

Screening for hepatocellular carcinoma

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Disclosure

This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at the Portland VA Medical Center, Portland, OR funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative (QUERI). 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.

Outline

- Epidemiology of HCC
- Current guideline recommendations
- Review of evidence
 - Methods
 - Results
 - Discussion
- Discussion of potential implications and future research needs by Drs Kelley and Ross

Increasing number of Vets at risk for, and with diagnosis of, HCC

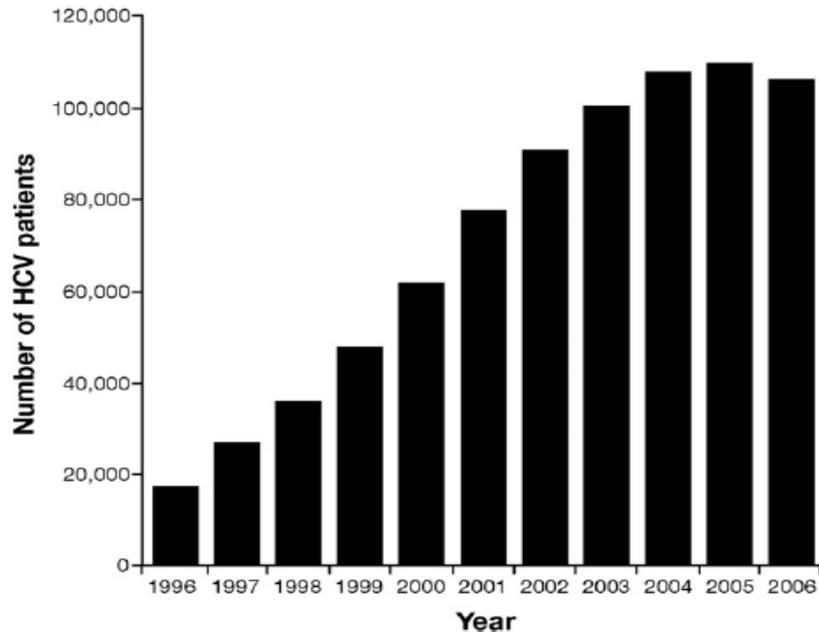


Figure 1. Change in HCV cohort size, 1996–2006.

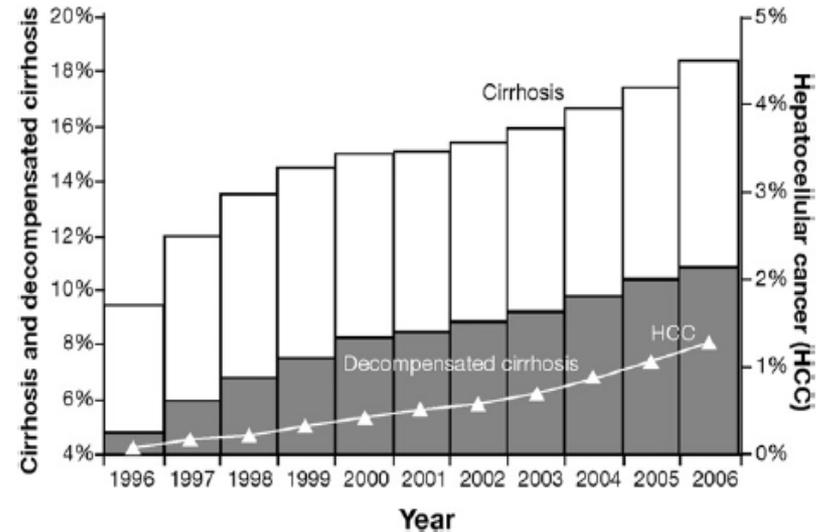
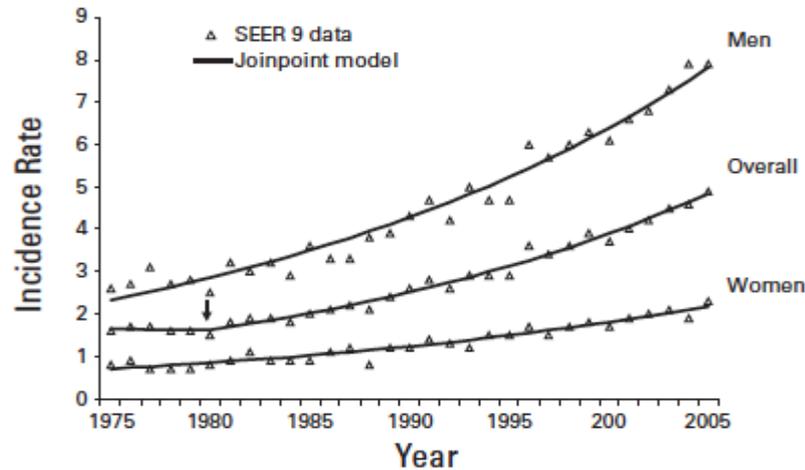


Figure 2. Crude prevalence of cirrhosis, decompensated cirrhosis, and HCC, 1996–2006.

Incidence of HCC in general population also increased, mostly because of the diagnosis of more localized tumors



	Diagnosis Years (%)				
	1992-1993	1994-1996	1997-1999	2000-2002	2003-2004

Patients by stage at diagnosis					
Localized	28	30	33	40	44
Regional	22	26	28	30	29
Distant	22	21	19	18	17
1-year survival by stage					
Localized	41	48	57	59	67
Regional	25	25	28	34	39
Distant	12	13	11	14	15

More recent trends

- From 2007-2010:
 - Overall HCC incidence rates did not significantly increase
 - Rates decreased among men aged 35-49 and Asian-Pacific Islanders
 - Liver cancer mortality rates decreased or remained stable

Current guidelines for HCC screening

	AASLD	APASL	EASL-EORTC
Overall recommendation (level of evidence)	Periodic screening of high-risk patients (Level I)	Periodic screening of high-risk patients (2a, B)	Periodic screening of high-risk patients (NR)
Screening modality, periodicity	US, 6 months	US + AFP, 6 months	US, 6 months
Specific subgroups who should be screened	HBV carriers, cirrhotic patients (any etiology), transplant wait list	HBV or HCV + cirrhosis	Child A/B cirrhosis; Child C cirrhosis awaiting transplant; HBV carriers with active hepatitis or family history of HCC; chronic HCV with advanced fibrosis

Practice in VA – HCV clinical case registry

- Patients with HCV + cirrhosis
 - 42% received US or AFP in year after cirrhosis dx
 - Additional 30% had tests done for reason other than screening
- Patients with HCV but no cirrhosis
 - 30% received screening test year following HCV Dx
- Patients with HCV + HCC
 - 78% received AFP or US between HCV and HCC dx
 - Only one-third received annual screening in the two years prior to HCC dx

Uncertainties

- Despite proliferation of guidelines, there is controversy regarding the strength of evidence supporting recommendations

Objectives of review

- To clarify the strength of the published evidence with regards to screening for hepatocellular carcinoma
- Key questions
 - What are the benefits and harms of screening for HCC in patients with chronic liver disease?
 - What are the benefits and harms of treating screen-detected HCC?

Evidence-based Synthesis Program (ESP) Overview

- Sponsored by VA Office of R&D and Quality Enhancement Research Initiative (QUERI).
- Established to provide timely and accurate syntheses/reviews of healthcare topics identified by VA clinicians, managers and policy-makers, as they work to improve the health and healthcare of Veterans.
- Builds on staff and expertise already in place at the Evidence-based Practice Centers (EPC) designated by AHRQ. Four of these EPCs are also ESP Centers:
 - Durham VA Medical Center; VA Greater Los Angeles Health Care System; Portland VA Medical Center; and Minneapolis VA Medical Center.

ESP Overview

- Provides evidence syntheses on important clinical practice topics relevant to Veterans, and these reports help:
 - develop clinical policies informed by evidence,
 - the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
 - guide the direction for future research to address gaps in clinical knowledge.
- Broad topic nomination process – e.g. VACO, VISNs, field – facilitated by ESP Coordinating Center (Portland) through online process:

<http://www.hsrd.research.va.gov/publications/esp/TopicNomination.cfm>

ESP Overview

- Steering Committee representing research and operations (PCS, OQP, ONS, and VISN) provides oversight and guides program direction.
- Technical Expert Panel (TEP)
 - Recruited for each topic to provide content expertise.
 - Guides topic development; refines the key questions.
 - Reviews data/draft report.
- External Peer Reviewers & Policy Partners
 - Reviews and comments on draft report
- Final reports posted on VA HSR&D website and disseminated widely through the VA.

<http://www.hsrd.research.va.gov/publications/esp/reports.cfm>

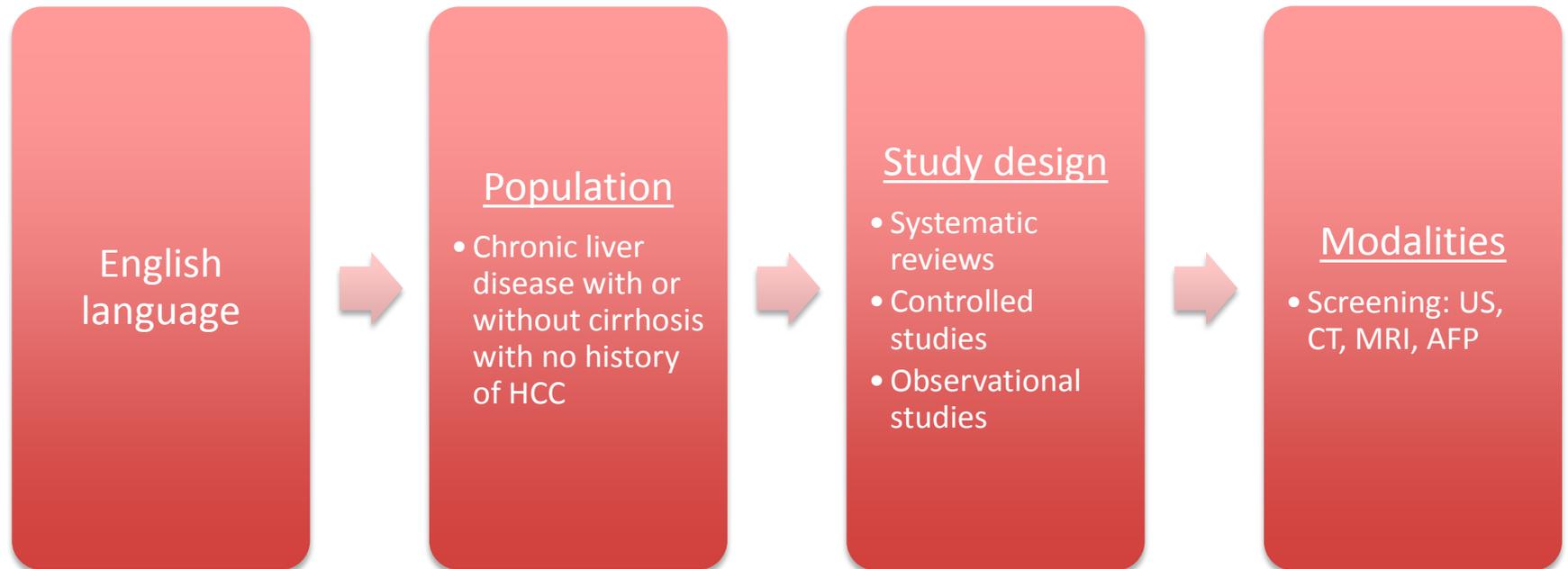
Methods – Search Strategy

- Systematic review of the literature
- Sources:
 - Medline, PsycInfo and Cochrane databases up through April 2014
 - Clinical trial registries, reference lists
 - Content experts
- Screening: Any surveillance or screening program in which testing was performed explicitly to detect HCC in asymptomatic patients

