The Chronic Liver Disease Foundation (CLDF) and the International Coalition of Hepatology Education Providers (IC-HEP) present:

THE LIVER SUMMIT

Certified by:

ANNENBERG CENTER FOR HEALTH SCIENCES AT EISENHOWER

Provided by:

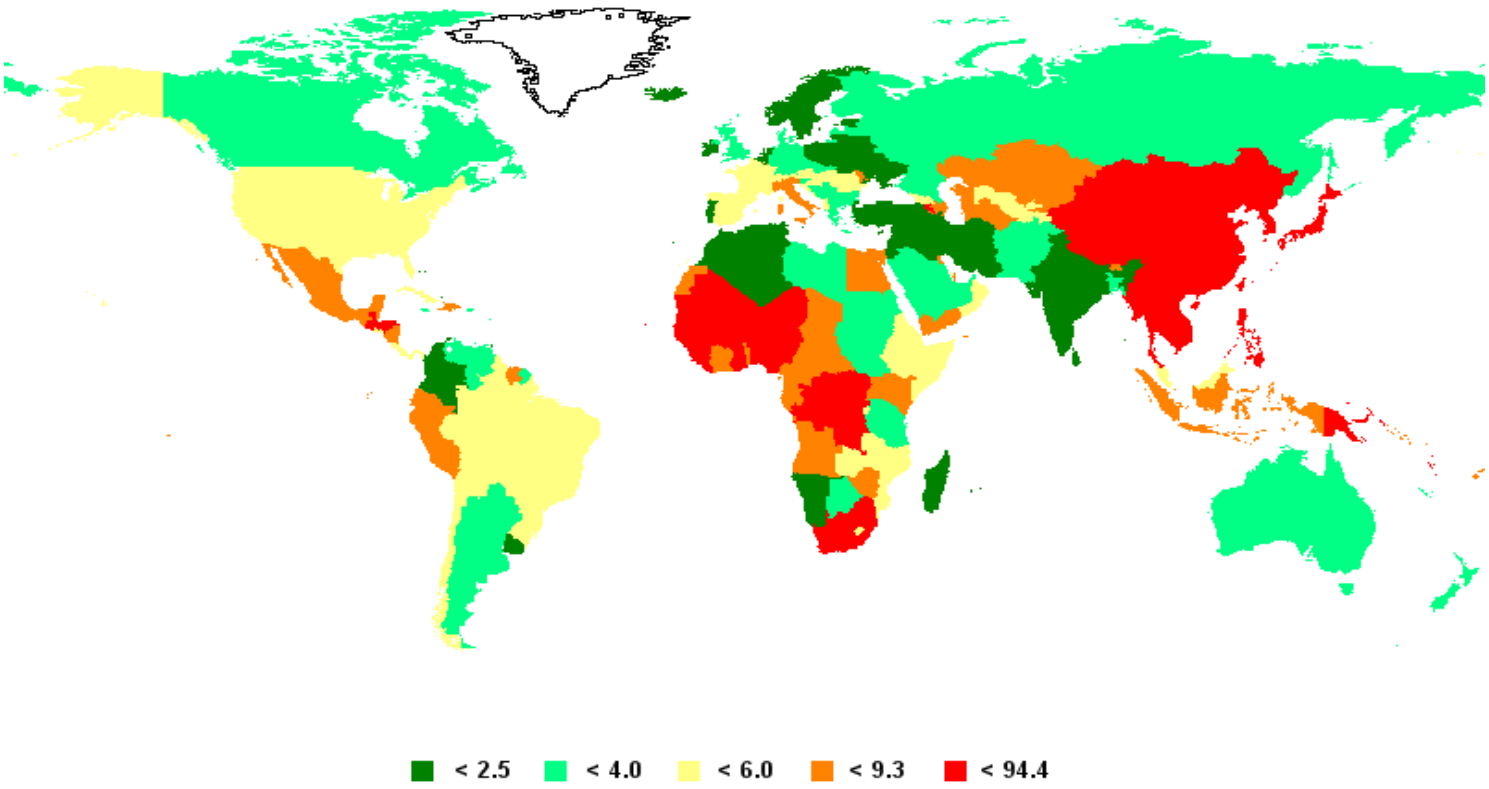
CLDF
Chronic Liver Disease Foundation

Endorsed by:

ICHEP
International Coalition of Hepatology Education Providers

Hepatocellular Carcinoma

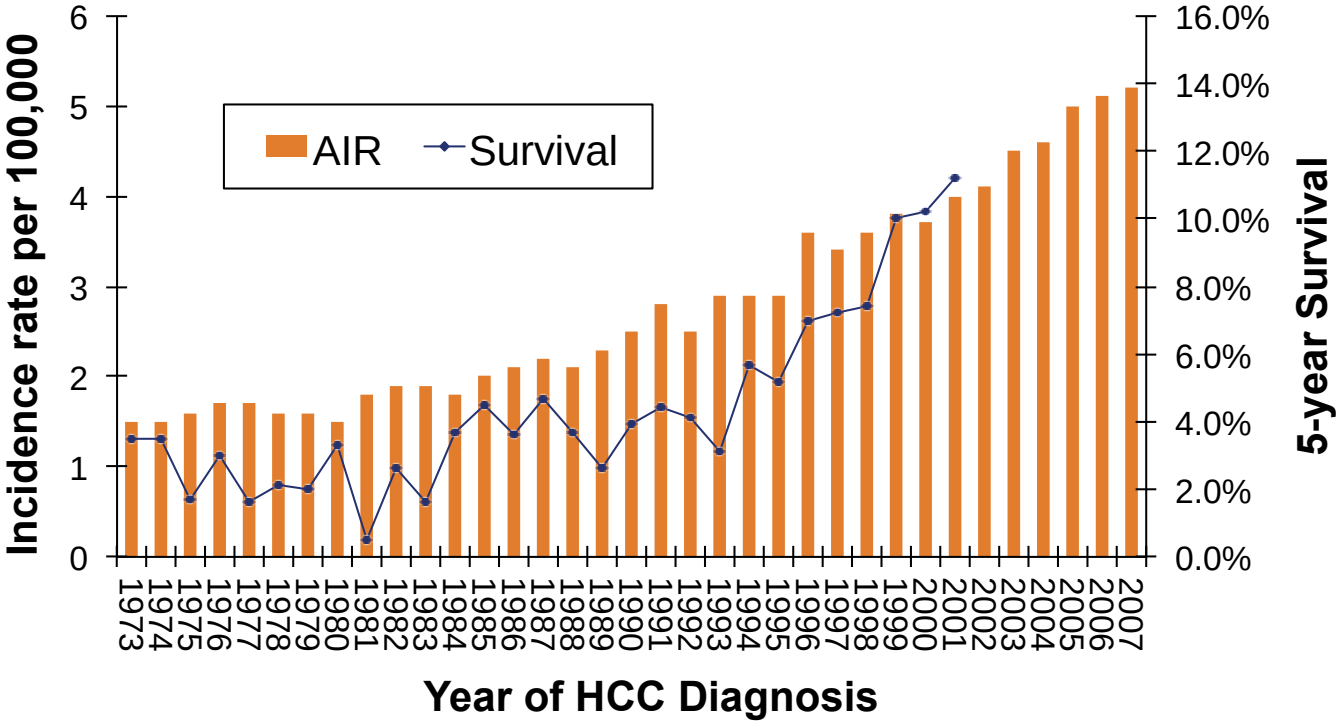
HCC: Age Standardized Incidence Rates 2005 (Men and Women)



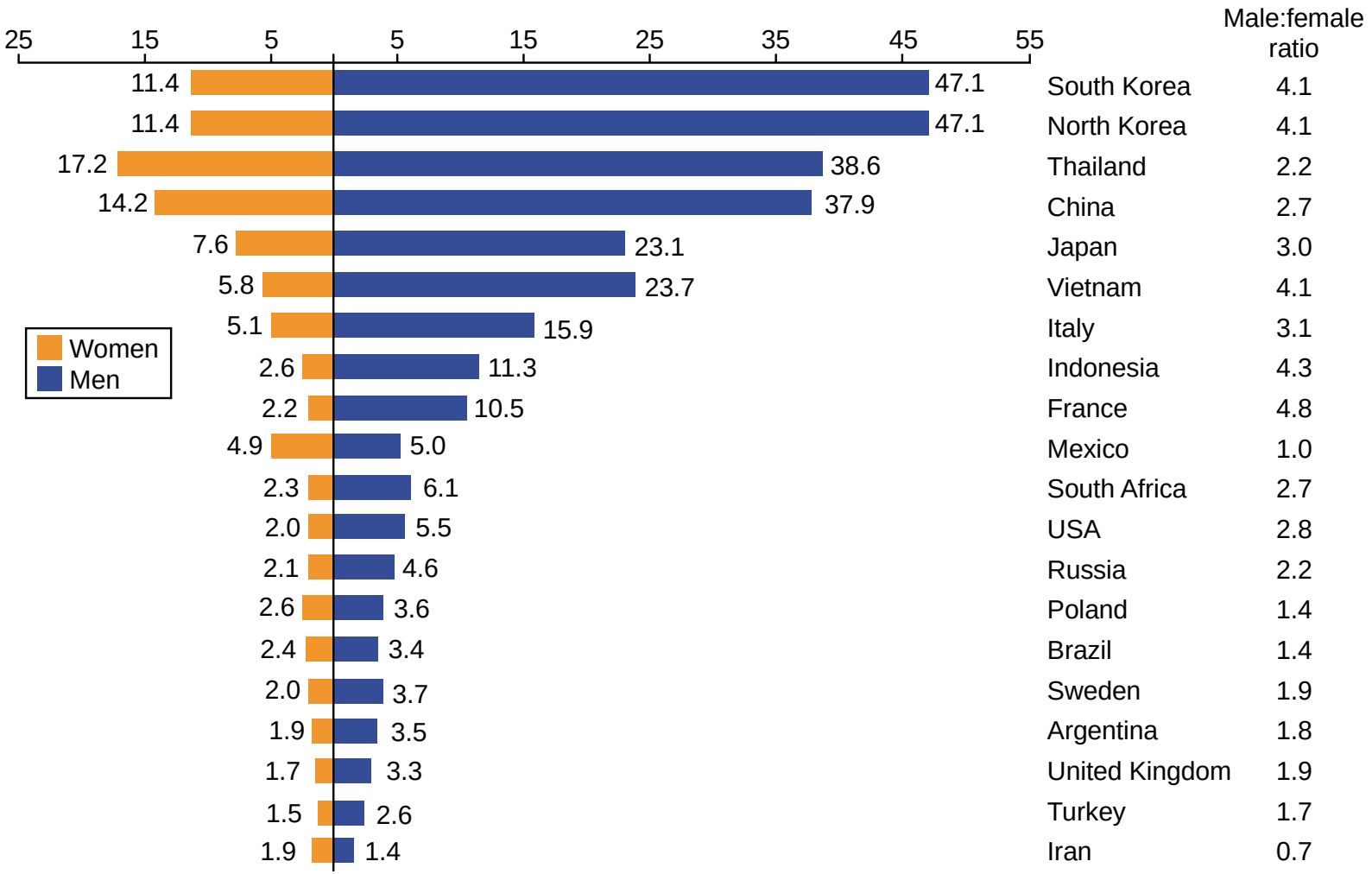
Global View of HCC

- Primary liver cancer increased from 437,408 cases in 1990 to 714,600 in 2002
- Incidence and mortality rates
  - Decreasing in areas of high and intermediate incidence, including China and Japan
  - Increasing in low-incidence areas, including the United States and Canada

