



# Reconsidering Liver Transplantation for HCC in a Era of Organ shortage

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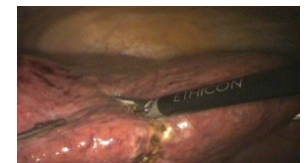
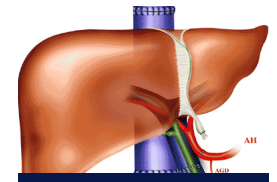
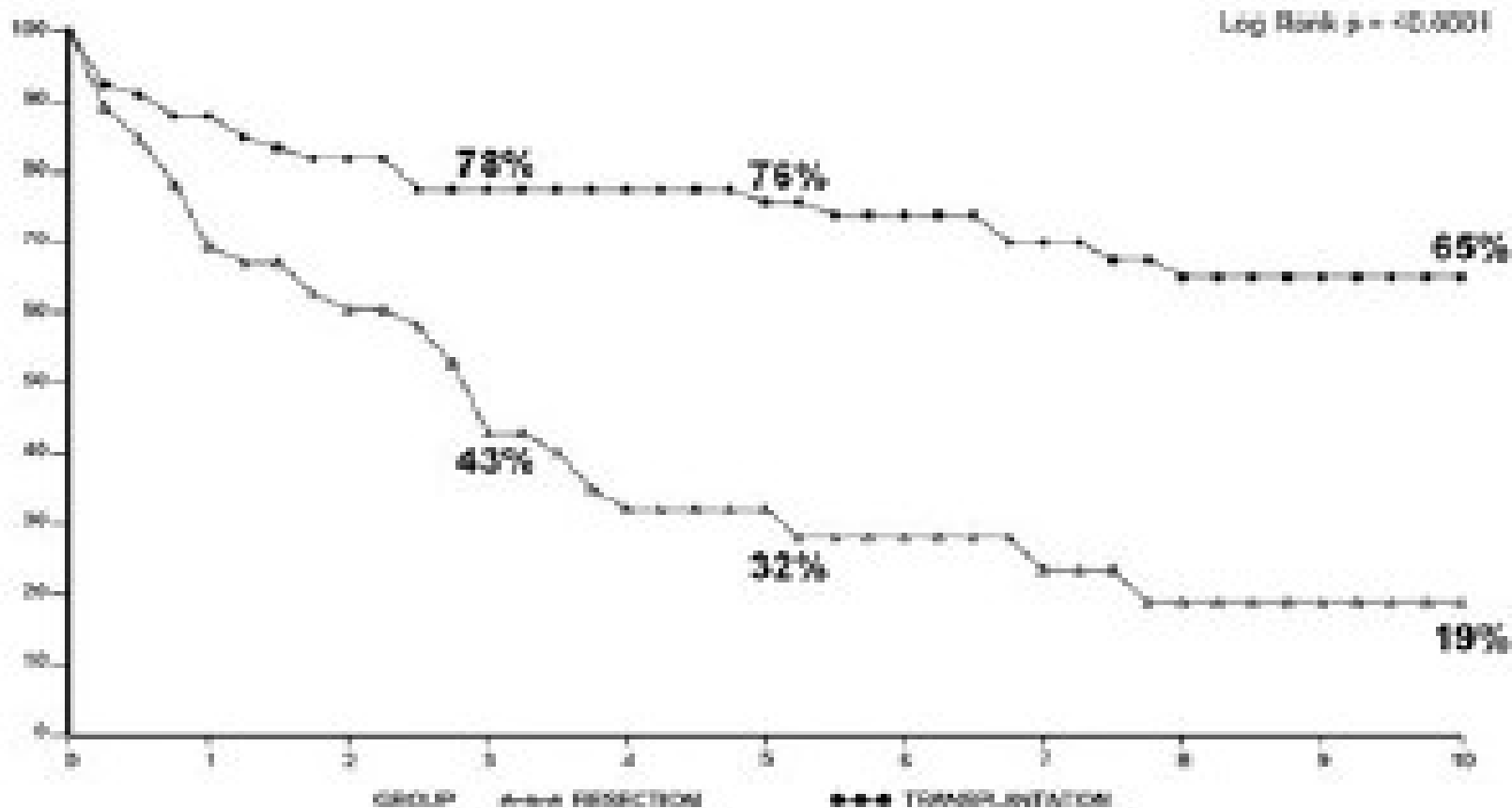
**Villejuif, France**



# Resection or Transplantation for Early Hepatocellular Carcinoma in a Cirrhotic Liver

## Does Size Define the Best Oncological Strategy?

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 Gilles Pelletier, MD, PhD,\* Jean-Charles Duclos-Vallée, MD, PhD,\*†‡ Didier Samuel, MD, PhD,\*†‡  
 Catherine Guettier, MD,\* and Denis Castaing, MD\*†‡



# Independent Prognostic Factors of Recurrence Free Survival After Resection for HCC

Factor	Hazard ratio (95%CI)	P value
AFP > 200	1.5 (1.07-2.2)	0.02
Intraoperative Transfusions	2.6 (1.5-3.1)	0.0001
Poor Differentiation	1.9 (1.2-2.9)	0.009
Microvascular Invasion	1.71 (1.2-2.4)	0.002
Cirrhosis	1.69 (1.2-2.39)	0.003

***Kluger, Cherqui. J Hepatol 2015***

# Liver Transplantation for HCC

## Effective but Small Part of the treatment

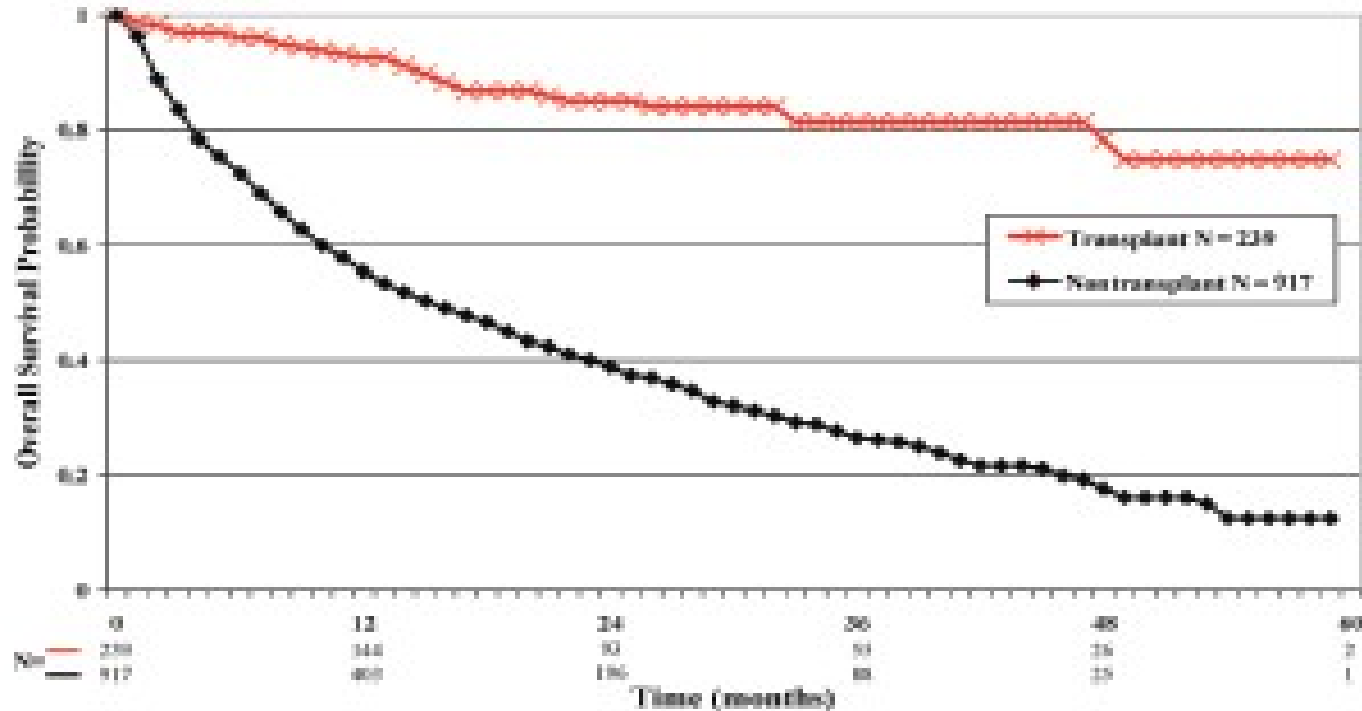


Figure 1. Kaplan-Meier survival curves for transplant versus nontransplant for hepatocellular carcinoma.

**Surveillance, Epidemiology, and End Results Program 1998-2002, USA**

**Patients with small HCC  $\leq 5$ cm**

**21% were transplanted**

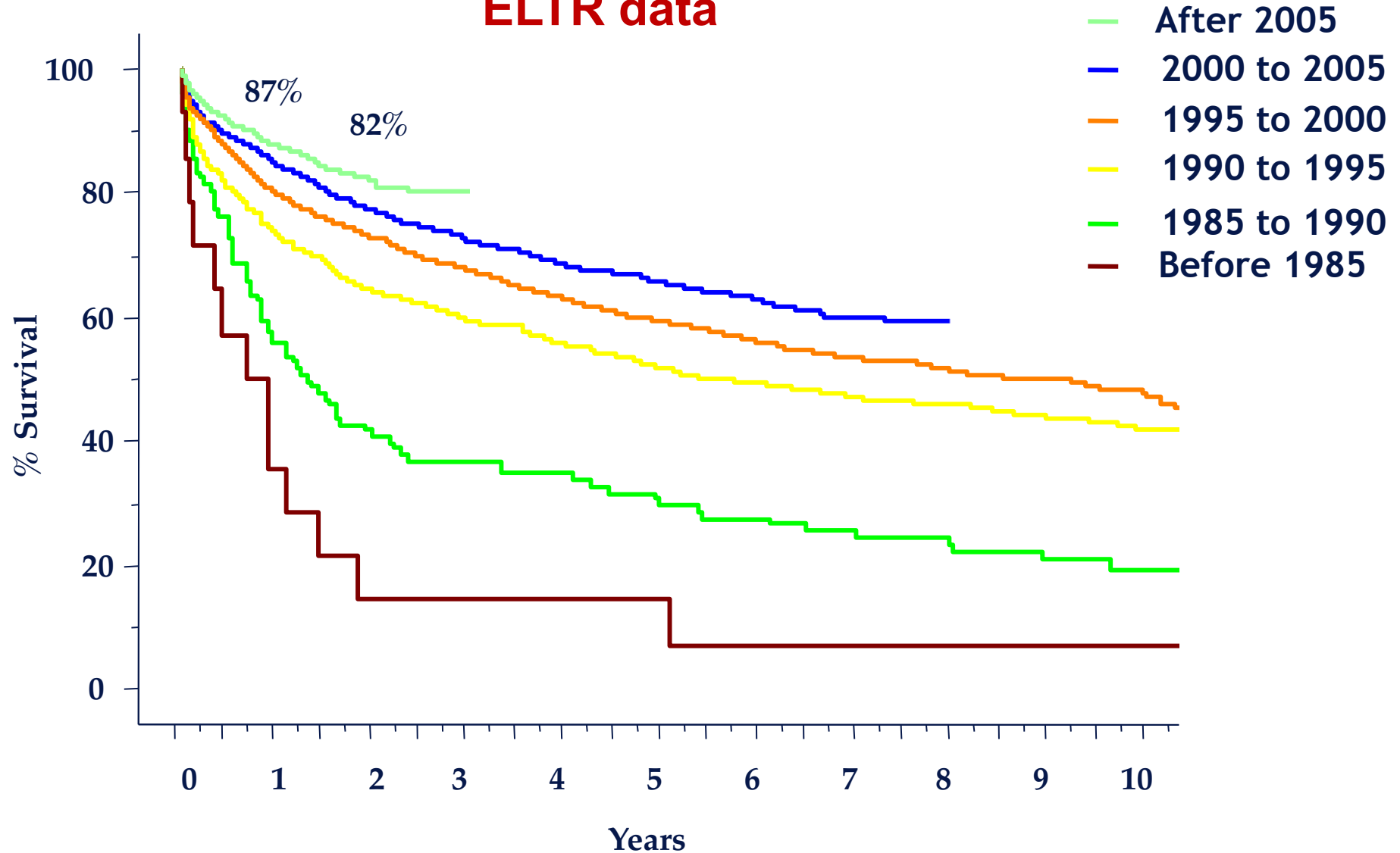
## Limitations of LT for HCC

- Survival < OLT for benign disease: recurrence
- Competition with other indications
- Strict patient selection required
- Organ shortage
- Progression and drop out from waiting list

# Patient survival according to the year of LT

## For Hepatocellular Carcinoma

ELTR data



# Resection vs Liver transplantation

3-year survival (Disease free)

	Resection	OLT	p
1 ou 2 nodules, < 3 cm	41% (18%)	83% (83%)	<0.05
≥ 3 nodules, ≥ 3 cm	-	46% (44%)	<0.01

« We believe that hepatic transplantation should be restricted to small lesions (<3cm) with one or two nodules. »

# 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.

*Ann Surg, 1993*

## LIVER TRANSPLANTATION FOR THE TREATMENT OF SMALL HEPATOCELLULAR CARCINOMAS IN PATIENTS WITH CIRRHOSIS

VINCENZO MAZZAFERRO, M.D., ENRICO REGALIA, M.D., ROBERTO DOCI, M.D., SALVATORE ANDREOLA, M.D.,  
ANDREA PULVIRENTI, M.D., FEDERICO BOZZETTI, M.D., FABRIZIO MONTALTO, M.D., MARIO AMMATUNA, M.D.,  
ALBERTO MORABITO, PH.D., AND LEANDRO GENNARI, M.D., PH.D.

