

MÁSTER EN HEPATOLOGÍA

UAM
Universidad Autónoma
de Madrid

 Universidad
de Alcalá

Asignatura 7: Hepatocarcinoma

Criterios expandidos de resección y trasplante como tratamiento de rescate. Papel actual del Downstaging

Prof. Alejandro Forner
Hospital Clínic Barcelona

Advisory board/Consultancy:

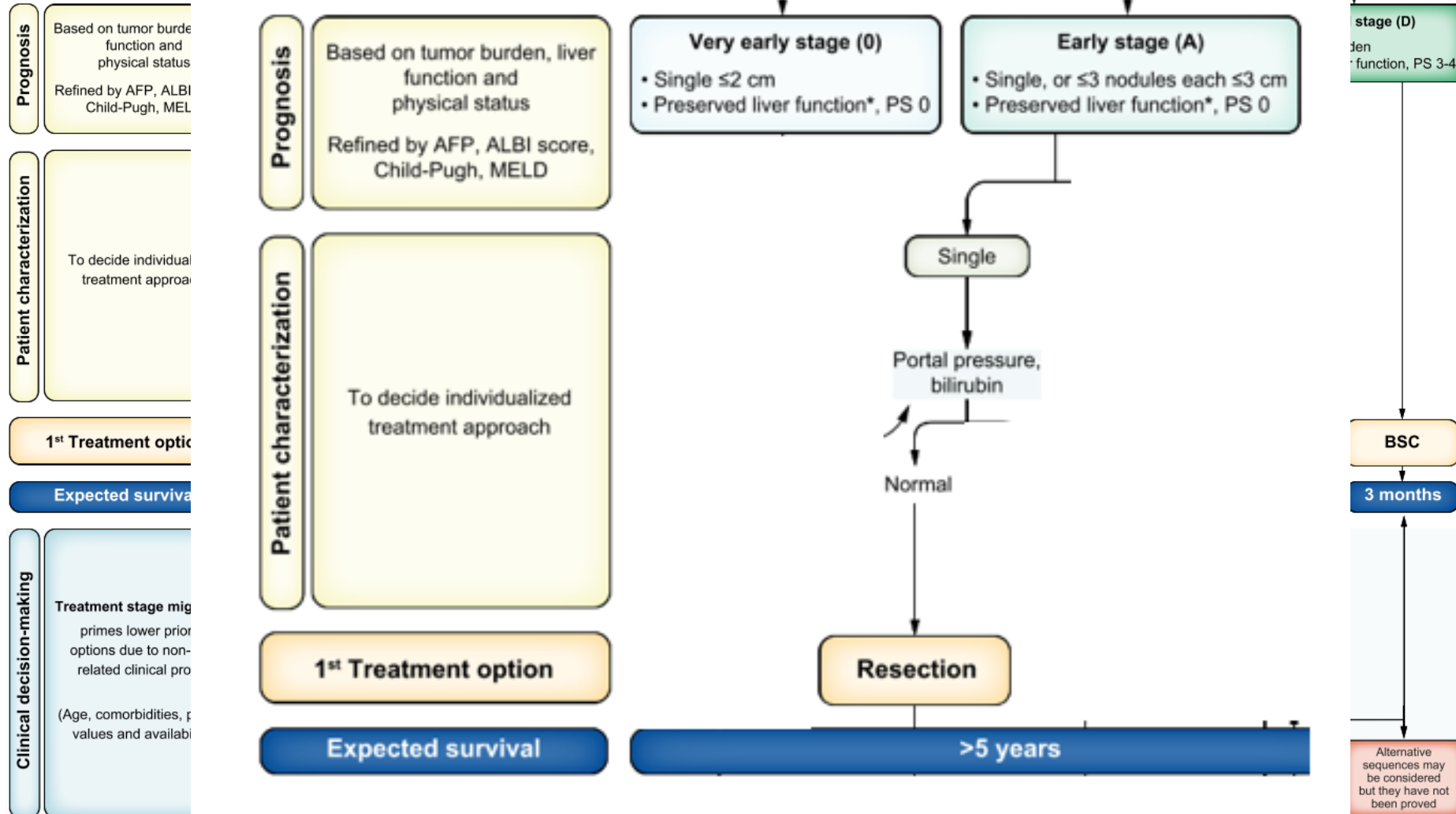
AstraZeneca, Roche, SIRTEX, AB Exact Science, Boston Science, and Taiho.

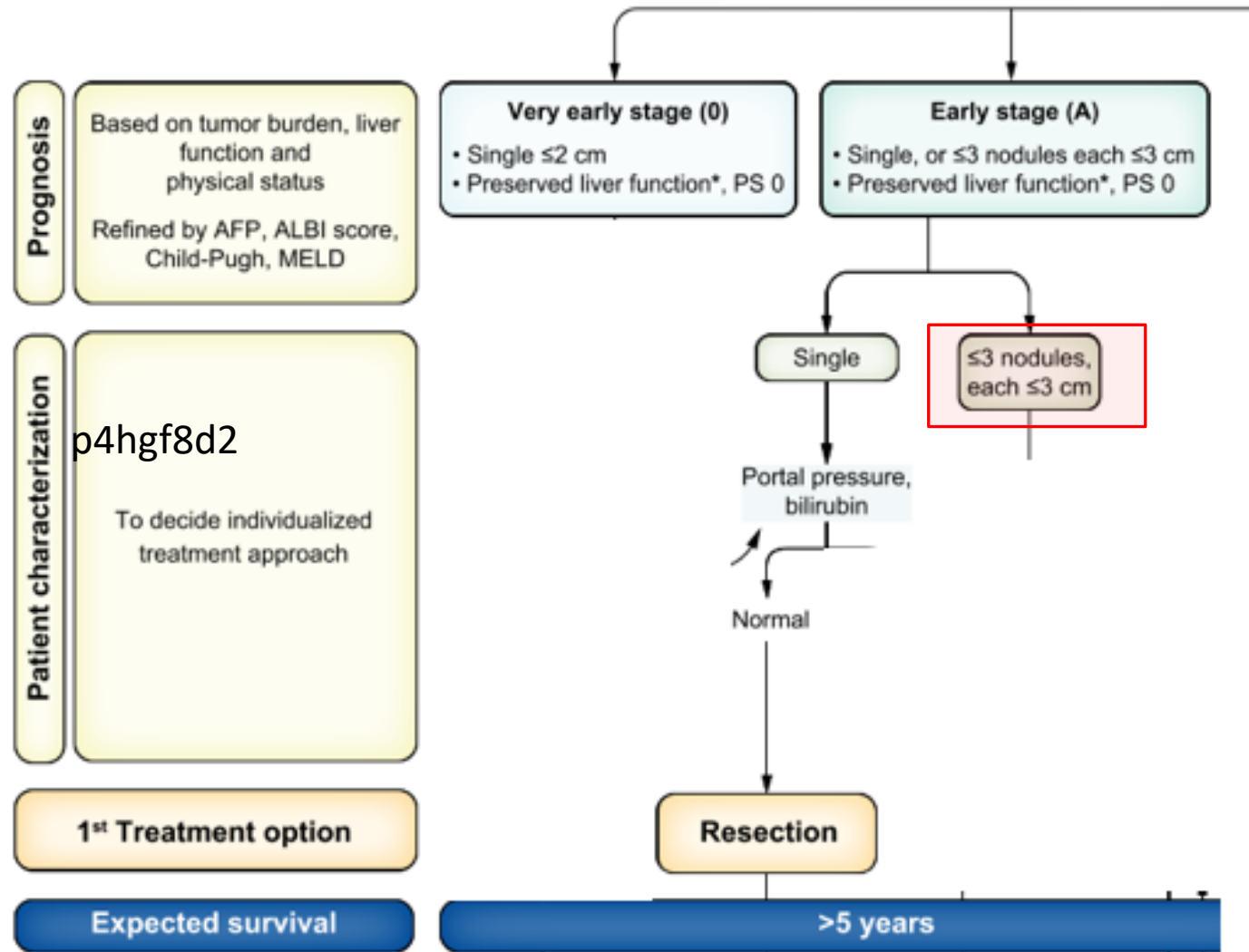
Lecture fees:

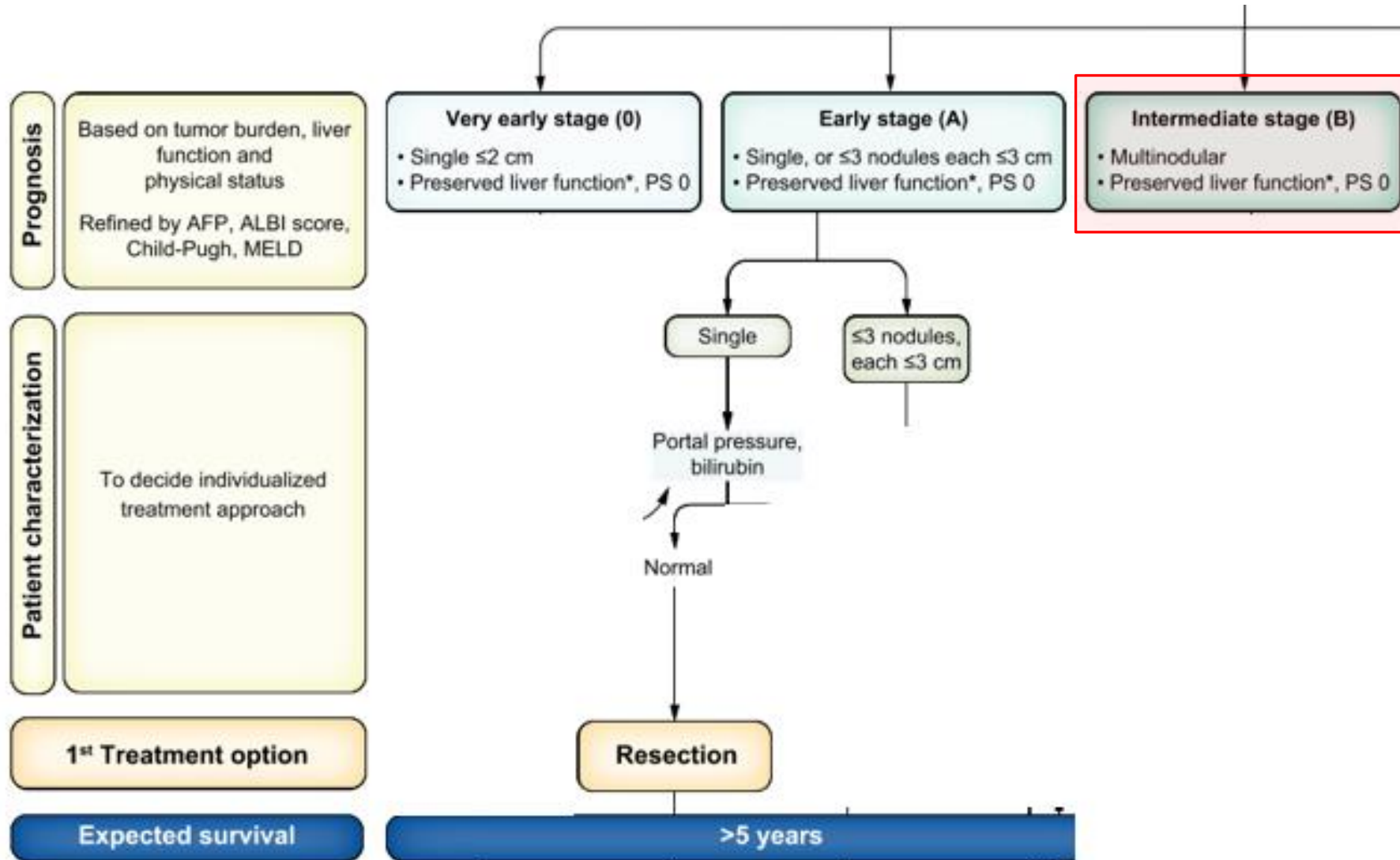
Gilead, Boston Scientific, Roche, and AstraZeneca

-
- Resection: Indications and challenging scenarios
 - Liver transplantation: Where are the limits?
 - Downstaging: Facts and hopes
 - Expansion of LT criteria for HCC

-
- Resection: Indications and challenging scenarios
 - Liver transplantation: Where are the limits?
 - Downstaging: Facts and hopes
 - Expansion of LT criteria for HCC

