How Far is Too Far in HCC for Liver Transplantation?

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Sept 23rd 2023

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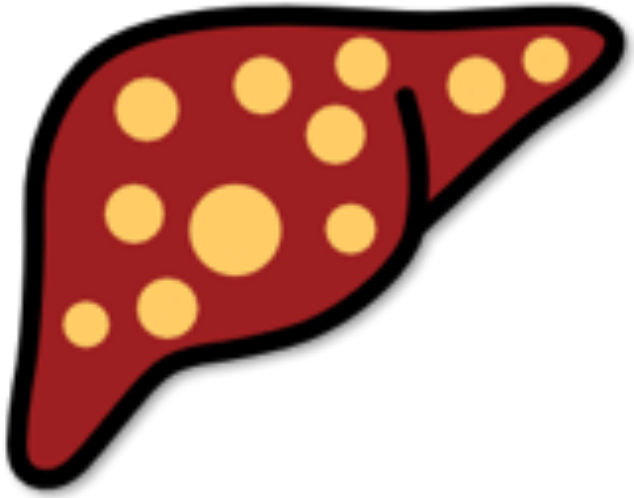
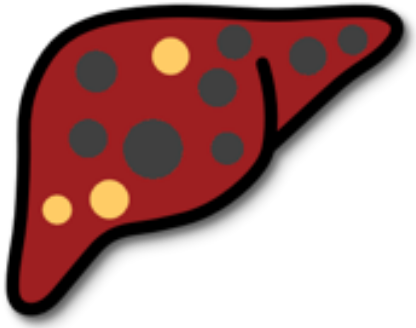
Disclosures

- Bayer
- Boston Scientific
- AstraZeneca

Case # 1



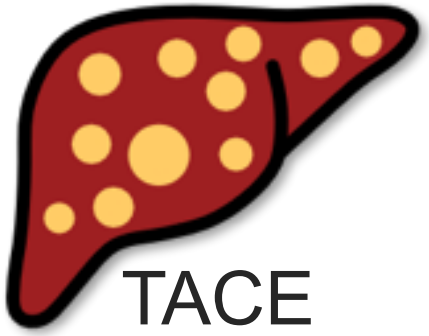
- 61 M HCV cirrhosis
- Multiple lesions outside of UCSF criteria
- AFP 500



TACE

AFP 40

Within MC



TACE

AFP 700

Progression of disease

Acceptable criteria for liver transplant?

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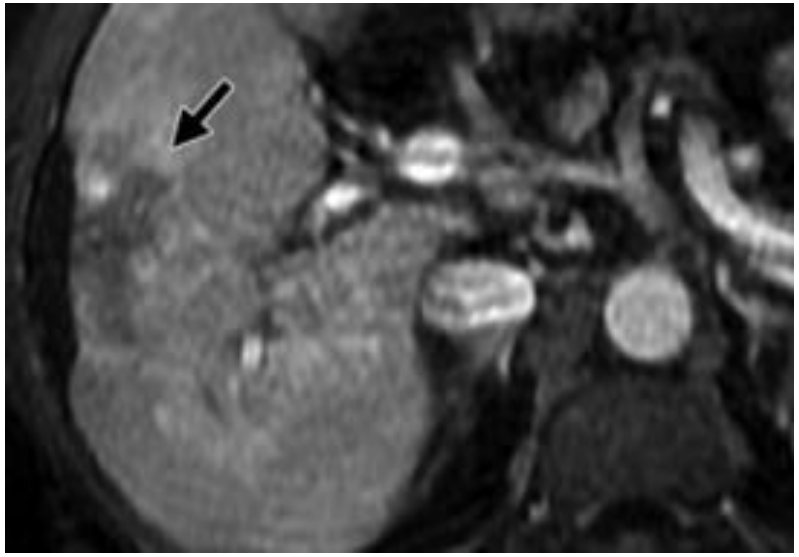
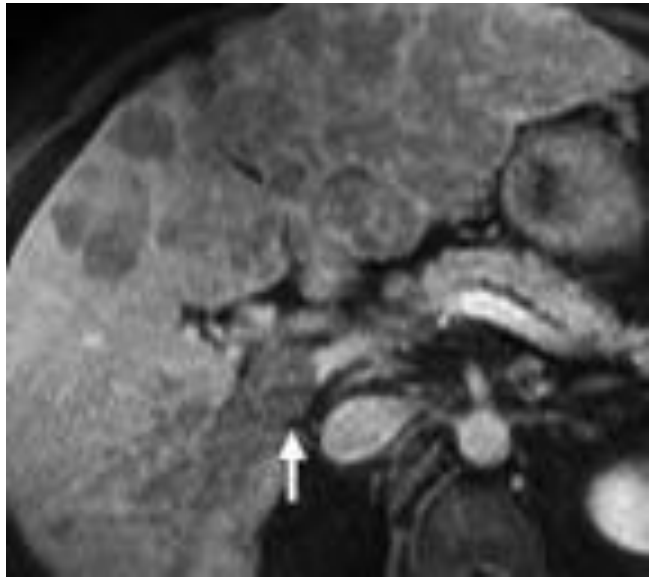
Case # 2



SBRT
AFP <20
Within MC
14 months



- 58 M ETOH cirrhosis
- Infiltrating HCC, no extrahepatic spread
- AFP 18,000

Acceptable criteria for liver transplant?

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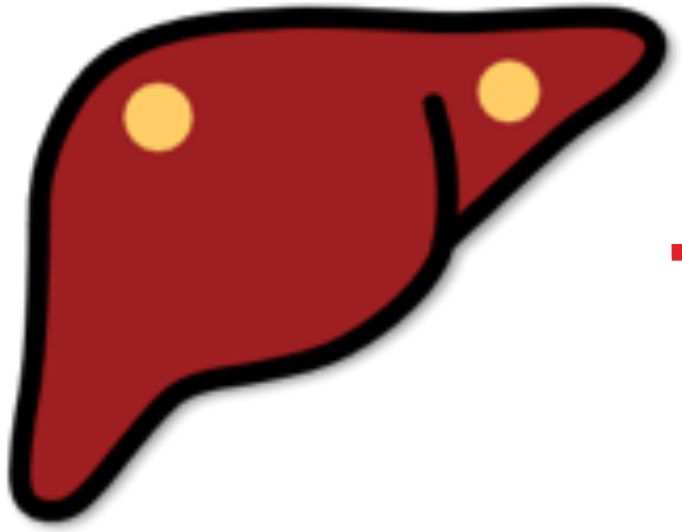
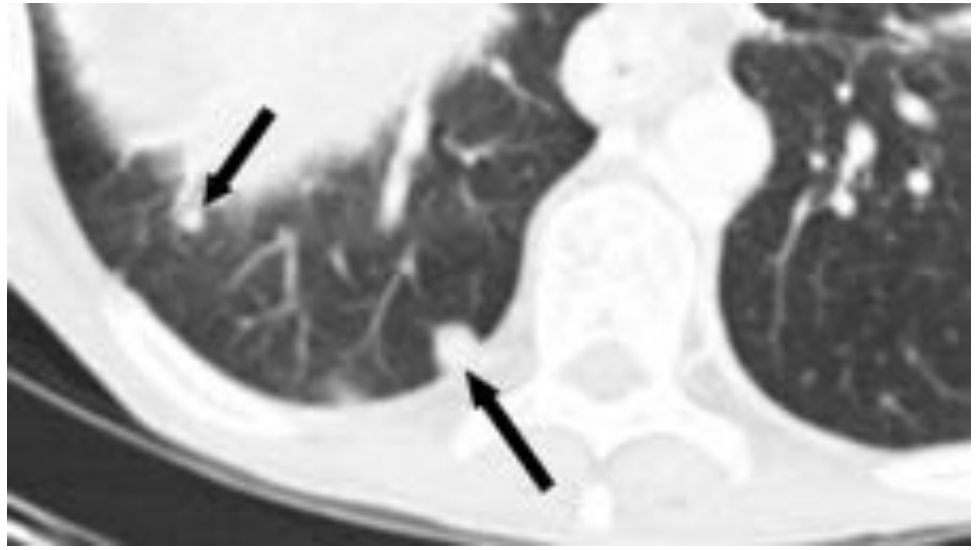
Case # 3





- 58 M NASH cirrhosis
- 2 x HCC within MC
- AFP 50, Y 90
- Recurrence 1 year later, 3 cm HCC TARE

- Treatment with IO
- Complete response for 1.5 years

Acceptable criteria for liver transplant?

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ANNALS OF SURGERY

Vol. 202 October 1985 No. 4

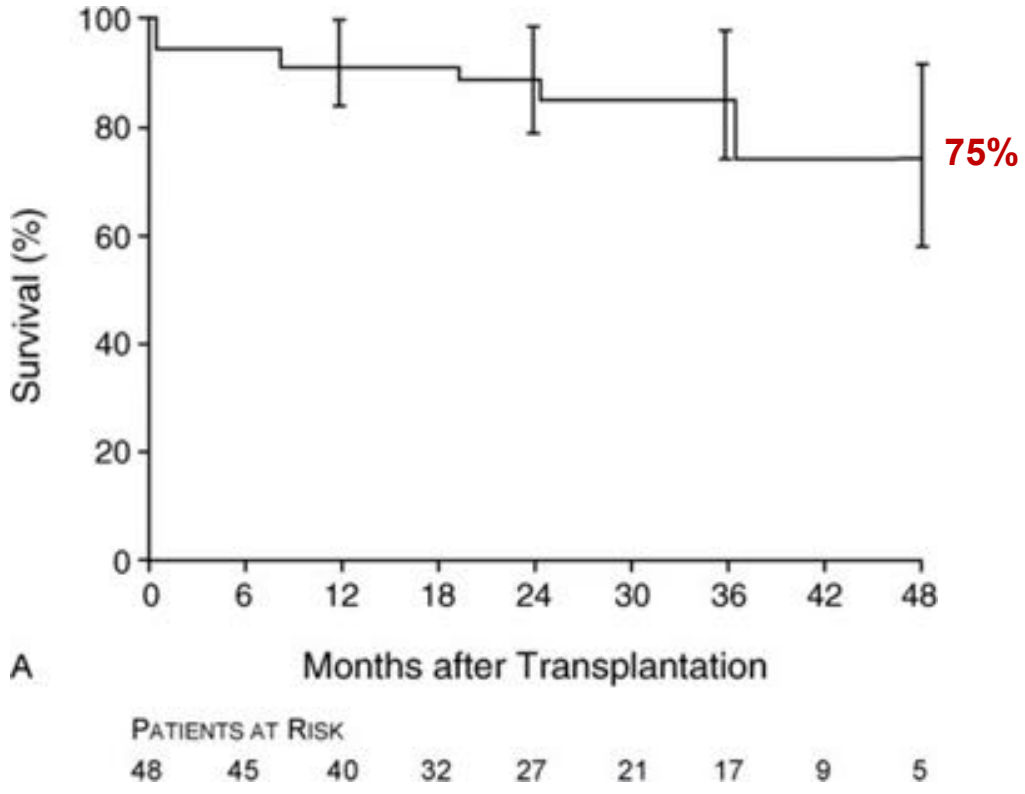
Role of Liver Transplantation in Cancer Therapy

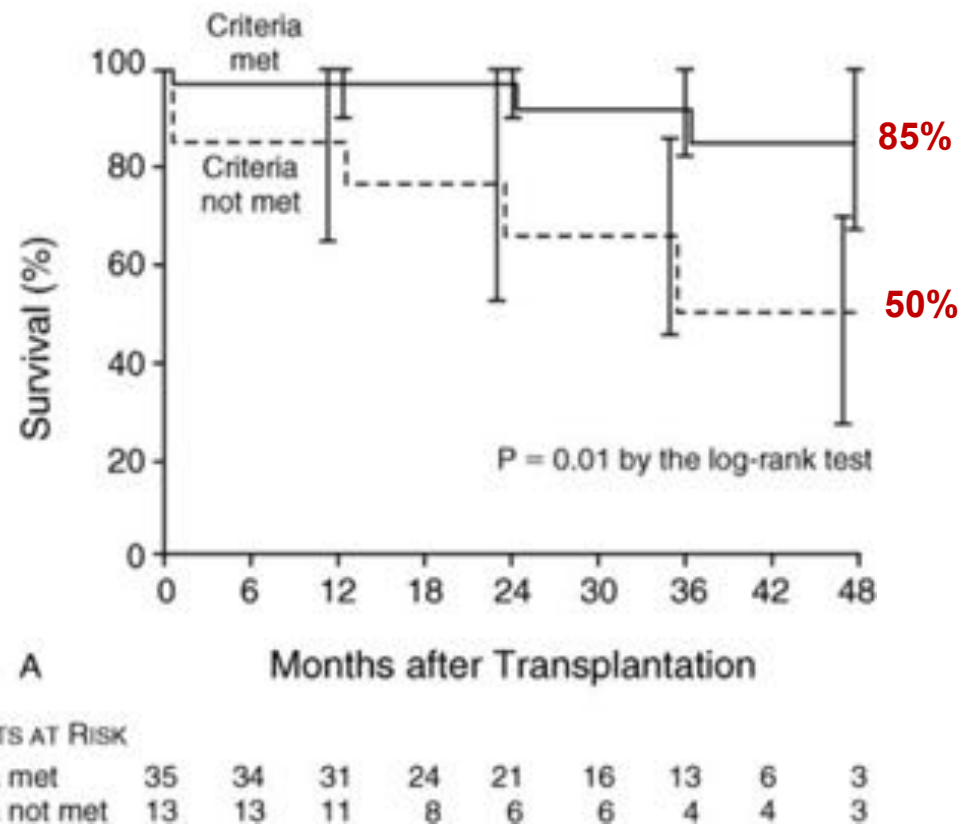
SHUNZABURO IWATSUKI, M.D., ROBERT D. GORDON, M.D., BYERS W. SHAW, JR., M.D.,
THOMAS E. STARZL, M.D., PH.D.

