# Pancreatic Ductal Carcinoma

M. Lisa Zhang, MD

Massachusetts General Hospital

Harvard Medical School
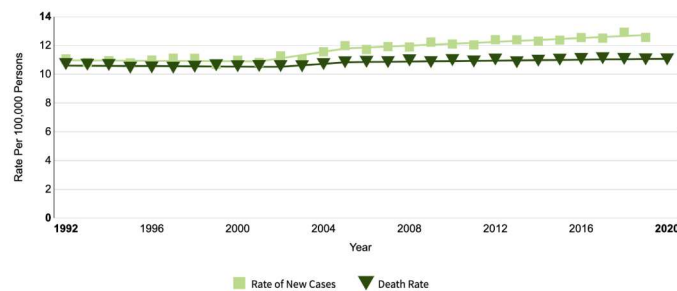
---

# Outline

- Background
- Normal pancreas elements
- Conventional pancreatic ductal adenocarcinoma (PDAC)
  - Differential diagnosis
  - Challenging scenarios
  - Immunohistochemistry
- PDAC variants

# Pancreatic Cancer

| Estimated New Cases in 2022 | 62,210 |
|---|---|
| % of All New Cancer Cases | 3.2% |

| Estimated Deaths in 2022 | 49,830 |
|---|---|
| % of All Cancer Deaths | 8.2% |

5-Year
Relative Survival

**11.5%**

2012–2018

---

# Pancreatic Ductal Adenocarcinoma (PDAC)

- 3rd leading cause of cancer-related deaths in the U.S.
- >90% of all pancreatic neoplasms
- Highest incidence in ages 60-80, M>F
- Mutational profile
    - 4 main mutations: *KRAS*, *CDKN2A/p16*, *p53*, *SMAD4*: no targeted therapy
    - ~2.5% *BRCA1/2* mutations: PARP inhibitors (olaparib FDA-approved 12/2019)
    - ~1% MSI-high/MMR-deficient: pembrolizumab
- Only cure is early detection and complete surgical resection
    - 50-55% of patients present with metastatic disease
    - 25-30% present with locally advanced/unresectable tumors (neoadjuvant therapy)

# Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA)

Know the path of the needle:
- Often transduodenal for pancreatic head lesions
- Often transgastric for pancreatic body/tail lesions
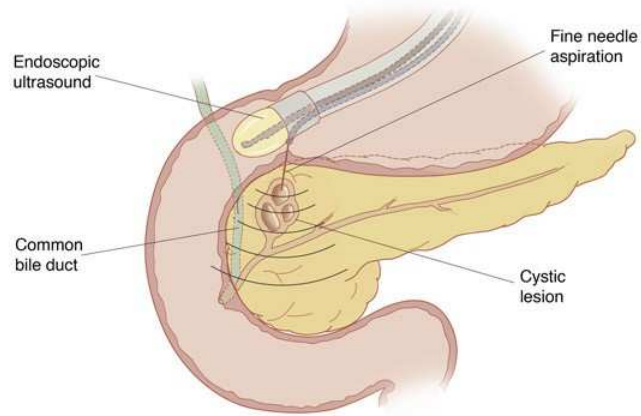


Endoscopic ultrasound
Fine needle aspiration
Common bile duct
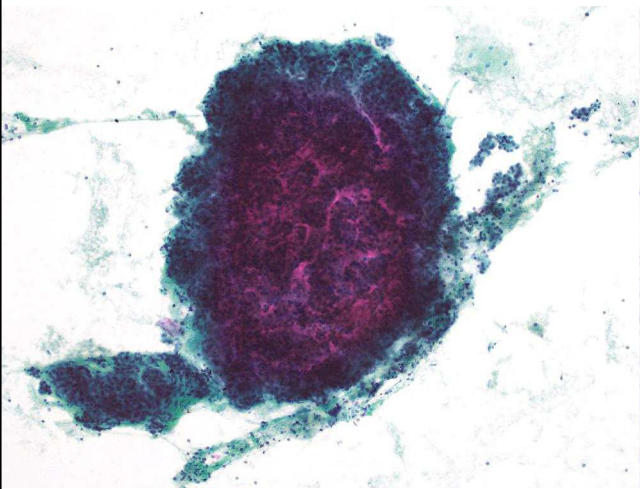Cystic lesion

