Diagnosis and Management of Primary Sclerosing Cholangitis: The Role of the Endoscopist

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Role of ERC in PSC

- Diagnosing PSC
- Managing complications of PSC
  - Bile duct stones
  - Acute cholangitis
  - Dominant strictures
- Diagnosing cholangiocarcinoma
A chronic, progressive destructive biliary disease of unknown cause, characterized by multiple, fibrosing, inflammatory strictures of the extra hepatic and/or intrahepatic bile ducts.

Bergquist and Broomé
PSC: Diagnosis

- **Diagnosis:**
  - Clinical
  - Biochemical
  - Histologic
  - RADIOLOGICAL
  - Irregularity and beading of the intrahepatic or extrahepatic bile ducts.
  - ERC vs MRC vs PTC
PSC: Diagnosis

**MRCP**
- Non-invasive
- Operator dependent
- Accuracy < 100%
- Non-therapeutic
- No sampling

**ERCP**
- Invasive
- Operator dependent
- Gold standard
- Therapeutic
- Tissue sampling
- Stage portal HTN
# PSC: Diagnosis

## MRCP in PSC

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Sens</th>
<th>Spec</th>
<th>Acc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrara et al Pediatr Radiol 2002;32:413</td>
<td>21</td>
<td>81%</td>
<td>100%</td>
<td>85%</td>
</tr>
<tr>
<td>Angulo et al J Hepatol 2000;33:659</td>
<td>73</td>
<td>NR</td>
<td>NR</td>
<td>90%</td>
</tr>
<tr>
<td>Textor et al Endoscopy 2002;34:984</td>
<td>150</td>
<td>88%</td>
<td>99%</td>
<td>NR</td>
</tr>
<tr>
<td>Weber et al Rofo Fortsch Geb Rontgenstr 2003;175:203</td>
<td>55</td>
<td>97%</td>
<td>64%</td>
<td>84%</td>
</tr>
</tbody>
</table>
PSC: Diagnosis
PSC: Diagnosis

- Exclude secondary biliary sclerosis
  - Biliary Surgery
  - Biliary Stones
  - Biliary Neoplasms
  - Hepatic artery injury
  - Intra hepatic arterial FUDR
  - HIV Cholangiopathy
Intra-hepatic artery FUDR
PSC: Diagnosis

Beware of radiologic “look a likes”

Cirrhosis
HCC
Polycystic Liver Disease
Sub massive necrosis
Histocytosis X

Amyloid
Intrahepatic PV Thrombosis
Liver Mets
Leukemia
Lymphoma
Inflammatory pseudo tumors
Endoscopic Therapy in PSC

- Treatment Endoscopic:
  - Acute cholangitis
  - Stones
  - Dominant strictures (seen in up to 50% pts but no consensus definition) with or without symptoms
Endoscopic Therapy in PSC

- Initially limited to acute cholangitis (stents or nasobiliary drains).
- Stone extraction can be performed effectively but may be challenging with stone above stricture.
- Treatment of “dominant stricture”: Multiple non-controlled series reporting positive responses for stents ± dilation.
- Early experience with high incidence of complications, mainly infectious.
Endoscopic Therapy: Dominant Strictures

- 32 patients with PSC and dominant stricture.
- All treated with stenting 10Fr (n=21) 7Fr then 10Fr (n=6) 7Fr (n=5).
- 5 patients underwent balloon dilation.
- Stents removed mean=11 days (range 1-23 days).
- Scores for pruritus, fatigue and pain improved in 83%.
- Jaundice resolved in 12/14 and LFT significantly decreased.
- 80% and 60% intervention-free at 1 and 3 yrs.
- 15% complication rate (none severe).

Ponsioen et al Am J Gastroenterol 1999;94:2403
Endoscopic Therapy: Dominant Strictures

Baluyut et al Gastrointest Endosc 2001;53:308

- Retrospective study of 63 pts with dominant strictures.
- Dilations performed with balloons (61) or catheters (2).
- Stents used for poor fluoroscopic response to dilation (32).
- Median f/u 34 months.
- Predicted 5yr survival by Kaplan-Meier was greater than estimated survival by Mayo model (within 3mos prior to ERCP).
Endoscopic Therapy of PSC: Are we altering natural history of disease?

Critique of Baluyut et al:

- Used the Mayo Risk Score which was designed to follow progression of disease over years:
  
  \[ R = (0.03 \text{Age, yrs}) + (0.54 \log(e) \text{Bili mg/dL}) + (0.54 \log(e) \text{AST U/mL}) + (1.24 \text{Bleed hx}) - (0.84 \text{Albumin gm/dL}) \]

- This will be profoundly impacted acutely (days) by stenting a dominant stricture.

