Osher Mini Medical School – 11/13/2019

HEPATOCELLULAR CARCINOMA (HCC)

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Assistant Clinical Professor

HEPATOCELLULAR CARCINOMA

- Risk factors and epidemiology
- Surveillance for HCC
- Diagnosis and staging
- Treatment decisions
    - Surgical options and criteria
    - Local regional therapy
    - Systemic therapy

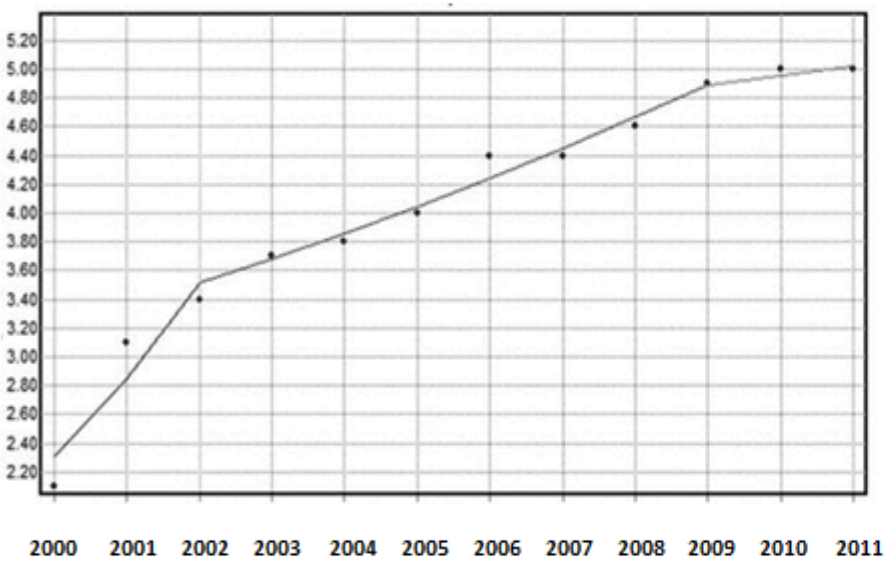
HEPATOCELLULAR CARCINOMA

- Hepatocellular carcinoma (HCC) is the 5th most common cancer worldwide, and the 3rd leading cause of cancer-related deaths[1]
- In Asia and Sub-Saharan Africa alone, >500,000 new HCC cases develop each year[2]
- Most HCC cases are associated with an underlying risk factor[1]

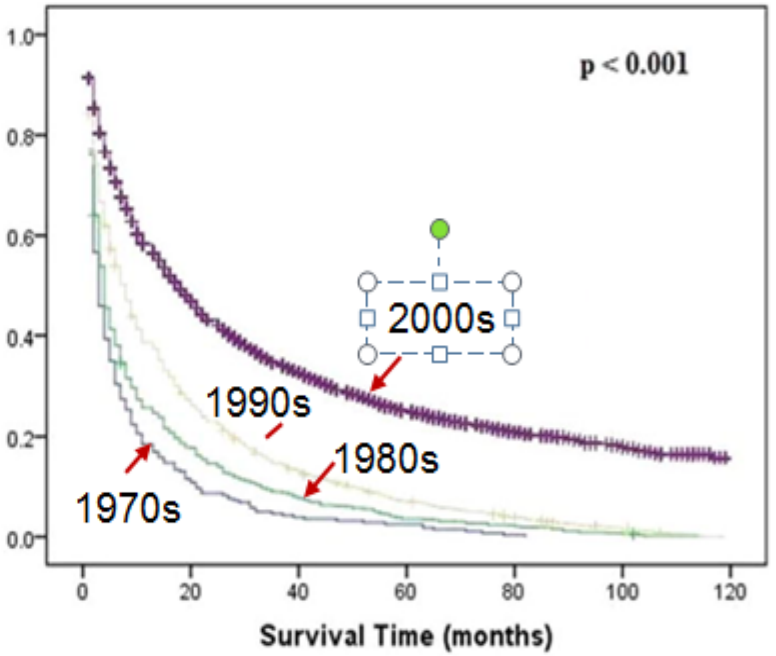
[1]Ferenci P, et al. J Clin Gastroenterol. 2010;44(4):239-245.
[2]Thomas and Zhu. J Clin Oncol. 2005;23(13):2892-2899.

Rising Incidence of HCC in the U.S.

Age-adjusted rates/ trend 2000-2011



Cumulative Survival by Decade



Njei B. et al. Hepatology 2015;61:191-199

WHO IS AT RISK FOR HCC?

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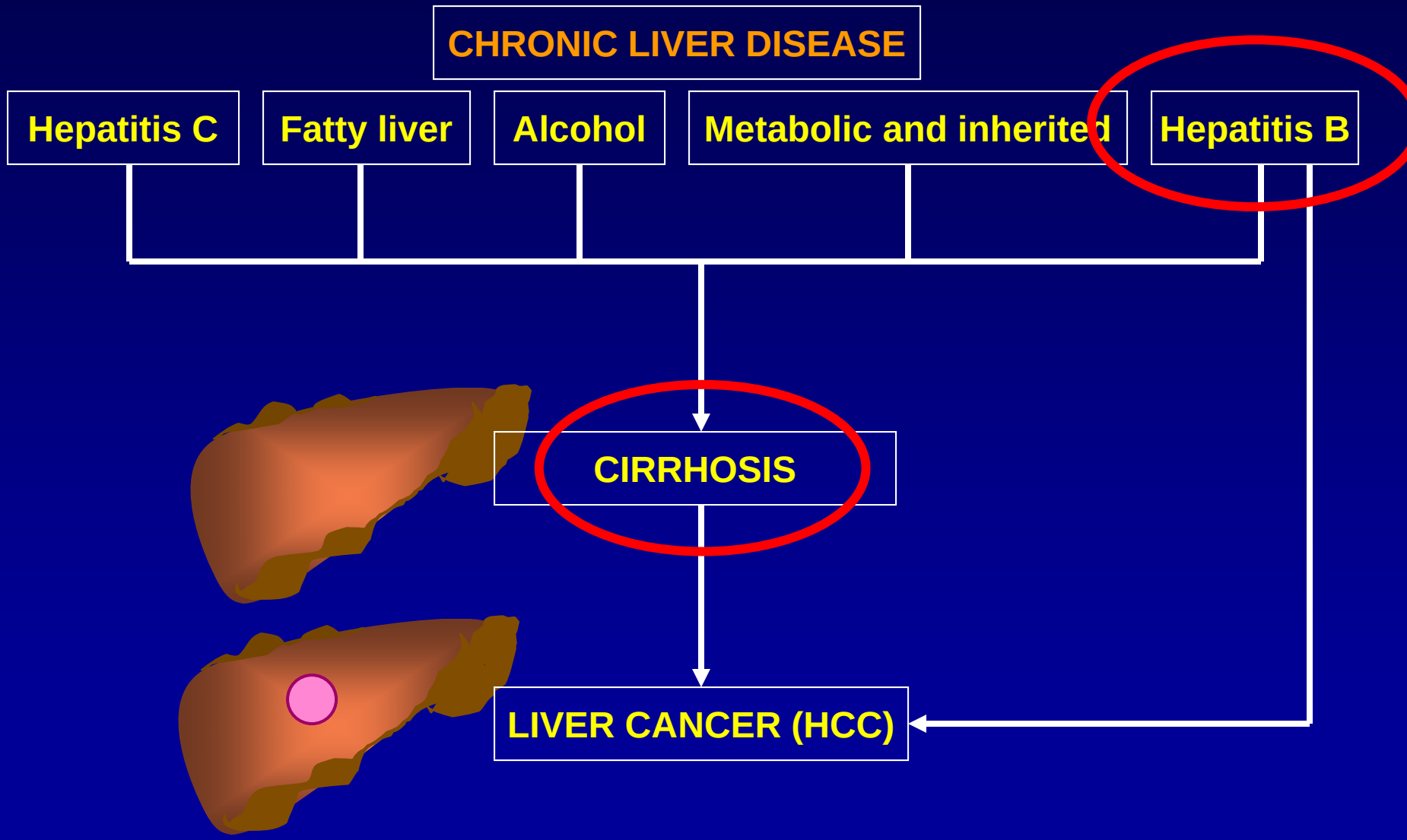
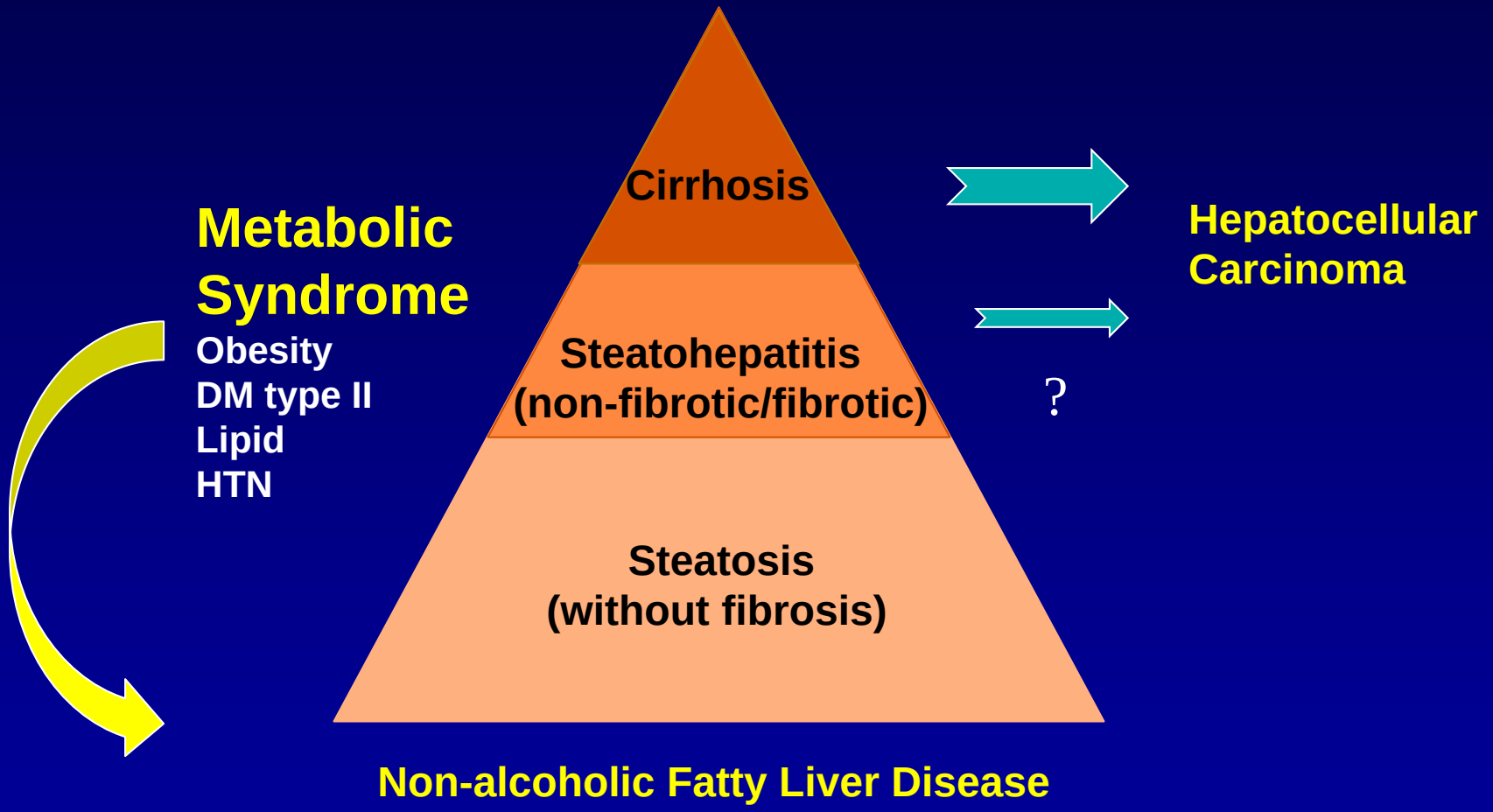


METABOLIC SYNDROME/ NAFLD AND HCC



Adopted from Baffy G, Brunt EM, & Caldwell SH. J Hepatol 2012;56:1384-1391

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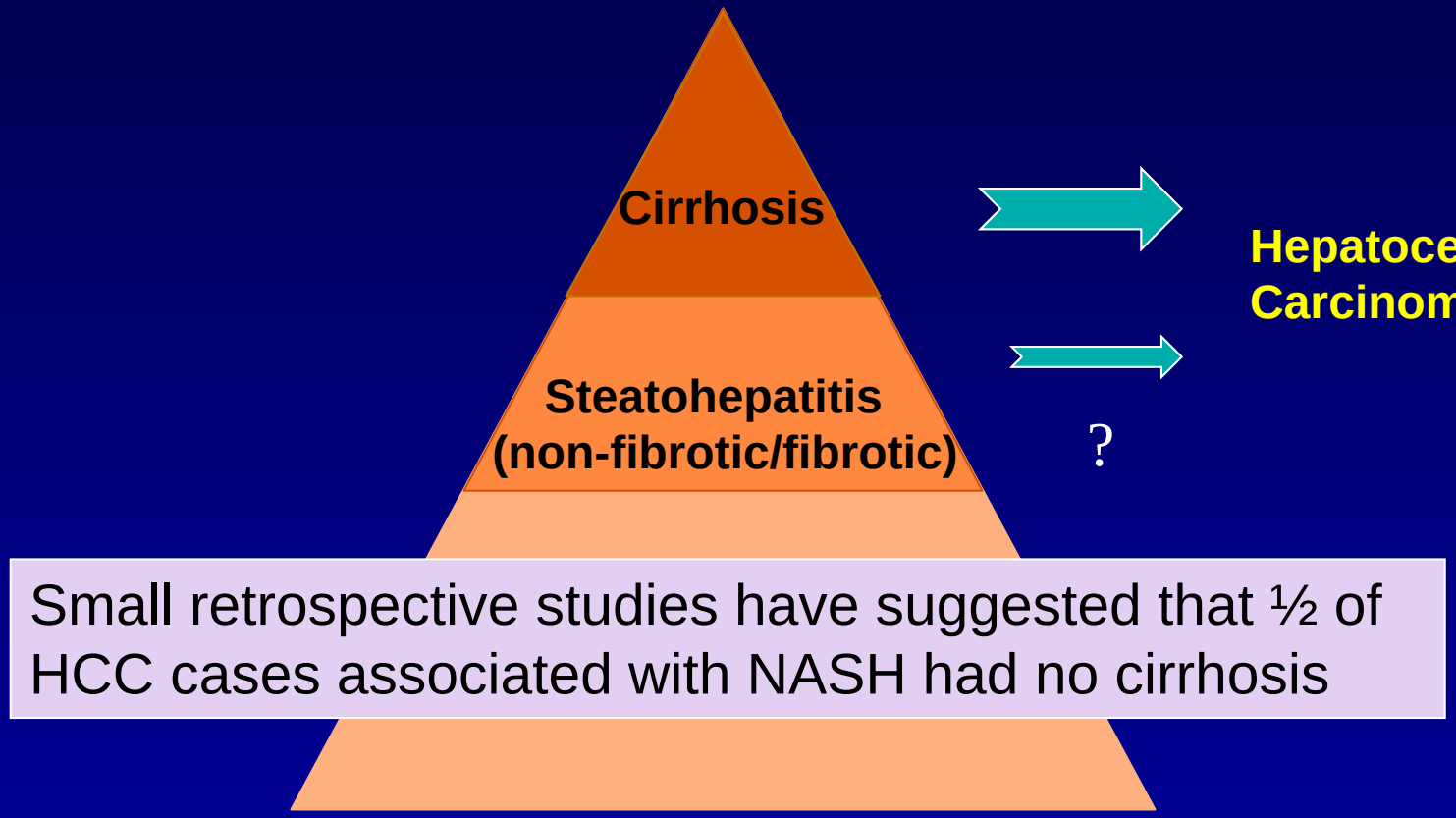


Mittal S, et al. Clin Gastroenterol Hepatol 2015;56:13;594-601

METABOLIC SYNDROME/ NAFLD AND HCC

Multiple Logistic Regression Analysis

Pre-existing conditions	Adjusted OR*	p-value
HBV	19.87	< 0.0001
HCV	62.92	< 0.0001
Unspecified viral	13.46	< 0.0001
Alcoholic liver disease	35.29	< 0.0001
Non-specified cirrhosis	50.15	< 0.0001
Smoking	2.97	< 0.0001
Metabolic syndrome	2.58	< 0.0001
Impaired glucose tolerance/ diabetes mellitus	2.90	< 0.0001
Dyslipoproteinemia	1.35	< 0.0001
Hypertension	1.93	< 0.0001
Obesity	2.58	< 0.0001

*Adjusted for age and sex, race

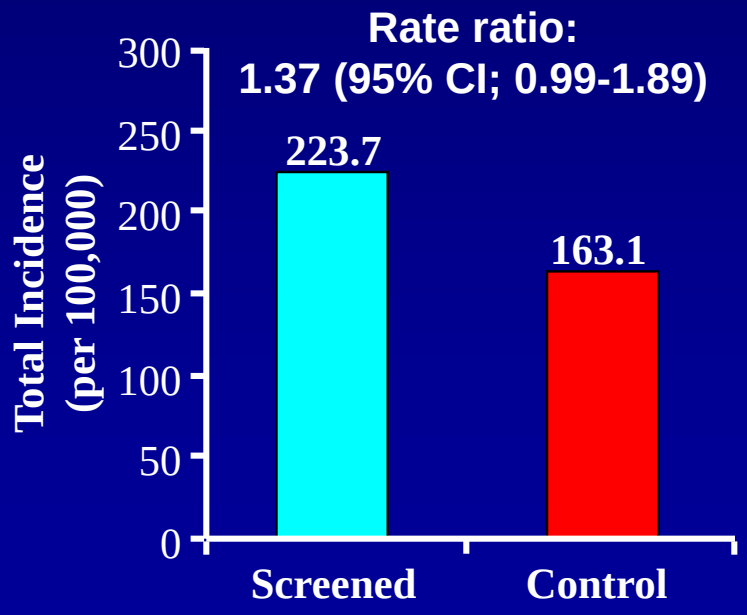
Welzel TM et al. Hepatology 2011;54:463-471

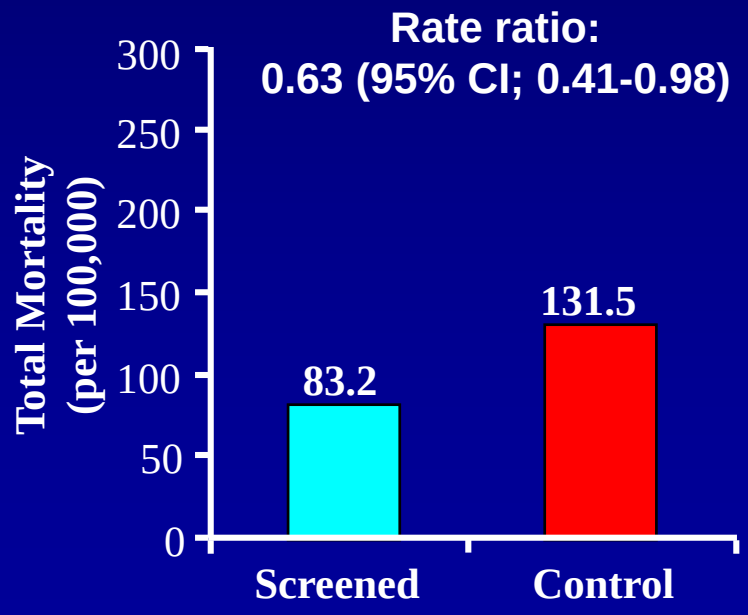
SURVEILLANCE OF HCC

- Surveillance = applying screening tests at regular intervals in patients at risk for HCC.
- Most commonly used surveillance in clinical practice = ultrasound + alpha-fetoprotein (AFP) every 6 months.
- The added value of AFP to ultrasound in surveillance has been questioned. AFP no longer included in AASLD guidelines.