*NEJM, 1996*

# Liver Transplantation for Hepatocellular Carcinoma: Validation of the UCSF-Expanded Criteria Based on Preoperative Imaging

*Am J Transp, 2007*



# Liver Transplantation for Hepatocellular Carcinoma: Beyond the Milan Criteria

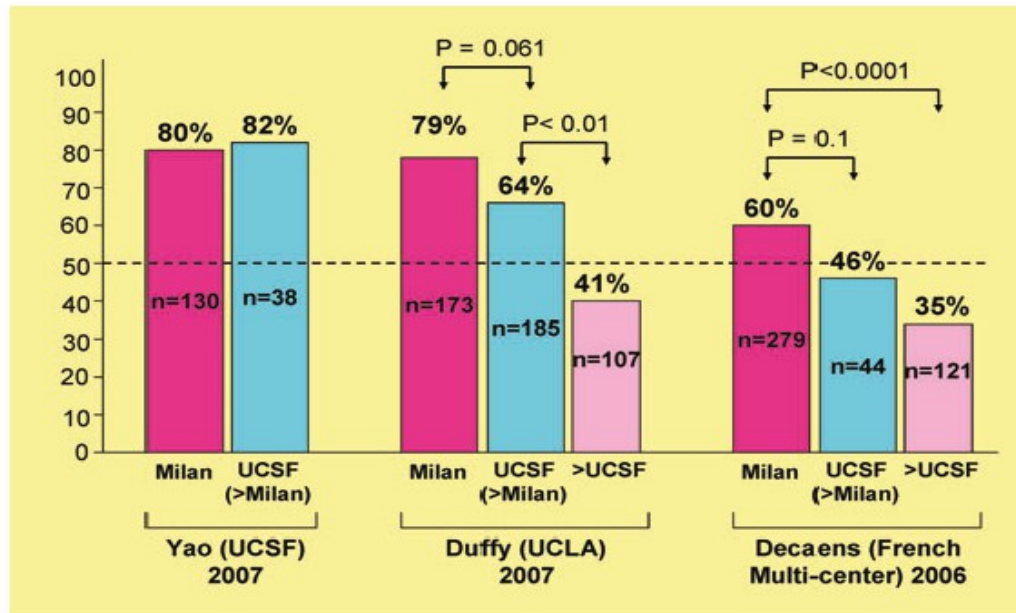
F. Y. Yao\*

## MILAN

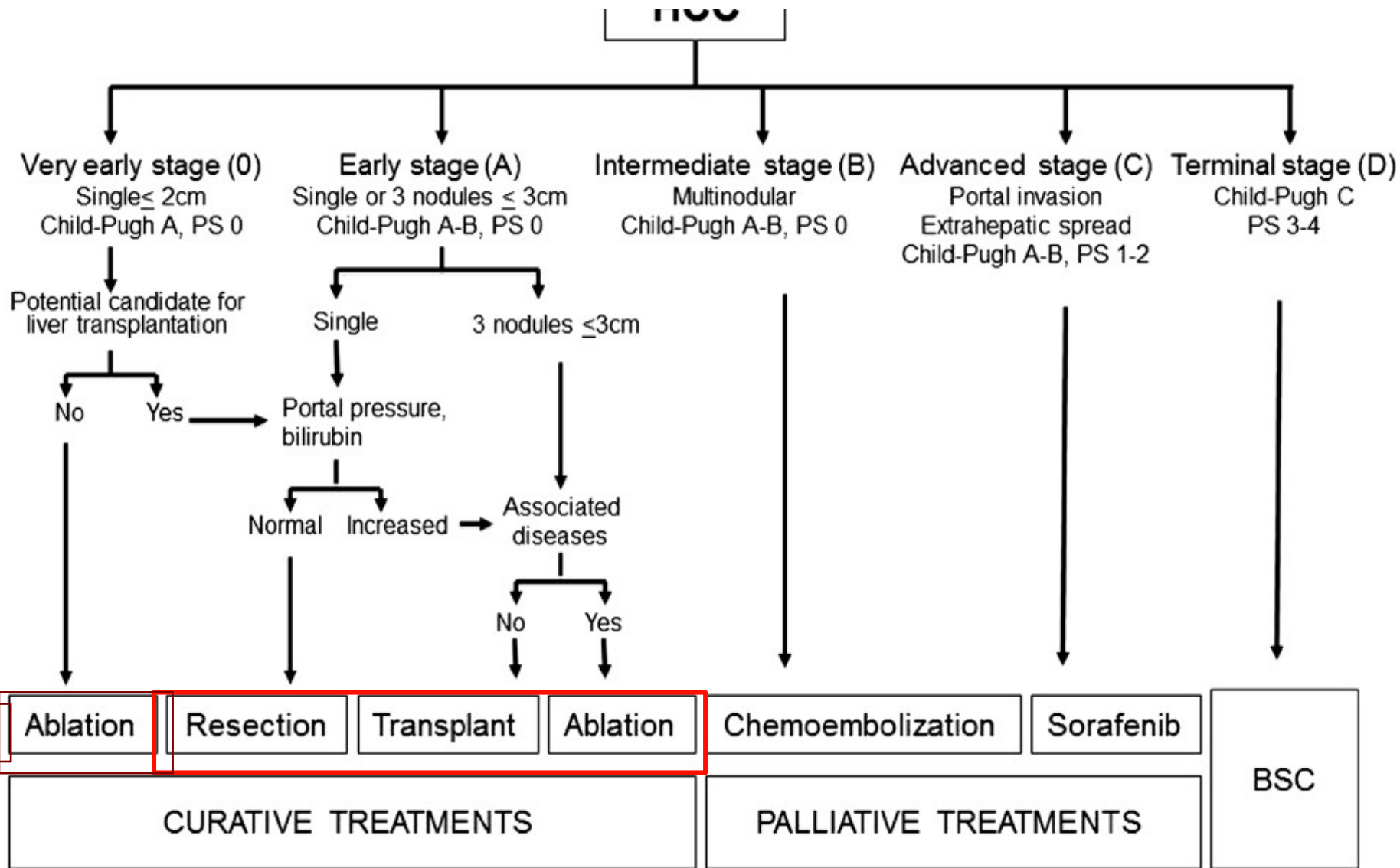
1 nodule  $\leq 5$  cm  
Or  $n \leq 3$  et  $\emptyset \leq 3$  cm

## UCSF

1 nodule  $\leq 6.5$  cm  
Or  $n \leq 3 / \emptyset \leq 4.5$  ou  $\Sigma \emptyset \leq 8$  cm



# Guidelines for Treatment of HCC



Missing: Child C with 1-3 nodules <3cm

# Organ Allocation USA - 2002

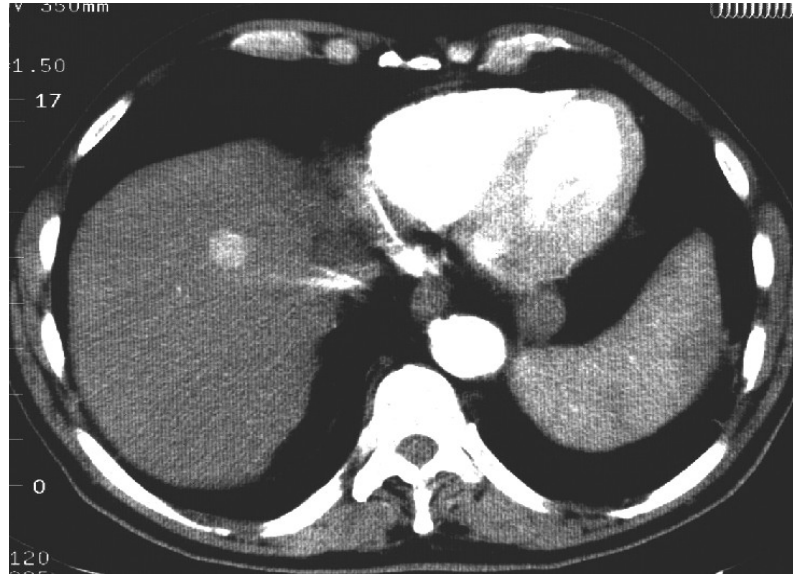
- **MELD measuring severity of liver disease**
- Utility: sickest first Policy
  - **HCC exception points for TNM1 and TNM2**
  - Equity
  - HCC MELD (increase / 3 months)
  - Transplant within 3-6 months

# Organ Allocation

## USA 2002. Europe 2004-2007

- **MELD: severity of liver disease**
- **HCC exception points**
  - TNM 1: 0 points
  - TNM 2 : HCC MELD
  - increment / 3 months: 6 – 12 months

# Liver Transplantation for Small HCC



30 % of TNM 1 (<2cm) patients had no cancer on hepatectomy specimen

Wiesner Gastroenterology 2004

# Can we Refine the Criteria of Selection of HCC

- **Size and Number of Nodules:**
  - Insufficient and Simplistic
  - Empirical extension
- **Tumor Biology**
  - Pathology excellent but usually unavailable preoperatively
  - Surrogates
    - AFP
    - Tumor progression
    - Response to Locoregional treatment
    - Genomics and Molecular biology...