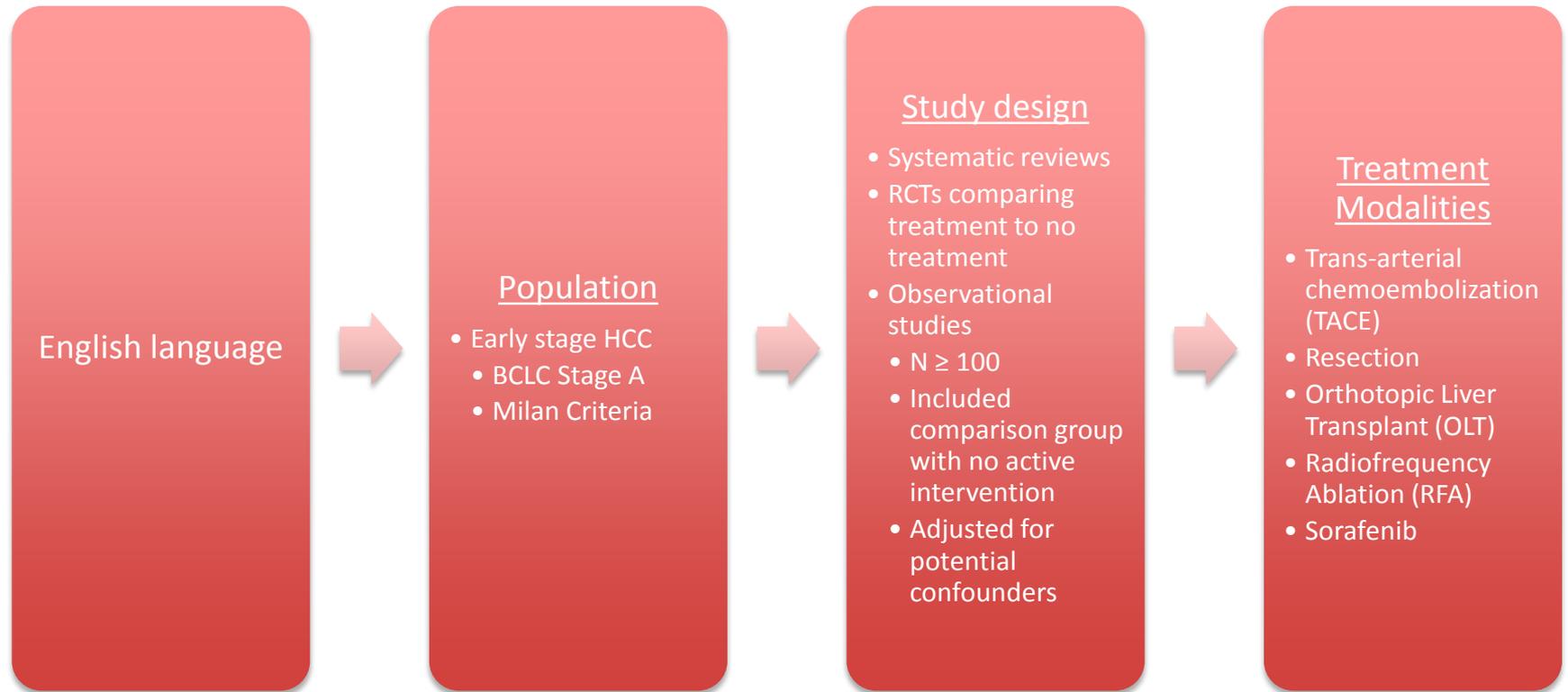
Methods – Outcomes of Interest

- Screening:
 - Benefits: Mortality
 - Harms: Liver biopsy complications, renal insufficiency, psychological effects, overdiagnosis
- Treatment:
 - Benefits: Mortality
 - Harms: Hospitalization, bleeding, pain, acute liver injury, infections and adverse events

Methods – Screening Inclusion Criteria



Methods – Treatment Inclusion Criteria



Methods – Evaluation

- Single investigator reviewed abstracts for inclusion
- Two investigators independently reviewed selected full texts for inclusion
- Second reviewer confirmed data abstraction for accuracy

Methods – Evaluation

Risk of Bias

- Two reviewers independently assessed the quality of each trial including overall risk of bias using Cochrane Collaboration tool

Risk of bias	Interpretation	Within a study
Low	Plausible bias unlikely to seriously alter the results	Low risk of bias for all key domains
Unclear	Plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key domains
High	Plausible bias that seriously weakens confidence in the results	High risk of bias for one or more key domains

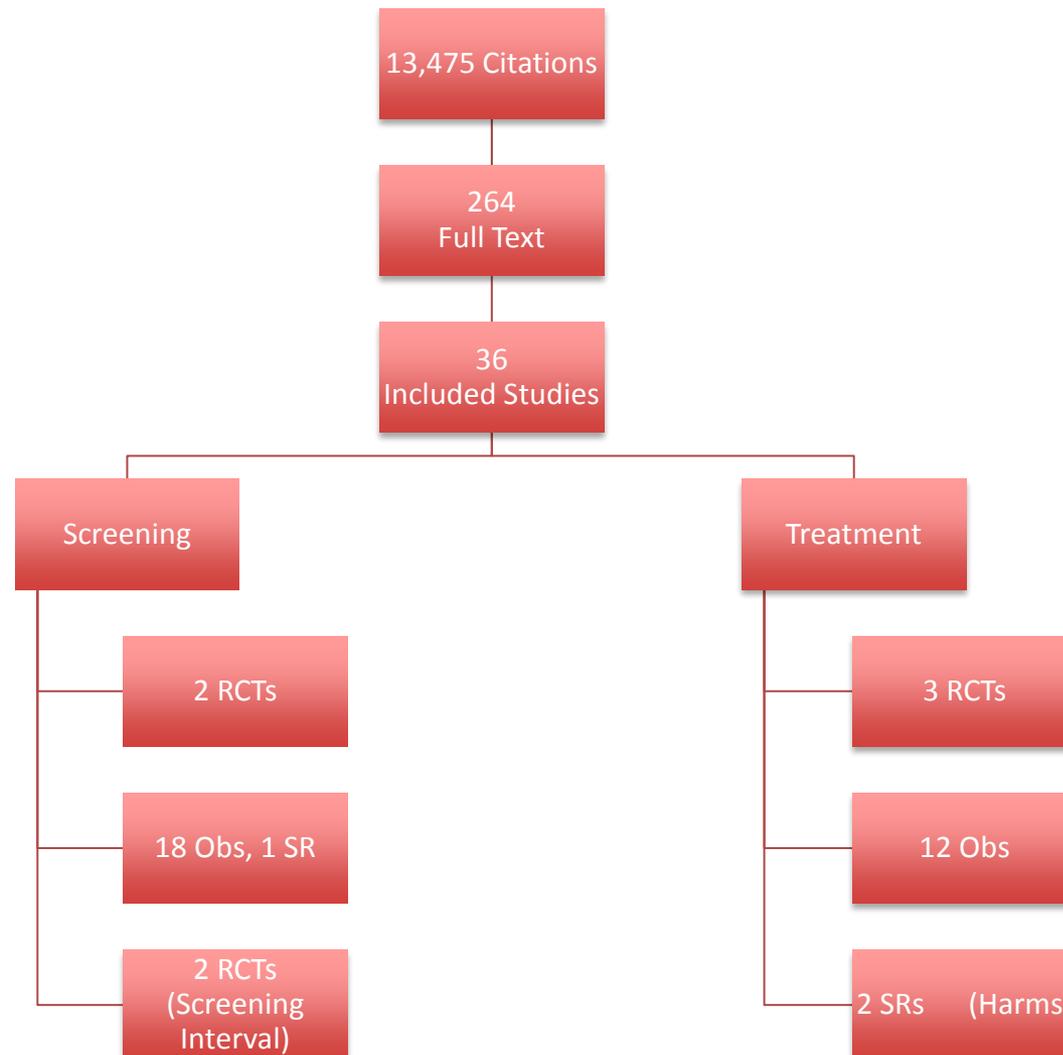
Methods – Evaluation

Strength of Evidence

- The strength of evidence was graded based on GRADE working group criteria

Grade	Definition
High	Further research is very unlikely to change confidence in 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

Results – search yield



Effects of Screening on Mortality - RCTs

	Zhang, et al 2004	Chen, et al 2003
Setting	China	China
Population	HBV	HBV
N (screening v control)	9757 v 9443	3712 v 1869
Screening modality	US + AFP	AFP
Frequency	Q6 months	Q6 months
HCC mortality	RR 0.63 (0.41 – 0.98)	1,138/100,000 v 1,114/100,000 person- years, $P = 0.86$
All-cause mortality	Not reported	1,843/100,000 v 1,788/100,000 person- years, $P = NS$

Risk of Bias in RCTs of HCC Screening

	Zhang 2004 (N > 19,000)	Chen 2003 (N > 5,000)
Sequence generation	Unclear risk of bias	Unclear risk of bias
Allocation concealment	Unclear risk of bias	Unclear risk of bias
Blinding	Unclear risk of bias	Low risk of bias
Incomplete data	High risk of bias	Low risk of bias
Selective outcome reporting	High risk of bias	Low risk of bias
Overall	High risk of bias	Unclear risk of bias

