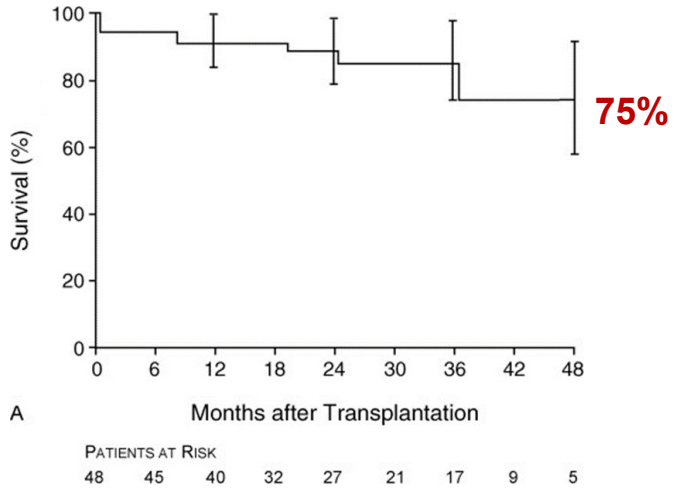
Liver Transplant for HCC

Norah Terrault, MD
Professor of Medicine
Chief, Gastrointestinal and Liver Diseases
University of Southern California

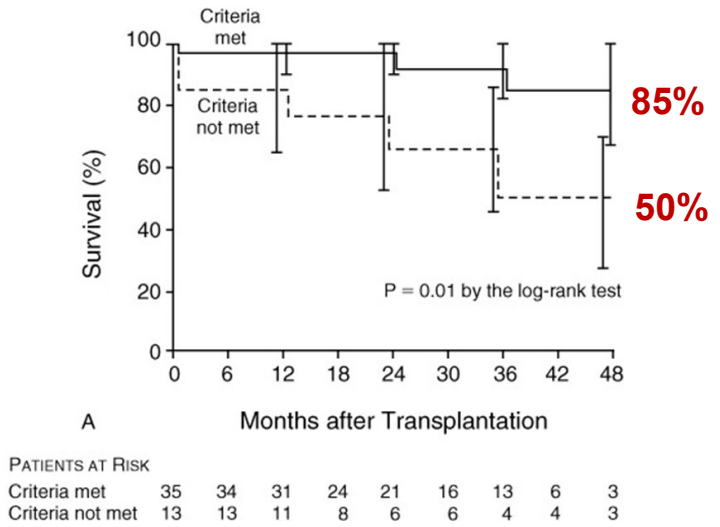
@norahterrault

Keck Medical Center of USC
Keck Medicine of USC

Landmark Study Establishes LT as Effective Treatment for ”Small” HCC



75%

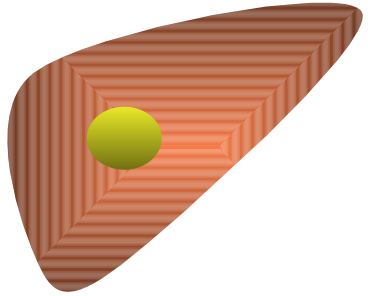


85%

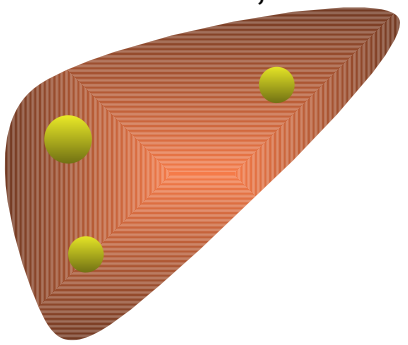
50%

The Milan Criteria

Single tumor, not > 5 cm



Up to 3 tumors, none > 3 cm

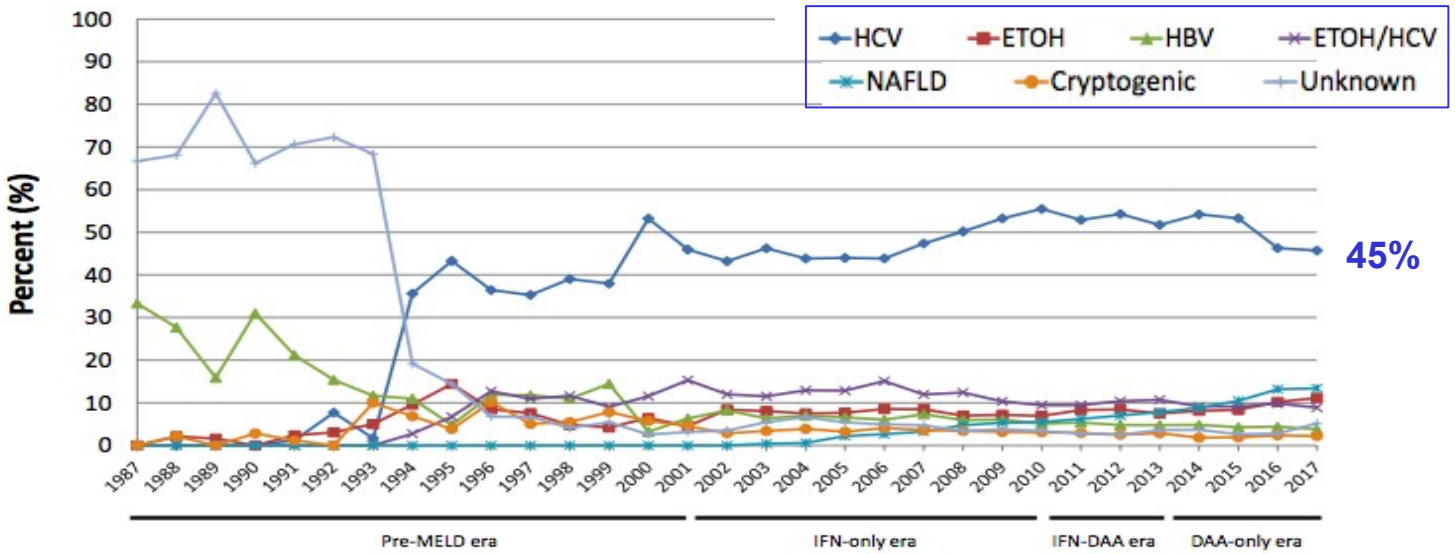


No vascular invasion or extrahepatic spread

Mazzaferro et al. NEJM 1996

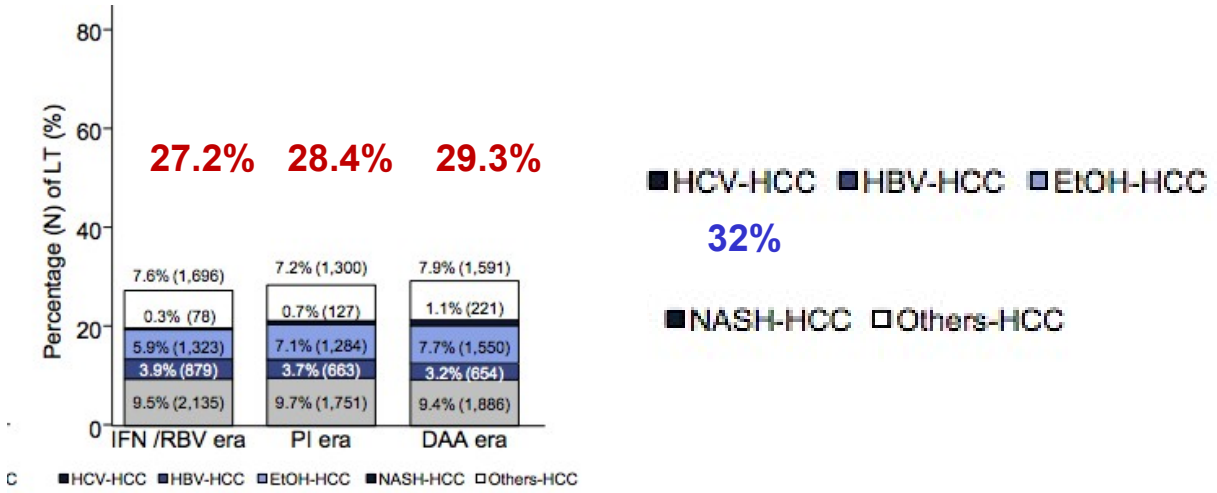
HCC is Primary Indication for LT in ~30%

