Management of polycystic liver disease and other liver complications

Joost PH Drenth

KDIGO Controversies Conference on
Autosomal Dominant Polycystic Kidney Disease (ADPKD)
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Radboudumc

KDIGO Questions

1. What are the indications for intervention in PLD? How to choose the most appropriate treatment?
2. What are the medical therapies in PLD?
3. What are the side effects of somatostatin analogues?
4. Should hepatic cystic disease impact on choice of immunosuppression?
5. What are the barriers to clinical trials for PLD?
6. How to diagnose and treat liver cyst infections?
7. How to evaluate and follow PLD: Need to develop a clinical score or a specific questionnaire?
8. What advice can be given to pre- and post-menopausal women with PLD regarding contraception and estrogen replacement therapies?

Q1

What are the indications for intervention in PLD?
How to choose the most appropriate treatment?

Invasive treatment options

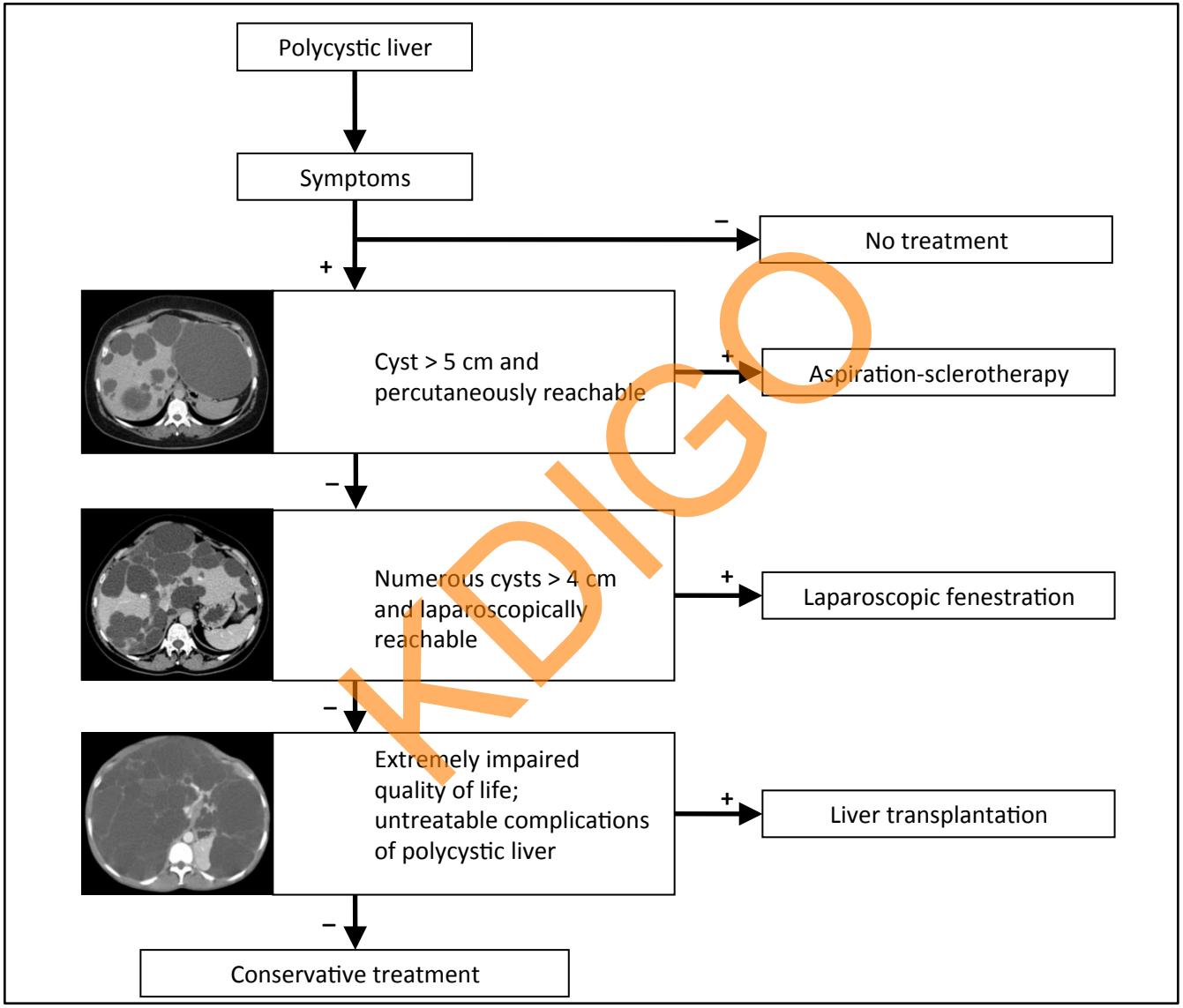
- Aim:
  - Improvement of Quality of Life
  - Reduction of symptoms
- Means:
  - Reduction of liver volume
- Invasive treatment options:
  - Radiological
    - Aspiration and sclerotherapy
    - Transcatheter arterial embolization
  - Surgical
    - Cyst fenestration
    - Liver resection
    - Liver transplantation

Interventions in PLD

Population	Intervention	Effect	Side effects	P.O.
Dominant Cysts	Aspiration sclerotherapy	Total regression in 22%	Cyst bleeding infection	OK
Superficial large cysts	Fenestration	Symptom relief 92%	Complications 23%	OK
Segmental PLD	Hepatic Resection	Symptom relief 86%	Complications 51%	Do not try, unless…
Massive PLD	Embolization of hepatic artery	TLV 4% ↓	3-year survival 70%	Only in Japan
Massive PLD	Liver transplantation	QoL 91% ↑	Morbidity 41%	Do if out of options

Drenth Hepatology 2010;52(6):2223-2230.