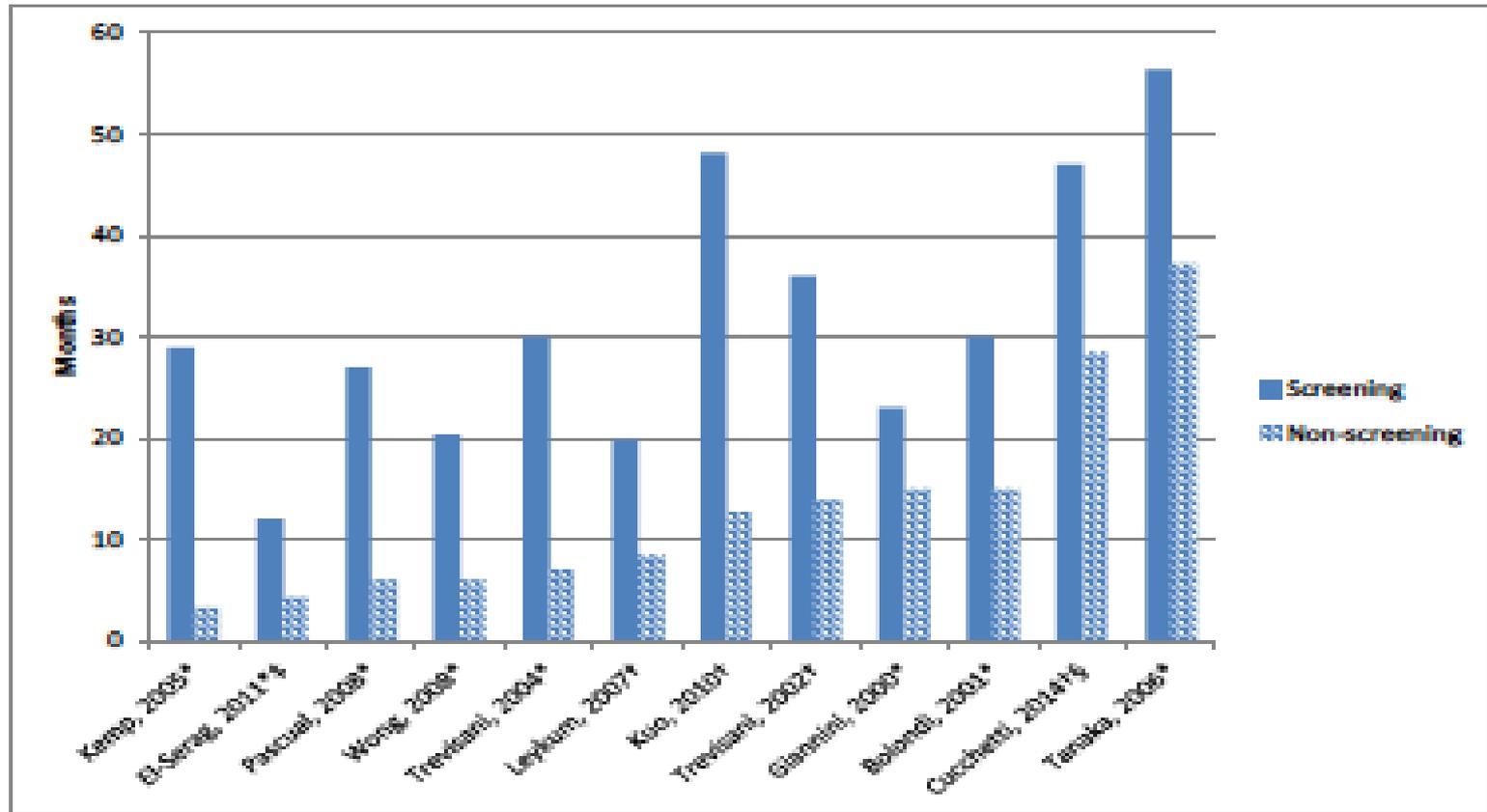
Effect of screening on mortality – observational studies

- 18 mostly single-center, retrospective studies across a range of geographic settings
- Most included patients with hepatitis B or C
 - Majority of patients had Child A or B cirrhosis, though control groups tended to have more severe liver disease
- Ultrasound with or without AFP was the screening modality in nearly all studies

Observational studies - findings

- Screened patients had earlier-stage HCC
 - 60-100% screened patients vs 19.6-56.5% clinically diagnosed patients
- More screened patients received treatments such as RFA, resection, or transplant
 - Relatively few patients overall underwent hepatic resection or transplant
- Screened patients tended to have longer median survival from the time of diagnosis
 - A recent meta-analysis of observational studies found similar results (3-yr survival OR 1.9, 95% CI 1.67-2.17)

Figure 2. Median survival in cohort studies of HCC patients diagnosed through screening programs compared with no screening



* P < 0.05

† P-value was not reported.

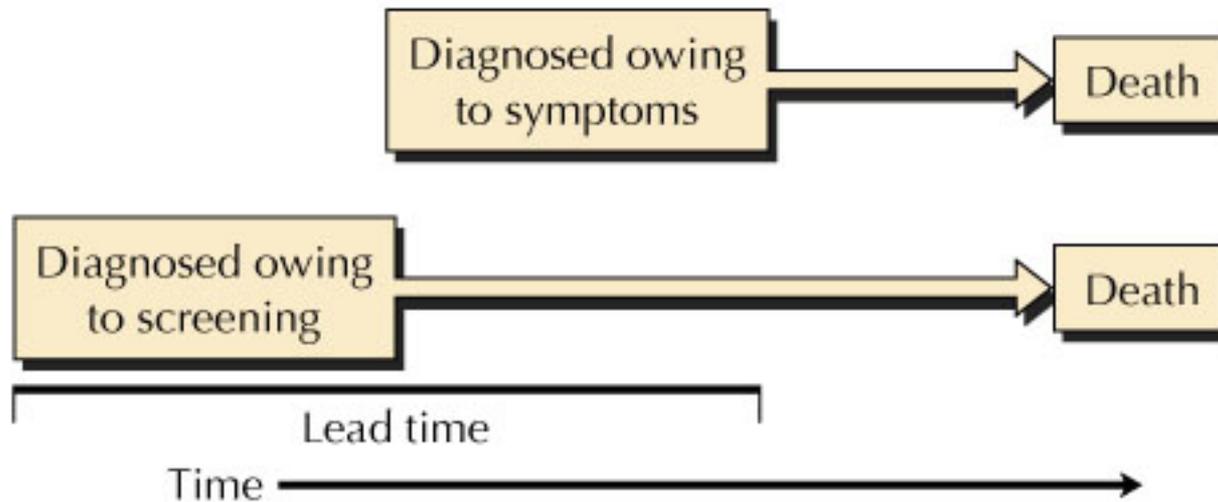
‡ Screening group includes patients screened at both 0-6 and 7-24 month intervals before HCC diagnosis.

§ Sixty-one percent of screening group received semi-annual surveillance; 17% received annual surveillance.

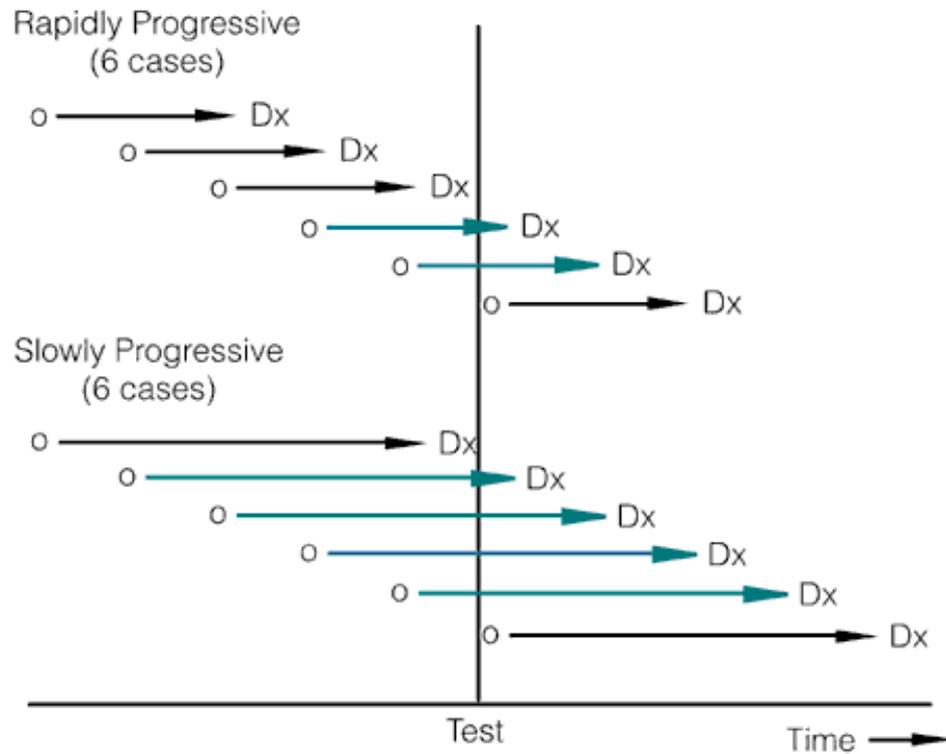
Methodologic issues of observational studies

- Retrospective, single center
- Unclear assessment of screening status
- Selection bias
- Unclear follow-up
- Lead-time and length-time bias

Lead-time bias



Length-time bias



o = Time of disease onset.

Dx = Time when disease is clinically obvious without testing.

