UMC Utrecht

Surveillance for hepatocellular carcinoma: current practice and future developments

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Disclosure of speaker's interest

- No (potential) conflict of interest

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Outline of presentation

1. Background

2. Evidence that surveillance reduces HCC mortality

3. Tools for surveillance

4. Effectiveness of HCC surveillance in clinical practice

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1. **Background**
2. Evidence that surveillance reduces HCC mortality
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Hepatocellular carcinoma (HCC)

- Most frequent form of primary liver cancer
- 90% of patients have underlying chronic liver disease (cirrhosis)
- Worldwide: 5th most common cancer, 3th cancer-related mortality (approx. 650,000 deaths each year: 50% in China)
- In the Netherlands: relatively low HCC incidence, but increasing (NAFLD, immigrants)

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Patient and clinical characteristics of 1223 HCC patients (approx. 60% of all HCC patients in the Netherlands) in the period 2005-2012

Patient nr	1223 (100%)
Etiology	
Chronic viral hepatitis	
- Hepatitis B	197 (16%)
- Hepatitis C	249 (20%)
- Co-infection	19 (2%)
Hemochromatosis	37 (3%)
Alcohol	349 (29%)
NAFLD	134 (11%)
Others	42 (3%)
No risk factors	196 (16%)

Van Meer et al. Eur J Gastroenterol Hepatol. 2016;28:352-9

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- 90% of patients have underlying chronic liver disease (cirrhosis)
- Worldwide: 5th most common cancer, 3th cancer-related mortality (approx. 650,000 deaths each year: 50% in China)
- In the Netherlands: relatively low HCC incidence, but increasing (NAFLD, immigrants)
- Prognosis in general poor: in 2011, in the Netherlands 47% of all patients any treatment, 20% resection or transplantation, 10% RFA (van Meer *et al*. Ned Tijdschr Geneeskd. 2014;158:A7074)

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CHANGE

Surveillance in cancer

Definition:

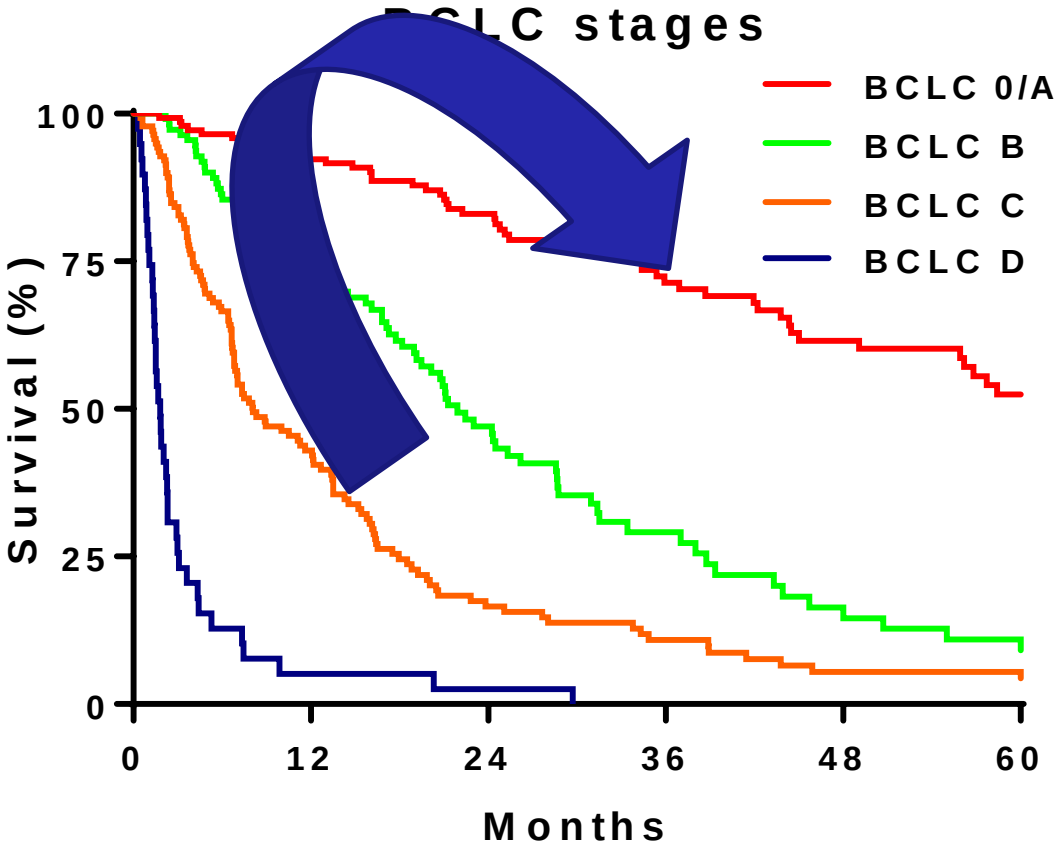
Repeated application of a test over time with the aim of reducing disease-specific mortality

Criteria:

1. Common disease with substantial morbidity and mortality
2. Identification of the target population
3. Screening test is acceptable
4. Screening test with low morbidity and high diagnostic accuracy
5. Well-defined recall strategy

Prorok PC. Am J Pediatr Hematol Oncol. 1992;14:117-28.

Aim of surveillance: HCC detection at earlier stage may improve outcome



Bruix J et. Al, Gastroenterology 2016; 150:835-853

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Welke patienten moet surveillance voor hepatocellulair carcinoom aangeboden worden?

- A) alle patienten met levercirrose
- B) high risk patienten met levercirrose + high risk hepatitis B “dragers” zonder cirrose
- C) alle patienten met levercirrose bij wie evt HCC behandeling mogelijk is
- D) high risk patienten met levercirrose + high risk hepatitis B “dragers” zonder cirrose wie evt HCC behandeling mogelijk is

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Current recommendations for HCC surveillance
(only ultrasound at 6-month interval)

Cirrhosis		
Hepatitis B cirrhosis		
Hepatitis C cirrhosis		
Hemochromatosis cirrhosis		
Alcoholic cirrhosis		
Stage 4 primary biliary cholangitis		
No cirrhosis		
East asian male hepatitis B carriers over age 40		
East asian female hepatitis B carriers over age 50		
African/North Am. Blacks >20 yrs		
Hepatitis B carrier with family history of HCC		

AASLD: Dutch Guidelines

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HCC surveillance: randomized controlled trials

-Cirrhosis: NONE

-Hepatitis C: NONE

-Hepatitis B (mainly carriers):

2 trials from China:

one showed no benefit (AFP alone every 6 months)

one showed benefit (ultrasound + AFP every 6 months)

-other underlying causes of liver disease: NONE

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HCC surveillance: randomized controlled trials

-Cirrhosis: NONE

-Hepatitis C: NONE

-**Hepatitis B (mainly carriers):**

2 trials from China:

one showed no benefit (AFP alone every 6 months)

one showed benefit (ultrasound + AFP every 6 months)

-other underlying causes of liver disease: NONE

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Randomized controlled study from China

-5581 HBV carriers randomized to AFP determination at 6-month intervals or control group.

