TORONTO
Liver Transplant Program

TORONTO
Liver and Pancreas Surgery

The Liver Transplant Symposium: Pushing Boundaries in Transplant Oncology
Singapore September 2023

Selecting the Ideal Candidate for Dowsntaging

Gonzalo Sapisochin MD, PhD, MSc
Associate Professor of Surgery
University of Toronto
Abdominal Transplant & HPB Surgical Oncology
University Health Network, Toronto

UHN Ajmera Transplant Centre

TORONTO
Liver Transplant Program

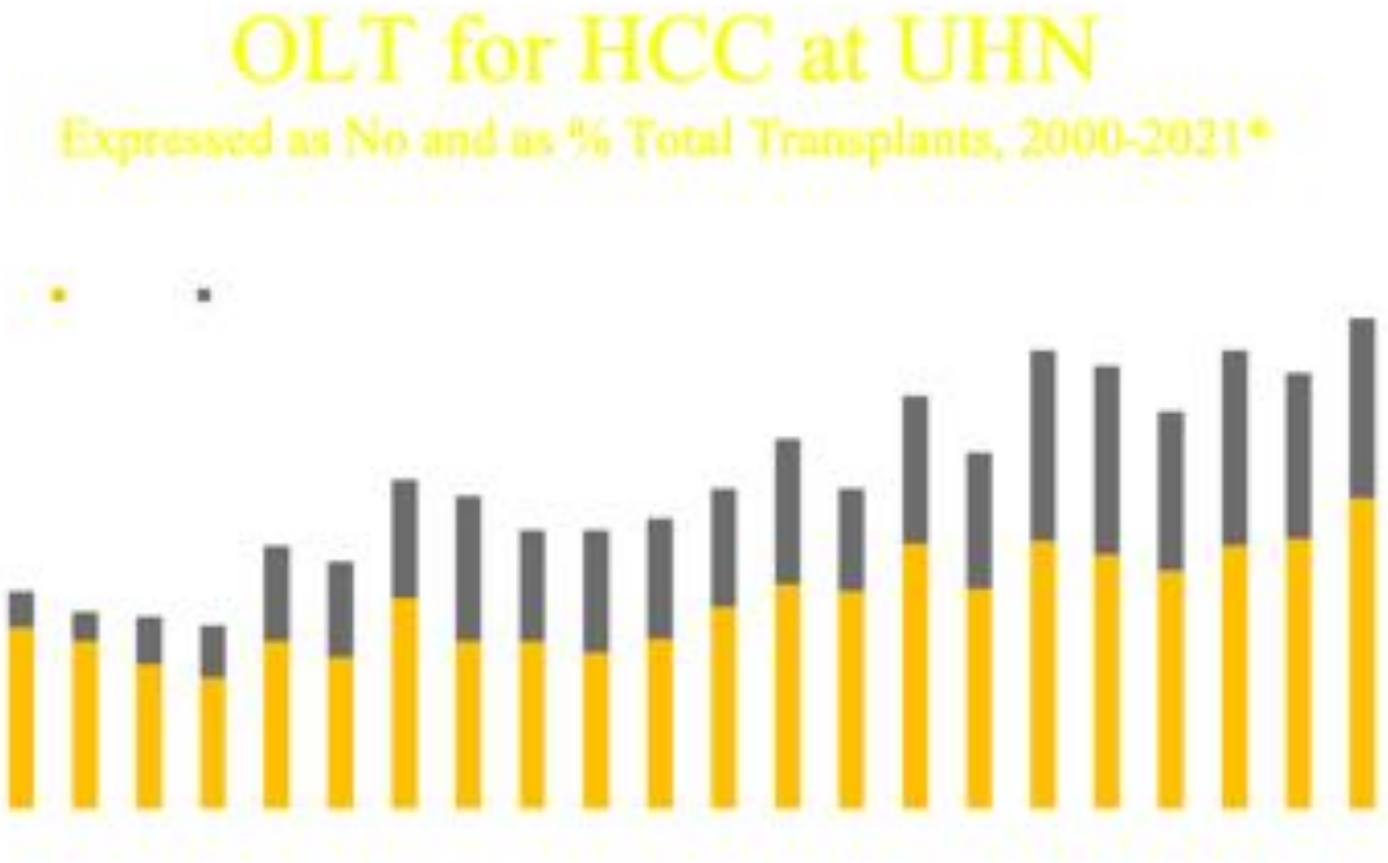
Disclosures

Grant Support from Bayer®, Roche®
Consultant for Novartis®, Integra®, Roche®, AstraZeneca®, Chiesi®, Eisai®, HepaRegeniX®.

UHN Ajmera Transplant Centre

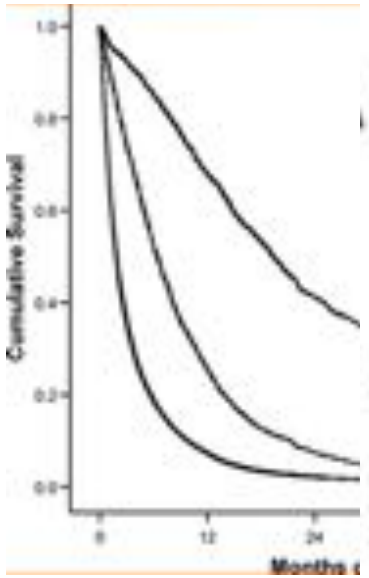
Liver Transplantation for HCC represents the best treatment option

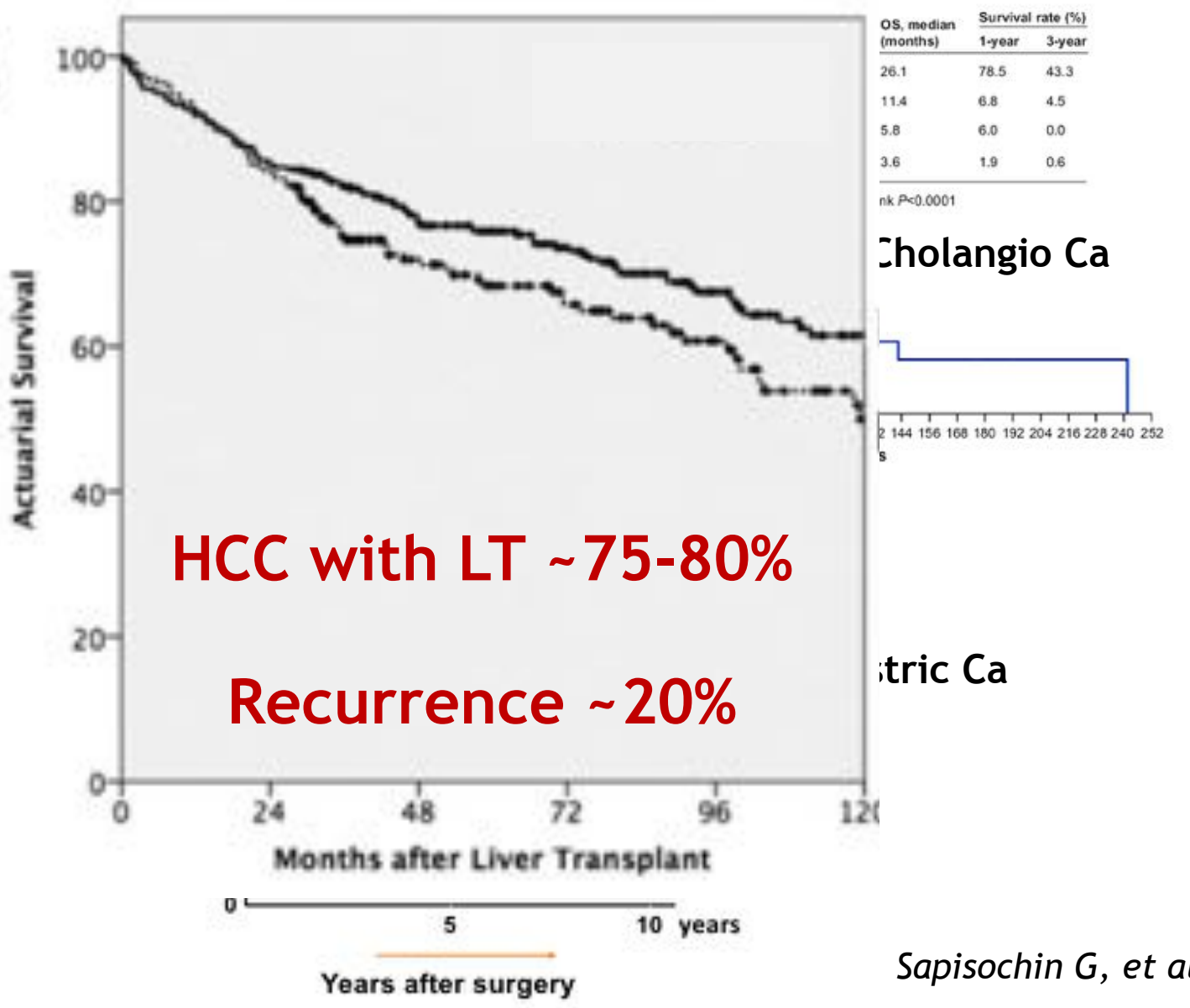
- Liver transplantation treats both the cancer with the widest margins and the underlying liver disease.



UHN Ajmera Transplant Centre

Outcomes: 5-year survival for abdominal malignancies





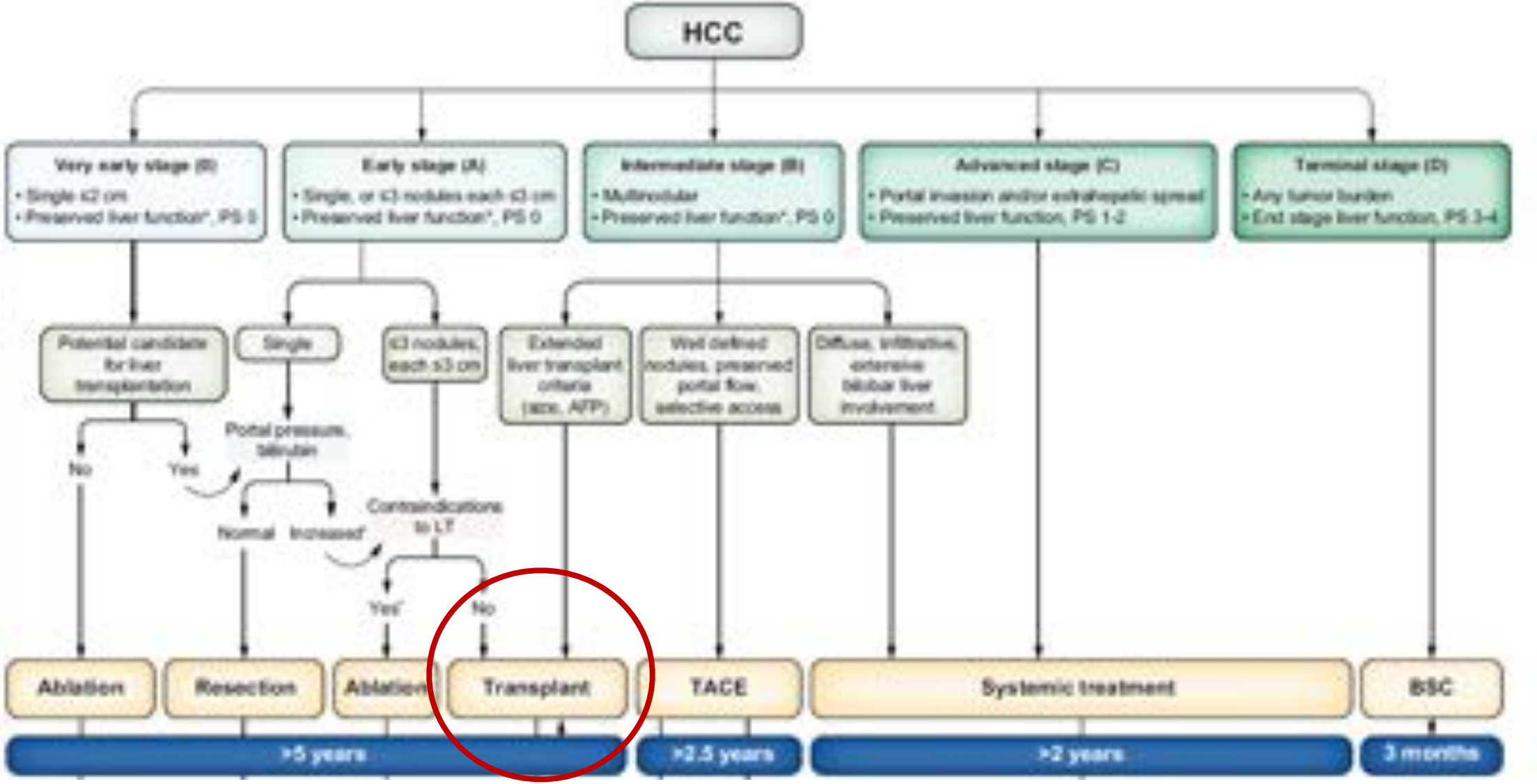
HCC with LT ~75-80%

Recurrence ~20%

UHN Ajmera Transplant Centre

Sapisochin G, et al. Hepatology 2016

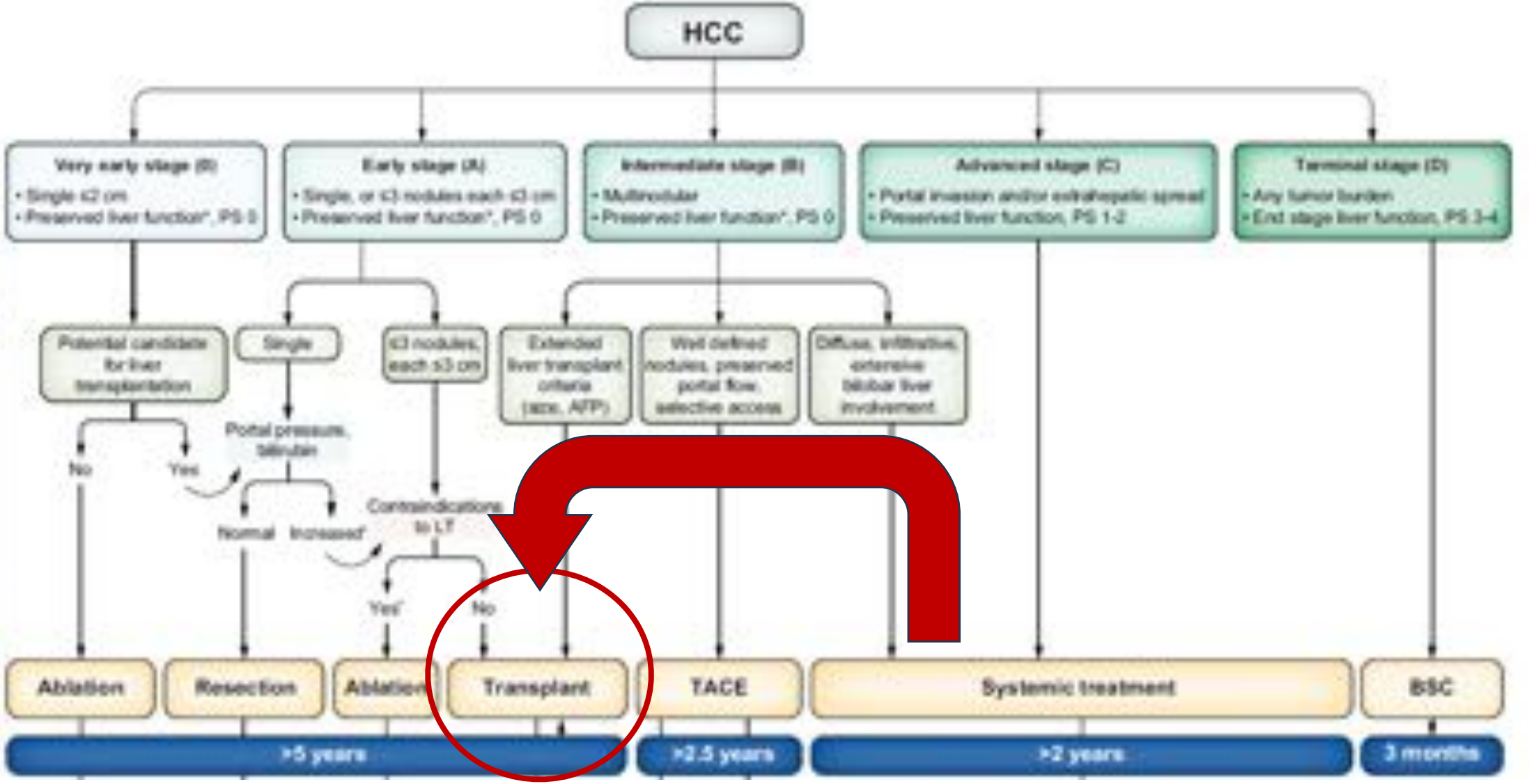
BCLC Staging System and LT



UHN Ajmera Transplant Centre

Reig M, et al. J Hepatol 2022

BCLC Staging System and LT



UHN Ajmera Transplant Centre

Reig M, et al. J Hepatol 2022

How can we Transplant Patients Beyond Milan Criteria?

Extended Criteria
(biological markers?)

Downstaging

Downstaging

62 yo man – NASH cirrhosis
CPT A, MELD 12, with Portal Hypertension (plt count 50.000)

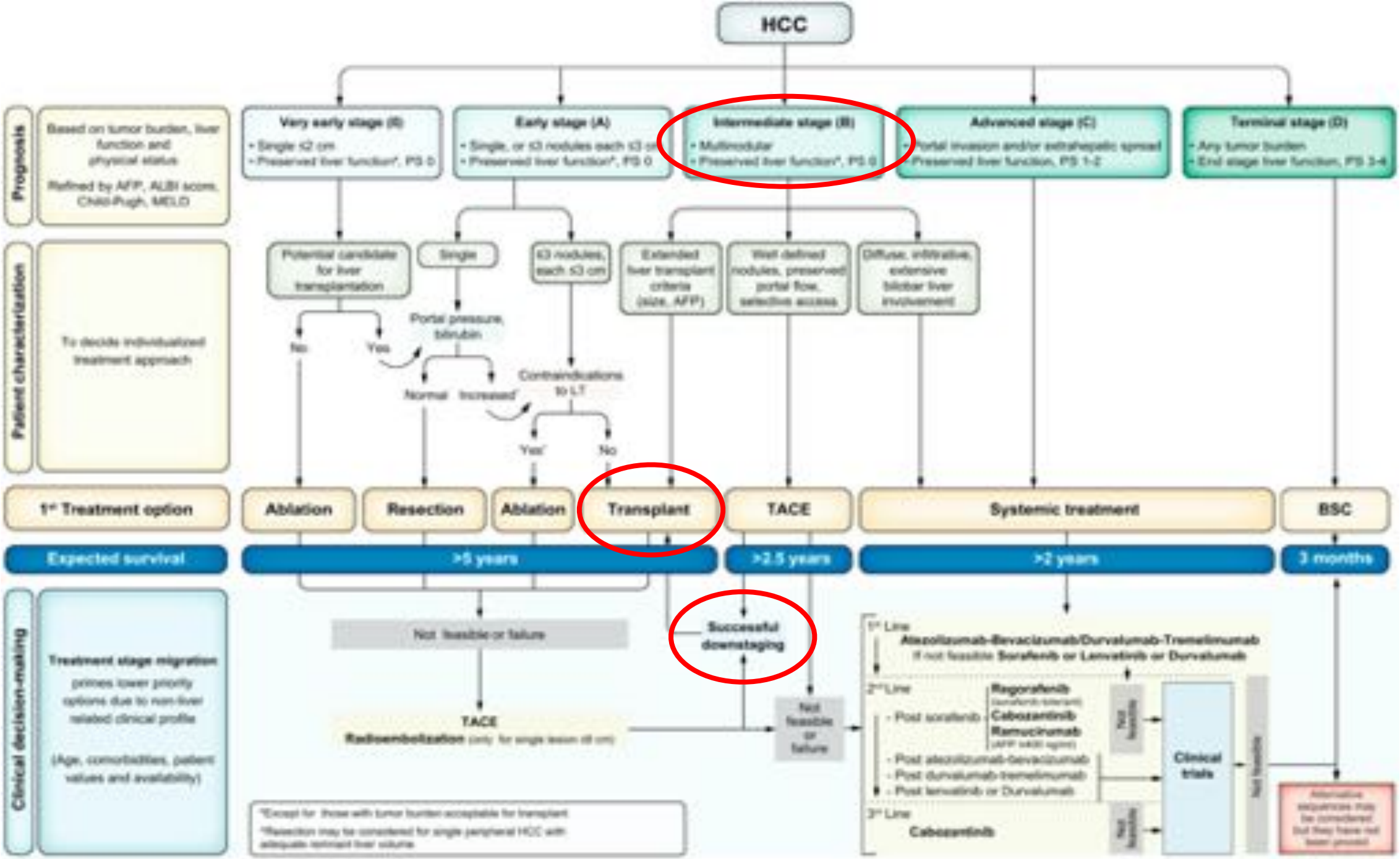
Tumor Burden:
6 HCCs.
2 are 5.5 cm and 4.3 cm
The other 4 are 3 cm, 2.4 cm, 1.5 cm and 1 cm
TTV=155

Excellent Functional Status – ECOG 0

AFP 3200 ng/mL

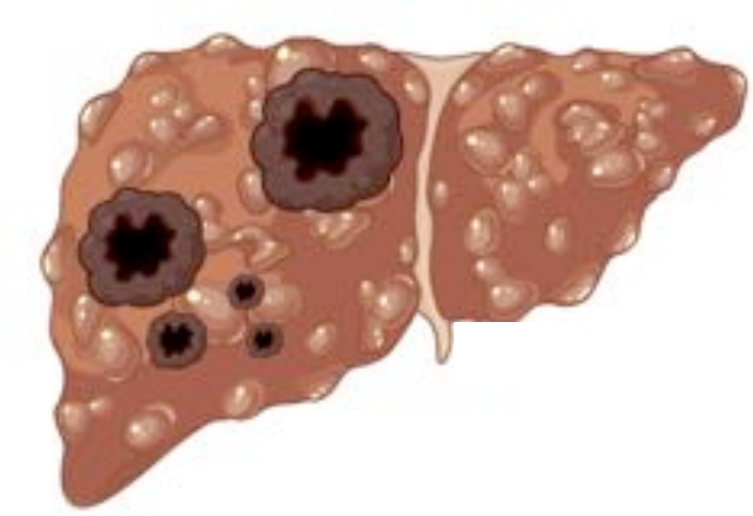
Treatment Options:

- Currently not a candidate for LT.
- Not a candidate for resection.
- TACE/TARE palliative – Median OS ~30 months
- Systemic Therapy – Median OS ~ 16-20 months


HCC
Prognosis
Based on tumor burden, liver function and physical status
Refined by AFP, ALBI score, Child-Pugh, MELD
Very early stage (0)
• Single ≤2 cm
• Preserved liver function*, PS 0
Early stage (A)
• Single, or ≤3 nodules each ≤3 cm
• Preserved liver function*, PS 0
Intermediate stage (B)
• Multinodular
• Preserved liver function*, PS 0
Advanced stage (C)
• Portal invasion and/or extrahepatic spread
• Preserved liver function, PS 1-2
Terminal stage (D)
• Any tumor burden
• End stage liver function, PS 3-4
Patient characterization
To decide individualized treatment approach
Potential candidate for liver transplantation
Single
≤3 nodules, each ≤3 cm
Extended liver transplant criteria (size, AFP)
Well defined nodules, preserved portal flow, selective access
Diffuse, infiltrative, extensive bilobar liver involvement
No
Yes
Portal pressure, bilirubin
Normal
Increased
Contraindications to LT
Yes
No
1st Treatment option
Ablation
Resection
Ablation
Transplant
TACE
Systemic treatment
BSC
Expected survival
>5 years
>2.5 years
>2 years
3 months
Clinical decision-making
Treatment stage migration
primes lower priority options due to non-liver related clinical profile
(Age, comorbidities, patient values and availability)
Not feasible or failure
Successful downstaging
TACE
Radioembolization (only for single lesion ≤8 cm)
Not feasible or failure
1st Line
Atezolizumab-Bevacizumab/Durvalumab-Tremelimumab
If not feasible Sorafenib or Lenvatinib or Durvalumab
2nd Line
- Post sorafenib
Regorafenib
Cabozantinib
Ramucirumab
(AFP ≥400 ng/ml)
- Post atezolizumab-bevacizumab
- Post durvalumab-tremelimumab
- Post lenvatinib or Durvalumab
Not feasible
Clinical trials
3rd Line
Cabozantinib
Not feasible
Not feasible
*Except for those with tumor burden acceptable for transplant
*Resection may be considered for single peripheral HCC with adequate remnant liver volume

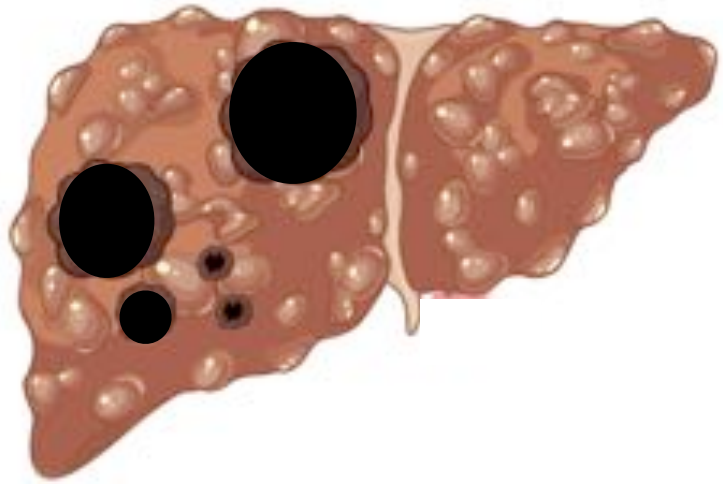
Downstaging

Extended/expanded institutional criteria
(usually UNOS DS)



LRT / ?systemic

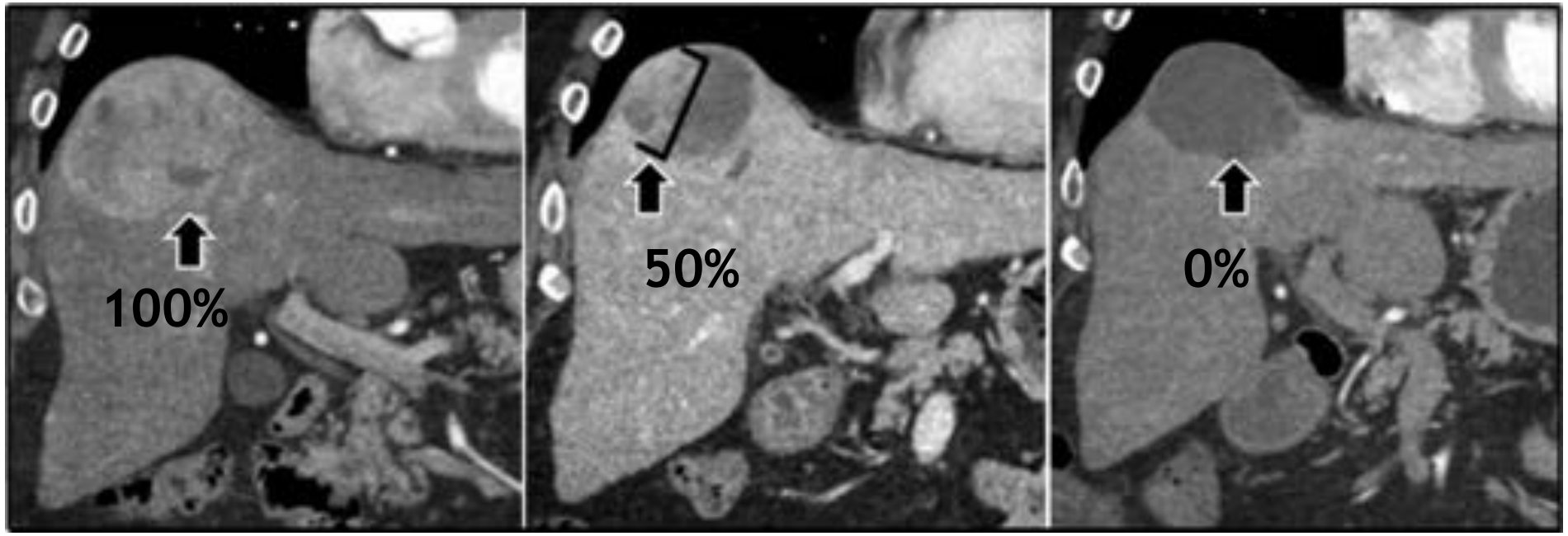
Downstaged institutional criteria
(usually Milan criteria – *viable tumour mRECIST*)



UHN Ajmera Transplant Centre

mRECIST Definition of Downstaging in HCC

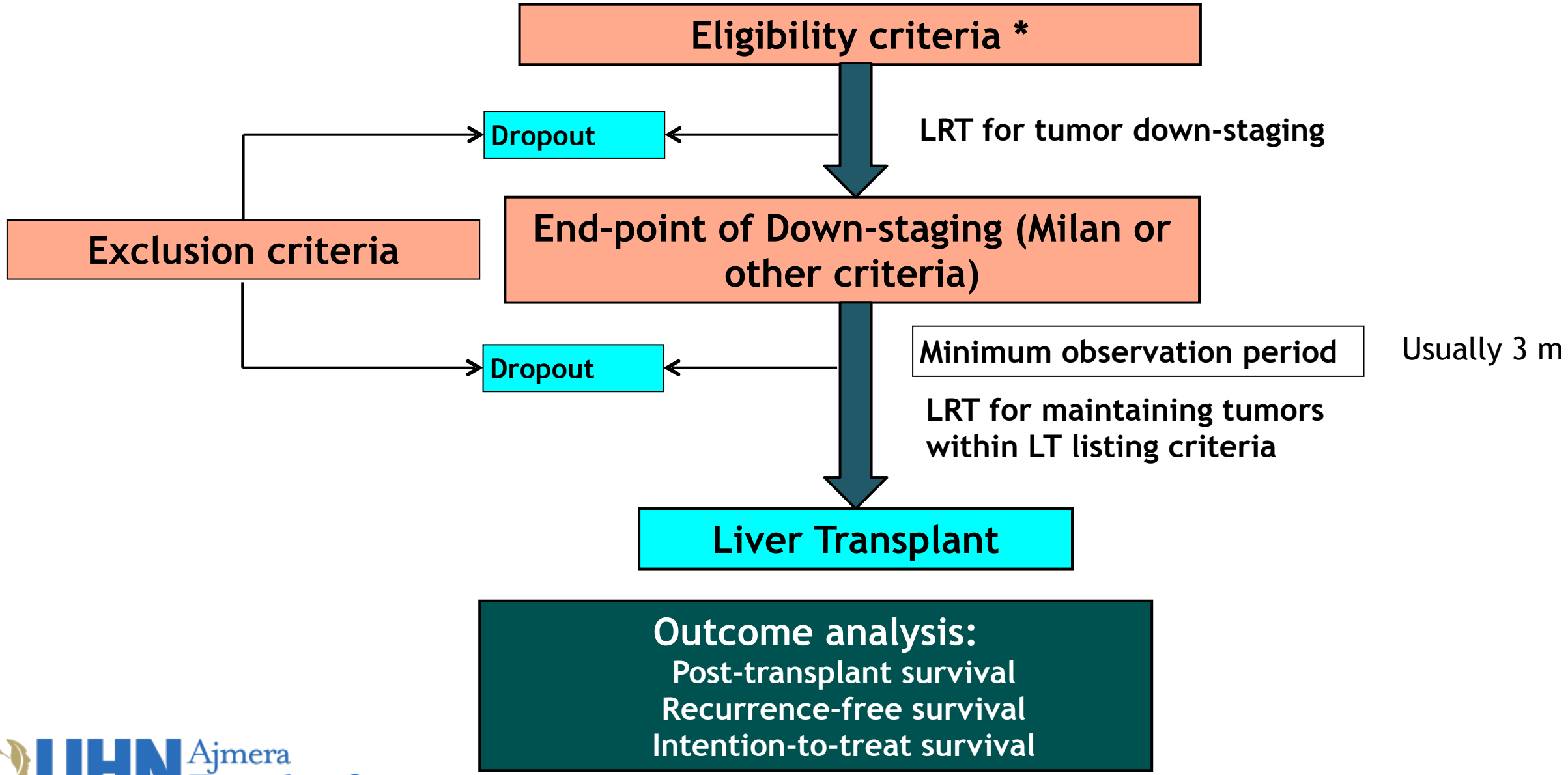
The radiological evaluation of the response to LRT is based on measurements of the maximum tumor diameter of ONLY viable tumors (mRECIST)



UHN Ajmera Transplant Centre

Lencioni R, et al. Semin Liver Dis 2010
Yao FY, et al. Hepatology 2016

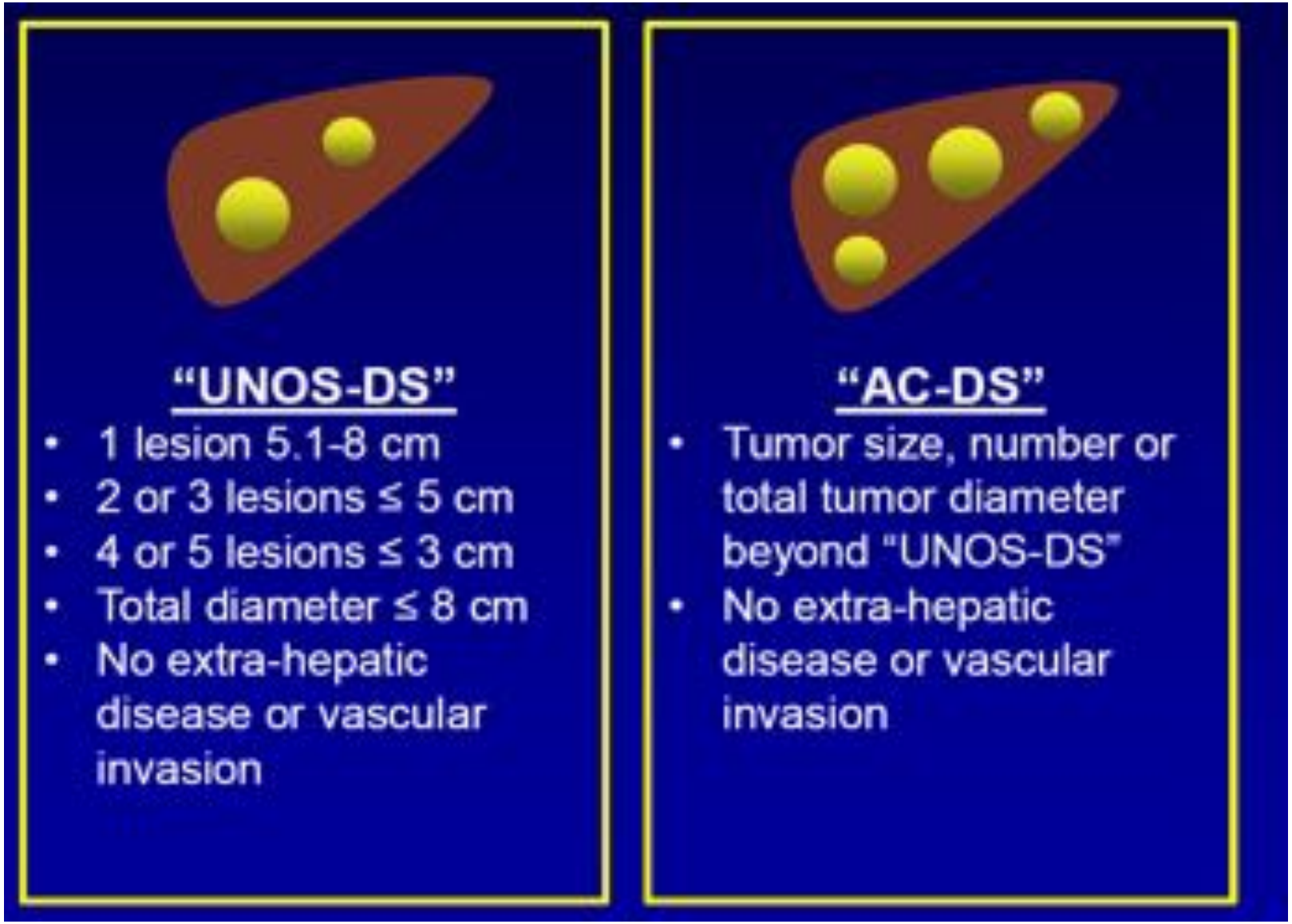
Down-Staging Protocol



UHN Ajmera Transplant Centre

Courtesy of F. Yao and N. Mehta

Down-Staging Protocols – Inclusion Criteria



UHN Ajmera Transplant Centre

Courtesy of F. Yao and N. Mehta - UCSF

End-Point of Down-Staging

- End point of down-staging should be viable tumor (mRECIST)
- Most centers end-point is MILAN criteria (UNOS/UCSF)
- In Toronto end-point is TTV 145 cm^3 and AFP <1000 ng/mL
- Geneva TTV 115 cm^3 and AFP <400 ng/mL

Based on Size and Number – Other markers?
discrepancy number/size tumors imaging and explant

UHN Ajmera Transplant Centre

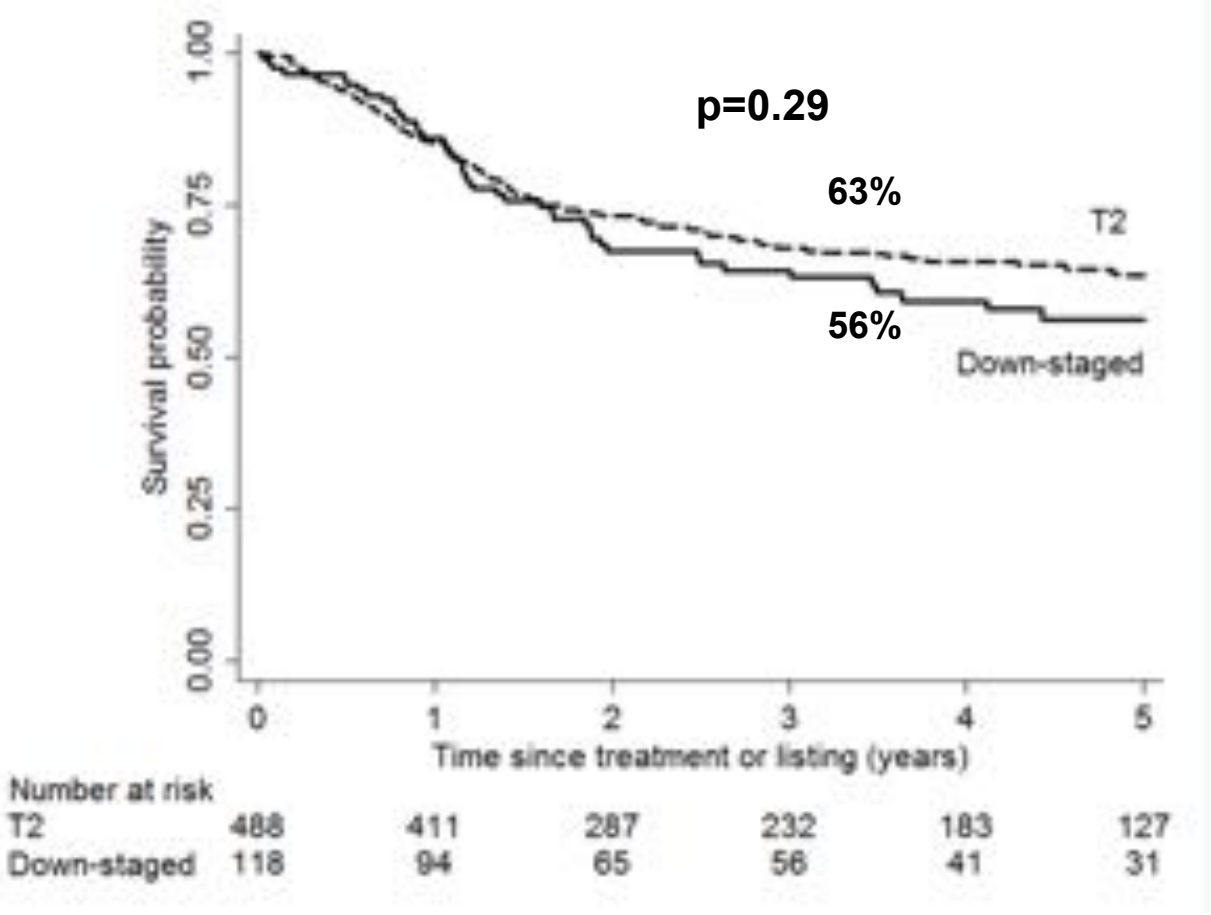
Yao FY, et al. Liver Transpl 2011
Jeng KS, et al. Transpl Proc 2019
Toso C, et al. Tranpl Int 2019

Minimum Observation Period After Down-Staging

- An observation period after down-staging is likely needed (tumor biology)
- The optimal time is unknown
- Most centers will accept a 3 month observation period. However, the time to transplant will be longer, except for LDLT

Outcomes of LT after Down-Staging

Intention-to-treat Survival

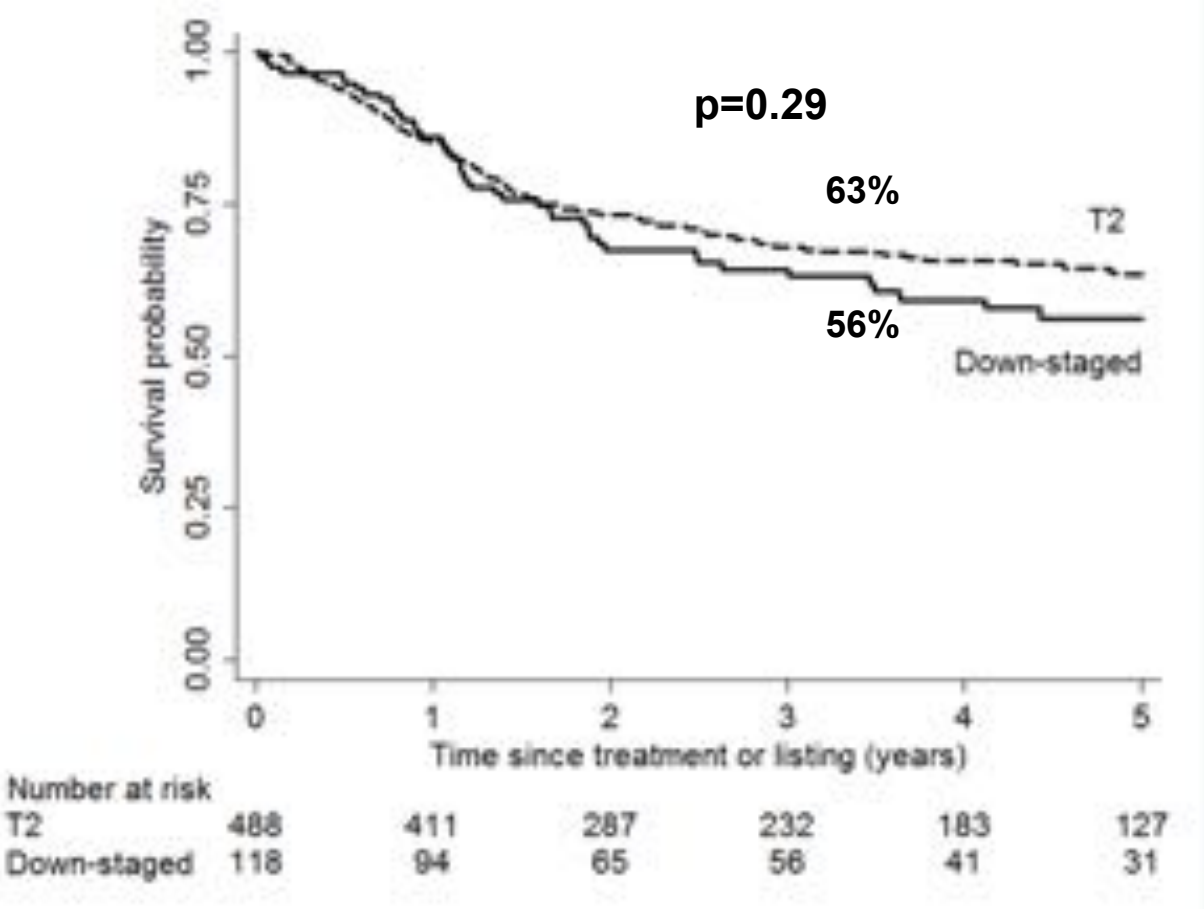


UHN Ajmera Transplant Centre

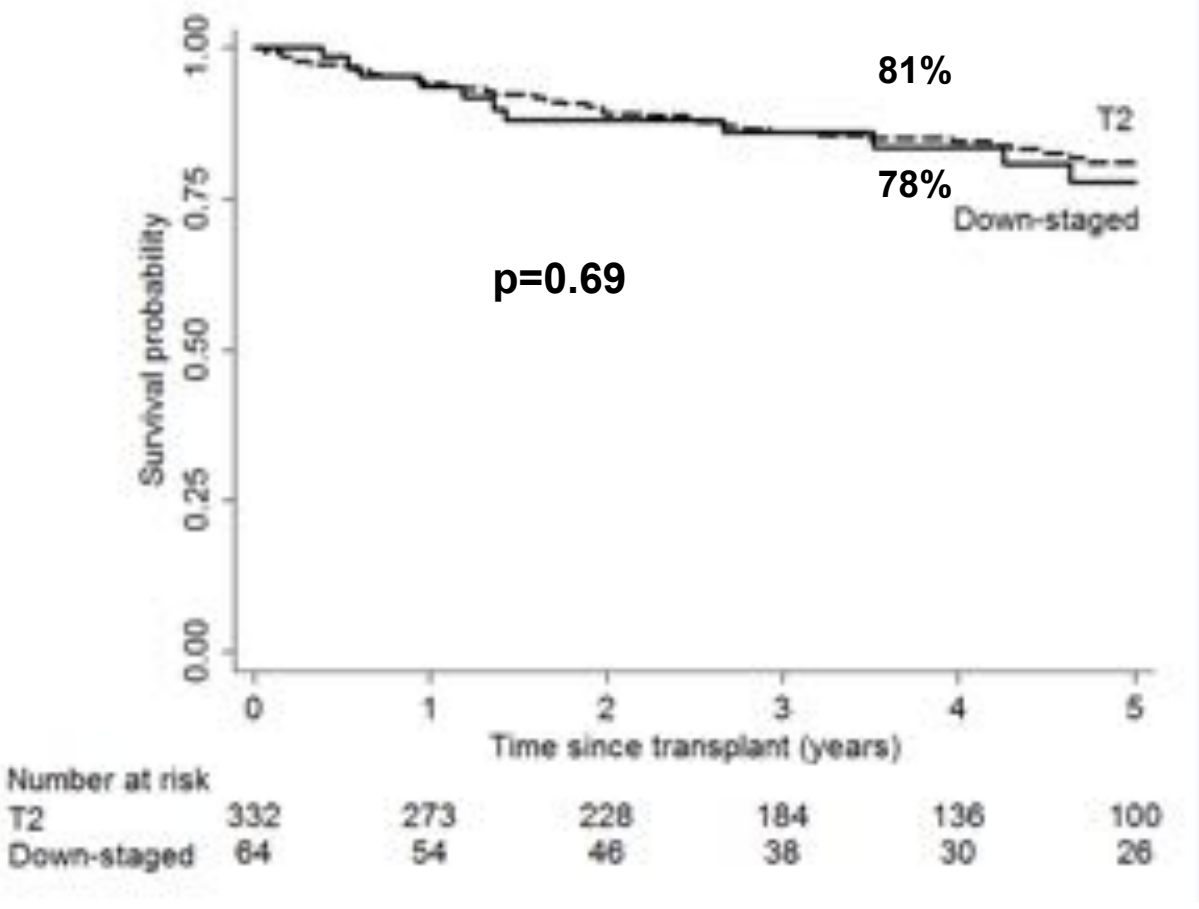
Yao et al. Hepatology 2015;61:1968-1977

Outcomes of LT after Down-Staging

Intention-to-treat Survival



Post-Transplant Survival



UHN Ajmera Transplant Centre

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

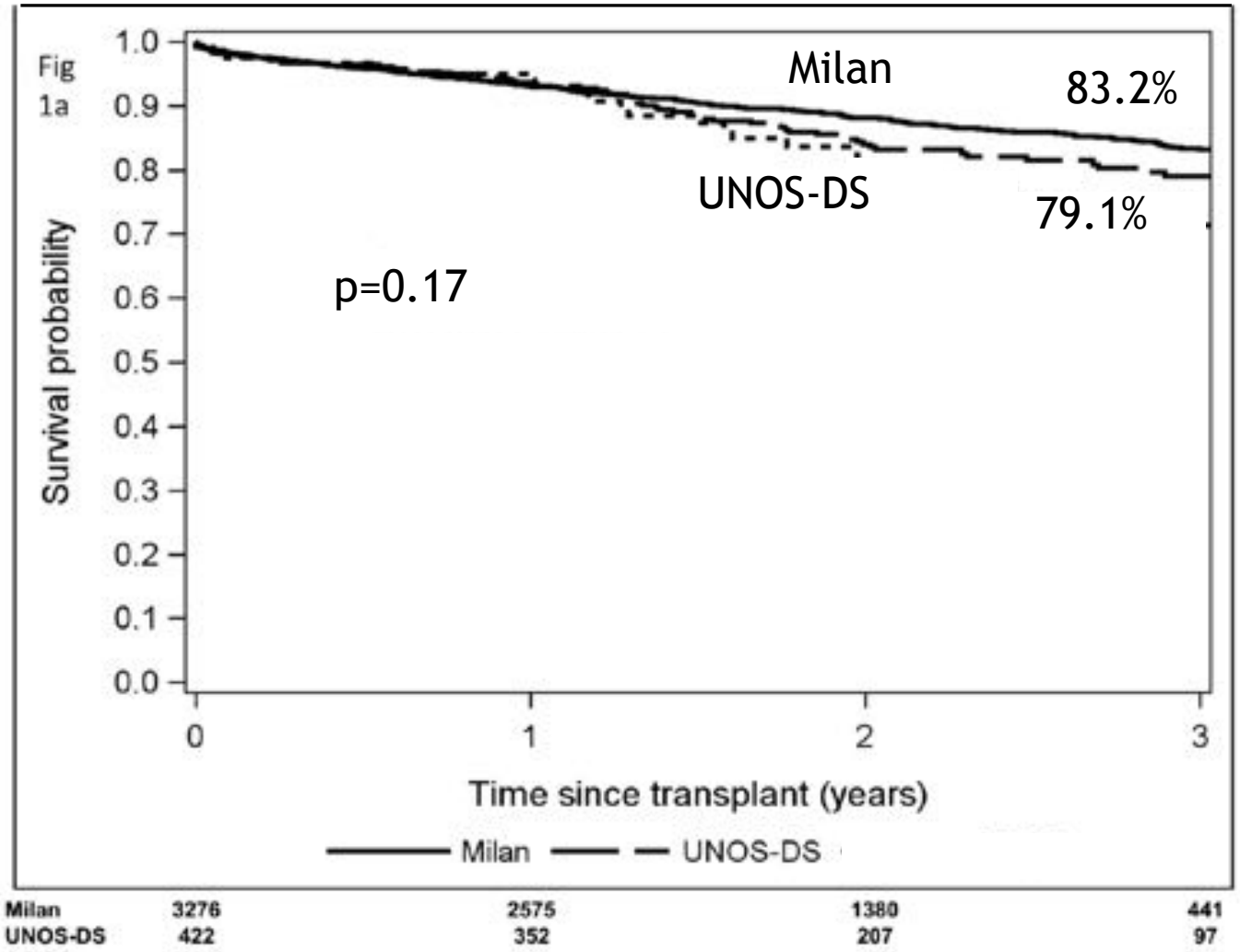
Outcomes of LT after Down-Staging

UNOS Database

3276 patients MILAN
422 DS to MILAN from UNOS-DS
Protocol

1 lesion 5-8 cm
2-3 lesions 3-5 cm with TTD <8 cm
4-5 lesions all <3 TTD <8

3-year Recurrence Probability
6.9% Milan vs. 12.8% UNOS-DS



UHN Ajmera Transplant Centre

Mehta N et al. Hepatology 2019

Should there be an upper tumor burden to attempt Down-staging?

