

Hepatocellular Carcinoma: The growing disease burden

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Your Liver. Your Life.

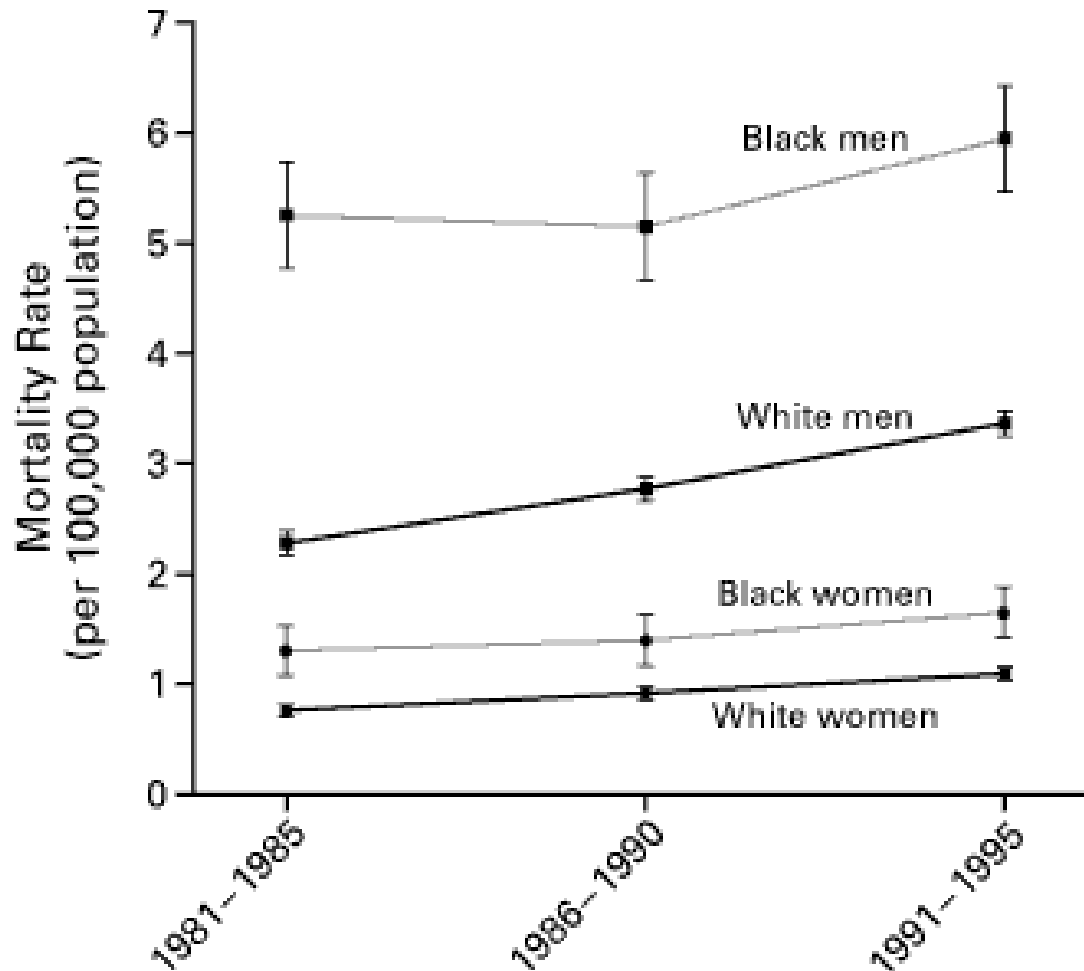
Hepatocellular Carcinoma (HCC)

- Hepatocellular carcinoma (HCC) is the 6th most common cancer in the world
- Third leading cause of cancer related death
- Age-adjusted US incidence has increased 2-fold: 1985-1998
- American Cancer Society statistics for liver cancer in 2008
 - Most patients with HCC in US have liver cirrhosis mainly by hepatitis B and C viruses
 - Estimation of new cases: 21,370
 - Estimation of deaths: 17,000

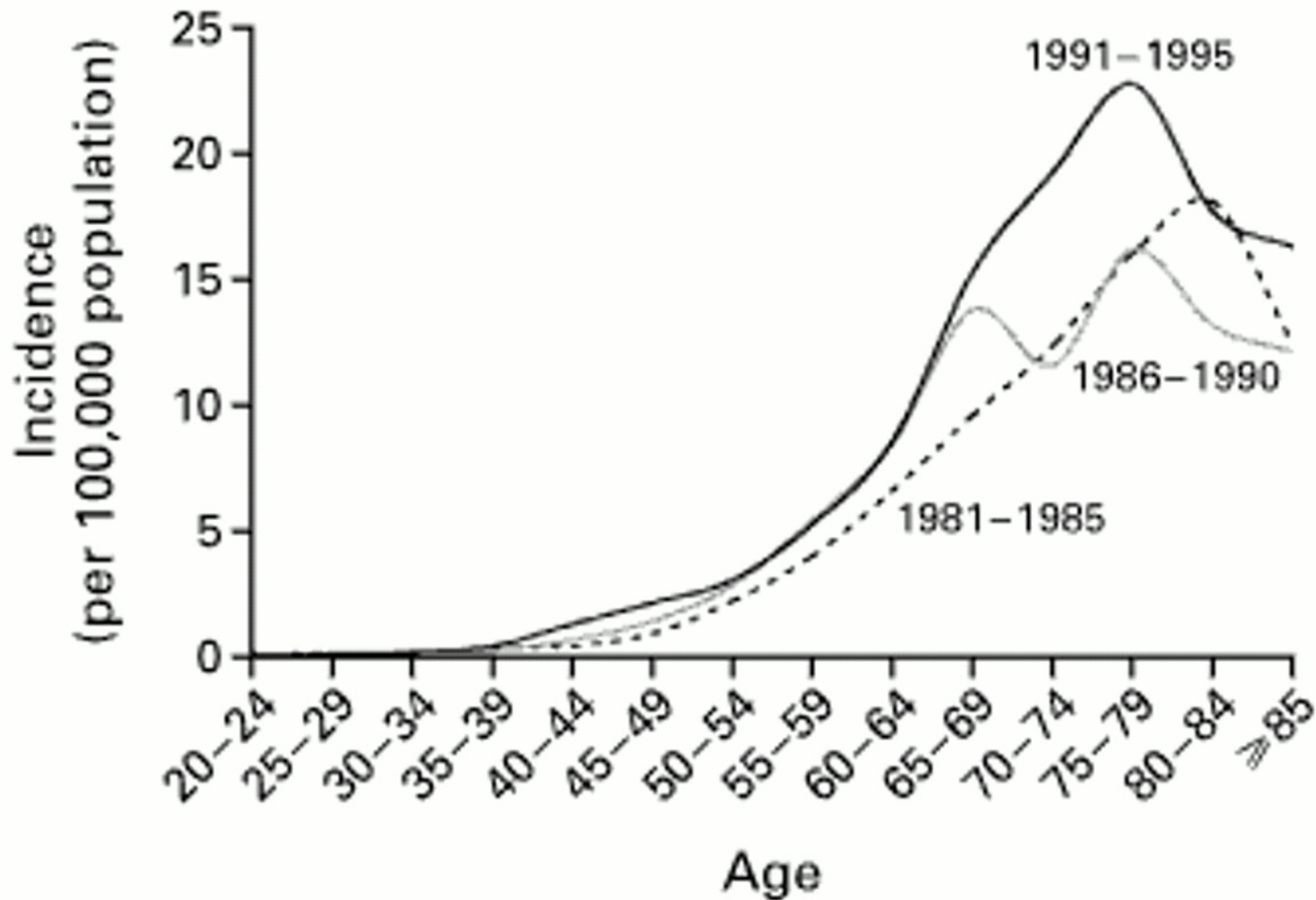
HCC: Epidemiology

- Hepatitis B virus is the most frequent underlying cause world wide
- 85% of HCC cases occur in Eastern and Southeastern Asian and Sub Saharan Africa (endemic HBV infection)
- In the US, HCV-related HCC is a rapidly rising cancer (50-70% of cases)
- Other risk factors in the United States include alcohol use, nonalcoholic fatty liver disease , inherited liver disease, smoking*
 - Hemochromatosis (highest risk, though low disease penetrance)
- Cirrhosis is a pre-malignant condition

Rising Mortality Rate from HCC in US (Age Adjusted)



Age-Specific Incidence of HCC among White Men in SEER Database



Origin of HCC

- Cirrhotic liver
 - All causes
- Noncirrhotic liver
 - Hepatitis B
 - Fibrolamellar variant
 - Rare metabolic diseases
(eg, glycogenosis, porphyria)
 - Hepatitis C (rare)
 - Other

Incidence of HCC as it relates to etiology of cirrhosis

Cirrhosis: High incidence of HCC (>15%)

Hemochromatosis

HCV-related

HBV-related

Alcoholic cirrhosis with HCV

Cirrhosis: Intermediate incidence of HCC (5%-15%)

Alcoholic cirrhosis without HCV

Non-alcoholic fatty liver disease

Cirrhosis: Low incidence of HCC (<5%)

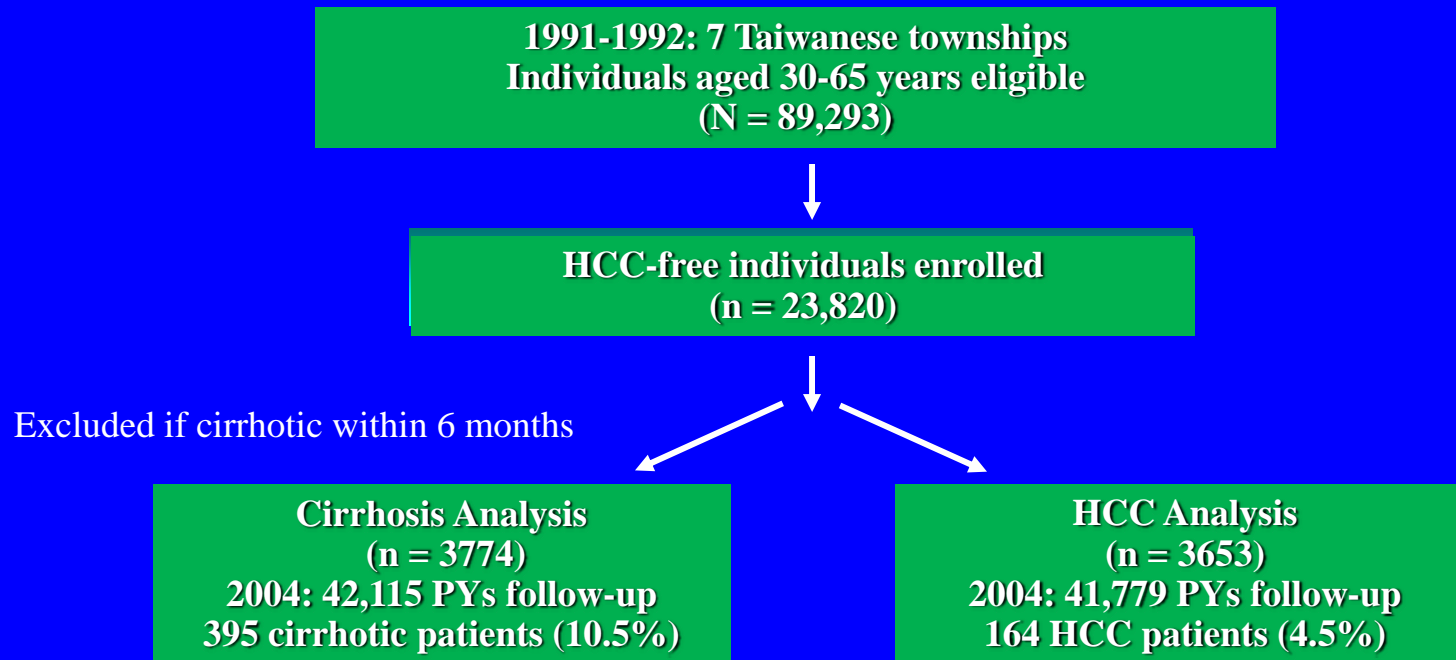
Primary biliary cirrhosis

Wilson disease cirrhosis

Autoimmune hepatitis

REVEAL: Baseline HBV DNA and Liver Disease Progression

Prospective, multicenter, observational cohort study



Chen CJ, et al. *JAMA* 2006;295:65-73.