- Is it an appropriate use of this instrument?
Endoscopic Therapy: Dominant Strictures

Stiehl et al J Hepatol 2002;36:151-156

- Prospective experience with 106 PSC pts on 15mg/kg URSO followed for a median of 5 yrs.
- Dominant strictures in 10% at enrollment and 40% in follow-up defined as <1.5mm extra and <1mm intrahepatic.
- All treated with balloon dil and short-course stents.
- Observed survival by Kaplan Meier > than predicted survival by old Mayo score.
Endoscopic Therapy: Dominant Strictures

Critique:

Stiehl et al J Hepatol 2002;36:151-156

“Attempts to use the more recent Mayo survival model...... were not successful. ....the majority of our patients had a negative risk factor with the updated Mayo model which indicates improved survival. ....we concluded that this model is not applicable...
Endoscopic Therapy: Dominant Strictures

Bjornsson et al Am J Gastroenterol 2004;99:502

- 125 pts with PSC
- DS defined as <1.5mm in CBD and < 1mm IHD (irregardless of the status of the pre-stenotic biliary tree), and was seen in 45% pts.
- No difference in change in ALP and bili pre ERC and 1 yr later in pts with or without DS, independent of endoscopic therapy (n=9).
- Authors conclude endoscopic therapy of DS should not be “routine”.
- I conclude that these were not “dominant” strictures.
Dilation of Dominant Strictures in PSC: technical notes

<table>
<thead>
<tr>
<th>Catheters</th>
<th>Balloons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro</td>
<td>Pro</td>
</tr>
<tr>
<td>Easy</td>
<td>Easy</td>
</tr>
<tr>
<td>Wire-guide</td>
<td>Wire-guide</td>
</tr>
<tr>
<td>Inexpensive</td>
<td>Larger diameter/Greater force</td>
</tr>
</tbody>
</table>

Con

Limited diameter
Limited force

Screw Catheter
Refractory strictures

Con

Expensive
Bends in duct
Balloon Dilation of Dominant Stricture in PSC
Catheter dilation in PSC
Balloon dilation of dominant stricture
Dominant strictures in PSC can be treated at ERC.

More important than the stricture is the state of the prestenotic biliary tree.

Tissue sampling and liberal antibiotics are mandatory.

I reserve treatment for patients with symptomatic jaundice.
Endoscopic Therapy of Dominant Strictures: Summary

- Concomitant dilation with stenting may improve results.
- Long term stenting has been reported anecdotally, I avoid.
- I prefer balloon dilation and short term (10-14 day) stenting.
- I avoid sphincterotomy if possible.
- No convincing data we are altering long term natural history.
Cholangiocarcinoma may develop in 15% patients with PSC.

Desmoplastic nature of tumor and presence of multiple non-neoplastic strictures makes diagnosis challenging.
DIAGNOSING CCA IN PSC: Tissue Sampling

- Brush Cytology
- Needle (FNA)
- Forceps

All with low sensitivity
All with high specificity
Multi-modal increases sens
Forceps best for bile duct CA

Highly suspicious for cancer does not equal cancer in PSC
Dominant Stricture: Forceps biopsy
Clinical Characteristics of PSC Patients with and without CCA

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CCA + PSC (n=44)</th>
<th>PSC (n=289)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of PSC (yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2.86 ± 2.35</td>
<td>4.90 ± 4.49</td>
<td>0.03*</td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>IBD n(%)</td>
<td>32 (72.7)</td>
<td>229 (79.2)</td>
<td>0.33#</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>43.54 ± 12.22</td>
<td>41.58 ± 11.82</td>
<td>0.55*</td>
</tr>
<tr>
<td>Median</td>
<td>43</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Male %</td>
<td>77</td>
<td>69</td>
<td></td>
</tr>
</tbody>
</table>

*Comparisons by Mann-Whitney U test.

#Comparisons by X² test.
**Tissue Sampling**

Performance Characteristics of BC for Diagnosing CCA Based on the Number of Sampling Sessions

<table>
<thead>
<tr>
<th>Results (%)</th>
<th>1 BC</th>
<th>2 BC</th>
<th>≥ 3BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>32.1</td>
<td>39.2</td>
<td>46.4</td>
</tr>
<tr>
<td>Specificity</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>86.6</td>
<td>87.8</td>
<td>89.1</td>
</tr>
<tr>
<td>Accuracy</td>
<td>87.4</td>
<td>88.7</td>
<td>90.1</td>
</tr>
</tbody>
</table>

Of 151 patients undergoing brush cytology, 72 (47.7%) had 1 BC while the remainder had 2 or more with a mean of 2.1 sessions/patient and a range of 1-10.
# DIAGNOSING CCA IN PSC: Tumor Markers

CEA and CA19-9 Serum Levels in PSC Patients With and Without CCA

<table>
<thead>
<tr>
<th></th>
<th>PSC CCA +</th>
<th></th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CEA (n=25) ng/mL</td>
<td>CA19-9 (n=12) U/mL</td>
<td>CEA (n=119) ng/mL</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>68.4 ± 206.7</td>
<td>5994 ± 11521.5</td>
<td>3.5 ± 2.8*</td>
</tr>
<tr>
<td>Median</td>
<td>8.2</td>
<td>377.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Range</td>
<td>0.7 – 959</td>
<td>6.5 – 34600</td>
<td>0.7 – 16.7</td>
</tr>
</tbody>
</table>

