29º CONGRESO

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Palexco

TOP PAPERS EN TRASPLANTE HEPÁTICO

DORA GÓMEZ PASANTES

UNIDAD HBP Y TRASPLANTE HEPÁTICO HOSPITAL UNIVERSITARIO DE A CORUÑA

cancers

MDPI

Review

Liver Transplantation for Hepatic Metastases from Colorectal Cancer: Current Knowledge and Open Issues

Marianna Maspero [1,†], Carlo Sposito [1,2,†], Matteo Virdis [1], Davide Citterio [1], Filippo Pietrantonio [1], Sherrie Bhoori [1], Filiberto Belli [1] and Vincenzo Mazzaferro [1,2,*]

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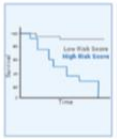
		Available evidence	Open Issues
	**Post-transplant survival**	Disease free-survival after LT seems to be comparable to progression-free survival after chemotherapy, however LT seems to offer better long-term survival to patients with unresectable CRLM than any available chemotherapeutic regimen.	• No randomized controlled trial on chemotherapy versus transplantation • No data on quality of life after LT versus "chronic" chemotherapy
	**Prognostic factors**	Some selection criteria for LT are now considered well-established. LT should be avoided in patients with • Progressive disease • Extrahepatic dissemination • BRAF mutation	Many potential prognostic factors and selection criteria have been identified through retrospective analyses, however those results may change with the emergence of prospective evidence and larger datasets.
	**Transplant vs resection**	Retrospective studies have identified LT as superior to LR in case of high tumor burdens requiring portal vein embolization.	Some patients with tumors that are technically resectable may benefit from LT. No comparison has been made between parenchymal-sparing resection and LT. The definition of resectability is not univocal.
	**Endpoints**	Recurrence-free survival may not be an appropriate endpoint. Recurrence is common after LT, however overall survival may be excellent also after recurrence.	Establishing appropriate trial endpoints is going to be crucial if CRLM become an established indication for LT. Overall survival and transplant benefit may be candidate endpoints.
	**Ethical considerations**	The current number of patients eligible to LT for CRLM is low and unlikely to have a substantial impact on a waiting list. Patients who have been on systemic chemotherapy for 1-2 years are likely to be stable enough to wait 3-4 months for LT without progressing and dropping out of the wailist. For now, prioritization should be tailored on the local situation.	• The number of eligible patients would dramatically increase if resectable patients were included • Whether LDLT is an acceptable option for this indication remains to be established • The RAPID procedure may be an option, however the risk of tumor diffusion between the two steps needs to be investigated
	**Medical management**	Patients should remain on maintenance chemotherapy while on the waiting list. Most trials involved an immunosuppressive switch to mTOR.	There is limited evidence of the effect of different immunosuppressive regimens on post-LT outcomes.
	**Treatment of recurrent disease**	Post-recurrence survival can be good in case of curative-intent treatment. Post-LT recurrences should be managed aggressively.	Treatment of post-LT recurrence should follow oncological principles.

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Objetivo: dar una visión integral de la evidencia disponible del trasplante hepático en las metástasis de CCR


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SUPERVIVENCIA DESPUÉS DE TRASPLANTE HEPÁTICO EN METÁSTASIS DE CCR

- Los resultados esperados a largo plazo pueden ser extrapolados de menos de 100 pacientes.

Compagnons Hépato-Biliaires group
n=12

Centros americanos n=21

Noruega
n=56
SECA I: OS 26.1% a 10 años (58 m)
SECA II: OS 83% a 5 años (36 m)

Donante cadáver
Donante vivo
Técnica RAPID
Técnica RAVAS

SUPERVIVENCIA DESPUÉS DE TRASPLANTE HEPÁTICO EN METÁSTASIS DE CCR

Resection and Partial Liver Segment 2/3 Transplantation With Delayed Total Hepatectomy					
NCT02215889	2014–2028	Norway	RAPID	- Unresectable CRLM - ≥8 weeks of CT	20
RAPID-Padova NCT04865471	2020–2025	Italy	RAPID	- Unresectable CRLM (validation committee) - BRAF wild type - At least 3 months of CT - At least 6 months from primary resection and listing - At least 8 weeks of tumor control - No extrahepatic disease or local recurrence	18

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FACTORES PRONÓSTICOS

	Currently Accepted	Currently Debated
Hepatic tumor burden	Unresectable disease	A trial testing the benefit of LT versus reseection in case of resectable CRLM is ongoing (SECA II Arm A, see Table 1). "Biologic non-resectable CRLM" can be considered for LT. Biologic non resectability can be inferred in: • Patients with resectable liver-only disease but high tumor burden (TBS >9) lacking pan-RAS mutations [survival benefit of LT over resection has been observed in retrospective reports] [36] • Patients candidate to advanced liver resection strategies considering remnant liver regenerative techniques with predicted mortality >10% (i.e., complex PVE, unfeasible second step of ALLPS); complex resections with liver inflow/outflow reconstructions [survival benefit of LT has been observed vs. PVE-associated resections in retrospective comparisons] [37] • Patients with resectable and repeatedly recurring liver-only metastases (lacking pan-RAS mutations) after ≥3 curative hepatectomies performed in experienced Centers Comparison of LT with parenchimal-sparing R1par vs. R1vasc resection of CRLM [38,39] needs to be investigated
	Synchronous and metachronous metastases	No current limitation/stratification are applied with respect to the time from primary tumor to CRLM detection
	No BRAF mutation	Some specific molecular mutations [40] may be associated with better prognosis and may not be contraindications to transplantation k-RAS mutations are debated and not considered as contraindication in some studies
Molecular characteristics	CEA < 80 ng/mL	Various CEA cutoffs at the time of transplant. No current limitations with respect to CEA level at the time of first referral
Biomarkers	Circulating cancer byproducts (liquid biopsy)	ctDNA monitoring is increasingly utilized for decision making in CRC patients [41,42]
	At least 1 year between resection of the primary and transplant	At least 2 years between resection of the primary and transplant
Timing	At least 1 year between resection of the primary and transplant	At least 2 years between resection of the primary and transplant

