2016 Northern CA Society for Clinical GI: Post-AASLD Symposium

Hepatocellular Carcinoma Management

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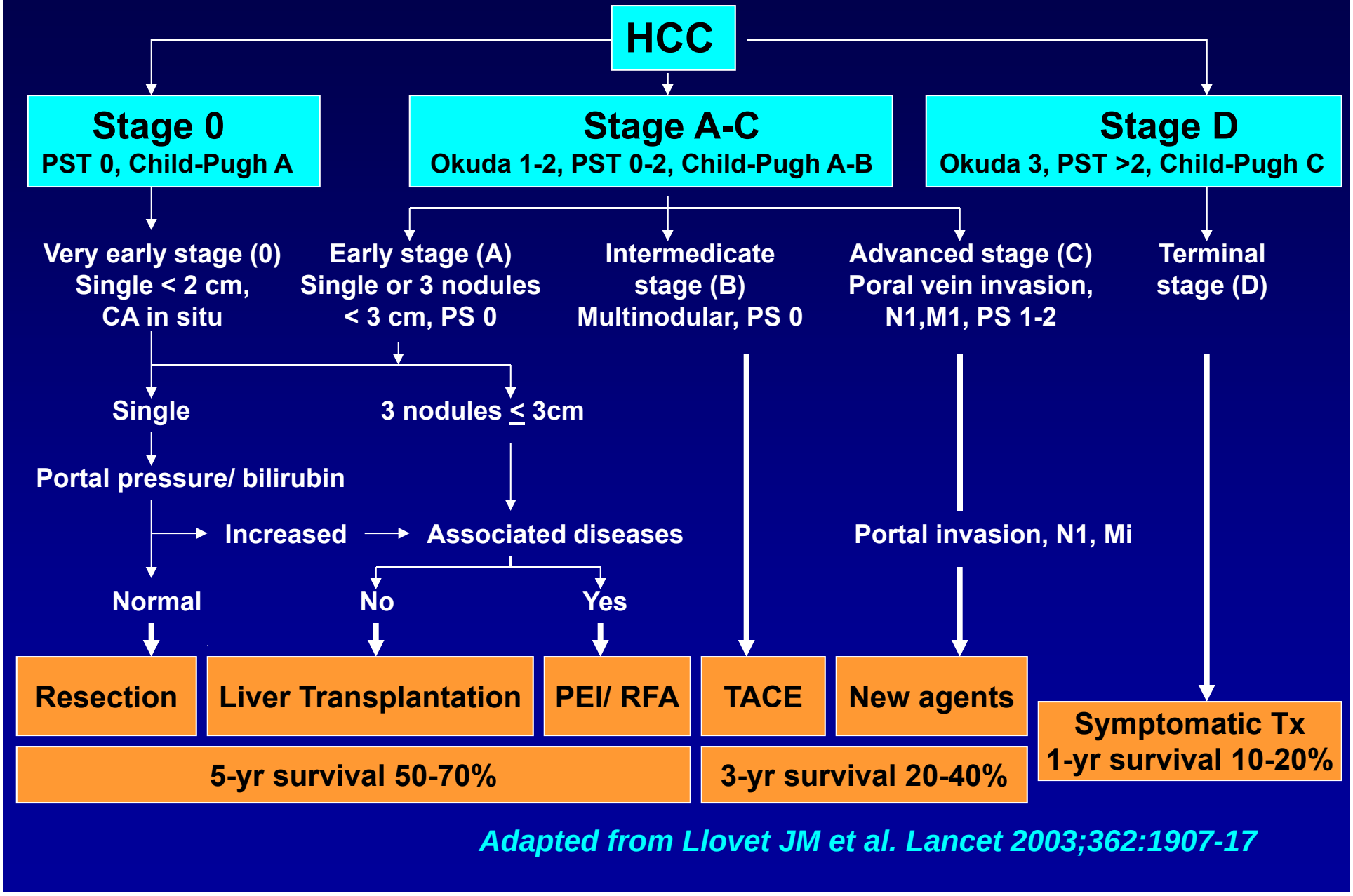
12/10/16

UCSF Division of Gastroenterology and Hepatology

OVERVIEW

- Current state of liver transplantation (LT) for HCC
  - Refining selection criteria for LT
  - Updates in down-staging outcomes
  - Proposed UNOS policy changes
  - HCV: Should we treat before LT??
- Updates in chemo- and immunotherapy

BCLC STAGING CLASSIFICATION



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

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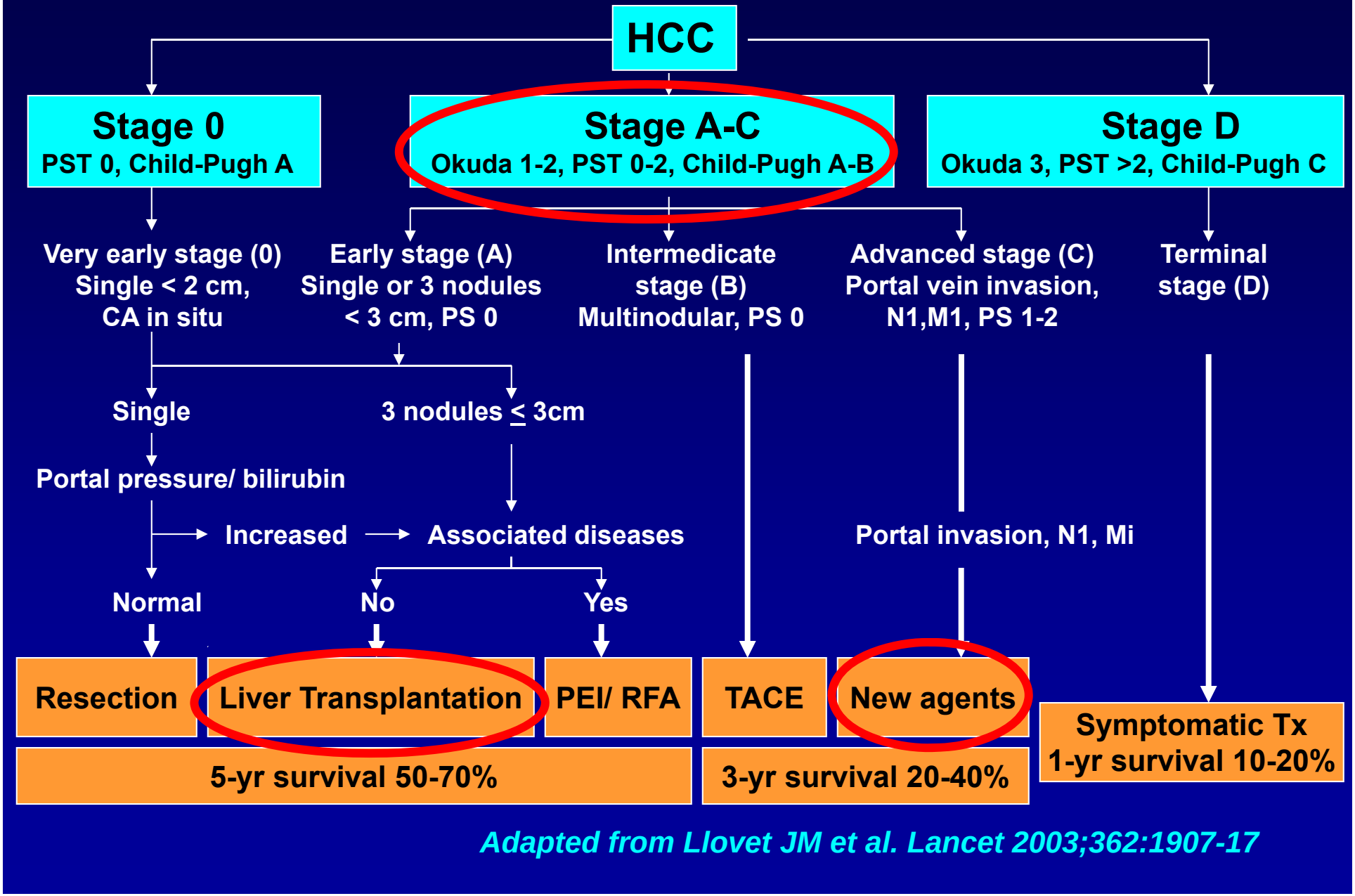

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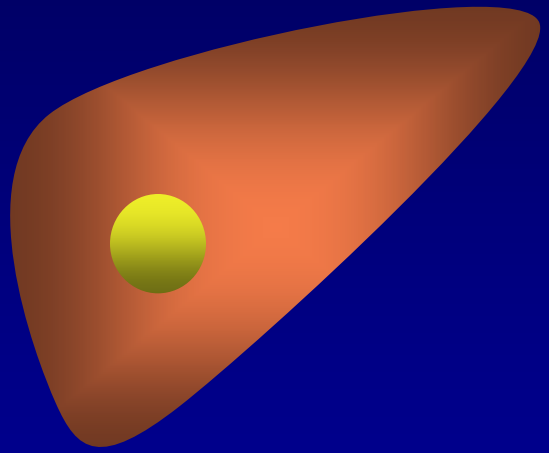
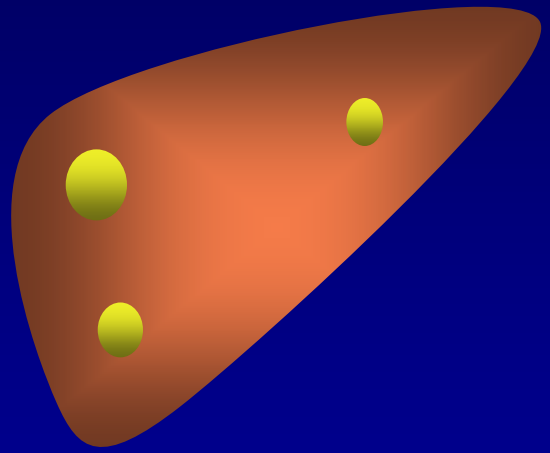
LIVER TRANSPLANTATION FOR HCC
MILAN CRITERIA

1 lesion ≤ 5 cm



2 to 3, none > 3 cm



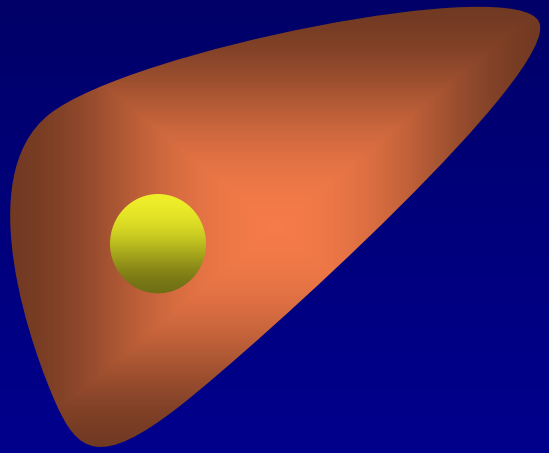
+

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
T2 CRITERIA

1 lesion 2-5 cm



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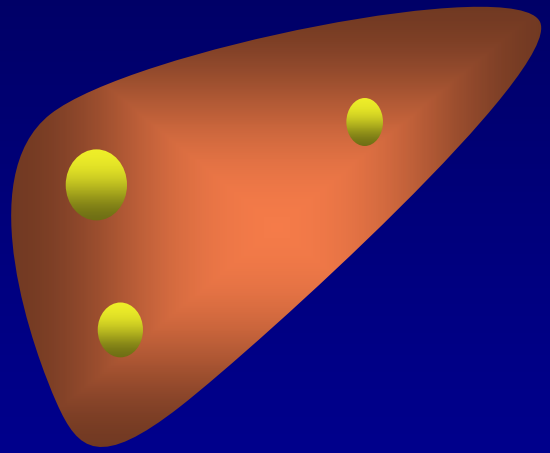

Post-LT

5 year survival: 70-80%

5 year HCC recurrence: ~15%

LIVER TRANSPLANT FOR HCC: RECENT CHANGES

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

LIVER TRANSPLANT FOR HCC: RECENT CHANGES

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  - Only pts w/ T2 HCC and LI-RADS 5 lesions are eligible to receive priority listing
    - LI-RADS 5: Definite HCC
    - LI-RADS 4: Probable HCC
    - LI-RADS 3: Indeterminate

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	LIRADS 3	LIRADS 3	LIRADS 3	LIRADS 3	LIRADS 4
	One	LIRADS 3	LIRADS 4	LIRADS 4	LIRADS 4	LIRADS 5
	≥ Two	LIRADS 4	LIRADS 4	LIRADs 4	LIRADS 5	LIRADS 5

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LIVER TRANSPLANT FOR HCC: RECENT CHANGES

- Uniform diagnostic criteria (OPTN/ LIRADS) + standardized reporting
- 6-month mandatory waiting period before MELD exception of 28
- Cap at MELD of 34

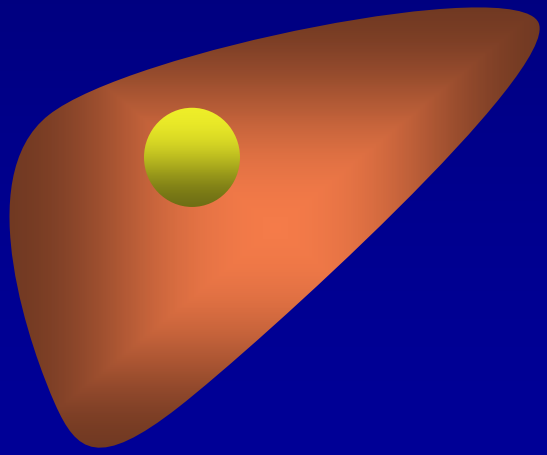
DELAYED HCC-MELD EXCEPTION SCORE

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 TRANSPLANTATION FOR HCC: OPTIMIZING SELECTION CRITERIA

Scenario: Your patient with a 3.5 cm HCC is at the top of the wait list and is expecting a liver offer at any time. Today in clinic he asks you what his expected outcomes are after transplant.