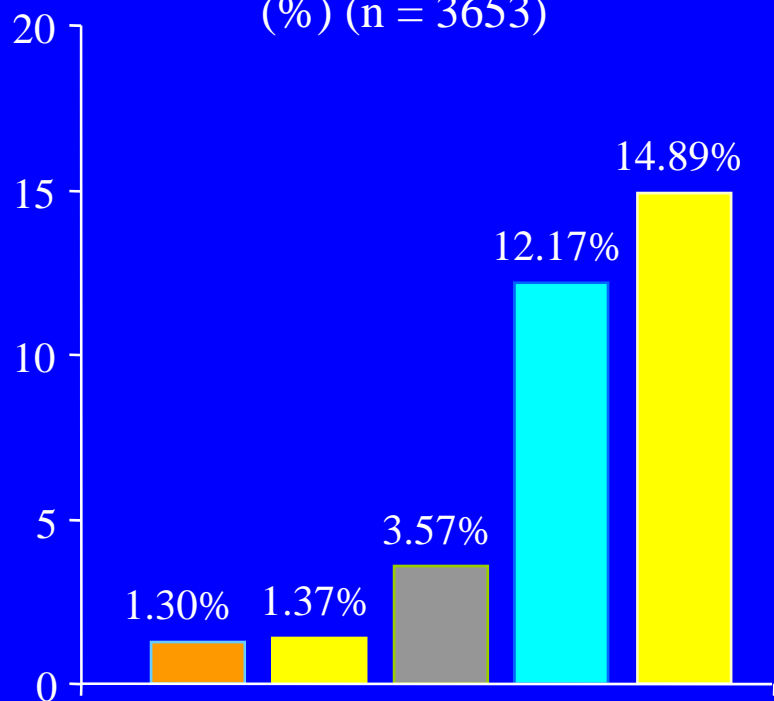
Iloeje UH, et al. *Gastroenterology* 2006;130:678-686.

REVEAL Study: HBV DNA Levels and Long-Term Outcomes

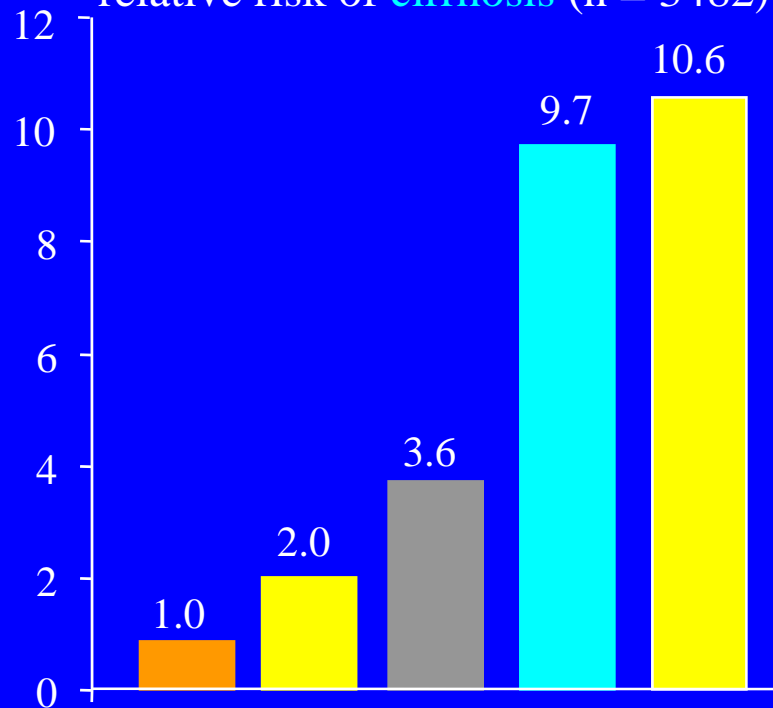
Viral Load at Baseline



Cumulative incidence of **HCC** (%) (n = 3653)



Multivariate-adjusted relative risk of **cirrhosis** (n = 3482)

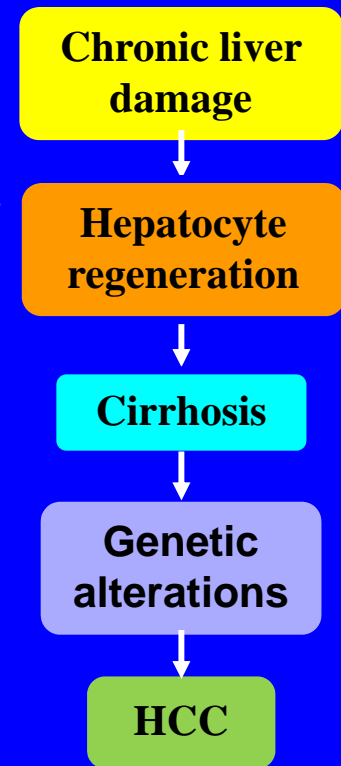


HCC: Pathogenesis

- Carcinogenesis is typically a stepwise process
 - Sequential genetic mutations
 - Oncogene activation
 - Tumor suppressor gene inactivation
- No dominant pathways of hepatocellular carcinogenesis have been identified

Molecular Pathogenesis of HCC

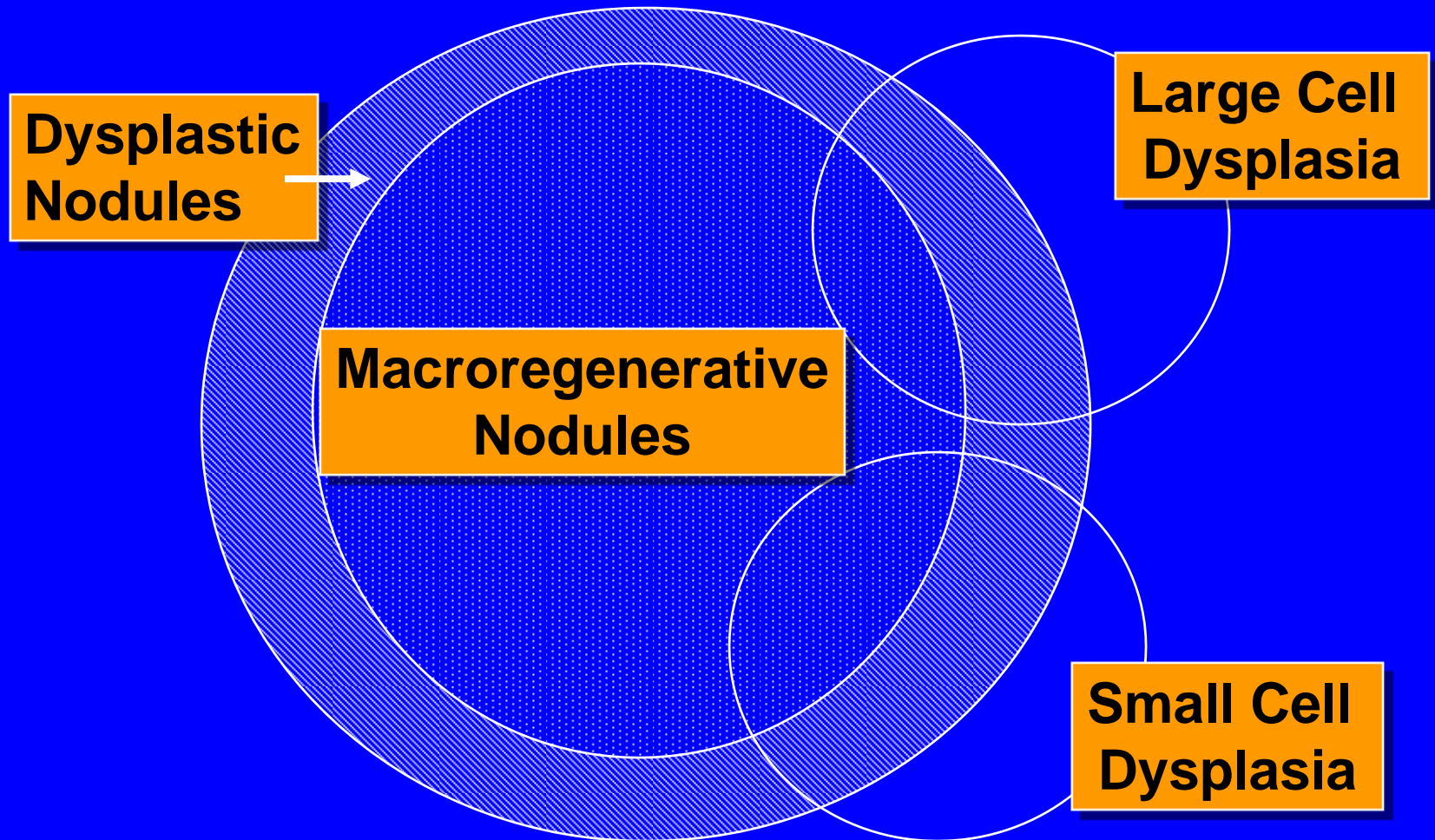
- 2 key mechanisms implicated in development of HCC
 - Liver cirrhosis following tissue damage (infectious or toxic damage)
 - Mutations occurring in 1 or more oncogenic or tumor suppressor genes
- Abnormalities in cellular signaling pathways
 - Raf/MEK/ERK
 - PI3K/AKT/mTOR
 - Wnt/ β -catenin
 - Angiogenic signaling



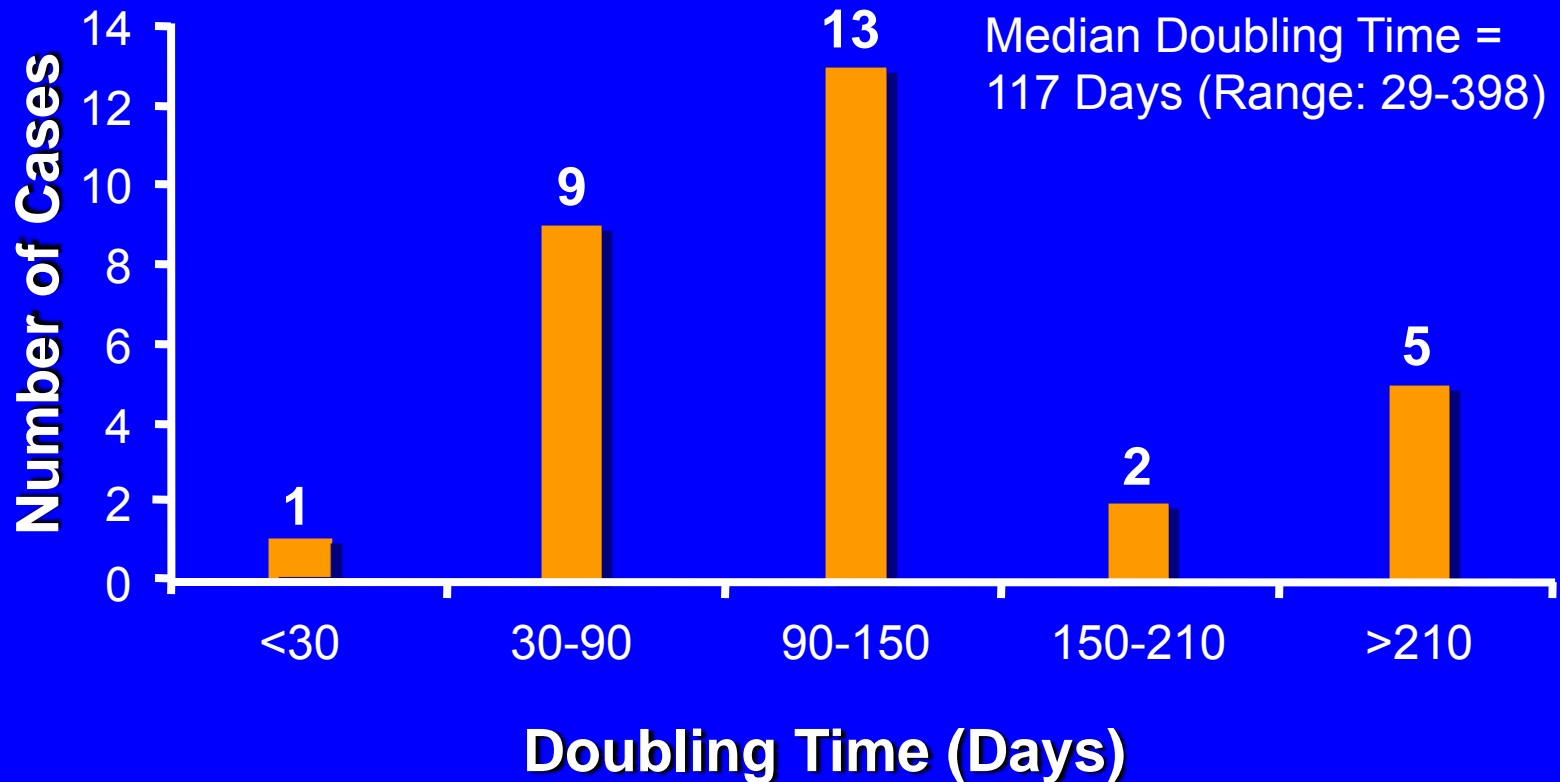
Marotta F et al. Clin Ter. 2004;155:187-199. Thorgeirsson SS, et al. Nat Genet. 2002;31:339-346. Wiesenauer CA, et al. J Am Coll Surg. 2004;198:410-421. Wang XW, et al. Toxicology. 2002;181-182:43-47. Feitelson MA, et al. Surg Clin North Am. 2004;84:339-354. Avila MA, et al. Oncogene. 2006;25:3866-3884. Adapted from CCO

