



# Improving Diagnostic Yield of Pancreatic Serous Cystadenoma with Cyst Fluid Ancillary Testing, Adjunct Immunohistochemistry, and Additional Fine Needle Biopsy Sampling

Xi Wang<sup>1</sup>, Xuchen Zhang<sup>1</sup>, Pei Hui<sup>1</sup>, Guoping Cai<sup>1,2</sup>

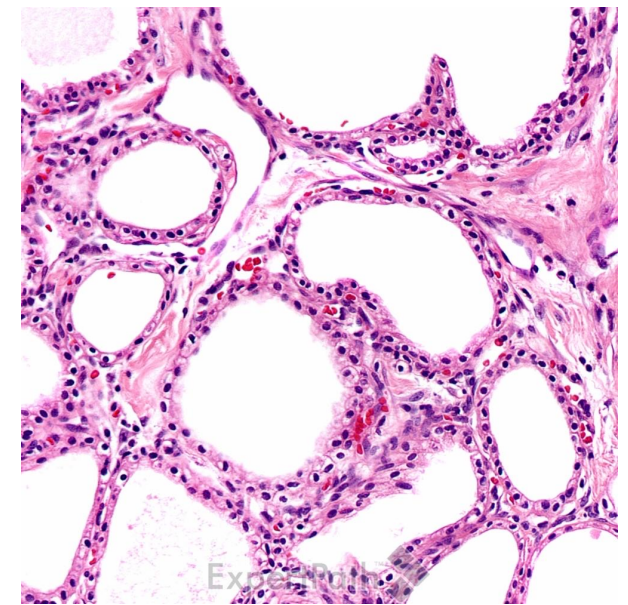
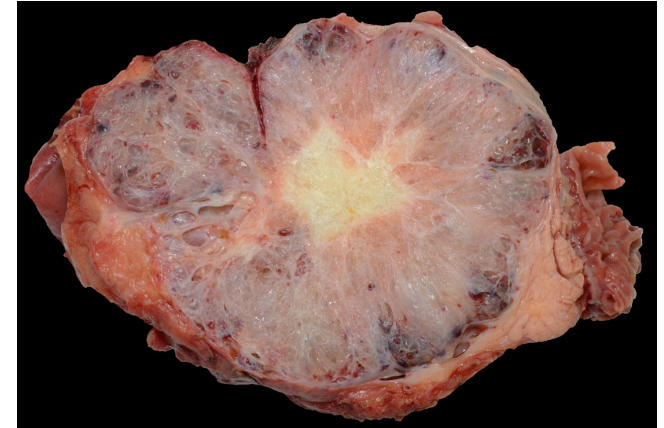
<sup>1</sup> Department of Pathology, Yale University School of Medicine, New Haven, CT

<sup>2</sup> Yale Cancer Center, Yale University School of Medicine, New Haven, CT

