MÁSTER EN HEPATOLOGÍA

ORGANIZA:

UAM UNIVERSIDAD AUTONOMA DE MADRID

Universidad de Alcalá

Asignatura: Oportunidades en Hepatología

“Poliquistosis hepática”

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Caso clínico #1

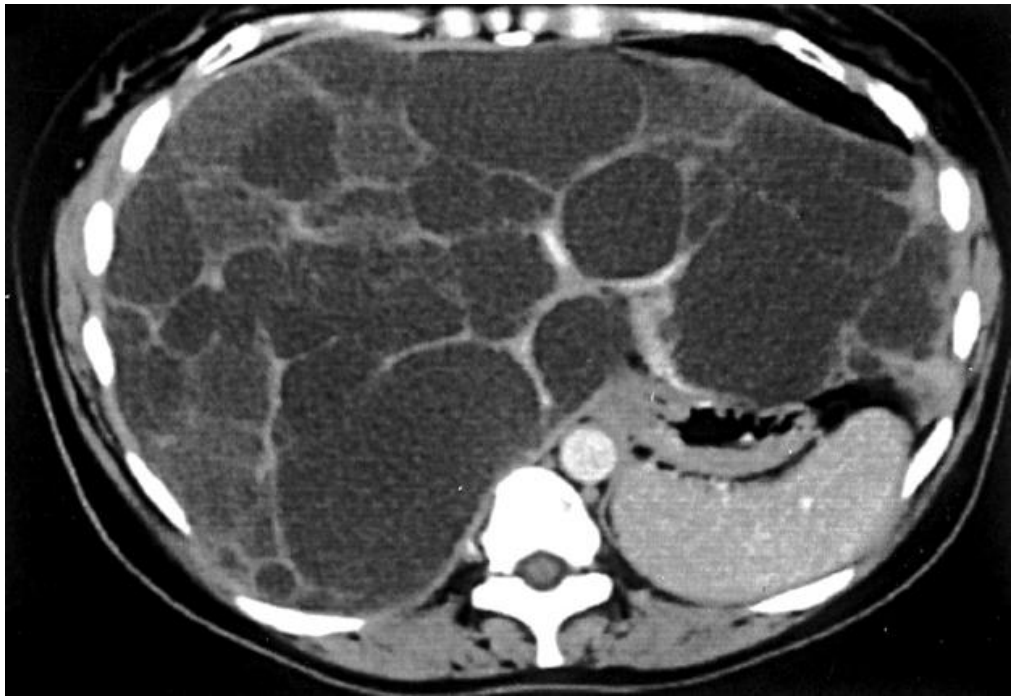
1999 34 años, aumento perímetro abdominal
TAC: múltiples quistes hepáticos y menos renales
no HTA

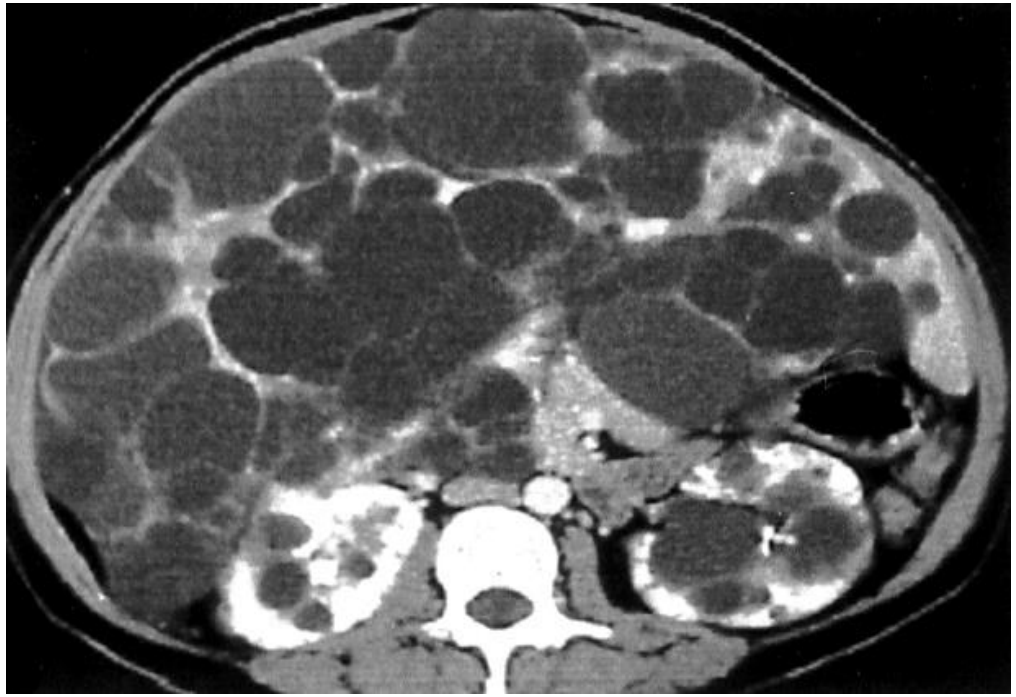
2004 Everolimus durante 1 año sin respuesta

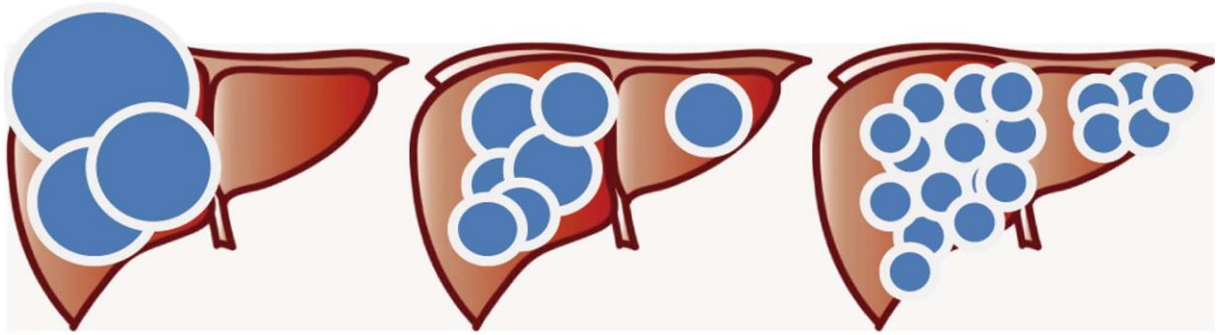
2009 46 años, trasplante hepático por deterioro calidad vida, malnutrición
creat 0.9 mg/dl, albúmina 3.7 g/dl, bili 0.8 mg/dl, GGT 69 UI/ml, FAL 103 UI/ml, INR 1