HCC

Possible Premalignant Lesions

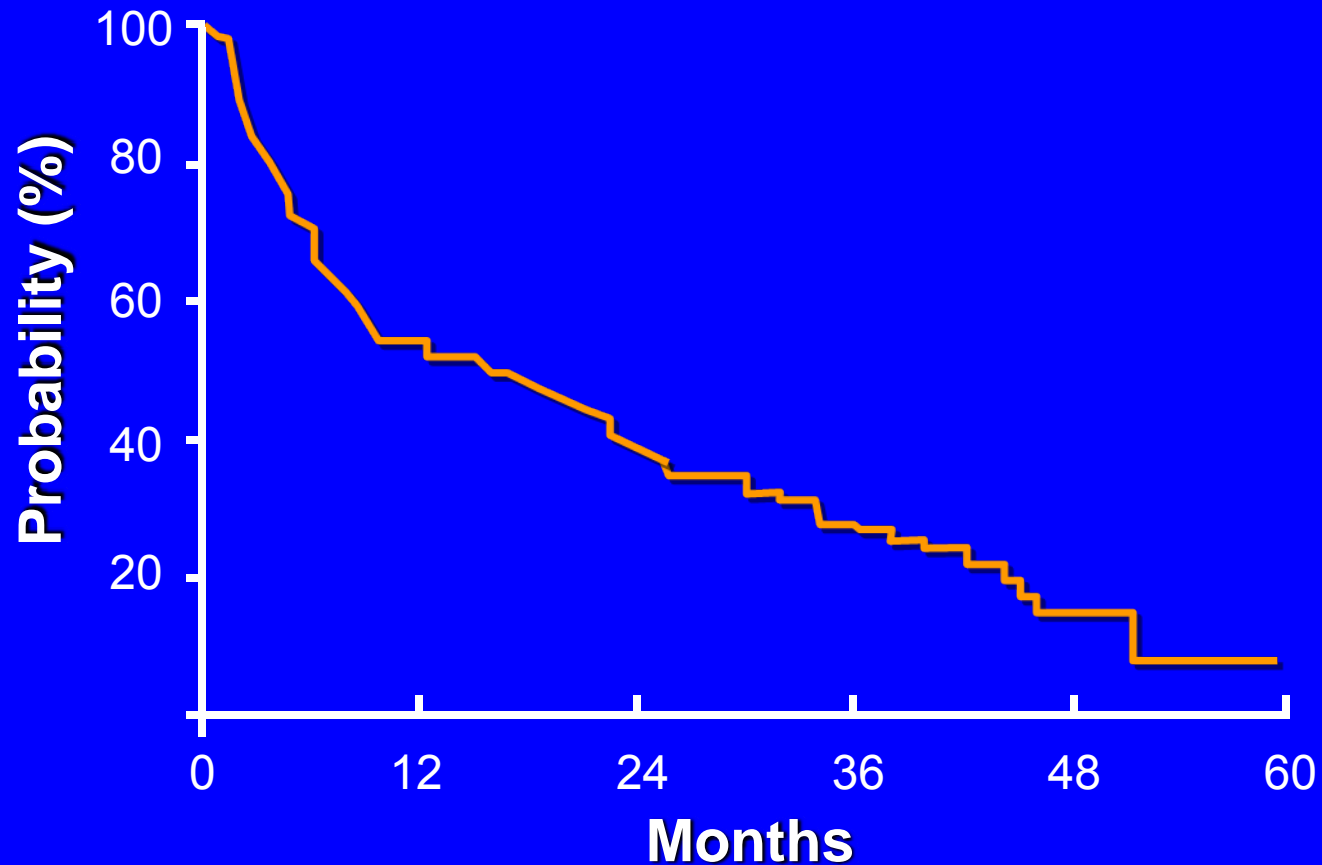


Growth Rates of HCC



Sheu J-C, et al. *Gastroenterology*. 1985;89:259.

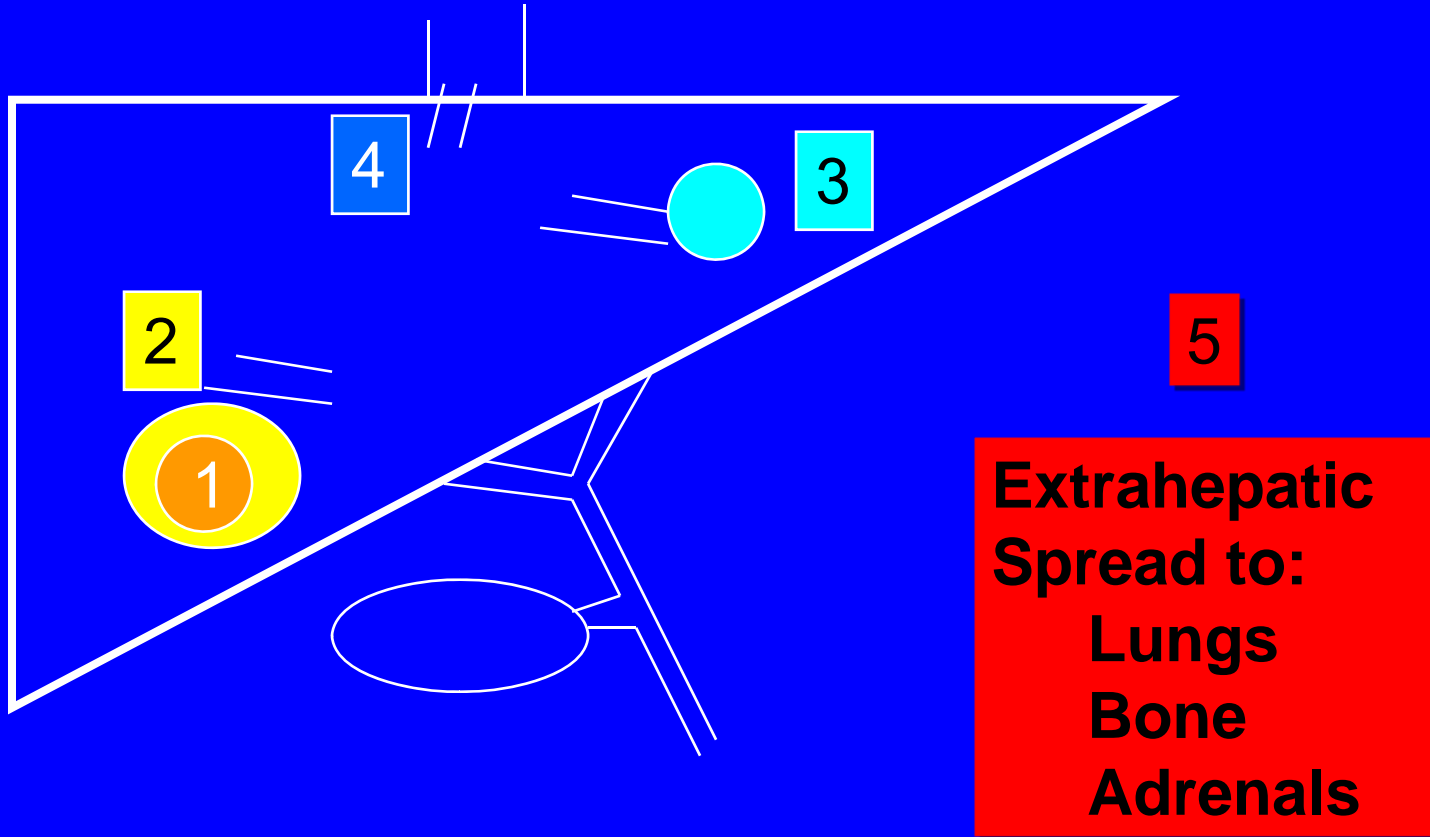
Actuarial Survival of Patients With Untreated HCC



Patients at Risk 102 57 40 21 8 1

Llovet JM, et al. *Hepatology*. 1999;29:62.

Spread of HCC



How do we screen for HCC

- No studies define unequivocally the best modality for diagnosing HCC
- Ultrasonography (US) every 6-12 months with alpha-fetoprotein (AFP) every six months is current standard of care for screening high risk patients
 - US has technical limitations (operator dependence, reduced efficacy in those with elevated BMI)
 - US if subject has normal BMI
- AFP alone is not sufficient unless imaging modalities are not available
- Our practice at IU: MRI every 9 months or Dual Phase Spiral CT, or US every 6-12 months if normal BMI
 - MRI or US preferred due to radiation risk with CT scan

AASLD Guidelines

- Surveillance recommended in at-risk groups
 - Specific hepatitis B carriers
 - Nonhepatitis B cirrhosis
- US preferred surveillance tool
 - AFP alone should not be used unless US unavailable
- Patients should be screened at 6- to 12-month intervals

HCC Screening: Caveats with Ultrasound

- Detection of hypo- or hyperechoic nodule should raise suspicion of HCC in a cirrhotic patient
 - Less than half of nodules less than 1 cm size correspond to hepatocellular carcinoma
 - Nodules less than 1 cm are followed with repeat ultrasound every three months until lesion greater than 1 cm
 - Absence of growth does not rule out HCC

How is HCC Diagnosed: Dynamic Imaging (CT scan or MRI)

- HCCs have blood supply from hepatic artery
- Dual Phase Spiral CT scan or MRI with intravenous contrast allows rapid acquisition of images during hepatic arterial phase and portal venous phases
- Lesions seen during the arterial phase and which are less well seen during portal venous phase are suspicious for HCC
 - Requires relatively preserved renal function for both

