



UNIVERSITÉ
DE GENÈVE

FACULTÉ DE MÉDECINE
Département de chirurgie



Hôpitaux
Universitaires
Genève

Current trends in liver transplantation

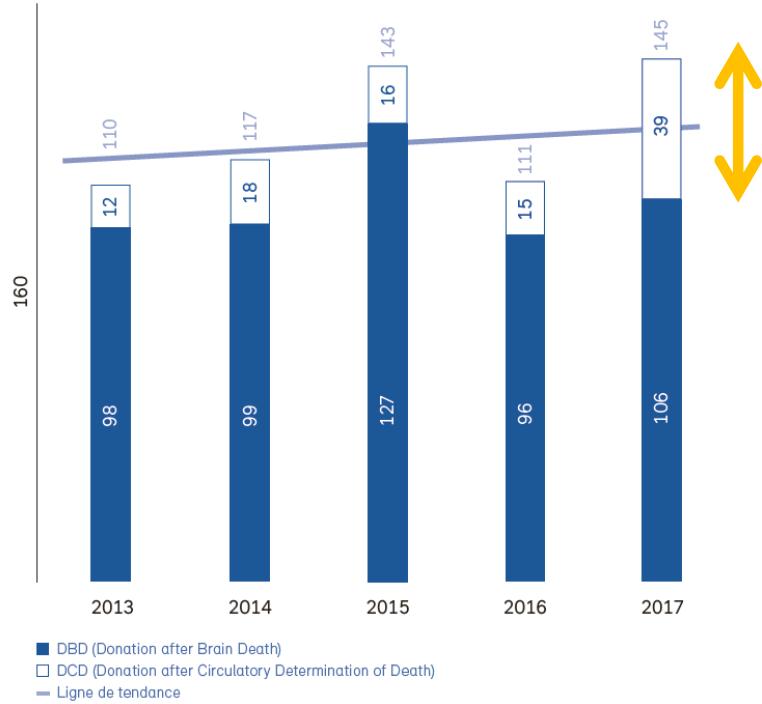
Christian Toso MD, PhD

Head of abdominal surgery
Professor
Geneva University Hospitals
University of Geneva

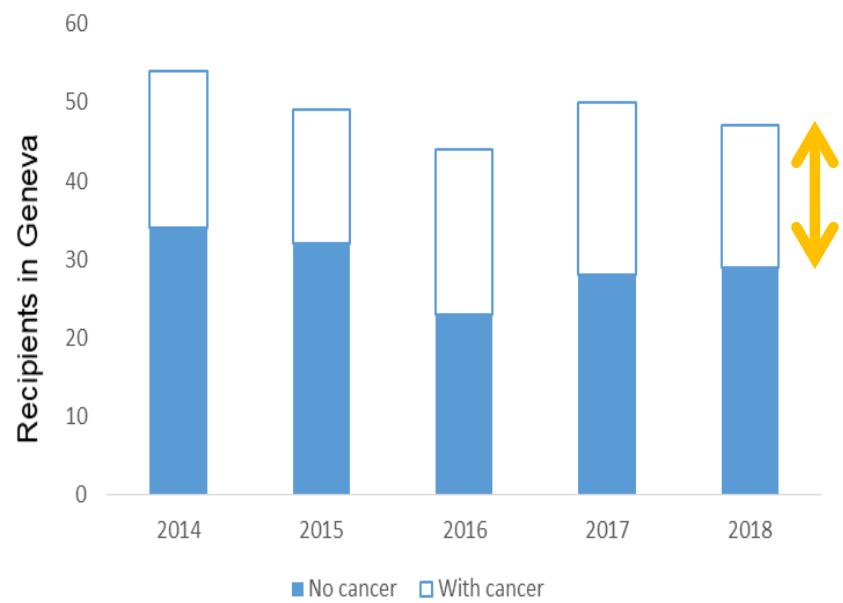
Lausanne, January 2019

Current trends

Swiss donors



Geneva recipients



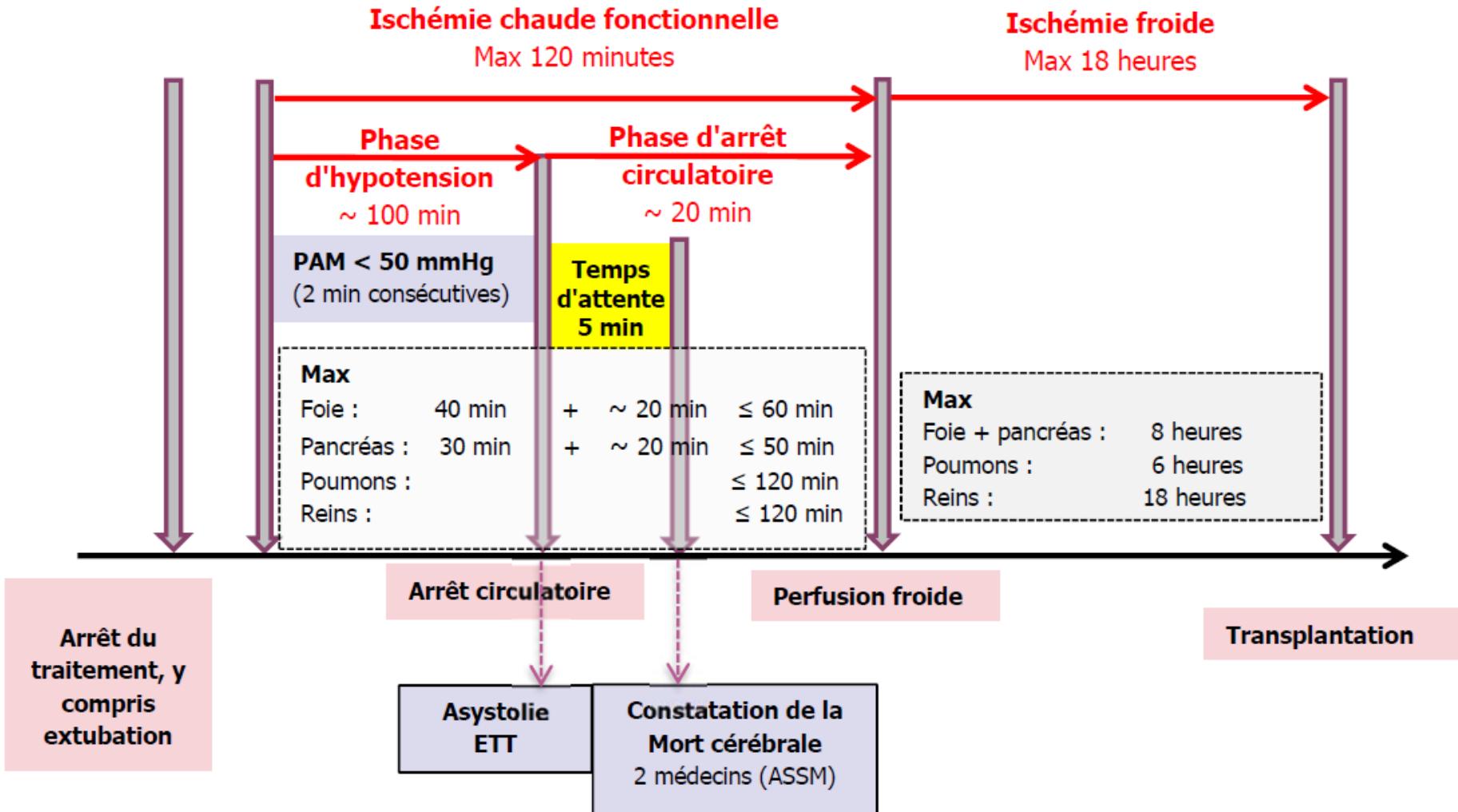
DCD and machine
perfusion

Transplant oncology

DCD and machine perfusion

Category	Description	Circumstances
Type I	Dead on arrival (irreversible cardiac arrest on the street)	Uncontrolled
Type II	Unsuccessful resuscitation (includes patients brought into the emergency room while being resuscitated by the ambulance crew)	Uncontrolled
→ Type III	Imminent cardiac arrest in intensive care (ventilator switch-off)	Controlled
Type IV	Cardiac arrest during or after the brain death diagnostic procedure	Controlled
Type V	Unexpected cardiac arrest in intensive care	Uncontrolled

DCD –Maastricht 3 protocole National (sans ECMO-R)
(Un centre ne peut exiger d'un autre centre le recourt à l'ECMO)



- DCD donors now represent 27% of the donors in Switzerland
- At increased risk of delayed graft function (\approx 20-30% without machine perfusion)
- At increased risk of ischemic cholangiopathy (\approx 30% without machine perfusion)

Donor:

- Age < 70 years,
- BMI < 25-30
- Functional warm ischemia: < 30 min
- No chronic liver disease (steatosis < 20%)
- AST/ALT< 4N et/ou profil +++
- Heparine +++
- CIT < 8h +++

Recipient:

- Age <66 years
- First transplant,
- No major co-morbidity or prior surgery
- MELD < 25

Machine perfusion

- HOPE: Hypothermic Oxygenated PErfusion
- NMP: Normothermic Machine Perfusion
- NRP: Normothermic Regional Perfusion (ECMO in donor)

HOPE

American Journal of Transplantation 2010; 10: 372-381
Wiley Periodicals Inc.

Hypothermic Machine Preservation in Human Liver Transplantation: The First Clinical Series

J. V. Guarerra^{a,*}, S. D. Henry^a, B. Samstein^a,
R. Odeh-Ramadan^a, M. Kinkhabwala^a,
M. J. Goldstein^b, L. E. Ratner^a, J. F. Renz^c,
H. T. Lee^b, R. S. Brown, Jr.^a and J. C. Emond^a

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American Journal of Transplantation 2015; 15: 161-169
Wiley Periodicals Inc.

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Transplantation and the American Society of Transplant Surgeons
doi: 10.1111/j.1600-6143.2009.02932.x

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doi: 10.1111/ajt.12958

Hypothermic Machine Preservation Facilitates Successful Transplantation of "Orphan" Extended Criteria Donor Livers

J. V. Guarerra^a, S. D. Henry, B. Samstein,
C. Musat, T. I. Lukose, L. E. Ratner,
R. S. Brown, Jr., and J. C. Emond

Research Article

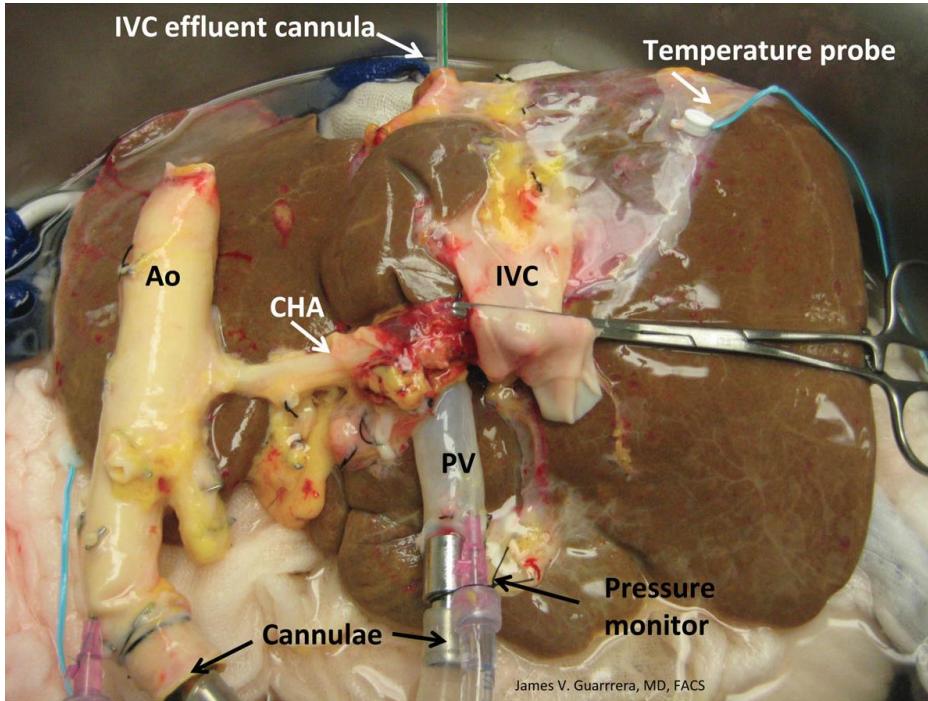
 **EASL** | JOURNAL OF HEPATOLOGY

UNOS, United Network for Organ Sharing; UW,
University of Wisconsin
Received 01 May 2014, revised 21 July 2014 and

