Advances in the Endoscopic Evaluation of PSC

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PSC: Definition

A chronic, progressive destructive biliary disease of unknown cause, characterized by multiple, fibrosing, inflammatory strictures of the extra hepatic and/or intrahepatic bile ducts.

Bergquist and Broomé

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Role of ERC in PSC

- Diagnosing PSC
- Managing complications of PSC
  - Bile duct stones
  - Acute cholangitis
  - Dominant strictures
- Diagnosing cholangiocarcinoma

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DIAGNOSING CCA IN PSC

- Cholangiocarcinoma may develop in 15% patients with PSC.
- Desmoplastic nature of tumor and presence of multiple non-neoplastic strictures makes diagnosis challenging.
- Risks highest in first years after diagnosis.

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DIAGNOSING CCA IN PSC: Tissue Sampling

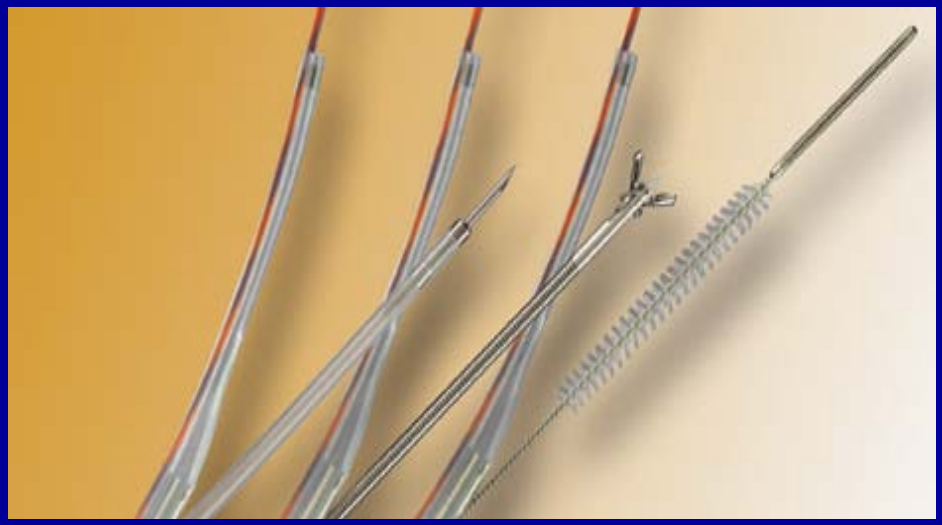
- **Brush Cytology**
- **Needle (FNA)**
- **Forceps**

All with low sensitivity

All with high specificity

Multi-modal increases sens

Forceps best for bile duct CA



Highly suspicious for cancer does not equal cancer in PSC

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DIAGNOSING CCA IN PSC:
Strategies to improve diagnostic accuracy

- Multimodal tissue sampling
- Serum tumor markers
- Improvement in analysis of tissue obtained???
- New imaging modalities

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DIAGNOSING CCA IN PSC

Siqueira et al Gastrointest Endosc 2002;56:40

Clinical Characteristics of PSC Patients with and without CCA

Characteristics	CCA + PSC (n=44)	PSC (n=289)	*p*
Duration of PSC (yrs) Mean ± SD Median	 2.86 ± 2.35 2	 4.90 ± 4.49 4	 0.03*
IBD n(%)	32 (72.7)	229 (79.2)	0.33#
Age (yrs) Mean ± SD Median	 43.54 ± 12.22 43	 41.58 ± 11.82 43	 0.55*
Male %	77	69	

*Comparisons by Mann-Whitney U test.

#Comparisons by X^2 test.

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DIAGNOSING CCA IN PSC: Tissue Sampling

Performance Characteristics of BC for Diagnosing CCA Based on the Number of Sampling Sessions

	Results (%)		
	1 BC	2 BC	≥ 3BC
Sensitivity	32.1	39.2	46.4
Specificity	100	100	100
Positive Predictive Value	100	100	100
Negative Predictive Value	86.6	87.8	89.1
Accuracy	87.4	88.7	90.1

Of 151 patients undergoing brush cytology, 72 (47.7%) had 1 BC while the remainder had 2 or more with a mean of 2.1 sessions/patient and a range of 1-10.

