LIVER TRANSPLANTATION

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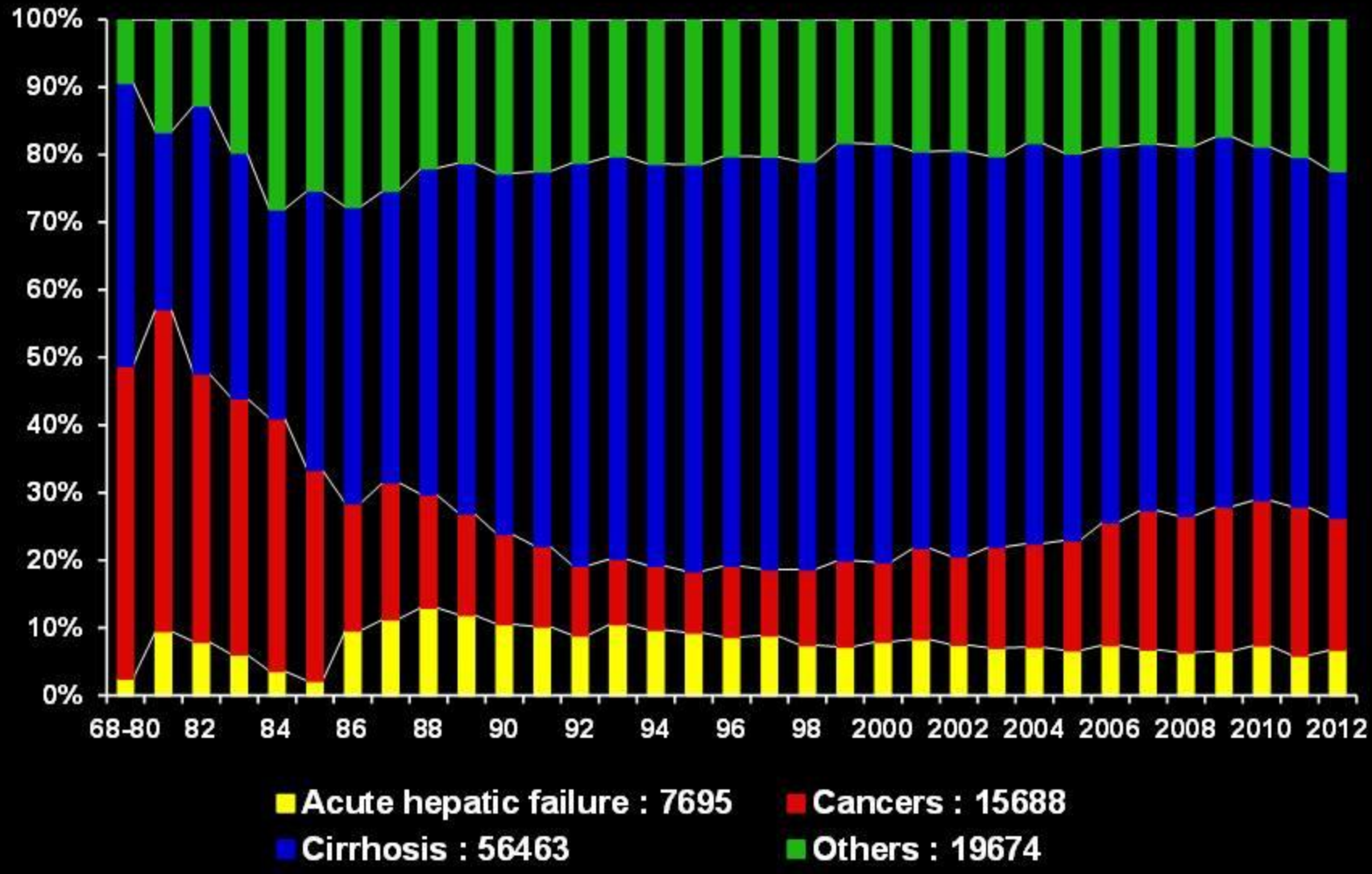
INDICATION

- **Non-resectability**
  - Extent
  - Degree of cirrhosis
- **Radicality**
- **Removal of the cancerigenic liver**

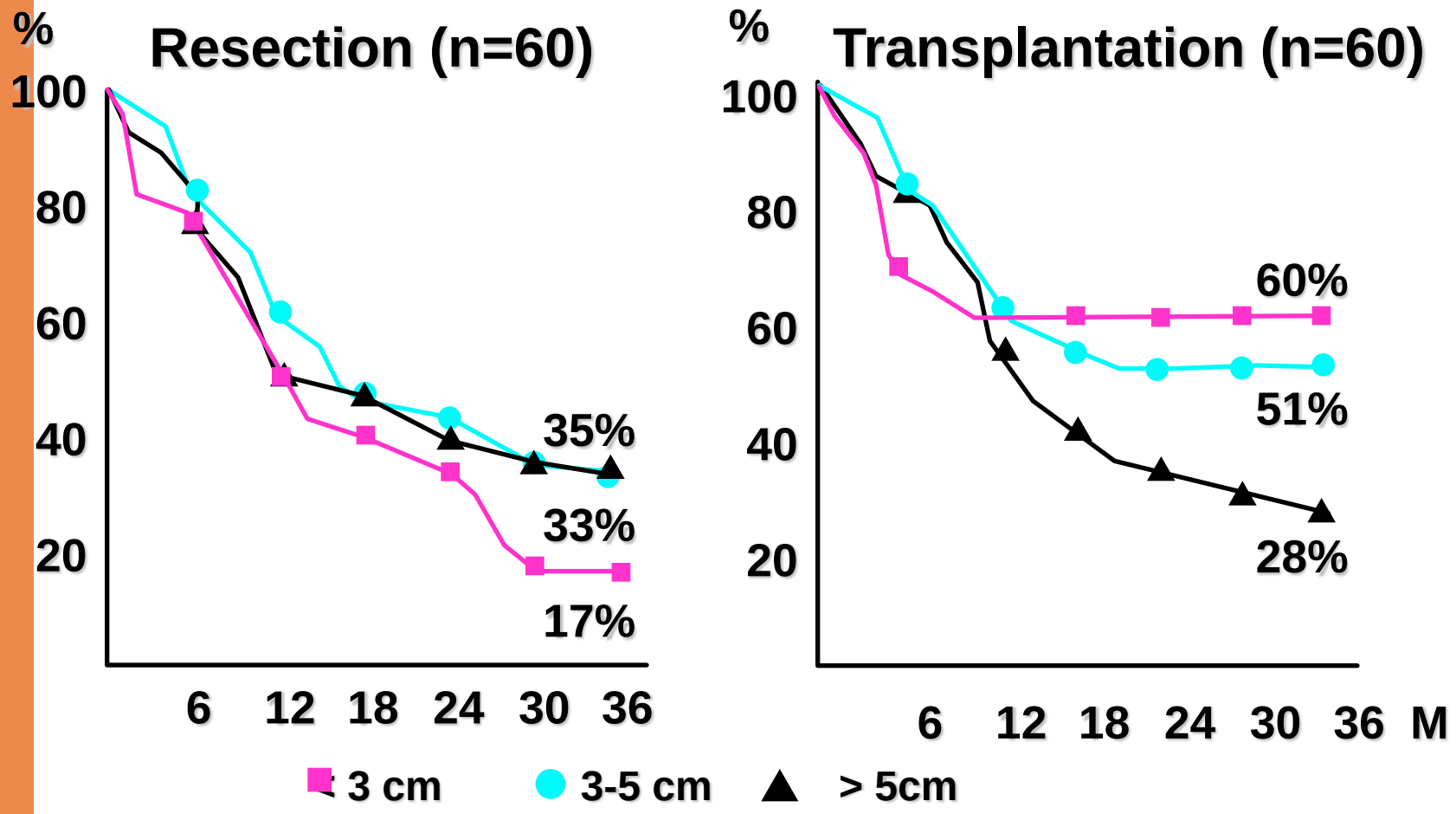
Evolution of Primary Diseases leading to Liver Transplantation in Europe

