Diagnosis and Management of Primary Sclerosing Cholangitis:

The Role of the Endoscopist

Adam Slivka MD-PhD
Associate Chief of the Division
Gastroenterology Hepatology and Nutrition
University of Pittsburgh Medical Center

Role of ERC in PSC

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

PSC: Diagnosis

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

PSC:Diagnosis

- **Diagnosis:**
  - **Clinical**
  - **Biochemical**
  - **Histologic**
  - **RADIOLOGICAL**
    - Irregularity and beading of the intrahepatic or extrahepatic bile ducts.
    - ERC vs MRC vs PTC

PSC:Diagnosis

MRCP

- Non-invasive
- Operator dependent
- Accuracy < 100%
- Non-therapeutic
- No sampling

ERCP

- Invasive
- Operator dependent
- Gold standard
- Therapeutic
- Tissue sampling
- Stage portal HTN

PSC:Diagnosis
MRCP in PSC

Study	N	Sens	Spec	Acc
Ferrara et al Pediatr Radiol 2002;32:413	21	81%	100%	85%
Angulo et al J Hepatol 2000;33:659	73	NR	NR	90%
Textor et al Endoscopy 2002;34:984	150	88%	99%	NR
Weber et al Rofo Fortsch Geb Rontgenstr 2003;175:203	55	97%	64%	84%

PSC:Diagnosis

PSC:Diagnosis

- **Exclude secondary biliary sclerosis**
  - **Biliary Surgery**
  - **Biliary Stones**
  - **Biliary Neoplasms**
  - **Hepatic artery injury**
  - **Intra hepatic arterial FUDR**
  - **HIV Cholangiopathy**

Intra-hepatic artery FUDR

PSC:Diagnosis

Beware of radiologic "look a likes"

Cirrhosis

HCC

Polycystic Liver Disease

Sub massive necrosis

Histocytosis X

Amyloid

Intrahepatic PV Thrombosis

Liver Mets

Leukemia

Lymphoma

Inflammatory pseudo tumors

Endoscopic Therapy in PSC

- **Treatment Endoscopic:**
    - **Acute cholangitis**
    - **Stones**
    - **Dominant strictures (seen in up to 50% pts but no consensus definition) with or without symptoms**

Endoscopic Therapy in PSC

- **Initially limited to acute cholangitis (stents or nasobiliary drains).**

- **Stone extraction can be performed effectively but may be challenging with stone above stricture.**

- **Treatment of "dominant stricture": Multiple non-controlled series reporting positive responses for stents $\pm$ dilation.**

- **Early experience with high incidence of complications, mainly infectious.**

Endoscopic Therapy: Dominant Strictures

Ponsioen et al Am J Gastroenterol 1999;94:2403

- 32 patients with PSC and dominant stricture.
- All treated with stenting 10Fr (n=21) 7Fr then 10Fr (n=6) 7Fr (n=5).
- 5 patients underwent balloon dilation.
- Stents removed mean=11days (range 1-23days).
- Scores for pruritus, fatigue and pain improved in 83%.
- Jaundice resolved in 12/14 and lft significantly decreased.
- 80% and 60% intervention-free at 1 and 3yrs.
- 15% complication rate (none severe).

Endoscopic Therapy: Dominant Strictures

Baluyut et al Gastrointest Endosc 2001;53:308

- **Retrospective study of 63 pts with dominant strictures.**

- **Dilations performed with balloons (61) or catheters (2).**

- **Stents used for poor fluoroscopic response to dilation (32).**

- **Median f/u 34 months.**

- **Predicted 5yr survival by Kaplan-Meier was greater than estimated survival by Mayo model (within 3mos prior to ERCP)**

Endoscopic Therapy of PSC: Are we altering natural history of disease?

