

Liver Disease in ADPKD

WEBINAR, July 13th 2010.

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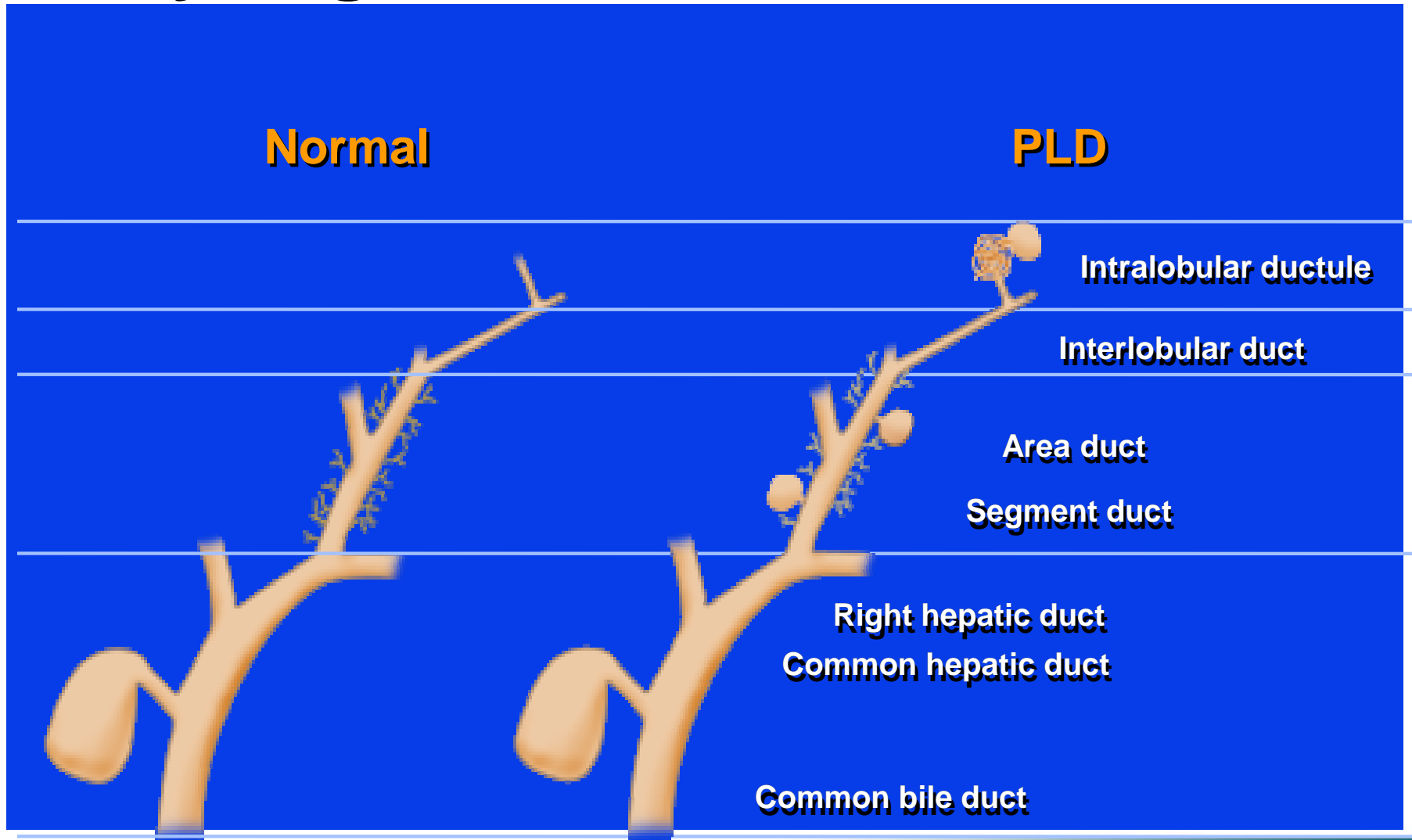
Outline

- Historical
- Natural History
- How do you get liver cysts?
- Symptoms
- Medical management
- Surgical management
- New treatments

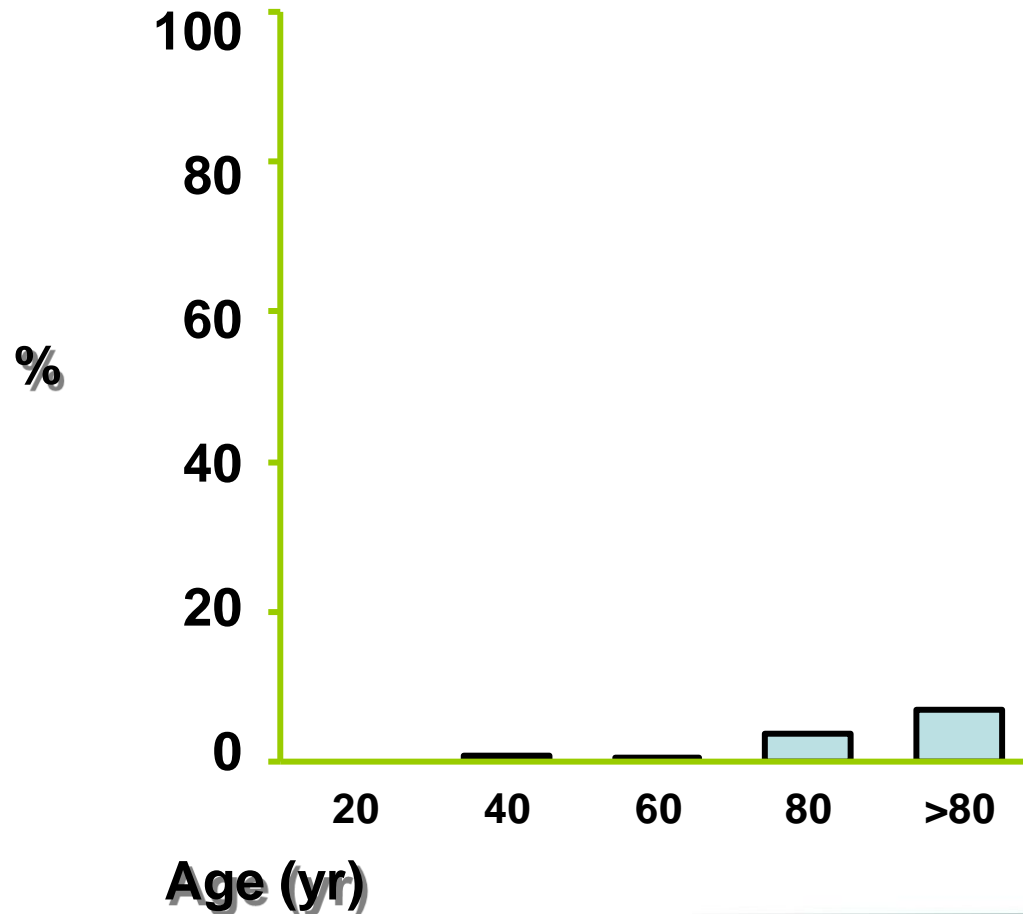
Polycystic Liver Disease

Disease	Gene	Chromosome	Protein	Function
ADPKD	PKD1	16p13.3	Polycystin 1	Membrane receptor
	PKD2	4q21-23	Polycystin 2	Calcium channel
ADPLD	PLD1	19 p13.2	Glucosidase II	ER protein processing
	PLD2	6	SEC63	ER protein processing

Cystogenesis in ADPKD/ADPLD



Prevalence of Liver Cysts in the General Population



MRI Evaluation of Hepatic Cysts in Early ADPKD: CRISP Cohort.

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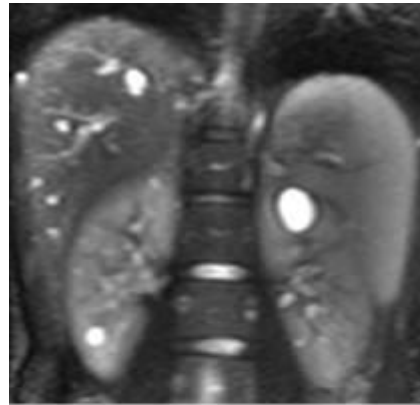
**Departments of Radiology, Medicine, and **Division of Biostatistics, Washington University, St. Louis, Missouri; [†]Emory University School of Medicine, Atlanta, Georgia; [‡]Mayo Foundation, Rochester, Minnesota; [§]Departments of Medicine (Renal Division) and Radiology, University of Alabama at Birmingham, Birmingham, Alabama; [¶]University of Kansas Medical Center, Kansas City, Missouri; [¶]Northwest Renal Clinic, Portland, Oregon; and [#]National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland*

- **Quantitative MRI scans: 3mm slices**
- **Prevalence of liver cysts in early ADPKD**
 - **58% in 15-24yo**
 - **85% in 25-34yo**
 - **94% in 35-46yos**

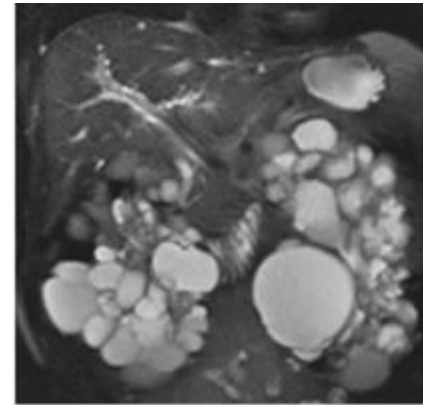
Bae T et al CJASN 2006;1:64-69.

T2-weighted MRI From Four Different Patients With Variable Severity Of Hepatic And Renal Cysts

24yo man liver
cysts (6.3ml) renal
cysts (15.4 ml).



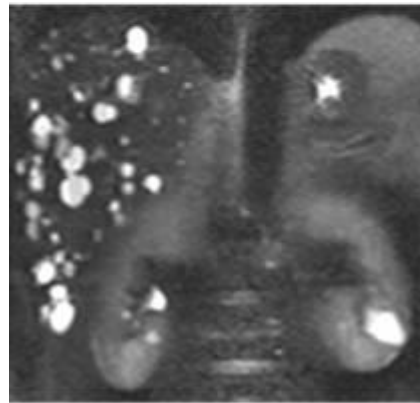
(A)



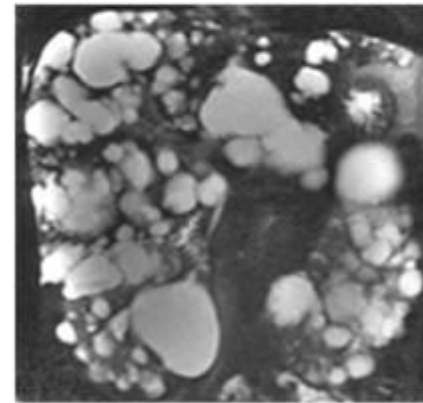
(B)

46yo man mild hepatic
cyst (9.3 ml)severe
renal cysts (1940 ml).

44yo man
hepatic
cysts(318.7 ml)
but mild renal
cyst burden
(37.6 ml).



(C)



(D)

30yo woman
hepatic cysts
(2368.8 ml) and
renal cysts
(1084.5 ml).

Symptomatic Polycystic Liver Disease (1)



- Mass Effect (by dominant cyst/massive PLD)**
- Abdominal distension/pain
 - Early satiety, heartburn, emesis
 - Malnutrition, loss of muscle/fat
 - Dyspnea, orthopnea
 - Change in bowel pattern, hemorrhoids
 - Back pain
 - Hernias, uterine prolapse, rib fractures
 - Venous obstruction (hepatic, IVC, porta)
 - Bile duct obstruction

Symptomatic Polycystic Liver Disease

Complications

- Hemorrhage
- Rupture
- Infection

Rare Associations

- Bile duct dilatation
- Congenital hepatic fibrosis
- Cholangiocarcinoma

Liver Cyst Infection

- **Risk Factors**
 - Recent abdominal surgery
 - Kidney Transplant
 - Chronic dialysis
- **Symptoms**
 - Fever + new onset RUQ pain
 - Leukocytosis ↑ ESR
 - ↑ ALP
 - Bacteremia
 - Cultures of undrained cyst fluid +ve

Symptomatic Polycystic Liver Disease

Nonsurgical Treatment Options

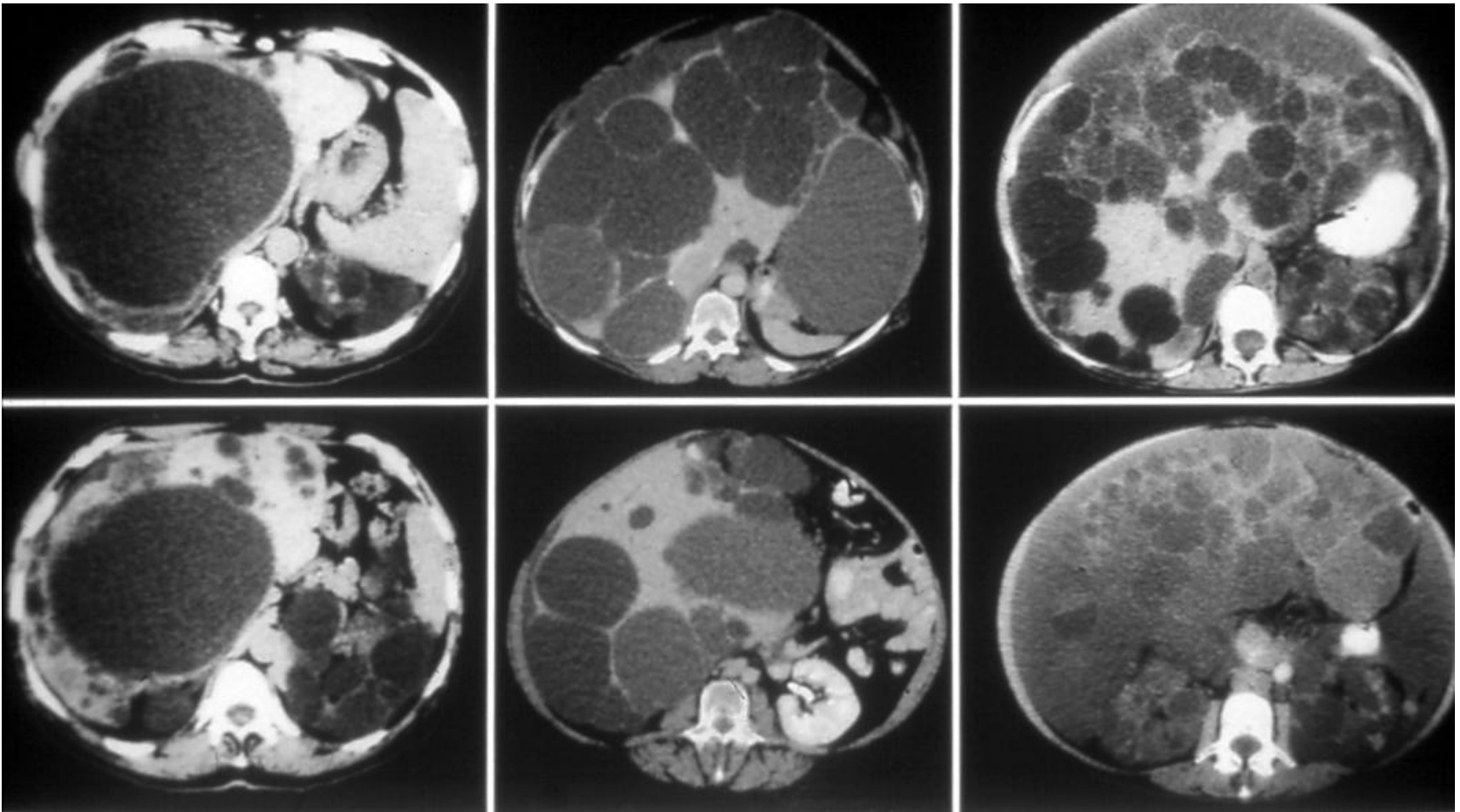
- **Avoid estrogens**
- **Avoid caffeine**
 - Caffeine stimulates cAMP
- **H₂-blocker or H⁺/K⁺ ATPase inhibitor**
 - ↓ secretion rates from unroofed liver cysts, possibly by inhibiting gastric acidity and secretion of secretin
- **Somatostatin analogues**
 - Long-acting octreotide/ lanreotide