The Incidence and 5-Year Survival of HCC in United States

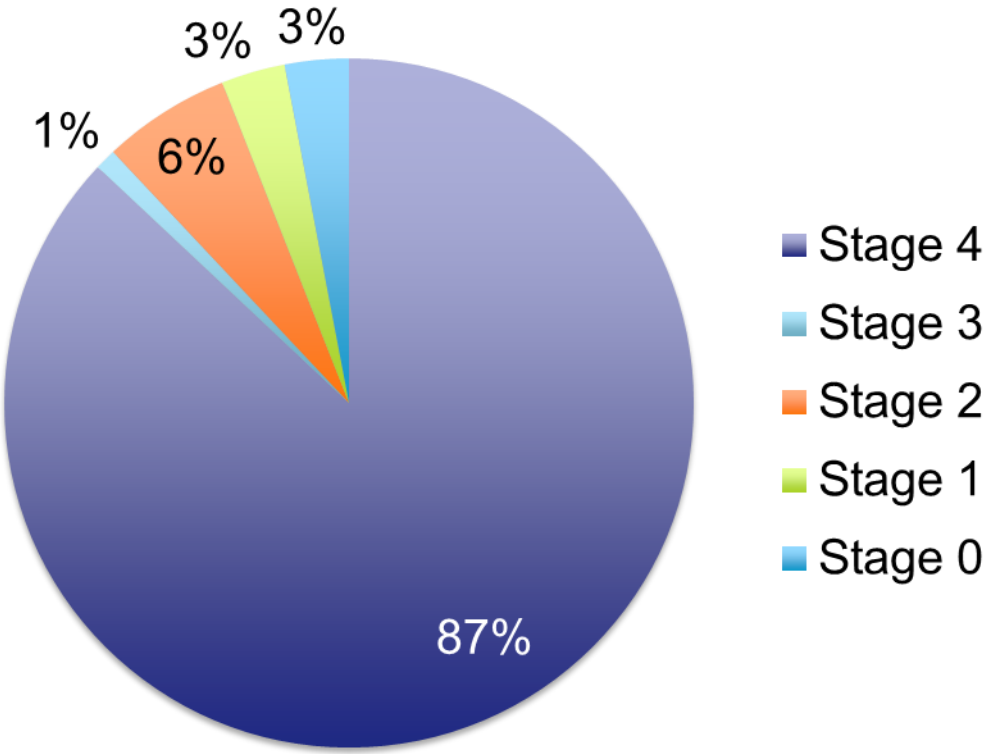


El-Serag HB. *N Engl J Med* 2011


25
15
5
5
15
25
35
45
55
Male:female ratio
Women
Men
11.4 47.1 South Korea 4.1
11.4 47.1 North Korea 4.1
17.2 38.6 Thailand 2.2
14.2 37.9 China 2.7
7.6 23.1 Japan 3.0
5.8 23.7 Vietnam 4.1
5.1 15.9 Italy 3.1
2.6 11.3 Indonesia 4.3
2.2 10.5 France 4.8
4.9 5.0 Mexico 1.0
2.3 6.1 South Africa 2.7
2.0 5.5 USA 2.8
2.1 4.6 Russia 2.2
2.6 3.6 Poland 1.4
2.4 3.4 Brazil 1.4
2.0 3.7 Sweden 1.9
1.9 3.5 Argentina 1.8
1.7 3.3 United Kingdom 1.9
1.5 2.6 Turkey 1.7
1.9 1.4 Iran 0.7

Liver Fibrosis and HCC

HCC can occur in non-cirrhotic livers, but most HBV patients with HCC have cirrhosis.



Yang JD, et al. *Clin Gastroenterol Hepatol*. 2011;9:64-70.

HCC in HCV

- Prevalence of HCV+ HCC (20-90%)
- Relative Risk of HCC
  - Compared to HCV- controls (25 fold)
- Absolute Risk of HCC
  - HCC in HCV (1 per 100 at 30 years)
  - HCC in HCV-related cirrhosis (3.5 per 100 [1-7])

Risk Factors for HCC in Chronic HCV: Host Factors

- Older age
- Duration of HCV infection
- Male sex
- Race
- Alcoholism
- Obesity
- Diabetes
- HBV co-infection
- HIV co-infection

HCV Viral Factors and Risk of HCC

- HCV Viremia (HCV RNA)
  - Any level (vs. none)
  - High level (vs. low)
    - Taiwan study show high HCC risk
    - US studies only as predictor of treatment response
- HCV Genotype
  - Possibly GT 1b
    - Meta analysis (1.78 increase in HCC odds)
  - GT 3

HCV Genotype 3 in the VA HCV Clinical Case Registry 2000-2009: Cirrhosis and HCC

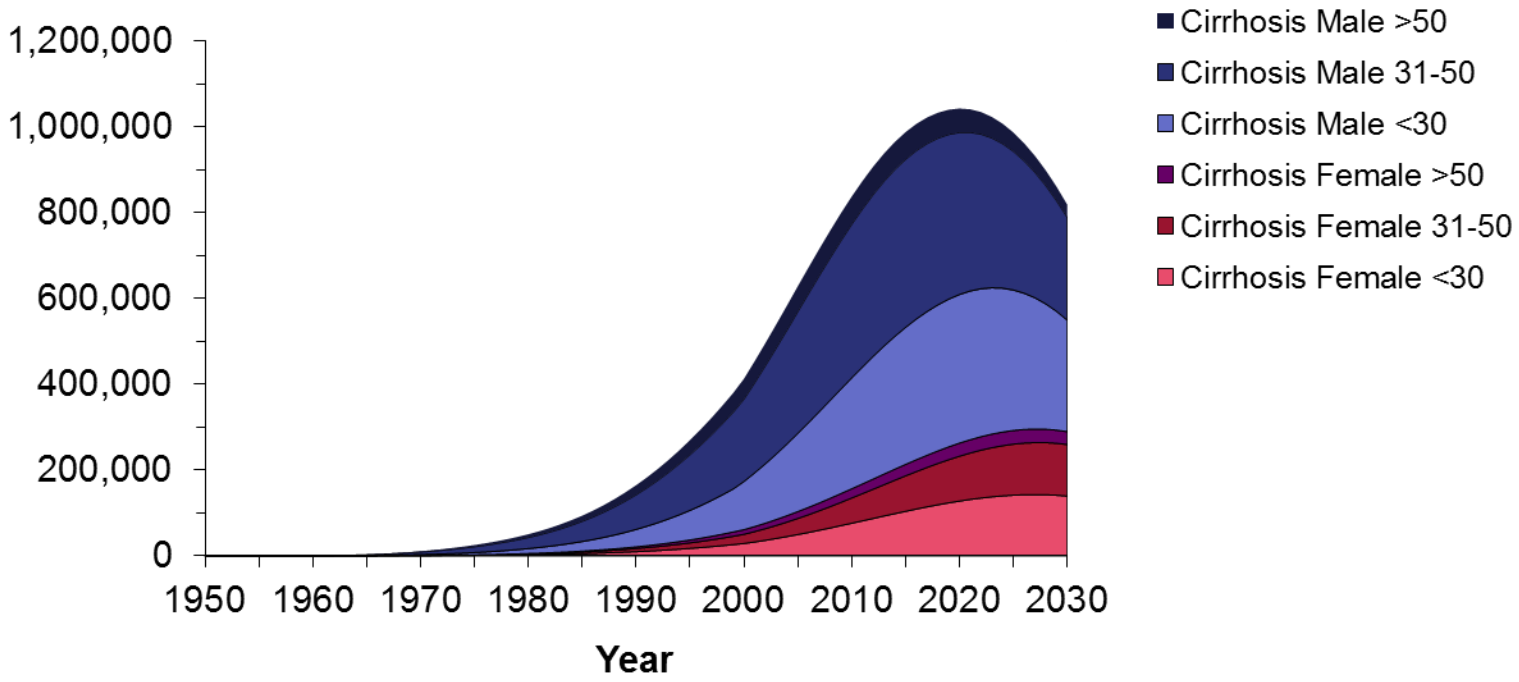
- 88,348 patients with genotype 1 (80%)
- 13,077 genotype 2 (12%)
- 8,337 genotype 3 (7.5%)
- Mean followup 5.4 years
- After adjustment for demographic, clinical and antiviral treatment factors, comparison between genotypes 3 and 1:

	Hazard Ratio	Confidence Interval
Cirrhosis	1.31	1.22.-1.39
HCC	1.80	1.61-2.03

Conclusion: Genotype 3 is associated with a significantly higher risk of cirrhosis and HCC vs genotype 1, independent of age, diabetes, BMI or antiviral treatment

Kanwal F et al, Hepatology 2014;60:98-105

HCV-related Cirrhosis by Cohort



Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings L *Gastroenterology* 2010