FACTORES PRONÓSTICOS

Factor	Evidence	Rational for Transplantation
Potential transplant benefit		
Tumor bunder score (TBS) > 9 [44] Increasing number and size of metastases [45]	A TBS > 9 has been associated with reduced OS Increasing number (HR 1.3, 1.1–1.6) and diameter (HR 1.1, 1–1.2) associated with reduced OS.	Recurrence in the presence of these factor is likely to be due to microscopic, undetectable disease left behind during resection. The complete hepatectomy performed during LT may reduce this recurrence risk by eliminating all intrahepatic disease.
Need for intraoperative ablation [46]	Associated with early recurrence, OR 1.6 (1.1–2.5)	
Surgical margin 0 mm [46]	Associated with early recurrence, OR 1.5 (1–2.2)	
R1 resection [47] †	Associated with early recurrence, HR 2.2 (1.2–4.2)	
Need for portal vein embolization [37,48]	Associated with reduced OS, HR 1.48 (1.09–1.98) In patients with high tumor load, median OS 19.2 months (95% CI, 0.0–39.5 months) after PVE vs. 40.5 months (95%CI, 26.3–54.7 months) after LT (p = 0.007)	
Initially unresectable disease [47]	Associated with early recurrence (HR 1.9, 1.02–3.7)	
More metastases detected intraoperatively [49]	Associated with reduced OS (HR 3.19, 1.28–7.97)	
Need for preoperative chemotherapy [45]	Associated with reduced OS, HR 1.7 (1.2–2.5)	

Factor	Evidence	Rational for Transplantation
Transplant benefit unlikely		
More than 1 preoperative chemotherapy line [48]	Associated with early recurrence, RR 1.6 (1.1–2.4)	Recurrence in the presence of these factors is likely to be due to aggressive biological characteristics, thus a liver transplant is unlikely to change the prognosis
Progression during last-line chemotherapy [48]	Associated with early recurrence, RR 2.18 (1.11–4.47)	
Higher CEA levels [47]	CEA > 30 ng/m associated with early recurrence, HR 2.3 (1.2–4.7)	
Higher CA 19-9 [48] levels	CA 19-9 levels > 60 U/mL associated with early recurrence, RR 2.21 (1.44–3.43).CA 19-9 levels > 100 U/mL associated with reduces OS, HR 1.86 (1.37–2.48)	
Primary tumor T stage > 2 [45,46]	Associated with reduced OS, HR 1.4 (1.1–2) Associated with early recurrence, OR 2.6 (1.4–4.8)	
Right-sided primary tumor [45]	Associated with reduced OS, HR 1.5 (1–2.1)	
Primary tumor lymphovascular invasion [47]	Associated with early recurrence, HR 2.5, 1.3–4.8	
Nodal positive primary [48]	Associated with reduced OS, HR 1.46 (1.13–1.89)	

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TRASPLANTE HEPÁTICO VS RESECCIÓN HEPÁTICA

Actualmente CRLM 1-2% TH
Enfermedad resecable→potenciales candidatos
Problemas:recursos limitados

CONSIDERACIONES ÉTICAS

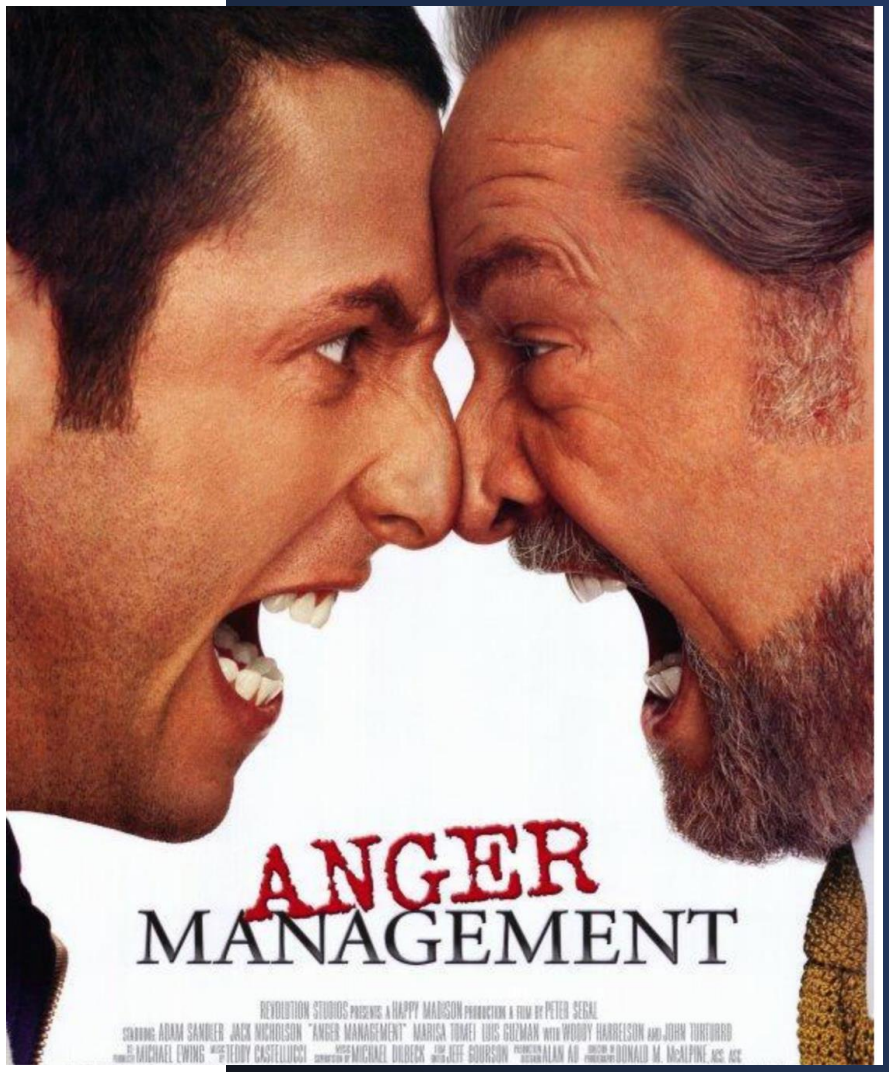
- 1-2% pacientes pacientes CRLM → 0.24-0.51 pacientes por millón habitantes/año.
- TH en pacientes resecables??

