ADPKD & ADPLD

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Radboudumc

DLW 21 june 2018

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Structure

- Autosomal Dominant Polycystic Kidney Disease (ADPKD)
- Autosomal Dominant Polycystic Liver Disease (ADPLD)
- Case
- 3 questions

Question 1

Which is the most common extrahepatic manifestation of ADPKD?

1. Cardiac valve abnormalities
2. Colonic Divericulae
3. Hepatic cysts
4. Hypertension

Question 2

- ADPKD is a genetic disorder. You are approached by a family member of a patient with ADPKD who desires to be screened for ADPKD. Which test do you order ?

1. Creatinine
2. CT kidney & bladder
3. Gene test
4. Renal ultrasound

Question 3

- A patient with ADPKD does develop hypertension. Which class of anti-hypertensives is the most appropriate

1. Angiotensin receptor blocker
2. Beta blocker
3. Calcium channel blocker
4. Loop diuretic

What is ADPKD?

- Autosomal dominant polycystic kidney disease (ADPKD)

- **Presentation**
  - presents clinically in the third or fourth decade of life

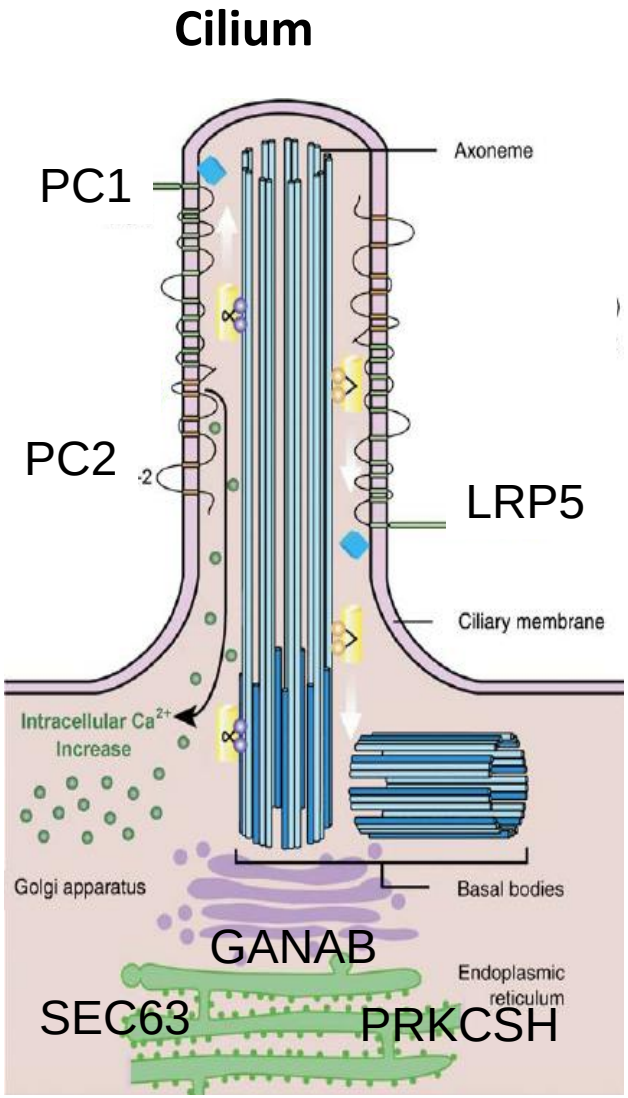
- **Renal phenotype:** continuous development of renal cysts
  - increase in total kidney volume
  - hypertension
  - glomerular filtration rate reduction
  - end-stage renal disease in the majority of patients

- **Frequent** inherited disorder
  - point prevalence for ADPKD of ~3–5/10 000
  - ~10% of cases with end-stage renal disease

What causes ADPKD?

- **Genetic mutations**
- PKD1 (85%) vs. PKD2 (15%)
- localize to the primary cilium

- Effect of mutations
- High cAMP, low Ca
- ↑ secretion and proliferation of renal epithelial cells



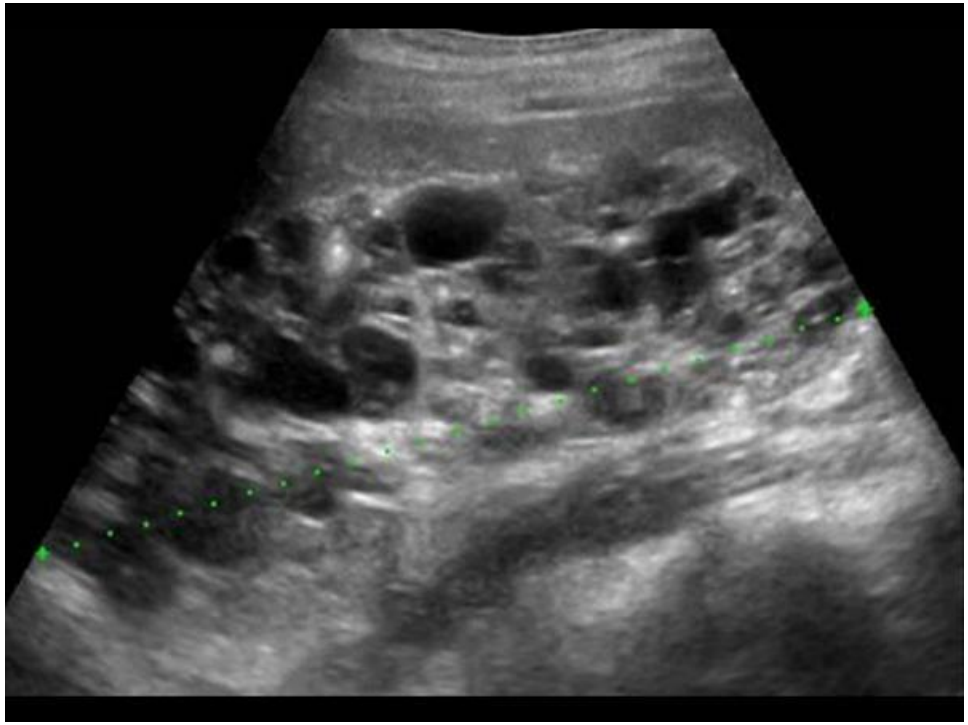
Proc Natl Acad Sci U S A. 2014 Apr 8;111(14):5343-8

How do I diagnose ADPKD

TABEL Criteria van Ravine voor het stellen van de diagnose 'autosomaal dominante polycysteuze nierziekte'[3]

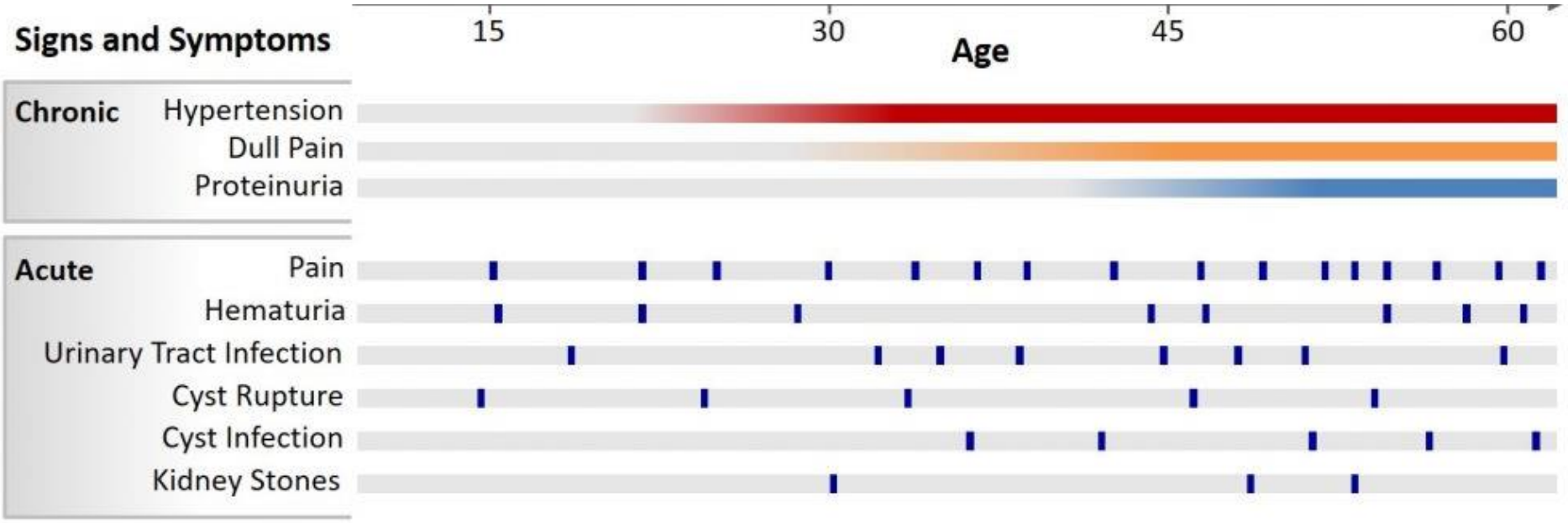
leeftijd in jaren	aantal cysten bij	
	positieve familieanamnese	negatieve familieanamnese
15-29	> 2 niercysten	> 10 cysten per nier
30-59	> 2 cysten per nier	> 10 cysten per nier
≥ 60	> 4 cysten per nier	> 10 cysten per nier

Ultrasound in ADPKD



Polycystic kidney

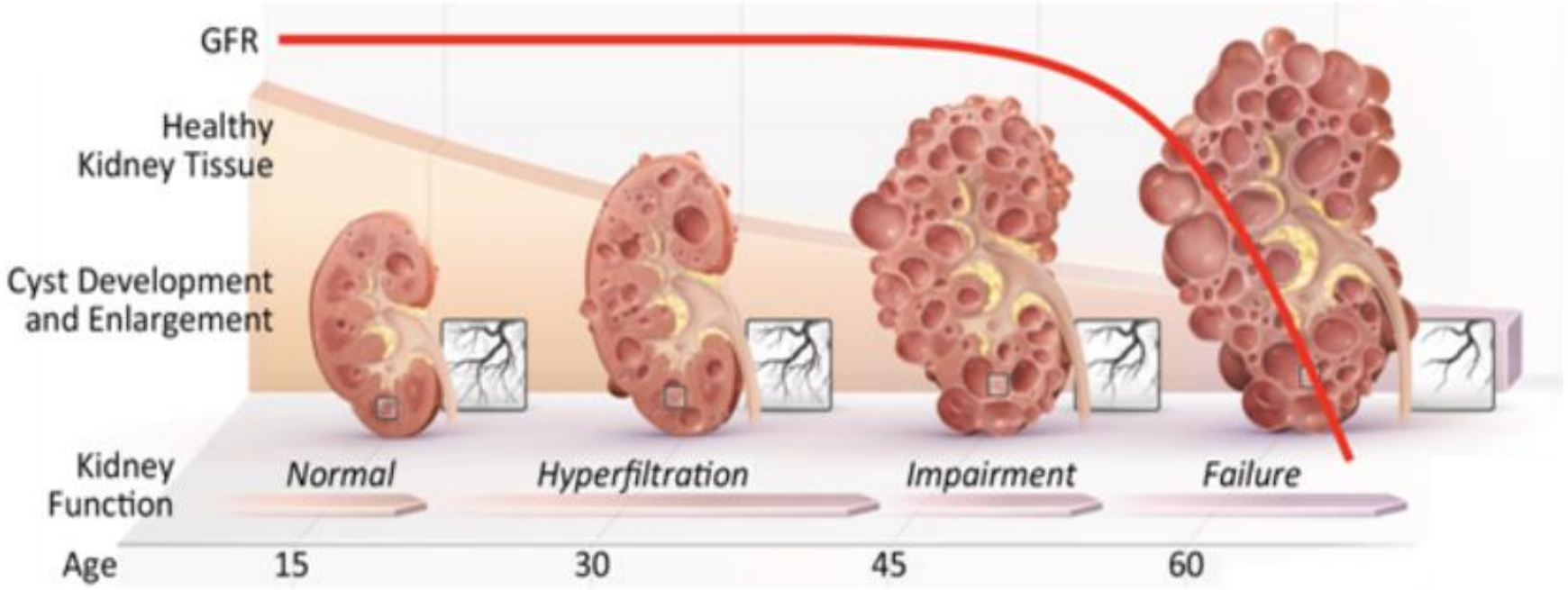
Renal Phenotype of ADPKD



N Engl J Med 2006; 354:2122-2130

Renal failure in ADPKD

- Renal function remains compensated for considerable time



N Engl J Med 2006; 354:2122-2130

CKD stages

Stage	GFR*	Description
1	90+	Normal kidney function, but urine findings, structural abnormalities, or genetic trait point to kidney disease
2	60-89	Mildly reduced kidney function and other findings (as for stage 1) point to kidney disease
3A	45-59	Mild to moderately reduced kidney function
3B	30-44	Moderate to severely reduced kidney function
4	15-29	Severely reduced kidney function
5	<15 or on dialysis	Very severe or ESRD (sometimes called established kidney failure)

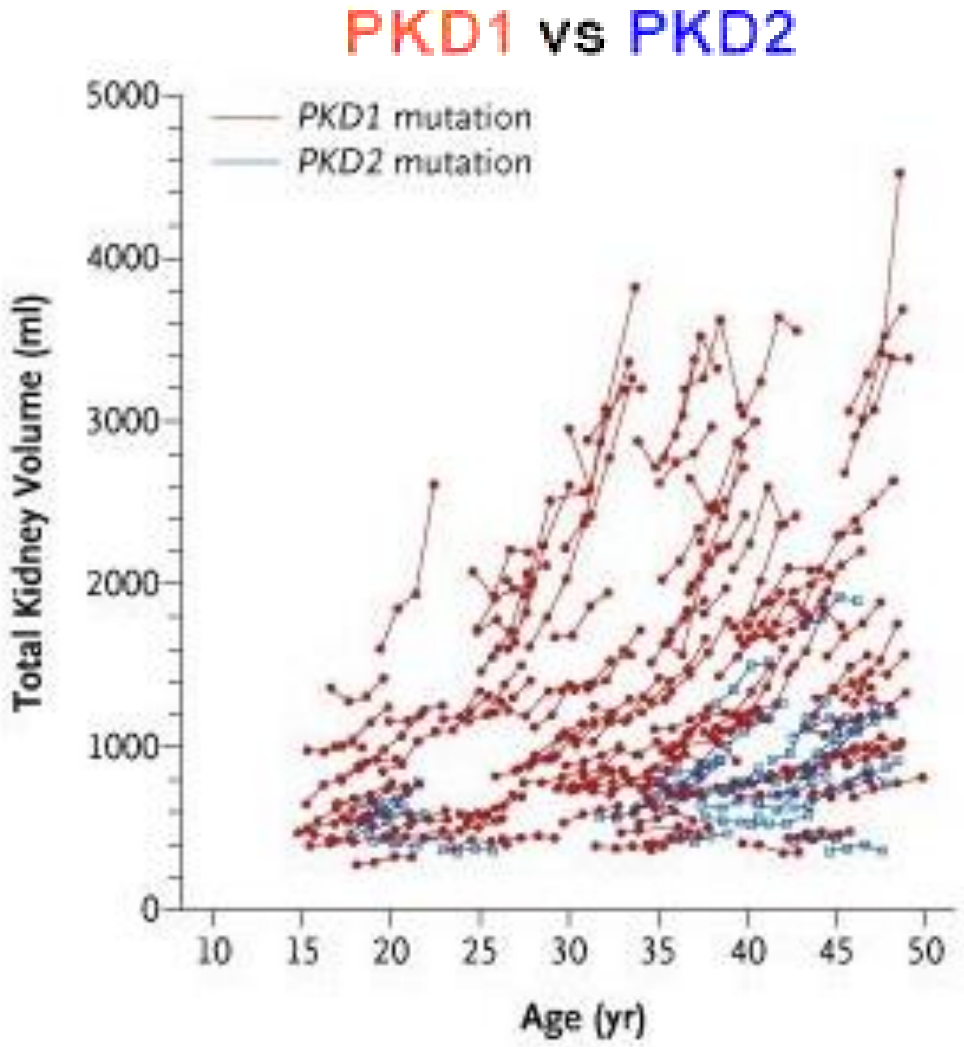
How do I predict renal prognosis?