HOPE for human liver grafts obtained from donors after cardiac death

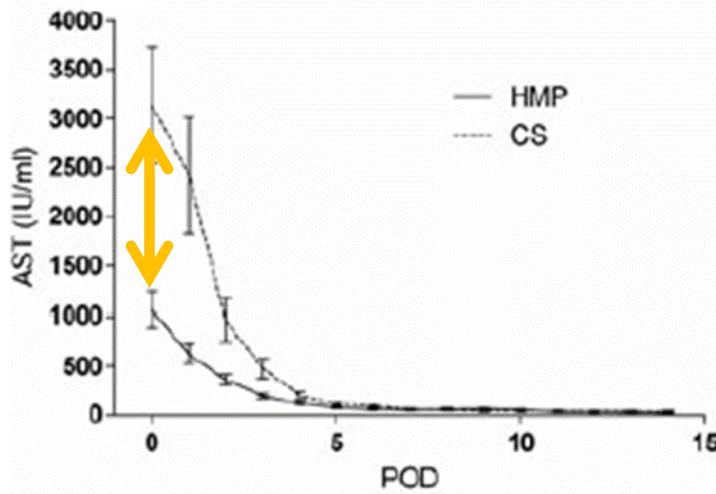
Philipp Dutkowski^{1,†}, Andrea Schlegel^{1,†}, Michelle de Oliveira¹, Beat Müllhaupt², Fabienne Nau³,
Pierre-Alain Clavien^{1,*}
First Comparison of Hypothermic Oxygenated Liver Transplantation
Static Cold Storage of Human Donation after Circulatory Death
Liver Transplantation
An International Study
Dual hypothermic oxygenated machine perfusion in liver
transplants donated after circulatory death
Philippe Dutkowski, MD, * Wojciech G. Polak
Cornelia J. Verhoeven, † Irene Scalera, MD,
Pierre-Alain Clavien, MD, *
R. van Rijn^{1,2}, N. Karimian^{1,2}, A. P. M. Matton^{1,2}, L. C. Burlage^{1,2}, A. C. Westerkamp^{1,2},
A. P. van den Berg³, R. H. J. de Kleine¹, M. T. de Boer¹, T. Lisman^{1,2} and R. J. Porte^{1,2},
J. V. Guarerra, S. D. Henry, B. Samstein, C. Musat, T. I. Lukose, L. E. Ratner, R. S. Brown, Jr., and J. C. Emond

Hypothermic machine perfusion in human



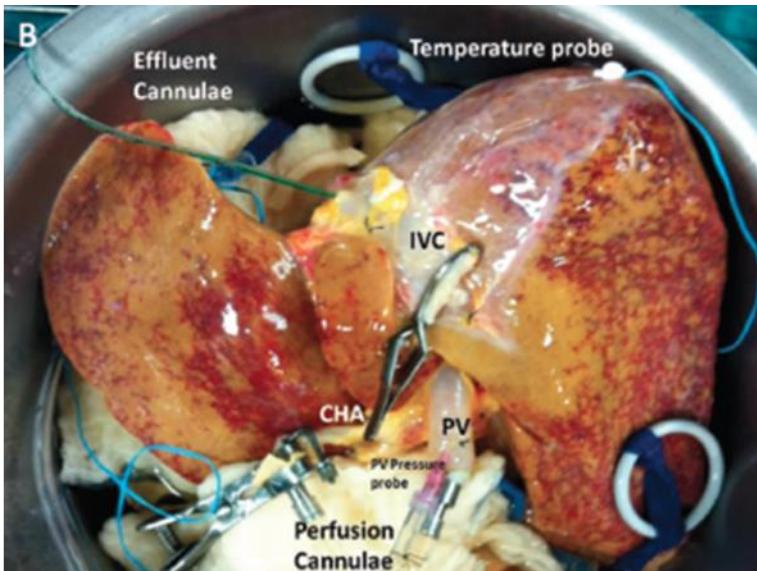
- Standard donors
- Perfusion after static preservation
- Dual (arterial and portal) perfusion
- Non-oxygenated perfusate
- 20 liver grafts

Hypothermic machine perfusion in human



	Machine perfusion (HMP)	Cold storage (CS)
Primary nonfunction	0	0
Early allograft dysfunction	1* (5%) ¹	5 (25%)
Vascular complications (total)	0	1
Hepatic artery stenosis		1
Biliary complications (total)	2	4

Hypothermic machine perfusion in human (marginal donors)



	Machine perfusion	Cold storage	p-Value
Number of patients	31	30	
Primary nonfunction	1 (3%)	2 (7%)	0.612
→ Early allograft dysfunction	6 (19%)	9 (30%)	0.384
Postoperative complications			
HAT	1 (3%)	2 (7%)	0.612
PVT	2 (6%)	0	0.492
→ Biliary complications	4 (13%)	13 (43%)	0.001
Bile leak	1 (3%)	3 (10%)	0.354
Biliary stricture	3 (10%)	10 (33%)	0.031
Reoperation for bleeding	2 (6%)	7 (23%)	0.081
Acute kidney injury	3 (10%)	8 (27%)	0.106
Incisional hernia	4 (13%)	5 (17%)	0.732
→ Hospital length of stay (days)	13.6 ± 10.9	20.1 ± 11.1	0.001
One year survival	26/31 (83.8%)	24/30 (80.0%)	0.761

HOPE in human

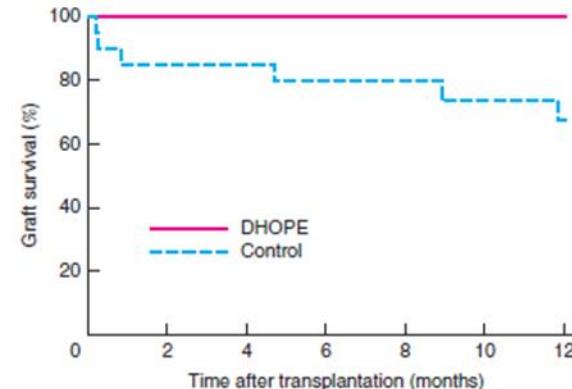
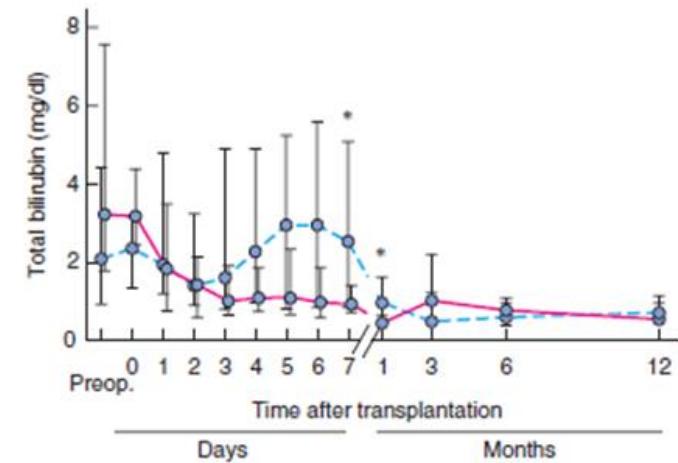
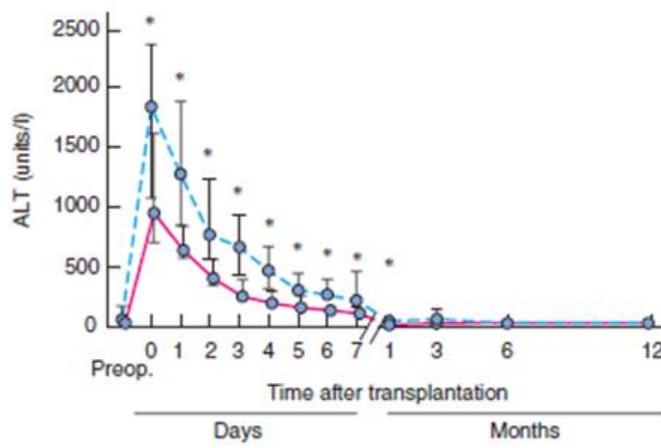
- DCD donors (n=8)
- Similar outcomes as with standard donors
- Median follow-up: 8 months



HOPE-treated DCD livers (n=25) vs. cold-stored DCD livers (n=25)

- ↓ peak ALT (1239 vs. 2065 U/L, p<0.02)
- ↓ IH cholangiopathy (0 vs. 22%, p<0.015)
- ↓ biliary complications (20 vs. 46%, p<0.042)
- ↓ graft failure, retransplant (0 vs. 18%, p<0.05)
- 1-year graft survival (90 vs. 69%, p<0.035)

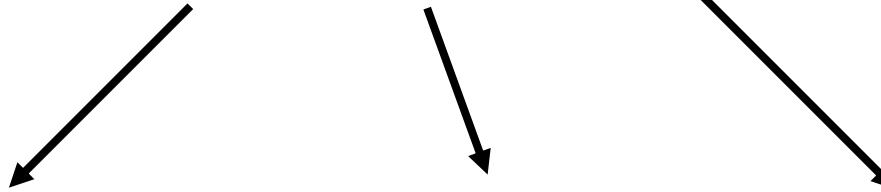
Dual HOPE-treated DCD livers (n=10) vs. cold-stored DCD livers (n=20)



	No. at risk						
DHOPE	10	10	10	10	10	10	10
Control	20	16	15	15	15	12	11

Normothermic machine perfusion

Recreate physiological environment



Deliver oxygen

Physiological temperature

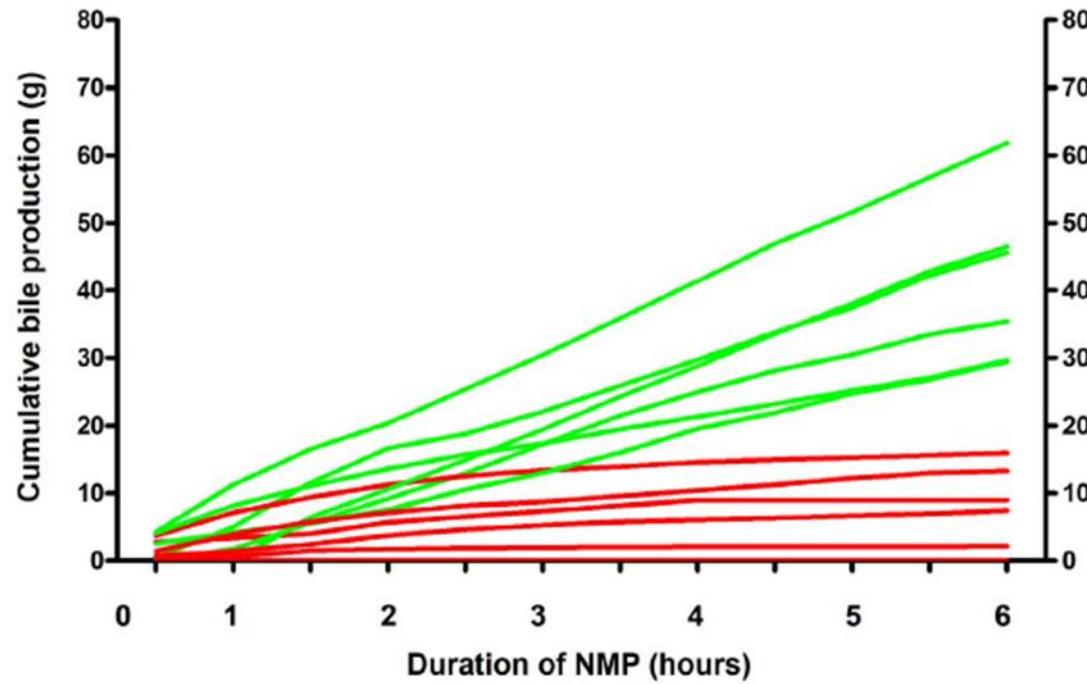


Provide nutrients

- Allow normal metabolic activity
- Avoid ischemia-reperfusion
- Assess viability +++