# Can we Refine the Criteria of Selection of HCC UCSF Criteria

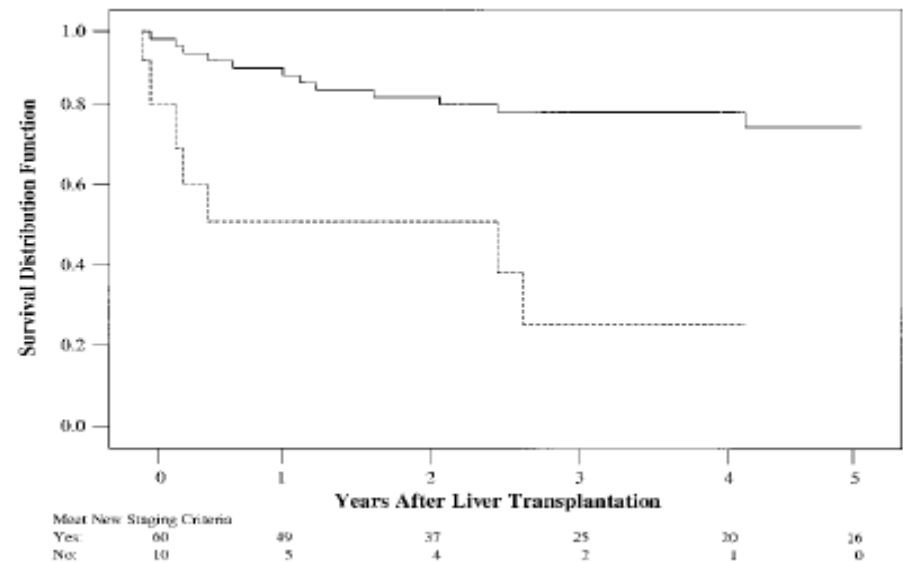
*LT for HCC : expansion of the tumor size does not adversely impact survival*  
*Yao et al. Hepatology 2001*

## Modified staging\*

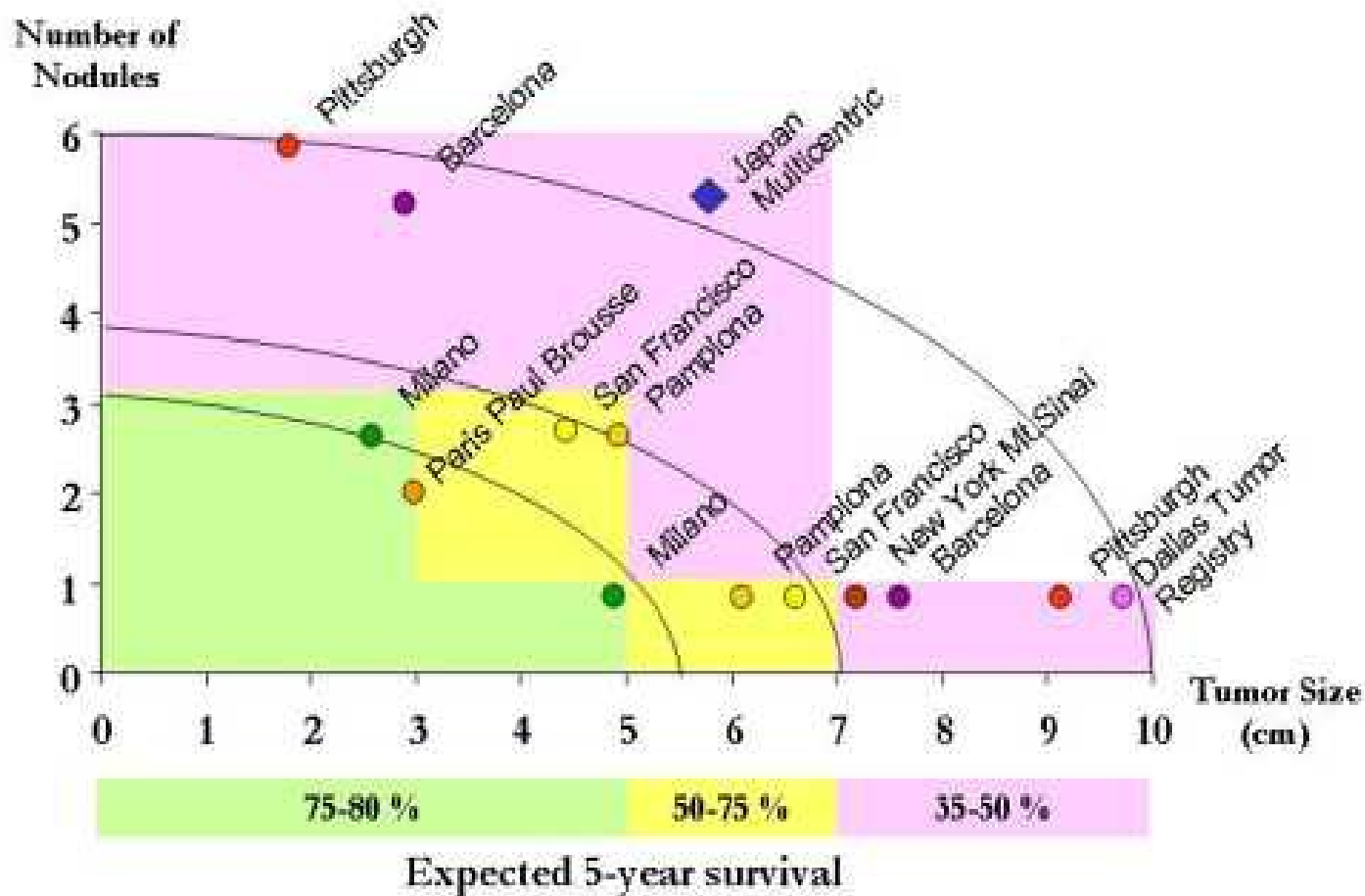
- Single nodule < 6.5 cm

OR

- $\leq 3$  nodules,  $\leq 4.5$  cm diameter and total diameter  $\leq 8$ cm



# The Metro Ticket



Mazzaferro et al.

Lancet Oncol 2009



# Up to Seven:

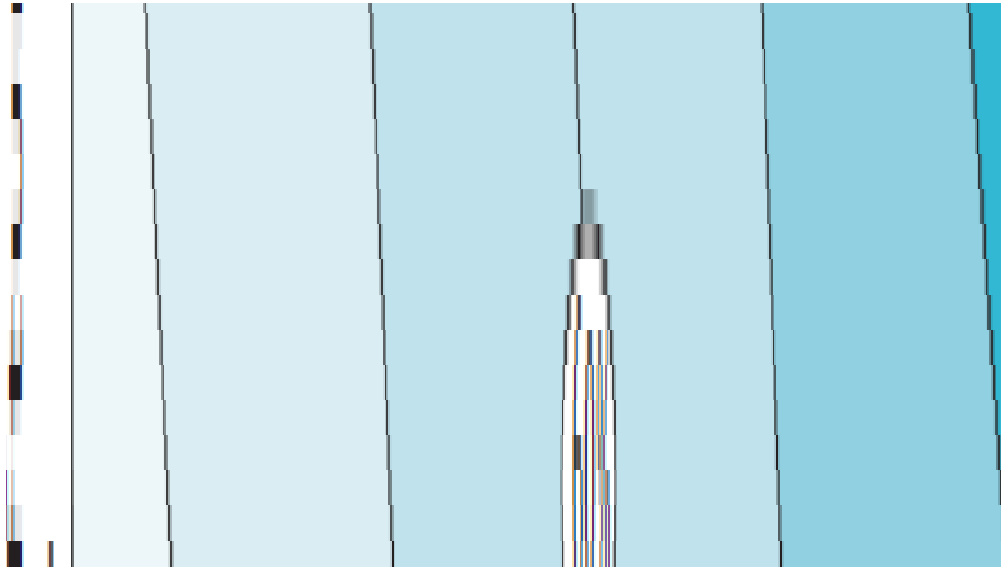
**HCC with 7 as the sum of the size of the largest tumour  
and the number of tumours**

1 tumor - 6 cm: 6+1

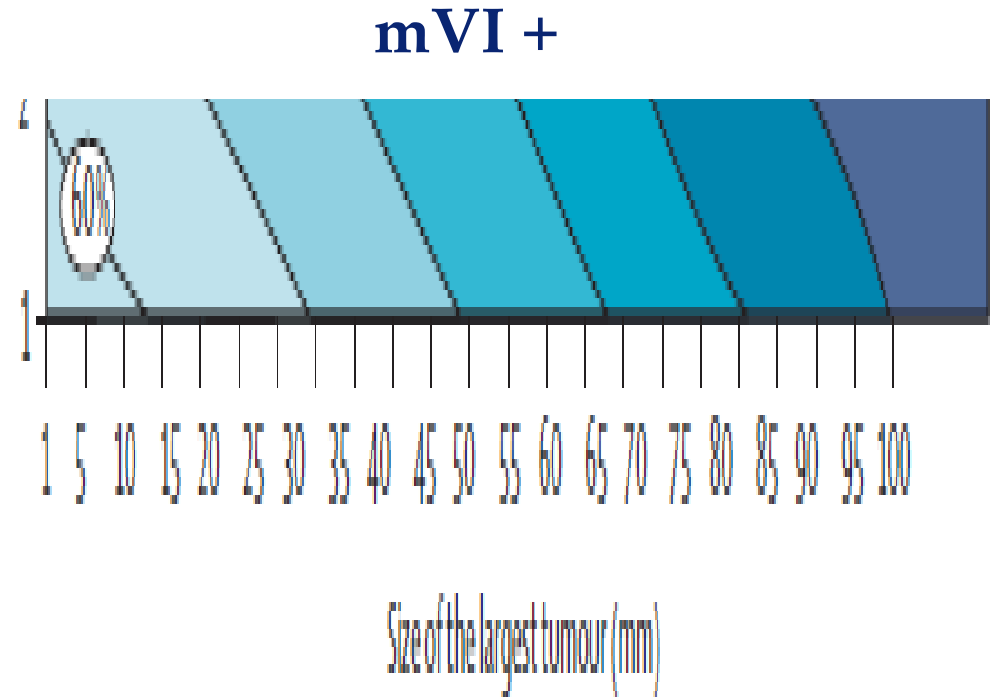
4 tumors - max 3 cm: 4+3

5 tumors – max 2 cm: 5+2

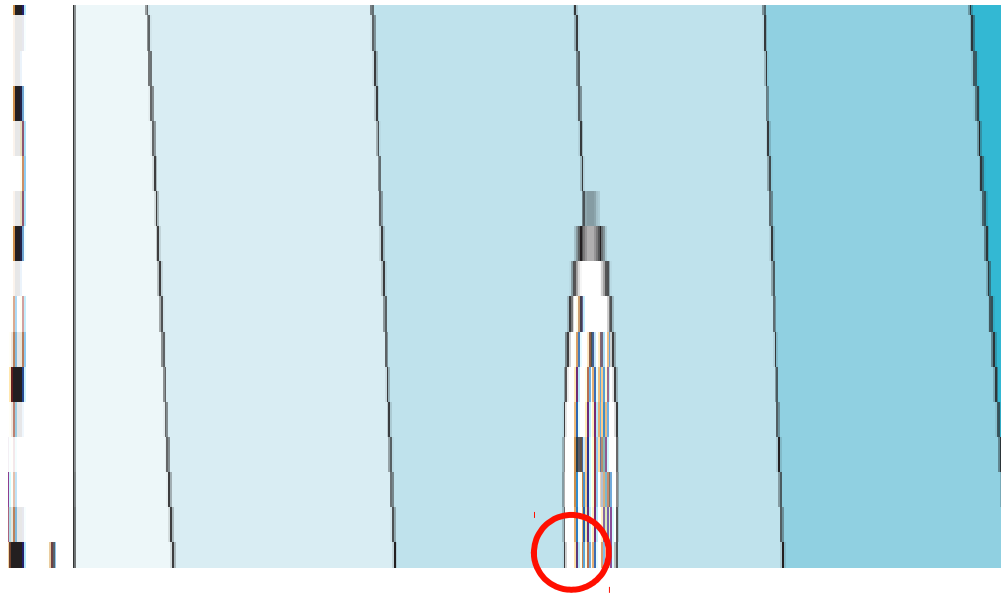
# Up to Seven: Role of Microvascular Invasion