- **Parameters for poor prognosis**

- **Rate of GFR decline**
  - Decrease in eGFR of ≥5 mL/min/1.73m2 in 1 year
  - Decrease in eGFR of ≥2.5 mL/min/1.73m2 per year over 5 years

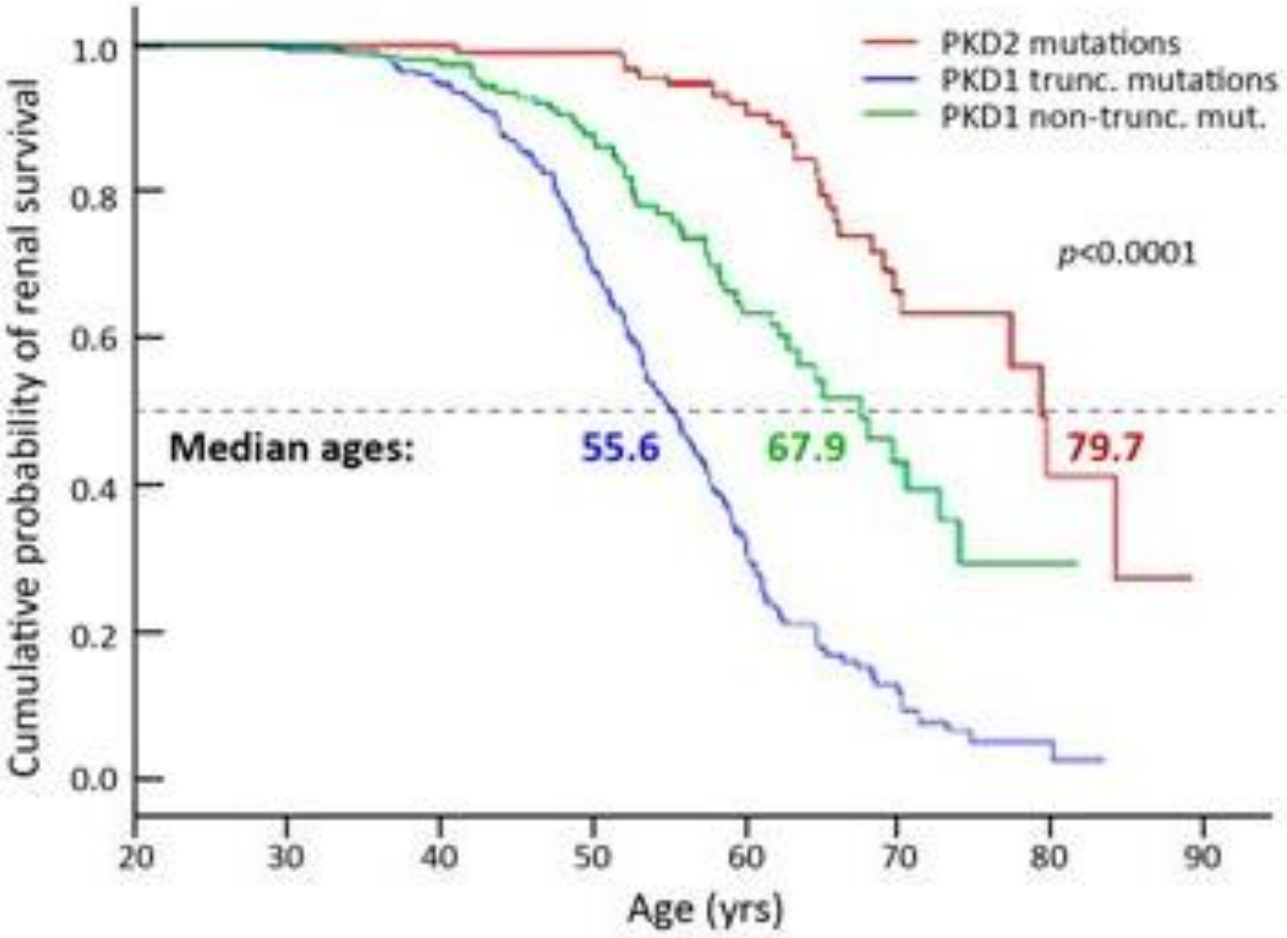
- **Rate of kidney growth**
  - An annual increase in TKV of ≥5% per year

PKD gene associates with renal volume



N Engl J Med 2006 354 2128

PKD mutation class predicts renal survival



1. Cornec-Le Gall E, *et al. J Am Soc Nephrol* 2013; 24(6):1006-13.
2. Pei Y, *et al. Kidney Int* 2012; 81(4):412-7.

Basic management

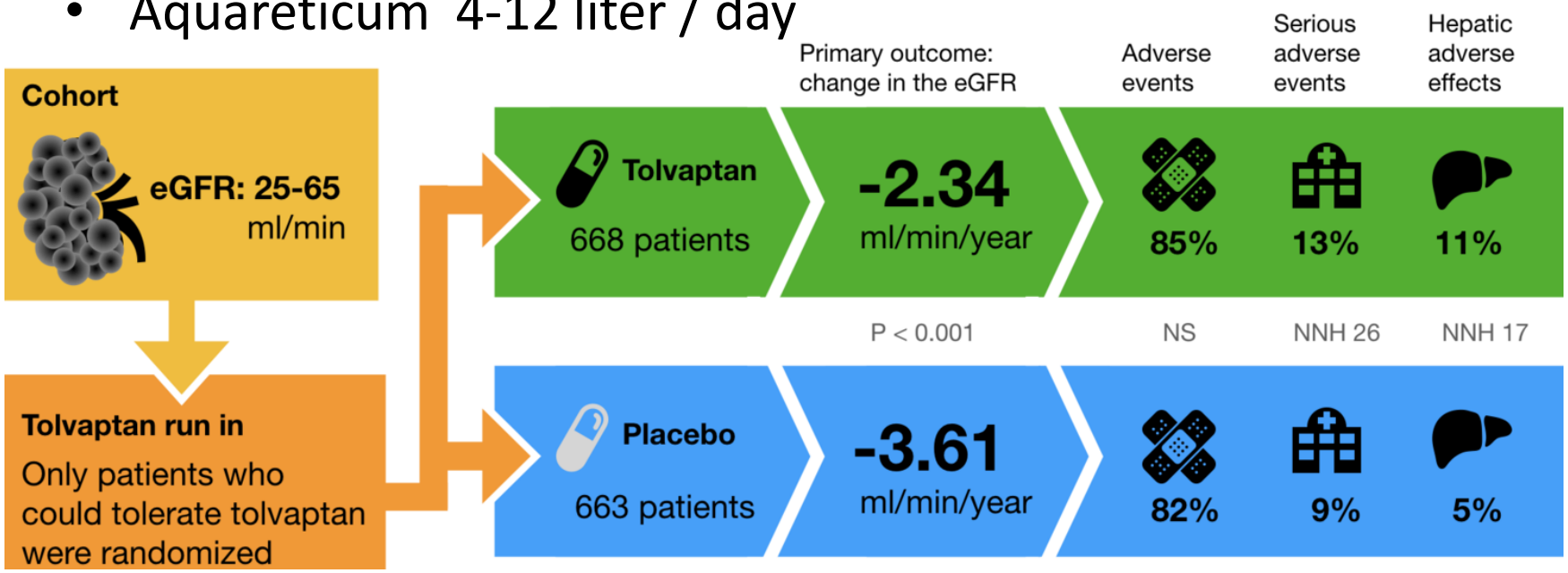
- **Fluid intake**
  - Water intake 2-4 liter / day
  - Low-salt diet
  - Low-protein diet (CKD4)

- **Blood pressure control**
  - Target blood pressure target of ≤140/90 mmHg
  - Angiotensin-converting enzyme inhibitors
  - Angiotensin receptor blockers

Is there a treatment for ADPKD?

Tolvaptan

- Vasopressin antagonist
- Aquareticum 4-12 liter / day



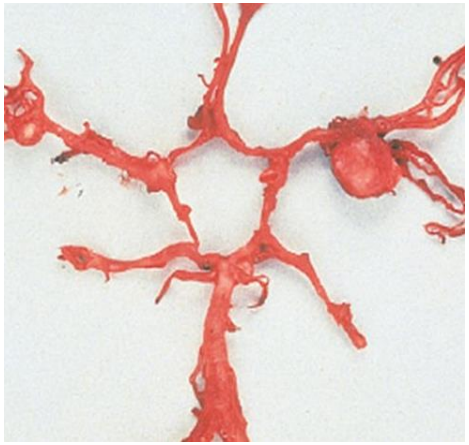
Tolvaptan

- 4 year treatment gives 1 year saved from dialysis

https://www.nejm.org/doi/full/10.1056/NEJMoa1710030

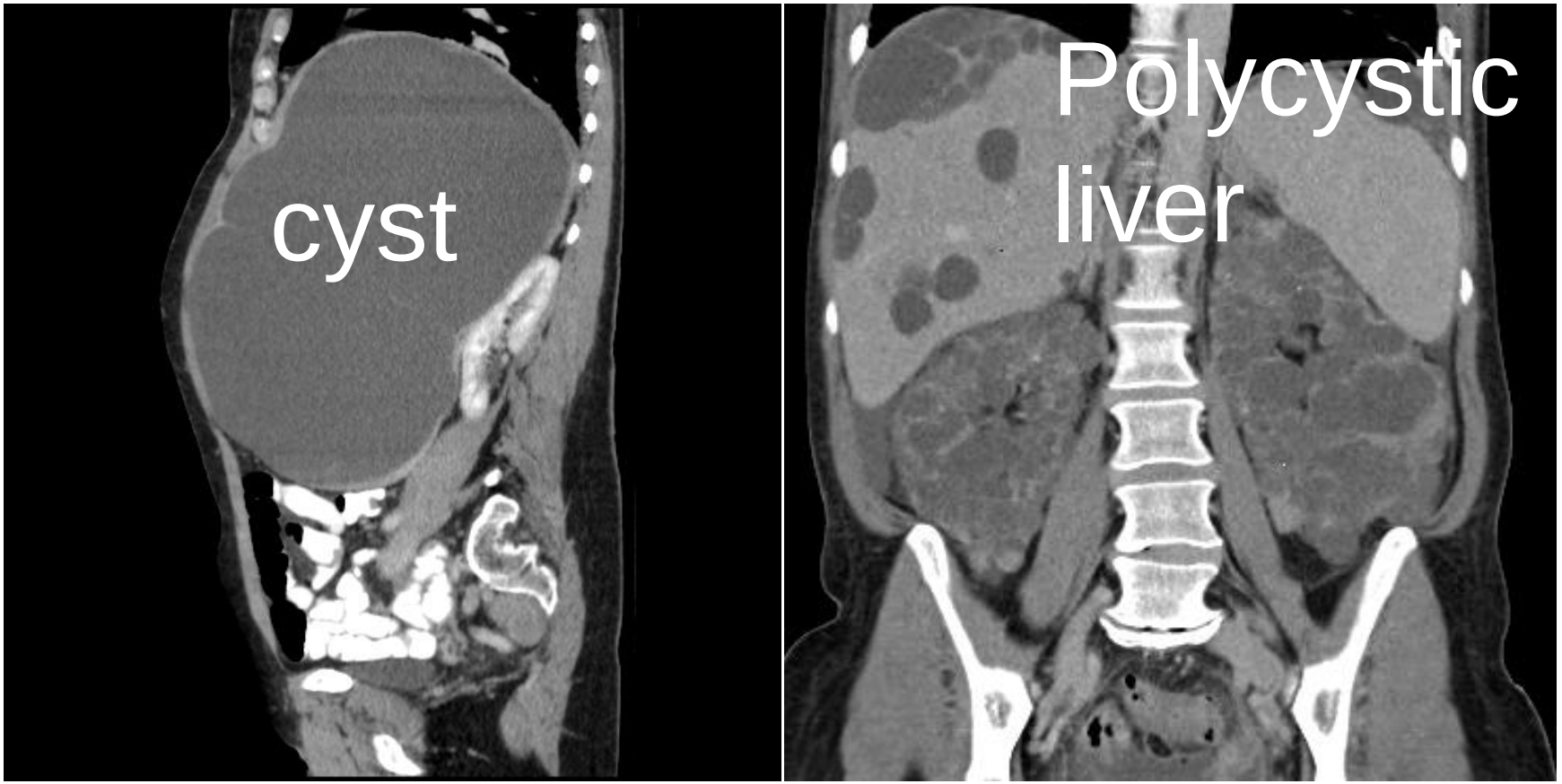
ADPKD extra renal manifestations

- **Major extrarenal complications of ADPKD**
  - Cerebral aneurysms
  - Hepatic cysts
  - Cardiac valve disease
  - Colonic diverticula
  - Abdominal wall and inguinal hernia

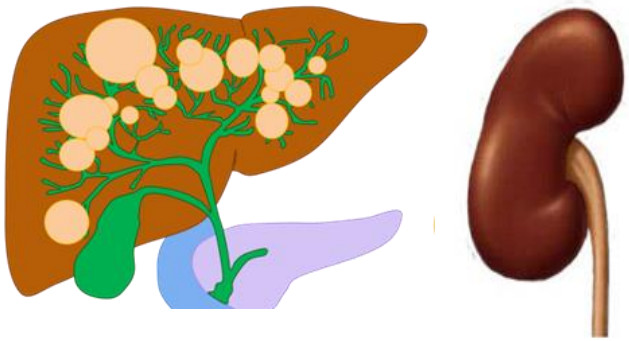


Aneurysm of cerebral vasculature

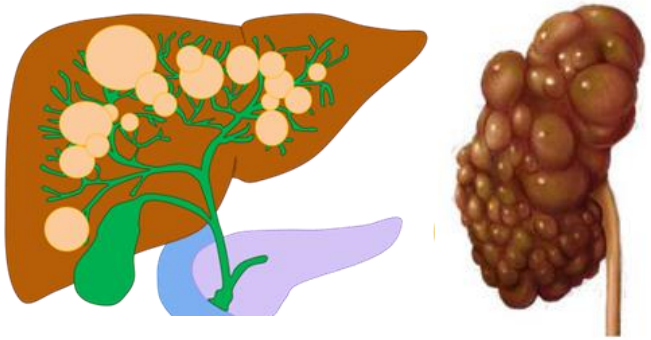
Hepatic Cysts: large / polycystic



Polycystic liver



ADPLD
Autosomal dominant polycystic **liver** disease



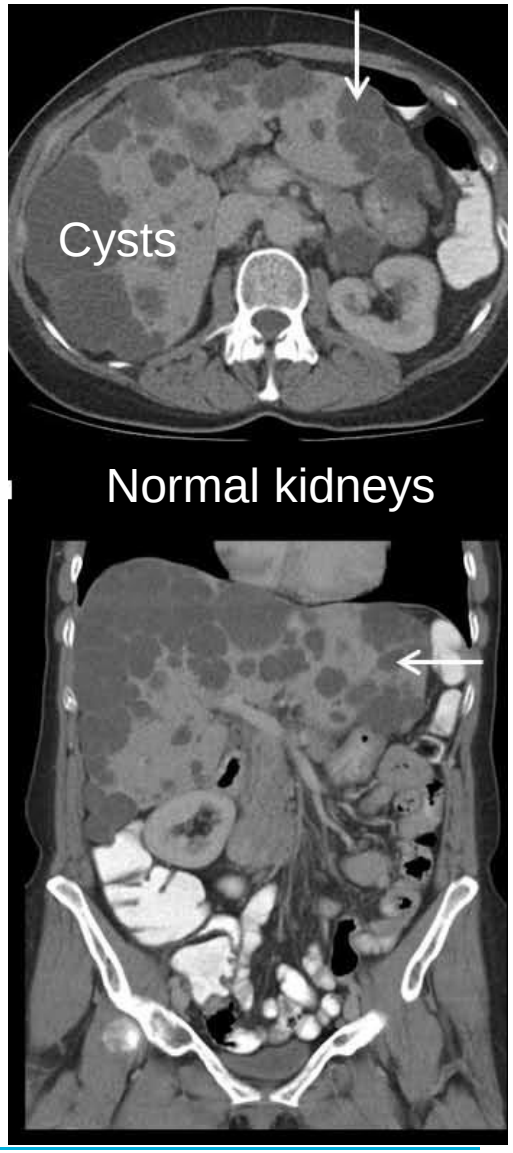
ADPKD
Autosomal dominant polycystic **kidney** disease

Autosomal dominant polycystic liver disease (ADPLD)

- Primarily a **hepatic** disease

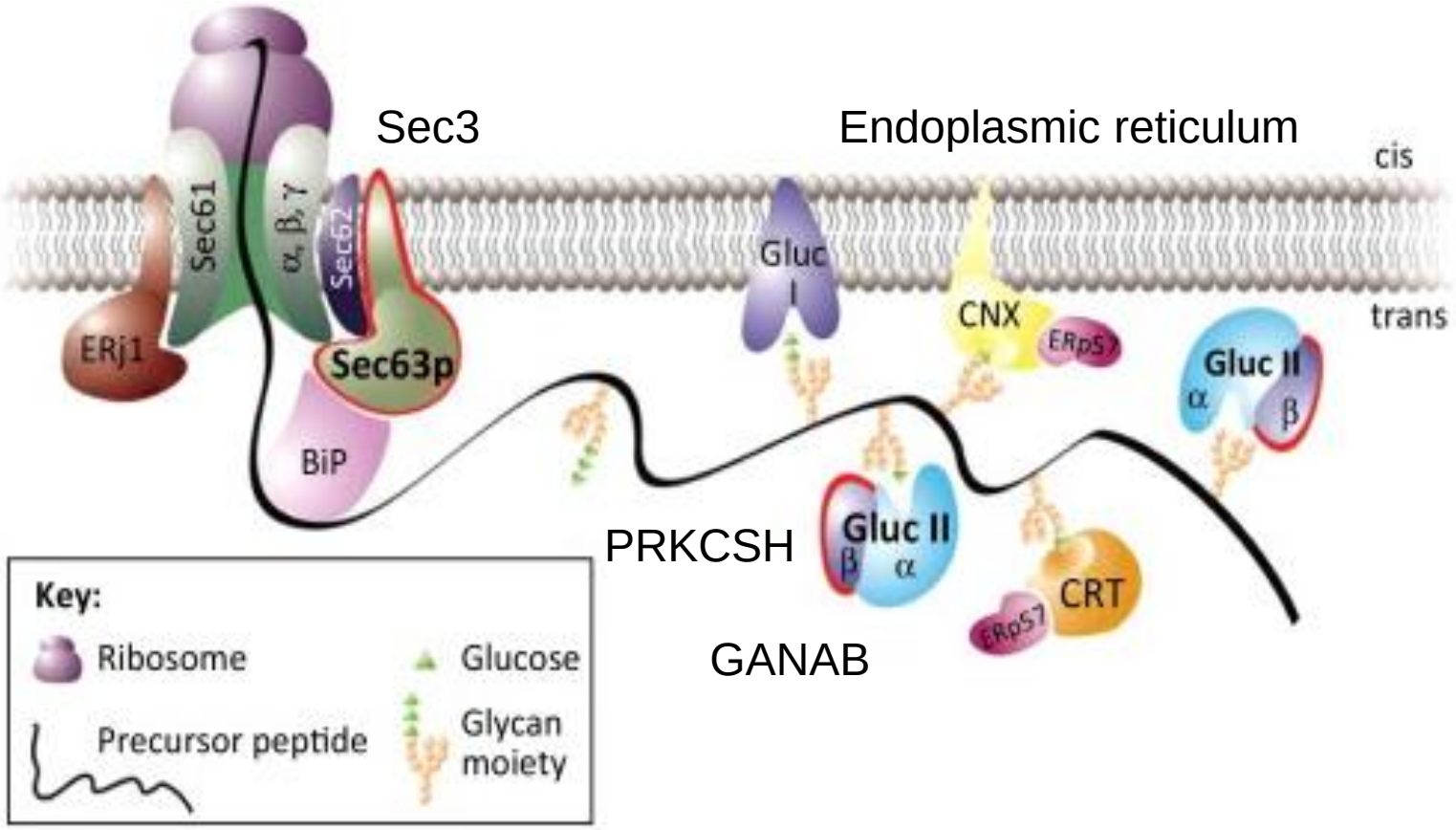
- **Frequency**
  - Not very common (1/158000)

- **Phenotype**
  - Multiple non-communicating liver cysts
  - Severe: spleen / pancreas cysts
  - No renal cysts
  - Onset 30-40 years-of-age
  - Mitral valve abnormalities ~ 20%