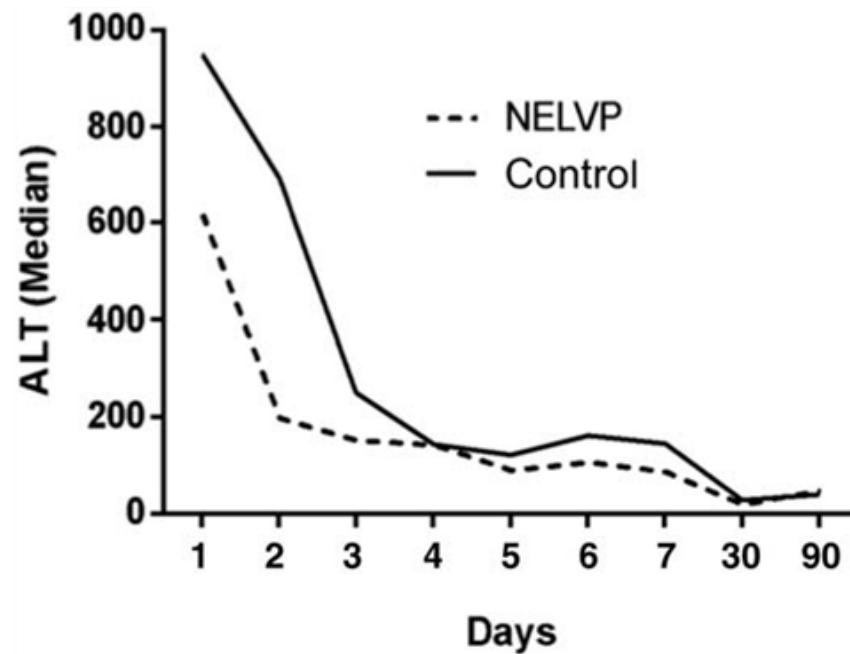
Imber CJ, Am J Transpl 2002
St Peter SD, Br J Surg 2002
Reddy SP, Transplantation 2004

Normothermic machine perfusion



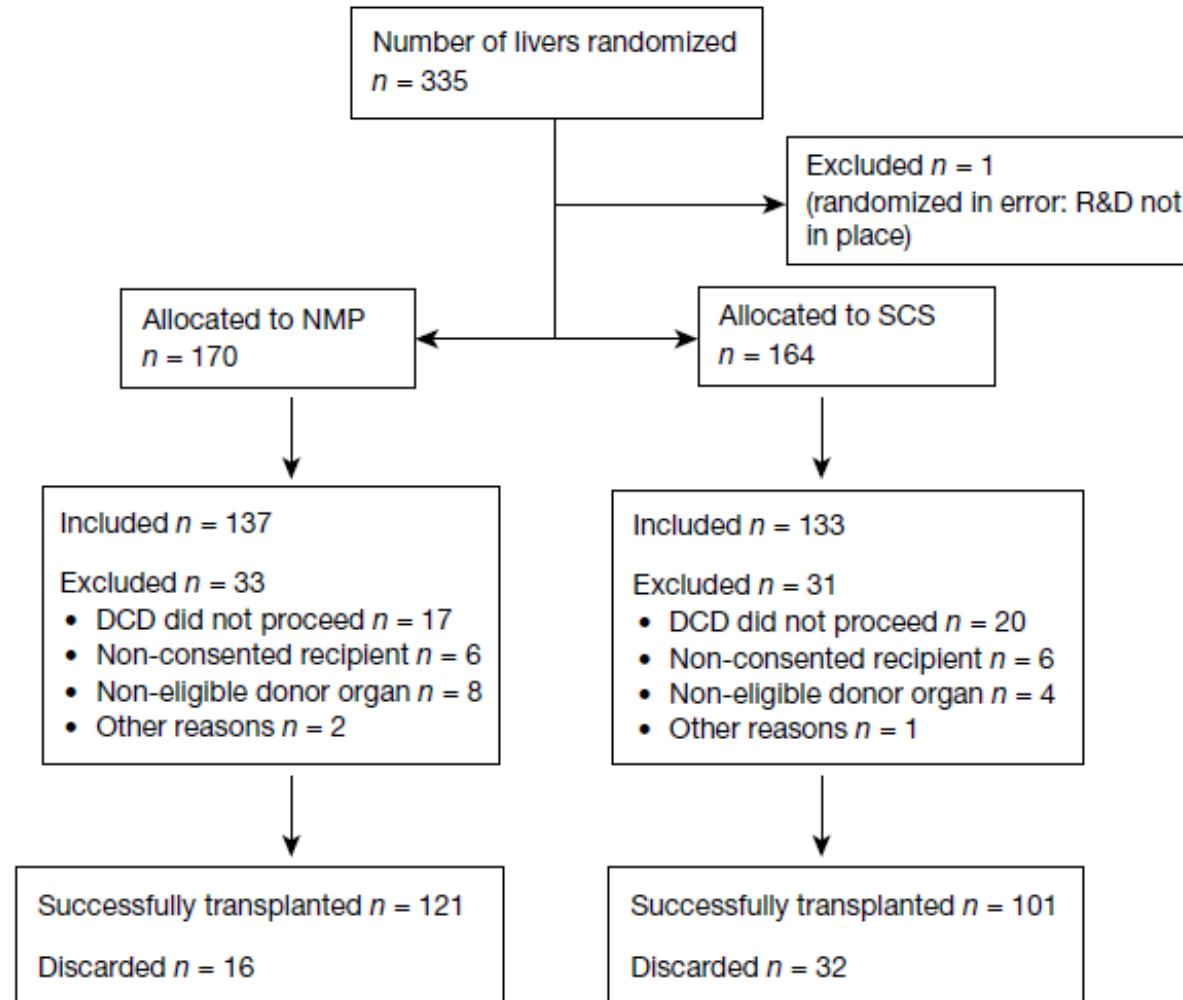
Testing the liver (>30g vs. <20g)

Normothermic machine perfusion of standard livers vs. cold-storage



Bral et al. AJT 2016
Selzner et al. Liver Transplant 2016
Ravikumar et al. AJT 2016

Randomized clinical trial normothermic machine perfusion of standard livers vs. cold-storage



Randomized clinical trial normothermic machine perfusion of standard livers vs. cold-storage

- DCD and DBD donors
- 50% ↓ peak ALT
- 50% ↓ organ discard
- 54% ↑ preservation time
- Similar bile duct complications, and graft and patient survival



Warm vs. cold perfusion techniques to rescue rodent liver grafts

Andrea Schlegel, Philipp Kron, Rolf Graf, Philipp Dutkowski[†], Pierre-Alain Clavien^{*†}

Department of Surgery, University Hospital Zurich, Swiss HPB and Transplant Center, Zurich, Switzerland

Journal of Hepatology 2014 vol. 61 | 1267–1275

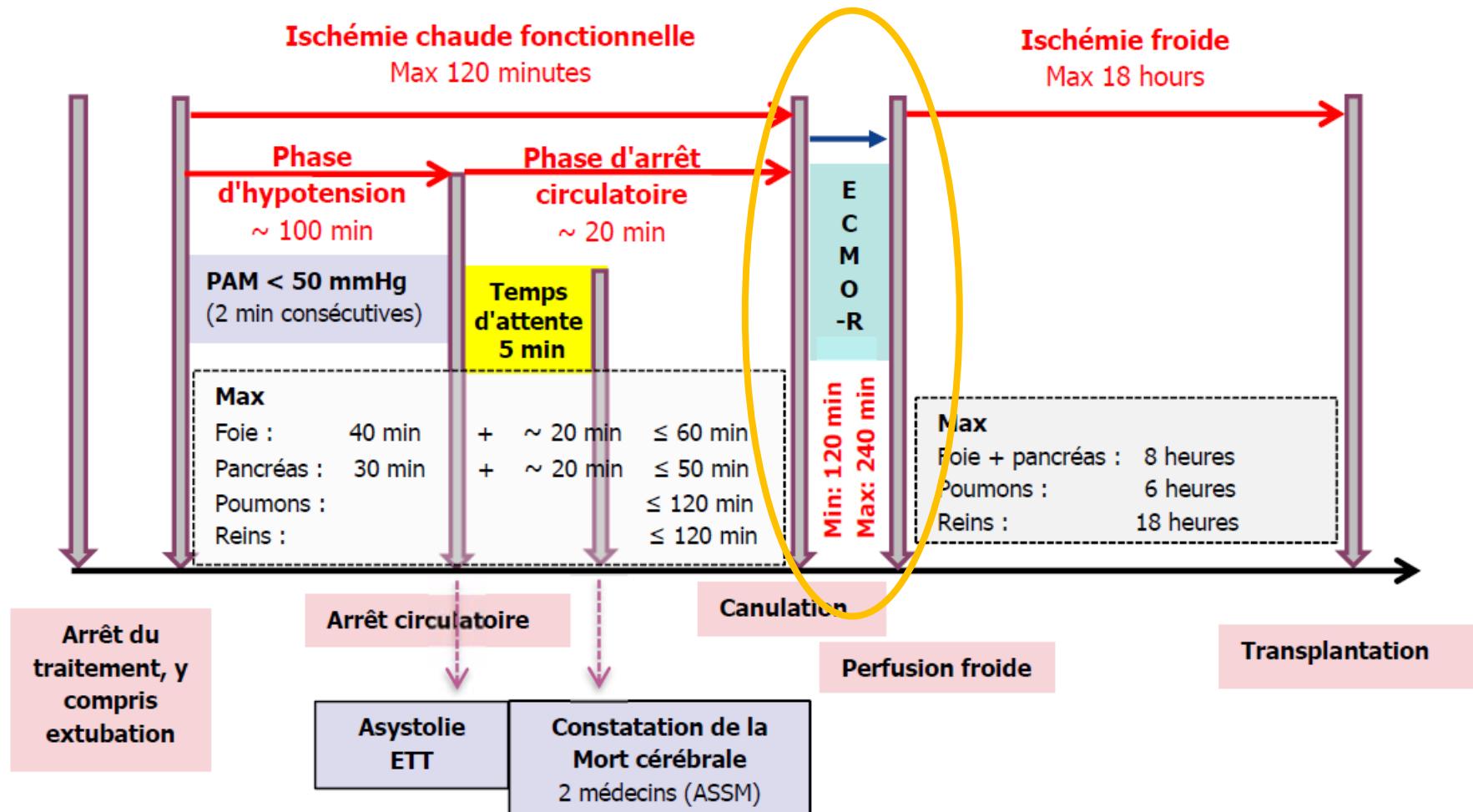


Liver Assist®

Normothermic Regional Perfusion



- Less expensive
- Can be applied early

DCD –Maastricht 3 protocole National avec ECMO régionale*(Un centre ne peut exiger d'un autre centre le recourt à l'ECMO)*

Normothermic Regional Perfusion (NRP)

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doi: 10.1111/ajt.14214

American Journal of Transplantation 2017; 17: 2165–2172
Wiley Periodicals Inc.

Improving the Outcomes of Controlled Donation After Using Abdominal Normothermic Perfusion

E. Miñambres^{1,*}, B. Suberviola², B. Dominguez-Gil³, E. Rodrigo⁴, J. C. Ruiz-San Millán⁴ , J. C. Rodríguez-San Juan⁵ and M. A. Ballasteros²

Journal of Transplantation 2014; 14: 2846–2853
Wiley Periodicals Inc.

CURRENT OPINION

Organs Obtained From Circulatory Death Donors by Perfusion

Abdominal regional *in-situ* perfusion in donor after circulatory determination of death donors

Amelia J. Hessheimer, Juan C. García-Valdecasas, and Constantino Fondevila

Purpose of review

Provide an overview regarding the current state of abdominal regional perfusion (ARP) in donor circulatory determination of death (DCD) organ transplantation, including the principles behind functions and the most recent results of its clinical application.

