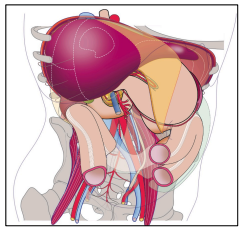


Hépatocarcinome: Place de la chirurgie

Dr Olivier Detry

Chirurgie Abdominale & Transplantation

CHU Liège

Hépatocarcinome

- Sur foie sain
- Sur foie cirrhotique

Les cirrhoses asiatiques ne sont pas les mêmes que les nôtres…

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

Liver transplantation for unresectable hepatocellular carcinoma in normal livers

Hynek Mergental[1,39,†], Rene Adam[2,†], Bo-Goran Ericzon[3,†], Piotr Kalicinski[4,†], Ferninand Mühlbacher[5,†], Krister Höckerstedt[6,†], Jürgen L. Klempnauer[7,†], Styrbjörn Friman[8,†], Christoph E. Broelsch[9,†], Georges Mantion[10,†], Carlos Fernandez-Sellez[11,†], Bart van Hoek[12,†], Josef Fangmann[13,†], Jacques Pirenne[14,†], Paolo Muiesan[15,†], Alfred Königsrainer[16,†], Darius F. Mirza[1,†], Jan Lerut[17,†], Olivier Detry[18,†], Yves-Ptrice Le Treut[19,†], Vincenzo Mazzaferro[20,†], Florian Löhe[21,†], Marina Berenguer[22,†], Pierre-Alain Clavien[23,†], Xavier Rogiers[24,†], Jacques Belghiti[25,†], Laslo Kóbori[26,†], Patrizia Burra[27,†], Philippe Wolf[28,†], Wolfgang Schareck[29,†], Przemyslaw Pisarski[30,†], Aksel Foss[31,†], Franco Filipponi[32,†], Marek Krawczyk[33,†], Martin Wolff[34,†], Jan M. Langrehr[35,†], Keith Rolles[36,†], Neville Jamieson[37,†], Wim C.J. Hop[38,†], Robert J. Porte[39,*,†]

Journal of Hepatology **2012** vol. 57 | 297–305

Conclusions: This is the largest reported series of patients transplanted for NC-HCC. Selection of patients without macrovascular invasion or lymph node involvement, or patients ⩾12 months after previous liver resection, can result in 5-year survival rates of 59%. In contrast to HCC in cirrhosis, tumor size is not a predictor of post-transplant survival in NC-HCC.

HCC & chirurgie

- Destruction (éthanol et RFA)
- Résection: quel patient? quel type de résection?
- Transplantation hépatique après résection
- Transplantation hépatique
    - Milan
    - Extented criteria

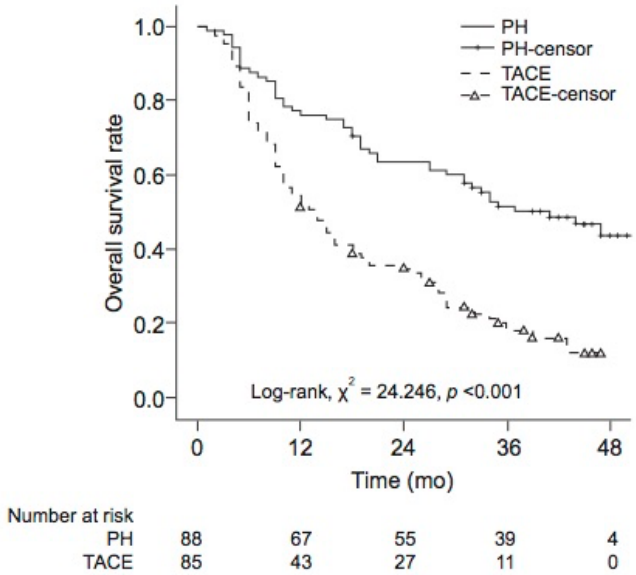
Research Article

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

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,*]

[1]*The Third Depart ment of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai 200438, China;* [2]*The Department of Dermatology, Changhai Hospital, Second Military Medical University, Shanghai 200438, China;* [3]*Faculty of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong Special Administrative Region*



Résection? Quel type de résection

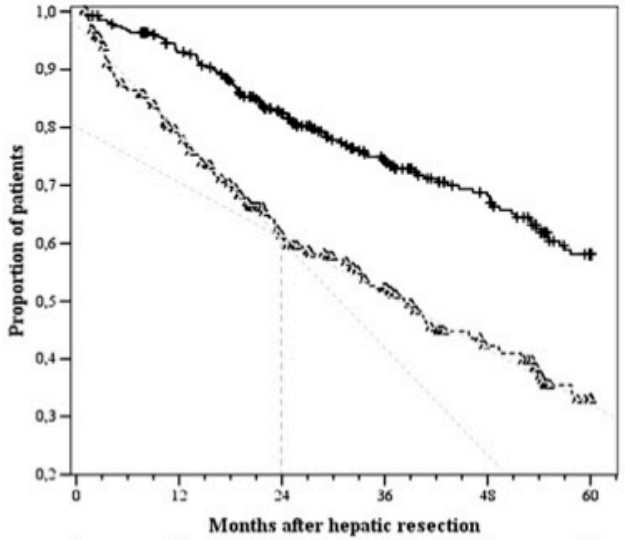
- Open / laparoscopique
- Anatomique / non-anatomique

Anatomic versus nonanatomic resection in cirrhotic patients with early hepatocellular carcinoma

Alessandro Cucchetti, MD,[a] Guo-Liang Qiao, MD,[b] Matteo Cescon, MD, PhD,[a] Jun Li, MD,[b] Yong Xia, MD,[b] Giorgio Ercolani, MD,[a] Feng Shen, MD,[b] *and* **Antonio Daniele Pinna, MD, PhD,[a]**
Bologna, Italy, and Shanghai, China

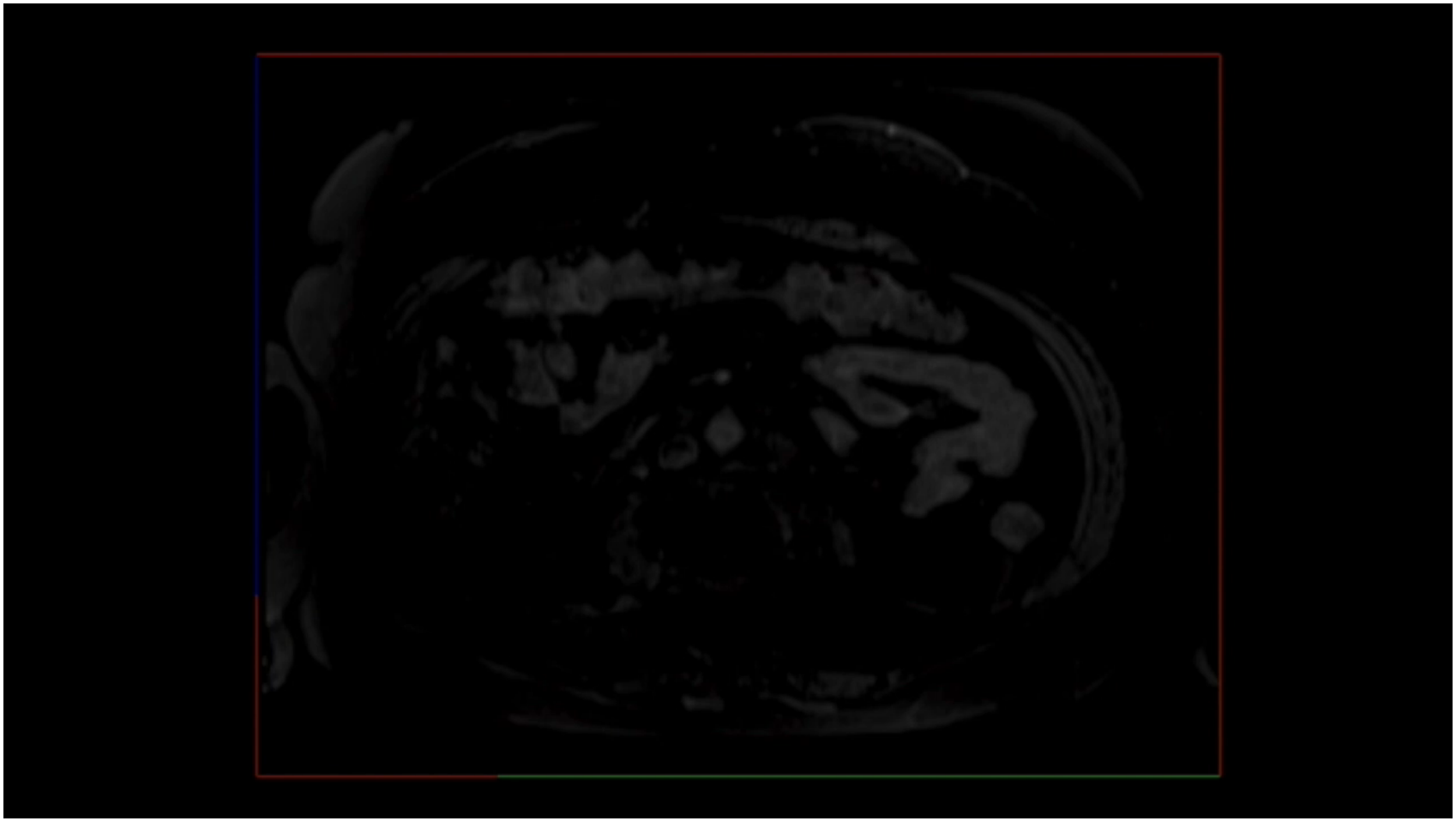
Background. *Whether anatomic resection (AR) for hepatocellular carcinoma (HCC) can really confer a survival advantage over non-AR (NAR), especially for cirrhotic patients, remains unclear.*
Methods. *Prospectively collected data of 543 cirrhotic patients in Child–Pugh class A submitted to AR (n = 228) versus NAR (n = 315) for early HCC in an Eastern (n = 269) and a Western (n = 274) surgical unit, were reviewed. To control for confounding variable distributions, a 1-to-1 propensity score match was applied to compare AR and NAR outcomes (n = 298).*
Results. *The 5-year recurrence-free and overall survivals of the 543 patients were 32.3% and 60.0%, respectively, without differences between the 2 centers (P = .635 and .479, respectively). AR conferred better overall and recurrence-free survival than NAR (P = .009 and .041, respectively), but NAR patients suffered from significantly worse hepatic dysfunction. After 1-to-1 match, AR (n = 149) and NAR (n = 149) patients had similar covariate distributions. In this matched sample, AR still conferred better recurrence-free survival over NAR (P = .044) but the beneficial effect of AR was limited to the reduction of early recurrence (<2 years) of poorly differentiated tumors and of tumors with microvascular invasion (P < .05), resulting in better overall survival (P = .018).*
Conclusion. *In cirrhotic patients, AR for early HCC can lead to a lower early recurrence rate in tumors with unfavorable tumor features, whereas NAR will not worsen the recurrence rate in well/moderately differentiated tumors or in the absence of microvascular invasion. (Surgery 2014;155:512-21.)*

From the Liver and Multiorgan Transplant Unit,[a] S. Orsola Hospital, Alma Mater Studiorum – University of Bologna, Bologna, Italy; and the Eastern Hepatobiliary Surgery Hospital,[b] Shanghai, China



At Risk	0m	12m	24m	36m	48m	60m
Patient Survival	298	264	208	155	122	83
Recurrence-free	298	218	151	110	73	45

Fig 1. Overall (upper plot) and recurrence-free (lower plot) survivals of the matched cohort of 298 cirrhotic patients. Recurrence-free survival changes its slope from year 2 after surgery onward, dividing early from late recurrences. Linear interpolation for early recurrence: Constant = 0.977; b1 = −0.016; $r^2 = 0.984$. For late recurrence: constant = 0.801; b1 = −0.008; $r^2 = 0.988$.



