BRIGHAM AND WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL

Emerging Role of Endoscopic Ultrasound in Liver Disease

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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

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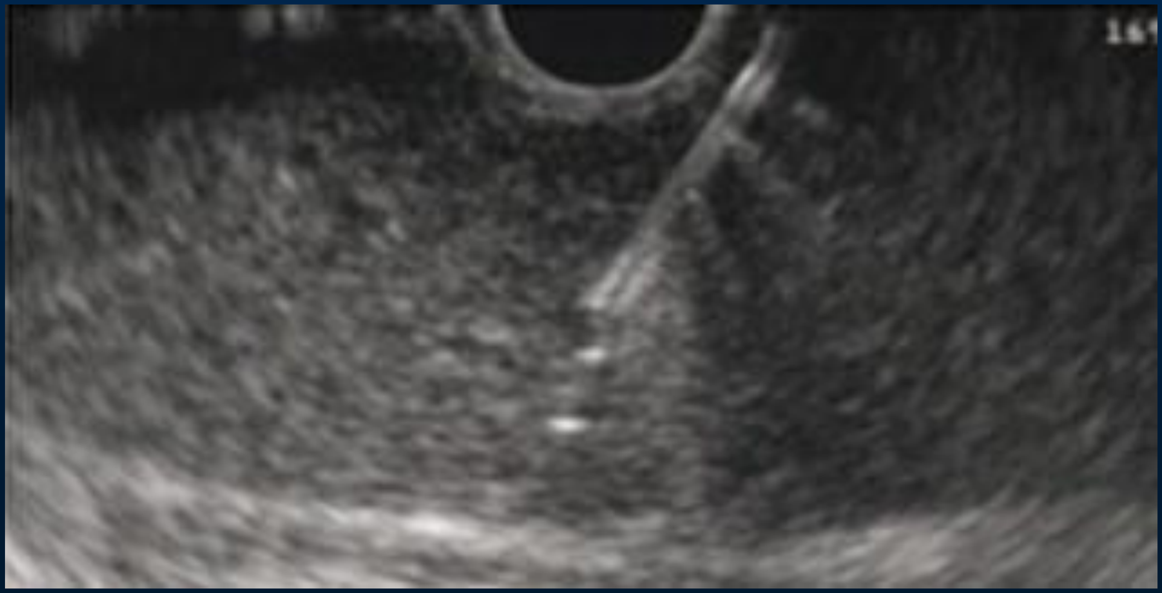
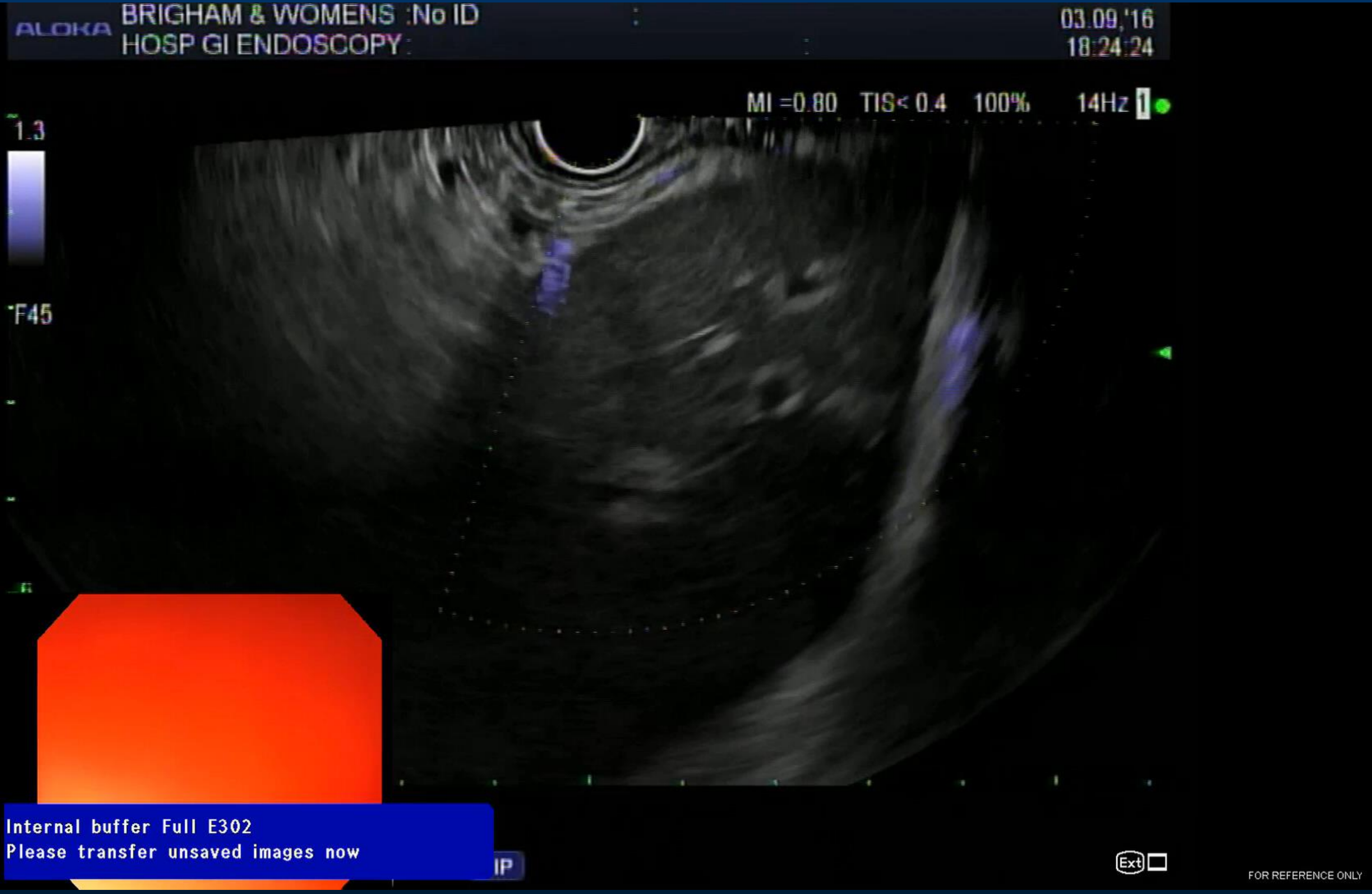
Background

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



EUS Liver Biopsy



Background

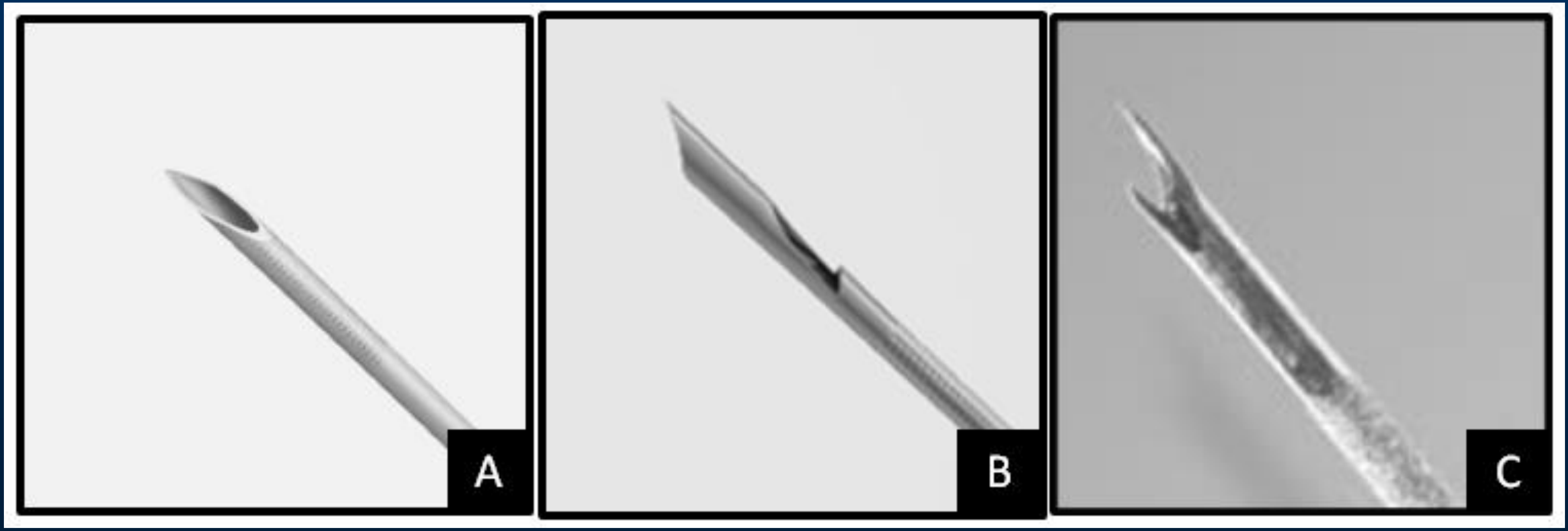
- Potential advantages of EUS liver biopsy
  - Technically simple
  - Does not require percutaneous puncture (painful)
  - Image-guided, allows avoidance of blood vessels >1 mm in diameter
  - Simultaneous comprehensive assessment of UGI tract, biliary tree, gallbladder, pancreas
- Preliminary reports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