Symptomatic Polycystic Liver Disease

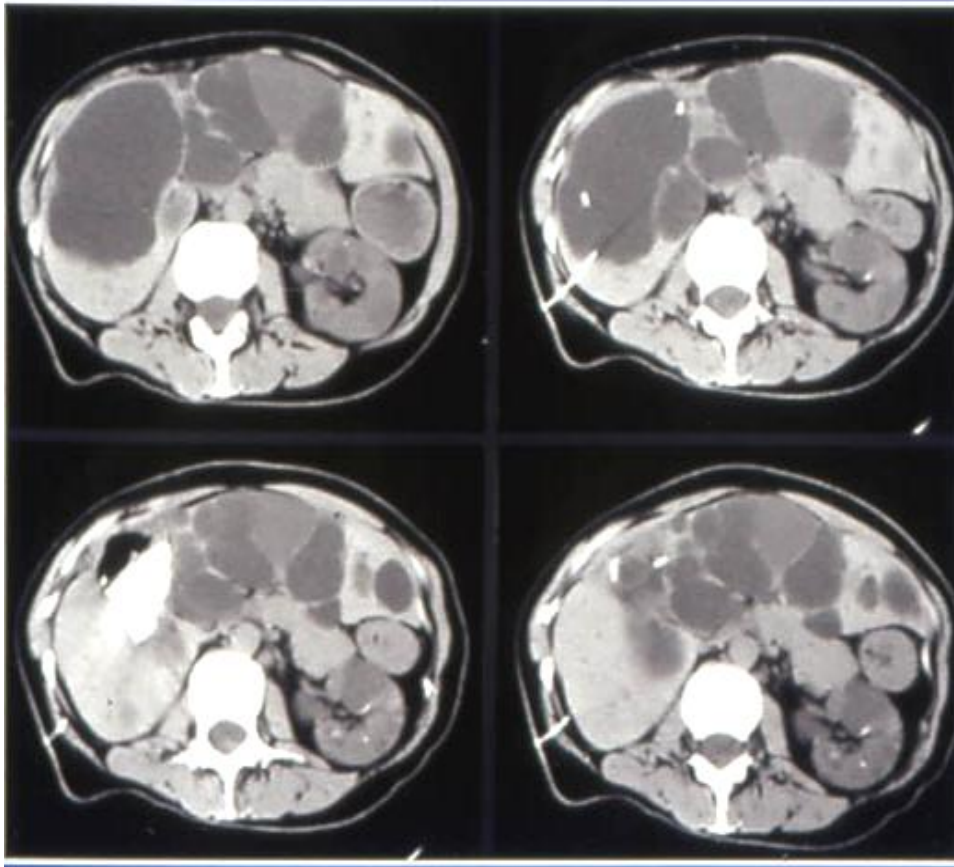
Surgical Treatment Options

- 1. Percutaneous aspiration/sclerosis**
- 2. Fenestration (laparoscopic or open)**
- 3. Hepatic resection/fenestration**
- 4. Liver transplantation**

Symptomatic Polycystic Liver Disease



Autosomal Dominant Polycystic Liver Disease: Alcohol Sclerosis of Liver Cysts



Success rate:

Primary: 69%

Secondary: 23%

Failure: 8%

Complications:

Major: None

Minor: Transient pain

Autosomal Dominant Polycystic Liver Disease Laparoscopic Fenestration For Polycystic Liver



INTRAOPERATIVE COMPLICATIONS

Hypothermia

Hypercapnia

POSTOPERATIVE COMPLICATIONS

Transient ascites (46%)

SYMPTOMATIC RELIEF

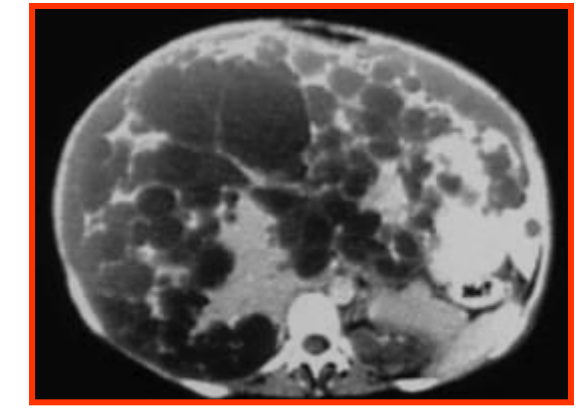
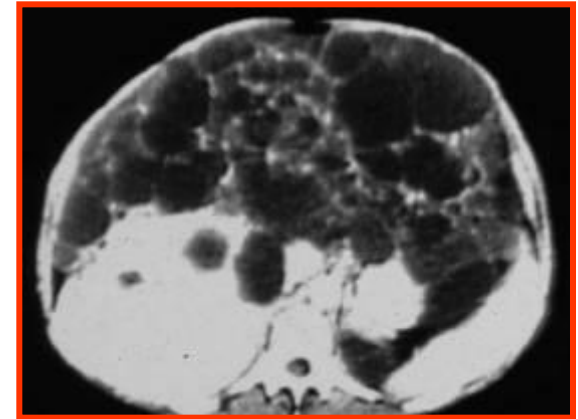
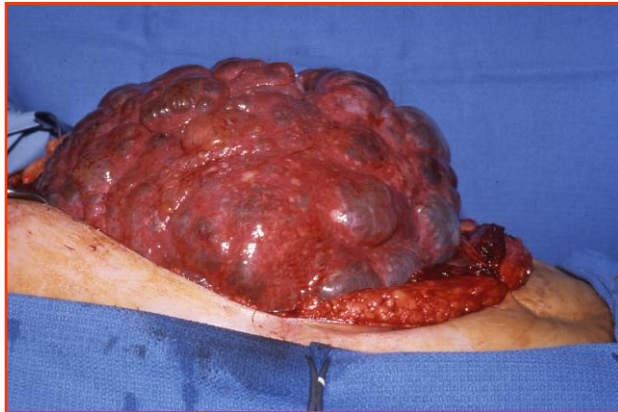
85%

RECURRENCE of SYMPTOMS

73%

Useful for few large cysts

Massive Polycystic Liver Disease



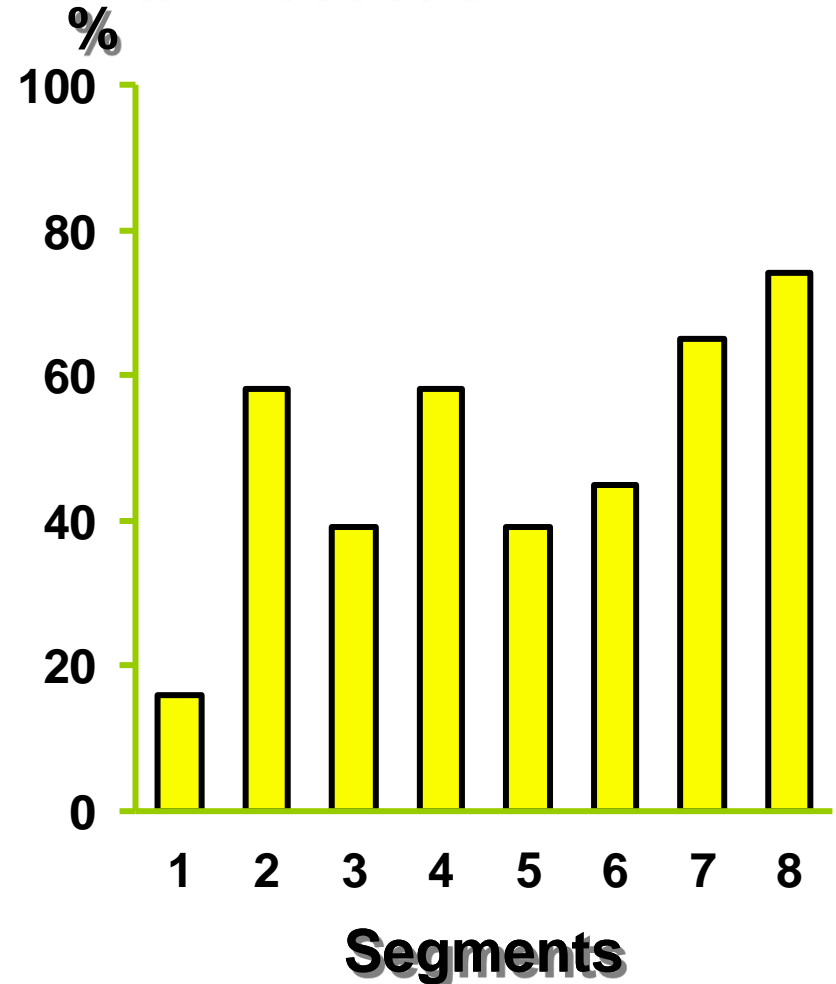
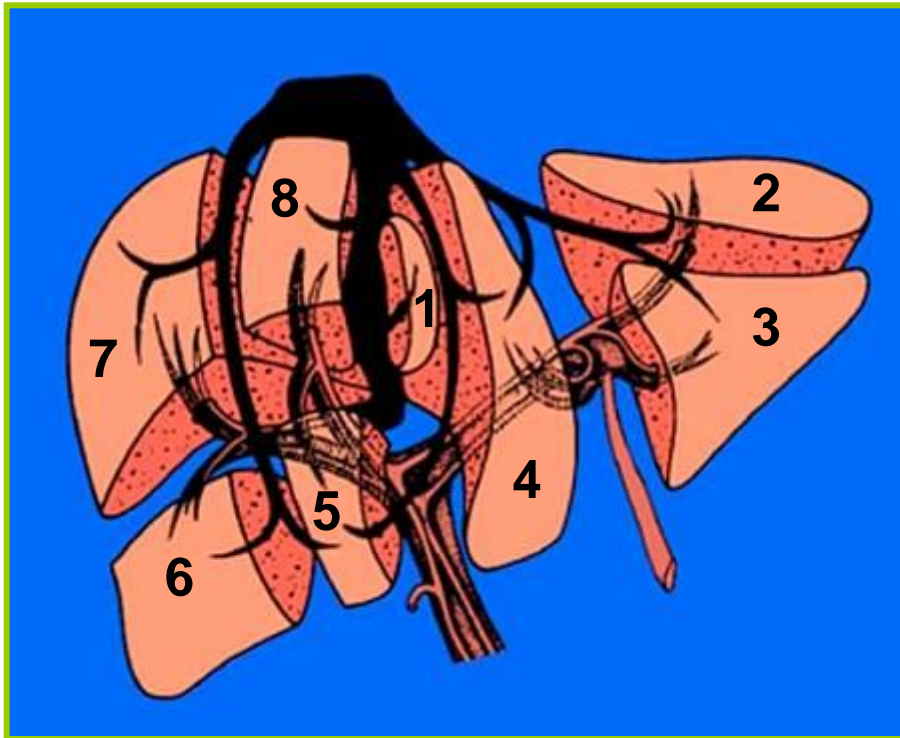
- Focal (preserved liver segments in >80% of patients)
- Parenchymal volume constant

Nagorney et al: KI 33:202, 1988

Everson et al: Hepatology 8:1627, 1988

Resection-Fenestration for Polycystic Liver Disease

Distribution of Segmental Resection



A Critical Appraisal of Hepatic Resection, Cyst Fenestration, and Liver Transplantation.

- Performance status normalized or improved in 75% of patients and 73% returned to work full-time.
- At follow-up, health survey scores were similar to the general population despite subsequent recurrence of symptoms in 73% of patients.

TABLE 1. ECOG Performance Status Before and After Operative Treatment for PLD ($P < 0.0001$)

	Immediate Preoperative (n = 141)	At Follow-Up (n = 78)
ECOG-PS 0	15%	68%
ECOG-PS 1	57%	22%
ECOG-PS 2	24%	10%
ECOG-PS 3	4%	0%
ECOG-PS 4	0%	0%

Schnelldorfer et al.

Annals of Surgery • Volume 250, Number 1, July 2009

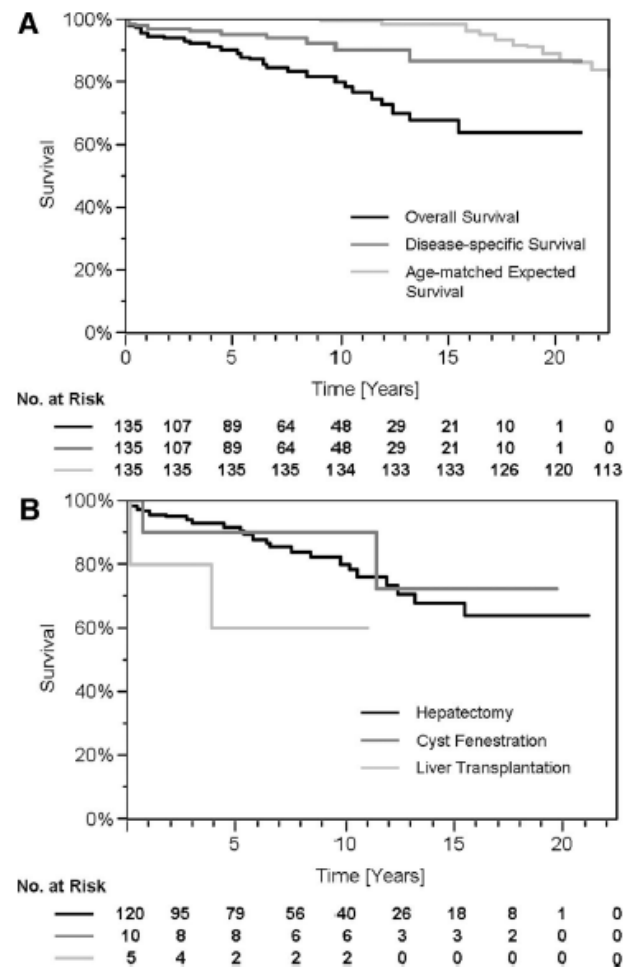
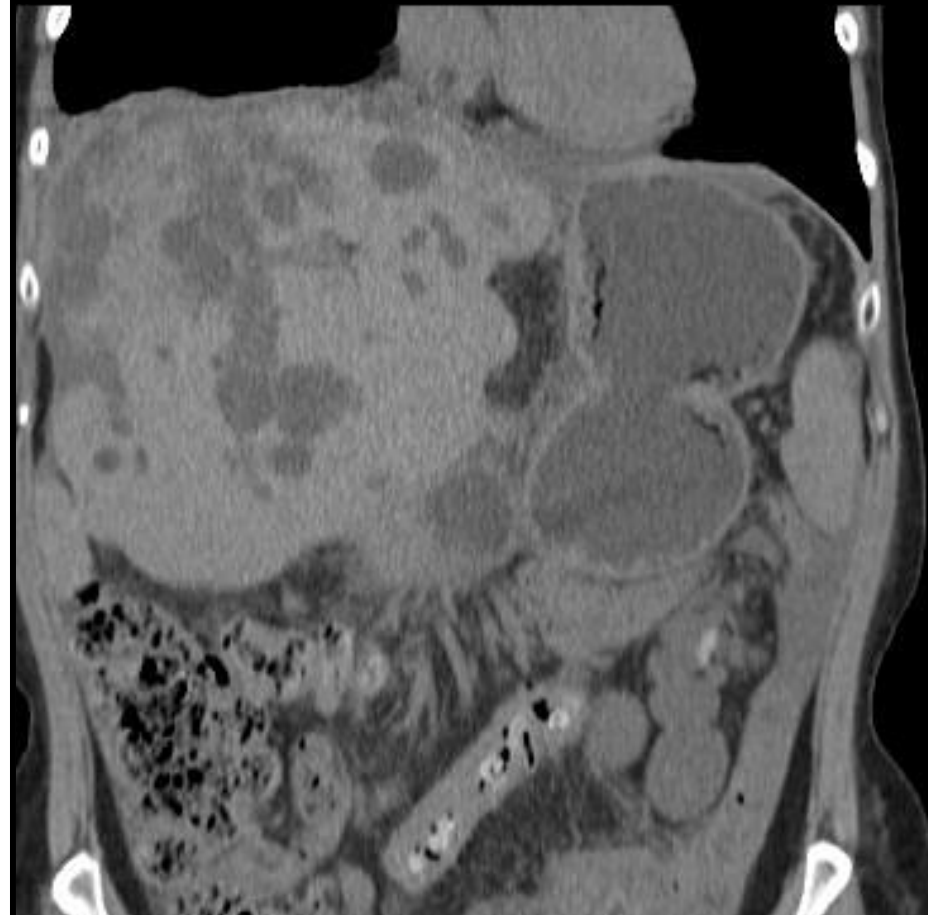
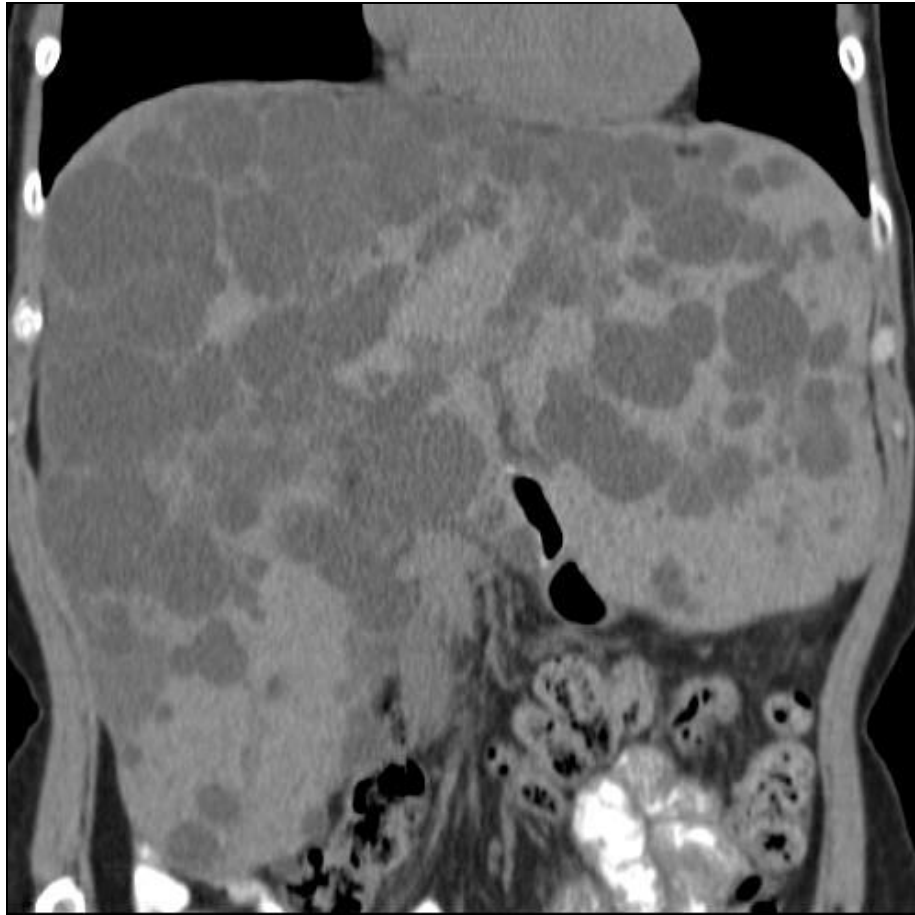
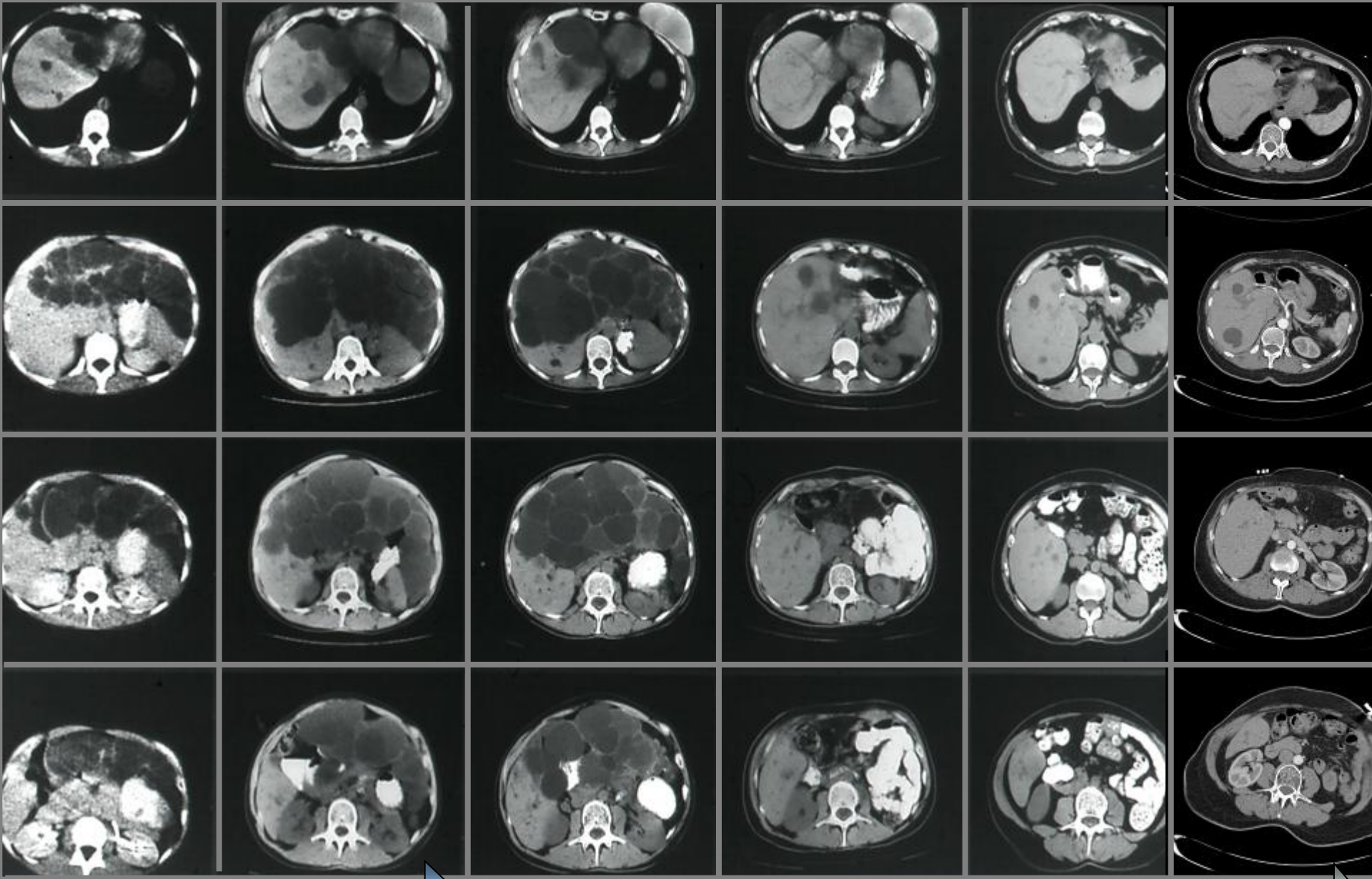


