Hepatocellular Carcinoma

Screening and Surveillance Strategies

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Is Surveillance “Worthwhile”?

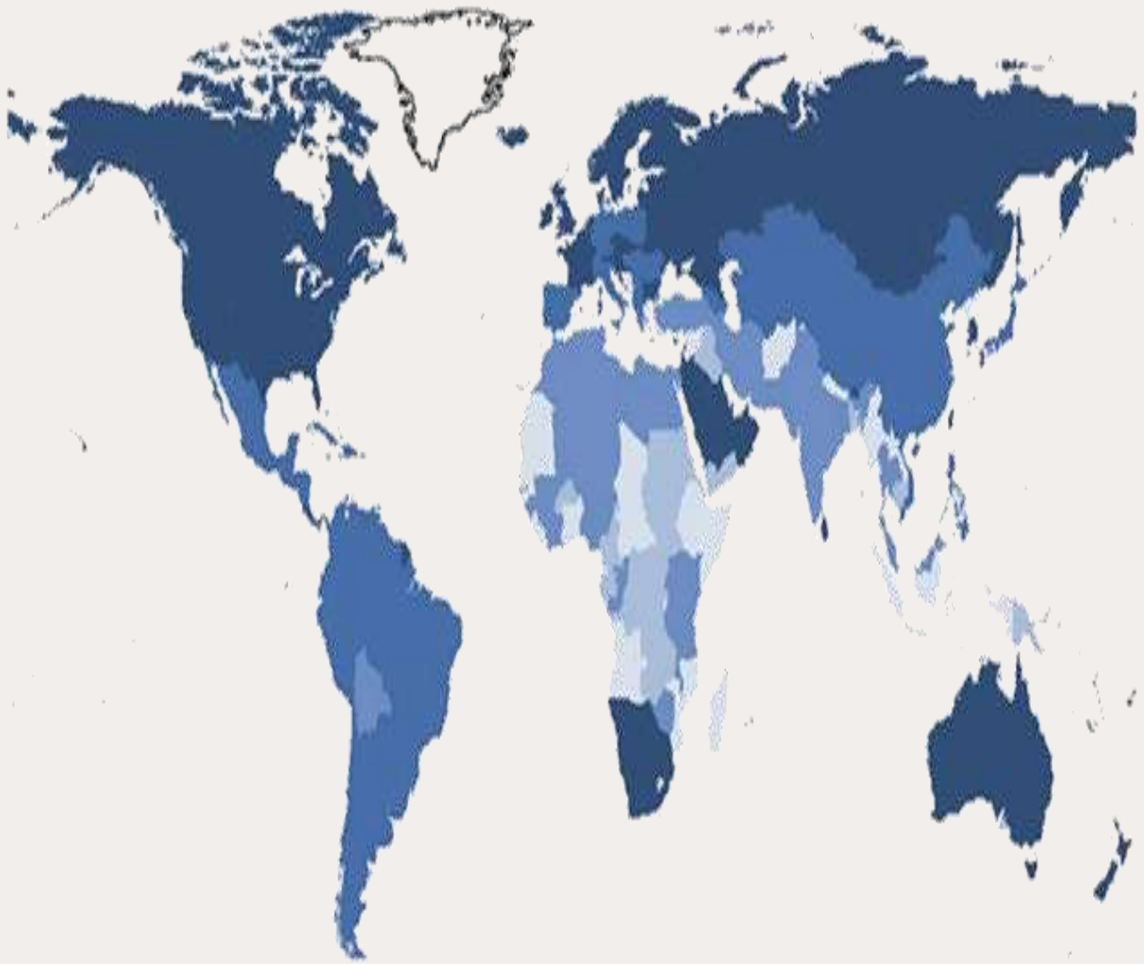
- How can we determine whether surveillance is worthwhile (effective)?
- How do we define “worthwhile”?
  - Improvement in survival of 3 months[1]
- Surveillance considered cost-effective if it achieves this >3-month improvement in survival at a cost of < $50,000 per life-year saved[2]
- Early diagnosis allows application of potentially curative treatment
- Detect 70% of tumors at early stage asymptomatic when it is possible to intervene.

1. Naimark D, et al. J Gen Intern Med. 1994;9:702-707.
2. Laupacis A, et al. CMAJ. 1992;146:473-481.

Identification of At-Risk Population for HCC Surveillance

- What level of risk makes surveillance worthwhile?
  - Incidence
- According to randomized controlled trials
  - Hepatitis B: 0.28% per year[1]
- According to cost-efficacy analyses
  - Hepatitis B: 0.2% per year[3]
  - Non-hepatitis B cirrhosis: > 1.4% per year[4]

1. Zhang BH, et al. J Cancer Res Clin Oncol. 2004;130:417-422. 2. Sarasin FP, et al. Am J Med. 1996;101:422-434. 3. Morris Sherman, MB BCh, PhD, FRCP(C). Data on file. 4. Arguedas MR, et al. Am J Gastroenterol. 2003;98:679-690.



1: National incidence data

2: Local incidence data and national mortality data

3: Local incidence data. No mortality data

4: Frequency data

5: No data

HCC: Epidemiology

- HCC is the most common primary liver malignancy
- Worldwide incidence >600,000 new cases per year; (rising)

- More common in men than women (4:1)
- 80% occurs in developing countries particularly Asia
- In HBV endemic areas: >10 in 100,000
- 500,000 deaths worldwide per year

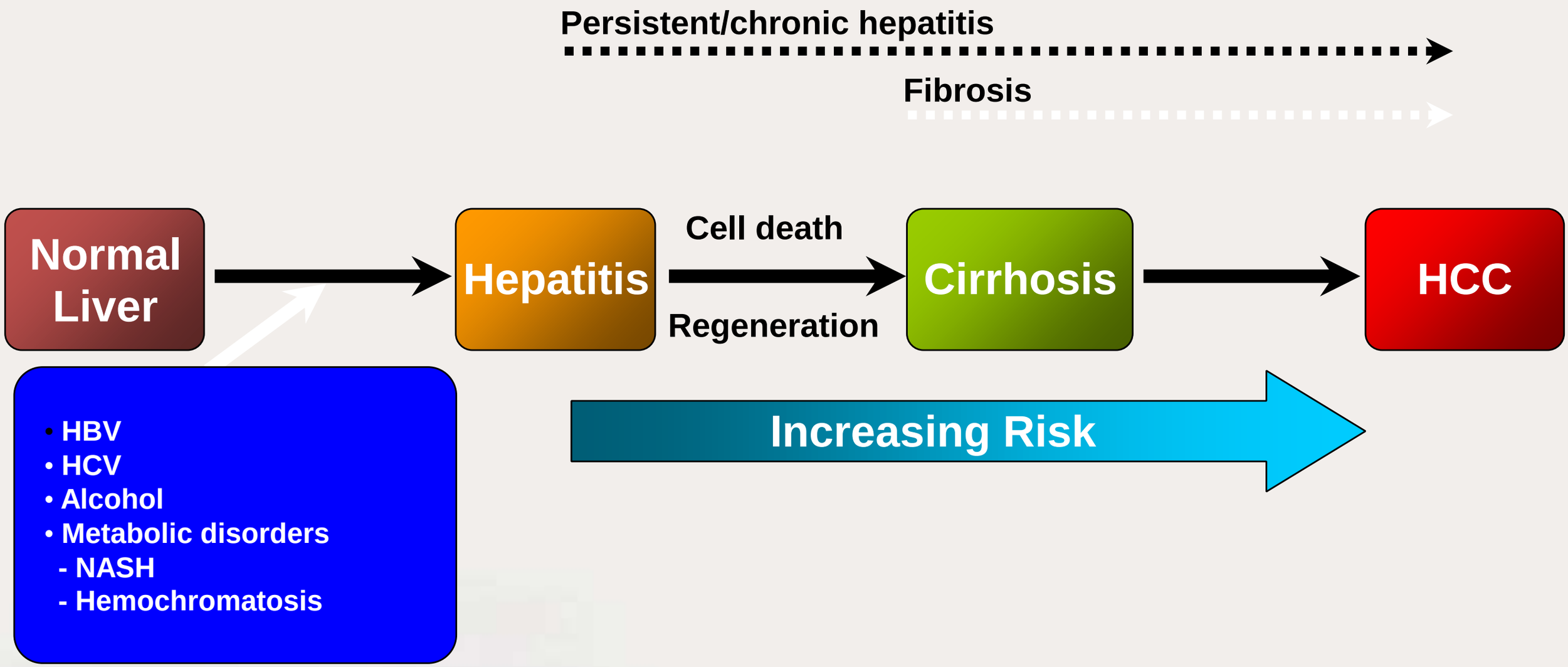
- For resection, rate of recurrence can be as high as 50% at 2 years