Critique of Baluyut et al:

- **Used the Mayo Risk Score which was designed to follow progression of disease over years:**

- **R=(0.03 Age,yrs) + (0.54 log(e) Bili mg/dL) + (0.54 log(e) AST U/mL) + (1.24 Bleed hx) – (0.84 Albumin gm/dL)**

- **This will be profoundly impacted acutely (days) by stenting a dominant stricture.**

- **Is it an appropriate use of this instrument?**

Endoscopic Therapy: Dominant Strictures

Stiehl et al J Hepatol 2002;36:151-156

- **Prospective experience with 106 PSC pts on 15mg/kg URSO followed for a median of 5 yrs.**

- **Dominant strictures in 10% at enrollment and 40% in follow-up defined as <1.5mm extra and <1mm intrahepatic.**

- **All treated with balloon dil and short-course stents.**

- **Observed survival by Kaplan Meier > than predicted survival by old Mayo score.**

Endoscopic Therapy: Dominant Strictures

Critique:

Stiehl et al J Hepatol 2002;36:151-156

- "Attempts to use the more recent Mayo survival model…… were not successful. ….the majority of our patients had a negative risk factor with the updated Mayo model which indicates improved survival. ….we concluded that this model is not applicable…

Endoscopic Therapy: Dominant Strictures

Bjornsson et al Am J Gastroenterol 2004;99:502

- **125 pts with PSC**
- **DS defined as $\leq$1.5mm in CBD and $\leq$ 1mm IHD (irregardless of the status of the pre-stenotic biliary tree), and was seen in 45% pts.**
- **No difference in change in ALP and bili pre ERC and 1 yr later in pts with or without DS, independent of endoscopic therapy (n=9).**
- **Authors conclude endoscopic therapy of DS should not be "routine".**
- **I conclude that these were not "dominant" strictures.**

