HCC and Surgical Rx Options

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Overview

- HCC diagnosis/staging (LI-RADS + BCLC)
- Resection versus LT for HCC
  - Criteria for surgical management of HCC
  - Comparison of surgical outcomes
  - Salvage transplant

Case Presentation

55-year-old man with alcohol-associated cirrhosis, found on screening ultrasound to have a 3 cm lesion in the right lobe. Quad-phase CT of the abdomen confirmed the presence of a 3.5 cm lesion in the right lobe along with mild ascites. Examination showed no spider nevi. Spleen tip palpable.

Laboratory evaluation showed bilirubin 1.7, ALT 28, AST 42, albumin 3.5, INR 1.3, platelets 85,000, AFP 36.

Questions:

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

HCC – Is Biopsy Necessary?

Biopsy is not necessary to confirm HCC diagnosis if the lesion meets radiologic criteria in the appropriate clinical setting (e.g. LI-RADS 5)

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

Tumor seeding along the biopsy tract rare (<1%)

Biopsy in selected cases if atypical radiologic appearance (e.g. LI-RADS M) or lack of strong risk factor for HCC

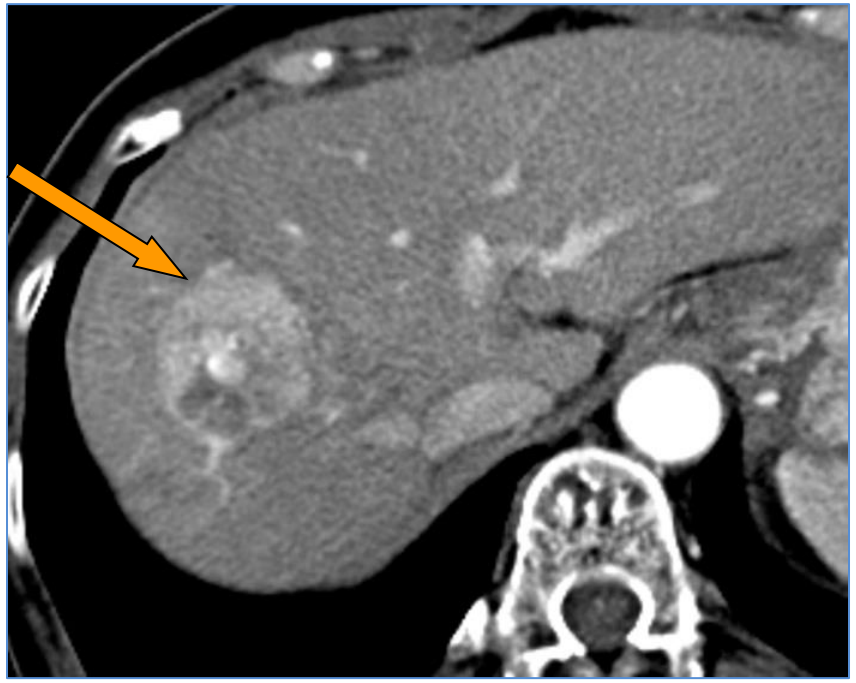
Liver Imaging Reporting And Data System (LI-RAD) Major Diagnostic Criteria

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

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

HCC – Radiologic Diagnosis

Arterial Phase



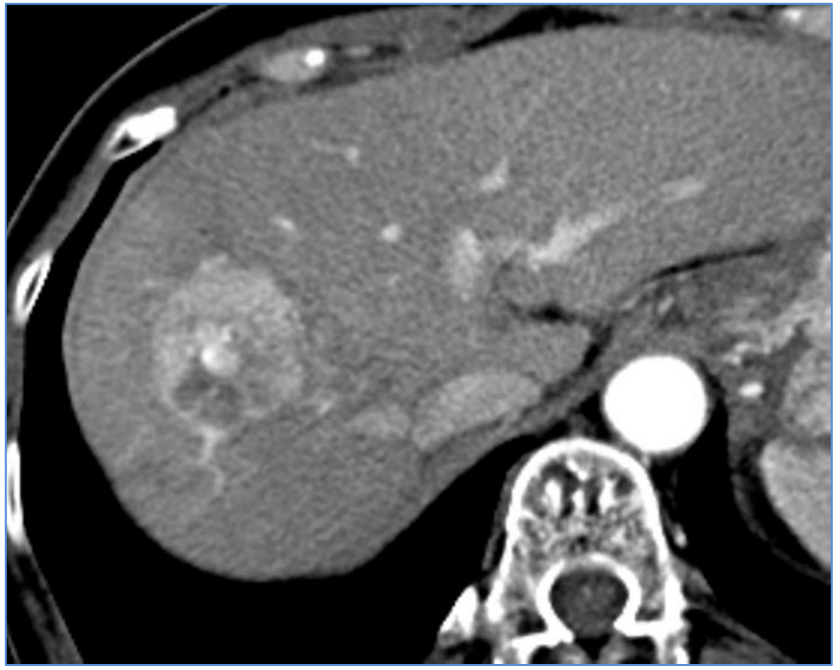
Hyper-enhancement

Portal Venous phase

“washout”

HCC – Radiologic Diagnosis

Arterial Phase



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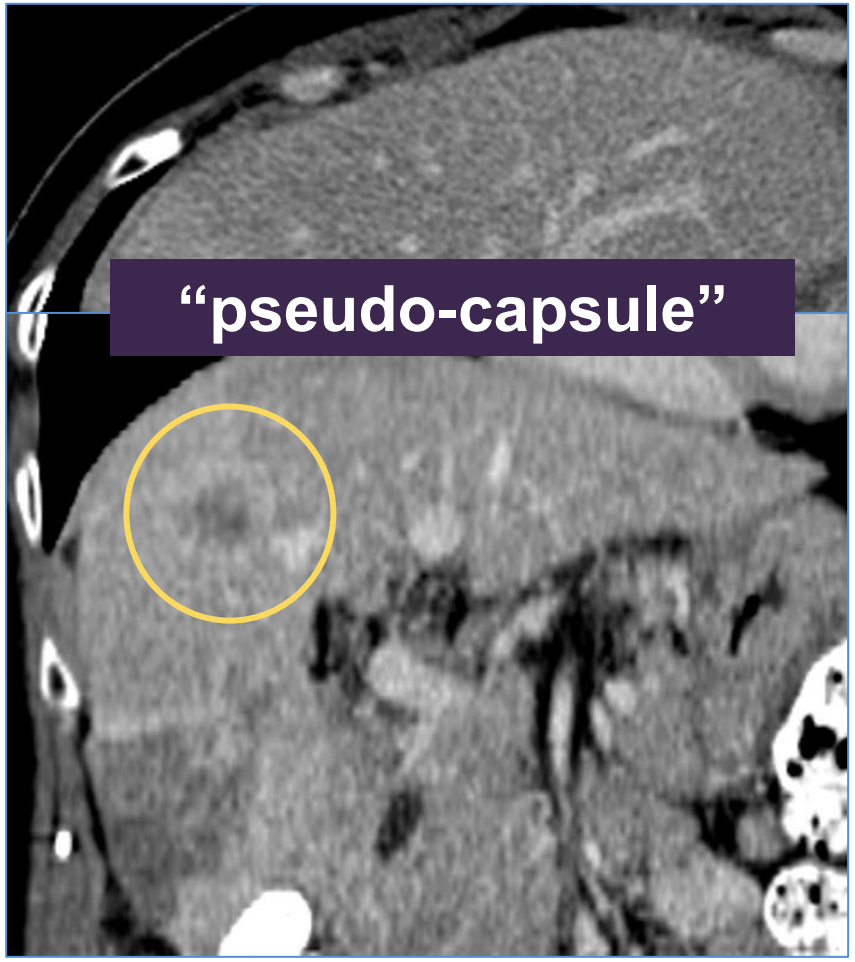


Liver Imaging Reporting and Data System (LI-RADS)

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

Li-RAD 1: Definite benign

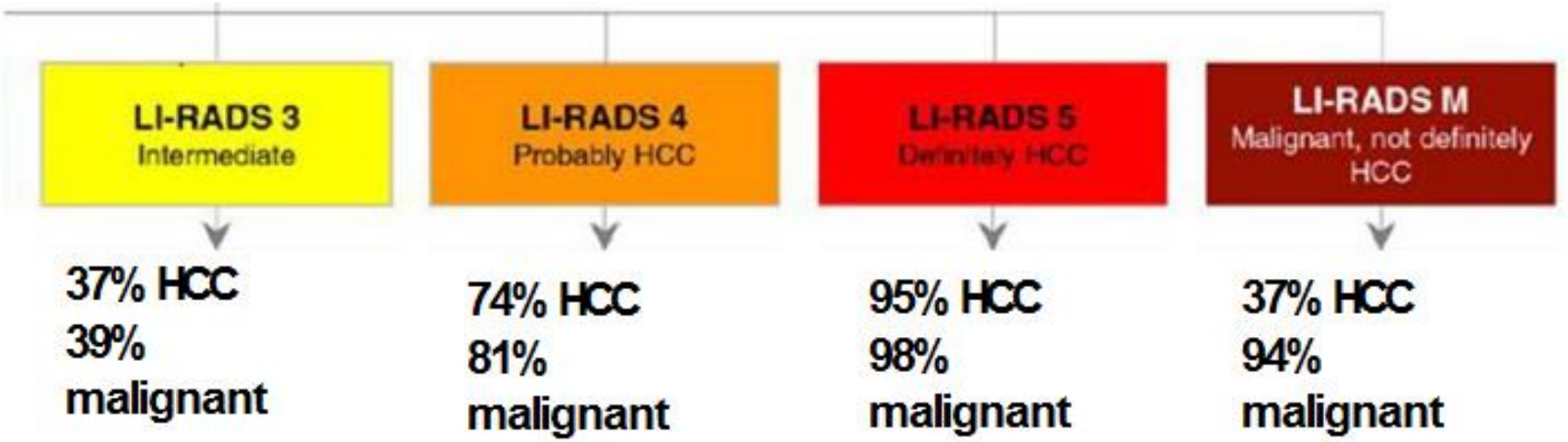
Li-RAD 2: Probable benign

Li-RAD 3: Indeterminate

Li-RAD 4: Probable HCC

Li-RAD 5: Definite HCC

LI-RADS Accuracy



CT/MRI LI-RADS v2018, accessed January 2019.

Liver Imaging Reporting and Data System (LI-RADS)

LIVER MASS

Diagnostic Criteria		Arterial phase hypo- or Iso-enhancement		Nonrim arterial phase hyper-enhancement		
		< 2 cm	≥ 2 cm	< 1 cm	1-1.9 cm	≥ 2 cm
"Washout" "Capsule" Threshold growth	None	LIRAD 3	LIRAD3	LIRAD3	LIRAD 3	LIRAD4
	One	LIRAD 3	LIRAD4	LIRAD4	LR - 4/5	LIRAD 5
	≥ Two	LIRAD 4	LIRAD4	LIRAD4	LIRAD 5	LIRAD 5

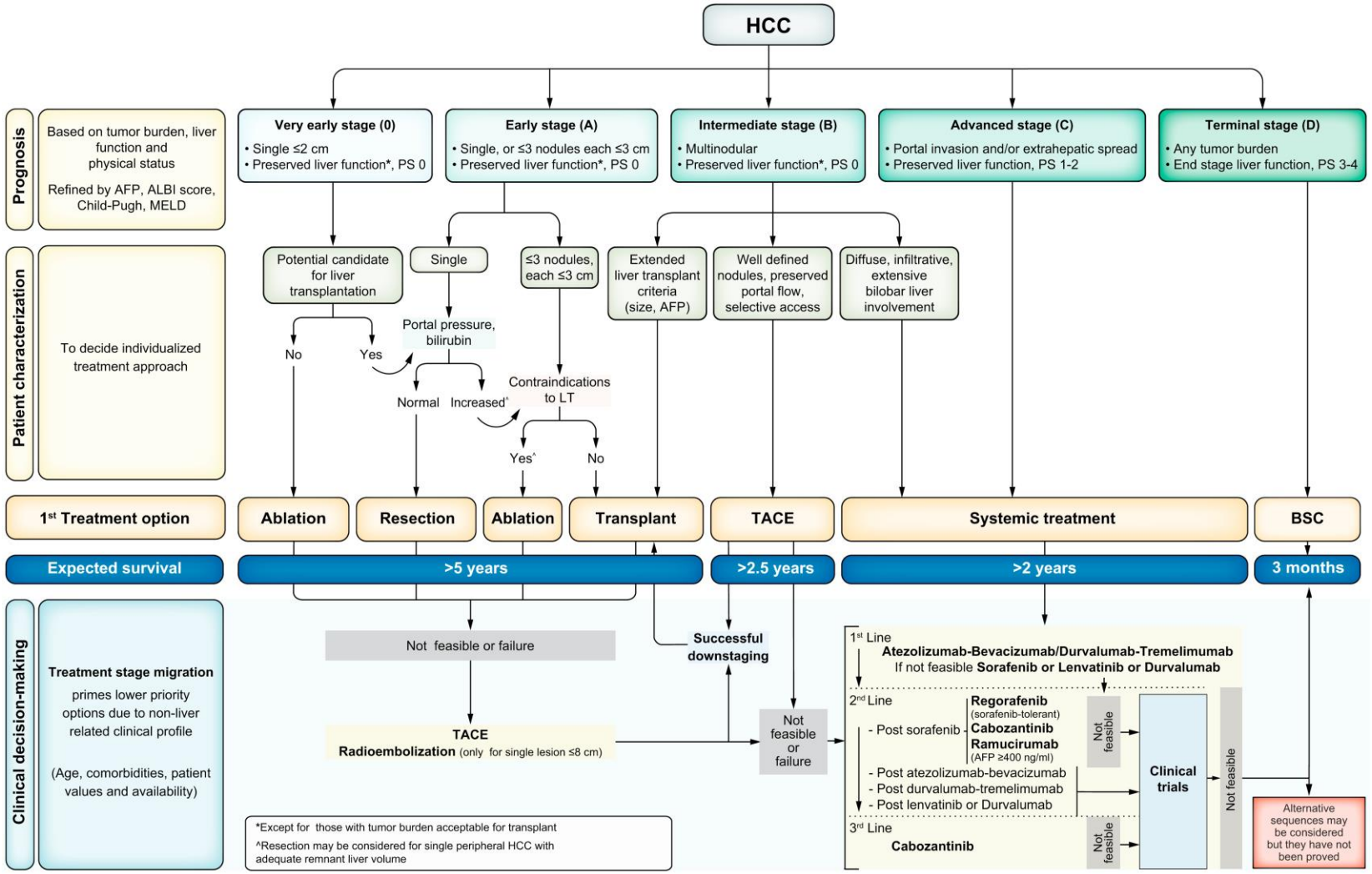
UNOS imaging criteria for HCC in determining MELD exception listing: LI-RADS 5 only

1-1.9 cm lesion with enhancing capsule: LIRADS-4

1-1.9 cm lesion with washout or threshold growth: LIRADS-5

•Example: 2 lesions 1.5 cm both LR-5 IS eligible for MELD exception

Hepatocellular Carcinoma
BCLC Staging Classification



Reig M et al. *Journal of Hepatology*. 2022.

Case Presentation

55-year-old man with chronic hepatitis C and biopsy proven cirrhosis, found on screening ultrasound to have a 3 cm lesion in the right lobe. Quad-phase CT of the abdomen showed a 3.5 cm arterial enhancing lesion in segment 6 with washout. No symptoms other than mild fatigue. No history of substance abuse. Examination showed no spider nevi. Spleen tip palpable. Dx: LI-RADS 5 per Tumor Board review.