Similar a otras indicaciones de TH oncológico

- ColangioCa perihiliar tras neoady QTRDT
- HCC con tto local y respuesta parcial
- Dowstaging de HCC.

TRATAMIENTO DE LA RECIDIVA

- DFR 1 año: 53% SECA II, 56% Compagnons Hépato-Biliaires Study, 62% estudio norteamericano.
- No predice OS.
- SECA registry/RAPID study: 56 → 44 recurrencia → 56% intención curativa (OS a 5 años 51.3%).



Liver transplantation

JOURNAL
OF HEPATOLOGY

A multicenter randomized-controlled trial of hypothermic oxygenated perfusion (HOPE) for human liver grafts before transplantation

Andrea Schlegel[1,2], Matteo Mueller[1], Xavier Muller[1,3], Janina Eden[1], Rebecca Panconesi[4], Stefanie von Felten[5], Klaus Steigmiller[5], Richard X. Sousa Da Silva[1], Olivier de Rougemont[1], Jean-Yves Mabrut[3], Mickaël Lesurtel[3], Miriam Cortes Cerisuelo[6], Nigel D. Heaton[6], Marc Antoine Allard[7], Rene Adam[7], Diethard Monbaliu[8,9], Ina Jochmans[8,9], Martijn P.D. Haring[10], Robert J. Porte[10], Alessandro Parente[2], Paolo Muiesan[2,11], Philipp Kron[1,12], Magdy Attia[12], Dagmar Kollmann[13], Gabriela Berlakovich[13], Xavier Rogiers[14], Karin Petterson[1], Anne L. Kranich[15], Stefanie Amberg[15], Beat Müllhaupt[16], Pierre-Alain Clavien[1,†], Philipp Dutkowski[1,*,†]

