HCC Case Presentation

Neil Mehta, MD
UCSF Division of GI/Hepatology

12/8/18

INITIAL PRESENTATION

- 51-year-old man with presumed EtOH cirrhosis complicated by multi-focal hepatocellular carcinoma who presents for phase 1 liver transplant evaluation in February 2018

- First diagnosed with cirrhosis in October 2014
  - Had presented with variceal bleeding and underwent band ligation then and several sessions thereafter
  - Quit alcohol at time of bleed
  - Metabolic risk factors include obesity with BMI 36 down from 48 accomplished through diet

INITIAL PRESENTATION

- He has had intermittent mild encephalopathy in the past and takes rifaximin a few times per week

- He also has had lower extremity edema and ascites farily controlled on lasix 40 mg and aldactone 100 mg daily

INITIAL PRESENTATION: HCC

- Initial CT abdomen 1/3/18 showed 2 arterially enhancing hepatic lesions concerning for HCC including:
  1) 5.5 cm dome lesion with possible washout
  2) 3.5 cm lesion in segment 8 with subtle washout
- The larger dome lesion per report had been seen on a 5/8/17 CT abdomen at which time it measured 3.7 cm
- AFP has always been normal

LTX EVALUATION : PMHX/PSHX

- Alcoholic cirrhosis of liver w/ HE/ascites/variceal bleeding
- HCC (hepatocellular carcinoma)
- Obesity (BMI 36)
- Osteoarthritis
- Sleep apnea
- Vitamin D deficiency

- No past surgical hx

LTX EVALUATION: MEDICATIONS

- Furosemide 40 mg daily
- Spironolactone 100 mg daily
- Rifaximin 550 mg 1-2x per week
- Nadolol 40 mg daily

LTX EVALUATION : SOCIAL HX

- Married, no children; lives in Cotati with his wife who would be his primary caregiver
- Works full-time, owns a trucking business
- Former chewing tobacco, quit April 2017
- Former heavy alcohol abuse, typically 4-6 drinks per day until quitting in 2014
- No alcohol-related issues (DUI/arrests etc)
- No illicit substances
- Deemed low risk candidate from psychosocial perspective

LTX EVALUATION: PEX

- Vital Signs: BP 92/54 | Pulse 65 | Ht 6’0” | Wt 272 lb | BMI 36.9 | SpO2 99%
- Constitutional: NAD, well appearing, robust
- Cardiovascular: Regular rate and rhythm, no peripheral edema
- Gastrointestinal: Soft, non tender abdomen without fluid wave, hernias or masses
- Neurologic: No asterixis. Alert and oriented x3
- Psychiatric: Normal mood and affect

INITIAL PRESENTATION: LABS

- Bilirubin 2.4, Direct bilirubin 1.2, INR 1.5, Sodium 132, Creatinine 0.94, Albumin 3.3, MELD 16
- WBC 2.6, Hct 39.6, Plt 49
- AFP 2.2 ng/ml
- AFP-L3 12% (ref <10%), DCP 15.4 ng/ml (ref <7.5)
- BT O+, Utox and ETG/ETS negative

INITIAL PRESENTATION: TUMOR BOARD

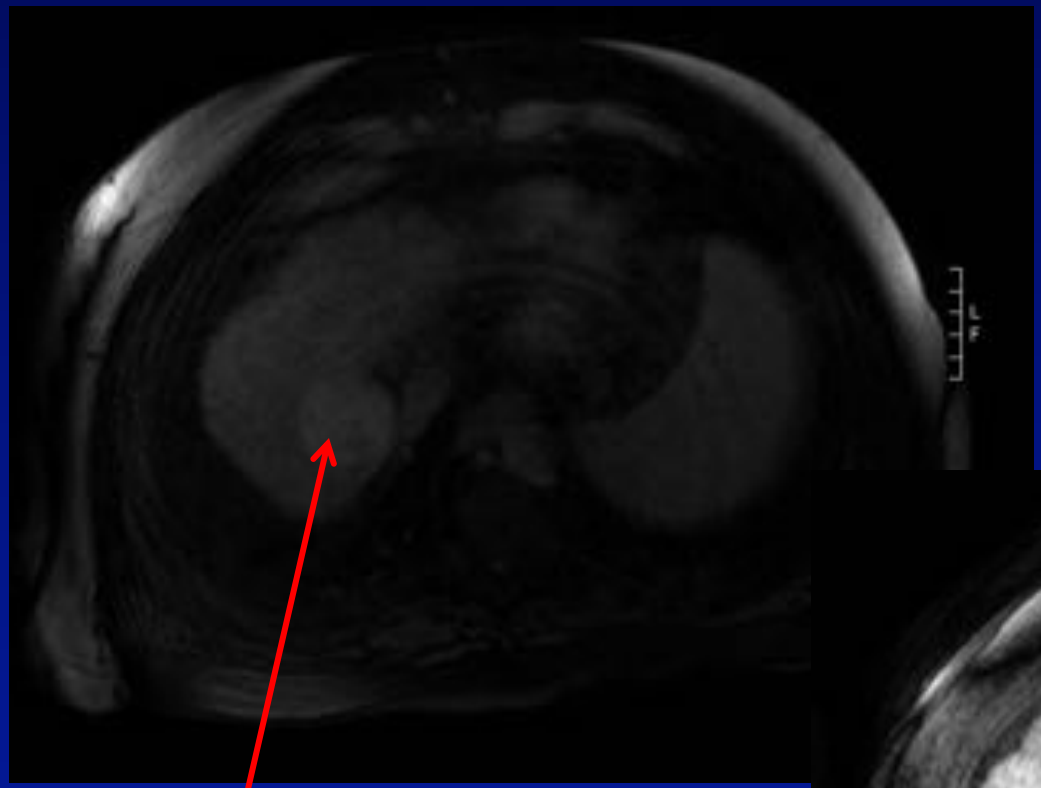
- MRI abdomen 2/16/18:

  - Arterially enhancing lesion at the hepatic dome with likely washout, measuring 5.5 cm in size, LI RADS 5.

  - Ill-defined arterially enhancing lesion in segment 8 with subtle washout measuring 4.5 cm in size, concerning for LI-RADS 5.
  - Cirrhotic liver with portal HTN resulting in splenomegaly and perigastric, perisplenic, esophageal varices, and ascites.

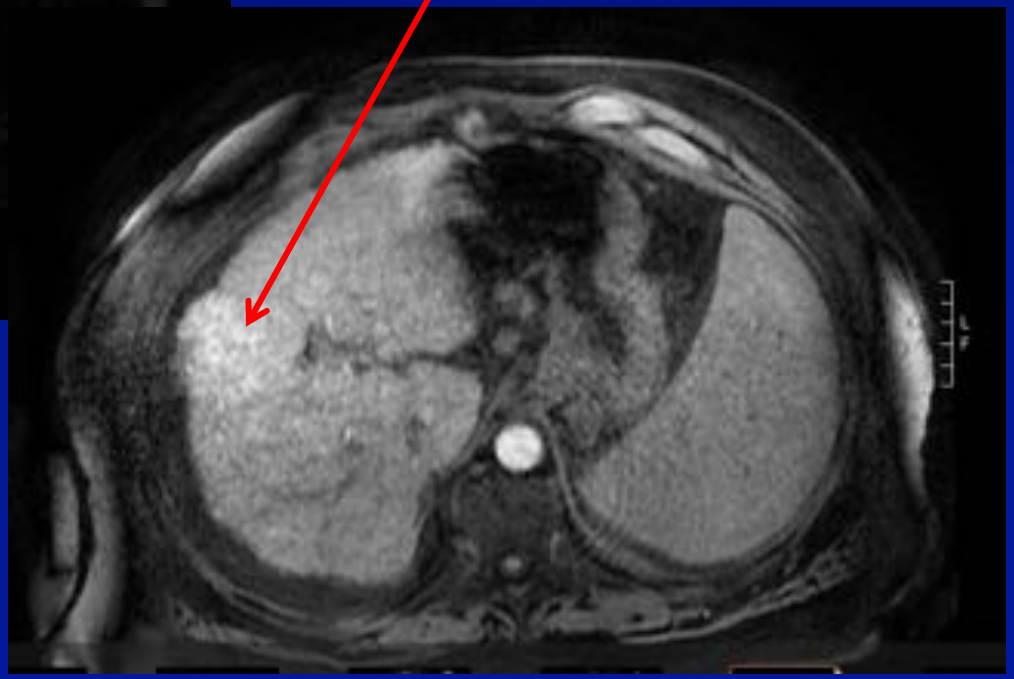
  - Portal Vein: Chronic partial occlusion of the portal vein and superior mesenteric vein. Thrombus in the splenic vein.

INITIAL PRESENTATION: TUMOR BOARD

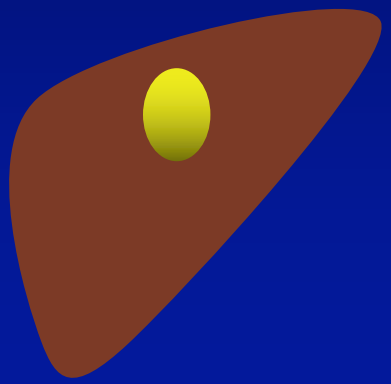


5.5 cm LR-5
dome lesion

Ill defined 4.5 cm
LR-5 in seg 8

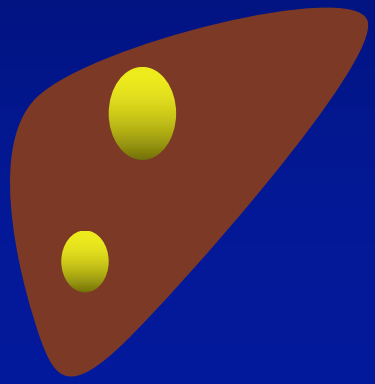


HCC Transplant Criteria



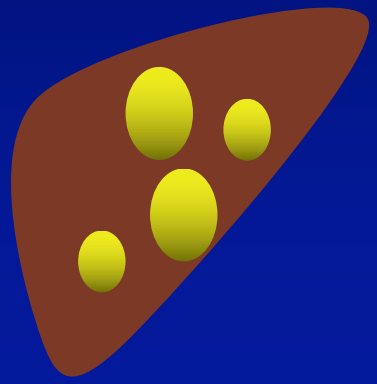
MILAN CRITERIA

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



UNOS 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
- TTD > 8cm
- No extra-hepatic dz

SUMMARY

- MRI abdomen 2/16/18:
  - Arterially enhancing lesion at the hepatic dome with likely washout, measuring 5.5 cm in size, LI RADS 5.
  - Ill-defined arterially enhancing lesion in segment 8 with subtle washout measuring 4.5 cm in size, concerning for LI-RADS 5.

- Child-Pugh C10, MELD 16, decompensated
- Tumor burden = 2 lesions, 10 cm TTD → "All-comers"
- AFP normal

NOW WHAT?

- MRI abdomen 2/16/18:
  - Arterially enhancing lesion at the hepatic dome with likely washout, measuring 5.5 cm in size, LI RADS 5.
  - Ill-defined arterially enhancing lesion in segment 8 with subtle washout measuring 4.5 cm in size, concerning for LI-RADS 5.

- Child-Pugh C10, MELD 16, decompensated
- Tumor burden = 2 lesions, 10 cm TTD → "All-comers"
- AFP normal

What are our treatment options??

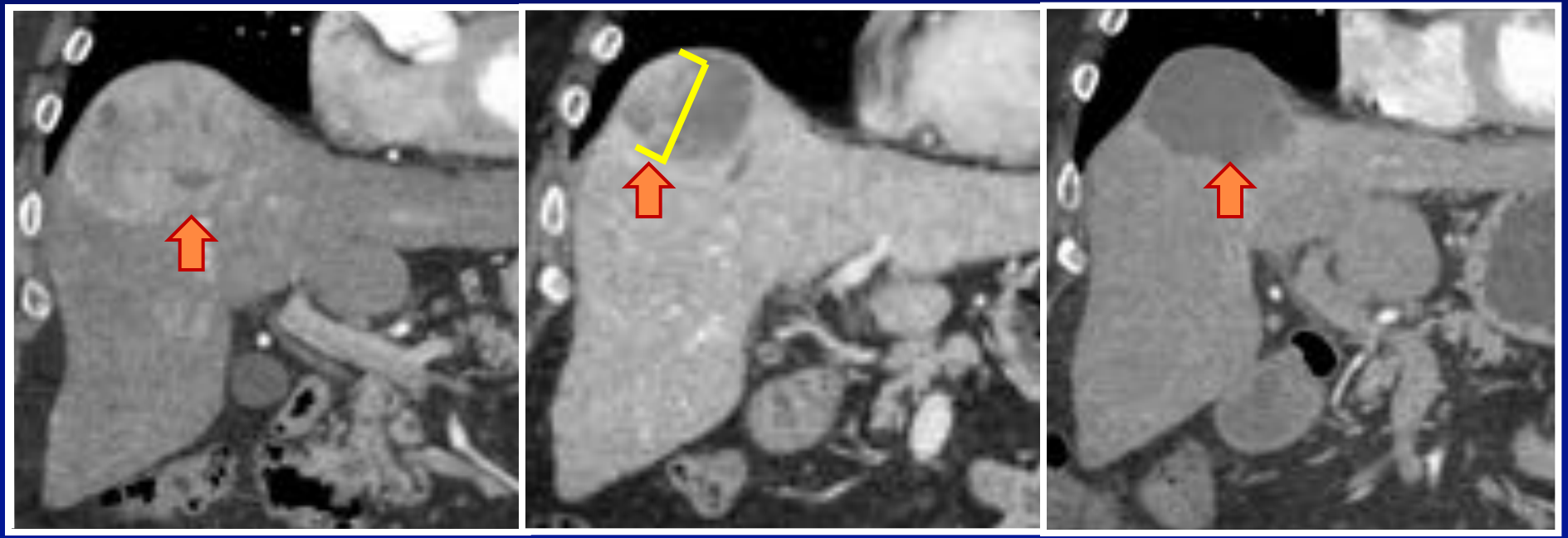
Down-staging of HCC for Transplant

- 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

LOCAL REGIONAL THERAPIES FOR HCC

CHEMOEMBOLIZATION

Transarterial (TACE)

ABLATIONS

CHEMICAL

Percutaneous ethanol injection (PEI)

THERMAL

Radiofrequency ablation (RFA)

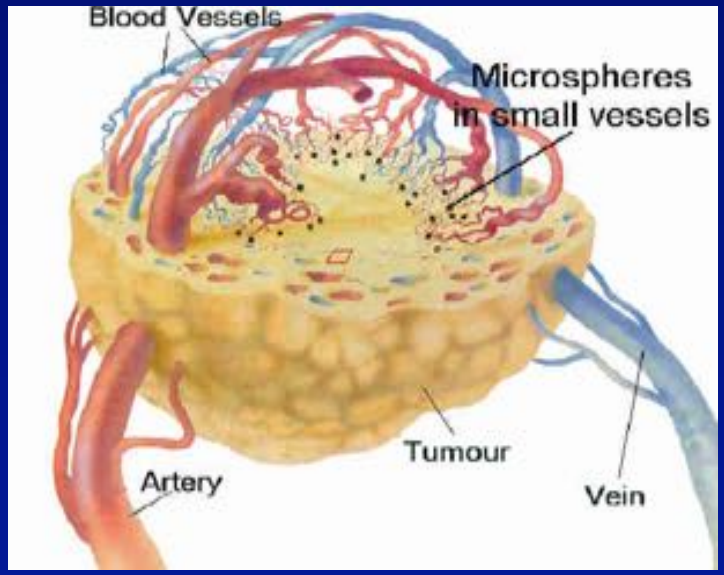
(Laparoscopic, percutaneous or open)

Microwave/ Cryo- ablation

RADIOEMBOLIZATION (YITTRIUM - 90)
& EXTERNAL BEAM IRRADIATION (SBRT)

