Can We Find Cholangiocarcinoma in Primary Sclerosing Cholangitis (PSC)

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Outline

- Risk of cholangio Ca in PSC
- Surveillance
- Evaluation of suspected cholangio Ca
Cholangio Ca (CCA) in PSC

- Risk of CCA in pts with PSC is increased ~ 400 fold
- Annual risk ~ 2%
- Lifetime risk 10-15%
- Major contributor to mortality
- More than 50% are diagnosed in the 1st yr after diagnosis of PSC

Rizvi S. Clinical Gastroenterology & Hepatology 2015;13:2152

Take Home Message

- Have a high index of suspicion for CCA around the time of diagnosis of PSC
Cholangiocarcinoma in PSC

**Cumulative Survival**

- **CCA (n=48; 12%)**
- **Not CCA (n=346)**
- **All patients (n=394)**

**Time (years)**

**Median survival from diagnosis of PSC:**
- 12.2 years without CCA vs. 1.9 years with CCA

Boberg et al. Scand J of Medicine 2002

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**Risk factors for CCA in PSC**

- Older age at diagnosis
- Tobacco, ETOH
- Elevated bilirubin and Alk Phos
- Bleeding varices
- Dominant strictures
- Duration of IBD*
- Proctocolectomy
- Genetic predisposition – risk alleles for NKG2D receptor

*Gulamhusein AF. Am J Gastroenterol 2016;111:705
Take Home Message

• At this time we cannot reliably select population of PSC patients that is at higher risk of CCA
• Screen all patients

Screening Tools

• LFT 3 to 6 months
• MRI/MRCP once a year?
• CA 19-9 once a year?
• ERCP not indicated for screening

Rizvi S. Clinical Gastroenterol Heptatol 2015;13:2152
When to Initiate Evaluation for CCA?

- Increasing LFTs *
- Elevated/increasing CA 19-9
  - 7-10% of the general population do not produce CA 19-9
- Intrahepatic dilation on MRCP
- Focal bile duct thickening with enhancement on MRI
- Dominant stricture on MRCP


Dominant Strictures

- Stenosis with diameter ≤ 1.5 mm in CBD or ≤ 1 mm in right/left hepatic duct
- Stricture that stands out among all others in patients with PSC
- Occur in 45-50% of patients

Dominant Strictures

- May cause sudden worsening with jaundice and cholangitis
- More frequently benign, but ~25% are malignant
- Associated with reduced transplant-free survival

Actuarial survival free of OLT


Take Home Message

- Dominant strictures carry worse prognosis
  - Initiate referral to transplant center
- Most dominant stricture are benign but approximately 1/4 are malignant
  - Promptly evaluate for CCA
What is the Evaluation for Suspected CCA?

- CA 19-9
- CT
- ERCP

ERCP in PSC

- Technically more challenging
- Higher complication rate
- Consider referral to tertiary center with expertise in management of PSC and OLT capabilities
ERCP in PSC Technical Considerations

- Give antibiotic prophylaxis
- Minimize contrast injection
- Take multiple (early) images
- Avoid sphincterotomy?
- Obtain brushing and biopsy
- May consider obtaining FISH
- Dilate strictures but avoid stenting????

Should we Avoid Stenting in PSC?

- 71 PSC patients: 34 dilation/37 stent (19 PTC, 14 ERCP, 4 both)
- Stent had more complications: 30 vs 6 (p=0.001)
- “Stenting was associated with more complications, and its role should be assessed in a randomized trial rather than being accepted as routinely indicated in this setting”

Muhsin Kaya M. Am J Gastroenterol 2001; 96, 1059
Should we Avoid Stenting in PSC?

### Table 1. The Incidence of Intervention-Related Complications

<table>
<thead>
<tr>
<th>Procedure-Related Complication</th>
<th>Balloon Group (n)</th>
<th>PTC Group (n)</th>
<th>ERCP Group (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholangitis</td>
<td>1</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Biliary duct perforation</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Choledochoduodenal fistula</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Biliary leak</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Tube site infection</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>23*</td>
<td>7†</td>
</tr>
</tbody>
</table>

Muhsin Kaya M. Am J Gastroenterol 2001; 96, 1059
Take Home Message

• Give balloon a try at the initial ERCP
• Do not hesitate to stent if no response to the balloon dilation

Biliary Brush Cytology

• Meta-analysis of brush cytology in PSC
  – 11 studies
  – 747 patients
• Sensitivity 43%, Specificity 97%