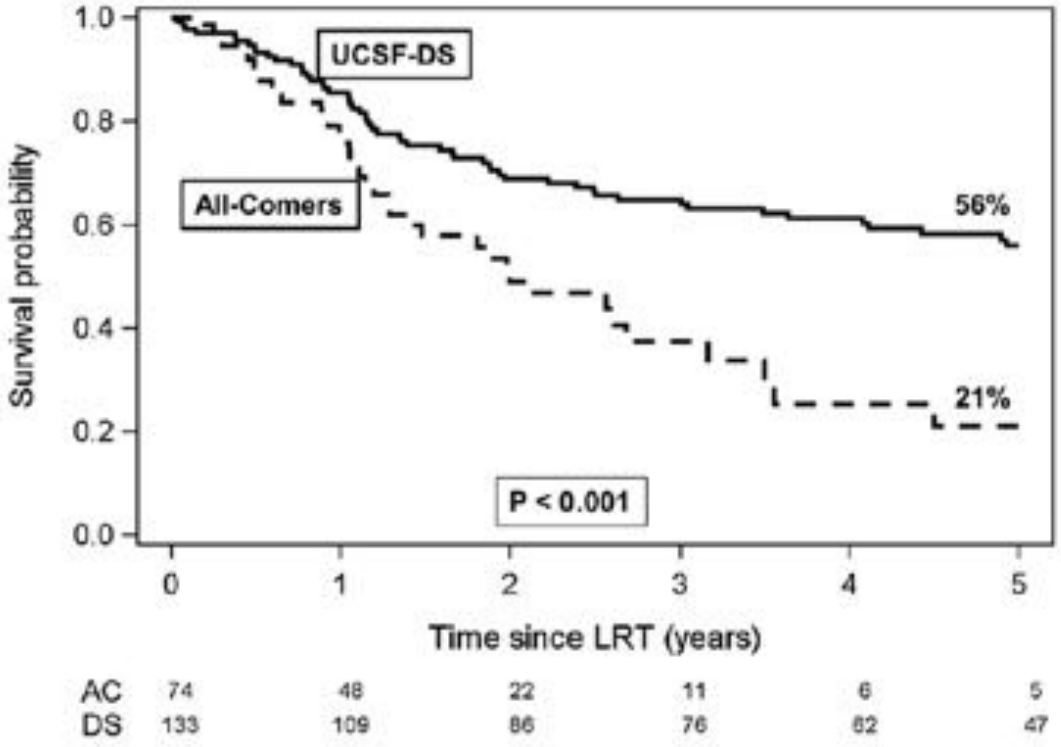
UCSF DS Criteria

Inclusion Criteria

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

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

Absence of vascular invasion based on cross-sectional imaging

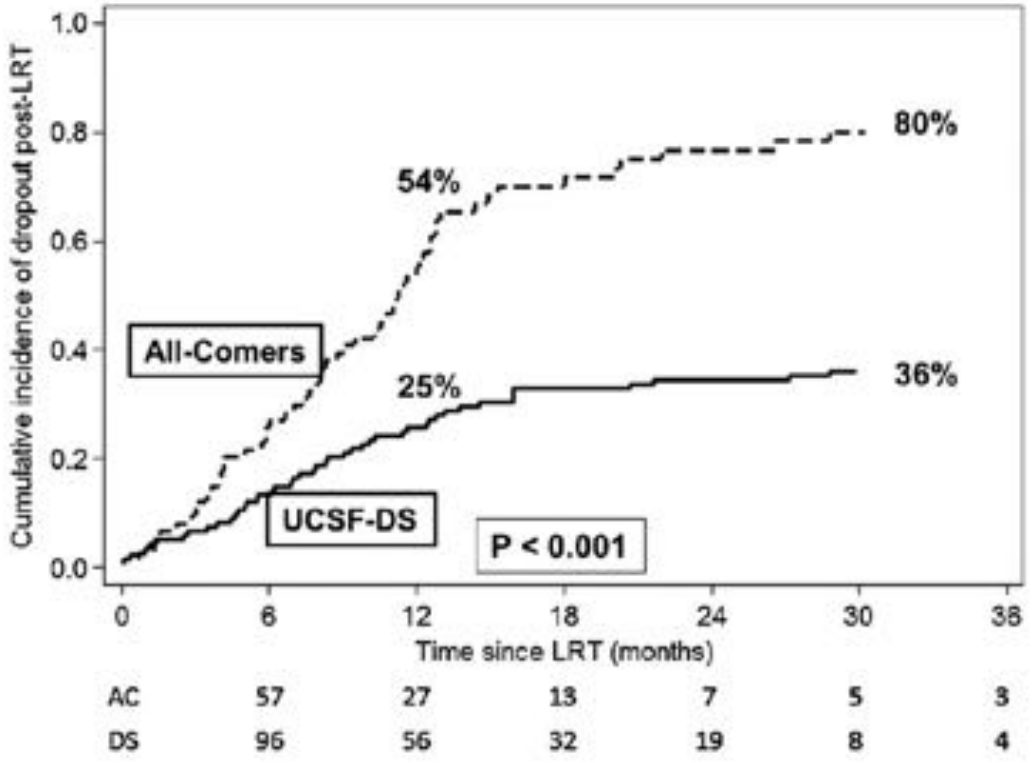


All-comers Criteria

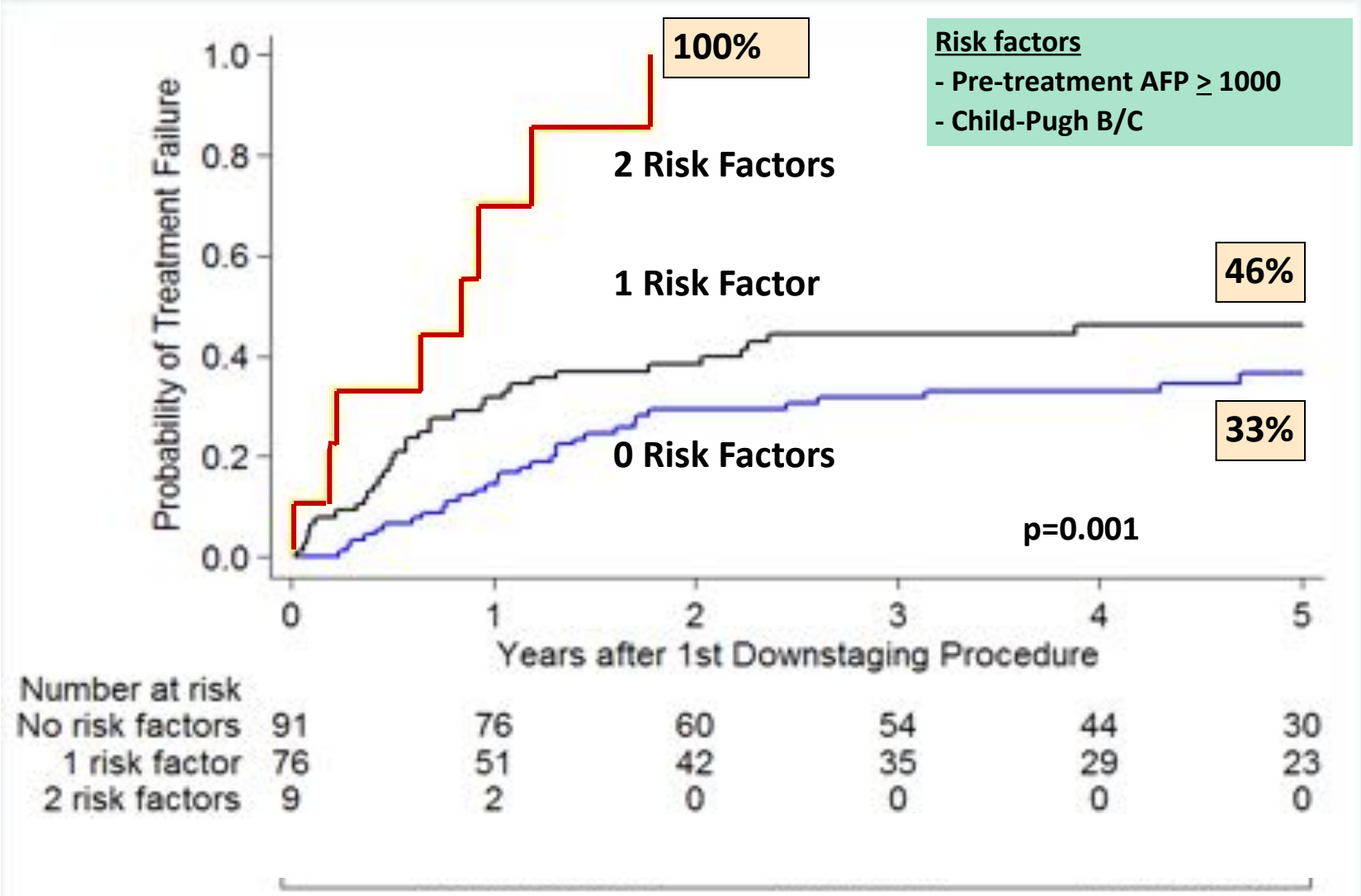
HCC exceeding UCSF-DS protocol by any of the following:

1. HCC tumor number
2. HCC tumor size
3. Total HCC tumor diameter

Absence of vascular invasion based on cross-sectional imaging



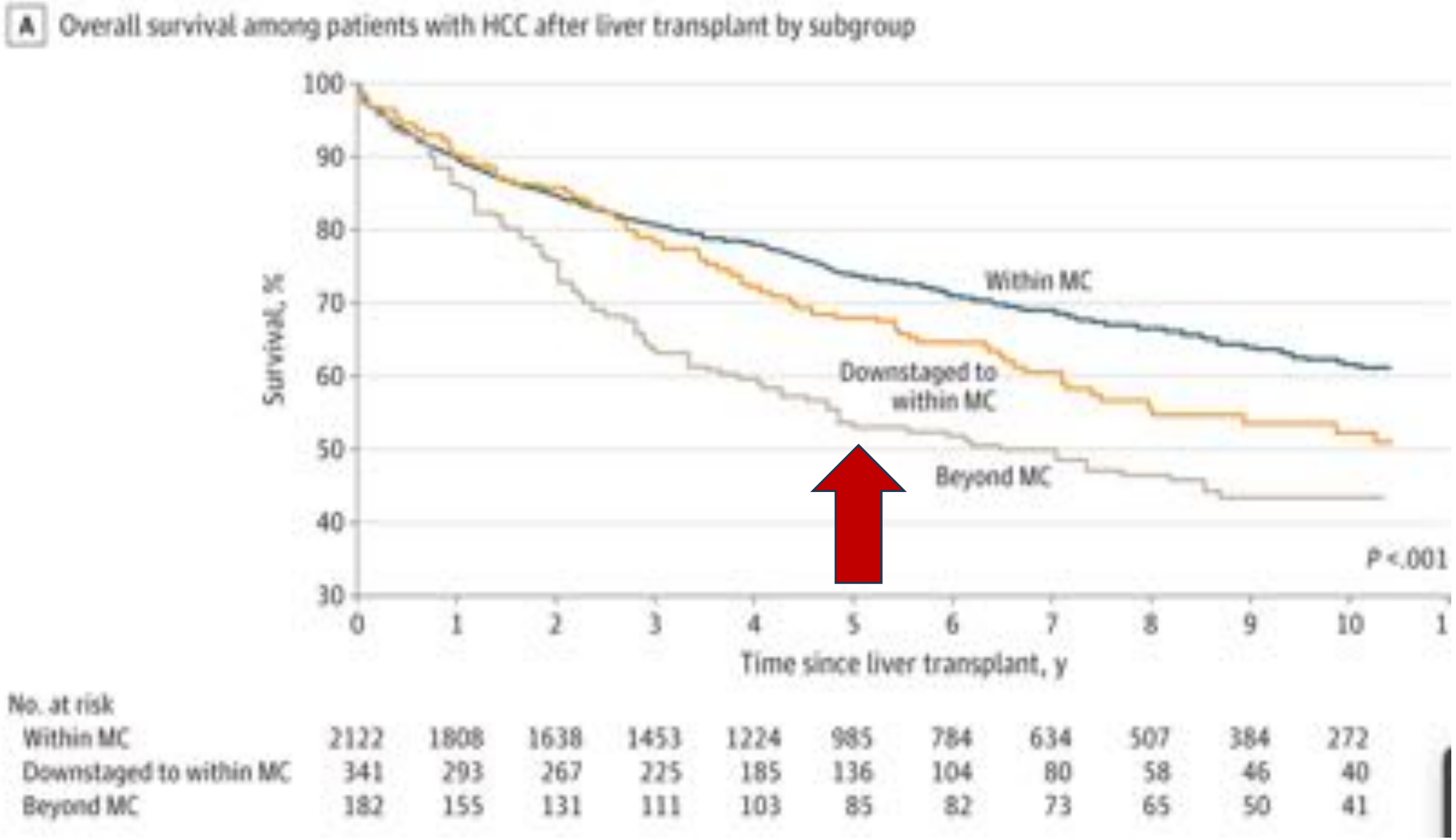
Treatment Failure: AFP and Child's Class



UHN Ajmera Transplant Centre

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

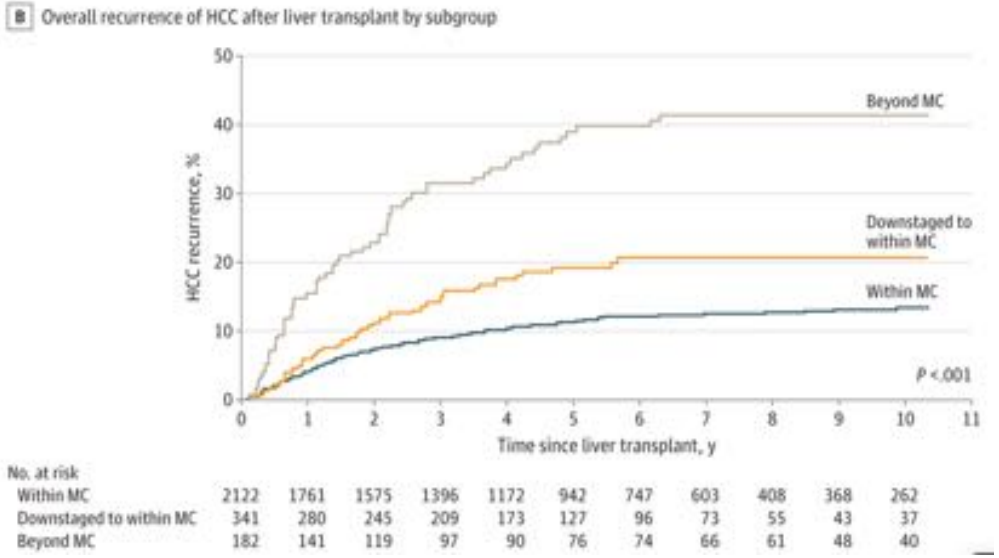
Multicenter Downstaging Study

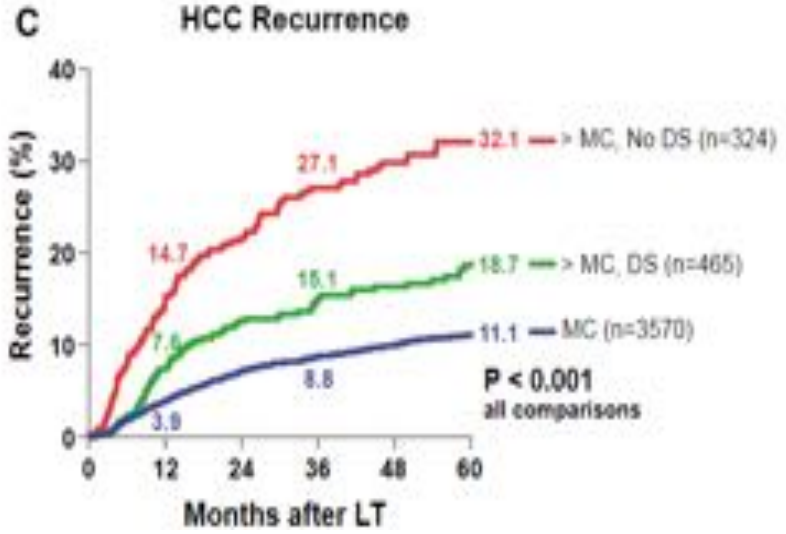


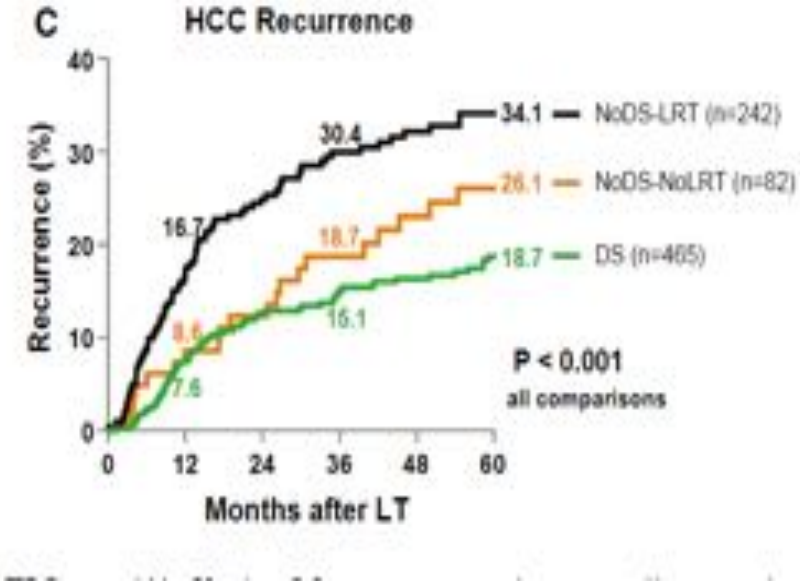
UHN Ajmera Transplant Centre

P Tabrizian et al. JAMA Surgery 2022

Multicenter Downstaging Study



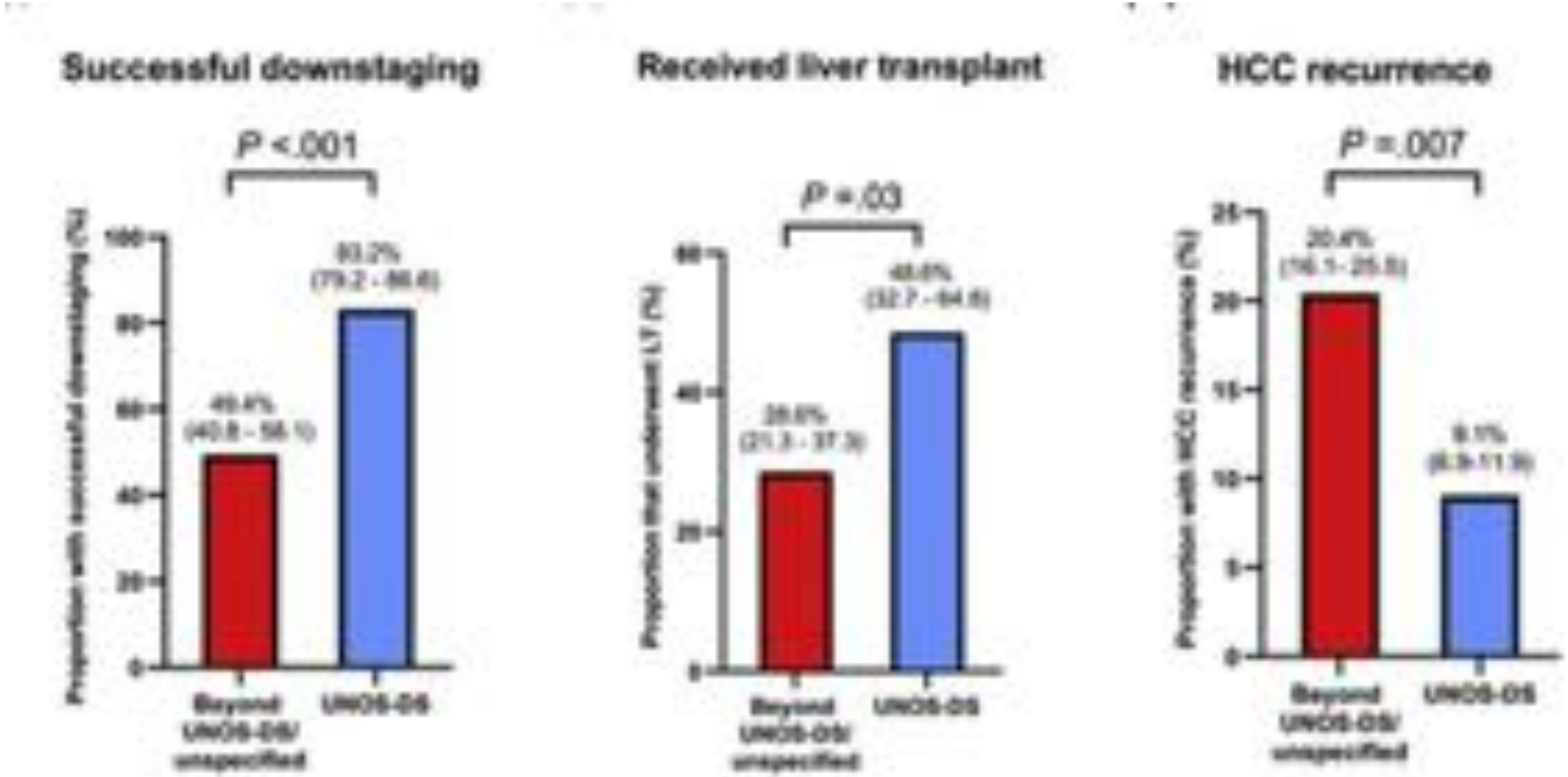




UHN Ajmera Transplant Centre

P Tabrizian et al. JAMA Surgery 2022; A Kardashian et al. Hepatology 2020

Within and Beyond UNOS-DS Protocols



UHN Ajmera Transplant Centre

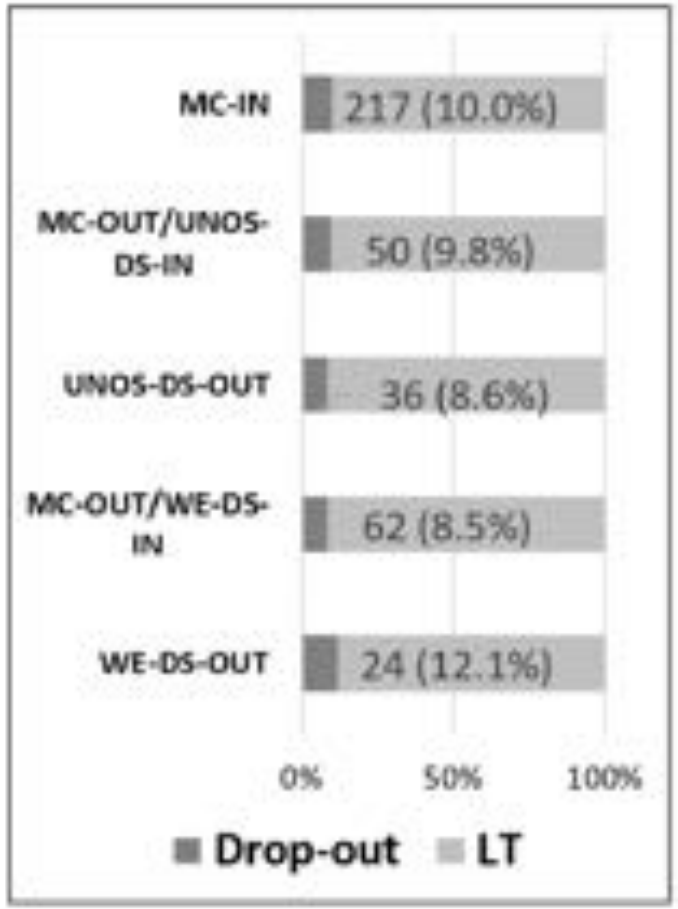
Tan et al, CGH 2022

Upper Limit for Downstaging

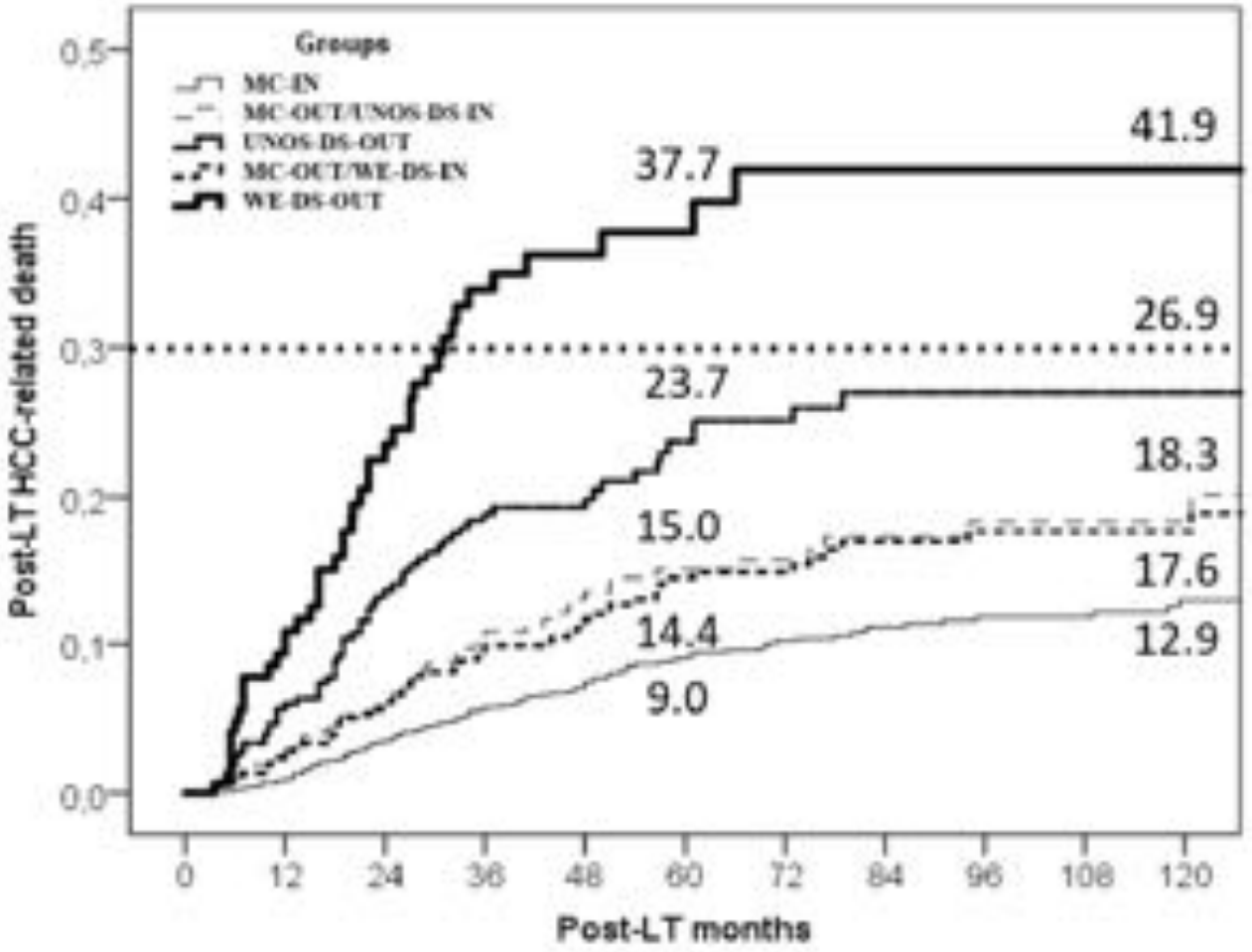
WE-DS Criteria

- AFP <20 plus diameter and number <12
- AFP 21-200 and <10
- AFP 201-500 <7
- AFP 501-1000 <5

Similar Drop-out Rates



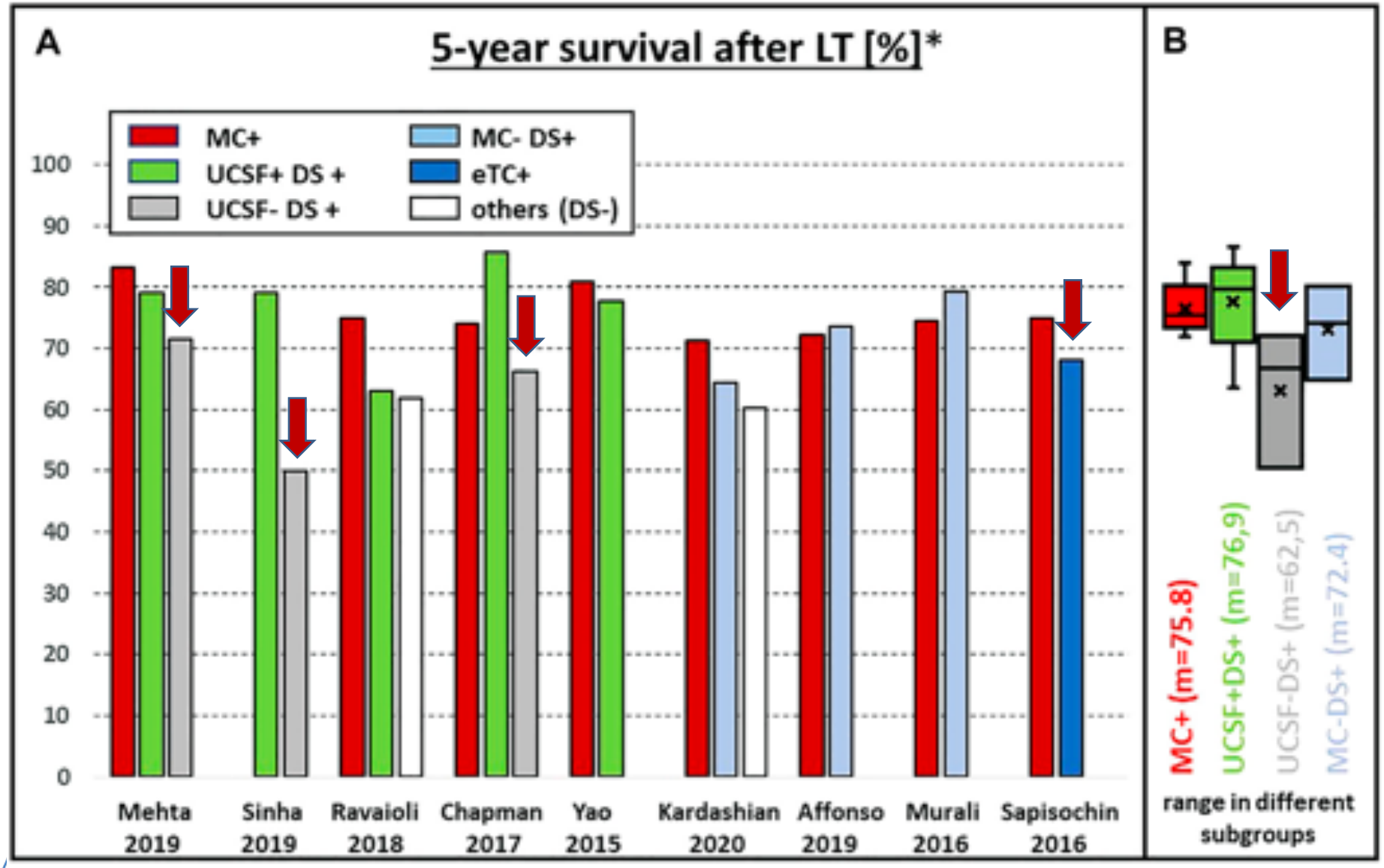
10y OS HCC related-death 82% within WE-DS 58 % if WE-DS out



UHN Ajmera Transplant Centre

Lai Q et al. Cancers 2020

Upper Limit for Downstaging



UHN Transplant Centre

Seehofer D, Sapisochin G et al. Tranpl Int 2022

Upper Limit for Downstaging

- An upper limit in tumor burden probably exists beyond which successful LT after down-staging becomes an unlikely goal
  - Significantly worse rates of down-staging, ITT survival, waitlist dropout, and post-LT survival for HCC pts initially beyond UNOS-DS compared to Milan and UNOS-DS patients
  - But what that limit is?

- Could adding systemic therapy in this population be helpful to improve outcomes

Some Caveats

- A proportion of patients without downstaging to Milan (and tumor response) would have done very well after LT.

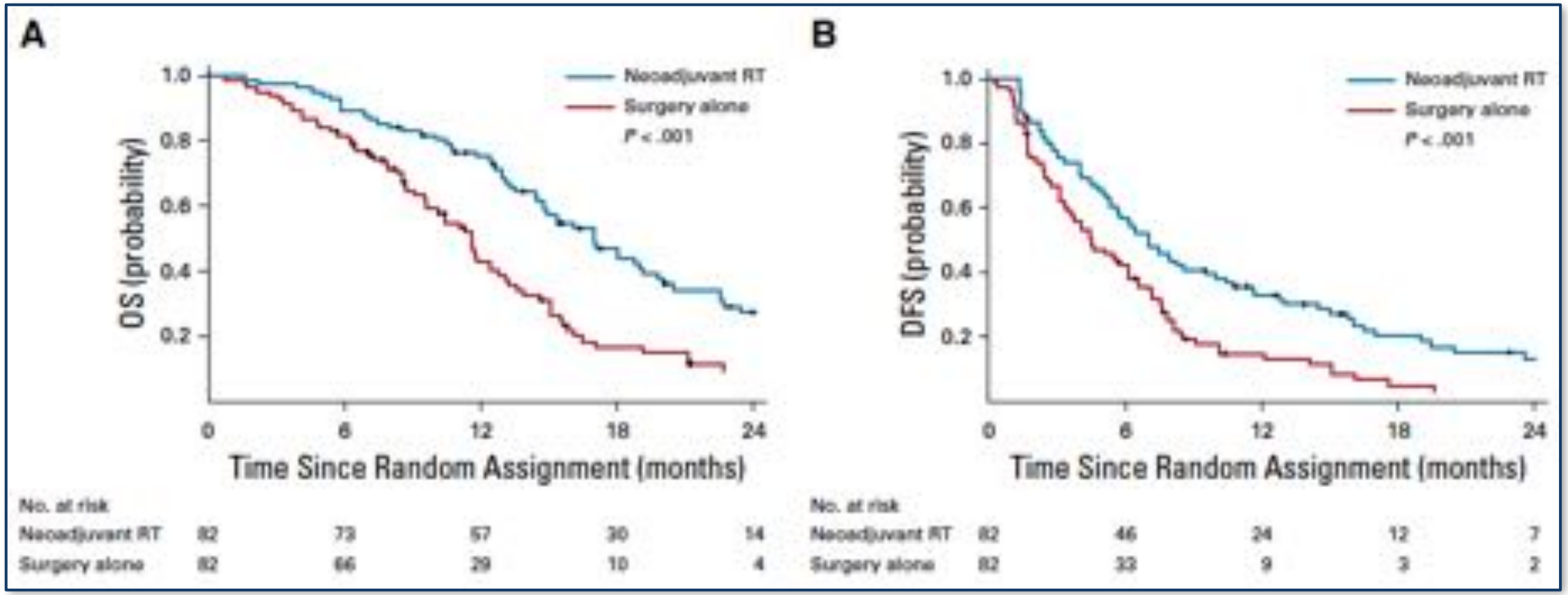
- Do we need downstaging? Or response to therapy is enough?

- Should this be different in the setting of LDLT, were the threshold of 5y OS may be different?

- What is the goal of therapy in those with high tumor burder? When to start immunotherapy?

Can we successfully Down-stage patients with Macrovascular Invasion?

Neoadjuvant Three-Dimensional Conformal Radiotherapy for Resectable Hepatocellular Carcinoma With Portal Vein Tumor Thrombus: A Randomized, Open-Label, Multicenter Controlled Study



UHN Ajmera Transplant Centre

Wei X, et al. J Clin Oncol 2019

Experience With LDLT in Patients with Hepatocellular Carcinoma and Portal Vein Tumor Thrombosis Postdownstaging

Category of patient → Characteristics ↓	HCC-cirr, PVTT, LDLT post downstaging N = 25	HCC-cirr, PVTT, LDLT without downstaging N = 21	HCC-cirr, no PVTT, LDLT N = 405	p value
Recurrence Patterns				
Number of patients (%)	6 (24%)	10 (48%)	95 (23%)	0.043*
Time to recurrence [months] Median (range) Mean ± SD	 5 (1-39) 9 ± 15	 12 (2-44) 13 ± 13	 14 (1-108) 19 ± 17	0.006*
Recurrence type n (single or multiple sites)				
Hepatic	3 (50%)	2 (20%)	31 (33%)	0.460
Lung	5 (83%)	7 (70%)	42 (44%)	0.065
Bone	2 (33%)	4 (40%)	12 (13%)	0.042*
Lymph nodes, soft tissue	-	3 (30%)	8 (8%)	0.013*
Brain	-	1 (10%)	2 (2%)	0.425

5-y OS 57%

5-y OS 45%

5-y OS 65%

Median Follow-up 33 months

UHN Ajmera Transplant Centre

Soin A, et al. Transplantation 2020

Future Directions

- With newer LRT and systemic therapies all patients eligible for transplant without EH disease should be considered in “downstaging protocols”.

- With immunotherapy being used more in the pre-LT setting – upper limits of downstaging protocols likely to disappear (safety data awaited).

Unmet Needs

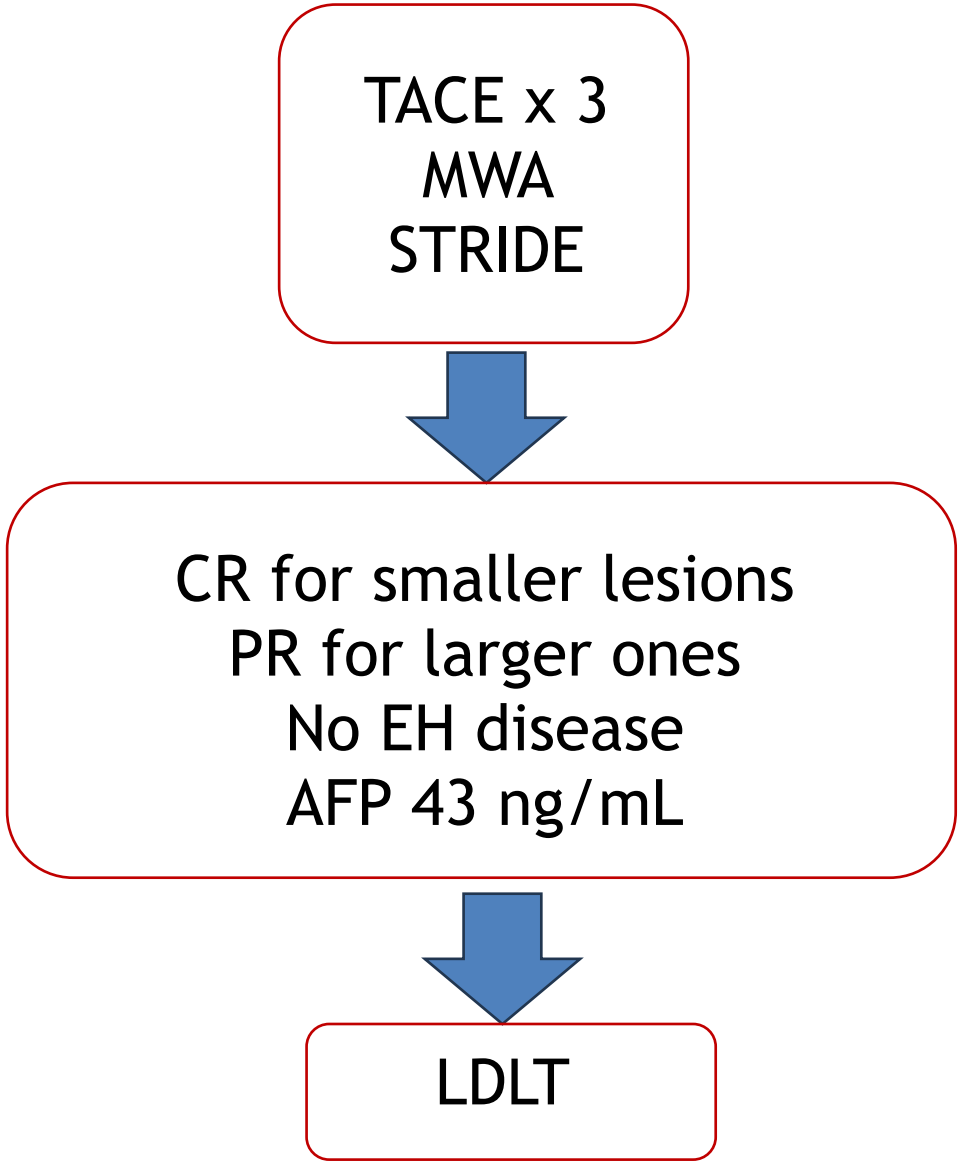
- What is the optimal Down-staging Protocol?
- Utilization of immunotherapy in this setting
- Down-staging to what? And how to monitor therapy (biomarkers)?
  - PET
  - ctDNA
  - Radiomics

62 yo man – NASH cirrhosis
CPT A, MELD 12, with Portal Hypertension
(plt count 50.000)

Tumor Burden:
6 HCCs.
2 are 5.5 cm and 4.3 cm
The other 4 are 3 cm, 2.4 cm,
1.5 cm and 1 cm
TTV=155

Excellent Functional Status – ECOG 0

AFP 3200 ng/mL



Who is the Ideal Candidate for Downstaging?

- Ideal are those just beyond Milan DS to Milan; BUT
- Most patients with no EH disease and no MVI should be considered into a DS strategy.
- Patients should receive the SOC treatment but transplant should be always a consideration down the road.

Summary

- Liver Transplantation plays a very important role in the global management of HCC – best treatment – and its utilization likely to increase (new therapies).

- "Downstaging" or "response to therapy" can increase the eligibility of patients.

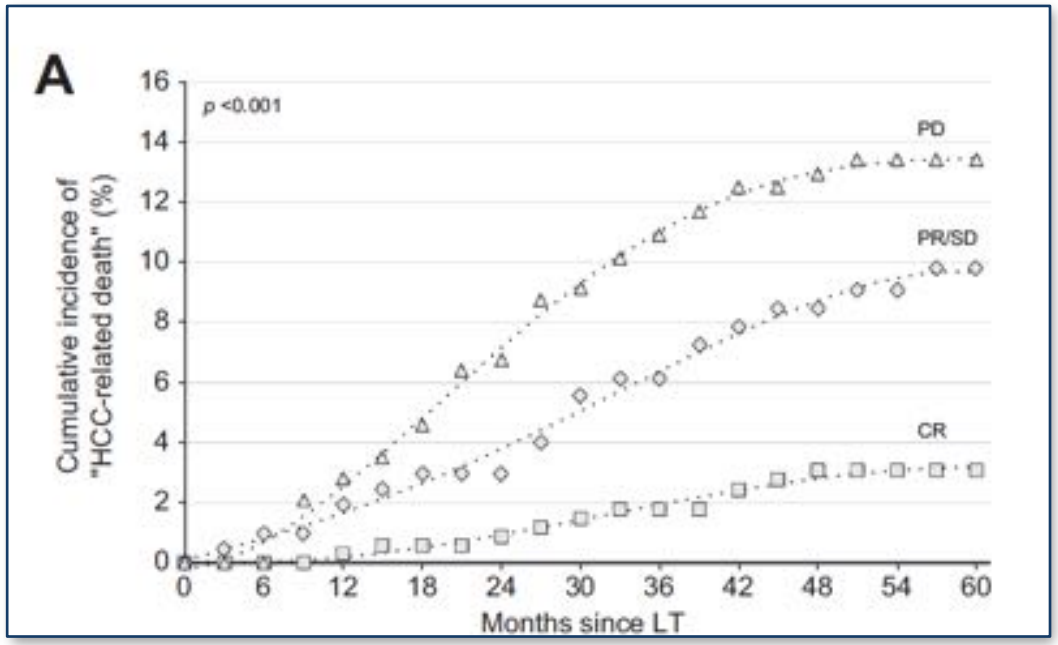
- Most patients "without EH" disease should likely be considered potential candidates for LT if sustained response to therapy.