FEATURE

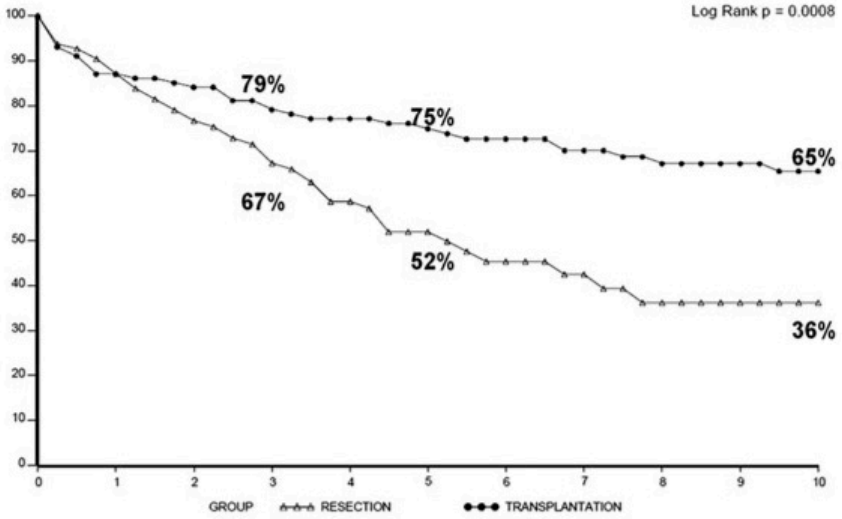
Resection or Transplantation for Early Hepatocellular Carcinoma in a Cirrhotic Liver

Does Size Define the Best Oncological Strategy?

Rene Adam, MD, PhD,†‡ Prashant Bhangui, MS,* Eric Vibert, MD,*†‡ Daniel Azoulay, MD, PhD,*†§ Gilles Pelletier, MD, PhD,* Jean-Charles Duclos-Vallée, MD, PhD,*†‡ Didier Samuel, MD, PhD,*†‡ Catherine Guettier, MD,* and Denis Castaing, MD*†‡*

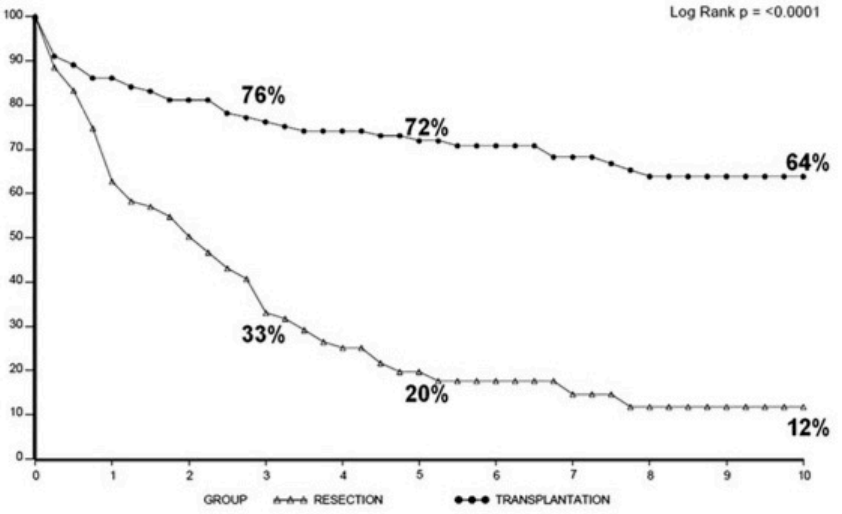
Annals of Surgery • Volume 256, Number 6, December 2012

(A)



	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
RESECTION	97	78	61	48	37	27	17	15	11	9	6
TRANSPLANTATION	101	88	85	79	74	66	63	50	44	39	34

(B)



	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
RESECTION	96	57	43	26	17	10	6	5	4	3	2
TRANSPLANTATION	101	87	82	76	71	63	61	49	43	38	34

FIGURE 1. A, OS for solitary HCC-cirr (≤5 cm), resection versus transplantation. B, RFS for solitary HCC-cirr (≤5 cm), resection versus transplantation.

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*†§*

Annals of Surgery • Volume 264, Number 1, July 2016

Summary Background Data: In compensated cirrhotics with early hepatocellular carcinoma (HCC-cirr), upfront liver resection (LR) and salvage liver transplantation (SLT) in case of recurrence may have outcomes comparable to primary LT (PLT).

Objective: An intention-to-treat (ITT) analysis comparing PLT and SLT strategies.

Methods: Of 130 HCC-cirr patients who underwent upfront LR (group LR), 90 (69%) recurred, 31 could undergo SLT (group SLT). During the same period, 366 patients were listed for LT (group LLT); 26 dropped-out (7.1%), 340 finally underwent PLT (group PLT). We compared survival between groups LR and LLT, LR and PLT, and PLT and SLT.

Results: Feasibility of SLT strategy was 34% (31/90). In an ITT analysis, group LLT had better 5-yr/10-yr overall survival (OS) compared with group LR (68%/58% vs. 58%/35%; $P = 0.008$). Similarly, 5-yr/10-yr OS and disease-free survival (DFS) were better in group PLT versus group LR (OS 73%/63% vs. 58%/35%, $P = 0.0007$; DFS 69%/61% vs. 27%/21%, $P < 0.0001$). Upfront resection and microvascular tumor invasion were poor prognostic factors for both OS and DFS, presence of satellite tumor nodules additionally predicted worse DFS. Group SLT had similar postoperative and long-term outcomes compared with group PLT (starting from time of LT) (OS 54%/54% vs. 73%/63%, $P = 0.35$; DFS 48%/48% vs. 69%/61%, $P = 0.18$, respectively).

Conclusions: In initially transplantable HCC-cirr patients, ITT survival was better in group PLT compared with group LR. SLT was feasible in only a third of patients who recurred after LR. Post SLT, short and long-term outcomes were comparable with PLT. Better patient selection for the "resection first" approach and early detection of recurrence may improve outcomes of the SLT strategy.

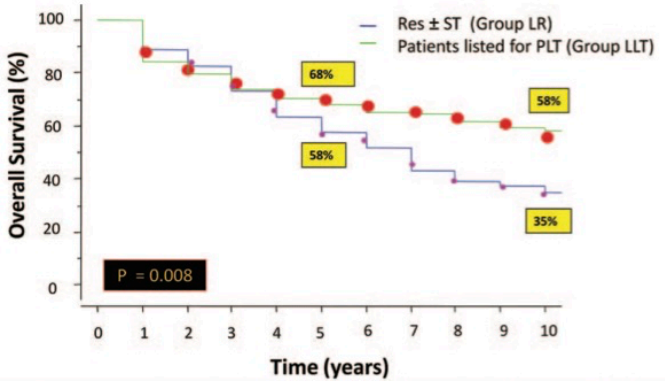


FIGURE 2. Overall survival resection ± salvage LT [group LR] (n = 130) versus patients listed for PLT (including drop-outs) [group LLT] (n = 366). Res, resection.

Liver Resection as a Bridge to Transplantation for Hepatocellular Carcinoma on Cirrhosis

A Reasonable Strategy?

René Adam, MD, PhD, Daniel Azoulay, MD, PhD, Denis Castaing, MD, Rony Eshkenazy, MD, Gérard Pascal, MD, Kentaro Hashizume, MD, Didier Samuel, MD, PhD, and Henri Bismuth, MD, FACS Hon.

Objective: To assess the viability of a strategy of primary resection with secondary liver transplantation (LT) for hepatocellular carcinoma (HCC) on cirrhosis

Summary Background Data: LT is the optimal treatment of HCC with cirrhosis. Owing to organ shortage, liver resection is considered as a reasonable first-line treatment of patients with small HCC and good liver function, with secondary LT as a perspective in case of recurrence. The viability of such strategy, positively explored in theoretical models, is not documented in clinical practice.

Methods: Among 358 consecutive patients with HCC on cirrhosis treated by liver resection (n = 163; 98 of whom were transplantable) or transplantation (n = 195), the feasibility and outcome of secondary transplantation was evaluated in a 2-step fashion. First, secondary LT for tumor recurrence after resection (n = 17) was compared with primary LT (n = 195), to assess the risk and the outcome of secondary LT in patients who effectively succeeded to be treated by this approach. Second, primary resection in transplantable patients (n = 98) was compared with that of primary LT (n = 195) on an intention-to-treat basis, to assess the outcome of each treatment strategy and to determine the proportion of resected patients likely to be switched for secondary LT. Transplantability of resected patients was retrospectively determined according to selection criteria of LT for HCC.

Results: Operative mortality (≤2 months) of secondary LT was significantly higher than that of primary LT (28.6% versus 2.1%; $P = 0.0008$) as was intraoperative bleeding (mean transfused blood units, 20.7 versus 10.5; $P = 0.0001$). Tumor recurrence occurred more frequently after secondary than after primary LT (54% versus 18%; $P = 0.001$). Posttransplant 5-year overall survival was 41% versus 61% ($P = 0.03$), and disease-free survival was 29% versus 58% ($P = 0.003$) for secondary and primary LT, respectively.

Of 98 patients treated by resection while initially eligible for transplantation, only 20 (20%) were secondarily transplanted, 17 of whom (17%) for tumor recurrence and 3 (3%) for hepatic decompensation. Transplantability of tumoral recurrence was 25% (17 of 69 recurrences). Compared with primarily transplanted patients, transplantable resected patients had a decreased 5-year overall survival (50% versus 61%; $P = 0.05$) and disease-free survival (18% versus 58%; $P < 0.0001$), despite the use of secondary LT.

On a multivariate analysis including 271 patients eligible for transplantation and treated by either liver resection or primary LT, liver resection alone ($P < 0.0001$; risk ratio [RR] = 3.27) or liver resection with secondary LT ($P < 0.05$; RR= 1.87) emerged as negative independent factors of disease-free survival as compared with primary LT. A number of nodules > 3 ($P = 0.002$; RR= 2.02) and a maximum tumor size exceeding 30 mm ($P < 0.0001$; RR=1.93) were also predictive of lower disease-free survival.

