COLLEGE of AMERICAN PATHOLOGISTS
Education

CAP19
Knowledge
Relationships
Expertise

Cytologic Atypia on EUS-FNA

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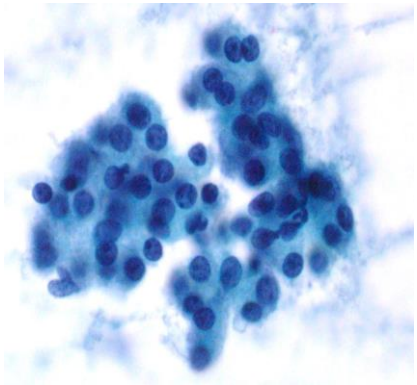
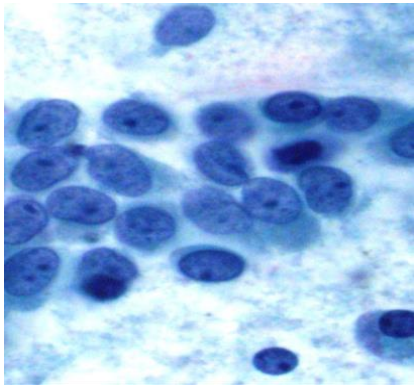
Indeterminate Diagnosis : What?

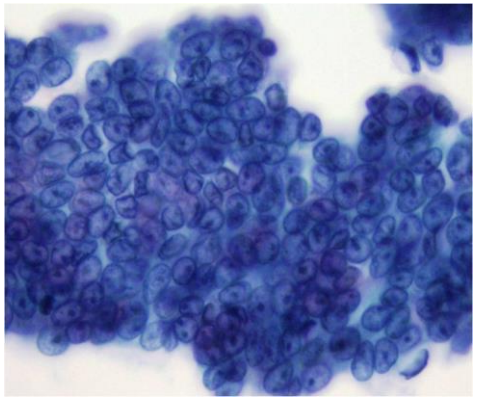
Benign

Indeterminate Diagnosis

Malignant





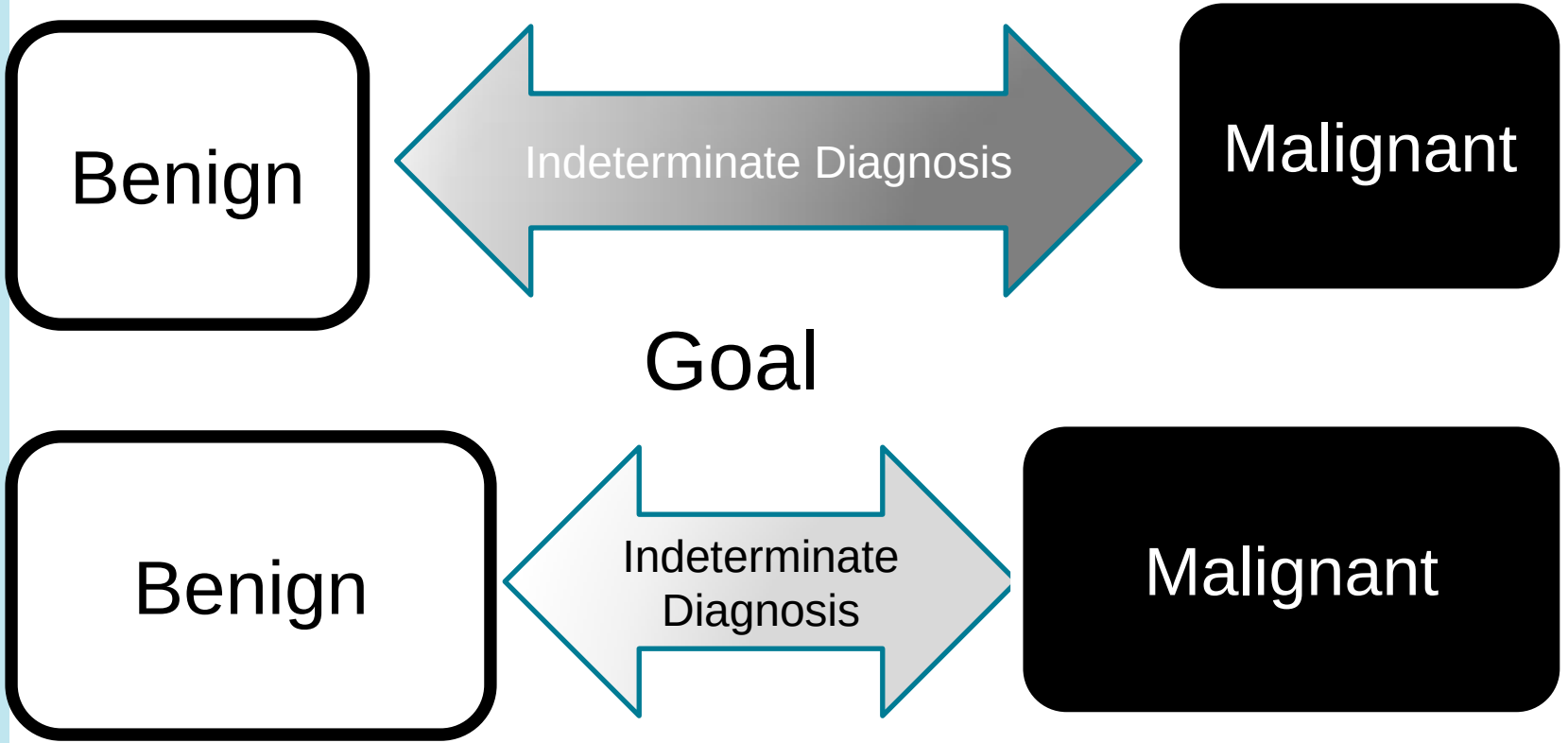


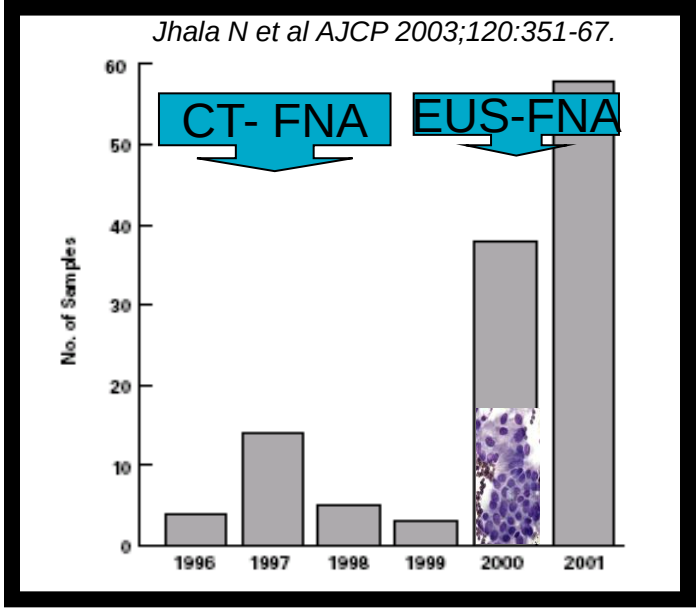
Our Challenges
Indeterminate Diagnosis

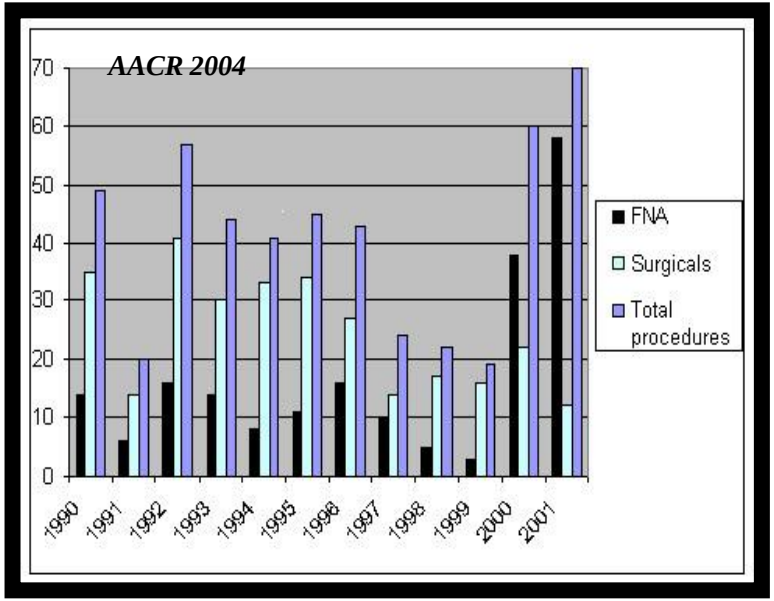
Cytology Diagnosis	# of cases	Follow Up of Cancer
Benign	85	18 (21%)
Indeterminate	25	17 (68%)
Positive	20	

J Mol Diagn 2010, 12:780–786.

Indeterminate Diagnosis : What?







	Unsat	Positive	Negative	Atypical	Total Cases
Percutaneous FNA (1990-1999)	13%	42%	26%	19%	84 (100%)
EUS-FNA (2000- 2002)	3%	66%	25%	6%	96 (100%)

JOP. J Pancreas (Online) 2004; 5(4):282-288.

ROUND TABLE

Pancreatic Fine Needle Aspiration: To Do or not To Do?

William R Brugge

Qian and Hecht suggested that US/CT-guided biopsies may be more accurate and sensitive for documenting malignancy than EUS, but noted that EUS-guidance was used in more difficult lesions [41]. In contrast,…….

"Jhala et al. demonstrated that EUS-FNA was superior to CT-FNA in obtaining adequate cells from neuroendocrine tumors of the pancreas for the diagnosis and performing additional imunohistochemical stains [42]."

42. Jhala D, Eloubeidi M, Chhieng DC, Frost A, Eltoum IA, Roberson J, Jhala N. Fine needle aspiration biopsy of the islet cell tumor of pancreas: a comparison between computerized axial tomography and endoscopic ultrasound-guided fine needle aspiration biopsy. Ann Diagn Pathol 2002; 6:106-12. [PMID 12004358]

Endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB): past, present, and future

Kenji Yamao[1], Akira Sawaki[1], Nobumasa Mizuno[1], Yasuhiro Shimizu[2], Yasushi Yatabe[3], and Takashi Koshikawa[4]

Table 1. History of EUS-FNAB

1980	DiMagno et al.[3]	Linear array echoendoscope
	Strohm et al.[4]	Mechanical radial echoendoscope
1984	Tio and Tytgat[5]	Possibility of EUS-FNAB
1989	Kouzu[a]	Possibility of EUS-FNAB
1991	Harada et al.[6]	Experimental study of EUS-FNAB
	Calletti et al.[7]	EUS-assisted FNA for gastric submucosal tumor using guillotine needle biopsy
1992	Vilmann et al.[2]	EUS-FNAB using convex linear array echoendoscope for pancreatic cancer
1993	Vilmann et al.[8]	Development of a new needle (steel needle with Teflon sheath) and EUS-FNAB for upper gastrointestinal tract lesion
	Wiersema et al.[9]	EUS-FNAB for mediastinal lymph node
	Tio et al.[10]	EUS-FNAB using mechanical radial echoendoscope for pancreatic cancer