U.S. UNOS



45%

Europe ELTR



Relevant is assessing **post-LT survival** among HCC patients: HCV was competing risk of death in the pre-DAA era

Puigvehi M, Am J Transplant 2020;20:220-230
Belli L, J Hepatol 2018; 69(4):810-817

Outcome of LT for HCC in the MELD Era (2002-2007)

2002-2007	N	Adjusted * HR (95% CI)	Patient Survival (%) 1 yr	2 yr	3 yr	4 yr	
No HCC	14351	1	88.3	83.8	80.8	78.0	
HCC, MELD exception	4453	1.27 (1.1-1.4)	89.0	81.4	76.5	72.7	
HCC, MELD exception (≥ 2 cm)	3595	1.33 (1.2-1.5)	88.3	80.4	74.8	70.7	

*Adjusted for MELD score, underlying liver disease, age, gender, race/ethnicity, BMI, and donor age (+ other donor factors)

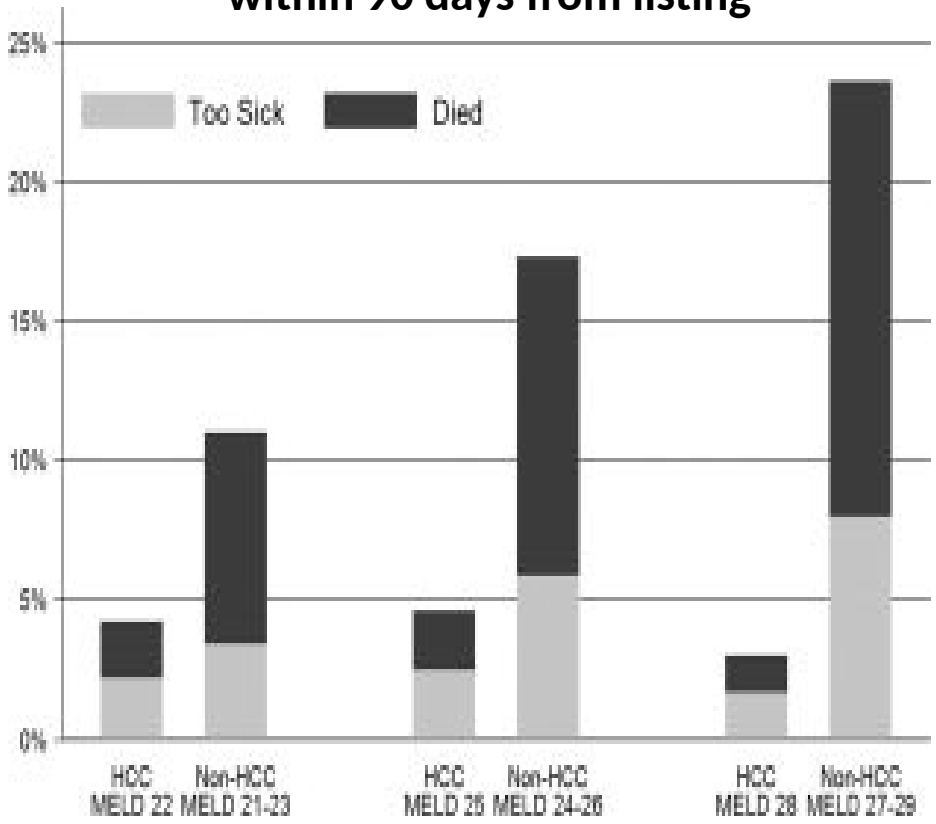
- **Overall recurrence rate post-LTx for HCC approximately 10%**
- **<u>Consensus</u> : LT should be reserved for HCC patients who have a predicted 5-year survival comparable to non-HCC patients**

Ioannou GN, et al. Gastroenterology 2008, Pomfret et al, Liver Transplantation 2010; Clavien et al, Lancet Oncology 2012

Waiting List Dynamics

UNOS: January 1, 2005 to May 31, 2009

% Pts who dropped out or died within 90 days from listing



HCC prioritization increased disparity in access to LT for non-HCC

90-Day Wait List Mortality and Dropout for HCC Candidates vs. Non-HCC Candidates

Within Each MELD Category

HCC MELD	Reference Group	Adjusted OR (95% CI)	*P* Value
22	Non-HCC MELD 21-23	0.32 (0.27-0.39)	<0.001
25	Non-HCC MELD 24-26	0.21 (0.17-0.27)	<0.001
28	Non-HCC MELD 27-29	0.09 (0.05-0.14)	<0.001

Multivariate model was adjusted for the recipient's age at listing, sex, race/ethnicity, blood type, and insurance status (private versus public)

Goldberg et al, Liver Transplantation 2012

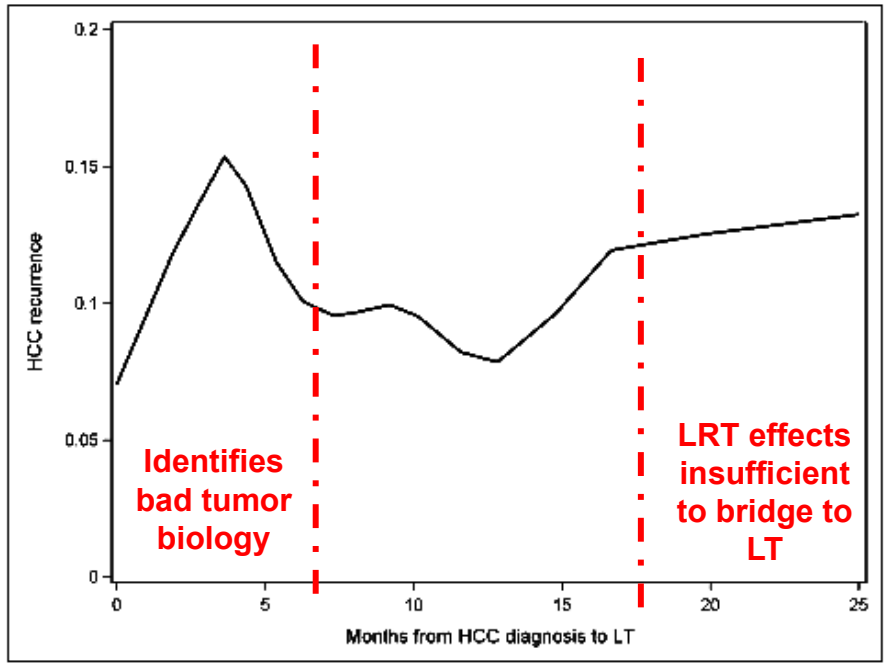
Changes to Prioritization for HCC to Reduce Disparity in Access to LT (vs Decompensated Cirrhosis)

2002	2003	2004	2005	2015
29 exception points T2 lesions 24 exception points T1 lesions	24 exception points T2 lesions 20 exception points T1 lesions	24 exception points T2 lesions No exception points T1 lesions	22 exception points T2 lesions No exception points T1 lesions	28 exception points after 6 months of listing Maximum of 34 MELD exception

