

Management of Early/Intermediate Stage Hepatocellular Carcinoma (HCC) Including Liver Transplantation

Neil Mehta, MD
Associate Clinical Professor of Medicine
UCSF Division of GI/Hepatology



DISCLOSURES

- I have no relevant commercial interests or relationships to report

HCC AND LT: OVERVIEW

- HCC diagnosis and staging
- Selection criteria for liver transplant
- Local-regional therapy (LRT)
- Down-staging and “all-comers”
- RETREAT + post-LT mgmt (if time permits)

CASE PRESENTATION

55 year-old man with alcohol-associated 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 3.5 cm lesion in the right lobe along with mild ascites. Examination showed no spider nevi. Spleen tip palpable.

Laboratory evaluation showed bilirubin 1.7, ALT 28, AST 42, 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. Should we biopsy the lesion and why?

LIVER IMAGING REPORTING AND DATA SYSTEM (LI-RADS)

MAJOR DIAGNOSTIC CRITERIA

- Arterial phase hyper-enhancement
- Delayed phase “washout”
- Pseudo-capsule
- Interval growth $\geq 50\%$ 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”

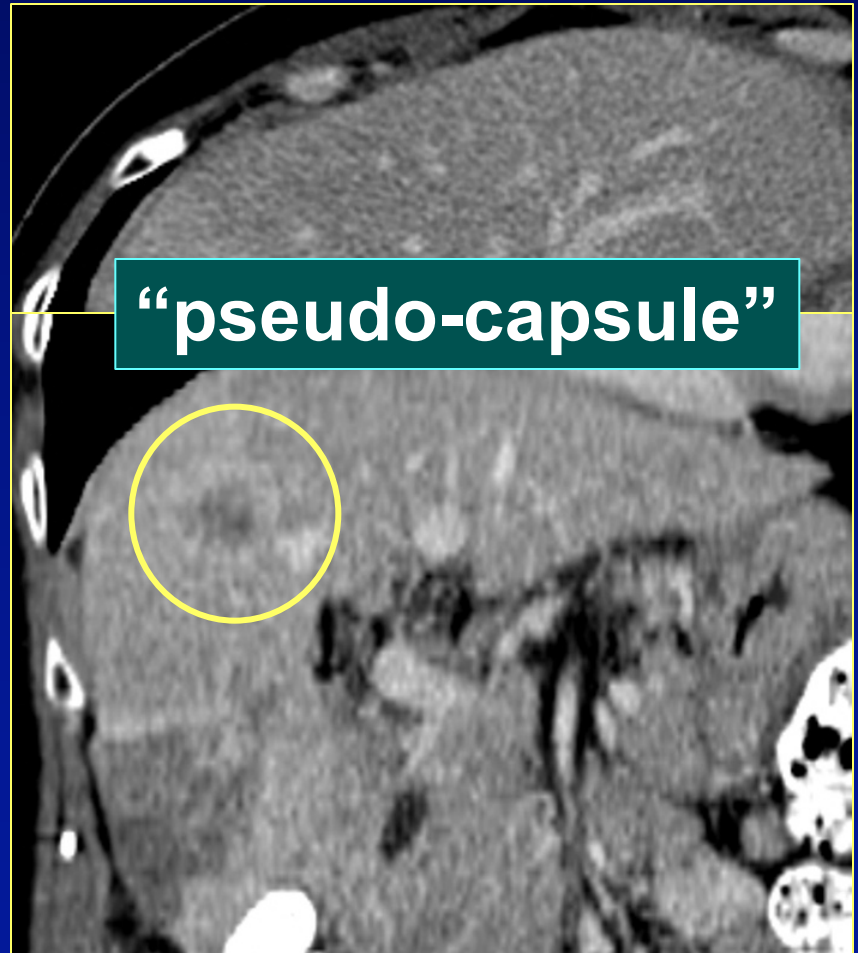
HCC – RADIOLOGIC DIAGNOSIS

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)

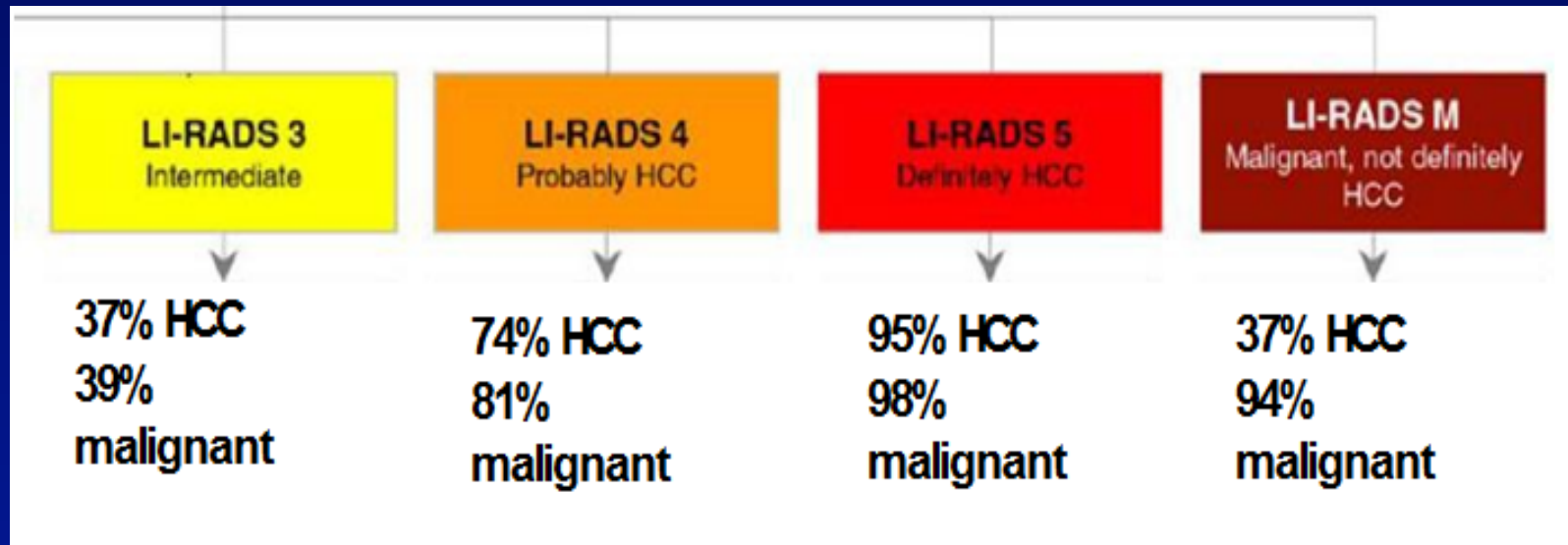
LIVER MASS

Diagnostic Criteria

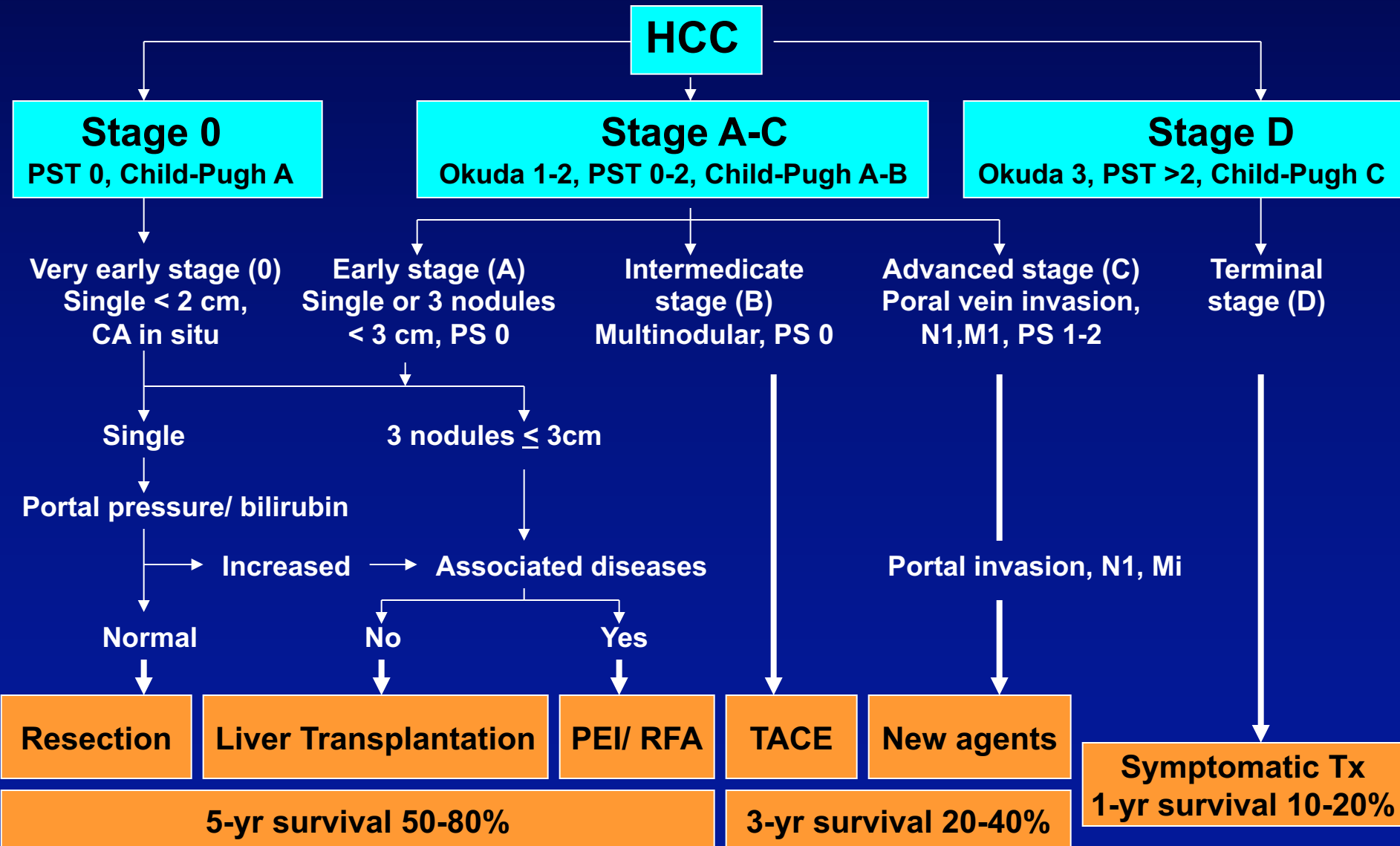


		Arterial phase hypo- or Iso-enhancement		Arterial phase hyper-enhancement		
		< 2 cm	≥ 2 cm	< 1 cm	1-1.9 cm	≥ 2 cm
“Washout” “Capsule” Threshold growth	None	LIRAD 3	LIRAD 3	LIRAD 3	LIRAD 3	LIRAD 4
	One	LIRAD 3	LIRAD 4	LIRAD 4	LIRAD 4	LIRAD 5
	≥ Two	LIRAD 4	LIRAD 4	LIRAD 4	LIRAD 5	LIRAD 5

LI-RADS ACCURACY



BCLC STAGING CLASSIFICATION



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

CASE PRESENTATION

55 year-old man with alcoholic cirrhosis, found on screening u/s to have a 3 cm lesion in the right lobe. Quad-phase CT abdomen showed a **3.5 cm arterial enhancing lesion in the right lobe with “washout”** along with mild ascites. Examination showed no spider nevi. Spleen tip palpable. No alcohol in 3 years

Dx: **LI-RADS 5** HCC per Tumor Board review

Laboratory evaluation showed bilirubin 1.7, ALT 28, AST 42, 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)

CASE PRESENTATION

55 year-old man with alcoholic cirrhosis, found on screening u/s to have a 3 cm lesion in the right lobe. Quad-phase CT abdomen showed a 3.5 cm arterial enhancing lesion in the right lobe with “washout” along with **mild ascites**. Examination showed no spider nevi. **Spleen tip palpable**. No alcohol in 3 years

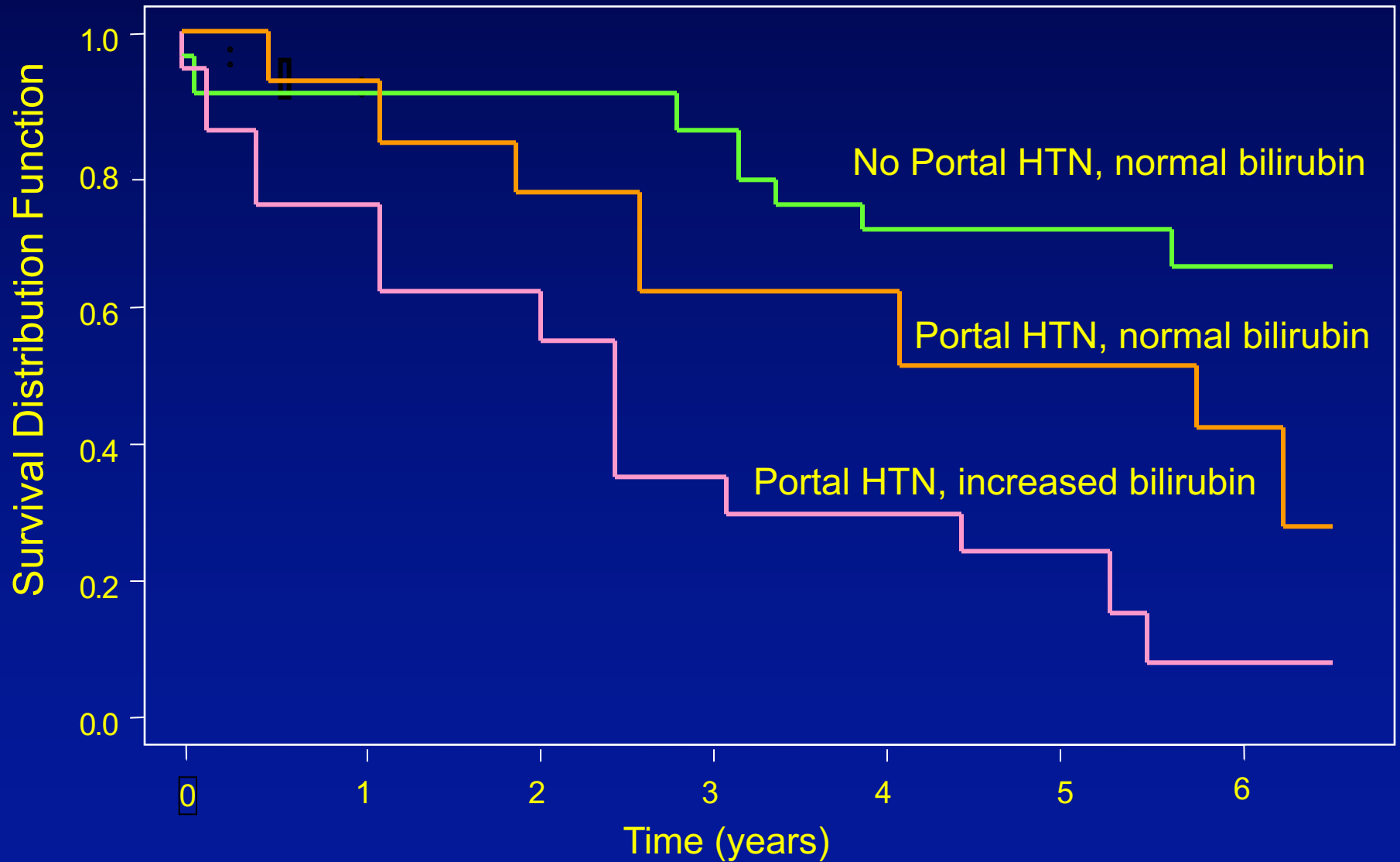
Dx: LI-RADS 5 HCC per Tumor Board review

