MÁSTER EN HEPATOLOGÍA

UAM Universidad Autónoma de Madrid

Universidad de Alcalá

Asignatura : Hepatocarcinoma

“Criterios expandidos de resección y trasplante como tratamiento de rescate”

Alejandro Forner

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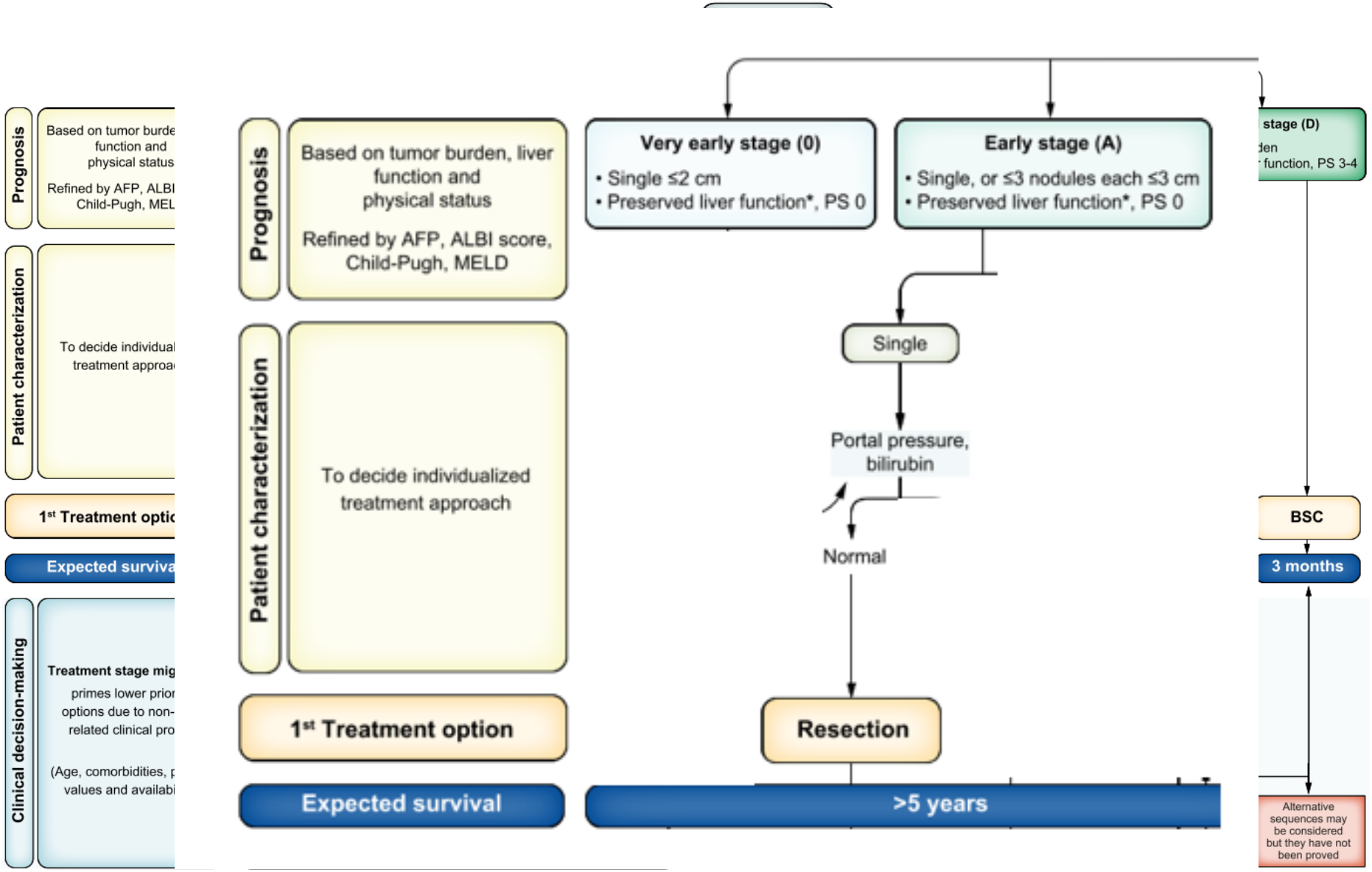
Agenda

- Resection: Indications and challenging scenarios
- Liver transplantation: Where are the limits?
- Resection vs. Liver transplantation

Agenda

- Resection: Indications and challenging scenarios
- Liver transplantation: Where are the limits?
- Resection vs. Liver transplantation

BCLC Staging and Treatment Strategy, 2022



Reig M, Forner A, Rimola J, et al. J Hepatol. 2022;Mar;76(3):681-693.

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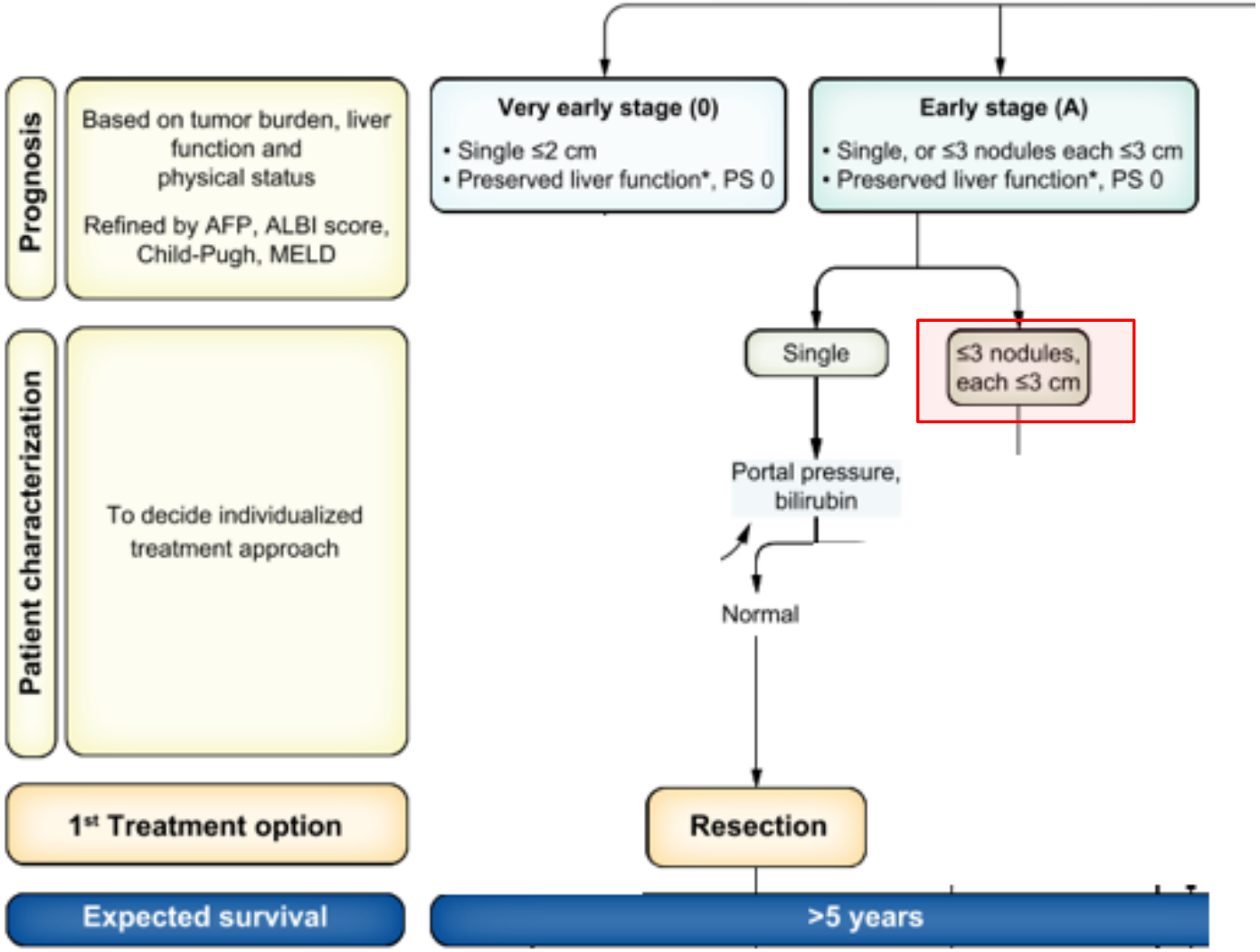

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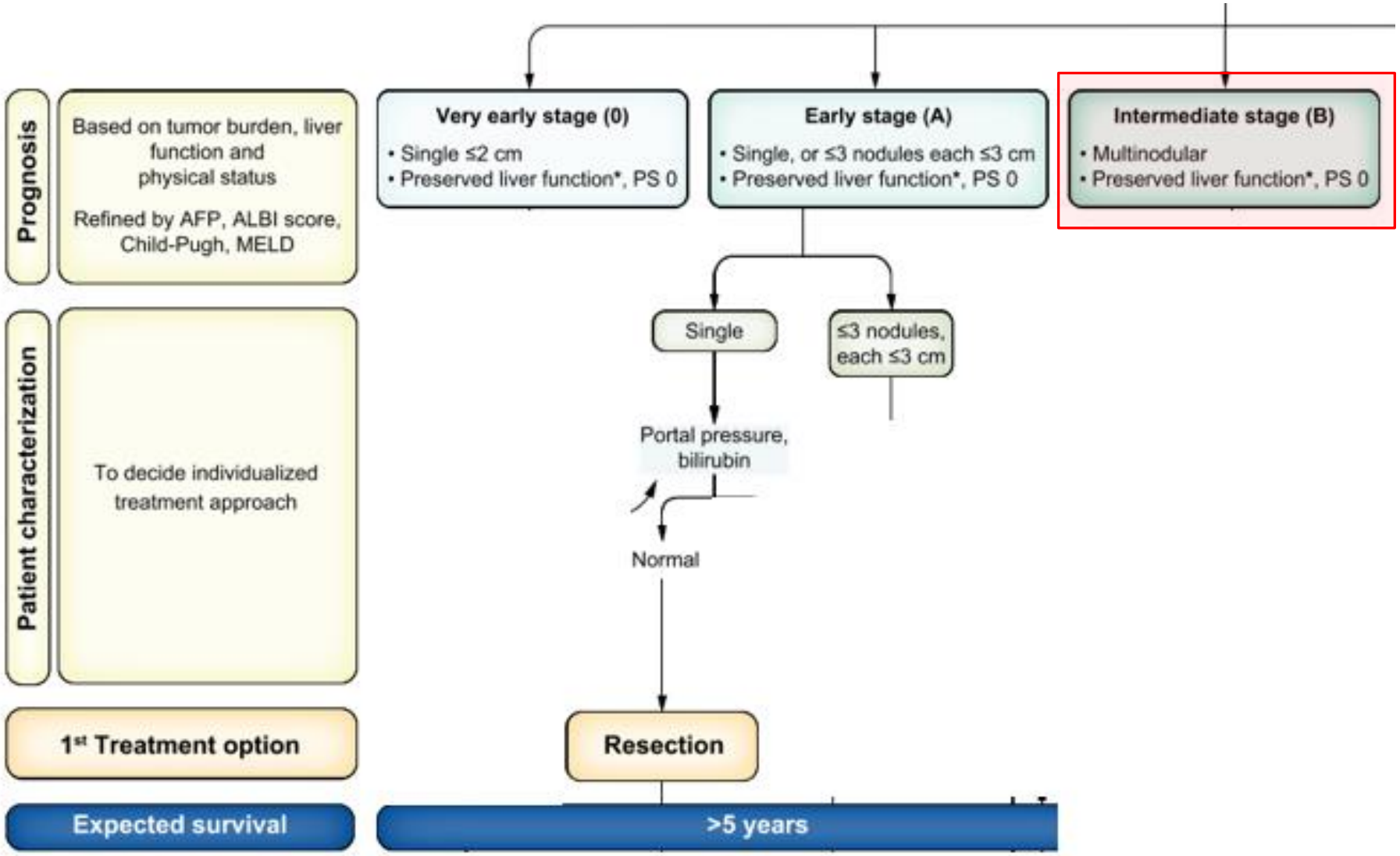

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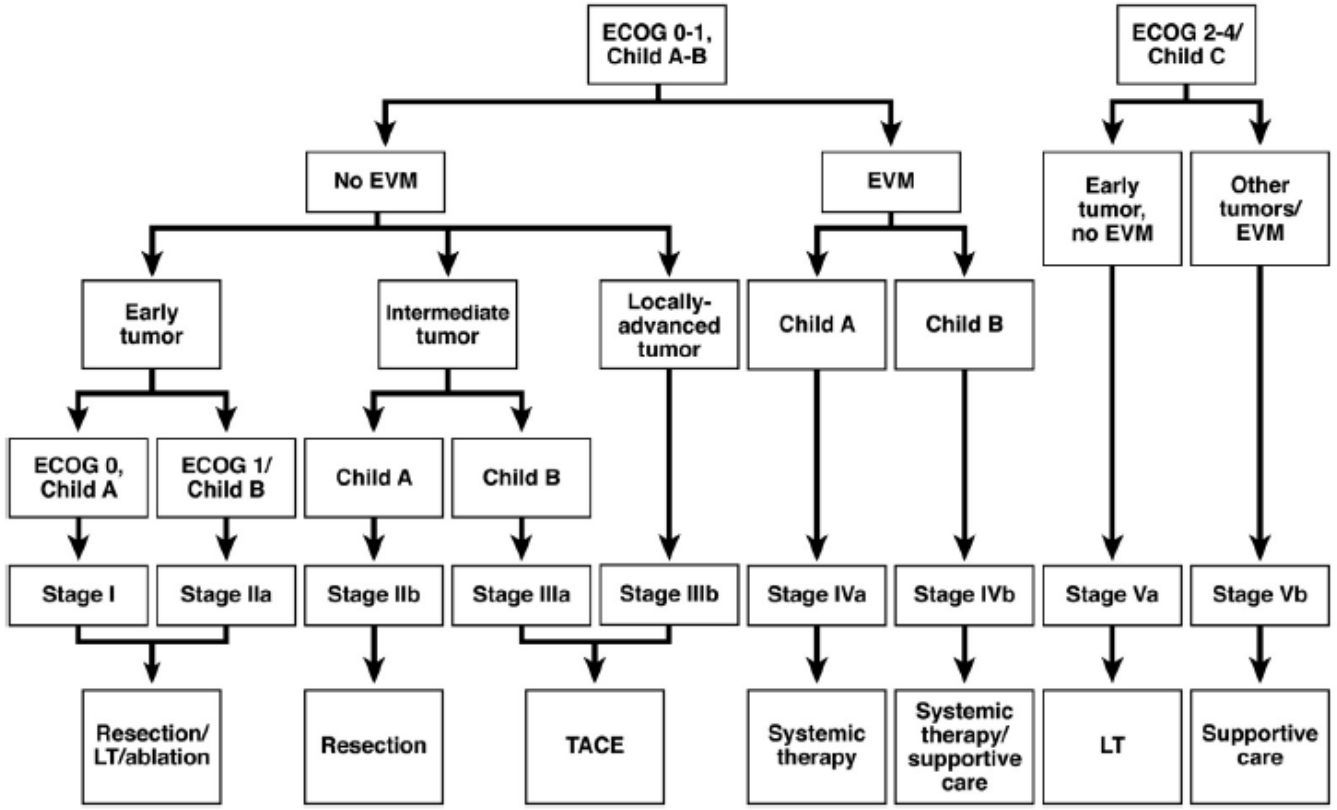
Curative treatments: Surgical Resection

Resection in intermediate HCC



Yau et al. Gastroenterology 2014;146:1691-1700.

