NCSCG Liver Symposium 2019

HCC and Transplant Debate: Small tumors as well as tumors outside of transplant areas

Presenters:

Renu Dhanasekaran (Stanford)

Francis Yao (UCSF)

Case 1

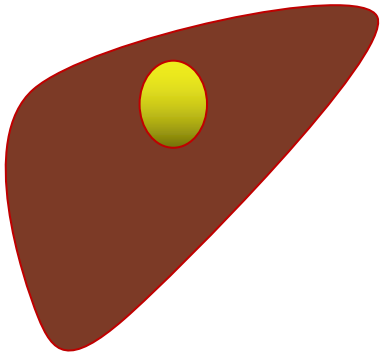
- 55 year-old man with HCV-cirrhosis, history of sustained virologic response after anti-viral therapy, now with a 1.5 cm hypervascular lesion with washout and capsule in the right lobe on MRI of the abdomen (LI-RADS 5).
- He has normal liver function (total bilirubin 1.0, INR 1.1) and no ascites or encephalopathy (Child's A cirrhosis); platelet count of 75, splenomegaly, no varices on EGD. His alpha-fetoprotein was 5.0. His BMI was 25.
- Debate: Transplant or no transplant

  Renu: Transplant

  Francis: No transplant, ablate

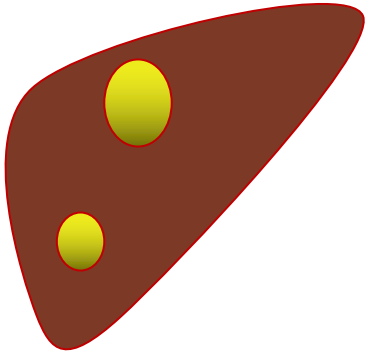
HCC Transplant Criteria in the US

1 lesion 1.5 cm (T1)



Milan Criteria (T2)

- 1 lesion 2-5 cm
- 2-3 lesions $\leq$ 3 cm
- No extra-hepatic disease



UCSF Down-staging Criteria

- 1 lesion 5.1-8 cm
- 2-3 lesions ≤ 5 cm
- 4-5 lesions ≤ 3 cm
- Total Tumor Diameter ≤ 8 cm
- No extra-hepatic disease

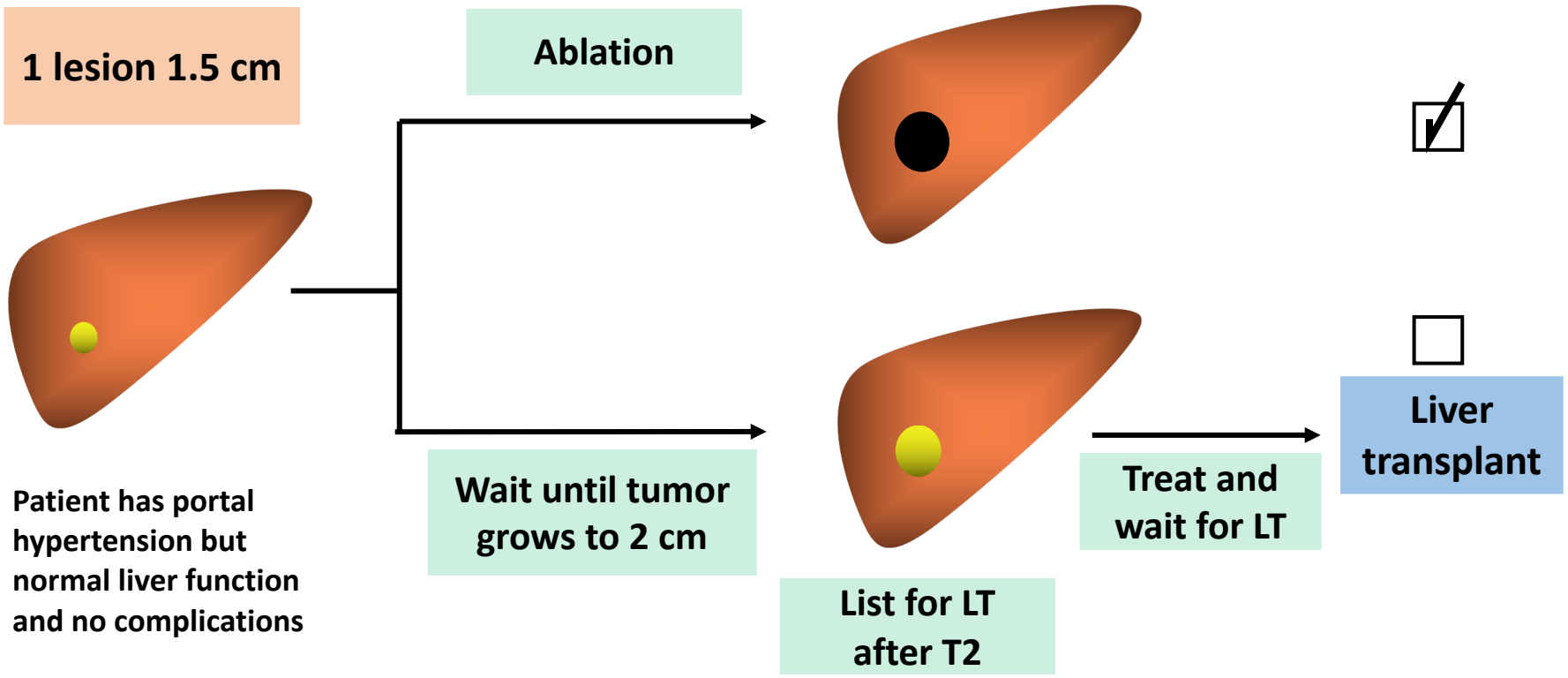
NCSCG Liver Symposium 2019

HCC and Transplant Debate #1:
No transplant for small T1 tumors

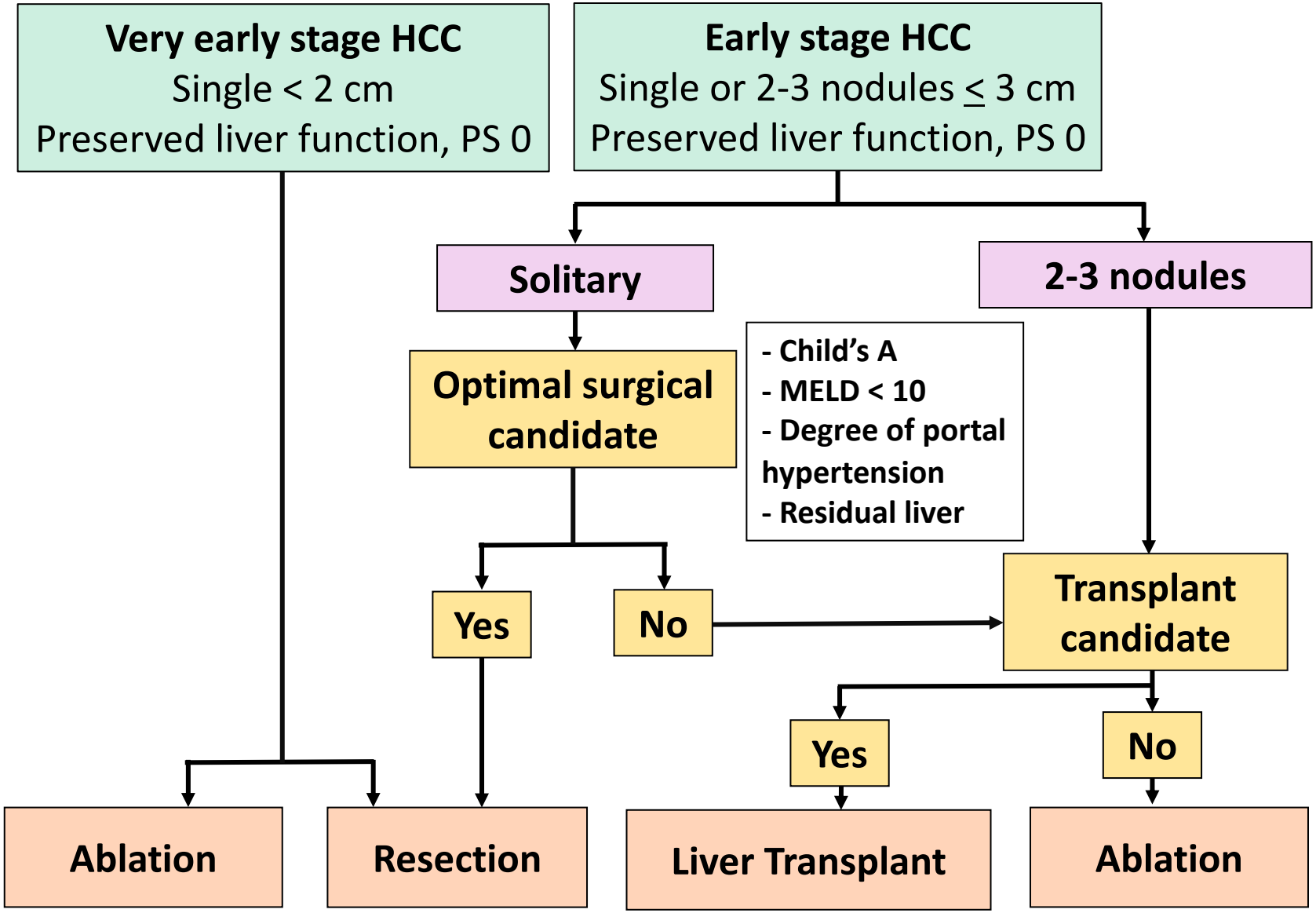
Francis Yao, M.D., FAASLD

Professor of Clinical Medicine and Surgery
Director, Hepatology
Medical Director, Liver Transplantation
University of California, San Francisco

Small HCC < 2 cm: Ablate versus Transplant



EASL 2018 algorithm for curative treatments of HCC



EASL Clinical Practice Guidelines. J Hepatol 2018;69:182-236

RCT of resection versus RFA in HCC

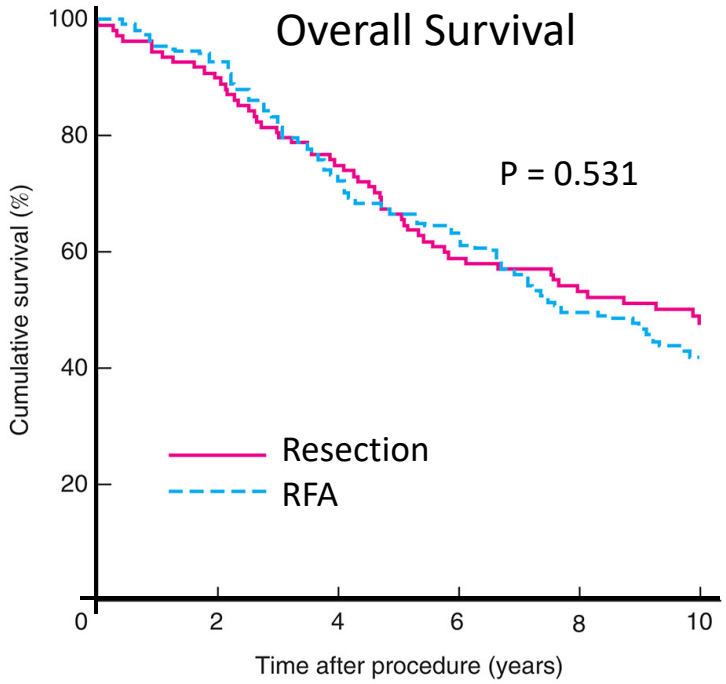
	Inclusion Criteria	Overall Survival	Other outcomes
Chen et al. 2006 [1] Resection (n=90) RFA (n=71)	1 lesion ≤ 5 cm	No difference	More complications with resection
Huang et al. 2010 [2] Resection (n=115) RFA (n=115)	Milan criteria	Better survival with resection	Lower HCC recurrence with resection
Feng et al. 2012 [3] Resection (n=84) RFA (n=84)	Up to ≤ 4 cm and ≤ 2 lesions	No difference	
Fang et al. 2014 [4] Resection (n=60) RFA (n=60)	1 lesion ≤ 3 cm	No difference	More complications with resection
Ng et al. 2017 [5] Resection (n=109) RFA (n=109)	Milan criteria	No difference	Trend for better disease-free survival with resection

1. *Chen MS et al. Ann Surg 2006;243:321-328*
2. *Huang J et al. Ann Surg 2010;252:903-912*
3. *Feng K et al. J Hepatol 2012;57:794-802*
4. *Fang Y et al. J Gastroenterol Hepatol 2014;29:193-200*
5. *Ng KKC et al. Br J Surg 2017;104:1775-1784*