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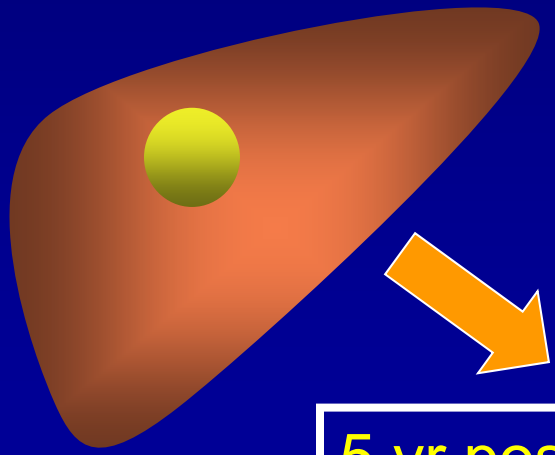

5 yr post-LT survival: 75-80%
5 yr HCC recurrence: ~15%

LIVER TRANSPLANTATION FOR HCC: OPTIMIZING SELECTION CRITERIA

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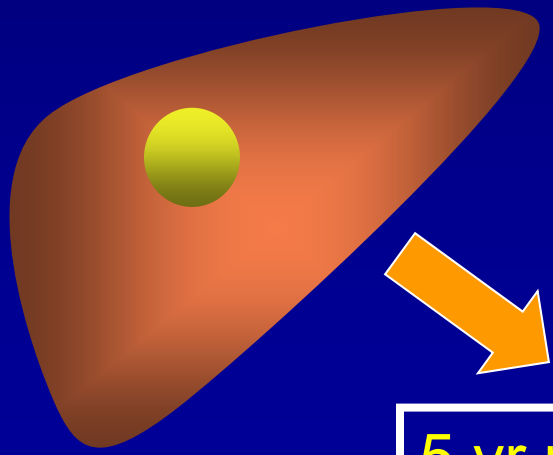
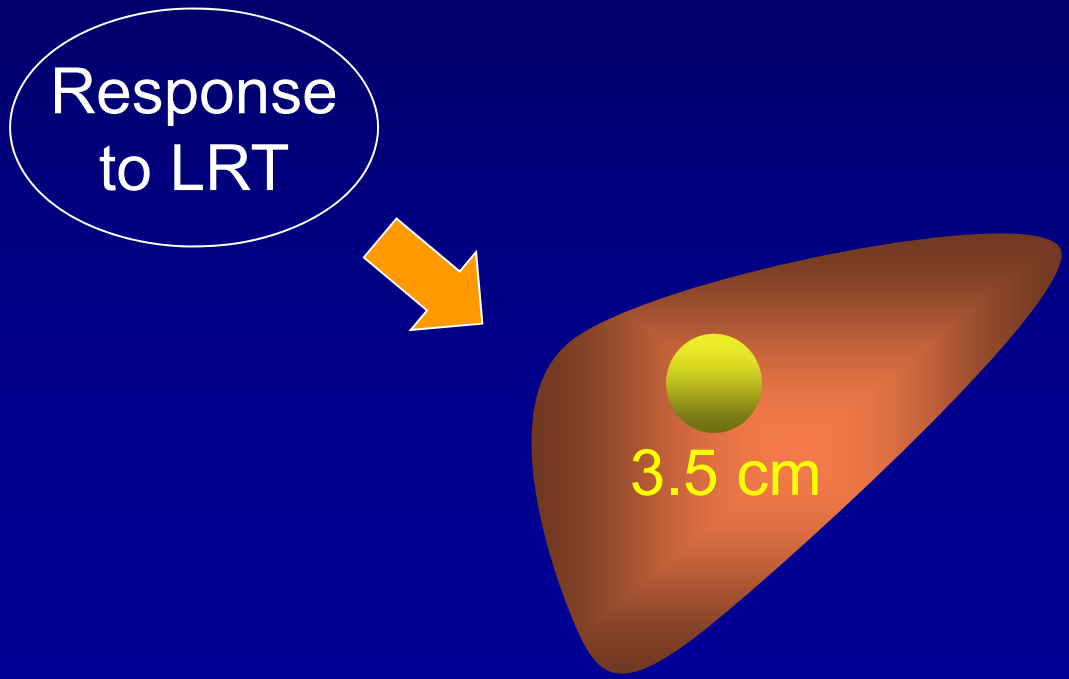


5 yr post-LT survival: ???
5 yr HCC recurrence: ???

LIVER TRANSPLANTATION FOR HCC: OPTIMIZING SELECTION CRITERIA



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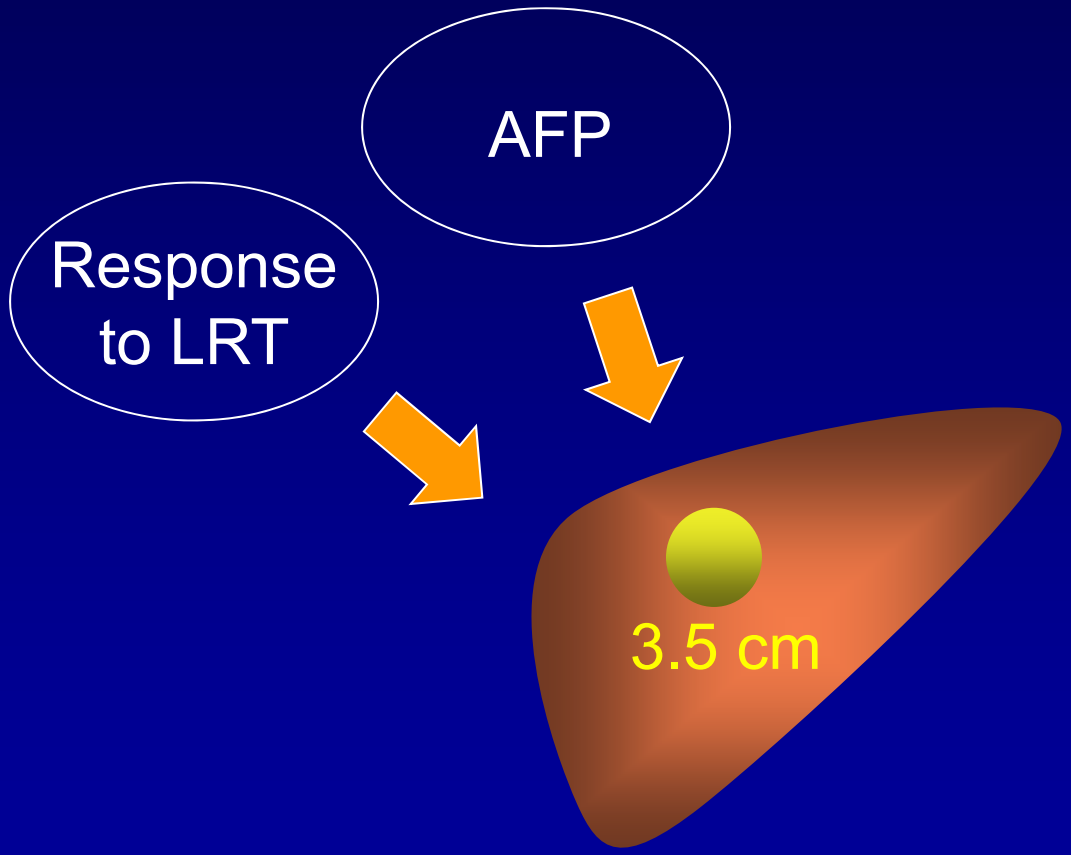

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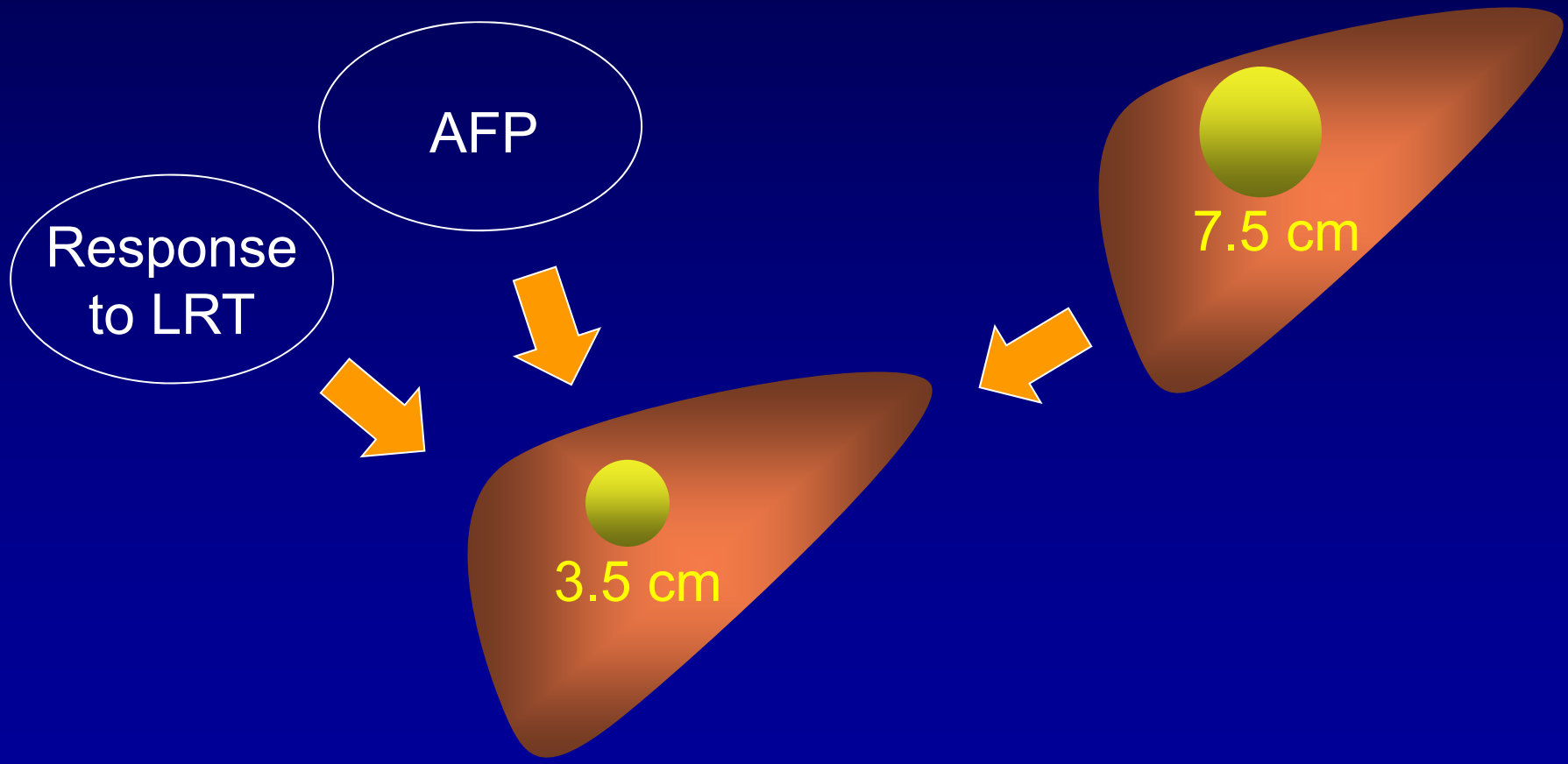

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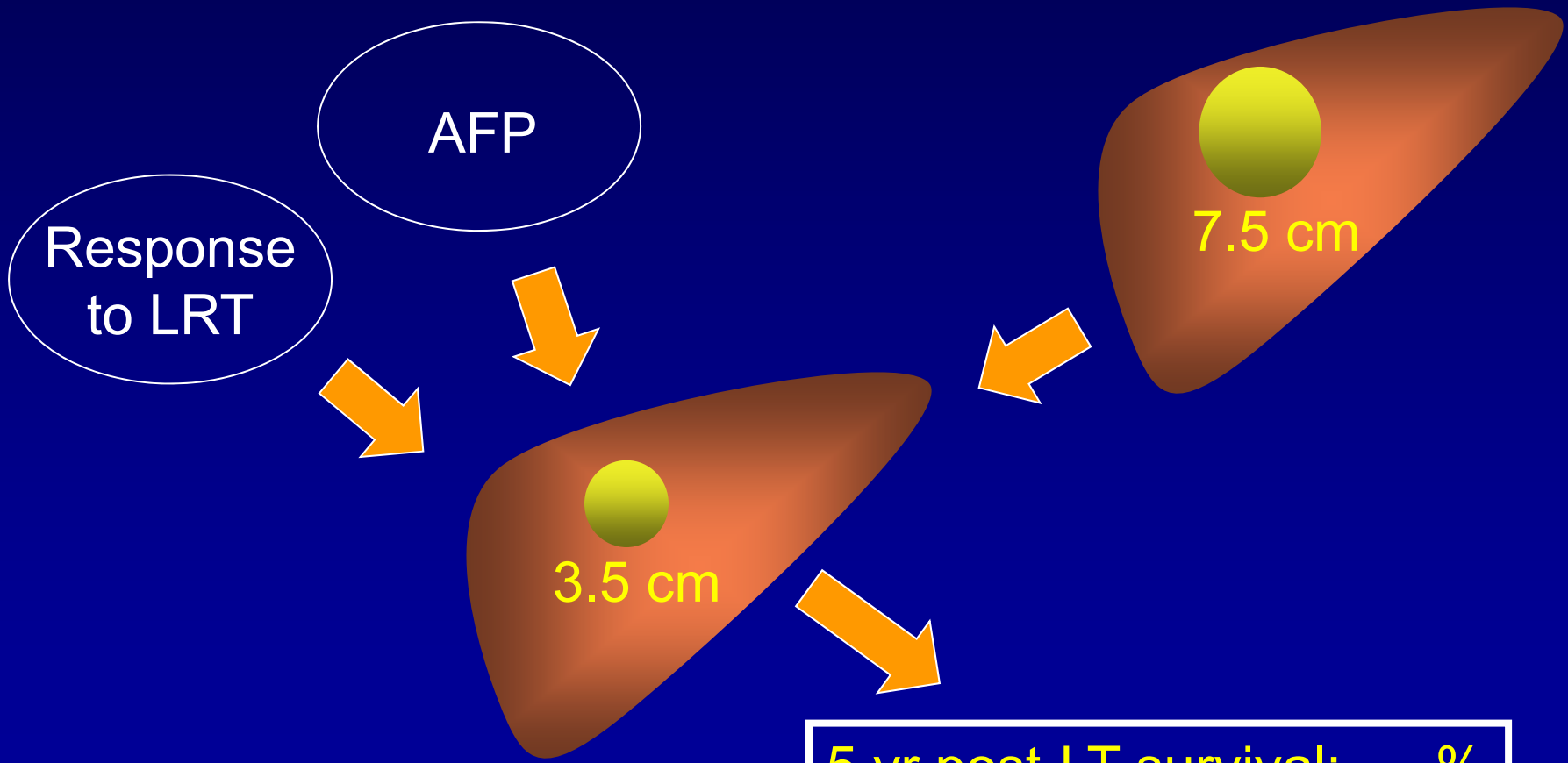
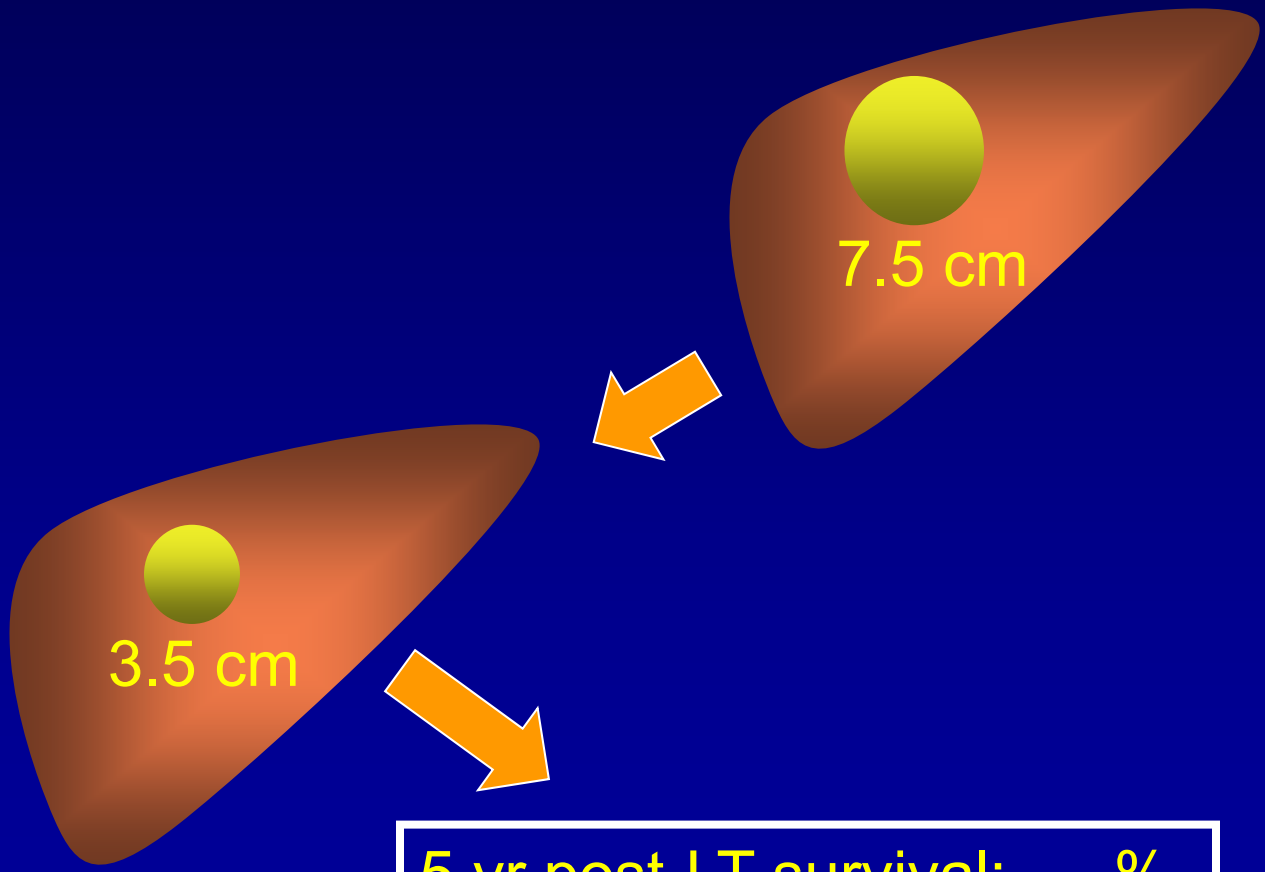


