment (54.2 vs 20%, p = 0.049), the 1-, 2-, and 4-year survival rates among patients with HCC were similar (95.8/78.8/57.4% vs 80/64/56%, p = 0.399). The trial used clustered randomization and carried an unclear risk of bias because of poor reporting of outcome assessment and statistical analyses.

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 (11.3 vs 12.1%, p = 0.38).[31] A similar number of patients were diagnosed with HCC in both groups (8.3 vs 11.0%, p = 0.13), and most met Milan criteria (79.2 vs 71.4%, p = 0.40).

Effects of screening on mortality: Observational studies

We included 16 observational studies which compared survival in patients with HCC diagnosed with screening to HCC diagnosed incidentally as part of another work-up or because of symptoms (Appendix D, Table 3).[32-47]

Studies represented a range of geographic settings including Asia (6 studies), Europe (5 studies), Australia (1 study), and the US (4 studies, of which 3 were conducted in the VA). The vast majority of patients included in these studies had hepatitis B or C with Child-Pugh class A or B cirrhosis, though in many studies, liver disease severity was significantly higher in the non-screening groups. Ultrasound with or without AFP measurement was the screening method used in nearly all studies, except for 2 US studies in which a small number of patients underwent CT.[34,39]

In general, patients who had undergone screening had earlier stage HCC than those who had HCC diagnosed incidentally or due to symptoms (% range meeting equivalent of Milan criteria: 60.0-100 vs 19.6-56.5 in 10 studies). More screen-detected patients received potentially curative treatment, though only a small proportion of screening group patients underwent hepatic resection (range 2.8-23.9% in 12 studies,[32,34,36-39,41-46] and 53.5% in one outlier study[47]) or liver transplantation (1-15% in 5 studies,[36,39,40,44,46] and 26-30.1% in 2 other studies).[32,43] Survival from the time of HCC diagnosis was generally higher among screening group patients than non-screening group patients (Appendix D, Table 3). Median survival ranged among studies from 12-56 months in the screening group, and from 3-37 months in the non-screening group (Appendix B, Figure 3). Three-year survival ranged from 22-67% in the screening group, and from 15-51 percent in the non-screening group. Unadjusted mortality risk was significantly lower in the screening group in some studies[35,38,39,47] although this survival advantage was not statistically significant in one study.[33]

Three of the observational studies reported objective and replicable methods for distinguishing screening from non-screening patients, and had comparatively fewer issues with selection bias by drawing patients from the VA – a single, large integrated health system.[34,35,39] The largest of these used the national VA HCV clinical case registry to identify 1,480 HCC patients, and was the only study to assess survival from the time at-risk for HCC (in this case, the HCV diagnosis date), rather than from the date of HCC diagnosis.[35] Patients who had had screening done both 0-6 months and 7-24 months prior to HCC diagnosis had modestly longer survival than those with no screening (median survival from HCV diagnosis 1,951 vs 1,782 days; HR=0.82; 95% CI: 0.72-0.95). Those with screening in either, but not both, time periods had similar survival as those with no screening. In models adjusted for lead-time, the survival advantage of recurrent screening was attenuated with longer lead-time assumptions. The other 2 studies were also conducted in VA and included patients with HCV and HCC. One of the studies found that screening was not associated with improved survival, but rates of screening were low and cited as a possible reason for the lack of observed survival effect.[34] The other study found HCC screening was not associated with improved survival, though receipt of potentially curative therapy was associated with improved survival.[39]

Overall, there are several methodologic considerations which temper the confidence with which one can draw conclusions from the body of observational literature (Appendix D, Table 4). Most of the studies were single center retrospective cohort studies in which all patients with diagnosed HCC were first identified and screening status was subsequently determined. Few studies

reported data about loss to follow-up, and many studies did not report using a comprehensive method to assess mortality outcomes equally in screening and non-screening groups. In most studies, the comparison group was drawn from a referral population and there are likely unmeasured patient, treatment, health care access and other factors that are different between groups. Even in the VHA studies in which all patients are part of the same health system, most screen-detected patients were followed by hepatologists and it is possible that co-interventions unrelated to HCC treatment differed between groups.

In addition to the methodologic issues specific to individual studies detailed in Appendix D, Tables 2 and 4, the potential for lead-time bias, in which the "lead-time" between cancer diagnosis in screened and unscreened groups adds to the apparent survival advantage, is inherent in any observational study of screening effects.[48] Though there is no infallible way to circumvent the threat of lead-time bias other than the conduct of a well-designed RCT, 4 studies used statistical techniques to adjust for lead-time bias.[35,41,43,46] These studies used various assumptions about tumor doubling time to estimate the lead-time of screening diagnosis. Three of the studies adjusted for lead-time and found the survival advantage for screening patients disappeared when the tumor doubling time was assumed to be 90-120 days or longer.[35,41,46] A fourth study used serial ultrasound data from 13 patients to estimate a tumor doubling time of 216 days, though survival among screening patients remained higher even after adjusting for lead-time.[43]

Of note, length-time bias, in which screening identifies patients with slower growing tumors, may complicate lead-time estimates.