J Gastroenterol 2005; 40:1013–1023
DOI 10.1007/s00535-005-1717-6

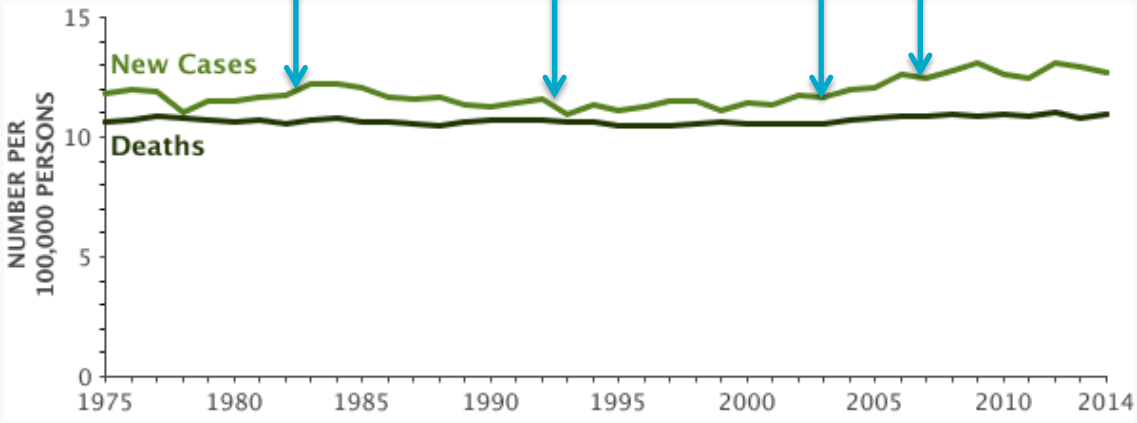
2002	Jhala et al.[30]	EUS-FNAB for pancreatic endocrine tumor
	Gress et al.[34]	EUS-FNT (tattooing)
	Wiersema et al.[35]	Development of a new needle (Trucut biopsy needle)
	Jacobson et al.[31]	EUS-FNAB for gallbladder
2003	Matsumoto et al.[32]	EUS-FNAB for autoimmune pancreatitis
	Fritscher-Ravens et al.[33]	EUS-FNAB for splenic lesion

- Pitfalls Highlighted
- Data suggested that EUS will become standard of care

EUS

EUS – FNA

NCCN Guidelines changed



Year	1975	1980	1985	1990	1995	2000	2005	2009
5-Year Relative Survival	3.0%	3.3%	3.2%	3.7%	3.6%	5.1%	6.2%	8.5%

SEER 9 Incidence & U.S. Mortality 1975–2014, All Races, Both Sexes. Rates are Age-Adjusted.

Pancreatic FNA : Atypia Frequency

	2002	2004	2015	2017	2019
Unsatisfactory	44	3	52	172	39
Benign	10	23	224	404	100
Atypical	17 **(9.4)**	5 **(5.9%)**	129 **(10.6%)**	91 **(7.48%)**	25 **(7.5%)**
Suspicious	12 **(6.7%)**	4 **(4.7%)**	35 **(2.8%)**	30 **(2.4%)**	6 **(1.7%)**
Neoplasm	6		140		70
Malignant	85	49	632	520	94
Total	179	84	1212	1217	334

Cancer Cytopathol2002;96:174 – 80 ,
Cancer Cytopathol. 2015;123:98-107.
J Am Soc Cytopathol 2019; 8:120-127

Cancer Cytopathol 2004;102:239 – 46
Diag Cytopathol 2018; 45:3-13

Factors That May Impact Diagnostic Performance

Reducing Atypia: Lessons learned

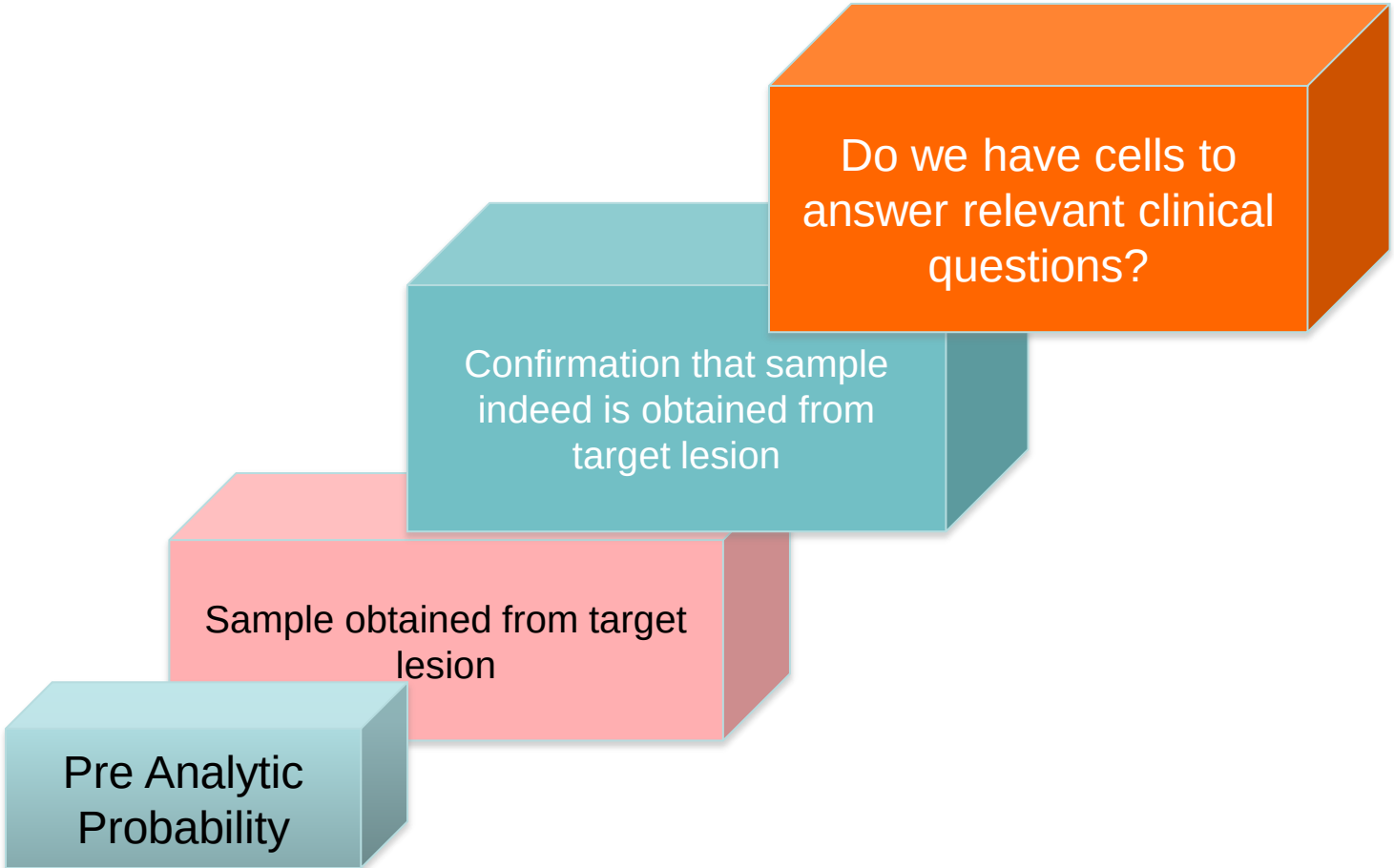
1. Tissue is the issue –

   Adequate Cells – Adequate Diagnosis
2. Effective communication
3. Identifying pitfalls – Reduce Atypia rates
4. Recognizing Morphologic features
5. Algorithmic approach for diagnosis – reduce interpretive pitfalls
6. Judicious use of ancillary tests.

Cytopathology 2007;18:143-50.
Ann Diagn Pathol. 2007;11:176-81.
Am J Clin Pathol 2006; 126:572-579
Diag Cytopathol 2017; 45:3-13.

Cancer 2004; 110: 239-46;
Am J Clin Pathol 2003; 102:351-362
Diagn Cytopathol 2014; 42:351-362.
Cancer Cytopathol 2018; 376-380

Adequate cytology sample



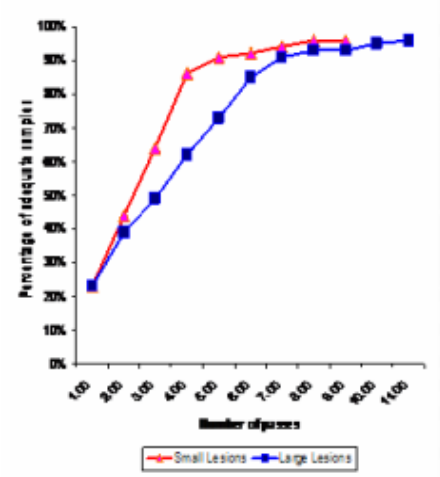
EUS-FNA: Towards Improving Diagnostic Performance

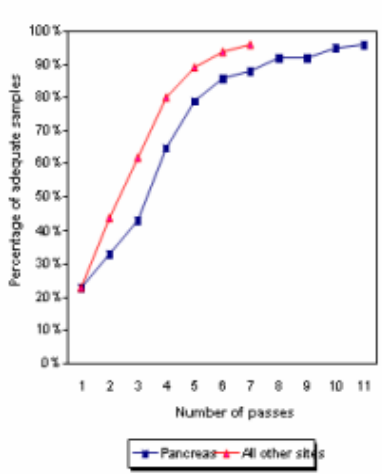
Size of lesion has little effect on operating characteristics.

	≤ 25 mms* (n=100)	**> 25 mms* (n=109)**
Sensitivity :	96% (92%)	96% (90%)
Specificity:	100%	100%

Frequency of Inconclusive diagnoses (atypical diagnosis/ suspicious diagnoses): 5- 25%

Cancer 2004; 102:239-46.





Reference	EUS-FNAs	Adequacy (%)	Pathologist Presence
Wiersema et al 1997[15]	554	524 (94.6)	Present
Williams et al 1999[18]	333	327 (98.2)	Present
Shin et al, 2002[23]	**179**	**156 (87.2)**	**Absent**
Klapman et al , 2003[30]	130	118 (90.7)	Present
	113	**90 (79.6)**	**Absent**
Jhala et al, 2004	209	201 (96)	Present

Endoscopic Ultrasound–Guided Fine-Needle Aspiration

A Cytopathologist's Perspective

Nirag C. Jhala, MD, MIAC,[1*] Darshana N. Jhala, [1]

Am J Clin Pathol 2003;120:351-367
DOI: 10.1309/MFRFJ0XYJLN8NVDP

Table 2
Approaches for Performing Endoscopic Ultrasound–Guided Fine-Needle Aspiration From Various Topographic Locations in the Pancreas