mVI -

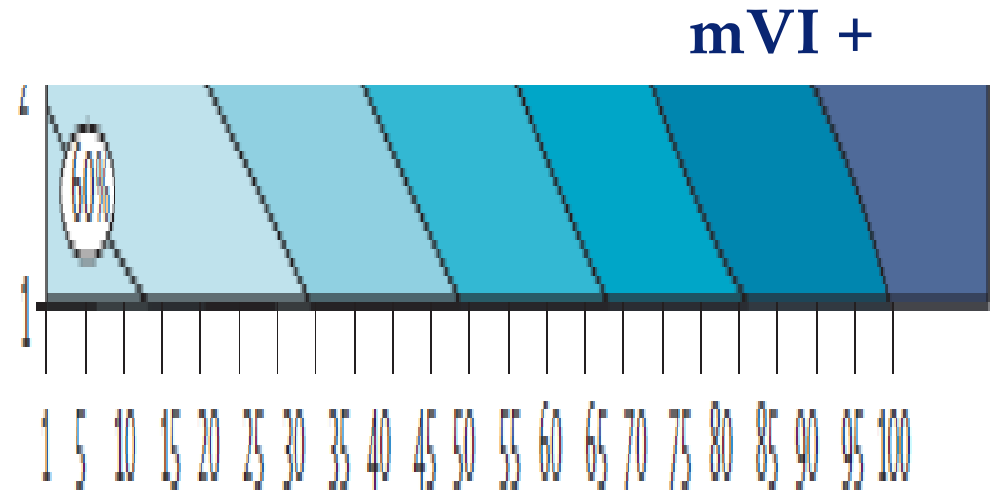


# Up to Seven: Role of Microvascular Invasion



mVI -

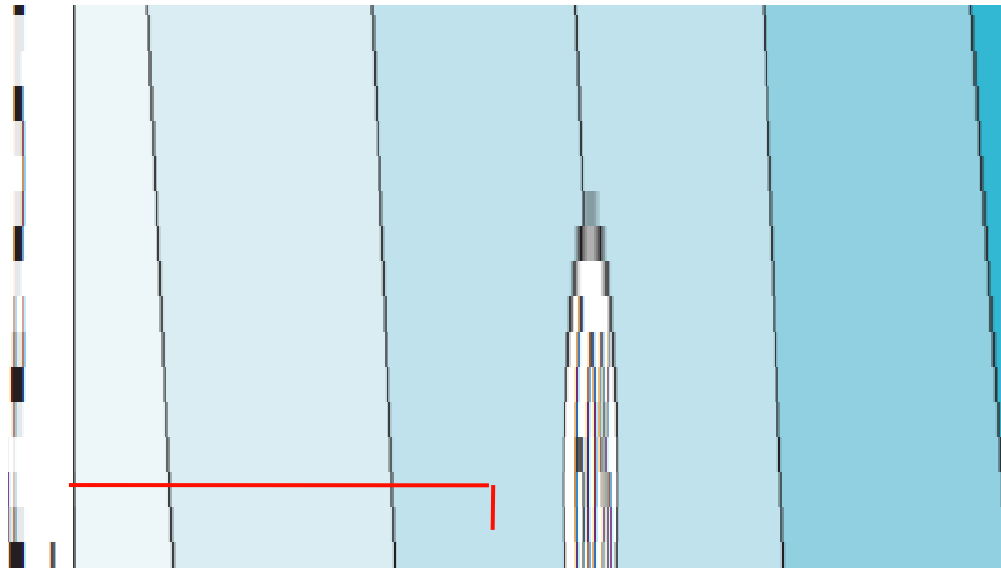
1 tumor - 6 cm: 6+1  
mVI- 68% 5y  
mVI+ 46% 5Y



mVI +

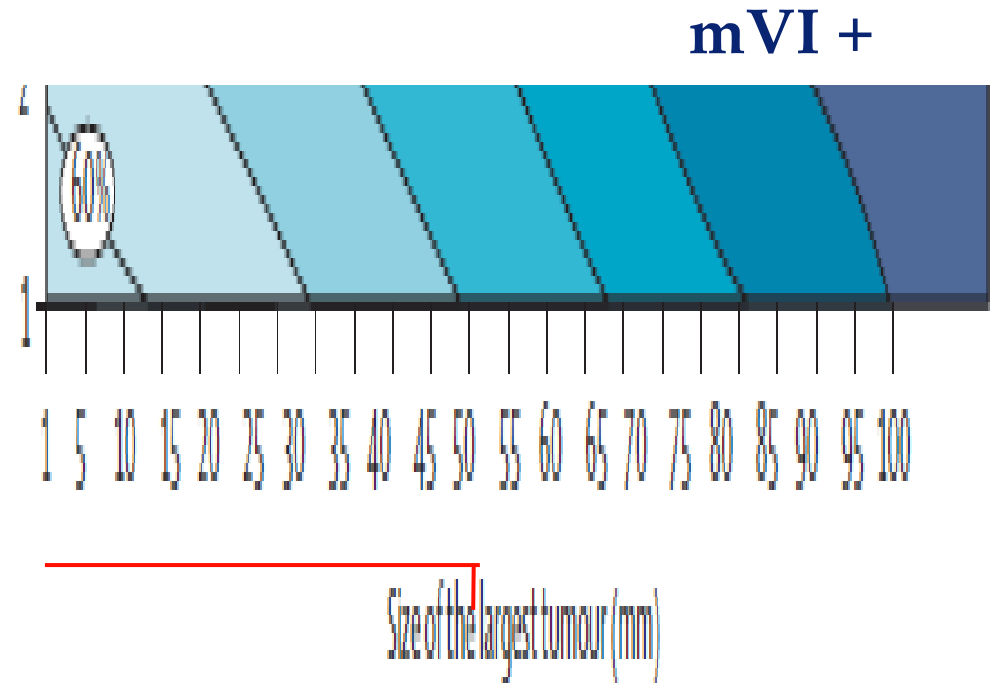
Size of the largest tumour (mm)

# Up to Seven: Role of Microvascular Invasion

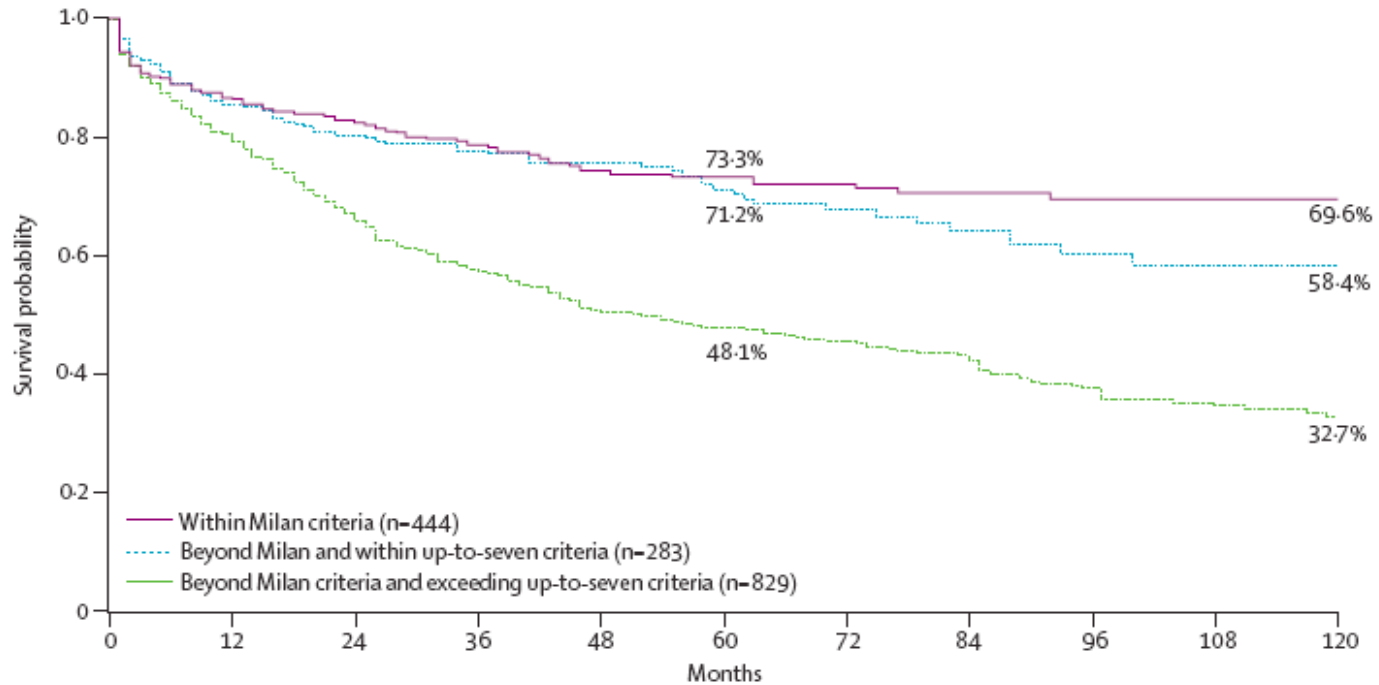


mVI -

5 tumors – max 2 cm: 5+2  
mVI- 68% 5y  
mVI+ 48% 5Y



# Up to Seven without Microvascular Invasion



	Patients at risk										
	0	12	24	36	48	60	72	84	96	108	120
Within Milan criteria	444	340	278	219	176	140	124	94	71	71	71
Beyond Milan within up-to-seven	283	217	173	137	121	90	68	57	44	32	32
Exceeding Milan and up-to-seven	829	593	429	323	250	202	155	120	87	66	48

**Figure 3: Up-to-seven criteria**

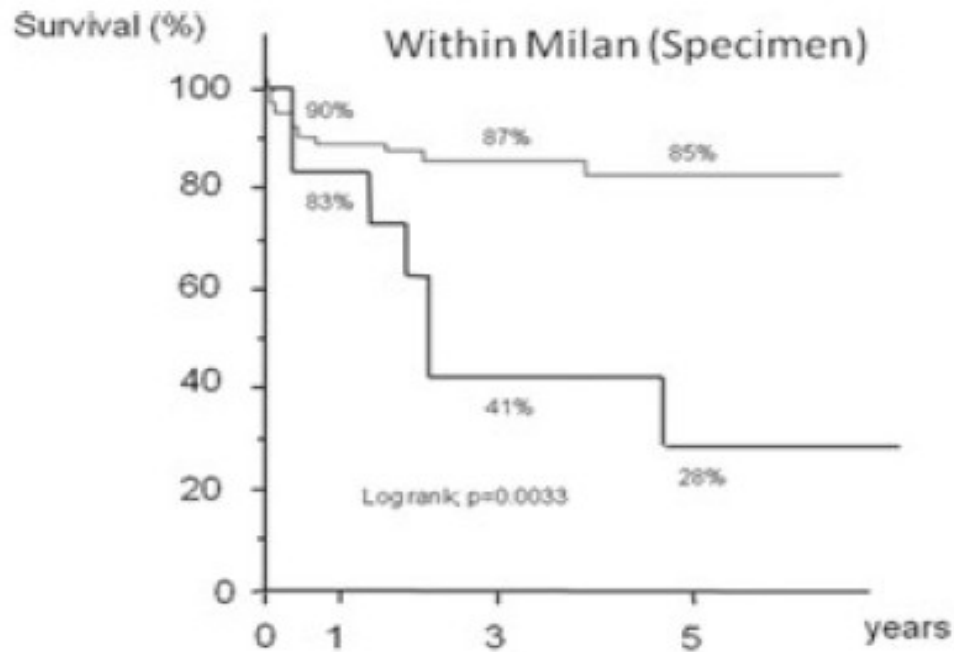
Kaplan-Meier overall survival curves of the three subgroups: within Milan criteria (n=444); beyond Milan and within up-to-seven criteria (n=283); and beyond Milan and exceeding up-to-seven criteria (n=829). Patients with hepatocellular carcinomas beyond Milan criteria, but within up-to-seven criteria 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).

# Can we Refine the Criteria of Selection of HCC

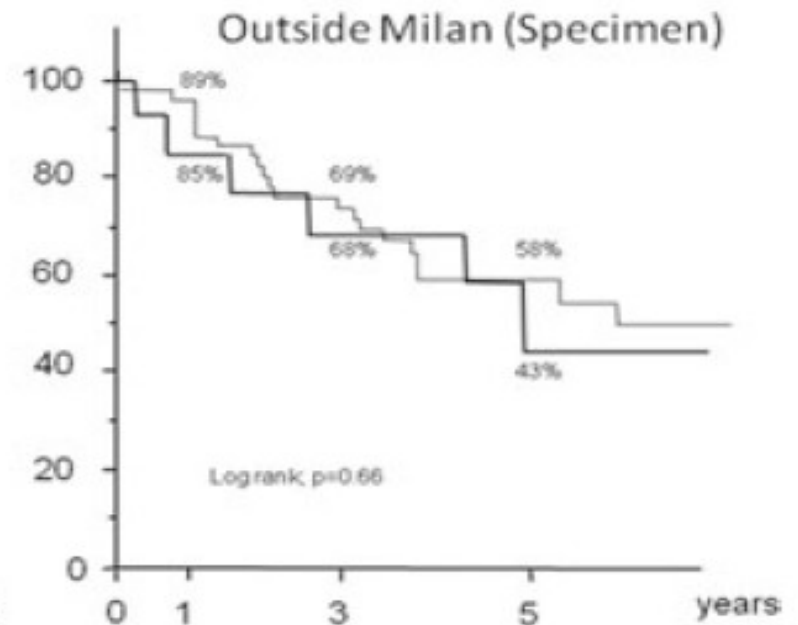
## UCSF Criteria

- **Size and Number of Nodules:**
  - Insufficient and Simplistic
  - Empirical extension
- **Tumor Biology**
  - Pathology excellent but usually unavailable preoperatively
  - Surrogates
    - AFP
    - Tumor progression
    - Response to Locoregional treatment
    - Genomics and Molecular biology...