Treatment Algoritm

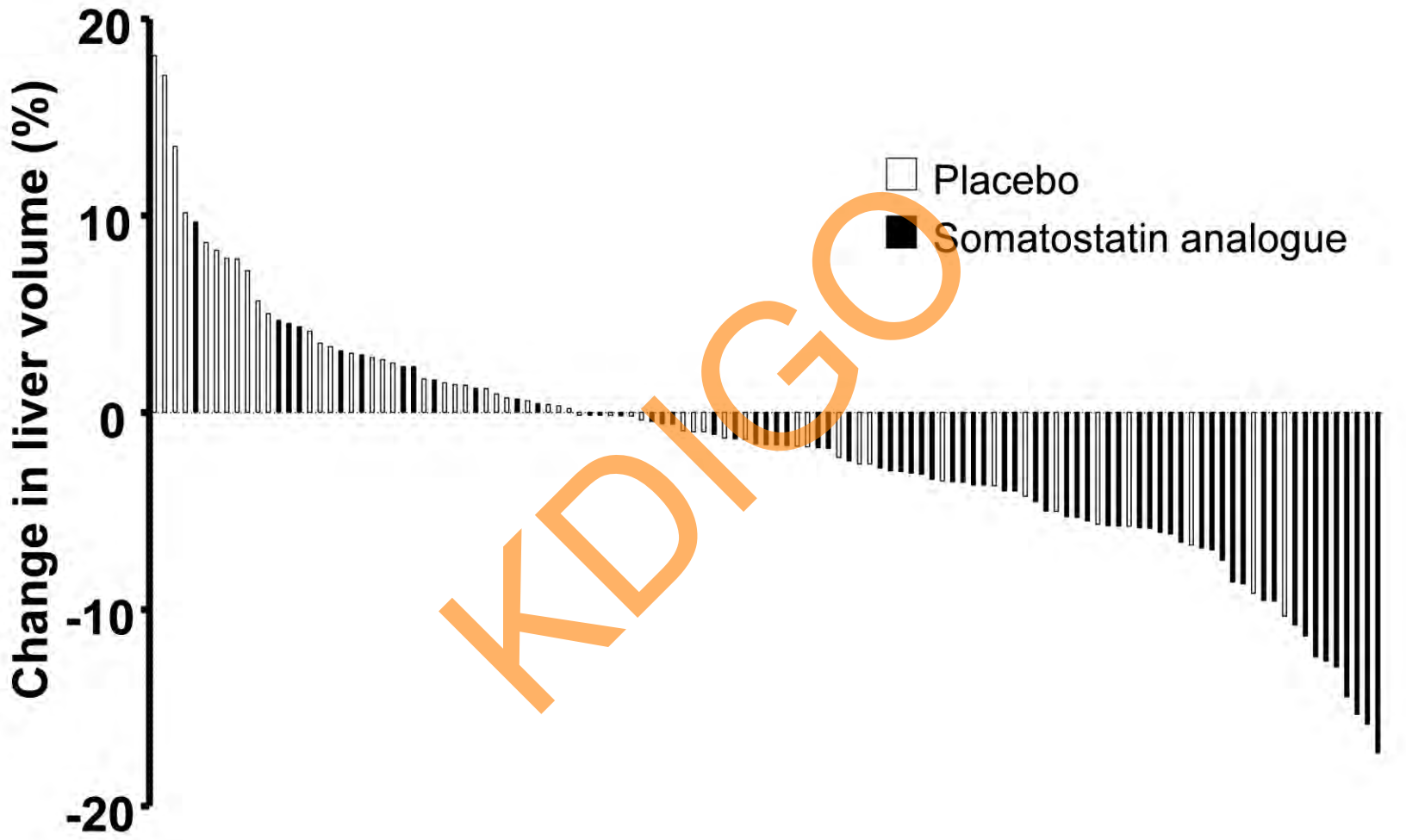


[Fig] Keimpema, Br J Surg 2009

Q2

What are the medical therapies in PLD?

Individual responses in somatostatin trials

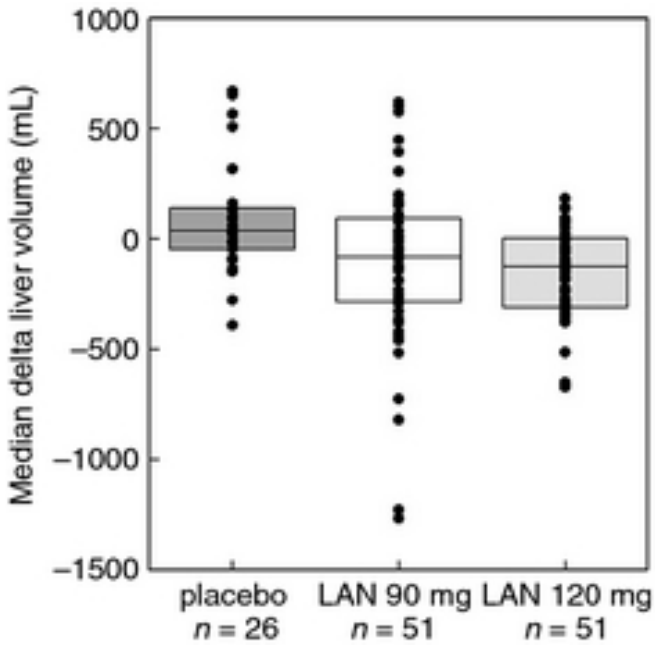


[Fig] Gevers et al, Gastroenterology. 2013

Starting dose somatostatin analogues

- Lanreotide
  - 120 & 90 mg every 4 weeks decrease liver volume after 6 months dose-dependently[1]
  - Less pronounced side-effect profile in LAN 90 mg[1]
  - No correlation with serum levels and treatment response[2]
  - Start with 120 mg /4 weeks

- Octreotide
  - No dose-finding studies
  - Start with 40 mg every 4 weeks



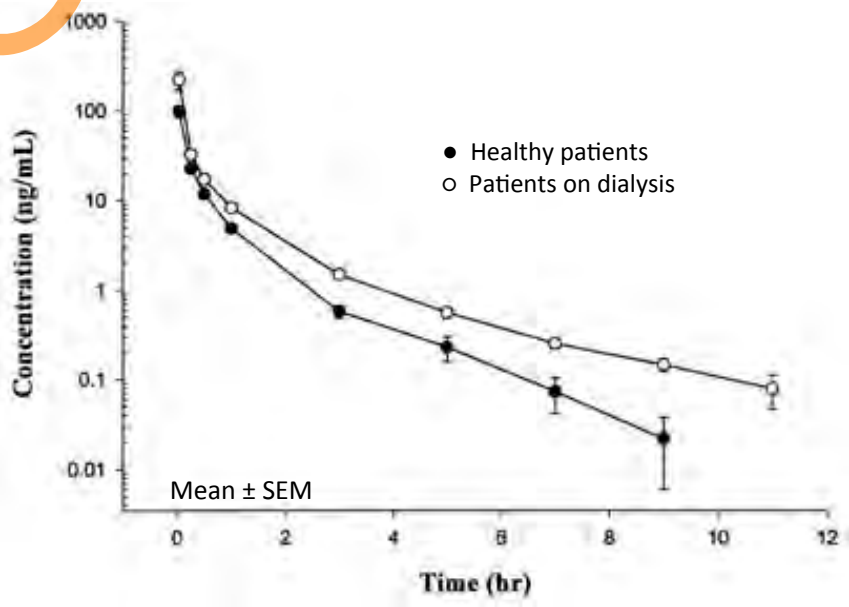
[1] Temmerman, AP&T. 2013
[2] Keimpema et al, Gastroenterology, 2009

Starting dose in reduced renal function

- Limited pharmacokinetic data

- Reduced clearance of lanreotide in 12 patients on dialysis[1]
  - Including 3 ADPKD patients
  - After 1 bolus of 7 µg/kg lanreotide

- Dose reduction in ↓ GFR?
  - 120 → 90 mg in eGFR < 30 ml/min in DIPAK trial[2]



[1] Barbanoj et al, Clin Pharmacol Ther .1999
[2] Meijer et al, Am J Kidney Dis. 2013

Somatostatin analogues in PLD

- Lanreotide & Octreotide reduce liver volume in PLD
  - Effect
    - Majority (80%) responds
    - Dose dependency (Lanreotide)
    - Within 3-6 monnths
    - Largest effect < 6 months, beyond: maintenance
    - Stopping = recurrence
    - Females > Males
    - Young > Old
    - Adding everolimus: no use
    - Curtails kidney volume?

Q3

What are the side effects of somatostatin analogues?

