Il Nodulo Epatico

dalla Diagnosi ... alla Terapia

Terapia dell'HCC

L'approccio chirurgico

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IRCCS San Martino-IST

Genova, 21 Settembre 2013

HCC
Approccio Chirurgico

- Resezione
- Trapianto
- Terapie combinate: Radiofrequenza con accesso open o laparoscopico.

  «Surgical Resection versus Open-Approach Radiofrequency Ablation for small Hepatocellular Carcinomas within Milan criteria after successfull Trasncatheter Arterial Chemoembolization» (J. Lei, J Gastrointest Surg, August 2013)
- Linee guida AISF

Confronto

Resezione		Trapianto
SI	Trattamento tumore	SI
NO	Trattamento cirrosi/epatopatia	SI
20%	Morbilità	40-48%
2-3%	Mortalità perioperatoria	3% e a 1 anno ≤ 10%
/	Complicanze Immunosoppressione	-Incidenza neoplasia de novo: 13% e 26% a 5 e 8 aa -IRC: 18.5% a 5 anni -Sepsi: 37% nei primi 3 mesi (mortalità: 30%, ma 50% in caso di shock settico)
50% a 3 aa e 70% a 5 aa (sede Intraepatica)	Recidiva HCC post resezione/trapianto	15-20% a 5 aa (88% Extraepatica)
/	Organs shortage	Drop out: 10% a 6 mesi
-EC: Mediana 1.9 U -PFC: Mediana 3.7 U -PLT: Mediana 0 U -ICU stay post op: Mediana 1.6 gg -Hospital stay post op: Mediana 8 gg - 20.000 €	Costi	-EC: Mediana 2-10 U -PFC: Mediana 10 U -PLT: Mediana 4 U -ICU stay post op: Mediana 2 gg -Hospital stay post op: Mediana 20 gg - 40.000 €

Criteri allocazione graft epatico

URGENCY

Priorità assegnata in base alla gravità del paziente in lista

UTILITY

Priorità assegnata in base all'outcome atteso nel post trapianto

BENEFIT

Priorità assegnata al paziente con maggior differenza tra la sopravvivenza attesa post trapianto e la sopravvivenza attesa in lista

ID no.	Future lifetime (*patient*) WL	LTx	B = LTx – WL	Total future lifetime (*patient population*) if assigned to candidate (ID no.)
1	7	10	3	17 = 10 + 2 + 5 = 3 + (7 + 2 + 5)
2	2	3	1	15 = 7 + 3 + 5 = 1 + (7 + 2 + 5)
3	5	9	4	18 = 7 + 2 + 9 = 4 + (7 + 2 + 5)

B = transplant benefit.
ID = patient identification number.
LTx = predicted post transplant lifetime.
WL = predicted waiting list lifetime.

Schaubel AJOT 2009

Criteri per inserimento in lista trapianto UK

- Gli organi sono una risorsa della società

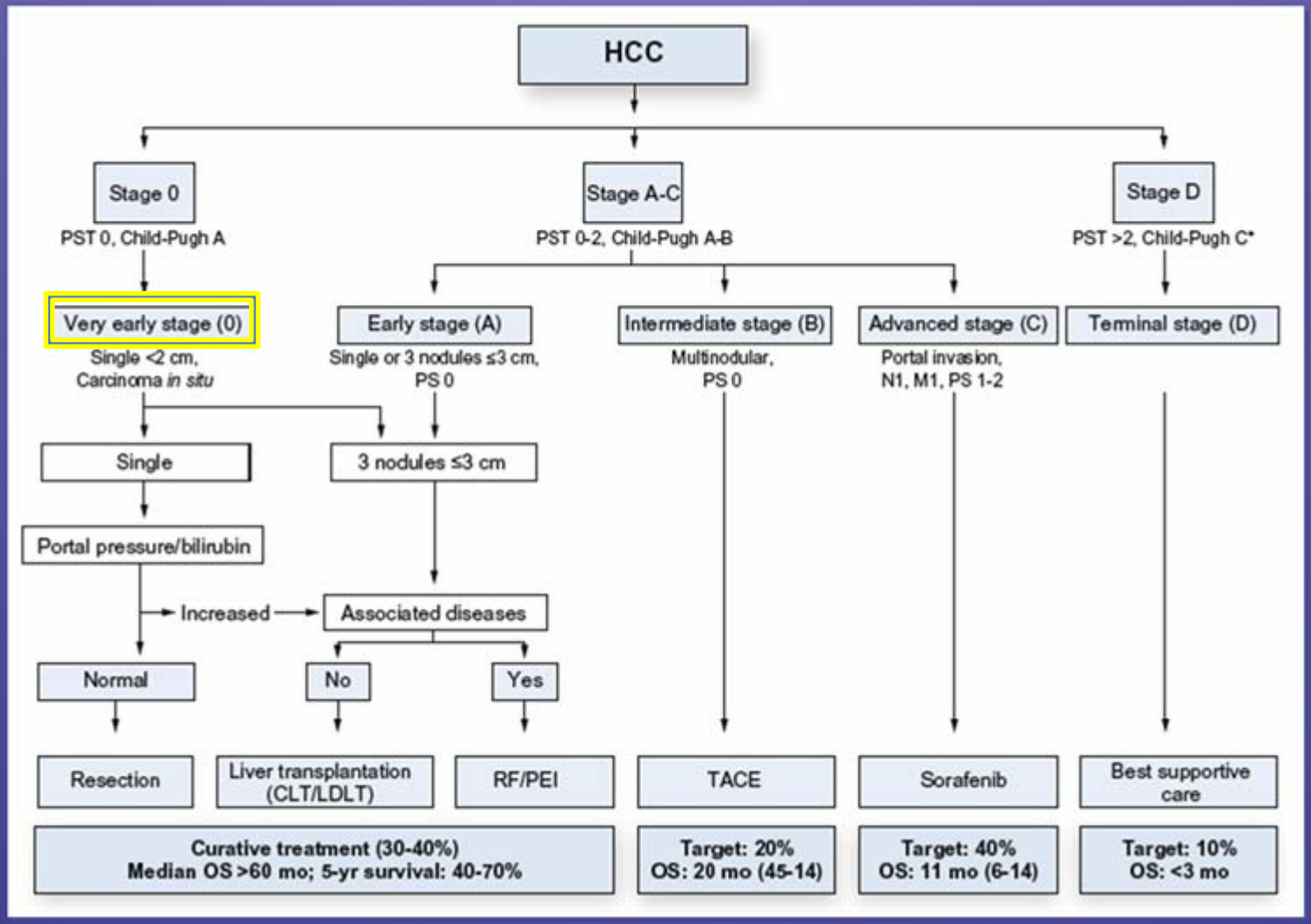
- I pazienti dovrebbero essere selezionati se l'aspettativa di vita senza il trapianto risulta essere ≤ 1 anno o se il paziente presenta una qualità di vita inaccettabile a causa della malattia epatica

- I pazienti trapiantati dovrebbero avere una probabilità di sopravvivenza di almeno il 50% a 5 anni con una accettabile qualità di vita

(Conferenza di Edimburgo 1996, medici-pazienti-eticisti-media)

Neuberger J, Hepathology 2013

Barcelona-Clinic Liver Cancer (BCLC) Classification



EASL conference – 2012; AASLD guidelines – 2012

Resezione epatica: Fattori Prognostici

Portal hypertension:

HVPG < 10 mmHg:
IPLF 0%
5-ys Overall survival 70%

HVPG > 10 mmHg:
Liver decompensation (ascites)
5-ys Overall survival 50%

MELD:

Validated for:

1. Predictor mortality of patient receiving TIPS
2. Priority in WL for liver transplant
3. Predictor 3 months & 1 years mortality of of cirrhotic patient
4. Mortality after digestive hemorrage
5. Morbidity & Mortality after surgery (hepatic and non)

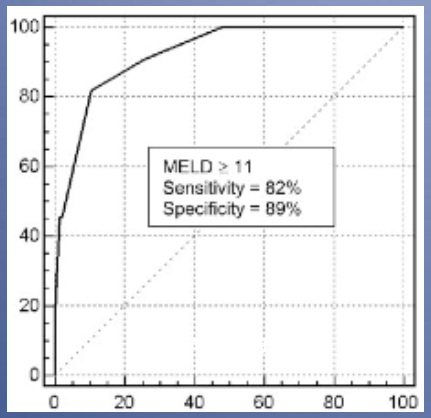
Conseguences of portal hypertension:

-Splenomegaly
-Abdominal collaterals
-Platelets < 100.000
-Esophageal varices

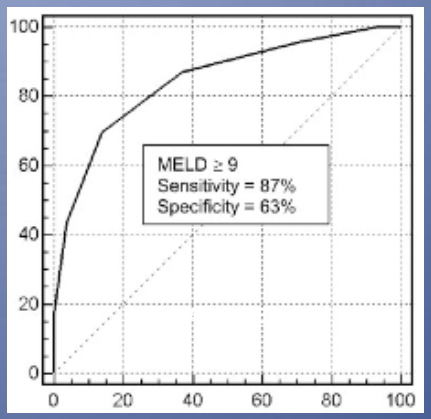
→ *+ 25-28% postoperative death*

Resezione epatica: ruolo del MELD

Evaluation of MELD impact on prognosis after hepatectomy for HCC



IPLF 7.1%
with MELD 11 *p 0.001*



Complication 29.9%
with MELD 9 *p 0.001*

Variables	MELD score <9 (n = 74)	MELD score between 9 and 10 (n = 56)	MELD score ≥11 (n = 24)	P*
Postoperative liver failure	0 (0%)	2 (3.6%)	9 (37.5%)	0.001
Postoperative complications	6 (8.1%)	20 (35.7%)	20 (83.3%)	0.001
Refractory ascites	5 (6.8%)	15 (26.8%)	20 (83.3%)	0.001
Jaundice	2 (2.7%)	10 (17.9%)	19 (79.2%)	0.001
Alteration of coagulation factors	3 (4.1%)	12 (21.4%)	19 (79.2%)	0.001
Renal impairment	0 (0%)	4 (7.1%)	6 (25%)	0.001
Hospital stay (days)	8 (5-38)	9 (6-33)	25 (6-166)	0.001
1-year survival	100%	94%	74%	0.001

Cescon Arch Surg 2009

Surgical resection

Selection criteria

Indication to extent hepatectomy for HCC on cirrhosis by simple algorithm based on preoperative variables

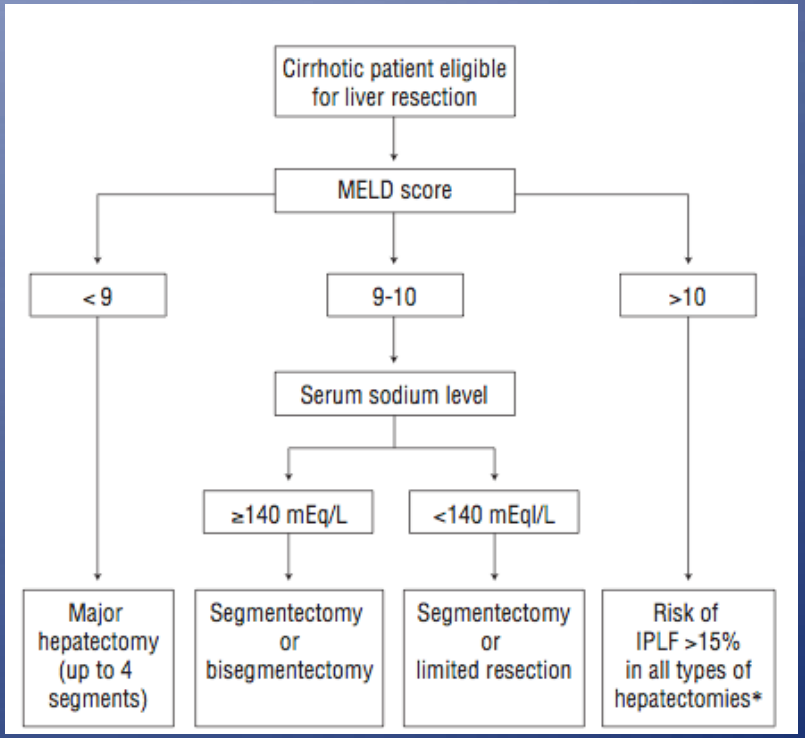
466 pazienti, multicentrico, retrospettivo, CTP A/B 439/27, MELD 8.9 (>10 17%), Major/Minor (>/up to 2 segm) hepatectomy 58/408
Endopoint: relationship between preoperative characteristics and surgical planning with postoperative morbidity

Results
IPLFn 23 (4.9%) → 4 treated by LT
3-months mortality 4.6%

Preoperative predictors of IPLF
Multivariate ansluysis
MELDscore *(p 0.01)*
Extent of hepatectomy *(p 0.01)*
Na level *(p 0.09)*

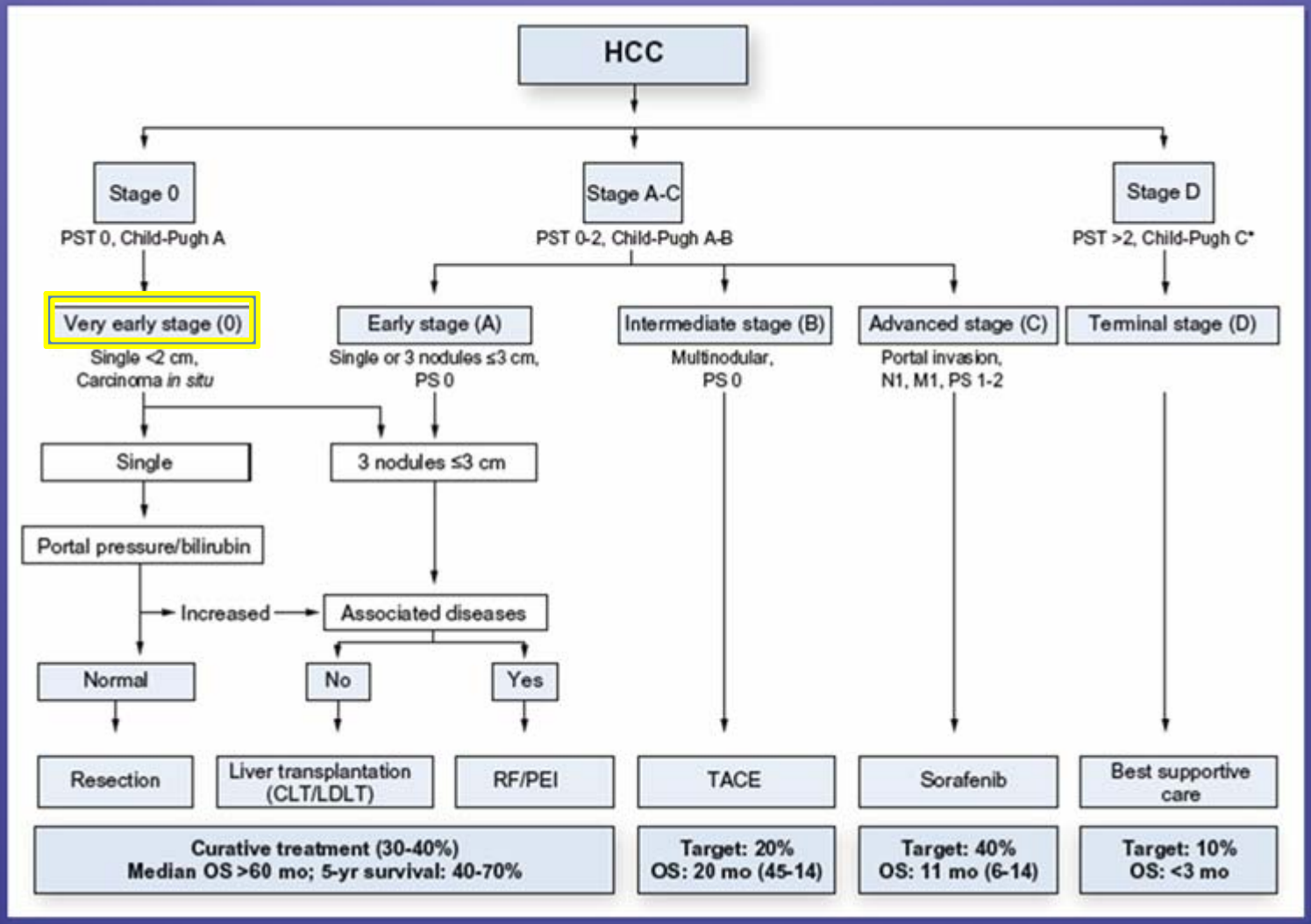
MELD score and extent of hepatectomy
MELD < 9 IPLF 0.4%] *p 0.02*
MELD 9-10 IPLF 3.8%] *p 0.001*
MELD >11IPLF 20.3%

Subgroup MELD 9-10
Na level predict IPLF (Sens 100% AUC 0.77)
Risk of IPLF related to type of hepatectomy
•< 1 segm 2.5%
•1-2 segm 9.1%
•> 2segm 28.6%



Cescon Arch Surg 2009

Barcelona-Clinic Liver Cancer (BCLC) Classification



EASL conference – 2012; AASLD guidelines – 2012

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Management of HCC

Carlos Rodríguez de Lope[1], Silvia Tremosini[1], Alejandro Forner[1,2], María Reig[1,2], Jordi Bruix[1,2*]