@sapisochin

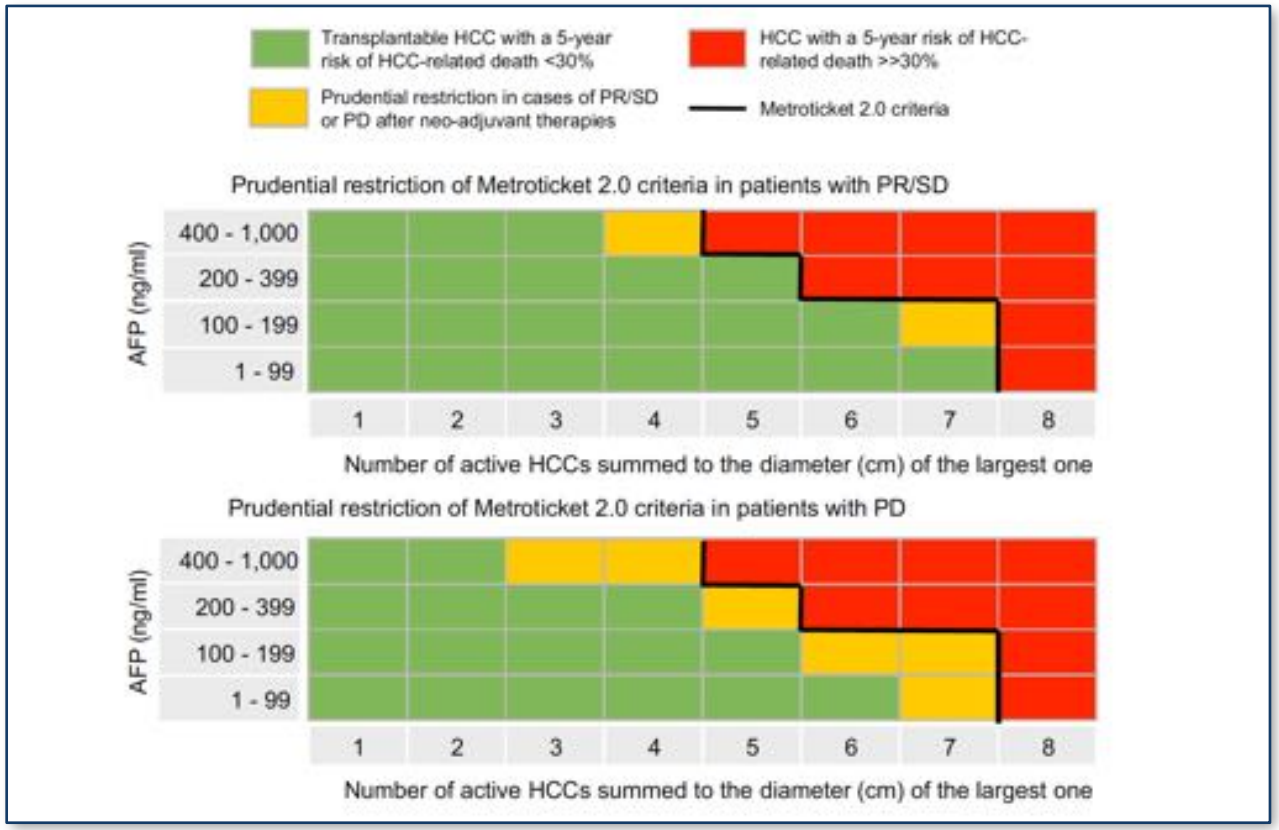
UHN Ajmera Transplant Centre

Gonzalo.Sapisochin@uhn.ca

Including mRECIST in the Metroticket 2.0 criteria improves prediction of hepatocellular carcinoma-related death after liver transplant



5-year *"HCC-related death"*
CR: 3.1%
PR/SD: 9.6%
PD: 13.4% (p<0.001)



UHN Ajmera Transplant Centre

Cuchetti A, et al. J Hepatol 2020

University of Toronto Experience

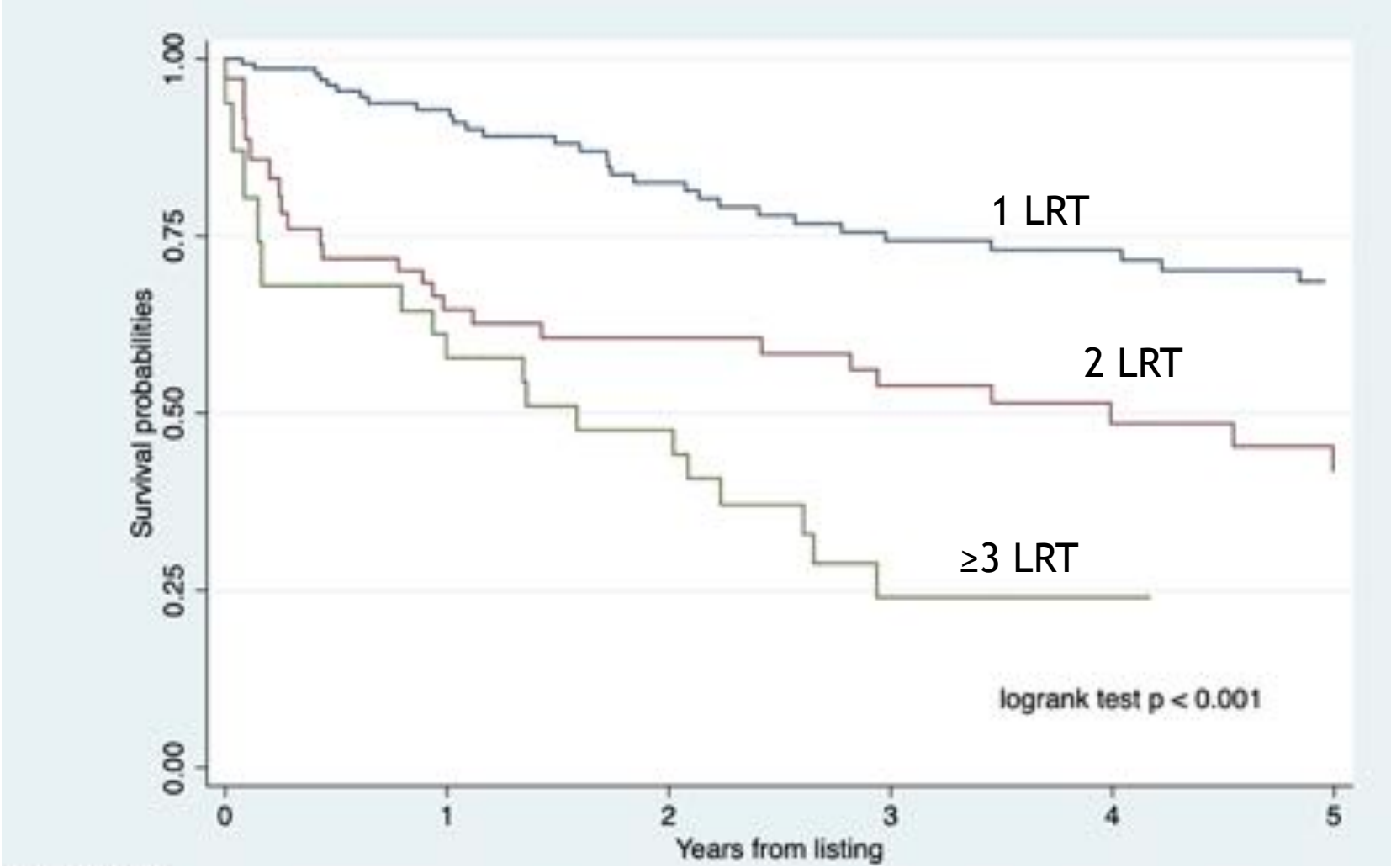
n=196

BEYOND MILAN

Multivariate Analysis

LRT >2 HR 2.19 (1.27-3.78)
LRT ≥3 HR 4.35 (2.32-8.16)

Intention-to-treat Analysis

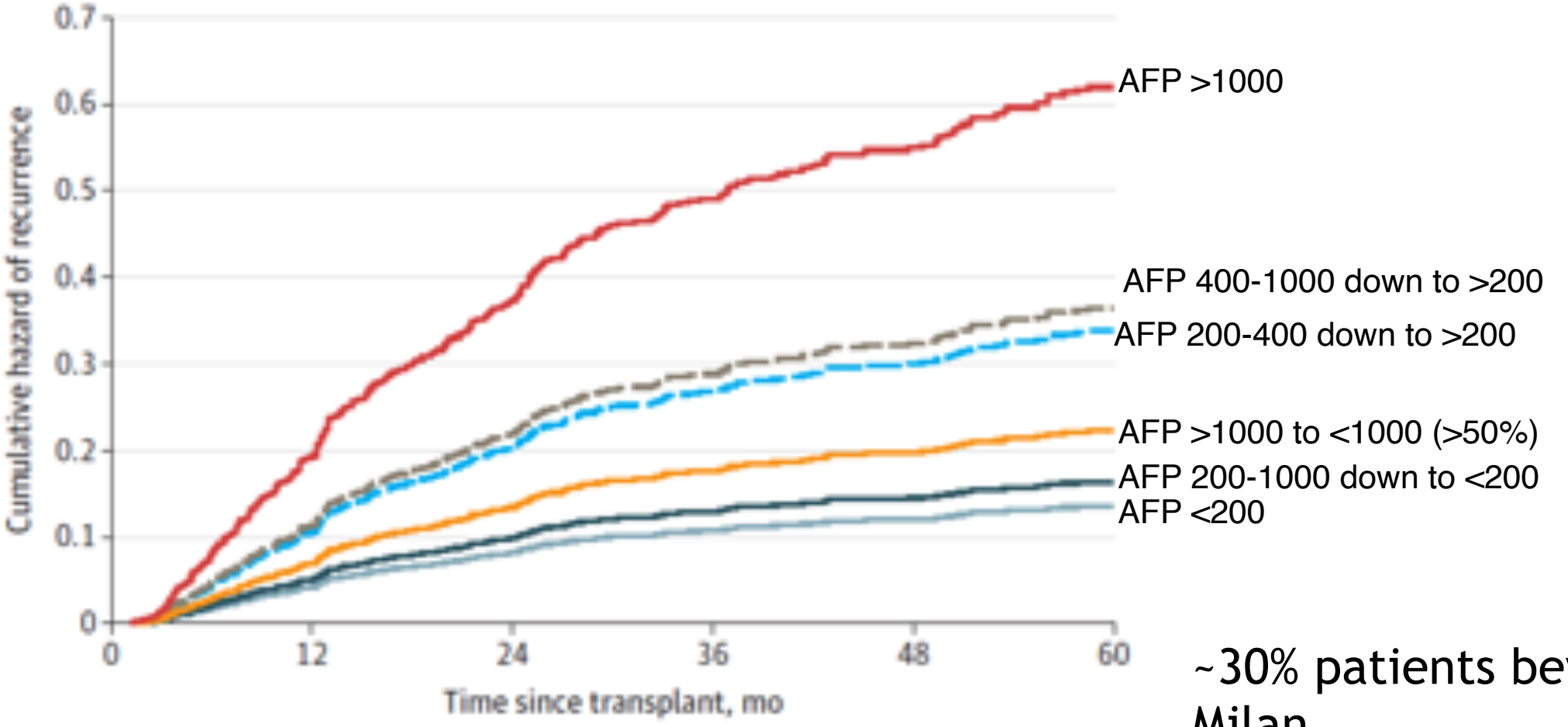


UHN Ajmera Transplant Centre

Gorgen A, Sapisochin G, et al. ILTS 2019 O-088

JAMA Surgery | Original Investigation

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



~30% patients beyond Milan

UHN Ajmera Transplant Centre

Halazun K, Sapisochin G et al. JAMA Surg 2021

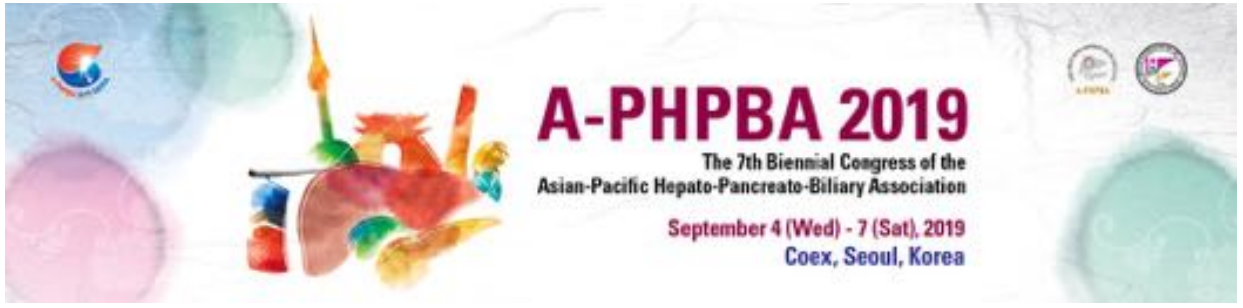
Response to LRT by decrease in tumor markers (AFP)

Down-Staging for HCC: Future Directions

- What is the optimal Down-staging Protocol?

- Down-staging to what? And how to monitor therapy
- PET
- ctDNA
- Radiomics

- Do we really need to Down-stage, or is response enough?



7th Biennial Congress of the Asian-Pacific HPB Association

How to Improve Oncological Outcomes of Liver Transplantation for HCC

Downstaging

Gonzalo Sapisochin, MD, PhD, MSc

Assistant Professor of Surgery. HPB & Multi Organ Transplant Program

Division of General Surgery. University Health Network

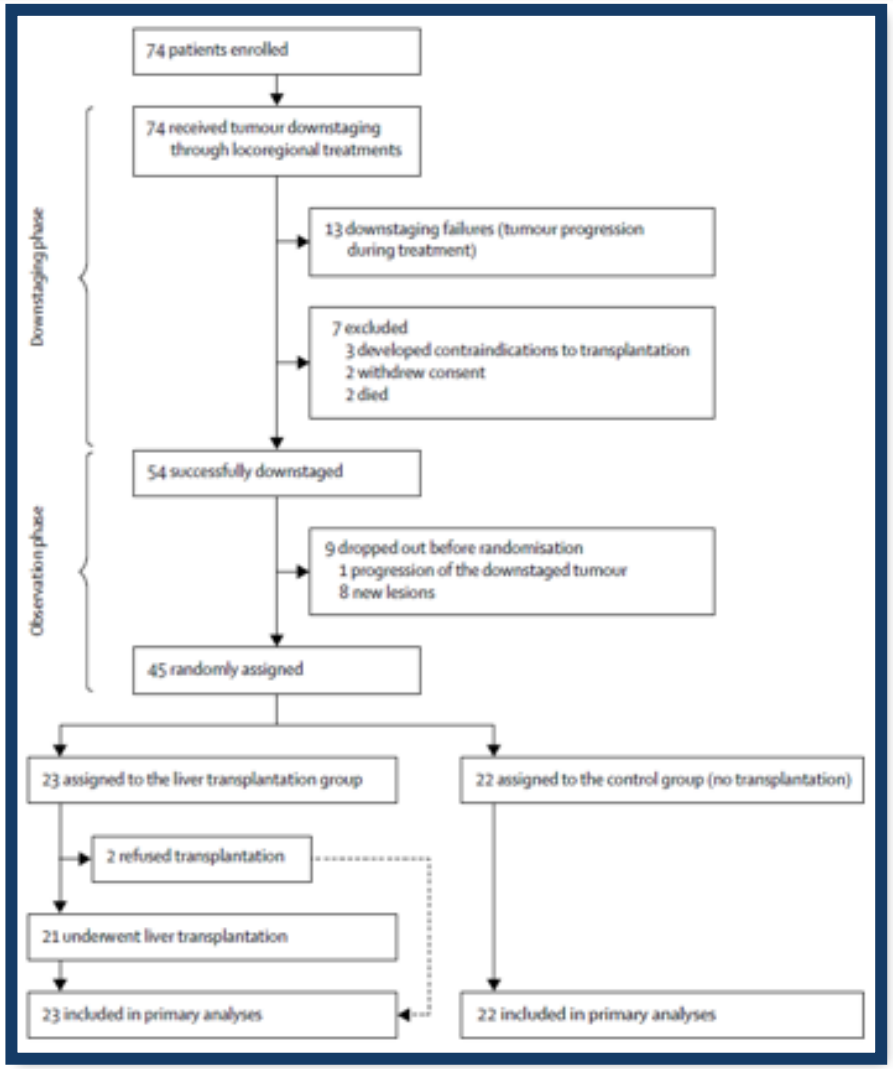
University of Toronto

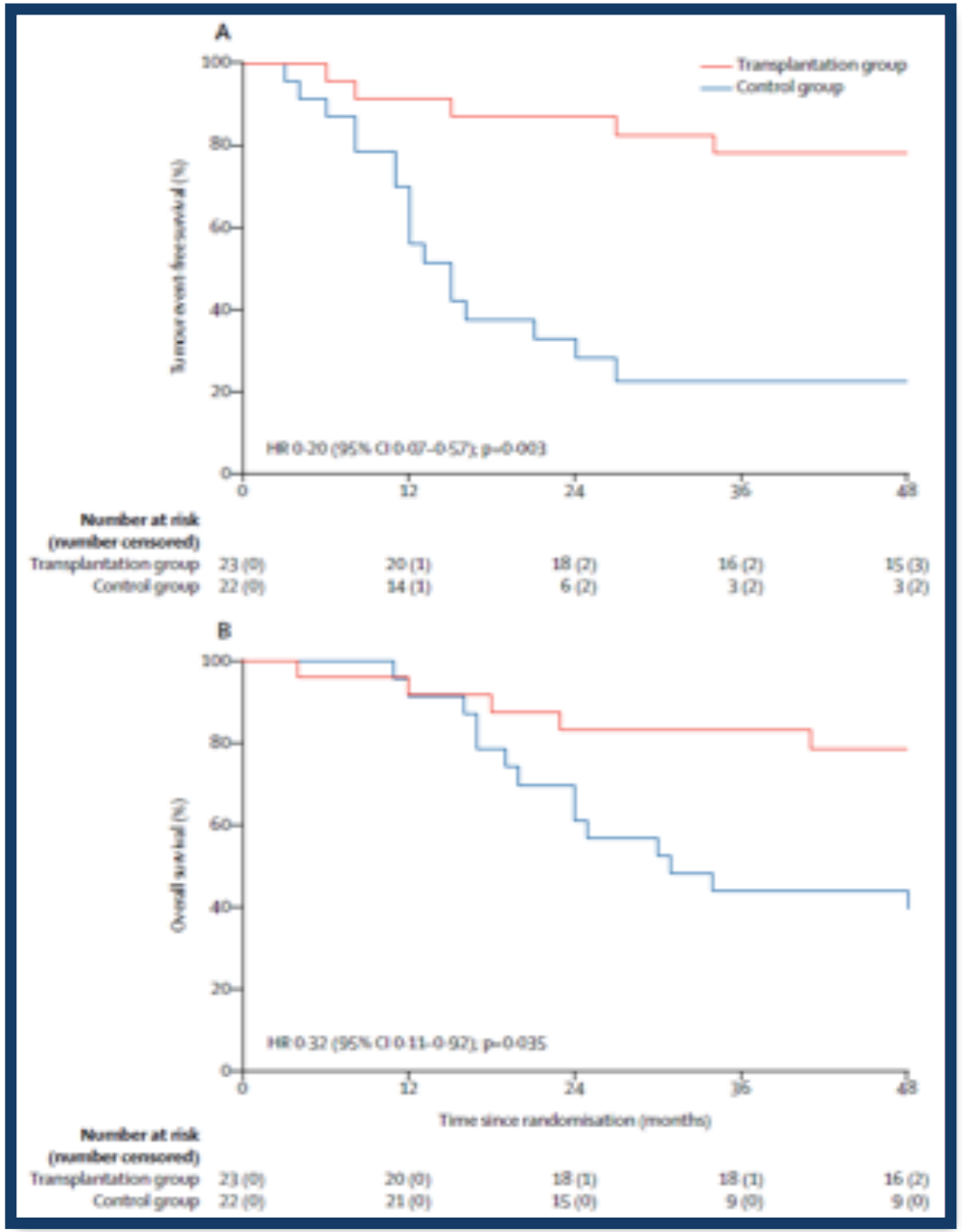
UNIVERSITY OF TORONTO

nt Centre

MULTI ORGAN Transplant PROGRAM

Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial





UHN Ajmera Transplant Centre

Mazzaferro V, et al. Lancet Oncol 2020

Bridging Therapy as a surrogate of tumor biology

Disclosure

In relation to this presentation, I declare that there are no conflicts of interest.

A conflict of interest is any situation in which a speaker or immediate family members have interests, and those may cause a conflict with the current presentation. Conflicts of interest do not preclude the delivery of the talk, but should be explicitly declared. These may include financial interests (eg. owning stocks of a related company, having received honoraria, consultancy fees), research interests (research support by grants or otherwise), organisational interests and gifts.

Introduction

- Optimal transplant criteria for HCC has been based on static tumor size and number in most jurisdictions. In many cases this criteria has thought to be restrictive (Milan criteria)

- Limitations of size and number criteria:

  - Does not account for changes in tumor burden.
  - Accuracy of imaging techniques?
  - Biological behavior?
  - Other cancers (i.e. Colorectal Liver Metastases, importance of response to chemotherapy)

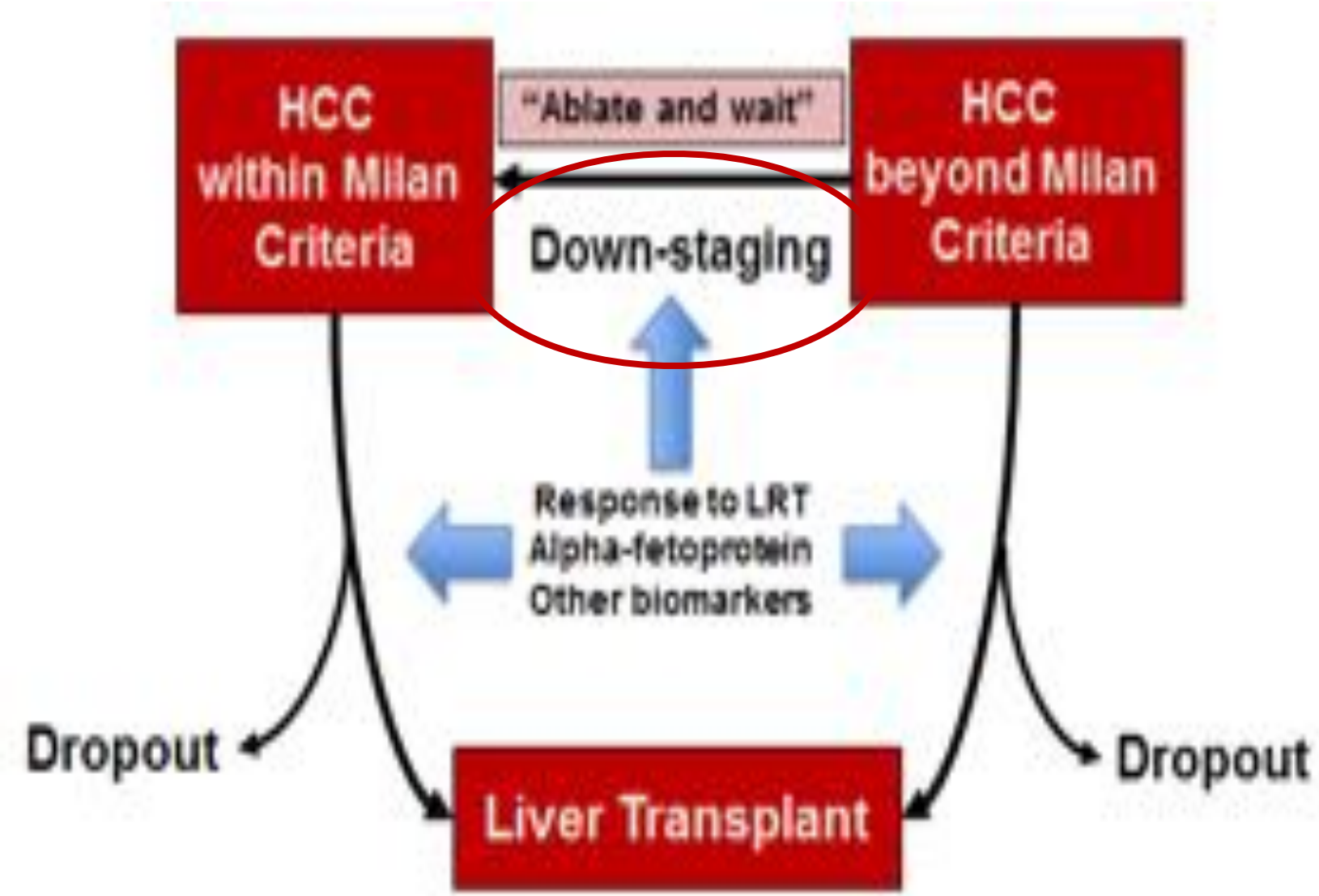
Transplantation criteria	Intention-to-treat survival	Disease-free survival	Post-transplantation survival	Comments
Milan criteria[51] • Single tumour ≤5 cm or 3 tumours all ≤3 cm	N/A	92% 4 years	85% 4 years	Based only on size and number
UCSF criteria[58] • Single tumour ≤6.5 cm or 3 tumours all ≤4.5 cm with TTD ≤8 cm	N/A	90.9% 5 years	80.9% 5 years	Based only on size and number
Up-to-7 criteria[48] • The sum of the maximum tumour diameter and number <7	N/A	• Beyond Milan but within Up-to-7 • 64.1% 5 years	• Beyond Milan but within Up-to-7 • 71.2% 5 years	Based only on size and number
Total Tumour Volume (TTV)[47] • Total tumour volume ≤115 cm^3 • AFP ≤400 ng/mL	• Beyond Milan but within TTV/AFP • 53.8% 4 years	• Beyond Milan but within TTV/AFP • 68% 4 years	• Beyond Milan but within TTV/AFP • 74.6% 4 years	Size and number and biological marker (AFP)
Extended Toronto Criteria (ETC)[43] • No limit in size and number • No vascular invasion • No extrahepatic disease • No cancer-related symptoms • Biopsy of largest tumour not poorly differentiated	• Beyond Milan but within ETC • 55% 5 years	• Beyond Milan but within ETC • 30% 5 years • (Cumulative risk of recurrence)	• Beyond Milan but within ETC • 68% 5 years	No size and number limit but biological behaviour (cancer-related symptoms and tumour differentiation)
Kyoto Criteria[55] • Number ≤10 tumours • Size ≤5 cm • DCP ≤400 mAU/mL	N/A	• Beyond Milan but within Kyoto • 30% 5 years • (Cumulative risk of recurrence)	• Beyond Milan but within Kyoto • 65% 5 years	Size and number and biological marker

UHN Ajmera Transplant Centre

Sapisochin G et al. Nature Rev. 2017

Can we expand the indications of Liver Transplantation for HCC by Tumor Downstaging?

Can response to LRT and other surrogates of tumor biology be integrated in the decision making of LT candidacy in patients with HCC?



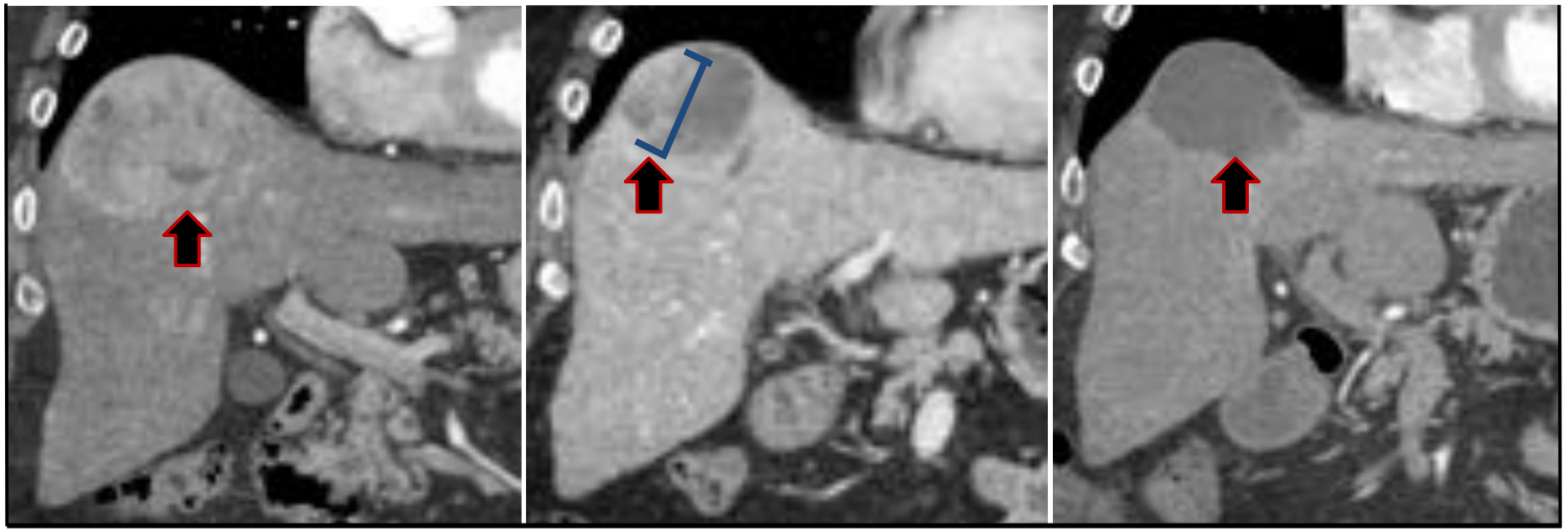
UHN Ajmera Transplant Centre

Mehta N, et al. Clin Liver Dis 2019

Definition of Down-Staging

Reduction in tumor size using LRT to meet “acceptable LT criteria”

- Tumor response based on radiographic measurement of size of viable tumors



UHN Ajmera Transplant Centre

Yao F et al. Hepatology 2015
Mehta N et al. Clinical Gastro & Hepatology 2018
EASL guidelines, RECIST

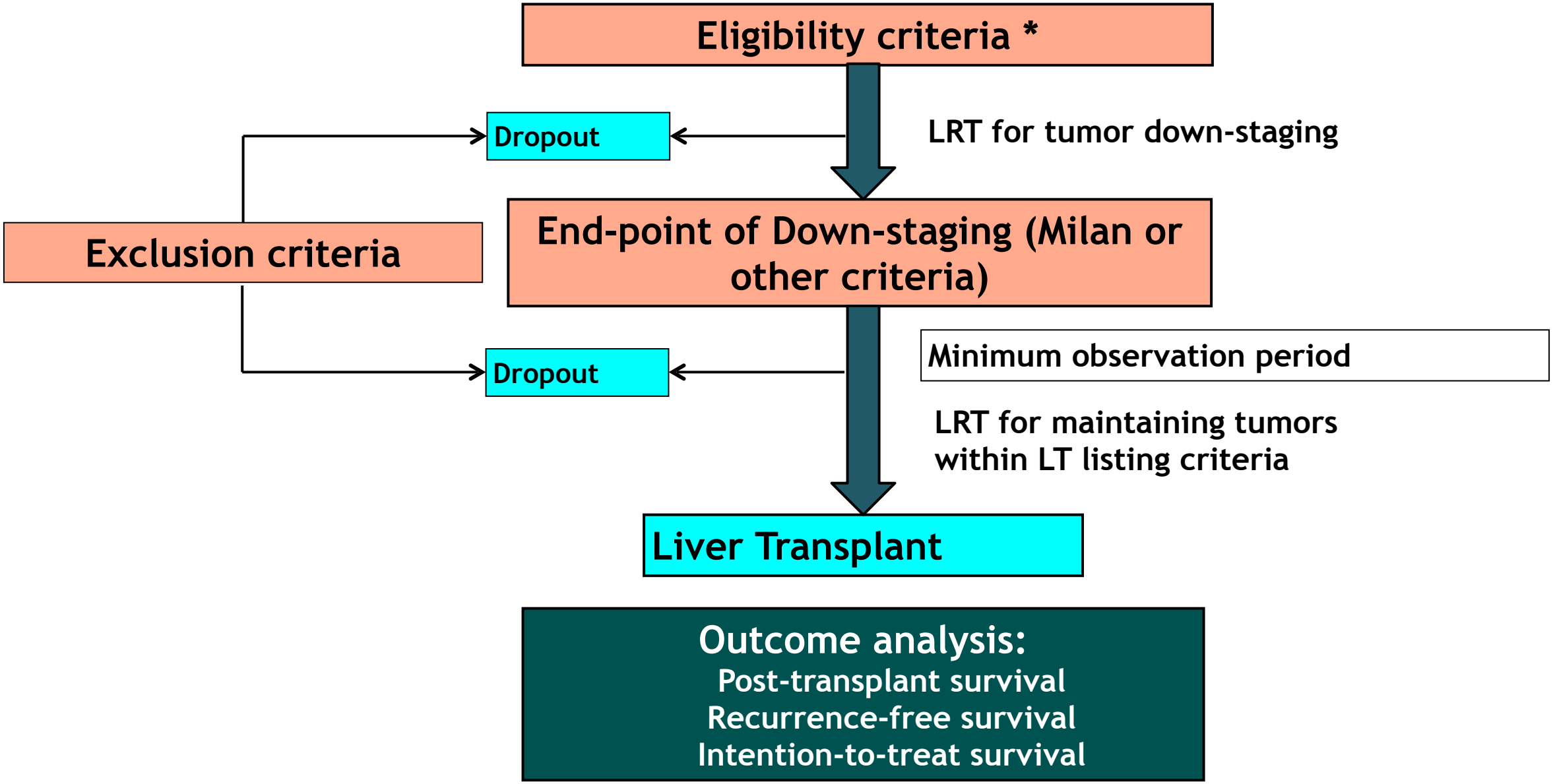
Goals and Expectations of Down-Staging

- The goal of down-staging is to decrease the tumor burden to meet acceptable criteria for liver transplant._

- Down-staging may allow selection of tumors with more favorable biology that respond to down-staging treatment and also do well after liver transplant.

- Down-staging should yield 5-year post-transplant survival similar to that achieved for patients who meet criteria for liver transplant without down-staging.

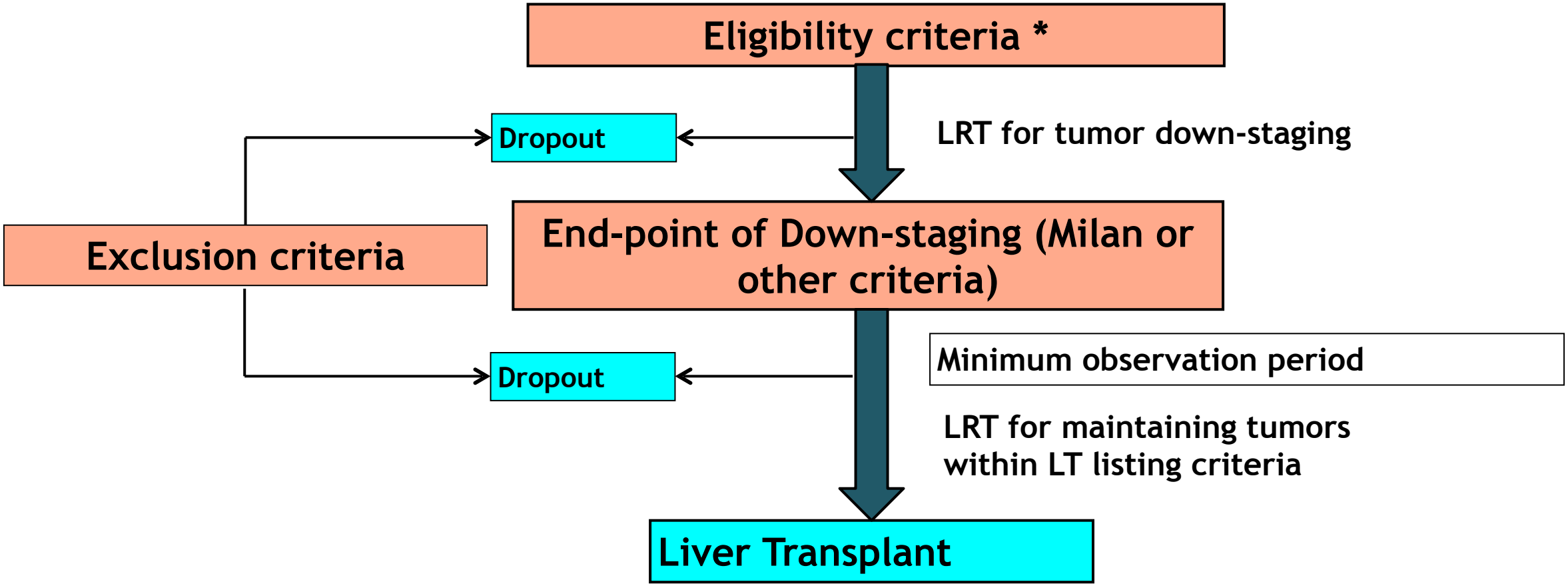
Yao FY, et al Liver Transpl 2011
Lo CM. Am J Transpl 2008



* Based on HCC number and diameter initially beyond LT listing criteria

UHN Ajmera Transplant Centre

Courtesy of F. Yao and N. Mehta

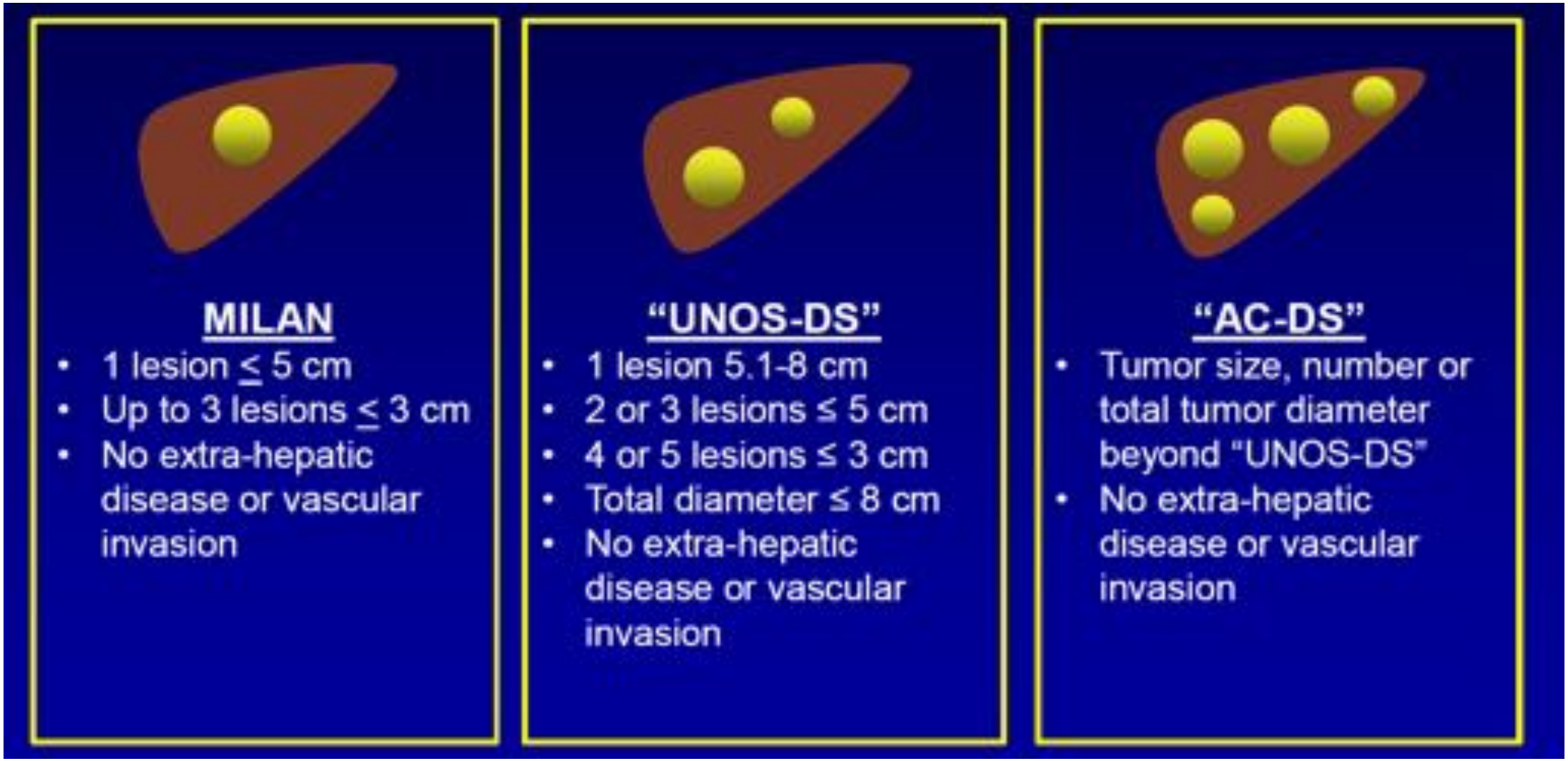


5-yr survival the same as those meeting criteria without down-staging

UHN Ajmera Transplant Centre

Courtesy of F. Yao and N. Mehta
Clavien PA, et al. Lancet Oncol 2012

Down-Staging Protocols – Inclusion Criteria



UHN Ajmera Transplant Centre

Courtesy of F. Yao and N. Mehta - UCSF

End-Point of Down-Staging

- End point of down-staging should be viable tumor (mRECIST)
- Most centers end-point is MILAN criteria (UNOS/UCSF)
- In Toronto end-point is TTV 145 cm^3 and AFP <1000
- Geneva TTV 115 cm^3 and AFP <400

Based on Size and Number – Other markers?
discrepancy number/size tumors imaging and explant

UHN Ajmera Transplant Centre

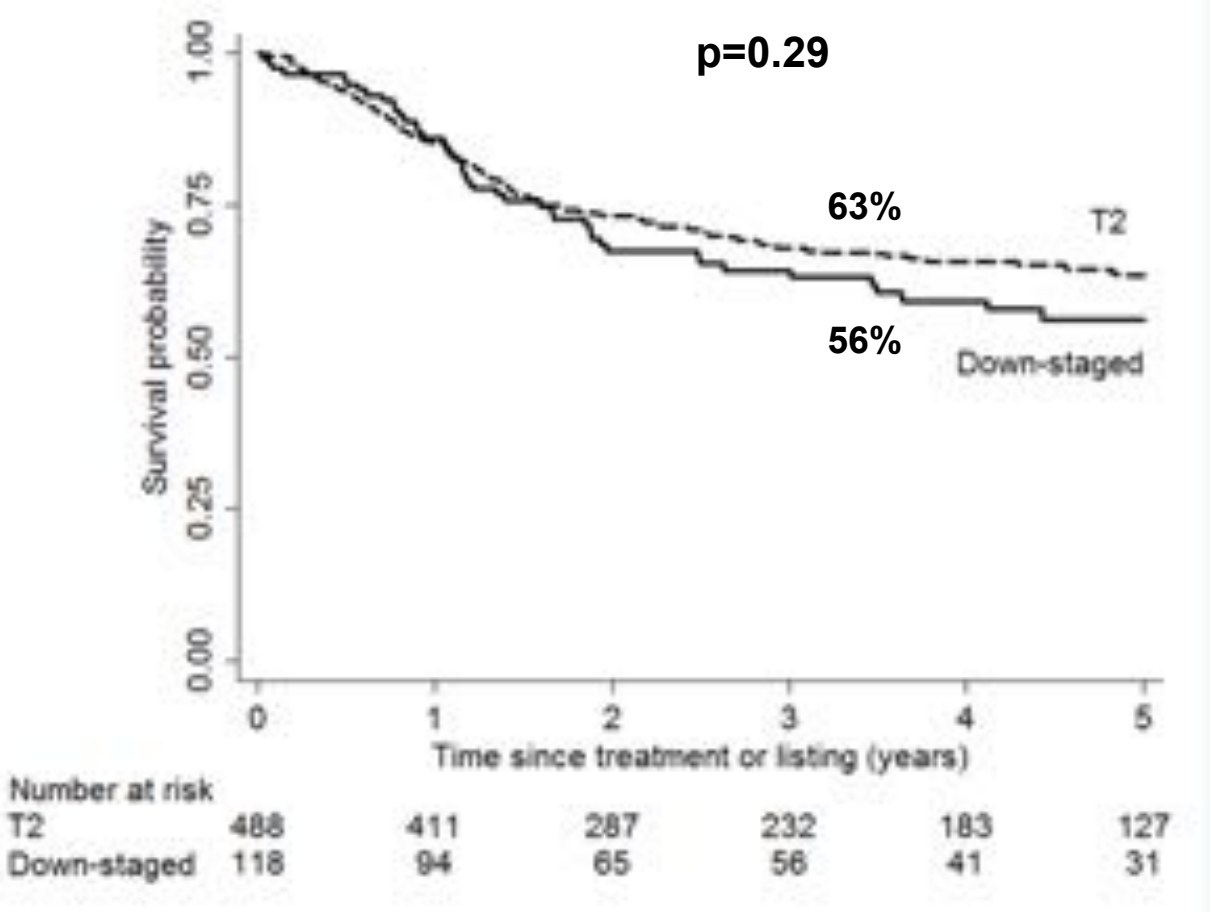
Yao FY, et al. Liver Transpl 2011
Jeng KS, et al. Transpl Proc 2019
Toso C, et al. Tranpl Int 2019

Minimum Observation Period After Down-Staging

- An observation period after down-staging is likely needed (tumor biology)
- The optimal time is unknown
- Most centers will accept a 3 month observation period. However, the time to transplant will be longer, except for LDLT

Outcomes of LT after Down-Staging

Intention-to-treat Survival

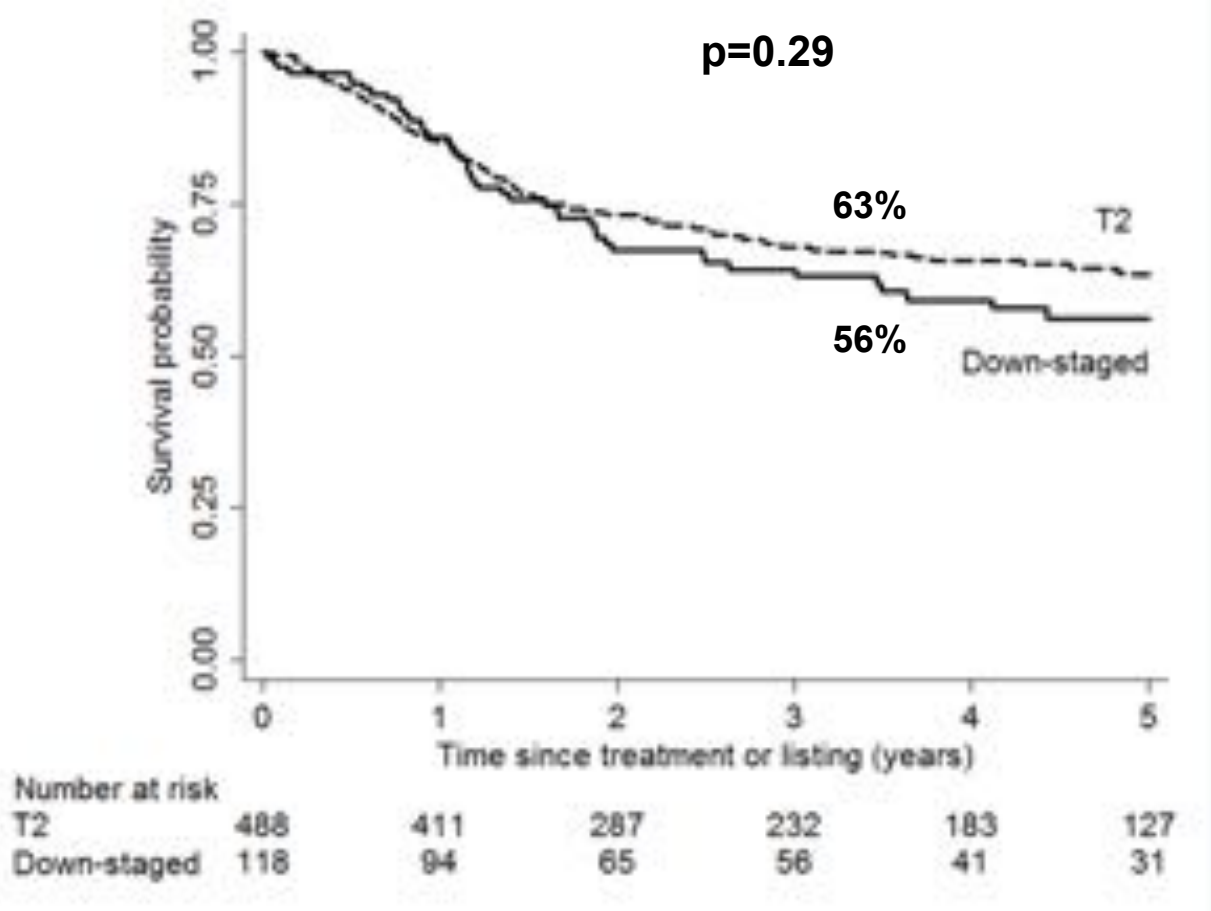


UHN Ajmera Transplant Centre

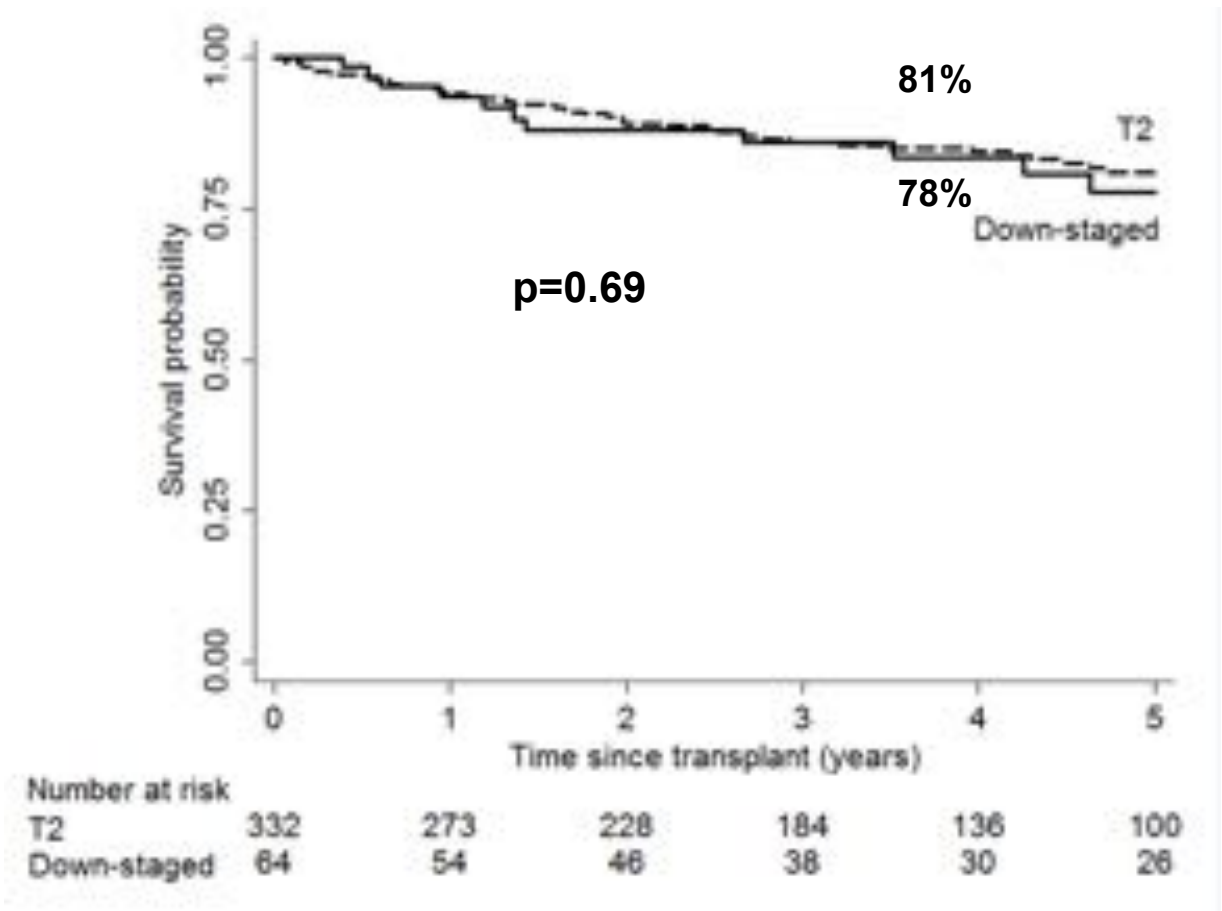
Yao et al. Hepatology 2015;61:1968-1977

Outcomes of LT after Down-Staging

Intention-to-treat Survival



Post-Transplant Survival



UHN Ajmera Transplant Centre

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

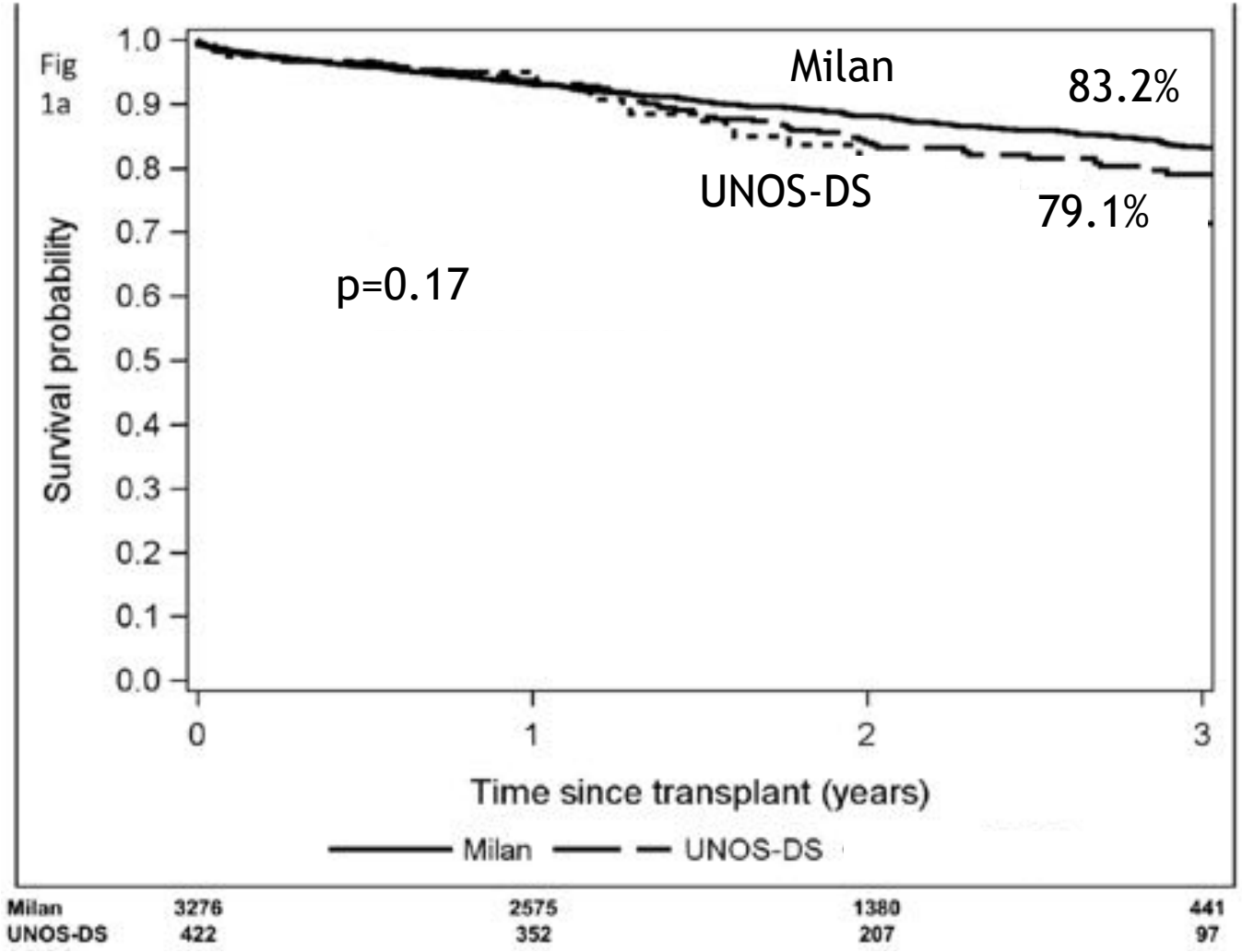
Outcomes of LT after Down-Staging

UNOS Database

3276 patients MILAN
422 DS to MILAN from UNOS-DS
Protocol

1 lesion 5-8 cm
2-3 lesions 3-5 cm with TTD <8 cm
4-5 lesions all <3 TTD <8

3-year Recurrence Probability
6.9% Milan vs. 12.8% UNOS-DS



UHN Ajmera Transplant Centre

Mehta N et al. Hepatology 2019

Should there be an upper tumor burden to attempt Down-staging?