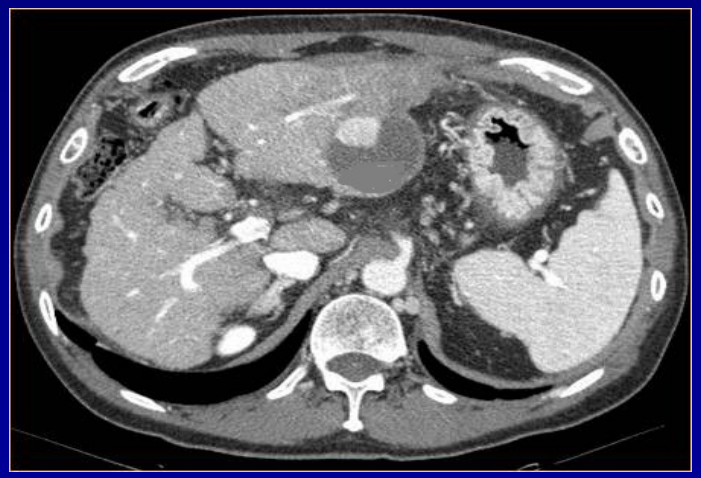
LIVER TRANSPLANTATION FOR HCC: DOWNSTAGING

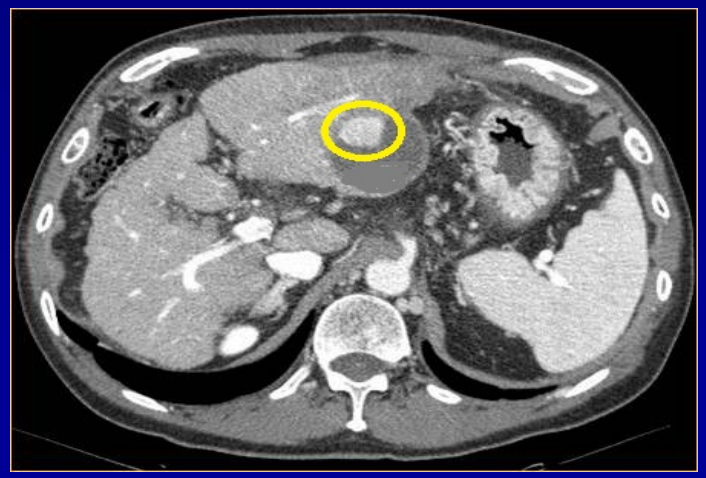


5 yr post-LT survival: __%
5 yr HCC recurrence: __%

DOWN-STAGING

- Down-staging: Reduction in the size of tumor(s) using LRT to meet acceptable LT criteria
- Tumor response to down-staging treatment is based on radiographic measurement of the size of viable tumors





Yao FY, et al, Liver Transpl 2011; Ravaioli et al. Am J Transpl 2008; Pomfret et al. Liver Transplant 2010; Bruix, J et al EASL Practice Guidelines, J Hepatology 2012

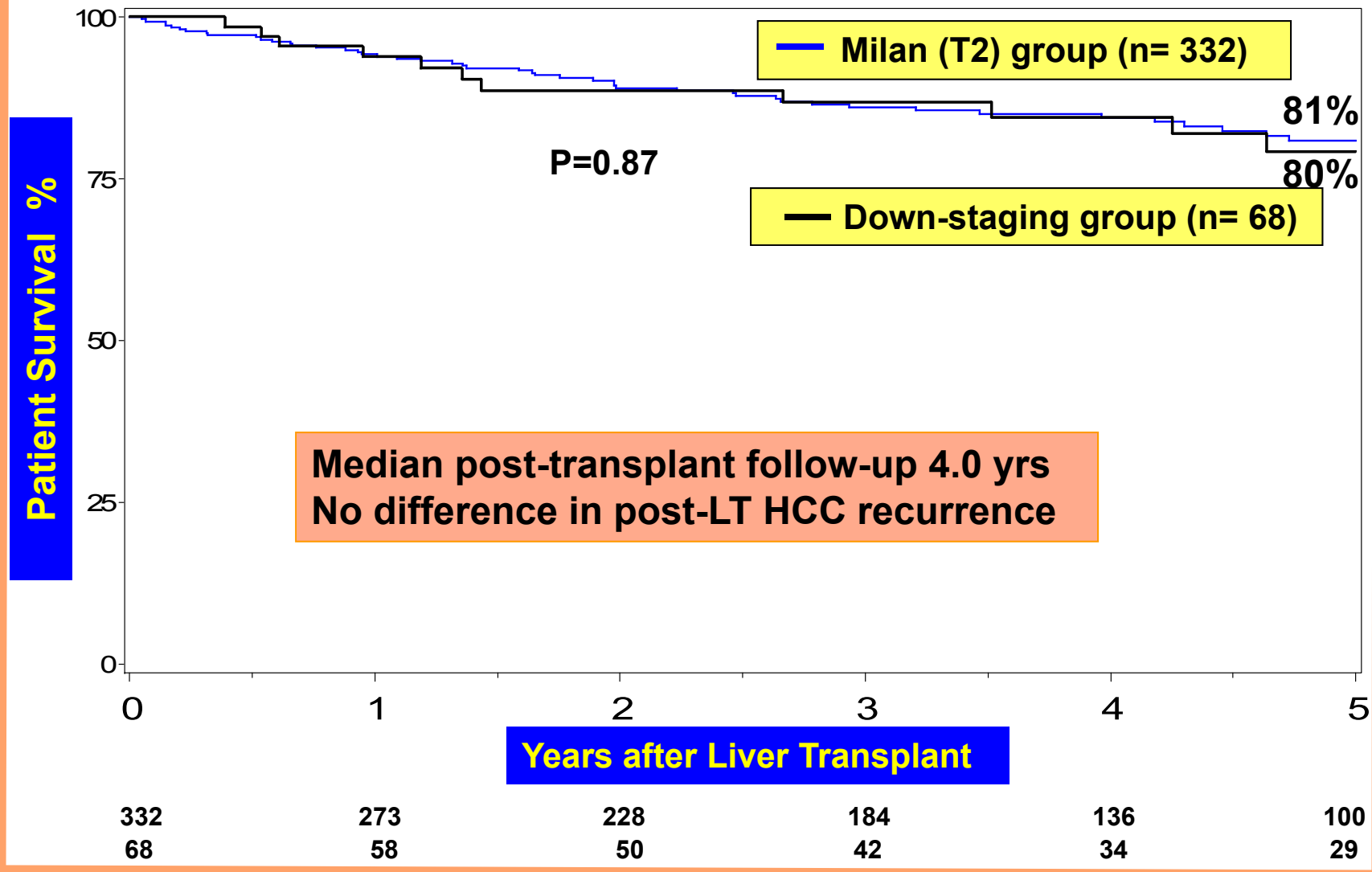
REGION 5
DOWN-STAGING PROTOCOL

- 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

- Candidates can undergo deceased-donor LT 3 months after down-staging if within Milan criteria

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

POST-TRANSPLANT SURVIVAL



Yao et al. Hepatology 2015; 1968-77

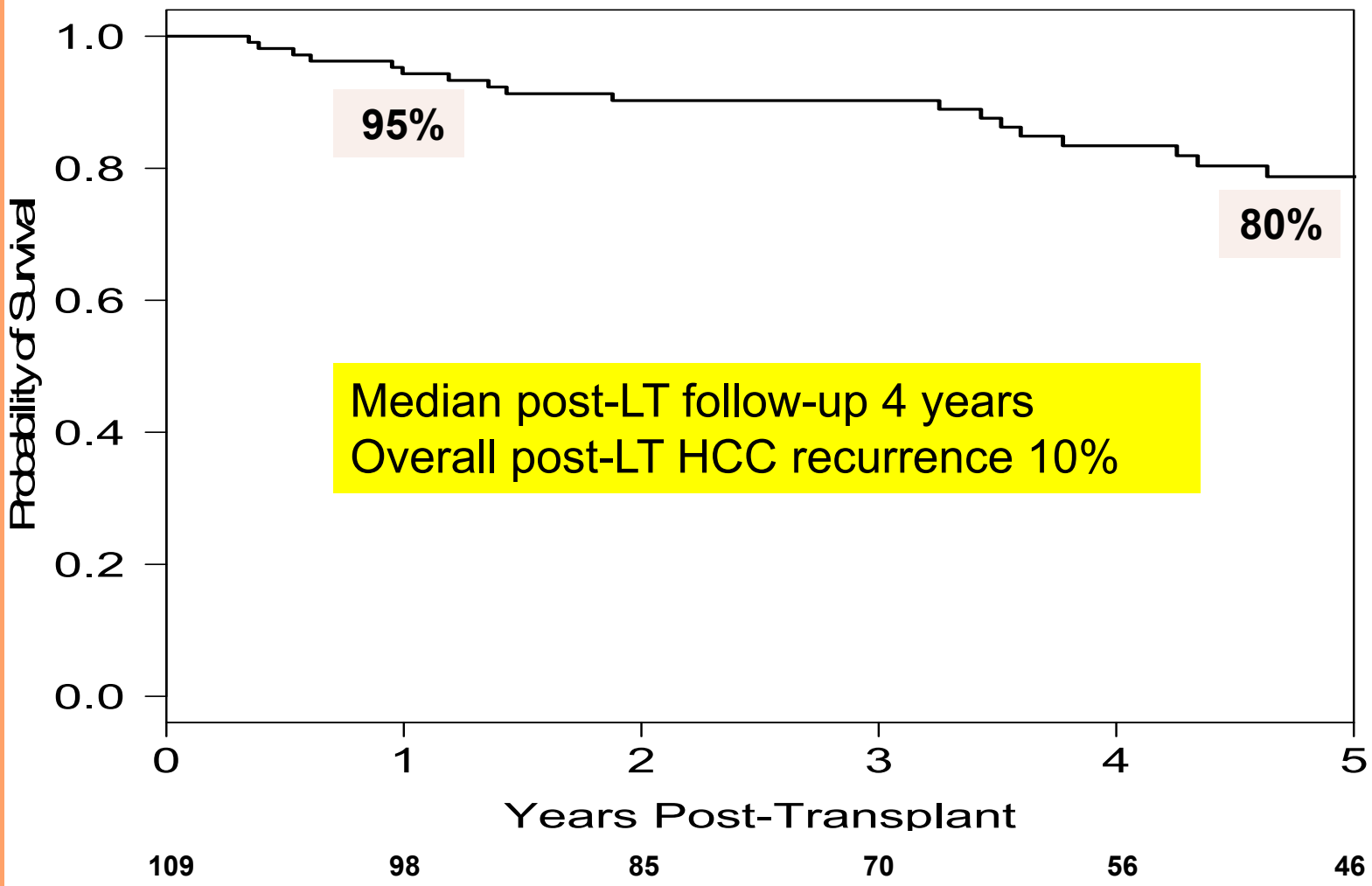
REGION 5 DOWN-STAGING RESULTS

- 187 patients at UCSF, CPMC, and Scripps
- Successful down-staging: residual tumor(s) within Milan criteria

- 58% underwent LT a median of 13 months from 1st down-staging procedure
- Favorable explant characteristics
    - 81% within Milan
    - 6% microvascular invasion
    - 1% poorly differentiated tumor grade

Mehta N et al. Hepatology 2014; 60 (Suppl):253A (AASLD 2014)

POST-TRANSPLANT SURVIVAL



Mehta et al. AASLD 2014

PROPOSED UNOS POLICY CHANGES

Down-staging

- Candidates that meet the Region 5 down-staging protocol and then complete LRT must be successfully down-staged into Milan criteria to receive a MELD exception

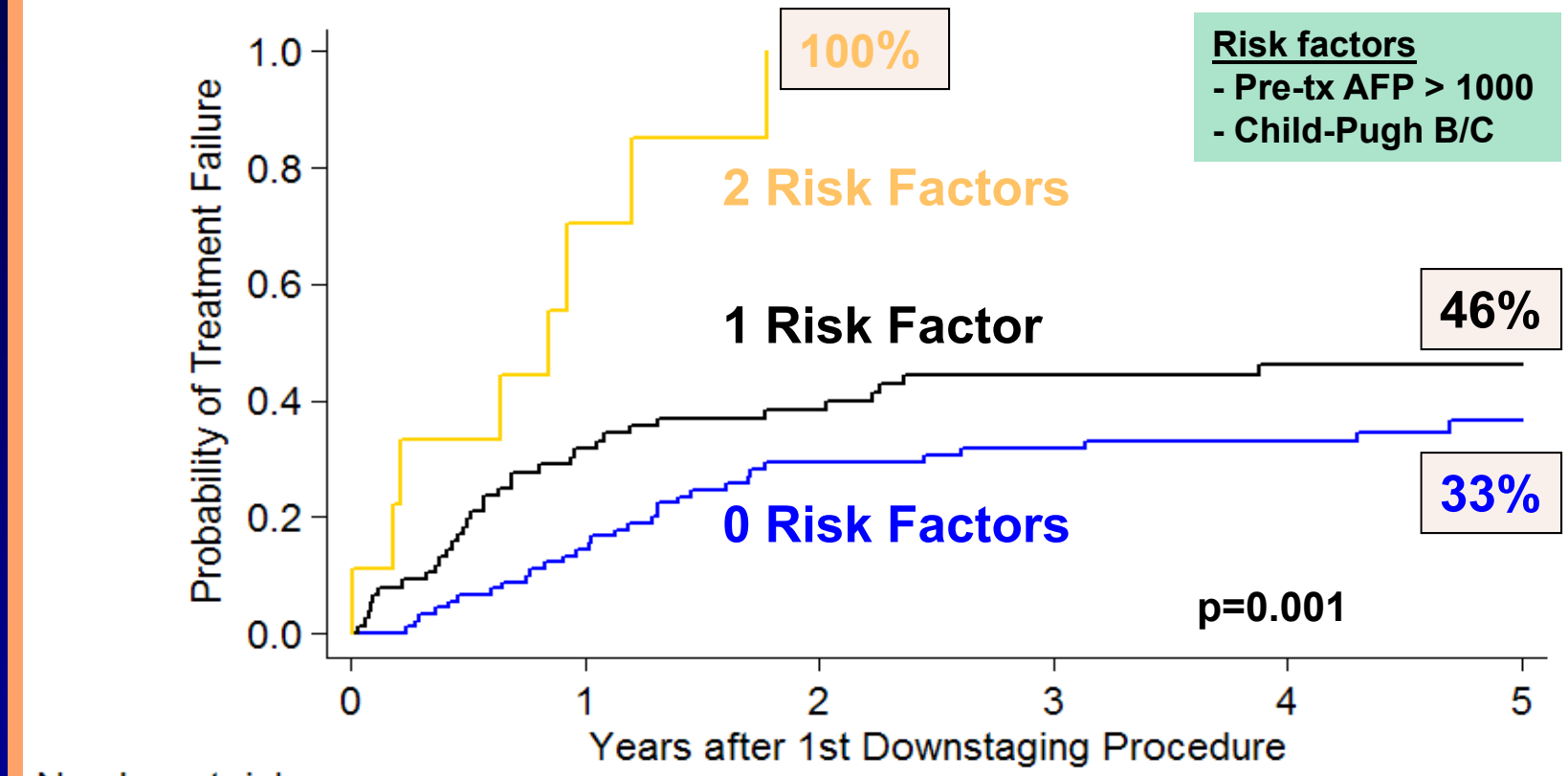
TREATMENT FAILURES

- ***Can we better refine our selection criteria for entry into the down-staging protocol by looking at our treatment failures?***