# Impact of Pre-LT Increasing AFP > 15 ng/ml/mth on Post-LT Recurrence Free Survival



Nb of patients at risk	1 yr	3 yrs	5 yrs
No progression group (n=77)	66	51	36
Progression group (n=12)	9	4	3



Nb of patients at risk	1 yr	3 yrs	5 yrs
No progression group (n=77)	43	27	12
Progression group (n=12)	10	7	3

# Liver Transplantation for Hepatocellular Carcinoma: A Model Including $\alpha$ -Fetoprotein Improves the Performance of Milan Criteria

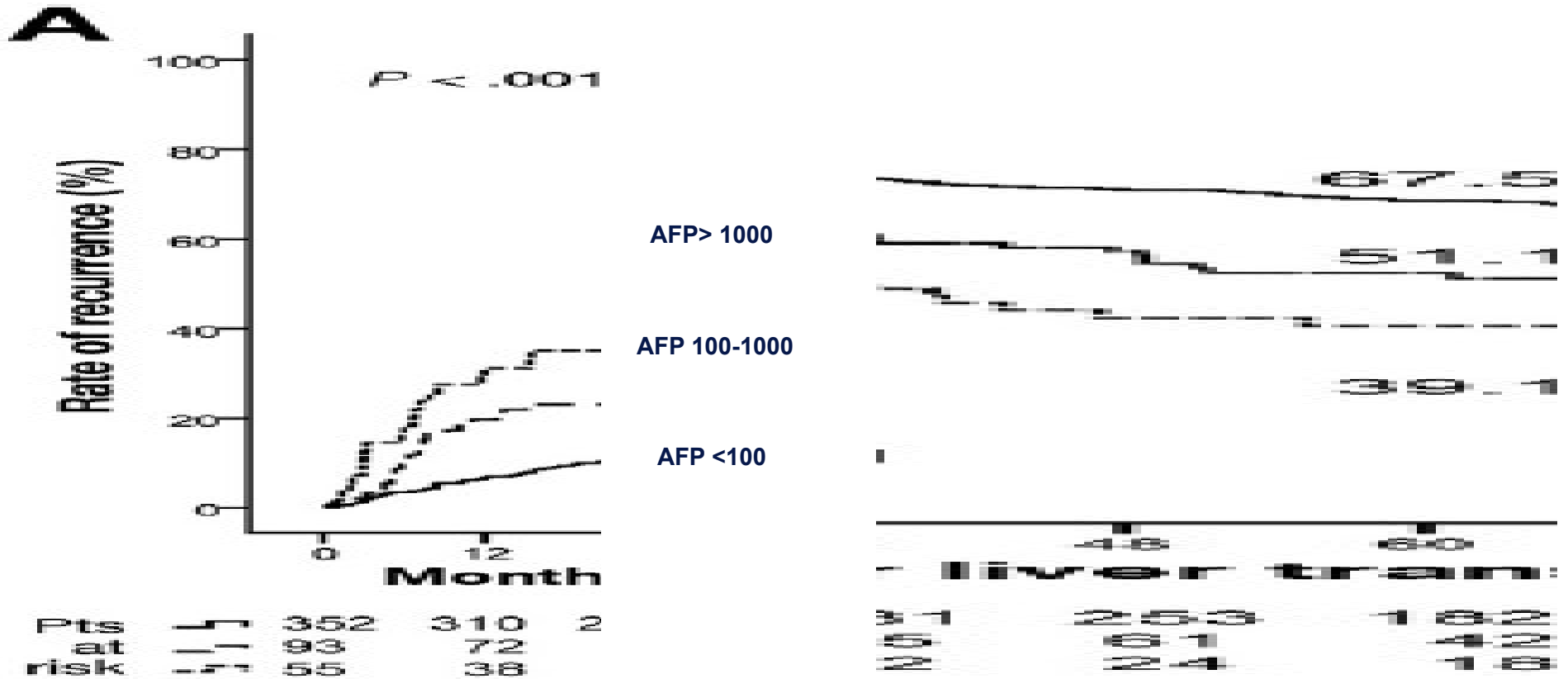
CHRISTOPHE DUVOUX,<sup>1,2</sup> FRANÇOISE ROUDOT-THORAVAL,<sup>2,3</sup> THOMAS DECAENS,<sup>1,2,4</sup> FABIENNE PESSIONE,<sup>5</sup> HANAA BADRAN,<sup>1</sup> TULLIO PIARDI,<sup>6</sup> CLAIRE FRANCOZ,<sup>7</sup> PHILIPPE COMPAGNON,<sup>8</sup> CLAIRE VANLEMMENS,<sup>9</sup> JÉROME DUMORTIER,<sup>10</sup> SÉBASTIEN DHARANCY,<sup>11</sup> JEAN GUGENHEIM,<sup>12</sup> PIERRE-HENRI BERNARD,<sup>13</sup> RENÉ ADAM,<sup>14</sup> SYLVIE RADENNE,<sup>15</sup> FABRICE MUSCARI,<sup>16</sup> FILOMENA CONTI,<sup>17</sup> JEAN HARDWIGSEN,<sup>18</sup> GEORGES-PHILIPPE PAGEAUX,<sup>19</sup> OLIVIER CHAZOUILLÈRES,<sup>17</sup> EPHREM SALAME,<sup>20</sup> MARIE-NOELLE HILLERET,<sup>21</sup> PASCAL LEBRAY,<sup>22</sup> ARMAND ABERGEL,<sup>23</sup> MARILYNE DEBETTE-GRATIEN,<sup>24</sup> MICHAEL D. KLUGER,<sup>25</sup> ARIANE MALLAT,<sup>1,2,4</sup> DANIEL AZOULAY,<sup>2,25</sup> and DANIEL CHERQUI,<sup>2,25</sup> on behalf of the Liver Transplantation French Study Group

GASTROENTEROLOGY 2012;143:986-994

- **1032 patients transplanted for HCC in 16 French Centers (> Milan : 32%)**
  - **Training cohort 597**
  - **Validation cohort 435**
- **Uni- and multivariate analysis for predictors of recurrence**
- **Design of a predictive model of recurrence**
  - **Design of a simplified, user-friendly version of the model**
  - **Comparison against Milan criteria**



# AFP level and Post LT Survival and Recurrence

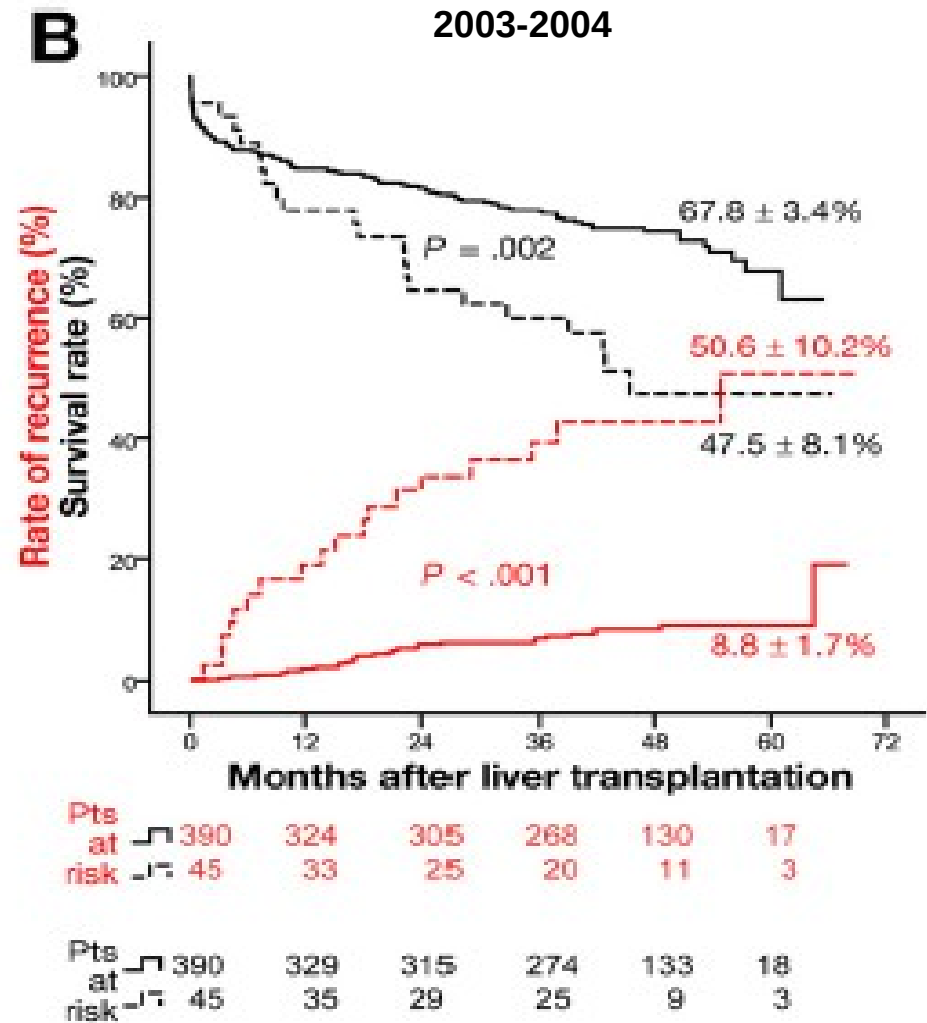
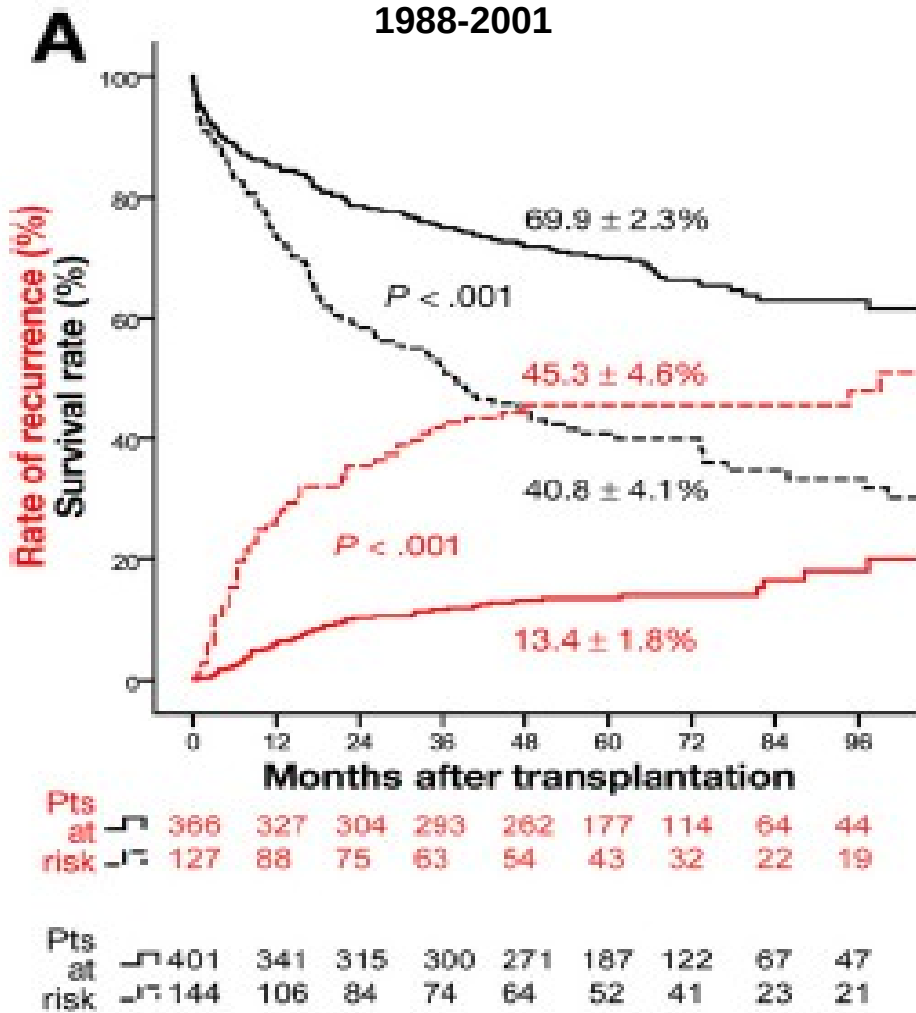


