Indeterminate Strictures of Biliary System – Role of Advanced Imaging

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Professor University of Queensland, Australia
Indeterminate Biliary Strictures:

- Inflammatory – Autoimmune, PSC, Chronic Pancreatitis
- Trauma / Ischemia
- Chemoembolization
- Transplant / Biliary surgery
- Infections
- Choledochal cyst
- Malignant - Cholangiocarcinoma
Diagnostic Challenge

Traditionally: EUS (IDUS), ERCP, Biomarkers (Poor sensitivity)

20% of biliary strictures remain indeterminate and need surveillance or surgery

No standard prescription how to evaluate – use tailored approach based on available technology
Pathway Diagnosis:

- History
- Radiologic Imaging
- Endoscopy - Brushing, FISH (polysomy)
- Biomarkers - CA 19-9
- Advanced Imaging: Single operator Cholangioscopy, Endomicroscopy
PSC strictures / Cholangio CA:

- Increase yield with more samples
- EUS staging and FNA
- FISH also has not increased sensitivity
- Spyglass / Spybite forceps (limited data, small numbers, cholangitis)
- Recently Endomicroscopy to improve yield and target biopsies
Case: Indeterminate

- 73 Y/O with mild elevated liver tests
- Ca-19-9 normal, IgG4 Normal
- No Alarm symptoms
- Enlarged Lymph nodes Hilum
- Enlarged HOP
- MRCP
Hilar Lesion: Single operator cholangioscope
Probe Based Endomicroscopy : pCLE
IgG4 Negative Autoimmune Cholangitis:
Proposed diagnostic approach to biliary strictures.

Jaundice

Abdominal US

Proximal Obstruction

MRI/MRCP

Hilar Mass

ERCP‡ +/- SOC with biopsy

No Malignancy

EUS-FNA

No Malignancy

IDUS

High likelihood of malignancy

Surgery

Low likelihood of malignancy

Close observation and follow-up

Distal Obstruction

CT

Mass

Surgery vs. EUS-FNA

No Mass

EUS-FNA

No Malignancy

ERCP‡

No Malignancy

Consider repeat ERCP with other modalities (SOC with biopsy, IDUS, CLE)

* Once malignancy is confirmed by any modality, surgical and oncology referral should be obtained

‡ Includes brushings (for cytology and FISH analysis), fluoroscopic biopsies, needle aspiration, fluid aspiration
Proximal biliary stricture

ERCP with SOC
Biopsy or cytology or FISH

Cytology or biopsy (+)

CCA

CA19-9 ≥ 129 U/mL

Probable CCA

Cytology (+)

Probable CCA

MRI surveillance, consider EUS

Cytology or biopsy (-)
FISH (polysomy)

Probable CCA

Cytology (-) FISH (polysomy)

EUS +/- FNA or repeat ERCP

CA19-9 < 129 U/mL

Repeat ERCP

Cytology (-) FISH (-)

Nature Reviews | Gastroenterology & Hepatology
Distal:

Distal biliary structure

- IgG4 < 1.4 g/l
  - EUS ± FNA
    - Cytology (+)
      - Cancer
    - Cytology (-)
      - Follow Figure 4

- IgG4 < 1.4 g/l or meeting HISORt criteria
  - Prednisone 40 mg/d
    - Response

Nature Reviews | Gastroenterology & Hepatology
Intraductal Imaging of CBD:

- Challenging
- SOC (Spyglass)
- Endomicroscopy – CLE
Indeterminate Strictures: pCLE Operating Characteristics

- kappa statistic, stent changes

Table 1: Studies examining efficacy of probe-based confocal laser endomicroscopy in diagnosis for indeterminate biliary strictures

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Classification</th>
<th>Patients</th>
<th>Sen (%)</th>
<th>Spe (%)</th>
<th>NPV (%)</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meining, et al.</td>
<td>GIE 2011</td>
<td>Miami</td>
<td>89</td>
<td>98</td>
<td>67</td>
<td>97</td>
<td>71</td>
</tr>
<tr>
<td>Meining, et al.</td>
<td>Endo 2012</td>
<td>Miami</td>
<td>47</td>
<td>97</td>
<td>33</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Slivka, et al.</td>
<td>GIE 2015</td>
<td>Paris/Miami</td>
<td>136</td>
<td>89</td>
<td>71</td>
<td>78</td>
<td>84</td>
</tr>
</tbody>
</table>
## Miami Criteria: 2009