Keimpema. Liver Int. 2011;31: 92-8

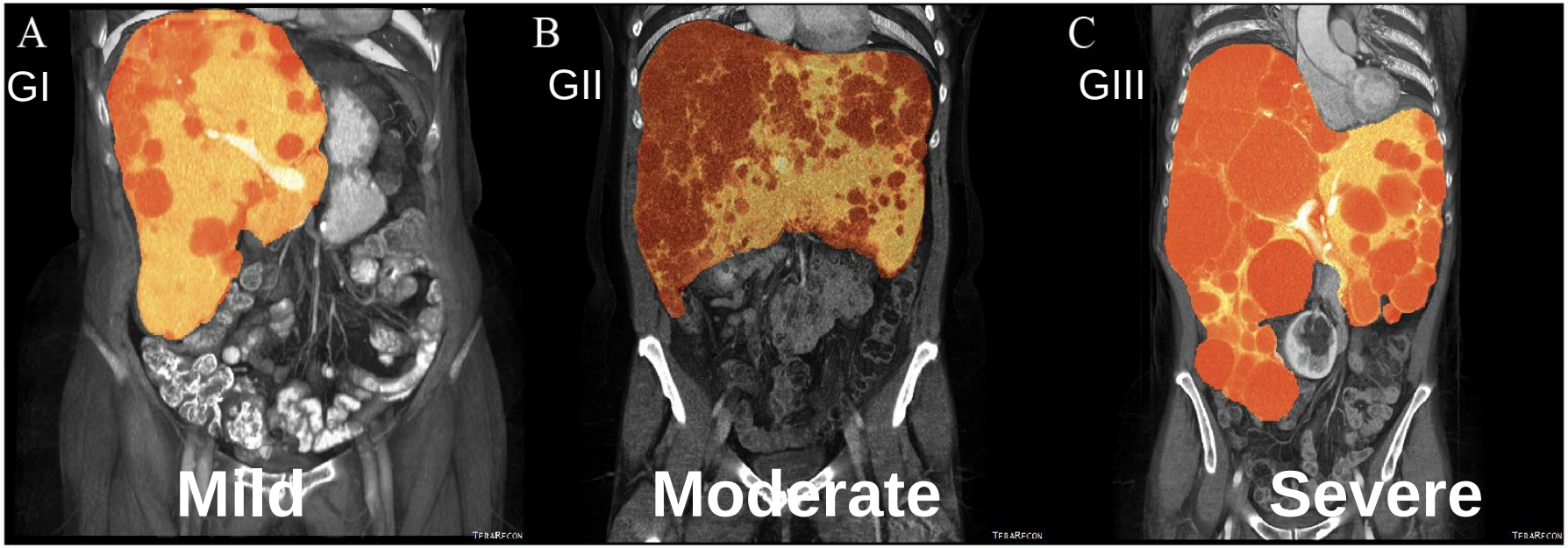
Genes in ADPLD



Genes in ADPLD encode endoplasmic reticulum proteins
Involved in quality control of folding & processing of glycoproteins
Account for ~25% of ADPLD cases

Polycystic liver disease (PLD)

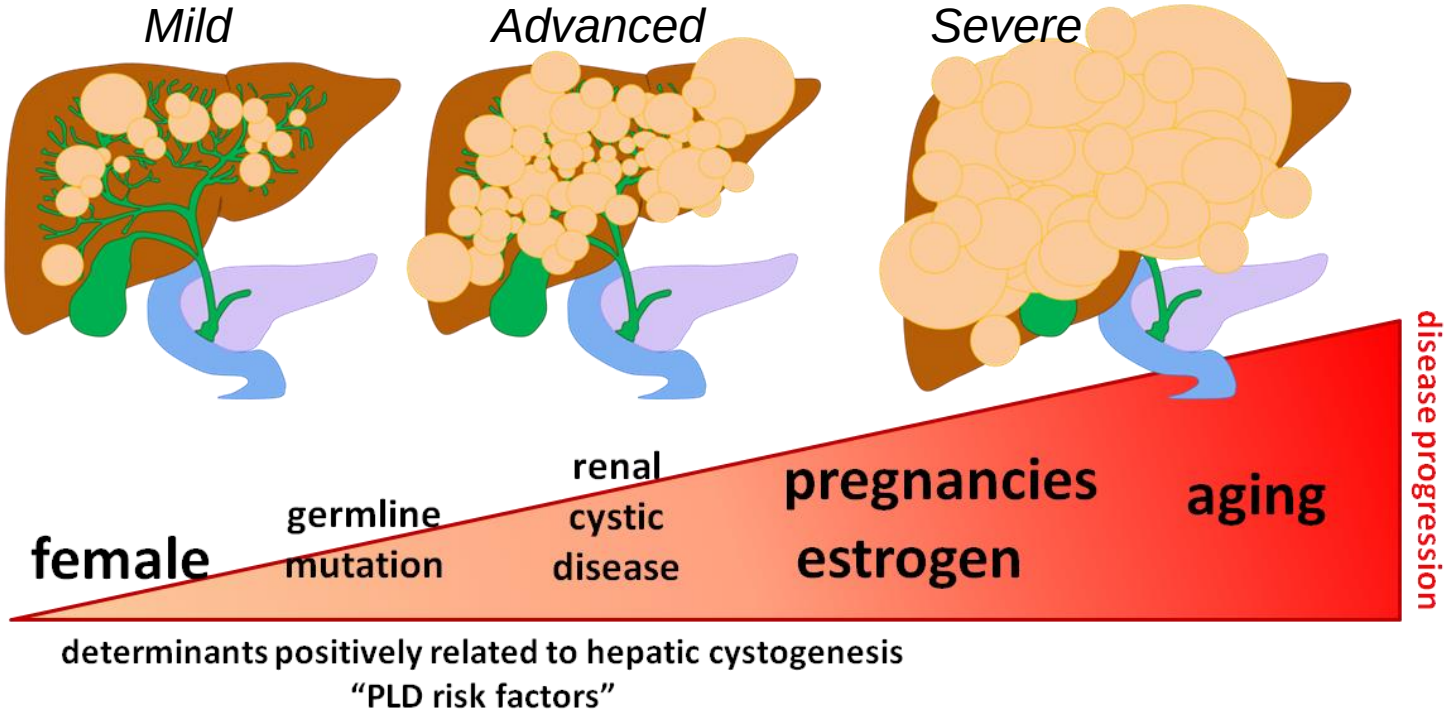
- Liver volume displaces other abdominal organs
- Gigot classification



Journal of Hepatology DOI: (10.1016/j.jhep.2017.11.024)

Risk factors for massive PLD

- *PKD1, PKD2* [1,2]
- Somatic hits, transheterozygous mechanisms [3]
- Modifier genes, multiple mutations [4,5]
  De novo, mosaicism
- Proven:
  [6-8]



[1] Hateboer et al. Lancet 1999
[2] Torres et al. Kidney Int. 2012
[3] Koptides et al. Hum Mol Genet. 2000
[4] Kleffmann et al. J Hepatology 2012
[5] Bergmann et al. JASN 2011
[6] Gabow et al. Hepatology 1990
[7] Sherstha et al. Hepatology 1998
[8] Chapman et al. Adv Ren Repl Th 2003

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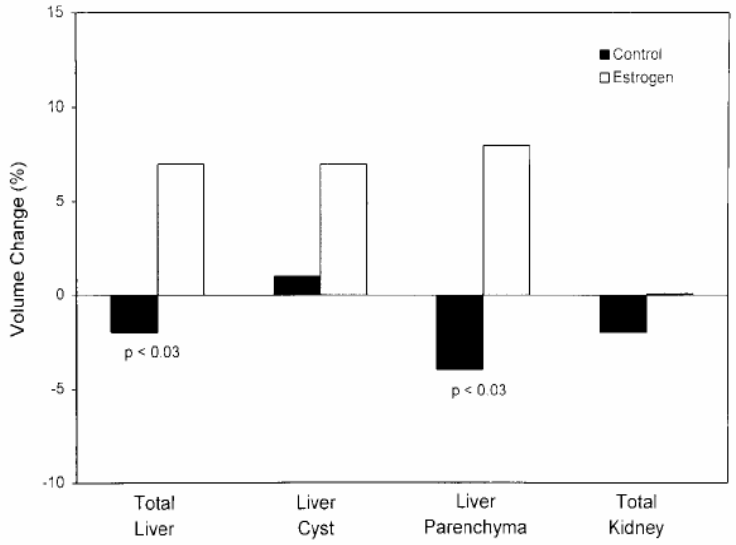
Estrogens use

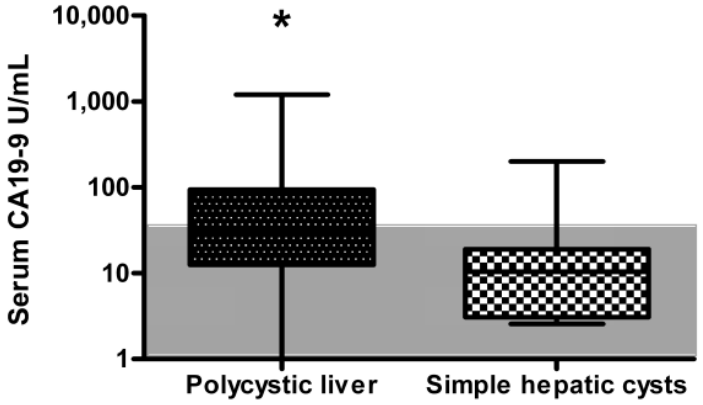
- Female sex, estrogens use and multiple pregnancies are risk factors polycystic liver growth
- 20 postmenopausal ADPKD patients
  - Estrogens use versus no treatment for one year
  - Estrogen treatment associated increase in liver volume; no increase in kidney volume
- Discourage the use of exogenous estrogens in symptomatic PLD patients



Shertsha, Hepatology.1997; 26(5):1282-6.
Gevers, Nat Rev Gastroenterol Hepatol 2013;10(2):101-108.

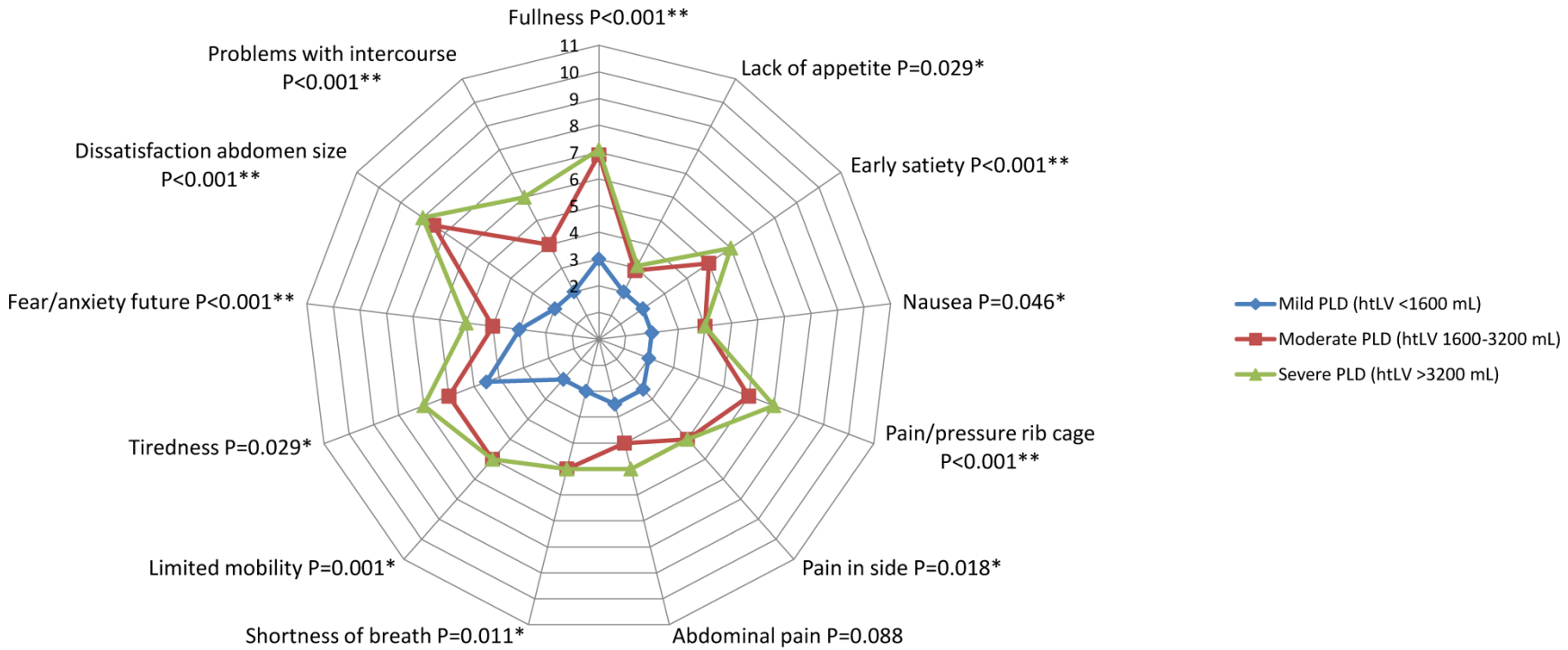
Lab in PLD

- No abnormalities in liver synthesis
- Abnormalities in liver enzymes may occur:
  - ↑ γGT ; ↑ AP
- ↑ Carbohydrate antigen 19-9
  - Raised in cyst infections
  - Possible follow up biomarker?



Van Keimpema L et al., Liver Int. 2011 Jan; 31(1):92-8
Waanders, E., et al., Liver Int, 2009. 29(9): p. 1389-95.

Qol impairment depends on PLD volume



Liver Int. 2014 Nov;34(10):1578-83.

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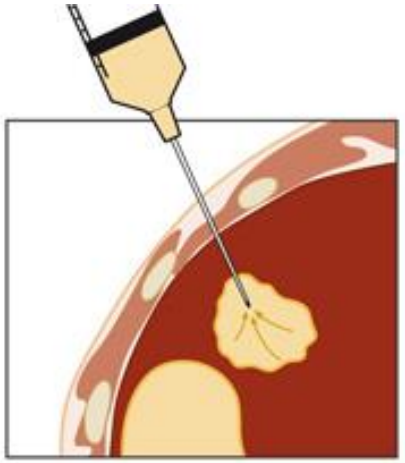
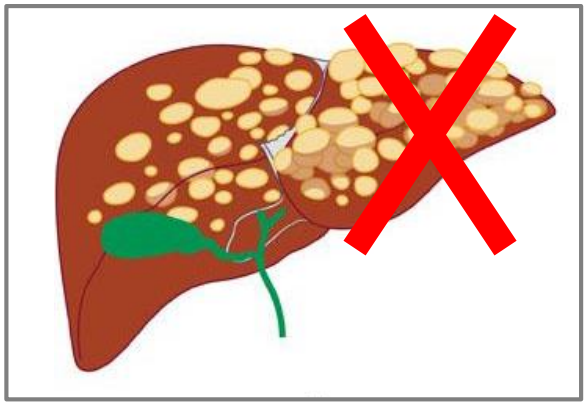
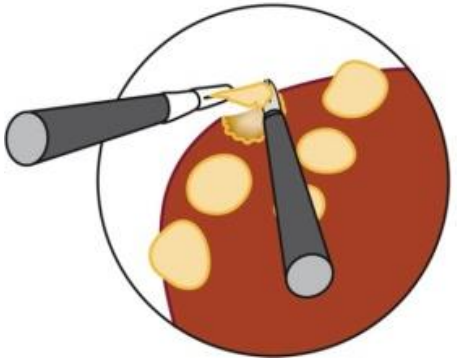
Treatment