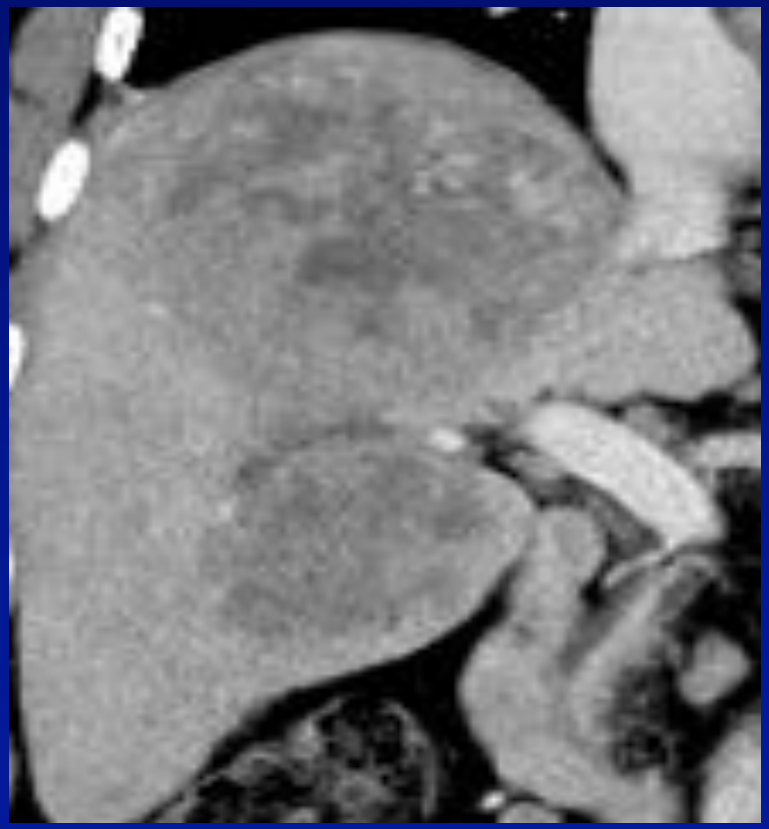
Y-90 RADIOEMBOLIZATION

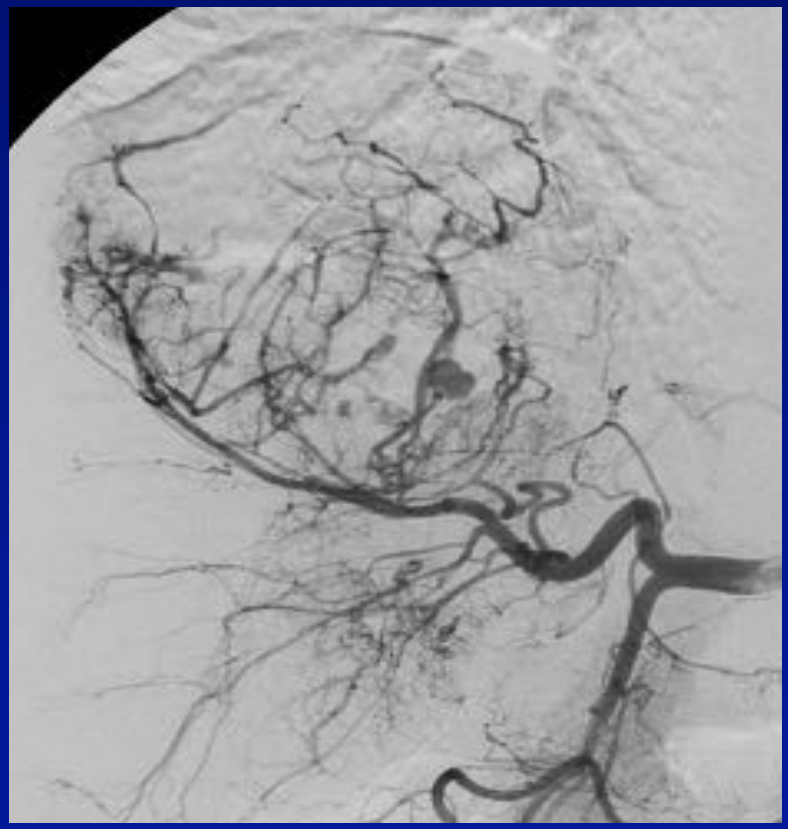
- TheraSphere (glass microspheres)
- SIR-Spheres (resin microspheres)
- Radiographic response up to 90%
- Survival benefit unknown
- Risks of radiation damage
- Advanced tumor stage and preserved liver function (bilirubin < 2mg/dl)



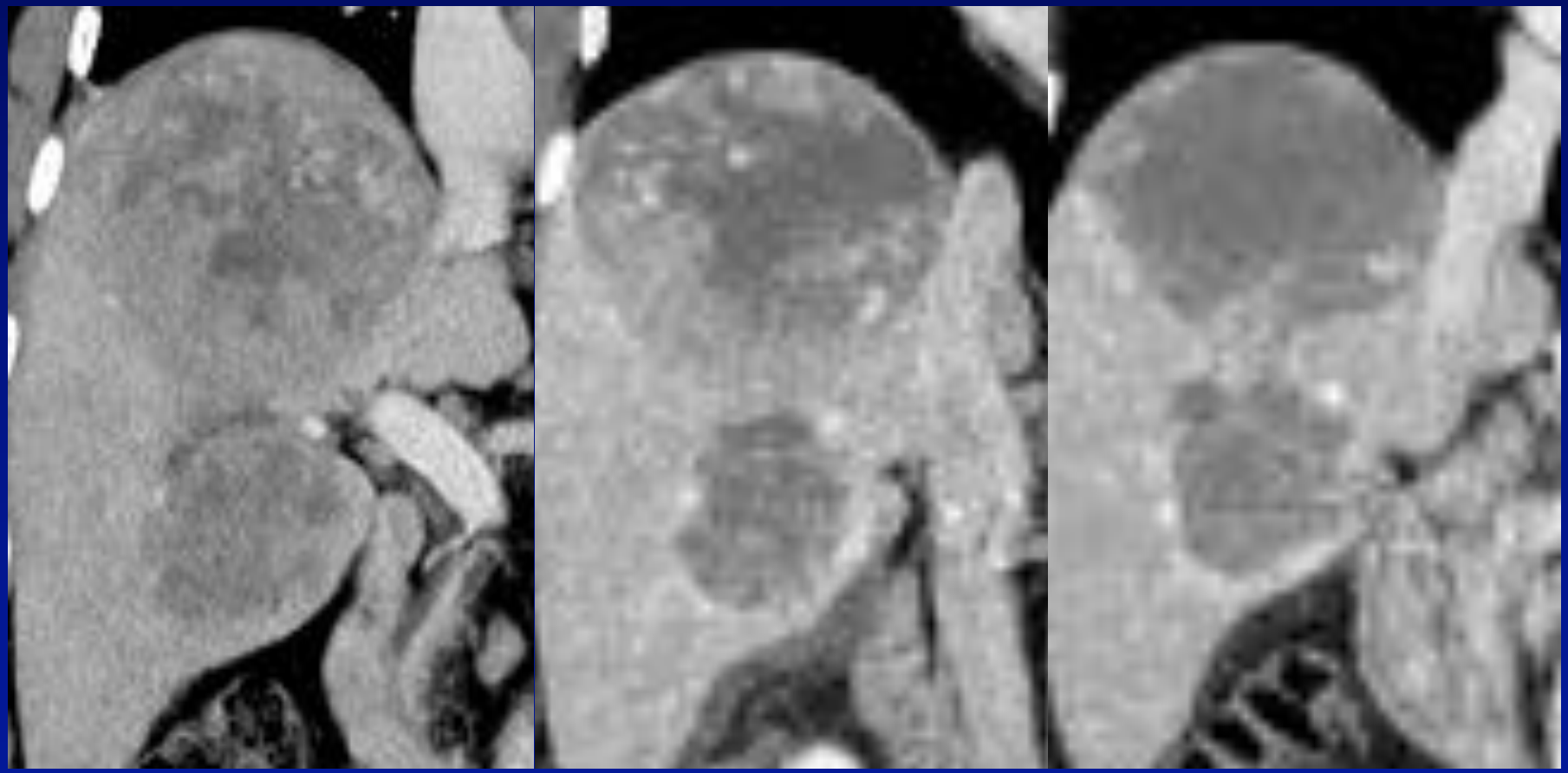
56M with HCV and large HCC

Radioembolization with TheraSphere/Y-90





56M with HCV and large HCC

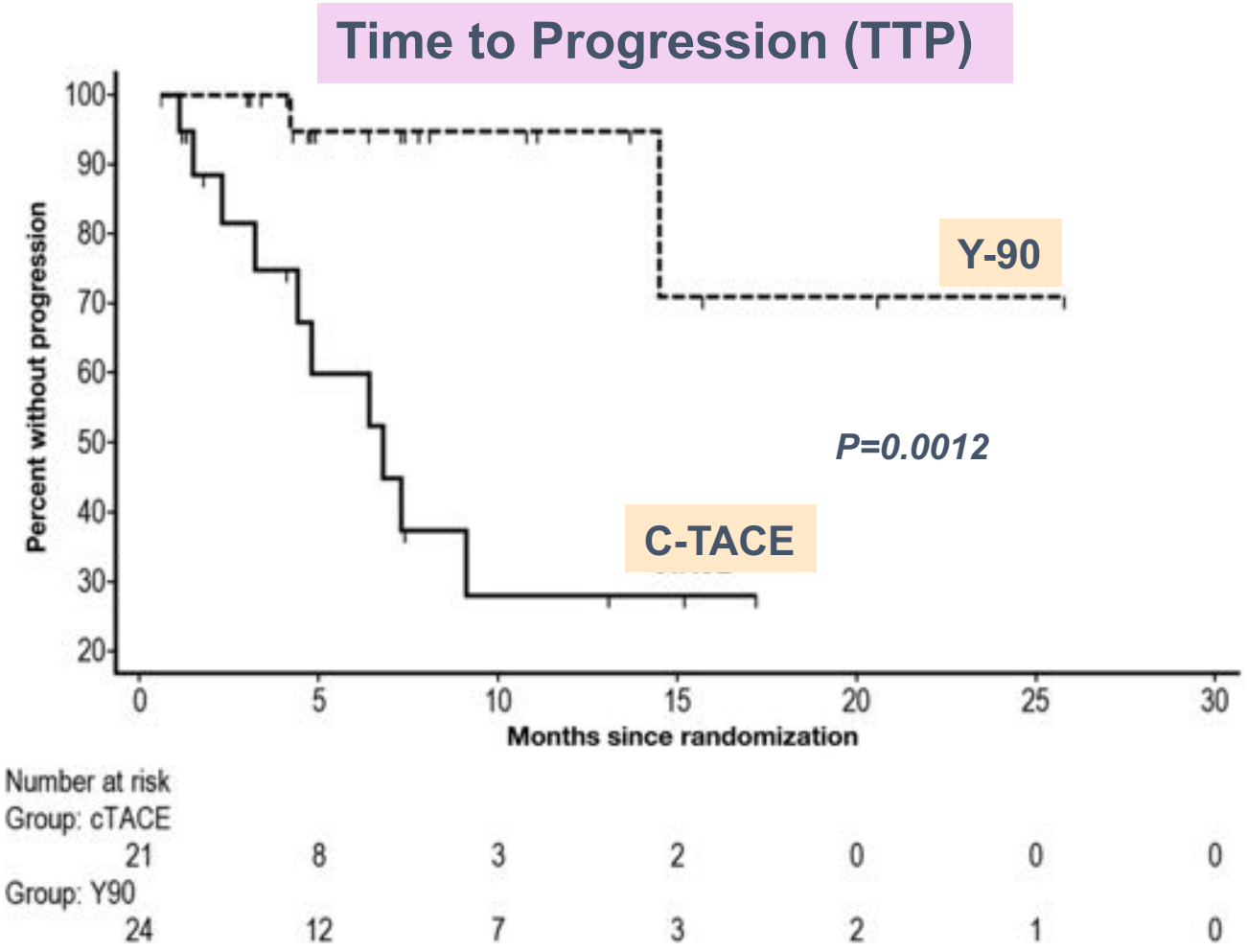


Pre-treatment

1 mo after Y-90 #1

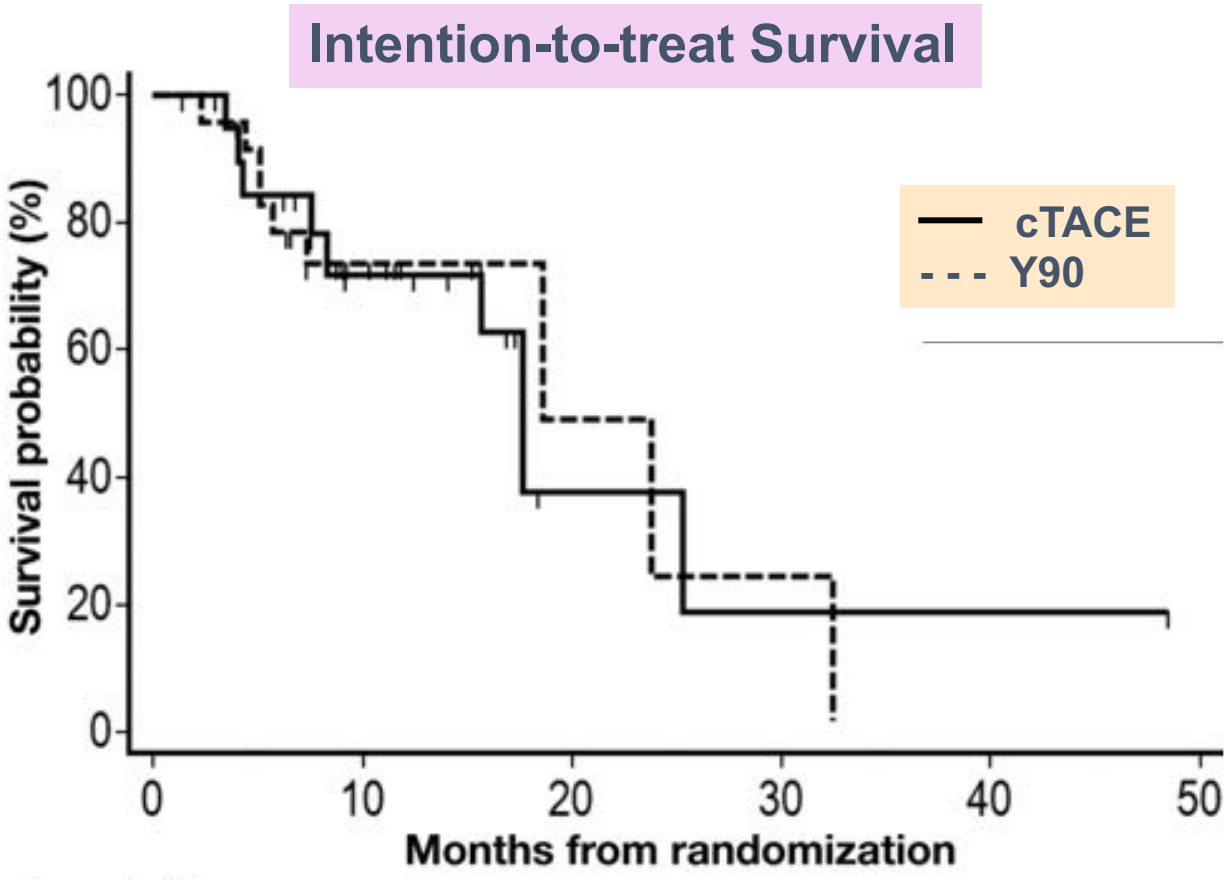
1 mo after Y-90 #2
4 mo after Y-90 #1

SIRT (Y-90) versus TACE (PREMIERE)