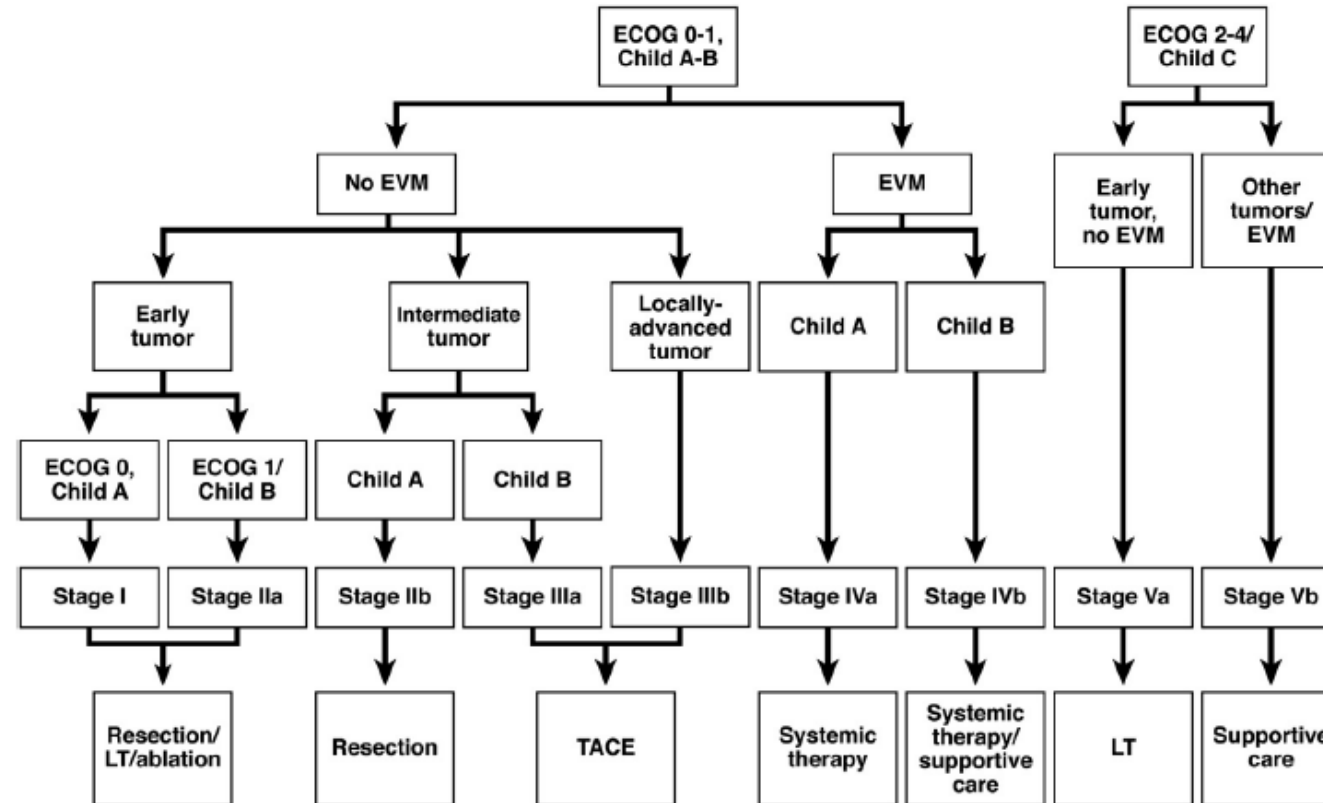






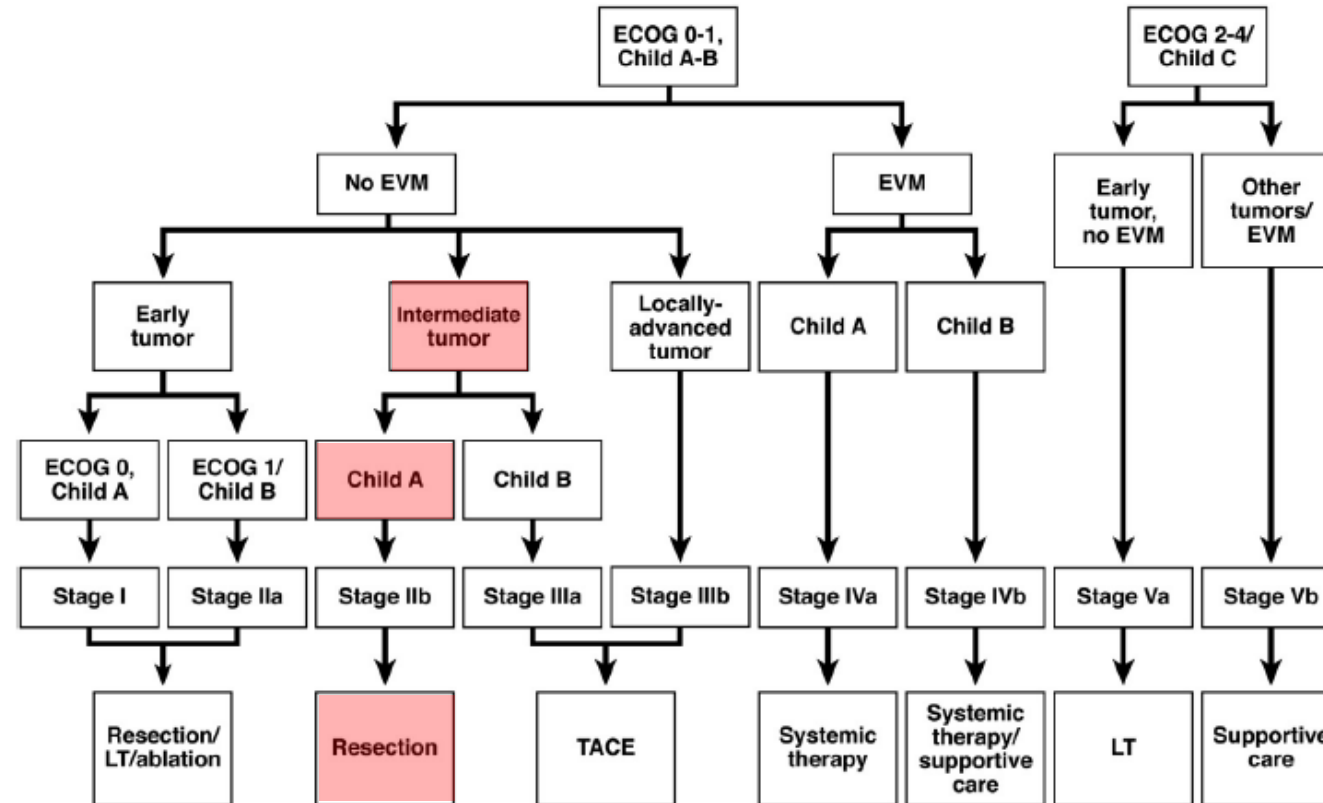
Curative treatments: Surgical Resection

Resection in intermediate HCC



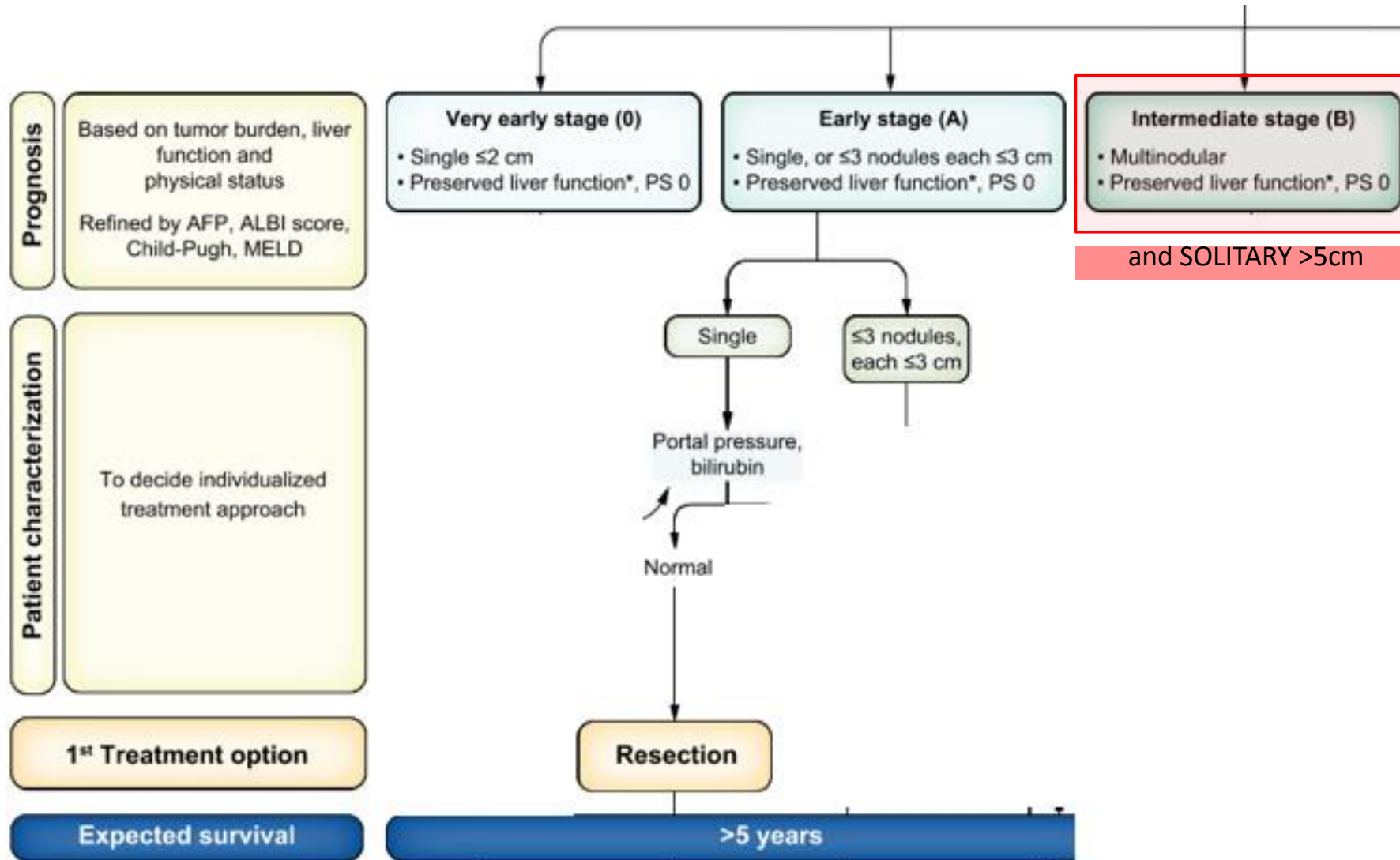
Curative treatments: Surgical Resection

Resection in intermediate HCC



Resection in intermediate HCC

- The problem of definition



Resection in intermediate HCC: the problem of definitions

When to Perform Hepatic Resection for Intermediate-Stage Hepatocellular Carcinoma

Alessandro Cucchetti,¹ Benjamin Djulbegovic,² Athanasios Tsalatsanis,² Alessandro Vitale,³
Iztok Hozo,⁴ Fabio Piscaglia,¹ Matteo Cescon,¹ Giorgio Ercolani,¹ Francesco Tuci,³
Umberto Cillo,³ and Antonio Daniele Pinna¹

Table 1. Baseline Characteristics of Patients With Cirrhosis Undergoing Hepatic Resection for Intermediate HCC

Variable	In Study (n = 247)
Age, years	65 (57-71)
Male gender (%)	201 (81.4)
HBsAg ⁺ (%)	57 (23.1)
Anti-HCV ⁺ (%)	126 (51.0)
Mild ascites (%)	24 (9.7)
Presence of varices (%)	58 (23.5)
Serum albumin, g/dL	3.8 (3.4-4.0)
Total bilirubin, mg/dL	0.85 (0.59-1.25)
Platelet count, ×10 ³ /mmc	149 (105-218)
INR	1.13 (1.07-1.21)
Child-Pugh score	5 (5-6)
A5 (%)	141 (57.1)
A6 (%)	86 (34.8)
B7 (%)	18 (7.3)
B8 (%)	2 (0.8)
MELD score	8 (7-9)
Radiological tumor number	1 (1-2)
Single tumor (%)	124 (50.2)
Two or three tumors (%)	93 (37.7)
More than three tumors (%)	30 (12.1)
Radiological largest tumor size, cm	6.0 (5.0-7.7)
OS	
1 year (95% CI)	77.8% (72.1-82.6)
3 year (95% CI)	48.7% (41.4-55.5)
5 year (95% CI)	33.8% (26.2-41.5)

Continuous variables are reported as medians and IQRs (25th-75th percentiles).

Abbreviations: HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

Curative treatments: Surgical Resection

Resection in intermediate HCC: the problem of definitions

- The problem of definitions
- The problem of selection bias

“all of these retrospective comparisons were almost certainly associated with selection bias: the patients who were selected for resection instead of TACE probably had clinical characteristics that gave the surgeon confidence of a good outcome, whereas those selected for TACE likely lacked such features, immediately introducing a bias against TACE”

Curative treatments: Surgical Resection

Resection in intermediate HCC: the problem of definitions

- The problem of definitions
- The problem of selection bias
- **The problem of comparator**

Curative treatments: Surgical Resection

Resection in intermediate HCC: the problem of comparator

Partial hepatectomy vs. transcatheter arterial chemoembolization for resectable multiple hepatocellular carcinoma beyond Milan criteria: A RCT

Lei Yin¹, Hui Li^{2,†}, Ai-Jun Li^{1,†}, Wan Yee Lau^{1,3}, Ze-ya Pan¹, Eric C.H. Lai^{1,3}, Meng-chao Wu¹, Wei-Ping Zhou^{1,*}

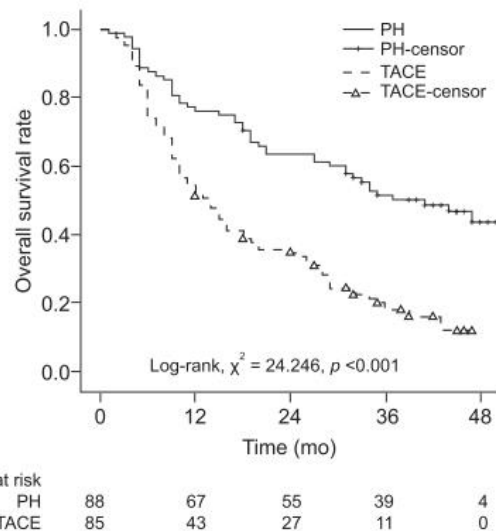


Fig. 2. Overall survival curves for PH and TACE.

Results: The 1-, 2-, and 3-year OS rates were 76.1%, 63.5%, and 51.5%, respectively, for the PH group compared with 51.8%, 34.8%, and 18.1%, respectively, for the TACE group (Log-rank test, $\chi^2 = 24.246$, $p < 0.001$). Multivariate Cox proportional hazards regression analysis revealed the type of treatment (hazard ratio, 0.434; 95% CI, 0.293 to 0.644, $p < 0.001$), number of tumor (hazard ratio, 1.758; 95% CI, 1.213 to 2.548, $p = 0.003$) and gender (hazard ratio, 0.451; 95% CI, 0.236 to 0.862, $p = 0.016$) were significant independent risk factors associated with OS.

Curative treatments: Surgical Resection

Resection in intermediate HCC: the problem of comparator

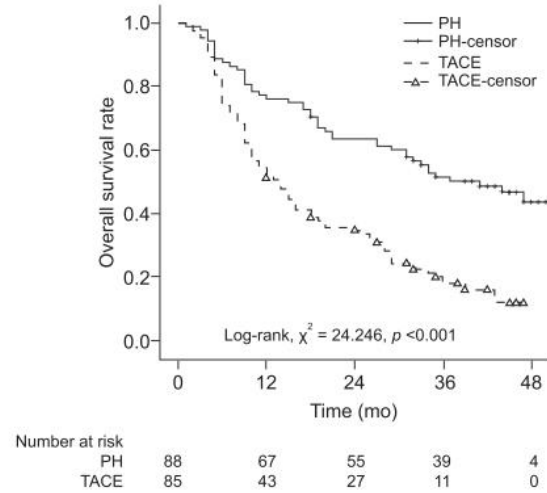
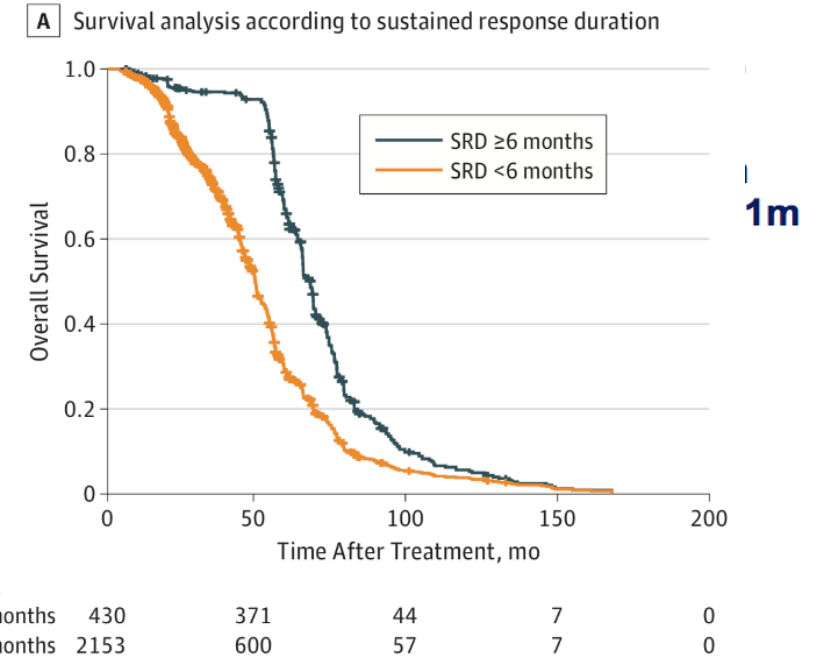


Fig. 2. Overall survival curves for PH and TACE.