Monitoring side-effects

Adverse event	Somatostatin analogue n/N (%)[a]	Placebo n/N (%)[a]
Diarrhea/Loose stools	34/67 (51)	7/52 (13)
Abdominal cramps	23/67 (34)	1/52 (2)
Flatulence, bloating and gas	20/67 (30)	3/52 (6)
Persistent injection site swelling	17/67 (25)	1/52 (2)
Steatorrhea	10/67 (15)	0/52 (0)
Nausea	9/67 (13)	3/52 (6)
Constipation	4/67 (6)	1/52 (2)

[a]Denominator is total of patients in treatment arm

- Management
  - Most symptoms disappear after repeated injections
  - Dose reduction
  - Pancreatic enzyme suppletion

Gevers et al, Gastroenterology. 2013

Monitoring side-effects

- Cholelithiasis [1,2]
  - No patient developed (symptomatic) cholelithiasis in trials (6-24 months)
    - However, no ultrasound follow-up

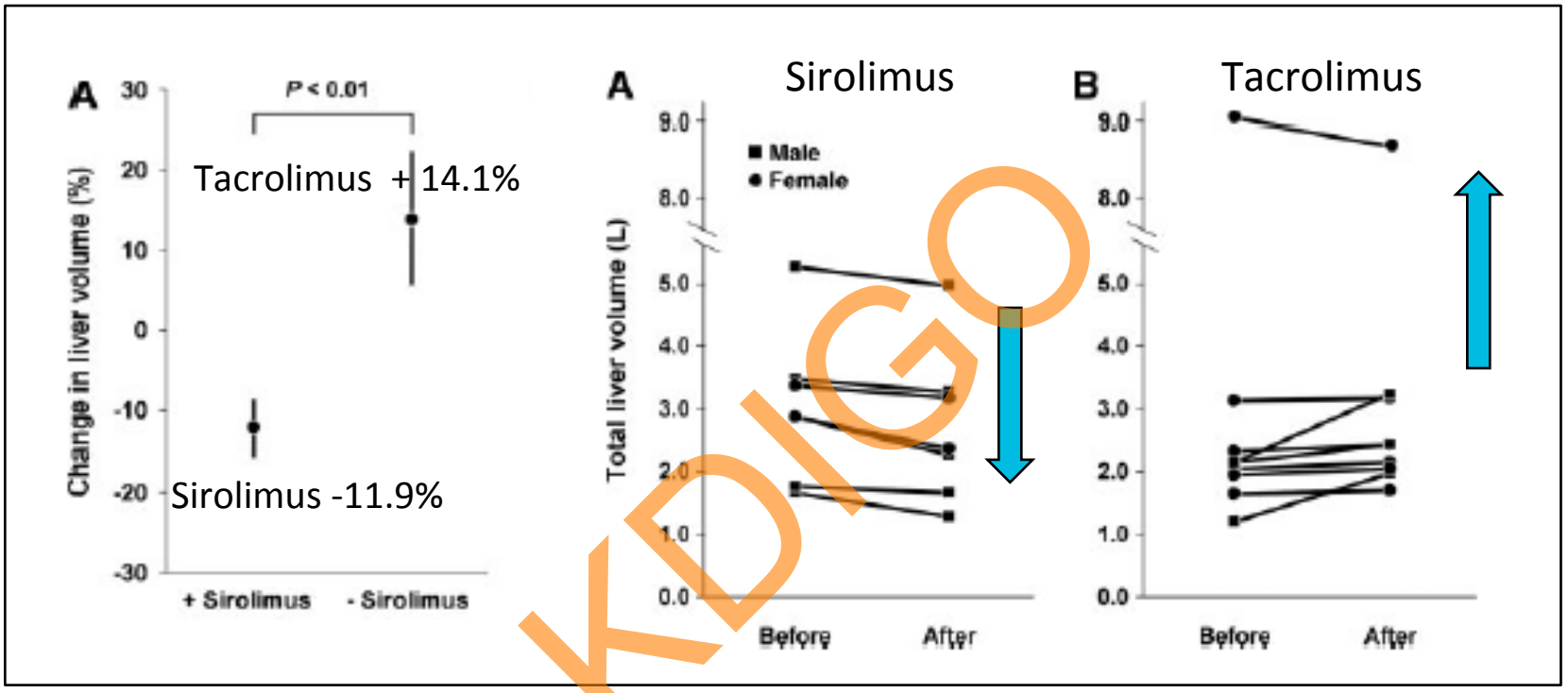
- Plasma glucose levels [3]
  - Significantly increases after SA therapy (+0.4 mmol/L in 6-12 months)
  - No patient developed diabetes or required antidiabetic therapy in trials
  - Dose reduction in case of hyperglycemia

[1] Chrispijn et al, Aliment Pharmacol Ther. 2012
[2] Hogan et al, Nephrol Dial Transplant. 2012
[3] Gevers et al, Gastroenterology. 2013

Q4

Should hepatic cystic disease impact on choice of immunosuppression?

mTOR inhibitors after kidney transplantation

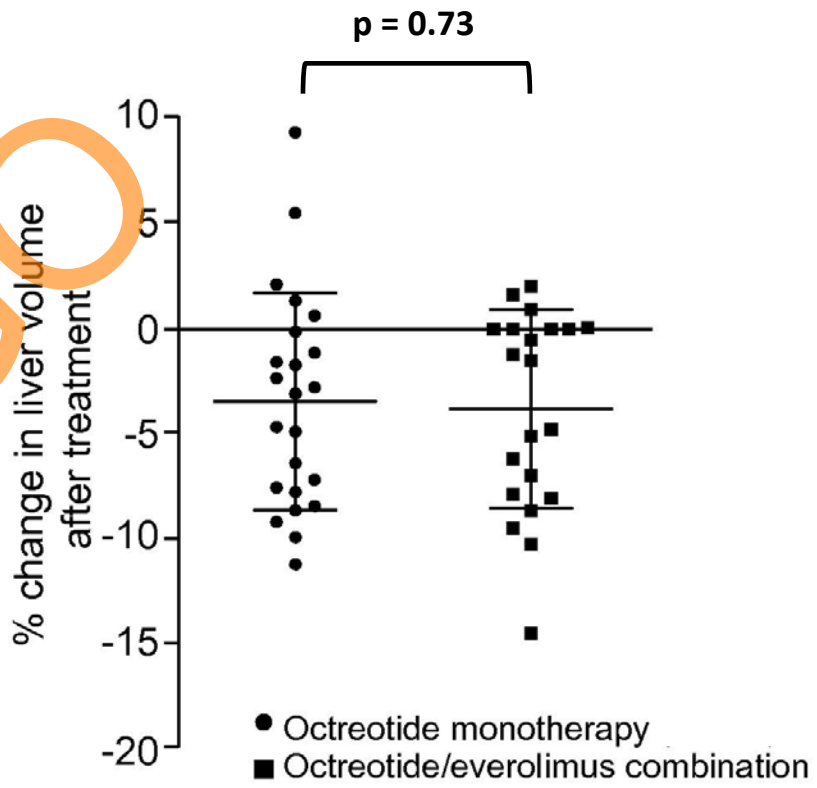


- 16 ADPKD patients: renal transplantation
- RCT: immunosuppressive effects sirolimus (n=7) vs. tacrolimus (n=9)
- Length of treatment 9.4 months; Abdominal imaging studies (-11 to + 7 months)

Qian et al, J Am Soc Nephrol, 2008.

mTOR does not potentiate effect of somatostatins

- mTOR inhibitors combined with somatostatin analogues
- 44 severe PLD patients
- Treatment 1 year
  - Octreotide LAR
  - Octreotide LAR and everolimus
- Everolimus does not improve volume-reducing effect of octreotide



Chrispijn et al, J Hepatol. 2013

Q5

What are the barriers to clinical trials for PLD?