# Outline

- Background
- **Normal pancreas elements**
- Conventional pancreatic ductal adenocarcinoma (PDAC)
  - Differential diagnosis
  - Challenging scenarios
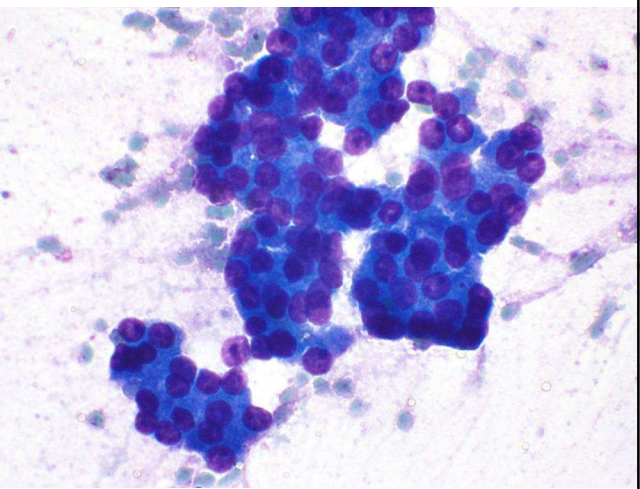  - Immunohistochemistry
- PDAC variants

# Normal pancreas



Acinar cells

Ductal cells
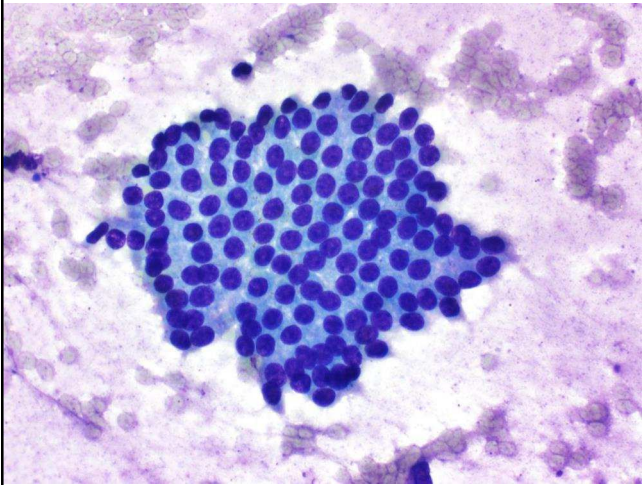
Acinar cells

Neuroendocrine cells
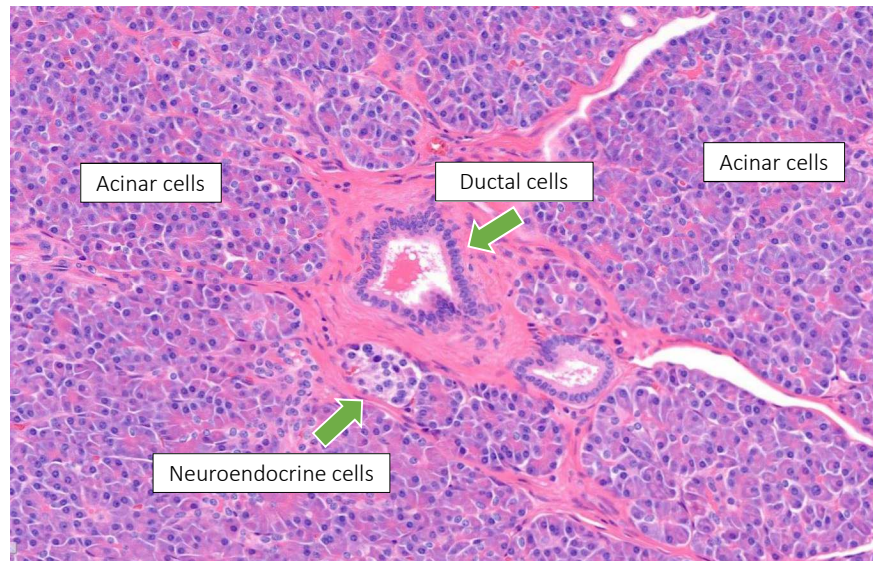