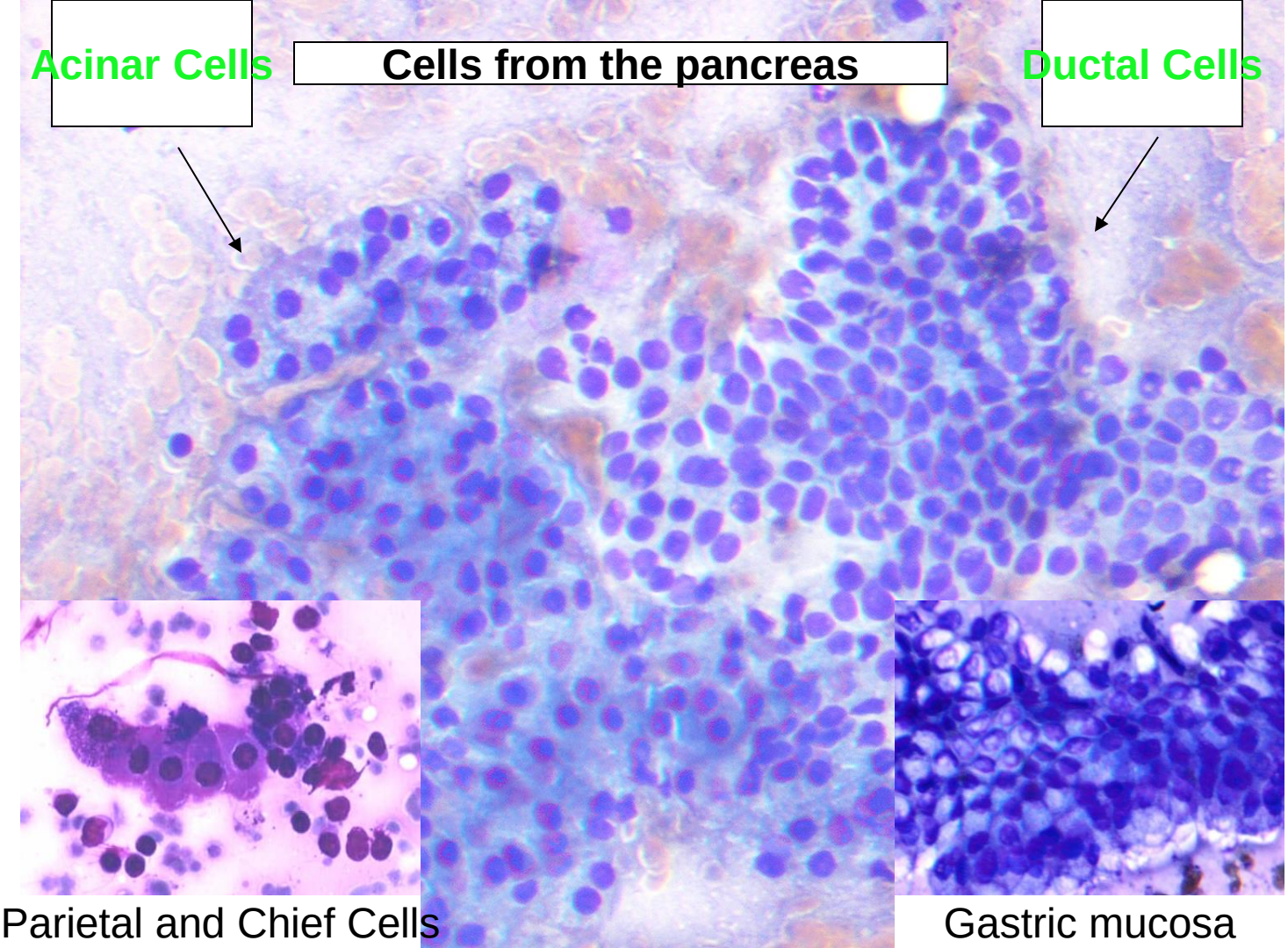
Location of Lesion	Approach	Additional Cells
Head/uncinate	Transduodenal	Tightly cohesive glandular cells with honeycomb appearance and goblet cells
Body/tail	Transgastric	Parietal cells, superficial glandular cells (Image 3)

Avoiding Pitfalls

CAP TODAY

January 2005 Special Section: PAP/NGC Program Review

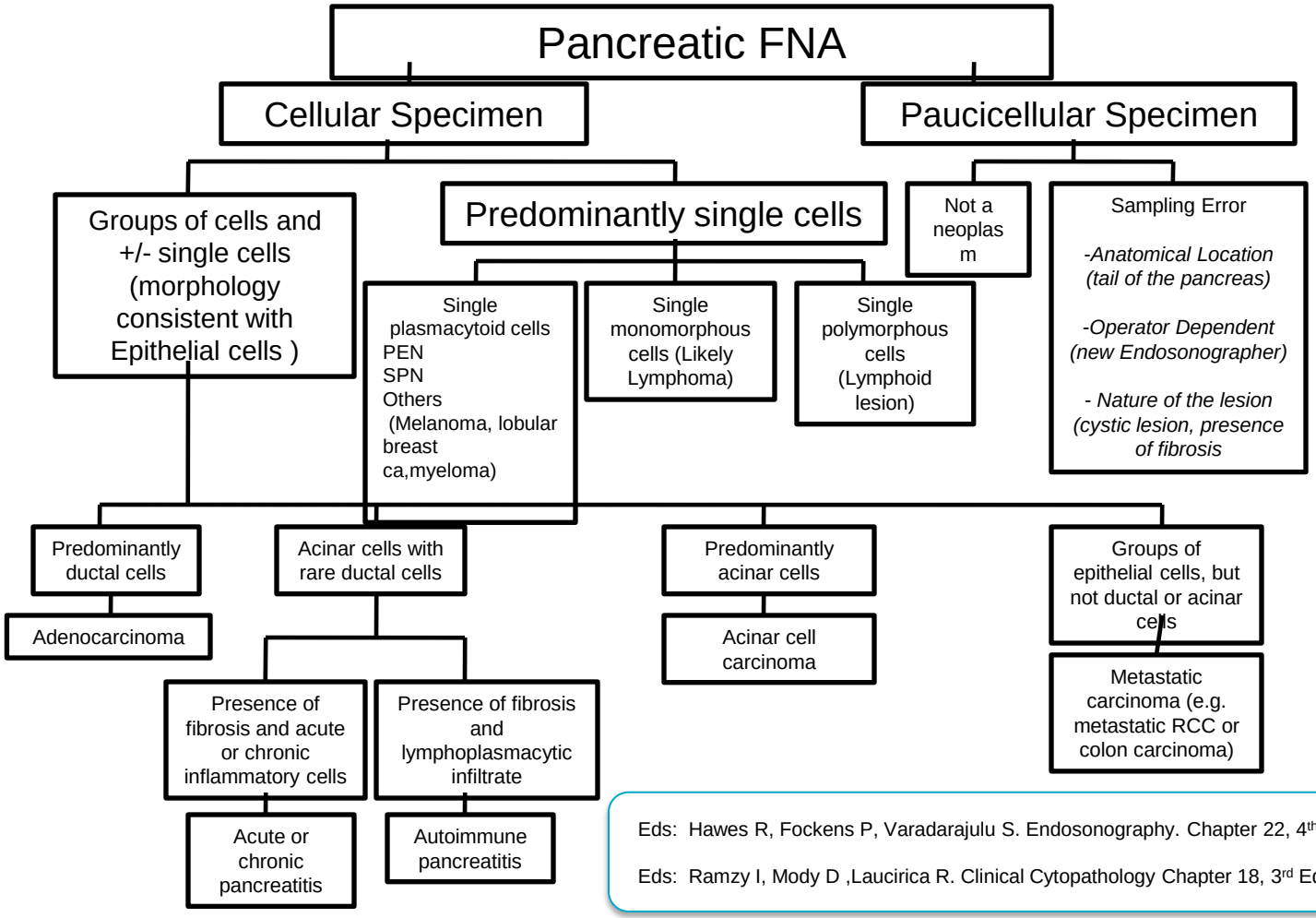
Pancreas. Jhala has described many of the interpretive pitfalls associated with EUS-FNA of the pancreas. Depending on the topographic location of the lesion in the pancreas, the EUS-FNA will sample different types of normal gastrointestinal tract structures.



Parietal and Chief Cells

Gastric mucosa

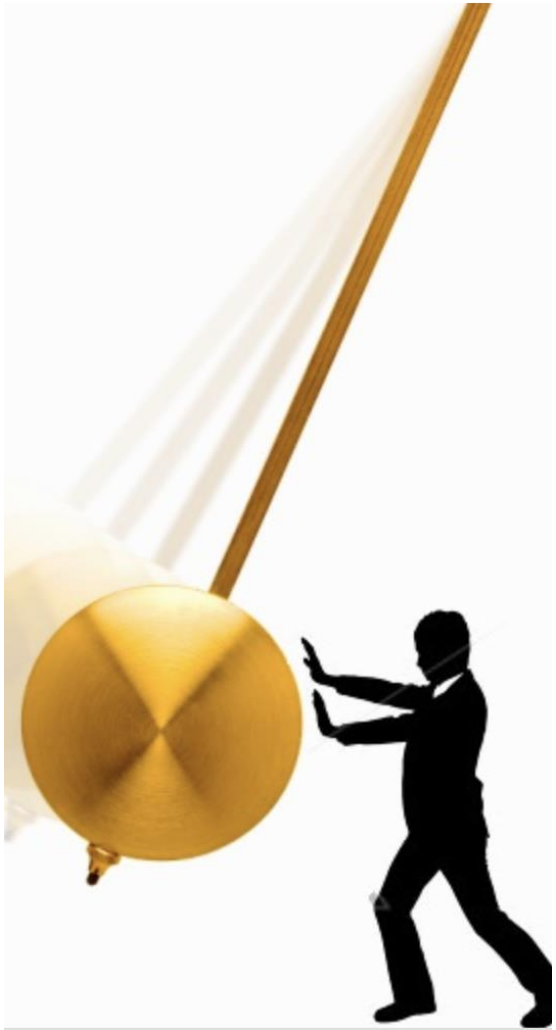
Jhala Algorithm



Eds: Hawes R, Fockens P, Varadarajulu S. Endosonography. Chapter 22, 4th Ed, Elsevier, 2019

Eds: Ramzy I, Mody D ,Laucirica R. Clinical Cytopathology Chapter 18, 3rd Ed. McGraw Hill, 2018

Jhala Algorithm - Impact



The changing Paradigm in EUS- guided Tissue acquisition

“ The pendulum has swung from histology to cytology ……..…..”

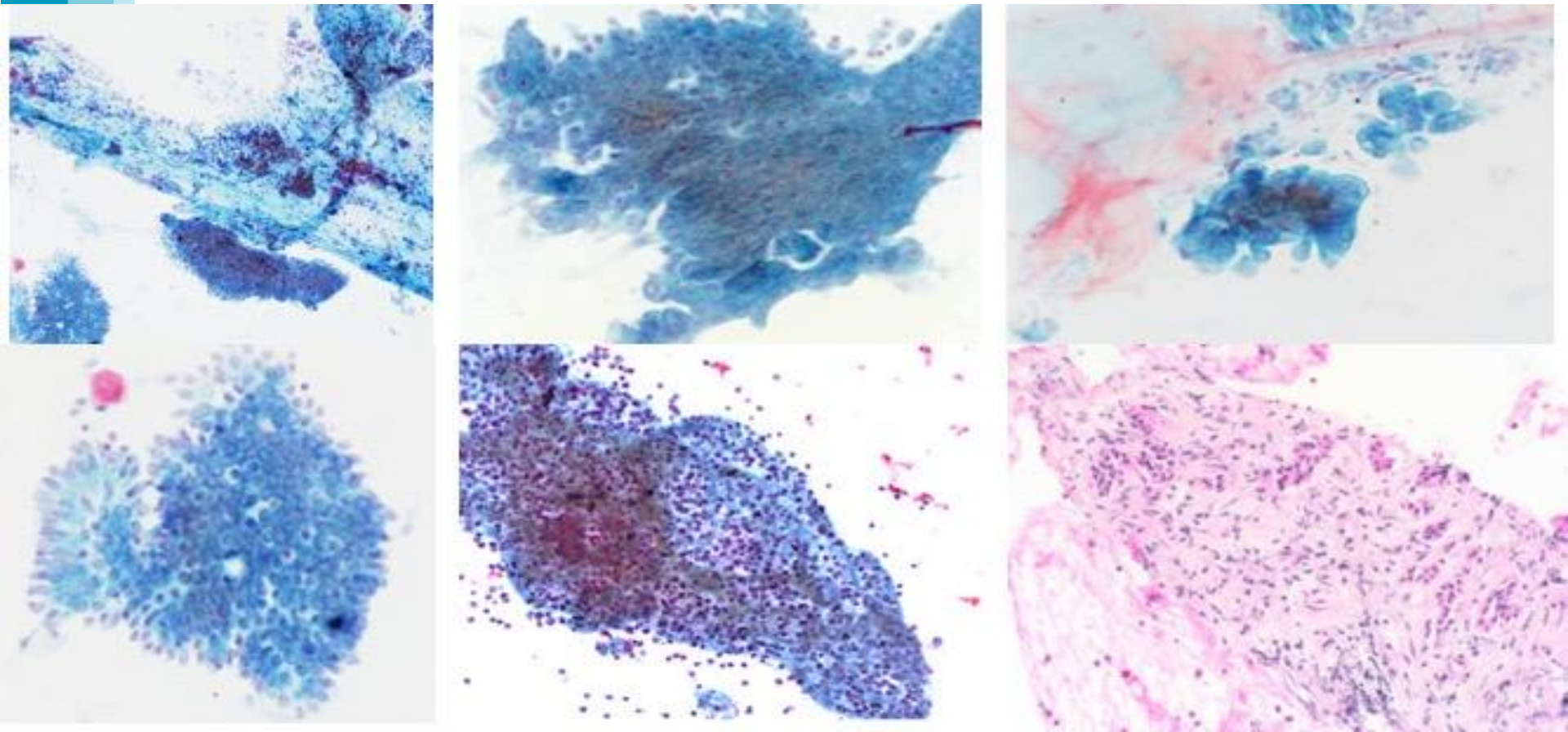
Gastrointest Endoscopy Clinic N Am 2014; 24:1-7

The focus of Endosonogrpahers today is to determine if Rapid Onsite Specimen Evaluation (ROSE) …..