Barriers

- Somatostatin analogues
  - May be perceived as standard of care
  - Placebo no clinical equipoise
- Inclusion criteria
  - Liver volume
  - Symptoms
- Primary endpoint?
  - Symptoms: no validated questionnaire
  - Liver volume:
    - Time consuming (not automated)
    - CT scan (radiation exposure)
    - MRI (expensive)

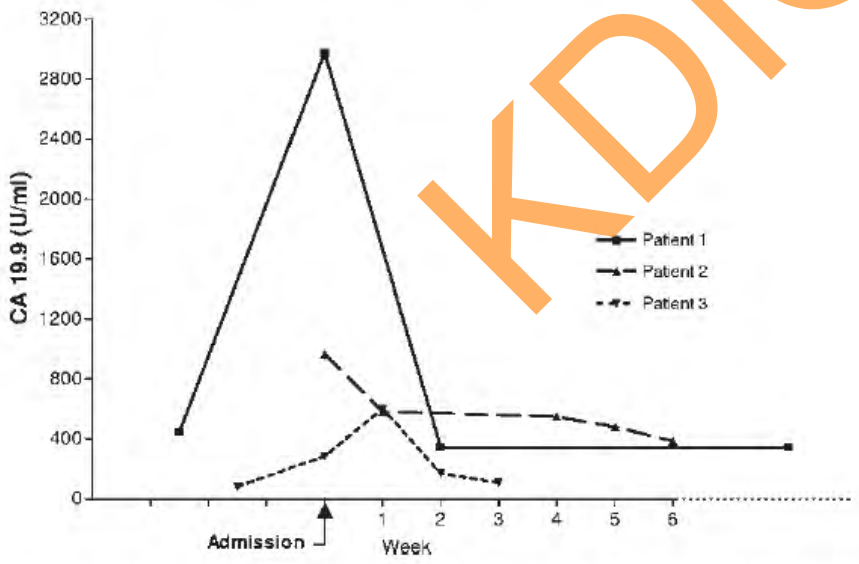
Q6

How to diagnose and treat liver cyst infections?

Cyst infection: diagnosis

- No validated diagnostic criteria [1,2]
  - mix of elements: pain + fever + CRP
  - gold standard?

- CA 19.9 [3]
  - increased in hepatic cyst infection (serum and cyst)
  - however: CA 19.9 raised in 40% of ADPKD patients

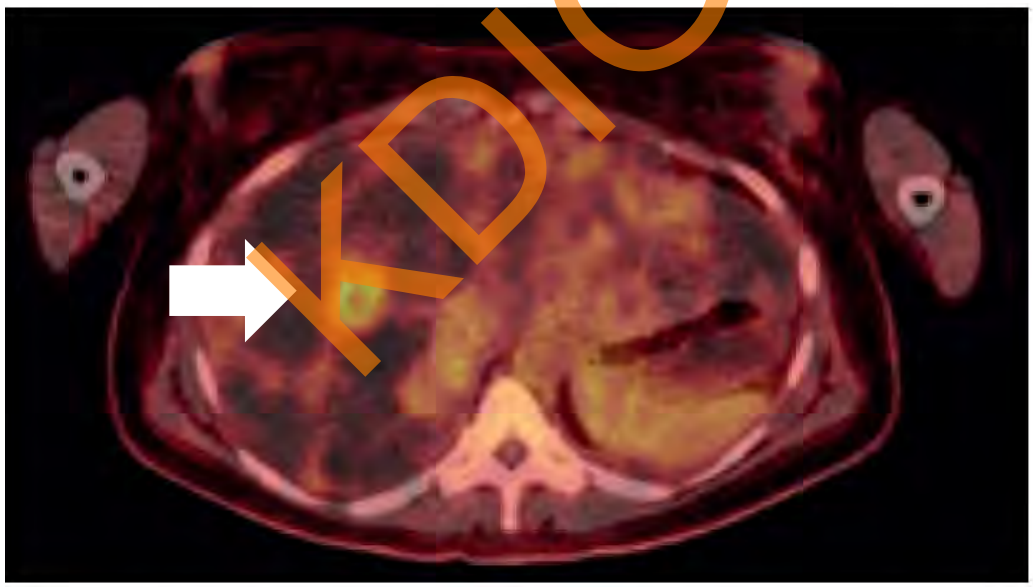


Serum CA 19.9 level
in 3 ADPKD patients admitted
for hepatic cyst infection

[1] Salleé et al. cJASN 2009
[2] Jouret et al. NDT 2012
[3] and [Fig] Kanaan et al. AJKD 2010

Cyst infection: diagnosis

- Imaging?
  - CT and MRI: contrast use, poor sensitivity/specificity
  - most promising technique: ^{18}F-FDG-PET CT [1-4]
    - limitations: costs, availability
    - sensitivity: effect of antibiotic treatment on result?
    - specificity: cholangitis, neoplasm?



[1] Bleeker –Rovers et al. AJKD 2003
[2] Jouret et al. cJASN 2011
[3] Piccoli et al. BMC Nephrology 2011
[4] Jouret et al. NDT 2012
[Fig] Lantinga et al. MAGMA 2013

Cyst infection: management

- Antibiotic therapy?
  1. adequate hepatic cyst penetration
     - limited data: fluoroquinolones (ciprofloxacin) [1]
  2. efficacy against common pathogens
     - resistance?
  3. duration and follow-up
     - short- vs. longterm?
     - usefulness of CRP and/or ^{18}F-FDG-PET CT? [2]

- Cyst drainage?
  - identification and accessibility of infected cyst?
  - risk of infection spread?

- Perceived increased risk of infection after RTX [3,4]

[1] Telenti et al. Mayo Clinic Proc 1990
[2] Lantinga et al. *unpublished*
[3] Rodrigues et al. Transpl Proc 2012
[4] Fitzpatrick et al. AJKD 1990

Q7

How to evaluate and follow PLD: Need to develop a clinical score or a specific questionnaire?

Follow up

- Follow up liver volume
  - Growth rate: 0.9-1.6% in ½ - 1 year

- Physical examination
  - Weight
  - Abdominal girth
  - Nutritional state (midarm circumference)
  - Signs of caval vein compression/portal hypertension

- Symptoms
  - Adjusted MELD score
  - Disease specific questionnaire (available spring 2014)
    - Captures PLD specific symptoms
    - Assesses improvement/decline in PLD specific symptoms
    - Outcome measure clinical trials