# Acinar cells

Pap stain, low power

Diff-Quik stain, high power

# Ductal cells

Diff-Quik stain

Pap stain
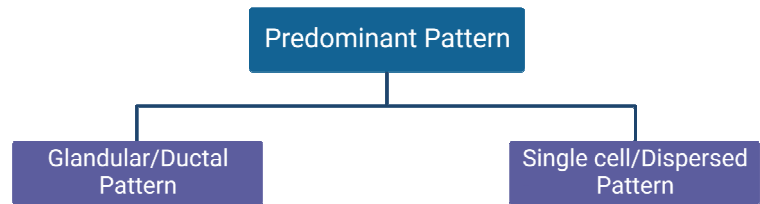
---

# Outline

- Background
- Normal pancreas elements
- Conventional pancreatic ductal adenocarcinoma (PDAC)
  - Differential diagnosis
  - Challenging scenarios
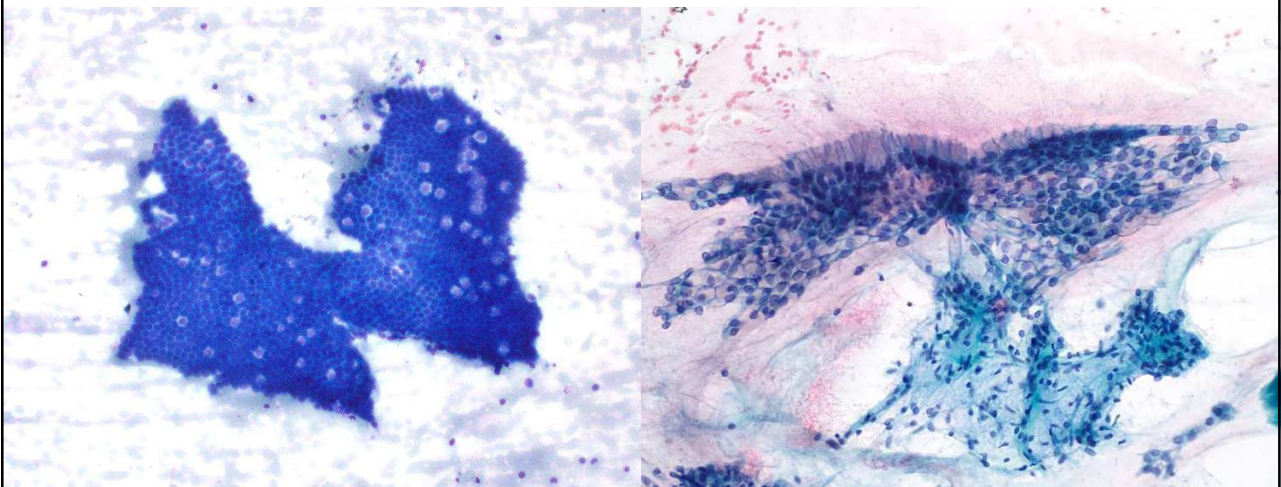  - Immunohistochemistry
- PDAC variants