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

What treatment would you recommend?

1. Anatomic resection
2. Wedge resection
3. Liver transplantation
4. Percutaneous microwave ablation (MWA)

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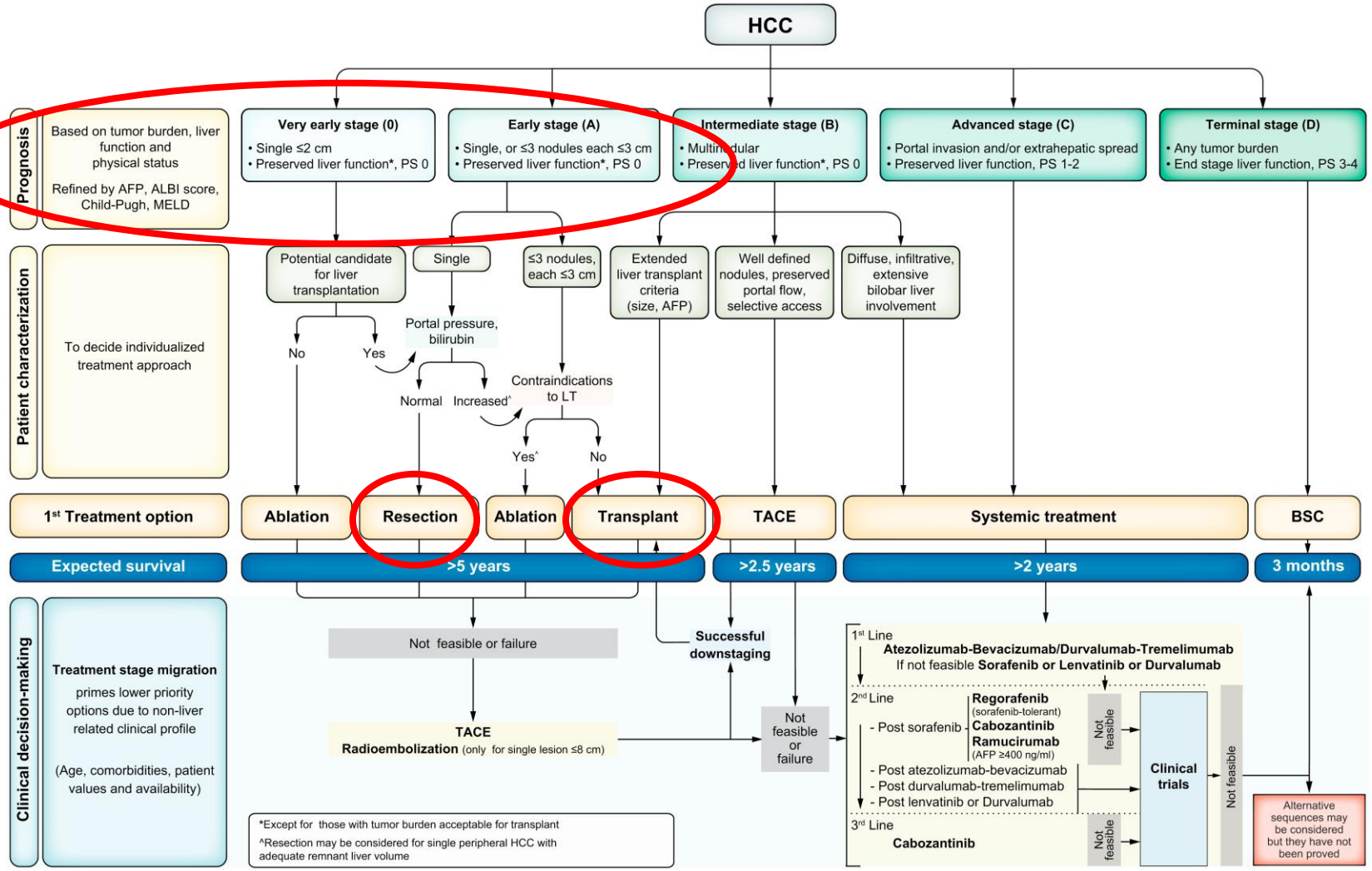

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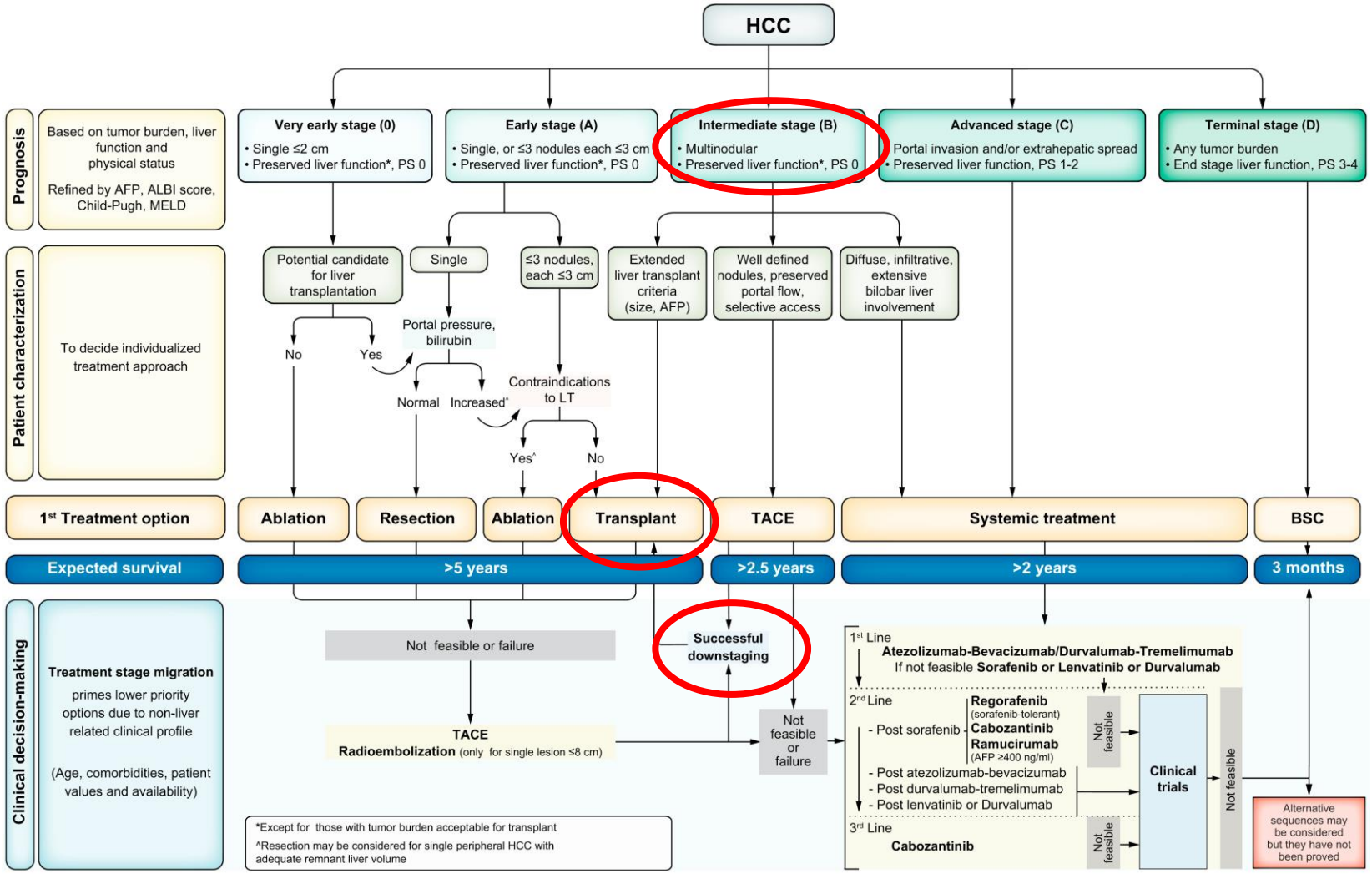
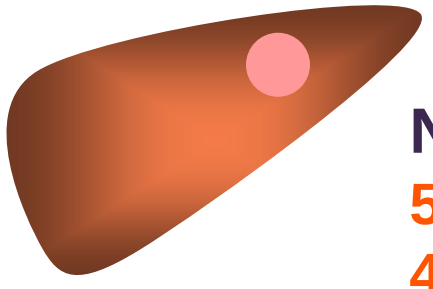
Hepatocellular Carcinoma
BCLC Staging Classification



Reig M et al. *Journal of Hepatology*. 2022.

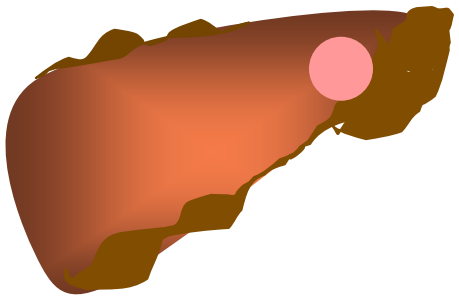
Surgical Treatment for HCC
Cirrhosis and Liver Function



NON-CIRRHOTIC → **RESECTION**

5% in Western countries

40% in Asia



CIRRHOTIC

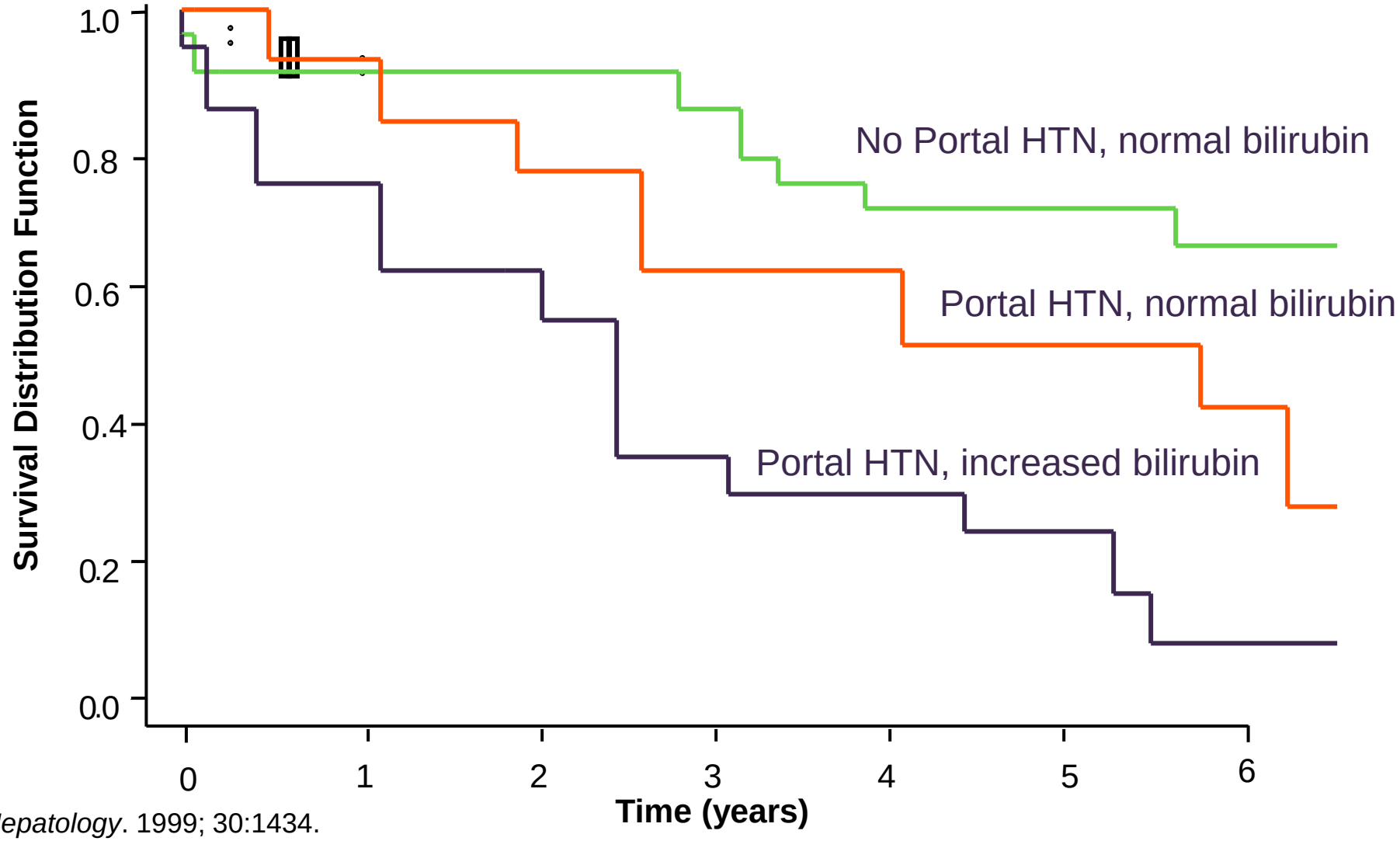
Child's A

Child's B

Child's C

→ **TRANSPLANT**

Survival Following Resection: Impact of Portal Hypertension



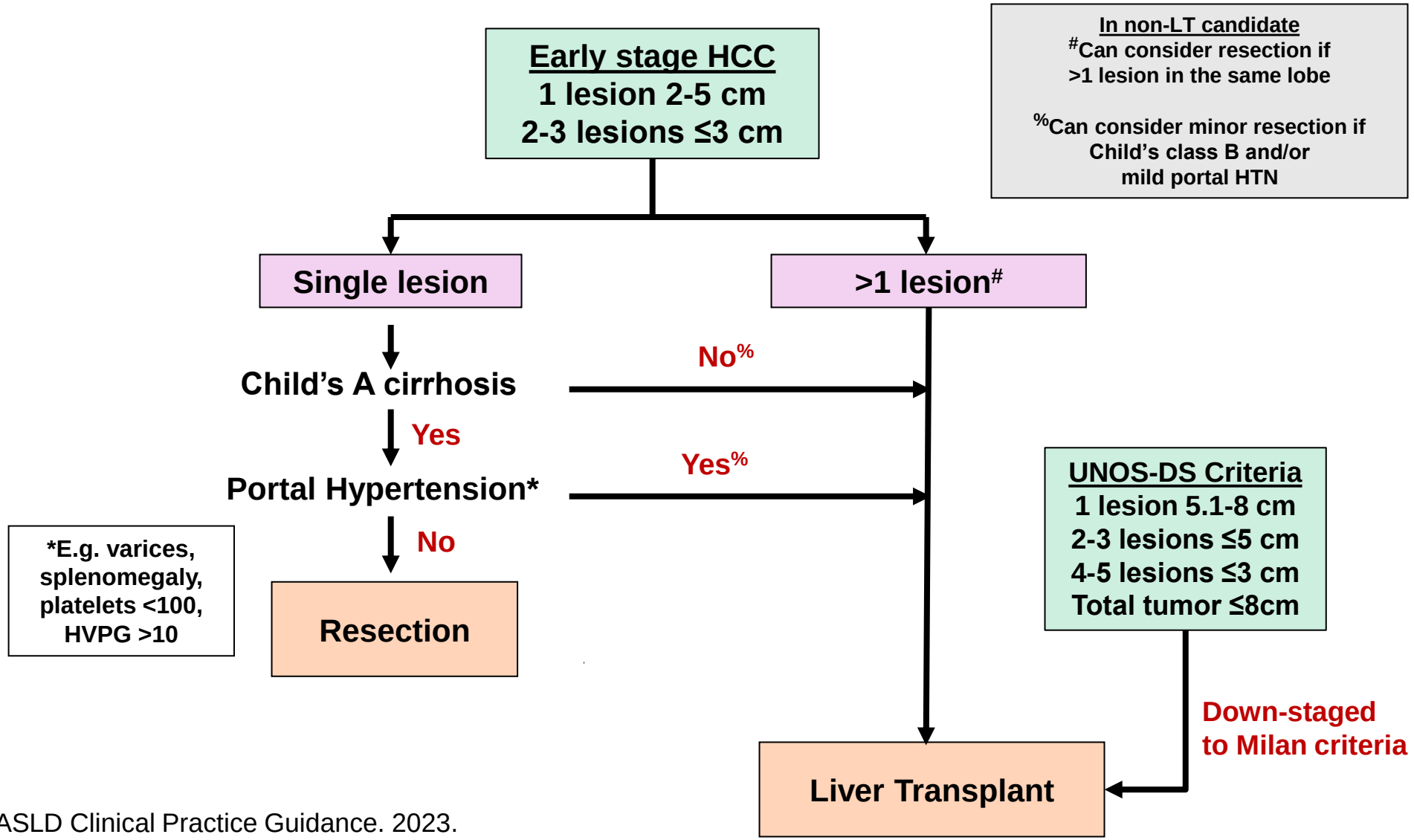
Llovet et al. *Hepatology*. 1999; 30:1434.