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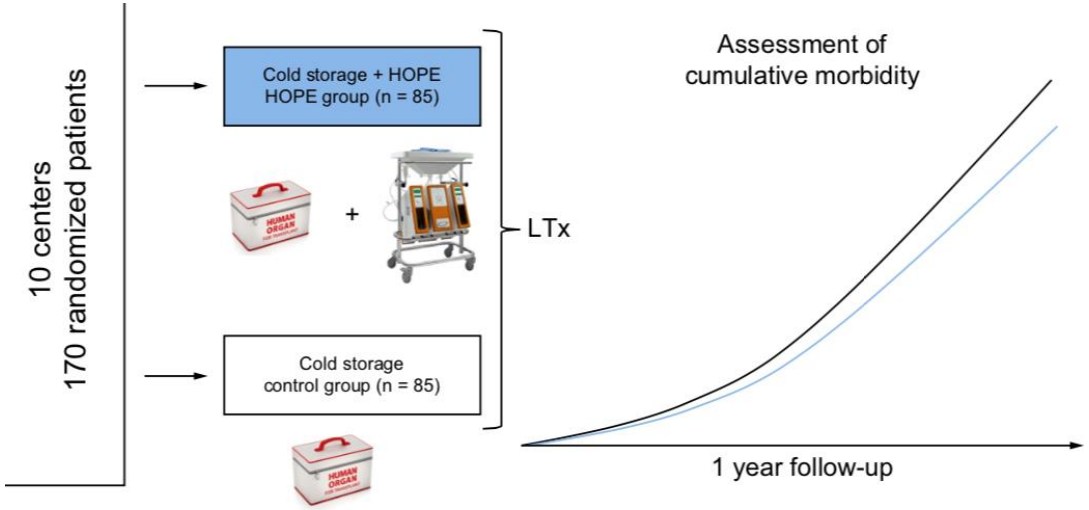
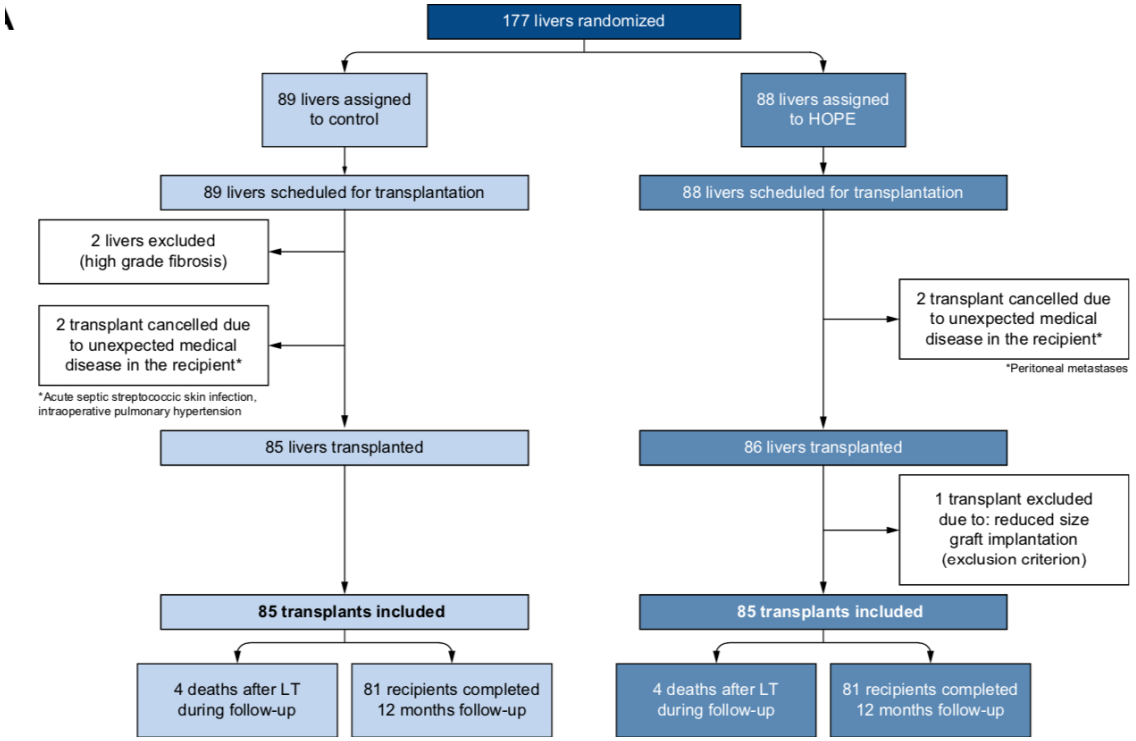
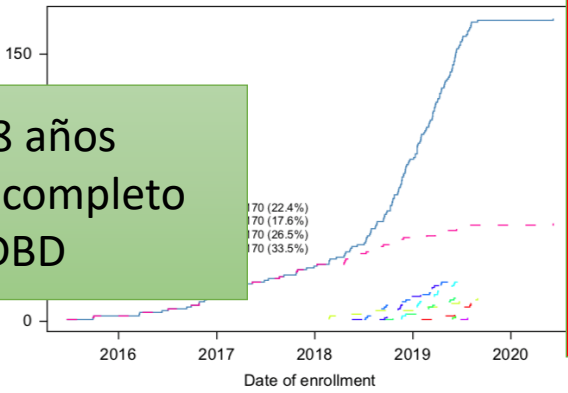




> 18 años
Injerto completo
DBD



< 18 años
Parcial o combinado
T isquemia fría > 15h
Contraindicación inesperada de Tx

PARÁMETROS HOPE

- Perfusión portal
- Flujo 150-300 ml/min
- Presión 3 mmHg
- Temperatura 8 ºC y 12 ºC
- Perfusato: 3 L Belzer MPS
- Oxigenación: 70-110 kPa
- Mínimo tiempo perfusión: 1 h.

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ENDPOINTS

- **PRINCIPAL:**

  ≥ 1 complicación mayor → Clavien Score ≥ III por paciente 1º año postTH.

- **SECUNDARIOS:**

  * *Comprehensive complication index (CCI)*

  * Datos laboratorio (AST, ALT,BRB,FA,GGT, INR, Factor V)

  * Complicaciones biliares

  * Tiempo de estancia en UCI (ICU)

  * Tiempo de estancia hospitalaria

  * Supervivencia del injerto y del receptor al año

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RESULTADOS ANALIZADOS POST HOC

Varios pacientes > 1 complicación mayor en el 1er año postTH.

Post hoc: nº complicaciones por paciente

Clavien scrore final controlado por dos clínicos independientes ciegos

Recipient-related complications: opportunistic infections, myocardial infarction, lung embolism, lung infections, hypertension, gastric ulcer, colitis, ileus, diabetes, diarrhea, pyelonephritis, seizures, cerebral ischemia, cerebral bleeding, mesenteric ischemia, ascites (without the need to drain), incarcerated umbilical or inguinal hernias (with the need for surgical repair), accidental traumas, recurrence of hepatocellular carcinoma, secondary cancer.

Liver graft-related complications: primary non-function, biliary necrosis, biliary strictures (anastomotic and non-anastomotic), bile leaks, hepatic artery thrombosis, hepatic artery stenosis, hepatic artery aneurysms, portal vein thrombosis, hepatic vein thrombosis, acute biopsy proven liver rejection, cholangitis, cholangiosepsis, hepatic encephalopathy, elevated liver enzymes (three-fold over normal values), cholestasis, ascites (with the need for drainage).

Transplant procedure-related complications: post-transplant hematoma in the first week (with the need for lavage), intermittent kidney failure (with the need for renal replacement therapy), wound infections (with the need for wound opening), elective incisional hernias (transplant incision).