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and the American Society of Transplant Surgeons
doi: 10.1111/ajt.12927

In Situ Normothermic Regional Perfusion for Controlled Donation After Circulatory Death—The United Kingdom Experience

G. C. Oniscu^{1,*}, L. V. Randle², P. Muiesan³, A. J. Butler², I. S. Currie¹, M. T. P. R. Perera³, J. L. Forsythe¹ and C. J. E. Watson²

extra-corporeal mem-
brane recircula-
tion

Normothermic Regional Perfusion (NRP): UK DCD score

Risk category	DCD NRP transplants	Ischaemic cholangiopathy	Primary non-function
Low risk	1	0	0
High risk	9	0	0
Futile transplants	8	0	0

DCD, donation after circulatory death; NRP, normothermic regional perfusion.

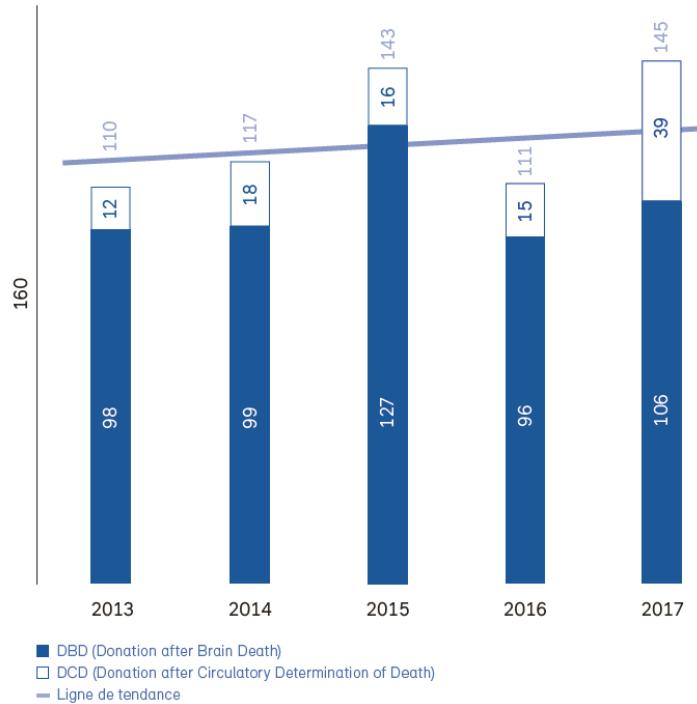
16% 27%

Current strategy in Geneva

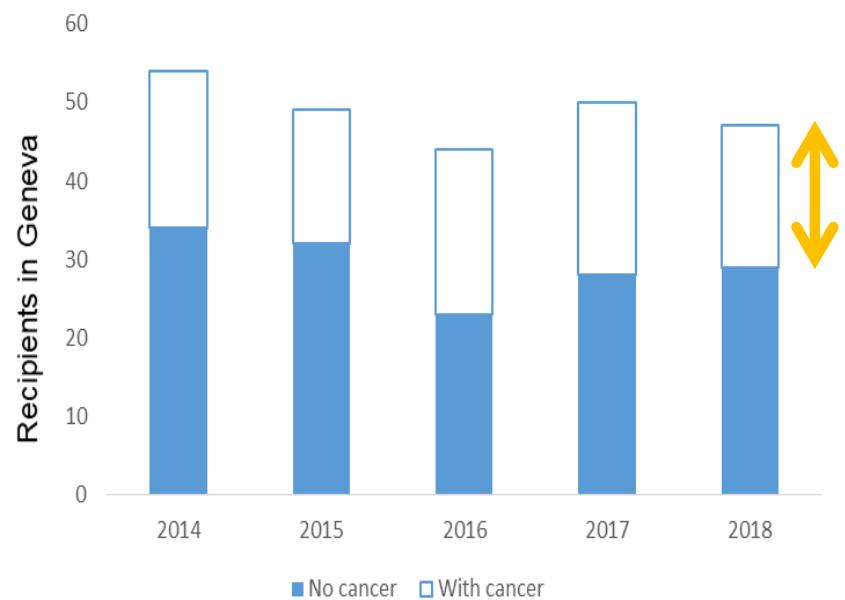
- DCD donor in Geneva
→ **NRP (normothermic regional perfusion)**
- Liver of a DCD donor offered to Geneva
→ **Cold storage to Geneva followed by HOPE (hypothermic oxygenated perfusion)**

Current trends

Swiss donors



Geneva recipients



Transplant oncology

Transplant oncology

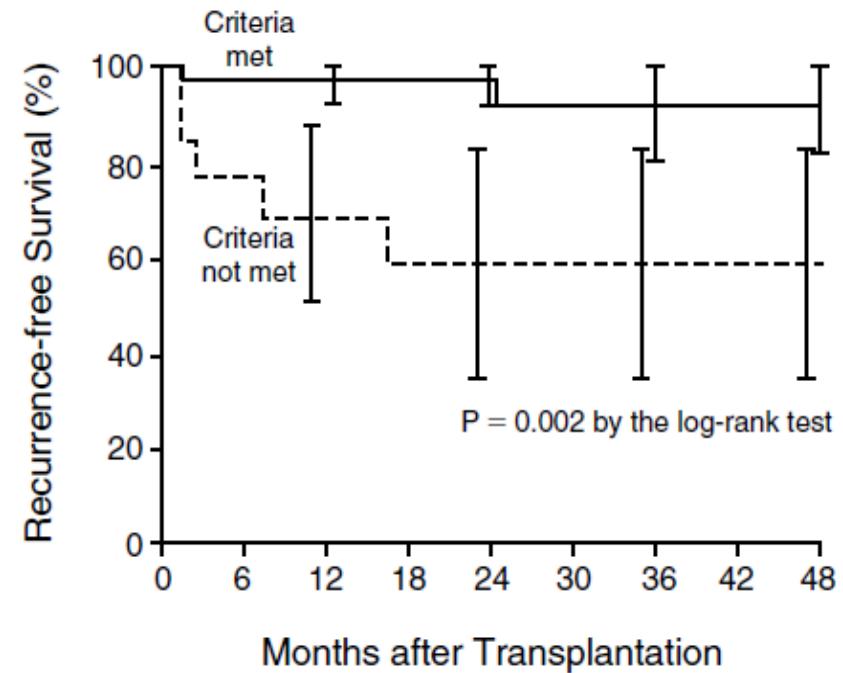
- Primary liver cancer
 - Hepatocellular carcinoma
 - Intrahepatic cholangiocarcinoma
 - Combined hepatocellular-cholangiocarcinoma
 - Hepatic epithelioid hemangioendothelioma
 - Hepatoblastoma
- Bile duct cancer
 - Perihilar cholangiocarcinoma
- Secondary liver cancer
 - Colorectal liver metastases
 - Neuroendocrine tumor (NET) liver metastases