Conclusions: LT after liver resection is associated with a higher operative mortality, an increased risk of recurrence, and a poorer outcome than primary LT. In addition, liver resection as a bridge to LT impairs the patient transplantability and the chance of long-term survival of cirrhotic patients with HCC. Primary LT should therefore remain the ideal choice of treatment of a cirrhotic patient with HCC, even when the tumor is resectable.

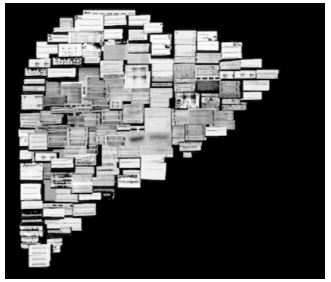
(*Ann Surg* 2003;238: 508–519)

Liver transplantation for HCC: do size & number really matter??

Pr Olivier Detry

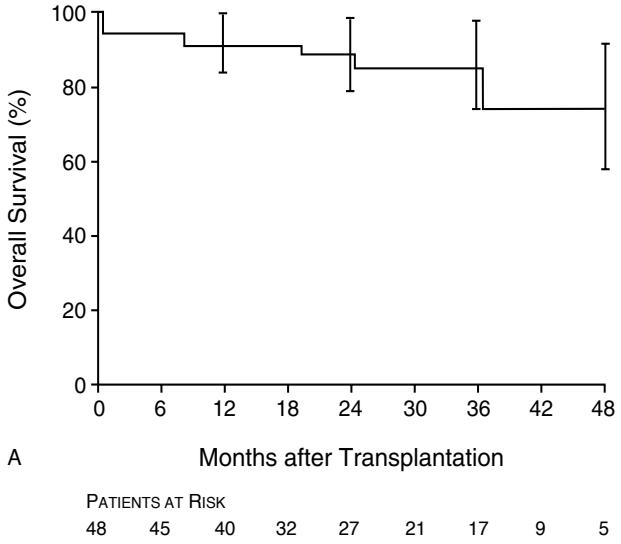
Dpt of Abdominal Surgery & Transplantation
CHU Liege, University of Liege

20th BASL Wintermeeting &
11th Interuniversitary Liver Course
Friday 4th and Saturday 5th of December 2015



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.



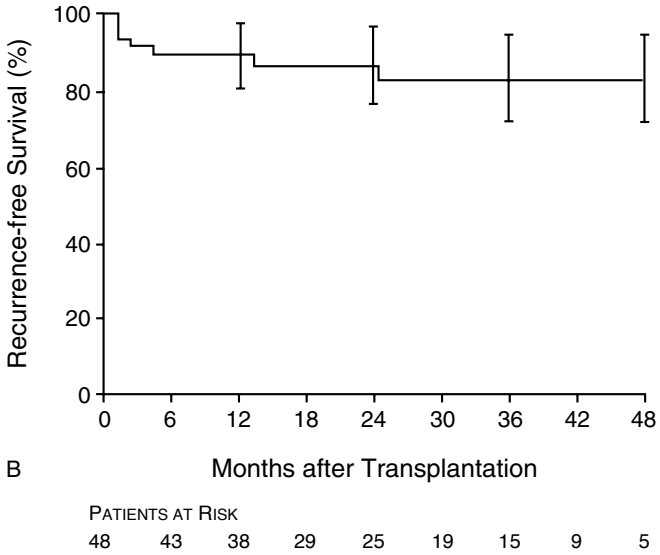


Figure 1. Overall Survival (Panel A) and Recurrence-free Survival (Panel B) after Liver Transplantation in 48 Patients with Small Hepatocellular Carcinomas and Cirrhosis.

N Engl J Med 1996; 334: 693-699

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

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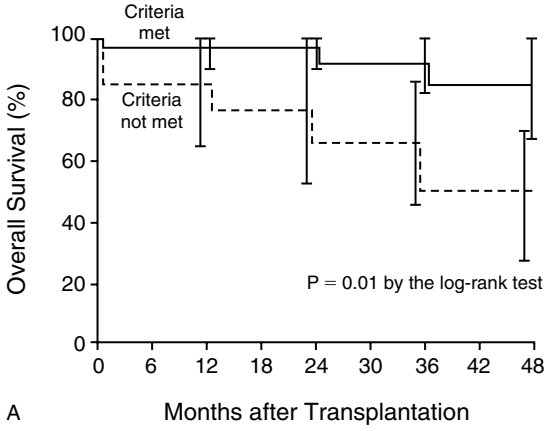
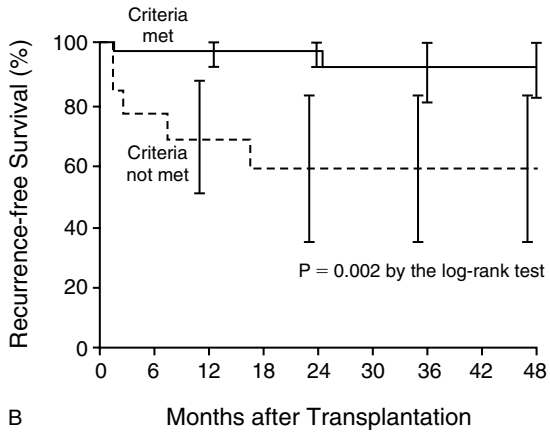


PATIENTS AT RISK

Criteria met	35	34	31	24	21	16	13	6	3
Criteria not met	13	13	11	8	6	6	4	4	3



PATIENTS AT RISK

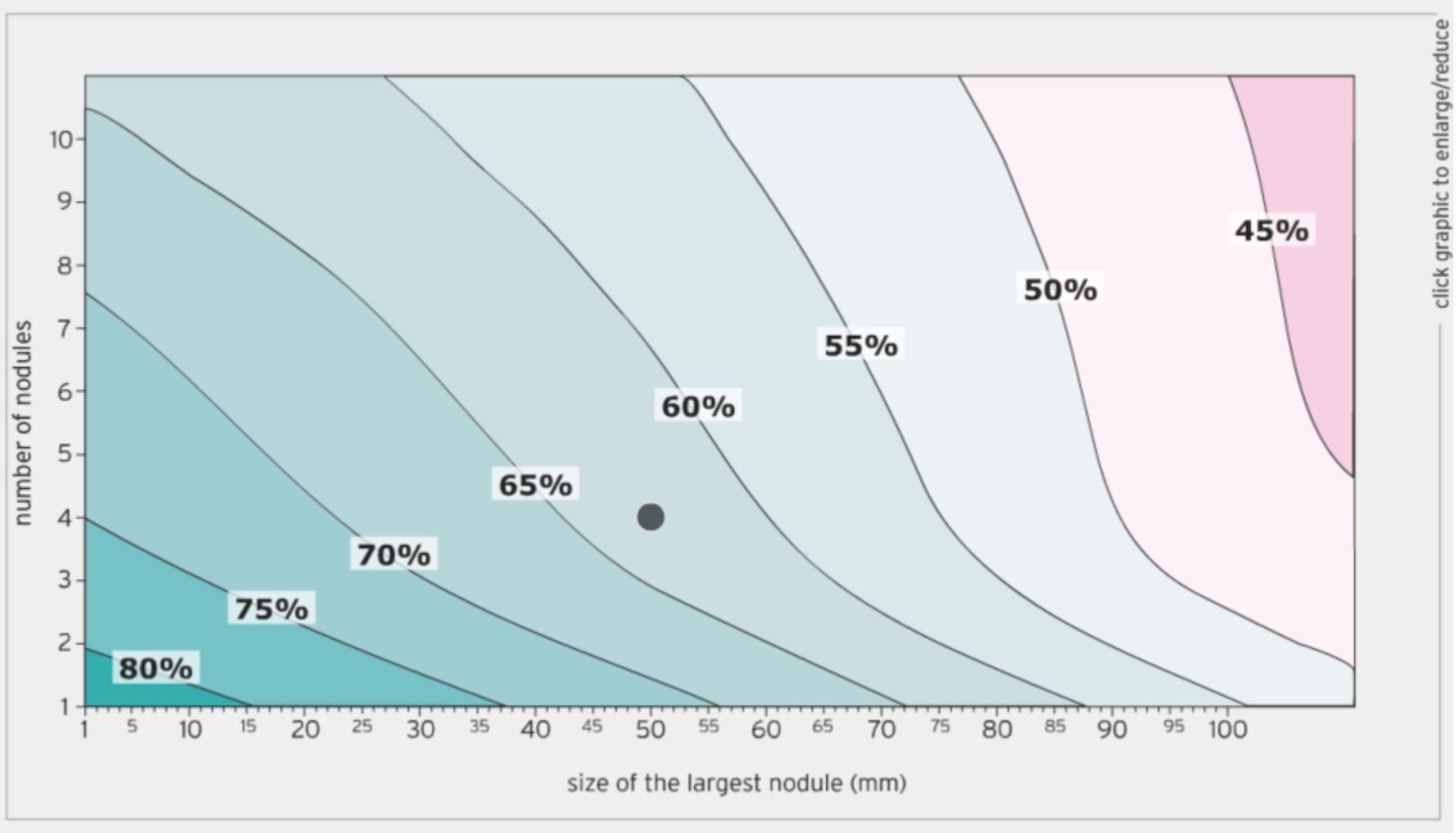
Criteria met	35	34	31	24	21	15	12	6	3
Criteria not met	13	10	9	5	5	5	4	3	3

Figure 3. Correlation of Post-Transplantation Pathological Confirmation of Early-Stage Hepatocellular Carcinoma with Overall Survival (Panel A) and Recurrence-free Survival (Panel B) among 48 Patients with Cirrhosis.

N Engl J Med 1996; 334: 693-699

Milan out HCC criteria

- UCSF: 1 nodule ≤ 6.5 cm, ≤ 3 nodules (largest 4.5 cm & total ≤ ⦸ 8 cm
- up-to-7: ≤ 7 nodules, largest ≤ 7 cm
- Tokyo: 5-5 rule: ≤ 5 nodules, largest ≤ 5 cm
- Hangzou: total ≤ ⦸ 8 cm or > ⦸ 8 cm with AFP < 400ng/ml
- Asan (South Korea): ≤ 5 cm, ≤ 6 nodules
- Shangai: 1 nodule ≤ 9 cm, ≤ 3nodules (largest 5 cm & total ≤ ⦸ 9 cm


number of nodules
size of the largest nodule (mm)
80%
75%
70%
65%
60%
55%
50%
45%
click graphic to enlarge/reduce