HARMS OF SCREENING

Potential harms of screening can relate to the physical effects of the screening tests themselves, to testing triggered by a positive screening test, or to the psychologic effects of having a positive screening test. 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. In 2 studies, HCC diagnosis was based on biopsy in 33-80.3% of cases.[32,39] 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%.[26] One single-center study published after this meta-analysis found 0.12% of patients experienced needle track seeding.[49] 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 contrast-enhanced CT was associated with adverse events in 13-15% of patients, while another found mild-moderate adverse events in 25% patients receiving gadoxetic acid-enhanced MRI.[50] We found no studies evaluating the psychologic harms of screening.

HCC SCREENING IN VHA

Three observational studies, all comparing outcomes in patients with screen-detected HCC to those incidentally diagnosed, were conducted in the VHA; the results are summarized

above.[34,35,39] The bulk of the remaining screening literature is less directly applicable to VA, where HCV cirrhosis is the major risk factor for HCC. The screening trials included only patients with HBV. While many of the remaining observational studies included subgroups with HCV, subgroup-specific data were not available (Appendix D, Table 3).

Studies suggest the practice of HCC screening in VA is inconsistent. The VA HCV Clinical Case Registry study of 1480 HCV-infected patients with HCC found that, though the vast majority had received one AFP test (89%) or ultrasound exam (78%) between HCV and HCC diagnoses, only 21.2% of the ultrasounds were classified as screening tests and about one-third of patients (34.4%) had received annual testing in the 2 years prior to HCC diagnosis.[35] The other 2 VA studies examined patients at 1-3 VA centers and similarly found low rates of routine screening.[34,39]

Another VHA HCV Clinical Case Registry study examining screening practices found that, of the 10.1% of HCV-infected Veterans with cirrhosis, 42% received at least one screening US or AFP test in the first year after diagnosis of cirrhosis.[51] However, an additional 30% of these patients had had one of these tests done for reasons other than screening in the same time frame. Rates of screening declined in each year after cirrhosis diagnosis, and several clinical factors such as higher comorbidity burden, more advanced liver disease, and higher rates of alcohol use were associated with lower use of screening. On the other hand, nearly 30% of HCV patients without cirrhosis received a screening test the year following HCV diagnosis.

In contrast to the inconsistent observed use of screening in VHA, a majority (71%) of VHA providers reported recommending HCC screening in a recent survey.[52] Providers specializing in the care of patients with liver disease, and those practicing at centers where HCC treatment was readily available were more likely to report recommending HCC screening.

EFFECTS OF TREATING HCC DETECTED AS A RESULT OF SCREENING

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 with which to draw conclusions about the net benefits of actively treating early-stage HCC compared to conservative treatment. The few trials comparing active to conservative treatment of early stage HCC examined TACE. Observational studies do show that patients selected for treatment with OLT, resection, or RFA had good long-term survival, which was substantially higher than patients not selected for such therapy, but it is unclear whether such effects reflect a true effect of treatment or reflect confounding by indication.

Three clinical trials that included patients with early-stage HCC compared TACE to conservative treatment, but these studies were limited by small sample size and lack of subgroup information specific to patients with early-stage disease (Appendix D, Tables 5-6). Low strength evidence from 2 trials found no survival benefit from TACE in patients with alcoholic liver disease. One of these was a multicenter trial with low risk of bias which was stopped early for futility after enrolling 96 patients,[53] and the other was a smaller study with unclear risk of bias of 42 patients in France.[54] Low strength evidence from one trial with unclear risk of bias, about half of whom

had early-stage HCC, found TACE was associated with improved survival in HBV patients (RR 0.49; 95% CI 0.29-0.81).[55] We excluded a fourth trial because it included only patients with advanced HCC.[56]

Low strength evidence from one large cohort study of patients with early-stage HCC found lower mortality among those that had undergone resection compared to those treated conservatively, after adjusting for tumor size and basic demographic characteristics (adjusted HR 0.45; 95% CI 0.34-0.59, $p < 0.01$).[57] The 4 other comparative observational studies were difficult to interpret because they compared more than one treatment across heterogeneous groups of patients with early- and late-stage disease (Appendix D, Tables 7-8). However, many patients selected for treatment had good long-term (4- or 5-year) survival: 53-73% for OLT,[58-61] 33-75% for resection,[57,62] and 27-77% for RFA.[58,62-64]