-HCC related mortality rates not significantly different (1138/100,000 vs 1114/100,000, P=0.86)

Chen et al. J Med Screen 2003;10:204

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Rationale for surveillance in HCC

- 18,816 HBV+ patients recruited in China
- Randomized to:
  - Surveillance by US/6 months + AFP
  - No surveillance
- Cluster randomization
- Adherence: 60%
- HCC-related mortality was reduced by 37% in the surveillance arm

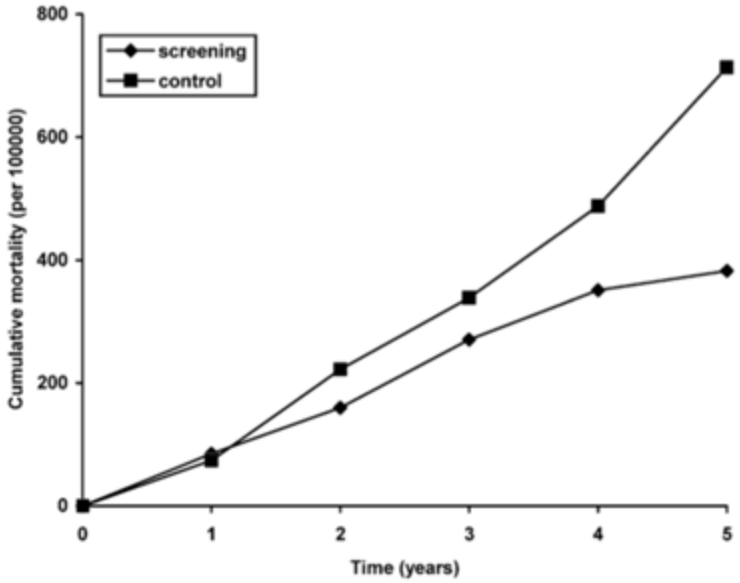

Fig. 5 Cumulative survival in different stages HCC patients

Zhang BH et al. J Cancer Res Clin Oncol. 2004;130:417-22.

Effect of HCC surveillance: lower level evidence

- Several non-randomized trials and observational and case-control studies from high incidence countries

McMahon BJ et al. *Hepatology* 2000; **32:** 842-846
Wong LL et al. *Liver Transpl* 2000; **6:** 320-325
Gebo KA et al. *Hepatology* 2002; **36:** S84-S92
Solmi L et al. *Am J Gastroenterol* 1996; **91:** 1189-1194

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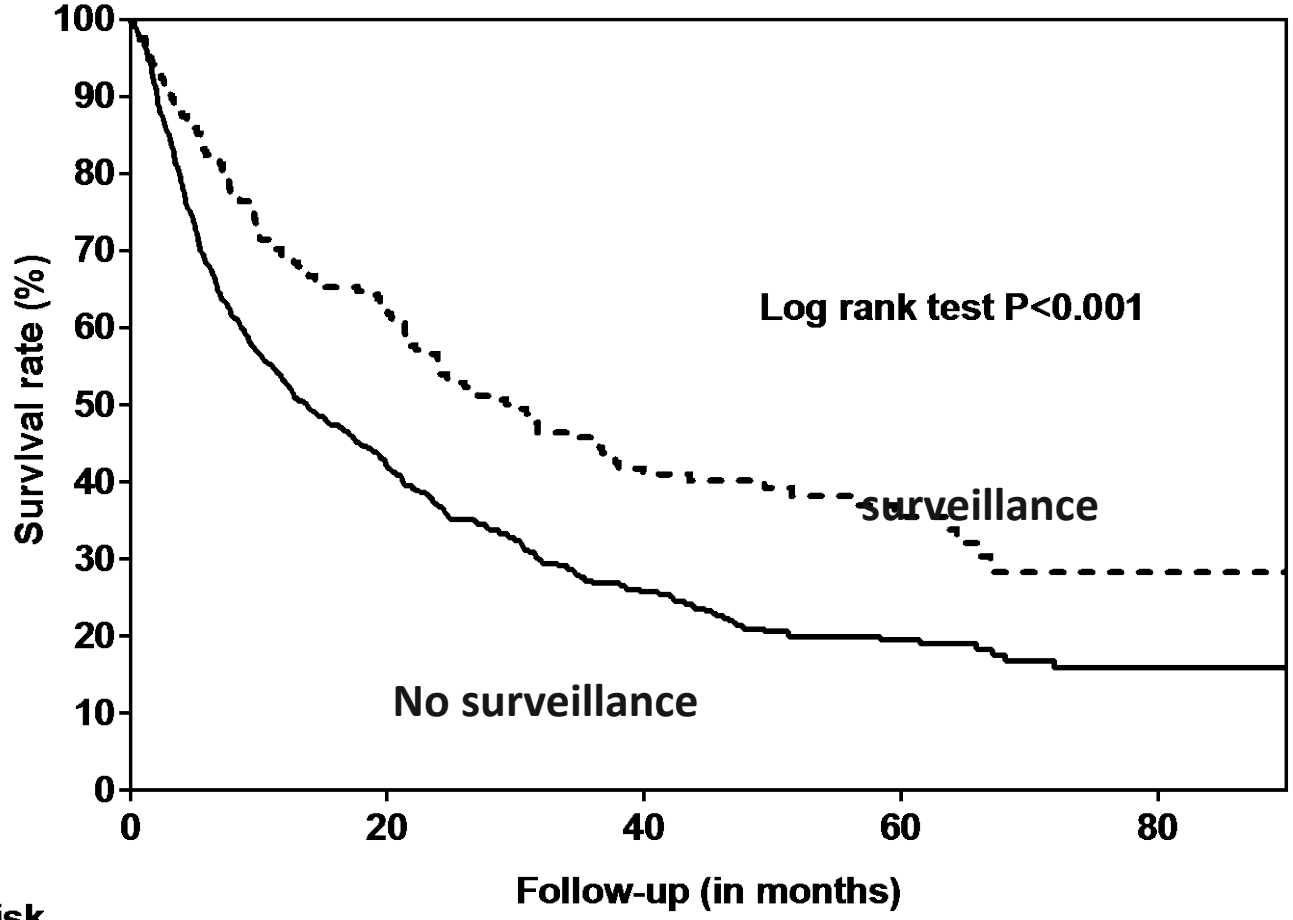
Results from a large cohort in the Netherlands: surveillance independent predictor of survival



Number at risk					
Surveillance:	279	123	57	24	6
Non-surveillance:	720	216	86	43	8

Van Meer et al. J Hepatol. 2015 Nov;63(5):1156-63

Clinical and tumor characteristics in the surveillance and non-surveillance groups

In the surveillance group:

- tumor size significantly smaller (2.7 cm vs 6 cm)
- AFP level significantly lower (16 vs 44 µg/L)
- earlier tumor stage (BCLC 0 and A combined: 61% vs 21%)
- resection/transplantation (34% vs 25%) and RFA (23% vs 7%) more often applied

Van Meer et al. J Hepatol. 2015 Nov;63(5):1156-63

Patient characteristics surveillance and non-surveillance groups

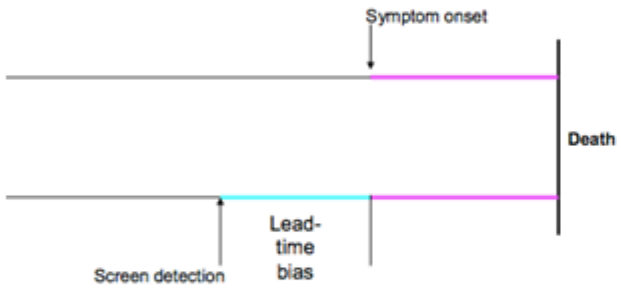
	Surveillance group	Non-surveillance group	P-value*
Patient no.	295 (27%)	779 (73%)	
Male gender	229 (78%)	585 (75%)	0.387
Age at HCC diagnosis (median, range)	**60 (19-90)**	**64 (8-91)**	<0.001
Etiology			<0.001
Chronic viral hepatitis			
- HBV	**58 (20%)**	**113 (14%)**	
- HCV	**113 (38%)**	**93 (12%)**	
- Co-infection	8 (3%)	8 (1%)	
Hemochromatosis	2 (1%)	18 (2%)	
Alcohol	71 (24%)	235 (30%)	
NAFLD	**22 (7%)**	**154 (20%)**	
Others	13 (4%)	20 (3%)	
No risk factors known	**8 (3%)**	**138 (18%)**	
Presence of cirrhosis	**286 (97%)**	**470 (60%)**	<0.001
Results indicate nrs and, between brackets, percentages, unless otherwise indicated.			