PACIENTES

177 pacientes (abril 2015-Agosto 2019)

Excluídos
CONTROL 4
HOPE 3

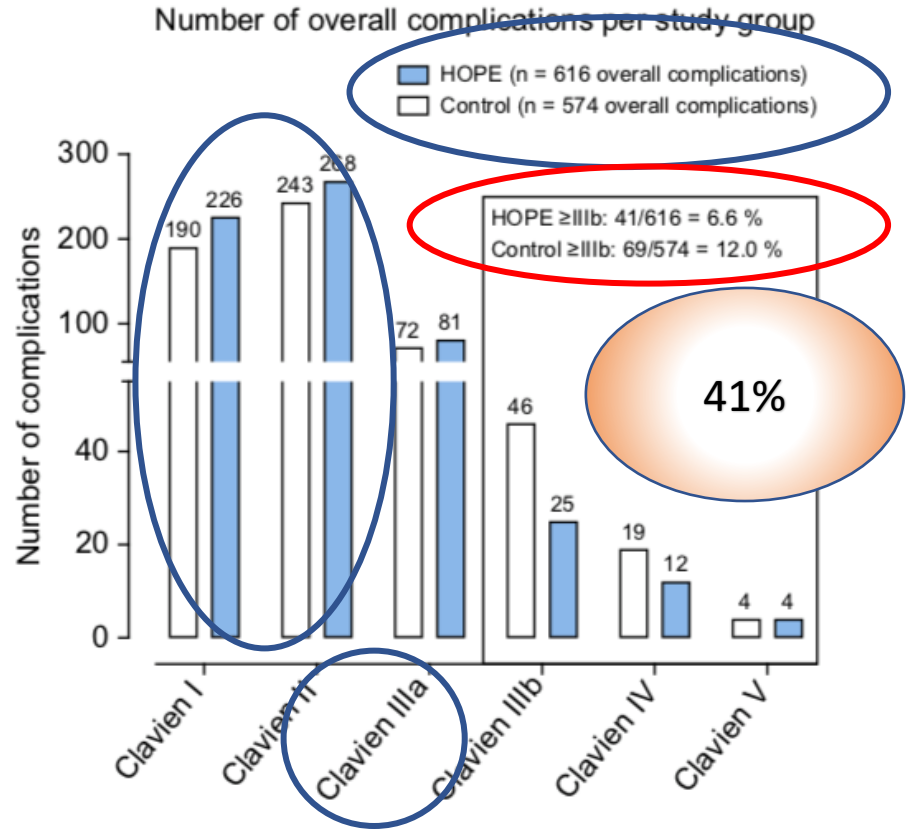
170 pacientes

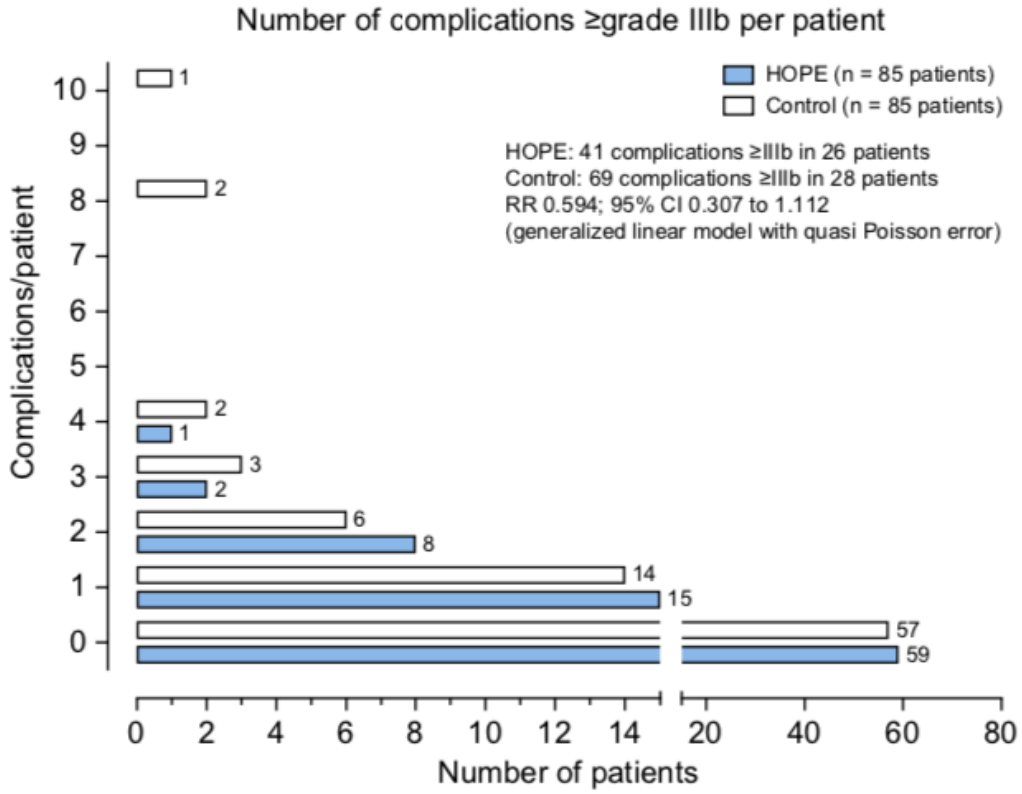
Variable	Overall	Control	HOPE	Missing (%)
N	170	85	85	
Before randomization				
Donor age, years	60.5 (47.0–72.0)	62.0 (44.0–71.0)	59.0 (48.0–72.0)	0
Donor sex, female	82 (48.5)	42 (50.0)	40 (47.1)	0.6
Donor height, m – mean (SD)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.2
Donor weight, kg – mean (SD)	76.3 (15.8)	77.8 (16.9)	74.9 (14.5)	1.2
Donor cause of death				6.5
Cerebral hemorrhage	73 (45.9)	39 (48.8)	34 (43.0)	
Cerebral trauma	37 (23.3)	18 (22.5)	19 (24.1)	
Anoxia	23 (14.5)	12 (15.0)	11 (13.9)	
Cerebral disease	1 (0.6)	0	1 (1.3)	
Suicide	4 (2.5)	3 (3.8)	1 (1.3)	
Other	21 (13.2)	8 (10.0)	13 (16.5)	
After randomization				
Preservation solution				0.6
Histidin-Tryptophan-Ketoglutarat (HTK)	4 (2.4)	1 (1.2)	3 (3.6)	
University of Wisconsin (UW)	53 (31.4)	27 (31.8)	26 (31.0)	
Institute George Lopez (IGL)-1	112 (66.3)	57 (67.1)	55 (65.5)	
Duration of cold storage, min	393.0 (320.0–482.0)	427.0 (356.0–487.0)	373.0 (299.2–471.8)	7.6
Duration of HOPE, min	95.5 (73.0–137.0)	—	95.5 (73.0–137.0)	57.6
Duration of total preservation time, min	451.0 (371.0–552.5)	427.0 (356.0–487.0)	474.0 (403.5–588.0)	13.5
Liver weight, g – mean (SD)	1517.0 (591.8)	1,583.0 (759.0)	1,457.3 (378.6)	17.1
AST HOPE perfusate, U/L		—	117.6 (60.0- 266.9)	76.1
ALT HOPE perfusate, U/L		—	177.1 (75.0-467.0)	76.1