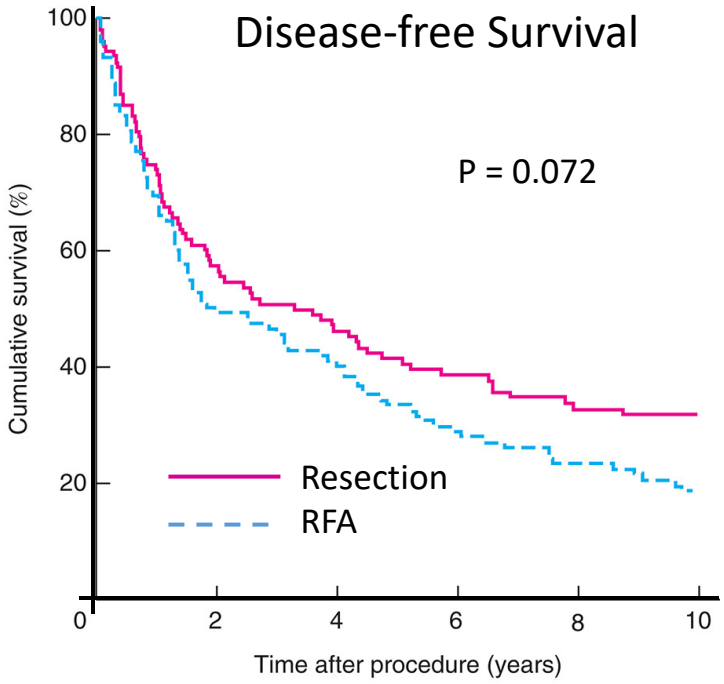
UCSF Transplant

RCT of Resection versus RFA in HCC

All Patients; 1 lesion ≤5 cm



Resection	109	97	80	63	54	38
RFA	109	99	78	67	53	35

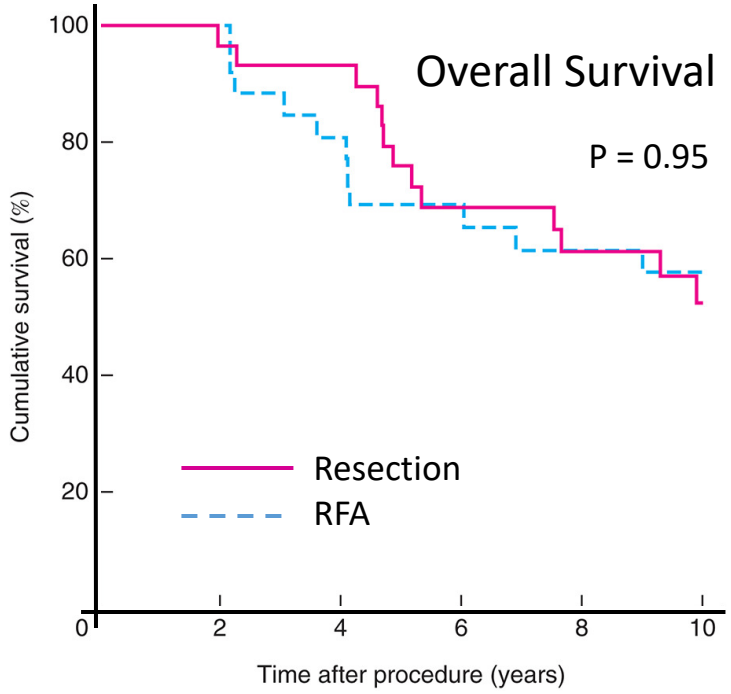


Resection	108	62	49	41	34	26
RFA	109	53	44	31	25	25

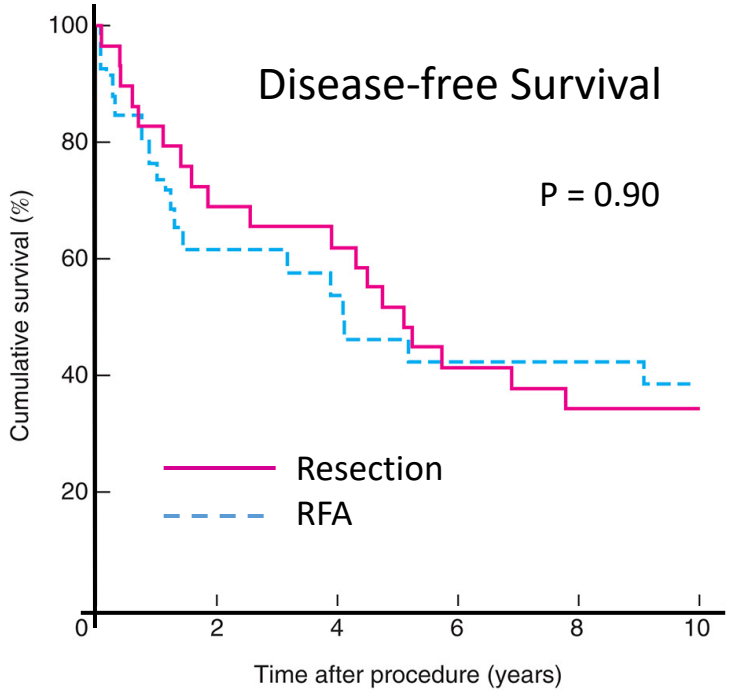
Ng KKC et al. Br J Surg 2017;104:1775-1784

RCT of Resection versus RFA in HCC

Very early HCC; 1 lesion ≤2 cm



Resection	29	28	27	20	16	11
RFA	26	26	21	18	16	8



Resection	29	20	18	12	10	8
RFA	26	16	14	11	11	8

Ng KKC et al. Br J Surg 2017;104:1775-1784

Thermal Ablation: Very early HCC

Single Tumor ≤ 2 cm

- A multi-center study on 218 patients with single lesion <= 2cm, median follow-up 31 months.
- Sustained complete response in 97% after 1 (86%) or 2 (12%) sessions.
- 5-year survival 55%, perioperative mortality 0% and major complication rate 1.8%.
- 5-year disease free survival rate 26%.

UCSF Transplant

Livraghi T, et al. Hepatology 2008;47:82-89

Thermal Ablation: Very early HCC

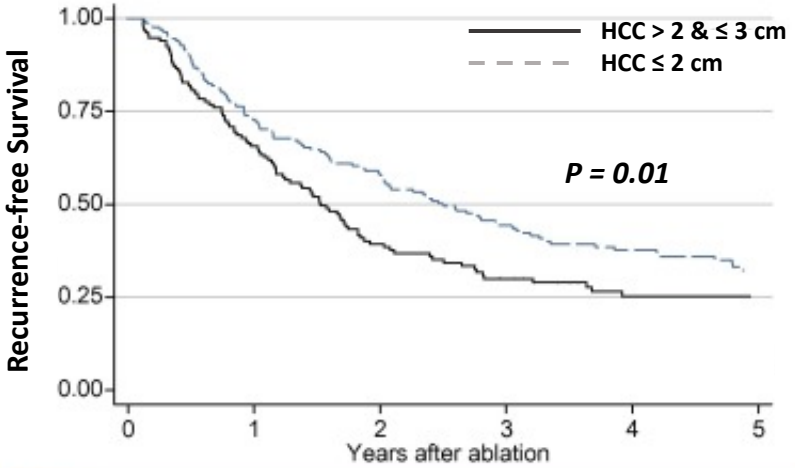
Single Tumor < 2 cm

- Systematic review and meta-analysis of 17 studies (3996 treated with resection and 4424 with ablation), with cost-effectiveness using a Markov model.
- Very early HCC < 2 cm in Child's class A patients: RFA provides similar life expectancy and quality-adjusted life expectancy at a lower cost compared to resection.

Cucchetti A, et al. J Hepatol 2013;59:300-307

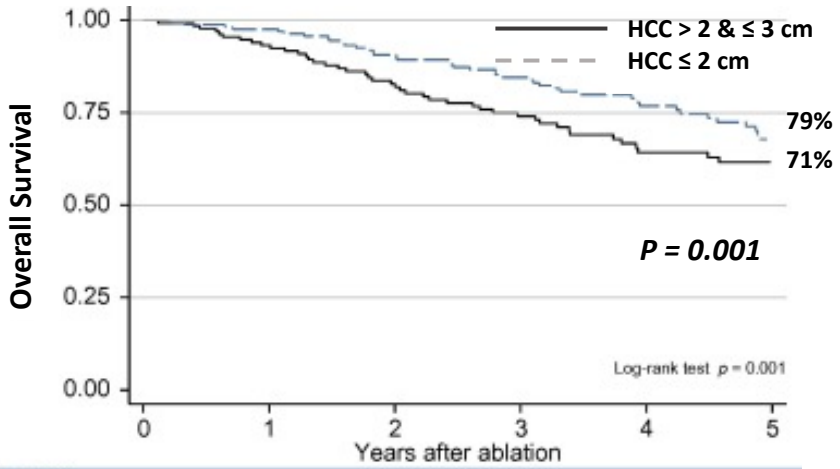
Survival outcome after RFA for HCC ≤ 3 cm

Recurrence-free Survival



N° at risk						
HCC >2 cm	134	87	49	32	18	12
HCC ≤2 cm	167	119	92	64	43	34

Overall Survival



N° at risk						
HCC >2 cm	134	122	97	79	52	38
HCC ≤2 cm	167	160	140	116	73	58

Doyle A, et al. J Hepatol 2019;70:866-873

HCC recurrence after RFA for HCC ≤ 3 cm

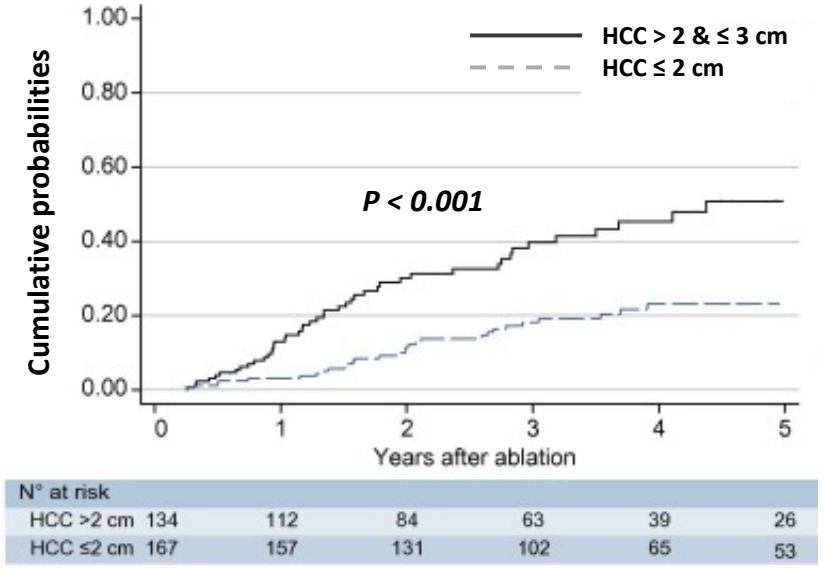
Recurrence pattern	Total (n=301)	≤ 2 cm (n=167)	> 2 and ≤ 3 cm (n= 134)	P-value
HCC recurrence	199 (66%)	105 (63%)	94 (70.1%)	0.18
Beyond Milan				
Total	83 (28%)	36 (22%)	47 (36%)	***0.01***
At first recurrence	38 (13%)	15 (9%)	23 (17%)	***0.03***
Reasons > Milan				
Tumor size/ number	29 (35%)	11 (31%)	18 (38%)	0.78
Vascular invasion	30 (36%)	15 (42%)	15 (32%)	0.36
Metastatic disease	24 (29%)	10 (28%)	14 (30%)	0.84

