Optimizing Patient Selection, Organ Allocation, and Outcomes in Liver Transplant (LT) Candidates with Hepatocellular Carcinoma (HCC)

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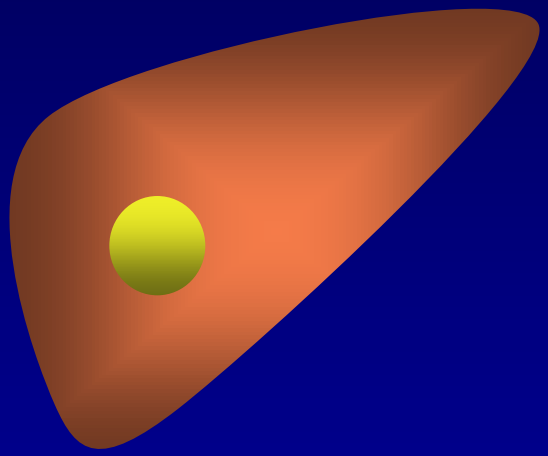
OVERVIEW

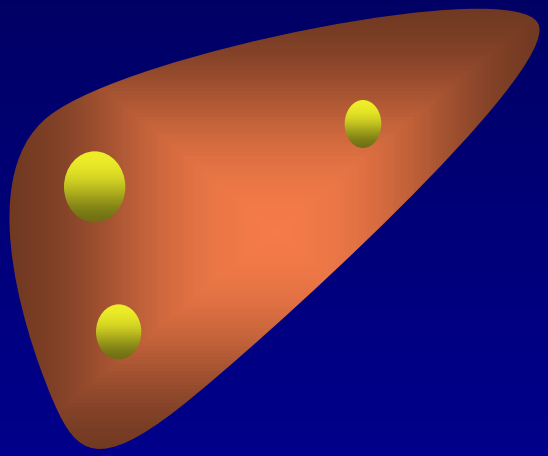
- Current state of LT for HCC worldwide
- Pushing beyond Milan criteria
  - Down-staging and “All-comers” results
  - Identifying important recurrence risk factors
  - Does the donor matter?
- Assessing individualized post-LT HCC recurrence risk
  - Novel risk scores using explant pathology
  - Standardize surveillance regimens
  - Tailor post-LT immunosuppression

Liver Transplant for HCC
Milan Criteria

1 lesion ≤ 5 cm



2 to 3, none > 3 cm



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Absence of Macroscopic Vascular Invasion
Absence of Extra-hepatic Spread

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

LT FOR HCC: EXPANDED CRITERIA

Table 1 | **Liver transplantation criteria for patients with hepatocellular carcinoma**

Transplantation criteria	Intention-to-treat survival	Disease-free survival	Post-transplantation survival	Comments
Milan criteria[51] • Single tumour ≤5 cm or 3 tumours all ≤3 cm	N/A	92% 4 years	85% 4 years	Based only on size and number
UCSF criteria[39] • Single tumour ≤6.5 cm or 3 tumours all ≤4.5 cm with TTD ≤8 cm	N/A	90.9% 5 years	80.9% 5 years	Based only on size and number
Up-to-7 criteria[49] • The sum of the maximum tumour diameter and number <7	N/A	• Beyond Milan but within Up-to-7 • 64.1% 5 years	• Beyond Milan but within Up-to-7 • 71.2% 5 years	Based only on size and number
Total Tumour Volume (TTV)[47] • Total tumour volume ≤115 cm^3 • AFP ≤400 ng/mL	• Beyond Milan but within TTV/AFP • 53.8% 4 years	• Beyond Milan but within TTV/AFP • 68% 4 years	• Beyond Milan but within TTV/AFP • 74.6% 4 years	Size and number and biological marker (AFP)
Extended Toronto Criteria (ETC)[43] • No limit in size and number • No vascular invasion • No extrahepatic disease • No cancer-related symptoms • Biopsy of largest tumour not poorly differentiated	• Beyond Milan but within ETC • 55% 5 years	• Beyond Milan but within ETC • 30% 5 years • (Cumulative risk of recurrence)	• Beyond Milan but within ETC • 68% 5 years	No size and number limit but biological behaviour (cancer-related symptoms and tumour differentiation)
Kyoto Criteria[55] • Number ≤10 tumours • Size ≤5 cm • DCP ≤400 mAU/mL	N/A	• Beyond Milan but within Kyoto • 30% 5 years • (Cumulative risk of recurrence)	• Beyond Milan but within Kyoto • 65% 5 years	Size and number and biological marker

AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin; TTD, total tumour diameter; UCSF, University of California San Francisco.

Sapisochin, G. & Bruix, J. 2017 Nat. Rev. Gastroenterol. Hepatol.

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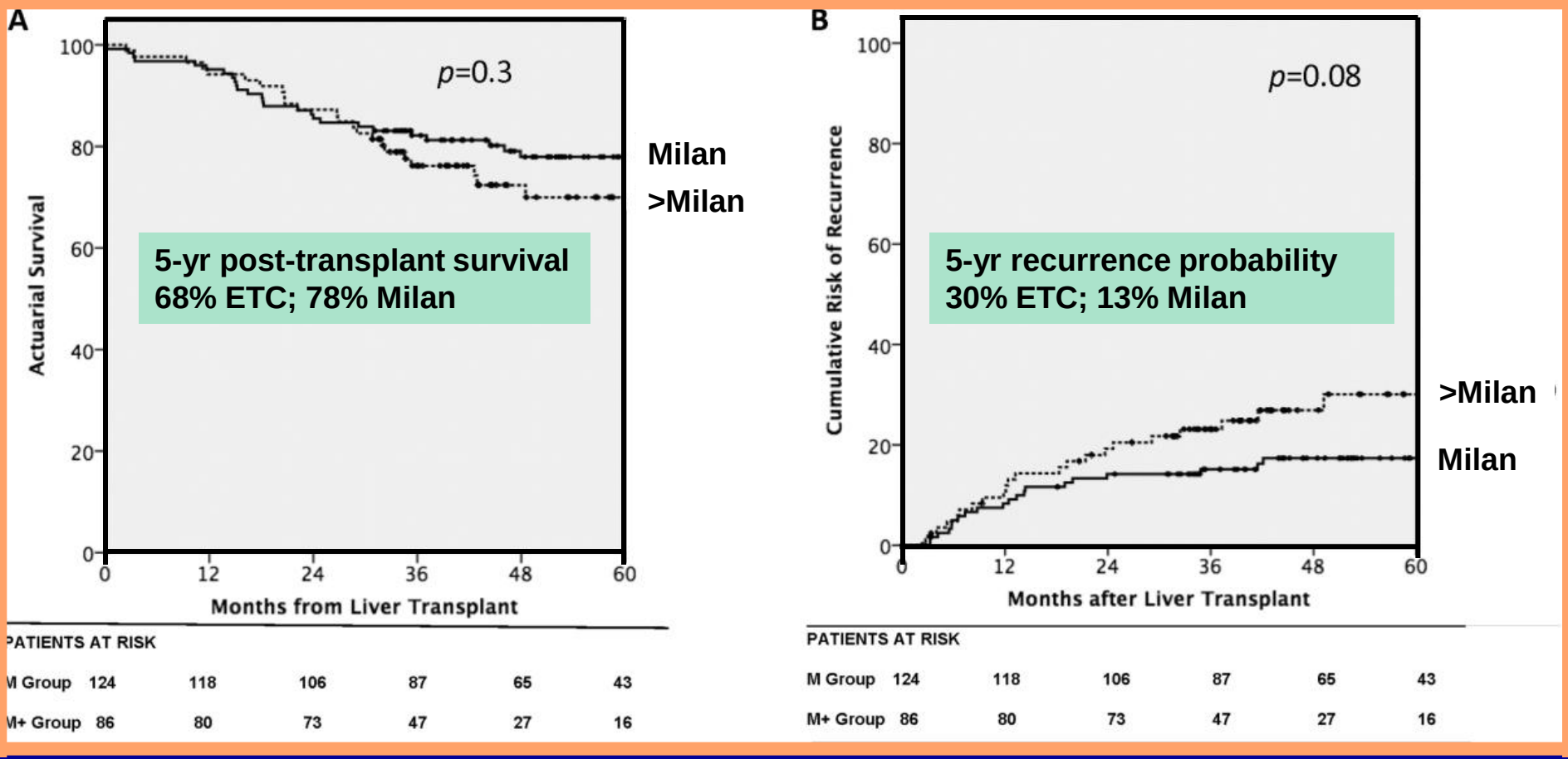
Extended Toronto Criteria



Sapisochin G et al. Hepatology 2016;64:2077-2088

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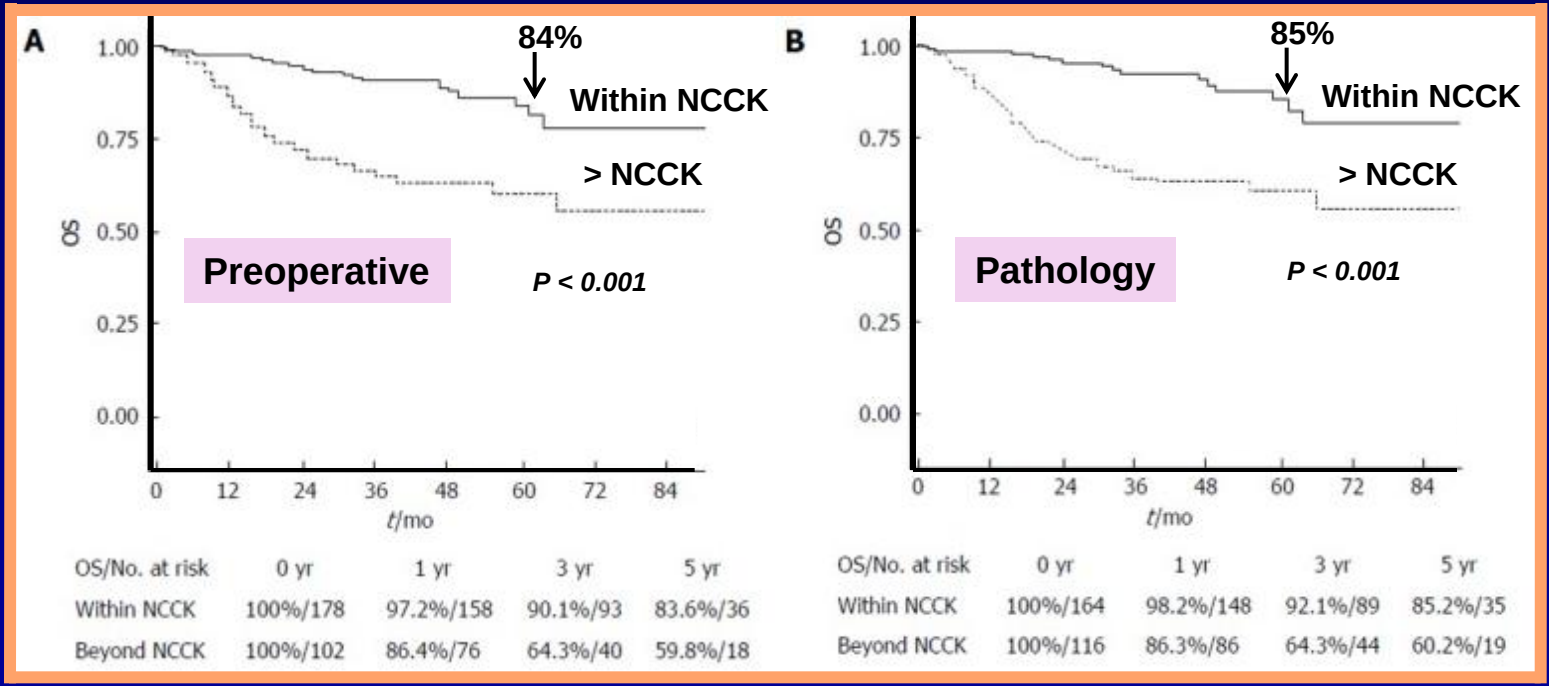
Extended Criteria & FDG PET/CT

The National Cancer Korea Criteria

- Total tumor diameter < 10 cm
- Negative ^{18}F-FDG PET/ CT



Lee SD, et al. World J Transpl 2016;6:411-422

HCC MELD EXCEPTION WORLDWIDE

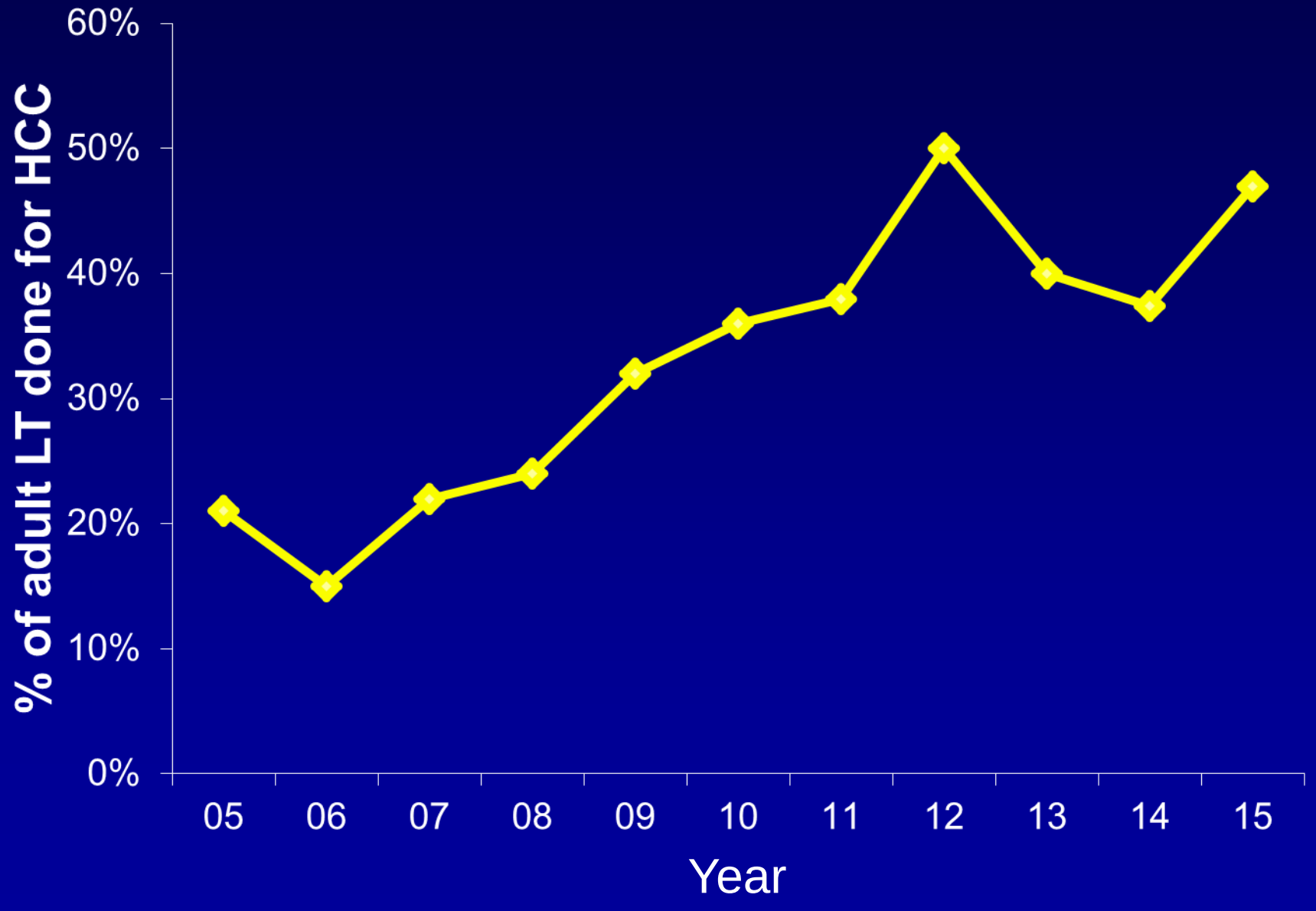
Table 2 | **Models using hepatocellular carcinoma exception points to allocate liver grafts**

Organ procurement organization (region)	Tumour burden to qualify for exception points	Exception points granted	Exception points progression	Exception point cap	Waiting period before receiving exception points
OPTN/UNOS (USA)	T2	28	First 3 months assignment of MELD score equivalent to 35% mortality risk. Following months additional MELD score equivalent to 10% increase in mortality	Yes: 34	6 months from listing (calculated MELD score)
Eurotransplant (Austria, Belgium, Germany, Holland, Slovakia, Croatia)	T2	22	Add point equivalent to a 10% increase in candidate mortality every 3 months	No	No
Human organ precurement and exchange program (Alberta, Canada)	TTV ≤115 cm^3 & AFP ≤400 ng/ml (T1 excluded)	22	Add 2 points every 2 months	No	No
Human organ precurement and exchange program (Ontario, Canada)	UCSF criteria or TTV≤115 cm^3 & AFP ≤400 ng/ml (T1 excluded)	22	Add 3 points every 3 months	No	No
Brazil	T2	20	Increase to 24 at 3 months and to 29 at 6 months	Yes: 29	No
Organització catalana de trasplantaments (Cataluña, Spain)	Single HCC <3 cm and AFP >200 ng/mL, or single HCC ≥3 cm and <5 cm or 2–3 HCCs ≤3 cm	19	Add one point every 3 months	No	No
Nord Italian transplant (Italy)	None	No exception points	Prioritization according to risk of progression and response to bridging therapies[87] (system under assessment)	No	No

AFP, α-fetoprotein; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; OPTN, Organ Procurement Transplantation Network; TTV, total tumour volume; UCSD, University of California San Francisco; UNOS, United Network for Organ Sharing. Modified with permission from Wiley © Toso, C. *et al.* Am. J. Transplant. **14**, 2221–2227 (2014).

Sapisochin, G. & Bruix, J. 2017 Nat. Rev. Gastroenterol. Hepatol.

RISING INCIDENCE OF LIVER TRANSPLANT FOR HCC AT UCSF



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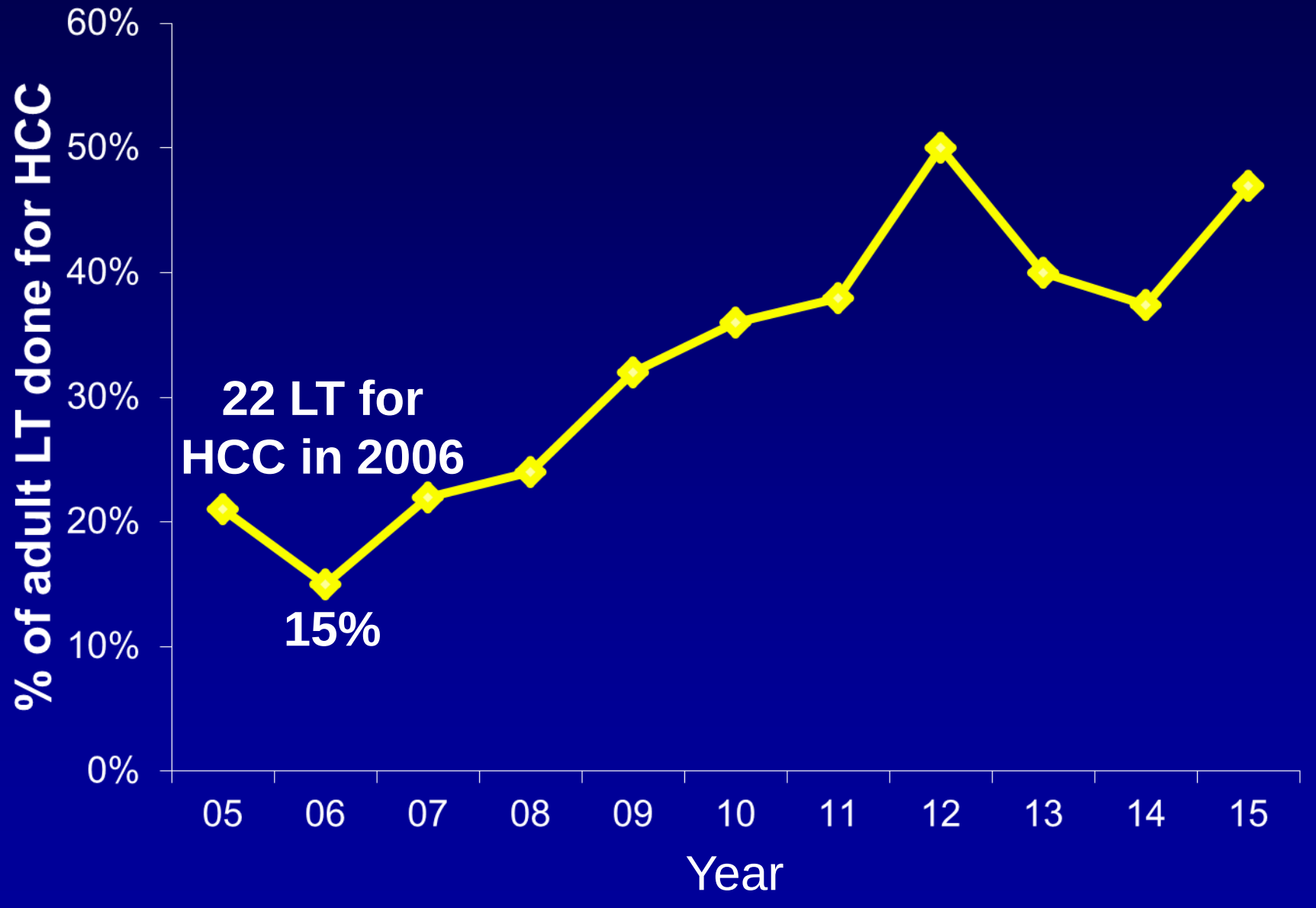

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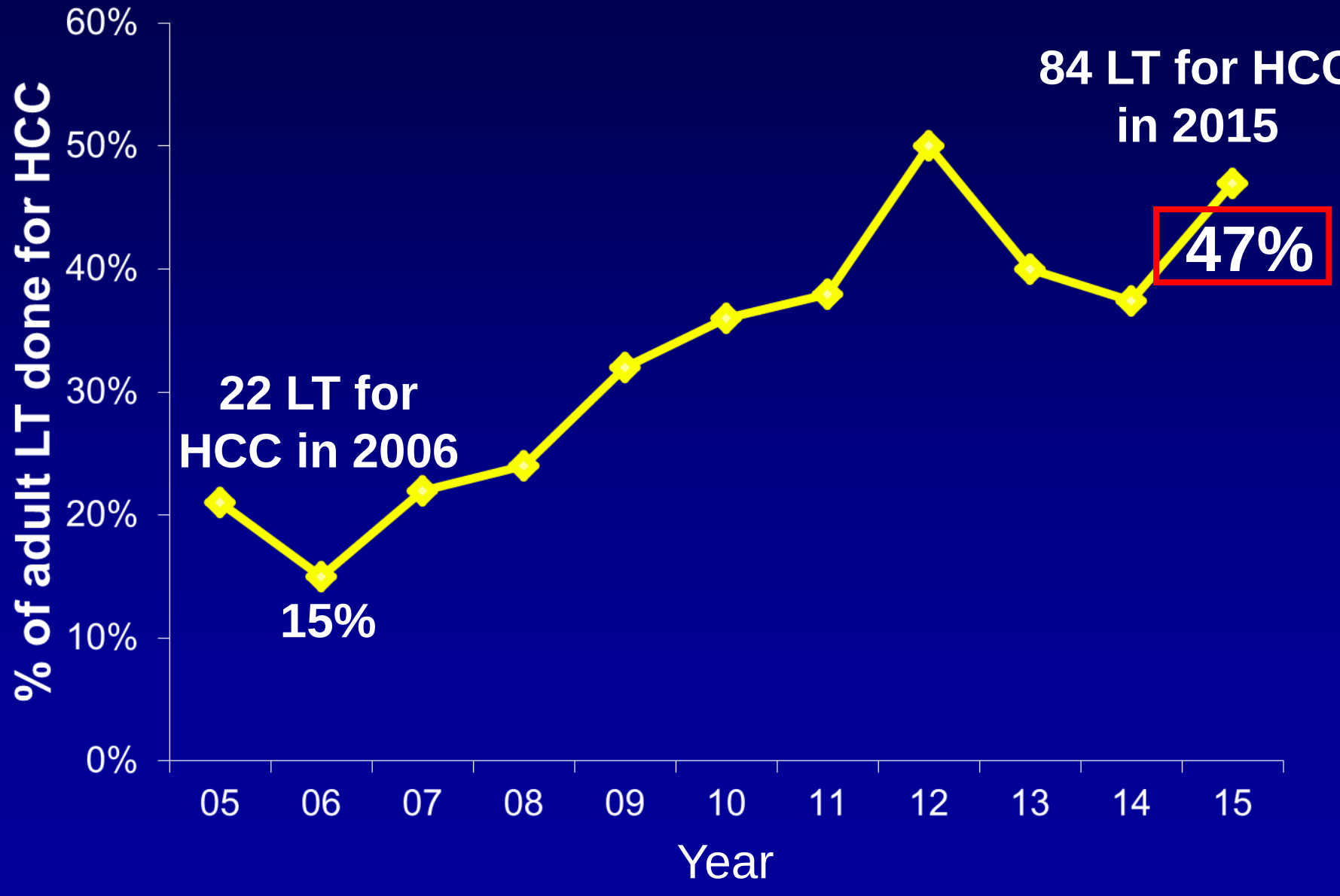
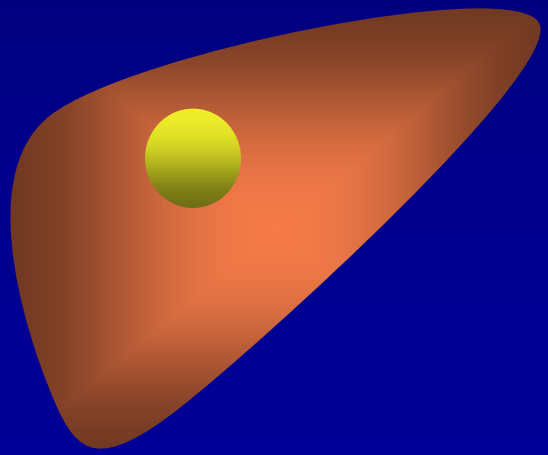


LIVER TRANSPLANTATION FOR HCC: OPTIMIZING SELECTION CRITERIA

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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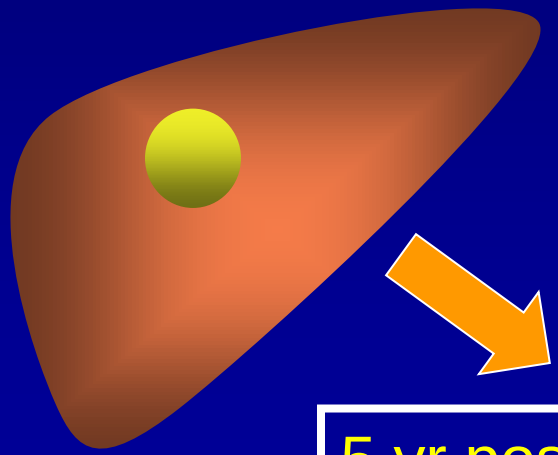

5 yr post-LT survival: 75-80%
5 yr HCC recurrence: ~15%

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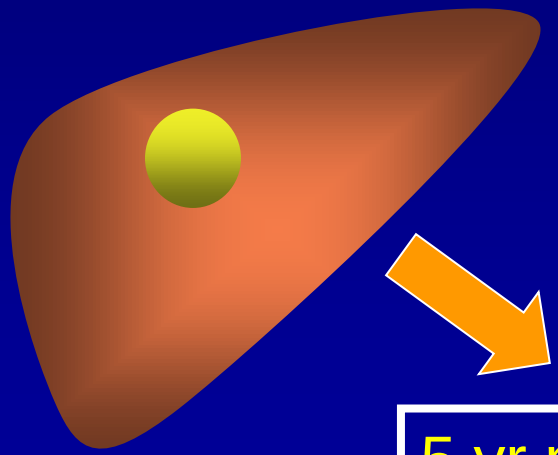
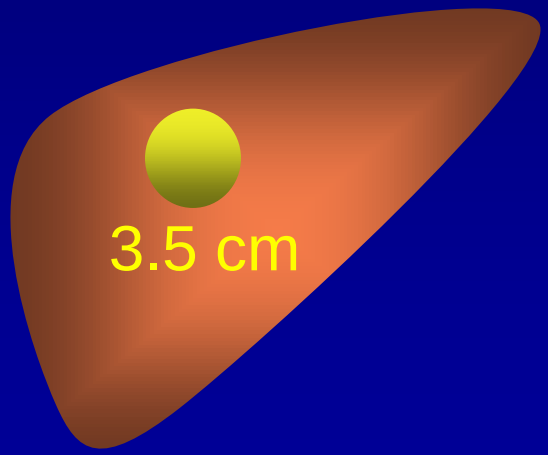


5 yr post-LT survival: ???
5 yr HCC recurrence: ???