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

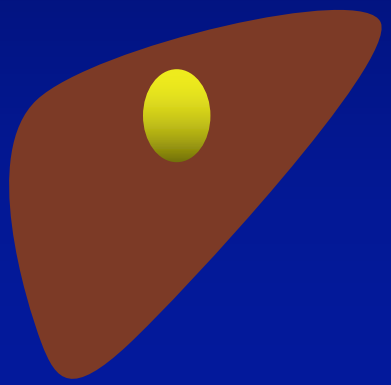
SIRT (Y-90) versus TACE (PREMIERE)



cTACE	21	10	2	1	1	0
Y90	24	9	2	1	0	0

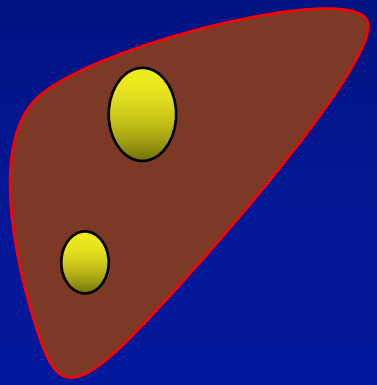
Salem R, et al. Gastroenterology 2016;151:1155-1163

HCC Transplant Criteria



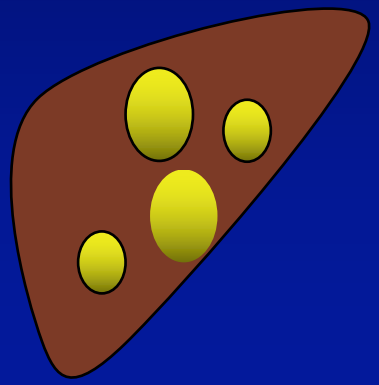
MILAN CRITERIA

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



UNOS DOWNSTAGING CRITERIA

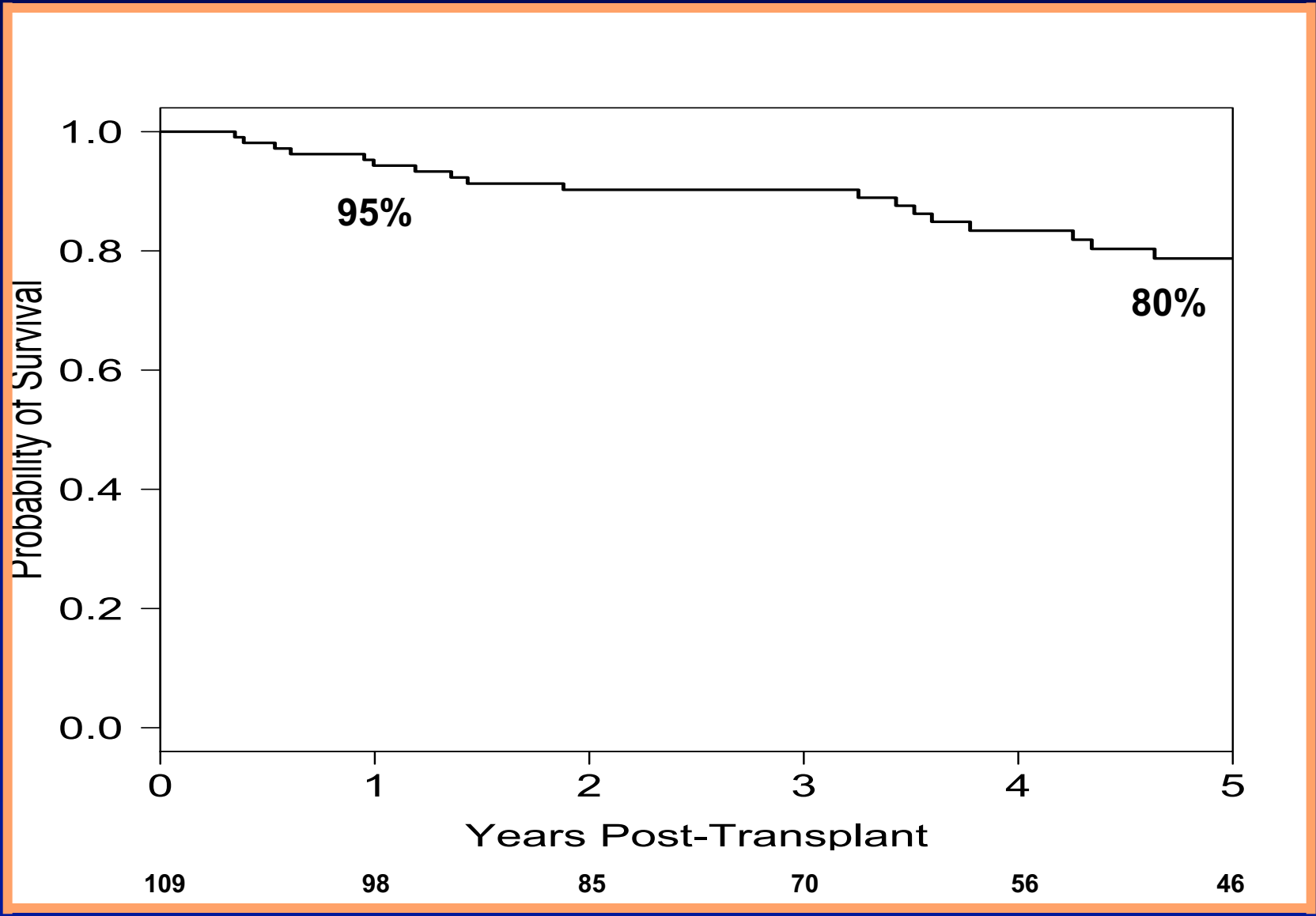
- 1 lesion 5.1-8cm
- 2-3 lesions ≤ 5 cm
- 4-5 lesions ≤ 3 cm
- TTD ≤ 8 cm
- No extra-hepatic dz



ALL-COMERS CRITERIA

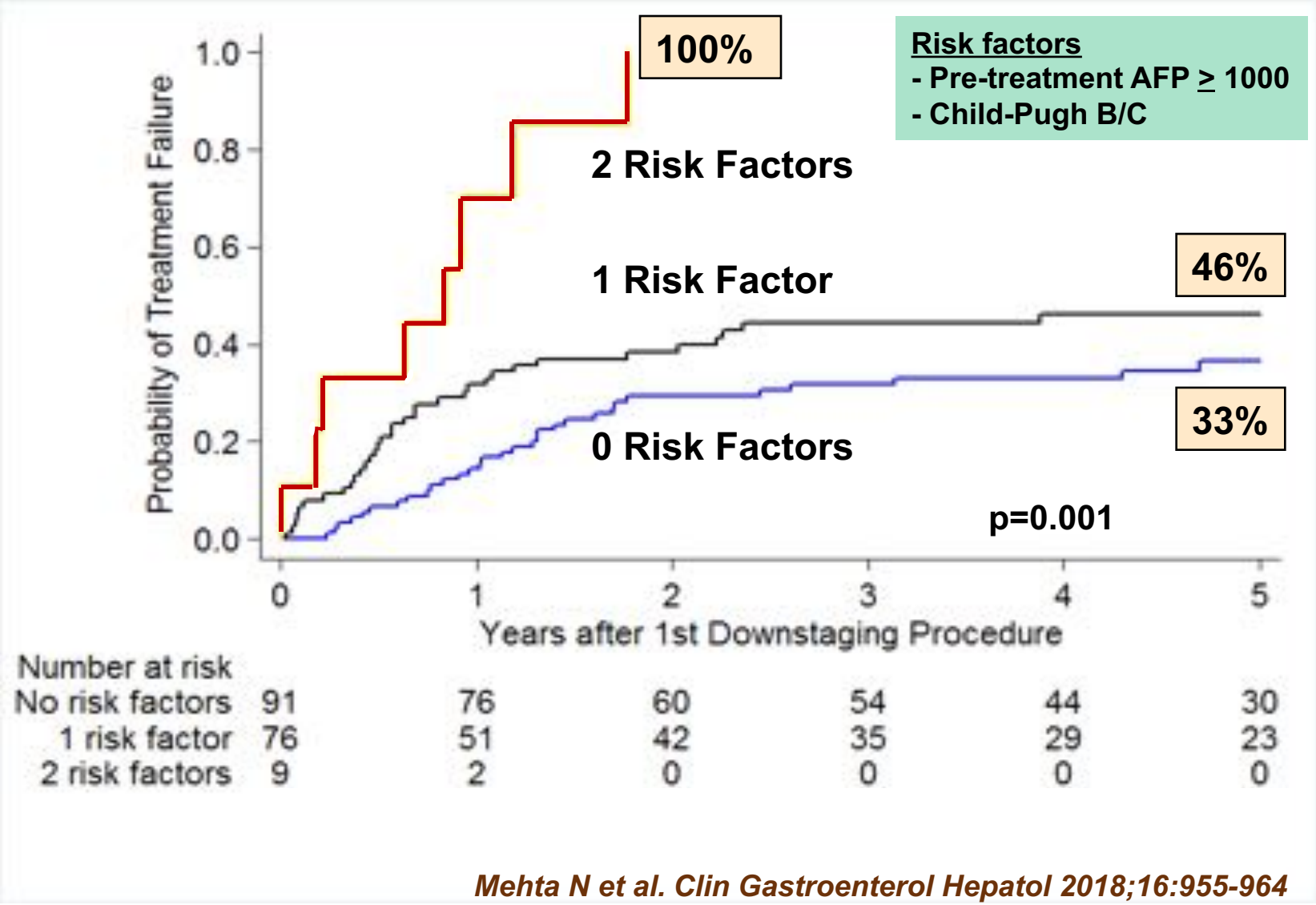
- Any number of tumors
- TTD > 8cm
- No extra-hepatic dz

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

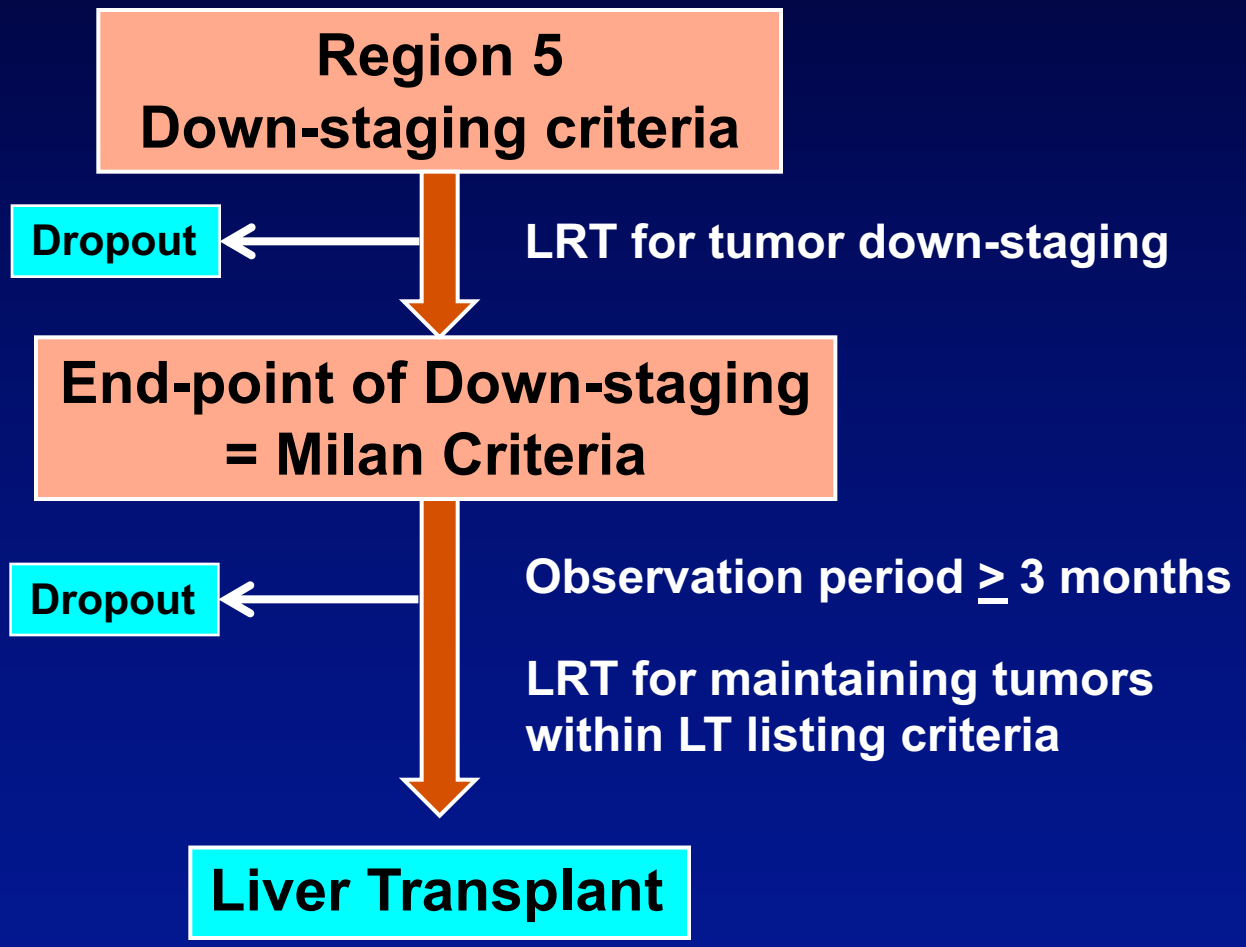


Mehta N et al. Clinical Gastroenterology and Hepatology 2017

Treatment Failure: AFP and Child's Class



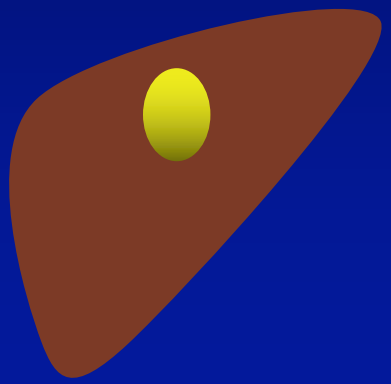
Mehta N et al. Clin Gastroenterol Hepatol 2018;16:955-964



5-yr survival same as Milan criteria without down-staging

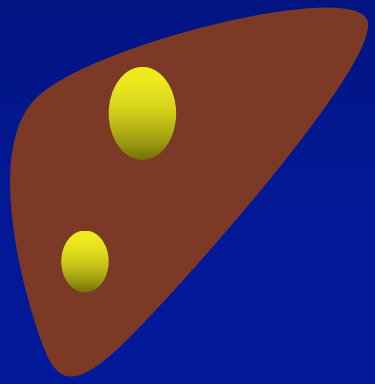
Region 5 Down-staging protocol recently accepted as national policy