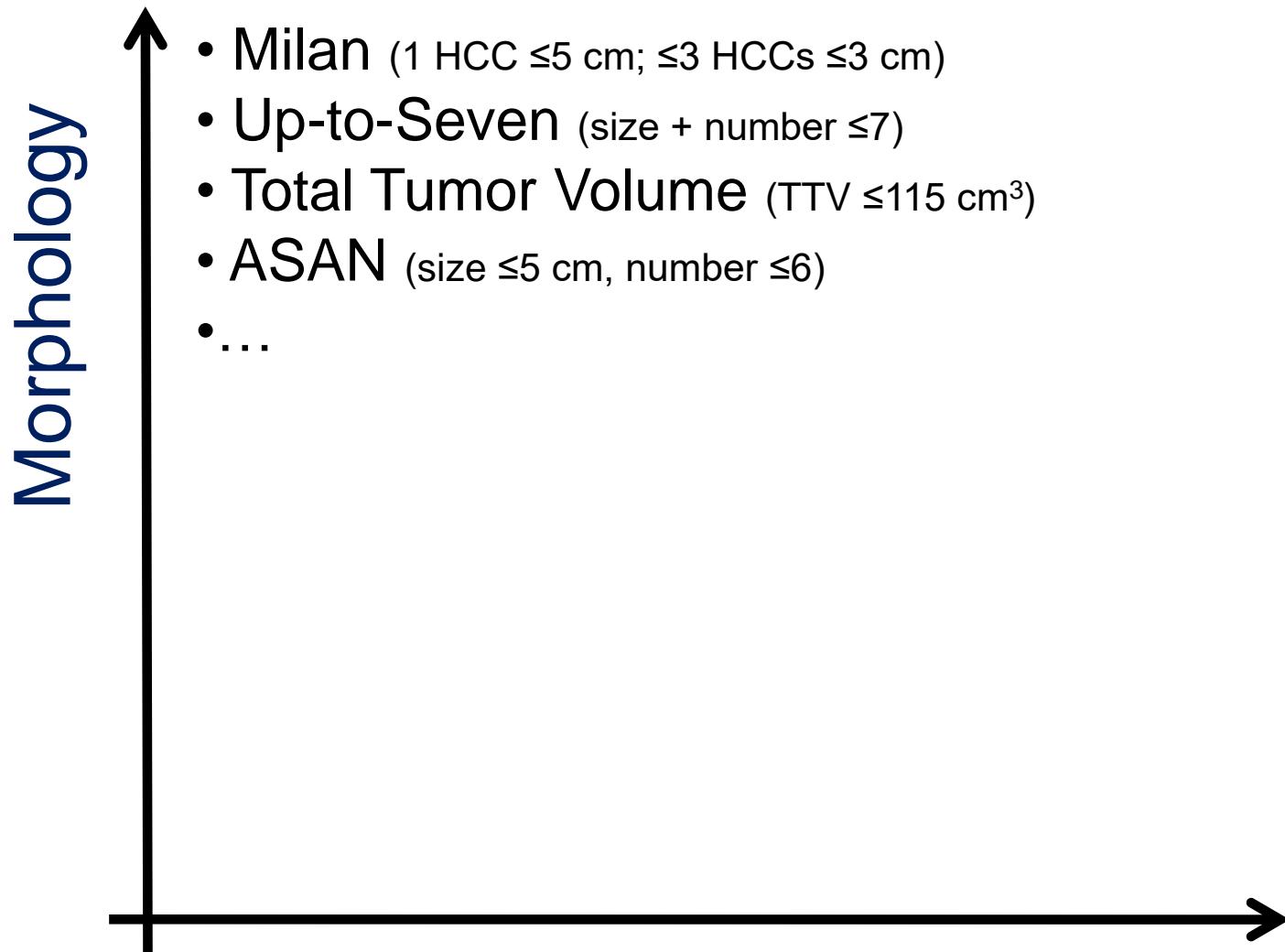
Transplantation for HCC

- Recipient characteristics
- Donor characteristics

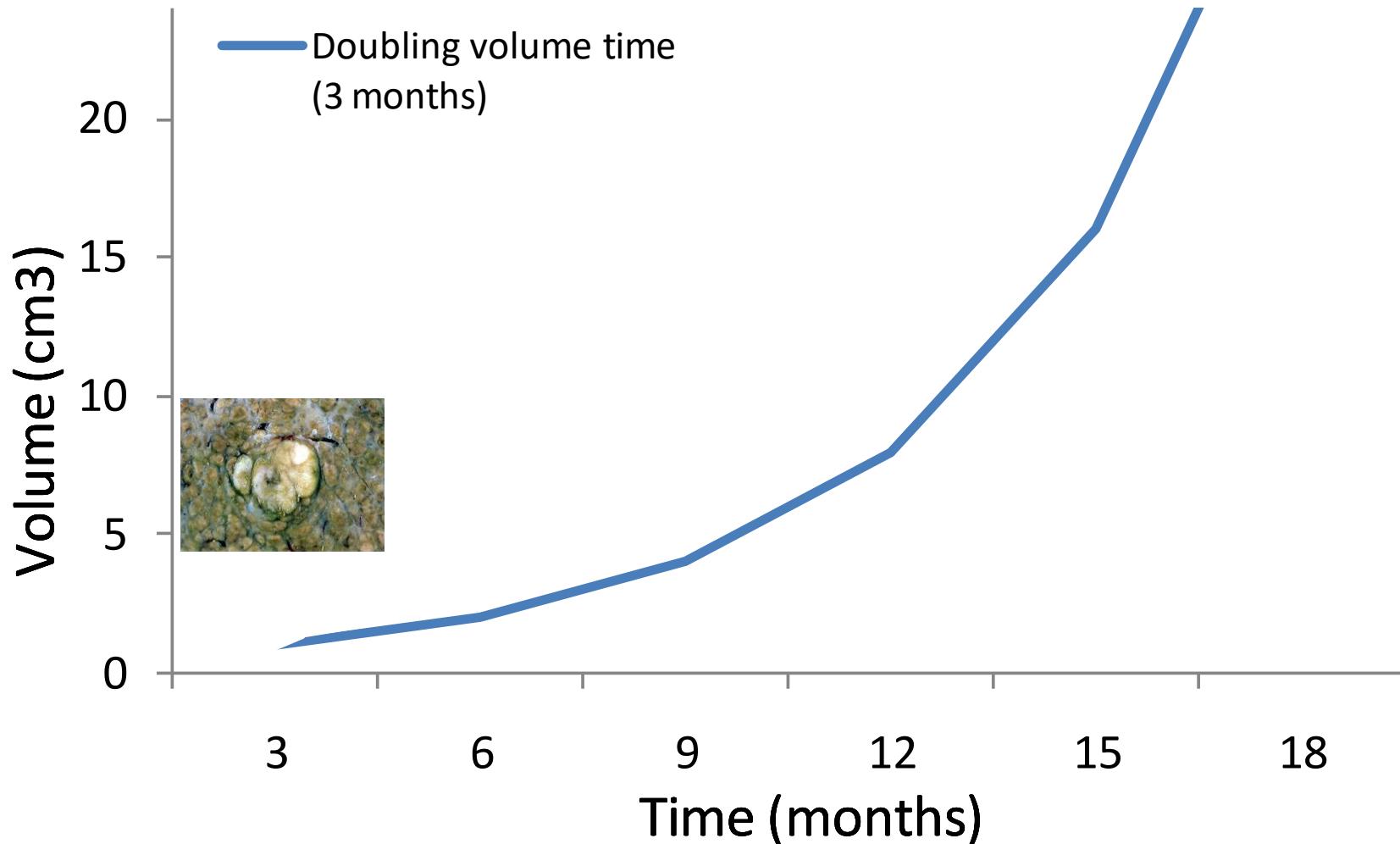
Transplantation for cancer: HCC

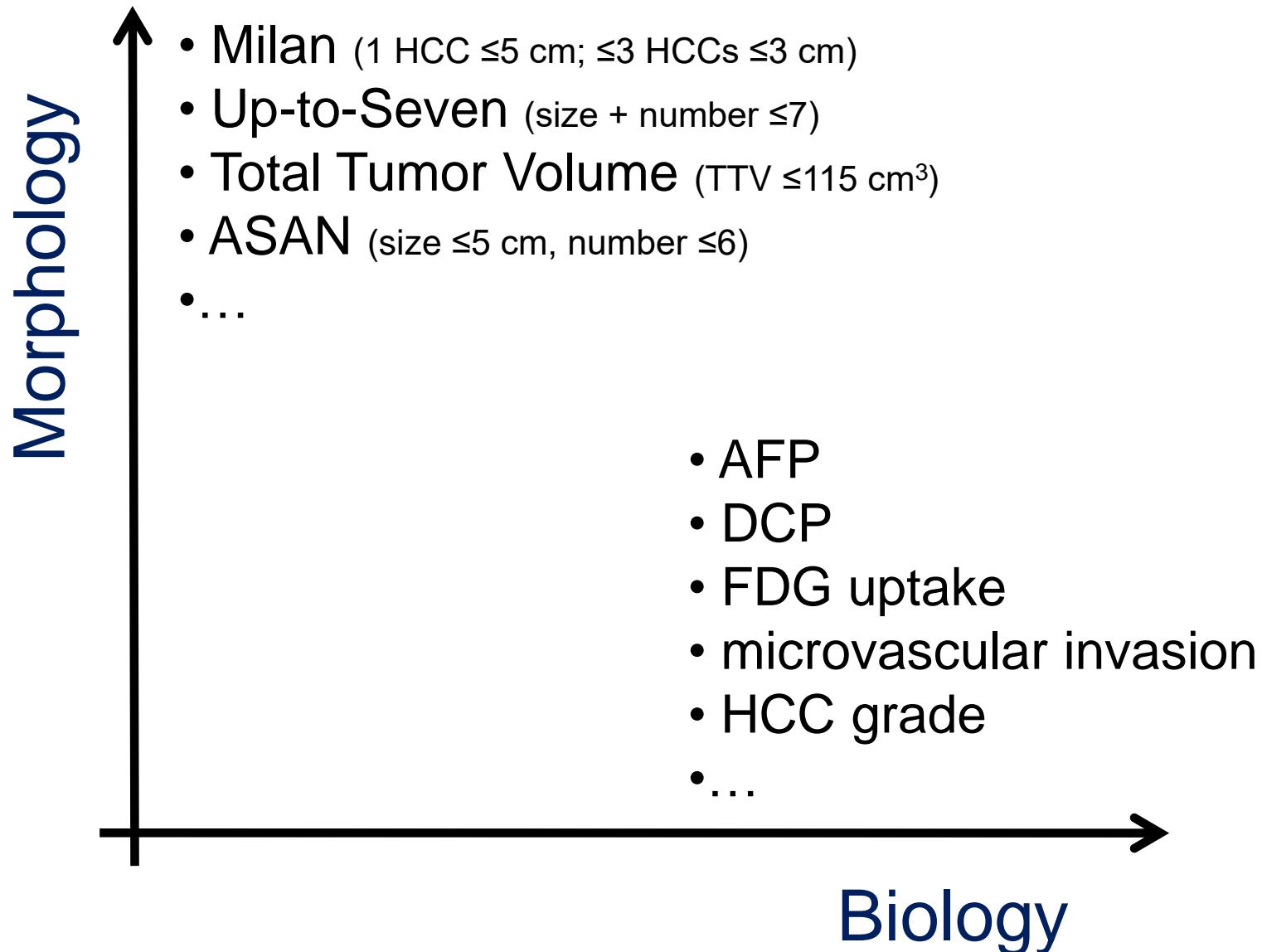
- HCC unique ≤ 5 cm
- ≤ 3 HCC ≤ 3 cm





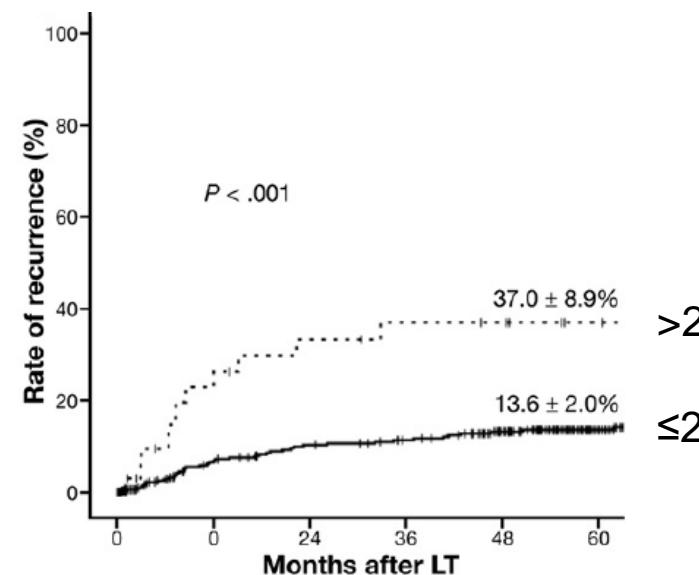
HCC biology





AFP model

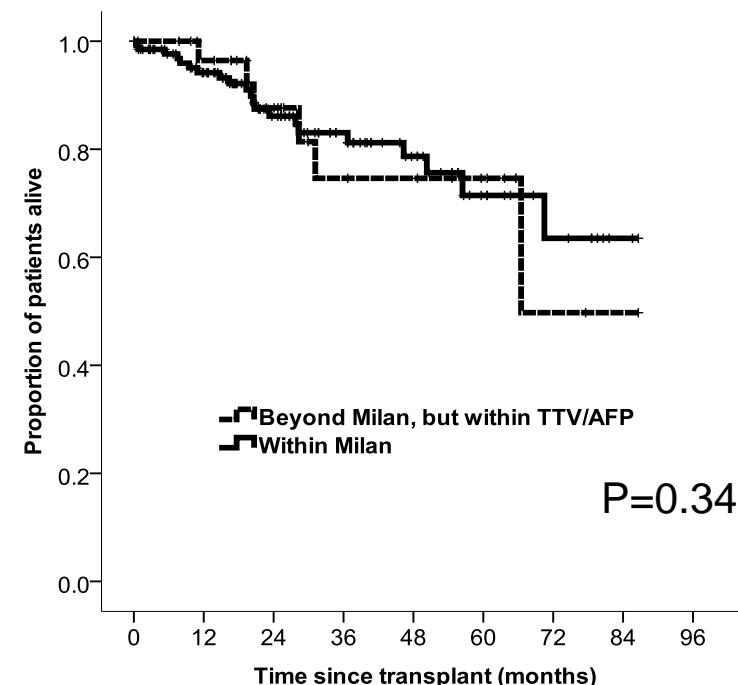
Variables	β coefficient	Hazard ratio	Points
→ Largest diameter, cm			
≤3	0	1	0
3–6	0.272	1.31	1
>6	1.347	3.84	4
→ Number of nodules			
1–3	0	1	0
≥4	0.696	2.01	2
→ AFP level, ng/mL			
≤100	0	1	0
100–1000	0.668	1.95	2
>1000	0.945	2.57	3



Pinero et al. Liver Int 2016
 Notarpaolo et al. J Hepatol 2016
 Duvoux et al. Gastroenterology 2012

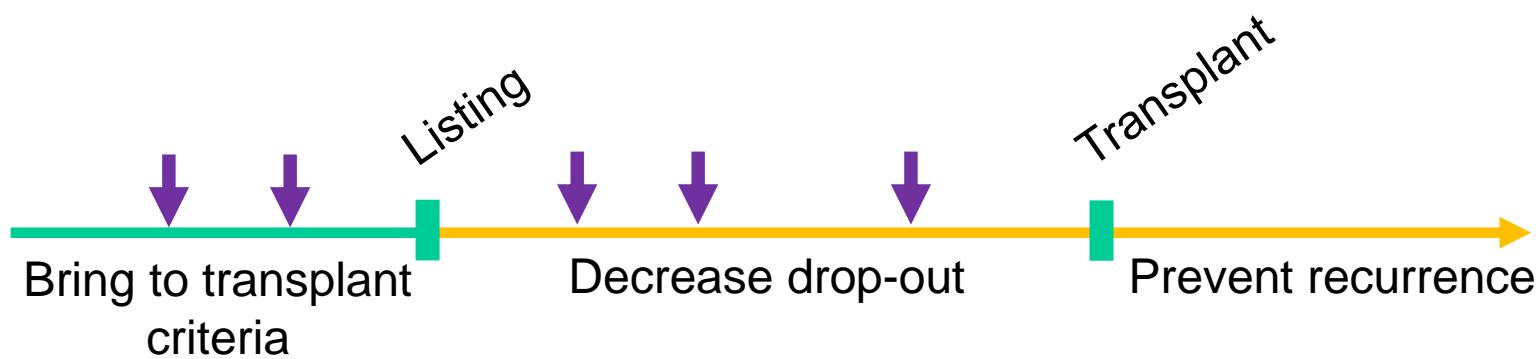
Total Tumor Volume /AFP

TTV \leq 115 cm³
AFP \leq 400 ng/ml



Toso et al. Hepatology 2015
Toso et al. Hepatology 2009
Toso et al. Liver Transplantation 2008