12/2012

05/1968 - 12/2012



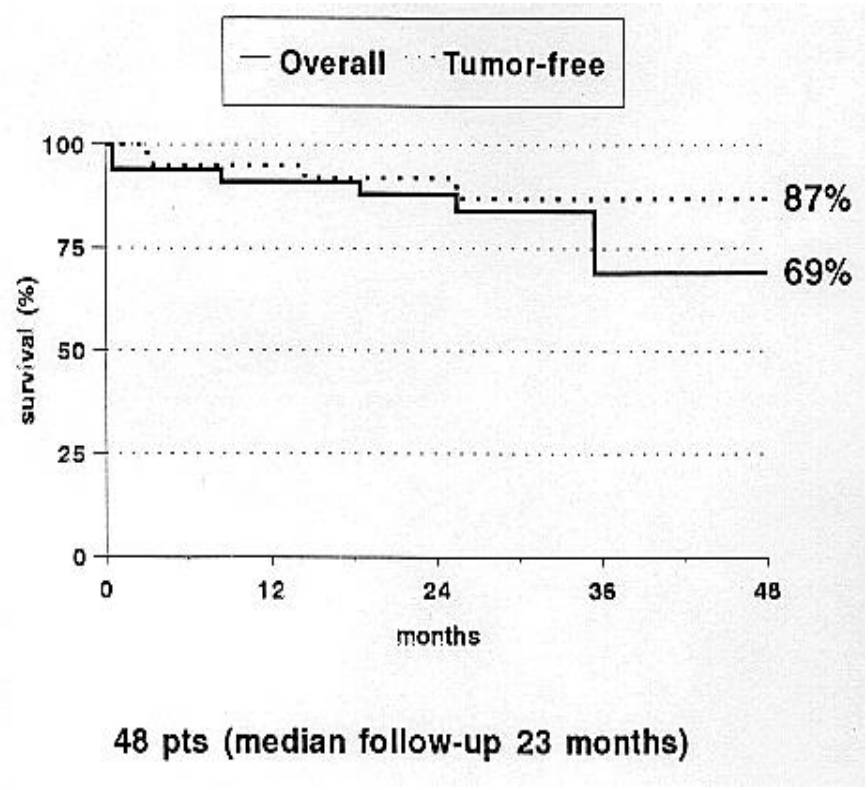
Transplantation vs. Resection



H. Bismuth et al. Ann Surg 1993

HCC : Milan criteria

- **Cirrhosis**
- **Biopsy HCC or AFP > 300 µg**
- **Solitary tumor:**
  - size < 5cm
- **Multiple nodules :**
  - max. 3
  - size < 3 cm
- **No vascular invasion**
- **No lymphnode involvement**



Mazzaferro et al. 1994

Table 2 | Reported 5-year overall survival rates in patients undergoing liver transplantation for hepatocellular carcinoma within Milan criteria (solitary tumour $\leq$50 mm in diameter or $\leq$3 tumours $\leq$30 mm in diameter)

Reference (year)	5-year overall survival (%)	
	Pre-operative imaging	Explant pathology
Mazzaferro (1996)[7]	75*	85*
Yao (2001)[28]		72.4
Fernandez (2003)[119]		68
Lohe (2005)[120]		70
Duffy (2007)[34]	79	86
Ito (2007)[44]	72	
Kwon (2007)[48]		>80
Poon (2007)[64]	81	
Takada (2007)[45]	73	
Herrero (2008)[39]	70	
Lee (2008)[43]		76
Silva (2008)[41]	69	
Toso (2008)[37]		82
Zheng (2008)[47]		78.3
Chen (2009)[19]	74.3	77.1
Mazzaferro (2009)[23]		73.3
Muscari (2009)[121]	77	
Santoyo (2009)[122]		65
Gabrielli (2010)[123]		94.7
DuBay (2011)[50]	72	

* Results reported at 4 years.

Maggs et al. APT 2012

ET SE criteria for HCC

N°	exceptional MELD criteria	A	B/L	G	NL	SLO	CRO
	Patient fulfills the Milan criteria at the time of request, one from 2a or 2b and both 3 and 4 have to be met	0	0	0	0	0	0
2a	Recipient has 1 lesion >= 2 cm and <= 5cm	✓	✓	✓	✓	✓	✓
2b	Recipient has 2 or 3 lesions, >= 1cm and <= 3cm in size	✓	✓	✓	✓	✓	✓
2c	Recipient has no extrahepatic metastases	✓	✓	✓	✓	✓	✓
2d	Recipient has no macrovascular invasion	✓	✓	✓	✓	✓	✓

HEPATOCELLULAR CARCINOMA

Liver Transplantation: Extended Criteria

Author, year	Proposed criteria
Yao, UCSF, 2001	1 nodule < 6.5 cm or ≤3 nodules, ≤4.5 cm, total < 8 cm
Sugawara, Tokyo 2007	<5 nodules, <5 cm
T	**ALL WITH OS RANGING FROM 50% TO 75%**
Soejima, Fukuoka 2007	Any number, ≤5 cm
Herrero, Navarra 2007	1 nodule < 6 cm or ≤3 nodules, ≤ 5 cm
Kwon, Seoul 2007	Any number, ≤5 cm, AFP ≤ 400 ng/ml
Zheng, Hangzhou 2008	total < 8 cm or total > 8 cm, Grade I/II and AFP < 400 ng/ml
Mazzaferro, Milan 2009	Up to 7, no microvascular invasion