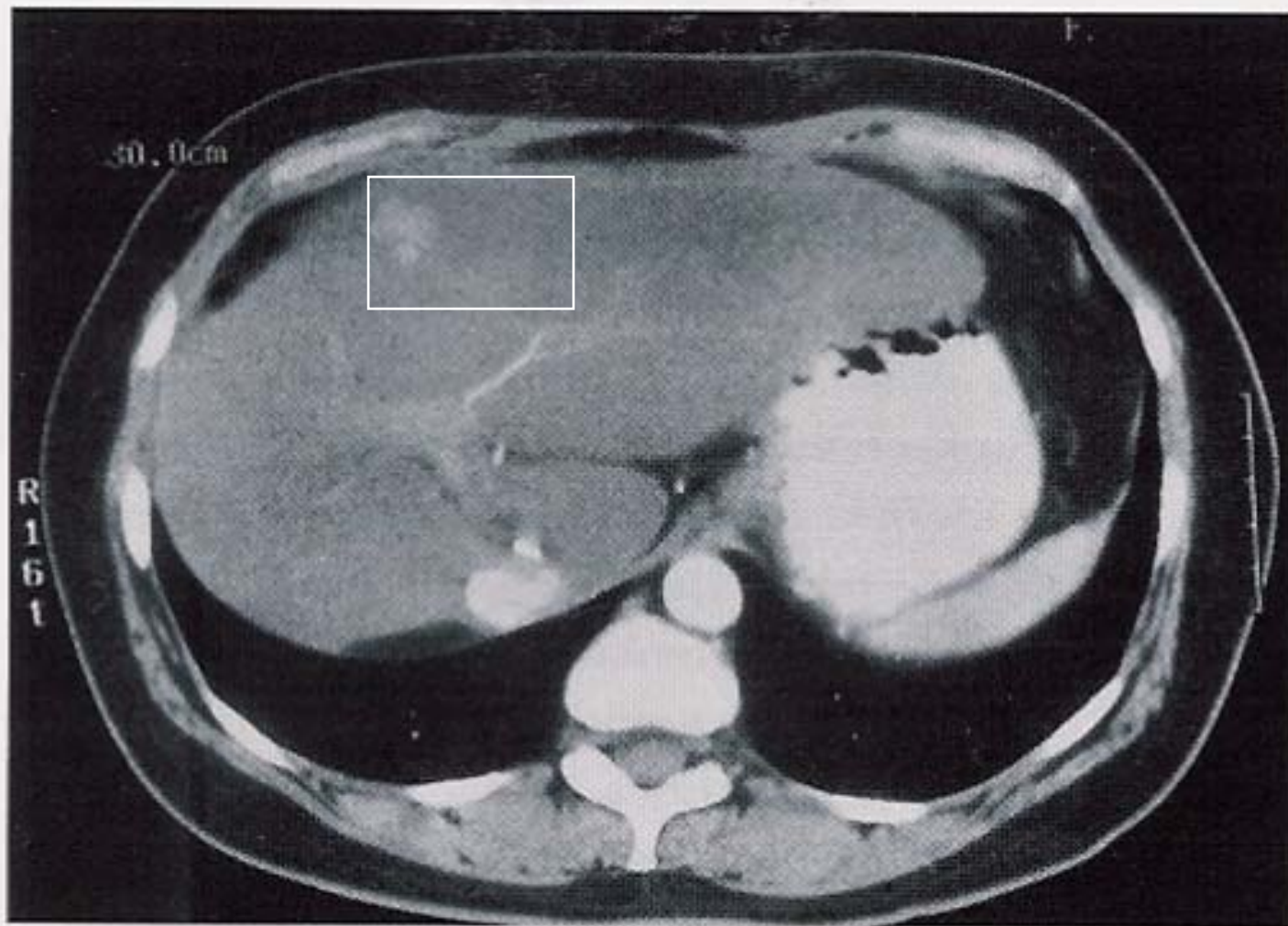


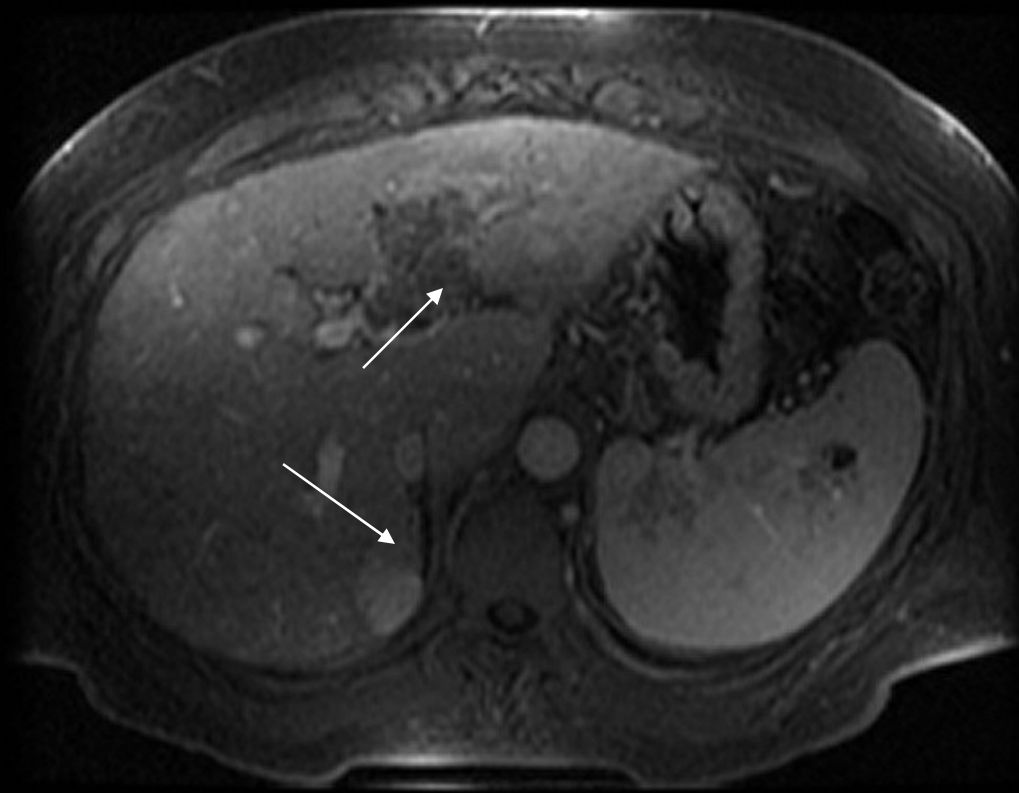
Figure 2. CT scan of the liver demonstrating an early HCC. This lesion is hypervascular, thus enhancing after contrast injection and appearing as a hyperdense nodule.

How is HCC Diagnosed: MRI

- MRI provides another way of distinguishing hepatocellular carcinoma from normal liver tissue
- Most tumors have a low signal intensity on T_1 -weighted images and a high signal intensity on T_2 -weighted images
- Gradient-echo sequences and turbo spin-echo sequences have greatly reduced the time needed for MRI.
 - (breath holding for 40 seconds for optimal images)
- Less dependent on normal renal function

MRI demonstrating HCC/Tumor Thrombosis

Se: 8
Im: 106
SL: -7.9



TruRez: Full
ZF: 2.32
DYN FAME+C
TR: 3.7
TE: 0.87
20CC MAGNEVIST

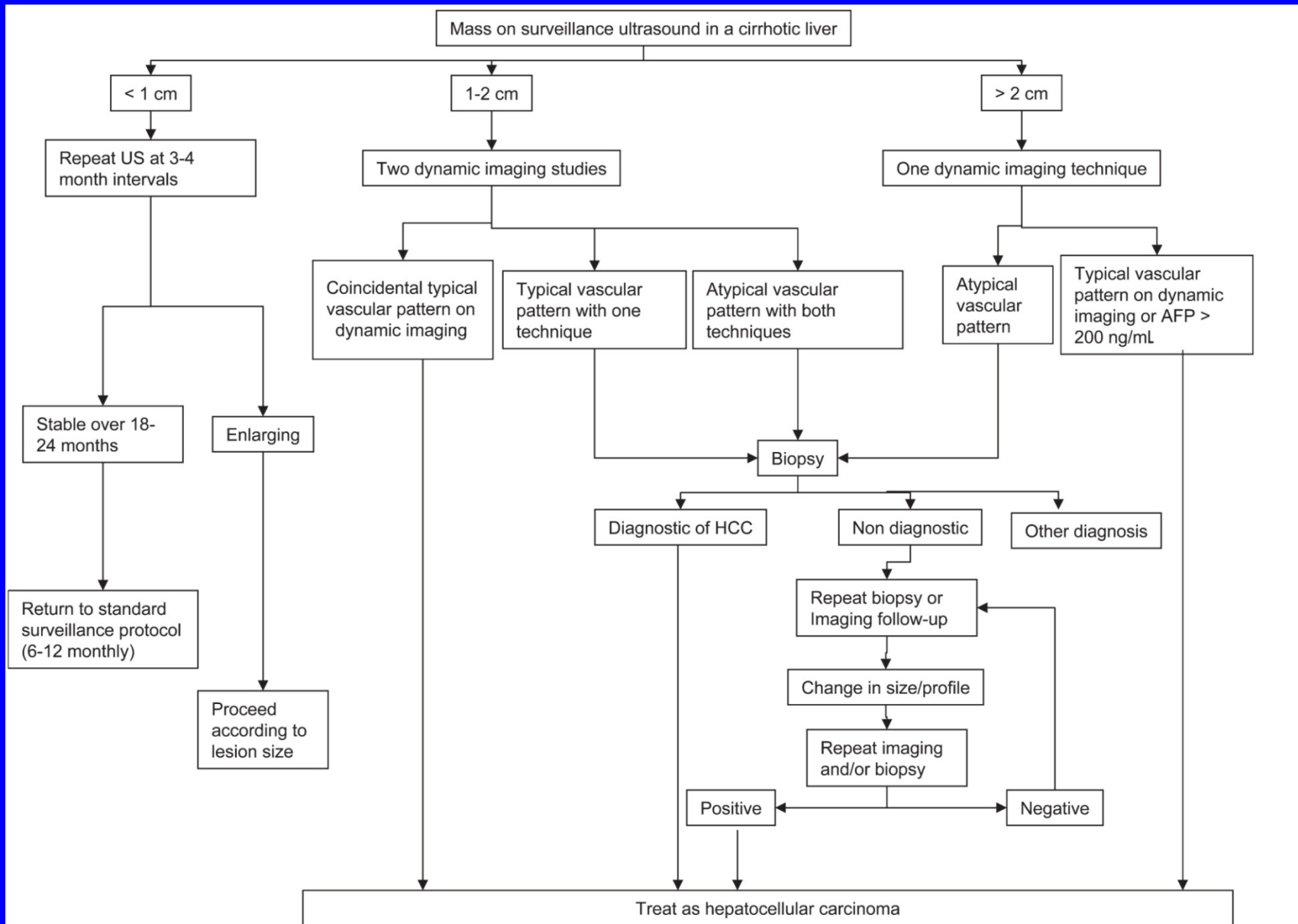
P

W: 124
L: 62 38

How is HCC Diagnosed?

- Nodules >2 cm can be confidently diagnosed with CT or MRI without needing a biopsy positive for HCC
- If lesion 1-2 cm need 2 dynamic imaging studies with typical washout, otherwise, biopsy
- A biopsy of a nodule negative for HCC should never be accepted as having excluded malignancy

Mass found with surveillance



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.

Dec. 9, 2008 on-line liver cancer video program for medical professionals by Paul Kwo, MD and American Liver Foundation

Alpha-fetoprotein Levels

- Values greater than 400 ng/ml have been validated as confirming hepatocellular carcinoma
- Viral liver disease often associated with transient increases of AFP coinciding with inflammatory flares of disease
- Values > 200 ng/ml with mass associated with high likelihood of HCC

Staging of HCC

- Staging systems
 - TNM nomenclature
 - Okuda system
 - BCLC (Barcelona Clinic Liver Cancer)
 - CLIP (Cancer of the Liver Italian Program)
- Key features
 - Tumor size
 - Liver function
 - Performance status of the patient

HCC

Factors Affecting Survival

- Constitutional syndrome
- Performance status
- Vascular invasion
- Extrahepatic spread

Llovet JM, et al. *Hepatology*. 1999;29:62.

Prognosis of Patients With HCC

Patient Survival

Therapy	1 Year	3 Years
No “radical” therapy	54%	28%
Surgical resection	81%	44%
Ethanol injection	82%	38%
Transplantation	84%	74%

Castells A, et al. *Hepatology*. 1993;18:11211. Llovet JM, et al. *Hepatology*. 1998;27:1572. Llovet JM, et al. *Hepatology*. 1999;29:62.

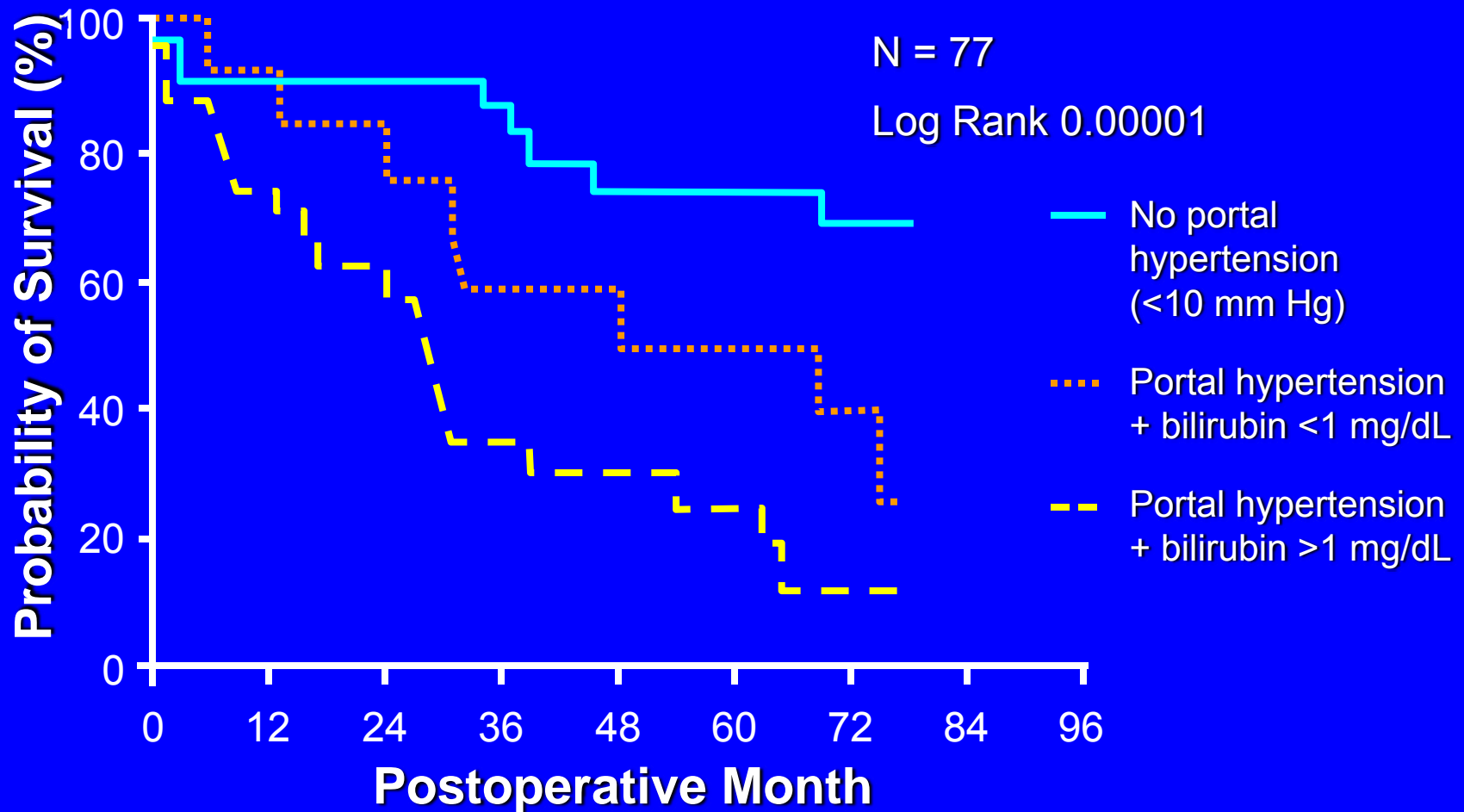
HCC Treatment Options: 2008

- Surgical resection
- Liver transplantation
- Transarterial Chemo-embolization or Radioembolization (Yttrium-90 microspheres)
- Radiofrequency ablation
- Sorafenib

Surgical Resection

- Small group of cirrhotics with HCC (<5% of HCC patients) are candidates
- HCC without cirrhosis are also candidates
- Criteria
 - Child-Pugh class A
 - Normal bilirubin
 - Absence of portal hypertension
 - <5 cm in diameter
- 5-year survival rate: 60%-70%
- Tumor recurrence: 50% in 3 years