FIGURE 1. Long-term survival in 135 patients after operative treatment for PLD: A, Overall survival compared with disease-specific survival and survival in an age-matched US standard population (log-rank test: $P < 0.0001$); B, Survival dependent on type of operative treatment (log-rank test: $P = 0.310$).

Massive Polycystic Liver Disease Combined Resection-Fenestration





-10yrs

-3yrs

-Pre-op

+1 year

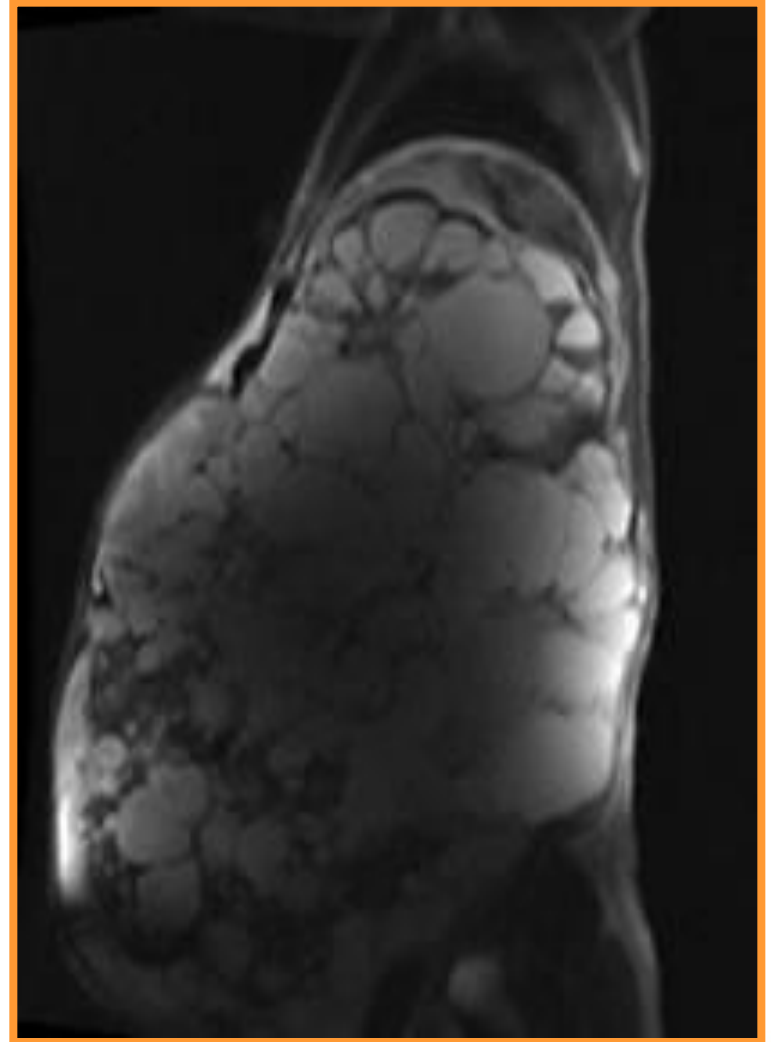
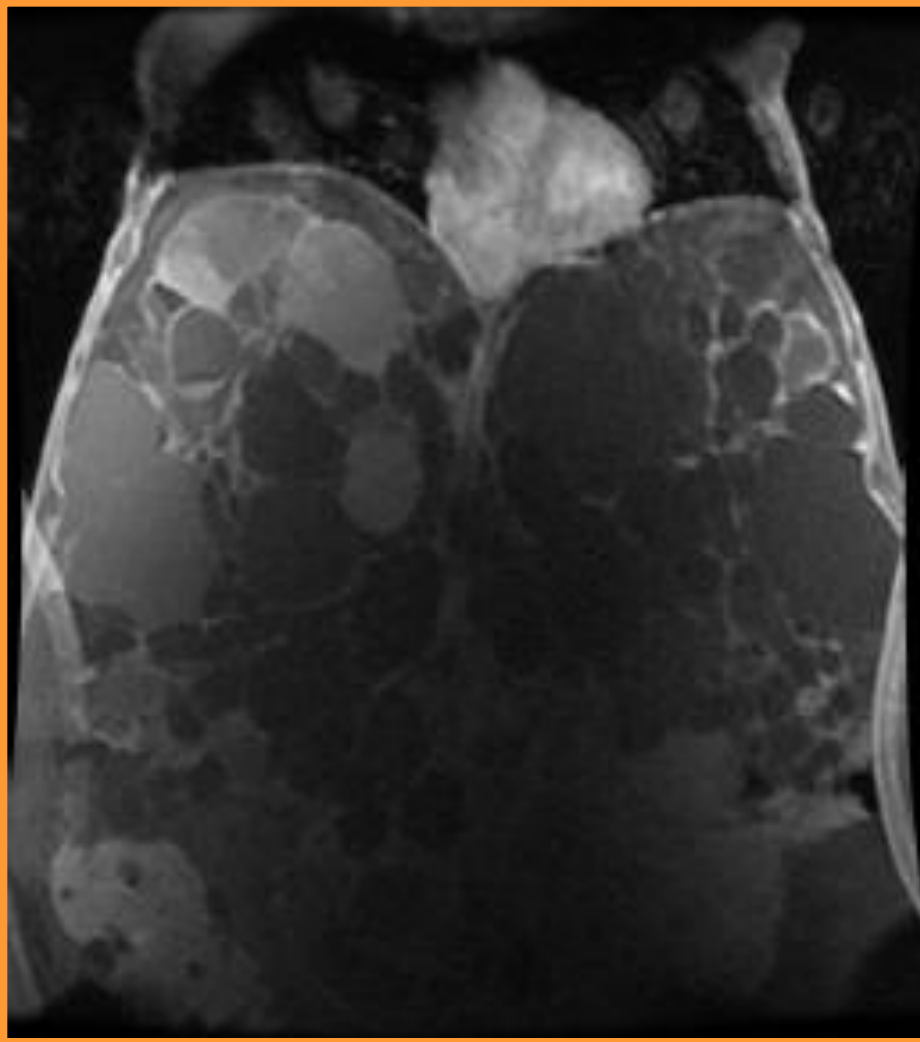
+3years

+10years

Courtesy of Vicente E. Torres.

www.pkdcure.org

Liver Transplantation for Massive Polycystic Liver Disease



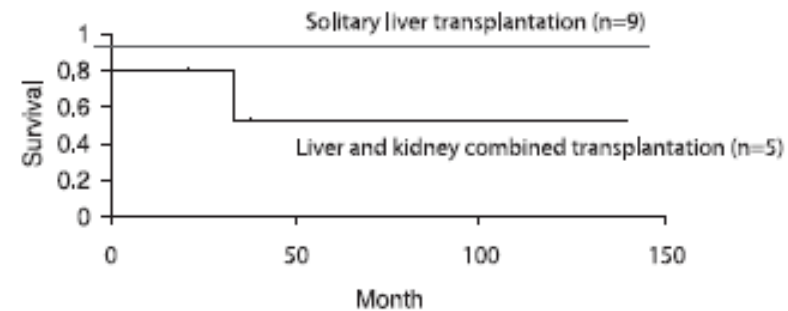
Model for End-Stage Liver Disease (MELD)

Numerical system that ranks (from 6 to 40) patients waiting for a liver based on three lab test results:

- Bilirubin (how effectively the liver excretes bile)
- INR (prothrombin time, ability to clot blood)
- Creatinine (kidney function)

Liver & Kidney Transplantation for PLD

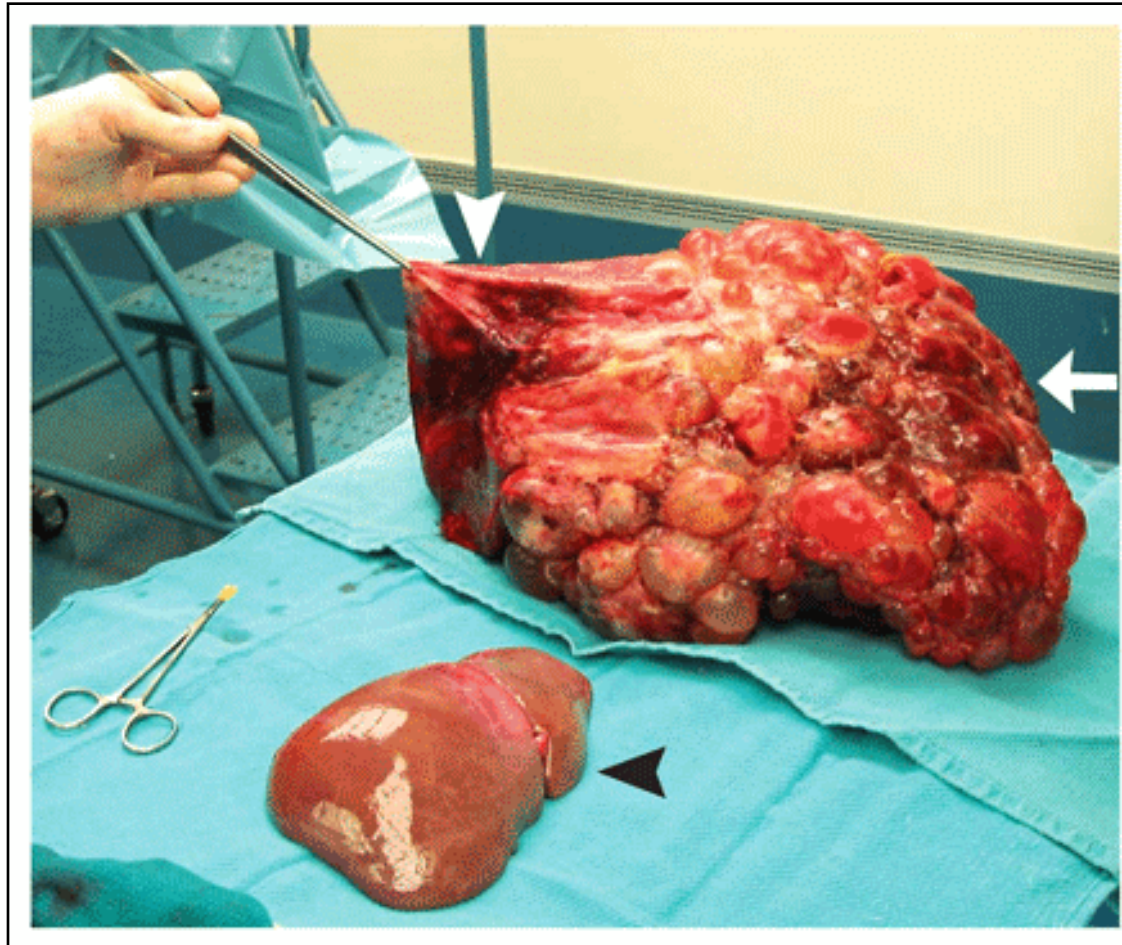
- First done 1988
- Malnutrition and failure to thrive
- Baylor/ Dallas Transplant Institute: 14 patients: 1987-2003
 - MELD= 15 7.5
 - Liver weight 2.6–12.6 kg
- 5-year survival for liver transplant considering all published studies ~ 85%
- Excellent Quality of Life
- Most of the mortality occurring in the first 3 months.



Kaplan-Meier survival curve.