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DIAGNOSING CCA IN PSC: Tumor Markers

CEA and CA19-9 Serum Levels in PSC Patients With and Without CCA

	PSC + CCA		PSC	
	CEA (n=25) ng/mL	CA19-9 (n=12) U/mL	CEA (n-119) ng/mL	CA19-9 (n=43) U/mL
Mean ± SD	68.4 ± 206.7	5994 ± 11521.5	3.5 ± 2.8*	66.7 ± 128.7*
Median	8.2	377.1	2.9	39.1
Range	0.7 – 959	6.5 – 34600	0.7 – 16.7	0.2 - 839

*p<0.01 compared to patients with CCA by Mann-Whitney U test.

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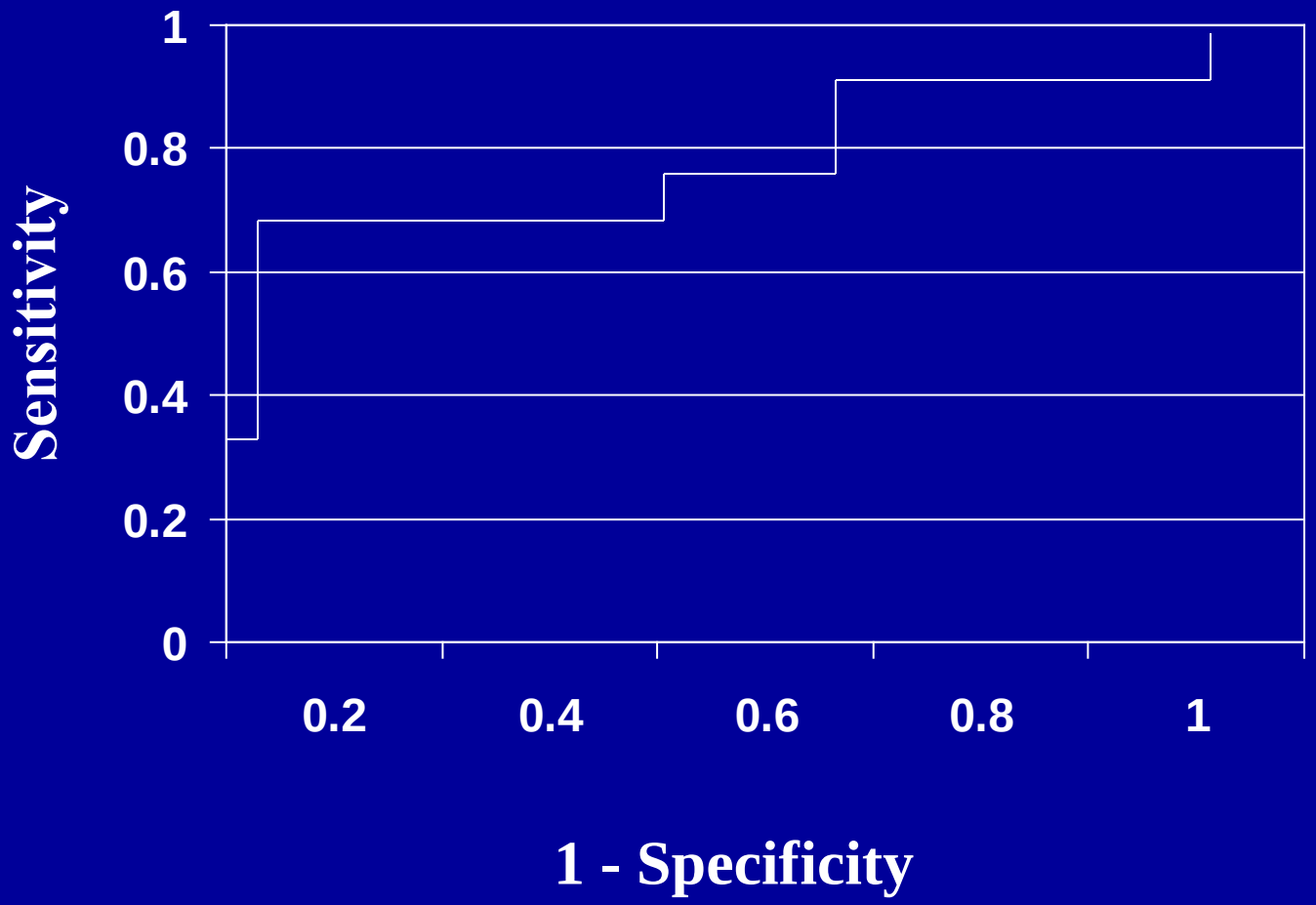
DIAGNOSING CCA IN PSC: ROC CA19-9; cut point 180 U/mL