HCC Transplant Criteria



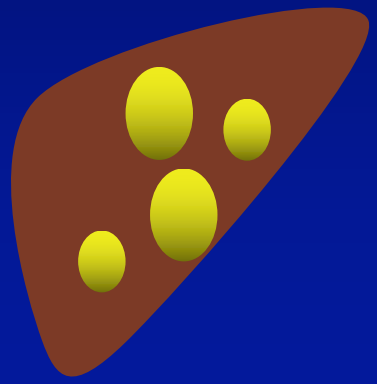
MILAN CRITERIA

- 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

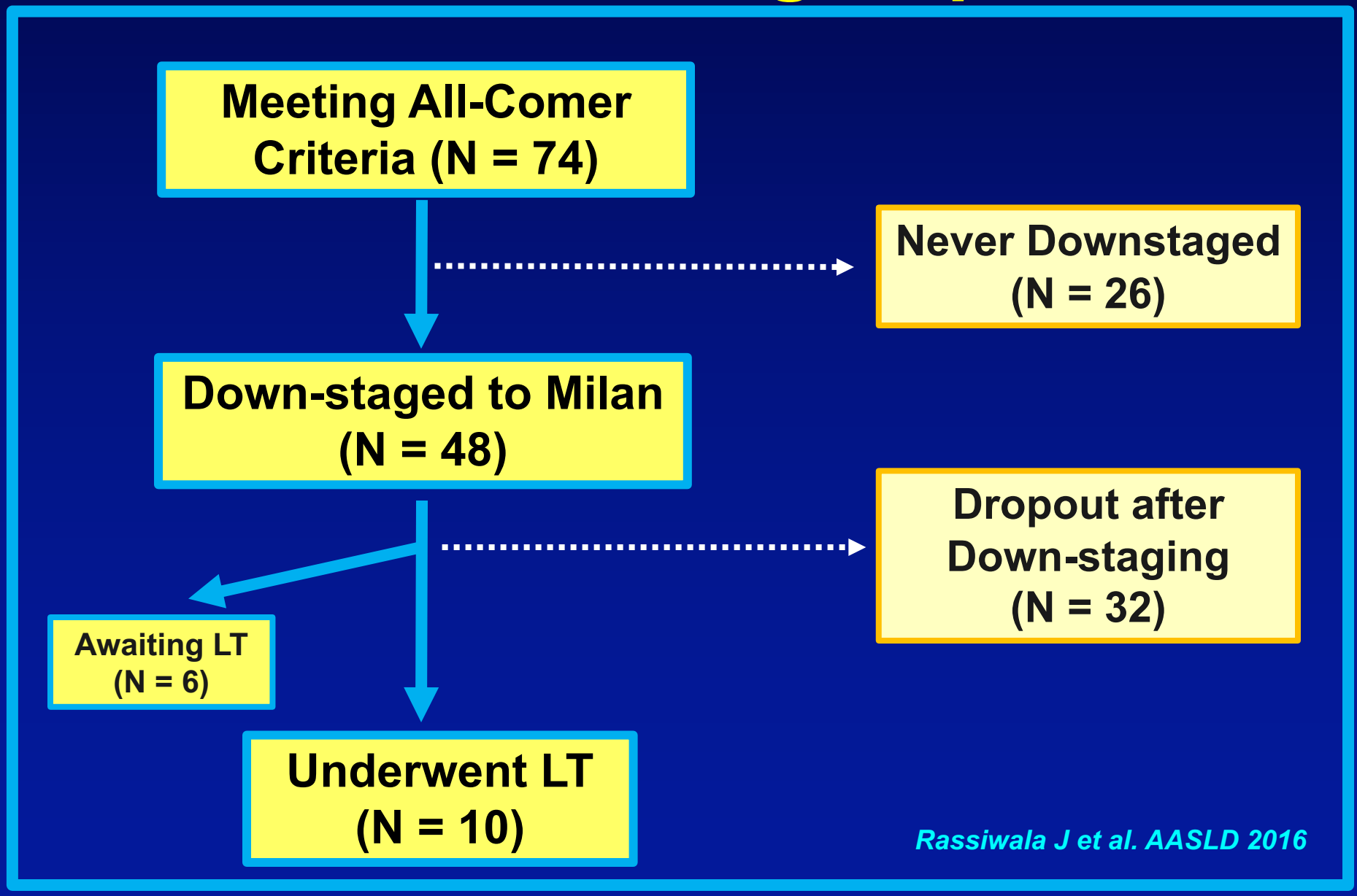
- Any number of tumors
- TTD > 8cm
- No extra-hepatic dz

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

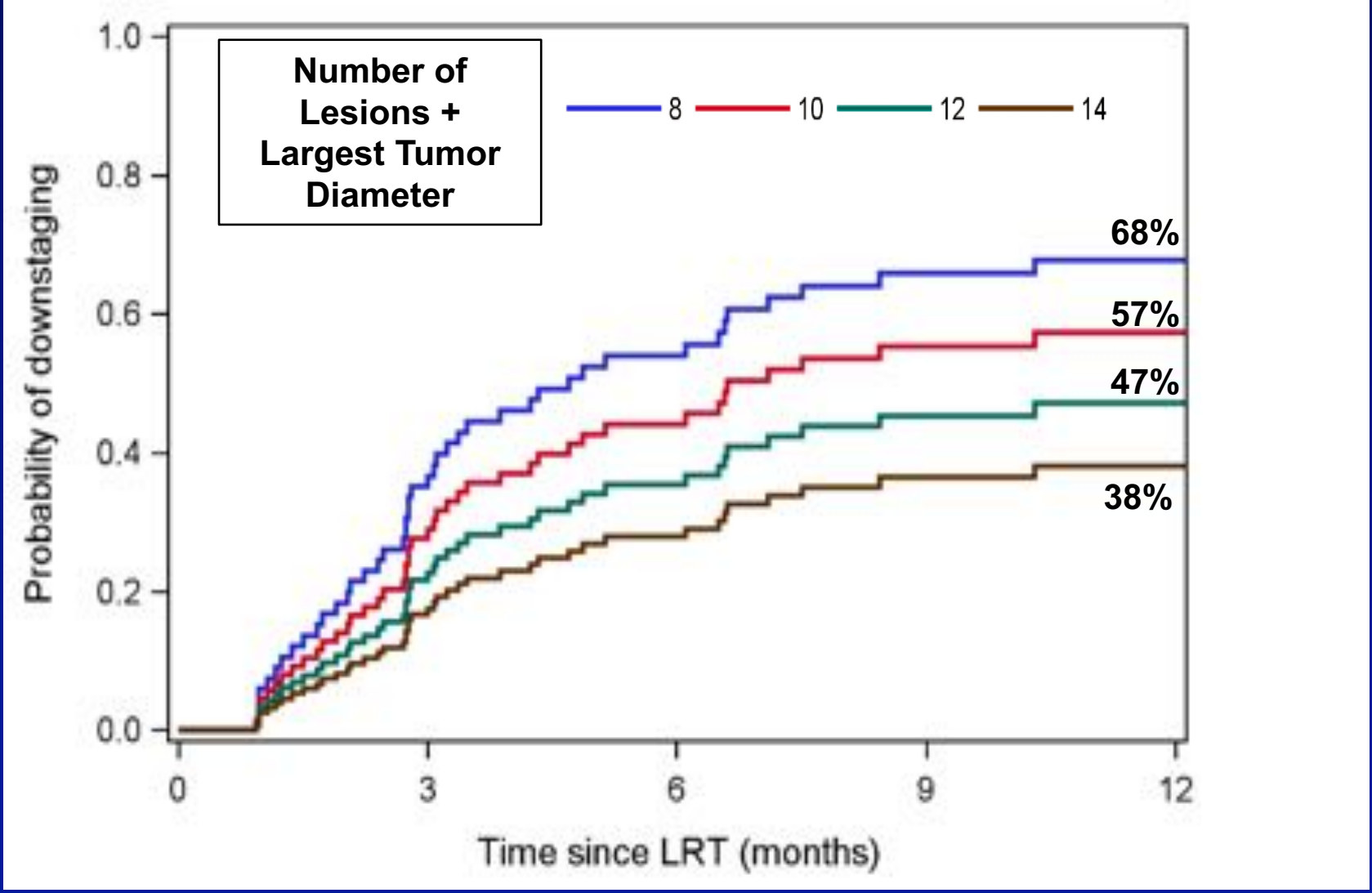
Rassiwala J et al. AASLD 2016

All-comers group



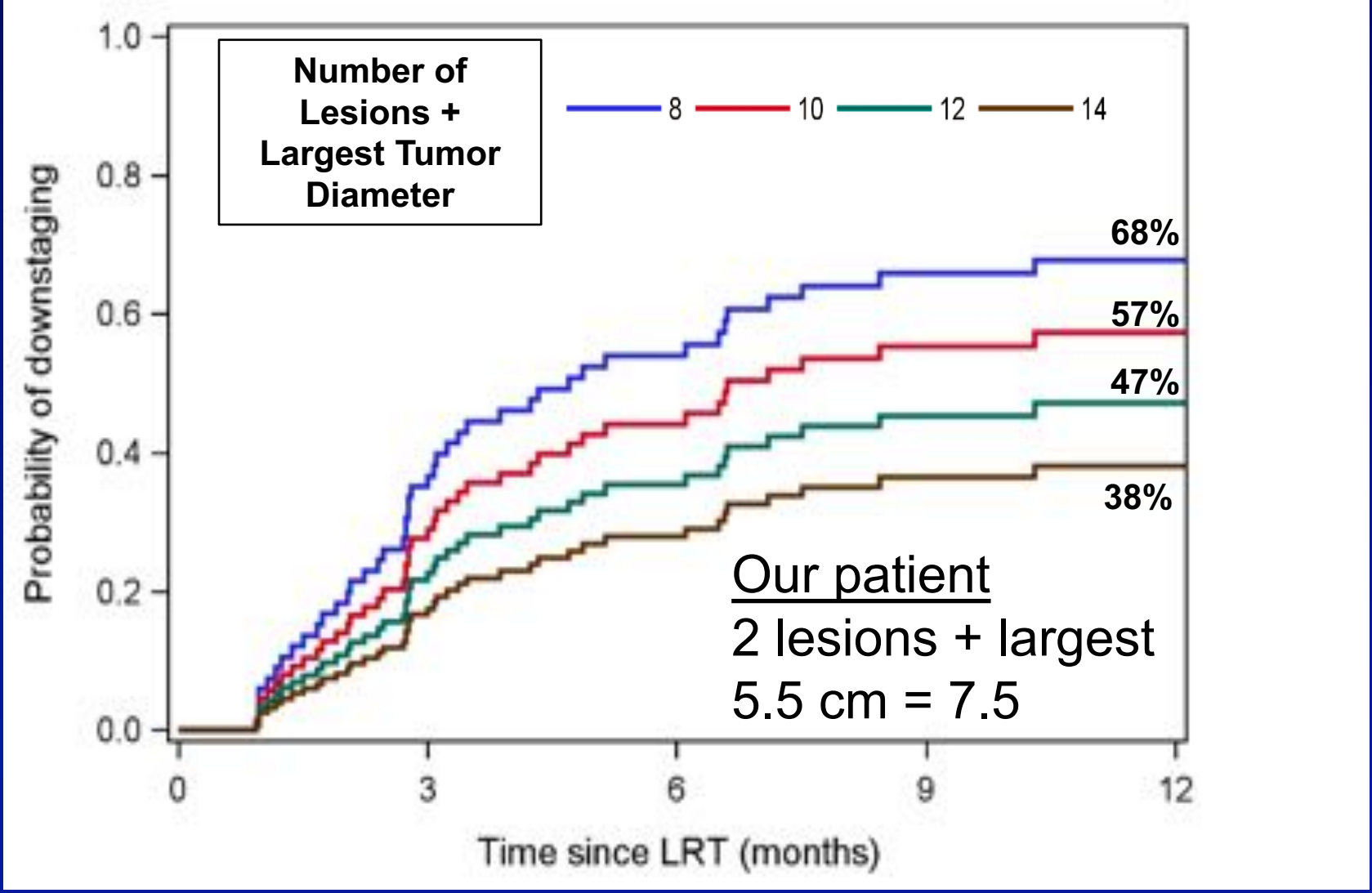
Rassiwala J et al. AASLD 2016

Probability of Downstaging by Initial Tumor Burden



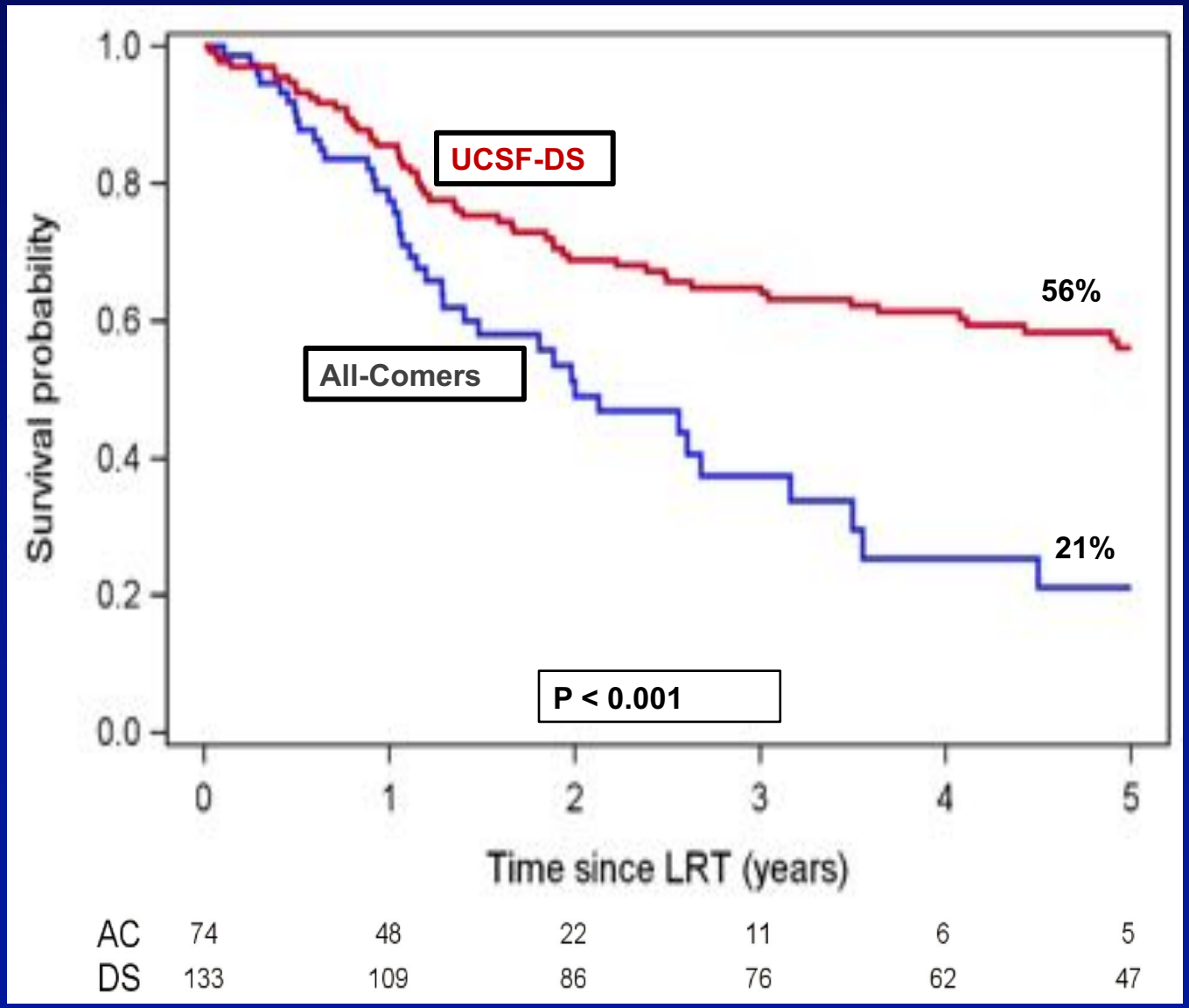
Rassiwala J et al. AASLD 2016

Probability of Downstaging by Initial Tumor Burden



Rassiwala J et al. AASLD 2016

Intention-to-Treat Survival



HCC TX COURSE

- He underwent TACE at UCSF on April 2018
- F/u MRI abdomen May 2018 showed:
  - Treated 4 cm dome lesion
  - Ill-defined segment 8 lesion now measures 8 cm (up from 4.5 cm in February)
  - Re-demonstrated chronic occlusion of main PV, SMV, and splenic vein

HCC TX COURSE

- TACE at UCSF on April 2018
- F/u MRI abdomen May 2018 showed:
  - Treated 4 cm dome lesion
  - Ill-defined segment 8 lesion now measures 8 cm (up from 4.5 cm in February)
  - Re-demonstrated chronic occlusion of main PV, SMV, and splenic vein

How do we know if this is bland or tumor thrombus?