T Ueno. Transplantation. 82 (4) 501-7. 2006

51yo(59kg) With ADPKD With A 9.1-kg Liver Underwent Liver Transplant



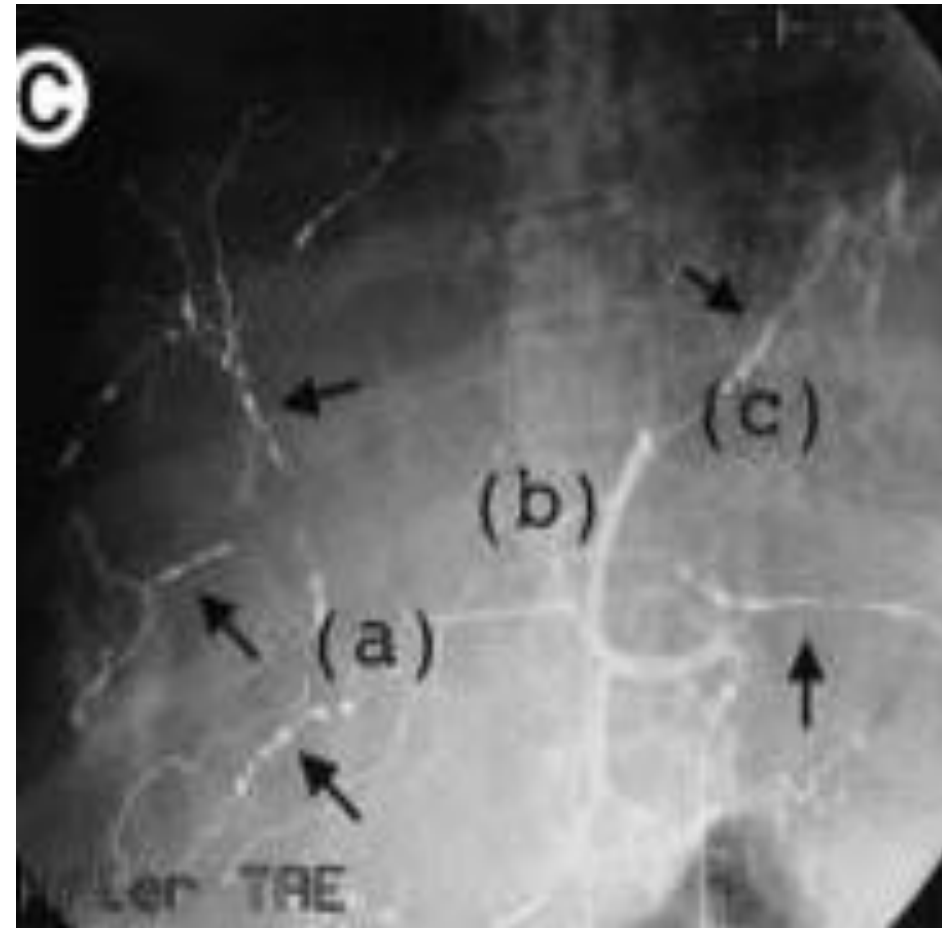
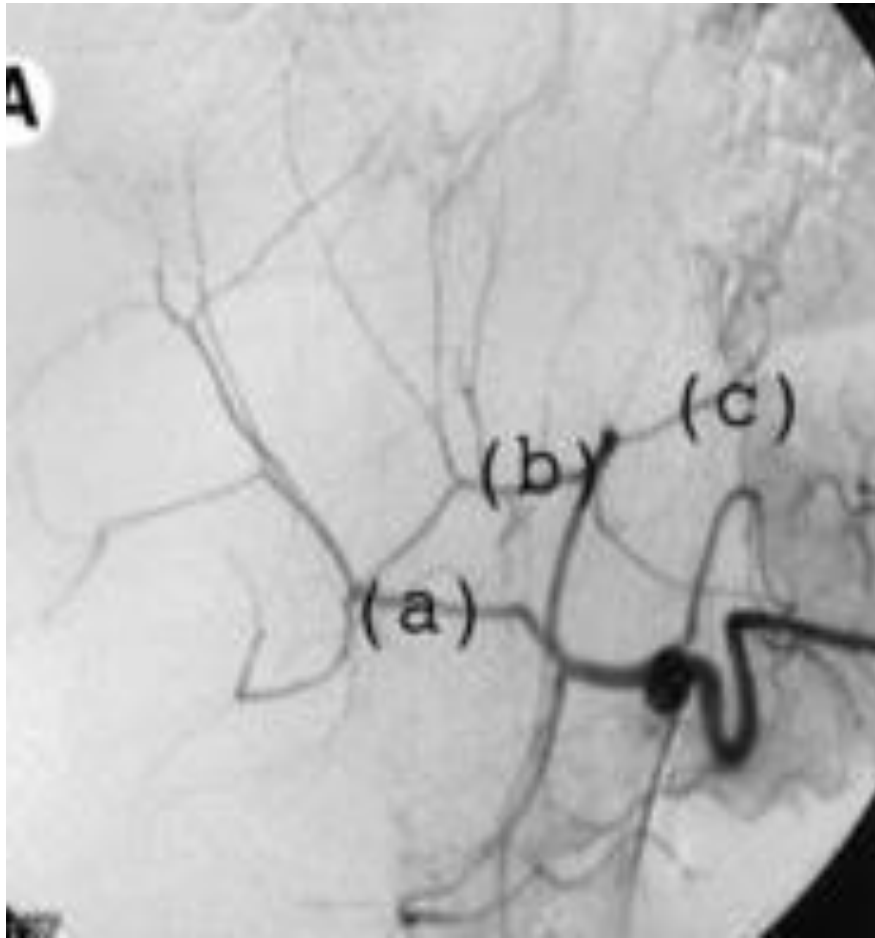
Symptomatic Polycystic Liver Disease

Alternative Treatment Options

- **Hepatic artery embolization**
- **Endovascular stent**
- **Transjugular intrahepatic portosystemic shunt (TIPS)**
- **La Veen shunt**

Severe Polycystic Liver Disease

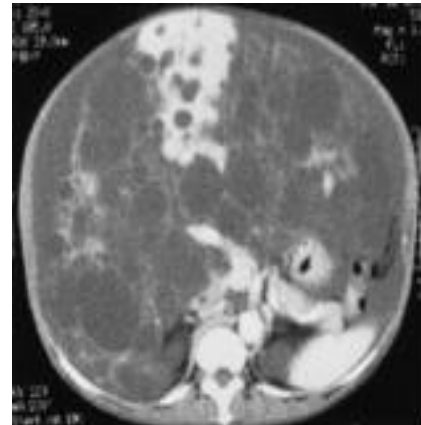
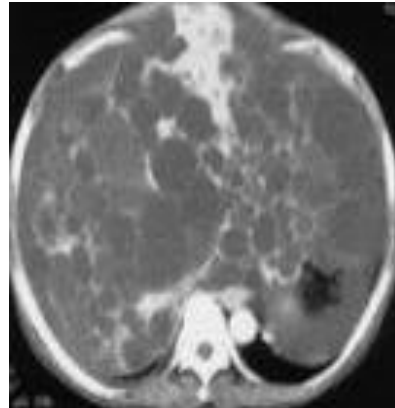
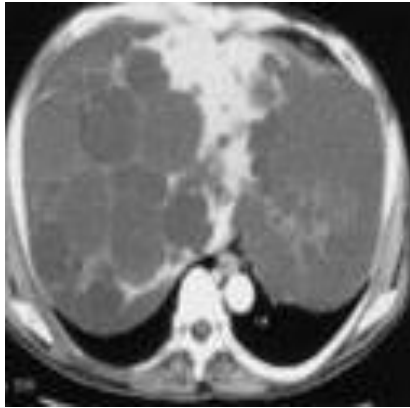
Hepatic Artery Embolization



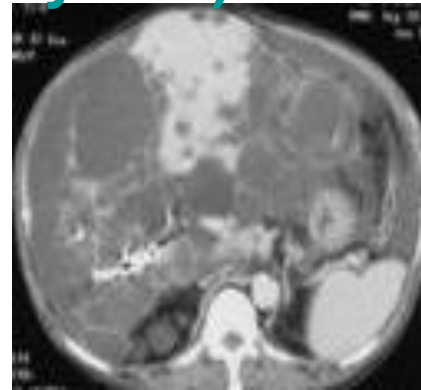
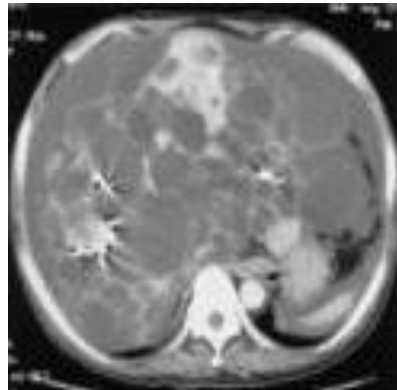
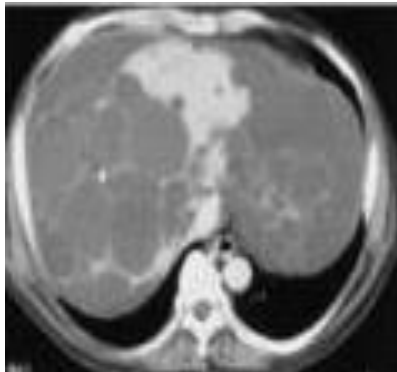
Severe Polycystic Liver Disease

Hepatic Artery Embolization

Pre

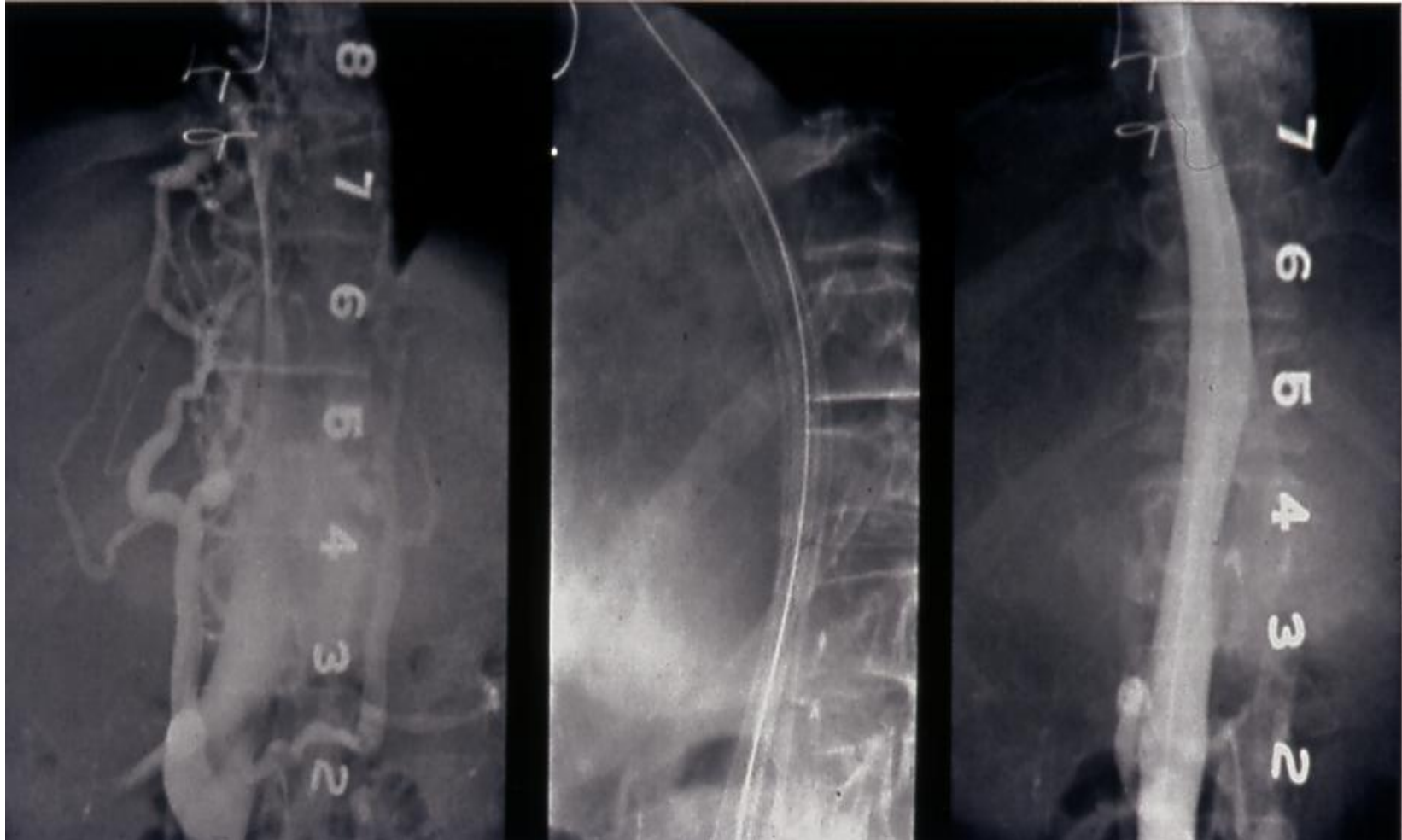


Post (2 years)

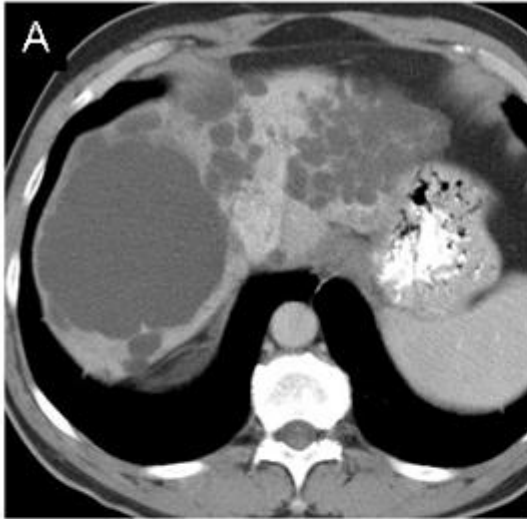


POLYCYSTIC LIVER DISEASE

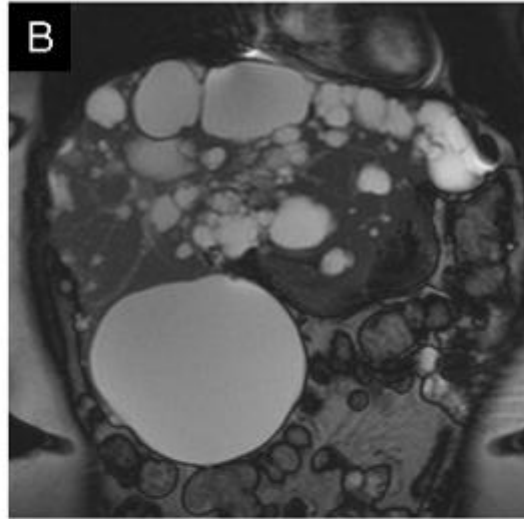
STENTING for INFERIOR VENA CAVA OBSTRUCTION



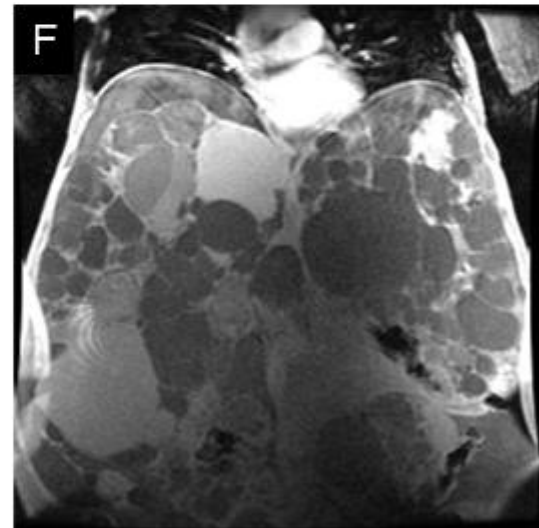
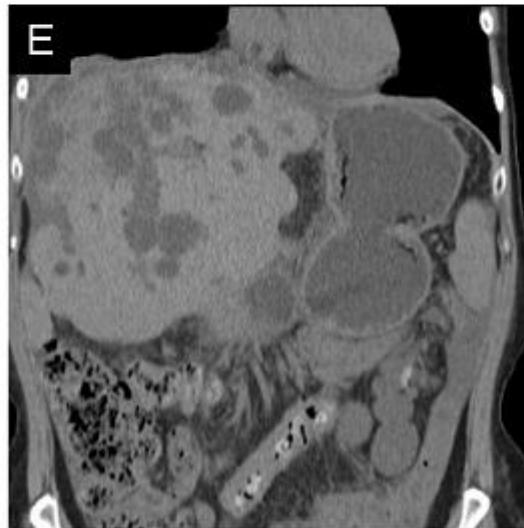
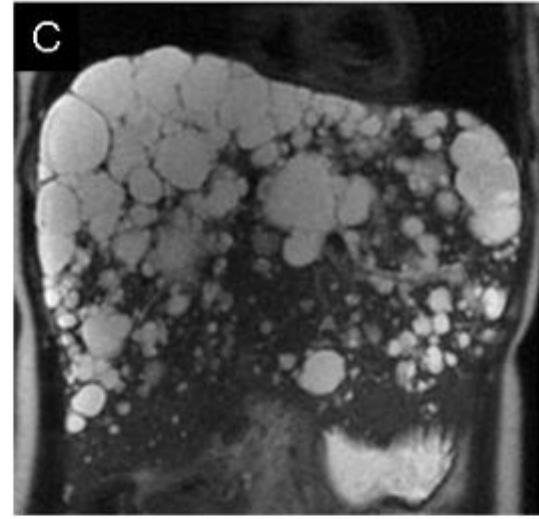
Aspiration and alcohol sclerosis