  - Only 12% are eligible for resection or LT

  - 80-90% of HCC cases occur in cirrhotic livers

World Health Organization. Available at: http://www.who.int/whosis/en/. Accessed October 6, 2008. American Cancer Society. Cancer facts & figures 2008. Atlanta: American Cancer Society; 2008.

Multifactorial Pathogenesis of HCC



HBV = hepatitis B virus; HCV = hepatitis C virus; NASH = nonalcoholic steatohepatitis.

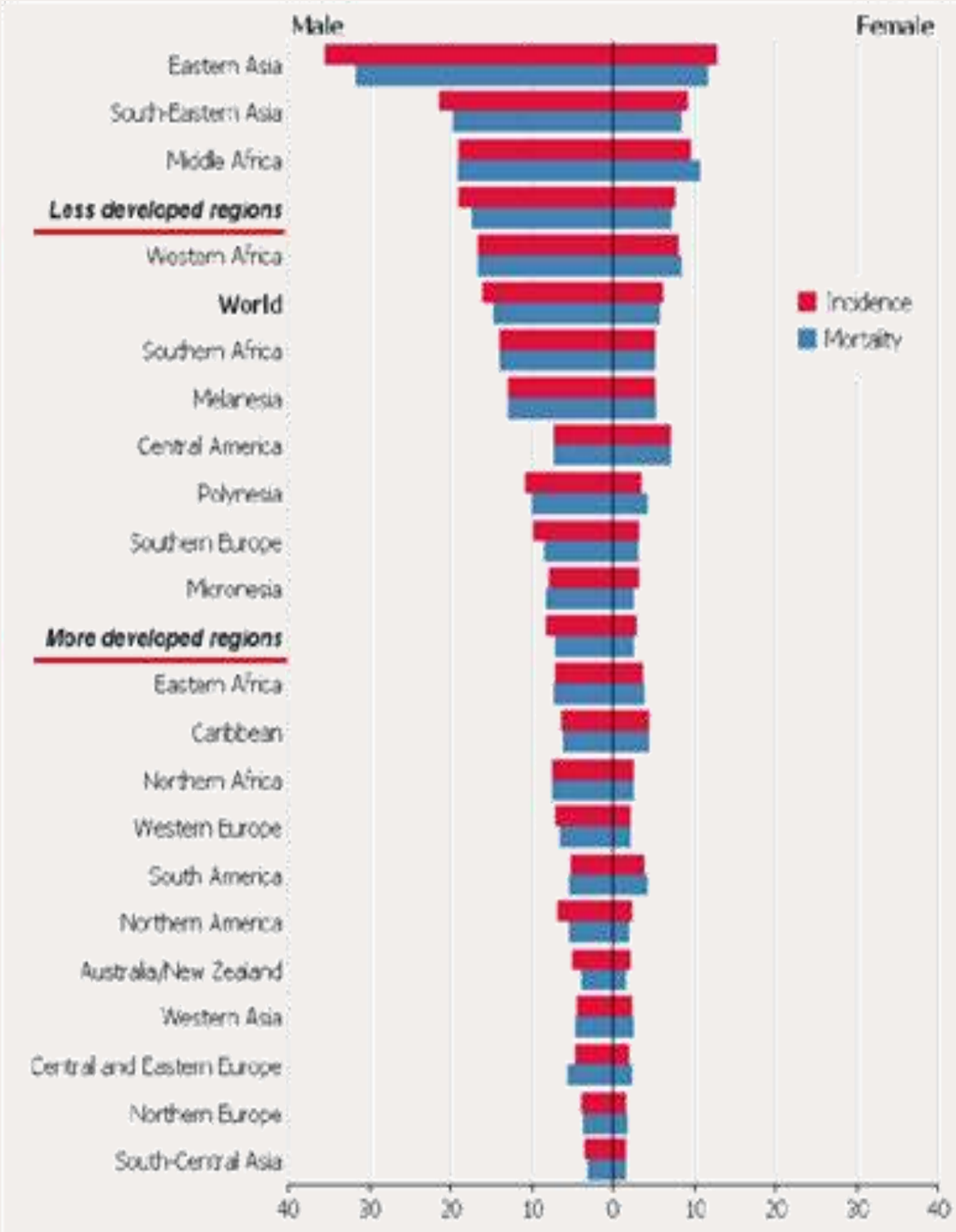
1. Adapted from Rivenbark AG, et al. *Clin Cancer Res.* 2007;13:2309-2312; 2. Marotta F, et al. *Clin Ther*. 2004;155:187-199;
3. Thorgeirsson S, et al. *Nat Genet*. 2002;31:339-346; 4. Wang XW, et al. *Toxicology*. 2002;181-182:43-47;
5. Koike K. *Hepatol Res*. 2005;33:145-150.

Risk Factors for Hepatocellular Carcinoma Estimates of the Attributable Fractions (%)

Risk factors	Europe/US	Japan	Africa/Asia
Hepatitis B virus	22 (4-58)	20 (18-44)	60 (40-90)
Hepatitis C virus	60 (12-72)	63 (48-94)	20 (9-56)
Alcohol	45 (8-57)	20 (15-33)	- (11-41)
Tobacco	12 (0-14)	40 (9-51)	22 -
Aflatoxin	Limited	Limited	High exposure
Other	<5	-	<5

Bosch and Ribes Viruses and Liver Cancer, 2002

Estimated Age-Standardized Incidence and Mortality Rates for Liver Cancer



Ferlay et al. Int J Cancer 2010;127:2893-2917;

Hepatocellular Carcinoma: Distinct Features

1. The tumor develops in the context of well-known environmental risk factors. The dominant role of HBV and HCV

2. The tumor is strictly associated with chronic liver disease, mainly cirrhosis.

3. One of the few cancers not requiring histology for diagnosis in all cases. Radiological diagnosis possible in cirrhotics and HBV patients.