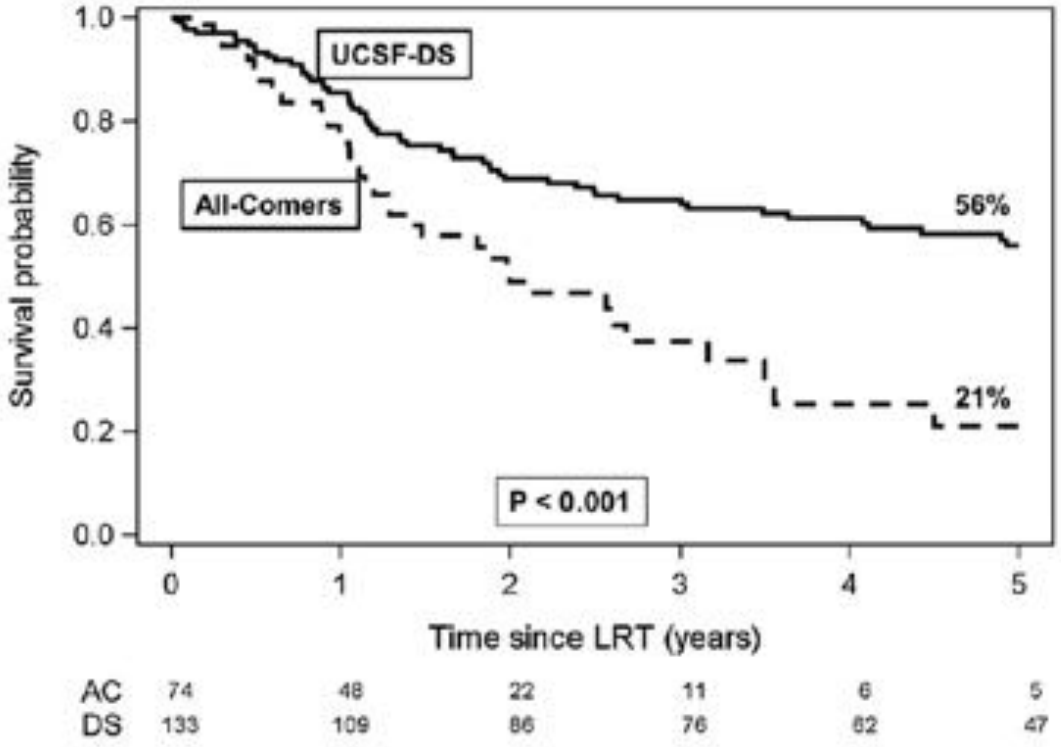
UCSF DS Criteria

Inclusion Criteria

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

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

Absence of vascular invasion based on cross-sectional imaging

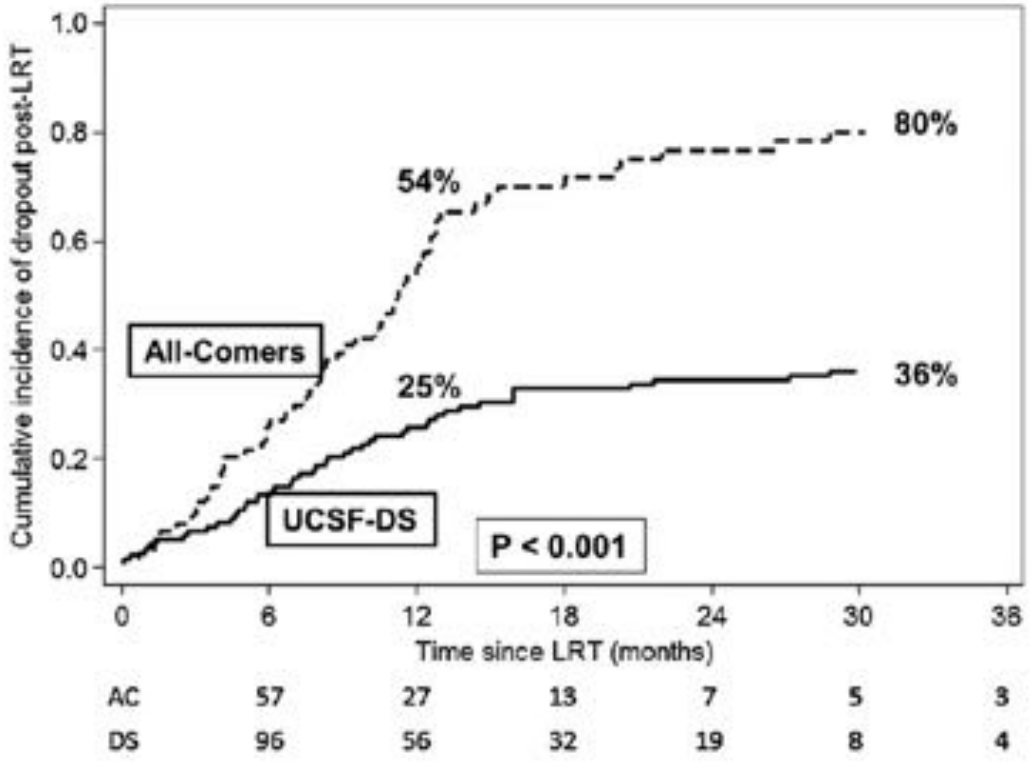


All-comers Criteria

HCC exceeding UCSF-DS protocol by any of the following:

1. HCC tumor number
2. HCC tumor size
3. Total HCC tumor diameter

Absence of vascular invasion based on cross-sectional imaging



Should there be different Down-staging protocols for LDLT vs. DDLT?

Downstaging Macrovasc Invasion??

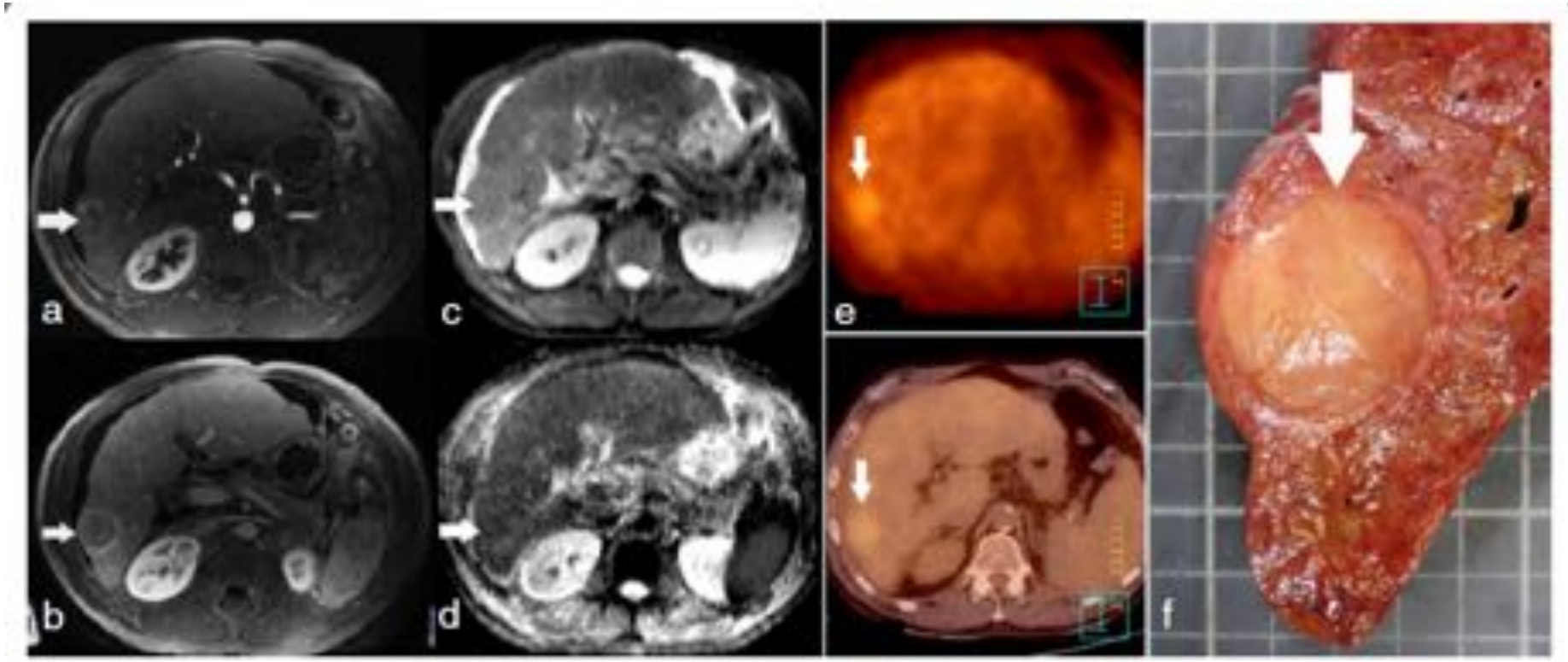
- Trial of SBRT in Resection…
- Korean Paper…

Future/Unanswered questions

- Optimal DS protocol? DS to what?
- Monitoring DS? Do we really need DS or Response is enough!!
- Biomarkers – ctDNA?
- DS with systemic therapy?

Functional imaging of hepatocellular carcinoma using diffusion-weighted MRI and ^{18}F-FDG PET/CT in patients on waiting-list for liver transplantation

Predicting Poorly Differentiated Nodules

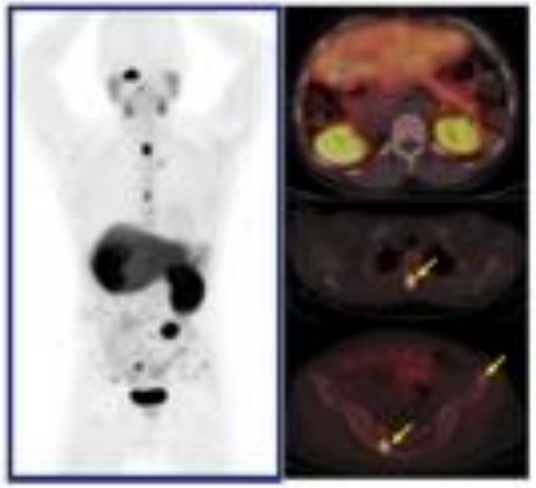


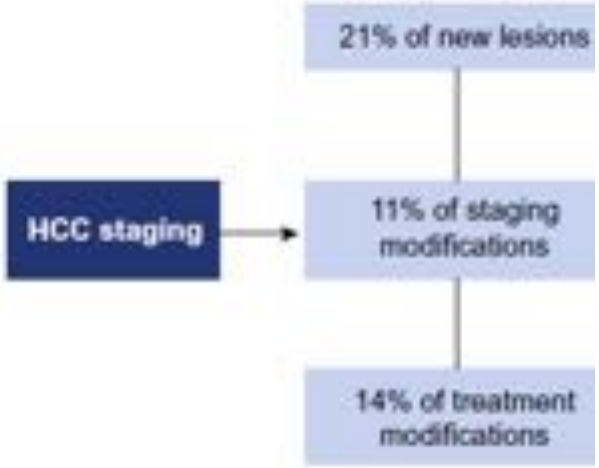
UHN Ajmera Transplant Centre

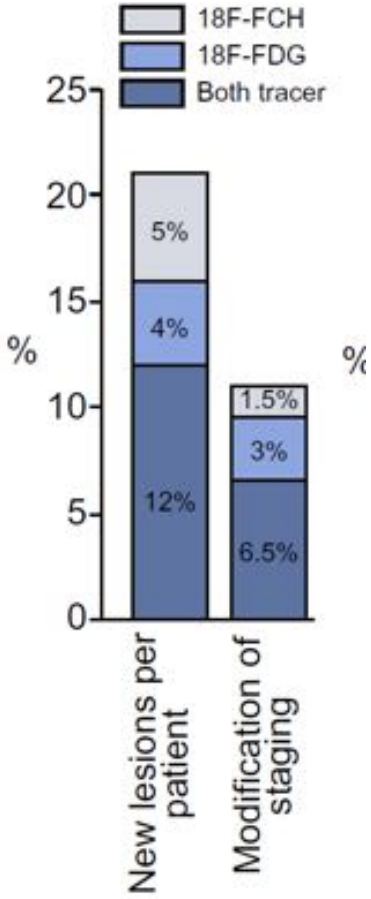
Boussouar S, et al. Cancer Imaging 2016

Positron emission tomography/computed tomography with 18F-fluorocholine improve tumor staging and treatment allocation in patients with hepatocellular carcinoma

Dual tracer PET/CT in patients with HCC



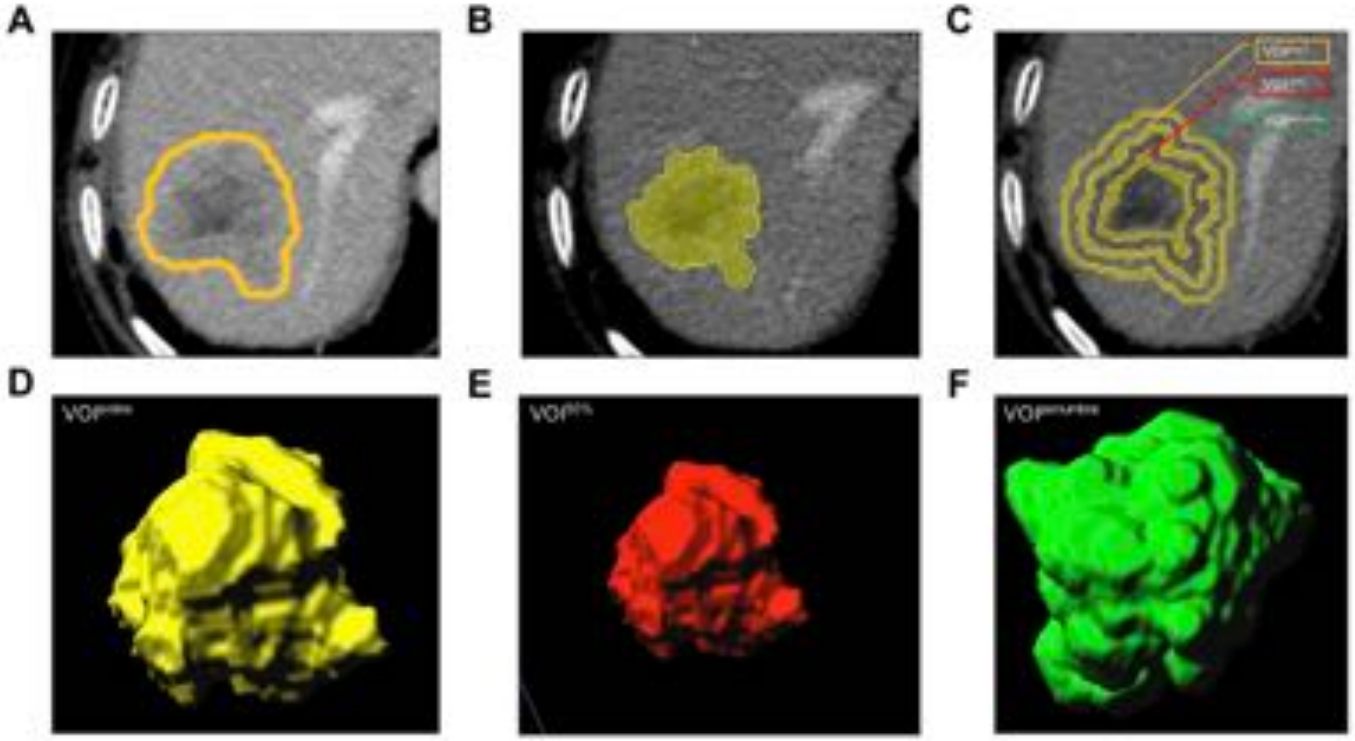


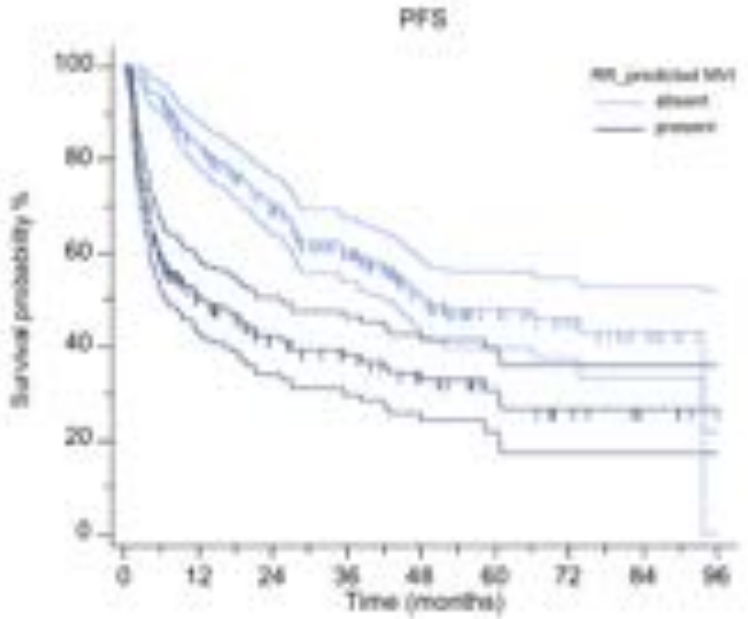


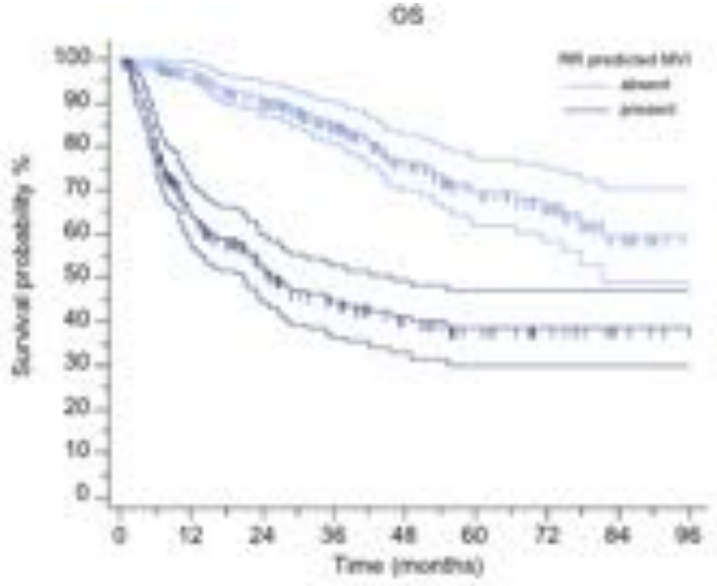
UHN Ajmera Transplant Centre

Chalaye J, et al. J. Hepatol 2018

Future Perspectives: Radiomics





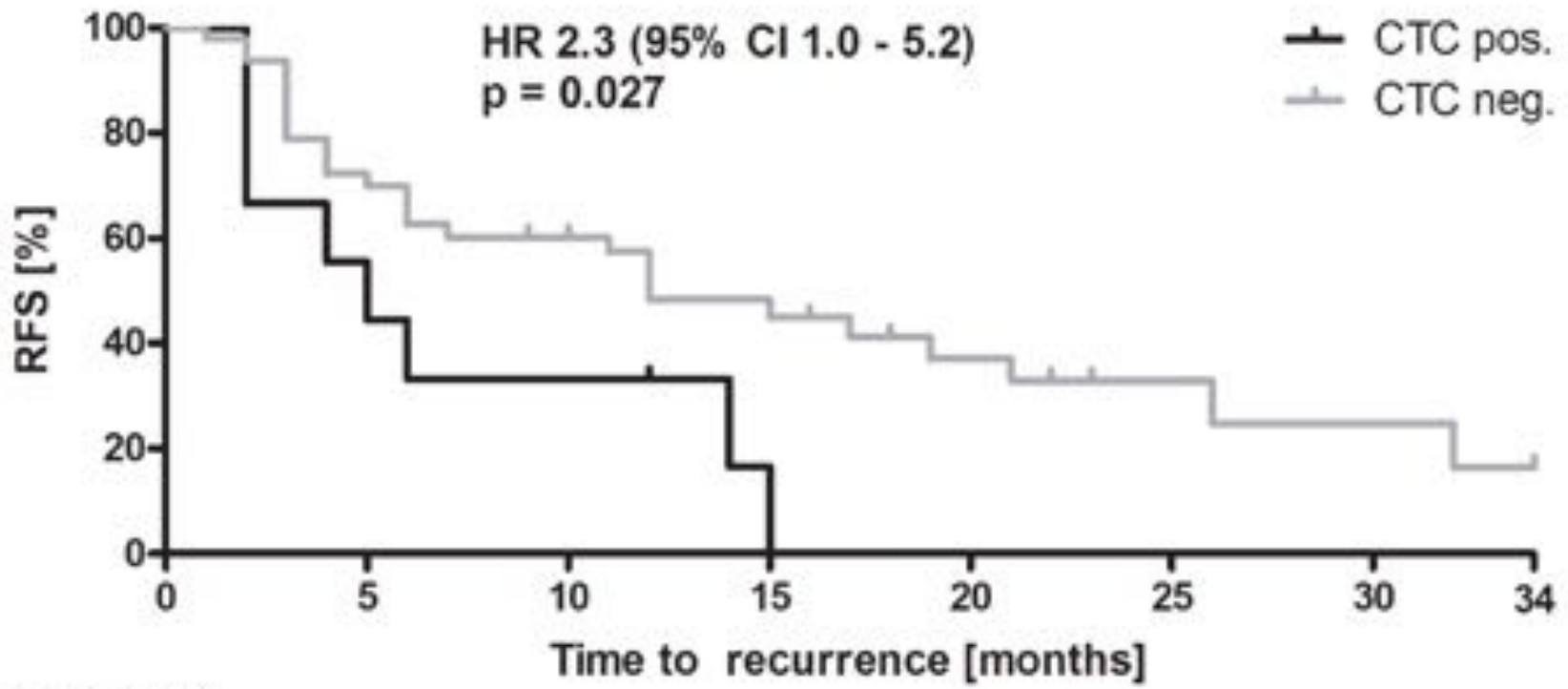


UHN Ajmera Transplant Centre

Xu et al. J Hepatol 2019

Circulating tumor cells as liquid biomarker for high HCC recurrence risk after curative liver resection

A



UHN Ajmera Transplant Centre

Von Felden J, et al. Oncotarget 2017

Circulating tumor cells as liquid biomarker for high HCC recurrence risk after curative liver resection

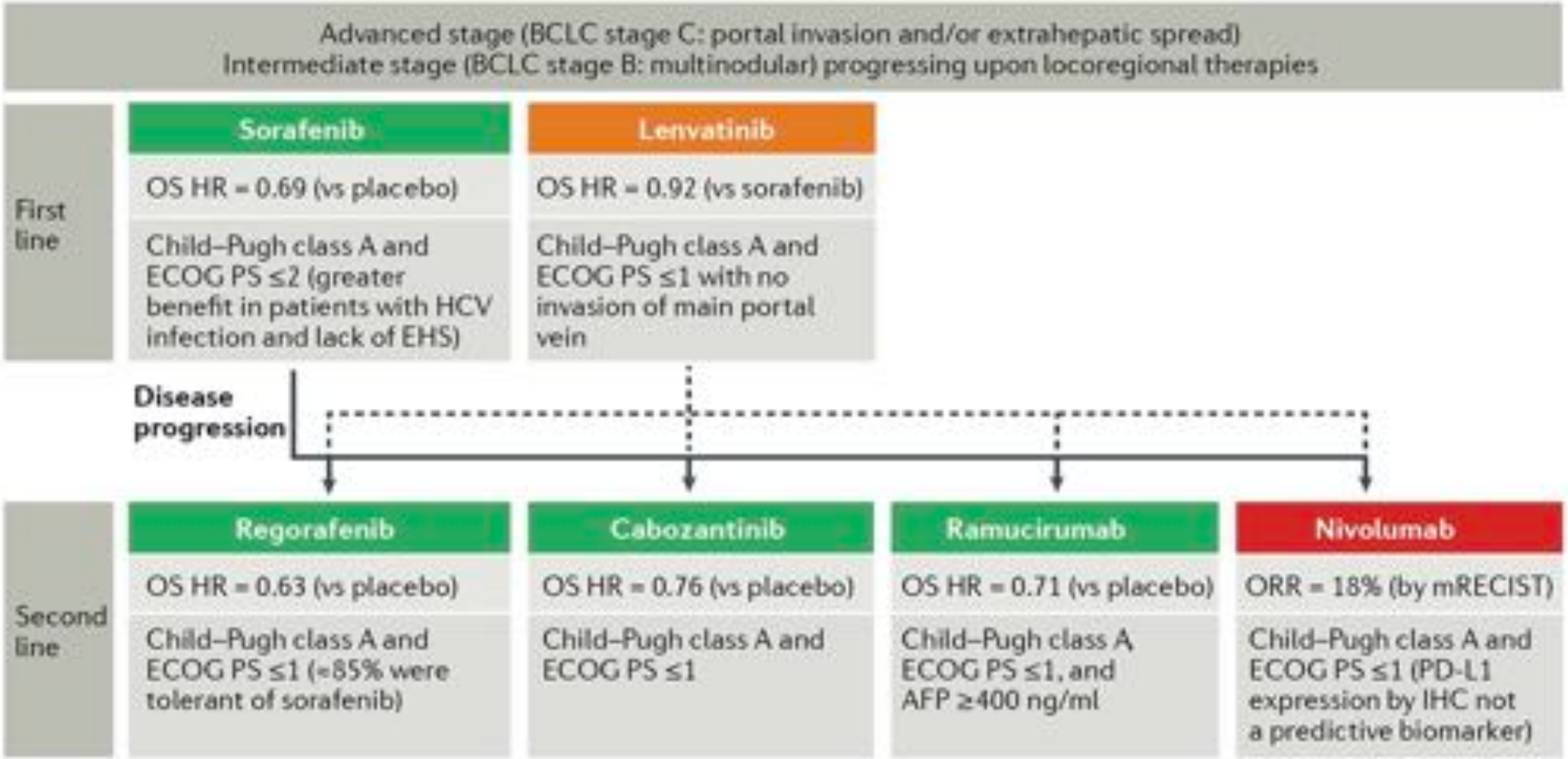
Table 3. Univariate and multivariate Cox regression analysis regarding recurrence of HCC

	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)	P-value
CTC status	2.3 (1.0-5.2)	0.027	3.1 (1.0-9.4)	0.043
Tumor status	1.3 (0.9-1.9)	0.226		
Grading	2.6 (0.9-8.9)	0.107		
Vascular invasion	0.8 (0.4-1.7)	0.634		
Resection margin	2.6 (1.1-6.4)	0.035	3.7 (1.4-10.3)	0.011
Liver cirrhosis	1.1 (0.6-2.2)	0.754		
Viral etiology	1.3 (0.6-2.8)	0.438		

Cox regression analysis on the risk of HCC recurrence after resection, n=57. Abbreviations: HR, hazard ratio; CI, confidence interval.

UHN Ajmera Transplant Centre

Von Felden J, et al. Oncotarget 2017



UHN Ajmera Transplant Centre

Llovet et al. Nature Rev. 2018

- Is there going to be any immunotherapy drug used in transplant population?
- Neoadjuvant therapies?
- Selection based on biological/genomic features?

Response to LRT by imaging/explant

mRECIST provides insight into tumor biology for patients with hepatocellular carcinoma awaiting liver transplantation

N=772 HCC patients treated LRT
94% within MILAN

mRECIST criteria
CR
PR ≥30% decrease
PD ≥20% increase
SD no changes

Risk of Drop-out

	OR	*p value*
No response to LRT	2.26 (1.31-3.88)	<0.01
Progression to LRT	8.24 (4.34-15.66)	<0.01
Number or LRT	1.29 (1.1-1.5)	<0.01

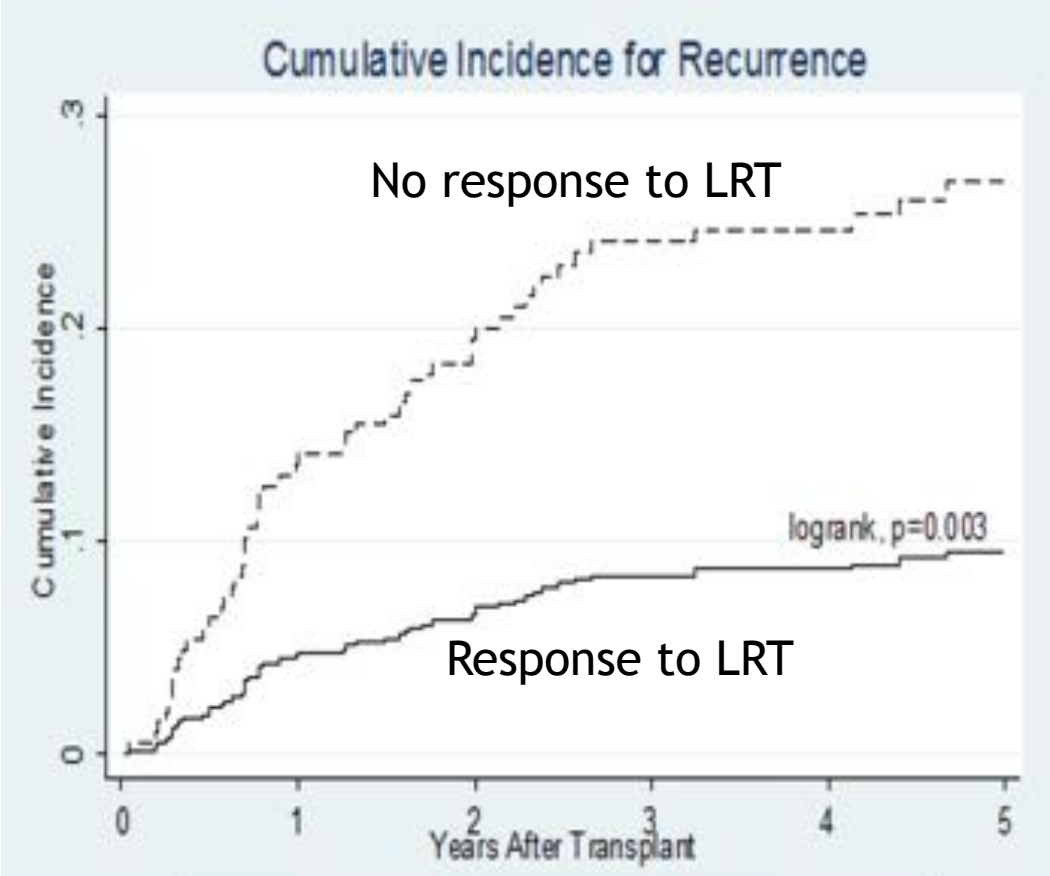
Cumulative incidence of Recurrence

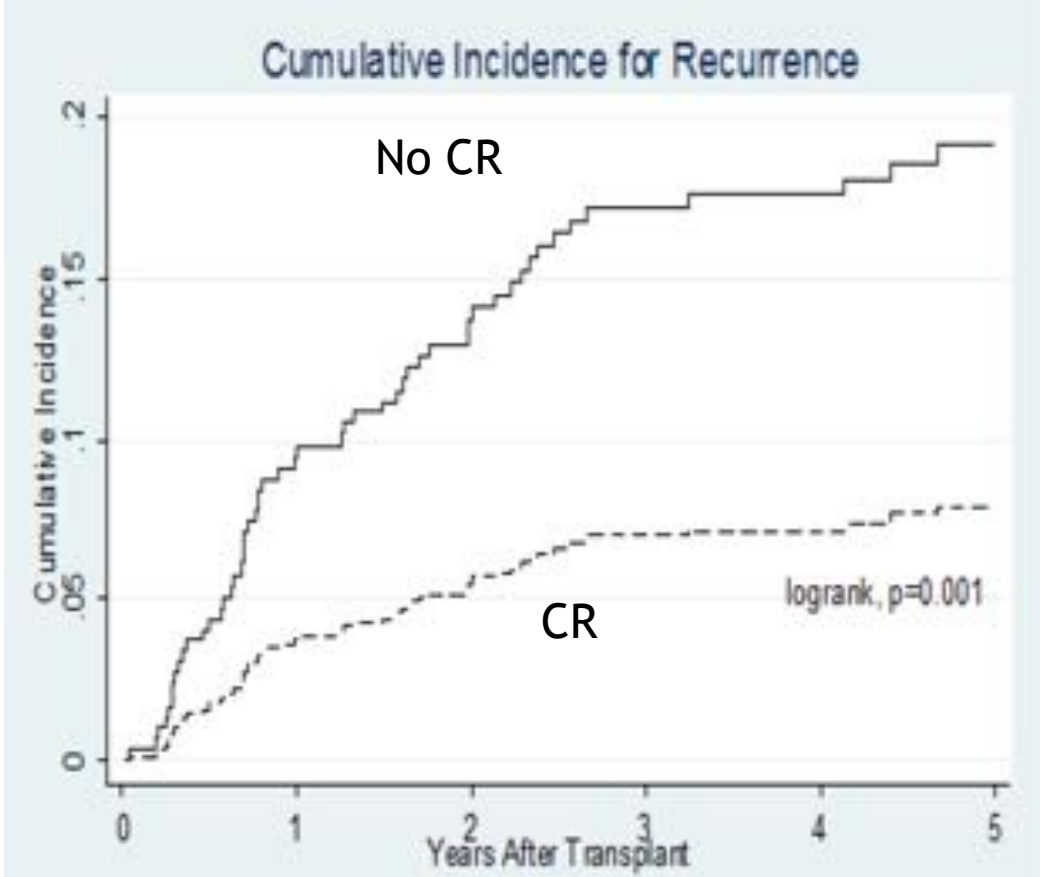
	OR	*p value*
No response to LRT	3.13 (1.25-7.89)	0.02
Number or LRT	1.49 (1.1-1.88)	0.01

UHN Ajmera Transplant Centre

Lee D. et al, Liver Transp 2019

mRECIST provides insight into tumor biology for patients with hepatocellular carcinoma awaiting liver transplantation





UHN Ajmera Transplant Centre

Lee D. et al, Liver Transp 2019

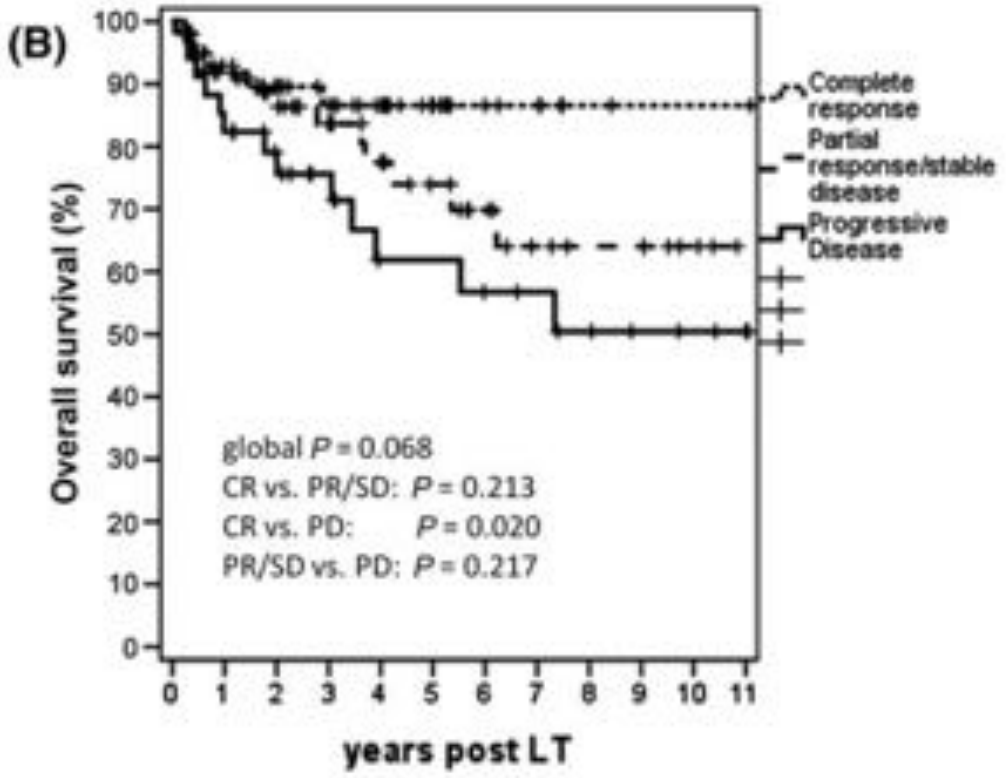
Liver
INTERNATIONAL

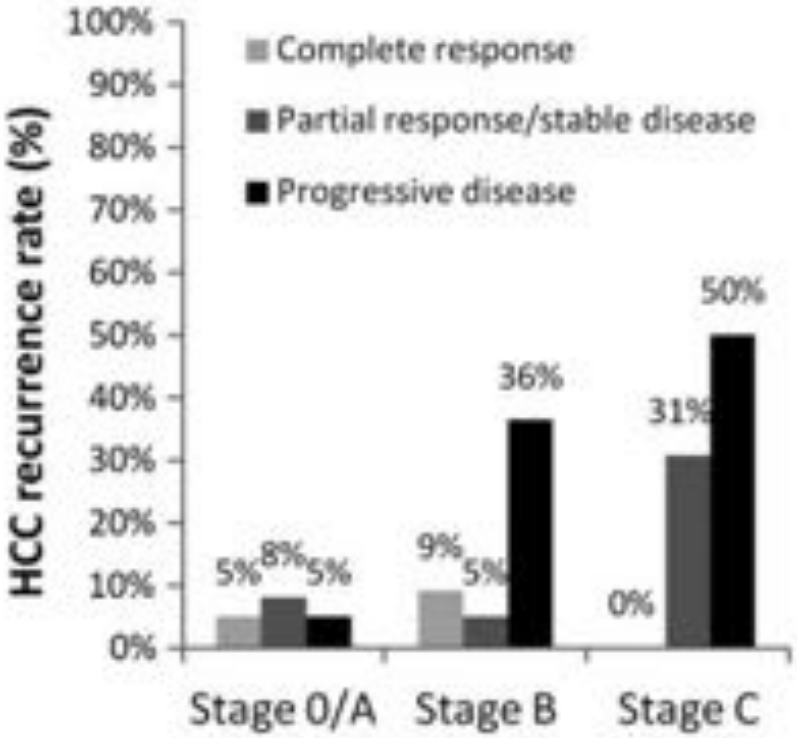
Liver International ISSN 1478-3223

LIVER TRANSPLANTATION

Excellent post-transplant survival in patients with intermediate stage hepatocellular carcinoma responding to neoadjuvant therapy

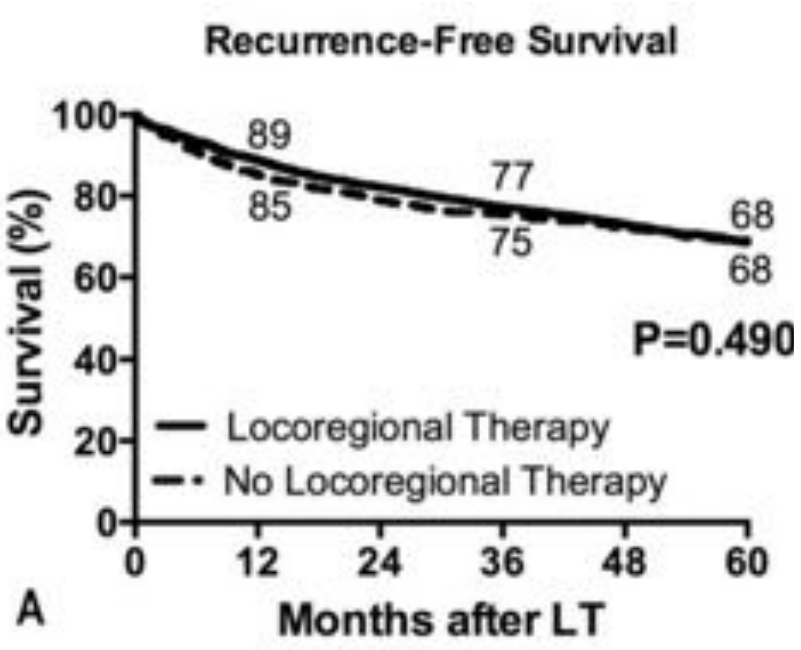
Armin Finkenstedt[1], Anja Vikoler[1], Manuela Portenkirchner[2], Kerstin Mülleder[2], Manuel Maglione[3], Christian Margreiter[3], Patrizia Moser[4], Wolfgang Vogel[1], Reto Bale[2], Martin Freund[2], Anna Luger[2], Herbert Tilg[5], Johannes Petersen[2], Stefan Schneeberger[3], Ivo Graziadei[6], Heinz Zoller[1] and Bernhard Glodny[2]