Curative treatments: Surgical Resection

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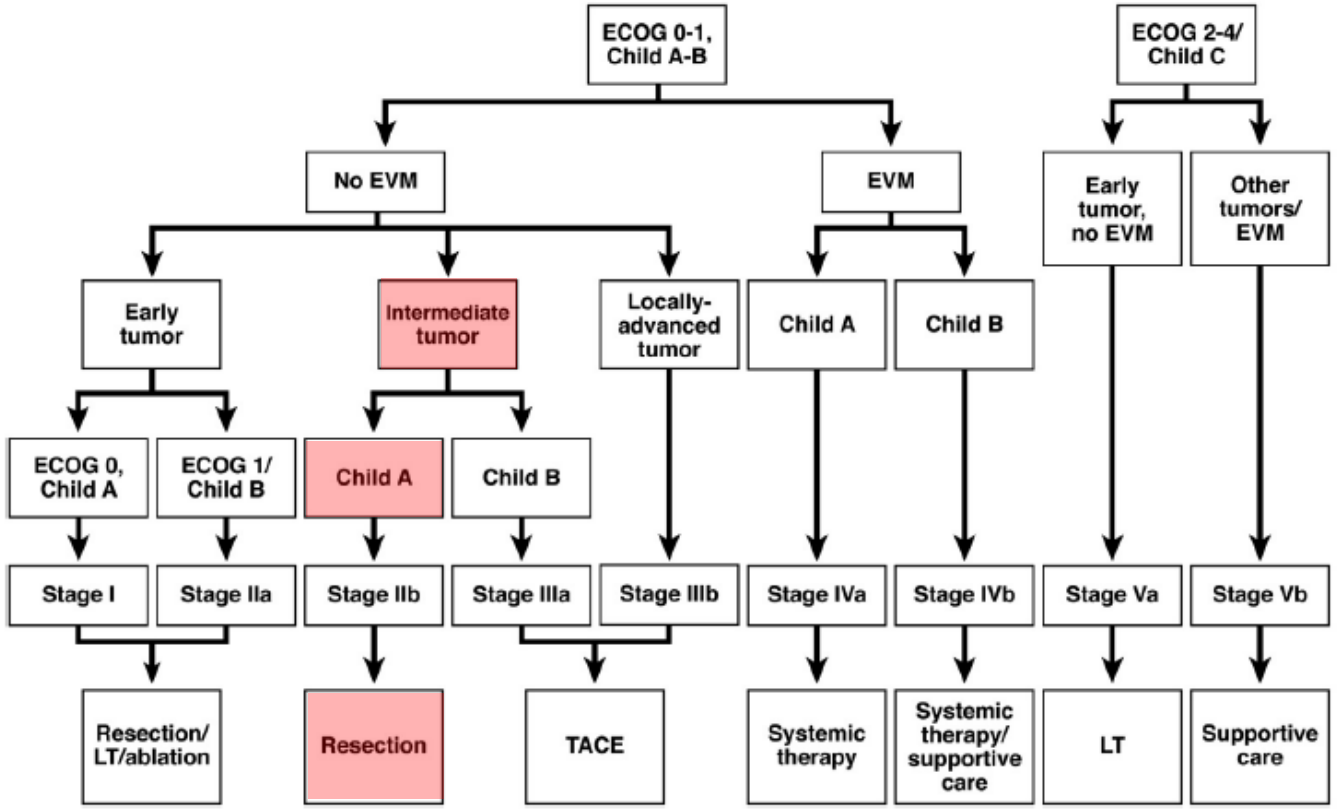

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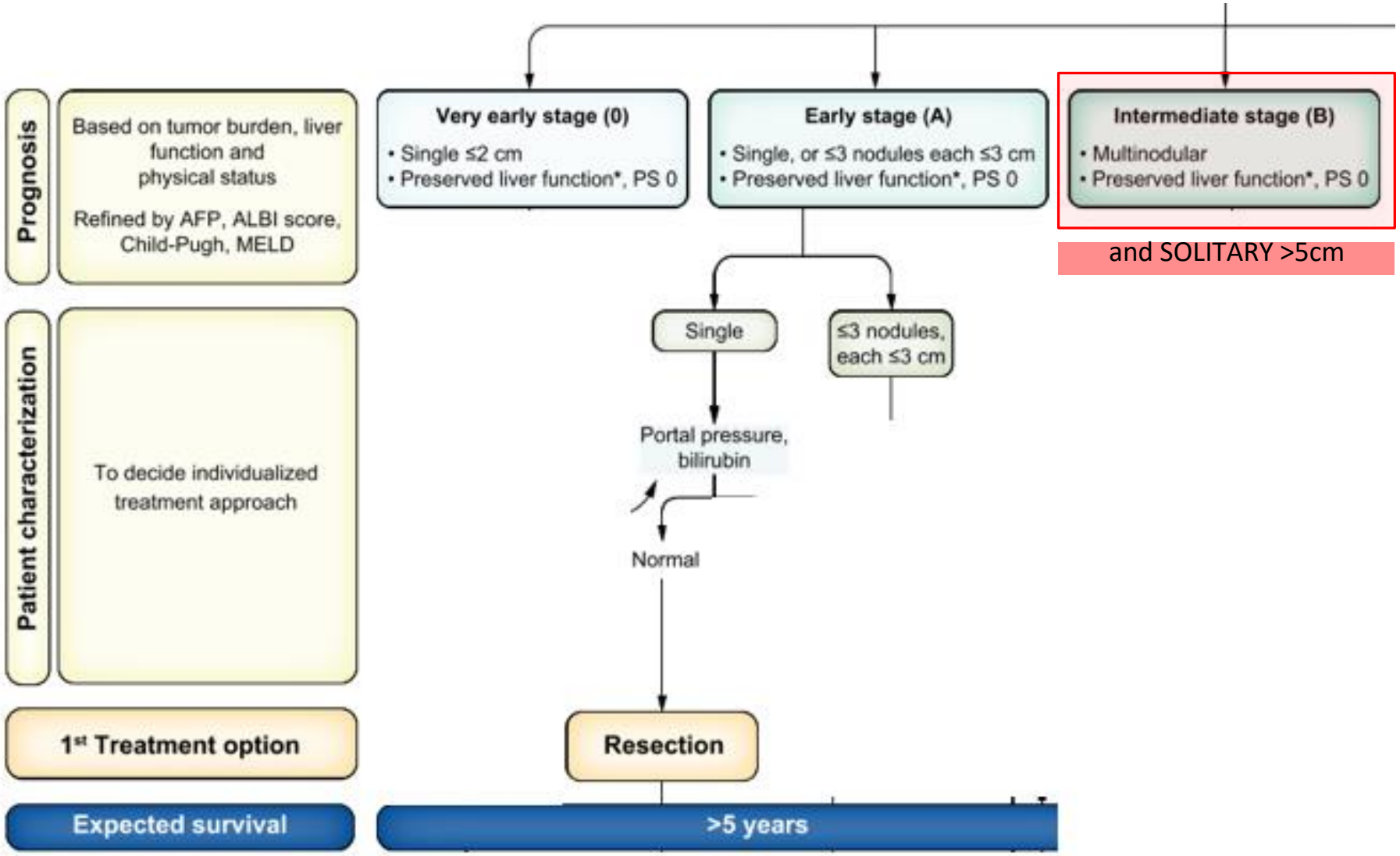
Curative treatments: Surgical Resection

Resection in intermediate HCC

- The problem of definition

BCLC Staging and Treatment Strategy, 2022



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Curative treatments: Surgical Resection

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 Pinna[1]

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)
$Anti\text{-}HCV^+$ (%)	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, $\times 10^3$/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.

Cucchetti A et al. Hepatology. 2015:61(3):905-914

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"

Forner A et al. Nature Reviews Clinical Oncology. 2015:12; 295.
EASL Guidelines. J Hepatol 2018;69:182–236.

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 Yin[1], Hui Li[2,†], Ai-Jun Li[1,†], Wan Yee Lau[1,3], Ze-ya Pan[1], Eric C.H. Lai[1,3], Meng-chao Wu[1], Wei-Ping Zhou[1,*]

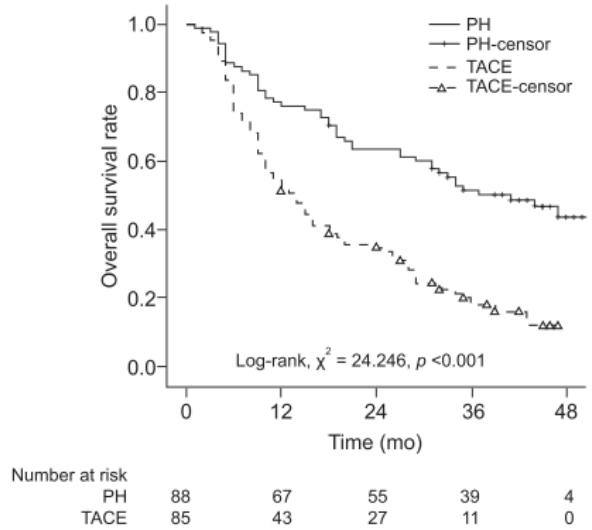


Fig. 2. Overall survival curves for PH and TACE.

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.

Yin L, et al. J Hepatol. 2014 Jul;61(1):82–8.

Curative treatments: Surgical Resection

Resection in intermediate HCC: the problem of comparator

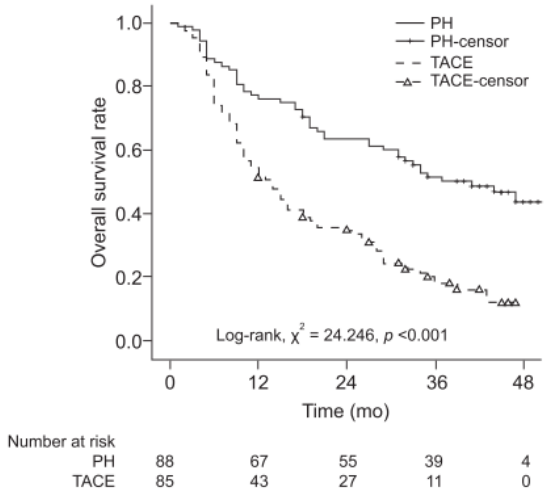
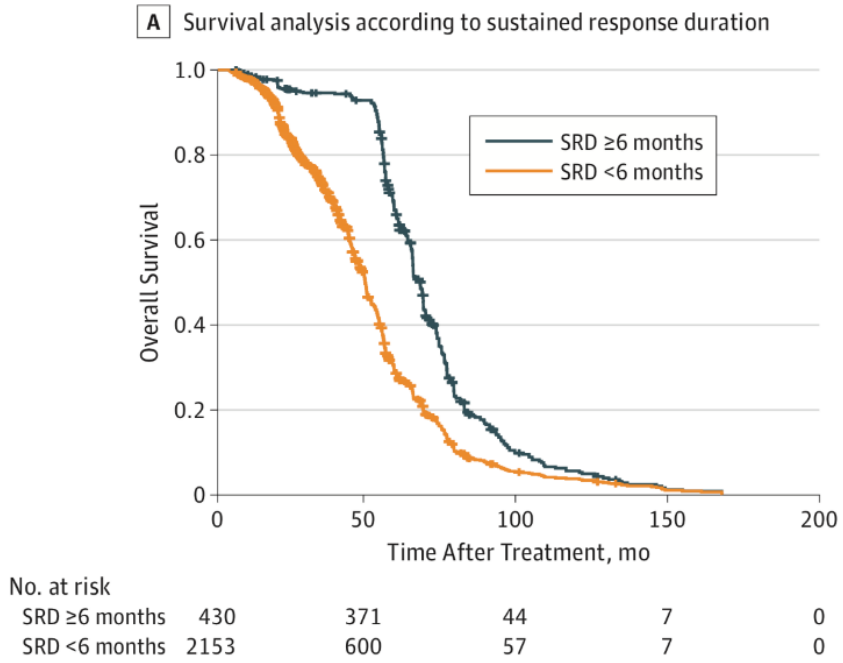


Fig. 2. Overall survival curves for PH and TACE.

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



2 5 8 1 4 7 0 3 6 9 2 5

Time since treatment start (months)

group

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)

Yin L, et al. J Hepatol. 2014 Jul;61(1):82–8.

Zhang Y, et al. JAMA Netw Open. 2018;1(6):e183213. doi:10.1001/jamanetworkopen.2018.3213

Curative treatments: Surgical Resection

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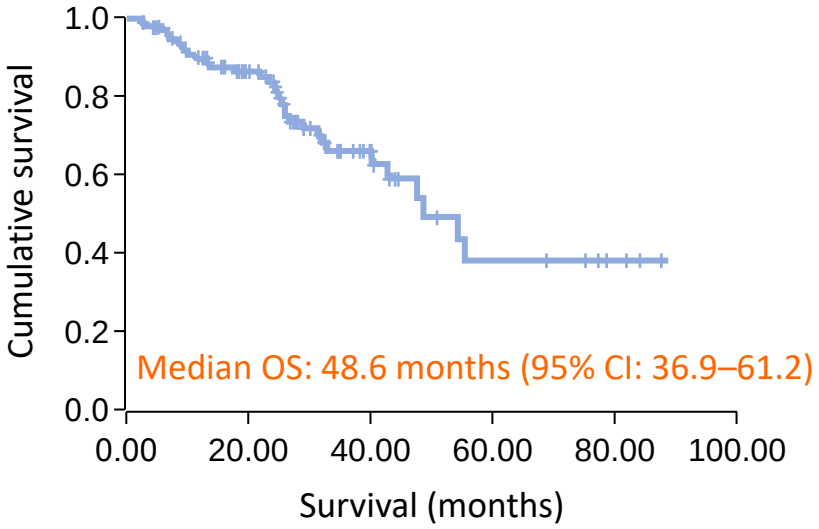


Child class (*n*)		1 year (%)	2 year (%)	3 year (%)	4 year (%)	5 year (%)
A						
21	One dominant ≤ 5 cm	100	95.2	71.4	66.6	47.6
37	One dominant > 5 cm	97.3	89.1	85.1	43.3	32.4
31	Multinodular ≤ 5 cm	93.5	90.3	61.3	41.9	25.8
13	Multinodular > 5 cm	84.6	69.2	46.1	15.3	0
102	Overall	95	88.2	61.7	45	29.4
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

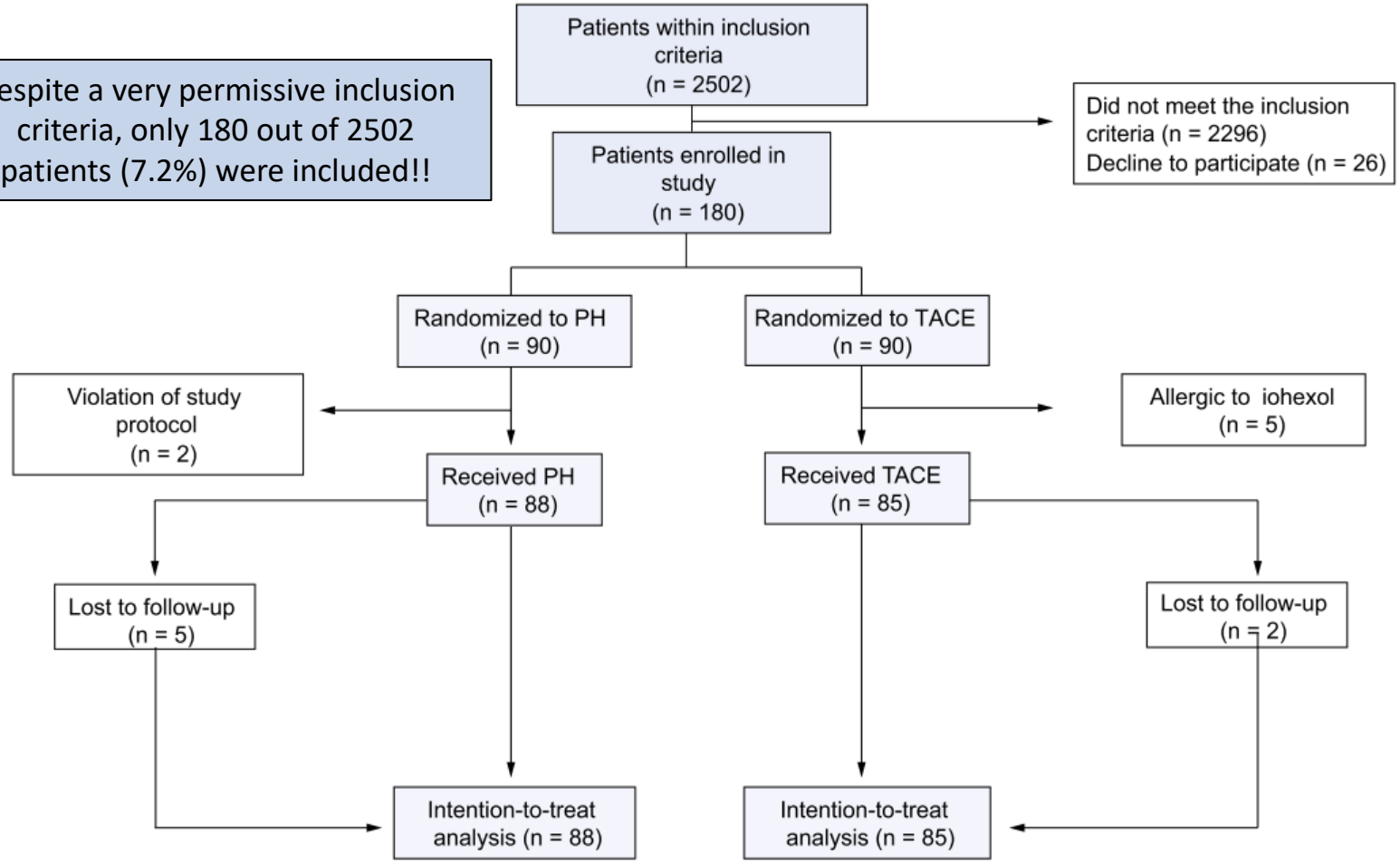
Burrel M, Reig M, et al. J Hepatol. 2012:56(6);1330-5

Malagari K, et al. CVIR 2012; 35: 119-1128

Curative treatments: Surgical Resection

Resection in intermediate HCC: the problem of comparator

Despite a very permissive inclusion criteria, only 180 out of 2502 patients (7.2%) were included!!