HARMS ASSOCIATED WITH TREATMENT OF EARLY-STAGE HCC

Serious harms occurred in 1.8-20% of patients, depending on the intervention (Appendix D, Tables 5, 7, and 9). Across the 3 trials examining the effects of TACE, 8-20% of patients experienced serious treatment related complications though it is unclear what proportion of these patients had early- versus late-stage disease. A systematic review of 23 studies found an aggregate perioperative mortality rate among 3,366 patients undergoing resection of 4%.[27]

One single-center cohort study of 1,031 consecutive patients found 3.2% of patients developed needle-track seeding after undergoing RFA for HCC.[65] Two single-center cohort studies found serious complications in 1.8-9.9% of patients including peritoneal bleeding, hemothorax, and portal vein thrombosis.[63,66] Harms of OLT were not well-reported.

CURRENT HCC SCREENING GUIDELINES

We found 26 guidelines addressing HCC screening. We focused on the 3 most widely disseminated guidelines representing North America, Europe, and Asia (see Appendix D, Table 10 for a summary of the screening recommendations from the 3 guidelines). All 3 recommend that those at high risk for HCC should be routinely screened every 6 months by US (AASLD & EASL)[8,9] or by US and AFP (APASL).[10] The 3 guidelines provide different specific recommendations about high risk groups and screening schedules based on initially positive screening results. We critically appraised the guidelines using the AGREE II framework and identified several methodological flaws (Appendix D, Table 11 describes the AGREE II ratings for each guideline). None of the guidelines reported a systematic review of the literature and none reported critically appraising included studies to assess their internal validity. The guidelines lacked a description of the strengths and weaknesses of the overall body of evidence and, rather, cited levels of evidence based simply on study design (Level I evidence based on RCT in the case AASLD, level 2a evidence based on consistent evidence from cohort studies in the case of APASL) or did not define the level of evidence (EASL). Each of the guidelines cited the Zhang 2004 trial as the major source of evidence supporting recommendations, though, as we describe above, the methodologic flaws of this trial and many of the observational studies limit their internal validity which, in turn, weakens the strength of evidence.

DISCUSSION

We systematically reviewed and critically appraised trials and observational studies examining the risks and benefits of HCC screening in patients with chronic liver disease. Periodic ultrasound and/or alpha-fetoprotein testing have been the most commonly evaluated screening modalities. Patients with viral hepatitis have been the most frequently studied populations. Although screening identifies patients with early-stage HCC and some patients with early-stage HCC selected for curative therapy do well, there is very low strength evidence from which to draw conclusions about the balance of benefits and harms of screening for HCC and treating HCC found as a result of screening across a population of patients.

The body of evidence was limited in part by the paucity and substantial methodologic shortcomings of screening trials. Indeed, the one large-scale trial conducted among hepatitis B infected patients in China that serves as the primary evidence base for these recommendations has serious methodologic limitations which undermine the validity of its findings.[28] The other trial found serial AFP screening offered no survival advantage.[29] Limited applicability, because of more widespread imaging use, higher rates of incidental diagnosis, and a smaller proportion of patients whose main risk is hepatitis B, further diminish the strength of evidence.

Though we found a large body of observational studies, they did not substantively add to the strength of evidence. Most were single center studies retrospectively evaluating patients with HCC and had several methodologic flaws, in addition to lead- and length-time biases. Four studies attempted to account for lead-time bias and 3 of them found, in doing so, that the survival advantage of screening was greatly attenuated. However, estimates of lead-time bias are uncertain at best in part because there are few data available about the natural history of early-stage or screen-detected HCC from which to estimate tumor doubling times. The small amount of information that does exist comes from older studies that suggest tumor growth patterns can differ markedly among patients, with some patients exhibiting steady growth, others no growth followed by a period of rapid growth, and others still with little to no long-term growth.[67-70] Another study of a mixed population of patients with early- and late-stage disease randomized to no treatment in 2 trials found 2 very different survival patterns depending on the presence or absence of an invasive tumor pattern and poor performance status (8 vs 50% 3-year survival, p=0.00010).[71]

