

## Screening for Hepatocellular Carcinoma

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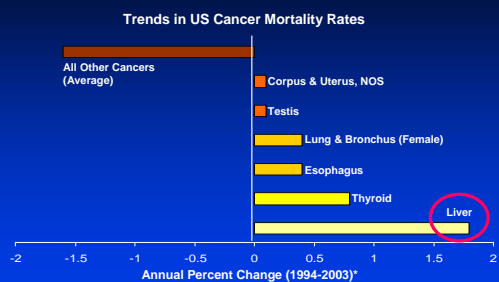
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## Liver Cancer Has the Fastest Growing Death Rate in the US



\*Represents the annual percent change over the time interval  
National Cancer Institute Website.  
Available at: <http://www.aicr.org/resources/pubs/cancerfactsheets/cfs010.pdf> Accessed September 21, 2006.

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## Why HCC is Rising?

Increasing prevalence of patients with cirrhosis

- Rising incidence of cirrhosis
  - HCV (main reason)
  - HBV
  - ?NAFLD / insulin resistance
- Improved survival of patients with cirrhosis

El-Serag HB, Gastroenterology 2004

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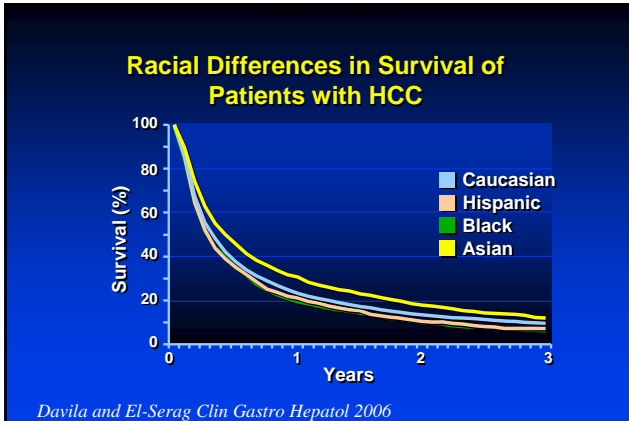
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Learning Luncheon 2: Hepatocellular Cancer  
 Screening: In Whom and How?




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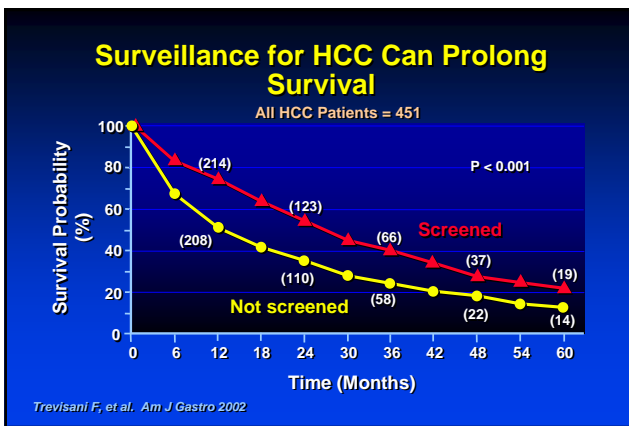
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### Surveillance for HCC Improves Mortality

A Randomized Controlled Trial

	Screened group	Control group
Person-years in study	38,444	41,077
HCC occurrence		
Cases	86	67
Total incidence (per 100,000)	223.7	163.1
Rate ratio (95% CI)	1.37 (0.99, 1.89)	
Deaths from HCC		
Deaths	32	54
Total mortality (per 100,000)	83.2	131.5
Rate ratio (95% CI)	0.63 (0.41, 0.98)	

*Zhang BH, et al. J Cancer Res Clin Oncol 2004*

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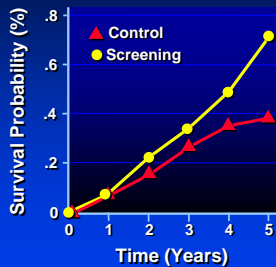
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### Surveillance for HCC Reduces Mortality: A Randomized Controlled Trial



Zhang BH, et al. J Cancer Res Clin Oncol 2004

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### Outcomes of HCC Surveillance