Laboratory evaluation showed **bilirubin 1.7**, ALT 28, AST 42, 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)

Survival following resection: Impact of portal hypertension



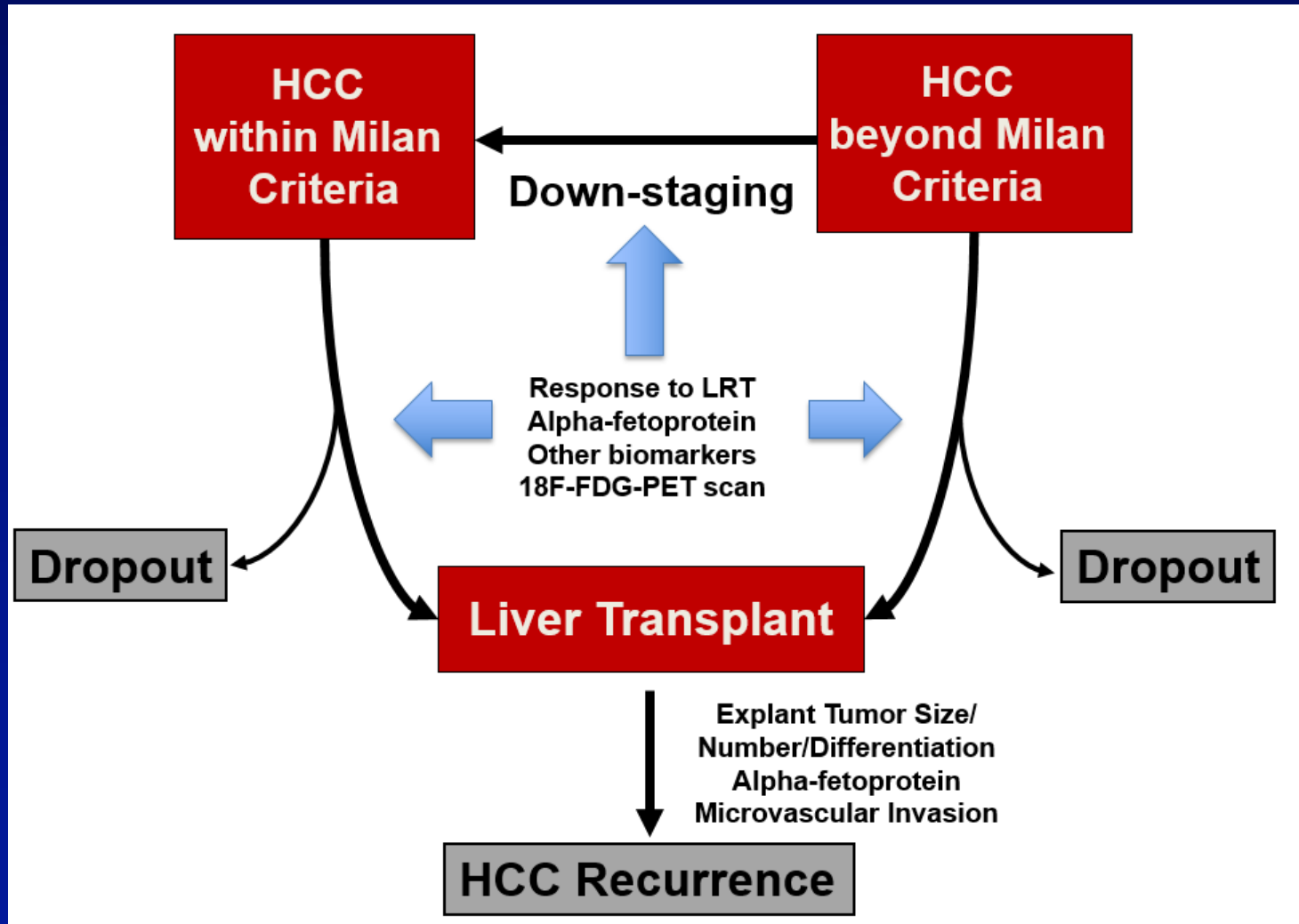
Llovet et al. Hepatology 1999; 30:1434

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

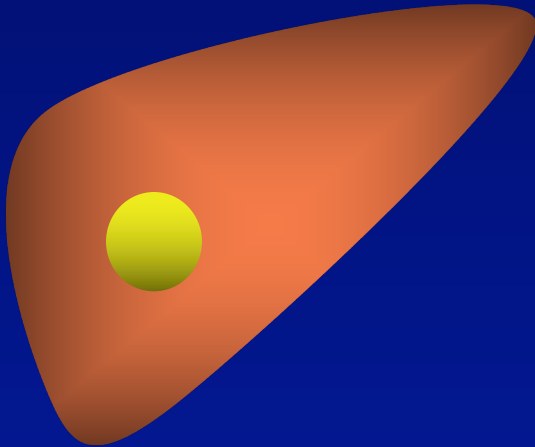
LIVER TRANSPLANTATION FOR HCC



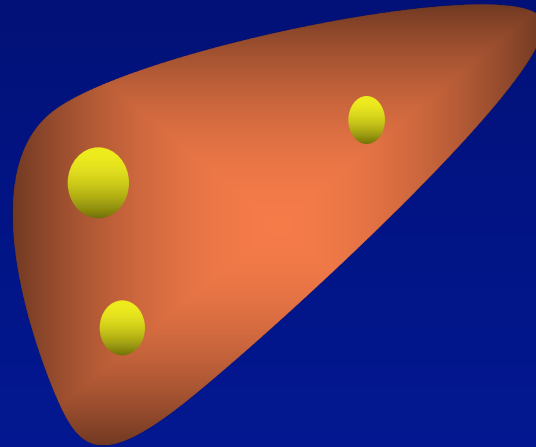
LIVER TRANSPLANTATION FOR HCC

MILAN CRITERIA

1 lesion ≤ 5 cm



2 to 3, none > 3 cm



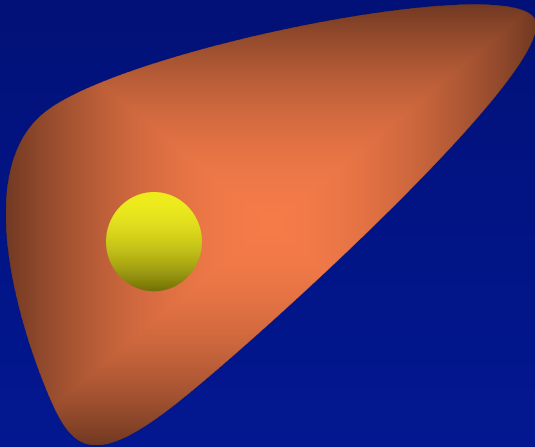
+

Absence of Macroscopic Vascular Invasion
Absence of Extra-hepatic Spread

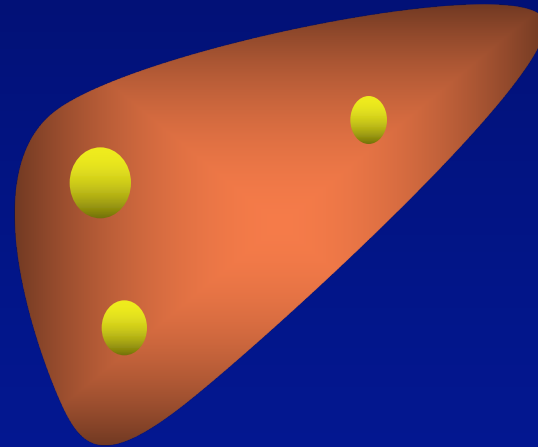
LIVER TRANSPLANTATION FOR HCC

STAGE T2 CRITERIA

1 lesion 2-5 cm



2 to 3, none > 3 cm



Post-LT

5 year survival: 75-80%

5 year HCC recurrence: 10-15%

POST-LT HCC RECURRENCE

- HCC recurrence is the most common cause of death after liver transplant for HCC
- Median survival after HCC recurrence < 1 year after diagnosis
- **Patient selection is the key to prevent recurrence**

*Massie AB, et al. Am J Transpl 2011; 11:2362-2371
Zimmerman MA, et al. Arch Surg 2008; 143:182-188
Clavien PA, et al. Lancet Oncology 2012; 13:11-22*

LIVER TRANSPLANT FOR HCC: RECENT CHANGES


- Uniform diagnostic criteria (OPTN/ LIRADS)
+ standardized reporting
 - Only HCC pts within T2/Milan criteria with LI-RADS 5 lesions are eligible to receive priority listing

LIVER TRANSPLANT FOR HCC:

RECENT CHANGES

- Uniform diagnostic criteria (OPTN/ LIRADS)
+ standardized reporting
- 6-month mandatory waiting period before
awarding MELD exception

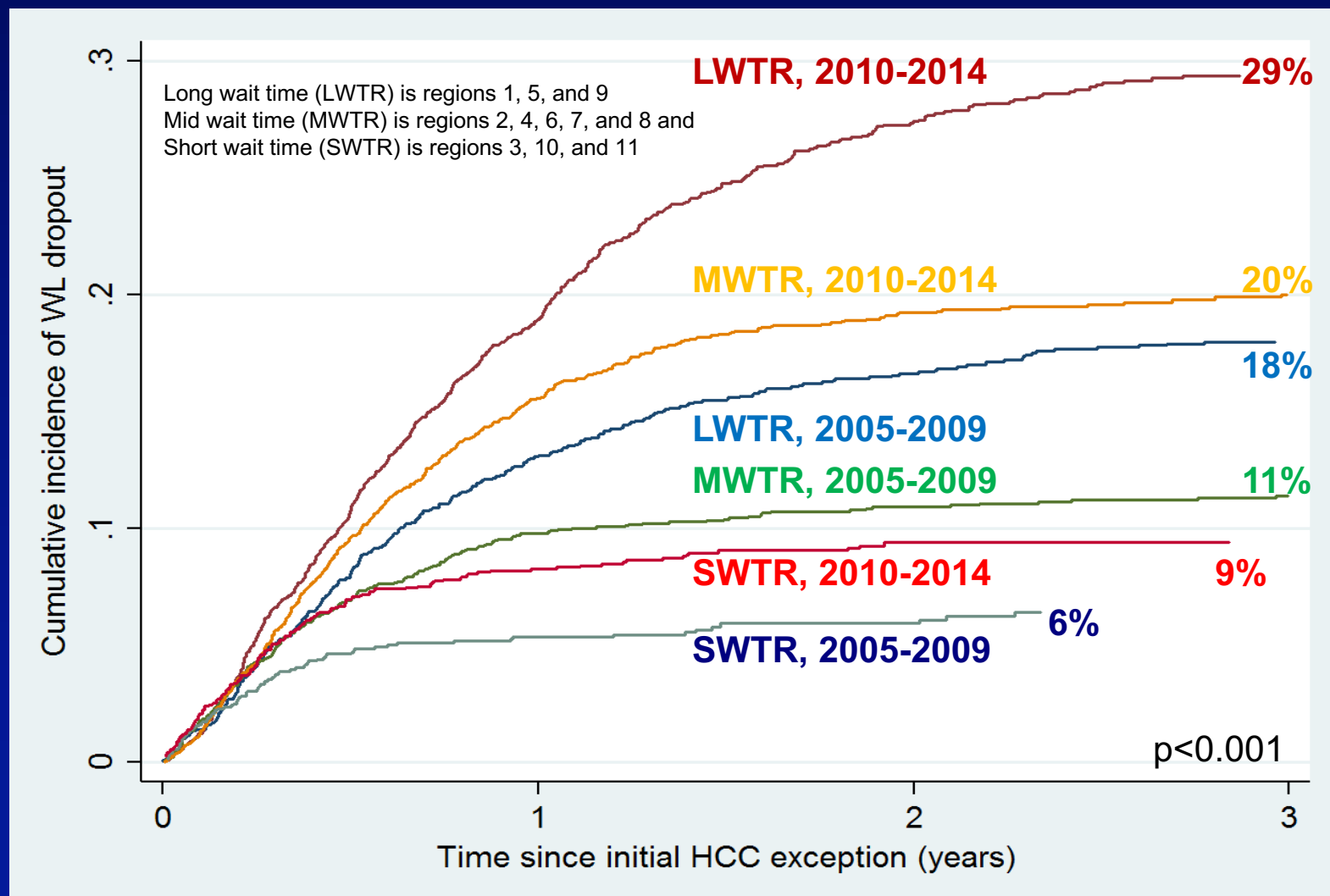
DELAYED HCC-MELD EXCEPTION SCORE

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

LIVER TRANSPLANT FOR HCC: RECENT CHANGES

- Uniform diagnostic criteria (OPTN/ LIRADS)
+ standardized reporting
- 6-month mandatory waiting period before
awarding MELD exception
- Regional variation in access to LT for HCC

PROBABILITY OF WAITLIST DROPOUT BY WAIT TIME REGION AND LISTING PERIOD



LIVER TRANSPLANT FOR HCC:

RECENT CHANGES

- HCC MELD ladder system has recently been replaced by awarding median MELD at transplant minus 3 points (MMAT-3) for the area where the candidate is listed
 - CPMC/Stanford/UCSF MMAT currently is 30 points so HCC patient will receive 27 points after 6 month wait and remain there until LT

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

CASE PRESENTATION



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

What treatment would you recommend?

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

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

What treatment would you recommend?