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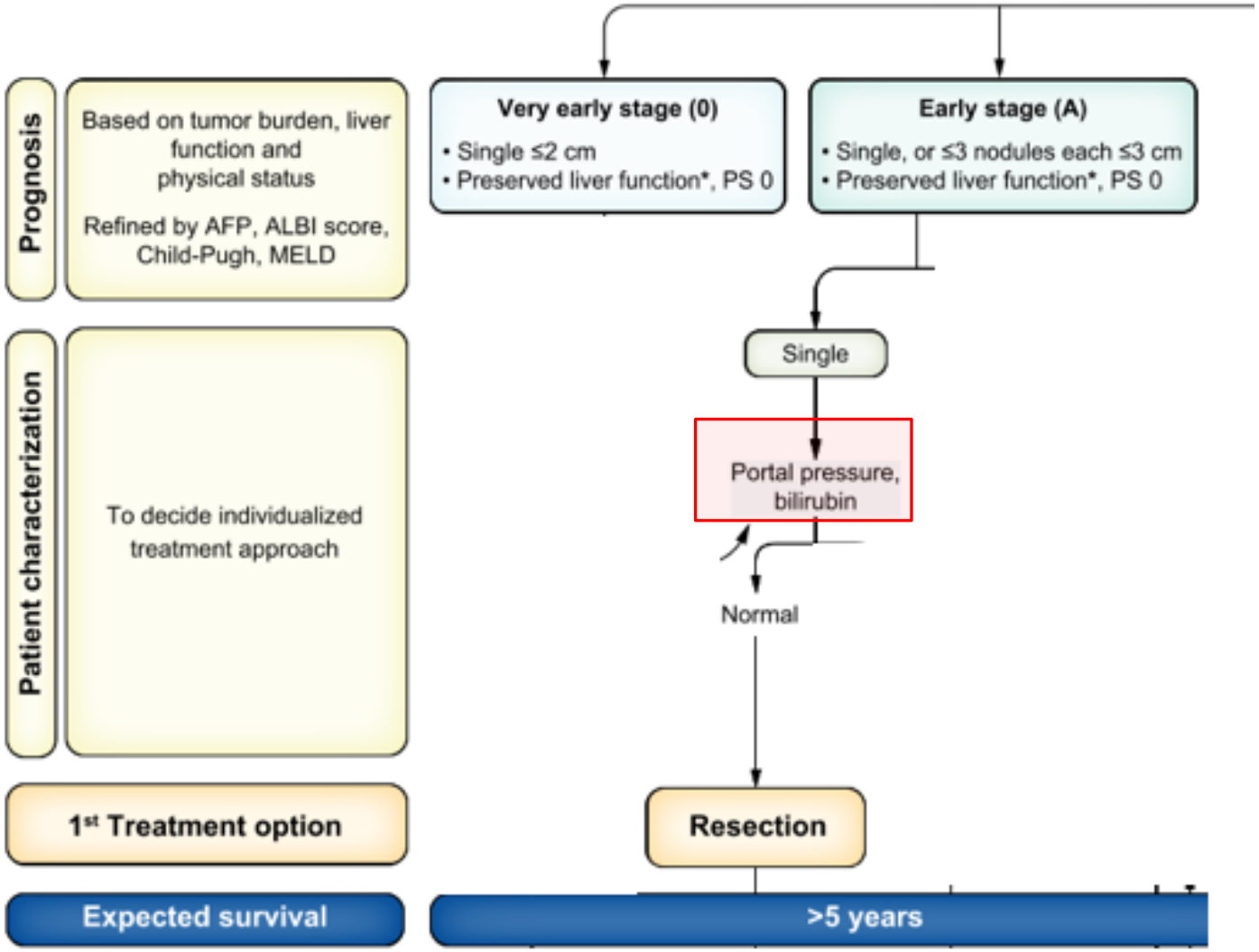
BCLC Staging and Treatment Strategy, 2022



Reig M, Forner A, Rimola J, et al. J Hepatol. 2022;Mar;76(3):681-693.

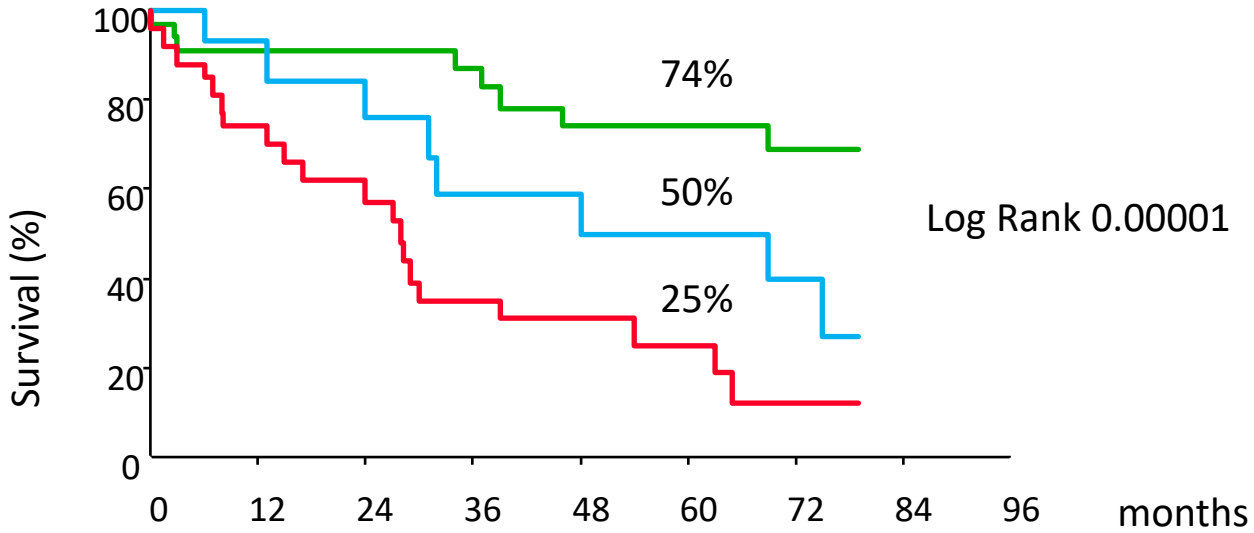
Curative treatments: Surgical Resection

Prognostic role of clinically significant portal hypertension

Best candidates: - Solitary HCC

- Child-Pugh A: No portal hypertension (HVPG < 10 mmHg)

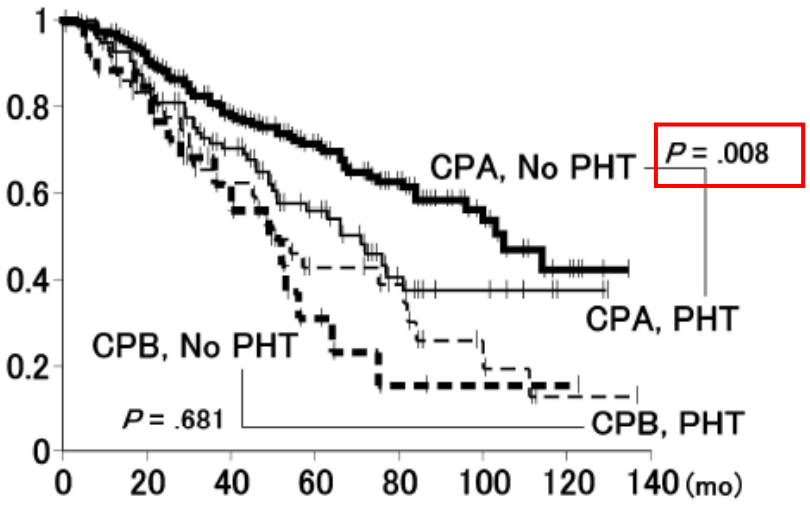
Normal Bilirubin (< 1 mg/dl)



Llovet JM, et al. Hepatology. 1999;30:1434-40.

Curative treatments: Surgical Resection

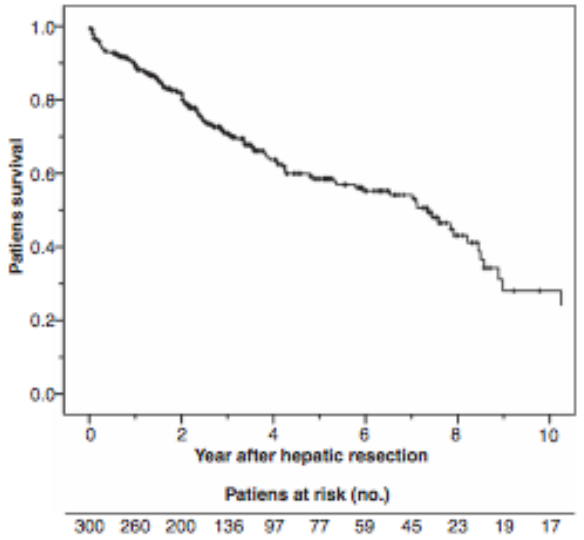
Prognostic role of clinically significant portal hypertension



5-years survival:

CP A, No PHT: 71%

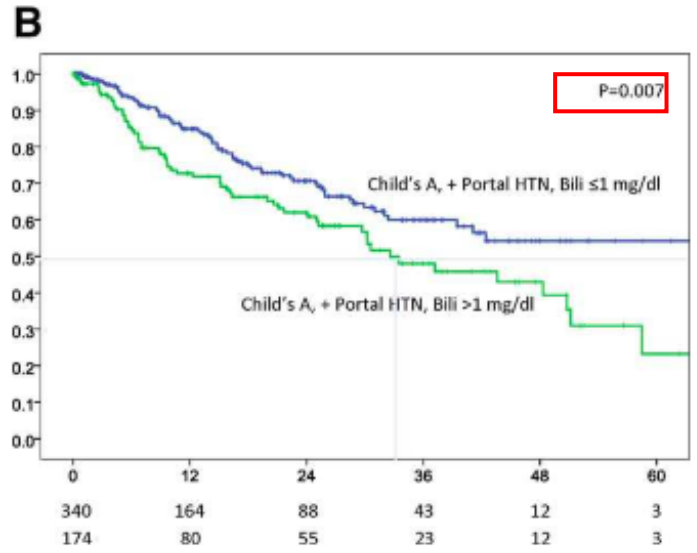
CP A, PHT: 56%



5-years survival:

Overall: 57.7%

CP A, No PHT: 63.8%



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

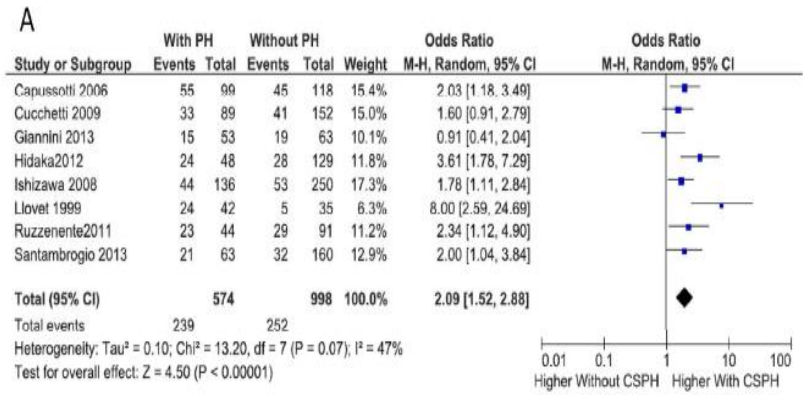
Cucchetti A, et al. Clin Cancer Res. 2012:18(16);4397-4405.