- Treatment failure defined as dropout due to tumor progression, liver-related death without LT, or post-LT HCC recurrence

Mehta N et al. AASLD 2015

TREATMENT FAILURE: AFP AND CHILD-PUGH



Number at risk						
No risk factors	91	76	60	54	44	30
1 risk factor	76	51	42	35	29	23
2 risk factors	9	2	0	0	0	0

Mehta N et al. AASLD 2015

UPDATED DOWN-STAGING PROTOCOL

Consortium expansion

- Region 5: UCSF, CPMC, Scripps, Stanford

- Region 2: U Pennsylvania
- Region 6: Oregon Health & Science (OHSU), Swedish
- Region 10: Michigan

UPDATED DOWN-STAGING PROTOCOL

Exclusion criteria

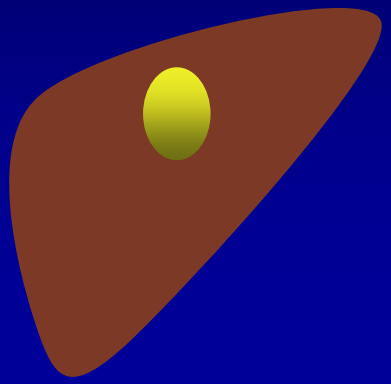
- AFP > 1000 ng/ml + Child's B or C cirrhosis
- Total bilirubin ≥ 4 mg/dL
- Medical or psychosocial contraindications to liver transplant

BEYOND DOWN-STAGING CRITERIA?

- What about patients whose tumor burden exceeds even the Region 5 down-staging protocol?

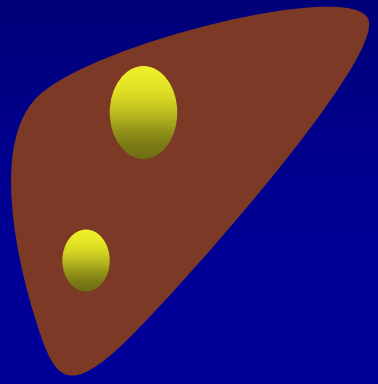
- **Is there an upper limit of tumor burden beyond which LT is a bad idea?**

HCC Transplant Criteria @ UCSF



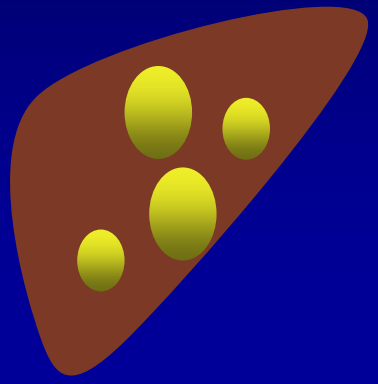
MILAN CRITERIA

- 1 lesion ≤ 5 cm
- 2-3 lesions ≤ 3 cm
- No extra-hepatic dz



DOWNSTAGING CRITERIA

- 1 lesion 5.1-8cm
- 2-3 lesions ≤ 5 cm
- 4-5 lesions ≤ 3 cm
- TTD ≤ 8 cm
- No extra-hepatic dz



ALL-COMERS CRITERIA

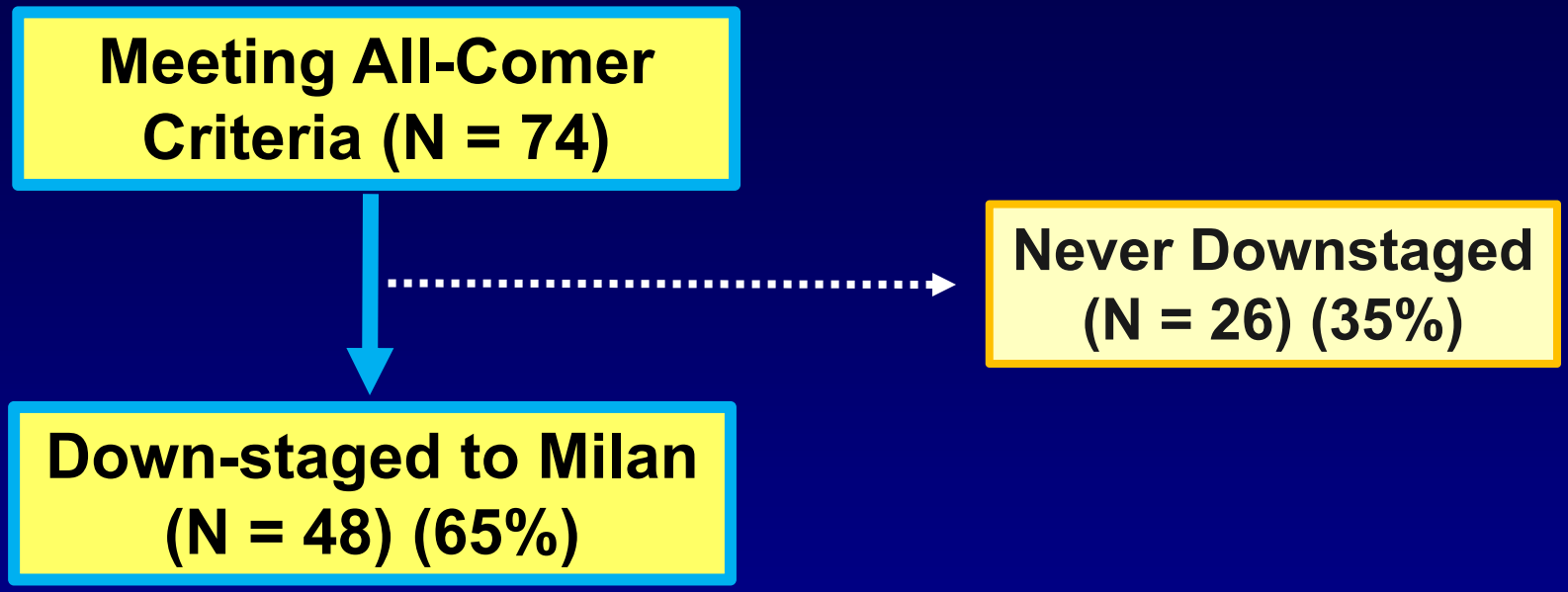
- Any number of tumors
- Total tumor burden beyond DS criteria
- No extra-hepatic dz

All-comers vs DS group Baseline Tumor Characteristics

	All-Comers N = 74	UCSF-DS N = 133	P-Value
Median MELD	10	10	0.69
Median AFP	24	22	0.42
Number of tumors at diagnosis (median, range)	3 (1 - 8)	2 (1 - 5)	< 0.01
Number of lesions + largest tumor diameter (median, range)	8.4 (6.3 - 16.0)	6.8 (5.2 - 9.0)	< 0.01
Largest tumor diameter of those with only 1 tumor (median, range)	12.0 (8.1 - 13.0)	6.3 (5.2 - 8.0)	< 0.01

Rassiwala J et al. AASLD 2016

All-comers group



Rassiwala J et al. AASLD 2016

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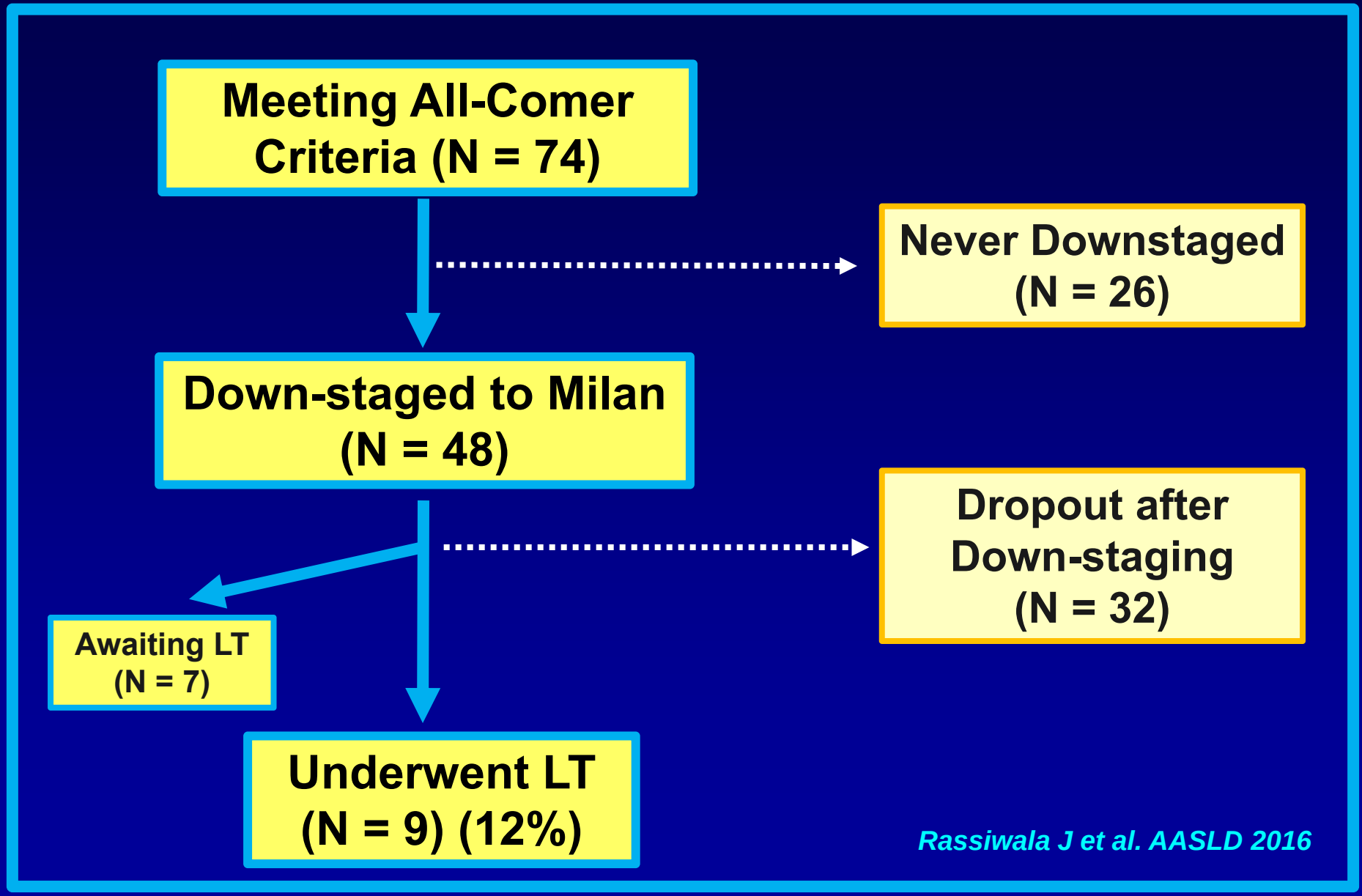
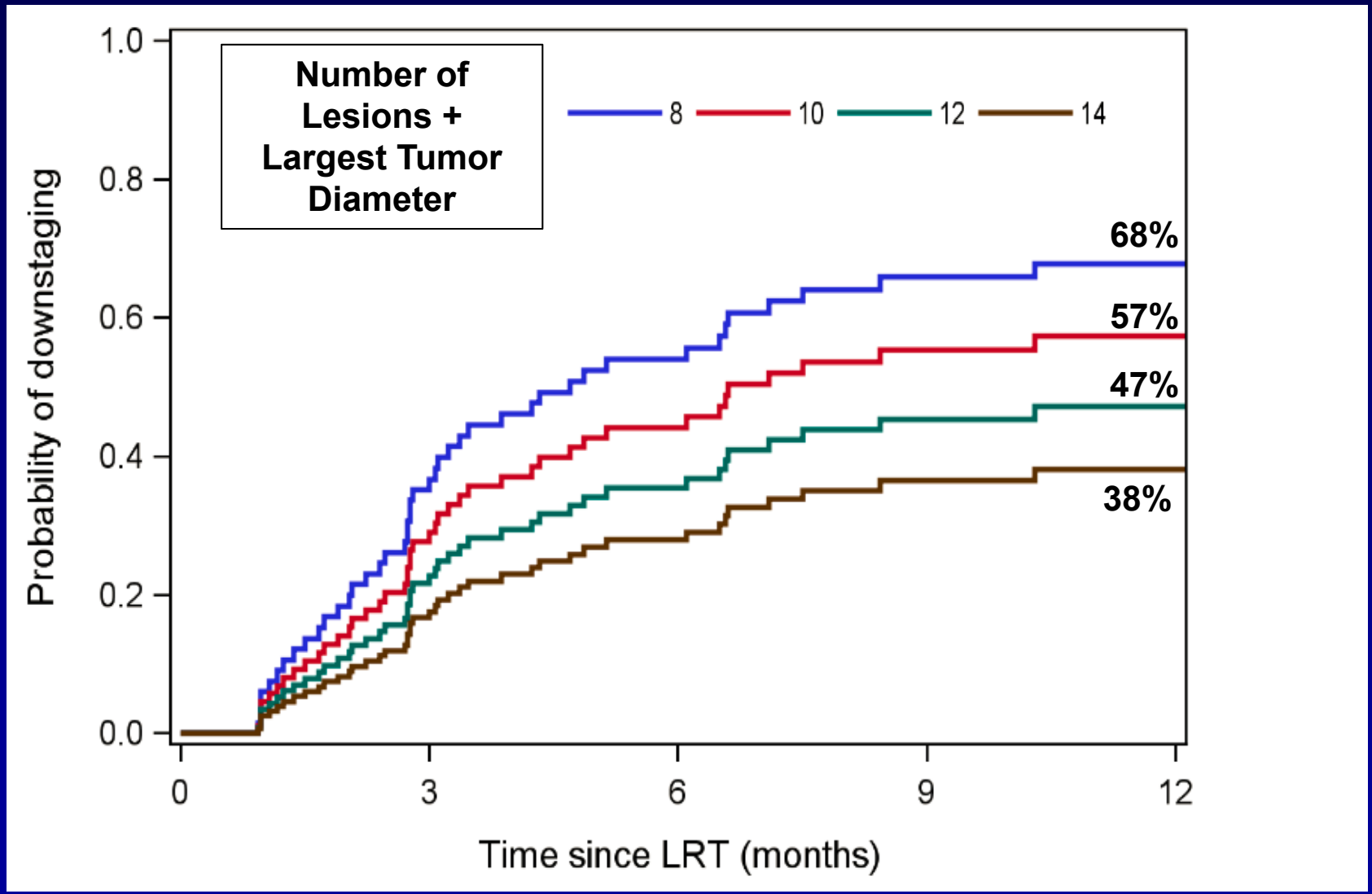