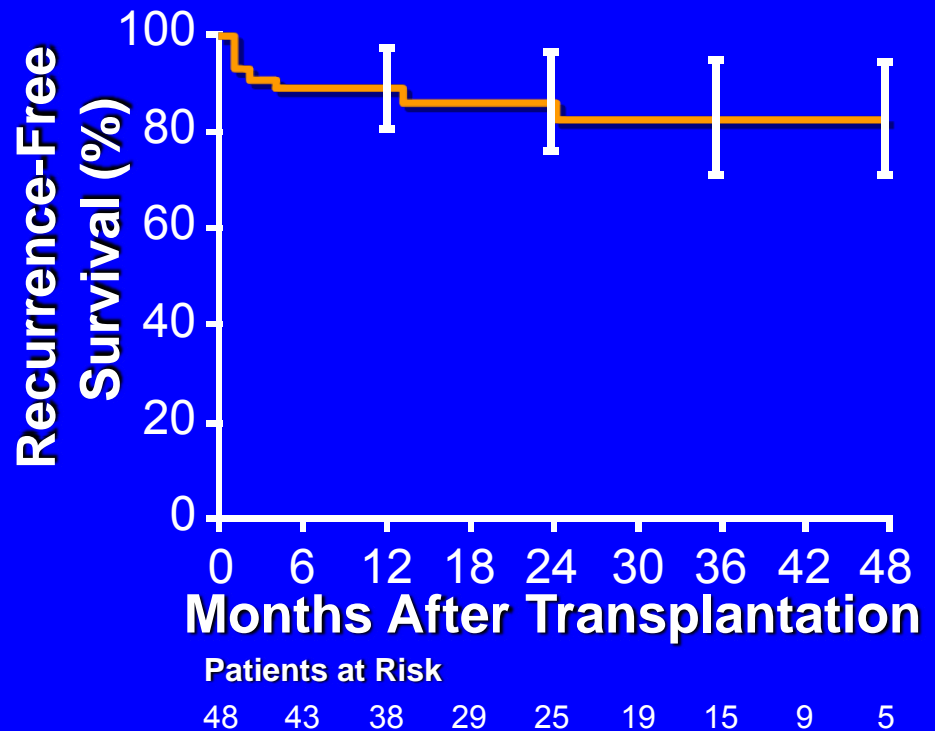
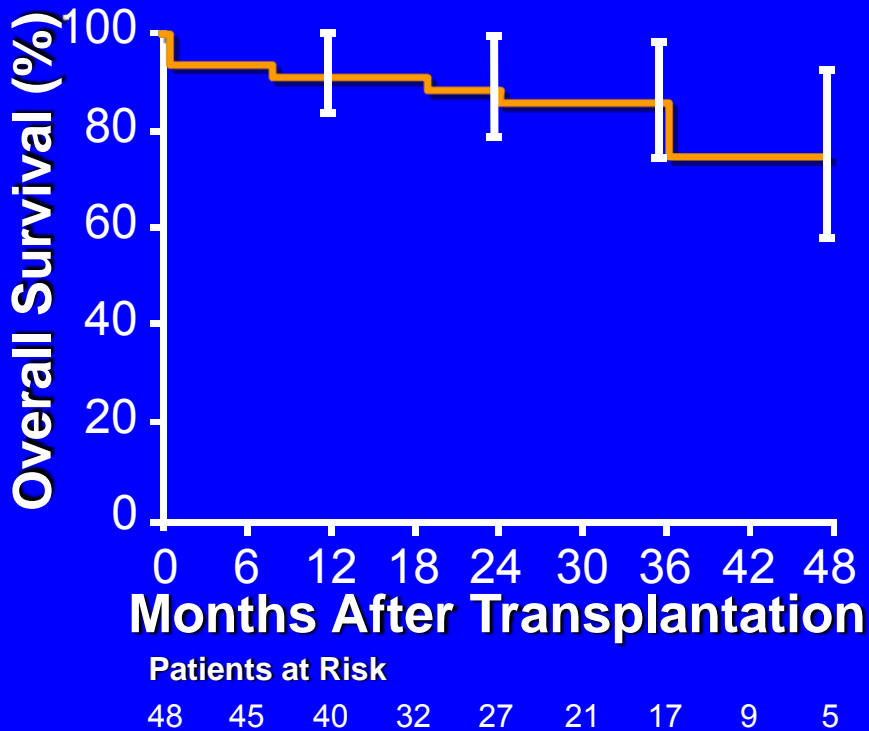
Survival Following Surgical Resection for HCC



Transplantation for HCC: Milan Criteria

- 1 lesion \leq 5 cm
- 3 lesions \leq 3 cm
- No vascular invasion
- No extrahepatic metastases

Survival and Recurrence-Free Survival Following Liver Transplantation for HCC

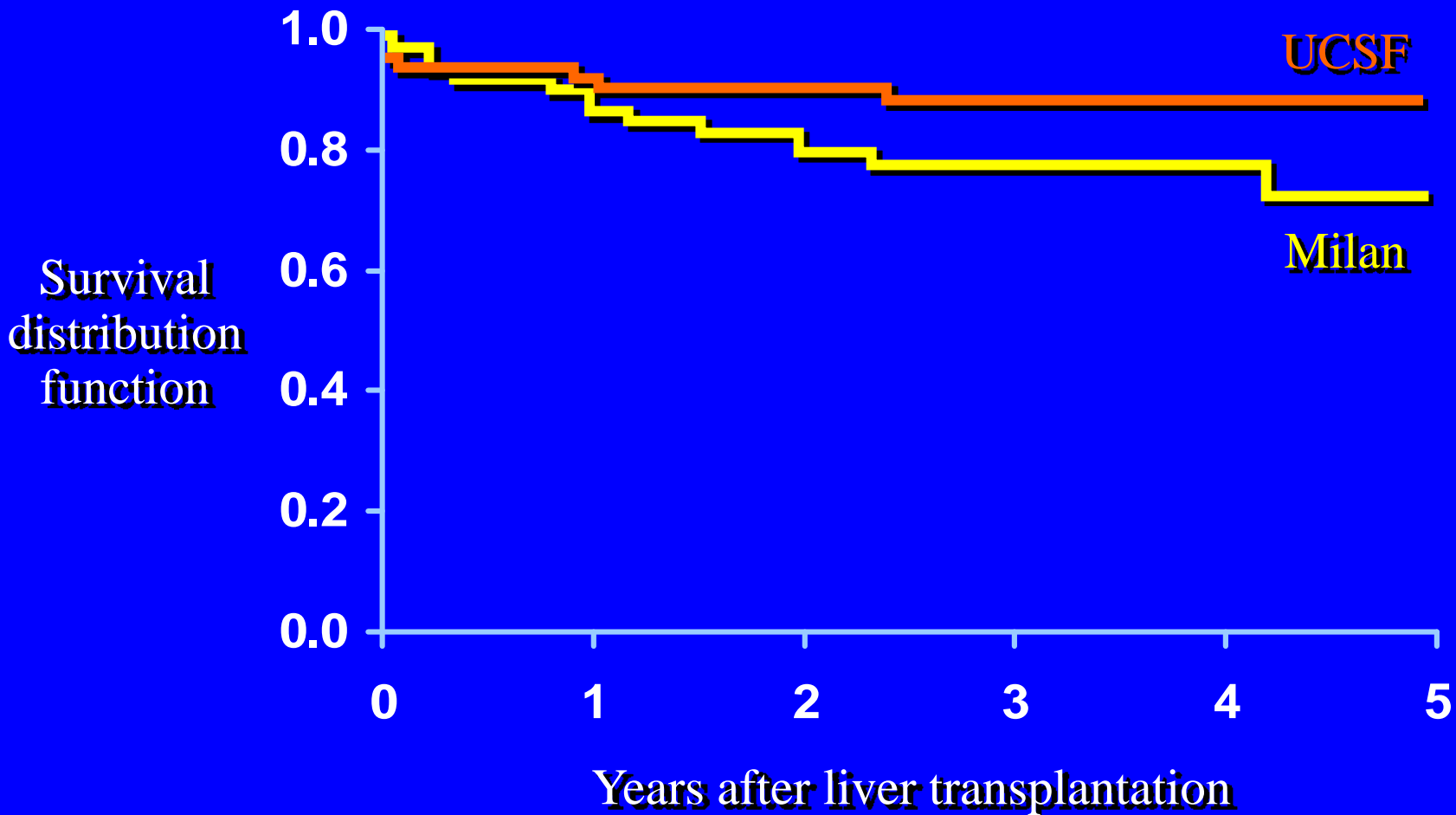


Transplantation for HCC: UCSF Criteria

- Lesion ≤ 6.5 cm
- 2-3 lesions
 - - largest ≤ 4.5 cm
 - - total < 8 cm diameter
- No vascular invasion
- No extrahepatic metastases

Survival Following OLT for HCC

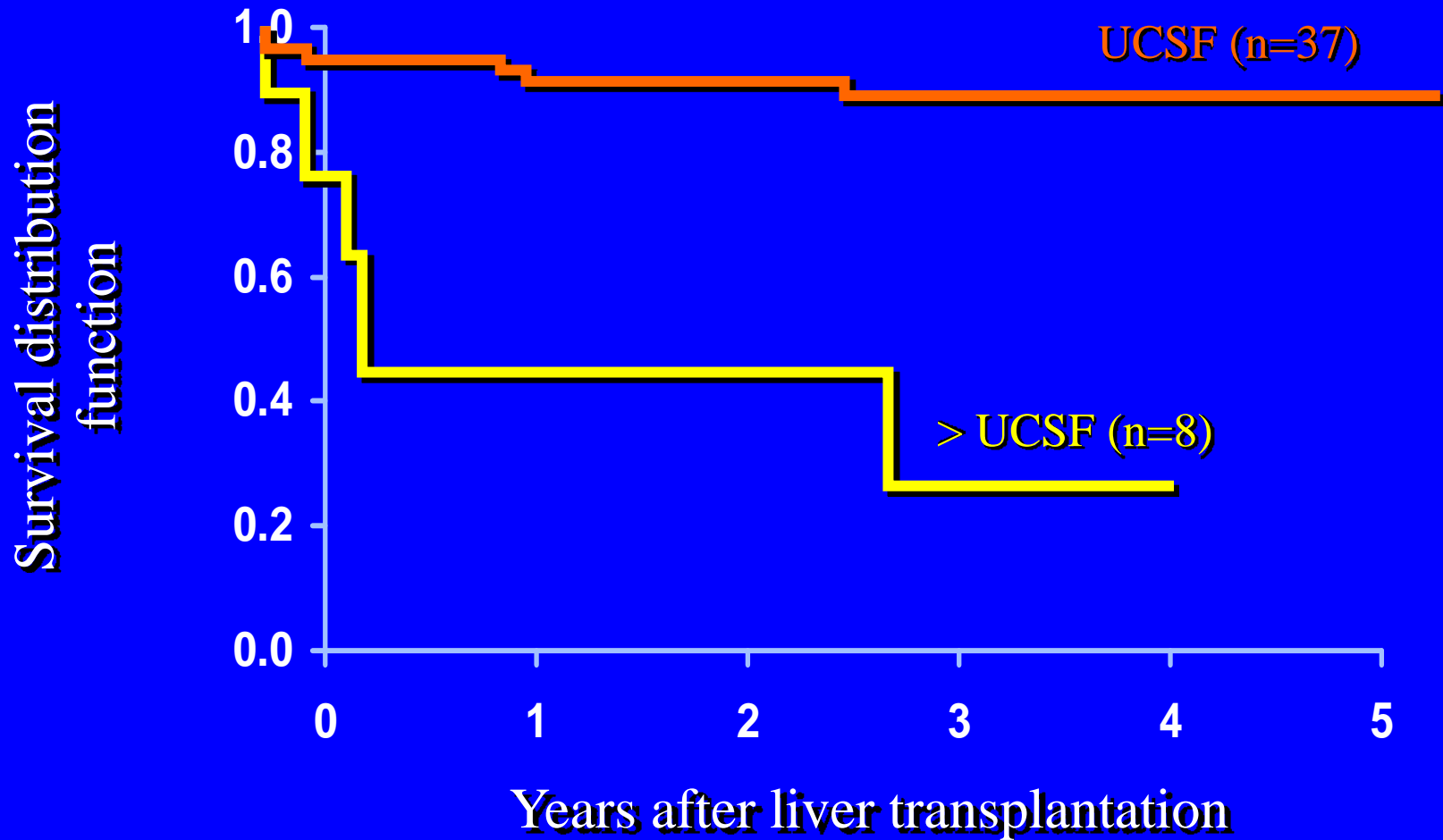
Milan and UCSF Criteria



Liver Transplantation 8:769, 2002

Dec. 9, 2008 on-line liver cancer video program for medical professionals by Paul Kwo, MD and American Liver Foundation