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

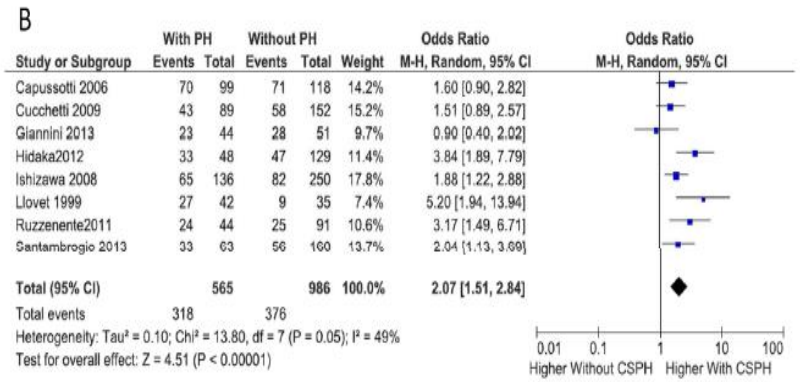
Curative treatments: Surgical Resection

Meta-analysis of the impact of CSPH on postoperative outcomes

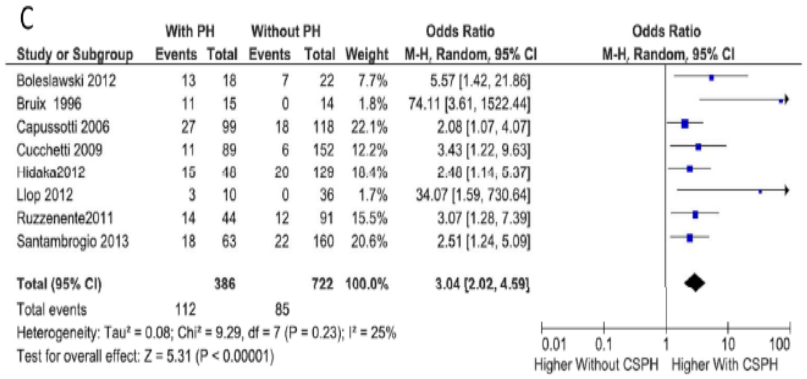
Panel A: 3-year mortality



Panel B: 5-year mortality



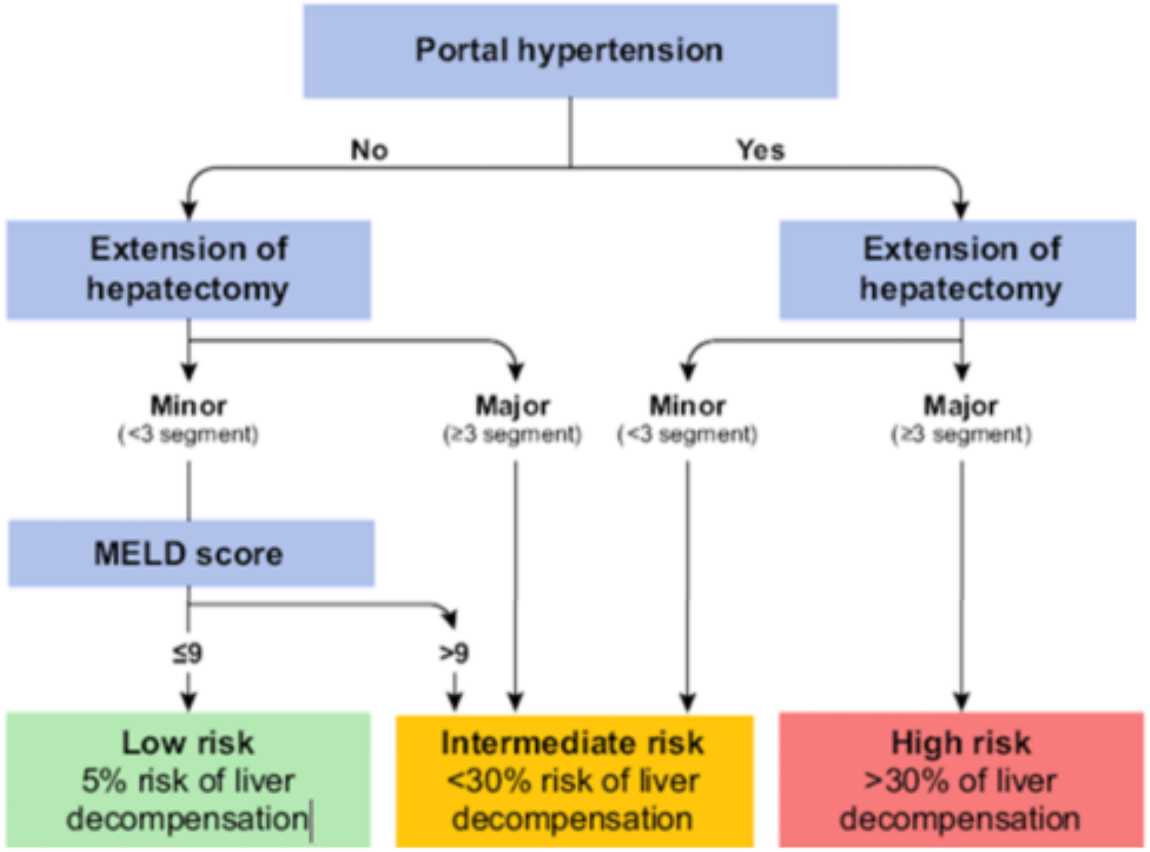
Panel C: clinical decompensation

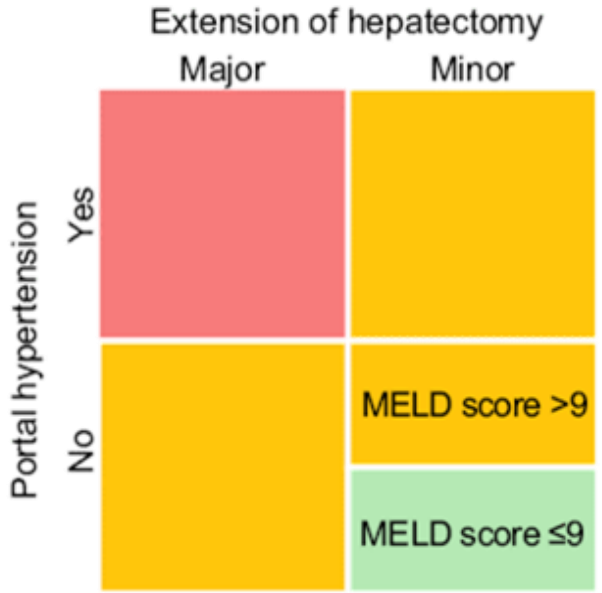


Berzigotti A, Reig M, et al, Hepatology. 2015 Feb;61(2):526-36.

Curative treatments: Surgical Resection

Redefinition of CSPH as a contraindication for surgical resection





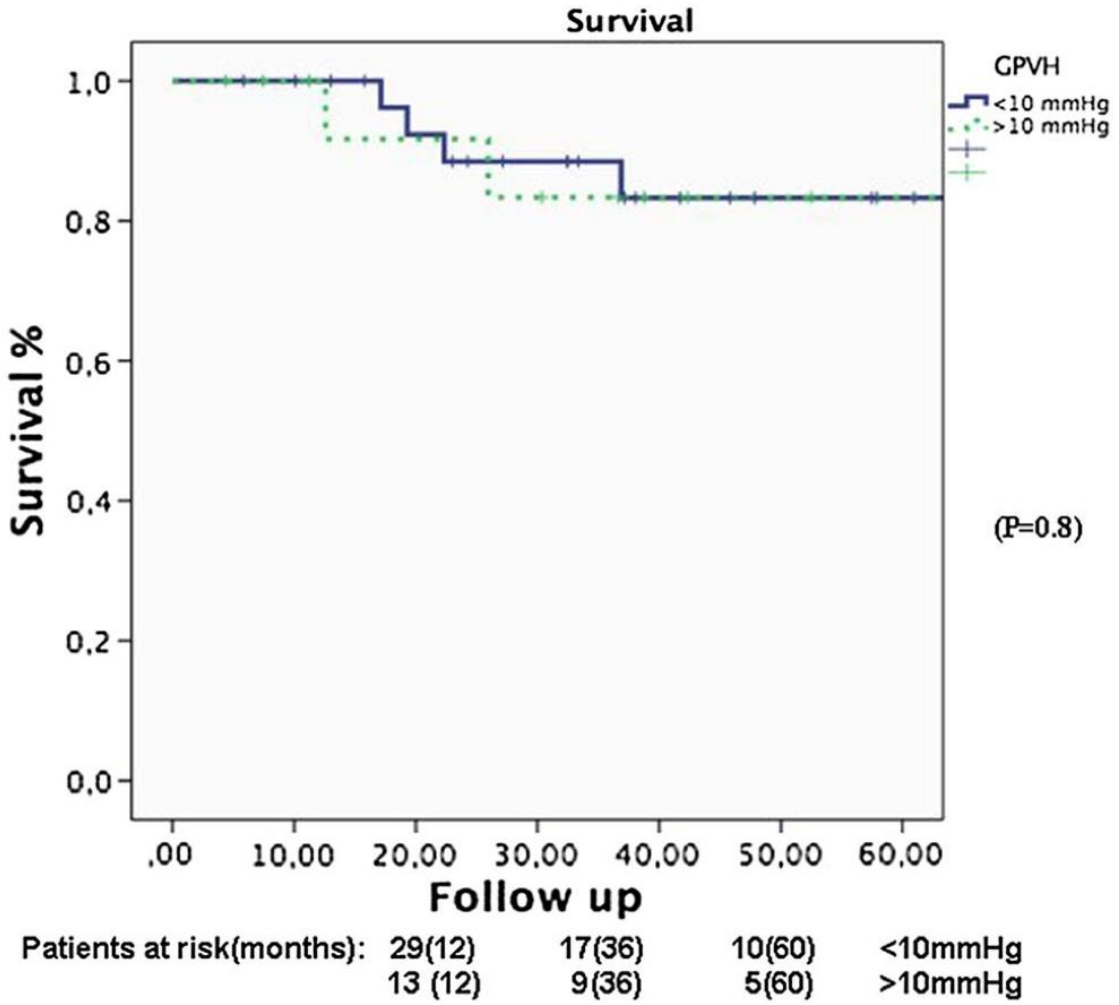
Citterio D, et al. JAMA Surg. 2016 Sep 1;151(9):846-53.

Curative treatments: Surgical Resection

Laparoscopic approach may expand resection in patients with CSPH

Table 5 Postoperative data

Variable	Non-CSPH $N=30$	CSPH $N=15$	p 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



Molina V, et al Surg Endosc. 2018;32(5):2345-2354. doi:10.1007/s00464-017-5930-1

Resection: Indications and challenging scenarios

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

Agenda

- Resection: Indications and challenging scenarios
- Liver transplantation: Where are the limits?
- Resection vs. Liver transplantation

Curative treatments: Liver transplantation

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

Beyond Milan criteria

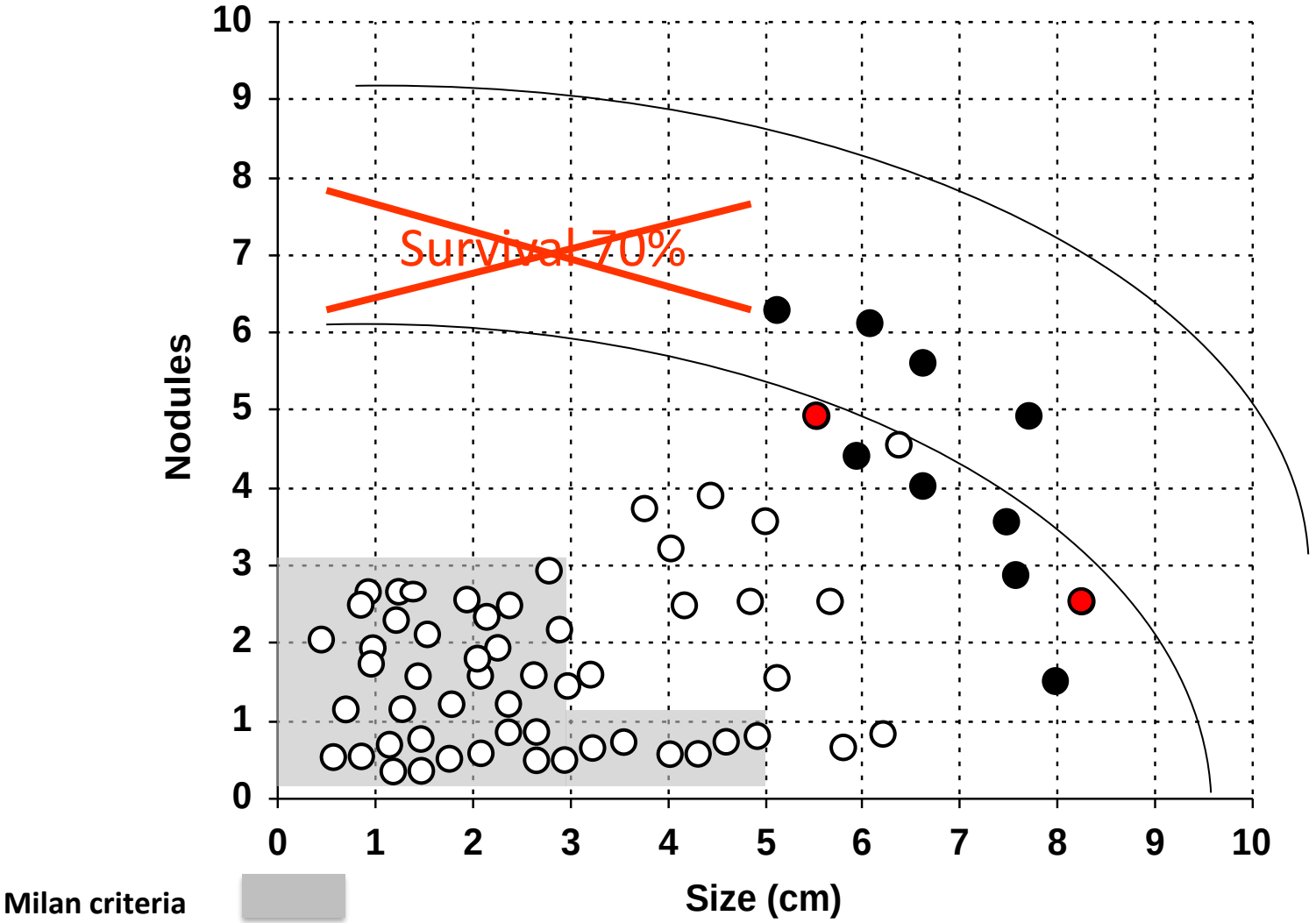
Expanded criteria

		5-year survival	
Author (year)	Criteria	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



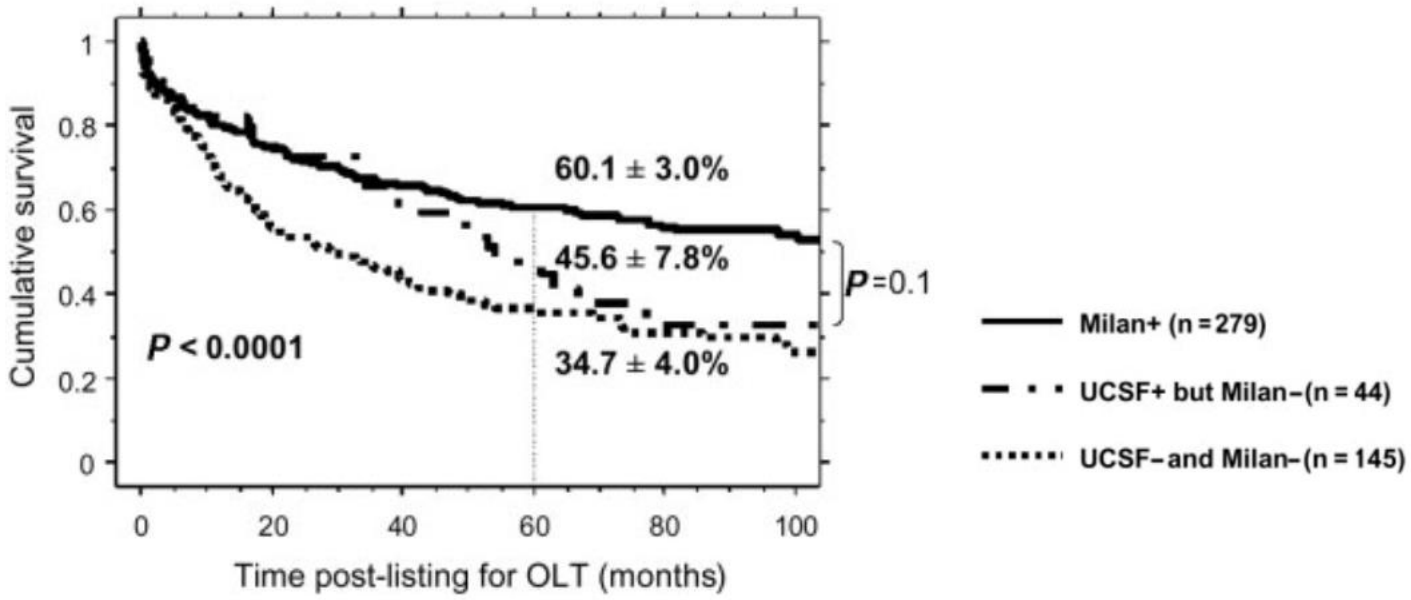
Majno P, Mazzaferro V. Liver Transpl. 2006;12:896-8.