Lead-time bias in observational studies

- 5 studies attempted to adjust for lead-time bias
 - In 3 studies, survival advantage disappeared when the tumor doubling time was assumed to be 90-120 days or longer
 - In another study, lead-time did not account for all the survival advantage
 - A recent study found that lead-time accounted for survival advantages seen over 3 years, but not over longer periods of time

El-Serag HB, Gut, 2011

Tanaka H, Liver Int, 2006

Tong MJ, Dig Dis Sci, 2010

Wong GL, Liver Int, 2008

Cucchetti A, J Hepatol, 2014

Trials comparing screening intervals

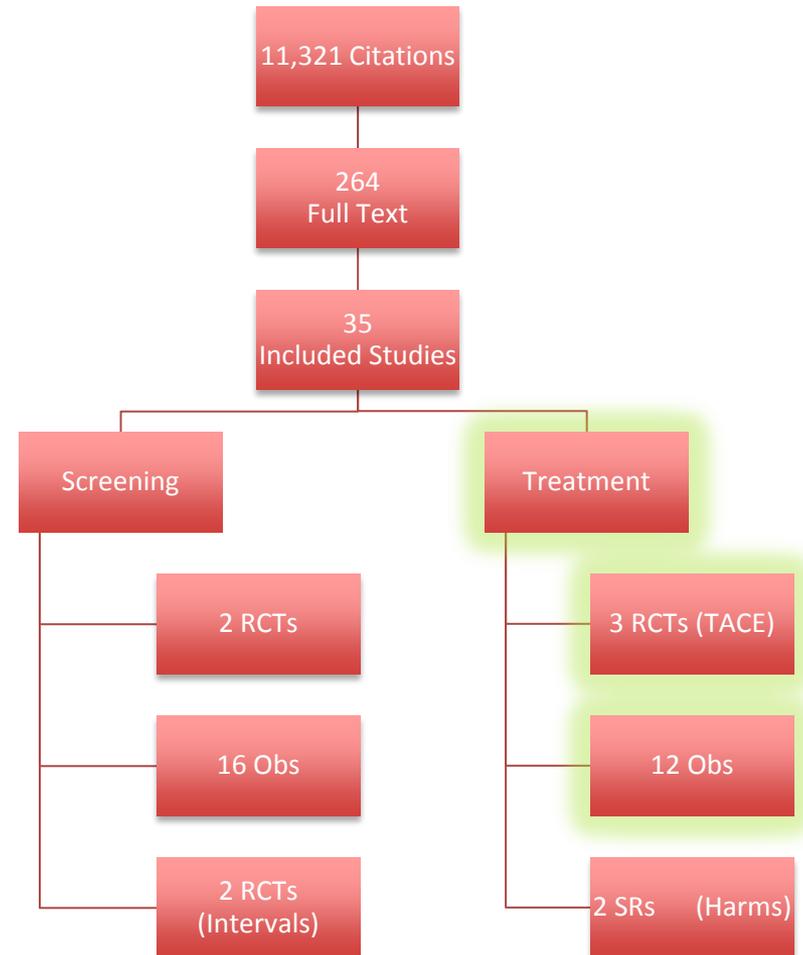
- 4 vs 12 month interval
 - Frequent screening found more very early-stage tumors (37.6 v 6.7%)
 - More patients underwent curative rx
 - No difference in 4 year survival
- 3 vs 6 month interval
 - More small focal lesions were detected
 - No difference in HCC detection
 - No difference in mortality

Harms of Screening

- Potential harms of screening:
 - Physical effects of screening (probably low)
 - Further testing triggered by positive screen
 - Needle-track seeding: 2.7%
 - Contrast-enhanced CT: 13-15%
 - Overdiagnosis
 - Psychological effects of positive screen
- None of the included studies reported harms of screening

Effects of Treatment on Mortality

- No studies specifically enrolled patients with screen-detected HCC
- Examined studies with early stage HCC as an approximation



Effects of Treatment on Mortality - RCTs

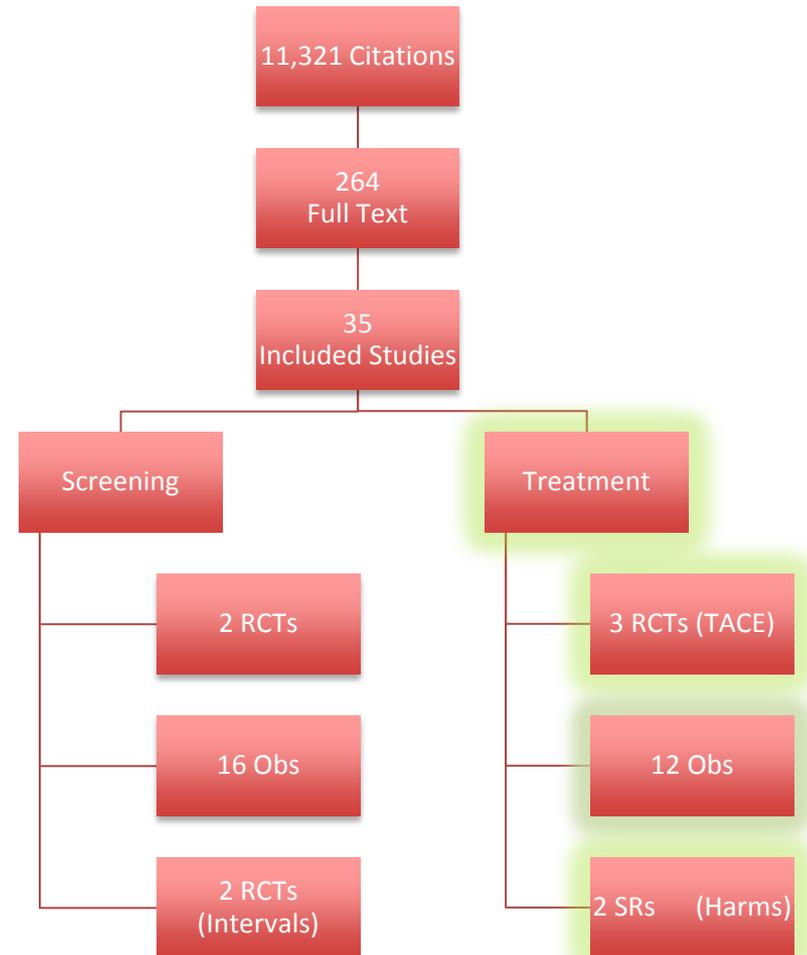
	Groupe d'Etude 1995	Pelletier 1990	Lo 2002
Population	EtOH	EtOH	HBV
N (TACE vs Supportive)	50 vs 46	21 vs 21	40 vs 39
Results (Adjusted)	No survival benefit (RR 0.77, 95% CI 0.48-1.25)	No survival benefit	Improved survival with TACE (RR 0.49, 95% CI 0.29-0.81)
Harms	Stopped due to deaths in both arms	2 deaths (Renal failure and GIB)	38 patients had treatment stopped
Risk of bias	Low	Unclear	Unclear

Effects of Treatment on Mortality – Observational Studies

- Patients receiving treatment with OLT, resection or RFA had good long-term (4-5 year) survival
 - OLT – 40-73%
 - Resection – 40-70%
 - RFA – 27-77%
- 5 comparative observational studies
 - Difficult to draw conclusions given heterogeneity of treatments examined
 - One study found lower mortality in patients selected for resection after adjusting for tumor and basic demographic characteristics (HR 0.45; 95% CI 0.34-0.59)

Harms of Treatment

- Serious harms:
 - TACE 8-20%
 - Resection 4% periop mortality
 - RFA 3.2% needle-track seeding; 1.8-9.9 other serious complications



Summary of results

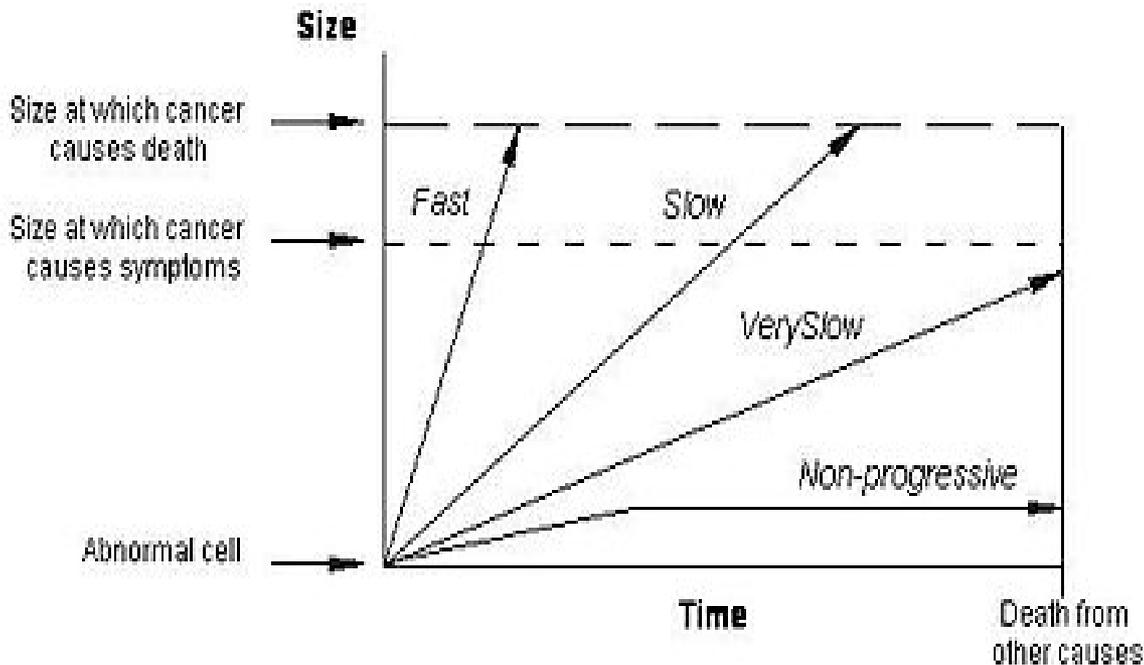
- Overall, evidence about the balance of mortality benefits and harms of screening for hepatocellular carcinoma is inconclusive
 - No methodologically sound trials of ultrasound screening
 - Observational studies limited by lead-time, length-time, and selection biases

Summary of results

- Screening can identify HCC at earlier stages and long-term survival in patients selected for curative therapy is often good
- The harms of screening have not been well studied
- Treatment of HCC can be associated with serious harms in 3-20% of patients