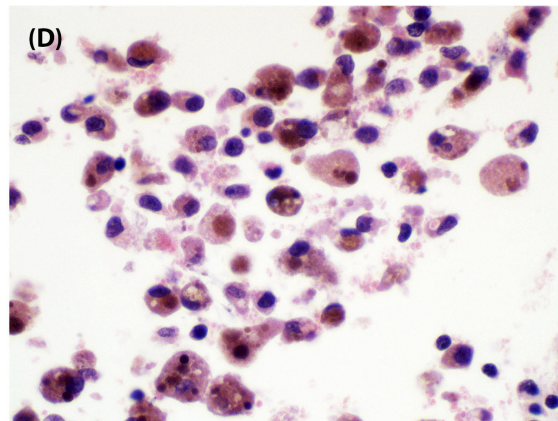
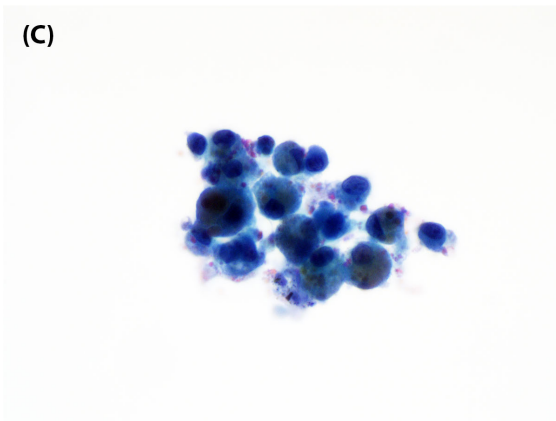
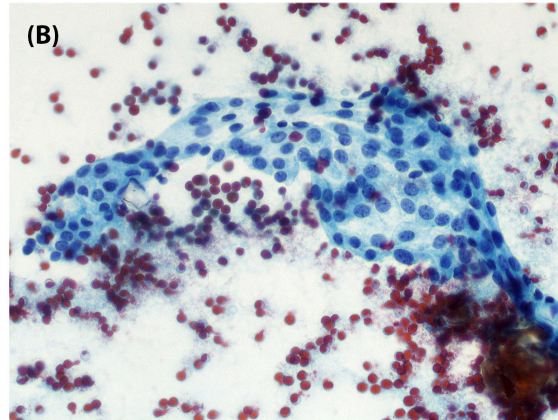
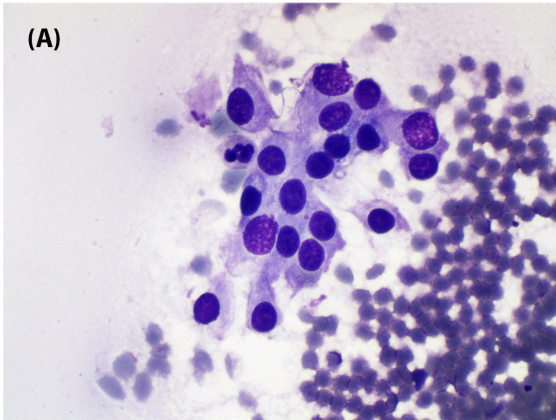
Xi Wang, MD/PhD, PGY-4  
Connecticut Society of Pathologists Education Meeting  
Feb 24<sup>th</sup> 2024

## Serous Cystadenoma (SCA) of the Pancreas

- Benign non-mucinous neoplasm representing 10-16% of pancreatic cystic lesions.
- Ultrasound-guided fine-needle aspiration (EUS-FNA) has been increasingly used for the diagnosis preoperatively
- Histologically composed of multiple cysts lined by bland cuboidal epithelium.



## The cytologic diagnosis of SCA has been challenging



- The specimen is usually paucicellular
- The aspirate is often bloody
- Reported diagnostic sensitivity ranges from 0-20%

# One of the major changes in WHO involves SCA

Papanicolaou System	WHO international System
I Nondiagnostic	I Nondiagnostic
II Negative for Malignancy	II Negative for Malignancy <b>Serous Cystadenoma</b>
III Atypical	III Atypical
IV Neoplasm-Benign <b>Serous Cystadenoma</b>	IV Pancreatic Neoplasm/Low-Risk <b>IPMN or MCN (low/intermediate-grade)</b>
Neoplasm-Other <b>IPMN or MCN (low/intermediate-grade)</b>	V Pancreatic Neoplasm/High-Risk <b>IPMN or MCN (high-grade)</b>
<b>IPMN or MCN (high-grade)</b>	VI Suspicious for Malignancy
<b>PanNET</b>	VII Malignant <b>PanNET</b>
<b>SPN</b>	<b>SPN</b>
V Suspicious for Malignancy	
VI Malignant	

## Aims of the study

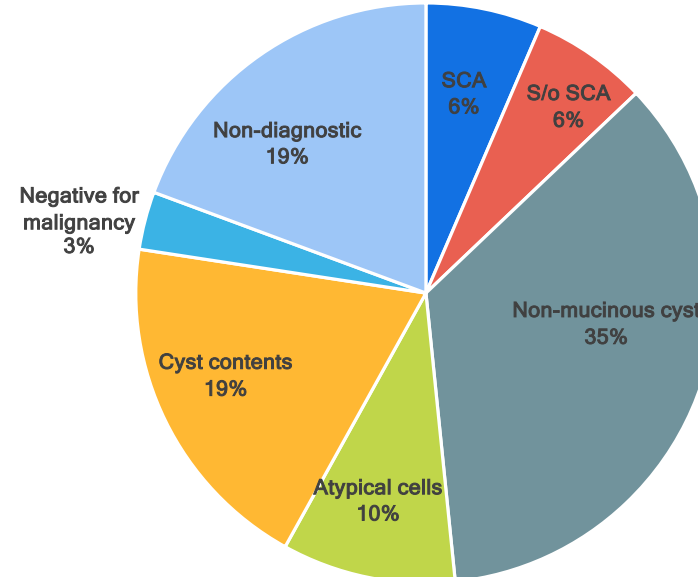
- 1) How confident cytopathologists are in rendering a diagnosis of SCA with or without cyst fluid ancillary testing?
- 2) Could adjunct immunostaining help improve the diagnosis?
- 3) Is there an additive value of concurrent fine needle biopsy (FNB) sampling for the diagnosis of SCA?