Beyond Milan criteria

External validation of UCSF criteria

Retrospective analysis of 479 HCC patients:

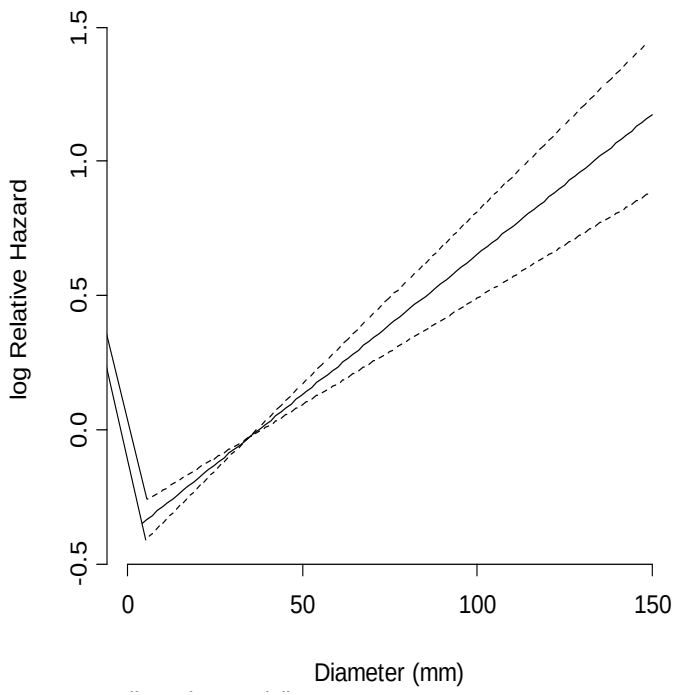
- 279 patients Milan in
- 44 patients Milan out but UCSF in (10% of total cohort)
- 145 patients Milan and UCSF out



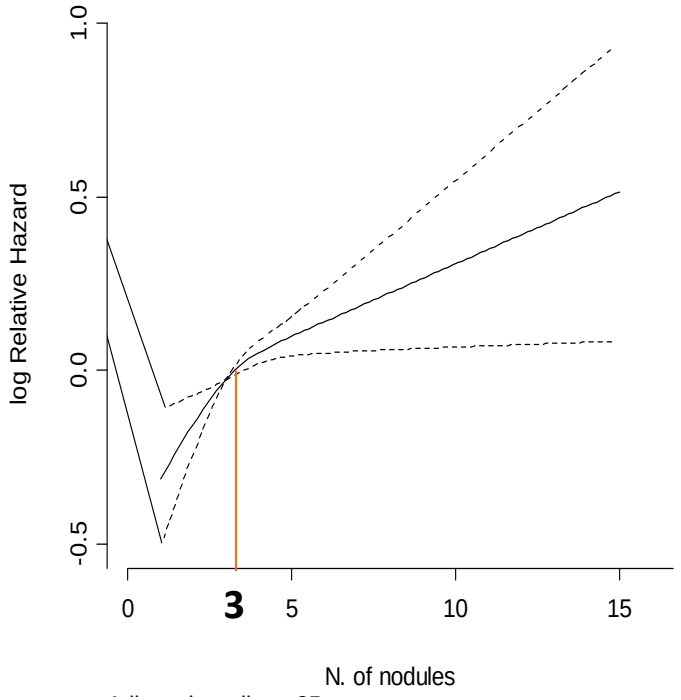
Decaens T et al. Liver Transpl. 2006:12:1761-1769.

Beyond Milan criteria

Metroticket study (n=1.556)



Adjusted to number nodules=3



Adjusted to diameter= 35 mm

The risk of death exponentially increase with the size

The risk increase up to 3 nodules, achieving afterwards a plateau

Mazzaferro V, et al. Lancet Oncol. 2009;10:35-43.

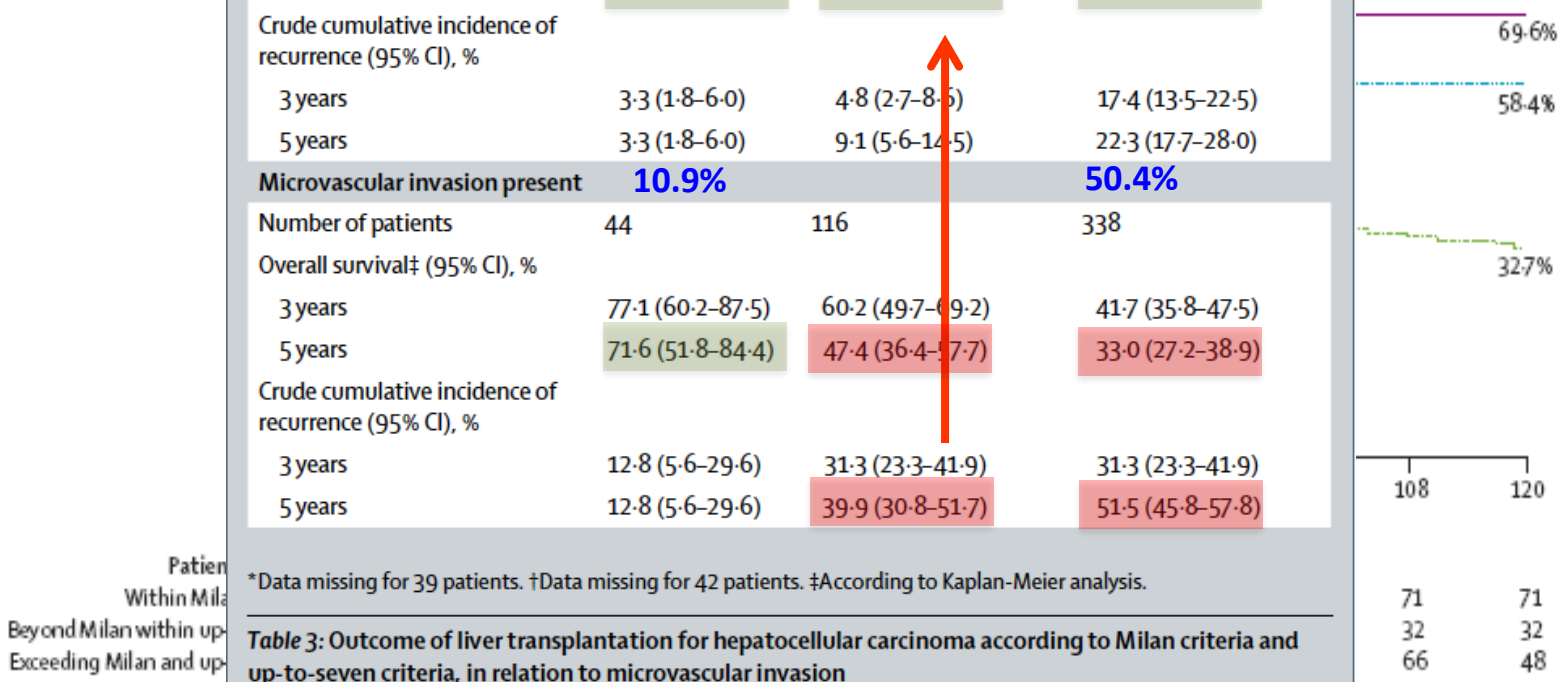
Metroticket analysis

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 (2·7–8·6)	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)

*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**



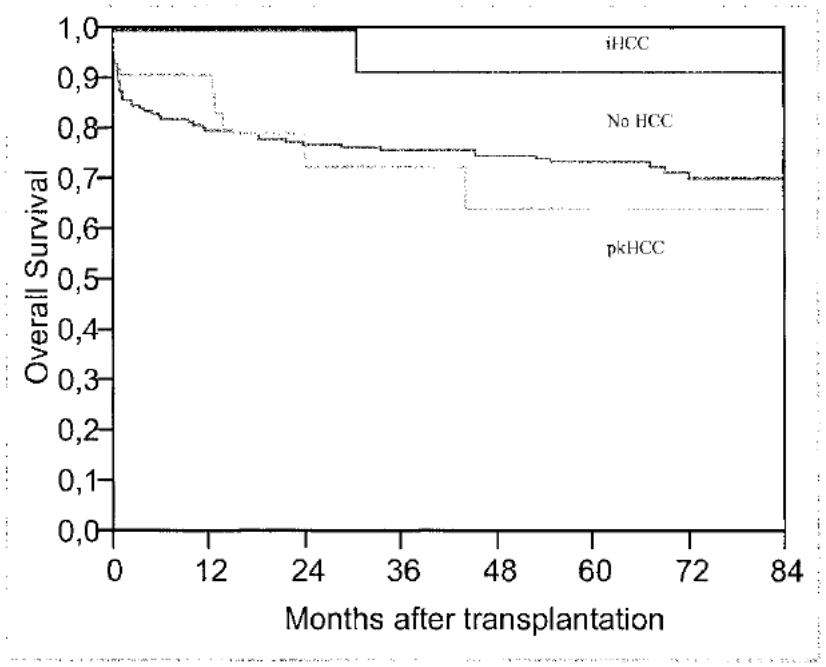
Median follow-up: 53 months

Mazzaferro V, et al. Lancet Oncol. 2009;10:35-43.

Biological markers as selection criteria

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)

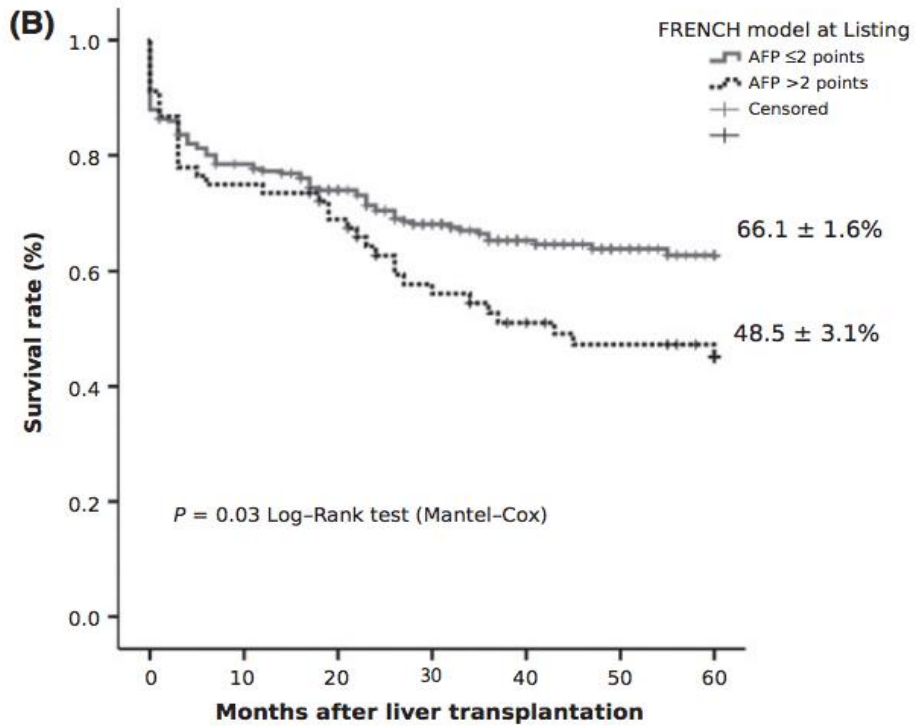


Limitations:
-Tumor heterogeneity
-No specific information regarding the survival in those outside Milan
-Retrospective: Only those transplanted are analyzed

Cillo U et al. Ann Surg. 2004;239(2):150-159.

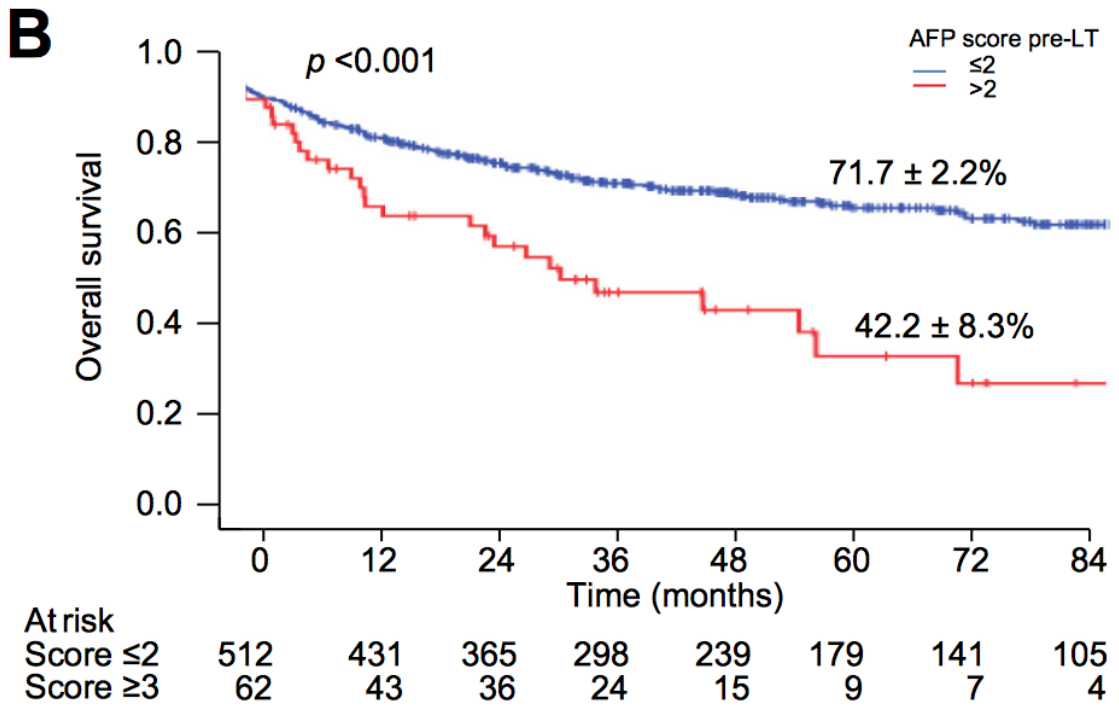
Biological markers as selection criteria

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

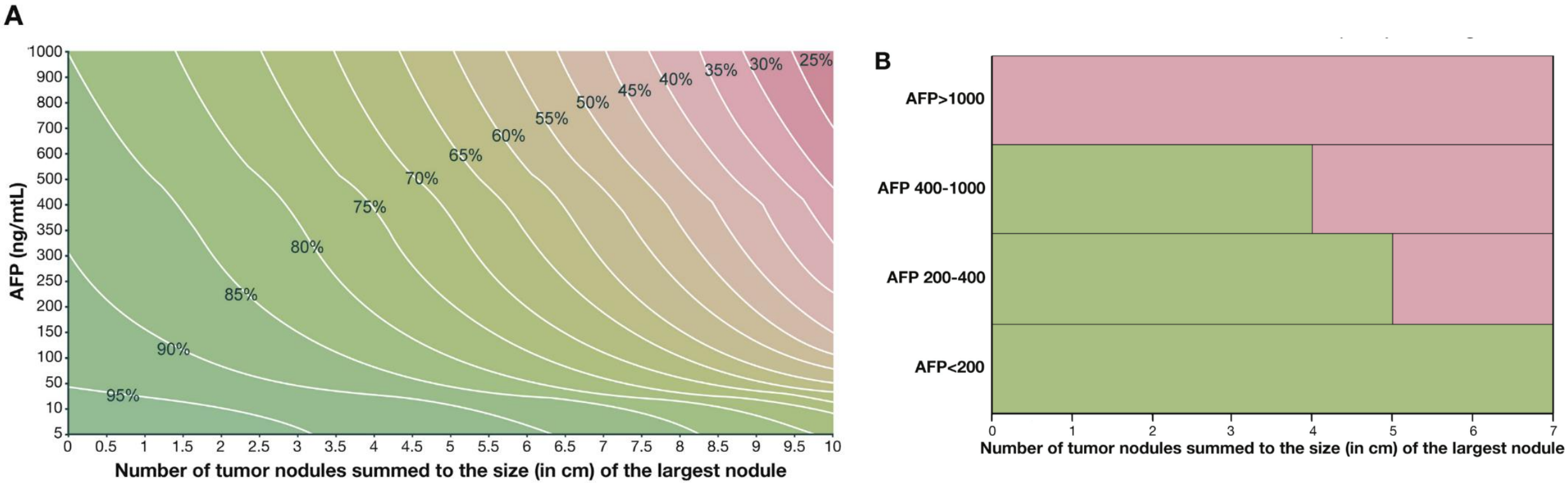
Piñero F et al. Liver Int. 2016 Nov;36(11):1657-1667.



Notarpaolo A, et al. J Hepatol. 2017;66:552–9.

Biological markers as selection criteria

Metroticket 2.0: The value of AFP



Mazzaferro V, et al . Gastroenterology 2018;154:128–39.

Beyond Milan criteria

Expanded criteria

		5-year survival		5-year survival Exceeding Milan criteria	
Author (year)	Criteria	Patients	Survival	Patients	Survival
Yao, 2001	Post-LT, explant Solitary tumor ≤ 6.5 cm or ≤ 3 tumors ≤ 4.5 cm	70	75%	N/A	N/A
Duffy, 2007	Post-LT, radiology/explant Solitary tumor ≤ 6.5 cm or ≤ 3 tumors ≤ 4.5 cm	208	64-81%	82	N/A
Onaca, 2007	Post-LT, explant Solitary tumor ≤ 6 cm or ≤ 4 tumors ≤ 5 cm	758	60%	130	N/A
Lee, 2008	Pre-LT, radiology Larger tumor ≤ 5 cm ≤ 6 nodules	186	76%	N/A	N/A
Toso, 2008	Post-LT, explant Total tumor volume ≤ 115 cm^3	274	74%	N/A	N/A
Herrero, 2008	Pre-LT, radiology One tumor ≤ 6 cm or 3 nodules ≤ 5 cm	85	70%	26	66%
Mazzaferro, 2009	Post-LT, explant "Up-to-seven" criteria	727	74%	283	71.2%

Yao F et al. Hepatology. 2001:33(6);1394-1405.
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.
Mazzaferro V, et al. Lancet Oncol. 2009;10:35-43.