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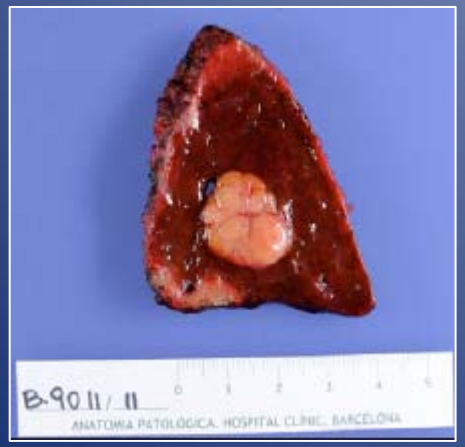
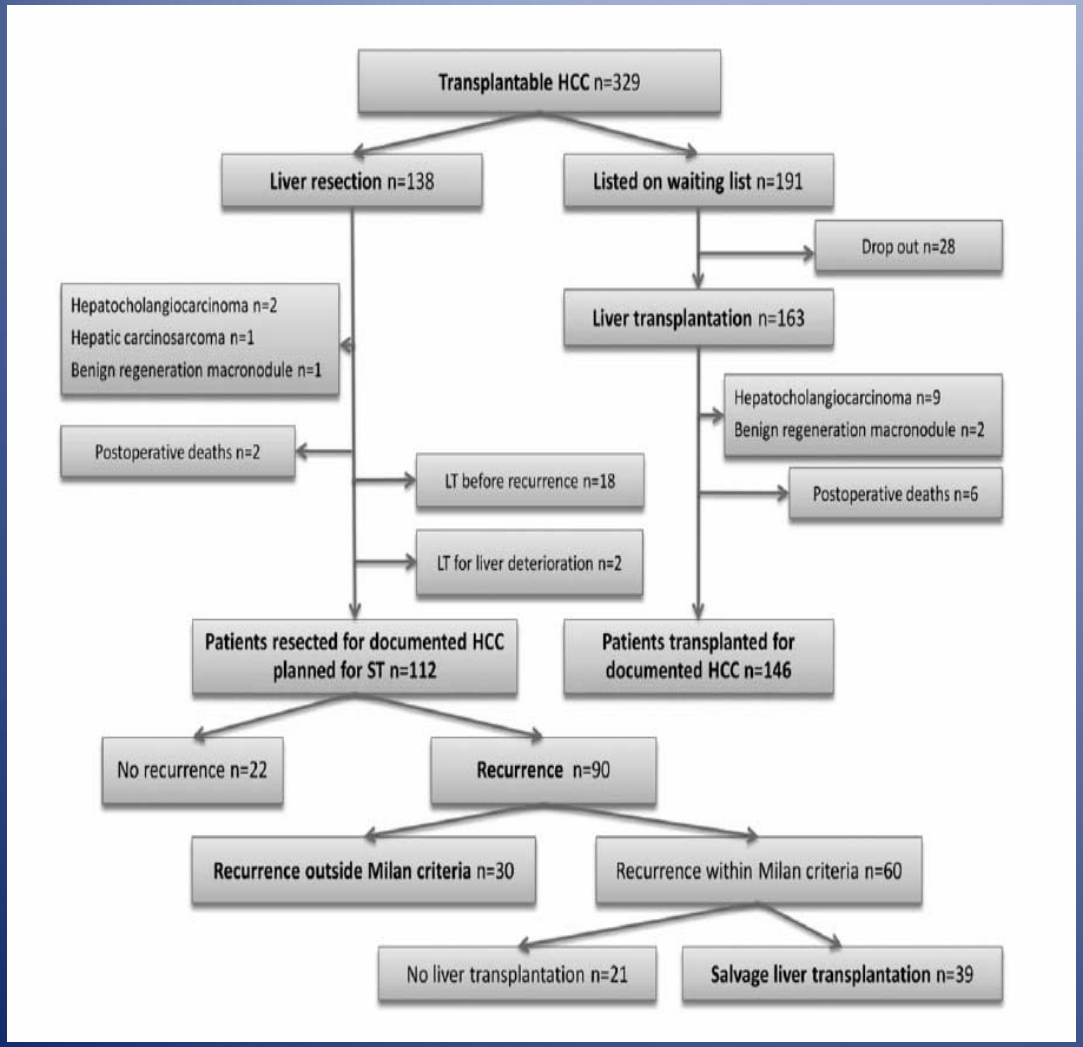


Pathology examination disclosed microscopic vascular invasione reflecting high risk of recurrence. This prompted the indication of liver transplantation (ab initio indication)

J of Hepathology 2012

Salvage Liver Transplantation (SLT)

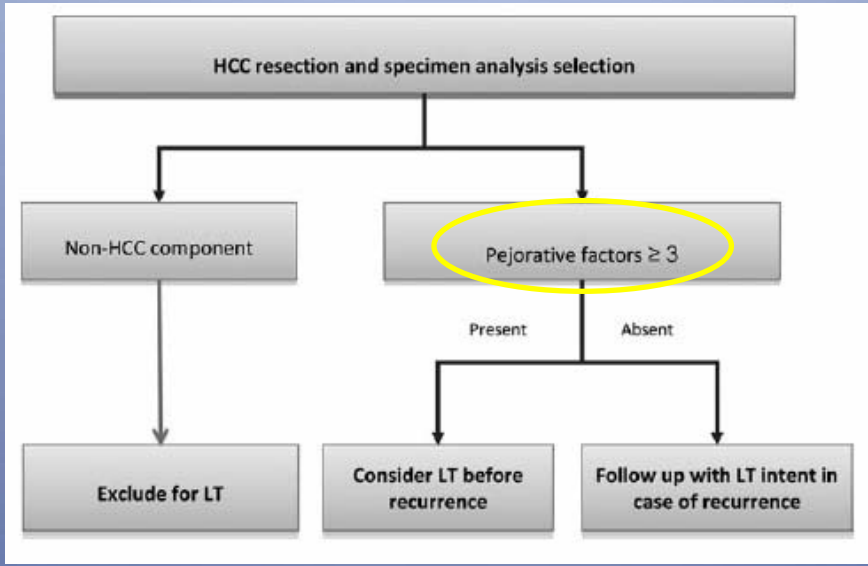


SLT:

-39/138 (28%) intention to treat population
-39/90 (40%) dei pazienti con recidiva post resezione
-39/60 (65%) dei pazienti con recidiva Milano In post resezione

Fuks, Hepatology 2012

Salvage Liver Transplantation

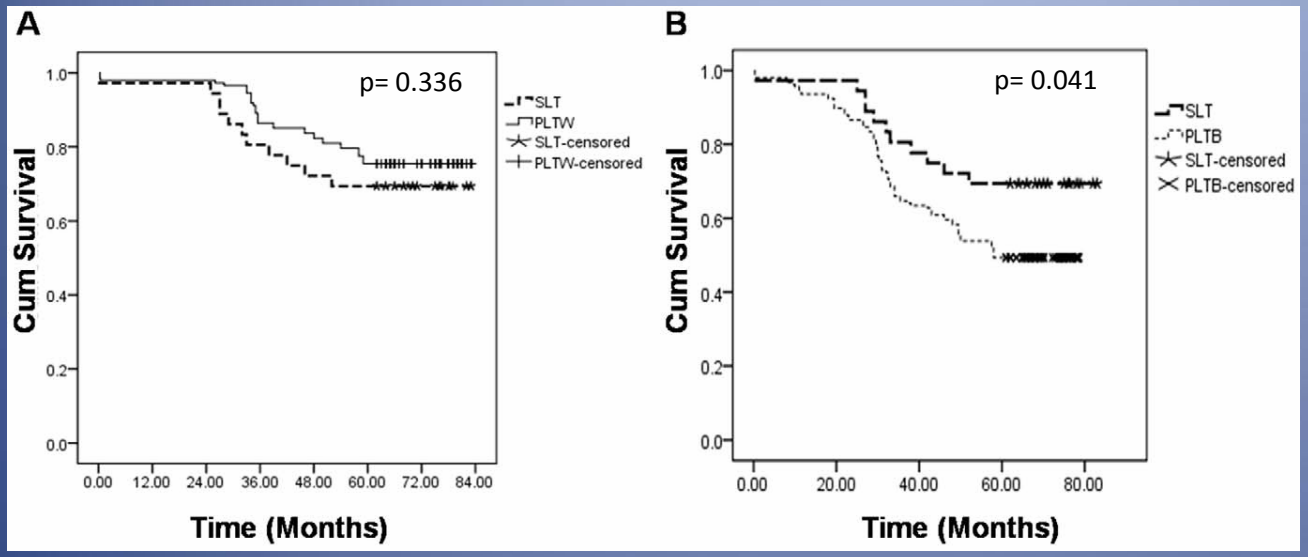


	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P	HR	95% CI	P
Male sex	0.63	0.24-1.63	0.34			
Age > 60 years	3.18	1.46-6.92	0.003	1.78	0.62-5.11	0.28
AFP > 400 ng/mL	1.88	0.87-4.04	0.11			
VHC	0.61	0.27-1.41	0.25			
VHB	1.55	0.67-3.58	0.30			
Chronic alcoholism	0.75	0.29-1.97	0.46			
Cryptogenic	2.05	0.92-4.53	0.07	1.02	0.40-2.57	0.96
Hemochromatosis	0.89	0.12-6.13	0.90			
Presence of cirrhosis	3.12	1.31-7.69	0.01	1.90	1.04-4.01	0.02
Anatomic resection	0.89	0.39-2.04	0.79			
Major resection	0.89	0.47-2.65	0.79			
Diameter > 3 cm	5.30	1.78-15.8	0.002	1.34	1.03-3.12	0.03
Single tumor	1.19	0.68-2.08	0.53			
R0 resection	2.31	0.86-6.19	0.09	3.36	0.74-15.2	0.11
Microscopic vascular invasion	2.2	1.05-4.68	0.003	2.83	1.10-7.29	0.003
Macroscopic vascular invasion	7.1	2.37-21.3	0.0001	2.20	0.90-5.57	0.07
Satellite nodules	5.0	2.39-10.8	0.0001	2.46	1.01-6.68	.04
Poor differentiation	6.0	2.86-12.9	0.0001	3.18	1.31-7.70	0.01

Abbreviations: AFP, α-fetoprotein; HCC, hepatocellular carcinoma; HR, hazard ratio; MC, Milan criteria; VHB, viral hepatitis B; VHC, viral hepatitis C.

Fuks, Hepatology 2012

Salvage Liver Transplantation (SLT= n 36) vs Primary Liver Transplantation (PLT= n 303)



PLTW (n 147): HCC Milano In
PLTB (n 156): HCC Milano Out

Intervallo tra LR e SLT: 35 mesi (1-63)

Group	Cases	Follow-up (month)	Recurrence		Overall survival rate (%)			Tumor-free survival rate (%)		
			Rate	time (month)	1 yr	3 yrs	5 yrs	1 yrs	3 yrs	5 yrs
SLT	36	58.7±20.7	5/36	28.2±15.1	97.2	80.6	69.4	97.1	87.9	74.2
PLTW	147	64.2±18.1	15/147	30.4±11.8	98.0	86.4	75.5	97.9	89.9	80.3
PLTB	156	57.2±33.1	63/156	22.5±14.9	96.2	64.7	48.7	88.5	53.2	33.6
P value		0.065	<0.001	<0.001	0.657	<0.001	<0.001	0.002	<0.001	<0.001

Wu, Plosone 2012

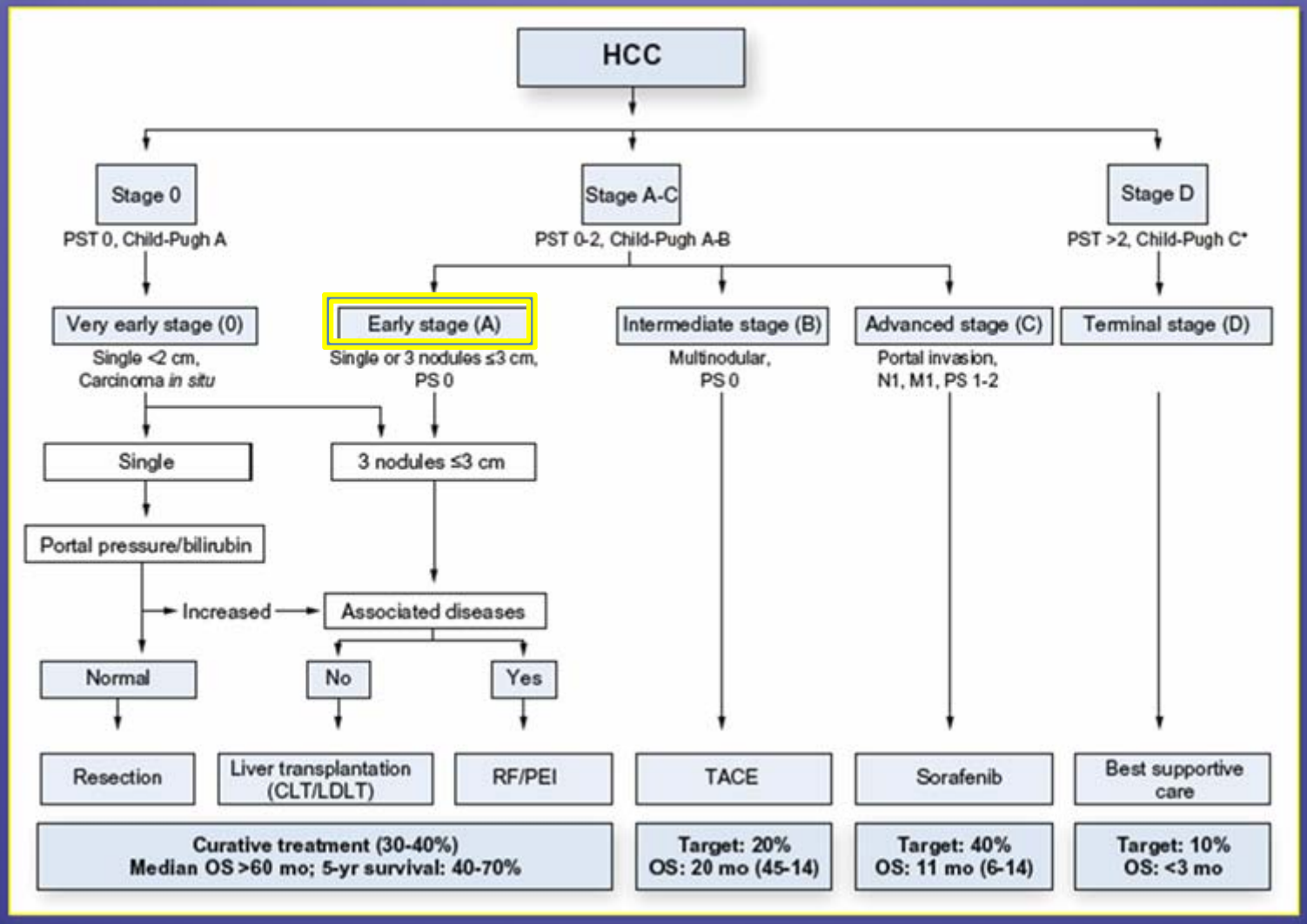
Salvage Liver Transplantation (SLT= n 36) vs Primary Liver Transplantation (PLT= n 303)

	SLT ($n=36$)	PLTW ($n=147$)	t value or χ^2 value	P value
Donor liver cold ischemic time (h)	8.1±2.5	7.4±2.8	1.37	0.127
Anhepatic time (min)	39.6±5.2	38.3±6.9	1.06	0.268
Operative time (min)	340±77	302±81	2.54	0.024*
Application of arterial jump grafts	3	2	5.29	0.021
Roux-n-Y	4	3	6.47	0.011
Intraoperative bleeding volume (ml)	1560±670	1180±910	2.35	0.028*
Intraoperative transfusion volume (ml)	1060±780	820±910	2.02	0.043*
Postoperative ICU time (h)	34±12	29±16	1.76	0.078
Primary graft nonfunction	0	0	–	–
Delayed graft function	1	4	<0.001	0.985
Intra-abdominal bleeding	0	4	1.001	0.317
Infections	2	14	0.571	0.450
Renal failure	1	3	0.073	0.786
Acute rejection	2	15	0.742	0.389
Biliary complications	2	14	0.571	0.450
Vascular complications	0	3	0.747	0.387
Recurrence of hepatitis	0	2	0.495	0.482

Abbreviation: SLT, salvage liver transplantation; PLTW, primary liver transplantation for HCC within Milan criteria; ICU, intensive care unit.

Wu, Plosone 2012

Barcelona-Clinic Liver Cancer (BCLC) Classification



EASL conference – 2012; AASLD guidelines – 2012

Recommendations from the International Consensus Conference on Liver Transplantation for HCC

Criteria for listing candidates with HCC in cirrhotic livers for deceased donor liver transplantation – Milan Criteria

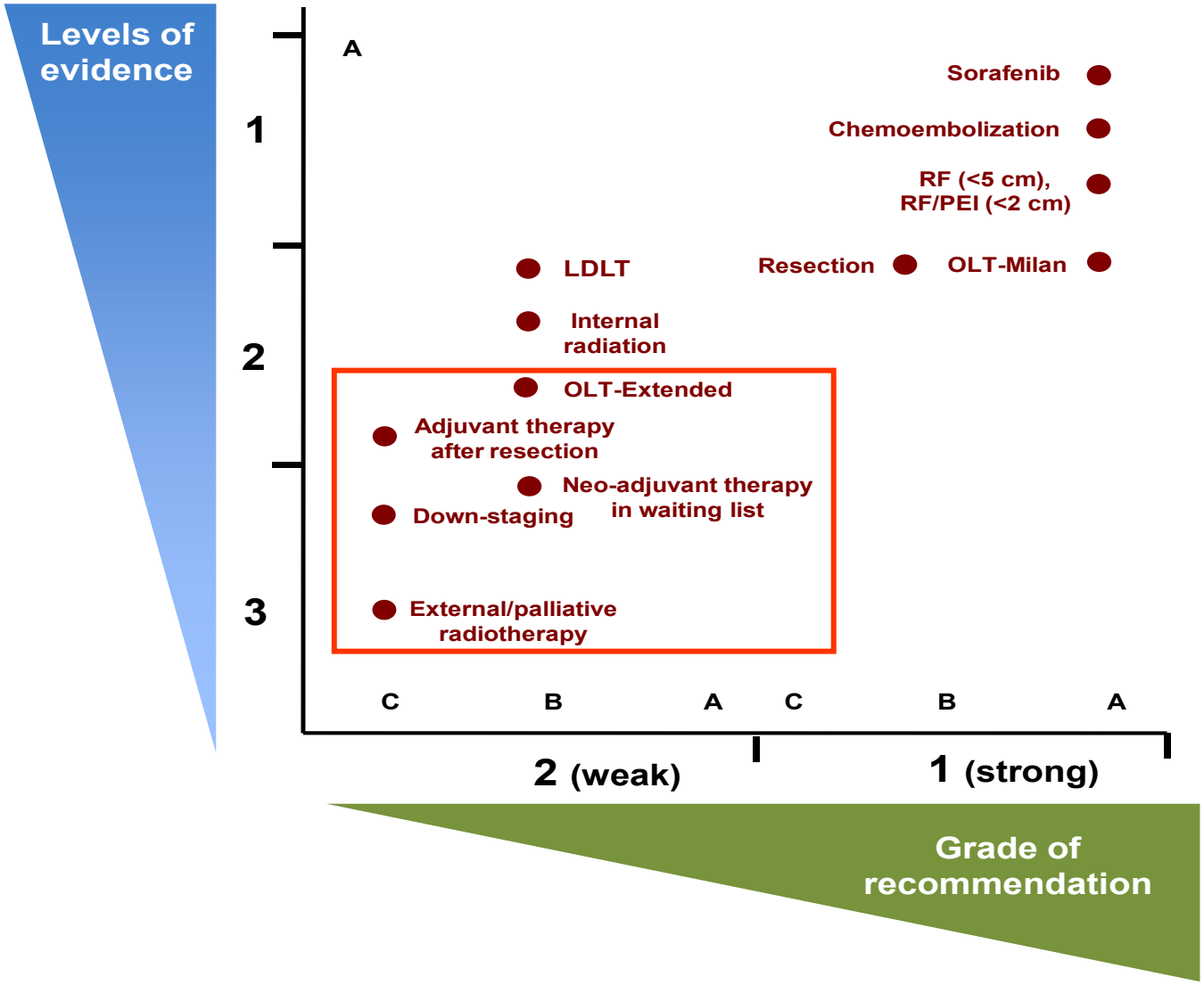
- The Milan Criteria are currently the benchmark, and the basis for comparison with other suggested criteria. (evidence 2a , Strong)