## Case selection

- ✓ We retrospectively searched for histologically proved serous cystadenoma cases which had been FNA sampled between May 2004 to May 2022.
- ✓ A total of 31 cases with SCA diagnosis confirmed on either concurrent fine needle biopsy (FNB) (N=11) or surgical resection (N=20) were identified.

## Clinical features, cytologic diagnosis, and cyst fluid ancillary tests of pancreatic SCA

Age, year	
Mean	65
Range	30-80
Gender, n (%)	
Male	13 (42%)
Female	18 (58%)
Tumor location, n (n%)	
Head/neck/uncinate	12 (39%)
Body/tail	19 (61%)
Tumor size, cm	
Mean	4.8
Range	1.5-13
Imaging findings, n (%)	
Cystic mass	23 (74%)
Solid mass	6 (19%)
Unknown	2 (6%)
Cytologic diagnosis, n (%)	
Serous cystadenoma	2 (6%)
Suggestive of serous cystadenoma	2 (6%)
Non-mucinous cyst	11 (35%)
Atypical cells	3 (10%)
Cyst contents	6 (19%)
Negative for malignancy	1 (3%)
Nondiagnostic	6 (19%)
CEA level, n (%)	
≥ 192 ng/ml	0
< 192 ng/ml	17 (100%)
Amylase level, n (%)	
≥ 250 U/L	3 (18%)
< 250 U/L	14 (82%)
KRAS mutation	
Mutant	0
Wild-type	14 (100%)

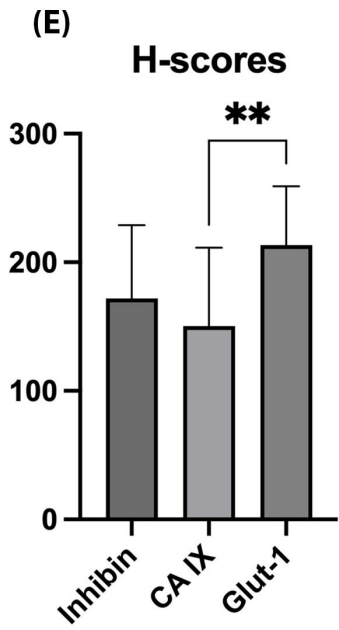
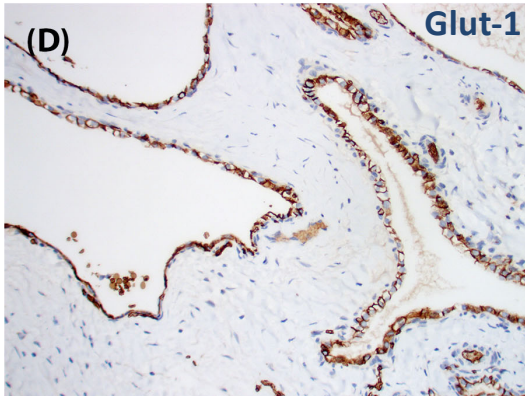
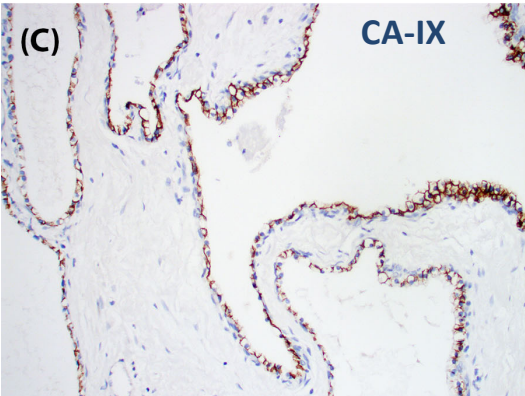
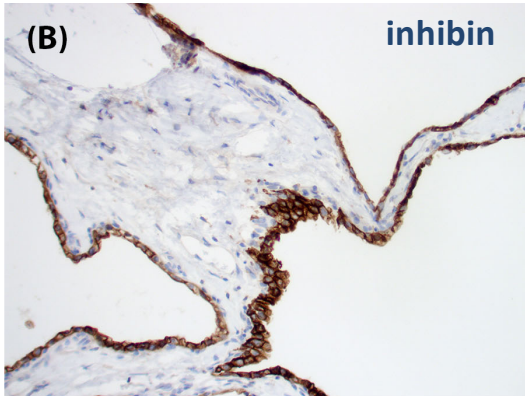
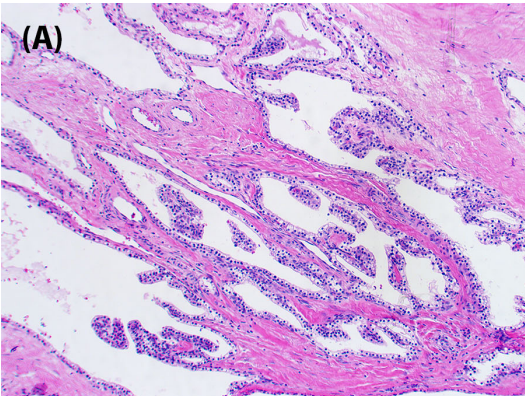