Hepatic Resection for HCC With Cirrhosis

“Ideal” candidate

- Good liver function - Child’s A
- No portal hypertension (suggested by varices, enlarged spleen, platelets <100)
- Normal bilirubin
- Single lesion ≤5 cm
- Location of tumor in left lobe (i.e. laparoscopic approach; minor hepatectomy)

Algorithm for Surgical Treatment of Early-Stage HCC



Modified for AASLD Clinical Practice Guidance. 2023.

Tumor Recurrence Post-Resection

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

Cha et al. *JACS*. 2003.

Tumor Recurrence Post-Resection

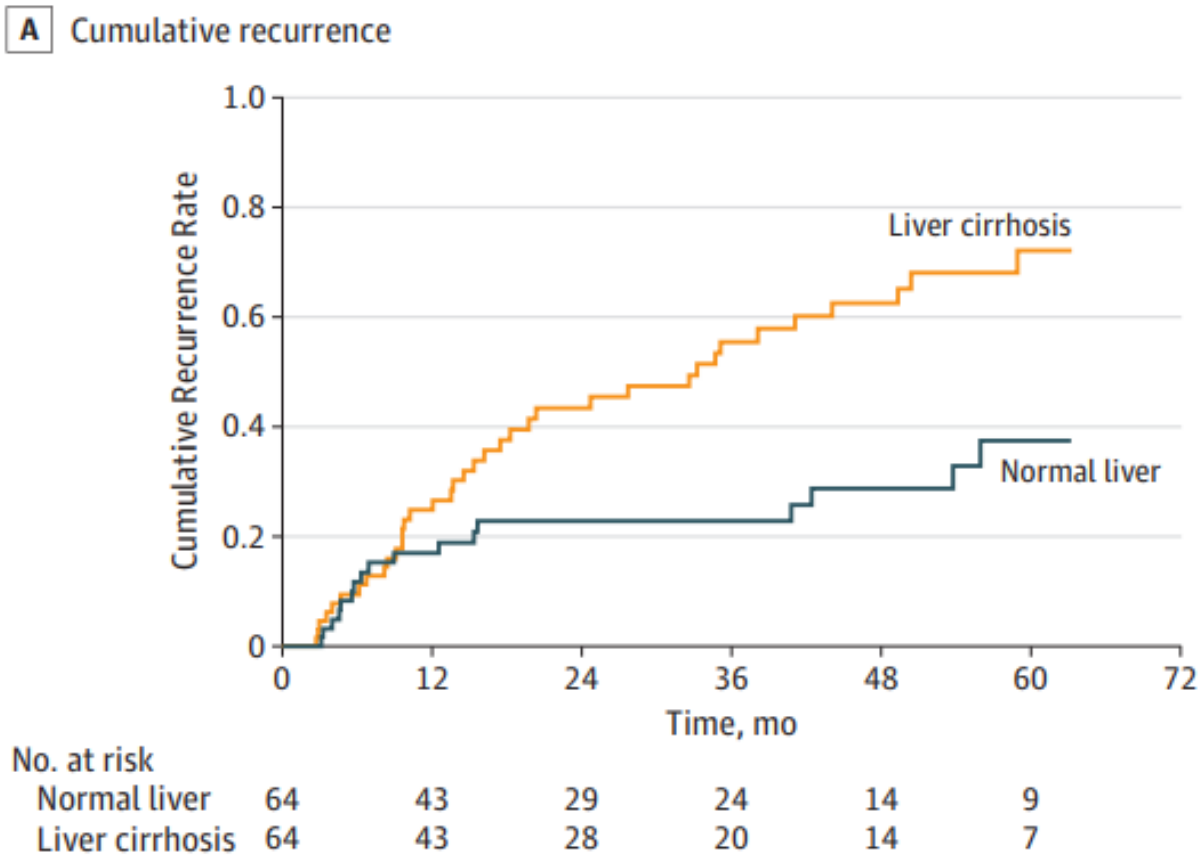
Approx 40-50% at 3 yrs and 60-70% at 5 yrs

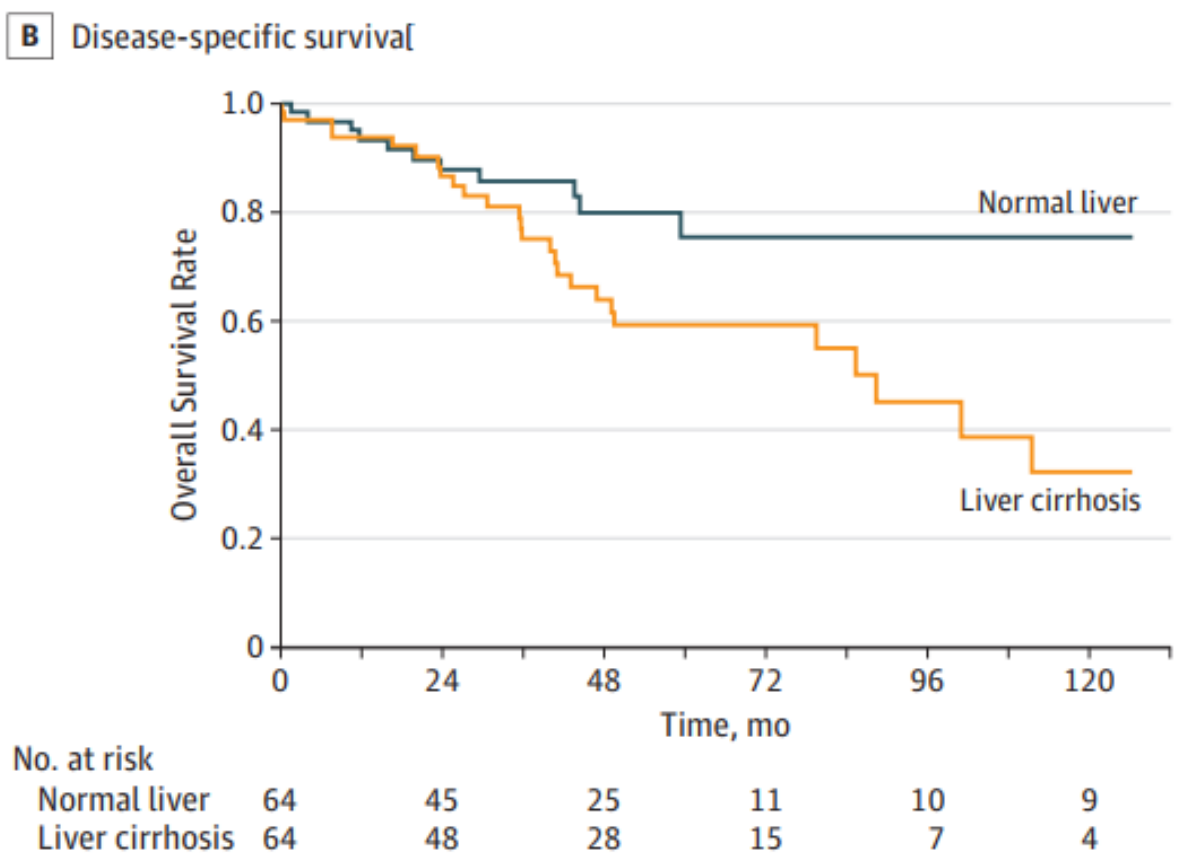
Predictors of tumor recurrence

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

Cha et al. *JACS*. 2003.

Resection Outcome Cirrhosis Vs. “Normal” Liver





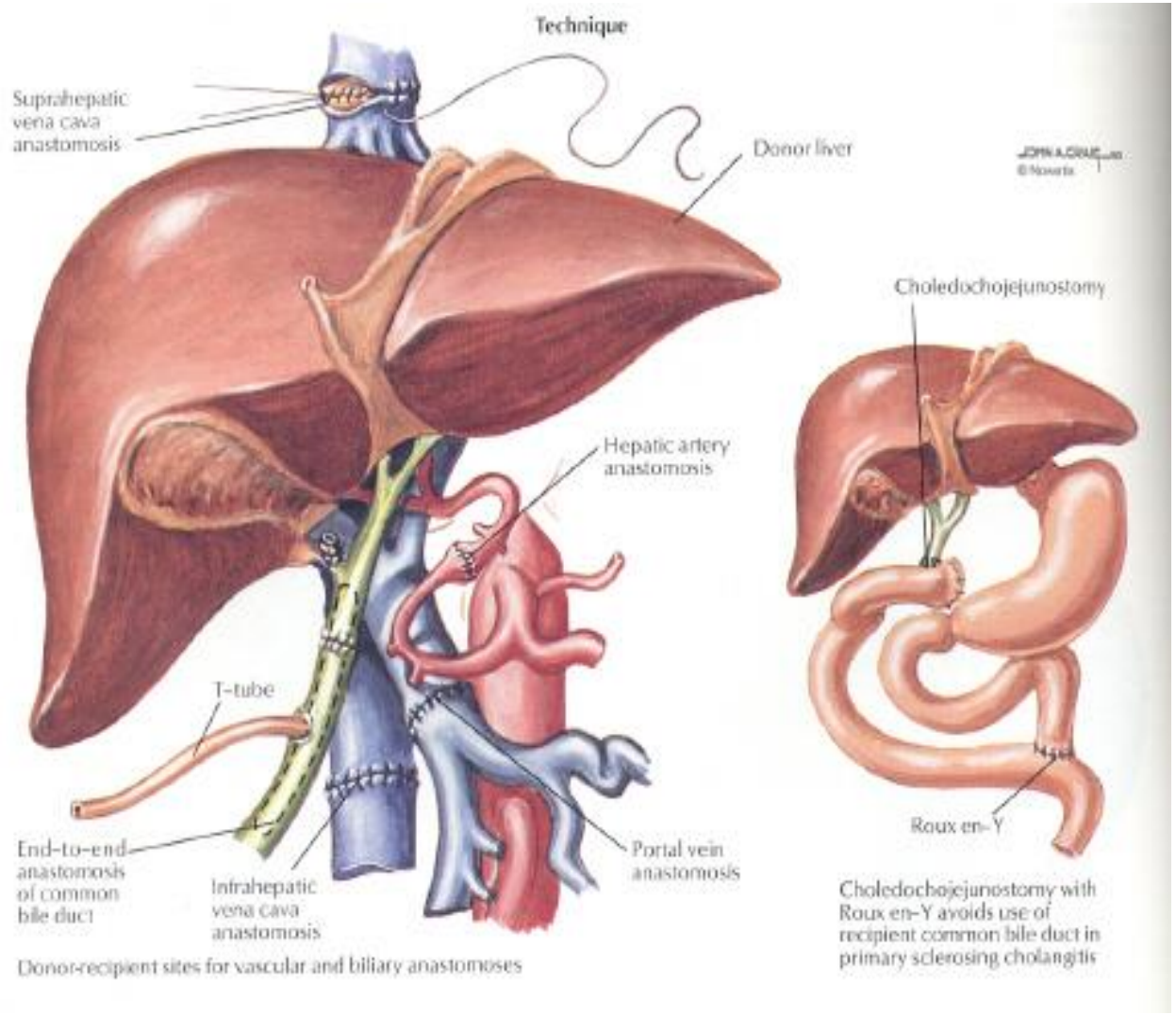
Sasaki K et al. *JAMA Surgery*. 2018.

Advantages of Liver TX

Best oncologic resection

Replaces diseased liver

Restores normal hepatic function

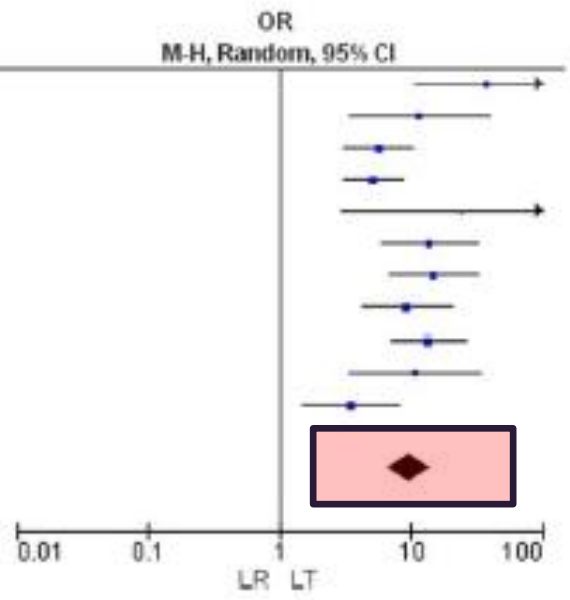


Intention-to-Treat Analyses
Meta-Analyses - Recurrence

Resection | Transplantation

Study or Subgroup	LR Events	LR Total	LT Events	LT Total	Weight	OR M-H, Random, 95% CI	Year
Llovet et al.[6] (1999)	44	77	3	87	6.3%	37.33 (10.84-128.61)	1999
Margarit[38] (2005)	22	37	4	36	6.3%	11.73 (3.43-40.11)	2005
Shah et al.[12] (2007)	53	121	17	140	12.4%	5.64 (3.03-10.50)	2007
Baccarani et al.[13] (2008)	123	245	22	134	13.7%	5.13 (3.05-8.64)	2008
Bellavance et al.[23] (2008)	13	38	1	48	2.8%	24.44 (3.02-197.80)	2008
Koniaris et al.[14] (2011)	21	31	31	234	9.7%	13.75 (5.92-31.94)	2011
Adam et al.[15] (2012)	60	97	10	101	10.5%	14.76 (6.83-31.90)	2012
Sogawa et al.[16] (2012)	40	56	16	75	10.2%	9.22 (4.14-20.53)	2012
Sapisochin et al.[17] (2013)	68	95	19	122	11.8%	13.65 (7.04-26.47)	2013
Jiang et al.[18] (2014)	23	33	6	34	6.9%	10.73 (3.39-33.99)	2014
Li[39] (2014)	105	243	7	39	9.5%	3.48 (1.48-8.19)	2014
Total (95% CI)		**1073**		**1050**	**100.0%**	**9.61** (6.57-14.06)	
Total events	572		136				

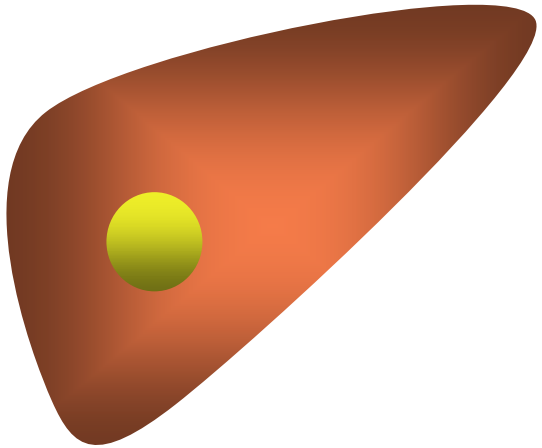
Heterogeneity: Tau² = 0.20; chi-square = 21.57, df = 10 (P = 0.02); I² = 54%
Test for overall effect: Z = 11.65 (P < 0.00001)



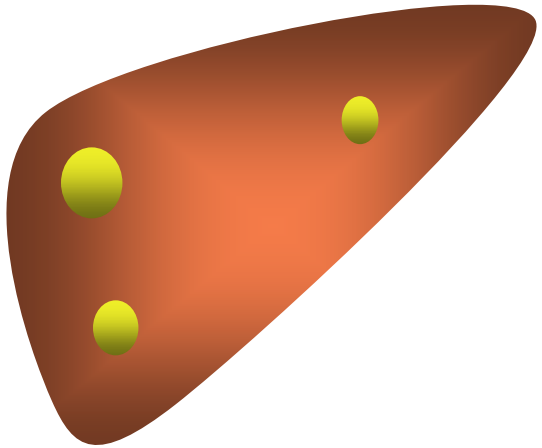
Menahem et al. *Liver Transplantation*. 2017.