AFP model

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

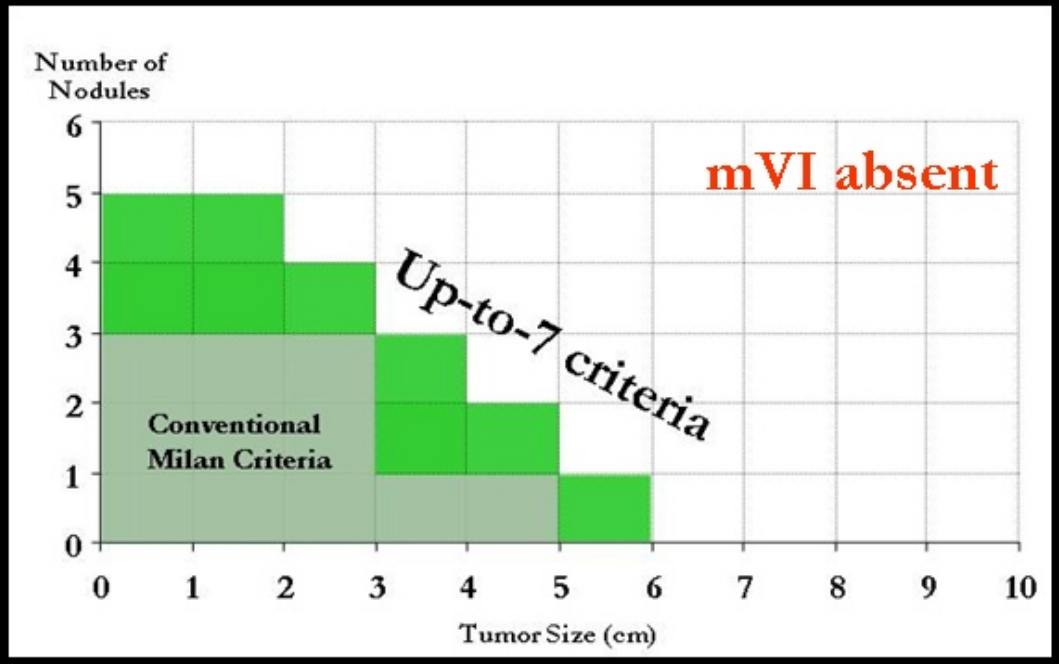
Variables	β coefficient	Hazard ratio	Points
Largest diameter, *cm*			
≤3	0	1	0
3–6	0.272	1.31	1
>6	1.347	3.84	4
Number of nodules			
1–3	0	1	0
≥4	0.696	2.01	2
AFP level, *ng/mL*			
≤100	0	1	0
100–1000	0.668	1.95	2
>1000	0.945	2.57	3

NOTE. The score is calculated by adding the individual points for each obtained variable. A cut-off value of 2 separates between patients at high and low risk of recurrence. In this simplified version, a cut-off value of 2 selected exactly the same patients as the original Cox score cut-off value of 0.7.

Low risk: ≤ 2
High risk: > 2

GASTROENTEROLOGY 2012;143:986–994

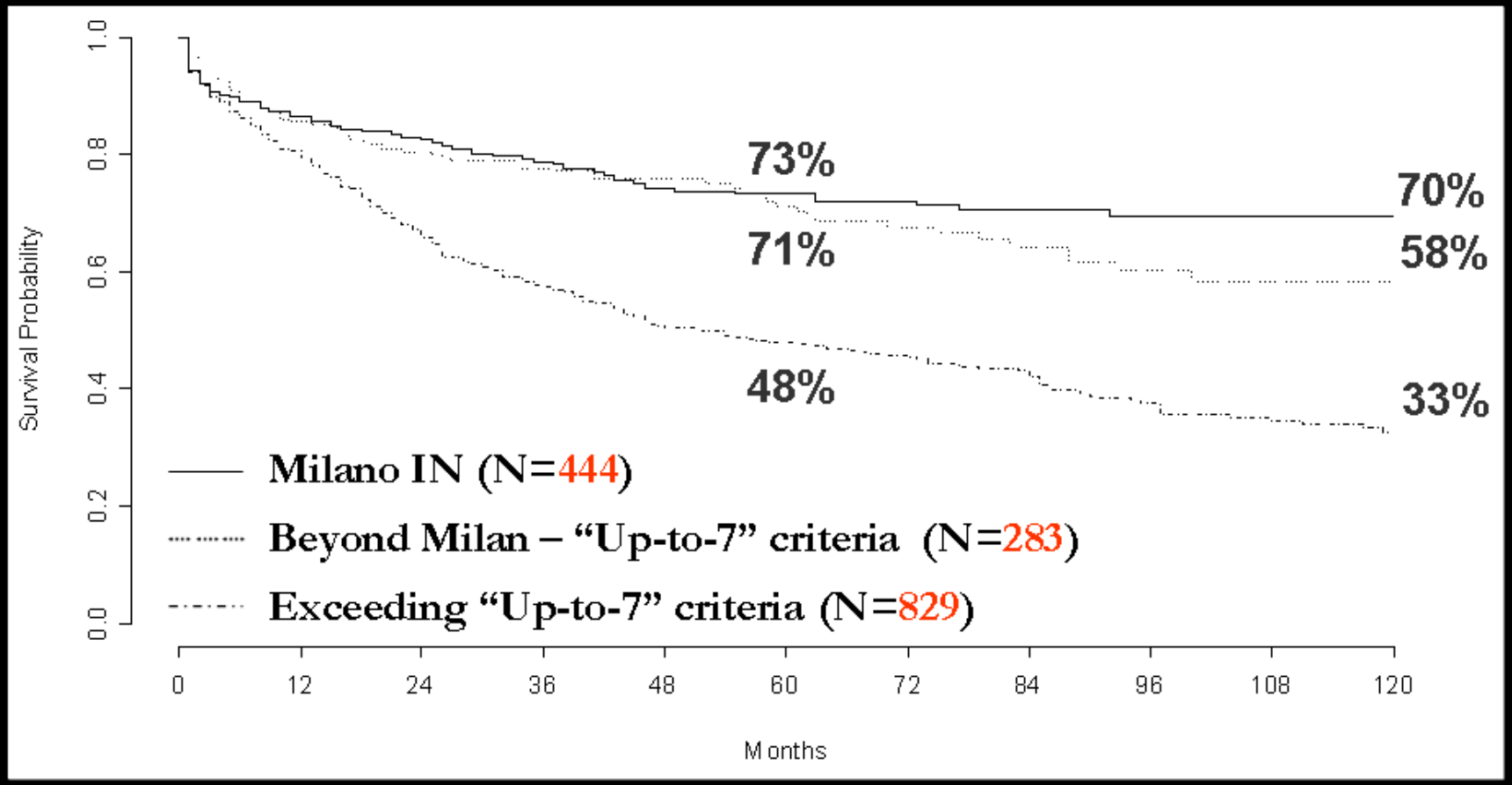
The "up-to-7 Criteria"



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]

Proving the existence of a good outcome group ("up-to-7") outside the Conventional Milan Criteria

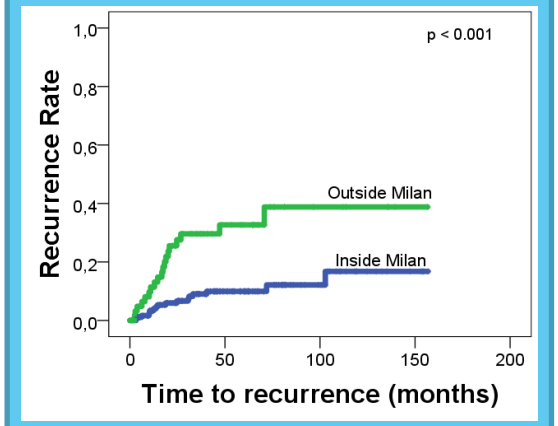


Median follow-up: 53 months

[Mazzaferro et al, Lancet Oncology 2009

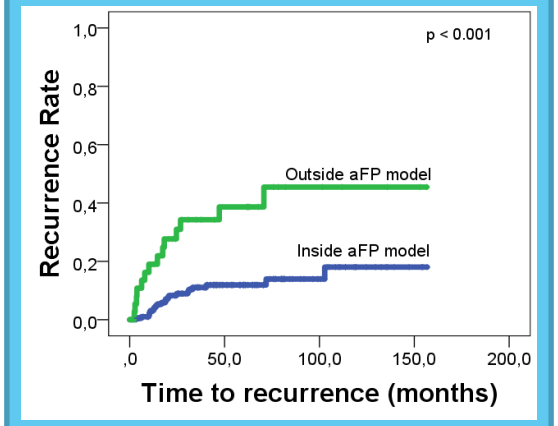
Be-LIAC cohort

Milan Criteria



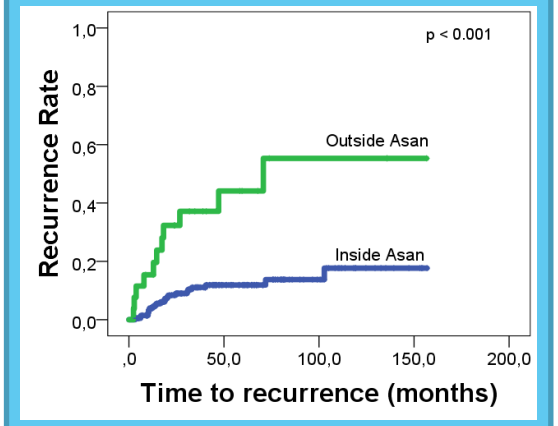
	5 yr Recurrence rate
IN	10 % +- 2.5
OUT	33 % +- 7

aFP model



	5 yr Recurrence rate
IN	12% +- 2.5
OUT	39 % +- 9

Asan Criteria



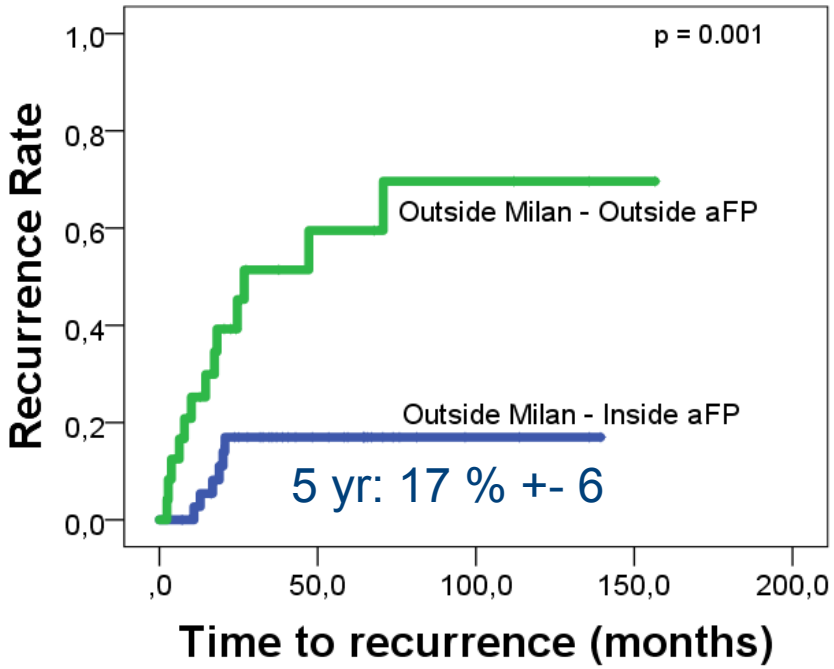
	5 yr Recurrence rate
IN	12% +- 2.5
OUT	44 % +- 11

