Endoscopic treatment of primary sclerosing cholangitis: Is there something new?

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AGENDA

- Introduction
- Diagnosis of PSC
- Use of ERCP
- Details of ERCP procedure
- Tools for cholangiocarcinoma exclusion
- PSC and colorectal cancer
- conclusion
72y male
Normal ileo-colonoscopy

Bilirubin N
ALP 231 UI/L
gGT 550 IU/L
AST 70 IU/L
ALT 230 IU/L

Fever / Cholangitis
This is not a PSC: IgG4 cholangitis and pancreatitis!
Chronic cholestatic liver disease characterized by inflammatory and fibrotic process involving intra- and extrahepatic bile ducts

- 1-16/100,000 (1-5% if UC)
- 60-70% in men; mean age of diagnosis 40y/o

**Symptoms**: pruritus, fatigue, RUQ pain, fever/chills, weight loss

- Increased risk for cholangiocarcinoma and colon cancer
- Progressive disorder: might evolve to **cirrhosis** and **liver failure**

**Diagnosis**:
- clinical + biological + imaging + pathology

Aabakken et al. Endoscopy 2017
Is there something new?

Yes ! ESGE guidelines
Role of endoscopy in primary sclerosing cholangitis: European Society of Gastrointestinal Endoscopy (ESGE) and European Association for the Study of the Liver (EASL) Clinical Guideline

Authors
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Endoscopy 2017; 49:588-608
J. Hepatol 2017; 66:1265-1281
PSC diagnosis
1. PSC DIAGNOSIS

**MRCP** to predict the diagnosis of PSC: Meta-analysis of 6 studies

Sensitivity: 0.86
Specificity: 0.94

<table>
<thead>
<tr>
<th>Strategy</th>
<th>MRCP→ERCP</th>
<th>ERCP→MRCP</th>
<th>ERCP→ERCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost*, average, $</td>
<td>413.1</td>
<td>1098</td>
<td>1123.3</td>
</tr>
<tr>
<td>Incremental cost, $</td>
<td>684.8</td>
<td>710.2</td>
<td></td>
</tr>
<tr>
<td>Effectiveness, probability of correct diagnosis</td>
<td>0.99754</td>
<td>0.99697</td>
<td>1.00000</td>
</tr>
<tr>
<td>Incremental effectiveness, probability of correct diagnosis</td>
<td>– 0.00057</td>
<td>0.00246</td>
<td></td>
</tr>
<tr>
<td>Cost–effectiveness ratio, $/correct diagnosis</td>
<td>414</td>
<td>1101</td>
<td>1123</td>
</tr>
<tr>
<td>Incremental cost–effectiveness ratio (ICER), $/correct diagnosis</td>
<td>(Dominated)</td>
<td>289292</td>
<td></td>
</tr>
</tbody>
</table>

* All costs are in Canadian dollars in 2004

Dave et al. Radiology 2010; 256:387
Meagher et al. Endoscopy 2007;39:222
RECOMMENDATION

1. ESGE/EASL recommend that, as the primary diagnostic modality for PSC, magnetic resonance cholangiography (MRC) should be preferred over endoscopic retrograde cholangiopancreatography (ERCP). Moderate quality evidence, strong recommendation.
MRCP SPECIFICITY FOR THE DIAGNOSIS OF PSC WITHOUT CLINICAL DATA IS POOR

29F
Asthma

Eosinophilic cholangitis

41M
Complicated cholecystectomy

Post-cholecystectomy bile duct injury

51M
Previous OLTx

Post-OLTx ischemic cholangitis
1. **Visualization of distal CBD and peripheral IHBD sometimes suboptimal by MRCP:**
   ... less and less with improvement of MRCP
   ...MRCP in expert center

2. *If high clinical suspicion and negative MRCP*
   ➔ liver biopsy (small IHBD PSC?)