Liver Transplantation for HCC Milan Criteria

1 lesion ≤ 5 cm



2 to 3, none > 3 cm



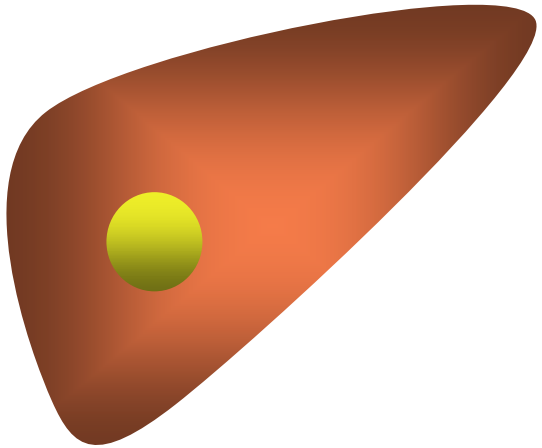
+

Absence of Macroscopic Vascular Invasion
Absence of Extra-hepatic Spread

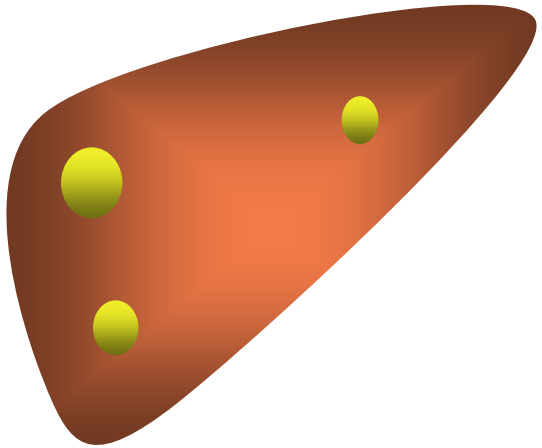
Mazzaferro et al. *N Engl J Med*. 1996;334:693-699.

Liver Transplantation for HCC Stage T2 Criteria

1 lesion ≤ 5 cm



2 to 3, none > 3 cm



<u>Post-LT</u>

5 year survival: ~80%

5 year HCC recurrence: 10-15%

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

Post-LT HCC Recurrence

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

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

Liver Transplant for HCC: Recent Changes

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

Liver Transplant for HCC: Recent Changes

- 6-month mandatory waiting period before awarding MELD exception

Delayed HCC-MELD Exception Score

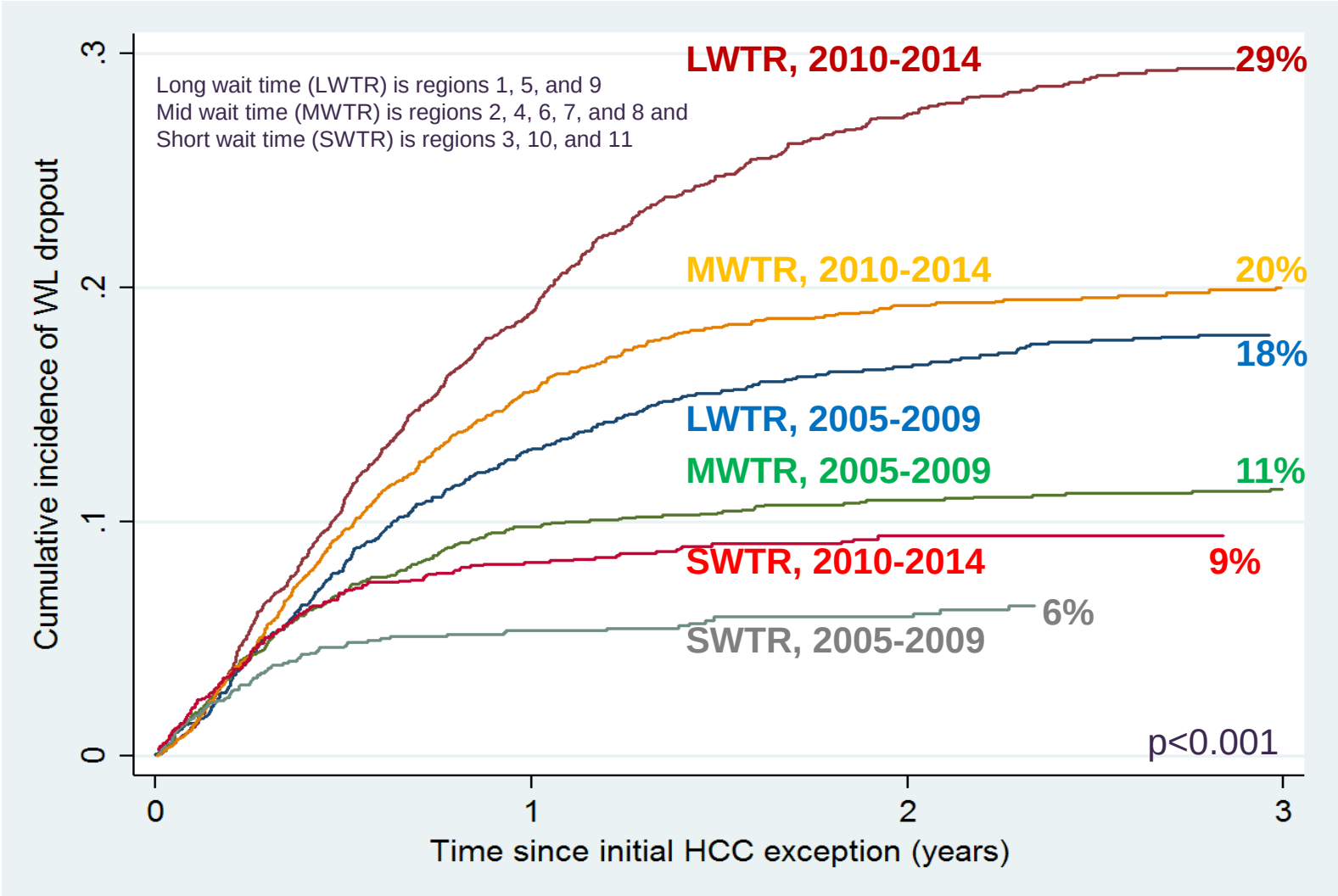
Delays in HCC-MELD exception	HCC Transplant rates (per 100 person-years)	Non-HCC Transplant rates (per 100 person-years)
0	108.7	30.1
3 months	65.0	32.5
6 months	44.2	33.9
9 months	33.6	34.8

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

Liver Transplant for HCC: Recent Changes

- 6-month mandatory waiting period before awarding MELD exception
- Regional variation in access to LT for HCC still exists

Probability of Waitlist Dropout by Wait Time Region and Listing Period

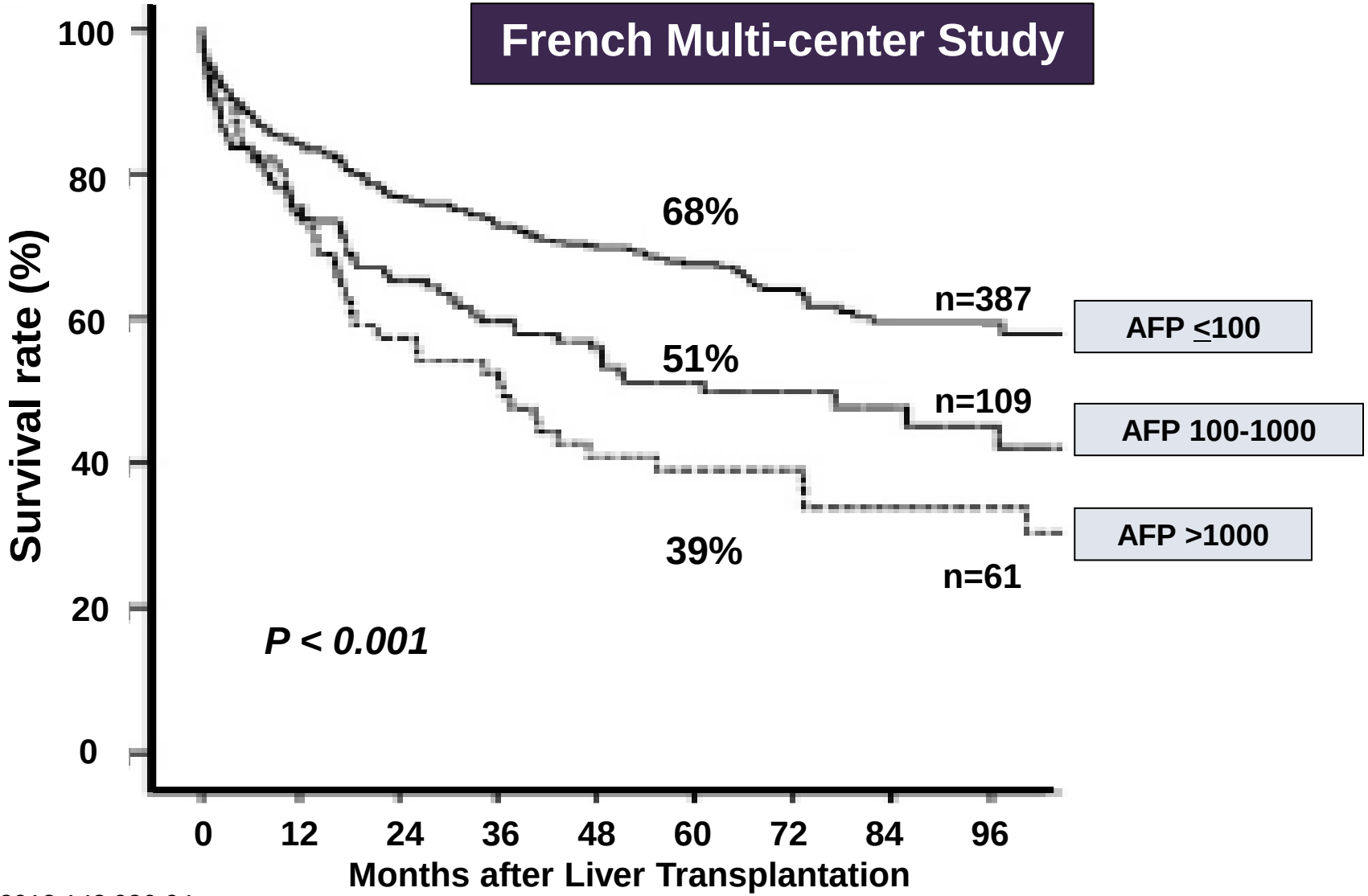


Mehta N et al. *Liver Transplantation*. 2018.

Liver Transplant for HCC: Recent Changes

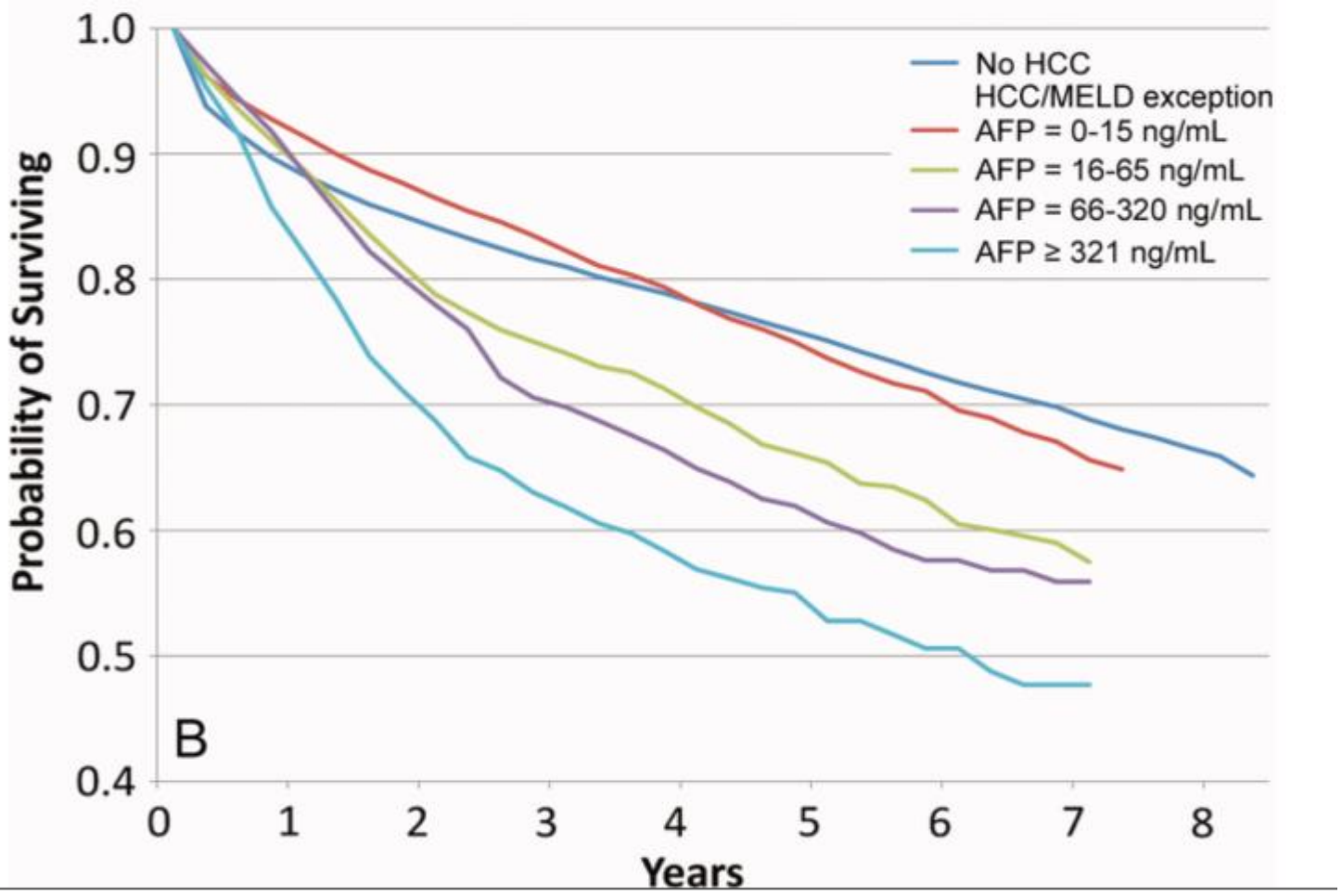
- HCC MELD ladder system has been replaced by awarding median MELD at transplant minus 3 points (MMAT-3) for the donor hospital
  - 6 month waiting period still in effect

AFP and Post-transplant Outcome – France



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

AFP and Post-LT HCC Survival



Berry et al. *Liver Transplantation*. 2013; 634-45.