Doyle A, et al. J Hepatol 2019;70:866-873

HCC recurrence after RFA for HCC ≤ 3 cm

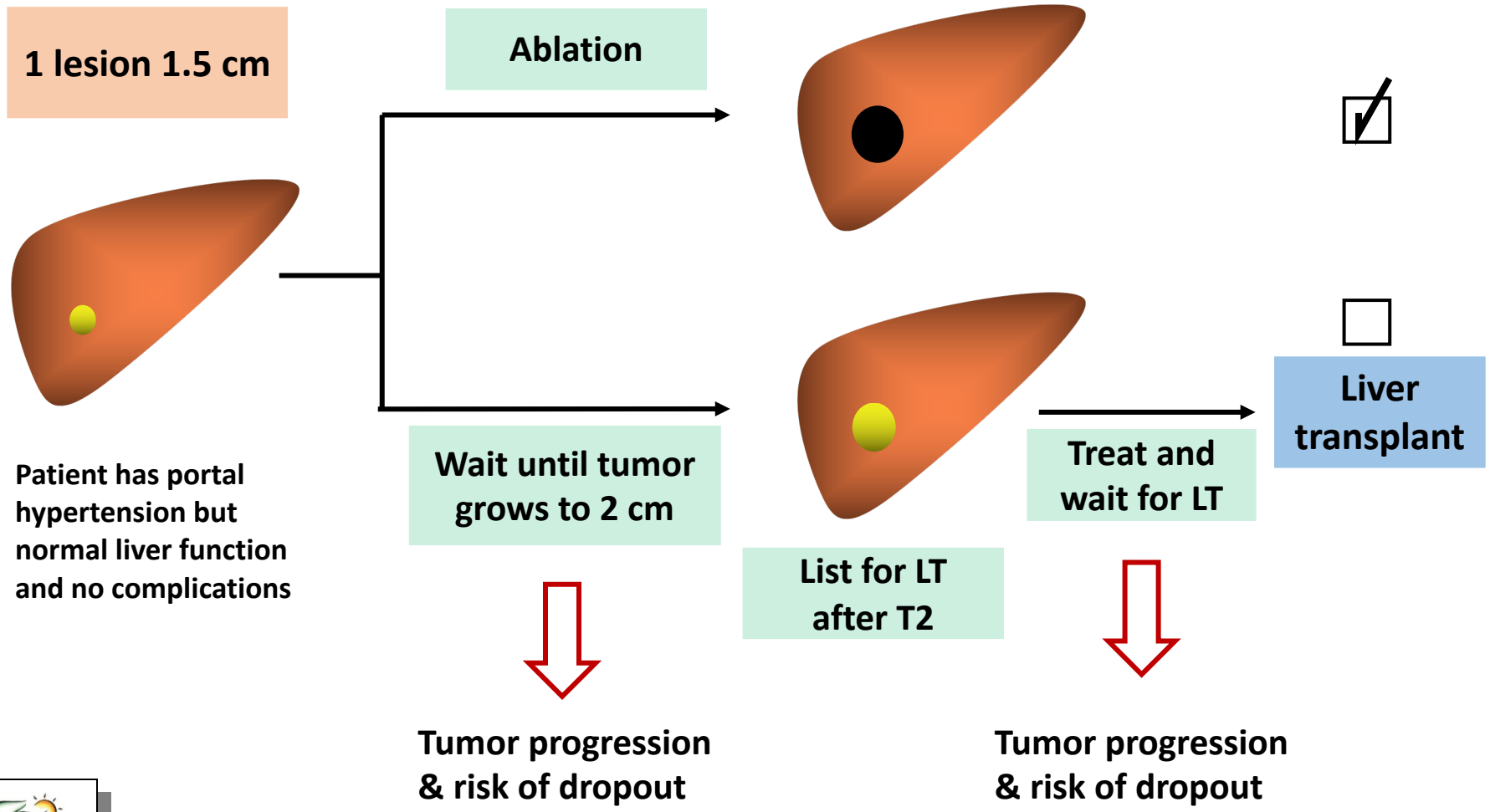
HCC Recurrence > Milan Criteria

Factors (multivariate)	HR
HCC size > 2 cm (vs ≤ 2 cm)	1.94 (p=0.01)
AFP 101-1000	2.05 (p=0.02)
AFP > 1000	2.06 (p=0.12)

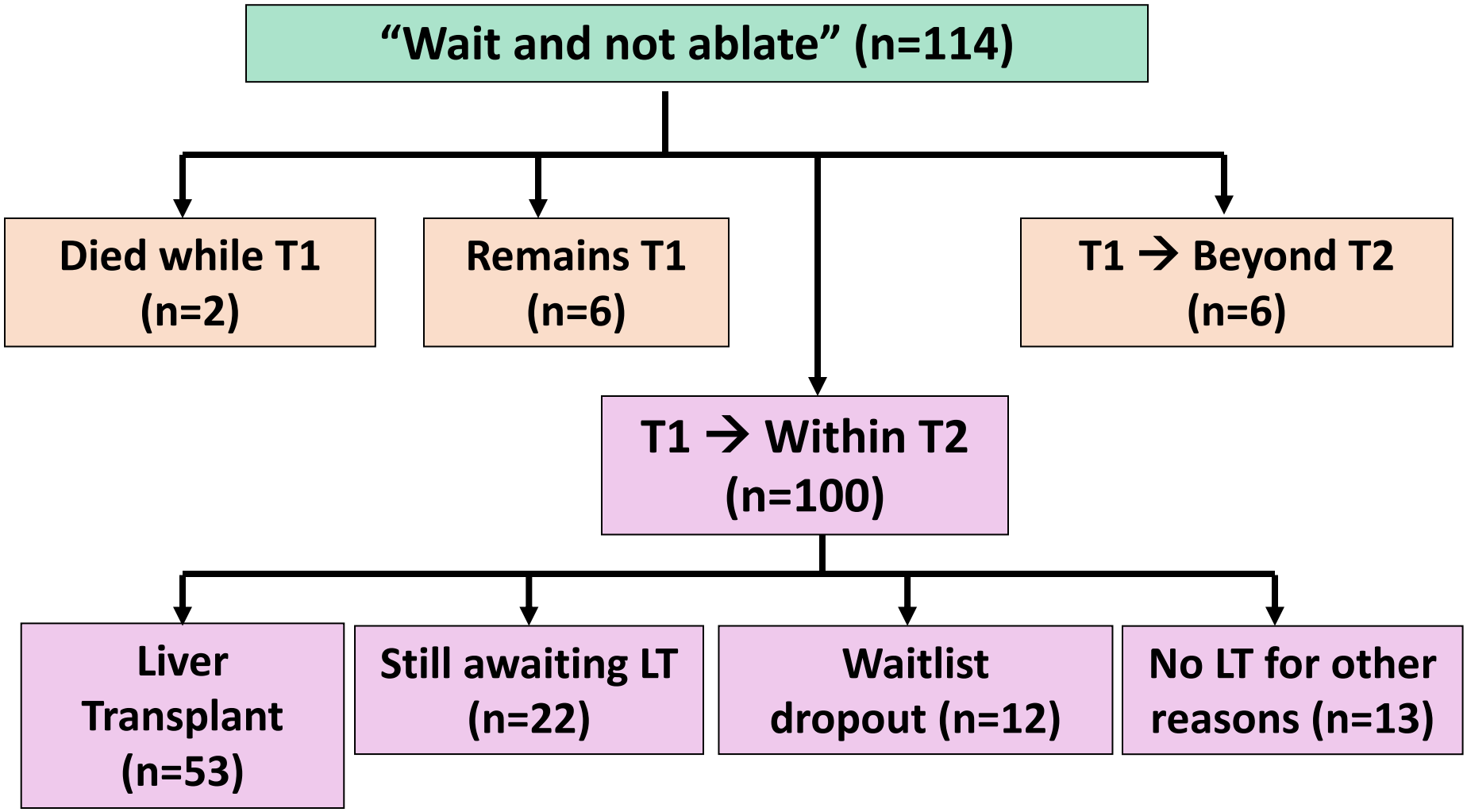


Doyle A, et al. J Hepatol 2019;70:866-873

Small HCC < 2 cm: Ablate versus Transplant

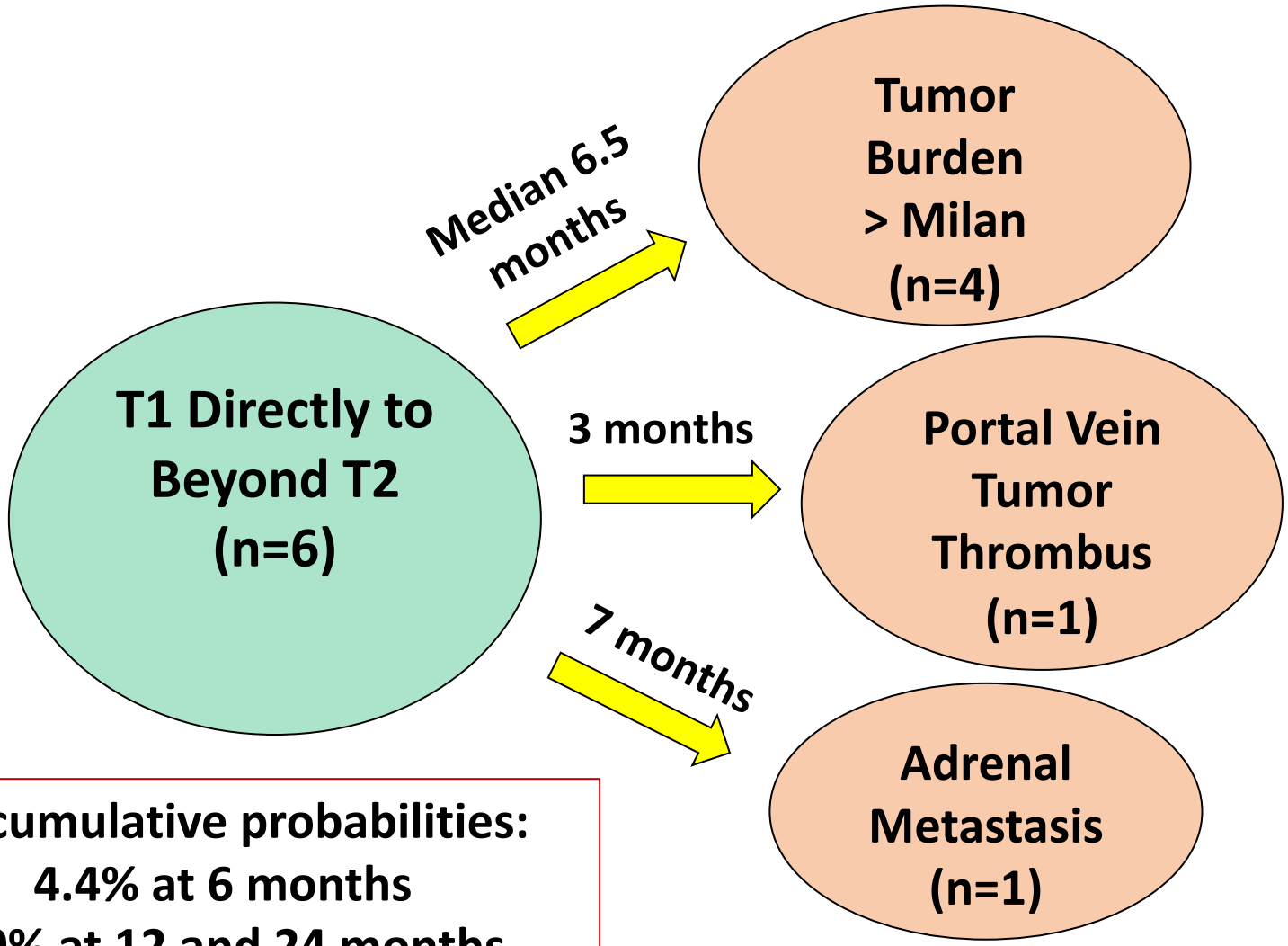


"Wait and not ablate" until T1 → T2



Mehta N, et al. Liver Transpl 2016;22:178-187

T1 (1 lesion < 2 cm) directly to Beyond Milan

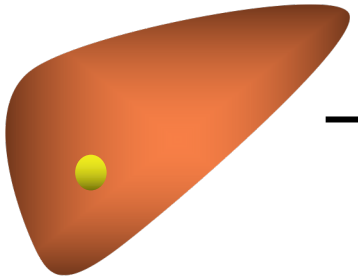


CR cumulative probabilities:
4.4% at 6 months
9.0% at 12 and 24 months

Mehta N, et al. Liver Transpl 2016;22:178-187

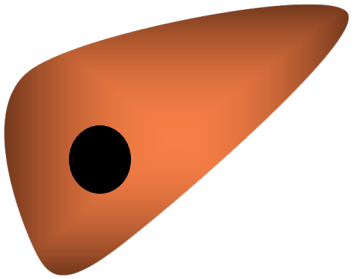
Small HCC < 2 cm: Ablate versus Transplant