2009 **Trasplante hepático**
Cirugía: desgarro VCI hasta AD, anastomosis VCI del injerto con AD
con ligadura VCI del paciente. Injerto 82 años, isquemia fría 10 h
ACVA parietal derecho en postoperatorio por shunt D-I
Alta a los 15 días
Inmunosupresión con tacrolimus y MMF

46 años, PLD grave, desplazamiento VCI,
enfermedad renal quística leve







Gigot criteria (I-III)

- number and size of the liver cysts
- amount of remaining liver parenchyma
- candidates for fenestration

Gigot I, not PLD (<10 quistes)

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Caso clínico #1

2017 Hepatología:
FS F4, 17 kPa
Endoscopia oral: varices esofágicas grandes
GPVH 21 mmHg, presión VCI 7 mmHg, no BHT por angulación
Ascitis moderada

Nefrología: ERC estadio 5: poliquistosis, ICN
creat 9.8 mg/dl, hemodiálisis

2020 Riesgo inaceptable retrasplante hepático
albúmina 3.1 g/dl, bili 2.3 mg/dl, INR 1.3
Hemodiálisis 3 veces/sem

Polycystic liver disease (PLD)

	ADPLD	ADPKD
Prevalencia	0.01% ~1:100 000	**0.2%** ~1:500-1000
Herencia	AD	AD
Mutaciones	PRKCSH SEC63	PKD1 90% PKD2 10%
Producto codificado	Hepatocistina Mutación SEC-63 (25-40%) ~50% sin PRKCSH/SEC63 Con mutaciones: más grave	Poliquistina-1 (90%) (más grave) Poliquistina-2 (10%) Fenotipo heterogéneo
Fenotipo	**Quistes hepáticos múltiples** (→ ± renales)	**Quistes renales múltiples** (→ ± hígado 80%) **y** anomalías vasculares

Natural history and symptoms

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Natural history of liver cysts

Progressive growing

Prevalence increases with age:

58% at 15-24 yr, **85%** at 25-34 yr, **95%** at 35-46 yr

Growth rate of polycystic livers: 0.9-1.6% in 6-12 m

Severity of liver disease: ADP**L**D with mutations > ADP**L**D > ADP**K**D

Symptoms

80-95% of symptomatic patients and LT ♀, mean age 50 yr

Majority of patients are asymptomatic

Hepatomegaly and symptoms related with liver size

Risk factors for liver cyst growth

- Advancing patient age
- Female gender
- Estrogen exposure: pregnancies, OCPs, estrogen replacement therapy (also in postmenopausal women)
- Severity of renal dysfunction and renal cyst volume

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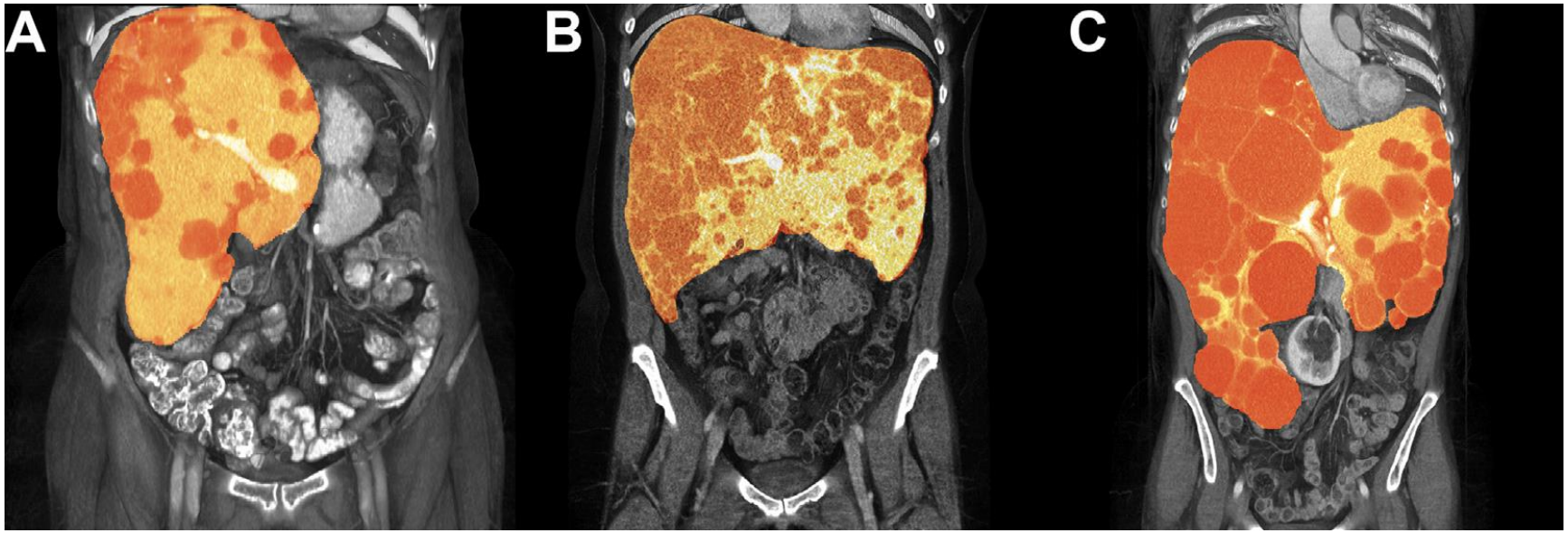
Mild, moderate and severe phenotypes of PLD

htTLV, **height-adjusted total liver volume**

Mild	**Moderate**	**Severe**
<1600 ml/m	1600 - 3200 ml/m	>3200 ml/m



Normal liver volume 1,300 - 1,700 ml

Natural history and symptoms

Complications (rare)