Consequence: Patients with HCC are waiting longer for LT

Wait-Time and Post-Transplant HCC Recurrence

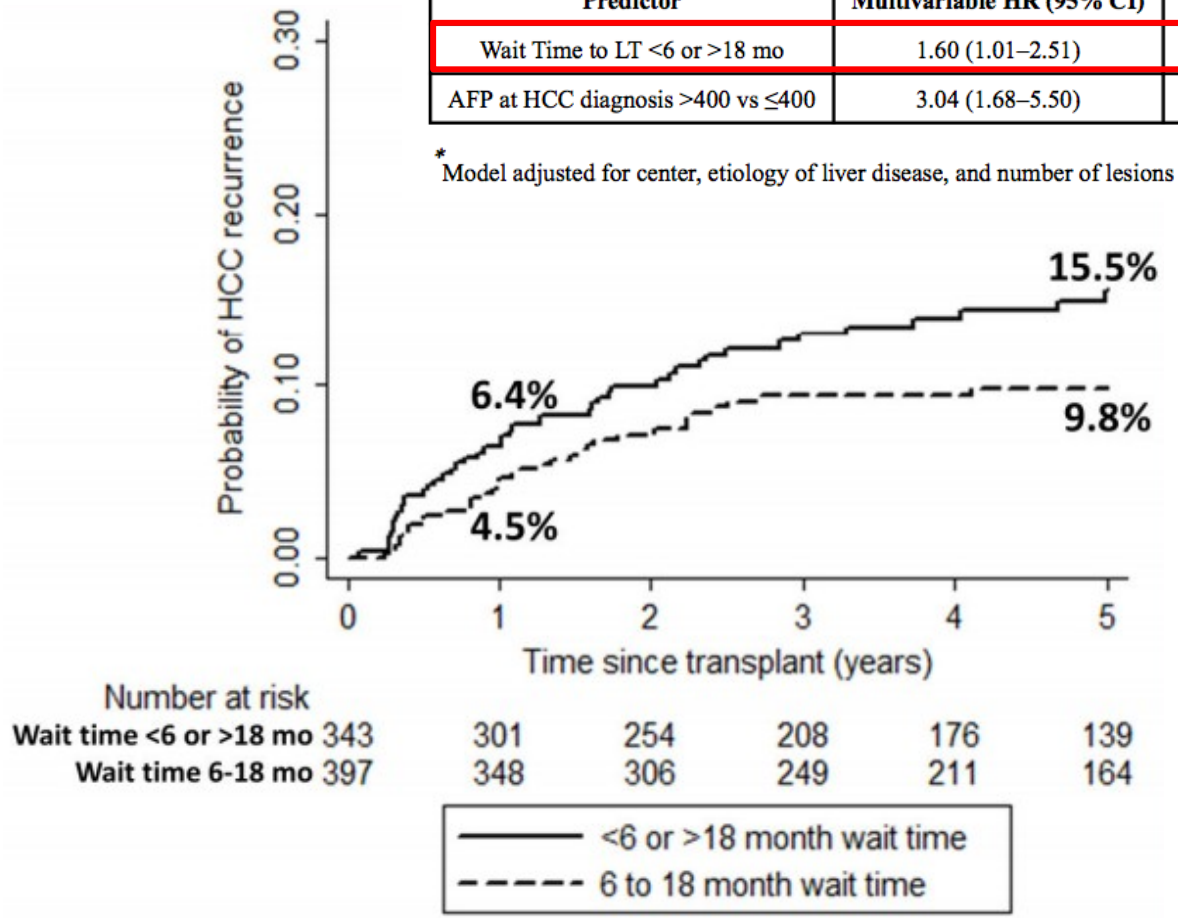
- **Multi-center study, N=911 from 3 LT centers with short, medium and long wait times (median of 4, 7, and 13 months, respectively) who received MELD exception listing for HCC from 2002–2012**



"Sweet Spot" for LT between 6-18 months from listing for HCC

Predictor	Multivariable HR (95% CI)	p value
Wait Time to LT <6 or >18 mo	1.60 (1.01–2.51)	0.04
AFP at HCC diagnosis >400 vs ≤400	3.04 (1.68–5.50)	<0.001

*Model adjusted for center, etiology of liver disease, and number of lesions



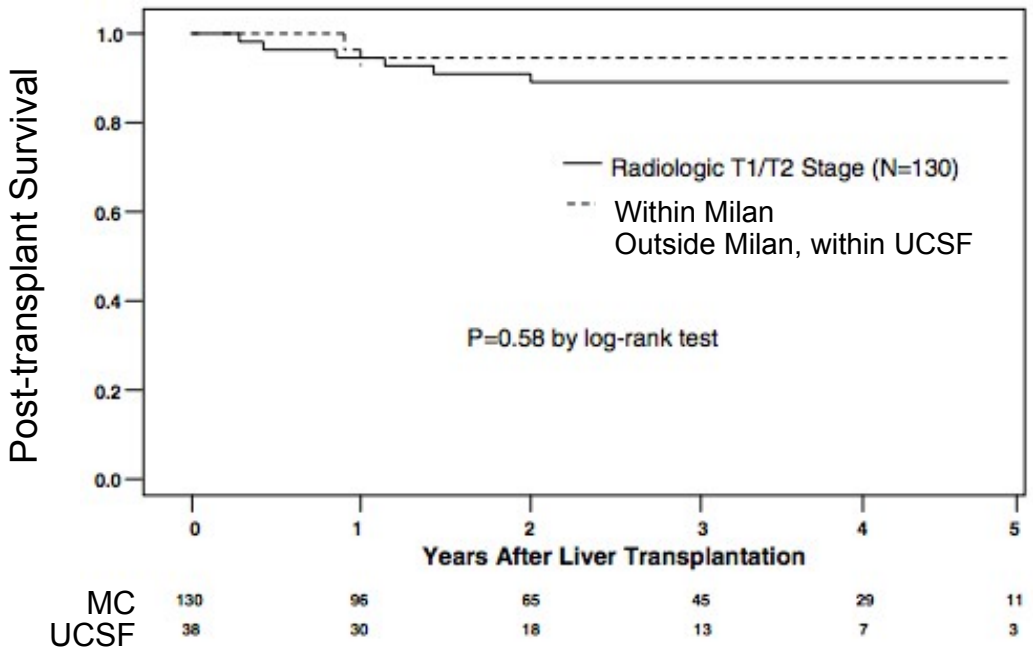
Mehta N, Transplantation 2017;101:2071-2078

Transplantation of HCC Beyond Milan

Modest Expansion Beyond Milan Yields Acceptable Survival

UCSF Criteria

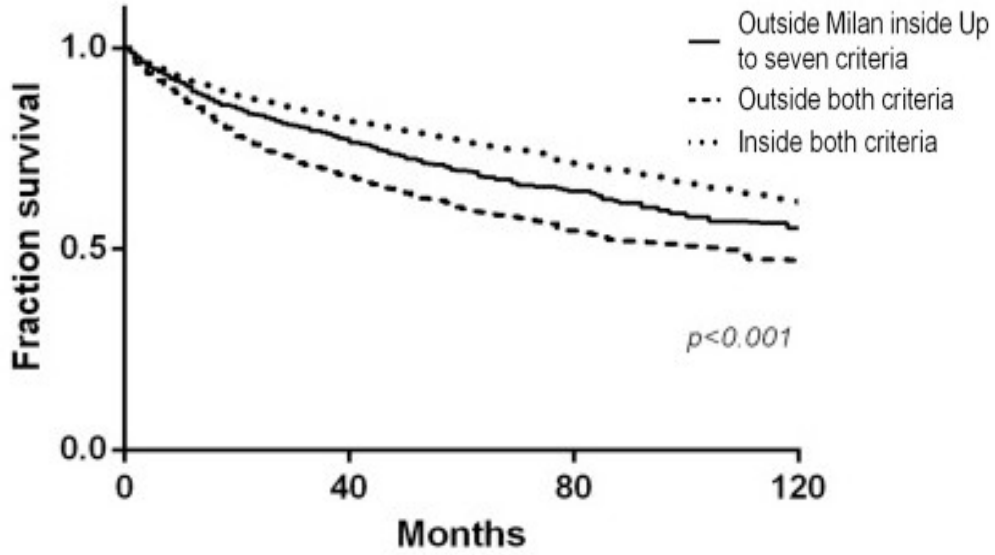
- Single tumor ≤ 6.5 cm, or
- 2-3 lesions, none exceeding 4.5 cm, with total tumor diameter ≤ 8 cm
- No vascular invasion and/or extrahepatic spread



Yao F, Hepatology 2001; 33(6):1394-403
Yao F, Am J Transplant 2007;7(11):2587-96

Up-to-7 Criteria

- Sum of the size of the largest tumor **in** cm and the total number of tumors



Follow-up time		40 months	80 months	120 months
Outside Milan inside Up to seven	*Numbers at risk*	473	186	58
	Survival (%)	73.5	61.8	55.0
Outside both	*Numbers at risk*	688	251	54
	Survival (%)	64.9	51.7	43.8
Inside both	*Numbers at risk*	2026	783	193
	Survival (%)	79.1	69.2	60.0