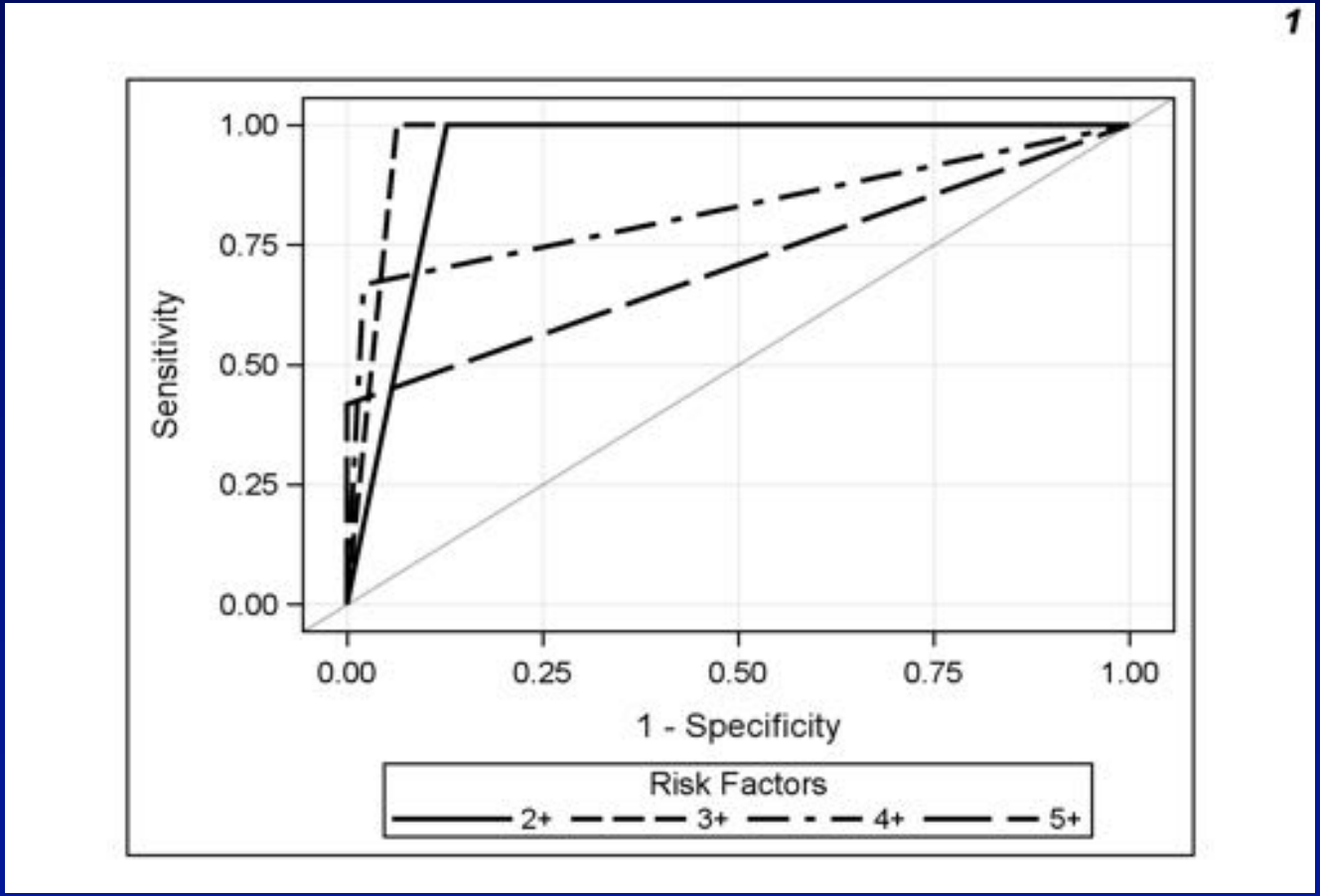
HCC TX COURSE

- TACE at UCSF on April 2018
- F/u MRI abdomen May 2018 showed:
  - Treated 4 cm dome lesion
  - Ill-defined segment 8 lesion now measures 8 cm (up from 4.5 cm in February)
  - Re-demonstrated chronic occlusion of main PV, SMV, and splenic vein

- A-VENA Criteria to distinguish bland and tumor PVT:
  - AFP >1000, Venous expansion, thrombus Enhancement, Neovascularity, and Adjacent to HCC
  - Our patient had none of these five risk factors

Sherman C et al. Liver Txp 2018

HCC TX COURSE

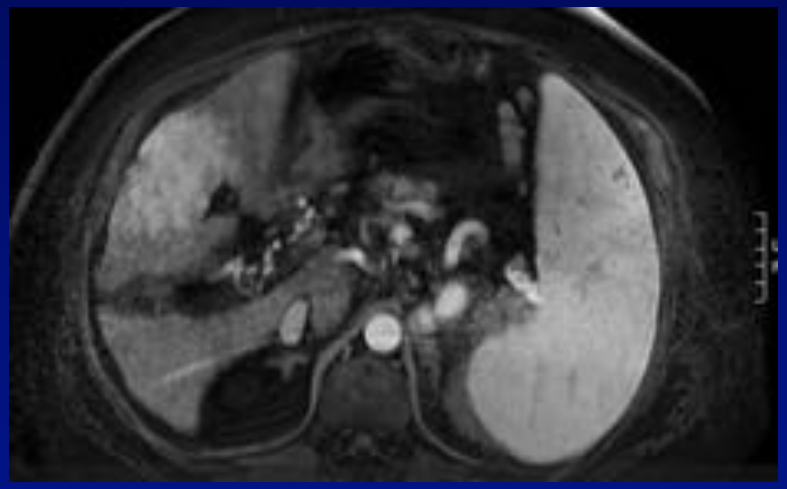


- 3+ criteria best characterized tumor PVT
  - 100% sensitive, 94% specific

Sherman C et al. Liver Txp 2018

HCC TX COURSE

- TACE at UCSF on April 2018
- F/u MRI abdomen May 2018:
  - Treated 4 cm dome lesion
  - Ill-defined segment 8 lesion now measures 8 cm (up from 4.5 cm in February)
  - Re-demonstrated chronic occlusion of main PV, SMV, and splenic vein



- T bili 3.0, D bili 1.1, INR 1.6, Plt 36, AFP 2.2
- He tolerated TACE well
- Next steps for 8 cm segment 8 lesion?

HCC TX COURSE

- Underwent 3 sessions of SBRT in July 2018 to this large anterior lobe lesion
- Bilirubin up to 6.2 on 9/4/18, INR remained 1.5, AFP <2
- Abdominal MRI 10/1/18 showed extensive ill-defined HCC in segment 8 lesion. Significant residual enhancing tumor remains interspersed with the newly non-enhancing treatment sites measuring up to 6.5 cm

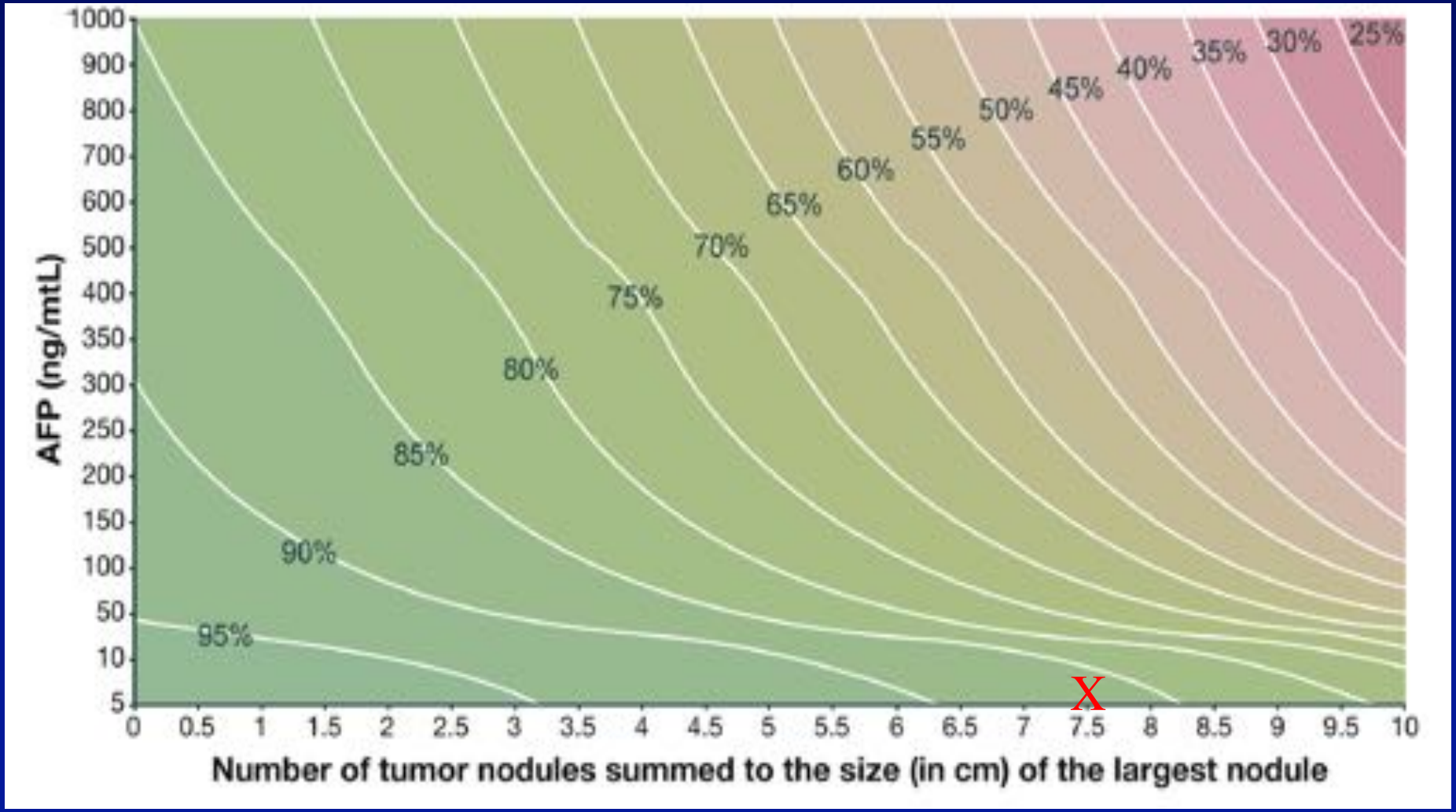
HCC TX COURSE

- Underwent 3 sessions of SBRT in July 2018 to this large anterior lobe lesion
- Bilirubin up to 6.2 on 9/4/18, INR remained 1.5, AFP <2
- Abdominal MRI 10/1/18 showed extensive ill-defined HCC in segment 8 lesion. Significant residual enhancing tumor remains interspersed with the newly non-enhancing treatment sites measuring up to 6.5 cm
- 10/4/18: Sodium 120, Tbili 32, Cr 2.0, INR 1.5
- MELD-Na 35 → he is directly admitted to the hospital

OK TO MOVE FORWARD WITH LT?

LT FOR HCC: METROTICKET 2.0

HCC Specific Survival



Mazzaferro V et al. Gastroenterology 2017

OK TO MOVE FORWARD WITH LT?

- Not sure - we need more information!!

- DCP up to 38.2 ng/ml
- AFP-L3 slightly up to 16.3

DCP + AFP + AFP-L3 (Mayo Clinic)

- Retrospective study; 2 sites (n=313)
- 70% within Milan Criteria
- 15% HCC recurrence
- Subset of 127 with available samples (33% with HCC recurrence)

AFP = 250 ng/mL	DCP = 7.5 mg/mL	HR (p-value)
HIGH	HIGH	5.2 (p< 0.001)
LOW	HIGH	3.2 (p=0.005)
HIGH	LOW	2.3 (p=0.1)
LOW	LOW	1

Chaiteerakij et al. Liver Transpl 2015; 21:599-606

OK TO MOVE FORWARD WITH LT?

- Not sure - we need more information!!

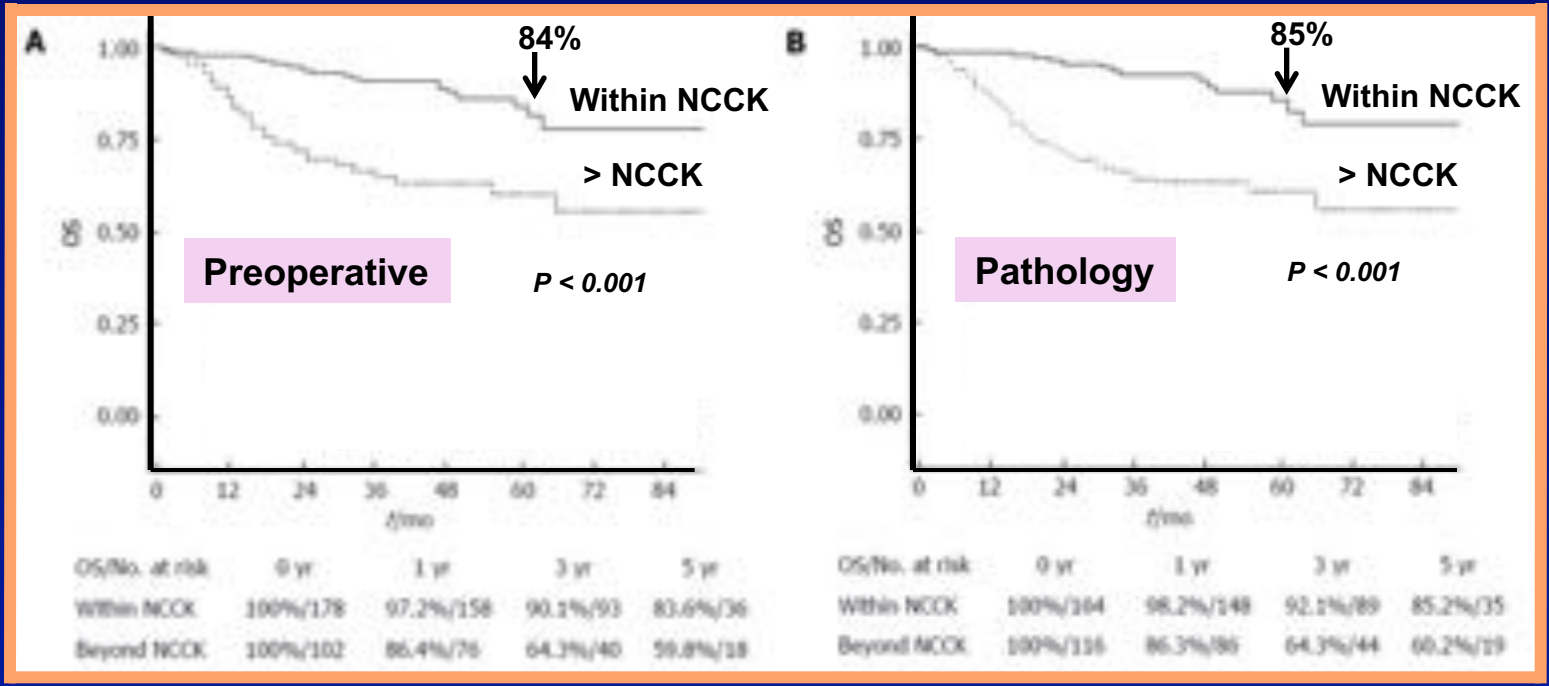
- DCP up to 38.2 ng/ml
- AFP-L3 slightly up to 16.3

- FDG PET/CT scan negative for hypermetabolic disease

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

OK TO MOVE FORWARD WITH LT?