Potentially curative treatments for HCC such as liver transplant and resection exist, but have the potential for substantial perioperative morbidity and mortality. Trials comparing screening intervals show that most of the HCC identified as a result of periodic screening were small, early-stage HCC.[30,31] If many of the HCC found as a result of routine screening would progress and cause morbidity before patients' underlying illness did, then the net balance of benefits and harms might favor widespread screening. If, on the other hand, HCC identified as a result of screening were more indolent, then the risks of treating disease that would not have otherwise been clinically relevant (ie, overdiagnosed HCC) might tip the balance away from routine screening. Unfortunately, we found no evidence examining rates of overdiagnosis. Many HCC are diagnosed with imaging alone, in part because of concerns over the risks of liver biopsy. The accuracy of such diagnoses – and the corresponding risk of overtreatment – may also be important considerations in evaluating the balance of benefits and harms of screening. A

forthcoming systematic review examining the diagnostic accuracy of imaging tests for HCC should help address this knowledge gap.[72]

Most patients with HCC diagnosed with screening had smaller tumors that would be potentially amenable to curative therapies such as resection or liver transplantation. Cohort studies suggest that long-term survival of patients undergoing liver resection or transplantation for HCC is quite high, but such treatments may be associated with substantial perioperative morbidity and mortality.[27,73] Whether there is a net benefit from aggressive treatment of all early stage HCC is unclear from current data. We found little trial data focused on early-stage HCC treatment, and reporting of harms was inconsistent. The reasons why patients were not selected for surgical therapy are not clear. If there were random variations in patient selection practices, then the observational studies showing that surgically treated patients had markedly increased survival compared to nonsurgically treated patients would be quite compelling. If, on the other hand, patient factors such as comorbidity burden, performance status, and social determinants of health were the main considerations in influencing the decision to undergo treatment then the potential for confounding may be considerable. A recent US study found that tumor stage and performance status were the factors associated with receipt of curative therapy.[74] There is also emerging evidence that the waiting period for OLT selects patients with more indolent HCC, since patients with more aggressive disease lose candidacy while awaiting transplant.[75]

We found few other systematic reviews examining HCC screening studies. A recent Cochrane review similarly found insufficient evidence for screening, but focused only on studies of HBV patients and did not examine observational studies.[14] Several widely disseminated guidelines recommend HCC screening in high-risk patients with liver disease,[8-10] but none used a systematic review which critically appraised included studies as a basis for the recommendations. Other systematic reviews have evaluated HCC treatment trials but, apart from the TACE trials discussed above, they included trials of patients with late-stage HCC.[76,77]

Our finding that the strength of published evidence examining HCC screening is very low neither supports nor refutes current clinical policy recommendations for HCC screening. Transparency about the strength of evidence on which these recommendations are based is important, but policy recommendations also take into account other factors such as patient values and preferences, expert opinion, and cost considerations.[78] It is likely to be the case that there is variation in the natural history of screen-detected HCC. Additional information clarifying natural history patterns and ways of distinguishing patients with more aggressive tumors from those with more indolent tumors might facilitate patient selection practices that would optimize the benefits of screening while minimizing the risks of overdiagnosis.

LIMITATIONS

One limitation of our review was the exclusion of articles whose full-text was not in English. However, we mitigated the risk of missing relevant studies by searching multiple databases, bibliographies, speaking with experts, and searching trial registries. Moreover, there is evidence to suggest that language restrictions do not bias results of reviews of conventional therapies.[79] Our focus on studies comparing active treatment to conservative management admittedly may have missed important effects of current treatments for HCC, since many have been evaluated in

the context of comparative effectiveness studies. However, a comparative effectiveness review of current treatments for HCC was beyond the scope of our review and would not have provided direct evidence about the utility of treating screen-detected HCC. Also, we did include systematic reviews of current treatments as a way to broaden our understanding of the benefits and harms of current therapies. We excluded studies of patients with advanced stage HCC so our findings apply only to patients with early stage disease. While it is possible that screening would identify some patients with advanced stage disease, the incremental effects of routine screening compared to clinical or incidental diagnosis would mainly be to increase the number of early stage HCC detected.

FUTURE STUDIES

Overall, we found little high-quality direct evidence from which to draw conclusions about the balance of benefits and harms of routine HCC screening. There are a number of opportunities for further study and it is likely, given the current insufficient body of evidence, that future studies will have a substantial impact on the strength of evidence. The key evidence gaps and suggestions for corresponding future research opportunities are summarized in Table 1.

The current body of published evidence does not, in and of itself, appear to constitute a threat to clinical equipoise over the health outcome effects of HCC screening. Experts have, however, raised other concerns about the ethics and feasibility of conducting such a study. The research and health care community should continue discussions about the feasibility and equipoise of an HCC screening trial.