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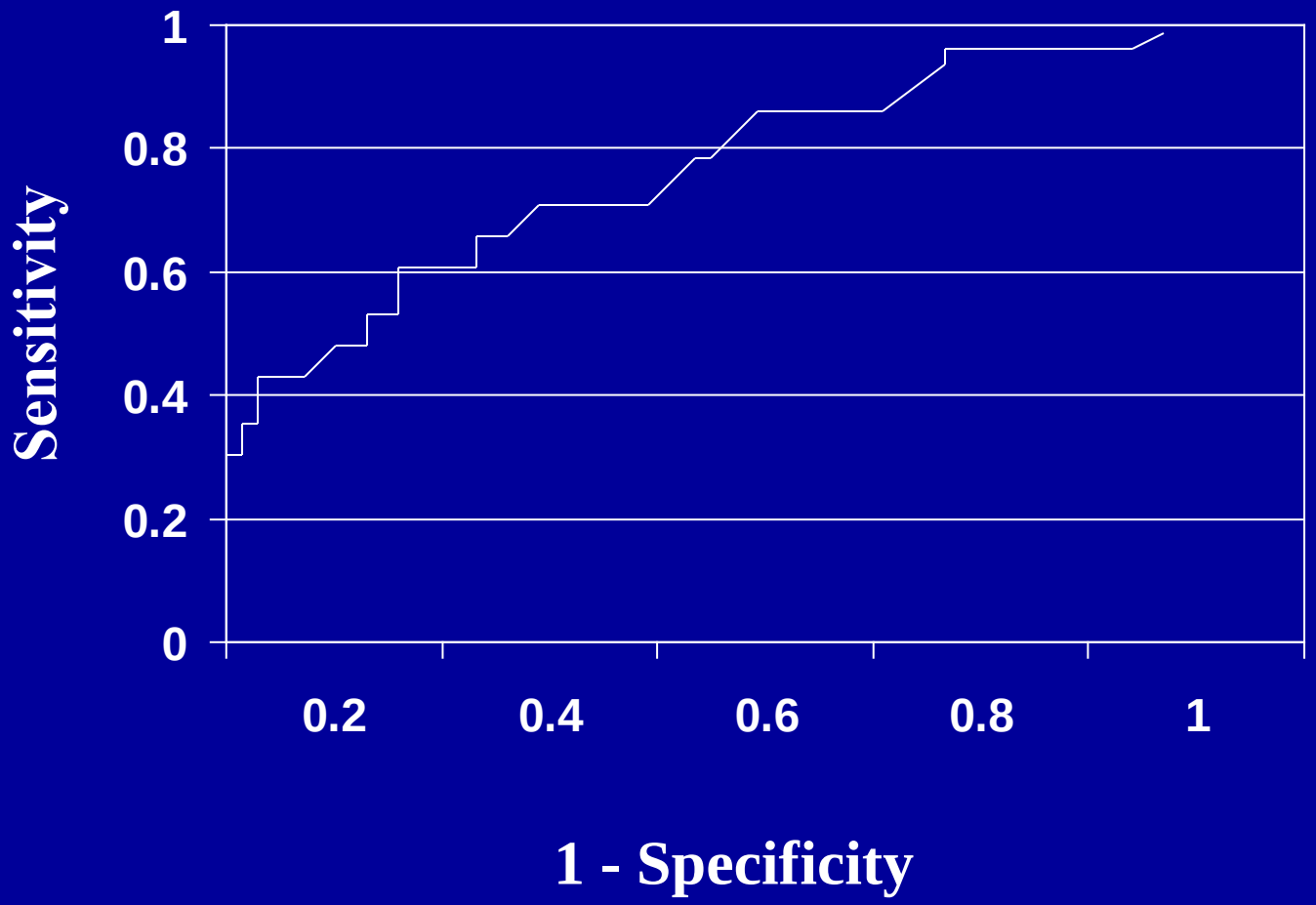
DIAGNOSING CCA IN PSC: ROC CEA; cut point 5 ng/mL