1 lesion 1.5 cm



Patient has portal hypertension but normal liver function and no complications

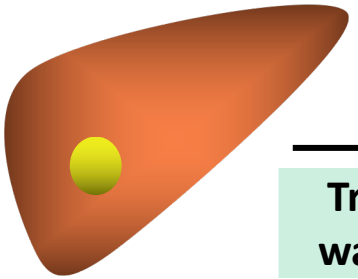
Ablation



5-yr survival (ITT) 60-70%

☑

Wait until tumor grows to 2 cm



List for LT after T2

Treat and wait for LT

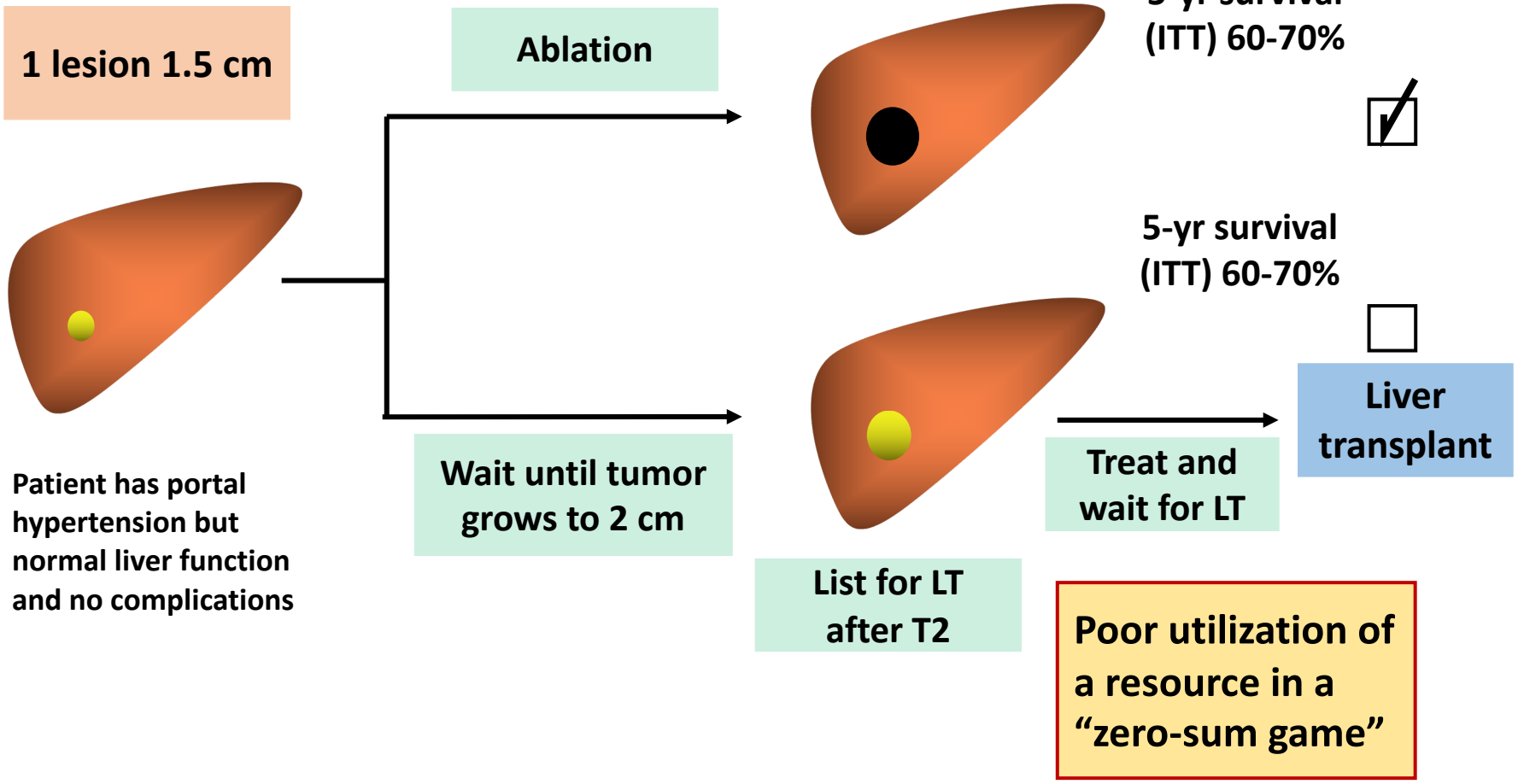
Liver transplant

5-yr survival (ITT) 60-70%

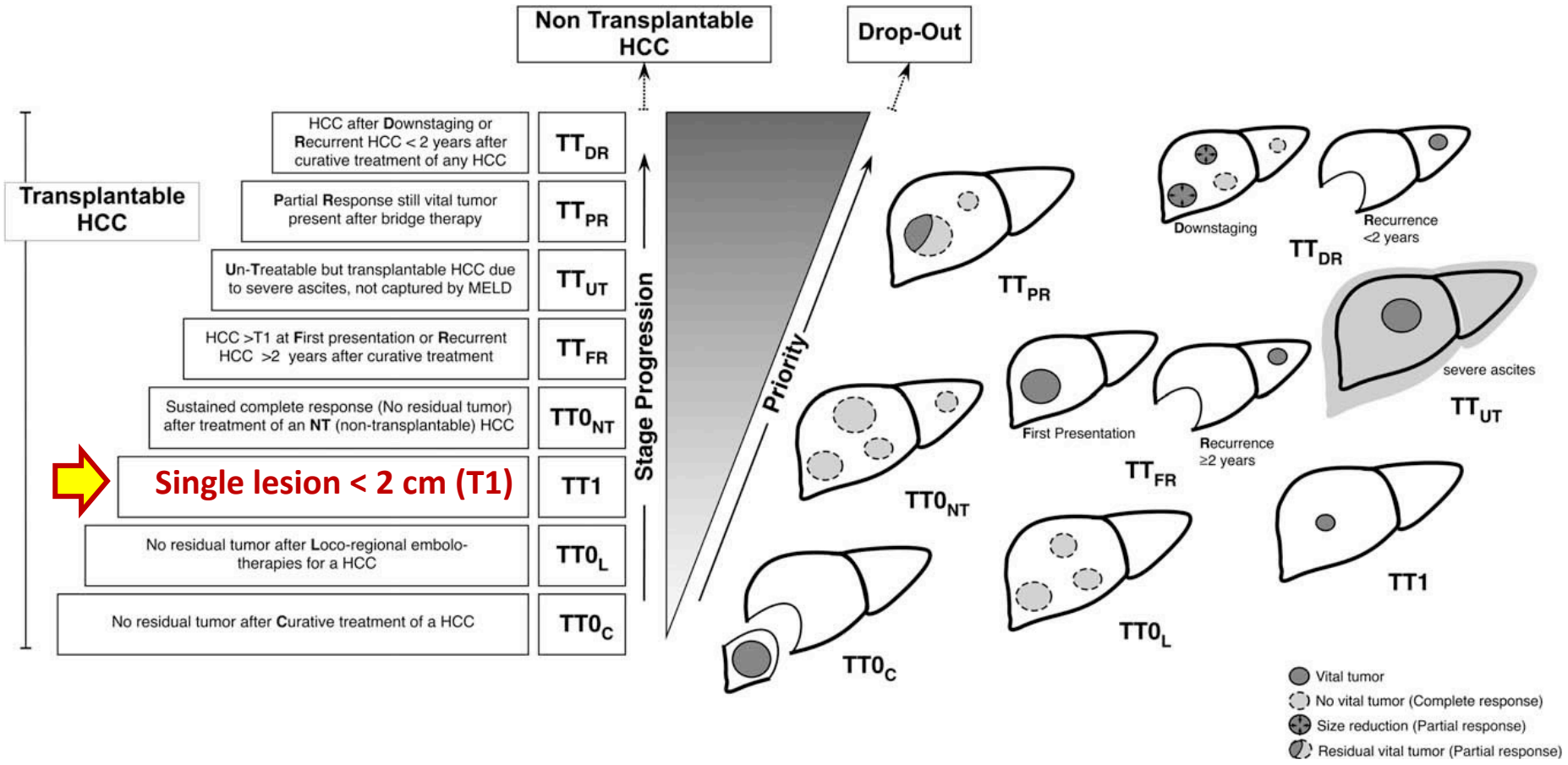
☐

Transplant Benefit marginal/very small (over the alternative treatment of ablation)

Small HCC < 2 cm: Ablate versus Transplant



Transplant benefit and priority for organ allocation



Mazzaferro V, et al. Hepatology 2016;63:1707-1717

Summary

- Ablation, not liver transplant, is recommended as treatment of choice in major guidelines for single lesion < 2 cm (very early HCC or T1 HCC).
- “Transplant benefit” marginal/ very small over ablation based on an intention-to-treat principle.
- Resource utilization must be considered in the decision of liver transplant for very small HCC < 2 cm given the increasing demand of liver transplant for HCC and the shortage of donors in a “zero-sum game”.

Thank You!

NCSCG Liver Symposium 2019

HCC and Transplant Debate #2:
YES for transplant for large tumors

Francis Yao, M.D., FAASLD

Professor of Clinical Medicine and Surgery
Director, Hepatology
Medical Director, Liver Transplantation
University of California, San Francisco

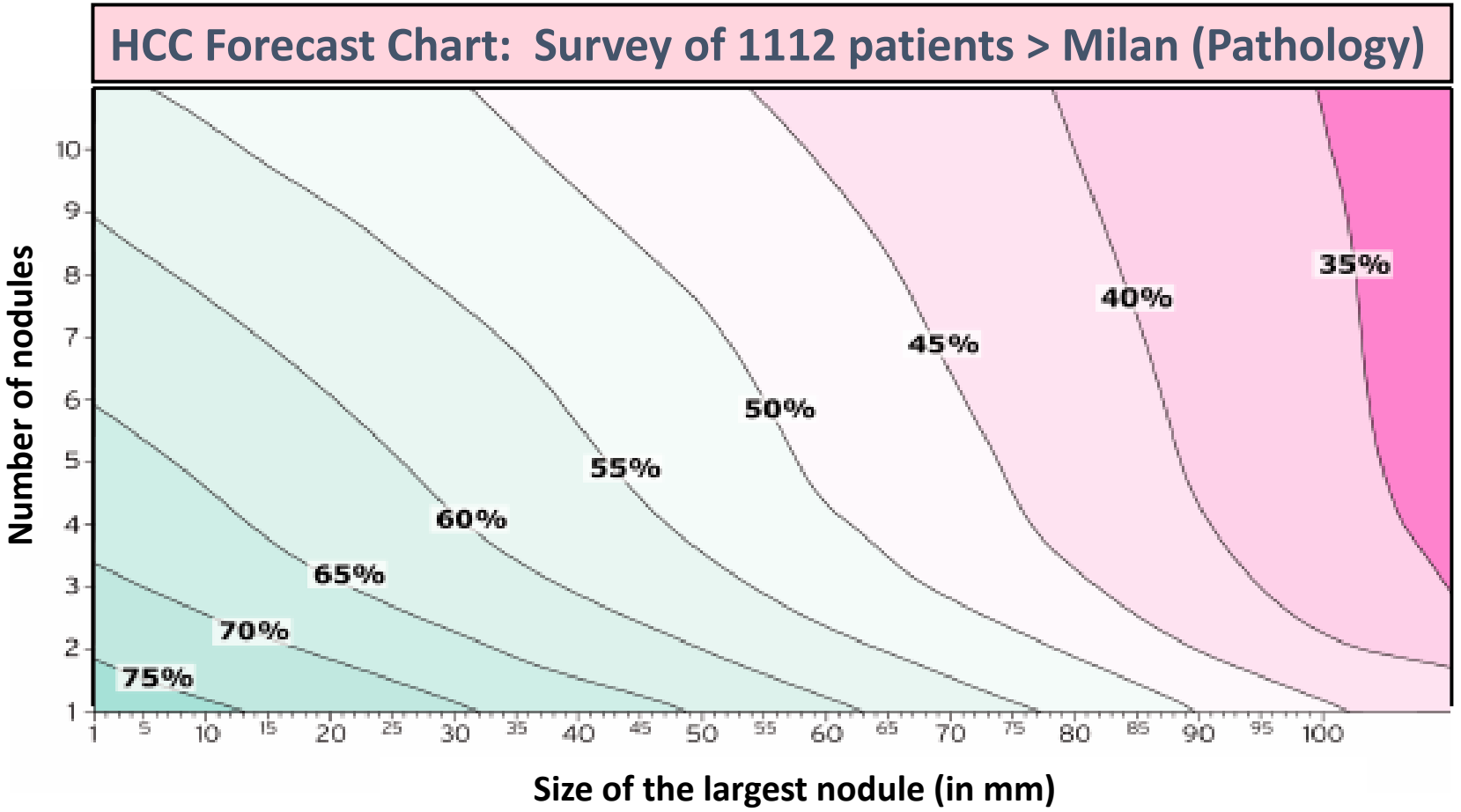
Case 2

- 55 year-old man with HCV-cirrhosis, history of sustained virologic response after anti-viral therapy, now with two hypervascular lesions with washout measuring 6.0 cm and 3.0 cm in the right lobe on MRI of the abdomen (LI-RADS 5).
- He has normal liver function (total bilirubin 1.0, INR 1.1) and no ascites or encephalopathy (Child's A cirrhosis); platelet count of 75, splenomegaly, no varices on EGD. His alpha-fetoprotein was 15. His BMI was 25.
- Debate: Transplant or no transplant

  Renu: No transplant

  Francis: Transplant (down-stage)