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

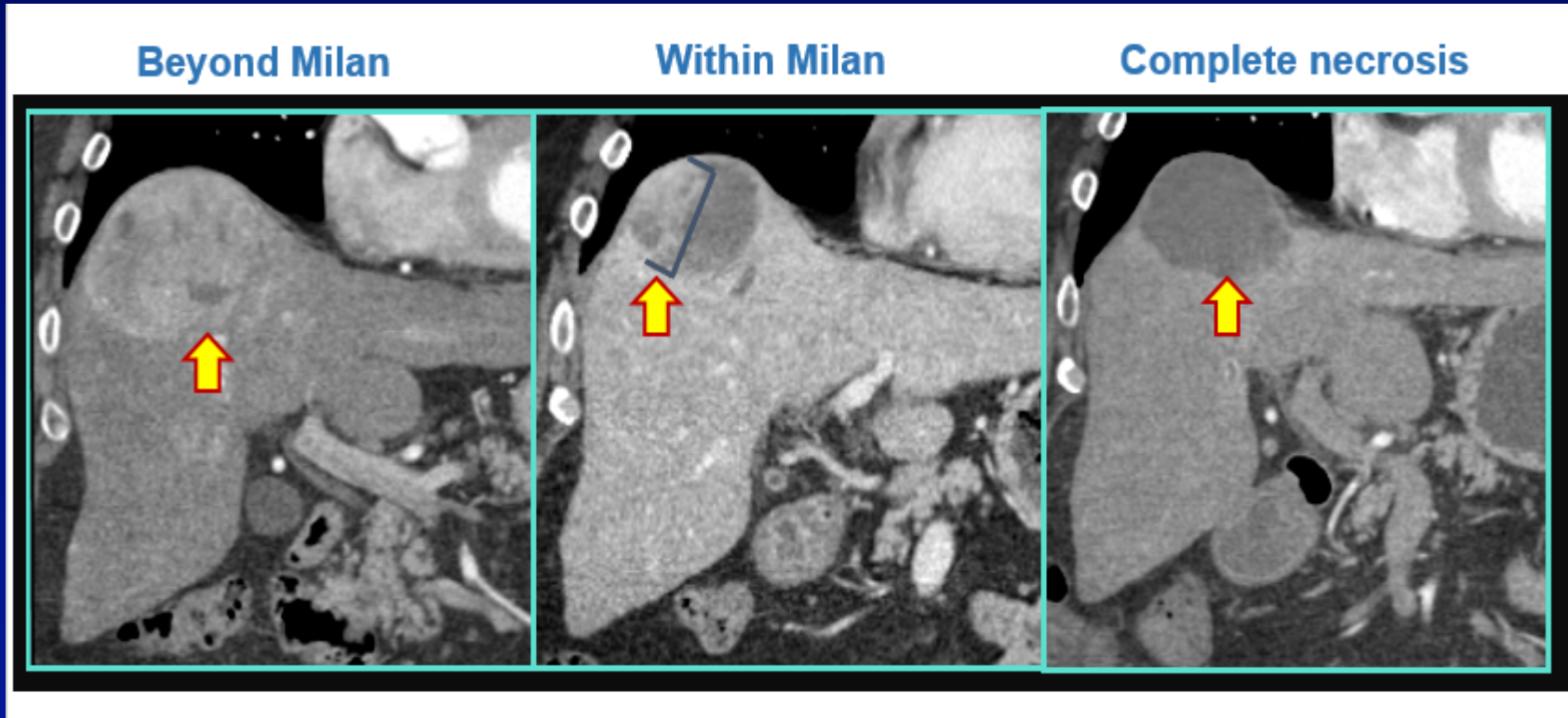
Down-staging of HCC for Transplant

- 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)

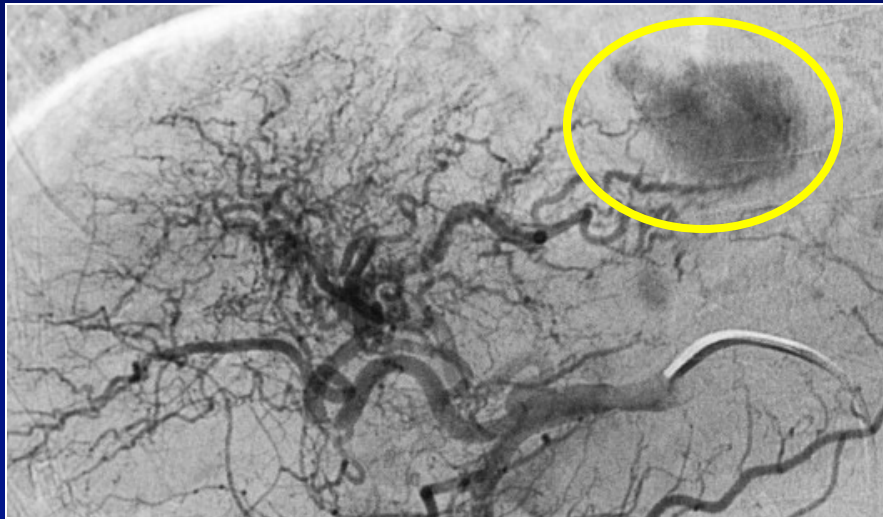
(Laparoscopic, percutaneous or open)

Microwave/ Cryo- ablation

RADIOEMBOLIZATION (YITTRIUM - 90)

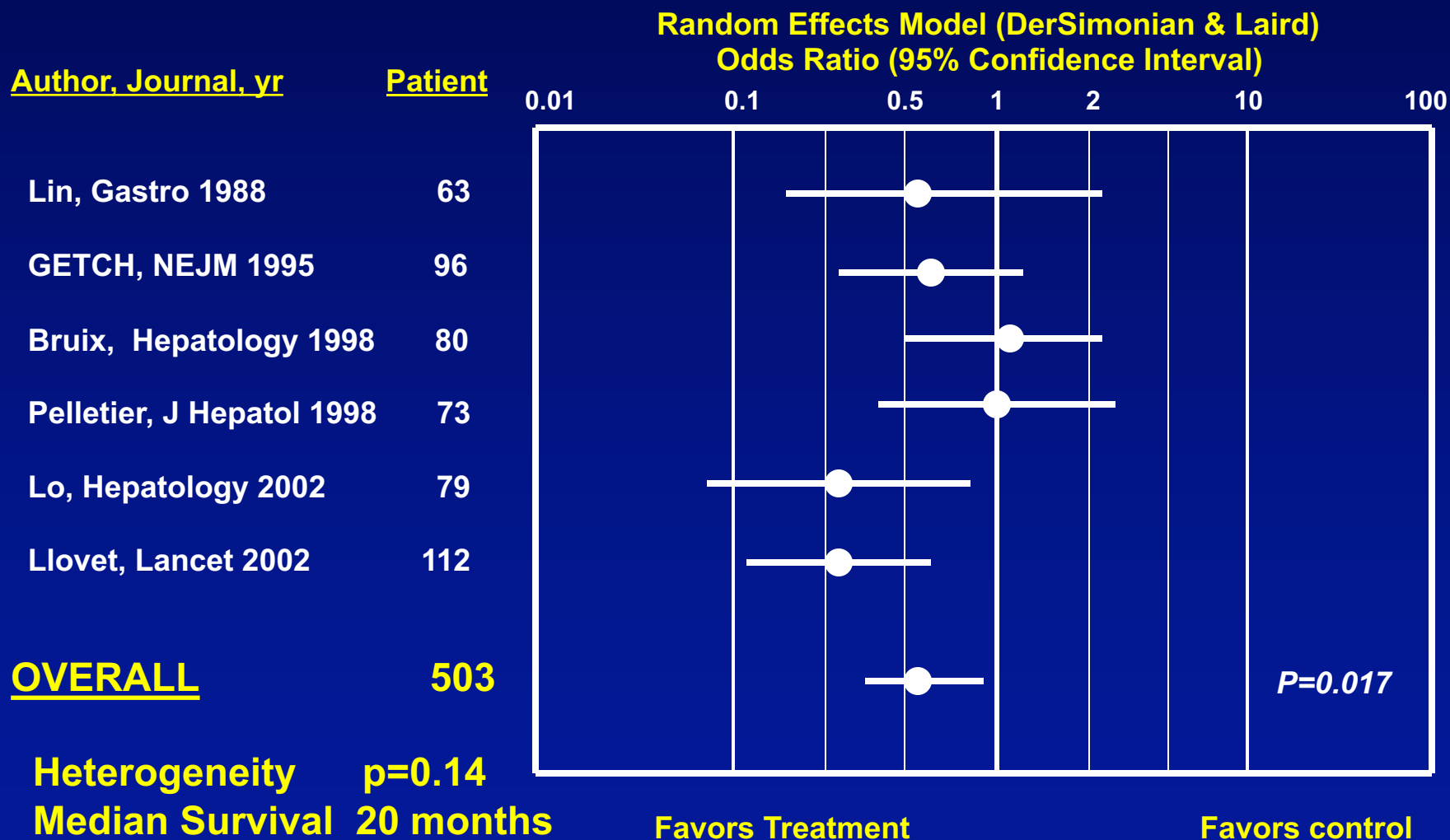
STEREOTACTIC BODY RADIATION (SBRT)

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

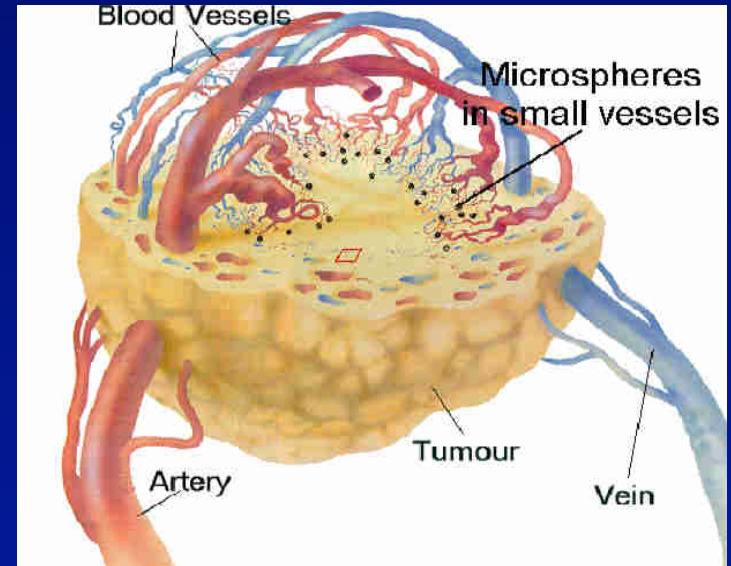
Meta-analysis of RCT for TACE/TAE vs. Placebo/ suboptimal Therapy



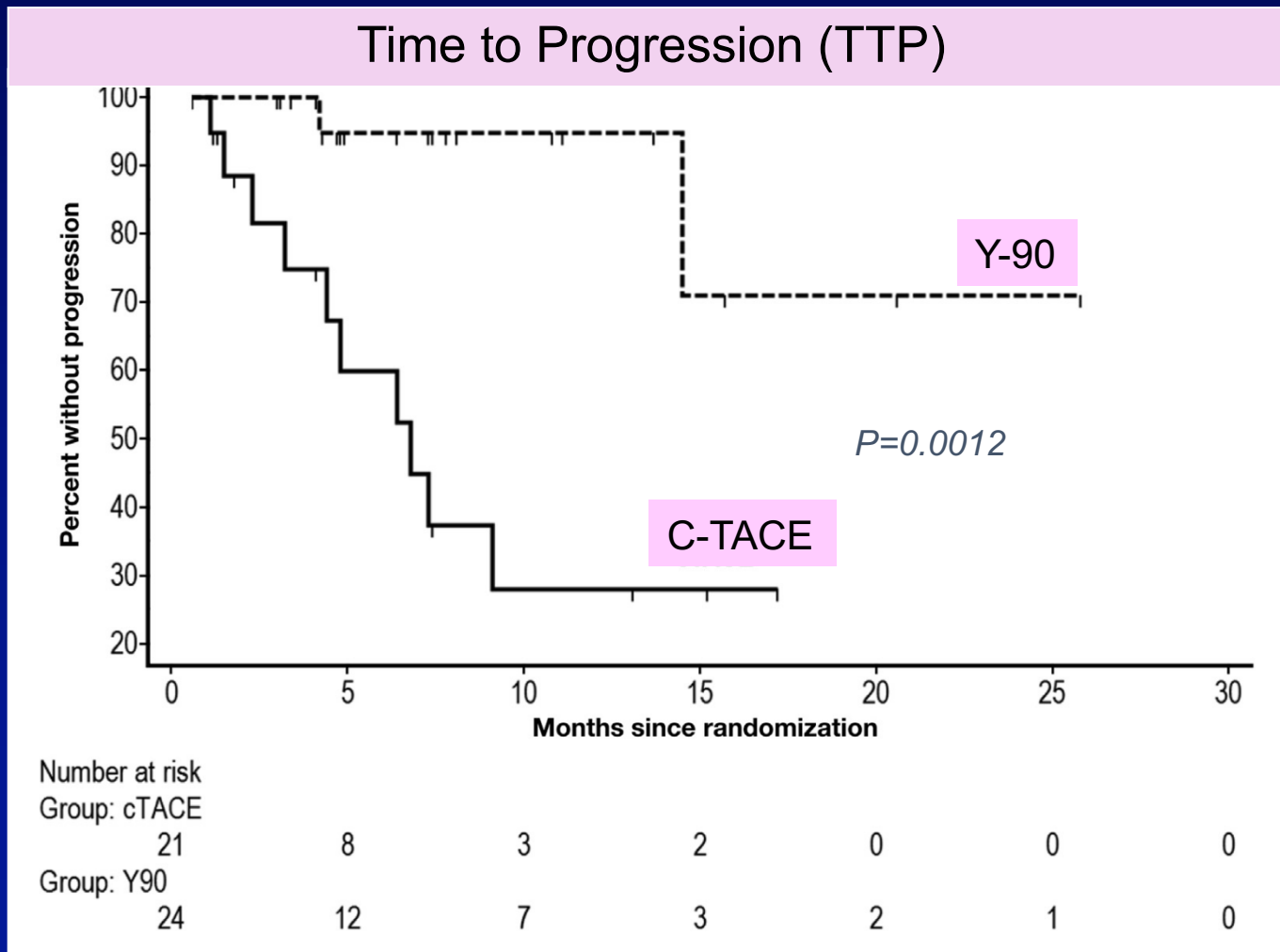
Llovet JM, Bruix J. Hepatology 2003;37:429-442

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 < 2-3 mg/dl)