## Aims of the study

- 1) How confident cytopathologists are in rendering a diagnosis of SCA with or without cyst fluid ancillary testing?
- 2) Could adjunct immunostaining help improve the diagnosis?
- 3) Is there an additive value of concurrent fine needle biopsy (FNB) sampling for the diagnosis of SCA?

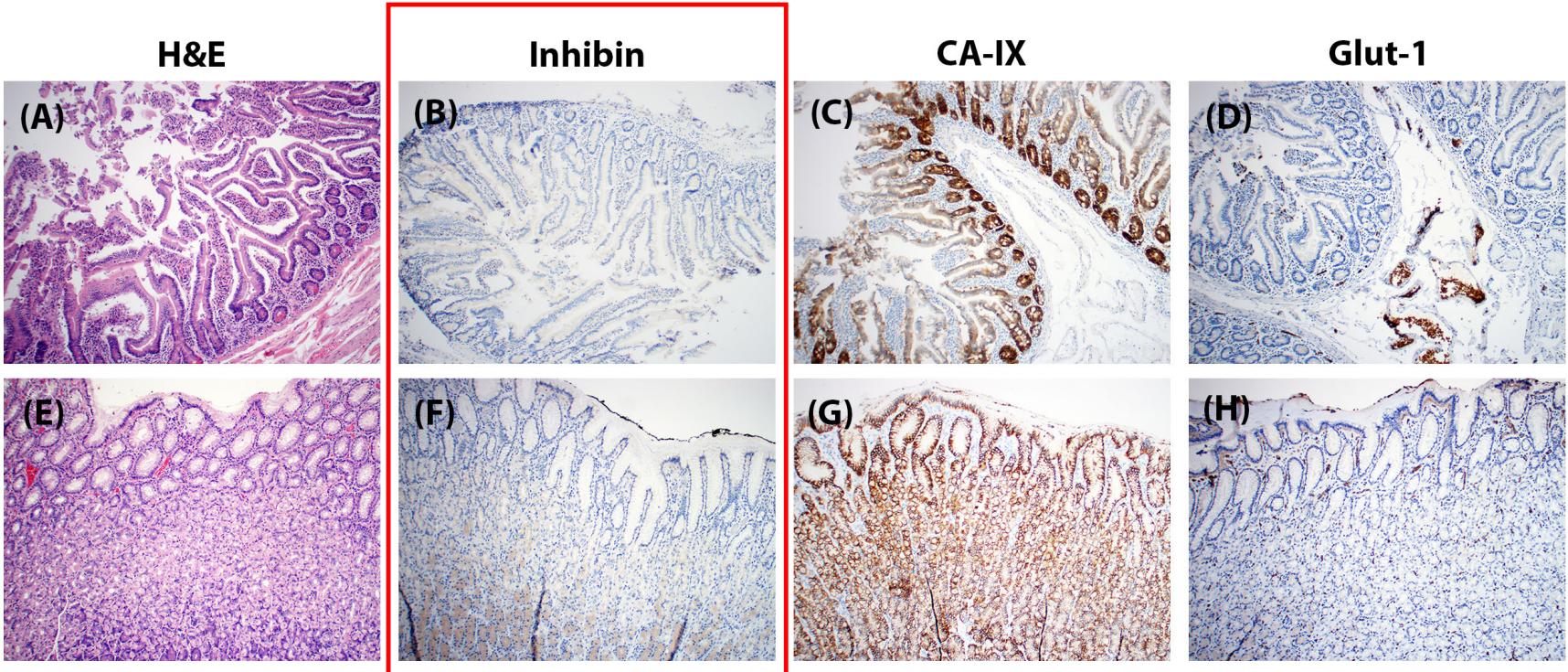


# Expression of inhibin, CA-IX and Glut-1 in SCAs



# Expression of inhibin, CA-IX and Glut-1 in normal gastric and duodenal epithelium

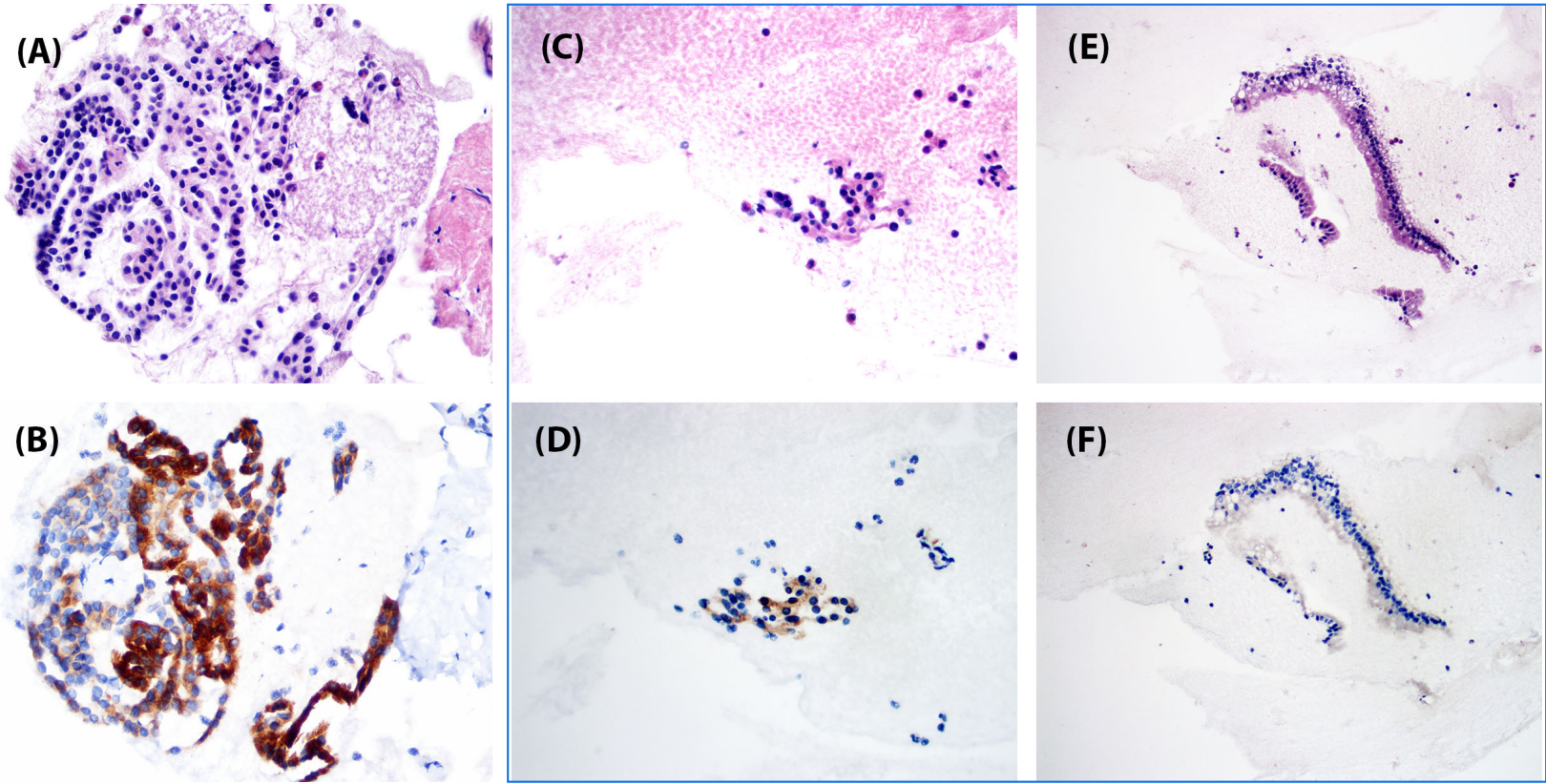
Normal duodenum epithelium



Normal gastric epithelium



# Expression of inhibin in FNA cell blocks



## The diagnostic yield was improved in 5 out of 7 cases

Case	Original Diagnosis	Cyst Fluid Ancillary Test	Immunohistochemistry
1	Consistent with serous cystadenoma	No cyst fluid analysis Scant cellularity	Inhibin +
2	Non-mucinous cyst	No cyst fluid analysis Scant cellularity	Inhibin +
3	Non-mucinous cyst	WT <i>KRAS</i> Scant cellularity	Inhibin +
4	Non-mucinous cyst	CEA 26 ng/ml, amylase 5288, WT <i>KRAS</i> Scant cellularity	Inhibin +