LIVER TRANSPLANTATION FOR HCC: OPTIMIZING SELECTION CRITERIA

Response to LRT



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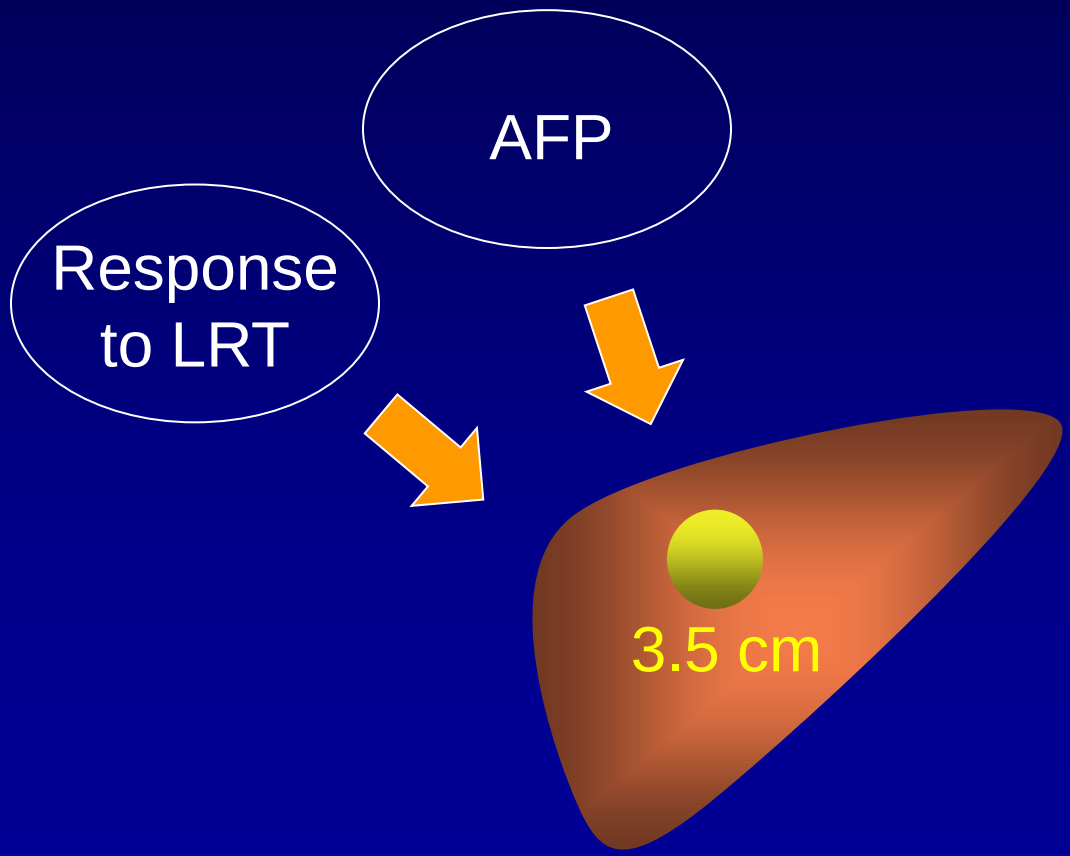

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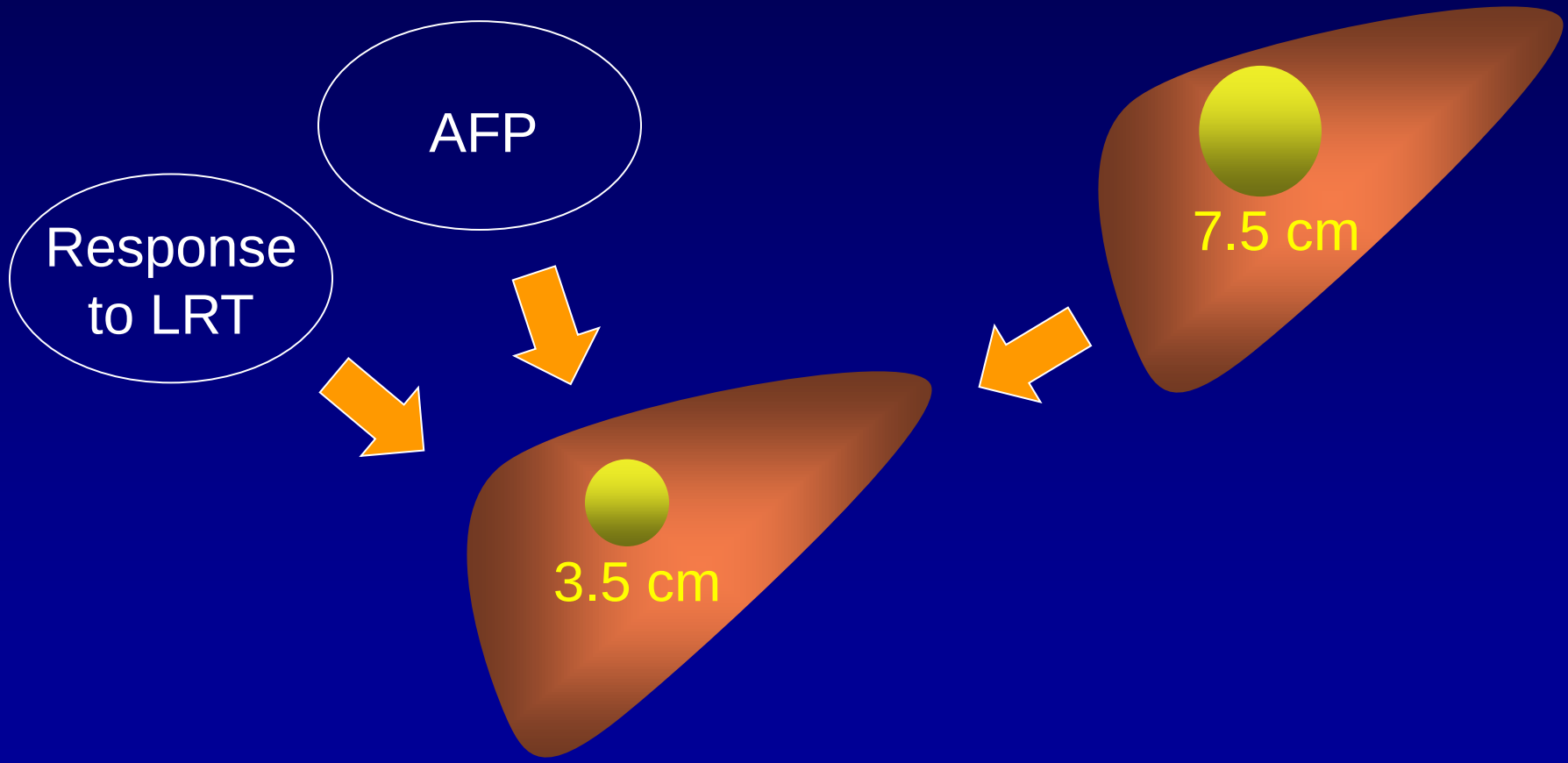

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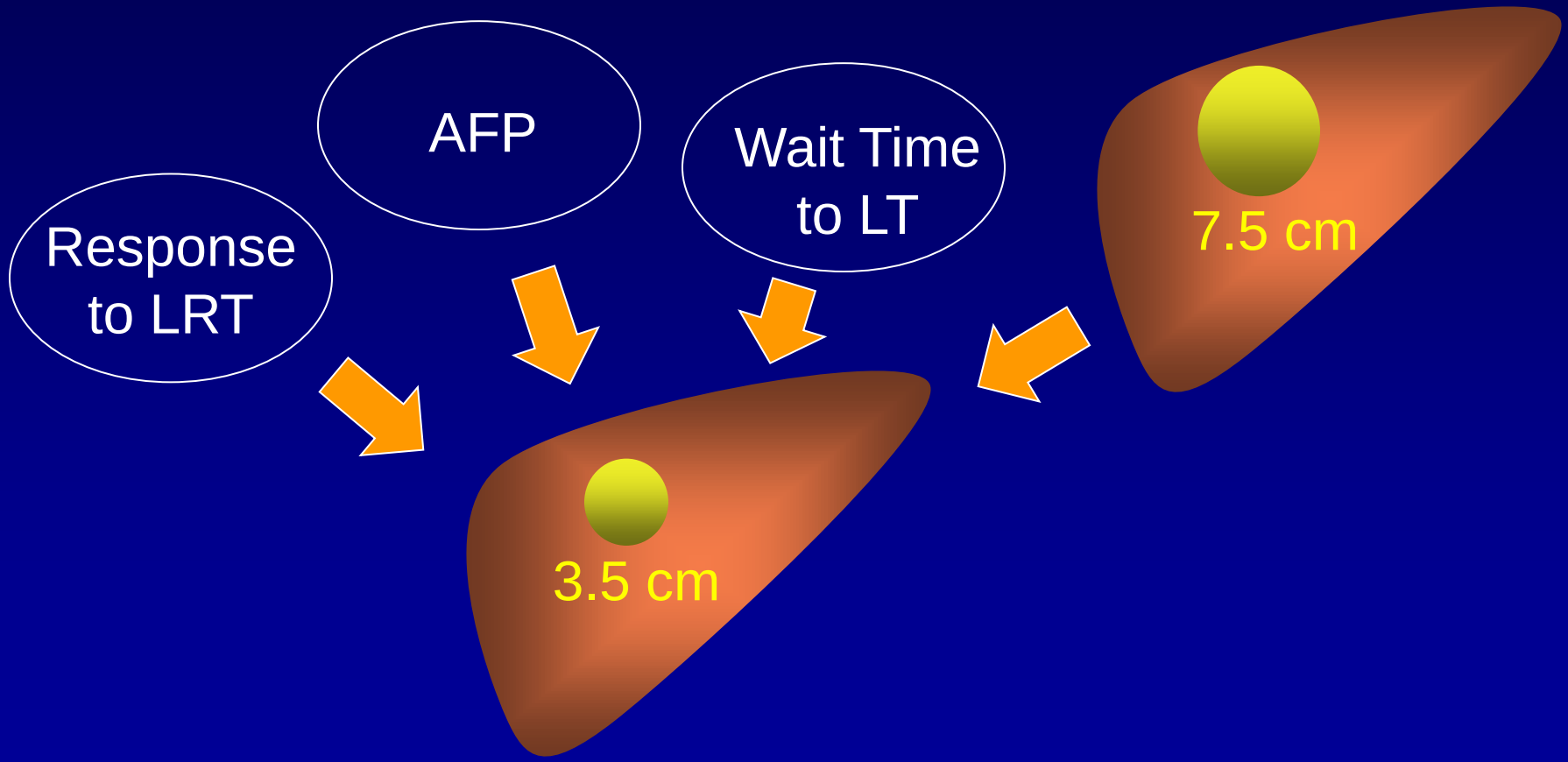

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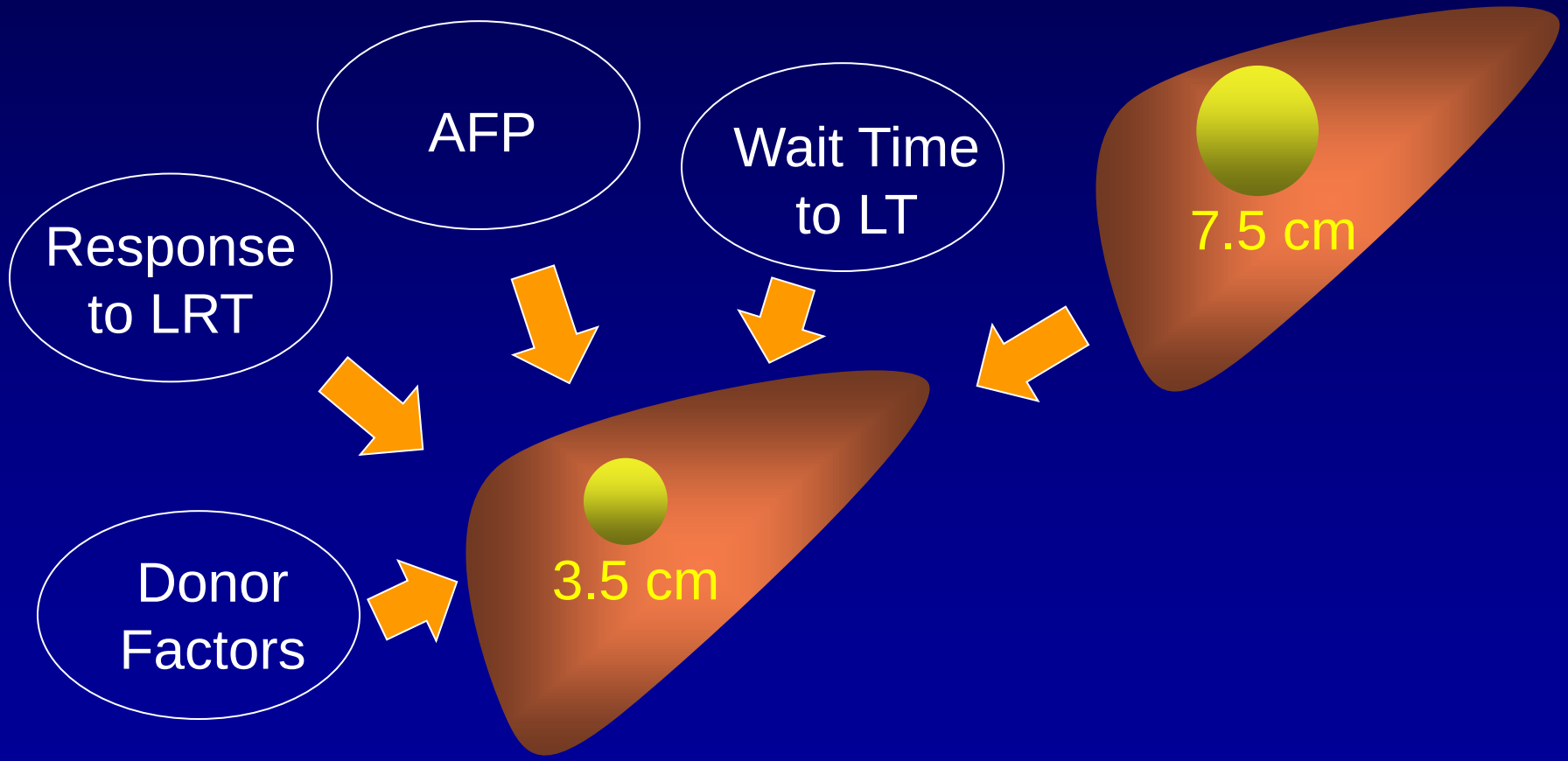

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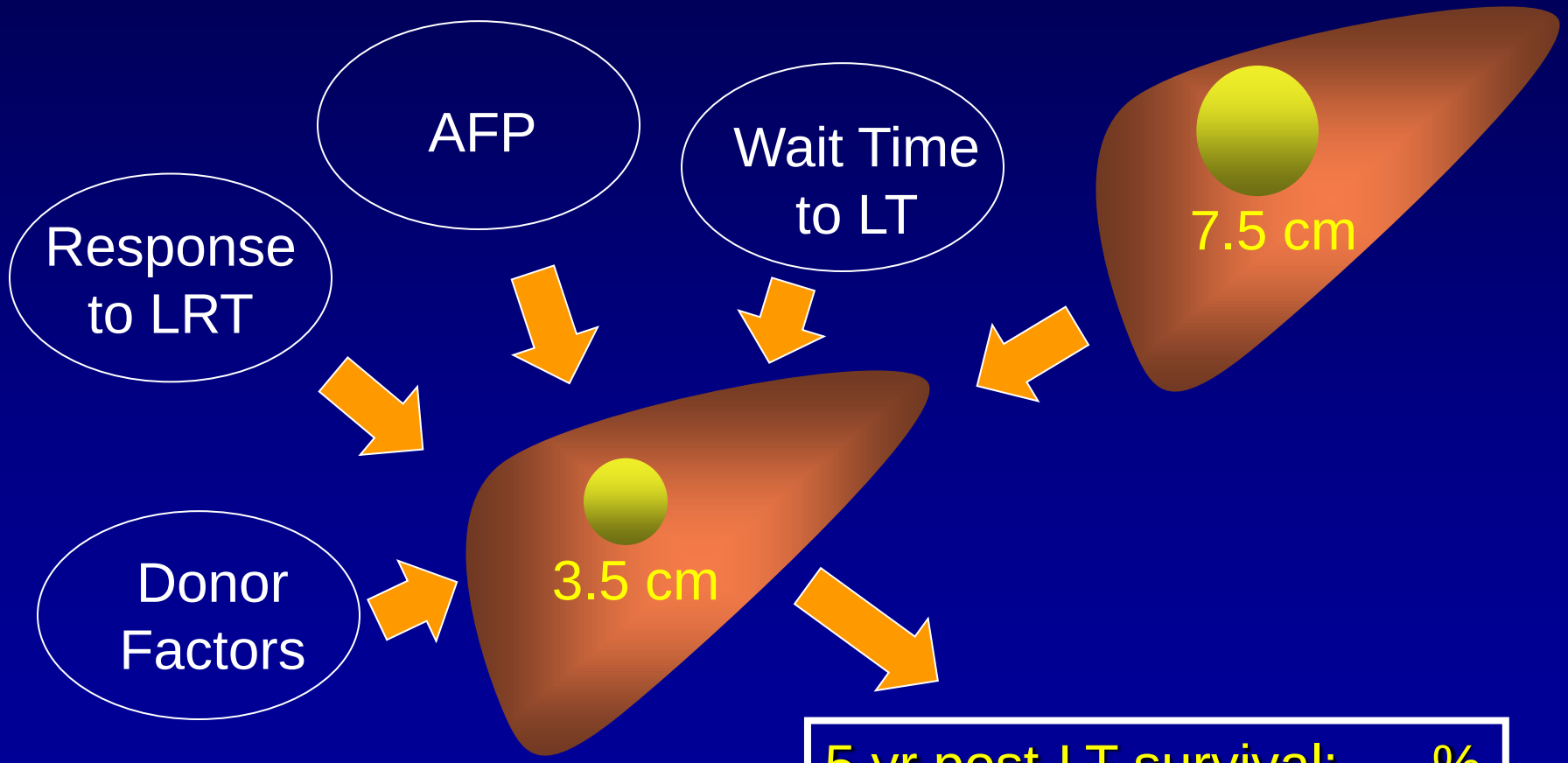
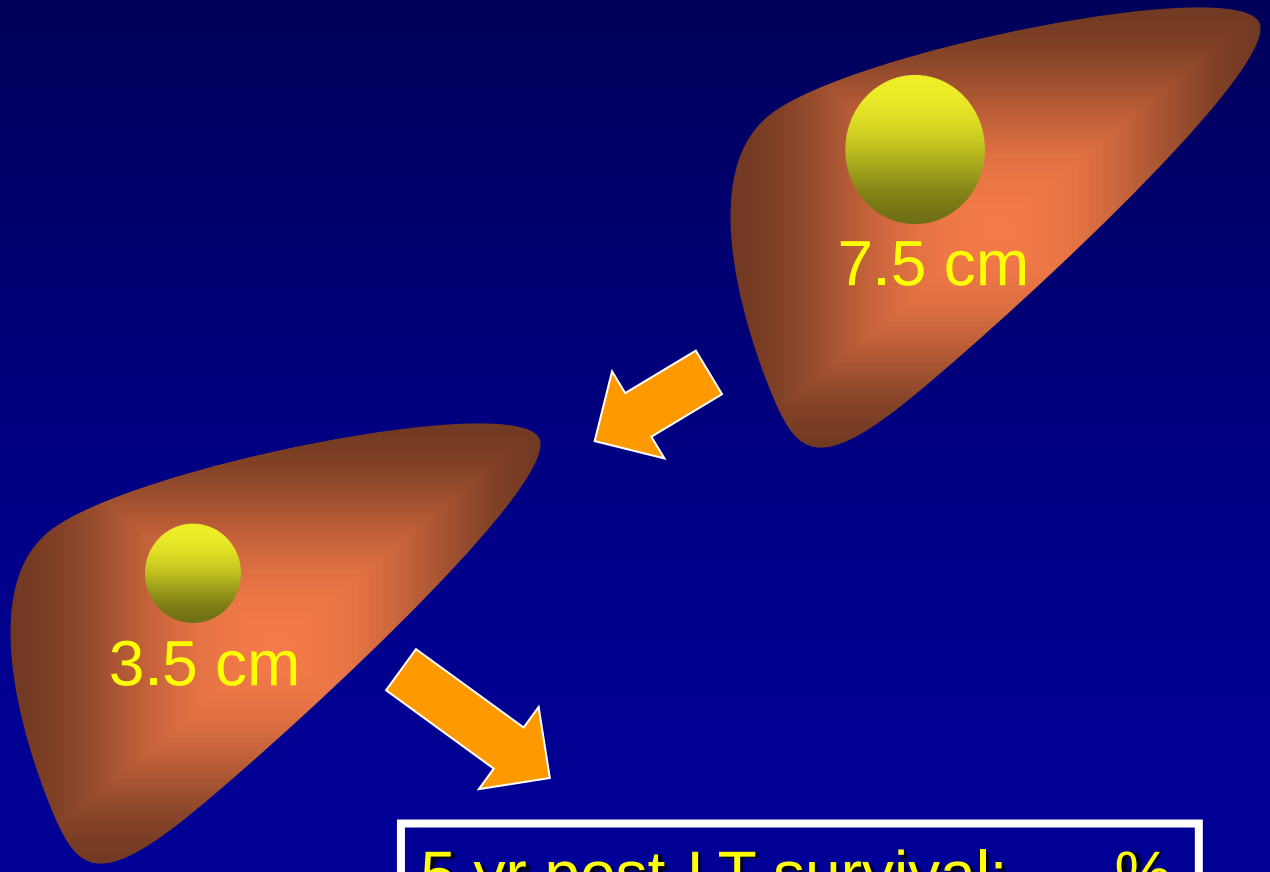


LIVER TRANSPLANTATION FOR HCC: DOWNSTAGING



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

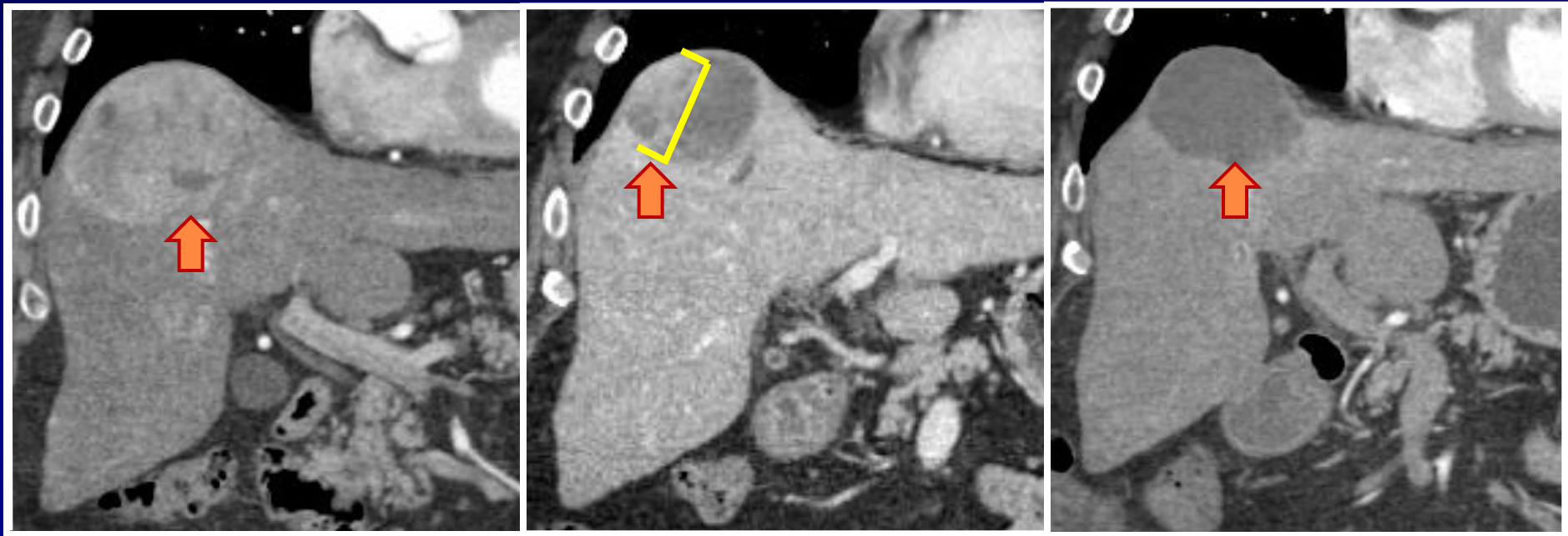
Down-staging of HCC for Transplant

- 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

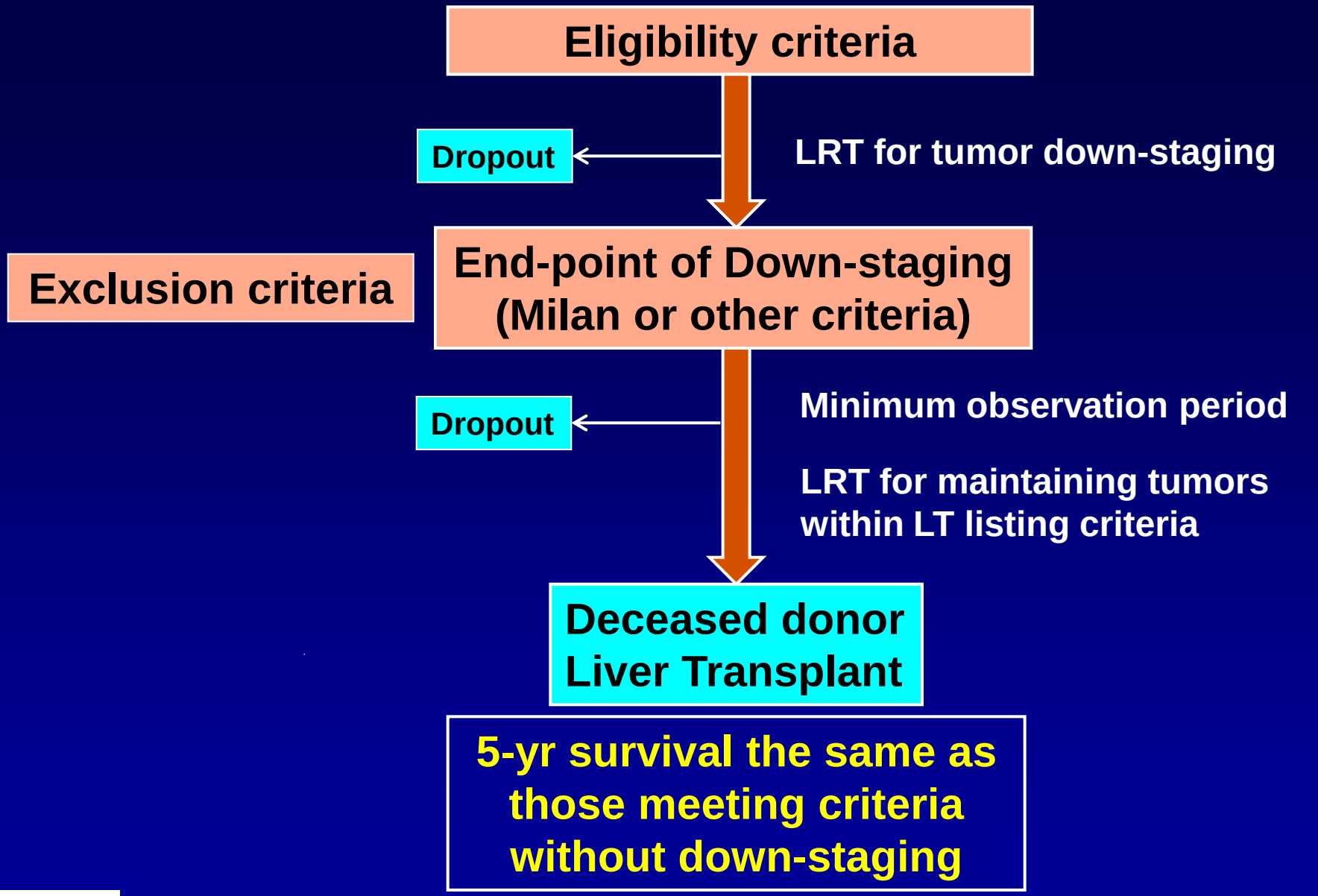
Tumor Down-staging Before Liver Transplant