*Duvoux et al. Gastroenterology 2012*

# AFP Score

Training (n=492)

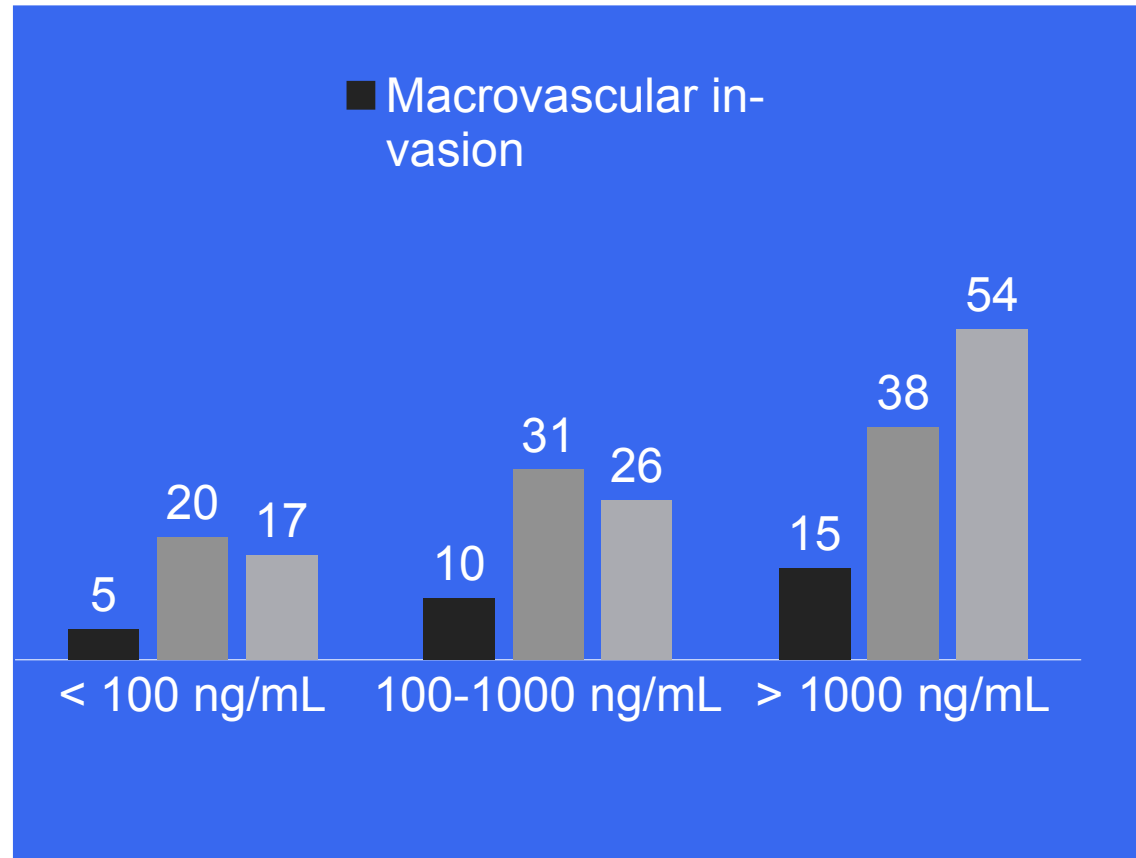
Validation (n=435)



LT recommended: Score  $\leq 2$

LT not recommended:  
Score  $> 2$

# Correlation AFP and Pathology



# The AFP score

Variable	Points
<b>Size</b> ≤ 3 cm 3-6 cm > 6 cm	0 1 4
<b>Number</b> 1-3 ≥ 4	0 2
<b>AFP (ng/mL)</b> ≤ 100 100-1000 > 1000	0 2 3

**Cut-off = 2**

**Risk of Recurrence**

**≤ 2 : Low**

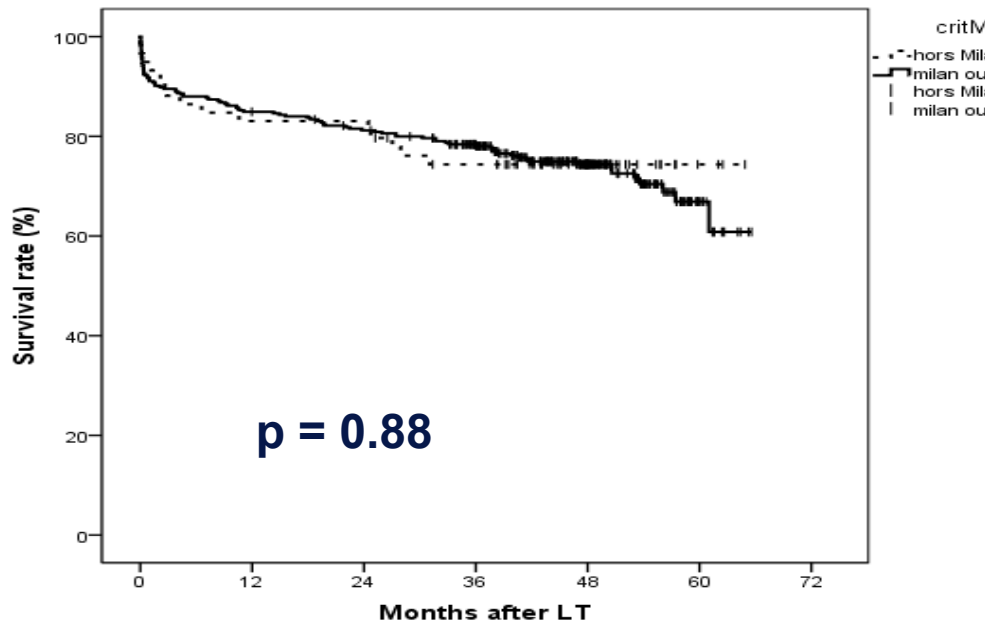
**> 2 : High**



# The AFP Score Improves Milan Criteria

Score  $\leq 2$  : 59 patients outside Milan

325 patients inside Milan



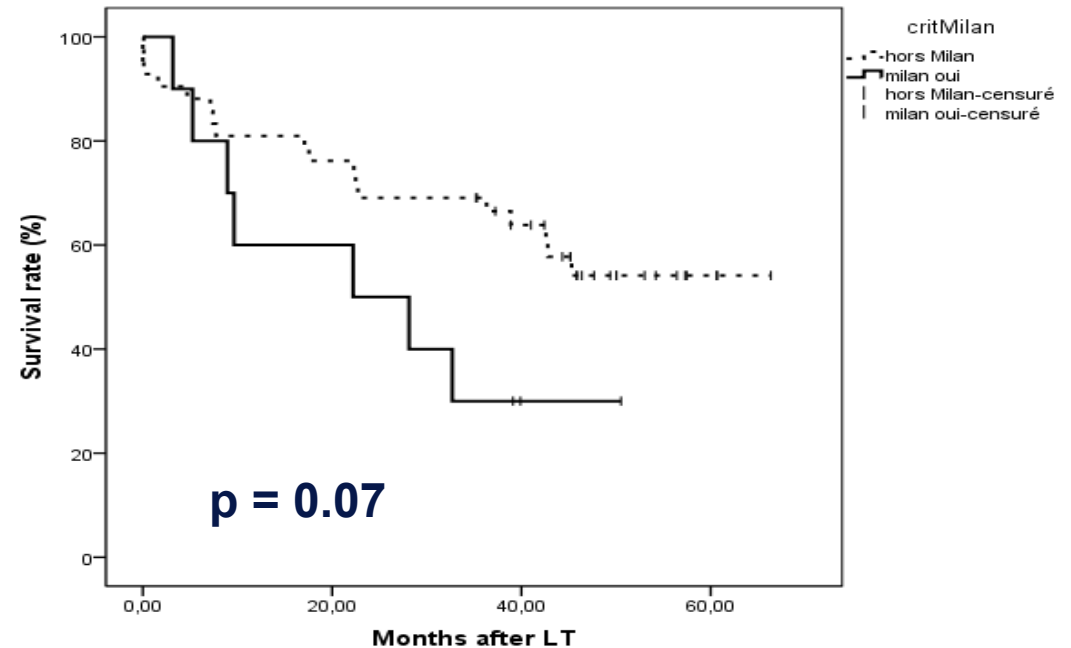
5 year survival :

Milan + :  $66.9 \pm 3.8$  %

Milan - :  $74.4 \pm 5.7$  %

Score  $\geq 3$  : 42 outside Milan

10 inside Milan



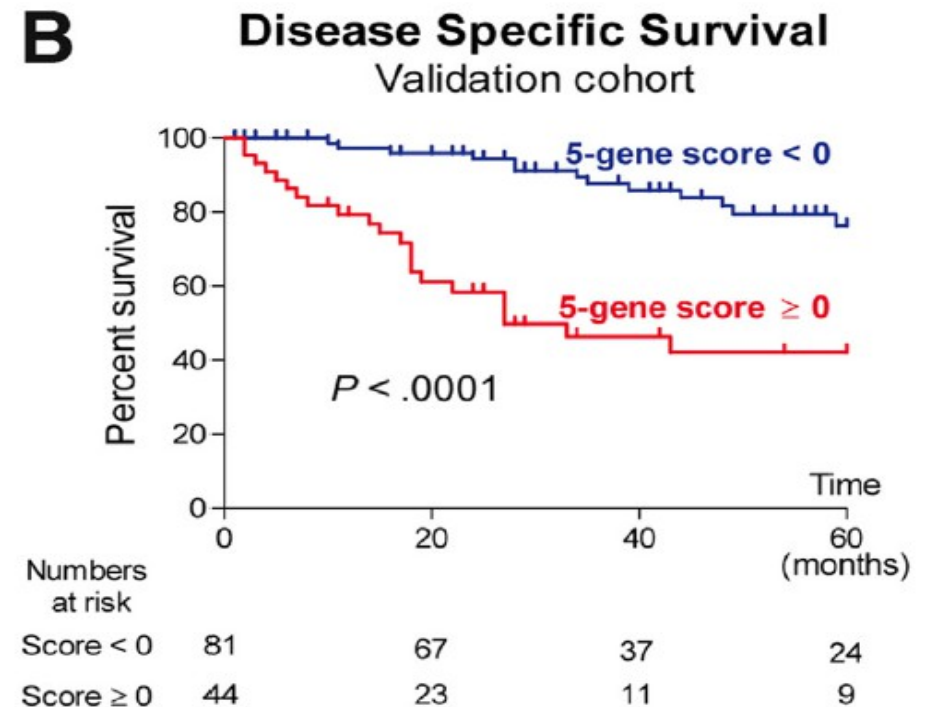
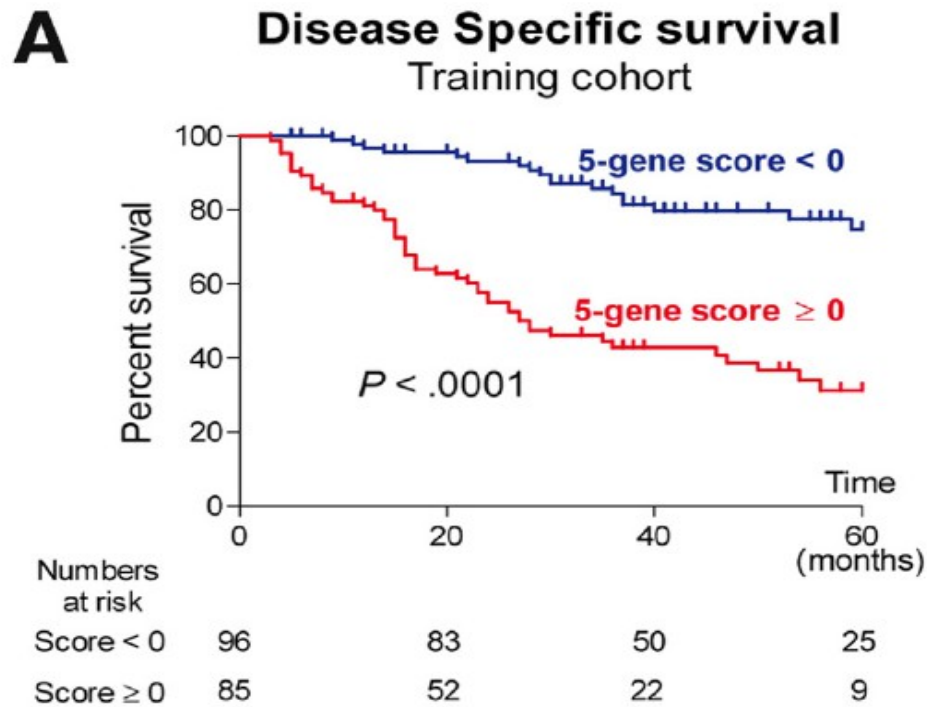
5 year survival :