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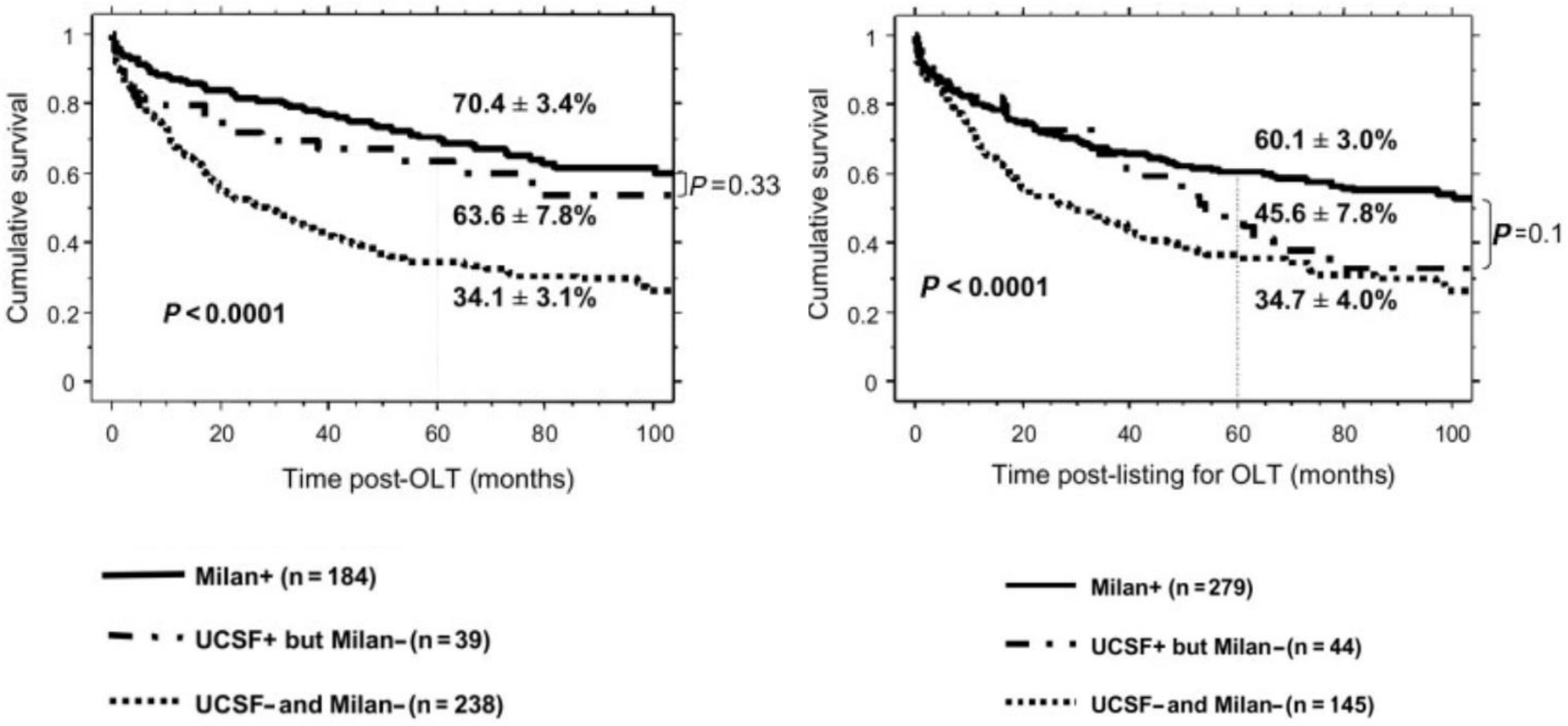
Mazzaferro V, et al. Lancet Oncol. 2009;10:35-43.

Beyond Milan criteria

Imaging versus explant



Decaens T et al. Liver Transpl. 2006:12:1761-1769.

Beyond Milan criteria

Imaging versus explant

Prospective evaluation based on imaging staging using UCSF criteria:
168 patients, 38 of them exceeding Milan criteria but within UCSF

Table 4: Histopathologic tumor characteristics in the liver explant

Pathologic tumor stage	No. of patients (N = 168)	No. with recurrence
T1	11 (6.5%)	0
T2	103 (61.3%)	3 (2.9%)
T3A	29 (17.3%)	1 (3.4%)
T3B	8 (4.8%)	4 (50%)
T4A	12 (7.1%)	1 (8.3%)
T4B	4 (2.4%)	2 (50%)
N1[1]	1 (0.6%)	1 (100%)
Histologic grade[2]	# of patients (N = 124)	# with recurrence
Well-differentiated (grade 1)	52 (41.9%)	0
Moderately differentiated (grade 2)	58 (46.8%)	8 (13.8%)
Poorly differentiated (grade 3)	14 (11.3%)	3 (21.4%)
Vascular invasion[3]	# of patients (N = 168)	# with recurrence
Micro-vascular	14 (8.3%)	5 (35.7%)
Macro-vascular	4 (2.4%)	2 (50%)
No	150 (89.3%)	5 (3.3%)

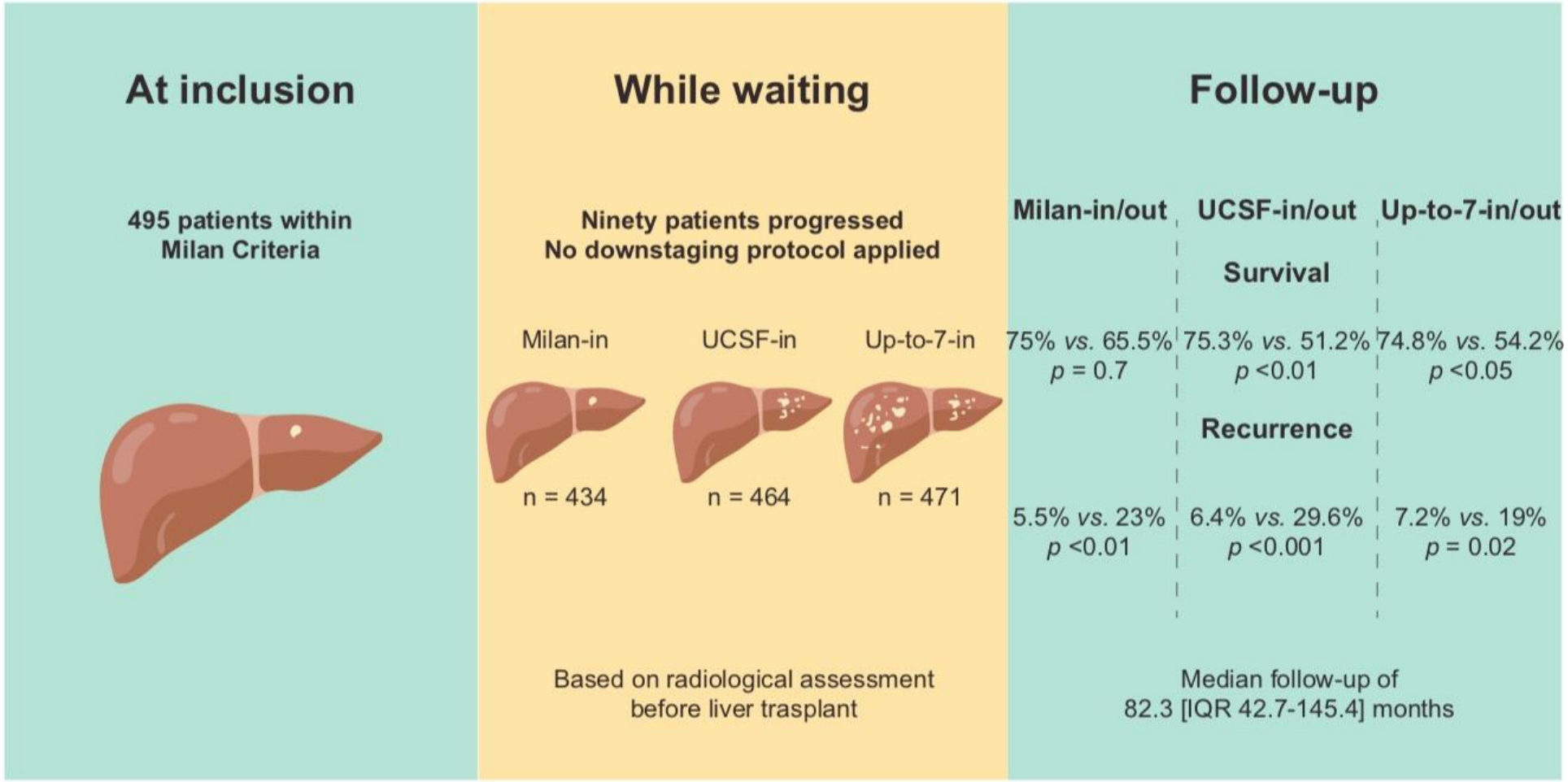
Table 6: Tumor under-staging by preoperative imaging studies

Pretransplant tumor stage	No. with under-staging[1]	No. with recurrence
T2 (N = 122)	24 (19.7%)	6 (25%)
	T3A = 10	1
	T3B = 4	2
	T4A = 7	0
	T4B = 2	2
	N1 = 1	1
T3A (N = 38)[2]	11 (28.9%)	2 (18.2%)
	T3B = 4	1
	T4A = 5	1
	T4B = 2	0

Yao FY. et al. Am J Transp. 2007:7(11):61(6):2587-2596.

Beyond Milan criteria

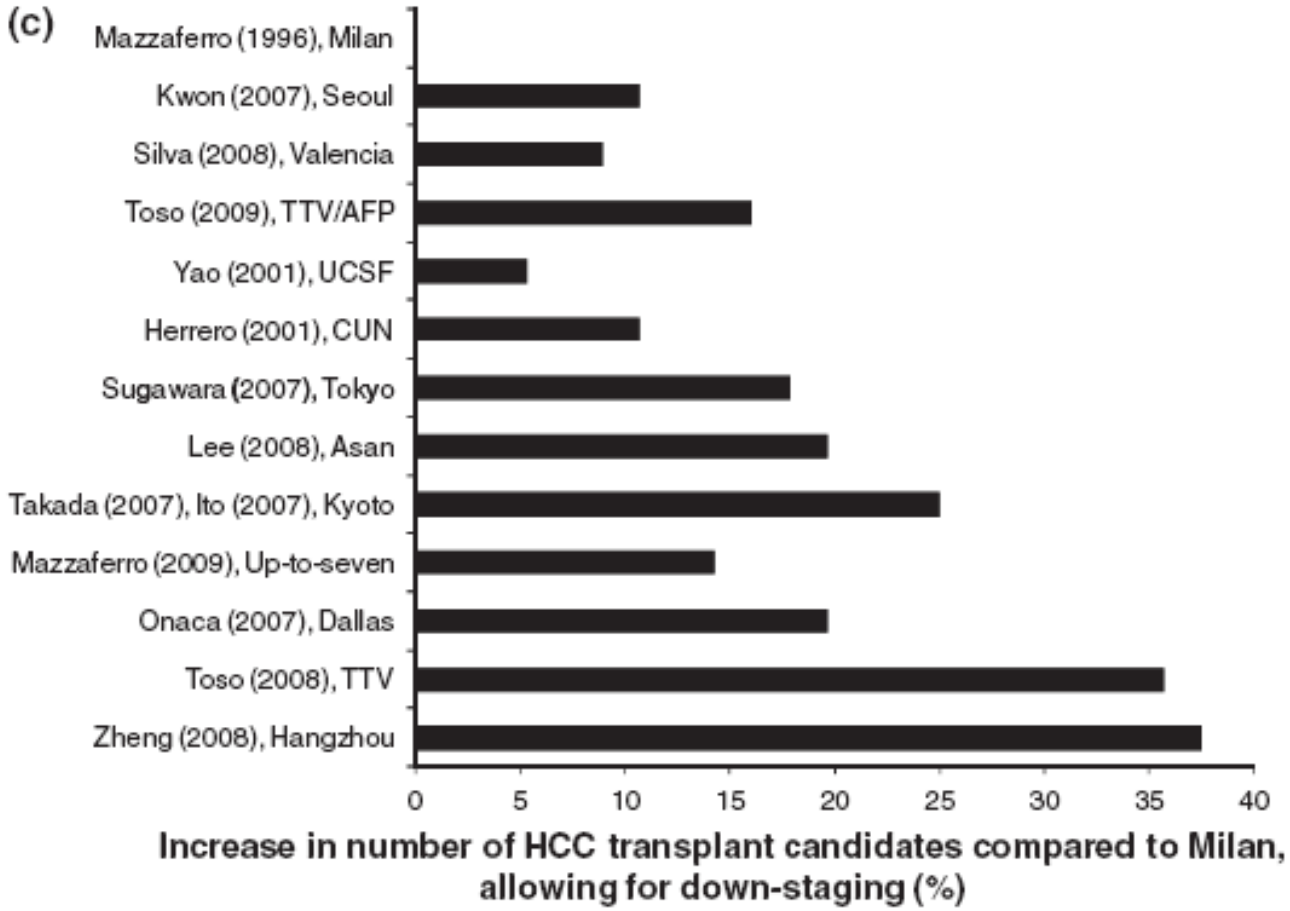
Progression beyond Milan criteria during waiting list



Ferrer-Fàbrega J, et al. J Hepatol. 2021;75:1154–1163.

Beyond Milan criteria

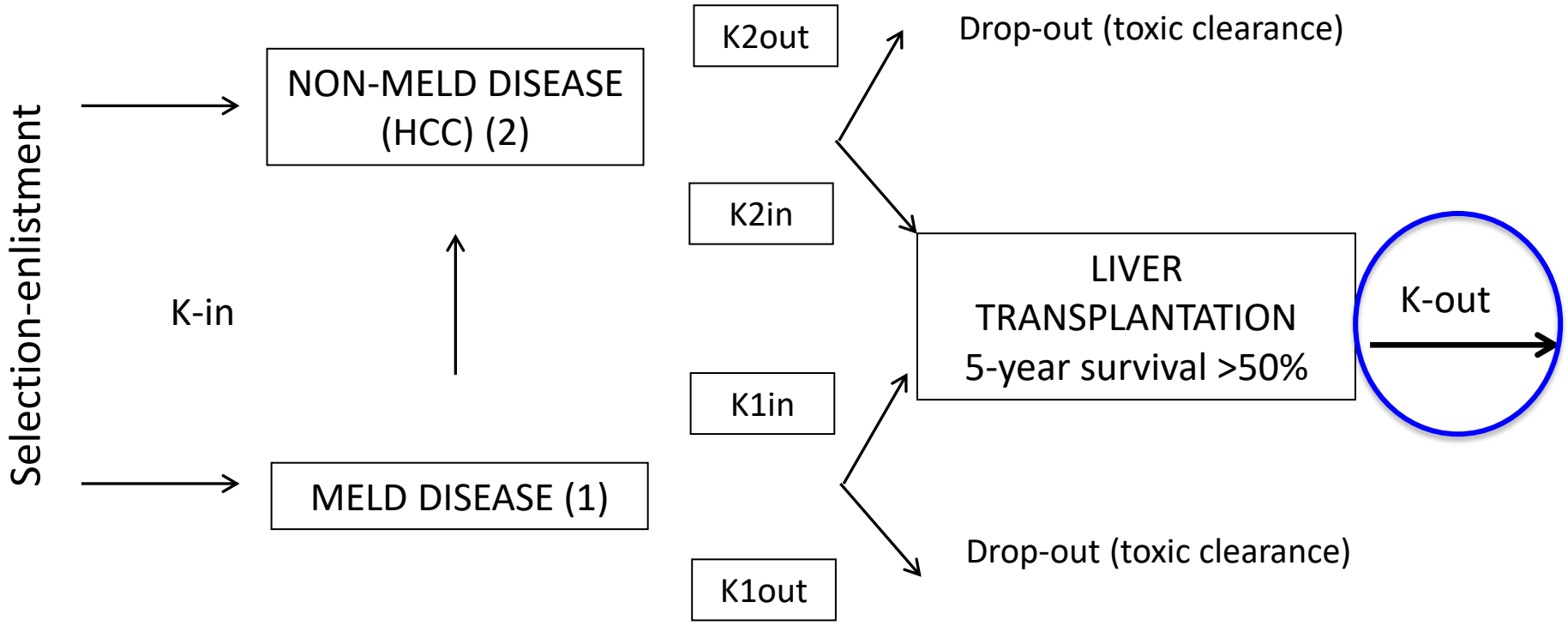
Increase of HCC patients in waiting list if criteria are expanded



Toso C, et al. Clin Transplant. 2010; 24:695-700.