- Cyst infection (punción, In-111 WBC or 67-Gallium scan, PET)
- Cyst bleeding
- Cyst rupture
- Portal hypertension, mostly due to HVOO
- Obstructive jaundice extremely rare

Associated diseases in ADP**K**D (ADPLD?), **systemic disease**

- Pancreatic cysts (10%)

- Arachnoid cysts
- Intracranial aneurysms, 16% and 6% with or w/o family history
  Screening: >30 yr, symptoms, family history (aneurysms, stroke),
  LTx/KTx candidate

- Valvular disease: mitral valve prolapse (25%), aortic regurgitation (10%)
- Arterial hypertension, 70%, <u>even before</u> KD (ADKPD)
- Left ventricular hypertrophy

- <u>NOT</u> increased risk of malignancy

Hepatic venous outflow obstruction in polycystic liver disease

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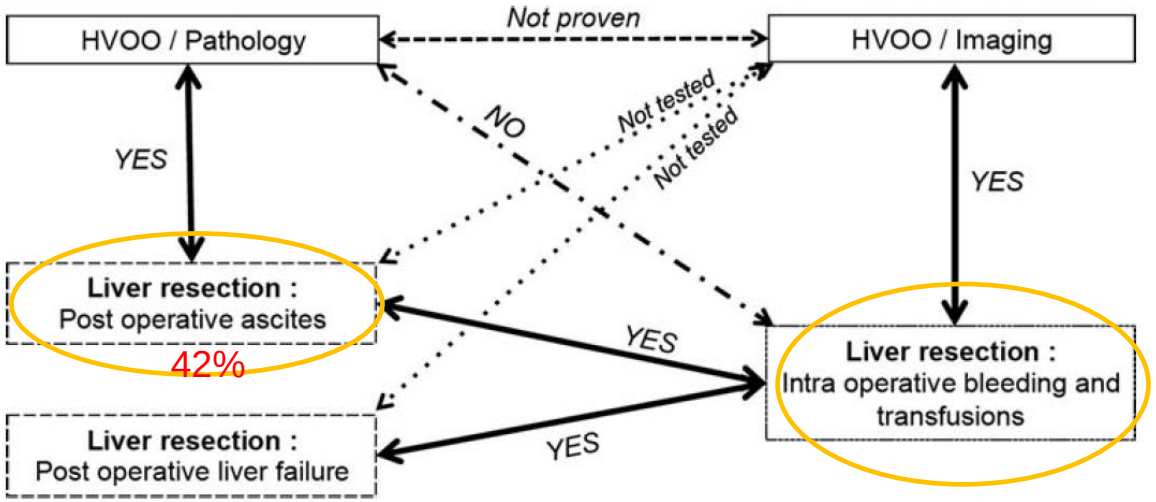
Retrospective study of **125 patients with ADPLD**
90 resection, 35 LT

Histology (n=125)	Imaging TC (n=45)
92% lesions of HVOO (47% sinusoidal dilatation) **Fibrosis 57%** (advanced 13%)	100% stenosis/obstruction 2 HV 87% 3 HV affected 84% intrahepatic collaterals