Determinants of HBV Disease Progression

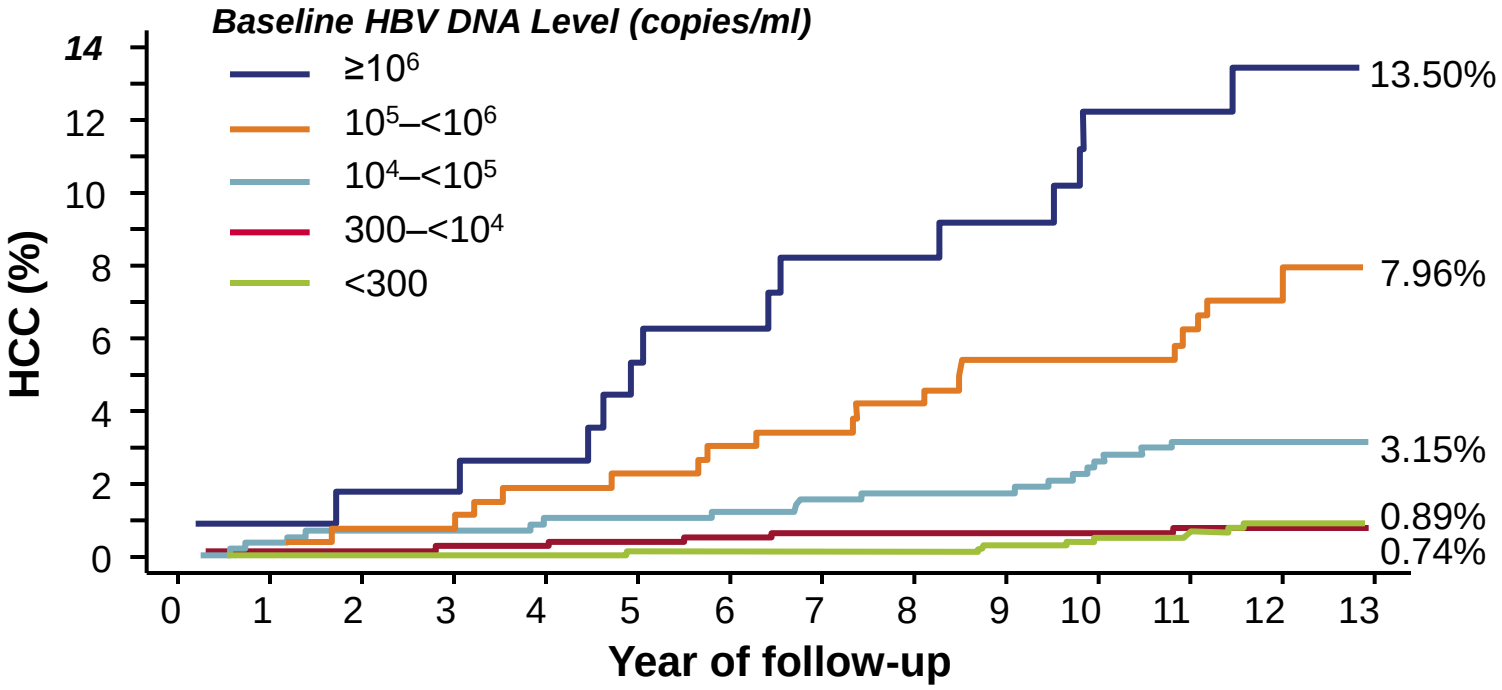
HBeAg-positive	HBeAg-negative
Prolonged interval before e-seroconversion	Persistent viral replication
Age > 40 Mildly, persistently abnormal ALT Genotype (C > B)	HBV-DNA Abnormal ALT Precore/BCP mutation
Male Alcohol Co-infection with HCV, HDV, HIV	

Yim HJ, et al. *Hepatology* 2006;43:S173-S181. Lai M, et al. *J Hepatol*. 2007;47:760-767.

Risk Factors for HCC in HBsAg-Positive Carriers

- Timing of HBV acquisition
- Older age
- Males > Females
- Cirrhosis > no cirrhosis
- Family History of HCC
- Heavy alcohol drinking
- Aflatoxin exposure
- HBeAg-positive carriers
- HBV genotype C
- HBV precore (decrease), core promoter (increase)
- Co-infection with HCV or HIV or HDV

Hepatitis B: Association Between Viral Load and Incidence of HCC



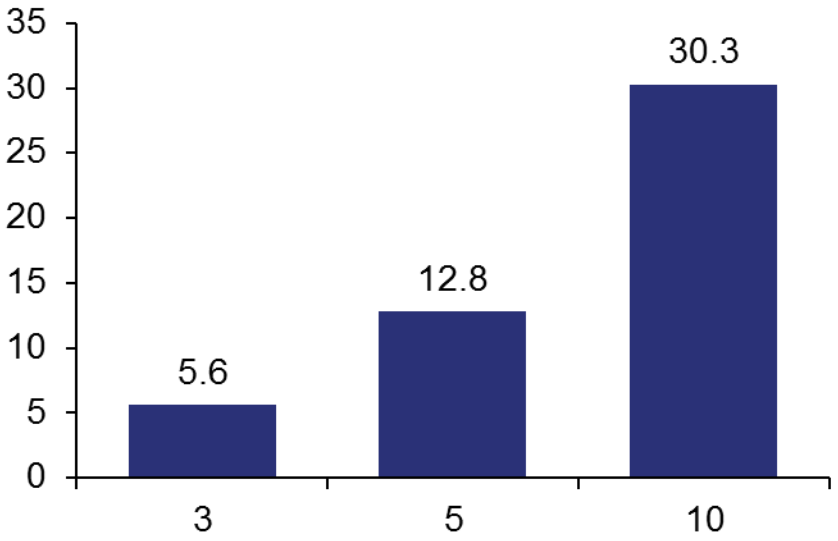
HBeAg negative, **normal ALT**, no liver cirrhosis at entry (n=2,925)

Chen CJ et al. *JAMA*. 2006;295:65–73

REACH-B Model

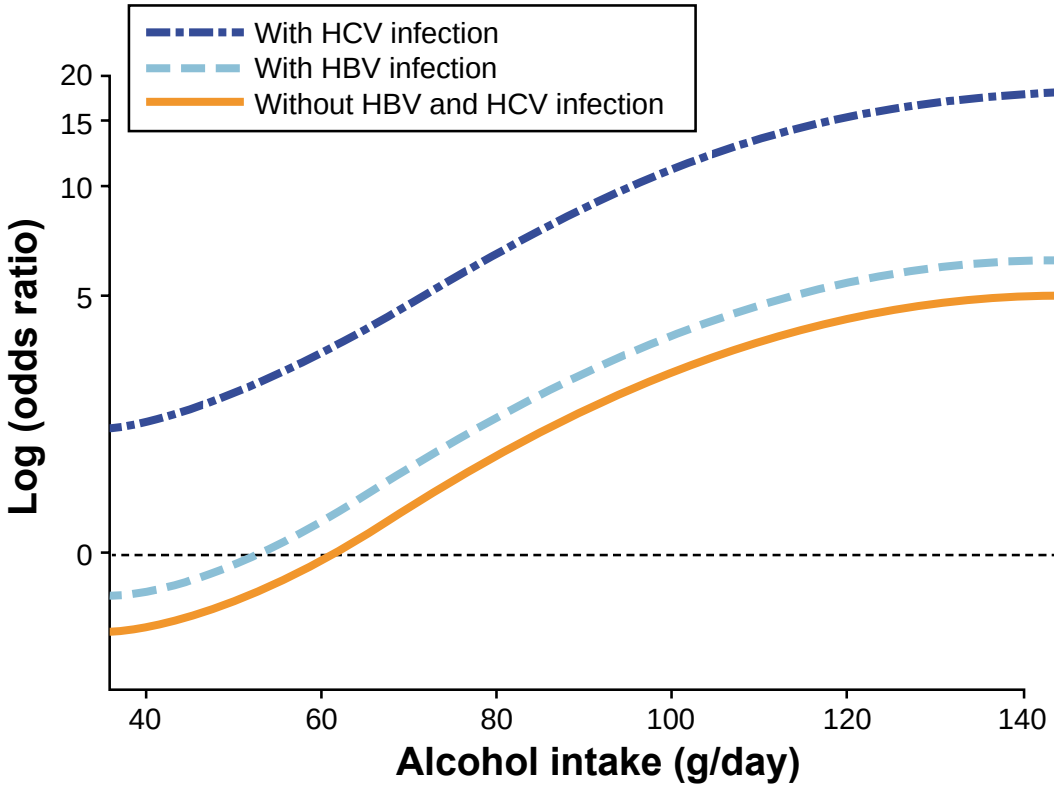
Variable	Data	Score
Sex	M/F	0-2
Age	Q 5 years over 30	0-6
ALT	<15 15-44 >45	0-2
HBeAg	+/-	0-2
HBV DNA	Und. ~10^4 ~10^5 ~10^6 >10^6	0-4

- 60 year-old HBeAg+ male ALT 47, HBV DNA 50,000
- REACH-B score=13



Yang HI. *Lancet Oncol* 2011; 12: 568–74

Alcohol and Viral Hepatitis

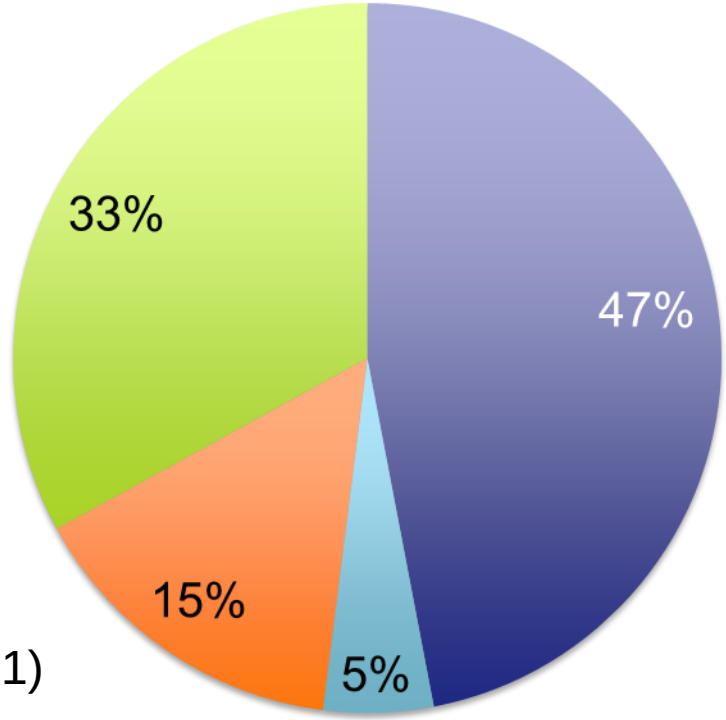


Gastroenterology 2012; 142:1264-1273.e1

Tobacco Smoking

- Smoking alone
  - Positive associations and no associations reported in different studies
- Smoking PLUS HBV and HCV infection
  - More than additive interaction between HBV infection and cigarette smoking
  - More than multiplicative interaction between HCV infection and cigarette smoking