Van Meer et al. J Hepatol. 2015 Nov;63(5):1156-63

Rationale for surveillance in HCC

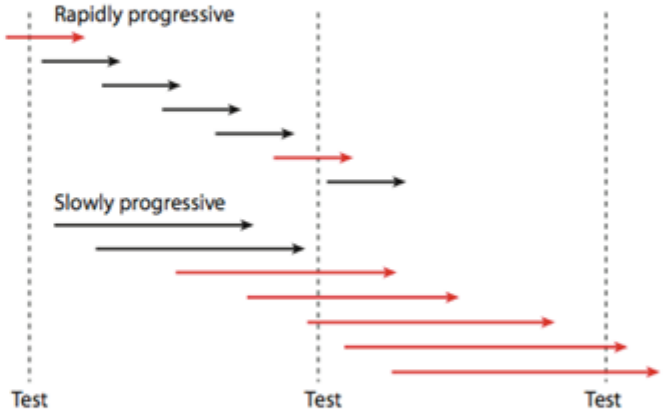
Uncontrolled studies are affected by several biases:

Lead-bias



Early detection advances what would have been the original date of diagnosis to an earlier point in time, but it does not necessarily follow that the patient's time of death will be delayed

Length-bias



Early diagnostic tools are more likely to pick up less aggressive lesions than rapidly lethal lesions

Croswell J et al. Semin Oncol 2010;37:202-15.
Kramer B et al. Annu Rev Med 2009;60:125-37.

Rationale for surveillance in HCC

Risk of overdiagnosis: the detection of cancer that would have otherwise not been identified in a patient's lifetime:

- Breast cancer: 15-25%
- Prostate cancer: 23-60%
- Lung cancer: 25%
- Thyroid cancer
- Renal cancer
- Neuroblastoma
- ...

Randomized controlled trials are needed to confirm the efficacy of surveillance in HCC!!!!

Sandhu G et al. J Natl Cancer Inst Monograph. 2012;45:146-51.
Veronesi G et al. Ann Intern Med 2012;157:776-84.
Welch, Black. J Natl Cancer Inst. 2010;102:605-13.

Rationale for surveillance in HCC

National Cancer Institute
at the National Institutes of Health

Benefits

Based on fair evidence, screening would not result in a decrease in mortality from hepatocellular cancer.

Magnitude of Effect: No reduction in mortality.

Study Design: Randomized controlled trials.
Internal Validity: Fair.
Consistency: Multiple studies, large number of participants.
External Validity: Fair.

Annals of Internal Medicine | IDEAS AND OPINIONS

Screening for Liver Cancer: The Rush to Judgment

Frank A. Lederle, MD, and Christine Pocha, MD, PhD

RCTs are requested in non-Asiatic populations

www.cancer.gov/cancertopics/pdq/screening/hepatocellular/HealthProfessional/page1.

Lederle FA, Pocha C. Ann Intern Med. 2012;156:387-9.

Rationale for surveillance in HCC

- The authors tested the feasibility of conducting a randomized controlled trial of HCC surveillance in patients with cirrhosis in Australia
- The proposed screening program comprised ultrasonography 6 monthly and serum alpha-fetoprotein every 3 months
- Among 205 patients, 204 (99.5%) declined randomization

A randomized study of HCC screening is not feasible when informed consent is required

Poustchi H et al. Hepatology 2011:54:1998-2004

Outline of presentation

1. Background

2. Evidence that surveillance reduces HCC mortality

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Hoe moet surveillance voor HCC verricht worden?

- A) Echografie elke 6 maanden
- B) Echografie elke 12 maanden
- C) Echografie + alfafoetoproteine elke 6 maanden
- D) Echografie + alfafoetoproteine elke 12 maanden

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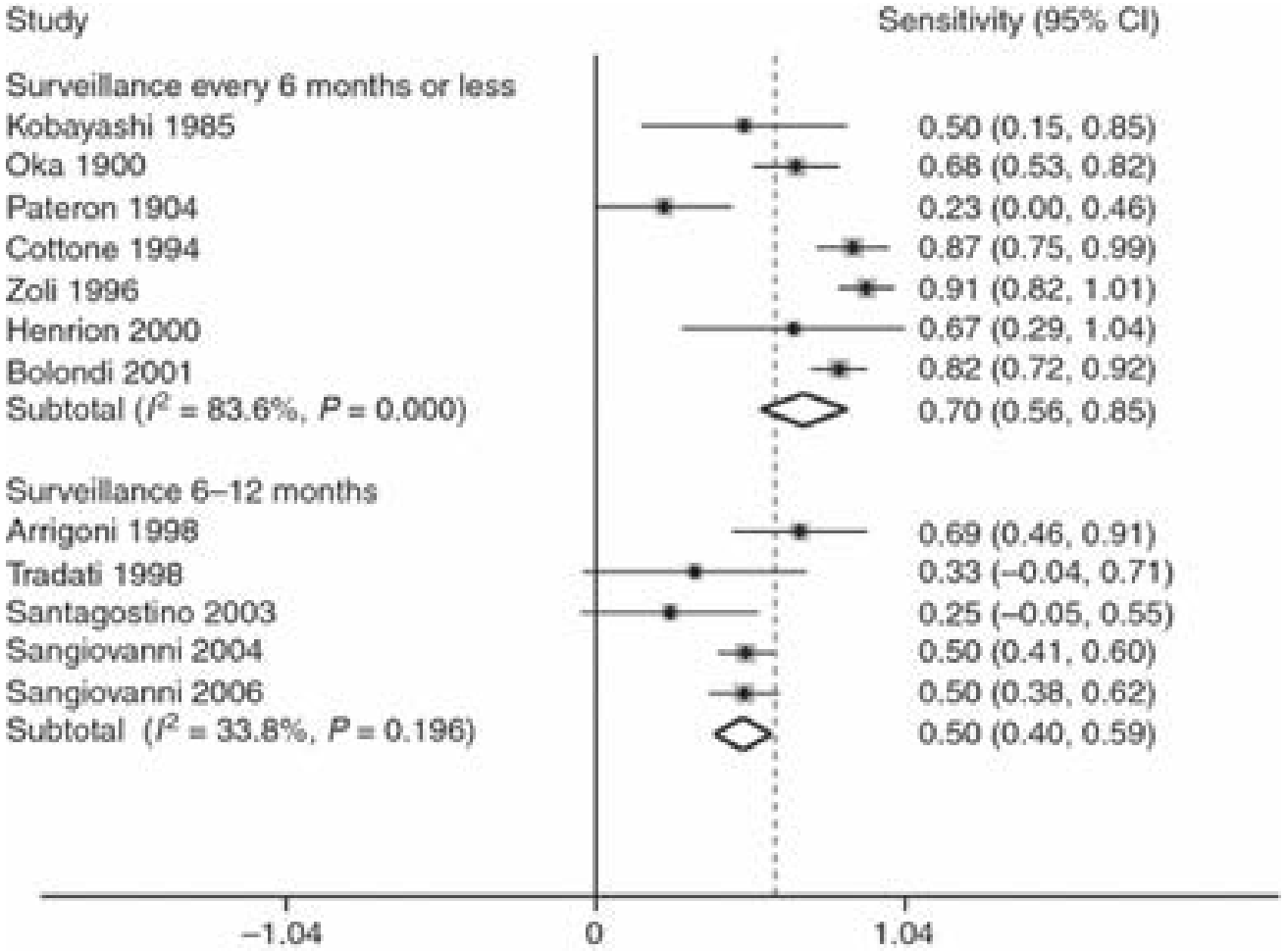
Sensitivity of ultrasound to detect early stage HCC (within Milan criteria): 6 vs 12-month intervals (Metaanalysis by Singal et al. APT 2009;30:37)