3. *If high clinical suspicion, still inconclusive:* « discuss diagnostic ERCP »
   (filling pressure on balloon occlusion, and visualization of the CBD)

**Balance risk of the procedure to benefit for the patient!**

Aabakken et al. *Endoscopy* 2017
RECOMMENDATION

2. ESGE/EASL suggest that ERCP can be considered if MRC plus liver biopsy is equivocal or contraindicated in patients with persisting clinical suspicion of PSC. The risks of ERCP have to be weighed against the potential benefit with regard to surveillance and treatment recommendations. Low quality evidence, weak recommendation.
RADIOLOGIC SEMIOLOGY: CHOLANGITIS

In Seo N et al. Korean J Radiol 2016
PSC DIAGNOSIS:

RECOMMENDATION

3. For the diagnosis of PSC, ESGE/EASL do not suggest routine use of endoscopic techniques other than ERCP (i.e., endoscopic ultrasound including intraductal ultrasound [IDUS], cholangioscopy, confocal endomicroscopy).

Weak recommendation, low quality evidence.
PSC endoscopic treatment: Strictures management
Clinical change:
- new symptoms (pruritus, jaundice, cholangitis)
- Rapid increase of cholestasis enzymes
- Change on MRCP
  
  (new dominant stricture / worsening of pre-existing stricture)

Goals of ERCP:
- Assess the likelyhood of cholangiocarcinoma
- Treat a dominant stricture
ERCP SEMIOLOGY

- Dominant stricture:
  - Stenosis ≤1.5mm CBD
  - Stenosis ≤1.0mm IHBD within 2 cm of the confluence

- Suspected cholangiocarcinoma:
  - Dilatation disproportionally severe relative to other concomittant biliary defects
  - ≥2cm for CBD
  - ≥1cm for RHBD / LHBD
  - ≥5mm for IHBD

Aabakken et al. Endoscopy 2017
6. ESGE/EASL suggest that, in patients with an established diagnosis of PSC, MRC should be considered before therapeutic ERCP.
Weak recommendation, low quality evidence.
RECOMMENDATION

7. ESGE/EASL suggest performing endoscopic treatment with concomitant ductal sampling (brush cytology, endobiliary biopsies) of suspected significant strictures identified at MRC in PSC patients who present with symptoms likely to improve following endoscopic treatment. Strong recommendation, low quality evidence.
ERCP IN CSP
ERCP IN CSP
ERCP IN CSP
ERCP IN CSP
Dilation / stenting of dominant strictures

- Aims:
  - Resolving symptoms (jaundice, pruritus, cholangitis)
  - Impact on prognosis (avoid progressive liver failure)?

In end-stage liver disease:

- Only cholangitis might improve after ERCP!
- If baseline bili > 5mg/dl: no change in bilirubin after treatment

Aabakken et al. Endoscopy 2017
## ERCP FOR PSC: EBM

### 1. Dilation ± stenting

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Procedure Details</th>
<th>Short-term Improvement in Cholestasis</th>
<th>Liver Transplantation-Free Survival</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gothardt, 2010 [42] (Extension of Stiehl 2002 study [33])</td>
<td>Prospective</td>
<td>96</td>
<td>Balloon dilation (8 mm in CBD, 6–8 mm for IHBD), plus stent in 5 patients with severe cholestasis and bacterial cholangitis</td>
<td>Short-term improvement in cholestasis, Liver transplantation-free survival Complications</td>
<td>Higher proportion of patients alive with no liver transplantation at 3 and 4 years than predicted using Mayo model ($P&lt;0.05$); at 1 and 2 years survival similar to Mayo prediction Adverse events in 21 therapeutic ERCPs (7.2% of 291 procedures, 25% of patients)</td>
<td>At 2 weeks, mean bilirubin level significantly decreased (by 56%); Improvement in symptoms and liver transplantation-free survival Comparison with Mayo model not reported (5-year and 10-year liver transplantation-free survival, 81% and 52%); Overall complication rate, 3.8%</td>
</tr>
<tr>
<td>Gluck, 2008 [35]</td>
<td>Retrospective</td>
<td>84</td>
<td>Balloon dilation and stenting (70% and 51% of patients, respectively)</td>
<td>Liver transplantation-free survival</td>
<td></td>
<td>Higher proportion of patients alive with no liver transplantation at 3 and 4 years than predicted using Mayo model ($P&lt;0.05$); at 1 and 2 years survival similar to Mayo prediction Adverse events in 21 therapeutic ERCPs (7.2% of 291 procedures, 25% of patients)</td>
</tr>
<tr>
<td>Stiehl, 2002 [33]</td>
<td>Prospective</td>
<td>52</td>
<td>Balloon dilation (8 mm in CBD, 6–8 mm for IHBD), plus stent in 5 patients with severe cholestasis and bacterial cholangitis</td>
<td>Liver transplantation-free survival</td>
<td></td>
<td>At 2 weeks, significant decrease in liver enzymes and bilirubin Improvement of jaundice in 24/24 and of pruritus in 12/13 patients Longer liver transplantation-free survival than predicted using 1992 Mayo model ($P&lt;0.0001$)</td>
</tr>
<tr>
<td>Baluyut, 2001 [44]</td>
<td>Retrospective</td>
<td>56</td>
<td>Balloon dilation (4–12 mm, $n=61$) Once per year, with stent if no significant radiological improvement following dilation ($n=33$)</td>
<td>Liver transplantation-free survival</td>
<td></td>
<td>Longer liver transplantation-free survival than predicted using 1999 Mayo model ($P=0.027$) 12% complications</td>
</tr>
</tbody>
</table>
### 2. Stenting