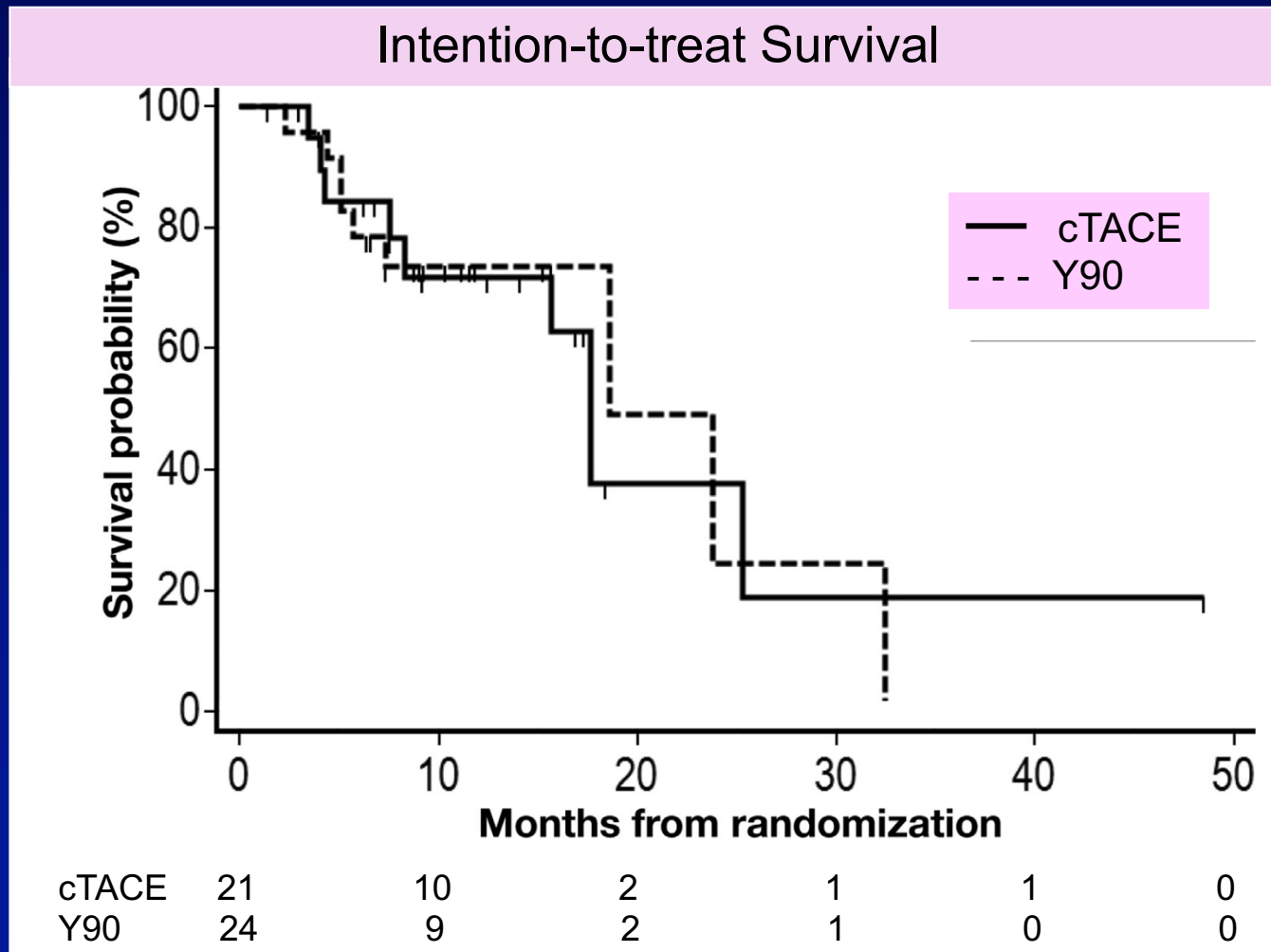


SIRT (Y-90) versus TACE (PREMIERE)



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

SIRT (Y-90) versus TACE (PREMIERE)

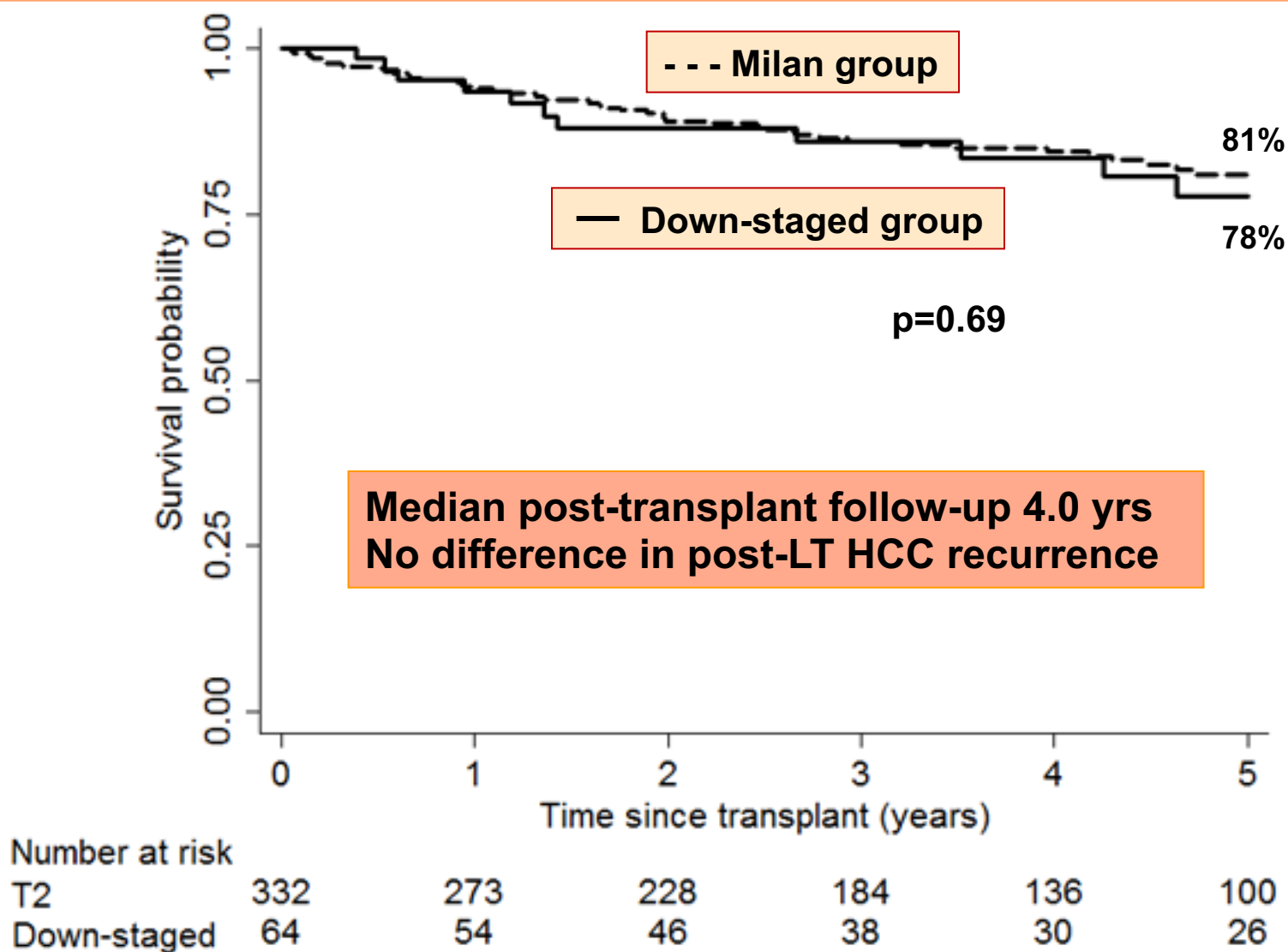


Salem R, et al. Gastroenterology 2016;151:1155-1163

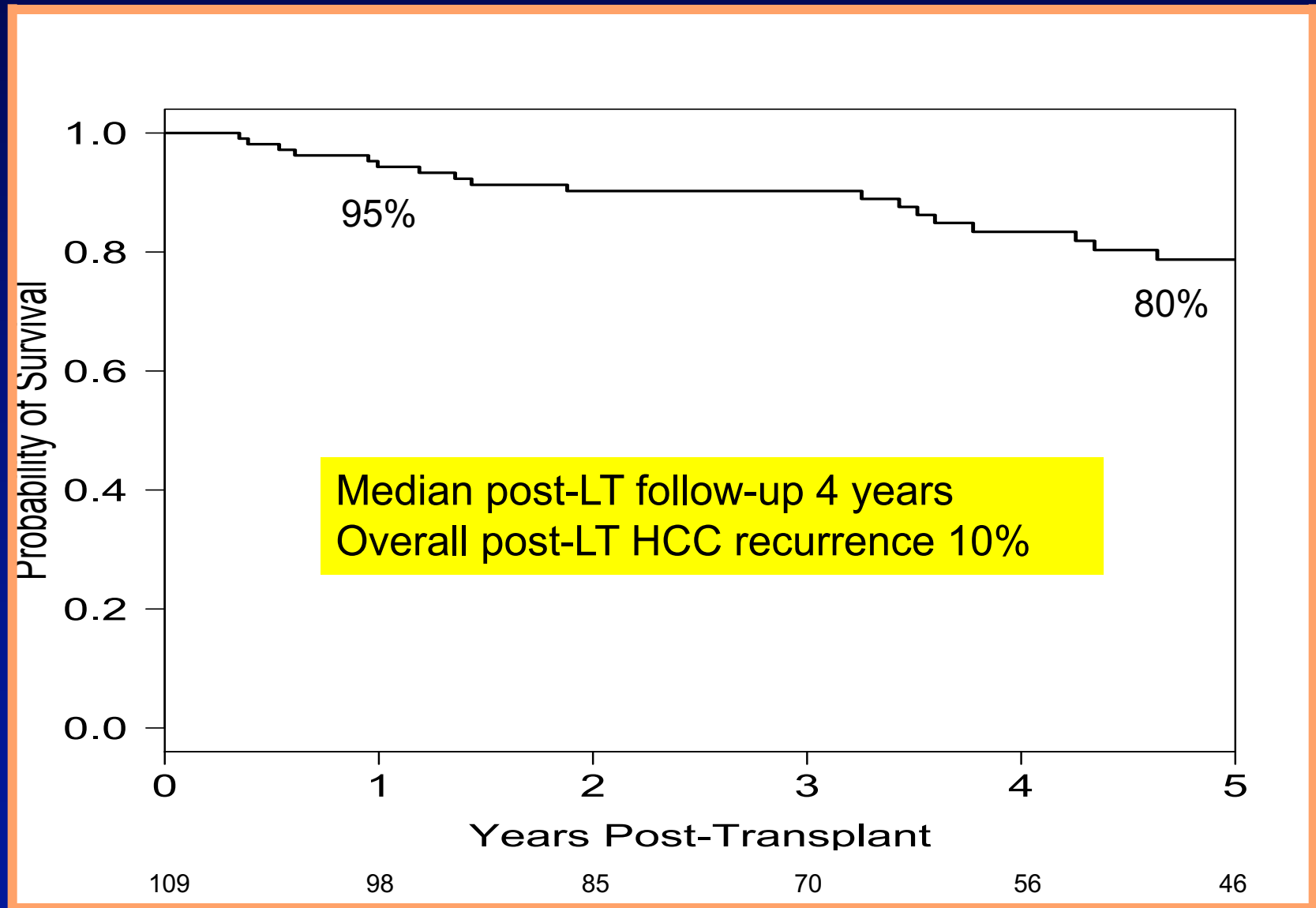
UNOS DOWN-STAGING PROTOCOL

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

Post-Transplant Survival



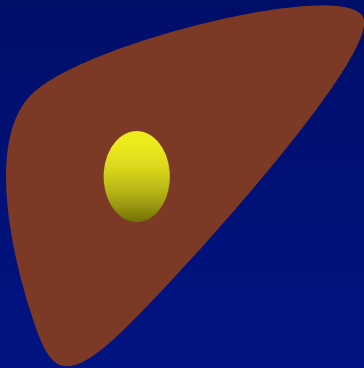
Region 5 D/S Multi-center Study: Post-LT Survival



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

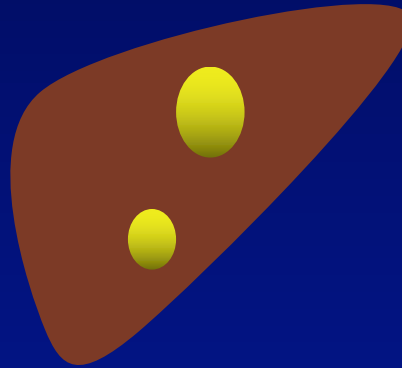
UNOS HCC COHORTS (N=3819)



MILAN

N=3,276 (86%)

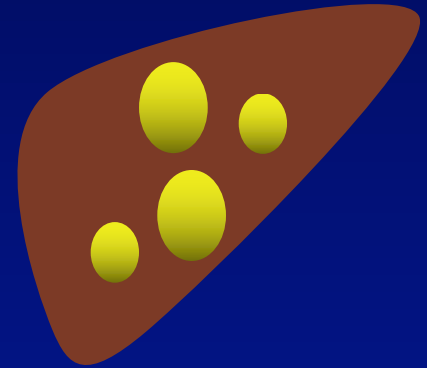
Total tumor diameter:
2.8 cm (2.3-3.7)



“UNOS-DS”

N=422 (11%)

Total tumor diameter:
5.8 cm (5.3-6.5)

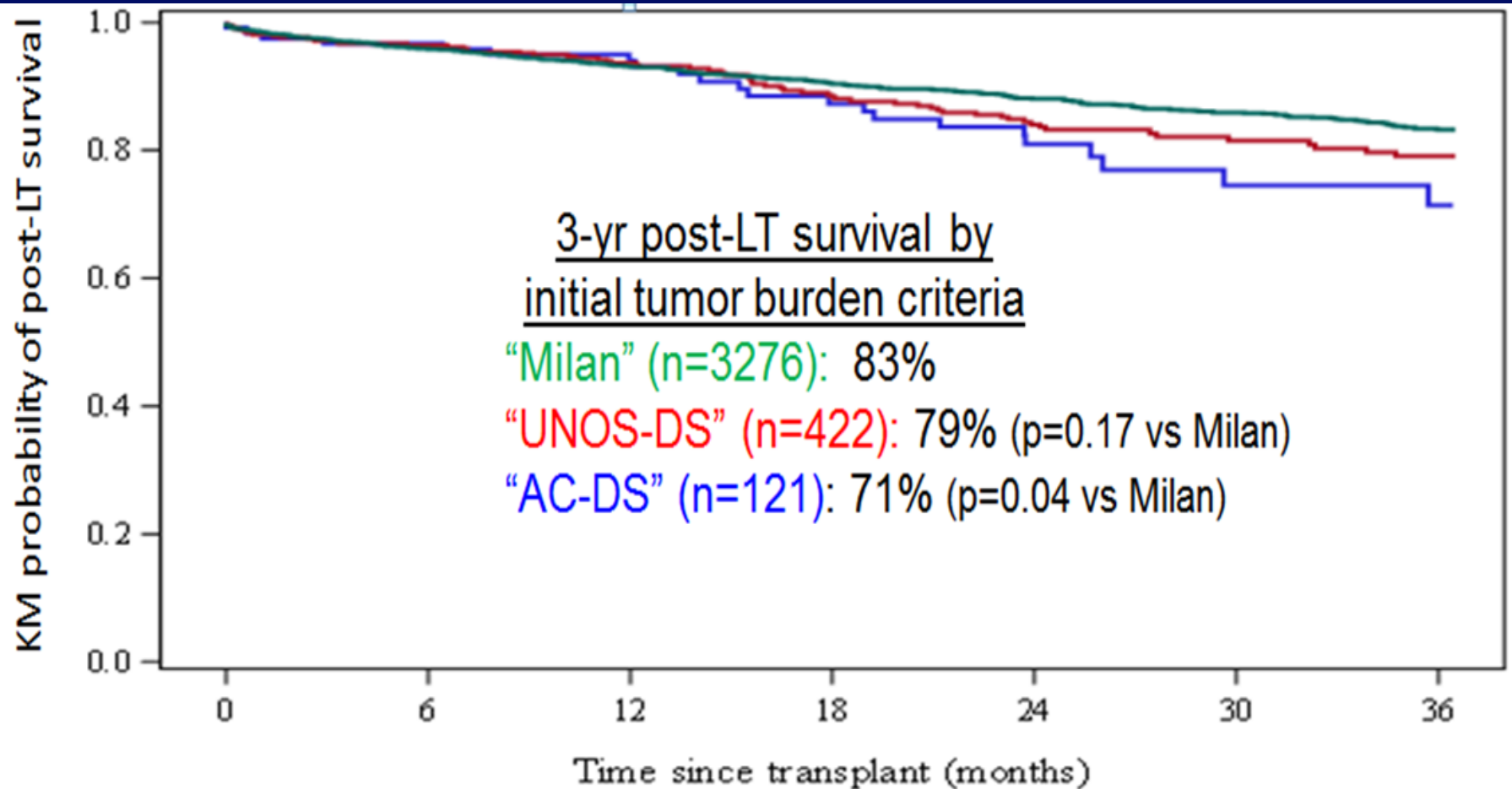


“All-comers”