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**
    Control group received no surveillance





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

TUMOR MARKERS

- Alpha-fetoprotein (AFP) as a screening test
  - 30-40% with HCC have normal AFP
  - 20-30% without HCC have abnormal AFP
  - The higher the AFP, the more likely the diagnosis of HCC
  - AFP 20 ng/ml performs best on ROC curve

- AFP as a prognostic marker
  - predicts overall mortality in HCC
  - predicts prognosis after resection
  - predicts prognosis after liver transplant

Marrero JA et al. Gastroenterology 2009;137:110-118
Tyson GL et al. Clin Gastro Hepatol 2012

CASE PRESENTATION

25 year-old Chinese woman with chronic hepatitis B and recent liver biopsy showing no fibrosis and minimal portal inflammation. No symptoms. Mother was diagnosed with liver cancer at age 55, treated with resection. Examination showed no spider nevi. Liver and spleen tip not palpable.

Laboratory evaluation showed bilirubin 1.0, ALT 19, AST 15, platelets 215,000, hepatitis B e antigen (-), hepatitis B DNA < 10 IU/mL. Previous labs last 3 years all showed normal ALT.

Your recommendations regarding HCC surveillance:

1. No screening until the age of 50
2. Screen with ultrasound and alpha-fetoprotein every 6 months
3. Screen with ultrasound and alpha-fetoprotein every 12 months
4. Screen if detectable hepatitis B DNA or elevated ALT during follow-up

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HCC Screening in Patients with Chronic HBV

- Patients at high risk for HCC should be screened with Ultrasound (+ AFP) every 6 months

  1) Cirrhosis
  2) Family history of HCC
  3) Age ≥ 40 for male and ≥ 50 for female (≥ 20 for Africans)
  4) Active replication (HBV DNA+) and or active necro-inflammatory activities

Marrero et al - AASLD guidelines; Hepatology 2018

HCC Surveillance in non-HBV cirrhosis

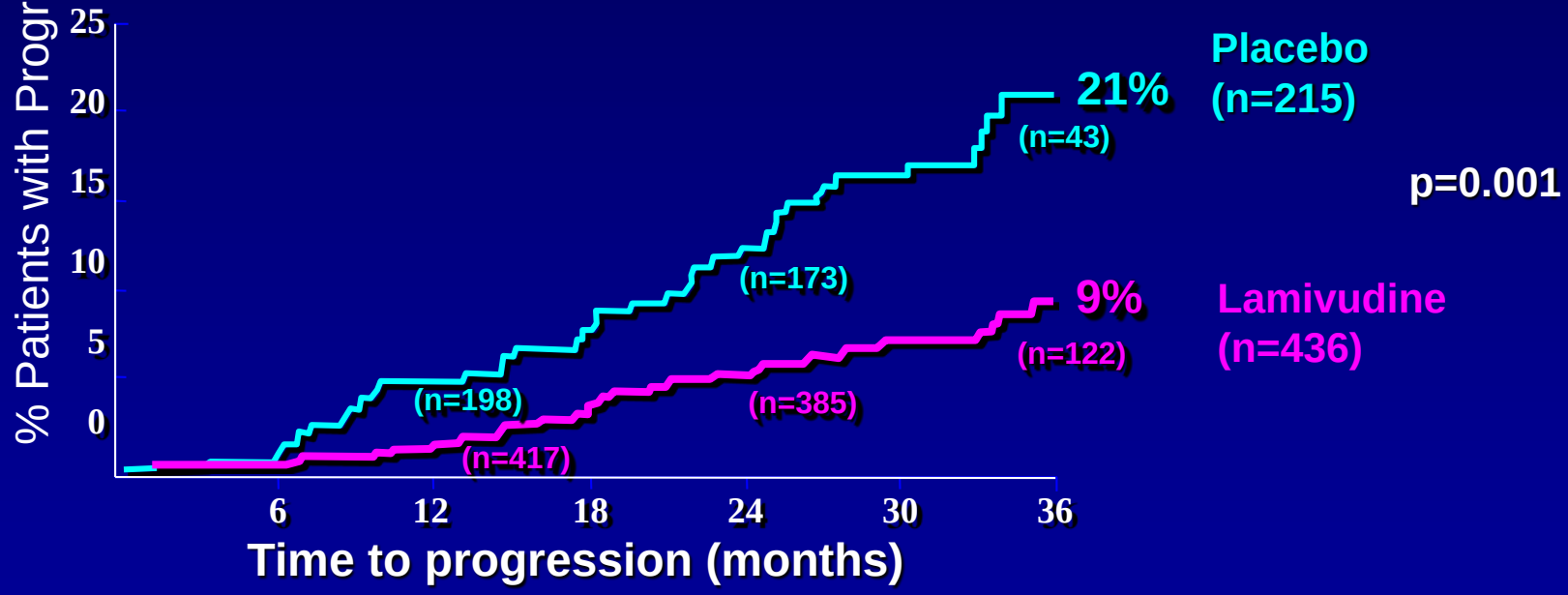
- HCC surveillance is recommended for all patients with cirrhosis
  - Unless Child-Pugh C disease and not on LT waitlist
- Insufficient evidence to suggest surveillance before development of cirrhosis (except HBV)
- The risk of HCC with HCV-related cirrhosis who develop SVR with DAA is lowered, but not eliminated
  - These pts should continue to undergo surveillance

Marrero et al - AASLD guidelines; Hepatology 2018

Lamivudine for Prevention of Liver-Related Complications in Patients with HBV-Cirrhosis

N=651 CHB patients with Ishak F4-6, evidence of viral replication, any ALT, compensated liver disease

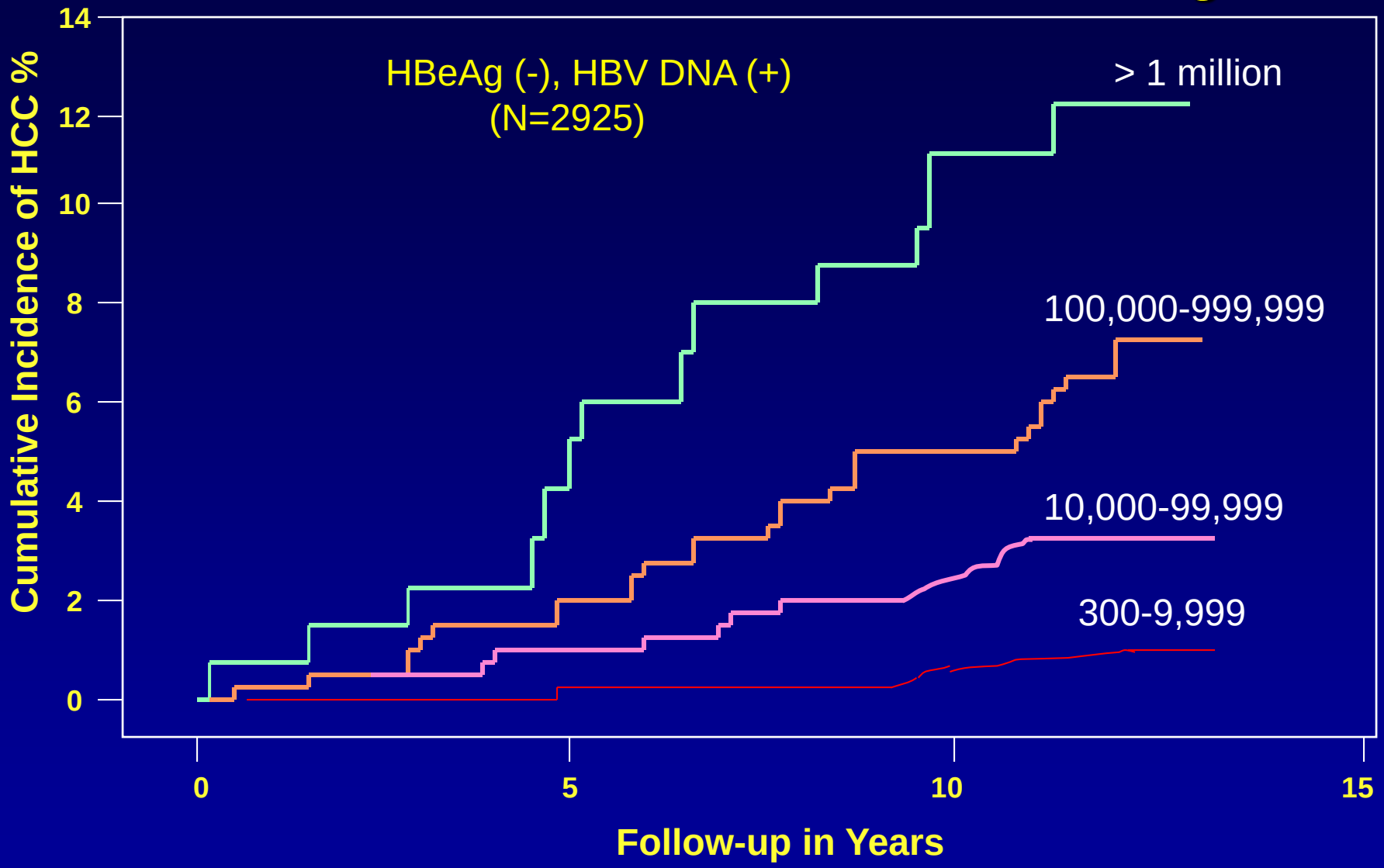
Treated with lamivudine 100mg daily for median 32 months



- **HCC in 3.9% lamivudine-treated patients vs 7.4% placebo controls HR=0.49, P=0.047**

Liaw YF, et al. N Engl J Med. 2004;351:1567

Cumulative Incidence of HCC across a HBV DNA gradient



Chen CJ and the REVEAL-HBV Study Group. JAMA 2006;295:65-73

SVR TO DAA THERAPY IN HCV/HCC: SYSTEMATIC REVIEW AND META-ANALYSIS

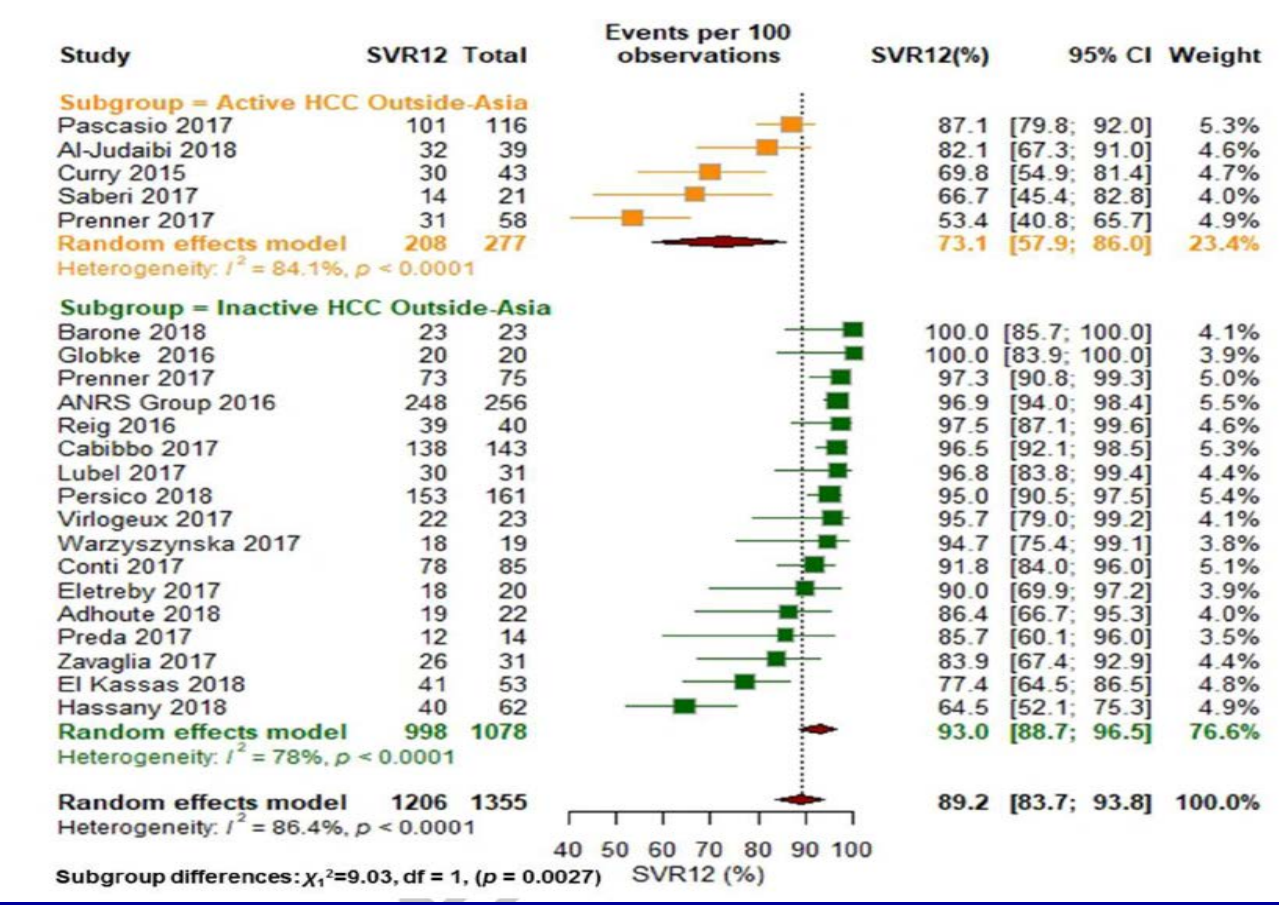
49 studies included from 15 countries (3341 HCC pts & 35701 non-HCC pts)

Pooled SVR (i.e cure) for HCC: 89.6% vs 93.3% for non-HCC (p=0.001)

Ji F, et al. J Hepatology 2019

SVR TO DAA THERAPY IN HCV/HCC: SYSTEMATIC REVIEW AND META-ANALYSIS

Pooled SVR for ACTIVE HCC: 73.1% vs 93.0% for non-HCC (p=0.001)



Ji F, et al.
J Hepatology 2019

CASE PRESENTATION

55 year-old man with chronic hepatitis C and biopsy proven cirrhosis, found on screening ultrasound to have a 3 cm lesion in the right lobe. Quad-phase CT of the abdomen confirmed the presence of a 2.5 cm lesion in the right lobe. No symptoms other than mild fatigue. No history of substance abuse. Examination showed no spider nevi. Spleen tip palpable.

Laboratory evaluation showed bilirubin 1.7, ALT 128, AST 98, albumin 3.5, INR 1.3, platelets 85,000, AFP 36.