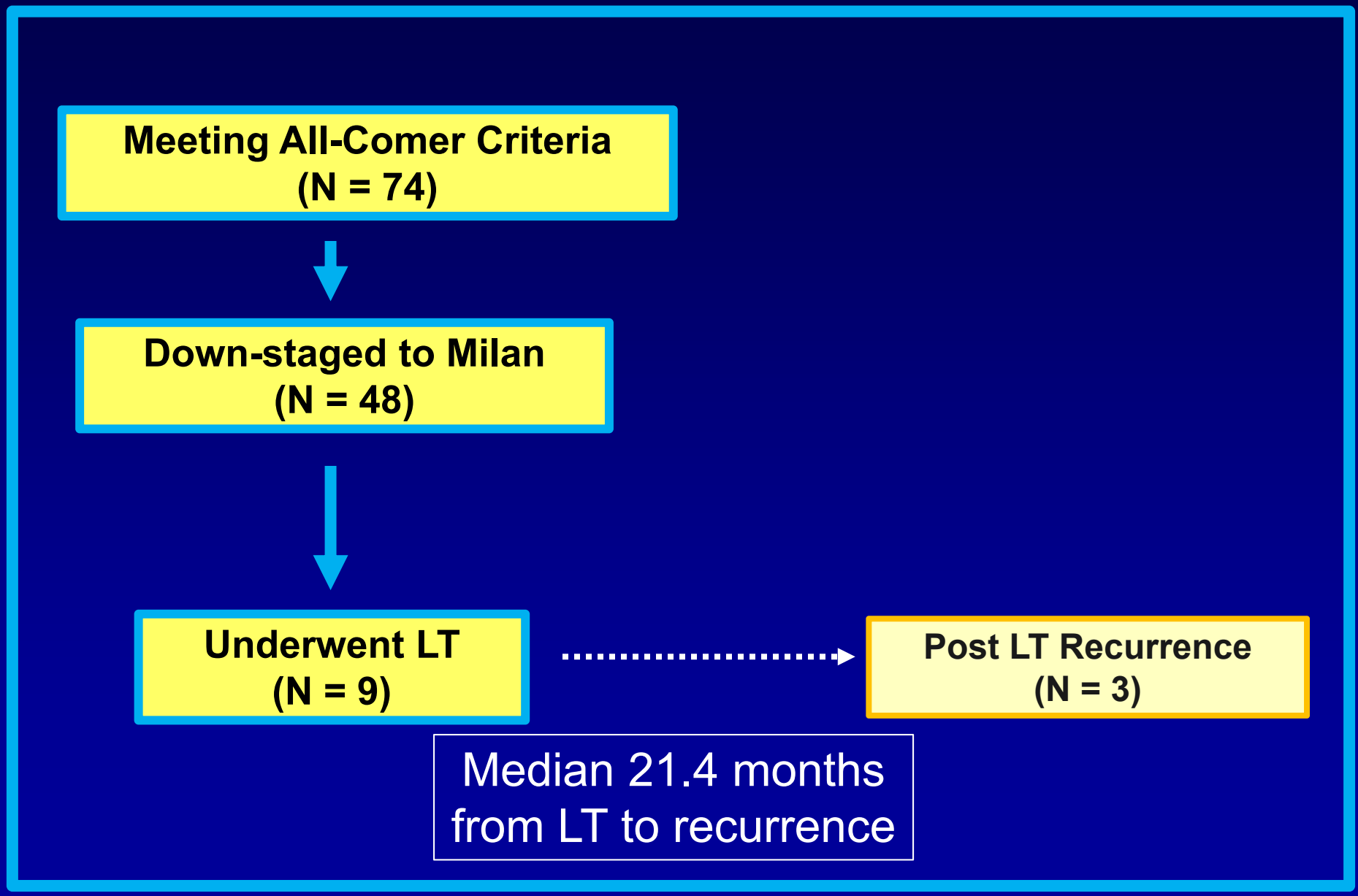
Rassiwala J et al. AASLD 2016

Probability of Downstaging by Initial Tumor Burden

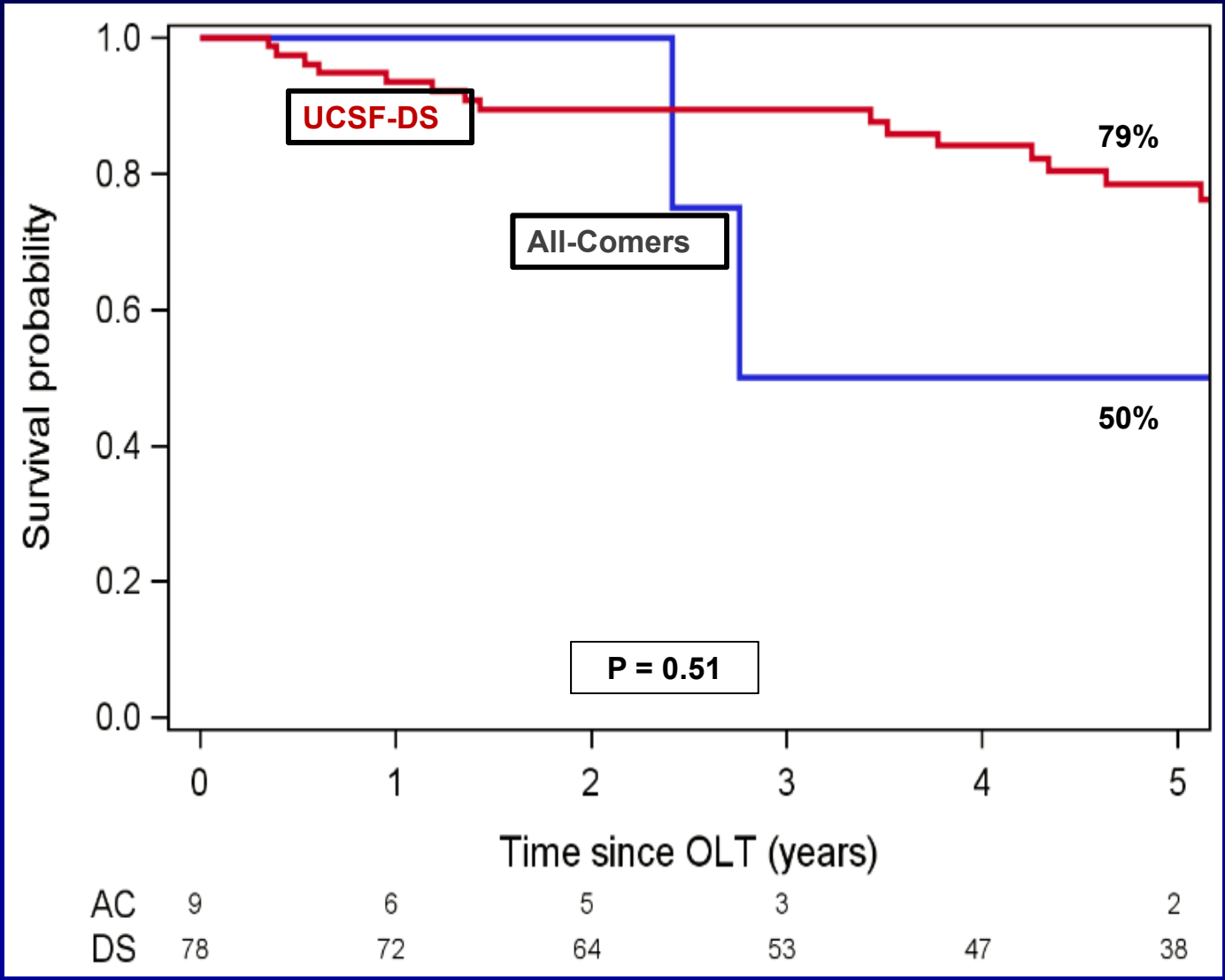


Rassiwala J et al. AASLD 2016

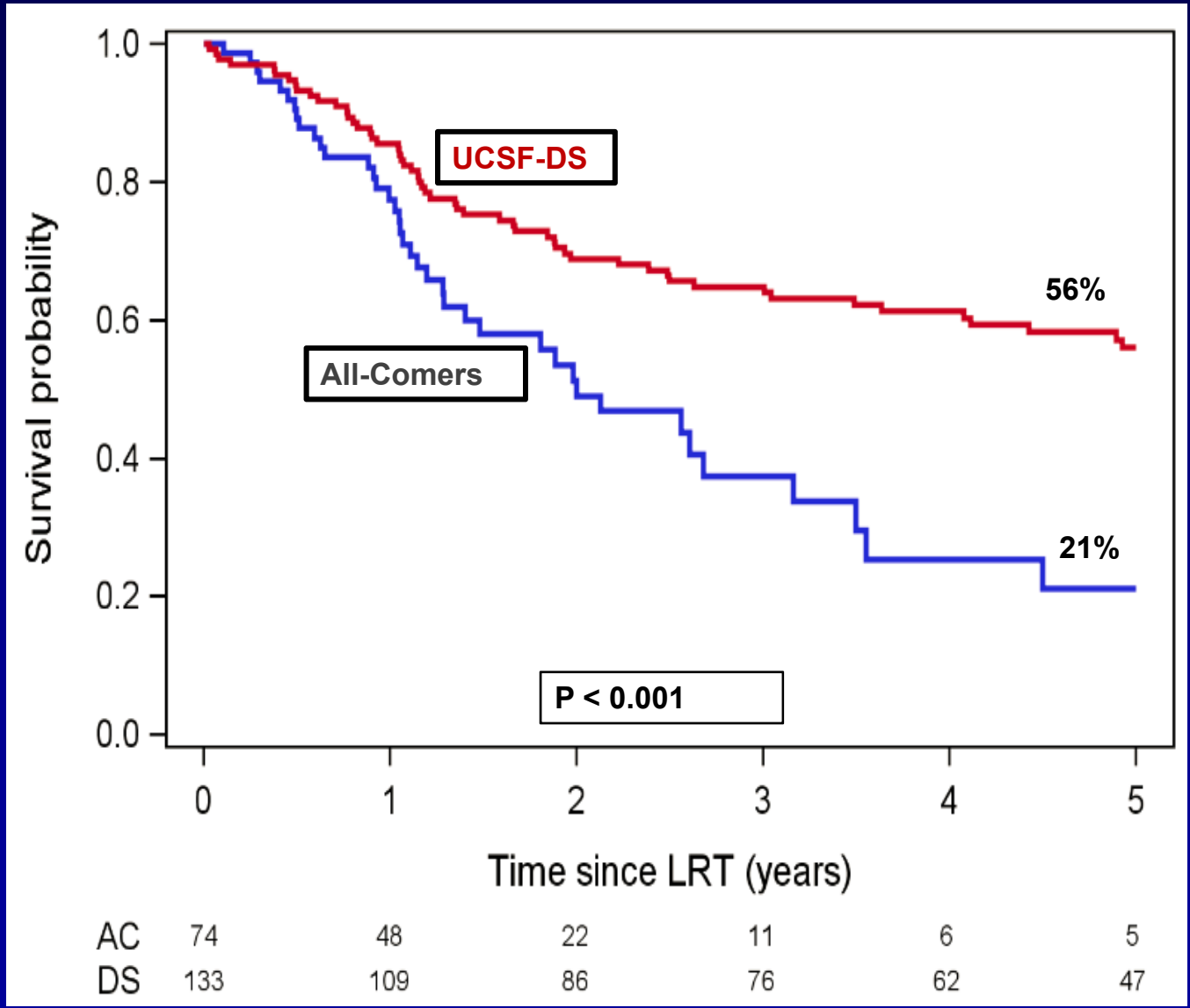
HCC Recurrence (All-comers group)



Post-Transplant Survival



Intention-to-Treat Survival



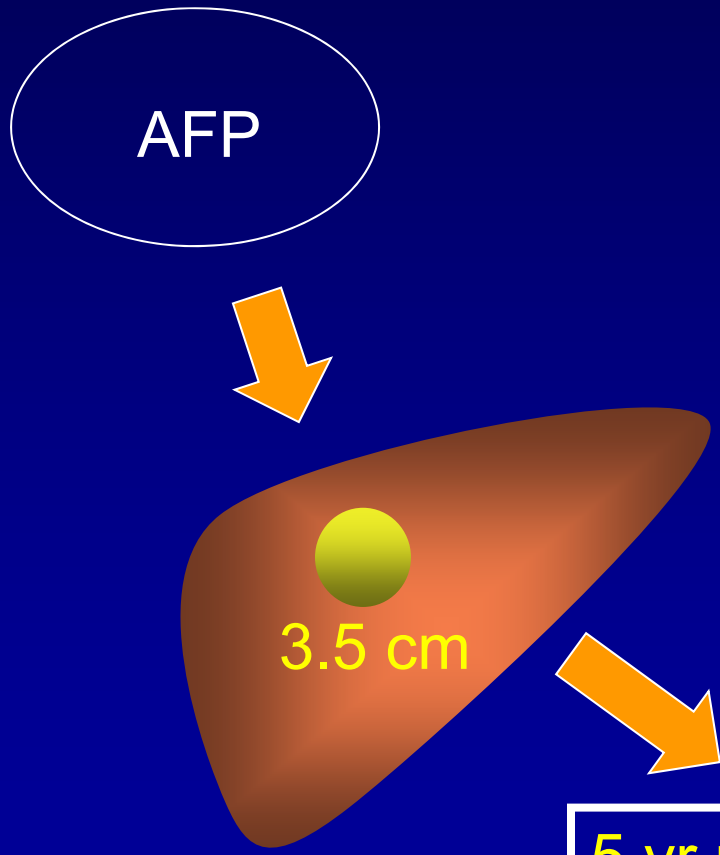
All-comers Summary

- An upper limit in tumor burden probably exists beyond which successful LT after down-staging becomes an unrealistic goal

- Patients with tumor burden exceeding the Region 5 down-staging criteria must be very carefully selected for any consideration of LT