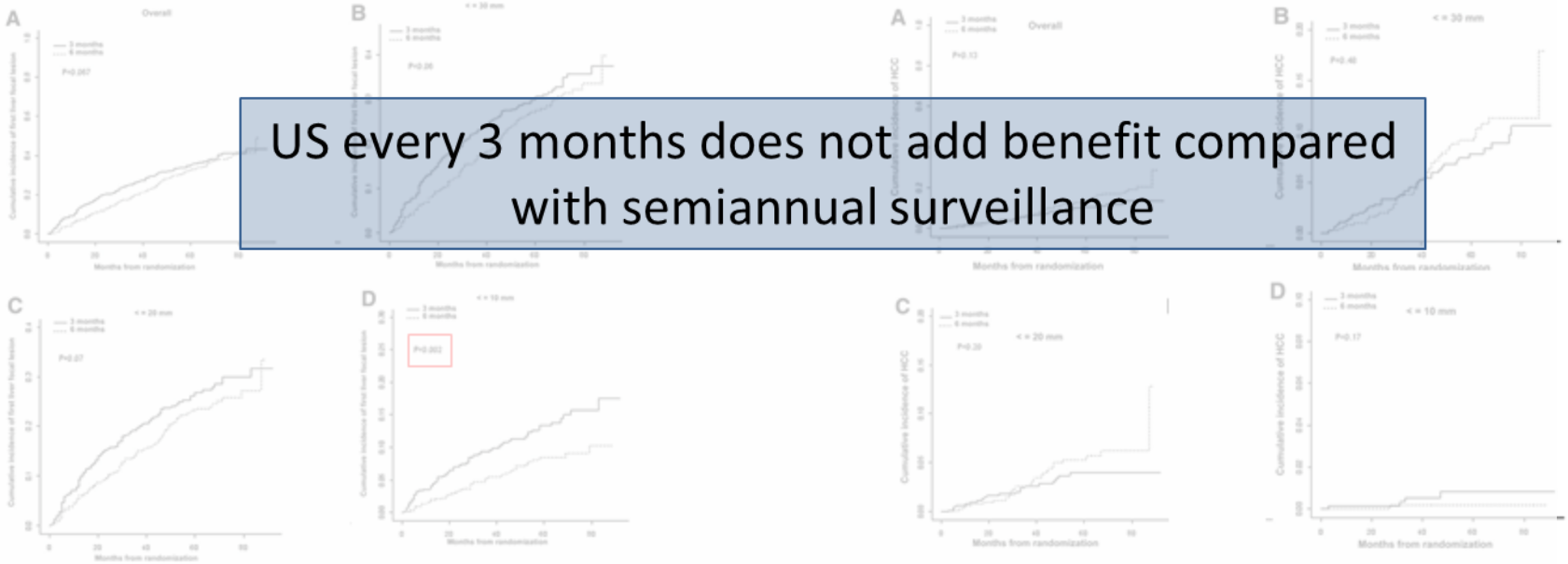
6 vs 12 months: pooled sensitivities 70 vs 50%, P=0.001. 95 % CI: 56-85% vs 40-59%

Surveillance interval

Multicenter (43 sites), RCT. A total of 1,278 patients were randomized (3m=640 vs 6m=638)

Nodule detection

HCC detection



US every 3 months does not add benefit compared with semiannual surveillance

Trinchet J et al. Hepatology. 2011;54:1987-97.

Alpha-fetoprotein for HCC surveillance

-Not recommended by AASLD, EASL, Dutch guidelines.
Recommended by APASL guideline in combination with US.

-20% of HCC cases are detected solely based on increased AFP (with normal ultrasound).

-available positive RCT from China used combined US + AFP

-Frequent false-positive results, related to increased transaminases.

-most of false positive results can be prevented by ordering AFP **only in case of relatively low transaminases**

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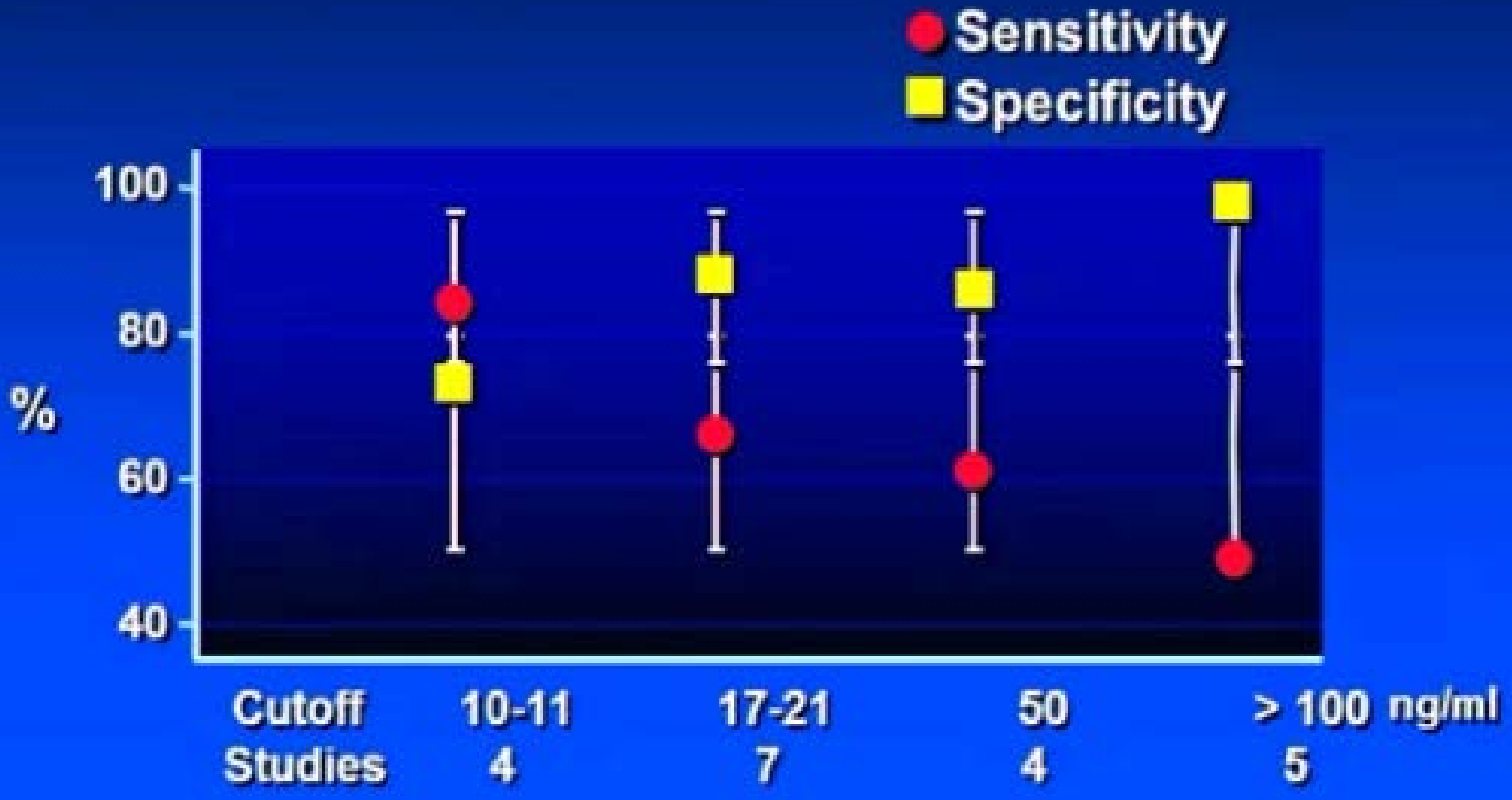
Performance Characteristics of AFP Based on Cutoff Level



Colli A, et al. Am J Gastro 2005

Outline of presentation

The controversities

1. Evidence that surveillance reduces HCC mortality?

2. High risk groups?

3. Ultrasound, alfa-fetoprotein or both and at what interval?

4. **Effectiveness of HCC surveillance in clinical practice?**

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Cost-effectiveness of HCC surveillance

The decision to enter in a surveillance program is determined by the risk of HCC, the life expectancy, and the cost you assume to expend

- An intervention is considered cost-effective if it provides an increase in longevity of about 100 days with a cost of less than about $50,000/year of life gained (QALY).....