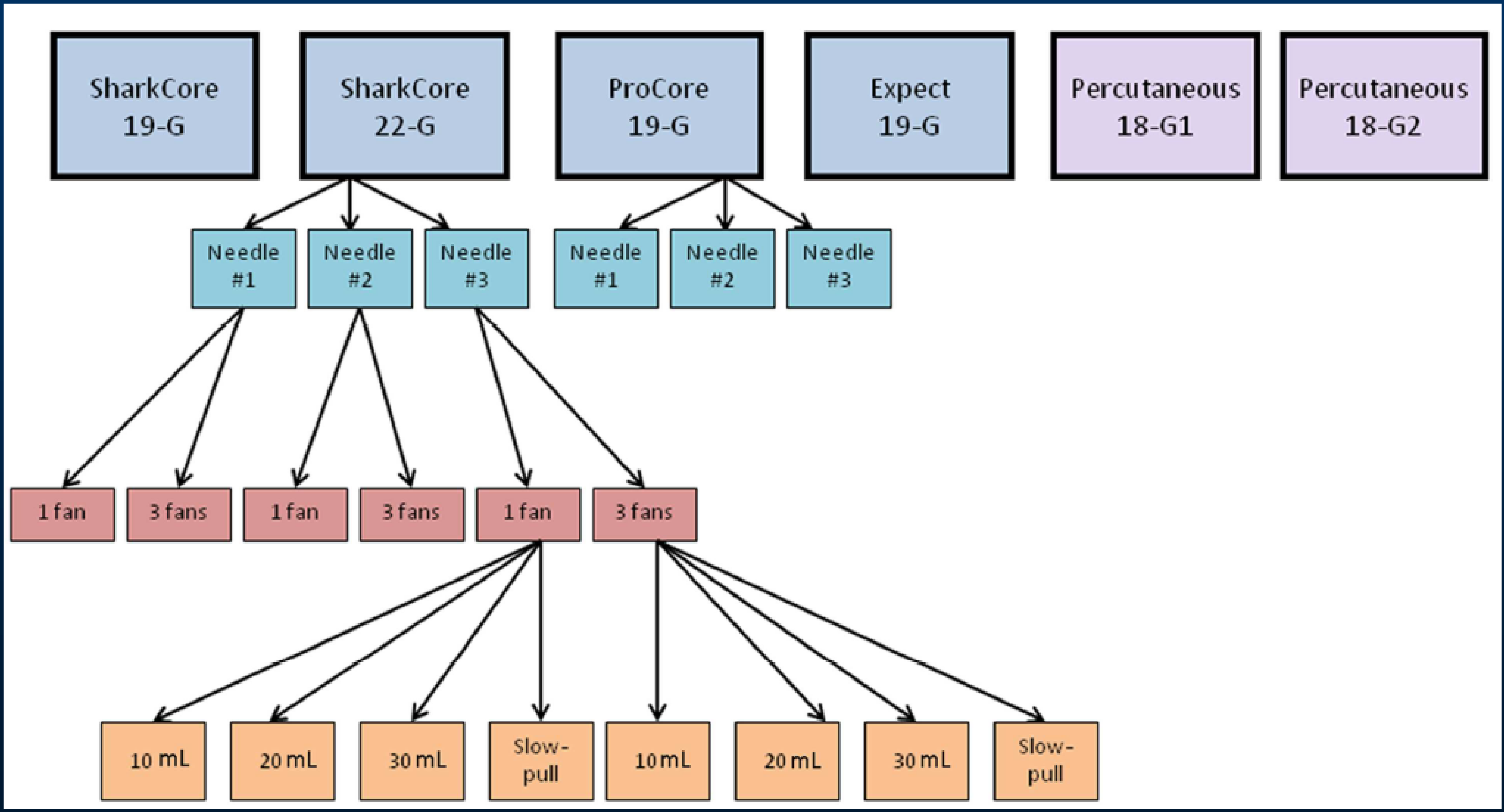


19-G Expect FNA

19-G ProCore

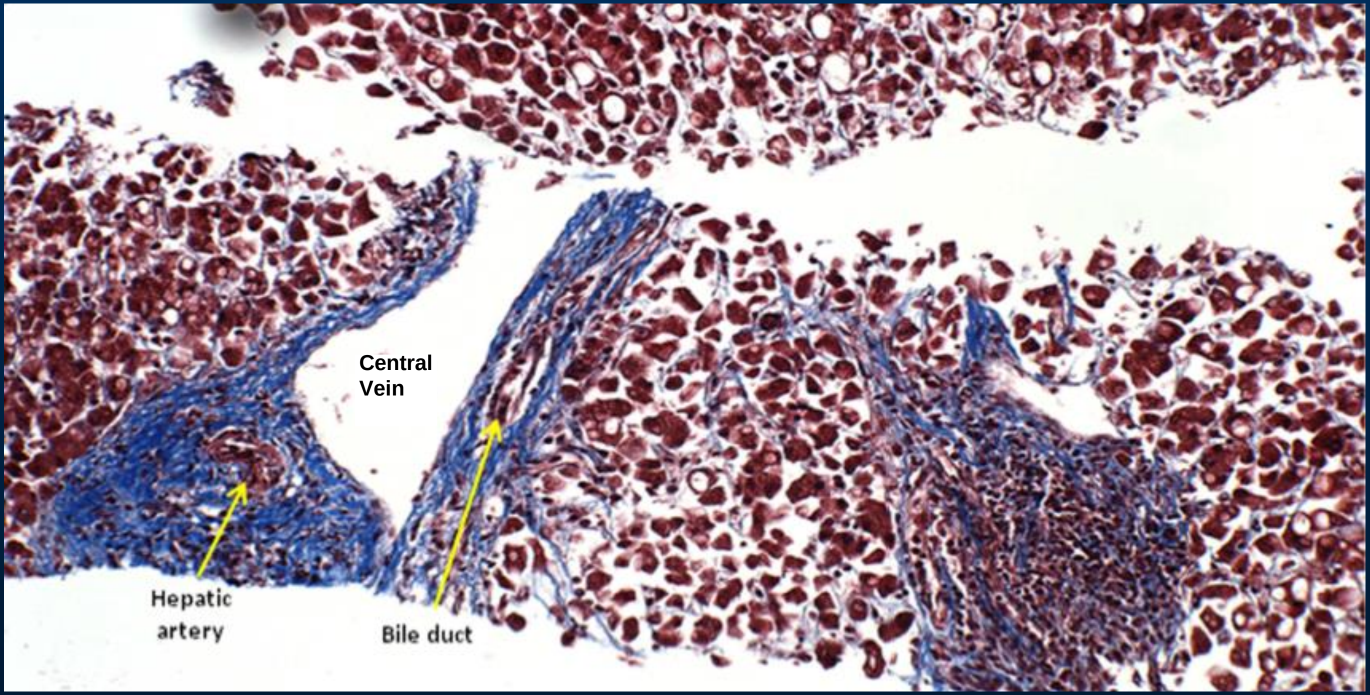
19-G SharkCore
22-G SharkCore

Methods


SharkCore 19-G
SharkCore 22-G
ProCore 19-G
Expect 19-G
Percutaneous 18-G1
Percutaneous 18-G2
Needle #1
Needle #2
Needle #3
Needle #1
Needle #2
Needle #3
1 fan
3 fans
1 fan
3 fans
1 fan
3 fans
10 mL
20 mL
30 mL
Slow-pull
10 mL
20 mL
30 mL
Slow-pull