#### Increased

- ✓ Detection of early cancer
- ✓ Detection of single tumor <5 cm
- ✓ Receipt of surgical therapy
- ✓ Survival

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### Cost-Effectiveness of HCC Surveillance

- Surveillance with bi-annual alpha-fetoprotein (AFP) and ultrasonography in Child class A cirrhotics had cost-effectiveness ratios between \$26,000 and \$55,000 per QALY
- 2 other studies show cost-benefits of HCC surveillance

Sarasin FP, et al. Am J Med 1996  
Arguedas MR, et al. Am J Gastroenterol. 2003  
Lin OS, et al. Aliment Pharmacol Ther. 2004

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*Learning Luncheon 2: Hepatocellular Cancer  
Screening: In Whom and How?*

**Criteria for Cancer Screening Program**

- the disease should be an important health problem
- identifiable target population
- treatment of occult disease should offer advantages compared with the treatment of symptomatic disease.
- screening test should be affordable
- test must be acceptable to the target population and to health care professionals.
- standardized recall procedures
- screening tests must achieve an acceptable level of accuracy

*Cancer 2004;101:1107-17.*

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**Screening for HCC:  
AASLD Recommendations**

- Population in which screening should be done
  - Cirrhosis (any etiology)
  - HBV: older, family history, cirrhosis
- Surveillance for HCC should be performed with ultrasonography (level II)
- AFP alone should not be used for surveillance unless ultrasonography is not available (level II)
- Screening should occur every 6-12 months (level II)
- The surveillance interval does not need to be shortened for patients at higher risk of HCC (level III)

*Bruix J, et al. Hepatology 2005;42:1208*

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**Risk Factors for HCC in  
Chronic HCV**

- HCC unusual in persons with grade 0-2 fibrosis
- HCC rate increased in persons with grades 3-4 fibrosis (bridging fibrosis or cirrhosis)
  - Risk of 1%-4%/year
  - Platelet count < 130,000 or elevated AFP may reflect increase risk

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### Risk Factors for HCC in HBsAg-Positive Carriers

- Increasing age in males
  - 2 population-based cohort studies
- Males > Females
  - multiple studies
- Cirrhosis > no cirrhosis
  - population-based cohort study
- HBeAg-positive carriers
  - cohort studies
- Frequent reversions from HBeAg to anti-Hbe
- Family History (multiple studies)

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### Cirrhosis and HCC (1-3% per year)



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### Screening for HCC

- Non-hepatitis B cirrhosis
  - Hepatitis C
  - Alcoholic cirrhosis
  - Genetic hemochromatosis
  - Primary biliary cirrhosis
  - Possibly: Alpha1-antitrypsin deficiency, non-alcoholic steatohepatitis, autoimmune hepatitis

Bruix J, Sherman M. Hepatology 2005

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### Screening for HCC

- Hepatitis B carriers
  - Asian males > 40 years
  - Asian females > 50 years
  - All cirrhotic hepatitis B carriers
  - Family history of HCC
  - Africans over age 20

Bruix J, Sherman M. *Hepatology* 2005

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### Who To Screen? Difficult Decisions

- Age
- Comorbidity
- Drug and alcohol
  
- Be informed, Discuss, Document

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### Alpha-fetoprotein

- Alpha-Fetoprotein (AFP) was first recognized as a distinct band, next to albumin (hence *alpha*) by electrophoresis of human cord blood in 1956
- The association of AFP with HCC was not made until 1963 when Abelev detected AFP in the blood of mice with transplantable HCCs

Johnson P.J. *Clin Liv Disease* 2001

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Screening: In Whom and How?