- 72 % Recurrence rate for HCC
- Median 8 months RFS

Moratorium on liver transplantation for HCC

Milan criteria





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Mazzaferro et al. NEJM 1996

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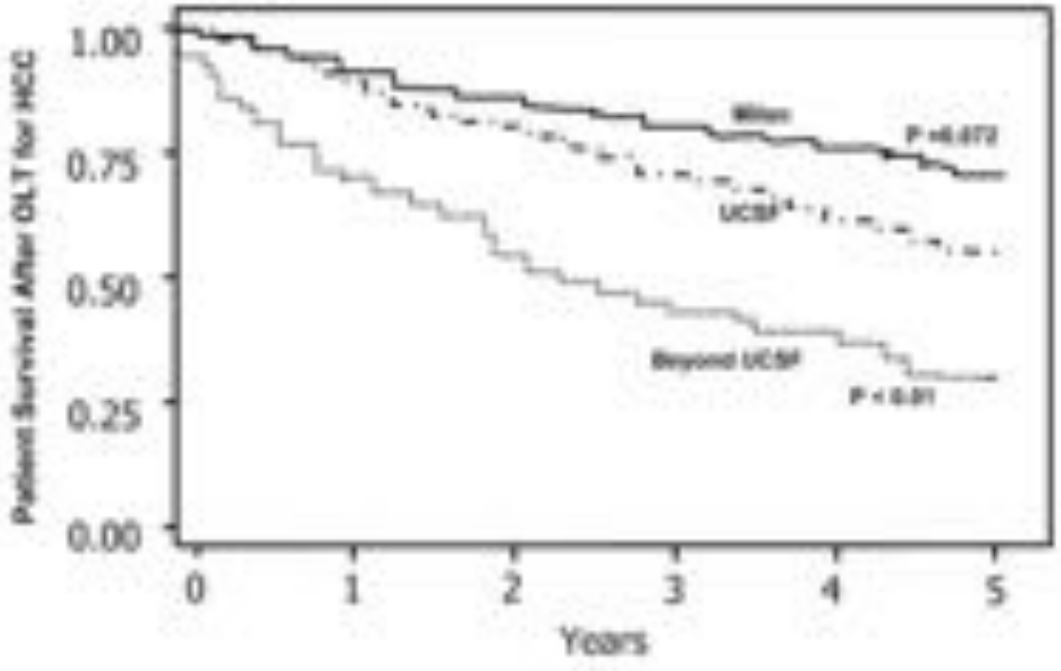
Liver Transplantation Criteria For Hepatocellular Carcinoma Should Be Expanded

A 22-Year Experience With 467 Patients at UCLA

John P. Duffy, MD, Andrew Vardanian, MD, Elizabeth Benjamin, MD, PhD, Melissa Watson, MD, Douglas G. Farmer, MD, Rafik M. Ghobrial, MD, PhD, Gerald Lipshutz, MD, Hasan Yersiz, MD, David S. K. Lu, MD, Charles Lassman, MD, Myron J. Tong, MD, PhD, Jonathan R. Hiatt, MD, and Ronald W. Busuttil, MD, PhD

ANNALS OF SURGERY
A Monthly Review of Surgical Science Since 1885



79%

64%

41%

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Duffy et al. Annals of Surgery 2007

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Selection criteria

Morphometric criteria

Tumor biology

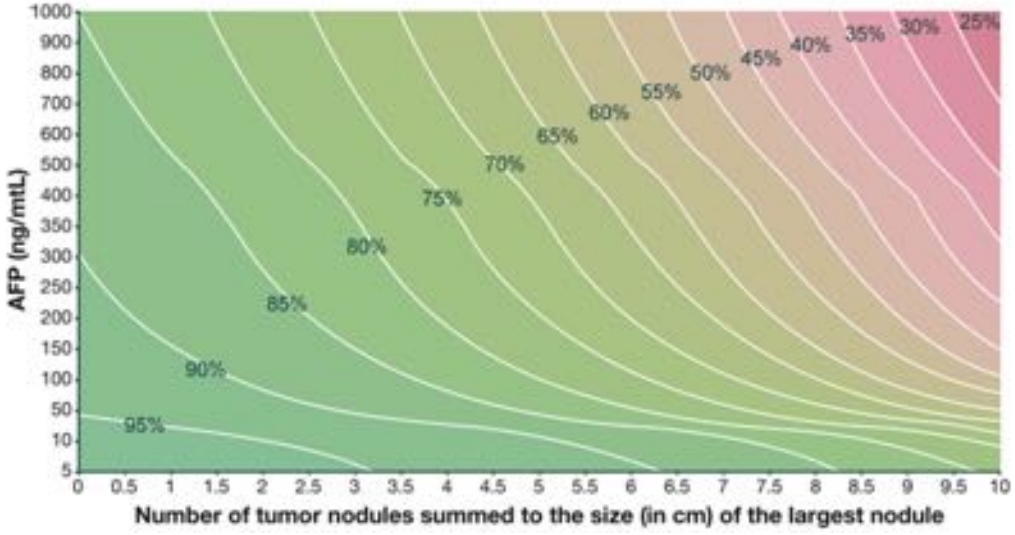
Waiting time
Response to bridge therapy
AFP

Sugawara *et al* 2007	78	≤ 5 HCC ≤ 5 cm	70% at 3 yr

Selection Criteria

Variables	β coefficient	Hazard ratio	Points
Largest diameter, cm			
≤3	0	1	0
3–6	0.272	1.31	1
>6	1.347	3.84	4
Number of nodules			
1–3	0	1	0
≥4	0.696	2.01	2
AFP level, ng/mL			
≤100	0	1	0
100–1000	0.668	1.95	2
>1000	0.945	2.57	3

↑ 20%



JAMA Surgery | Original Investigation

Dynamic α-Fetoprotein Response and Outcomes After Liver Transplant for Hepatocellular Carcinoma

Karim J. Halazun, MD; Russell E. Rosenblatt, MD, MS; Neil Mehta, MD; Quirino Lai, MD; Kaveh Hajifathalian, MD, PhD; Andre Gorgen, MD; Gagan Brar, MD; Kazunari Sasaki, MD; Maria B. Majella Doyle, MD; Parissa Tabrizian, MD; Vatche G. Agopian, MD; Marc Najjar, MD; Tommy Ivanics, MD; Benjamin Samstein, MD; Robert S. Brown Jr, MD, MPH; Jean C. Emond, MD; Francis Yao, MD; Jan Lerut, MD, PhD; Massimo Rossi, MD; Gianluca Mennini, MD; Samuele Iesari, MD; Armin Finkenstedt, MD; Benedikt Schaefer, MD; Jans Mittler, MD; Maria Hoppe-Lotichius, MD; Cristiano Quintini, MD; Federico Aucejo, MD; William Chapman, MD; Gonzalo Sapisochin, MD

NYCA score	Recurrence Risk	5-Year RFS
0-2	Low Risk	90%
3-6	Acceptable Risk	70%
7 or More points	High Risk	42%

> 85% MC out → low/acceptable risk

Mazzaferro et al, Gastroenterology 2018
Halazun et al, Annals of Surg 2018
Duvoux et al, Gastroenterology 2012

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Downstaging outcomes

Inclusion Criteria:

HCC exceeding UNOS T2 criteria but meeting one of the following:

- Single lesion ≤ 8 cm
- 2 or 3 lesions each ≤ 5 cm with the sum of the largest tumor diameters ≤ 8 cm
- 4 or 5 lesions each ≤ 3 cm with the sum of the largest tumor diameters ≤ 8 cm

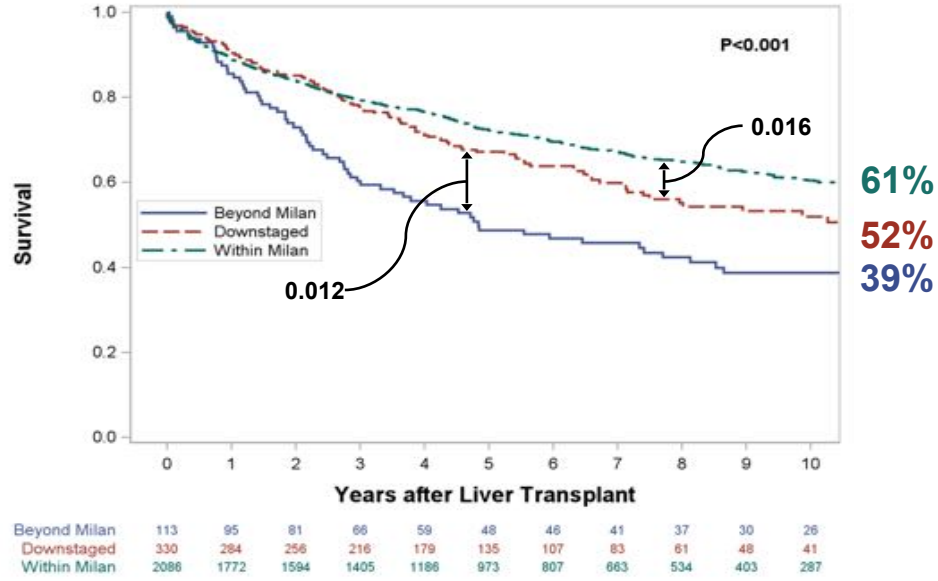
No vascular invasion

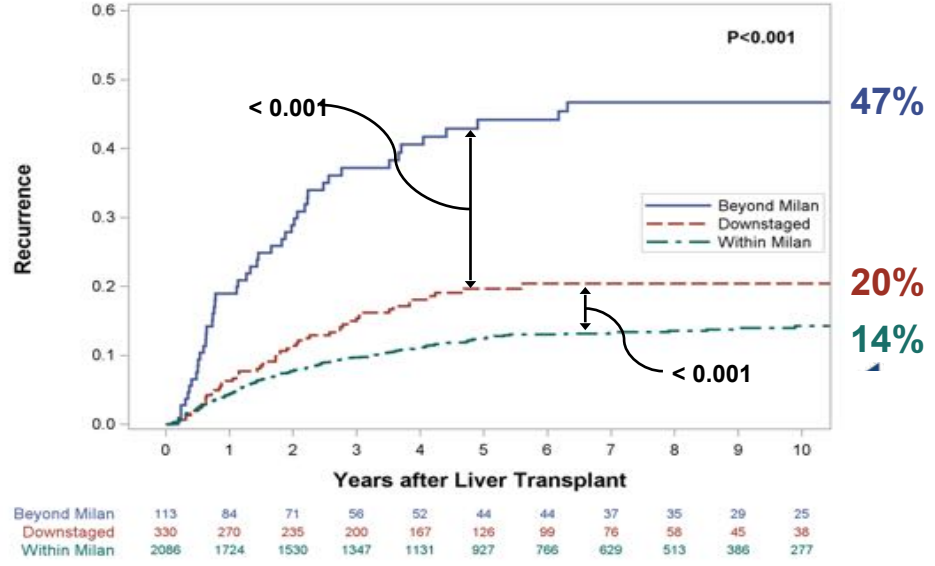
Successful downstaging → Residual tumor(s) within MC