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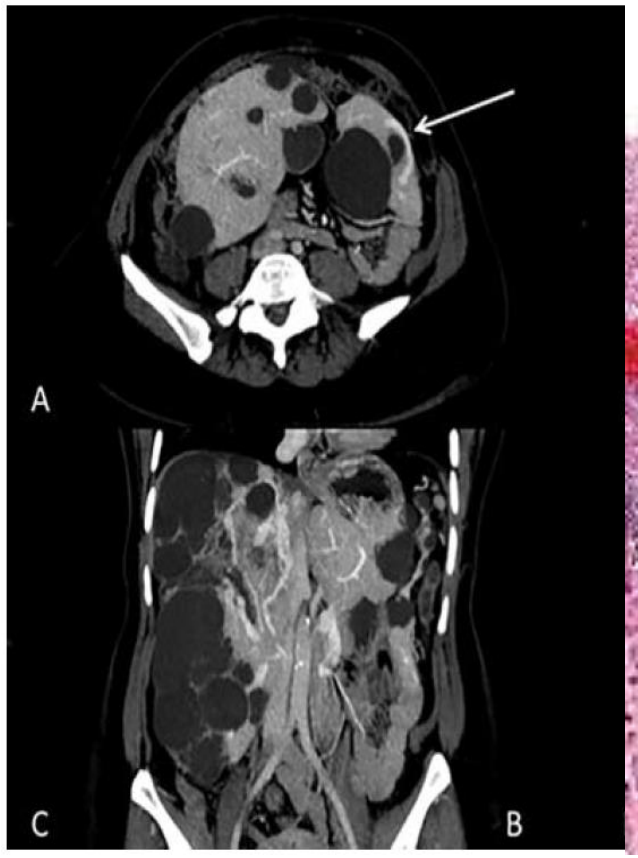
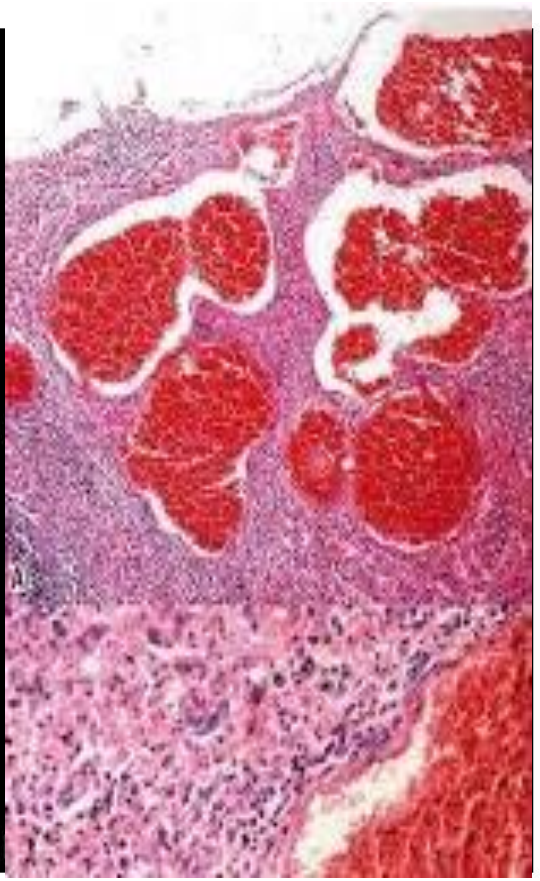
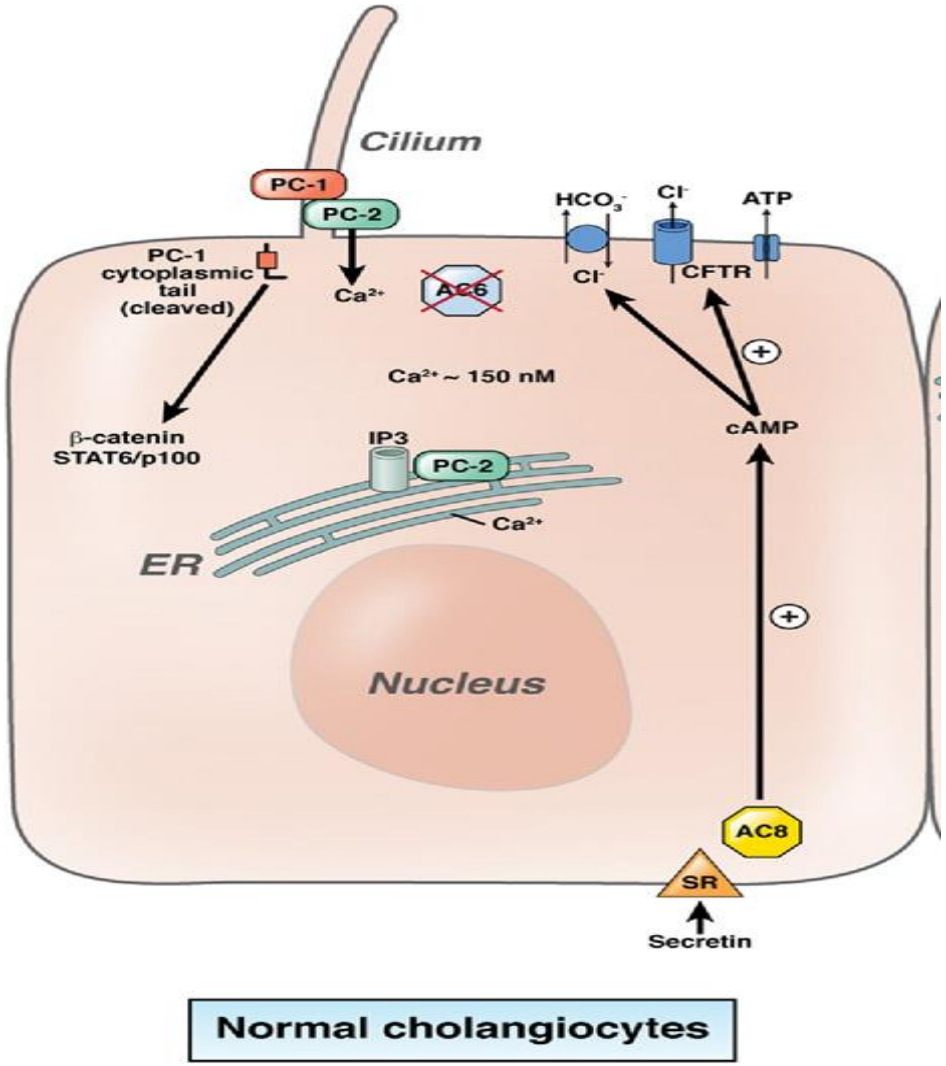
HVOO lesions: sinusoidal dilatation, congestion, peliosis, nodular regenerative hyperplasia