Survival

The 1-, 2-, and 3-year OS rates and median survival were 76.1%, 63.5%, 51.5%, and 41 months (range 1–50 months) respectively, in the PH group. The corresponding figures for the TACE group were 51.8%, 34.8%, 18.1%, and **14 months** (range 5–47 months), respectively. The PH group had significantly better OS than the TACE group (log-rank test, $\chi^2 = 24.246$, $p < 0.001$) (Fig. 2). The



For patients with SRD of 6 months or more, the median (range) OS was 67.7 (64.8-72.1) months, which was better than that of patients with SRD of less than 6 months (median [range] OS, 53.5 [52.5-55.4] months) (HR, 0.132; 95% CI, 0.112-0.168; $P < .001$)

Curative treatments: Surgical Resection

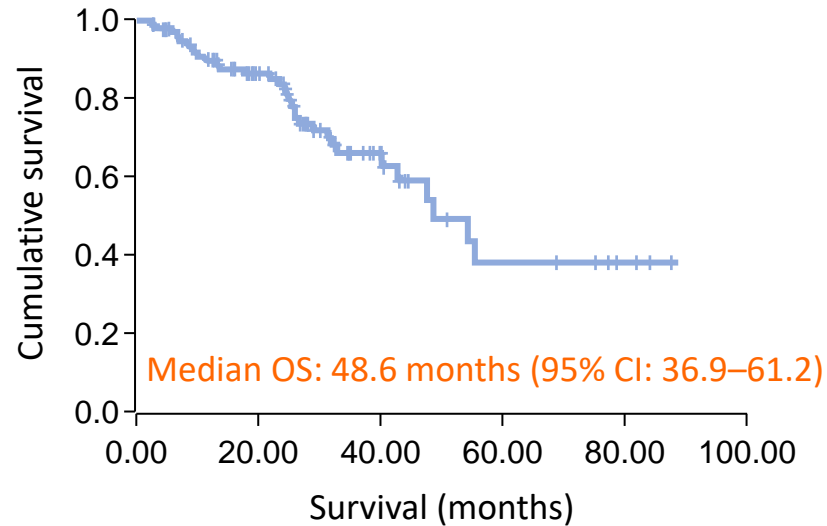
Resection in intermediate HCC: the problem of comparator

Table 1. Baseline Characteristics of Patients With Cirrhosis Undergoing Hepatic Resection for Intermediate HCC

Variable	In Study (n = 247)
Age, years	65 (57-71)
Male gender (%)	201 (81.4)
HBsAg ⁺ (%)	57 (23.1)
Anti-HCV ⁺ (%)	126 (51.0)
Mild ascites (%)	24 (9.7)
Presence of varices (%)	58 (23.5)
Serum albumin, g/dL	3.8 (3.4-4.0)
Total bilirubin, mg/dL	0.85 (0.59-1.25)
Platelet count, ×10 ³ /mmc	149 (105-218)
INR	1.13 (1.07-1.21)
Child-Pugh score	5 (5-6)
A5 (%)	141 (57.1)
A6 (%)	86 (34.8)
B7 (%)	18 (7.3)
B8 (%)	2 (0.8)
MELD score	8 (7-9)
Radiological tumor number	1 (1-2)
Single tumor (%)	124 (50.2)
Two or three tumors (%)	93 (37.7)
More than three tumors (%)	30 (12.1)
Radiological largest tumor size, cm	6.0 (5.0-7.7)
OS	
1 year (95% CI)	77.8% (72.1-82.6)
3 year (95% CI)	48.7% (41.4-55.5)
5 year (95% CI)	33.8% (26.2-41.5)

Continuous variables are reported as medians and IQRs (25th-75th percentiles).

Abbreviations: HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.



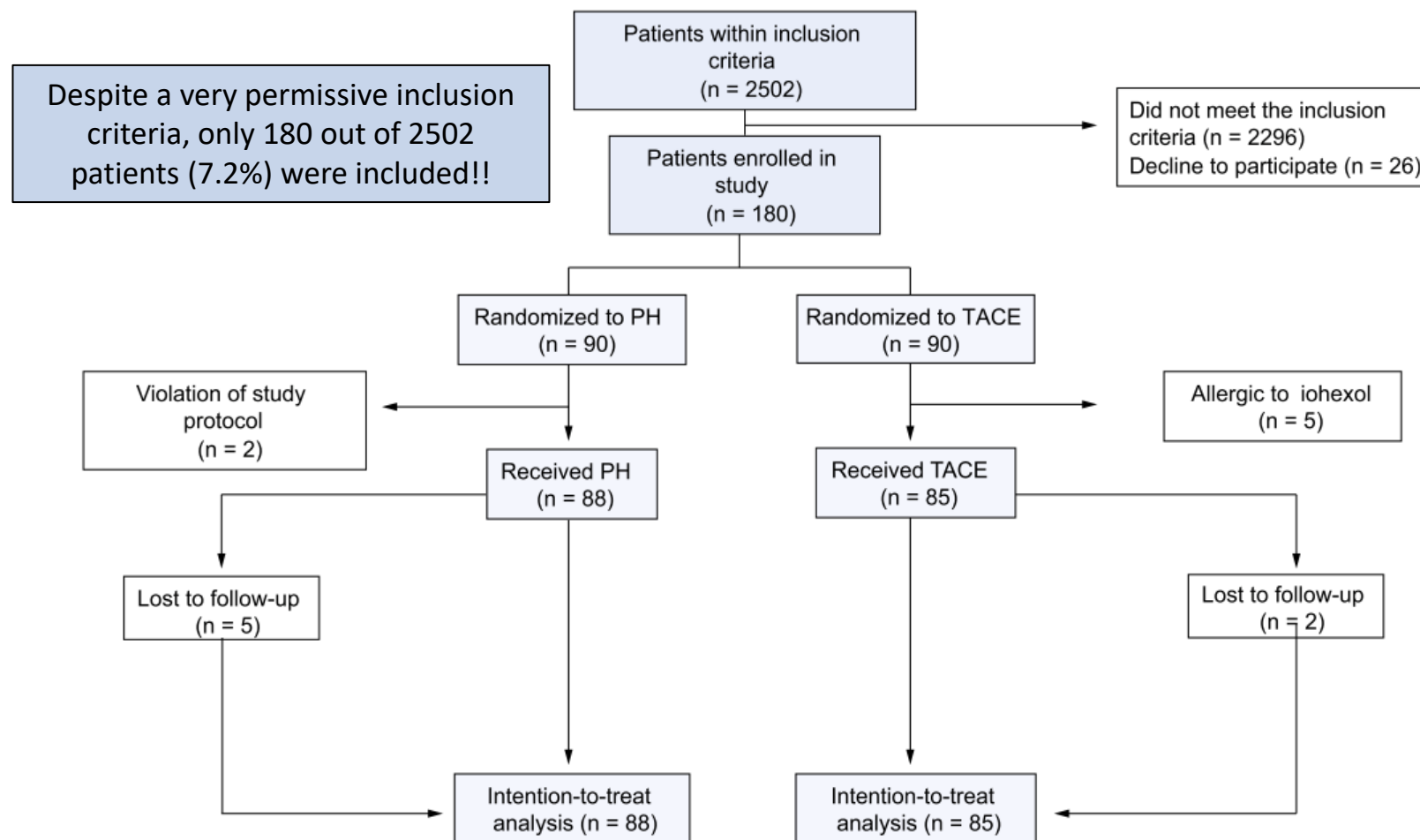
Child class (n)		1 year (%)	2 year (%)	3 year (%)	4 year (%)	5 year (%)
A						
21	One dominant ≤ 5 cm	100	95.2	71.4	66.6	47.6
37	One dominant > 5 cm	97.3	89.1	85.1	43.3	32.4
31	Multinodular ≤ 5 cm	93.5	90.3	61.3	41.9	25.8
13	Multinodular > 5 cm	84.6	69.2	46.1	15.3	0
102	Overall	95	88.2	61.7	45	29.4
B						
17	One dominant ≤ 5 cm	94.1	88.2	58.8	41.2	23.5
35	One dominant > 5 cm	91.4	71.4	54.2	37.1	11.4
14	Multinodular ≤ 5 cm	85.7	75	25	14.3	0
5	Multinodular > 5 cm	100	60	20	0	0
71	Overall	91.5	75	50.7	35.2	12.8
Total		93.6	83.8	62	41.04	22.5

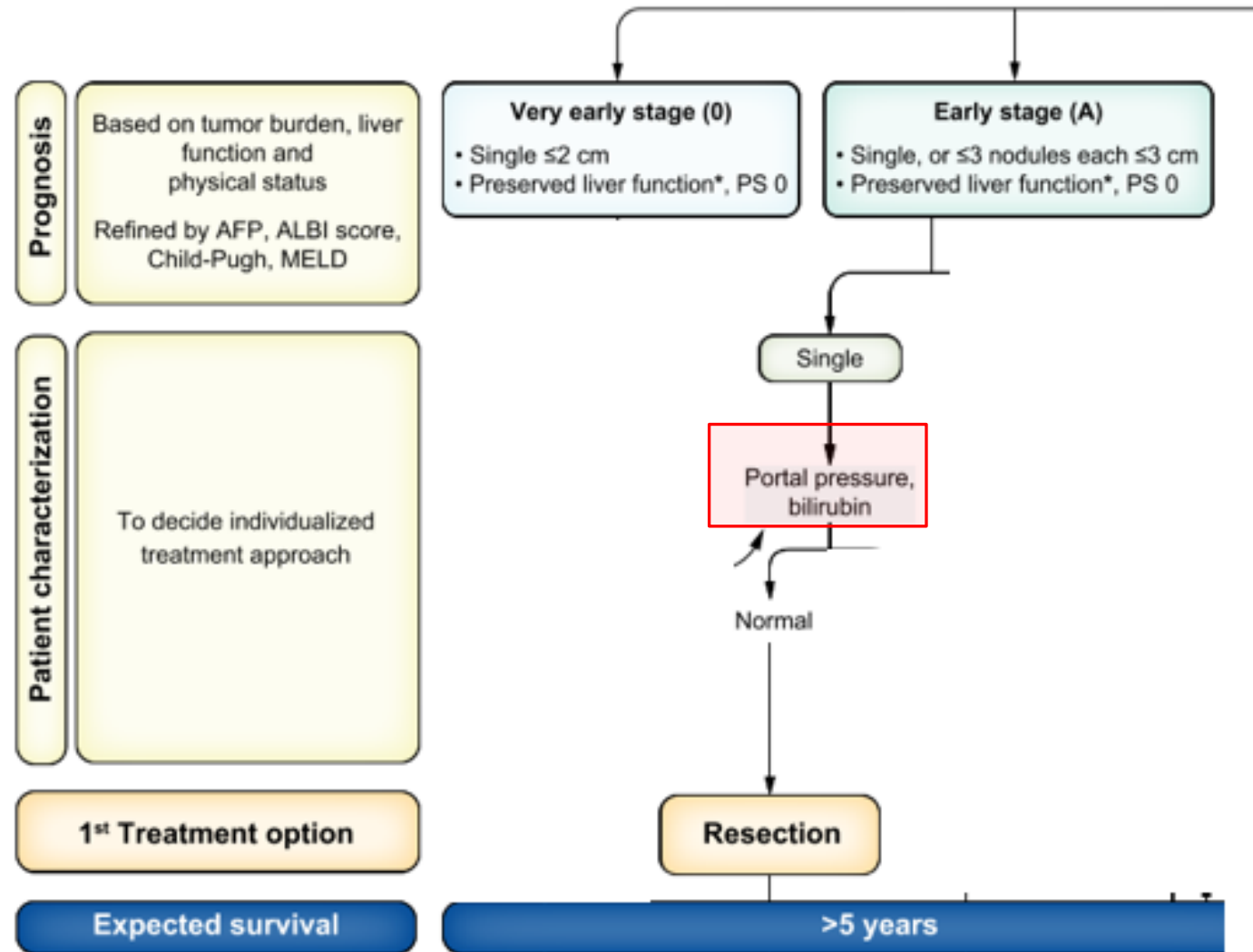
Mean overall survival: 43.8 months

Cucchetti A et al. Hepatology. 2015;61(3):905-914
 Burrel M, Reig M, et al. J Hepatol. 2012;56(6):1330-5
 Malagari K, et al. CVIR 2012; 35: 119-1128