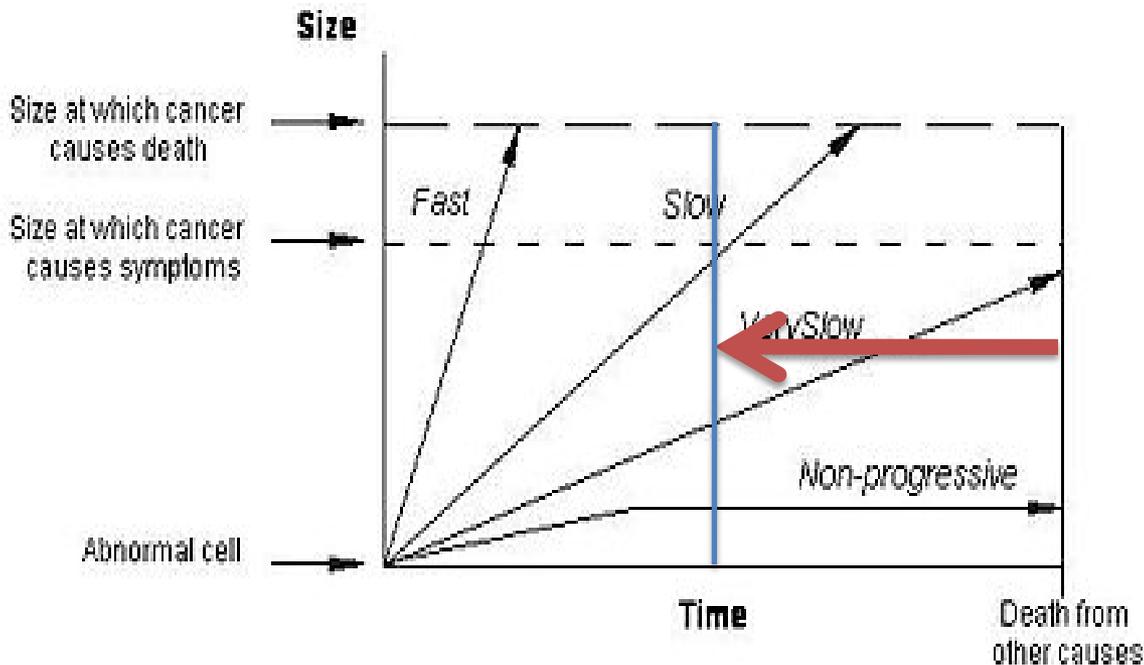
Discussion

- Net balance of benefits and harms depends in part on the natural history of HCC



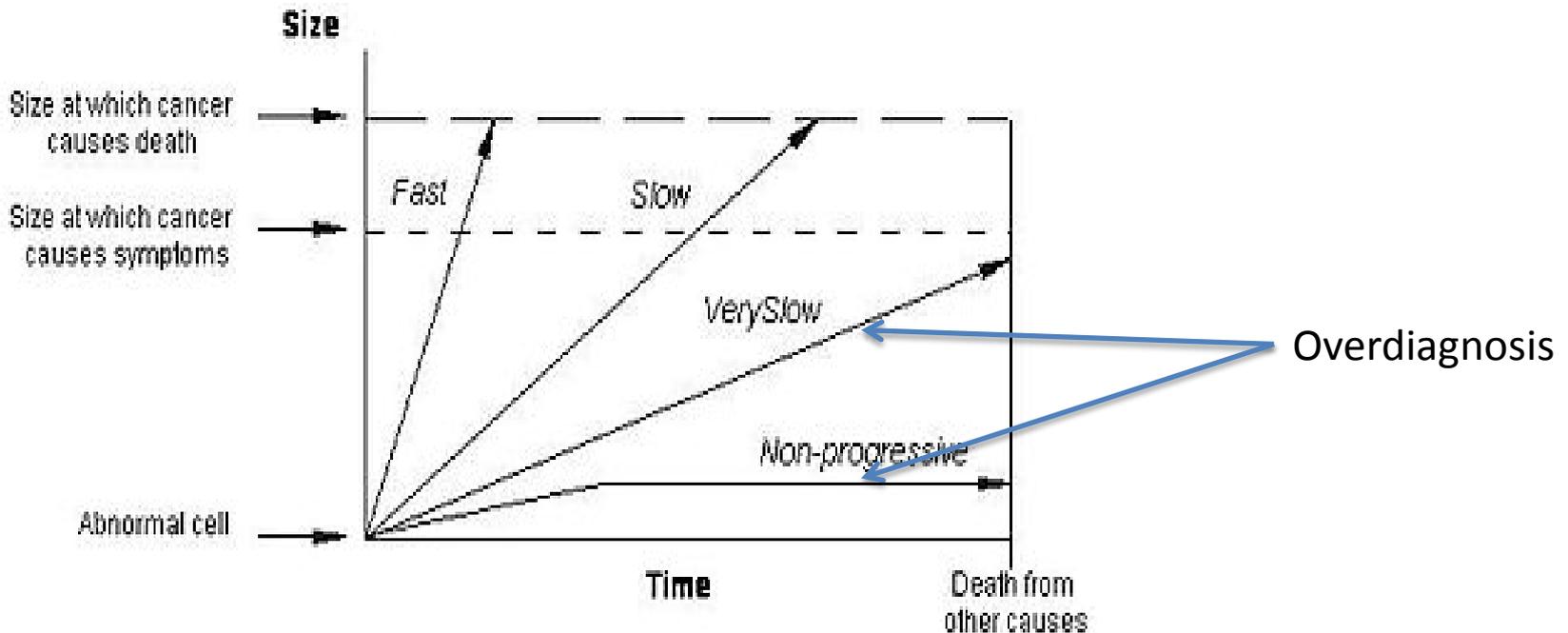
Discussion

- Net balance of benefits and harms depends in part on the natural history of HCC



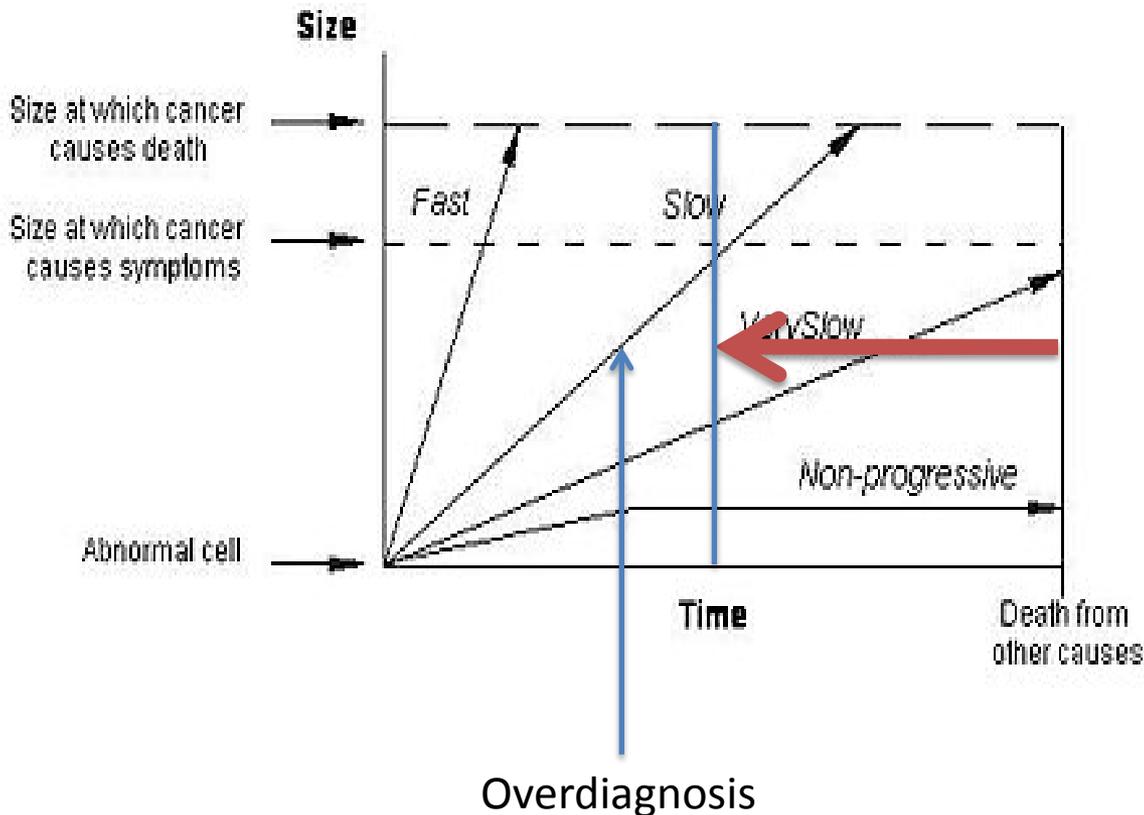
Discussion

- Net balance of benefits and harms depends in part on the natural history of HCC



Discussion

- Net balance of benefits and harms depends in part on the natural history of HCC



Discussion

- With more widespread screening, better imaging, what is the natural history of smaller lesions identified?
 - No direct evidence
 - Trial comparing 4 to 12 month screening intervals
 - More frequent screening identified more small tumors
 - More patients underwent curative rx, but survival did not differ

Discussion

- Natural history of screen detected HCC is unclear
 - Does early diagnosis and subsequent treatment of HCC alter the natural history of an aggressive HCC?
- New therapies for HCV also have the potential to alter the incidence and natural history of HCC

Implications

- “Absence of evidence is not evidence of absence”
 - Transparency about the strength of evidence is still important, however
 - Future research
 - Shared decision making
- Policy/guideline recommendations are based on many factors
 - Strength of evidence
 - Balance of benefits and harms
 - Patient values and preferences
 - Clinician expertise
 - Resource use considerations

Implications

- Important to minimize potential harms, maximize potential benefits
 - Target high-risk patients
 - Understand patient candidacy for treatment if HCC is found
- Given the overall very low strength of evidence, further research is very likely to be important

Questions?

If you have further questions,
feel free to contact:

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Devan.Kansagara@va.gov

The full report and cyber seminar presentation is available on the ESP
website:

<http://www.hsrdr.research.va.gov/publications/esp/>

The manuscript version of this research is: Kansagara D et al, Ann Int
Med, 2014 [E-pub ahead of print]

VA National Oncology Program Perspective

Michael Kelley MD

Current State

- Screening for HCC is common in VHA
 - 56% of the approximately 25 000 patients with cirrhosis and chronic hepatitis C in VHA had at least 1 imaging test within the past 12 months
- Insufficient evidence for or against screening

Harms of Screening

- Overdiagnosis. ~20% in breast and lung cancer screening
- Morbidity and mortality of “extra” treatment administered to screening patients who do not derive survival benefit from screening
- Anxiety and worry
- Time and cost to patient and society

Research Concepts (other than RTC)

- Cohort study
 - Patients eligible for screening (candidates for curative-intent treatment)
 - Collect baseline clinical variables
 - Long-term follow-up for all patients
 - Control for known and measurable independent variables
 - Instrumental variable or propensity scoring
 - Modest putative effect size of screening limits possible strength of conclusion

- Update cost-efficacy analyses
 - Current cost data
 - VHA adherence rates to screening and treatment
 - VHA long-term survival
 - Identify the necessary mortality benefit to make screening cost-effective
 - Is this magnitude of benefit consistent with estimation of HCC screening's possible benefit?