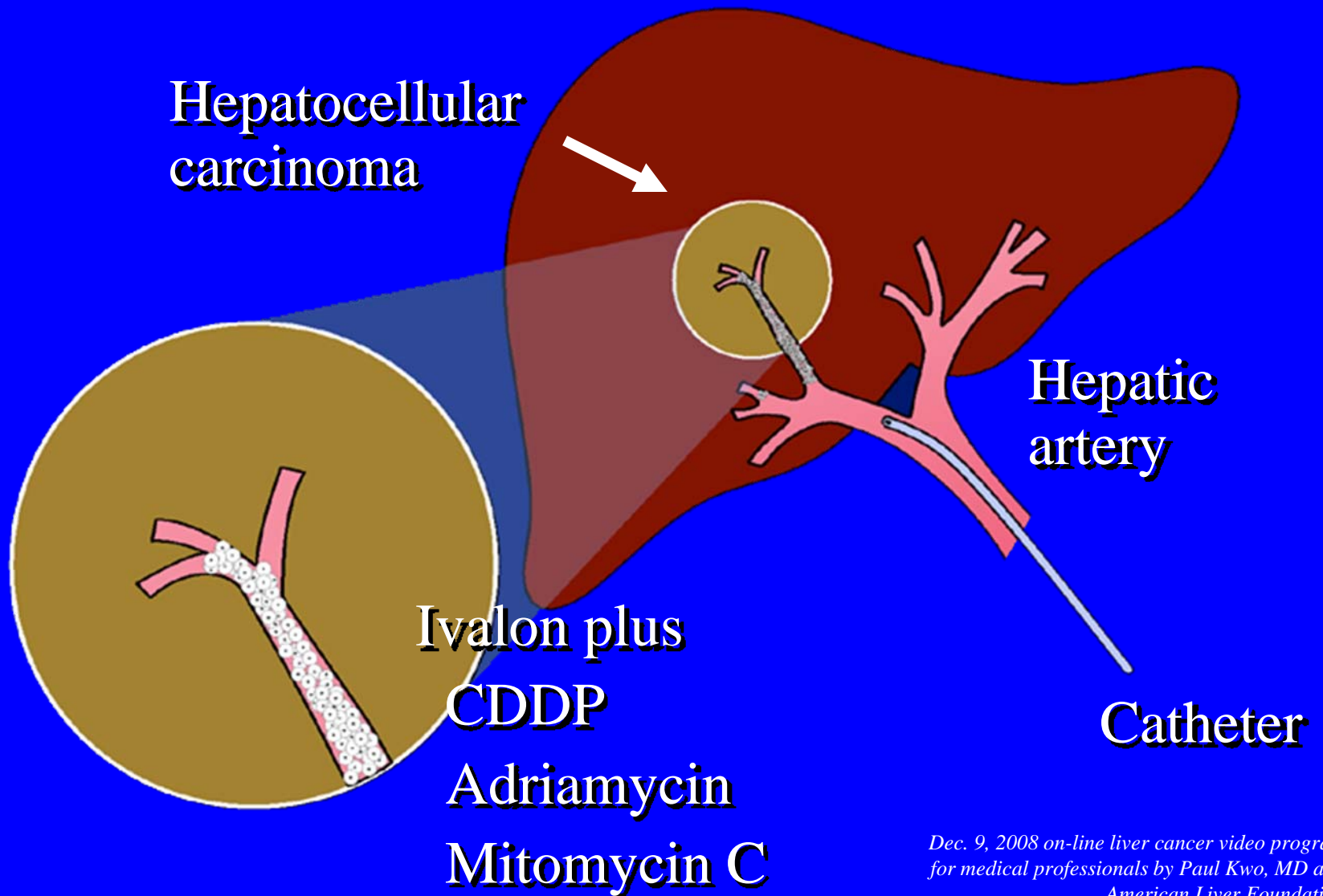
Survival Following LT for HCC



Yao et al: *Liver Transp* 8:765, 2002

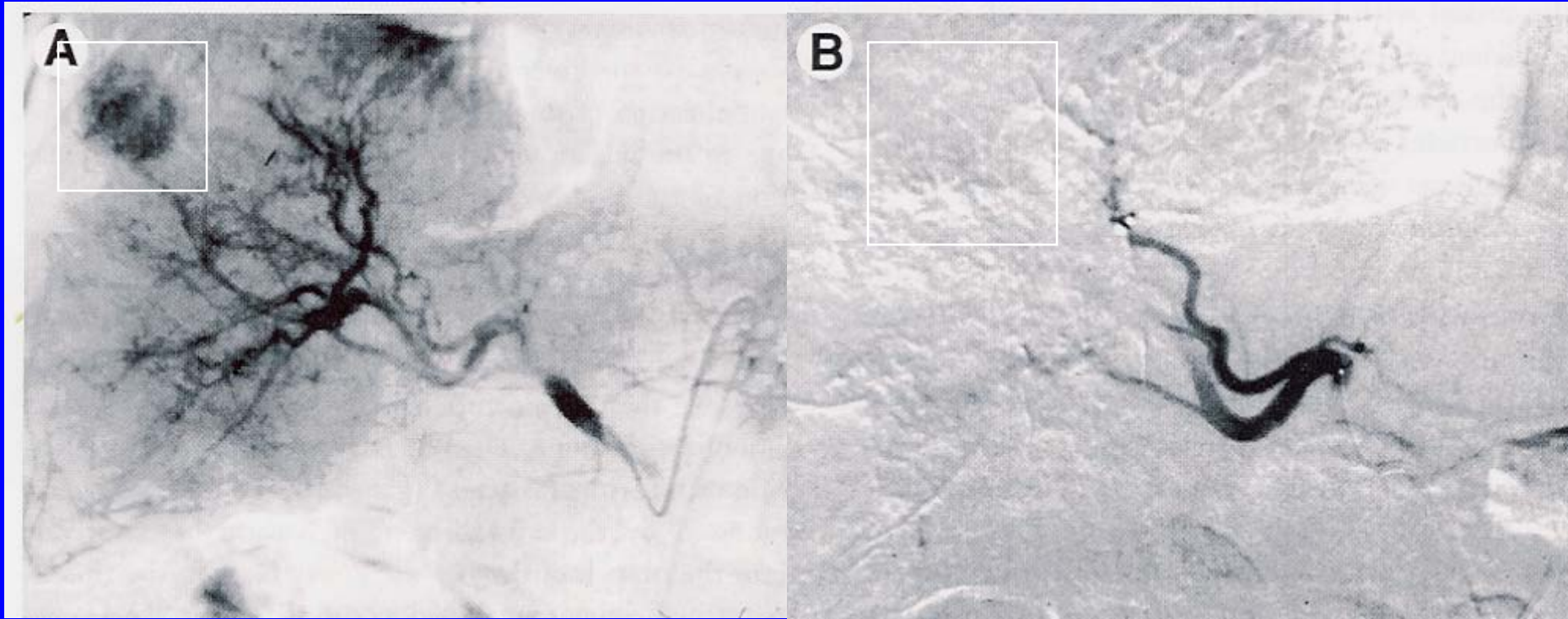
Dec. 9, 2008 on-line liver cancer video program for medical professionals by Paul Kwo, MD and American Liver Foundation

Chemoembolization



*Dec. 9, 2008 on-line liver cancer video program
for medical professionals by Paul Kwo, MD and
American Liver Foundation*

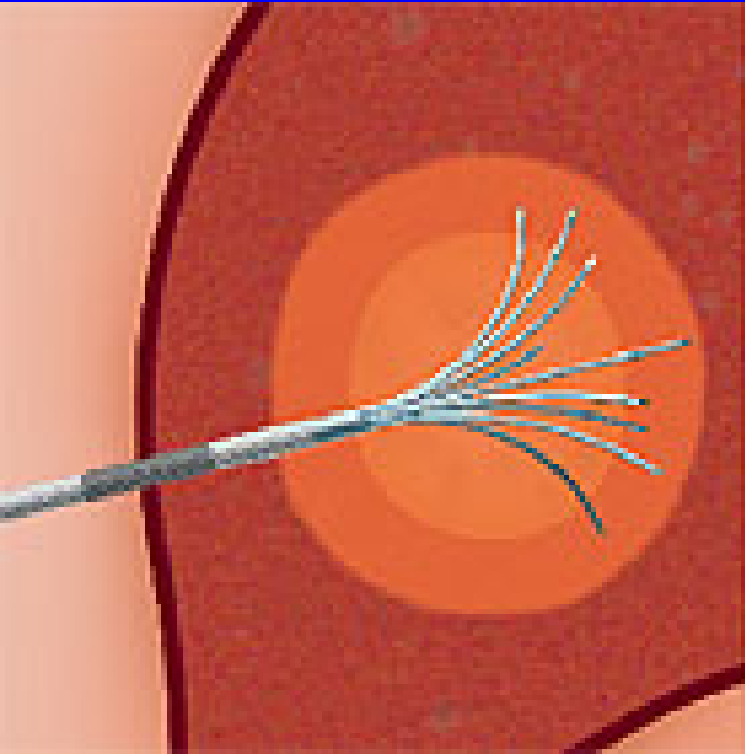
HCC: Transarterial Chemoembolization (TACE)