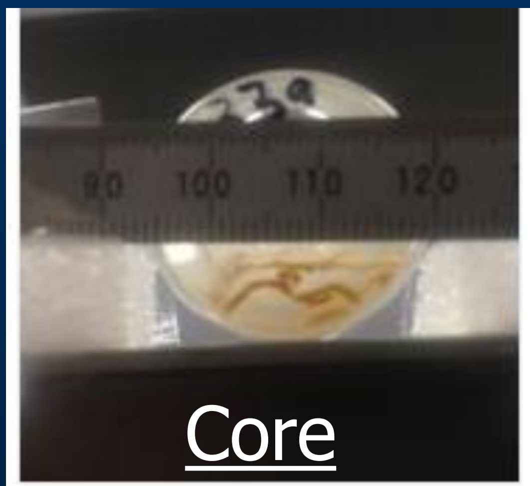
Methods

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



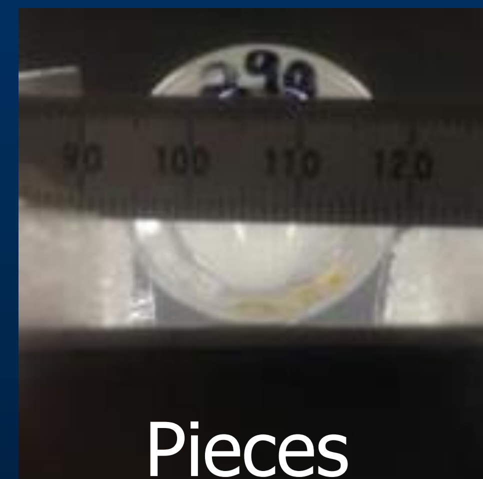
Methods

- **Secondary outcome:** Degree of fragmentation



Segment(s) > 15 mm

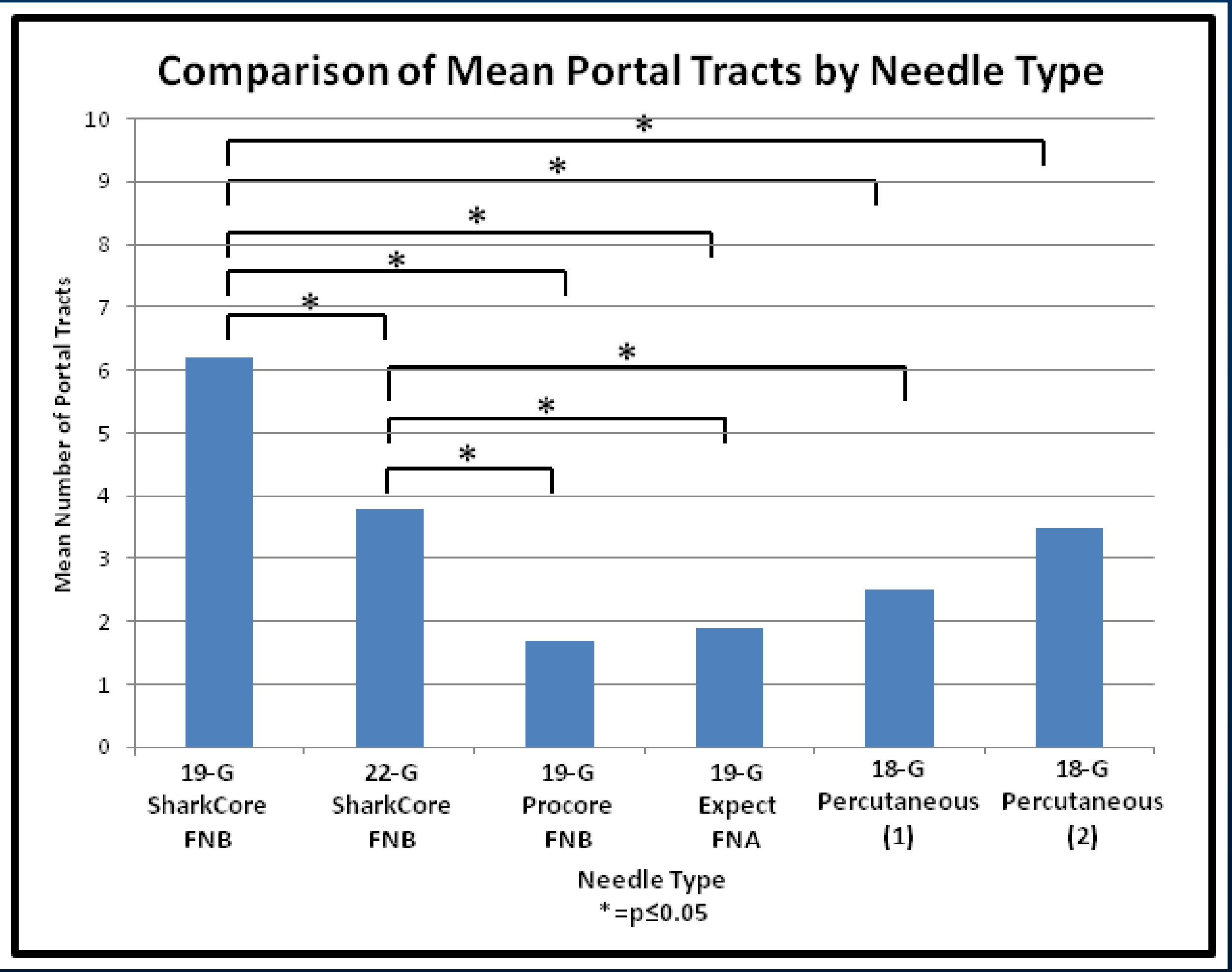
Segment(s) 5-15 mm



Segment(s) < 5mm

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

Results



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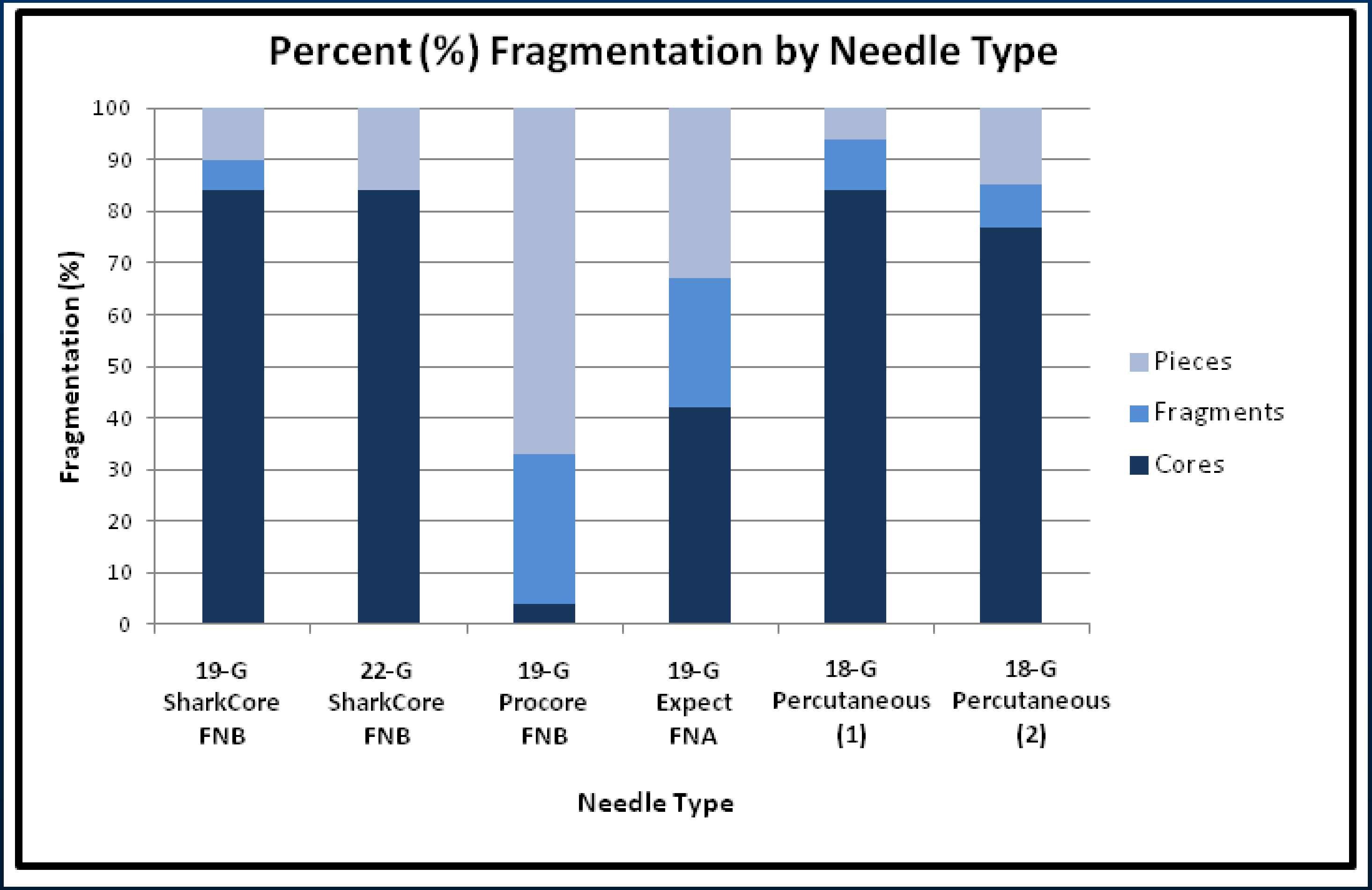
Results



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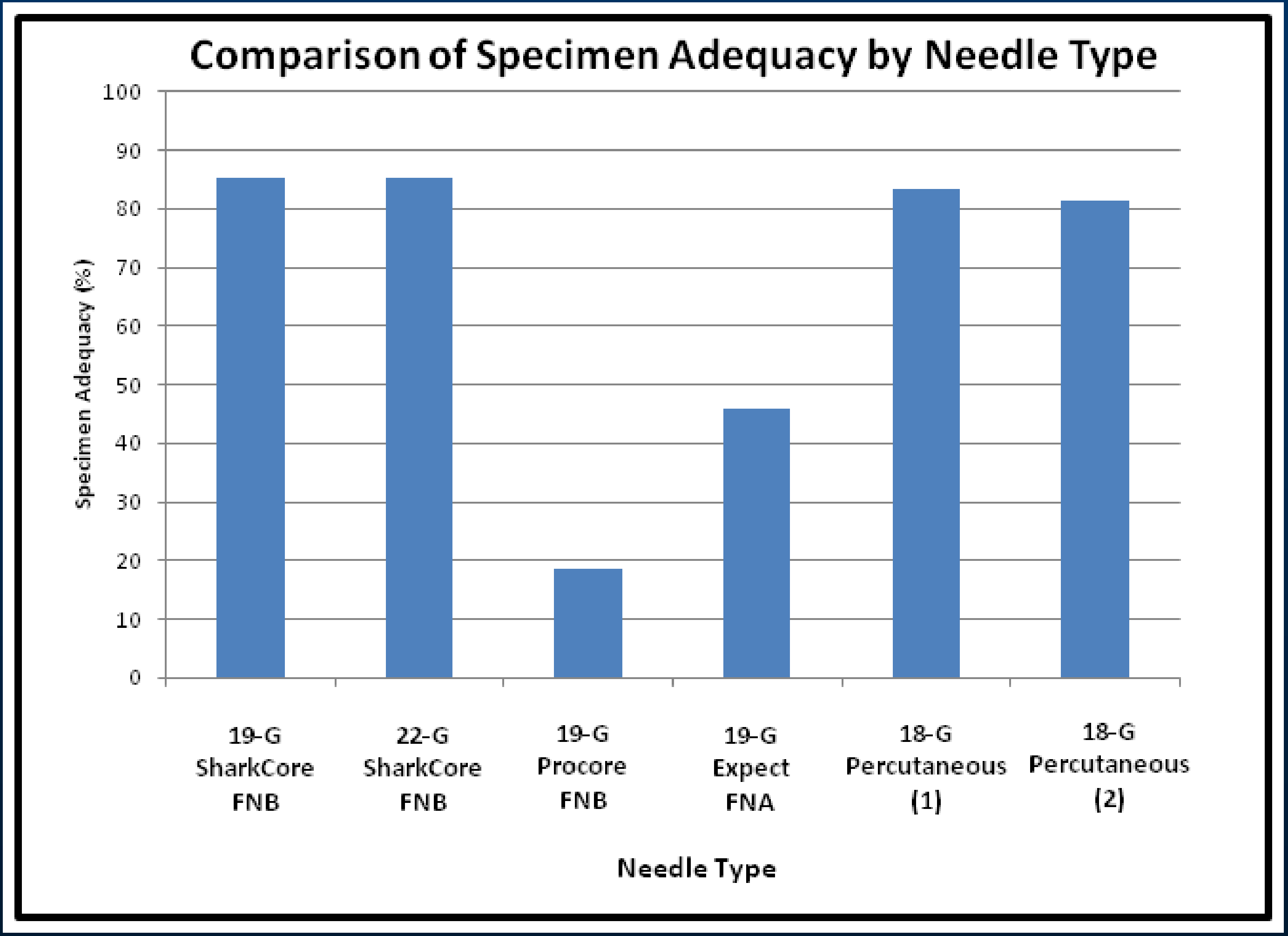
Results



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Multivariate Regression Analysis

	Effect Estimate	p-Value
Needle Type		
ProCore 19-G	---	---
Expect 19-G	0.17	0.848
SharkCore 19-G	3.23	<0.01*
SharkCore 22-G	2.38	<0.01*
Fans (#)		
1	---	---
3	1.33	0.03*
Location of biopsy		
Right	---	---
Left	0.53	0.62
Amount of Suction		
10 cc	---	---
20 cc	0.38	0.52
30 cc	0.56	0.34
Slow-Pull	0.83	0.67

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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

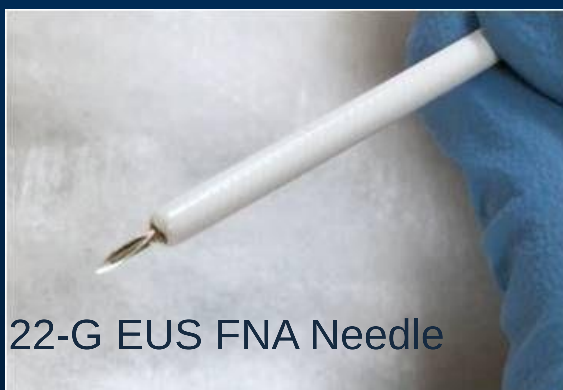
Research Programs

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

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

Background

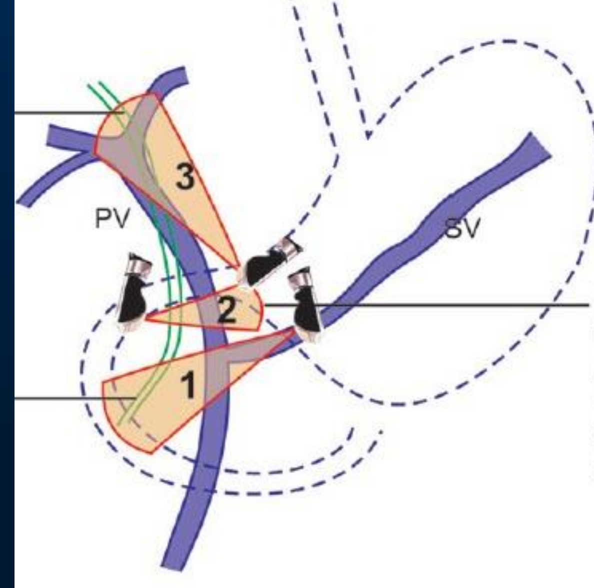
- We developed a novel EUS guided approach to obtain direct digital portal pressure measurements