- Refine identification of HCC risk
 - Clinical models
 - Biomarkers
- Refine prognostication and therapeutic response prediction for HCC
 - Identify those who need treatment (bad prognosis) and for whom current treatment is most likely to improve survival (prediction)

Policy Implications

- First, do no harm
- Current screening should not be expanded
- New screening programs should not be initiated
- Allow clinicians to offer screening
 - High risk of HCC
 - Good candidates for curative-intent treatment
 - Shared decision-making including explicit acknowledgement of limitation of evidence and potential for harm in addition to possible benefit

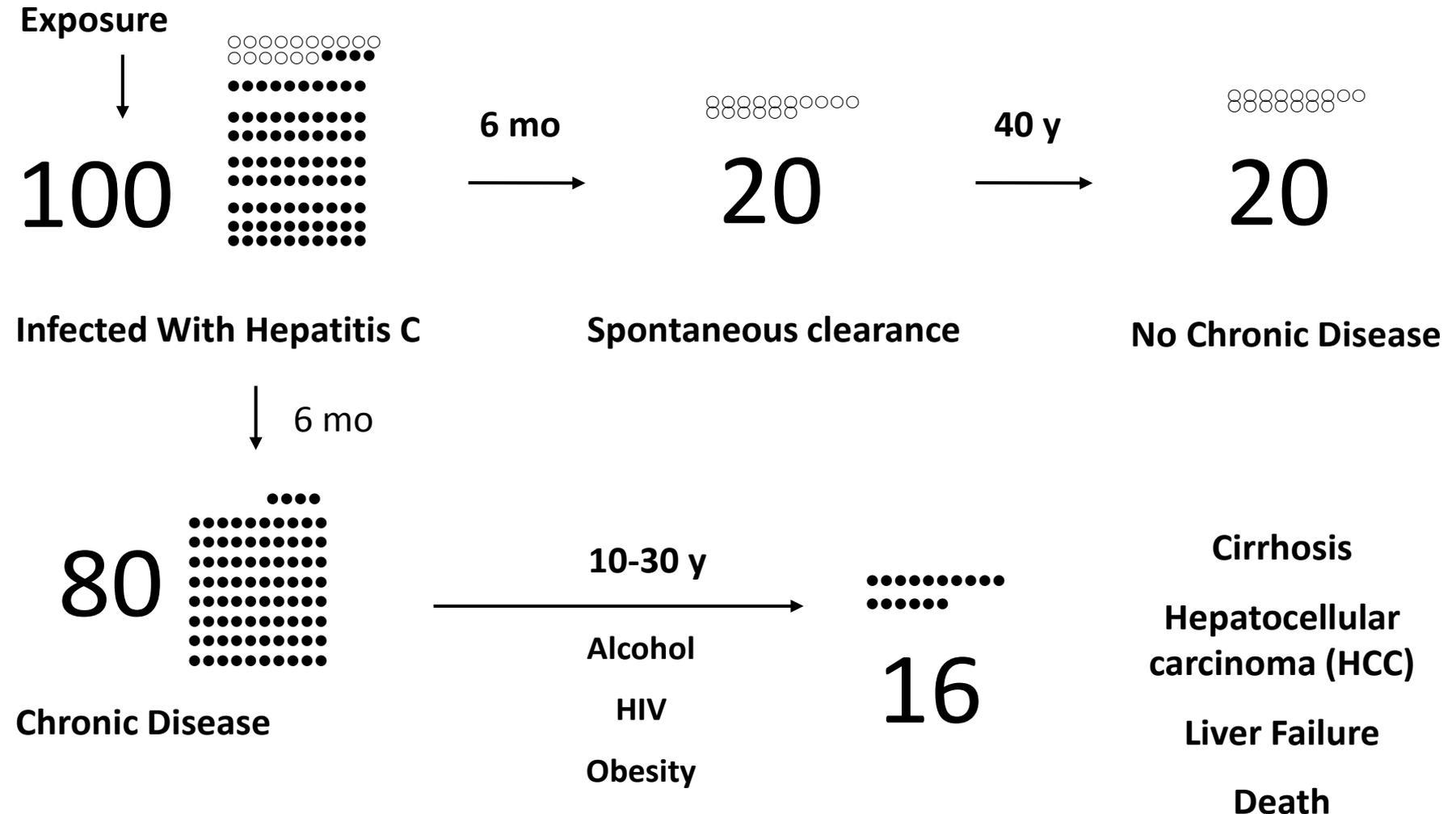
VA National Viral Hepatitis Program Perspective

David Ross, MD, PhD, MBI

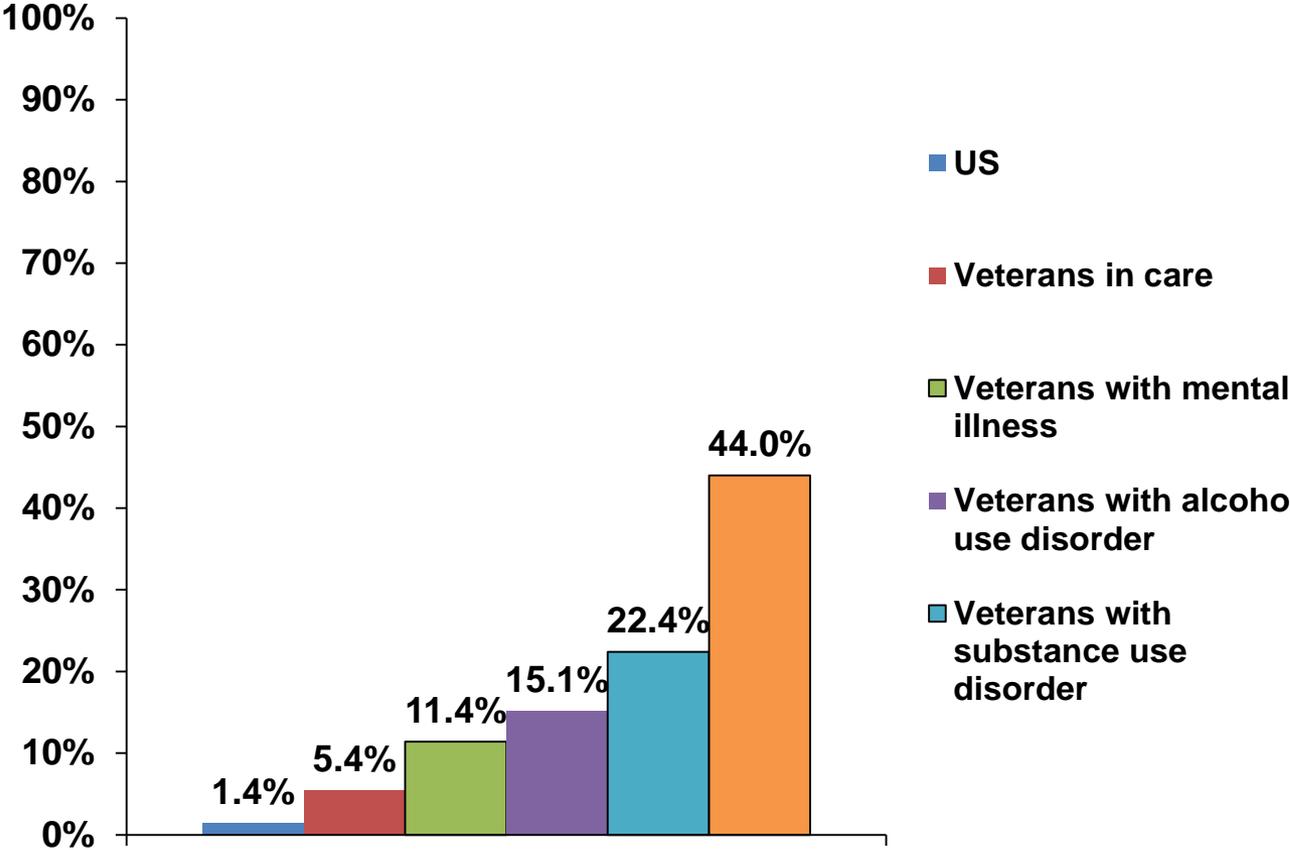
Key points

- VA patients at risk for hepatocellular carcinoma have a cumulative risk comparable to breast cancer risk in women with *BRCA1* mutations
- There is a limited window of opportunity to diagnose and treat the VA population at risk for HCC
- Early HCC can be treated effectively
- HCC surveillance is the standard of care for at-risk patients in the US
- Veterans deserve the same access to standard of care as other US patients