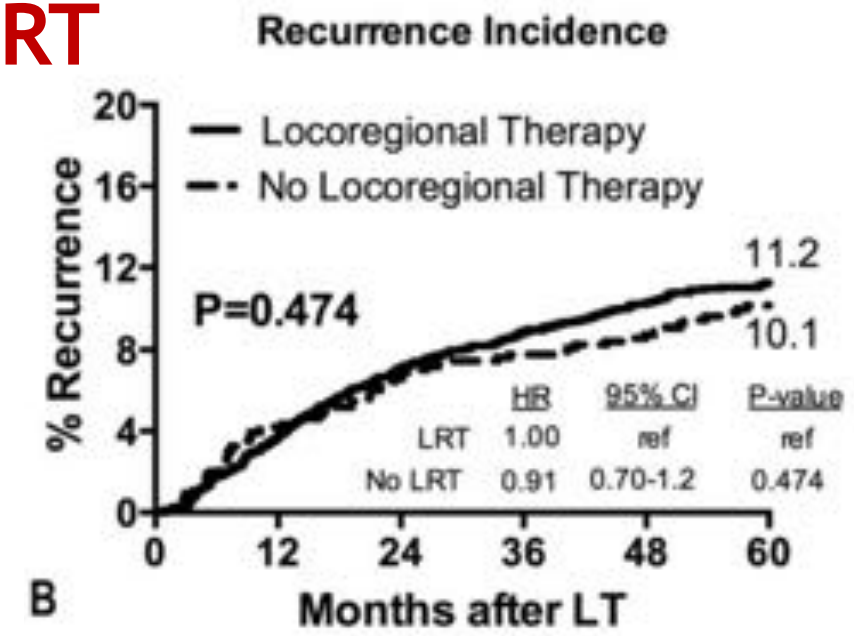


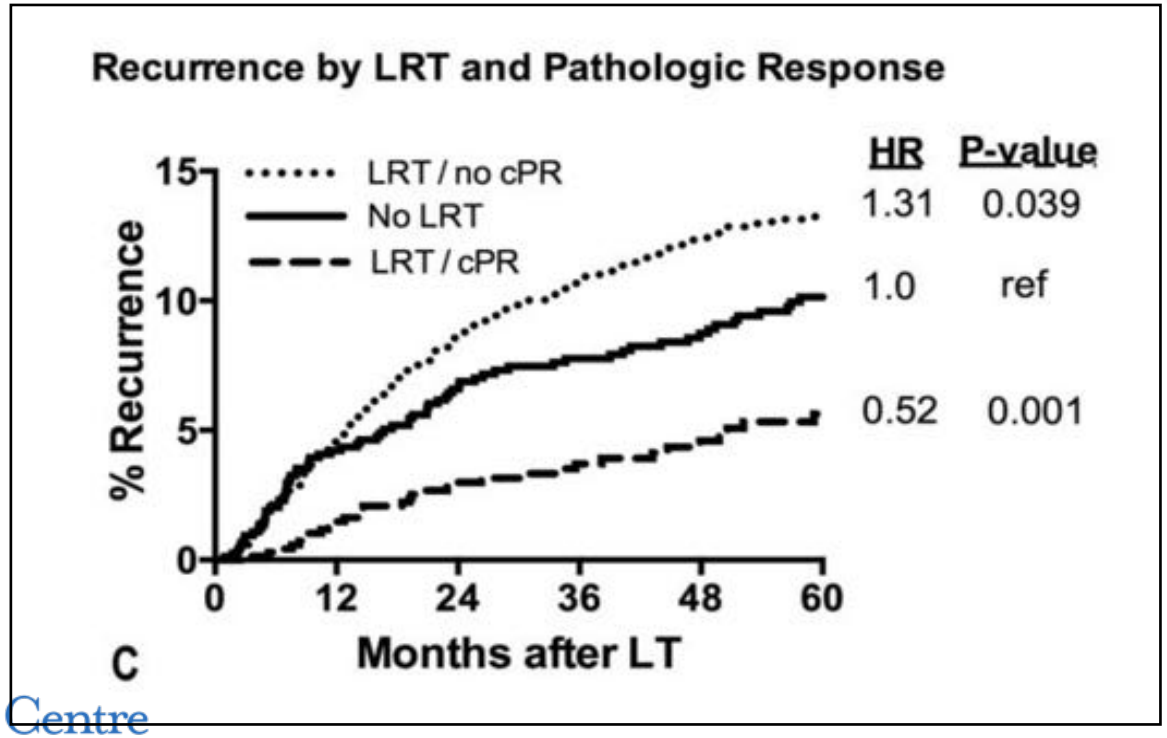


UHN Ajmera Transplan

Response to LRT







UHN Ajmera Transplant Centre

Agopian V et al. Ann Surg, 2017

University of Toronto Experience

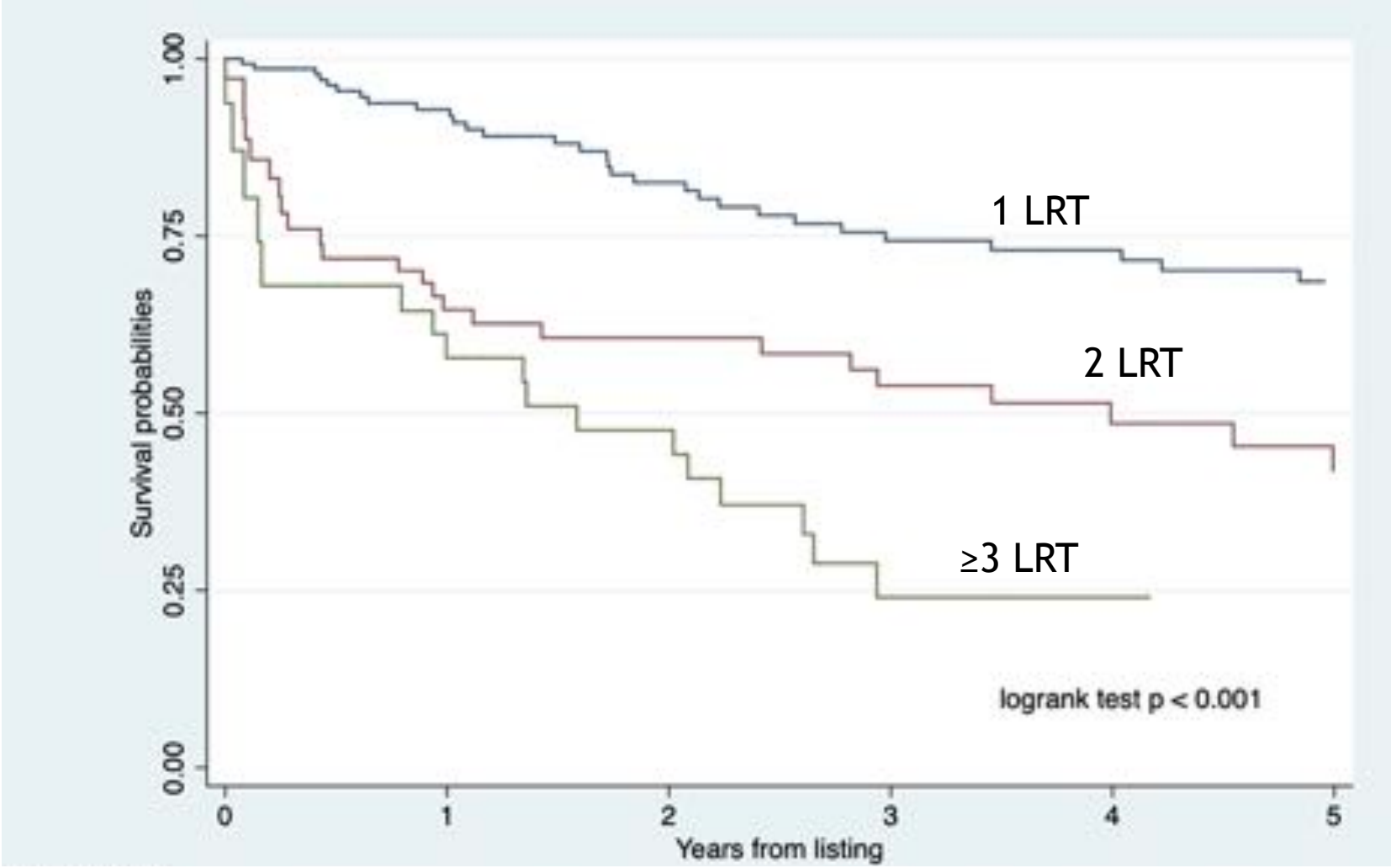
n=196

BEYOND MILAN

Multivariate Analysis

LRT >2 HR 2.19 (1.27-3.78)
LRT ≥3 HR 4.35 (2.32-8.16)

Intention-to-treat Analysis



UHN Ajmera Transplant Centre

Gorgen A, Sapisochin G, et al. ILTS 2019 O-088

University of Toronto Experience

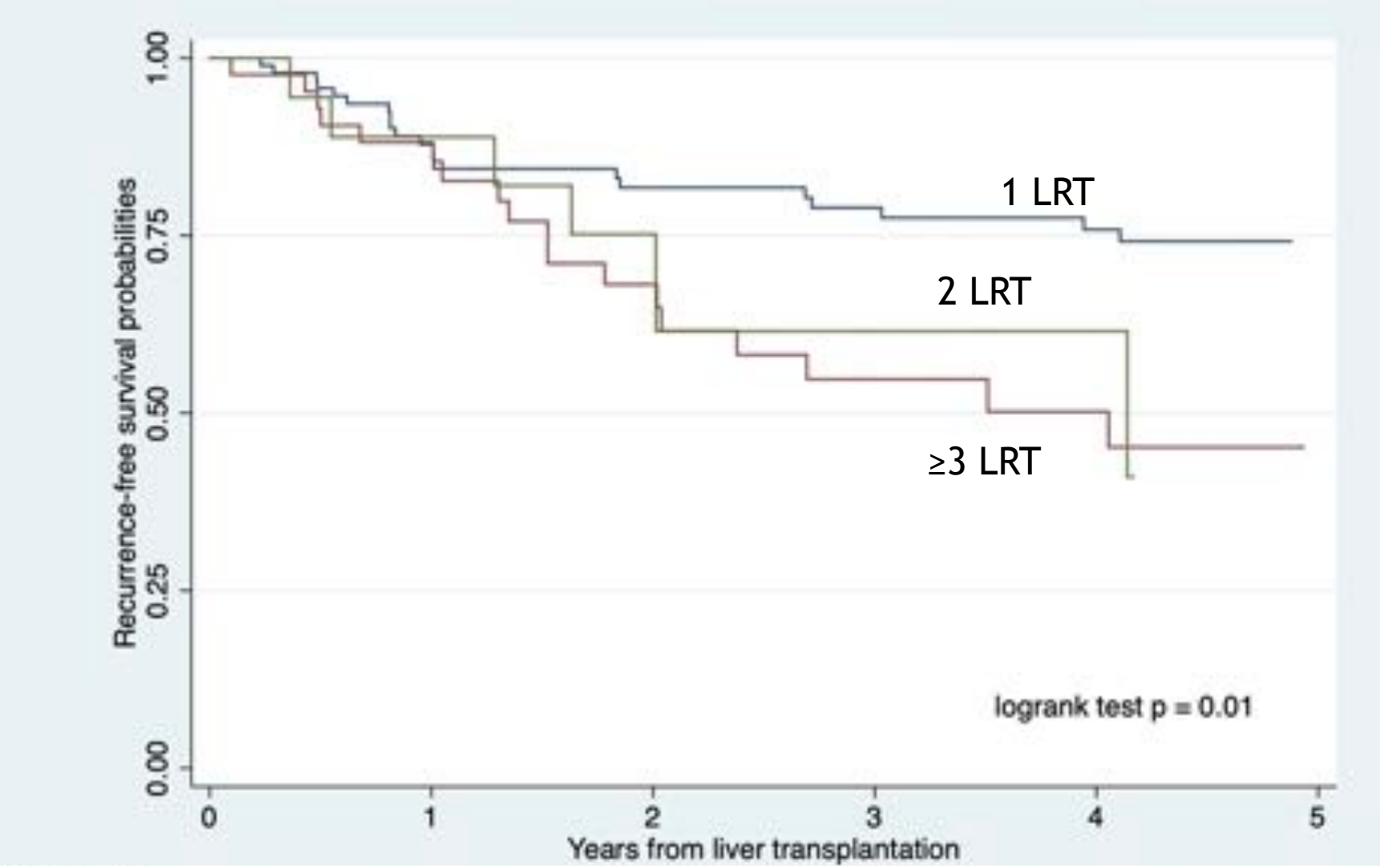
n=161 Transplanted

BEYOND MILAN

Multivariate Analysis

LRT >2 HR 2.39 (1.28-3.43)

Disease-Free Survival

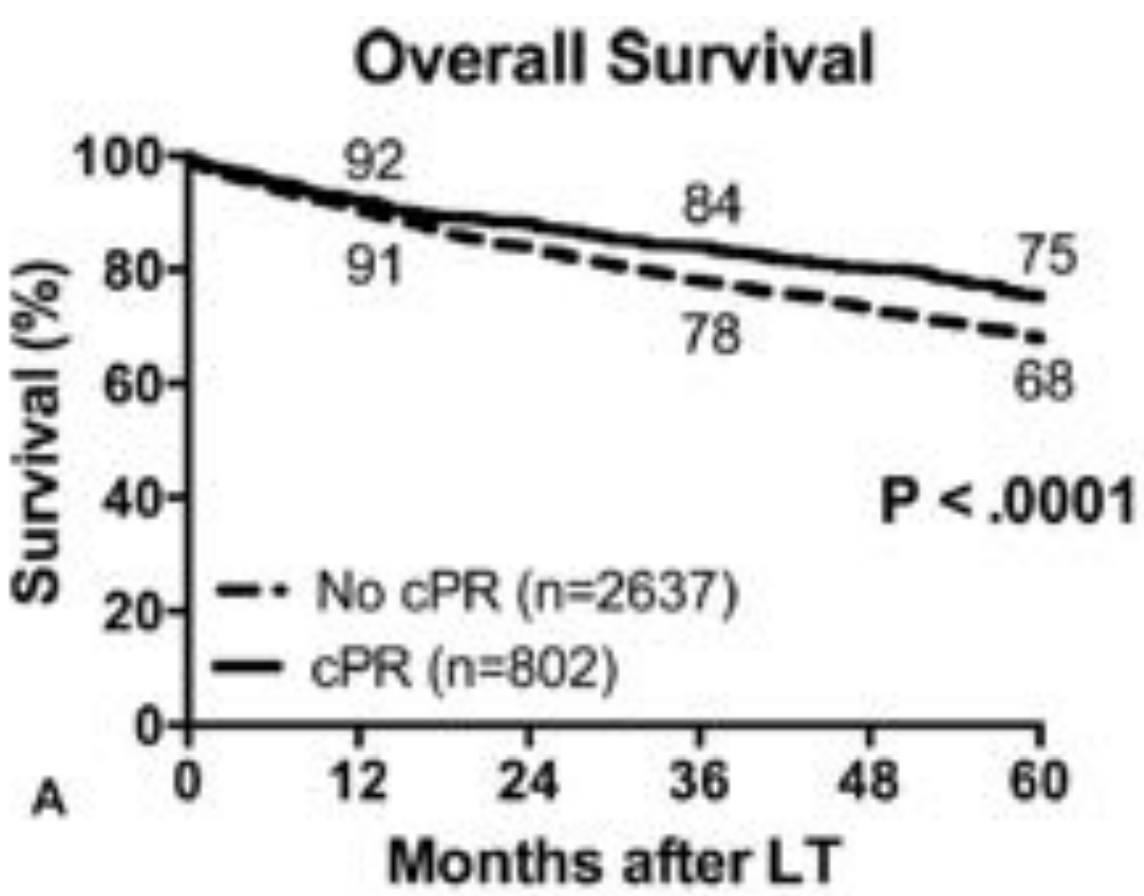


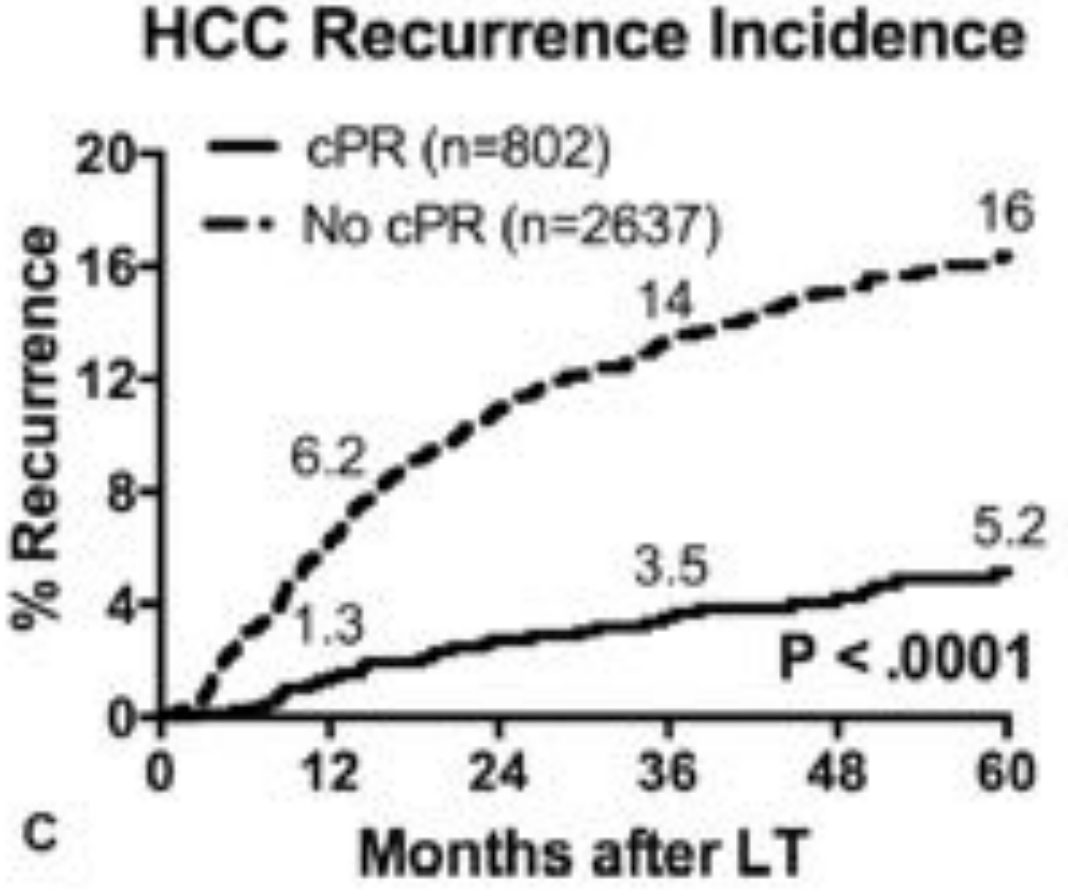
UHN Ajmera Transplant Centre

Gorgen A, Sapisochin G, et al. ILTS 2019 O-088

Pathologic Response to Pretransplant Locoregional Therapy is Predictive of Patient Outcome After Liver Transplantation for Hepatocellular Carcinoma

Analysis From the US Multicenter HCC Transplant Consortium





UHN Ajmera Transplant Centre

DiNorcia J et al. Ann Surg 2019

Hepatobiliary MRI as novel selection criteria in liver transplantation for hepatocellular carcinoma

Table 2. Significant prognostic factors in preoperative data, including MRI and Lab findings, in predicting HCC recurrence.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Age (year)	0.99	0.94–1.05	0.729			
Male	2.83	0.68–11.82	0.155			
Beyond the Milan criteria	3.21	1.61–6.40	<0.001	1.12	0.40–3.11	0.828
Morphological type	2.20	1.05–4.63	0.038	0.92	0.34–2.45	0.859
Non-smooth tumour margin	1.84	0.87–3.87	0.108			
Distinctive tumour margin	0.48	0.20–1.11	0.085			
Satellite nodule	5.90	2.62–13.29	<0.001	3.97	1.41–11.17	0.009
Peritumoural enhancement in AP	5.37	2.24–12.91	<0.001	1.36	0.36–5.15	0.655
Tumour capsule/pseudocapsule	0.72	0.36–1.43	0.344			
Peritumoural hypointensity in HBP	6.19	2.92–13.11	<0.001	4.24	1.40–12.82	0.011
Apparent diffusion coefficient	0.13	0.03–0.57	0.007	0.29	0.04–1.97	0.203
AFP (log ng/ml)	1.24	1.07–1.44	0.004	1.17	0.97–1.42	0.095
PIVKA-II (log mAU/ml)	1.35	1.09–1.67	0.007	1.06	0.81–1.40	0.676

UHN Ajmera Transplant Centre

Kim AY, et al. J. Hepatol 2018

Hepatobiliary MRI as novel selection criteria in liver transplantation for hepatocellular carcinoma

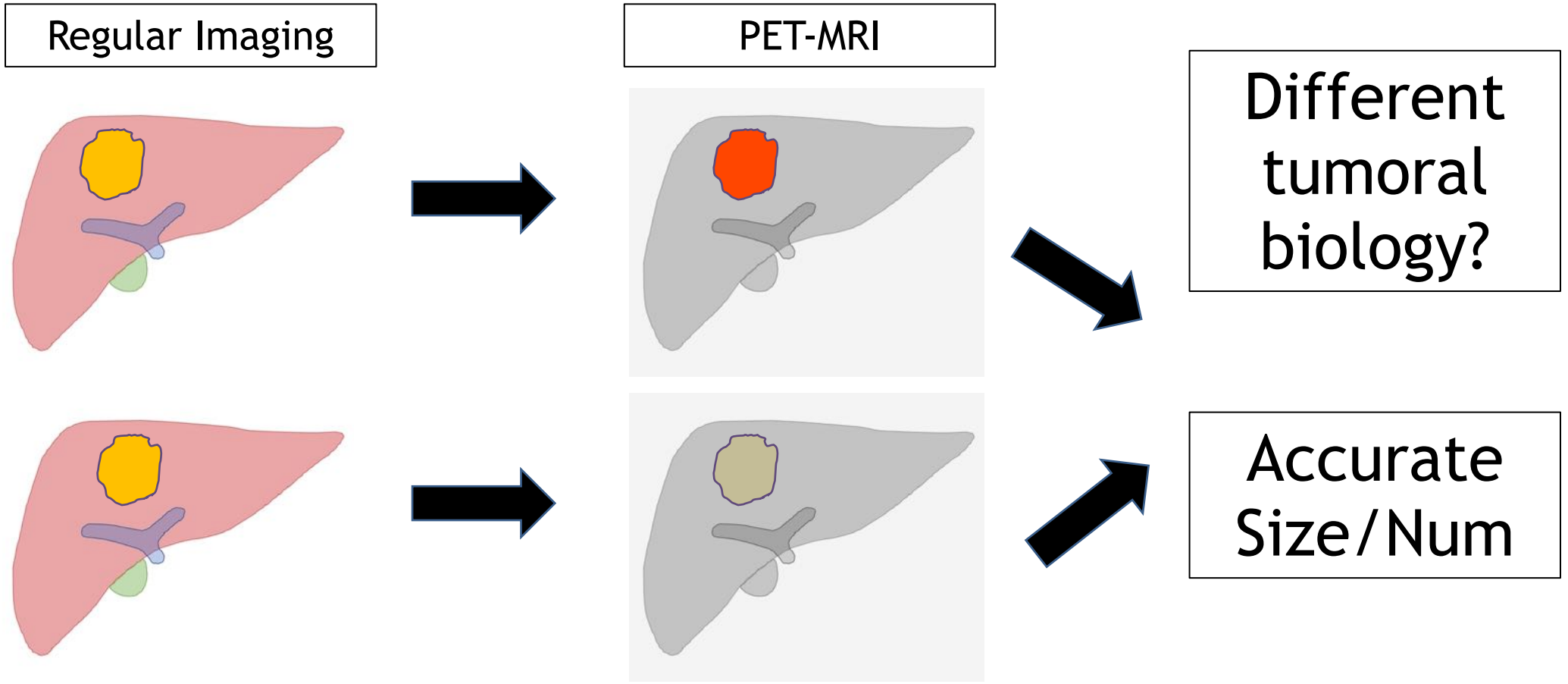
Table 3. MRI findings associated with microvascular invasion and intrahepatic metastasis.*

Variables	Microvascular invasion (+) (n = 55)	Microvascular invasion (−) (n = 45)	p value
Beyond the Milan criteria	27	5	<0.001
Morphological type†	40	15	<0.001
Non-smooth tumour margin	42	17	<0.001
Distinctive tumour margin	46	40	0.451
Satellite nodule	8	0	0.008
Peritumoural enhancement in AP	8	2	0.178
Tumour capsule/ pseudocapsule	28	21	0.673
Peritumoural hypointensity in HBP	13	1	0.002
Apparent diffusion coefficient‡	1.04 ± 0.20	1.11 ± 0.28	0.140
High-risk radiological findings	19	1	<0.001

UHN Ajmera Transplant Centre

Kim AY, et al. J. Hepatol 2018

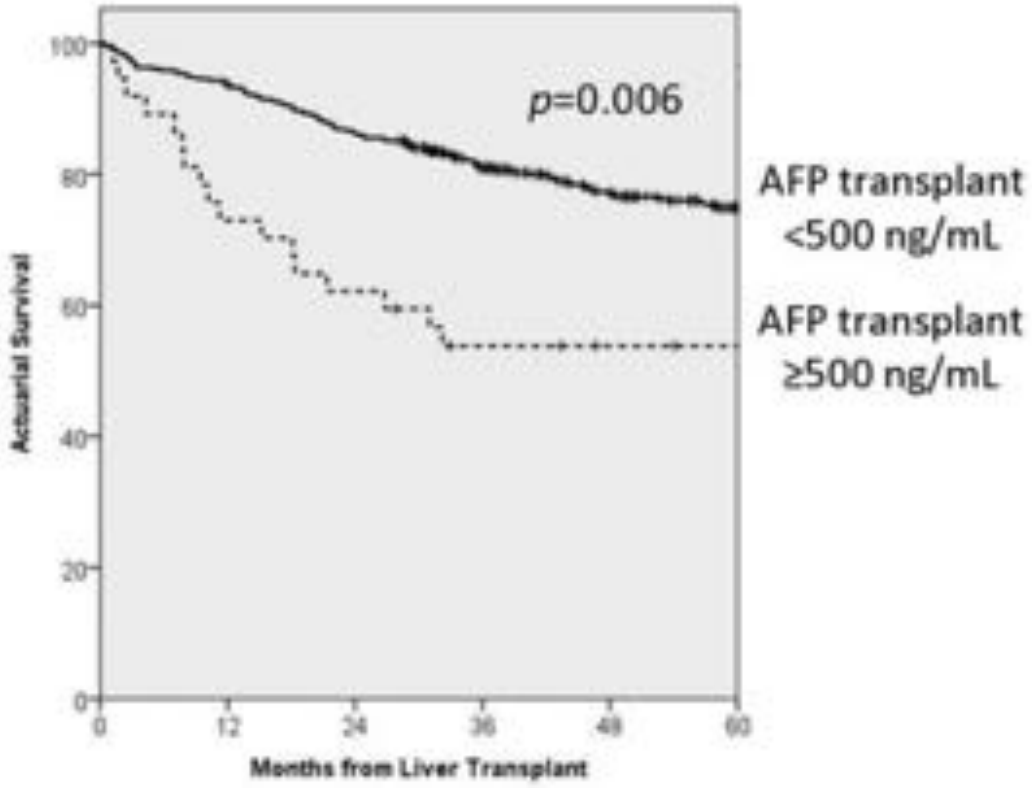
Future Perspectives: PET-MRI for Liver Cancer

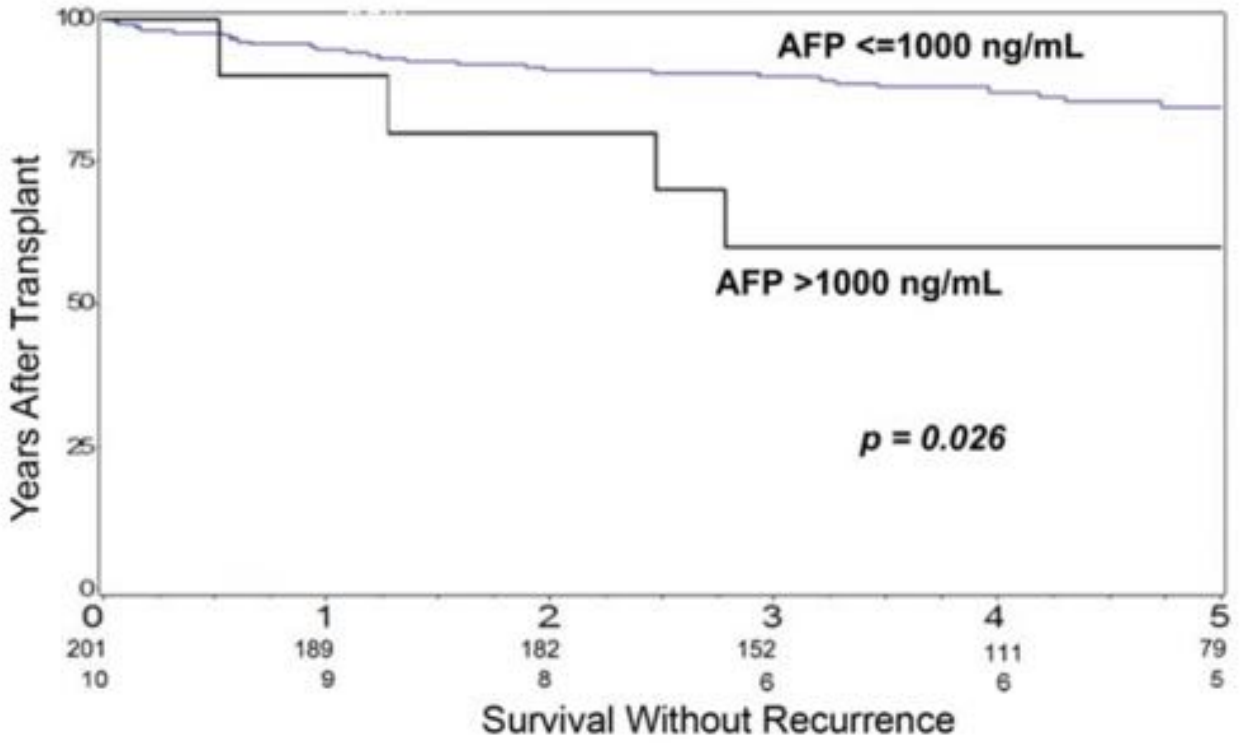


UHN Ajmera Transplant Centre

Response to LRT by decrease in tumor markers (AFP)

Static AFP





UHN Ajmera Transplant Centre

Sapisochin G et al. Hepatology 2016
Hameed et al. Liver Transpl 2014

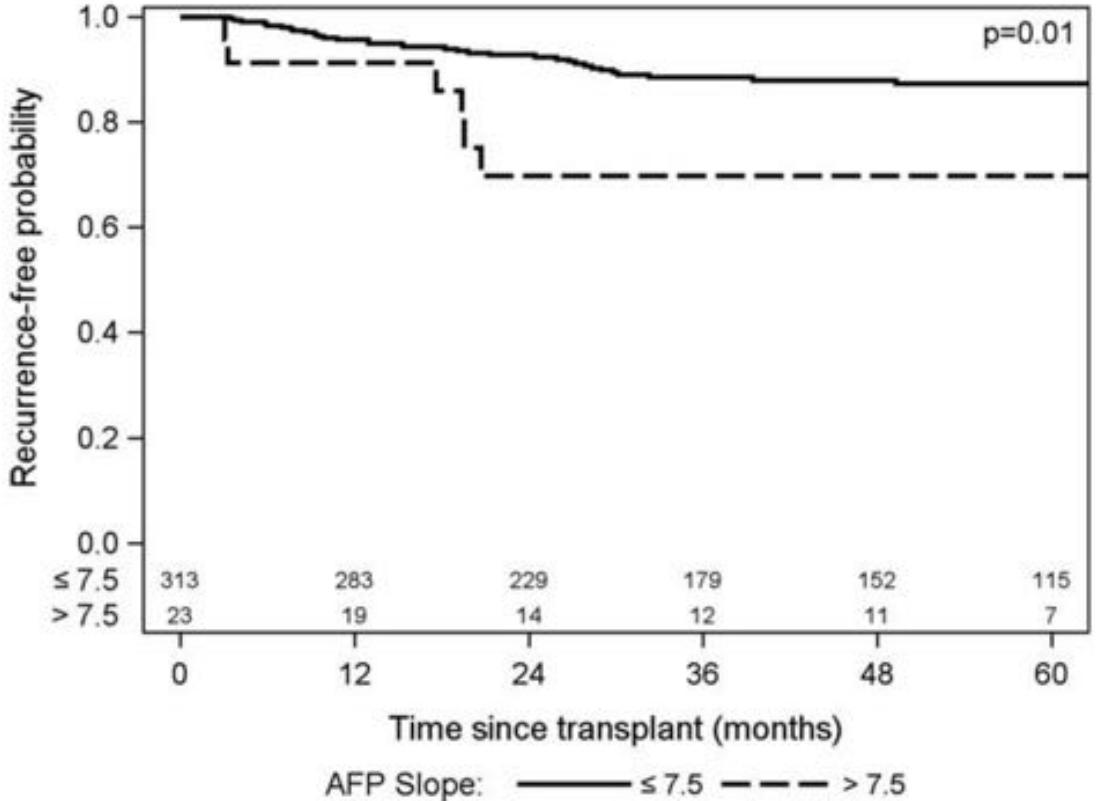
Alpha-Fetoprotein Slope >7.5 ng/mL per Month Predicts Microvascular Invasion and Tumor Recurrence After Liver Transplantation for Hepatocellular Carcinoma

Jeanne-Marie Giard, MD, MPH,[1] Neil Mehta, MD,[1] Jennifer L. Dodge, MPH,[2] John P. Roberts, MD,[2] and Francis Y. Yao, MD[1,2]

TABLE 4.

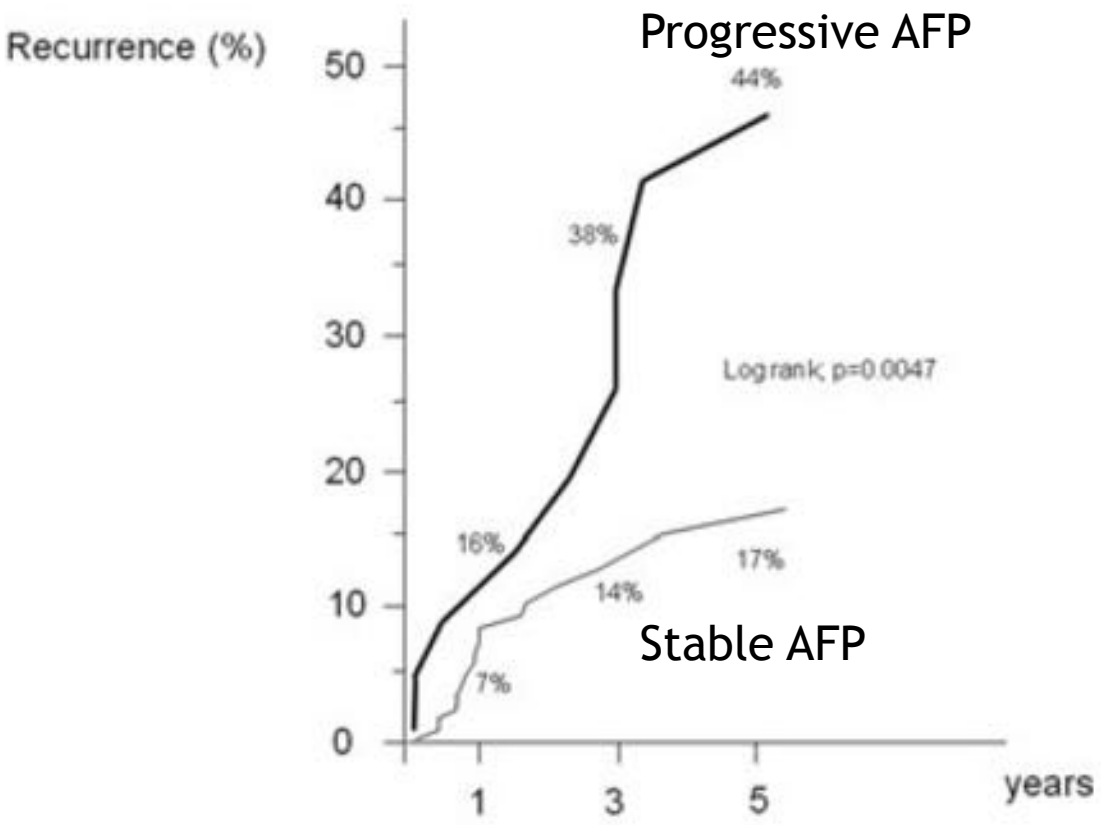
Multivariate analysis of predictors of HCC recurrence (pre-LT variables)

Predictor	HR (95% CI)	*P*
3 tumor nodules	7.6 (3.0-19.6)	<0.001
AFP slope > 7.5 ng/mL per month	3.0 (1.1-8.1)	0.03
Female sex	2.5 (1.2-5.0)	0.01



UHN Ajmera Transplant Centre

AFP slope



AFP increase ≥15 ng/mL per month

Overall Survival

	Risk Ratio
Progressive AFP (≥15 ng/mL per month)	2.06 (1.16-3.9)

Disease-Free Survival

	Risk Ratio
Progressive AFP (≥15 ng/mL per month)	2.45 (1.27-4.7)

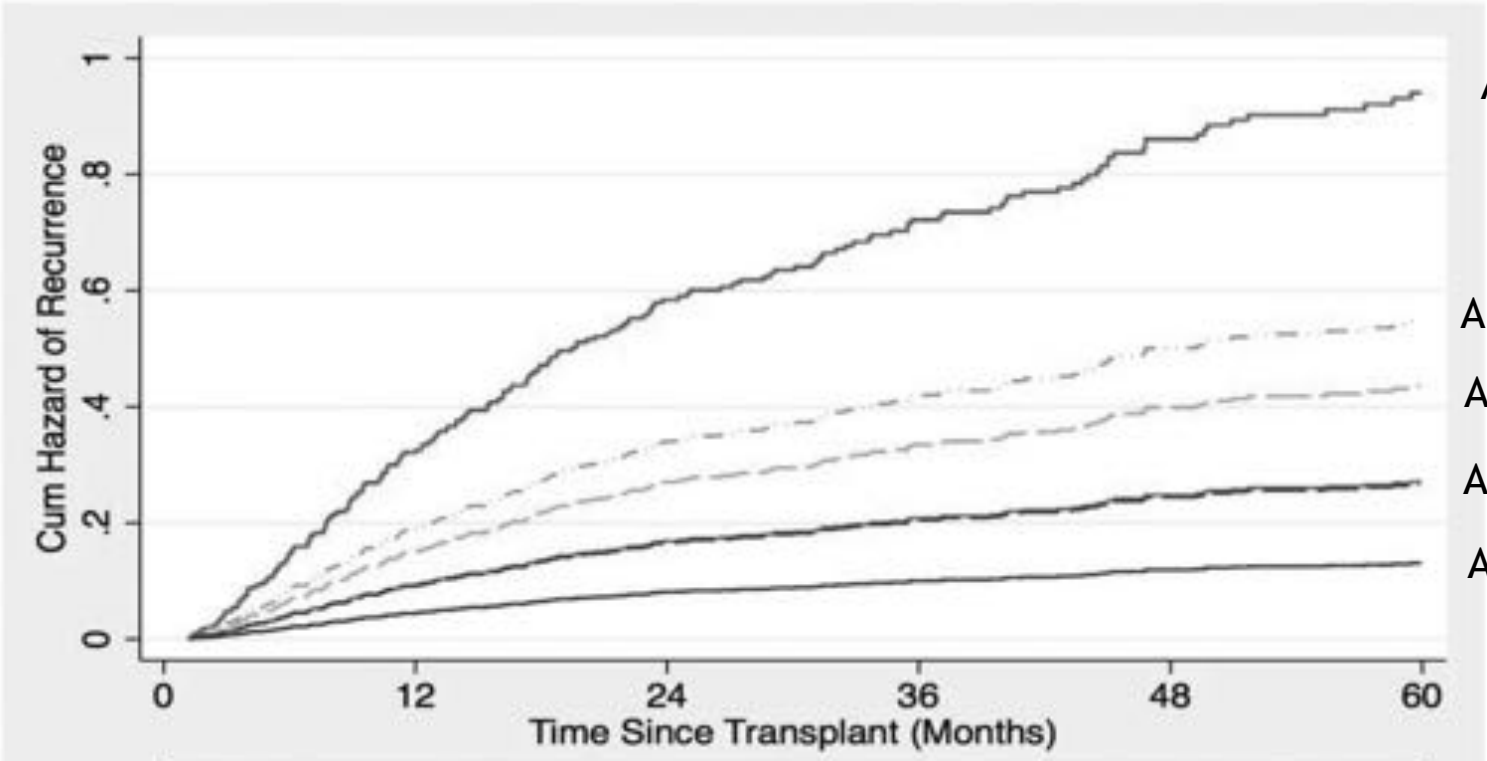
UHN Ajmera Transplant Centre

Vibert E, et al. AJT 2010

Is it Time to Abandon the Milan Criteria?

Results of a Bicoastal US Collaboration to Redefine Hepatocellular Carcinoma Liver Transplantation Selection Policies

AFP Response



AFP >1000

AFP 400-1000 down to >200

AFP 200-400 down to >200

AFP >1000 to <1000 (>50%)

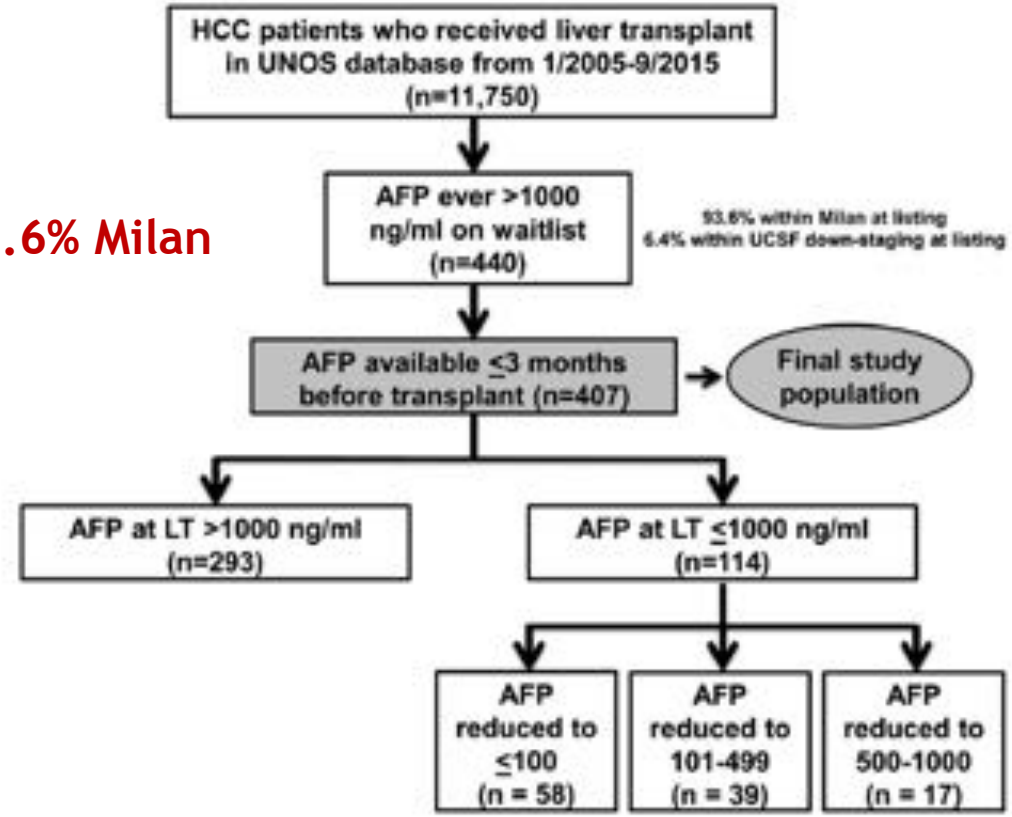
AFP <200

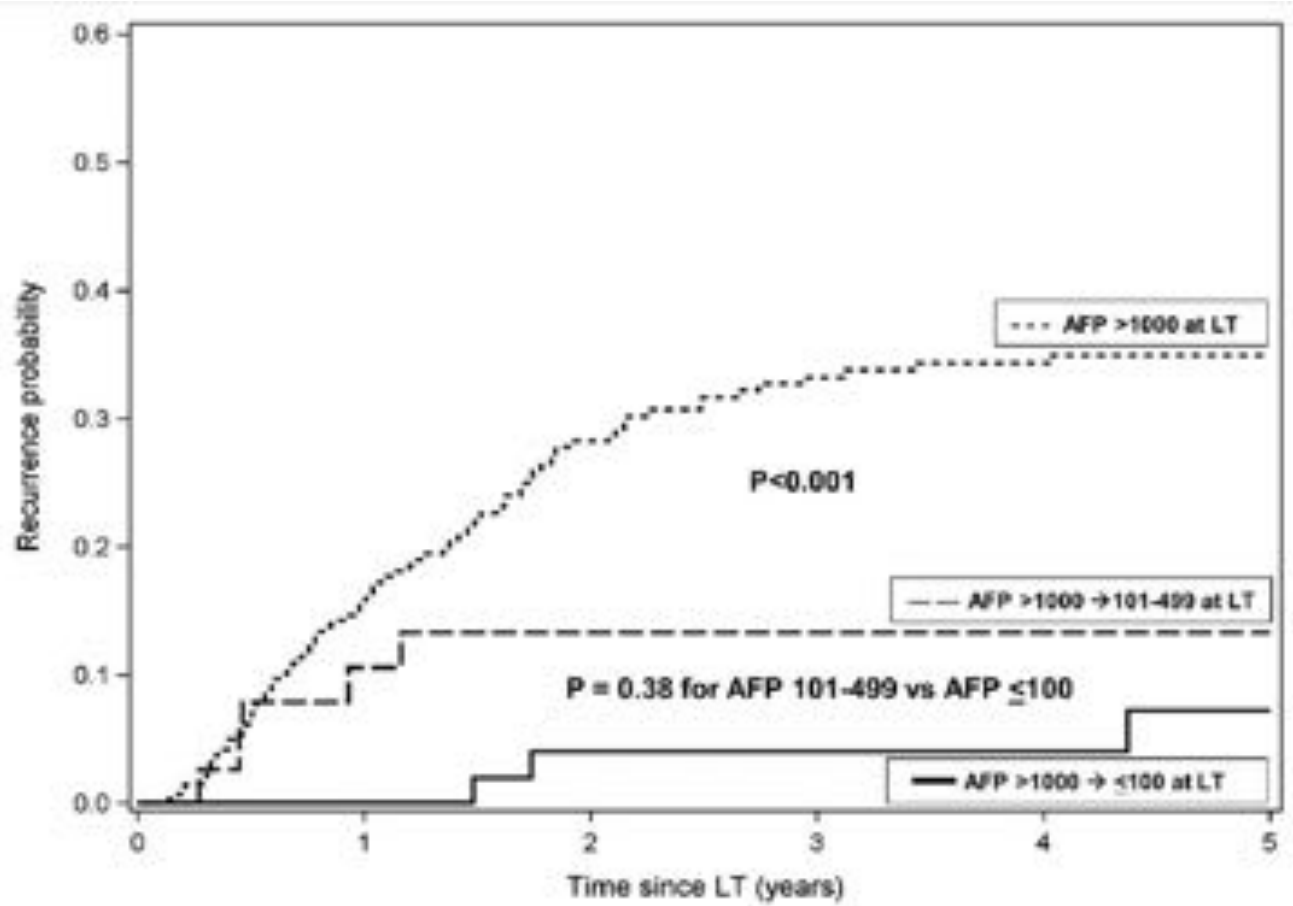
UHN Ajmera Transplant Centre

Halazun K, et al. Ann Surg 2018

AFP Response

93.6% Milan





UHN Ajmera Transplant Centre

Mehta N, et al. Hepatology 2019

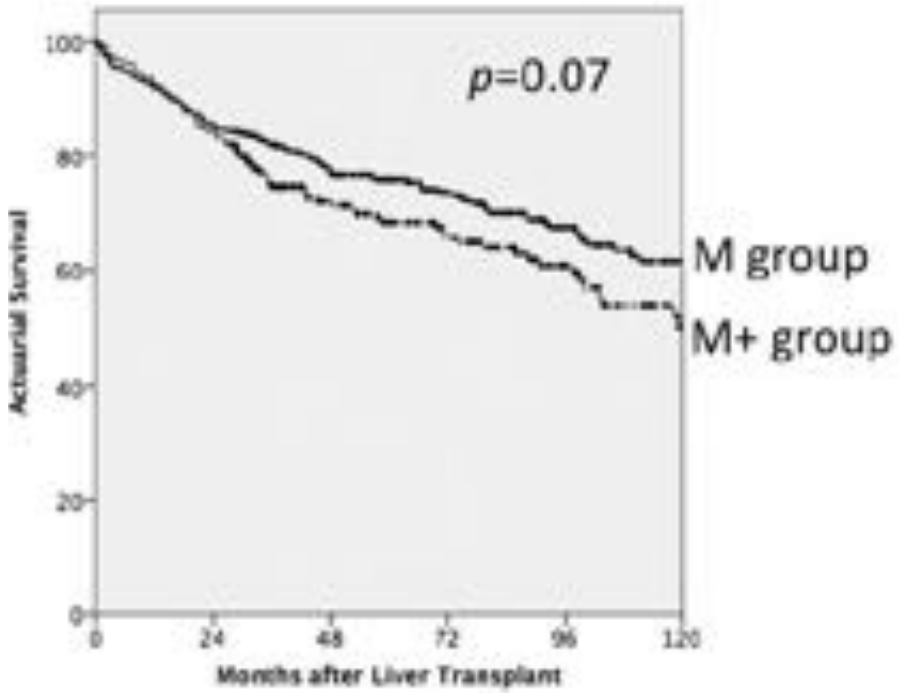
Other surrogates of tumor biology

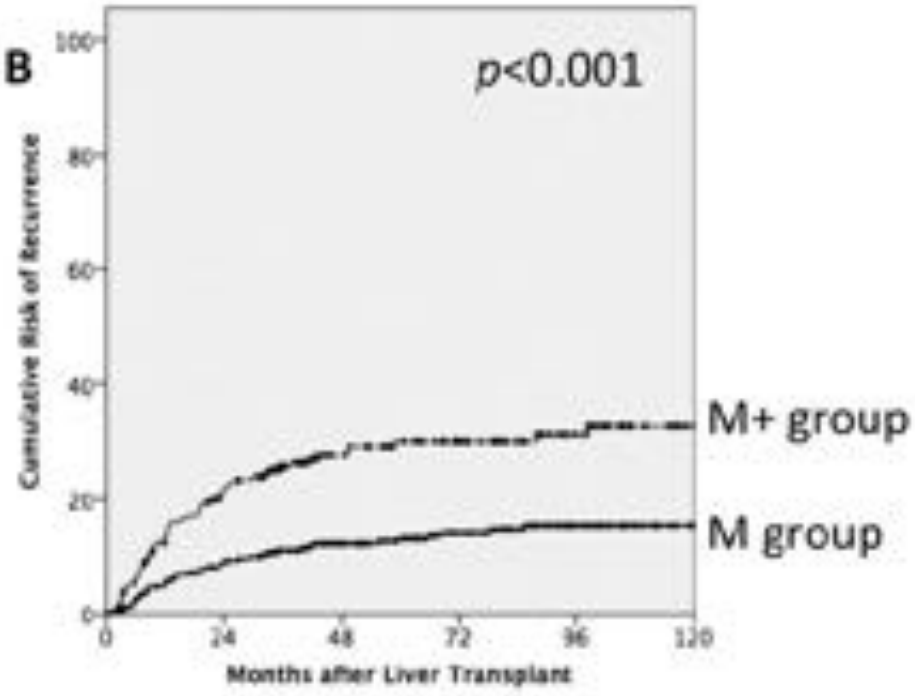
Tumor Differentiation

Extended Toronto Criteria

No limit size and number HCC
No constitutional symptoms
No Macrovascular Invasion
No Poorly Differentiation

***Limitation:**
Accuracy of biopsy
Heterogeneous tumor





UHN Ajmera Transplant Centre

Sapisochin G, et al. Hepatology 2016

Neutrophil-to-Lymphocyte Ratio (NLR)

A Novel Prognostic Index in Patients With Hepatocellular Cancer Waiting for Liver Transplantation

Time–Radiological-response–Alpha-fetoprotein–INflammation (TRAIN) Score

TABLE 2. Multivariable Cox Regression Analysis for the Risk of Intention-to-treat Death in the Training Set Population (Backward Conditional Method)

Variables	HR	95% CI	*P*
mRECIST PD (Y/N)	2.7	1.6–4.5	<0.001
AFP slope ≥15.0 ng/mL/mo (Y/N)	2.3	1.3–4.0	0.003
NLR ≥5.0 at LT or DO (Y/N)	1.6	1.0–2.6	0.08
WT slope (per month)	1.0	0.9–1.0	0.08

-2Log likelihood: 625.3.