Downstaging failure → Progression of tumor(s) beyond MC

→ Vascular invasion, extrahepatic disease

Minimum observation period of 3 months before LT





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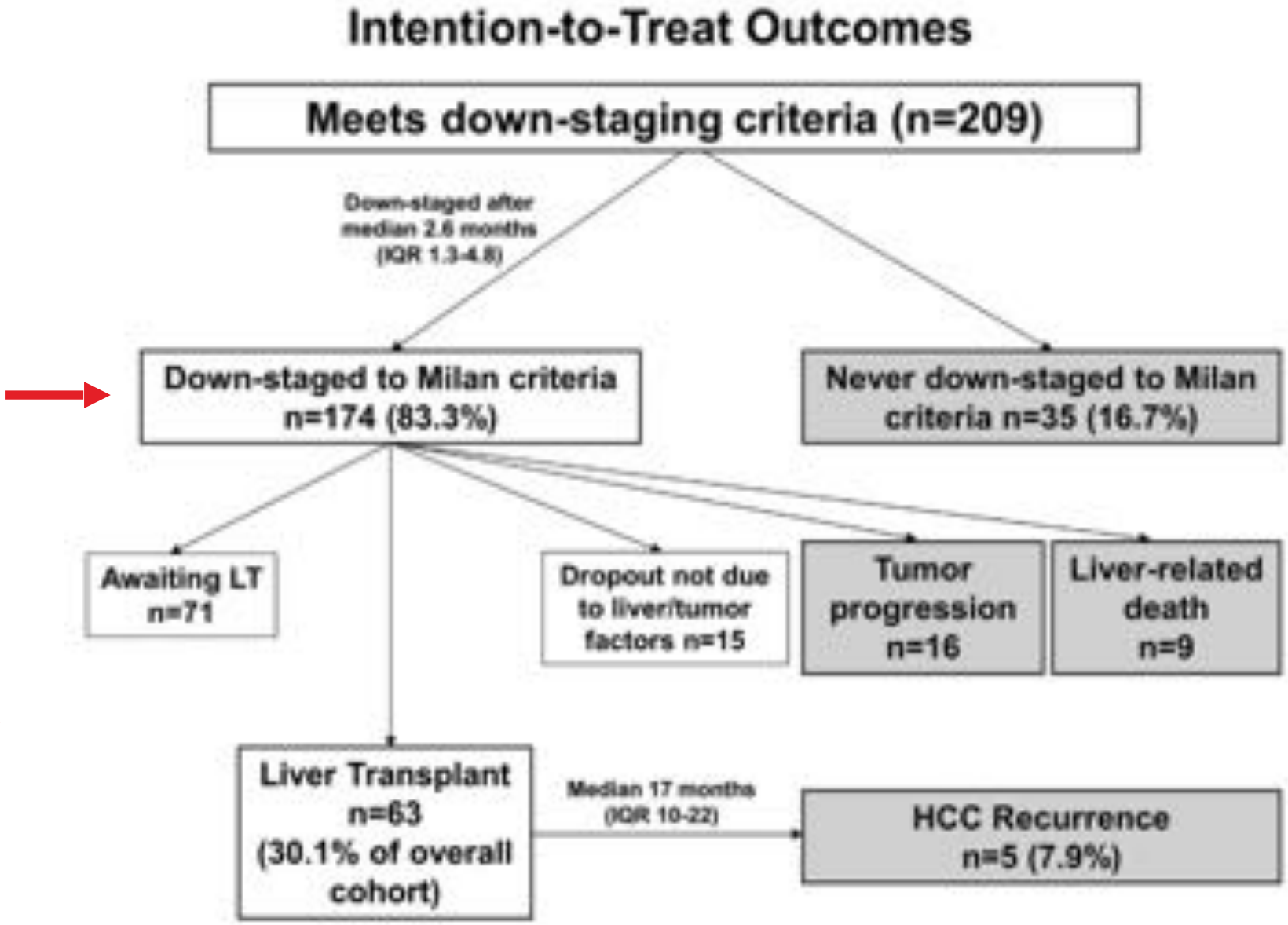
Yao et al. Hepatology 2015

2 yr OS: 95%, RR: 7.9%



Probability of LT at 3 years 46%

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Mehta et al. Gastroenterology Nov 2021

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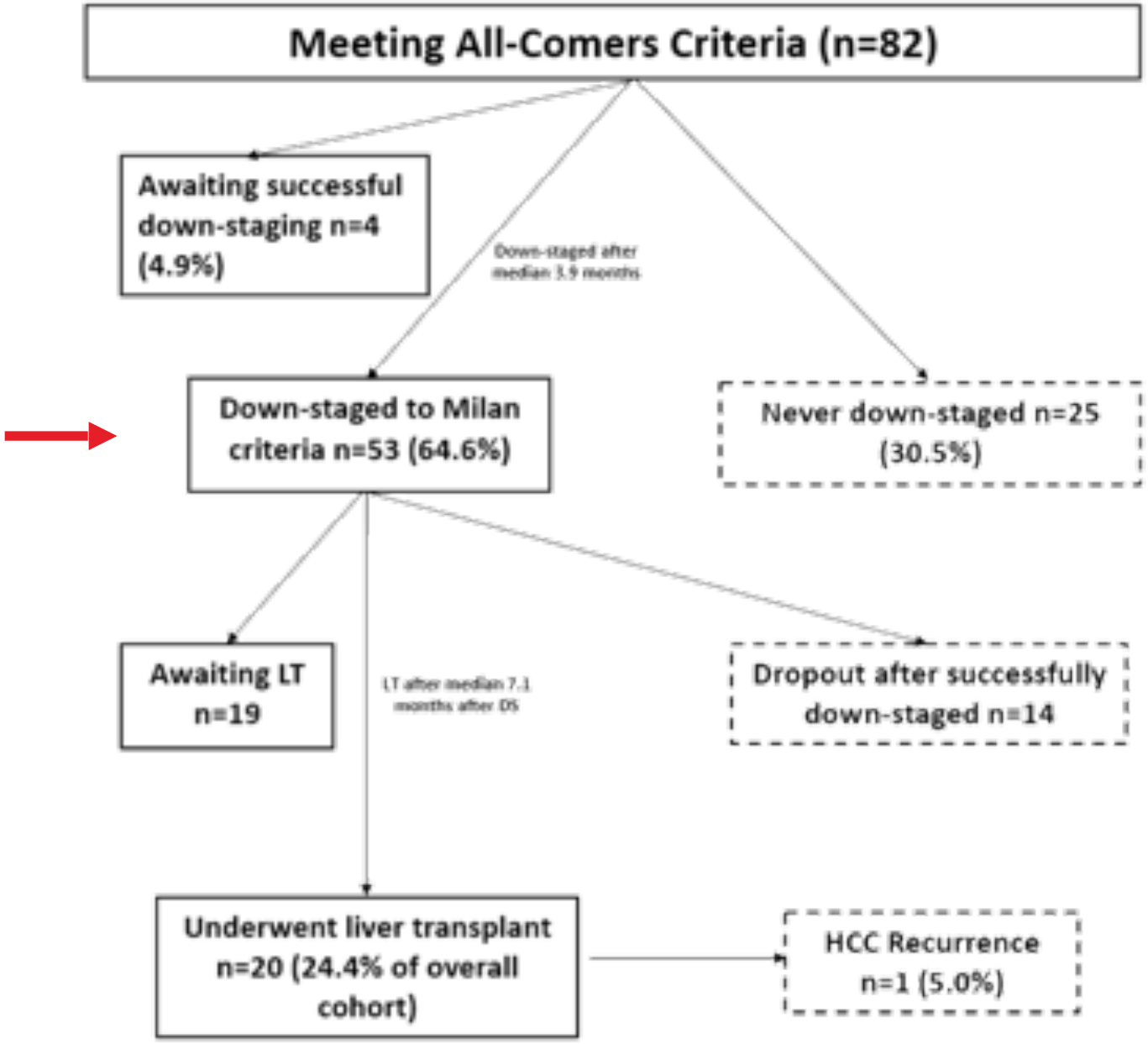

Exceeding UNOS DS

- Any number
- Any size
- Any diameter

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Mehta et al. under review

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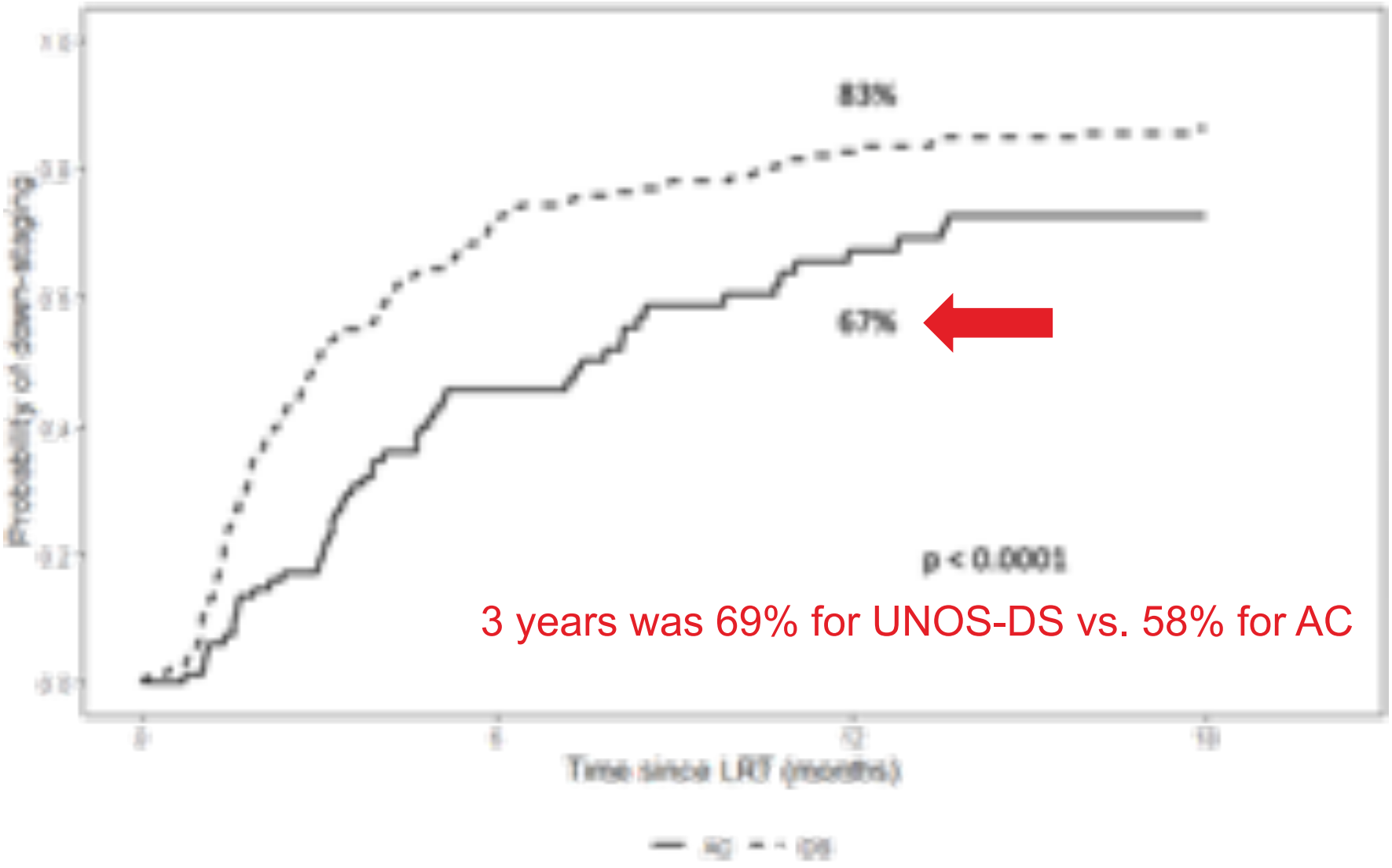

3 years was 69% for UNOS-DS vs. 58% for AC

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Mehta et al. unpublished

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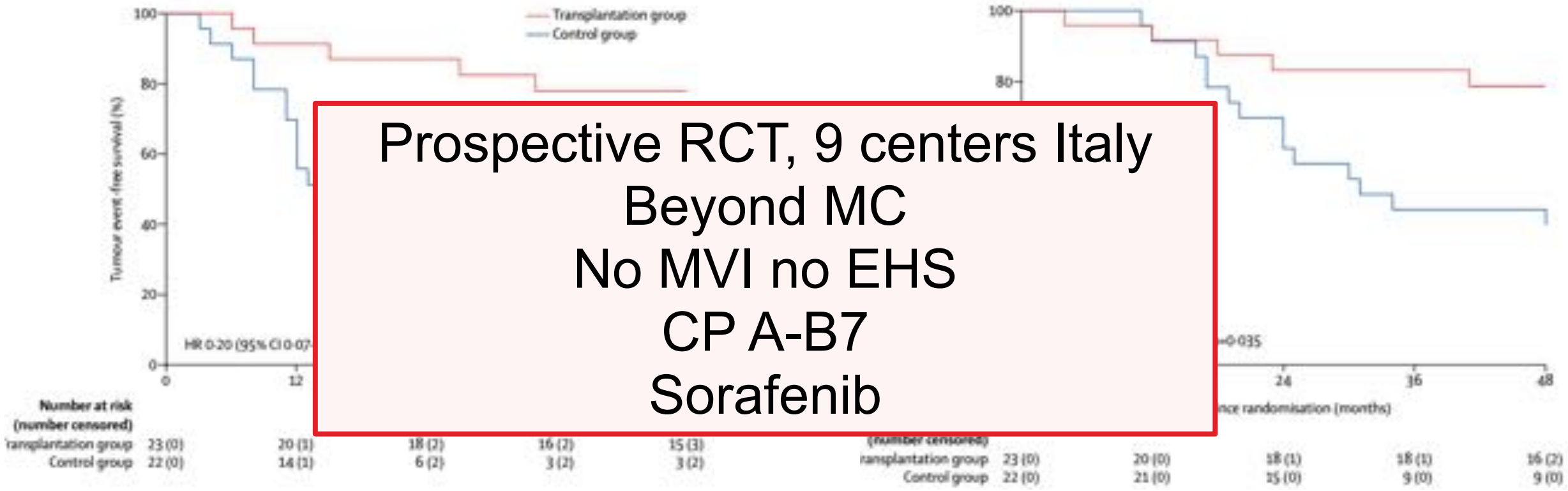
RTC downstaging