5	Non-mucinous cyst	No cyst fluid analysis Scant cellularity	Inhibin +
6	Cyst contents	CEA 1.1 ng/ml, amylase 20 U/L Scant cellularity	Inhibin +/-
7	Nondiagnostic	No cyst fluid analysis Scant cellularity	Inhibin +

## Aims of the study

- 1) How confident cytopathologists are in rendering a diagnosis of SCA with or without cyst fluid ancillary testing?
- 2) Could adjunct immunostaining help improve the diagnosis?
- 3) Is there an additive value of concurrent fine needle biopsy (FNB) sampling for the diagnosis of SCA?

## Concurrent FNA and FNB diagnosis for SCAs

Case	FNA Diagnosis	Ancillary Testing	FNB Diagnosis	Ancillary Testing
1	Cyst contents	WT <i>KRAS</i> Acellular block	SCA	AE1/AE3+, inhibin+, chromogranin-
2	Non-mucinous cyst	CEA 0.2 ng/ml; amylase 181 U/L; WT <i>KRAS</i> Acellular block	S/O SCA	CK7+, CK19+, inhibin+, PAS+
3	Non-mucinous cyst	CEA 30 ng/ml; amylase 7854 U/L; WT <i>KRAS</i> No cell block	LG neoplasm	AE1/AE3+, Inhibin+, PAX8+, Synaptophysin+, chromogranin+
4	Non-mucinous cyst	CEA 26 ng/ml; amylase 5288 U/L; WT <i>KRAS</i> Scant cellularity	SCA	Inhibin+, CA-IX+, Synaptophysin-, PAX8-