Variables initially analyzed in the model and then excluded: year of LT (per year), recipient age at WT registration (per year), recipient male gender (Y/N), HCV positivity (Y/N), LRT number of procedures (per number), PLR ≥150 at LT or DO (Y/N), MC-OUT status (Y/N).

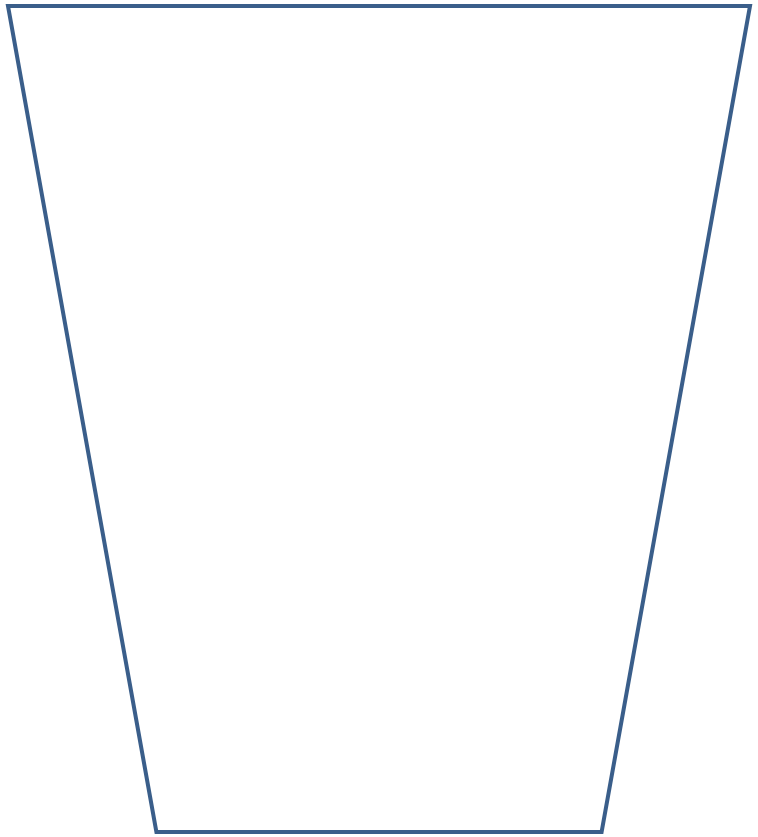
UHN Ajmera Transplant Centre

Lai Q, et al. Ann Surg 2016

AFP

NLR

...?



LRT

Diff.

UHN Ajmera Transplant Centre

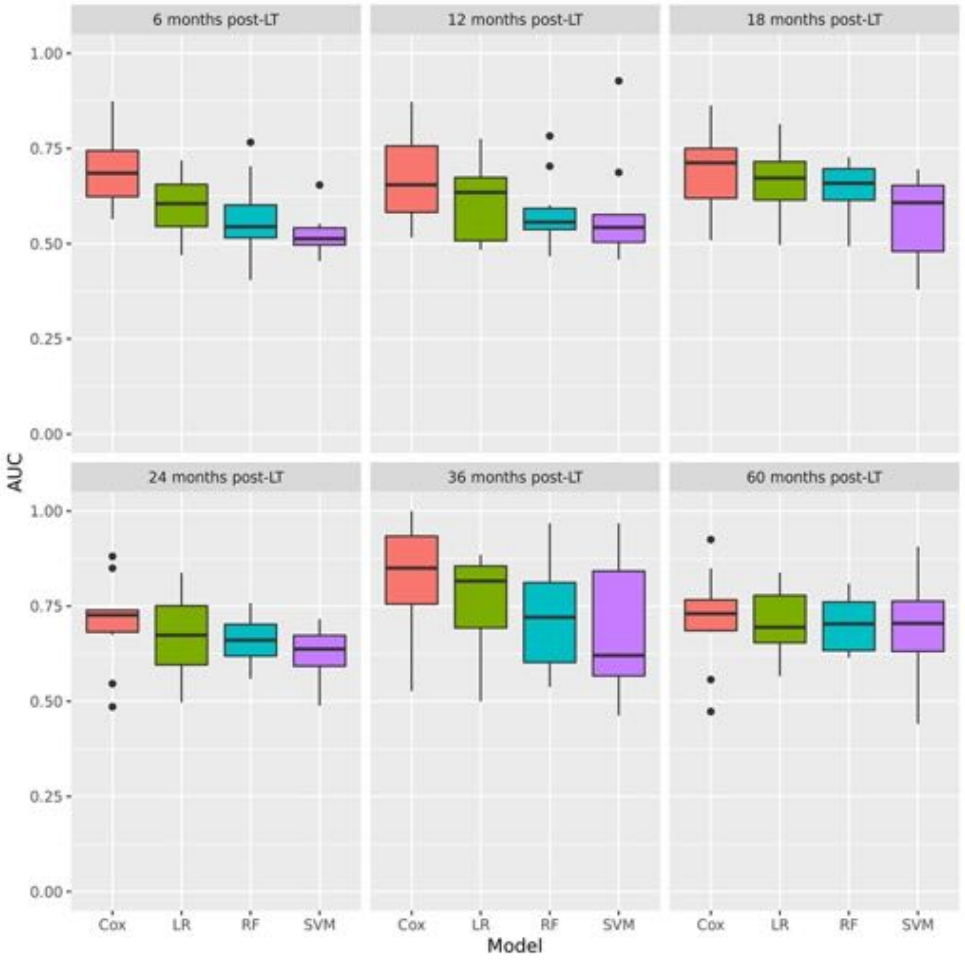
Pre-LT Selection Model	Tumor Burden	Biomarker(s)	Additional Criteria	5-Year Post-LT Overall Survival	AUROC
US National Policy[8]	Milan or down-staged to Milan	AFP > 1000 ng/mL reduced to <500 ng/mL		80%	
French AFP model[24]	Size and number (lowest risk: largest tumor ≤ 3 cm and ≤3 tumors)	AFP (lowest risk: ≤100 ng/mL)		68% if AFP model ≤ 2 versus 47% if AFP model > 2	0.7
Metro-Ticket 2[25]	Tumor number + size of largest tumor	AFP			0.72
TTV-AFP model[7]	TTV ≤ 115 cm^3	AFP ≤ 400 ng/mL		75% (at 4 years) for those beyond Milan criteria but within TTV-AFP	TTV: 0.8
ETC[26]	No limit		1. Biopsy of largest tumor with poorly differentiated excluded 2. No cancer-related symptoms	68% for those beyond Milan criteria but within ETC	
Pre-MoRAL[14]	Largest tumor size (lowest risk: ≤3 cm)	AFP (lowest risk: <200 ng/mL)	NLR (lower risk <5)	5-Year recurrence-free survival: 99% low risk 70% medium risk 56% high risk	0.82
HALT-HCC[27]	Hypotenuse between tumor number and largest tumor size*	Natural log (ln) AFP	MELD-Na		0.61
MoRAL[28] (LDLT)	No limit	$\sqrt{AFP}.\sqrt{DCP}$		83% for those beyond Milan criteria but low MoRAL score	0.84
National Cancer Center Korea[20] (LDLT)	Total tumor diameter < 10 cm		Negative ^{18}F-FDG-PET scan	84% (versus 60% in those exceeding criteria)	0.80
Kyoto criteria[15] (LDLT)	≤10 tumors, largest tumor ≤ 5 cm	DCP ≤ 400 mAU/mL		82% (versus 42% in those exceeding criteria)	Tumor #: 0.68 Size: 0.64 DCP: 0.71

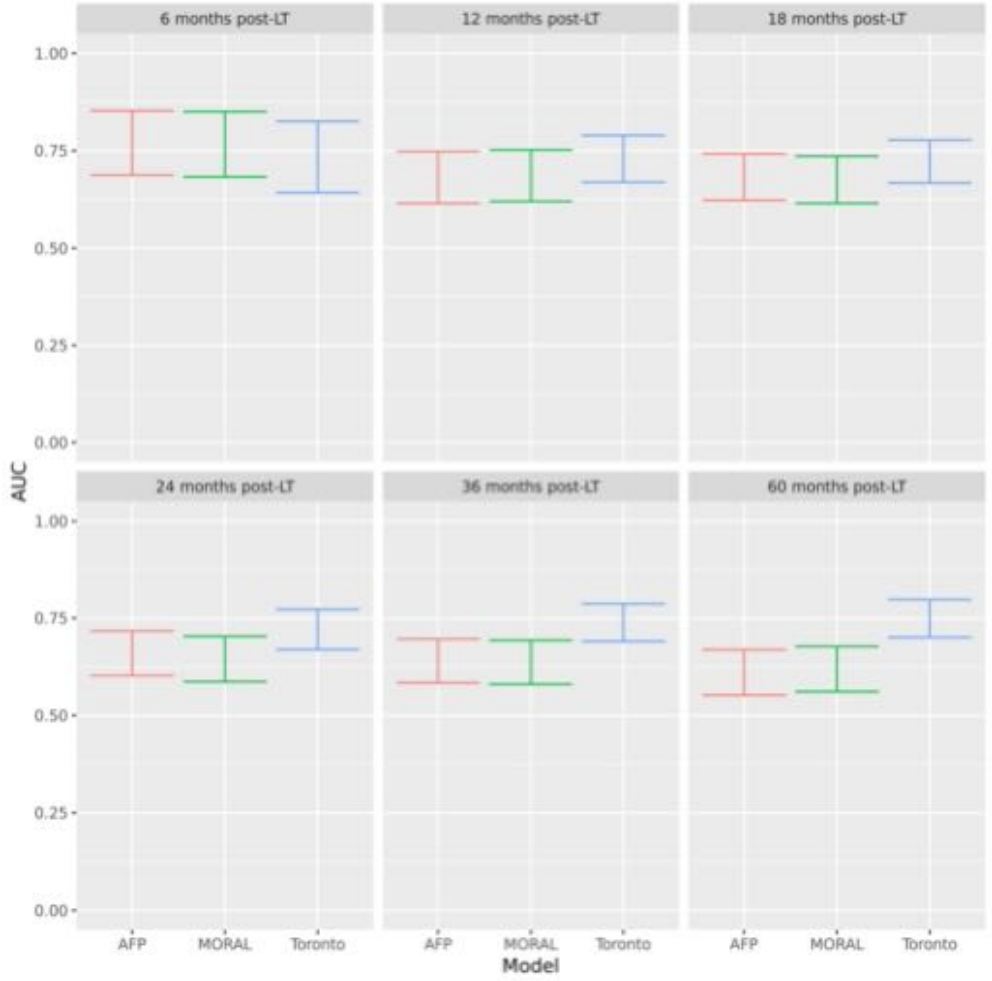
UHN Transplant Centre

Mehta N, et al. Clin Liver Dis 2019

Future Perspectives

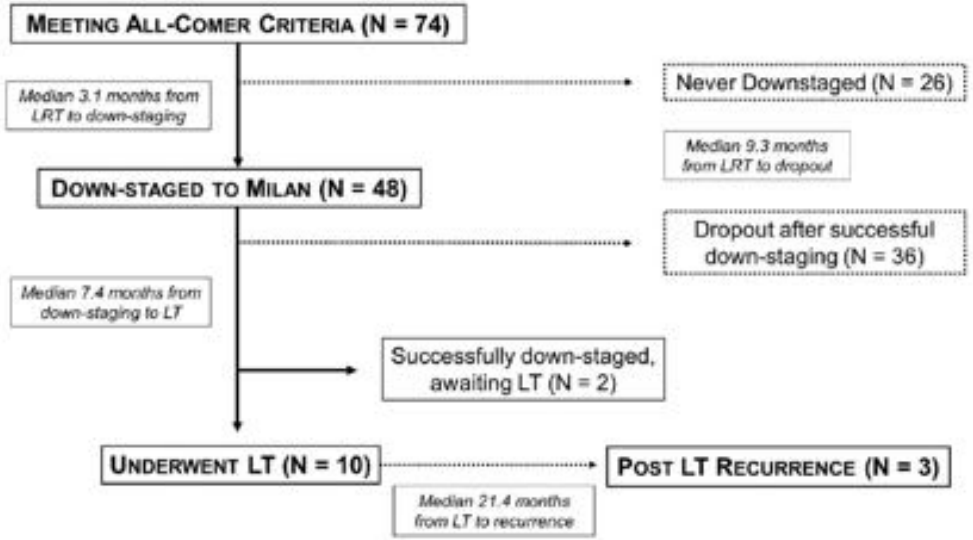
Will Machine Learning Algorithms (Artificial Intelligence) help with these Scores?

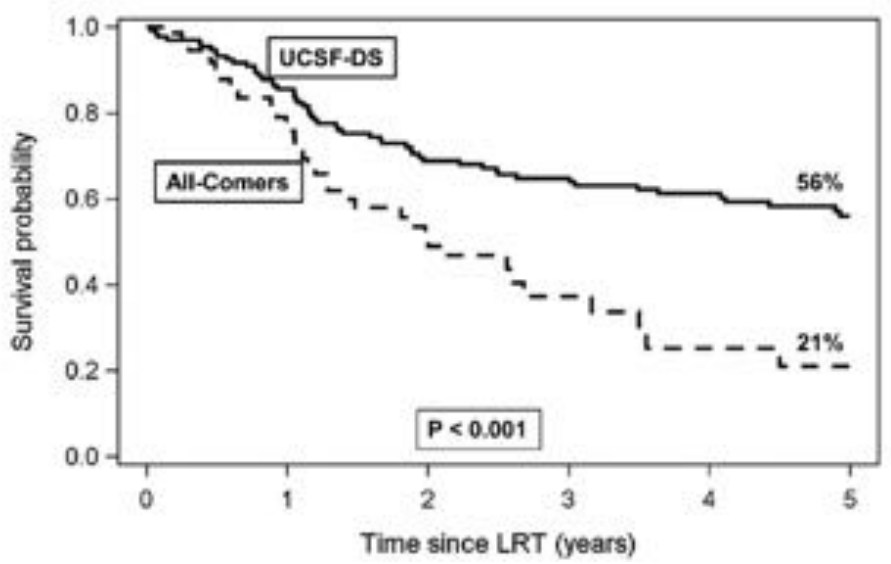


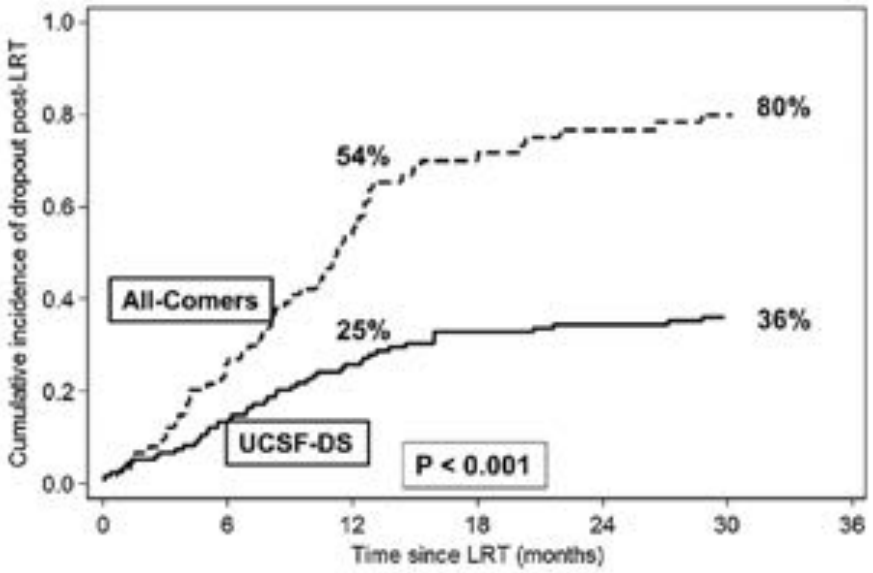


UHN Ajmera Transplant Centre

Lau L, Sapisochin G et al. ILTS 2019 P-



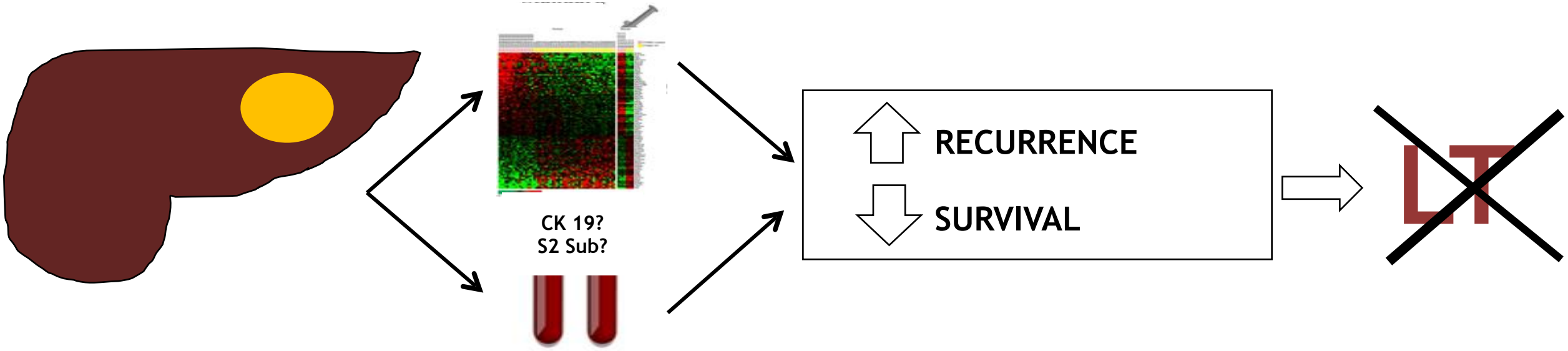




UHN Ajmera Transplant Centre

Sinha J. et al, Hepatology 2019

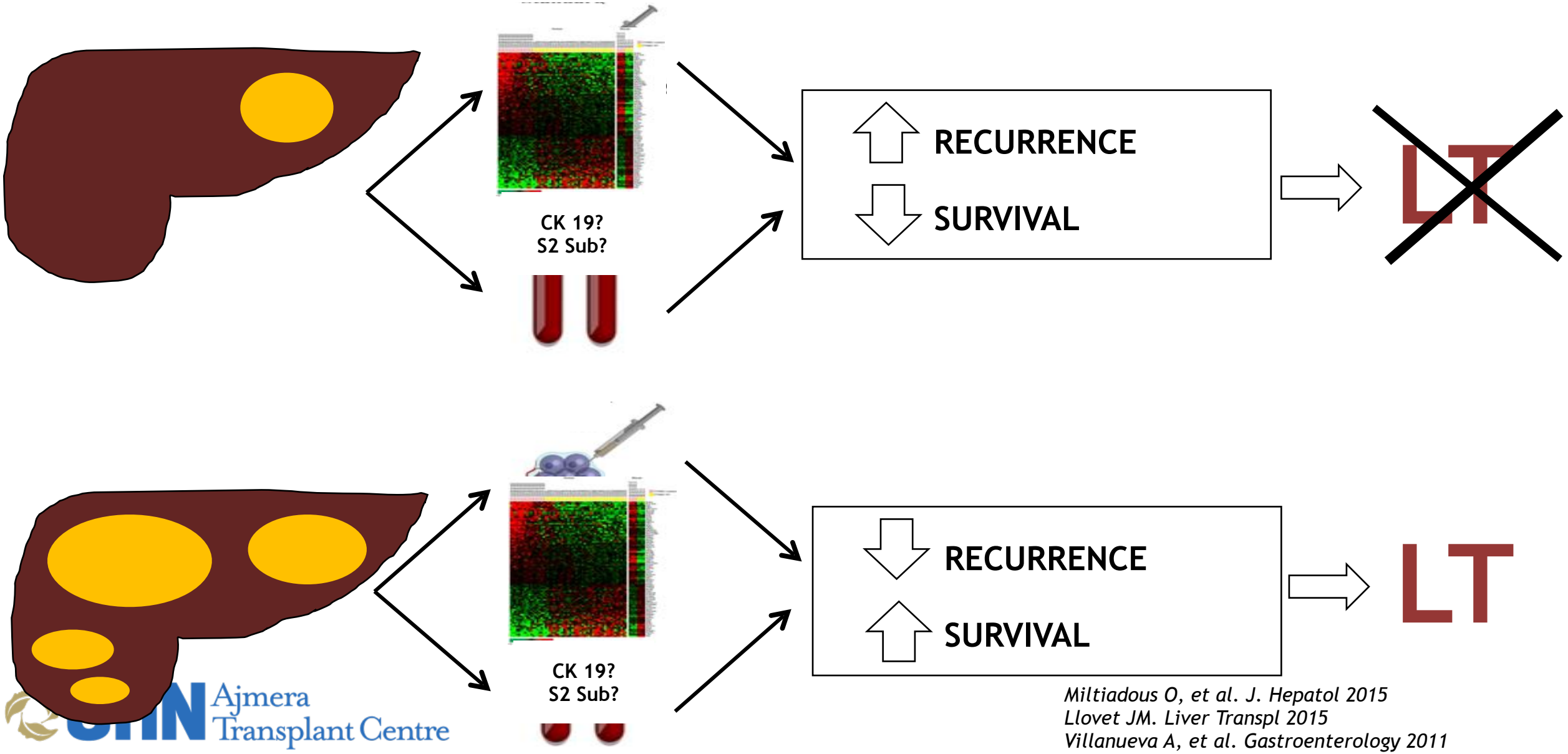
Moving beyond just SIZE & NUMBER
- Precision Medicine in HCC? -



UHN Ajmera Transplant Centre

Miltiadous O, et al. J. Hepatol 2015
Llovet JM. Liver Transpl 2015
Villanueva A, et al. Gastroenterology 2011

Moving beyond just SIZE & NUMBER
- Precision Medicine in HCC? -



Ajmera Transplant Centre

Miltiadous O, et al. J. Hepatol 2015
Llovet JM. Liver Transpl 2015
Villanueva A, et al. Gastroenterology 2011

Future Perspectives

Outline

- Why LRT?
- LRT response
- Biomarkers for LRT response
  - AFP
  - mRECIST
  - Pathological response
- Future perspectives

UHN Ajmera Transplant Centre

Locoregional therapies

- Aims:
  - Reduction of dropout risk
  - Downstaging
- Most applied methods:
  - TACE
  - RFA
  - Other: SBRT, Y90

DuBay et al HPB 2011
Frangakis et al. Cardiovasc Intervent Radiolo 2011
Sapisochin et al. J Hepatol 2017
Mohamed et al. Adv Radiat Oncol 2015

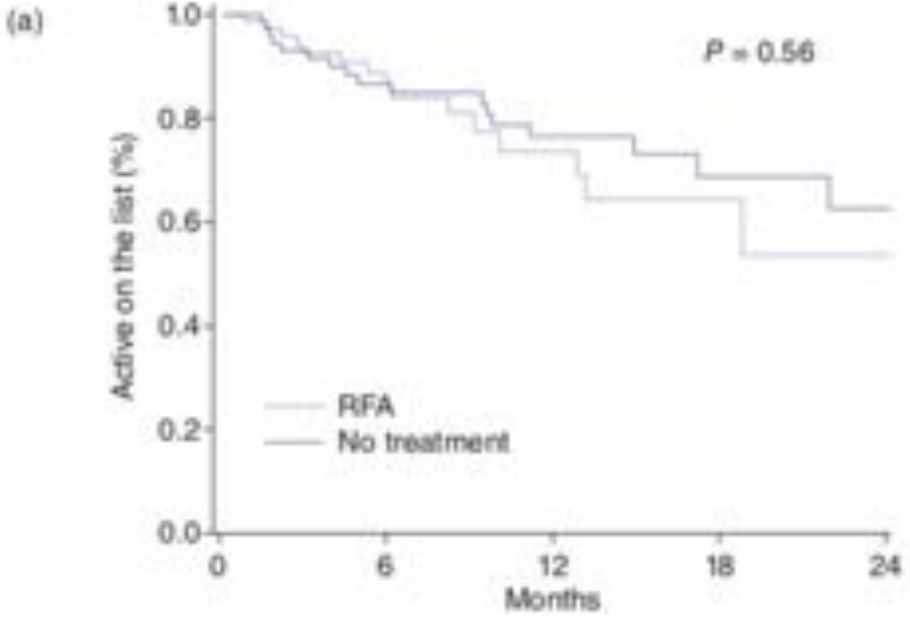
ORIGINAL ARTICLE

Radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation

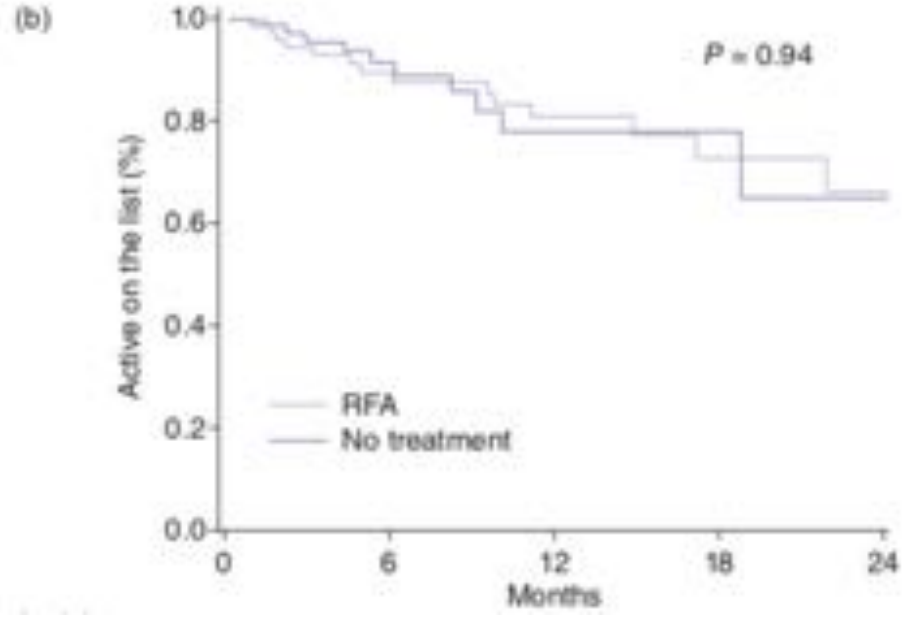
Derek A. DuBay[1]*, Charbel Sandroussi[1]*, John R. Kachura[2], Chia Sing Ho[2], J. Robert Beecroft[2], Charles M. Vollmer[3], Anand Ghanekar[1], Markus Guba[1], Mark S. Cattral[1], Ian D. McGilvray[1], David R. Grant[1] & Paul D. Greig[1]

[1]Liver Transplant Unit, Multiorgan Transplant Programme, University of Toronto, [2]Division of Vascular and Interventional Radiology, Department of Medical Imaging, Toronto General Hospital and Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada, and [3]Division of General Surgery, Beth Israel Deaconess Medical Center, Harvard School of Medicine, Boston, MA, USA

Overall dropout

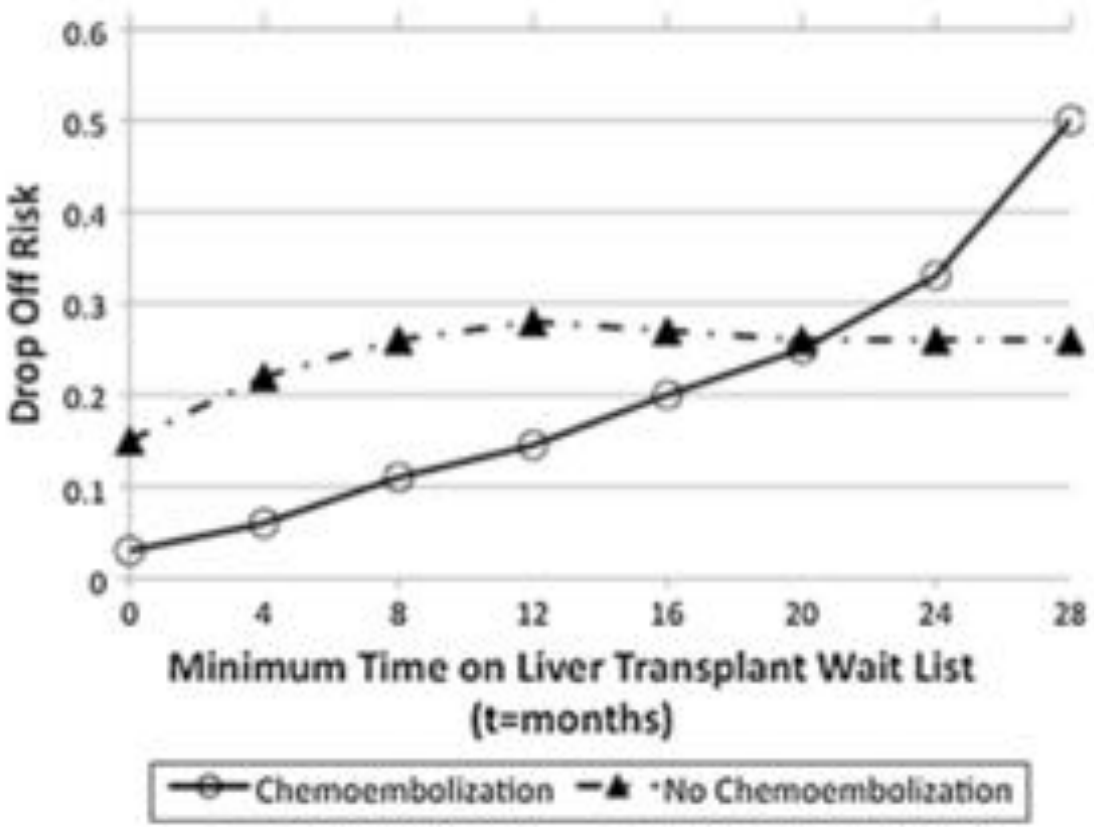


Dropout due to tumor progression



UHN Ajmera Transplant Centre

TACE and dropout risk



UHN Ajmera Transplant Centre

Frangakis et al. Cardiovasc Intervent Radiolo 2011

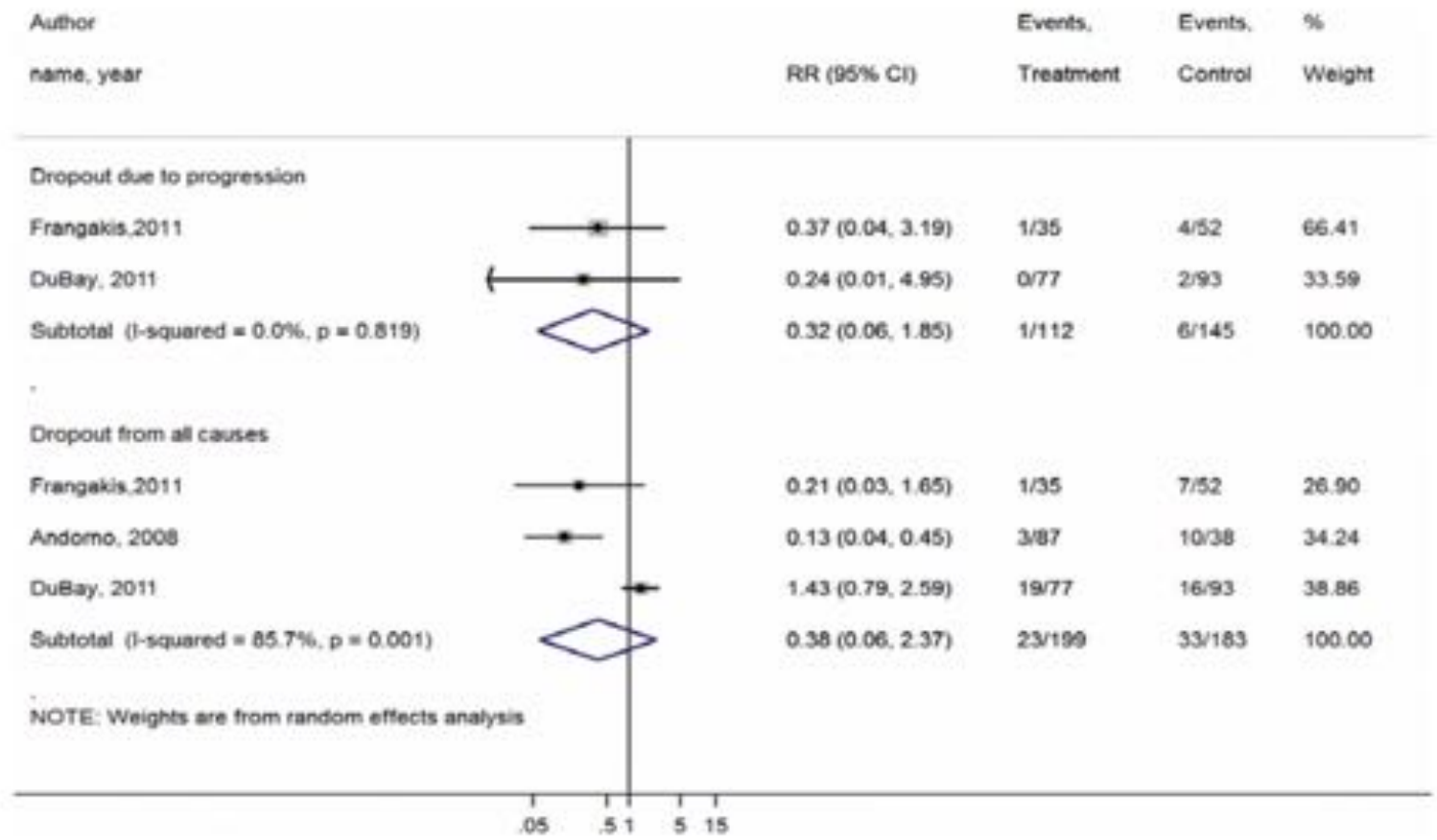
Preliminary Results of Liver Transplantation for Hepatocellular Carcinoma Among Allocation Organ Policy Strategies, Neoadjuvant Treatments, and Intention-to-Treat Analysis

E. Andorno, G. Bottino, N. Morelli, M. Casaccia, M. Gelli, D. Piredda, G. Immordino, R. Ferrante, I. Nardi, B.M. Troilo, S. Di Domenico, F. Ravazzoni, and U. Valente

Transplant Proc 2008

probabilities are constantly higher until 6 months from listing among patients with liver failure alone. Drop-out probabilities were 3.45% for patients who underwent neo-adjuvant therapies during the waiting list period and 27.02% in the nontreated group ($P < .0001$) regardless of histological response to treatment. In the study period, 49 (45.37%) grafts came from standard risk donors. The

LRT - Risk of dropout



UHN Ajmera Transplant Centre

Kulik et al. Hepatol. 2018

Response to LRT and progression beyond MC or death

TABLE 3. Cox Regression Models for Progression Outside the Milan Criteria or Death

	Transplant Censored			Transplant as Progression		
Variable	P Value	Hazard Ratio	95% Confidence Interval	P Value	Hazard Ratio	95% Confidence Interval
Age (years)	0.5001	1.01	0.98-1.05	0.4553	1.01	0.98-1.04
Albumin	0.0756	0.63	0.37-1.05	0.0221	0.64	0.43-0.94
Alkaline phosphatase	0.3382	1.00	0.99-1.00	0.0733	1.00	0.99-1.00
Creatinine	0.9671	1.02	0.44-2.35	0.3859	0.79	0.46-1.35
INR	0.0872	0.27	0.06-1.21	0.3447	0.59	0.20-1.76
Total bilirubin	0.7070	0.96	0.77-1.89	0.1905	1.10	0.95-1.26
Ascites	0.0098	3.45	1.35-8.85	0.3485	1.38	0.70-2.70
Encephalopathy	0.7553	1.22	0.34-4.40	0.9061	0.95	0.41-2.18
Performance status > 0	0.0978	13.77	0.62-307	0.7551	1.18	0.41-3.41
Total diameter	<0.0001	1.51	1.27-1.80	<0.0001	1.37	1.19-1.58
Recurrence/persistence	0.0001	2.75	1.65-4.60	<0.0001	2.82	1.91-4.16

UHN Ajmera Transplant Centre

De Giorgio et al. Liv Transpl 2010

Response to LRT and progression beyond MC or death

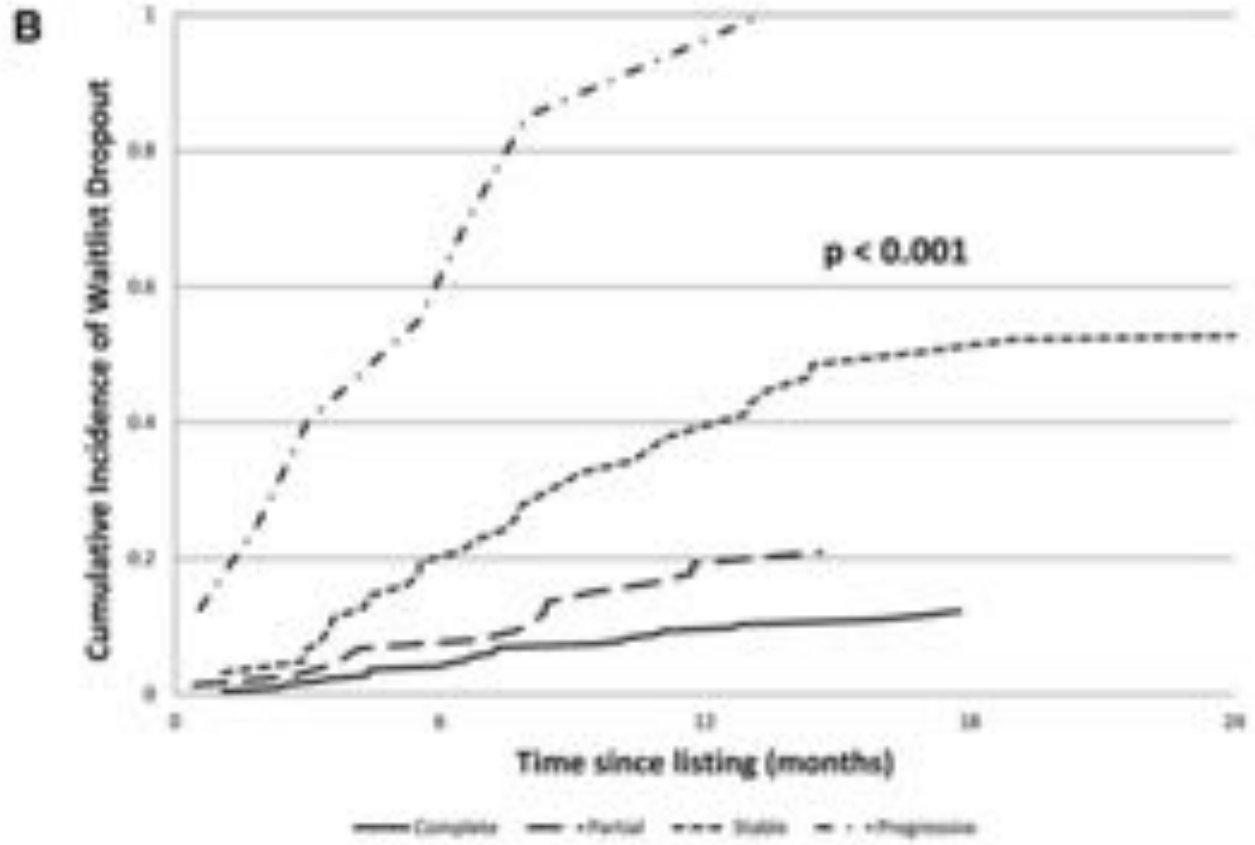
TABLE 3. Cox Regression Models for Progression Outside the Milan Criteria or Death

	Transplant Censored			Transplant as Progression		
Variable	P Value	Hazard Ratio	95% Confidence Interval	P Value	Hazard Ratio	95% Confidence Interval
Age (years)	0.5001	1.01	0.98-1.05	0.4553	1.01	0.98-1.04
Albumin	0.0756	0.63	0.37-1.05	0.0221	0.64	0.43-0.94
Alkaline phosphatase	0.3382	1.00	0.99-1.00	0.0733	1.00	0.99-1.00
Creatinine	0.9671	1.02	0.44-2.35	0.3859	0.79	0.46-1.35
INR	0.0872	0.27	0.06-1.21	0.3447	0.59	0.20-1.76
Total bilirubin	0.7070	0.96	0.77-1.89	0.1905	1.10	0.95-1.26
Ascites	0.0098	3.45	1.35-8.85	0.3485	1.38	0.70-2.70
Encephalopathy	0.7553	1.22	0.34-4.40	0.9061	0.95	0.41-2.18
Performance status > 0	0.0978	13.77	0.62-307	0.7551	1.18	0.41-3.41
Total diameter	<0.0001	1.51	1.27-1.80	<0.0001	1.37	1.19-1.58
Recurrence/persistence	0.0001	2.75	1.65-4.60	<0.0001	2.82	1.91-4.16

UHN Ajmera Transplant Centre

De Giorgio et al. Liv Transpl 2010

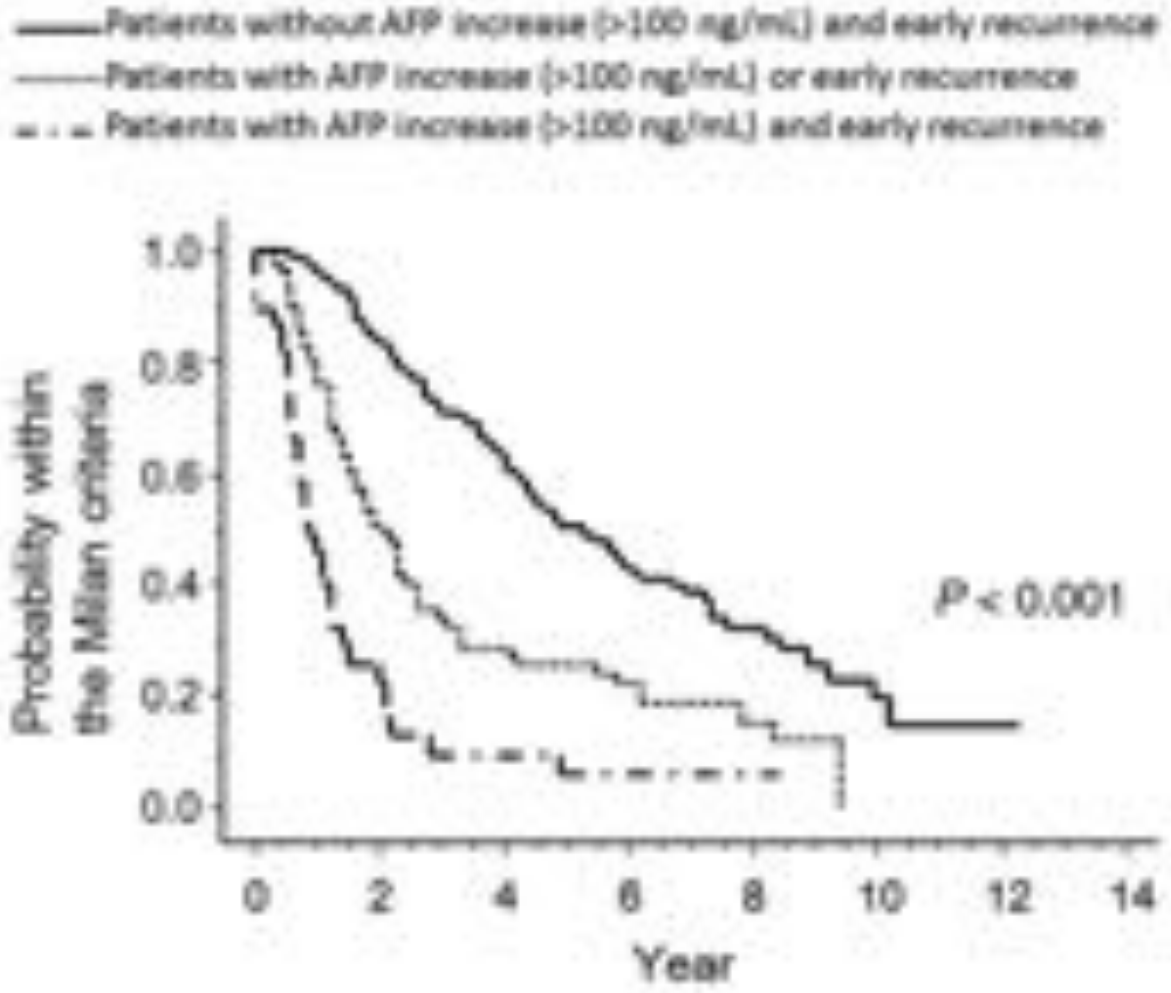
Response to LRT and dropout risk



UHN Ajmera Transplant Centre

Mehta et al. Liv Transpl 2013

Response to LRT and dropout risk



UHN Ajmera Transplant Centre

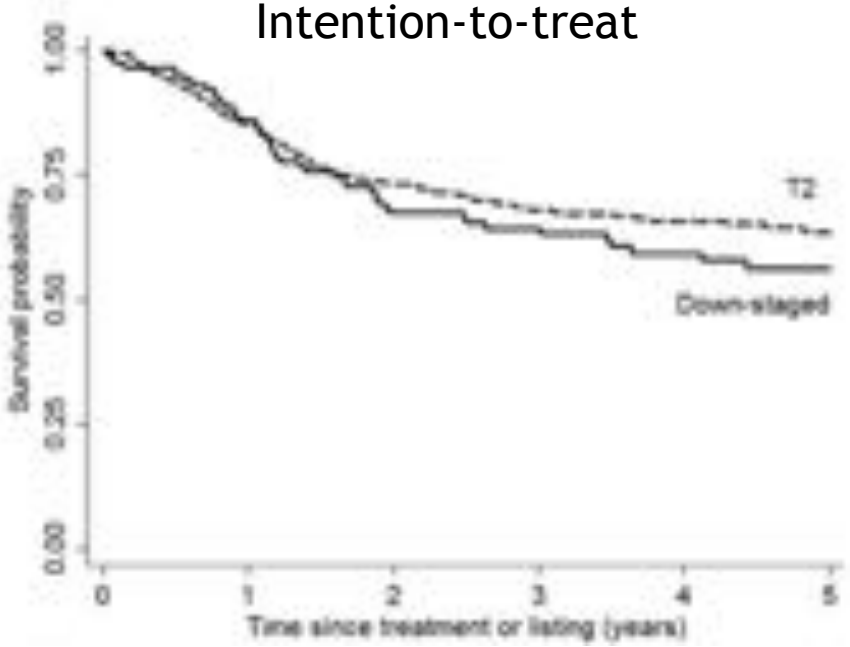
Tsuchiya et al. Liv Transpl 2014

HEPATOLOGY

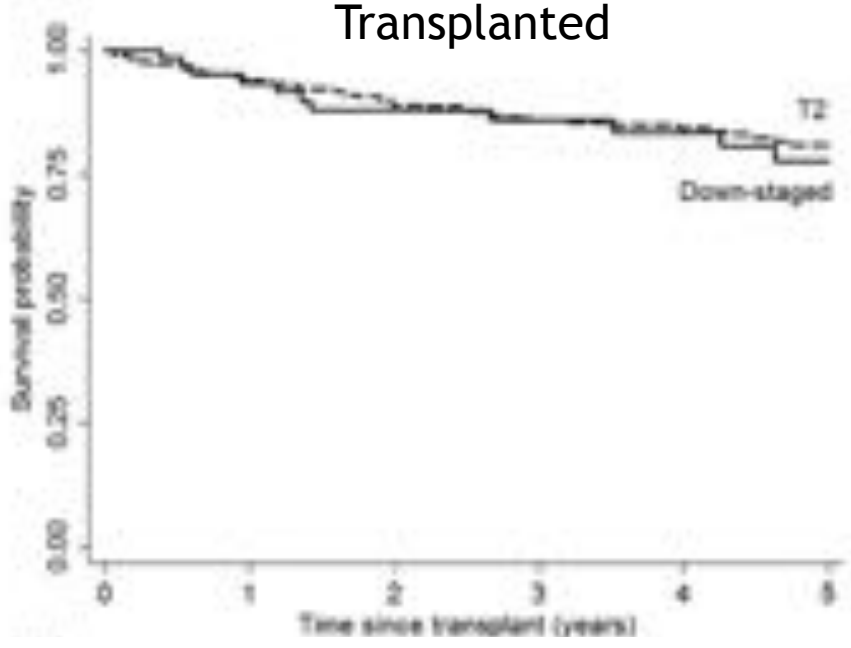
Downstaging of Hepatocellular Cancer Before Liver Transplant: Long-Term Outcome Compared to Tumors Within Milan Criteria