4. The sole solid cancer treatable by organ transplantation.

Surveillance for HCC as Recommended by AASLD, APASL and EASL

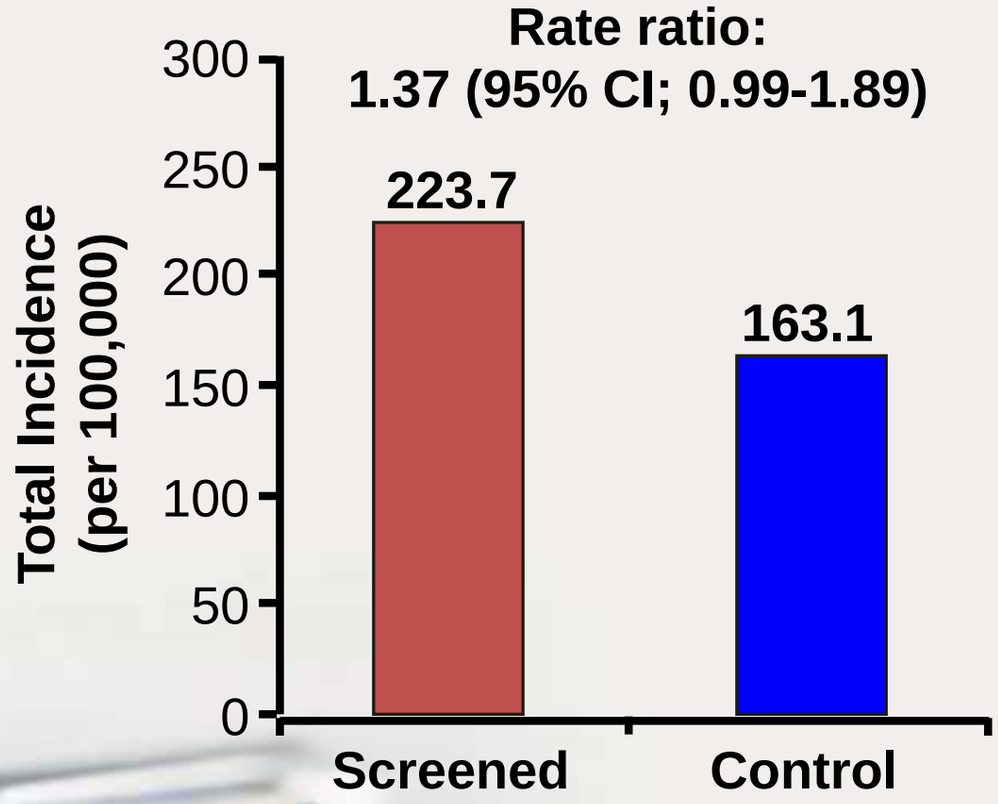
STRATEGY	AASLD 2010	APASL 2010	EASL 2012
Target population	Cirrhosis, CHB[1] NAFLD	Viral Cirrhosis	Cirrhosis, CHB[2] HCV F3

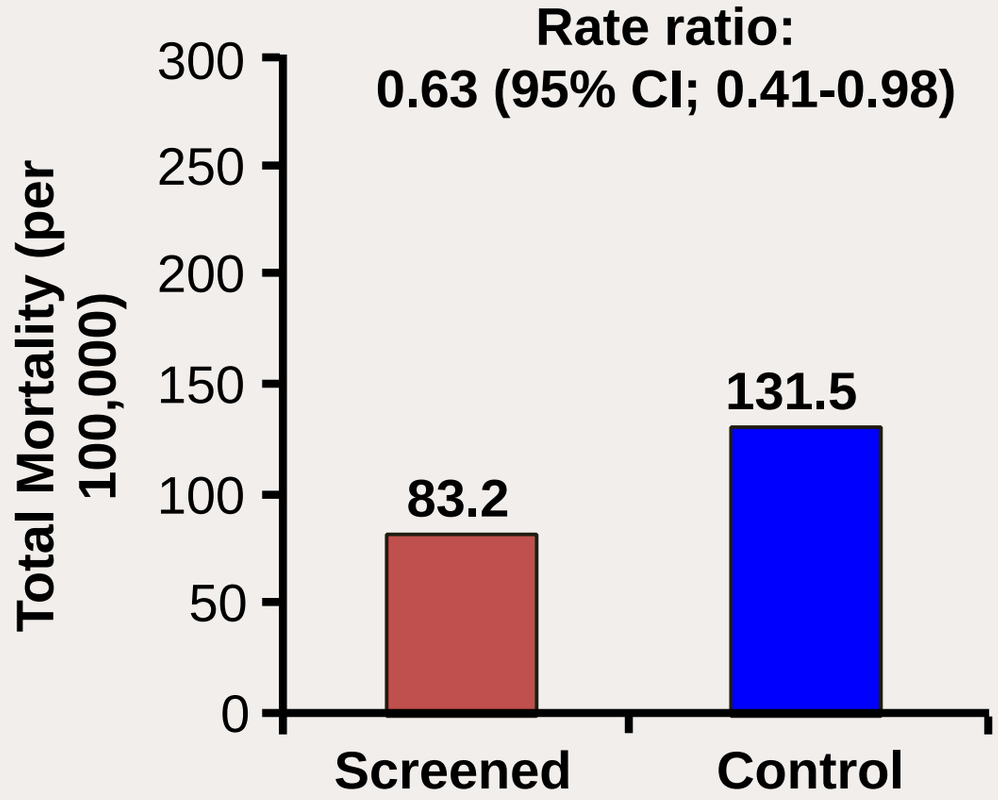
[1] Asian males >40 years and females >50 years
Family history of HCC
African/North American blacks > 20 years

[2] Active hepatitis
Family history of HCC

Outcome of HCC Surveillance

- 18,816 people with HBV infection or history of chronic hepatitis in urban Shanghai, China enrolled
  - Surveillance group offered US and AFP every 6 months (n = 9373)
  - Control group received no surveillance (n = 9443)

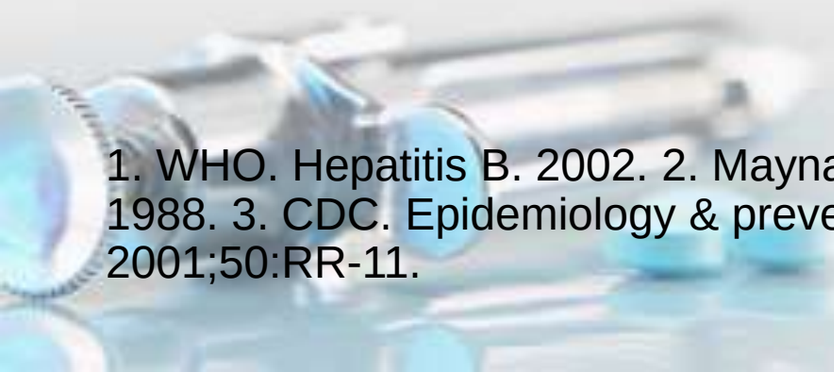




Zhang BH, et al. J Cancer Res Clin Oncol. 2004;130:417-422.

HBV: A Significant Cause of Worldwide Morbidity and Mortality

- > 2 billion have been infected[1]
- 4 million acute cases per year[1]
- 1 million deaths per year[1]
- 350-400 million chronic carriers[1]
  - 25% of carriers die from chronic hepatitis, cirrhosis, or liver cancer[1]
  - Nearly 75% of chronic carriers are Asian[2]
- Second most important carcinogen behind tobacco[3]
- Causes 60% to 80% of all primary liver cancer[1]
- HBV is 100 times more contagious than HIV[4]



1. WHO. Hepatitis B. 2002. 2. Maynard JE, et al. In: Viral Hepatitis and Liver Disease. New York: Alan R. Liss, Inc. 1988. 3. CDC. Epidemiology & prevention of vaccine-preventable diseases. The Pink Book. 8th ed. 4. CDC. MMWR. 2001;50:RR-11.