- A modest expansion of the number of potential candidates may be considered on the basis of several studies showing comparable survival for patients outside the Milan criteria. (evidence 3b, Weak)

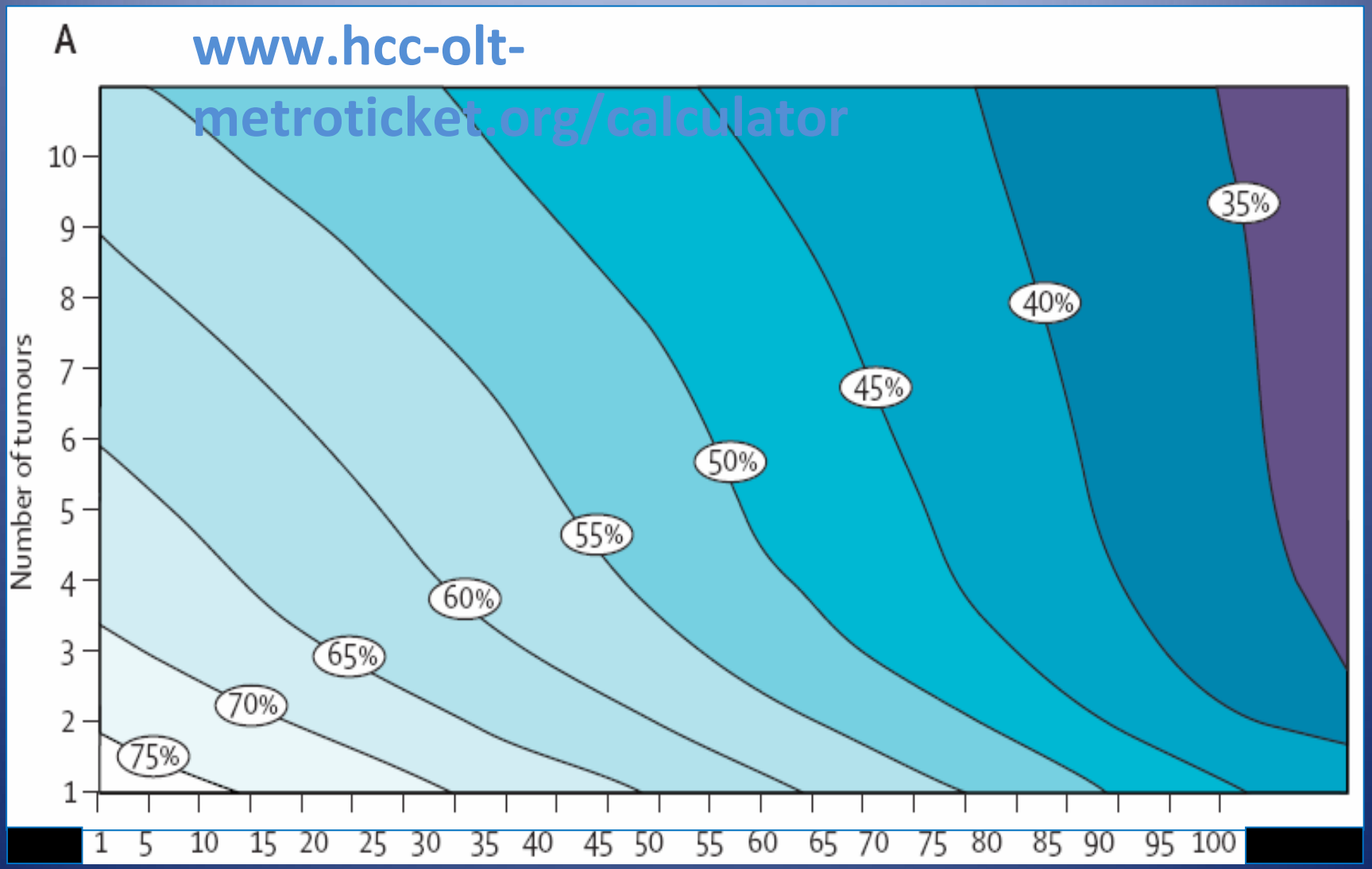
- Patients with worse prognosis may be considered for LT outside the Milan criteria if the dynamics of the waiting list allow it without undue prejudice to other recipients with a better prognosis. (no evidence, Weak)

Clavien PA Lancet Oncology 2011

Representation of EASL-EORTC 2011 recommendations for treatment according to levels of evidence (NCI classification) and strength of recommendation (GRADE system).



Individualization of prognosis in patients with HCC

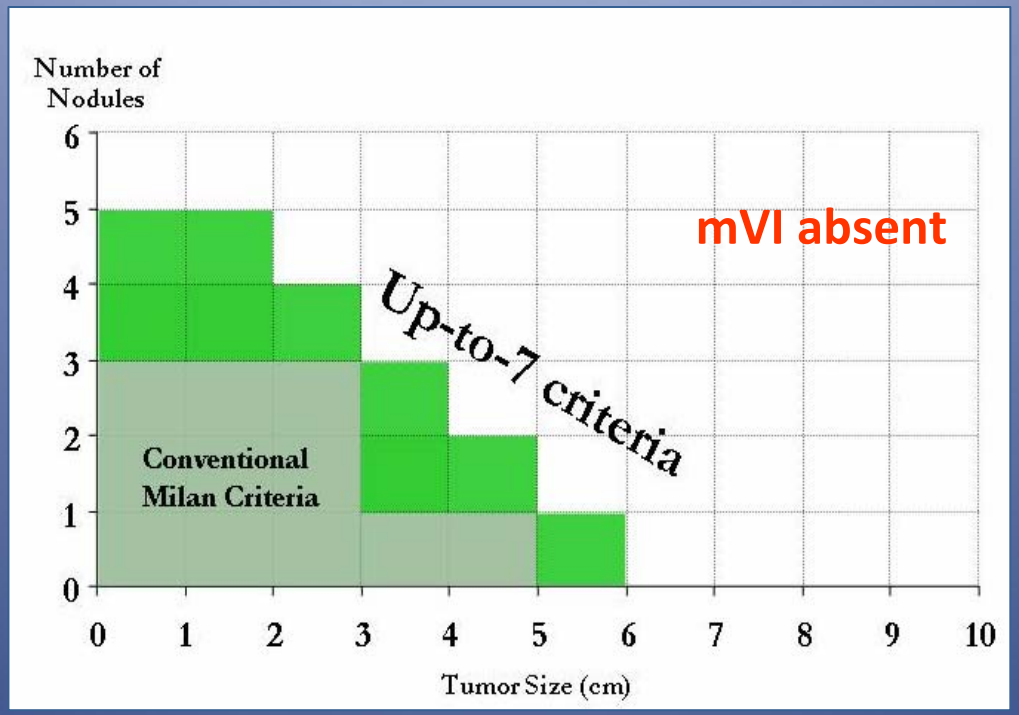


HCC FORECAST CHART

[Mazzaferro et al, Lancet Oncology 2009]

www.hcc-olt-metroticket.org
Predicting survival after liver transplantation in patients with HCC beyond the Milan Criteria: a retrospective, exploratory analysis

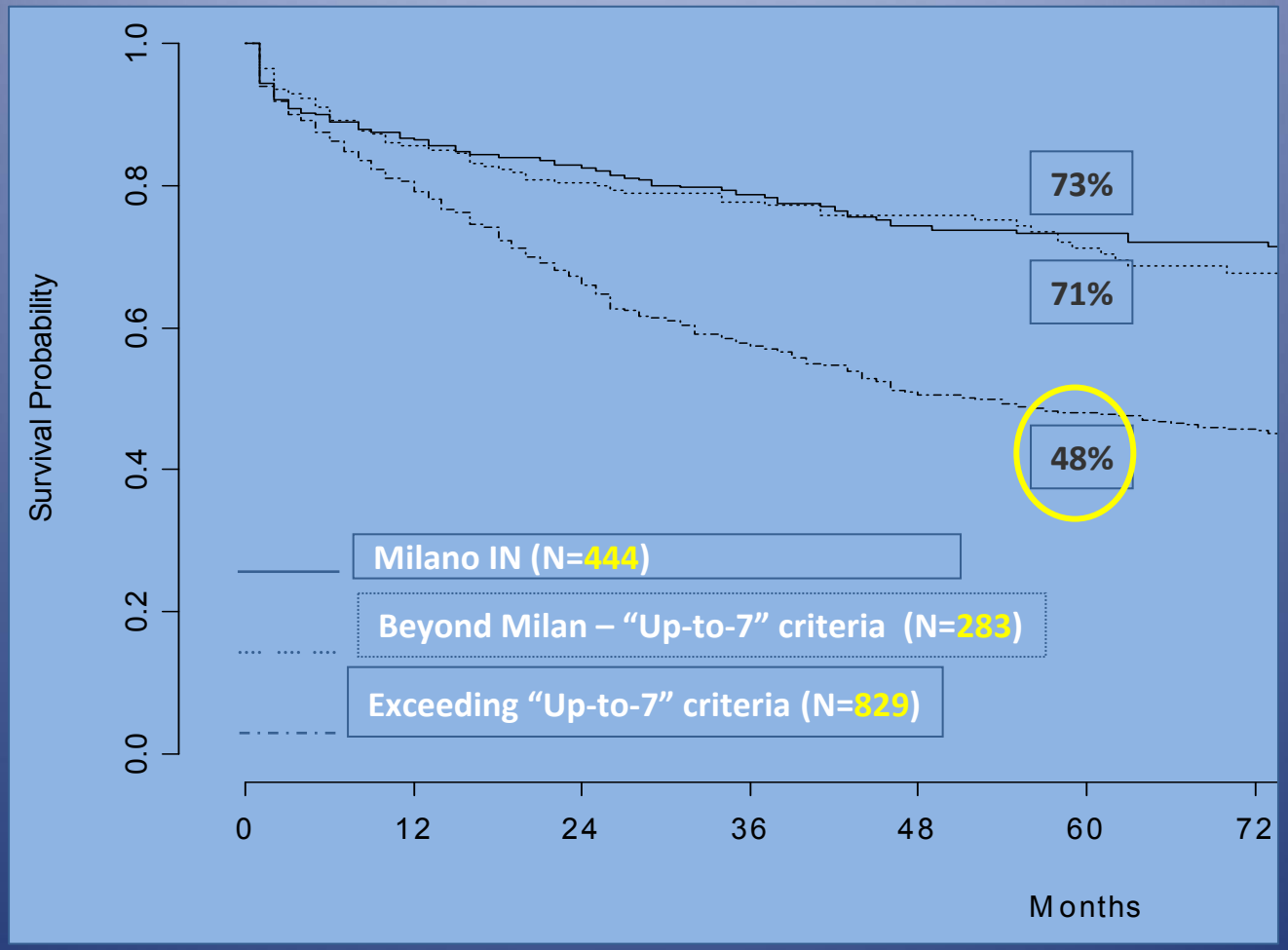
The “up-to-7 Criteria”



The “up-to-7” criteria could be a good starting point for prospective clinical trials on expansion of Milan Criteria

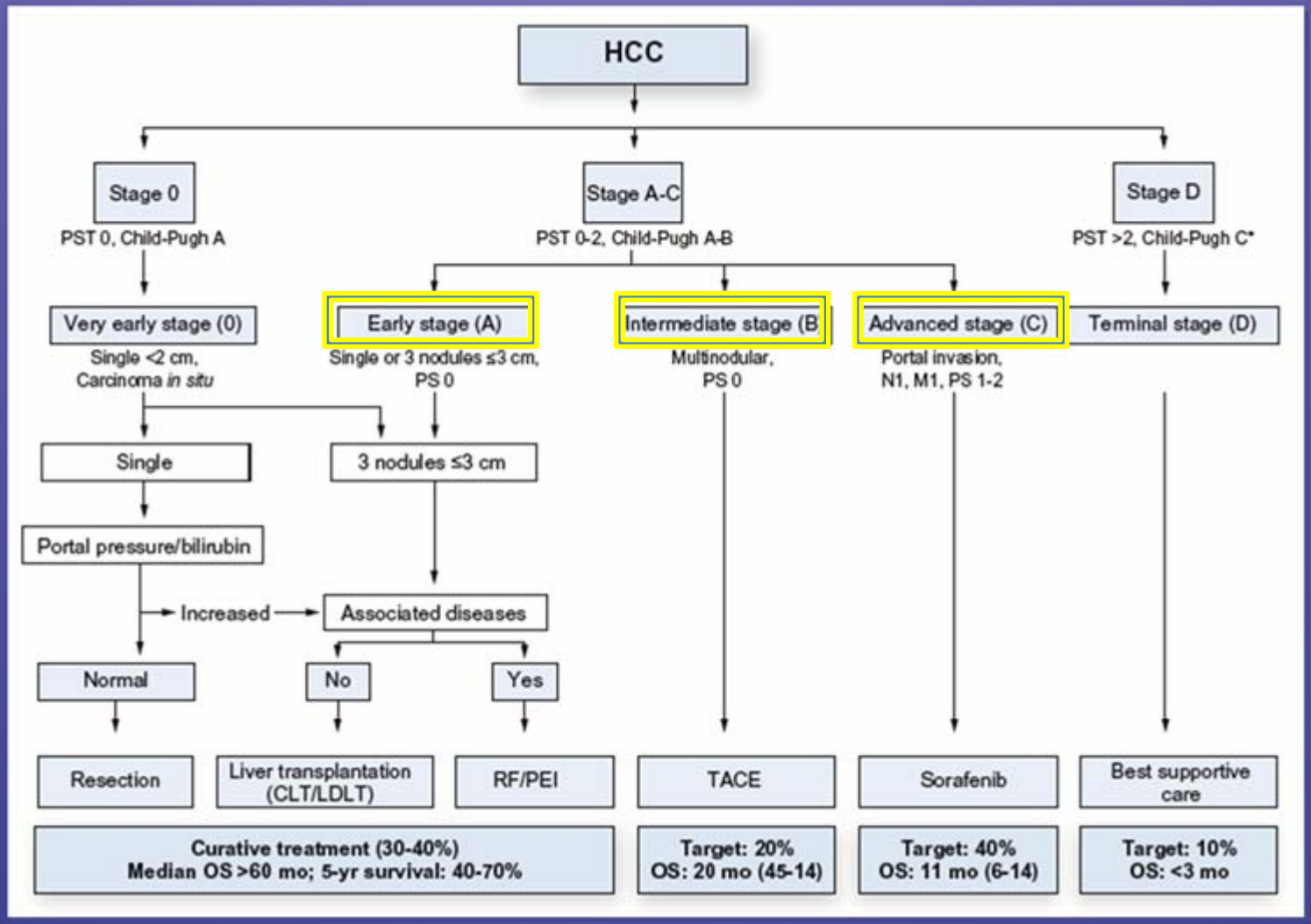
[Mazzaferro et al, Lancet Oncology 2009]

Unacceptable survival (< 50%) beyond the “up-to-7 Criteria”



[Mazzaferro, Lancet Oncology 2009]

Barcelona-Clinic Liver Cancer (BCLC) Classification



EASL conference – 2012; AASLD guidelines – 2012

Barcelona-Clinic Liver Cancer (BCLC) Classification

STAGE A (EARLY HCC)

Ruolo della resezione:

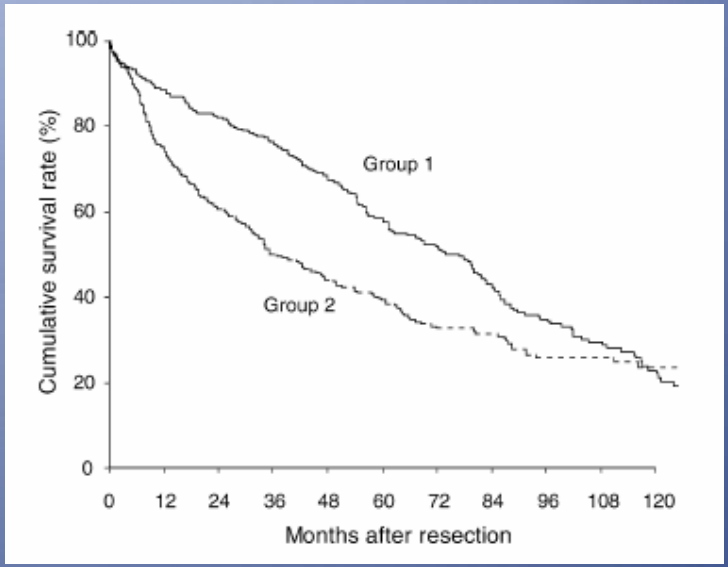
-cirrosi epatica ben compensata (CHILD A)→ mortalità perioperatoria 5-10%
-MELD < 9→ mortalità perioperatoria 0%
-sopravvivenza a 5 anni: 45-50%
-nei pazienti liberi da recidiva di HCC la sopravvivenza a 5 anni: 80%
-al contrario del trapianto che cura l'epatopatia sottostante, la resezione elimina la neoplasia
-selezionare paziente a basso rischio di recidiva HCC→ cirrosi HBV e cirrosi non epatitica
-scelta primaria giustificata se il trapianto salvataggio viene effettuato nei casi di pazienti con recidiva neoplastica
-terapia «PONTE» al trapianto al fine di prolungare il tempo di inserimento in lista secondario alla scarsità di organi
-terapia «PONTE» al trapianto migliore rispetto ai trattamenti locoregionali → caratteristiche anatomopatologiche dell'HCC e del parenchima epatico circostante

Pawlik TM, J Gastrointest Surg 2009

Barcelona-Clinic Liver Cancer (BCLC) Classification

STAGE B (INTERMEDIATE HCC)

Sopravvivenza cumulativa in resezione per Early HCC (Gruppo 1) *vs* Intermediate HCC (Gruppo 2)