Dilation of Dominant Strictures in PSC: technical notes

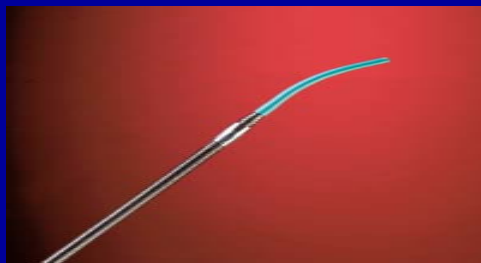- ## Catheters

Pro
Easy
Wire-guide
Inexpensive

Con
Limited diameter
Limited force

- ## Screw Catheter
Refractory strictures

- ## Balloons

Pro
Easy
Wire-guide
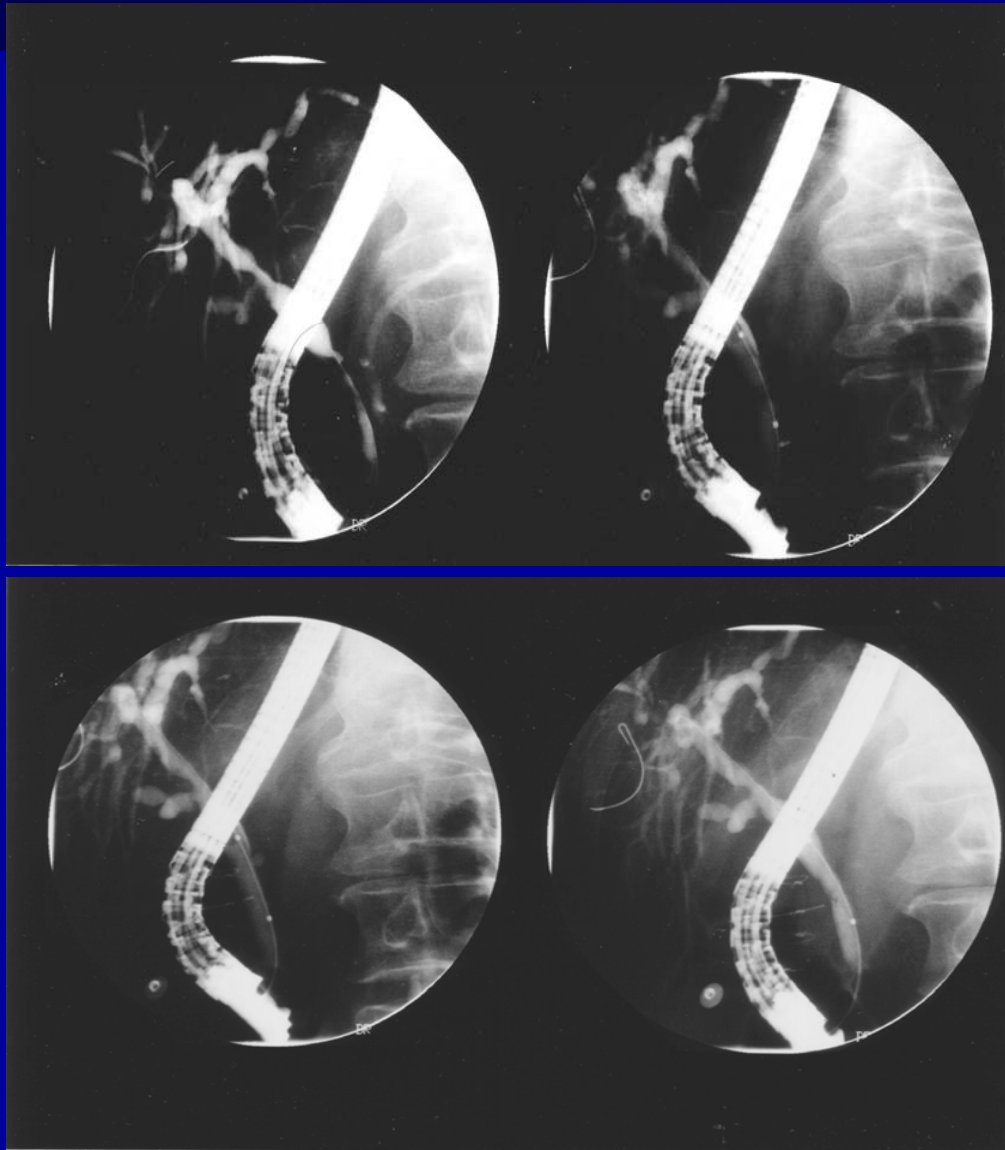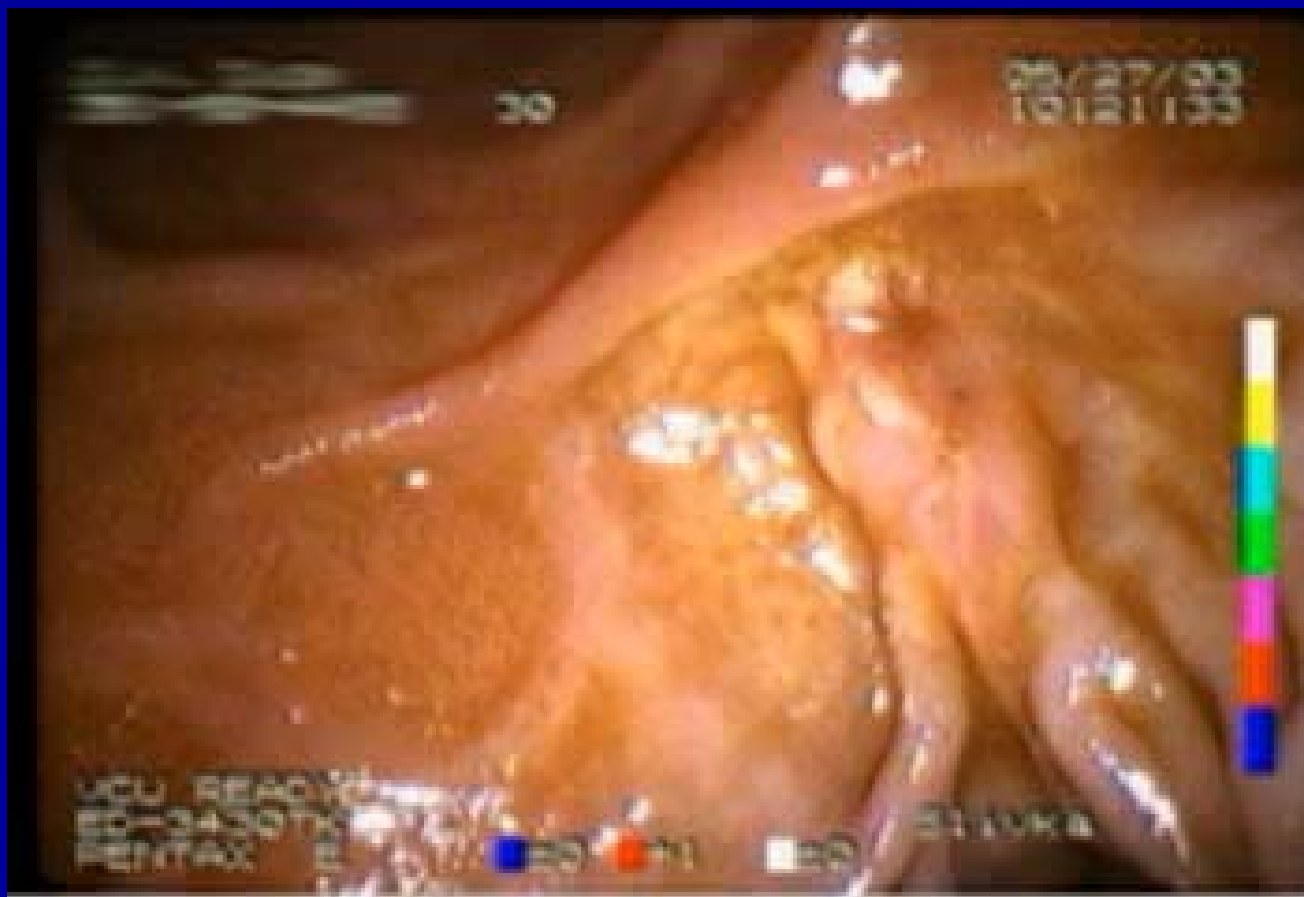Larger diameter/Greater force