HCV is the Dominant Risk Factor for HCC in the United States

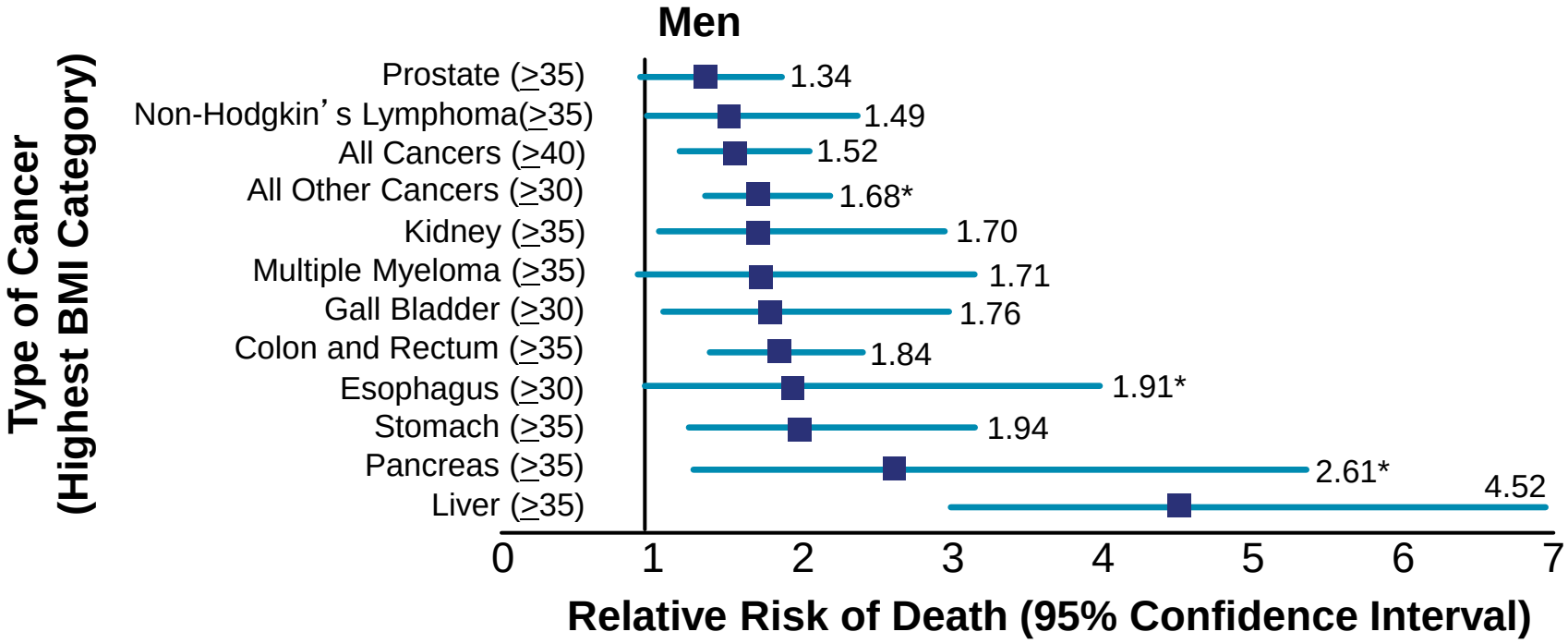


(N=691)

- HCV
- Both
- HBV
- Neither

- HBV most frequent in Asians
- HCV most frequent in whites and blacks

Mortality from Cancer in Obese US Men (n=900,053)

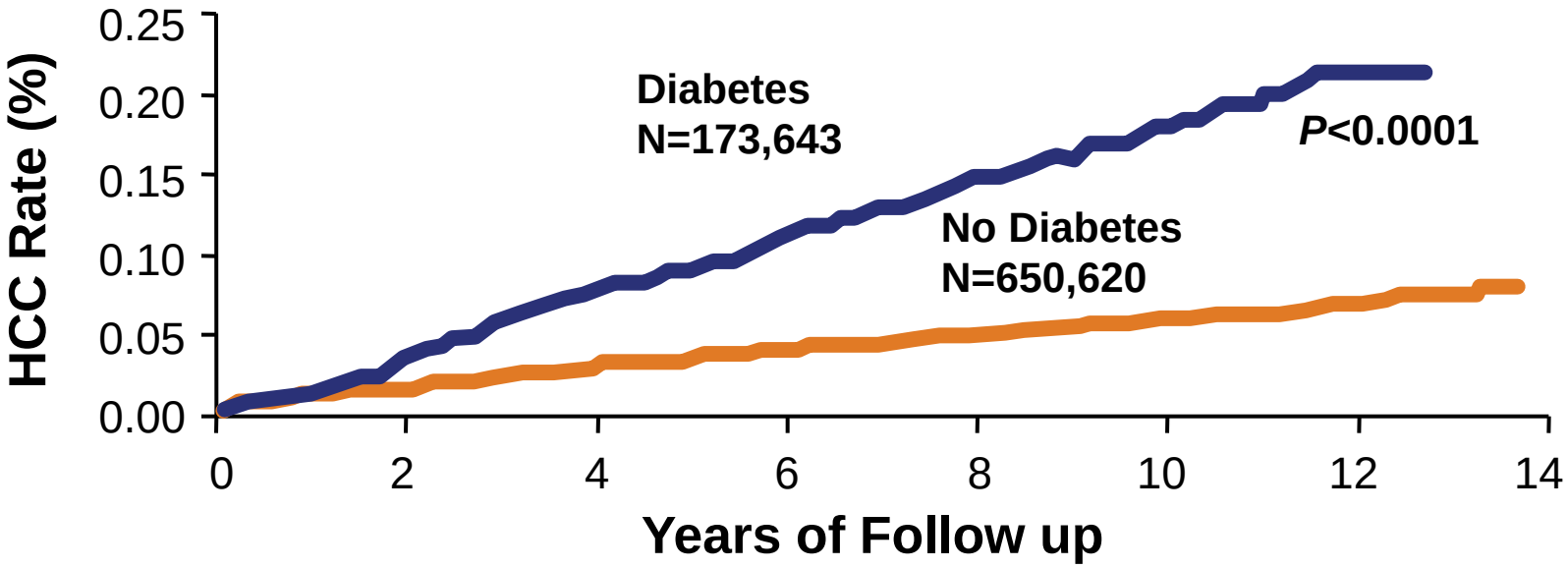


Calle, *NEJM* 2003

Obesity and Risk of HCC

- Systematic review of 10 cohort studies
  - Positive association between BMI and risk of HCC in 7 studies (relative risks ranging from 1.4 to 4.1)
  - No association in 2 studies
  - Inverse association in 1 study
- Limited by small number of cases with HCC, possibility of misclassification, and inconsistent adjustment for confounders

Diabetes Is Associated with a Two-fold Increase in Risk of HCC



El-Serag HB, et al, *Gastroenterology* 2004

NAFLD and Risk of HCC

- No evidence from population based data
- Possible increase in HCC risk in clinic based cohorts of NASH
  - ? Magnitude
  - ? Risk factors
- Consistent evidence from clinic based cohorts with NAFLD/NASH cirrhosis
  - Magnitude < HCV cirrhosis
  - Risk factors: obesity and diabetes

White D, Kanwal F, El-Serag. *Clin Gastro Hep* 2012

HCC in the Absence of Cirrhosis in United States Veterans

- ~13% of 1500 HCC cases developed in absence of cirrhosis
- These cases were more likely than HCC in cirrhosis to have
  - NAFLD or idiopathic compared to HCV or alcohol
  - Co-morbidities associated with metabolic syndrome
- While a small proportion, this poses logistical problems for HCC surveillance

El-Serag HB et al. DDW 2014

HCC Risk Factors:
Prevalence, Risk Estimates, Attributable Fraction?

	Prevalence in general population	Risk estimate of HCC	Current prevalence in HCC cases	Population attributable fraction
HBV	0.5-1%	20-25	10-15%	5-10%
HCV	1-2%	20-25	30-60%	20-25%
Alcoholic liver disease	10-15%	2-3	20-30%	20-30%
Metabolic syndrome	30-40%	1.5-2.5	20-50%	30-40%

Prevention of HCC

- HBV vaccination
- Treatment of viral hepatitis
- Coffee
- Statins
- Surveillance for HCC

HBV Vaccination and HCC: Taiwan Experience

ARTICLE

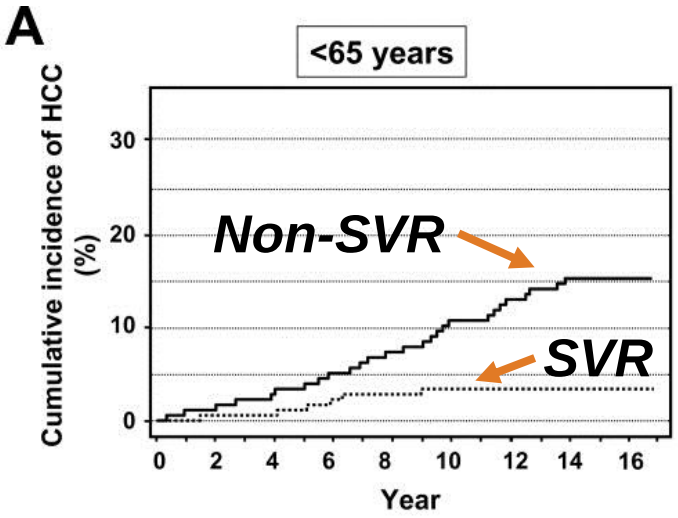
Decreased Incidence of Hepatocellular Carcinoma in Hepatitis B Vaccinees: A 20-Year Follow-up Study

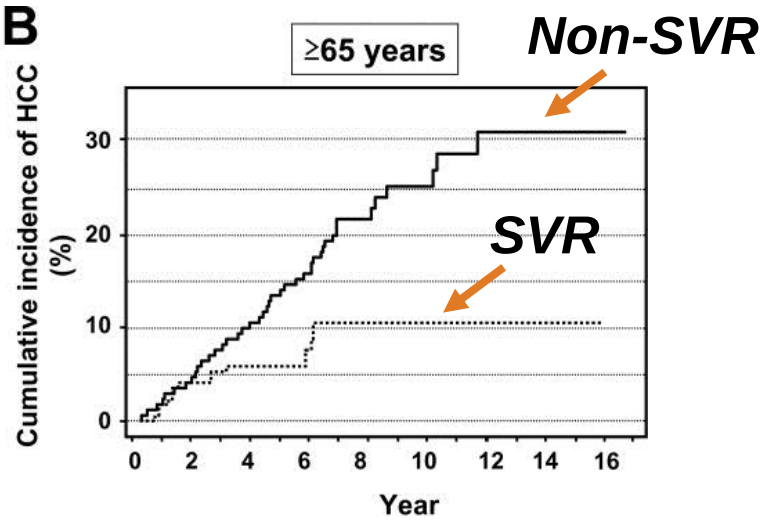
Mei-Hwei Chang, San-Lin You, Chien-Jen Chen, Chun-Jen Liu, Chuan-Mo Lee, Shi-Ming Lin, Heng-Cheng Chu, Tzee-Chung Wu, Sheng-Shun Yang, Hsu-Sung Kuo, Ding-Shinn Chen, the Taiwan Hepatoma Study Group

- HCC prevention extended from childhood to early adulthood
- Failures: incomplete vaccination, maternal HBsAg or HBeAg