Questions:

1. **What are the typical characteristics of HCC on quad-phase CT?**
2. **Would you biopsy the lesion and why?**

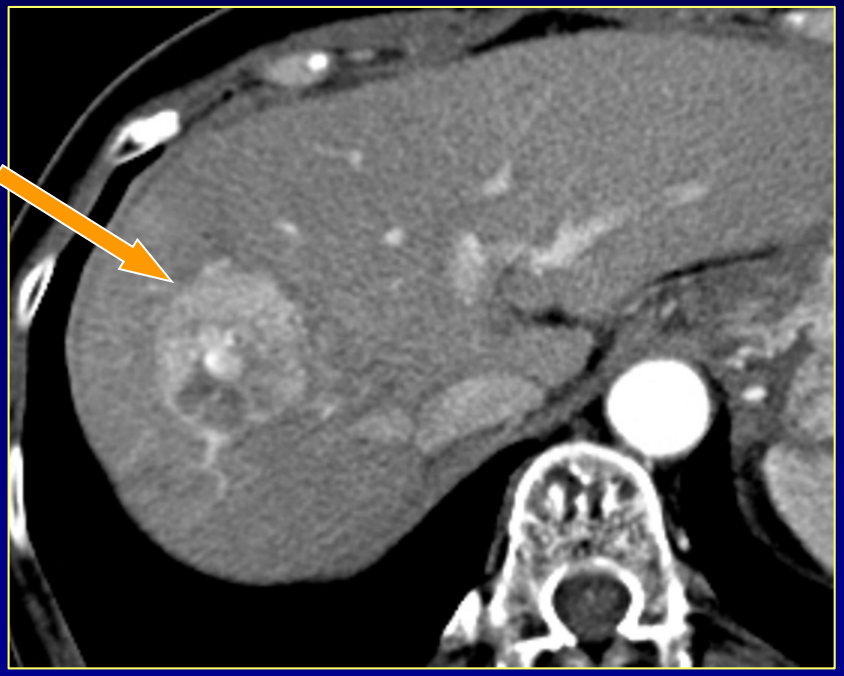
LIVER IMAGING REPORTING AND DATA SYSTEM (LI-RAD)
MAJOR DIAGNOSTIC CRITERIA

- Arterial phase hyper-enhancement
- Delayed phase “washout”
- Pseudo-capsule
- Interval growth ≥ 50% diameter within 6 mo

Different diagnostic criteria for lesion ≥2 cm versus < 2 cm

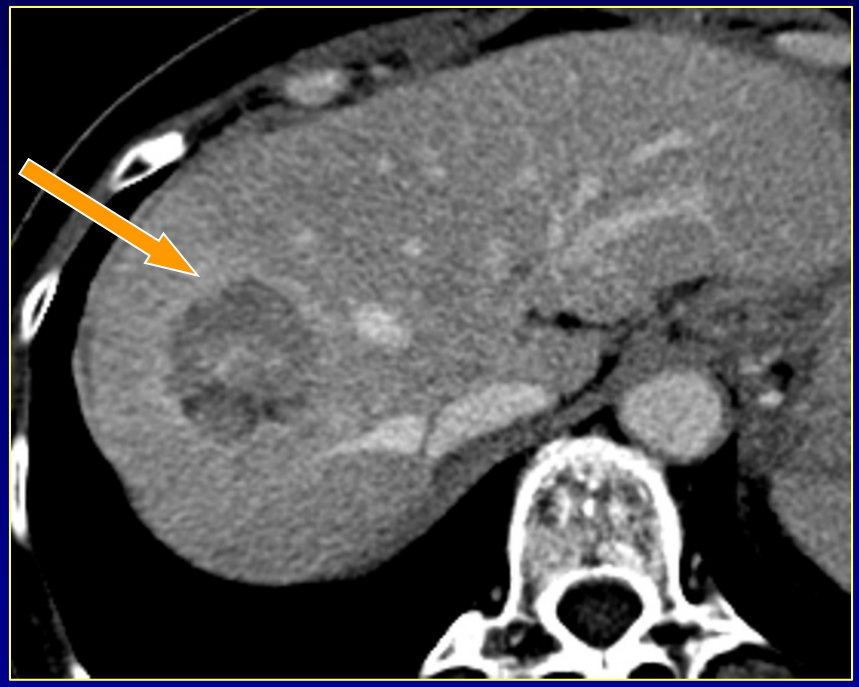
HCC – RADIOLOGIC DIAGNOSIS

Arterial Phase



Hyper-enhancement

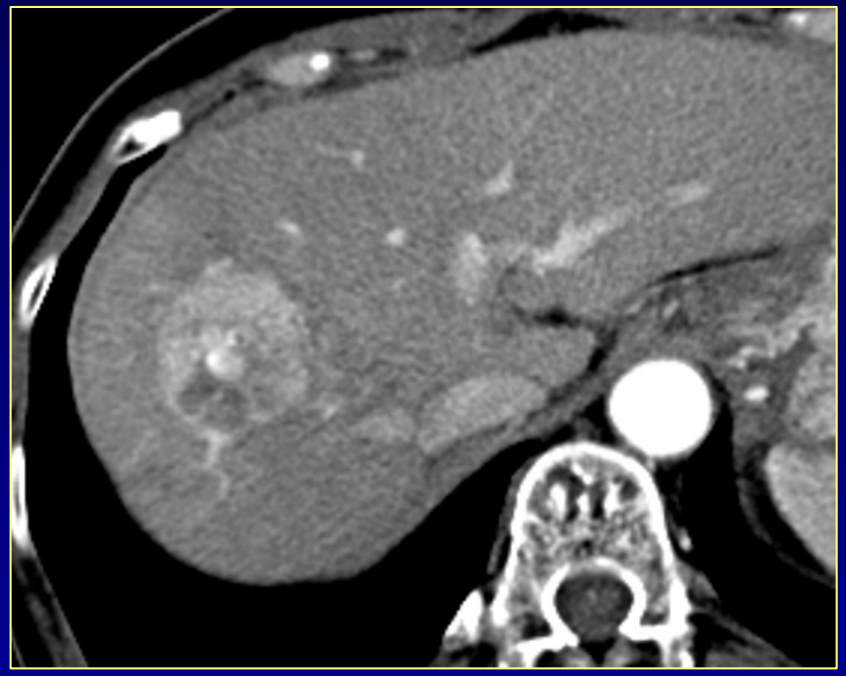
Portal Venous phase



“washout”

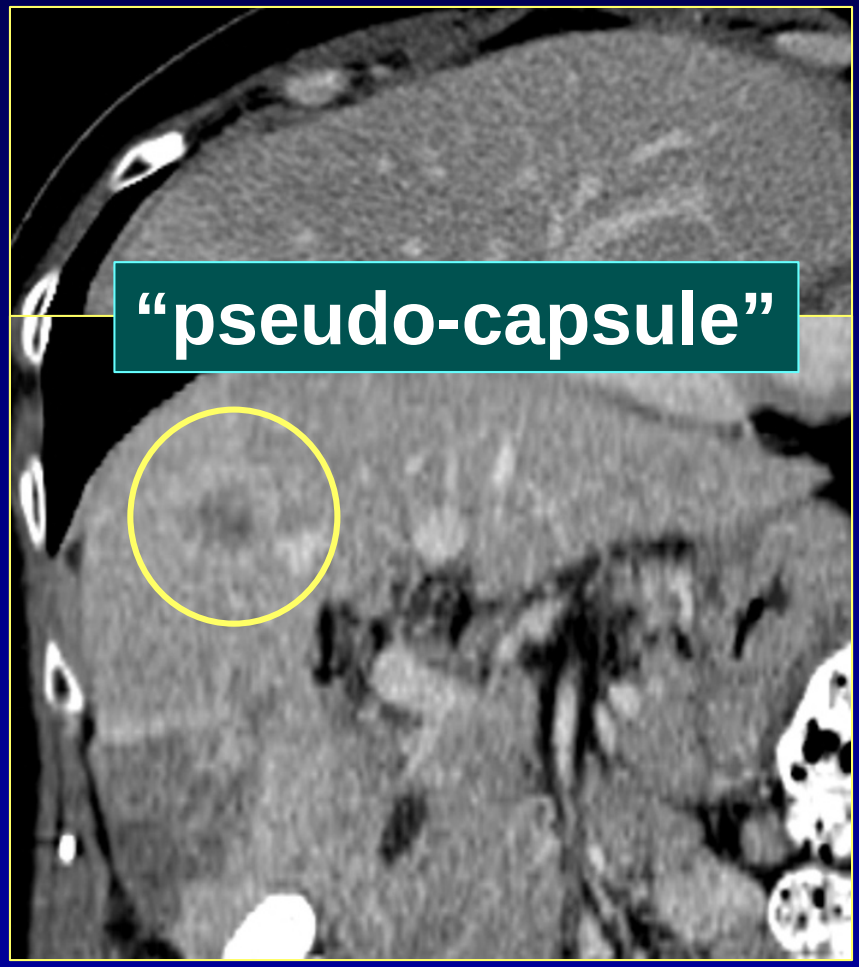
HCC – RADIOLOGIC DIAGNOSIS

Arterial Phase



Hyper-enhancement

Portal Venous phase



LIVER IMAGING REPORTING AND DATA SYSTEM (LI-RADS)

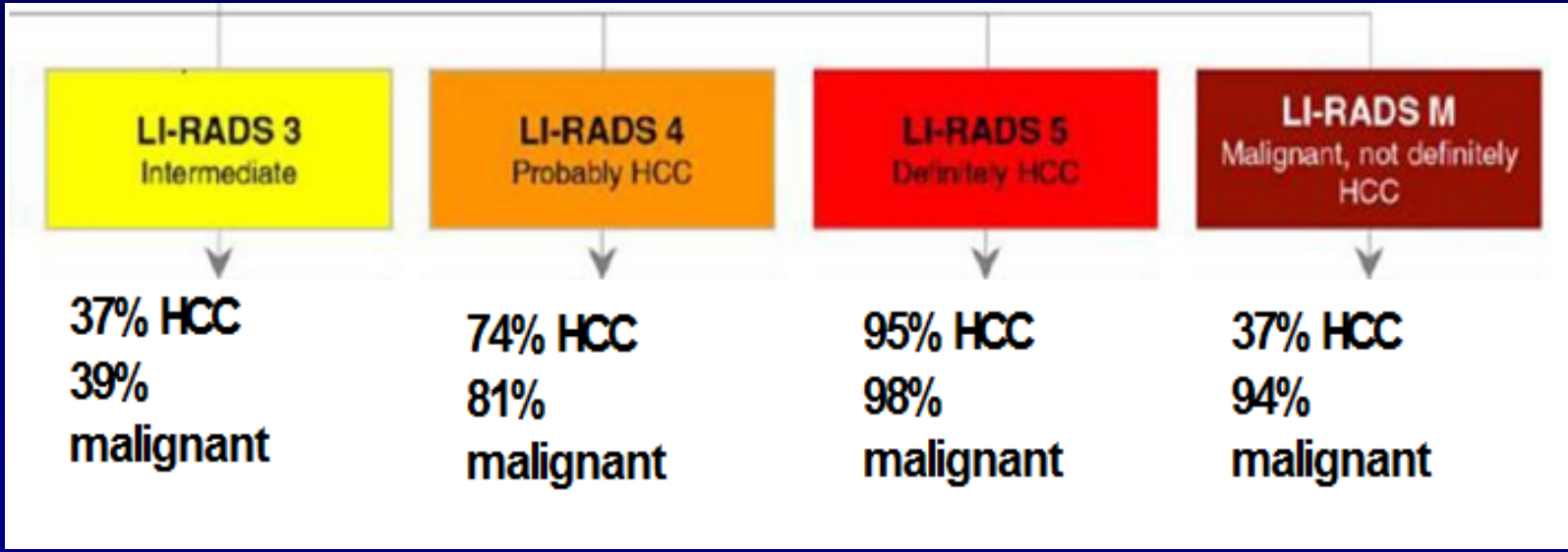
American College of Radiology: Standardized reporting of CT or MRI imaging for HCC in patients with cirrhosis or other risk factors

Li-RAD 1:	Definite benign
Li-RAD 2:	Probable benign
Li-RAD 3:	Indeterminate
Li-RAD 4:	Probable HCC
Li-RAD 5:	Definite HCC

LIVER IMAGING REPORTING AND DATA SYSTEM (LI-RADS)

Diagnostic Criteria		LIVER MASS				
		Arterial phase hypo- or Iso-enhancement		Arterial phase hyper-enhancement		
		< 2 cm	≥ 2 cm	< 1 cm	1-1.9 cm	≥ 2 cm
"Washout" "Capsule" Threshold growth	None	LIRAD 3	LIRAD 3	LIRAD 3	LIRAD 3	LIRAD 4
	One	LIRAD 3	LIRAD 4	LIRAD 4	LIRAD 4	LIRAD 5
	≥ Two	LIRAD 4	LIRAD 4	LIRAD 4	LIRAD 5	LIRAD 5

LI-RADS ACCURACY



CT/MRI LI-RADS v2018, accessed January 2019

HCC – IS BIOPSY NECESSARY?

Biopsy is not necessary to confirm HCC diagnosis if the lesion meets radiologic criteria in the appropriate clinical setting

False negative biopsy common in clinical practice and may lead to delay in diagnosis and treatment

Tumor seeding along the biopsy tract in 1-5%

Biopsy in selected cases if atypical radiologic appearance or lack of strong risk factor for HCC

MULTIDISCIPLINARY LIVER TUMOR BOARD

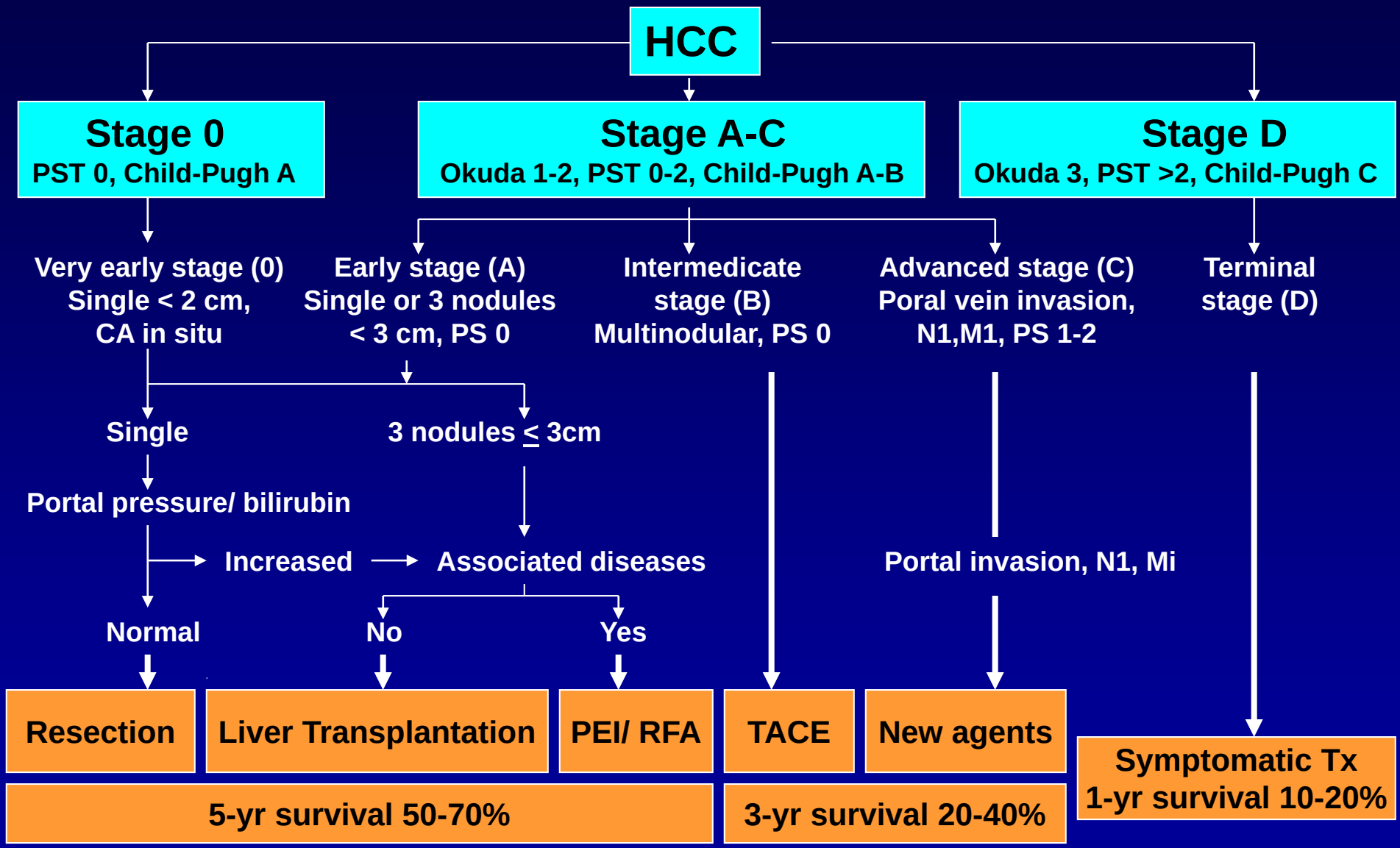
PARTICIPANTS

- Hepatologists
- Liver surgeons
- Interventional radiologists
- Radiologist - Abdominal imaging
- Oncologists
- Radiation Oncologists

OBJECTIVES

- Confirm diagnosis and staging
- Determine treatment strategies

BCLC STAGING CLASSIFICATION



Adapted from Llovet JM et al. Lancet 2003;362:1907-17

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Laboratory evaluation showed bilirubin 1.7, ALT 128, AST 98, albumin 3.5, INR 1.3, platelets 85,000, AFP 36.

What treatment would you recommend?