Bruix J, Sherman M. Hepatology. 2011;53:1020-22.
EASL-EORTC GP Guidelines. J Hepatol. 2012;56:908-43.
Neumann P et al. NEJM. 2014;371(9):796-797.

Target population for surveillance

Surveillance is cost-effective if the estimated HCC incidence is > 1.5% in cirrhotic patients and > 0.2% in non-cirrhotics

Bruix J, Sherman M. Hepatology. 2011;53:1020-22.
EASL-EORTC GP Guidelines. J Hepatol. 2012;56:908-43.

High risk groups proposed for HCC surveillance
(ultrasound at 6-month interval)

Only consider surveillance in patients suitable for active HCC therapy

AASLD guideline committee: Dutch Guideline

Insufficient evidence to propose surveillance

Population group ***Cirrhosis***	Threshold incidence for cost effectiveness of surveillance (%/year)	Incidence of HCC
Cirrhosis due to non-alcoholic steatohepatitis	???	↑
Cirrhosis from autoimmune hepatitis	1.5	1.1%/yr
Cirrhosis from α1 antitrypsin deficiency	??	??
Cirrhosis due to cystic fibrosis	??	??
No cirrhosis		
Severe fibrosis from viral hepatitis,alcohol, hemochromatosis, PBC	??	??
Hep B pt, no cirrhosis but other risk factors	??	??

AASLD guideline committee: AASLD 2010

Controversies in HCC surveillance (1): NAFLD/NASH

- NAFD/NASH contributes large proportion of HCC pts in western world but:
- In cirrhotics only modest HCC risk (cumulative incidence ranging from 2.4% over 7 yrs to 12.8% over 3 yrs)
- 40% of all HCCs in NAFLD in non-cirrhotics
- Surveillance by ultrasound ultrasound often not reliably because of morbid obesity
- Curative HCC treatment often not feasible because of comorbidities

White D, Kanwal F, El Serag H. Clin Gastro Hep 2012;10:1342

Controversies in HCC surveillance (2): alcoholic cirrhosis

Recent large cohort study from Denmark (Jepsen P. *et al.* Ann Int Med 2012 ;156:841-7)

8482 patients in period: 1993-2005

- HCC incidence 1th year 9.8/1000 → excluded
- HCC incidence 2nd year 3.8/1000

Total mortality after 5 years: 44%

- 88% not related to HCC
- Only 1.8% HCC related
- 10% unknown

Conclusion:

- Annual HCC risk 0.25-0.5% (< 1.5%)
- Surveillance not justified??

Research Article

EASL JOURNAL OF HEPATOLOGY

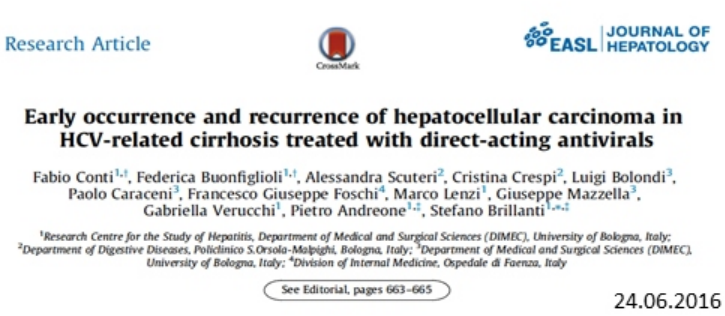
Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy☆

María Reig[1,†], Zoe Mariño[2,†], Christie Perelló[3], Mercedes Iñarrairaegui[4], Andrea Ribeiro[1], Sabela Lens[2], Alba Díaz[5], Ramón Vilana[6], Anna Darnell[6], María Varela[7], Bruno Sangro[4], José Luis Calleja[3], Xavier Forns[2,‡], Jordi Bruix[1,*,‡]

[1]Barcelona Clínic Liver Cancer (BCLC) Group, Liver Unit, Hospital Clínic Barcelona, IDIBAPS, University of Barcelona, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain; [2]Liver Unit, Hospital Clínic, IDIBAPS, University of Barcelona, CIBERehd, Barcelona, Spain; [3]Liver Unit, Hospital Universitario Puerta de Hierro, CIBERehd, IDIPHIM, Madrid, Spain; [4]Unidad de Hepatología, Clínica Universidad de Navarra, IDISNA, CIBERehd, Pamplona, Spain; [5]Department of Pathology, BCLC Group, Hospital Clínic Barcelona, IDIBAPS, University of Barcelona, Spain; [6]Department of Radiology, BCLC Group, Hospital Clínic Barcelona, University of Barcelona, Spain; [7]Liver Unit, Hospital Universitario Central de Asturias, Oviedo, Spain

See Editorial, pages 663–665

13.04.2016



Research Article

EASL JOURNAL OF HEPATOLOGY

Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals

Fabio Conti[1,†], Federica Buonfiglioli[1,†], Alessandra Scuteri[2], Cristina Crespi[2], Luigi Bolondi[3], Paolo Caraceni[3], Francesco Giuseppe Foschi[4], Marco Lenzi[1], Giuseppe Mazzella[3], Gabriella Verucchi[1], Pietro Andreone[1,2], Stefano Brillanti[1,*,‡]

[1]Research Centre for the Study of Hepatitis, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Italy; [2]Department of Digestive Diseases, Policlinico S.Orsola-Malpighi, Bologna, Italy; [3]Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Italy; [4]Division of Internal Medicine, Ospedale di Faenza, Italy

See Editorial, pages 663–665

24.06.2016

Letters to the Editor

High incidence of hepatocellular carcinoma following successful interferon-free antiviral therapy for hepatitis C associated cirrhosis

Direct antiviral agents and risk for HCC early recurrence: Much ado about nothing

Direct acting antiviral therapy and tumor recurrence after liver transplantation for hepatitis C-associated hepatocellular carcinoma

Reply to "Direct antiviral agents and risk for hepatocellular carcinoma (HCC) early recurrence: Much ado about nothing"

Hepatocellular carcinoma recurrence after treatment with direct-acting antivirals: First, do no harm by withdrawing treatment

Unexpected high incidence of hepatocellular carcinoma in patients with hepatitis C in the era of DAAs: Too alarming?