Con
Expensive
Bends in duct

Balloon Dilation of Dominant Stricture in PSC

Catheter dilation in PSC

Balloon dilation of dominant stricture

Endoscopic Therapy of Dominant Strictures:Summary

- **Dominant strictures in PSC can be treated at ERC.**

- **More important than the stricture is the state of the prestenotic biliary tree.**

- **Tissue sampling and liberal antibiotics are mandatory.**

- **I reserve treatment for patients with symptomatic jaundice.**

Endoscopic Therapy of Dominant Strictures:Summary

- **Concomitant dilation with stenting may improve results.**

- **Long term stenting has been reported anecdotally, I avoid.**

- **I prefer balloon dilation and short term (10-14 day) stenting.**

- **I avoid sphincterotomy if possible.**

- **No convincing data we are altering long term natural history.**

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.**
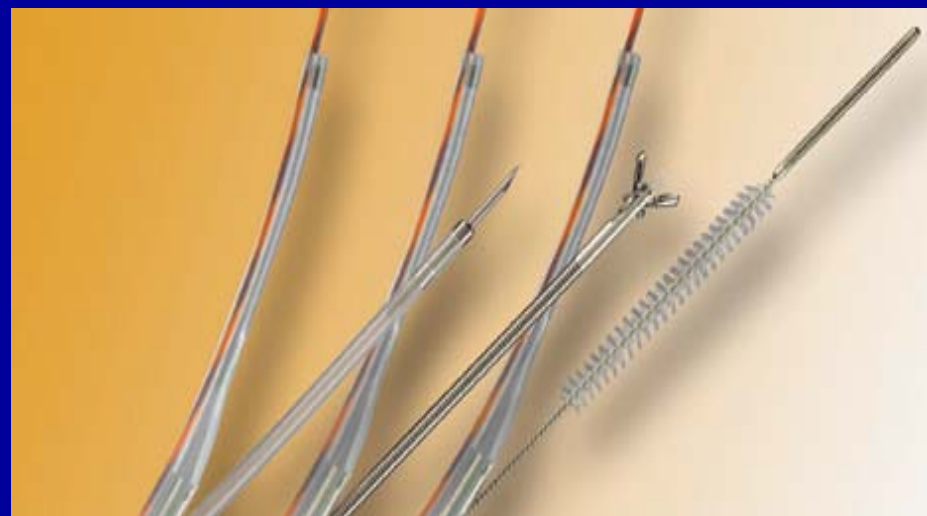
DIAGNOSING CCA IN PSC: Tissue Sampling