1. **Anatomic resection**
2. **Wedge resection**
3. **Liver transplantation**
4. **Percutaneous radiofrequency ablation (RFA)**

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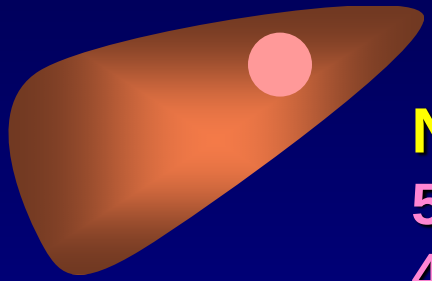
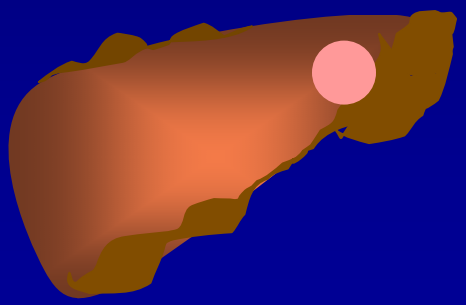
SURGICAL TREATMENT FOR HCC
CIRRHOSIS AND LIVER FUNCTION



NON-CIRRHOTIC → **RESECTION**

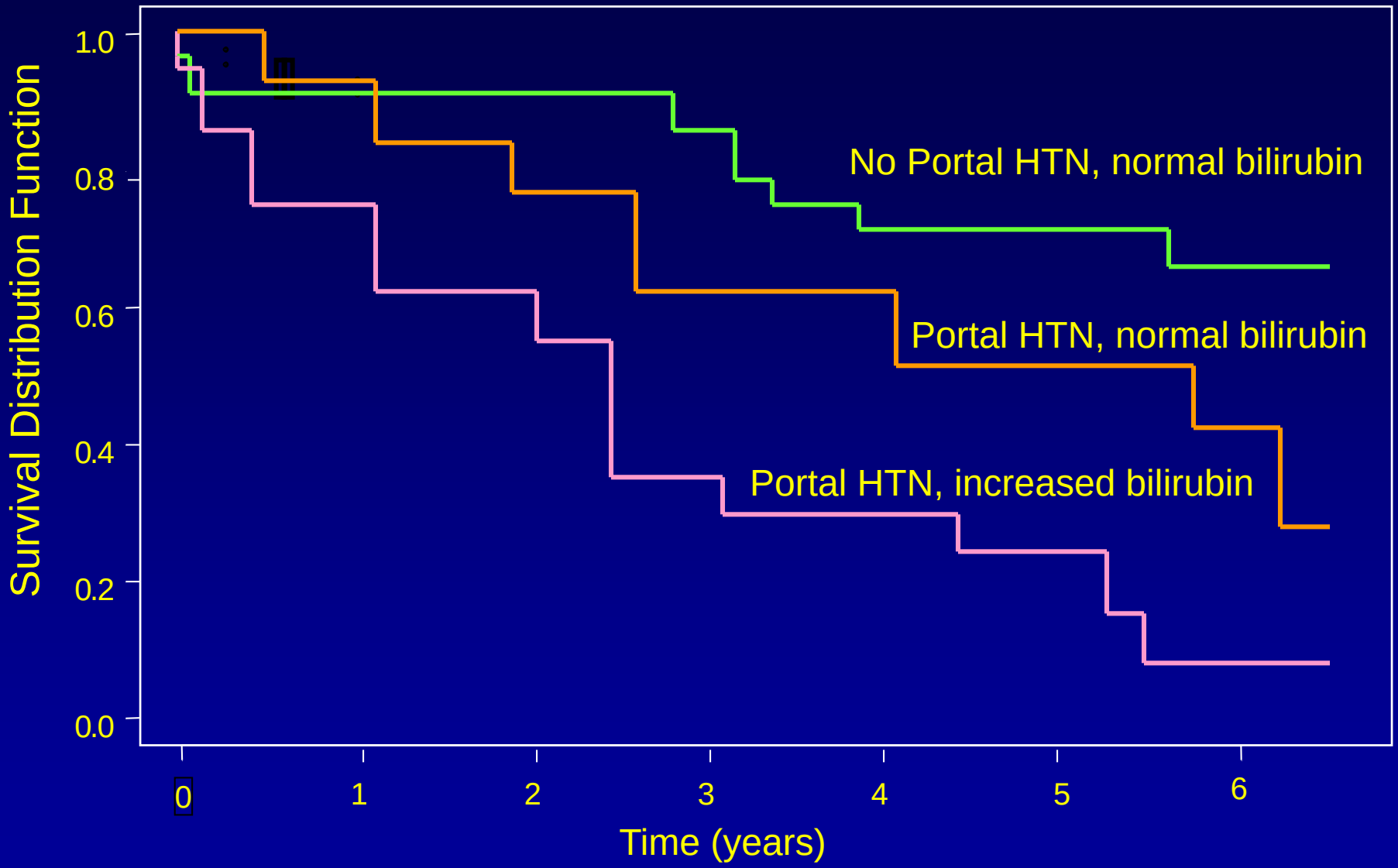
5% in Western countries
40% in Asia



CIRRHOTIC

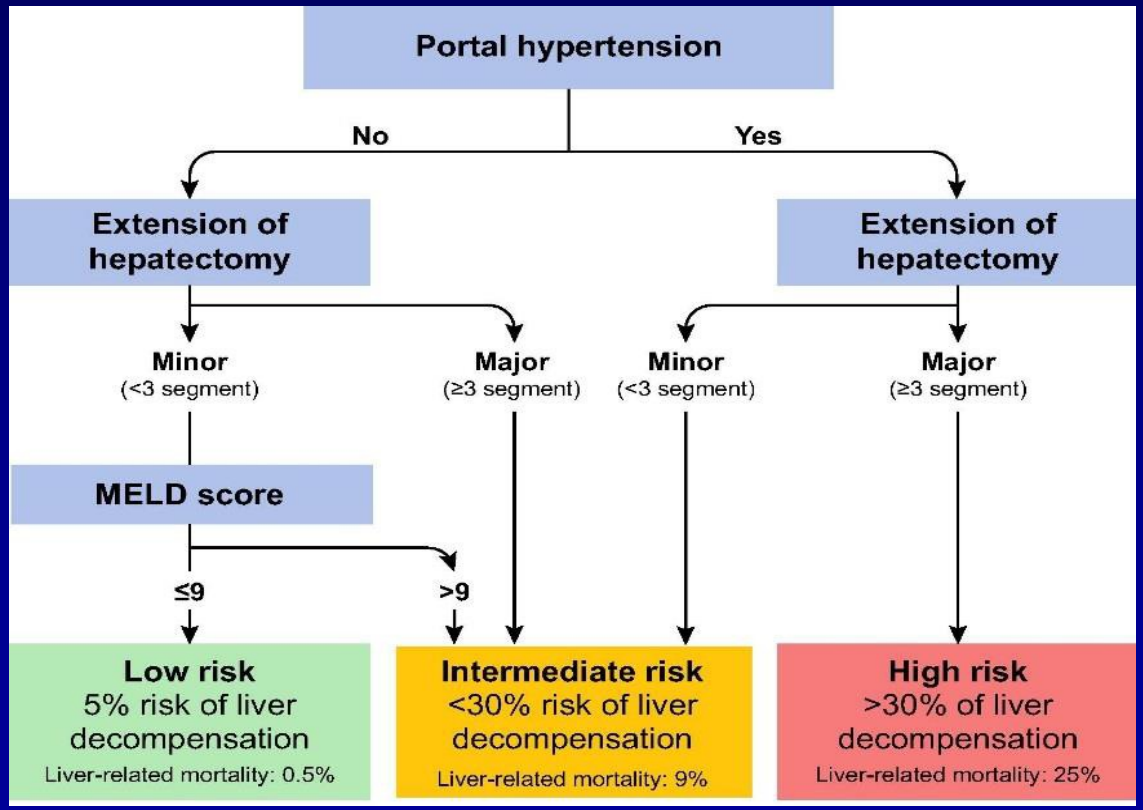
Child's A → **TRANSPLANT**
Child's B → **TRANSPLANT**
Child's C → **TRANSPLANT**

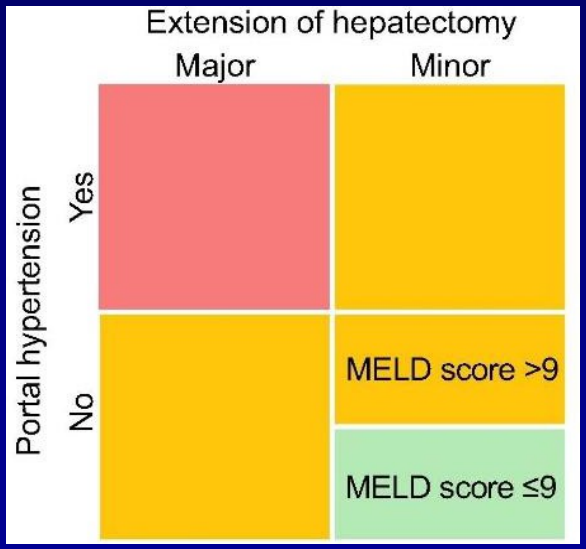
Survival following resection: Impact of portal hypertension



Llovet et al. Hepatology 1999; 30:1434

BCLC Definition of Optimal Surgical Candidate





EASL Clinical Practice Guidelines 2018

HEPATIC RESECTION FOR HCC WITH CIRRHOSIS

"Ideal" candidate

- Good liver function - Child's A
- No portal hypertension (suggested by varices, enlarged spleen, platelets < 100)
- Normal bilirubin
- Single lesion ≤ 5 cm
- Location of tumor in left lobe

TUMOR RECURRENCE POST-RESECTION

Approx 40-50% at 3 yrs and 60-70% at 5 yrs

Predictors of tumor recurrence

- Vascular invasion
- Multi-focal HCC/ satellite tumor nodules
- Tumor size > 5 cm
- Positive resection margins
- Lymph node involvement
- High alpha-fetoprotein

Cha et al JACS 2003

LIVER TRANSPLANTATION FOR HCC
MILAN CRITERIA

1 lesion ≤ 5 cm

2 to 3, none > 3 cm

+

Absence of Macroscopic Vascular Invasion
Absence of Extra-hepatic Spread

Mazzaferro, et al. N Engl J Med 1996;334:693-699

LIVER TRANSPLANTATION FOR HCC
STAGE T2 CRITERIA

1 lesion 2-5 cm

2 to 3, none > 3 cm

Post-LT

5 year survival: >75%

5 year HCC recurrence: 10-15%

Mazzaferro, et al. N Engl J Med 1996;334:693-699

LIVER TRANSPLANT FOR HCC: RECENT CHANGES

- 6-month mandatory waiting period before awarding MELD exception

DELAYED HCC-MELD EXCEPTION SCORE

Delays in HCC-MELD exception	HCC Transplant rates (per 100 person-years)	Non-HCC Transplant rates (per 100 person-years)
0	108.7	30.1
3 months	65.0	32.5
6 months	44.2	33.9
9 months	33.6	34.8

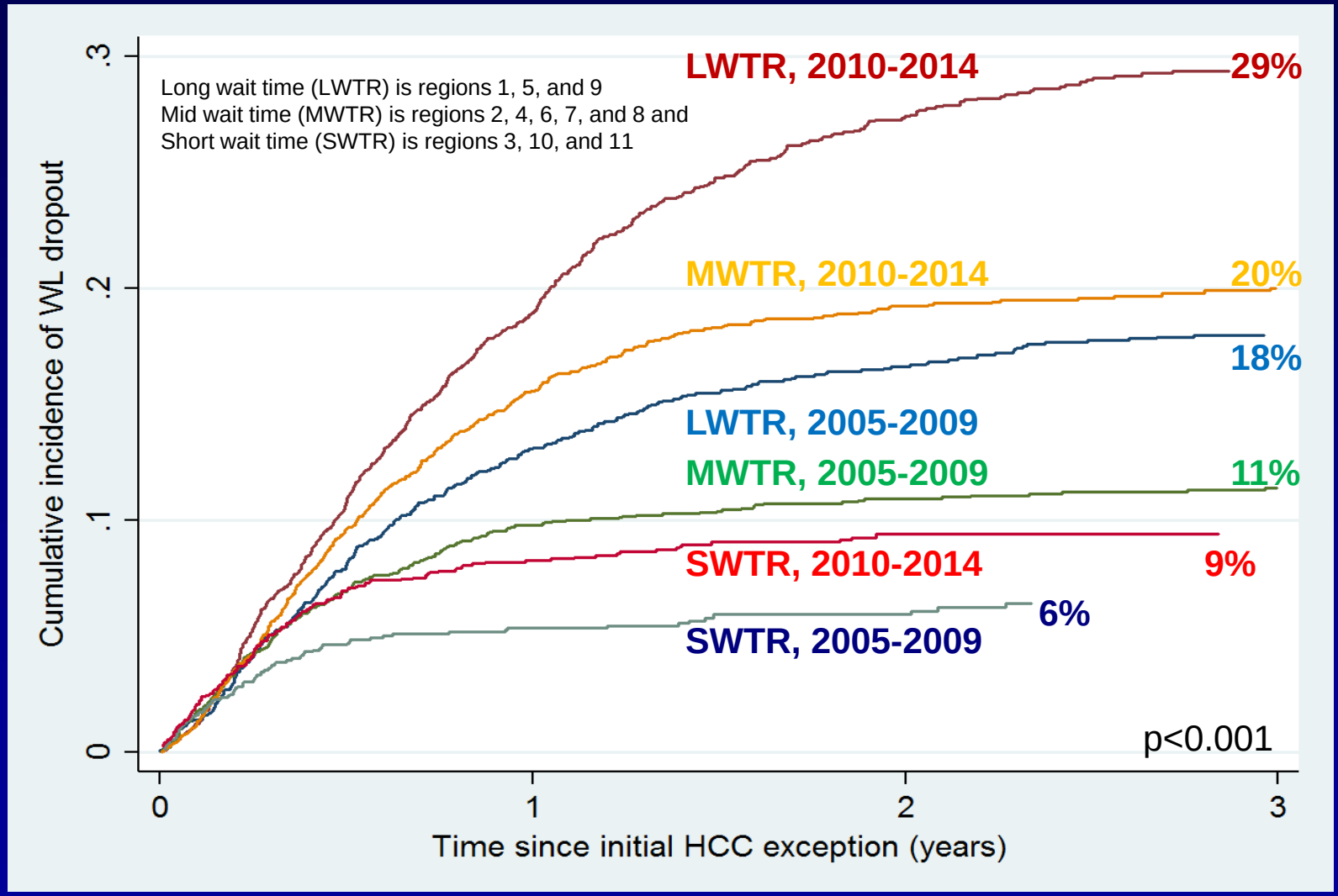
Heimbach J, et al. Hepatology 2015;61:1643-1650