KU LEUVEN

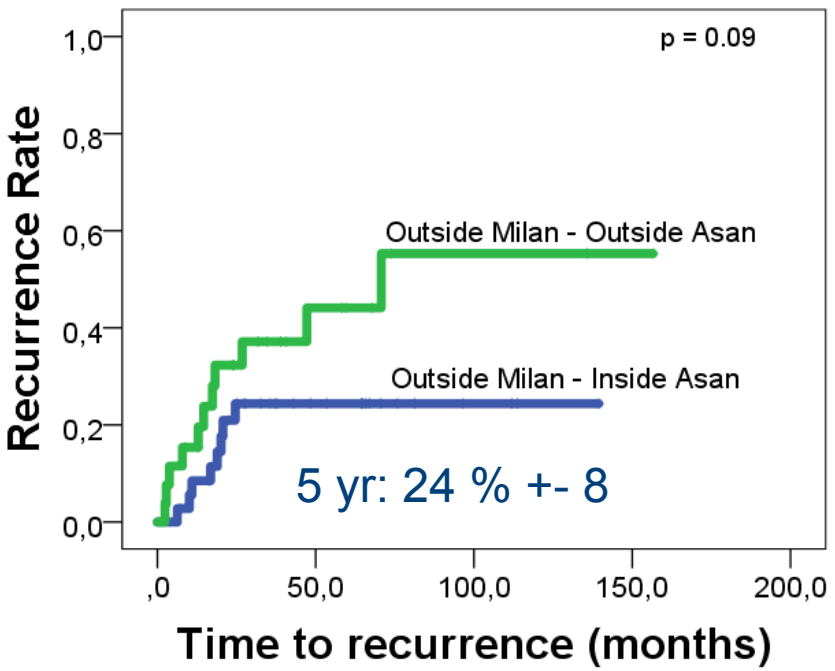
UZ LEUVEN

Be-LIAC cohort

		aFP model	
		IN	OUT
Milan	IN	167 (69 %)	13 (5%)
	OUT	38 (16%)	24 (10%)



		Asan criteria	
		IN	OUT
Milan	IN	177 (74 %)	0 (0 %)
	OUT	36 (15 %)	26 (11 %)



KU LEUVEN

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World J Gastroenterol 2015 March 14; 21(10): 3049-3054
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

Prognostic value of ^{18}F-FDG PET/CT in liver transplantation for hepatocarcinoma

Olivier Detry, Laurence Govaerts, Arnaud Deroover, Morgan Vandermeulen, Nicolas Meurisse, Serge Malenga, Noella Bletard, Charles Mbendi, Anne Lamproye, Pierre Honoré, Paul Meunier, Jean Delwaide, Roland Hustinx

Patients

- 52 LT for HCC during the study period
- 27 fulfilled the inclusion criteria
  - 13 Milan in (SE)
  - 14 Milan out (rescue allocation & DCD)

- Mean follow-up: 26 months
- Mean interval between PET & LT: 4 months

Original article

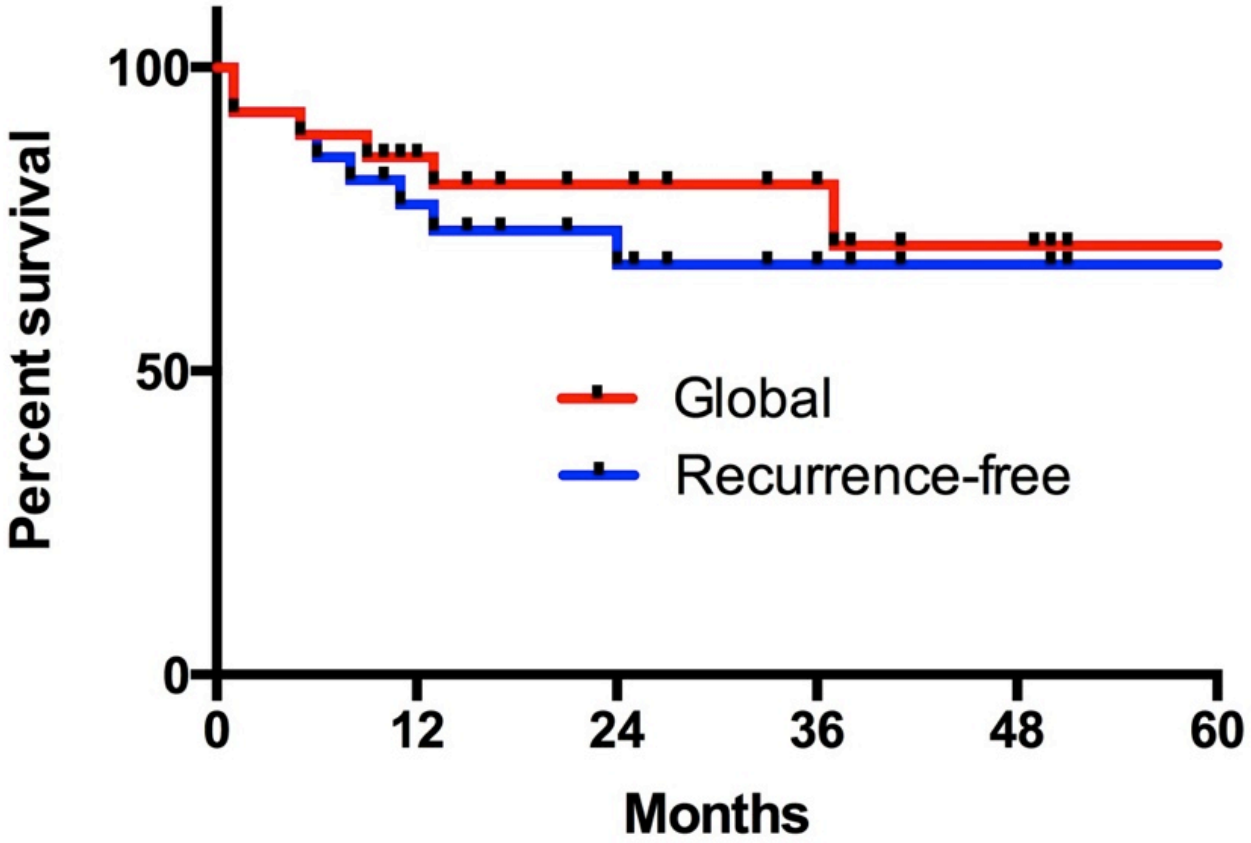
Donor age as a risk factor in donation after circulatory death liver transplantation in a controlled withdrawal protocol programme

O. Detry[1], A. Deroover[1], N. Meurisse[1], M. F. Hans[1], J. Delwaide[2], S. Lauwick[3], A. Kaba[3], J. Joris[3], M. Meurisse[1] and P. Honoré[1]

Departments of [1]Abdominal Surgery and Transplantation, [2]Hepato-Gastroenterology and [3]Anaesthesiology and Intensive Care, Centre Hospitalier Universitaire de Liège, University of Liège, Liège, Belgium

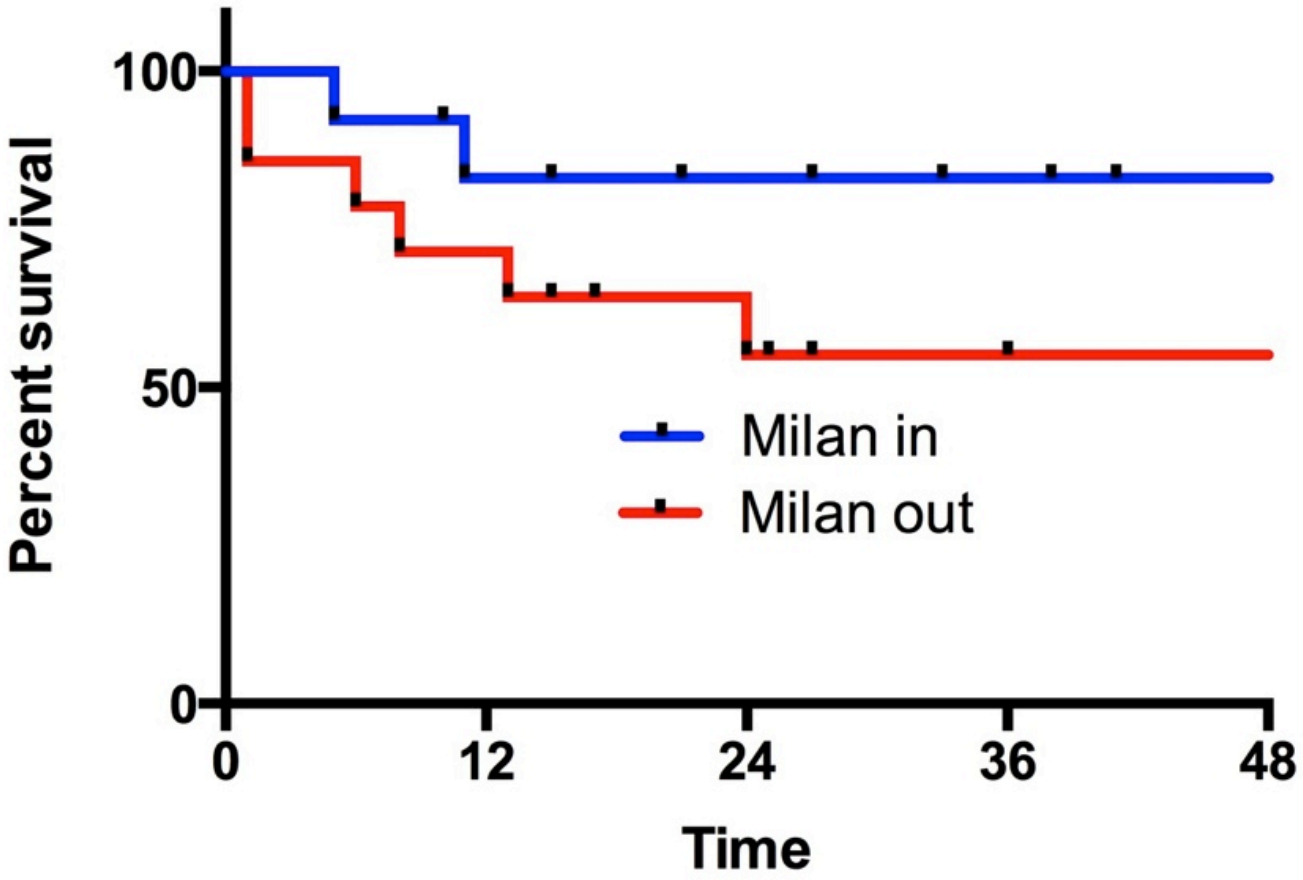
Correspondence to: Professor O. Detry, Department of Abdominal Surgery and Transplantation, CHU Liège, Sart Tilman B35, B4000 Liège, Belgium (e-mail: olivier.detry@transplantation.be)

