British Transplant Society 15th March 2018

Liver transplant for PSC :
Managing the dominant stricture
Timing of colectomy

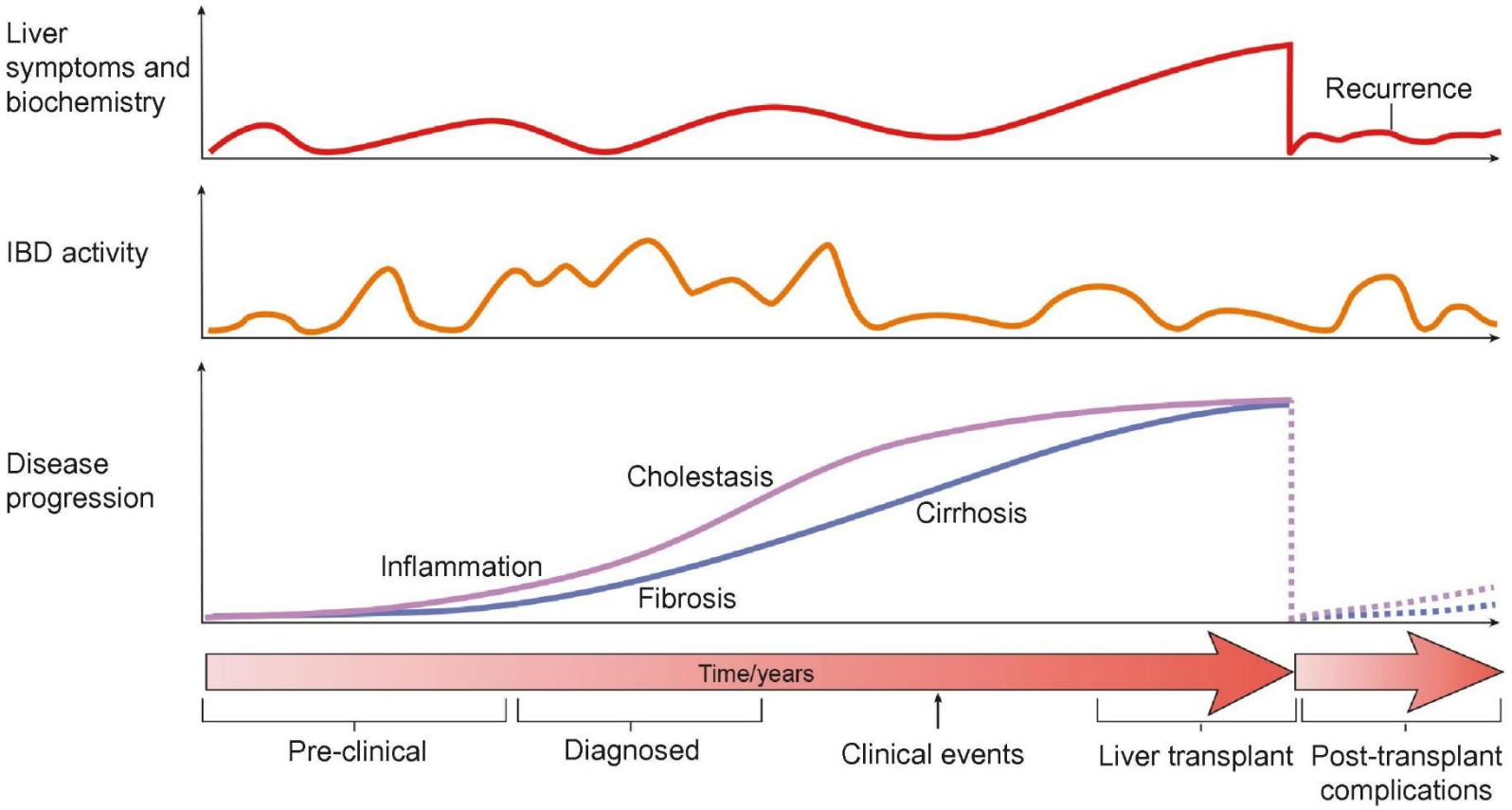
Brian Davidson

Prof of HPB and Liver Transplant Surgery
Royal Free London NHS Foundation Trust
Wellington Hospital London
University College London (UCL)

UCLPartners
Academic Health Science Partnership

UCL

Primary sclerosing cholangitis (PSC) and ulcerative colitis (UC)



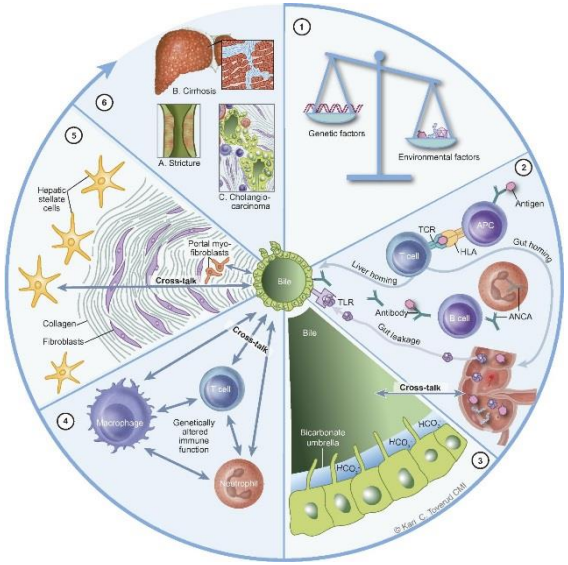
Kari C Toverud

Course of UC in PSC with cirrhosis

Presentation

- Patients with PSC and UC
  - Quiescent clinical symptoms
  - Extensive endoscopic disease
  - Rt sided predominant
  - Higher rates Ca