Milan + :  $30.0 \pm 14.5$  %

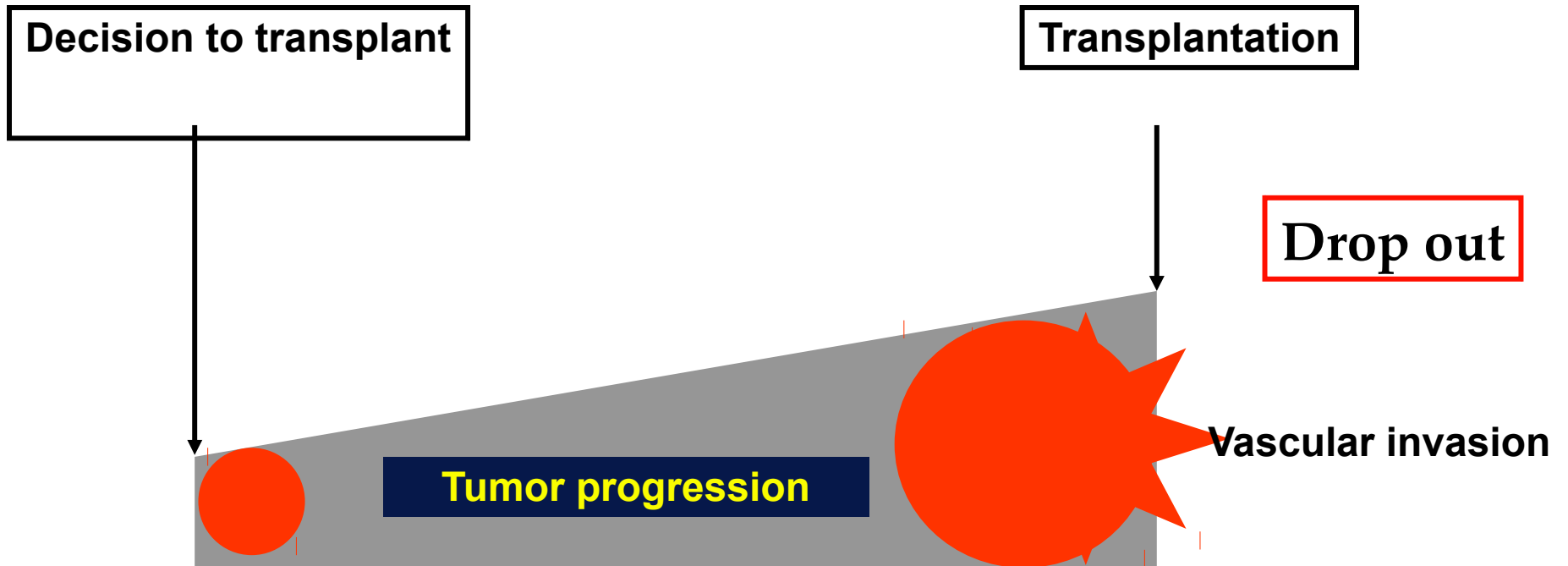
Milan - :  $54.1 \pm 8.2$  %

# A Hepatocellular Carcinoma 5-Gene Score Associated With Survival of Patients After Liver Resection

Nault et al. Gastroenterology 2013



# Liver Transplantation for HCC



**Bridge treatment**

**Intent to treat**



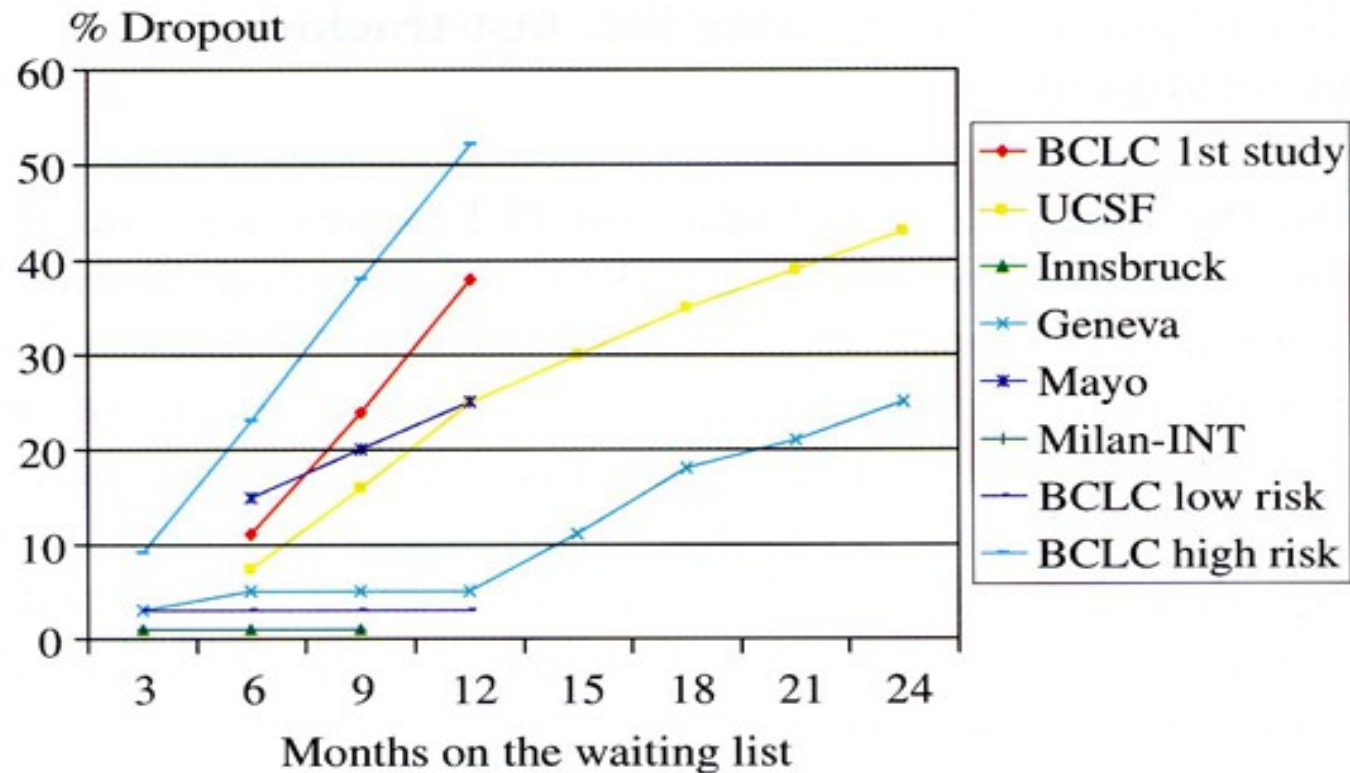
# DROP OUT FROM THE WAITING LIST

- Risk Increased with time
- Depends of the size and number of nodules at listing
- When to drop out?:
  - Increased HCC out of Milan criteria or UCSF criteria?
  - Vascular invasion?
- Interval of surveillance on the waiting list?
- Treatment of HCC to avoid drop out?

# STRATEGIES

- Depends of the waiting time
- Main possibilities:
  - Percutaneous treatment :
    - Radiofrequency
  - Transarterial chemoembolisation
  - Surgical Resection
  - Targeted Therapies?

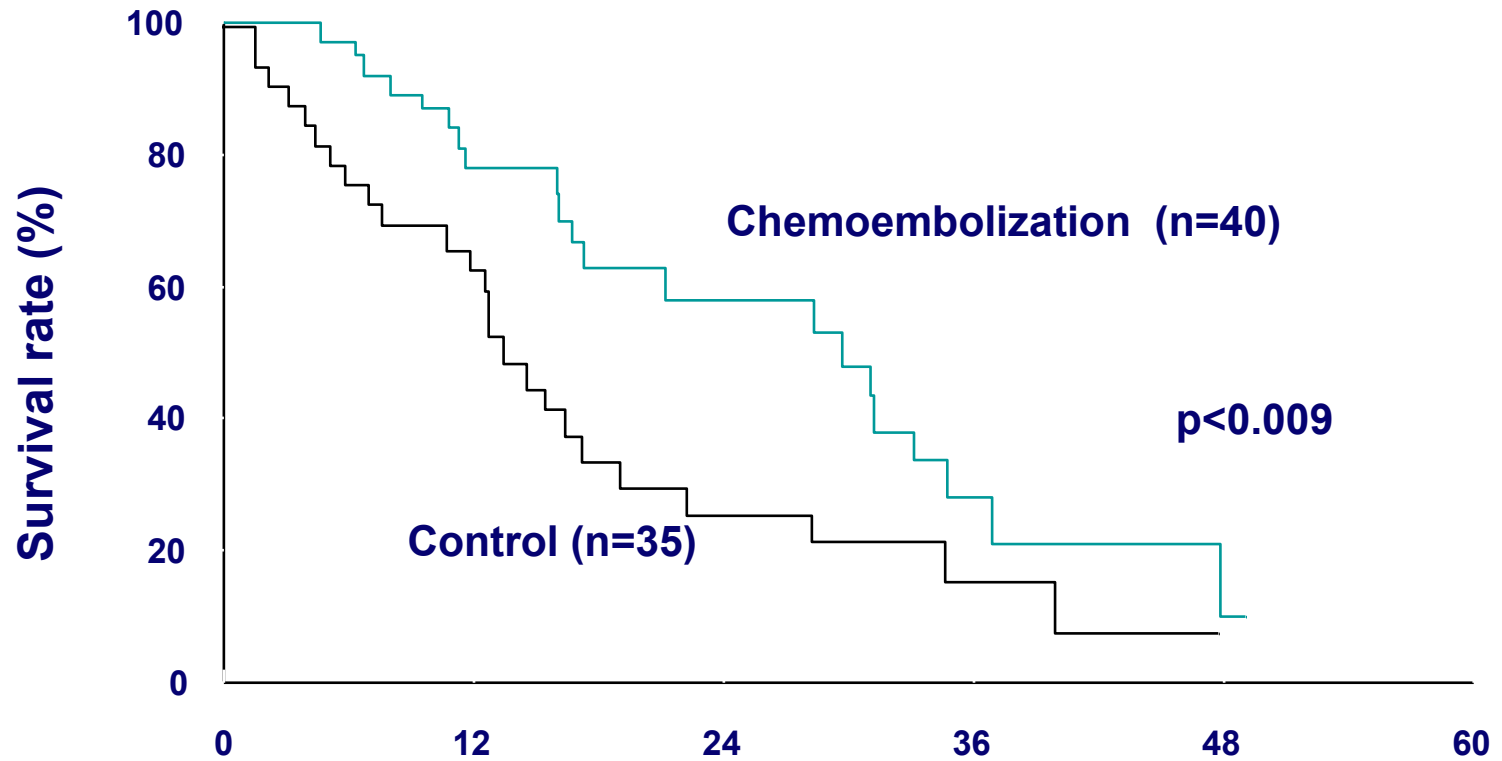
# Drop Out Rate In Patients With HCC Waiting For LT