Beyond Milan | **Within Milan** | **Complete necrosis**



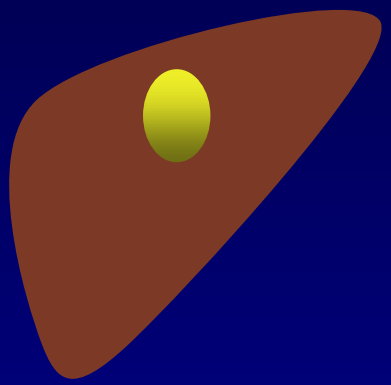
EASL and mRECIST

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



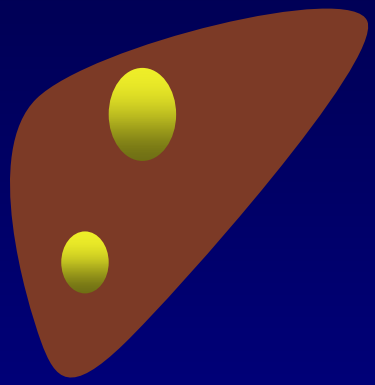
International Consensus Conference on OLT and HCC.
Clavien PA, et al. Lancet Oncology 2012:13;11-22

HCC Transplant Criteria @ UCSF



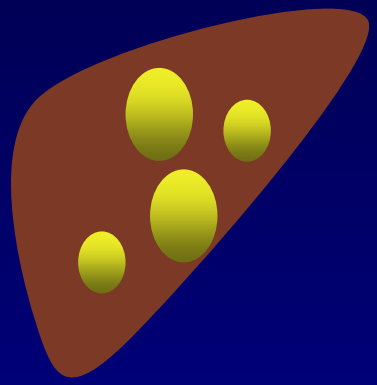
MILAN CRITERIA

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



DOWNSTAGING CRITERIA

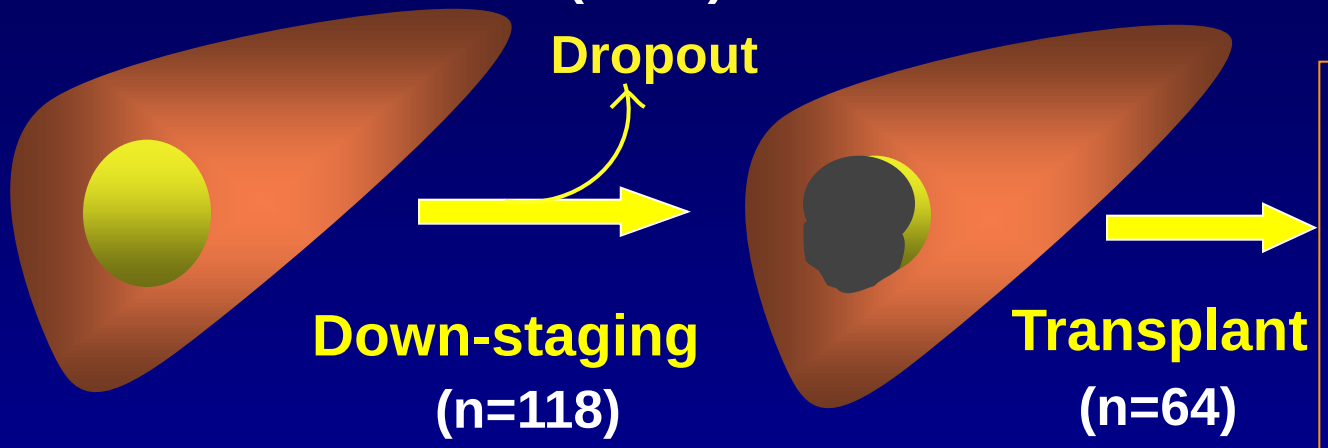
- 1 lesion 5.1-8cm
- 2-3 lesions ≤ 5 cm
- 4-5 lesions ≤ 3 cm
- TTD ≤ 8 cm
- No extra-hepatic dz



ALL-COMERS CRITERIA

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

Down-staging of HCC
Updated UCSF Data



Median f/u 3.8 years

78% 5-yr survival post-transplant

91% 5-yr recurrence- free probability

UCSF Criteria for Down-staging

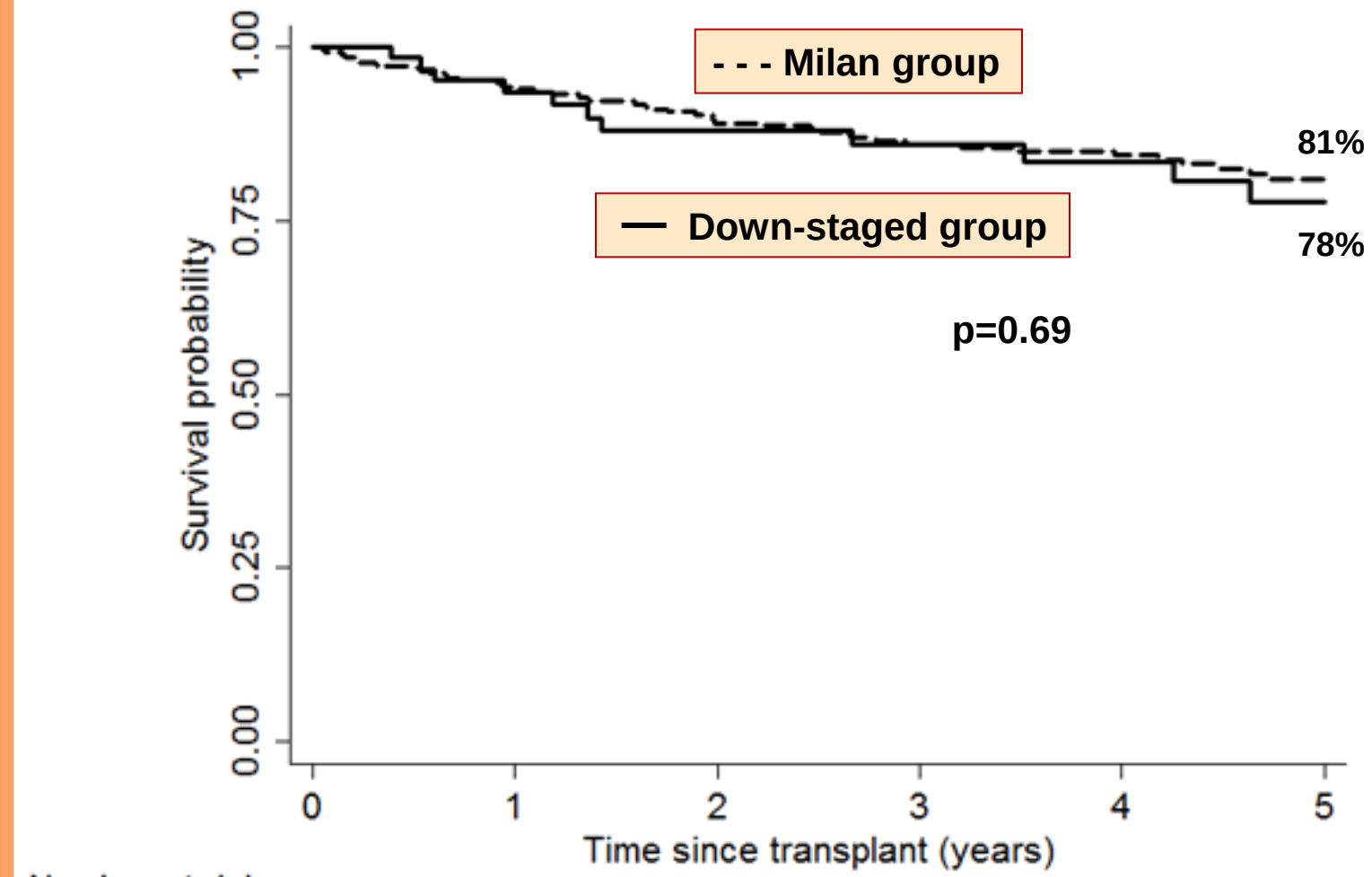
1 tumor ≤ 8 cm

2-3 tumor ≤ 5 cm + total diameter ≤ 8 cm

4-5 tumor ≤ 3 cm + total diameter ≤ 8 cm

Yao et al. Hepatology 2015;61:1968-1977

Post-Transplant Survival



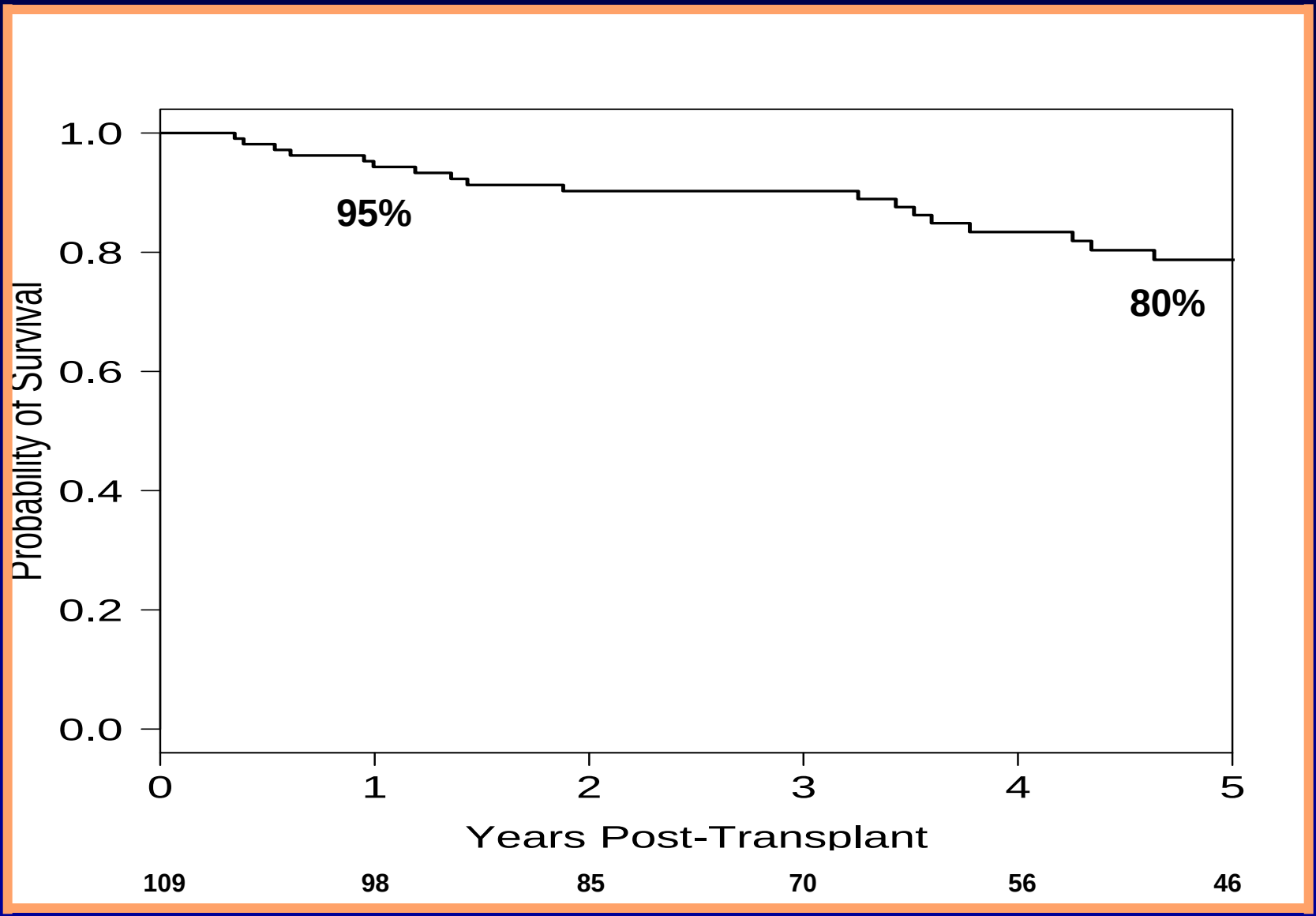
Yao FY, et al. Hepatology 2015;61:1968-1977

Region 5 Multi-center Experience

- 187 consecutive adult patients with HCC treated under Region 5 down-staging protocol from 3 centers (UCSF, CPMC, Scripps) between 2002 and 2012
- Uniform eligibility criteria, criteria for successful down-staging (within Milan criteria) and minimal observation period of 3 months
- Median time from down-staging to liver transplant of 12.6 months (IQR 6-19)
- Median post-transplant follow-up of 4.3 years

Mehta N et al. Clinical Gastroenterology and Hepatology 2017 (in press)

Post-Transplant Survival



Mehta N et al. Clinical Gastroenterology and Hepatology 2017 (in press)

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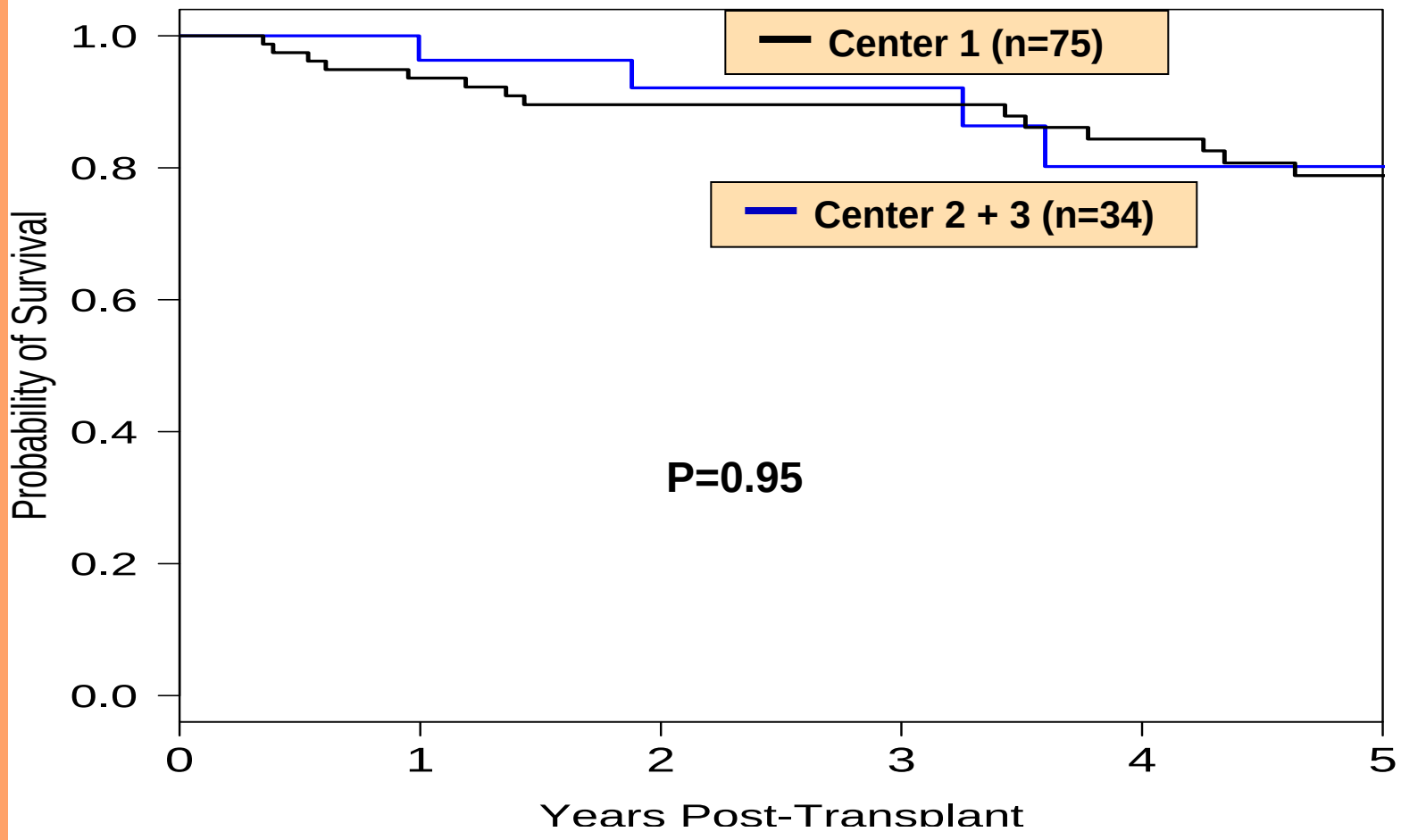

Center 1	75	71	63	53	44	38
Center 2/3	34	27	22	17	12	8

Mehta N et al. Clinical Gastroenterology and Hepatology 2017 (in press)

Region 5 Multi-center Experience

Explant Tumor Characteristics	n (%)
Pathologic Tumor Stage (n=109)	
Complete necrosis (no viable tumor)	38 (35%)
Within Milan criteria	50 (46%)
Beyond Milan criteria	21 (19%)
Vascular Invasion	
Micro-vascular/ Macro-vascular	7 (6%)/ 1 (1%)
Histologic Grade of Differentiation (n=71)	
Well differentiated	25 (35%)
Moderately differentiated	45 (63%)
Poorly differentiated	1 (1%)

Mehta N et al. Clinical Gastroenterology and Hepatology 2017 (in press)

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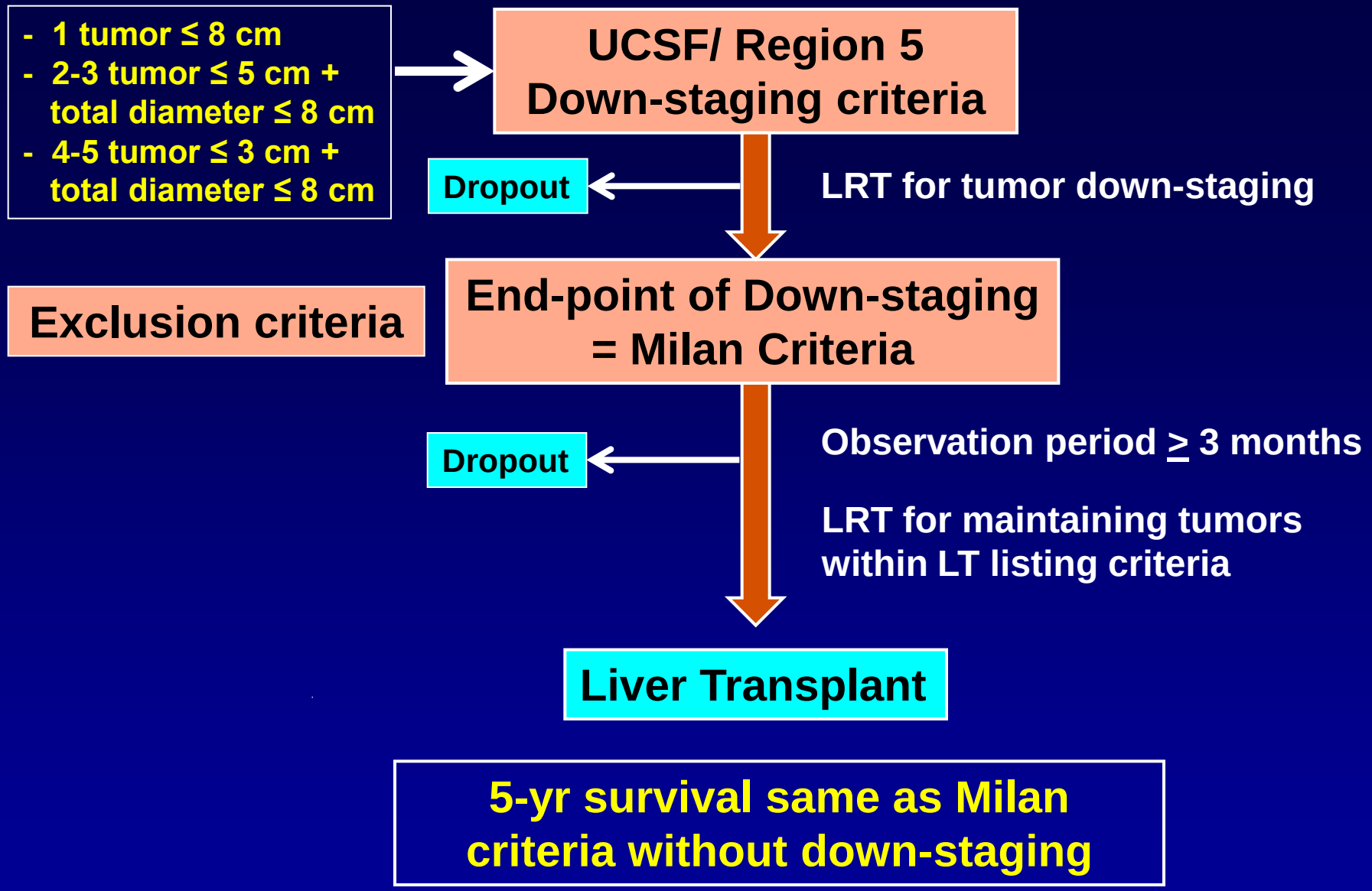


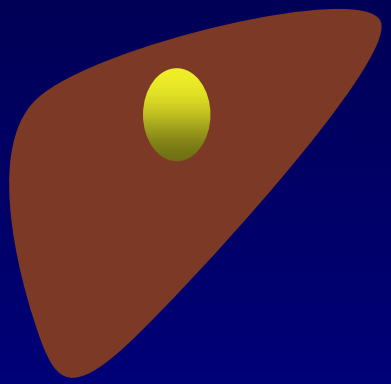
UCSF/ Region 5 Down-staging protocol recently accepted as national policy

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



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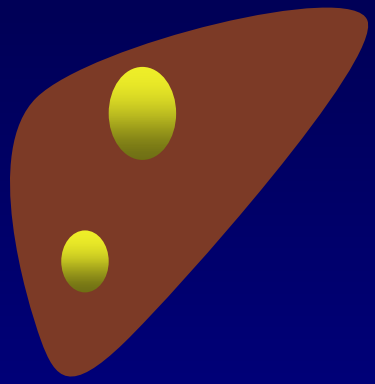

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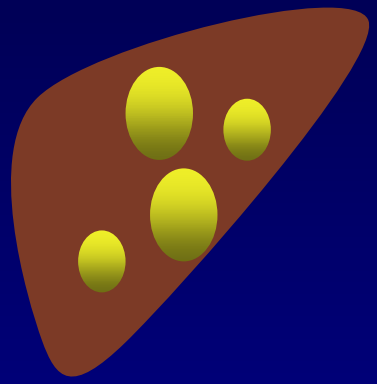
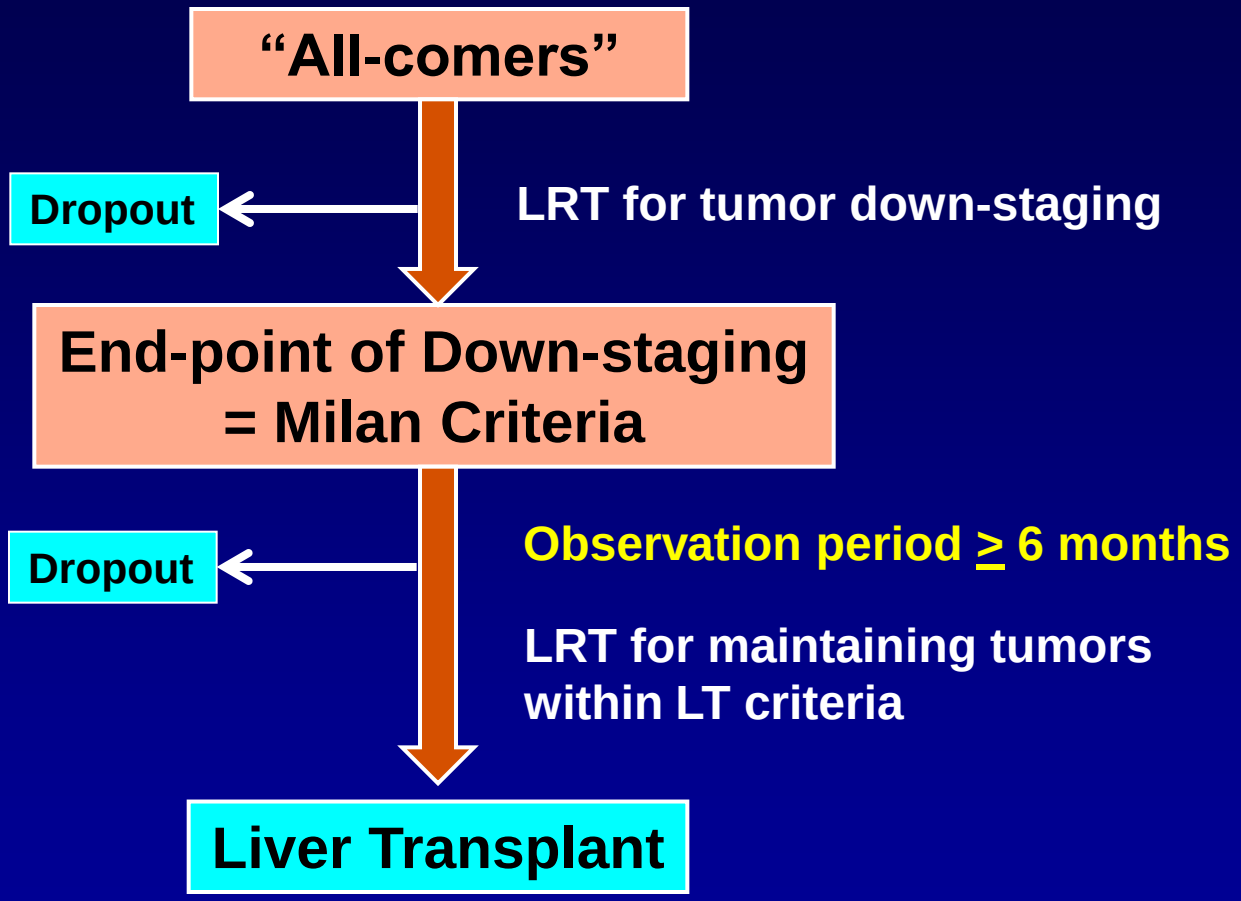
- TTD ≤ 8 cm
- No extra-hepatic dz