Up-to-seven criteria

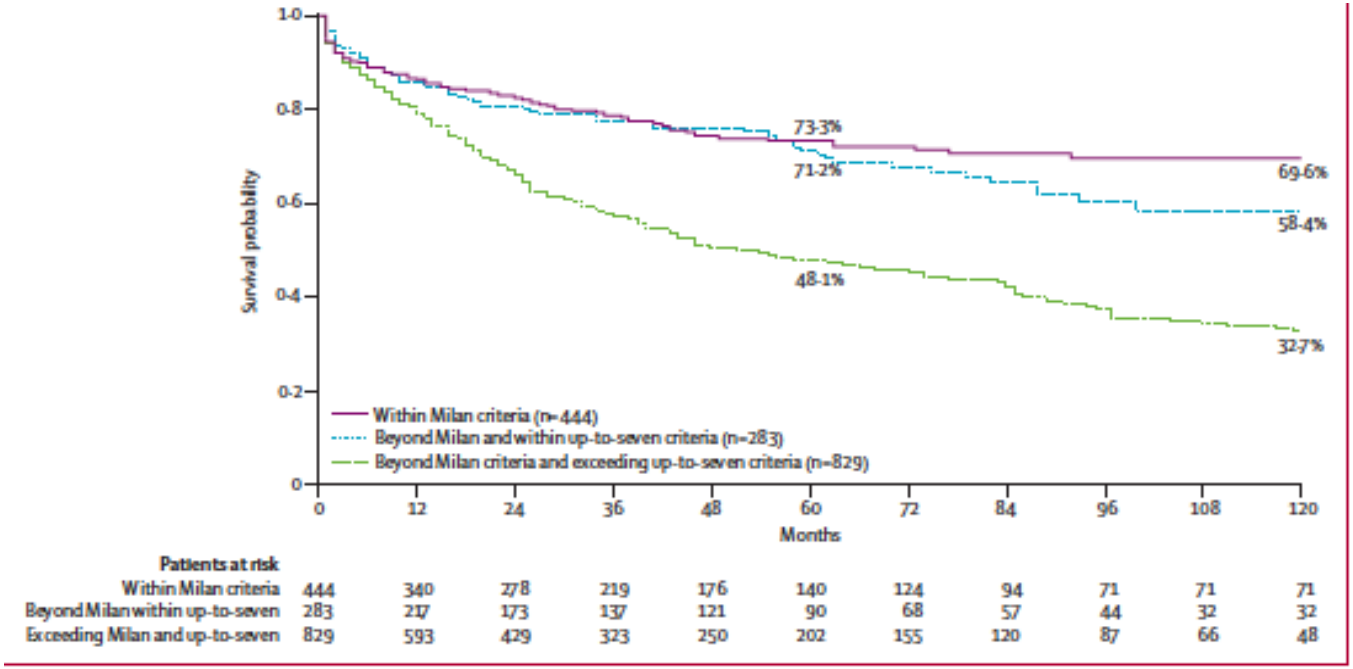
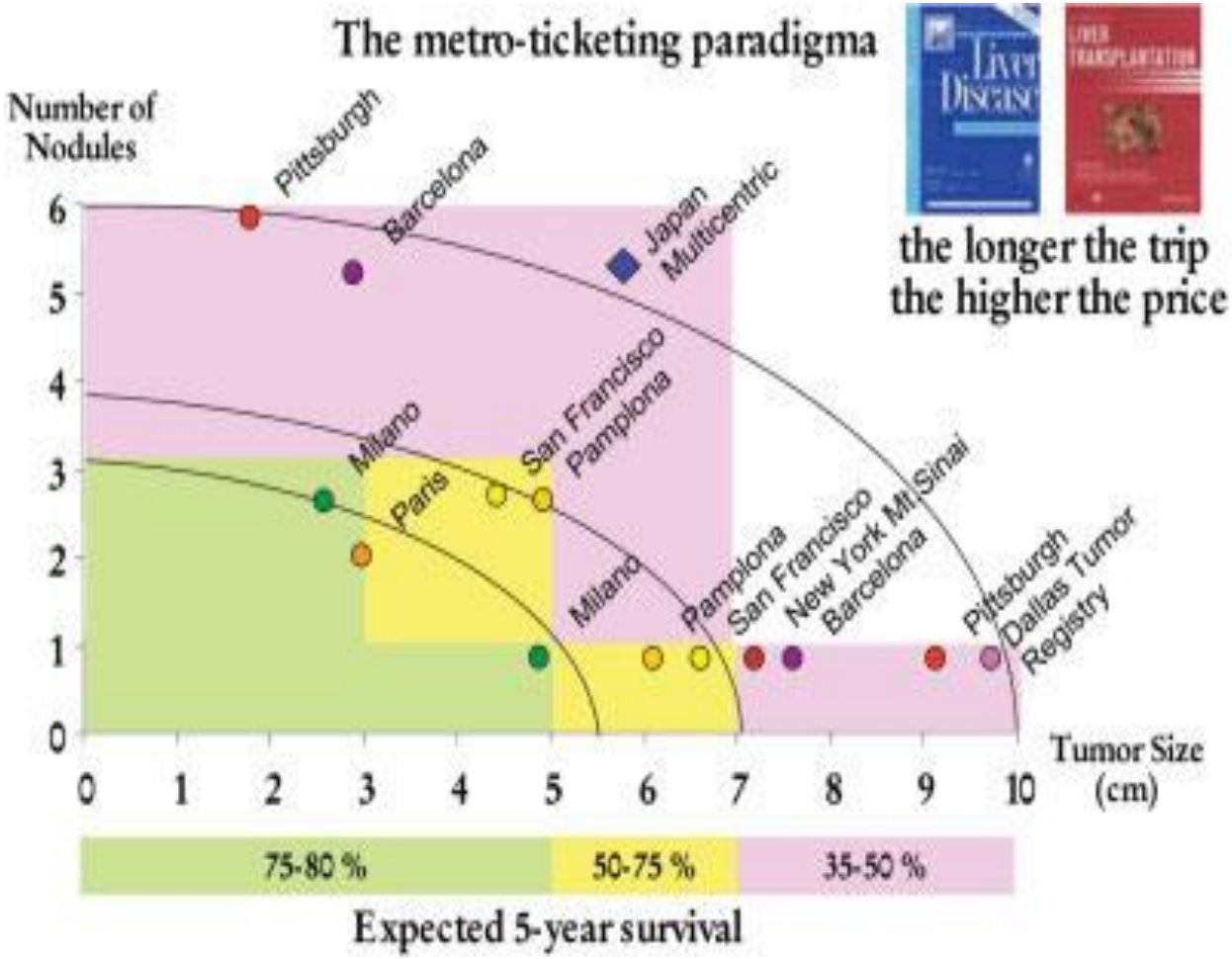


Figure 3: Up-to-seven criteria
Kaplan-Meier overall survival curves of the three subgroups: within Milan criteria (n=444); beyond Milan and within up-to-seven criteria (n=283); and beyond Milan and exceeding up-to-seven criteria (n=829). Patients with hepatocellular carcinomas beyond Milan criteria, but within up-to-seven criteria had a similar survival compared with patients within Milan criteria. Patients beyond up-to-seven criteria had a significant deterioration in survival (p<0·001).

Extended criteria – cave!

- More sensitive diagnostic methods
- Selection due to waiting time (no SE status)
- Selection by downstaging
- Study Design (retrospective) (postoperative pathology)
- AND : also the TX survival for non-HCC indications has improved