Hepatitis B Carriers Suitable for HCC Surveillance

Hepatitis B carriers[1-4]

- Asian males > ~ 40 years (incidence ~ 0.4% to 0.6% per year)
- Asian females > ~ 50 years (incidence ~ 0.2% per year)
- Africans older than 20 years of age (incidence unknown but likely > 0.2% per year)
- Cirrhosis (HCC incidence: 3% to 5%/year)
- Family history of HCC: mainly Asian and African

Beasley RP, et al. Lancet. 1981;2:1129-1133. Koike K, et al. Oncology. 2002;62(suppl 1):29-37. Beasley RP. Hepatology. 1982;2(suppl):21S-26S. Fattovich G, et al. Gut. 1991;32:294-298. Manno M, et al. Gastroenterology. 2004;127:756-763. Hsu YS, et al. Hepatology. 2002;35:1522-1527. Fattovich G. J Hepatol. 2003;39(suppl 1):S50-S58.

Surveillance for HCC as Recommended by AASLD, APASL and EASL/EORTC

Strategy	AASLD 2010	APASL 2010	EASL 2012
Target Population	Cirrhosis, HBV, NAFLD	Viral cirrhosis	Cirrhosis, HBV, HCV F3
Screening modality	Abdominal US	Abdominal US +AFP	Abdominal US
Optional CT/MRI	No	Yes	No
Additional markers DCP/AFP-L3	No	Yes	No
Screening intervals, mo.	6	6	6
Radiological Diagnosis	CT, MRI > 1 cm	CE-US, CT-MRI Any Size	CT,MRI >1 cm

Sensitivity/specificity of AFP Surveillance for HCC

Study	Sensitivity, %	Specificity, %	PPV, %
Case-control studies			
Trevisani 2001	**60**	**91**	**25**
Surveillance studies			
Tanaka 1990	**64**		
Pateron 1994	**50**	**86**	**33**
Borzio 1995	**47**		
Sherman 1995	**64**	**91**	**9**
Solmi 1996	**54**		
Zoli 1996	**62**		
McMahon 2000	**97**	**95**	**31**
Bolondi 2001	**41**	**82**	**46**
Tong 2001	**59**	**91**	**11**

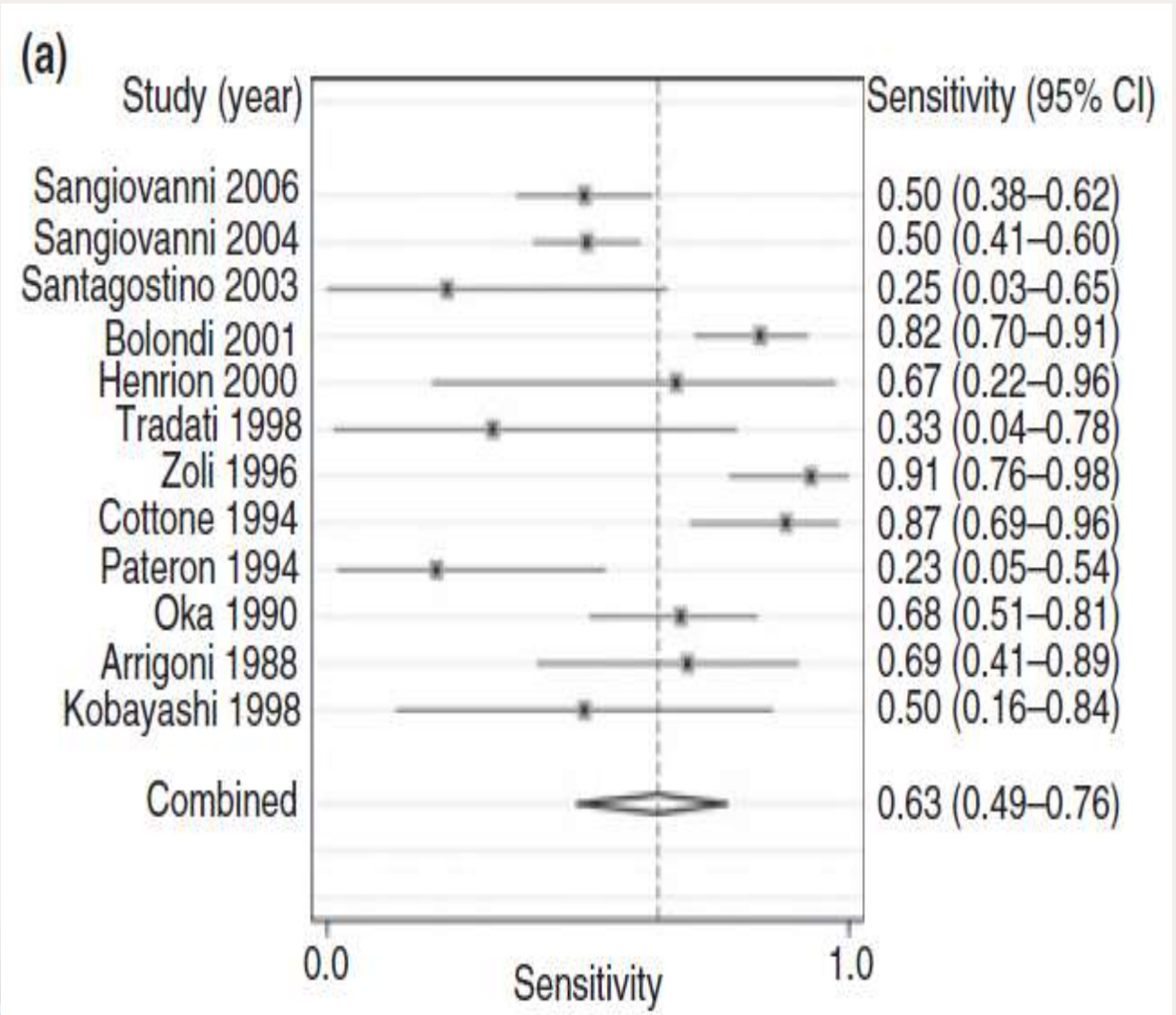
Serum AFP as a single test for the diagnosis of HCC has performed poorly and is not recommended as a surveillance test in management guidelines (41%-97% sensitivity)

*5% prevalence of HCC.