Francis Y. Yao,[1,2] Neil Mehta,[1] Jennifer Flemming,[1] Jennifer Dodge,[2] Bilal Hameed,[1] Oren Fix,[1] Ryutaro Hirose,[2] Nicholas Fidelman,[3] Robert K. Kerlan, Jr.,[3] and John P. Roberts[2]

Intention-to-treat



Transplanted



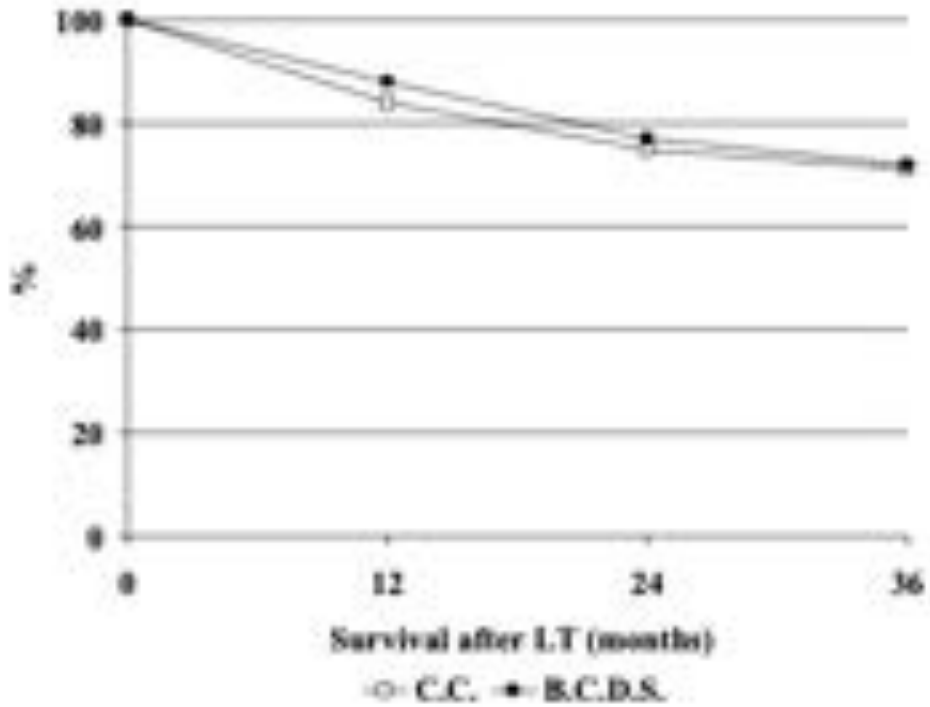
UHN Ajmera Transplant Centre

American Journal of Transplantation 2008; 8: 2547–2557
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2008.02409.x

Liver Transplantation for Hepatocellular Carcinoma: Results of Down-Staging in Patients Initially Outside the Milan Selection Criteria

M. Ravaioli[a], G. L. Grazi[a,*], F. Piscaglia[b], F. Trevisani[b], M. Cescon[a], G. Ercolani[a], M. Vivarelli[a], R. Golfieri[c], A. D'Errico Grigioni[d], I. Panzini[a], C. Morelli[a], M. Bernardi[b], L. Bolondi[b] and A. D. Pinna[a]



UHN Ajmera Transplant Centre

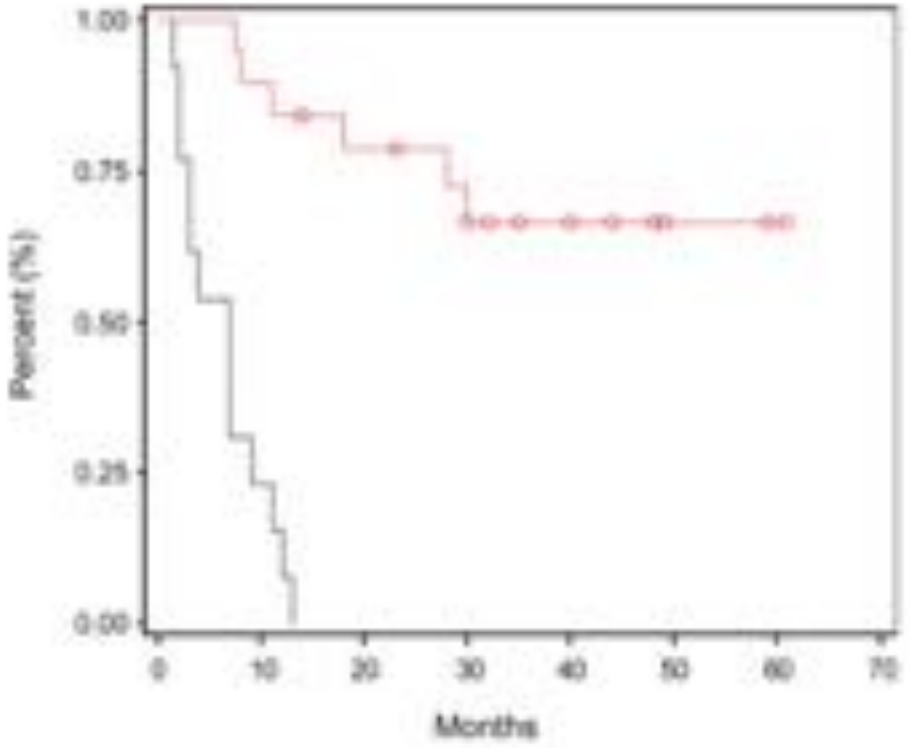
LIVER TRANSPLANTATION 16:289-299, 2010

ORIGINAL ARTICLE

Morphological Features of Advanced Hepatocellular Carcinoma as a Predictor of Downstaging and Liver Transplantation: An Intention-to-Treat Analysis

Omar Barakat,[1] R. Patrick Wood,[1] Claire F. Ozaki,[1] Victor Ankoma-Sey,[2] Joseph Galati,[2] Mark Skolkin,[3] Barry Toombs,[3] Mary Round,[3] Warren Moore,[3] and Luis Mieles[4]

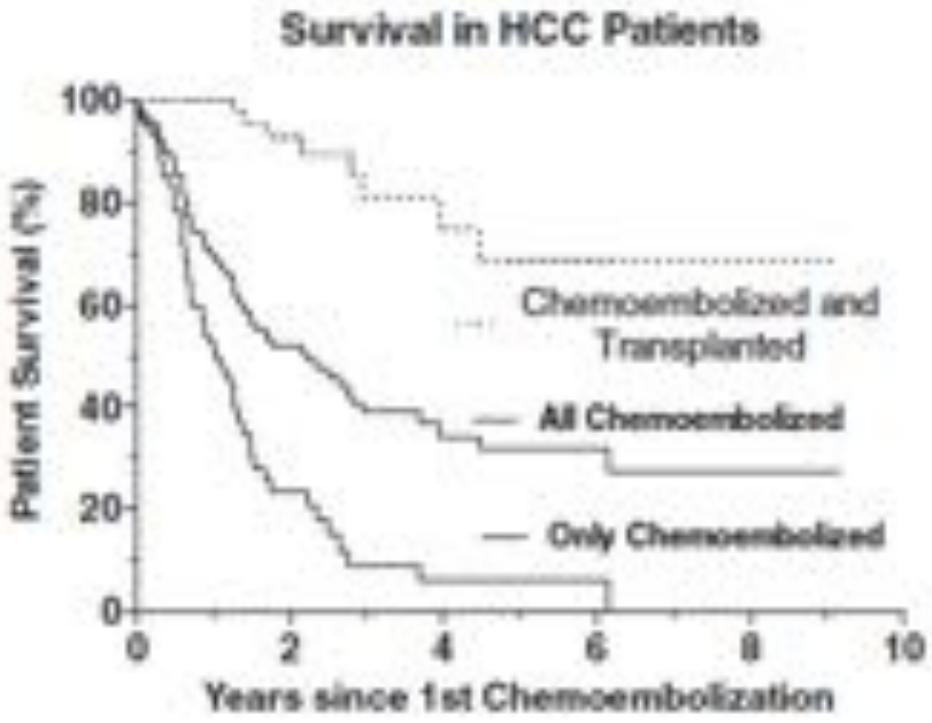
Downstaged vs. non-downstaged

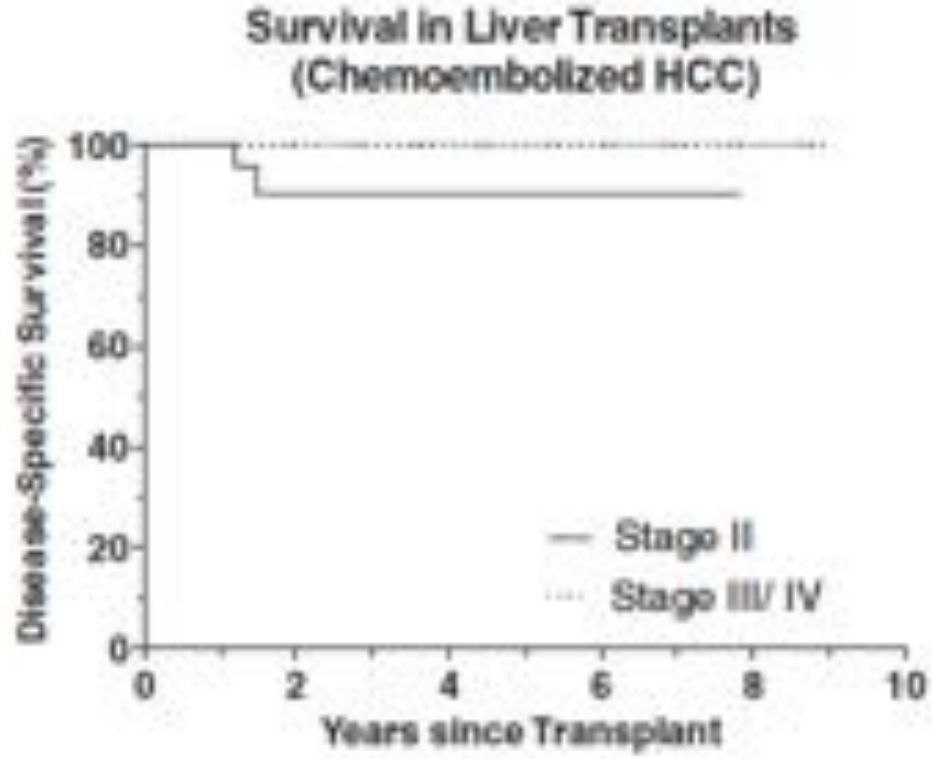


UHN Ajmera Transplant C

Outcomes of Neoadjuvant Transarterial Chemoembolization to Downstage Hepatocellular Carcinoma Before Liver Transplantation

William C. Chapman, MD, M. B. Majella Doyle, MD,* Jourdan E. Stuart,†*
Neeta Vachharajani, MD, Jeffrey S. Crippin, MD,‡ Christopher D. Anderson, MD,**
Jeffrey A. Lowell, MD, Surendra Shenoy, MD,* Michael D. Darcy, MD,† and Daniel B. Brown, MD§*





Response to LRT and pathological features

Table 3. Explant Histological Characteristics in the Downstaging Group and the T2 Group

	Downstaging Group (n = 64)	T2 Group (n = 332)	P Value
Pathological tumor stage (%)			
Complete necrosis (no viable tumor)	26 (40.6)	133 (40.1)	1.0
T1*	10 (15.6)	29 (8.7)	0.11
T2	18 (28.1)	115 (34.6)	0.39
T3	4 (6.3)	24 (7.2)	1.0
T4a (>4 lesions)	5 (7.8)	29 (8.7)	1.0
T4b (macrovascular invasion)	1 (1.6)	2 (0.6)	0.41
Histological grade of differentiation† (%)	N = 38	N = 199	
Well differentiated	13 (34.2)	79 (39.7)	0.59
Moderately differentiated	25 (65.8)	103 (51.8)	0.15
Poorly differentiated	0	17 (8.5)	0.08
Vascular invasion (%)	N = 64	N = 332	
Microvascular	1 (1.6)	18 (5.4)	0.33
Macrovascular	1 (1.6)	2 (0.6)	0.41

UHN Ajmera Transplant Centre

Yao et al. Hepatol 2015

Response to LRT and pathological features

Univariable and multivariable logistic regression for predictors of microvascular invasion among patients who underwent liver transplantation.				
Variable	Univariable		Multivariable	
	OR (95% CI)	p	OR (95% CI)	p
Serum AFP pre-LT (per 100 ng/mL)	1.04 (1.00 - 1.08)	0.04	1.02 (0.99 - 1.05)	0.21
AFP slope (ref.: stable)				
Regressive	1.13 (0.63 - 2.01)	0.68	1.53 (0.81 - 2.91)	0.19
Progressive	2.02 (1.11 - 3.68)	0.02	0.96 (0.52 - 1.78)	0.91
Tumor size pre-LT (per cm)	1.20 (1.13 - 1.27)	<0.001	1.12 (1.02 - 1.23)	0.02
Tumor number pre-LT (per lesion)	1.52 (1.32 - 1.74)	<0.001	1.18 (0.95 - 1.47)	0.13
Number of LRT (ref.: 1 LRT)				
2 LRT	1.94 (1.21 - 3.10)	0.01	1.85 (1.12 - 3.06)	0.02
≥ 3LRT	2.23 (1.22 - 4.09)	0.01	1.99 (1.03 - 3.84)	0.04

Complete Pathologic Response to Pretransplant Locoregional Therapy for Hepatocellular Carcinoma Defines Cancer Cure After Liver Transplantation

Analysis of 501 Consecutively Treated Patients

Vatche G. Agopian, MD, Maud M. Morshedi, MD, PhD,† Justin McWilliams, MD,†*
Michael P. Harlander-Locke, MPH, Daniela Markovic, MS,‡ Ali Zarrinpar, MD, PhD,* Fady M. Kaldas, MD,**
Douglas G. Farmer, MD, Hasan Yersiz, MD,* Jonathan R. Hiatt, MD,* and Ronald W. Busuttil, MD, PhD**

Impact of Pretransplant Bridging Locoregional Therapy for Patients With Hepatocellular Carcinoma Within Milan Criteria Undergoing Liver Transplantation

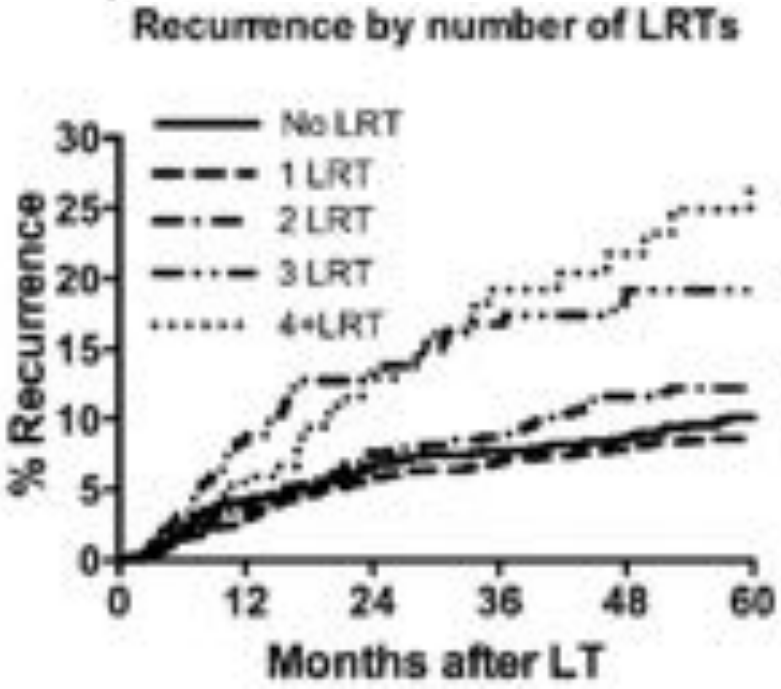
Analysis of 3601 Patients From the US Multicenter HCC Transplant Consortium

Vatche G. Agopian, MD, FACS, Michael P. Harlander-Locke, MPH,* Richard M. Ruiz, MD,† Goran B. Klintmalm, MD, PhD,† Srinath Senguttuvan, MS,† Sander S. Florman, MD,‡ Brandy Haydel, BS, CCRC,‡ Maarouf Hoteit, MD,§ Matthew H. Levine, MD, PhD,§ David D. Lee, MD,¶ C. Burcin Taner, MD,¶ Elizabeth C. Verna, MD, MS,|| Karim J. Halazun, MD,||** Rita Abdelmessih, MD,|| Amit D. Tevar, MD,†† Abhinav Humar, MD,†† Federico Aucejo, MD,‡‡ William C. Chapman, MD,§§ Neeta Vachharajani, BS,§§ Mindie H. Nguyen, MD, MAS,¶¶ Marc L. Melcher, MD, PhD,|||| Trevor L. Nydam, MD,*** Constance Mobley, MD, PhD,††† R. Mark Ghobrial, MD, PhD,††† Beth Amundsen, MD,‡‡‡ James F. Markmann, MD, PhD,‡‡‡ Alan N. Langnas, DO,§§§ Carol A. Carney, CCRC,§§§ Jennifer Berumen, MD,¶¶¶ Alan W. Hemming, MD,¶¶¶ Debra L. Sudan, MD,|||||| Johnny C. Hong, MD,**** Joohyun Kim, MD,**** Michael A. Zimmerman, MD,**** Abbas Rana, MD,†††† Michael L. Kueht, MD,†††† Christopher M. Jones, MD,‡‡‡‡ Thomas M. Fishbein, MD,§§§§ and Ronald W. Busuttil, MD, PhD**

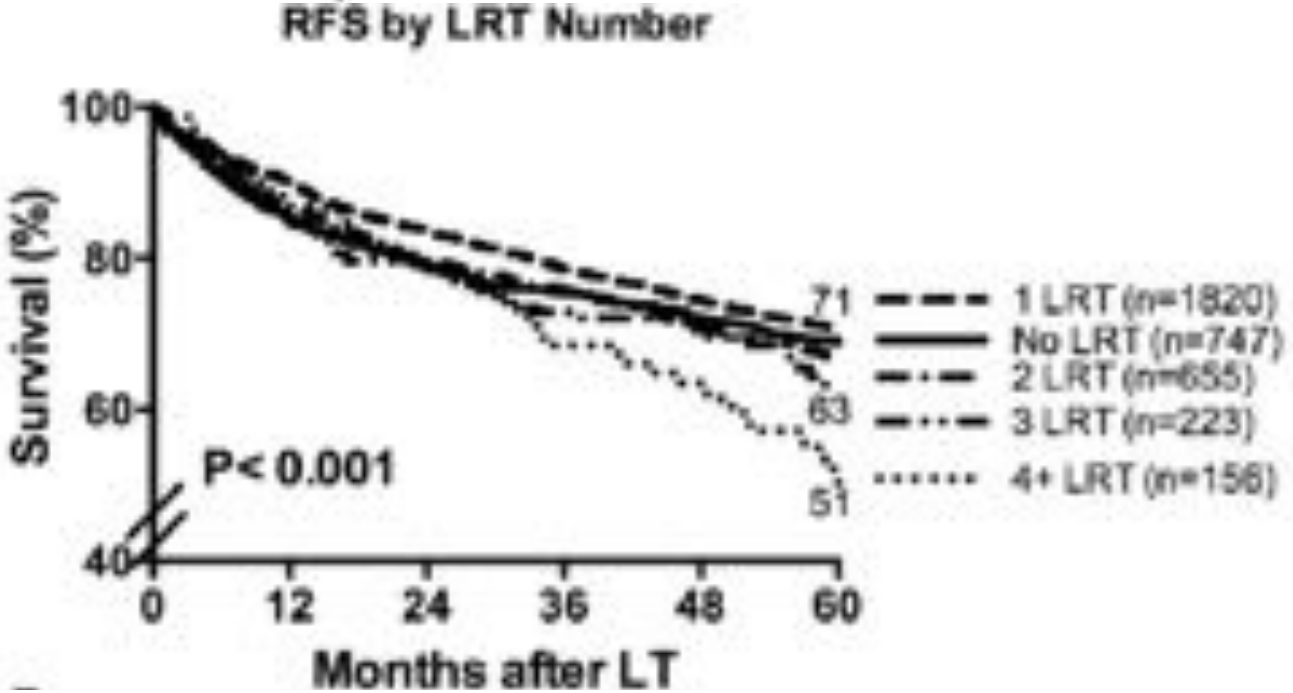
UHN Ajmera Transplant Centre

Impact of Pretransplant Bridging Locoregional Therapy for Patients With Hepatocellular Carcinoma Within Milan Criteria Undergoing Liver Transplantation

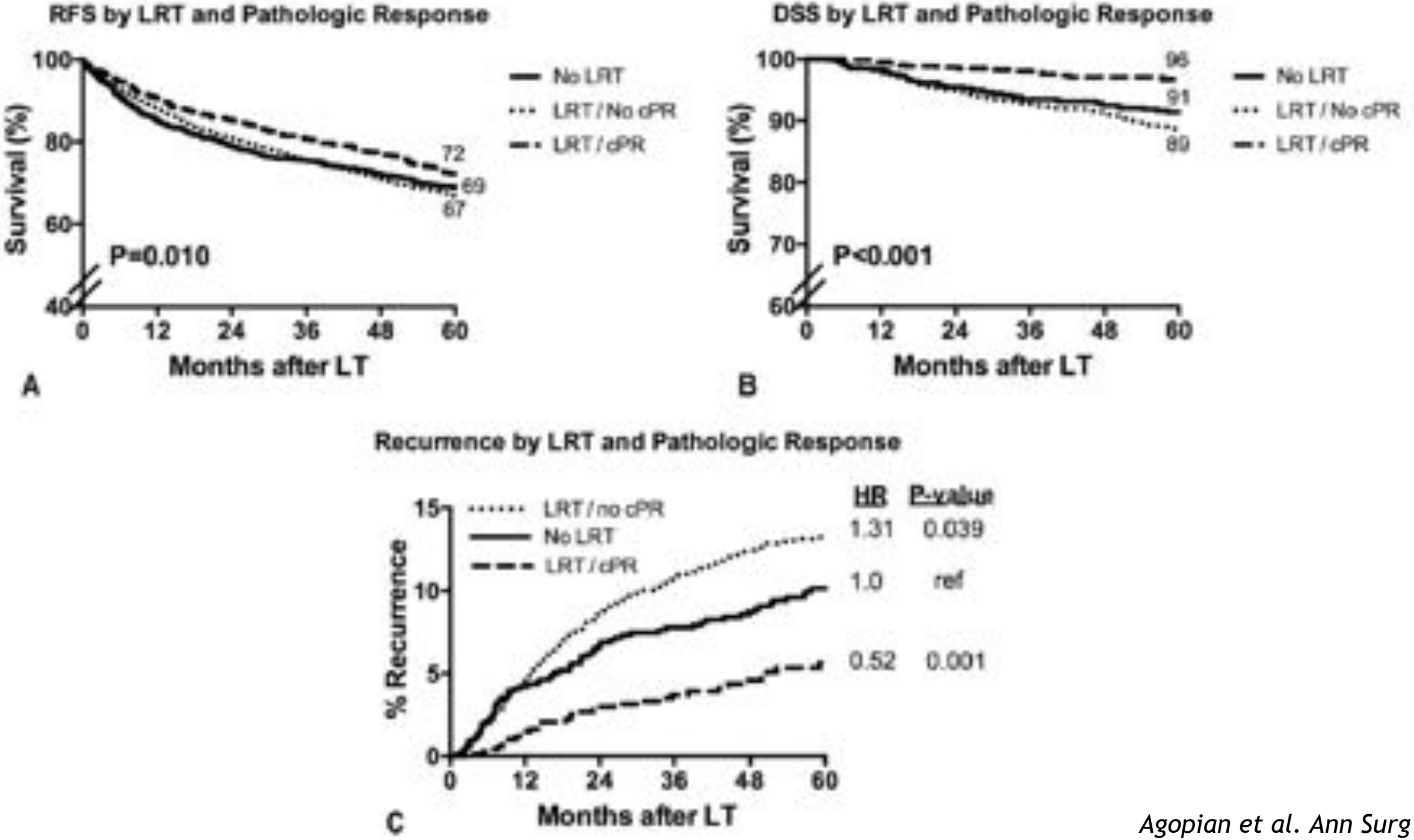
Analysis of 3601 Patients From the US Multicenter HCC Transplant Consortium



	HR	P-value
4+ LRT	2.5	<0.001
3 LRT	2.1	<0.001
2 LRT	1.2	0.313
No LRT	1	ref
1 LRT	0.86	0.304



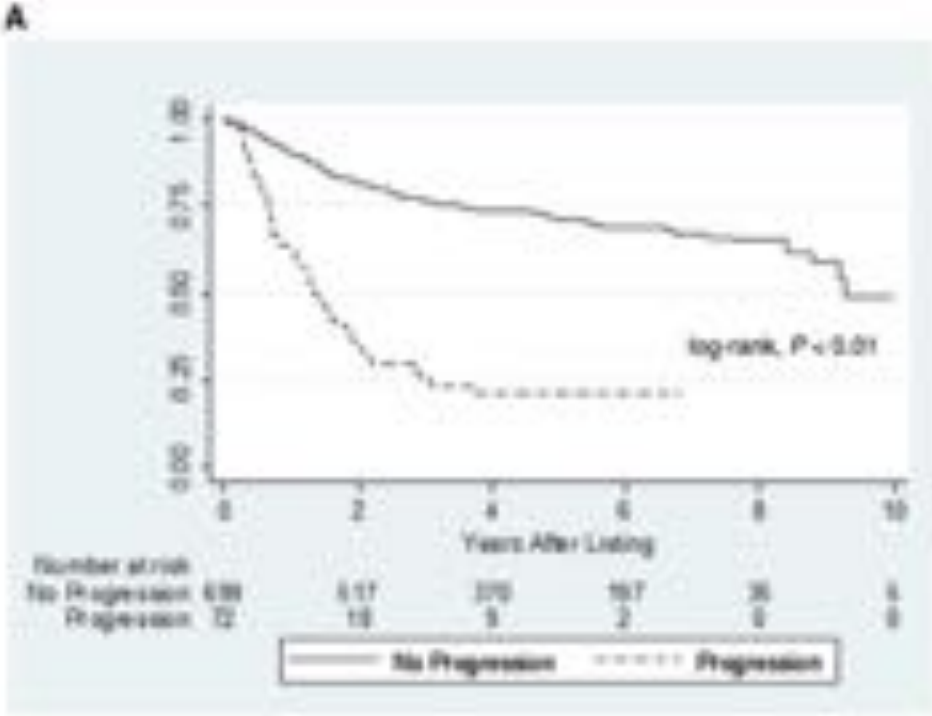
UHN Ajmera Transplant Centre

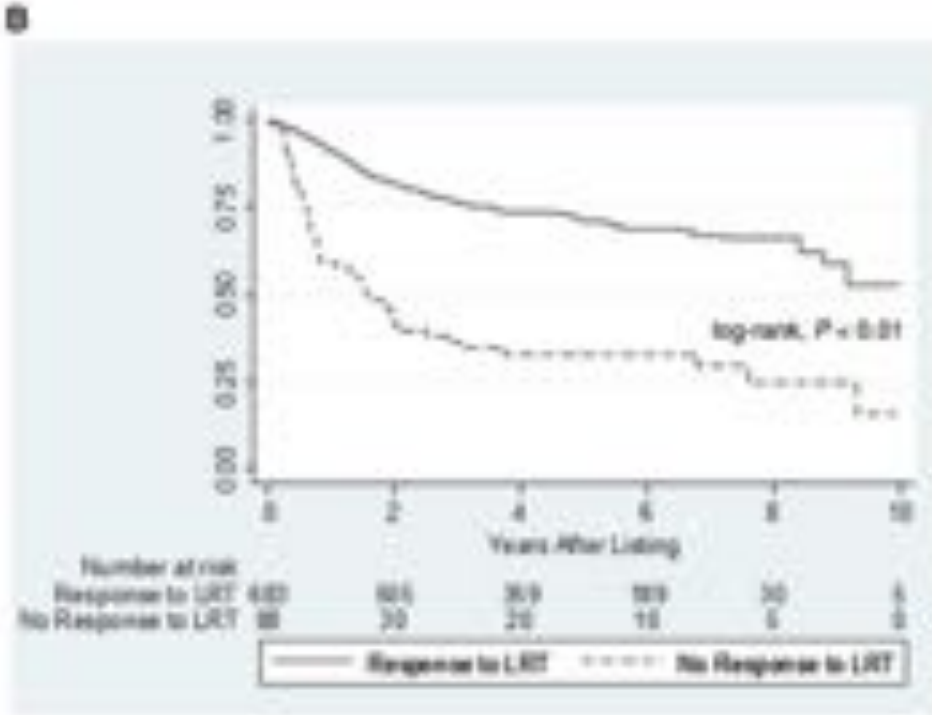


Agopian et al. Ann Surg 2017

The mRECIST Classification Provides Insight into Tumor Biology for Patients With Hepatocellular Carcinoma Awaiting Liver Transplantation

David D. Lee ,[1] Mariya Samoylova,[2,3] Neil Mehta ,[3] Kaitlyn R. Musto,[1] John P. Roberts,[4] Francis Y. Yao,[3] and Denise M. Harnois[1]

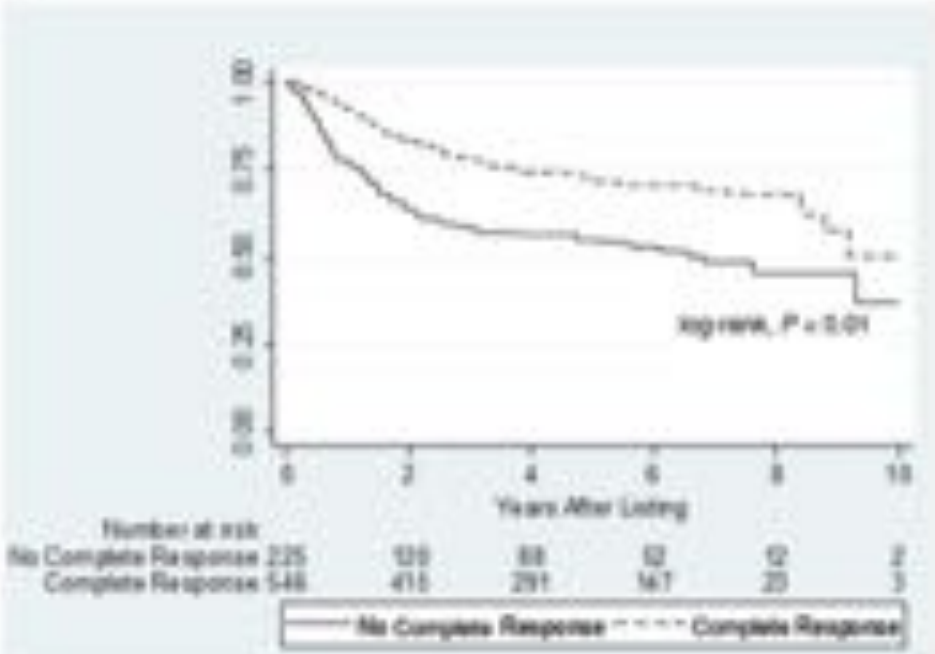




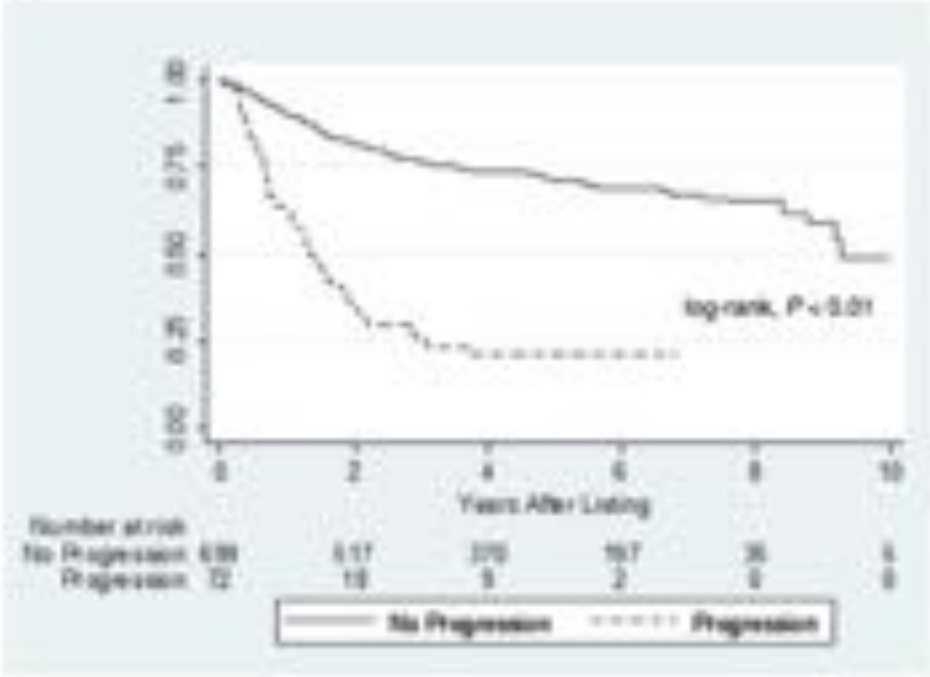
The mRECIST Classification P
Insight into Tumor Biology for P
With Hepatocellular Carcinoma
Liver Transplantation

David D. Lee ,[1] Mariya Samoylova,[2,3] Neil Mehta ,[3] Kaitlyn R. Musto
Francis Y. Yao,[3] and Denise M. Harnois[1]

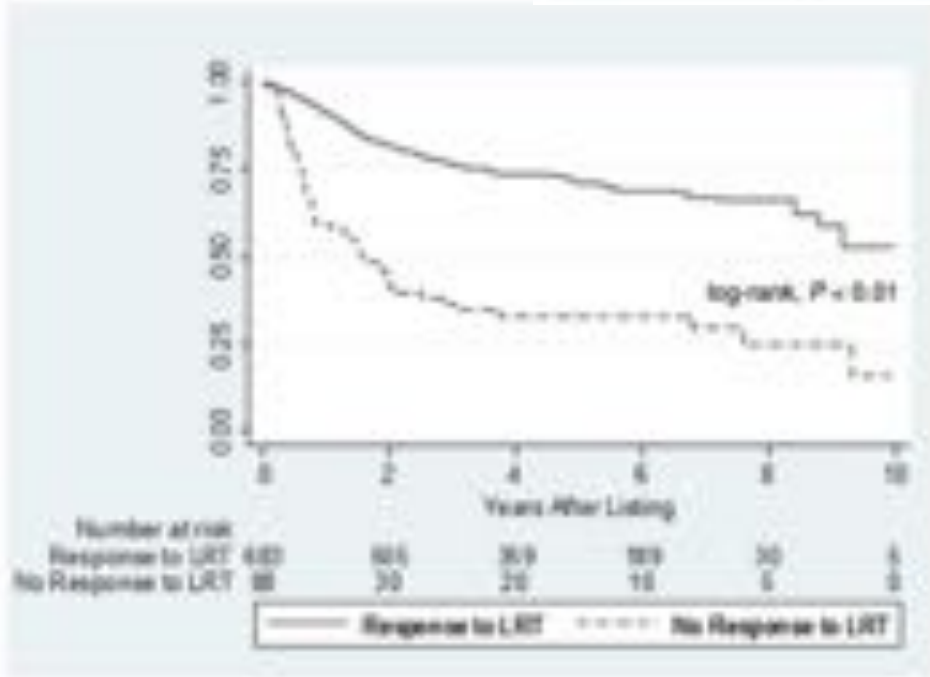
C



A



B

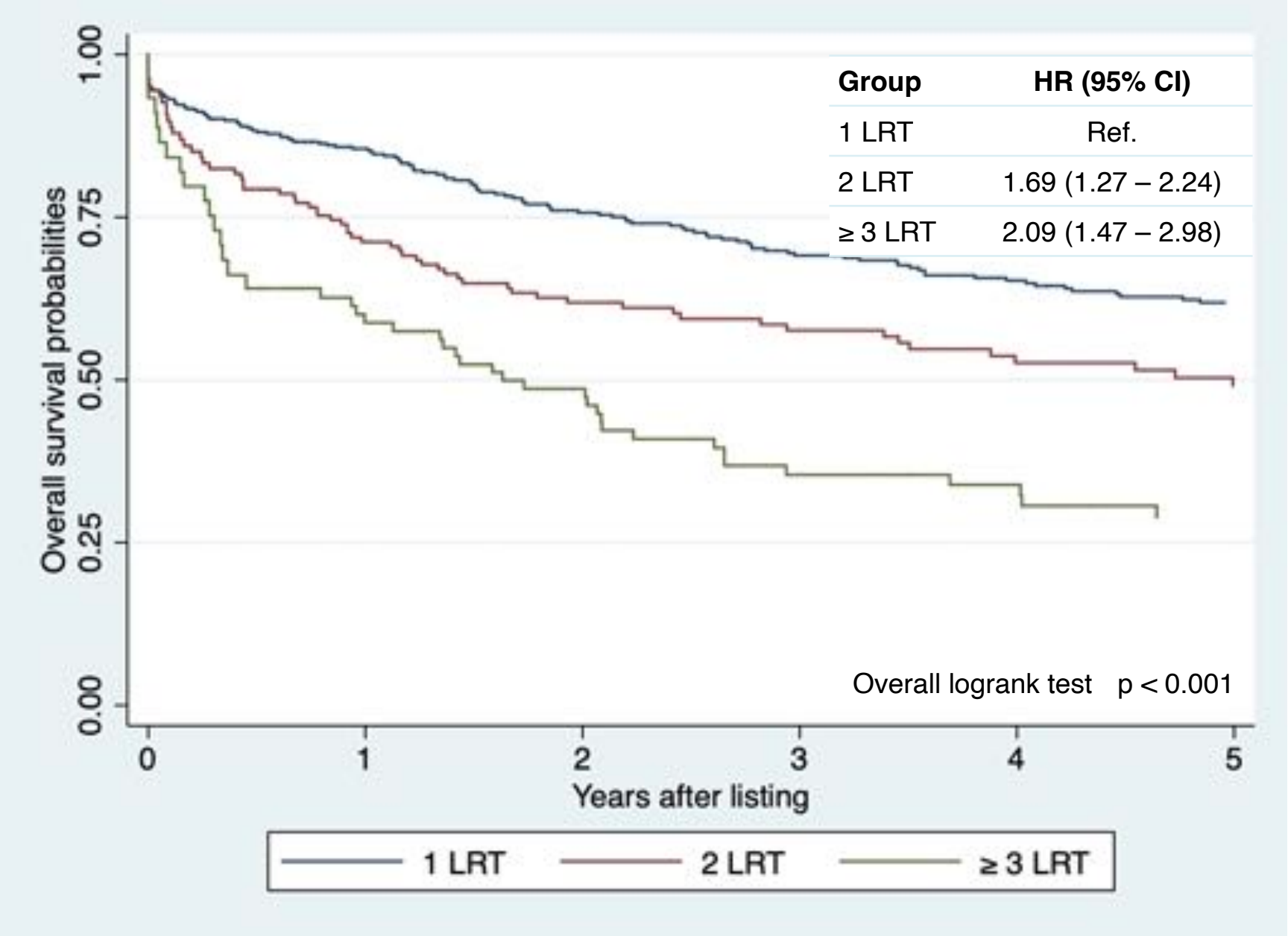


Pathologic Response to Pretransplant Locoregional Therapy is Predictive of Patient Outcome After Liver Transplantation for Hepatocellular Carcinoma

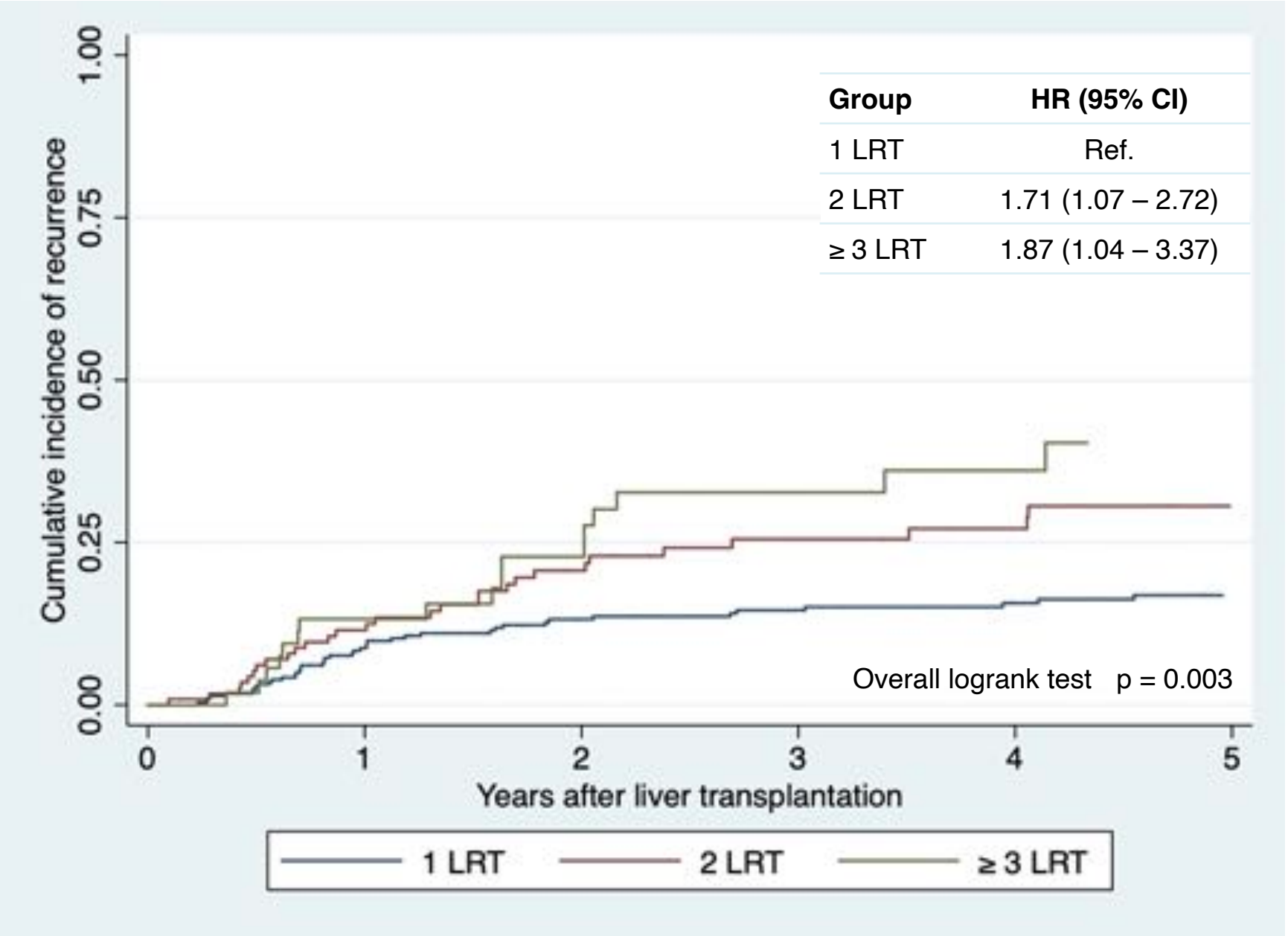
Analysis From the US Multicenter HCC Transplant Consortium

Joseph DiNorcia, MD, Sander S. Florman, MD,† Brandy Haydel, BS,† Parissa Tabrizian, MD,† Richard M. Ruiz, MD,‡ Goran B. Klintmalm, MD, PhD,‡ Srinath Senguttuvan, MS,‡ David D. Lee, MD,§ C. Burcin Taner, MD,§ Elizabeth C. Verna, MD, MS,¶ Karim J. Halazun, MD,|| Maarouf Hoteit, MD,** Matthew H. Levine, MD, PhD,** William C. Chapman, MD,†† Neeta Vachharajani, BS,†† Federico Aucejo, MD,‡‡ Mindie H. Nguyen, MD, MAS,§§ Marc L. Melcher, MD, PhD,¶¶ Amit D. Tevar, MD,|||| Abhinav Humar, MD,|||| Constance Mobley, MD, PhD,*** Mark Ghobrial, MD, PhD,*** Trevor L. Nydam, MD,††† Beth Amundsen, MD,‡‡‡ James F. Markmann, MD, PhD,‡‡‡ Jennifer Berumen, MD,§§§ Alan W. Hemming, MD,§§§ Alan N. Langnas, DO,¶¶¶ Carol A. Carney, CCRC,¶¶¶ Debra L. Sudan, MD,|||||| Johnny C. Hong, MD,**** Joohyun Kim, MD,**** Michael A. Zimmerman, MD,**** Abbas Rana, MD,†††† Michael L. Kueht, MD,†††† Christopher M. Jones, MD,‡‡‡‡ Thomas M. Fishbein, MD,§§§§ Daniela Markovic, MS,¶¶¶¶ Ronald W. Busuttil, MD, PhD,* and Vatche G. Agopian, MD**

UHN Ajmera Transplant Centre



UHN Ajmera Transplant Centre



UHN Ajmera Transplant Centre

Comparison between the accuracy of validated selection criteria for liver transplantation before and after the inclusion of one point in patients with increased need of locoregional therapies.			
Criteria	Before (95% CI)	After (95% CI)	p
Milan	0.61 (0.56 - 0.67)	0.66 (0.60 - 0.71)	0.07
AFP French score	0.66 (0.60 - 0.72)	0.69 (0.63 - 0.75)	0.03
Metroticket 2.0	0.65 (0.58 - 0.72)	0.67 (0.61 - 0.74)	0.01
ETC	0.56 (0.52 - 0.60)	0.64 (0.58 - 0.69)	0.01
UCSF	0.61 (0.55 - 0.66)	0.66 (0.60 - 0.71)	0.06

Selection Criteria: Pre-Listing AFP

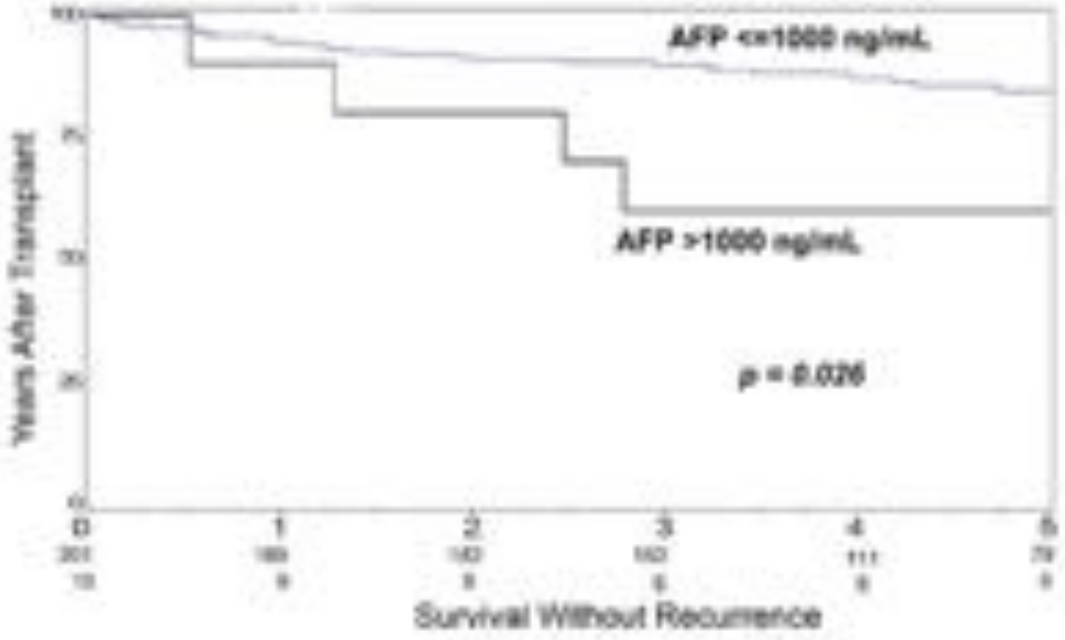


TABLE 4. Multivariate Analysis of Predictors of HCC Recurrence

Variable	HR	95% CI	P Value
Vascular invasion	5.6	1.6-19	0.0063
AFP level > 1000 ng/mL	1.54	0.36-6.5	0.056
Pathological stage beyond UCSF criteria*	2.2	0.6-7.6	0.23

*The UCSF criteria are as follows: 1 lesion ≤6.5 cm or 2 to 3 lesions, each ≤4.5 cm, with a total tumor diameter ≤8 cm.