Variable	Overall	Control	HOPE	Missing (%)
n	**170**	**85**	**85**	
Recipient age, years	59.0 (50.2–64.0)	57.0 (49.0–64.0)	60.0 (51.0–64.0)	0
Recipient sex, female	48 (28.2)	18 (21.2)	30 (35.3)	0
Underlying disease				0
Acute liver failure	1 (0.6)	1 (1.2)	0 (0)	
Cirrhosis Child-Pugh A	49 (28.8)	23 (27.1)	26 (30.6)	
Cirrhosis Child-Pugh B,C	93 (54.7)	50 (58.8)	43 (50.6)	
Other	27 (15.9)	11 (12.9)	16 (18.8)	
Laboratory MELD	20.0 (11.0–27.0)	19.0 (12.0–26.0)	20.0 (11.0–28.0)	0
Treatment before liver transplant				0
TACE, RFA	41 (24.1)	21 (24.7)	20 (23.5)	
TIPS	10 (5.9)	5 (5.9)	5 (5.9)	
Conservative	38 (22.4)	23 (27.1)	15 (17.6)	
No treatment	61 (35.9)	34 (40.0)	27 (31.8)	
Other	20 (11.8)	2 (2.4)	18 (21.2)	
Previous liver transplant	7 (4.1)	2 (2.4)	5 (5.9)	0
Transplant center				0
Birmingham	12 (7.1)	7 (8.2)	5 (5.9)	
Ghent	1 (0.6)	0 (0)	1 (1.2)	
Groningen	13 (7.6)	7 (8.2)	6 (7.1)	
Leeds	3 (1.8)	2 (2.4)	1 (1.2)	
Leuven	16 (9.4)	8 (9.4)	8 (9.4)	
London	23 (13.5)	11 (12.9)	12 (14.1)	
Lyon	24 (14.1)	12 (14.1)	12 (14.1)	
Paris	21 (12.4)	11 (12.9)	10 (11.8)	
Vienna	2 (1.2)	1 (1.2)	1 (1.2)	
Zürich	55 (32.4)	26 (30.6)	29 (34.1)	