Beyond Milan criteria

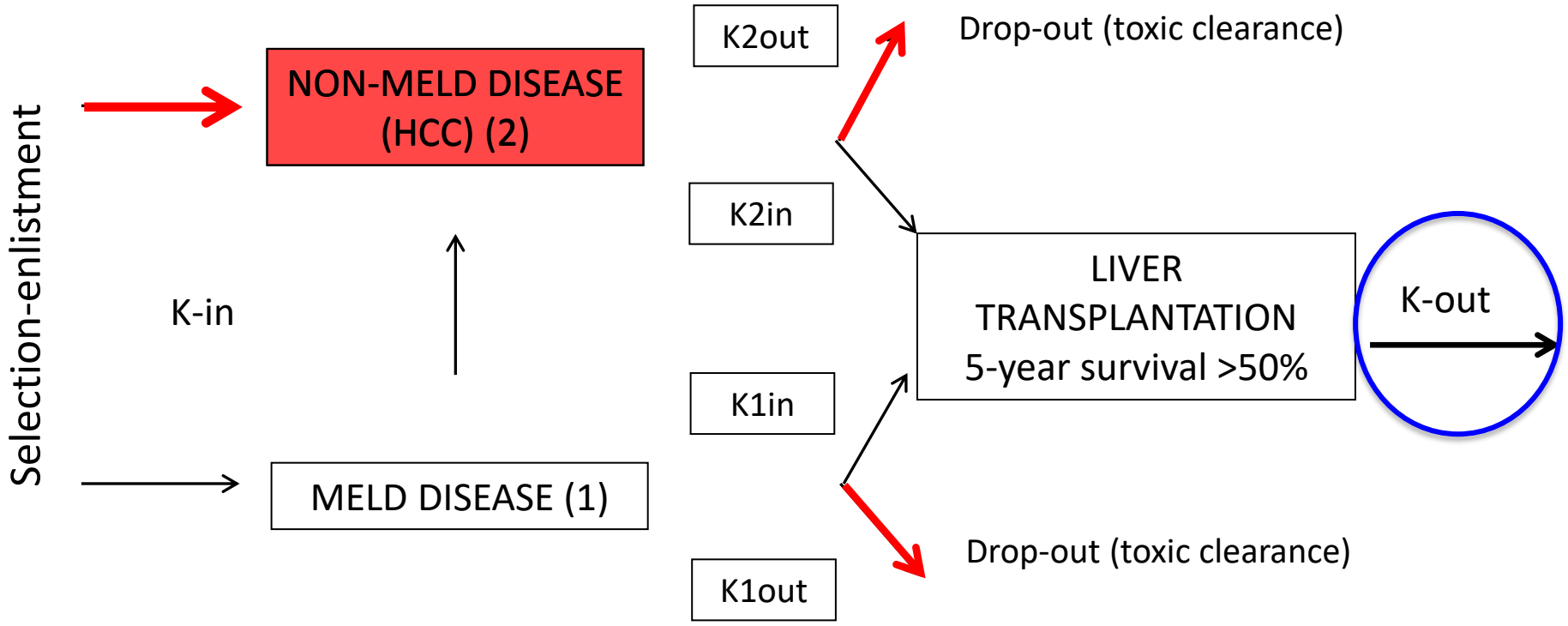
Increase of HCC patients in waiting list if criteria are expanded



Navasa M and Bruix J. Hepatology. 2010;51;12-15.

Beyond Milan criteria

Increase of HCC patients in waiting list if criteria are expanded



Navasa M and Bruix J. Hepatology. 2010;51;12-15.

Beyond Milan criteria

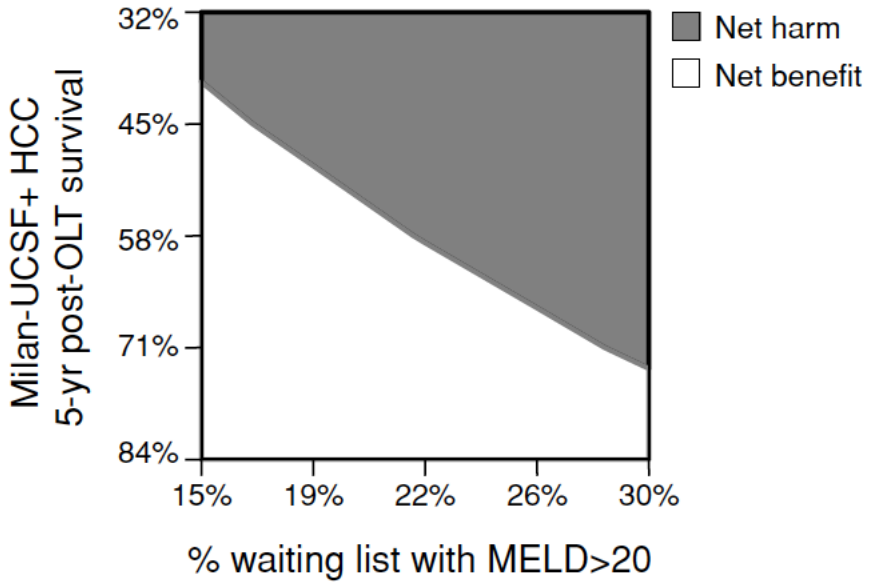
Impact on the waiting list if criteria are expanded

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 organ[1]

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

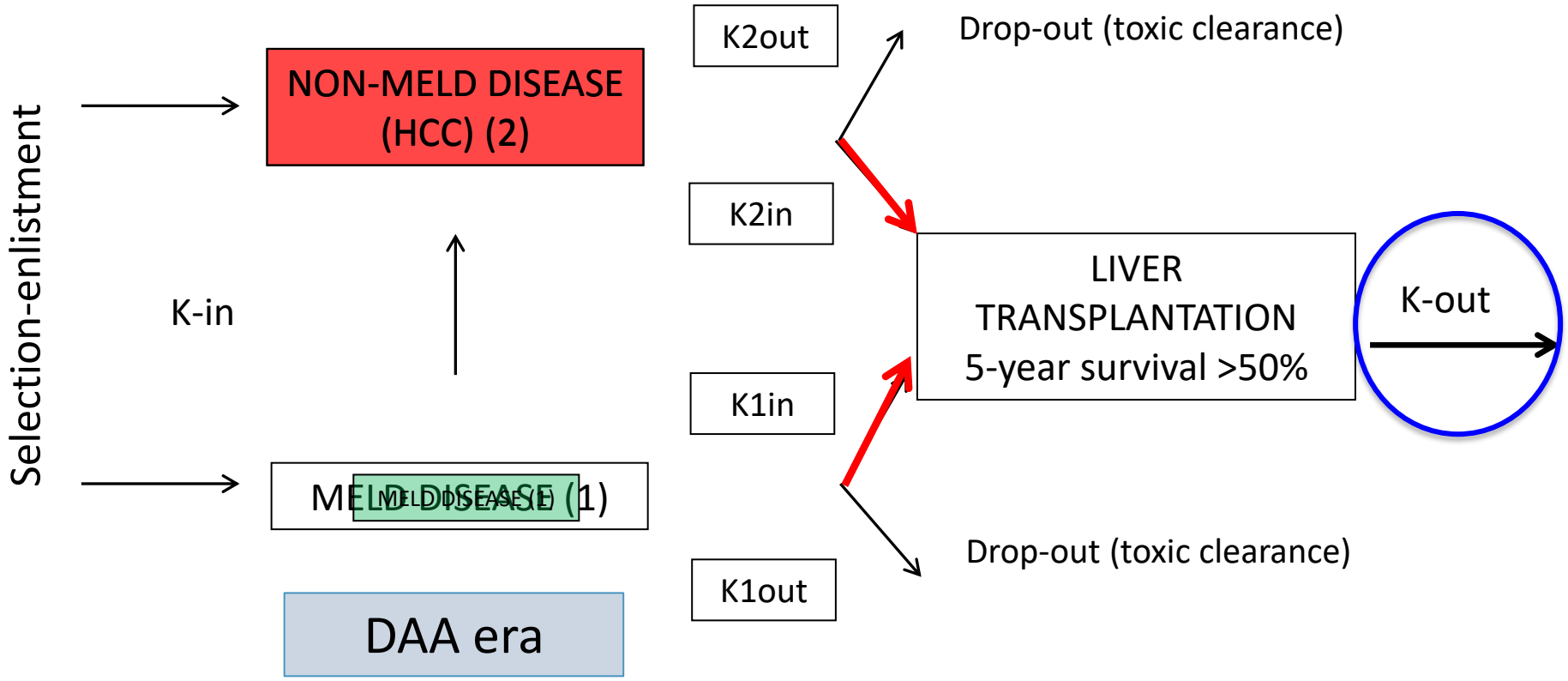
[1]Based on national averages for organ arrival rate.



Volk ML et al. Am J Transplant 2008;8:839-846.

Beyond Milan criteria

Increase of HCC patients in waiting list if criteria are expanded



Navasa M and Bruix J. Hepatology. 2010;51;12-15.

Expanded criteria for HCC: Controversies

Summary

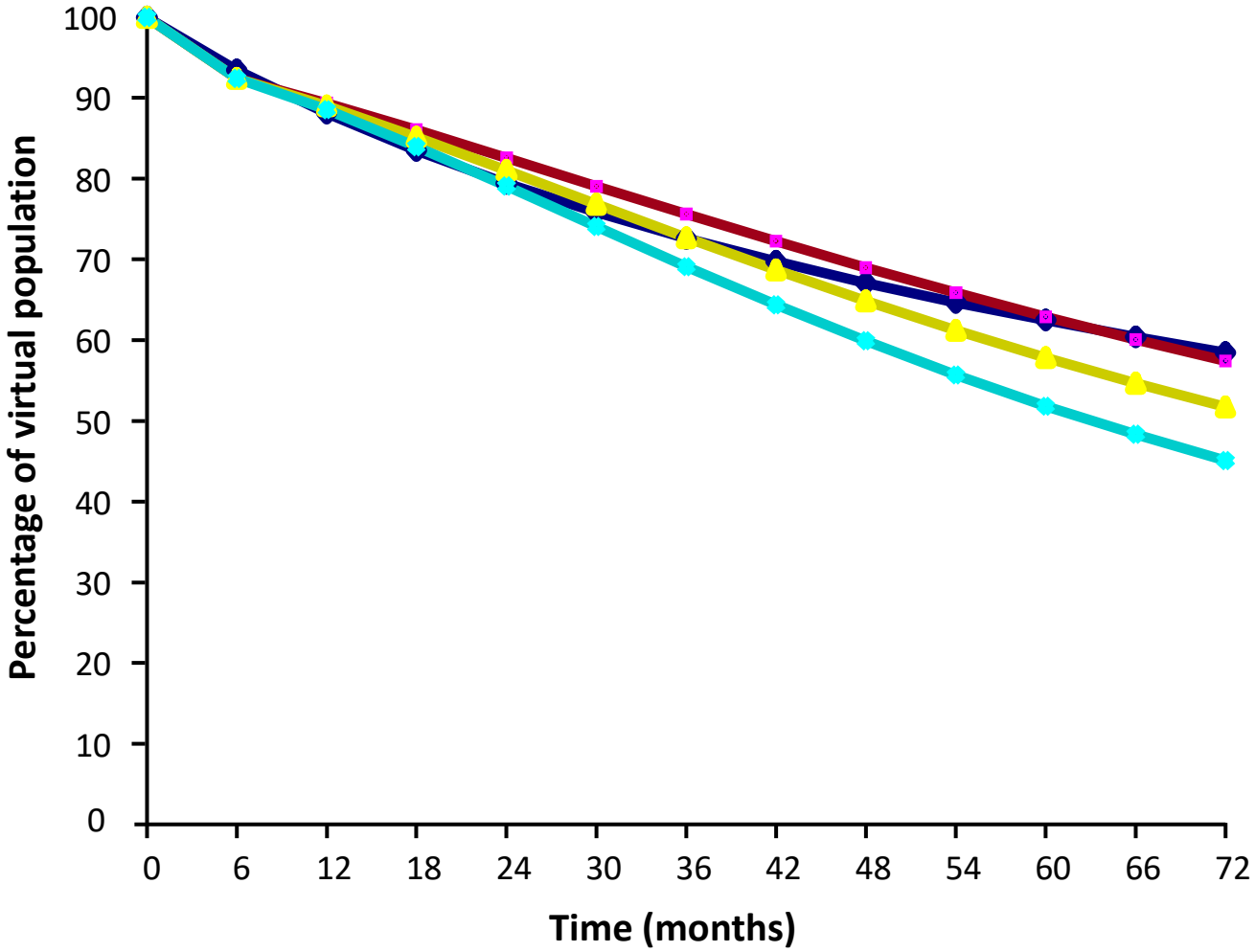
- There is life beyond “Milan”…..
- A discreet expansion will allow an acceptable results
- There is a need of surpassing the criteria based exclusively on size and number of nodules
- The application of expanded criteria should be done if the local dynamics of the waiting list does not harm the other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

Agenda

- Resection: Indications and challenging scenarios
- Liver transplantation: Where are the limits?
- Resection vs. Liver transplantation

Upfront OLT vs resection and salvage OLT

Survival curves of the virtual population



Best scenario:
recurrence 15% year
transplantability 80%

OLT

Salvage OLT scenarios

best
intermediate
worst

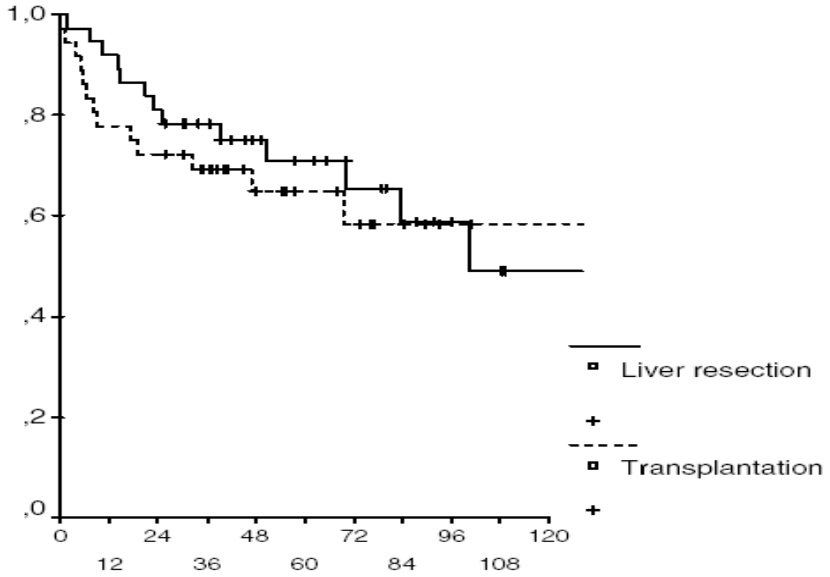
Worst scenario:
recurrence 25% year
transplantability 40%

Majno PE et al. Hepatology. 2000;31:899-906.