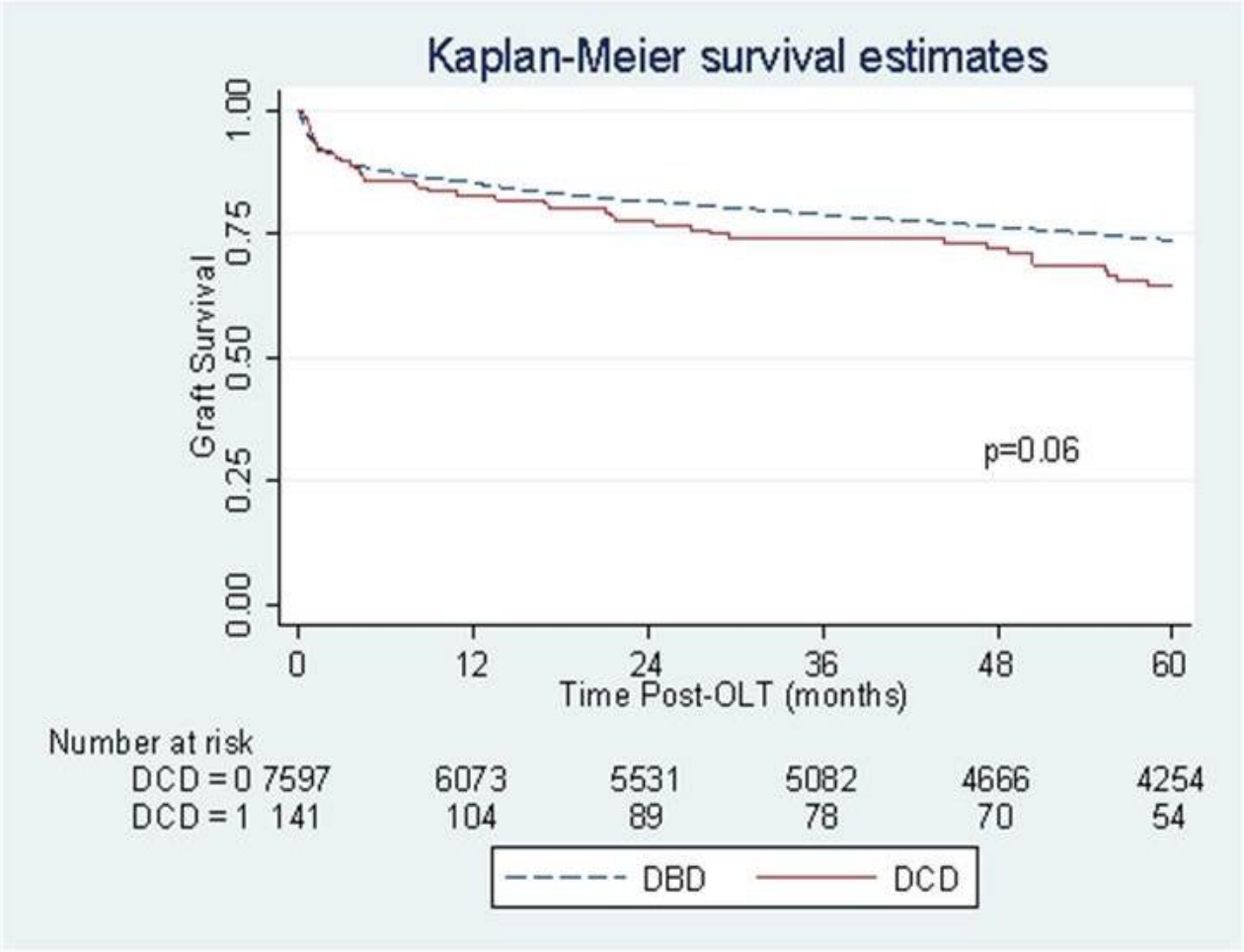
- Could PSC with UC may be a separate disease entity?



Treatment

- Patients with PSC and UC
  - Require less steroids
  - Fewer hospitalisations
  - Those requiring OLT have more quiescent disease
  - Lower incidence of colonic dysplasia
- Is liver disease protective to UC?