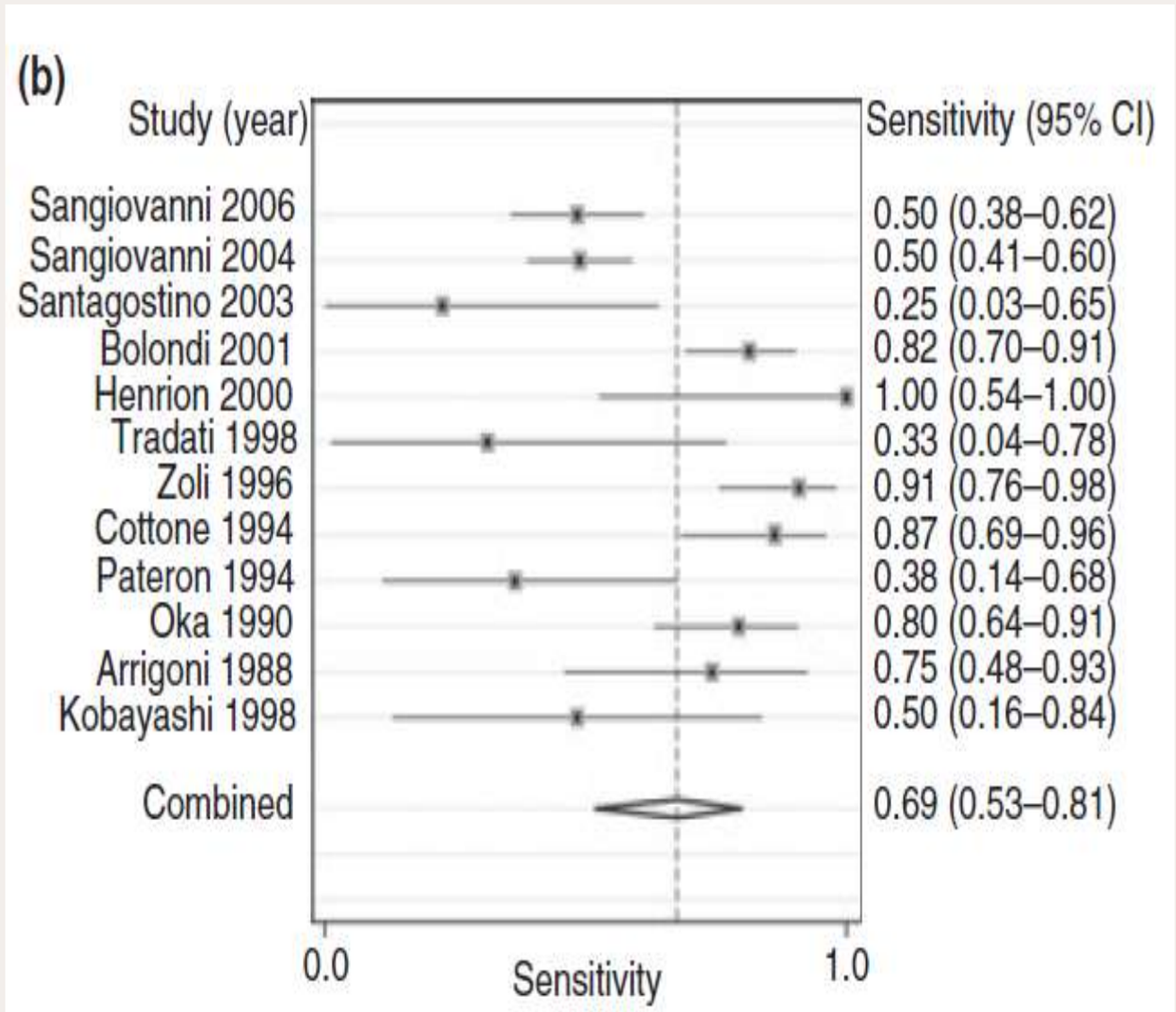
Trevisani F, et al. J Hepatol. 2001;34:570-575. Tanaka S, et al. Cancer. 1990;66:2210-2214. Pateron D, et al. J Hepatol. 1994;20:65-71. Borzio M, et al. Gastroenterology. 1995;108:812-817. Sherman M, et al. Hepatology. 1995;22:432-438. Solmi L, et al. Am J Gastroenterol. 1996;91:1189-1194. Zoli M, et al. Cancer. 1996;78:977-985. McMahon BJ, et al. Hepatology. 2000;32:842-846. Bolondi L, et al. Gut. 2001;48:251-259. Tong MJ, et al. J Gastroenterol Hepatol. 2001;16:553-559.

The Diagnostic Sensitivity of Ultrasound in the Early Diagnosis of HCC in Cirrhosis

Ultrasound alone



Ultrasound + AFP



Singal et al Aliment Pharmacol Ther 2009; 30:37-47

Combination of AFP and Ultrasound for Surveillance

- Combination increases detection, but increases false-positives and costs
- False-positive rates
  - AFP alone: 5.0%
  - Ultrasound alone: 2.9%
  - AFP/ultrasound combined: 7.5%
- Ultrasound costs $2000 per tumor found
- AFP/ultrasound costs $3000 per tumor found

Zhang B, et al. J Med Screen. 1999;6:108-110.

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Target Population	***Cirrhosis, HBV, NAFLD***	***Viral cirrhosis***	***Cirrhosis, HBV, HCV F3***
Screening modality	***Abdominal US***	***Abdominal US +AFP***	***Abdominal US***
Optional CT/MRI	***No***	***Yes***	***No***
Additional markers DCP/AFP-L3	***No***	***Yes***	***No***
Screening intervals, mo.	***6***	***6***	***6***
Radiological Diagnosis	***CT, MRI > 1 cm***	***CE-US, CT-MRI Any Size***	***CT,MRI >1 cm***

HCC Surveillance by CT Scan

- No evidence to support the use of CT scanning for routine HCC surveillance
  - PPV and NPV unknown
  - Accurate use of CT requires 4-phase contrast CT
    - Radiation exposure is significant
  - In the absence of contrast CT, false-positive rate very high
    - Cannot distinguish small HCC from dysplastic nodules or arterialized cirrhotic nodules
    - Flow abnormalities create diagnostic difficulty

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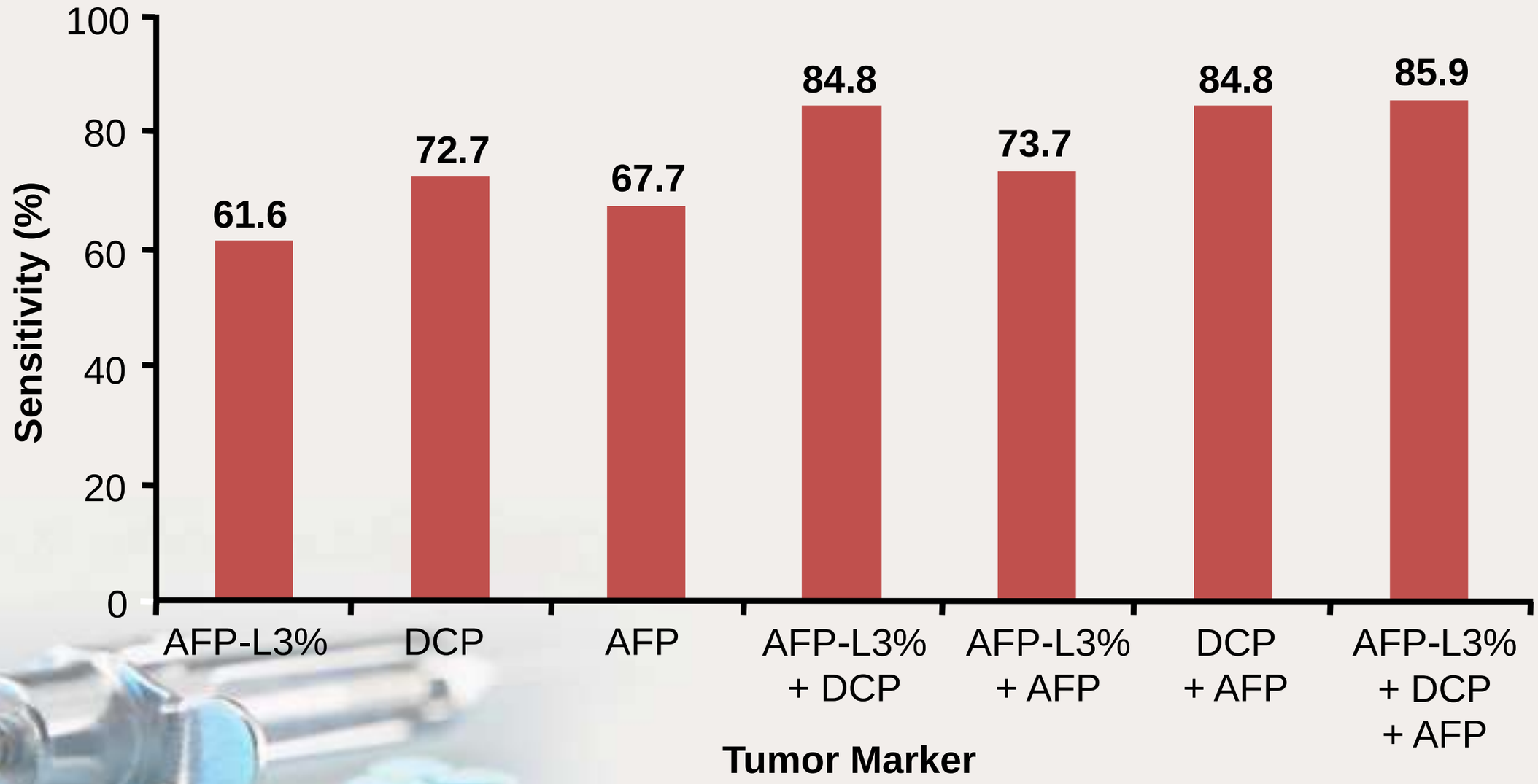
Current Surveillance Tests Are Not Sufficiently Sensitive

- Prospective analysis of 99 patients with histologically proven, unresectable HCC



Carr BI, et al. Dig Dis Sci. 2007;52:776-782.