Curative treatments: Surgical Resection

Resection in intermediate HCC: the problem of comparator



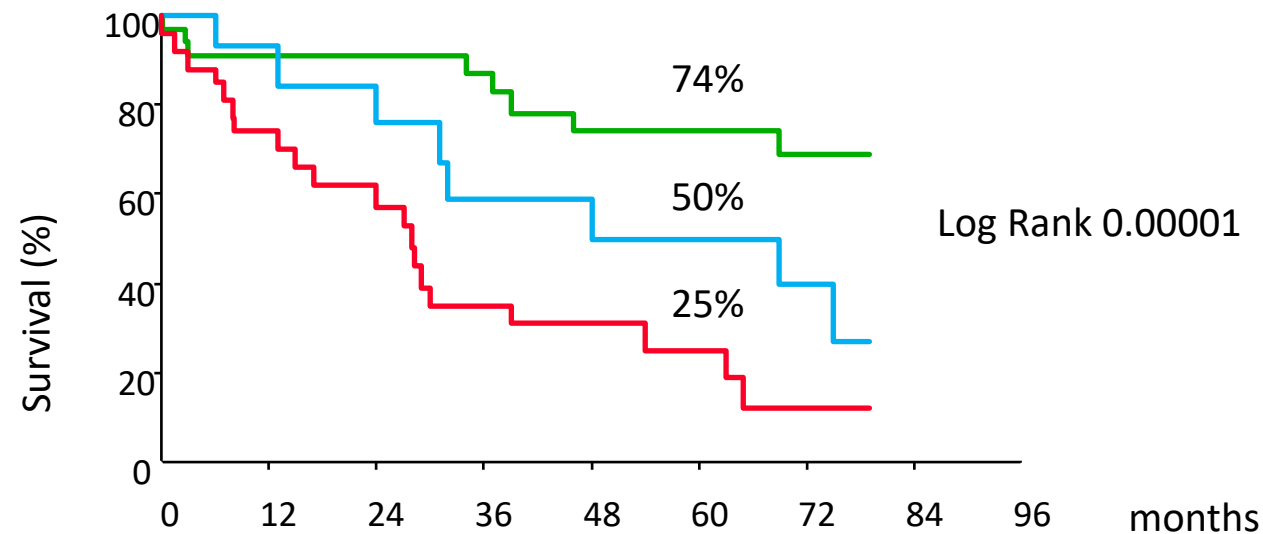


Curative treatments: Surgical Resection

Prognostic role of clinically significant portal hypertension

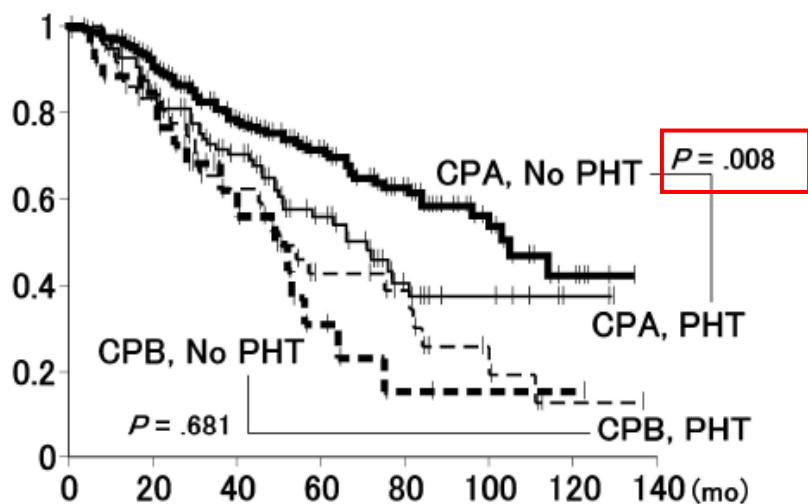
Best candidates:

- Solitary HCC
- Child-Pugh A: No portal hypertension (HVPG < 10 mmHg)
Normal Bilirubin (< 1 mg/dl)



- No portal hypertension and normal bilirubin (n= 35)
- Portal hypertension and normal bilirubin (n=15)
- Portal hypertension and Bilirubin ≥ 1 mg/dL (n=27)

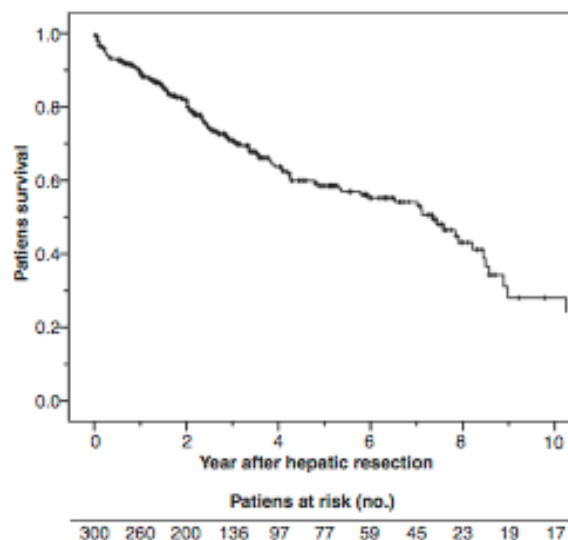
Prognostic role of clinically significant portal hypertension



5-years survival:

CP A, No PHT: 71%

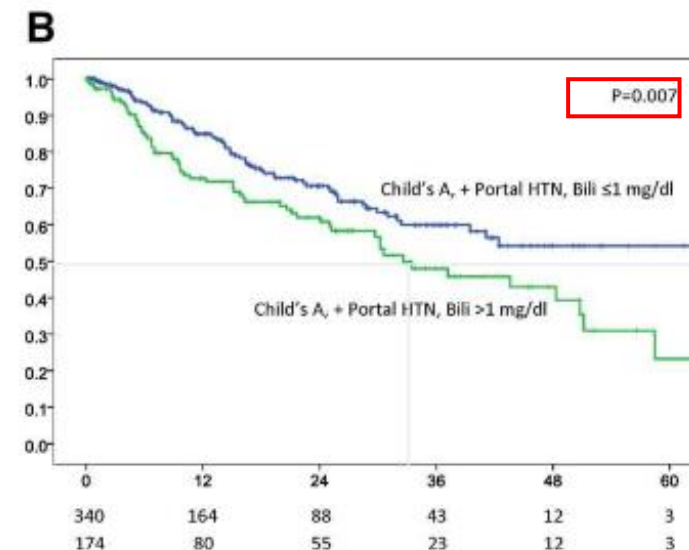
CP A, PHT: 56%



5-years survival:

Overall: 57.7%

CP A, No PHT: 63.8%



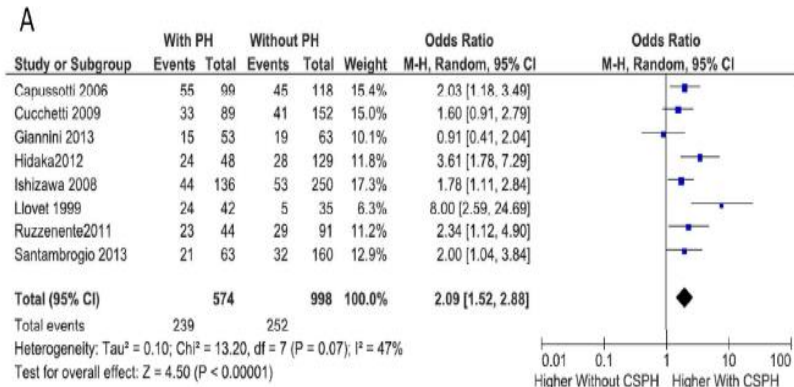
Ishizawa T, et al. Gastroenterology. 2008;134:1908-16.

Cucchetti A, et al. Clin Cancer Res. 2012;18(16):4397-4405.

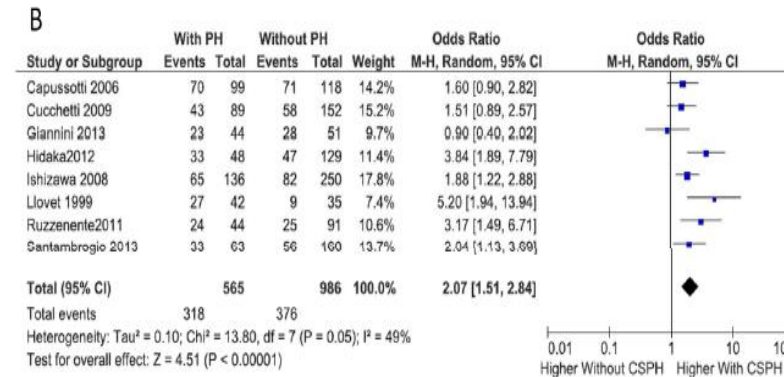
Roayaie S et al. Hepatology. 2015;62:440-451.

Meta-analysis of the impact of CSPH on postoperative outcomes

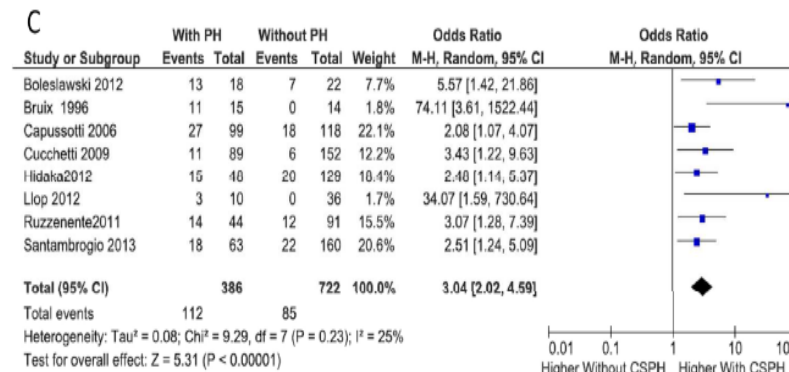
Panel A: 3-year mortality



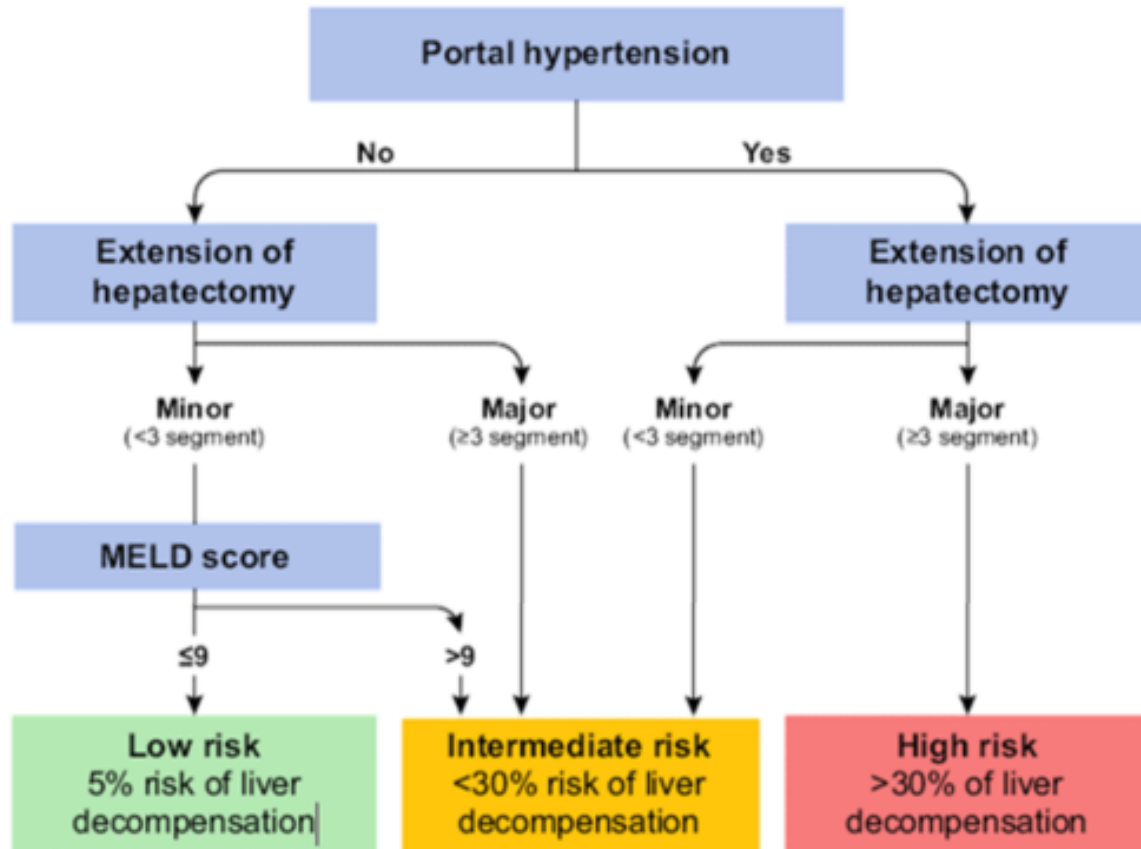
Panel B: 5-year mortality



Panel C: clinical decompensation



Redefinition of CSPH as a contraindication for surgical resection

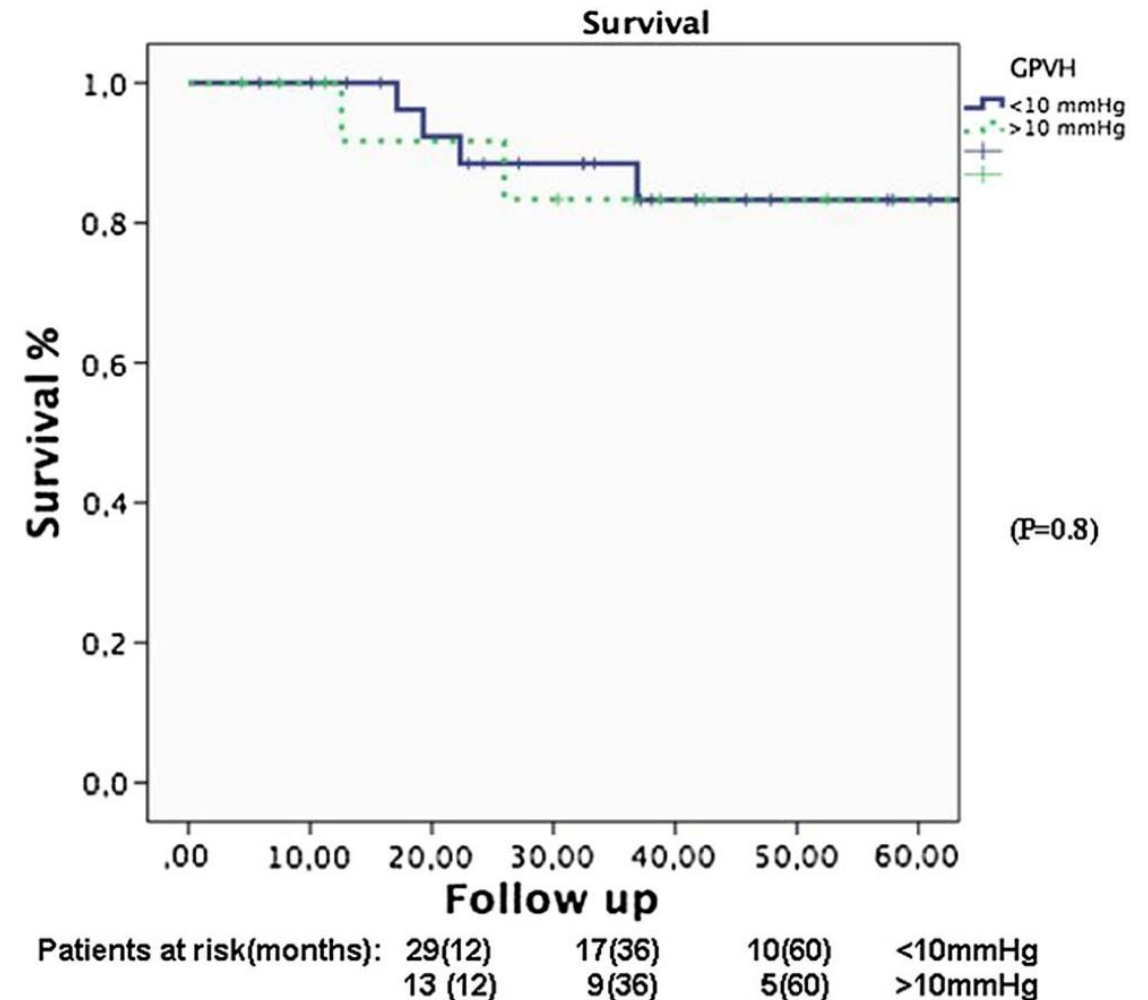


		Extension of hepatectomy	
		Major	Minor
Portal hypertension	Yes		
	No		MELD score >9 MELD score ≤9