**AFP (>20 ng/ml) in HCC Surveillance  
Prospective Cohort Studies**

Author	No. of Cirrhotics	No. of HCC	PPV %	NPV %
Pateron	118	14	33	-
Oka	260	55	32	82
Bolondi	313	61	46	85
Tong	602	31	12	99
Chalasani	285	27	30	-

Marrero JA. Clin Liver Dis 2005

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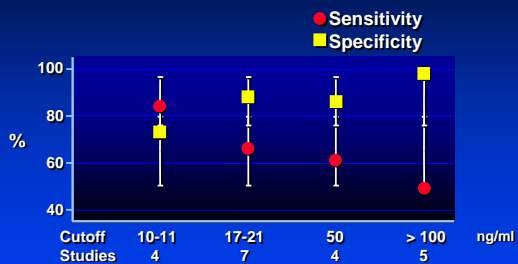
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**Performance Characteristics  
of AFP Based on Cutoff Level**



Colli A, et al. Am J Gastro 2005

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**Other Markers**

- Des-gamma-carboxy prothrombin (DCP)
  - Cohort studies of patients with cirrhosis
    - Sensitivity 23%-57%
  - 734 pts with cirrhosis, follow up 13 months, and 29 HCC
    - DCP: sensitivity 41%; specificity 90%
    - AFP: sensitivity 40%; specificity 62%
  - Possibly more specific than AFP
- AFP-L3
  - More specific than AFP
- Combination

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### Combination vs. AFP alone

- HCV-related cirrhosis were followed up prospectively for 2 years.
  - 34 of 298 who were free of HCC at entry.
- Only AFP (>20 ng/mL): sensitivity, specificity, and positive and negative predictive values: 61%, 71%, 34%, and 88%, respectively
- Combination: 77%, 59%, 32%, and 91%, respectively
- Marginal improvement in surveillance for early HCC

*Sterling RK et al Clin Gastro Hep 2009*

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### Ultrasound in HCC in Cohort Studies

Author	Year	Sensitivity (%)	Specificity (%)	Likelihood Ratio	
				Pos	Neg
Okazaki	84	86	99	66.0	0.14
Maringhni	84	92	86	6.5	0.09
Kobayashi	85	75	98	32.6	0.26
Tanaka	86	47	100	589.0	0.41
Dodd	92	43	98	21.5	0.58
Saada	97	33	100	333.0	0.67
Chalasanani	99	59	92	8.4	0.45
Rode	01	46	95	9.2	0.57
Bennett	01	30	97	7.4	0.72
Teefey	03	89	73	3.3	0.15
Libbrecht	03	40	100	400.0	0.60
<b>Pooled Estimates</b>		<b>60.5</b>	<b>96.9</b>	<b>17.7</b>	<b>0.5</b>

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### Ultrasound for HCC Screening

- Metaanalysis of prospective studies using ultrasound for the detection of early HCC.
  - Overall sensitivity of 72%.
- However, when only those studies that controlled for verification bias
  - Overall sensitivity drops to 35%
- Better quality studies are needed.

*Singal A, et al. APT 2009*

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### CT Scan, MRI for Screening

- No evidence
- Pros: less operator dependent, more sensitive and specific for HCC diagnosis
- Cons: expensive, limited availability, radiation, false positive, still operator/reader dependent

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### Screening for HCC: AASLD Recommendations

- Surveillance for HCC should be performed with ultrasonography (level II)
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### Surveillance Recommendations

- The target population for surveillance are those with liver cirrhosis (and HBV-infected patients without cirrhosis in special circumstances)
- AFP and US are the recommended screening tests for HCC in patients at the highest risk
- Based on tumor doubling time and studies, the recommended interval for surveillance is every 6 months in patients with cirrhosis
- Screening increases likelihood of HCC diagnosis
  - Small and potentially treatable
  - May reduce mortality

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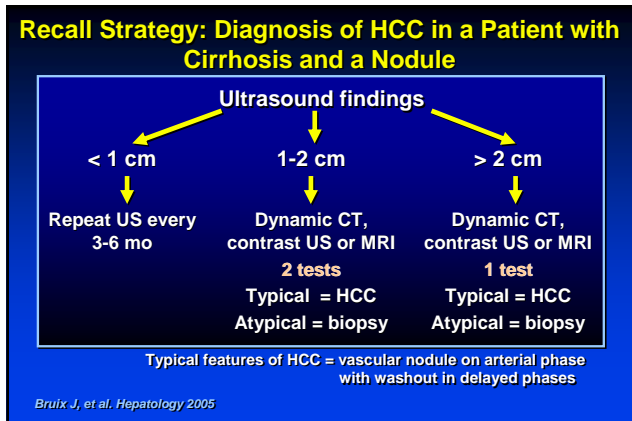
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# Learning Luncheon 2: Hepatocellular Cancer Screening: In Whom and How?