Downstaging patients outside transplant criteria



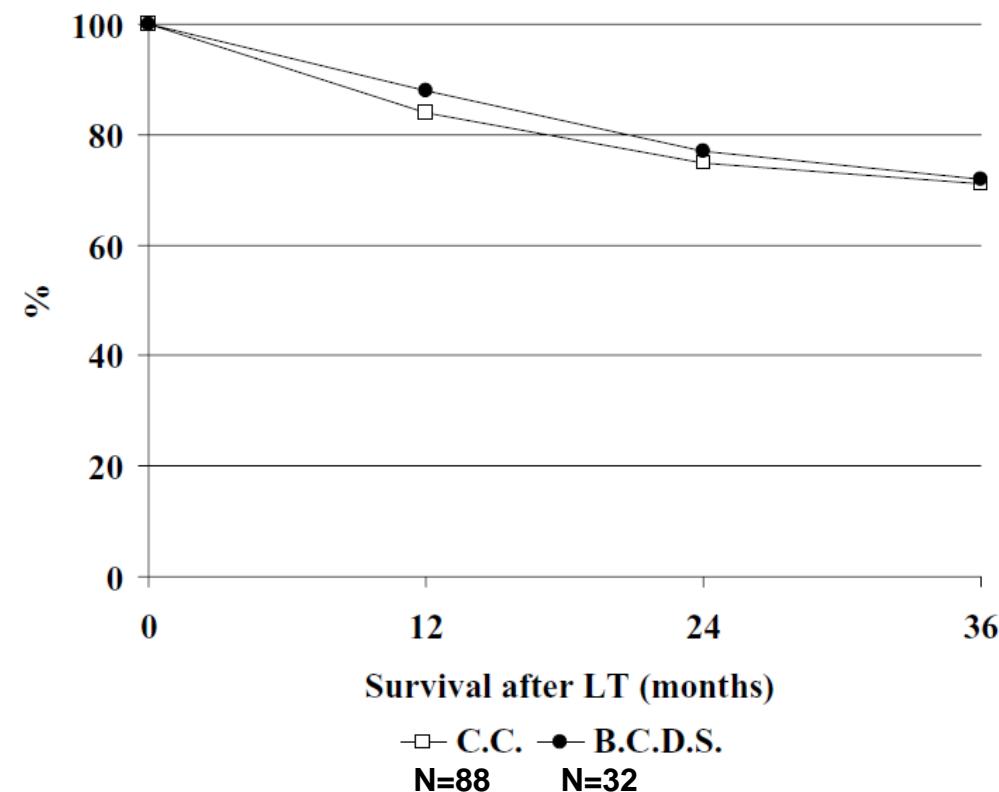
Downstaging: morphology

Inclusion criteria:

- single HCC ≤ 8 cm
- bifocal HCC ≤ 5 cm
- 3 to 6 HCCs ≤ 4 cm, and maximum total diameter of 12 cm

Downstaging success:

- within Milan criteria
- AFP <400 ng/ml
- stability for >3 months



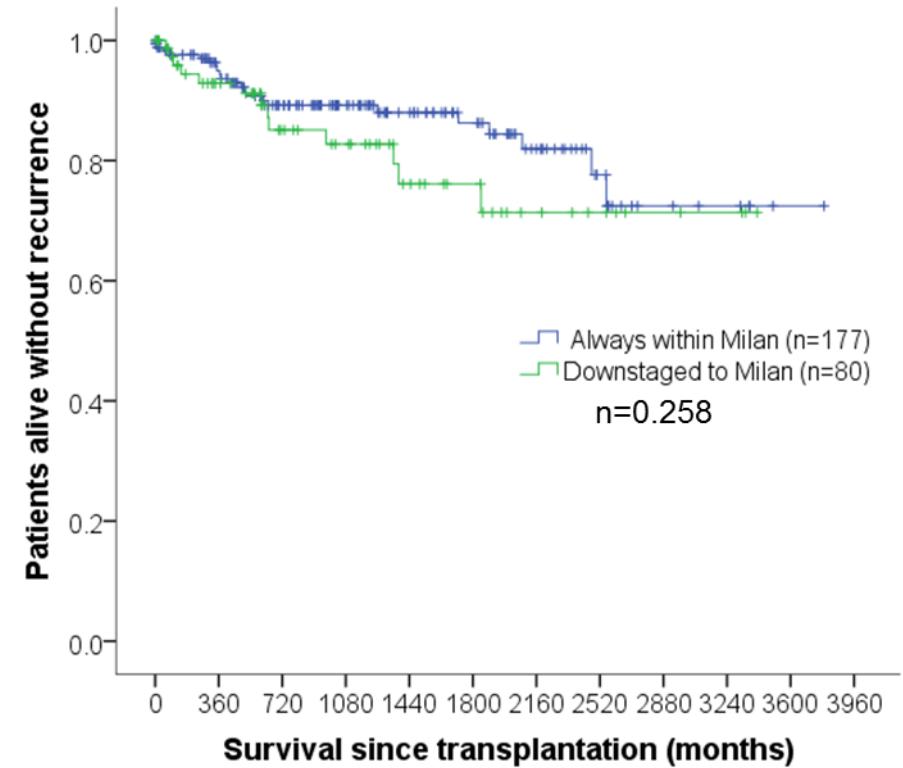
Downstaging : morphology

Inclusion criteria:

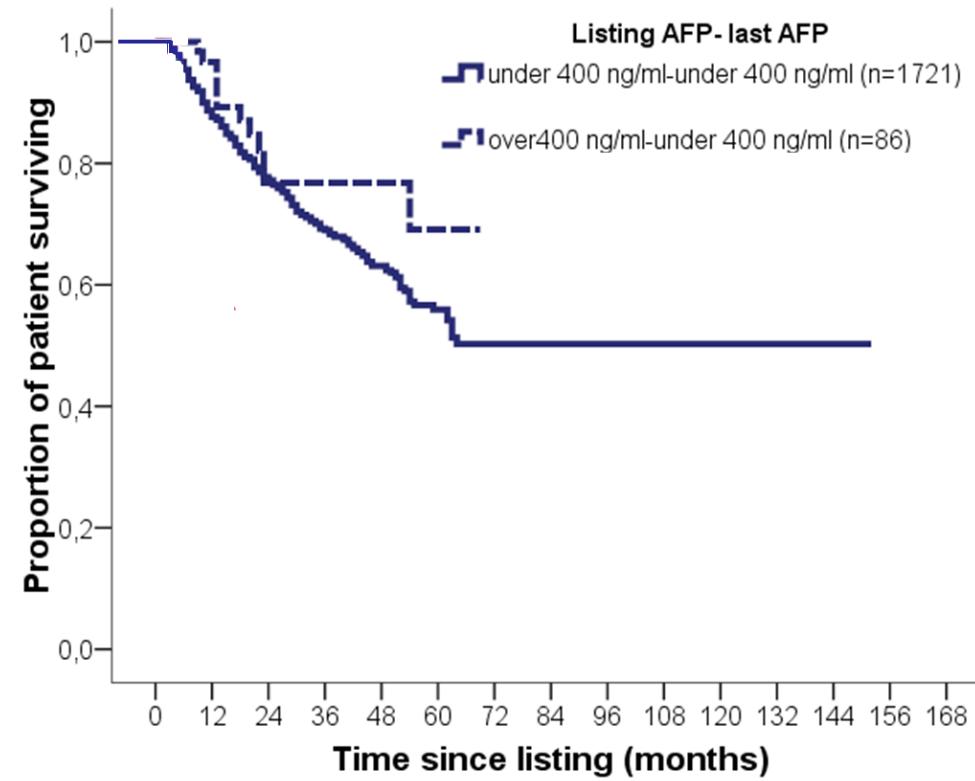
- no restriction

Downstaging success:

- within TTV/AFP
- stability for >3 months

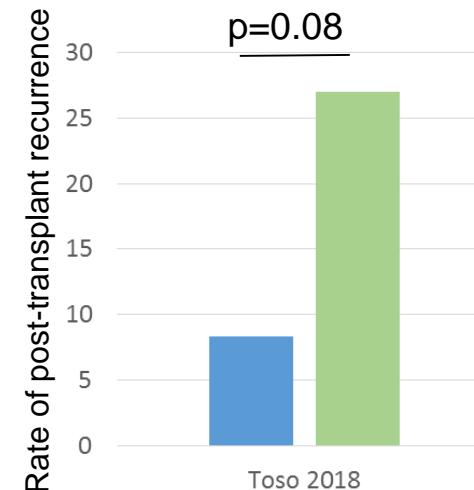


Downstaging: biology

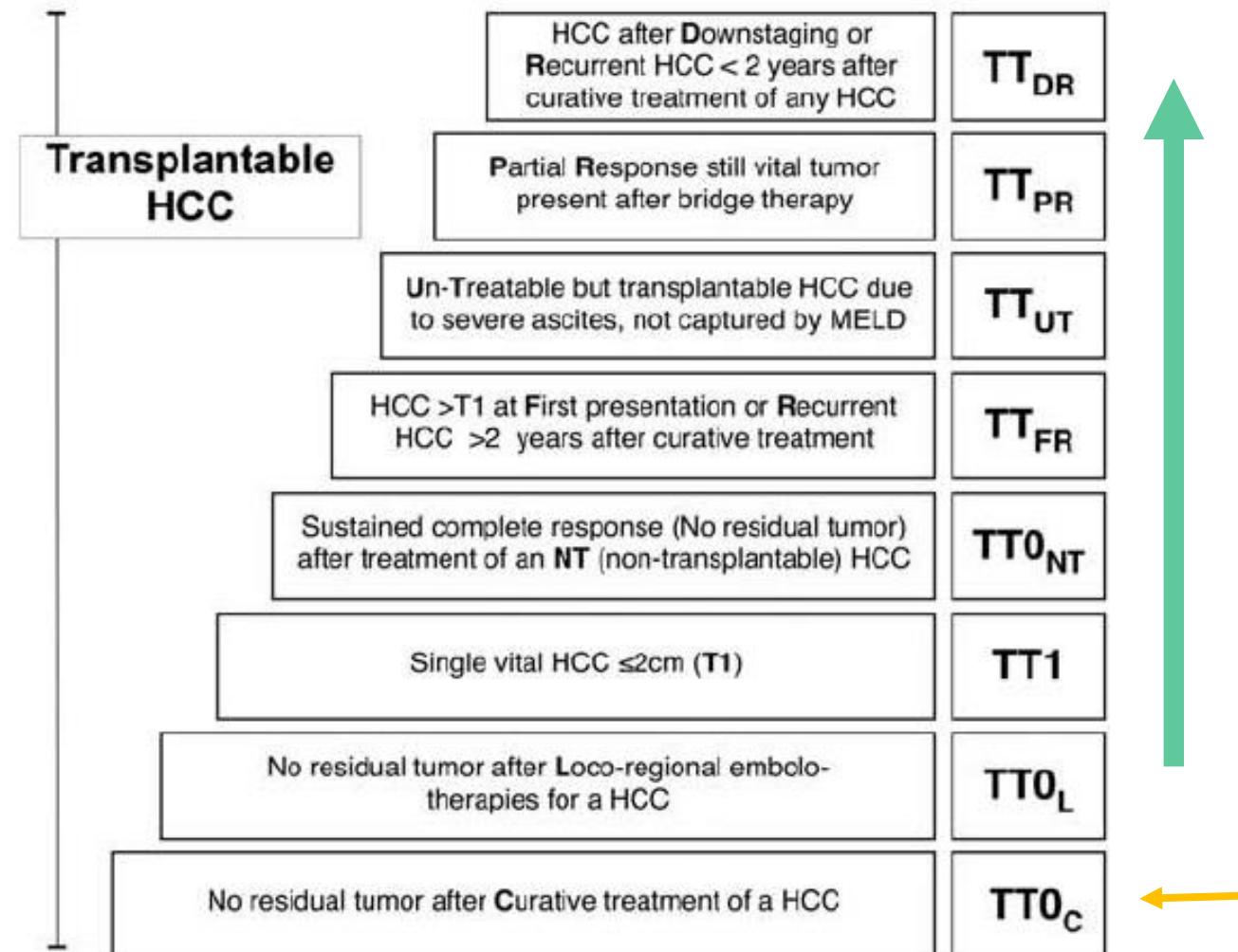


Waiting time should be

- Long enough to avoid transplanting patients with early and aggressive recurrences
- Not too long, in order to transplant (and save) patients with more indolent recurrences
- > 3 months



Too early for transplantation?