## Differential Diagnosis of Solid Lesions

Predominant Pattern

Glandular/Ductal Pattern

Single cell/Dispersed Pattern
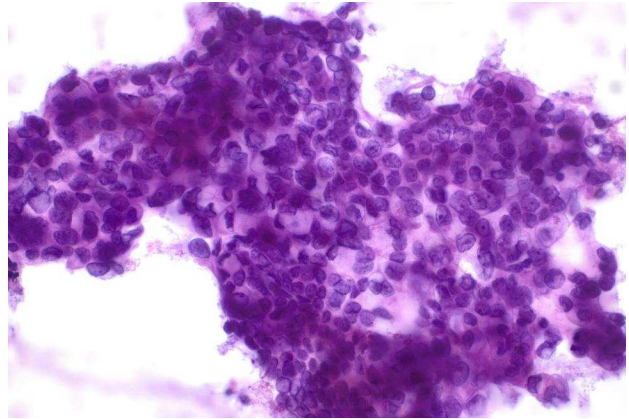
---

# GI Contamination

Duodenal contamination

Gastric contamination

# Pancreatic ductal adenocarcinoma (PDAC)
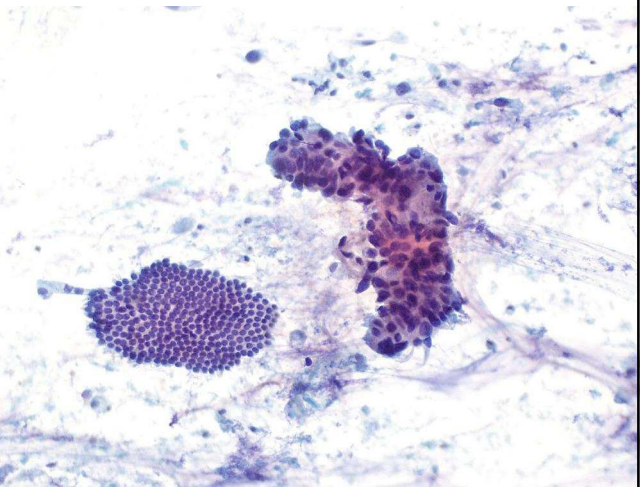
- Architecture
  - "Drunken honeycomb"
  - (Single atypical cells)
  - (Background necrosis)
- Cytomorphology
  - Anisonucleosis >4:1
  - Nuclear membrane irregularities
  - Nuclear hypo or hyperchromasia
  - Variably prominent nucleoli
  - Variably mucinous cytoplasm



# Pancreatic Ductal Adenocarcinoma (PDAC)
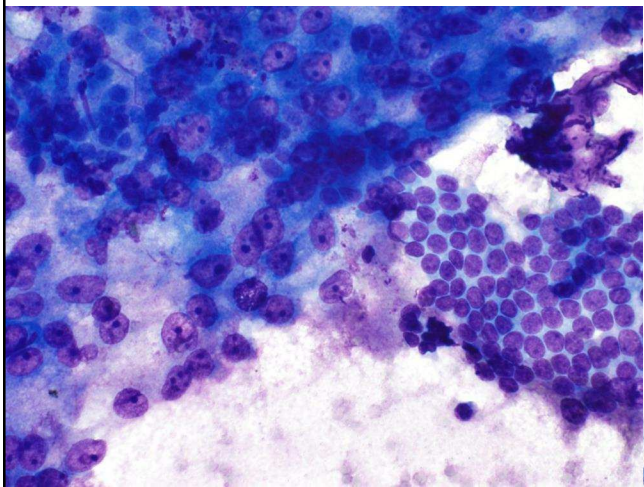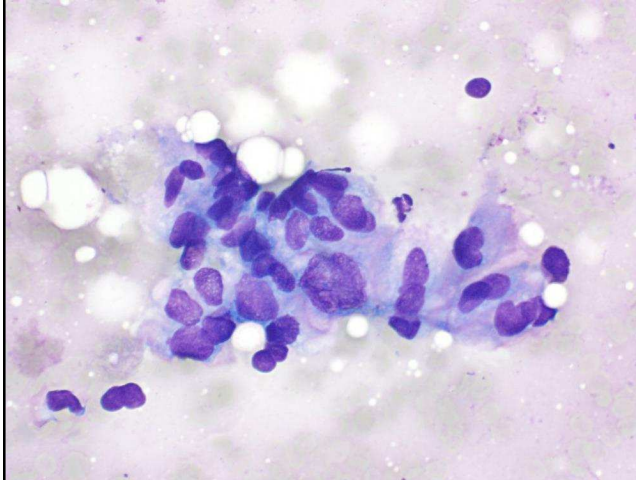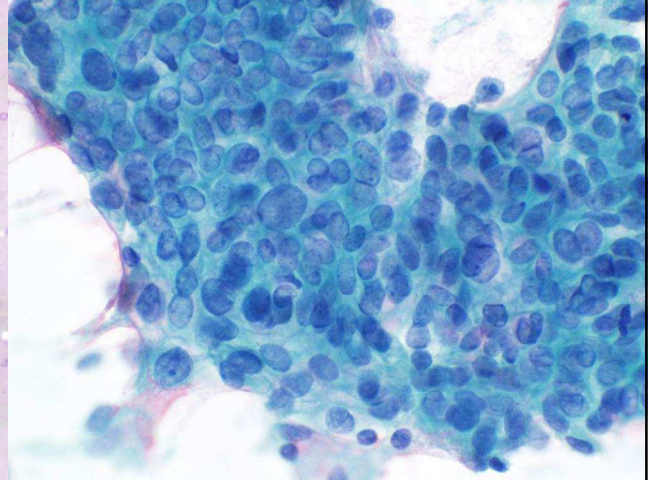