**Fig. 1. Summary of dropout probabilities in different centres. Missing intermediate values were interpolated from the mean of the adjacent values.**

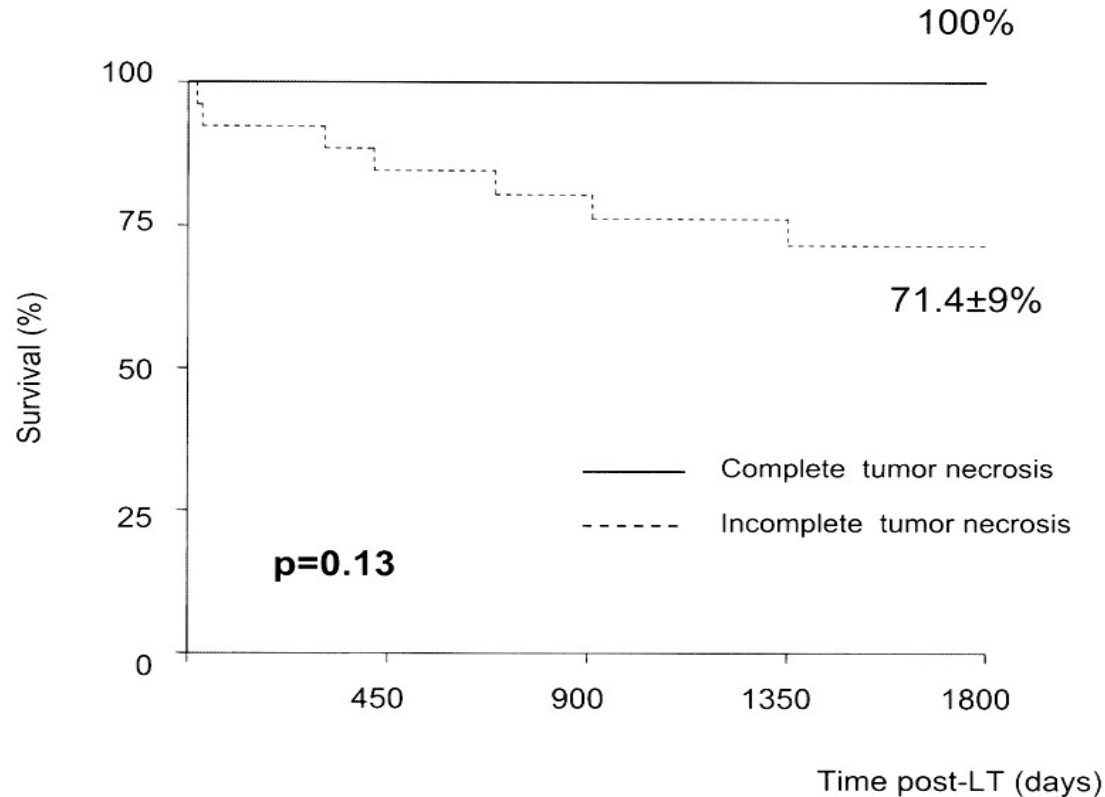
# TRANSARTERIAL LIPIODOL CHEMOEMBOLISATION

## Survival: chemoembolisation vs control



Chemoembolization	40	29	14	4	2
Control	35	19	7	3	0

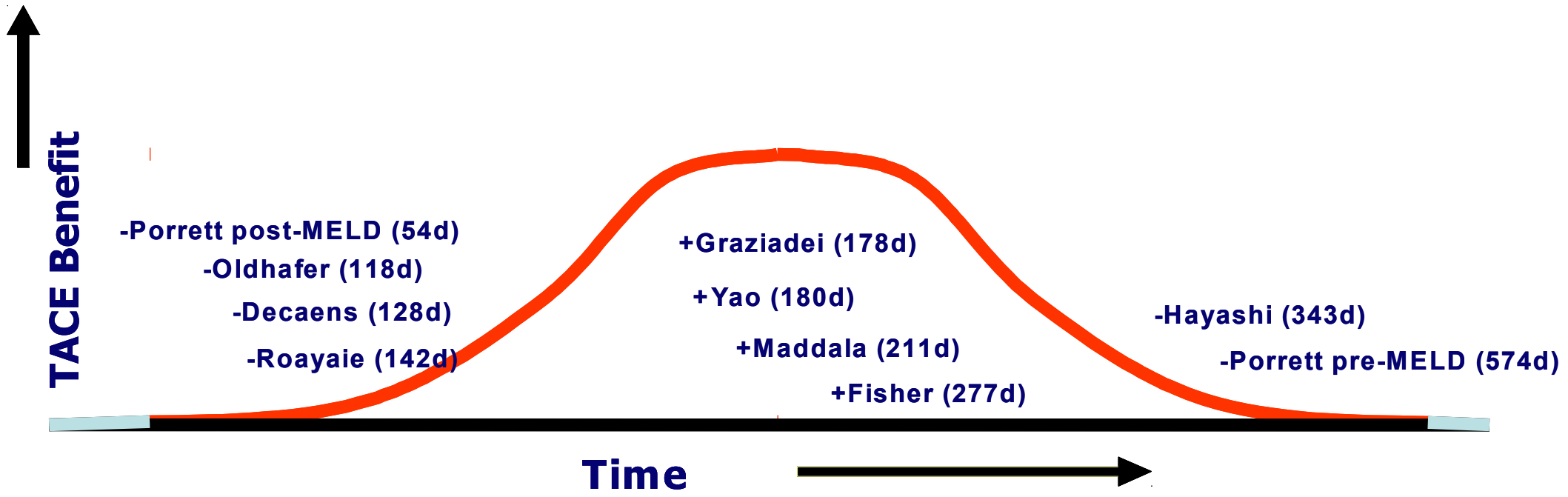
# 5-Year Disease Free Survival According to Complete Necrosis of One Nodule < 5cm after TACE or STACE



**Figure 3. Five-year disease-free survival in patients with single-nodule disease  $\leq 5$  cm, according to complete tumor necrosis. Solid line, patients with complete tumor necrosis (n = 6); dotted line, patients without complete tumor necrosis (n = 26).**

# TACE Benefit According to the Waiting Time Duration

## Benefit for Waiting time Between 4 to 9 months

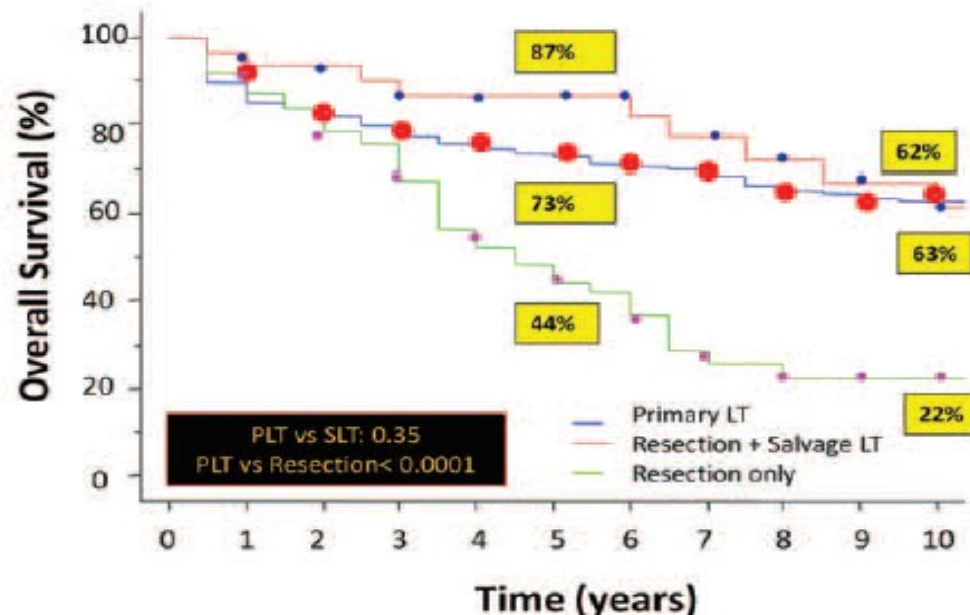
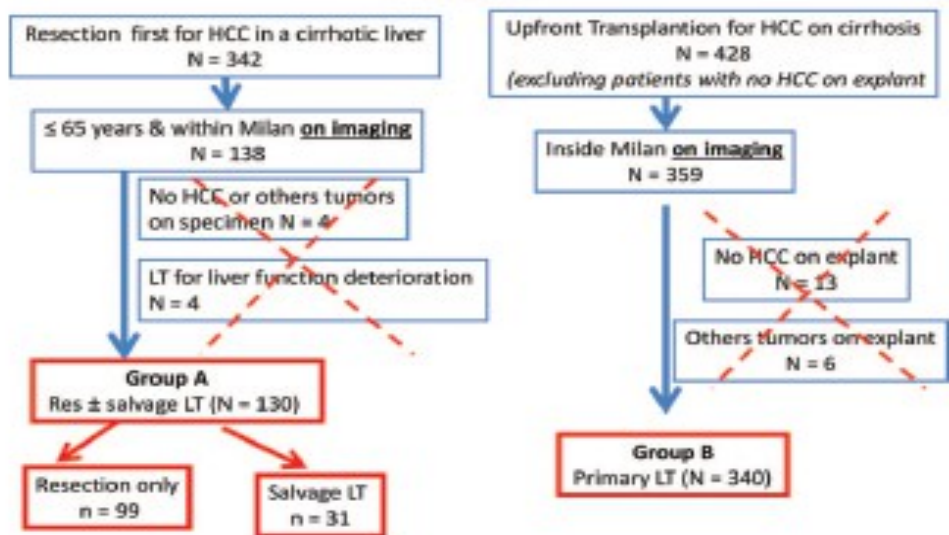


*Aloia T, Adam R, Samuel D, J Gastro Intest Surg 2007*

# Salvage Versus Primary Liver Transplantation for Early Hepatocellular Carcinoma: Do Both Strategies Yield Similar Outcomes?

Prashant Bhangui, MD,\*†‡ Marc Antoine Allard, MD,\*†§ Eric Vibert, MD, PhD,\*†¶ Daniel Cherqui, MD,\*†¶ Gilles Pelletier, MD,\*†¶ Antonio Sa Cunha, MD,\*†§ Catherine Guettier, MD,\*†¶ Jean-Charles Duclos Vallee, MD,\*†¶ Faouzi Saliba, MD,\*†¶ Henri Bismuth, MD,\*†¶ Didier Samuel, MD, PhD,\*†¶ Denis Castaing, MD,\*†¶ and René Adam, MD, PhD\*†§

1990-2012



**Feasibility of Salvage LT : 31/90 who recurred (34%)**

# Conclusion

Liver transplantation, by treating both the tumor and cirrhosis, is the best (only) curative treatment for HCC

Its intention to treat efficacy is limited by severe organ shortage and it can only be offered to a limited number of patients

Strict criteria based on the risk of tumor recurrence are therefore required for an effective utilization of limited organ supply



# Conclusion

## **Post transplant recurrences are correlated with**

Size and number of lesions

Tumor differentiation and vascular involvement

Preoperative AFP

## **Milan Criteria are widely adopted but have limitations**

Excessive for early and very early tumors (T1)

Too restrictive for lesions moderately above criteria

## **Preoperative AFP**

Improves patient selection

Allows reasoned extension of criteria

# Conclusion

**Bridge treatment is required** (TACE, Ablation, Resection)

To control tumor progression on waiting list

Improve patient selection

Downstage more advanced tumors

**Present trend:**

Ablation or Resection for early tumors in compensated cirrhosis and salvage transplantation in case of recurrence

Moderate extension of transplant criteria to patients with AFP < 100

**Thanks**



## **Medico–Surgical Team of the CHB**

**T. Antonini, A. Coilly, JC. Duclos-Vallée, G Pelletier  
B Roche, R Sobesky**

**P. Ichai, F Saliba, M Boudon, S André**

**D. Cherqui, D. Castaing, R Adam, A Sa Cunha, E Vibert,**

**O Ciaccio, G Pittau and all**