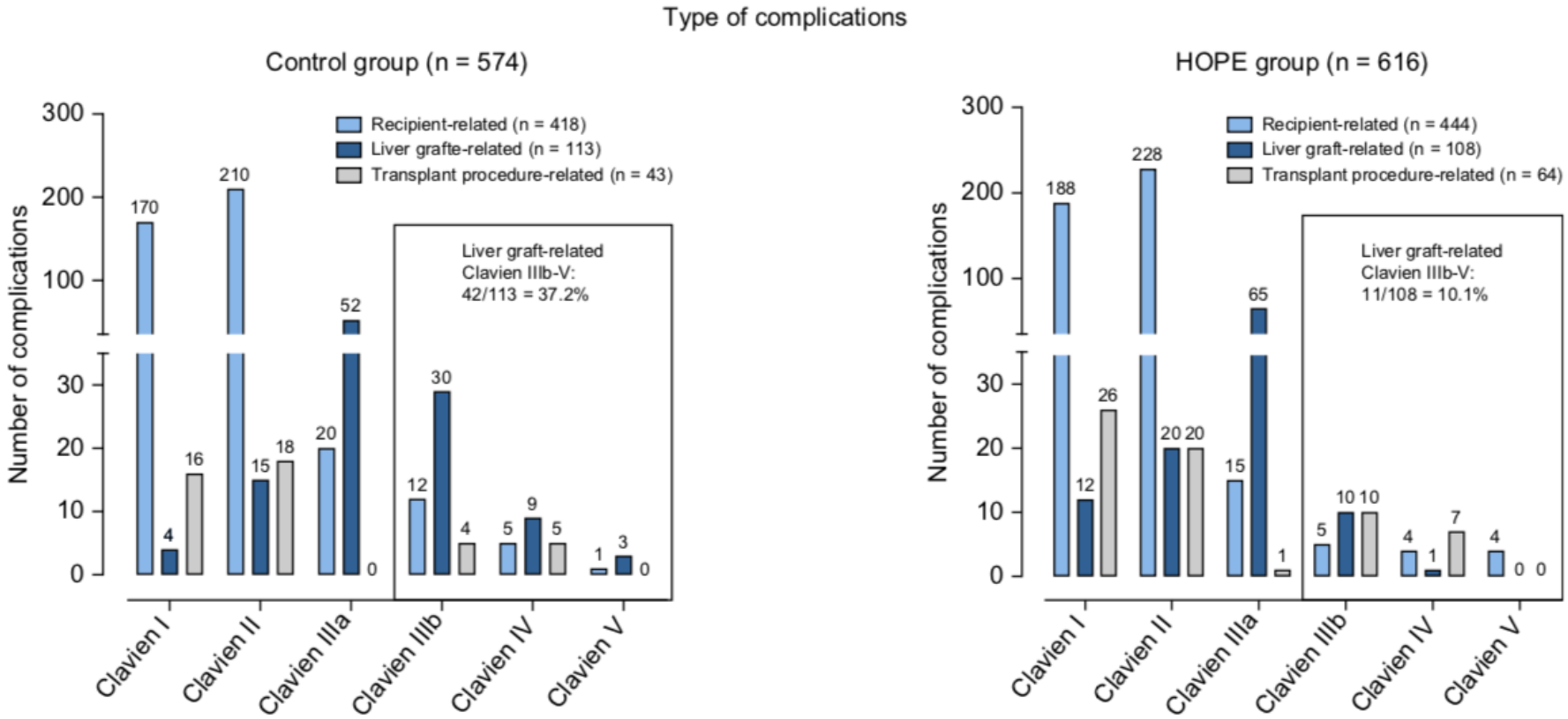
VARIABLE PRINCIPAL: COMPLICACIONES

1.190 complicaciones
Clavien ≥ IIIa
54.1% (46/85) Control
51.8% (44/85 HOPE)





VARIABLE PRINCIPAL: COMPLICACIONES



VARIABLES SECUNDARIAS

Table 3. Pre-specified secondary endpoints (recipient outcome within 12 months after LT) and additional outcome parameters.

Variable	Overall	Control	HOPE	*p* value	Effect size (95% CI)	Missing (%)
N	170	85	85			
CCI 12, months	49.4 (29.6–64.4)	49.5 (29.6–64.5)	49.4 (33.2–63.9)	0.89‡	MD 0.685–7.202 to 8.338)‡	0
Peak AST, U/L	825 (430–1,705)	896 (409–2,478)	803 (435–1,303)			0
AST AUC, U/L – day 1-7	1,147 (687–2,171)	1,147 (683–2,752)	1,149 (693–1,856)	0.25*	MD -0.157 (–0.42 to 0.11)*	1.8
Peak ALT, U/L	654 (365–1,188)	695 (379–1,575)	636 (341–1,055)			0
ALT AUC, U/L – day 1-7	2,022 (1,242–3,750)	1,978 (1,232–4,128)	2,048 (1,252–3,475)	0.49*	MD -0.089 (–0.34 to 0.16)*	0
INR AUC, day 1-7	7.1 (6.6–7.8)	7.1 (6.5–8.1)	7.1 (6.6–7.8)			0
Bilirubin AUC, µmol/L – day 1-7	199 (103–438)	202 (95–542)	200 (119–381)			11.2
GGT AUC, U/L – day 1-7	1,653 (806–2,615)	1,774 (761–2,621)	1,531 (918–2,610)			11.8
AP AUC, U/L – day 1-7	846 (622–1,320)	874 (637–1,255)	803 (619–1,323)			0.6
Hospital stay, days	15 (13.0–25.0)	15 (13.0,25.0)	17 (12.0–24.5)	0.79#	HR 0.958 (0.70 to 1.30)#	1.8
ICU stay, days	3.0 (2.0–5.0)	3.0 (2.0–6.0)	3.0 (2.0–5.0)	0.75#	HR 1.051 (0.77 to 1.43)#	0
Any biliary complication	34 (20.0)	19 (22.4)	15 (17.6)	0.44§	OR 0.744 (0.35 to 1.58)§	0
Overall graft loss in 1 year	11 (6.5)	7 (8.2)	4 (4.7)	0.36§	OR 0.550 (0.140 to 1.896)§	0
Recipient death in 1 year	8 (4.7)	4 (4.7)	4 (4.8)	1.00§	OR 1.000 (0.229 to 4.359)§	0
Additional outcome parameters after LT						
Duration of transplantation, min	380 (295–477)	384 (302–464)	371 (284–480)			3.5
Anastomotic biliary complications	32 (19.0)	18 (21.2)	14 (16.5)			0
Non-anastomotic biliary complications (NAS)	4 (2.4)	3 (3.5)	1 (1.2)##			0
Early allograft dysfunction**	53 (31.2)	39 (45.9)	14 (16.5)			0
Hepatic artery thrombosis	2 (1.2)	0	2 (2.4)			0
Hepatic artery stenosis	3 (1.8)	2 (2.4)	1 (1.2)			0
Liver-related graft loss due to:	6 (3.5)	6 (7.1)	0	0.004		0
Primary non function	3 (1.8)	3 (3.5)	0	0.015†		0
NAS	3 (1.8)	3 (3.5)	0			0
Recipient-related graft loss	5 (2.9)	1 (1.2)	4 (4.7)	0.223‡‡	HR 3.90 (0.44 to 34.90)‡‡	0
Primary tumor recurrence	1 (0.6)	0	1 (1.2)			0
Secondary tumor growth	3 (1.8)	1 (1.2)	2 (2.4)			0
Opportunistic infection	1 (0.6)	0	1 (1.2)			0
Retransplantation	3 (1.8)	3 (3.5)	0			0
CCI 3 month	41.8 (23.0–52.6)	42.4 (22.6–52.7)	41.8 (24.2–52.6)			0
CCI 6 month	46.0 (27.3–58.8)	42.4 (22.6–52.7)	46.8 (29.8–60.1)			0
CCI 9 month	48.3 (29.6–63.2)	48.2 (29.6–59.9)	48.9 (29.8–63.7)			0