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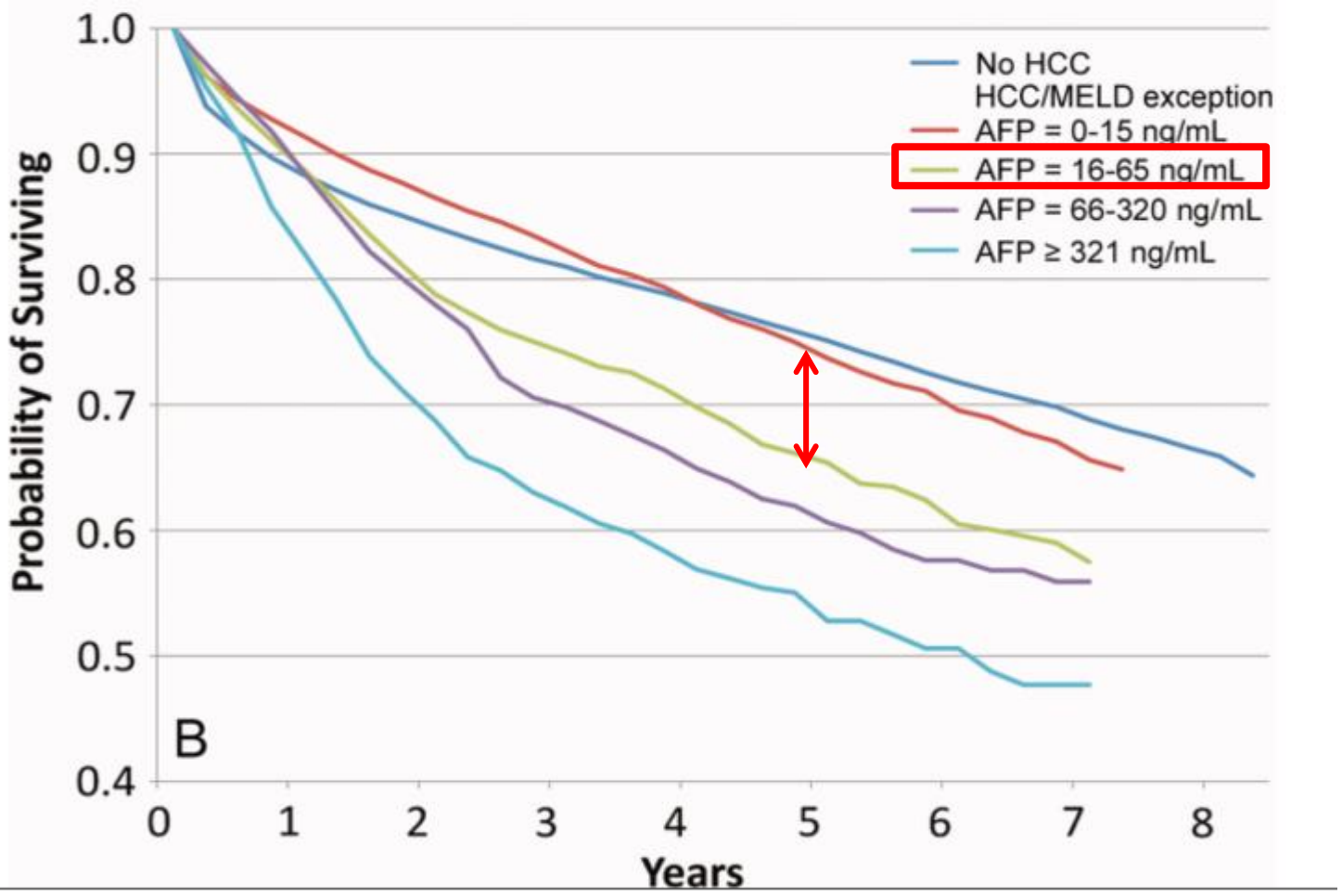
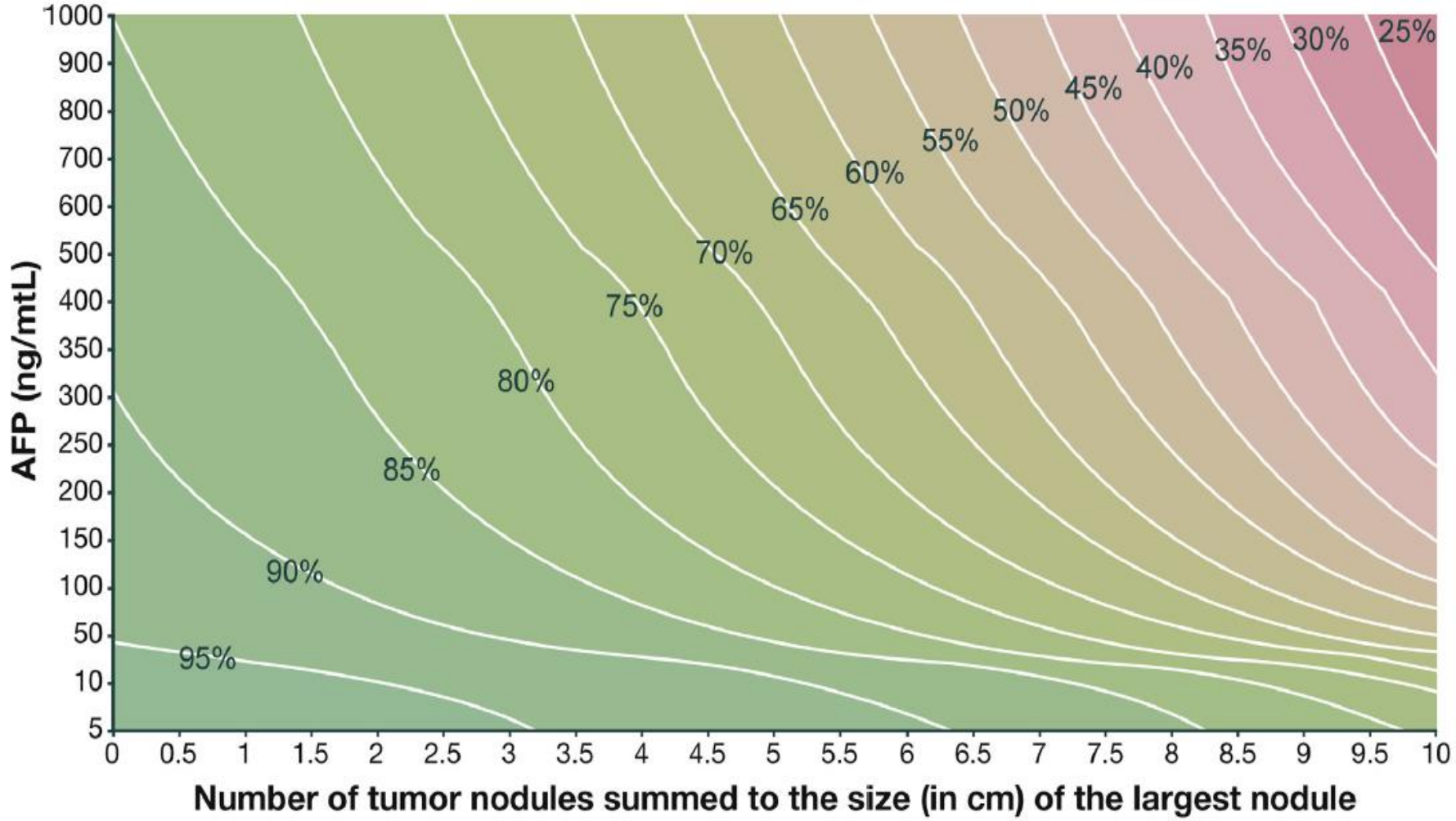


Berry et al. *Liver Transplantation*. 2013; 634-45.

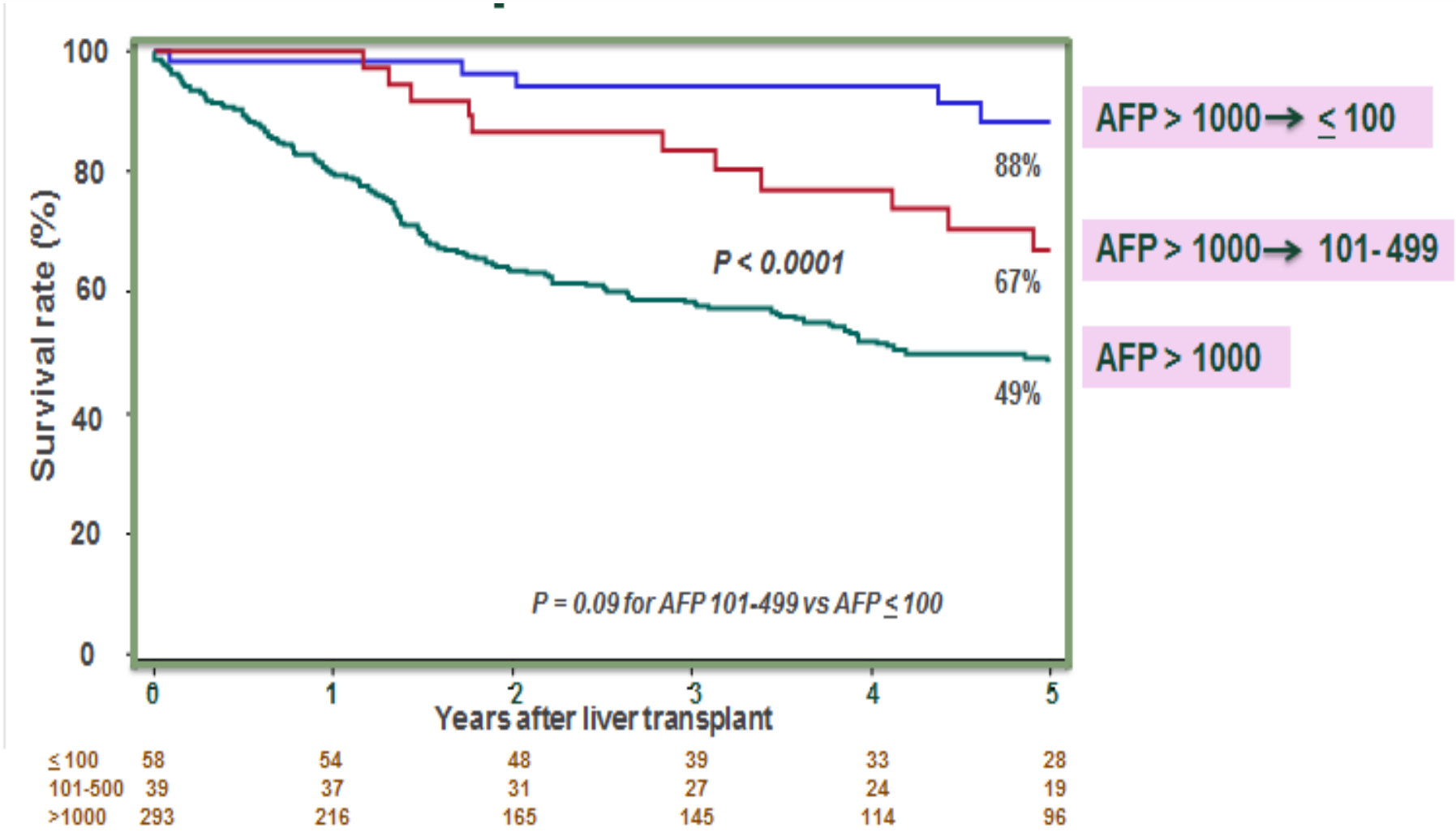
LT for HCC: Metroticket 2.0

HCC Specific Survival



Mazzaferro V et al. *Gastroenterology*. 2017.

Reducing High AFP Prior To LT



AFP > 1000 → ≤ 100

AFP > 1000 → 101-499

AFP > 1000

Mehta N. *Hepatology*. 2019.

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

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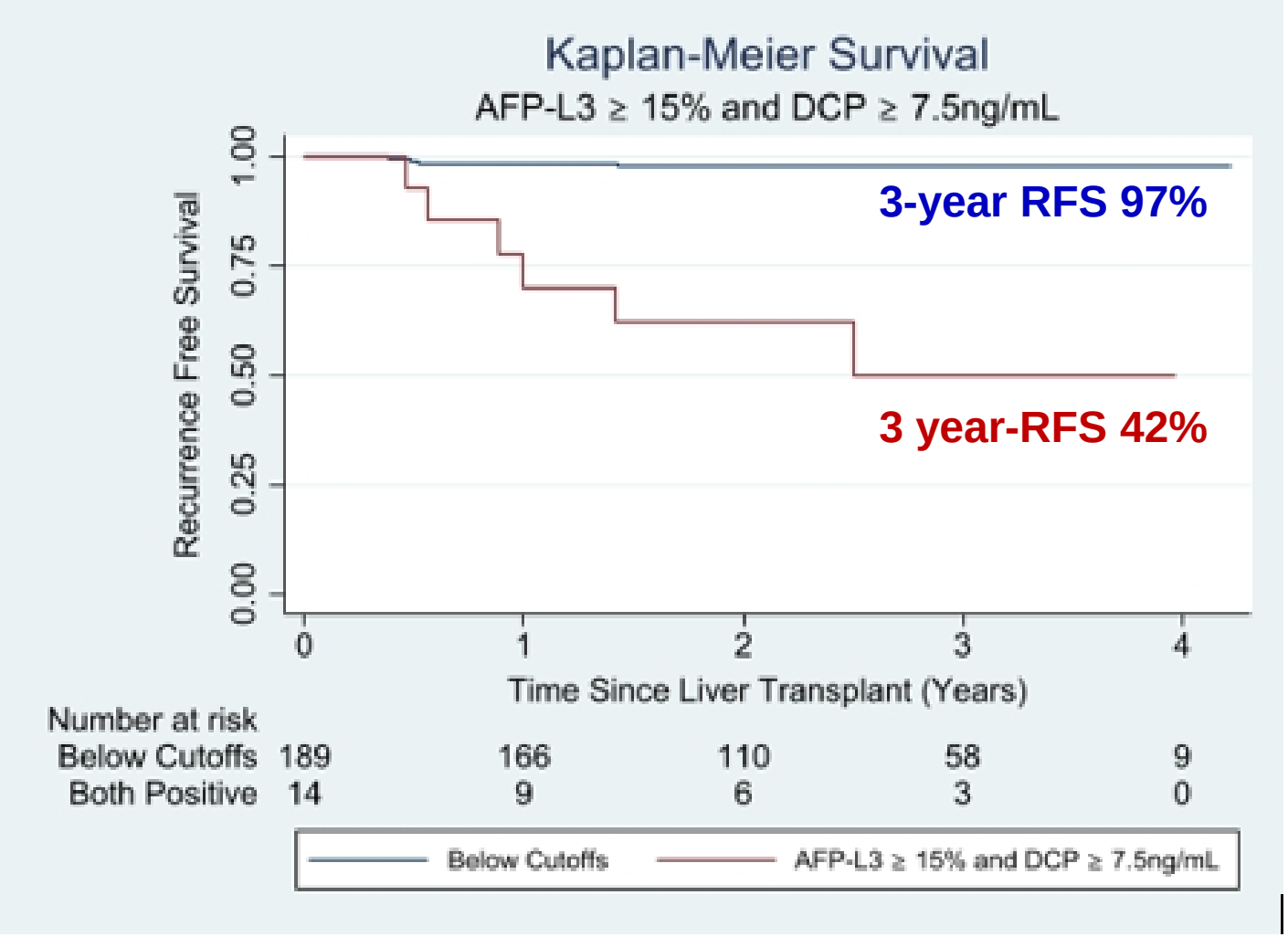
However, AFP reduction to <100 after LRT is ideal

DCP + AFP + AFP-L3 (Mayo Clinic)

Factors predicting HCC Recurrence	HR (p-value)	C statistic
Milan		0.63
Among tumors within Milan		
AFP ≥ 250	3.2 (p=0.01)	0.68
DCP ≥7.5	4.3 (p<0.001)	0.7
AFP-L3% ≥ 35	4.5 (p<0.001)	0.7
Absolute AFP-L3 ≥ 56	4.1 (p=0.001)	0.68

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

Dual Positivity for AFP-L3 >15% and DCP >7.5 Predicts Worse Post-lt Survival



Norman J, Mehta N. *AASLD Liver Meeting*. 2022.