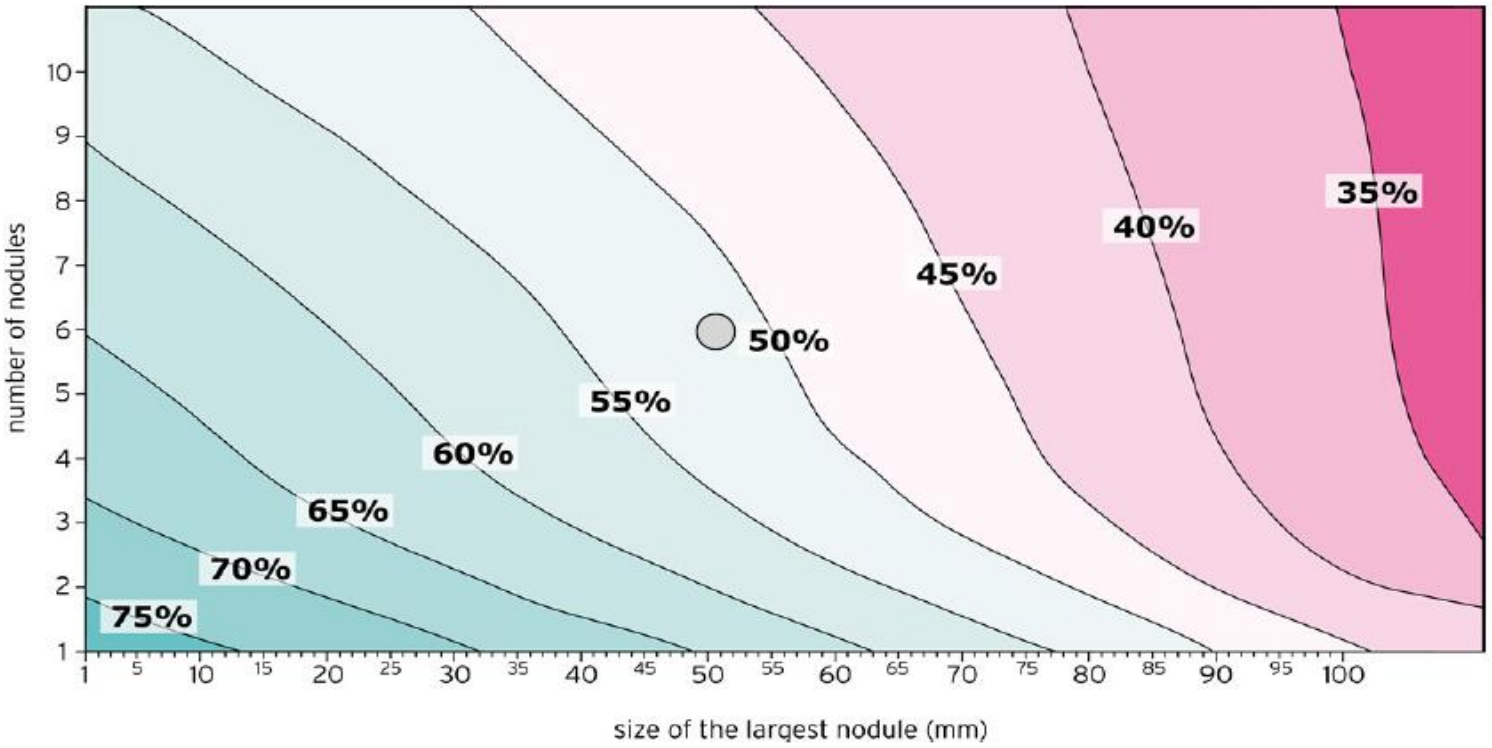


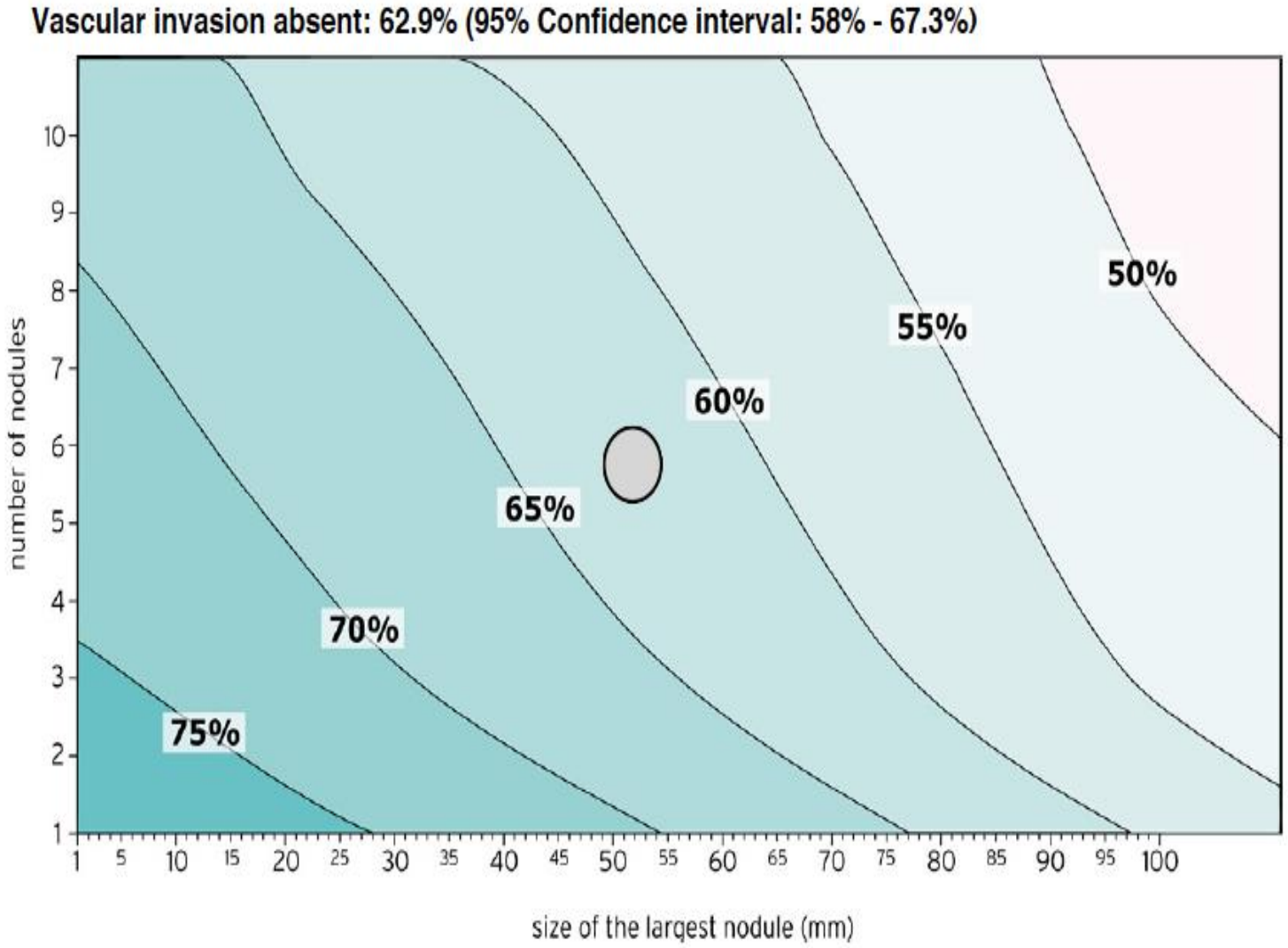
metroticketCalculator

Patient: Testpatient - Date of Birth: 50mm 6nodes

5-yr predicted survival

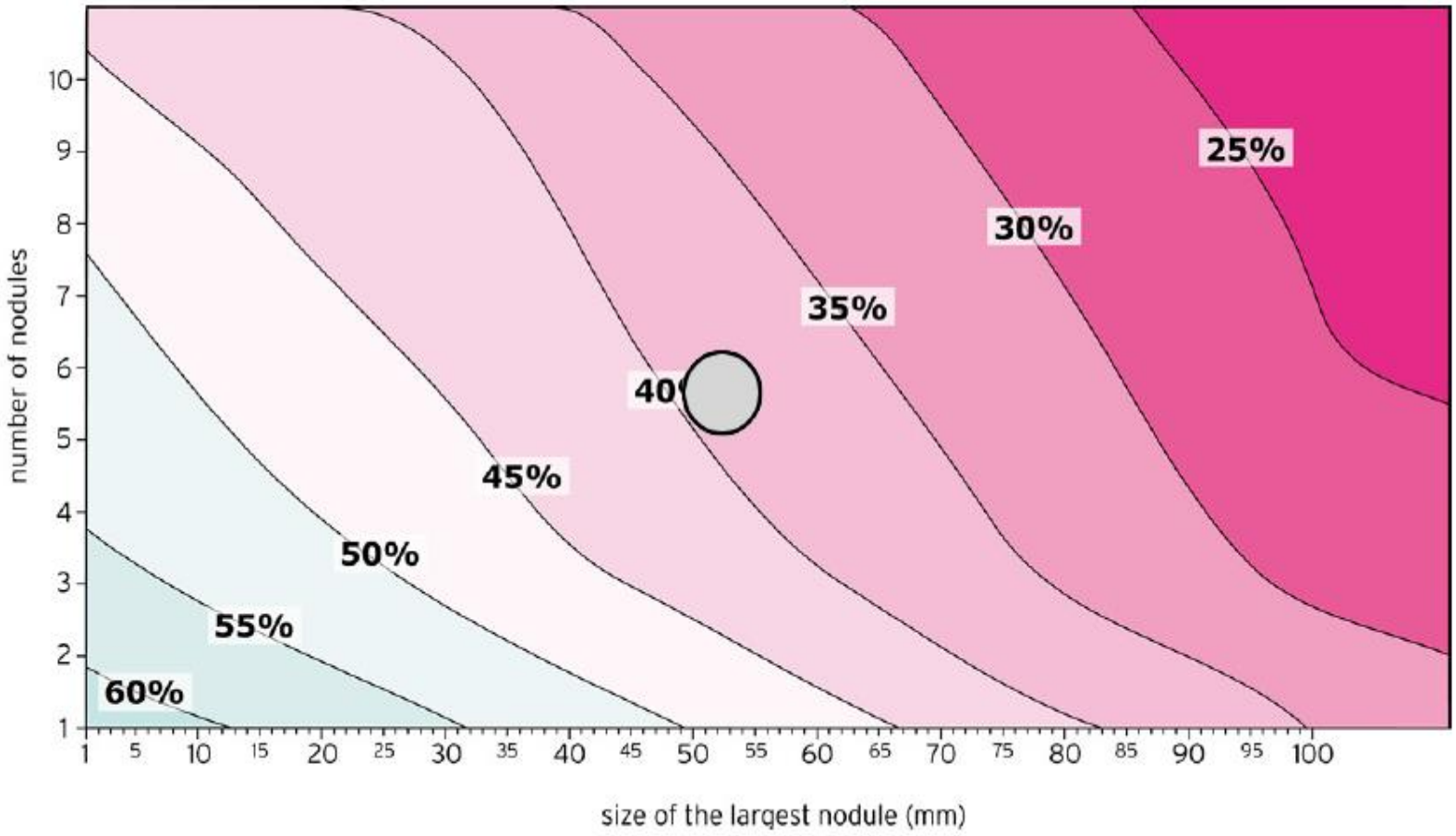
Vascular invasion unspecified: 51.6% (95% Confidence interval: 49% - 54.1%)