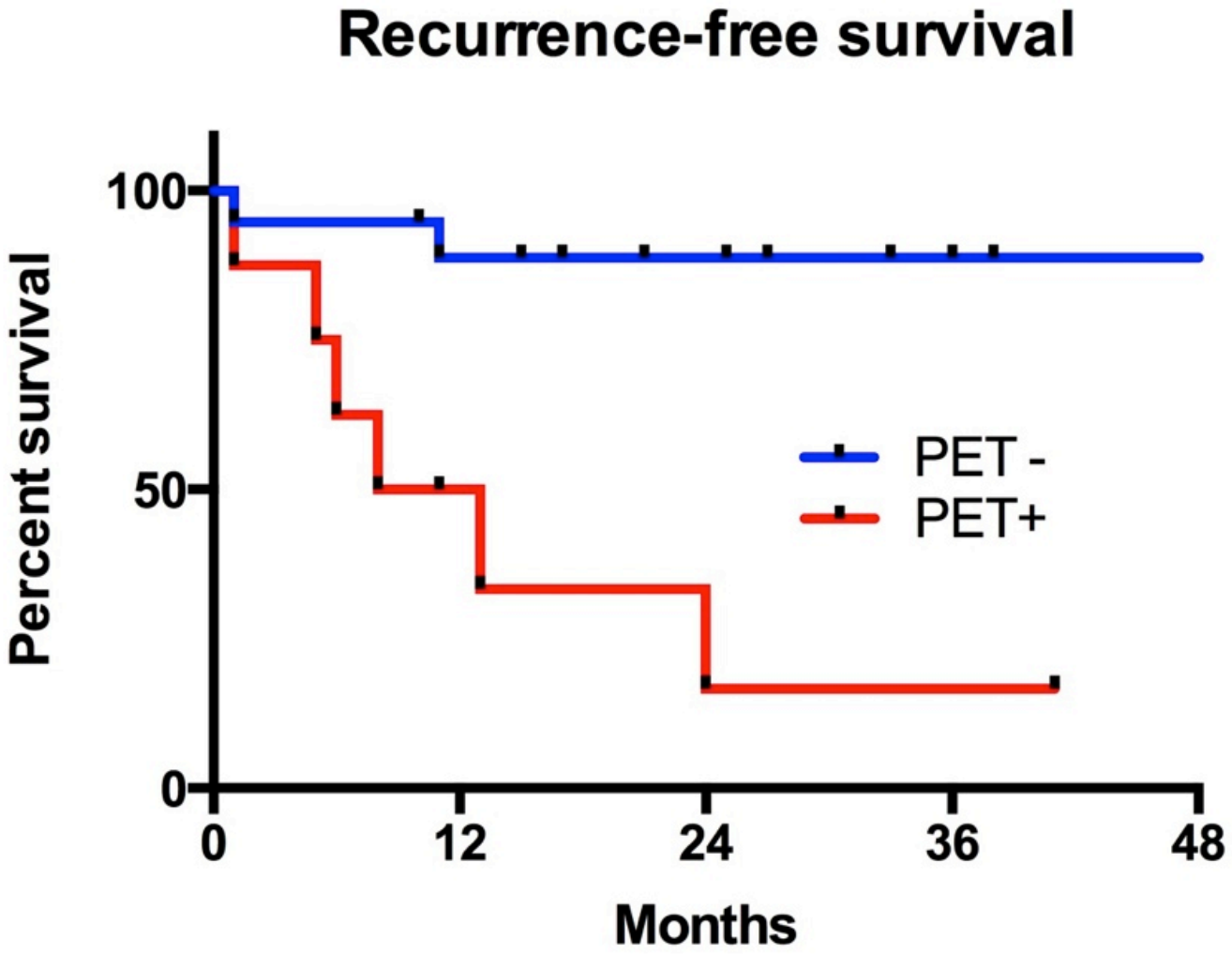
Patient survival

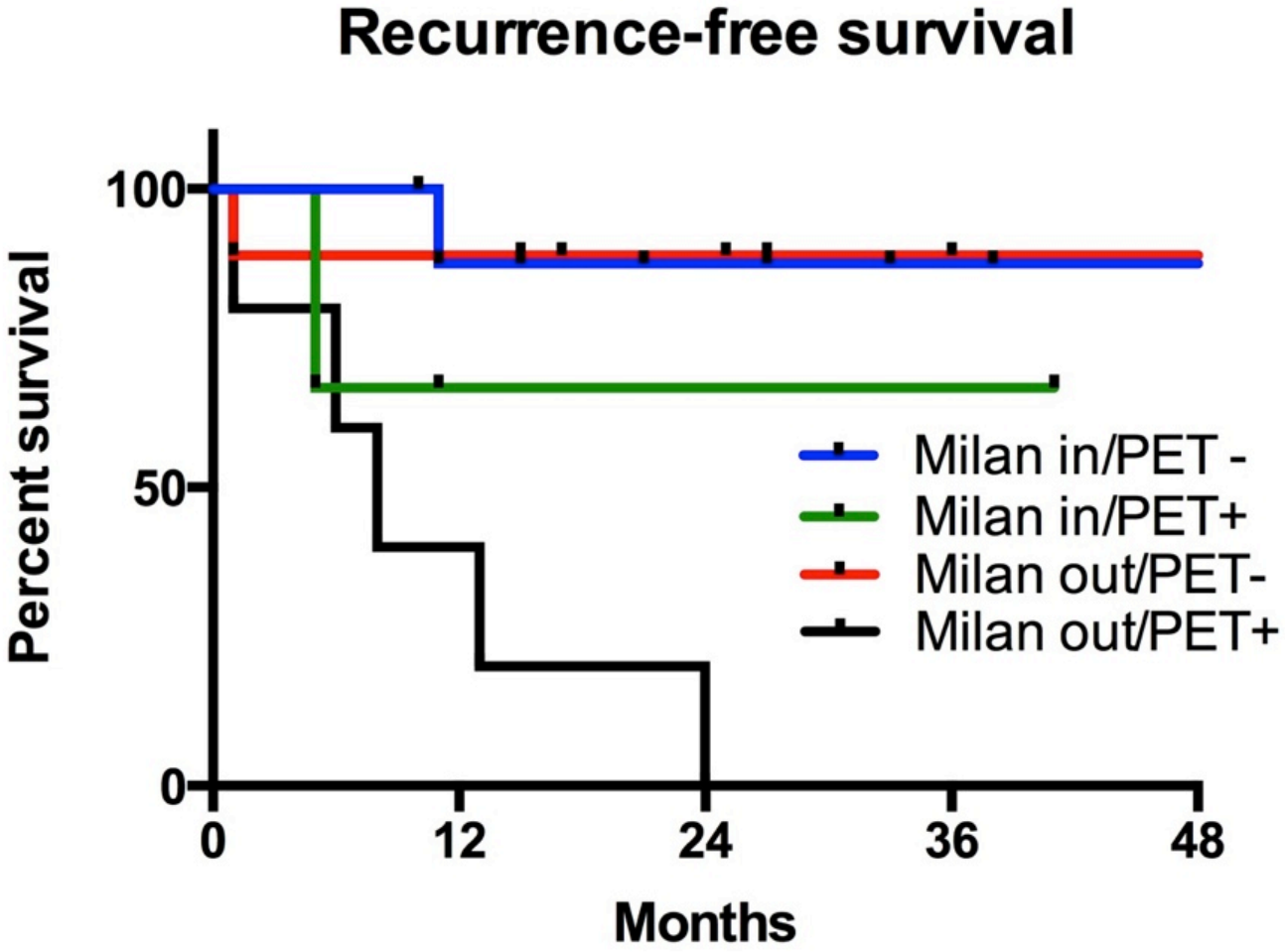


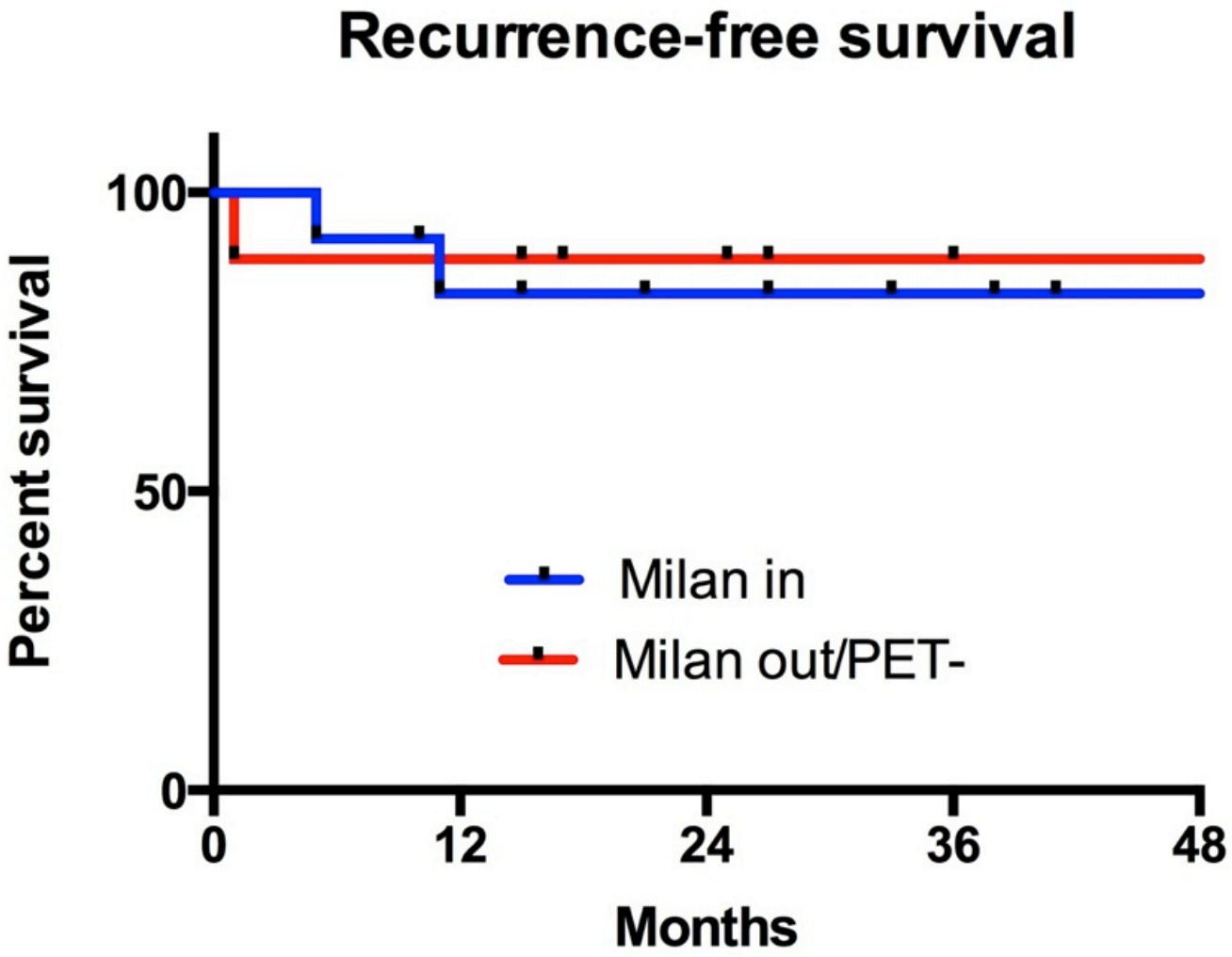
- One year survival: 85%
- Five-year survival: 70.6%

Recurrence-free survival




Recurrence-free survival
Percent survival
100
50
0
0
12
24
36
48
Months
PET -
PET+

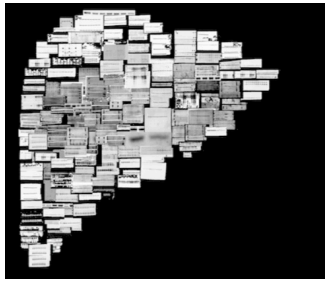

Recurrence-free survival
Percent survival
100
50
0
0
12
24
36
48
Months
Milan in/PET -
Milan in/PET+
Milan out/PET-
Milan out/PET+


Recurrence-free survival
Percent survival
100
50
0
0
12
24
36
48
Months
Milan in
Milan out/PET-

Liver transplantation for HCC: do size & number really matter??