Variable	Median survival (mo)	P value
Hepatitis B surface antigen carrier		
No (n = 99)	46.9	.03
Yes (n = 281)	32.1	
Serum alfa fetoprotein[a] (ηg/mL)		
≤ 222.5 (n = 211)	45.5	.01
>222.5 (n = 169)	25.4	
Symptomatic disease		
No (n = 170)	30.9	<.001
Yes (n = 210)	25.7	
Presence of cirrhosis		
No (n = 279)	42.3	.01
Yes (n = 101)	25.3	
No. of tumor nodules		
Solitary (n = 308)	46.9	<.001
Multinodular (n = 72)	14.3	
Microvascular tumor invasion		
No (n = 180)	63.8	<.001
Yes (n = 200)	23.1	
Tumor invasion of adjacent organs		
No (n = 349)	41.6	.003
Yes (n = 31)	16.1	
Histological margin involvement by tumor		
No (n = 356)	42.2	<.001
Yes (n = 24)	12.9	

Fattori prognostici di sopravvivenza post resezione epatica:

0→ 58% sopravvivenza a 5 anni (come in early HCC)

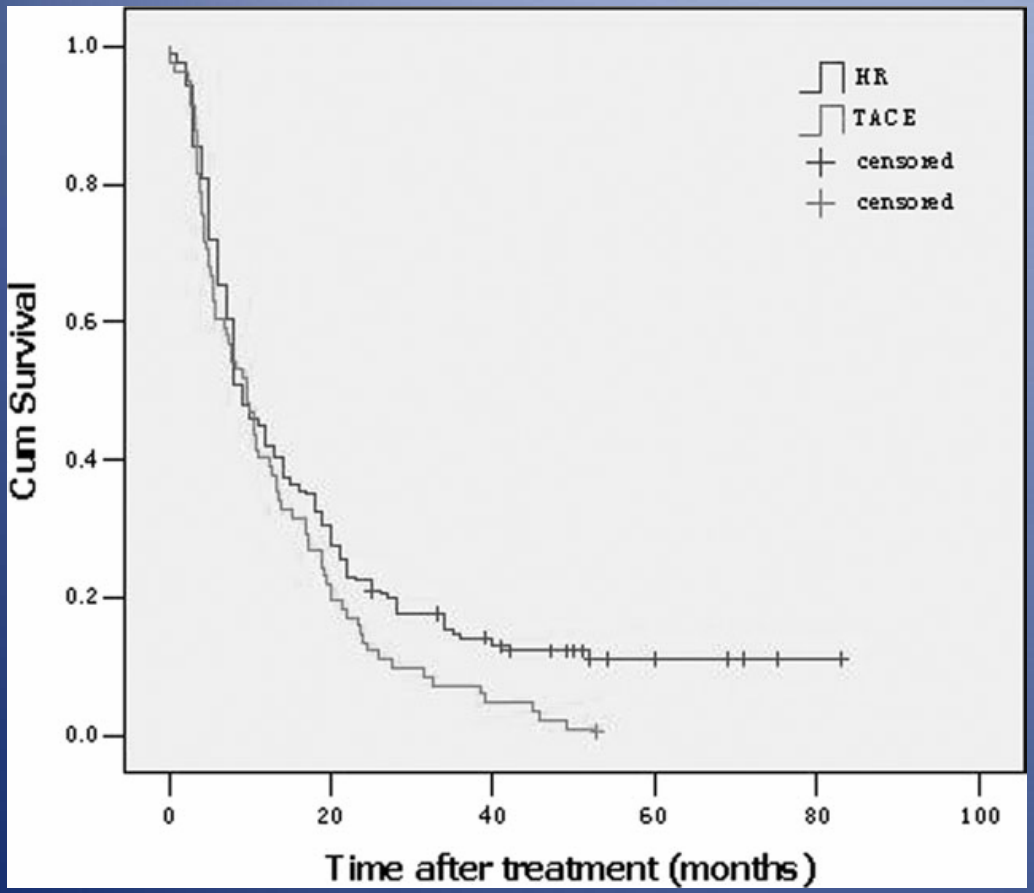
1-2→ 37% sopravvivenza a 5 anni (in post TACE 28% a 3 anni sec. EASL)

≥ 3→ 17% sopravvivenza a 5 anni (gruppo con peggiore outcome post resezione)

Poon Ann. Surg. Oncol. 2005

Barcelona-Clinic Liver Cancer (BCLC) Classification

STAGE C (ADVANCED HCC)



HR 1,3,5 anni 42, 14,11%
TACE 1,3,5 anni 37,7.3, 0.5%
P <0.001

Zhen –Wei Peng Cancer ott 2012

Barcelona-Clinic Liver Cancer (BCLC) Classification

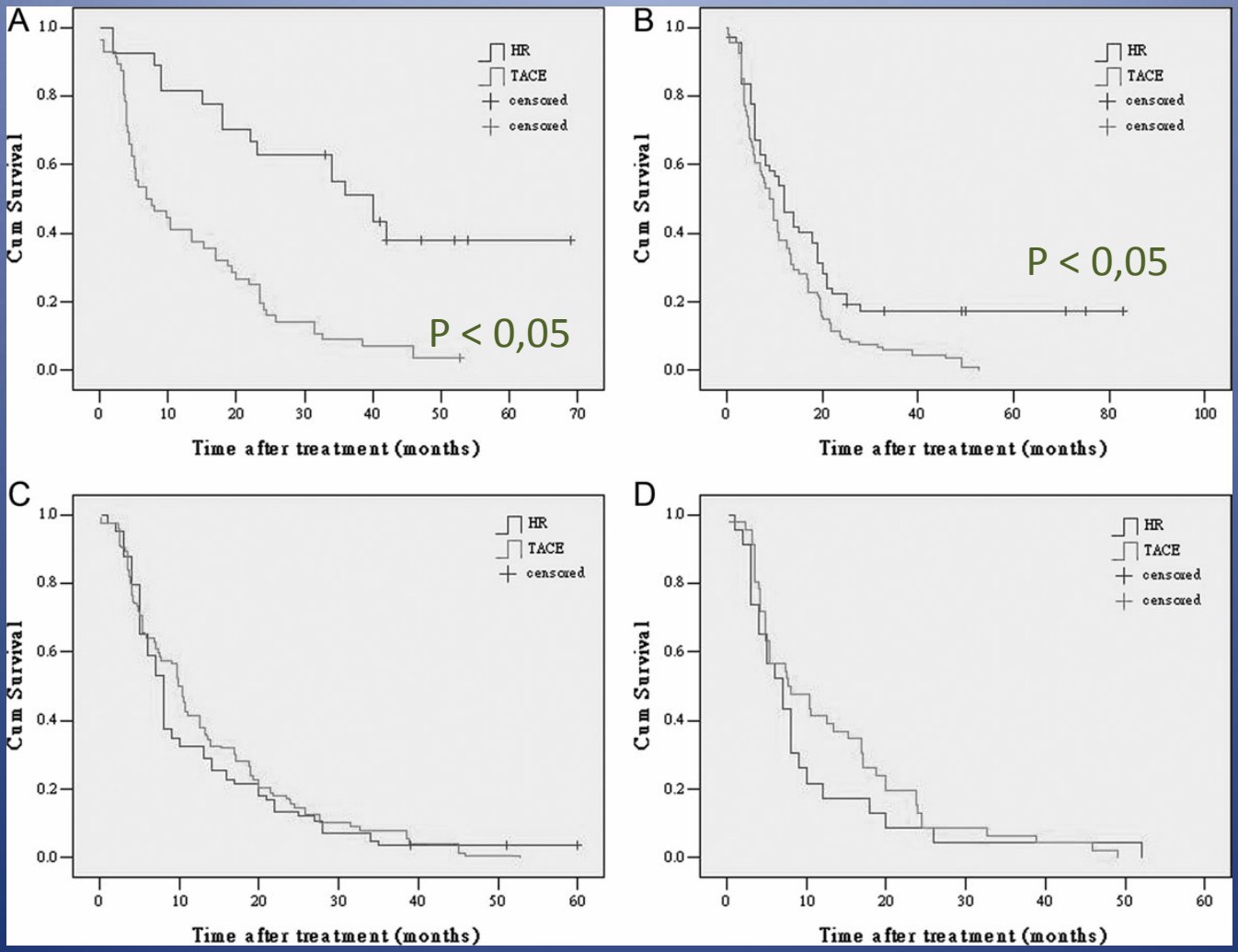
STAGE C (ADVANCED HCC)

PVT tipo 1

PVT tipo 2

PVT tipo 3

PVT tipo 4



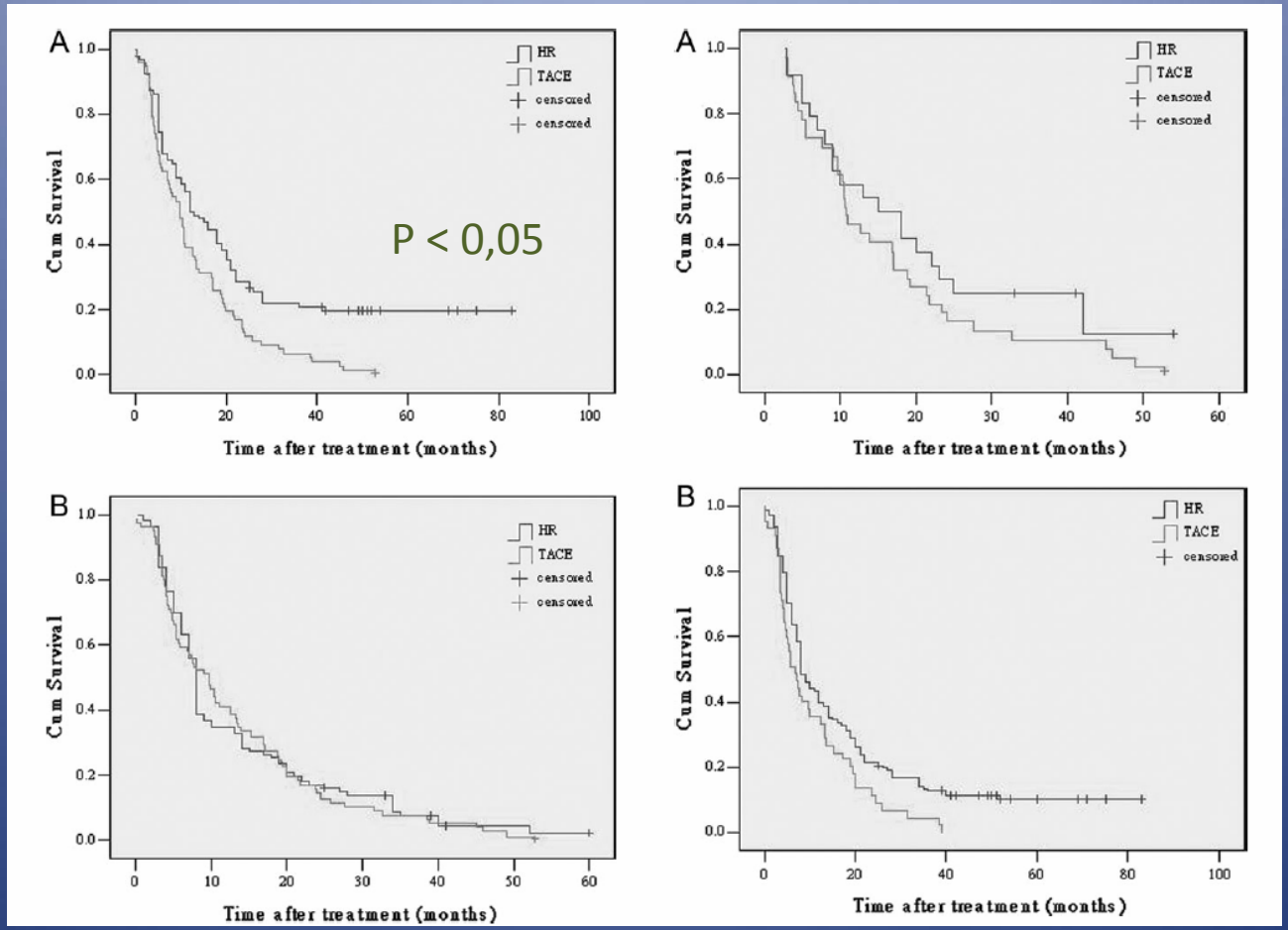
Zhen –Wei Peng Cancer ott 2012

Barcelona-Clinic Liver Cancer (BCLC) Classification

STAGE C (ADVANCED HCC)

HCC singolo

HCC multiplo



HCC < 5 cm

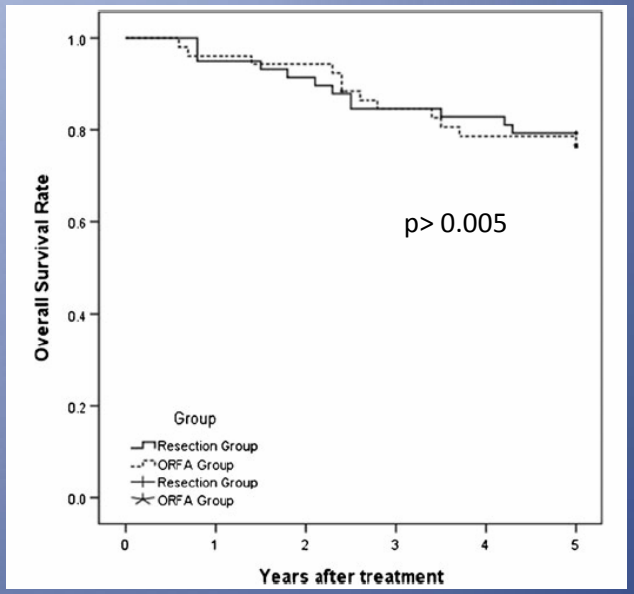
HCC > 5 cm

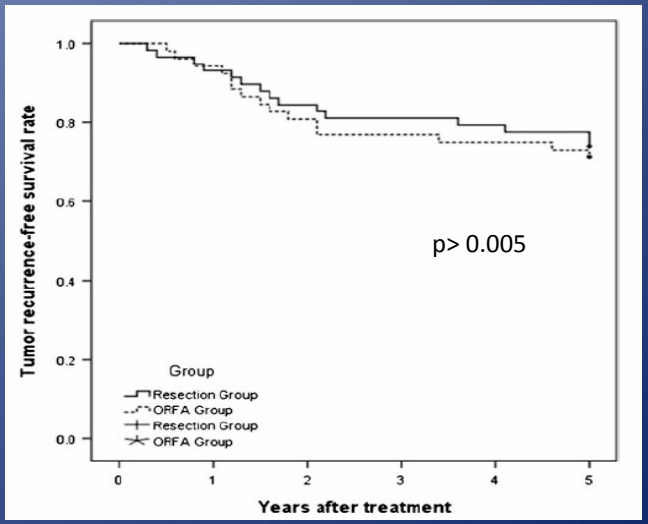
Zhen –Wei Peng Cancer ott 2012

Terapie combinate resezione epatica vs open RF (ORFA) per HCC Milano IN post TACE

	LR Group 58	ORFA Group 52	*P* Value
Operative time (h)	4.8±1.1	3.9±0.9	0.000
Blood loss (ml)	327.6±163.3	120.0±60.6	0.000
Blood transfusion (yes/no)	5/53	1/51	0.124
Length of stay (days)	10.6±4.5	7.3±2.7	0.000
Hospitalization costs	8454.0±3734.9	5882.0±2223.0	0.000
Complications			0.090
Grade I	4	3	
Bile leak	1	0	
Wound infection	1	1	
Pleural effusion	1	2	
Intestinal obstruction	1	0	
Grade II	5	2	
Postoperative hemorrhage	2	0	
Wound infection	1	1	
Pneumonia	1	1	
Bile leak	1	0	
Grade IIIa	2	0	
Pleural effusion	1	0	
Bile leak	1	0	
Grade IIIb	3	2	
Intraperitoneal hemorrhage	2	1	
Gastrointestinal bleeding	1	0	
Biloma	0	1	
Grade IVa	1	0	
Hepatic failure	1	0	
Grade IVb	0	0	
Grade V	0	0	

Outcomes Intraoperatorio e postoperatorio





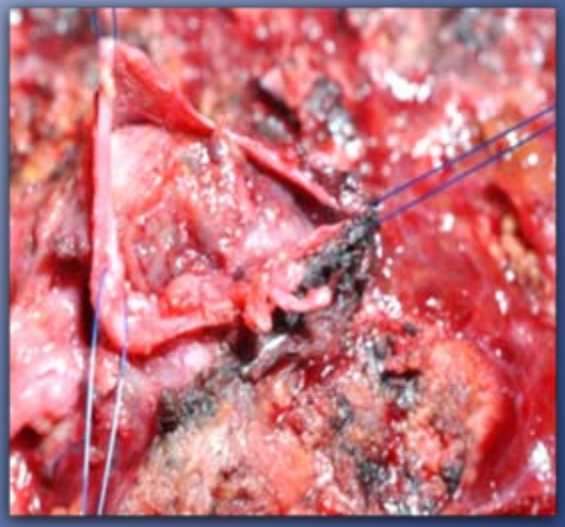
Lei J., J Gastrointest Surg 2013

Absolute contraindications to liver transplant

Macrovascular invasion

Liver Resection *Versus* Transplantation for Hepatocellular Carcinoma in Cirrhotic Patients

Henri Bismuth, M.D., F.A.C.S. (Hon), Laurence Chiche, M.D., René Adam, M.D., Denis Castaing, M.D., Tom Diamond, M.D., F.R.C.S., and Ashley Dennison, M.D., F.R.C.S.