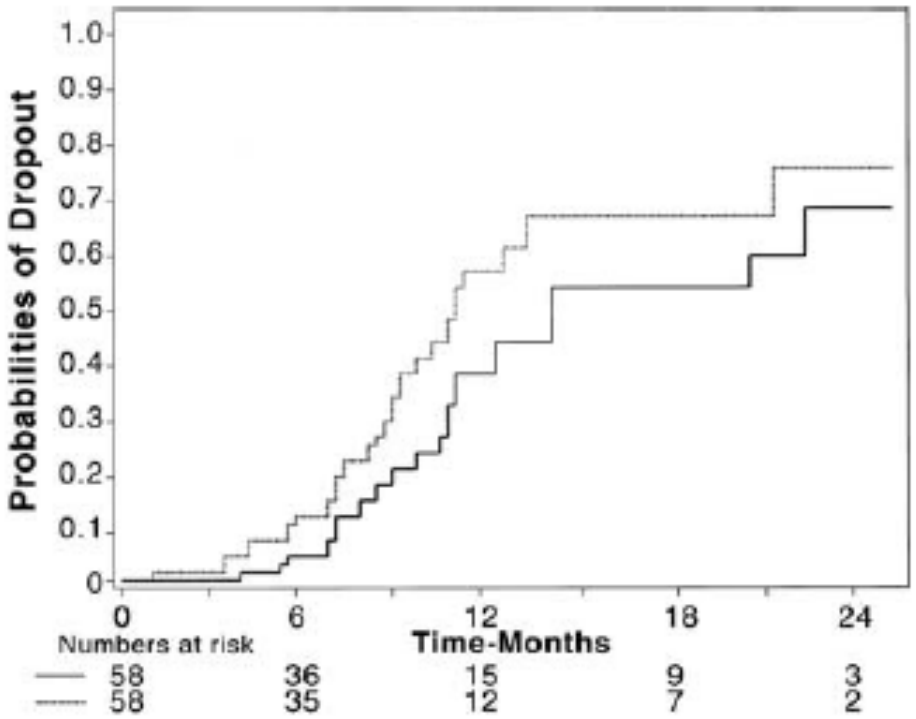


Patient: Testpatient - Date of Birth: 50mm 6nodes

Vascular invasion present: 39.1% (95% Confidence interval: 33.7% - 44.4%)



Drop out risk => bridging therapies



Yao et al. Liver Transplant 2003

Drop-out risk

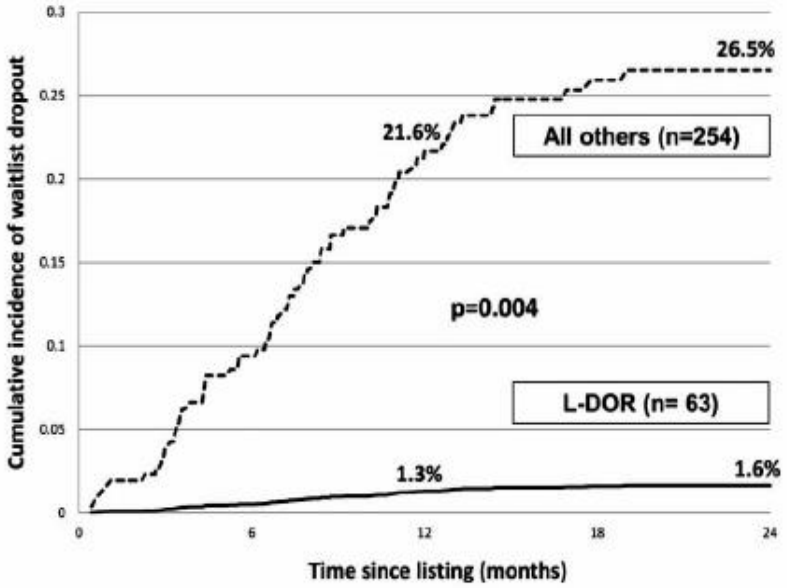


Figure 2. Cumulative incidence of wait-list dropout due to tumor progression or death by dropout risk groups (CRs). The low-risk group met the following criteria: a single tumor of 2 to 3 cm, a complete response to the first LRT, and an AFP level ≤ 20 ng/mL after the first LRT.

Single tumor 2-3 cm
Complete response to first LRT
AFP < or = 2O ng/ml

Resection vs. Transplantation for small HCC≤ 2cm

comparable OS rates

patients with normal LFT should be resected because

- No need of immunosuppression
- donor organ shortage

In patients with end-stage liver disease transplant preferred

resection used as bridging therapy for transplant

Recent Studies Comparing Long-Term Outcome of Patients with Hepatocellular Carcinoma Treated Primarily with Resection (and Salvage Transplantation) or Primary Liver Transplantation

First Author	Year Published	Primary Therapy	Sample Size	5-Year Overall Survival Rate (%)	5-Year Disease-Free Survival Rate (%)
Lee[127]	2010	Transplantation	78	68	75*
		Resection	130	52	50
Facciuto[128]	2009	Transplantation	119	62	—
		Resection	60	61	—
Del Gaudio[129]	2008	Transplantation	147	58	54
		Resection	80	66	41
Shah[130]	2007	Transplantation	140	64	78*
		Resection	121	56	60
Poon[17]	2007	Transplantation	85	44	—
		Resection	228	60	—
Margarit[18]	2005	Transplantation	36	50	64*
		Resection	37	78	39
Bigourdan[19]	2003	Transplantation	17	71	80*
		Resection	20	36	40*
Adam[131]	2003	Transplantation	195	61†	58*
		Resection	98	50	18
Belghiti[132]	2003	Transplantation	70	—	59
		Resection	18	—	61
Figueras[134]	2000	Transplantation	85	60	60*
		Resection	35	51	31

*Significant difference as reported in the original study.
†Fourth-year survival rates are reported for patients meeting the Milan criteria.
Adapted from Rahbari NN, Mehrabi A, Mollberg NM, et al. Hepatocellular carcinoma: current management and perspectives for the future. Ann Surg 2011;253:453–469; Table 2, with permission from Lippincott Williams & Wilkins.

LOCAL REGIONAL THERAPIES FOR HCC

- **CHEMOEMBOLIZATION**
  - Conventional and Drug-eluting beads
- **ABLATIONS**
- **CHEMICAL**
  - Percutaneous ethanol injection (PEI)
- **THERMAL**
  - Radiofrequency ablation (RFA)
    - (Laparoscopic, percutaneous or open)
  - Microwave/ Cryo- ablation
  - RADIOEMBOLIZATION (YITTRIUM - 90)

Downstaging to within Milan criteria?

Reference	Outcome measure	Rate (%)		P	Method of analysis
		Within Milan criteria	Initially beyond Milan criteria		
De Luna *et al.*[15]	3-year absolute survival	85	79	0·90	Log rank comparison of Kaplan–Meier curves
Chapman *et al.*[8]	5-year recurrence-free survival	63	50	0·34	Log rank comparison of Kaplan–Meier curves
Cillo *et al.*[18]	5-year absolute survival	69	79	> 0·05	Not clear
Otto *et al.*[17]	5-year recurrence-free survival	94	75	0·42	Log rank comparison of Kaplan–Meier curves
Graziadei *et al.*[19]	4-year absolute survival	94	41	< 0·001	Log rank and Wilcoxon comparison of Kaplan–Meier curves

Systematic review of outcome of downstaging hepatocellular cancer before liver transplantation in patients outside the Milan criteria