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DIAGNOSING CCA IN PSC:

Performance Characteristics of Brush Cytology and Serum Tumor Markers for Diagnosing CCA (n=45)

	BC	CEA	CA19-9	CA19-9 or BC	CEA or CA19-9	BC or CEA
Sens (%)	37.5	62.5	75.0	87.5	100	87.5
Spec (%)	100	78.4	97.3	97.3	78.4	78.4
PPV (%)	100	38.5	85.7	87.5	50.0	46.7
NPV (%)	88.1	90.5	94.7	97.3	100	96.7
ACC (%)	88.8	75.5	93.3	95.6	82.2	80.0

Sens=sensitivity; PPV=positive predictive value; NPV=negative predictive value; ACC=accuracy

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DIAGNOSING CCA IN PSC: Beyond routine cytology

- Flow cytometry
- FISH
- KRAS
- LOH
- Oncogenes

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DIAGNOSING CCA IN PSC
Novel imaging:PET

Keiding et al Hepatology 1999;28:700

- FDG-PET was able to differentiate 6 pts with psc/cca from 9 psc and 5 controls.

Prytz et al Hepatology 2006;44:1572

- FDG-PET in 24 psc pts without evid CCA 2 weeks prior to OLTx.
- 3 pts with CCA correctly identified (blinded).
- PET neg in HGD (n=1).
- 1 false positive PET (epitheliod granuloma).

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DIAGNOSING CCA IN PSC
Novel imaging:Cholangioscopy

Tischendorf Endoscopy 2006;38:665

- **Prospective study of 53 PSC pts with dominant strictures.**
- **Cholangiography performed with a 9Fr scope and videotaped.**
- **Subsequent tissue sampling routine.**
- **Video's scored 1=benign, 2=probably benign, 3=probably malignant, 4=malignant.**

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DIAGNOSING CCA IN PSC
Novel imaging:Cholangioscopy

Tischendorf Endoscopy 2006;38:665

- **Malignant features=polypoid mass, villous mass, or irregular ulceration.**
- **12/53 pts (23%) had CCA.**
- **Cholangioscopy identified 11/12 CCA pts and 38/41 non-CCA pts**