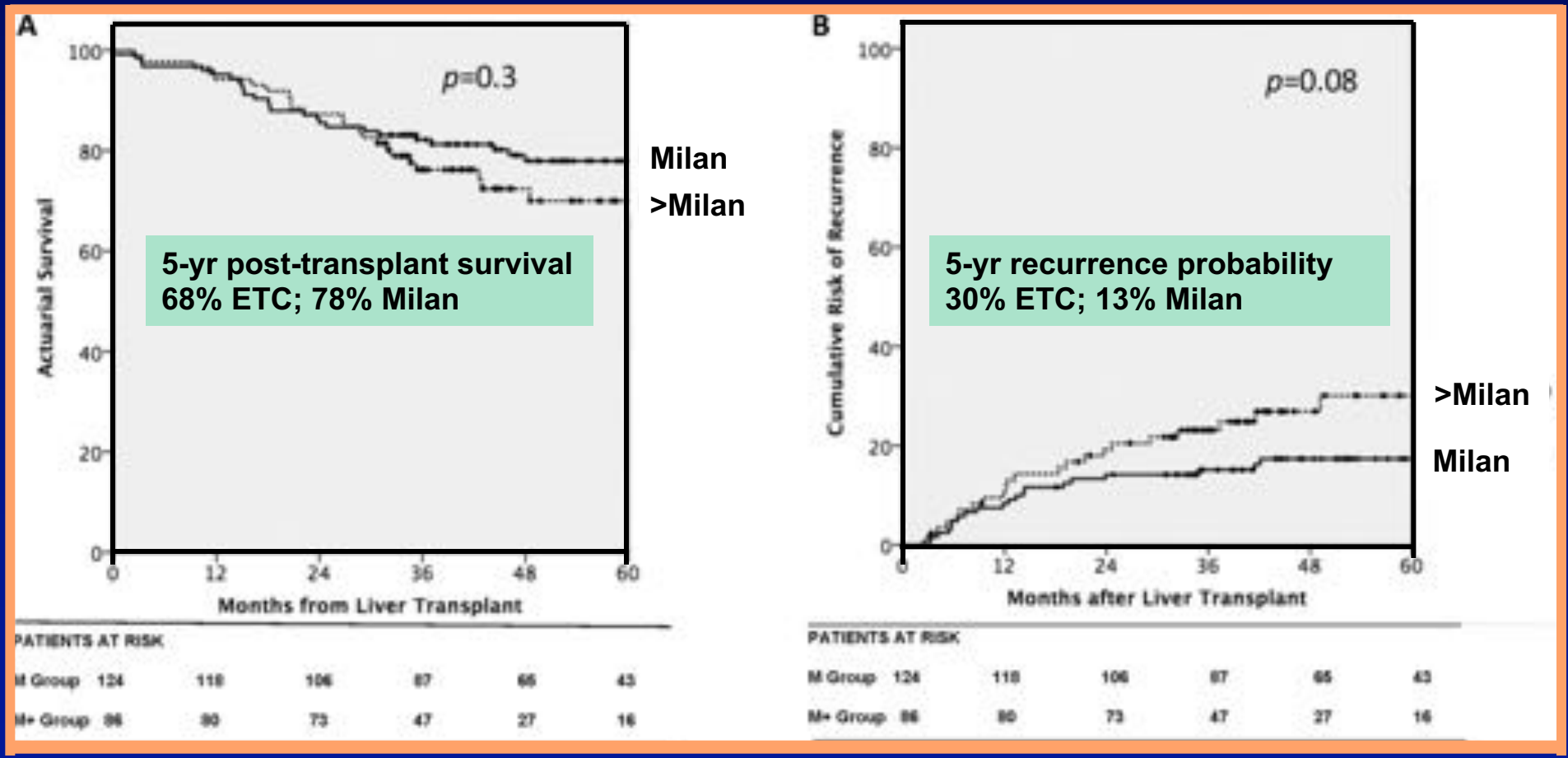
- Not sure - we need more information!!

- DCP up to 38.2 ng/ml
- AFP-L3 slightly up to 16.3

- FDG PET/CT scan negative for hypermetabolic disease

- Preoperative biopsy of the ill-defined tumor?

Extended Toronto Criteria



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

OK TO MOVE FORWARD WITH LT?

- Not sure - we need more information!!

- DCP up to 38.2 ng/ml
- AFP-L3 slightly up to 16.3

- FDG PET/CT scan negative for hypermetabolic disease

- Pathology from intraoperative biopsies of the tumor show well to moderately differentiated HCC

LIVER TRANSPLANT FOR HCC
SELECTION CRITERIA

PROS	CONS
AFP 2 ng/ml AFP-L3 16% Well to moderately differentiated grade PET scan negative Partial response to LRT Wait time ~8 months	Beyond Milan criteria (but appears to be within UCSF extended criteria) DCP 38.2 ng/ml

√

Mehta N and Yao F.
Clinical Liver Disease 2018

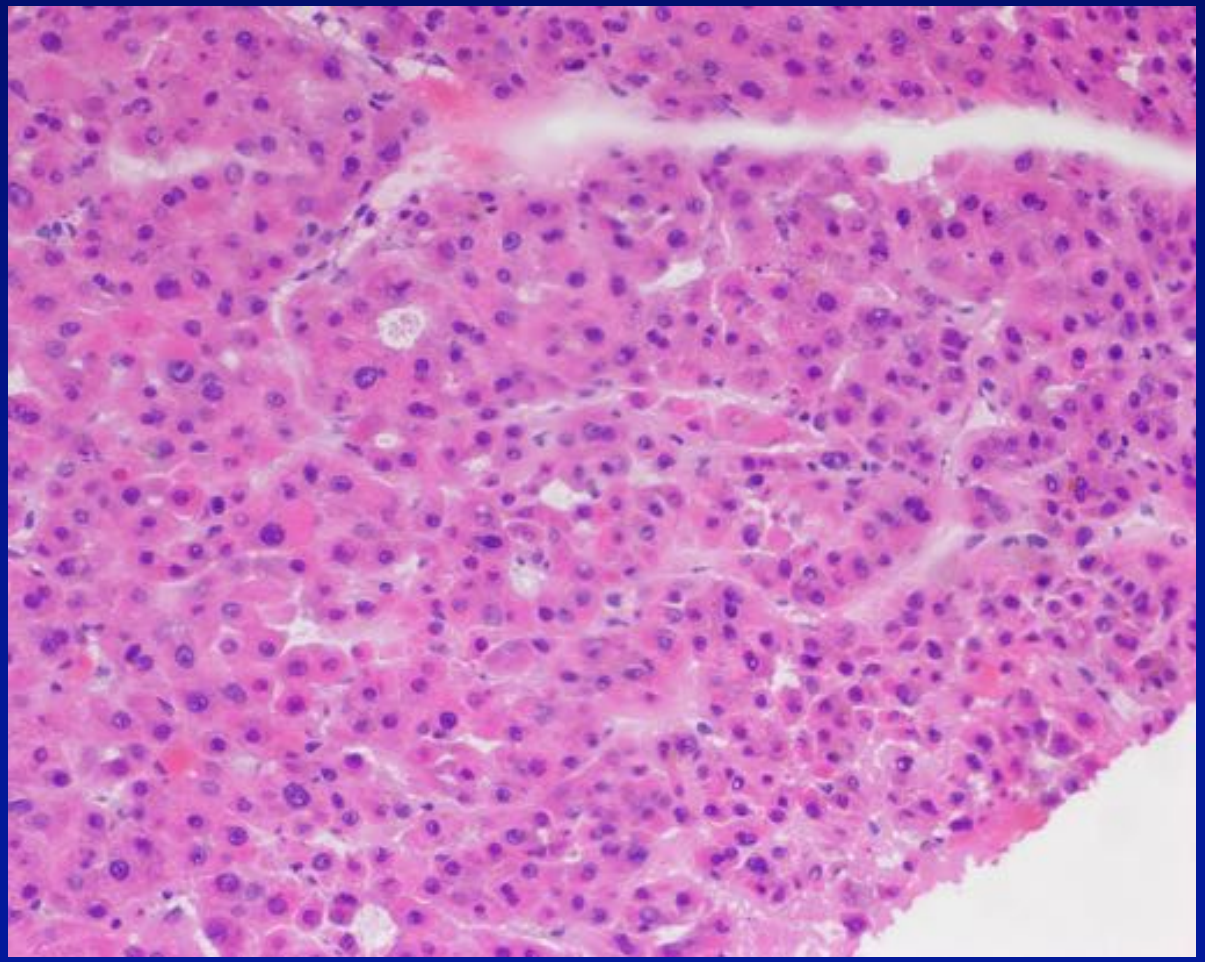
LTX

- Underwent LT on 10/13/18

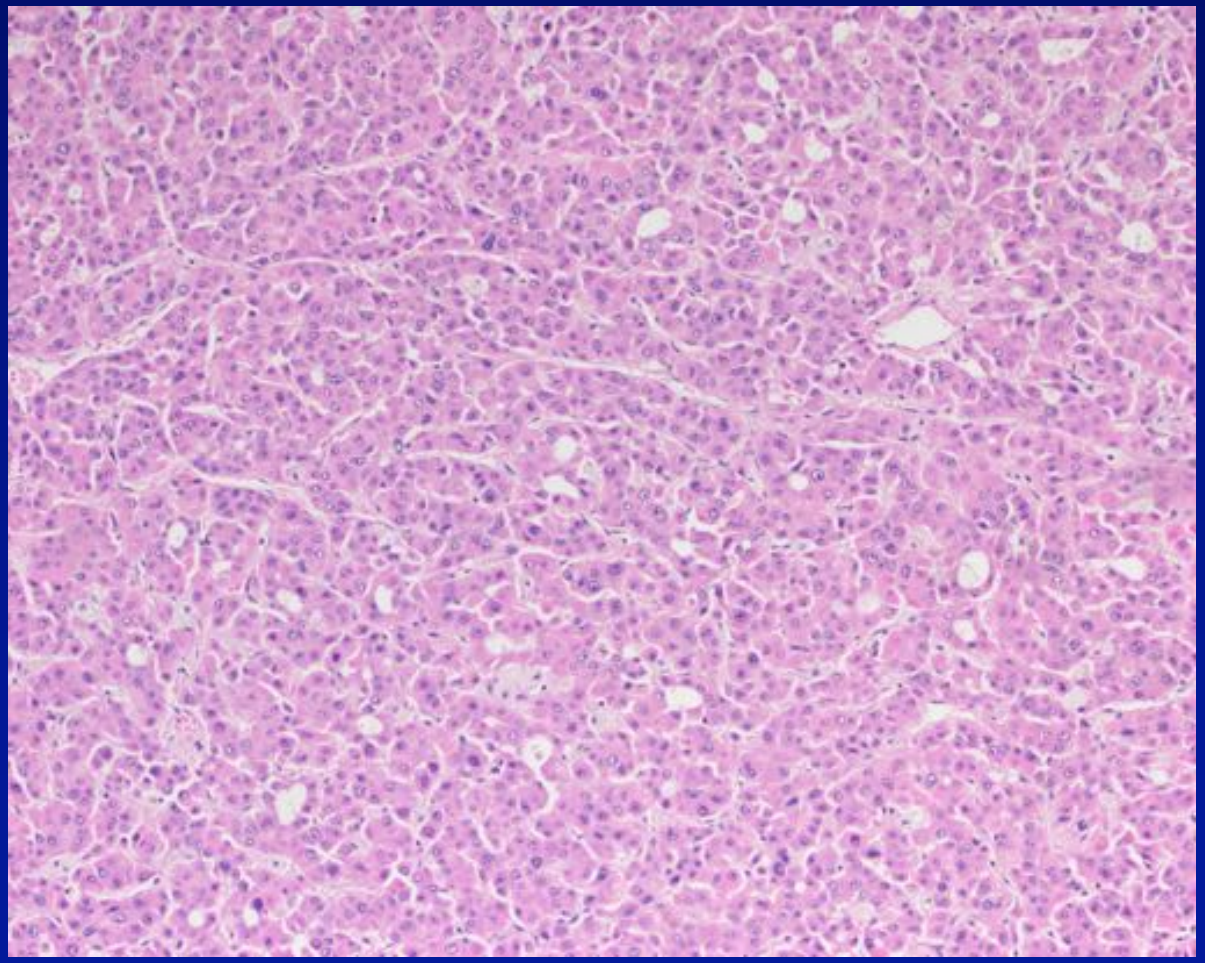
- Explant
  - Tumor #1: Size: 7.5 cm, viable 5 cm, moderately differentiated
  - Tumor #2: Size: 4.5 cm, viable 0.5 cm, well-differentiated

  - Vascular invasion: None.
  - Local extension of tumor: Confined to liver.

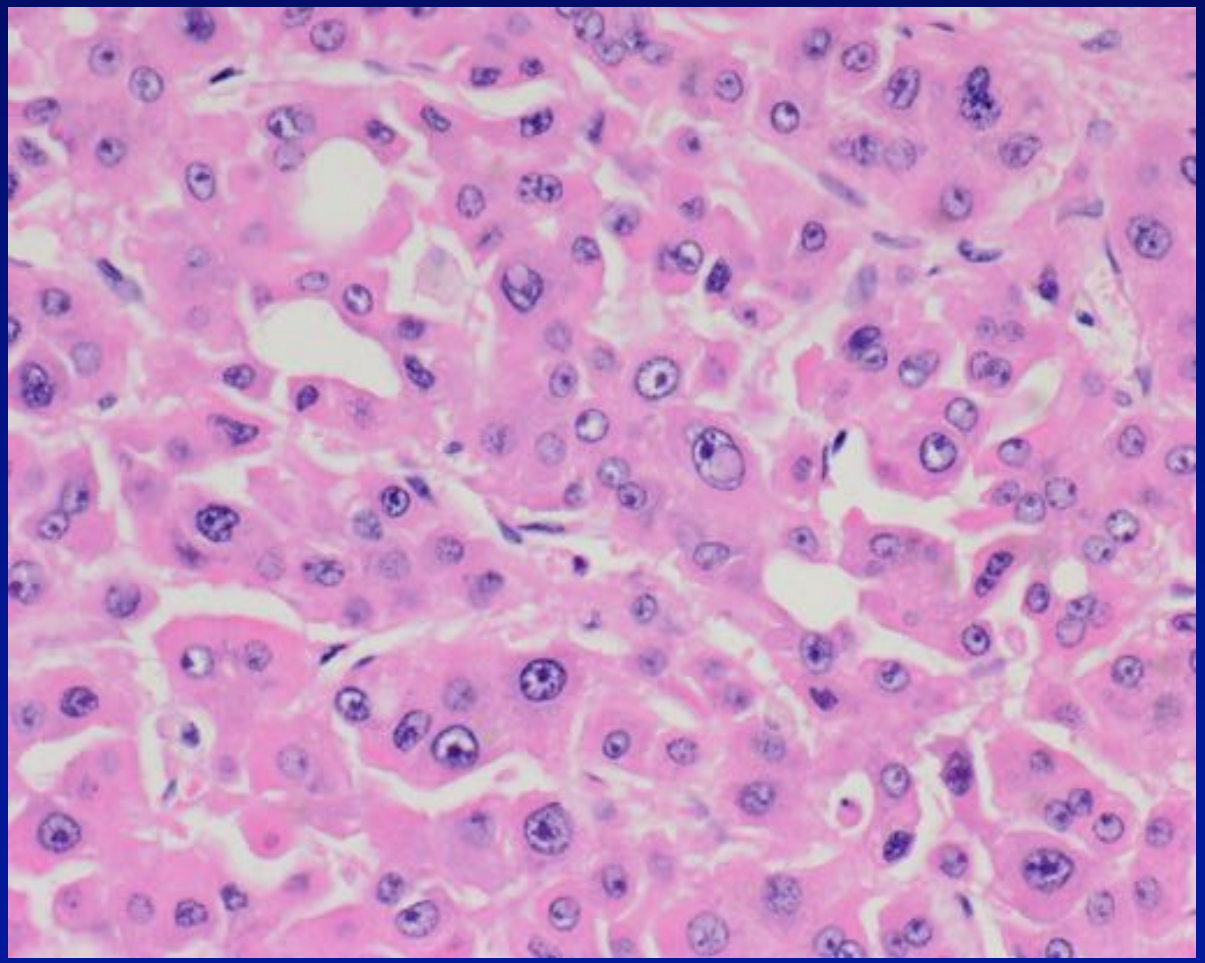
Frozen Section – Hepatocellular neoplasm, favor HCC