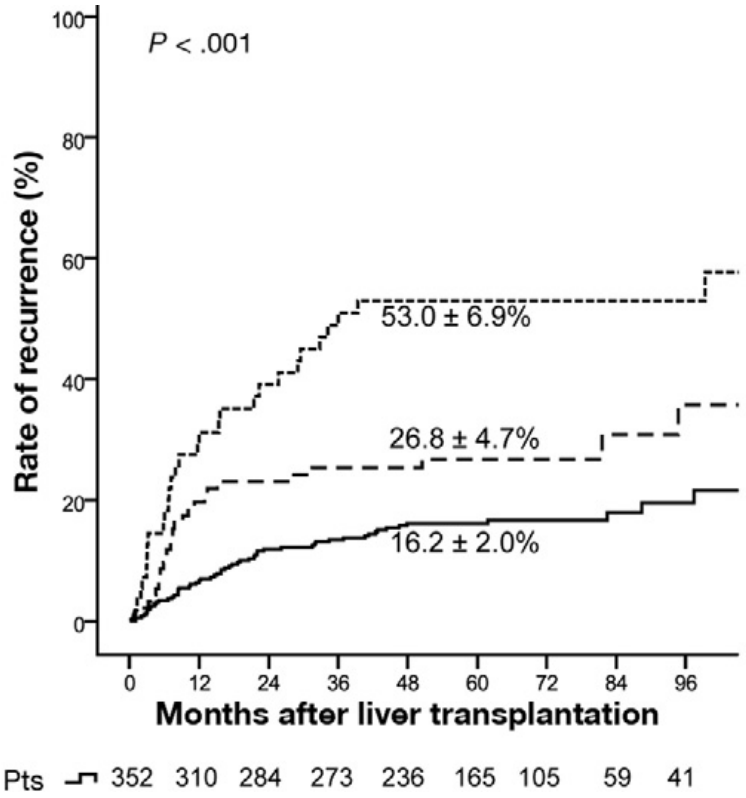
A. N. Gordon-Weeks1, A. Snaith1, T. Petrinic1, P. J. Friend1, A. Burls2 and M. A. Silva1

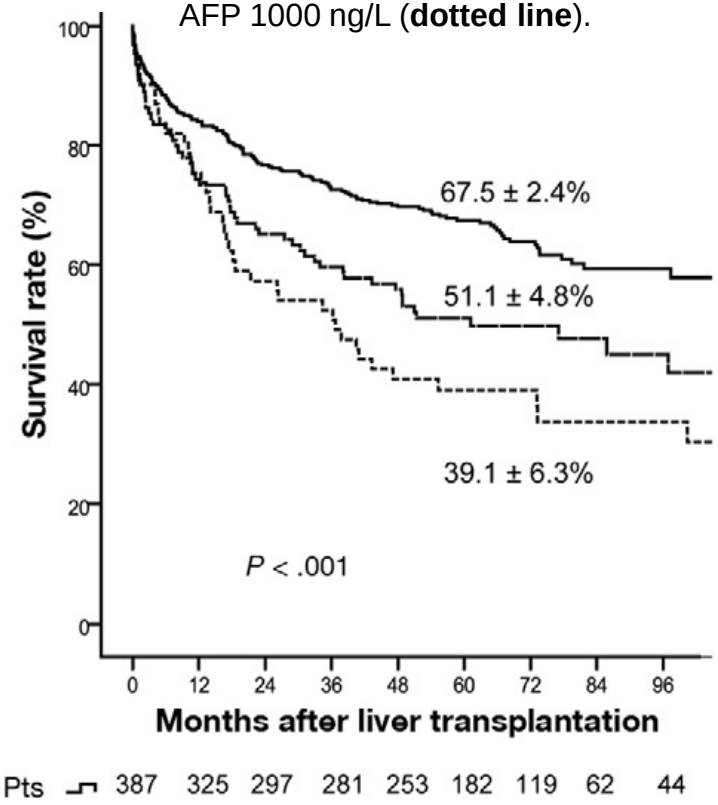
Brit J Surg 2011

N°	Additional guidelines	A	B/L	G	NL	SLO	CRO
	Patient does not fulfill the Milan criteria at the time of request, but was initially diagnosed with HCC (only 1 possible)	O	O	O	O	O	O
3a	inside the Milan criteria, and after treatment presenting with one lesion <2cm or no lesion at all at time of SE request, is still considered to be a transplant candidate.	✓	✓	✓	✓	✓	✓
3b	inside the Milan criteria, and has lesion(s) exceeding the Milan criteria at time of SE request; must be submitted to the national audit group.		✓		✓		
3c	outside the Milan criteria, and fulfilling the criteria only after downstaging at time of SE request; must be submitted to the national audit group.		✓		✓		

Tumor biology?

Figure 1. Rates of (**A**) recurrence and (**B**) overall survival rates according to -fetoprotein level in the training cohort. AFP 100 ng/L (**solid line**); AFP 100–1000 ng/L (**dashed line**); AFP 1000 ng/L (**dotted line**).

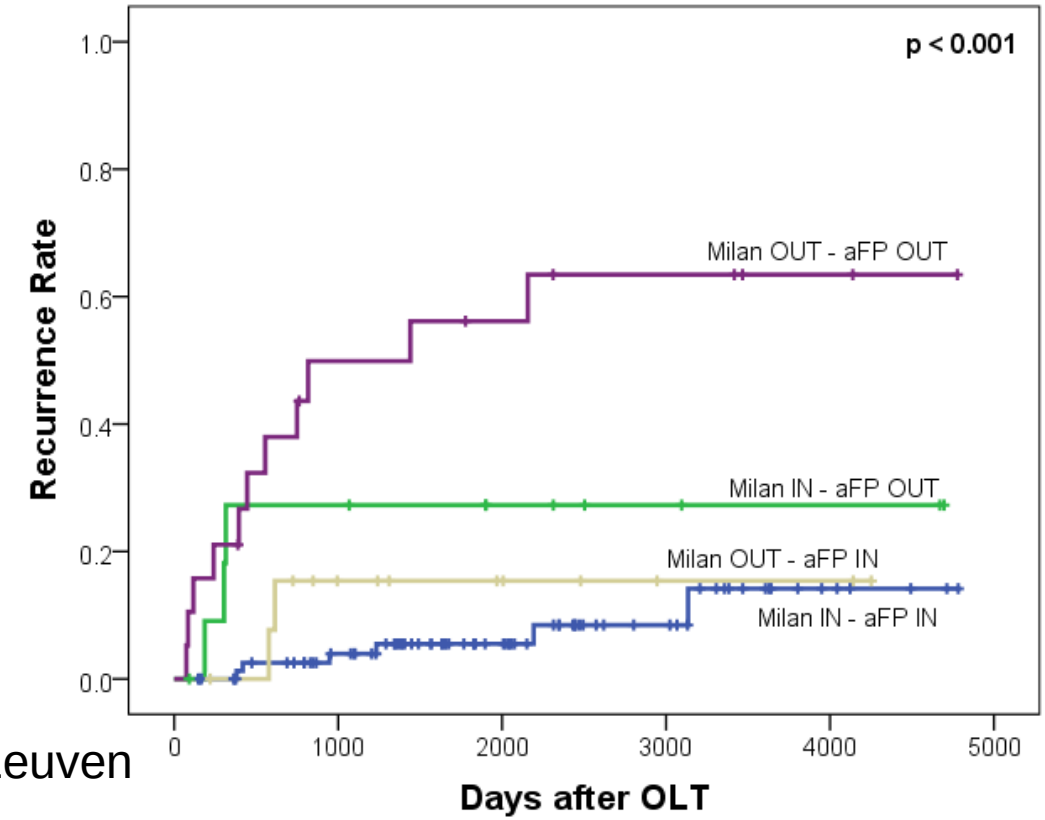




Duvoux et al. GASTROENTEROLOGY 2012;143:986–994

First validation in UZ Leuven cohort

	Frequency	Percent
Milan IN - aFP IN	85	63.9
Milan IN - aFP OUT	12	9.0
Milan OUT - aFP IN	14	10.5
Milan OUT - aFP OUT	19	14.3