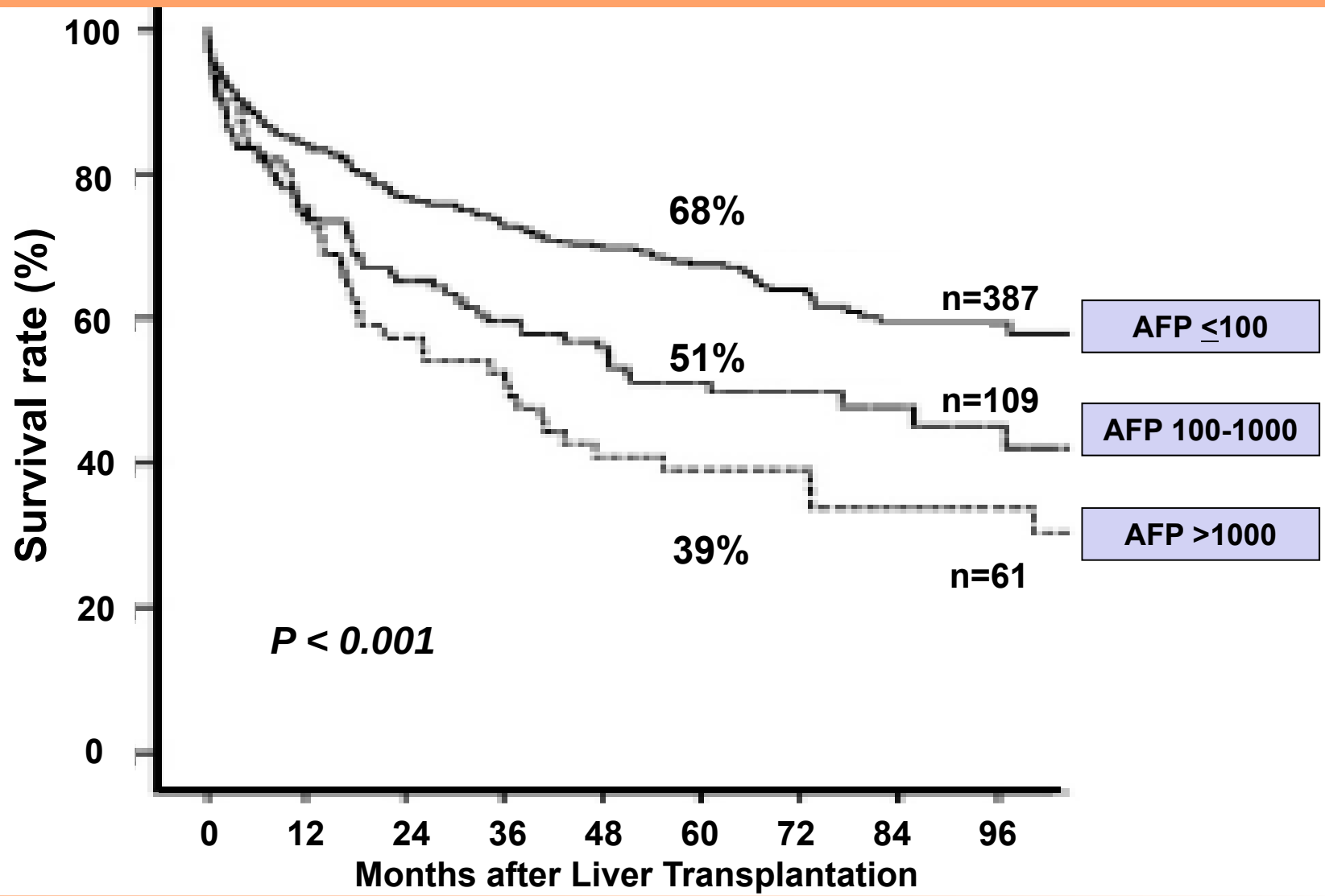
Rassiwala J et al. AASLD 2016

LIVER TRANSPLANTATION FOR HCC: AFP



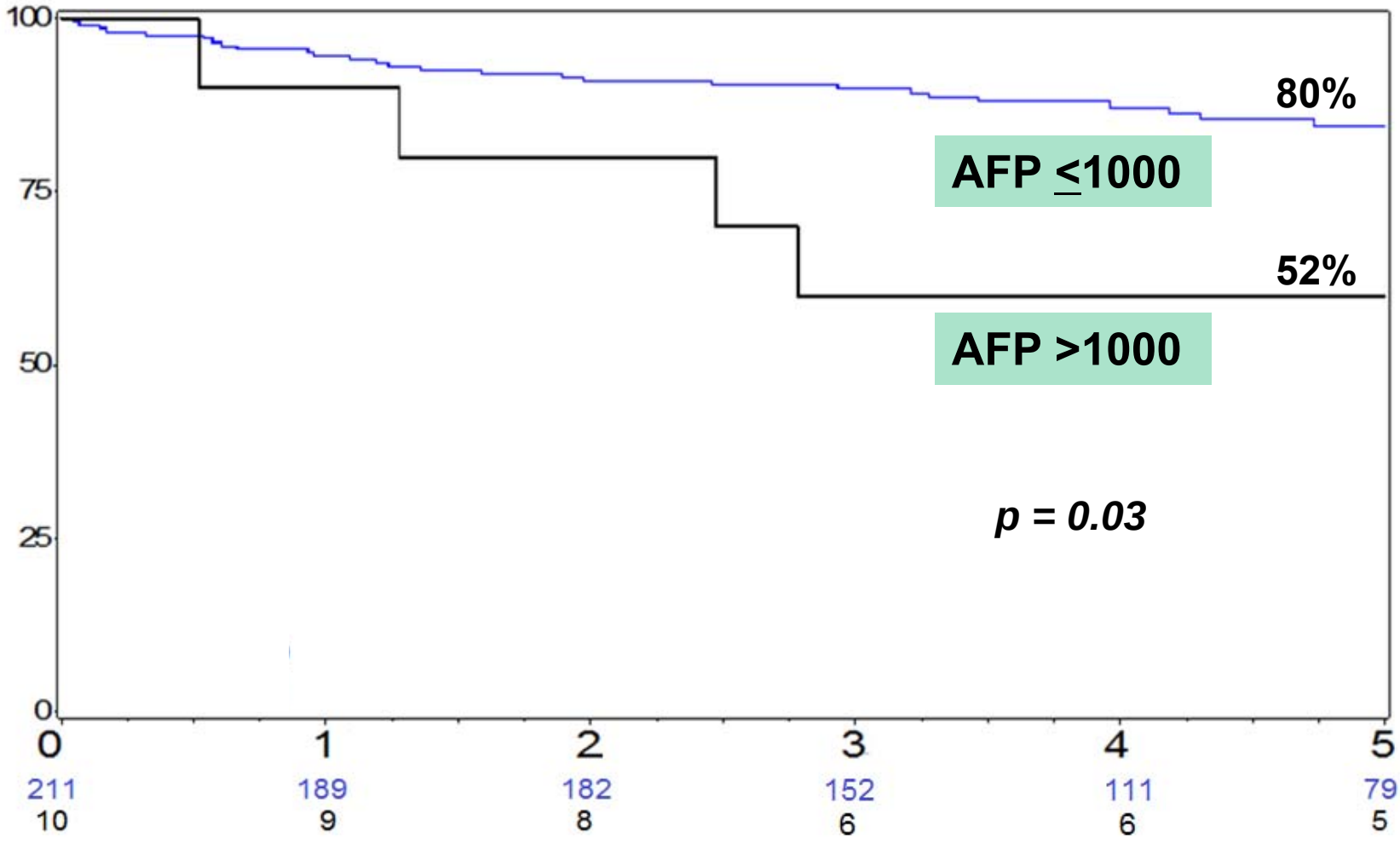
5 yr post-LT survival: __%
5 yr HCC recurrence: __%

AFP and Post-transplant Outcome- France



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

AFP and Post-transplant Outcome - UCSF



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

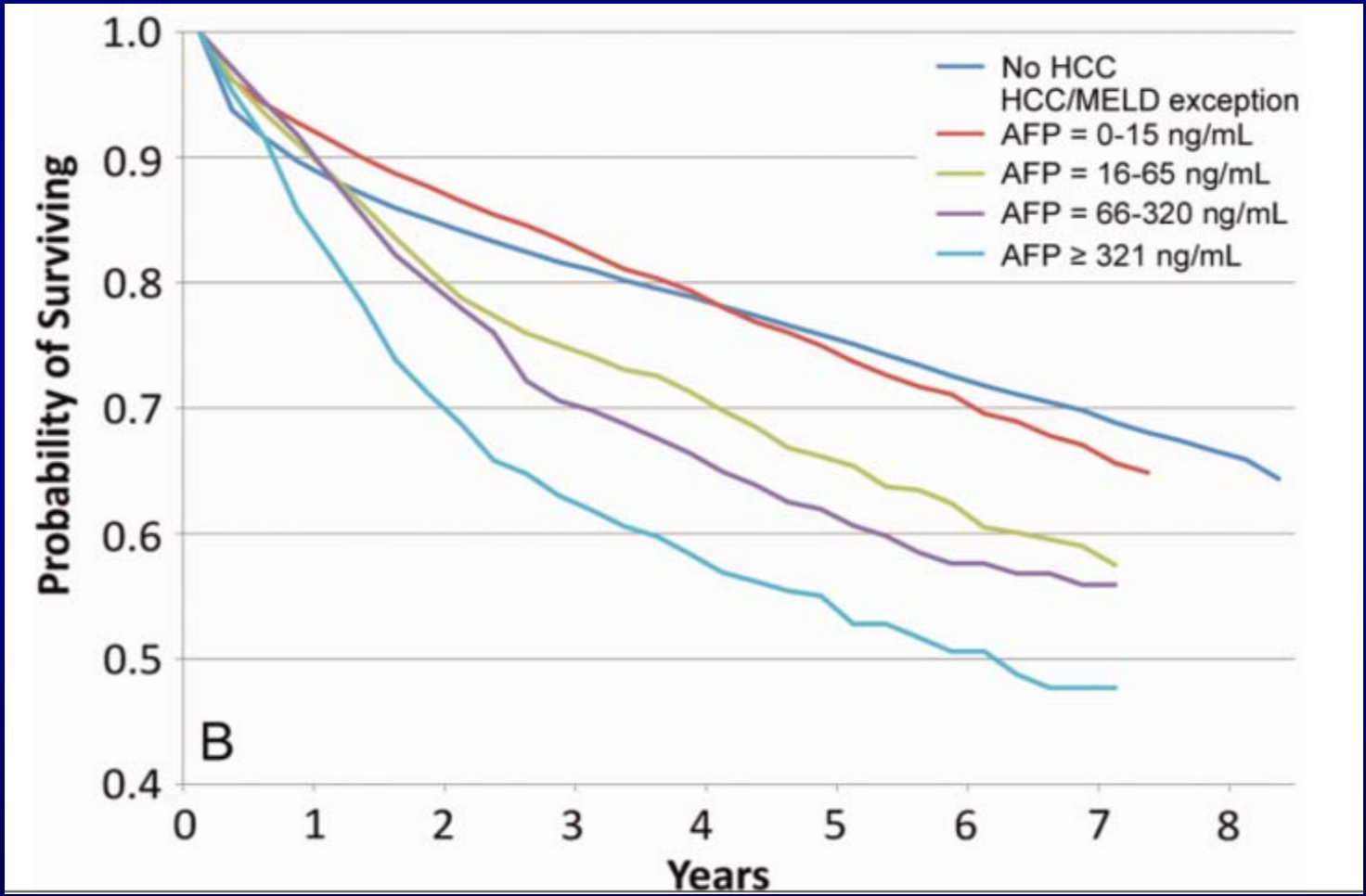
PROPOSED UNOS POLICY CHANGES

High AFP Threshold

- Candidates with lesions meeting T2 criteria but with an AFP >1000 are not eligible for a standardized MELD exception
- If these lesions fall <500 after LRT, the candidate is eligible for a standardized MELD exception
- Candidates with an AFP level ≥500 at any time point following LRT will be referred to the review board

AFP AND POST-LT HCC SURVIVAL

UNOS Database from 2002-11 (n=45,267)



Berry et al. Liver Transplantation 2013; 634-45

AFP AND POST-LT HCC SURVIVAL

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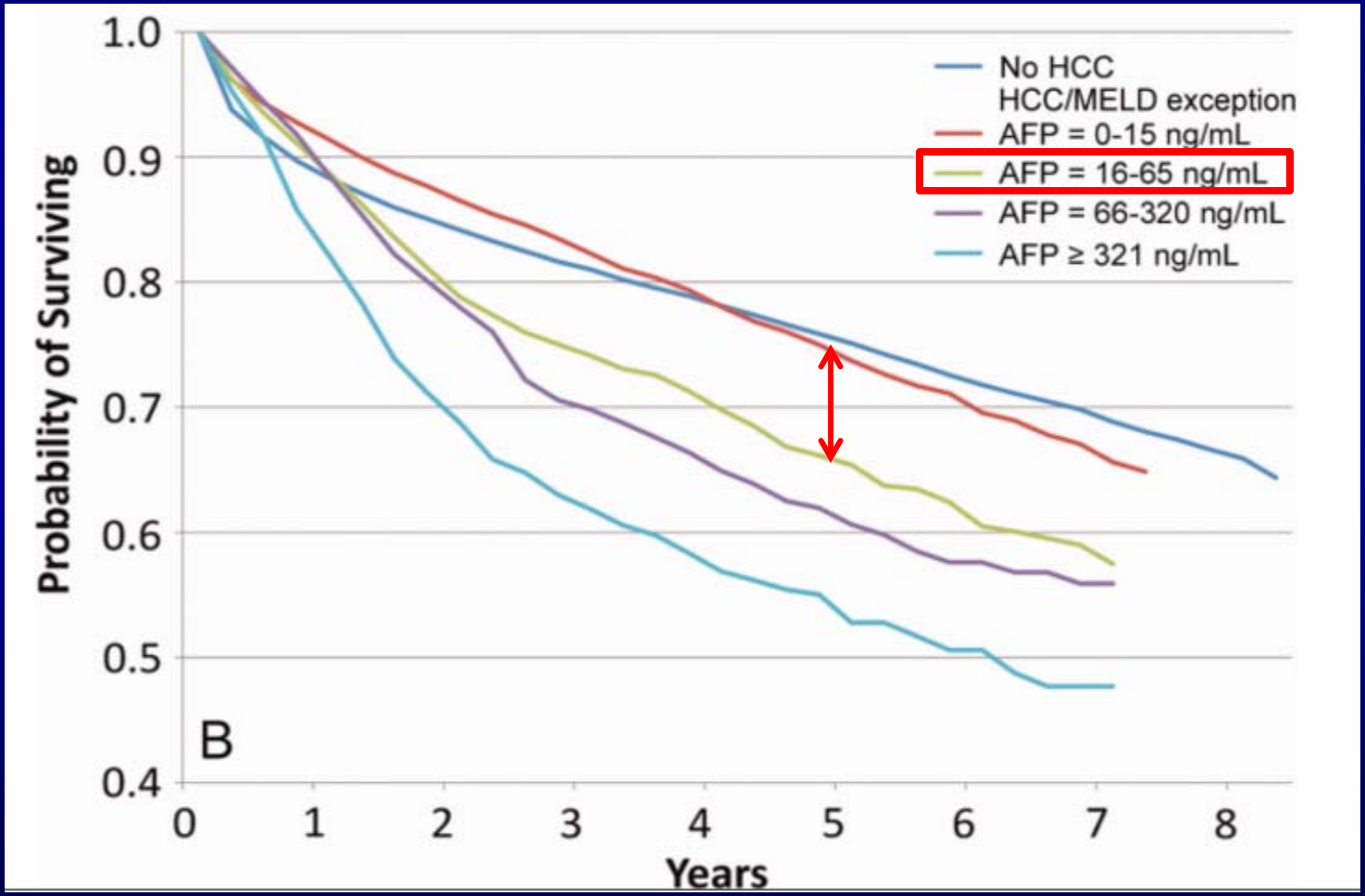
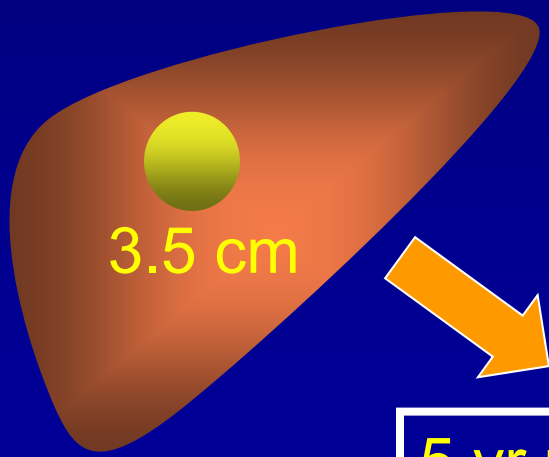