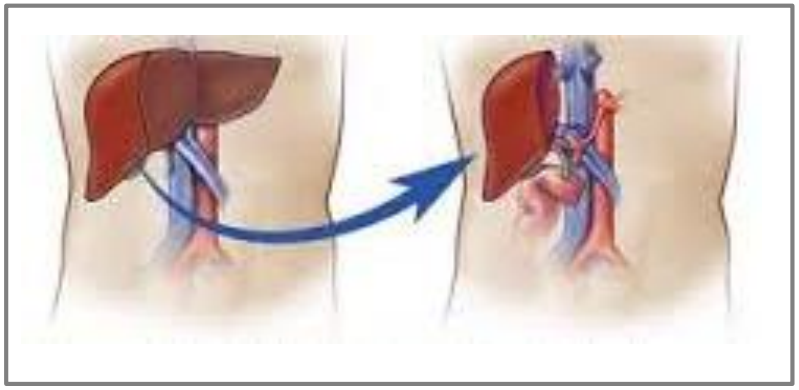
1. Aspiration-sclerotherapy



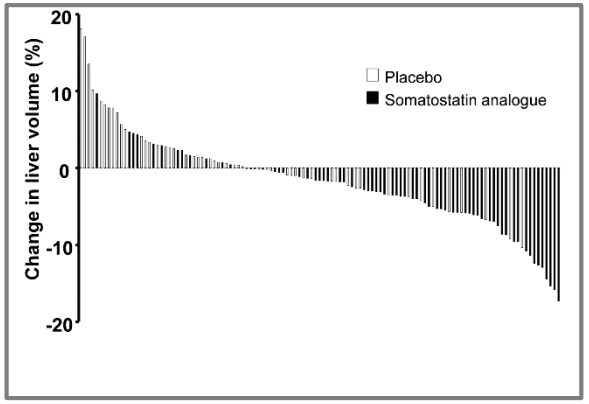
2. Resection



3. Fenestration



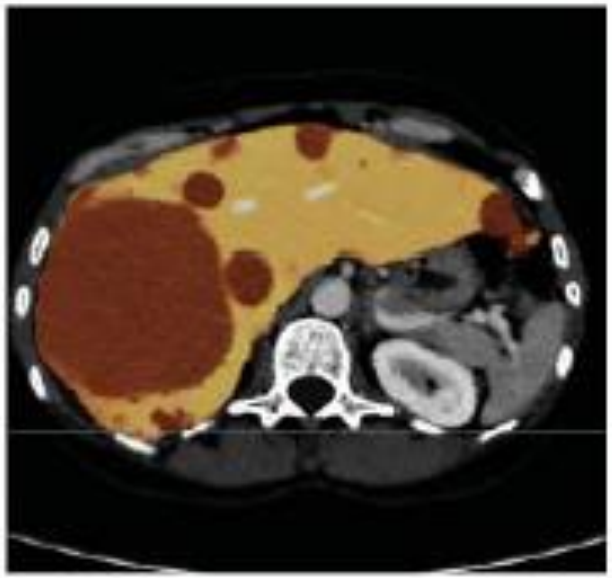
4. Liver transplantation



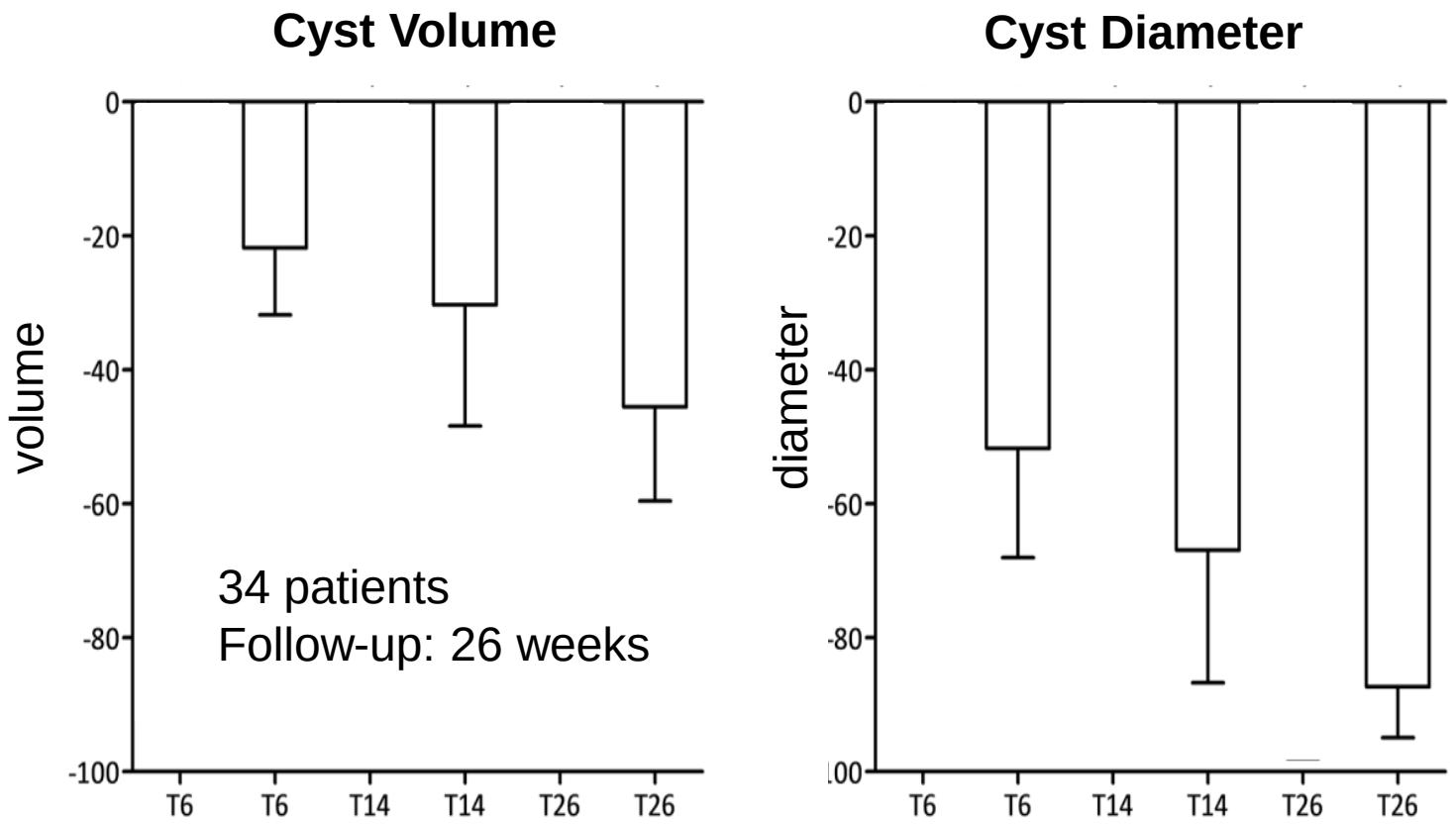
5. Somatostatin analogues

Aspiration Sclerotherapy

Aspiration - Sclerotherapy
Dominant cyst (>~8cm) percutaneously accessible



Aspiration Sclerotherapy: effects

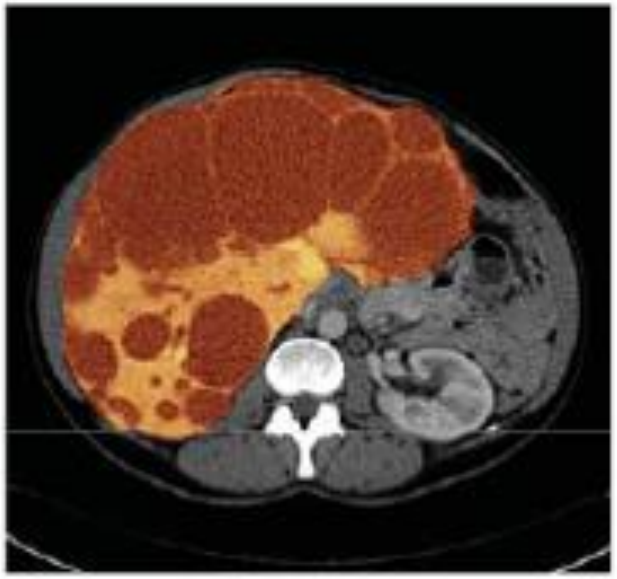


Continuous Reduction of Cyst Volume and Diameter with time

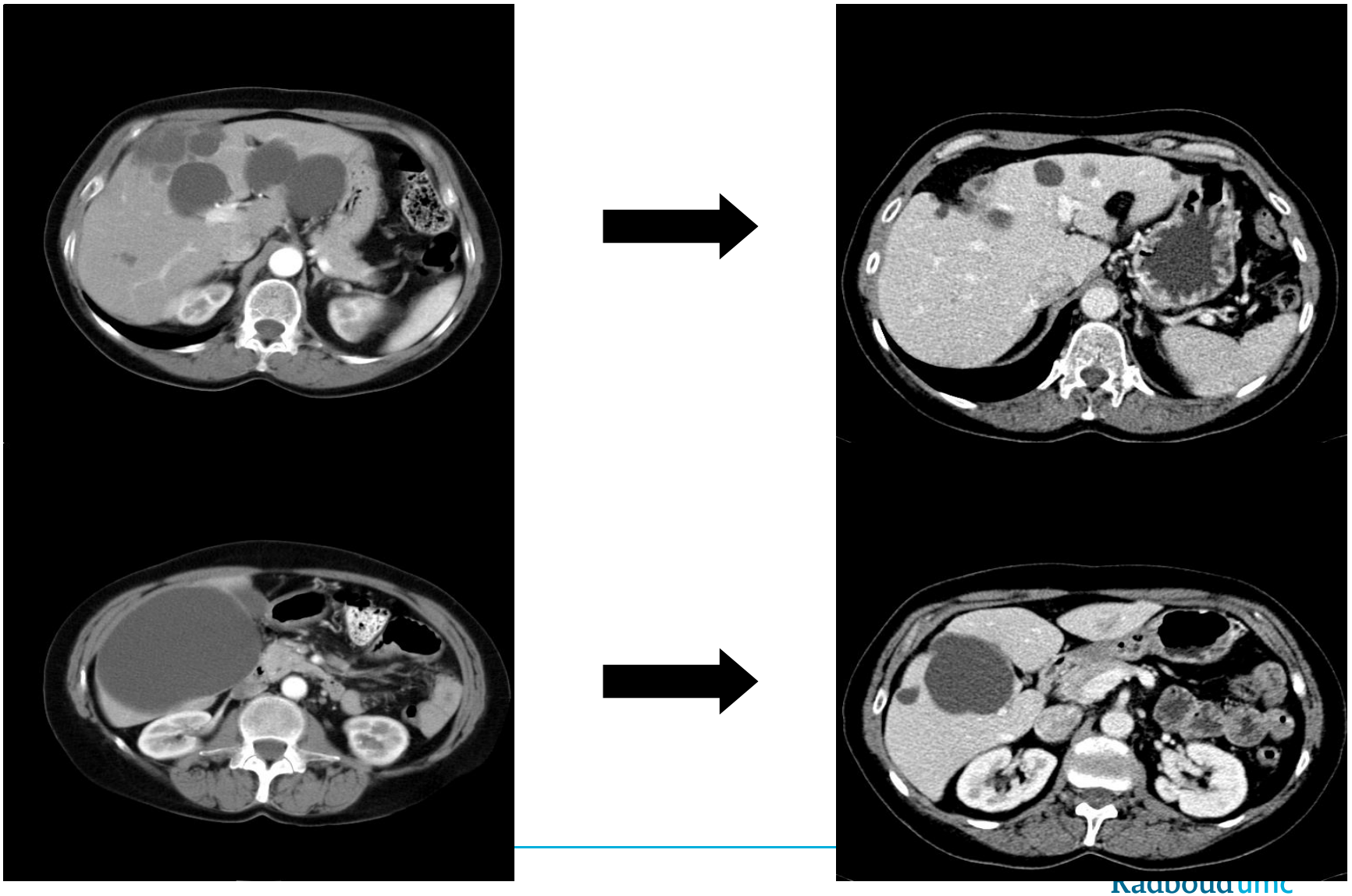
Eur Radiol. 2018 Jan 9. doi: 10.1007/s00330-017-5205-1.

Laparoscopic fenestration

Fenestration
Multiple large cysts located in the anterior segmentsof the liver and laparoscopic accessible

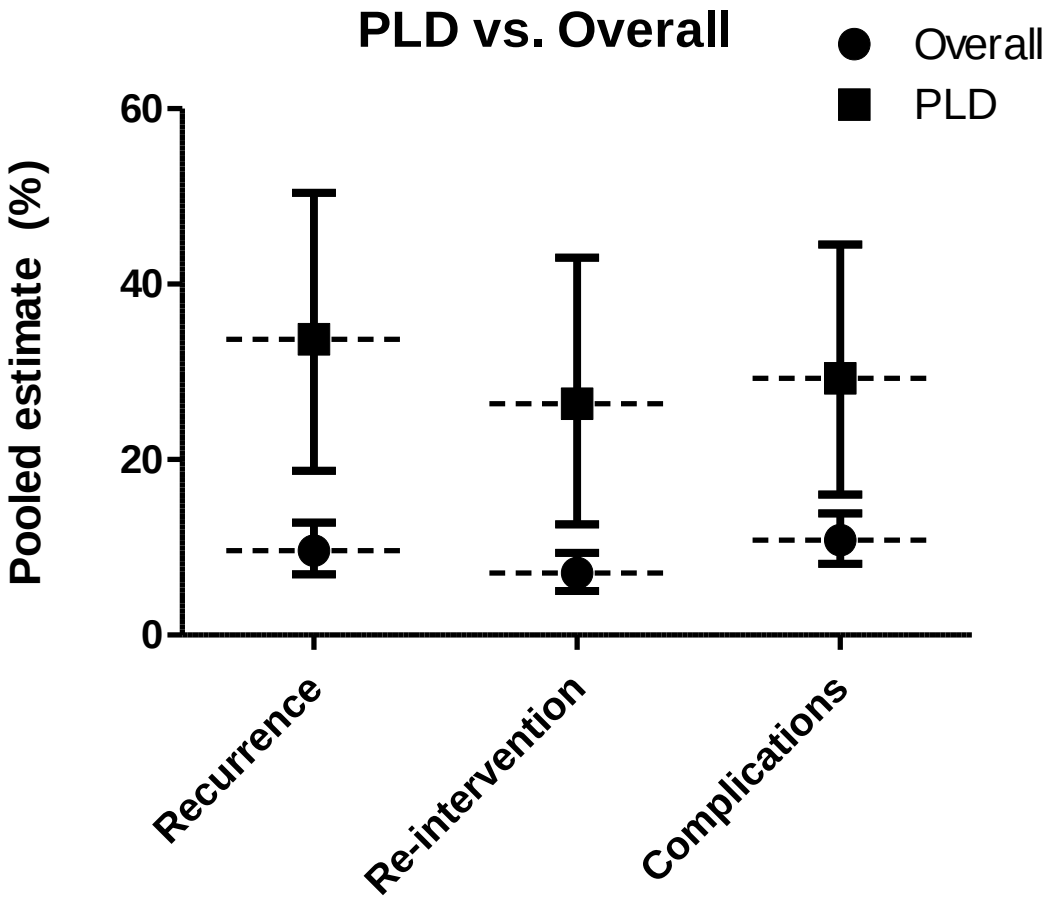


Laparoscopic fenestration



Laparoscopic fenestration
for PLD vs. single cysts

- Meta-analysis outcomes
- PLD population
  - Medium recurrence
  - Medium reintervention rates
  - Medium complication rates

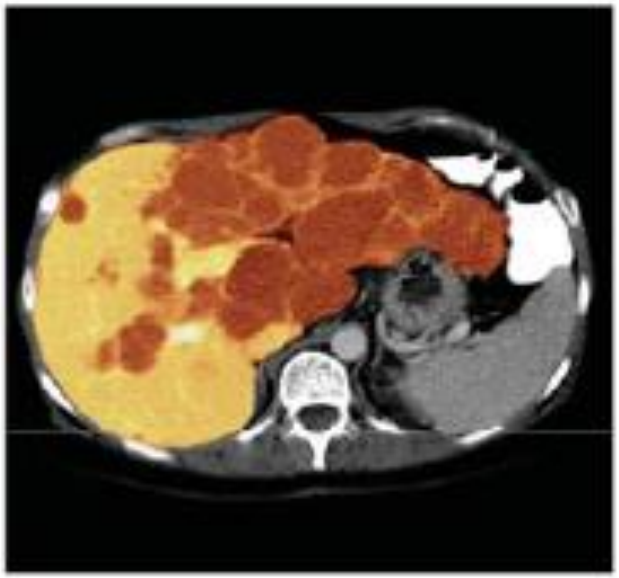


Bernts: submitted

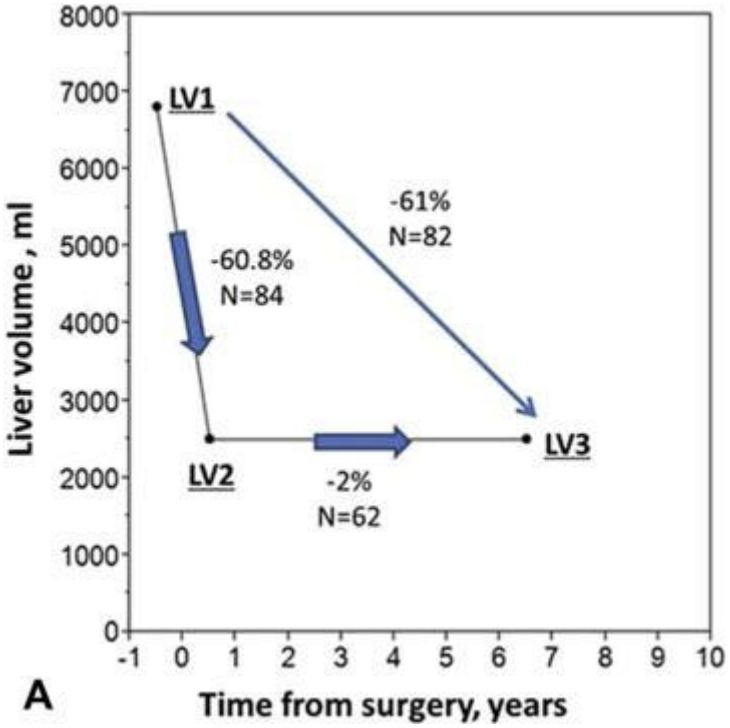
Liver resection

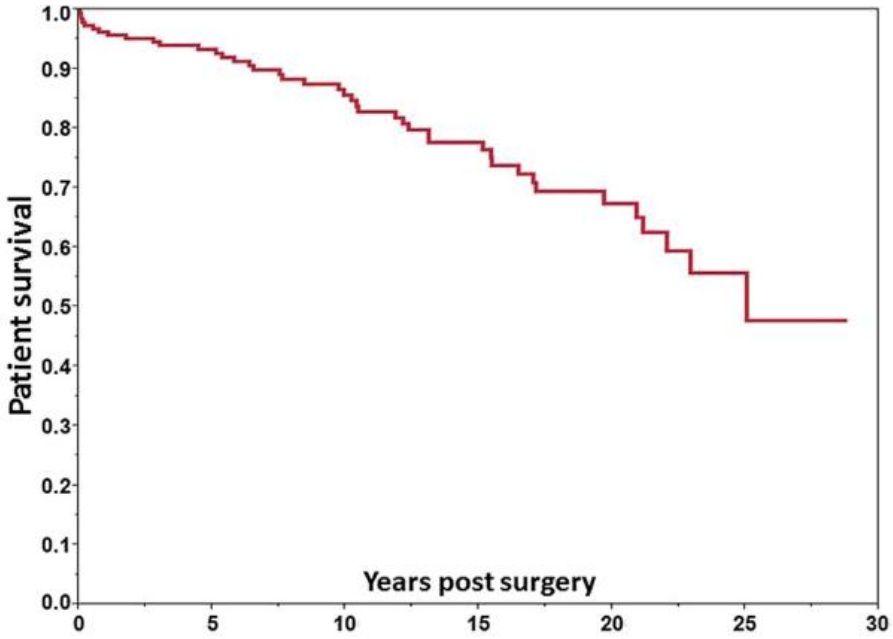
Resection

Moderate to severe PLD with cysts clustered in a few segments in presence of some less affected segments; fenestration and AS not possible



Resection



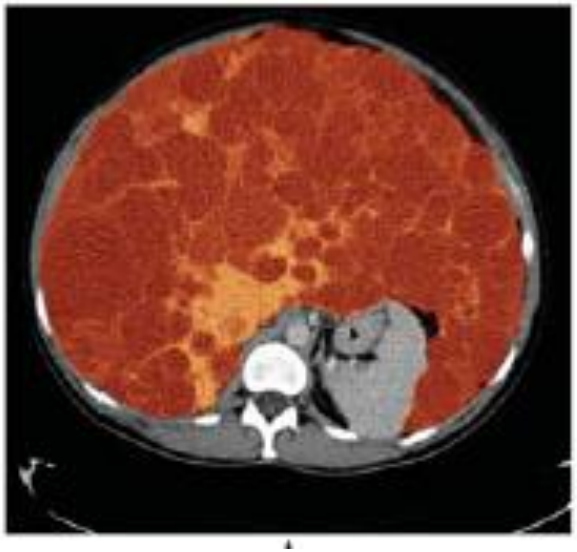


Message: Liver volume rapidly drops, only in experienced hands, reasonable survival

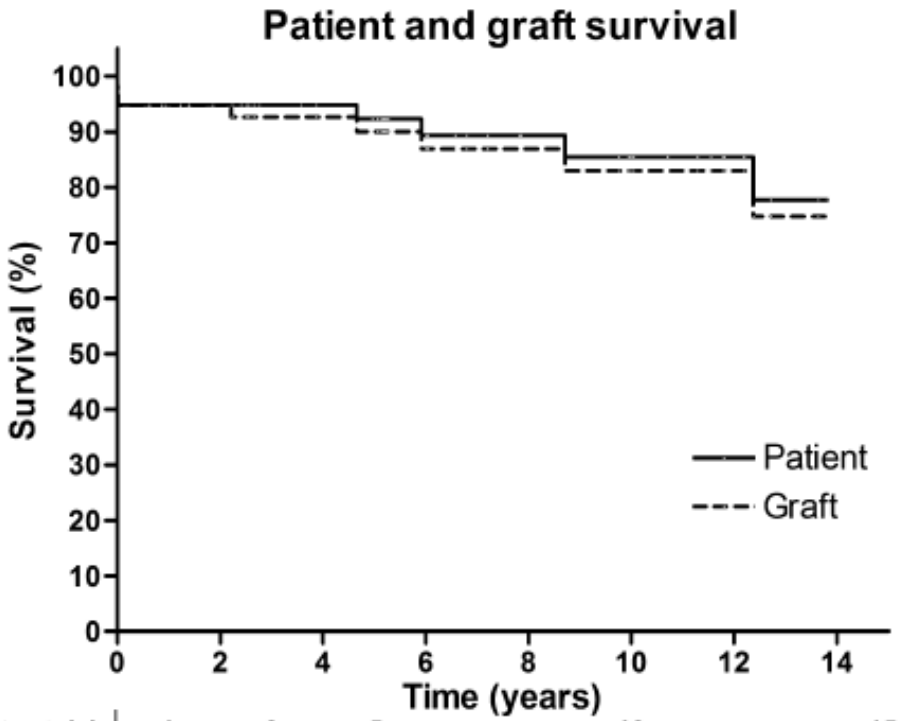
J Am Coll Surg. 2016 Jul; 223(1): 118–126.e1.