Portal thrombosis (main branches) is significantly associated with a dismal prognosis (20% at 3 years)

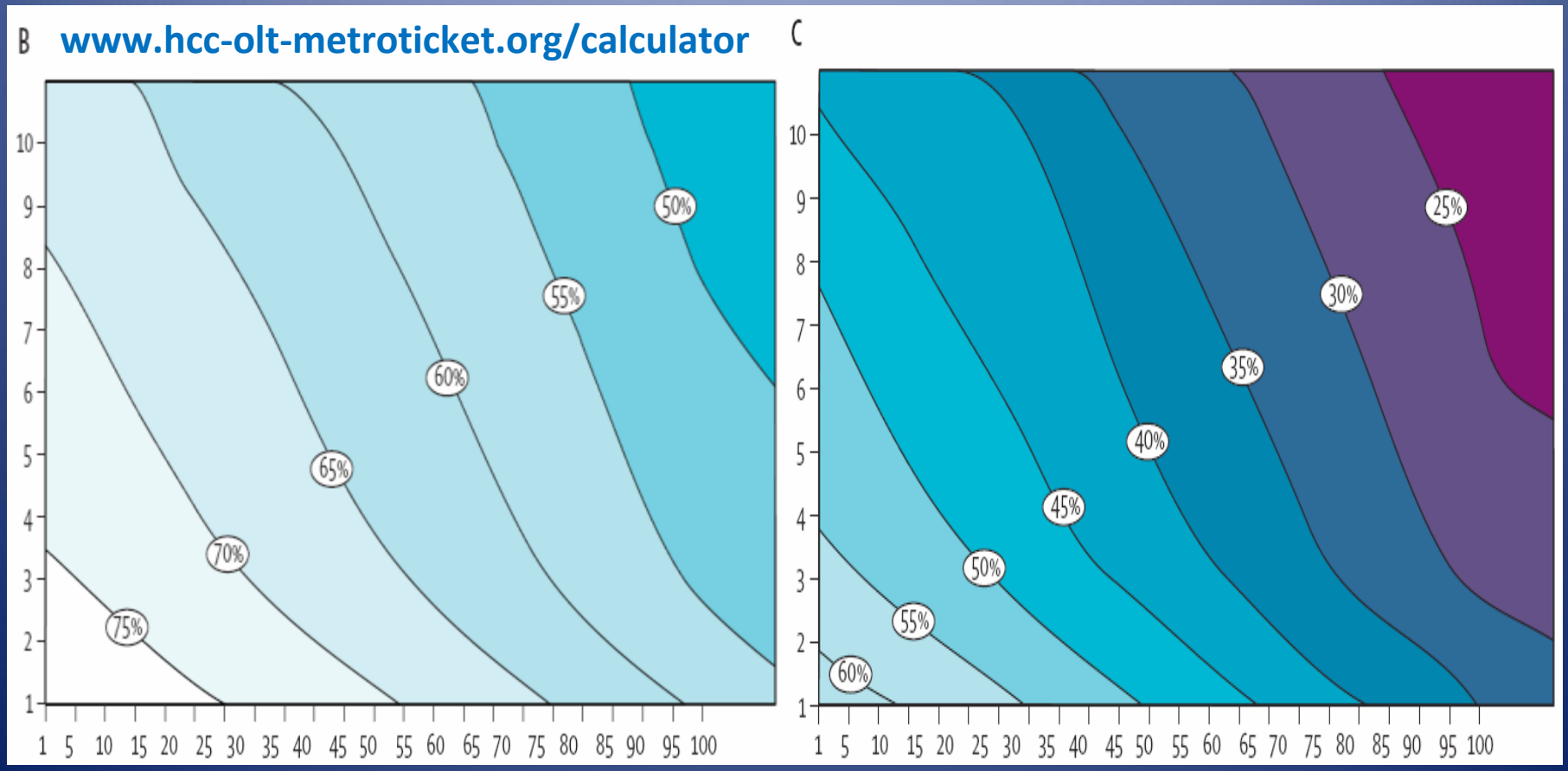
[Bismuth H, Ann Surg 1993]

The role of pathological features: mVI

Influence of micro-Vascular Invasion on patient outcome

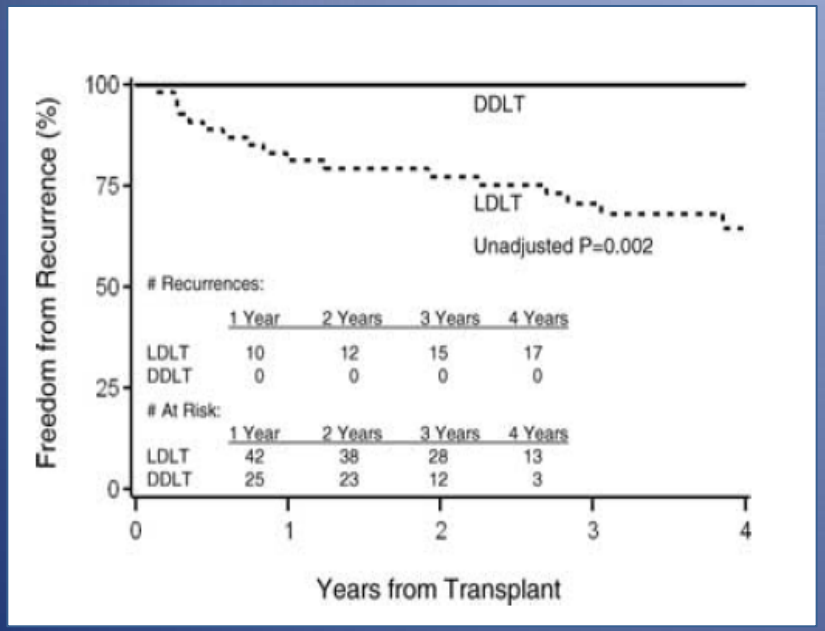
Absent

Present



[Mazzaferro et al, Lancet Oncology 2009]

Fast track effect in LDLT for HCC: transforming potential drop-outs into recurrences



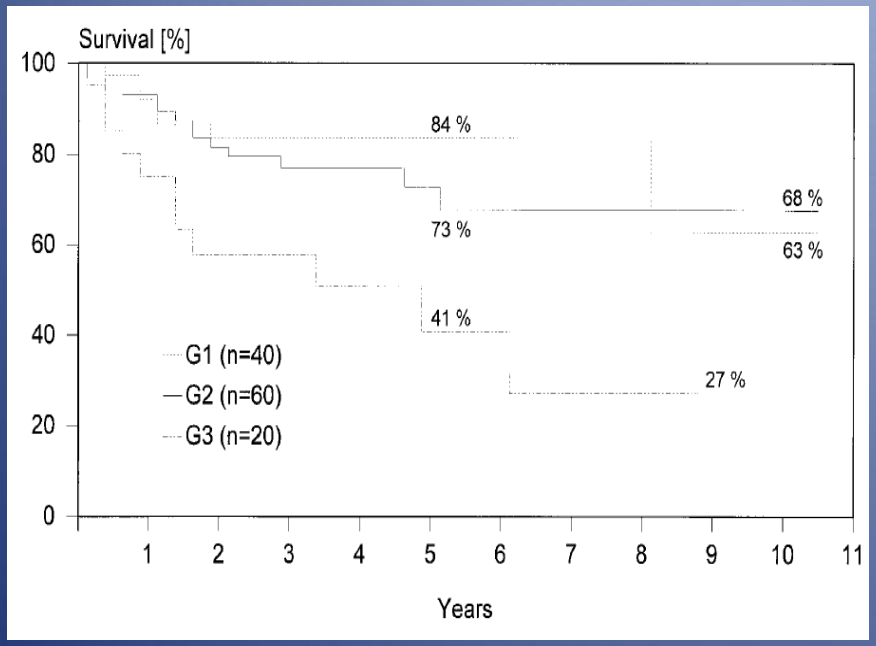
High recurrence-rate may be observed in patients with biologically aggressive tumor, whose drop-out from the list because of tumor progression may be prevented by the prompt availability of the graft.

- Mean waiting time:160 vs 469 days (p<.0001)
- Median follow-up: 4 vs 3.4 years (p<.05)
- Recurrence rate: 29% vs 0 (p=.002)

[Fisher et al, Am J Transplant 2007]

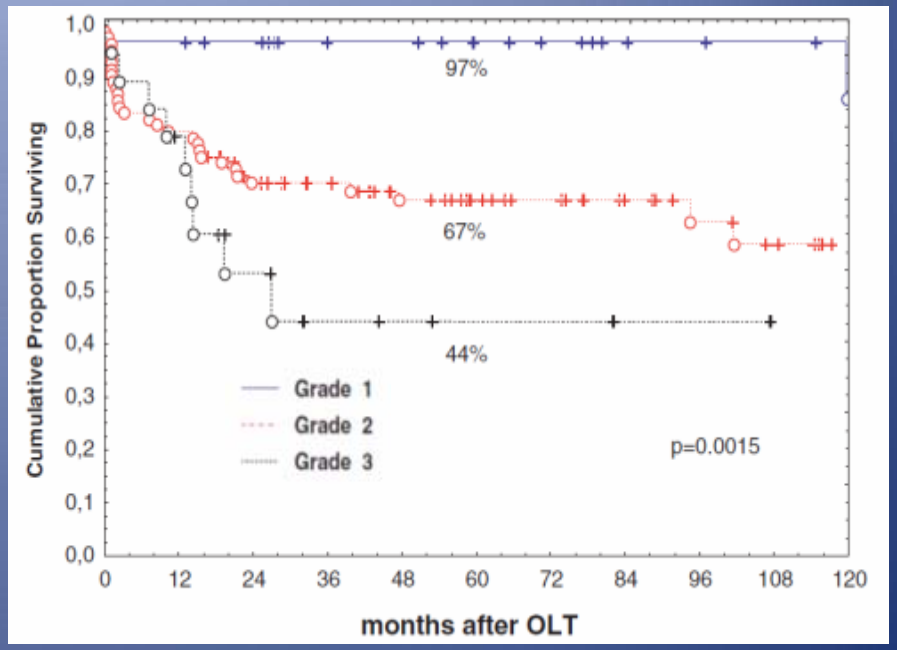
The role of pathological features: grading

120 patients – 86.5% within MC



[Jonas S, Hepatology 2001]

155 patients – 84% within MC

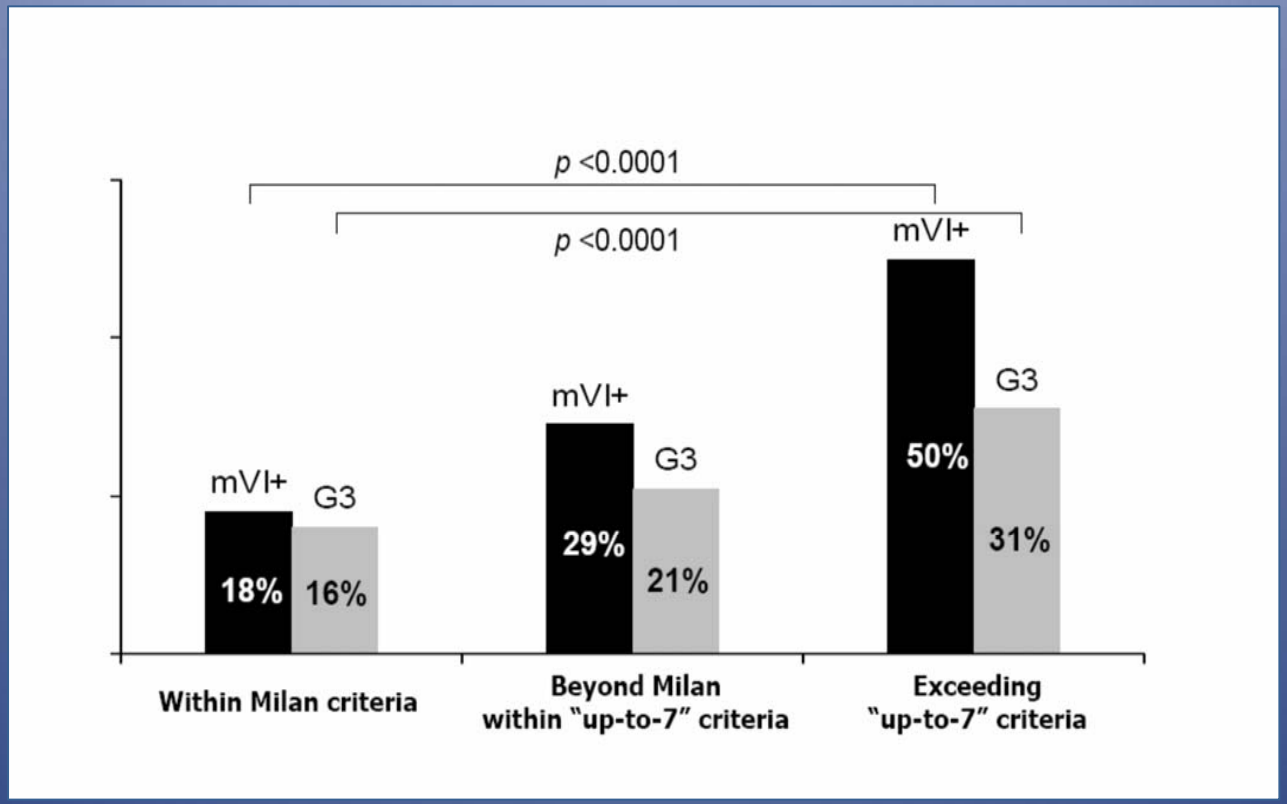


[Zavaglia C, Am J Gastroenterol 2005]

Overall survival for G3 HCC is inferior to 50% at 5 yrs

The role of pathological features

Correlation mVI and grading among size-and-number categories



A significant increment of G3 parallels the size/number grouping and incidence of mVI

[Mazzaferro, Lancet Oncology 2009]

Stadiazione dell'HCC su cirrosi
EASL conference – 2012; AASLD guidelines – 2012

IDEAL PROGNOSTIC SYSTEM → Patients stratification → Survival prediction
Treatment algorithm
RCT planning

HCC prognostic factors

Tumor characteristics

(n° and size of nodules, vascular invasion)

Patient general health condition

Liver function

Treatment efficacy

EASL conference – 2012; AASLD guidelines – 2012

BCLC staging system

STAGE Treatment efficacy	PST	TUMOR STATUS Tumor stage	Okuda	LIVER FUNCTION
Very early HCC	0	Single < 2cm	I	No CRPH / Bil.N
Early stage HCC	0 0 0	Single Single 3 nodules ≤ 3 cm	I I I - II	CRPH/ bil. N CRPH/ bil. Child A-B
intermediate HCC	0	Multinodular	I-II	Child A-B
Advanced HCC	1-2	Vascular invasion or extrahepatic spread	I-II	Child C
End stage HCC	3-4	Any	III	Child C

EASL conference – 2012; AASLD guidelines – 2012

Barcelona-Clinic Liver Cancer (BCLC) Classification

STAGE 0 (VERY EARLY HCC)

-Singola neoplasia con diametro < 2 cm

-Assenza di invasione vascolare/satellitosi

-Child A

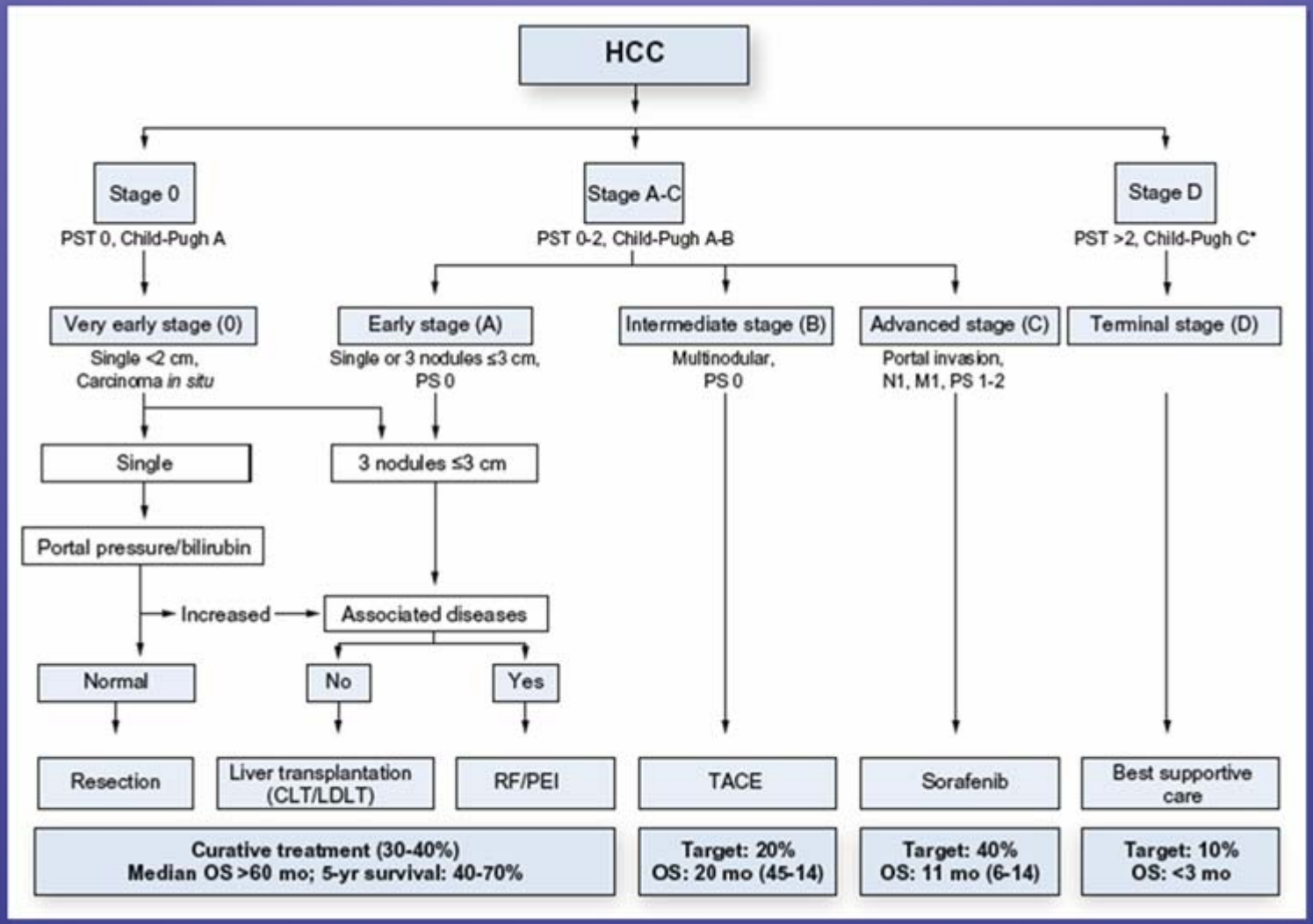
-Sopravvivenza a 5 anni:

per resezione e Trapianto → 80-90%

per ablazione locale → 70%

EASL conference – 2012; AASLD guidelines – 2012

Barcelona-Clinic Liver Cancer (BCLC) Classification



EASL conference – 2012; AASLD guidelines – 2012

Barcelona-Clinic Liver Cancer (BCLC) Classification

STAGE A (EARLY HCC)