HCV: Natural history

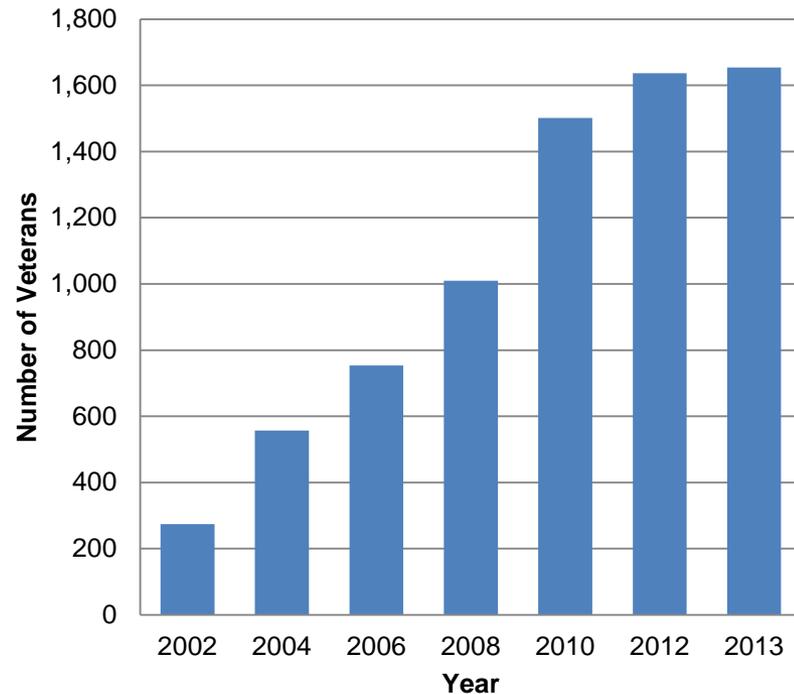


HCV is a major clinical and public health issue for VA

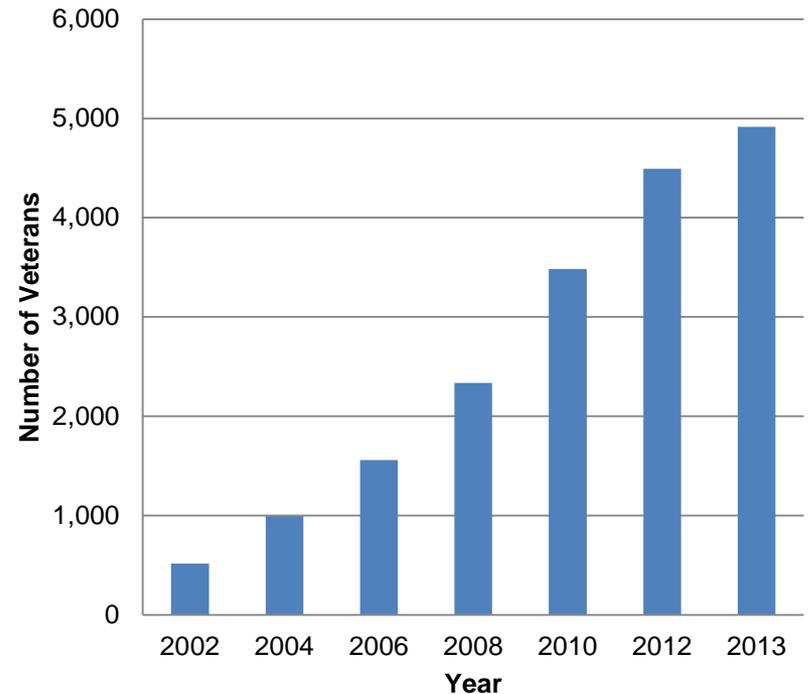


The incidence and prevalence of HCC in VA HCV patients is skyrocketing

HCV+ Veterans with first diagnosis of HCC



HCV+ Veterans ever diagnosed with HCC



HCC median survival differs by stage at diagnosis

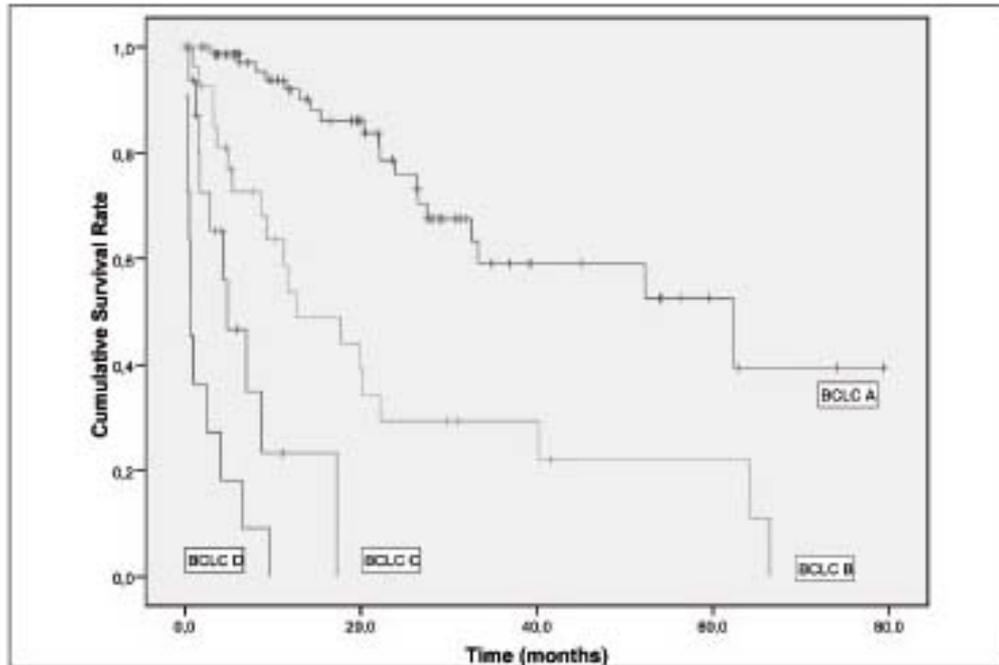
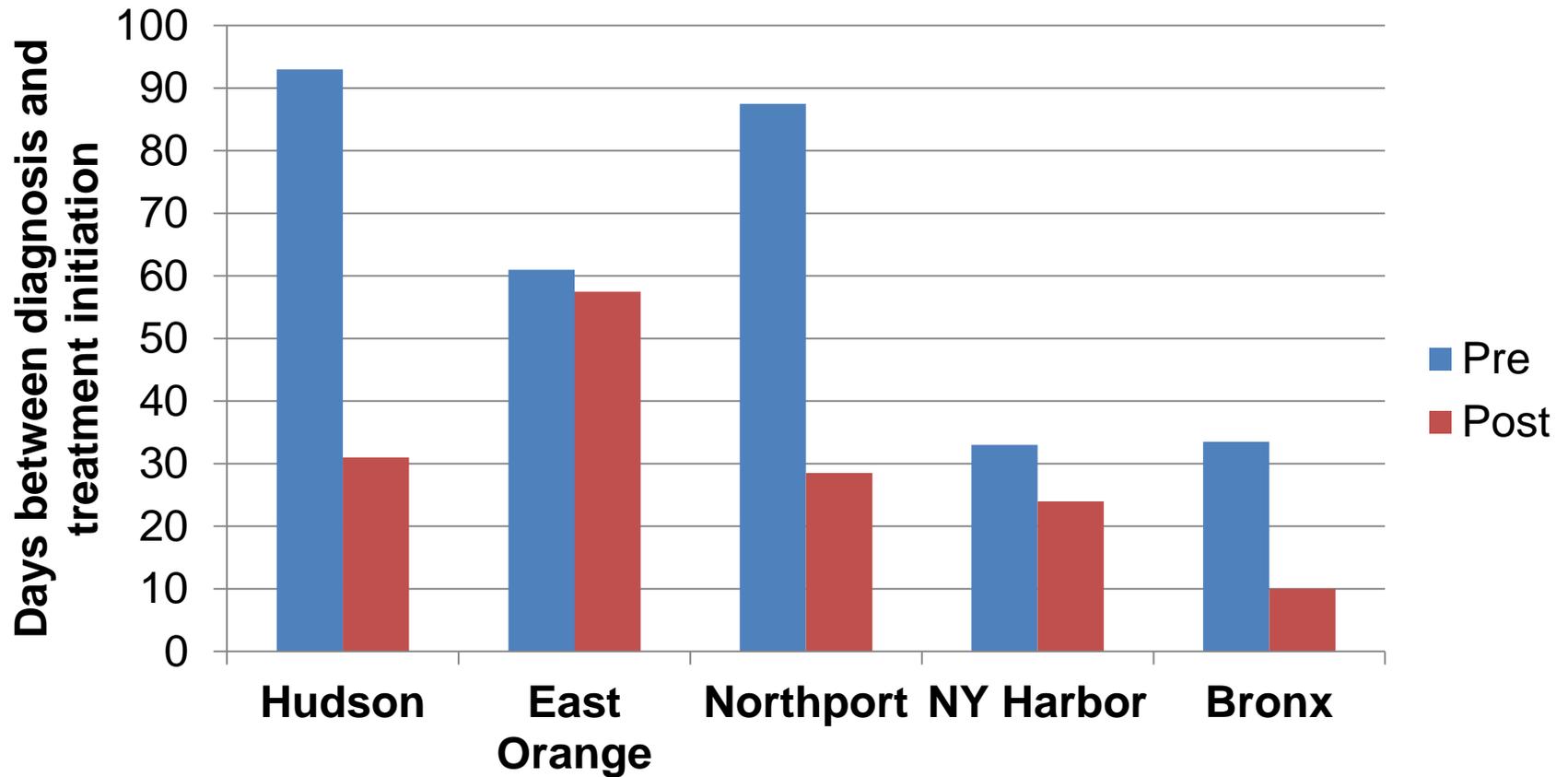


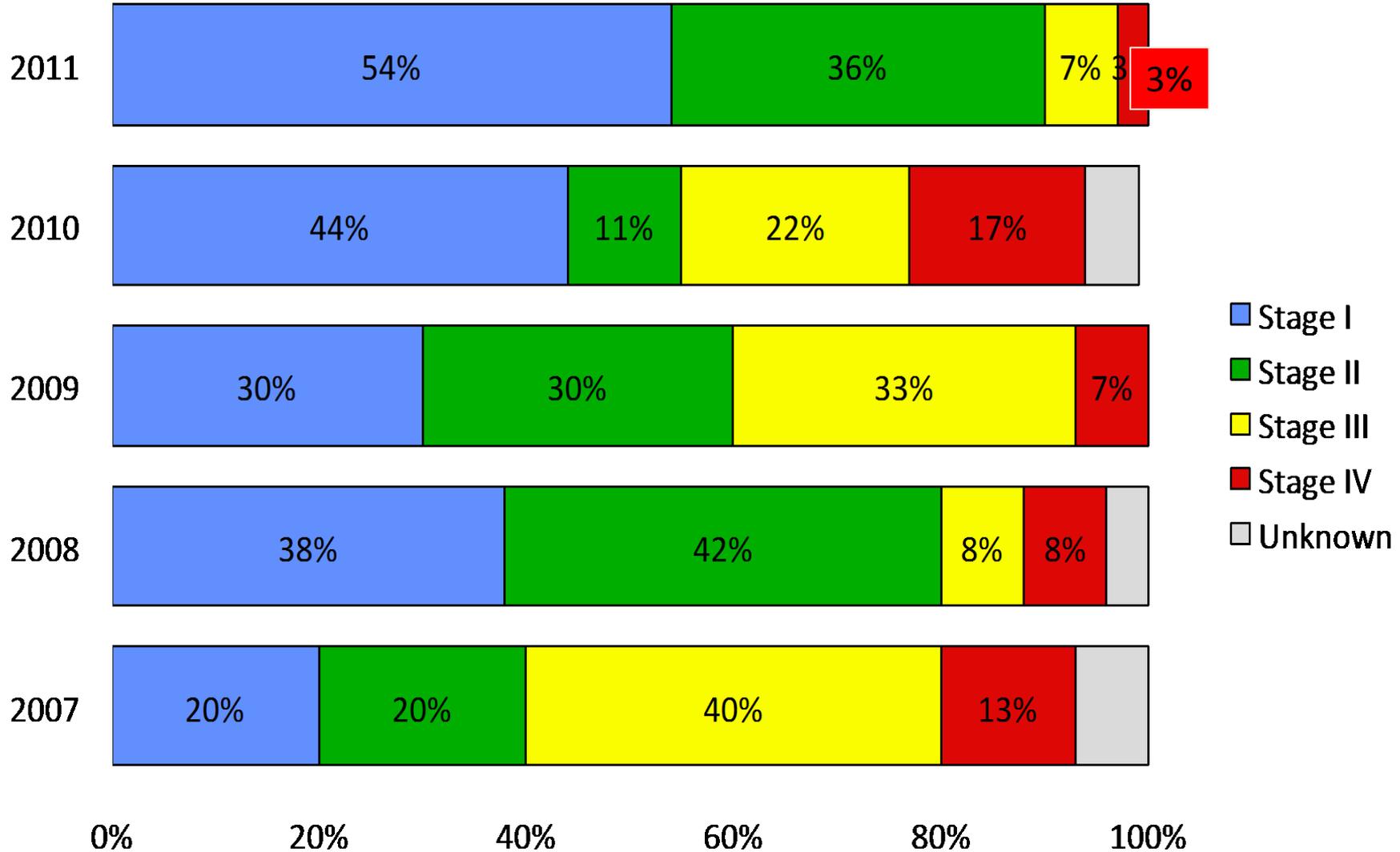
Fig. 2. Survival according BCLC system. There were statistically significant differences in survival rates among each group ($p < 0.0001$). BCLC: The Barcelona Clinic Liver Cancer.