LIVER TRANSPLANT FOR HCC: RECENT CHANGES

- 6-month mandatory waiting period before awarding MELD exception

- Regional variation in access to LT for HCC still exists

PROBABILITY OF WAITLIST DROPOUT BY WAIT TIME REGION AND LISTING PERIOD

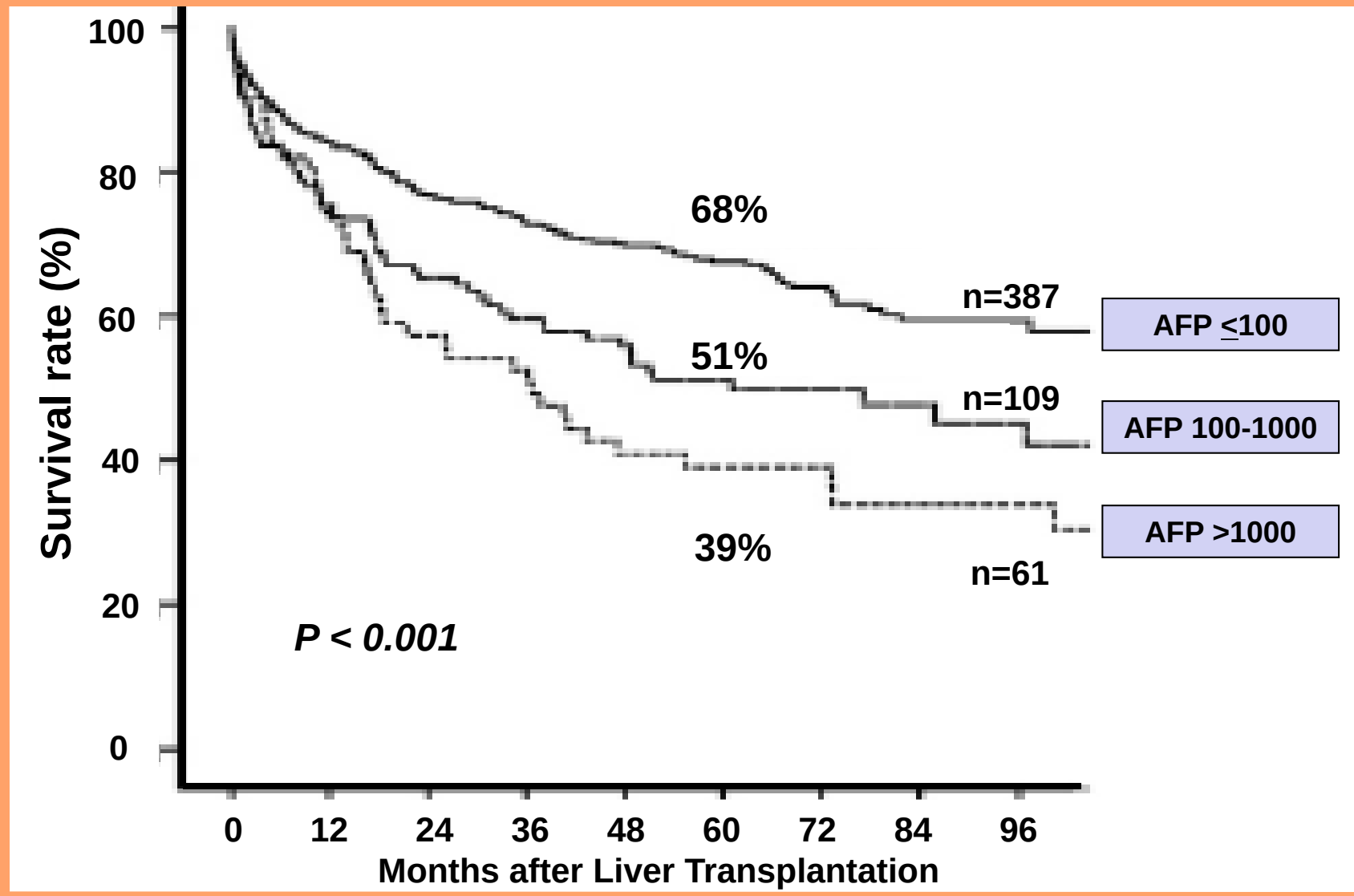


Mehta N et al, Liver Transplantation 2018

LIVER TRANSPLANT FOR HCC: RECENT CHANGES

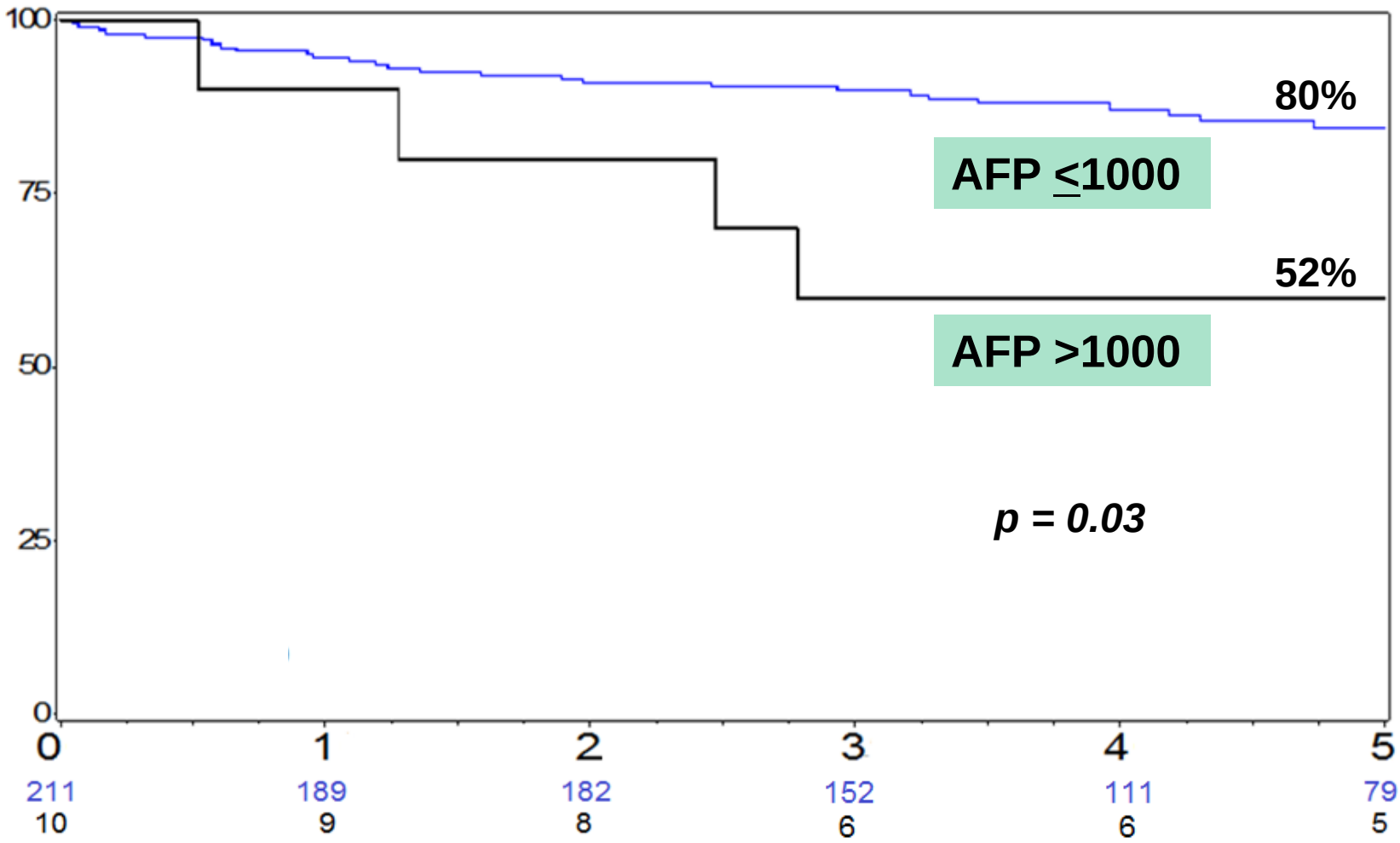
- As of May 2019, HCC MELD ladder system has been replaced by awarding median MELD at transplant (MMAT) for the donor service area (DSA) minus 3 points
  - 6 month waiting period still in effect

AFP and Post-transplant Outcome- France



Duvoux et al. Gastroenterology 2012;143:986-94

AFP and Post-transplant Outcome - UCSF



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Hameed B. et al. Liver Transplantation 2014; 945-951

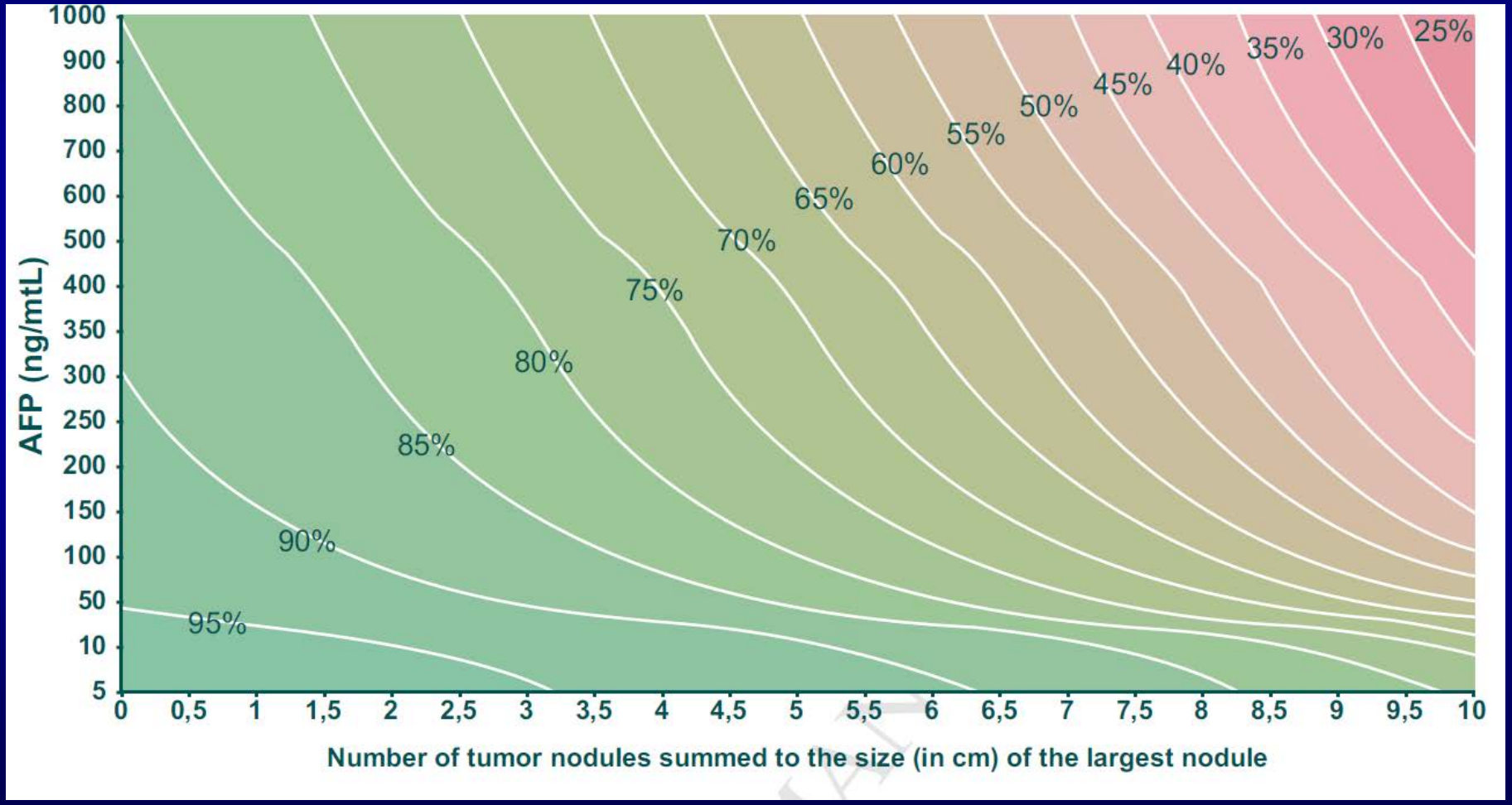
RECENT UNOS POLICY CHANGE

High AFP Threshold

- Candidates with lesions meeting T2 criteria but with an AFP >1000 are not eligible for a standardized MELD exception

- If AFP falls <500 after LRT, the candidate is eligible for a standardized MELD exception

LIVER TRANSPLANTATION FOR HCC
METROTICKET 2.0



Mazzaferro V et al. Gastroenterology 2018;154:128-39

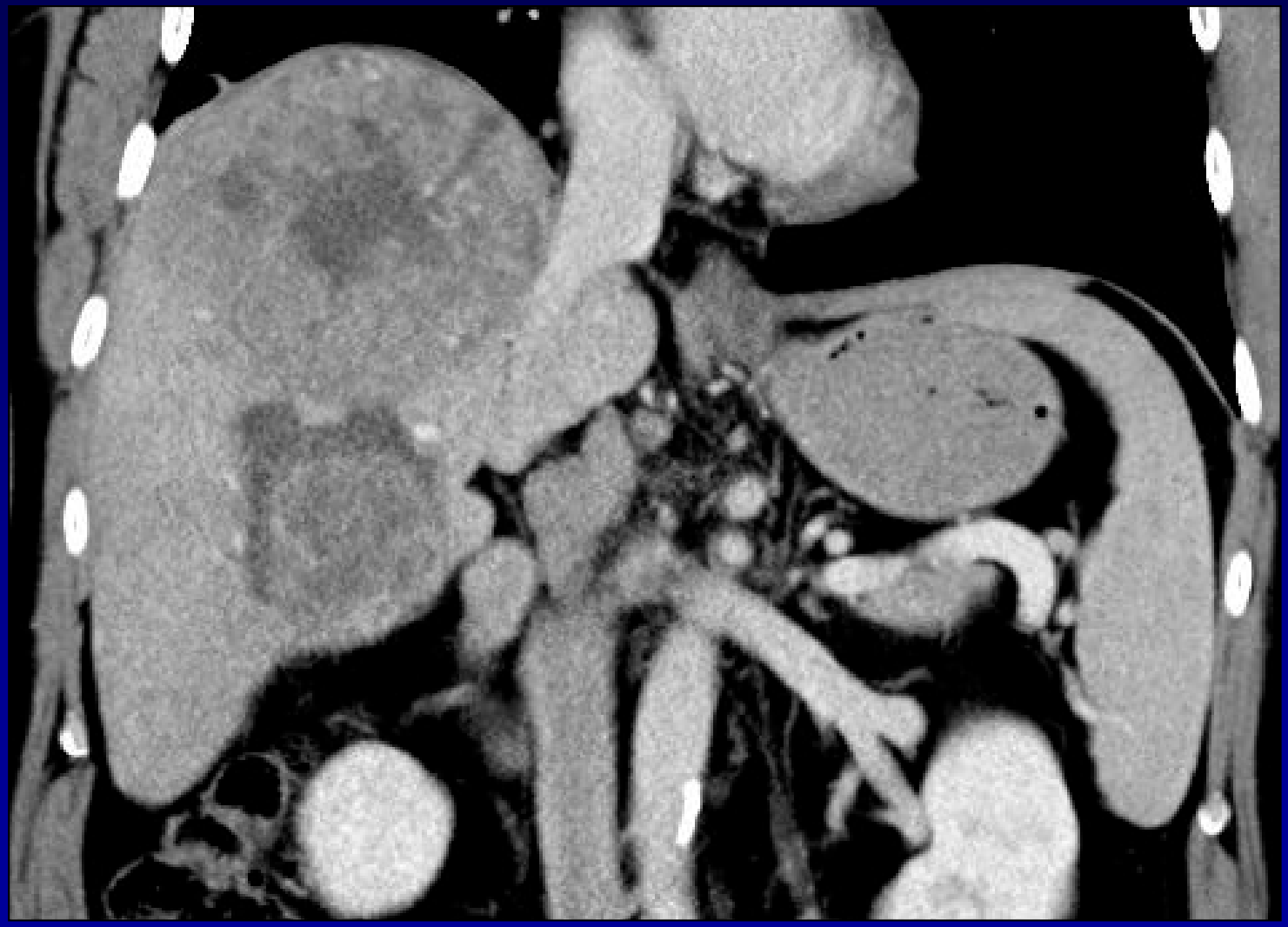
CASE PRESENTATION

56 year-old man with chronic HBV, well suppressed on anti-viral therapy. He received inadequate HCC surveillance and was found to have two LI-RADS 5 tumors in the right lobe measuring 5 cm and 3 cm. Asymptomatic (ECOG 0). No substance abuse. No significant medical history.

Laboratory: HCT 42.4, platelets 84,000, creatinine 0.6, total bilirubin 0.9, albumin 4.2, hepatitis B DNA (-), AFP 49 ng/mL

Hepatocellular Carcinoma

CASE PRESENTATION



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2) Microwave ablation
3) Sorafenib
4) Liver transplant after down-staging to within Milan criteria

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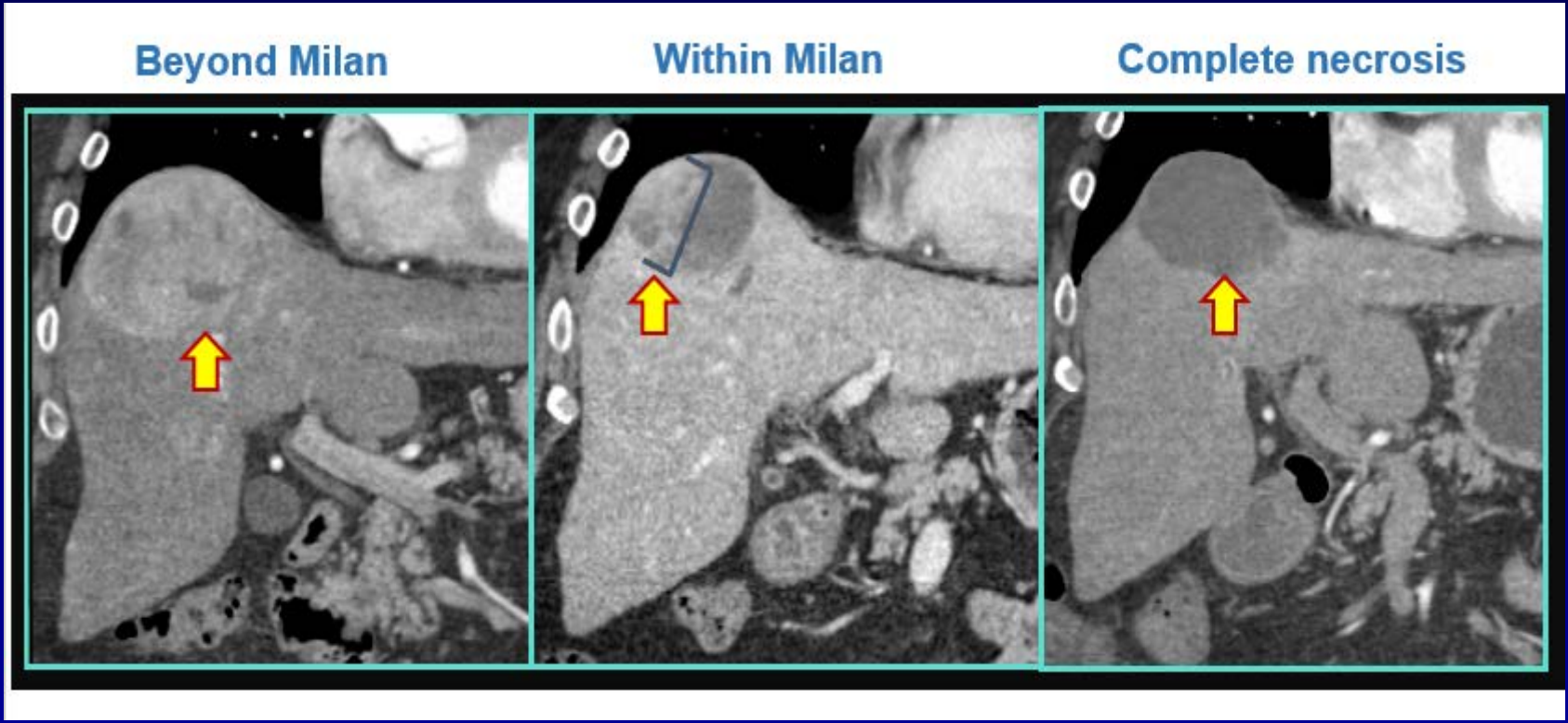
Down-staging of HCC for Transplant

- Definition: Reduction in the size of tumor using local regional therapy to meet acceptable criteria for liver transplant [1]
- Tumor response: Based on radiographic measurement of the size of all viable tumors, not including the area of necrosis from local regional therapy [2]
- A selection tool for tumors with more favorable biology that respond to down-staging treatment and also do well after liver transplant [1]

1. Yao & Fidelman. Hepatology 2016;63:1014-1025
2. EASL Guidelines - Briux J. et al. J Hepatol 2001;35: 421–430

Down-staging of HCC for Transplant



Yao & Fidelman. Hepatology 2016;63:1014-1025

LOCAL REGIONAL THERAPIES FOR HCC

CHEMOEMBOLIZATION (TACE)

Conventional versus Drug-eluting beads

ABLATIONS

CHEMICAL

Percutaneous ethanol injection (PEI)

THERMAL

Radiofrequency ablation (RFA)