Pre-treatment

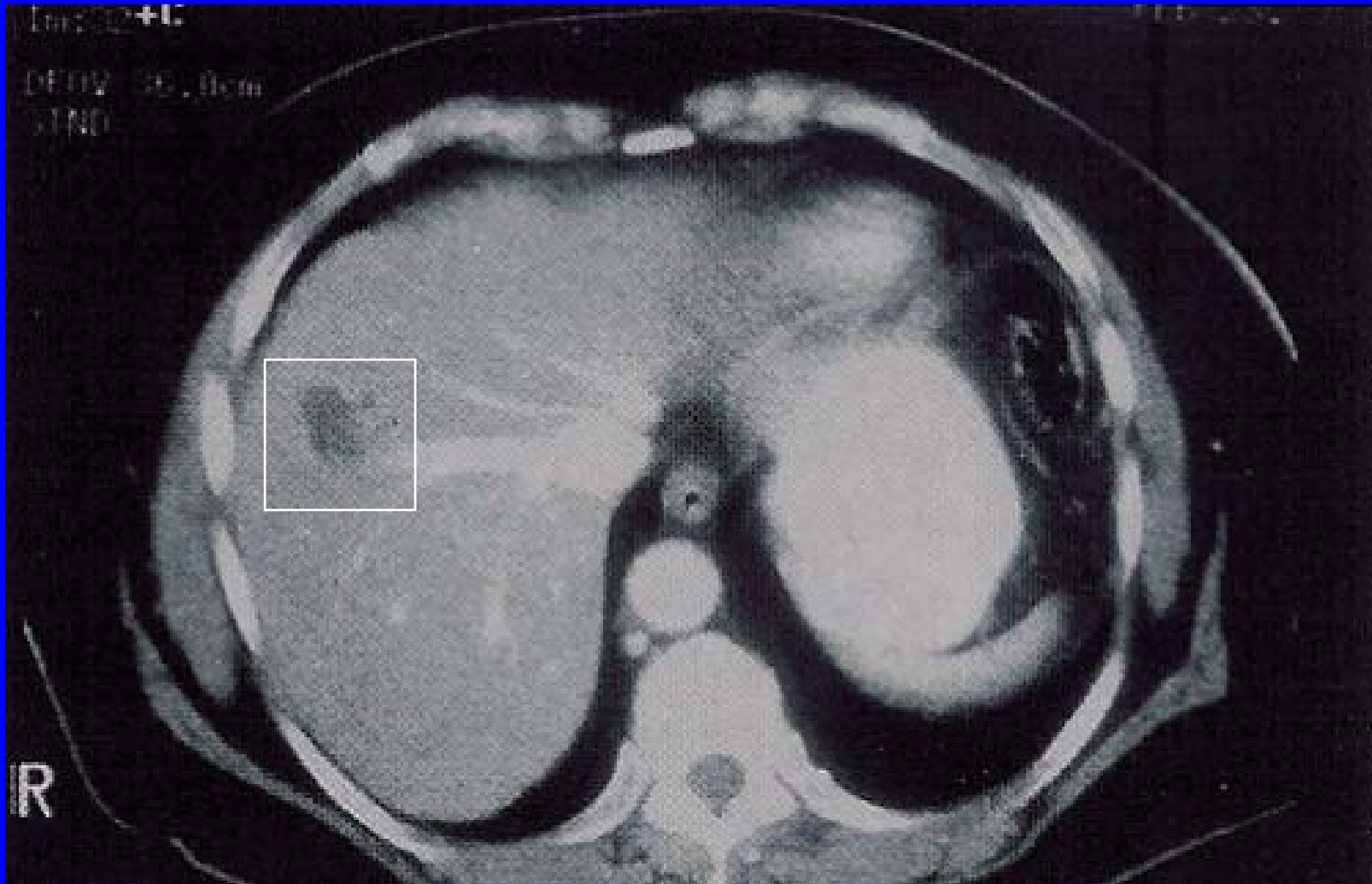
Post-treatment

Radiofrequency Ablation

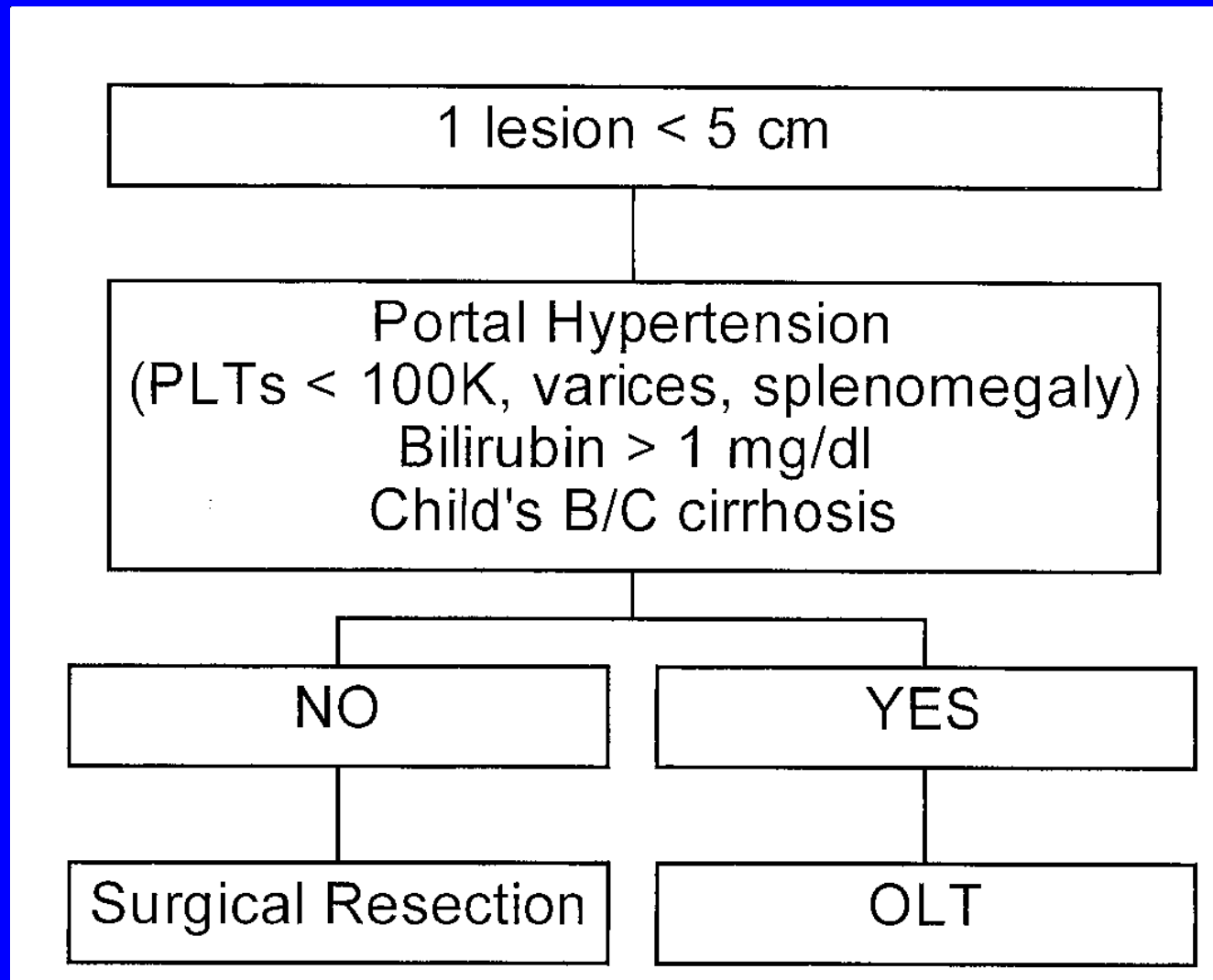


A 14 gauge needle is directed into the tumor by ultrasound or CT guidance and an alternating current is applied, similar to microwave, Best in tumors less than 5 cm.

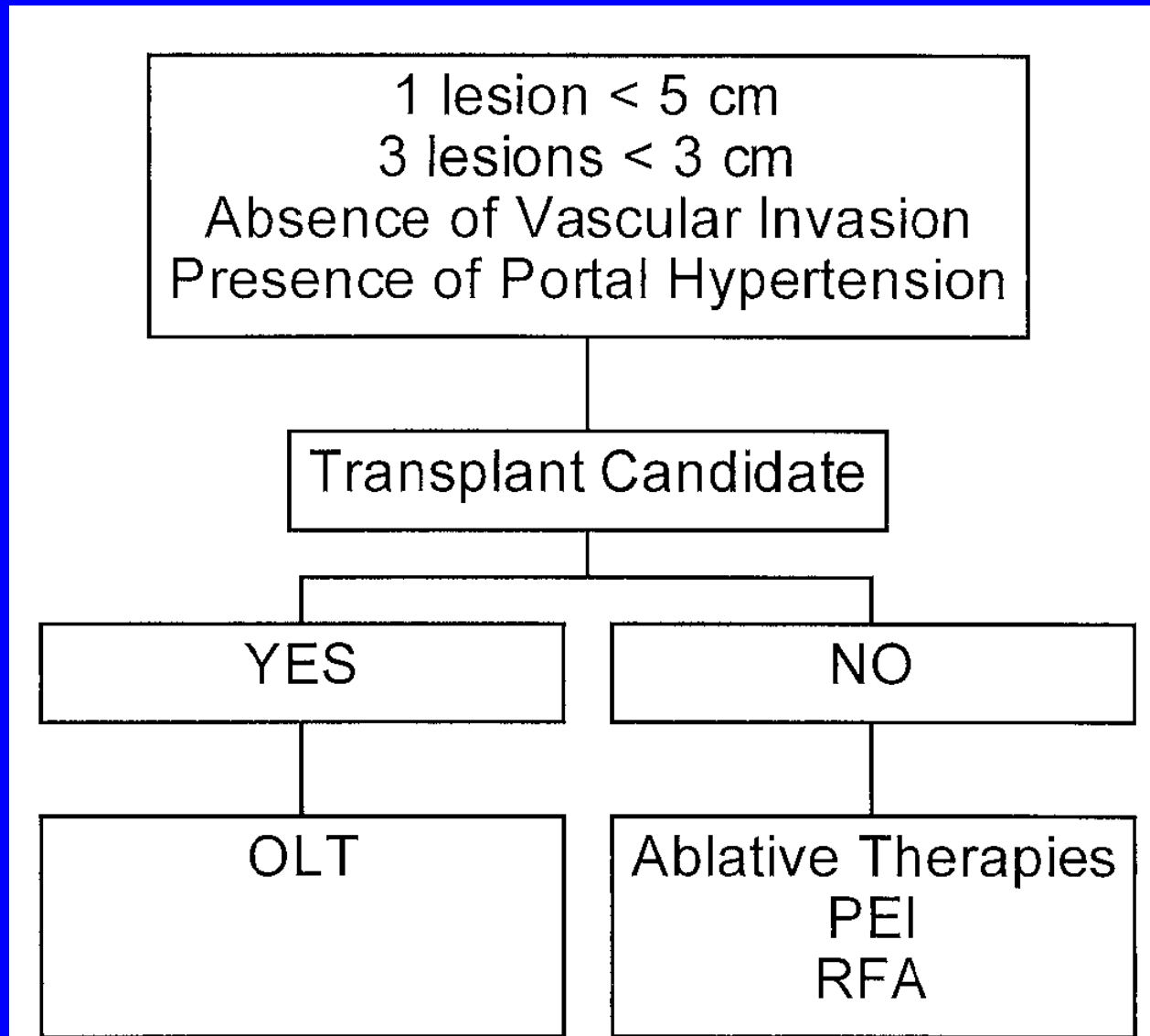
HCC: Post RFA Treatment



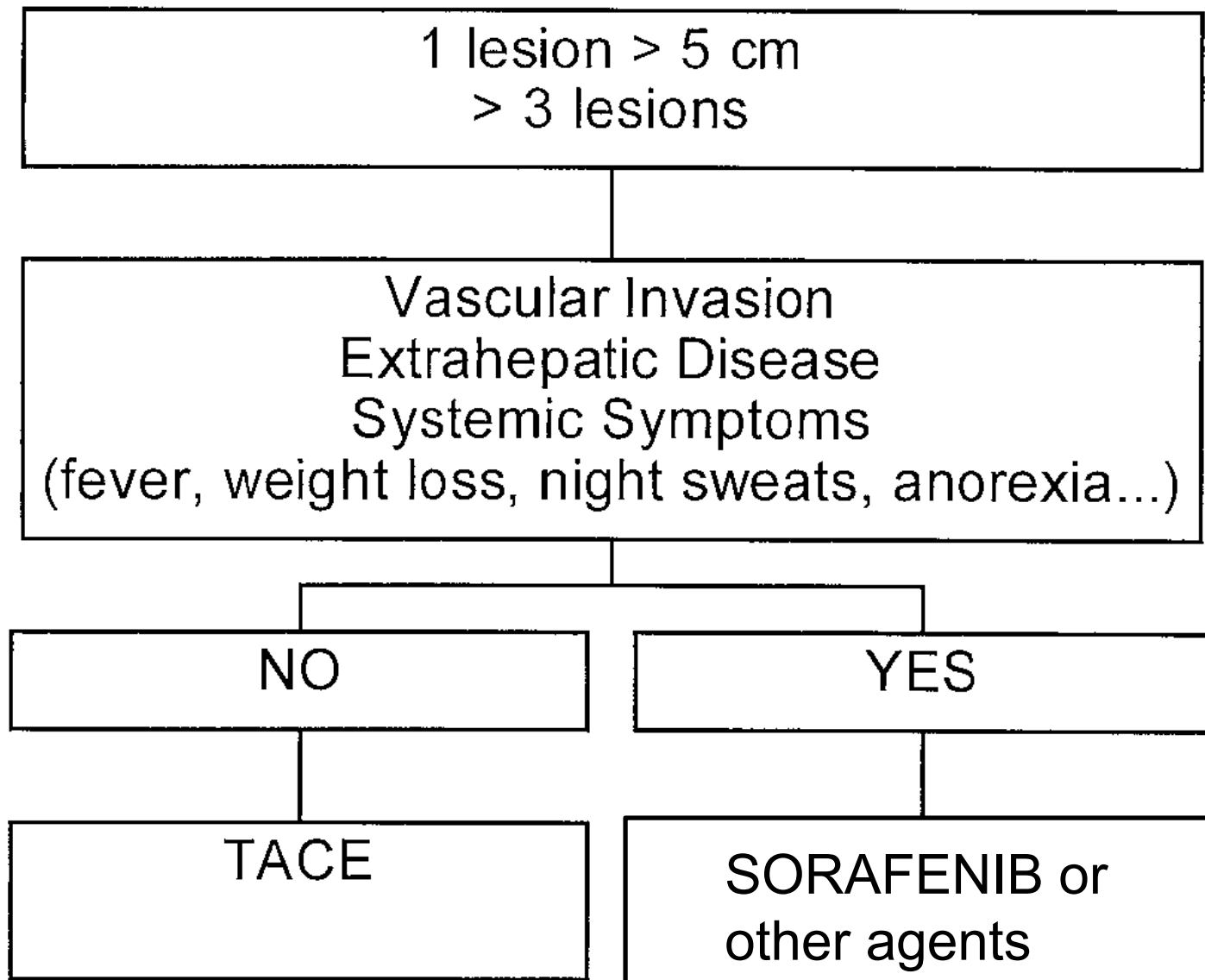
Management Algorithm for a Solitary HCC nodule



Management Algorithm for Early HCC nodule



Management Algorithm for Large Solitary or Multicentric HCC

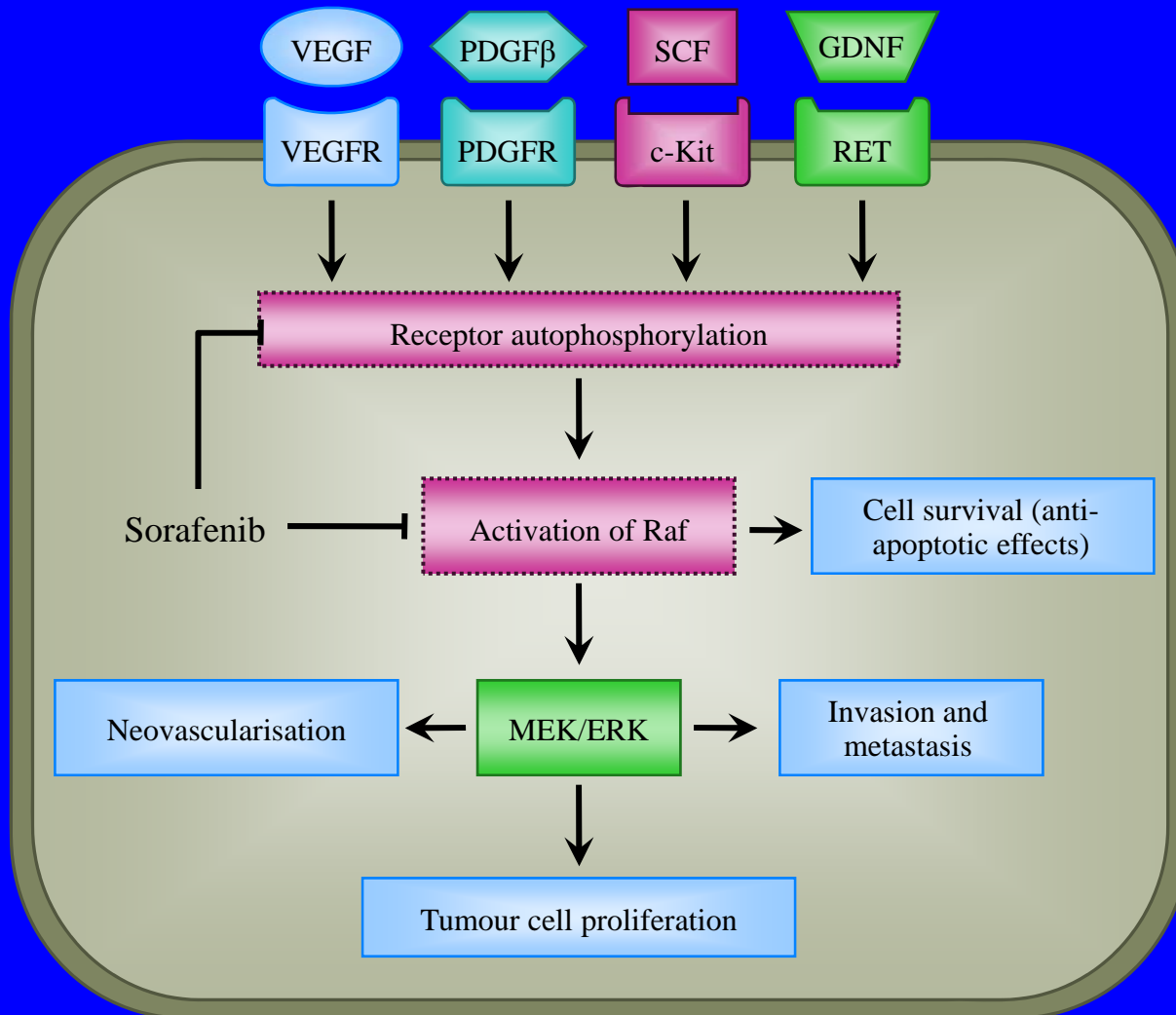


Sorafenib Improves Survival in Hepatocellular Carcinoma: Results of a Phase III Randomized, Placebo-Controlled Trial