Barbier L et al. Hepatology 2018

Signalling in normal and cyst cholangiocytes

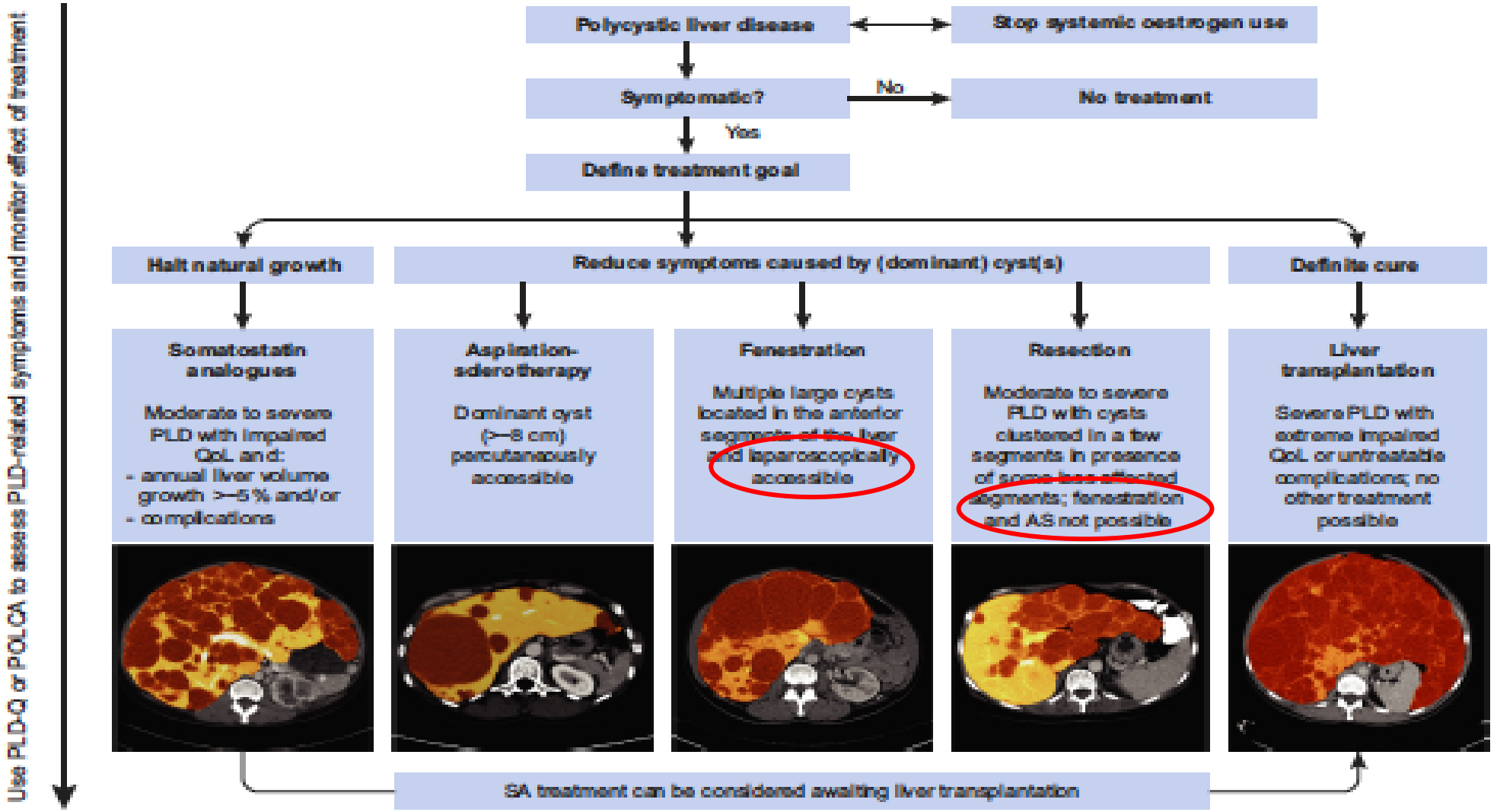


Phenotypic changes in cyst cholagiocytes

- Less differentiated phenotype
- ↑ cAMP levels (drive fluid secretion and proliferation)
- ↑ proliferation/apoptosis
- ↑VEGF and VEGFR2 expression
- ↑ cytokines and chemokines expression
- ↓ cytoplasmic [Ca^{2+}]
- ↑ expression of mTOR, pERK1/2
- Changes in ER functions

M Strazzabosco et al. Gastroenterology 2011

Treatment algorithm for polycystic liver disease



R van Aerts et al. *JHEP 2018*

Young women with Polycystic Liver Disease respond better to somatostatin analogues: A Pooled Analysis of Individual Patient Data

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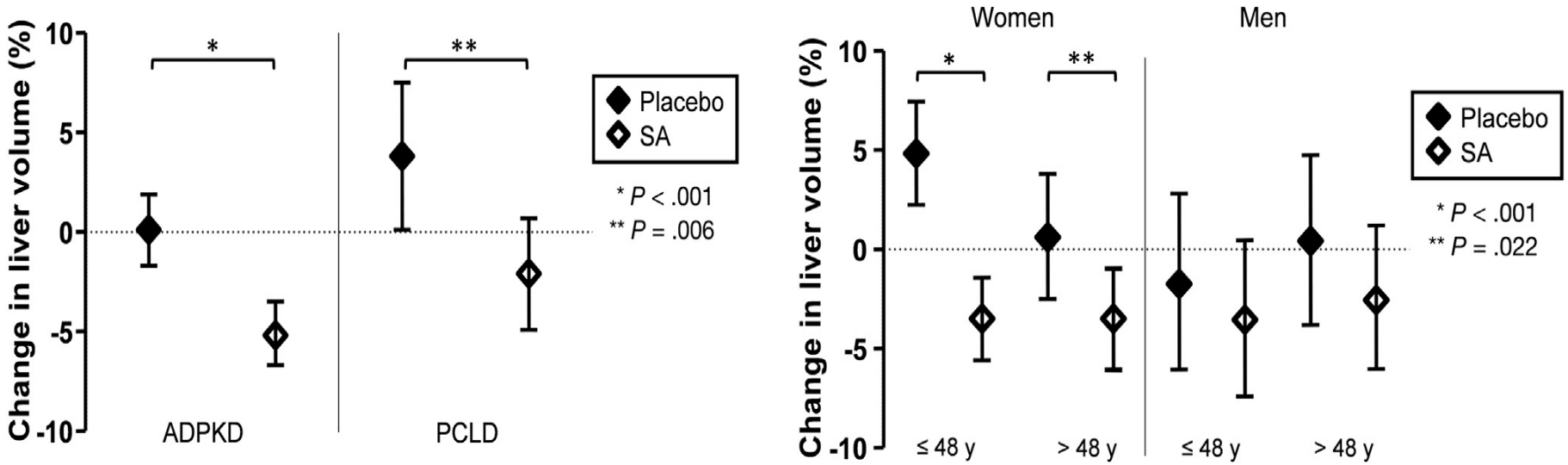
Primary outcome: change in liver volume after 6-12 m

Lanreotide 120 mg/4 wks sc / **Octreotide** 40 mg/4 wks sc / **Placebo**



- Heterogeneity in response: <u>15% non-response</u>
- Underlying diagnosis**: little influence**
- **Young women** (<48 yr) largest increase in liver volume, best response
- Ineffective in men, modestly effective in older women
- ~~Treatment beyond 24 m little benefit. Once stopped, liver volume rebounds~~
- ~~No effect on kidney volume~~
- **Target population:** women with <u>extensive</u> PLD and symptoms

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TG Gevers et al. Gastroenterology 2013

Lanreotide reduces liver growth in patients with autosomal dominant polycystic liver and kidney disease

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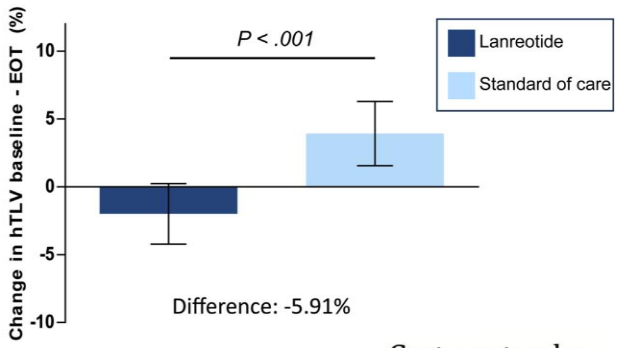
A 120-week randomized clinical trial