N=121 (3.2%)

Total tumor diameter:
9.3 cm (8.5-10.6)

UNOS DOWN-STAGING PROTOCOL

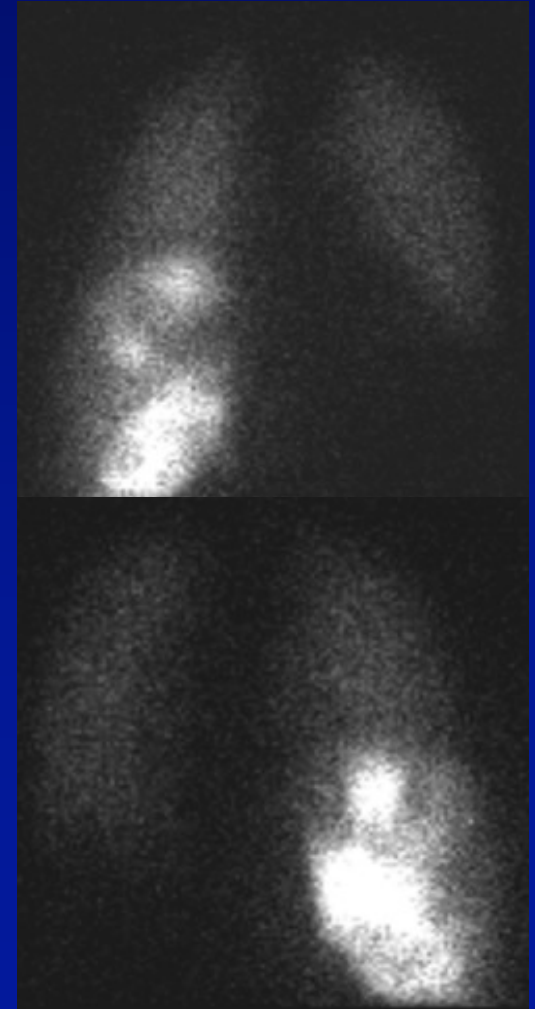


CASE PRESENTATION

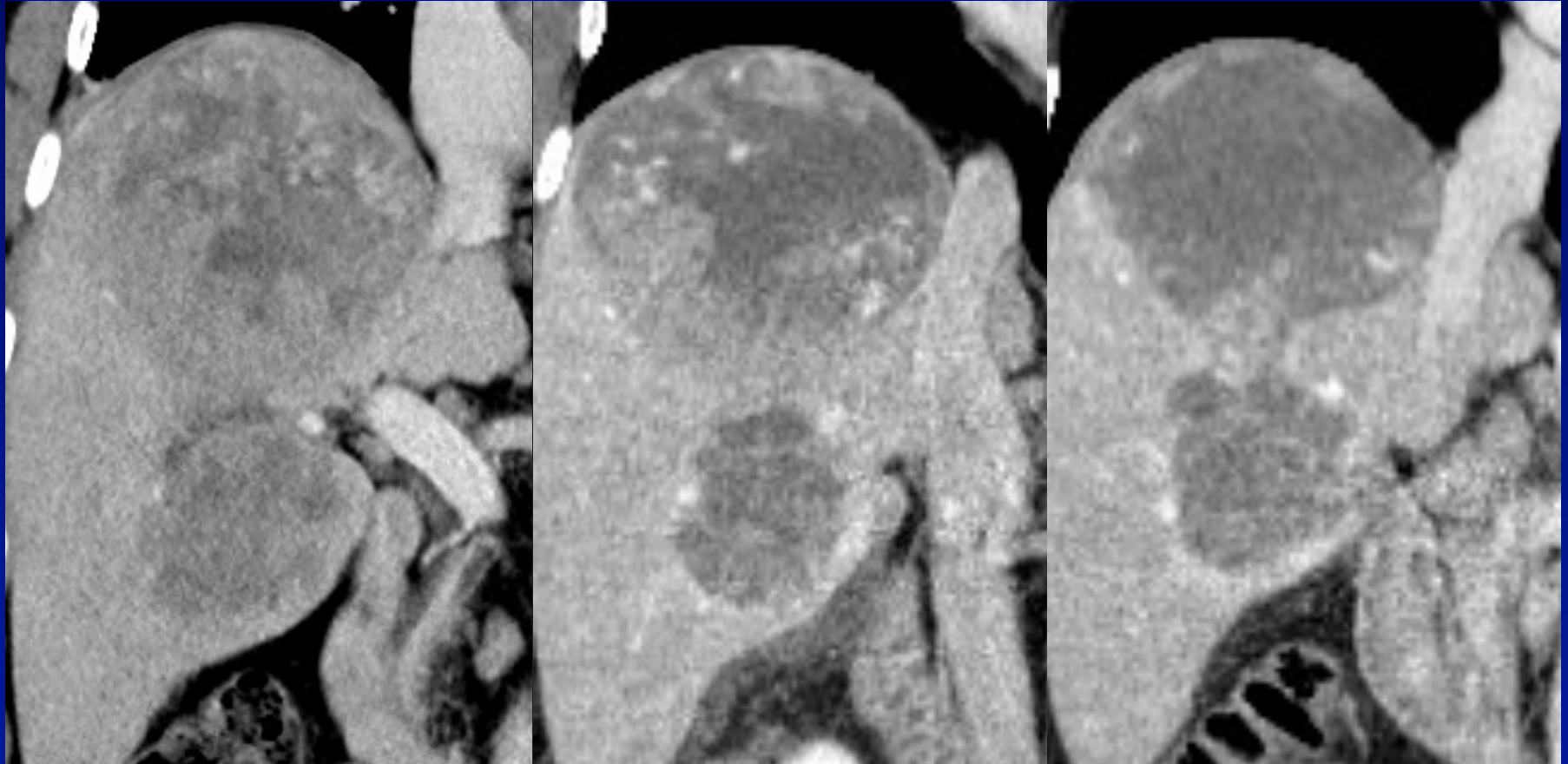
Radioembolization with TheraSphere/Y-90



Tc-MAA



CASE PRESENTATION

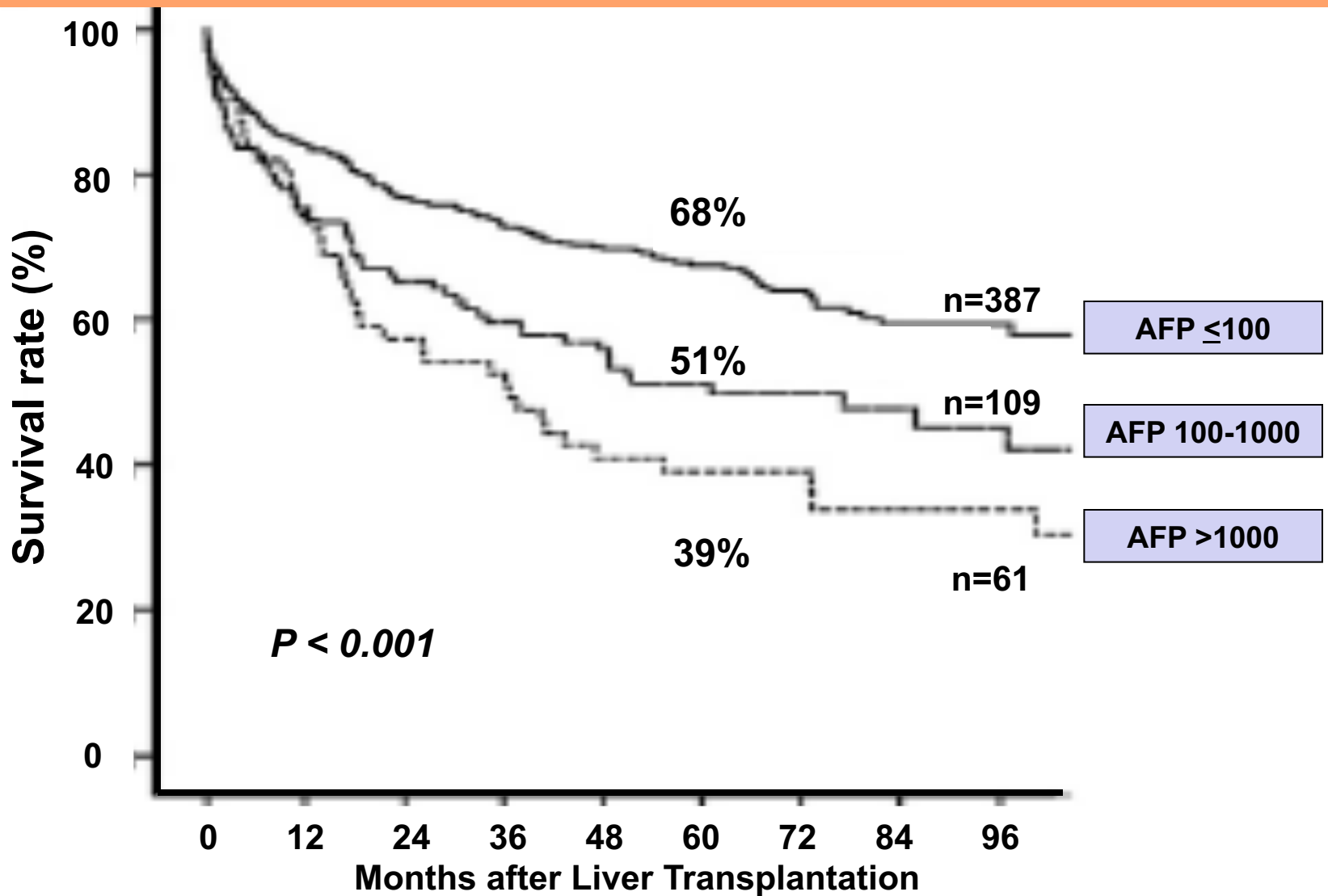


Pre-Y90

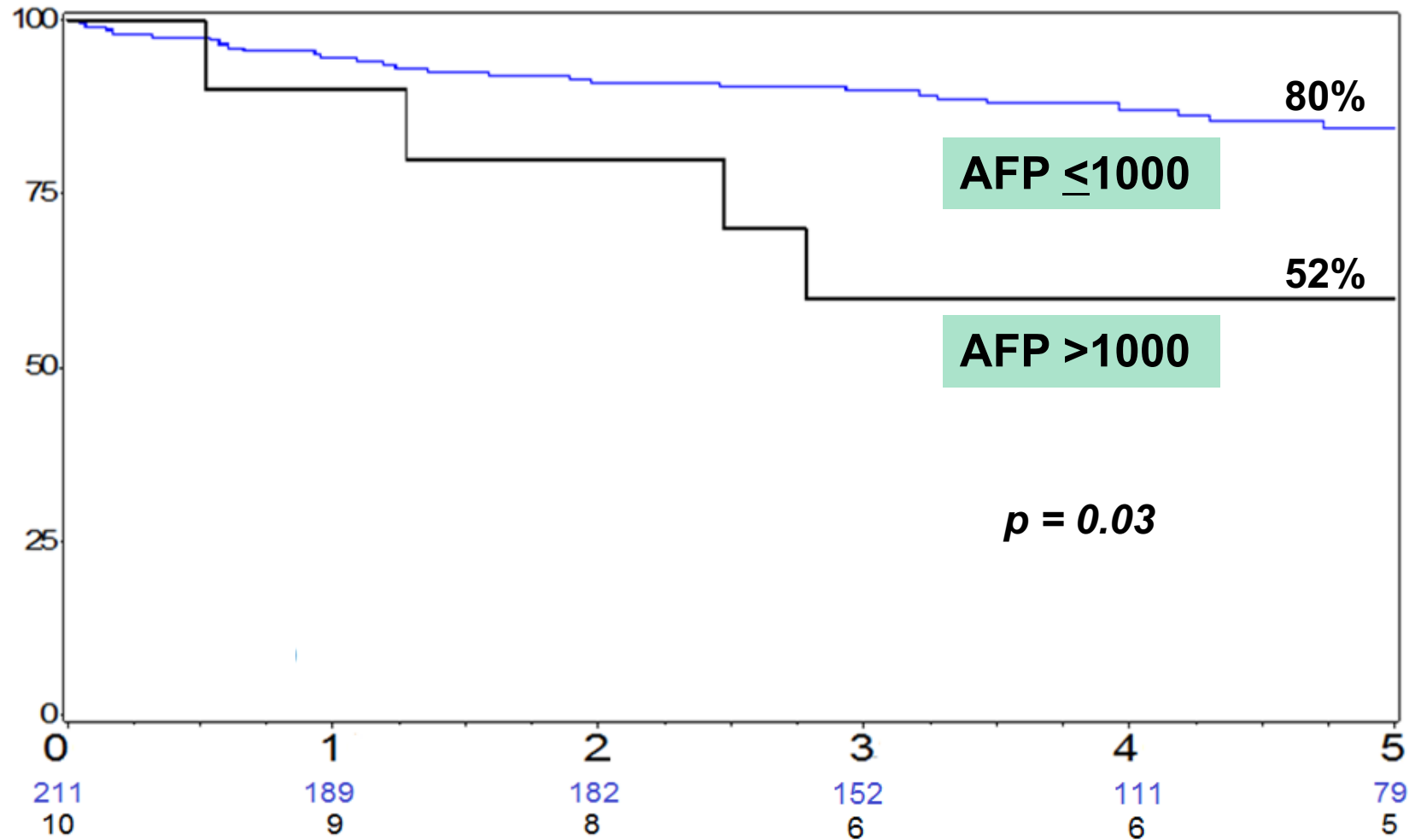
1 mo p Y90#1

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

AFP and Post-transplant Outcome- France



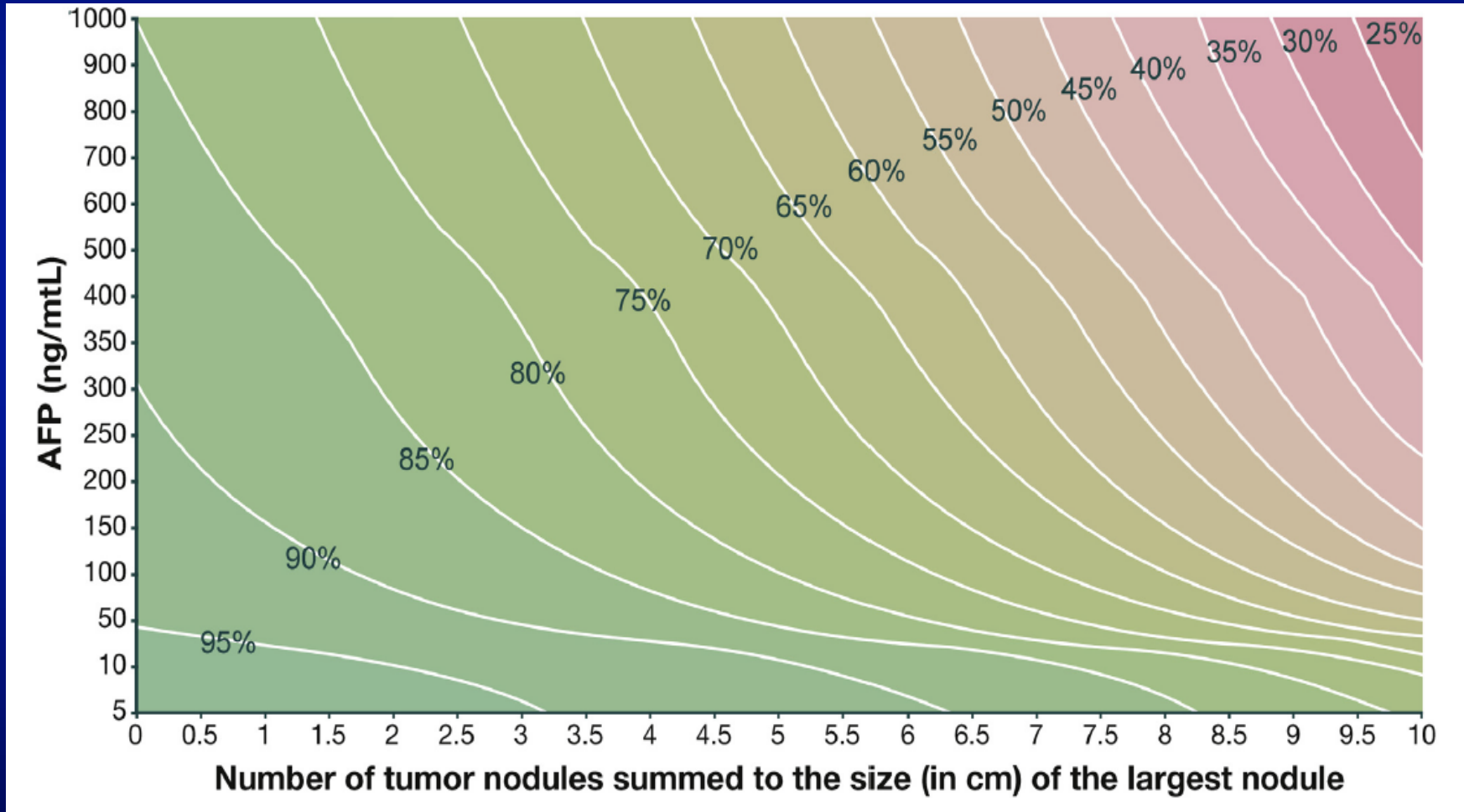