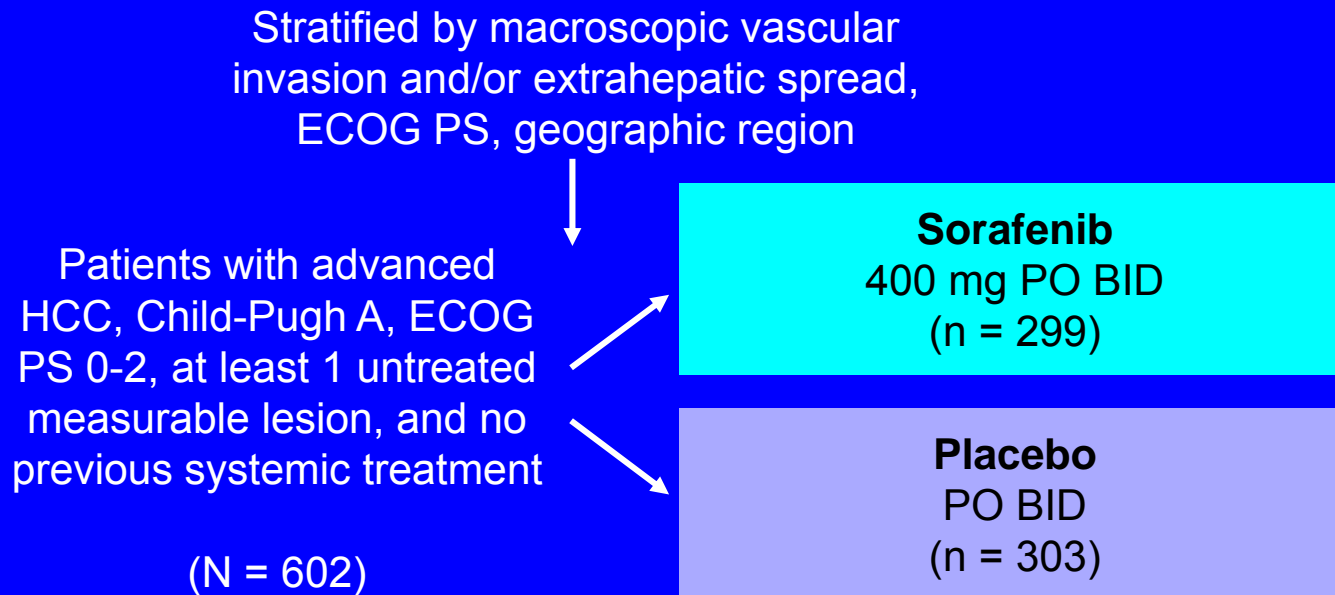
Josep M Llovet, Sergio Ricci, Vincenzo Mazzaferro, Philip Hilgard, Jean-Luc Raoul, Stefan Zeuzem, Armando Santoro, MinghuaShan, Marius Moscovici, Dimitris Voliotis, and Jordi Bruix,
for the SHARP Investigators Study Group

Supported by Bayer HealthCare and Onyx Pharmaceuticals

Cellular targets of sorafenib

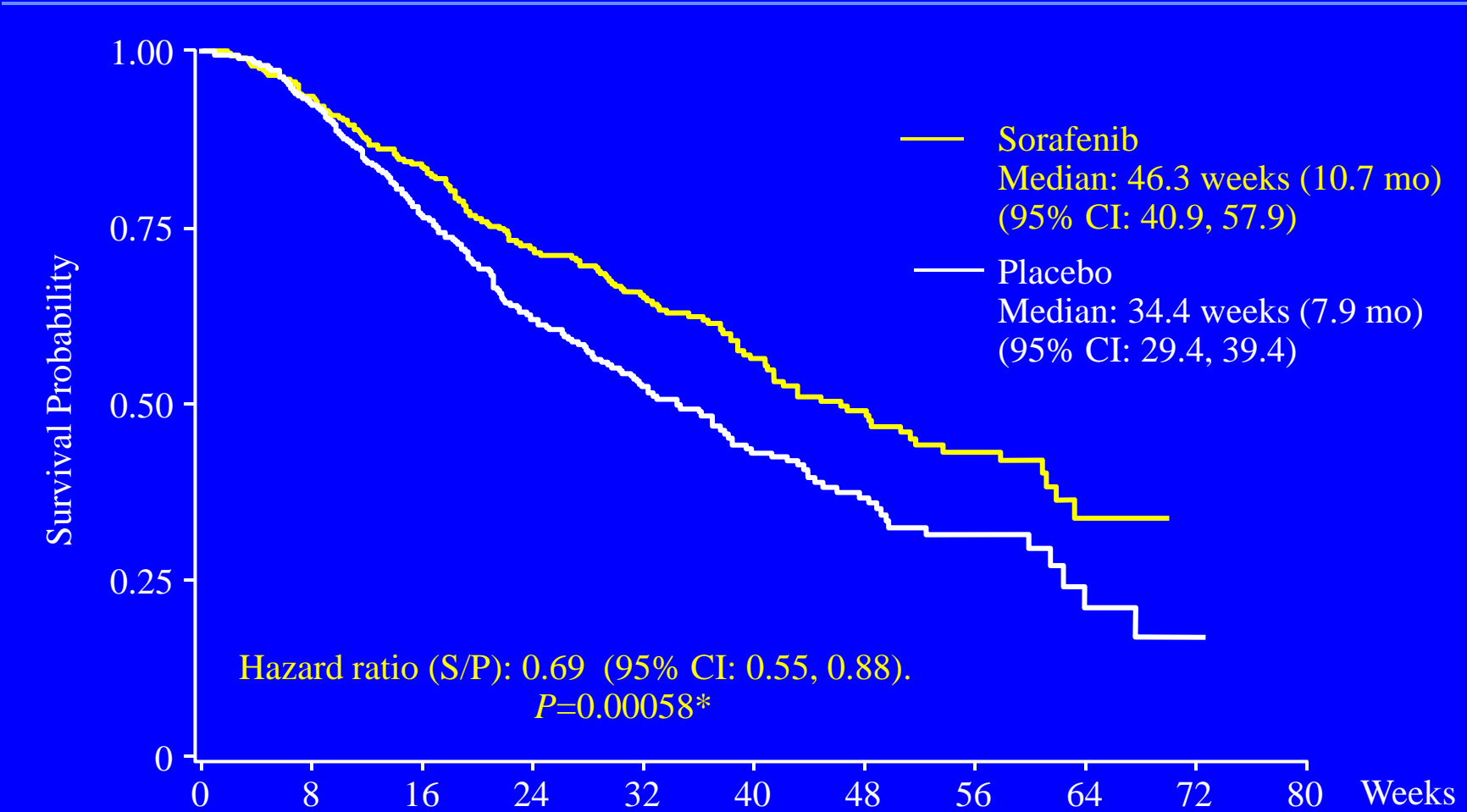


SHARP: Phase III Study of Sorafenib in HCC



Phase III SHARP Trial

Overall survival (Intention-to-treat)



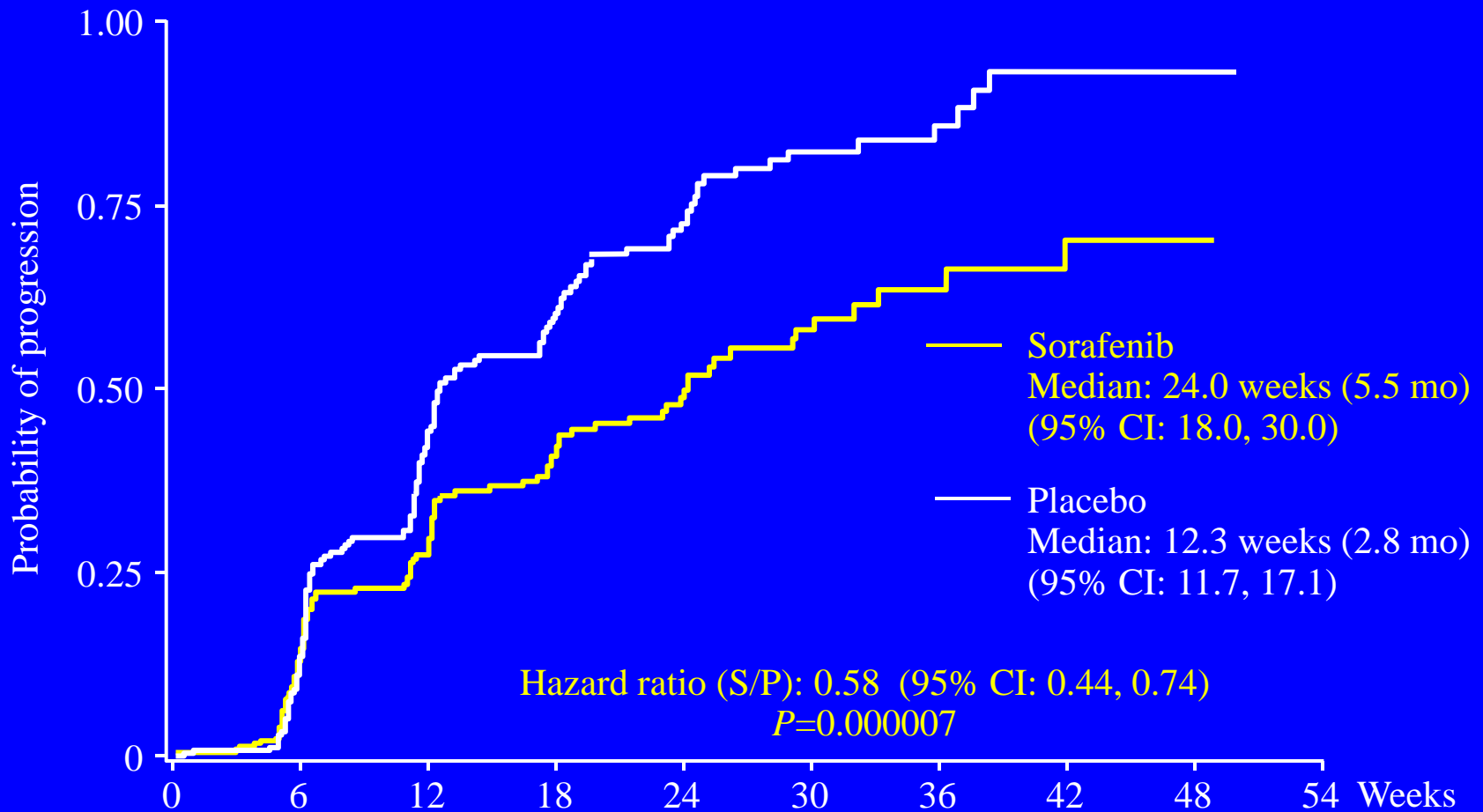
Patients at risk

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

*O'Brien-Fleming threshold for statistical significance was $P=0.0077$.

Phase III SHARP Trial

Time to Progression (Independent central review)



Patients at risk

Sorafenib:	299	196	126	80	50	28	14	8	2	0
Placebo:	303	192	101	57	31	12	8	2	1	0

Summary

- HCC usually arises in cirrhotic liver
- Growth rate varies
- Long asymptomatic phase
- Child-Pugh stage and performance status are important determinants of survival

Conclusions

- Liver transplantation offers best chance for cure in selected cases (preoperative chemoembolization may provide additional benefit)
- Living donor liver transplantation may provide timely transplantation
- Radical (PEI and RFA) therapies are effective for small tumors before OLT

Conclusions

- The role of TACE in non-transplant patients remains to be defined but appears to improve survival
- Sorafenib conferred a survival benefit in unresectable HCC is being studied in multiple patient populations with HCC
- Important to identify patients with end stage liver disease and other high risk groups, particularly Hepatitis B and C carriers as well as NAFL-D in the US