Pommergaard HC, HPB 2018;20:768-775

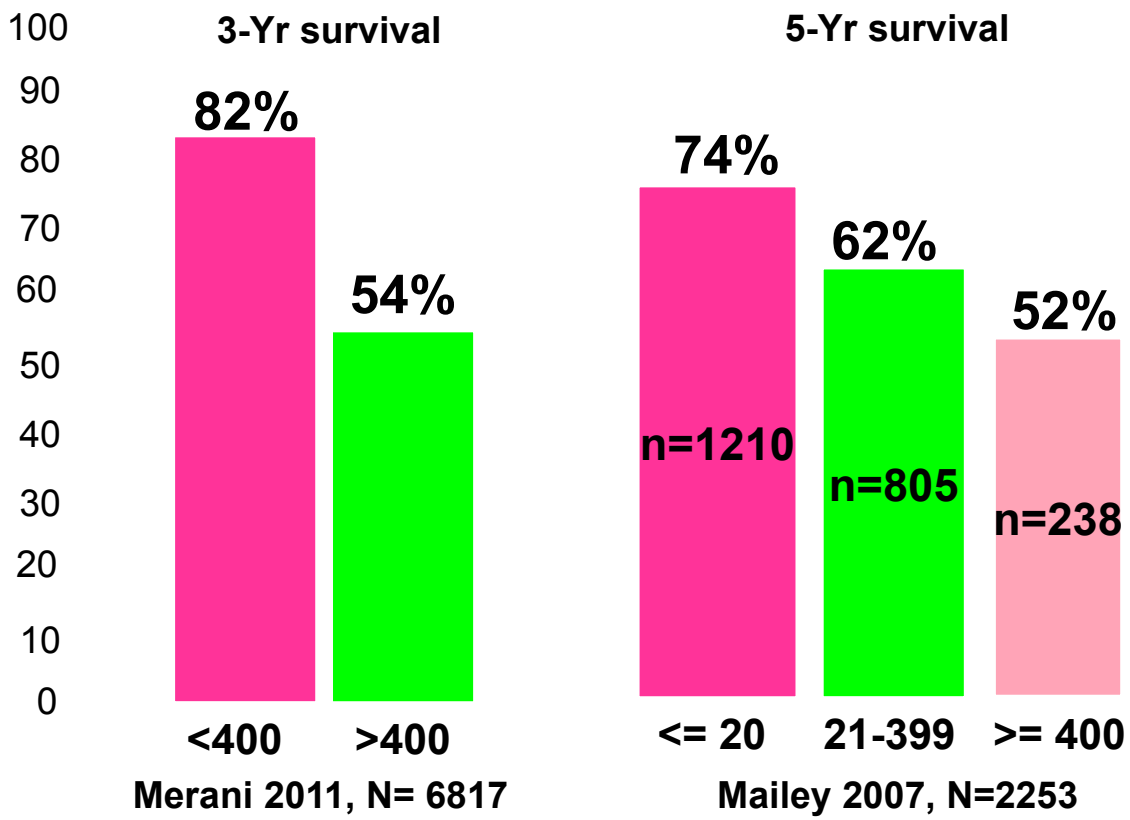
Expanding Eligibility Beyond Milan Criteria

Criteria (country, city, author)	Tumor number	Tumor diameter (cm)	Additional criteria	Overall survival (1 year/ 3 years)
USA [1]	≤3	3–5	No vascular invasion	75–80% (5 year)
Canada Toronto [3]	Any	Any	-No extrahepatic disease -No vascular invasion -No cancer related symptoms/ECOG 0 -Biopsy NOT poorly differentiated	94%/76%
UK [4]	1–5	3–7	-No evidence of progression (volume increase <20%) -No extrahepatic spread -No new nodules over 6 months *Tumor rupture and AFP >10K are absolute contraindications	No data
France [5]	Not defined 1–3 ≥4	Not defined ≤3 3–6 >6	-AFP cut-offs ≤100 100–1000 >1000	67.8% (5 year)
China				
Hong Kong [6]	1 ≤3	≤6.5 ≤4.5	No diffuse type, no vascular invasion	78%/66%
Hangzhou [7]	Not identified	Total ≤8	Grade I or II with AFP ≤400 if tumor >8 cm	70.7%/70.7%
Japan				
Tokyo [10]	≤5	≤5	None	82%/75%
Kyoto [11]	≤10	≤5	PIVKA-II ≤400 mAU/mL	NA/87%
South Korea				
Seoul (AMC) [8]	≤6	≤5	No gross vascular invasion	87.5%/81.6%
Seoul (CMC) [9]	≤7	≤7	None	NA/86.3%

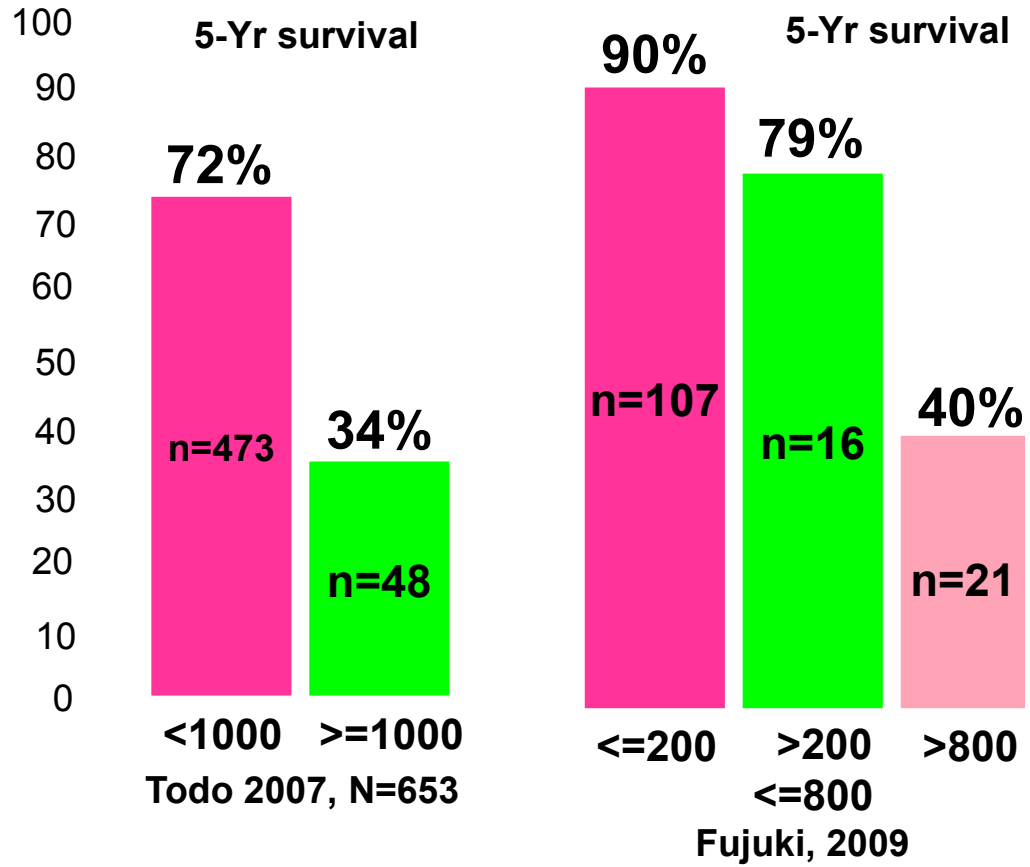
Rudnick & Russo, Exp Rev Gastroenterology & Hepatology 2018;12:3:265-275

Pre-LT AFP is a Useful Biomarker in Patients with HCC Undergoing Liver Transplantation