Research to more definitively evaluate the balance of benefits and harms of treating early stage HCC is imperative. Even in the absence of randomized controlled trials of screening, observational studies using well-designed registries of HCC patients, their treatments, complication rates, and long-term outcomes could prove useful. These registries should include consecutive patients and prospectively collect clinical information about potential adverse effects over time. Studies examining the psychologic impact of screening are also needed.

Imaging tests can clearly identify small, early-stage HCCs. Future studies should evaluate the contemporary natural history of such lesions and consideration should be given to treatment trials that include a watchful waiting arm for very early HCC.

Table 1. Gaps in evidence and recommendations for future research

Topic	Evidence gap	Potential future research
Screening		
	No methodologically sound trials have examined the effects of screening on health outcomes in patients with chronic liver disease.	Trials examining the health outcome effects of screening should be considered, including patients with hepatitis B, hepatitis C, and other forms of chronic liver disease.
	The feasibility of conducting randomized trials of screening in patients with chronic liver disease has been questioned.	Future studies should evaluate public willingness to participate in screening studies based on available evidence in the US and including patients with hepatitis C.
	Observational studies are limited by selection bias, limited generalizability (mostly single-center), retrospective design, and inability to identify time at risk for HCC.	Large registries of patients with chronic liver disease, with prospective recording of date of diagnosis of chronic liver disease, date of cirrhosis diagnosis, screening practice, imaging findings, HCC diagnosis, and treatment received.
	The contemporary natural history of early-stage HCC detected by imaging tests is not well understood.	Prospective cohort studies examining the growth patterns of small (< 2 cm) liver lesions suspicious for HCC should be considered. Studies would ideally examine and compare independent interpretations of serial imaging studies.
	The harms of screening have not been well-explored.	Studies examining the psychologic effects of screening (anxiety, depression) should be considered. Registry studies should include information about the cost of initial screening as well as the rates of repeat imaging required for initial positive results and associated resource use and harms.
	Current guidelines recommend 6 month screening intervals. Two trials demonstrate that 3- or 4-month screening intervals are not associated with benefit compared to 12-month intervals. However, no trials have compared 6 to 12 month screening intervals.	Trials comparing 6 to 12 month screening intervals should be considered.
Treatment		
Overall	The benefits and harms of treating very early stage HCC compared to a watchful waiting strategy are unknown.	Trials comparing various treatment strategies to watchful waiting for very early stage HCC should be considered.
TACE	Trials of TACE have included mixed populations with early and late stage disease. Trials have been small and have not included patients with hepatitis C.	Trials examining the effects of TACE on health outcomes in patients with early-stage HCC should be considered. Trials should include patients with hepatitis C.

Topic	Evidence gap	Potential future research
RFA	No trials have examined the health outcome effects of RFA. Observational studies are limited by biases such as confounding by indication.	Trials comparing RFA to conservative treatment in patients with early stage disease may be considered. In the absence of such trials, prospective cohort studies using well-designed registries of patients with chronic liver disease should be conducted, using techniques such as propensity scoring to control for confounding factors related to patient selection. Rates of needle-track seeding and other complications should be examined in these prospective studies.
OLT	No trials have examined the benefits and harms of OLT for patients with HCC compared to conservative treatment. Harms associated with OLT for HCC have not been well reported in observational studies.	Prospective cohort studies using well-designed registries of patients with chronic liver disease should be conducted, using techniques such as propensity scoring to control for confounding factors related to patient selection. Rates of perioperative morbidity and mortality, as well as longer-term harms such as infectious complications should be examined in prospective studies.
Resection	No trials have examined the benefits and harms of resection for patients with HCC compared to conservative treatment. One observational study did attempt to control for patient selection factors and found resection was associated with lower mortality, but did not explicitly account for some important confounding factors such as patient comorbidity and performance status. While perioperative mortality had been well-examined, most of the data are over a decade old and applicability to current practice is unclear.	Prospective cohort studies using well-designed registries of patients with chronic liver disease should be conducted, using techniques such as propensity scoring to control for confounding factors related to patient selection. Rates of perioperative morbidity and mortality, as well as longer-term harms should be examined in contemporary prospective studies.
Sorafenib	No trials have examined the benefits and harms of sorafenib in patients with early stage HCC.	Trials and prospective cohort studies of sorafenib in patients with early-stage HCC should be considered.

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 harm. Trials examining the balance of benefits and harms of HCC screening in patients with chronic liver disease should be considered.

Table 2. 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 0-5.8%, most recent study not in meta-analysis found risk of 0.12%. 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		
Effects of treatment of screen-detected or early-stage HCC compared to no treatment						

	Outcome	For each study design: N studies: N studies by liver disease etiology; N=combined number of participants	Findings	Strength of Evidence*	Comments
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 8-20% 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; KQ = key question; 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.

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