Q8

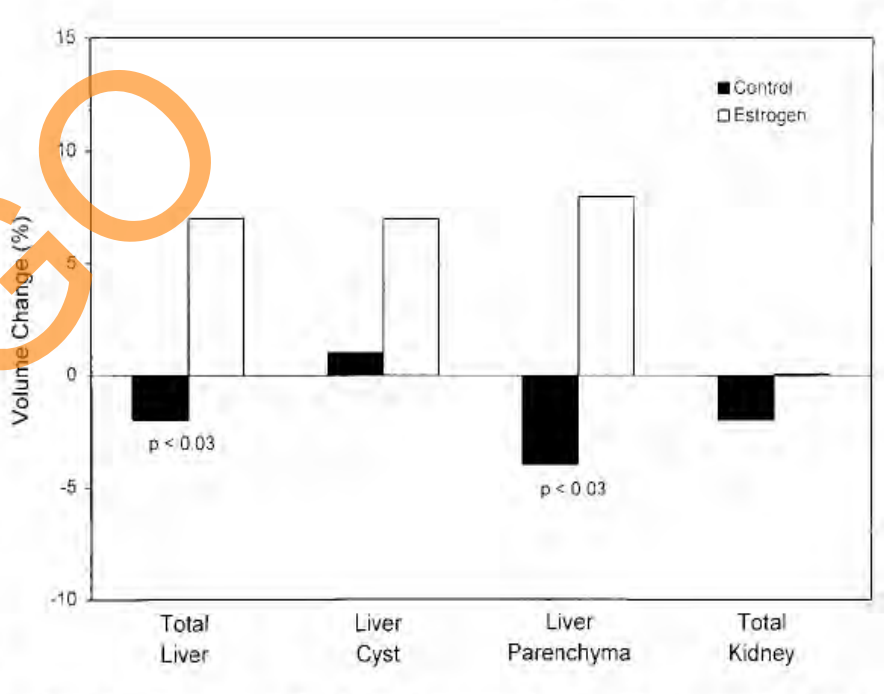
What advice can be given to pre- and post-menopausal women with PLD regarding contraception and estrogen replacement therapies?

Estrogens use

- Female sex, estrogens use and multiple pregnancies are risk factors polycystic liver growth

- 20 postmenopausal ADPKD pts [1]
  - Estrogens use vs. no treatment
  - Estrogen treatment associated increase in liver volume; no increase in kidney volume

- Discourage the use of exogenous estrogens in symptomatic PLD patients [2]



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

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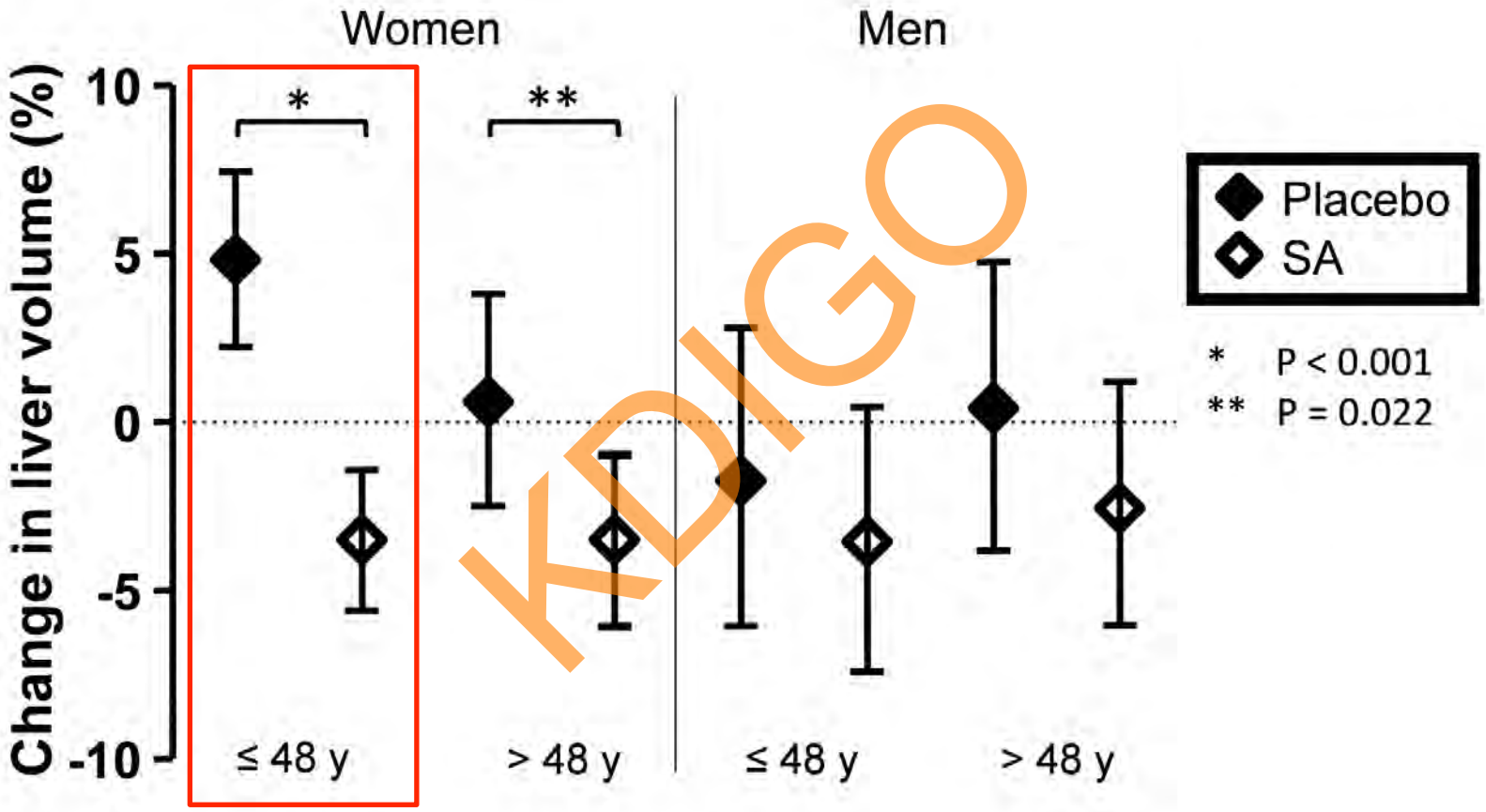
What should patients be told about PLD? Is enough known about potential lifestyle modifications (good and bad) to affect this frightening PKD-related condition?