Autosomal Dominant Polycystic Kidney and Liver Disease patients with liver volume ≥ 2000mL

Lanreotide 120 mg sc every 28 days

Standard of care

Primary outcome
% change in height adjusted total liver volume (hTLV) from baseline to end of treatment (EOT)



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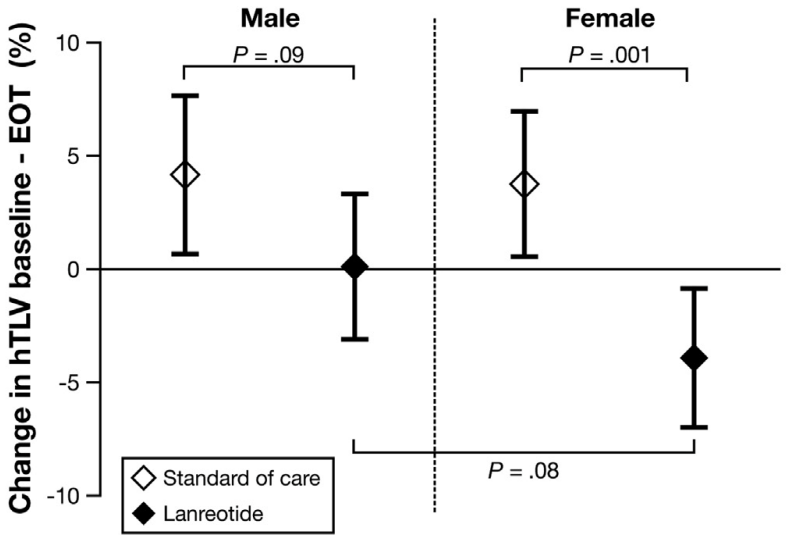
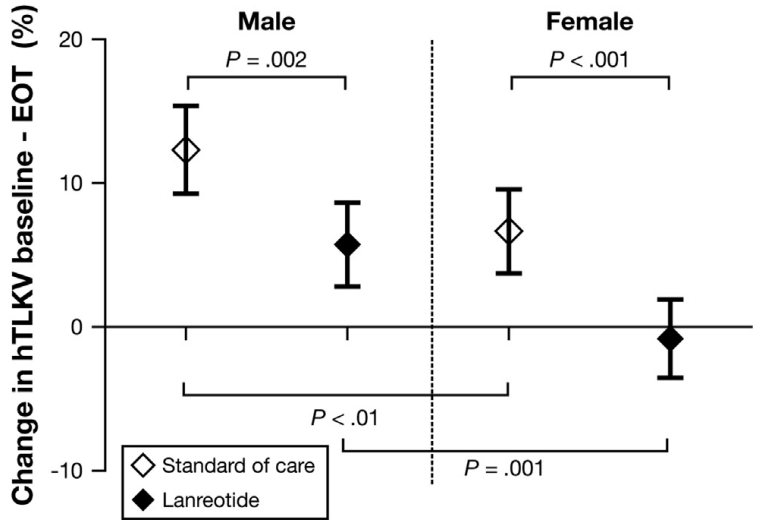
hTLV at the end of treatment



hTLKV at the end of treatment



hTLV still reduced by 3.87% at 4 months after last injection of lanreotide (P .04)

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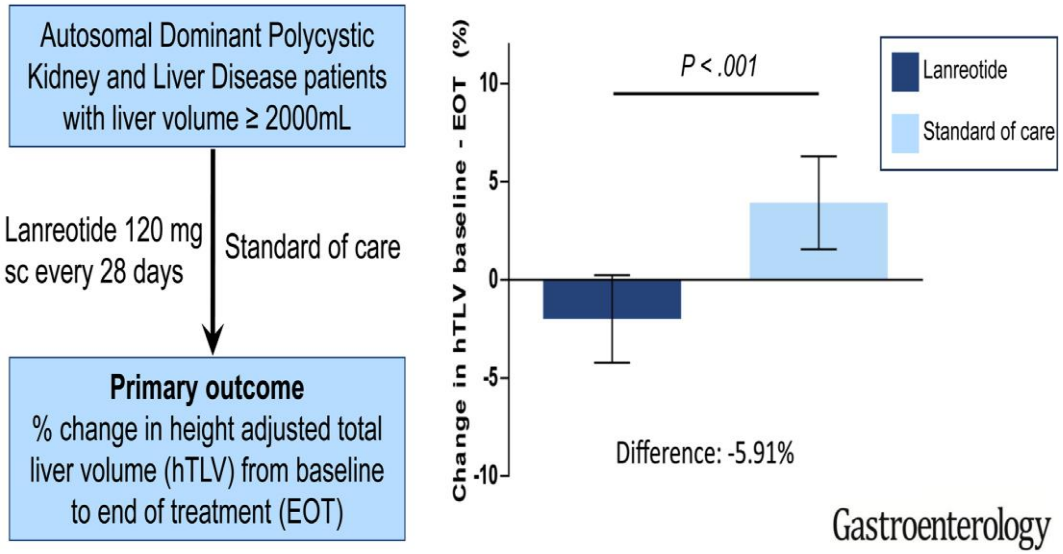
RM van Aerts et al. Gastroenterology 2019

Lanreotide reduces liver growth in patients with autosomal dominant polycystic liver and kidney disease