Laparoscopic approach may expand resection in patients with CSPH

Table 5 Postoperative data

Variable	Non-CSPH N= 30	CSPH N= 15	<i>p</i> value
Mortality (90 days)	0	0	
Clavien–Dindo classification			
I	6 (27%) 2 ileus 4 fever unknown origin	–	
II	3 (10%) 2 ascites 1 heart failure	2 (14%) 1 ascites 1 haemorrhage	
IIIa	1 (3%) 1 wound infection	–	
IIIb	1 (3%) 1 haemorrhage	1 (7%) 1 evisceration	
Reintervention rate	1 (3%)	1 (7%)	ns
Hospital stay (days, median, range)	4 (2–11)	3 (2–20)	ns



Summary

- Solitary HCC in patients without CSPH are the best candidates for resection
- Portal hypertension and multifocality are robust predictors of worse outcome but are not absolute contraindications
- According to the current scientific evidence, TACE should be considered the first treatment option for intermediate HCC. The role of resection should be evaluated in RCTs

-
- Resection: Indications and challenging scenarios
 - **Liver transplantation: Where are the limits?**
 - Downstaging: Facts and hopes
 - Expansion of LT criteria for HCC

Outcomes applying restrictive selection criteria

Authors, year	n	Selection criteria	Recurrence	Survival at 5y
Mazzaferro, 1996	48	Milan	8%	75%*
Jonas, 2001	120	Milan	--	71%
Cillo, 2004	30	Milan	6.7%	72%
Herrero, 2008	47	Milan	8.5%	70%
Mazzaferro, 2009	444	Milan	--	73.3%

* Survival at 4 years
 ~ 5-y recurrence rate
 ~ 100-(5-y RFS)

Mazzaferro V et al. N Engl J Med. 1996;334:693-9
 Jonas S et al. Hepatology. 2001;33:1080-6
 Cillo U et al. Ann Surg. 2004;239:150-9
 Herrero JI et al. Liver Transpl. 2008;14:272-8
 Mazzaferro V et al. Lancet Oncol. 2009;10:35-43

Expanded criteria

Author (year)	Criteria	5-year survival	
		Patients	Survival
Yao, 2001	Post-LT, explant Solitary tumor ≤ 6.5 cm or ≤ 3 tumors ≤ 4.5 cm	70	75%
Duffy, 2007	Post-LT, radiology/explant Solitary tumor ≤ 6.5 cm or ≤ 3 tumors ≤ 4.5 cm	208	64-81%
Onaca, 2007	Post-LT, explant Solitary tumor ≤ 6 cm or ≤ 4 tumors ≤ 5 cm	659	55-63%
Lee, 2008	Pre-LT, radiology Larger tumor ≤ 5 cm ≤ 6 nodules	186	76%
Toso, 2008	Post-LT, explant Total tumor volume ≤ 115 cm ³	251	80%
Herrero, 2008	Pre-LT, radiology One tumor ≤ 6 cm or 3 nodules ≤ 5 cm	85	70%

Yao F et al. Hepatology. 2001;33(6);1394-1403.

Duffy JA et al. Ann Surg. 2007;246(3):502-511.

Onaca N et al. Liver Transpl. 2007;13(3):391-399.

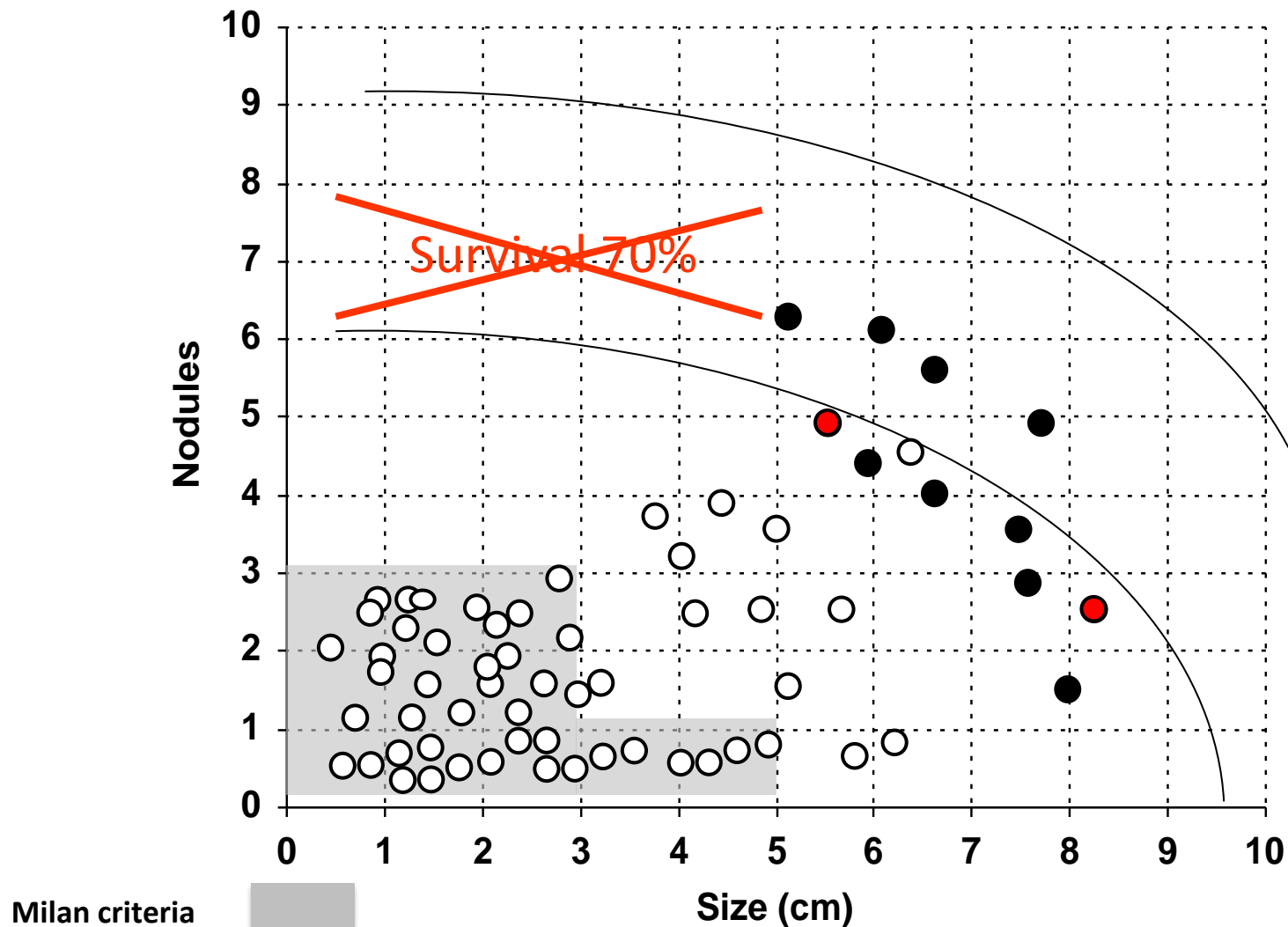
Lee S et al. Liver Transpl. 2008;14(7):935-945.

Toso C. et al. Liver Transpl. 2008;14(8):1107-1115.

Herrero JI et al. Liver Transpl. 2008;14(3):272-278.

Beyond Milan criteria...chaos!

There is not uniform criteria for reporting results

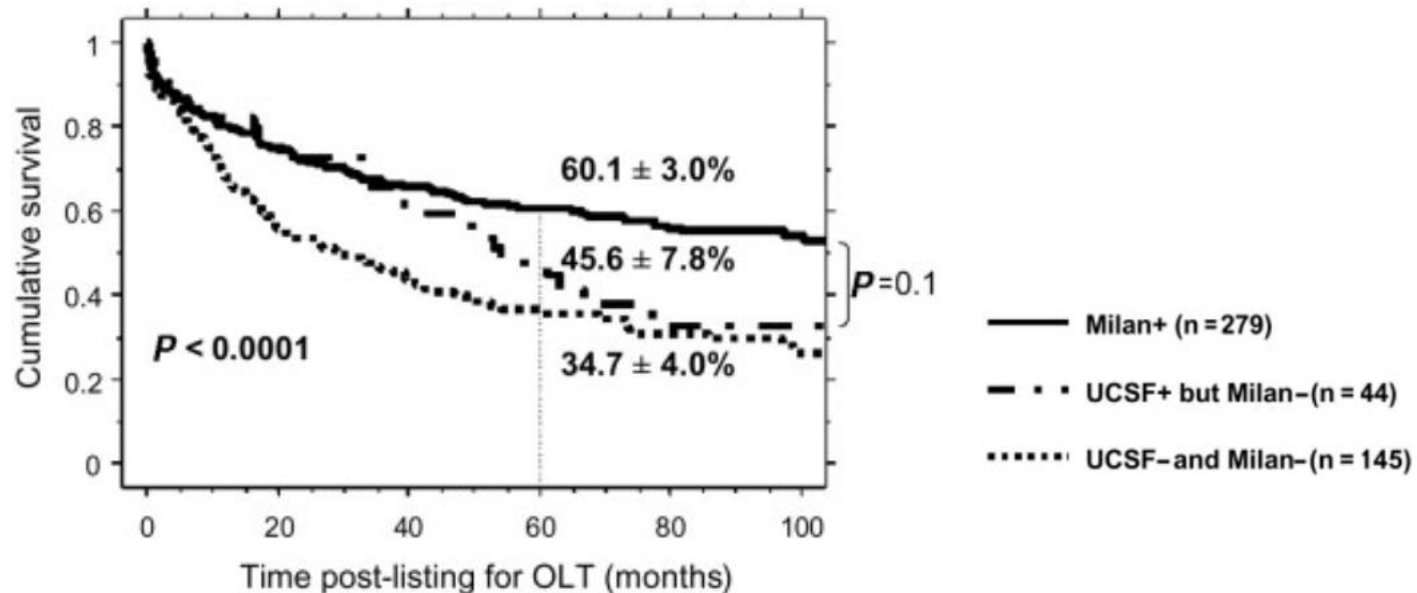


Beyond Milan criteria

External validation of UCSF criteria

Retrospective analysis of 479 HCC patients:

- 279 patients Milan in
- 44 patients Milan out but UCSF in (10% of total cohort)
- 145 patients Milan and UCSF out



Up to seven criteria

	Milan (within)*	Milan (outside)†	
		Within up-to-seven criteria	Exceeding up-to-seven criteria
Microvascular invasion absent			
Number of patients	361	283	333
Overall survival‡ (95% CI), %			
3 years	81.8 (77.1-85.7)	77.7 (72.0-82.5)	71.8 (66.2-76.7)
5 years	76.1 (70.6-80.7)	71.2 (64.3-77.0)	64.0 (57.7-69.5)
Crude cumulative incidence of recurrence (95% CI), %			
3 years	3.3 (1.8-6.0)	4.8 (2.7-8.5)	17.4 (13.5-22.5)
5 years	3.3 (1.8-6.0)	9.1 (5.6-14.5)	22.3 (17.7-28.0)
Microvascular invasion present	10.9%		50.4%
Number of patients	44	116	338
Overall survival‡ (95% CI), %			
3 years	77.1 (60.2-87.5)	60.2 (49.7-69.2)	41.7 (35.8-47.5)
5 years	71.6 (51.8-84.4)	47.4 (36.4-57.7)	33.0 (27.2-38.9)
Crude cumulative incidence of recurrence (95% CI), %			
3 years	12.8 (5.6-29.6)	31.3 (23.3-41.9)	31.3 (23.3-41.9)
5 years	12.8 (5.6-29.6)	39.9 (30.8-51.7)	51.5 (45.8-57.8)



Patient
Within Milan
Beyond Milan within up-
Exceeding Milan and up-

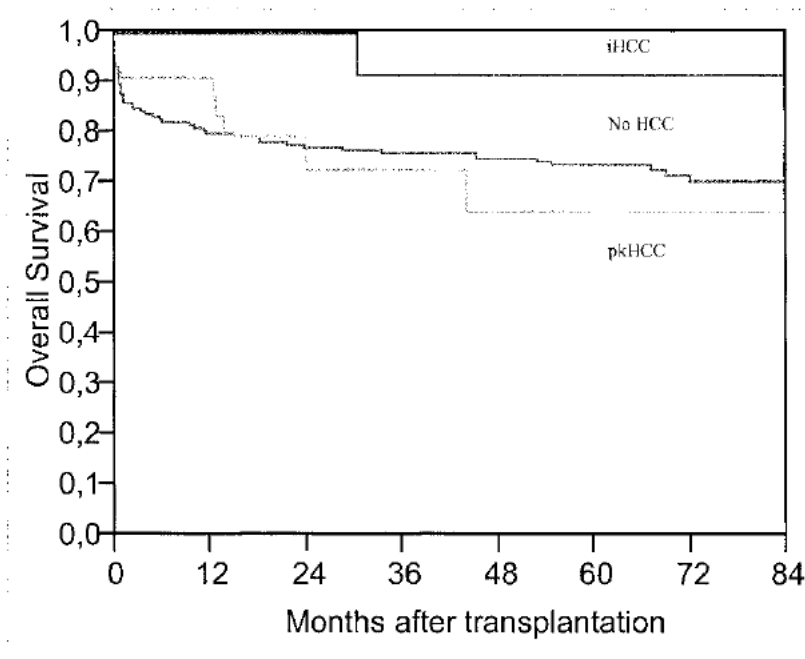
*Data missing for 39 patients. †Data missing for 42 patients. ‡According to Kaplan-Meier analysis.