Outcome OLT for PSC (UNOS)



Mousa et al ATC 2017

PSC and dominant strictures

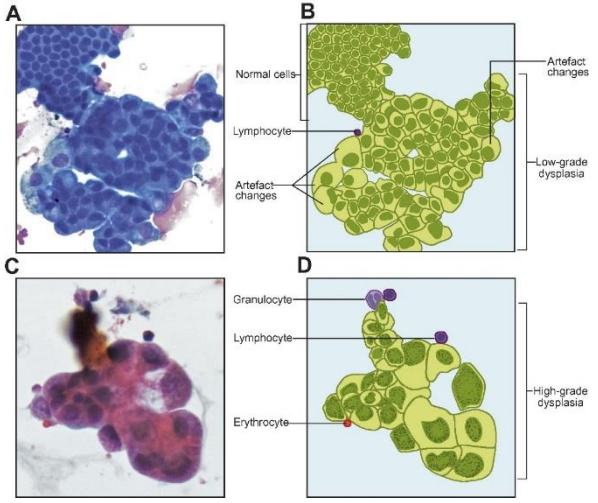
PSC diagnosis

- EASL guidelines 2009
  (J Hepatol 2009 ; 51 : 237)
  - Unexplained biochemical cholestasis 6/12
  - Characteristic changes on MRCP or liver biopsy

Dominant stricture

- CBD <1.5mm
- Rt or Lt hepatic duct <1mm

- Isolated stricture in PSC rare (<5%)
  - Consider CCA



Management of the dominant stricture in PSC

EASL recommendation 2009

- Dominant bile duct strictures with significant cholestasis should be treated with biliary dilatation.
- Biliary stent for failed stricture dilatation.
- Prophylactic antibiotic coverage is recommended.

Should we balloon/ stent the dominant stricture?

Advantages

- Improves liver biochemistry
- Reduces pruritus
- Stenting can reverse fibrotic liver disease
- Improves survival

Disadvantages

- Introduces sepsis into biliary tree
- Increased risk of OLT
- Delays OLT and hence increases risk of OLT
- Ineffective

No controlled trial has evaluated endoscopic therapy for dominant PSC strictures

Evidence for treatment?

No benefit of endoscopic therapy in PSC

Bjornsson AJ Gastro 2004; 99 : 502

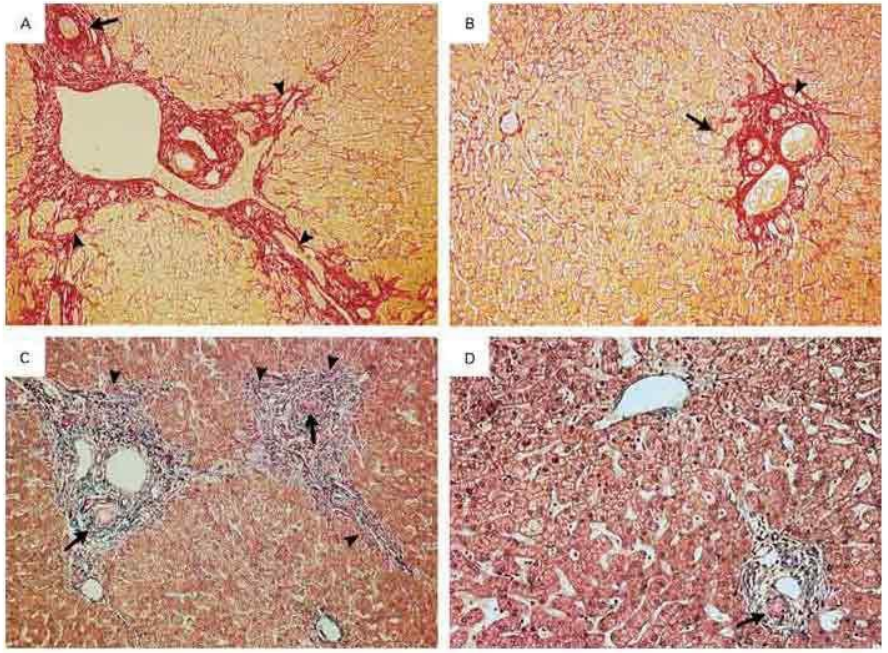
- Review of 125 patients with PSC
- 56 of 125 (45%) treated dominant strictures.
- No difference Bil or ALP between stricture and no stricture.

	Bil umol/l	ALP Ukat/l
Stent	42	16
No stent	35	15.2
Diff p	ns	ns

Stenting can reverse fibrotic liver disease

Hemmel P NEJM 2001; 344 : 418-423

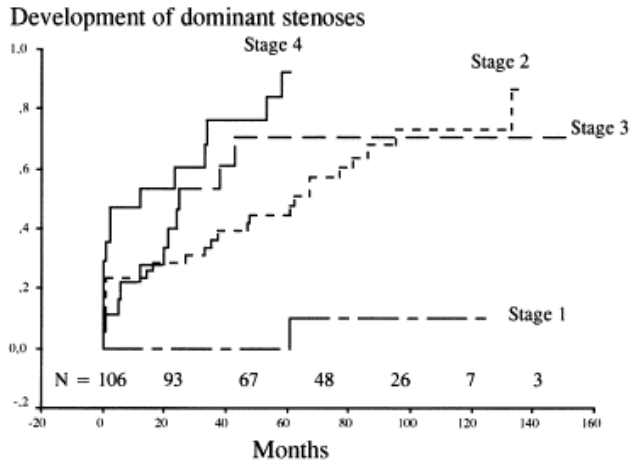
- 11 patients with CBD strictures from chronic pancreatitis
- Liver Bx at time of surgical bypass
- Follow up liver Bx
- Median 2.5 years
- 9 improved fibrosis
  - 2 grades, 2 patients
  - 1 grade, 4 patients
  - 3 patients unchanged.