Liver transplantation

Liver Transplantation
Severe PLD with extreme impaired QoL or untreatable complications; no other treatment possible



LTX in PLD



Patients at risk	1	3	5	10	15
Patient	51	40	36	19	5
Graft	50	38	34	18	4

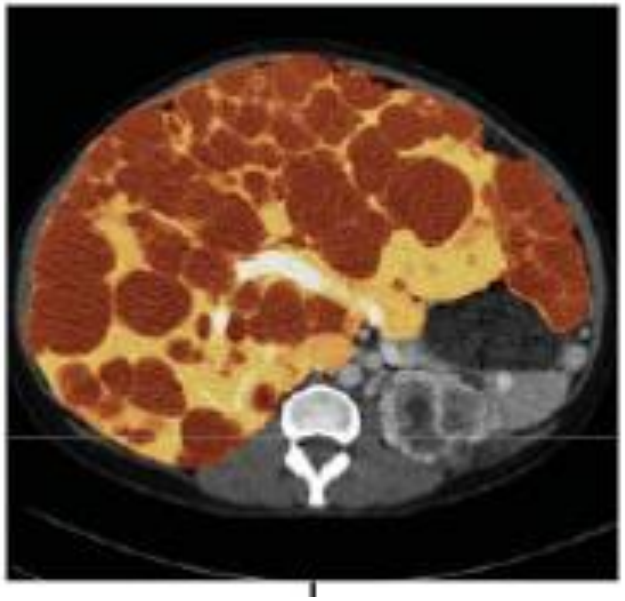
- European Liver Transplant Registry (ELTR) database
- 58 PLD patients

Transpl Int. 2011 Dec;24(12):1239-45

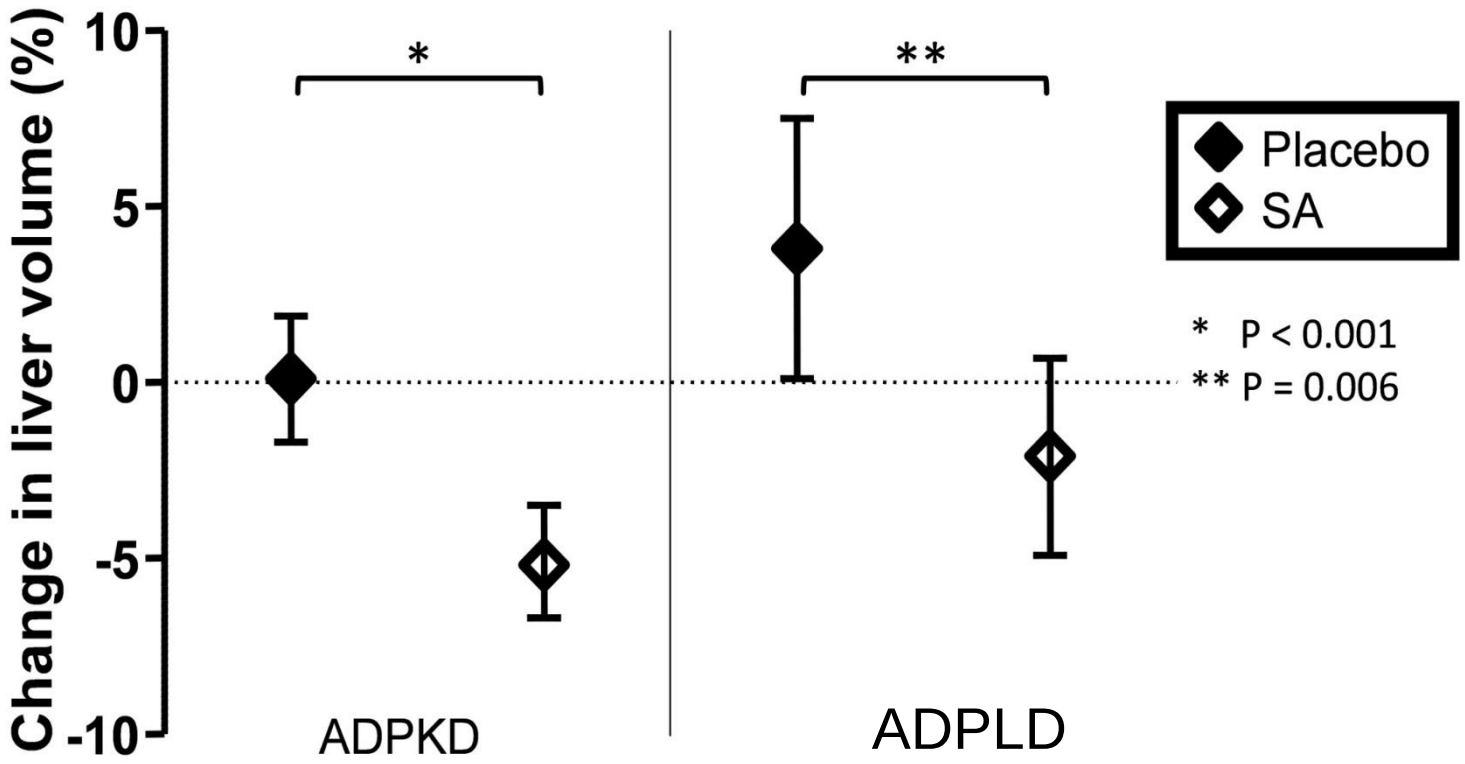
Somatostatin Analogues

Moderate to severe PLD with impaired QoL and:

- annual liver volume growth ≥~5% and/or
- complications



ADPKD vs. ADPLD

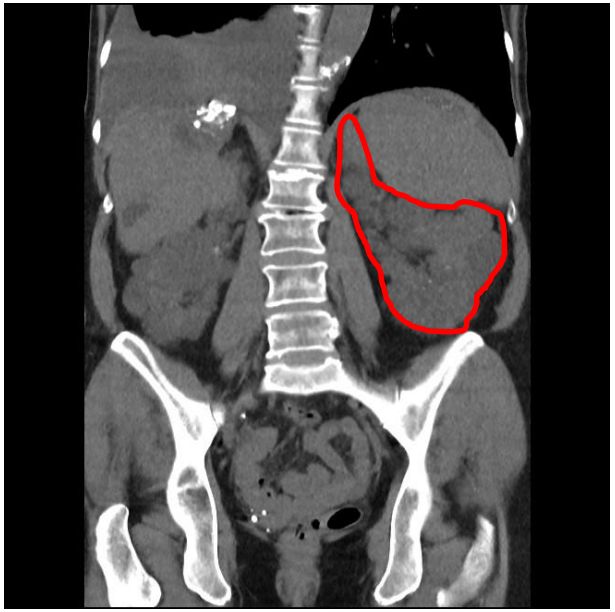


Effect of somatostatin analogues is independent of genetic disorder

Gastroenterology. 2013 Aug;145(2):357-65.e1-2.

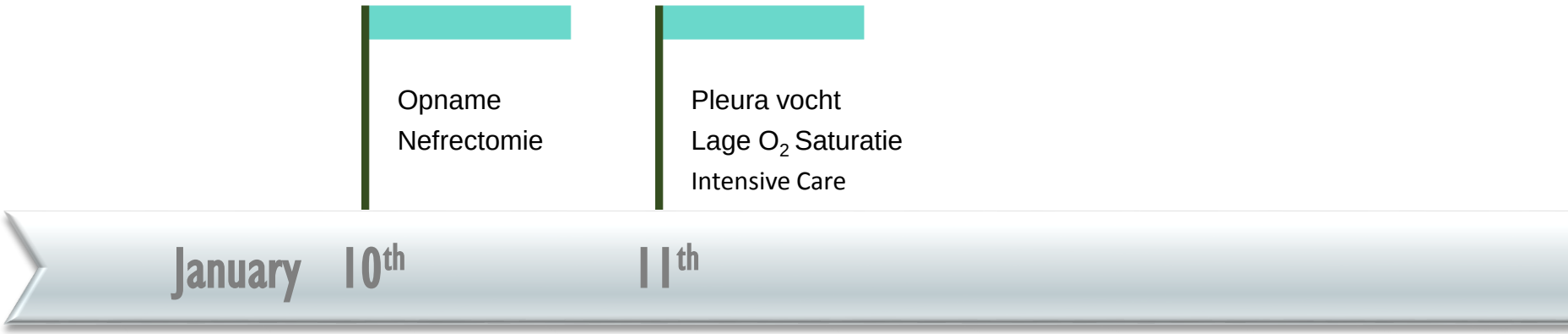
Casus

- Vrouw, 67 jaar oud
- ADPKD:
  - Nierinsufficiëntie
  - Polycysteuze leverziekte (PLD)
  - 2003 Niertransplantatie
- Opname op 10-01-2018 voor linkszijdige nefrectomie wegens:
  - Buikpijn
  - Vol gevoel
  - Snel verzadigd
  - Blaas prolaps.



Casus

- Vrouw, 67 jaar oud, ADPKD met nierfalen
- Opname op 10-01-2018 voor linkszijdige nefrectomie

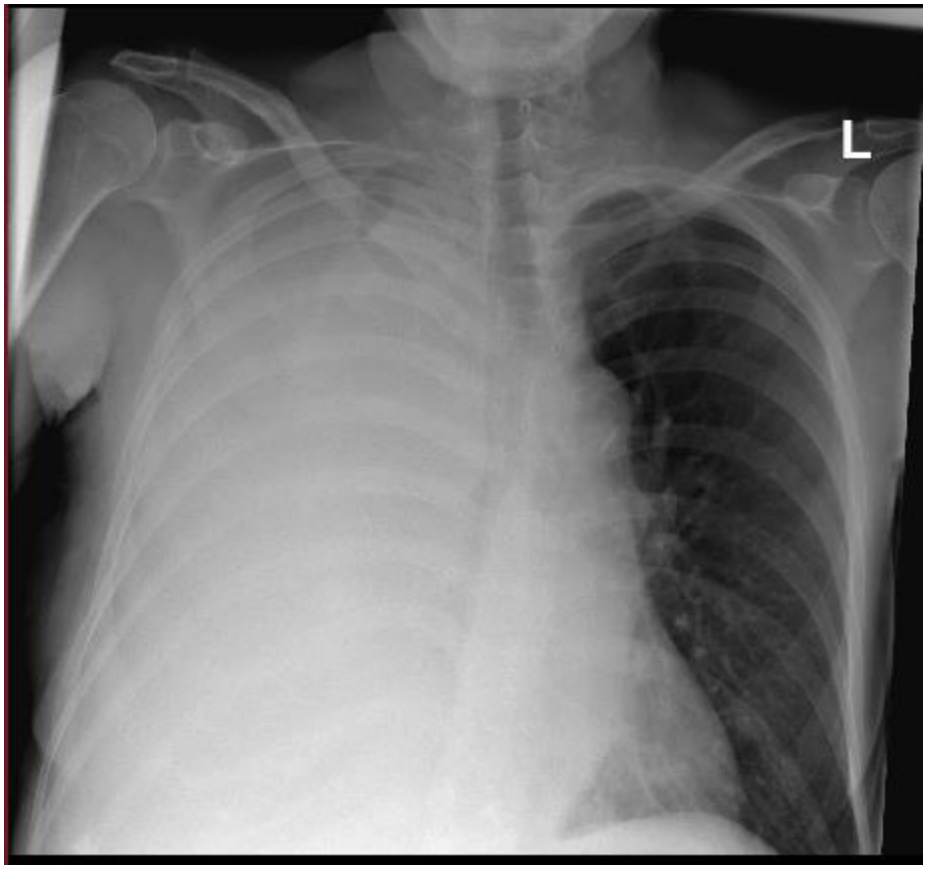


Eerste presentatie

Symptomen:

- Dyspnoe
- Geen hoesten
- Geen koorts
- Saturatie: 88%

- X-thorax:

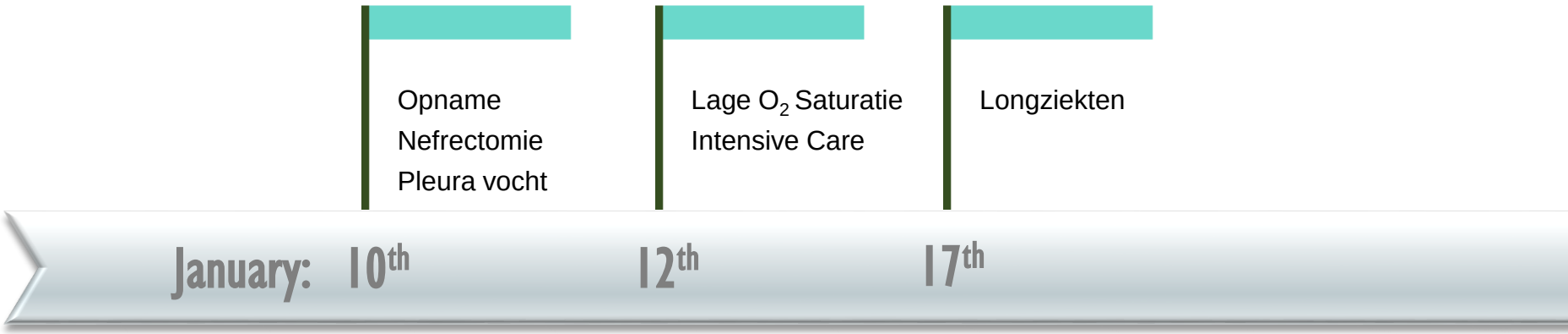


Wat is hier aan de hand?

