Emerging Role of Endoscopic Ultrasound in Liver Disease

Marvin Ryou, MD
Assistant Professor of Medicine
Advanced Endoscopy, Gastroenterology
Research Programs

- EUS-Based Hepatobiliary Diagnostics
  - EUS Liver Biopsy
  - EUS Digital Portal Pressure Measurements
  - EUS Elastography

- EUS-Based Hepatobiliary Therapeutics
  - EUS TIPS
  - EUS Gallbladder
Research Programs

- EUS-Based Hepatobiliary Diagnostics
  - EUS Liver Biopsy
  - EUS Digital Portal Pressure Measurements
  - EUS Elastography

- EUS-Based Hepatobiliary Therapeutics
  - EUS TIPS
  - EUS Gallbladder
Background

- EUS-guided liver biopsy is emerging as a novel method of obtaining benign hepatic tissue
- New coring needles (fine needle biopsy [FNB]) are available
Background

- Potential advantages of EUS liver biopsy
  - Technically simple
  - Does not require percutaneous puncture (painful)
  - Image-guided, allows avoidance of blood vessels >1 mm in diameter
  - Simultaneous comprehensive assessment of UGI tract, biliary tree, gallbladder, pancreas

- Preliminary reports show safety/feasibility but specimen adequacy equivocal (9-91%)
Aims

- To compare the histologic yield of 4 different EUS-based needles and 2 percutaneous needles on human cadaveric liver model

- To identify optimal degree of suction and optimal number of needle excursions for maximal histologic yield
Methods

EUS needles tested

19-G Expect FNA
19-G ProCore
19-G SharkCore
22-G SharkCore
Methods

- **Primary outcome:** Number of portal triads
Methods

- **Secondary outcome:** Degree of fragmentation

- **Secondary outcome:** Specimen adequacy
  - ≥ 5 portal triads and/or segment ≥ 15mm (i.e. core)
Results

Comparison of Mean Portal Tracts by Needle Type

Mean Number of Portal Tracts

- 19-G SharkCore FNB
- 22-G SharkCore FNB
- 19-G Procore FNB
- 19-G Expect FNA
- 18-G Percutaneous (1)
- 18-G Percutaneous (2)

Needle Type

* = p ≤ 0.05

Schulman AS, Ryou M. GIE 2016
# Results

![Percent (%) Fragmentation by Needle Type](chart.png)

- **19-G SharkCore FNB**: 80% pieces, 20% fragments, 0% cores
- **22-G SharkCore FNB**: 70% pieces, 30% fragments, 0% cores
- **19-G Procore FNB**: 90% pieces, 10% fragments, 0% cores
- **19-G Expect FNA**: 80% pieces, 20% fragments, 0% cores
- **18-G Percutaneous (1)**: 70% pieces, 30% fragments, 0% cores
- **18-G Percutaneous (2)**: 60% pieces, 40% fragments, 0% cores

Schulman AS, Ryou M. GIE 2016
Results

Comparison of Specimen Adequacy by Needle Type

<table>
<thead>
<tr>
<th>Needle Type</th>
<th>Specimen Adequacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19-G SharkCore FNB</td>
<td>90</td>
</tr>
<tr>
<td>22-G SharkCore FNB</td>
<td>90</td>
</tr>
<tr>
<td>19-G Procore FNB</td>
<td>50</td>
</tr>
<tr>
<td>19-G Expect FNA</td>
<td>50</td>
</tr>
<tr>
<td>18-G Percutaneous (1)</td>
<td>80</td>
</tr>
<tr>
<td>18-G Percutaneous (2)</td>
<td>80</td>
</tr>
</tbody>
</table>

Schulman AS, Ryou M. GIE 2016
# Multivariate Regression Analysis

<table>
<thead>
<tr>
<th>Needle Type</th>
<th>Effect Estimate</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ProCore 19-G</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Expect 19-G</td>
<td>0.17</td>
<td>0.848</td>
</tr>
<tr>
<td>SharkCore 19-G</td>
<td>3.23</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>SharkCore 22-G</td>
<td>2.38</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fans (#)</th>
<th>Effect Estimate</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>1.33</td>
<td>0.03*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location of biopsy</th>
<th>Effect Estimate</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Left</td>
<td>0.53</td>
<td>0.62</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amount of Suction</th>
<th>Effect Estimate</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 cc</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>20 cc</td>
<td>0.38</td>
<td>0.52</td>
</tr>
<tr>
<td>30 cc</td>
<td>0.56</td>
<td>0.34</td>
</tr>
<tr>
<td>Slow-Pull</td>
<td>0.83</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Schulman AS, Ryou M. GIE 2016
Conclusions

- SharkCore FNB provides superior histologic yield compared to existing 19-G FNA/FNB needles and 18-G percutaneous needles.
- 22-G SharkCore also performed at least equivalent to 18-G percutaneous needle.
- 3 needle excursions outperform 1 excursion.
- Degree of suction and location in liver did not appear to matter.
Research Programs