-Singola neoplasia con diametro ≥ 2 cm o 3 noduli con diametro < 3 cm

-Child A/B

-Sopravvivenza mediana senza alcun trattamento: 36 mesi

-Sopravvivenza a 5 anni per resezione, Trapianto o ablazione locale → 50-70%

-TUMOR STATUS: dimensioni del nodulo maggiore e multicentricità (singolo nodulo 2-5 cm, 3 noduli ≤ 3 cm)

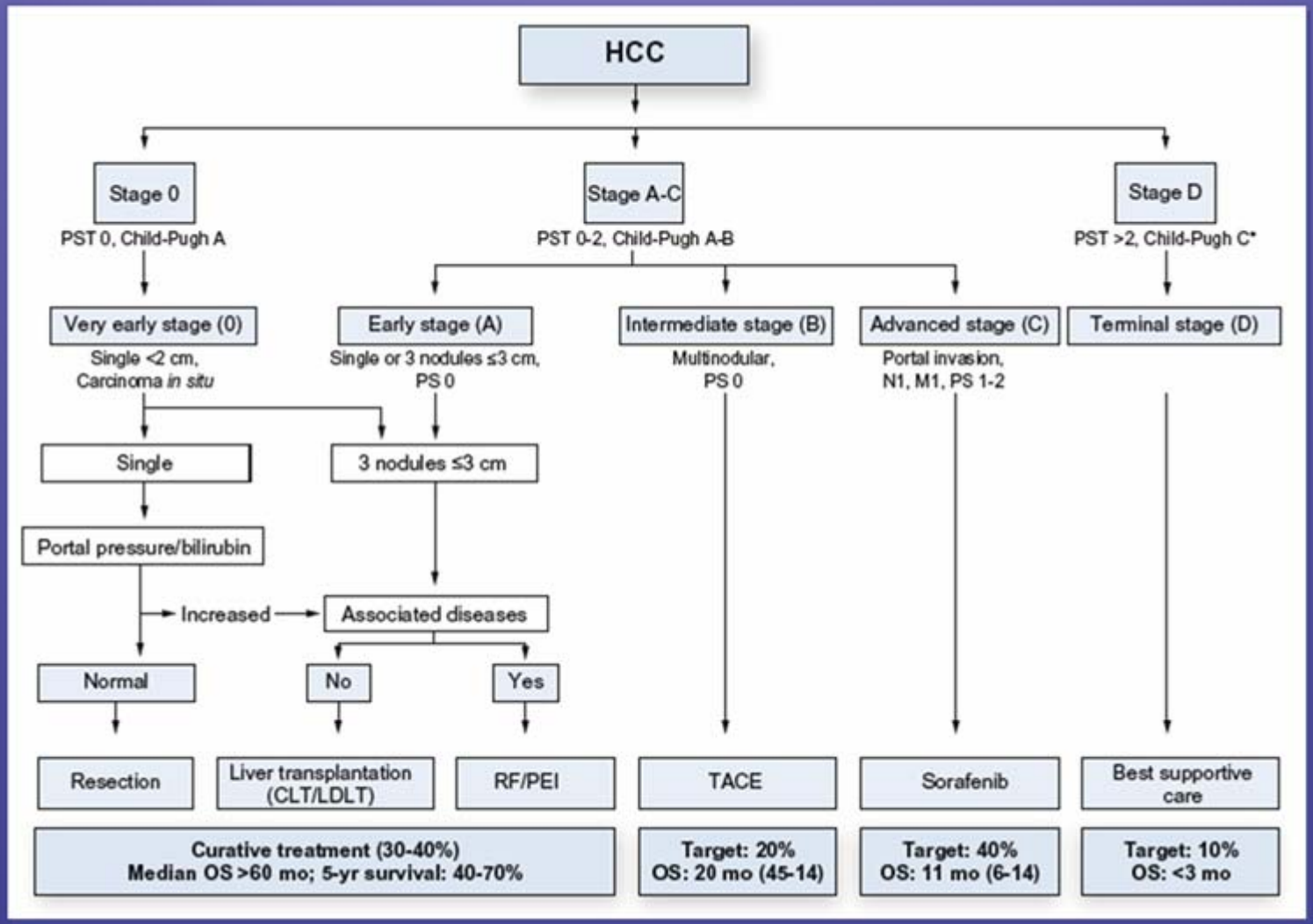
-Predittori di sopravvivenza post resezione per neoplasia singola: grado di ipertensione portale e bilirubinemia nella norma

-Predittori di sopravvivenza post ablazione locale: Child A

-Predittori di sopravvivenza post Trapianto: Criteri di Milano per HCC

EASL conference – 2012; AASLD guidelines – 2012

Barcelona-Clinic Liver Cancer (BCLC) Classification



EASL conference – 2012; AASLD guidelines – 2012

Barcelona-Clinic Liver Cancer (BCLC) Classification

STAGE B (INTERMEDIATE HCC)

-Neoplasia multinodulare in paziente asintomatico

-Child A/B

-Sopravvivenza mediana senza trattamento → 16 mesi o 49% a 2 anni

-Sopravvivenza mediana con trattamento→ aumento della sopravvivenza mediana di 19-20 mesi,MA :

se buone risposta a TACE: sopravvivenza mediana→ 36-45 mesi

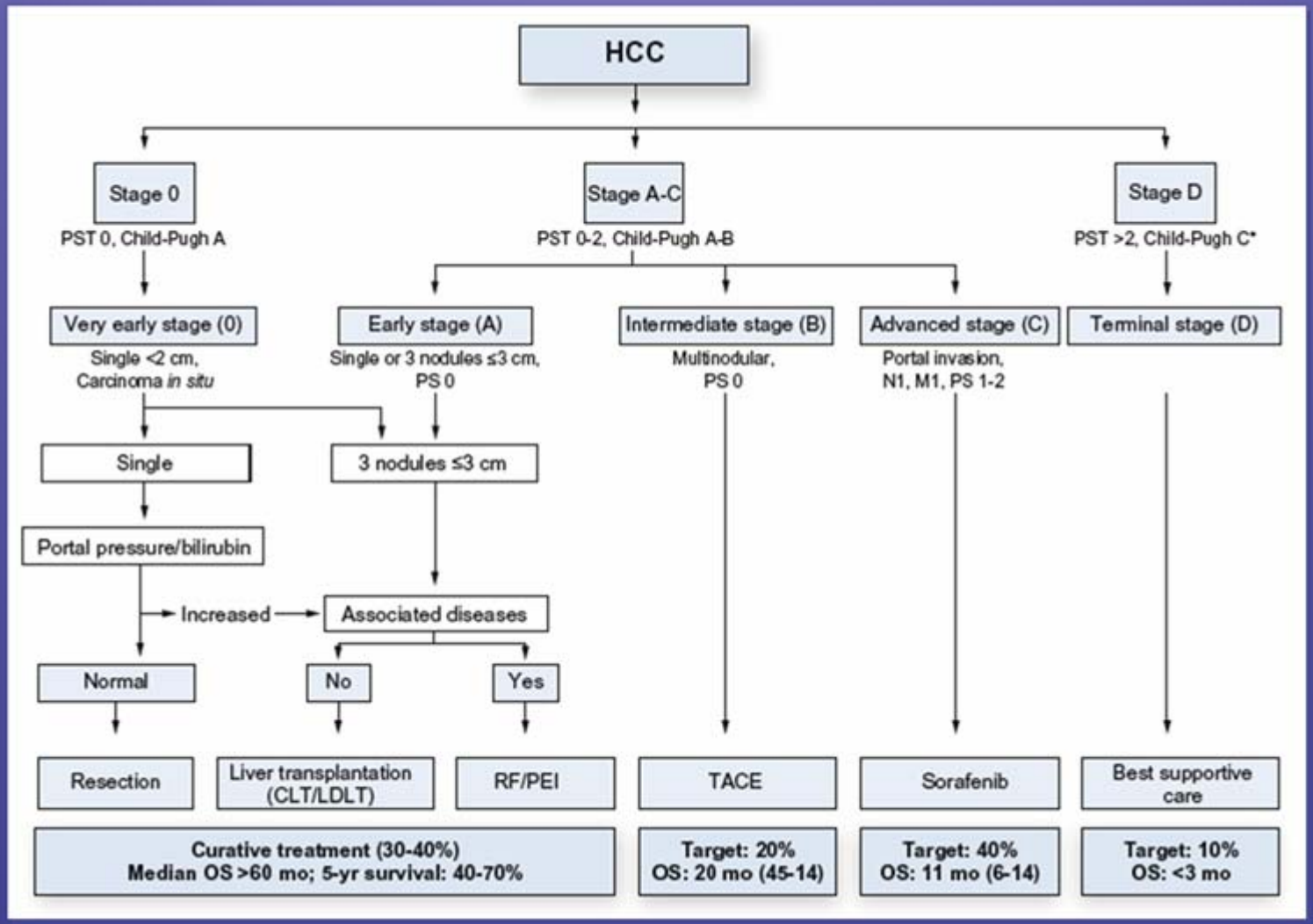
se pessima risposta a TACE: soprevvivenza mediana → 11 mesi

-Sopravvivenza mediana se in terapia con Sorafenib→ 14.7 mesi

-Predittori di sopravvivenza post TACE: presenza di ascite

EASL conference – 2012; AASLD guidelines – 2012

Barcelona-Clinic Liver Cancer (BCLC) Classification



EASL conference – 2012; AASLD guidelines – 2012

Barcelona-Clinic Liver Cancer (BCLC) Classification

STAGE C (ADVANCED HCC)

-Neoplasia multinodulare in paziente sintomatico

-Invasione macrovascolare (vasi portali) o extraepatica (MTS linfonodale o a distanza)

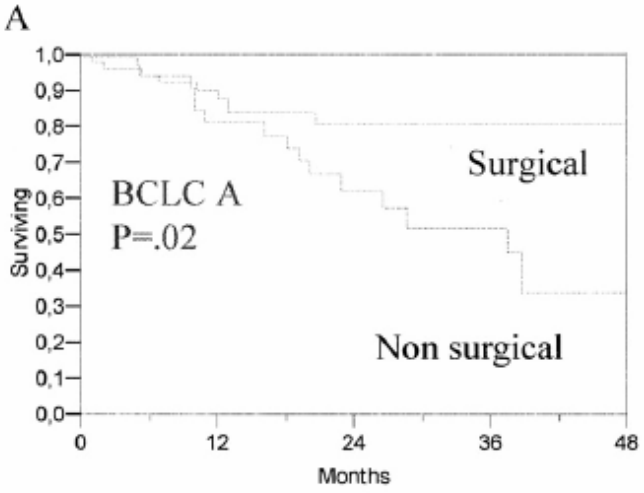
-Child A/B

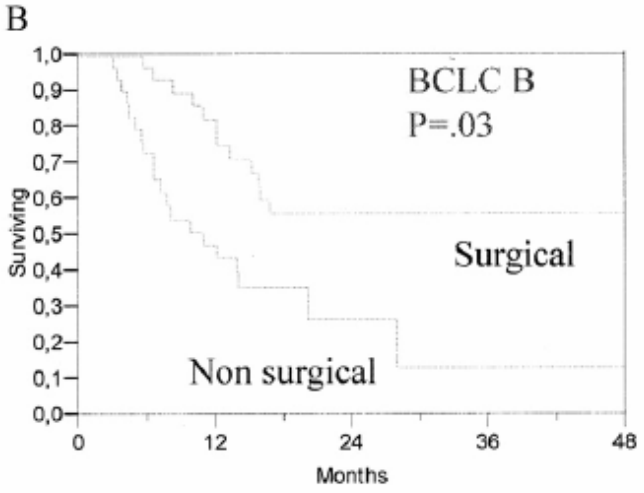
-Sopravvivenza mediana → 6 mesi (+/- 1 mese se Child A oppure B) o 25% a 1 anni

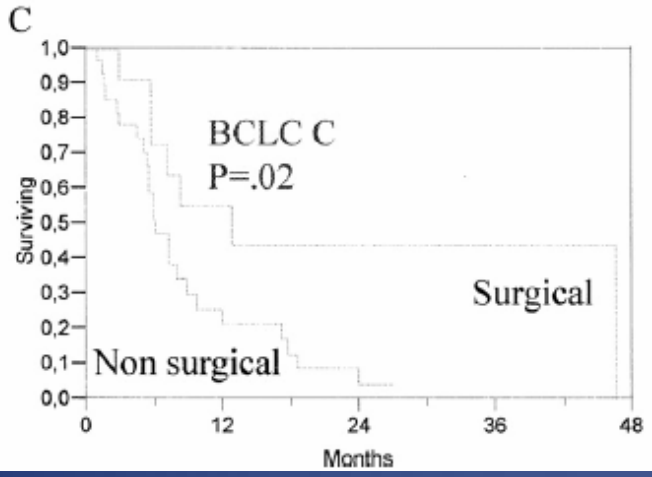
-Sopravvivenza mediana se in terapia con Sorafenib→ 9.5 mesi

EASL conference – 2012; AASLD guidelines – 2012

Ruolo della Chirurgia come ruolo prognostico nella BCLC







Groups of patients	BCLC	No. (%)	Survival rates (%) 1yr	3yr	4yr	P value
SURGICAL (400 pts)	A	228 (57)	90	81	81	<0.01
	B	124 (31)	82	56	56	
	C	48 (12)	55	44	0	
	D	-	-	-	-	
NON SURGICAL (315 pts)	A	110 (35)	81	52	34	<0.01
	B	91 (29)	47	13	0	
	C	82 (26)	26	0	0	
	D	32 (10)	30	0	0	

Vitale A. Transplantation Proceedings 2009

Barcelona-Clinic Liver Cancer (BCLC) Classification

STAGE D (END-STAGE HCC)

-Neoplasia multinodulare in paziente gravemente sintomatico

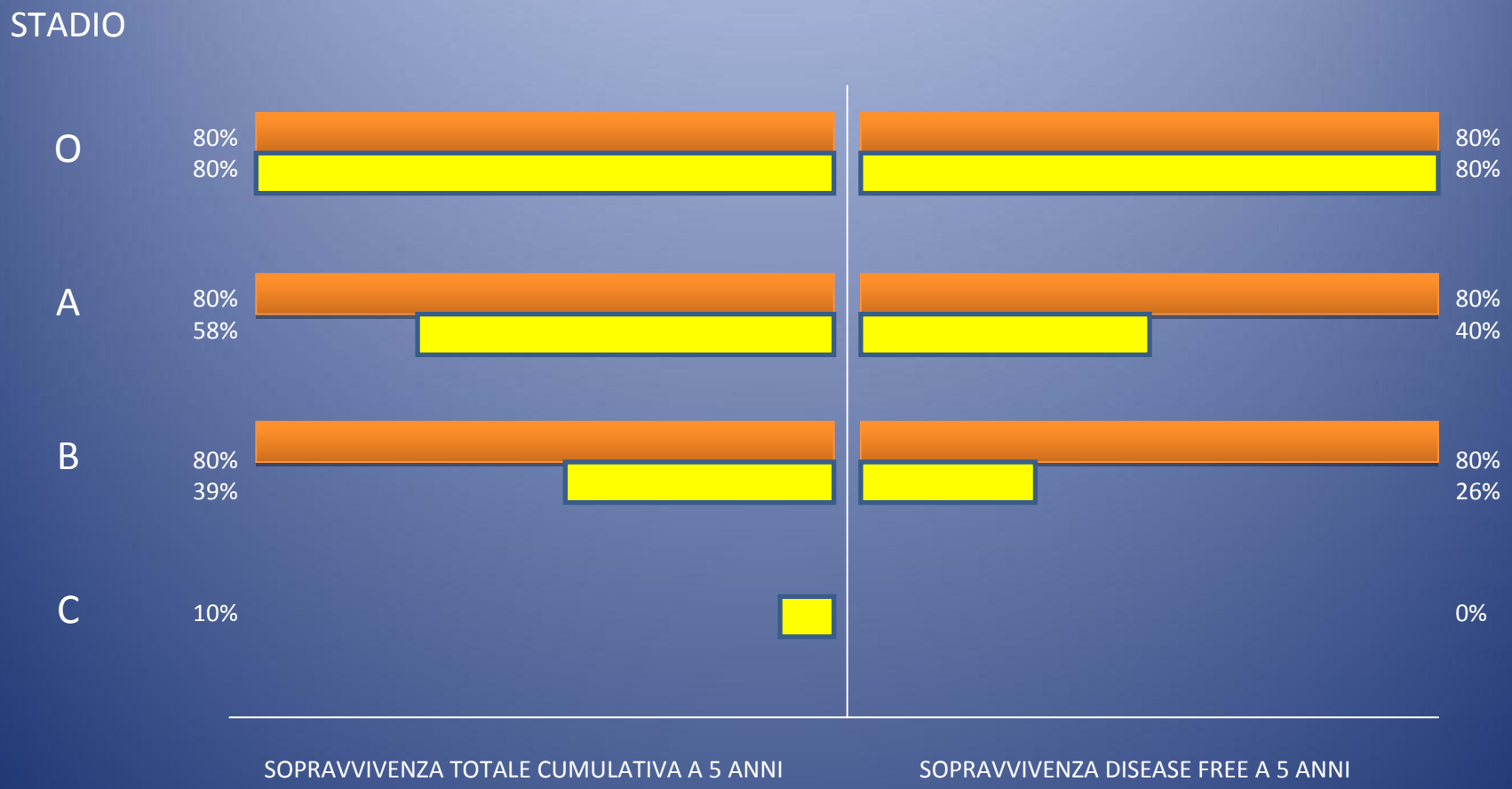
- Basso valore di Performance Status: ECOG 3-4