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

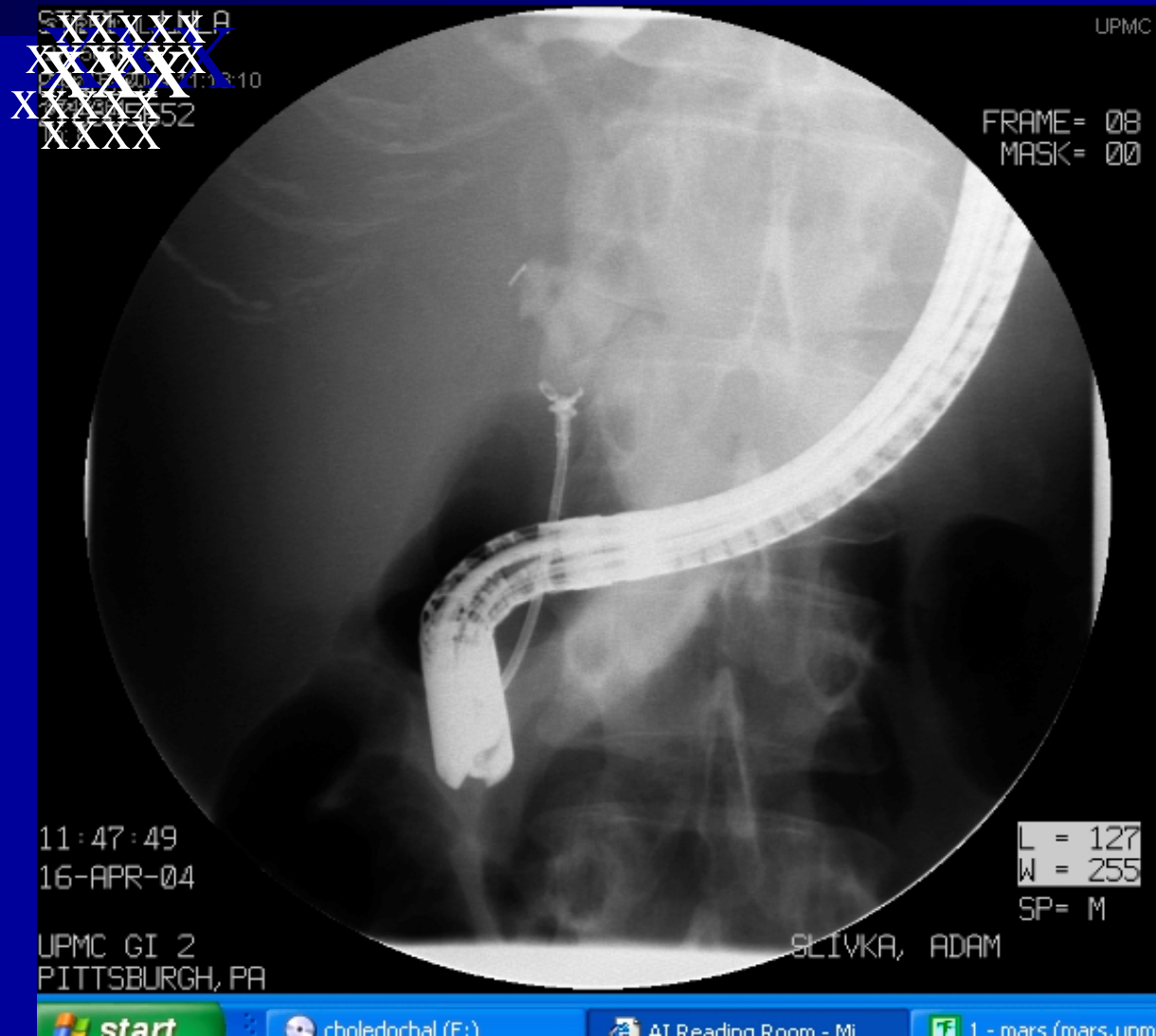**All with low sensitivity**

All with high specificity

Multi-modal increases sens

Forceps best for bile duct CA

Highly suspicious for cancer does not equal cancer in PSC

Dominant Stricture: Forceps biopsy

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	2.86 ± 2.35	4.90 ± 4.49	0.03*
Median	2	4	
IBD n(%)	32 (72.7)	229 (79.2)	0.33#
Age (yrs)			
Mean ± SD	43.54 ± 12.22	41.58 ± 11.82	0.55*
Median	43	43	
Male %	77	69	

*Comparisons by Mann-Whitney U test.

#Comparisons by X^2 test.

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	$\geq$ 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.