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Procedure</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ponsioen, 1999 [36]</td>
<td>Retrospective</td>
<td>32</td>
<td>Stenting</td>
<td>1-week stenting (10-Fr stent) with no balloon dilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2-month symptomatic and biochemical improvement, Actuarial curve of re-intervention-free patients</td>
</tr>
<tr>
<td>van Milligen de Wit, 1996 [45]</td>
<td>Retrospective</td>
<td>25</td>
<td>Stenting</td>
<td>Stenting for a median of 3 months (plus 8-mm dilation in 3 patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Change in symptoms and biochemical tests within 6 months following stent insertion</td>
</tr>
</tbody>
</table>

- Improvement of symptoms in 83%
- Significant decrease in bilirubin (44% had increased conjugated bilirubin at baseline) and cholestasis enzymes
- Re-intervention-free patients (actuarial): 60% at 3 years

### 3. Dilation vs. dilation + stenting

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Procedure</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaya, 2001 [46]</td>
<td>Retrospective</td>
<td>71</td>
<td>Dilation</td>
<td>Balloon dilation (4 – 8 mm, n = 34) vs. Balloon dilation with 3 – 4-month stenting (n = 37) Intervention via PTBD in 0/34 of balloon group vs. 23/37 of stent group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Biochemical course up to 24 months</td>
</tr>
</tbody>
</table>

- Both strategies improved liver biochemistry; fever resolved only in the dilation without stent group. No additional benefit of stenting after balloon dilation
- More complications in stent vs. dilation alone group (P = 0.001)
- More complications in PTBD vs. ERCP group (P < 0.001)
- (No multivariate analysis)

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**Improved Prognosis (comparaison to Mayo model Tx-free survival): only with dilation**

Few data on stenting (more cholangitis < clogging?)

Dilation vs stenting: more PTC performed in stent group / more complications

*Aabakken et al. Endoscopy 2017*
ERCP DETAILS FOR PSC

- Sphincterotomy?
  - Small EST if difficult cannulation *(strong recommendation, weak quality)*
  - Balance risk-benefit (ascending cholangitis / repeated procedures)

- Dilation:
  - Balloon size: up to caliber of bile duct (8mm CBD / 6mm IHBD)
  - Repeat dilation if previous response / recurrence of stricture and symptoms attributed to that stricture

- Stenting:
  - One 10fr CBD stent or two 7Fr hilar stents
  - Stent must be removed 1-2 weeks after insertion *(stent extraction without opacification)*

*Aabakken et al. Endoscopy 2017*
RECOMMENDATION

8. ESGE/EASL suggest that the choice between stenting and balloon dilation should be left to the endoscopist’s discretion.
Weak recommendation, low quality evidence.
Dominant benign stenosis occur in approximately 50% of patients with PSC

**PSC (N = 65)**
Non-endstage and non-cirrhotic, ERCP for treatment of dominant stricture (narrowing to ≤1.5 mm in the common hepatic duct or common bile duct, or ≤1.0 mm in the left or right hepatic ducts)