Diff-Quik stain

Pap stain

# Pancreatic Ductal Adenocarcinoma (PDAC)



Diff-Quik stain



Pap stain

---

# Causes of reactive atypia

| Clinical scenario: | | |
|---|---|---|
| inflammatory process that appears mass-forming on imaging<br>→ FNA to rule out malignancy | Acute pancreatitis | Dirty background (debris, necrosis) |
| | | Acute inflammation |
| | | Fat necrosis |
| | | Calcifications |
| | Chronic pancreatitis | Background amorphous/granular debris |
| | | Variable mixed inflammation |
| | | Fibrotic tissue fragments |
| | | Late stage: lack of acinar tissue, residual islet cells |
| | Autoimmune pancreatitis | Type 1 (IgG4-related): lymphoplasmacytic sclerosing |
| | | Type 2: granulocytic epithelial lesions (more marked atypia) |
| | Paraduodenal/groove pancreatitis | Spindle cell proliferation (fibroblasts, smooth muscle) |
| | | Brunner glands (foamy cells) |
| | | Variable neutrophils and macrophages |

Table 1. Comparison of Reactive Atypia, Well-Differentiated Adenocarcinoma, and Moderately or Poorly Differentiated Adenocarcinomas in Fine-Needle Aspiration Samples

| Criteria | Reactive Atypia | Well-Differentiated Adenocarcinoma | Moderately or Poorly Differentiated Adenocarcinoma |
|---|---|---|---|
| Cellularity | <6 atypical groups | Variable | Variable |
| Background | Inflammatory, clean, debris | Clean or bloody | Coagulative necrosis |
| Architecture | Minimal crowding, loss of polarity | Large, folded groups, nuclear crowding, and overlapping | More 3-dimensional groups; smaller atypically formed groups |
| Dyshesion | Cohesive | Infrequent; cohesion more typical | Present |
| Anisonucleosis | Mild: 2:1 to 3:1; moderate: 3:1 to 4:1 (not >4:1) | >4:1 | More variability in the degree of anisonucleosis |
| Nuclear enlargement | Nuclear size increases | 1.5× red blood cells on air-dried smears, 2.5× normal duct nuclei on alcohol-fixed smears | Larger than well differentiated, more variability in nuclear size |
| Chromatin appearance | Granular, evenly distributed | More often hypochromatic | Hyperchromasia and abnormal parachromatin clearing |
| Nuclear membrane abnormalities | Minimal | Elongations and angulations | More obvious notches and convolutions |
| Mitoses | Can be present, no abnormal forms | Infrequent | Abnormal forms, more frequent |
| Macronucleoli | Present in moderate atypia | Absent | Present |