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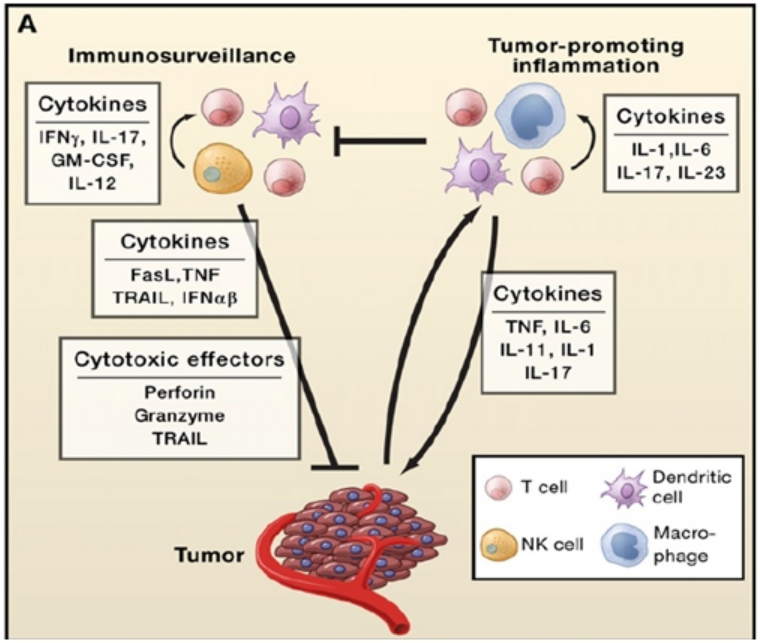
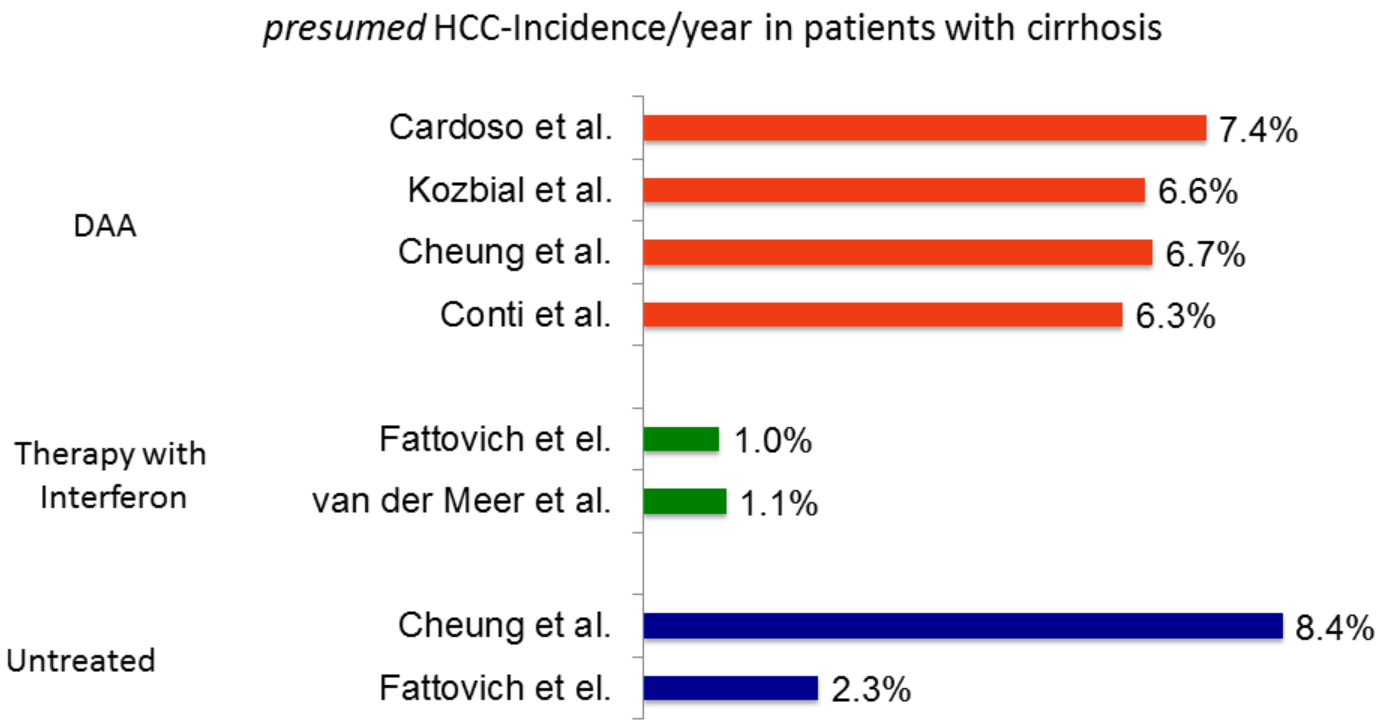
DAA and HCC: A potential explanation



SVR

Grivennikov et al. Cell 2010; Spaan et al, CID 2016

DAA-Therapy and “de-novo” HCC



Cardoso et al. J Hepatol 2016, Kozbial et al. J Hepatol 2016, Cheung et al., Journal of Hepatology 2016, Conti et al. J Hepatol 2016, Fattovich et al., J Hepatol 1997, van der Meer et al. J Hepatol 2016

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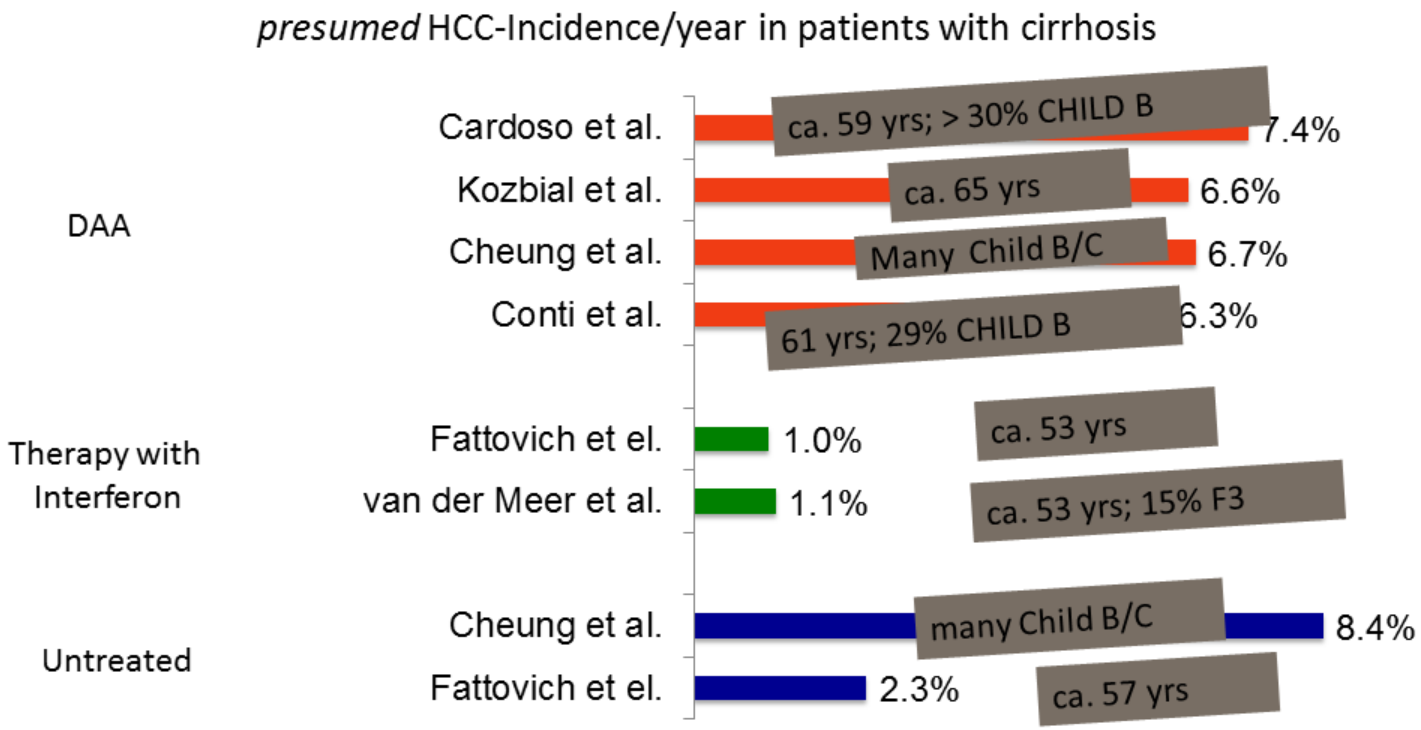
DAA-Therapy and “de-novo” HCC



Cardoso et al. J Hepatol 2016, Kozbial et al. J Hepatol 2016, Cheung et al., Journal of Hepatology 2016, Conti et al. J Hepatol 2016, Fattovich et al., J Hepatol 1997, van der Meer et al. J Hepatol 2016