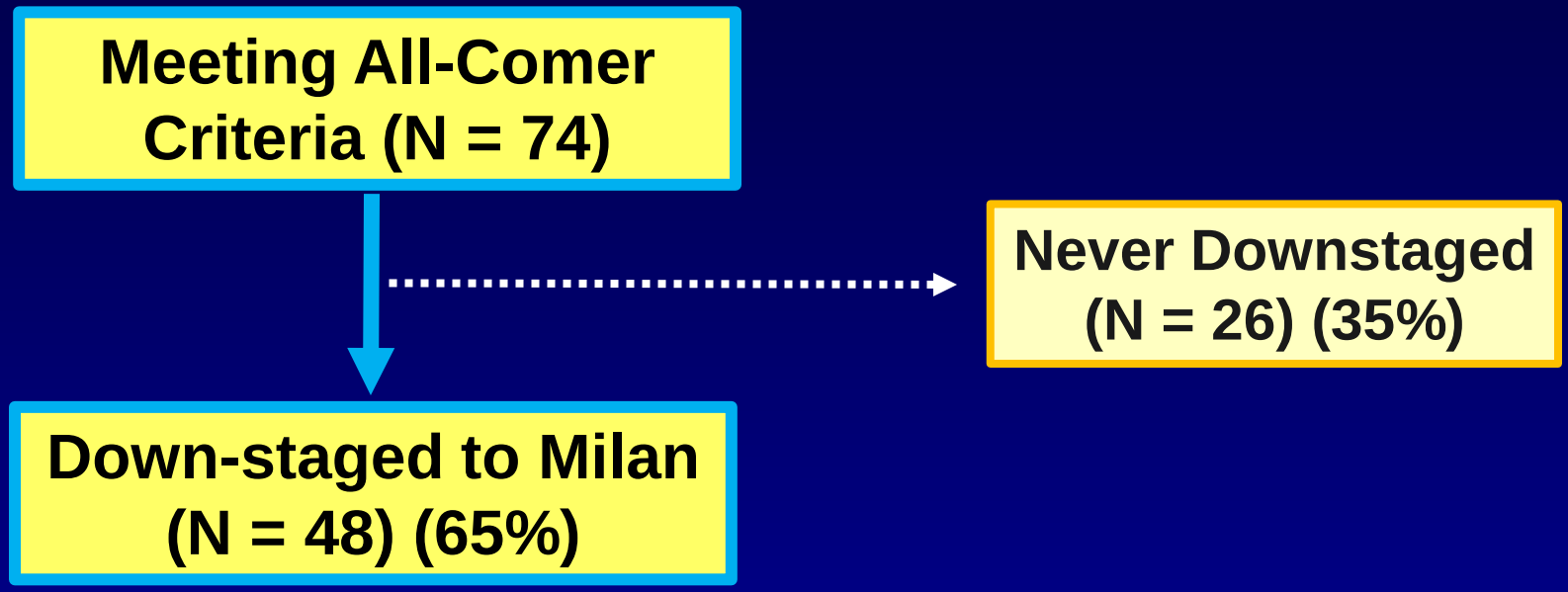
ALL-COMERS CRITERIA

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

“All-comers” Down-staging Protocol

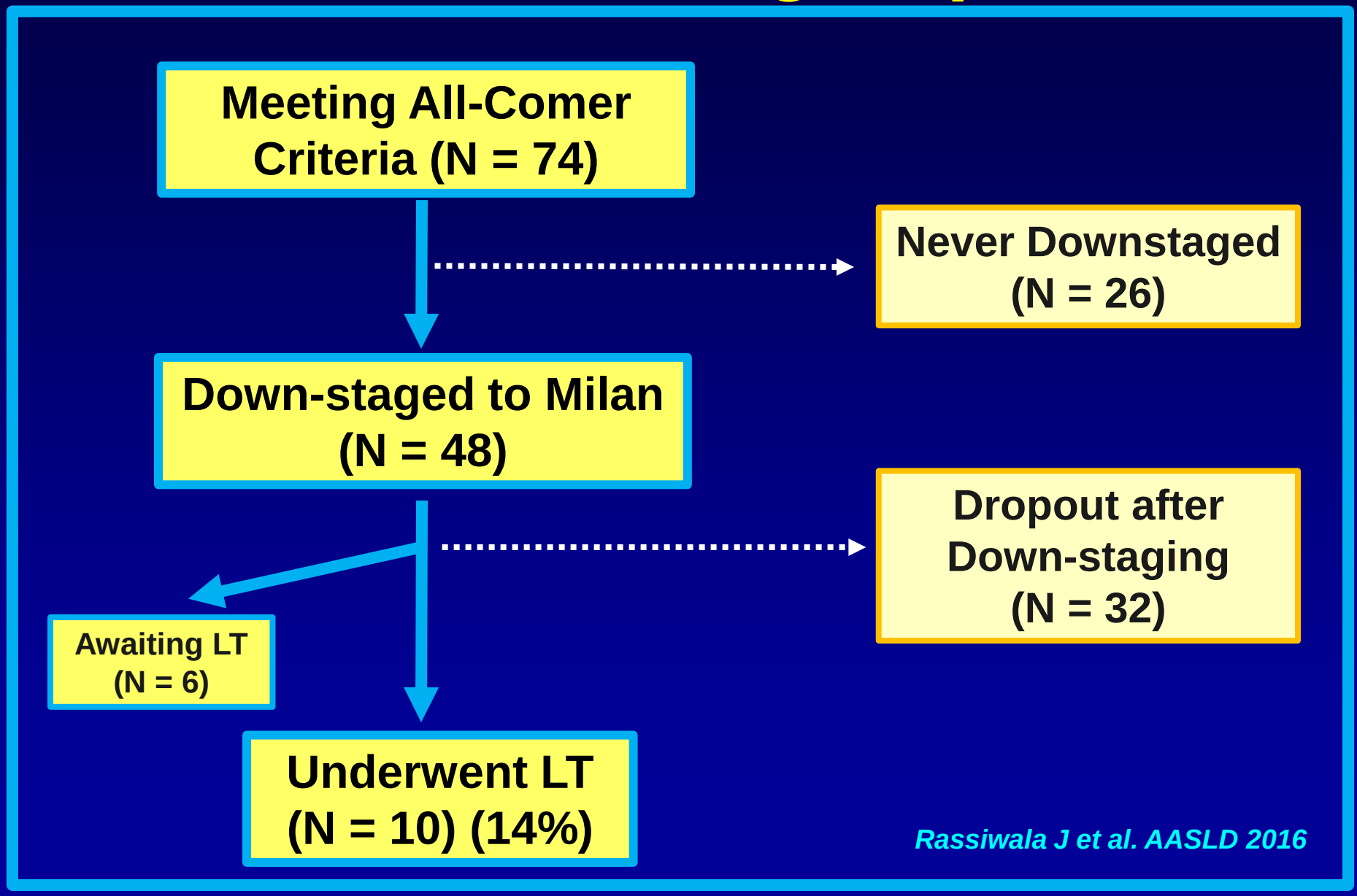


All-comers group



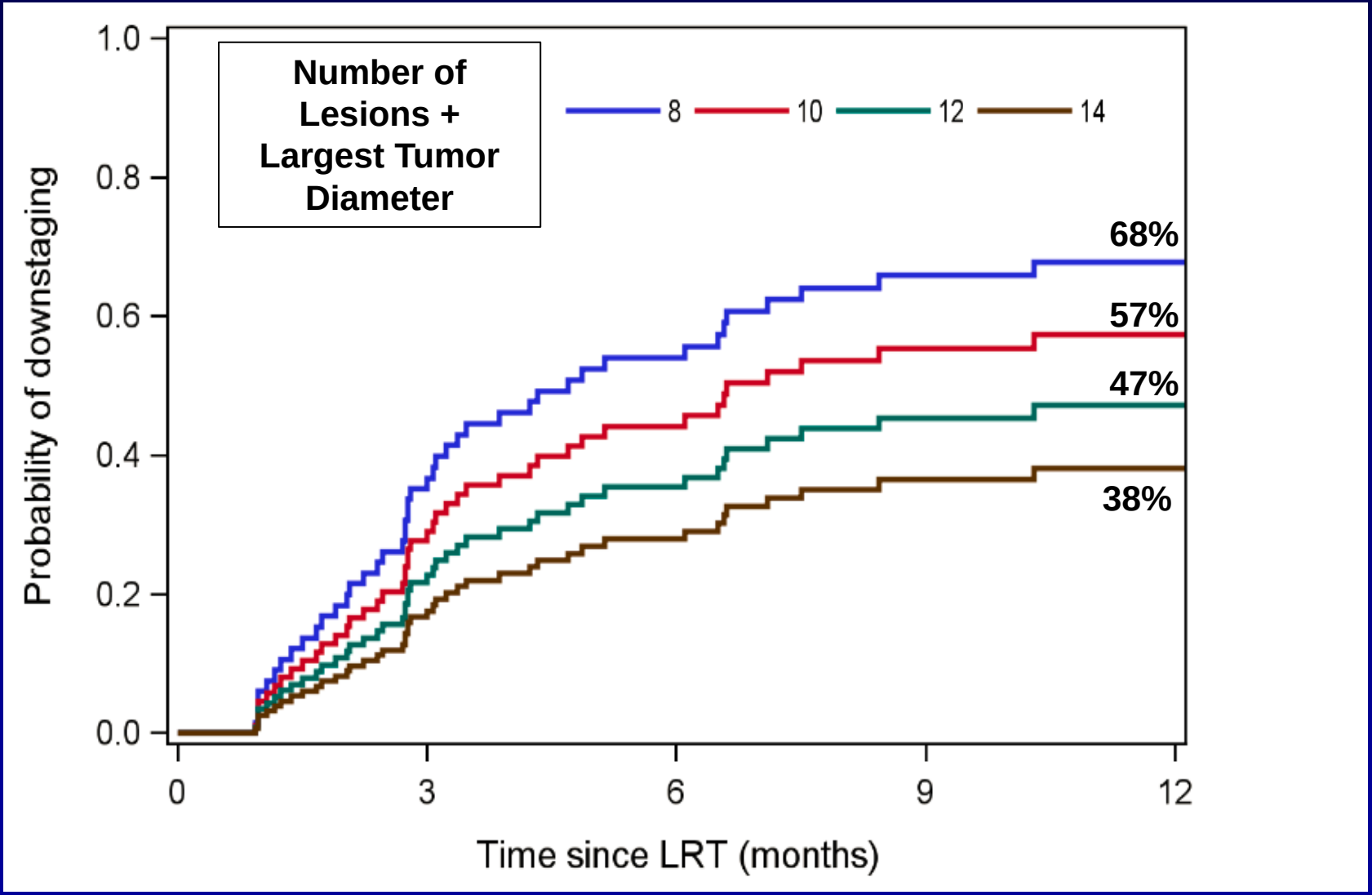
Rassiwala J et al. AASLD 2016

All-comers group



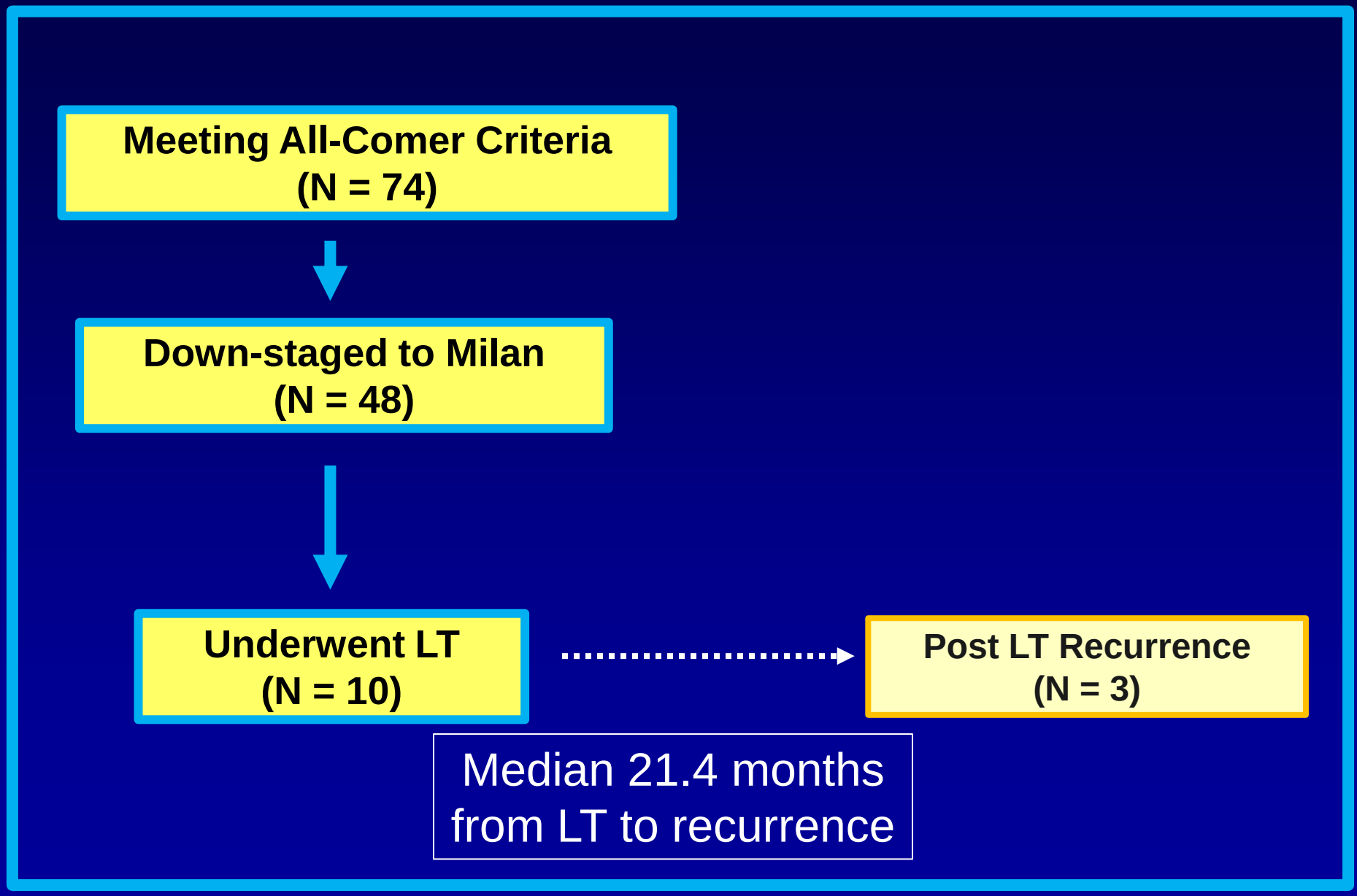
Rassiwala J et al. AASLD 2016

Probability of Downstaging by Initial Tumor Burden

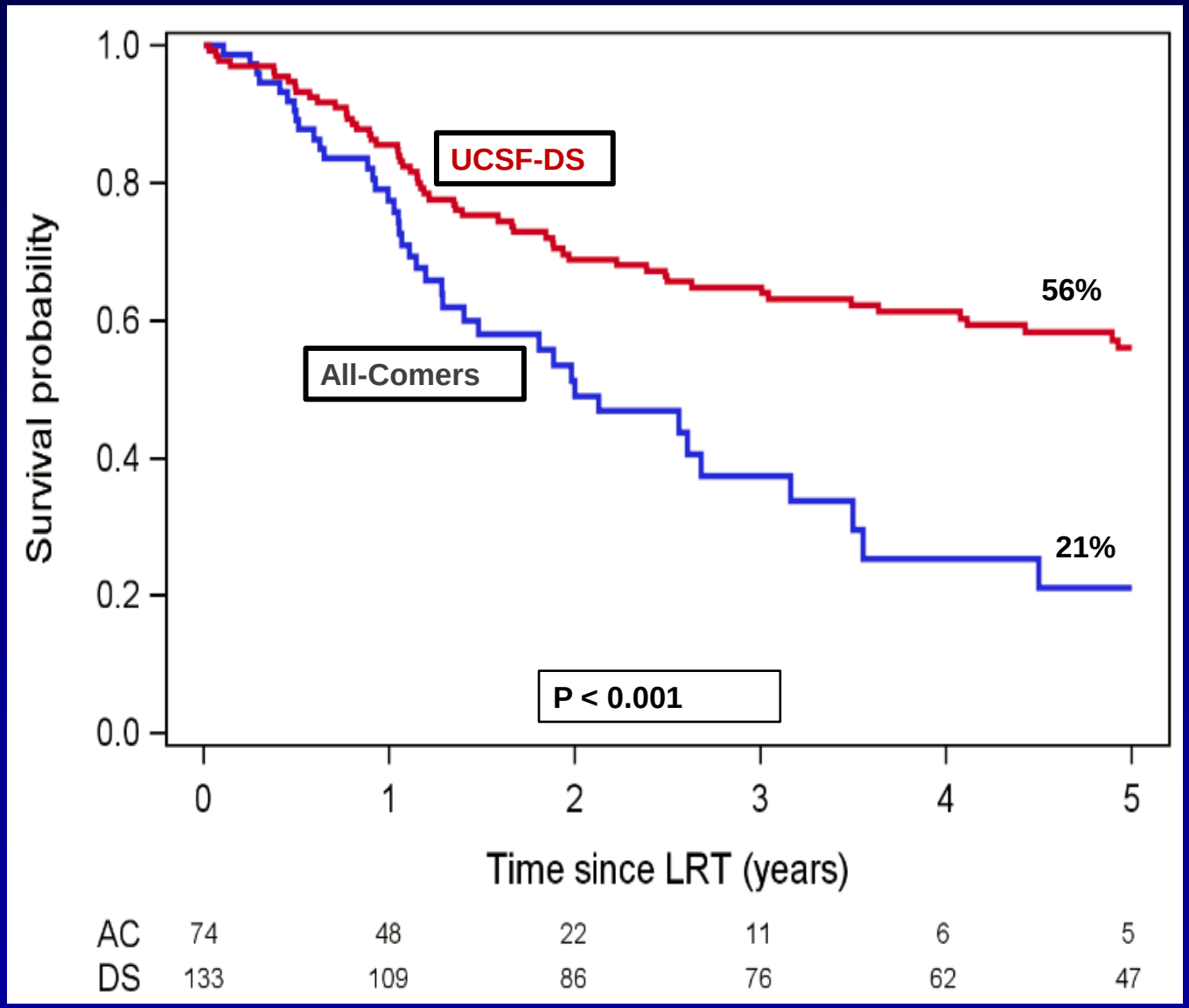


Rassiwala J et al. AASLD 2016

HCC Recurrence (All-comers group)



Intention-to-Treat Survival



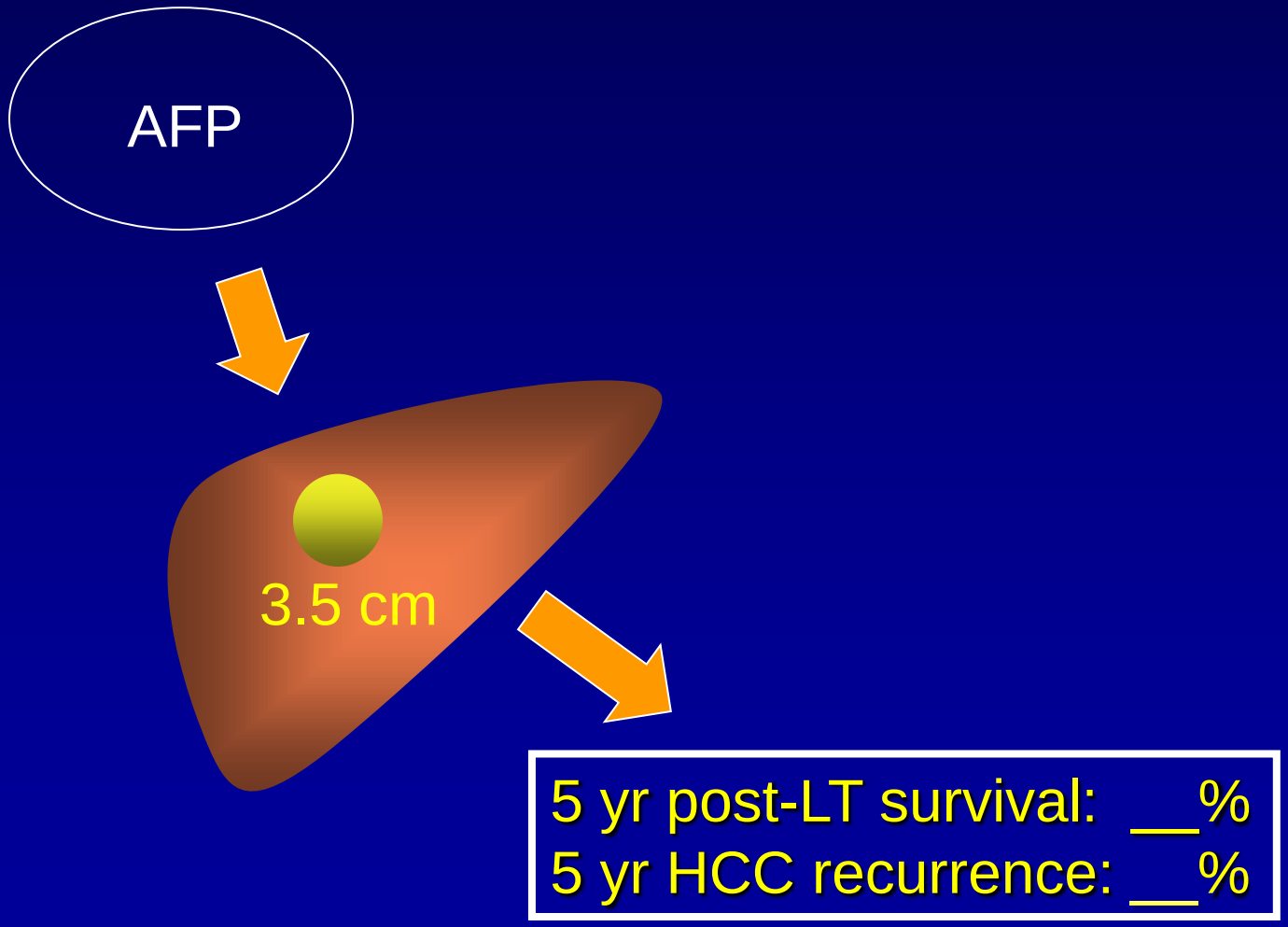
All-comers Summary

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

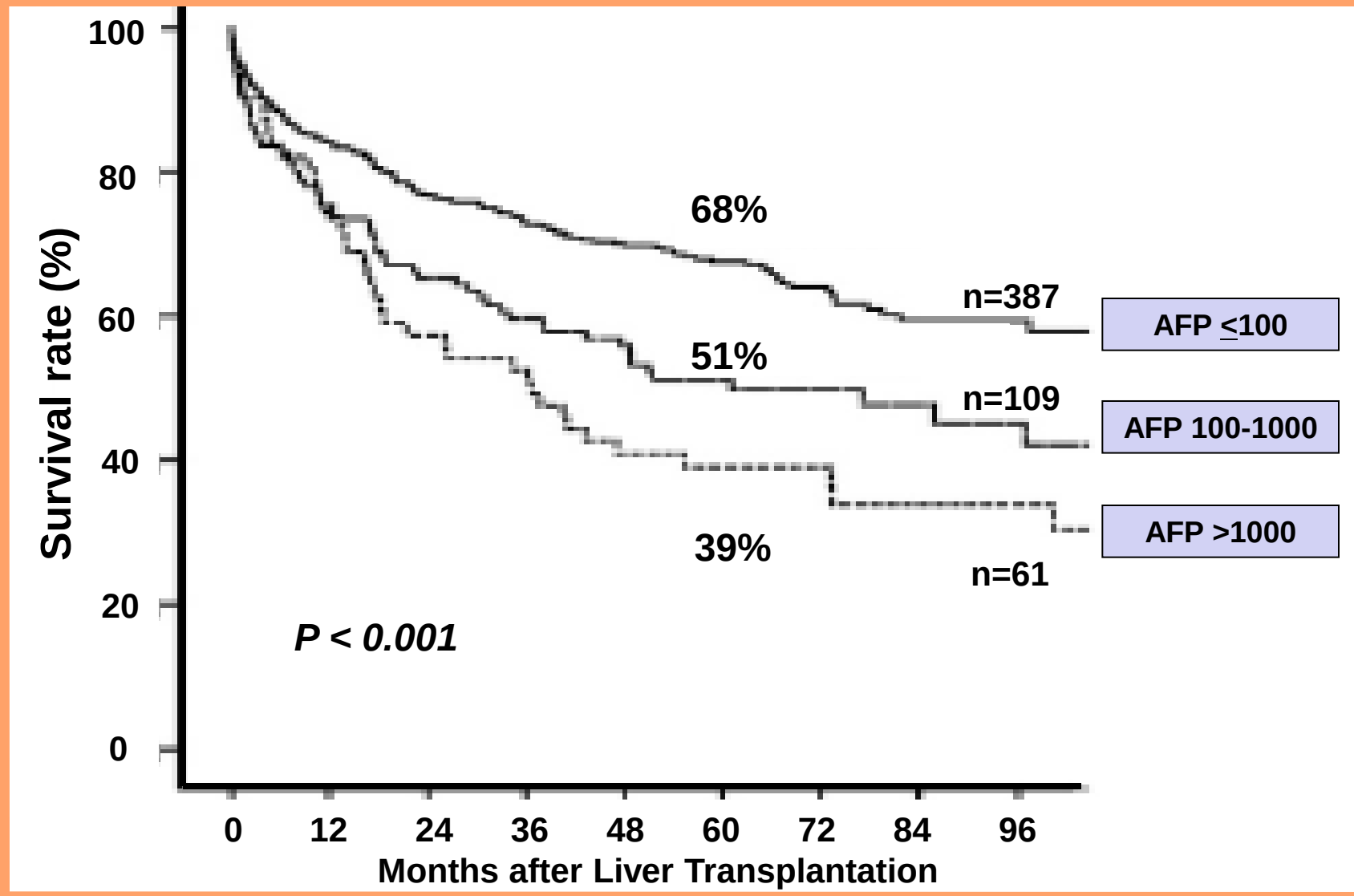
- Patients with tumor burden exceeding the Region 5 down-staging criteria must be very carefully selected for consideration of LT

Rassiwala J et al. AASLD 2016

LIVER TRANSPLANTATION FOR HCC: AFP



AFP and Post-transplant Outcome- France



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

Prognostic Model: Tumor size, number and AFP

Variables	Points
Largest tumor diameter, cm	
≤ 3	0
3-6	1
> 6	4
Number of tumor nodules	
1-3	0
≥ 4	2
AFP level, *ng/mL*	
≤ 100	0
100-1000	2
> 1000	3

UCSF Transplant

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

Prognostic Model: Tumor size, number and AFP

Variables	Points
Largest tumor diameter, cm	
≤ 3	0
3-6	1
> 6	4
Number of tumor nodules	
1-3	0
≥ 4	2
AFP level, *ng/mL*	
≤ 100	0
100-1000	2
> 1000	3