Case Presentations

EUS FNA of the pancreas -
58 year old - ill defined mass in the head

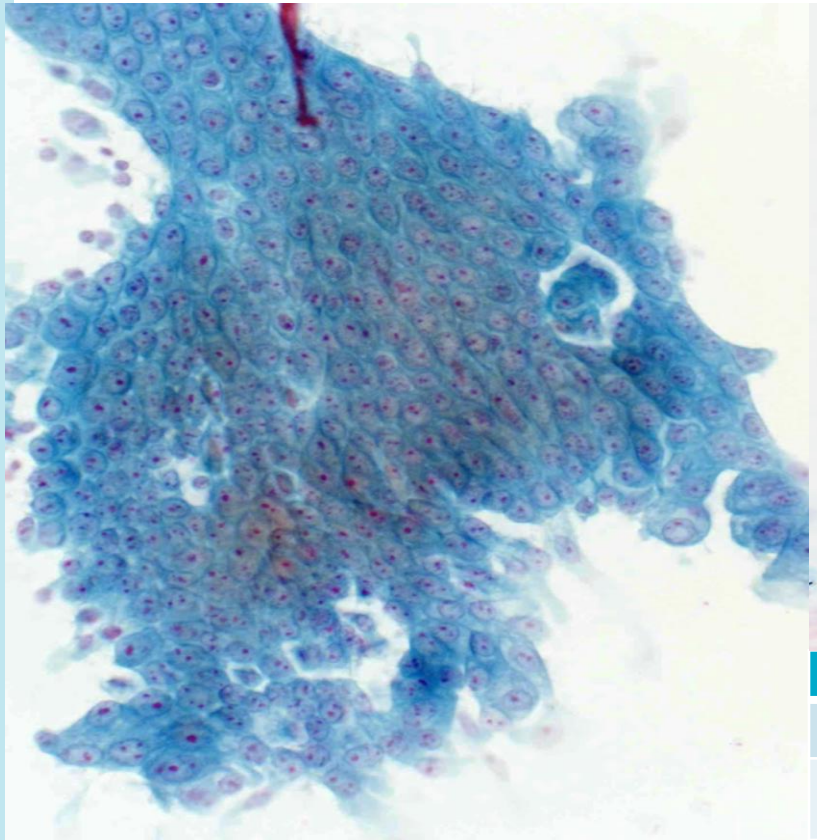
EUS FNA of the pancreas -
58 year old - ill defined mass in the head

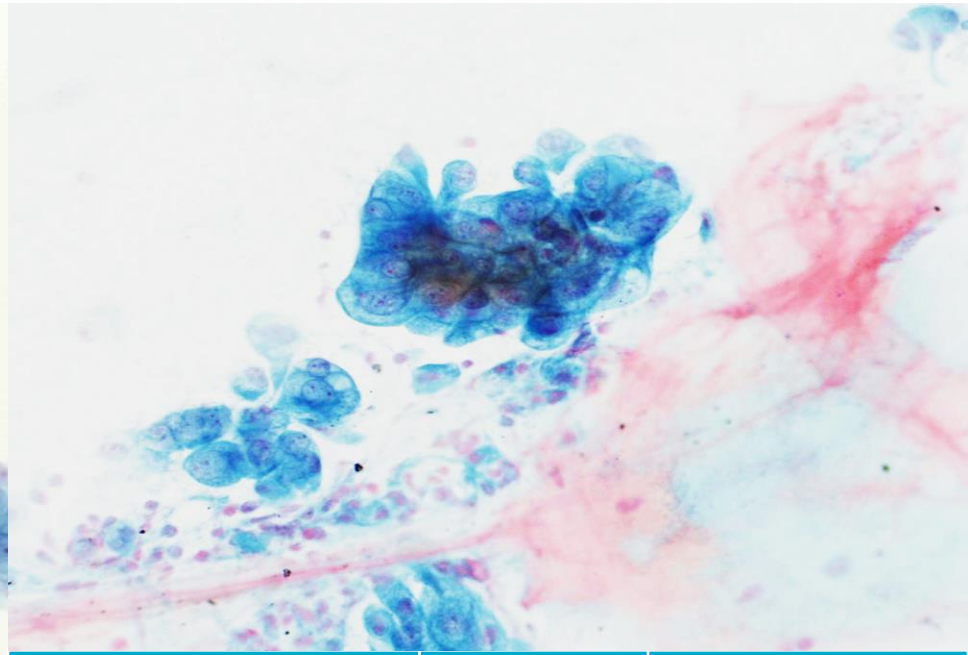


Benign

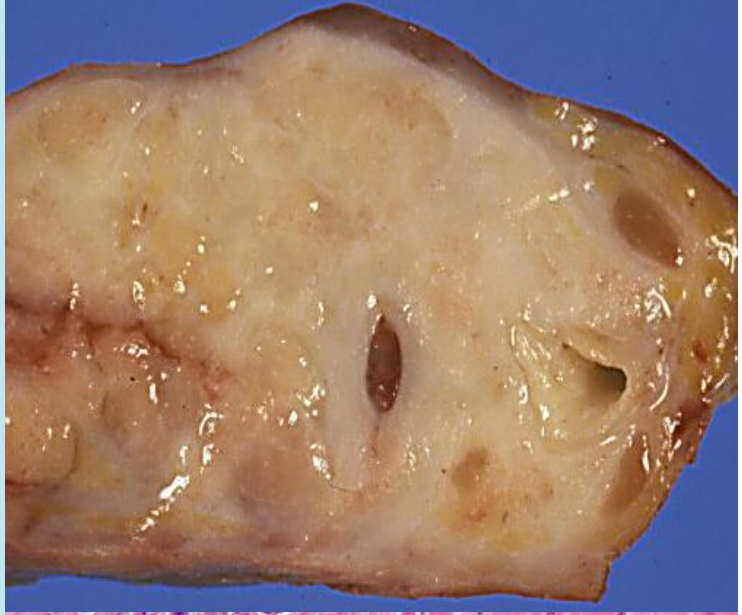
Indeterminate Diagnosis

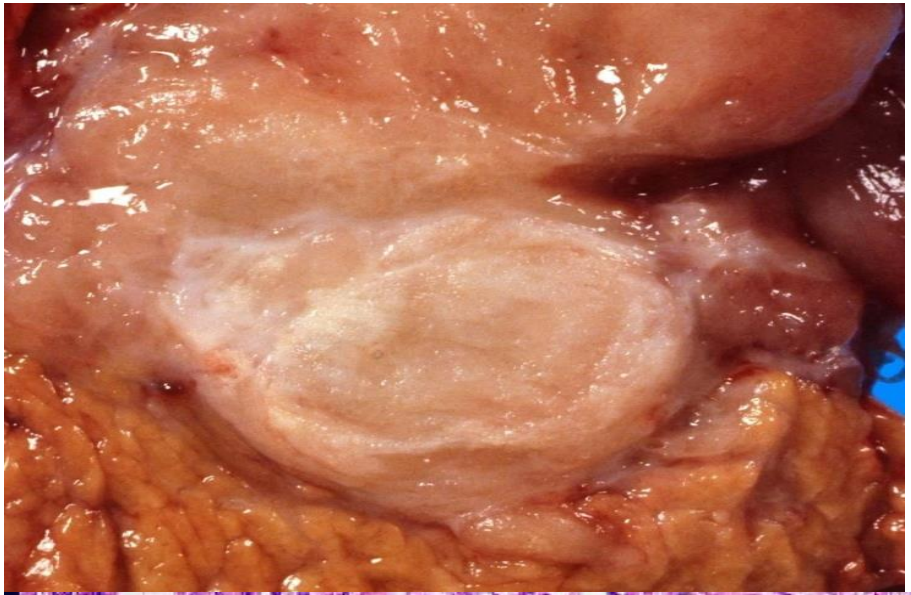
Malignant

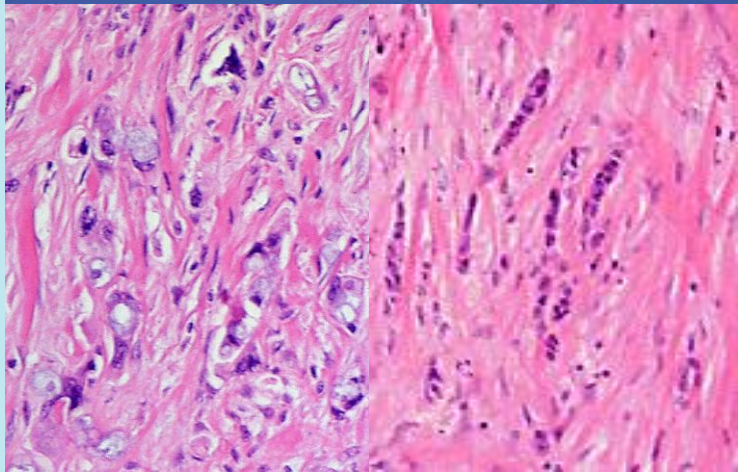


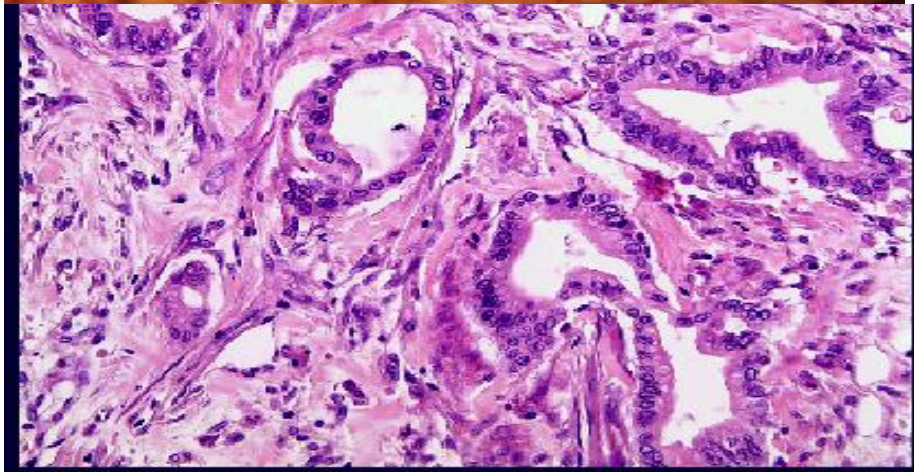


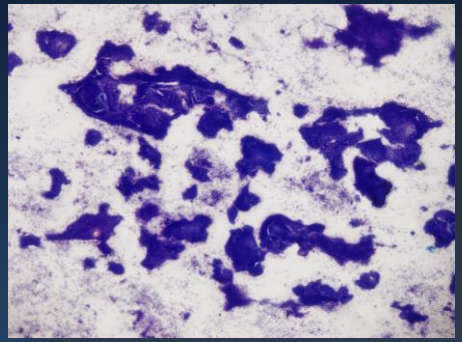
		False Pos
Siddiqui AA et al	GIE 2011	4/367 (1%)
Gleeson et al	GUT 2010	27/377 (7.2%)