J Natl Cancer Inst 2009;101:1348-1355

HCC and Hepatitis C Treatment



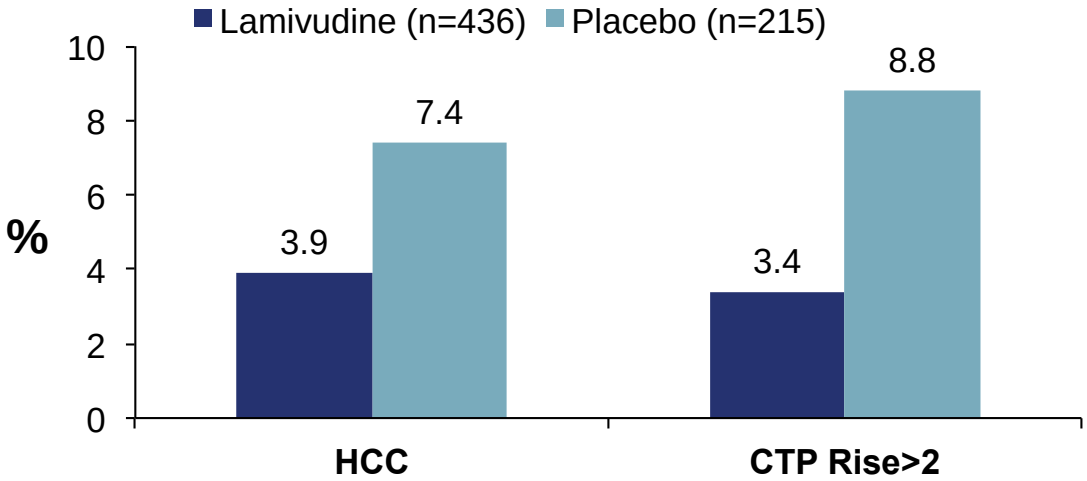


		0	5 yrs.	10 yrs.	15 yrs.
SVR	Patients with HCC	0	6	12	12
	Patients at risk	565	376	164	56
	Cumulative incidence of HCC	0%	1.2%	3.3%	3.3%
Non SVR	Patients with HCC	0	33	72	85
	Patients at risk	980	723	345	141
	Cumulative incidence of HCC	0%	3.6%	10.9%	15.5%

		0	5 yrs.	10 yrs.	15 yrs.
SVR	Patients with HCC	0	7	10	10
	Patients at risk	121	67	21	5
	Cumulative incidence of HCC	0%	6.0%	11.0%	11.0%
Non SVR	Patients with HCC	0	46	61	64
	Patients at risk	376	179	43	25
	Cumulative incidence of HCC	0%	14.1%	25.5%	31.1%

Impact of HBV Treatment on HCC

- Randomized controlled trial comparing lamivudine versus placebo
  - Patients with advanced fibrosis or cirrhosis
  - HBV-DNA (>10^5 copies/mL) or HBeAg+
  - Study terminated prematurely by DSMB (median Tx=32.4 mo)



Liaw Y-F, et al. *N Engl J Med.* 2004;351:1521-1531.

Prevention of HCC (Antiviral Treatment)

Efficacy in
Clinical Trials and
Research Centers

≠

Effectiveness in
Community Practice

↓

Efficacy x Access x
Correct Diagnosis x Recommendation x
Acceptance x Adherence

El-Serag HB. et al. *Gastroenterology.* 2007;132:8-10.

Statins and HCC

Systematic Review

- Ten studies
  - 7 observational, 3 clinical trials
- Pooled OR: 0.63 (0.52-0.76)
  - Not in the 3 clinical trials
- Not other lipid lowering medications
- Unclear
  - Dose, duration, type

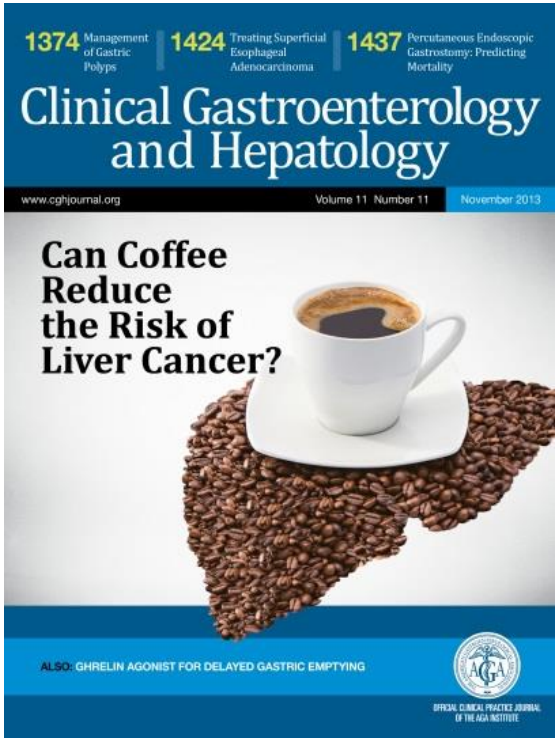
Metformin and Reduced Risk of HCC in Diabetic Patients: a Meta-analysis

- Seven studies:
  - Three cohort studies
  - Four case-control studies
- Significantly reduced risk of HCC in metformin users versus nonusers in diabetic patients
  - RR: 0.24, 95% CI 0.13–0.46, $p < 0.001$

Zhang H et al. *Scand J Gastroenetrol* 2013

Coffee and Hepatocellular Carcinoma

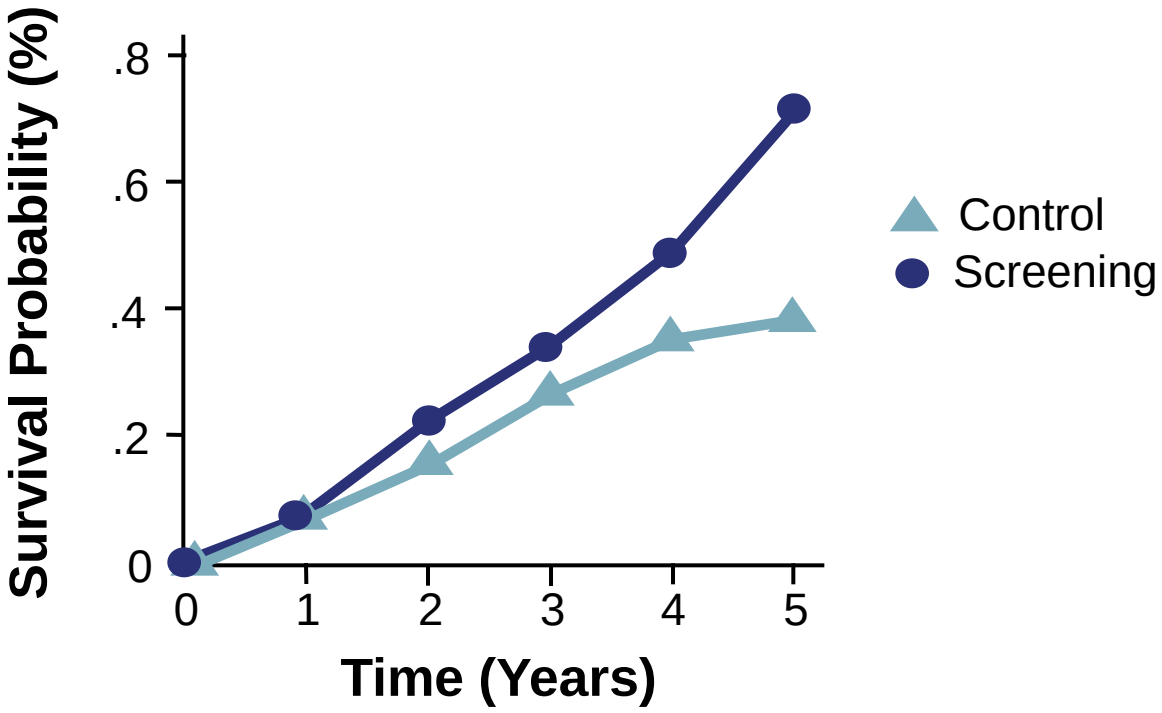
- Epidemiologic studies: coffee consumption is inversely related to
  - Serum liver enzyme activity
  - Liver cirrhosis
  - HCC
- For each additional 1 cup of coffee:
  - Case-control studies
    - (0.77, 0.72-0.83)
  - Cohort studies
    - (0.75, 0.65-0.85)



HCC Surveillance: Randomized Controlled Trials

- Cirrhosis (NONE)
- Hepatitis C infection (NONE)
- Hepatitis B infection carriers
  - China
  - Two trials
  - One showed benefit (Zhang et al. 2004)
  - One did not show benefit (Chen et al. 2003)

Surveillance for HCC Reduces Mortality:
A Randomized Controlled Trial of AFP+US q 6 months



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

Recommended Groups for HCC Surveillance

Population Group	Threshold Incidence for Efficacy of Surveillance (>0.25 LYG)(%/year)	Incidence of HCC (%/year)
Asian male hepatitis B carriers > age 40	0.2	0.4–0.6
Asian female hepatitis B carriers > age 50	0.2	0.3–0.6
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African/North American Blacks	0.2	HCC occurs at a younger age
Cirrhotic hepatitis B carriers	0.2-1.5	3–8
Hepatitis C cirrhosis	1.5	3–5

Sherman M. *Semin Liver Dis*. 2010;30(1):3-16.