### Table 2  Miami Criteria of probe-based confocal laser endomicroscopy for predicting biliary neoplasmia in the pancreaticobiliary system

<table>
<thead>
<tr>
<th>Malignant Criteria</th>
<th>Benign Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thick, dark bands (&gt; 40 μm)</td>
<td>Thin, dark (branching) bands</td>
</tr>
<tr>
<td>Thick, white bands (&gt; 30 μm)</td>
<td>Thin, white bands</td>
</tr>
<tr>
<td>Dark clumps</td>
<td></td>
</tr>
<tr>
<td>Epithelium visualized (villi)</td>
<td></td>
</tr>
<tr>
<td>Fluorescein leakage</td>
<td></td>
</tr>
</tbody>
</table>
Malignant:
Paris Criteria:

**Healthy bile duct**
1. Reticular network of thin dark branching bands (<20µm) - *thin collagen bundle*
2. Light grey background - *lymphatic sinuses*
3. Vessels (<20µm)

**Inflammatory stricture**
1. Multiple white bands - *vessels*
2. Dark granular pattern in scales
3. Enlarged space between scales
4. Thickened reticular structures

**Malignant stricture**
1. Thick white bands (>20µm) - *vessels*
2. Thick dark bands (>40µm) - *Bundles with increased diameter*
3. Epithelium
4. Dark clumps
Table 3 Paris Classification of probe-based confocal laser endomicroscopy for differentiating benign inflammatory strictures

<table>
<thead>
<tr>
<th>Benign inflammatory criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular congestion</td>
</tr>
<tr>
<td>Roughness aspect</td>
</tr>
<tr>
<td>Increased interglandular space</td>
</tr>
<tr>
<td>Thickened reticular structure</td>
</tr>
</tbody>
</table>
Benign Stricture
Inflammatory:

Post-Stent Inflammatory Stricture
Validation with Paris Criteria:

BILIARY AND PANCREATIC

Improved classification of indeterminate biliary strictures by probe-based confocal laser endomicroscopy using the Paris Criteria following biliary stenting

Pushpak Taunk, * Satish Singh, †,‡ David Lichtenstein, † Virendra Joshi, § Jason Gold ‡ and Ashish Sharma ¶

*University of South Florida, Tampa, Florida, †Boston University Medical Center, ‡Boston VA Medical Center, Boston, Massachusetts, §Ochsner Health System, New Orleans, Louisiana, and ¶Kaiser Permanente Health System, Sacramento, California, USA

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<table>
<thead>
<tr>
<th>Demographics</th>
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</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>21</td>
</tr>
<tr>
<td>Total videos</td>
<td>27</td>
</tr>
<tr>
<td>Total malignant videos</td>
<td>7</td>
</tr>
<tr>
<td>Total benign videos</td>
<td>20</td>
</tr>
<tr>
<td>Average age</td>
<td>64.5</td>
</tr>
<tr>
<td>Males</td>
<td>17</td>
</tr>
<tr>
<td>Females</td>
<td>4</td>
</tr>
<tr>
<td>Videos s/p plastic stent</td>
<td>11</td>
</tr>
<tr>
<td>Videos s/p metal stent</td>
<td>3</td>
</tr>
<tr>
<td>Average time w/ plastic stent</td>
<td>5.3 months</td>
</tr>
<tr>
<td>Average time w/ metal stent</td>
<td>3.3 months</td>
</tr>
</tbody>
</table>
### Table 5
Performance of probe-based confocal laser endomicroscopy (pCLE) on indeterminate biliary strictures using the Miami Criteria

<table>
<thead>
<tr>
<th>pCLE imaging</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-stent placement (%)</td>
<td>88</td>
<td>75</td>
<td>64</td>
<td>92</td>
<td>79</td>
</tr>
<tr>
<td>Post-stent placement (%)</td>
<td>88</td>
<td>36</td>
<td>23</td>
<td>93</td>
<td>45</td>
</tr>
</tbody>
</table>

### Table 6
Performance of probe-based confocal laser endomicroscopy (pCLE) on indeterminate biliary strictures using the Paris Classification

<table>
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<tbody>
<tr>
<td>Pre-stent placement (%)</td>
<td>63</td>
<td>88</td>
<td>71</td>
<td>82</td>
<td>79</td>
</tr>
<tr>
<td>Post-stent placement (%)</td>
<td>63</td>
<td>73</td>
<td>31</td>
<td>91</td>
<td>71</td>
</tr>
</tbody>
</table>