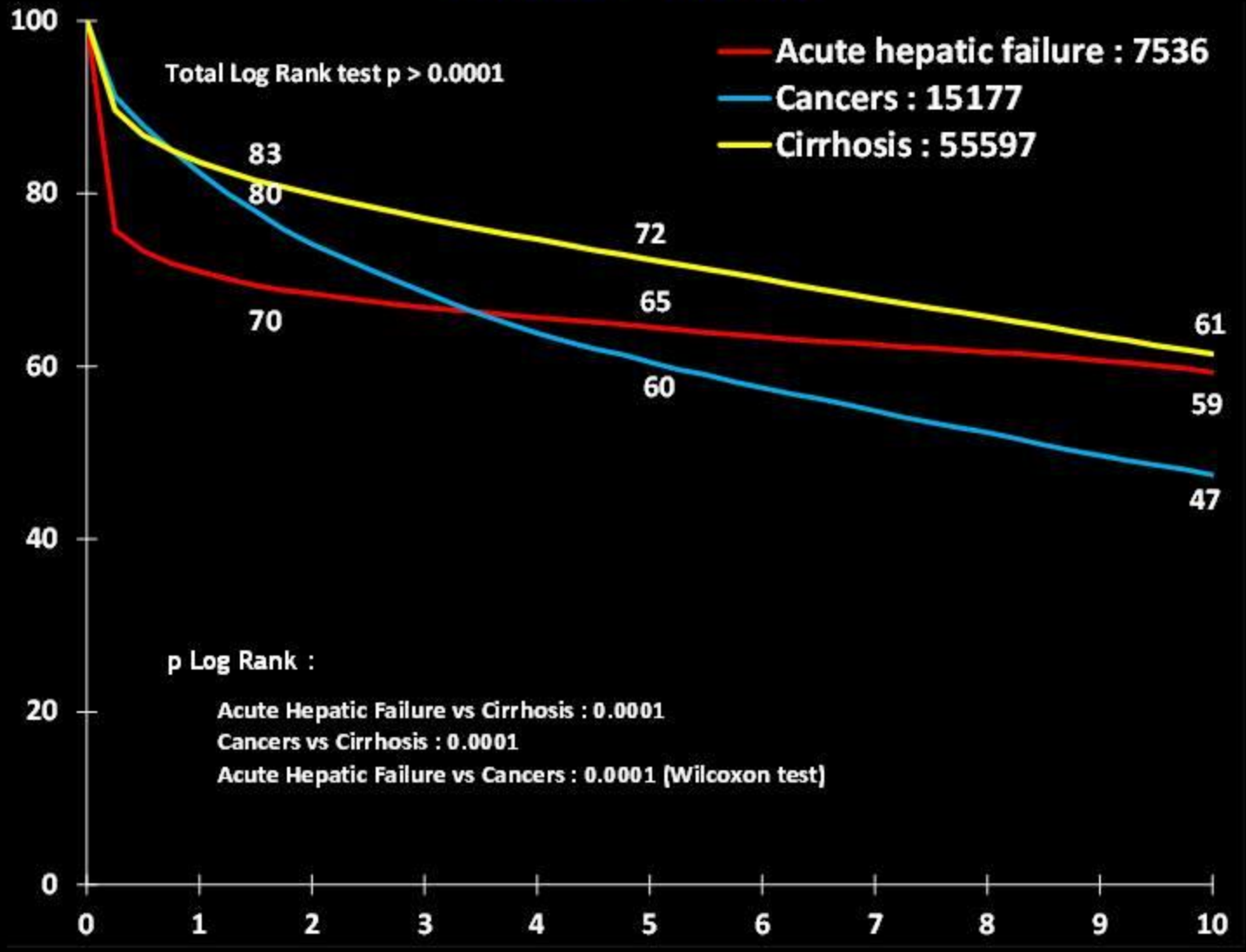


Courtesy J. Dekervel, UZ Leuven

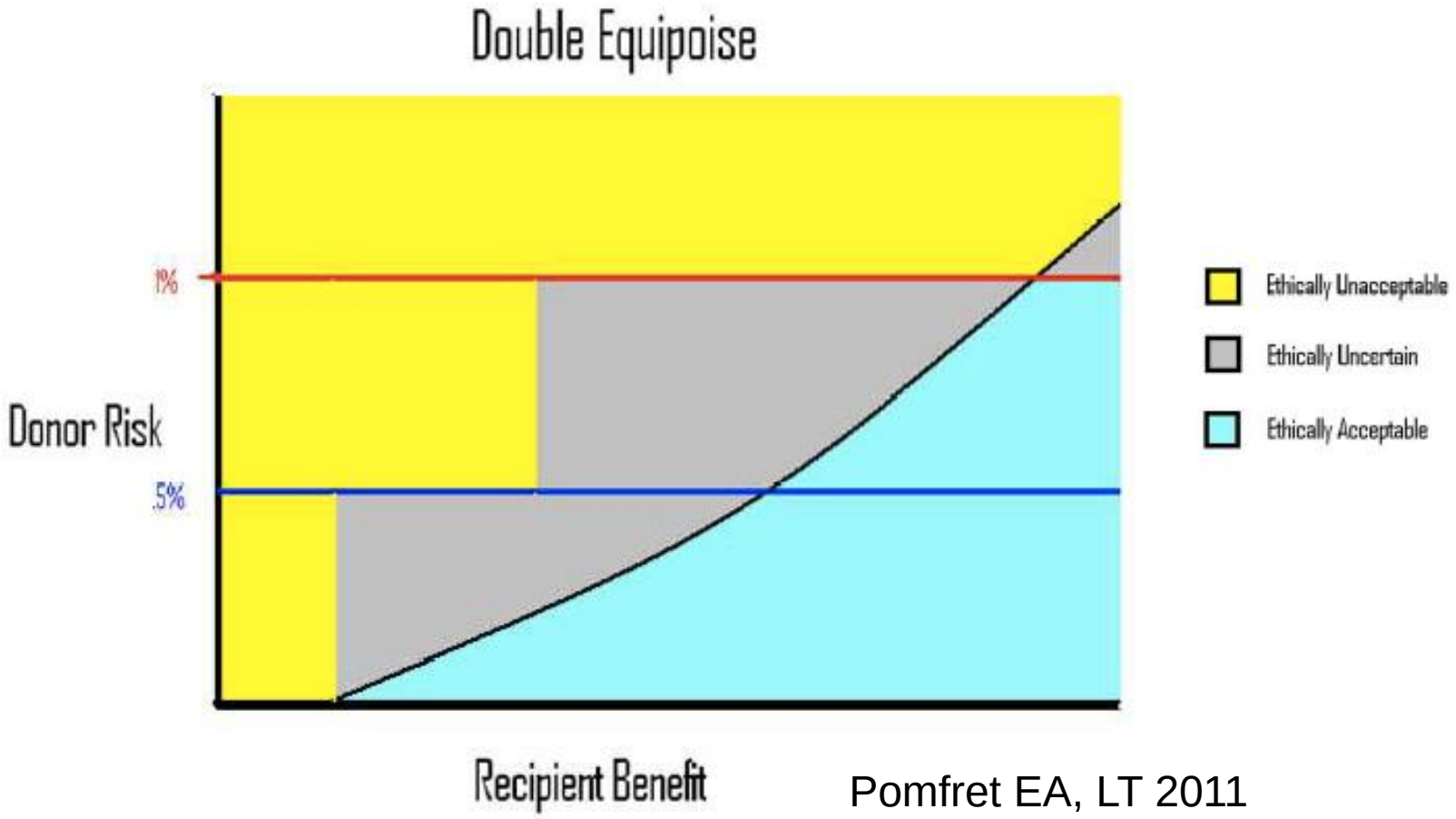
Patient Survival according to the Indication

01/1988 - 12/2012

12/2012



Living donor LTX



Pomfret EA, LT 2011

Living Donor Liver Transplantation for Hepatocellular Carcinoma: Increased Recurrence but Improved Survival

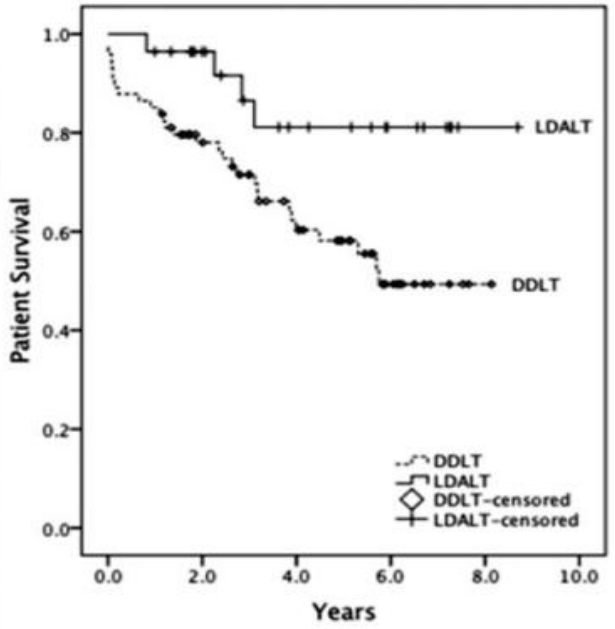


Figure 5. Overall survival of the living donor adult liver transplantation (LDALT) and deceased donor liver transplantation (DDLT) groups ($P = 0.023$).