- BCLC stage
 - A: 6 y
 - B: 20 m
 - C: 10 m
 - D: <3 mo
- VA
 - Median: 10 mo
 - 5 years: 8%

Delays in HCC diagnosis and treatment are due to inadequate programs



Finding Liver Cancer At Earlier Stages



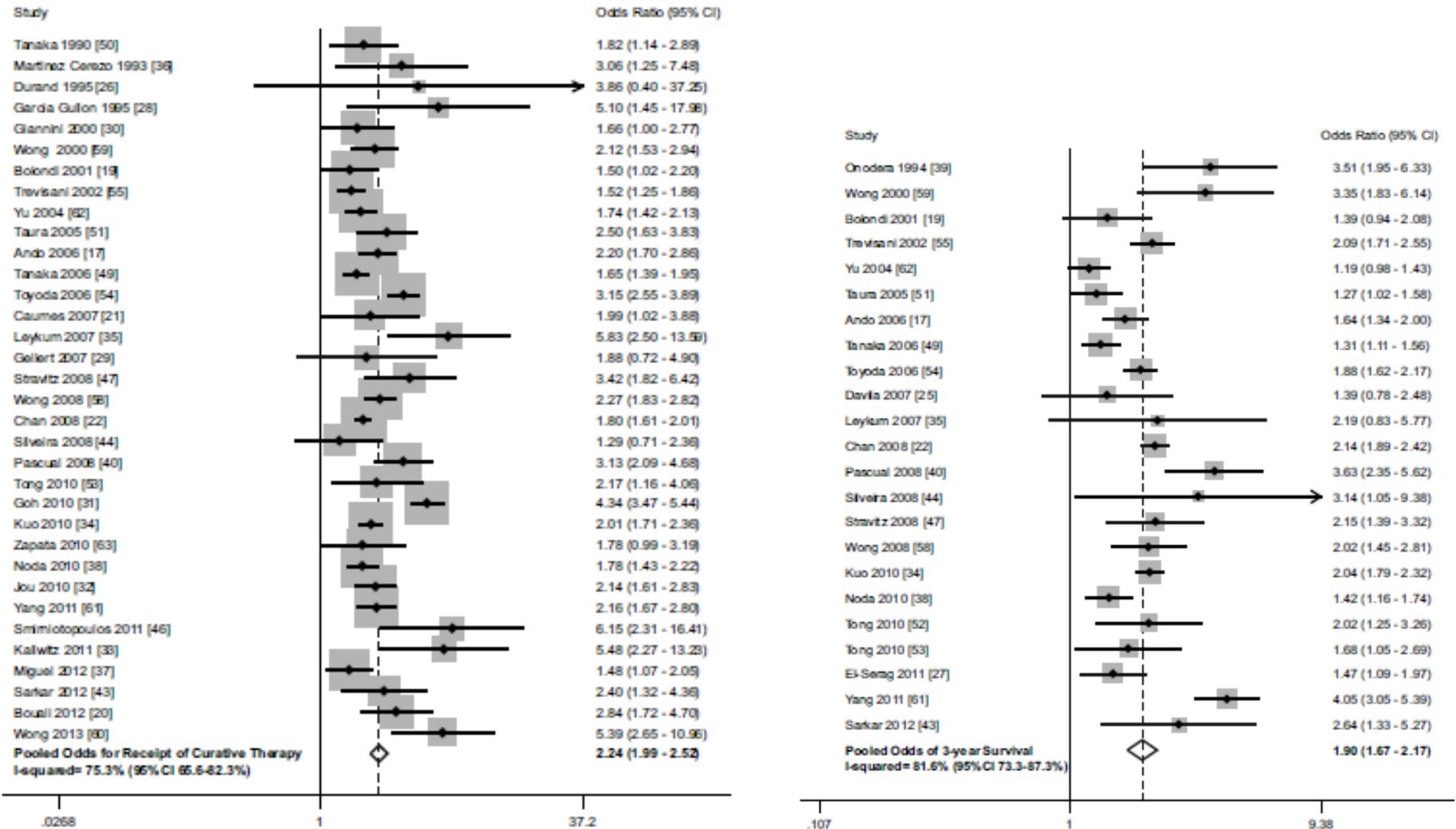
T. Taddei, unpublished

Major limitations of evidence synthesis

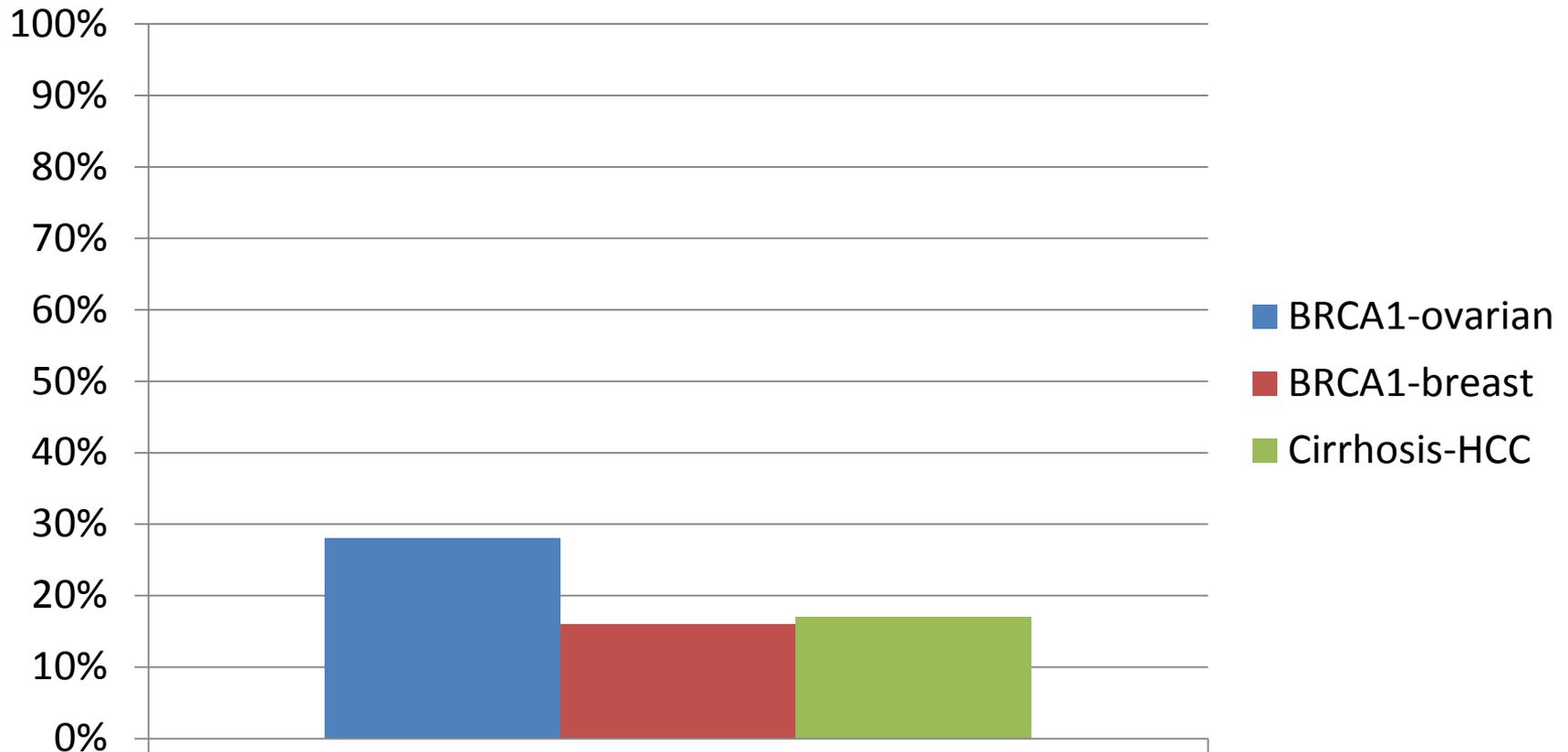
- Surveillance
 - Natural history assumed to be highly heterogeneous
 - Biopsy assumed to be major diagnostic platform
 - Hypothetical harms not quantified or modeled with regard to morbidity or mortality
- Treatment
 - Natural history assumed to be highly heterogeneous, artificially inflating significance of confounding by indication
 - Active-controlled trials largely excluded

Is Screening Controversial?

Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: A meta-analysis.



Cumulative cancer incidence in high-risk populations



Liede A, *et al.*. J Clin Oncol. 2002 Mar 15;20(6):1570-7; Fattovich G, *et al.* Gastroenterol 2004 Nov;127(5 Suppl 1):S35-50.

Other cancer screening practices with “insufficient evidence”

- Ovarian cancer - Regular transvaginal ultrasonography and CA125 testing for women with *BRCA1* or mismatch repair gene mutations
- Breast cancer – Annual mammography and/or breast MRI for women with *BRCA1* or *BRCA2* mutations
- Colon cancer - Flexible sigmoidoscopy starting at age 10 for patients with familial adenomatous polyposis
- Colon cancer – FOBT for average risk patients prior to 1995

Do no harm ≠ Do nothing

- Current outcomes from HCC in VA are awful.
- Mean age of VA HCV patients is 56 years: Results from a RCT or prospective cohort study may be uninterpretable. They certainly will be moot.
- Imperfect evidence is not the same as insufficient evidence. Suspending surveillance in VA because of a single study that the evidence is “insufficient” is not acceptable.
- VA’s strategic plan for HCC cannot be to stop looking for it.
- HCC surveillance is the standard of care in the US. VA cannot unilaterally announce its own standard of care.