A 120-week randomized clinical trial



Adverse events

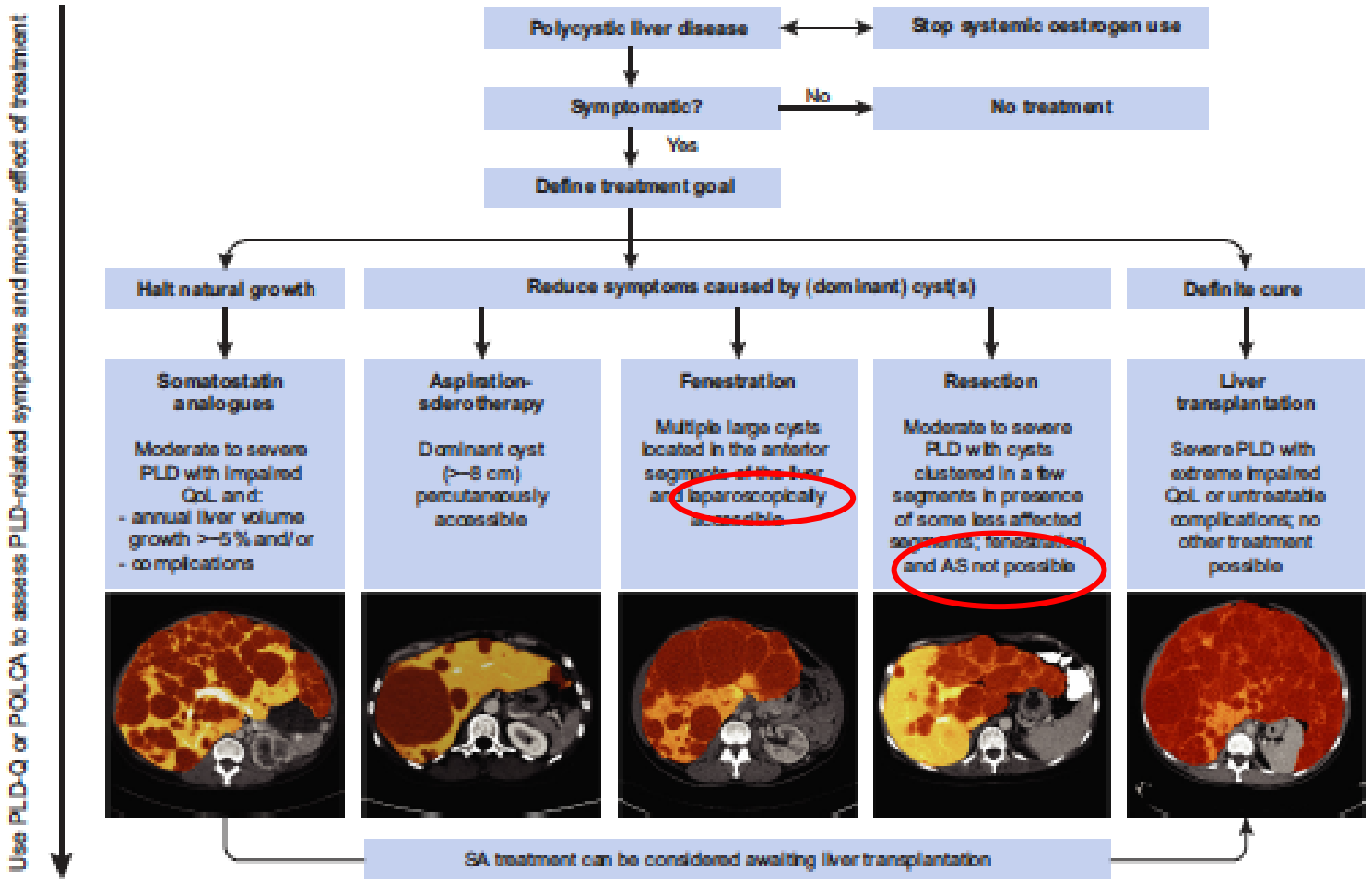
- 15/93 (16%) patients dose reduction, 6 stopped
(7 GI complains→abdominal pain and diarrhea, 3 malaise,
2 bradycardia, 1 hypoglycemia, 1 hair loss, 1 cyst infection)
- **6 liver cyst infection**

Limitations

- No change in QoL
- Most w/o hepatomegaly-related complains
(hTLV >3200 ml/m)(14% LAR, 6% SOC)

RM van Aerts et al. Gastroenterology 2019

Treatment algorithm for polycystic liver disease



R van Aerts et al. *JHEP 2018*

Liver transplantation in polycystic liver disease

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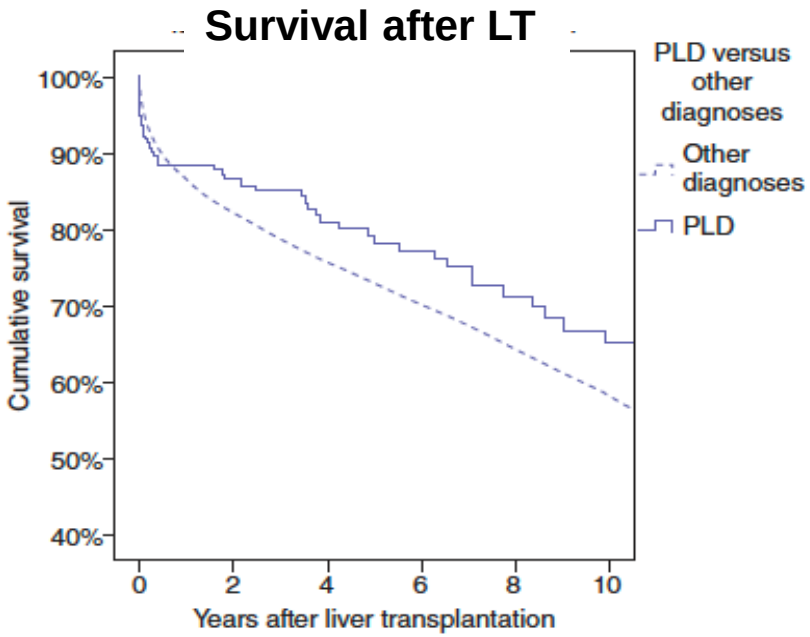
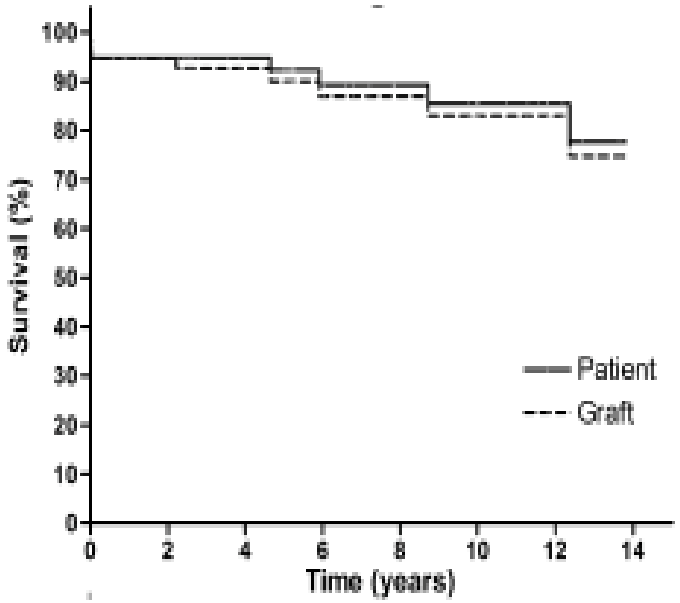
Retrospective UNOS database
107 411 LT (**1988-2010**) → 0.3% PLD