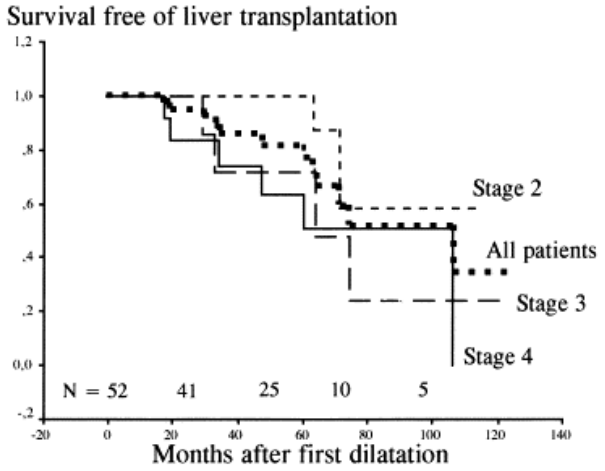


Not PSC, small study, histological grading

Outcome of endoscopic treatment of dominant stenoses in PSC

Stiehl J Hepatol 2002; 36 : 151-156





- 106 patients with PSC
- On trial of UDCA
- 52 developed dominant strictures.
- 5 yr survival stage 2 100%, stage 3 72%, stage 4 50%
- 2 of 52 patients undergoing dilatation developed CCA

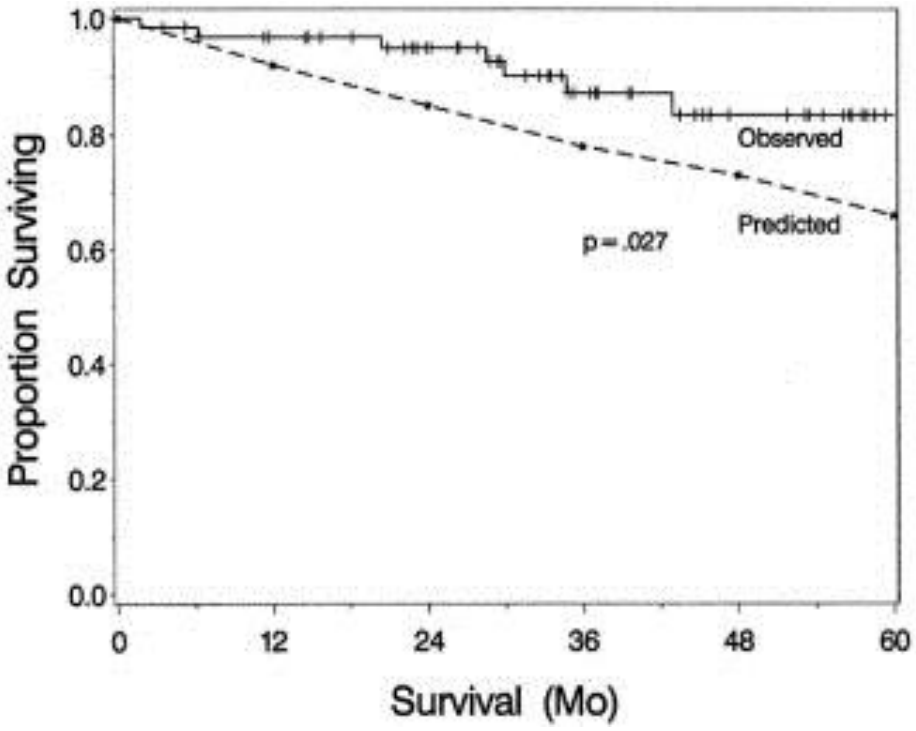
Histological stages of PSC (Ludwig G 1989)
Stage 1: portal tract changes
Stage 2 : periportal fibrosis
Stage 3 : Bridging fibrosis
Stage 4 : Cirrhosis

Dominant stricture with early stage liver disease (stage 1, 2) not indication for transplant.

Stenting improves survival in PSC

Balayut AR Gastro Endosc 2001

- 63 patients with PSC undergoing endotherapy
- Repeat balloon dilatations of dominant strictures
- Follow up 3 years
- Predicted survival at presentation using Mayo clinic model.
- Actual survival at 5 years

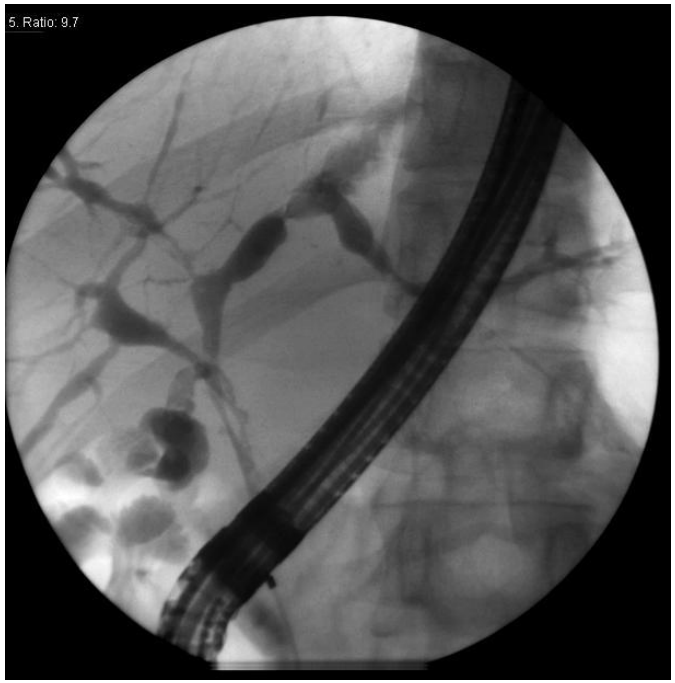


Mayo Risk Score was calculated by using the equation R = (0.03 Age, years) + (0.54 loge Bilirubin mg/dL) + (0.54 loge Aspartate aminotransferase U/mL) + (1.24 Bleed history) – (0.84 Albumin gm/dL).