ASGE
AMERICAN SOCIETY FOR GASTROINTESTINAL ENDOSCOPY

DIAGNOSING CCA IN PSC:
Tumor Markers
CEA and CA19-9 Serum Levels in PSC Patients With and Without CCA

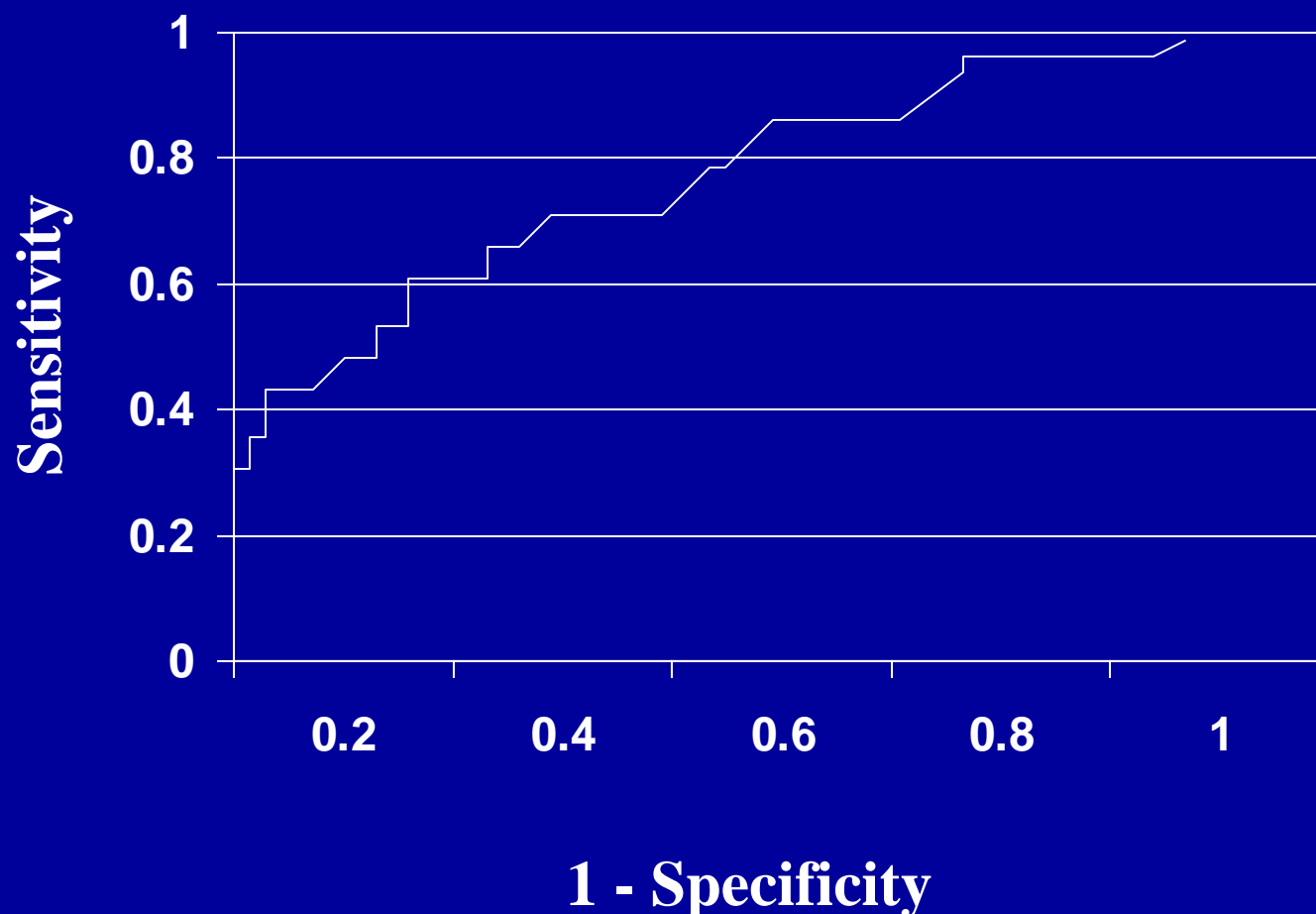|	PSC CCA +		PSC	
	CEA (n=25) ng/mL	CA19-9 (n=12) U/mL	CEA (n-119) ng/mL	CA19-9 (n=43) U/mL
Mean ± SD	68.4 ± 206.7	5994 ± 11521.5	3.5 ± 2.8*	66.7 ± 128.7*
Median	8.2	377.1	2.9	39.1
Range	0.7 – 959	6.5 – 34600	0.7 – 16.7	0.2 - 839