UHN Ajmera Transplant Centre

Hameed et al. Liver Transpl 2014

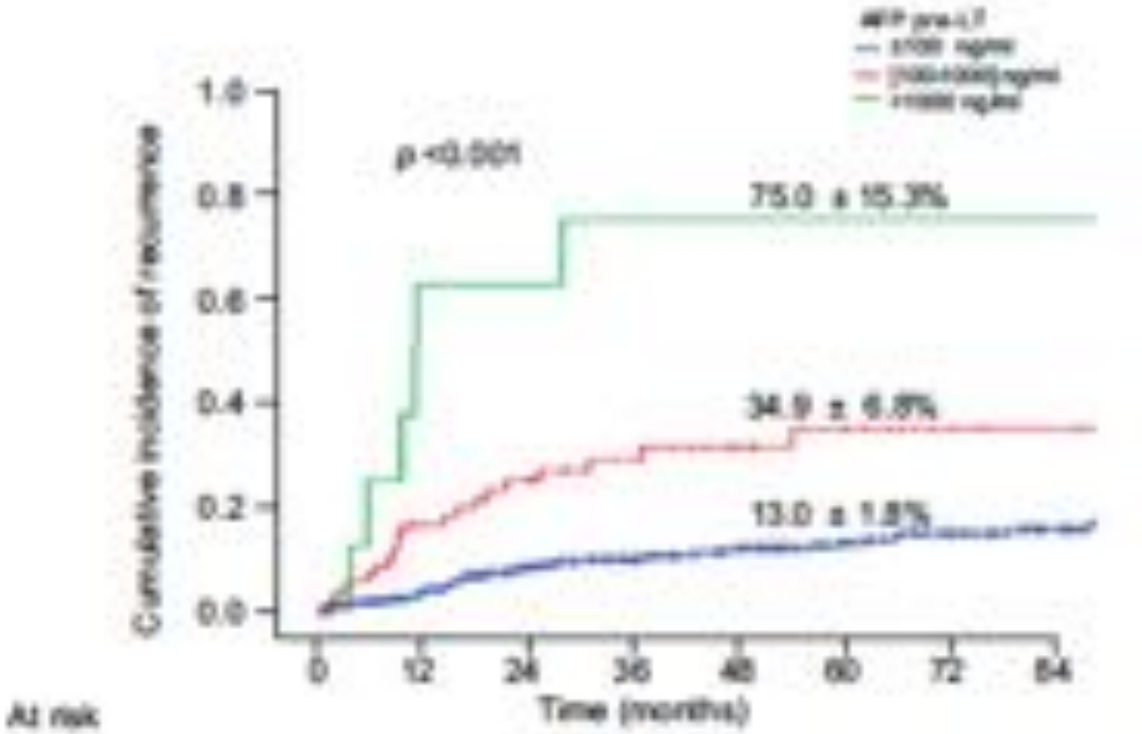
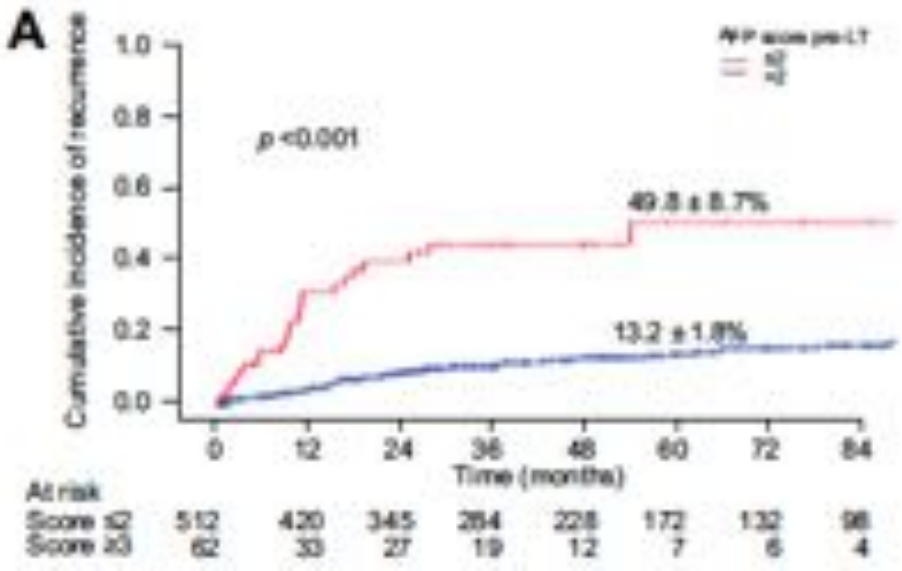
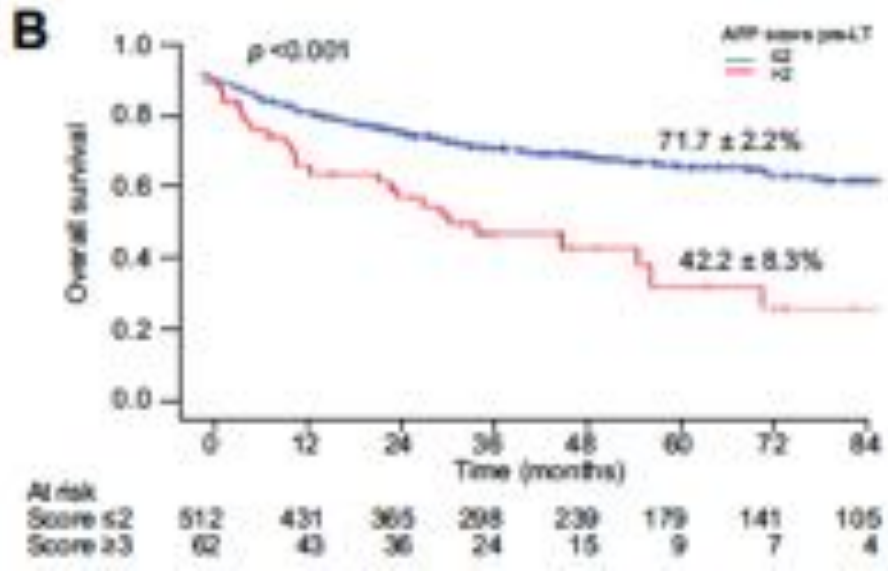


Table 1. Simplified, user-friendly version of the AFP model.

Variables	β coefficient	Hazard ratio	Points
Largest diameter			
≤3 cm	0	1	0
3–6 cm	0.272	1.31	1
>6 cm	1.347	3.84	4
Number of nodules			
1–3	0	1	0
4 and more	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





Notarpaolo et al. J Hepatol 2017

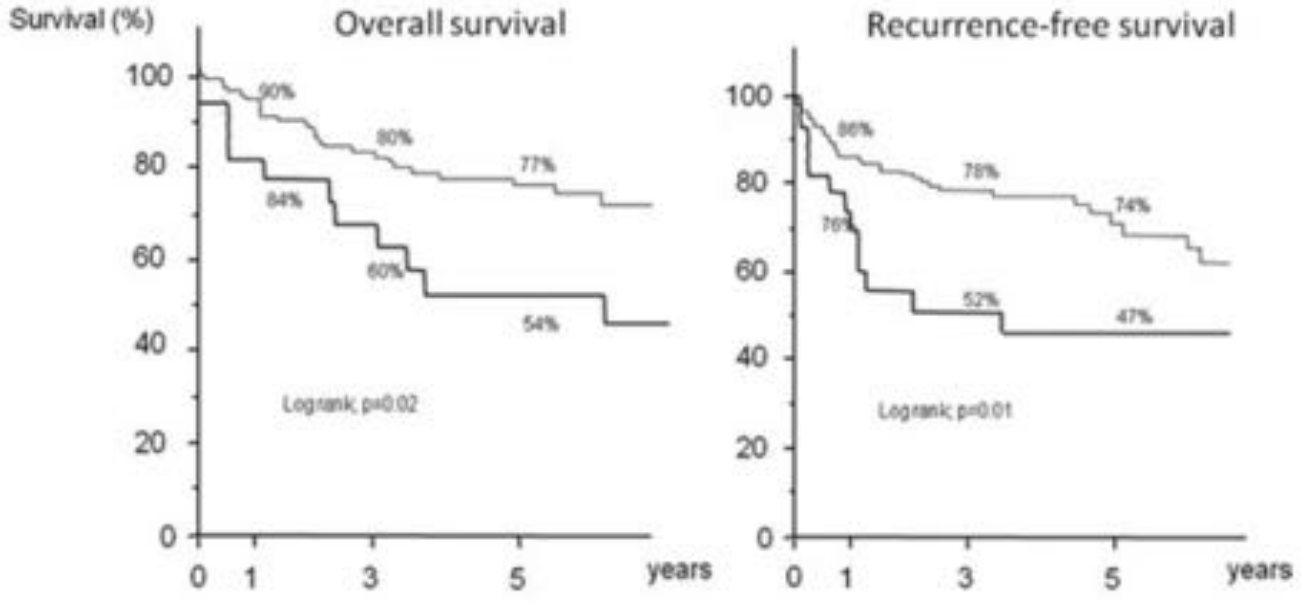
AFP slope

American Journal of Transplantation 2010; 10: 129–137
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2009.02750.x

Progression of Alphafetoprotein Before Liver Transplantation for Hepatocellular Carcinoma in Cirrhotic Patients: A Critical Factor

E. Vibert[a,b,d], D. Azoulay[a,c,d], E. Hoti[a], S. Iacopinelli[a], D. Samuel[a,b,d], C. Salloum[a], A. Lemoine[a,c,d], H. Bismuth[a], D. Castaing[a,b,d] and R. Adam[a,e,d,*]



UHN Ajmera Transplant Centre

DOI:10.1111/hpb.12486 HPB

ORIGINAL ARTICLE

Delta-slope of alpha-fetoprotein improves the ability to select liver transplant patients with hepatocellular cancer

Quirino Lai[1,2], Milton Inostroza[3], Juan M. Rico Juri[4], Pierre Goffette[5] & Jan Lerut[1]

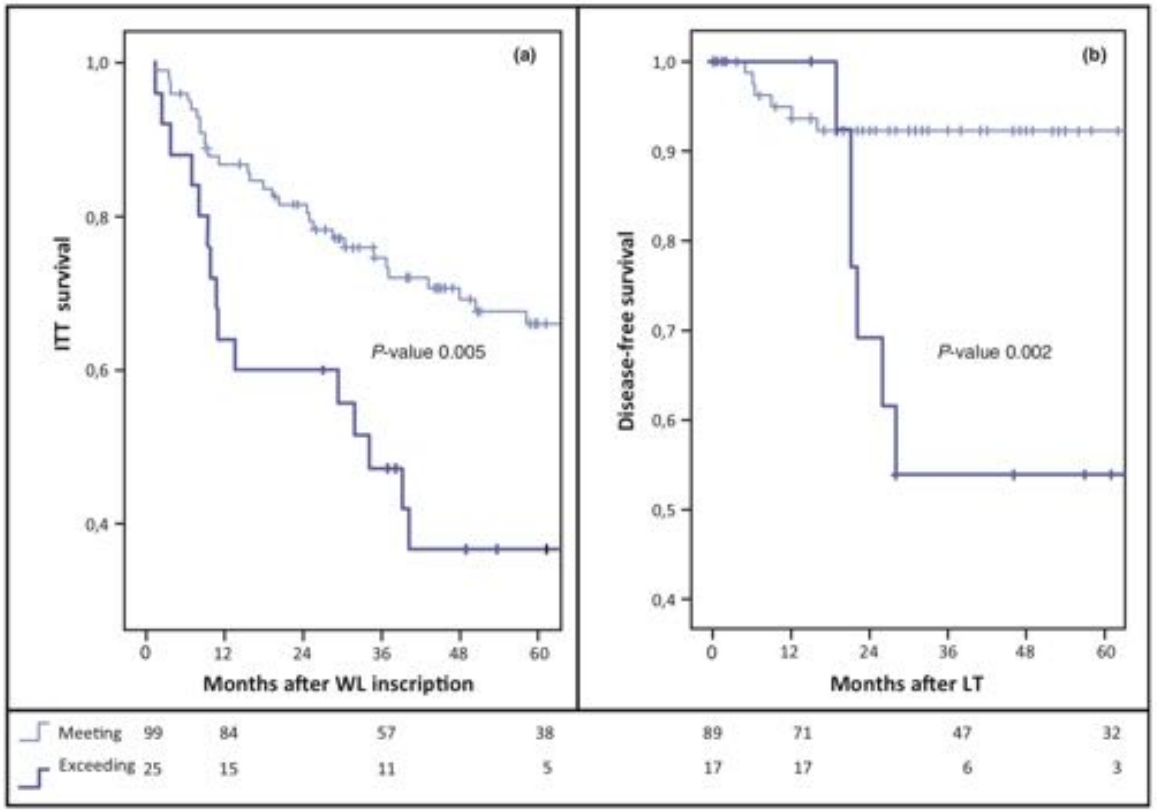
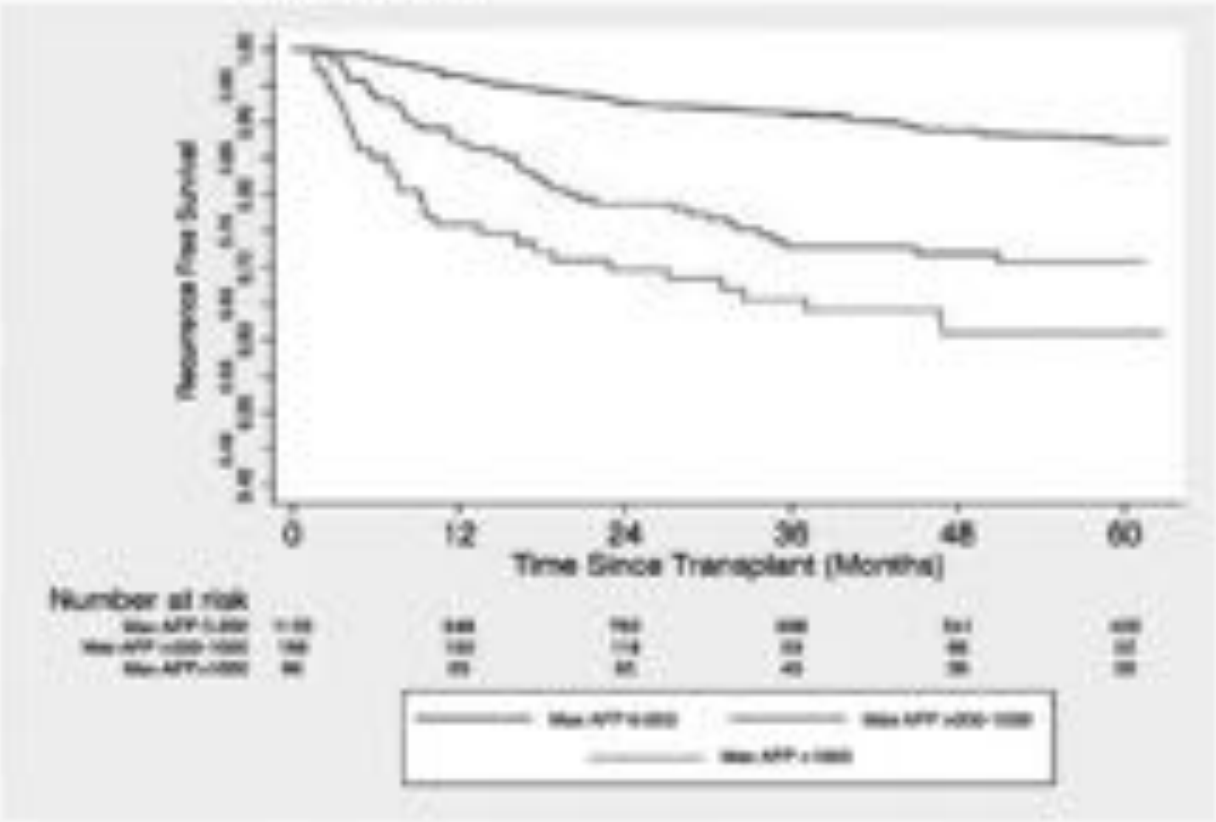


Figure 2 (a) Intention-to-treat survival rates according to the alpha-fetoprotein (AFP) delta-slope model; (b) disease-free survival rates according to the AFP delta-slope model

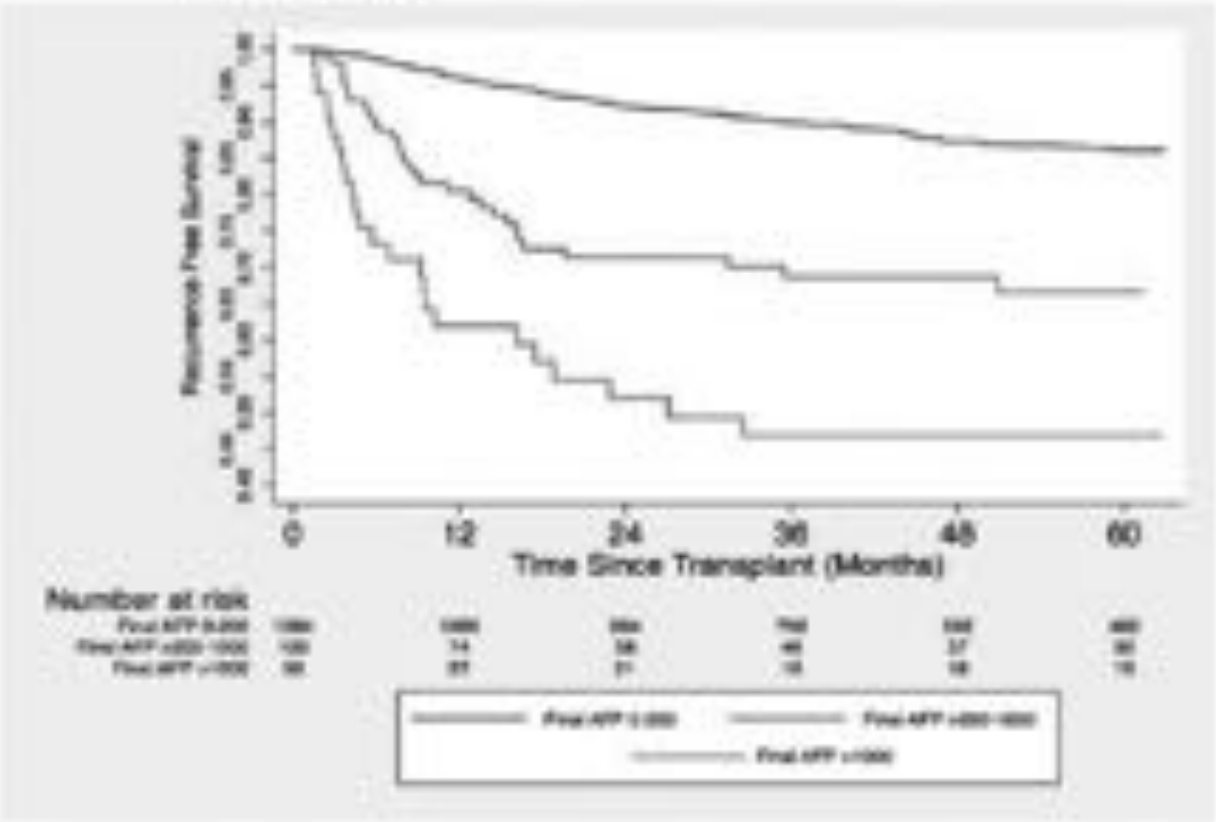
Subanalysis #1: AFP delta-slope and mRECIST response

Stratifying the entire cohort according to the pre-LT radiological response based on the mRECIST classification, a greater number of patients with a pre-LRT AFP delta-slope ≥15 ng/ml/month was observed in patients with progressive pathology (10/27, 37.0%) compared with patients with a stable (5/40, 12.5%), partial response (5/37, 13.5%) or complete response (1/10, 10.0%) (*P*-value 0.022).

Max AFP

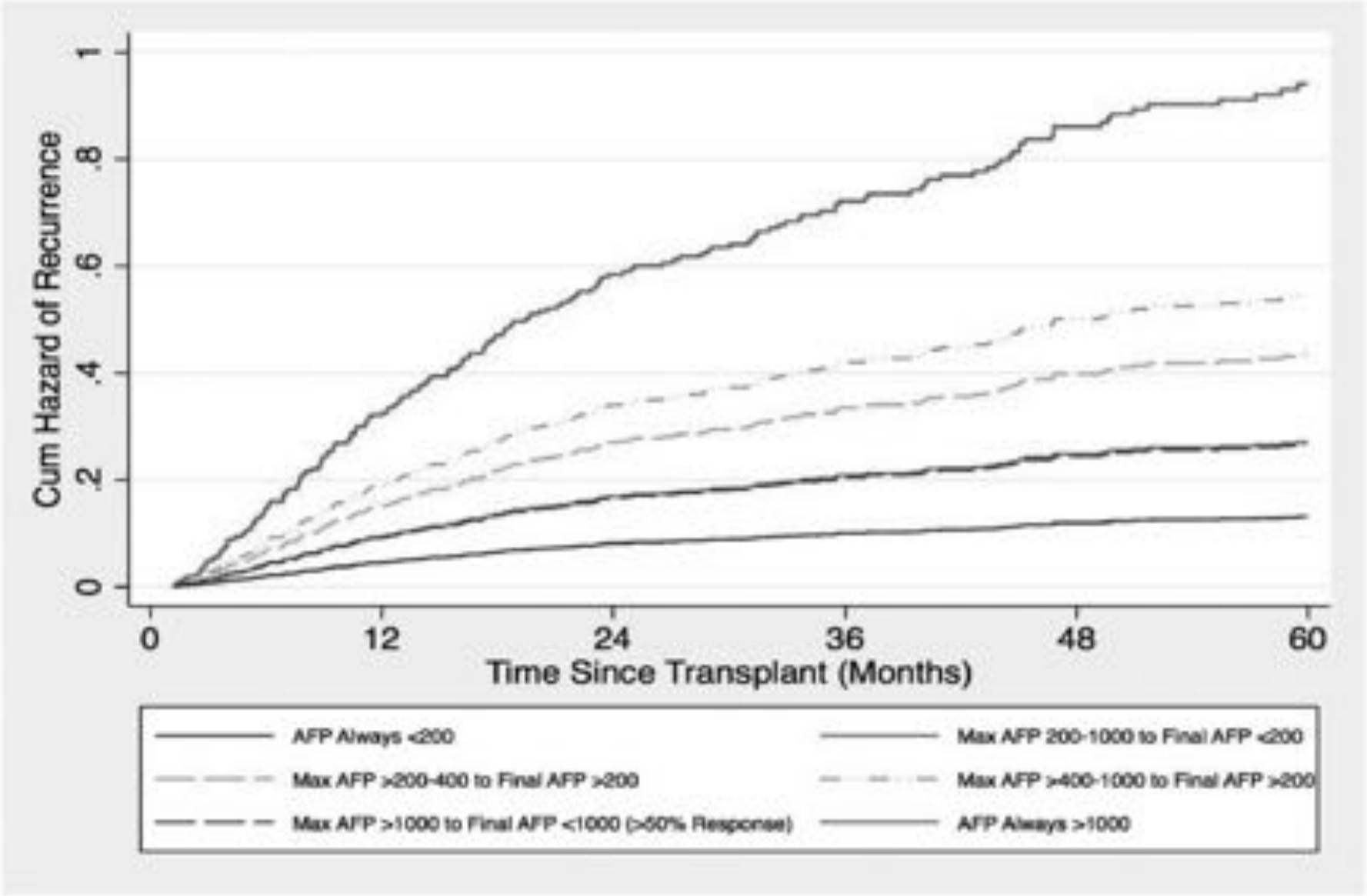


Final AFP



UHN Ajmera Transplant Centre

Halazun et al. Ann Surg 2018



UHN Ajmera Transplant Centre

Halazun et al. Ann Surg 2018

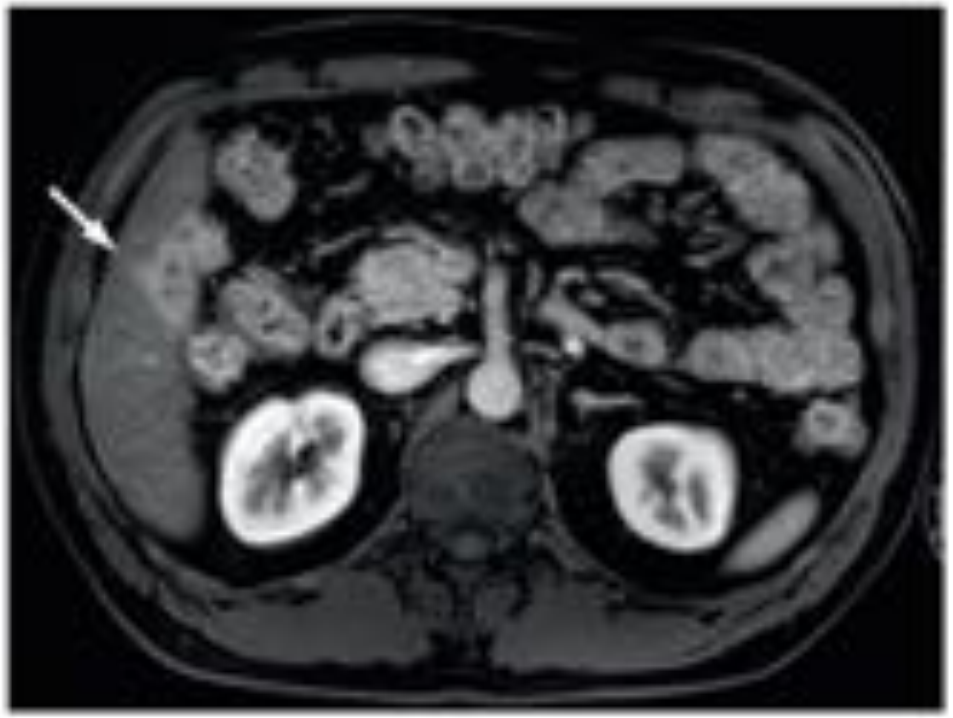
Selection tool: MRI

	Multivariate analysis		
	OR	95% CI	*p* value
Tumor size	0.976	0.641, 1.487	0.910
Arterial rim enhancement	1.296	0.462, 3.636	0.623
Arterial peritumoral enhancement	5.184	2.228, 12.063	<0.001*
Non-smooth tumor margin	3.555	1.627, 7.769	0.001*
Radiological capsule			
Tumor hypointensity on HBP			
Peritumoral hypointensity on HBP	4.705	1.671,13.246	0.003*
Tumor-to-liver SI ratio on DWI			
ADC ($\times 10^{-3}$ mm^2/sec)	0.191	0.031, 1.156	0.071

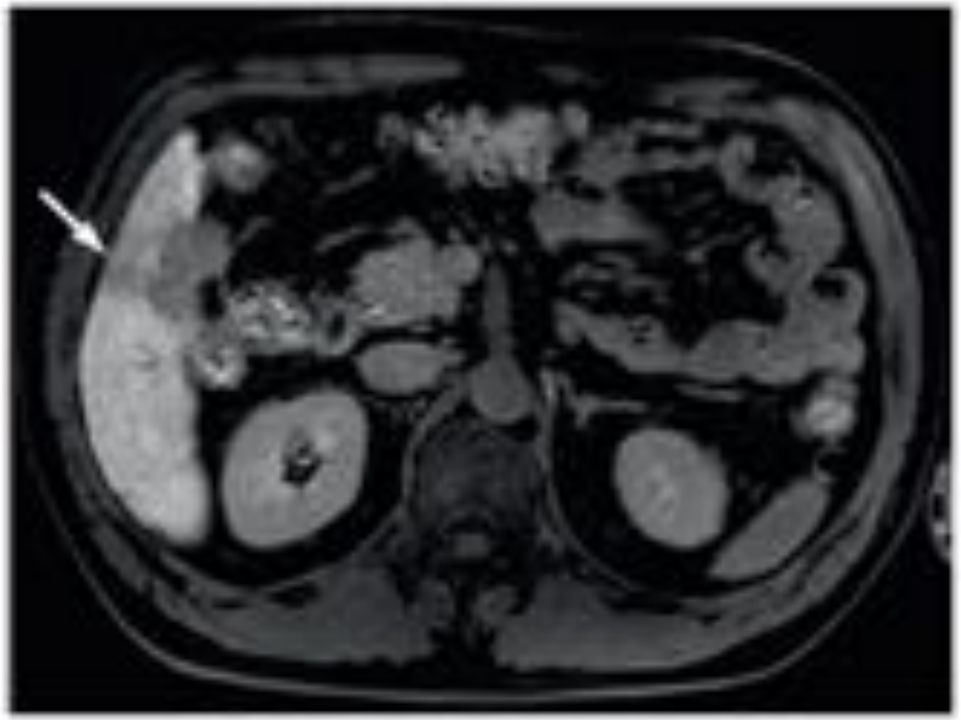
UHN Ajmera Transplant Centre

Lee et al. J Hepatol 2017

Peritumoral enhancement

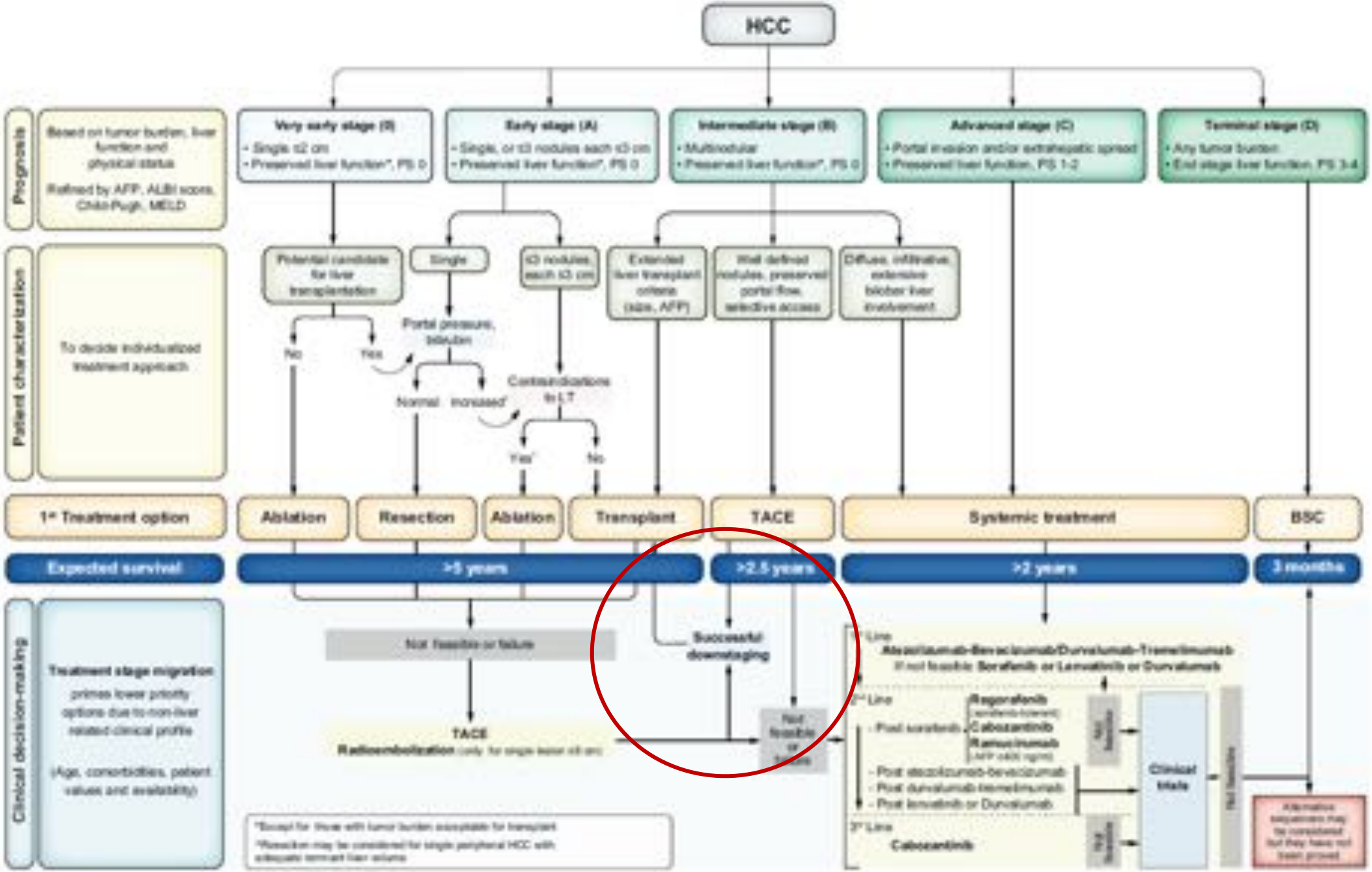


Non-smooth margin
Peritumoral hypodensity



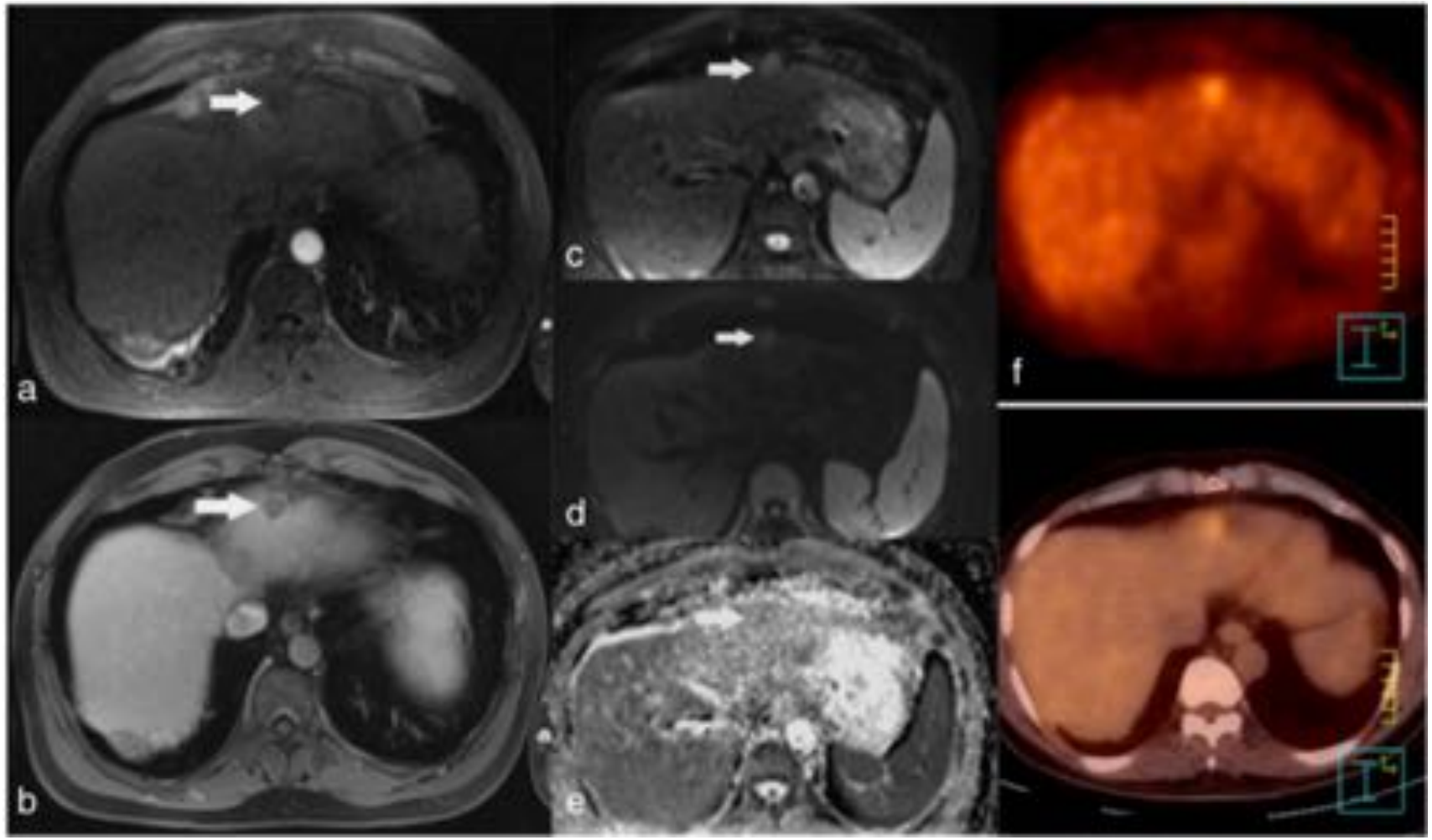
UHN Ajmera Transplant Centre

Lee et al. J Hepatol 2017



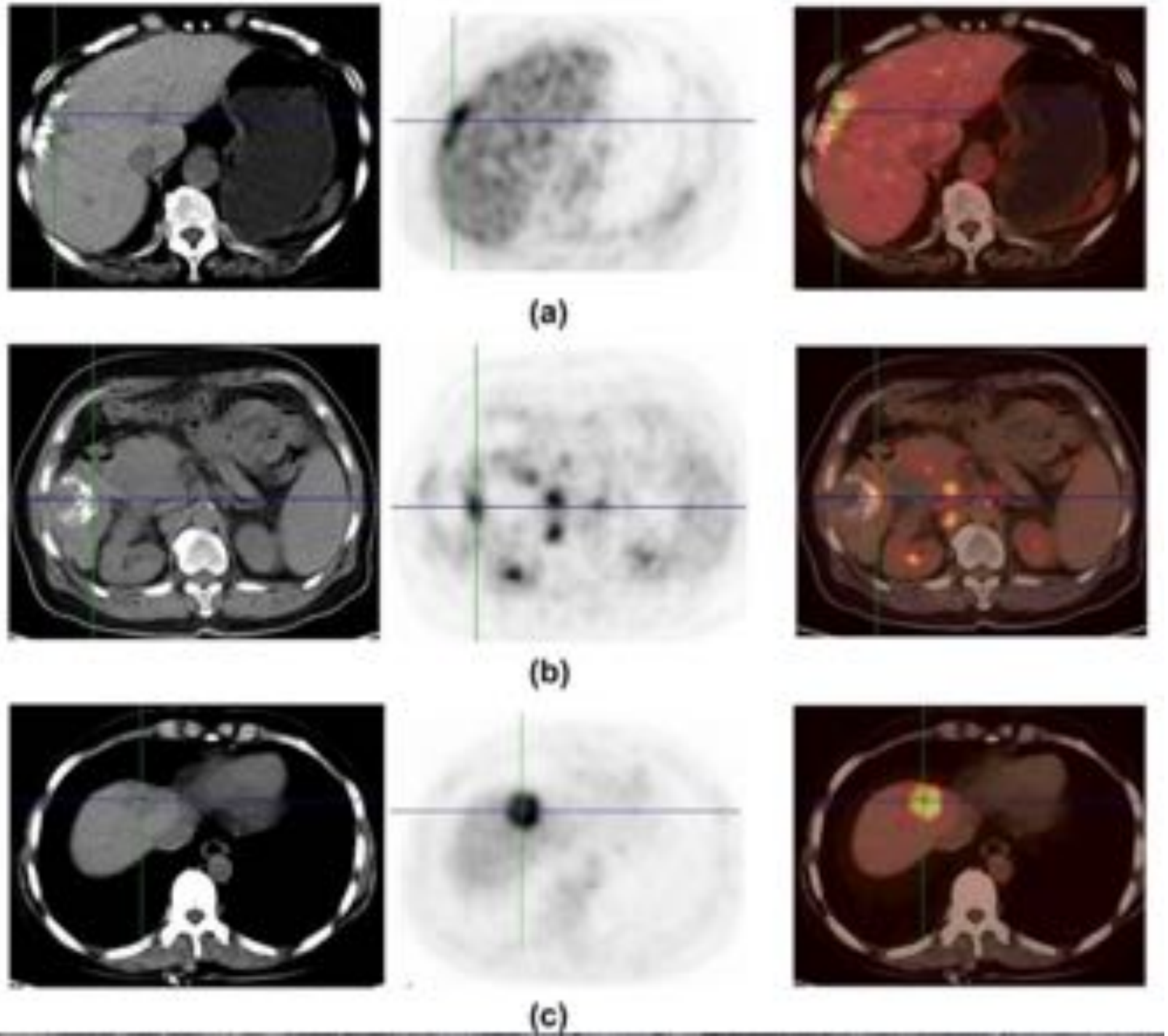
Reig M, et al. J Hepatol 2022

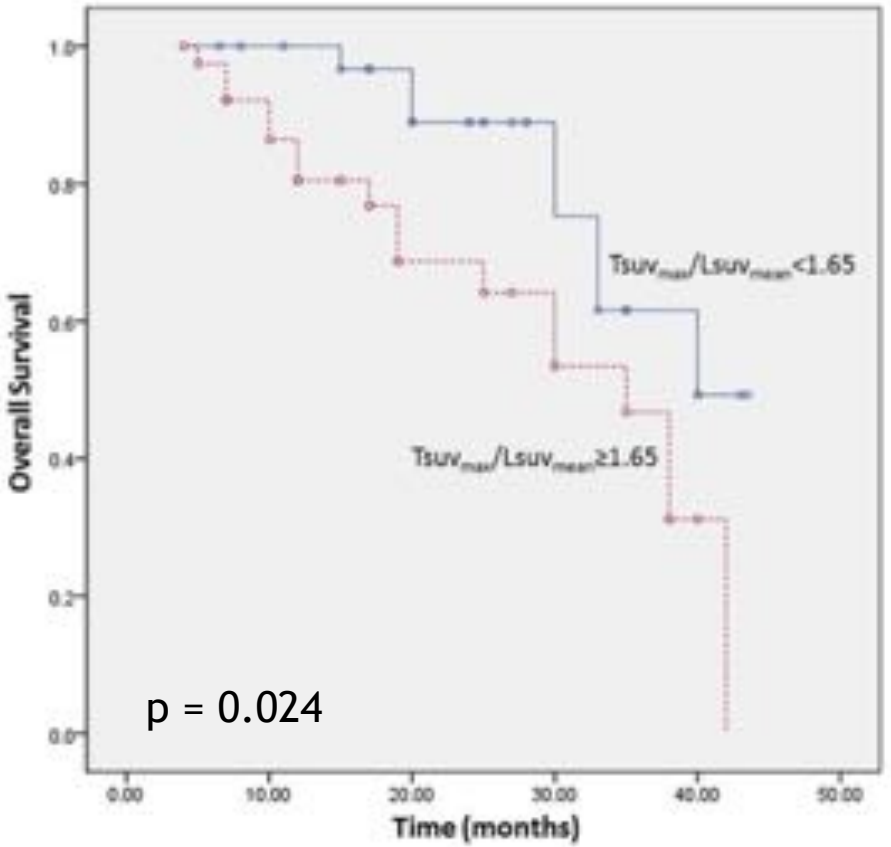
Selection Tool: PET MRI



UHN Ajmera Transplant Centre

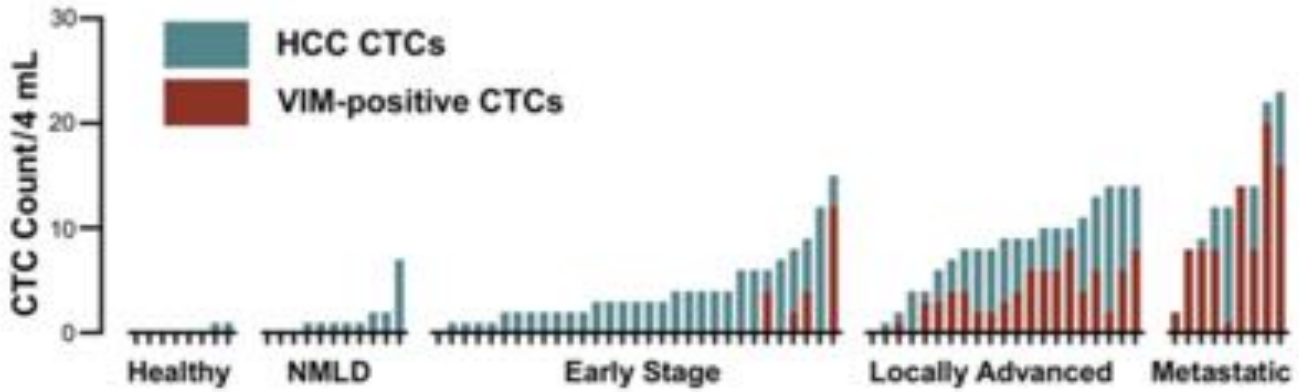
Boussouar et al. Cancer Imaging 2016

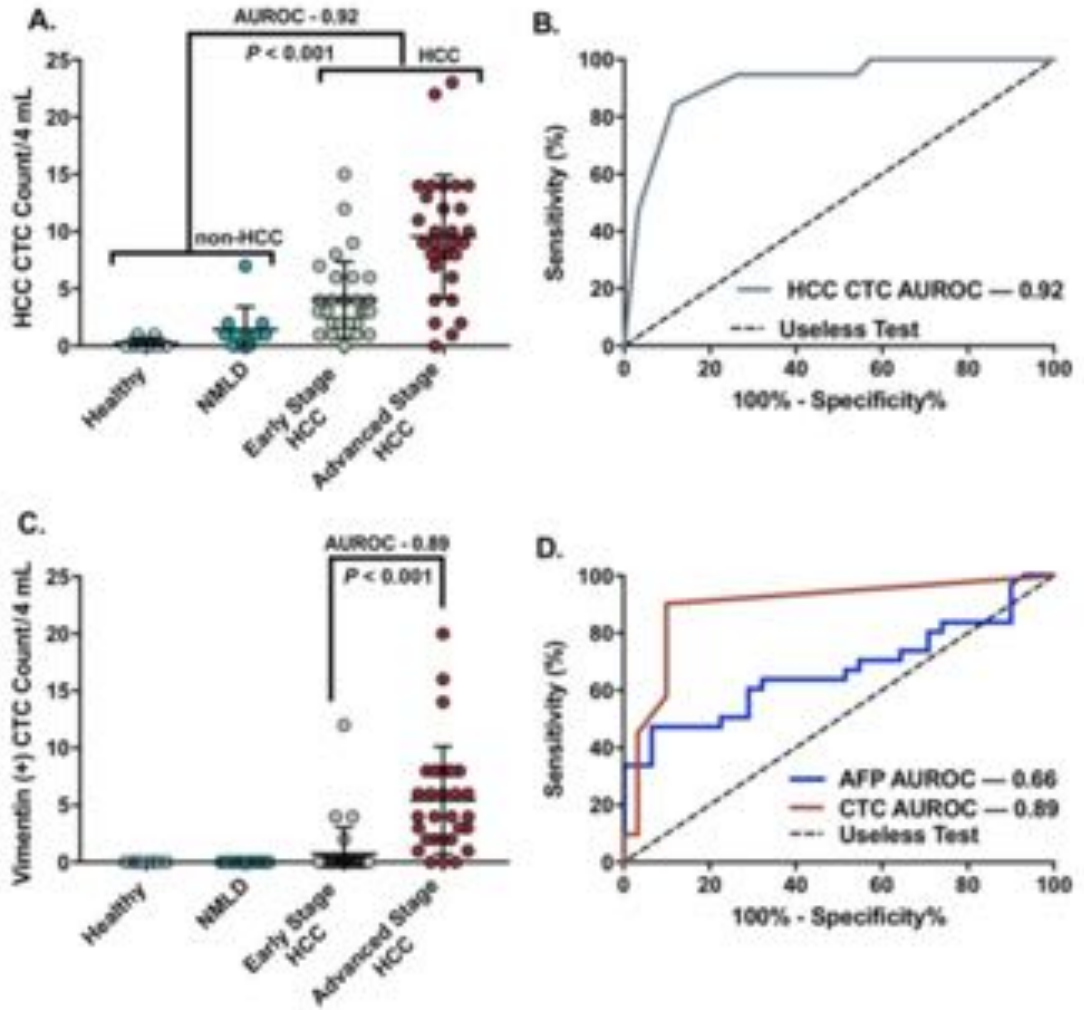


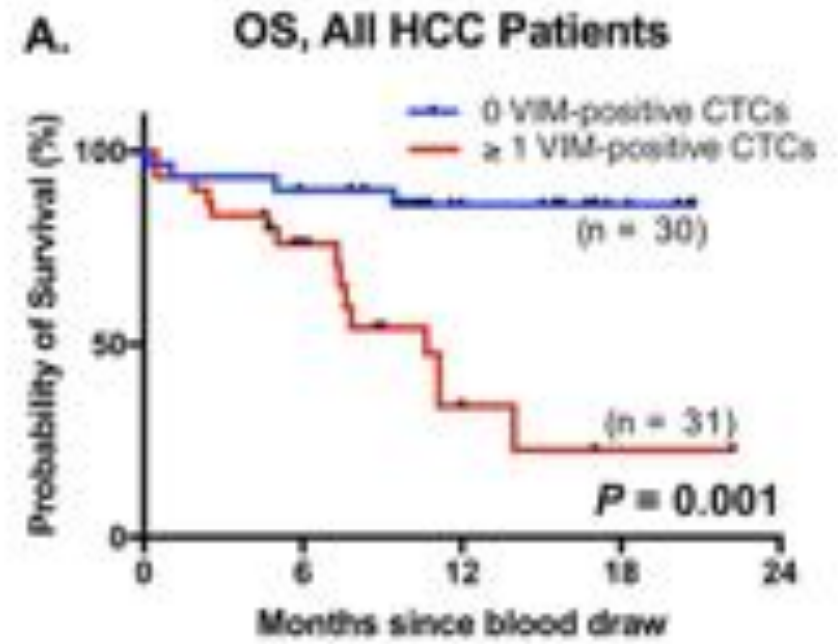


Song et al. Clinical Radiology 2015

Selection tool: circulating tumor cells







Court et al. Liver Transpl 2018

Conclusions

- LRT seems to be related to lower dropout rates, although the evidence level is low
- Good response to LRT is related to less aggressive pathological features in explanted livers
- Patients with intermediate stage HCC and good response to LRT could benefit from LT