Groups in Whom the Risk of HCC is Increased, but in Whom Efficacy of Surveillance Has **Not** Been Demonstrated

Population Group	Threshold Incidence for Efficacy of Surveillance (>0.25 LYG)(%/year)	Incidence of HCC (%/year)
Hepatitis B carriers <40 (males) or 50 (females)	0.2	<0.2
Hepatitis C and stage 3 fibrosis	1.5	<1.5
Noncirrhotic NAFLD	1.5	<1.5

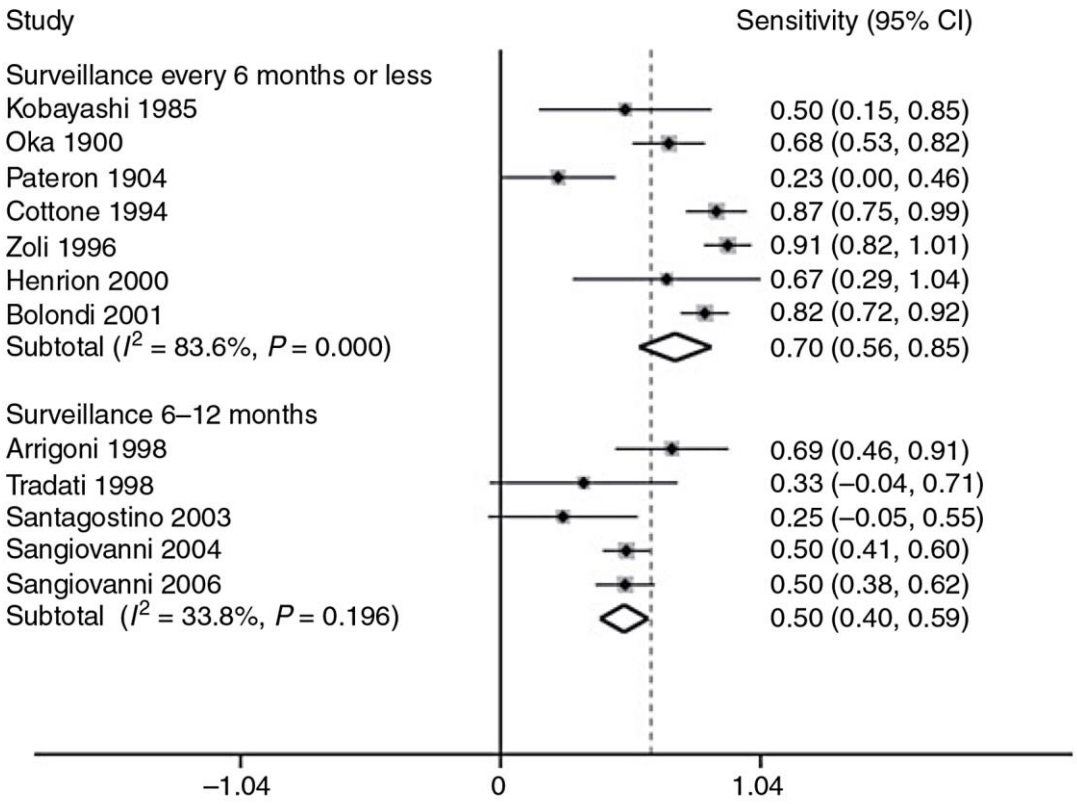
Sherman M. *Semin Liver Dis*. 2010;30(1):3-16.

AFP and Des-gamma-carboxy Prothrombin (DCP) in the Early Diagnosis of HCC

- 1031 patients randomized in the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) Trial
  - Nested case-control study of 39 HCC cases and 77 controls
- Testing within one month prior to HCC diagnosis
- DCP: sensitivity (74%) and specificity (86%) at a cutoff of 40 mAU/mL
- AFP: sensitivity (61%) and specificity (81%) at a cutoff of 20 ng/mL
- Combining both markers increased the sensitivity to 91% at month 0 but the specificity decreased to 74%

Lok, et al. *Gastroenterology* 2009

Ultrasound Surveillance in Early HCC: Systematic Review

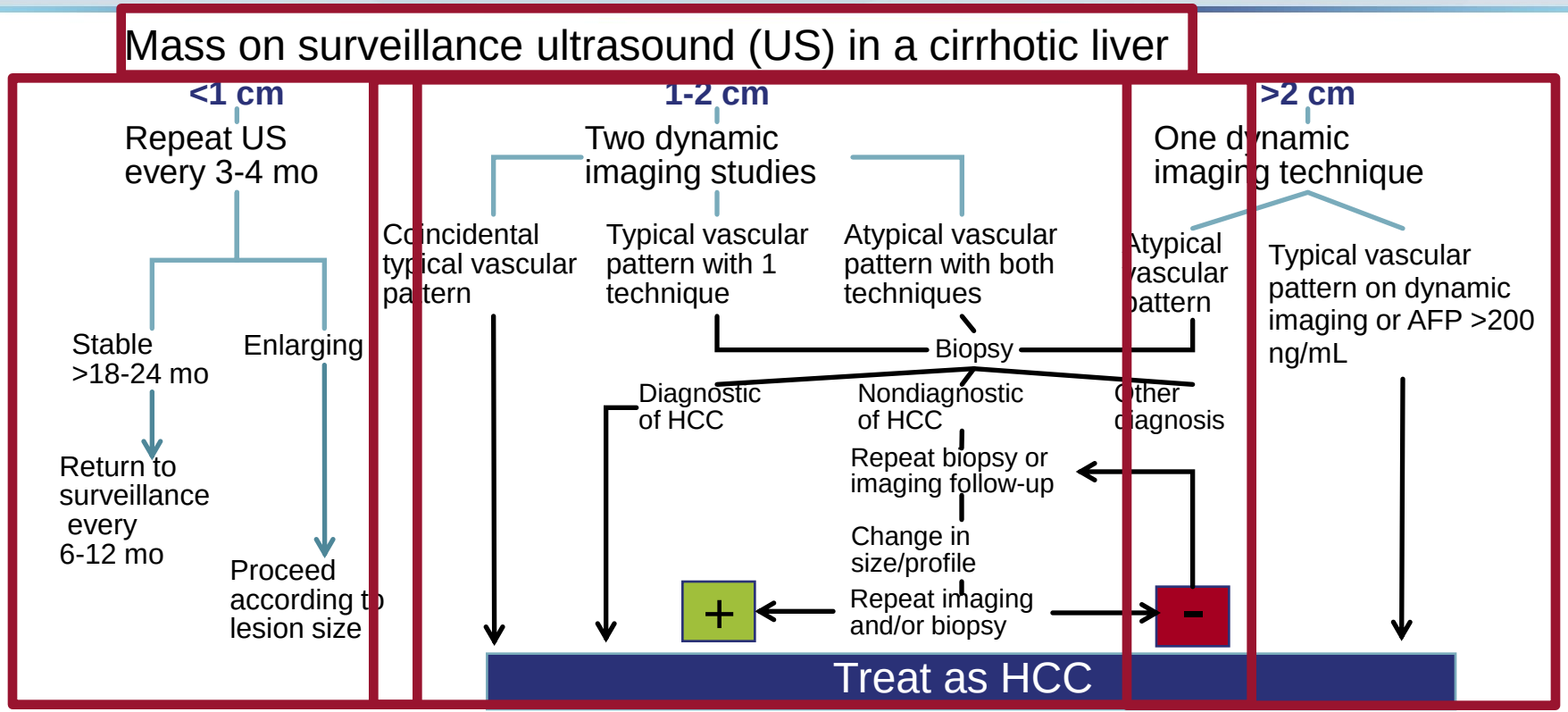


Singal A, et al. APT 20

HCC Surveillance Recommendations

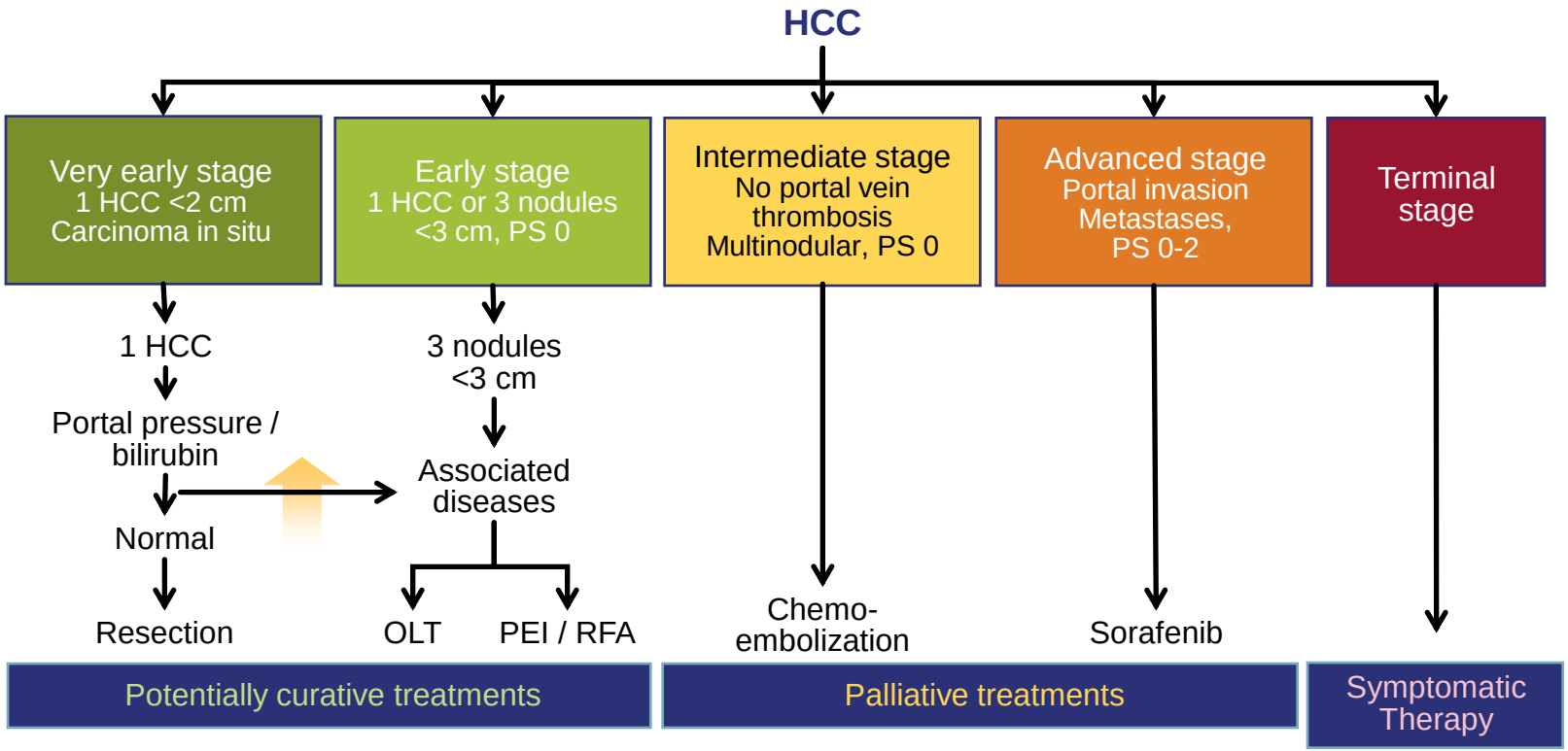
- The target population for surveillance are those with liver cirrhosis (and HBV-infected patients without cirrhosis in special circumstances)
- US and AFP are the recommended screening tests for HCC in patients at the highest risk
  - US is central
  - Not AFP alone
  - Premature to recommend dropping AFP