22-G EUS FNA Needle

.035” Digital Pressure Wire

Portal vein easily accessed from duodenal bulb



Background

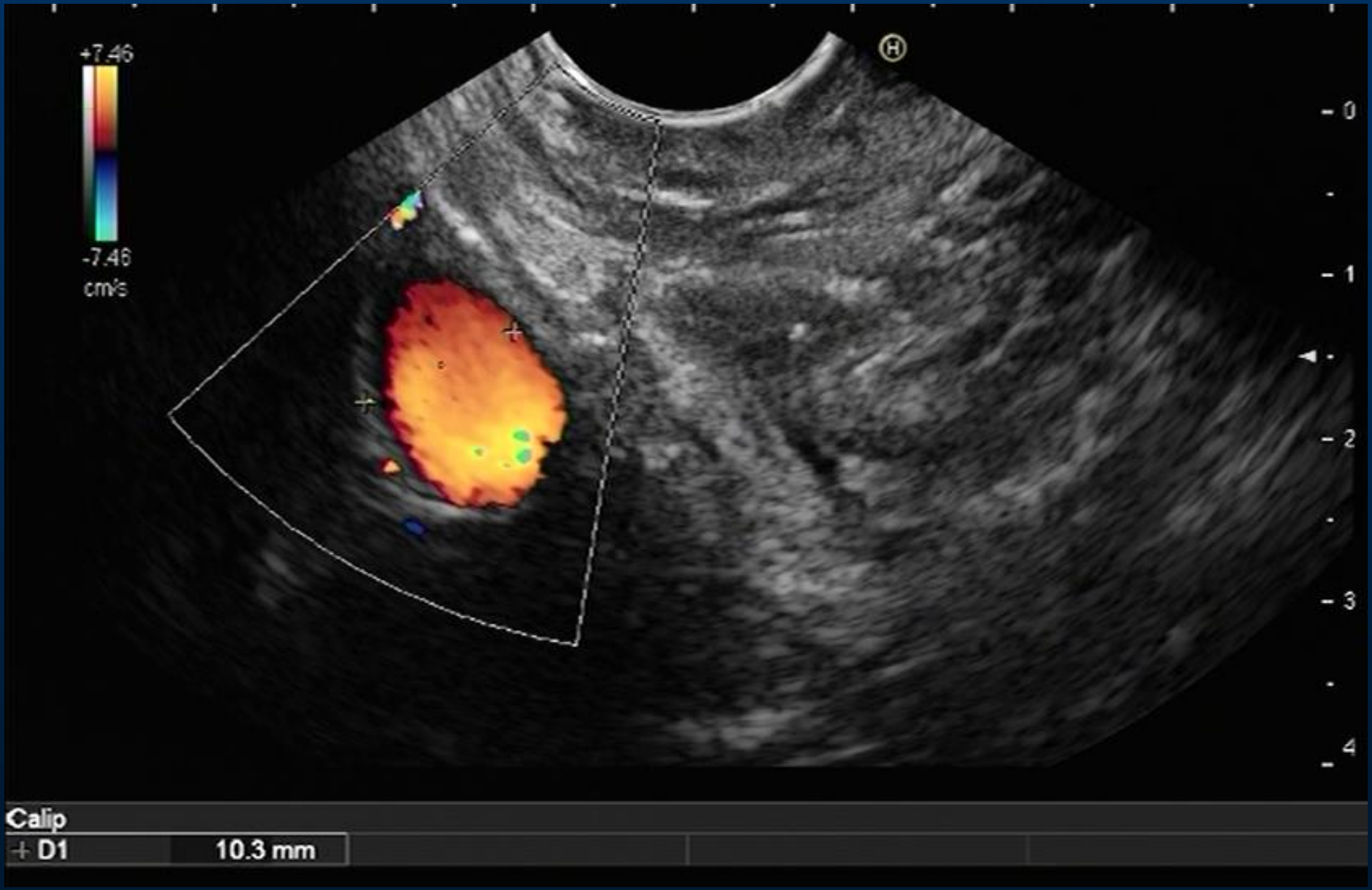
- Portal pressures provides important information re: risks of decompensation and mortality
- Portal pressures currently estimated using surrogate HVPG, not widely performed

Classification		Stages			
METAVIR	F1-F3	F4	F4	F4	F4
HVPG (mmHg)		>6 mmHg	>10 mmHg	>12 mmHg	>16 mmHg
Clinical class		Stage 1	Stage 2	Stage 3	Stage 4
	No cirrhosis	Compensated	Compensated	Decompensated	Decompensated
			Varices	Variceal bleeding Ascites Encephalopathy	Variceal bleeding Ascites Encephalopathy Bacterial infection Hepatorenal syndrome
1-yr mortality		1%	3%	10-30%	60-100%

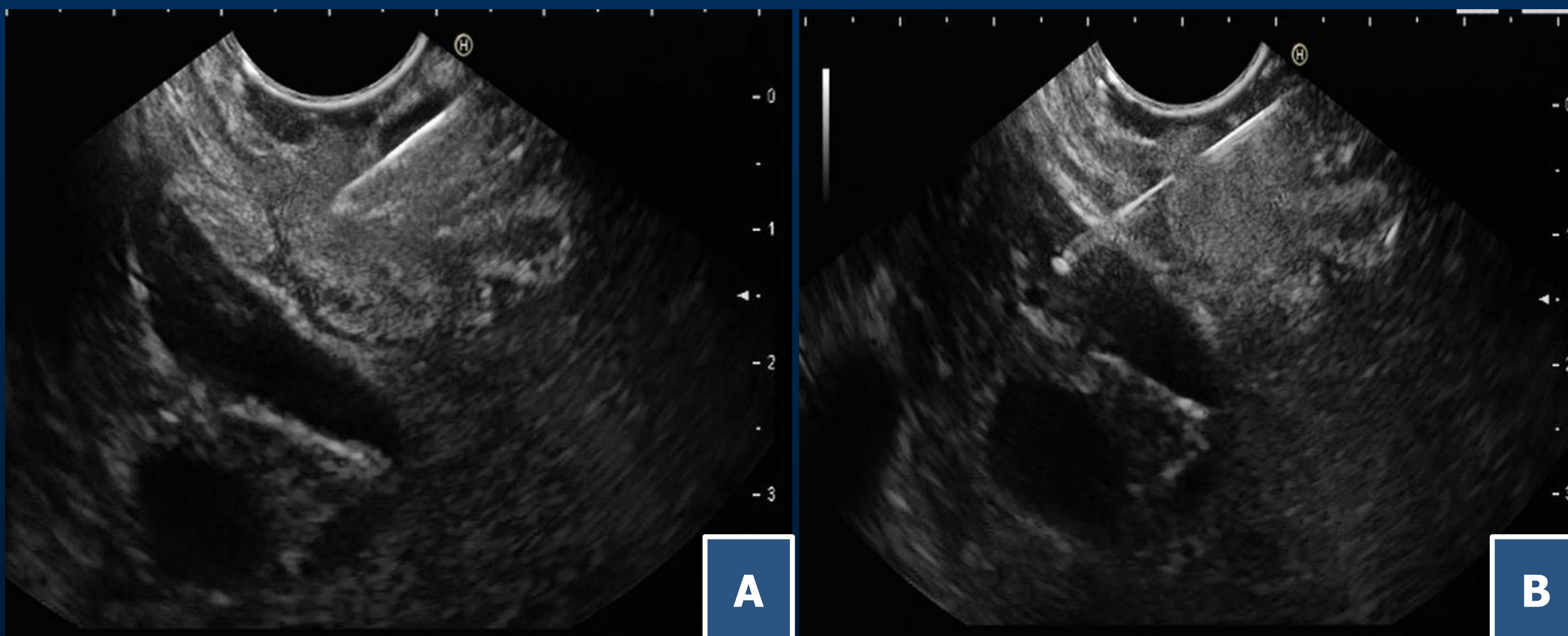
Aims

- 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



EUS Approach



Transjugular HVPG

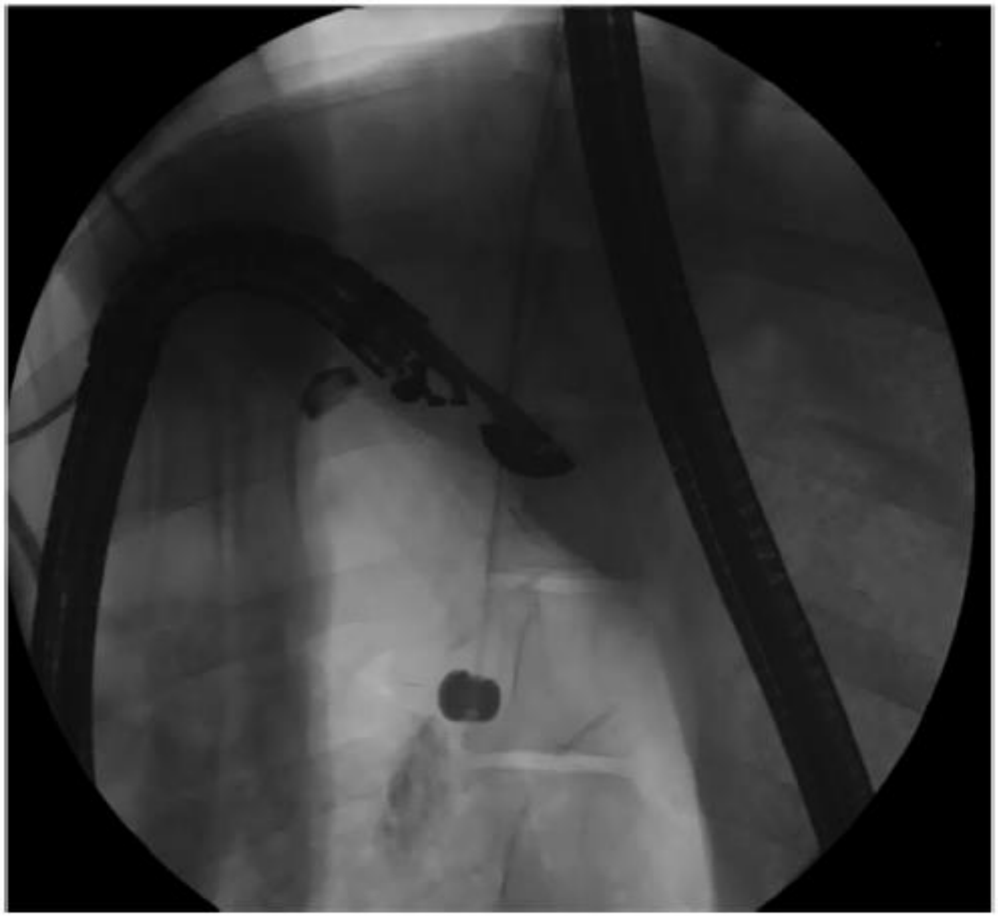


Figure 3. Transjugular catheterization with balloon occlusion catheter perfomed under fluoroscopy.