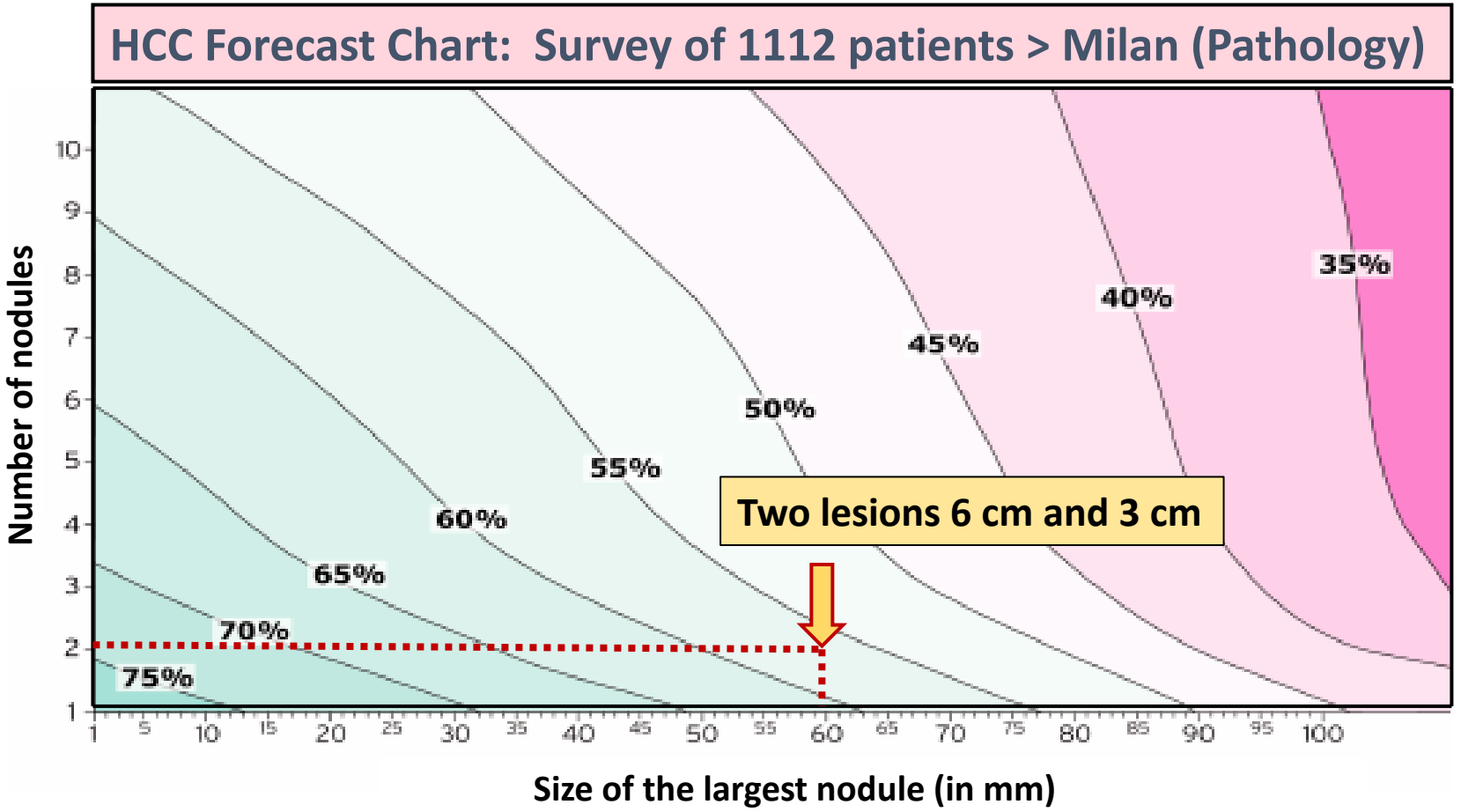
The HCC "Metro-ticket" – Tumor Size and Number



Courtesy of Dr. Vincenco Mazzaferro, with permission

Mazzaferro et al. Lancet Oncology 2009;10:35-43

The HCC "Metro-ticket" – Tumor Size and Number

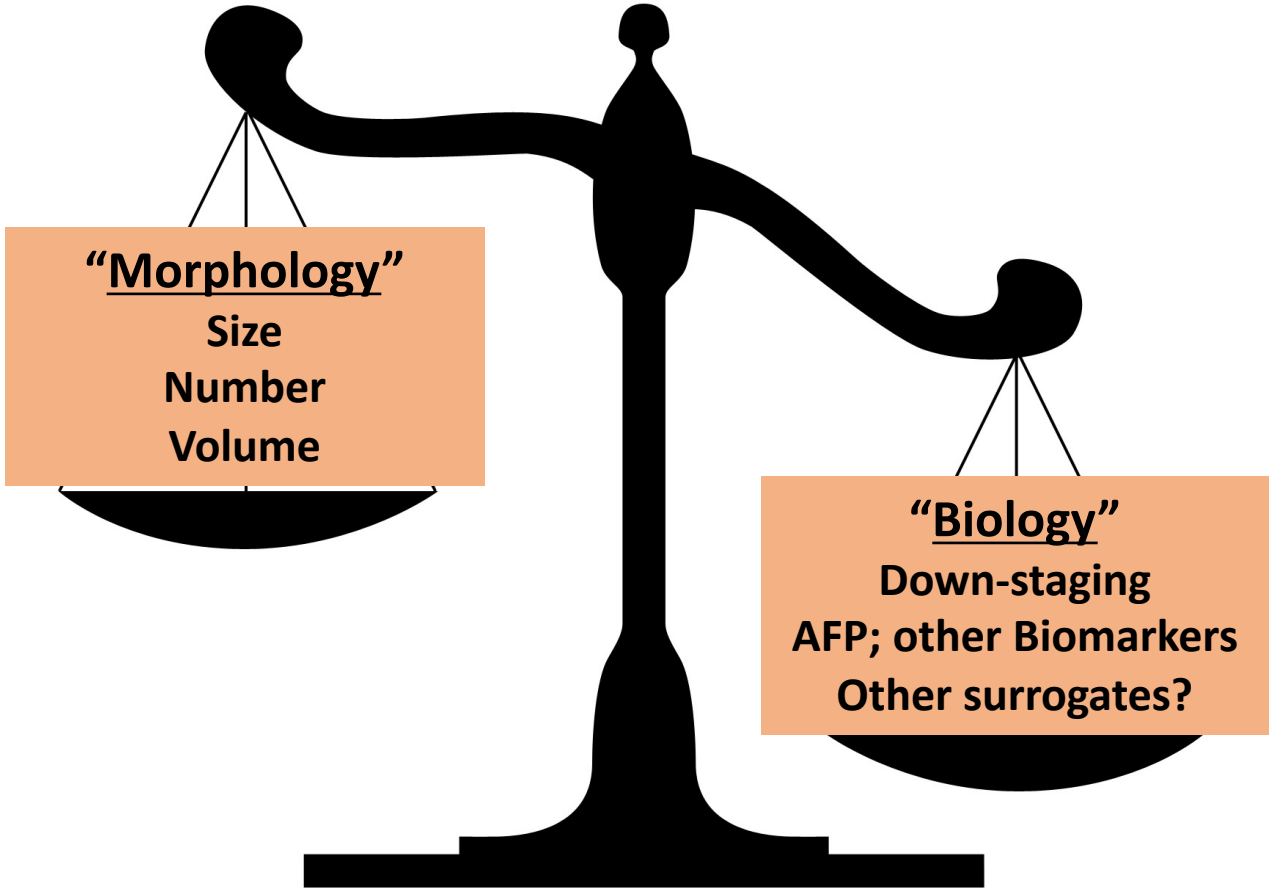


Courtesy of Dr. Vincenco Mazzaferro, with permission

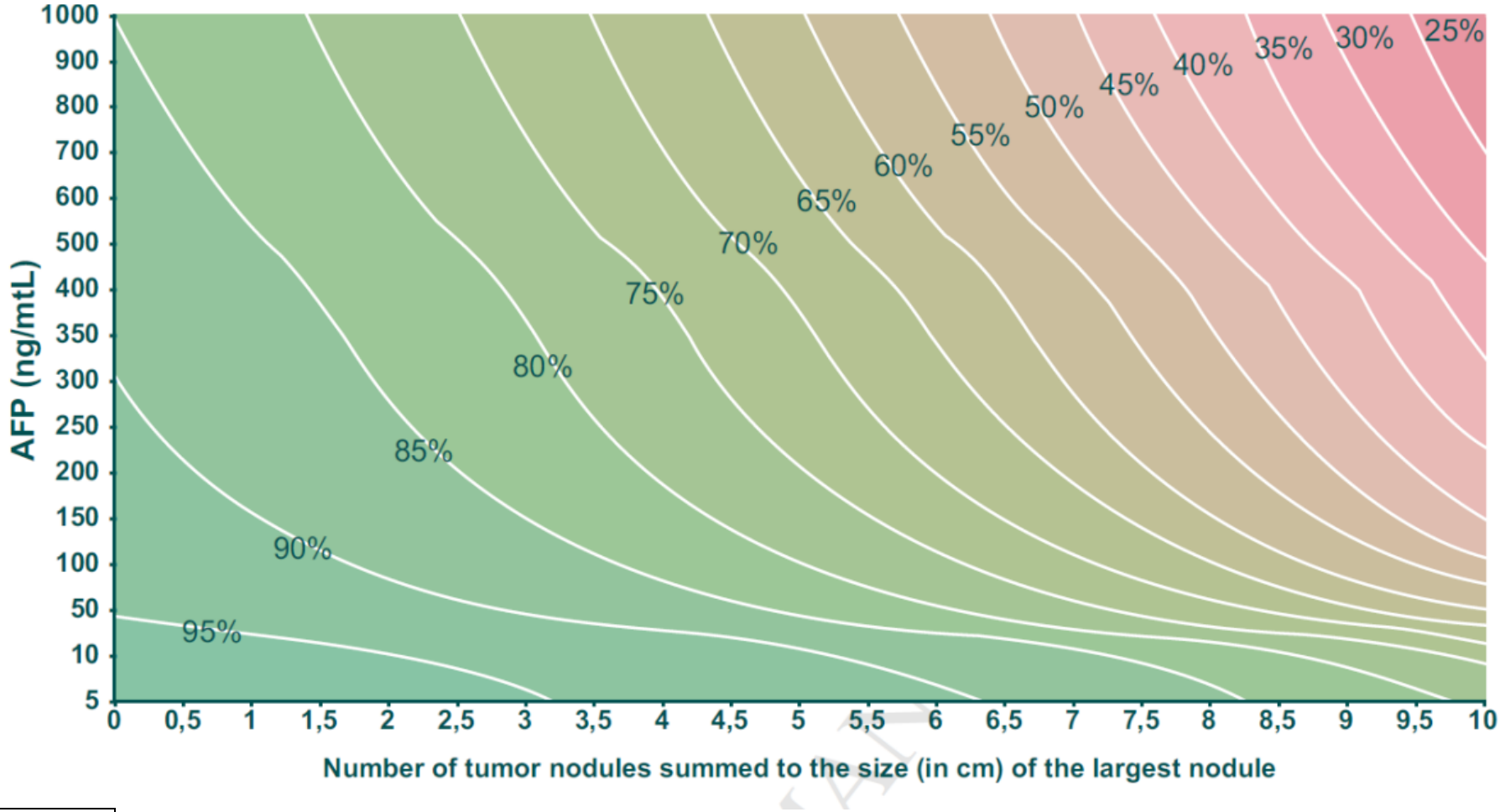
Mazzaferro et al. Lancet Oncology 2009;10:35-43