Diagnostic Criteria for HCC



Adapted from Bruix J and Sherman M. *Hepatology*. 2005; 42(5):1208

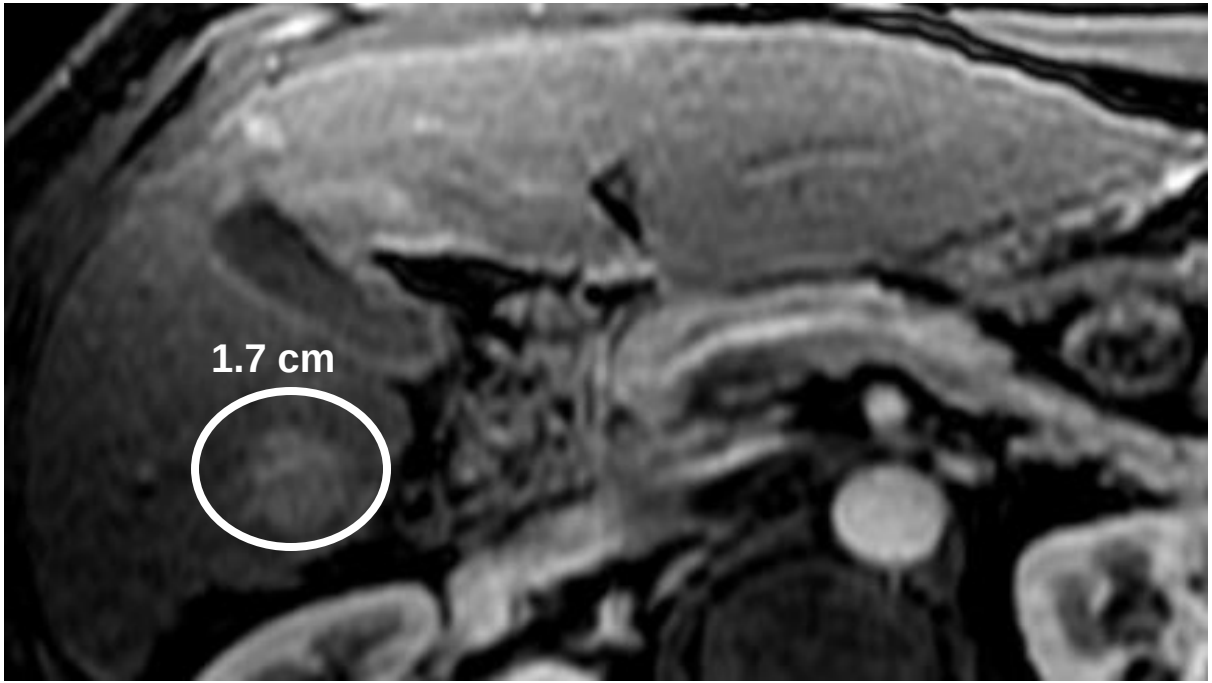
Hepatocellular Carcinoma: Treatment



El-Serag HB, et al. *Gastroenterology* 2008

Hepatocellular Carcinoma: Treatment

Very Early Stage HCC



Tumors < 2 cm with normal synthetic function

Hepatocellular Carcinoma: Treatment

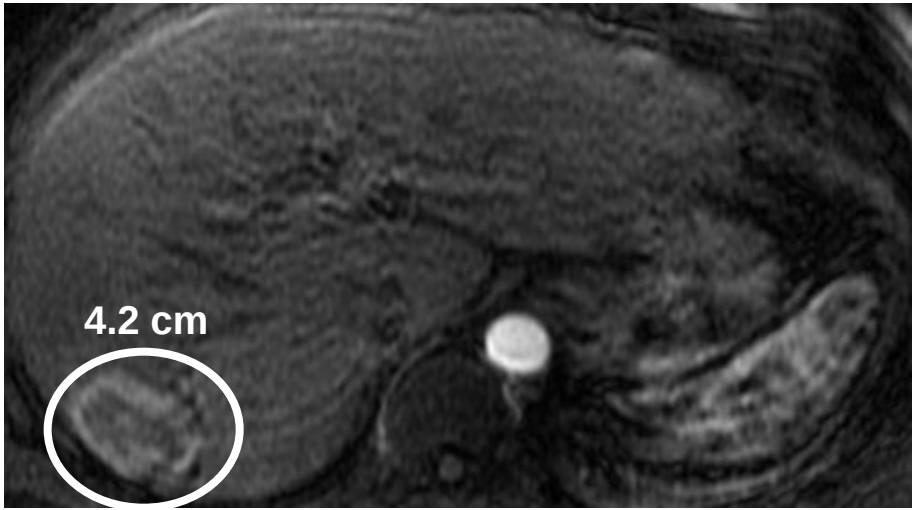
Randomized Trial of RFA versus Resection for Very Early HCC

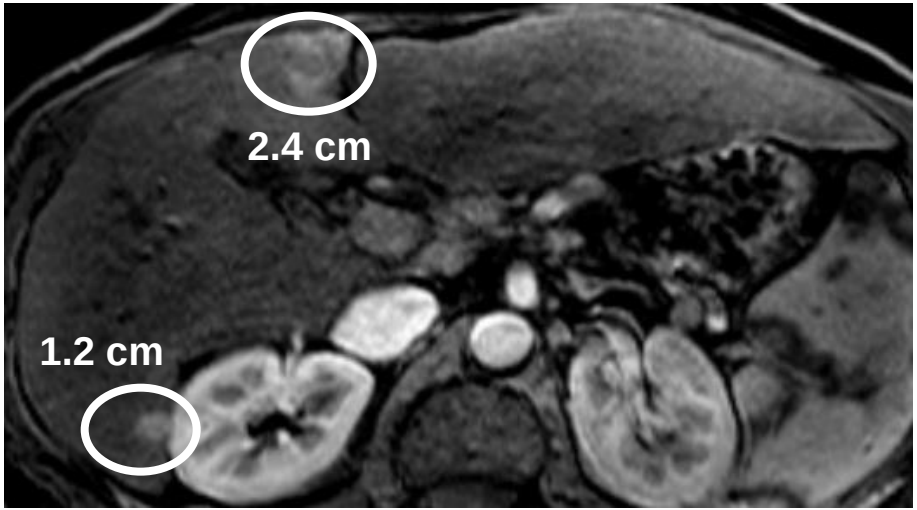
- Study Groups: RFA = 71; Resection =90
- No difference among groups in terms of liver function, performance status and tumor burden (all < 3 cm)

Chen MS, et al. *Ann Surgery* 2006; 243(3):321

Hepatocellular Carcinoma: Treatment

Early Stage HCC (Milan)





Single Tumor 2-5 cm or < 3 lesions each < 3 cm
with Child class A or B

Hepatocellular Carcinoma: Treatment

Transplantation (LT)

- Curative for HCC and chronic liver disease
- MELD exception points for HCC
- Live donor LT considered for HCC progression outside MILAN criteria
- UCSF criteria not implemented in current MELD exception allocation policy

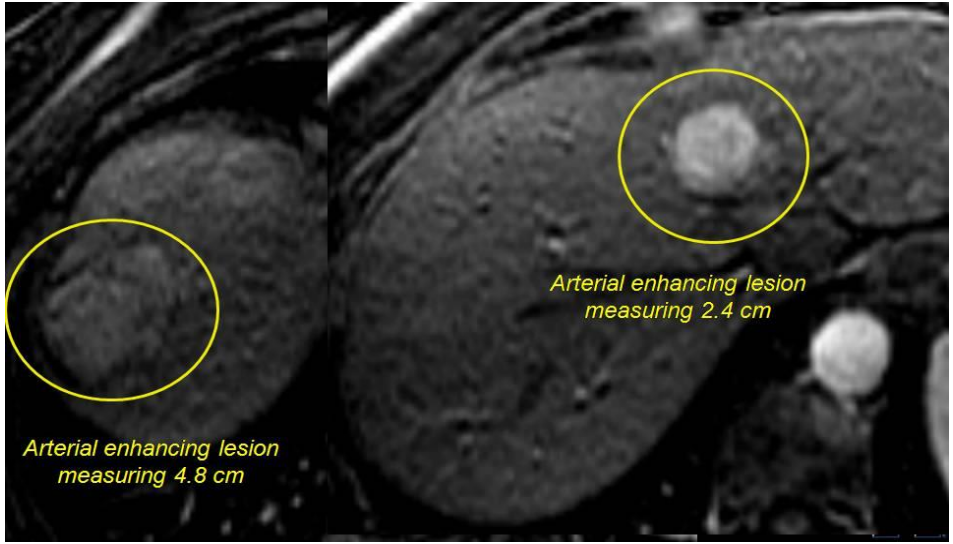
Survival

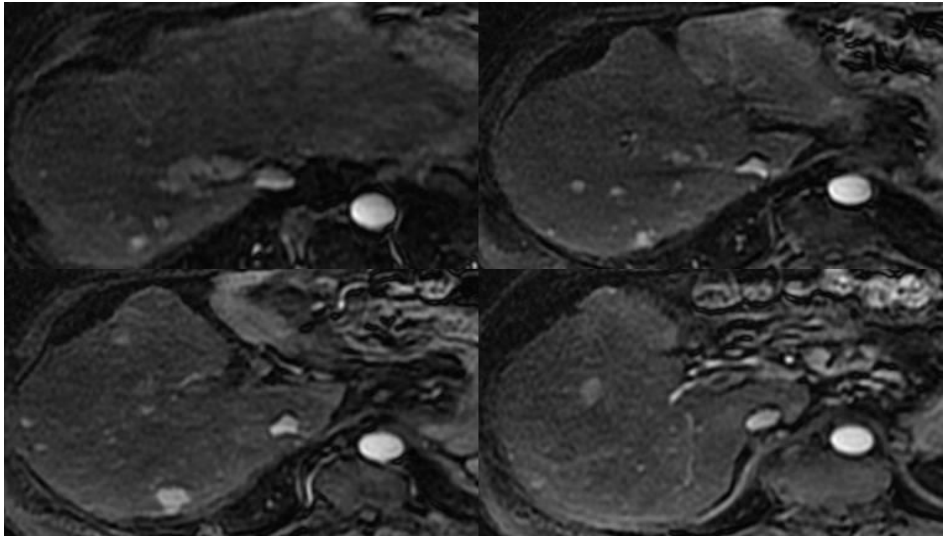
1 year	91%
2 year	75%
5 year Milan	>70%
5 year (extended)	~50%

Sala M,et al. *Liver Transpl* 2004;10(Suppl 2):S4-S9.
Mazzaferro V, et al. *N Engl J Med* 1996;334;693-699.
Shetty K, et al. *Liver Transpl* 2004;10:911-918.
Yao F, et al. *Hepatology* 2001;33:1394-1403.