Table 3: Outcome of liver transplantation for hepatocellular carcinoma according to Milan criteria and up-to-seven criteria, in relation to microvascular invasion

Median follow-up: 53 months

Differentiation degree as a selection criteria

- Exclusion criteria for LT: Vascular invasion, extrahepatic spread and/or poor differentiated tumors
- During 11 years 133 HCC patients were evaluated: 93 excluded, 10 due to poor differentiated HCC (5 of them within Milan)



Limitations:

- Tumor heterogeneity
- No specific information regarding the survival in those outside Milan
- Retrospective: Only those transplanted are analyzed

AFP as a selection criteria

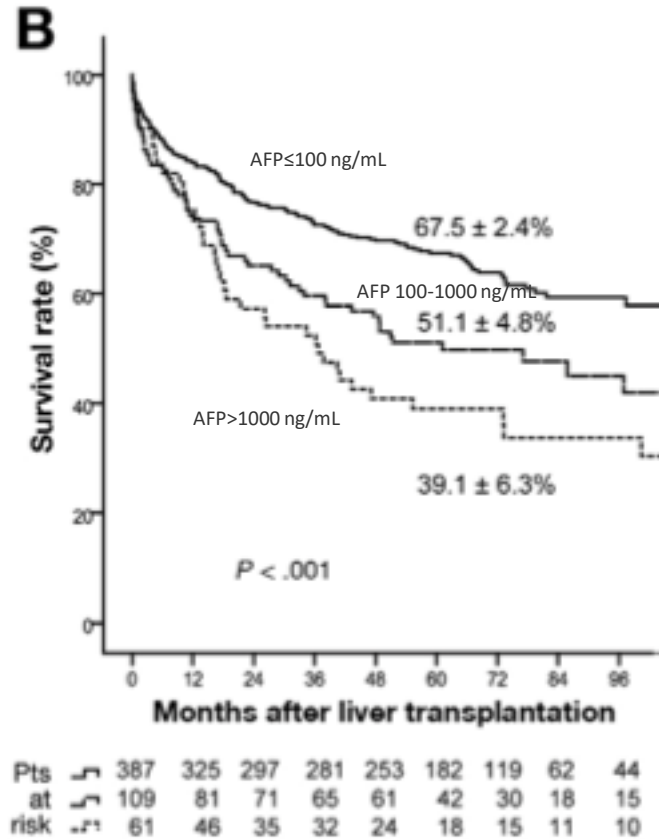
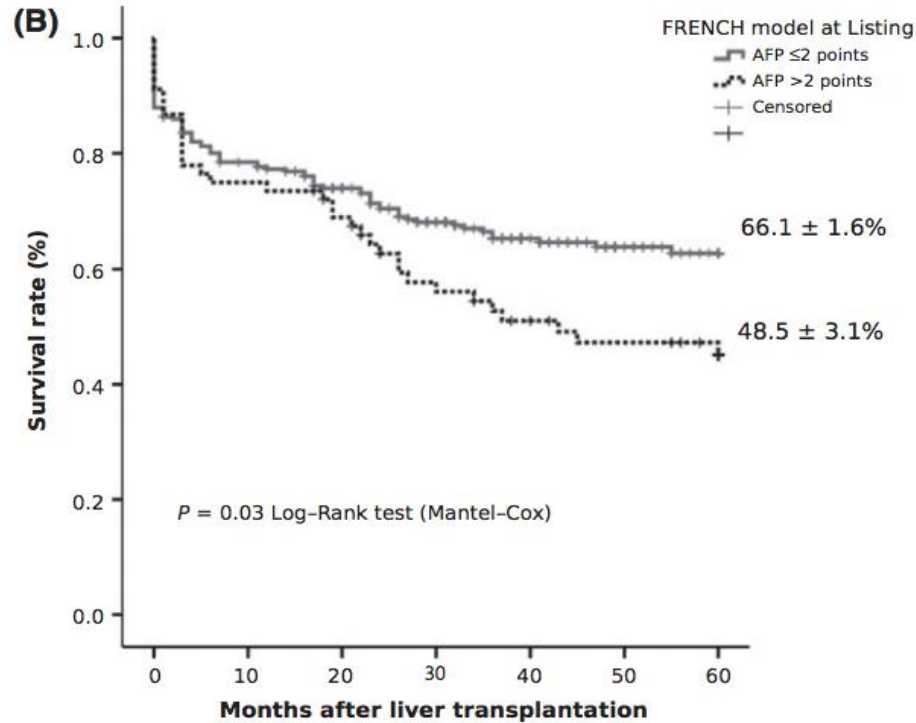


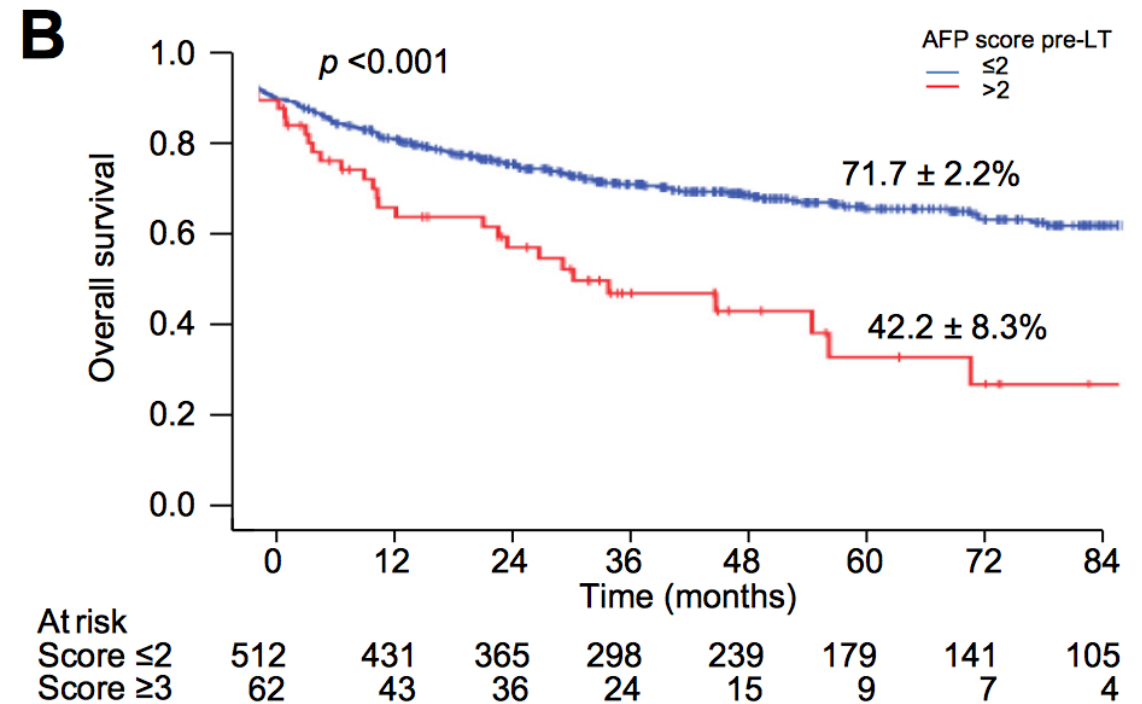
Table 2. Simplified, User-Friendly Version of the AFP Model

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

AFP as a selection criteria: External validation

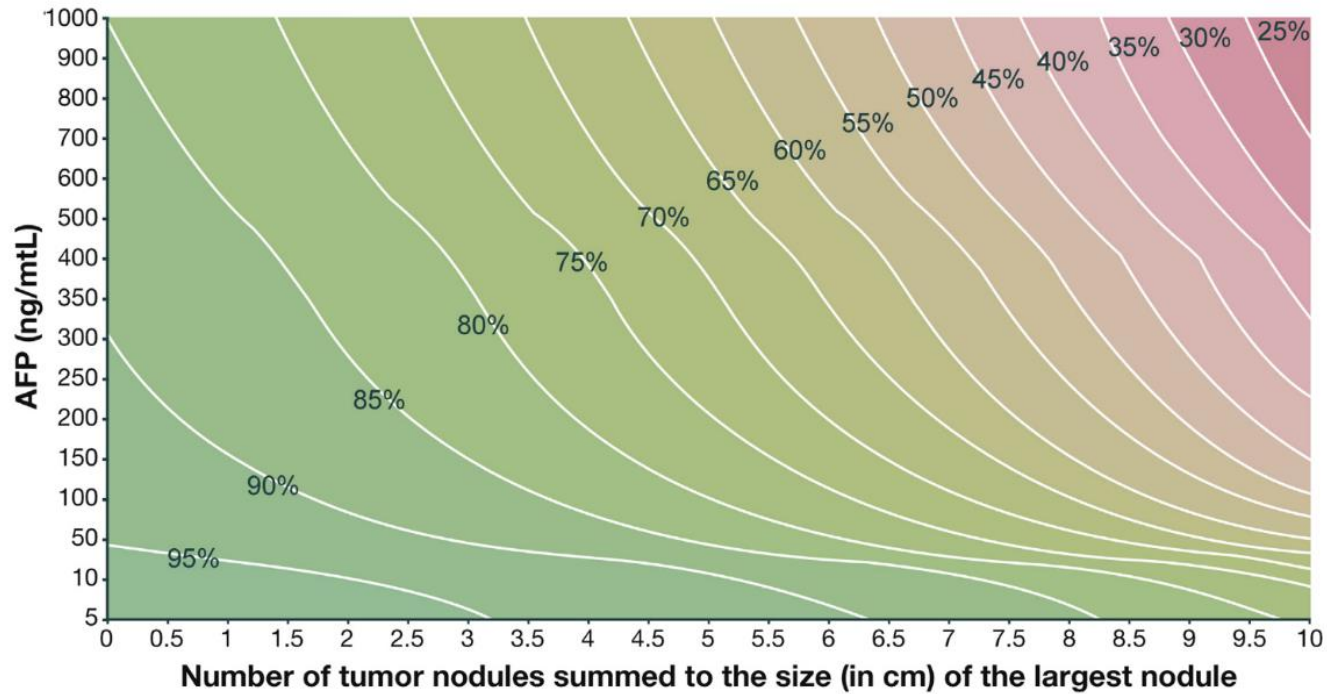


Patients at Risk/ Time (months)	12	36	60
French ≤ 2 (n = 257)	192	114	49
French > 2 (n = 68)	50	30	21

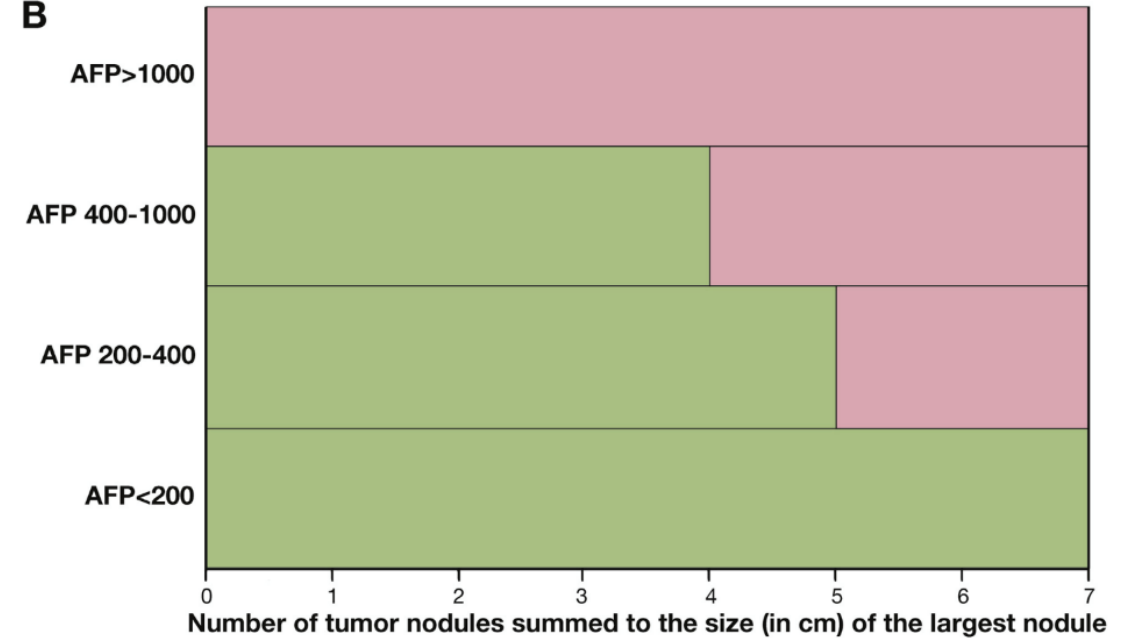


Metroticket 2.0: The value of AFP

A

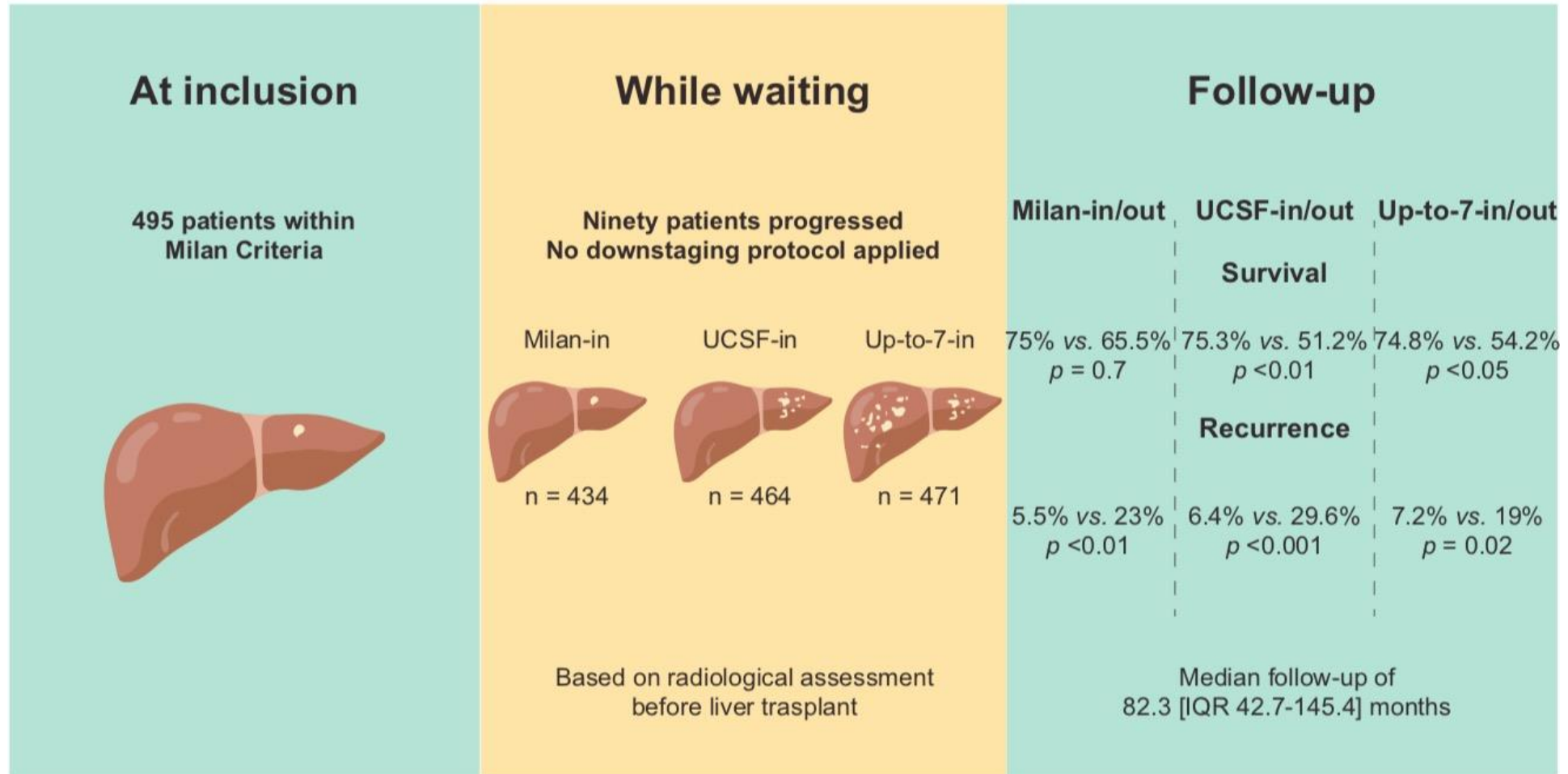


B



Beyond Milan criteria

Progression beyond Milan criteria during waiting list



-
- Resection: Indications and challenging scenarios
 - Liver transplantation: Where are the limits?
 - **Downstaging: Facts and hopes**
 - Expansion of LT criteria for HCC