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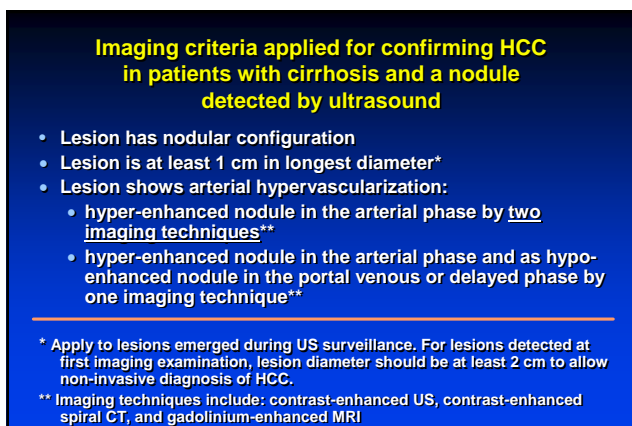
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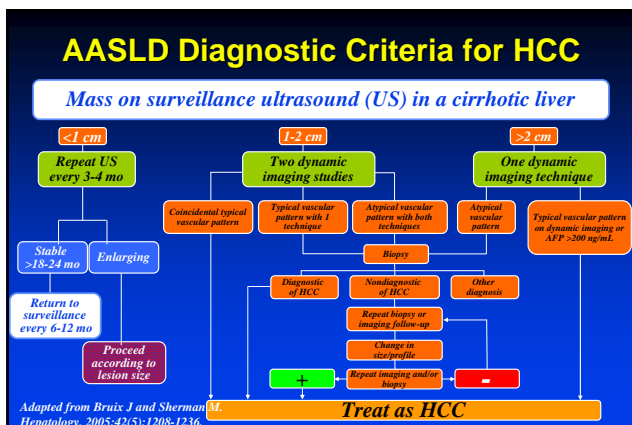
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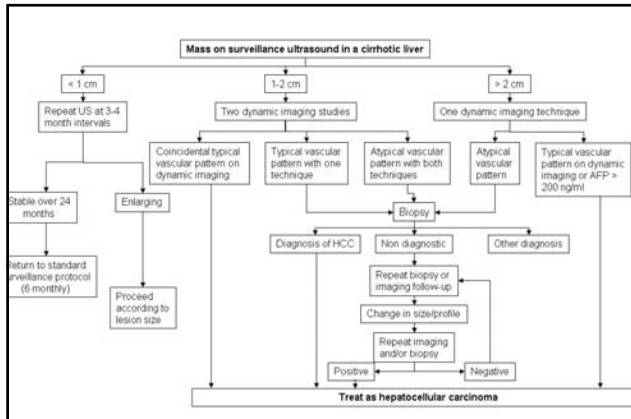
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## Learning Luncheon 2: Hepatocellular Cancer Screening: In Whom and How?




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### Outcomes of HCC Screening

Is it used?  
How is it used?  
frequency, type, patient population  
Recall strategy?  
Is appropriate therapy given?

Clinical Trials

Clinical Practice

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### Efficacy and Effectiveness Big Difference

	Efficacy	Access	Diagnose	Recommend	Accept	Adhere	Effectiveness
Screen A	50%	80%	85%	85%	85%	70%	17%
Screen B	70%	80%	85%	85%	85%	70%	24%
Screen A modified	50%	90%	90%	90%	90%	80%	26%

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### HCC Surveillance in VA

- Three VA Centers
- 1998-2003
- 157 HCC cases
- Only 44 (28%) received any HCC screening within 3 yrs prior to HCC diagnosis
- Younger age and specific risk factor (HCV or ALD) increase likelihood of screening

*Davila J, et al. J Clin Hepatol 2007*

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### HCC Screening in Non VA SEER-Medicare