5	S/O SCA	CEA 17 ng/ml; amylase 13 U/L; WT <i>KRAS</i> Scant cellularity	S/O SCA	Inhibin+
6	Non-mucinous cyst	CEA 15 ng/ml; amylase 76 U/L; WT <i>KRAS</i> No cell block	S/O SCA	Inhibin+, PAS+
7	Non-mucinous cyst	No cyst fluid analysis No cell block	S/O SCA	AE1/AE3+, Inhibin+, Synaptophysin-, PAS+
8	Non-mucinous cyst	CEA 154 ng/ml; amylase 483 U/L; WT <i>KRAS</i> No cell block	S/O SCA	CK7+, CK19+, inhibin+, PAS+
9	Nondiagnostic	No cyst fluid analysis No cell block	Nondiagnostic	Inhibin-, Synaptophysin-
10	Nondiagnostic	No cyst fluid analysis No cell block	SCA	AE1/AE3+, CK7+, Inhibin+, CEA-
11	Atypical cells	No cyst fluid analysis No cell block	SCA	N/A
12	Non-mucinous cyst	No cyst fluid analysis Low cellularity	SCA	CK7+, PAS+
13	Non-mucinous cyst	No cyst fluid analysis No cell block	S/O SCA	N/A
14	Non-mucinous cyst	No cyst fluid analysis Scant cellularity; inhibin, Glut-1 noncontributory	SCA	AE1/AE3+, inhibin+
15	Cyst contents	No cyst fluid analysis Scant cellularity; inhibin noncontributory	SCA	AE1/AE3+, inhibin+, Synaptophysin-, INSM1-