Liver Transplant for HCC

Changing views on Selection Criteria

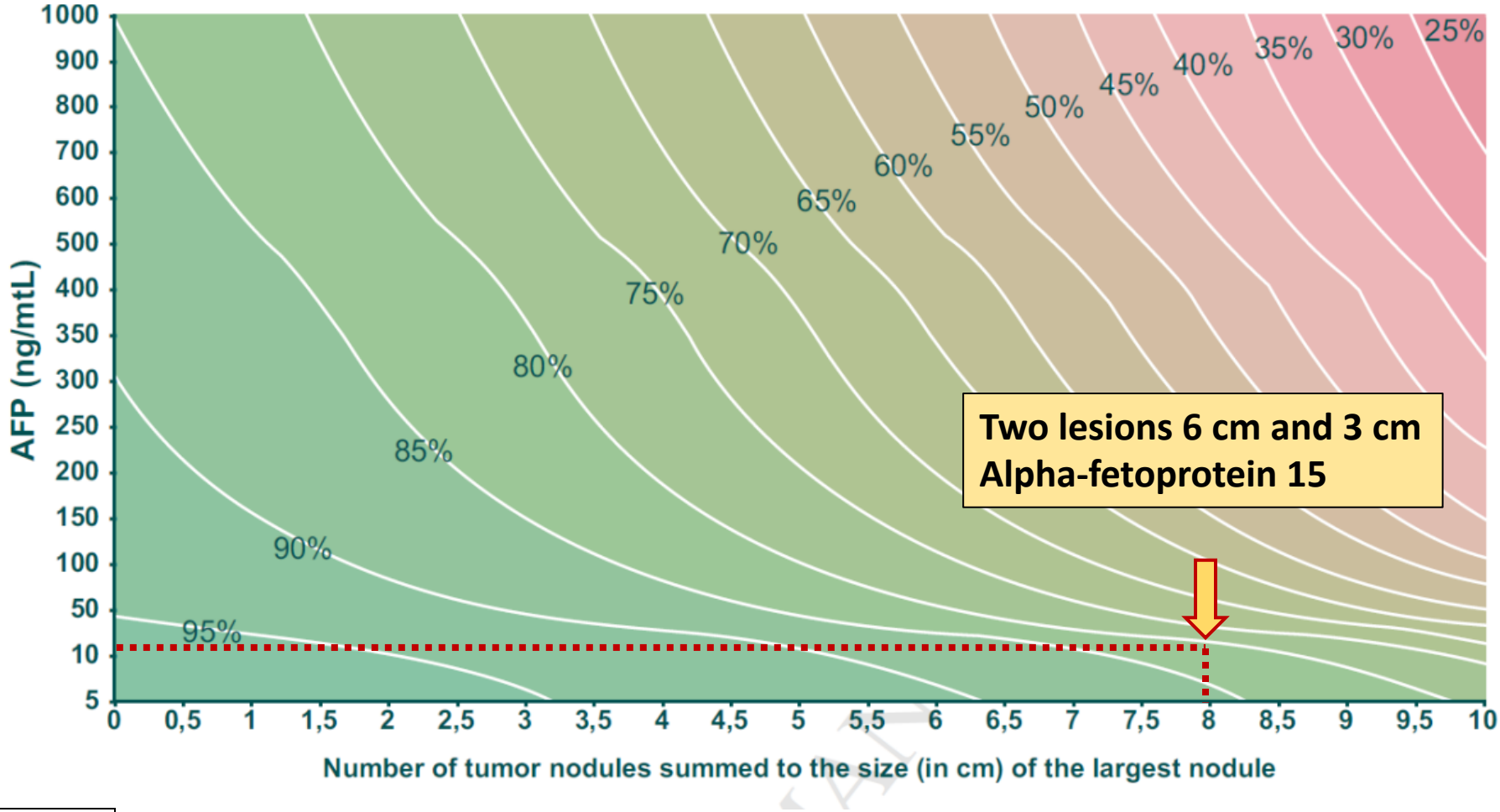


Metro-ticket 2.0: AFP + Tumor Burden



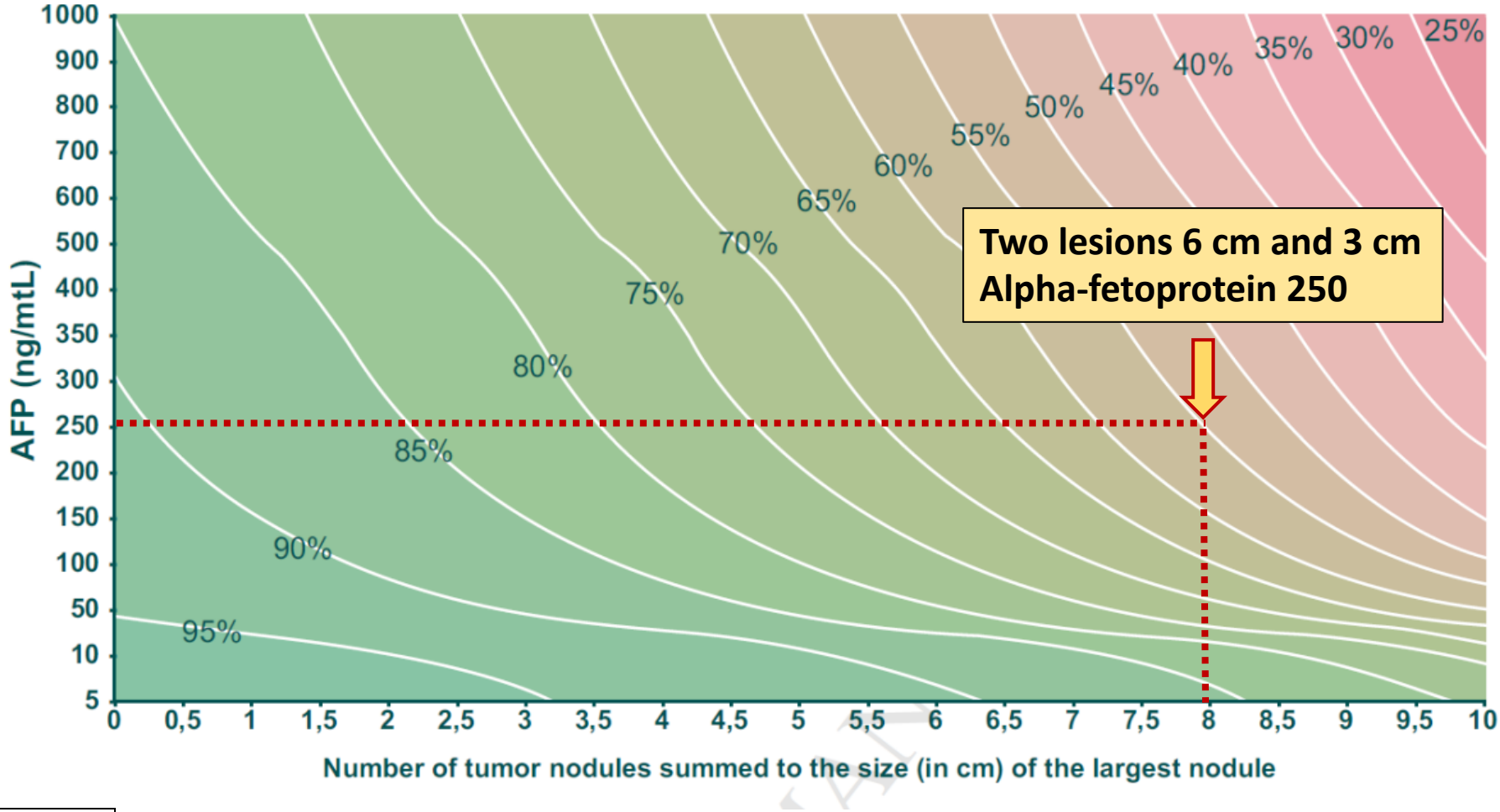
Mazzaferro et al. Gastroenterology 2018;154:128-139

Metro-ticket 2.0: AFP + Tumor Burden



Mazzaferro et al. Gastroenterology 2018;154:128-139

Metro-ticket 2.0: AFP + Tumor Burden



Mazzaferro et al. Gastroenterology 2018;154:128-139

Pre-transplant Prognostic Models (selected)

Pre-Transplant Selection	Tumor Burden	Biomarkers	AUROC
US National Policy [1,2]	Milan or Down-staged to Milan	No AFP ≥ 1000 (reduced to < 500)	
French AFP Model [3]	Largest tumor Size and total number	AFP	0.7
Metro-ticket 2 [4]	Largest tumor Size and total number	AFP	0.72
HCC-HALT* [5]	Tumor burden score (size and number)	AFP	0.61
TTV + AFP [6]	TTV ≤ 115 cm^3	AFP ≤ 400 ng/ml	
Pre-MORAL [7]	Largest tumor size	AFP, NLR	0.82

**Include MELD-Na*

1. Yao FY, et al. Hepatology 2015;61:1968-1977
2. Hameed B. et al. Liver Transpl 2014;20:945-951
3. Duvoux et al. Gastroenterology 2012;143:986-94
4. Mazzaferro et al. Gastroenterology 2018;154:128-139
5. Sasaki et al. Lancet Gastroenterol Hepatol 2017; 2:595-603
6. Toso et al. Hepatology 2015;62:158-165
7. Halazun KJ, et al. Ann Surg 2017;265:557-564

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]

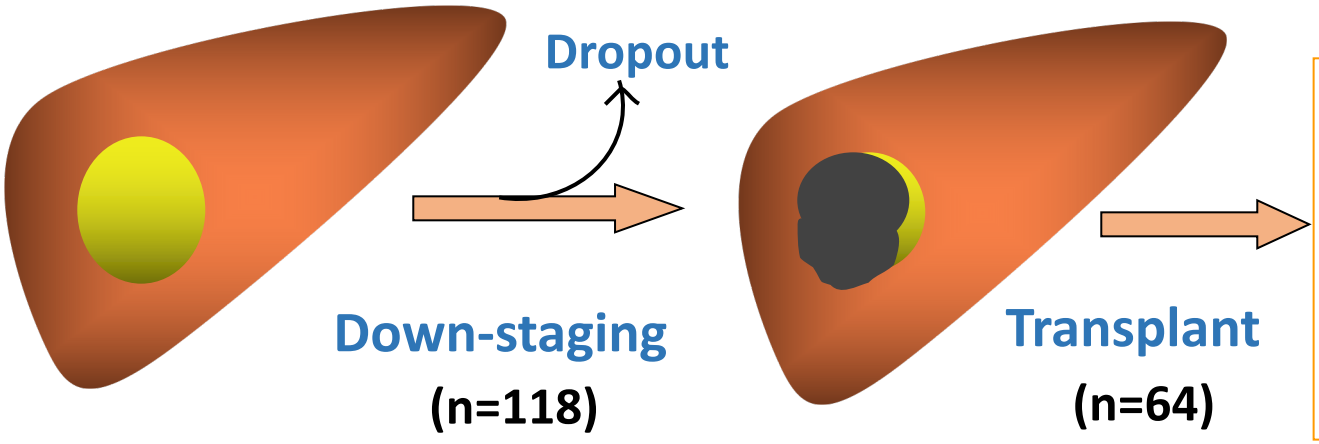
1. Yao & Fidelman. Hepatology 2016;63:1014-1025

2. EASL Guidelines - Briux J. et al. J Hepatol 2001;35: 421–430

UCSF Down-Staging Protocol for Transplant

Minimum observation 3 months

Meeting Milan criteria



(n=41)

Dropout

Down-staging

(n=118)

Transplant

(n=64)

Median f/u 3.8 years

- 5 HCC recurrence (8%)
- 78% 5-yr survival post-transplant
- 91% 5-yr recurrence free probability
- 56% 5-yr intention-to-treat survival

Inclusion Criteria for Down-staging

1 tumor ≤ 8 cm

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

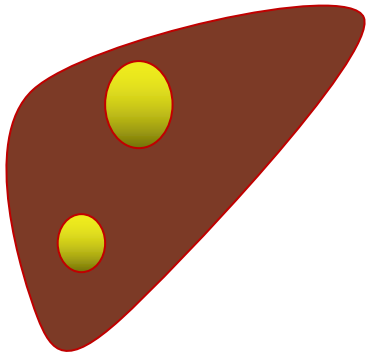
4-5 tumor ≤ 3 cm + total diameter ≤ 8 cm

→ US national policy

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

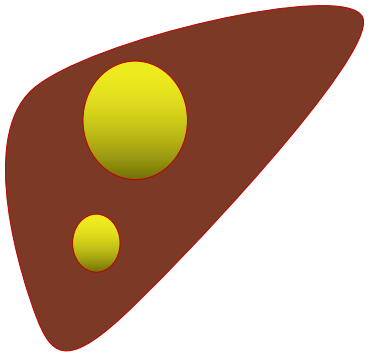
HCC Transplant Criteria at UCSF

Two lesions 6 cm & 3 cm
Outside these criteria



UCSF Down-staging Criteria

- 1 lesion 5.1-8 cm
- 2-3 lesions ≤ 5 cm
- 4-5 lesions ≤ 3 cm
- Total Tumor Diameter ≤ 8 cm
- No extra-hepatic disease