Hepatocellular Carcinoma

Case Presentation

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

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

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3. Atezolizumab/Bevacizumab
4. Liver transplant after down-staging to within Milan criteria

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What treatment would you recommend?

1. Resection
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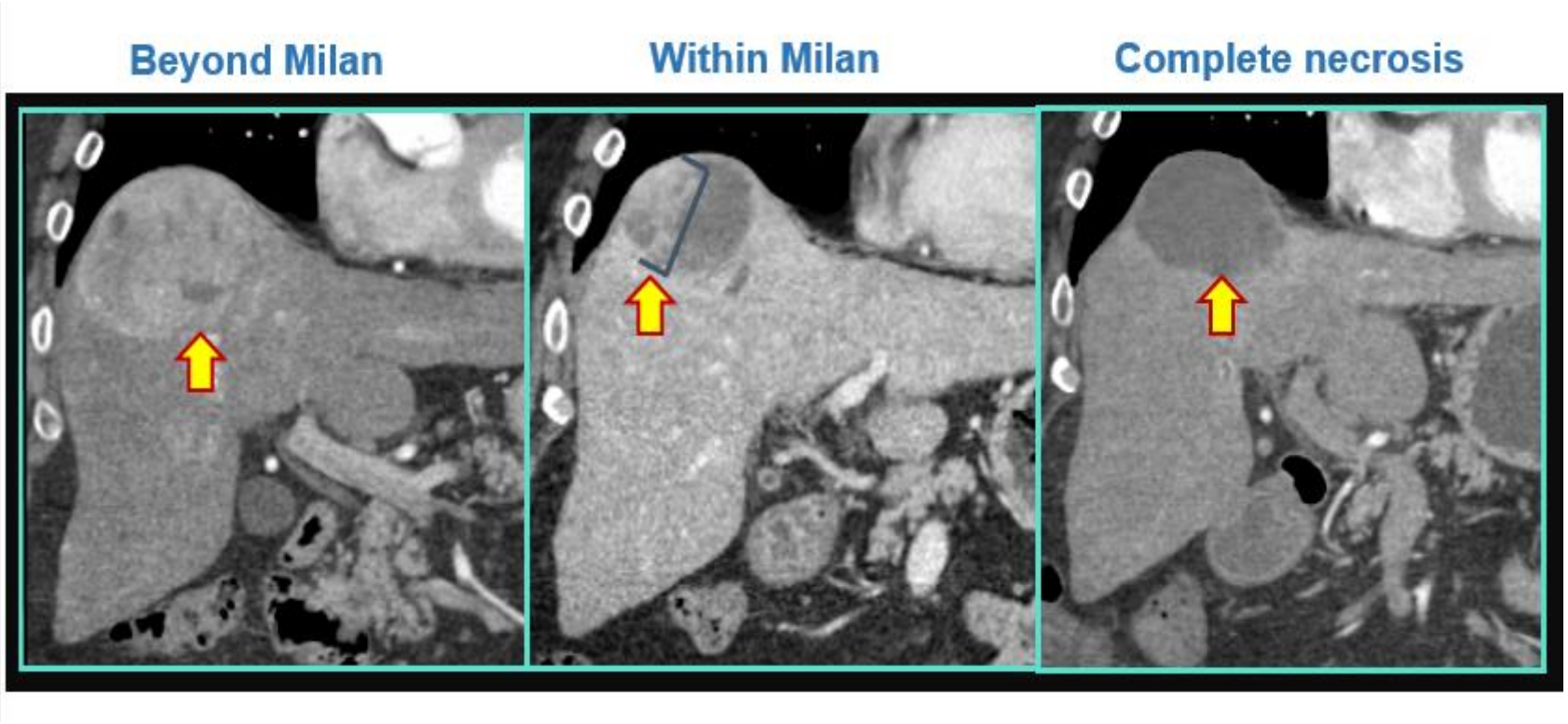
3. Atezolizumab/Bevacizumab
4. **Liver transplant after down-staging to within Milan criteria**

Down-Staging of HCC for Transplant

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

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

Down-Staging of HCC for Transplant



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

Local Regional Therapies for HCC

CHEMOEMBOLIZATION (TACE)

- Conventional versus Drug-eluting beads

ABLATIONS

CHEMICAL

- Percutaneous ethanol injection (PEI)

THERMAL

- Radiofrequency ablation (RFA)
  - (Laparoscopic, percutaneous or open)
- Microwave/ Cryo- ablation

RADIOEMBOLIZATION (YITTRIUM - 90)

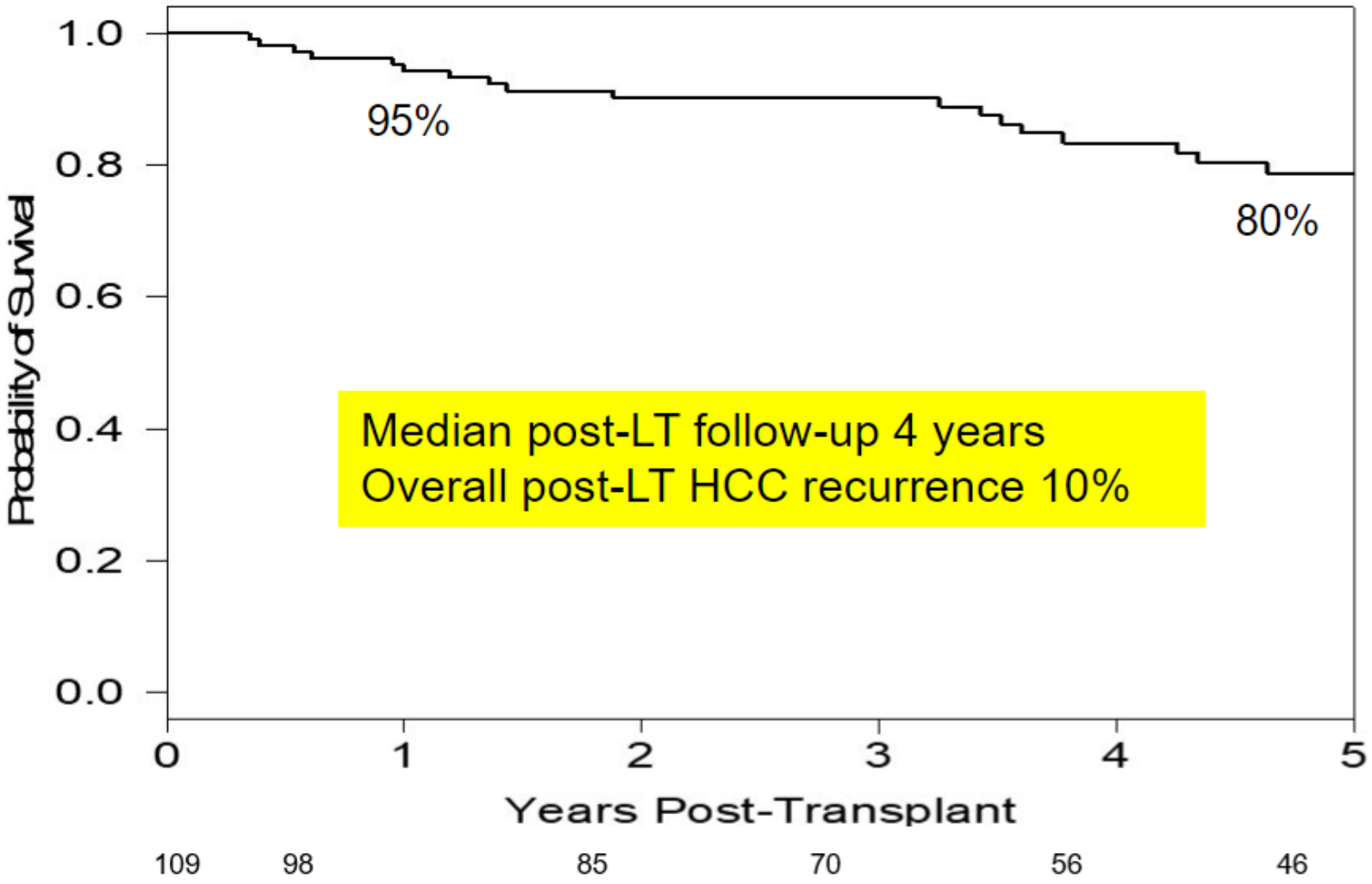
STEREOTACTIC BODY RADIATION (SBRT)

National Down-Staging Protocol (UNOS-DS)

- Inclusion criteria
  - 1 lesion > 5 cm and ≤ 8 cm
  - 2 or 3 lesions ≤ 5 cm w/ total tumor diameter ≤ 8 cm
  - 4 or 5 lesions ≤ 3 cm w/ total tumor diameter ≤ 8 cm
  - No vascular invasion on imaging
- Minimum 3-month observation period after successful down-staging into Milan before LT can be undertaken

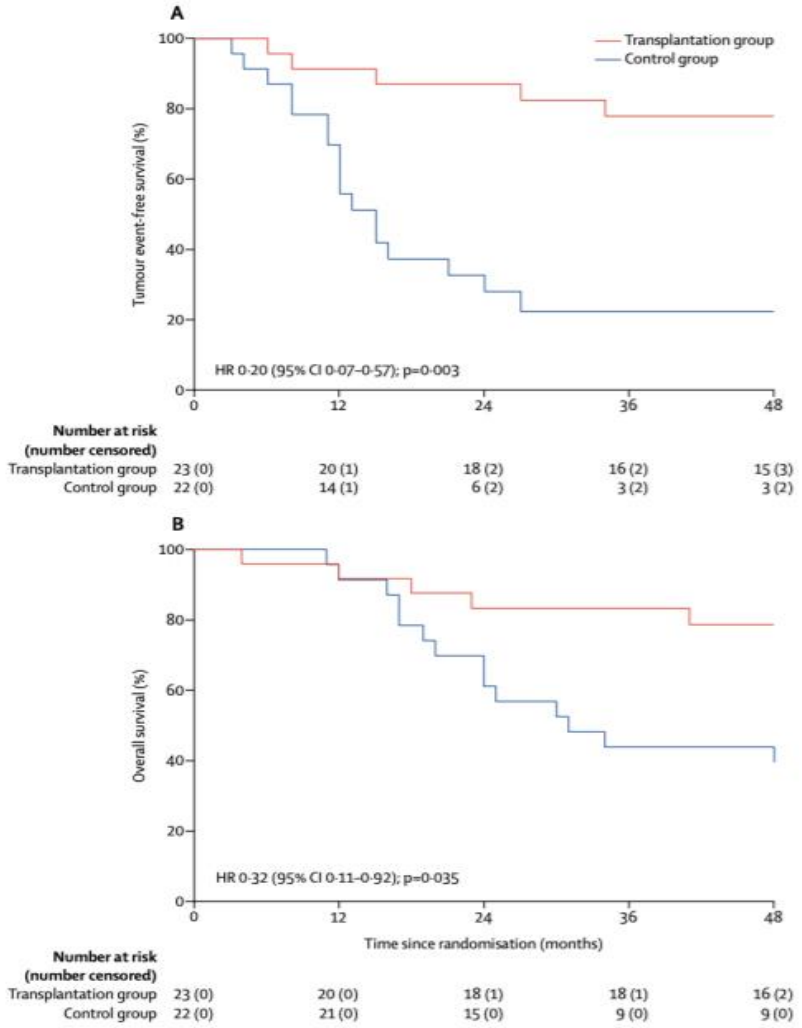
Yao et al. *Hepatology*. 2008;48:819-827.

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



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

Multicenter Down-Staging RCT: Italy



- From 2011-15, pts initially beyond Milan criteria with partial or complete response (mRECIST) randomly assigned to LT or non-transplantation therapies

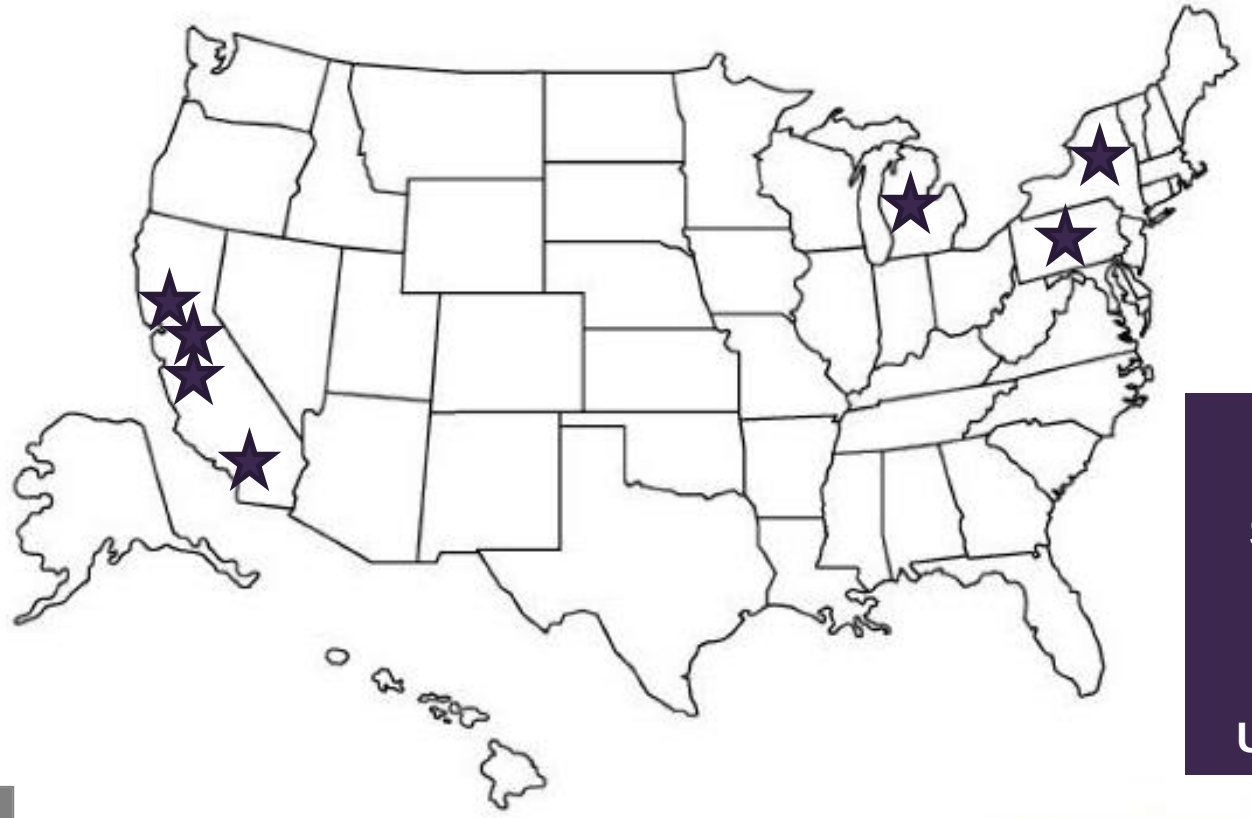
Mazzaferro et al. *Lancet Oncology*. 2020.