Prospective RCT, 9 centers Italy
Beyond MC
No MVI no EHS
CP A-B7
Sorafenib

5-year OS 77% vs 31%

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Mazzaferro et al. Lancet Oncol 2020

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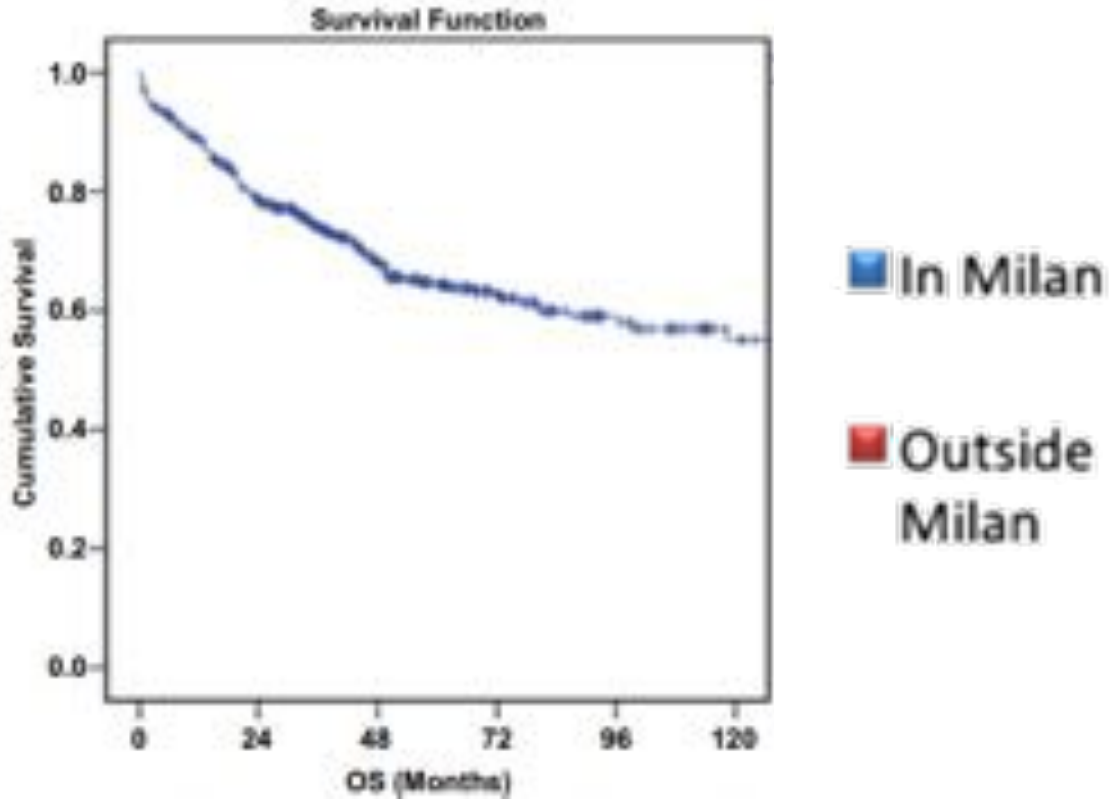
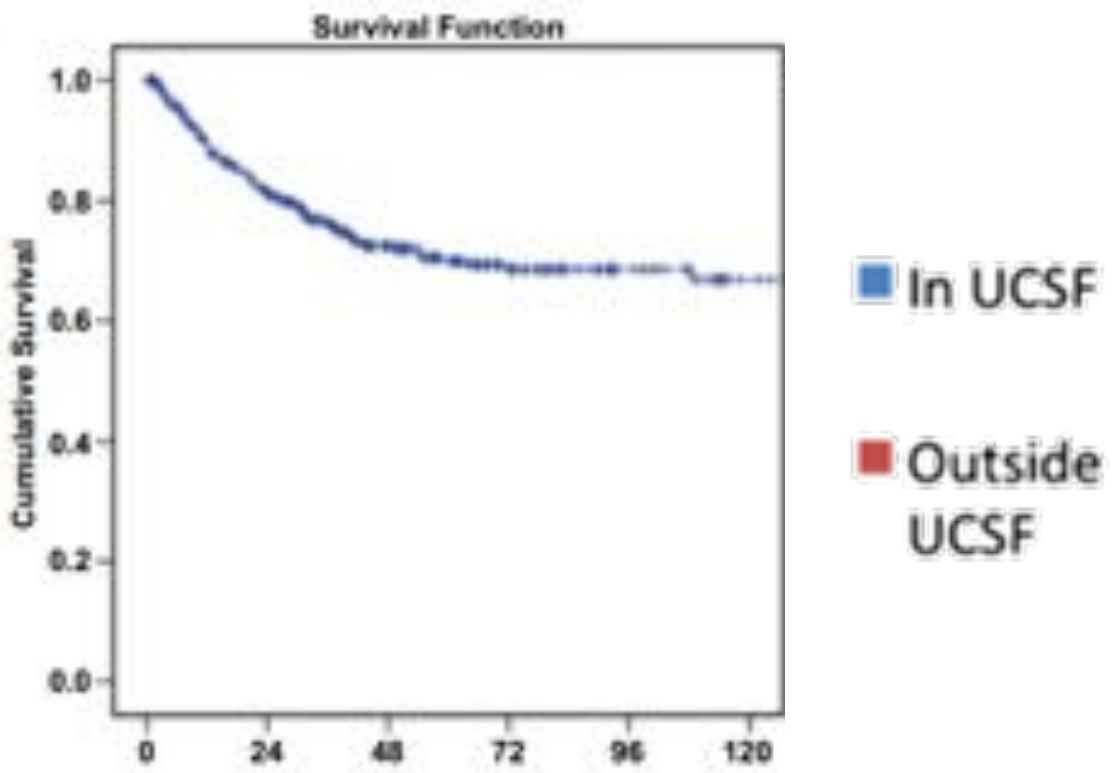
LDLT-expanded criteria

		Selection criteria
Tokyo (5-5 rule) 2007	78	≤ 5 nodules and ≤ 5 cm
Kyoto Criteria 2013	136	≤ 10 nodules, all ≤ 5 cm and DCP ≤ 400 mAU/ml
Asan Medical Center 2008	857	Tumor diameter ≤ 5 cm, ≤ 6 lesions, no Mv invasion
Kyushu Criteria 2009	90	Any # of tumors, ≤ 5 cm in size, and DCP < 300
Turkey 2012	92	No EHD, no Mv PV invasion
Samsung	180	≤ 7 tumors, diameter ≤ 6 cm, AFP ≤ 1000 ng/ml
Toronto Criteria 2015	294	Any size, any #, no Mv invasion, grade well-mod
Medanta 2021	405	No EHD, no Mv invasion, any size/number

LDLT-expanded criteria



5-yr OS 64%
5-yr RFS 70%



Three factors predicted recurrence:
Pre-LT AFP ≥ 100 ng/mL
Tumor burden beyond UCSF
18F FDG PET avidity

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Bhangui et al. Liver Transplantation 2021

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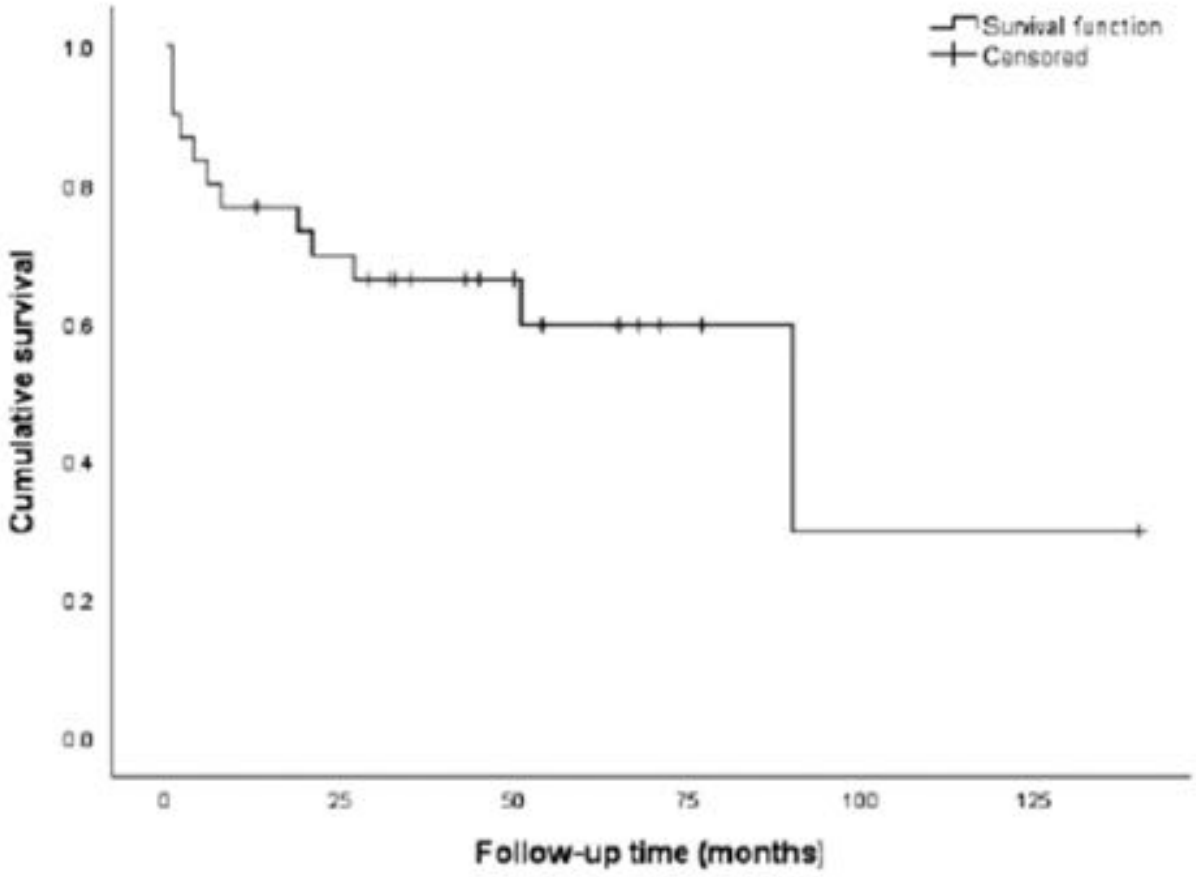
Macrovascular invasion?