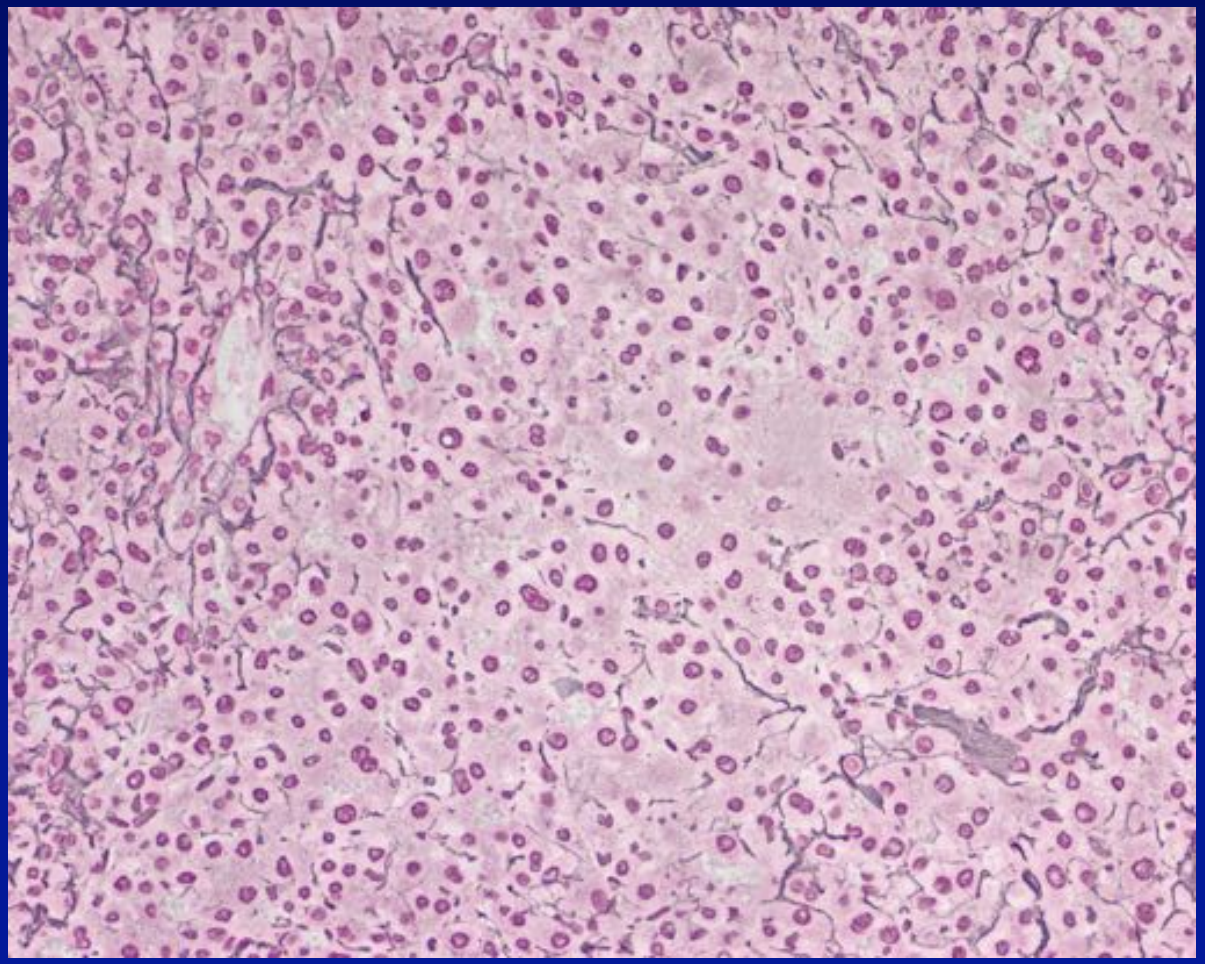
HCC – moderately differentiated (7.5 cm, partial necrosis)



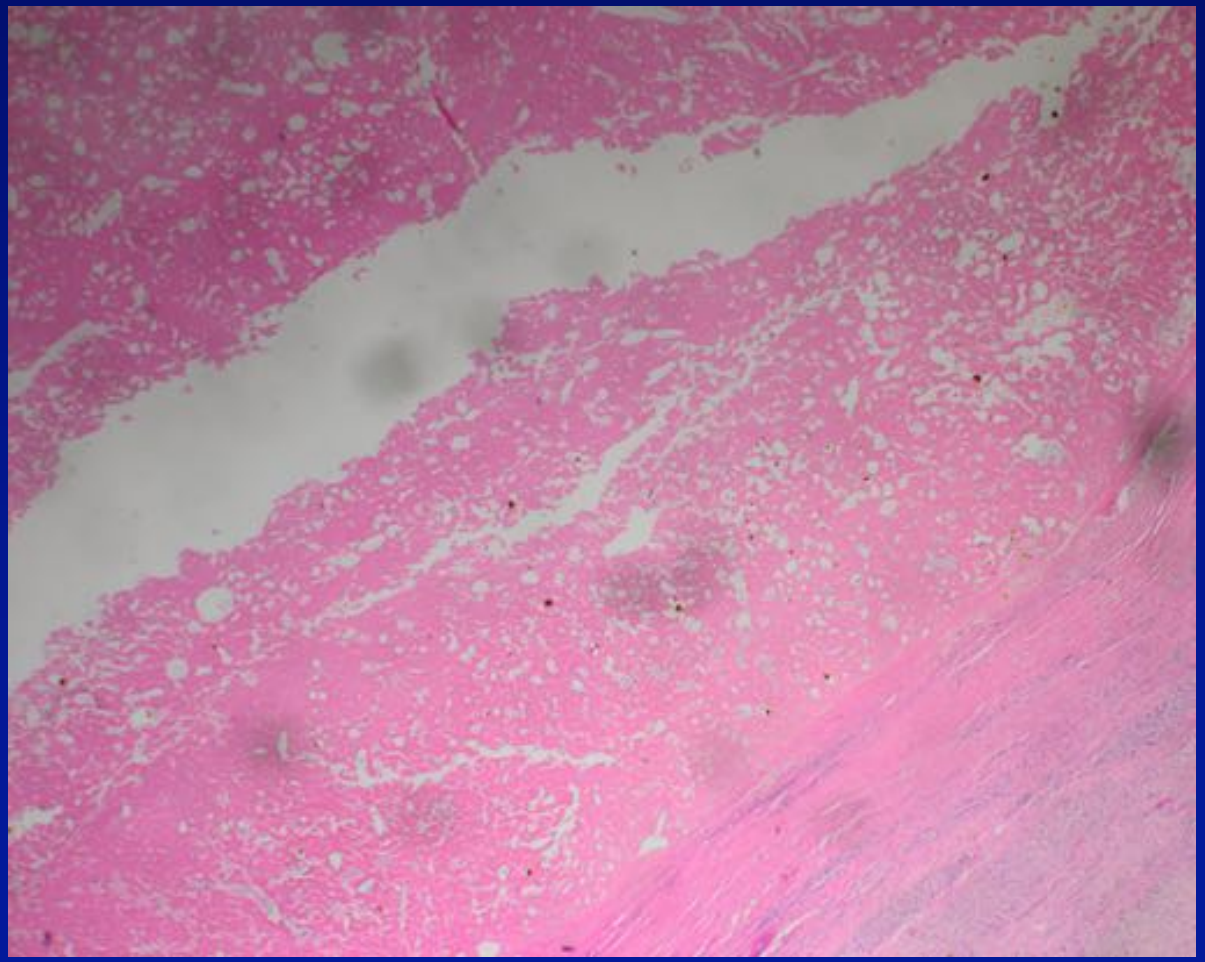
HCC – large pleomorphic nuclei



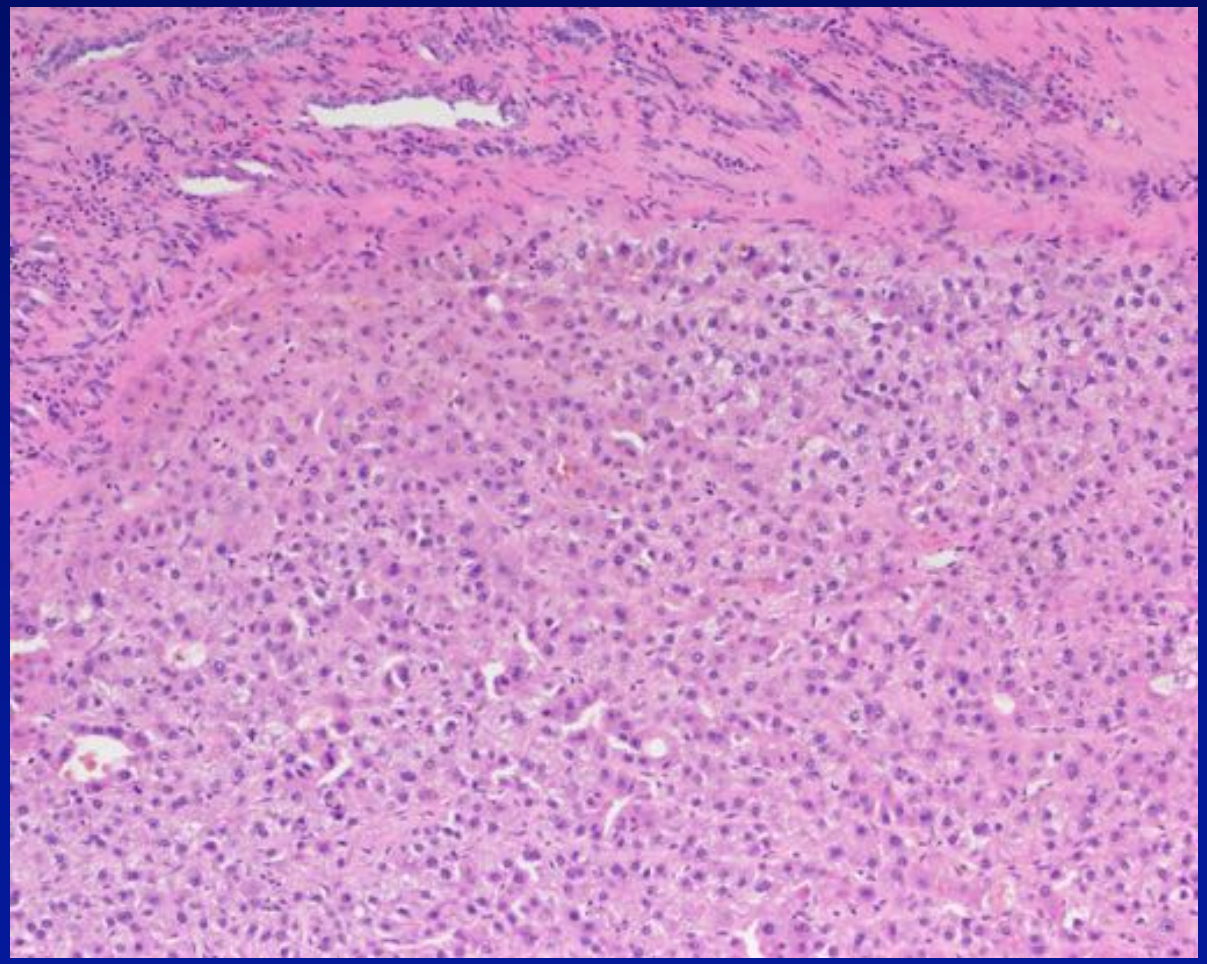
Tumor – reticulin loss



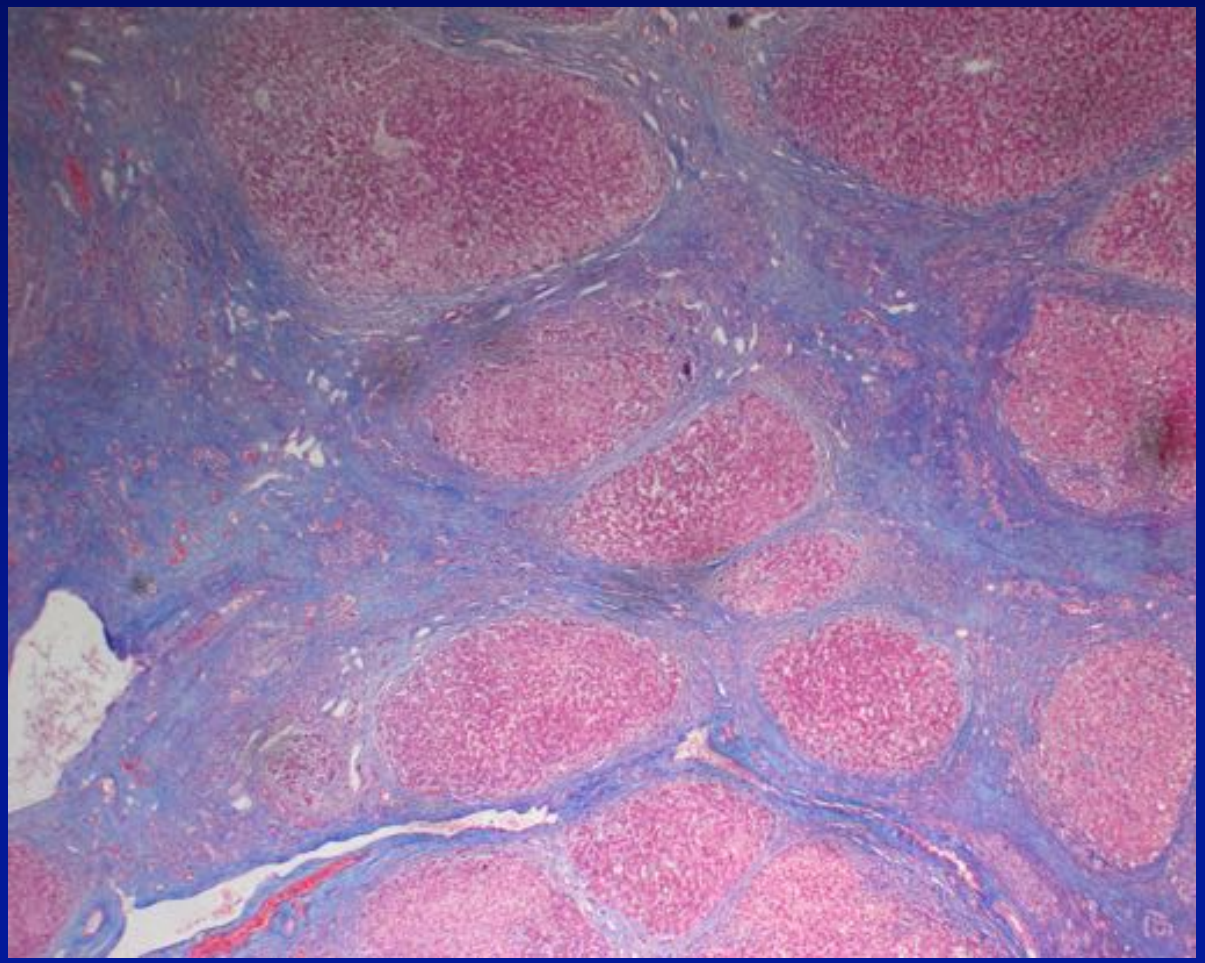
HCC - 4.5 cm(right lobe), 95% necrotic, well-differentiated



HCC - Moderately differentiated, 5 cm, 20% necrotic



Cirrhosis (trichrome)