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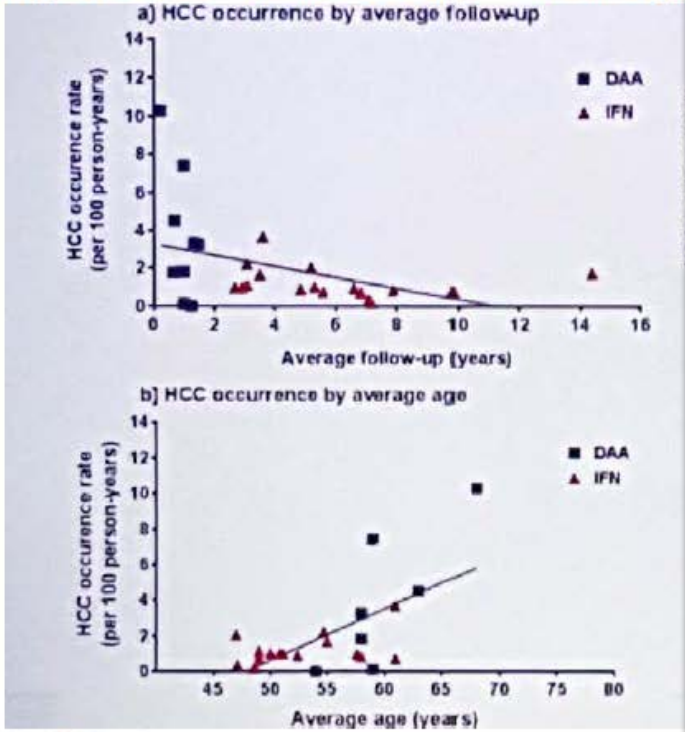
DAA and HCC?

Impact of follow-up and age



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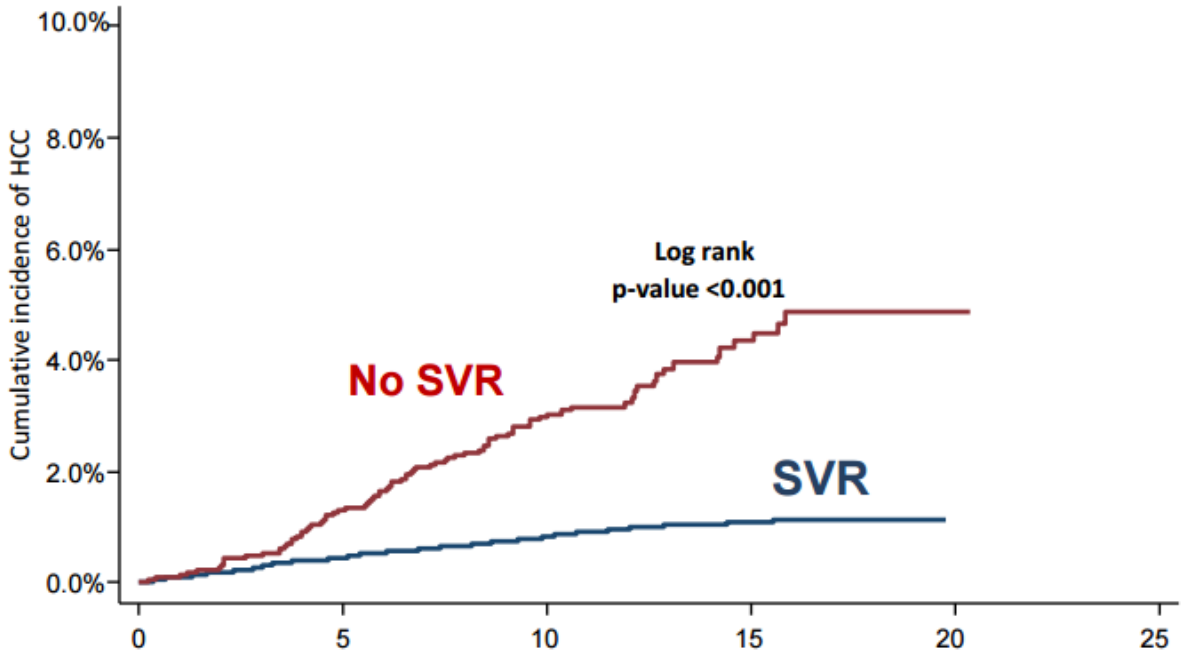
Results

Cumulative HCC incidence rates by SVR

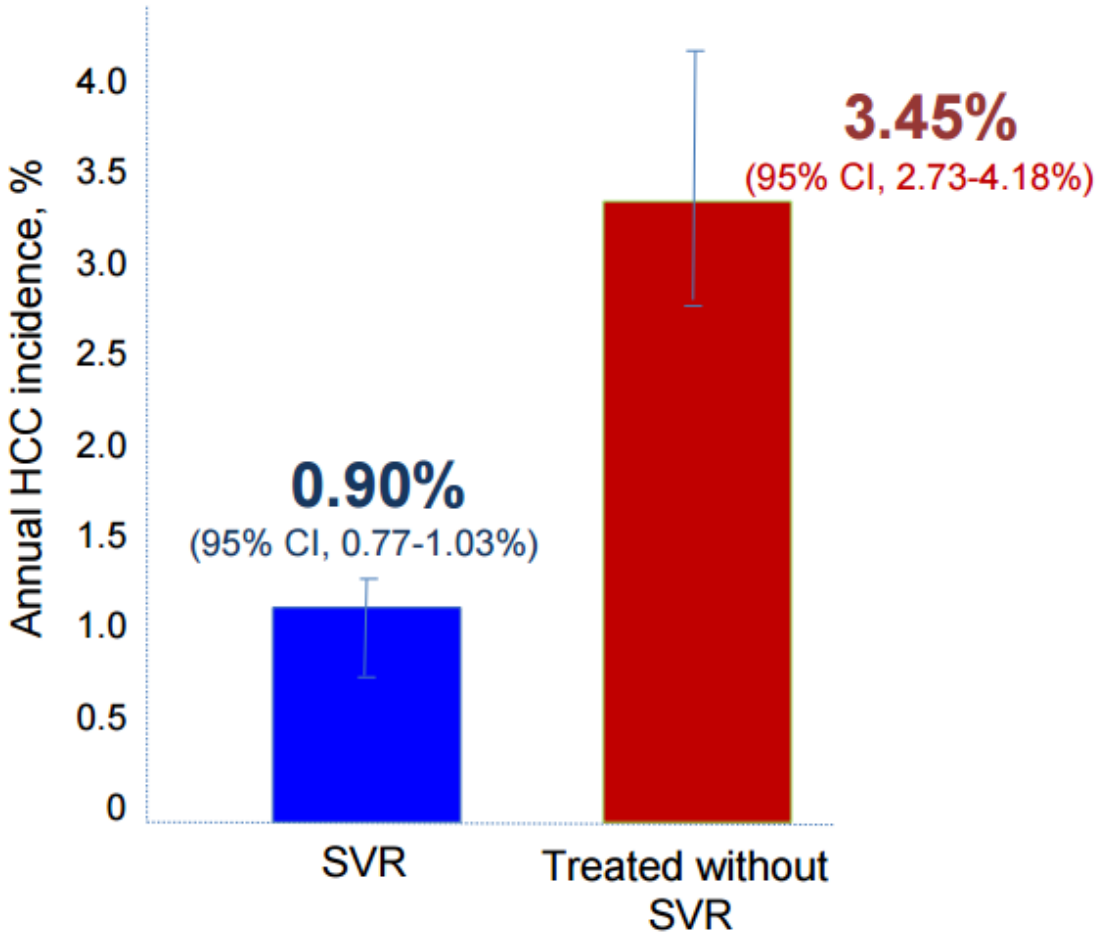


N at risk (N HCC)											
SVR	19518	(85)	19372	(68)	14364	(29)	6128	(1)	0	(0)	0
No SVR	2982	(35)	2453	(36)	1617	(14)	636	(3)	5	(0)	0