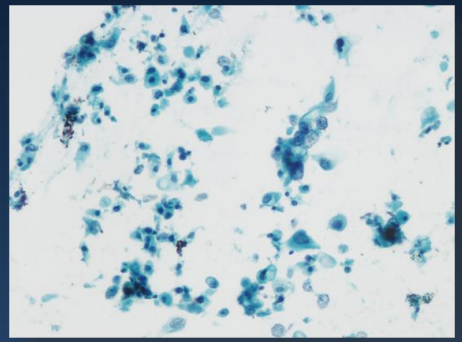




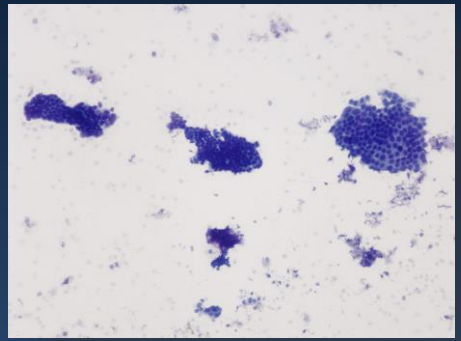




Hypercellularity

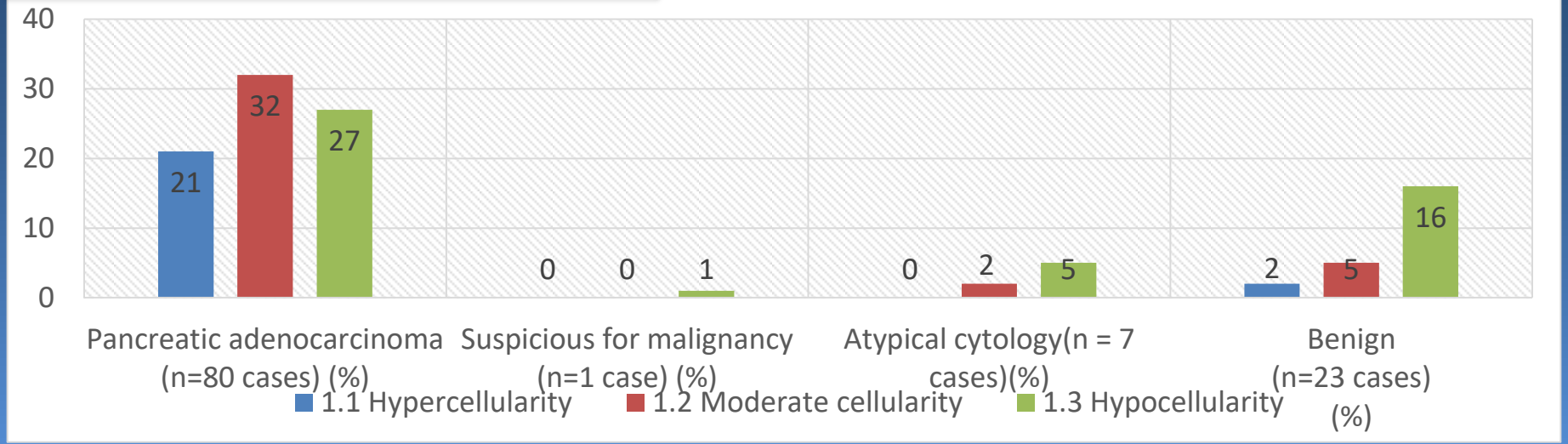


Moderate cellularity



Hypocellularity

Piyachat S .. Jhala N. ASC Nov2019



Pancreatic Cancer – Cytologic Features

3 dimensional groups

Abortive glands

Intranuclear Inclusions

Nuclear Enlargement

Nuclear Mb. Irregularity

Single Cells

Prominent Nucleoli

Chromatin Clumping

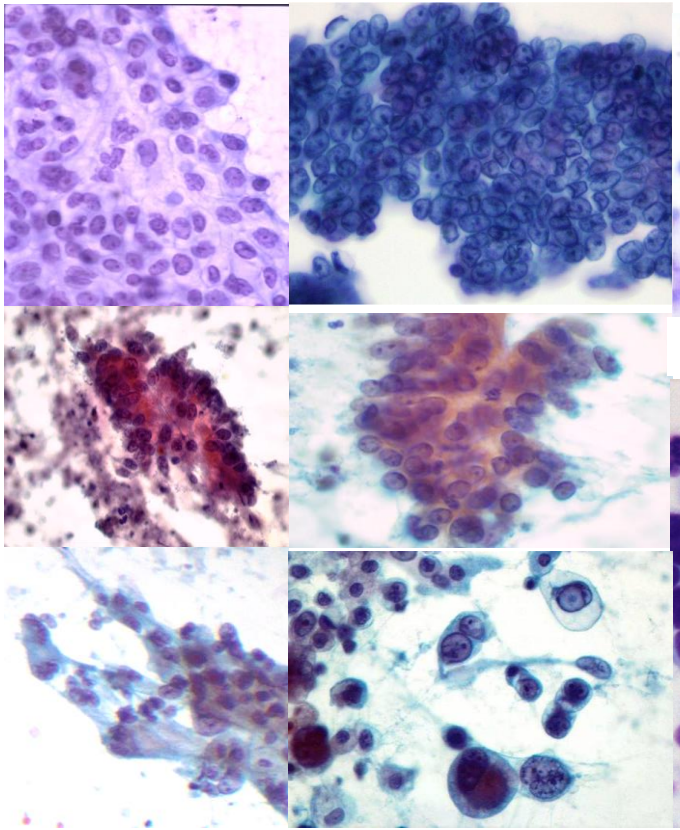
Necrotic Background

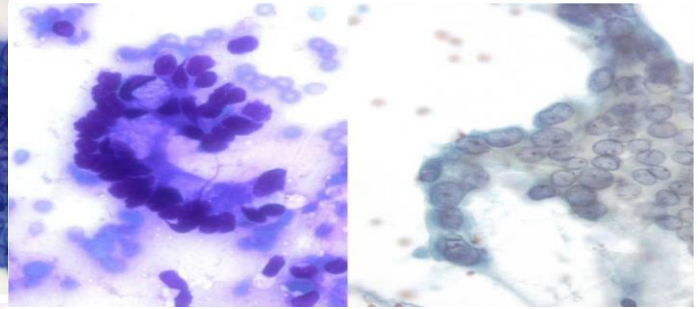
High n:c ratio

Abnormal Mitosis

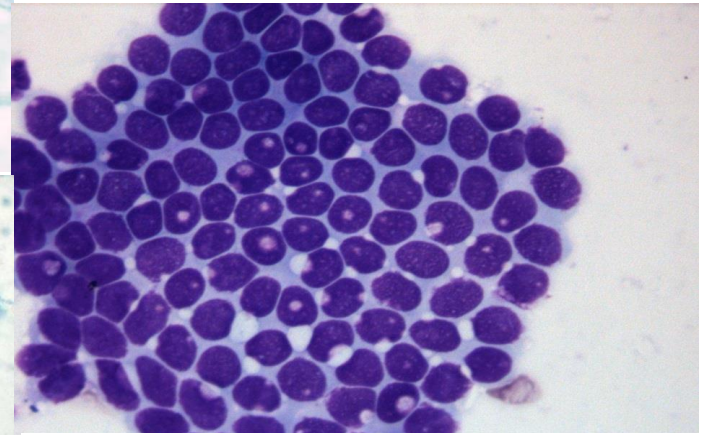
Nuclear Molding

Squamoid appearance





Cancer (Cancer Cytopathol) 2003;99:44 –50



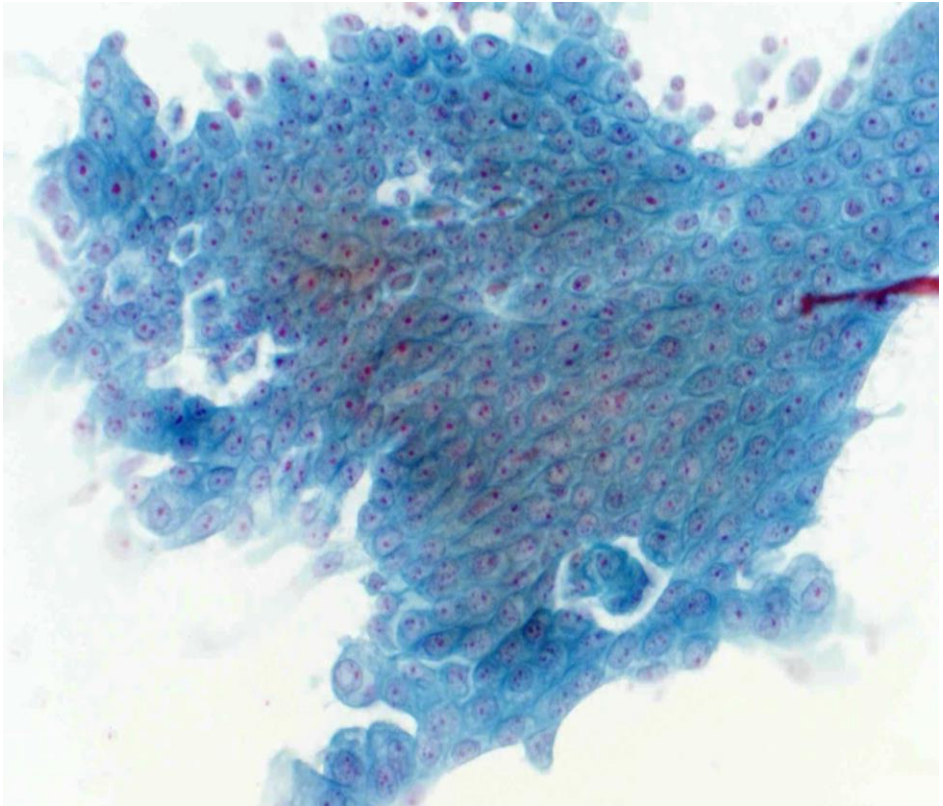
Ann Clin Cytol Pathol ; 2016:2(1): 1014

Diagn Cytopathol 1991;7:341 –345
Am J Clin Pathol 1985; 83:171-176
Diagn Cytopathol 1986; 2:301-306
Acta Cytol 1989; 42:341-347
Acta Cytol 1995; 39:1-10

Cytologic Criteria for Well Differentiated Adenocarcinoma of the Pancreas in Fine-Needle Aspiration Biopsy Specimens

Cancer (Cancer Cytopathol) 2003;99:44 –50.