- EUS-Based Hepatobiliary Diagnostics
  - EUS Liver Biopsy
  - EUS Digital Portal Pressure Measurements
  - EUS Elastography

- EUS-Based Hepatobiliary Therapeutics
  - EUS TIPS
  - EUS Gallbladder
We developed a novel EUS guided approach to obtain direct digital portal pressure measurements.
Portal pressures provides important information re: risks of decompensation and mortality

Portal pressures currently estimated using surrogate HVPG, not widely performed

<table>
<thead>
<tr>
<th>Classification</th>
<th>Stages</th>
<th>1-yr mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>METAVIR F1-F3</td>
<td>F4 &gt;6 mmHg</td>
<td>1%</td>
</tr>
<tr>
<td>HVPG (mmHg)</td>
<td>F4 &gt;10 mmHg</td>
<td>3%</td>
</tr>
<tr>
<td>Clinical class</td>
<td>F4 &gt;12 mmHg</td>
<td>10-30%</td>
</tr>
<tr>
<td>No cirrhosis</td>
<td>Stage 1 Compensated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage 2 Compensated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage 3 Decompensated</td>
<td>Varices</td>
</tr>
<tr>
<td></td>
<td>Stage 4 Decompensated</td>
<td>Variceal bleeding</td>
</tr>
<tr>
<td></td>
<td>Ascites</td>
<td>Variceal bleeding</td>
</tr>
<tr>
<td></td>
<td>Encephalopathy</td>
<td>Ascites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Encephalopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bacterial infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatorenal syndrome</td>
</tr>
<tr>
<td>1-yr mortality</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Aims

- To determine safety and technical feasibility in an animal survival model
- To determine accuracy compared to transjugular gold standard
- To compare direct portal vein versus transhepatic first order venule
EUS Approach
Transjugular HVPG

Figure 3. Transjugular catheterization with balloon occlusion catheter performed under fluoroscopy.
Results

- All procedure successfully performed in less than 10 minutes
- Portal pressure measurements performed in less than 4 minutes
- All animals recovered and survived 2 weeks without incident
- No bleeding, hematoma or abscesses at necropsy
Results

<table>
<thead>
<tr>
<th>Pig</th>
<th>HVPG measurement, mm Hg</th>
<th>EUS-guided portal pressure measurement, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

*HVPG, Hepatic venous pressure gradient.*
## Results

### Equivalent Pressures: Portal vein vs First-Order Venule

<table>
<thead>
<tr>
<th>Pig Number</th>
<th>Pressure Measurement (mmHg) at Baseline</th>
<th>Pressure Measurement (mmHg) at Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Portal Vein</td>
<td>First order venule</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

Schulman AS, Ryou M. GIE 2016
### Results

**Table 2. NASA Task Load Index for the endoscopist’s effort in EUS-guided portal pressure measurement based on a 10-cm visual analog scale**

<table>
<thead>
<tr>
<th>Category</th>
<th>Animals (N = 5)</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mental demand</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Physical demand</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Temporal demand</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Performance</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Effort</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Frustration</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Technical difficulty</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

*NASA, National Aeronautics and Space Administration.*

*The endoscopist specified his score by indicating a position along a continuous line between 2 endpoints from 0 (disagree) to 10 (strongly agree).*

Schulman AS, Ryou M. GIE 2016
Conclusions

- First report of direct EUS guided portal pressure measurement using digital wire
- Survival study demonstrated safety and feasibility
- Technically straightforward and requires minimal time
- Provides direct portal pressure measurements, unlike HVPG which is surrogate
Research Programs

- EUS-Based Hepatobiliary Diagnostics
  - EUS Liver Biopsy
  - EUS Digital Portal Pressure Measurements
  - EUS Elastography

- EUS-Based Hepatobiliary Therapeutics
  - EUS TIPS
  - EUS Gallbladder
Background

- Elastography: measures tissue stiffness and compressibility
- Fibroscan (transient elastography) has decreased clinical need for liver biopsies
- Fibroscan has shortcomings:
  - Ascites
  - Thick abdominal wall
  - Does not “see” most of liver
  - Difficulty distinguishing F2 from F3
Background

- **Real Time Elastography (RTE):**
  - Color mapping reflects underlying differences in tissue compressibility
  - More comprehensive measurements
  - Available on U/S processors
**Background**

- Validation of Real-Time Elastography (RTE) Using Trans-abdominal Probe for Liver Histology

**EUS Elastography:**
Elastography from the Inside!

ROC analysis differentiating F4 from F0-F3 fibrosis
Fujimoto et al., 2013
Works in Progress

- Standardizing EUS Elasto technique
- Assessing EUS Elasto’s ability to differentiate Normal, Fatty, and Cirrhotic
- Comparing EUS Elasto with Transabdominal Elasto
- Correlating EUS Elasto with risk of clinical decompensation
- Assessing EUS Elasto’s ability to differentiate F1, F2, F3, and F4.
Preliminary Results

- **Standardizing EUS Elastography Technique**
  - Choose Frames Delineating Perihepatic Fat (Red stripe)
  - Center ROI
  - Avoid bile ducts
  - Avoid vasculature
  - ROI up to 2 cm from transducer