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Selecting an HCC Surveillance Interval

- Dependent on
  - Tumor growth rate
  - Prognosis of HCC at different sizes
    - < 1-2 cm
    - 2-3 cm
    - > 3 cm
  - Ideal surveillance interval unknown
    - Tumor growth rates suggest every 4-12 months
- Does not depend on degree of risk

HCC Surveillance Interval

- Rationale for 6 month

- Doubling time: median = 6 mo (range, 1-19 mo)

  - Growth from 1 to 3 cm:

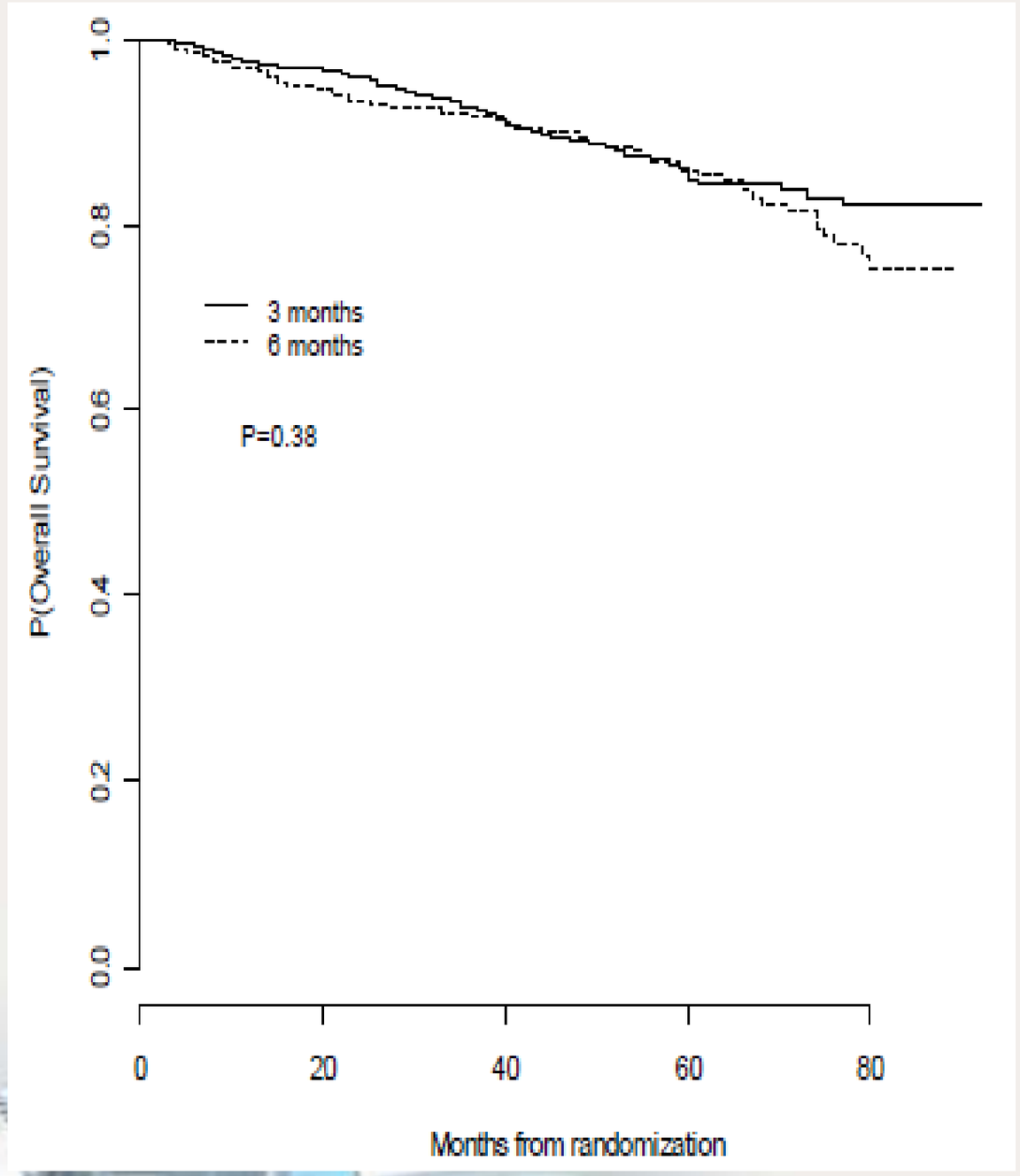
    4 mo for most aggressive,

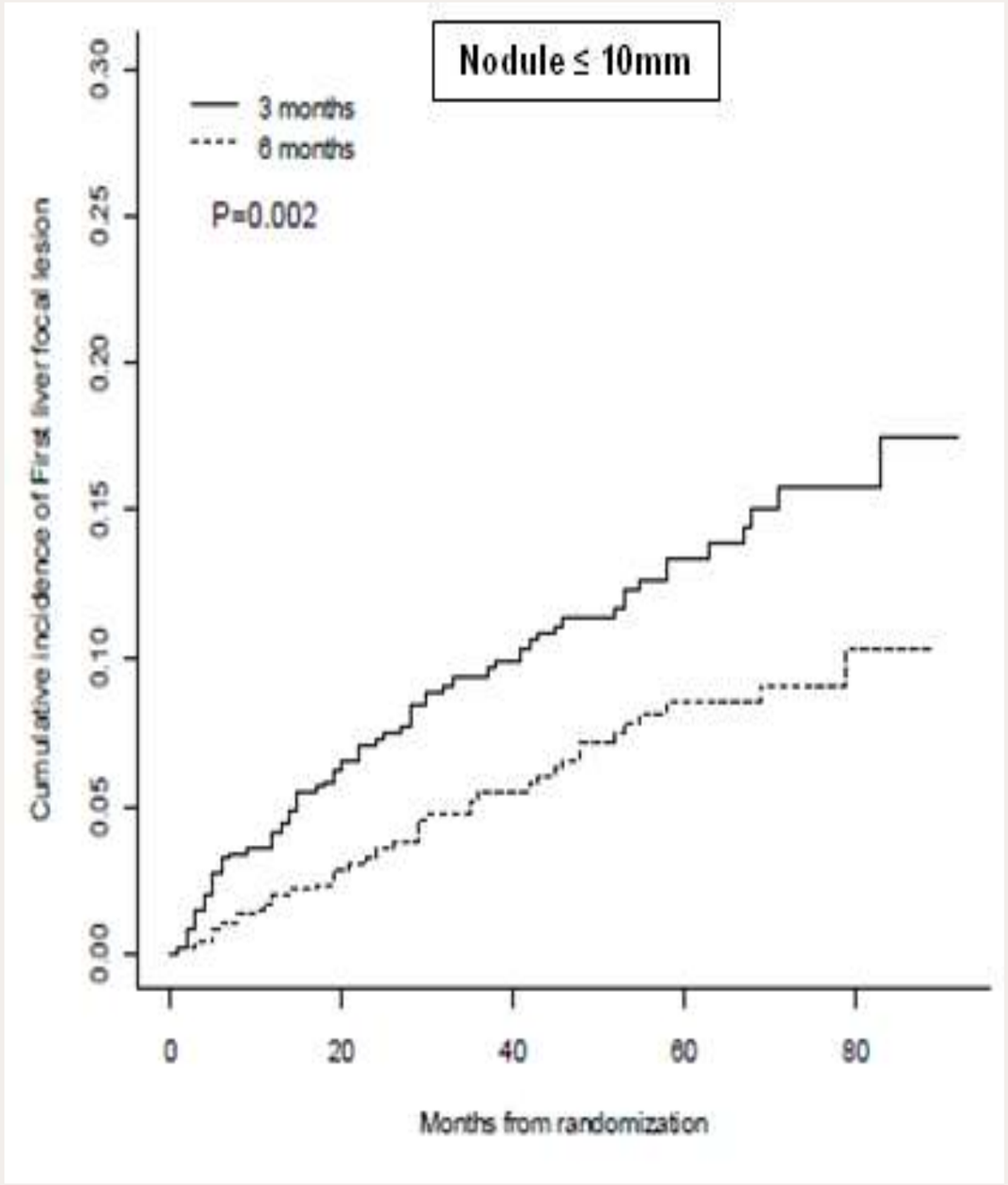
    18 mo for moderately aggressive,

    5 yr for indolent

- Median detectable subclinical priod for HCC = 3.2%

US Surveillance of HCC in Cirrhosis: Randomized Trial Comparing 3- and 6- Month Periodicity





Trinchet et al, Hepatology 2011; 54:1987-97

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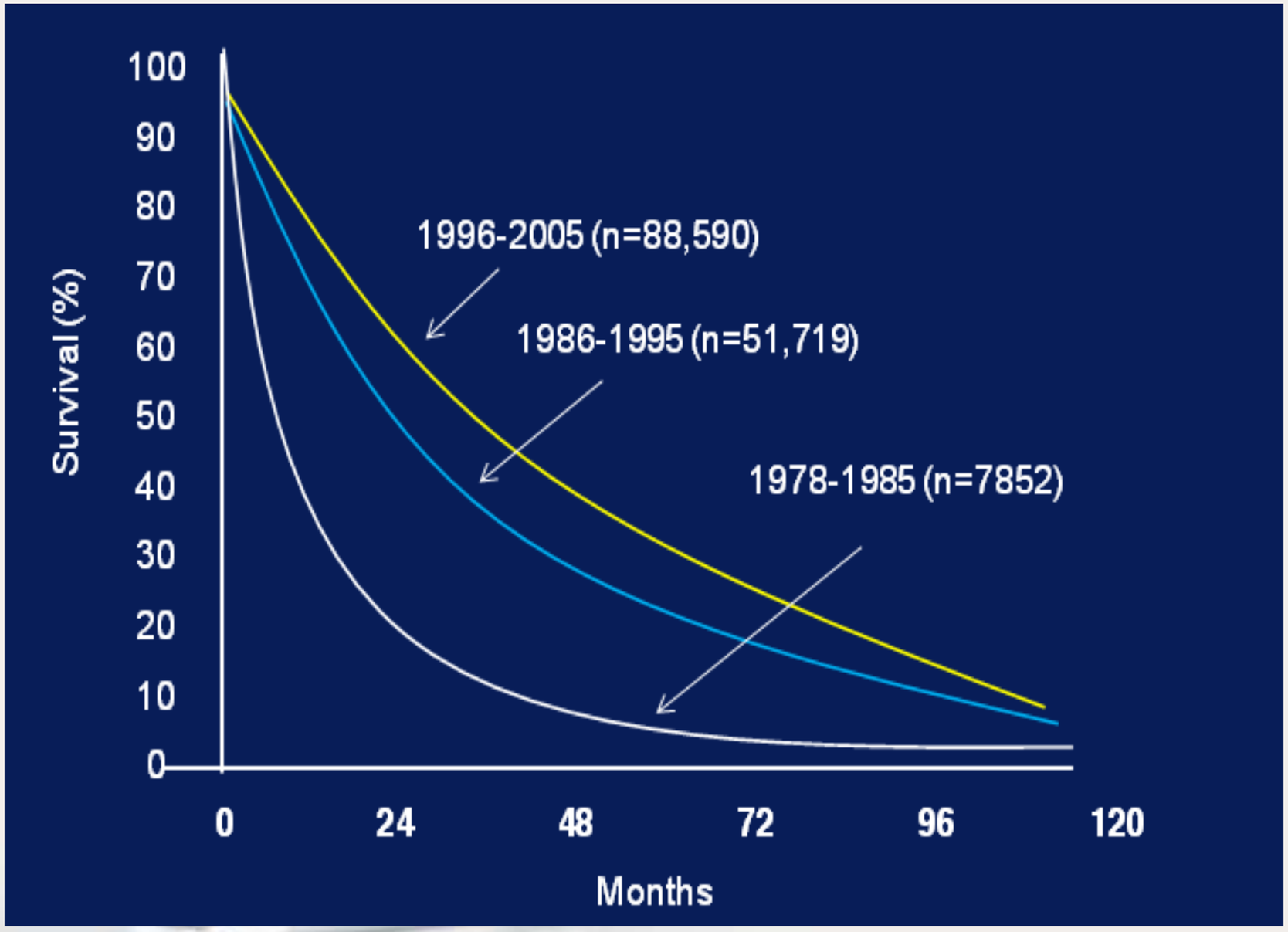
Radiological Diagnosis of 1-2 cm Nodules in Cirrhosis: A Surveillance study of 59 patients

	No HCC	Sensitivity	Imaging
CE-US	**34**	26%	**100%**
Contrast CT	**34**	**44%**	**100%**
MR gadalinium	**32**	**44%**	**100%**
Two coincidental technique of stepwise imaging diagnosis (AASLD 2005)		**35%**	**100%**
Sequential study with one imaging	**65%**		**100%**