3 dimensional groups
Nuclear Enlargement
Nuclear Mb. Irregularity
Single Cells
Prominent Nucleoli
Chromatin Clumping
Necrotic Background
High n:c ratio
Nuclear Molding
Mitosis
Squamoid appearance
Chromatin clearing
Hyperchromasia
Intranuclear Inclusions
Abortive glands



Utilization of Ancillary Studies in the Cytologic Diagnosis of Biliary and Pancreatic Lesions:

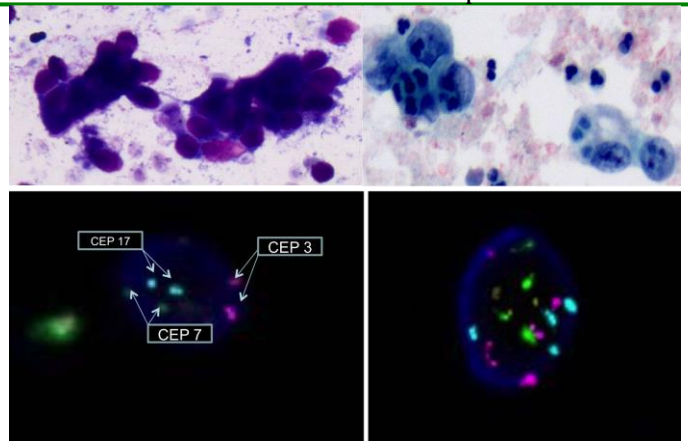
The Papanicolaou Society of Cytopathology Guidelines for Pancreatobiliary Cytology

Lester J. Layfield, M.D.[1,*], Hormoz Ehya, M.D.[2], Armando C. Filie, M.D.[3], Ralph H. Hruban, M.D.[4], Nirag Jhala, M.D.[5], Loren Joseph, M.D.[6], Philippe Vielh, M.D., Ph.D.[7], and Martha B. Pitman, M.D.[8]

	Sensitivity	Specificity	Reference
Mesothelin	74%	33%	Dim et al.
	62%	100%	Jhala et al.
	68%	91%	McCarthy et al.
SMAD4	**88%**	86%	Jhala, Iacobuzio C, Deshpande V.

FISH analysis

Jhala D and Jhala N Gastro Clin N Am 2015



Jhala Algorithm

Par

Cellular Specimen

Groups of cells and +/- single cells (morphology consistent with Epithelial cells)

Predomin

Single plasmacytoid cells
PEN
SPN
Others (Melanoma, lobular breast ca,myeloma)

Predominantly ductal cells

Adenocarcinoma

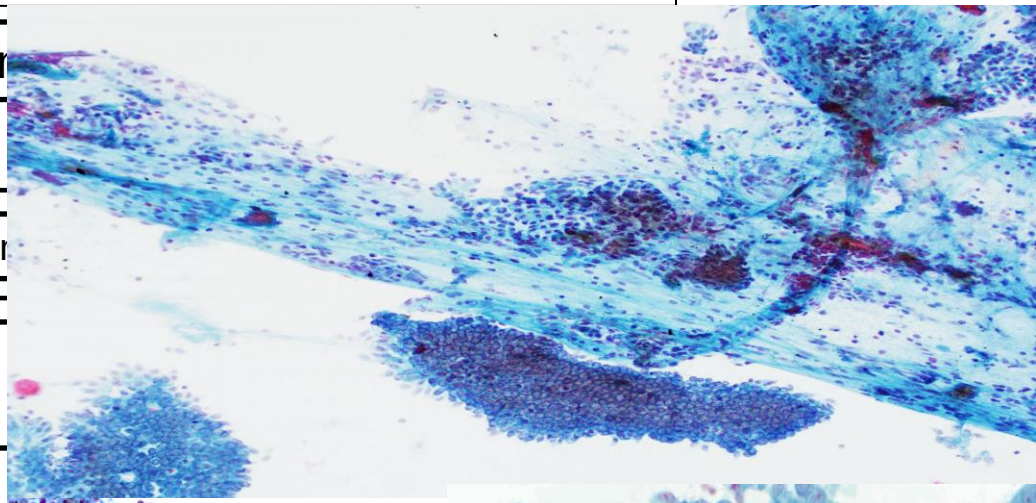
Acinar cells with rare ductal cells

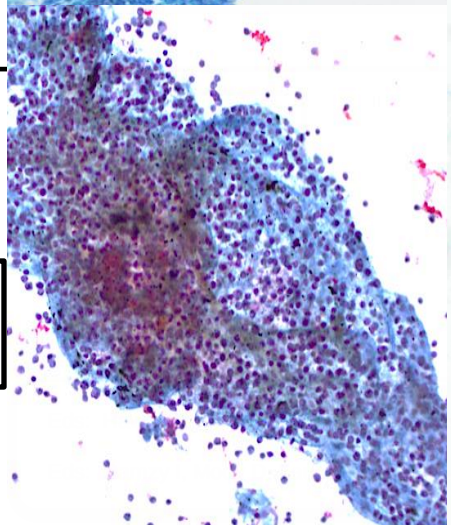
Presence of fibrosis and acute or chronic inflammatory cells

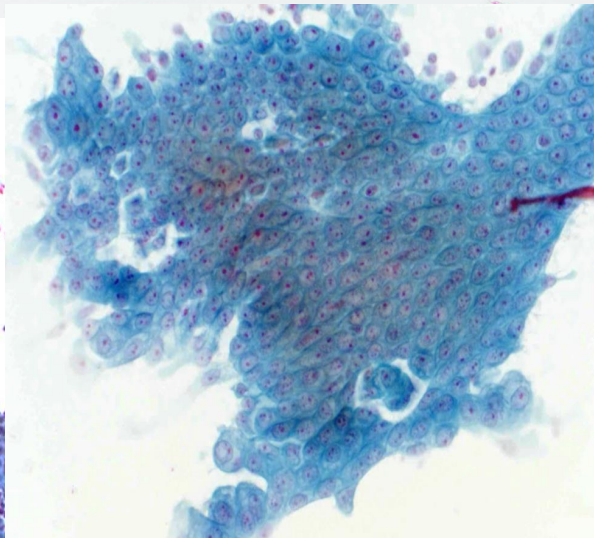
Acute or chronic pancreatitis

Presence of fibrosis and lymphoplasmacytic infiltrate

Autoimmune pancreatitis







Atypia and Autoimmune Pancreatitis

Diagnosis	# OF CASES
Malignant	1
Neoplasm (Mucinous)	1
Atypical	10
Benign	5
Non Diagnostic	3
Total	20

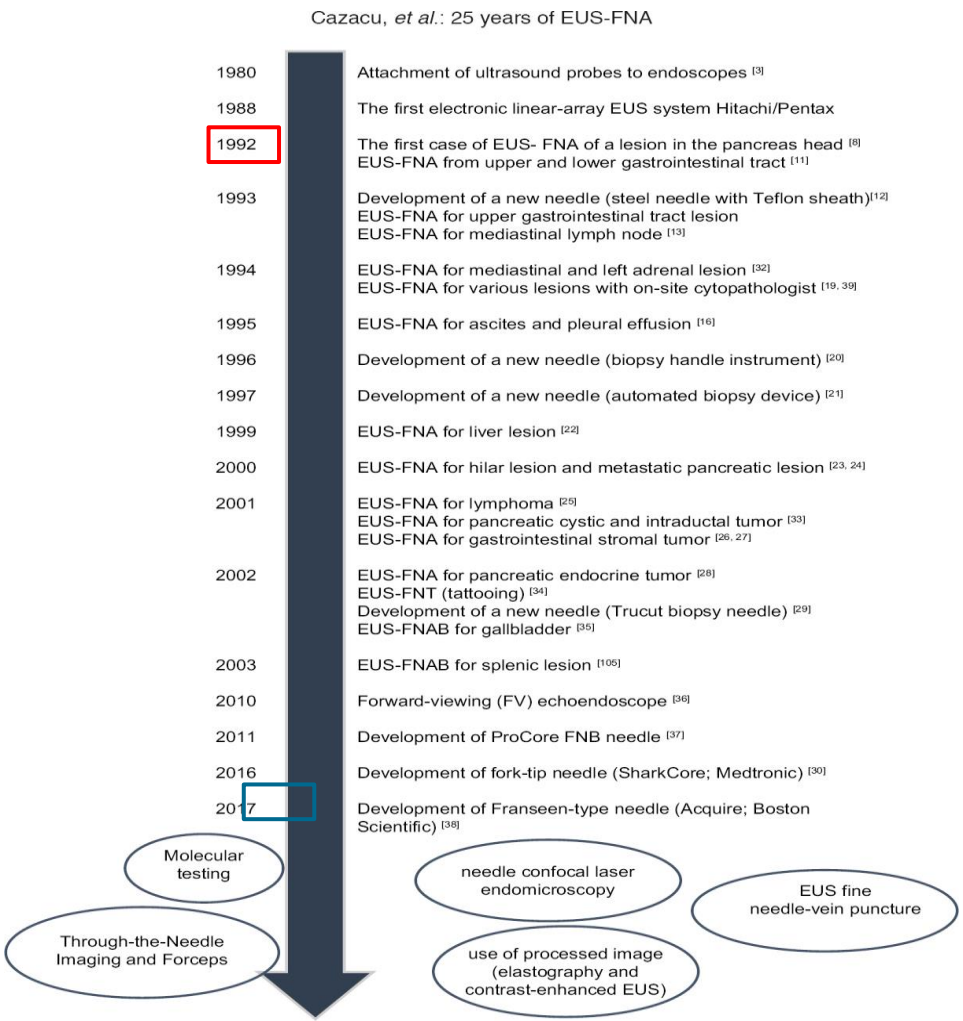
Atypical Diagnosis	# OF CASES
Suspicious for Malignancy	1
Cannot exclude NET	1
Markedly Atypical	1
Scattered Ductal Atypia	7
Total	10

Acta Cytol. 2012;56(3):228-32.

EUS-FNA

The first EUS-FNA was reported 25 years ago.

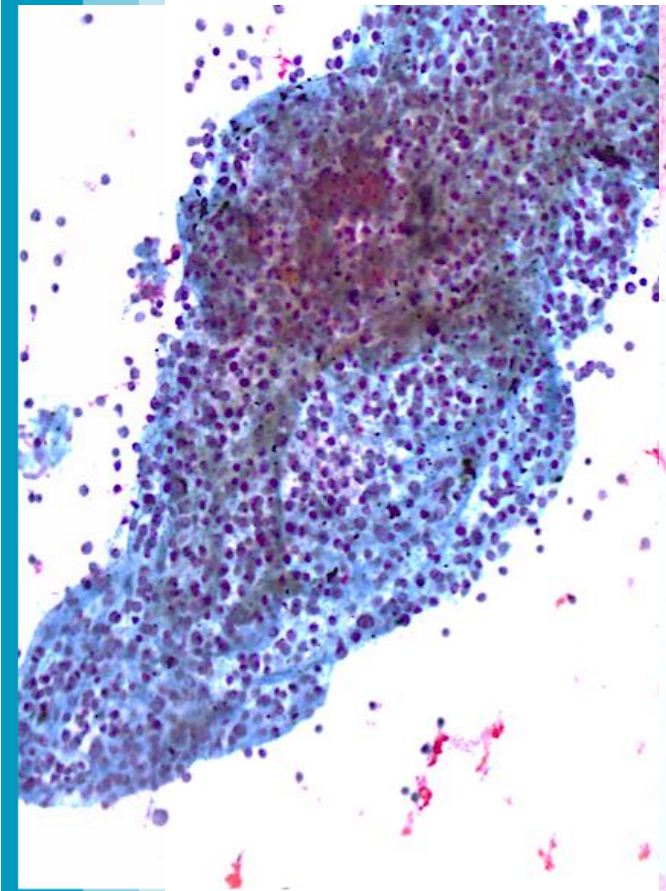
Now become a part of the diagnostic and staging algorithm for the evaluation of benign and malignant diseases of the GI tract and adjacent organs, including lung.