AFP and Post-transplant Outcome - UCSF



LIVER TRANSPLANTATION FOR HCC

METROTICKET 2.0

HCC Specific Survival

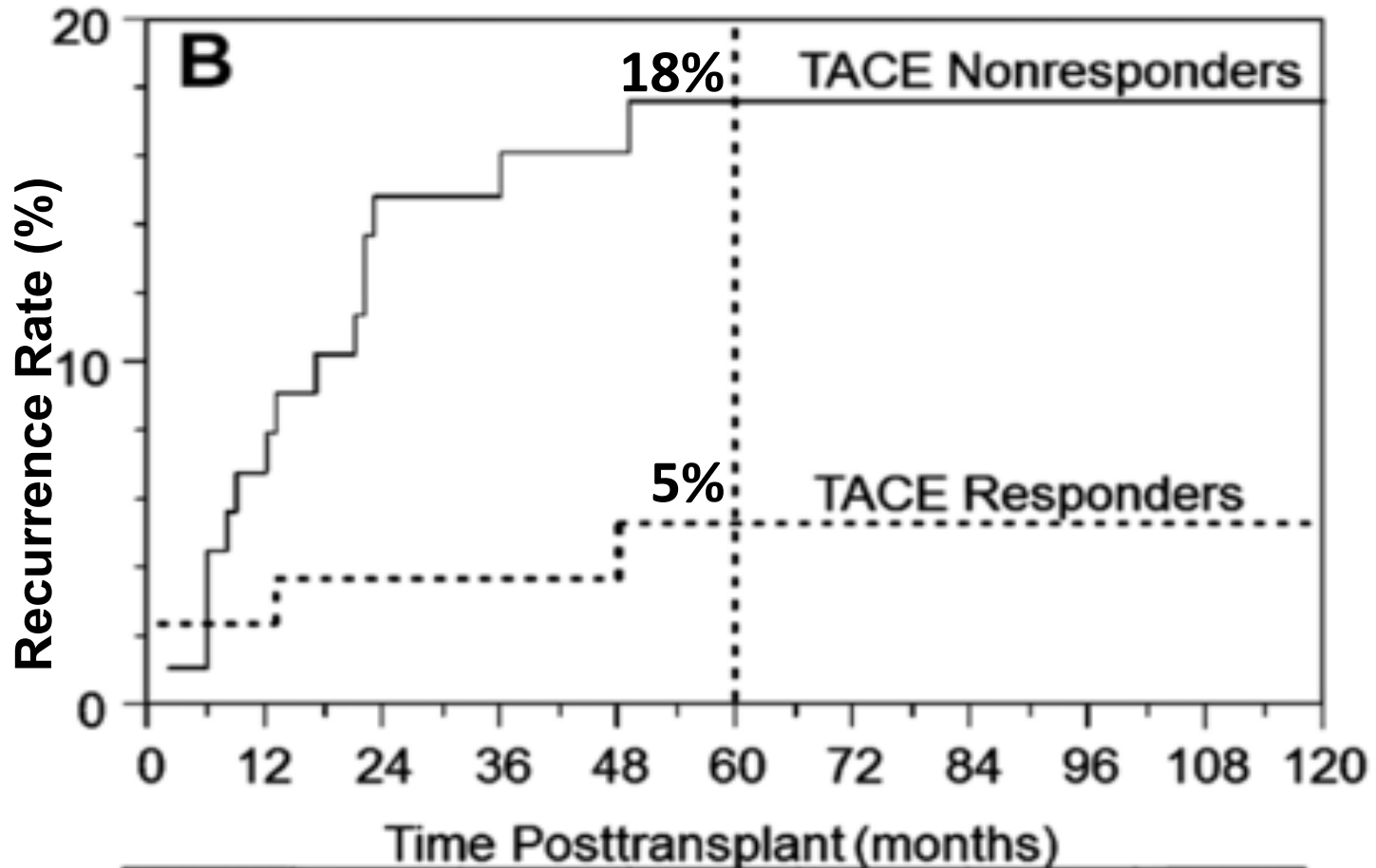


RECENT UNOS POLICY CHANGE

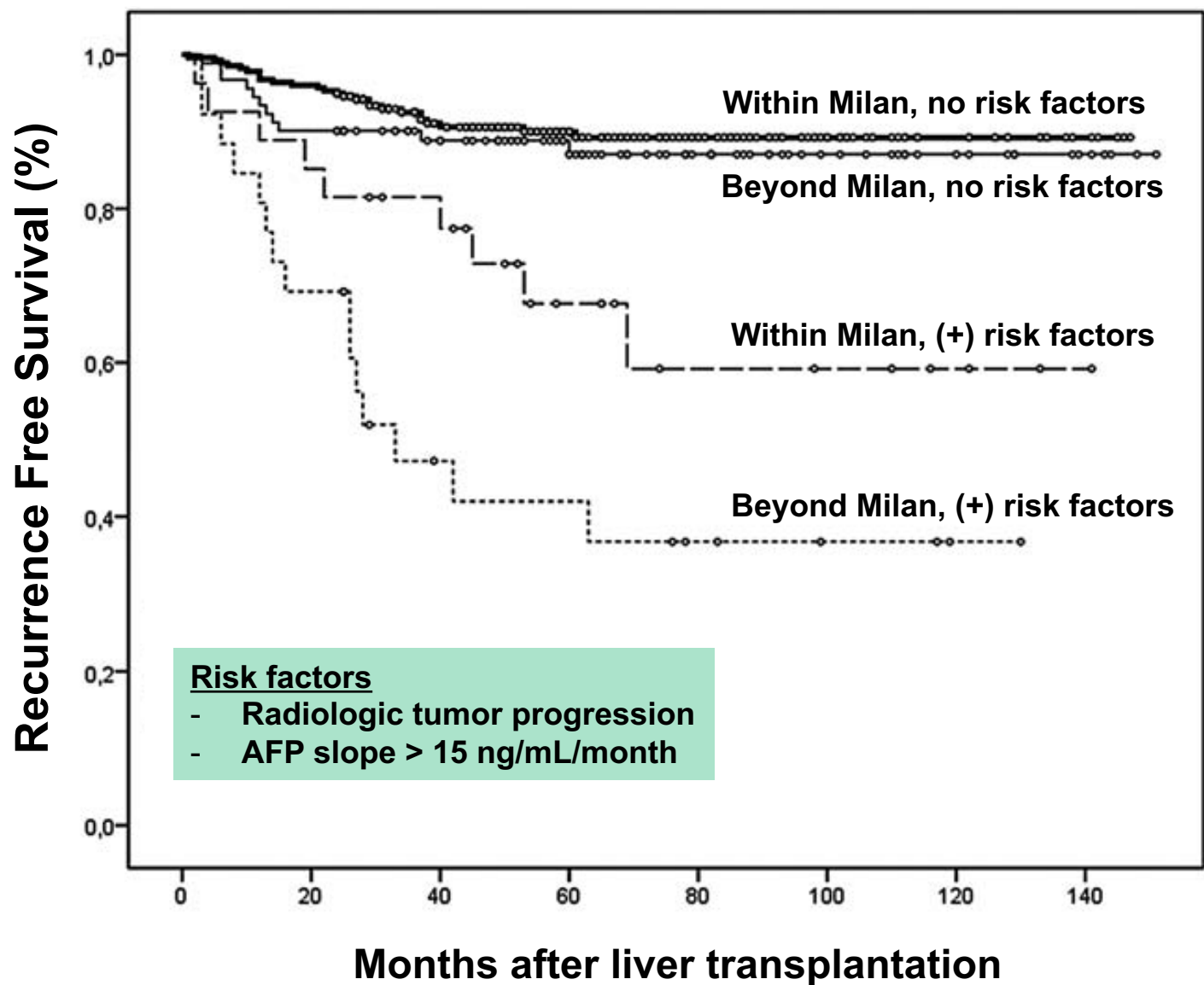
High AFP Threshold

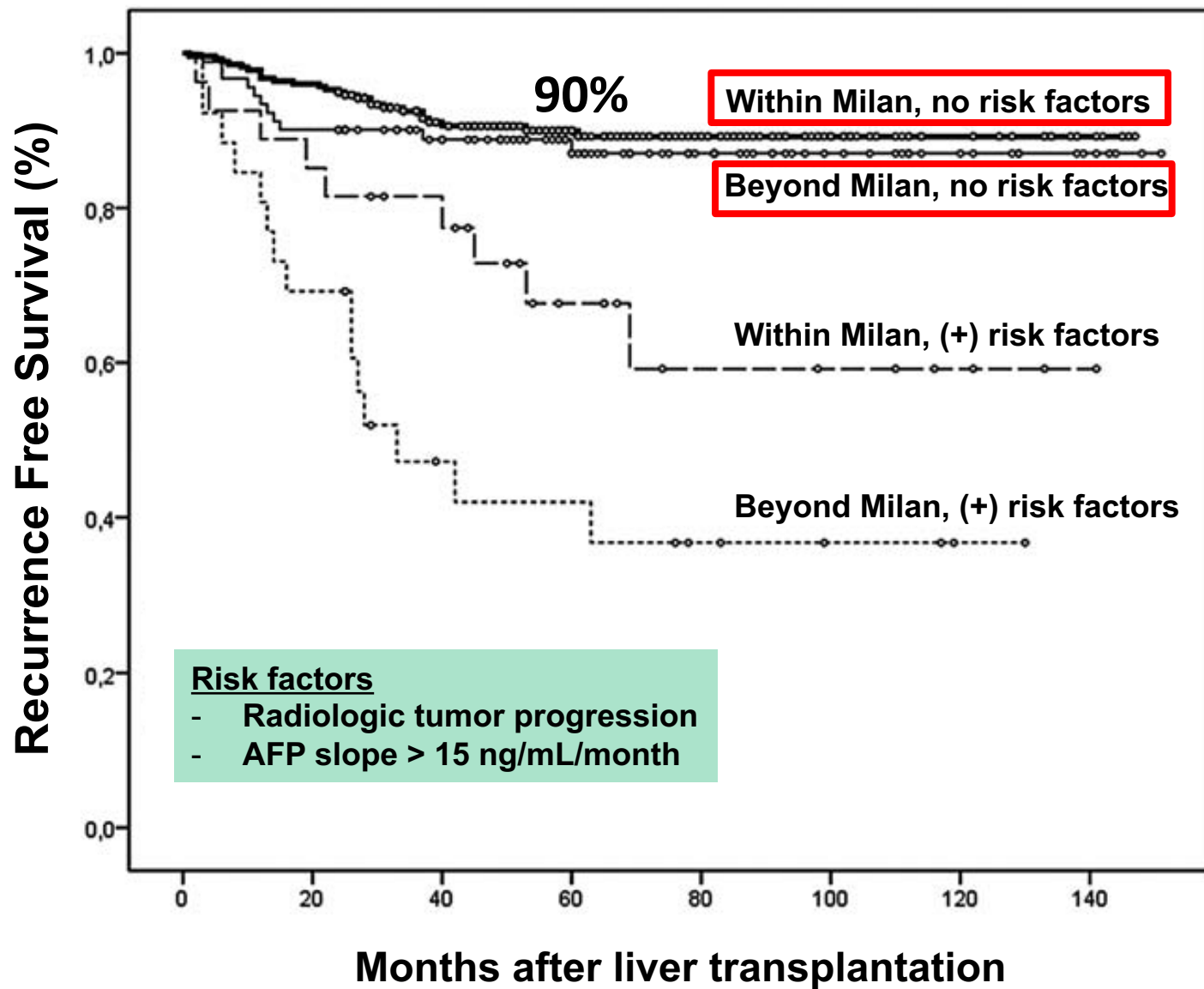
- Candidates with lesions meeting T2 criteria but with an AFP >1000 are not eligible for a standardized MELD exception
- If AFP falls <500 after LRT, the candidate is eligible for a standardized MELD exception