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

DIAGNOSING CCA IN PSC:
ROC CA19-9; cut point 180 U/mL
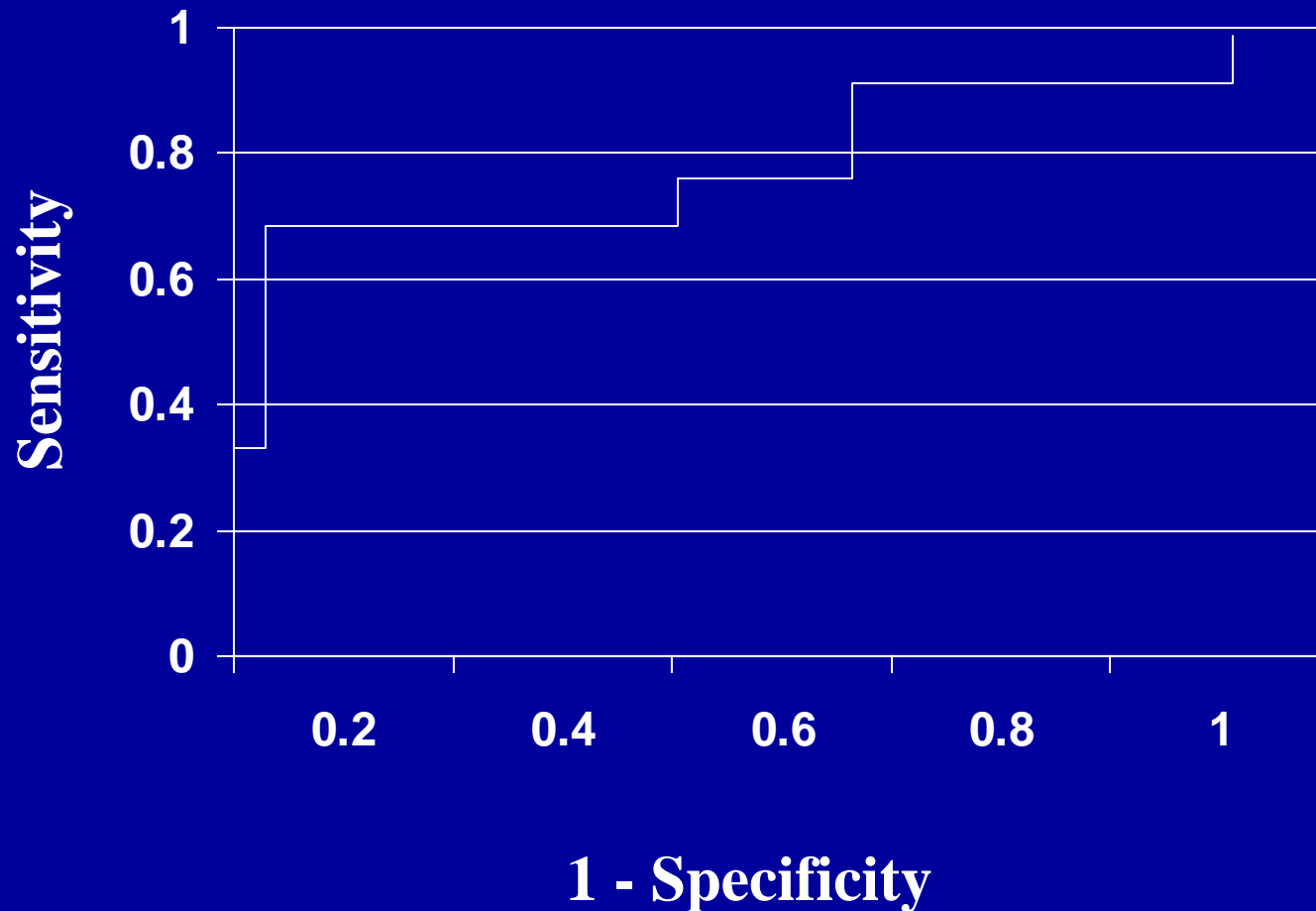
DIAGNOSING CCA IN PSC: ROC CEA; cut point 5 ng/mL