*p<0.01 compared to patients with CCA by Mann-Whitney U test.
DIAGNOSING CCA IN PSC: ROC CA19-9; cut point 180 U/mL
DIAGNOSING CCA IN PSC: ROC CEA; cut point 5 ng/mL
### Performance Characteristics of Brush Cytology and Serum Tumor Markers for Diagnosing CCA (n=45)

<table>
<thead>
<tr>
<th></th>
<th>BC</th>
<th>CEA</th>
<th>CA19-9</th>
<th>CA19-9 or BC</th>
<th>CEA or CA19-9</th>
<th>BC or CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sens (%)</strong></td>
<td>37.5</td>
<td>62.5</td>
<td>75.0</td>
<td>87.5</td>
<td>100</td>
<td>87.5</td>
</tr>
<tr>
<td><strong>Spec (%)</strong></td>
<td>100</td>
<td>78.4</td>
<td>97.3</td>
<td>97.3</td>
<td>78.4</td>
<td>78.4</td>
</tr>
<tr>
<td><strong>PPV (%)</strong></td>
<td>100</td>
<td>38.5</td>
<td>85.7</td>
<td>87.5</td>
<td>50.0</td>
<td>46.7</td>
</tr>
<tr>
<td><strong>NPV (%)</strong></td>
<td>88.1</td>
<td>90.5</td>
<td>94.7</td>
<td>97.3</td>
<td>100</td>
<td>96.7</td>
</tr>
<tr>
<td><strong>ACC (%)</strong></td>
<td>88.8</td>
<td>75.5</td>
<td>93.3</td>
<td>95.6</td>
<td>82.2</td>
<td>80.0</td>
</tr>
</tbody>
</table>

Sens=sensitivity; PPV=positive predictive value; NPV=negative predictive value; ACC=accuracy
DIAGNOSING CCA IN PSC:
Strategies to improve diagnostic accuracy

- Multimodal tissue sampling
- Tumor markers + brush cytology
- Improvement in analysis of tissue obtained???
DIAGNOSING CCA IN PSC: Beyond routine cytology

Lindberg et al Endoscopy 2002;34:909

- Brush for cytology and DNA content by flow cytometry with serum CEA and CA 19-9 in 20 patients with PSC.
- 7 ultimately diagnosed with cholangiocarcinoma.
- Sens 100%; Spec 85%
DIAGNOSING CCA IN PSC: Beyond routine cytology

Baron et al Clin Gastroenterol Hepatol 2004;2:214

- 100 pts with biliary strictures undergoing ERC with BC.
- Compared digital image analysis (DNA content; “ploidy analysis”) with routine cytology.
- 56 malignancies; 44 benign
- Sens, Spec and Acc for DIA vs RC were: 39% vs 18%, 77% vs 98%, and 56% vs 53%.
- DIA may be a valuable adjunct to RC.
DIAGNOSING CCA IN PSC: Beyond routine histology

Khalid et. al. GUT 2005

- 26 patients with biliary strictures underwent ERC with brush cytology.
- 11 patients with cholangiocarcinoma and 6 with pancreatic carcinoma
- BC + for CA in 7 and inconclusive in 10
- 9 patients benign strictures
- BC benign in 8 and inconclusive in 1.
DIAGNOSING CCA IN PSC: Beyond routine cytology

- Genomic DNA from cell clusters acquired from BC specimens and microdissected surgical malignant and normal tissue underwent PCR amplification.
- A panel of 12 polymorphic microsatellite markers linked to 6 tumor suppressor genes was developed: CMM/RIZ, VHL, p16, p53, PTEN and APC.
- The PCR products were compared for microsatellite allelic loss (LOH) and k-ras codon-12 mutations.
DIAGNOSING CCA IN PSC: Beyond routine histology

- Selected malignant appearing BC clusters and microdissected histologic samples from cancer showed abundant LOH.
- Brushings from 9 benign cases showed no LOH (p< 0.001).
- LOH and k-ras mutations profile of the cytological specimens was concordant with the tissue samples.
- Presence of k-ras mutation predicted malignancy of pancreatic origin (p<0.001).
- LOH and k-ras mutation analysis from biliary BC discriminates reactive from malignant cells, with 100% sens, spec and acc.
Diagnosing cholangiocarcinoma in PSC is usually a death sentence. How hard do we push?

Should PSC pts be transplanted for prophylaxis against CCA?

Should transplant be used as an oncologic procedure?

What is the role of living related donor transplants in PSC with possible CCA?

Does screening tumor markers make sense?

Will molecular markers allow for premalignant diagnoses?