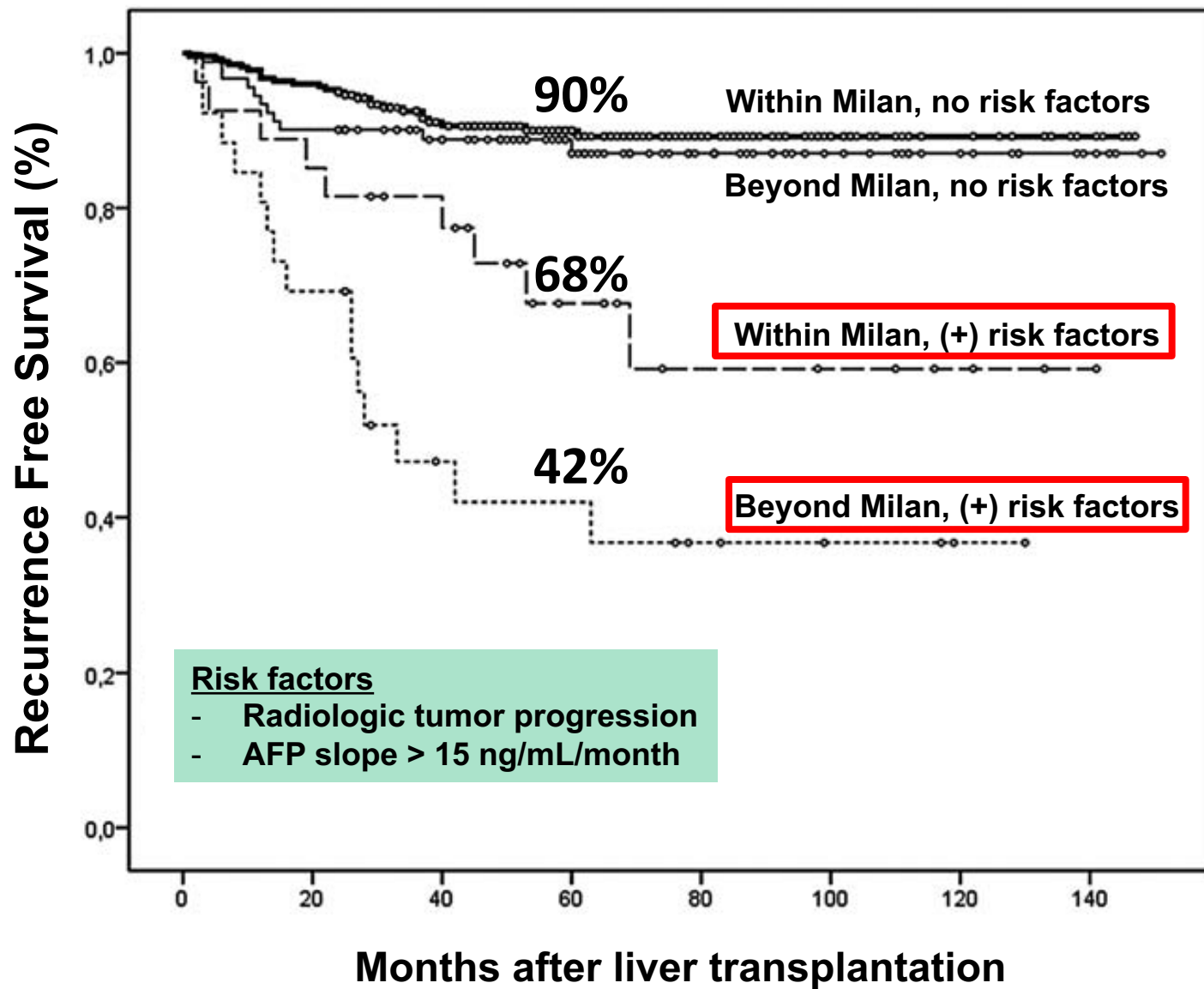
RESPONSE TO LOCAL-REGIONAL THERAPY AS PROGNOSTIC FACTOR



Months	6	12	24	36	48	60
NR (n=90)	4 (4.5%)	7 (7.9%)	13 (14.8%)	14 (16.1%)	14 (16.1%)	15 (17.6%)
RP (n=83)	2 (2.4%)	2 (2.4%)	3 (3.7%)	3 (3.7%)	4 (5.3%)	4 (5.3%)







HCC AND LT: OVERVIEW

- HCC diagnosis and staging
- Selection criteria for liver transplant
- Local-regional therapy (LRT)
- Down-staging and “all-comers”
- RETREAT score and post-LT mgmt

RETREAT SCORE

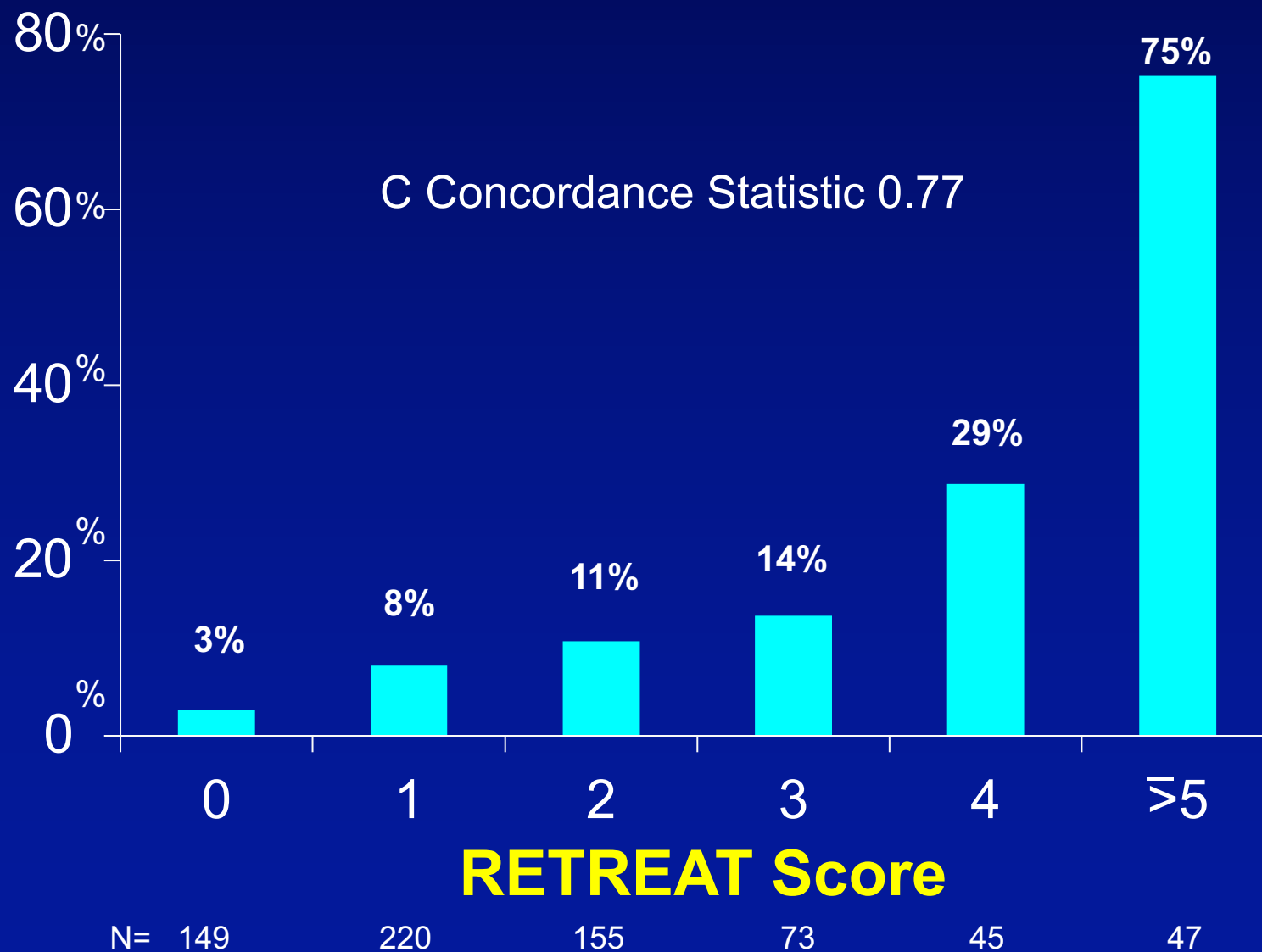
- Multi-center study, 1060 LT recipients w/ HCC meeting Milan criteria by imaging, developed + validated prediction index for HCC recurrence
- The Risk Estimation of Tumor Recurrence After Transplant (RETREAT) score incorporates 3 variables that independently predict recurrence
 - **Last AFP prior to LT**
 - **Microvascular invasion**
 - **Largest viable tumor diameter + number of viable tumors on explant**

RETREAT SCORE

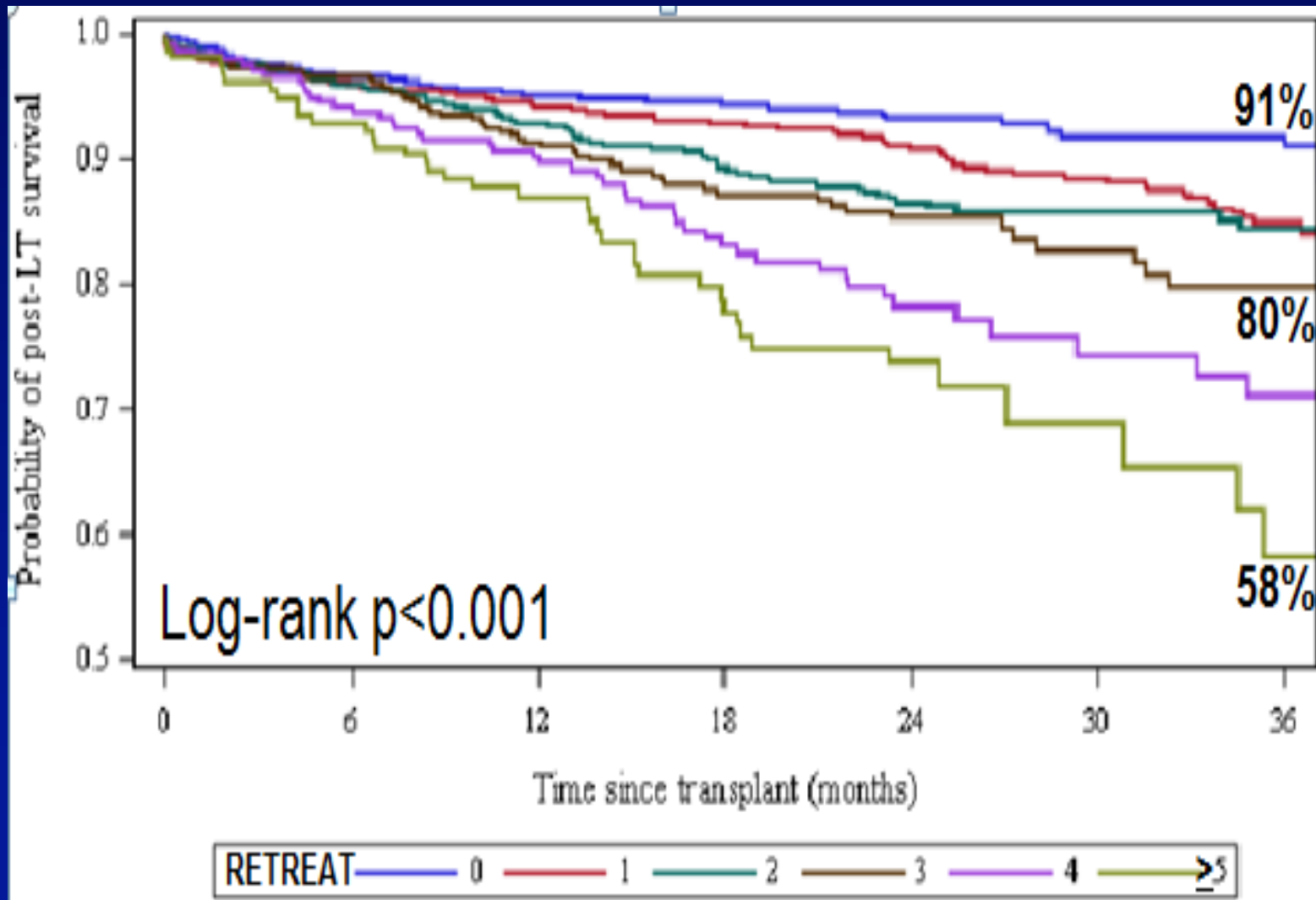
Predictor	Points
<u>AFP at LT</u>	
21-99	1
100-999	2
≥1000	3
<u>Micro-vascular Invasion</u>	
Yes	2
<u>Largest Viable Tumor Size (cm) + Number of Viable Lesions</u>	
1-4.9	1
5-9.9	2
≥10	3

No RETREAT points scored for: AFP 0-20, no microvascular invasion, and explant pathology stage score of 0

RETREAT SCORE: 5 YR RECURRENCE



OBSERVED 3-YR POST-LT SURVIVAL STRATIFIED BY RETREAT SCORE



RETREAT FOR HCC SURVEILLANCE

<u>RETREAT</u>	<u>Proposed surveillance regimen</u>
0	No surveillance (20-25% of the cohort)
1-3	HCC surveillance every 6 months for 2 years
4	HCC surveillance every 6 months for 5 years
5+	HCC surveillance every 3-4 months for 2 years; then every 6 months for years 2-5

Surveillance should be performed w/ multiphasic abdominal CT or MRI, chest CT, and AFP at the recommended interval

RETREAT: JBL 1/24/15

- AFP at Transplant- 42.3
- Explant
 - Evidence of HCC in explant: Necrotic nodule, no viable tumor.
 - Number of tumors: 1, well-circumscribed.
 - Largest Tumor: 3.6 cm, entirely necrosed.
 - Vascular invasion: Necrotic nodule abuts large vessel but does not invade it.
 - Local extension of tumor: Confined to liver.