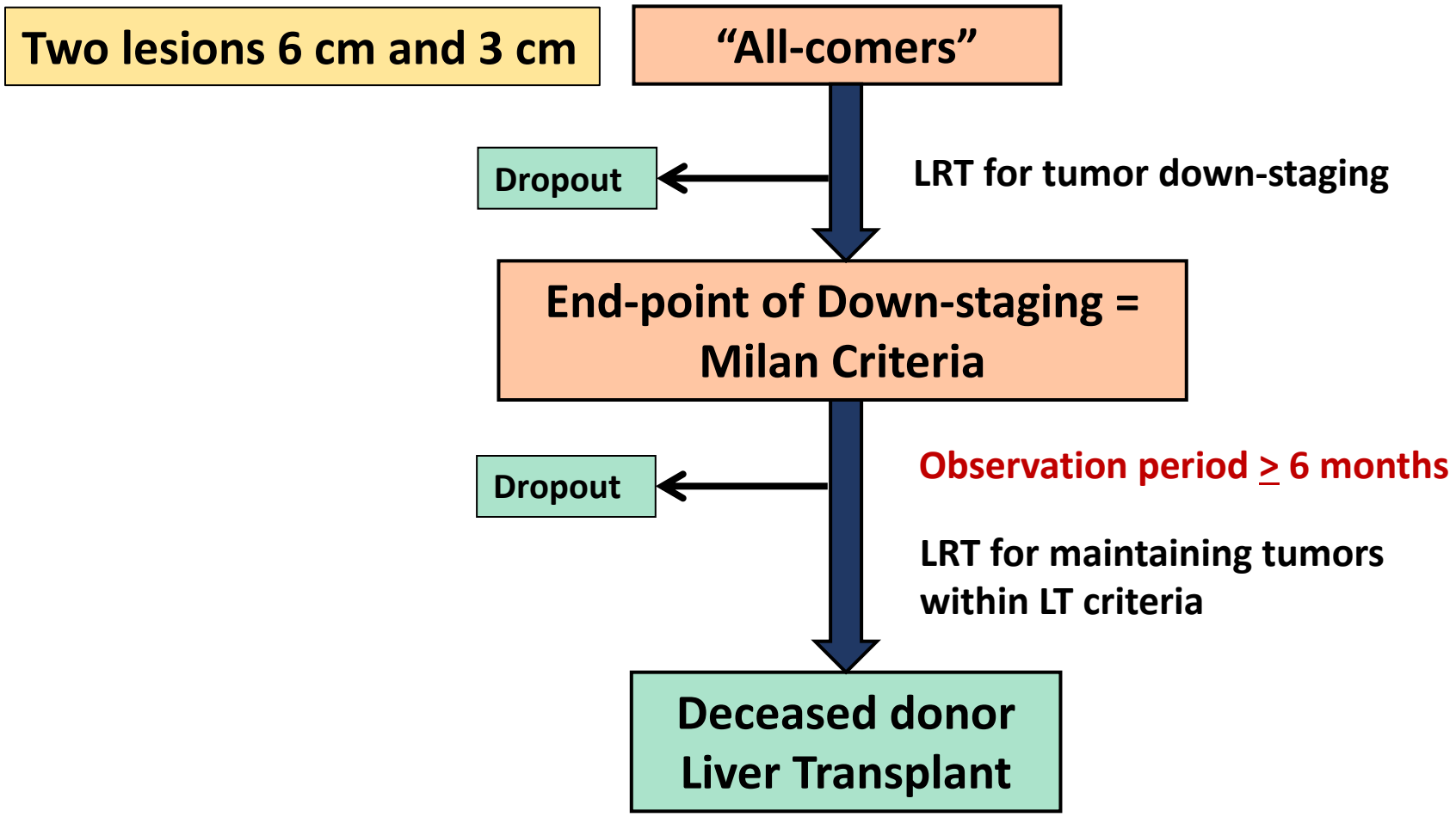


UCSF "All-Comers" Criteria

- Any number of tumors
- Total Tumor Diameter > 8 cm
- No extra-hepatic disease

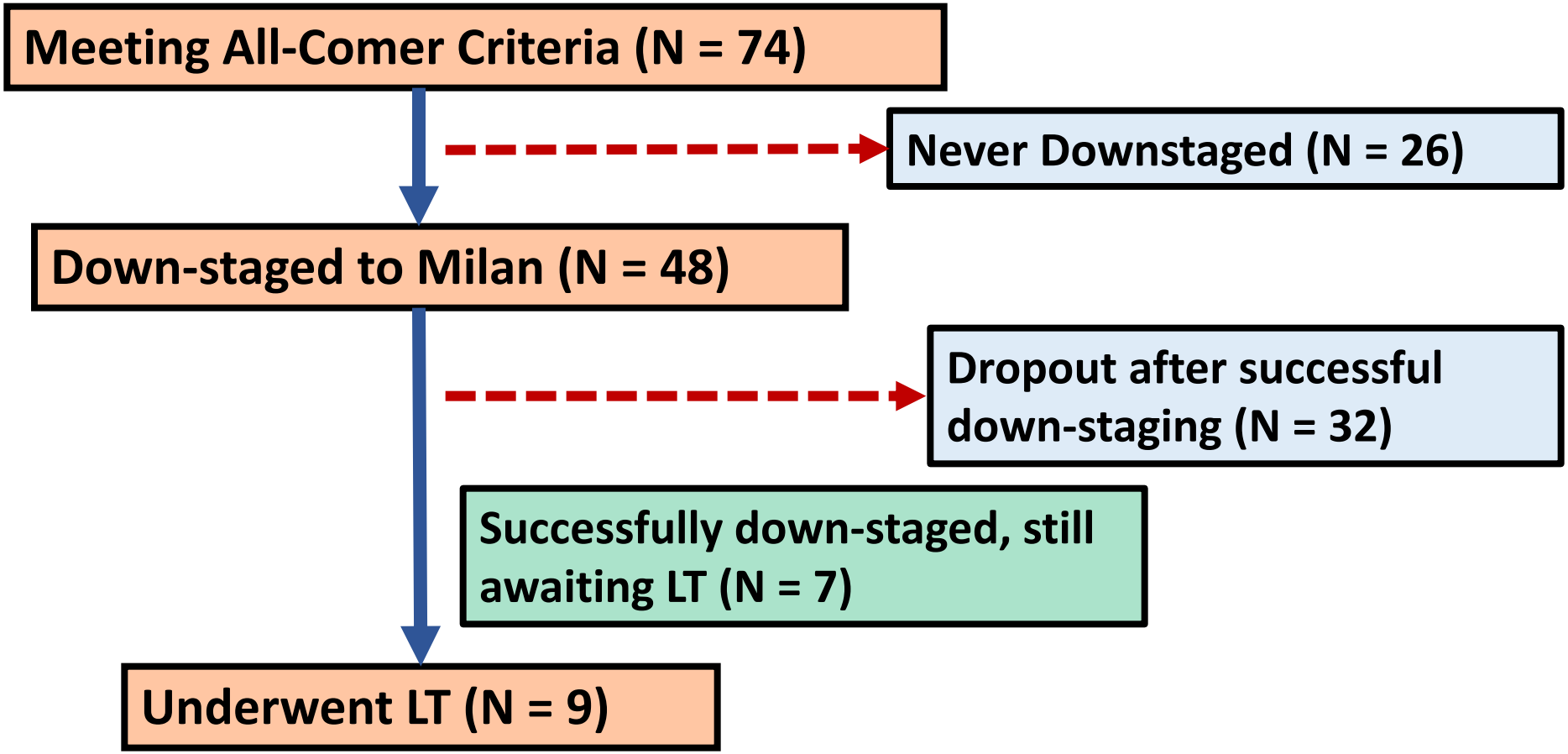
Require longer period of observation after down-staging (6 months)

“All-comers” Down-staging Protocol



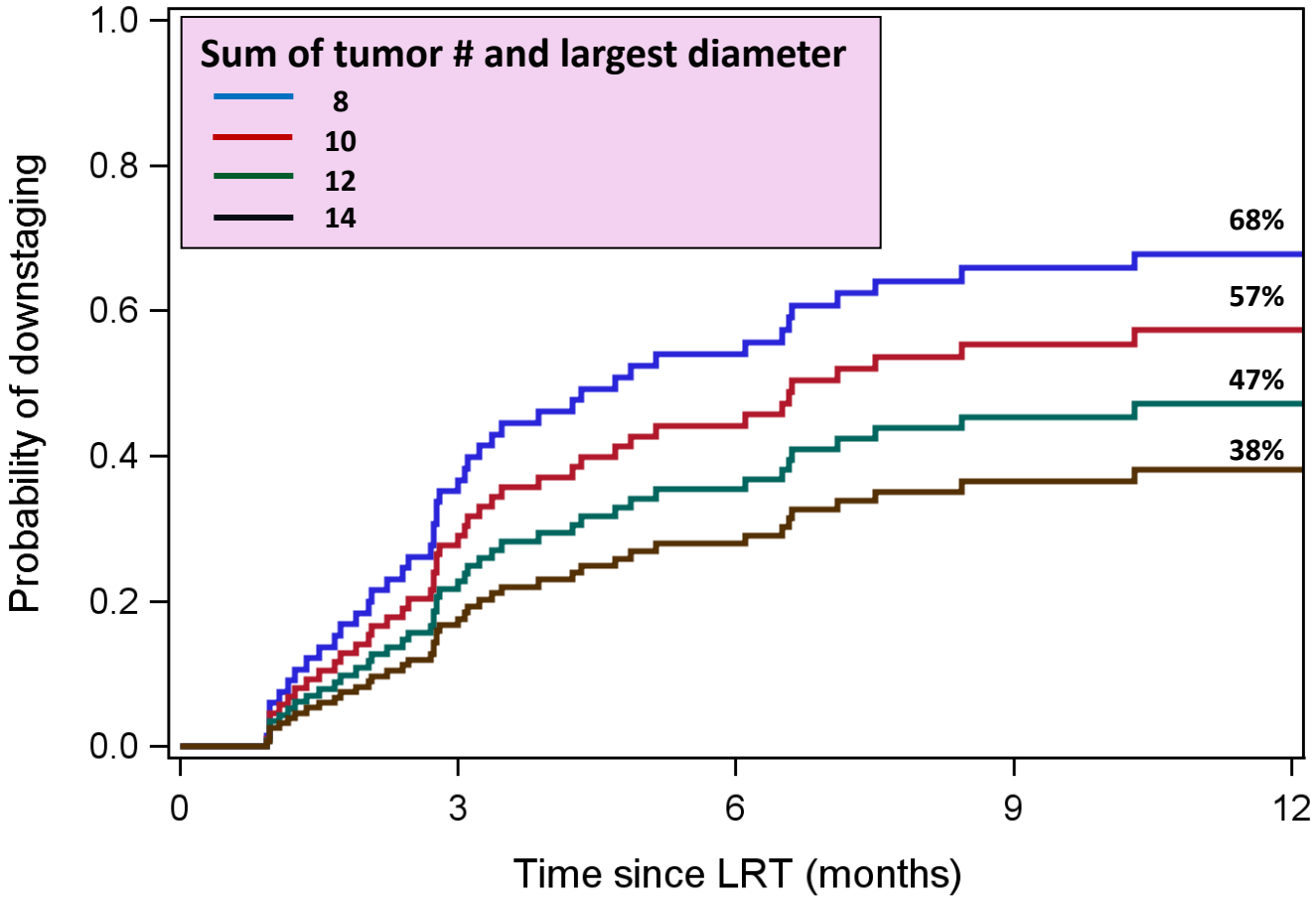
Sinha J et al. Hepatology 2019;70:1185-1196

“All-comers” Down-staging Protocol



Sinha J et al. Hepatology 2019;70:1185-1196

Probability of Down-staging (all-comers)



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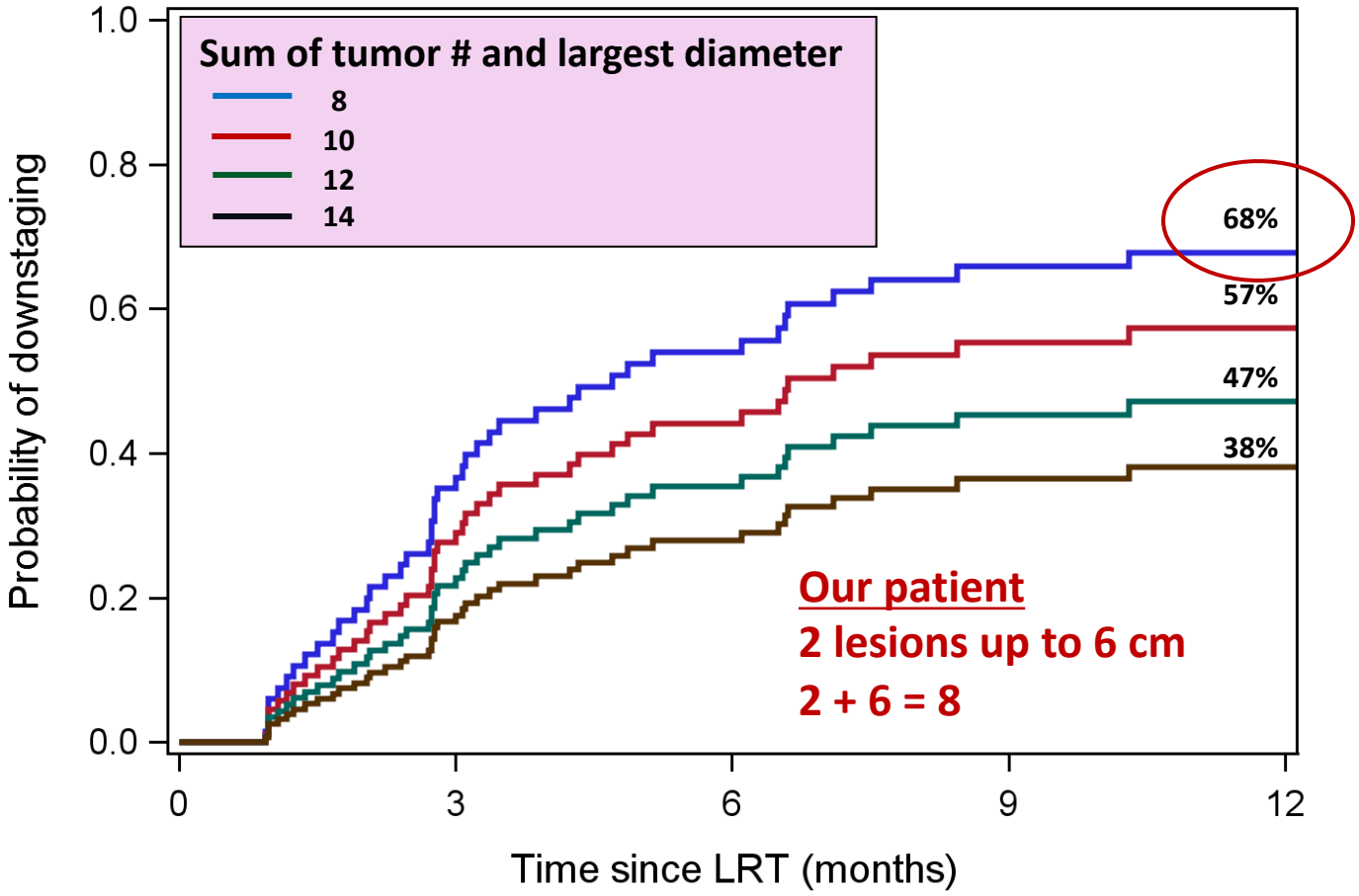
Probability of Down-staging (all-comers)