Multicenter study, 11 centers
N=30
+PVT (no PV4), OLT after CR
5 year OS 60%

Predictors of recurrence:

- AFP >10 ng/ml at time of LT
- Number of viable tumors
- Presence of residual HCC
- Satellite nodules
- Beyond Milan Criteria

IF AFP was ≤10 ng/ml, HCC recurrence was 11% vs 50%

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Assalino et al. Transplant international 2020

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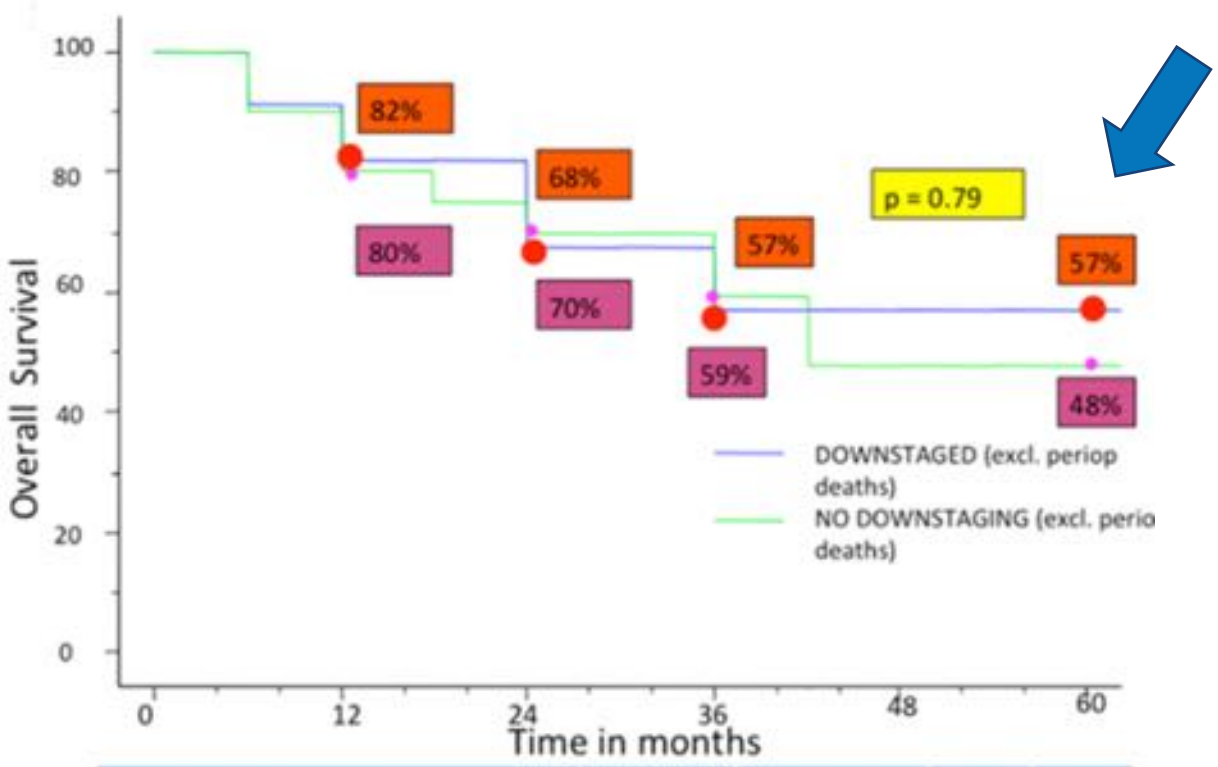
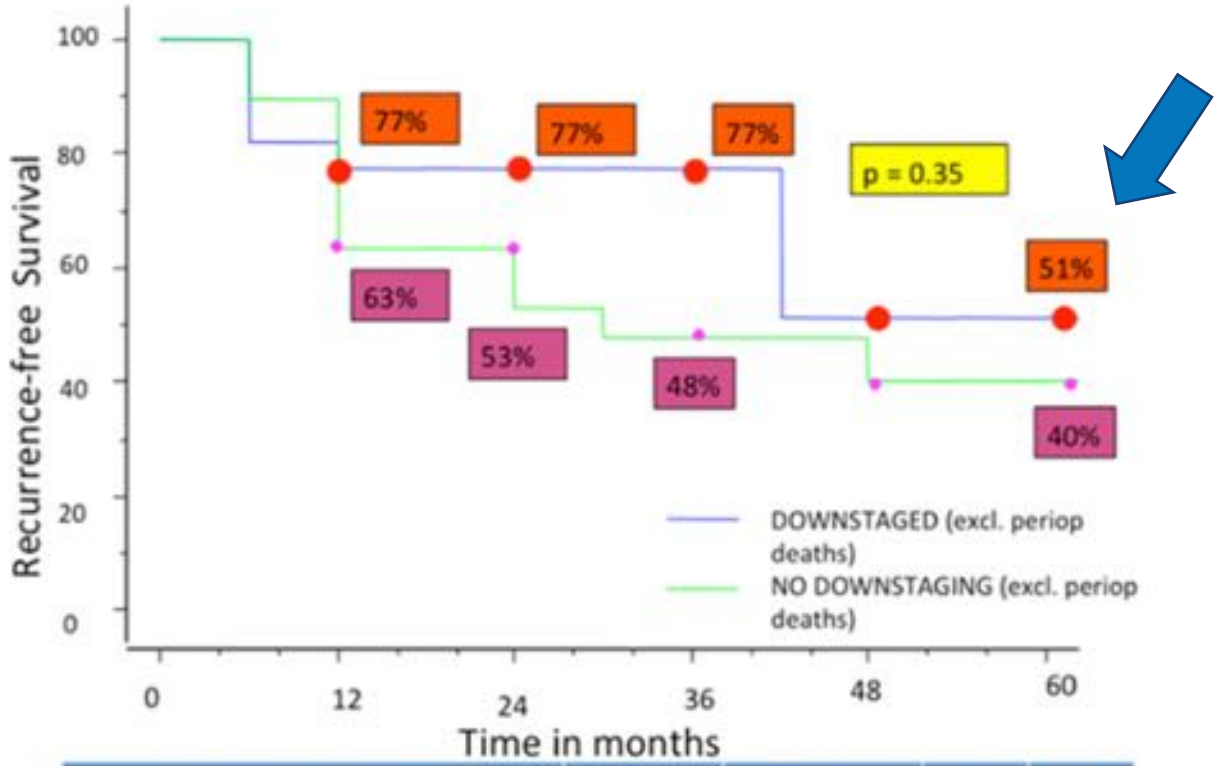
LDLT-PVT-Downstaging



No. of patients exposed	1 yr	2 yrs	3 yrs	4 yrs
Downstaged patients (23)	15	8	4	2
No downstaging (20)	16	14	11	5



No. of patients exposed	1 yr	2 yrs	3 yrs	5 yrs
Downstaged patients (23)	13	7	4	1
No downstaging (20)	12	10	8	4

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Soin et al. Transplantation 2020

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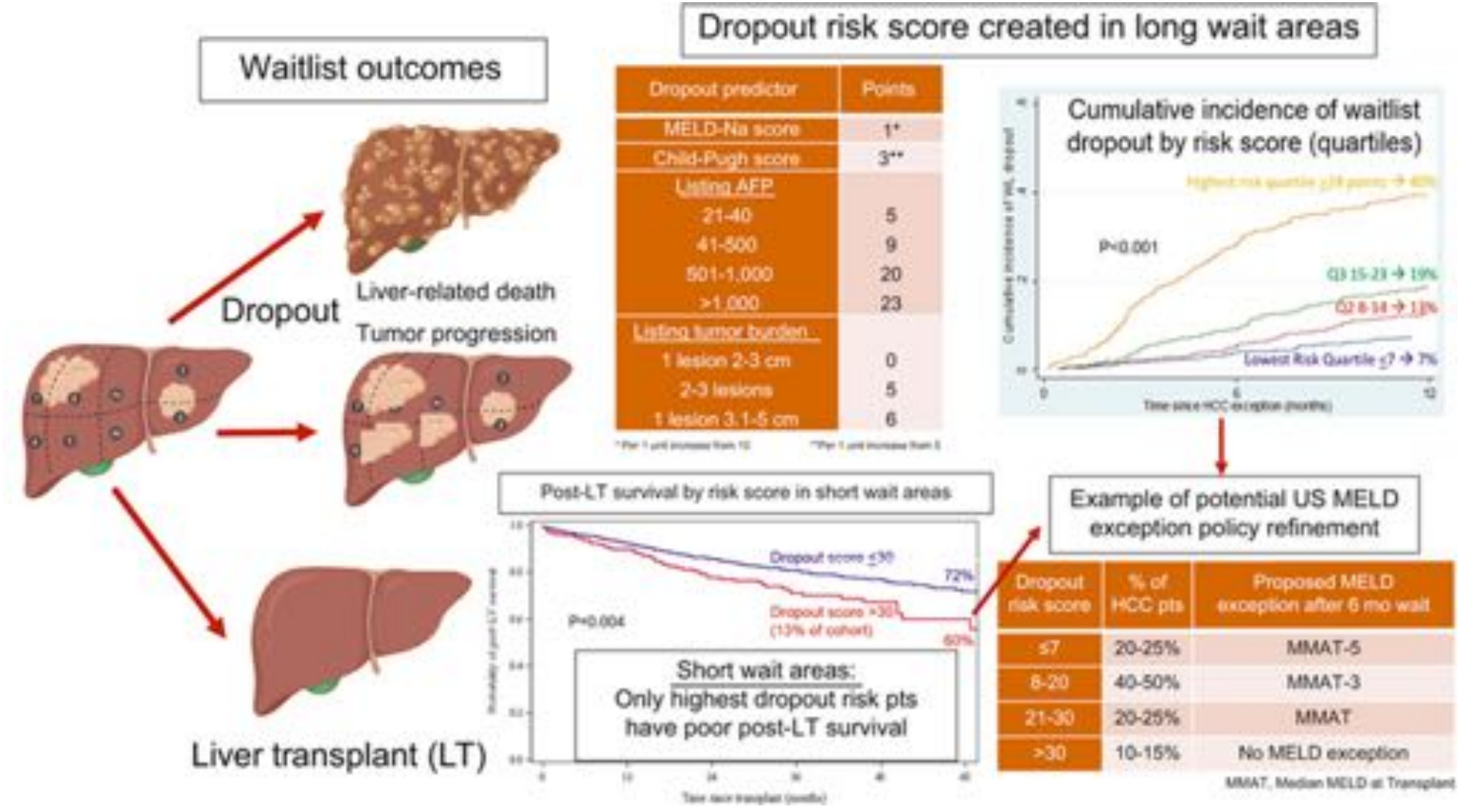
Dropout risk score



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Mehta et al, J Hep 2021

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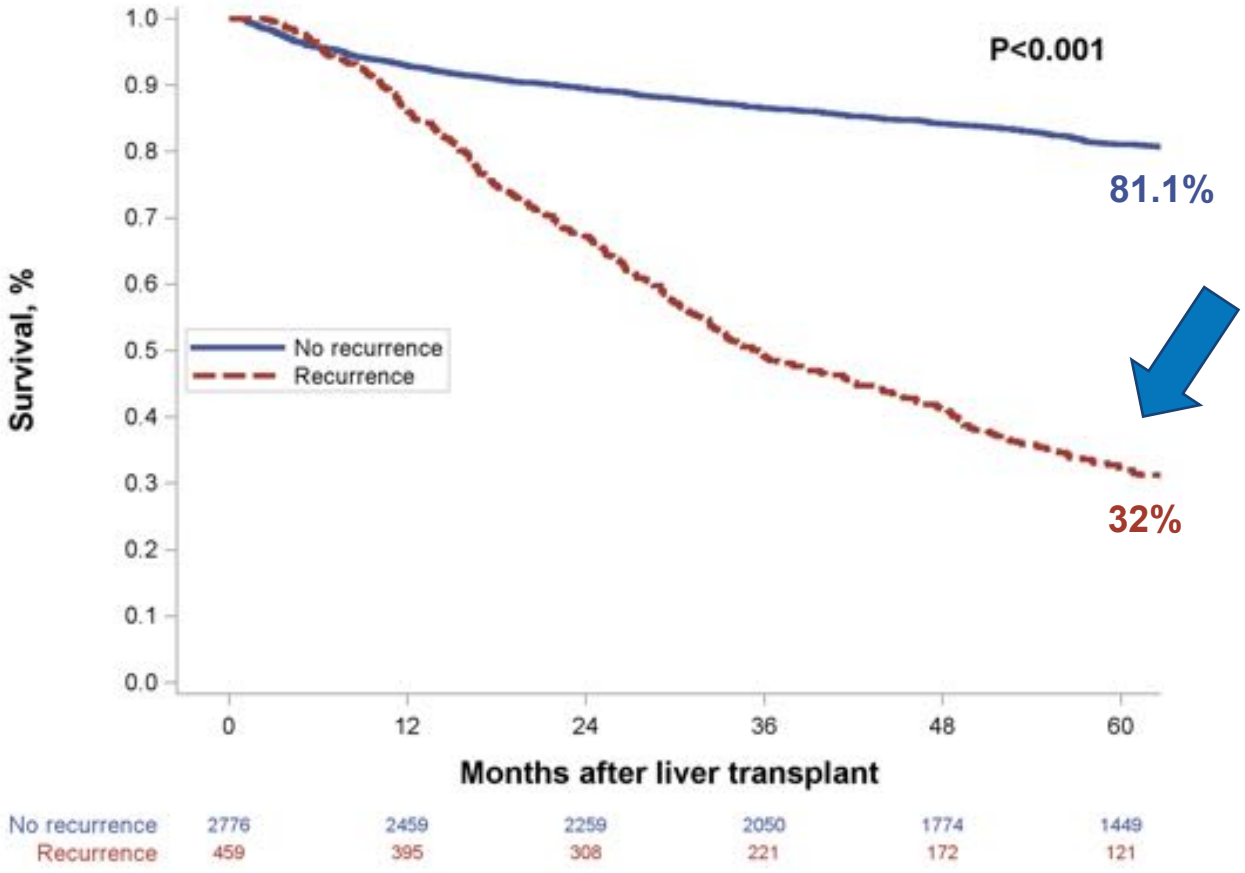
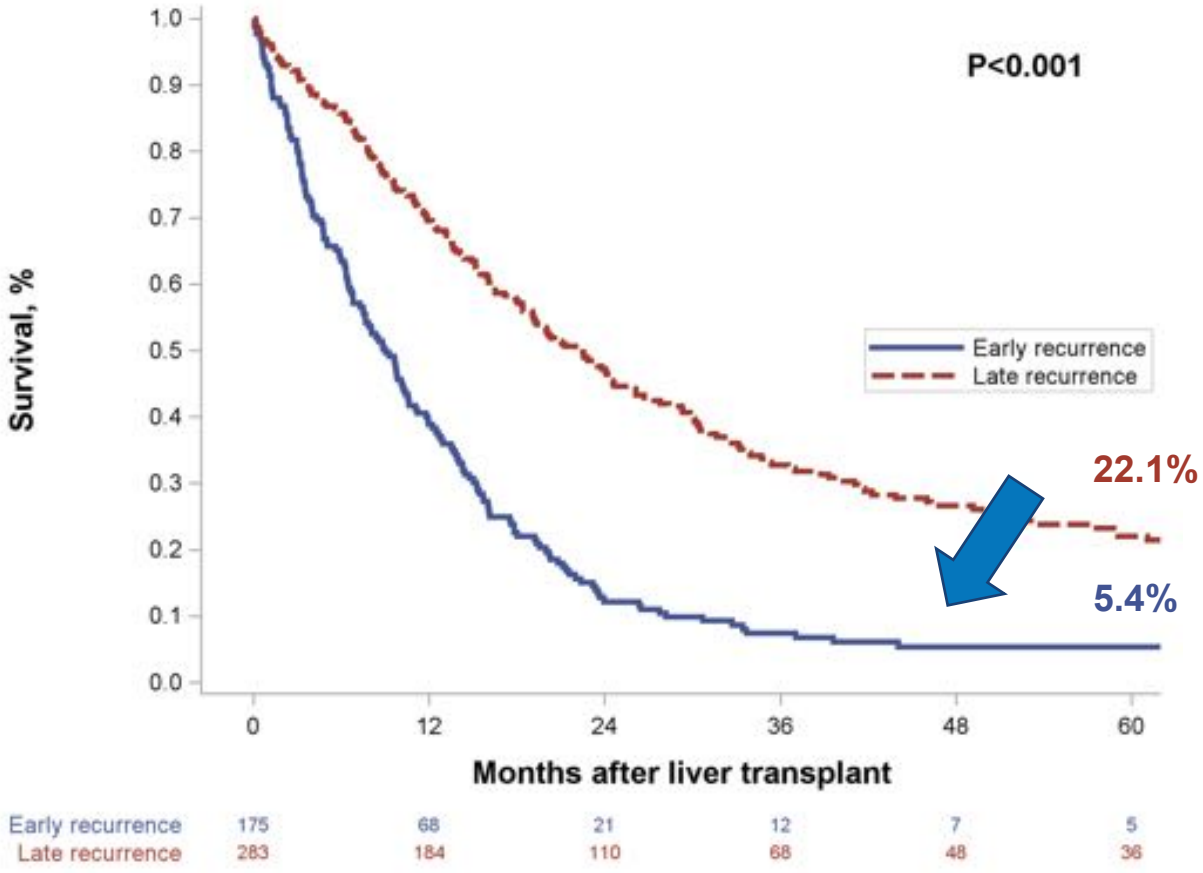
Recurrence!