RETREAT: JBL

Risk Factors for HCC Recurrence	Points
<u>AFP at LT</u>	
0-20	0
21-99	1
100-999	2
<u>≥1000</u>	3
<u>Microvascular Invasion</u>	
No	0
Yes	2
<u>Explant Largest Viable Tumor Size (cm) Plus Number of Viable Lesions</u>	
0	0
1-4.9	1
5-9.9	2
<u>≥10</u>	3

RETREAT: JBL

HCC Recurrence at 1 and 5 Years after LT		
Total Points Scored	Predicted HCC Recurrence at 1 yr	Predicted HCC Recurrence at 5 yrs
0	1.0%	2.9%
1	2.9%	8.0%
2	4.0%	10.8%
3	5.1%	13.7%
4	11.4%	28.7%
<u>≥5</u>	39.3%	75.2%

RETREAT FOR HCC SURVEILLANCE

RETREAT

Proposed surveillance regimen

1-3

HCC surveillance every 6 months for 2 years

Surveillance should be performed w/ multiphasic abdominal CT or MRI, chest CT, and AFP at the recommended interval.

RETREAT FOR HCC SURVEILLANCE

RETREAT

Proposed surveillance regimen

1-3

HCC surveillance every 6 months for 2 years

Surveillance should be performed w/ multiphasic abdominal CT or MRI, chest CT, and AFP at the recommended interval.

- Ongoing prospective multi-center study evaluating this surveillance protocol

LIVER TRANSPLANT FOR HCC: SUMMARY

- The Milan criteria remain the gold-standard for selection criteria in the US
- After 6 month delay, eligible HCC patients are now awarded MMAT-3 rather than the previous ladder upgrade system
- Similar post-LT survival observed for Milan and UNOS D/S patients → Down-staging now accepted as national policy

LIVER TRANSPLANT FOR HCC: SUMMARY

- Pts with initial tumor burden within “all-comers” should be carefully selected for LT given inferior post-LT outcomes
- AFP is an excellent marker of tumor biology with worse post-LT outcome as AFP rises. AFP >1000 is exclusion from LT nationally unless <500 ng/ml with LRT
- Tailor post-LT HCC surveillance regimens based on recurrence risk

neil.mehta@ucsf.edu

Thank You!



HEPATOCELLULAR CARCINOMA

- Hepatocellular carcinoma (HCC) is the 5th most common cancer worldwide, and the 3rd leading cause of cancer-related deaths¹
- In Asia and Sub-Saharan Africa alone, >500,000 new HCC cases develop each year²
- Most HCC cases are associated with an underlying risk factor¹

¹Ferenci P, et al. *J Clin Gastroenterol*. 2010;44(4):239-245.

²Thomas and Zhu. *J Clin Oncol*. 2005;23(13):2892-2899.

WHO IS AT RISK FOR HCC?

CHRONIC LIVER DISEASE

Hepatitis C

Fatty liver

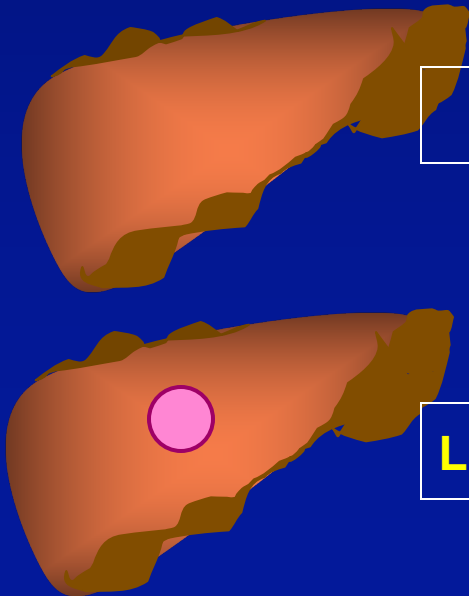
Alcohol

Metabolic and inherited

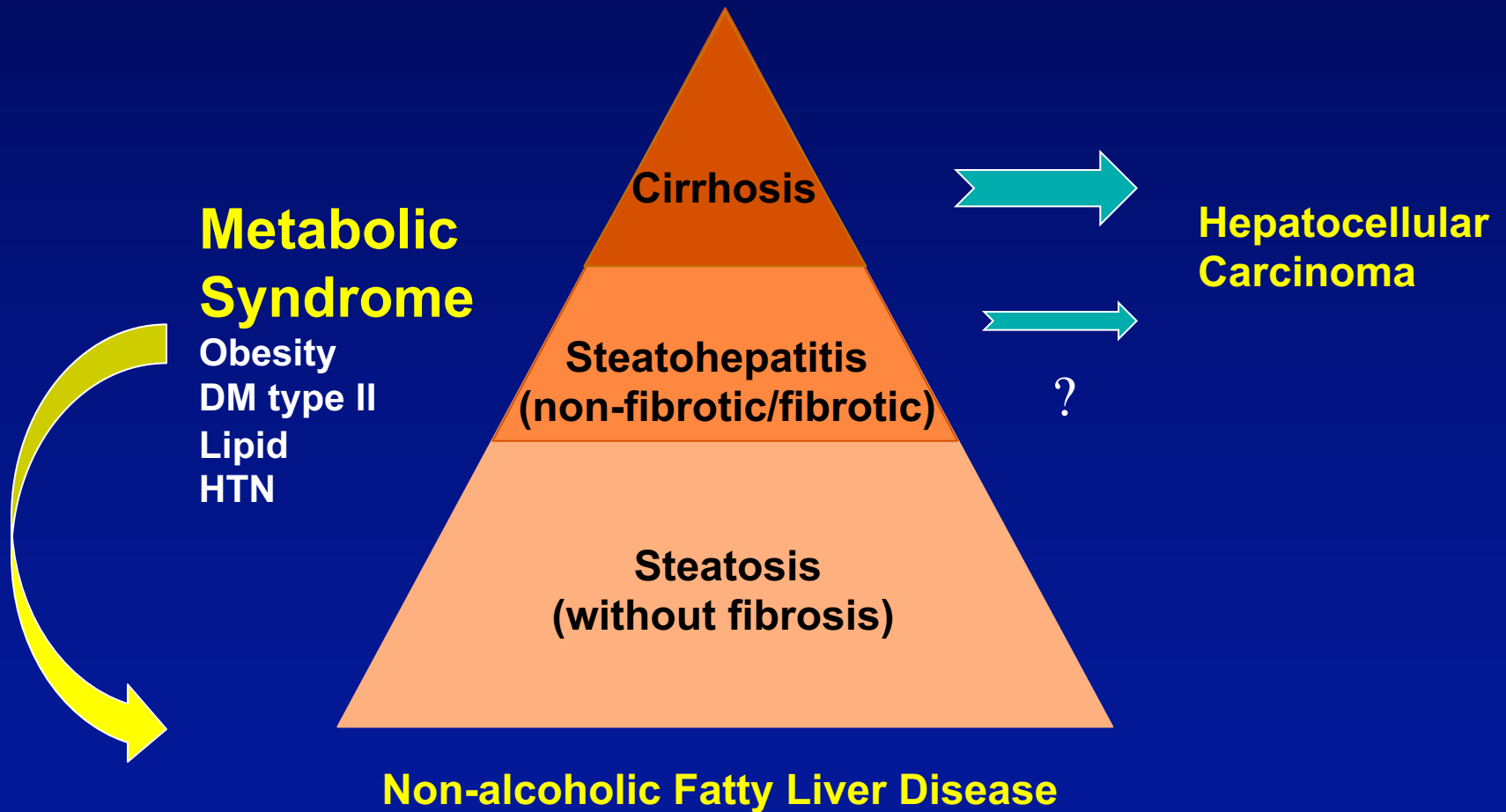
Hepatitis B

CIRRHOSIS

LIVER CANCER (HCC)



METABOLIC SYNDROME/ NAFLD AND HCC



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

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**

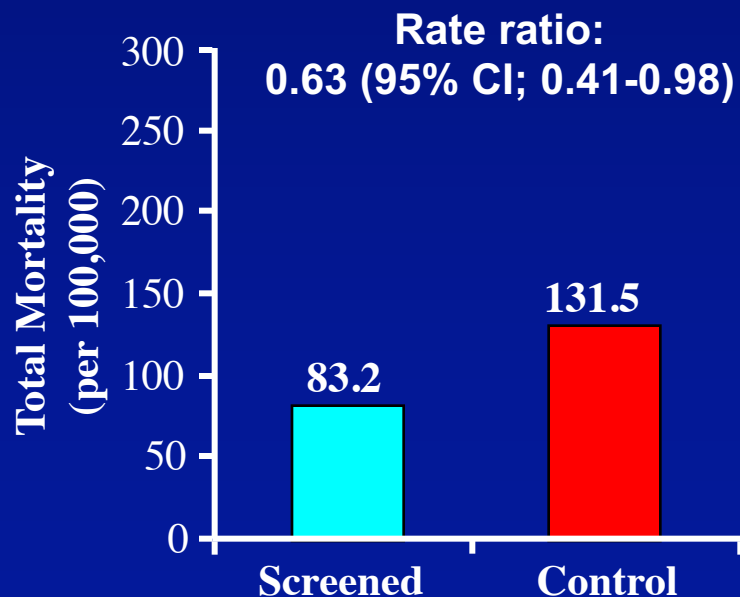
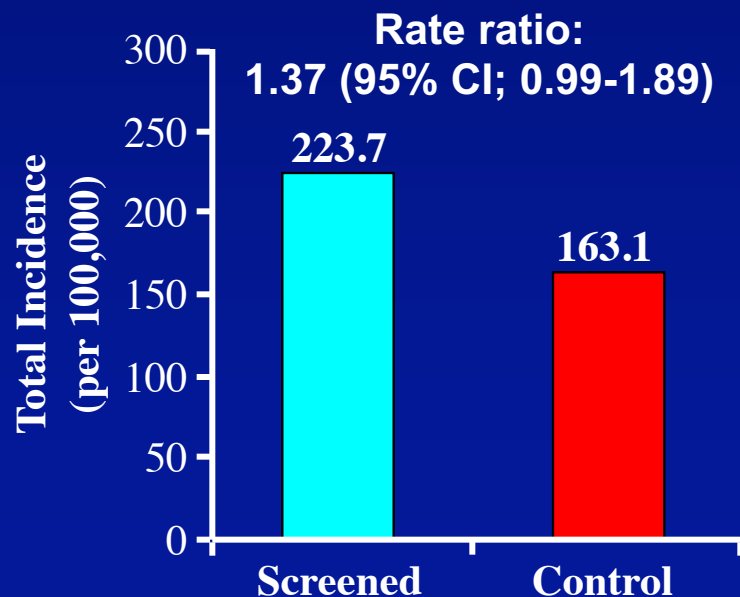
Welzel TM et al. Hepatology 2011;54:463-471

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.

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



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

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

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
 - 4) Active replication (HBV DNA+) and or active necro-inflammatory activities

HCC Surveillance in non-HBV cirrhosis

- HCC surveillance is recommended for nearly all patients with cirrhosis
- Insufficient evidence to suggest surveillance before development of cirrhosis (except HBV)
- The risk of HCC with HCV-related cirrhosis who are cured with the new anti-viral drugs (e.g. Harvoni) is lowered, but not eliminated
 - These pts should continue to undergo surveillance

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

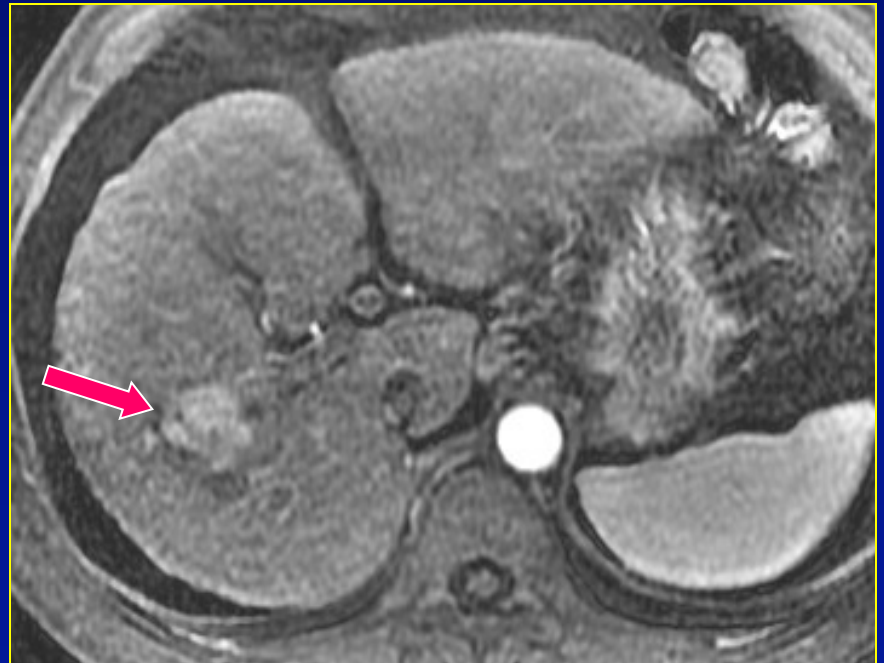
Tumor seeding along the biopsy tract in <1-2%

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

MICROWAVE/RADIOFREQUENCY ABLATION

Choice of treatment based on location and size

**Ideal location for
Percutaneous RFA**



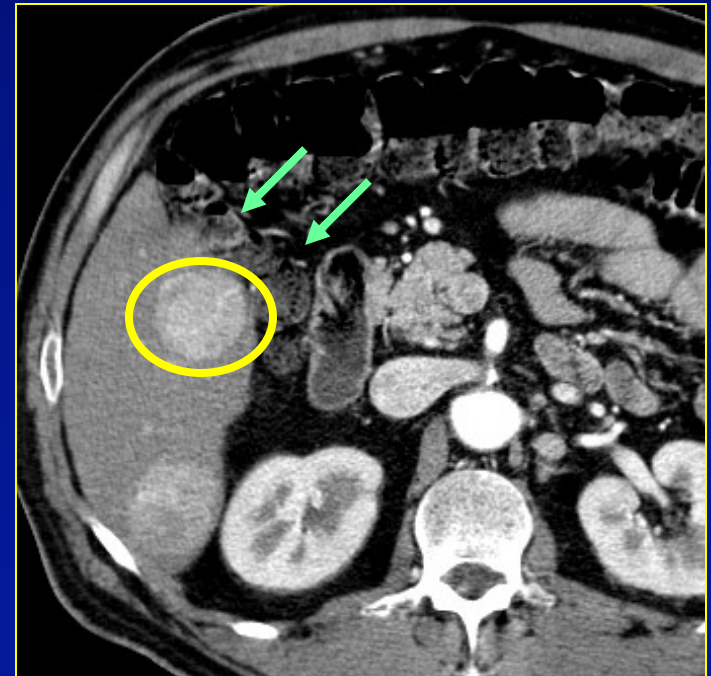
MICROWAVE/RADIOFREQUENCY ABLATION

Limitations of percutaneous RFA – Tumor location

Adjacent to diaphragm



Adjacent to bowel



MICROWAVE/RADIOFREQUENCY ABLATION

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