Kanwal F., El-Seragh H. *et al.* DDW 2017

Results

Annual HCC incidence rates by SVR



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Kanwal F., El-Seragh H. *et al.* DDW 2017

Summary and Conclusions

HCC incidence increasing in Western world, poor prognosis

Modest, but suggestive evidence for efficacy of surveillance in high risk groups

Ultrasound at 6-month interval is key, not AFP alone:

Continue at this moment HCC surveillance in DAA-cured HCV pts with F3/4 cirrhosis or comorbidities

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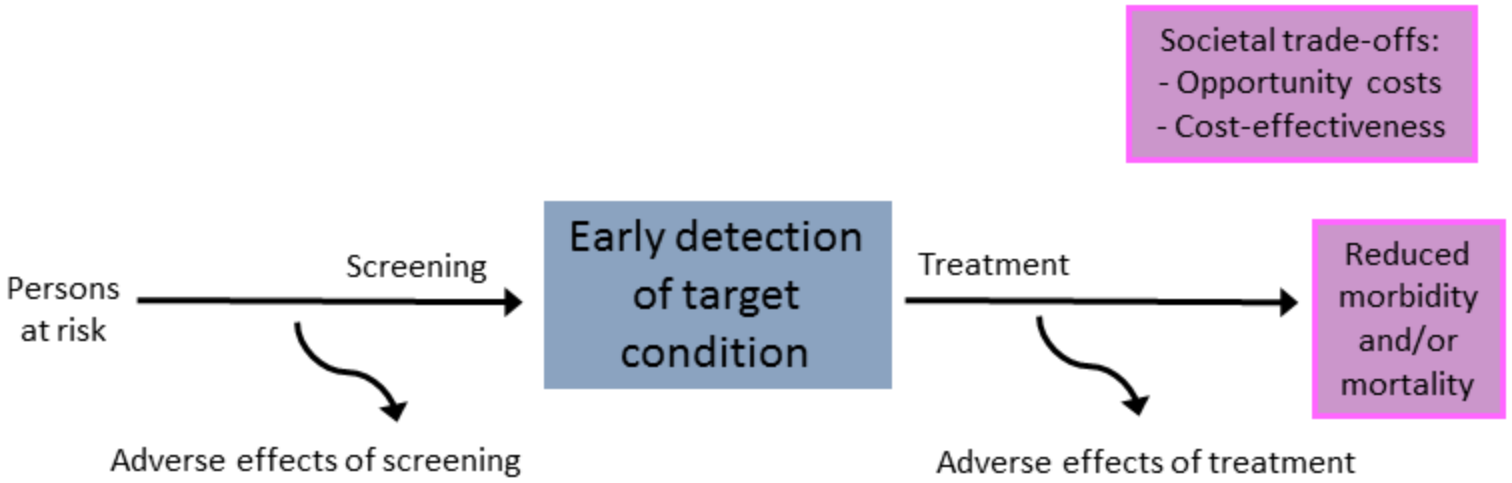
HCC Surveillance in 14,837 HCV-Infected Veterans with Cirrhosis (1997-2007)

AFP or ultrasound tests for HCC surveillance	n (%)
Routine surveillance	12.0
Inconsistent surveillance	55.9
No surveillance	32.1
1-year following cirrhosis diagnosis date	42.0
2-years	33.8
3-years	34.7
4-years	35.6

Davila J, et al. Ann Intern Med; 2011

Cost-effectiveness of HCC surveillance

Assessing the benefits and harms of early detection



False positive results:
-Negative psychological consequences
-Triggering of more invasive diagnostic procedures
-Substantial economic burdens

Complications of screening test

Croswell J et al. Semin Oncol 2010;37:202-15.
Kramer B et al. Annu Rev Med 2009;60:125-37.

Critical comments

- Not all deaths were reported
- Inadequate statistical analysis (did not account for cluster randomization)
- Some patients excluded after randomization
- Patients did not know that they were in randomized study
- May not be applicable to patients in Western world

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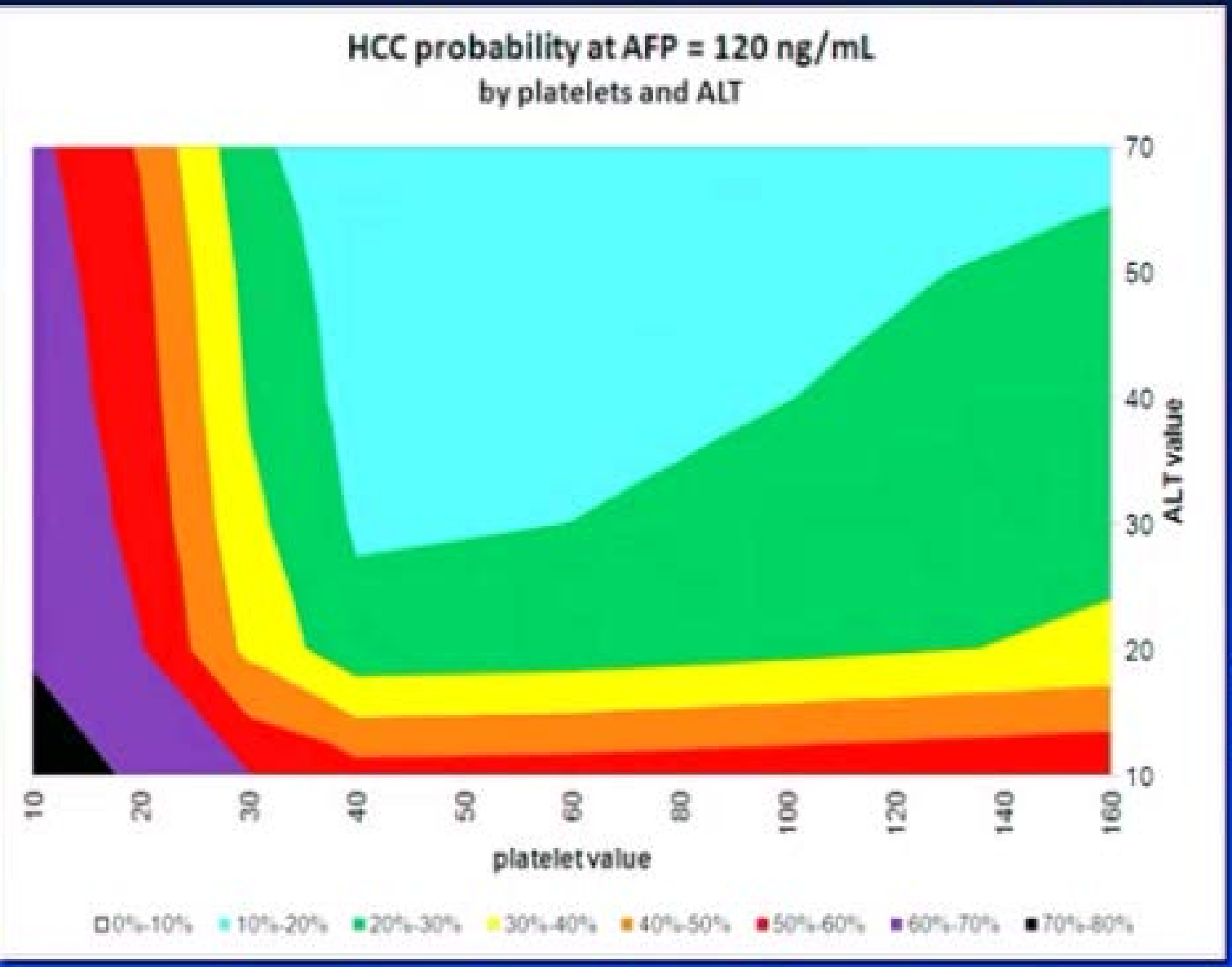
Adjusted AFP Algorithm



Richardson P.
DDW 2013