A single technique of stepwise imaging diagnosis of HCC led to a 23% reduction of FNB procedures (p=0.031)

Sangiovanni A GUT 2010:59:638-44

Cumulative Survival Rates of HCC in Japan
The XVIII report of LCSG



	Percent of 5 year survivial
1978-85	9.5%
1986-95	6.8%
1996-05	39.3%

Ikai, Hepatology Research **2010**

Effect of Surveillance on Outcomes

- Retrospective analysis of patients with cirrhosis and HCC (N = 269)
  - Standard-of-care surveillance (n = 172)
    - Ultrasound or other abdominal imaging ≥ 1 time/year
  - Substandard surveillance (n = 48)
    - Lack of abdominal imaging within 1 year of cancer diagnosis
  - Absence of surveillance (n = 59)

Outcomes, %	Standard-of-Care Surveillance (n = 172)	Substandard Surveillance (n = 48)	Absence of Surveillance (n = 59)	*P* Value
HCC diagnosis at stages 1/2	69	35	18	< .001
Liver transplantation	32	13	7	< .05
Mean 3-year survival from cancer diagnosis	40	27	13	< .005

Stravitz RT, et al. Am J Med. 2008;121:119-126.

NEVER ENDING: COST UTILITY RATIO

Use of Surveillance for HCC among patients with cirrhosis in US	
Study	1873 cirrhotics + HCC 1994-2002, SEER Medicare
Surveillance	17% regular 54% US
uptake	38% inconsistent 45% none

Elected for screening	Elected Usual Care
N= 182 (89%)	N=23(11%)

RUSH to JUDGEMENT?