Upfront OLT vs resection and salvage OLT

Survival curves in real population

	Resection + salvage OLT	Upfront OLT
Patients (N)	37	36
Mortality (overall) (n)	17	13
Recurrences (n)	22	4
Transplanted (salvage) (n)	6	36
Survival 5-10 years (%)	70–50	65–60



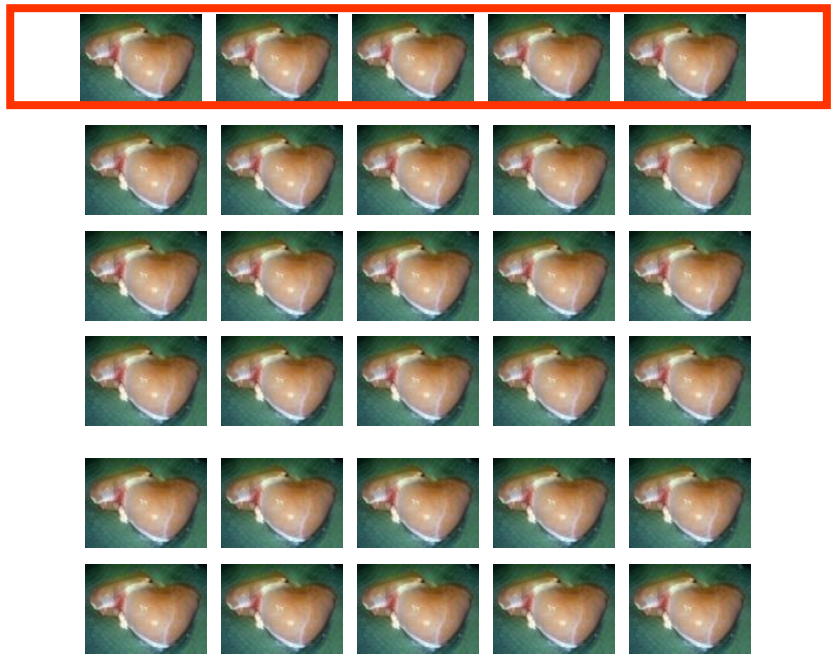
Margarit C, et al. Liver Transpl. 2005;11:1242-51.

Upfront OLT vs resection and salvage OLT

Survival curves in real population

For the same survival: grafts used …

Resection + salvage OLT



Available for the others!

Up-front OLT

Margarit C, et al. Liver Transpl. 2005;11:1242-51.

Curative treatments: Surgical Resection

Predictive factors for HCC recurrence after resection

Author, year	Vascular invasion	Satellites	Poor-diff.	Multifocal	Size	Cirrhosis	AFP	Others
Imamura, 2003	X			X		Hepatitis activity	X	Non-anatomical resection
Ishizawa, 2008	X			X		Child B		
Schiffman SC, 2010	X			X				
Fuks, 2012	X	X	X		> 3 cm	X		
Hasegawa, 2013				X	≥ 2 cm	Liver damage, platelets	X	Age, gender, HCV +, DCP
Park SK, 2013	X			UICC stage BCLC stage				
Li SH, 2013	X					X		Non-anatomical resection
Yin, 2013	X	X	X	BCLC stage	≥ 3 cm			Age, capsule, GGT, HBV DNA, antivirial

Upfront OLT vs resection and salvage OLT

Salvage liver transplantation for recurrence prevention

Variable	HR	CI 95%	p
Cirrhosis	1.9	1.04-4.01	0.02
Diameter> 3cm	1.34	1.03-3.12	0.03
mVI	2.83	1.10-7.29	0.003
Satellites	2.46	1.01-6.68	0.04
Poor diff.	3.18	1.31-7.70	0.01

Number of Pejorative Histological Factors*	Number of Patients	No Recurrence (n = 22) n (%)	Recurrence Within MC (n = 60) n (%)	Recurrence Beyond MC (n = 30) n (%)
0	41	10 (24)	31 (76)	0 (0)
1	43	10 (23)	24 (56)	9 (21)
2	14	2 (14)	5 (36)	7 (50)
3	8	0 (0)	0 (0)	8 (100)
4-5	6	0 (0)	0 (0)	6 (100)

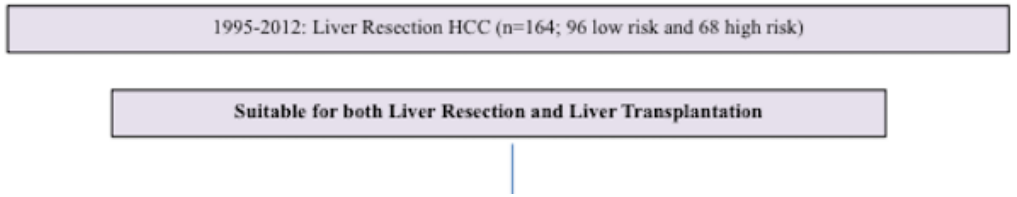
Pejorative Histological factors ≥3

Consider LT before recurrence

Sala M. et al. Liver Transpl. 2004;10:1294-1300.
Fuks D, et al. Hepatology 2012;55:132-140

Upfront OLT vs resection and salvage OLT

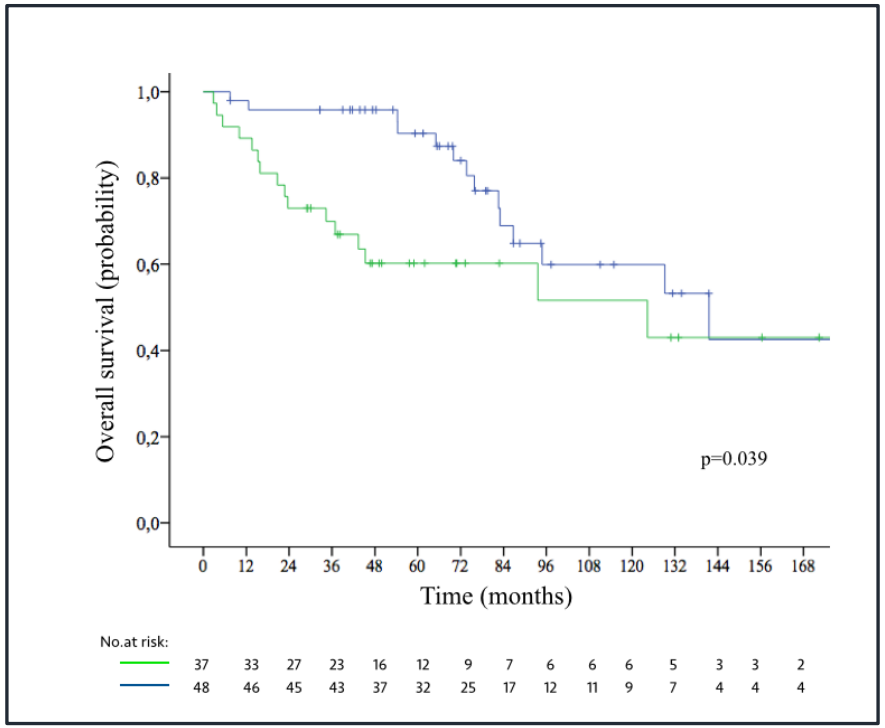
Salvage liver transplantation for recurrence prevention



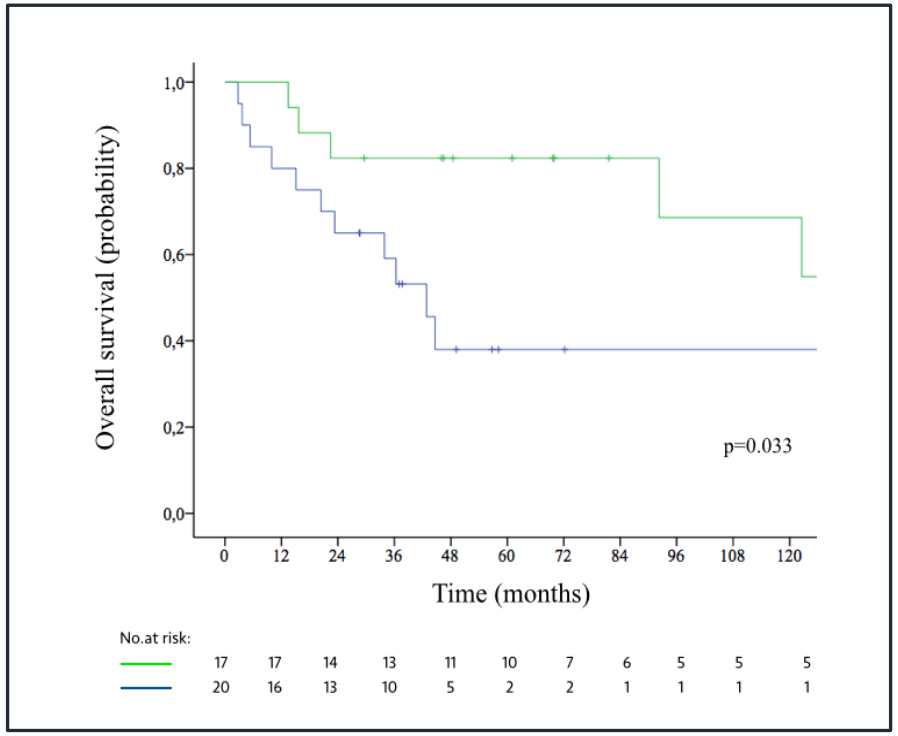
Sala M. et al. Liver Transpl. 2004;10:1294-1300.
Ferrer-Fàbrega J, Forner A et al. Hepatology. 2016;63(3):839-849.

Upfront OLT vs resection and salvage OLT

Salvage liver transplantation for recurrence prevention



Survival of the whole cohort from resection according to the pathological findings. The survival was significantly superior in low-risk compared to high-risk.

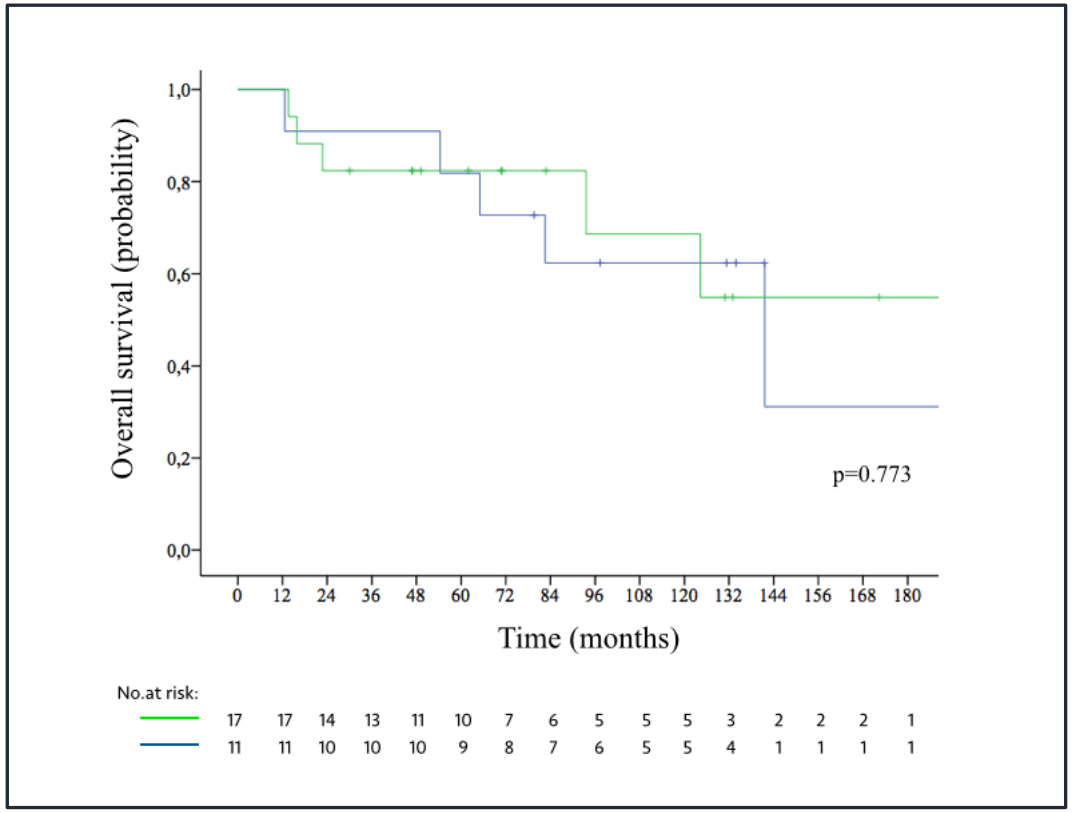


Survival of the high- risk patients (n=37) after resection. The survival was significantly superior in those finally transplanted compared to non-transplanted patients.

Sala M. et al. Liver Transpl. 2004;10:1294-1300.
Ferrer-Fàbrega J, Forner A et al. Hepatology. 2016;63(3):839-849.

Upfront OLT vs resection and salvage OLT

Salvage liver transplantation for recurrence prevention



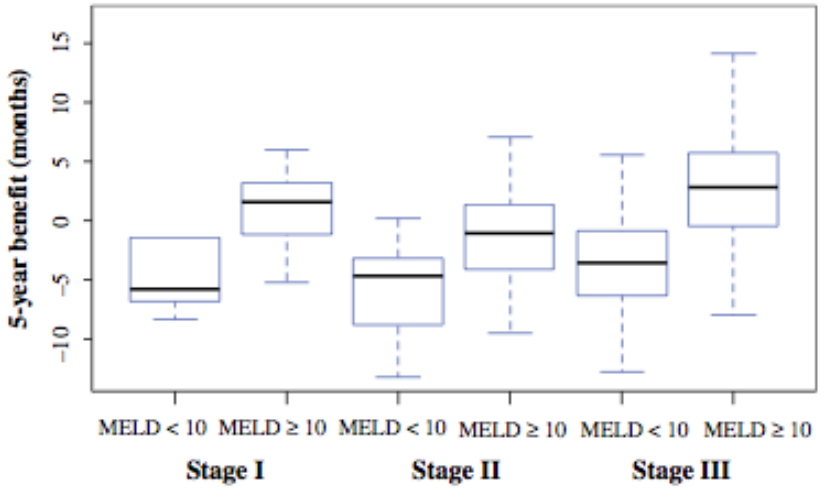
Survival of those patients finally transplanted (n=28) from the moment of liver transplantation. There were no statistically significant differences in survival.
(1, 3, and 5-year patient were 100% vs. 100%, 90.9% vs. 82.4%, 81.8% vs. 82.4%, respectively; p=0.773).

Sala M. et al. Liver Transpl. 2004;10:1294-1300.
Ferrer-Fàbrega J, Forner A et al. Hepatology. 2016;63(3):839-849.

Resection versus Liver transplantation

Survival benefit of LT vs HR: Impact of MELD score

- LT proved to be harmful in patients with resectable HCC with a low MELD score (<10) or with aggressive tumors (with MVI)
- As a result of a shortage of donors, only selected resectable tumors with a MELD score of >10 should be considered for transplantation.



Group	Stage I, benefit (n°)	Stage II, benefit (n°)	Stage III, benefit (n°)
MELD <10			
MVI			
No	−1.44 (171)	−3.27 (171)	−1.33 (182)
Yes	−6.90 (174)	−9.05 (137)	−6.15 (164)
p value based on MVI	<0.0001	<0.0001	<0.0001
D value based on MVI	|40.1585|	|40.0343|	|35.4404|
MELD ≥ 10			
MVI			
No	3.19 (178)	1.45 (162)	4.71 (150)
Yes	−1.14 (161)	−3.91 (174)	0.93 (176)
p value based on MVI	<0.0001	<0.0001	<0.0001
D value based on MVI	|19.1631|	|23.5837|	|16.2608|

Stage I: HCC within Milan criteria
Stage II: HCC within Up-to-7 criteria
Stage III: HCC beyond Up-to-7 criteria

Vitale A et al. Ann Surg Oncol. 2015 Jun;22(6):1901-7

Resection vs. Liver transplantation

Summary

- In patients with preserved liver function and single tumors, resection offers a similar outcome, preserving grafts for other patients
- Ab initio indication has shown excellent results
- An observational period (6 months?) may allow the identification of aggressive tumors

The BCLC group

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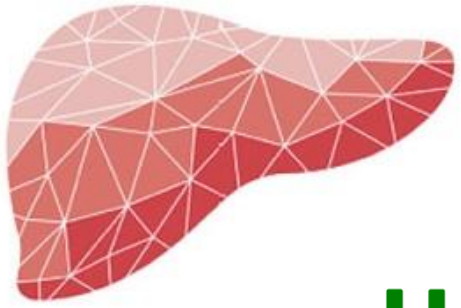
MÁSTER EN HEPATOLOGÍA



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