Polycystic liver disease

- Patient information
- Lifestyle modifications
- Risk of complications

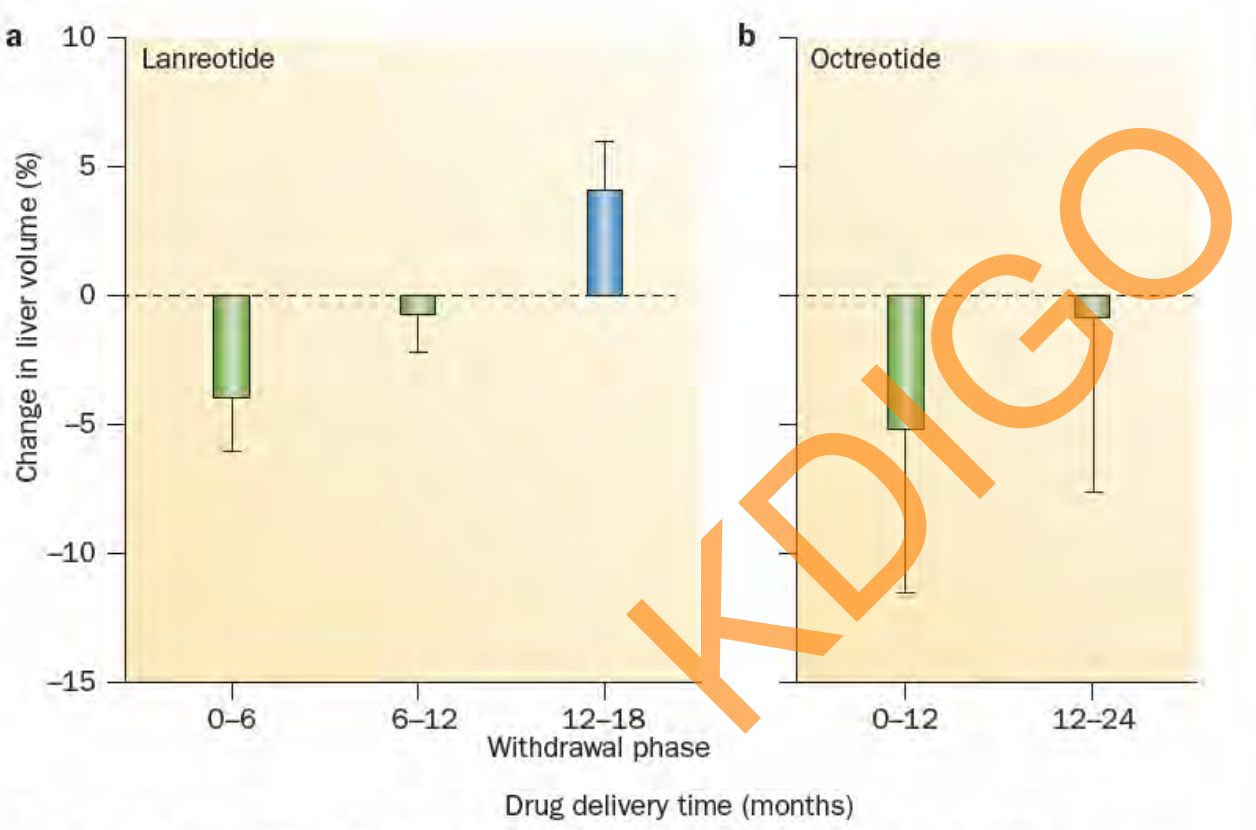
Practical Integrated Patient Support

Somatostatin analogues in age-gender subgroups



[Fig] Gevers et al, Gastroenterology. 2013

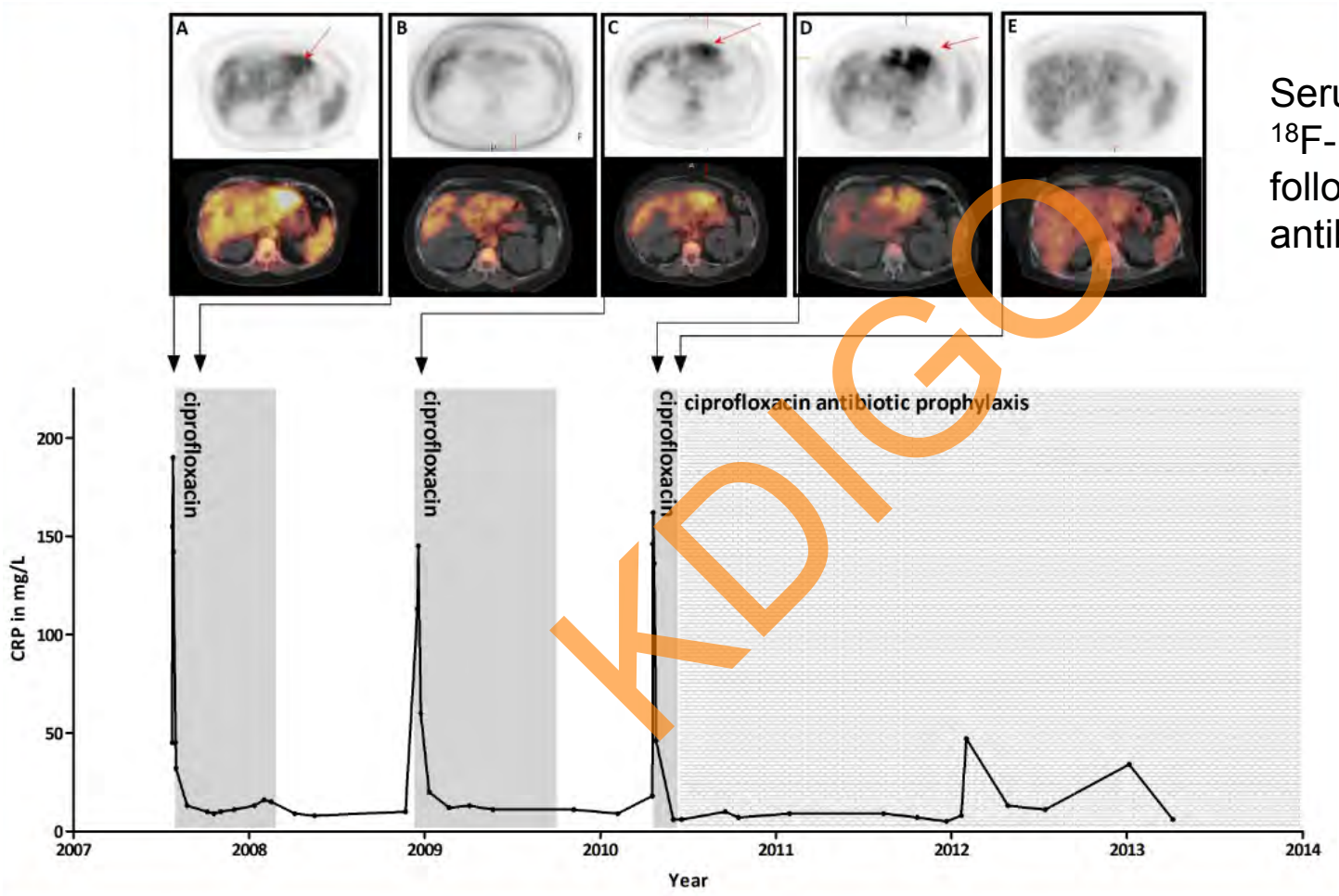
Extension trials



- Largest effect early in treatment
- Prolonging results in maintenance
- During follow-up: recurrence of liver growth

Chrispijn et al, Aliment Pharmacol Ther. 2012 and Hogan et al, Nephrol Dial Transplant. 2012

How to manage recurrent infection?



Serum CRP and ^{18}F-FDG PET/CT results following ciprofloxacin antibiotic therapy

[Fig] Lantinga et al. *unpublished*

Follow up: Severe PLD

Follow up liver volume

- Growth rate: 0.9-1.6% in ½ - 1 year [1]

Adjusted MELD-score [2]

- Massive polycystic liver (total cyst:parenchyma ratio > 1)
- Not a candidate/ failure other therapies
- Clinically significant manifestations of PLD
- Severe malnutrition
- Serum albumin <2.2 mg/dL
- Lean body mass: ↓ midarm circumference
  - ≤ 23.1 cm females; ≤ 23.8 cm males

eGFR >30: 15 points

eGFR <30: 20 points

[1] Gevers, T.J. and J.P. Drenth, Nat Rev Gastroenterol Hepatol, 2013. 10(2): p. 101-8.
[2] Arrazola, L., et al., Liver Transpl, 2006. **12**(12 Suppl 3): p. S110-1.