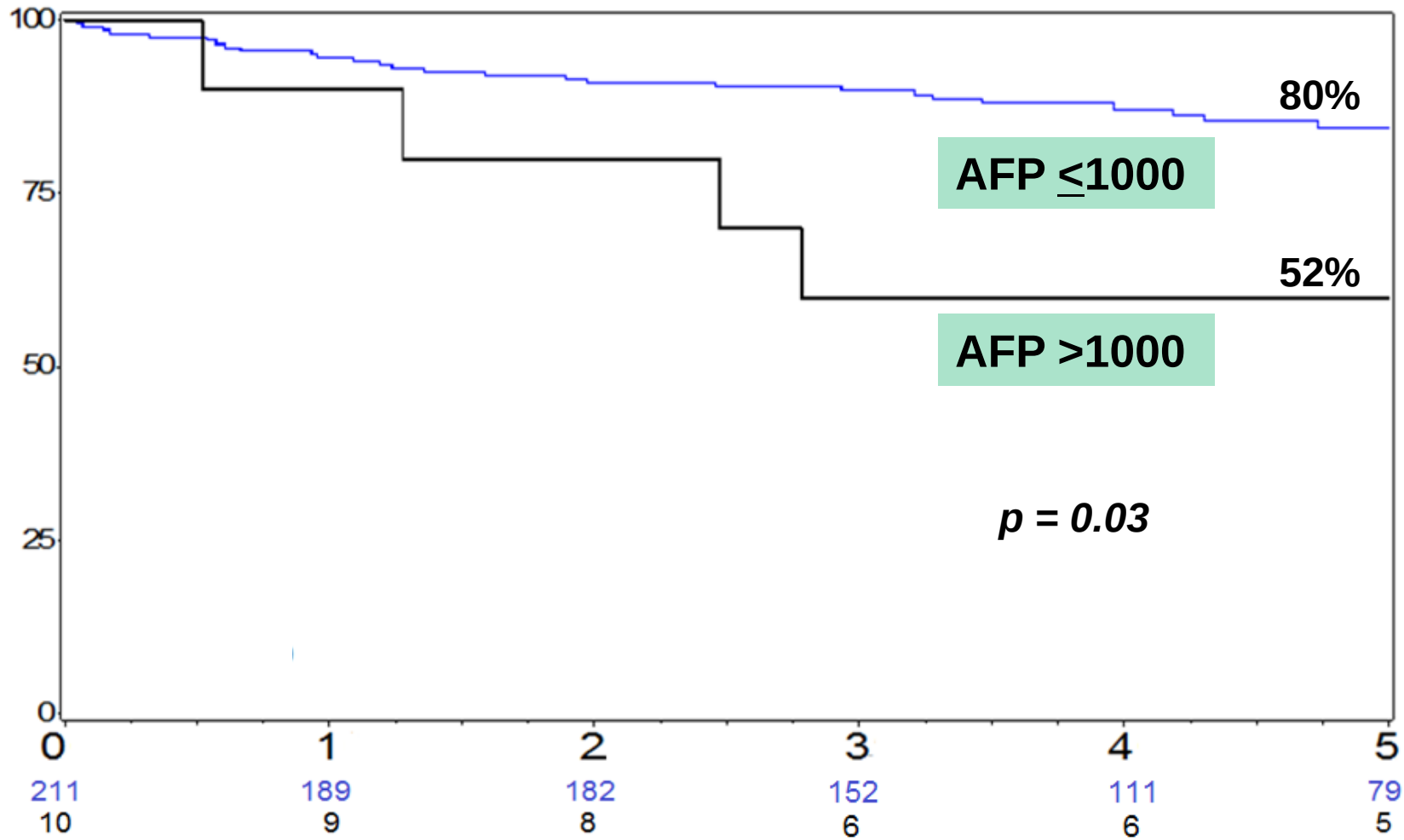
Low risk
≤ 2 points

Some HCC > Milan
but AFP ≤ 100
= Low risk

UCSF Transplant

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

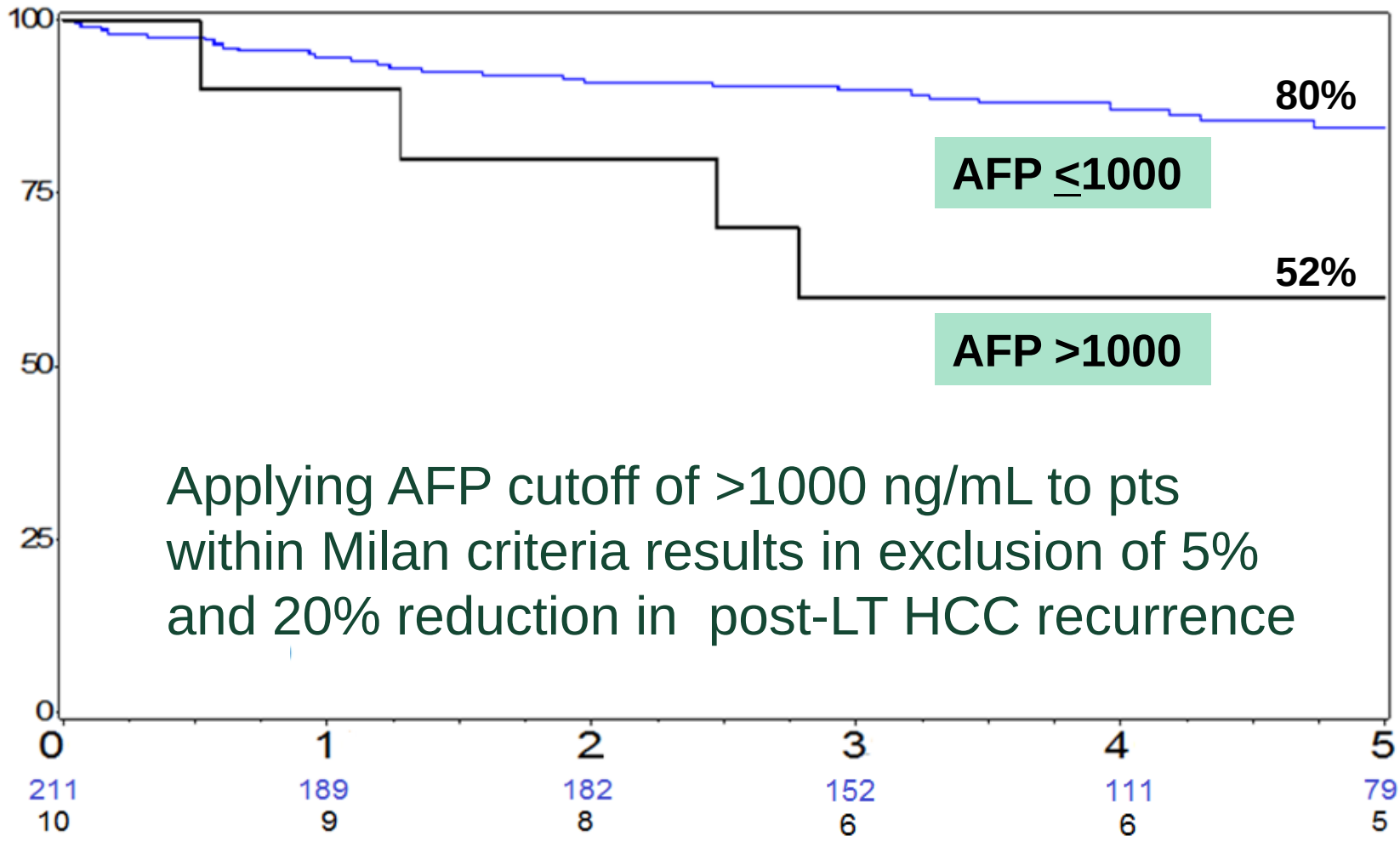
AFP and Post-transplant Outcome - UCSF



y

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

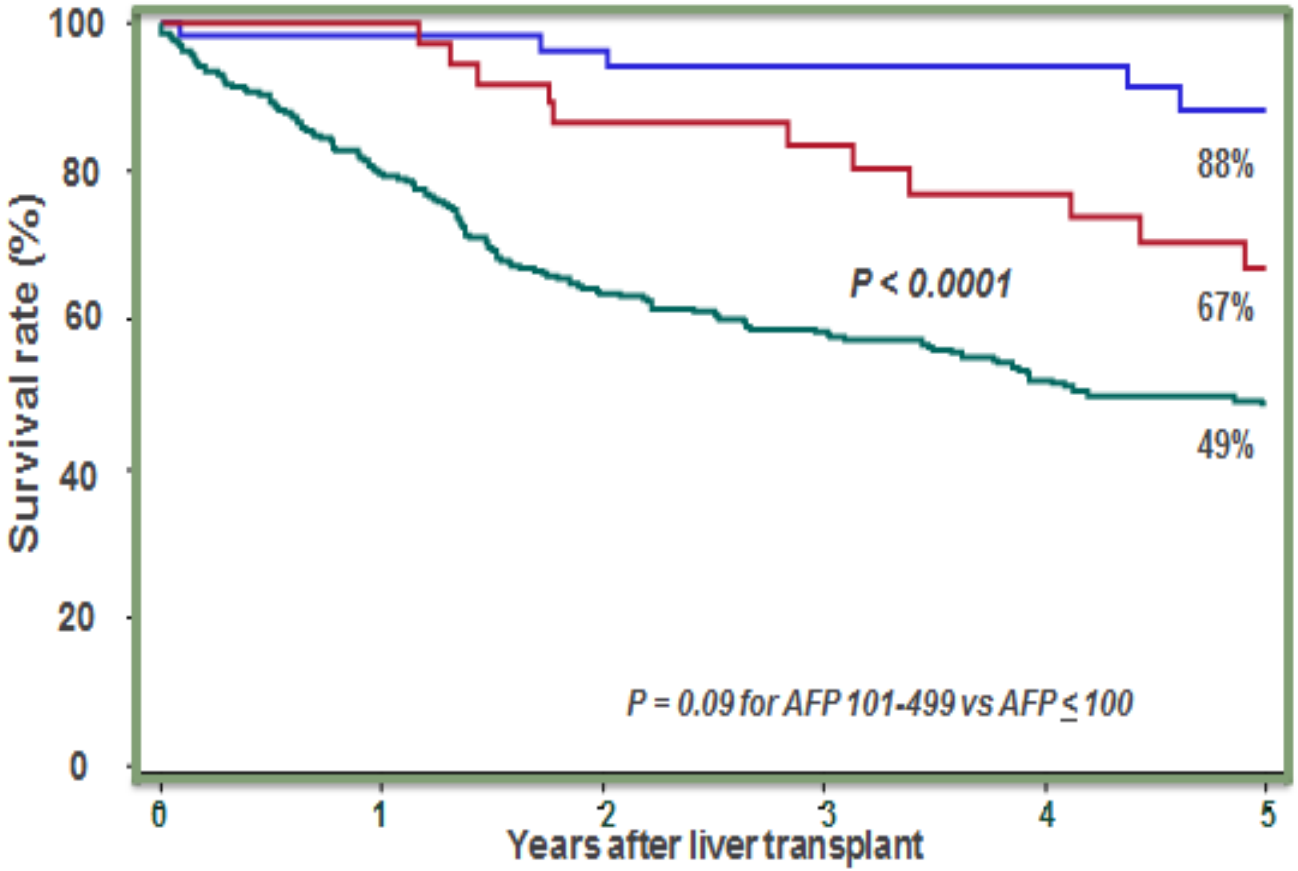
AFP and Post-transplant Outcome - UCSF



y

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

REDUCING HIGH AFP PRIOR TO LT



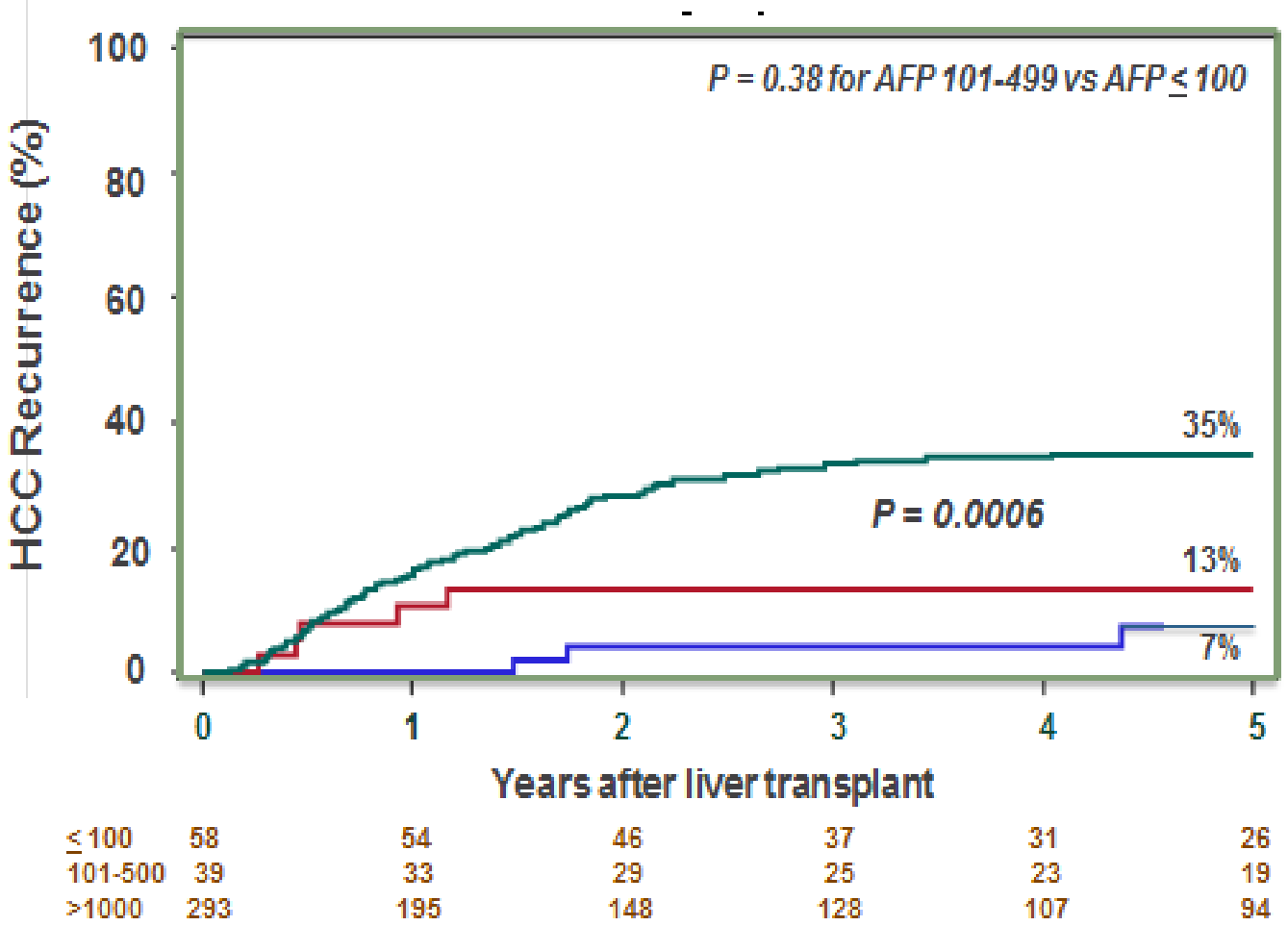
AFP > 1000 → ≤ 100

AFP > 1000 → 101-499

AFP > 1000

Yao F. et al. AASLD 2017

REDUCING HIGH AFP PRIOR TO LT



AFP > 1000

AFP > 1000 → 101-499

AFP > 1000 → ≤ 100

Yao F. et al. AASLD 2017

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

UNOS POLICY CHANGE

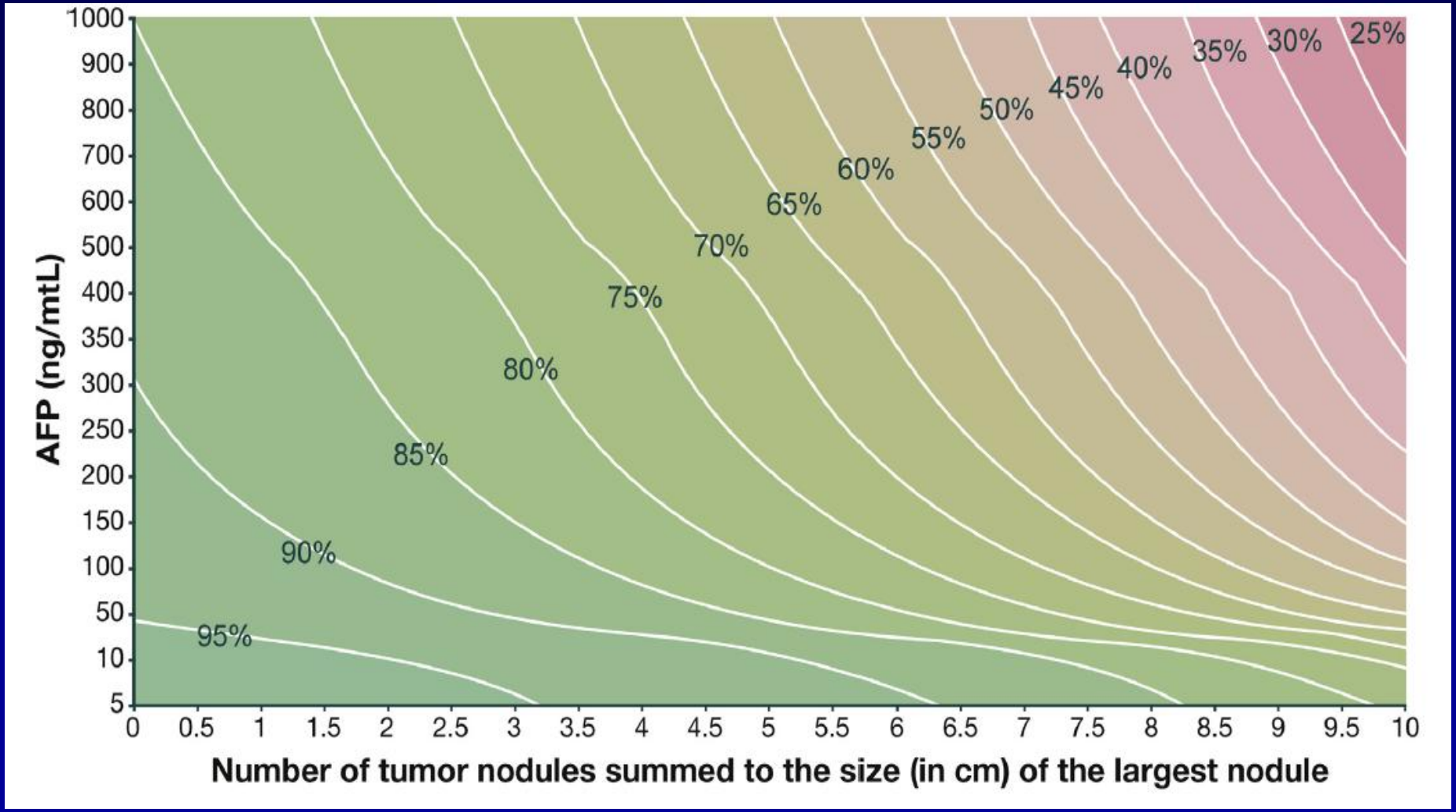
High AFP Threshold

- 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

However, AFP reduction to <100 after LRT is ideal

LT FOR HCC: METROTICKET 2.0

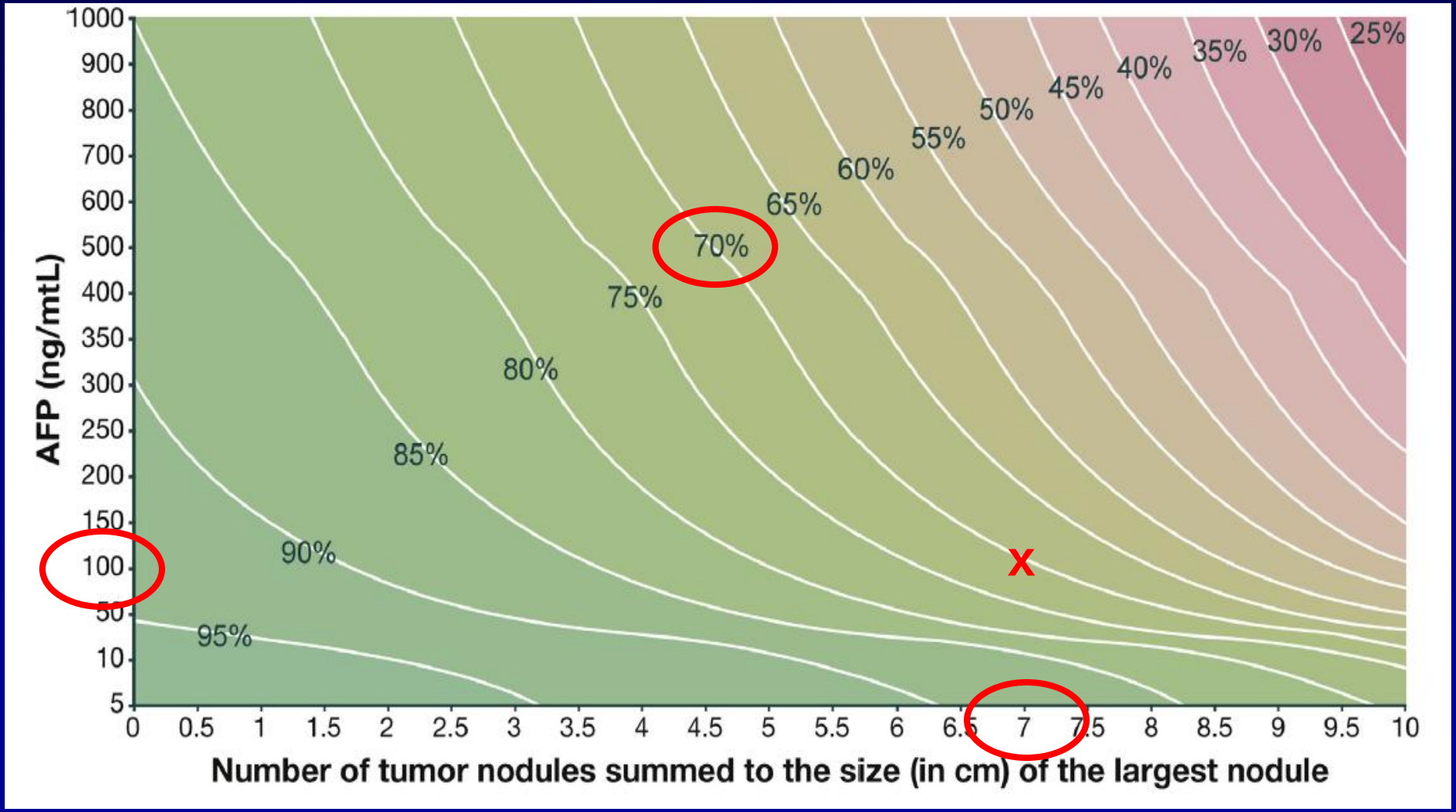
HCC Specific Survival



Mazzaferro V et al. Gastroenterology 2017 (in press)

LT FOR HCC: METROTICKET 2.0

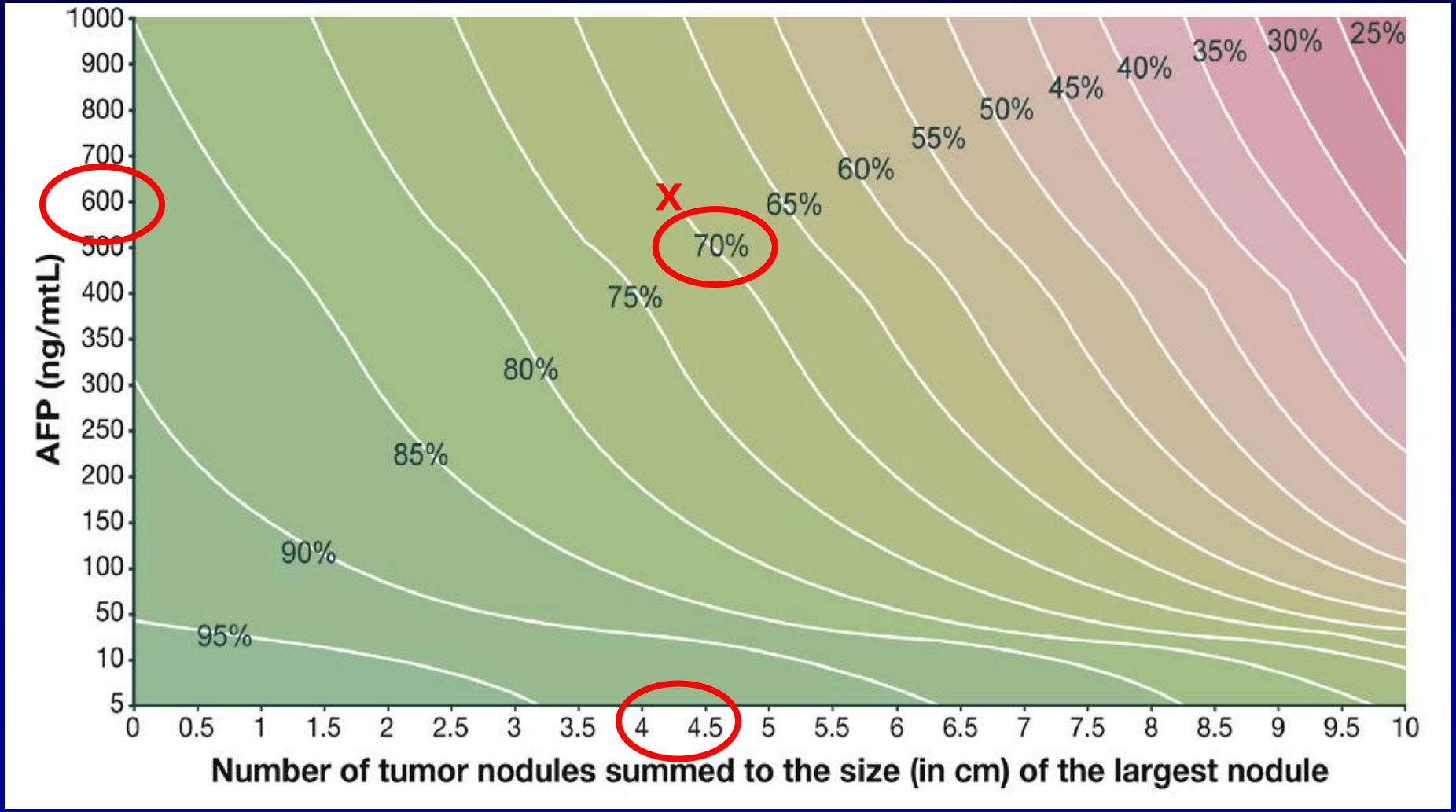
HCC Specific Survival



Mazzaferro V et al. Gastroenterology 2017 (in press)

LT FOR HCC: METROTICKET 2.0

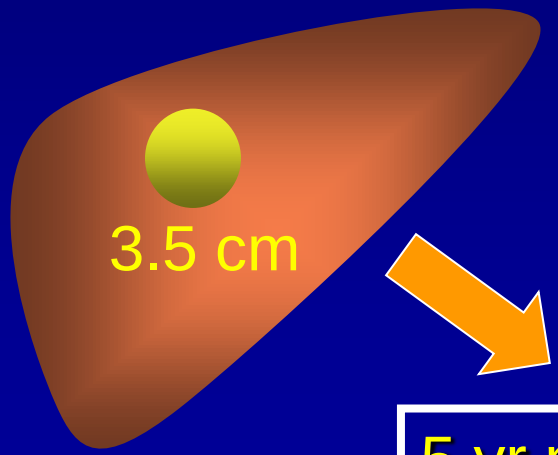
HCC Specific Survival



Mazzaferro V et al. Gastroenterology 2017 (in press)