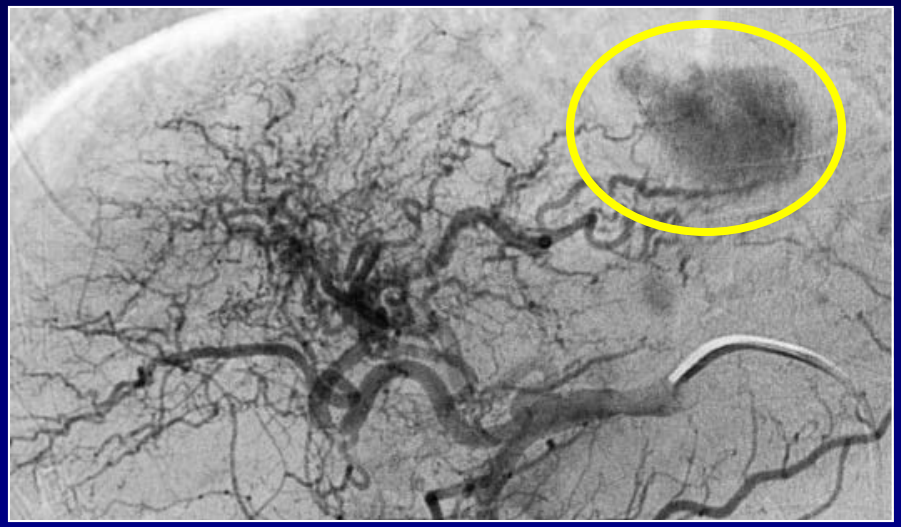
(Laparoscopic, percutaneous or open)

Microwave/ Cryo- ablation

RADIOEMBOLIZATION (YITTRIUM - 90)

STEREOTACTIC BODY RADIATION (SBRT)

TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION

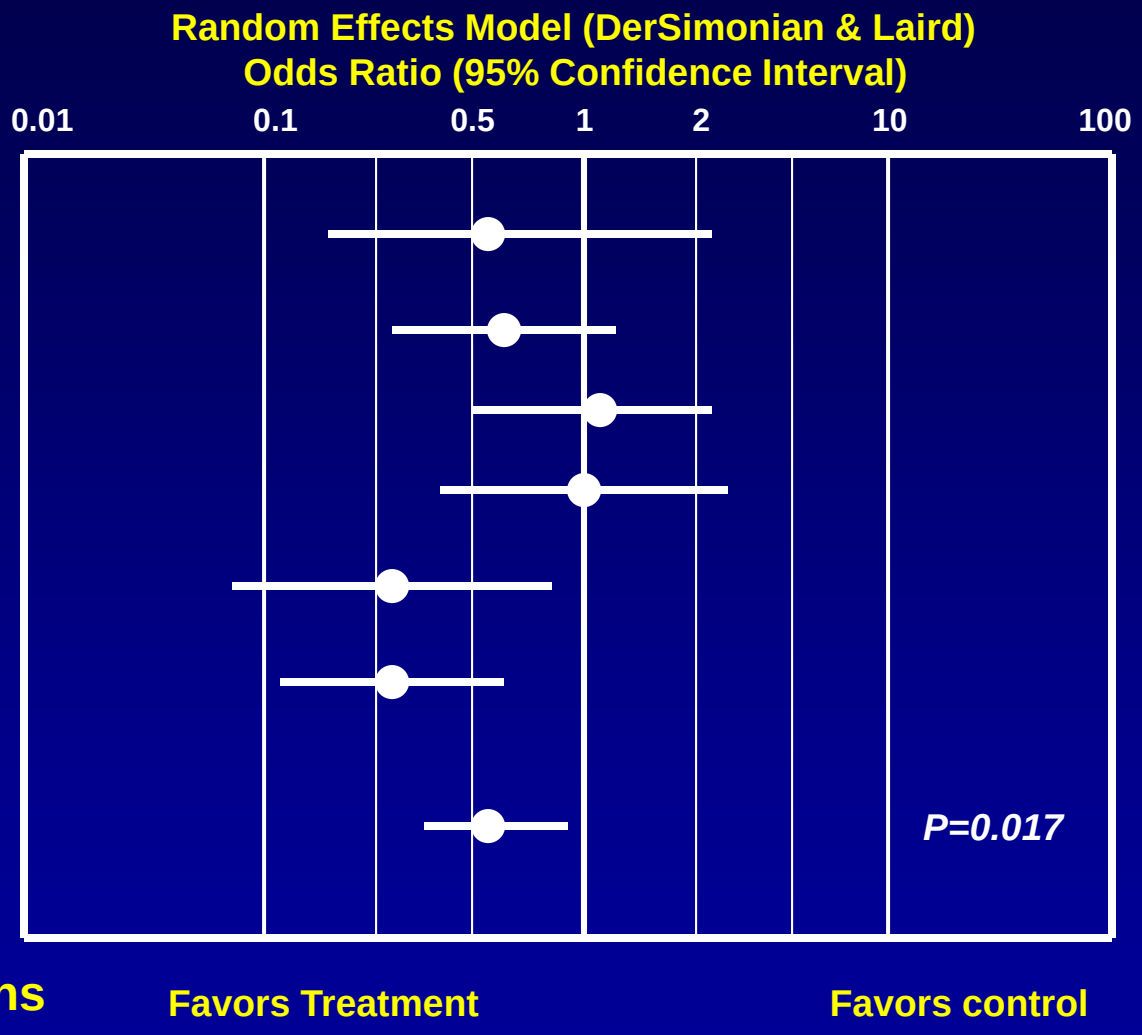


- Selective embolization of the hepatic arterial supply to tumor via the common femoral artery.
- Cytotoxic agent (Cis-platinum, Doxorubicin, Mitomycin-C, 5-FU) mixed with lipiodol or gelfoam particles.
- Complications include fever, abdominal pain, infection (abscess), hepatic arterial injury, hepatic decompensation

Meta-analysis of RCT for TACE/TAE vs. Placebo/ suboptimal Therapy

Author, Journal, yr	Patient
Lin, Gastro 1988	63
GETCH, NEJM 1995	96
Bruix, Hepatology 1998	80
Pelletier, J Hepatol 1998	73
Lo, Hepatology 2002	79
Llovet, Lancet 2002	112
OVERALL	**503**

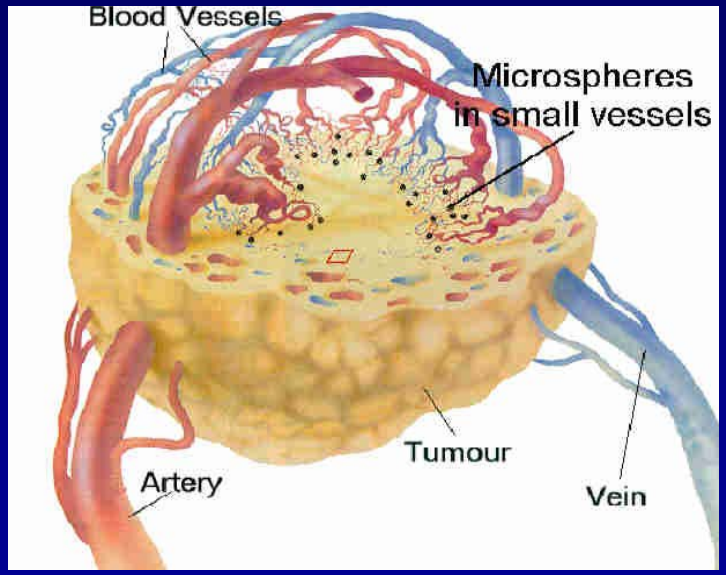
Heterogeneity p=0.14
Median Survival 20 months



Llovet JM, Bruix J. Hepatology 2003;37:429-442

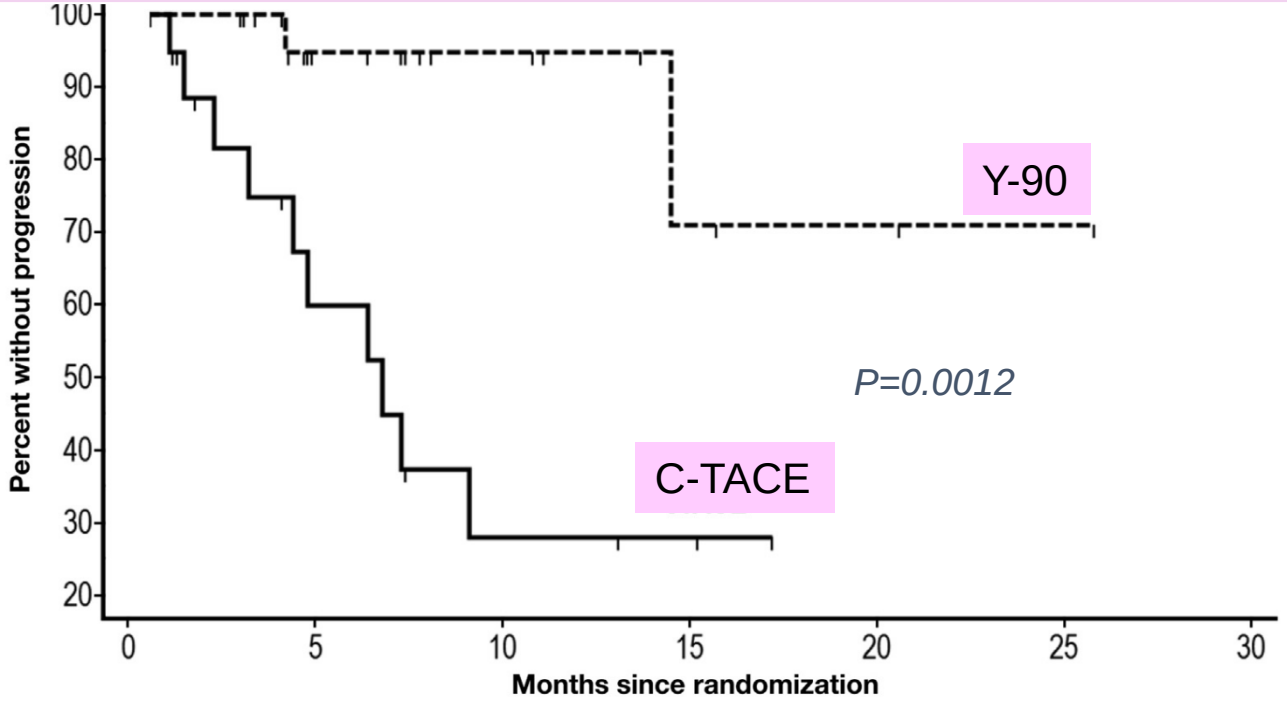
Y-90 RADIOEMBOLIZATION

- TheraSphere (glass microspheres)
- SIR-Spheres (resin microspheres)
- Radiographic response up to 90%
- Survival benefit unknown
- Risks of radiation damage
- Advanced tumor stage and preserved liver function (bilirubin < 2mg/dl)



SIRT (Y-90) versus TACE (PREMIERE)

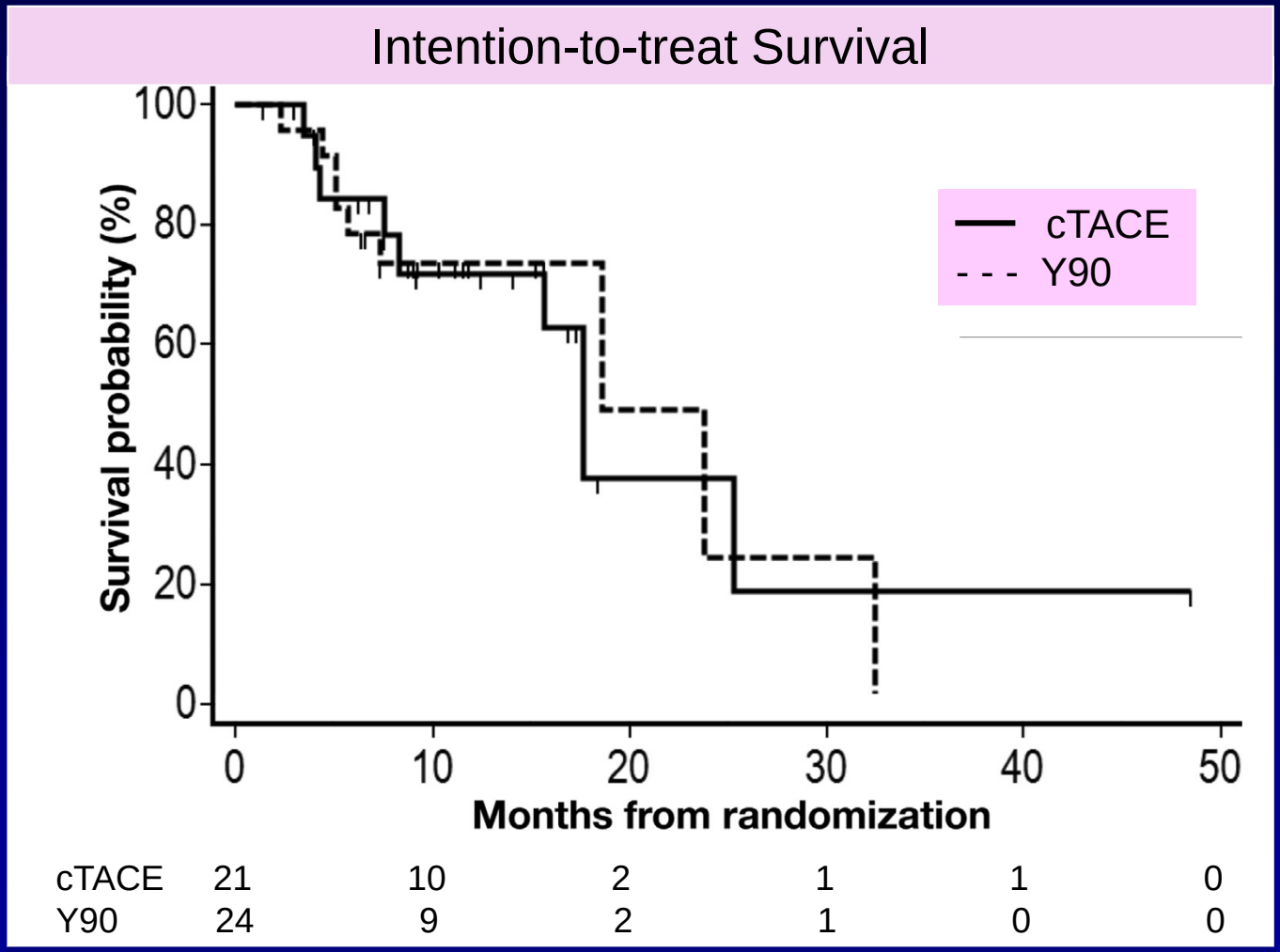
Time to Progression (TTP)



Number at risk						
Group: cTACE						
21	8	3	2	0	0	0
Group: Y90						
24	12	7	3	2	1	0

Salem R, et al. Gastroenterology 2016;151:1155-1163

SIRT (Y-90) versus TACE (PREMIERE)



Salem R, et al. Gastroenterology 2016;151:1155-1163

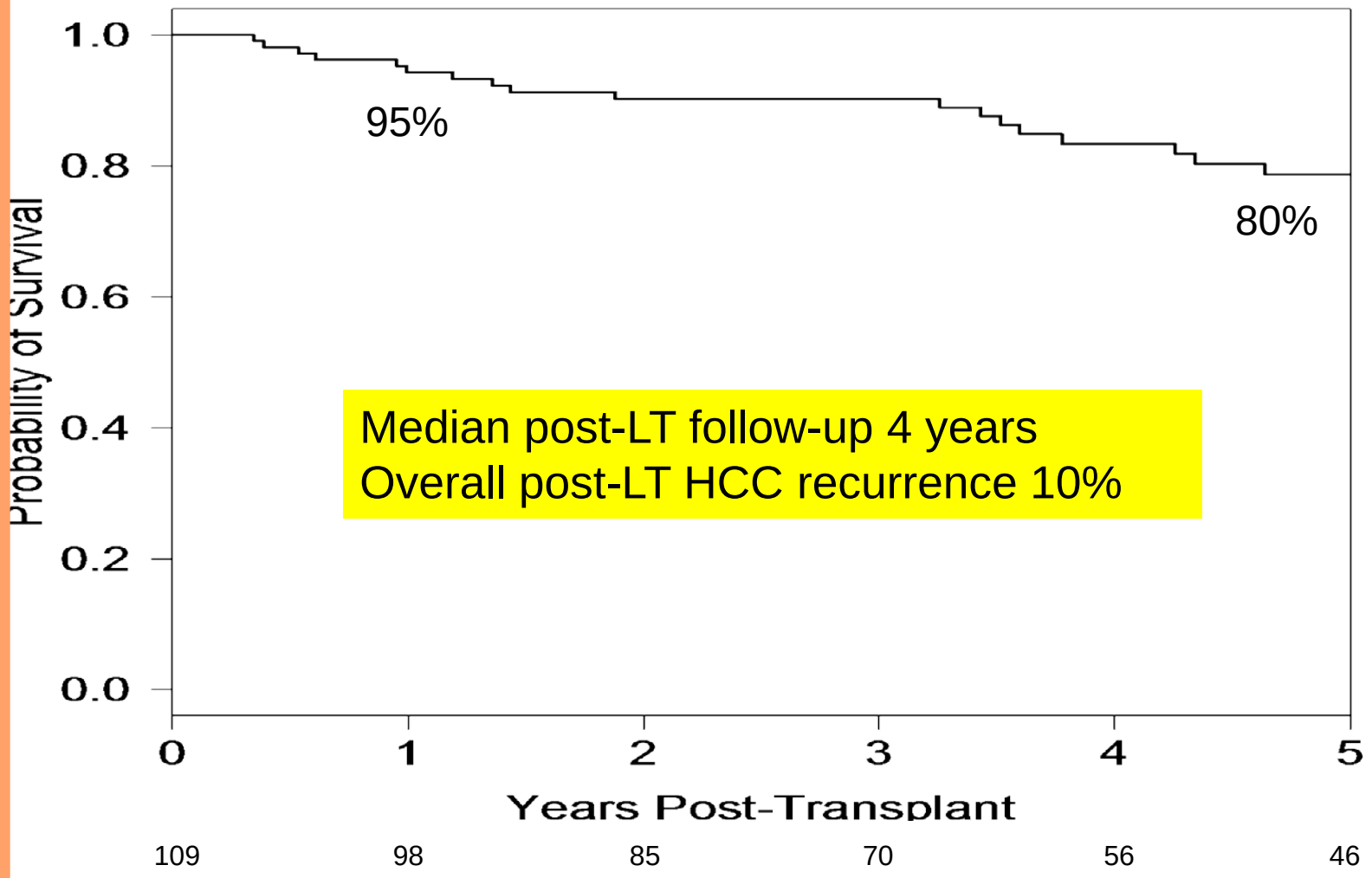
UCSF/REGION 5 DOWN-STAGING PROTOCOL

- Inclusion criteria
  - 1 lesion > 5 cm and ≤ 8 cm
  - 2 or 3 lesions ≤ 5 cm w/ total tumor diameter ≤ 8 cm
  - 4 or 5 lesions ≤ 3 cm w/ total tumor diameter ≤ 8 cm
  - No vascular invasion on imaging