Hepatocellular Carcinoma: Treatment

Intermediate Stage



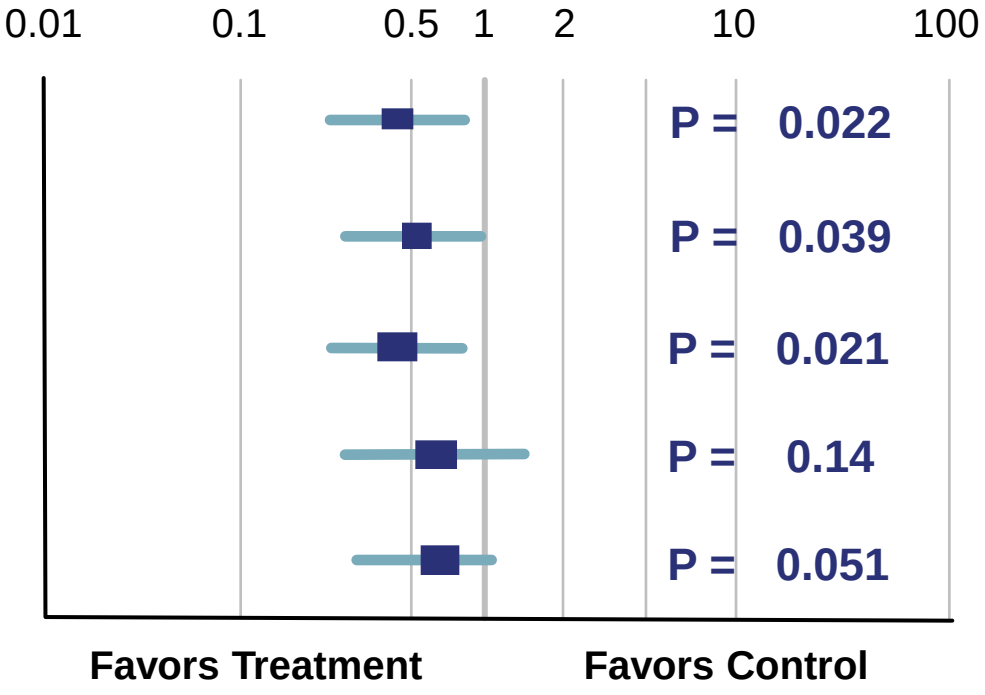


Single Tumor > 5 cm or multifocal tumor WITHOUT vascular Involvement; Child class A or B

Sensitivity Meta-Analysis of Core RCTs Reporting

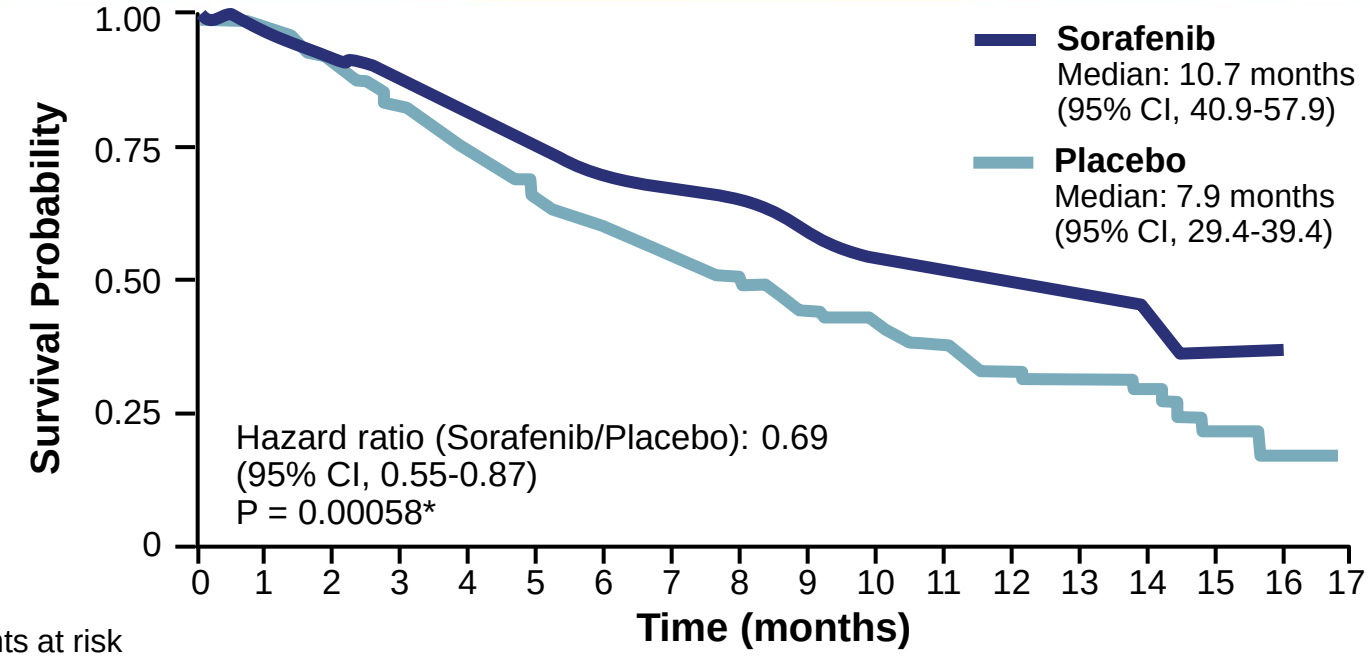
1 or 2-year Survival with Chemoembolization / Embolization: Various Treatment Comparisons

Comparison	Patients
Treatment vs no treatment 4 RCT	367
High quality trials 5 RCT	440
Chemoembolization vs control 4 RCT	323
Embolization vs control 3 RCT	215
Treatment vs control: 1 year survival 7 RCT	545



Adapted from Llovet JM, Bruix J. *Hepatology* 2003; 37:429

Phase III SHARP Trial: Overall Survival (Intent-to-Treat Population)



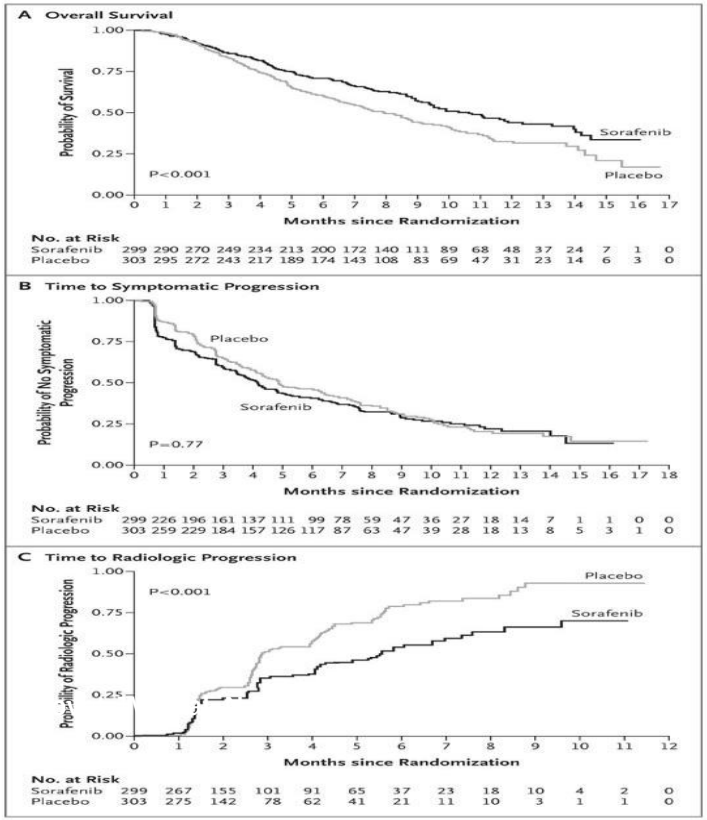
Patients at risk

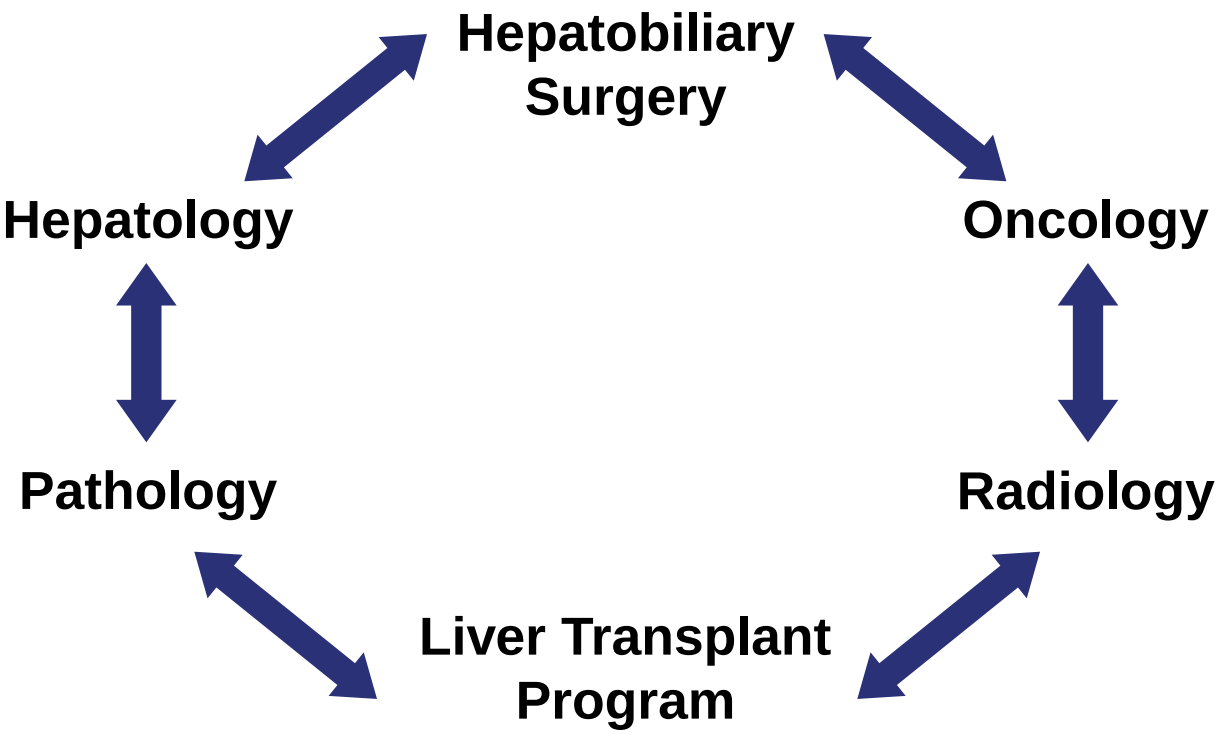
Sorafenib:	299	274	241	205	161	108	67	38	12	0
Placebo:	303	276	224	179	126	78	47	25	7	2

*O'Brien-Fleming threshold for statistical significance was *P* = 0.0077; CI=confidence interval

Llovet JM et al. *NEJM*. 2008; 359(4):378

Kaplan-Meier Analysis: Overall Survival, Time to Symptomatic Progression, Time to Radiologic Progression With Sorafenib



Llovet JM et al. N Engl J Med 2008;359:378-390

Management of Hepatocellular Carcinoma Requires a Multidisciplinary Approach