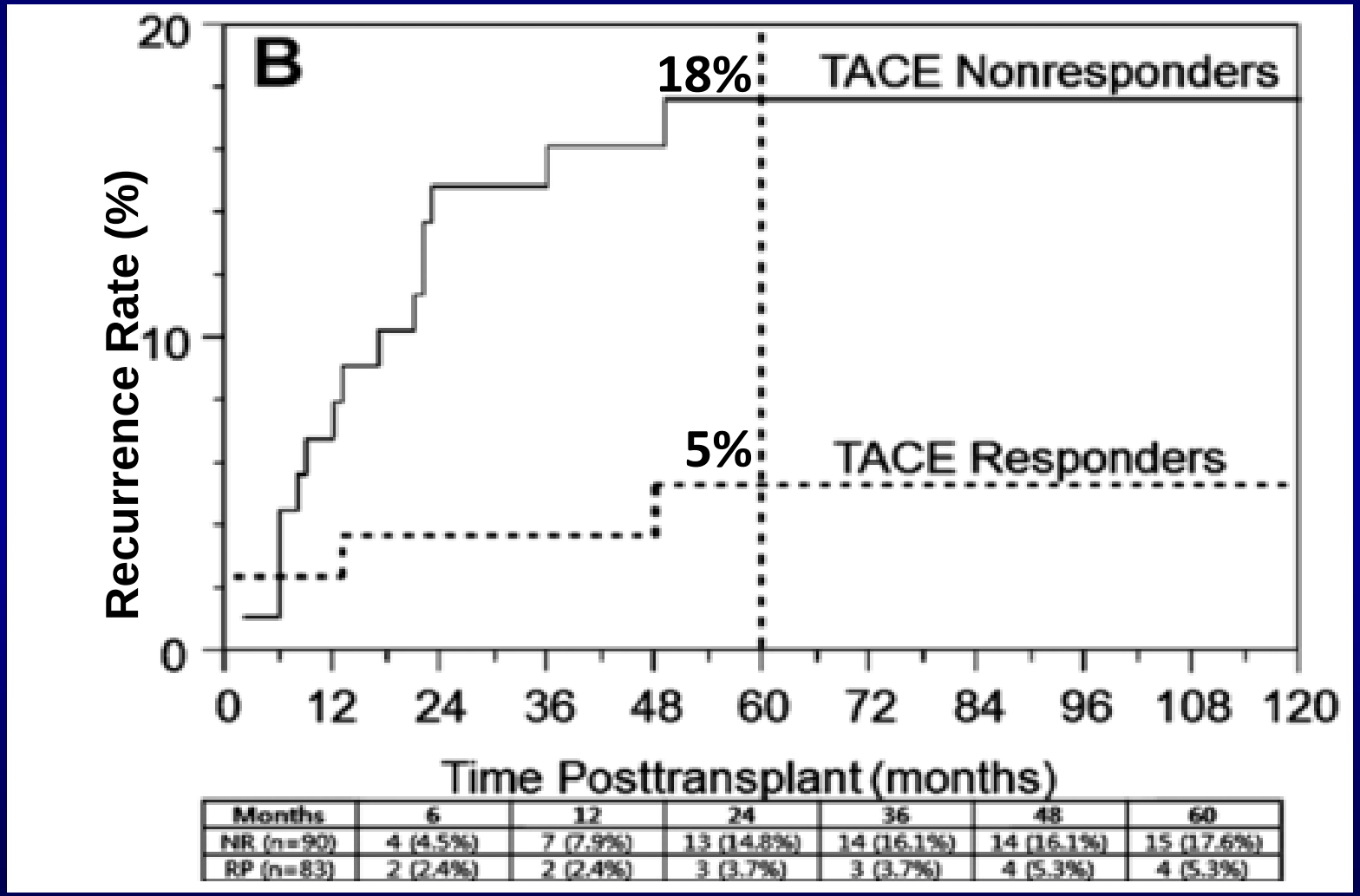
LIVER TRANSPLANTATION FOR HCC: OPTIMIZING SELECTION CRITERIA

Response to LRT



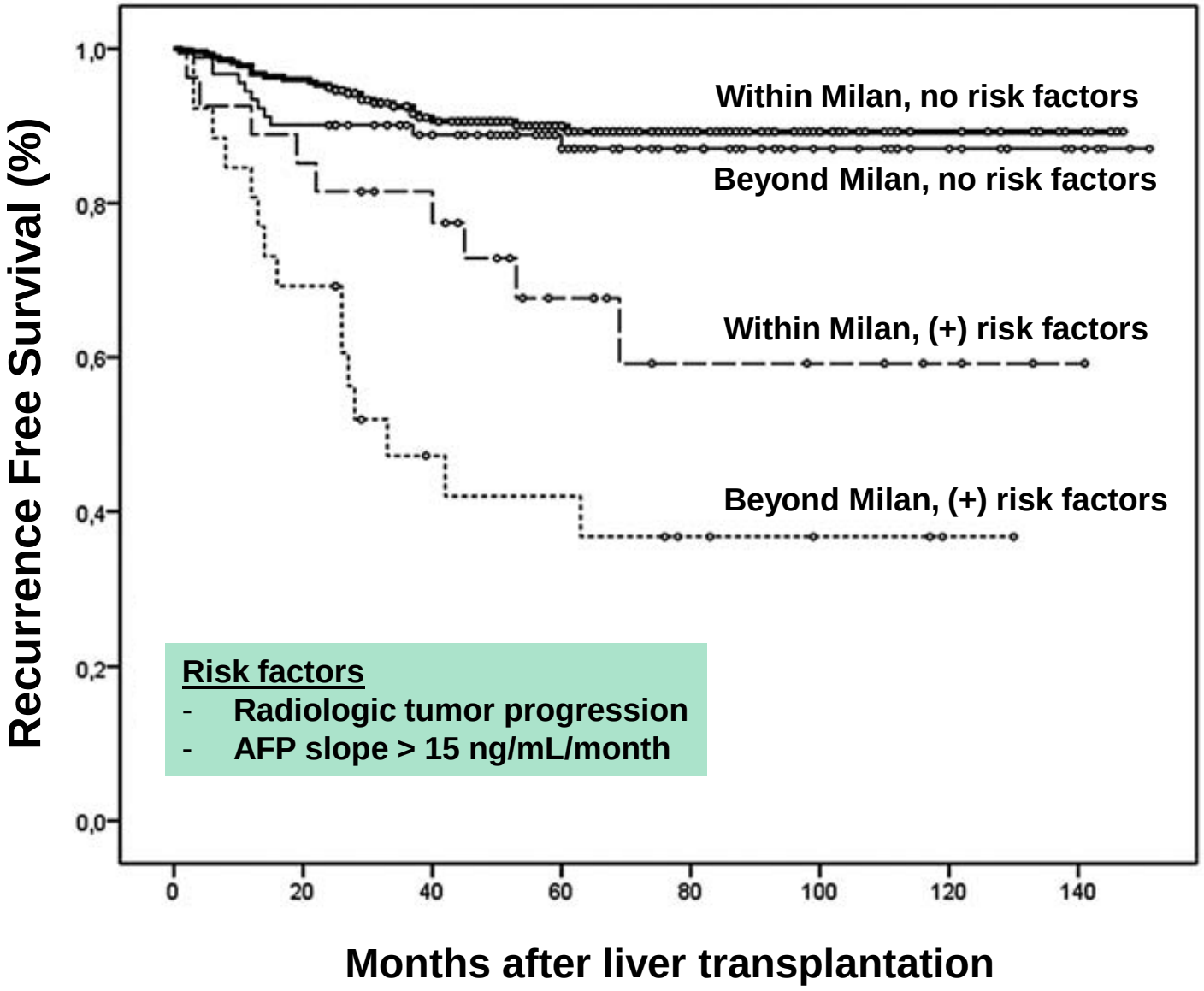
5 yr post-LT survival: __%
5 yr HCC recurrence: __%

RESPONSE TO LOCAL-REGIONAL THERAPY AS PROGNOSTIC FACTOR

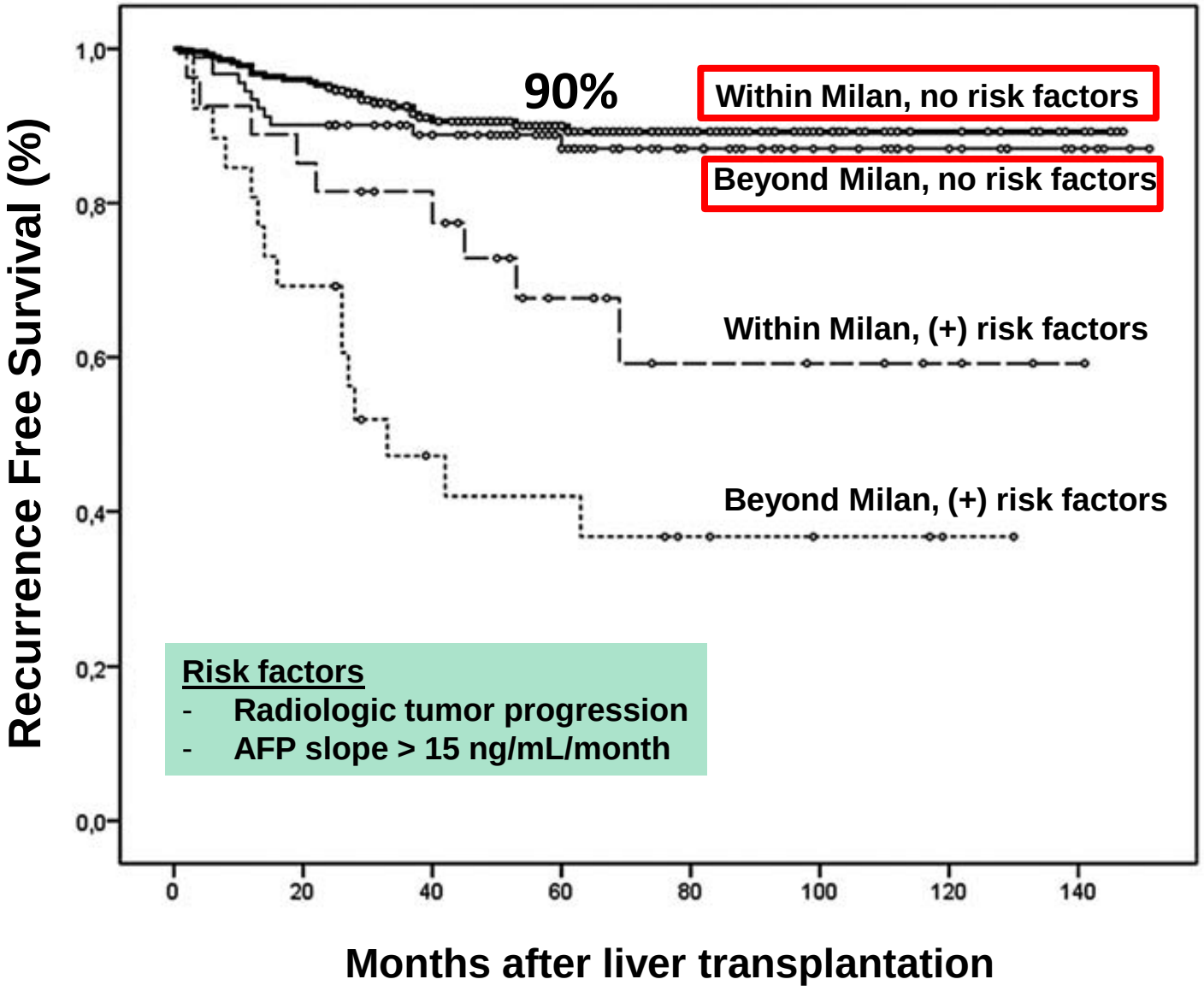


Months	6	12	24	36	48	60
NR (n=90)	4 (4.5%)	7 (7.9%)	13 (14.8%)	14 (16.1%)	14 (16.1%)	15 (17.6%)
RP (n=83)	2 (2.4%)	2 (2.4%)	3 (3.7%)	3 (3.7%)	4 (5.3%)	4 (5.3%)

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



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



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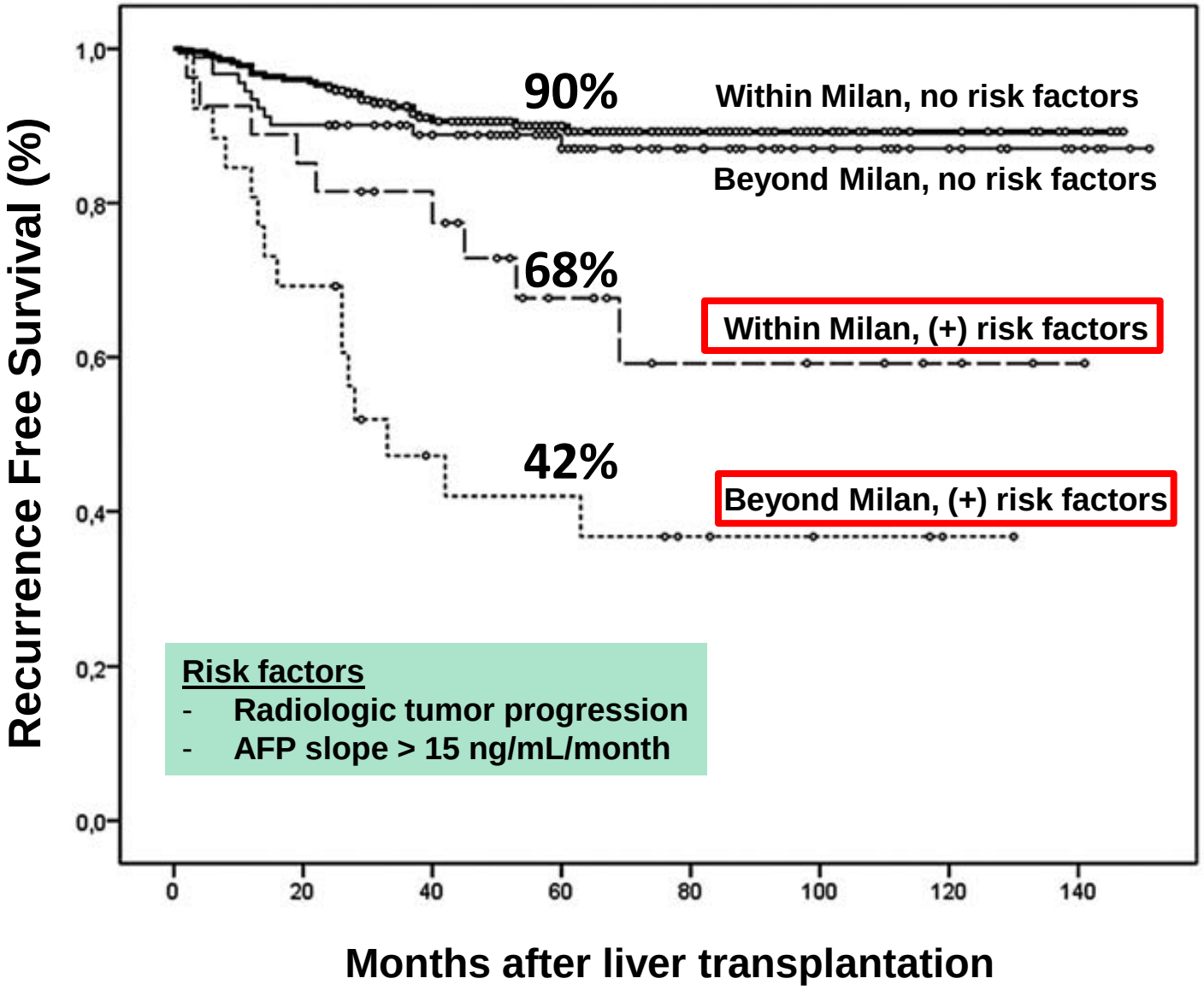
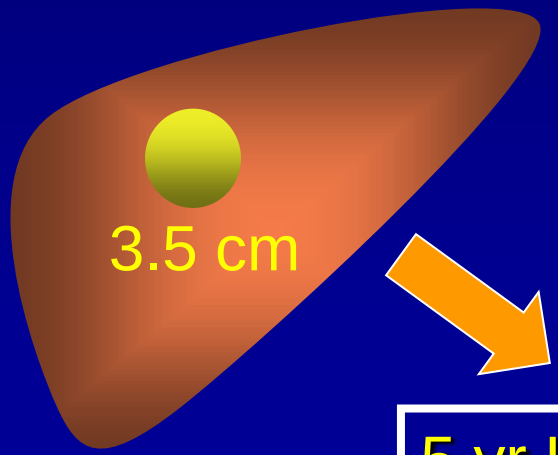


Lai Q, et al. Liver Transpl 2013;19:1108-1118

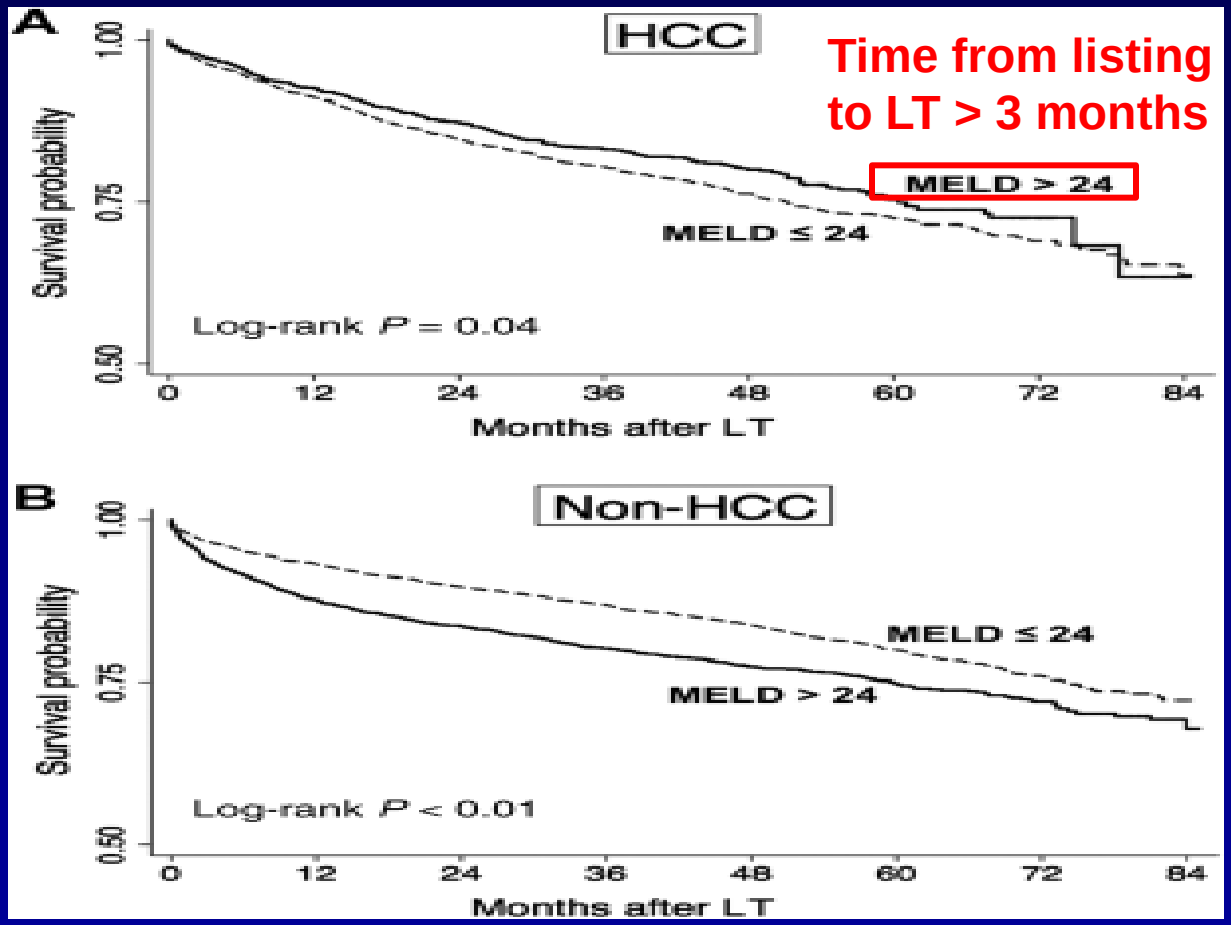
LIVER TRANSPLANTATION FOR HCC: OPTIMIZING SELECTION CRITERIA

Wait Time to LT



5 yr HCC recurrence: __%

POST-LT HCC SURVIVAL IN UNOS DATABASE: IMPACT OF WAITING TIME



Schlansky et al, Liver Transplantation 2014; 1045-56

U.S. MULTI-CENTER STUDY ON WAIT TIMES

- Multi-center cohort study of all adults with HCC within Milan criteria by imaging listed with MELD exception from 2002-2012 (n=911)

- 3 study centers chosen to capture spectrum of wait times:
  - Long (UCSF - Center 1)
  - Medium (Mayo Clinic Rochester - Center 2)
  - Short (Mayo Clinic Jacksonville - Center 3)

- Wait time started at HCC diagnosis

Mehta N, et al. Transplantation 2017

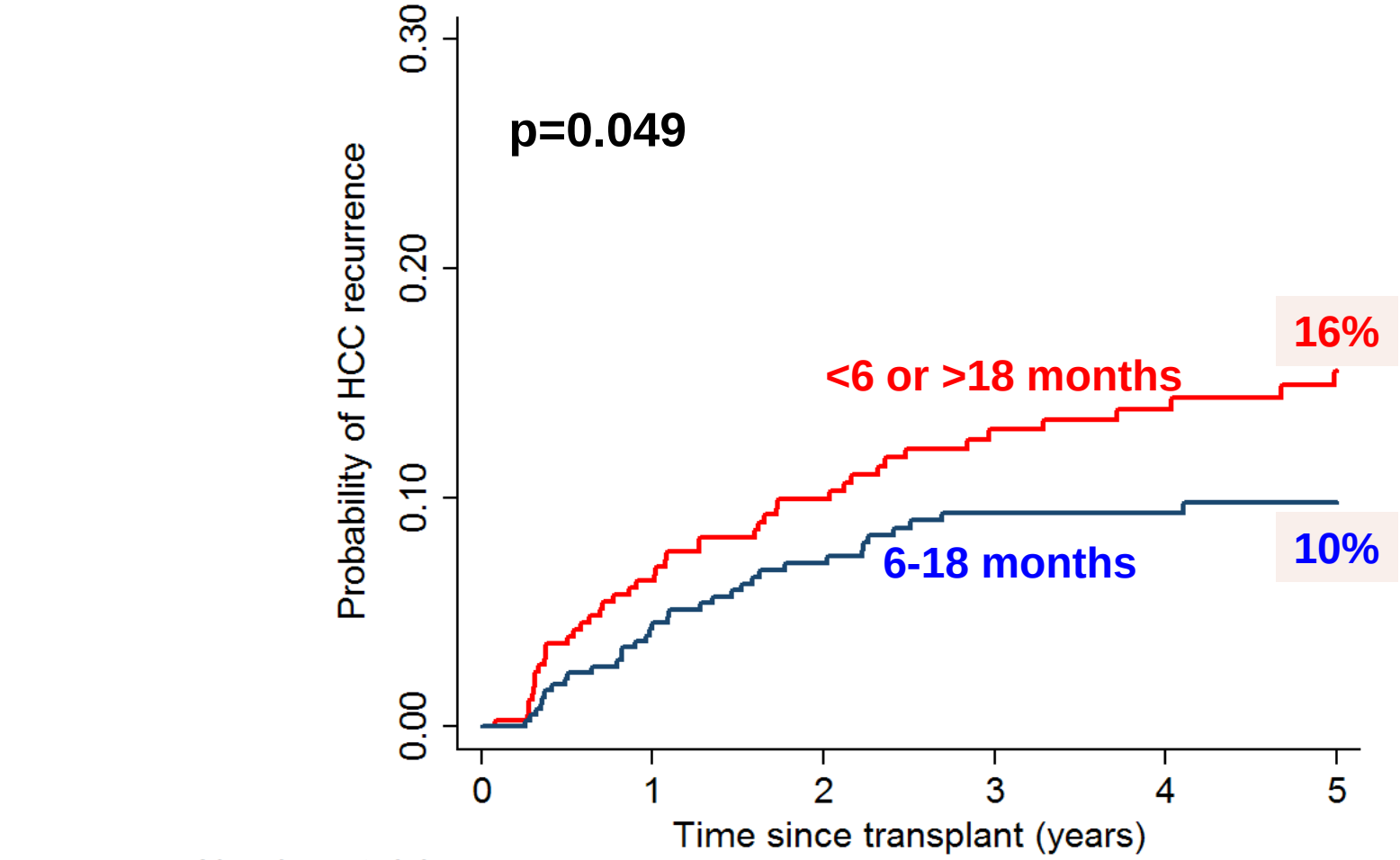
PREDICTORS OF RECURRENCE KNOWN PRIOR TO LT

Predictor	Multivariable HR (95% CI)	p-value
Wait Time to LT <6 or >18 mo	1.6 (1.01-2.5)	0.04
AFP at HCC dx >400 vs ≤400	3.0 (1.7-5.5)	<0.001

Wait time of <6 or >18 mo associated w/ AFP >100 at LT (HR 1.6, 95% CI 1.04-2.6, p<0.03)

Mehta N, et al. Transplantation 2017

THE WAIT TIME "SWEET SPOT": 6-18 MONTHS



Number at risk						
<6 or >18 month wait time	343	301	254	208	176	139
6 to 18 month wait time	397	348	306	249	211	164

Mehta N, et al. Transplantation 2017

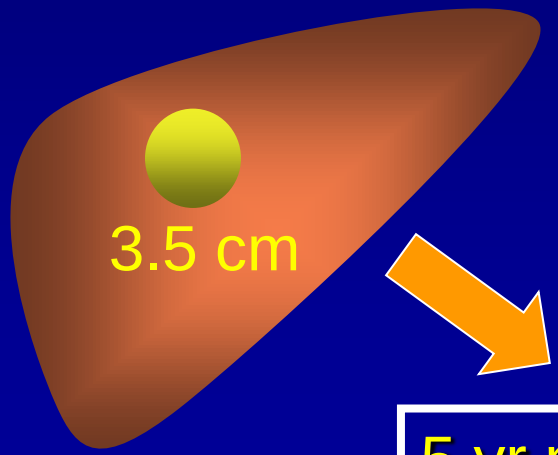
U.S. MULTI-CENTER STUDY ON WAIT TIMES

- The “sweet spot” wait time of 6-18 months from HCC diagnosis should be the target to:
  1) Minimize HCC recurrence after LT
  2) Avoid unnecessary dropout seen with very prolonged wait times

Mehta N, et al. Transplantation 2017

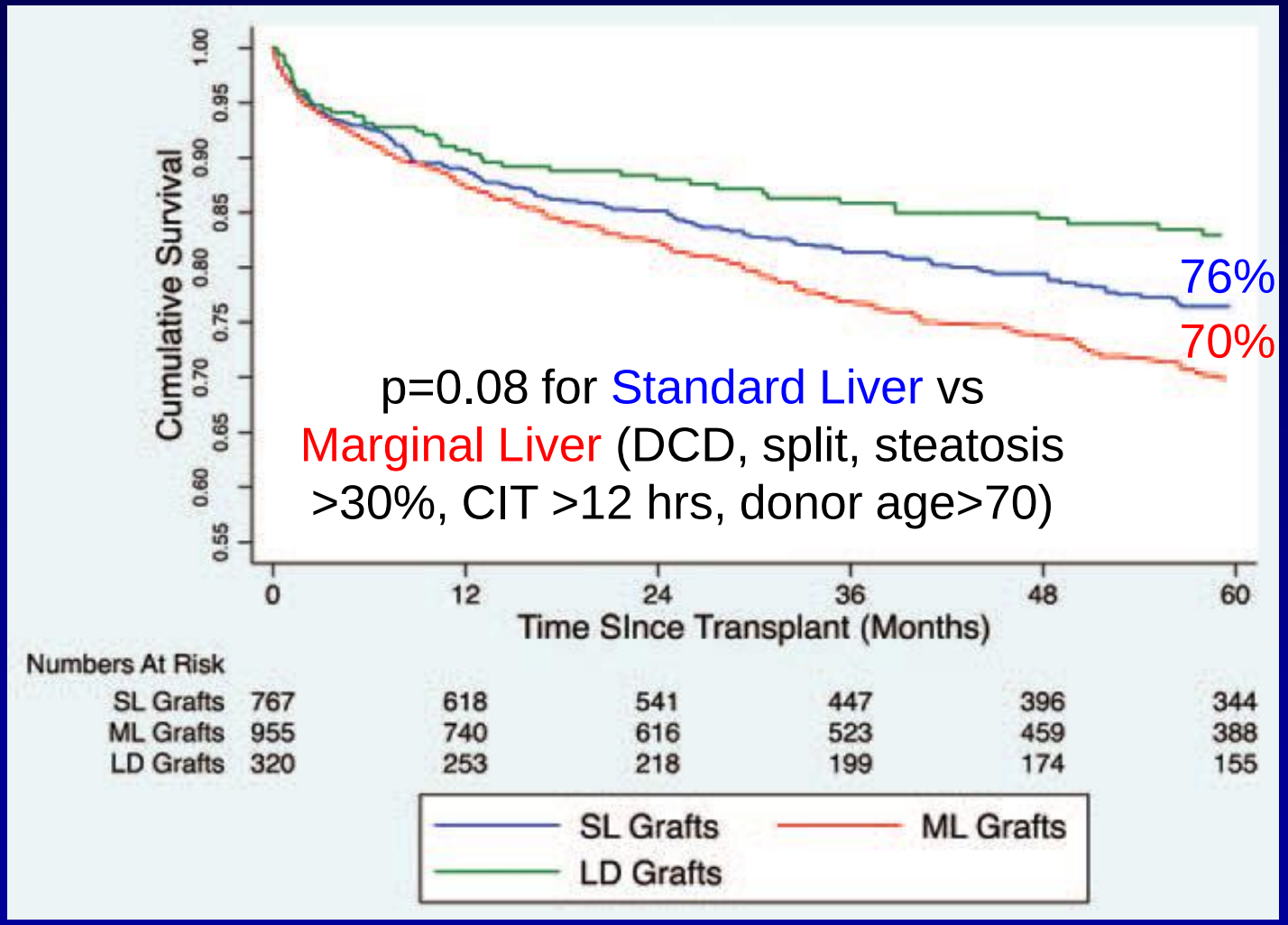
LIVER TRANSPLANTATION FOR HCC: DONOR INFLUENCE ON OUTCOMES?