Laparoscopic fenestration



Hepatic artery Embolization



Before right lobectomy & Cyst
Fenestration

After right lobectomy & Cyst
Fenestration

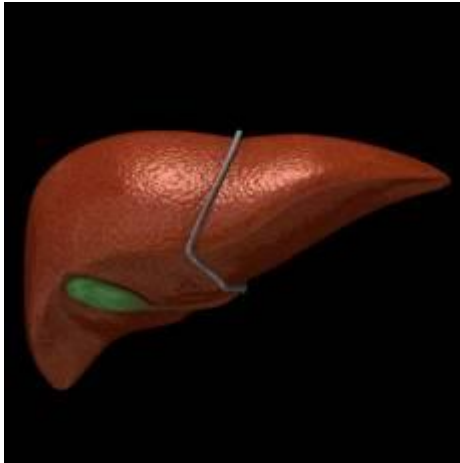
Liver Transplant

Symptomatic Polycystic Liver Disease

Nonsurgical Treatment Options

- **Avoid estrogens, caffeine**
- **H2-blocker or H⁺/K⁺ ATPase inhibitor**
- **Somatostatin analogues**
- **Sirolimus (?)**

Mechanisms of Cyst Development:



Normal liver

Mutations in ADPKD
(PKD1 and PKD2)

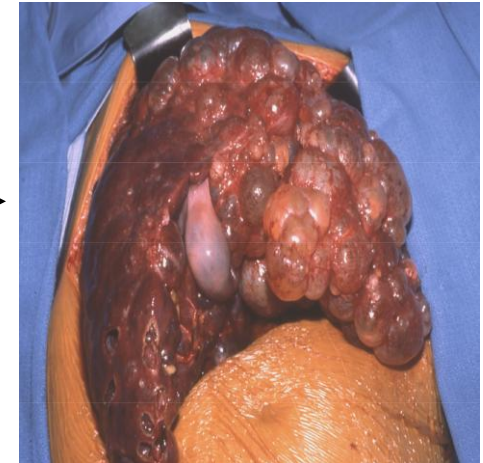
Mutations in ADPLD
(PRKCSH and SEC63)

- Defective cell planar polarity
- Centrosomal amplification
- Cell cycle dysregulation
- Increased apoptosis

- **Increased fluid secretion**
- **Increased cell proliferation**

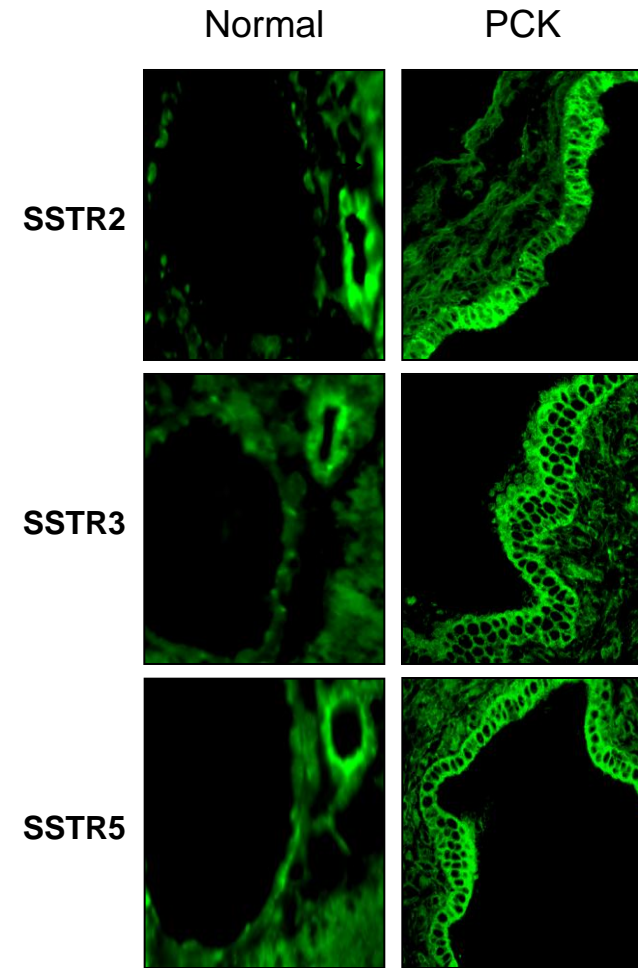
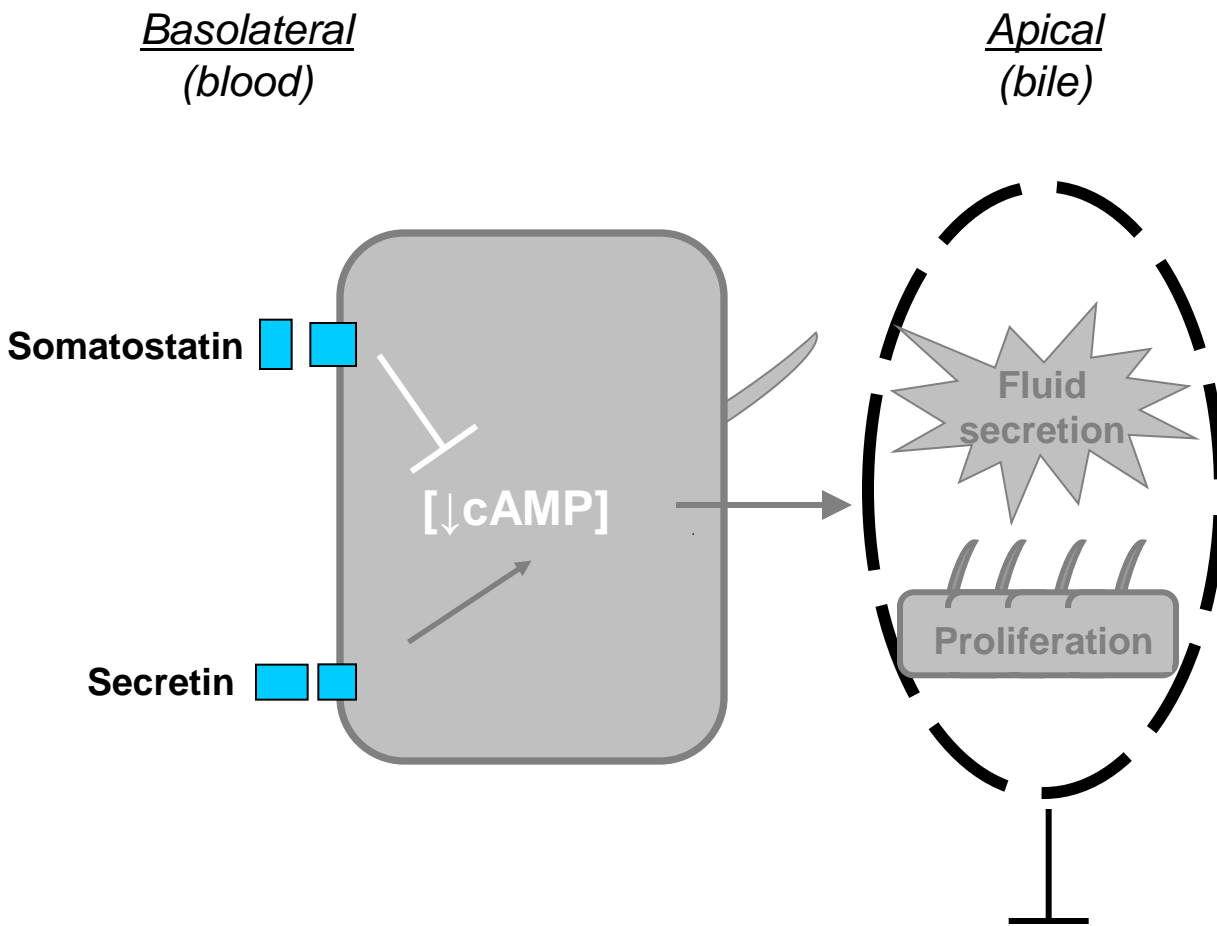


cAMP elevation



PLD

In Cholangiocytes, cAMP Facilitates Fluid Secretion & Proliferation

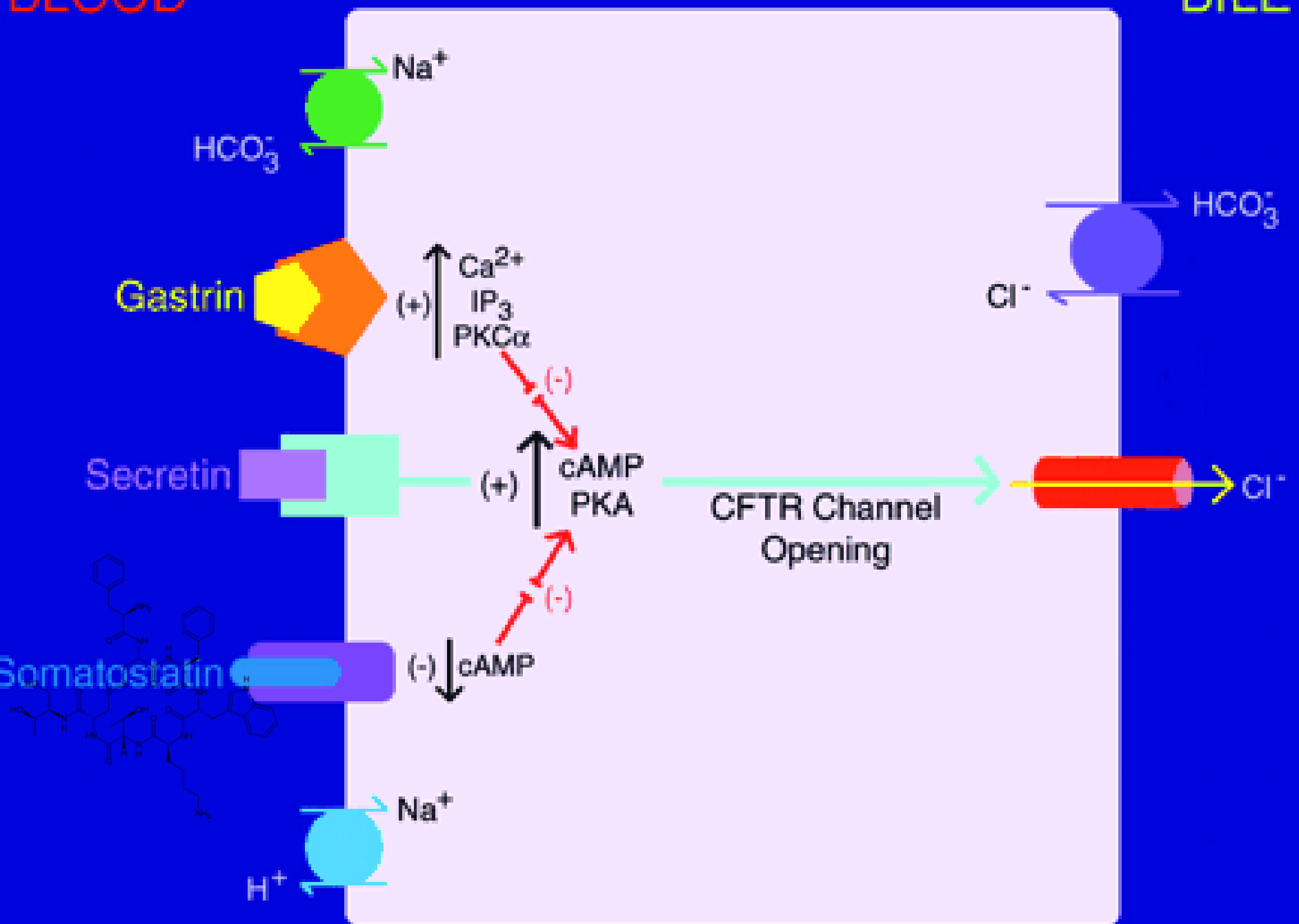


Cyst growth

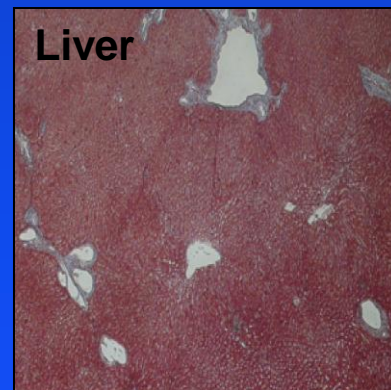
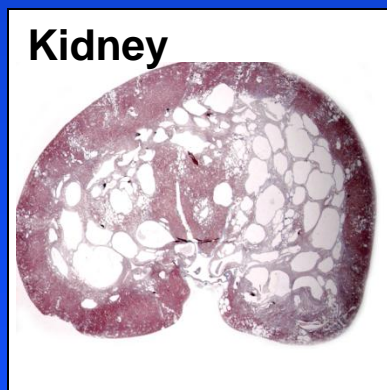
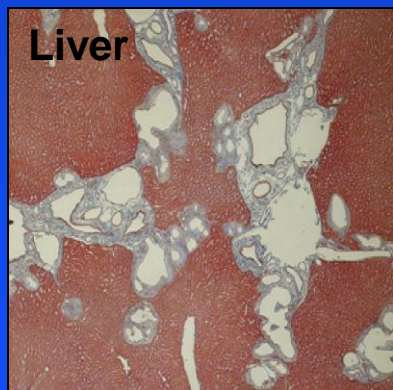
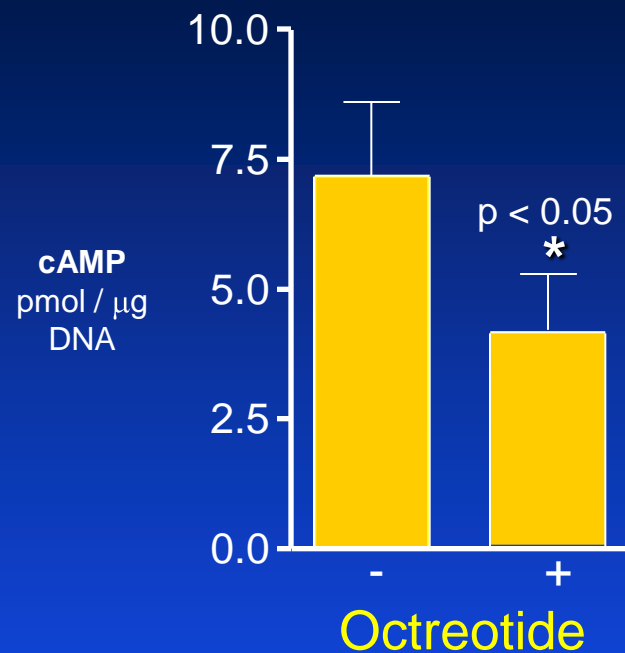
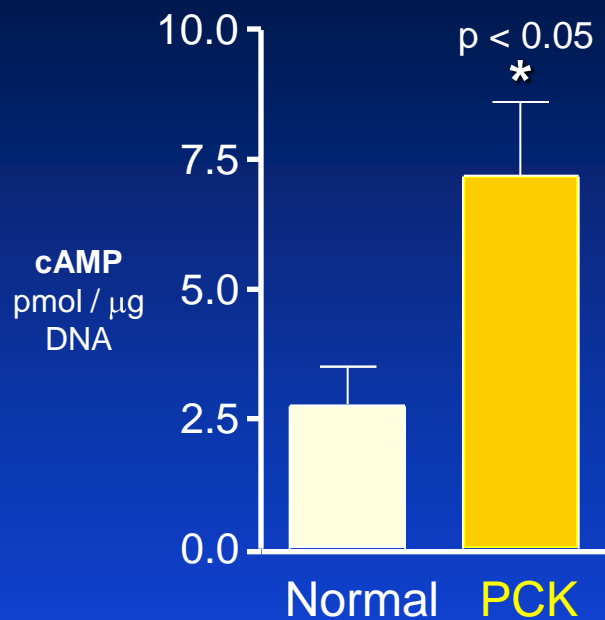
Masyuk, *Gastroenterology*, 2007