Small study, short follow up, model validated to assess response to treatment?

Conclusion (1) : Dominant stricture in PSC

- Isolated stricture rare : think CCA
- Good prognosis if early stage liver disease (Stage 1 and 2)
- Dominant stricture not in itself indication for OLT.
- Value of balloon dilatation/ stent unproven.
- Benefits and risks.
- No RCT.



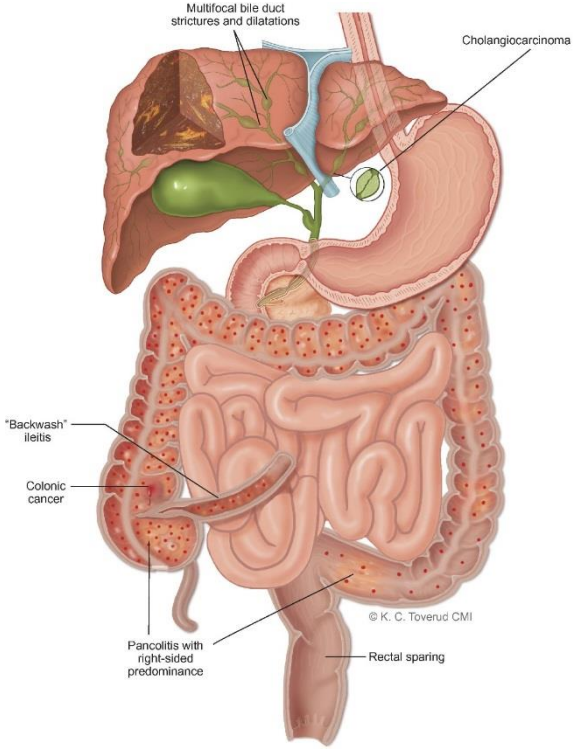
Liver transplant for PSC with UC
Timing of colectomy?

Colectomy prior to transplant

- Yes
  - Severe dysplasia
  - Severely symptomatic(cahexia) contraindicating OLT.
- ?
  - If high risk of UC progression post OLT.
  - If high risk bowel cancer post OLT

vs

  - **Risks of colectomy in cirrhosis**.

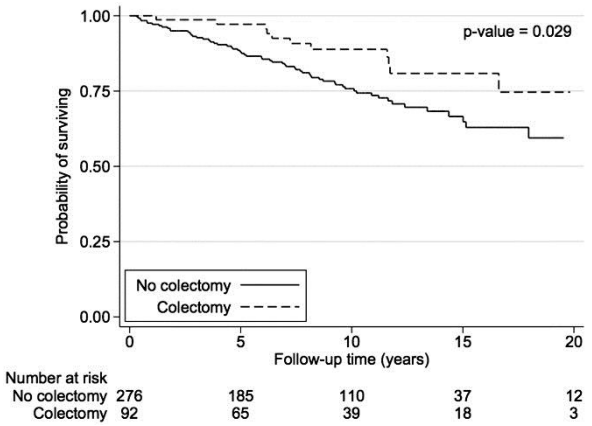


Risk factors and prognosis for recurrent PSC(rPSC) after OLT : A Nordic Multicentre study

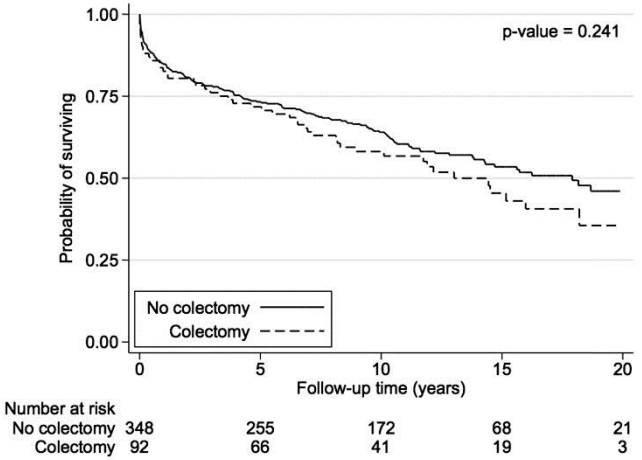
Lindstrom et al Scand J Gastro 2018 (in press)

- 440 patients with OLT for PSC (1984-2007)
- Follow up 3743 years
- rPSC in 19%(n=85)
- Risk of death or needing re-Tx increased by rPSC.
  - HR 7.3; 95% CI 4.1-12.8, p=0.0001
- Pre Tx colectomy associated with reduced risk of recurrent PSC (HR 0.49; 95% CI 0.26-0.94, p=0.033)
- Inflammation of UC not associated with rPSC
- FK 506 risk factor for rPSC (before 40yrs HR 7.3)