Donor Factors



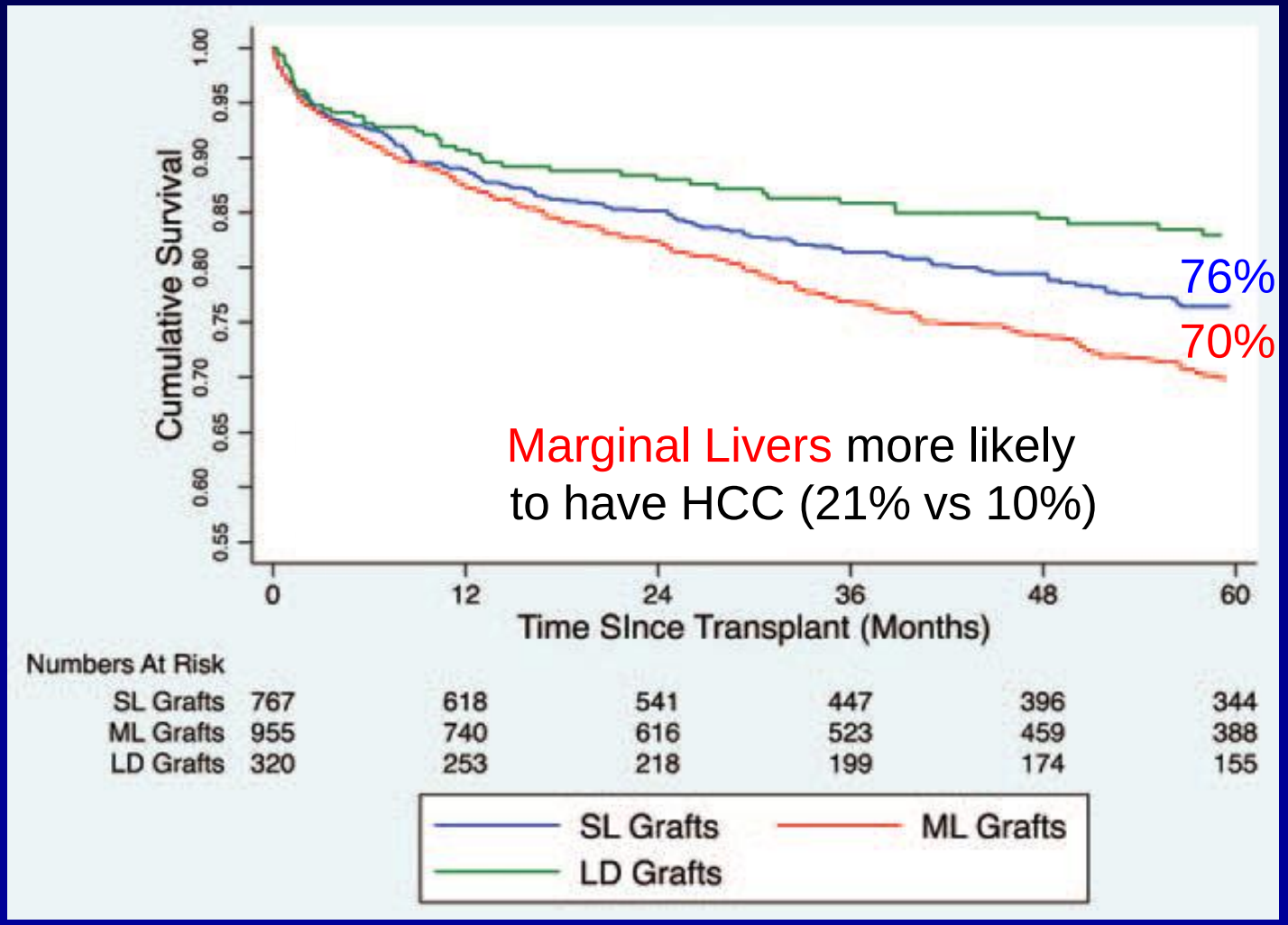
5 yr post-LT survival: __%
5 yr HCC recurrence: __%

MARGINAL LIVERS INFLUENCE ON OUTCOMES (HCC AND NON-HCC)



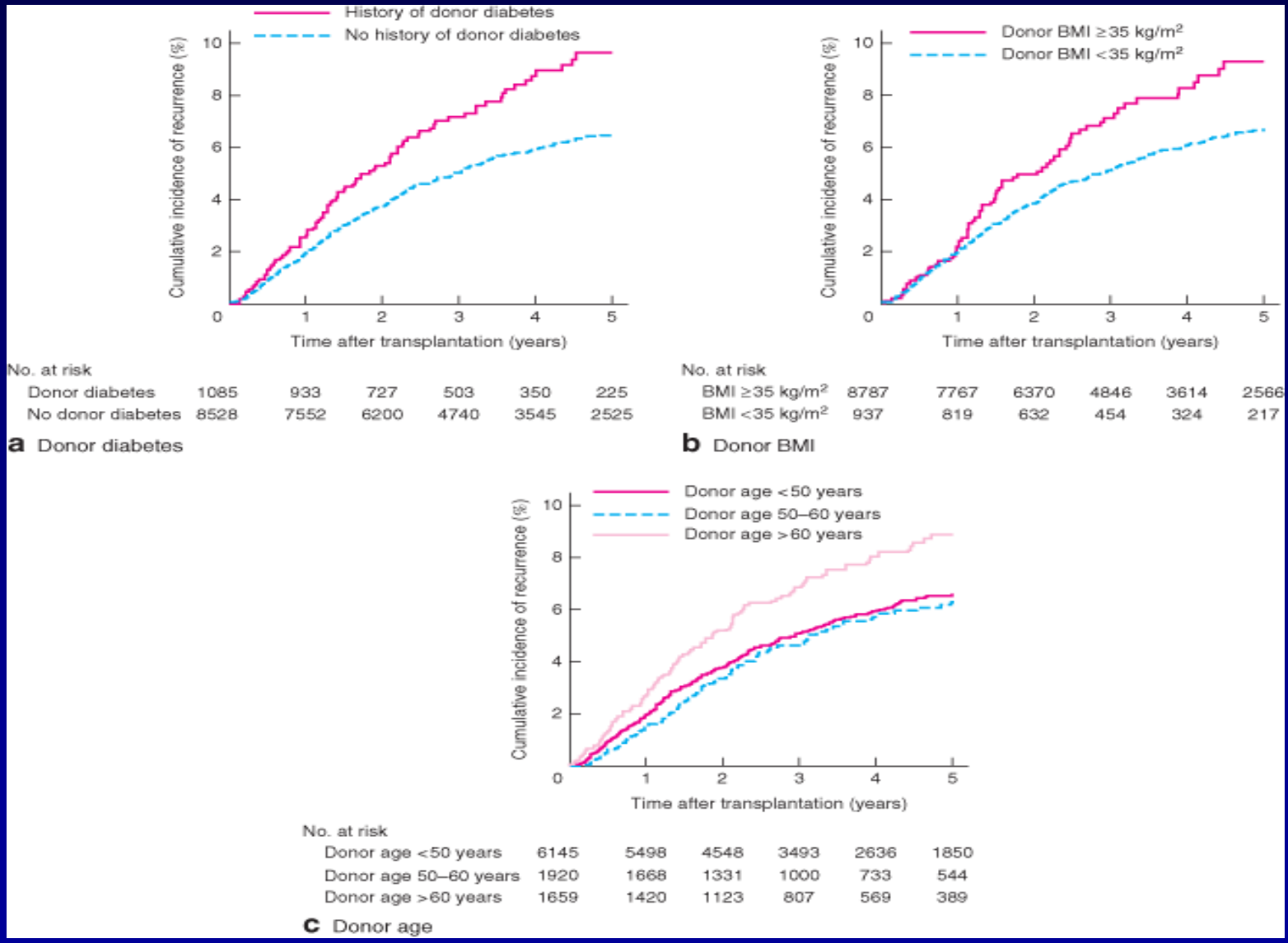
Halazun K et al. Ann Surgery 2016: 441-449

MARGINAL LIVERS INFLUENCE ON OUTCOMES (HCC AND NON-HCC)



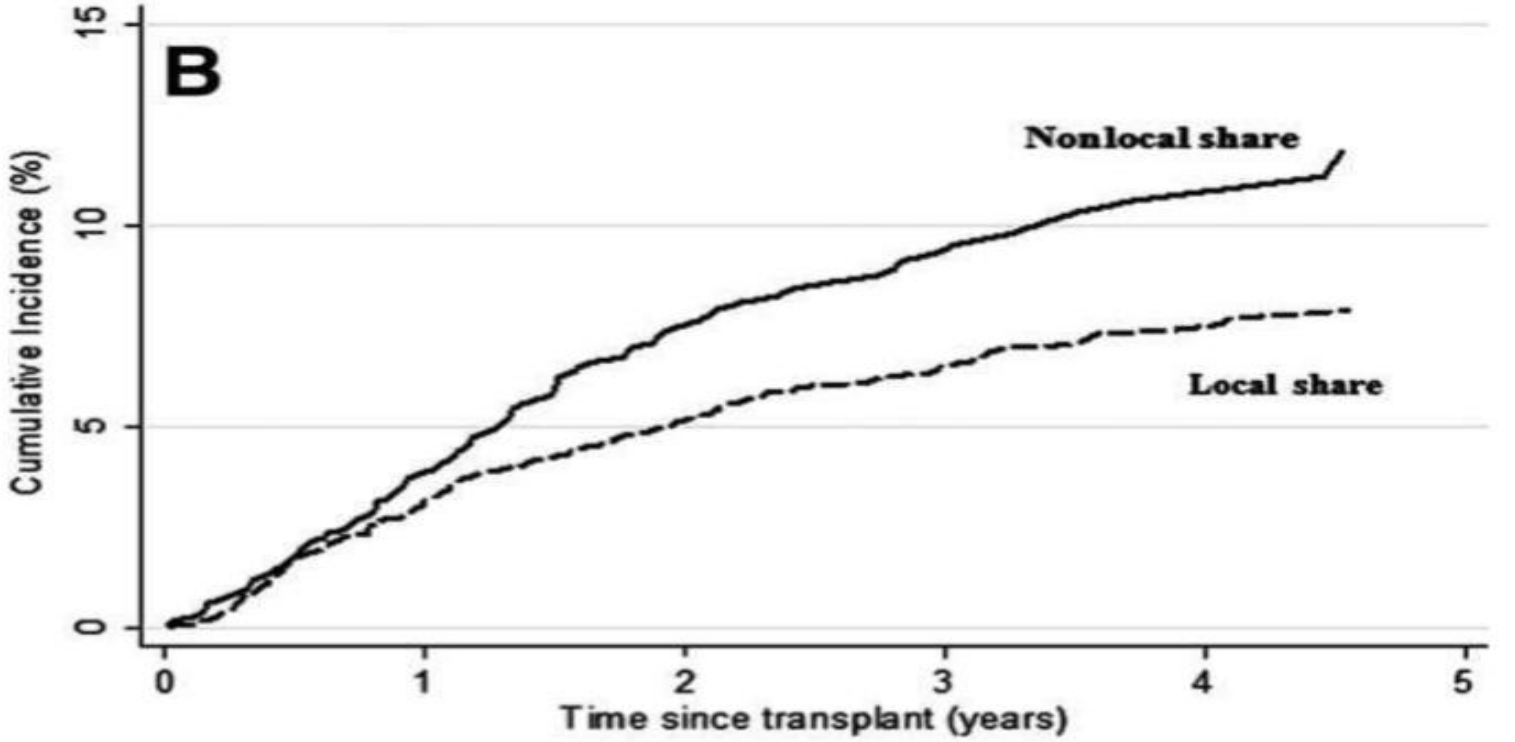
Halazun K et al. Ann Surgery 2017: 441-449

DONOR INFLUENCE ON HCC RECURRENCE?



Orci LA, et al.
Br J Surgery 2015: 1250-57

COLD ISCHEMIA TIME INFLUENCE ON HCC RECURRENCE?

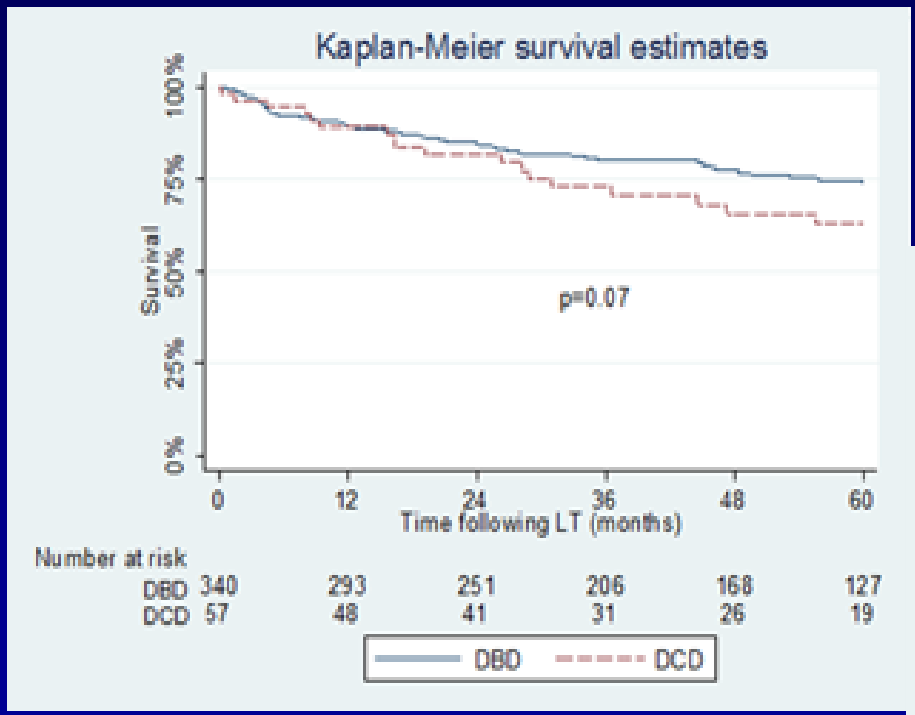


	1 year p=0.3	2 years p=0.009	3 years p<0.006	4 years p<0.004
Local share	3.2 (2.6-3.8)	5.1 (4.4-5.9)	6.5 (5.6-7.4)	7.4 (6.4-8.4)
Nonlocal share	3.8 (2.8-5.1)	7.4 (5.9-9.2)	9.3 (7.4-11.4)	10.6 (8.5-13.0)

Vagefi P, et al. Liver Txp 2015: 187-94

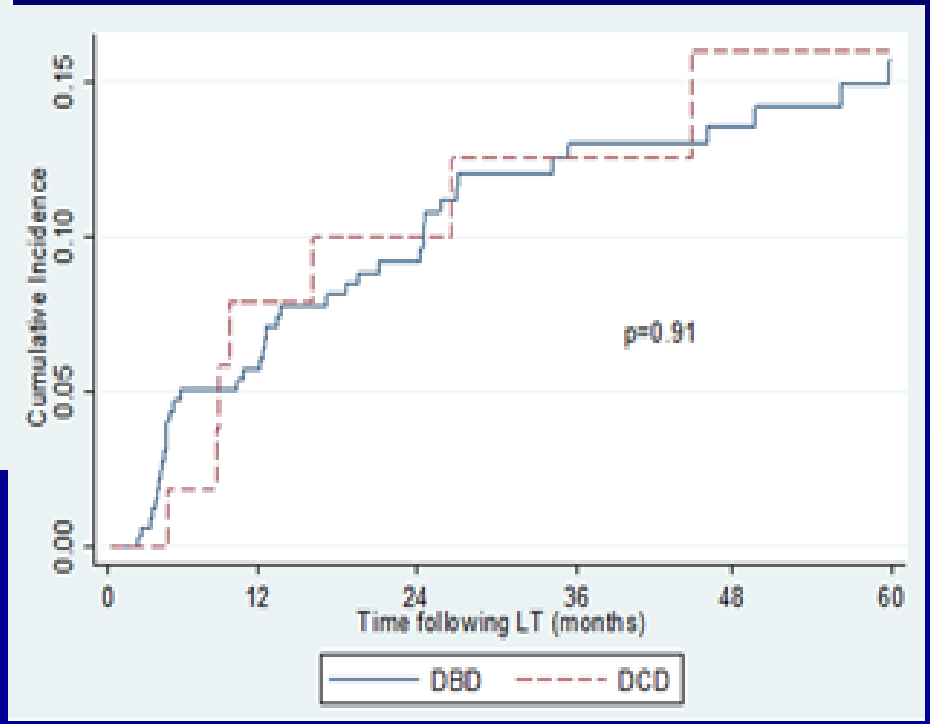
LIVER TRANSPLANTATION FOR HCC: DCD INFLUENCE ON OUTCOMES?

Post-LT HCC Survival



DBD and DCD Matched Cohorts with HCC

Post-LT HCC Recurrence



Croome KP, et al.
Am J Transpl 2015; 2704-11

LIVER TRANSPLANTATION FOR HCC: DONOR SUMMARY

- Donor age >60, donor steatosis/diabetes/ obesity, and increased cold ischemia time may lead to small increase in recurrence
- When using marginal livers for HCC, need to maximize chance of a good outcome whenever possible:
  - E.g. Well-compensated patient with well treated tumor likely will not benefit from DCD donor
  - Limit # of risk factors (e.g. if cold ischemia time >10 hours then hopefully donor age <60)
  - Normothermic perfusion for DCD or steatotic livers

Vining CC et al. 2017 Liver Txp; Sapisochin, G. & Bruix, J. 2017 Nat. Rev. Gastroenterol. Hepatol.

OVERVIEW

- Current state of LT for HCC worldwide
- Down-staging and “All-comers” results
- Pushing beyond Milan criteria
    - Identifying important recurrence risk factors
    - Does the donor matter?
- Assessing individualized post-LT recurrence risk using the explant to:
    - Standardized surveillance regimens
    - Tailor immunosuppression

ESTIMATING POST-LT HCC RECURRENCE

- Tumor recurrence is the most common cause of death after LT for HCC w/ median survival of ~1 year
- Explant provides a wealth of objective (?) data to better stratify recurrence risk
- Several post-LT models have been recently proposed to estimate post-transplant recurrence (and survival):
  - Post- or Combo-MORAL score
  - US Multicenter HCC Transplant Consortium nomogram
  - RETREAT score

Clavien PA, et al. Lancet Oncology 2012; 13:11-22; Halazun KJ et al. Ann Surg 2017; Mehta N et al. JAMA Oncology 2017; Agopian VG et al. ATC 2017

RETREAT SCORE

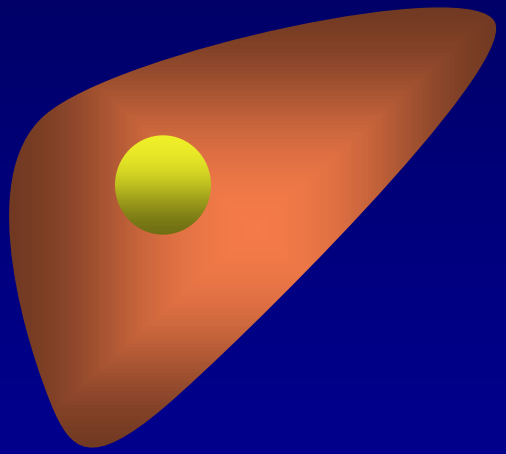
- Multi-center study, 1060 LT recipients w/ HCC meeting Milan criteria by imaging, developed + validated prediction index for HCC recurrence

- 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**

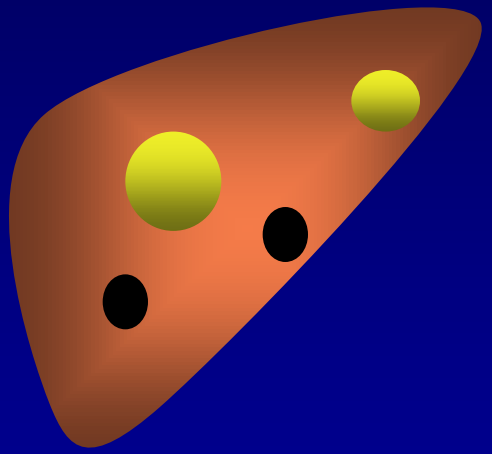
Mehta N, et al. JAMA Oncology 2017

RETREAT: EXPLANT TUMOR BURDEN

- Sum of the largest diameter of viable tumor + number of viable tumors on explant



1 viable lesion 4 cm = 5



2 viable lesions 4 cm & 2 cm = 6
2 completely necrotic lesions are not counted

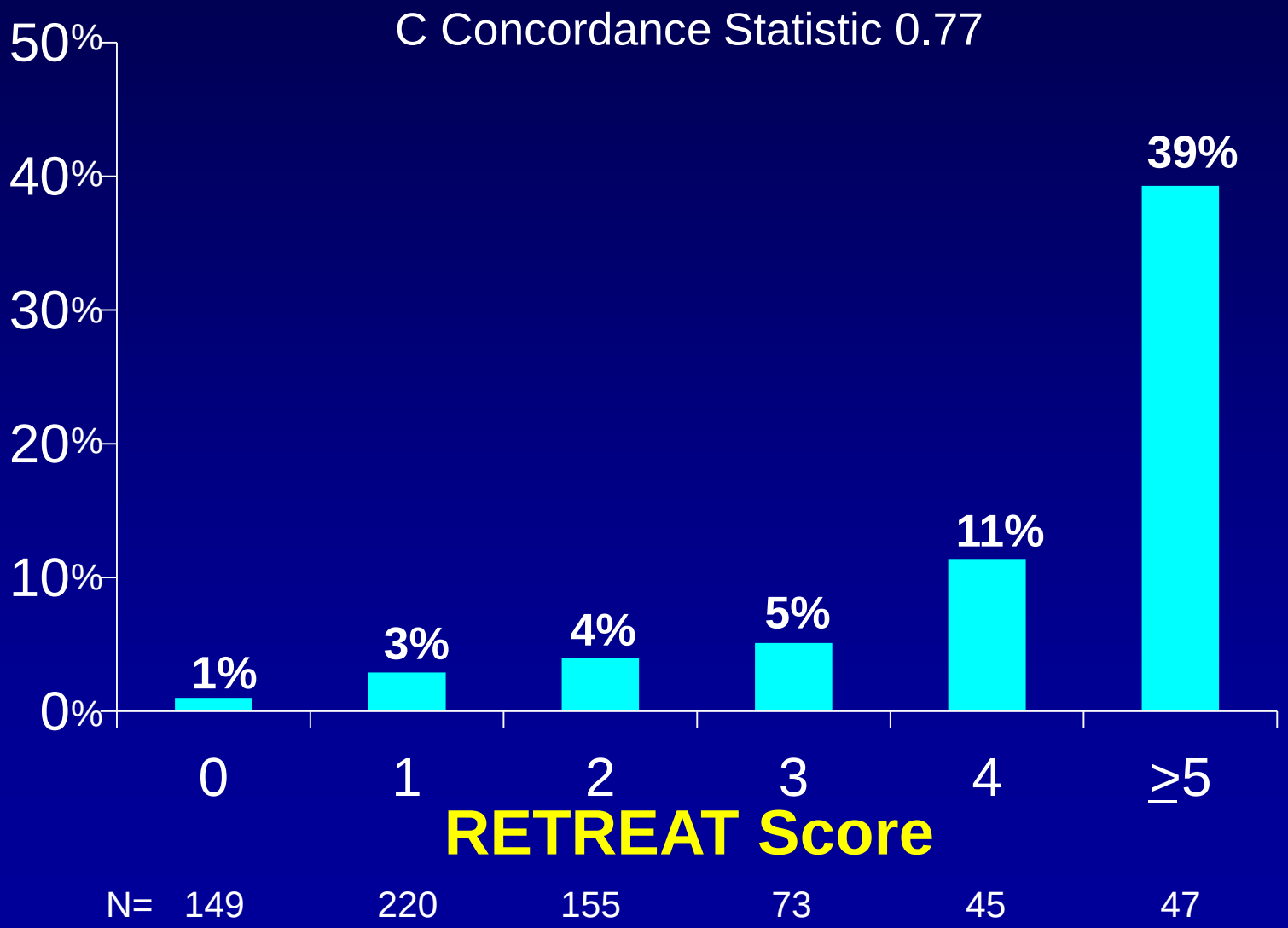
RETREAT SCORE

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

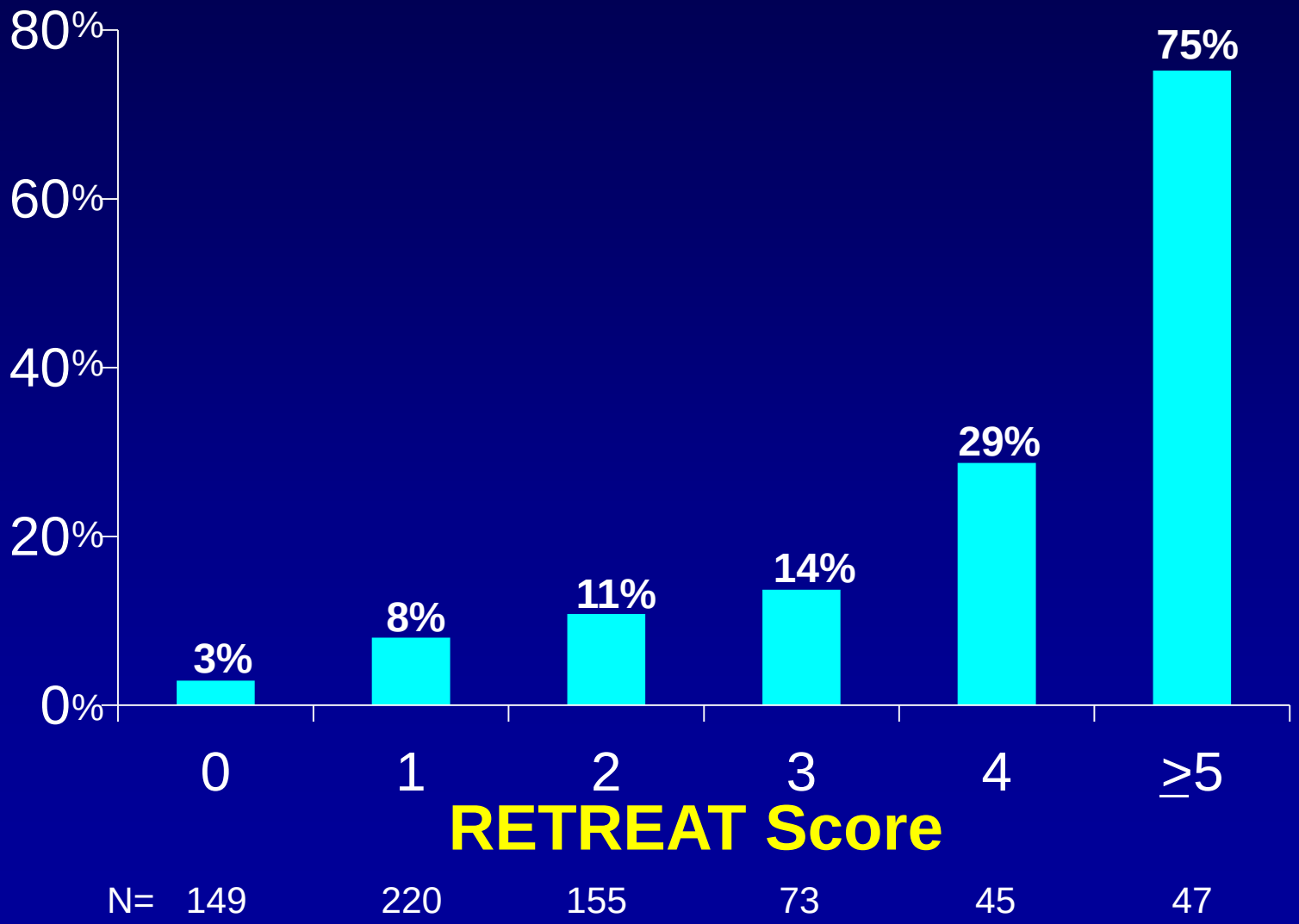
No RETREAT points scored for: AFP 0-20, no microvascular invasion, and explant pathology stage score of 0