Downstaging

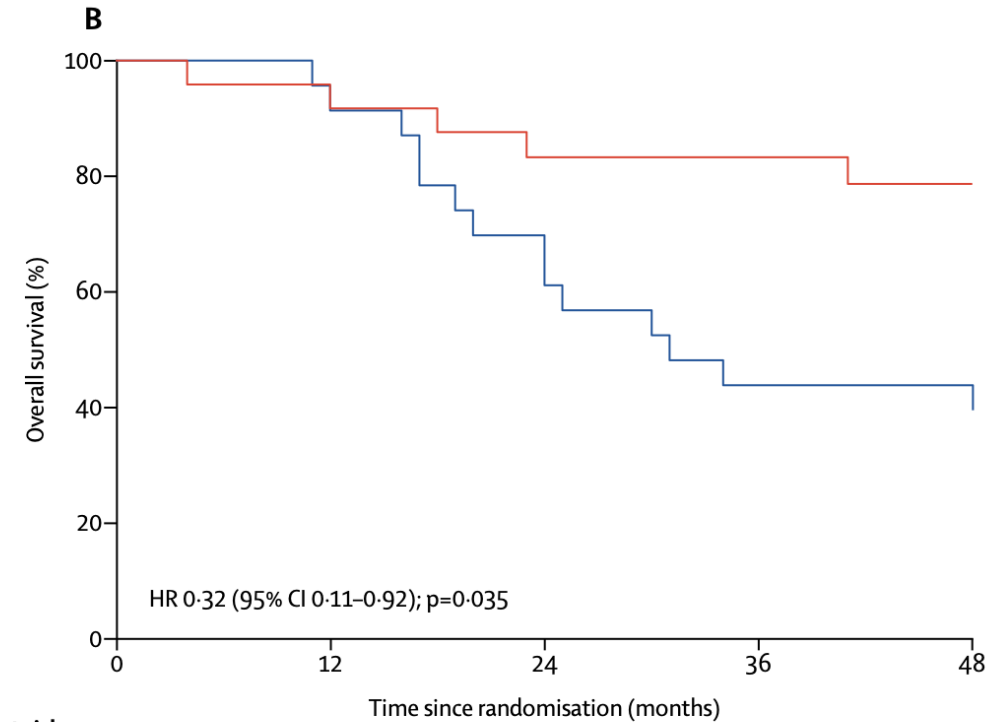
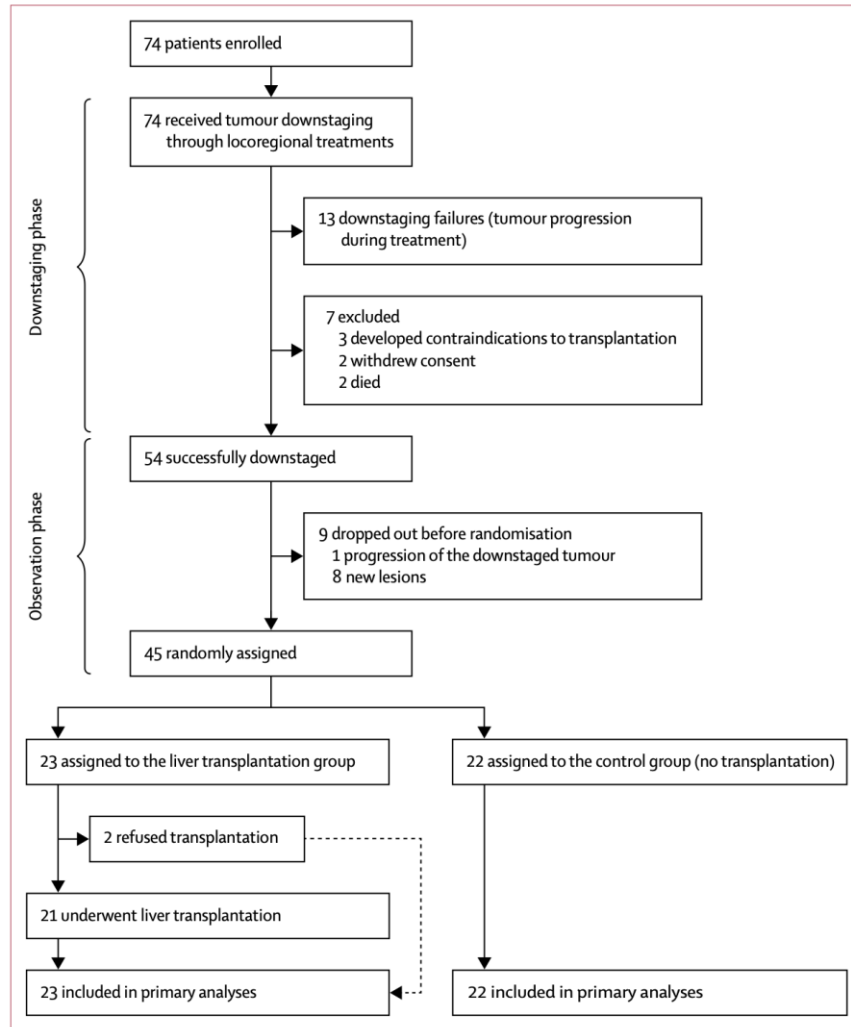
Author (year)	Baseline stage	Downstaging criteria	Survival	
			Patients: Included/Transplanted	5-year survival
Majno, 1997	Post-LT, explant 3 tumors ≤ 4.5cm	Necrosis ≥ 50%	54/28 (downstaged)	71% (recurrence-free survival)
Yao, 2005	Pre-LT, radiology 1 lesion 5-8cm or 2-3 nodules ≤ 3cm with sum of all diameters ≤ 8cm	USCF criteria at least 2 months	30/21	82% (2 years (6 months post-LT))
Otto, 2006	Post-LT, explant Any HCC stage	USCF criteria	61/34	51.0% (intention to treat)
Yao, 2015	Pre-LT, radiology Same as Yao 2005	Milan criteria	118/64	56.1% (intention to treat)

- There is not an homogeneous definition of successful downstaging
- Downstaging might allow to select tumors biologically less aggressive
- Up to now, there is not any RCT or controlled cohort study that has demonstrated its efficacy

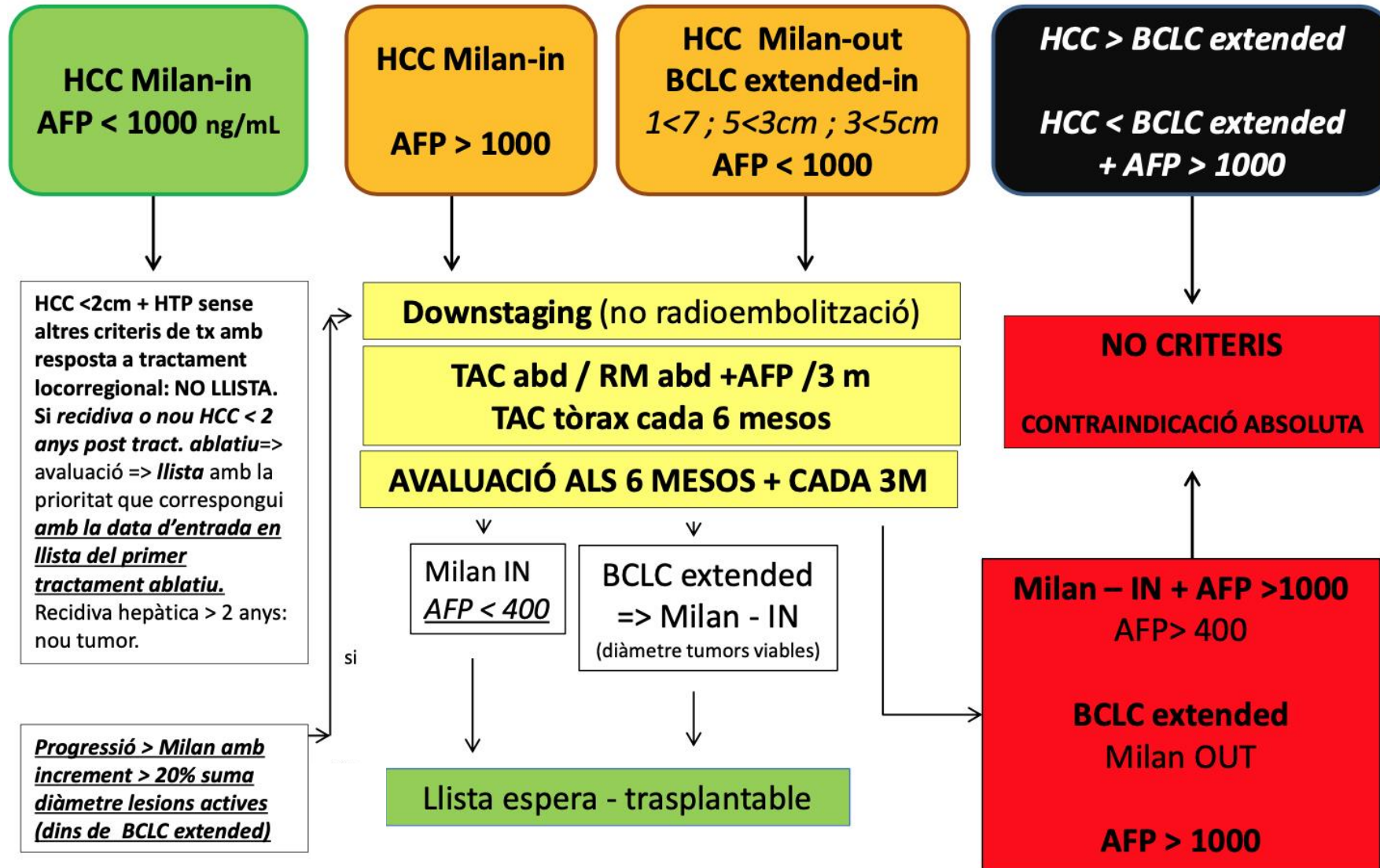
Clavien PA et al. Lancet Oncol. 2012;Jan;13(1):e11-22.
Vibert E, et al. J Hepatol. 2020 Feb;72(2):262–76.

Majno P et al. Ann Surg. 1997;226(6):688-701.
Yao FY et al. Liver Transpl. 2005;11(12):1505-1514.
Otto G et al. Liver Transpl. 2006;12(8):1260-1267.
Yao FY et al. Hepatology. 2015;61(6):1968-77.

Downstaging: XXL Randomised, phase 2b/3 Trial

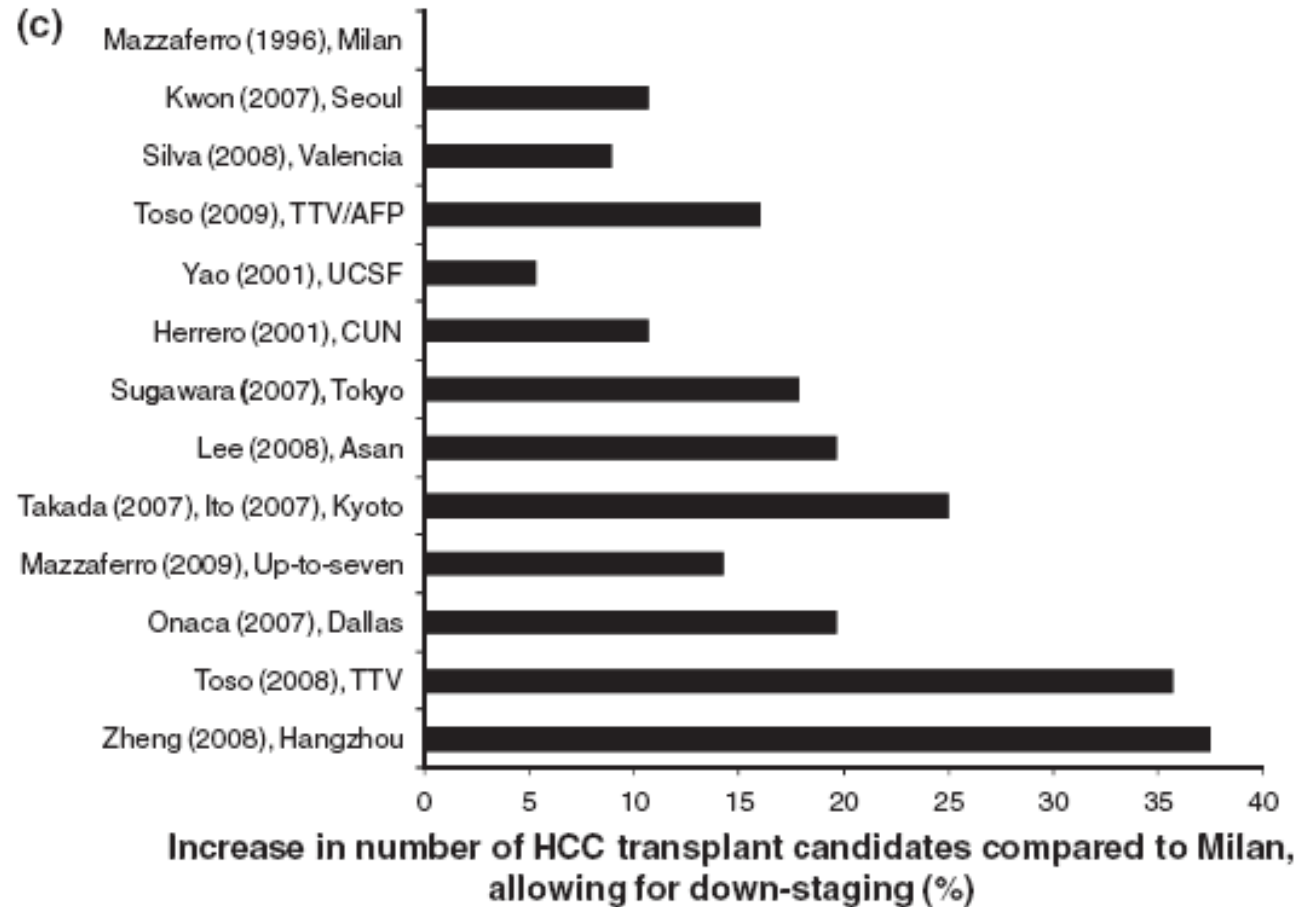


	Number at risk (number censored)				
	0	12	24	36	48
Transplantation group	23 (0)	20 (0)	18 (1)	18 (1)	16 (2)
Control group	22 (0)	21 (0)	15 (0)	9 (0)	9 (0)