YES!

20th BASL Wintermeeting &
11th Interuniversitary Liver Course
Friday 4th and Saturday 5th of December 2015



HCC

- Number of nodules & size is not the magic bullet
- MILAN criteria are too restrictive and should be enlarged
- **Tumor biology & differentiation**
  - AFP
  - Response to adjuvant therapy
  - PET scan ?
- Post transplant chemotherapy ?

Project

- Prospective multicentric national evaluation of the prognostic value of 18FDG PET/CT in liver transplantation for HCC

  – Primary investigator: ULg
  – 6 Belgian Centers: ULg, ULB, UCL, KUL, UZA, UZG

Stichting tegen Kanker
Fondation contre le Cancer

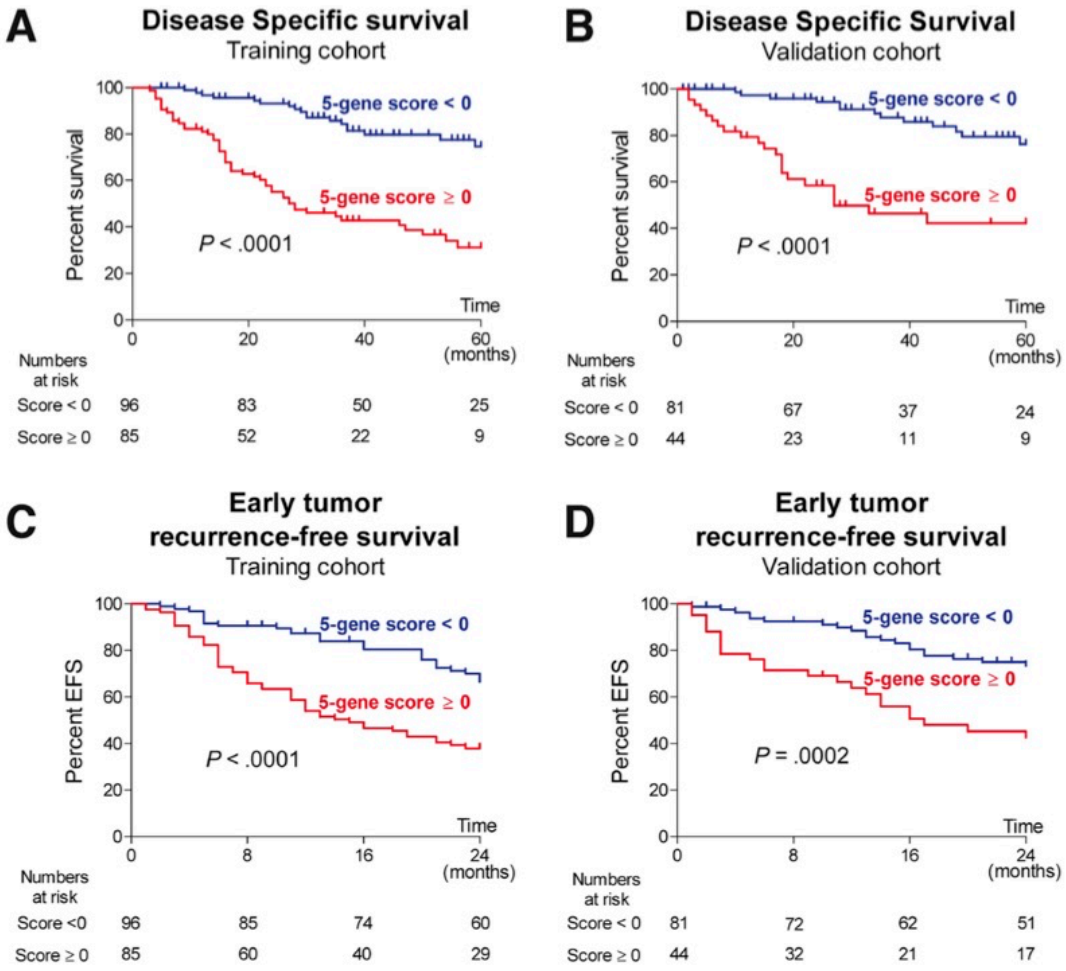
GASTROENTEROLOGY 2013;145:176–187

CLINICAL—LIVER

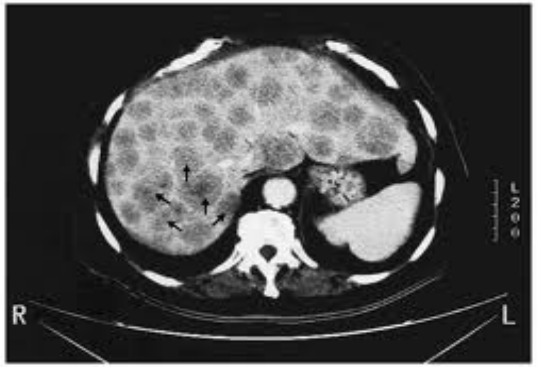
A Hepatocellular Carcinoma 5-Gene Score Associated With Survival of Patients After Liver Resection

JEAN–CHARLES NAULT,[1,2,*] AURÉLIEN DE REYNIÈS,[3,*] AUGUSTO VILLANUEVA,[4,5] JULIEN CALDERARO,[1,6,8] SANDRA REBOUISSOU,[1,2] GABRIELLE COUCHY,[1,2] THOMAS DECAENS,[7,8,9] DOMINIQUE FRANCO,[10] SANDRINE IMBEAUD,[1,2] FRANCIS ROUSSEAU,[11] DANIEL AZOULAY,[8,12] JEAN SARIC,[13] JEAN–FRÉDÉRIC BLANC,[14] CHARLES BALABAUD,[15] PAULETTE BIOULAC–SAGE,[15,16] ALEXIS LAURENT,[8,9,12] PIERRE LAURENT–PUIG,[17] JOSEP M. LLOVET,[4,5,18,19] and JESSICA ZUCMAN–ROSSI[1,2,20]

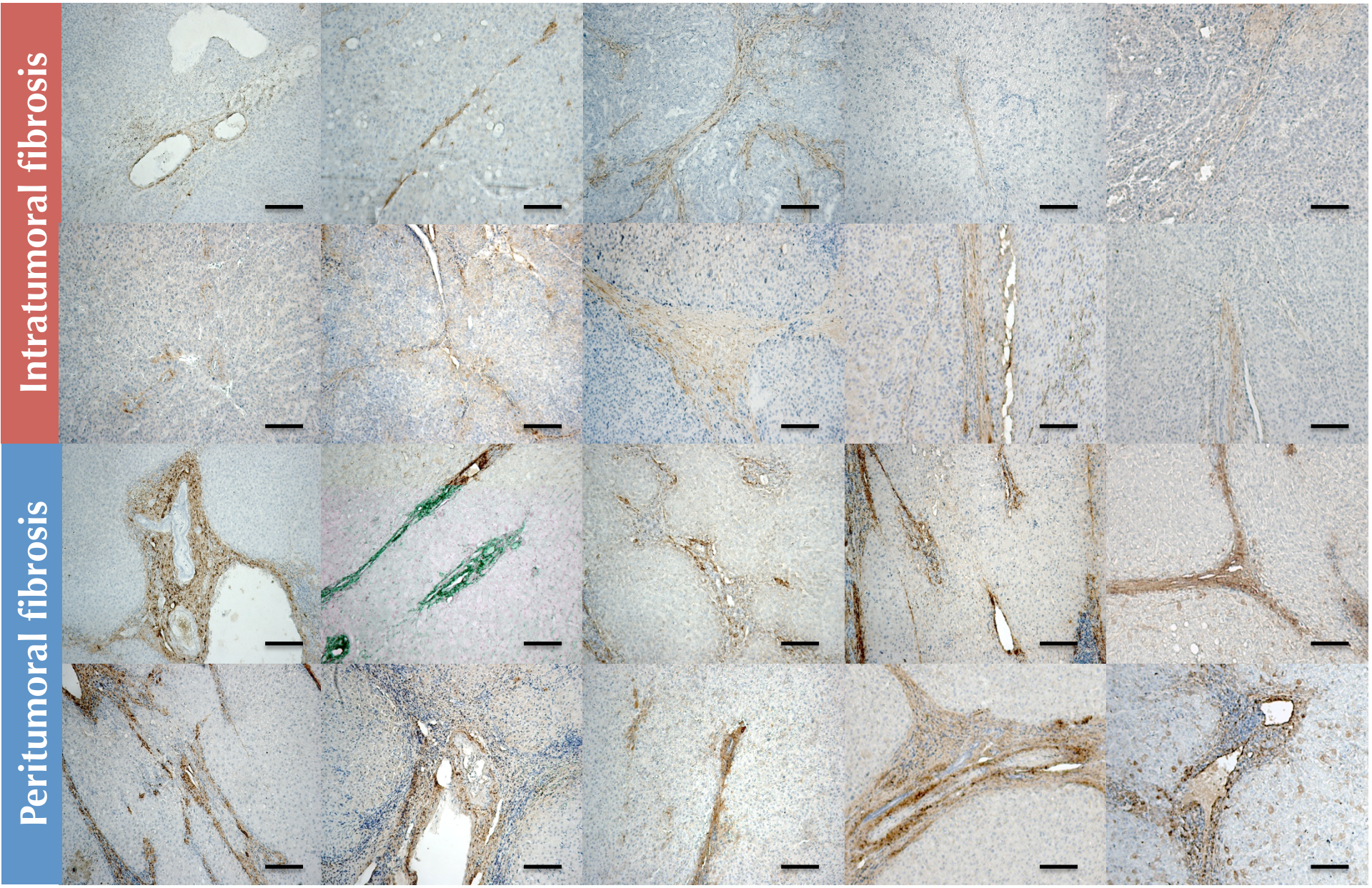
[1]Inserm, UMR-674, Génomique Fonctionnelle des Tumeurs Solides, IUH, Paris, France; [2]Université Paris Descartes, Labex Immuno-Oncology, Sorbonne Paris Cité, Faculté de Médecine, Paris, France; [3]Ligue Nationale Contre le Cancer, Paris, France; [4]HCC Translational Research Laboratory, Barcelona-Clinic Liver Cancer Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Liver Unit, Hospital Clinic, Barcelona, Spain; [5]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Instituto Carlos III, Barcelona, Spain; [6]AP-HP, Department of Pathology, Henri Mondor University Hospital, Créteil, France; [7]AP-HP, Department of Hepatology, Henri Mondor University Hospital, Créteil, France; [8]Université Paris-Est Créteil Val-de-Marne, Créteil, France; [9]Inserm U955, Pathophysiology and Therapy of Chronic Viral Hepatitis, Créteil, France; [10]AP-HP, Surgery Department, Hôpital Antoine Béclère, Clamart, France; [11]IntegraGen, Evry, France; [12]Digestive, Hepatobiliary and Liver Transplantation, Assistance Publique-Hôpitaux de Paris, Créteil, France; [13]Department of Surgery, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France; [14]Gastroenterology Unit, CHU Bordeaux, Saint André Hôpital, Bordeaux 33075, France; [15]Inserm U1053, Universite Bordeaux Segalen, Bordeaux, France; [16]Department of Pathology, CHU de Bordeaux, Pellegrin Hospital, Bordeaux, France; [17]Paris Descartes University, Paris Sorbonne Cité, INSERM UMR-S775, Paris, France; [18]Mount Sinai Liver Cancer Program, Divisions of Liver Diseases, Mount Sinai School of Medicine, New York, New York; [19]Institució Catalana de Recerca i Estudis Avançats, Barcelona, Catalonia, Spain; and [20]Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Paris, France