Trikudanathan G. GIE 2014;79:783
ERCP Guided Biopsy

• Increases yield of brush cytology
• May be technically more difficult in PSC patients with small duct and without sphincterotomy
• Recommended if technically feasible

ERCP Guided Multimodal Sampling
Brush + Biopsy

• Sensitivity 60-70%

Korc P. GIE 2016;84(4):557
Fluorescent in situ hybridization (FISH)

- Identifies the equivalent to aneuploidy
- If more than 2 spots are seen for more than 1 color → polysomy
- Results: Negative or Positive (trisomy, tetrasomy, polysomy)
- Serial polysomy is predictive of Ca

Long term outcomes according to FISH results

Survival of patients with a positive polysomy test was similar to that of patients with cholangiocarcinoma

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Chaiteerakij R. GIE 2016;83(6):1228
Navaneethan U. GIE;2014;79(6):943
Bangarulingam et al. Hepatology 2010
Problems with FISH

- Low sensitivity – 35 to 55%
- Cannot be used alone
- Hard to interpret
- Long turnover time (send out test)
- Expensive

FISH Optimized Probe

- Accurate in PSC and non-PSC patients

<table>
<thead>
<tr>
<th></th>
<th>Cytology</th>
<th>Old probe</th>
<th>New probe</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>19%</td>
<td>46%</td>
<td>65%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Specificity</td>
<td>93%</td>
<td>91%</td>
<td>100%</td>
<td>NS</td>
</tr>
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Barr Fritcher EG. Gastroenterology 2015;149:1813
FISH Optimized Probe

• Accurate in PSC and non-PSC patients

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FISH: Take Home Message

• FISH should not be used as screening modality
• Has only additive role to multimodal sampling*
  – 50 patients/22 cholangio Ca
  – Brush + biopsy + FISH: Sens 82%
• Use as a second line test if initial multimodal sampling (brush + biopsy) is unrevealing
• Polysomy is concerning finding

*Nanda A. Ther Adv Gastroenterol 2015;2:56
Cholangioscopy for Indeterminate Strictures

- Prospective paired control design
- Triple sampling: cholangioscopy-guided biopsy, cytology brushing and standard forceps biopsy

<table>
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<th>Cholangioscopy</th>
<th>Brush</th>
<th>Biopsy</th>
</tr>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>76%</td>
<td>6%</td>
<td>29%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>84%</td>
<td>38%</td>
<td>54%</td>
</tr>
<tr>
<td>NPV</td>
<td>70%</td>
<td>36%</td>
<td>43%</td>
</tr>
</tbody>
</table>

(p<0.0001) (p=0.02)

Draganov PV. GIE 2012 Feb;75(2):347
Cholangioscopy: Take Home Message

- Increases the yield of brush and standard biopsy but not much data specifically in cholangio Ca in PSC
- Technically challenging due to smaller ducts
- Consider if technically feasible if high index for suspicion for cholangio Ca and negative evaluation

EUS-FNA

- EUS has high yield in patients with cholangio Ca*
- Avoid doing EUS in patients with PSC and suspected cholangio Ca!!!
- If you do EUS limit to FNA of suspicious Ly nodes

*Sadeghi A. GIE 2016;83(2):290
Advanced Endoscopic Imaging Techniques and New Markers

• NBI
• pCLE
• IDUS
• Volatile organic compounds (VOC)*

*Navaneethan U. GIE 2015;81:943

• Volatile organic compounds (VOC)
• VOC change with change of metabolism
• Canine sent, gas chromatography, electronic nose
Conclusions

• Patients with PSC are at increased risk of cholangio Ca
• Have a high index of suspicion for cholangio Ca around the time of diagnosis of PSC
• Consider screening for cholangio Ca in PSC with LFT, ±CA19-9 and ±MRI/MRCP
• ERCP is not indicated for screening

Conclusion

• Initiate evaluation for cholangio Ca
  – Increasing LFTs and/or CA 19-9
  – Intrahepatic dilation on MRCP
  – Focal bile duct thickening with enhancement on MRI
  – Dominant stricture on MRCP
Conclusion

• Evaluation for cholangio Ca
  – CA 19-9
  – CT
  – ERCP
    • Brush for cytology and forceps biopsy
    • FISH?
    • Cholangioscopy in selected cases
  – Avoid EUS
• If above is negative then repeat in 3-6 months