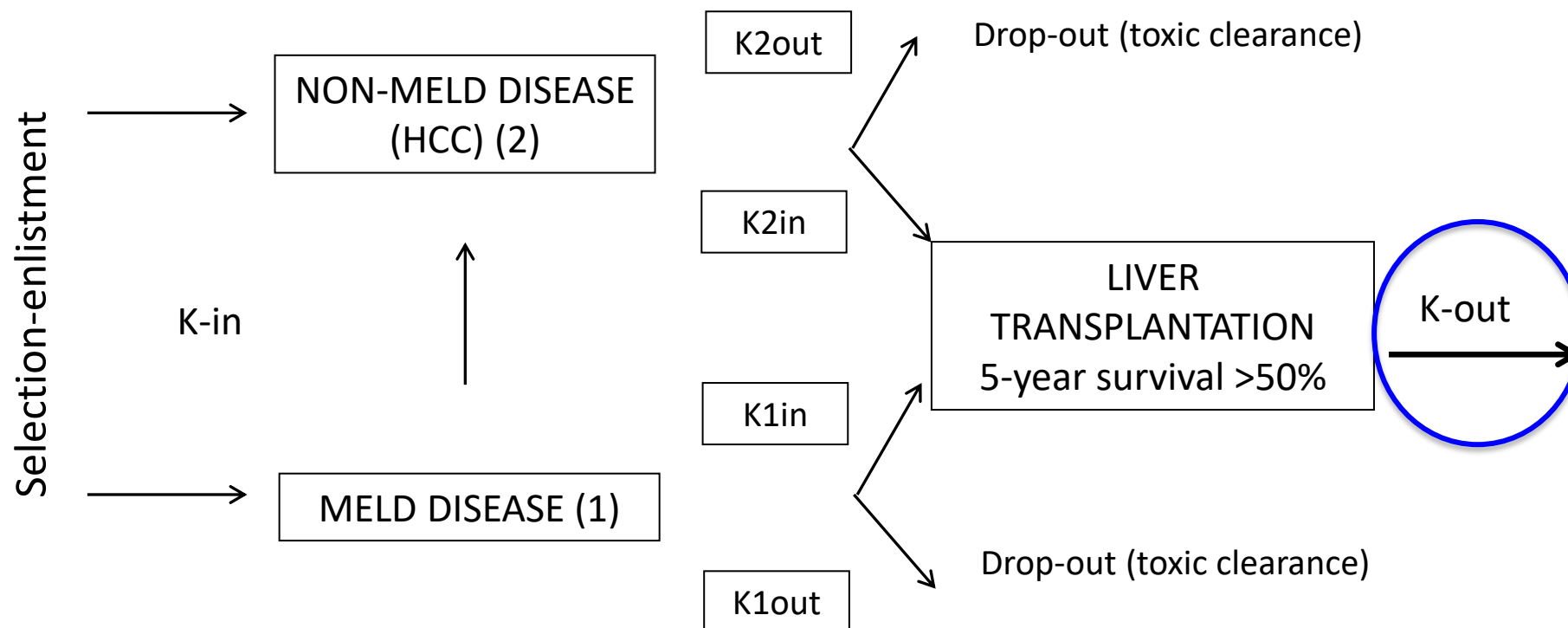


-
- Resection: Indications and challenging scenarios
 - Liver transplantation: Where are the limits?
 - Downstaging: Facts and hopes
 - **Expansion of LT criteria for HCC**

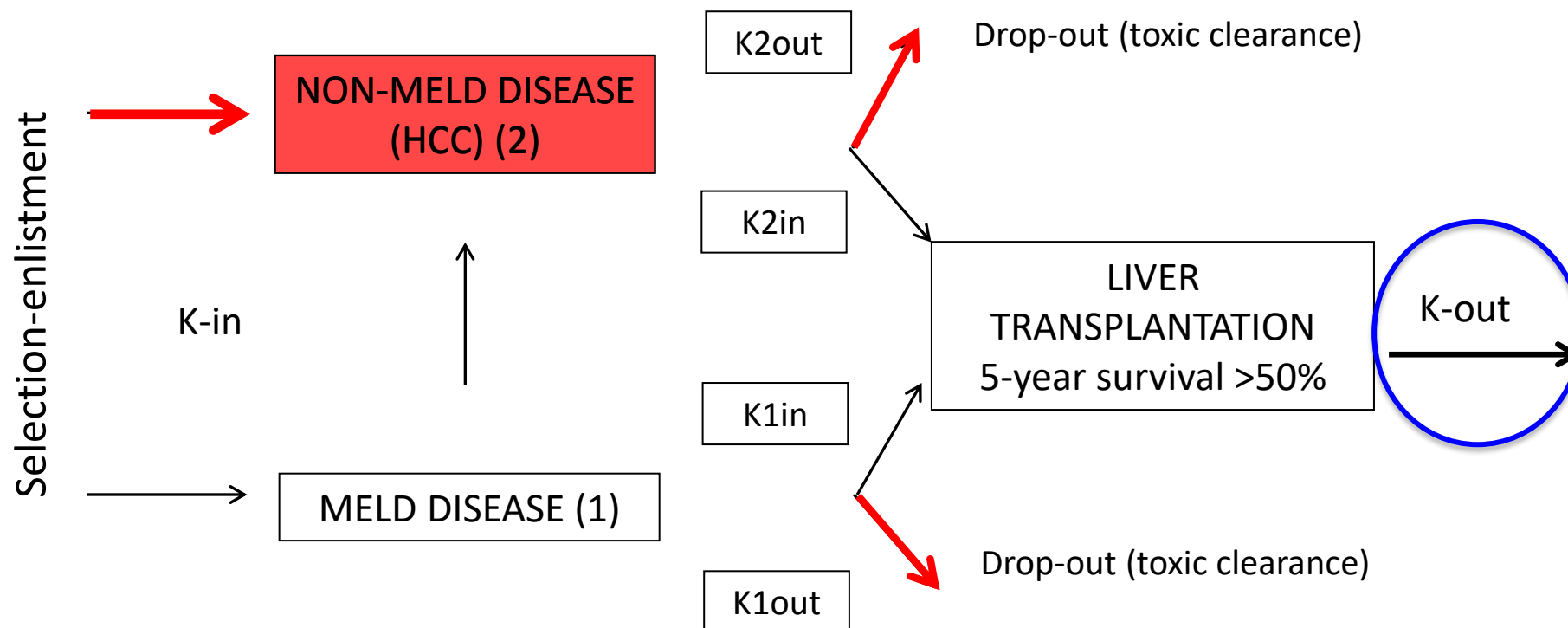
Increase of HCC patients in waiting list if criteria are expanded



Increase of HCC patients in waiting list if criteria are expanded



Increase of HCC patients in waiting list if criteria are expanded



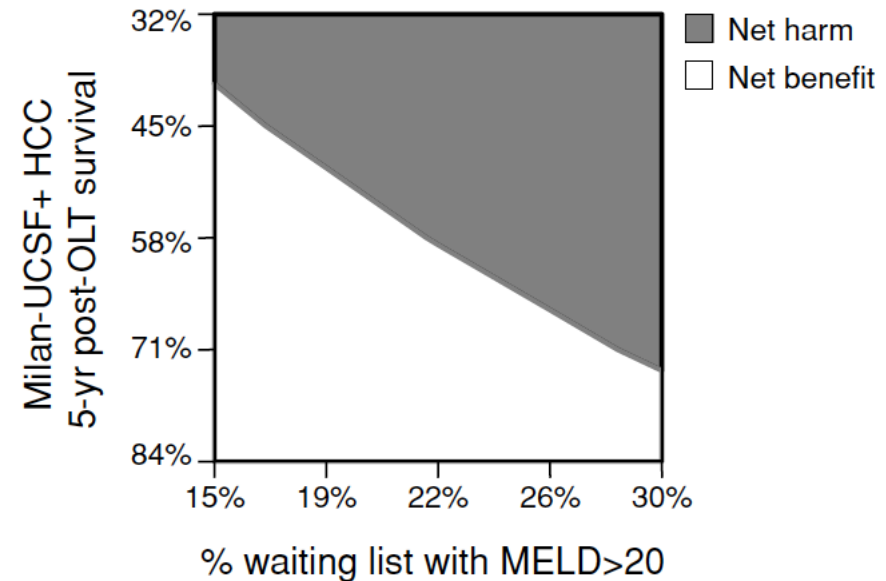
Impact on the waiting list if criteria are expanded

Cost-efficacy study using a Markov model for evaluating the benefit in survival of transplanting patients using expanded criteria compared with the harm caused to the other patients in the waiting list

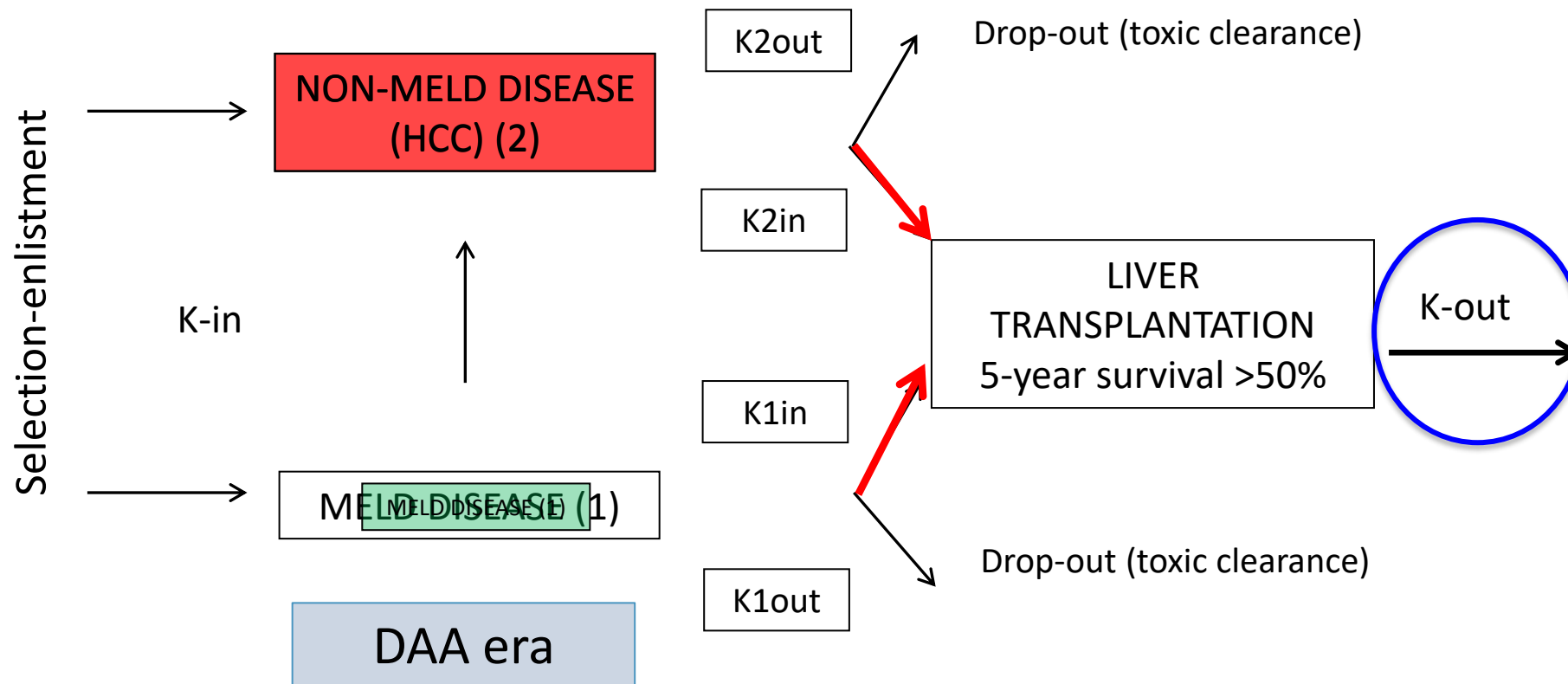
Table 3: Harm caused to individual patients on the waiting list when the patient with Milan-UCSF+ HCC receives an organ¹

Patient subgroup	Increase in mortality risk (per patient)	Quality-adjusted days of life lost (per patient)
HCC within Milan	0.4%	10
MELD 11–20	0.1%	3
MELD 21–30	1.1%	27
MELD >30	4.2%	108

¹Based on national averages for organ arrival rate.




Increase of HCC patients in waiting list if criteria are expanded



Summary

- There is life beyond “Milan”
- A discreet expansion will allow an acceptable results
- There is a need of surpassing the criteria based exclusively on size and number of nodules
- The application of expanded criteria should be done if the local dynamics of the waiting list does not harm the other included patients (both the HCC patients and those with advanced liver disease)



 @Alexfornergon
aforner@clinic.cat



MÁSTER EN HEPATOLOGÍA



UAM
Universidad Autónoma
de Madrid



Universidad
de Alcalá