Evaluation and follow-up

- Aim of SA therapy: reducing PLD-related symptoms by decreasing liver volume

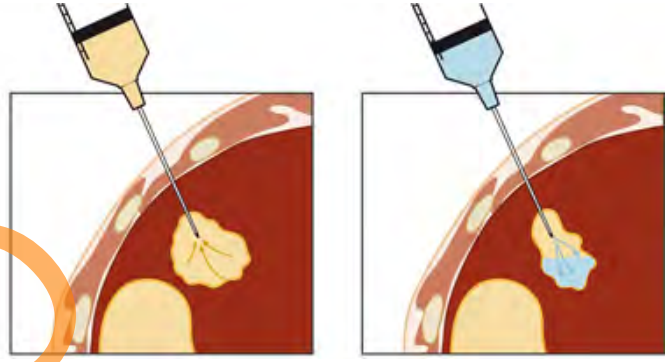
- Follow-up liver volume
  - CT or MRI volumetry
  - Time-consuming (± 1 hour)
  - Need for faster methods

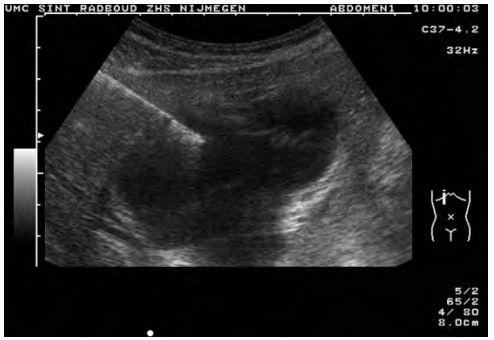
- Follow-up symptoms

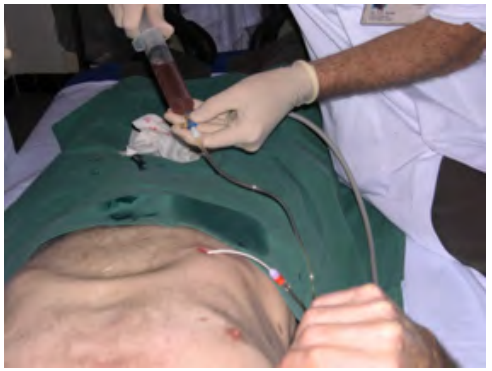
- Stopping rules?

Aspiration sclerotherapy

- Indication: large symptomatic solitary or dominant hepatic cyst (> 5 cm)
- Minimal invasive
- Procedure: percutaneous drainage with instillation of sclerosing agent [1]
  - Ethanol, minocycline, tetracycline, etc
  - Comparable results, ethanol most commonly used
- 22% total regression; 19% partial regression[2]
- 21% recurrence [2]



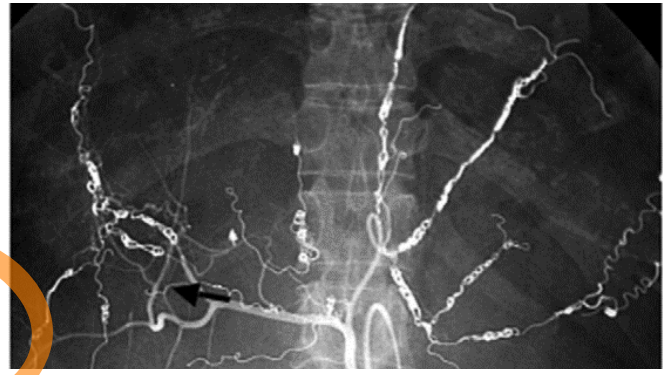




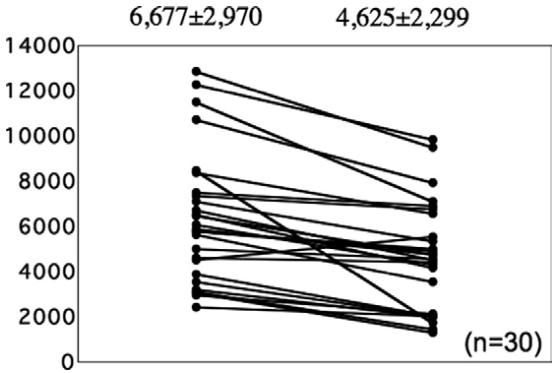
[1] Bean, W. J AJR Am J Roentgenol 144(2): 237-241.
[2] Drenth Hepatology 2010;52(6):2223-2230.

Transcatheter arterial embolization

- Procedure: selective embolization of hepatic artery branches that supply major cysts



- Experimental [1,2]
  - Two relatively small uncontrolled trails
    - Reduction liver volume by 23-36%
    - Symptomatic improvement

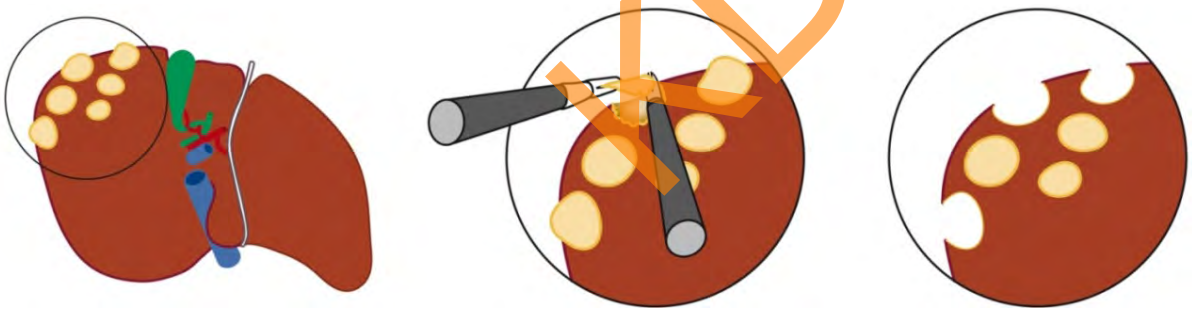


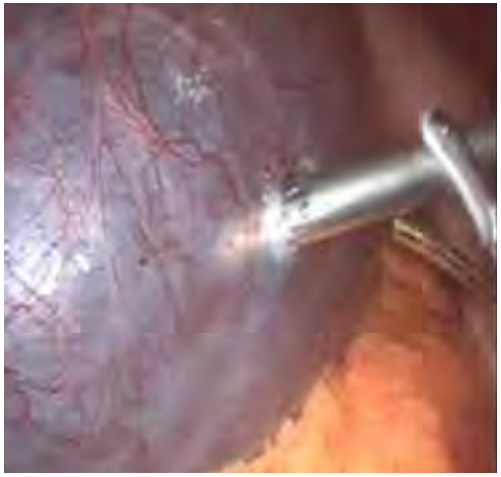
- Research in a controlled setting is needed before recommending TAE over conventional treatment options [3]

[1] Takei, R. Am J Kidney Dis 2007; 49: 744-752
[2] Wang, M. Abd Imaging 2013; 38(3):465-73
[3] Gevers, Nat Rev Gastroenterol Hepatol 2013;10(2):101-108

Cyst fenestration

- Indication: multiple symptomatic large superficial located cysts
- Procedure: deroofing cyst [1]
- 92% symptomatic relief; 24% cyst recurrence [2]
- Complications: laparoscopic 23% vs laporatomy 40% [2]

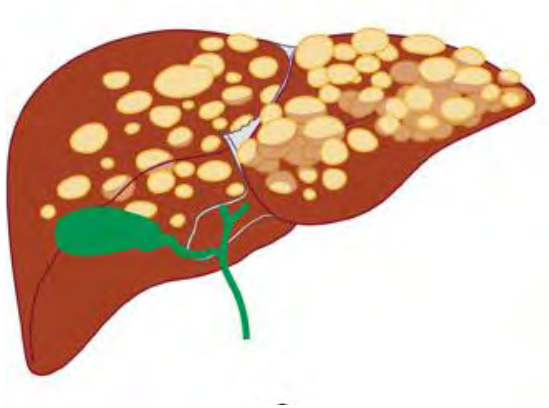




[1] Lin,T.Y. Jpn J Surg 1977;7(4):189-198.
[2] Drenth J.P. Hepatology 2010;52(6):2223-2230.