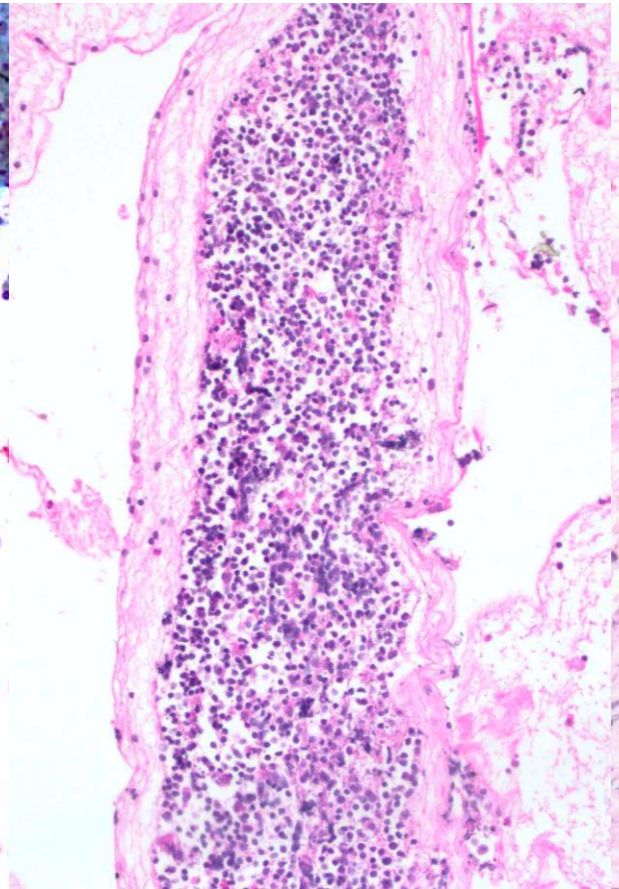


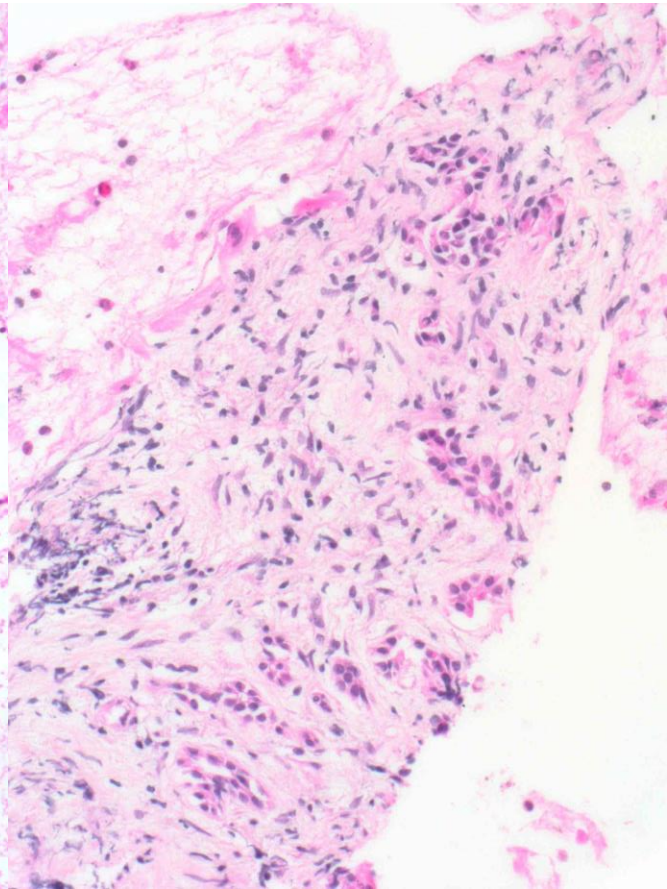
VARADARAJULU ET AL, CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2012;10:697–703

Cazacu IM et al., A quarter century of EUS-FNA: Progress, milestones, and future directions. Endosc Ultrasound 2018;7:141-60

EUS FNA of the pancreas -
58 year old - ill defined mass in the head





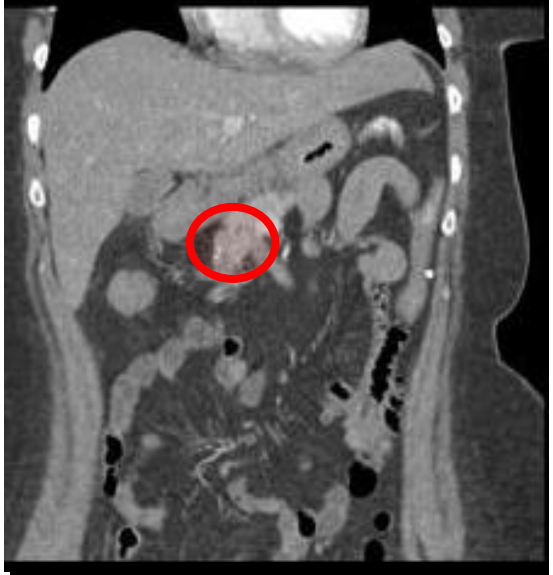


	LPSP (Resection)	**Core Biopsy**
H	At least 3 of the following: 1.Periductal lymphoplasmacytic infiltrate without granulocytic infiltration 2.Obliterative phlebitis 3.Storiform fibrosis 4.Abundant (>l0 cells/HPF) IgG4-+ cells	Any 2 of the following: 1.Periductal lymphoplasmacytic infiltrate without granulocytic infiltration 2.Obliterative phlebitis 3.Stoiform fibrosis 4.Abundant (>10 cells/HPF) IgG4-positive cells
I		Imaging Evidence
S		Serology
O	Other organ Involvement	Other organ Involvement
Rt.		Response to Steroids

Gastroenterol Clin N Am 2016; 45: 29–43

Autoimmune Pancreatitis

Case 2



2 cm, ill-defined, solid-cystic lesion
With calcifications (Head/ neck)

Well circumscribed 1 x 1.5 cm low attenuation lesion

Differential Diagnosis:

Pancreatic pseudocyst.

Serous cystadenoma

Much Less Likely:

Mucinous Cystadenoma

Pancreatic Adenocarcinoma

There was a 2 cm, ill-defined, solid-cystic lesion in the head/body of the pancreas with calcifications, preventing an accurate estimate of the entire size of the lesion, fine needle aspiration.

· **A second, small, anechoic simple cyst was noted in the body of the pancreas measuring 0.7cm.** The PD was not dilated.

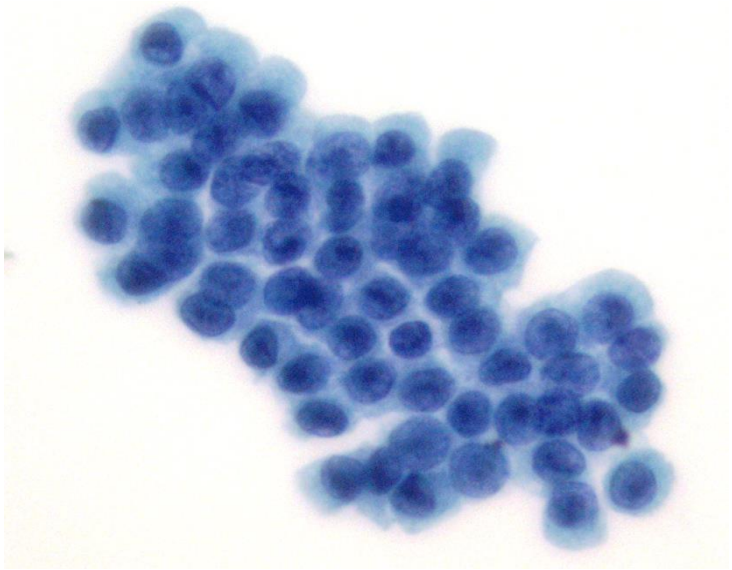
Received Clinical Information

Female 54 years

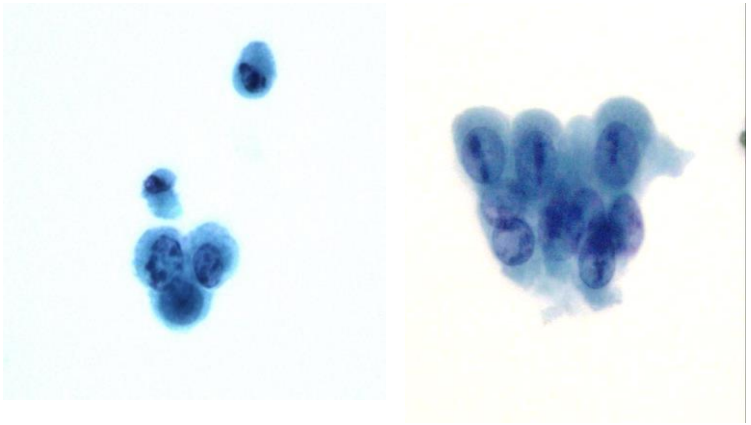
Cyst in the Head of the Pancreas

Cyst Size: 2 cm

Pancreas with calcifications



- No ROSE: Rapid Onsite Specimen Evaluation



Overview of Pancreatic Cysts

I. No lining	**“Pseudocyst”: Pancreatitis-associated**
II. True lining	**Mucinous** ***Intraductal papillary muc. neoplasm*** ***Mucinous cystic neoplasm***
	Serous
	Others (*squam., acinar, endothelial...*)
III. Degenerative /necrotic change in a neoplasm	***Solid-pseudopapillary neoplasm*** ***Cystic ductal adenocarcinoma*** **Others (*endocrine, mets., etc.*)**

Jhala N , Piyachat S, and Jhala D. Acta Cytol 2020;64:1–12

Pancreatic Cyst – Approach Overview

Is this A Mucinous or Non Mucinous Cyst?

Thick Mucin - Viscosity – String Sign
Mucinous Epithelium
Biochemical estimations
Molecular Studies

If this A Mucinous Cyst
Is it MCN vs IPMN ?

Imaging Studies
Molecular Studies

If this A Mucinous Cyst
Is it benign- Atypia/ Dysplasia - Malignant ?