Schulman AS, Ryou M. DDW 2016
Preliminary Results

- Standardizing EUS Elastography Technique

![Distribution of LFI Chart](chart.png)

Schulman AS, Ryou M. DDW 2016
EUS Elastography: Differentiating Normal, Fatty, and Cirrhotic

<table>
<thead>
<tr>
<th>Group</th>
<th>Number Enrolled</th>
<th>Mean LFI [+/- SD]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>39</td>
<td>0.79 [0.6]</td>
</tr>
<tr>
<td>Fatty liver</td>
<td>26</td>
<td>1.66 [0.9]</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>10</td>
<td>3.21 [0.9]</td>
</tr>
</tbody>
</table>
Preliminary Results

Distribution of LFI

F: 48.65
Prob > F: <.0001

Normal
Fatty
Cirrhosis

Schulman AS, Ryou M. DDW 2016
Conclusions

- EUS elastography can potentially differentiate Metavir scores (F1, F2, F3, F4)
- EUS elastography can potentially help in patients for whom transabdominal imaging would be inaccurate (e.g. ascites, thick abdominal wall)
Research Programs

- EUS-Based Hepatobiliary Diagnostics
  - EUS Liver Biopsy
  - EUS Digital Portal Pressure Measurements
  - EUS Elastography

- EUS-Based Hepatobiliary Therapeutics
  - EUS TIPS
  - EUS Gallbladder
Background

- Transjugular intrahepatic portosystemic shunt (TIPS)
  - Involves creation of low-resistance channel between portal vein and hepatic vein
  - Deployment of stent allows blood to return to systemic circulation
  - Performed under angiography
  - Associated with inadvertent biliary/arterial damage
Background

- **Endoscopic Intrahepatic Portosystemic Shunt (EIPS)**
  - Transgastric access across hepatic vein and portal vein
  - Measure pressures in both
  - Guidewire advanced through needle which is then removed
  - Balloon dilation of tract
Background

- Advance stent deployment catheter into portal vein
- Deploy distal flange
- Deploy proximal flange

Stent Deployment (EUS)

LAMS
10 mm length

Stent Deployment (Fluoro)
Background

- Dilate stent to 10 mm
- Doppler to confirm flow
- Direct pressure measurements repeated
- Site of bowel wall entry clipped as needed
Aims

- To determine safety and technical feasibility of EUS guided intrahepatic portosystemic shunt (EIPS) in a survival animal study

- To compare direct portal and hepatic vein pressure measurements before and after EIPS
Results

- EIPS successful in 5/5 animals
- Mean time required for EUS identification, needle access, pressure measurements, and stent placements was 43 min [31-55]
- No intraprocedural hemodynamic instability

Schulman AS, Ryou M, Thompson CC. GIE 2016
Results

Comparison of pressure measurements (mm Hg) at baseline and on two week follow-up in each animal

<table>
<thead>
<tr>
<th>Pig Number</th>
<th>Pressure Measurement (mmHg) at Baseline</th>
<th>Pressure Measurement (mmHg) at Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hepatic Vein</td>
<td>Portal Vein</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td><strong>5.0</strong></td>
<td><strong>7.0</strong></td>
</tr>
</tbody>
</table>

Schulman AS, Ryou M, Thompson CC. GIE 2016
Necropsy

- No intraabdominal or retroperitoneal bleeding
- In-stent thrombosis found in 3 animals
  - 2 undilated stents
  - 1 dilated stent
- Small liver abscesses
  - 2 animals

Schulman AS, Ryou M, Thompson CC. GIE 2016
Necropsy

Schulman AS, Ryou M, Thompson CC. GIE 2016
Conclusions

- EUS-guided intrahepatic portosystemic shunt using a lumen-apposing metal stent with simultaneous direct portal pressure measurement is technically feasible.
- Procedure can be performed quickly.
- Stent modification required.
Research Programs

- EUS-Based Hepatobiliary Diagnostics
  - EUS Liver Biopsy
  - EUS Digital Portal Pressure Measurements
  - EUS Elastography

- EUS-Based Hepatobiliary Therapeutics
  - EUS TIPS
  - EUS Gallbladder
Background

- EUS-guided lumen-apposing stents (LAMS) currently being used for **palliative** gallbladder drainage

- EUS-guided GB drainage could have wider applicability with a prosthetic-free device

Baron T, NEJM 2015
Jejuno-Ileal Anastomosis Creation

Clinical Studies

- Endoscopic delivery of magnets under general anesthesia
- Twin scope approach
- Magnets assembled and coupled - marks end of procedure
- Jejunal – Ileal anastomosis created at 5 days
- All coupled magnets pass
Background
Final Thoughts

- Endoscopic Ultrasound is a powerful diagnostic and therapeutic tool potentially of assistance in the patient with liver/biliary disease.

- Feasibility of performing EUS-guided liver biopsy, portal pressure measurements, elastography, TIPS, and gallbladder drainage could potentially unify and simplify hepatobiliary care.
Thank You