30-day mortality (1-survival)	<1 January 2000	≥1 January 2000	Wilcoxon's *P*-value
PLD	12% (*n* = 122)	7% (*n* = 235)	0.038
Other transplants	8% (*n* = 3520)	5% (*n* = 5782)	<0.001

Gedaly R et al. *HPB Surg* 2013

Retrospective **ELTR** database
58 PLD, **1985-2007**



Reasons for LT
- 74% mechanical difficulties
- 14% pain
- 12% complications

Difficulties in surgery, 38%
- 17% prior surgery!!
- 12% grossly enlarged liver

Keimpema L et al. *Transplant Int* 2011

Liver transplantation in polycystic liver disease

Criteria for LT

- massive PLD with symptoms
(exceptional *htTLV <3200ml/m, <5000ml*)
- severe malnutrition
(albumin <2.2 g/dl)
- portal hypertension, including HVOO
- recurrent cyst infection

MELD exception

• w/o renal insufficiency, GFR >30 ml/min, MELD 15 (plus 3 points/3 mo)
• with renal insufficiency, GFR <30 ml/min, MELD 20 (plus 3 points/3 mo)
→ combined hepatorenal transplant

Arrazola L et al. *Liver Transplant*. 2006

Ethical issues

UNOS database 2002-15
>70% more likely transplanted than cirrhosis

SD Doshi et al. Transplantation 2017

Combined liver/kidney transplantation in polycystic liver disease

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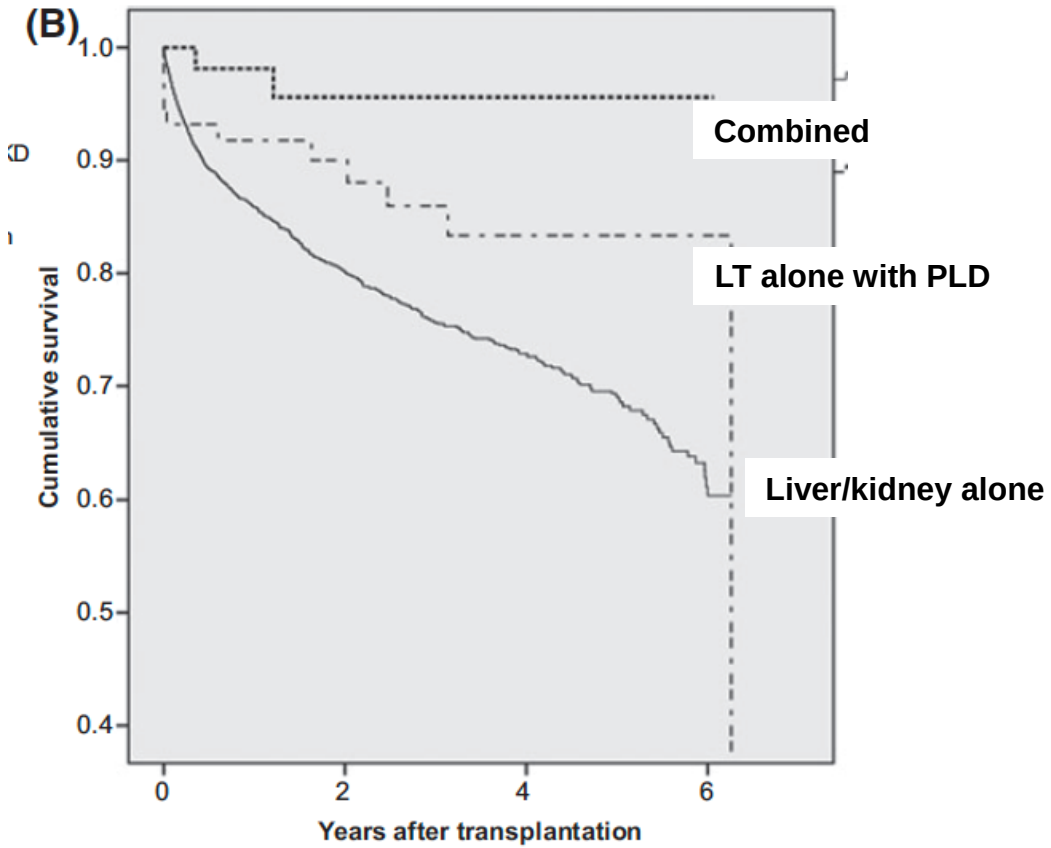
Survival after LT



Retrospective UNOS database
107 411 LT (**1988-2013**) → 107 liver/kidney T

	1-Year	3-Year	5-Year
	Patient survival	Patient survival	Patient survival
PLD/PKD	91%	90%	90%
PLD alone	87%	82%	77%
Other liver–kidney	82%	73%	67%

C Coquillard et al. *Liver Int 2016*

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Key points

— Cyst growth depends of female sex and age

— Hepatic vein outflow obstruction is common in massive PLD

— Young women with symptomatic disease are the target of somatostatin analogues

— Increased mortality of LT at short-term