U.S. Transplant Registries



LDLT Single and Multicenter Studies

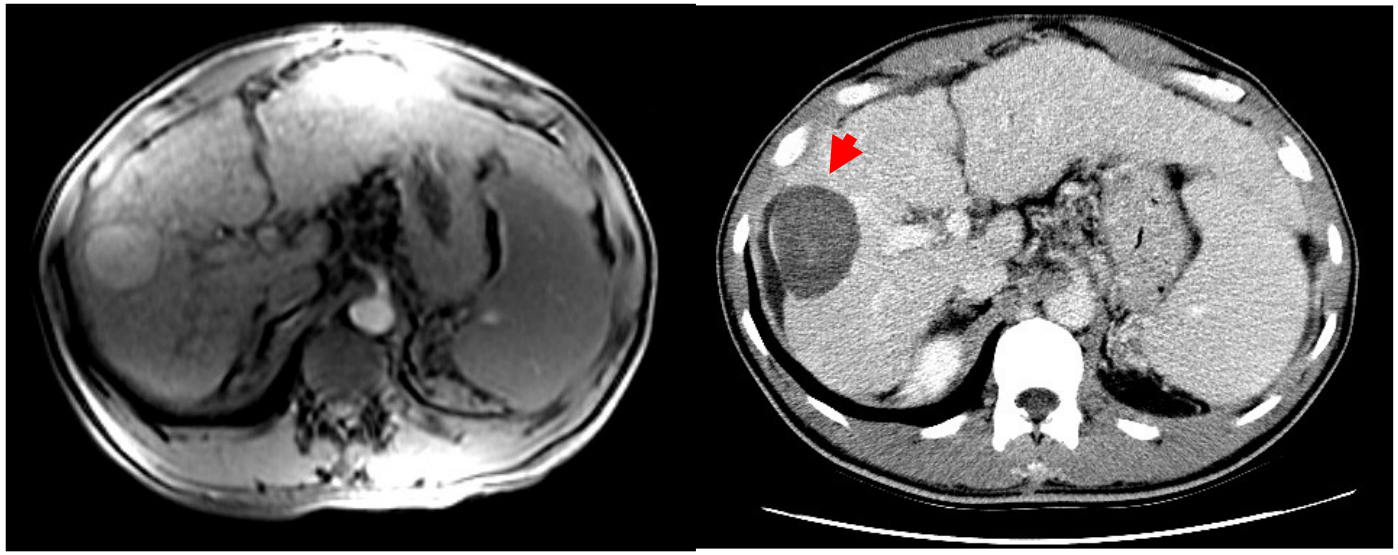


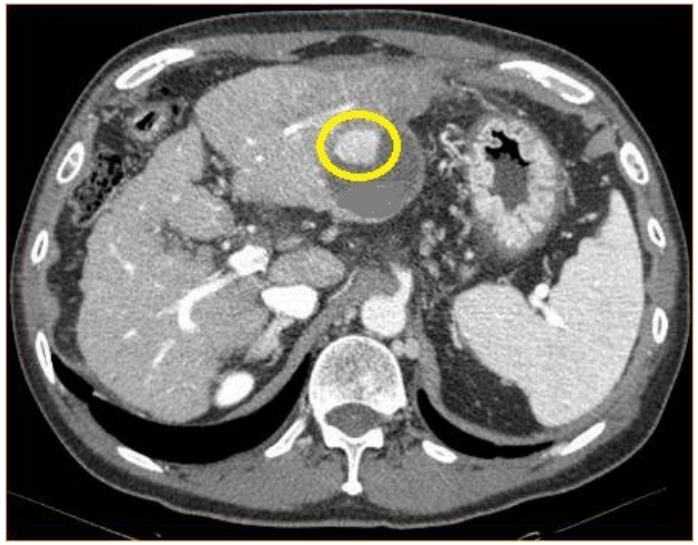
Merani J Hepatol 2011;55:814-819; Mailey B Arch Surg 2011;146:26-33; Todo S. Liver Transpl 2007;13:S48-54; Fujuki et al. Am J Transpl 2009;9:2362-2371

EASL Guidelines Use RECIST Criteria

Tumor response to down-staging treatments: Based on radiographic measurement of the size of all viable tumors

Target lesions		
Response category	RECIST	mRECIST
CR	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions
PR	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	At least a 30% decrease in the sum of the diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD	Any cases that do not qualify for either PR or PD	Any cases that do not qualify for either PR or PD
PD	An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

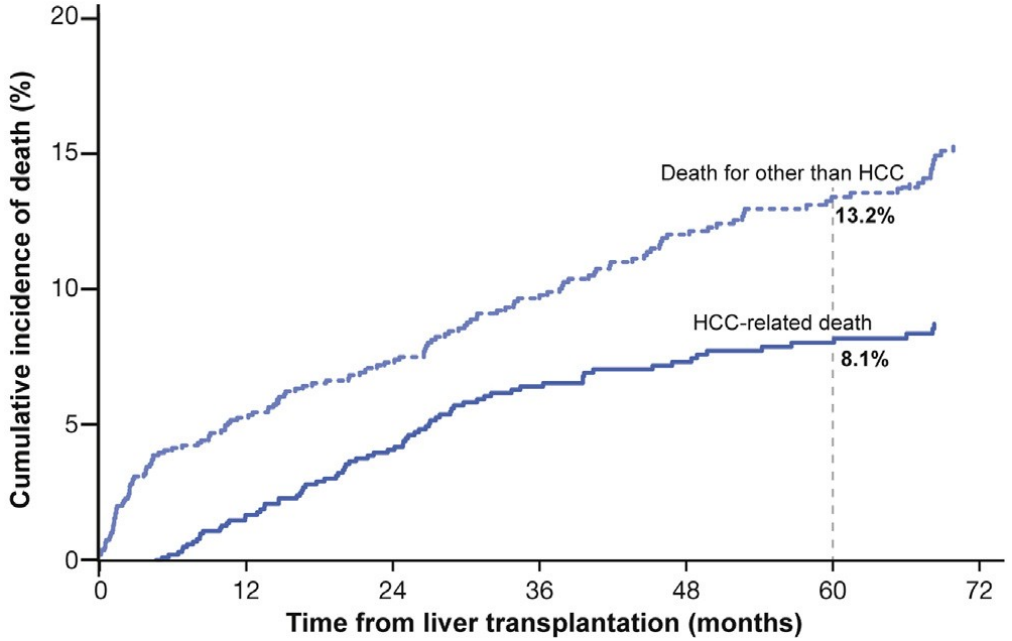




Bruix, J et al EASL Practice Guidelines, J Hepatology 2012

Incorporating Response to LRT into Prognosis

- N=1018 LT recipients from 2000-2010: 3 tertiary referral centers in Italy
- 84.5% underwent LRT, 89.4% with T2 criteria on last imaging
- Based on scan closest to time of LT (median 2.3 mos)
- Externally validated in 346 Asian LT recipients with HCC



Competing risks analysis: HCC and non-HCC deaths

- **Particularly relevant in pre-DAA era**

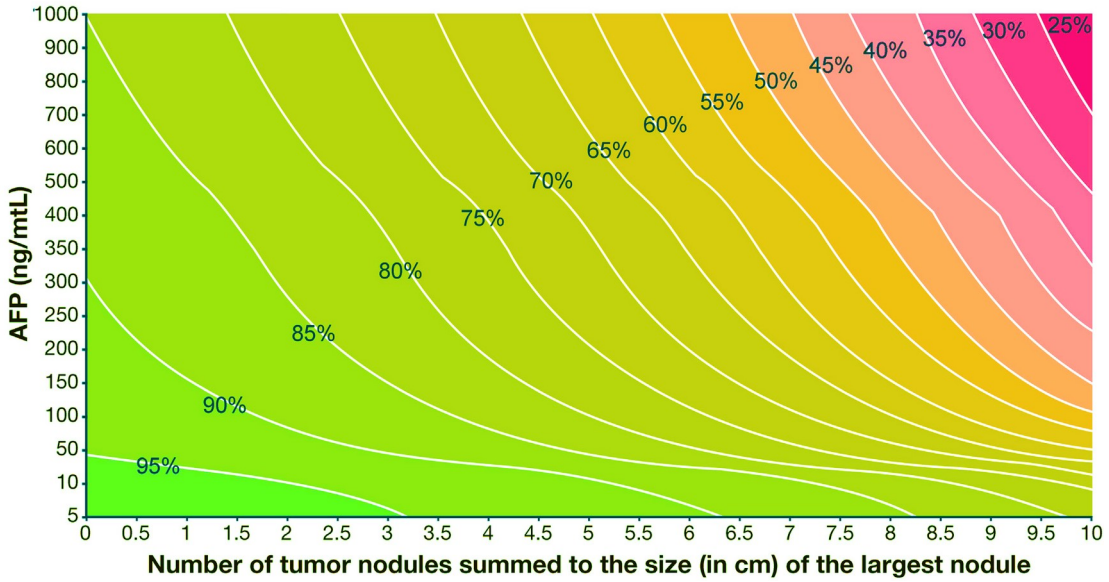
Metroticket 2.0

3 variables with survival:

- **# of viable tumors**
- **Diameter of largest viable tumor**
- **AFP**

Mazzaferro V, Gastroenterology 2018;154:128–139

MetroTicket 2.0



- More dynamic – captures response to LRT
- Highlights importance of AFP as biomarker and response to LRT

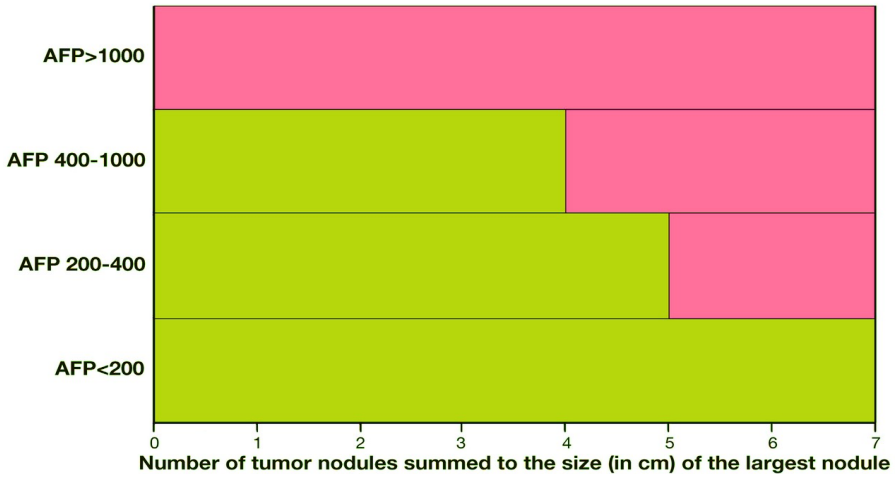
<u>Simplified version</u>:

AFP>1000 ng/dL should not be transplanted

AFP<200 ng/dL plus total # + diameter up to 7 is acceptable

AFP 400-100, up to 4 cm

AFP 200-400, up to 5 cm



Mazzaferro V, Gastroenterology 2018;154:128–139

Downstaging of HCC

- Definition of down-staging: Reduction in the size of tumor using loco-regional therapy to meet acceptable criteria for LT
- Milan criteria remains the gold standard to achieve prior to LT in those with HCC
- Tumor response to down-staging treatments: Radiographic measurement of viable tumors not including the area of necrosis from LRT
  - Approach used by MetroTicket 2.0
- UNOS eligibility for downstaging
  - Also, if initial AFP >1000 ng/mL, ng/mL

1 lesion > 5 cm & ≤8 cm or

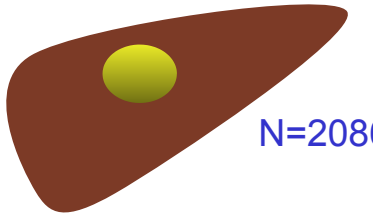
2-3 lesions ≤5cm & total diameter ≤8 cm or

4-5 lesions ≤3cm & total diameter ≤8cm

* principle of EASL HCC guidelines

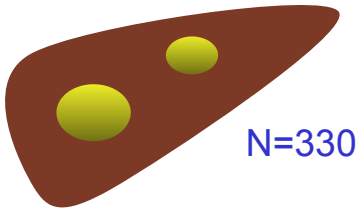
Wait-List Dropout Risk Among Beyond Milan Criteria: Comparison of "UNOS" and "All-Comers" Downstaged

- **Retrospective analysis of adult patients in the UNOS database who submitted a MELD exception application for HCC between January 2010 and December 2017**



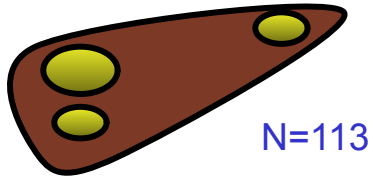
"MILAN"

- 1 lesion ≤ 5 cm
- 2-3 lesions ≤ 3 cm
- No extra-hepatic disease or vascular invasion



"UNOS-DS"

- 1 lesion 5.1-8 cm
- 2-3 lesions ≤5 cm
- 4-5 lesions ≤ 3 cm
- Total diameter ≤8 cm
- No extra-hepatic disease or vascular invasion



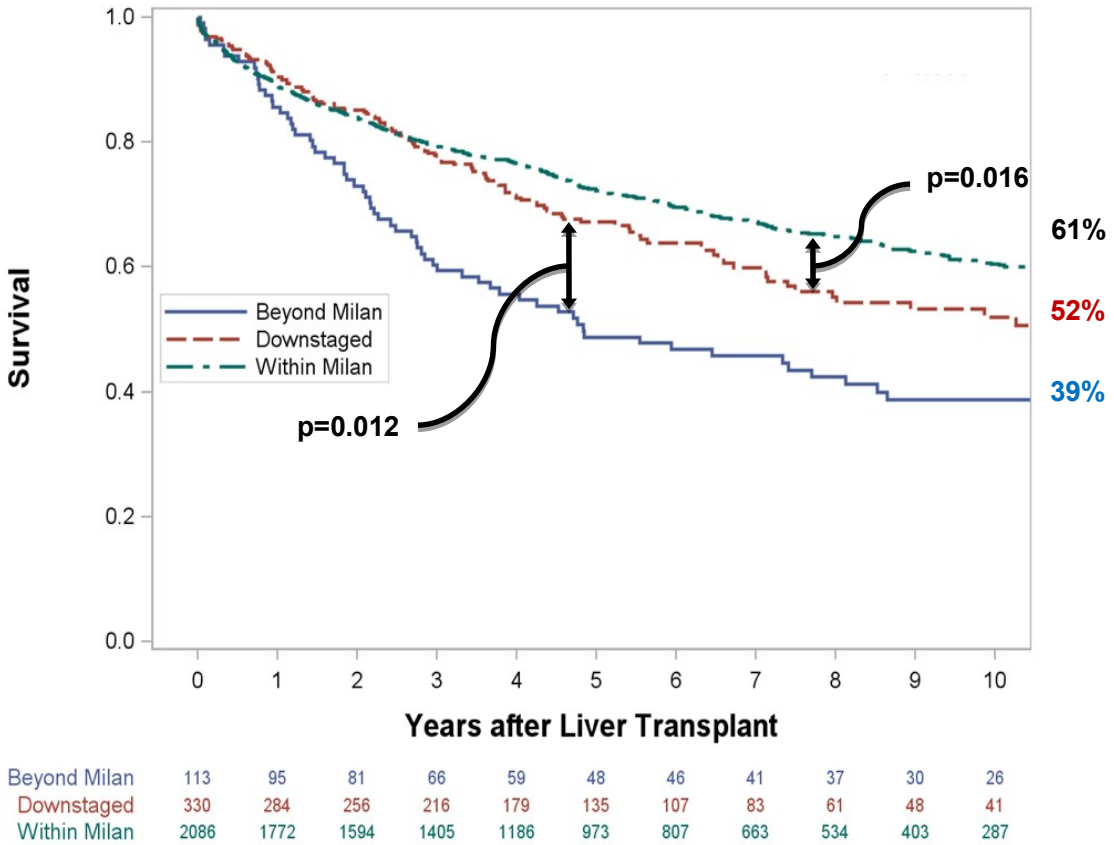
"AC-DS"