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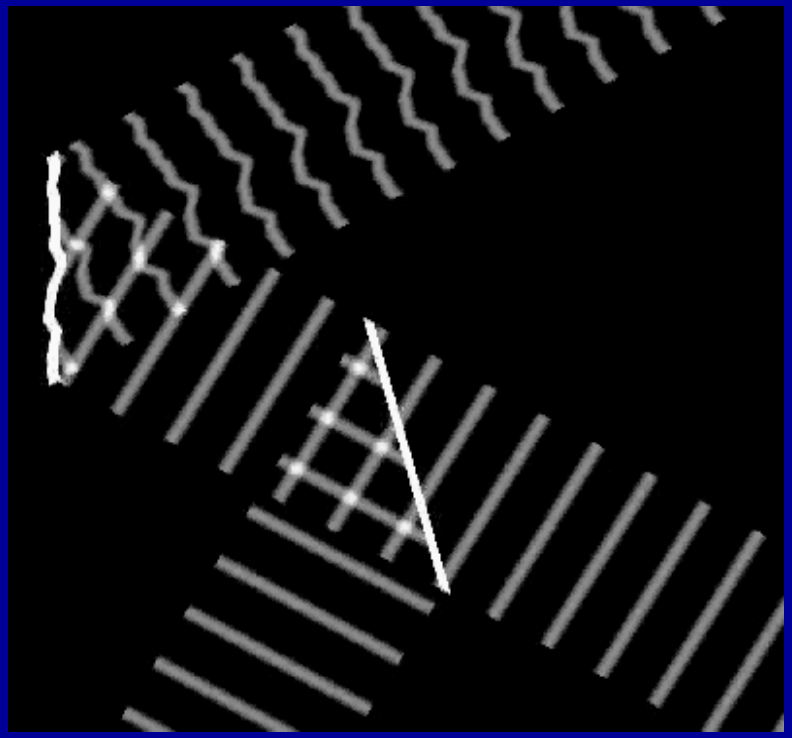
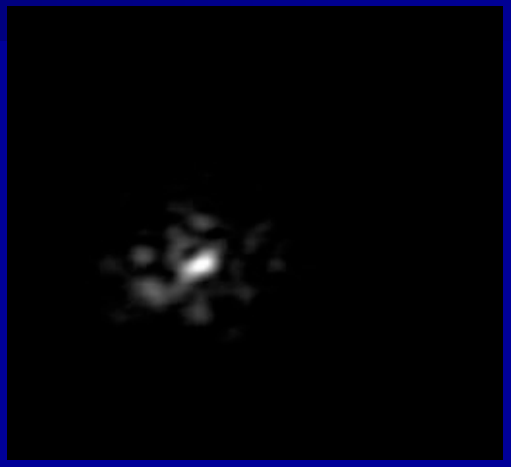
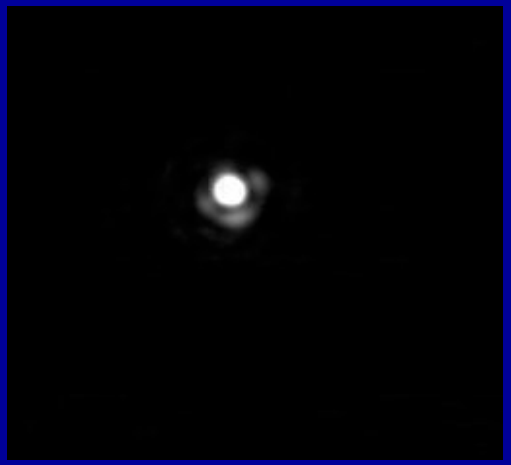
Adaptive Optics