BLOOD

BILE

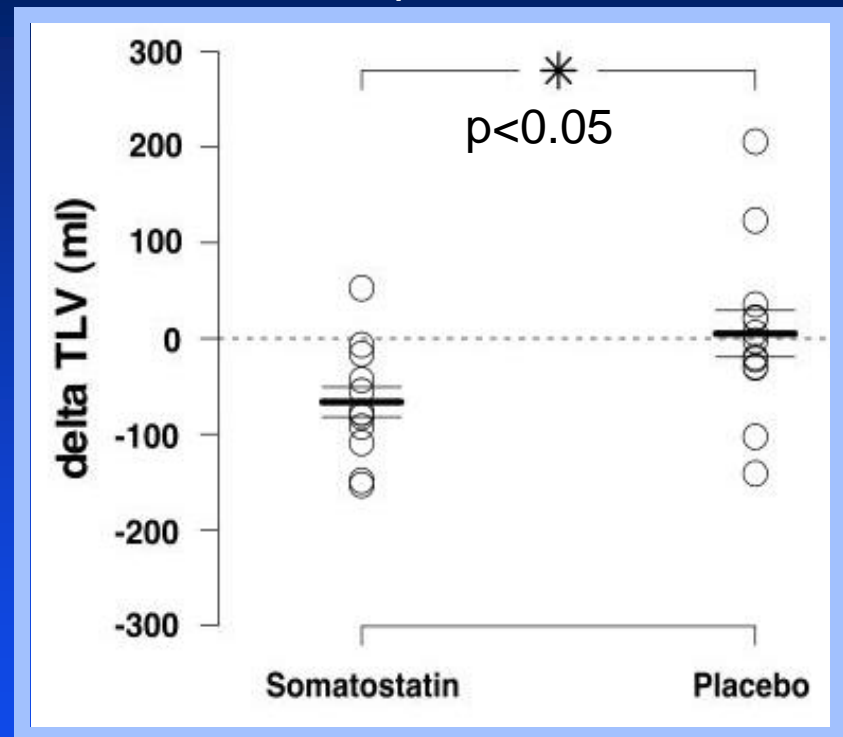
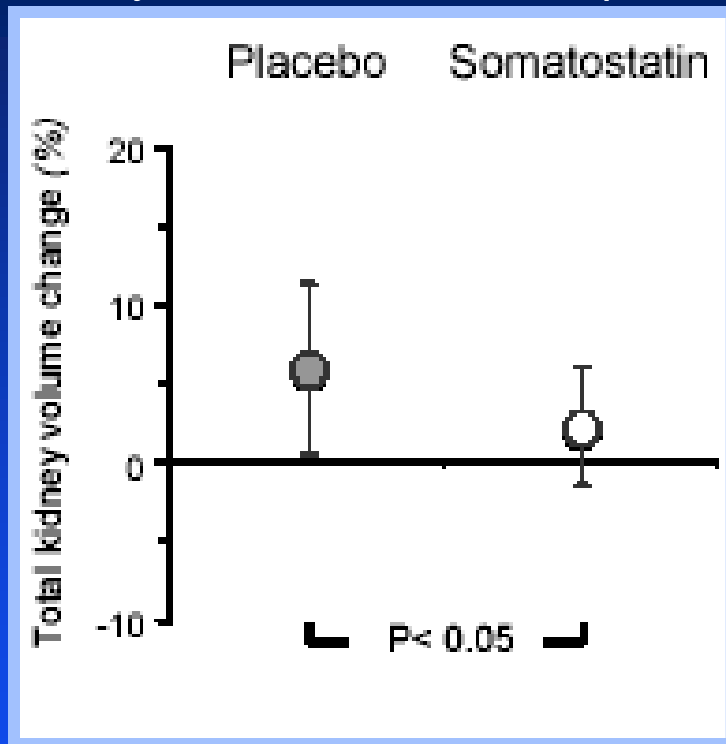


cAMP Targeting Attenuates Hepatic and Renal Cyst Growth in the PCK Rat, an Animal Model of PLD



Long-Acting Octreotide Trial in ADPKD

- Randomized, placebo-controlled, cross-over study x 6 months
- Small study (n=12)
- Good safety profile
- Dose adjustments advised for patients with severe renal impairment



TLV ↓ 1,641±486 to 1,574±469 ml (p<0.005).

Δ TLV (-66±56 vs +5±88 ml).

Ruggenti, Kidney Int, 2005.

LOCKCYSYT STUDY (Lanreotide)



Table 1: Demographics and baseline clinical characteristics. Data are mean (95% CI).

	Lanreotide group (N=27)	Placebo group (N=27)	p
Age (years)	49.6 (34.4–64.8)	50.3 (32.6–68.1)	0.752
Sex (male/female)	3/24	4/23	0.685
Diagnosis (ADPKD/PCLD)	12/15	20/7	0.027
Centre (Leuven/Nijmegen)	12/15	12/15	1.000
Body mass index (kg/m ²)	26.1 (18.7–33.5)	25.7 (18.6–32.8)	0.733
Liver volume (mL)	4606 (547–8665)	4689 (613–8765)	0.698
Right and left kidney volume (mL)*	1000 (-39–2039)	1115 (-519–2748)	0.673

*Only ADPKD patients

ADPKD, autosomal dominant polycystic kidney disease; PCLD, polycystic liver disease.

- Lanreotide 120mg x 6 months
- Therapeutic drug levels
- Equivalent to 60mg OctLAR



LOCKCYSY- Results:

Table 2: Outcomes Data are mean (95% CI).

	Diagnosis	Lanreotide			Placebo			p
		Baseline	End	Absolute change	Baseline	End*	Absolute change*	
Liver volume (mL)	Both	4606 (547–8665)	4471 (542–8401)	-134 (-476–207)	4689 (613–8765)	4896 (739–9053)	92 (-320–504)	<0.01
		-2.9% (-11.1–5.4)			1.6% (-5.2–8.4)			
Liver volume (mL)	PCLD	4195 (437–7952)	4138 (462–7814)	-57 (-337–223)	3855 (-338–8047)	4428 (-140–8996)	213 (-268–695)	<0.01
		-1.1% (-7.3–5.0)			3.8% (-3.9–11.4)			
Liver volume (mL)	ADPKD	5119 (762–9476)	4888 (645–9130)	-231 (-555–93)	4981 (1000–8963)	5036 (925–9148)	55 (-318–428)	<0.01
		-5.0% (-13.8–3.7)			9.9% (-5.2–7.2)			
Kidney volume (mL)	ADPKD	1000 (-39–2039)	983 (-62–2028)	-17 (-126–93)	1115 (-519–2748)	1165 (-541–2870)	50 (-99–199)	0.018
		-1.5% (-13.2–10.3)			3.4% (-7.1–14.0)			

*Not of all patients end data available: baseline n=27, end n=26

ADPKD, autosomal dominant polycystic kidney disease; PCLD, polycystic liver disease.

- Δ Mean LV -2.9%, 4606 mL (95%CI 547–8665)-> 4471 mL (95%CI 542–8401).
- Placebo group + 1.6%; 4689 mL (95% CI 613–8765) to 4895 mL (95% CI 739–9053) (p<0.01)
- Post-hoc stratification for patients with ADPKD or PCLD - similar changes in liver volume, with significant differences in patients on lanreotide (P<0.01 for both diseases).

LONG-ACTING OCTREOTIDE TRIAL (Mayo Clinic)

Prospective, double blind, placebo controlled (2:1), 42 patients

Octreotide LAR 40 mg IM every 4 weeks

Primary endpoint: % change in liver volume at 12 months (MRI)

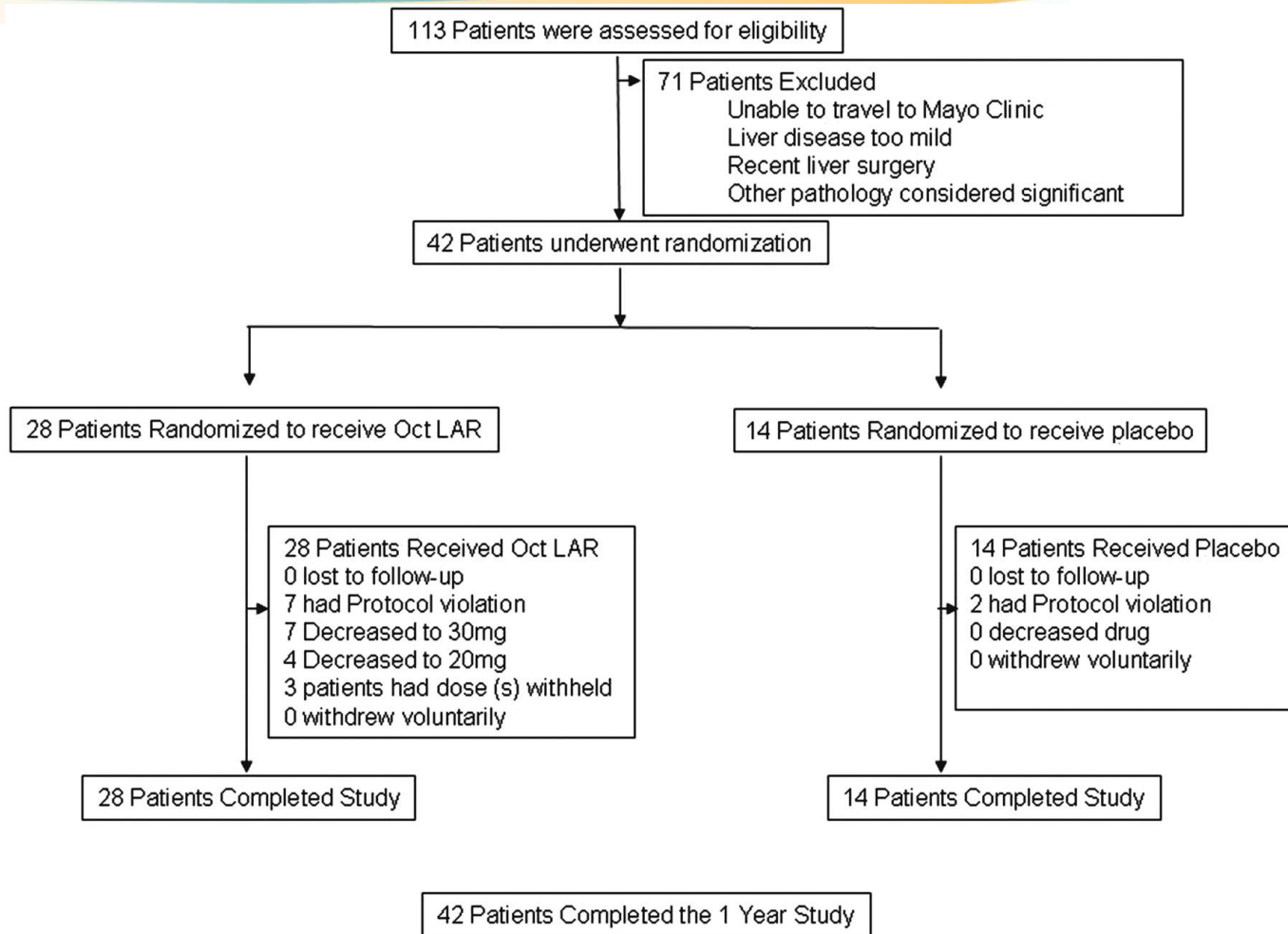
Secondary endpoints: % change in kidney and liver/renal cyst volumes

Patient Characteristics

- Age \geq 18 years
- PLD associated with ADPKD or isolated ADPLD
- Liver volume >4000 mL or symptomatic due to mass effects
- Not a candidate for or declining surgical intervention
- Serum creatinine <3 mg/dL
- Exclusion criteria (pregnancy, major illness, uncontrolled DM)

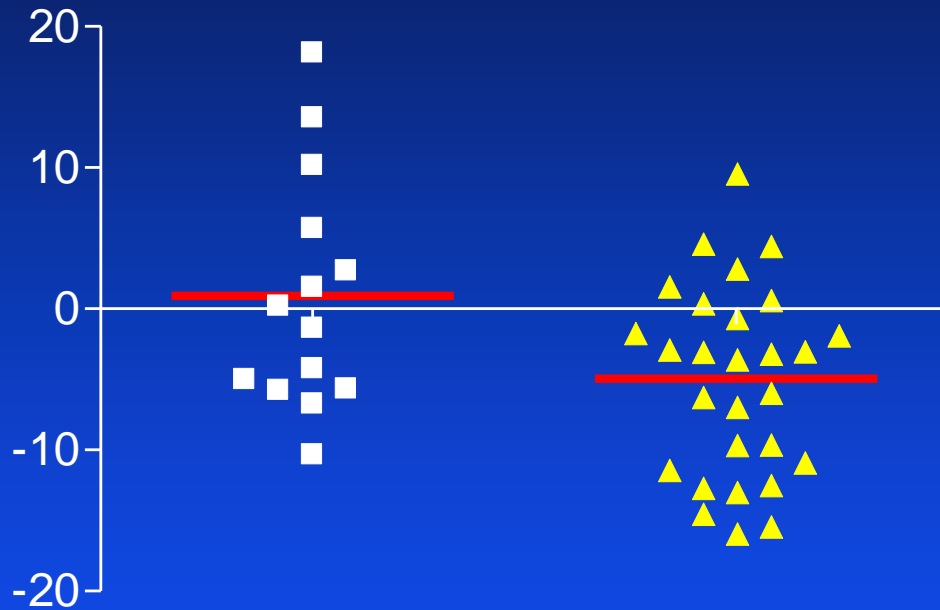
Open label extension

Study flow diagram

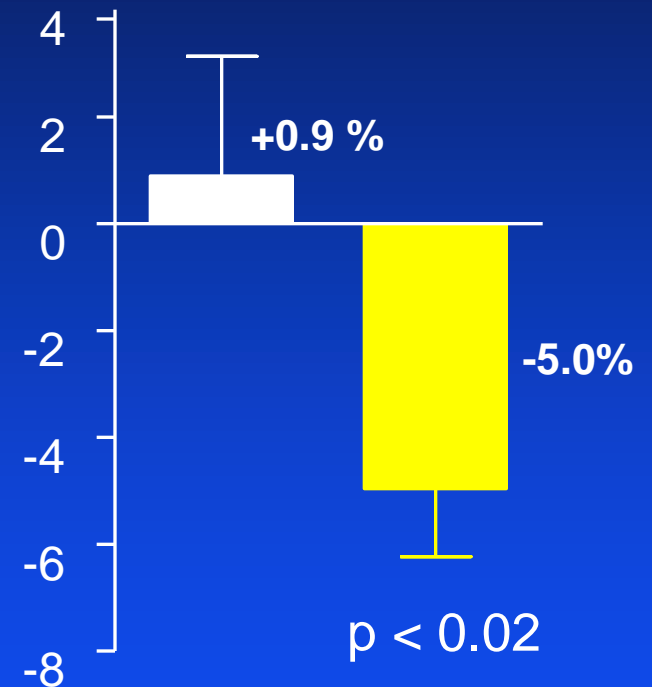


Liver Volume Decreases in OctLAR Patients

Individual patients
(% change compared to baseline)



Liver volume
(average % change
compared to baseline)

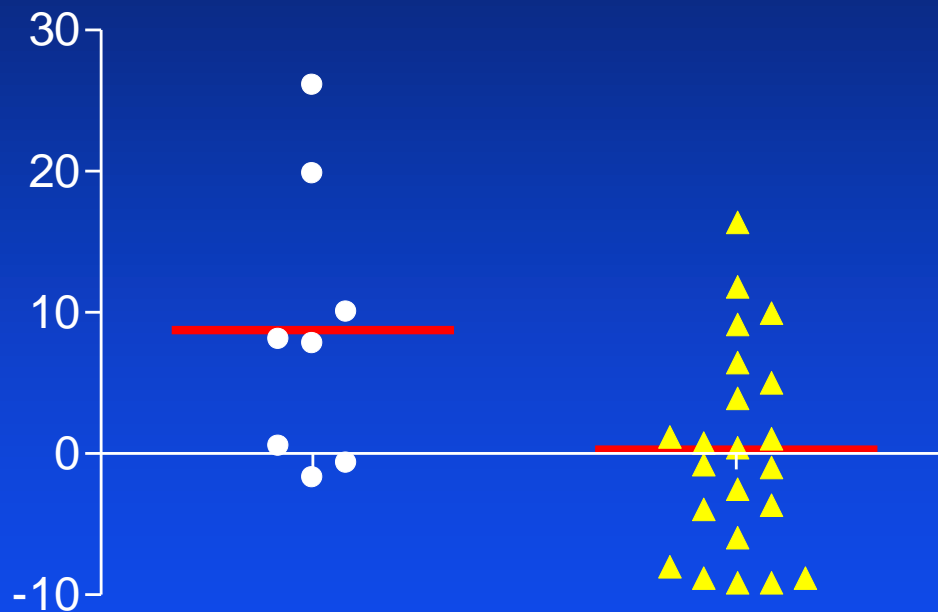


Placebo OctLAR

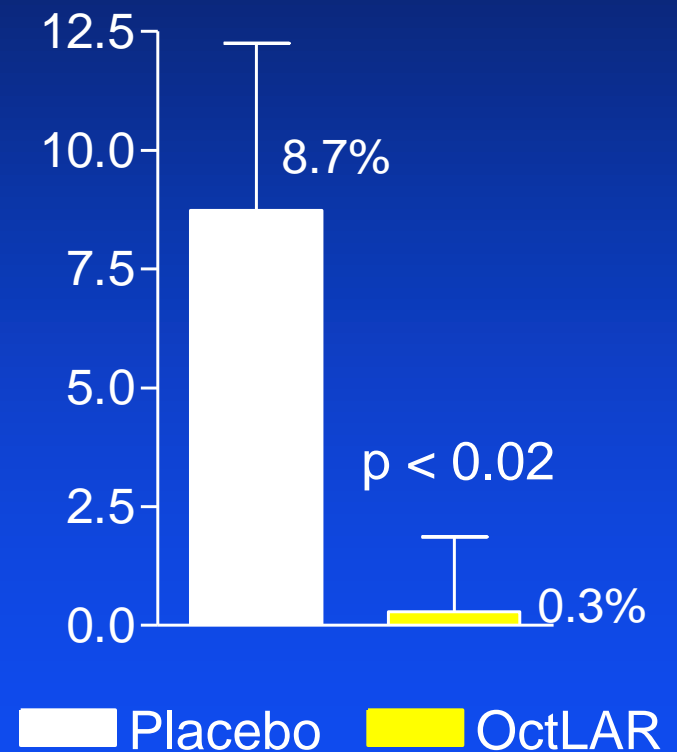
Hogan, M. C. et al. J Am Soc Nephrol 2010;21:1052-1061