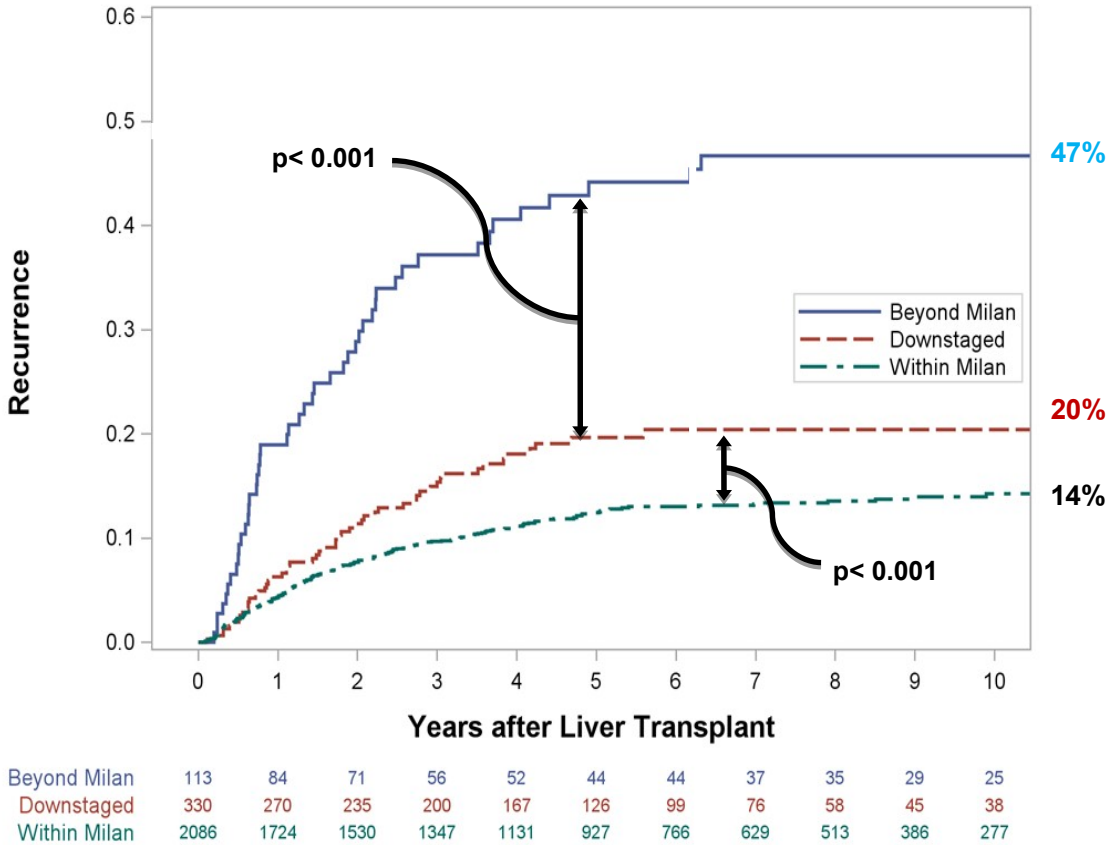
- Tumor size, number or total tumor diameter beyond "UNOS-DS"
- No extra-hepatic disease or vascular invasion

- **UNOS-DS and AC-DS groups required to have been down-staged to within Milan prior to LT**

Huang A, AASLD 2019, Abstract 136

10-Year Outcomes for LT Recipients with HCC
Within Milan, Downstaged and Beyond Milan





Acceptable 10-year outcomes for patients with HCC downstaged to within Milan
Patients beyond Milan have high risk of recurrence

Tabrizian P, AASLD 201

Recurrent HCC Post-LT

HCC Recurrence and Location in LT Recipieints

Study and time period, N	Patients with recurrence	Time to recurrence (months)	Hepatic recurrence	Extrahepatic recurrence/common sites	Multiple sites
Roayaie, 1998-2002 N=311	18%	12.3 (1.5-60.3)	16%	53%	32%
Cescon, 1997-2009 N=283	12%	12 (1-118)	9%	21% lung, bone, peritoneum	71%
Escartin, 1988-2005 N=184	15%	Early <12 mos=5.7 Late ≥12mos=33.5	25%	75% lung, bone	39%
Valdivieso, 1996-2008 N=182	9%	23.4	9%	70% lung, bone, adrenal, nodes	22%
Mehta, 2002-2012 N=721	12%	13	26%	100% lung, bone, peritoneum	25%
Fernandez-Sevilla, 1991-2013, N=493	14%	17	3%	73%	24%
Sapisochin, 2000-2012 N=780	16%	14	13%	52%	35%

Adapted from Verna E et al, Am J Transplant 2019 Nov 11

Recurrent HCC in Liver Transplant Recipients

Systematic review: 1021 recipients

N=61 studies: 13 case reports, 41 retrospective case series, and 7 retrospective comparative

Treatment	total # patients	Median survival (mos) ± SD (weighted)	# studies
Resection	27	42 ± 24.5	6
LRT (TACE)	40	11.2 ± 8.81	6
Sorafenib	76	12.1 ± 9.95	7
Sorafenib + mTOR	68	18.2 ± 6.53	5
Systemic chemotherapy	35	5.79 ± 2.7	2
Support care	54	3.3 ± 2.12	4

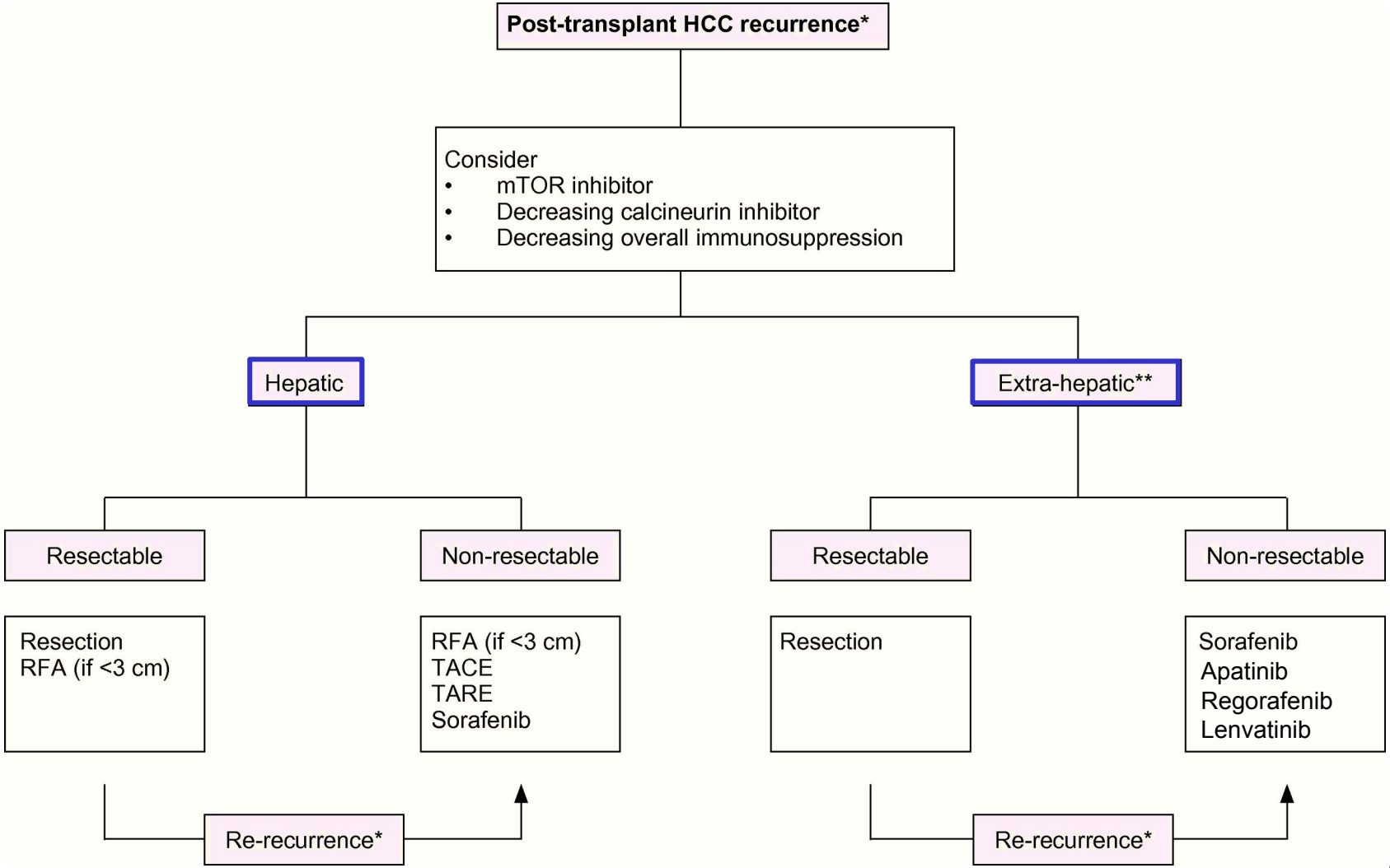
De'Angelis N, WJG 2015;21:11185-11198

Surveillance Recommendations for LT with HCC

Practice	Rationale
Surveil using cross-sectional imaging and AFP	Early detection is key; as desire to detect those that are resectable Use most sensitive tests available Value of AFP unclear but low cost
Surveil every 6 months for at least 2-3 years; consider up to 5 years	Most HCC recur within first 2 years
Include CT scan of chest in surveillance	Majority of recurrences are extrahepatic and lung is among the most common locations Bone is also common but surveillance methods lack sensitivity so base on symptoms/ALP elevation