- 3,903 patients diagnosed with HCC
- Mean age: 76 years ( $\pm$  sd); all >65
- 67% male, 33% female
- 6.6% received regular screening, as defined as at least 1 screening test per year during 2 or the 3 years prior to HCC screening

▪ *Davila J et al. Gastroenterology 2009 Accepted*

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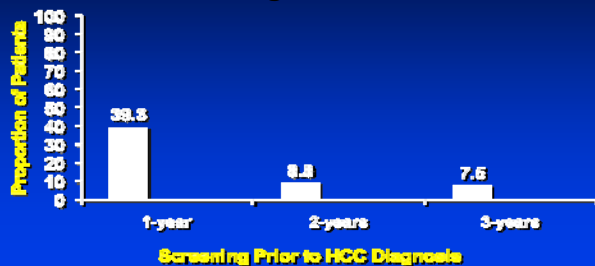
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### Receipt of Screening Prior to HCC Diagnosis



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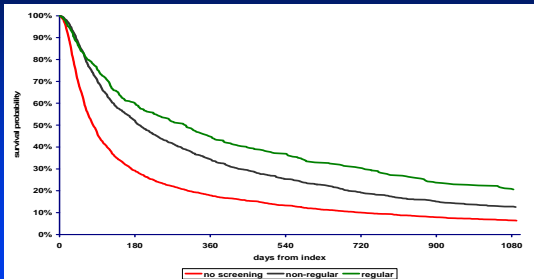
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## Learning Luncheon 2: Hepatocellular Cancer Screening: In Whom and How?

### Overall Survival by Screening Status



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### Is HCC Screening Effective?

- The pieces are present:
  - Increasing fatal disease
  - High risk population: liver cirrhosis (and HBV-infected patients)
  - OK tests: AFP and US
  - Recall strategy available (imaging, biopsy)
  - Treatment available: curative and palliative
- The whole thing?
- Effective in limited settings

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### Pros and Cons of HCC Screening

- Pro:
  - Possibility of early detection and prolonged survival
  - Liability of not screening
- Con
  - Costs of screening
  - Costs of evaluation of false positive tests
  - Anxiety of positive tests
  - Lack of recall strategy or effective therapy

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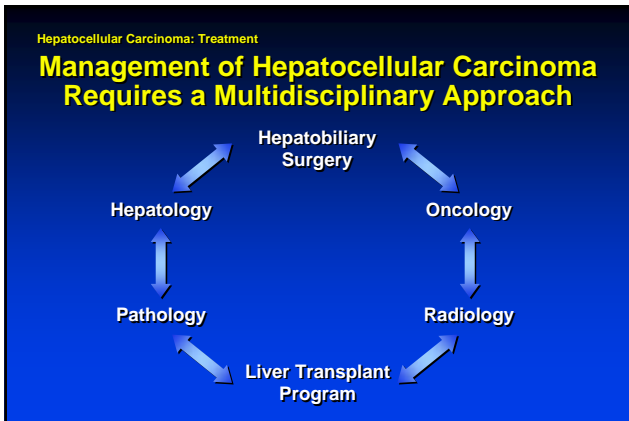
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Screening: In Whom and How?




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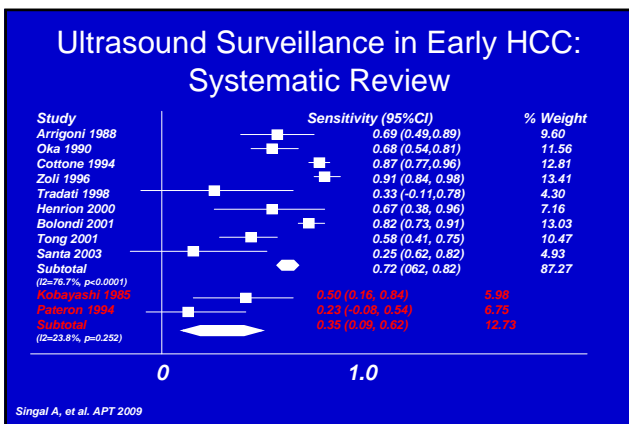
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Singal A, et al. APT 2009

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