Kidney Volume Decreases in OctLAR Patients

*Individual patients
(% change compared to baseline)*



*Kidney volume
(average % change compared to baseline)*



Hogan, M. C. et al. J Am Soc Nephrol 2010;21:1052-1061

Patient Reported Outcomes

- **SF-36v2 physical component summary (PCS) score ($p < 0.05$)**
- **Significantly improved in response to OctreotideLAR ($p < 0.05$):**
 - **physical ability**
 - **bodily pain**

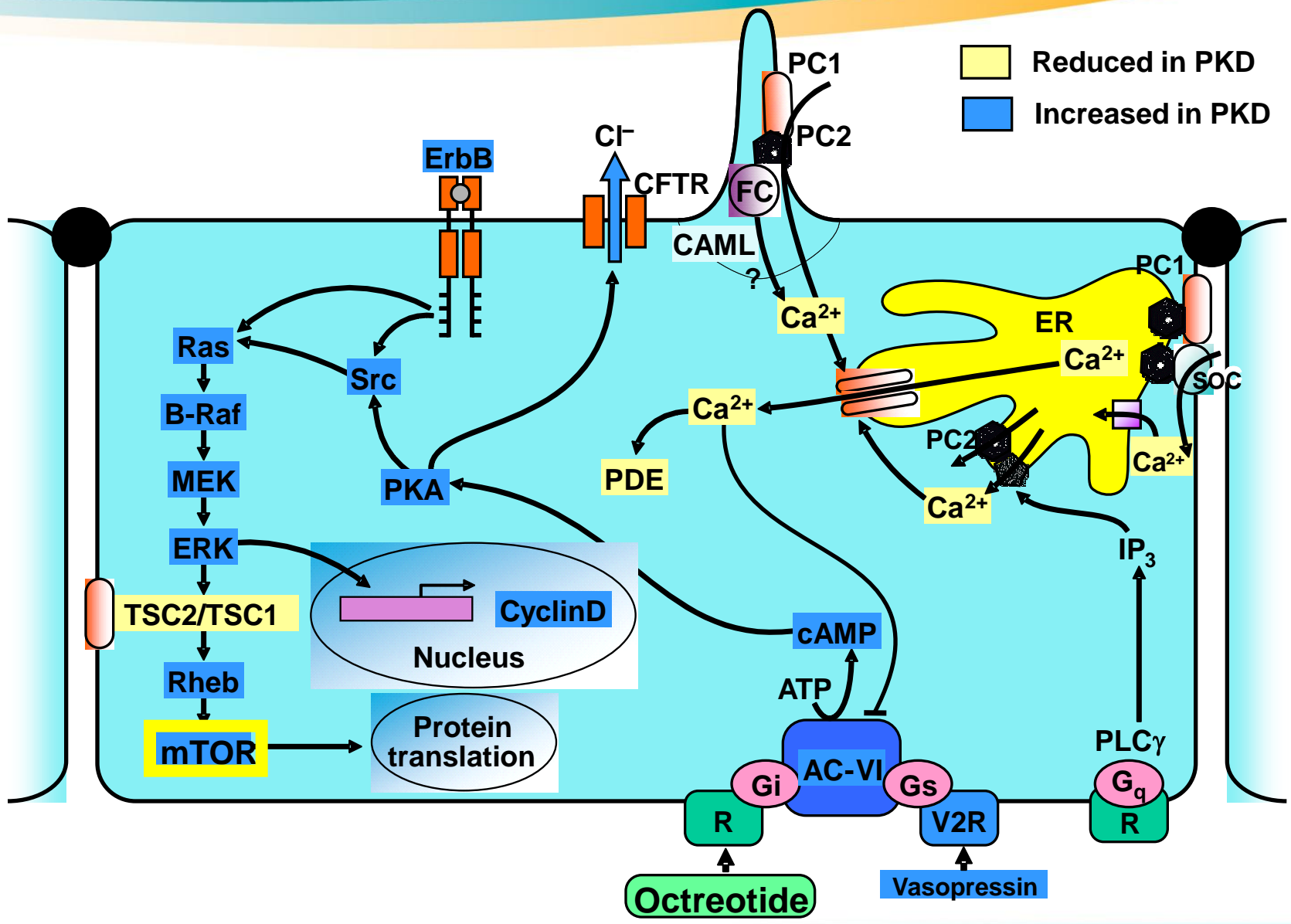
Adverse Events

- Serious: 3 hospitalizations unrelated to drug
- Transient pain on injection site (1-3 days post-injection)
- Granuloma on injection site
- Transient mild diarrhea (1-3 days post-injection)
- Other side effects:
 - gas
 - abdominal pain
 - headache

Hogan, M. C. et al. J Am Soc Nephrol 2010;21:1052-1061

Summary

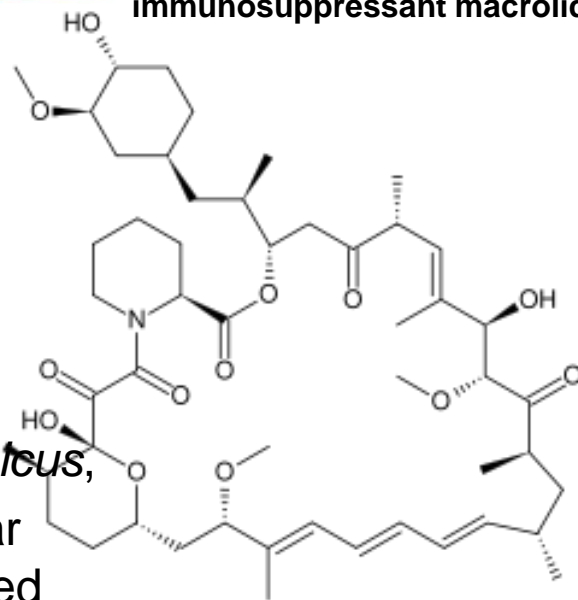
- **12 months of OctLAR treatment reduced liver and kidney volumes**
- **General health perception of PLD patients was improved on OctLAR**
- **Side effects of OctLAR were acceptable**



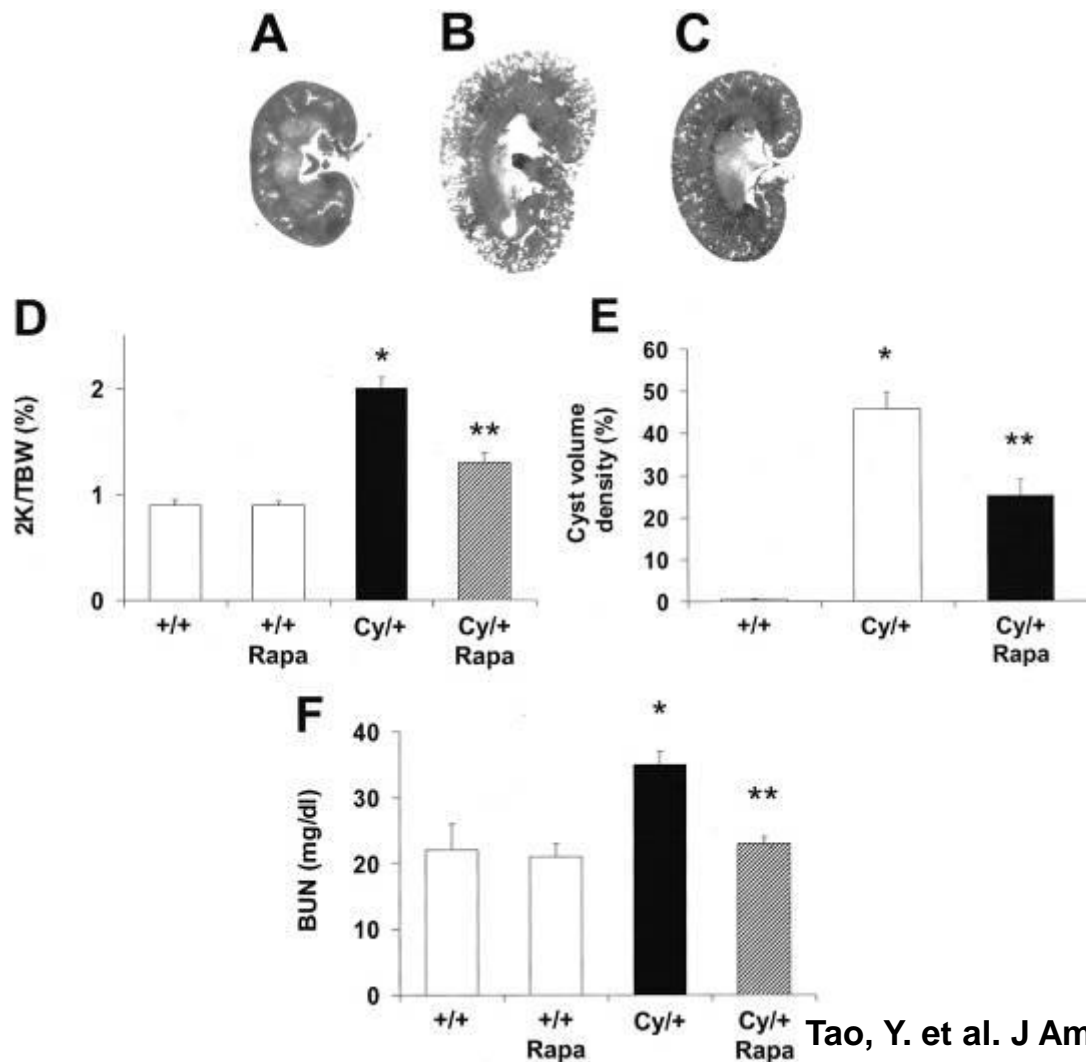
Wyeth, Inc Madison, NJ, an
immunosuppressant macrolide

Sirolimus (Rapamycin, Rapamune®)

- Discovered >30 years ago
- Found in an Easter Island soil sample around 1970. "Rapamycin" comes from Rapa Nui.
- Anti-cancer activity known since mid-1970s.
- Natural compound made by *Streptomyces hygroscopicus*,
- Binds FK506 binding protein (FKBP-12) in a molecular complex that involves the subunit regulatory associated protein of TOR (RAPTOR), and inhibits mTOR kinase activity.
- Inhibition of mTOR: downregulation of CDK complexes and p27 (Kip1) accumulation; blocks cell-cycle progression in late G1/S.
- Inhibits proliferation of endothelial & vascular smooth muscle cells required for tumor angiogenesis.

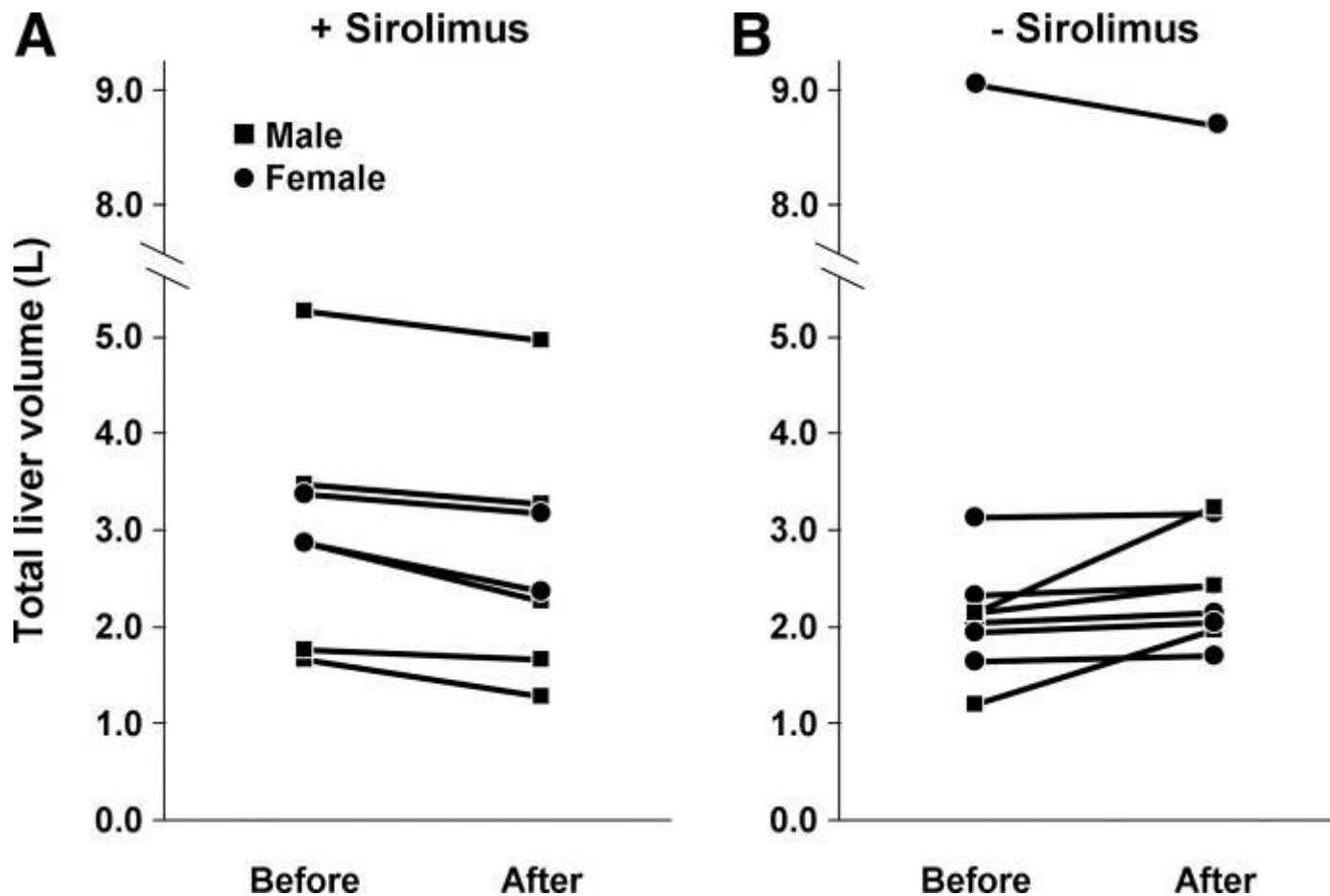


Effects of Rapamycin on development of PKD in Han:SPRD rats.