Berry et al. Liver Transplantation 2013; 634-45

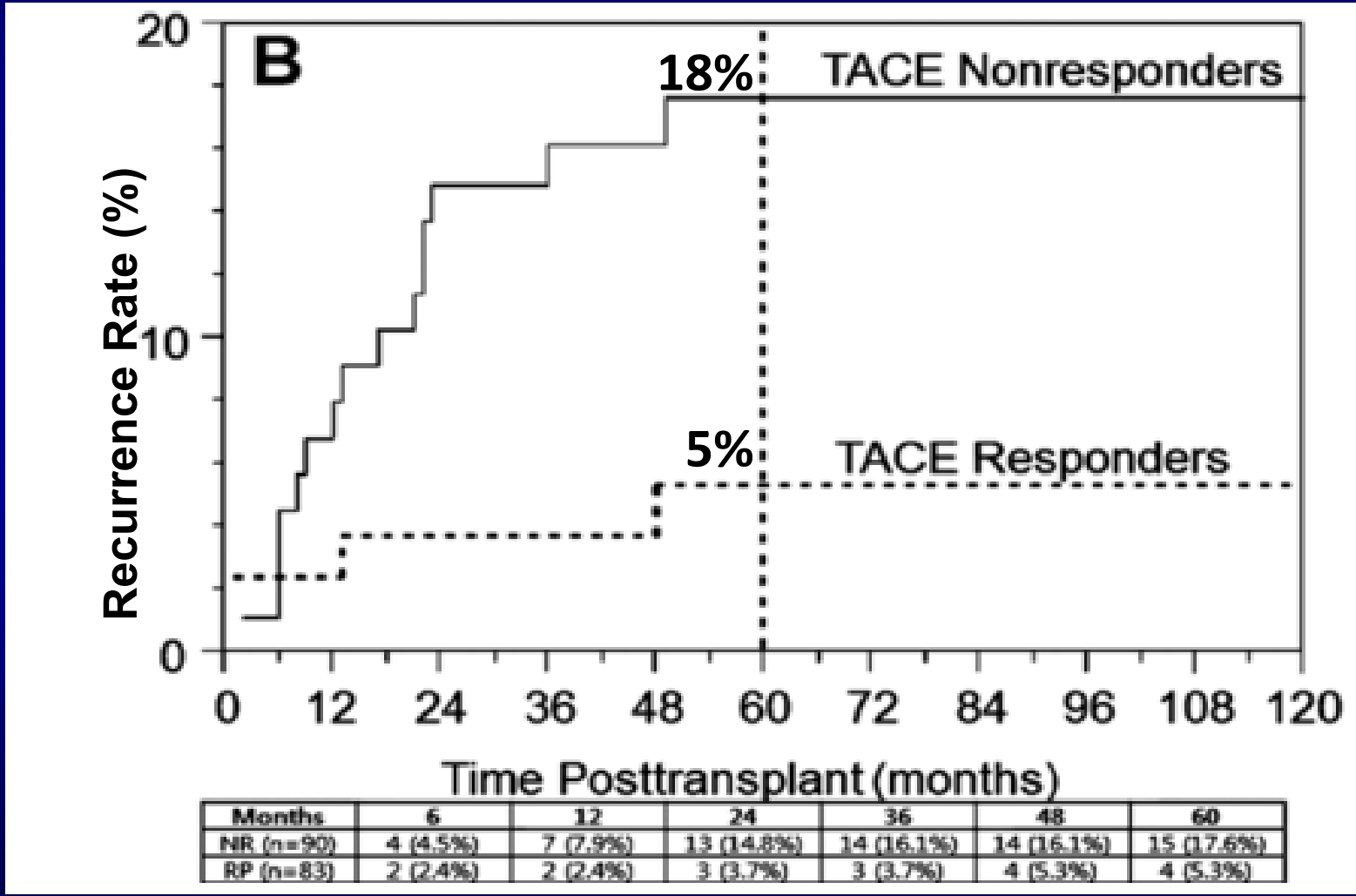
LIVER TRANSPLANTATION FOR HCC: OPTIMIZING SELECTION CRITERIA

Response to LRT



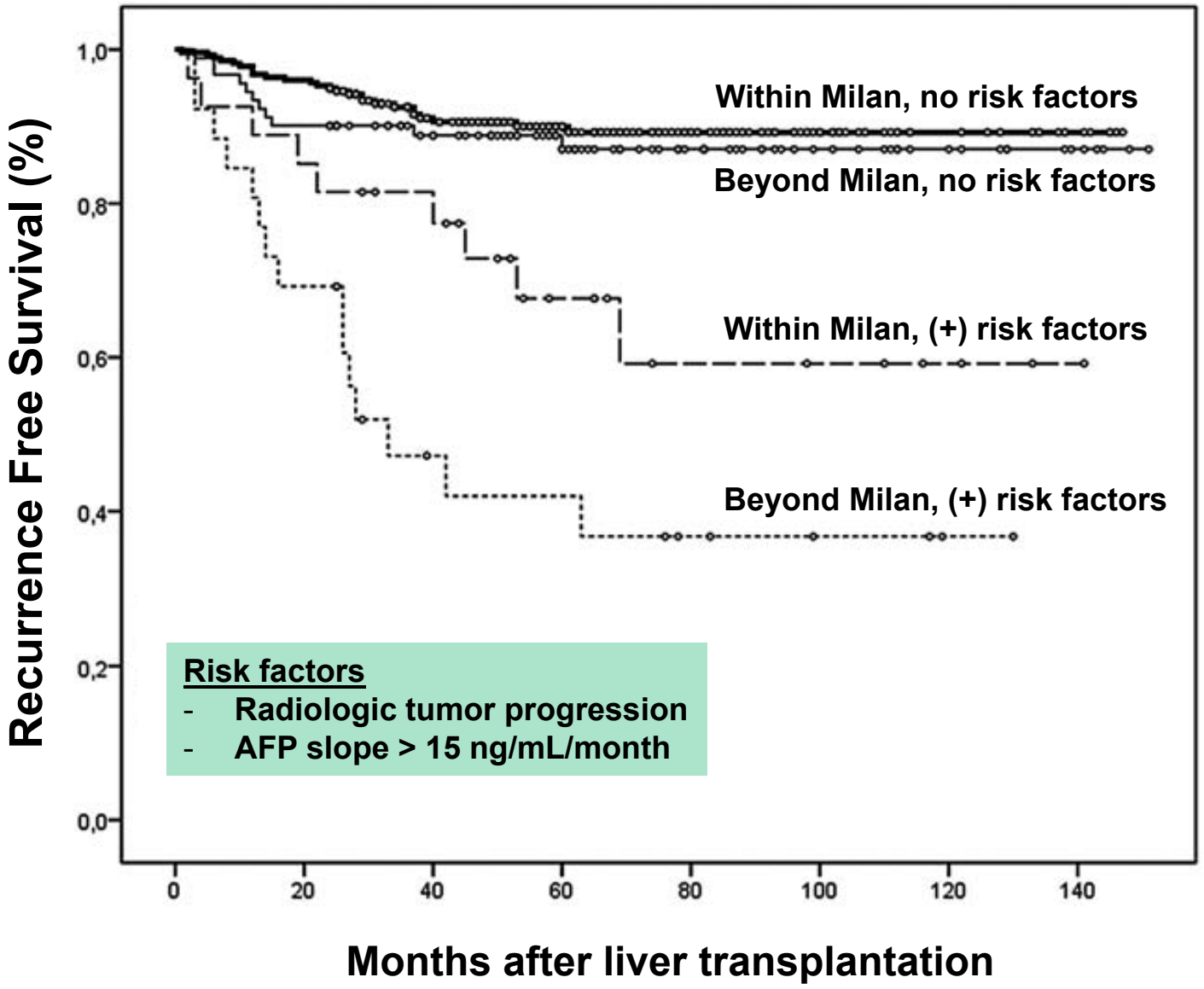
5 yr post-LT survival: __%
5 yr HCC recurrence: __%

RESPONSE TO LOCAL-REGIONAL THERAPY AS PROGNOSTIC FACTOR

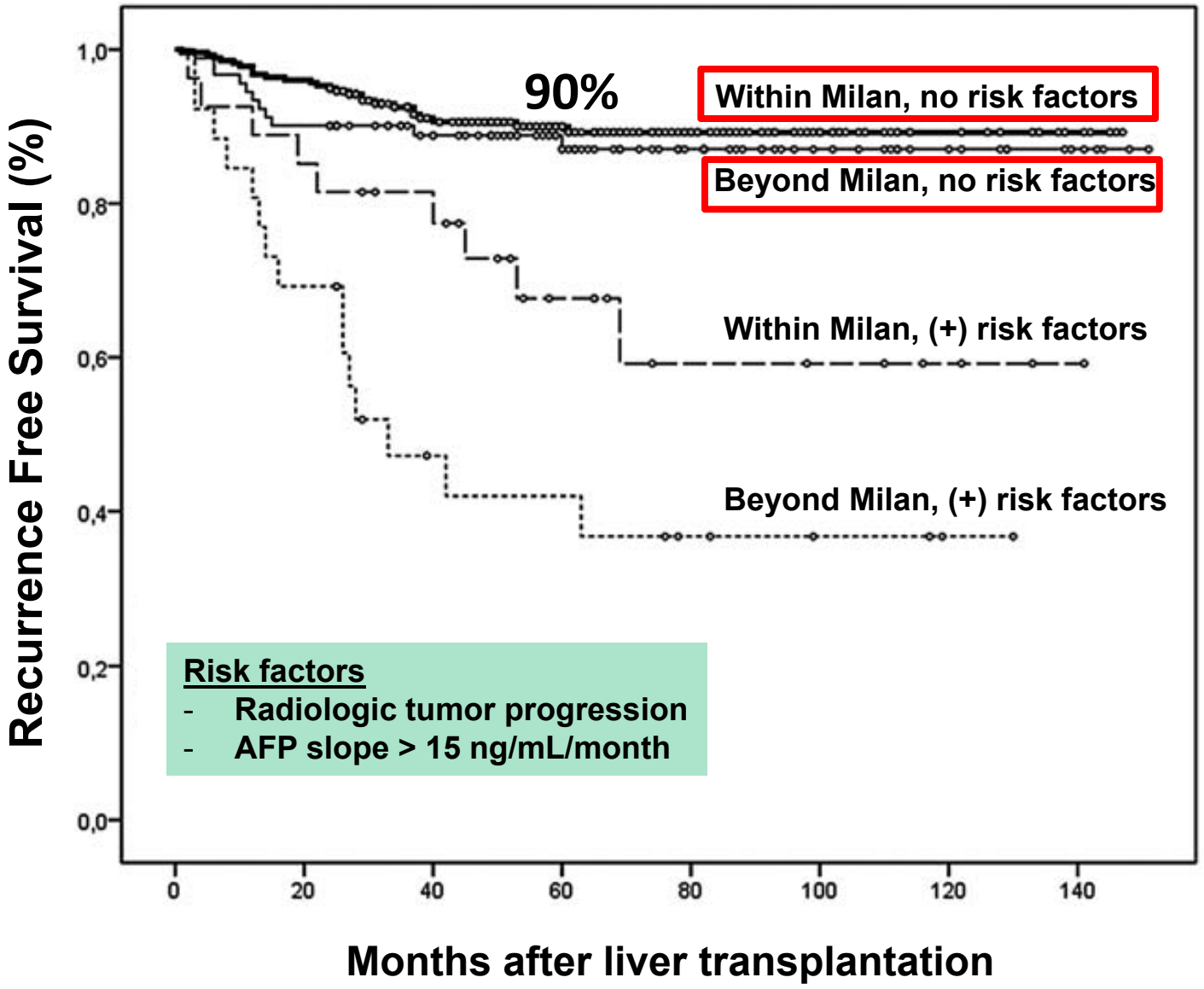


Months	6	12	24	36	48	60
NR (n=90)	4 (4.5%)	7 (7.9%)	13 (14.8%)	14 (16.1%)	14 (16.1%)	15 (17.6%)
RP (n=83)	2 (2.4%)	2 (2.4%)	3 (3.7%)	3 (3.7%)	4 (5.3%)	4 (5.3%)

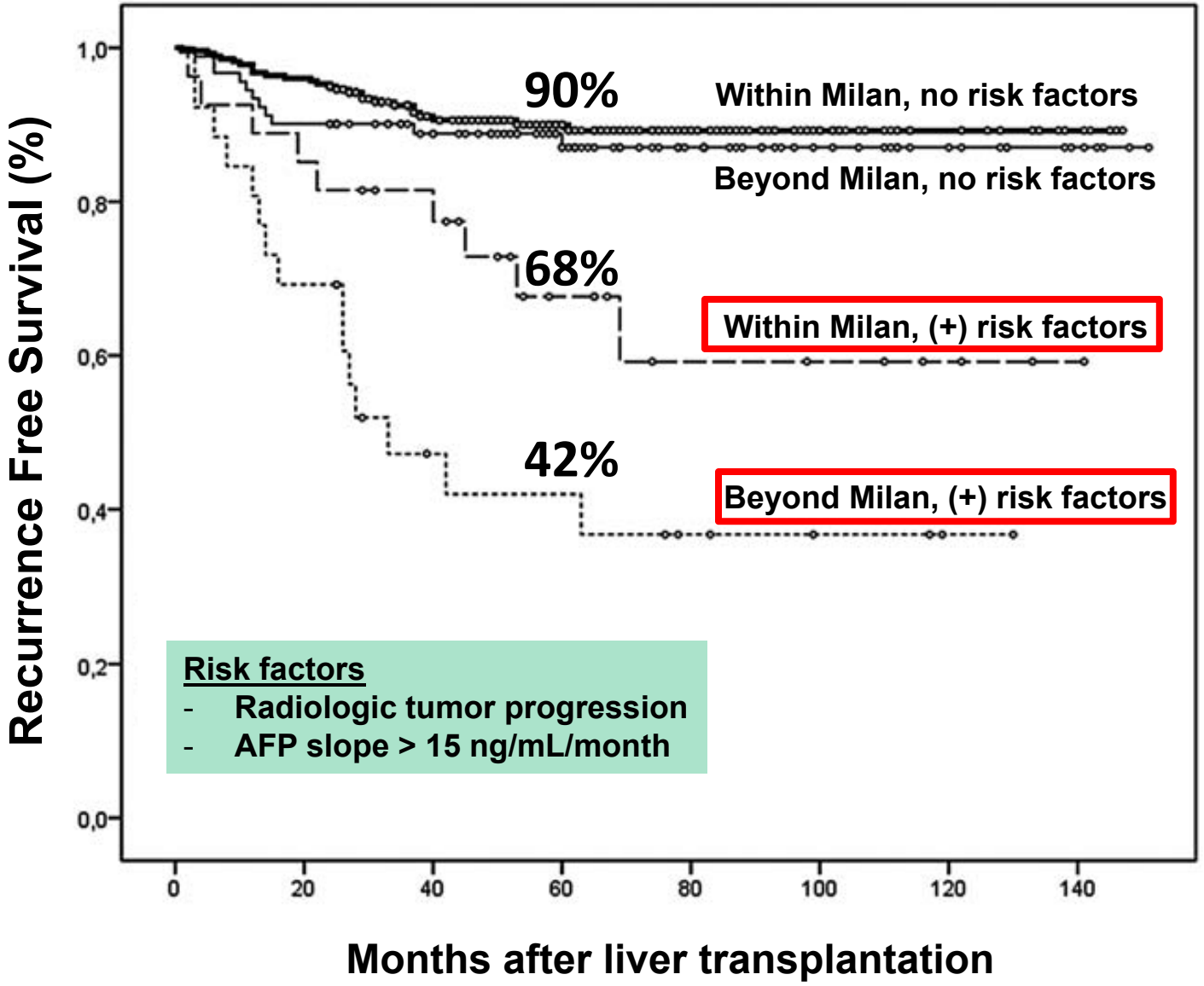
Kim DJ, et al. Am J Transpl 2014; 1383-90



Lai Q, et al. Liver Transpl 2013;19:1108-1118



Lai Q, et al. Liver Transpl 2013;19:1108-1118



Lai Q, et al. Liver Transpl 2013;19:1108-1118

OVERVIEW

- Current state of liver transplantation (LT) for HCC
  - Refining selection criteria for LT
  - Updates in down-staging outcomes
  - Proposed UNOS policy changes
  - HCV: Should we treat before LT??
- Updates in chemo- and immunotherapy

Spectrum of Cirrhosis Among Patients on the Waiting List

- Compensated cirrhosis
- Child-Pugh A
- MELD <10
- HCC as indication for LT

- Many DAA options
- Higher chance of SVR
- High chance of clinical benefits
- Cure before death likely

- Decompensated cirrhosis
- Child-Pugh B
- Mild-moderate portal HTN
- Mild-moderate altered liver synthetic function

- Fewer DAA options
- Slight reduction in SVR
- Cure before death likely
- Moderate chance of clinical benefits

- Decompensated cirrhosis
- Child-Pugh C
- Severe/refractory portal hypertensive complications
- Moderate-severe liver synthetic dysfunction

- Fewer DAA options
- Modest reduction in SVR
- Risk of dying before or with SVR
- Modest clinical benefits in short-term

HCC/HCV: To Treat or Not To Treat?