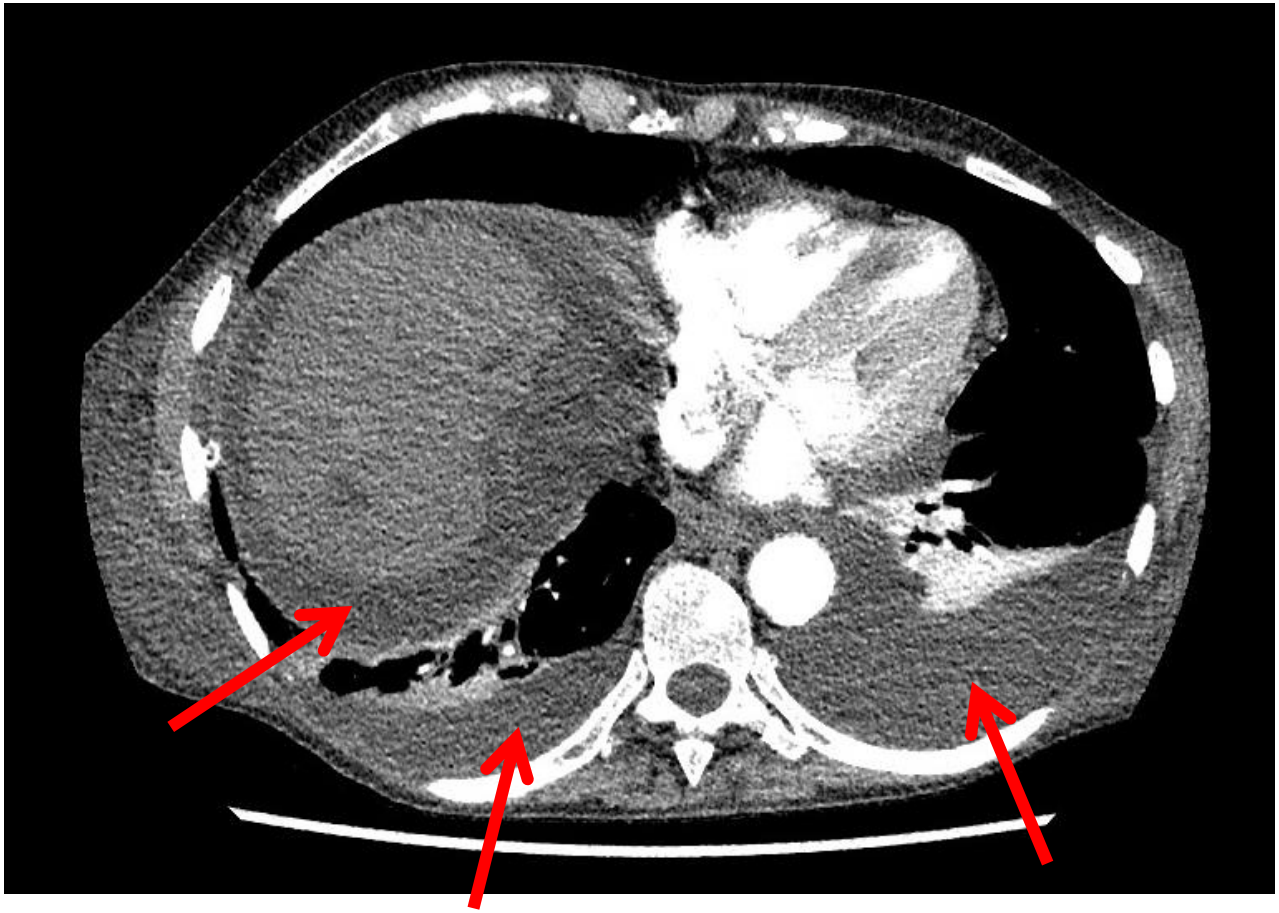
Pleuravocht

- Drainage:
  - 2 liter heldere, gelige vloeistof (transudaat)

- Differentiaal diagnose:
  - Secundair aan ascites
  - Reactief na nefrectomie
  - Auto-immuun
  - Pulmonaal probleem



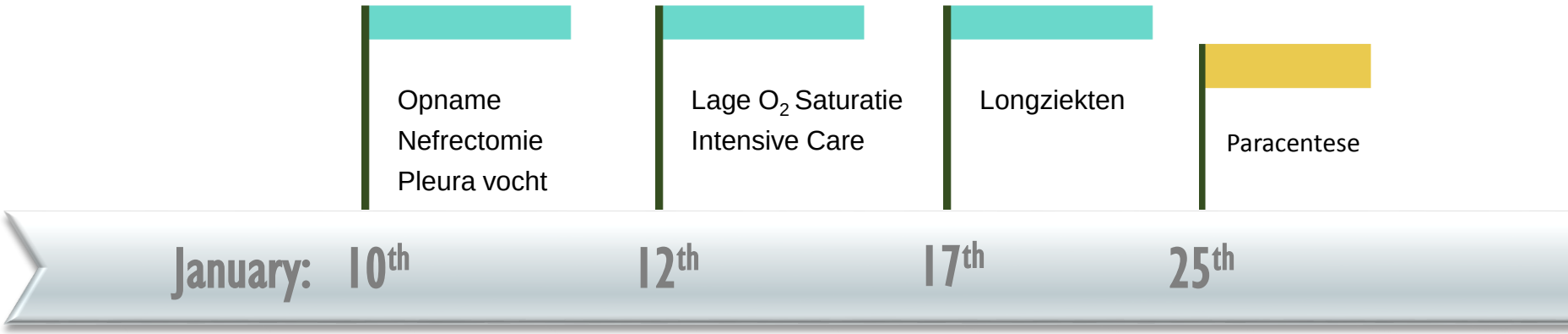
CT Thorax



Ascites

- Paracentese
  - Transsudaat
  - Geen SBP
  - Geen tekenen van maligniteit

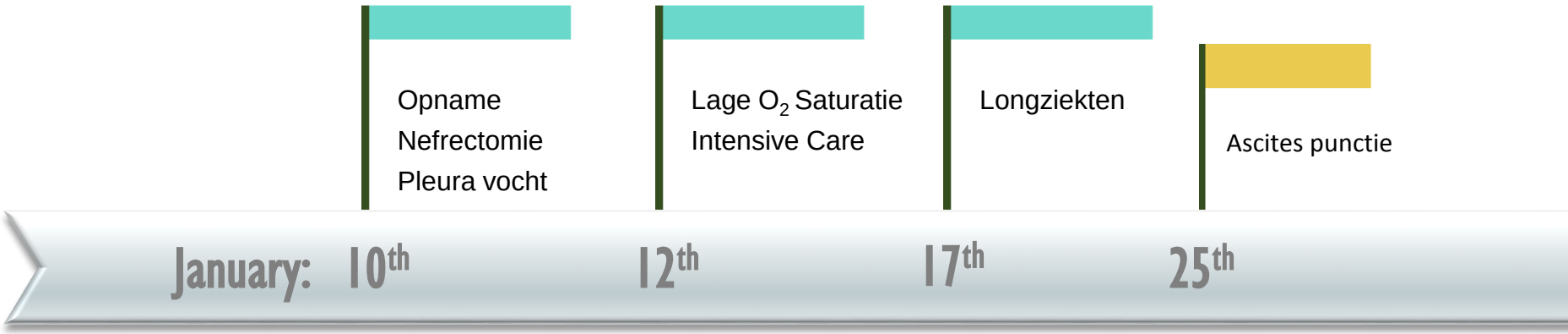
- Echo:
  - Normale portale flow.
  - Goede flow vena cava.
  - Levervenen beperkt a vue.
  - Geen aanwijzing voor trombose.



Ascites

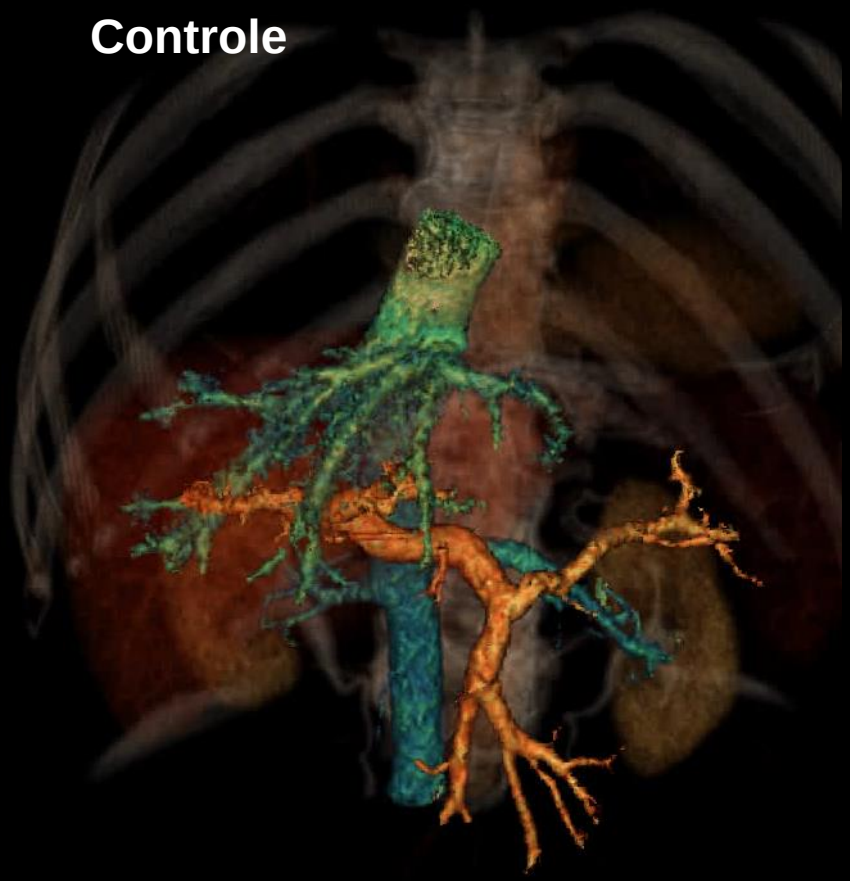
- Differentiaal diagnose:
  - Hepatic venous outflow obstruction (HVOO) bij ADPKD
  - Post-operatief (bijv. peritoneum letsel)
  - Portale hypertensie bij leverfibrose