Centeno BA. Arch Pathol Lab Med 2023.
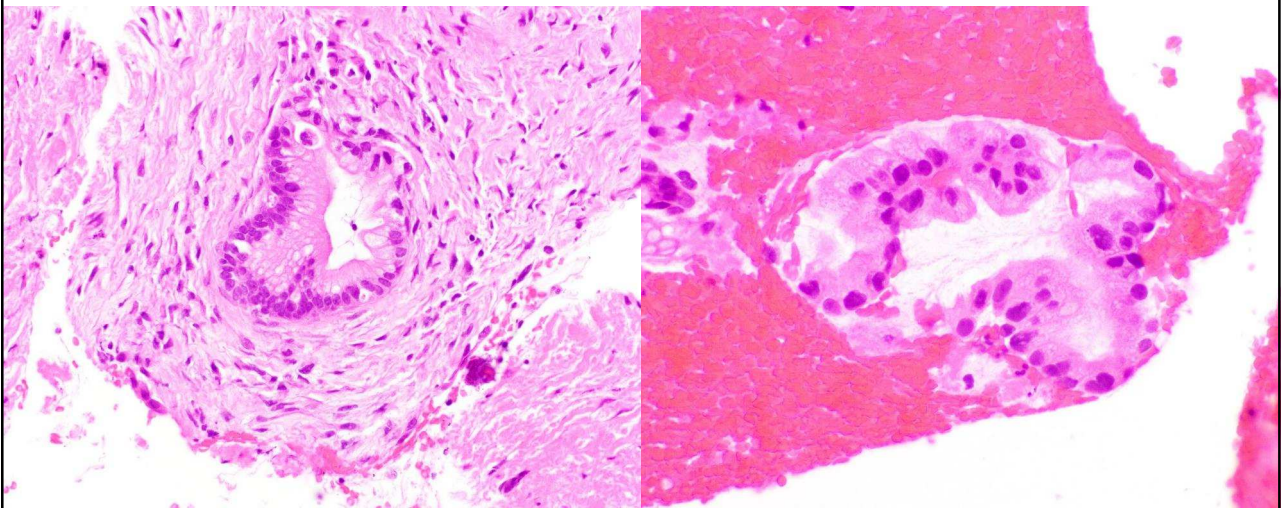


Well-diff adenocarcinoma vs. reactive atypia?
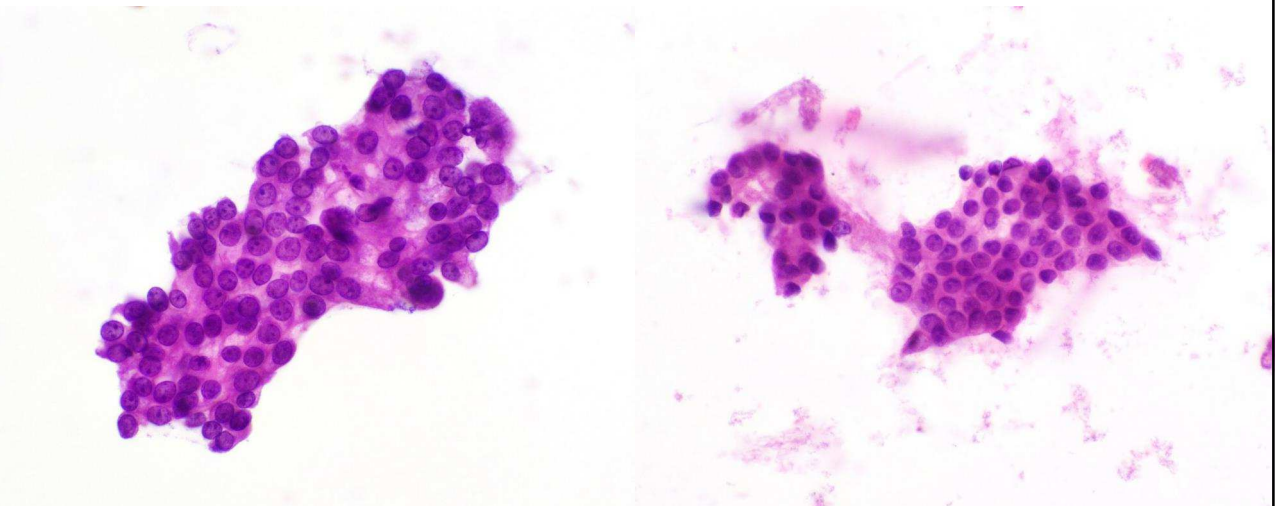
Rapid H&E stain, on-site evaluation