Verna E et al, Am J Transplant 2019 Nov 11

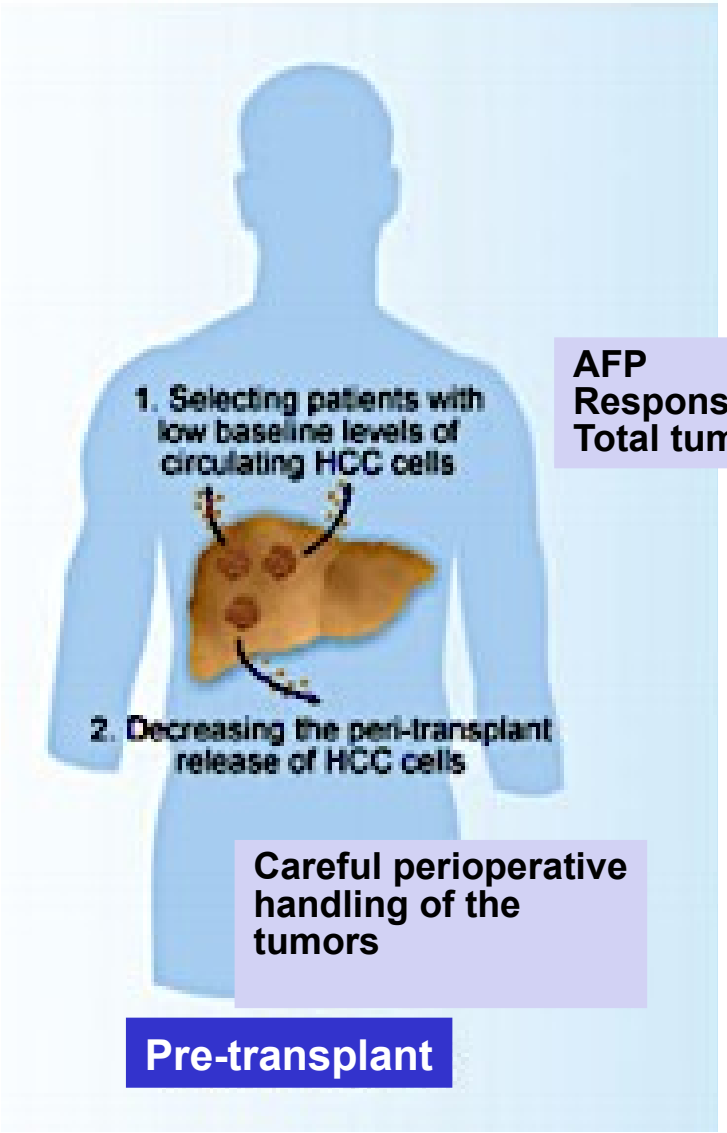
Suggested Management Algorithm for Recurrent HCC in Liver Transplant Recipients



Caution with CTL4 and anti-PD1 inhibitors → reports of rejection leading to graft failure

Toso C, J Hepatol 2013; 59: 3-5
Yu Z, Transplant Proc 2018;50:4042-4045
Iavarone M, Am J Transplant 2019;19:3176-3184
Lee B, Liver Transplant 2019;25:1845-1848

Prevention of HCC Recurrence After LT

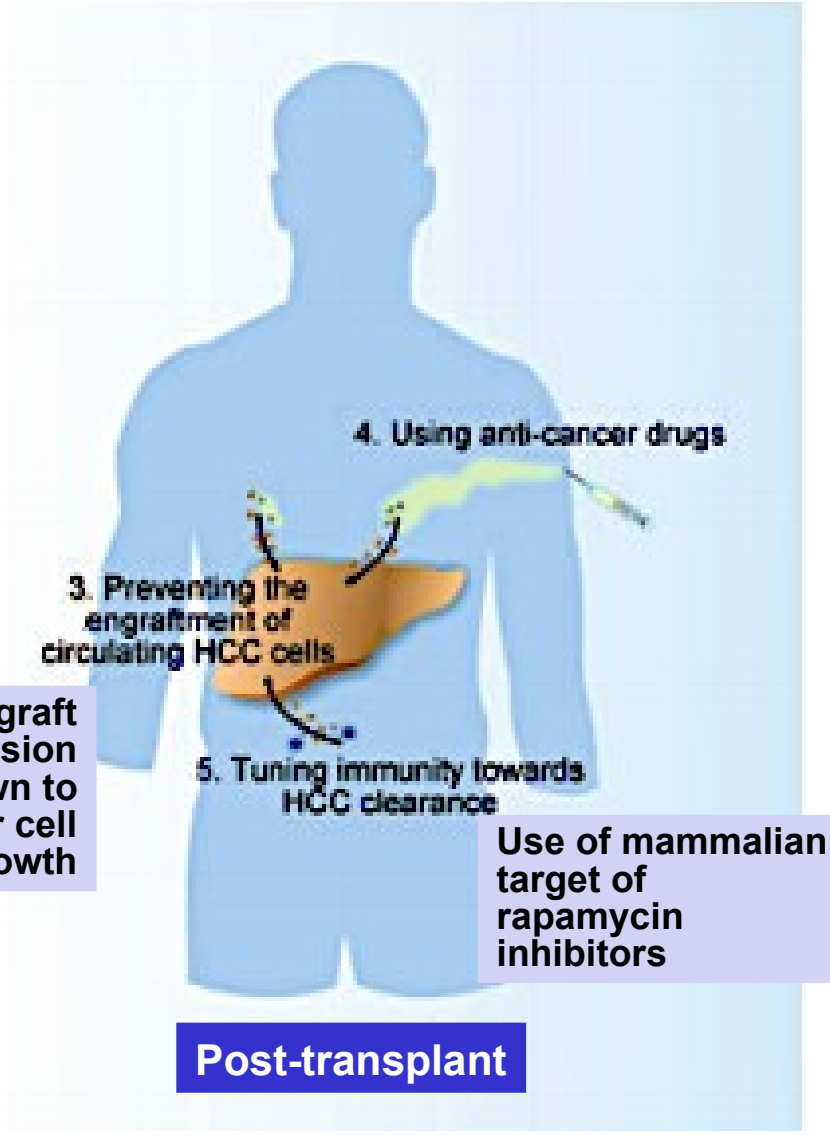


AFP
Response to LRT
Total tumor burden

Careful perioperative handling of the tumors

Pre-transplant

Decrease liver graft ischemia-reperfusion injury, → shown to promote cancer cell engraftment and growth



Use of mammalian target of rapamycin inhibitors

Post-transplant

Toso C et al Am J Transplant 2011;11(10):2031-5

Liver Transplant as Therapy for HCC
Summary I

- LT is an effective HCC therapy for well-selected patients
- LT for patients within MC or downstaged to within MC have excellent 5-10 year HCC-recurrence free survival 60-75%
- Biomarkers of tumor biology improve prediction of recurrence-free survival (beyond size and number)
  - AFP: if >1000 should be contraindication
  - Response to LRT: CR have best outcomes, but PR acceptable
- Wait-list drop-off highest for those beyond Milan or UCSF criteria
  - Consideration of futility required

Liver Transplant as Therapy for HCC
Summary II

- HCC recurrences are primarily within the first 2 years and often are extrahepatic
- With current LT policies, recurrence rates are only ~15% at 5 years but this rate may be anticipated as the criteria for LT are expanded
- Survival after recurrence is poor, especially if not a resection candidate
  - Emphasize on surveillance
- If no contraindications, consider using mTORi based IMS
- More studies on safety and efficacy of HCC-specific therapies in LT patients needed


Thank-you