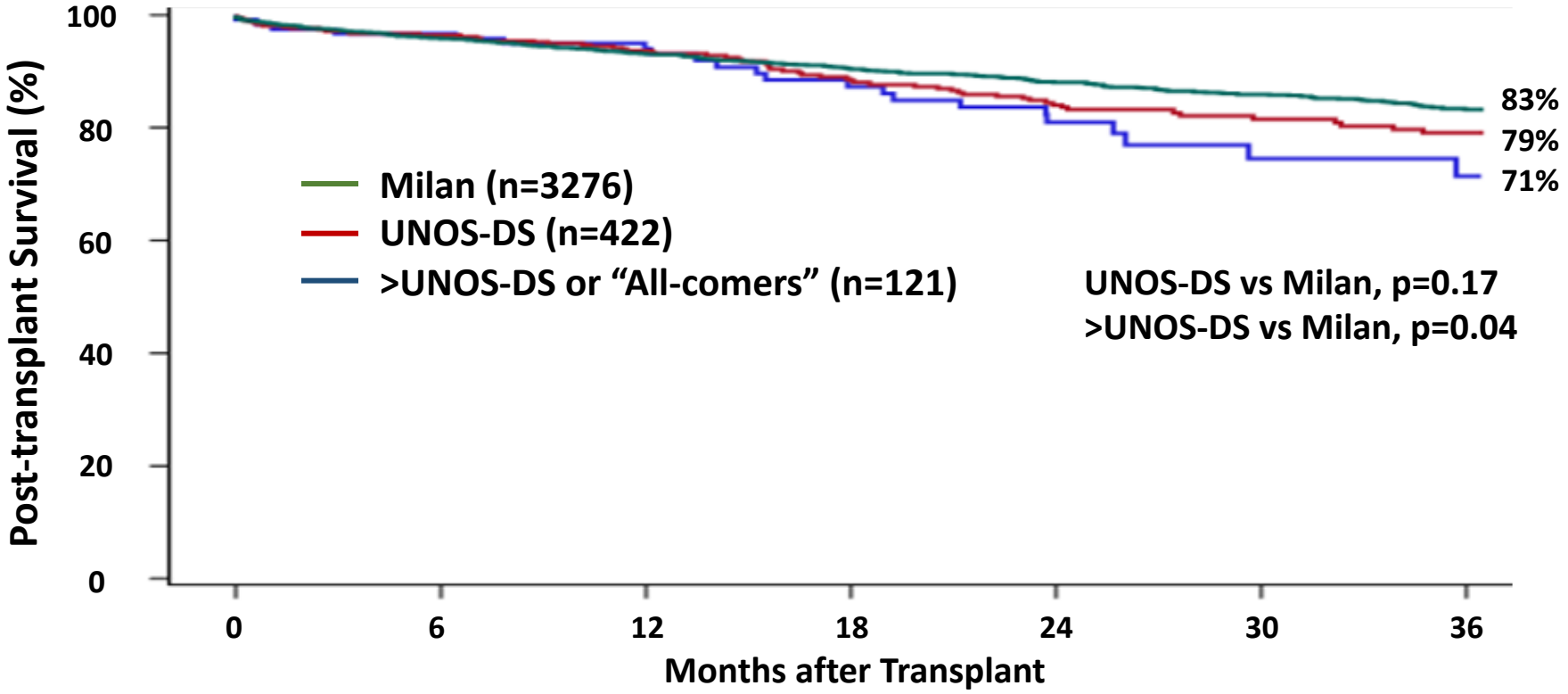
Sinha J et al. Hepatology 2019;70:1185-1196

“All comers” Down-Staging Protocol

- A subset of patients in the “all-comers” group may benefit from liver transplant
- There are upper limits in tumor burden beyond which successful liver transplant after down-staging becomes an unrealistic goal
- Strategies to shorten waiting time (high-risk donors) or living donor liver transplant

Post-transplant survival after down-staging

The effects of initial tumor burden



UCSF/ UNOS-down-staging Inclusion Criteria

1 tumor ≤ 8 cm

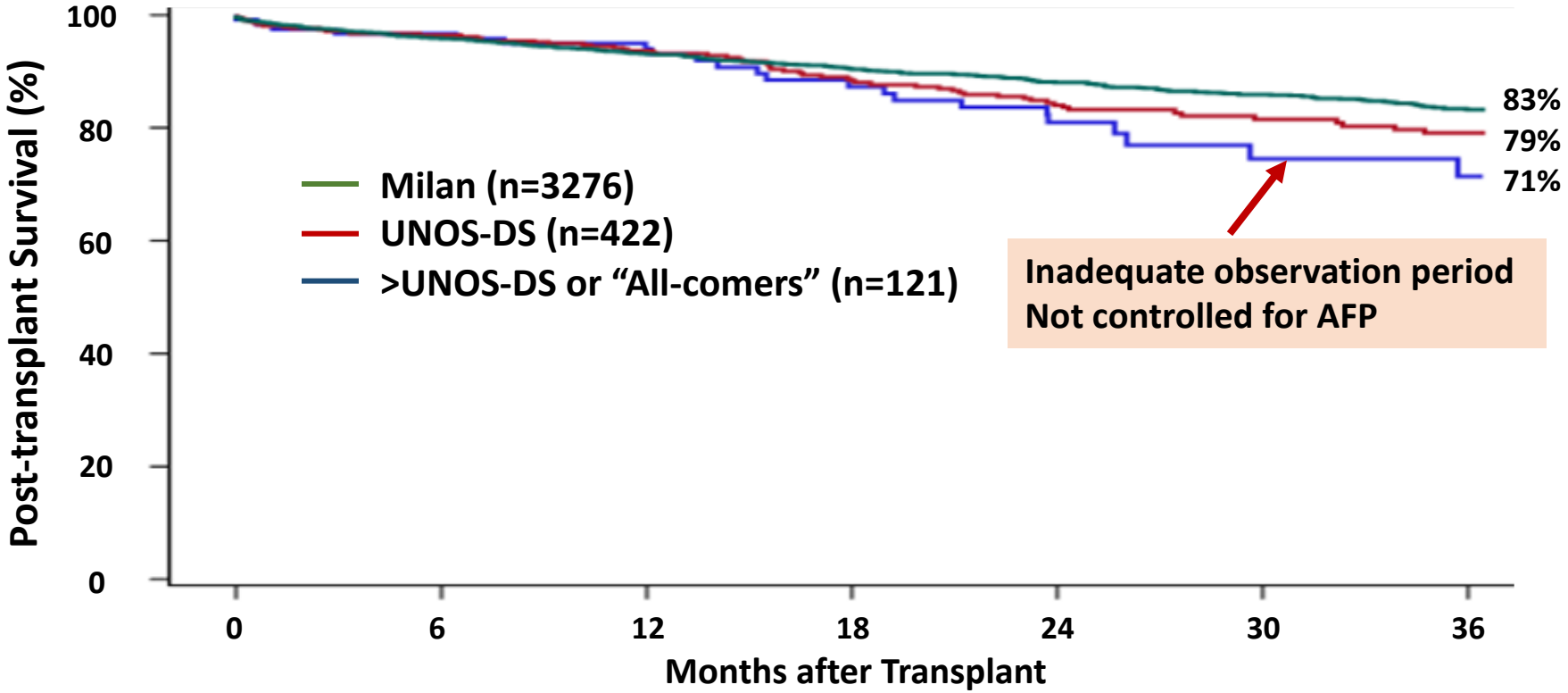
2-3 tumor ≤ 5 cm + total diameter ≤ 8 cm

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

Mehta N, et al. Hepatology [Epub]

Post-transplant survival after down-staging

The effects of initial tumor burden



UCSF/ UNOS-down-staging Inclusion Criteria

1 tumor ≤ 8 cm

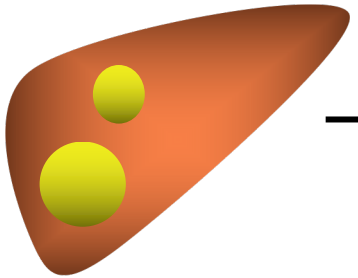
2-3 tumor ≤ 5 cm + total diameter ≤ 8 cm

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

Mehta N, et al. Hepatology [Epub]

Large tumors: Transplant or no transplant?

2 lesion 6 cm & 3 cm, AFP 15

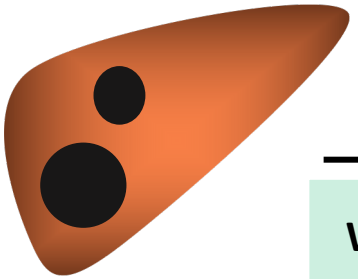


No transplant; TACE or Y-90 for "palliation"

5-yr survival 20-30%

☐

Down-staging



List for LT if successful down-staging to Milan

Wait for LT

☑

Liver transplant

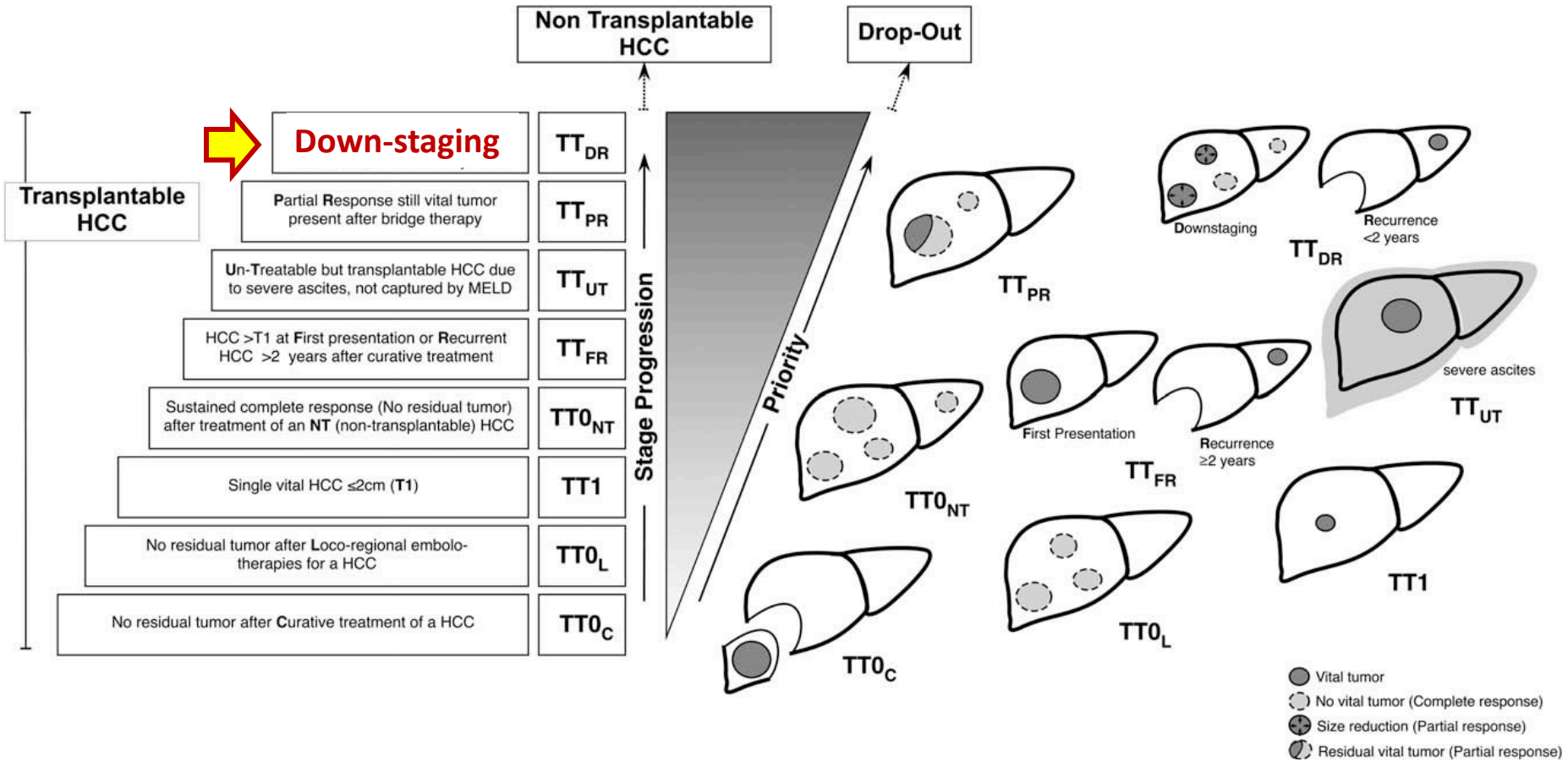
5-yr post-LT survival 70%

Tumor progression & dropout (selection)

Dropout due To long wait-time

Transplant benefit high (compared to alternatives)

Transplant benefit and priority for organ allocation



Mazzaferro V, et al. Hepatology 2016;63:1707-1717

Summary

- Paradigm shift in patient selection for liver transplant, incorporating response to local regional therapy/ down-staging and tumor markers (AFP) and not relying solely on tumor burden.
- Based on initial tumor burden in this case, at least 2/3 probability of successful down-staging to Milan.
- “Transplant benefit” high after successful down-staging for large tumors vs palliative TACE or Y-90 radioembolization.

Thank You!