-Child C

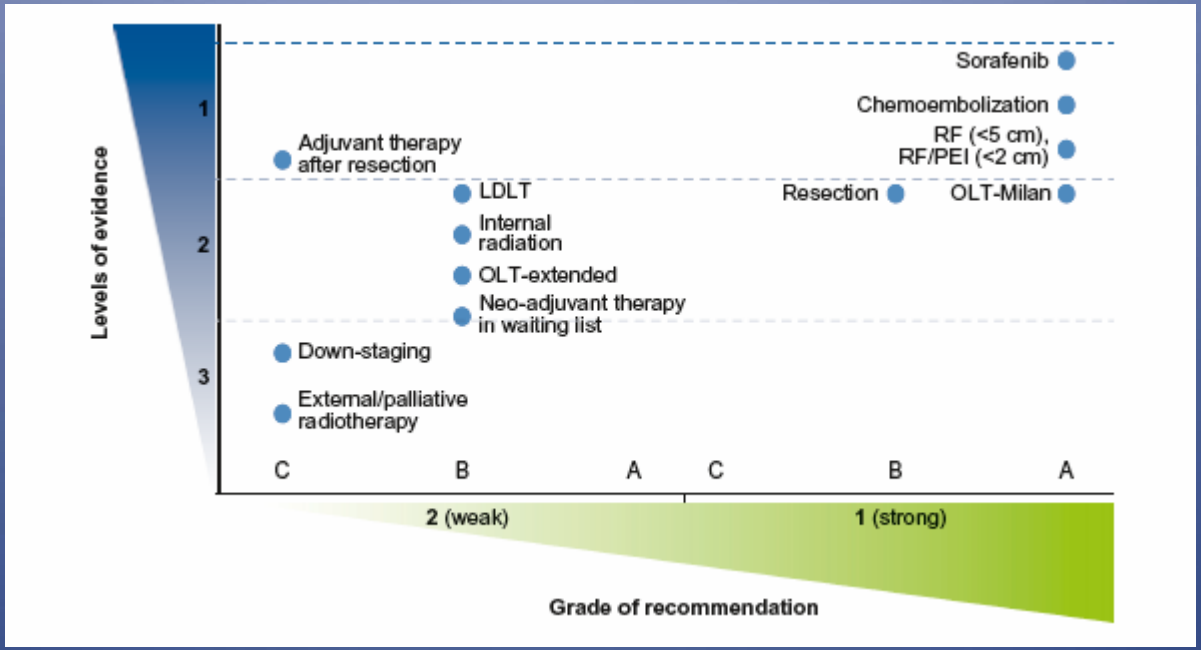
-Sopravvivenza mediana → 3-4 mesi o 11% a 1 anni

EASL conference – 2012; AASLD guidelines – 2012

Barcelona-Clinic Liver Cancer (BCLC) Classification-Sopravvivenza



Rapporto livello di evidenza/Grado di raccomandazione per HCC



EASL conference – 2012; AASLD guidelines – 2012

Resezione epatica: rischio di recidiva

Più importanti fattori predittivi di recidiva neoplastica:

-diametro della lesione→ sopravvivenza a 5 anni:
HCC < 2 cm: 66%
HCC 2-5 cm: 52%
HCC > 5 cm: 37%

-invasione microvascolare → associato a differenziazione istologica, grading e dimensioni del nodulo maggiore. Probabilità di presenza del suddetto:
diametro nodulo = 2 cm→ 20%
diametro nodulo 2-5 cm → 30-60%
diametro nodulo ≥ 5 cm→ 60-90%

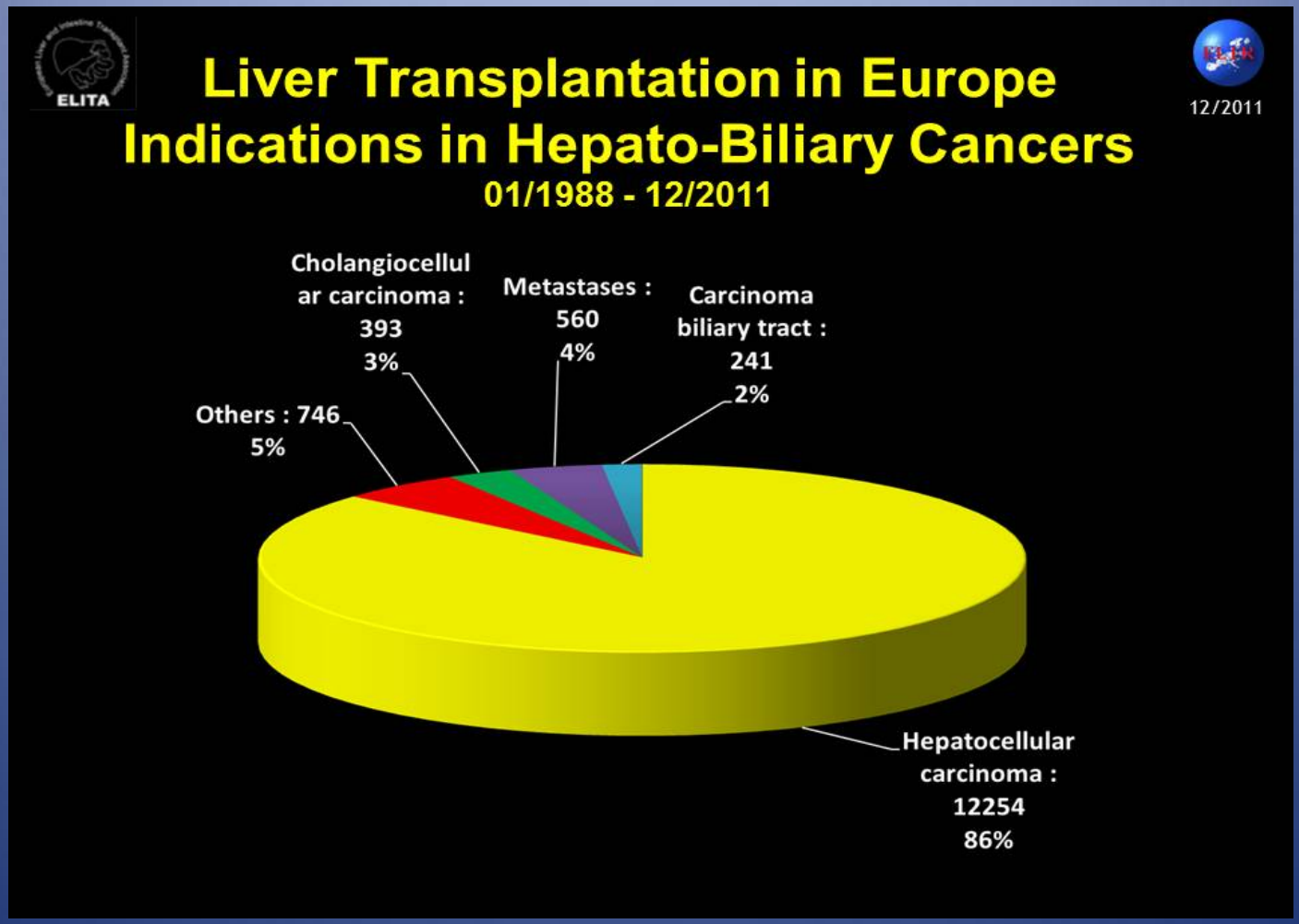
-numero lesioni → sopravvivenza a 5 anni:
1 nodulo: 57%
≥3 noduli: 26%

La recidiva neoplastica deriva dal tumore primitivo e non da tumori metacroni sviluppatisi nel fegato cirrotico (comunque la recidiva conseguente a disseminazione si manifesta durante i primi tre anni di followw up)

La chemioterapia pre o post resezione non migliora la probabilità di recidiva neoplastica

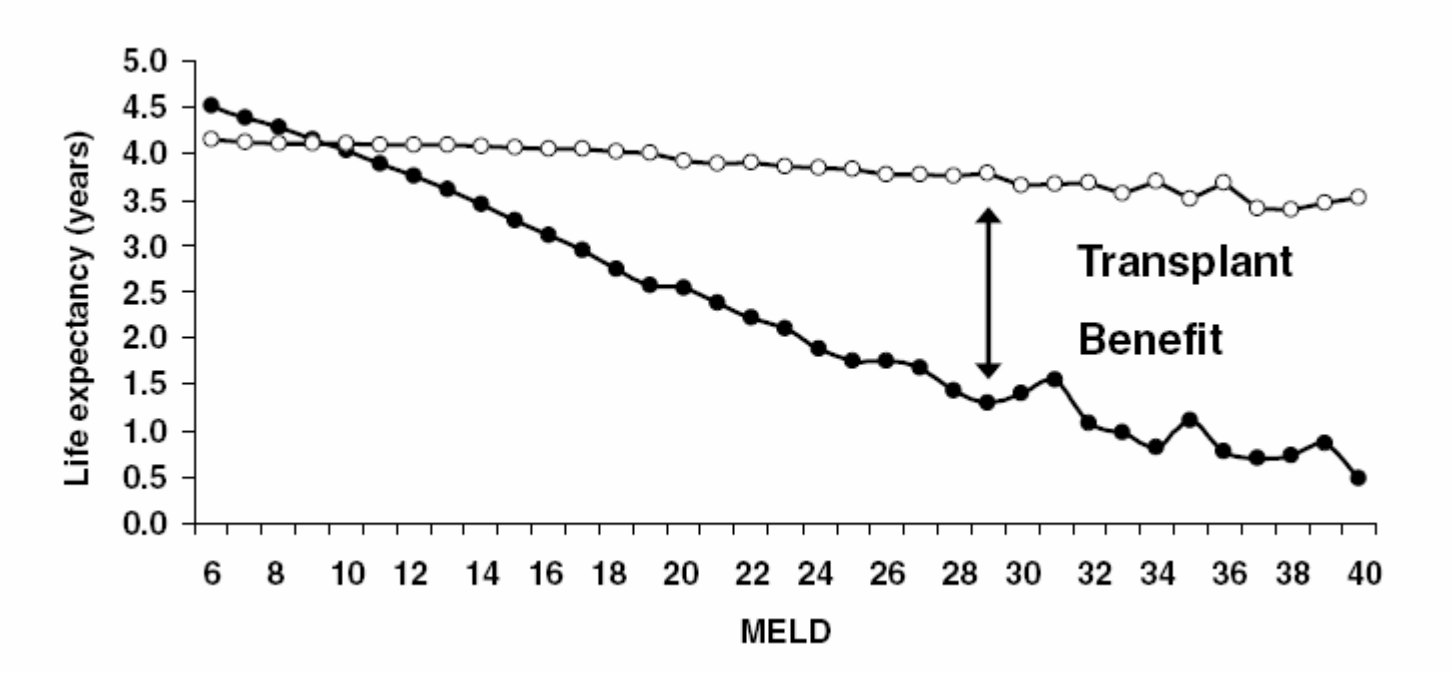
EASL conference – 2012; AASLD guidelines – 2012

Trapianto di Fegato: indicazioni per neoplasie epatiche



ELTR 2012

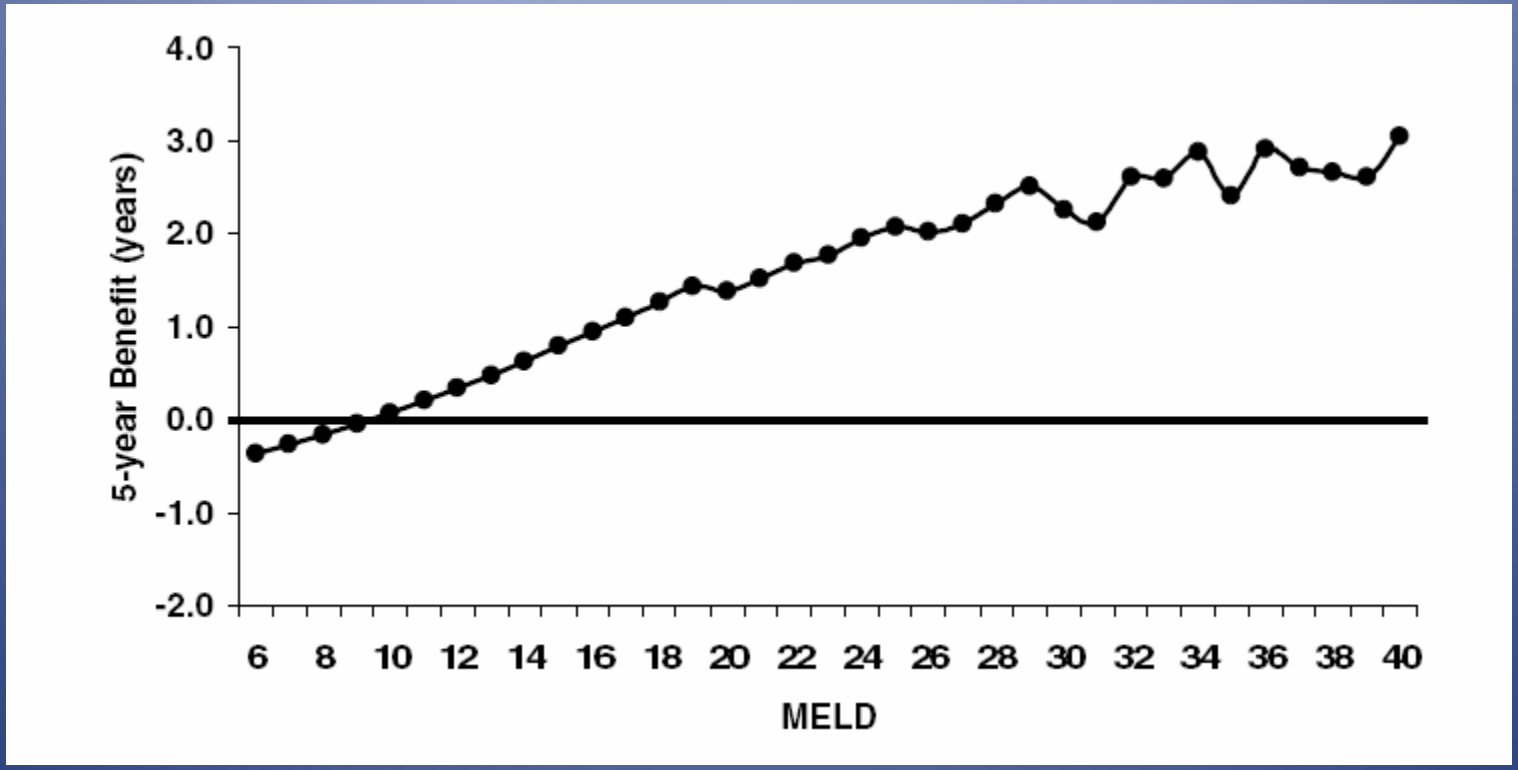
TRANSPLANT BENEFIT IN OLT



Aspettativa di vita in una media di 5 anni utilizzando il MELD score
(Rank correlation fra benefit score e MELD score = 0.67)

Schaubel AJOT 2009

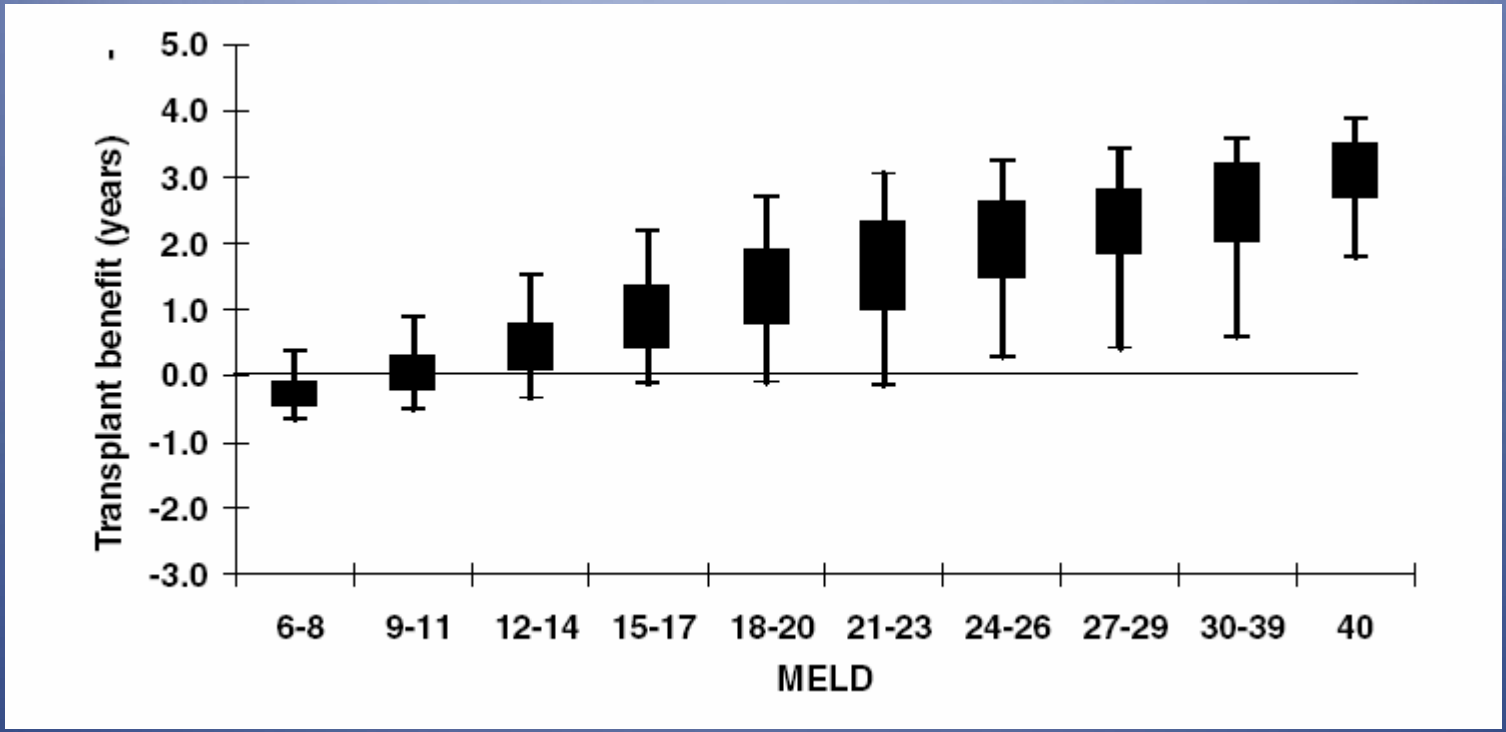
TRANSPLANT BENEFIT IN OLT



Transplant BENEFIT in una media di 5 anni utilizzando il MELD score

Schaubel AJOT 2009

TRANSPLANT BENEFIT IN OLT

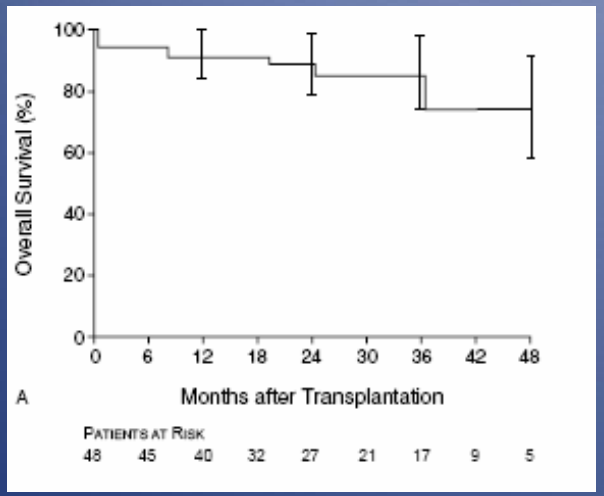


Variabilità nella distribuzione del benefit score ad ogni MELD score

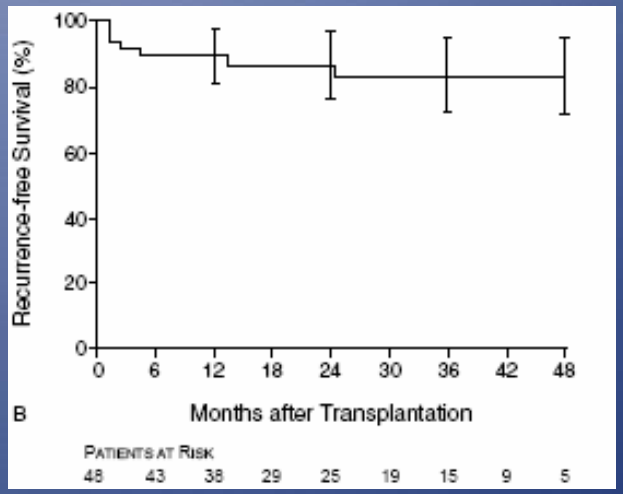
Schaubel AJOT 2009

Criteri di selezione HCC
Criteri di Milano

Nodulo singolo ≤ 5 cm
HCC multifocale fino a 3 noduli ≤ 3 cm
Assenza di invasione macrovascolare
Assenza di malattia extraepatica



Sopravvivenza globale a 4 anni: 75%



Sopravvivenza libera da malattia a 4 anni: 83%

Mazzaferro N Engl J Med 1996

Problematiche relative al trapianto per HCC

Le liste di attesa per LT sono caratterizzate dalla coesistenza di due distinte popolazioni (HCC e ESLD) ciascuna delle quali richiede il rispetto di legittime esigenze.