- Minimum 3 month observation period after successful down-staging into Milan before LT can be undertaken

Yao et al. Hepatology 2008;48:819-827

Region 5 D/S Multi-center Study: Post-LT Survival



Mehta N et al. Clin Gastroenterol Hepatol 2018;16:955-964

UNOS DOWN-STAGING PROTOCOL

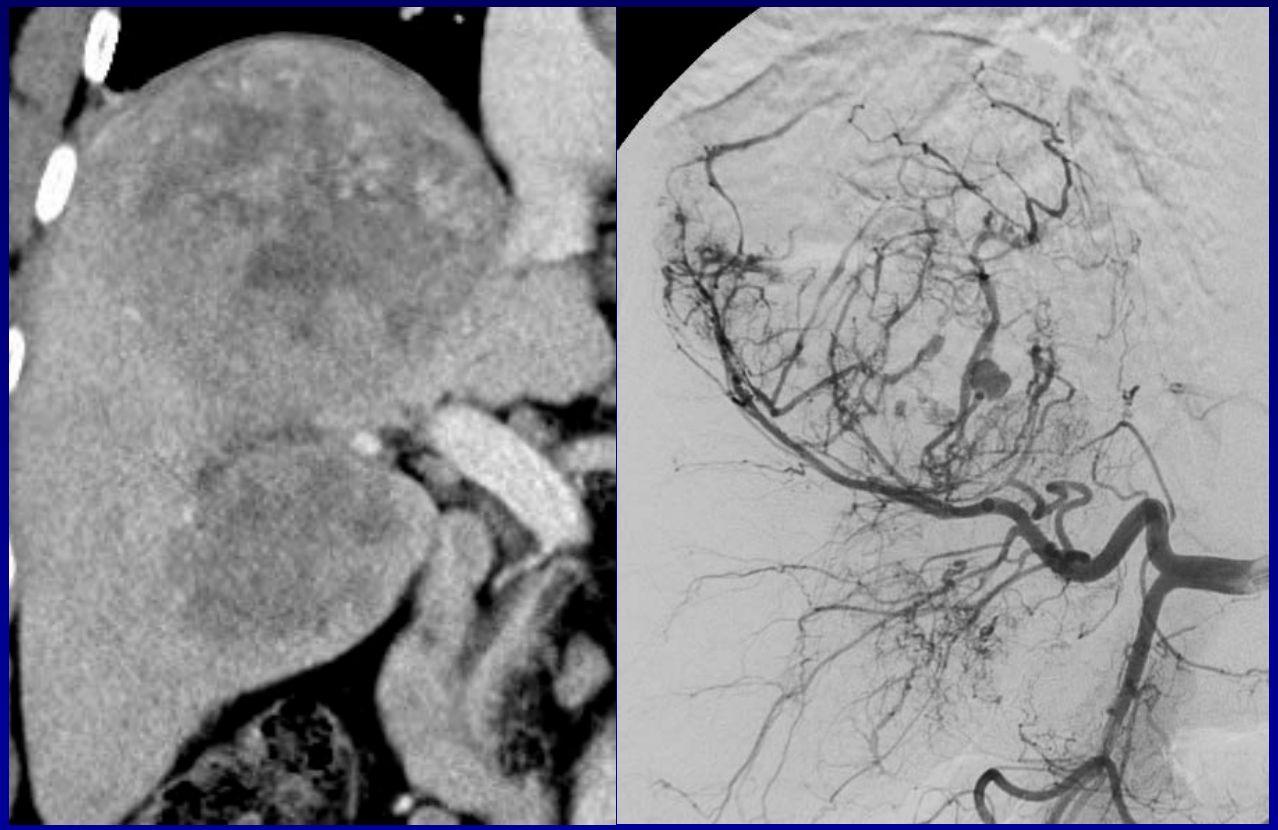
- Inclusion criteria
  - 1 lesion > 5 cm and ≤ 8 cm
  - 2 or 3 lesions ≤ 5 cm w/ total tumor diameter ≤ 8 cm
  - 4 or 5 lesions ≤ 3 cm w/ total tumor diameter ≤ 8 cm
  - No vascular invasion on imaging

- This protocol has recently been adopted as national policy for automatic priority listing in patients who have been successfully down-staged to within Milan criteria

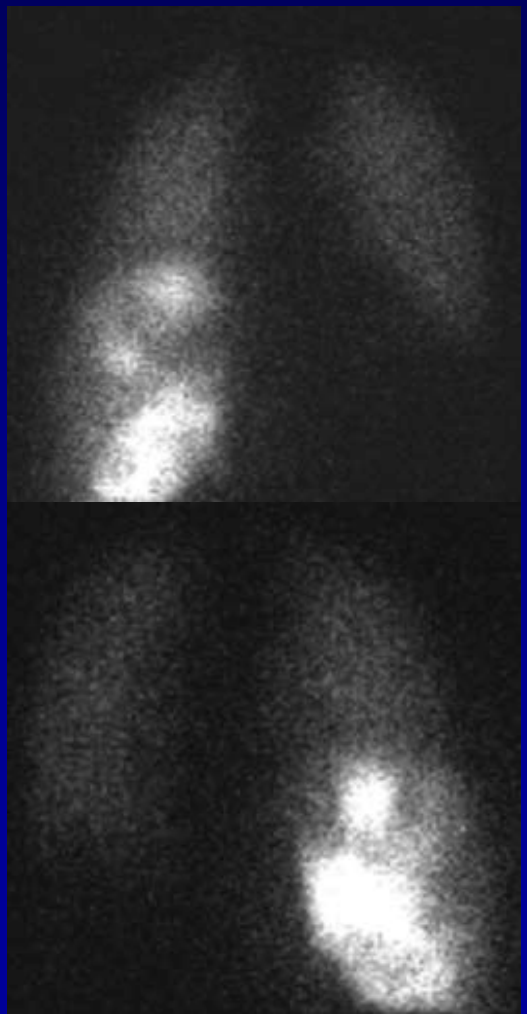
Yao et al. Hepatology 2008;48:819-827

CASE PRESENTATION

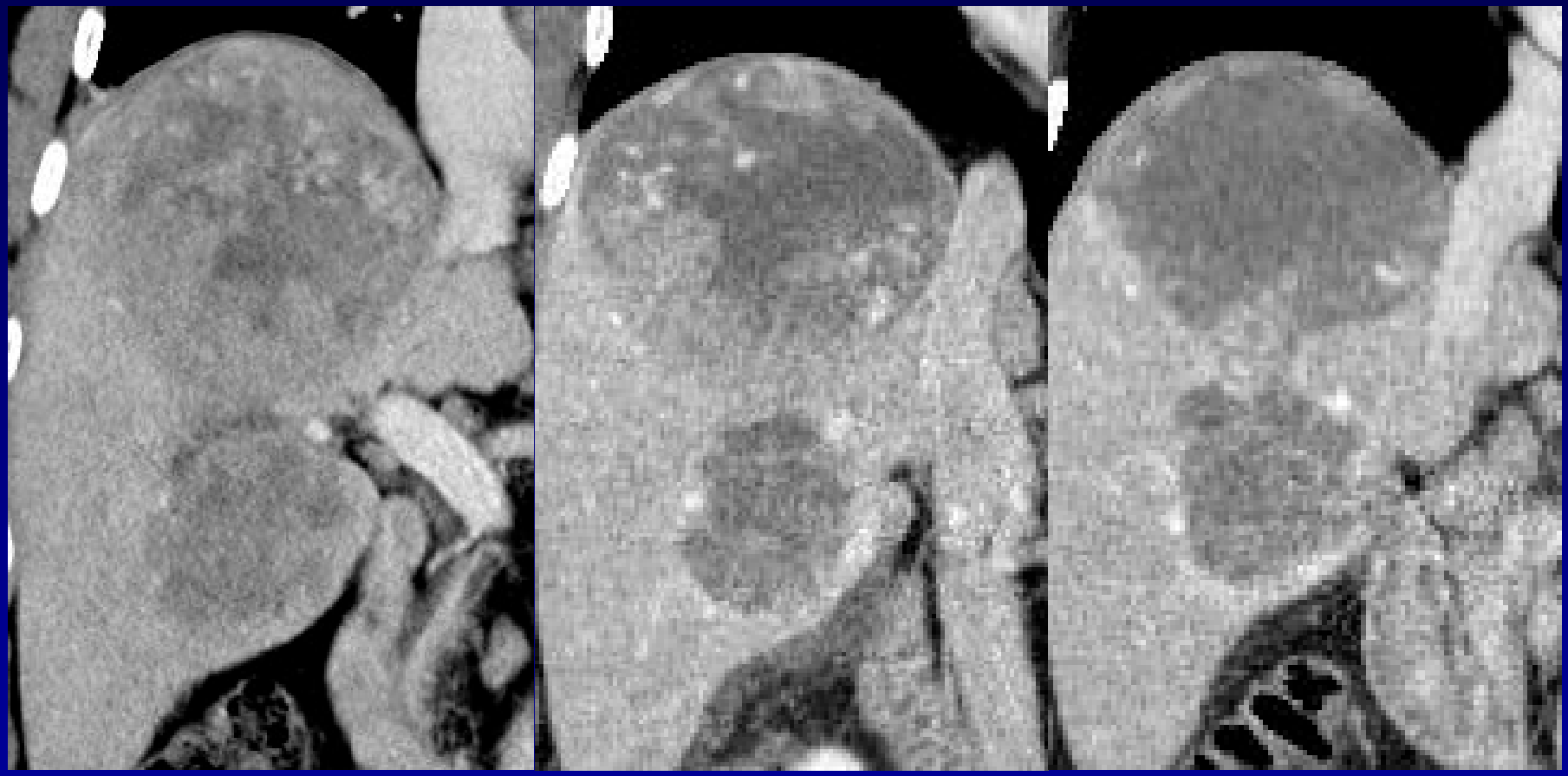
Radioembolization with TheraSphere/Y-90



Tc-MAA



CASE PRESENTATION



Pre-Y90

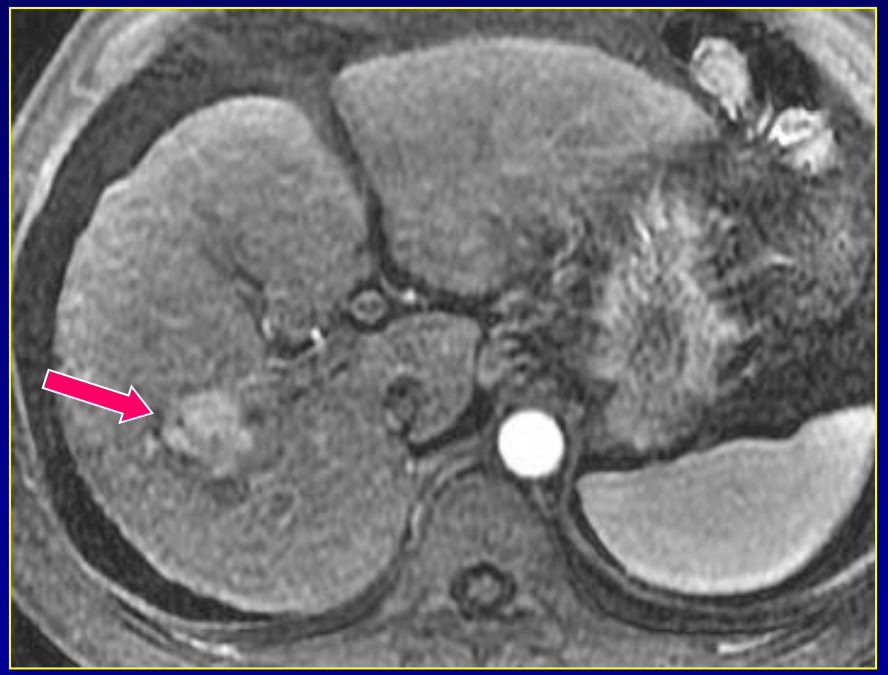
1 mo p Y90#1

1 mo p Y90#2
4 mo p Y90#1

MICROWAVE/RADIOFREQUENCY ABLATION

Choice of treatment based on location and size

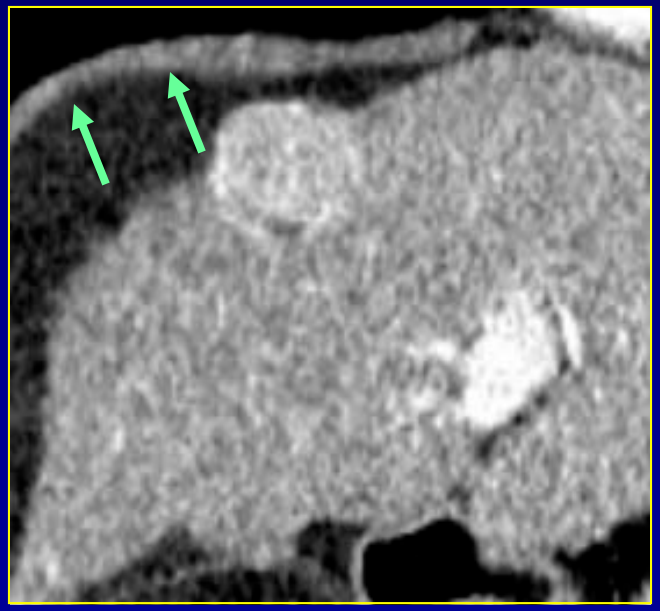
Ideal location for Percutaneous RFA



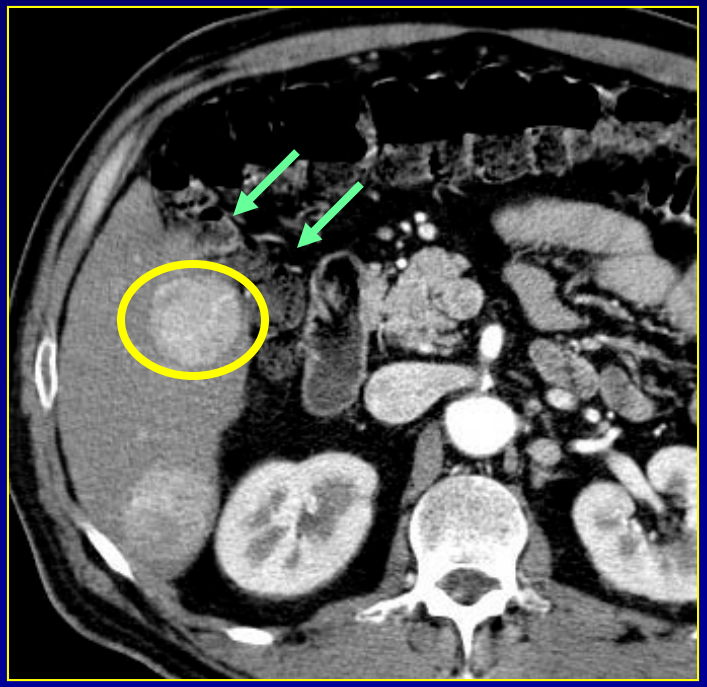
MICROWAVE/RADIOFREQUENCY ABLATION

Limitations of percutaneous RFA
– Tumor location

Adjacent to diaphram

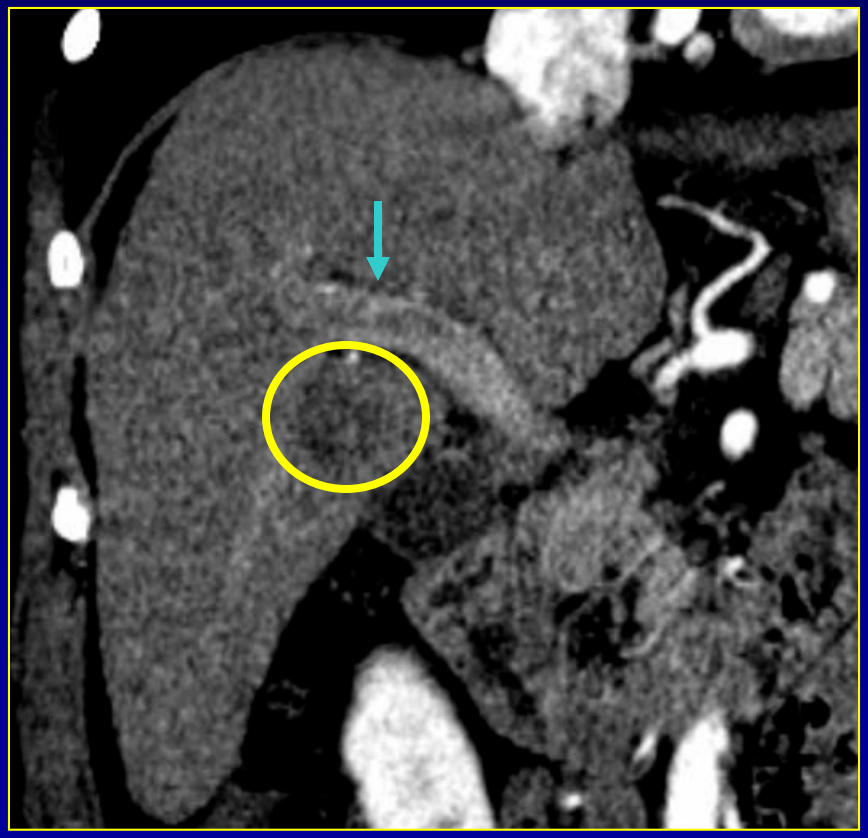


Adjacent to bowel



MICROWAVE/RADIOFREQUENCY ABLATION

Limitations of percutaneous RFA – Tumor location
Adjacent to large vessel (heat-sink)