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Tabrizian et al, ILCA 2020

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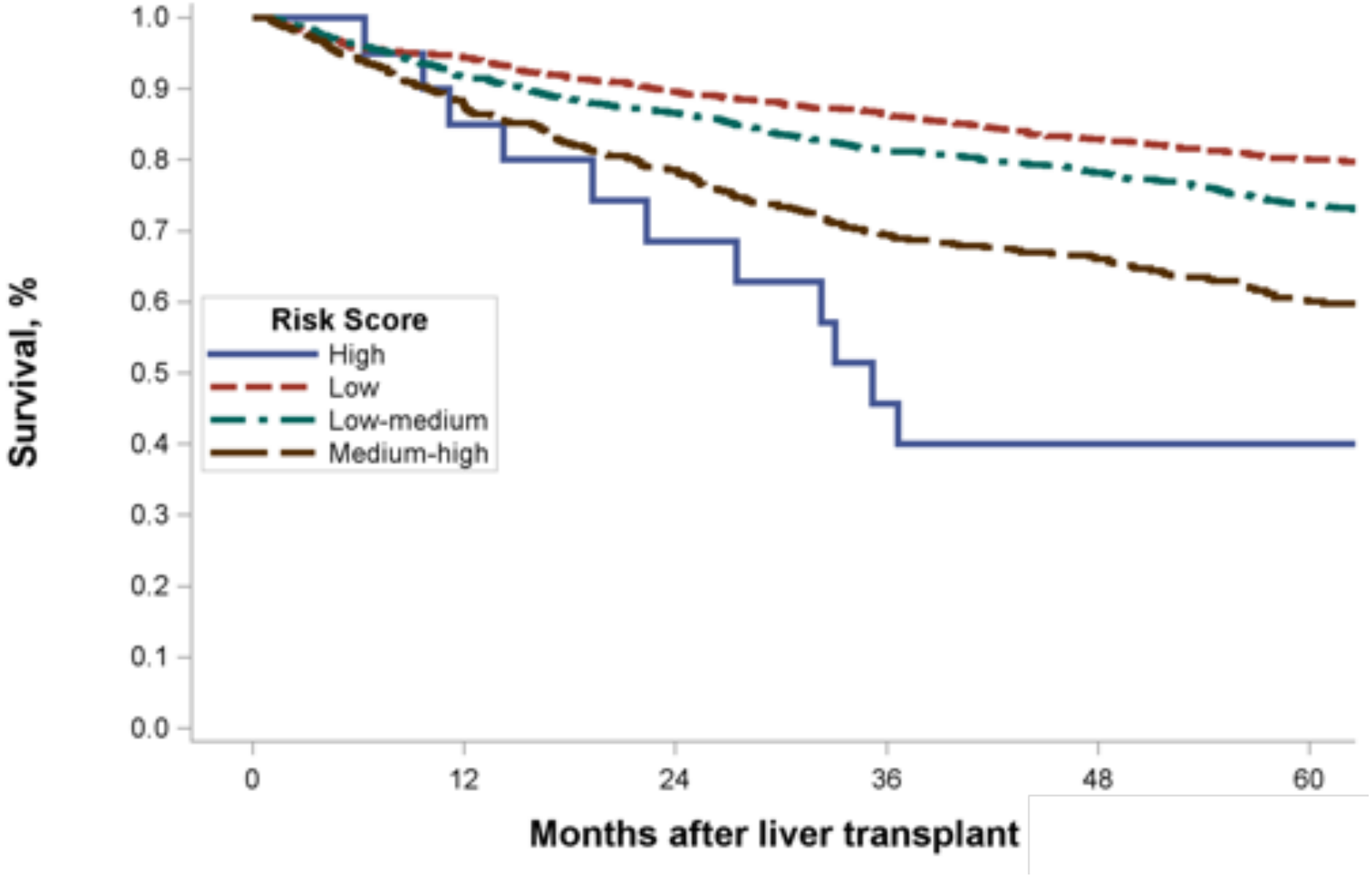
Predictors of Early Post - LT HCC Recurrence (n = 175)

Variable	HR (95% CI)	P - Value	Score
Number of initial tumors > 3	1.39 (0.77 - 2.53)	0.279	0
Maximum initial tumor size			
< 3 cm	Reference	-	
3 - 6 cm	1.53 (1.10 - 2.12)	0.012	2
> 6 cm	3.79 (2.28 - 6.30)	< 0.001	4
Pre - LT NLR > 5	1.64 (1.15 - 2.35)	0.007	2
3 or more pre - LT LRT	2.20 (1.36 - 3.58)	0.002	2
AFP at LT			
< 20, always < 20	Reference	-	
< 20, maximum > 20	1.41 (0.75 - 2.64)	0.286	0
> 20, > 75% decrease from maximum AFP	2.23 (0.91 - 5.48)	0.079	0
> 20, 25 - 75% decrease from maximum AFP	2.72 (1.45 - 5.11)	0.002	3
> 20, < 25% decrease from maximum AFP	4.48 (3.19 - 6.30)	< 0.001	4



Recurrence Risk Stratification Score

Score	Risk of Recurrence	Probability of 1-year Recurrence	5-year Survival
0	Low risk	1.80%	80%
2 - 4	Low-medium risk	5.40%	74%
5 - 8	Medium-high risk	12.20%	60%
> 8	High risk	44.90%	40%

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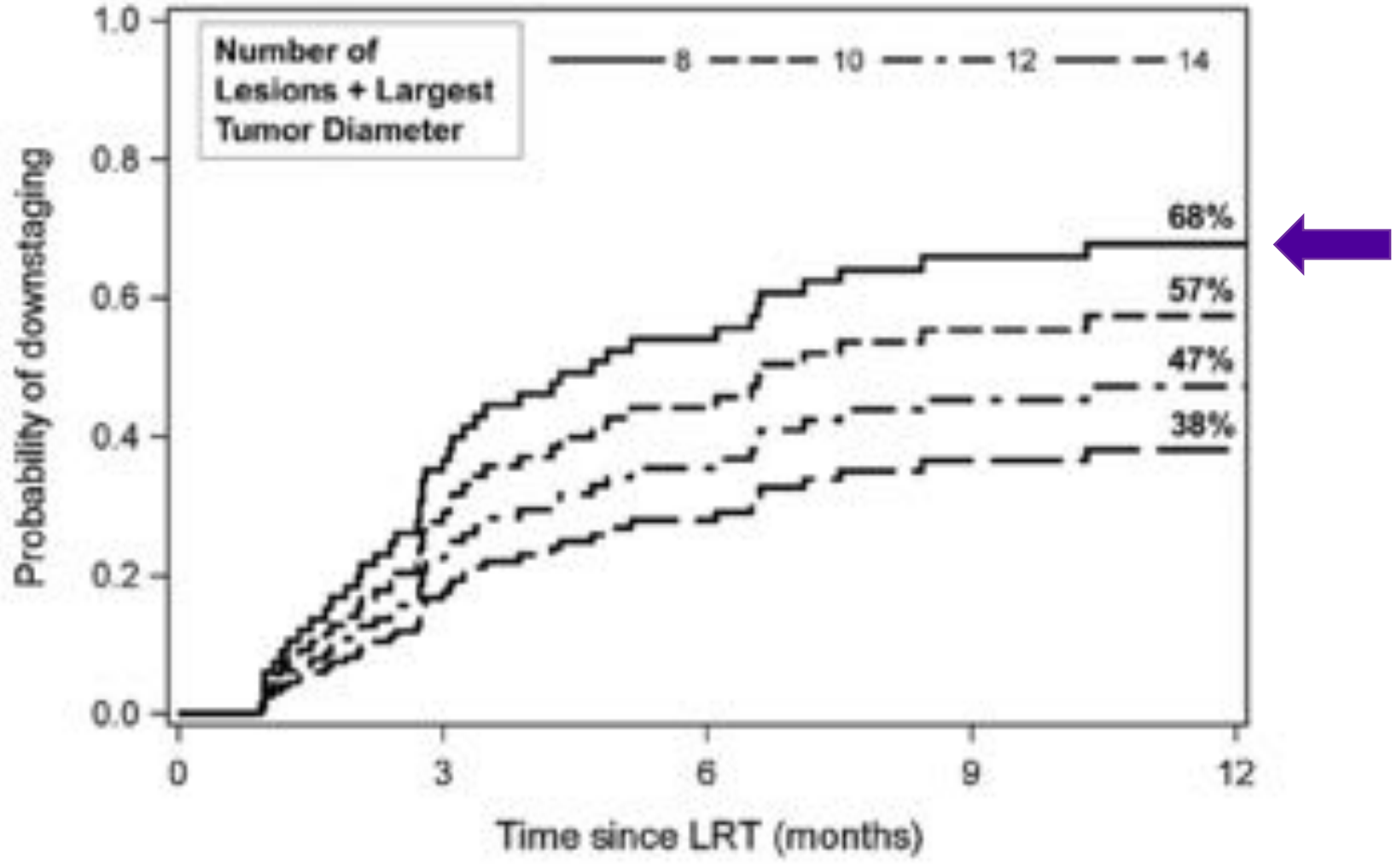
Upper limits in tumor burden?