Morphology

Biochemical estimations to distinguish Mucinous from Non Mucinous neoplastic Cysts

	IPMN	MCN	SCA
Viscosity	High	High	Low
CEA	High (>192 ng/ ml)*	High (>192 ng/ ml)*	Low
Amylase	Could be increased	Could be increased	Low

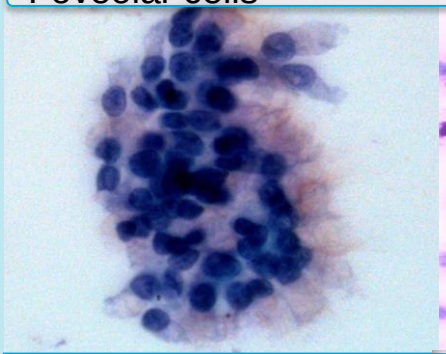
Molecular Testing in Cystic Neoplasms of the Pancreas

	IPMN	MCN	SCN
KRAS mutation	Present	Present	Absent
GNAS mutation	Present	Absent	Absent
RNF43 mutation	Present	Present	Absent
VHL gene	Absent	Absent	Present

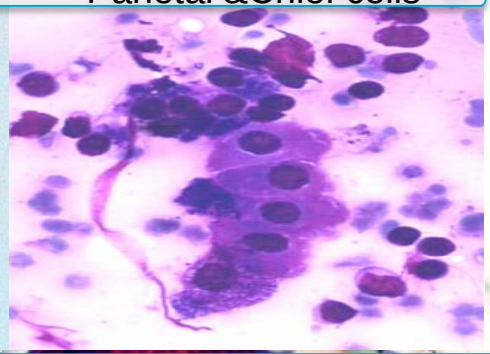
Pitman MB and Jhala N Cytology of Cystic Neoplasms of the Pancreas. Chapter 2. Eds: Chiaro MD, Haas SL and Schulick RD. Cystic Tumors of the Pancreas. Diagnosis and Treatment. Chapter 2 . Springer 2016

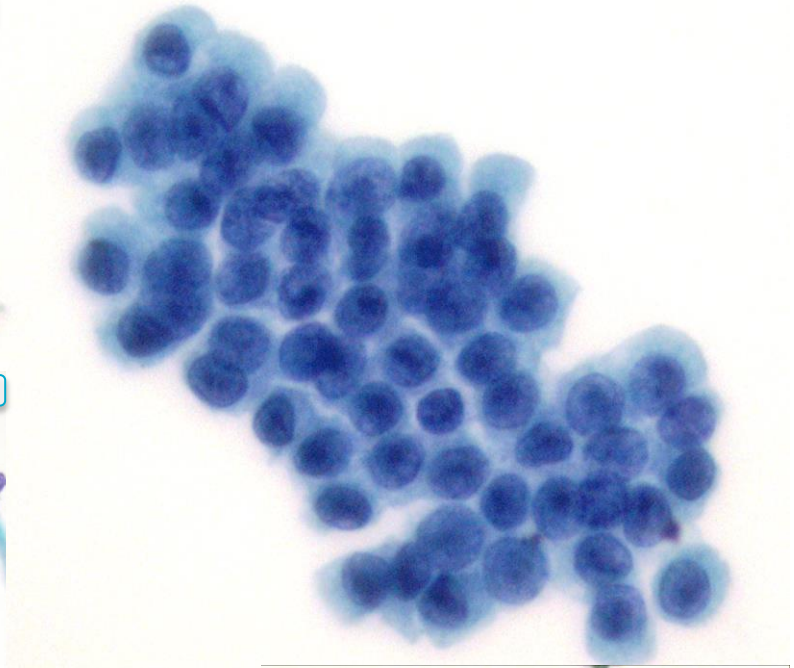
Jhala D and Jhala N . Pancreas. Chapter 18 . Eds: Ramzy I, Mody D, Laucirica R. Clinical Cytopathology ,McGraw Hill 2018

Foveolar cells



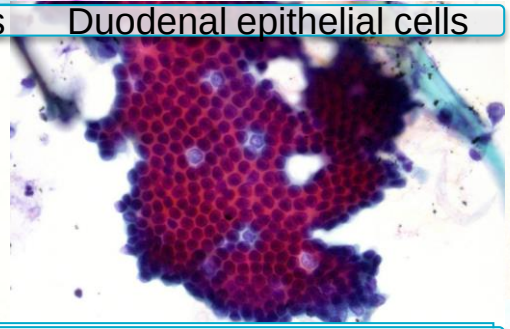
Parietal &Chief cells



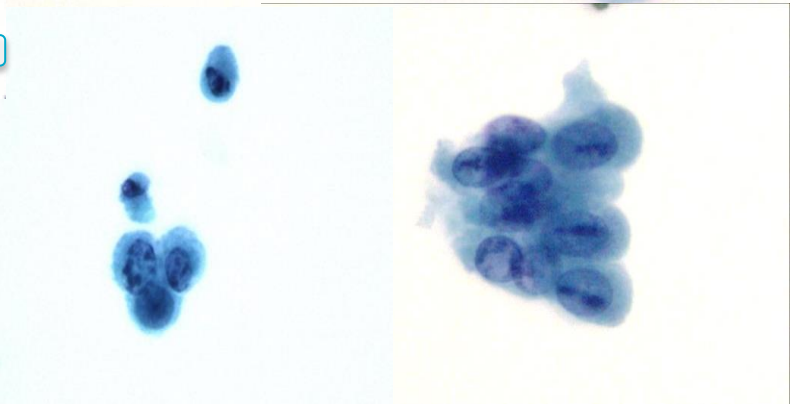


Duodenal epithelial cells

Duodenal epithelial cells



Pancreaticobiliary Epithelium



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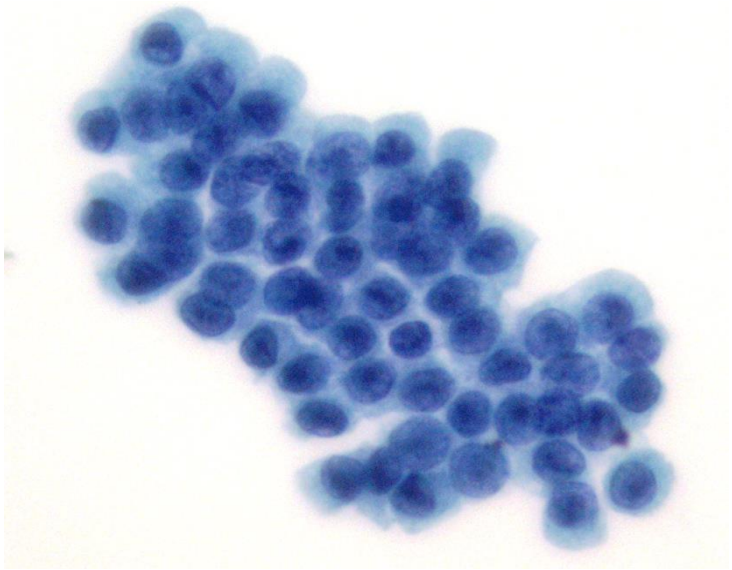
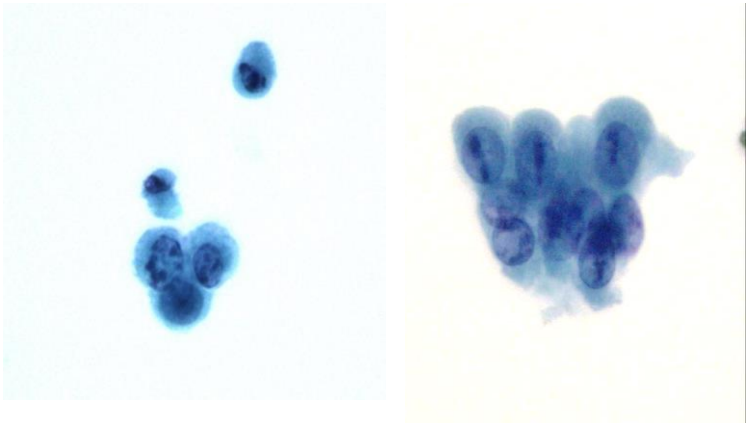


Biochemical and Molecular Studies

- CEA: 35ng/dl, Amylase : low
- Sample not collected for molecular studies

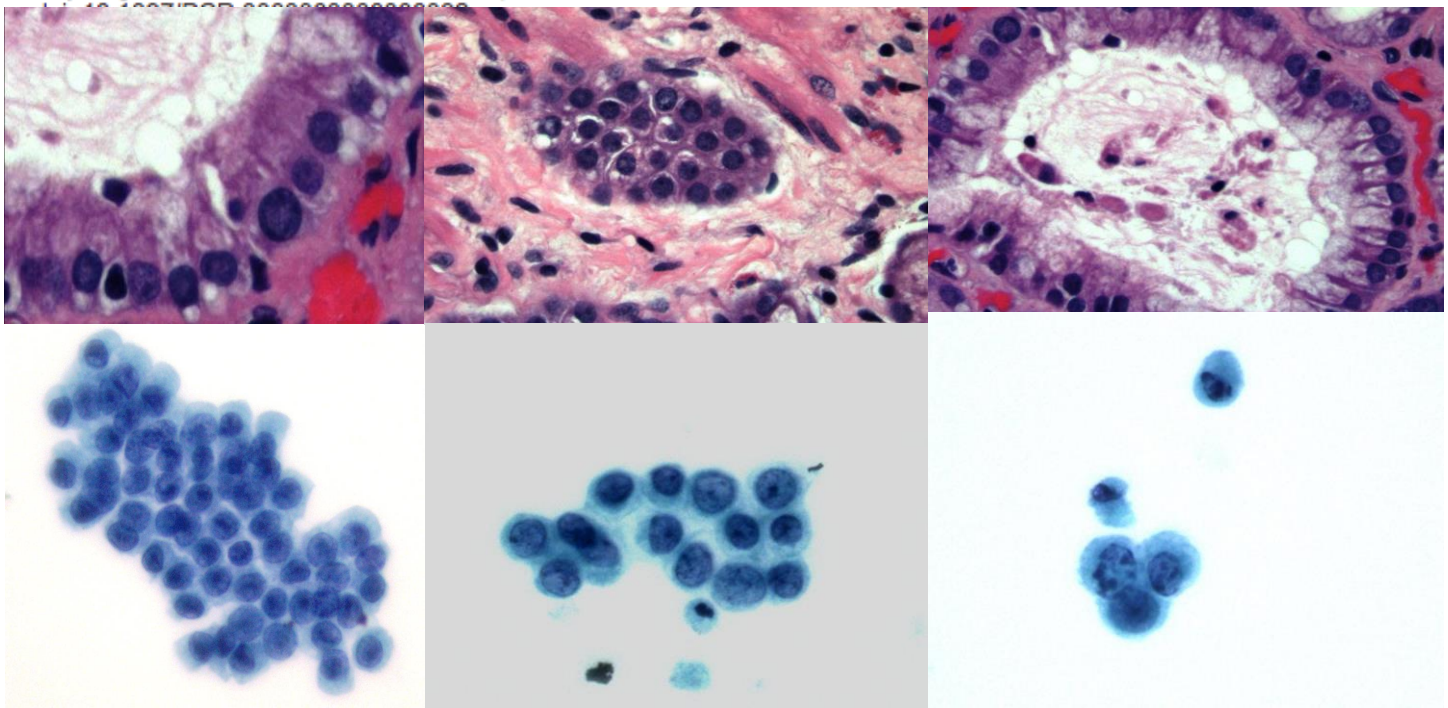


Pancreas, Head, 2.0 cm, EUS-FNA:
Markedly atypical glandular cells present and suspect a mucinous cystic neoplasm

Brunner Glands: A Major Pitfall in Assessing Endoscopic UltrasoundGuided Fine-Needle Aspiration Samples of the Pancreas

Lastra, Ricardo R. MD[*]; Jhala, Darshana N. MD[*†]; Ahmad, Nuzhat A. MD[‡]; Jhala, Nirag C. MD[§]

Pathology Case Reviews:
July/August 2015 - Volume 20 - Issue 4 - p 182–185



Risk of Malignancy for Pancreatic FNA
PSC Recommended
Neoplastic : Other Category (N= 332)

Classification	ROM
Non Diagnostic	7.7
Negative	1.0
Atypical	28.0
Neoplastic : Benign	0.0
Neoplastic : Other	30.3
Neoplastic : Other with HGA	90.0
Suspicious	100
Positive	100

J Am Soc Cytol 2019; 8:120-127

Take Home Points

Communication with clinical colleagues is important

Review imaging findings

Correlate morphology with Biochemical estimations
Understand pitfalls

If needed – Molecular testing may be of benefit

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PATHOLOGISTS