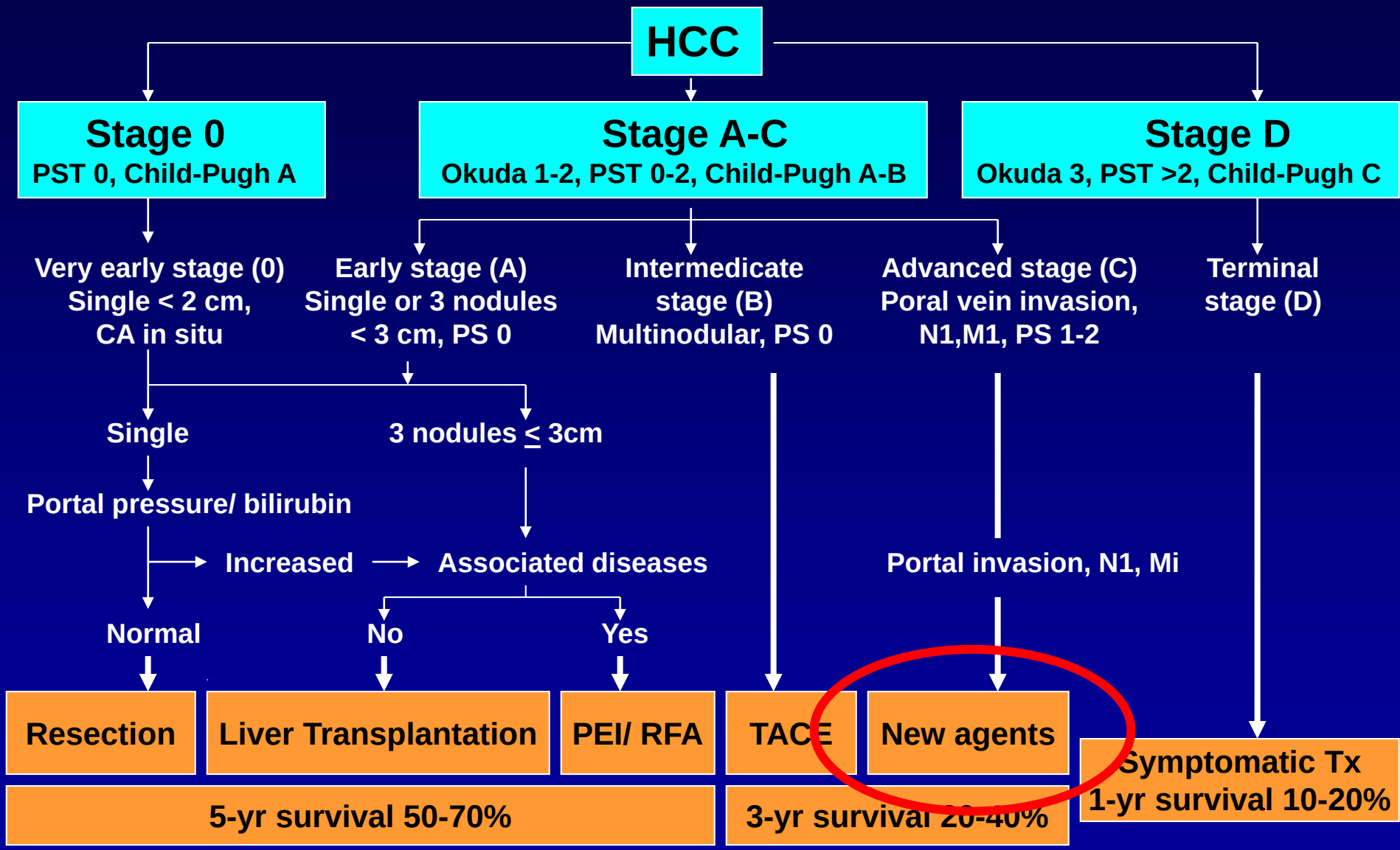
MICROWAVE/RADIOFREQUENCY ABLATION
IMPACT OF TUMOR SIZE

<= 3 cm versus > 3 cm

- Treatment response rate 70-95% for lesions ≤ 3 cm versus around 50% for lesions > 3 cm
- In lesions > 3 cm, overall 5-year survival 30-35%, 5-year recurrence rate up to 80%.

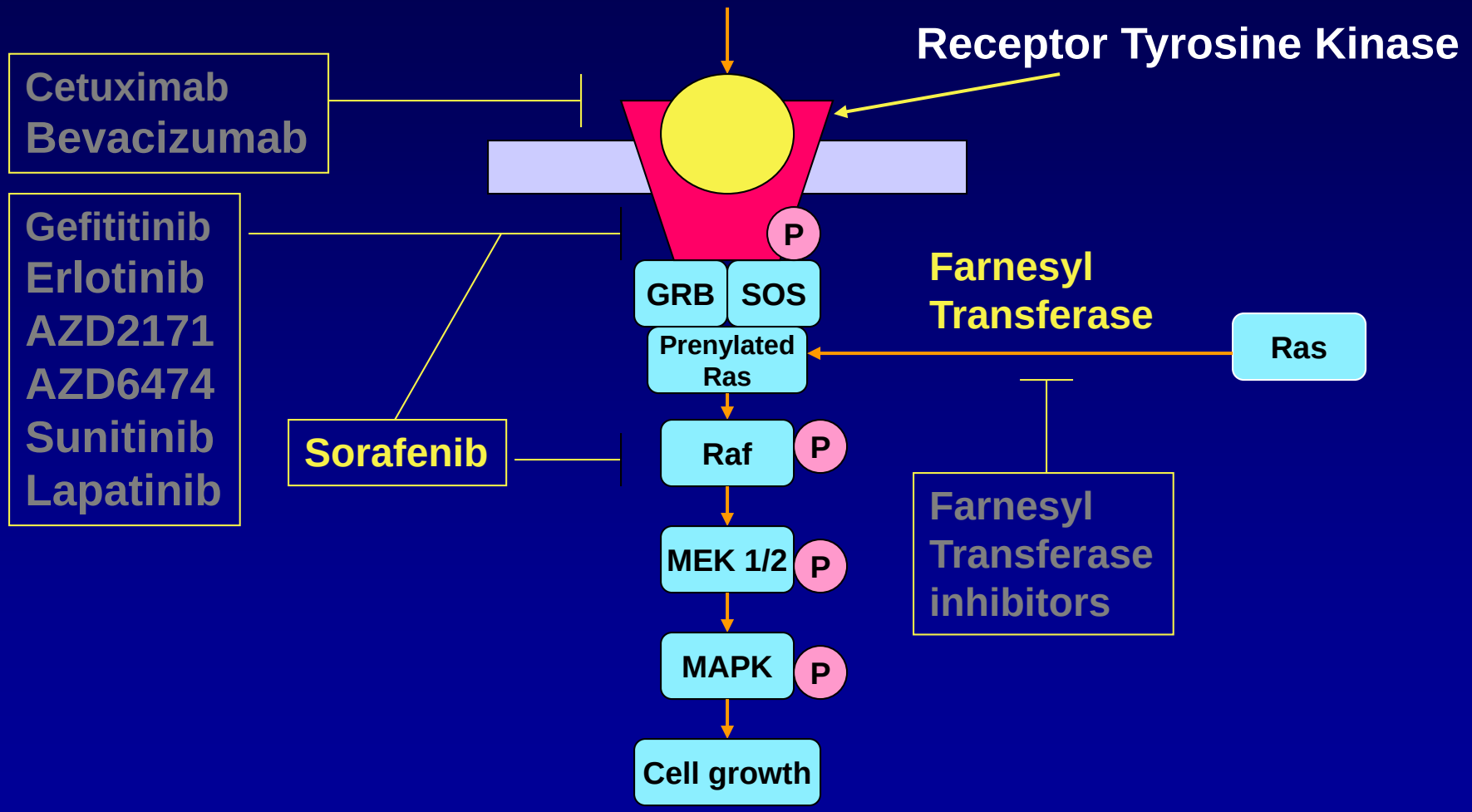
Sala M, et al. Hepatology 2004;40:1352-60
Lencioni R, et al. Radiology 2005;234:961-7
N'Kontchou G, et al. Hepatology 2009;50:1465-83
Santambrogio R, et al. Ann Surg Oncol 2009;16:3289-98

BCLC STAGING CLASSIFICATION



Adapted from Llovet JM et al. Lancet 2003;362:1907-17

TARGETED THERAPY FOR HCC
The Dawn of a New Era?



TARGETED THERAPY FOR HCC
SORAFENIB

- The Sorafenib HCC Assessment Randomized Controlled Protocol (SHARP) trial - 602 patients with advanced HCC (1/2 with vascular invasion or metastases) and Child's A cirrhosis randomized to oral sorafenib 400 mg bid versus placebo, showing a modest but significant survival benefit with sorafenib
  - Median survival 3 months longer (10.7 vs 7.9 mo)
- The safety of sorafenib has not yet been established in patients with Child's C cirrhosis and should be used only in the context of clinical trials (GIDEON)

Llovet JM et al. NEJM 2008; 359:378-390

TARGETED THERAPY FOR HCC
LENVATINIB

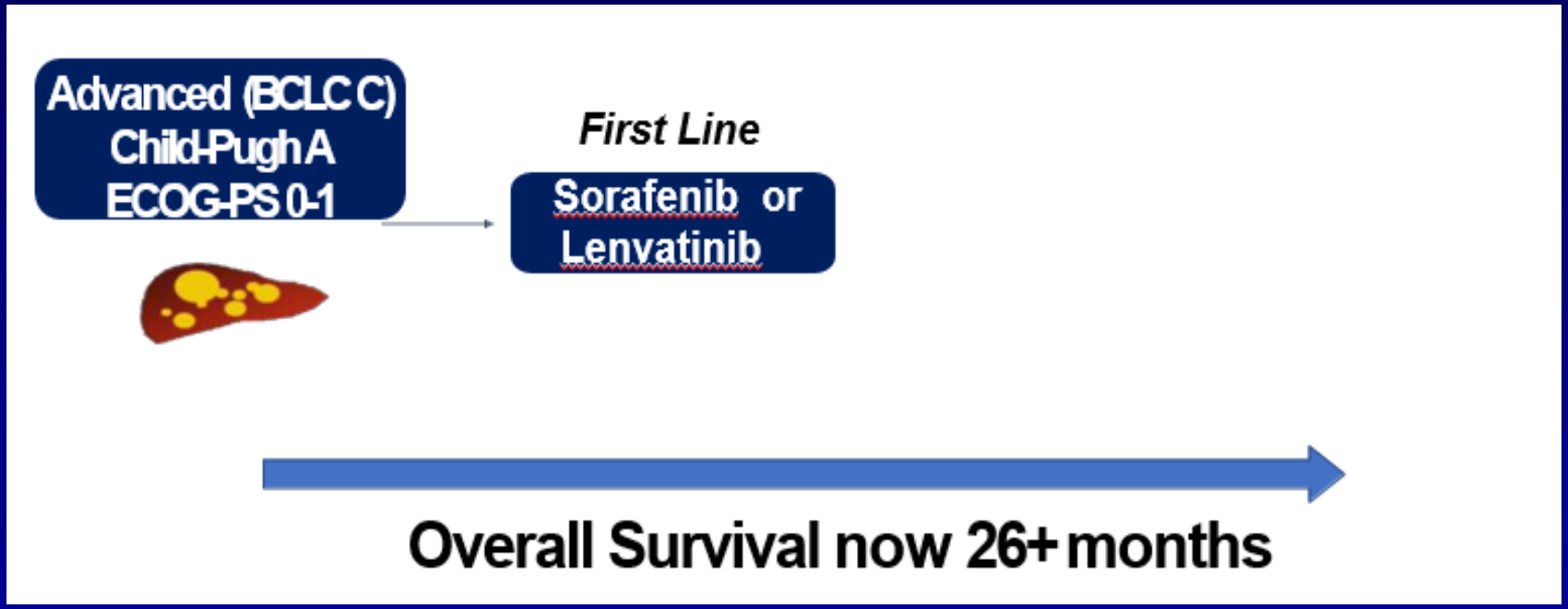
- Open label phase-3 study REFLECT compared 1st line lenvatinib vs sorafenib

- Lenvatinib was non-inferior to sorafenib
  - Median OS 13.6 vs 12.3 mo (HR 0.92)

- Lenvatinib had improvement in secondary endpts
  - PFS, TTP, and ORR all better w/ lenvatinib
- Discontinuation rate due to AEs fairly similar (9% vs 7%)
- In 2018, lenvatinib approved in US, Europe, and Japan

Kudo M et al. Lancet 2018;391:1163-73

TARGETED THERAPY FOR HCC



2nd LINE THERAPY FOR HCC

Tyrosine kinase inhibitors

Regorafenib[1]

- Phase-3 RESORCE study in patients who tolerated sorafenib ≥ 400 mg daily for 20 of prior 28 days
- OS: 10.6 months vs 7.8 months with placebo (HR 0.63)

Cabozantinib[2]

- Phase-3 CELESTIAL study
- OS: 10.2 months vs 8.0 months with placebo (HR 0.76)

Immunotherapy

Nivolumab[3]

- Phase-2 CHECKMATE-040 study
- ORR (mRECIST): 19%
- OS: 15.6 months

Pembrolizumab[4]

- Phase-2 KEYNOTE-224 study
- ORR (mRECIST): 15%
- OS: 12.9 months

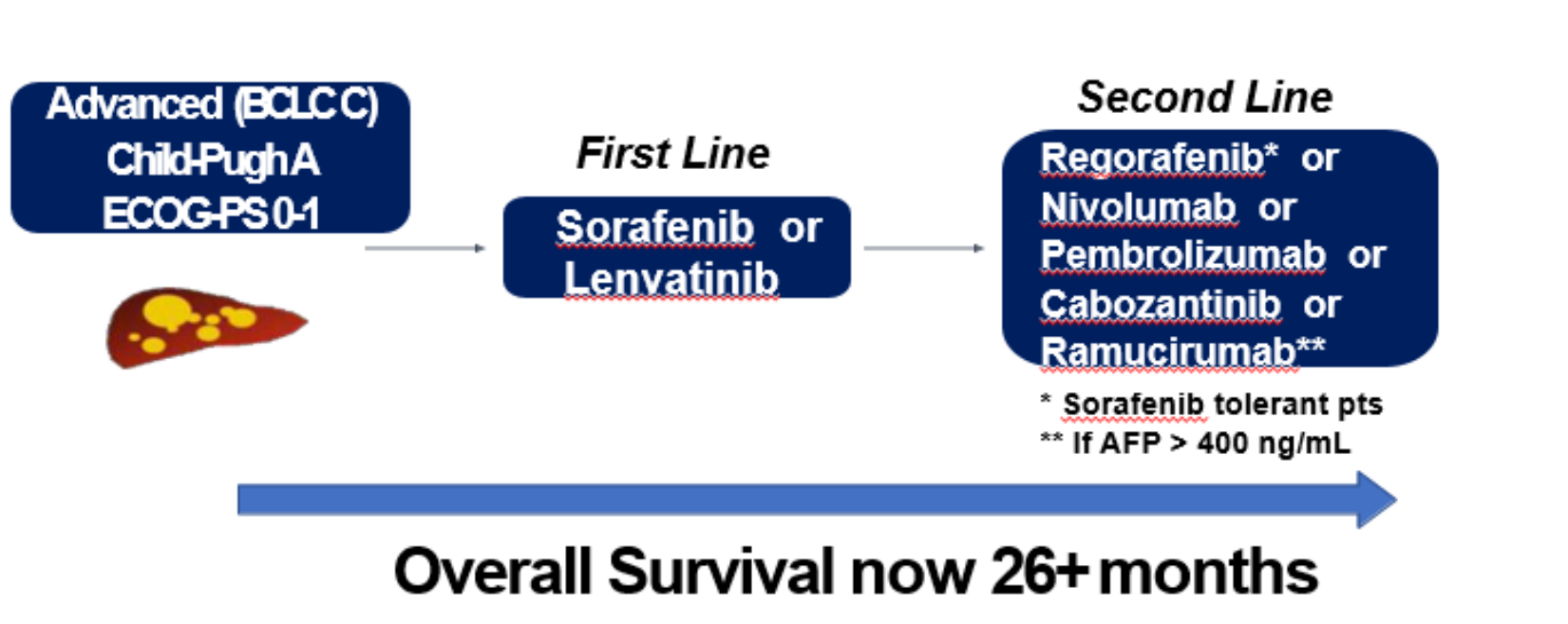
Anti-VEGF

Ramucirumab[5]

- Phase-3 REACH-2 study in patients with AFP > 400
- OS: 8.5 months vs 7.3 months with placebo (HR 0.71)

1. Bruix J, et al. *Lancet* 2017;389:56-66. 2. Abou-Alfa GK, et al. *N Engl J Med* 2018;379:54-63. 3. El-Khoueiry AB, et al. *Lancet* 2017;389:2492-2502. 4. Zhu AX, et al. *Lancet Oncol* 2018;9:940-952. 5. Zhu AX, et al. *J Clin Oncol* 2018;36:Suppl:4003

TARGETED THERAPY FOR HCC



Osher Mini Medical School – 11/13/2019

- Questions?
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