Mehta N, et al. JAMA Oncology 2017

RETREAT SCORE: 1 YR RECURRENCE



RETREAT SCORE: 5 YR RECURRENCE



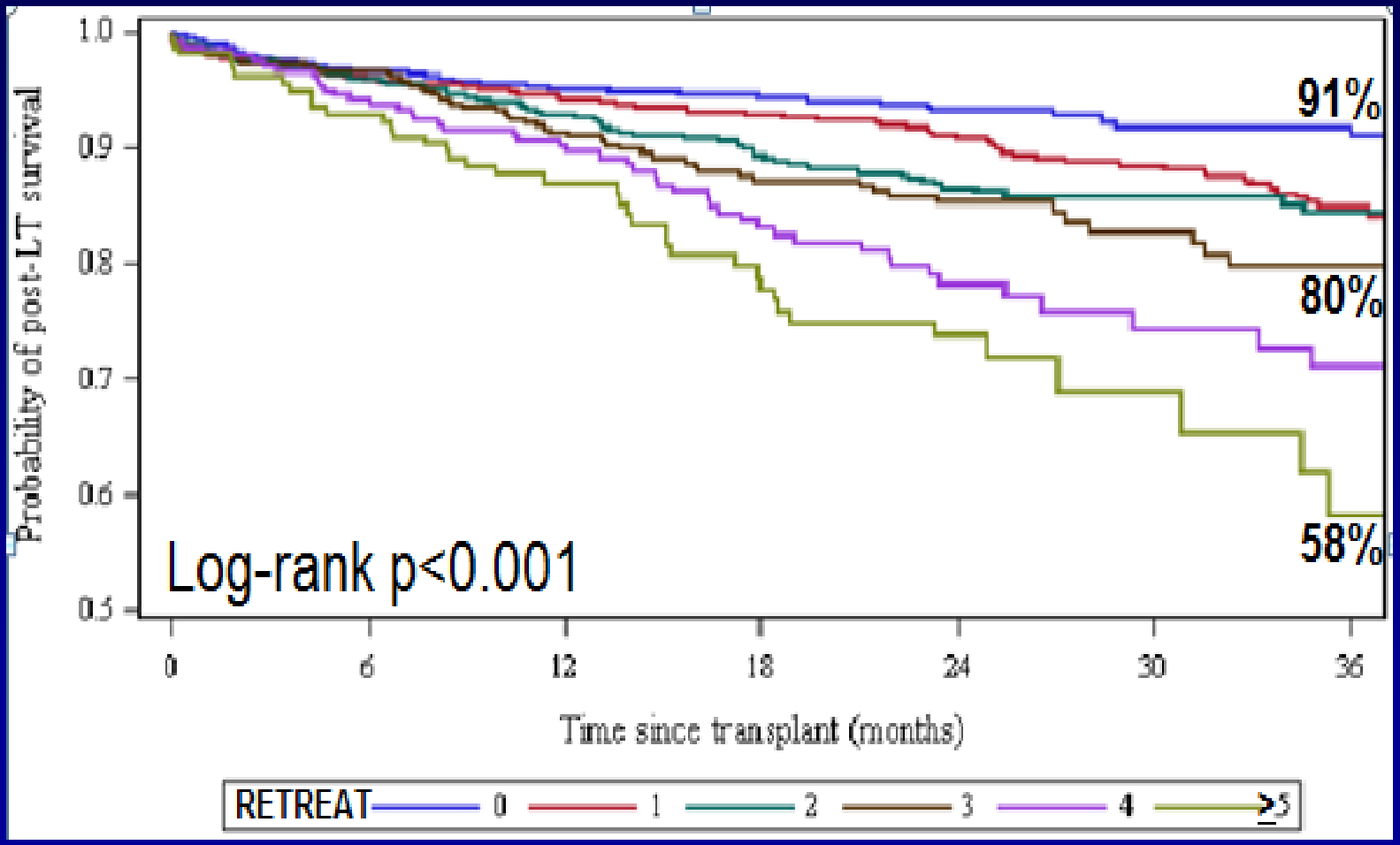
RETREAT VALIDATION IN UNOS (N=3392)

C Statistic 0.75 for HCC recurrence prediction in UNOS

Mehta N, et al. Am J Transplant 2017 (in press)

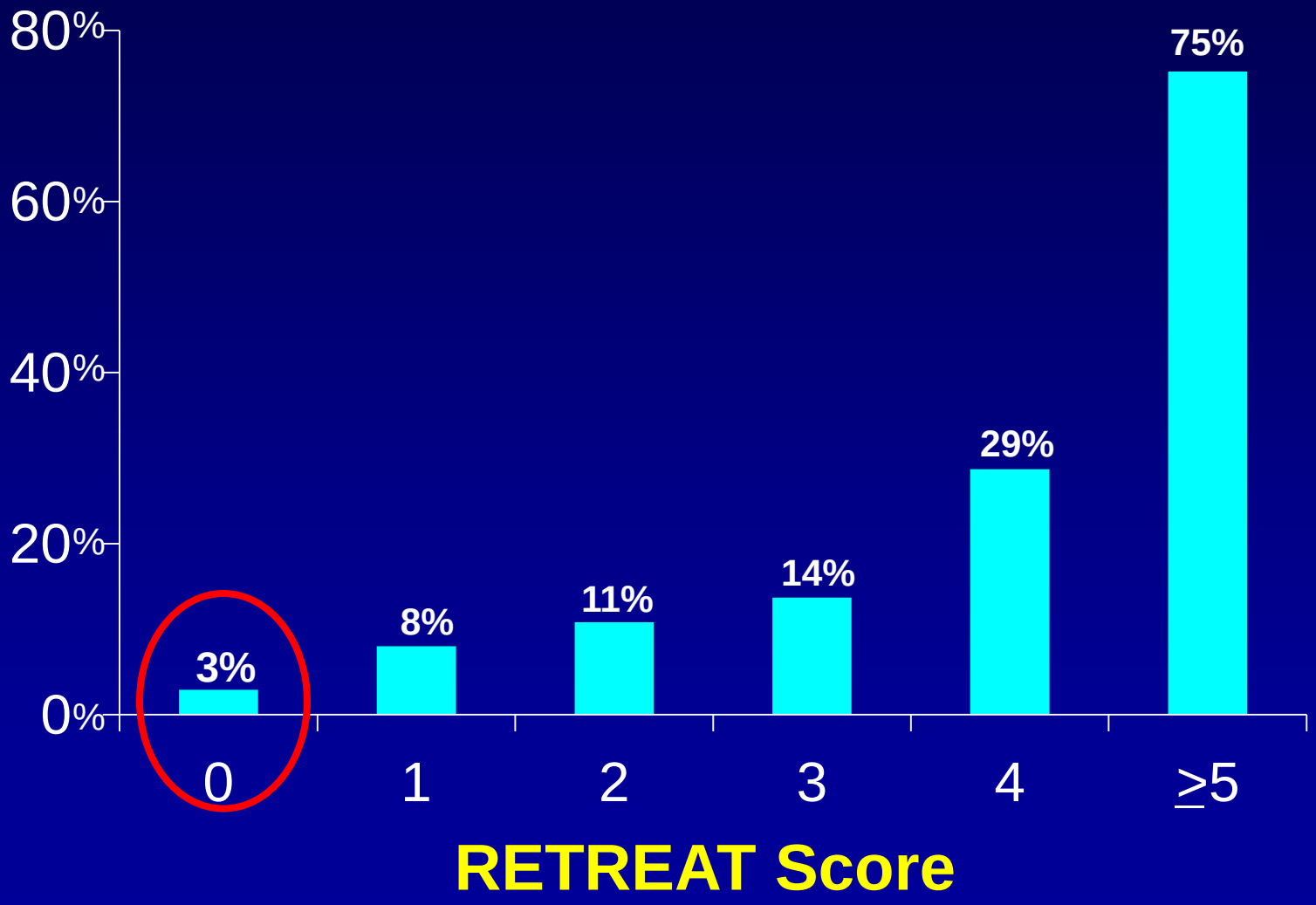
RETREAT VALIDATION IN UNOS (N=3392)

C Statistic 0.75 for HCC recurrence prediction in UNOS



Mehta N, et al. Am J Transplant 2017 (in press)

RETREAT FOR HCC SURVEILLANCE

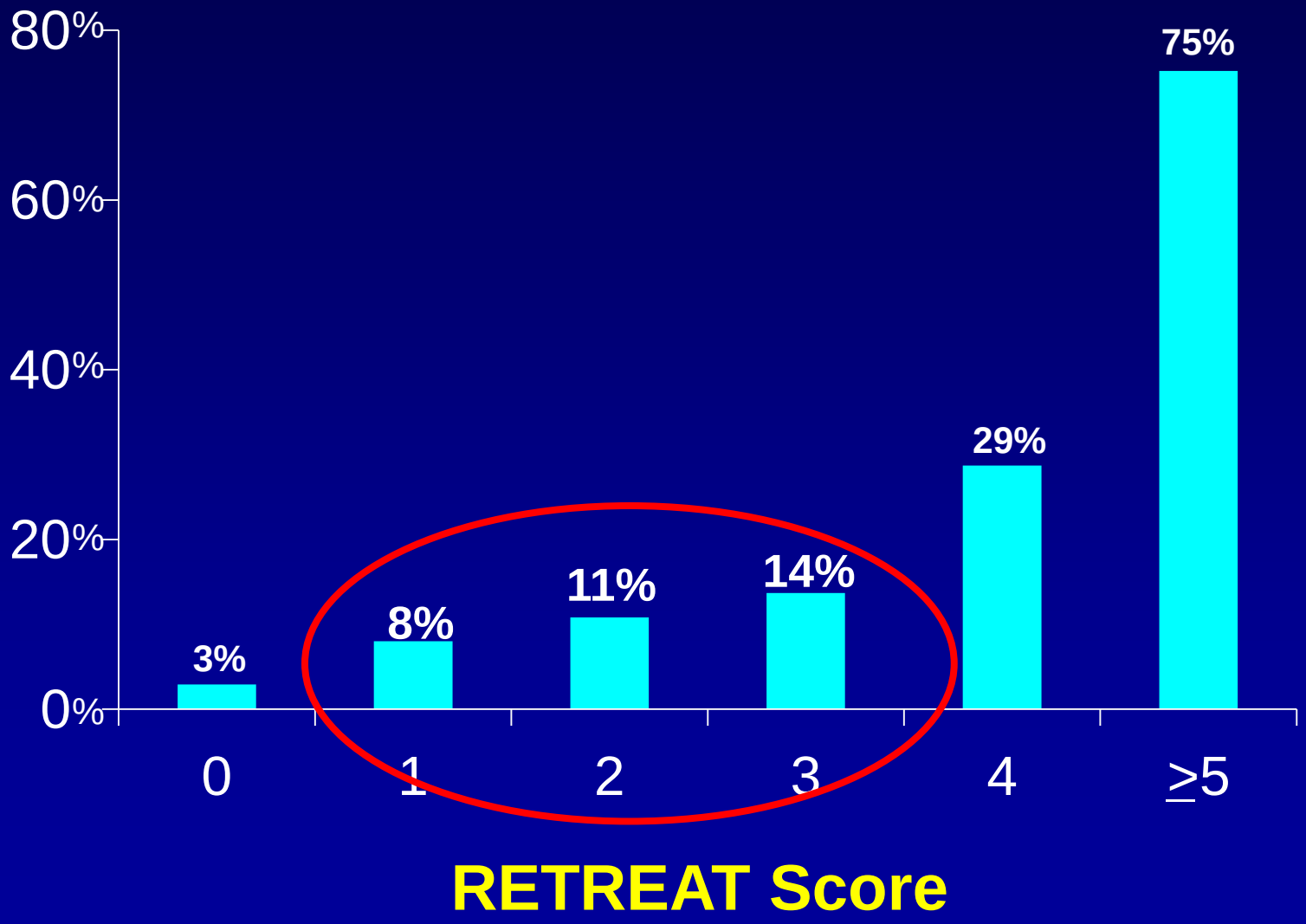


RETREAT FOR HCC SURVEILLANCE

RETREAT	Proposed surveillance regimen
0	No surveillance (20-25% of the cohort)

Mehta N, et al. JAMA Oncology 2017

RETREAT SCORE: 5 YR RECURRENCE

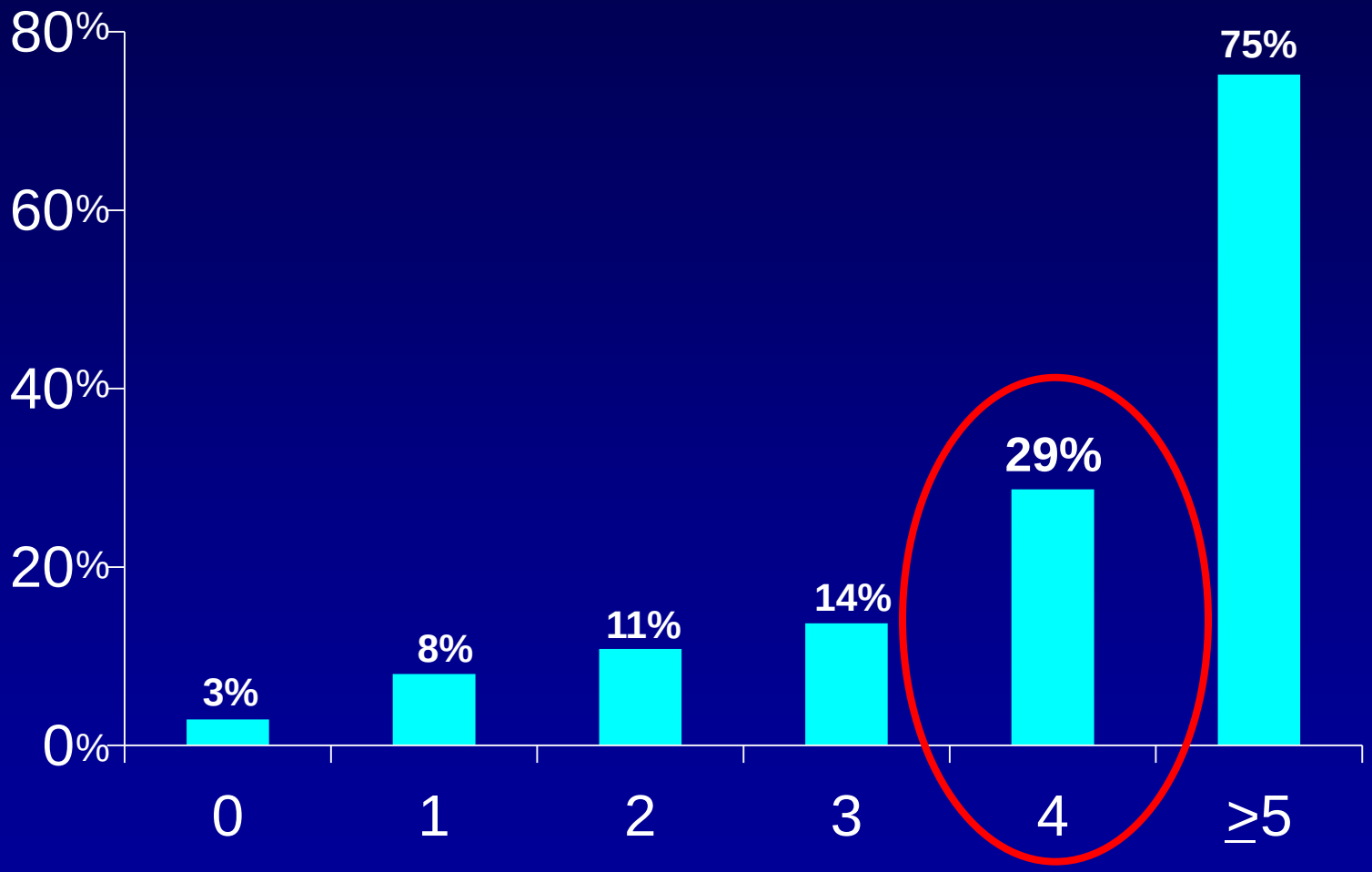


RETREAT FOR HCC SURVEILLANCE

RETREAT	Proposed surveillance regimen
0	No surveillance (20-25% of the cohort)
1-3	HCC surveillance every 6 months for 2 years

Mehta N, et al. JAMA Oncology 2017

RETREAT SCORE: 5 YR RECURRENCE



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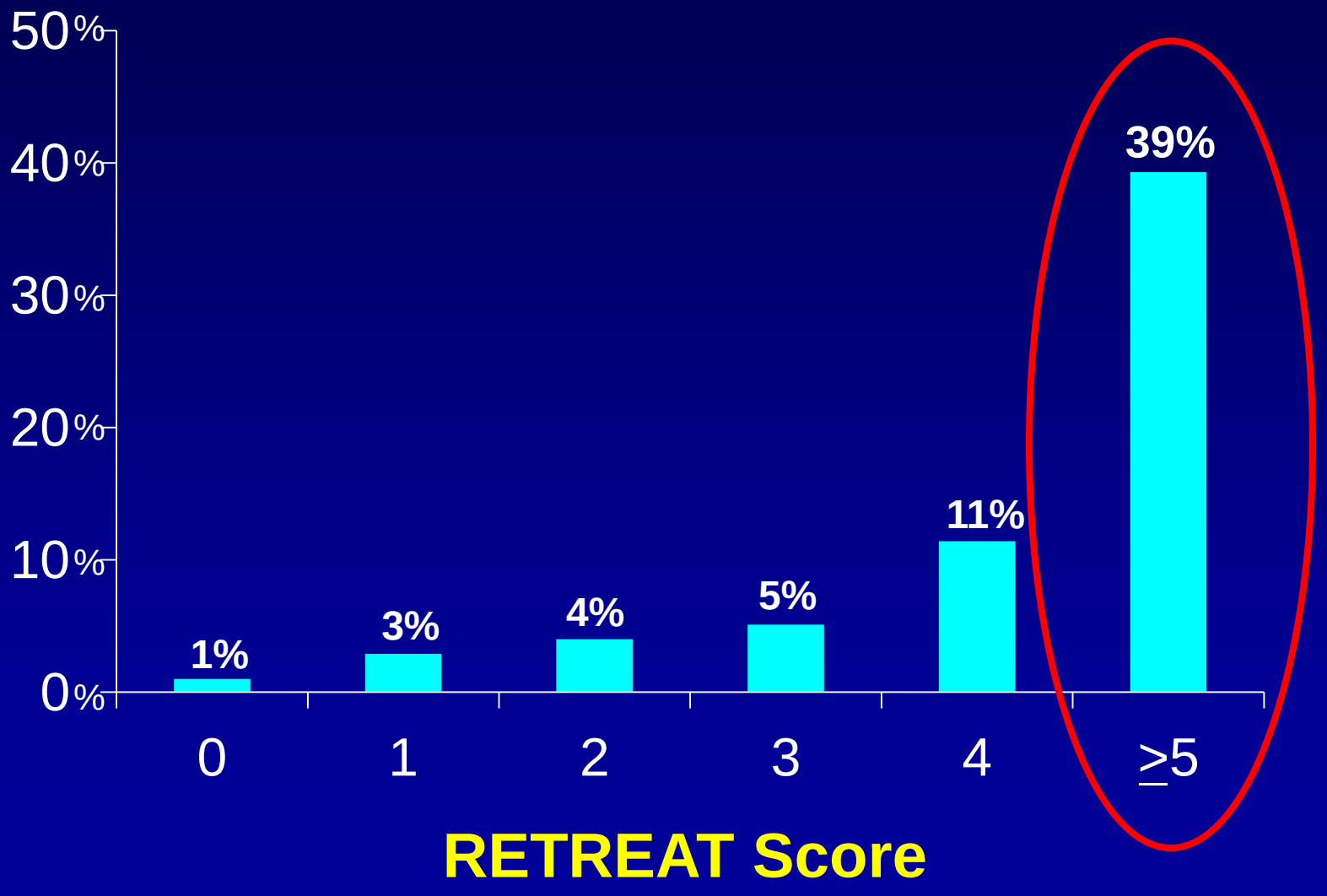
4	HCC surveillance every 6 months for 5 years

Mehta N, et al. JAMA Oncology 2017

RETREAT SCORE: 1 YR RECURRENCE



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

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Consensus statement from participating centers in the multi-center cohort (UCSF, Mayo Clinic Rochester, Mayo Clinic Jacksonville, U. Toronto)

Mehta N, et al. JAMA Oncology 2017

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
AFP at LT	
0-20	0
21-99	1
100-999	2
≥1000	3
Microvascular Invasion	
No	0
Yes	2
Explant Largest Viable Tumor Size (cm) Plus Number of Viable Lesions	
0	0
1-4.9	1
5-9.9	2
≥10	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%
≥5	39.3%	75.2%

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- Ongoing prospective multi-center study evaluating this surveillance protocol

POST-LT IMS: CNIs

- Standard post-LT IMS is CNI (e.g tacrolimus) w/ mycophenolate and prednisone
- Postulated that CNIs may increase HCC recurrence risk

Rodriguez-Peralvarez et al. J Hepatology 2013

POST-LT IMS: mTORi

- mTOR regulates cell growth, proliferation, metabolism, and aging
- mTOR inhibitors have shown anticancer properties in *in vitro* and animal models
  - Prevents angiogenesis by interfering with VEGF-mediated pathways, thus **potentially limiting tumor growth**
  - Induces extensive microthrombi, thus **potentially inhibiting tumor growth**
- mTOR pathway frequently up-regulated in HCC
- Many LT centers have shifted to using mTOR based IMS in HCC pts undergoing LT

Matter MS et al J Hepatology 2014

POST-LT IMS: MTORi

- Yanik et al: SRTR HCC LT recipients, 2002-2012
- 234 sirolimus within 3 mo of LT vs 3702 never treated with sirolimus
    - Linked w/ national pharmacy claims
- Sirolimus pts more likely to be outside Milan (11% vs 5%) but AFPs similar
- No significant differences between the groups in all-cause mortality, cancer-specific mortality, and HCC recurrence

Yanik EL et al, Liver Txp 2016

SILVER TRIAL

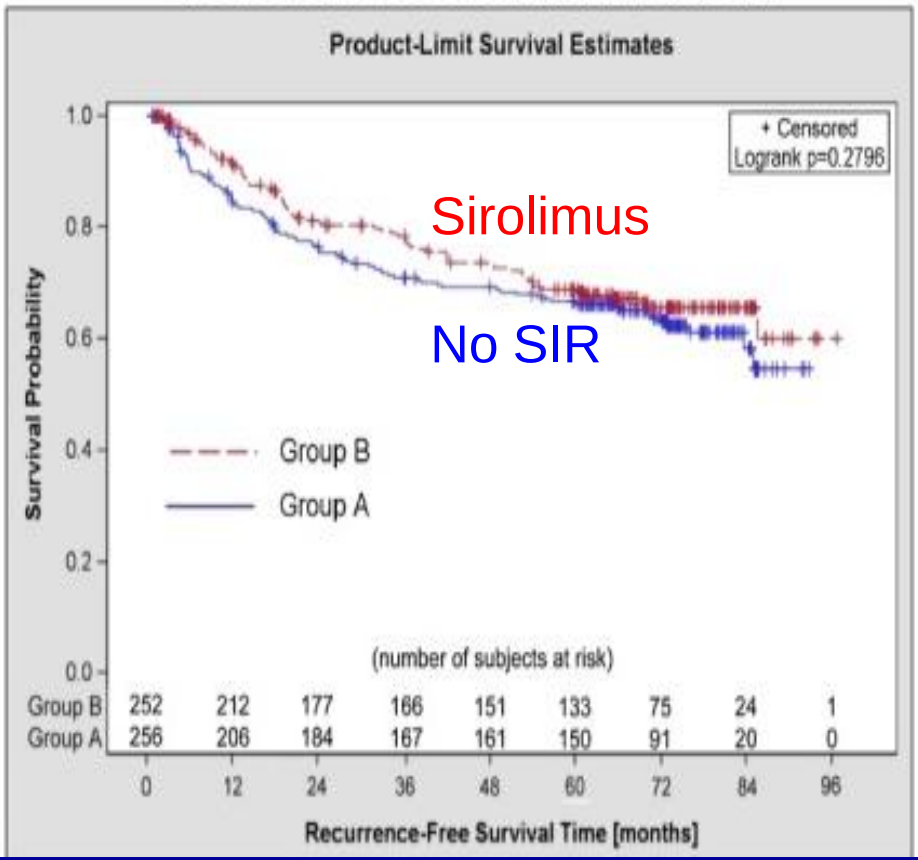
Prospective phase 3, multi-center international RCT

Geissler EK et al, Transplantation 2016

SILVER TRIAL: RFS

Prospective phase 3, multi-center international RCT

HCC recurrence-free survival (primary endpoint)



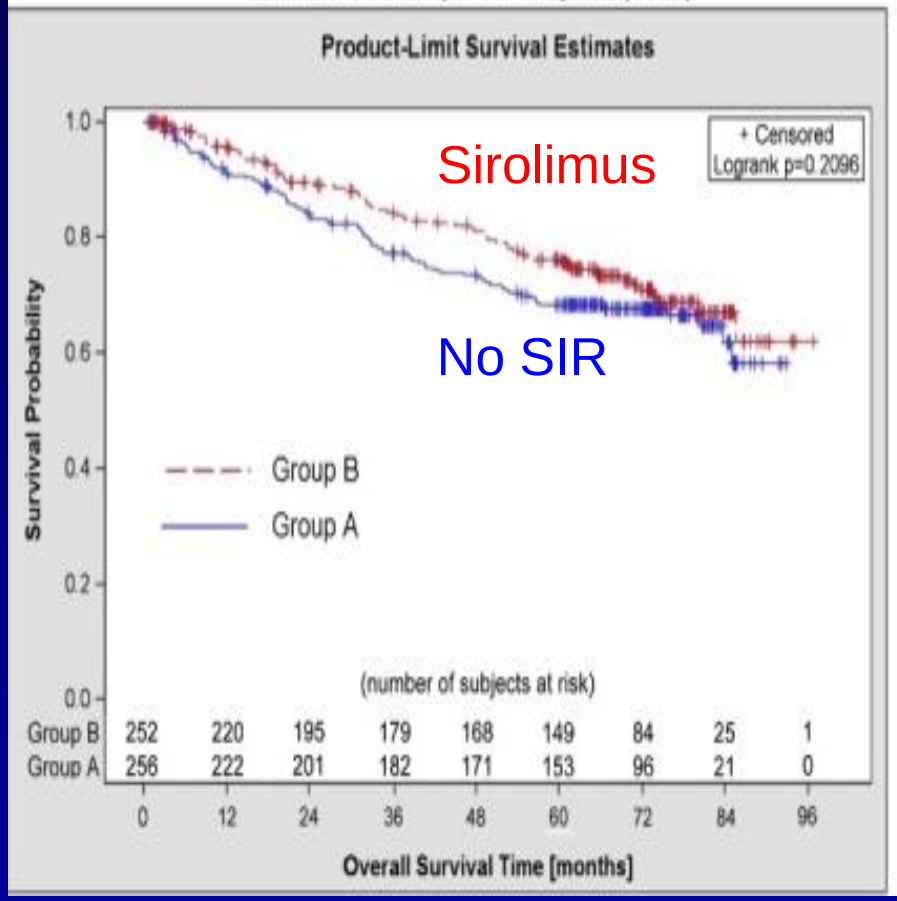
Recurrence-free survival over years (ITT population)

Time point after LTx	Group A (N=256)	Group B (N=252)	p-value (log-rank test)	HR [95% CI*]
1 year	218 (85.2%)	233 (92.5%)	0.0125	0.50 [0.29;0.87]
2 years	198 (77.3%)	209 (82.9%)	0.1434	0.75 [0.50;1.11]
3 years	185 (72.3%)	203 (80.6%)	0.0499	0.70 [0.48;1.00]
4 years	181 (70.7%)	192 (76.2%)	0.2193	0.81 [0.58;1.14]
5 years	175 (68.4%)	183 (72.6%)	0.3809	0.87 [0.63;1.19]
6 years	170 (66.4%)	178 (70.6%)	0.4325	0.88 [0.65;1.21]
7 years	166 (64.8%)	178 (70.6%)	0.2798	0.84 [0.67;1.15]
8 years	165 (64.5%)	177 (70.2%)	0.2796	0.84 [0.62;1.15]

Geissler EK et al, Transplantation 2016

SILVER TRIAL: OVERALL SURVIVAL

Overall survival (secondary endpoint)



Overall survival over years (ITT population)

Time point after LTx	Group A (N=256)	Group B (N=252)	p-value (log-rank test)	HR [95% CI*]
1 year	234 (91.4%)	242 (96.0%)	0.0414	0.47 [0.22;0.99]
2 years	217 (84.8%)	228 (90.5%)	0.0775	0.64 [0.38;1.06]
3 years	201 (78.5%)	217 (86.1%)	0.0503	0.66 [0.43;1.00]
4 years	192 (75.0%)	210 (83.3%)	0.0468	0.68 [0.46;1.00]
5 years	180 (70.3%)	200 (79.4%)	0.0479	0.70 [0.49;1.00]
6 years	179 (69.9%)	192 (76.2%)	0.1982	0.80 [0.57;1.12]
7 years	176 (68.7%)	189 (75.0%)	0.2104	0.81 [0.58;1.13]
8 years	175 (68.4%)	188 (74.6%)	0.2096	0.81 [0.58;1.13]

Geissler EK et al, Transplantation 2016

POST-LT IMS

- Consider moving away from studying mTOR inhibitors in all HCC LT recipients, but focus on those most likely to benefit

- Specifically target those with up-regulation of mTOR pathways, which occurs in ~50% of HCC pts
    - Molecular subtyping of explant tumor may prove important, especially w/ 2nd generation mTOR inhibitors that more widely block downstream targets

- At UCSF, pts w/ RETREAT score $\geq$4 are converted to MTOR based IMS at 4-12 wks post LT

Mehta N et al, Liver Txp 2016; Matter MS et al J Hepatology 2014

POST-LT HCC RECURRENCE SUMMARY

- Recent development of several risk scores to estimate individual HCC recurrence risk
- Tailor post-LT HCC surveillance regimens based on recurrence risk
    - Ongoing prospective studies to determine if this translates into improved outcomes
- Mixed results using mTOR inhibitors → focus on those most likely to benefit

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Thank You!