Well-diff adenocarcinoma vs. reactive atypia?
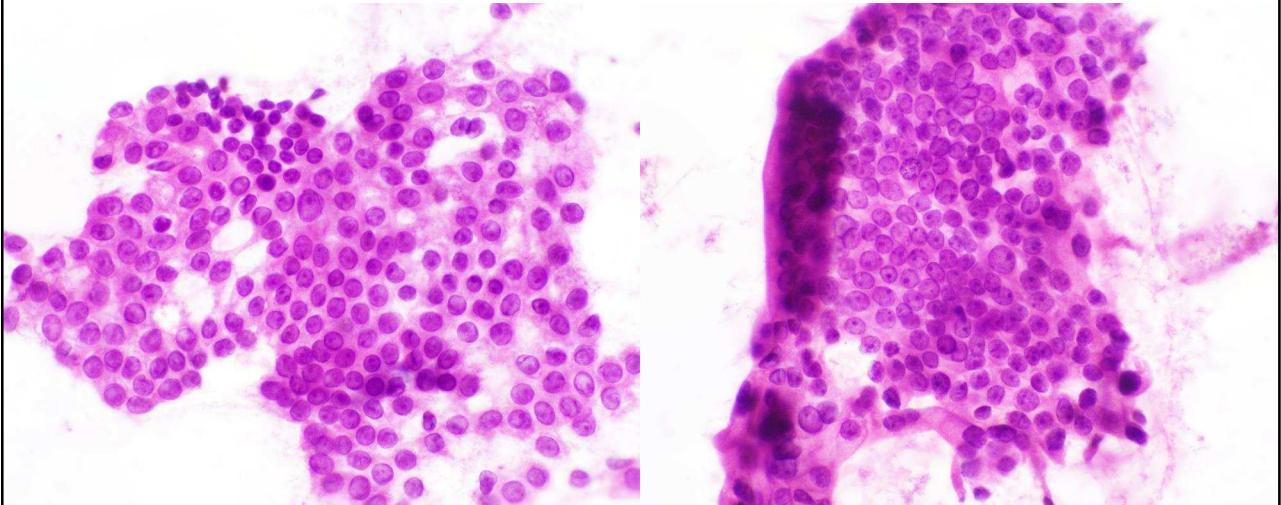
Rapid H&E stain, on-site evaluation



Well-diff adenocarcinoma

# Indeterminate diagnostic categories

**Table 3** Absolute risk and relative risk of malignancy of the diagnostic categories in the PCS system.

| Diagnostic category | Absolute risk of malignancy (%) | Relative risk | P value (relative to benign category) |
|---|---|---|---|
| I. Nondiagnostic | 7.7 | 7.7 | 0.07 |
| II. Negative for malignancy | 1.0 | 1.0 | NA |
| III. Atypical | 28.0 | 28.0 | 0.001[a] |
| IV. Neoplastic: benign | 0.0 | 0.0 | 1.00 |
| IV. Neoplastic: other, all grades of atypia | 30.3 | 30.3 | <0.001[a] |
| With low-grade atypia | 4.3 | 4.3 | 0.23 |
| With high-grade atypia | 90.0 | 90.0 | <0.001[a] |
| V. Suspicious for malignancy | 100.0 | 100.0 | <0.001[a] |
| VI. Positive or malignant | 100.0 | 100.0 | <0.001[a] |

Abbreviations: NA, not applicable; PCS, Papanicolaou Society of Cytopathology.
[a]Statistically significant ($P < 0.05$).