PSC Recurrence free survival with and without colectomy



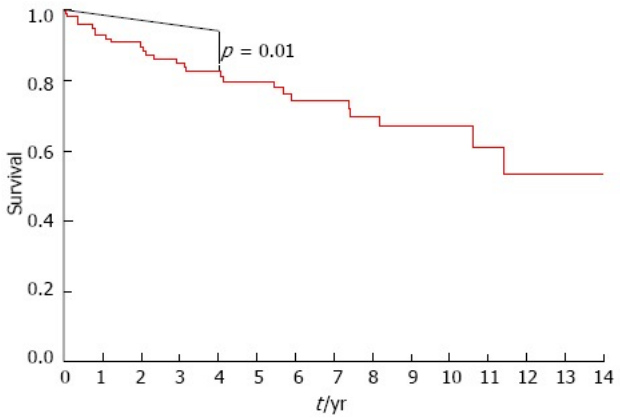
Patients survival post transplant for PSC



Risk of colectomy in patients with PSC

Treeprasertsuk S et al WJGI Pharm. Ther. 2013; 4(3) : 61-68

- Mayo Clinic 1995-2008
- 193 PSC/UC
- 104 underwent colectomy



General complications (34.6%)

- 2 deaths 10 and 20 days post op (2/104 = 1.9%)
- Most common
  - blood loss (10.6%) and abdo abscess (3.8%)

Liver complications (within1/12) (8.6%)

- Worsening LFTs (n=3)
- Liver failure and OLT (n=2)
- Acute cholangitis (n=3)
- Rt HV thrombus (n=1)

UC post OLT
Improved or stable

Study	*n*/UC patients	Immunosuppression (% of cohort)	Outcomes	Additional findings	Authors' comments
Gavaler et al. [5]	23/23	CYA + PRED; ± sulfasalazine	18 % unchanged, 82 % improved	8 patients required treatment of flares but no reported "worsening"	Patient questionnaire-based study
Shaked et al. [8]	36/29	CYA OR FK + PRED + AZT	14 % worse, 55 % unchanged, 17 % improved	Found preop active disease continued to be active	Assessment of preop disease based on a single visit pre-LT may not accurately reflect disease activity
Befeler et al. [7]	35/25	CYA + AZT + PRED (>3 months); FK + PRED (1 patient)	24 % worse, 76 % unchanged	No flares required IV steroids or surgery	10 patients of the cohort had undergone partial or total colectomies prior to enrollment
Graziadei et al. [10]	150/112	CYA + AZT + PRED (77) or FK + PRED (21)	13 % worse, 1 de novo case	Total number of acute rejection episodes and percentage of patients with at least 1 rejection episode was higher in the PSC population	Main study outcome was graft survival
Saldeen et al. [6]	47/39	CYA + PRED (>3 months) + AZT	6 % worse, 35 % unchanged, 59 % improved	Most favorable course in those on triple therapy	Patient questionnaire-based study
van de Vrie et al. [9]	18/14	CYA or FK, + PRED (2 years) + AZT (1–3 months in 75 %)	22 % worse, 67 % unchanged, 11 % improved, 1 de novo	Colorectal neoplasia was seen in 5/18 patients, all with prolonged disease course	75 % of patients were receiving concomitant AZT; 27 % incidence of dysplasia, but patients had long disease course and extensive disease