**Aim:** compare the efficacy between stenting vs dilatation, assess the re-intervention free recurrence rate during 2 years, safety, and improvement in cholestasis at 3 months

**Short-term stenting**
Stent removed no later than 2 weeks later

**Balloon dilatation**
Single session

Follow-up

24 months

Ponsioen C et al., abstr. GS-002 EASL 2017
MULTICENTER RANDOMIZED TRIAL COMPARING SHORT-TERM STENTING VERSUS BALLOON DILATATION FOR DOMINANT STRICTURES IN PSC (DILSTENT TRIAL)

After a follow-up of 2 years, there was no difference between the 2 treatment groups in the cumulative recurrence-free re-intervention rate ($p = 0.89$)

**Efficacy at 3 months**

<table>
<thead>
<tr>
<th></th>
<th>Stent</th>
<th>Balloon</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent</td>
<td>45%</td>
<td>7%</td>
<td>0.001</td>
</tr>
<tr>
<td>Balloon</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Serious adverse events**

<table>
<thead>
<tr>
<th></th>
<th>Stent</th>
<th>Balloon</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pancreatitis</td>
<td>24%</td>
<td>3%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Failure = early re-intervention, or no decrease of bilirubin or ALP or symptoms (pruritus/fatigue) at 3 months

“Balloon dilatation should be the initial treatment of choice in PSC patients without previous sphincterotomy”

Ponsioen C et al., abstr. GS-002 EASL 2017
COMPLICATIONS OF ERCP IN PSC

- Increased (4-6%):
  - Pancreatitis
  - Cholangitis
  - Ductal perforation

- Cannulation is more difficult in PSC

- Rectal NSAID, 5fr PPP
- Routine prophylactic Antibiotic
- balloon size adapted

RECOMMENDATION
14. ESGE/EASL suggest that ERCP in PSC patients should be undertaken by experienced pancreaticobiliary endoscopists. Strong recommendation, very low quality evidence.
PSC endoscopic treatment: Cholangiocarcinoma detection
CHOLANGIOCARCINOMA IN PSC

- Lifetime risk 10-20%
- X4 risk compared to general population
- Must be excluded if new « symptoms »
  - Increased cholestasis
  - Weight loss
  - Raised CA 19-9 (poor specificity)
  - New dominant stricture (5% of dominant strictures are CCA)
    - particularly if mass associated
    - 50% perihilar / 40% distal CBD

Aabakken et al. Endoscopy 2017
ENDOSCOPIC TOOLS TO DIAGNOSE CCA IN PSC

- Quality cholangiogramm: not enough!
  - Stricture location
  - Radiologic features
  - Palpation
- Always add cytology /biopsy sampling
- Add molecular biology (FISH/..) if equivocal

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytologic brush</td>
<td>45%</td>
<td>99%</td>
</tr>
<tr>
<td>Endobiliary biopsy</td>
<td>48%</td>
<td>99%</td>
</tr>
<tr>
<td>Brush+biopsy</td>
<td>59%</td>
<td>100%</td>
</tr>
<tr>
<td>pCLE</td>
<td>83%</td>
<td>67-77%</td>
</tr>
<tr>
<td>pCLE+ERCP</td>
<td>89%</td>
<td>67-77%</td>
</tr>
<tr>
<td>Cholangioscopy (biliary picture+biopsy)</td>
<td>84-96%</td>
<td>86-100%</td>
</tr>
</tbody>
</table>

Tringali Endoscopy 2015, Navaneethan GIE 2015
### CHOLANGIOSCOPY

<table>
<thead>
<tr>
<th></th>
<th>Dual operator « mother-baby » cholangioscopy</th>
<th>Single operator « mother-baby » cholangioscopy</th>
<th>Direct cholangioscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>endoscopists</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>directions</td>
<td>2</td>
<td>4</td>
<td>2-4</td>
</tr>
<tr>
<td>Diam canal op.</td>
<td>1.2mm</td>
<td>1.2mm</td>
<td>2mm</td>
</tr>
<tr>
<td>Picture quality</td>
<td>+</td>
<td>- -&gt; +</td>
<td>+</td>
</tr>
<tr>
<td>NBI</td>
<td>-/+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>cost</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Easiness</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Air embolism</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

*Tringali et al, Endoscopy 2015*
### Optimizing the detection of biliary dysplasia in primary sclerosing cholangitis before liver transplantation

**Table 4.** Sensitivity and specificity of different methods for the diagnosis of cholangiocarcinoma or high-grade dysplasia.