A
Disease Specific survival
Training cohort
Percent survival
5-gene score < 0
5-gene score ≥ 0
P < .0001
Time
(months)
Numbers at risk
Score < 0 96 83 50 25
Score ≥ 0 85 52 22 9
B
Disease Specific Survival
Validation cohort
Percent survival
5-gene score < 0
5-gene score ≥ 0
P < .0001
Time
(months)
Numbers at risk
Score < 0 81 67 37 24
Score ≥ 0 44 23 11 9
C
Early tumor recurrence-free survival
Training cohort
Percent EFS
5-gene score < 0
5-gene score ≥ 0
P < .0001
Time
(months)
Numbers at risk
Score <0 96 85 74 60
Score ≥ 0 85 60 40 29
D
Early tumor recurrence-free survival
Validation cohort
Percent EFS
5-gene score < 0
5-gene score ≥ 0
P = .0002
Time
(months)
Numbers at risk
Score < 0 81 72 62 51
Score ≥ 0 44 32 21 17

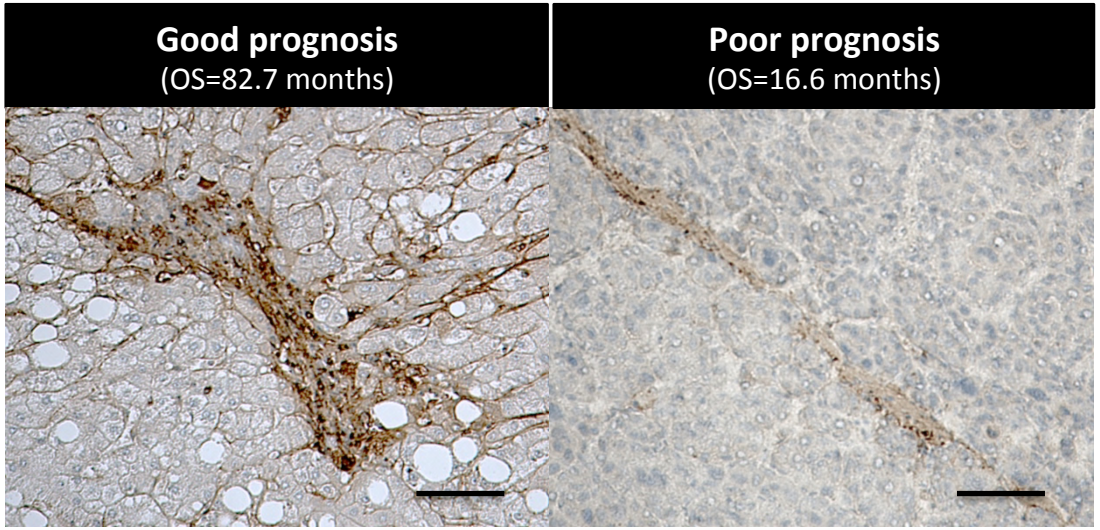
Role of Stromal Protein PRELP in The Hepatocellular Carcinoma

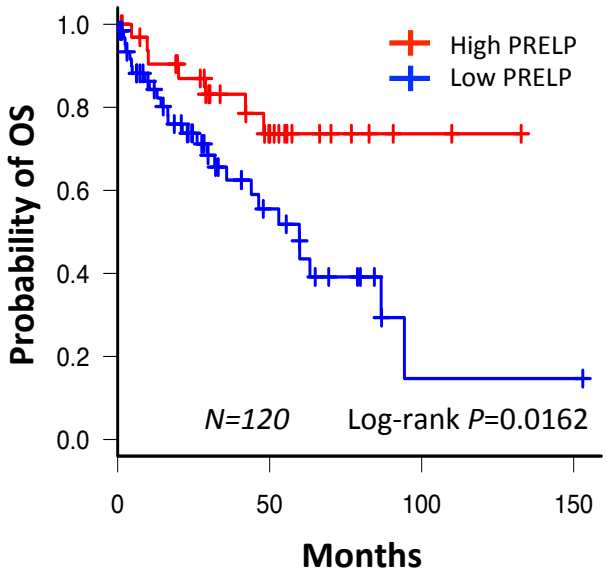


Intratumoral vs Peritumoral PRELP Expression in HCC



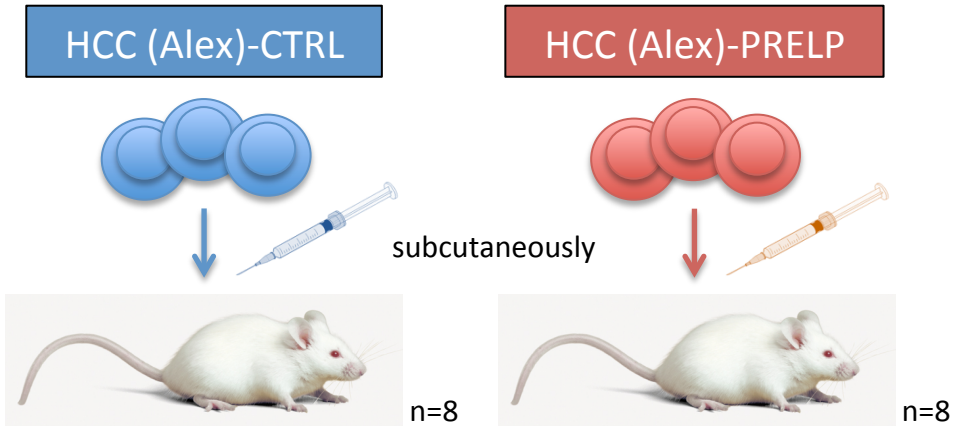
PRELP Overexpression in HCC Correlates With Good Outcome

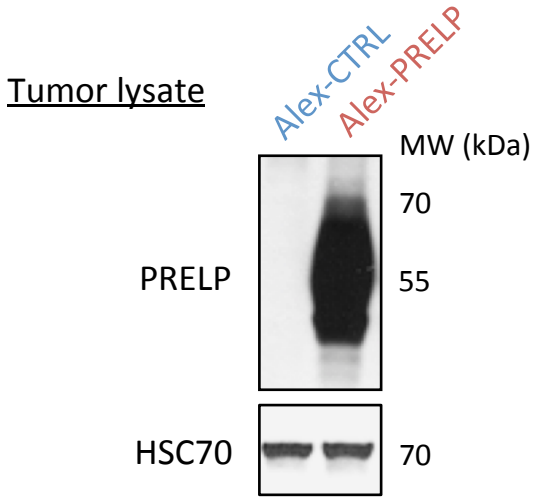


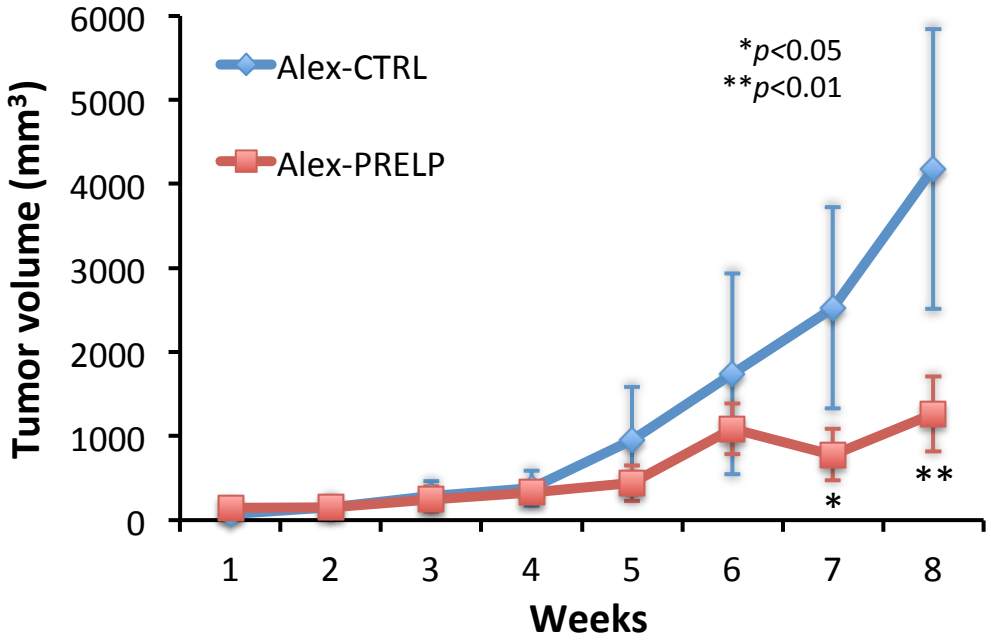


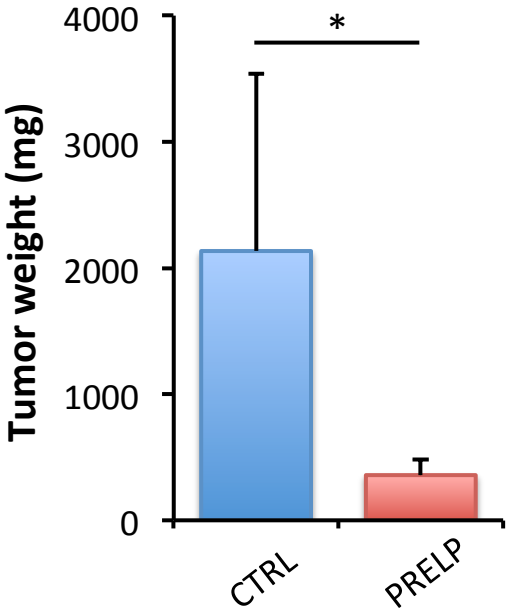
Anti-Tumor Effect of PRELP Overexpression in HCC

Experimental setup:









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BGDO Belgian Group of Digestive Oncology

Université de Liège

群馬大学 GUNMA UNIVERSITY

HCC

- Foie sain: résection ou transplantation
- Foie cirrhotique:

  Transplantation

  Résection

  Résection puis transplantation