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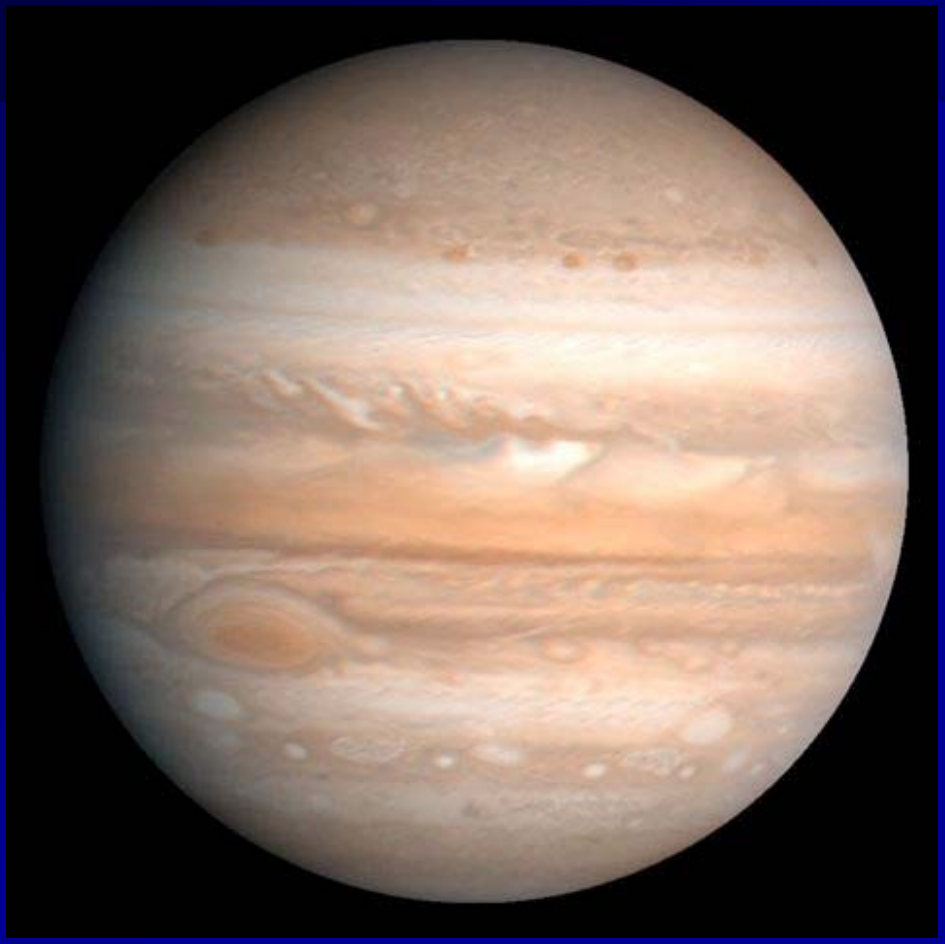
Jupiter



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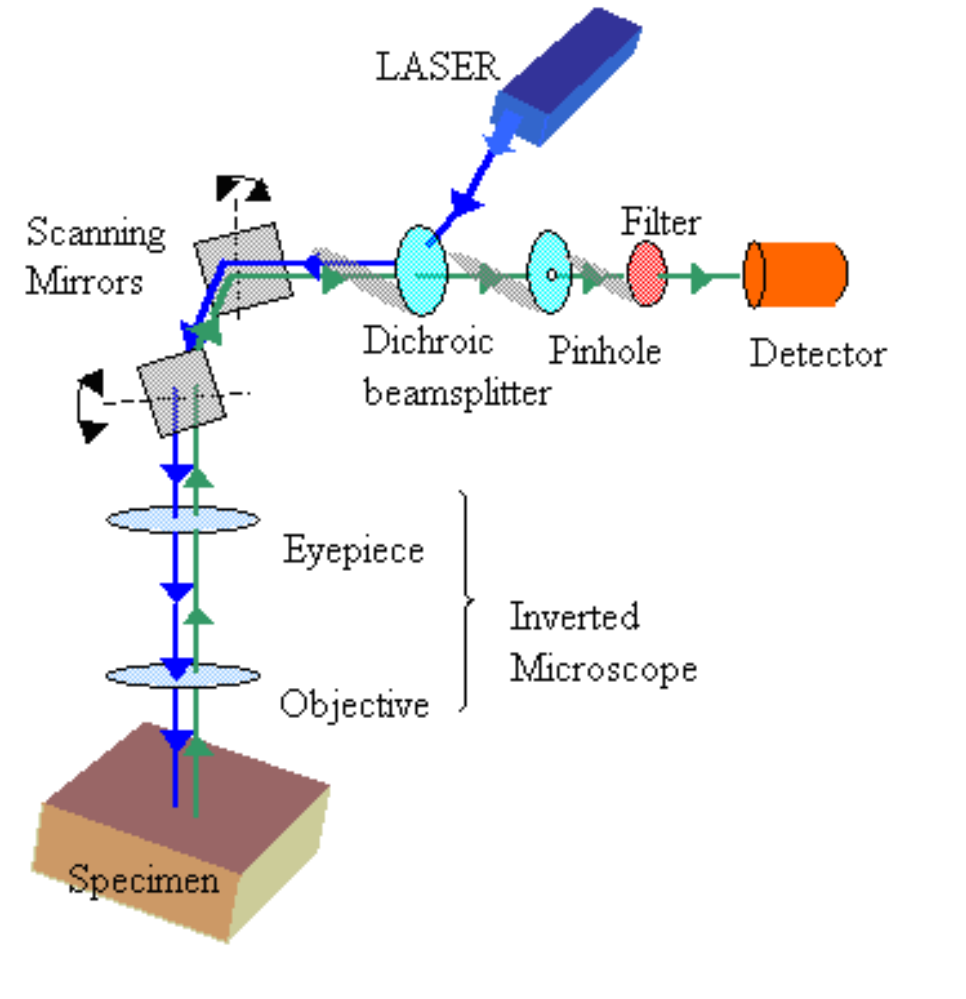
Confocal Microscopy