<table>
<thead>
<tr>
<th></th>
<th>CA19-9&lt;sup&gt;a&lt;/sup&gt;</th>
<th>FISH</th>
<th>Single brush</th>
<th>Repeated brush</th>
<th>Repeated brush cytology with cholangioscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>45% (25–67%)</td>
<td>84% (60–96%)</td>
<td>57% (20–88%)</td>
<td>82% (56–95%)</td>
<td>100% (56–100%)</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>59% (49–68%)</td>
<td>90% (75–97%)</td>
<td>94% (86–98%)</td>
<td>93% (84–97%)</td>
<td>97% (86–100%)</td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td>18% (09–31%)</td>
<td>80% (56–93%)</td>
<td>50% (17–83%)</td>
<td>74% (49–90%)</td>
<td>88% (47–99%)</td>
</tr>
<tr>
<td><strong>NPV</strong></td>
<td>84% (74–91%)</td>
<td>92% (78–98%)</td>
<td>96% (87–99%)</td>
<td>96% (87–99%)</td>
<td>100% (89–100%)</td>
</tr>
<tr>
<td>+LR</td>
<td>1.09 (0.7–1.8)</td>
<td>8.2 (3.2–21.2)</td>
<td>10.3 (3.3–3.4)</td>
<td>12.0 (5.0–28.8)</td>
<td>41.0 (5.9–284.1)</td>
</tr>
</tbody>
</table>

FISH: fluorescence in-situ hybridization; PPV: positive predictive value; NPV: negative predictive value; +LR: positive likelihood ratio.

<sup>a</sup>At cutoff of 34 U/mL.

Retrospective study on explanted liver (225 OLTx for PSC): pre-Tx tool to detect CCA sensitivity.

**Repeated brush cytology +/- SOC with targeted biopsies is superior to single brush cytology**

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Majeed et al. Scand J Gastro 2017
Systematic review with meta-analysis: endoscopic retrograde cholangiopancreatography-based modalities for the diagnosis of cholangiocarcinoma in primary sclerosing cholangitis

Conclusions
Single-operator cholangioscopy with targeted biopsies appears to be the most accurate ERCP-based modality for diagnosing cholangiocarcinoma in primary sclerosing cholangitis. However, future large, well-designed comparative diagnostic studies are warranted to validate these findings.

Cost utility of ERCP-based modalities for the diagnosis of cholangiocarcinoma in primary sclerosing cholangitis

Njei B et al; APT 2016
Njei B. GIE 2017
Normal bile duct

Grey background/ Vessels <20 µm / thin black stripes(<20 µm)

Thick white bands(>20 µm), black clumps, thick black stripes(>40 µm)

cholangiocarcinoma
IBD and PSC
CRC screening
CRC SCREENING

- Ileocolonoscopy at diagnosis of PSC
  (4 quadrant biopsy of every segment)
- Every year in case of IBD associated to PSC
- Every 5 years if PSC without IBD
- If IBD, dysplasia surveillance: chromoendoscopy
  (blue dye 0.1%+targeted biopsies)
  - (detection enhancement X2-3 compared to std colonoscopy)
- CRC risk
  - x 4 compared to UC without PSC
  - X 9 compared to general population

Aabakken et al. Endoscopy 2017
CONCLUSIONS

- PSC diagnosis relies on MRCP and clinical elements (! Mimickers)
- Avoid diagnostic ERCP
- Think about benefit of ERCP for the patient
- Treatment of dominant stricture
  - (sampling / dilation / short stenting period)
- Cholangiocarcinoma detection: new techniques
- ! Think also to colorectal cancer risk
- ! Think to gallbladder cancer risk (US 1X/y)
Gastroenterology and Endotherapy European Workshop
BRUSSELS - BELGIUM
June 18 – 20, 2018

www.live-endoscopy.com