Yes!

- High chance of cure with 12 weeks therapy
- Keep liver function stable for local-regional therapy
- Prevent worsening decompensation
- Eliminates the risk of HCV post-LT → simplifies management

HCC/HCV: To Treat or Not To Treat?

Maybe?

- **Effectiveness of DAAs in HCC pts appears to differ by genotype**

Study Setting

- National Veterans Affairs (VA) Healthcare System
- 167 medical centers around the country
- Largest integrated healthcare system in the USA
- Largest number of HCV-infected patients:
  n=174,000 (in 2013)
- Largest number of HCV + HCC:
  n= 5,139 (in 2013)

Ioannou et al, AASLD 2016

SVR Rates by Genotype

	No HCC	HCC	HCC/LT
Genotype 1	**93.1%** (92.6 - 93.5)	**79.1%** (74.4 - 83.1)	**96.4%** (90.1 - 98.7)
Genotype 2	**86.5%** (84.9 - 88.0)	**68.9%** (49.0 - 83.7)	N/A
Genotype 3	**75.9%** (73.3 - 78.5)	**47.0%** (33.5 - 61.1)	**88.9%** (61.0 - 97.6)

Ioannou et al, AASLD 2016

Why is HCC associated w/ lower SVR?

The lower SVR rate of HCC patients is not explained by:

Age, gender, race/ethnicity
Cirrhosis
Decompensated Cirrhosis
Bilirubin, Albumin, Platelet Count
Renal Function
Diabetes
HCV viral load, genotype, subgenotype
HCV regimen
Treatment experience

Ioannou et al, AASLD 2016

HCC/HCV: To Treat or Not To Treat?

No?

- **Expand potential donor pool to include HCV+ donors**
- **DAA curative therapy could increase the risk of HCC recurrence**

Risk of HCC Recurrence after Initial Successful Treatment in DAA-Treated Pts

Author, Country	N with HCC	N treated with DAA and Timing	Severity of Cirrhosis/HCC	HCC Treatment Given	HCC Recurrence Rate
Conti, Italy	59	59 (100%) Median 1 year post-HCC treatment	CP-A/B 56 within Milan	Resection, RFA, TACE, alcohol infection and combos	29% 24 weeks post-DAA therapy
Reig, Spain	58	58 (100%) Median 11.2 mo. post-HCC treatment	CP-A/B All within Milan	Resection, ablation, TACE	28% Median 3.5 mos after DAA therapy
Pol, France	79 CIRVIR Cohort	13 (16%)	CP-A 96% within Milan	Resection, ablation or both	1.73 (no DAA) vs 1.11 (DAA) per 100 p-yrs Median time to recur 16.5 months

Whether DAA curative therapy increases risk of HCC recurrence remains a controversial issue

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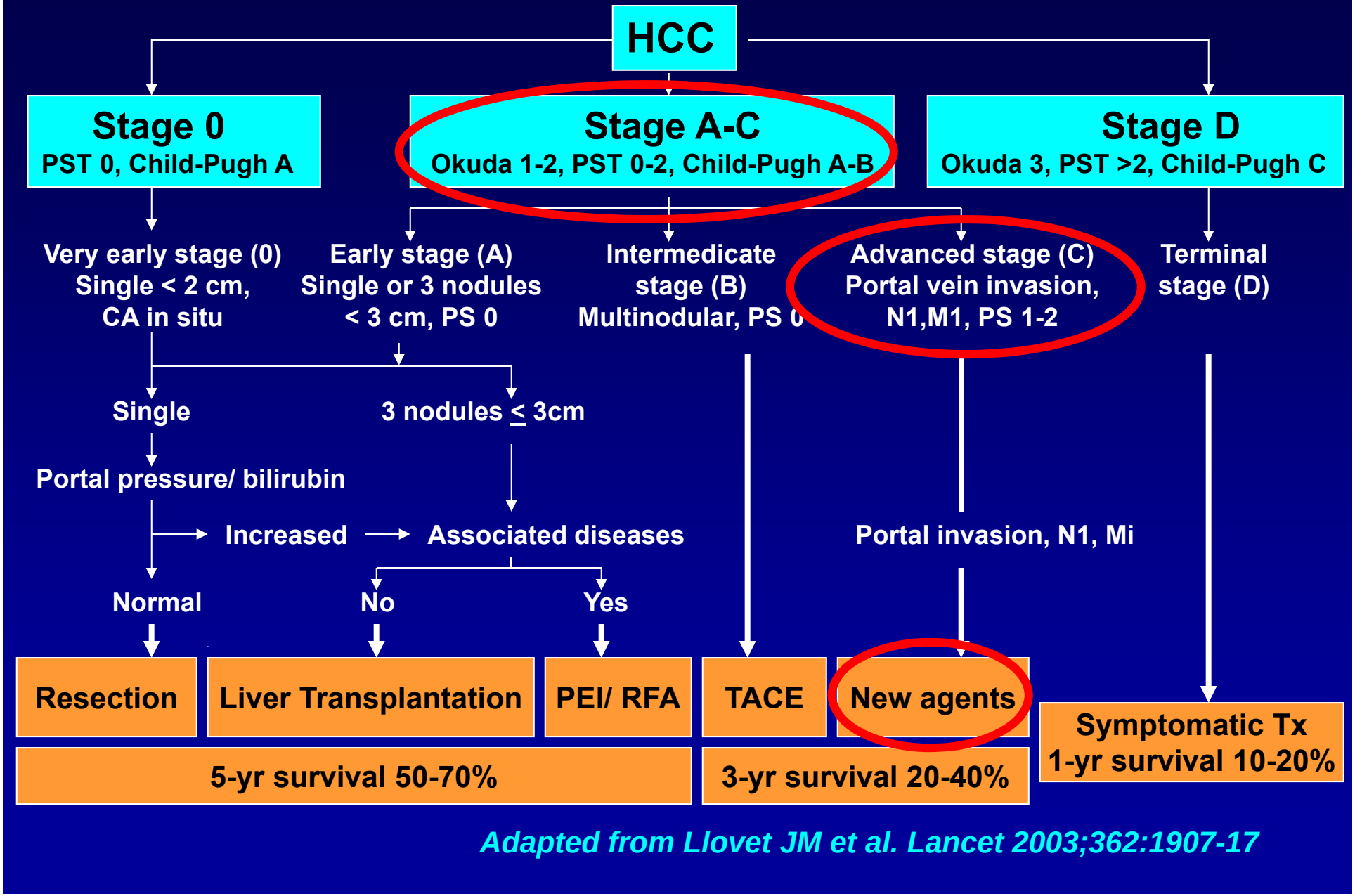
BCLC STAGING CLASSIFICATION



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

REGORAFENIB

- Sorafenib only systemic tx shown to significantly improve overall survival in pts w/ HCC unsuitable for local-regional therapy
- Oral multikinase inhibitor that blocks the activity of protein kinases involved in angiogenesis, oncogenesis, and tumor microenvironment
- Phase 3 RESORCE trial conducted to evaluate the efficacy and safety of regorafenib in pts who progressed on sorafenib

Int J Cancer 2011;129:245-55; 1. *N Engl J Med* 2008;359:378-90; 2. *Lancet Oncol* 2009;10:25-34;

REGORAFENIB

- RESORCE trial design (NCT01774344)
  - Pts stratified by geographic region, macrovascular invasion, extrahepatic disease, ECOG PS 0 vs 1, AFP (<400 vs ≥400)
  - BCLC B or C (majority), Child-Pugh A
- Regorafenib 160 mg daily (n=379) vs placebo (n=194)
- 152 centers, 21 countries
- Treated until progression, unacceptable toxicity, or withdrawal
- Groups well matched

Bruix J, et al. Presented at World Congress on Gastrointestinal Cancer 2016

REGORAFENIB

	Regorafenib N=379	Placebo N=194	
Median OS	**10.6 mo (9.1-12.1)**	**7.8 mo (6.3-8.8)**	HR 0.62, p<0.001
Progression Free Survival (mRECIST)	**3.1 mo (2.8-4.2)**	**1.5 mo (1.4-1.6)**	HR 0.46, p<0.001

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Survival benefit was maintained in all pre-defined subgroups

Regorafenib Gr 3/4 AEs: 13% HFSR, 9% fatigue, 15% HTN, 10% increased bili and AST

Bruix J, et al. Presented at World Congress on Gastrointestinal Cancer 2016

PD-1 Inhibitors

- Nivolumab is a fully human IgG4 monoclonal Ab inhibitor of the programmed death-1 (PD-1) receptor that restores T-cell mediated anti-tumor activity

- Tx with nivolumab has extended survival in multiple tumor types
    - Metastatic melanoma
    - Non-small cell lung CA
    - RCC
    - Hodkin lymphoma

Weber JS, et al. Lancet Oncol 2015; Borghaei H, et al NEJM 2015; Motzer RJ NEJM 2015

PD-1 Inhibitors

- CheckMate 040: Phase ½ study of nivolumab in patients with advanced HCC

- Study design
  - CP A pts who progressed on prior systemic therapy
  - Dose escalation (n=48)
  - Dose expansion (n=214)
  - HBV (n=66), HCV (n=61), uninfected (n=135)
  - Disease assessment with CT or MRI q6 weeks

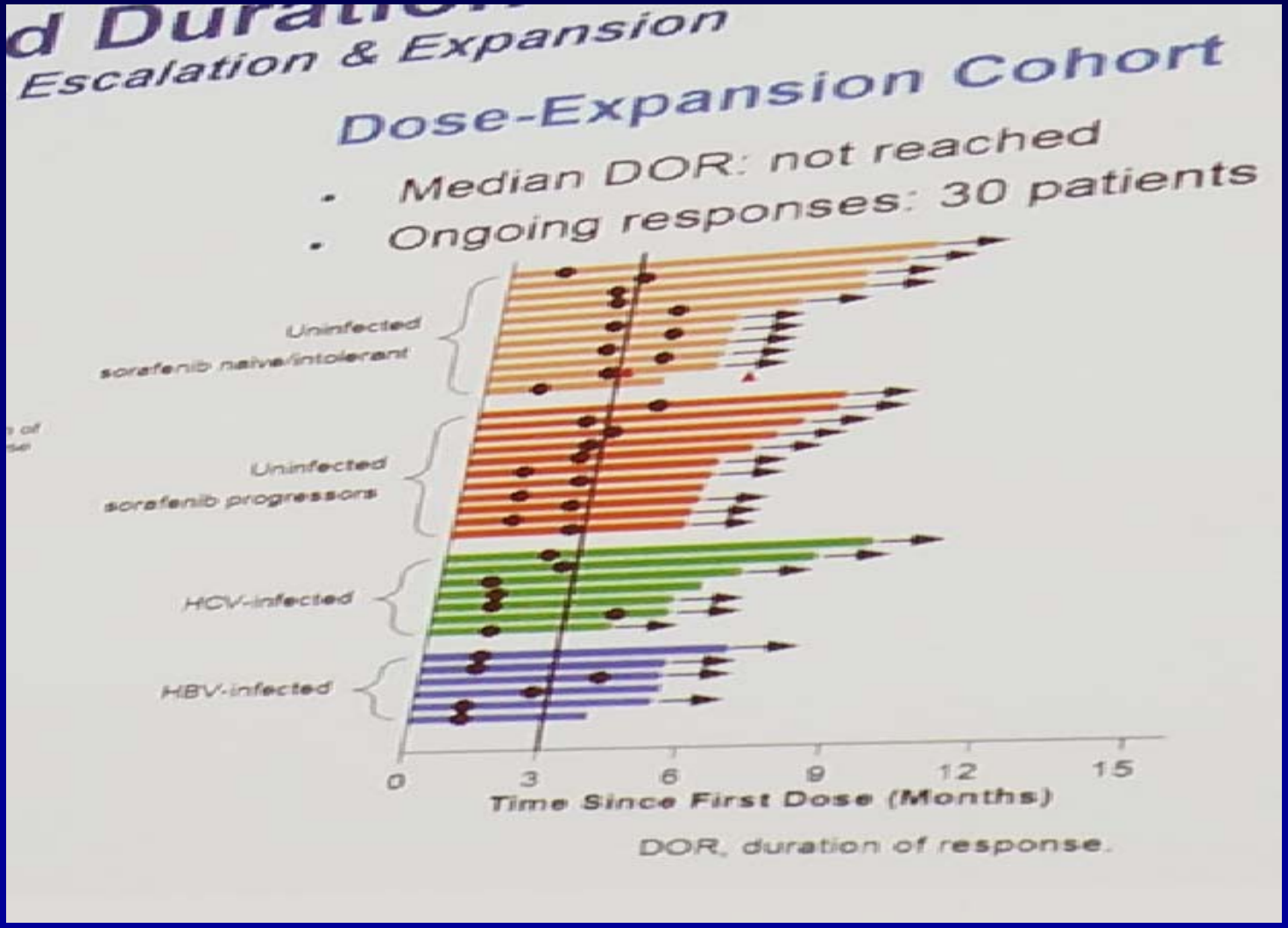
Melero et al, ESMO congress Copenhagen 2016

PD-1 Inhibitors

- Well tolerated
- 19% had at least 1 grade 3 or 4
  - 8% ALT or AST increase
  - 7% Lipase or amylase increase
  - 1% diarrhea, fatigue, and rash
- Objective response seen in 16% of cohort
  - 1% CR, 15% PR
  - 52% stable disease

Melero et al, ESMO congress Copenhagen 2016

PD-1 Inhibitors



Melero et al, ESMO congress Copenhagen 2016

PD-1 Inhibitors

Overall Survival % (95 CI)	Dose-escalation N=48	Dose-expansion N=214
At 6 months	66 (51-78)	83 (76-88)
At 9 months	66 (51-78)	71 (57-81)
At 12 months	59 (44-72)	NC
At 18 months	44 (29-58)	NC
Median OS	14.3 (9.6-18.9)	NC

Melero et al, ESMO congress Copenhagen 2016

PD-1 Inhibitors

- Objective responses:
  - Durable irrespective of infection status (HCV or HBV)
  - Observed regardless of prior sorafenib tx
  - Occurred in pts irrespective of PD-L1 expression
- Overall survival rate encouraging
- Safety and efficacy results consistent across dose-escalation and dose-expansion cohorts
- Phase 3 study of nivolumab ongoing

Melero et al, ESMO congress Copenhagen 2016

THANKS!

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