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

DIAGNOSING CCA IN PSC:
Strategies to improve diagnostic accuracy

- **Multimodal tissue sampling**
- **Tumor markers + brush cytology**
- **Improvement in analysis of tissue obtained???**

DIAGNOSING CCA IN PSC: Beyond routine cytology

Lindberg et al Endoscopy 2002;34:909

- Brush for cytology and DNA content by flow cytometry with serum CEA and CA 19-9 in 20 patients with PSC.

- 7 ultimately diagnosed with cholangiocarcinoma.

- Sens 100%; Spec 85%

DIAGNOSING CCA IN PSC: Beyond routine cytology

Baron et al Clin Gastroenterol Hepatol 2004;2:214

- **100 pts with biliary strictures undergoing ERC with BC.**
- **Compared digital image analysis (DNA content; "ploidy analysis") with routine cytology.**
- **56 malignancies; 44 benign**
- **Sens, Spec and Acc for DIA vs RC were: 39% vs 18%, 77% vs 98%, and 56% vs 53%.**
- **DIA may be a valuable adjunct to RC.**

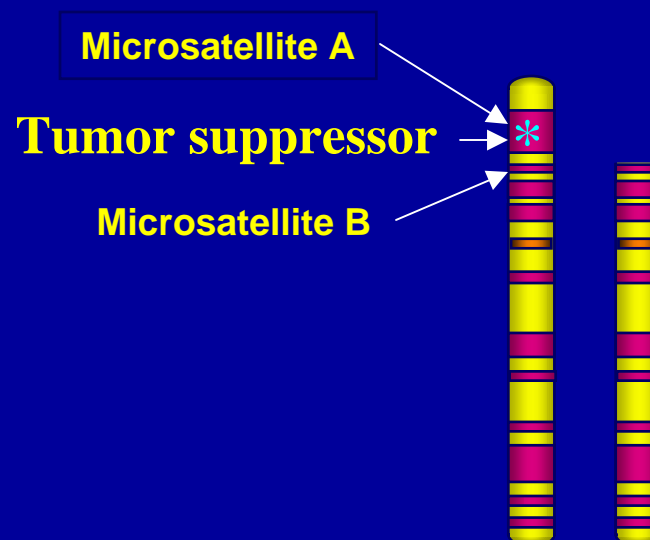# DIAGNOSING CCA IN PSC: Beyond routine histology

Khalid et. al. GUT 2005

- 26 patients with biliary strictures underwent ERC with brush cytology.
- 11 patients with cholangiocarcinoma and 6 with pancreatic carcinoma
- BC + for CA in 7 and inconclusive in 10
- 9 patients benign strictures
- BC benign in 8 and inconclusive in 1.

DIAGNOSING CCA IN PSC: Beyond routine cytology

- **Genomic DNA from cell clusters acquired from BC specimens and microdissected surgical malignant and normal tissue underwent PCR amplification.**

- **A panel of 12 polymorphic microsatellite markers linked to 6 tumor suppressor genes was developed: CMM/RIZ, VHL, p16, p53, PTEN and APC.**

- **The PCR products were compared for microsatellite allelic loss (LOH) and k-ras codon-12 mutations.**

Microsatellite A

Tumor suppressor

Microsatellite B

DIAGNOSING CCA IN PSC:
Beyond routine histology

- Selected malignant appearing BC clusters and microdissected histologic samples from cancer showed abundant LOH.

- Brushings from 9 benign cases showed no LOH (p< 0.001).

- LOH and k-ras mutations profile of the cytological specimens was concordant with the tissue samples.

- Presence of k-ras mutation predicted malignancy of pancreatic origin (p<0.001).

- LOH and k-ras mutation analysis from biliary BC discriminates reactive from malignant cells, with 100% sens, spec and acc.

DIAGNOSING CCA IN PSC: CONTROVERSIES

- **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?**

- **Does screening tumor markers make sense?**

- **Will molecular markers allow for premalignant diagnoses?**