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 1. Comparison of HVPG measurements and EUS-guided portal pressure measurements in each animal

Pig	HVPG measurement, mm Hg	EUS-guided portal pressure measurement, mm Hg
1	5	5
2	4	5
3	7	7
4	6	5
5	11	10

HVPG, Hepatic venous pressure gradient.

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Results

Equivalent Pressures: Portal vein vs First-Order Venule

Pig Number	Pressure Measurement (mmHg) at Baseline		Pressure Measurement (mmHg) at Day 14	
	Portal Vein	**First order venule**	**Portal Vein**	**First order venule**
1	3	4	5	4
2	10	11	9	9
3	5	4	4	4
4	4	4	5	4
5	6	6	5	7

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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*

	Animals (N = 5)					
Category	**1**	**2**	**3**	**4**	**5**	**Mean**
Mental demand	4	3	2	1	2	2.4
Physical demand	3	2	2	3	2	2.4
Temporal demand	2	1	2	2	1	1.6
Performance	3	2	1	2	1	1.8
Effort	3	2	1	2	2	2.0
Frustration	2	1	2	2	1	1.6
Technical difficulty	3	3	1	2	2	2.2

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).

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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
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  - EUS Elastography
- EUS-Based Hepatobiliary Therapeutics
  - EUS TIPS
  - EUS Gallbladder

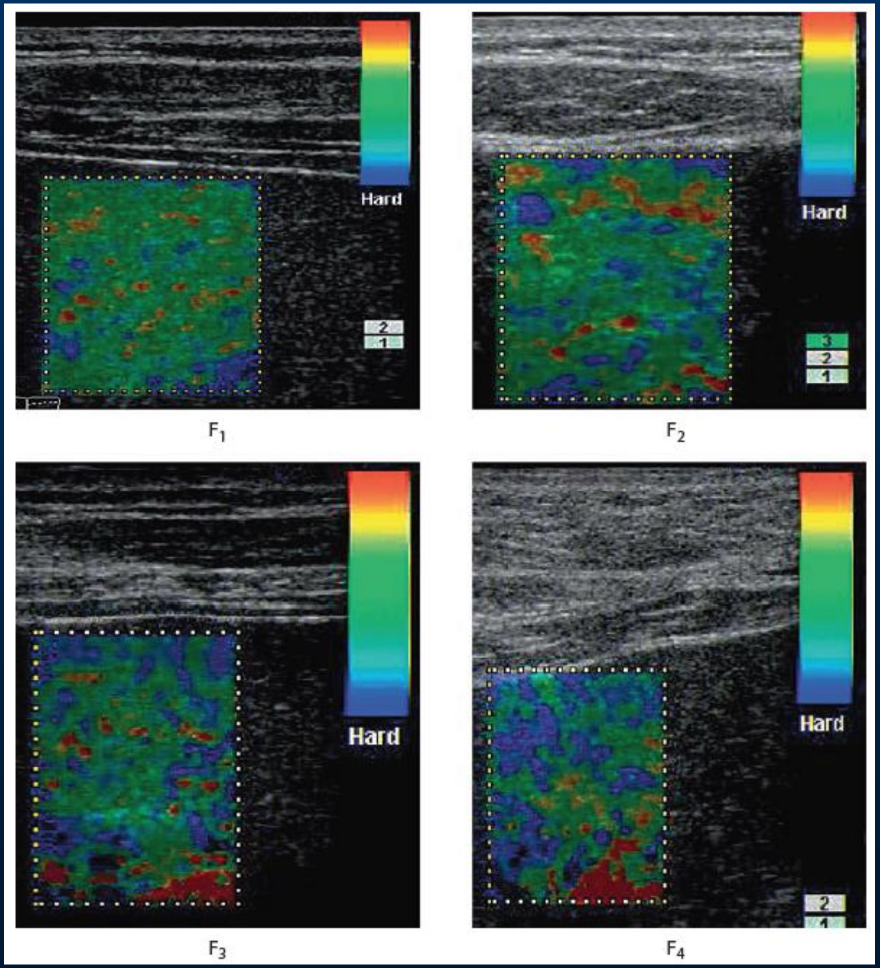
Background

- 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

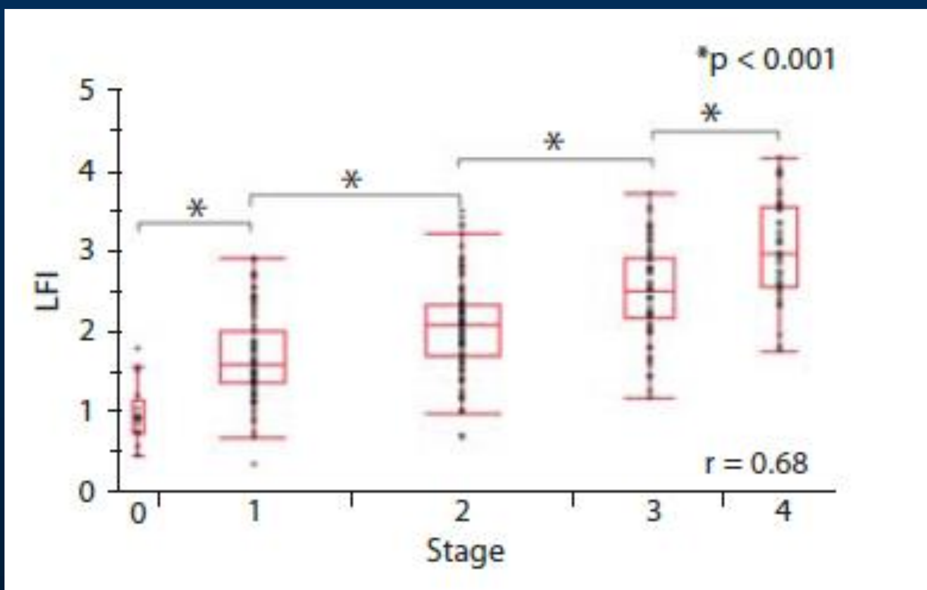
RTE Images for Metavir Scores F1-F4

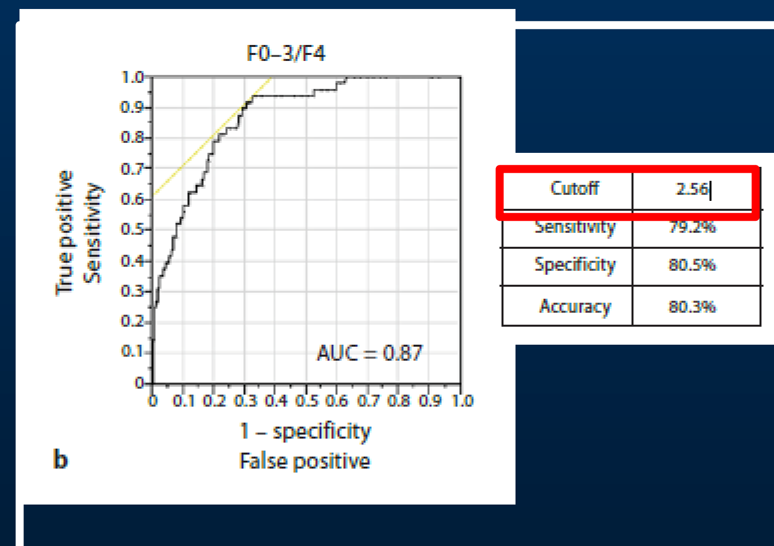


Fujimoto 2012

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

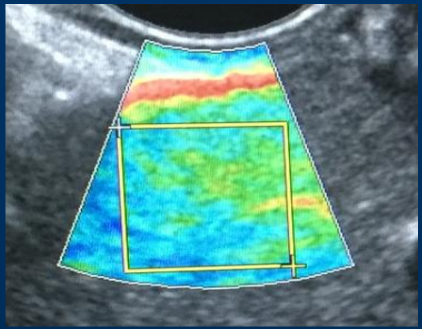
Works in Progress

- 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.