- CT thorax/abdomen – IV contrast



CT Abdomen

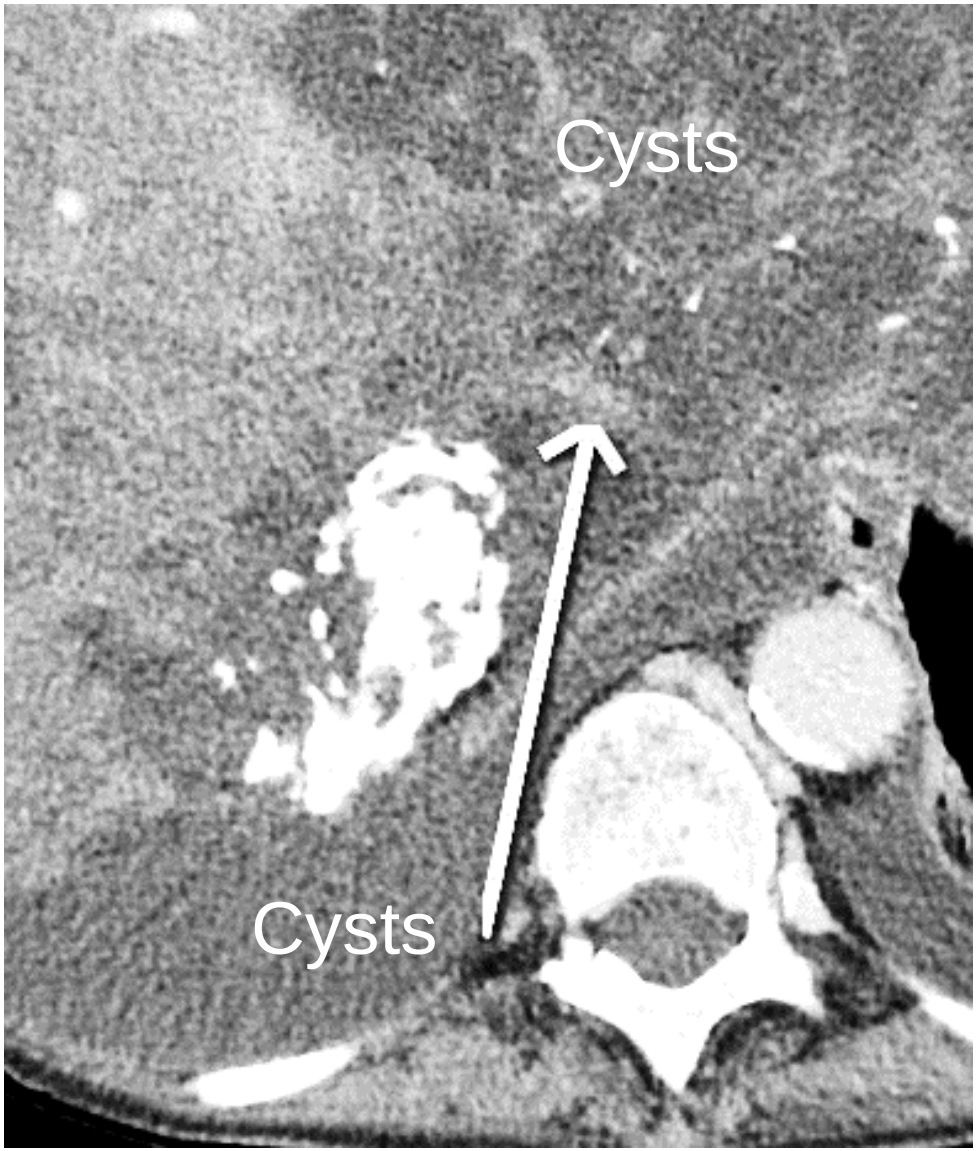
Controle

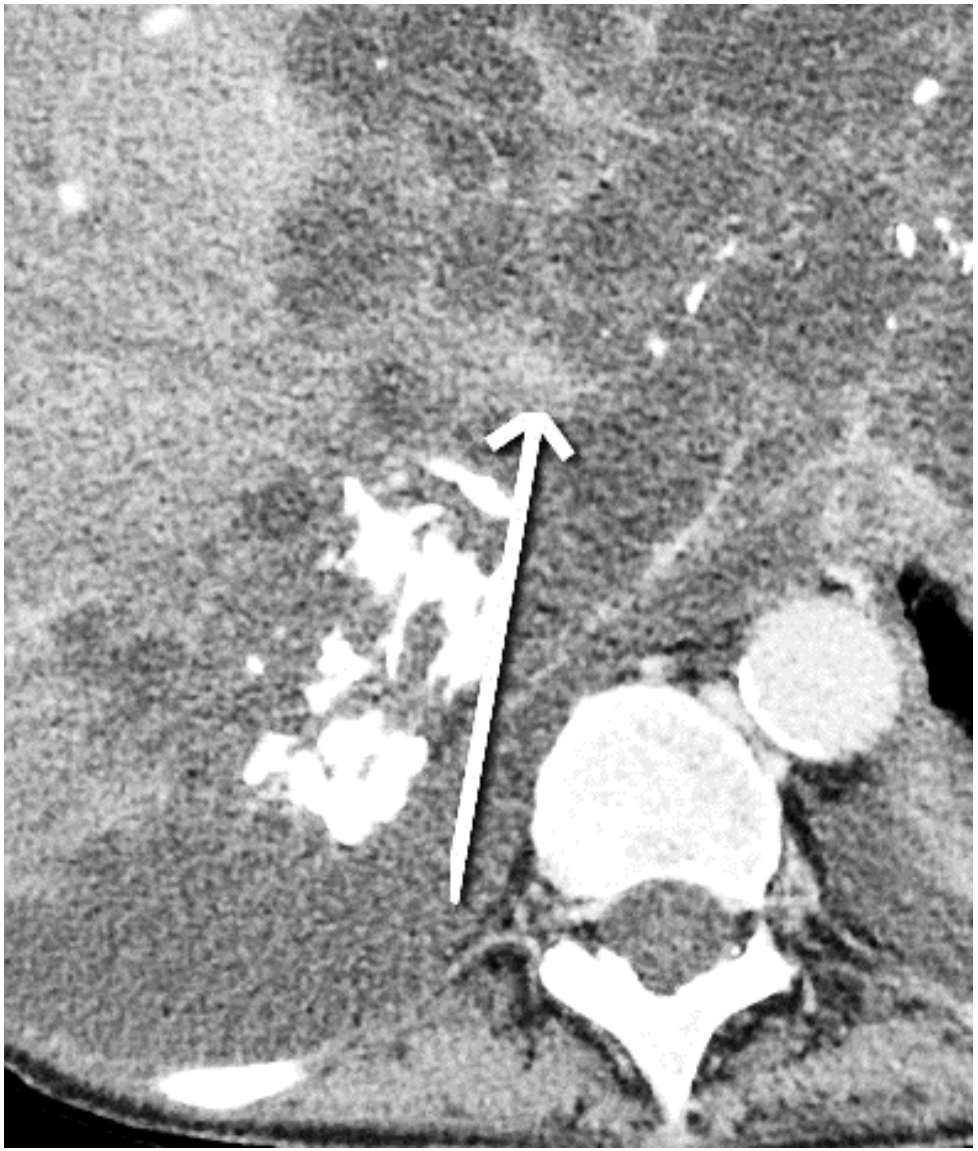


Casus

3D-reconstructies

1


Cysts
Cysts



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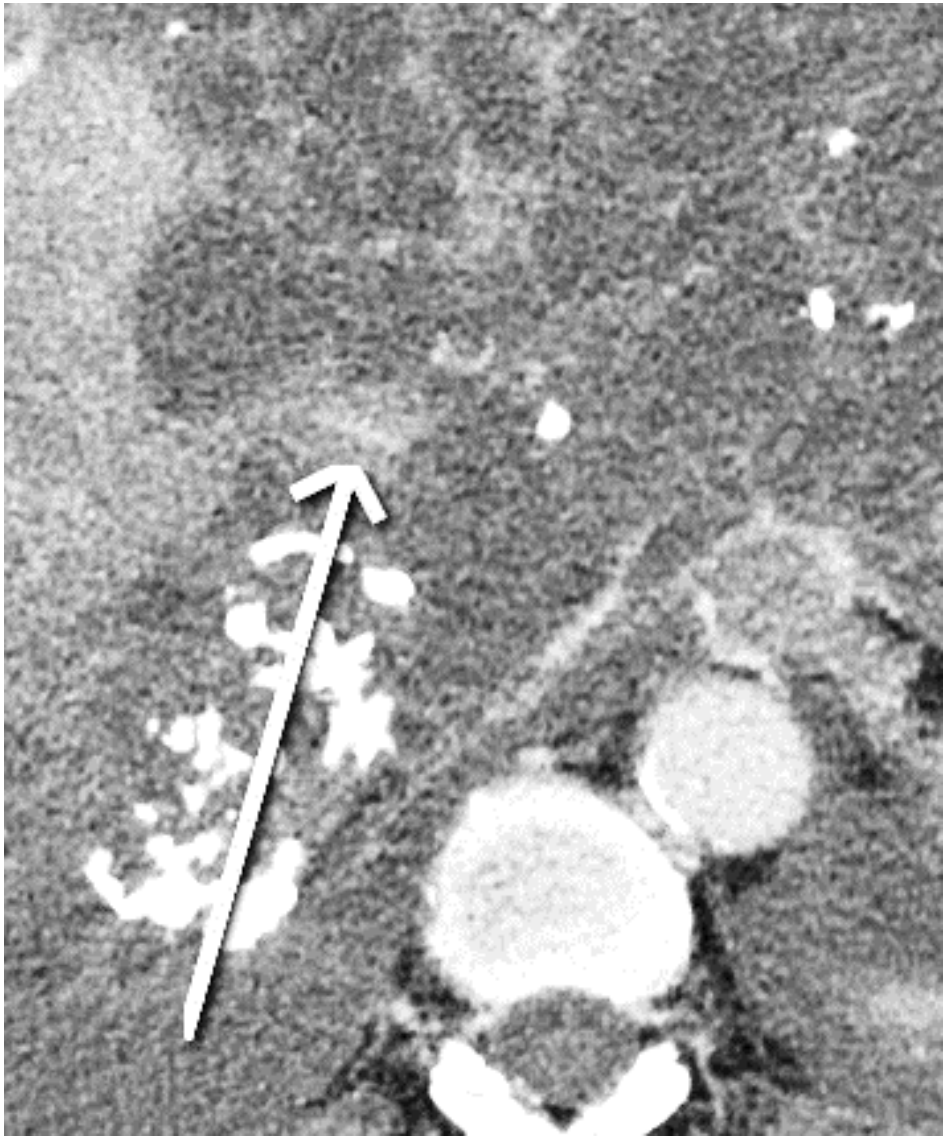
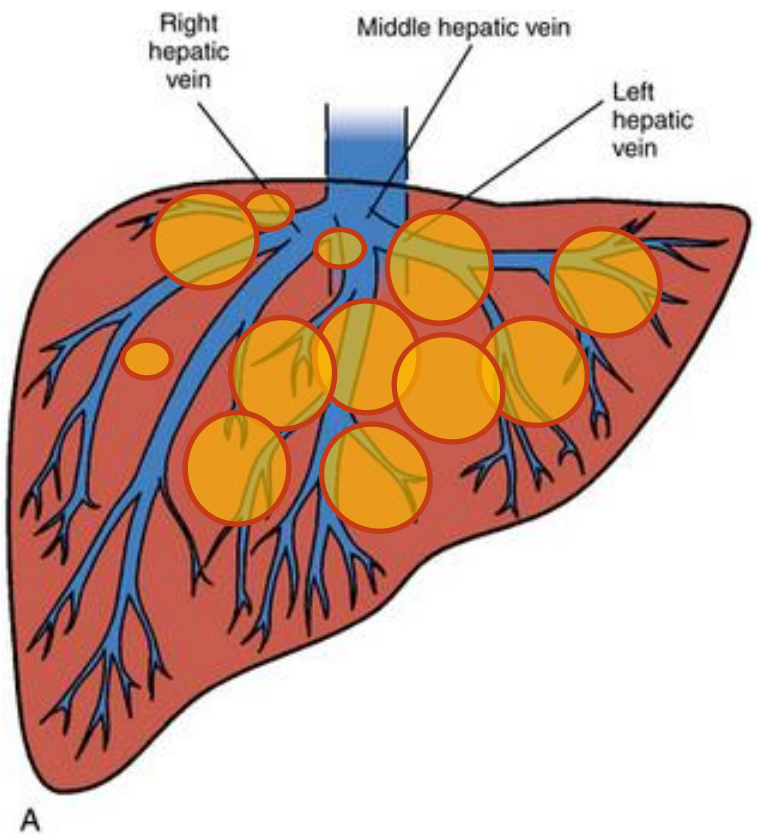
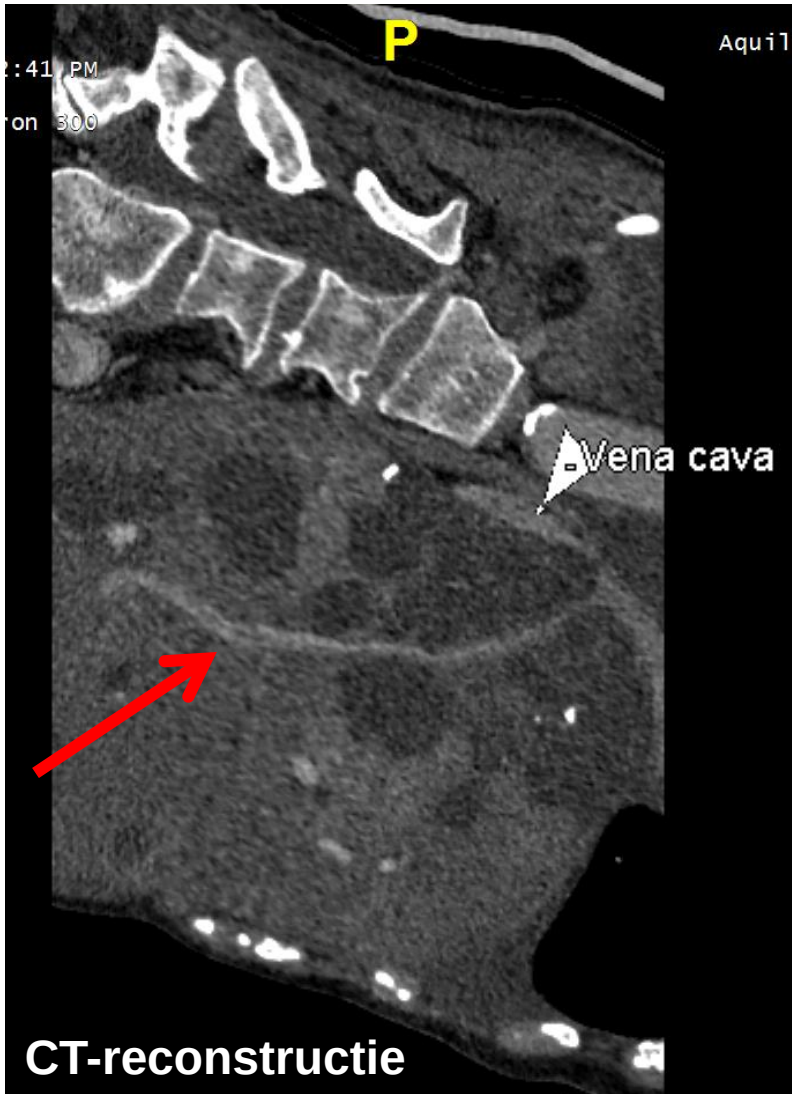


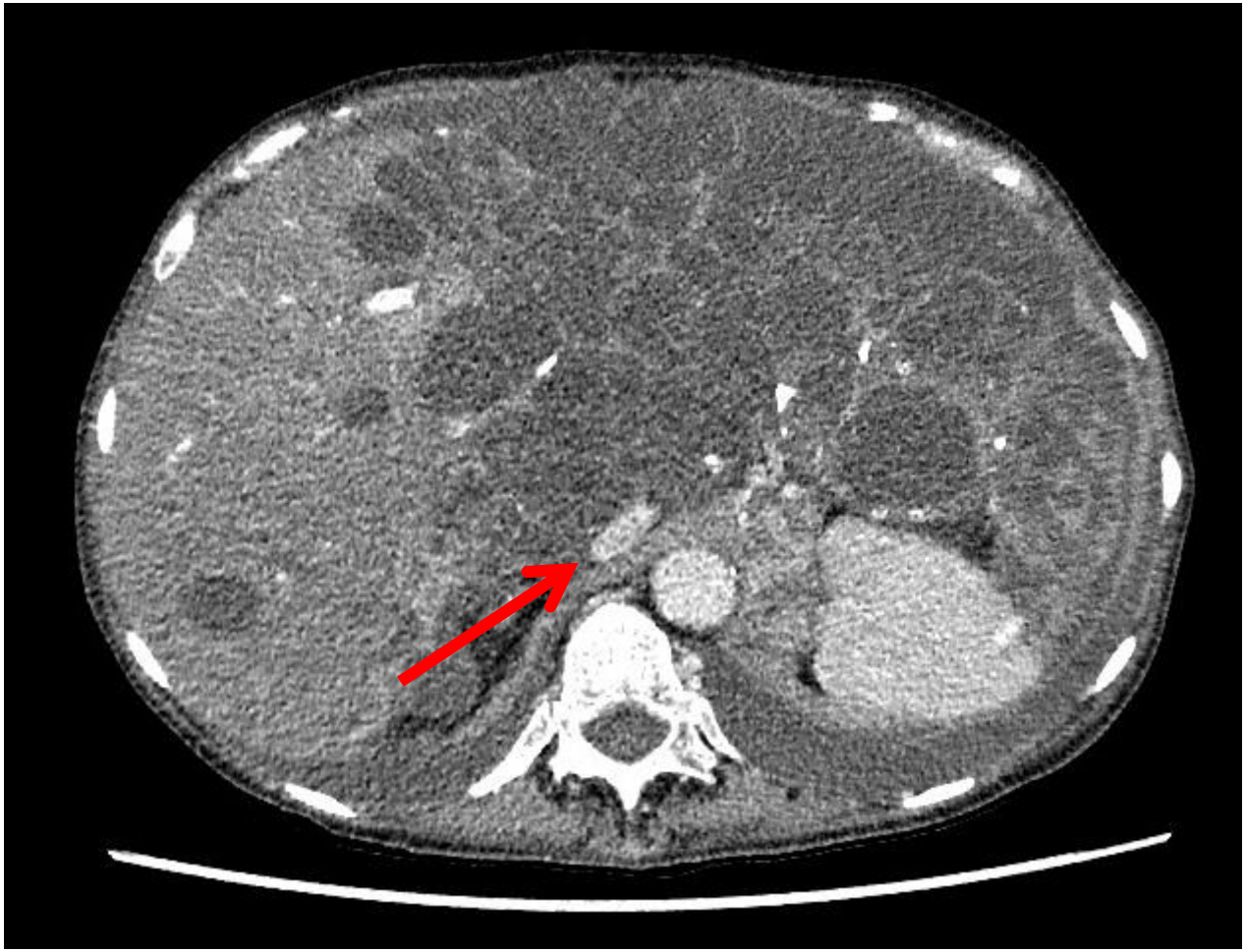
5

Rechter levervene (PLD)

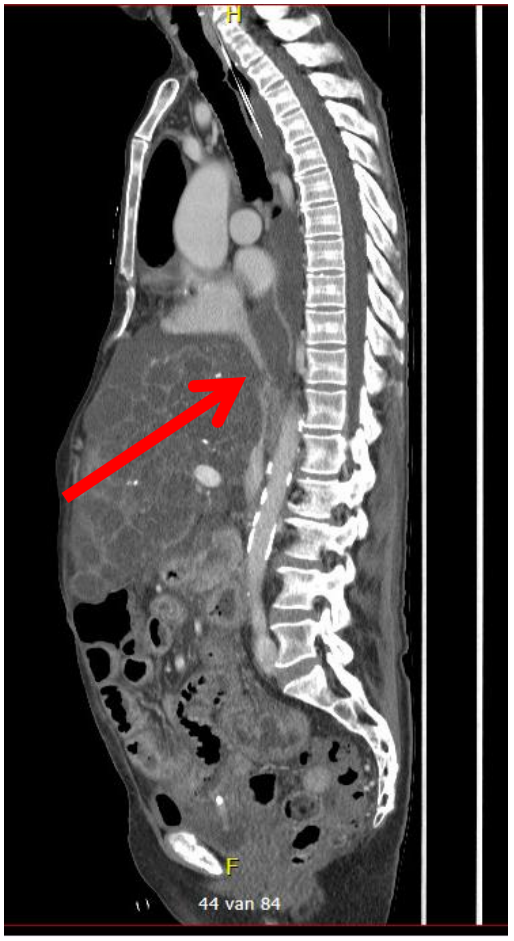




Vena cava compressie



Vena cava compressie



Tussenstand

- Dus:

- 67 jarige vrouw met ADPKD en polycysteuze lever
  Ascites, pleuravocht

- Vena hepatici : 2/ 3 taken zijn niet zichtbaar, slechts de rechter vena hepaticus is ‘gevuld’
- Compressie vena cava

Wat is hier aan de hand?

Hepatic venous outflow obstruction

- Prevalence
  - Underestimated
  - Case series [1-3,5-8]: 30 PLD with ascites [1]
  - Case series: association with Budd-Chiari syndrome [2,5-8]
  - Mainly ADPKD females who are prone to massive PLD [1]
  - First sign: 90-96% ascites [4]
    - Post-operative or *de novo* ascites: torsion, compression, operative narrowing
    - Multifactorial causes of ascites in PLD: cyst secretion, cyst rupture, lymphatic leak, chronic liver and kidney disease

- Management aims: [9]
  - Reduction portal hypertension/transudative ascites
  - Minimize detoriation of liver function (jaundice)

[1] Chauveau et al. Nephrol Dial Transplant 1997
[2] Uddin et al. Gut 1995
[3] Mudge et al. Nephrol Dial Transplant 2005
[4] Valla et al. Hypertension portale 1984
[5] Bhupalan et al. J R Soc Med 1992
[6] Ambrosetti et al. Gastroenterol Clin Biol 1992
[7] Clive et al. Am J Kid Disease 1993
[8] Johnstone et al. HPB Surg 1993
[9] Kohli et al. Lancet 1993

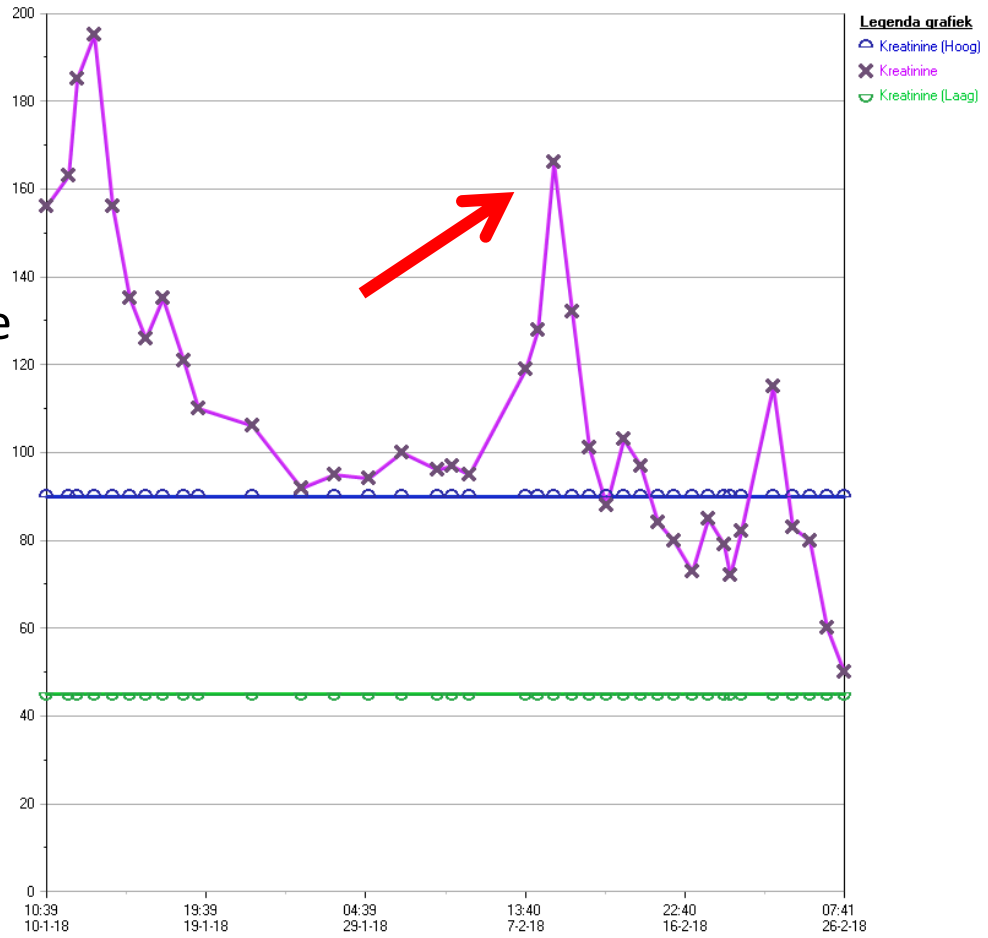
Behandeling:

Refractaire ascites door HVOO bij PLD

Behandeling

Refractaire ascites:

- Drainage met albumine suppletie
- Furosemide & Spironolacton
  → progressief nierfunctieverlies



Stop diuretica

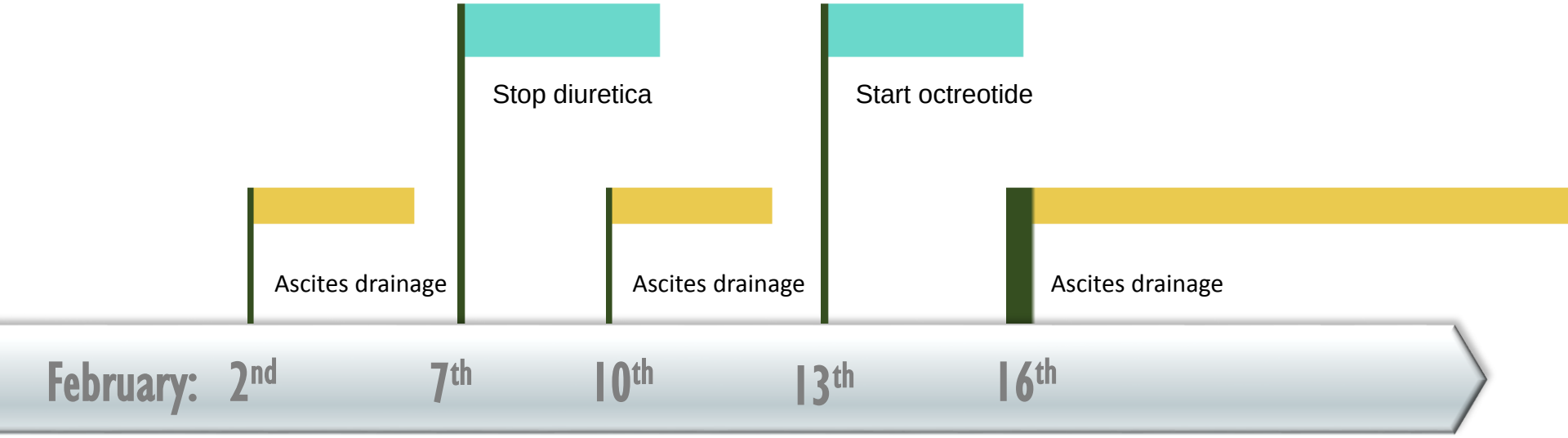
Ascites drainage

February: 2nd 7th

Behandeling

Refractaire ascites:

- Drainage
- ~~Furosemide & Spironolacton~~
- Octreotide 50 µg / uur

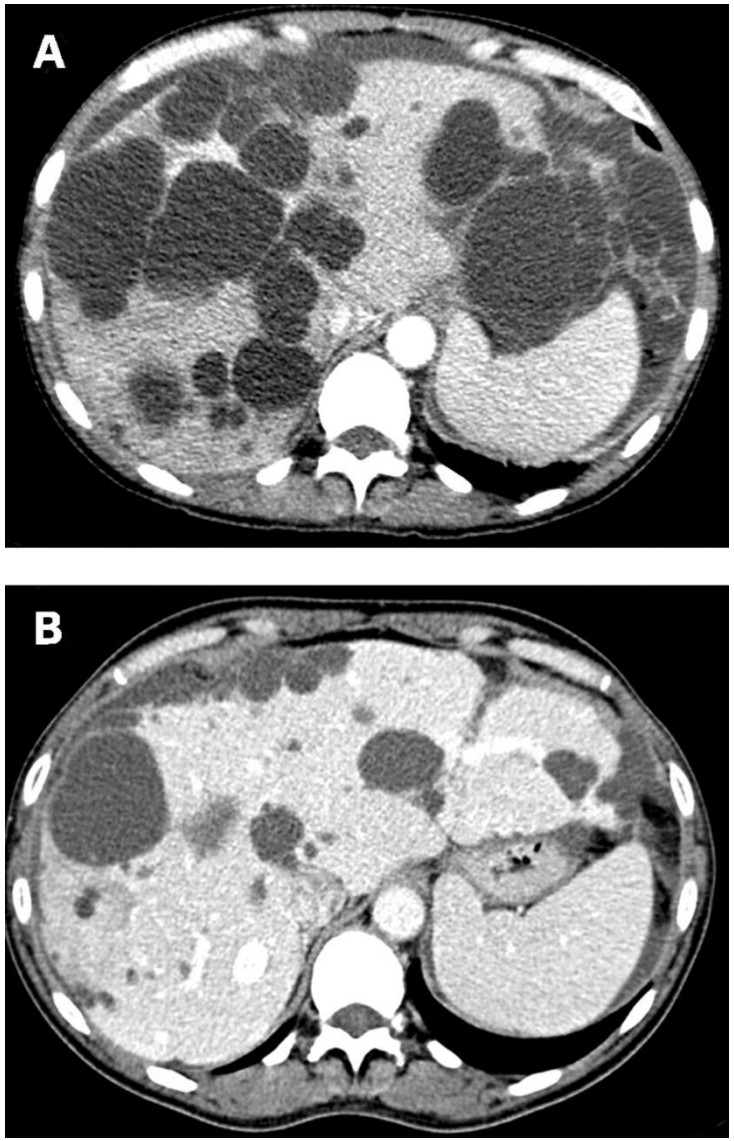


Octreotide

- “Somatostatin analogues reduce liver volume in polycystic liver disease”

- Vrouw , 43 jaar
- Polycysteuze lever (levervolume 8,2 L)
- Na laparoscopische fenestratie:
  - Ascites
  - Oedeem
  - Gewicht van 79 kg naar 94 kg
  - Vena cava inferior syndroom

- 6 maanden behandeld met somatostatine analogen:
  - Octreotide 3dd 100 µg
  - Lanreotide 120 µg elke 4 weken
- Goed resultaat: levervolume ↓ 14.9%



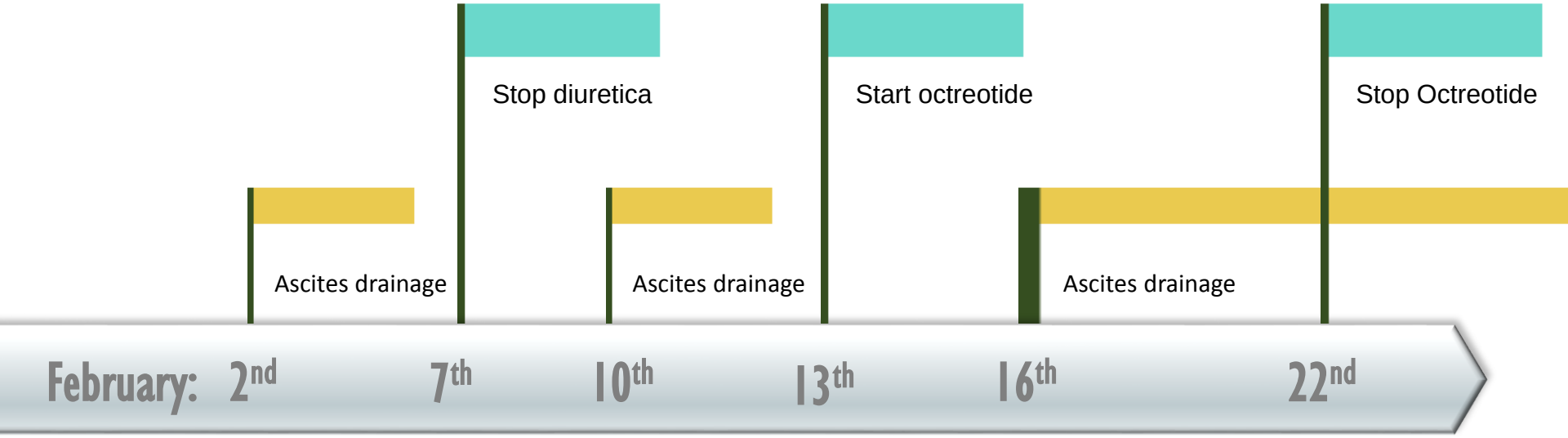
van Keimpema L, de Man RA, Drenth JP.
Gut. 2008 Sep;57(9):1338-9

Behandeling

Refractaire ascites:

- Drainage
- Octreotide

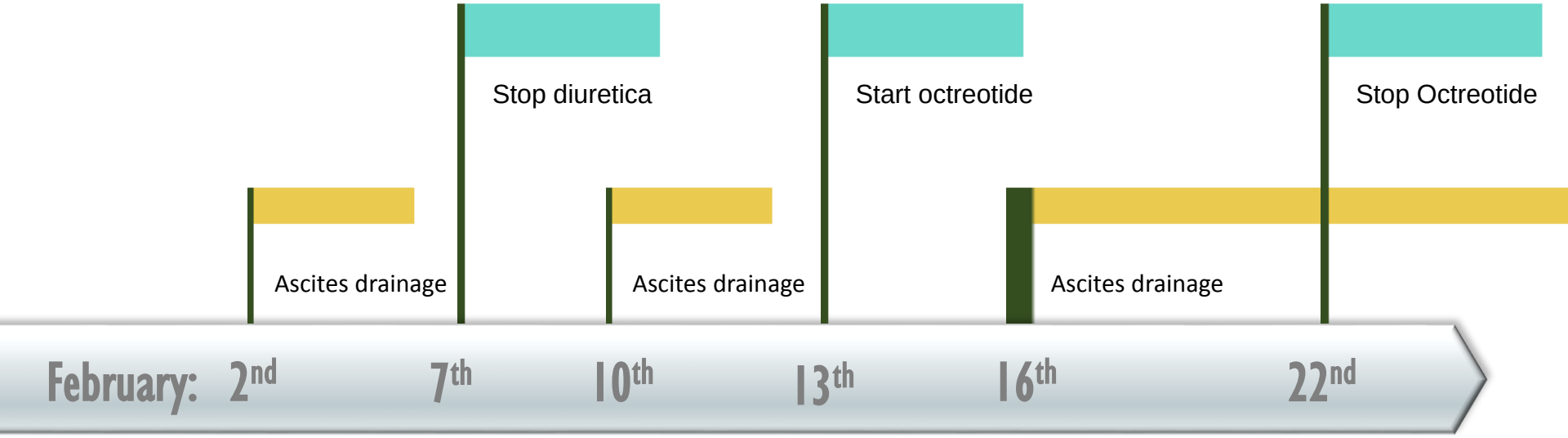
  → geen effect en ernstige diarree



Behandeling

Refractaire ascites:

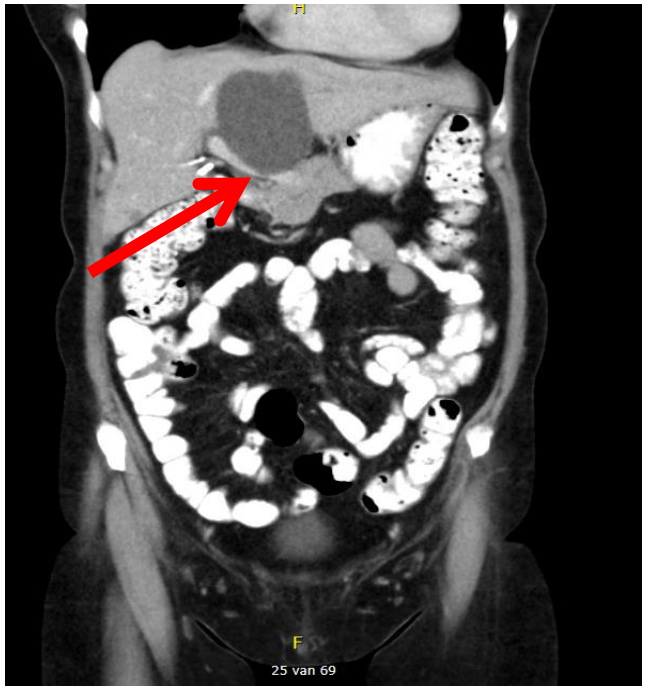
- Drainage
- ~~Furosemide & Spironolacton~~
- ~~Octreotide~~
- ?



Invasieve Behandeling

- Herstellen van flow:
  - Levervene stent
  - Vena cava inferior stent
  - TIPS

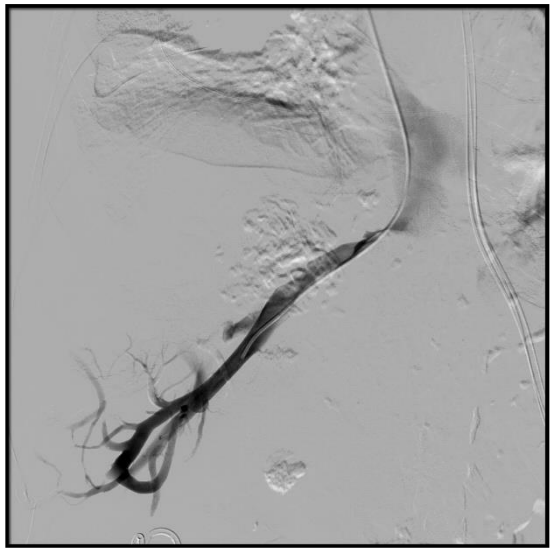
- Verwijderen van cyste(n):
  - Aspiratie sclerotherapie
  - Laparoscopische fenestratie
  - Segmentresectie
  - Levertransplantatie

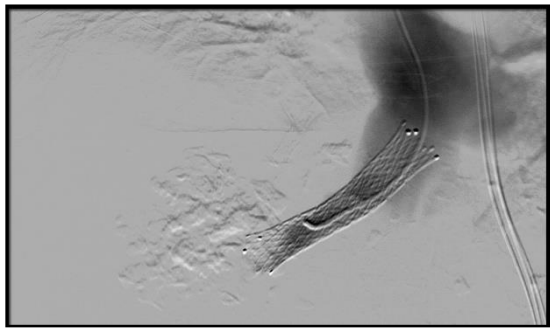


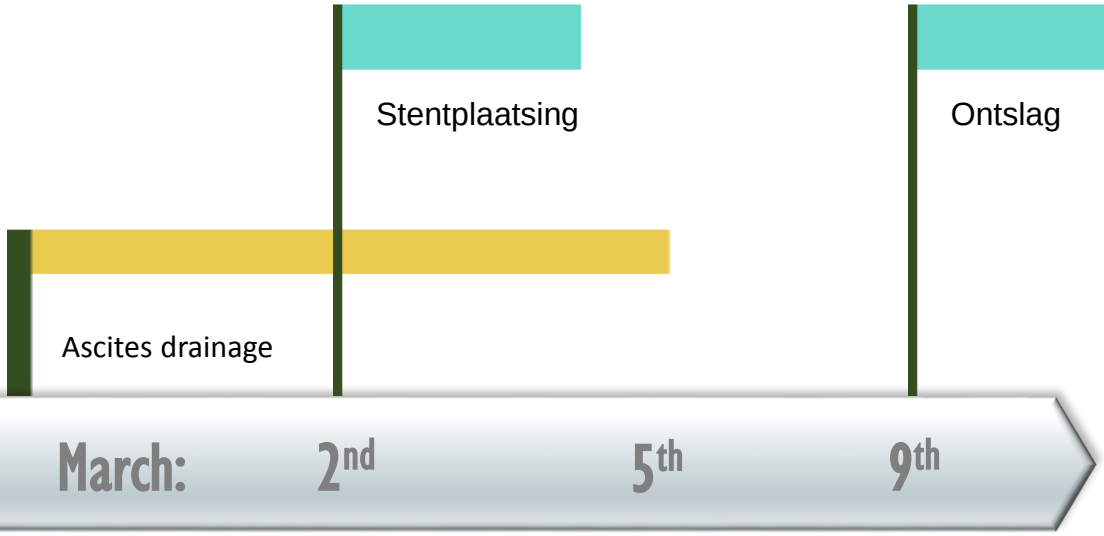
Behandeling

- Via vena jugularis ongecompliceerde stentplaatsing in de rechter levervene.

- Druk verval (levervene, atrium, Δ)
  - Pre: 33 mmHg, 7 mmHg (26 mmHg)
  - Post: 20 mmHg, 19 mmHg (1 mmHg)







CT 10-6-18

Key points

- Denk bij ascites bij polycysteuze leverziekte aan HVOO
- Overweeg medicamenteus beleid met somatostatine analogen
- Levervene stent bij gecompliceerde HVOO kan zeer effectief zijn
- Wees je bewust van de risico's van een nefrectomie bij ADPKD

Question 1

Which is the most common extrahepatic manifestation of ADPKD?

1. Cardiac valve abnormalities
2. Colonic Diverticulae
3. Hepatic cysts
4. **Hypertension**

Question 2

- ADPKD is a genetic disorder. You are approached by a family member of a patient with ADPKD who desires to be screened for ADPKD. Which test do you order ?

1. Creatinine
2. CT kidney & bladder
3. Gene test
4. **Renal ultrasound**

Question 3

- A patient with ADPKD does develop hypertension. Which class of anti-hypertensives is the most appropriate

1. **Angiotensin receptor blocker**
2. Beta blocker
3. Calcium channel blocker
4. Loop diuretic

ADPKD & ADPLD

Joost PH Drenth

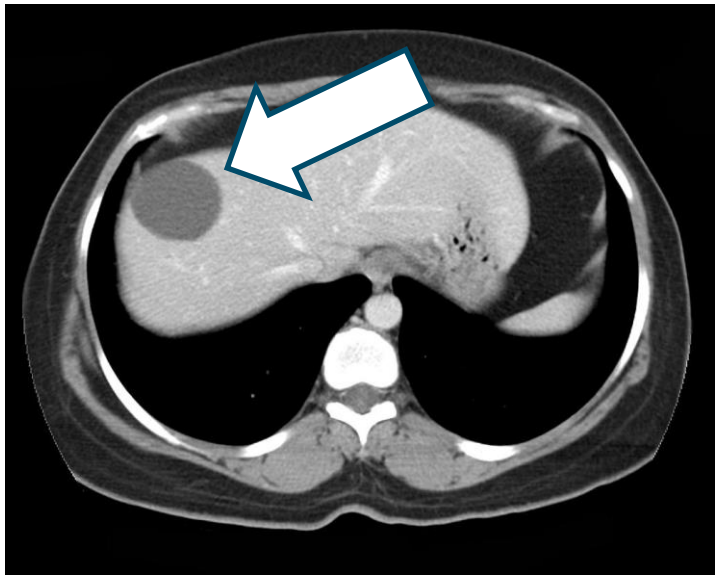
Radboudumc

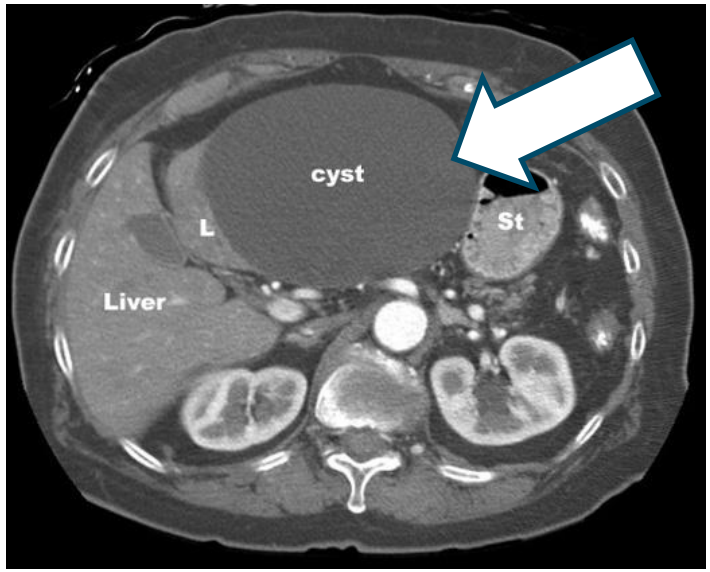
DLW 21 june 2018

Radboudumc

Hepatic cysts

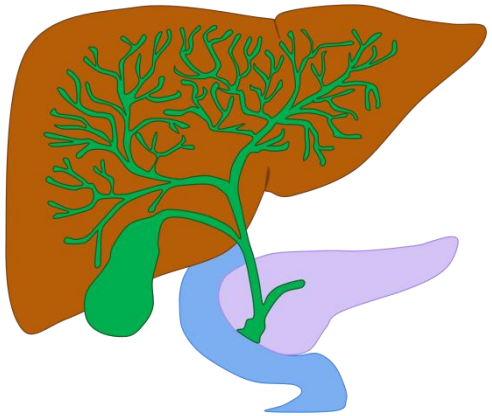
- Progressive dilatation of biliary microhamartomas
- Detached from biliary tract, lined with biliary epithelium

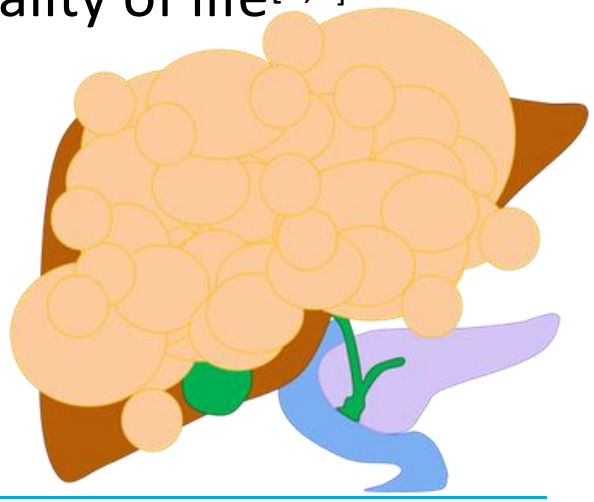




Definition of massive PLD

- **Anatomical**
  - ≥20 cysts, both lobes, variable cyst diameter, disconnected from the biliary tree
- **Clinical**
  - extra-hepatic symptoms of hepatomegaly
  - hepatic complications
- **Primairy end points**
  - hepatomegaly (> 1.5 liter); PLD total liver volume (> 4 liters)[1]
  - patients' perception/ health-related quality of life[2,3]





[1] Hogan et al. Nephrol. Dial. Transplant. 2012
[2] Kamphues et al. Updates Surg. 2011
[3] Wijnands et al. Liver int. 2013