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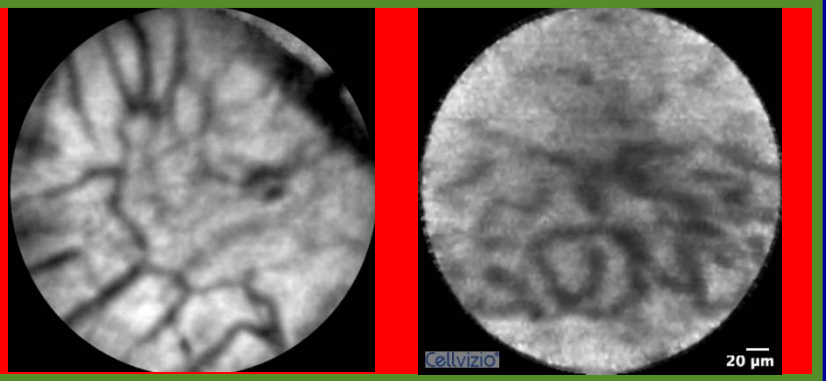
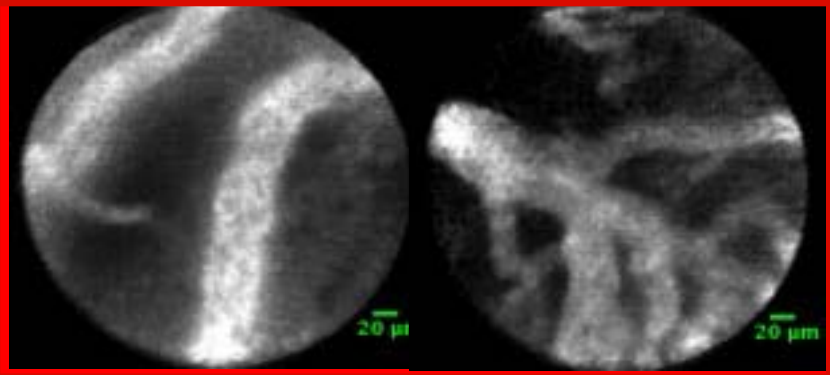
Diagnosing CCA
Confocal microscopy