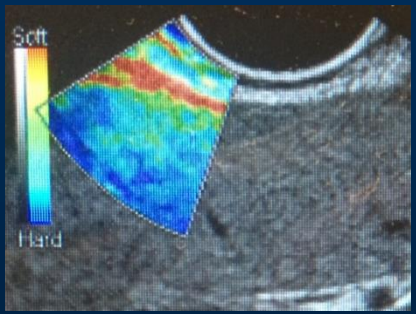
Preliminary Results

- 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

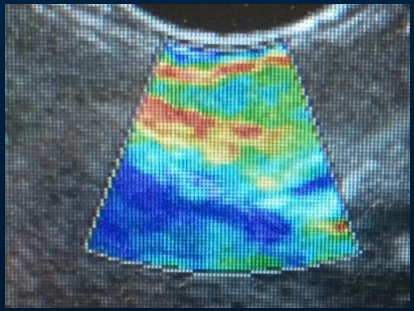
YES



NO



NO



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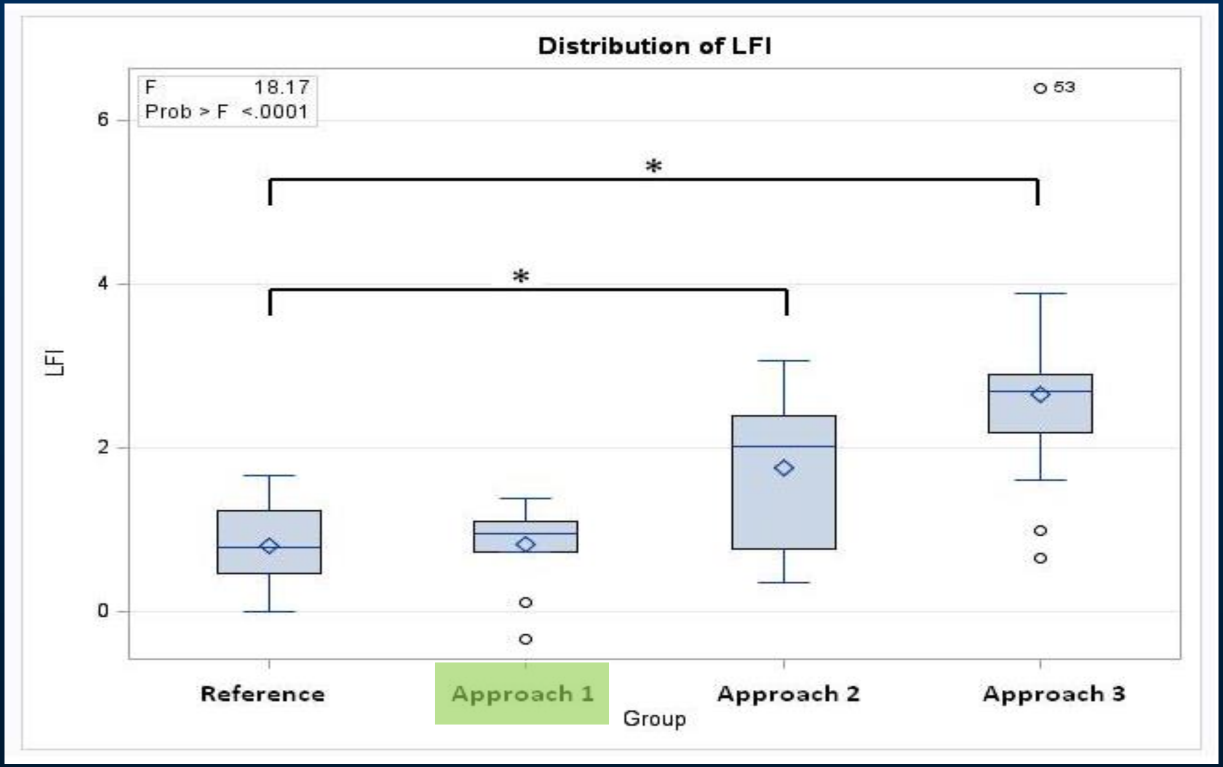
Preliminary Results

- Standardizing EUS Elastography Technique



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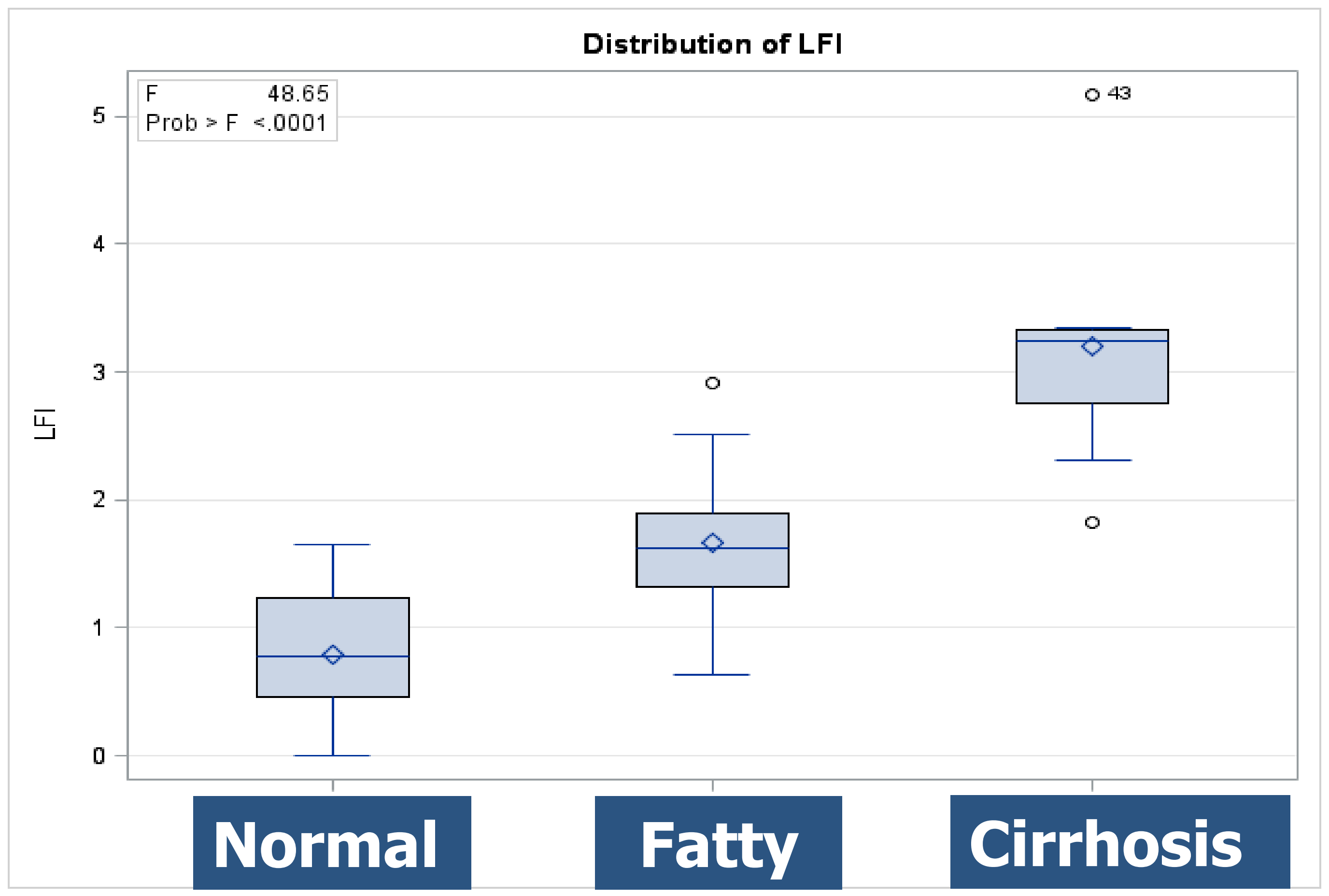
Preliminary Results

- EUS Elastography: Differentiating Normal, Fatty, and Cirrhotic

Group	Number Enrolled	Mean LFI [+/- SD]
Control	39	0.79 [0.6]
Fatty liver	26	1.66 [0.9]
Cirrhosis	10	3.21 [0.9]

Schulman AS, Ryou M. DDW 2016

Preliminary Results



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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)