UNOS Down-Staging Protocol

- Inclusion criteria
  - 1 lesion > 5 cm and ≤ 8 cm
  - 2 or 3 lesions ≤ 5 cm w/ total tumor diameter ≤ 8 cm
  - 4 or 5 lesions ≤ 3 cm w/ total tumor diameter ≤ 8 cm
  - No vascular invasion on imaging
- This protocol has recently been adopted as national policy for automatic priority listing in patients who have been successfully down-staged to within Milan criteria

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

Multicenter Evaluation of Reduction in Tumor Size before Liver Transplantation (MERITS-LT) Consortium



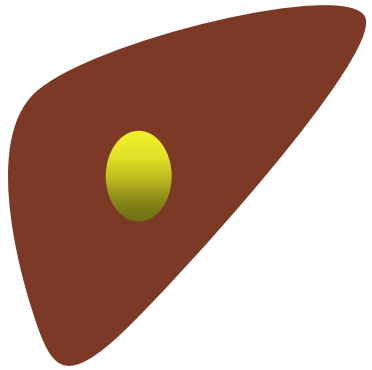
UCSF, CA
CPMC, CA
Scripps Clinic, CA
Stanford, CA
U Michigan, MI
Mt. Sinai, NY
U Pennsylvania, PA

Prospective Down-Staging Multi-Regional Study: MERITS-LT

- Among 209 HCC pts meeting UNOS-DS criteria, 2-yr probability of successful down-staging 88%
- No difference in probability of successful down-staging or liver transplant between TACE (n=132) and Y-90 (n=62)
- Tumor under-staging (explant > Milan) in 43%, and sum of the number of viable tumors + largest tumor diameter on last imaging only significant predictor of under-staging

Mehta N et al on behalf of MERITS-LT Consortium. *Gastroenterology*. 2021.

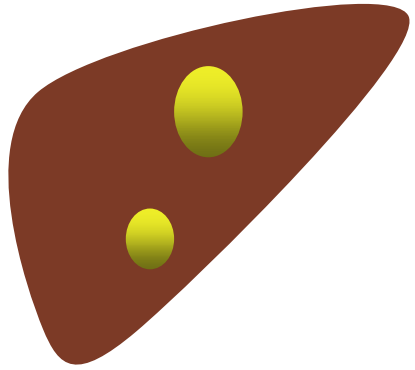
UNOS HCC COHORTS (N=3819)



MILAN

N=3,276 (86%)

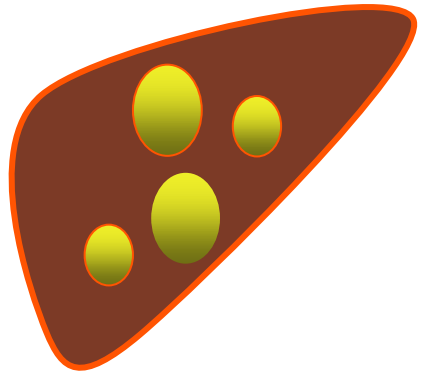
Total tumor diameter:
2.8 cm (2.3-3.7)



“UNOS-DS”

N=422 (11%)

Total tumor diameter:
5.8 cm (5.3-6.5)



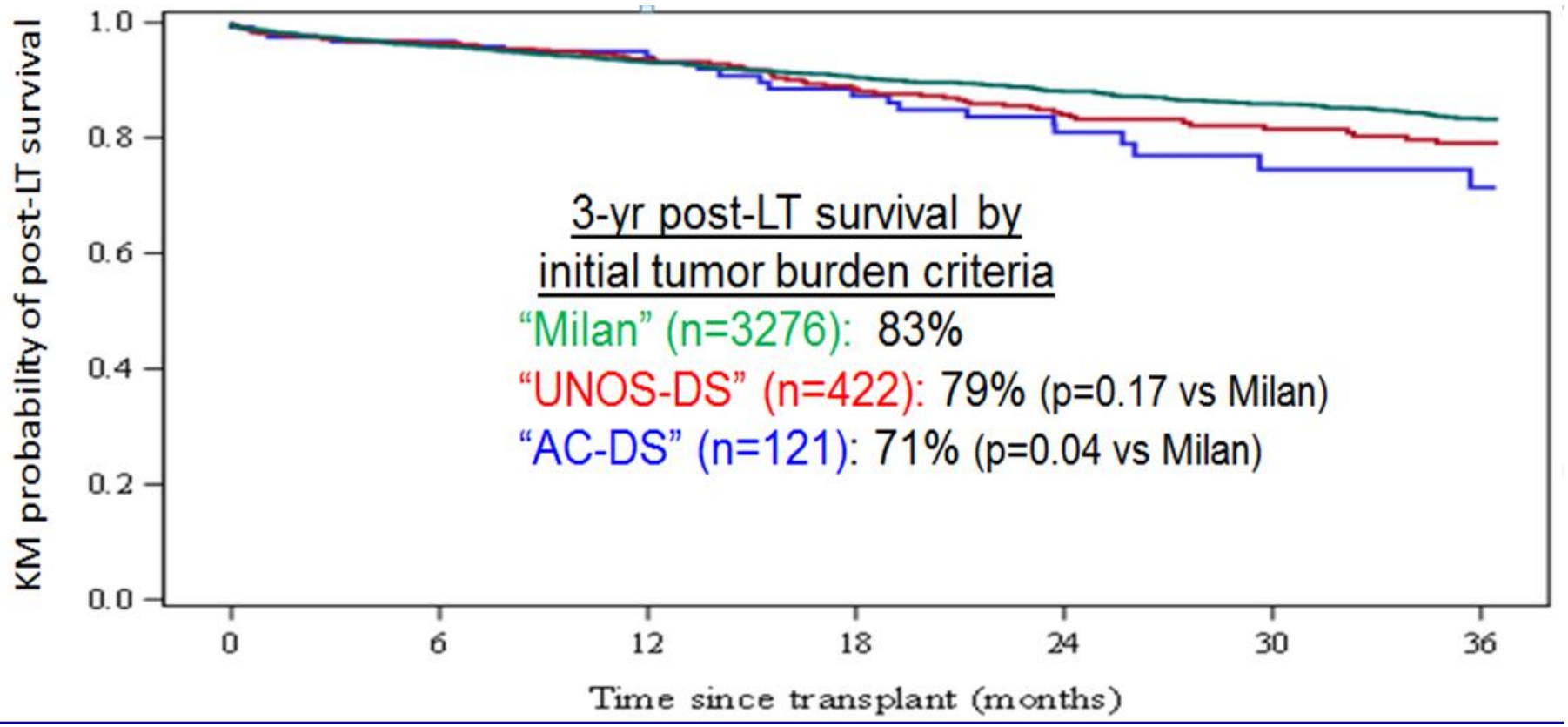
“All-comers”

N=121 (3.2%)

Total tumor diameter:
9.3 cm (8.5-10.6)

Mehta et al. *Hepatology*. 2020;71(3):943-54.

UNOS Down-Staging Protocol



Mehta et al. *Hepatology*. 2020;71(3):943-54.

Outcomes: Liver Resection vs. LT

Liver Transplantation and Hepatic Resection can Achieve Cure for Hepatocellular Carcinoma

Antonio Daniele Pinna, MD, Tian Yang, MD,† Vincenzo Mazzaferro, MD, PhD,‡ Luciano De Carlis, MD, FEBS,§ Jian Zhou, MD, PhD,¶ Sasan Roayaie, MD,|| Feng Shen, MD, PhD,† Carlo Sposito, MD, PhD,† Matteo Cescon, MD, PhD,* Stefano Di Sandro, MD, PhD,§ He Yi-feng, MD,¶ Philip Johnson, MD, FRCP,** and Alessandro Cucchetti, MD**

- Multinational study, N=3286 HCC pts treated with LT (n=1218) or resection (n=2068) to estimate statistical cure

A Pinna et al. *Ann Surg*. 2018.

Outcomes: Liver Resection vs. LT

Characteristics	LT (n: 1218)	HR (n: 2068)
Age, y		
Mean (SD)	53.7 (8.6)	59.1 (12.4)
Median (IQR)	54 (48–60)	60 (51–67)
Radiological number of vital HCCs before surgery		
None	329 (27.0%)	0 (0.0%)
Single nodule	504 (41.4%)	1597 (77.2%)
2–3 nodules	300 (24.6%)	399 (19.3%)
More than 3 nodules	85 (7.0%)	72 (3.5%)
Radiological largest vital HCC before surgery, cm †		
Mean (SD)	3.0 (2.0)	4.8 (3.3)
Median (IQR)	2.0 (2.0–4.0)	4.0 (2.5–6.0)
Last AFP before surgery, ng/mL		
Median (IQR)	10.1 (4.2–42.6)	12.0 (6.3–316)
Transplant criteria fulfilled		
Milan	993 (81.5%)	1271 (61.4%)
Radiological up-to-7	1109 (91.1%)	1509 (73.0%)
UCSF	1072 (88.0%)	1537 (74.3%)
AFP French model	1057 (86.8%)	1236 (59.8%)
Shangai–Fudan	1101 (90.4%)	1725 (83.4%)
Metroticket 2.0	1045 (85.8%)	1226 (59.2%)
MELD score at surgery		
Mean (SD)	12.2 (5.4)	8.6 (2.0)
Median (IQR)	11 (8–14)	8 (7–9)

A Pinna et al. *Ann Surg*. 2018.

Outcomes: Liver Resection vs. LT

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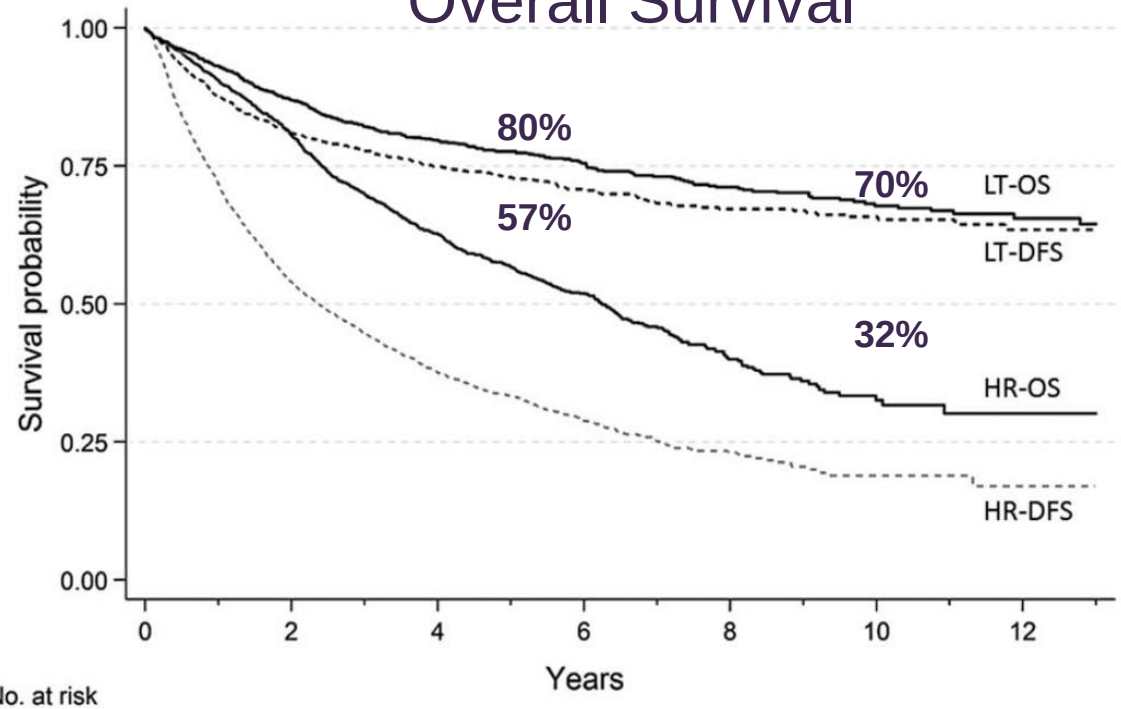
Overall Survival



No. at risk

HR – OS	2068	1420	855	444	144	40	6
HR – DFS	2068	980	537	253	73	25	5
LT – OS	1218	950	702	478	290	180	73
LT – DFS	1218	876	642	409	241	131	58

Cure: Liver Resection vs. LT

Liver Transplantation and Hepatic Resection can Achieve Cure for Hepatocellular Carcinoma

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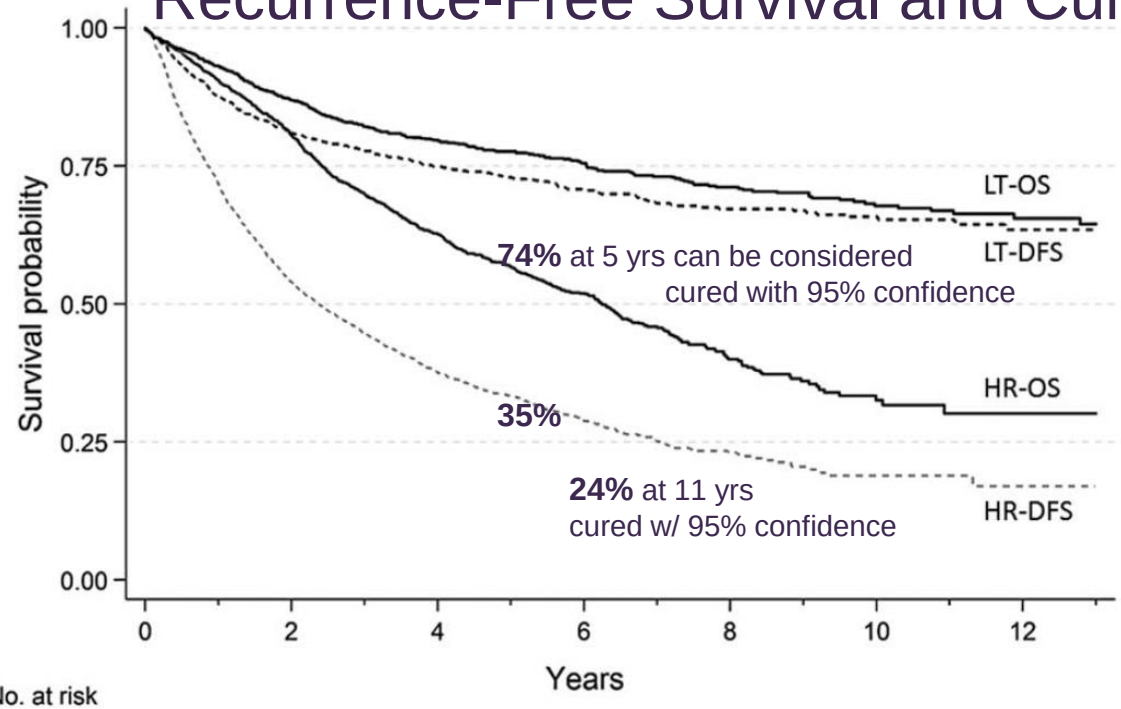
Recurrence-Free Survival and Cure