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Mehta et al, Hepatology 2019

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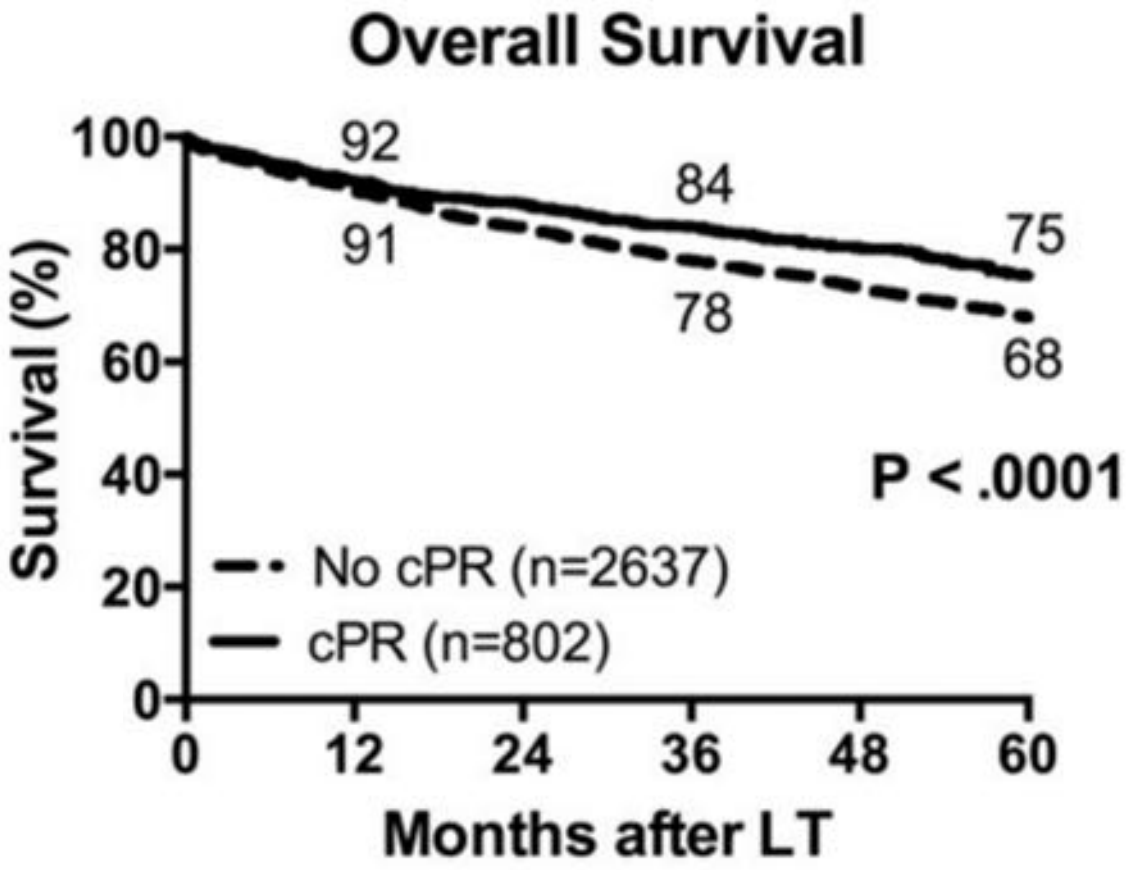
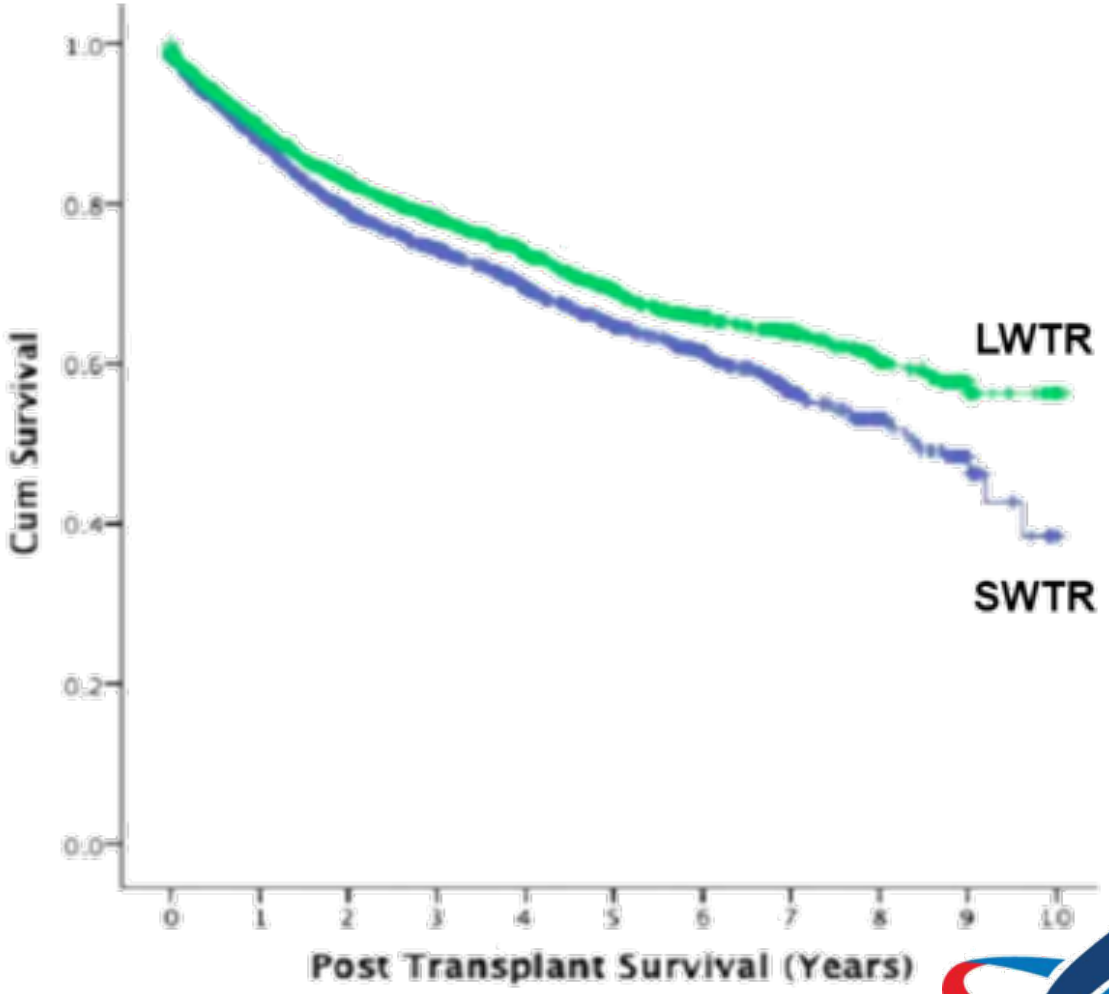
Pathologic response - Wait time





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DiNorcia et al. Hepatology 2020
Halazun et al. Hepatology 2014

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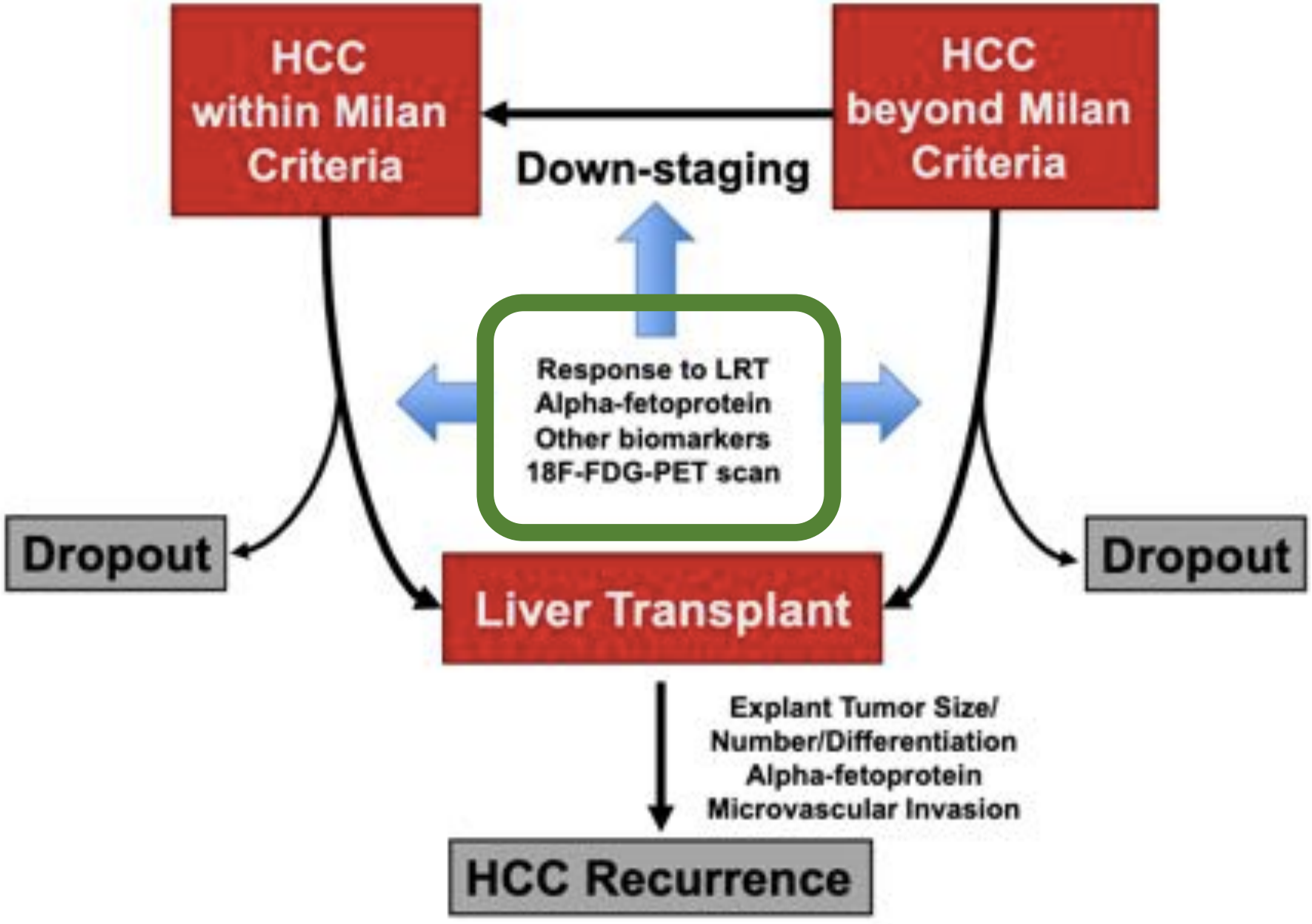
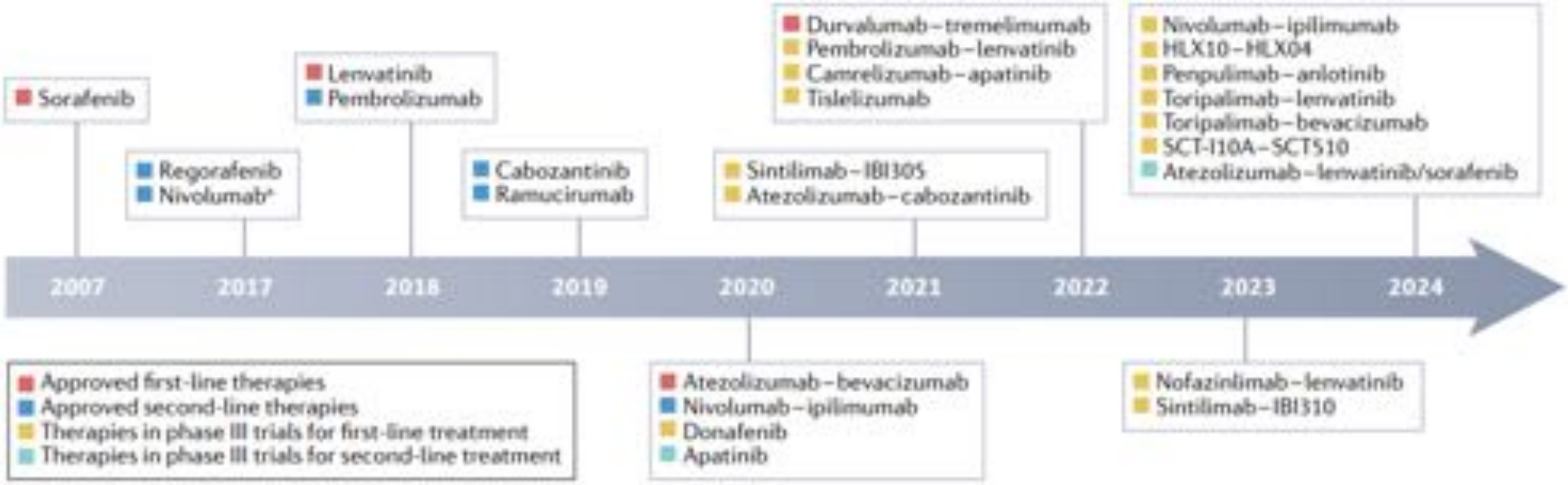

HCC within Milan Criteria
HCC beyond Milan Criteria
Down-staging
Response to LRT
Alpha-fetoprotein
Other biomarkers
18F-FDG-PET scan
Dropout
Dropout
Liver Transplant
Explant Tumor Size/
Number/Differentiation
Alpha-fetoprotein
Microvascular Invasion
HCC Recurrence