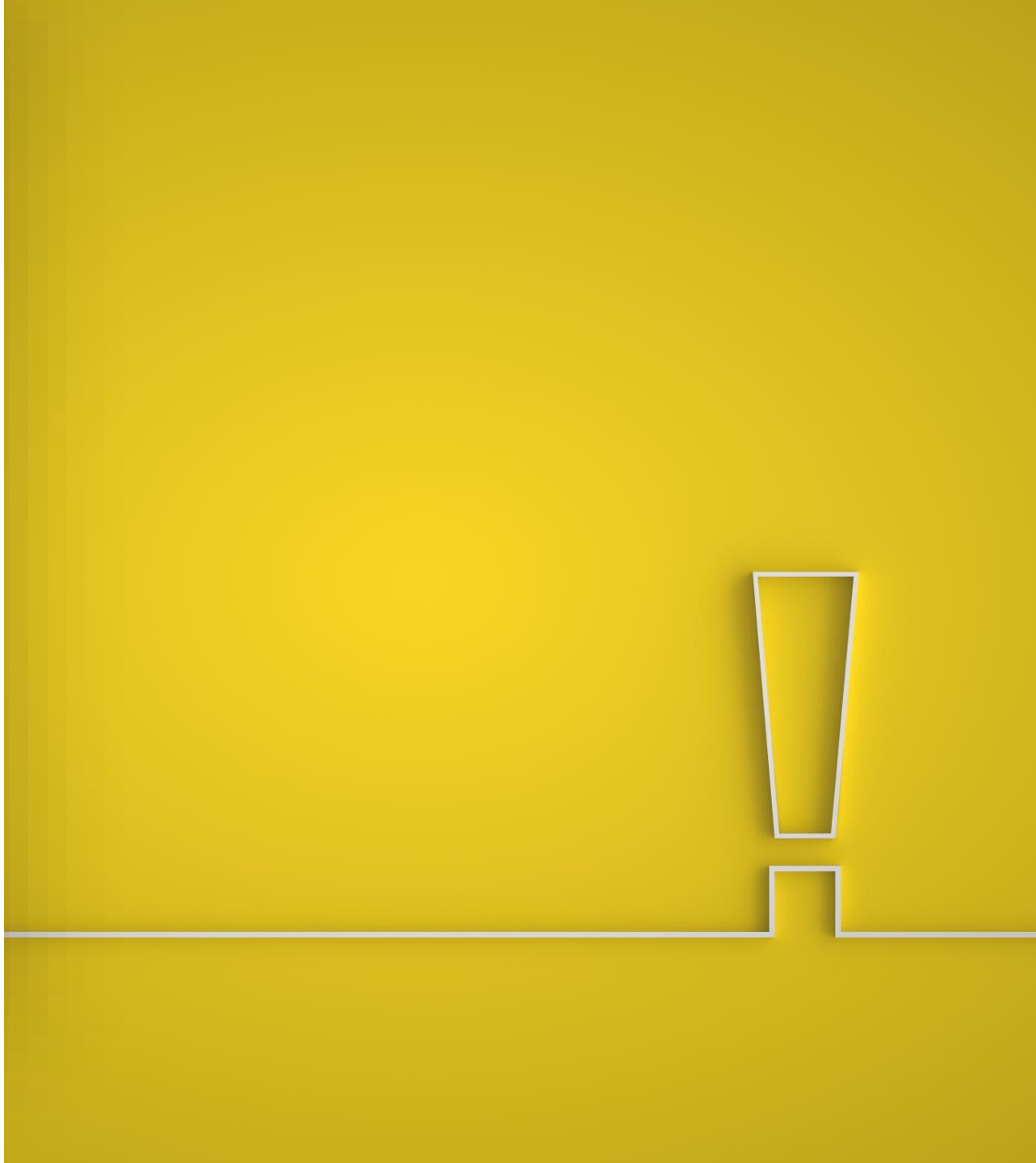
En análisis inicial
NO diferencias
estadísticamente
significativas

Análisis *post hoc CCI* 30.6
HOPE frente a 3.6 control

0 fallo injerto → HOPE
6 fallos injerto → Control

CONCLUSIONES DEL AUTOR

- HOPE es una técnica de perfusión sencilla y rápida que permite reducir las complicaciones graves relacionadas con el injerto en el primer año postTH.
- Necesitan más estudios para confirmar el importante potencial efecto clínico de HOPE en las complicaciones tras la cirugía.
- Parámetros analíticos, estancia hospitalaria,… podrían ser insuficientes para valorar la morbilidad relacionada con el injerto tras el TH.

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