Khosa et al 2014 Int J Colorectal Dis

Deterioration of IBD after OLT

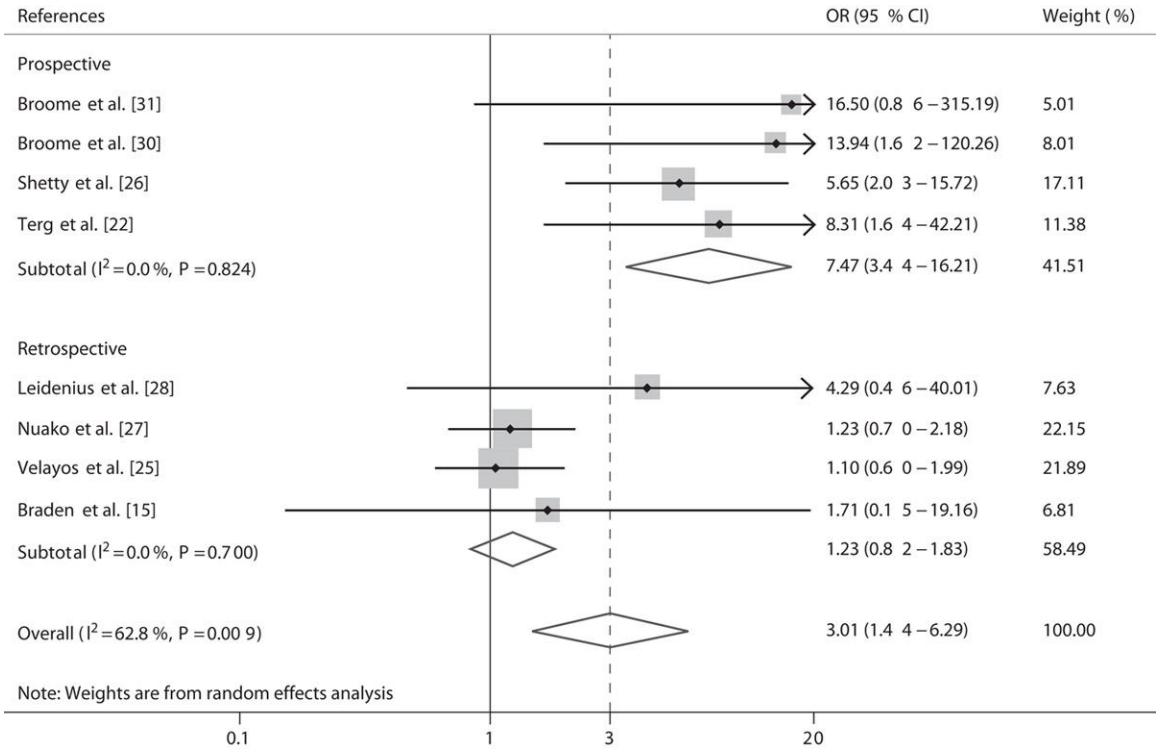
Study	*n*/UC patients	Immunosuppression (% of cohort)	Additional findings	Authors' comments
Dvorchik et al. [11]	192/165	CYA (50) or FK (50) + PRED; AZT or MMF (select few)	56 required colectomy (30 %); multivariate analysis showed transplant was only a risk factor for colectomy. The only risk factor for CRC was the duration of disease	The only outcome measured was colectomy, no evaluation of patient symptoms, medication requirements, etc. Note: immunosuppression was changed to FK in 37 patients
Ho et al. [12]	20/20	CYA (30) or FK (70) + PRED (>3 months); AZT (95)	Rate of relapse/year increased from 0.3 to 1.0/year ($p = 0.007$). 38 % (6/16) relapsed within 6 months; increase in corticosteroid tapers from 0.1 to 0.4/year ($p = 0.003$)	Relapse did not necessarily include endoscopic/histologic findings of active disease
Gelley et al. [13]	20/20	CYA (32) or FK (68)	Mayo disease activity index pre- and post-LT: 2.91 ± 0.9 increased to 6.64 ± 3.7 ($p = 0.009$); moderate activity (0 vs. 5, $p = 0.032$) and severe activity (1 vs. 8, $p = 0.02$)	No information available about drug regimens for IBD pre- or post-LT
Joshi et al. [14]	110/77	CYA or FK + PRED (>3 months); ± AZT (8); ± 5-ASA (62)	Worsening IBD course in 33 (39 %) with severe flare in 20/33; 6 required colectomy for failed medical therapy; univariate analysis showed older age, smokers, and active IBD pre-LT risk factors for flare. Multivariate analysis showed increased risk of flare with FK ($p = 0.08$)	

Khosa et al 2014 Int J Colorectal Dis

Reason for differences in outcome?

Increased risk of colorectal cancer in patients with PSC and IBD: metanalysis

Zheng H et al Eur J Gastro Hepatol 2016 ; 28 : 383-390



Chemoprevention of colorectal cancer in ulcerative colitis

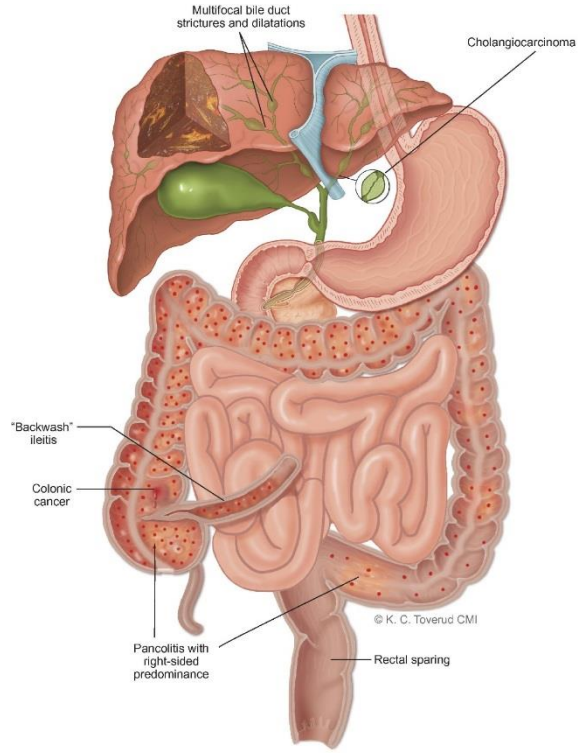
Cristina Bezzio et al Expert Rev Gastro Hepatol 2017 ; 11 : 339-347

- No RCT's
- Observational studies

• 5ASA	possible . Low level evidence
• Thiopurines	Nil
• Anti-TNF	Nil
• UCDA	Inconclusive