Segmental hepatic resection

- Indication: Severe polycystic liver with at least one unaffected segment
- Procedure: resection of affected segments and fenestration of residual cysts

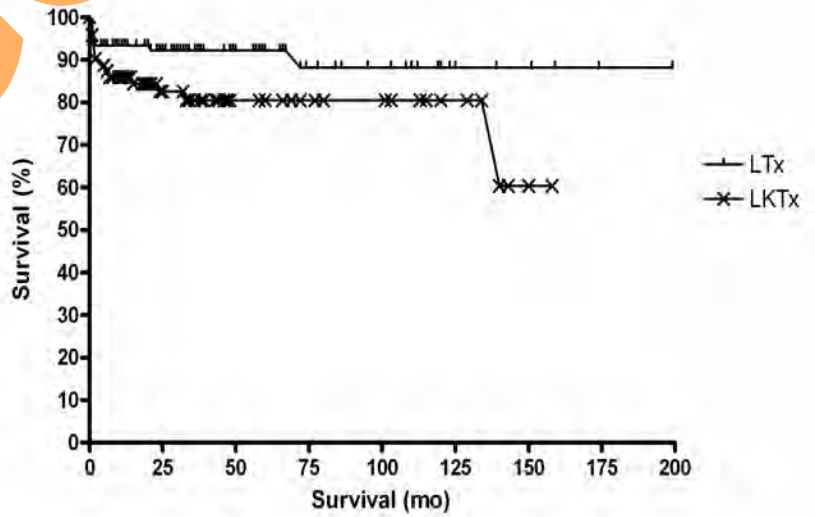


- 86% symptomatic relief [1]
- Complications in 51%; mortality 3% [1]
- Risk of subsequent adhesions might complicate future liver transplantation [2]

[1] Drenth J.P. Hepatology 2010;52(6):2223-2230.
[2] Gevers, Nat Rev Gastroenterol Hepatol 2013;10(2):101-108

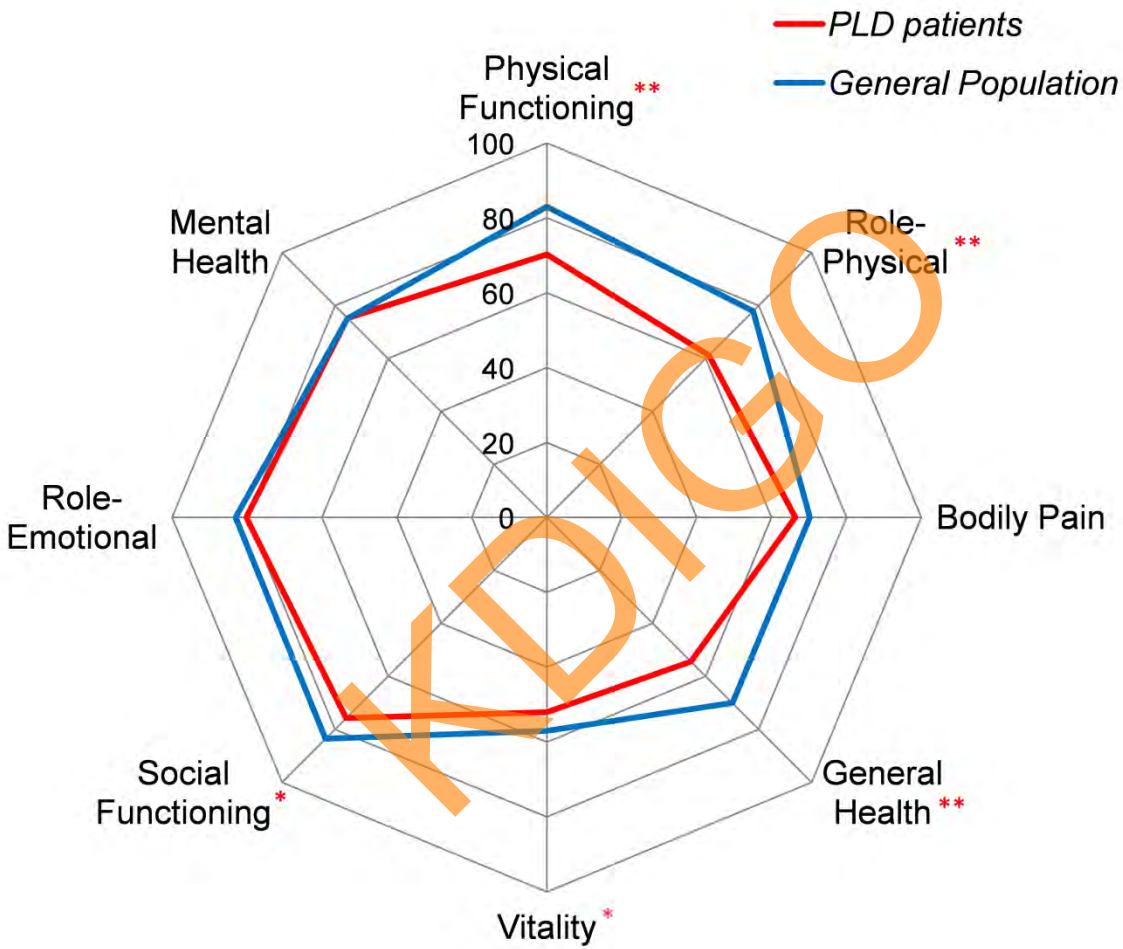
Liver transplantation

- Indication: severe diffuse polycystic liver with grave impaired quality of life and / or untreatable complications [1]
- Curative treatment option; 91% improvement of quality of life [2]
- Morbidity: 41%
- Liver and kidney transplantation
  - Consider in ADPKD patients undergoing maintenance dialysis
- 5 year survival rate: 92% LTx and 80% LKTx [3]



[1] Pirenne Transplant Proc 2001;33(1-2): 1364-1365.
[2] Kirchner, G. I Liver Transpl 2006; 12(8): 1268-1277.
[3] and [Fig] van Keimpema Transpl Int 2011; 24(12): 1239-1245

Follow up: Quality of life



[Fig] Wijnands, T.F. et al., Liver Int, 2013. **8**(10): p. 12430.

Follow up: Laboratory findings

- No abnormalities in liver synthesis
- Abnormalities in liver enzymes may occur:
  - ↑ γGT [1]
  - ↑ AP [1]
- ↑ Bilirubin by compression of bile ducts [1]
- ↑ Carbohydrate antigen 19-9 [2]
  - Positive correlation with liver volume (r = 0.3870, P = 0.0025)
  - Raised in cyst infections [3]
  - Possible follow up biomarker?

[1] Van Keimpema L et al., Liver Int. 2011 Jan; 31(1):92-8
[2] Waanders, E., et al., Liver Int, 2009. 29(9): p. 1389-95.
[3] Kanaan, N., et al., Am J Kidney Dis, 2010. 55(5): p. 916-22.