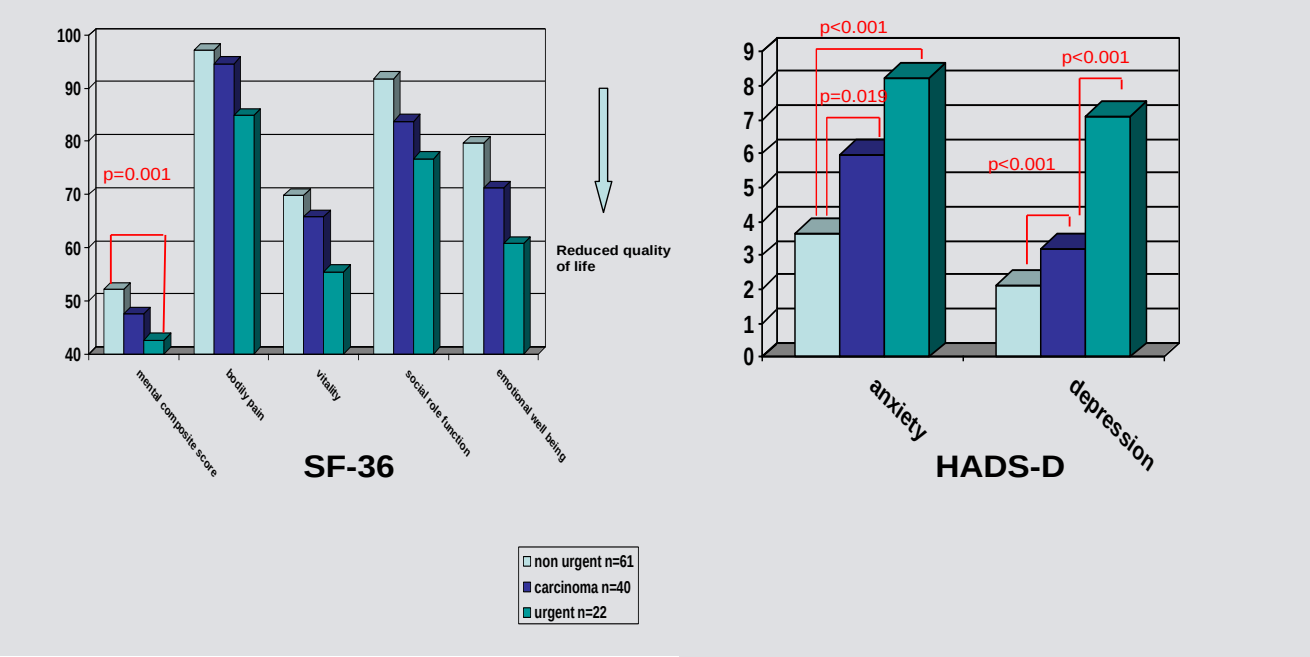
VAKILI K, LT 2009

- **8 y period; median 41 month FU**
- **Milan Criteria: 75%**
- **28 LDLT: 96% -81% 3 AND 5 Y OS**
- **28.6% HCC RECURRENCE (P=0.02)**

- 74 DDLT: 70%-58% 3 AND 5Y OS
- 12% HCC RECURRENCE (P=<0.05)

Psychological pressure depends on the type of indication

urgent TX / TX for HCC / non-urgent TX



Mental composite score, subscales of SF-36, anxiety and depression measured with HADS-D

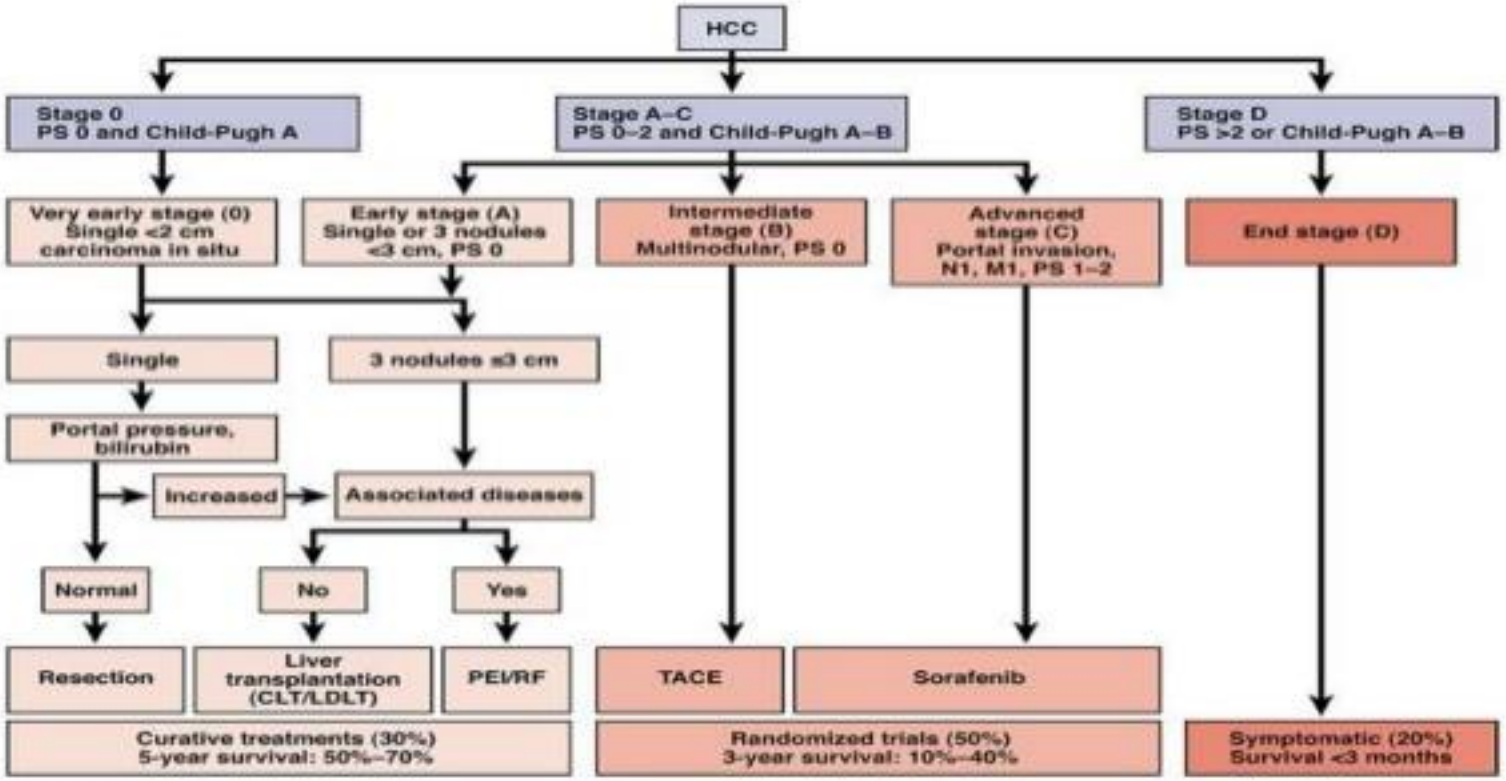
Erim, Schulz et al.

LIVING DONATION for HCC

- Latency time => tumour biology
- Informed consent of donor and recipient
- Attention to psychological pressure

Conclusion

- **LTX can be a curative option for treatment of HCC**
- **The chance of healing is determined by**
  - size and number of nodules
  - vascular invasion
  - tumour biology
- **The « freedom » of indications is co-determined by organ donation rates and the numbers of patients with other indications**
- **Living donor transplantation is a good option under certain conditions.**
- **Liver surgery/interventional techniques play a role :**
  - In the treatment of small lesions
  - As a bridge to transplantation
  - For downstaging to within Milan criteria



Llovet, J. M., Fuster, J., & Bruix, J. (2004). The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. *Liver Transplantation : Official Publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society*, *10*(2 Suppl 1), S115–S120.