No. at risk							
HR – OS	2068	1420	855	444	144	40	6
HR – DFS	2068	980	537	253	73	25	5
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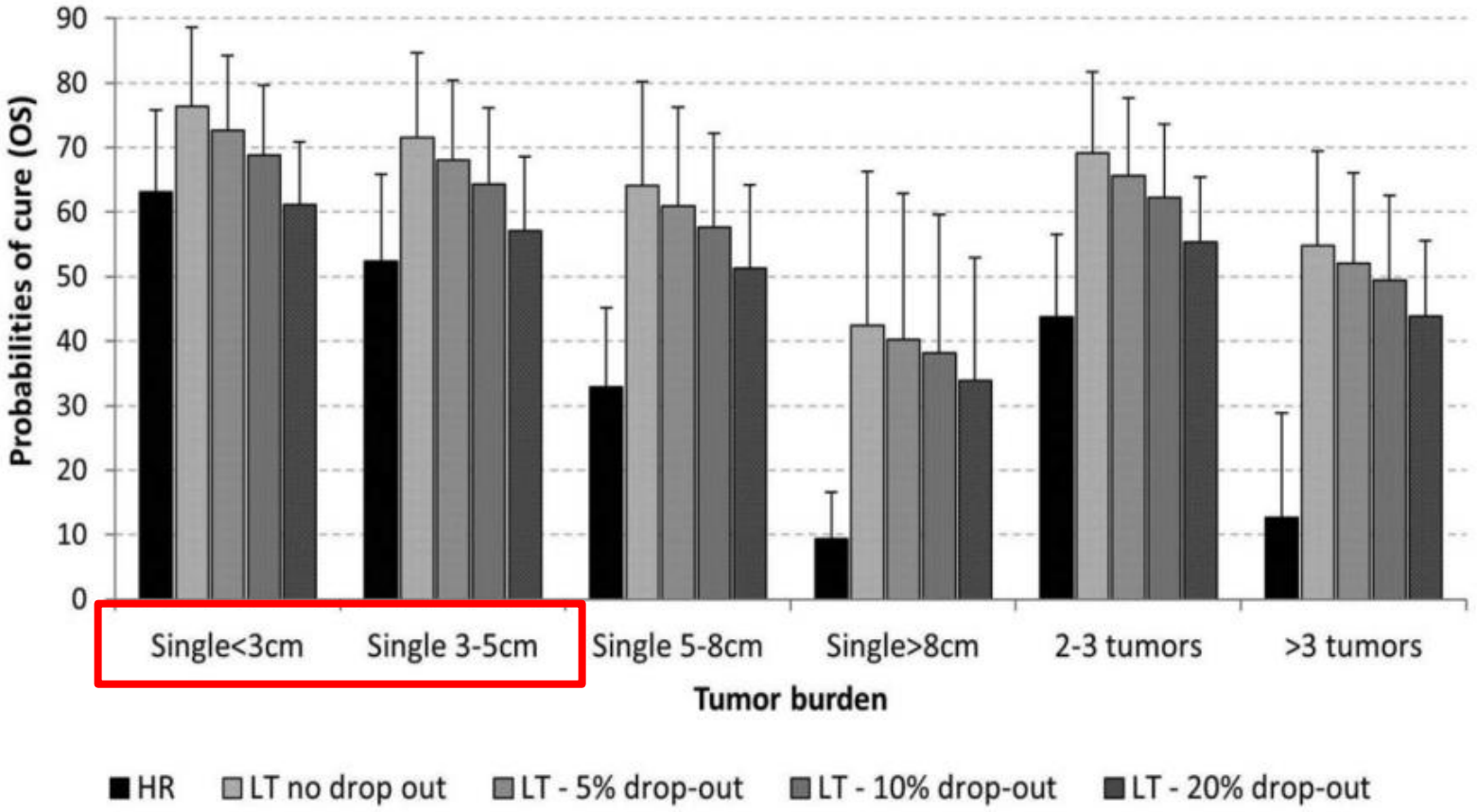
Cure: Resection vs. LT



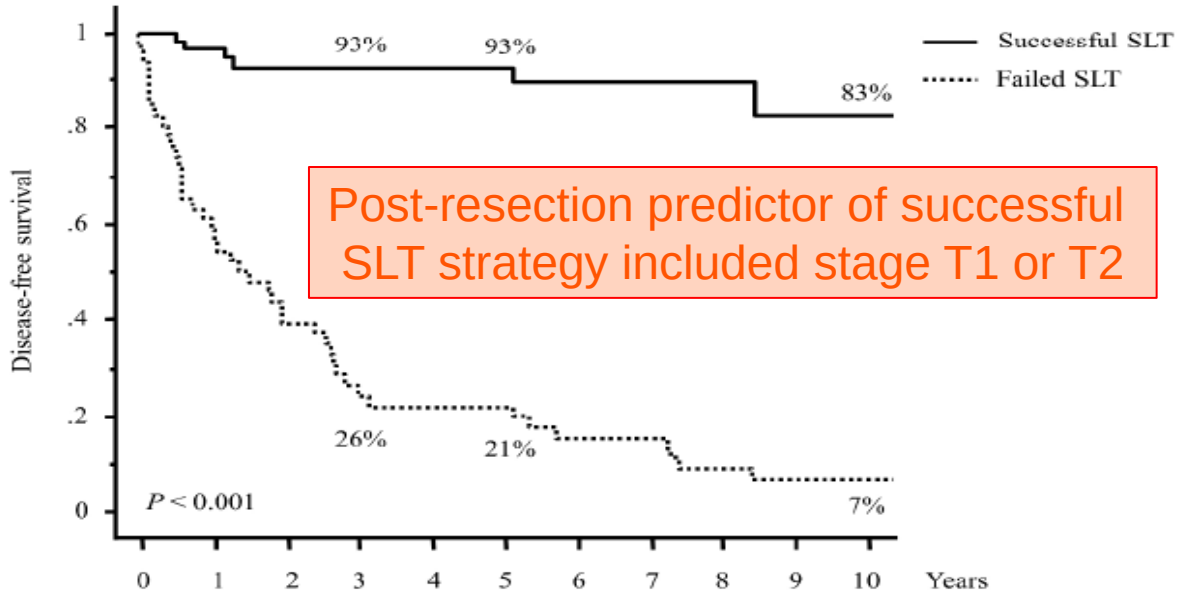
A Pinna et al. *Ann Surg*. 2018.

Post-Resection Recurrence: Salvage LTX

- Multiple studies performed assessing the strategy of resection and only if recurrence occurs within conventional transplant criteria to then pursue salvage LT

Michelakos T et al. *J Gastro Surg*. 2018.

Strategy of Salvage Liver Transplantation *Intention-to-Treat*



Patients at risk	Total	1 yr	2 yrs	3 yrs	5 yrs	10 yrs
Successful SLT	60	52	50	44	31	11
Failed SLT	48	28	18	12	10	3

Post-resection predictor of successful SLT strategy included stage T1 or T2

Successful SLT:
No recurrence
LT if recurred

Failed SLT:
Liver failure or
Recurrence w/o LT

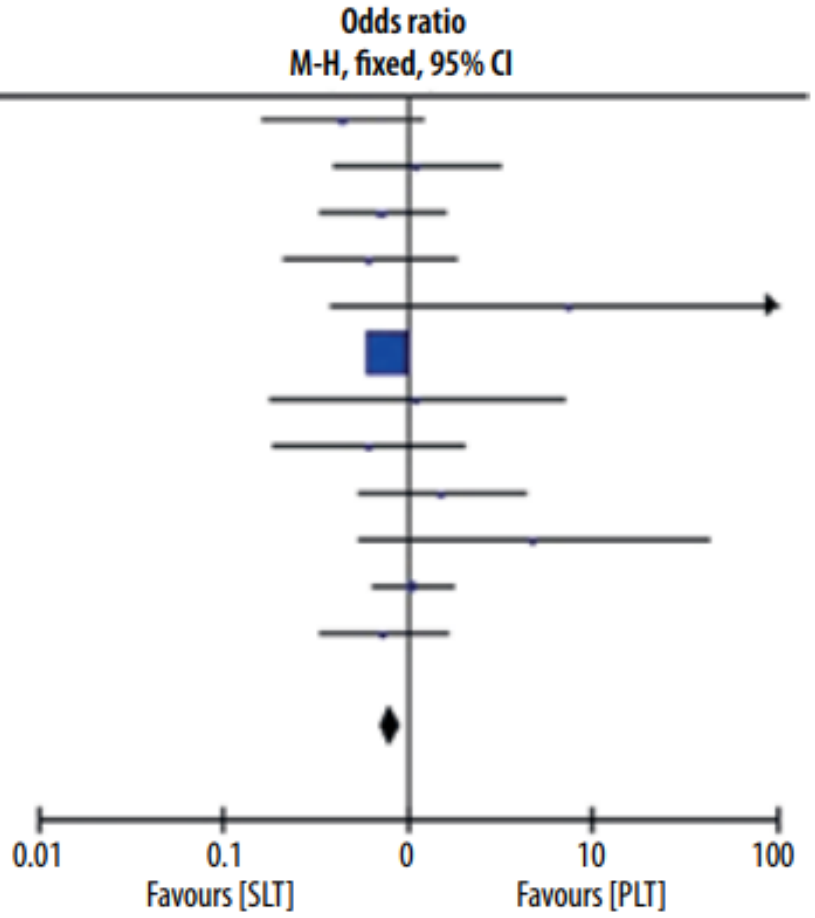
De Haas et al. *Hepatology*. 2018.

Salvage LT vs. Primary LT
5-yr *Post-LT Survival*

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, fixed, 95% CI
Adam 2003	7	17	119	195	2.2%	0.45 [0.16, 1.22]
Belghiti 2003	10	18	37	70	1.3%	1.11 [0.39, 3.16]
Bhangui 2016	10	31	135	340	3.0%	0.72 [0.33, 1.58]
Del Gaudio 2008	10	16	107	147	1.5%	0.62 [0.21, 1.83]
Faciutto 2008	5	5	19	32	0.1%	7.62 [0.39, 149.49]
Hu 2012	465	859	3454	5727	80.5%	0.78 [0.67, 0.90]
Margarit 2005	2	6	11	36	0.4%	1.14 [0.18, 7.15]
Sapisochin 2010	9	17	22	34	1.3%	0.61 [0.19, 2.00]
Scatton 2008	13	20	40	73	1.2%	1.53 [0.55, 4.28]
Vennarecci 2007	8	9	23	37	0.2%	4.87 [0.55, 43.18]
Wang 2006	35	76	131	295	5.6%	1.07 [0.64, 1.77]
Wu 2012	25	36	111	147	2.6%	0.74 [0.33, 1.64]
Total (95% CI)		**1110**		**7133**	**100.0%**	**0.81 [0.71, 0.92]**
Total events	599		4209			

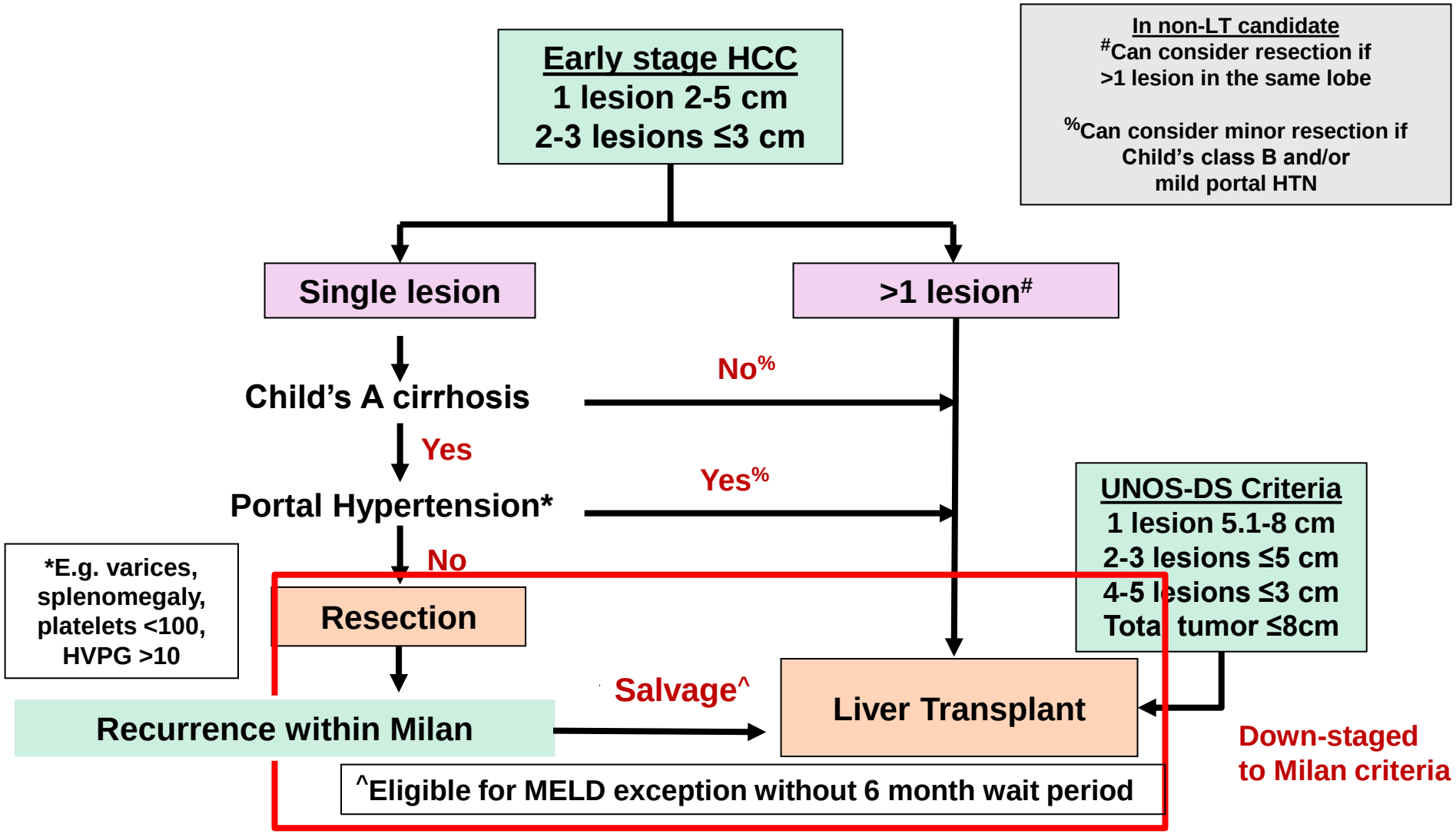
Heterogeneity: $Chi^2=10.12$, df=11 (P=0.52); $I^2=0\%$

Test for overall effect: Z=3.25 (P=0.001)



Yadav et al. *Ann Transplant*. 2018.

Algorithm for Surgical Treatment of Early-Stage HCC



Modified for AASLD Clinical Practice Guidance. 2023.

Take Away Slide (Resection)

- Resection status requires assessment of tumor burden, portal hypertension, MELD score, and extent of resection
- Resection associated with higher recurrence than LT but still 1st line tx, especially with single small tumor and in setting of organ shortages

Take Away Slide (Resection)

- The Milan criteria remain the gold-standard in the US though biomarkers should be incorporated for selection
  - E.g. AFP >1000 exclusion from LT unless decreases to <500 ng/ml with LRT
- After 6 month delay, eligible HCC pts now awarded MMAT-3 rather than previous ladder upgrade
- Similar post-LT survival observed for Milan and UNOS D/S patients
  → Down-staging now incorporated as national policy

Thank You!

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