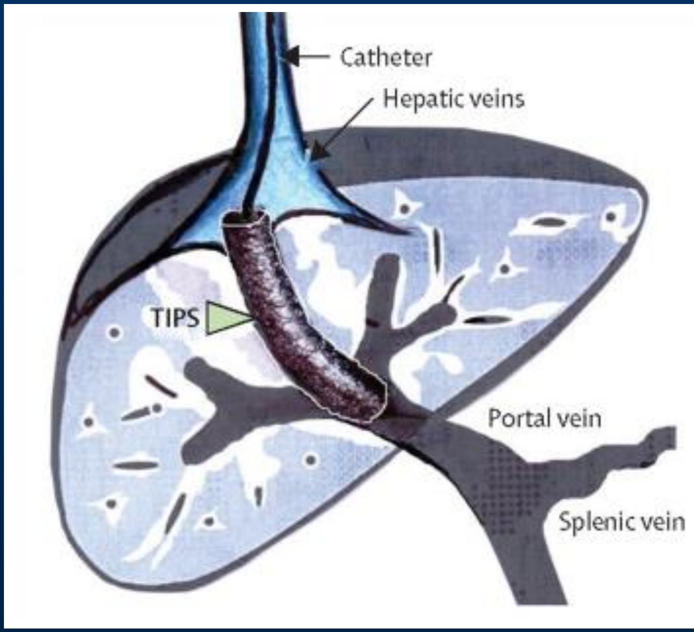
Research Programs

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

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

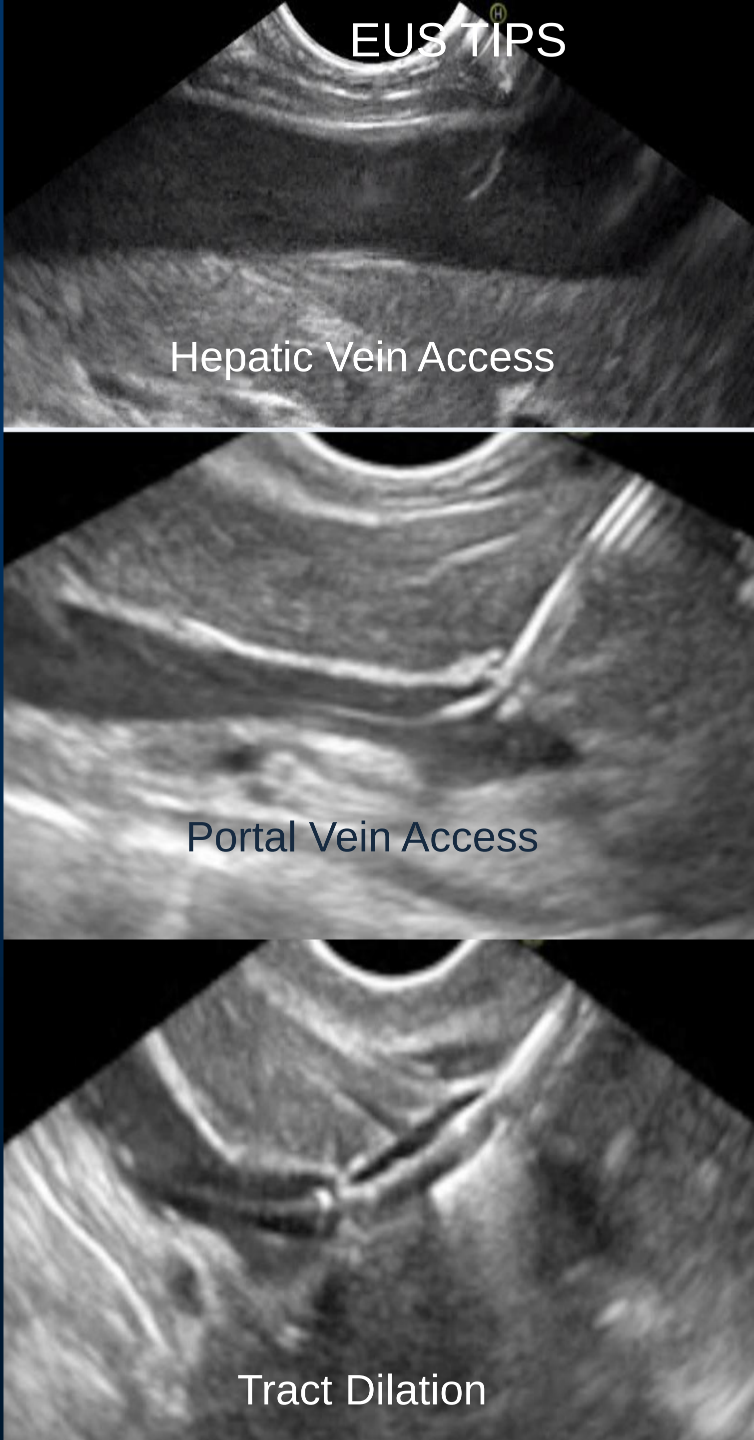
Background

- 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

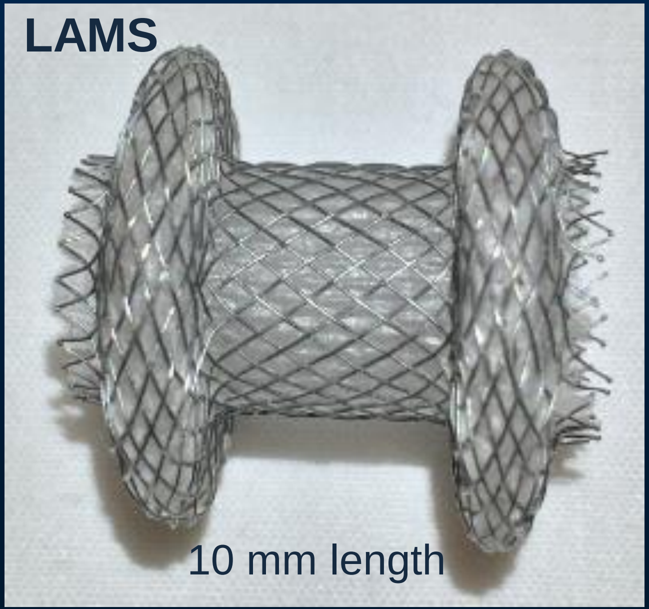
- Endoscopic Intrahepatic Portosystemic Shunt (EIPS)
  - Transgastric access across hepatic vein and portal vein
  - Measure pressures in both
  - Guidewire advanced through needle which is then removed
  - Balloon dilation of tract



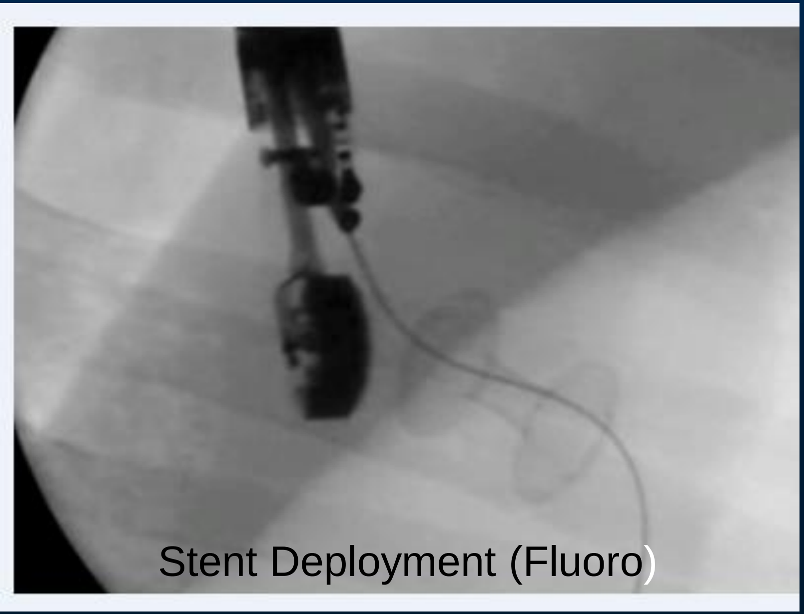
Background

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

Stent Deployment (EUS)

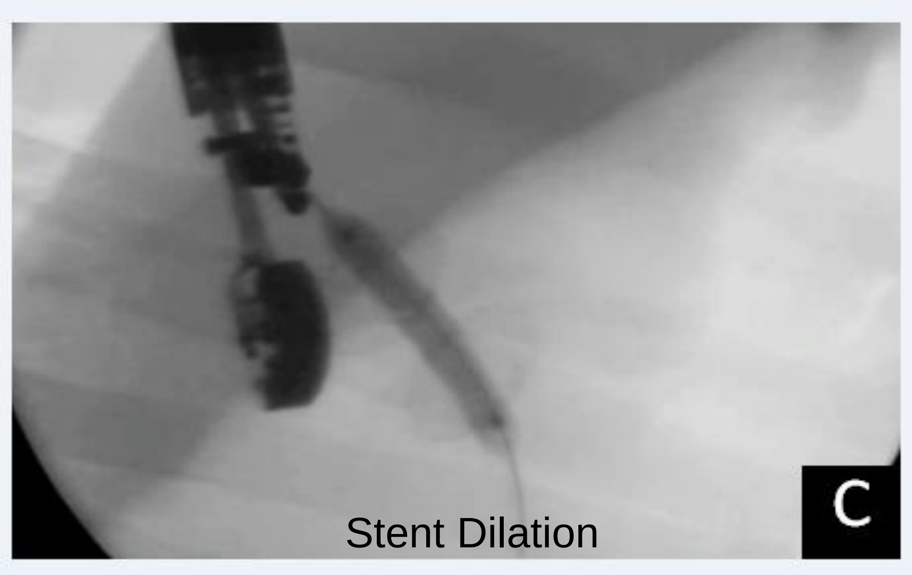

LAMS

10 mm length

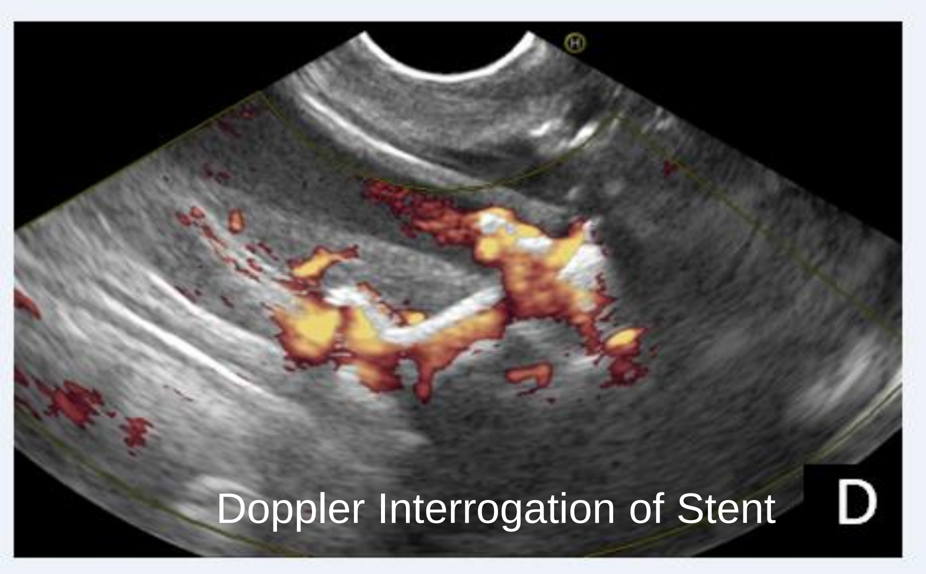

Stent Deployment (Fluoro)

Background

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



Stent Dilation



Doppler Interrogation of Stent

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

EUS TIPS

Schulman AS, Ryou M, Thompson CC. GIE 2016

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

Pig Number	Pressure Measurement (mmHg) at Baseline		Pressure Measurement (mmHg) at Day 14	
	Hepatic Vein	Portal Vein	Hepatic Vein	Portal Vein
1	3	5	4	5
2	5	7	6	7
3	5	6	6	6
4	7	9	7	7
5	5	8	7	6
Mean	5.0	7.0	6.0	6.3

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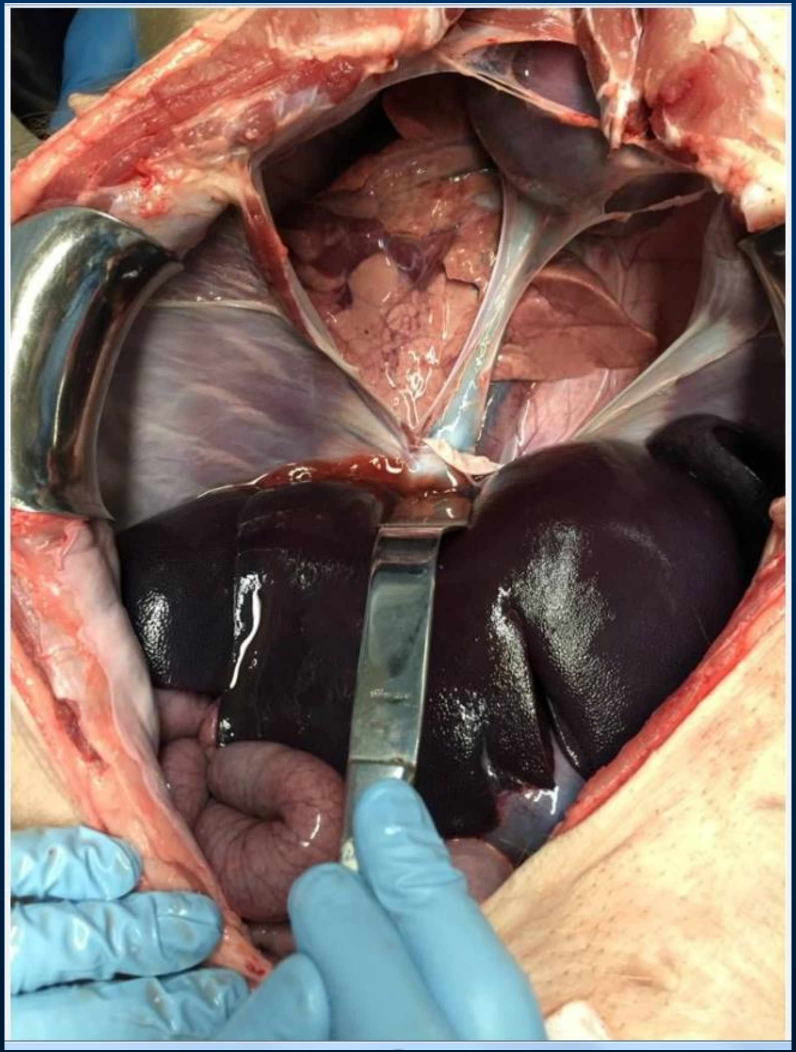
Necropsy