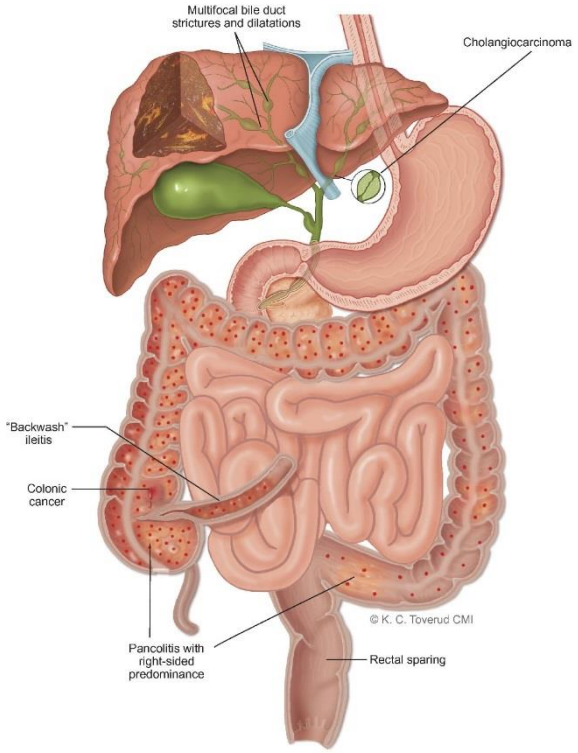
Liver transplant for PSC and UC
Timing of colectomy

- **Synchronous procedures**
  - OLT and colectomy
  - Treat liver and bowel disease.
  - Risks?
  - Complications?
  - No data



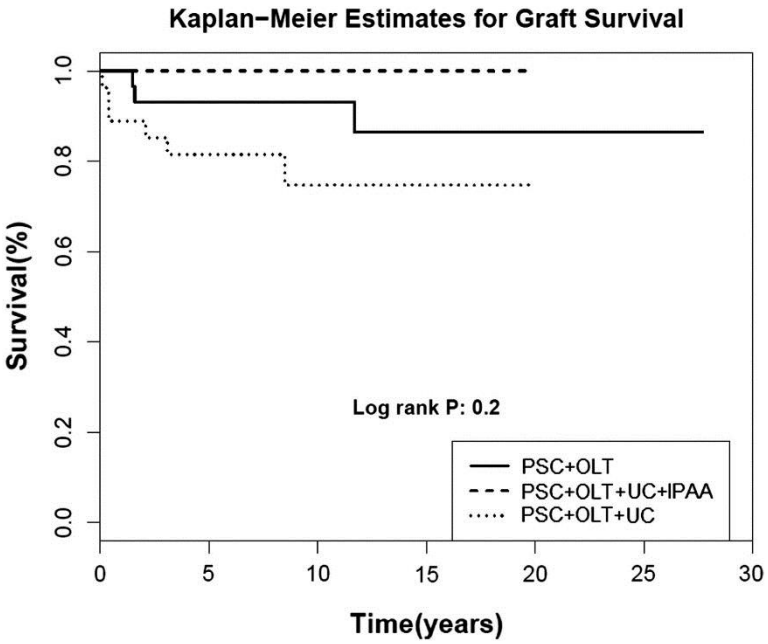
Liver transplant for PSC and UC
Timing of colectomy

- **Bowel resection post OLT for PSC**
  - Is it required?
    - 20%
  - What procedure?
    - Total colectomy and IPAA
  - Complications
  - Outcomes



Impact of ileal pouch-anal anastomosis on the surgical outcome of orthotopic liver transplantation for primary sclerosing cholangitis

Obusez EC et al J Cohns Colitis 2013 (Cleveland Clinic)



79 patients with OLT and PSC

OLT + PSc, no UC, n=30

OLT+PSC+ UC n=23

OLT + PSC+ IPAA, n=22

IPAA for UC after OLT for PSC : Is it safe? A Multi-institutional Analysis

Cho CS et al J Gastrointest Surg 2008; 12 : 1221-1226

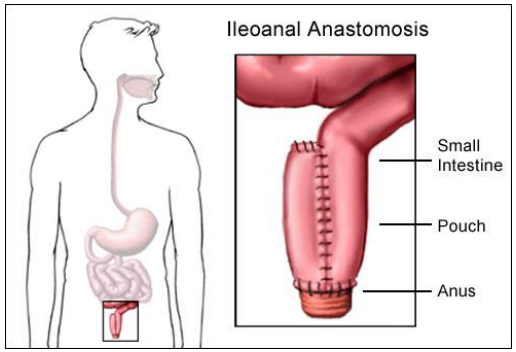
No mortality, peri-operative complications or allograft dysfunction

Hospitalisation data

	Values
Operative time, median (range)	6.1 h (2.5–8.7)
Estimated blood loss, median (range)	400 cc (100–1,400)
Pouch type (number)	S-IPAA (14)
	J-IPAA (7)
	W-IPAA (1)
	Rectal mucosectomy (17)
Length of hospitalization, median (range)	11 days (4–18)

Liver transplant for PSC and UC
Conclusions (2) : Timing of colectomy

- Colectomy prior to liver transplant
  - High grade dysplasia
  - Severe symptoms precluding OLT
  - May reduce recurrence of PSC post OLT
- Synchronous OLT and colectomy : no studies.
- Colectomy for UC post OLT
  - Required in about 20%
  - Total colectomy with IPAA safe with good long term outcomes.



Liver Transplant Unit,
Royal Free London NHS
Foundation Trust

UCLPartners
Academic Health Science Partnership

UCL