Kappa Statistic .56 (moderate)
pCLE Vs Tissue Sampling in Dominant PSC Strictures:

Multivariate Regression analysis

- A U.S. Multi-Center, Prospective Registry Study Utilizing Probe-Based Confocal Laser Endomicroscopy (PCLE) to Distinguish Benign From Malignant Dominant Biliary Strictures in Patients With Primary Sclerosing Cholangitis


1. pCLE superior to tissue sampling
2. Paris criteria may have some limitations in these strictures due to extensive scarring to detect neoplasia
Reflection / transmission - of Near infrared LASER light
Creates an Image pattern described as “hyper or hypo-reflective”
Why OCT in Bile duct? Can we better target biopsies?
Biliary Probe

9.5 cm
Distance from orange sheath to probe tip

1.3 cm
Distance from “start of scan” to tip

8.2 cm
Distance from orange sheath to “start of scan”

NO Balloon
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial Resolution</td>
<td>7 micron</td>
</tr>
<tr>
<td>Depth of Image</td>
<td>3mm</td>
</tr>
<tr>
<td>Lateral Resolution</td>
<td>40 micron</td>
</tr>
<tr>
<td>Focal Length</td>
<td>2.4mm</td>
</tr>
</tbody>
</table>
Normal
Duodenum

Normal CBD

DFI: 0.0cm
Normal Bile Duct

Epithelium/Single Layer

1mm
Normal Bile Duct

Different image

Epithelium/Single Layer

DFI: 36.4cm, Pos: 10:30
PSC/Inflammatory Disease

- Thickening of wall + inflammation
- Eroded Surface Epithelium
- Inflamed bile duct wall
Inflammation around peribiliary glands

PSC/Inflammatory Disease
Cholangiocarcinoma

Normal Surface Epithelium

Infiltrating Malignant Glands

DFI: 2.7cm
CCA Image 1

DFI: 2.7cm, Pos: 12:30
CCA Image 2

Cholangiocarcinoma

Bile Duct
A Pilot study of Safety and Efficacy of directed cannulation with a Low Profile catheter (LP) and imaging characteristics of bile duct wall using Optical Coherence tomography (OCT) for indeterminate biliary strictures – Initial report on in-vivo evaluation during ERCP:

Virendra Joshi1, 6, Sandeep N. Patel5, Hendrikus Vanderveldt4, Irma oliva3, Isaac Raijman5, Cris Molina1, David L. Carr-Locke2

Conclusion:
1. VLE of the bile duct using the Nvision platform and a novel LP catheter is feasible and safe
2. A two-layered structure in normal and inflammatory biliary strictures was seen consistently, malignant strictures demonstrated complete loss of layering
3. VLE of pancreatobiliary system has potential to define abnormalities, target sampling and therapy

DDW 2017, Chicago
Case Review:

- Pt. presents with normal appearing ampulla;

- cannulated the CBD with a standard sphincterotome and .025 wire, Ominpaque injected and the Cholangiogram showed a mid to distal CBD stricture approximately 2 cm in length. A sphincterotomy was then done. The wire was left in and then a VLE Low Profile probe was placed alongside the wire and a full scan was completed without any difficulty. VLE Tags were laid at frame 560 beginning of the stricture confirmed by flouro and 1059 end of stricture confirmed by flouro. Spyglass was then used to visualize the area of concern and bx’s were taken. Brushings were also taken of the suspected area.

- Pathology results: Atypical cells, adenocarcinoma
Cholangiogram
location of the LP PRobe
SpyGlass image of strictured area
SpyGlass Image and Spybite Image
Beginning of stricture

POSSIBLE INVASIVE MALIGNANT GLANDS, beginning of scalped appearance

DFI: 3.2cm
Middle of stricture Frame

764

- Loss of layering
- Eroded epithelium
- “Scalloping” look

DFI: 2.2cm
- Loss of layering
- Eroded epithelium
- “Scallopining” look

DFI: 2.2cm
Histology image from Spybite
Conclusion:

- CLE/VLE impact will only increase as enhanced user image interpretation capability and newly available technical improvements further the ability to identify and target advanced disease missed by other techniques.

- Artificial Intelligence and computer aided interpretation should be available in near future

- ..... And MILES to go before I sleep.... ( Sir Robert Frost )