# Conclusions

- Diagnosing SCA based on aspiration cytology alone is very difficult.
- There is an important role of cystic fluid ancillary testing.
- Inhibin is one of the best markers for cytologic materials.
- Most importantly, additional sampling with FNB will provide additive diagnostic value.

*This manuscript has been accepted by Cancer Cytopathology.*

# Acknowledgement

Dr. Guoping Cai

Dr. Xuchen Zhang

Dr. Pei Hui



**Thank you!**

**Supplemental Table 1.** Clinicopathologic features and ancillary tests of pancreatic serous cystadenoma diagnosed on FNA without surgical resection.

Case	Age, year	Gender	Location	Imaging findings	FNA diagnosis	Immunostain	CEA, ng/ml	Amylase, U/L	<i>KRAS</i> mutation
1	73	F	Body/Tail	Cystic lesion	SCA	Non-contributory	0.7	83	N/A
2	63	F	Head	Cystic lesion	S/O SCA	CD56+, SYN-, CHR-, PAS+	N/A	N/A	WT
3	77	F	Head	Large microcystic, S/O SCA	SCA	N/A	N/A	N/A	WT
4	72	M	Head	Cystic lesion	S/O SCA	N/A	0.2	52	WT
5	44	M	Body	Cystic lesion	S/O SCA	N/A	0.3	1441	WT
6	63	F	Body	Cystic lesion	SCA	N/A	0.2	16.2	N/A
7	54	F	Head	Cystic lesion, S/O SCA	S/O SCA	N/A	N/A	N/A	N/A
8	49	F	Tail	Cystic lesion, S/O SCA	S/O SCA	N/A	0.2	27	N/A
9	79	M	Head	Cystic lesion	S/O SCA	N/A	N/A	N/A	N/A
10	82	F	Head	Cystic lesion, S/O SCA	S/O SCA	N/A	0.5	47	N/A
11	63	M	Uncinate	Cystic lesion	S/O SCA	Inhibin+, CA-IX+, Glut1+	0.2	219	WT
12	67	F	Tail	Cystic lesion	S/O SCA	Inhibin+ on thin prep	0.2	21	WT

**Supplemental Table 2.** Rapid on-site evaluation interpretation and follow-up of selective serous cystadenoma cases.

Case #	ROSE interpretation	Additional aspirate	Cell block	Immunostain	Final FNA diagnosis
1	Pancreatic acinar cells	Yes	Acellular	N/A	Cyst contents
2	Rare inflammatory cells, paucicellular	No	Acellular	N/A	Non-mucinous
3	Mild atypical epithelium	Yes	Hemosiderin histiocytes	N/A	Non-mucinous
4	Predominantly blood and GI contaminant	Yes	No	N/A	Non-mucinous
5	Few cells	Yes	Acellular	N/A	Nondiagnostic
6	Blood, few cells	Yes	No	N/A	Nondiagnostic
7	Bland ductal epithelial cells, macrophages	Yes	Hemosiderin histiocytes	N/A	Serous cyst
8	Amorphous debris	Yes	No	N/A	Non-mucinous
9	Bland cuboidal cells, cannot exclude SCA	Yes	Low cellularity	Inhibin, Glut-1 suboptimal	Non-mucinous
10	Nondiagnostic	Yes	Acellular	N/A	Atypical

ROSE: Rapid on-site evaluation; SCA: serous cystadenoma; N/A, not performed.