Therapeutic landscape of advanced HCC



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Yang et al. Nature Reviews Gastroenterology and Hepatology 2022

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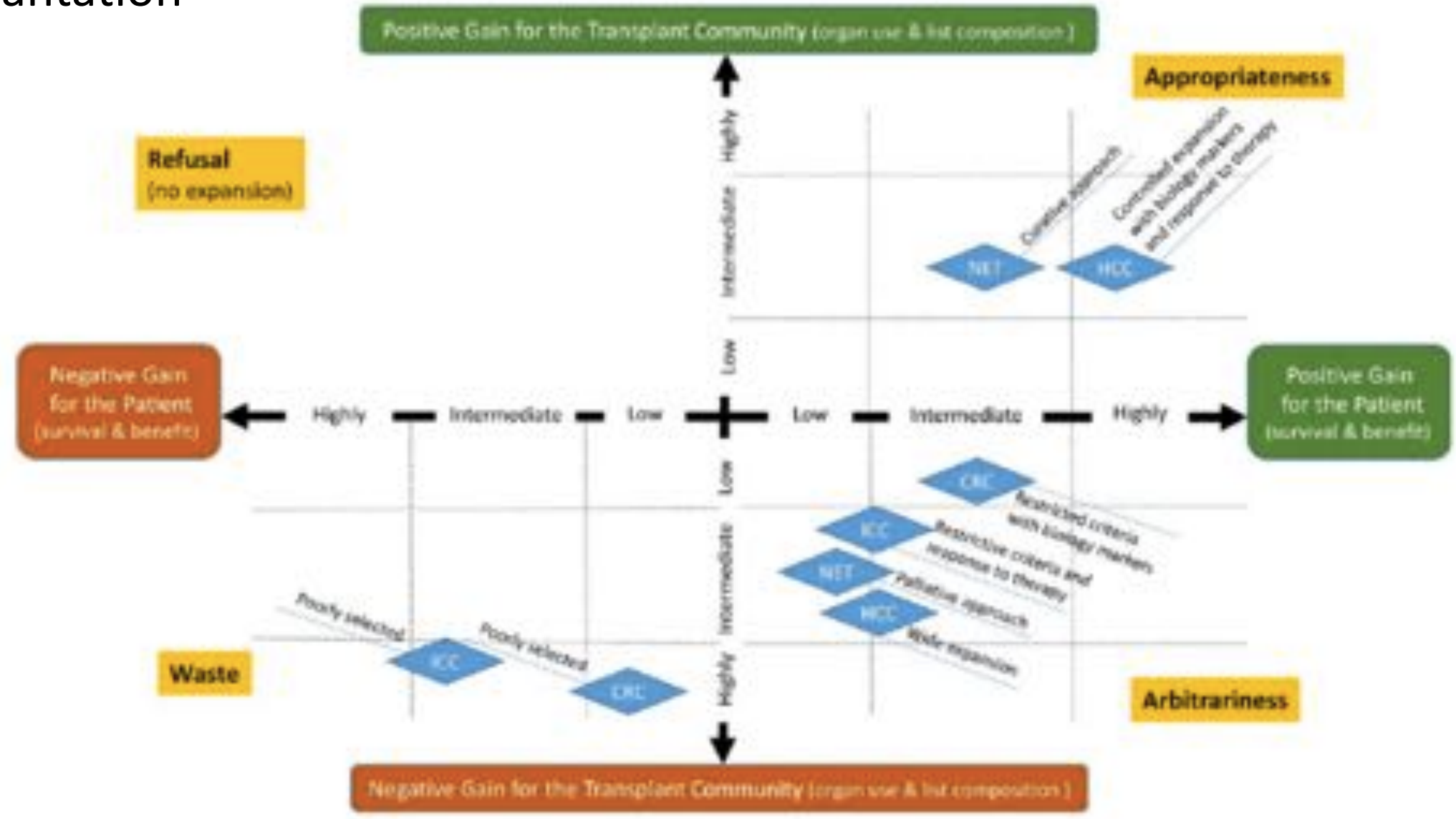
Transplantation



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Mazzaferro et al. Liver Transplant 2018

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Solid organ transplant recipients treated with ICI

Age	Gender	Immune-suppression	Years after LT	Doses	Graft outcome	Pathology of graft	Treatment of rejection	Outcome of cancer	Overall outcome
20	M	Sirolimus	3	Nivo, 2	Loss of function	Cellular/AB mediated rejection	Prednisone, IVIG	N/A	Death after 5 weeks
14	M	Tacrolimus	3	Nivo, 1	Loss of function	Cellular/AB mediated rejection	Prednisone	N/A	Death after 4 weeks
53	F	Everolimus	3	Nivo, 1	Loss of function	Cellular	Steroids	Progression	Death after 4 weeks
41	M	Tacrolimus	1	Nivo, 15	No rejection	N/A	N/A	Progression	Death > 7 mo
57	M	Tacrolimus	4	Pembro x10	No rejection	N/A	N/A	Radiologic resolution	Alive at 10 mo

n = 29, 14/29 kidney, 11/29 liver, 3/29 heart, 1 cornea
Graft loss/acute rejection: 45%

Gassmann et al. Transplantation direct 2018

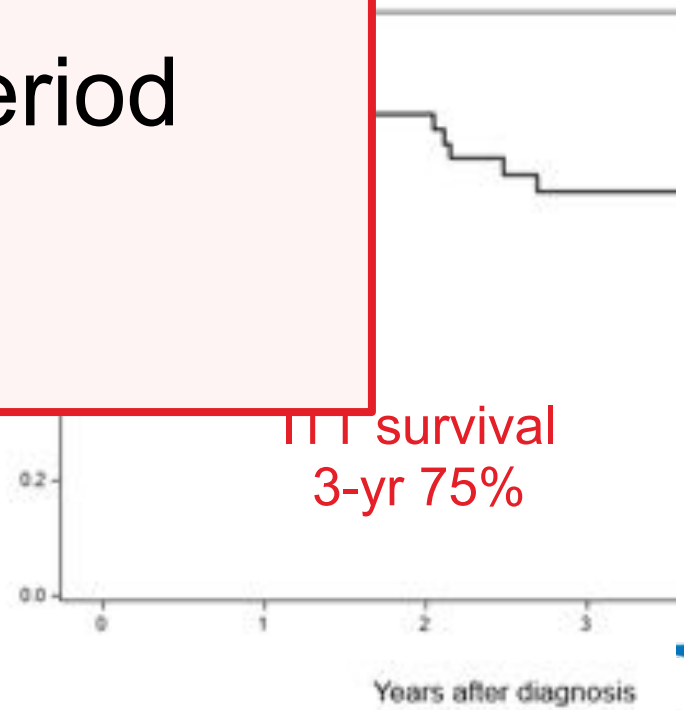
Immunotherapy and liver transplant

PD-1 inhibitor as bridge therapy to liver transplantation?

American Journal of TRANSPLANTATION

- Heterogeneous
- Case series/reports
- ICI type and washout period
- Lack of biopsy
- Immunosuppression

No ma
No
5
> 90 % maj



ITT survival
3-yr 75%

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Tabrizian et al. AJT 2020

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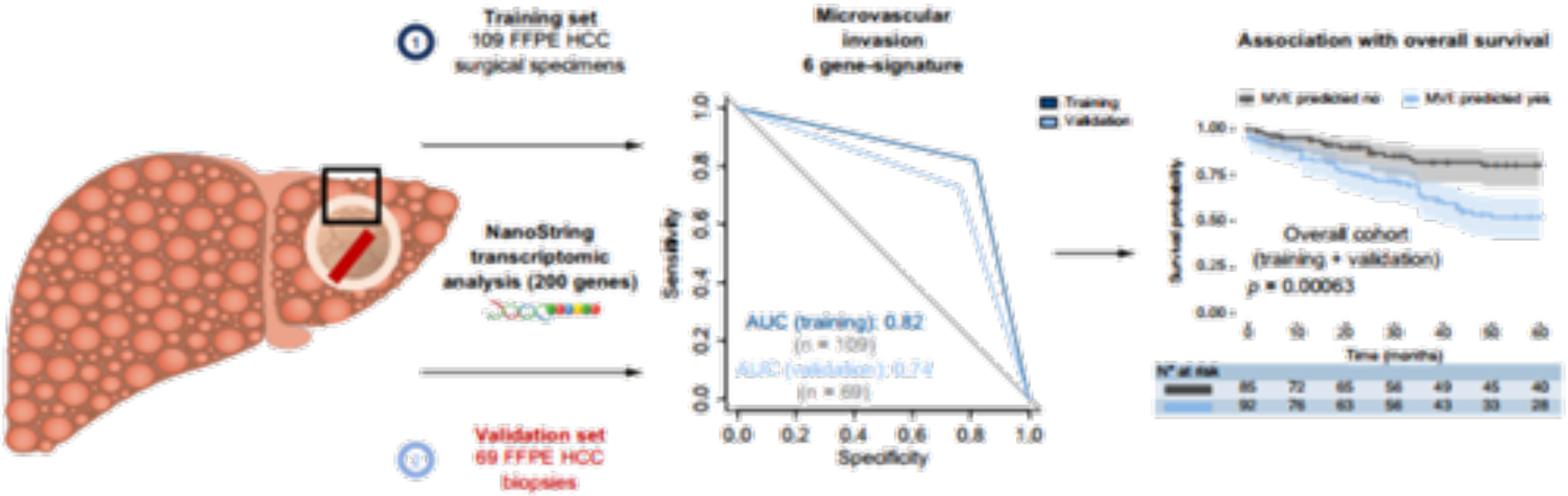
Future directions

- Future directions?

Trial	NCT	Phase	Treatment arms	Endpoint	Adjuvant	N=
Neoadjuvant pre LT						
PLENTY202001	NCT04425226	Phase 2	Pembro/Len	RFS	No	192
	NCT05185505	Phase 2	Atezo/Bev	Feasibility % rejection	No	24
	NCT05027425	Phase 2	Durva/Tremi	30d rejection rate	No	30
	NCT04443322	NA	Durva/Len	PFS/RFS	No	20

Gene expression signature

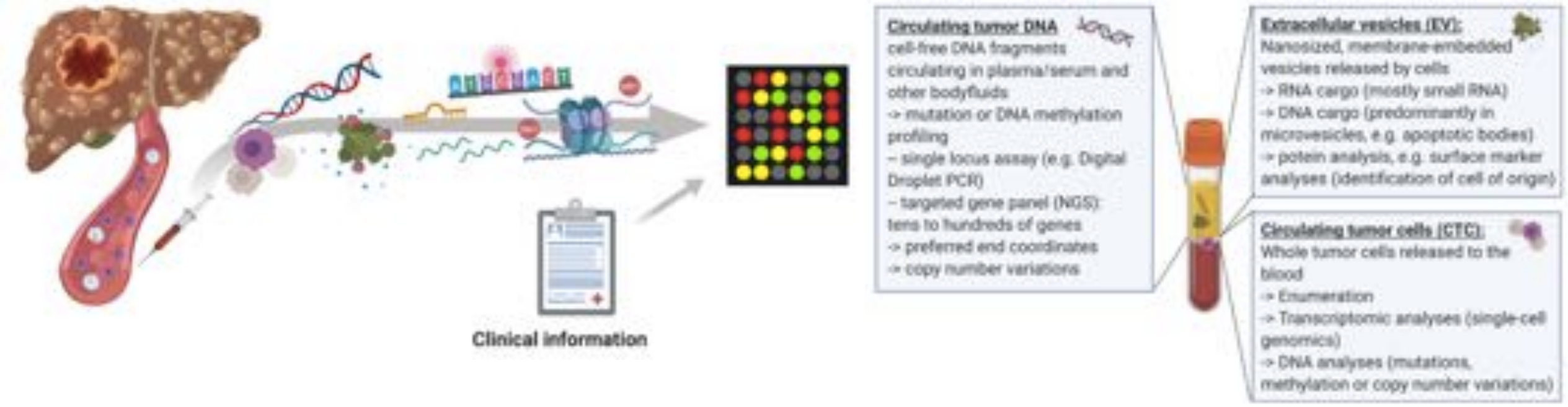


Mount Sinai Recanati/Miller Transplantation Institute

Beaufrere et al, J Hep 2022

The Liver Transplant Symposium 2023

Liquid biopsy in HCC



Mount Sinai Recanati/Miller Transplantation Institute

Von Felden et al, Git 2020

The Liver Transplant Symposium 2023

Where do we stand?

- Moving away from “size and number” criteria
- Patient selection/Personalization

- Understanding tumor biology:
    - Tumor differentiation
    - Heterogeneity of tumor growth
    - Boundaries of vascular invasion and DS therapies
    - Prognostic biomarkers (dynamic changes)
    - Other surrogates in predicting outcomes (e.g machine learning)

- Role and safety of ICI as bridge therapy
- Controlled clinical trial


Thank you