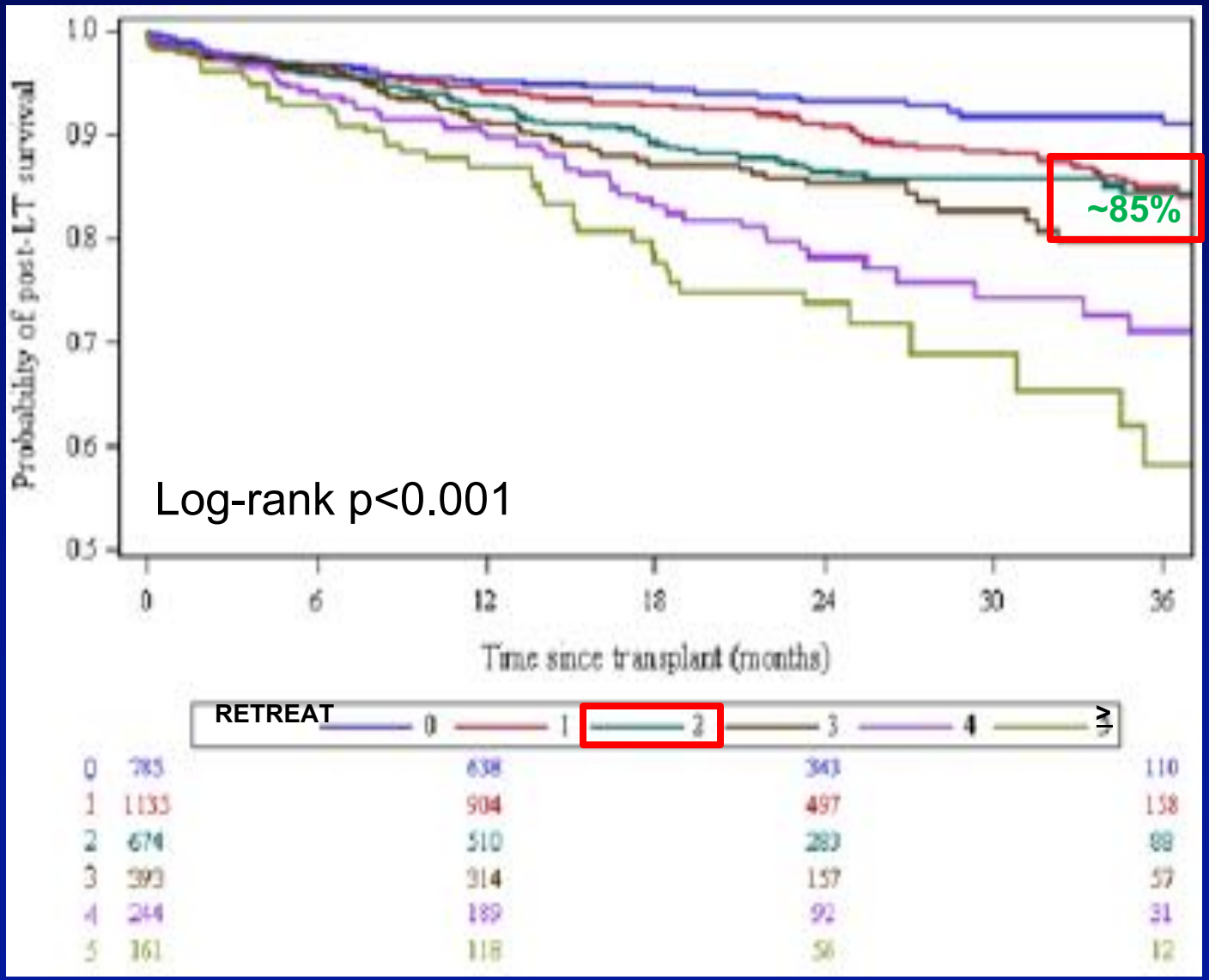


RETREAT SCORE

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

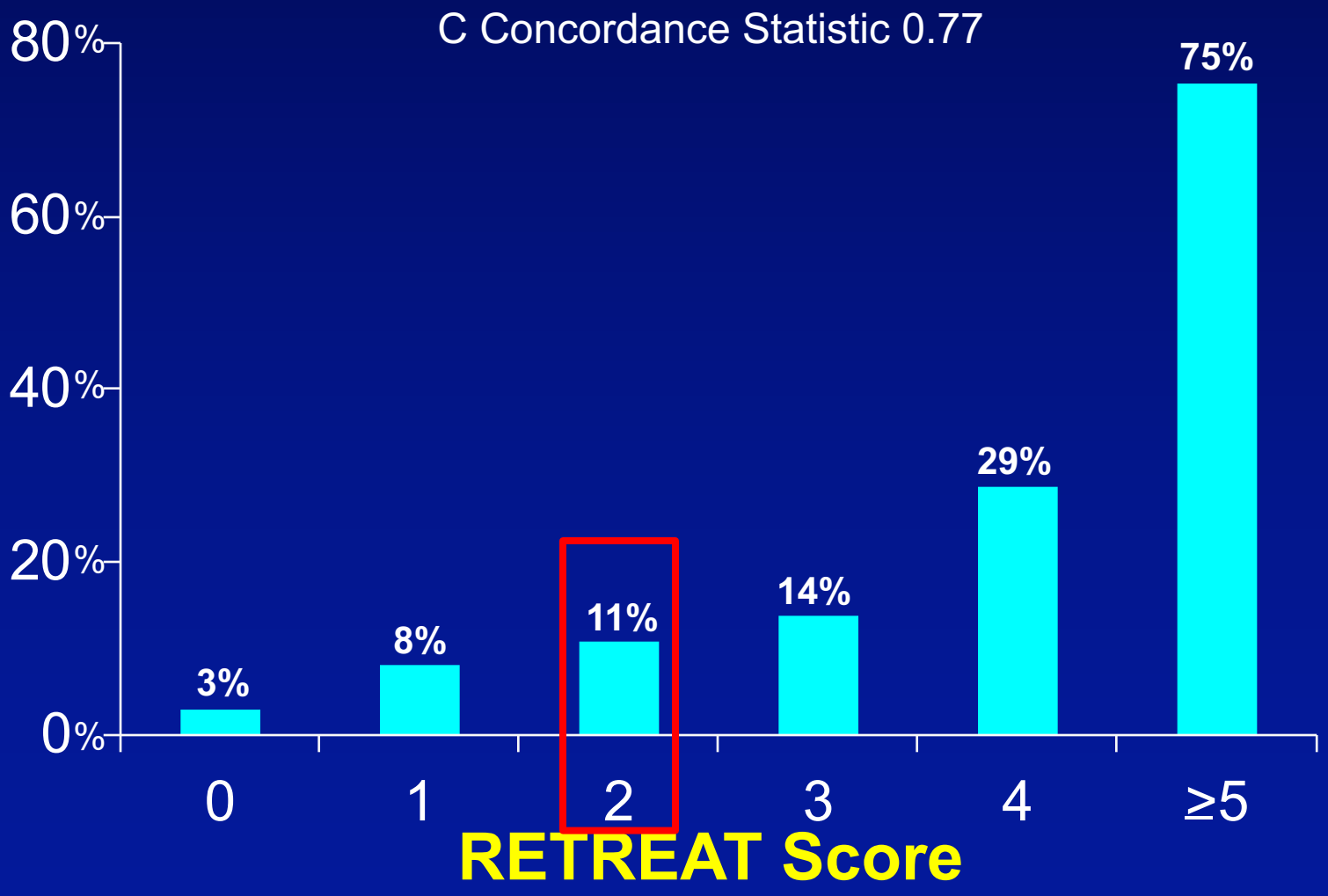
No RETREAT points scored for AFP 0-20 and no microvascular invasion

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



Mehta N, et al
AJT 2017

RETREAT SCORE: 5 YR RECURRENCE



Mehta N, et al. JAMA Oncology 2017

RETREAT FOR HCC SURVEILLANCE

RETREAT	Proposed surveillance regimen
1-3	HCC surveillance every 6 months for 2 years

Mehta N, et al. JAMA Oncology 2017

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**
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

Mehta N, et al. JAMA Oncology 2017

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
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

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

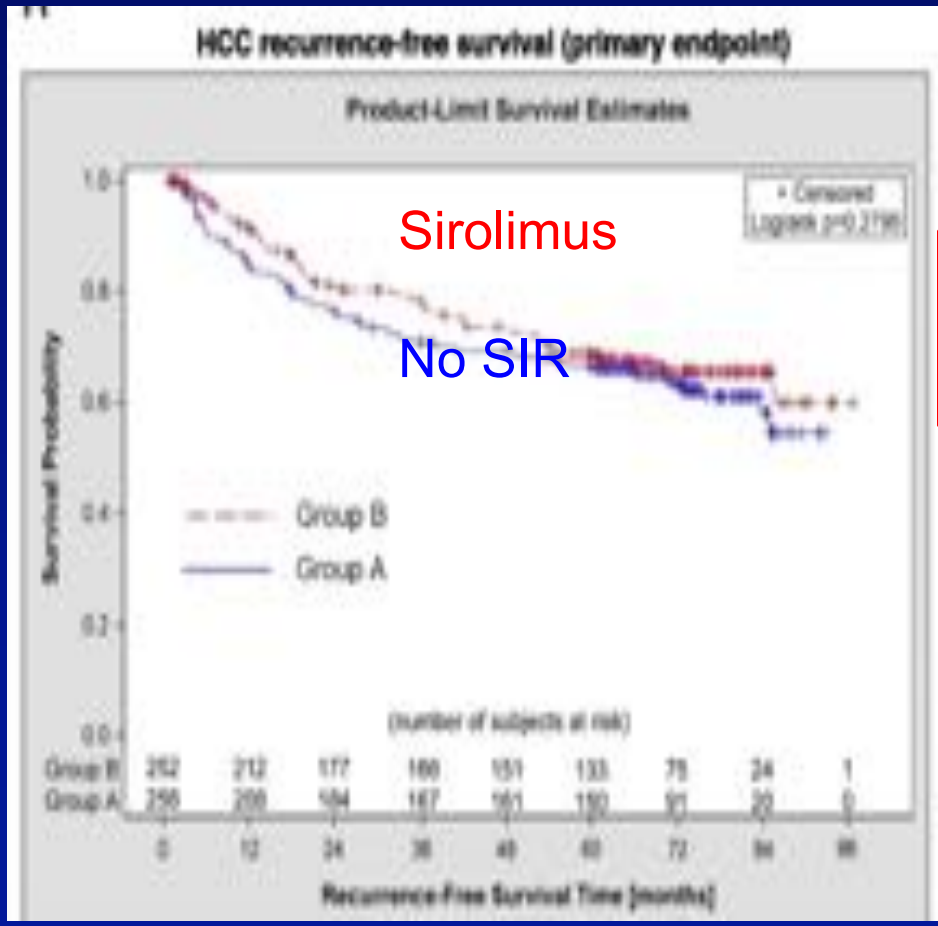
SILVER TRIAL

Prospective phase 3, multi-center international RCT

Geissler EK et al, Transplantation 2016

SILVER TRIAL: RFS

Prospective phase 3, multi-center international RCT

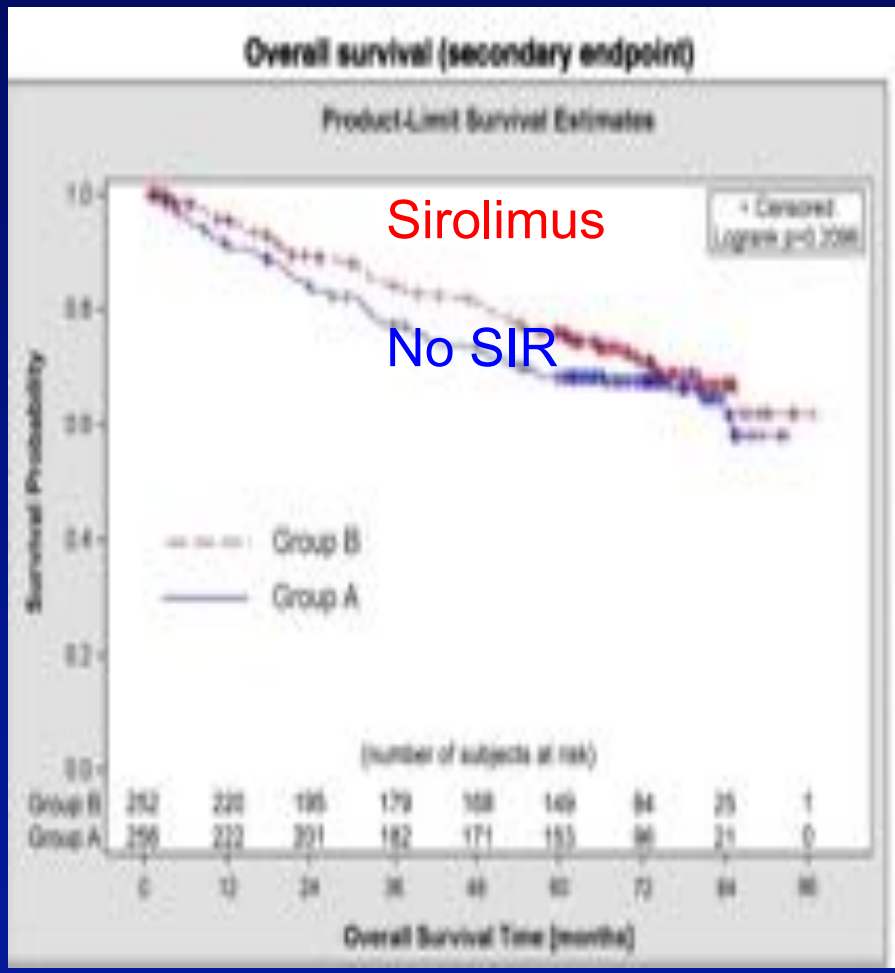


Recurrence-free survival over years (ITT population)

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

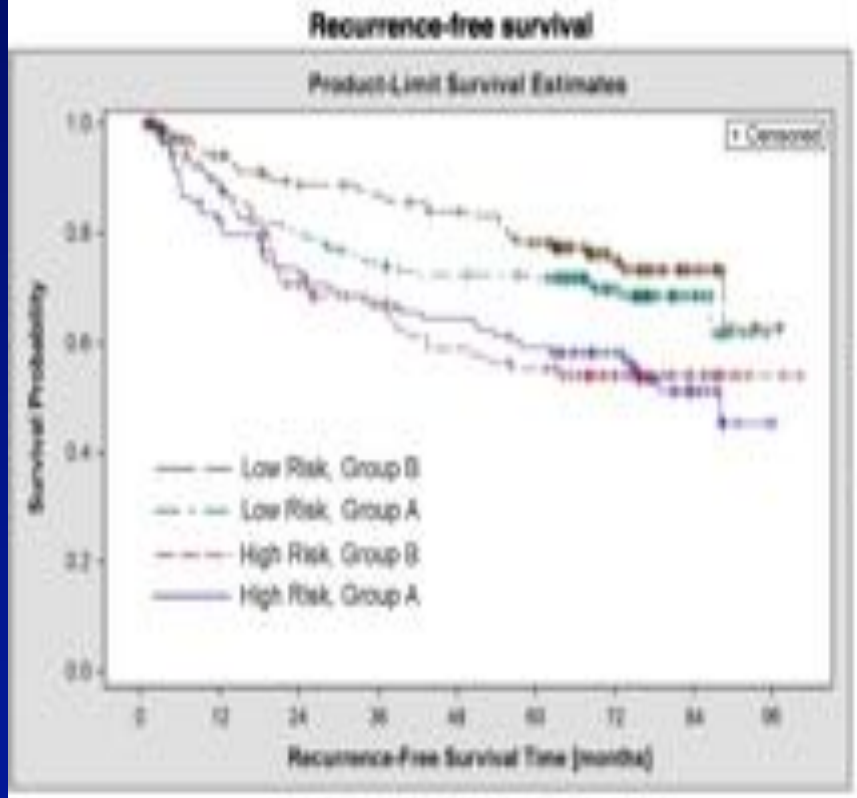


Overall survival over years (ITT population)

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

SILVER TRIAL



Recurrence-free survival over years (ITT population) - low risk

Time point after LTx	Group A (N=146)	Group B (N=146)	P-value (log-rank test)
1 year	128 (87.7%)	138 (94.5%)	0.0566
2 years	117 (80.1%)	131 (89.7%)	0.0383
3 years	109 (74.7%)	128 (87.7%)	0.0106
4 years	107 (73.3%)	124 (84.9%)	0.0280
5 years	106 (72.6%)	118 (80.8%)	0.1393
6 years	103 (70.5%)	114 (78.1%)	0.2103
7 years	102 (69.9%)	114 (78.1%)	0.1668
8 years	102 (69.9%)	113 (77.4%)	0.2047

Recurrence-free survival over years (ITT population) - high risk

Time point after LTx	Group A (N=110)	Group B (N=106)	P-value (log-rank test)
1 year	90 (81.8%)	95 (89.6%)	0.0970
2 years	81 (73.6%)	78 (73.6%)	0.9017
3 years	76 (69.1%)	75 (70.8%)	0.7606
4 years	74 (67.3%)	68 (64.2%)	0.6918
5 years	69 (62.7%)	65 (61.3%)	0.7939
6 years	67 (60.9%)	64 (60.4%)	0.8495
7 years	64 (58.2%)	64 (60.4%)	0.9257
8 years	63 (57.3%)	64 (60.4%)	0.8527

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 to be an important advance, especially w/ 2nd generation mTOR inhibitors that more widely block downstream targets

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

POST-LT IMS

- RCT currently in progress comparing everolimus plus tacrolimus vs mycophenolate mofetil plus tacrolimus for LT/HCC pts (clinicaltrials.gov: NCT02081755)
    - AFP, microvascular invasion, and explant tumor burden included w/ randomization
    - May shed light on the effects of mTORi in those truly at high risk for HCC recurrence

- 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

THANKS!

- neil.mehta@ucsf.edu