Key messages

HCC:

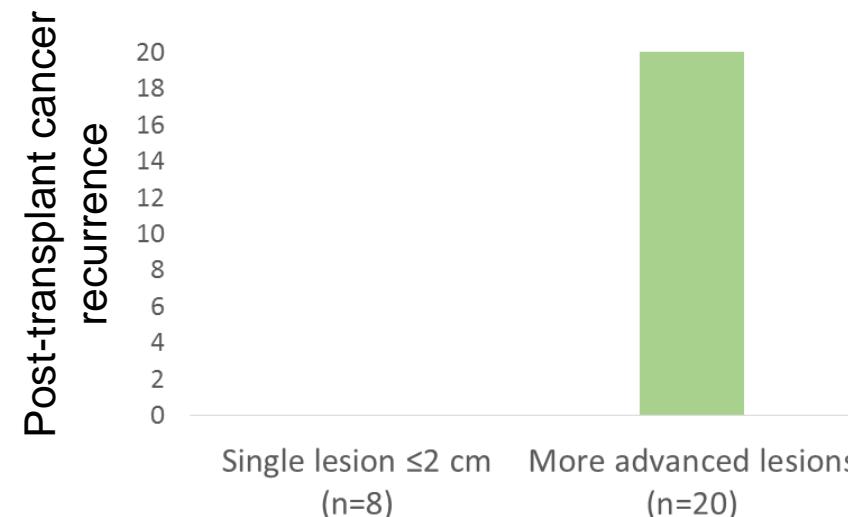
- Historical criteria can be expended (one HCC ≤ 6 cm)
- Historical criteria should be refined (AFP $\leq 400-1000$ ng/ml)
- Downstaging works
- Some patients may be too early for transplantation

Transplant oncology

- Primary liver cancer
 - Hepatocellular carcinoma
 - Intrahepatic cholangiocarcinoma
 - Combined hepatocellular-cholangiocarcinoma
 - Hepatic epithelioid hemangioendothelioma
 - Hepatoblastoma
- Bile duct cancer
 - Perihilar cholangiocarcinoma
- Secondary liver cancer
 - Colorectal liver metastases
 - Neuroendocrine tumor (NET) liver metastases

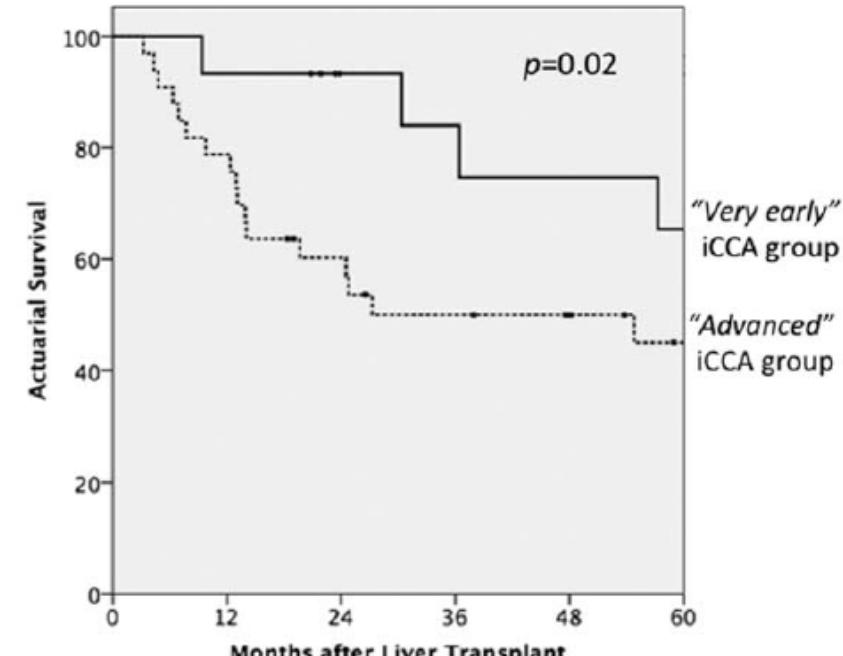
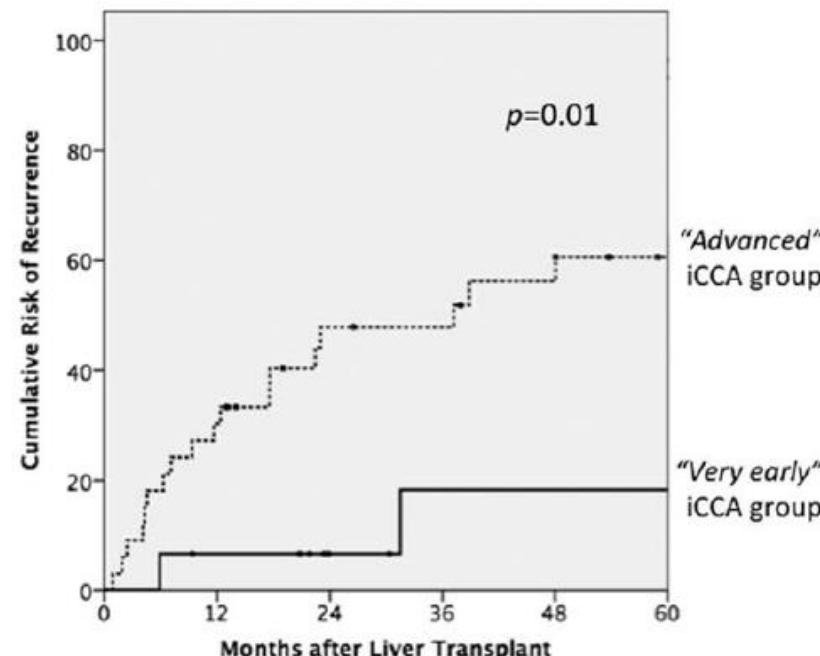
“Very early” intra-hepatic cholangiocarcinoma

- Retrospective multi-centric Spanish study
- 29 transplantations for intra-hepatic cholangiocarcinoma
- Risk of recurrence associated with:
 - size
 - tumor volume
 - microscopic vascular invasion
 - poor degree of differentiation



“Very early” intra-hepatic cholangiocarcinoma

- 15 “very early” (single lesion ≤ 2 cm)
- 33 more advanced
- Risk of recurrence associated with:
 - microscopic vascular invasion
 - poor degree of differentiation



Key messages

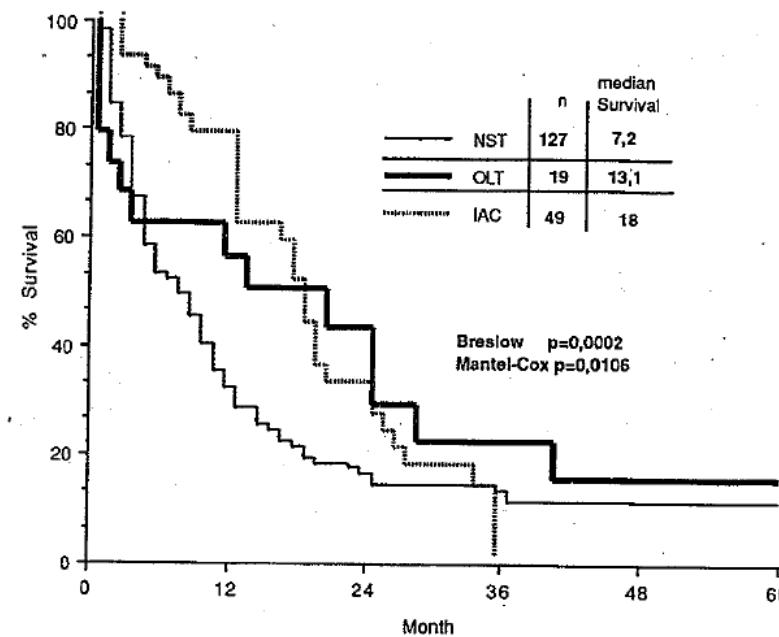
Intrahepatic cholangiocarcinoma:

- Transplantation for very early lesions (single ≤ 2 cm)
- Avoid micro-vascular invasion and poor differentiation

Transplant oncology

- Primary liver cancer
 - Hepatocellular carcinoma
 - Intrahepatic cholangiocarcinoma
 - Combined hepatocellular-cholangiocarcinoma
 - Hepatic epithelioid hemangioendothelioma
 - Hepatoblastoma
- Bile duct cancer
 - Perihilar cholangiocarcinoma
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 - Colorectal liver metastases
 - Neuroendocrine tumor (NET) liver metastases

Historical liver transplantation for CRLM



18 months median survival

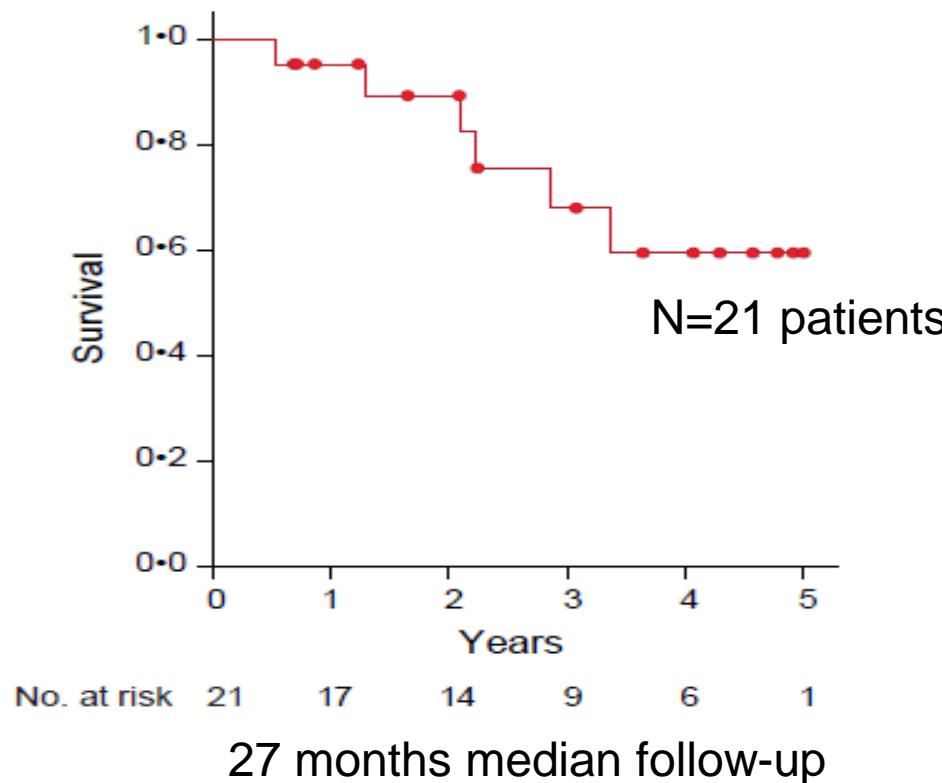
- 1983-1989
- 17 patients

Liver transplantation for CRLM

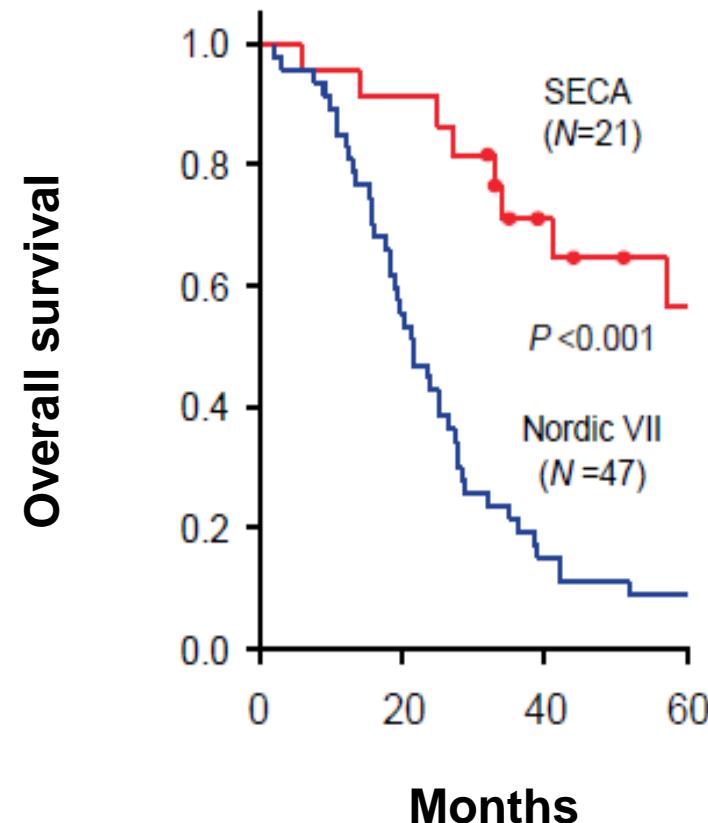
Things have changed

- Improved chemotherapy
- Improved transplantation
- Immunosuppression better tailored for oncological indications