Standard of Care and Not a Clinical Option

Davila, Hepatology 2010, Poustchi Hepatology 2011

Summary

- At-risk patients should be screened for HCC
- Ultrasound surveillance is preferable
  - AFP adds cost without significant benefit
- Serologic screening is not highly efficient
  - High false-positive and false-negative rates
- Surveillance should take place at 6-month intervals
  - Evidence for better survival than 12-month intervals

Screening and Surveillance are considered standard of care.

Cirrhosis (Non-HBV) Suitable for HCC Surveillance*

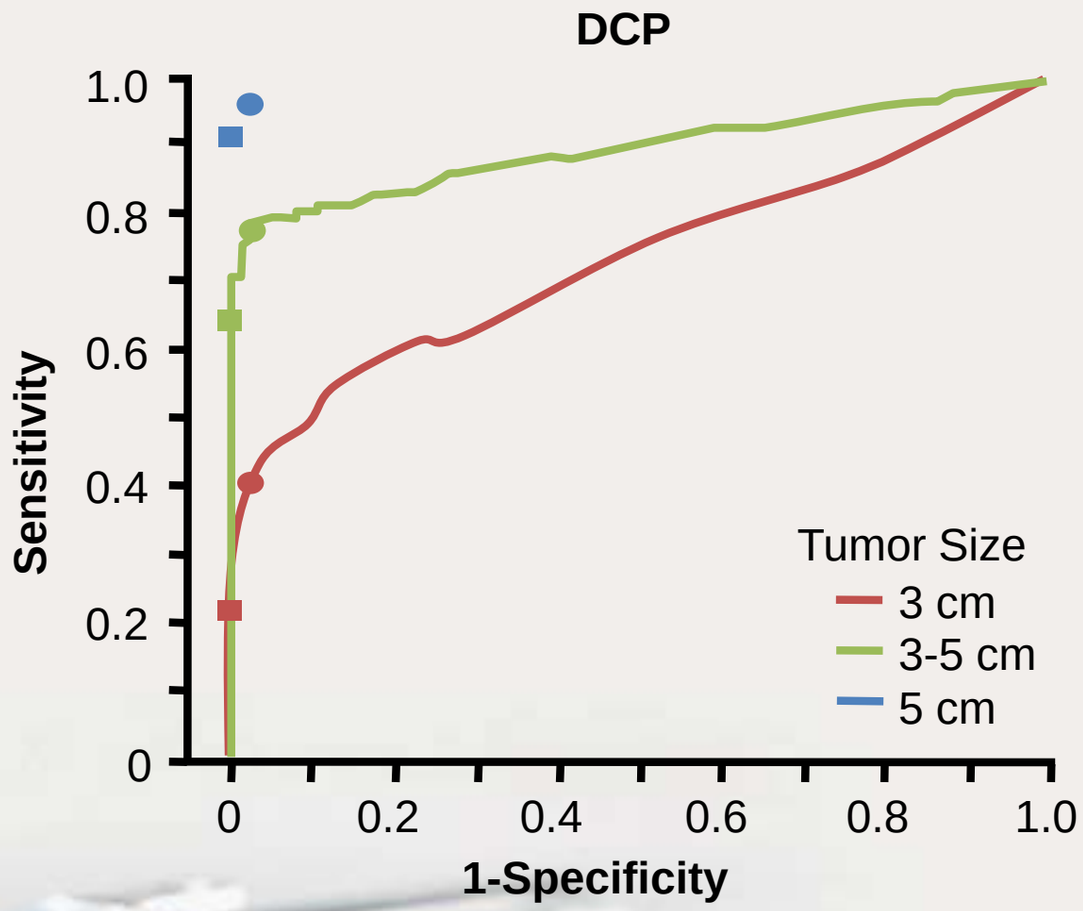
- Hepatitis C
  - Incidence of HCC ~ 2% to 8% per year
- Primary biliary cirrhosis
- Alcoholic cirrhosis
- Genetic hemochromatosis
- ? Nonalcoholic steatohepatitis
- ? Alpha1-antitrypsin deficiency
- ? Autoimmune hepatitis
- ? Cryptogenic cirrhosis

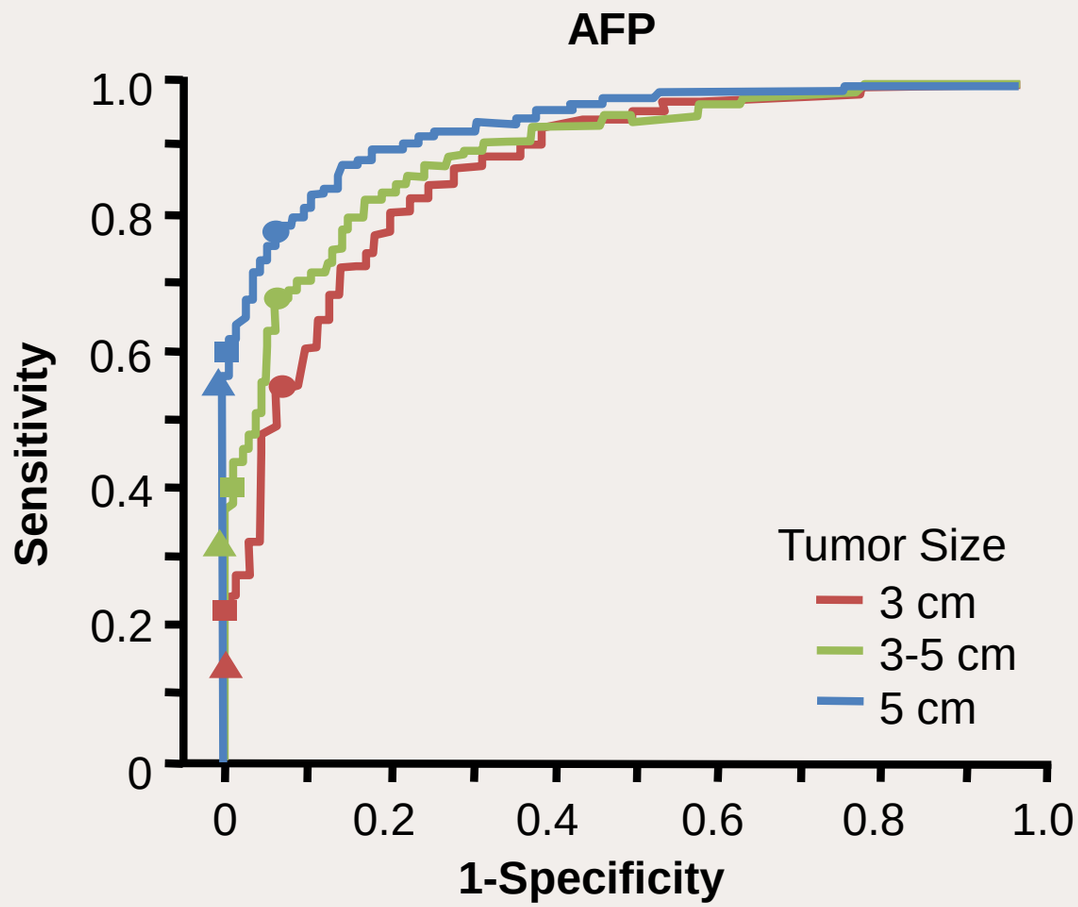
*Populations with an annual HCC incidence of ≥ 1.5%.

Takano S, et al. Hepatology. 1995;21:650-655. Tsukuma H, et al. N Engl J Med. 1993;328:1797-1801. Pateron D, et al. J Hepatol. 1994;20:65-71. Zaman SN, et al. Lancet. 1985;1:1357-1360.

Sensitivity/Specificity of DCP and AFP as a Function of Disease Stage

- Effect of tumor size on the diagnosis of HCC by DCP, AFP





Nakamura S, et al. Am J Gastroenterol. 2006;101:2038-2043.