Meining et al Clin Gastro Hep 2008

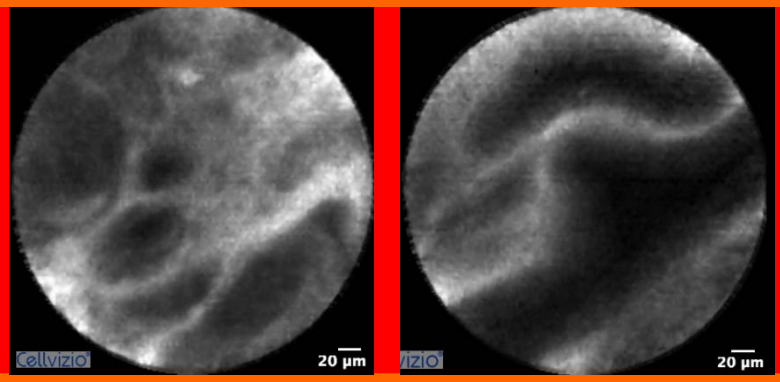
Normal Cells

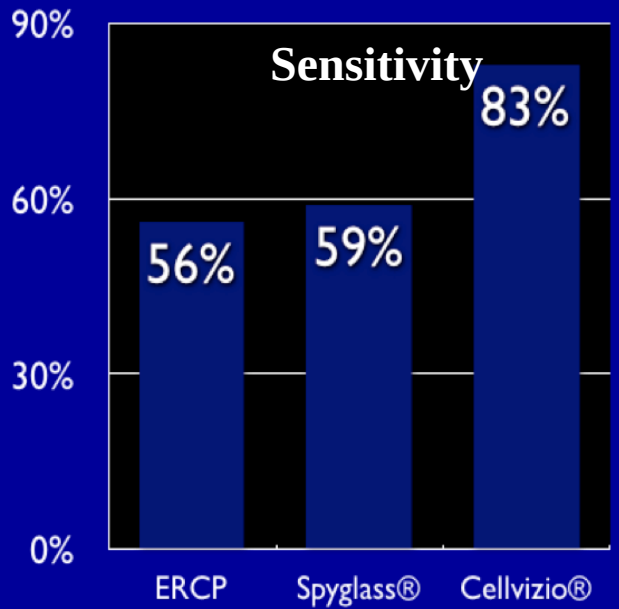


Abnormal Vessels



Abnormal Cells





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Prospective Series 2012

- **49 Benign : 40 malignant**

- **Bile duct malignancy detection**

	pCLE	Index pathology
Sensitivity	**98 %**	**45 %**
Specificity	67 %	100 %
PPV	71 %	100 %
NPV	**97 %**	69 %
Overall accuracy	81 %	75 %

- pCLE detected **39** malignant patients out of **40**, in real time
- Index pathology detected **18** malignant patients out of **40**

16 false positive patients identified with pCLE
No adverse events attributed to pCLE ocurred

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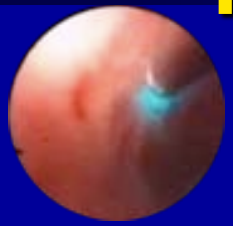
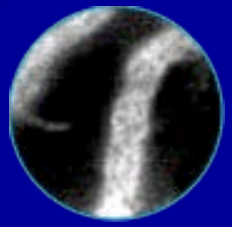
Conclusions: pCLE for diagnosing malignancy in indeterminant PB strictures



Cholangioscopy

Fluoroscopy



- Showed improved sensitivity compared to conventional pathology
- Allowed more patients to have CA detected early
- Can be delivered through a cholangioscope or catheter
- More work needed to reduce false positives

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pCLE in PSC

- Registry now open
- UPMC, U Denver, Yale, Columbia, Cornell, Rome, Marseilles

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DIAGNOSING CCA IN PSC: CONTROVERSIES

- Does screening tumor markers make sense?
- Will molecular markers allow for premalignant diagnoses?
- What are the performance characteristics of direct cholangioscopy and pCLE of dominant strictures for diagnosing CCA?
- Diagnosing cholangiocarcinoma in PSC is usually a death sentence. How hard do we push?
- Should PSC pts be transplanted for prophylaxis against CCA?
- Should transplant be used as an oncologic procedure?
- What is the role of living related donor transplants in PSC with possible CCA?

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