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



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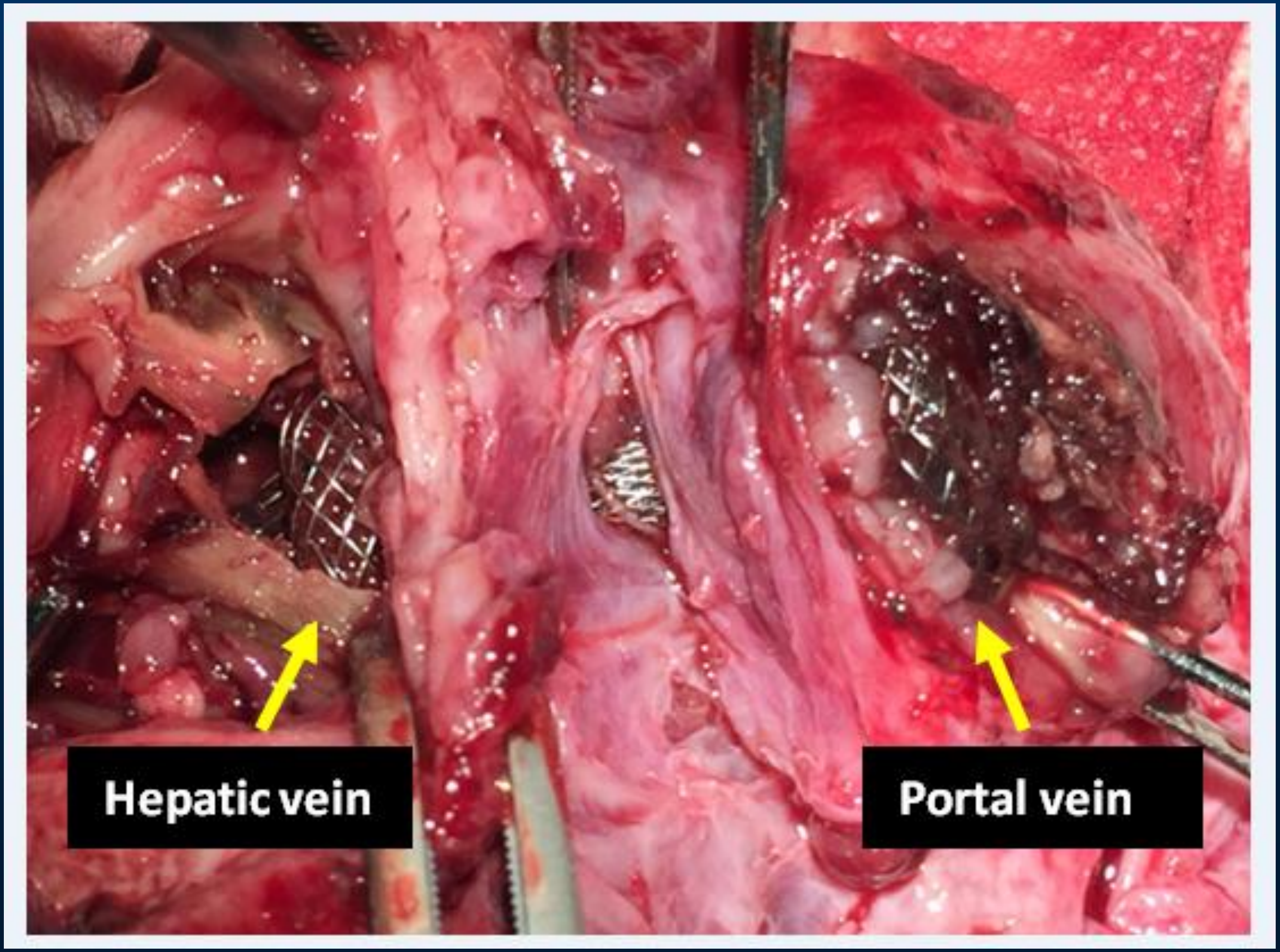
Necropsy



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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
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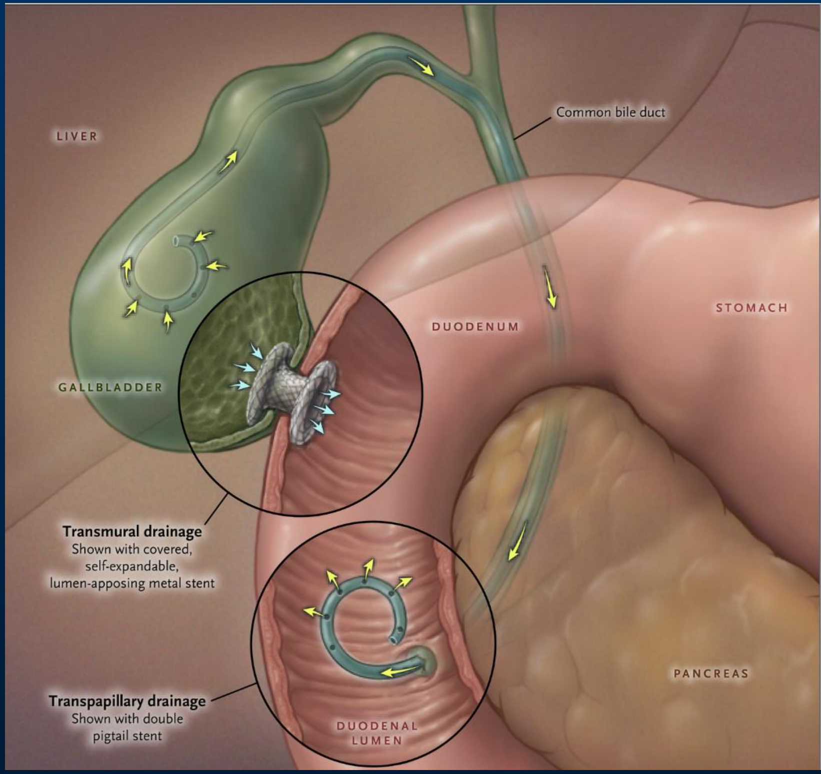
  - EUS Elastography
- EUS-Based Hepatobiliary Therapeutics
  - EUS TIPS
  - EUS Gallbladder

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

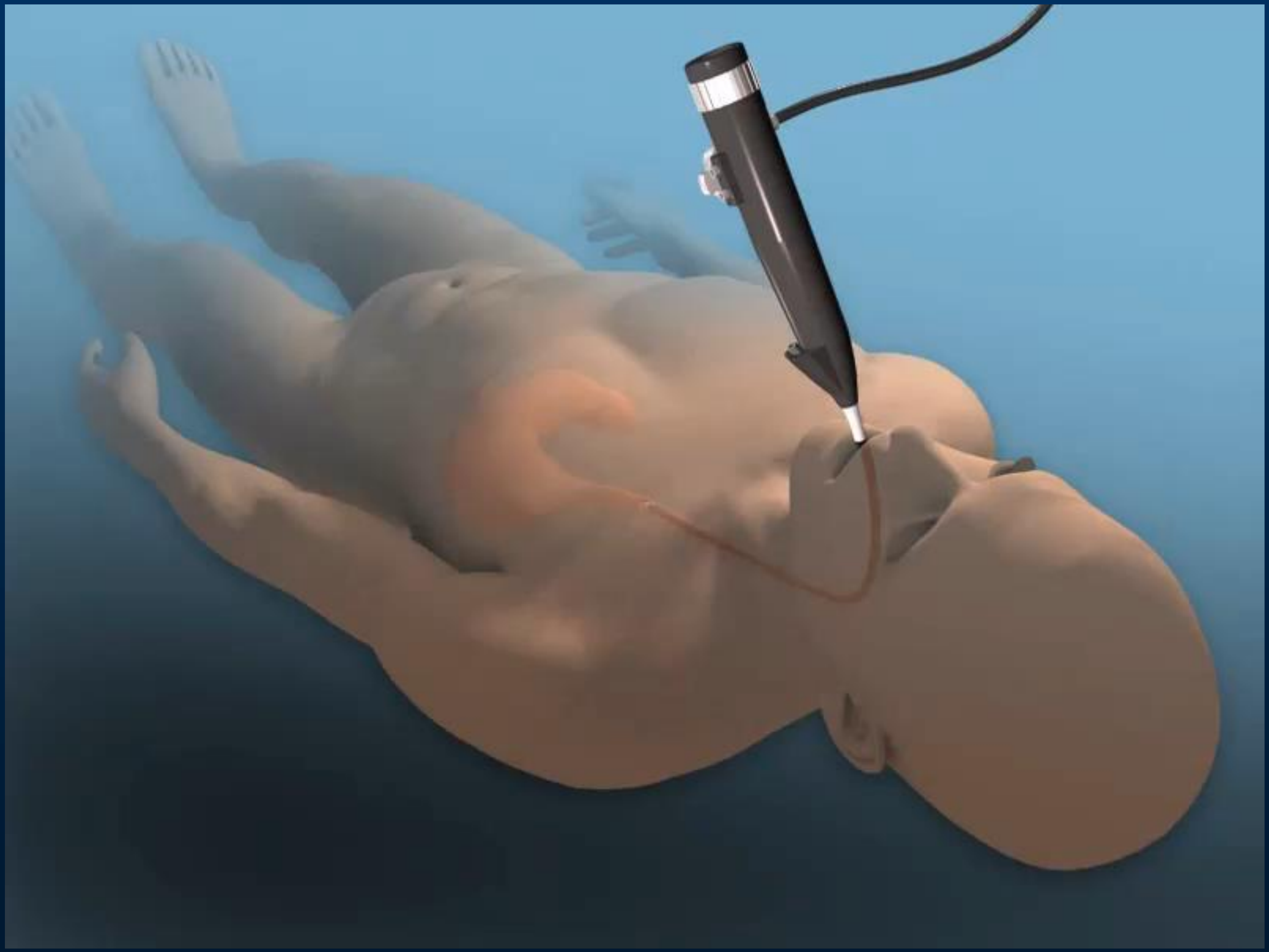
Jejuno-Ileal Anastomosis Creation

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

Ryou M, Thompson CC. GIE 2015

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