Indeterminate Biliary Strictures

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James A. Haley VA
I have no financial relationship relevant to the content of this educational activity.
Objectives

- Recognize indeterminate biliary strictures (IDBS) vs. malignant strictures
- Understand the most readily available instruments to diagnose and manage IDBS
- Know the benefits and limitations of diagnostic modalities
Indeterminate Biliary Strictures (IDBS)

- Biliary strictures without definite diagnosis after cross-sectional imaging and ERCP
- Substantial proportion of biliary strictures
- Broad differential
Dominant Stricture

- Subtype of IDBS with underlying PSC
  - CBD stenosis ≤ 1.5 mm
  - CHD stenosis ≤ 1 mm
- 1560-fold increased risk of cholangiocarcinoma
- ERCP-guided tissue acquisition with poor yield
  - Sensitivity 18-40%

Dominant Stricture

- Reasons for low sensitivity
  - Submucosal as opposed to radial tumor growth
  - Desmoplastic reaction
  - Inadequate access of endoscopic devices
  - Sampling under indirect visualization

Brush Cytology

- 16 studies reported overall biliary brush cytology sensitivity of 42% with NPV of 58%
- Poor sensitivity
  - Sampling error
  - Distinguishing cytopathology

Effectiveness of brush cytology vs intraductal biopsy

Brush Cytology

Effectiveness of brush cytology vs intraductal biopsy

Brush Cytology

![Graph showing specificity and 95% CI for various studies.]

Pooled Specificity = 0.99 (0.98 to 1.00)

Intraductal Biopsy

Effectiveness of brush cytology vs intraductal biopsy

Effectiveness of brush cytology vs intraductal biopsy

Intraductal Biopsy

![Graph showing specificity and 95% CI for various studies]

**Pooled Specificity** = 0.99 (0.98 to 1.00)

Effectiveness of brush cytology vs intraductal biopsy

Pooled Sensitivity

139 patients with suspected malignancy
  ▪ 116 malignant
Underwent 143 ERCPs
  ▪ Initial brushing of stricture (10x)
  ▪ Dilation performed
    ▪ 10 Fr Soehendra dilator or 4-8 mm TTS balloon
  ▪ Repeat brushings obtained with second brush

## Results

<table>
<thead>
<tr>
<th></th>
<th>Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-dilation Brushings</strong></td>
<td>40/116 (34.5%)</td>
</tr>
<tr>
<td><strong>Post-dilation Brushings</strong></td>
<td>36/116 (31%)</td>
</tr>
<tr>
<td><strong>Combined Pre- and Post-dilation</strong></td>
<td>51/116 (44%)</td>
</tr>
</tbody>
</table>

102 patients with suspicious biliary stricture
- Randomized to Cytolong or standard brush
- Stricture dilation not performed

# Longer brush length

<table>
<thead>
<tr>
<th></th>
<th>Proximal</th>
<th>Distal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytolong</strong></td>
<td>27%</td>
<td>31%</td>
</tr>
<tr>
<td><strong>Standard</strong></td>
<td>23%</td>
<td>28%</td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td></td>
<td>30%</td>
</tr>
</tbody>
</table>

Fluorescence in situ hybridization (FISH)

- Cytologic technique with fluorescently labeled DNA probes
- Reveals loss or gain of specific loci
- Abnormal cells quantified with fluorescence microscopy
- Positive if \( \geq 5 \) cells containing \( > 2 \) or more gains of FISH probes


CDKN2A locus

- Critical in cell cycle progression and senescence
- Detection of increases sensitivity to 76-89%
- Helpful in PSC
  - Serial polysomy
  - Multifocal polysomy
  - Even greater risk of cholangiocarcinoma

Barr Fritcher EG, Kipp BR, Voss JS, Clayton AC, Lindor KD, Halling KC, Gores GJ. Primary sclerosing cholangitis patients with serial polysomy fluorescence in situ hybridization results are at increased risk of cholangiocarcinoma. *Am J Gastroenterol* 2011; **106**: 2023-2028 [PMID: 21844920 DOI: 10.1038/ajg.2011.272]
Hepatobiliary system can be examined via EUS

- Gallbladder – gastric antrum
- Mid-CBD to confluence – duodenal bulb
- Periampullary region – second portion of duodenum
- Lymph nodes, vessels and presence of malignant ascites
Factors associated with malignancy

- Pancreatic head mass with biliary dilation
- Irregular outer edge of bile duct wall
  - Sensitivity 88%
  - Specificity 100%

Factors associated with malignancy

- Maximal bile duct wall thickness > 3 mm
  - Without pancreatic mass
  - Sensitivity 79%
  - Specificity 79%