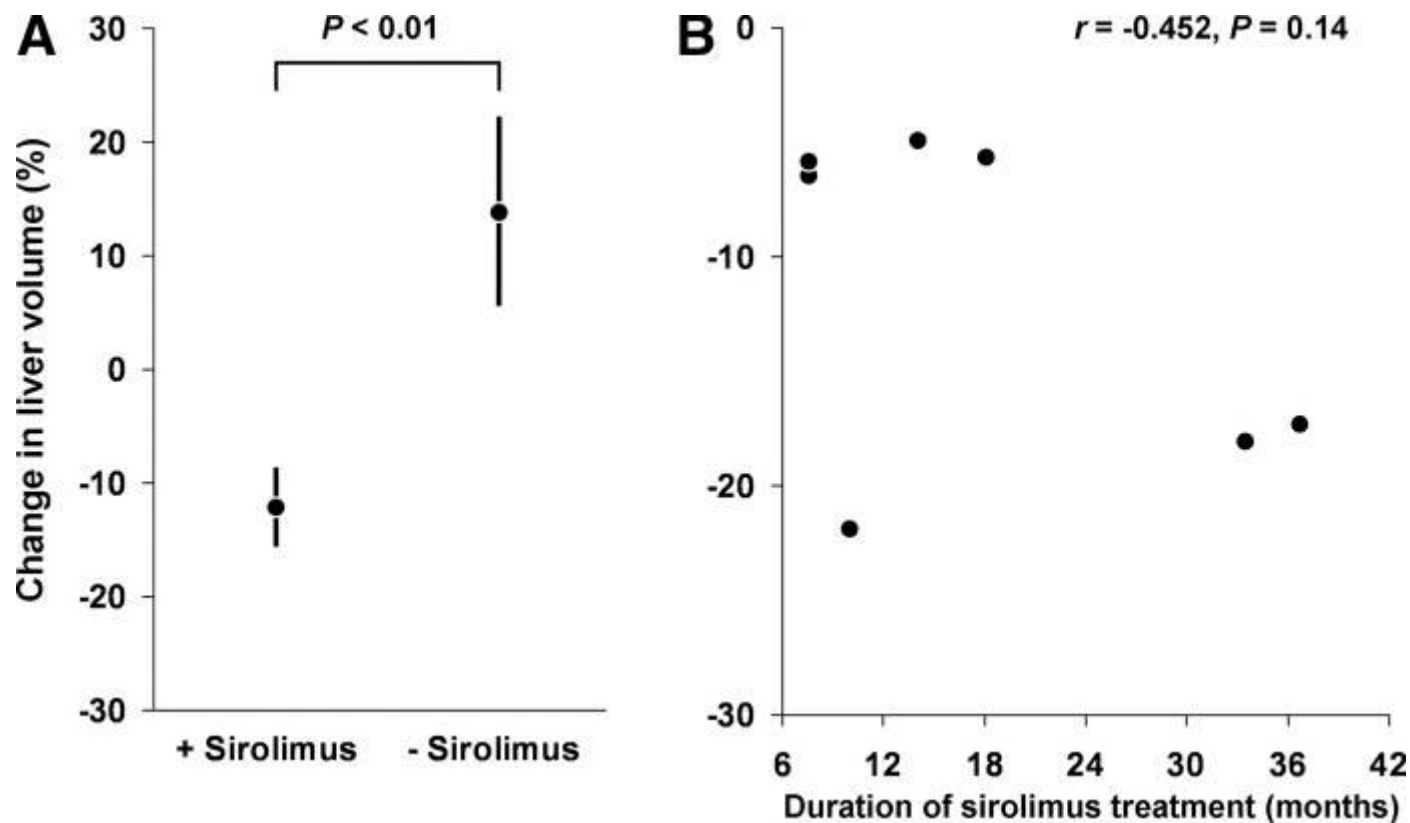
Tao, Y. et al. J Am Soc Nephrol 2005;16:46-51

TLV In Each Individual Patient At The First & Second Imaging Studies



Qian, Q. et al. JASN 2008;19:631-638

Average Changes in TLV in ADPKD Patients Sirolimus



Qian, Q. et al. J Am Soc Nephrol 2008;19:631-638

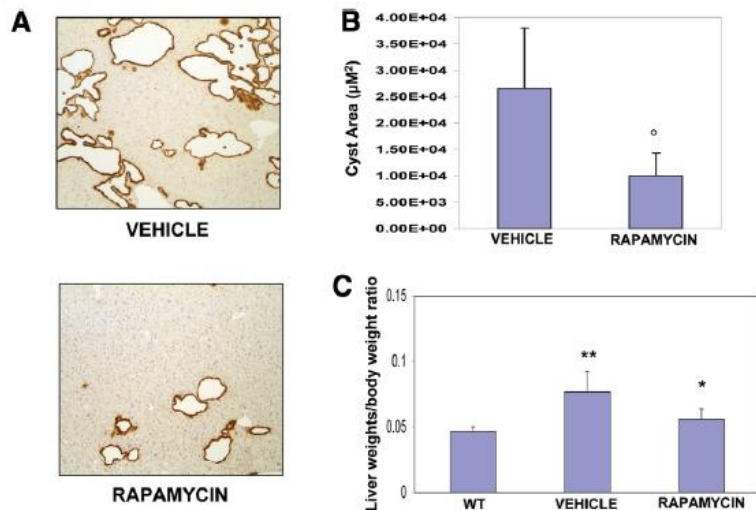


Fig. 2. Rapamycin reduced the cystic area and liver weight/body weight percentage in Pkd2KO mice. (A) The micrographs are representative of vehicle-treated mice (left) and rapamycin (1.5 mg/kg/day)-treated mice (right). (B) As shown in the bar graph, a significant reduction in the cystic area was observed in Pkd2KO-treated animals ($^{\circ}P < 0.001$, $n = 10$). (C) The decrease in cyst growth was also reflected in the significant reduction of the liver weight/body weight ratio. In fact, the liver weight/body weight ratio was higher in mice treated with the vehicle ($n = 10$) versus WT mice ($^{**}P < 0.001$, $n = 6$), and it was significantly reduced in rapamycin-treated mice ($^{*}P < 0.01$, $n = 10$).

Sirolimus reduced cystic area and liver weight in Pkd2 mouse

Spirli et al. Hepatology. May 2010.

Table 3. Effect of sirolimus on progression of hepatic disease in PCK rats and healthy controls

	PCK male		SD male		PCK female		SD female	
	Vehicle	Sirolimus	Vehicle	Sirolimus	Vehicle	Sirolimus	Vehicle	Sirolimus
LW/TBW (%)								
4 weeks	5.43 ± 0.27 ^b	5.41 ± 0.50 ^b	4.18 ± 0.4	4.29 ± 0.29	5.50 ± 0.58 ^b	6.12 ± 1.14 ^b	4.84 ± 0.2	4.70 ± 0.43
8 weeks	5.21 ± 1.22 ^b	5.34 ± 0.61 ^b	2.59 ± 0.31 [*]	2.75 ± 0.16 [*]	5.56 ± 0.80 ^b	5.46 ± 0.60 ^b	3.09 ± 0.85 [*]	2.88 ± 0.23 [*]
12 weeks	4.42 ± 0.74 ^b	4.77 ± 0.35 ^b	2.48 ± 0.10 [*]	2.50 ± 0.13 [*]	6.31 ± 1.40 ^b	5.71 ± 1.00 ^b	2.85 ± 0.54 [*]	2.86 ± 0.37 [*]
Cyst area/liver area (%)								
4 weeks	2.70 ± 0.77	3.47 ± 1.14			5.10 ± 2.60	4.82 ± 1.32		
8 weeks	7.67 ± 8.55	4.56 ± 0.99			5.16 ± 1.60	5.33 ± 1.93		
12 weeks	5.87 ± 2.69	8.23 ± 4.21			6.73 ± 4.14	6.31 ± 2.15	n.a.	
Fibrosis area/liver area (%)								
4 weeks	3.81 ± 0.45	6.20 ± 2.36			8.06 ± 3.26	6.85 ± 2.82		
8 weeks	8.26 ± 7.76	5.76 ± 2.91			5.58 ± 2.39	5.62 ± 3.00		
12 weeks	5.58 ± 2.50	5.39 ± 2.50			6.55 ± 2.66	6.63 ± 2.04		
BrdU-positive cells/field of view (liver)								
4 weeks	437 ± 146	704 ± 329	399 ± 67.4	407 ± 89.2	322 ± 084	435 ± 210	317 ± 62.1	419 ± 126
8 weeks	371 ± 227 ^b	447 ± 142 ^b	125 ± 18.4	160 ± 53.6	346 ± 157	369 ± 172	188 ± 34.6	155 ± 025.9
12 weeks	280 ± 068.9	438 ± 189 ^b	176 ± 97.9	213 ± 52.0	306 ± 104	243 ± 069	228 ± 61.2	268 ± 061.0
Bile acids (µmol/L)								
4 weeks	35.8 ± 08.87 ^b	83 ± 31.8 ^{a,b}	23.3 ± 9.3	21.9 ± 07.74	36.0 ± 21.5	63.6 ± 32.1 ^b	39.0 ± 35.6	15.0 ± 0.43
8 weeks	81.5 ± 55.7	121 ± 33.5 ^b	29.6 ± 9.43	33.1 ± 14.6	106.0 ± 48.8	68.9 ± 30.3	49.1 ± 16.3	28.6 ± 9.19
12 weeks	37.5 ± 20.0	104 ± 06.09 ^{a,b}	24.9 ± 6.36	18.6 ± 04.99	83.5 ± 19.4 ^b	86.0 ± 32.1 ^b	25.9 ± 08.85	20.2 ± 9.46
ALAT (U/L)								
4 weeks	59.9 ± 09.39	65.3 ± 24.8	44.0 ± 16.9	63.1 ± 12.8	64.7 ± 11.3	68.8 ± 21.0	71.1 ± 31.6	54.5 ± 16.7
8 weeks	92.4 ± 96.0	68.2 ± 45.5	41.6 ± 11.9	44.4 ± 12.7	72.5 ± 08.04	89.2 ± 27.7	60.8 ± 31.0	33.3 ± 01.57
12 weeks	66.4 ± 20.2 ^b	62.5 ± 17.0	42.5 ± 10.6	57.8 ± 16.6	67.3 ± 25.3	79.6 ± 14.2	71.7 ± 48.8	60.7 ± 45.0
ASAT (U/L)								
4 weeks	266 ± 049.9	586 ± 053.4	259 ± 112	320 ± 131	296 ± 86.6 ^b	372 ± 180	417 ± 93.2	221 ± 65.0
8 weeks	382 ± 106	390 ± 125	291 ± 066.6	360 ± 127	508 ± 219	521 ± 212	305 ± 74.1	223 ± 19.0
12 weeks	291 ± 081.7	477 ± 073.4 ^a	287 ± 073.4	307 ± 032.0	436 ± 79.3 ^b	579 ± 211	329 ± 74.5	246 ± 43.2

No effect of Sirolimus on liver disease in PCK rat.

Renken et al. ePub NDT 2010.

Results are given as mean ± SD.

^aP < 0.05 (sirolimus-treated animals versus vehicle-treated PCK and SD rats, respectively).

^bP < 0.05 (PCK rats versus SD rats of the respective treatment group).

^{*}P < 0.05 (SD rats treated for 8 and 12 weeks versus treatment for 4 weeks).

Symptomatic Polycystic Liver Disease

Nonsurgical Treatment Options

- **Avoid estrogens, caffeine**
- **H₂-blocker or H⁺/K⁺ ATPase inhibitor**
- **Somatostatin analogues**
- **mTor inhibitors (?)**

• May have a future role but because of toxicity is not likely to have a major impact as single drug.

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- Peter Harris PhD
- Chris Ward MD PhD
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 - page.linda@mayo.edu
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 - Mayo Foundation.
 - Novartis.

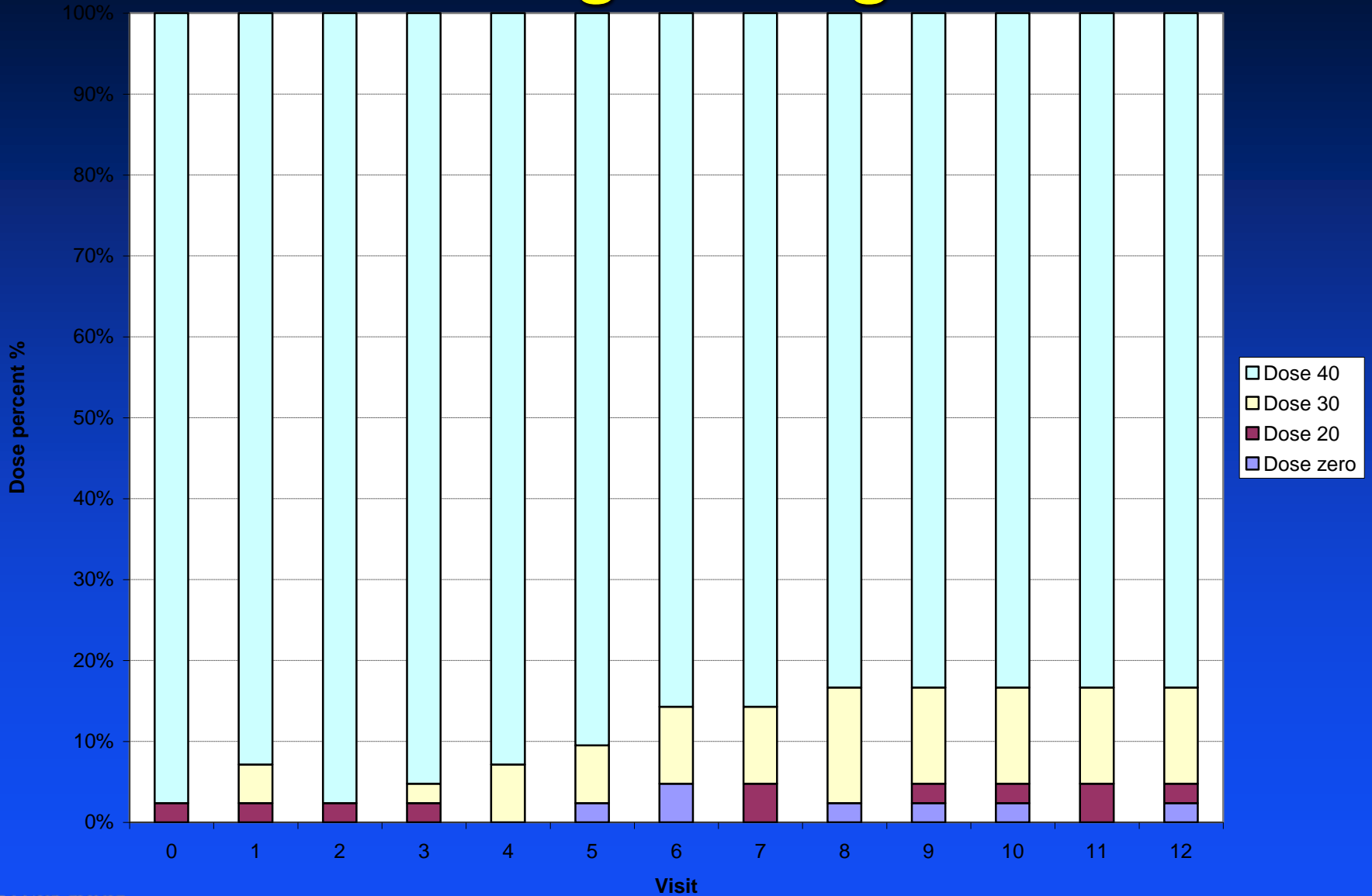
Liver Disease in ADPKD

WEBINAR, July 13th 2010.

Marie Hogan MD PhD
Assistant Professor, Division of Nephrology &
Hypertension,
Mayo Clinic, Rochester, MN.



Drug Dosing

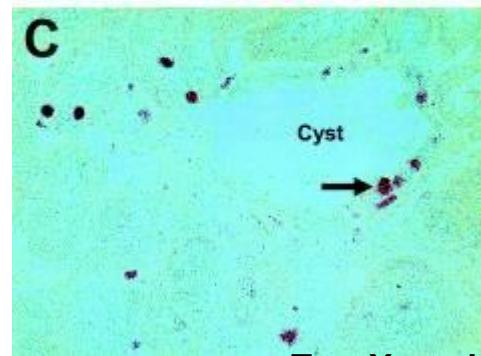
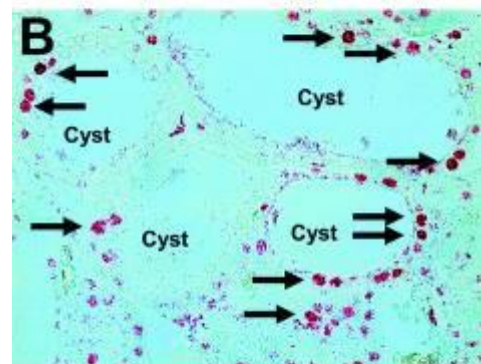
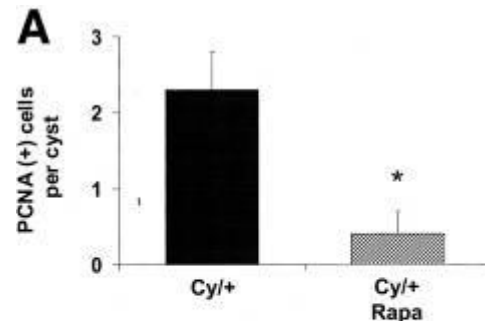


Tubular Cell proliferation in Cysts Markedly Reduced.

PCNA-positive cells in tubular epithelial cells lining the cysts was significantly decreased by rapamycin. * $P < 0.05$ versus vehicle-treated Cy/+ rats.

PCNA staining (arrows) in cysts of vehicle-treated Cy/+ rats.

PCNA staining (arrows) in cysts of rapamycin-treated Cy/+ rats.



Tao, Y. et al. JASN. 2005;16:46-51