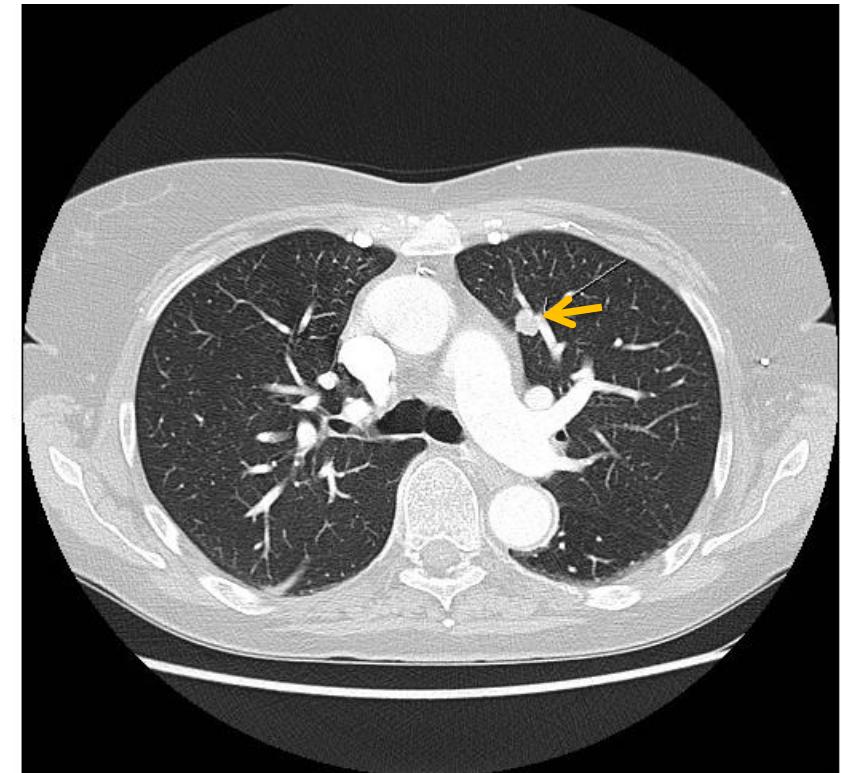
Liver transplantation for CRLM in Oslo



Better than chemotherapy



**Recurrence in almost
all patients (20/21)**



Patient characteristics

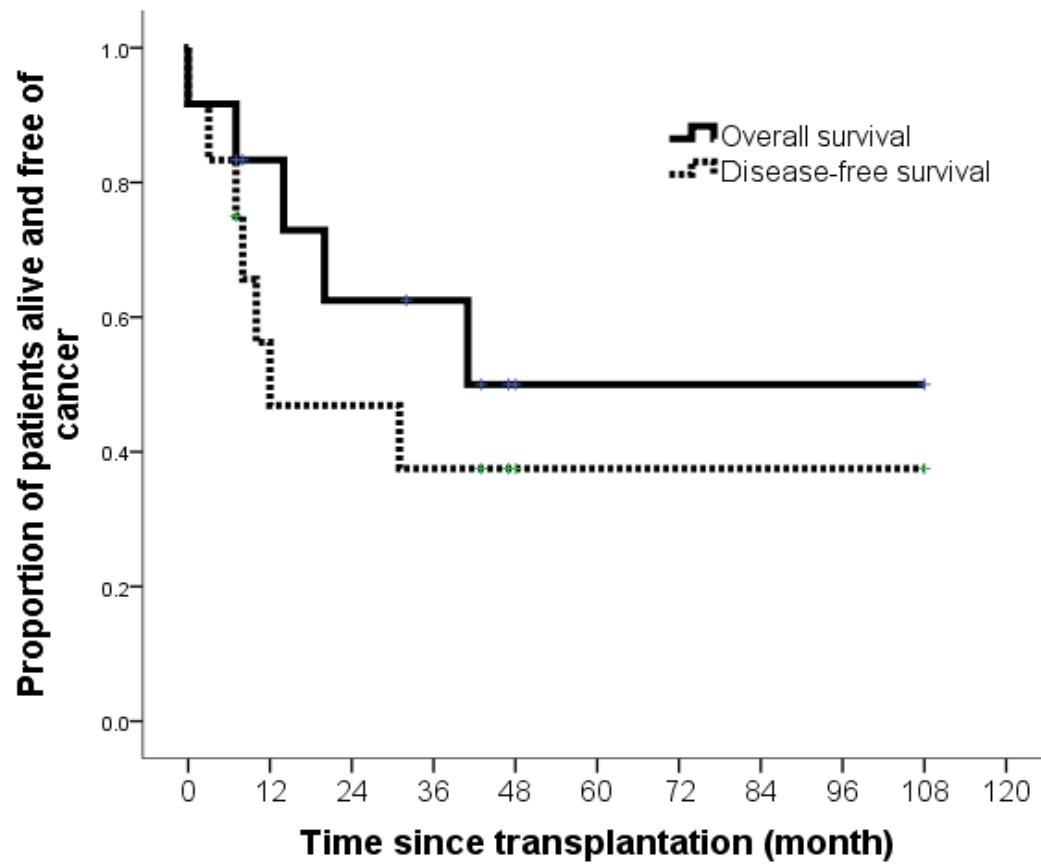
Patients (number)	12	
Median age (years, min-max)	56 (38-73)	
Gender	female:6/ male:6	
Location of primary cancer (%)		
colon	11 (92)	
rectum	1 (8)	
Pathological staging of primary cancer (%)		
T0*	1 (8)	
T2	1 (8)	
T3	8 (67)	
T4	2 (17)	
Node status of primary cancer (%)		
N0	5 (42)	
N1	5 (42)	
N2	2 (16)	

- Lisbon, n=8
- Coimbra, n=2
- Paris, n=1
- Geneva, n=1

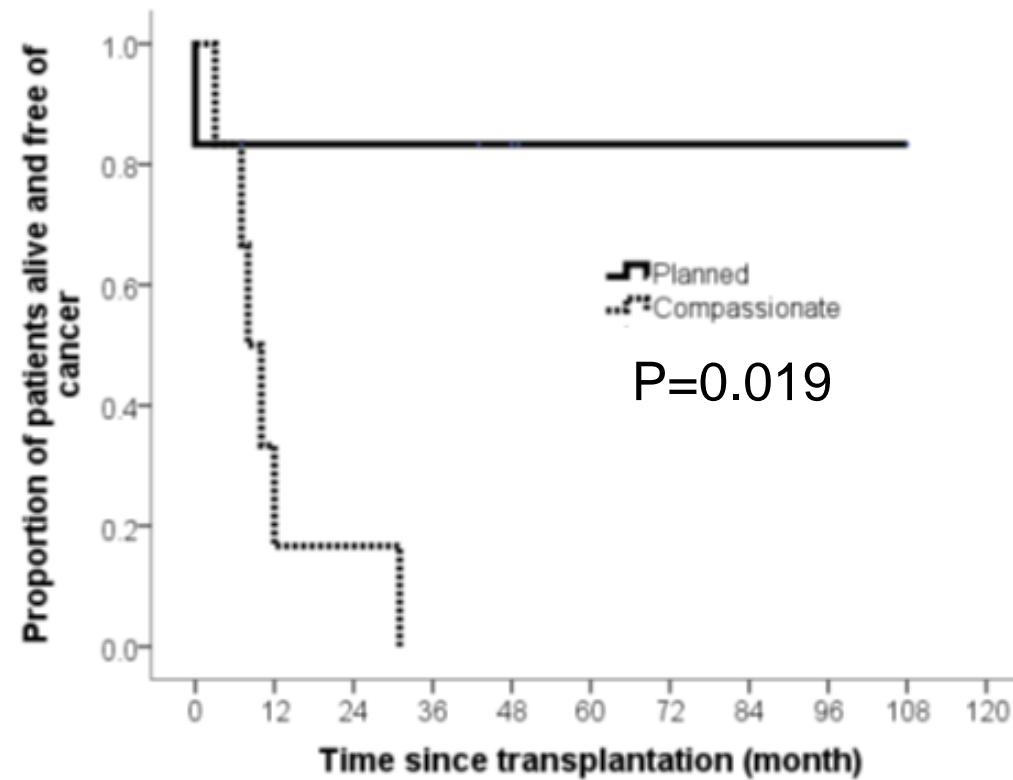
Peri-operative management

Median number of chemotherapy courses (min-max)	2 (0-4)	
Pre-transplant neo-adjuvant chemotherapy (%)	11 (92)	
Response to pre-transplant chemotherapy		
partial response	10	
stable diseases or progression	0	
Median number of liver resections (min-max)	1 (0-3)	

- Planned transplant in a long-term onco-surgical management, n=6
- Compassionate: up-front transplantations, n=2
- Compassionate: emergency transplantations, n=3
- Compassionate: IVC invasion discovered during transplant, n=1



5 patients alive and free of cancer 7, 43, 47, 48, and 108 months after transplantation

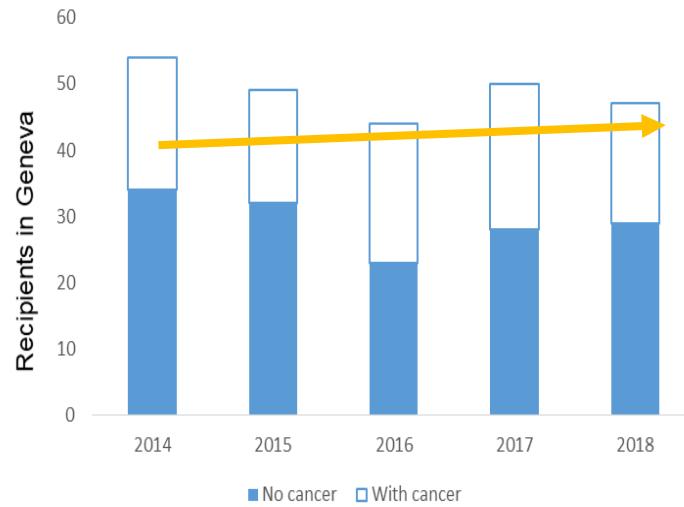
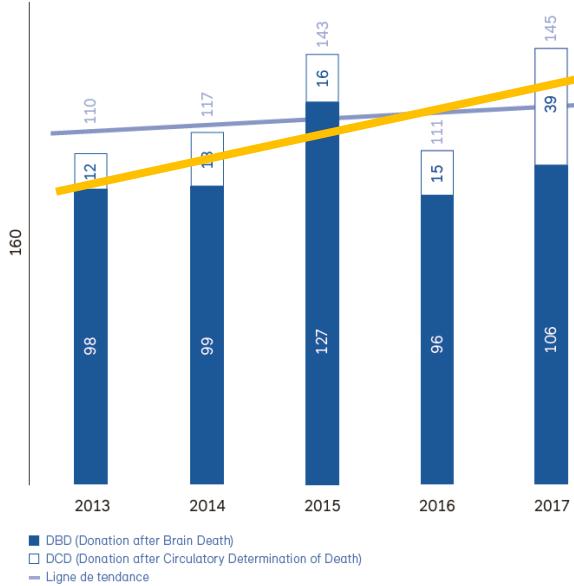


Key messages

CRLM:

- Disease-free survival can be achieved
- Favorable factors include a long time between diagnosis and transplant, a low CEA, and “planned” indication
- This indication should be further explored

The future of liver transplantation is bright! 😊



Thank you!

Prof. Ph. Compagnon

You for your excellent daily collaboration and for your attention today