Esigenze HCC:

- Tempi di attesa limitati
- Contenimento neoplasia entro limiti trapiantabilità
- Drop out

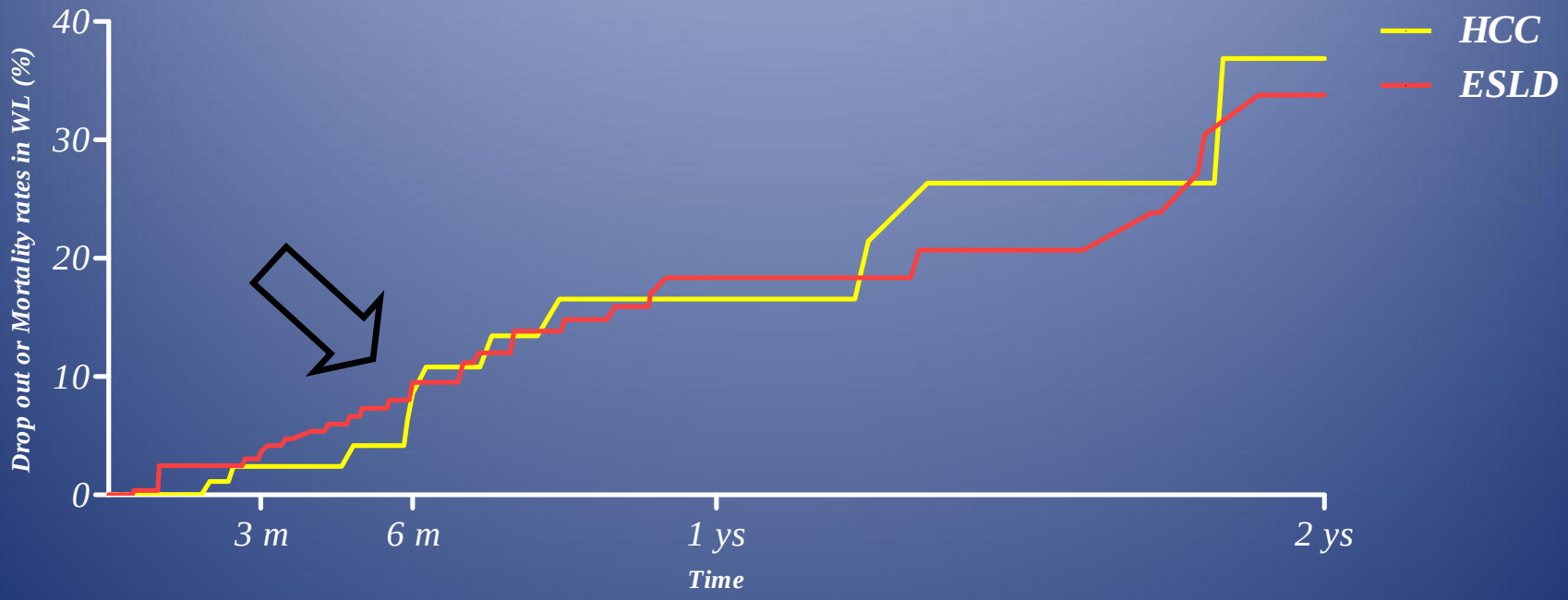
Esigenze ESLD:

- Nessuna alternativa terapeutica
- Lenta ma costante evoluzione
- Continuo incremento (Re-LT?)
- Mortalità in lista

Trattamenti pre LT
Disponibilità di organi costante

Richiesta di espansione dei Criteri per HCC

Drop out e Mortalità in lista in WL HCC *vs* ESLD

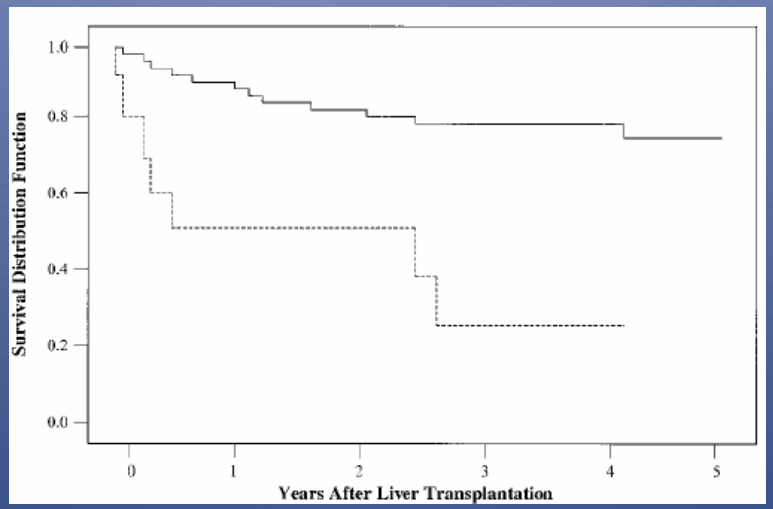


ELTR 2006

Criteri di selezione HCC
Criteri di San Francisco (UCSF)

Nodulo singolo ≤ 6,5 cm

HCC multifocale: ≤ 3 noduli con lesione maggiore ≤ 4,5 cm
e diametro totale ≤ 8 cm



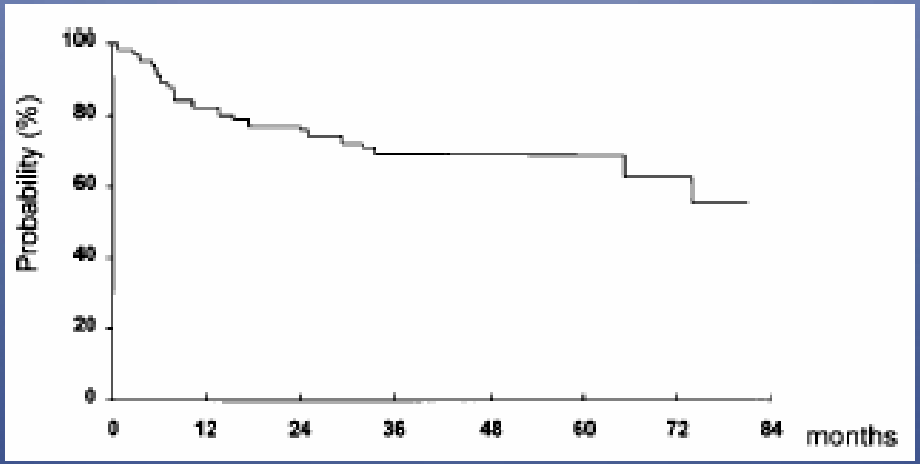
$p < 0.0005$

Sopravvivenza ad 1 e 5 anni: 90% e 75,2%

Yao Hepatology 2001

Criteri di selezione HCC
Criteri di Barcellona (BCLC)

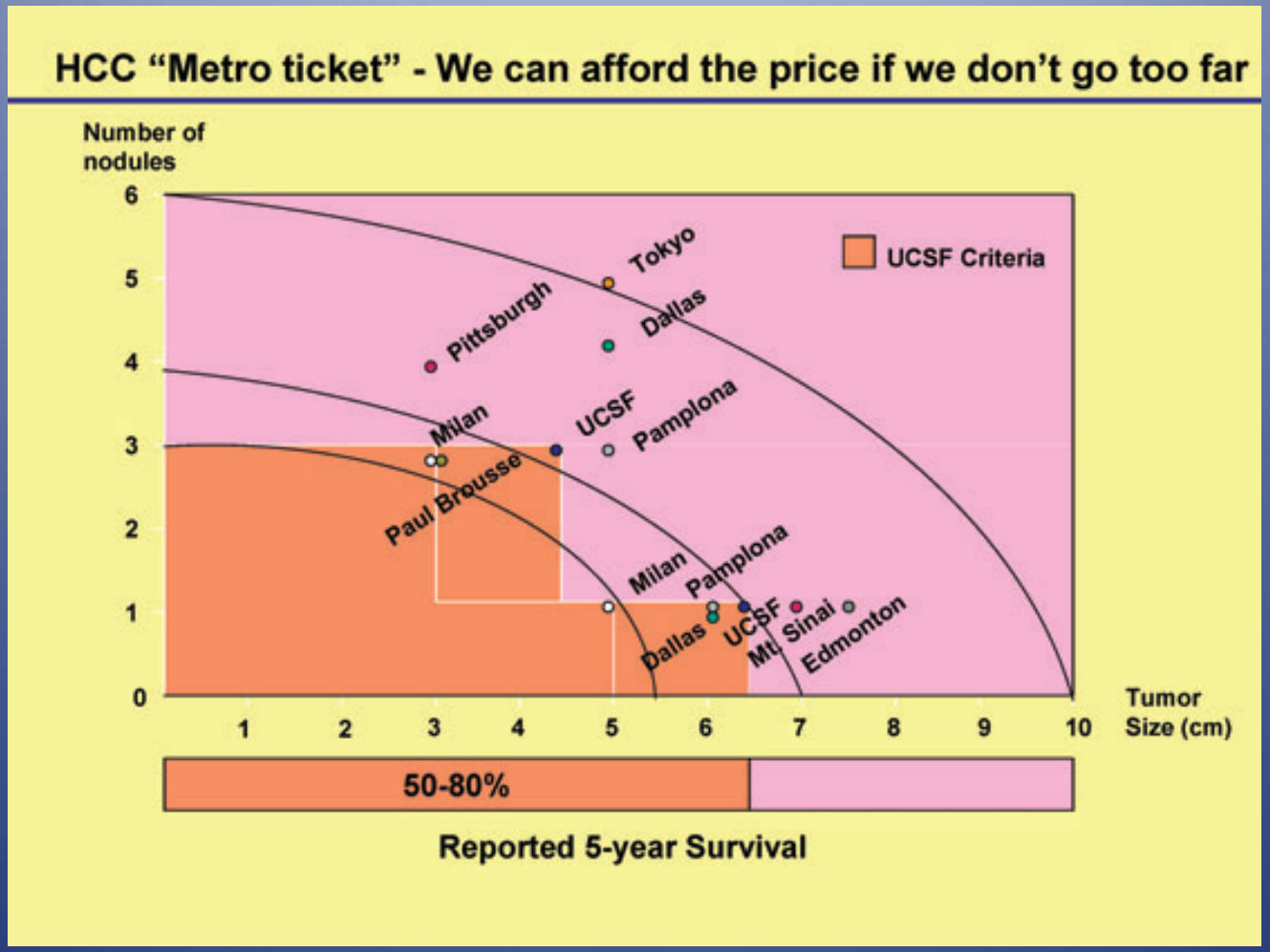
Nodulo singolo ≤ 7 cm
HCC multifocale ≤ 2-3 noduli tutti ≤ 5 cm
HCC multifocale ≤ 5 noduli tutti ≤ 3 cm



Sopravvivenza 5 anni di circa 69% in uno studio
"Intention to treat "

Yao Hepatology 2001

Criteri di selezione



Yao American Journal of Transplantation 2008

Trapianto di Fegato

Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria

A retrospective, exploratory analysis

Maximum tumour size, mm				<0·0001
Median (IQR)	35 (22–50)	20 (15–30)	40 (30–60)	
Range	1–200	1–50	4–200	
Grading, n (%)				0·003
G1	284/1113 (25·5)	50/197 (25·4)	234/916 (25·5)	
G2	550/1113 (49·4)	115/197 (58·4)	435/916 (47·5)	
G3	279/1113 (25·1)	32/197 (16·2)	247/916 (27·0)	
Not available	443 (··)	247 (··)	196 (··)	
Vascular invasion, n (%)				<0·0001
No	977/1475 (66·2)	361/405 (89·1)	616/1070 (57·6)	
Yes	498/1475 (33·8)	44/405 (10·9)	454/1070 (42·4)	
Not available	81 (··)	39 (··)	42 (··)	
Recurrence-free survival (95% CI), %				<0·0001
5 years	72·6 (69·6–75·3)	94·5 (91·4–96·5)	64·1 (60·3–67·6)	
10 years	68·2 (64·5–71·5)	94·5 (91·4–96·5)	58·1 (53·5–62·4)	
Overall survival (95% CI), %				<0·0001
5 years	59·1 (56·1–61·9)	73·3 (68·2–77·7)	53·6 (50·1–57·0)	
10 years	46·8 (43·0–50·5)	69·6 (63·7–74·8)	38·7 (34·2–43·1)	

Mazzaferro Lancet Onc 2009

Trapianto di fegato: Allocazione organi

Gen 2002: Sviluppo MELD score (INR, Creat, Bil)

permette di stimare il rischio di mortalità (3 months mortality risk) dei pazienti con ESLD con o senza cirrosi assumendo un ruolo fondamentale nella allocazione dei graft

Feb 2002: Introduzione MELD come parametro allocazione organi per ESLD

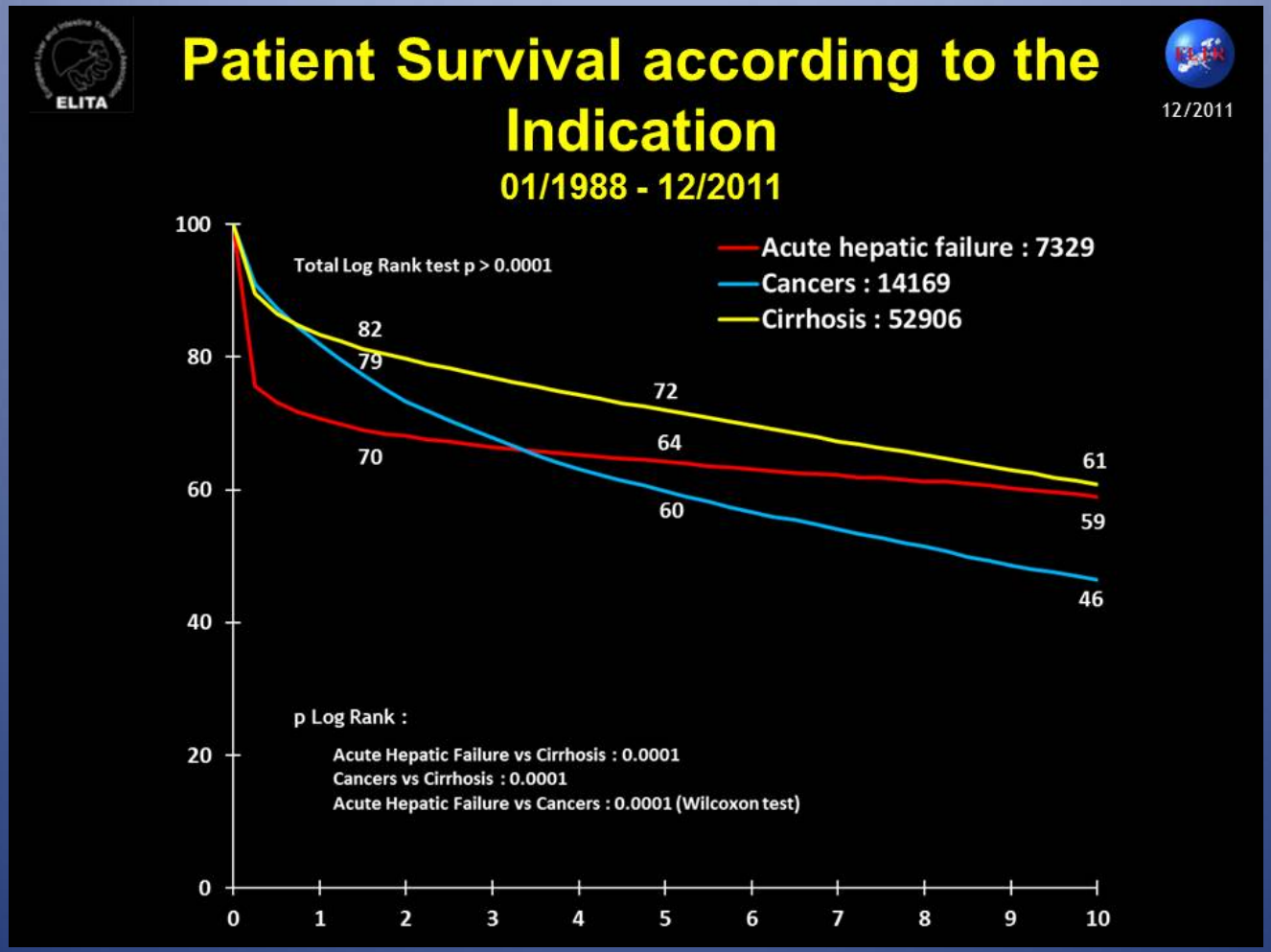
Attribuzione MELD corretto sulla base della stadiazione radiologica

HCC (T1): 3 months Drop out risk 15% → 24
HCC (T2): 3 months Drop out risk 30% → 29

2006: Correzione dei punteggi per HCC

HCC (T1): nessuna correzione
HCC (T2): 22 (Milan In)
HCC (T3): 22 (Milan Out)

Sopravvivenza post Trapianto di Fegato



ELTR 2012