Table 1  Main characteristics of nine studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>Age (average)</th>
<th>Sex (male/female)</th>
<th>Study design</th>
<th>Patients enrolment</th>
<th>Confirmation of EUS-FNA positive result selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fritsch-Ravens et al. [9]</td>
<td>10</td>
<td>59 (47-78)</td>
<td>7/3</td>
<td>Prospective</td>
<td>Consecutive</td>
<td>Surgery</td>
</tr>
<tr>
<td>Rösch et al. [10]</td>
<td>50</td>
<td>62 (31-86)</td>
<td>29/21</td>
<td>Prospective</td>
<td>Consecutive</td>
<td>Surgery</td>
</tr>
<tr>
<td>Lee et al. [11]</td>
<td>31</td>
<td>64 (43-89)</td>
<td>ND</td>
<td>Retrospective</td>
<td>ND</td>
<td>Follow-up and surgery</td>
</tr>
<tr>
<td>Eloubeidi et al. [12]</td>
<td>25</td>
<td>67 (56-78)</td>
<td>18/7</td>
<td>Prospective</td>
<td>ND</td>
<td>Follow-up and surgery</td>
</tr>
<tr>
<td>Fritsch-Ravens et al. [13]</td>
<td>44</td>
<td>59 (37-74)</td>
<td>31/13</td>
<td>Prospective</td>
<td>Consecutive</td>
<td>Follow-up and surgery</td>
</tr>
<tr>
<td>Byrne et al. [14]</td>
<td>35</td>
<td>68 (ND)</td>
<td>16/19</td>
<td>Retrospective</td>
<td>ND</td>
<td>Follow-up and surgery</td>
</tr>
<tr>
<td>DeWitt et al. [21]</td>
<td>24</td>
<td>68 (37-87)</td>
<td>14/10</td>
<td>Retrospective</td>
<td>ND</td>
<td>Follow-up and surgery</td>
</tr>
<tr>
<td>Meara et al. [22]</td>
<td>50</td>
<td>66 (37-84)</td>
<td>31/19</td>
<td>Prospective</td>
<td>ND</td>
<td>Follow-up and surgery</td>
</tr>
<tr>
<td>Hijjoka et al. [23]</td>
<td>15</td>
<td>66 (54-79)</td>
<td>7/8</td>
<td>Retrospective</td>
<td>Consecutive</td>
<td>Follow-up and surgery</td>
</tr>
</tbody>
</table>

EUS-FNA had a pooled sensitivity of 84% and a pooled specificity of 100%
Tumor Seeding

- Implantation of cells along needle path
- Not as concerning in pancreatic CA
- Porta hepatis lesion
- Significant impact on liver transplantation

<table>
<thead>
<tr>
<th></th>
<th>No biopsy</th>
<th>Positive TP biopsy</th>
<th>Negative TP biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritoneal metastasis at staging</td>
<td>14/175 (8%)</td>
<td>5/6 (83%)</td>
<td>0/9</td>
</tr>
</tbody>
</table>

Intraductal Ultrasound

- High resolution
- Limited penetration
- Scan from hilum to papilla
- 3D reconstruction

Tringali A¹, Lemmers A¹, Meves V³, Terheggen G⁴, Pohl J², Manfredi G⁵, Häfner M⁶, Costamagna G¹, Devière J², Neuhaus H⁴, Caillol F⁷, Giovannini M⁷, Hassan C⁸, Dumonceau JM⁹. **Intraductal biliopancreatic imaging: European Society of Gastrointestinal Endoscopy (ESGE) technology review.** Endoscopy. 2015 Aug;47(8):739-53.
# Intraductal Ultrasound

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCA</td>
<td>98%</td>
<td>98%</td>
<td>92%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>94%</td>
<td>90%</td>
<td>91%</td>
</tr>
<tr>
<td>Ampullary</td>
<td>81%</td>
<td>90%</td>
<td>89%</td>
</tr>
</tbody>
</table>

Real-time magnification of the mucosal layer
- 9-12 frames per second
- Requires IV fluorescein

Tringali A¹, Lemmers A², Meves V³, Terhoggen G⁴, Pohl J⁵, Manfredi G⁶, Häfner M⁷, Costamagna G¹, Devière J², Neuhaus H⁶, Caillol F¹, Giovannini M⁷, Hassan C⁸, Dumonceau JM⁹. *Intraductal biliopancreatic imaging: European Society of Gastrointestinal Endoscopy (ESGE) technology review.* Endoscopy. 2015 Aug;47(8):739-53.
Miami Classification

- Presence of two:
  - White bands > 20 µm
  - Dark bands > 40 µm
  - Dark clumps
  - Epithelial structures
  - Fluorescein leakage
- Sensitivity 97%
- Specificity 33%

Tringali A¹, Lemmers A², Meves V³, Terheggen G⁴, Pohl J³, Manfredi G⁵, Hafner M⁶, Costamagna G¹, Deviere J², Neuhaus H⁴, Caillol F⁷, Giovannini M⁷, Hassan C⁸, Dumonceau JM⁹. *Intraductal biliopancreatic imaging: European Society of Gastrointestinal Endoscopy (ESGE) technology review.* Endoscopy. 2015 Aug;47(8):739-53.
SpyGlass Cholangioscopy

Diagnostic accuracy

- 26 patients (17 malignant)
- Triple sampling
  - Cholangioscopy-guided mini-forceps
  - Cytology brushing
  - Standard forceps
- Findings compared to final status

### Diagnostic accuracy

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Accuracy</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology brush*</td>
<td>5.9%</td>
<td>38.5%</td>
<td>36%</td>
</tr>
<tr>
<td>Standard forceps</td>
<td>29.4%</td>
<td>53.8%</td>
<td>42.8%</td>
</tr>
<tr>
<td>Mini-forceps</td>
<td>76.5%</td>
<td>84.6%</td>
<td>69.2%</td>
</tr>
</tbody>
</table>

SpyGlass biopsies

- Systematic review through 2014
- 10 studies involving 456 patients