Hoda RS et al. J Am Soc Cytopathol. 2019

---

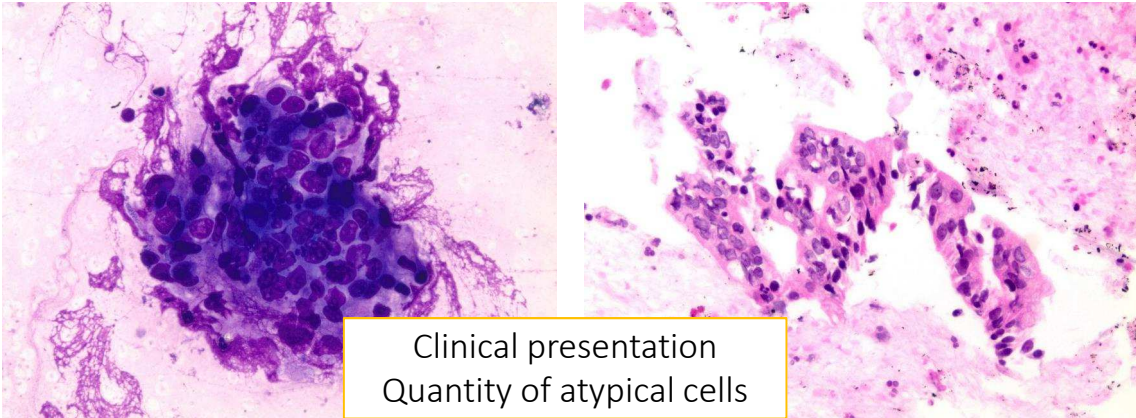# Example case: final diagnosis "Atypical"

- 81-year-old female with pancreatic head mass, prior biopsy with "reactive epithelial changes and acute inflammation"



Quality/Degree of atypia
? Reactive/injured epithelium
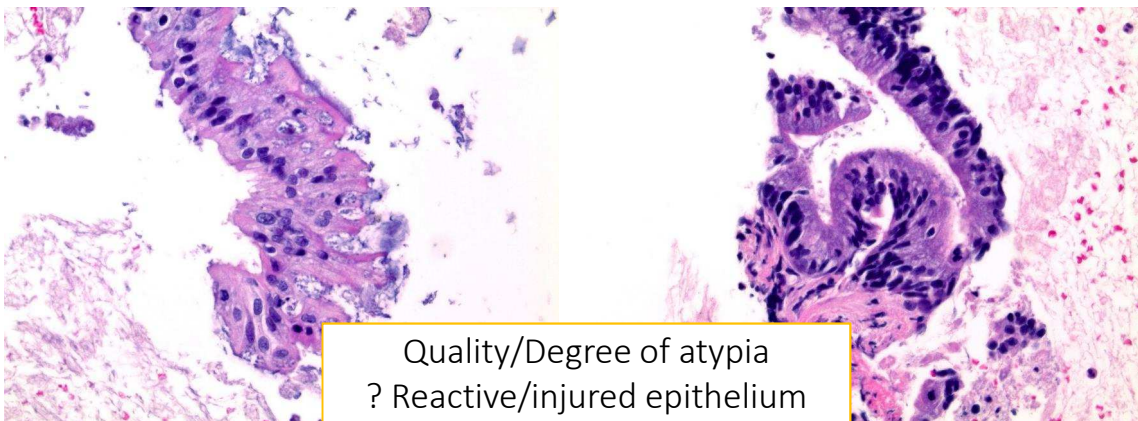
# Example case: final diagnosis "Atypical"

- 29-year-old female with pancreatic duct dilatation and possible obstructive mass in the pancreatic head, ?pancreatitis vs. PDAC



Clinical presentation
Quantity of atypical cells

# Example case: final diagnosis "Suspicious"

- Very rare highly atypical cells in a background of desmoplastic stroma
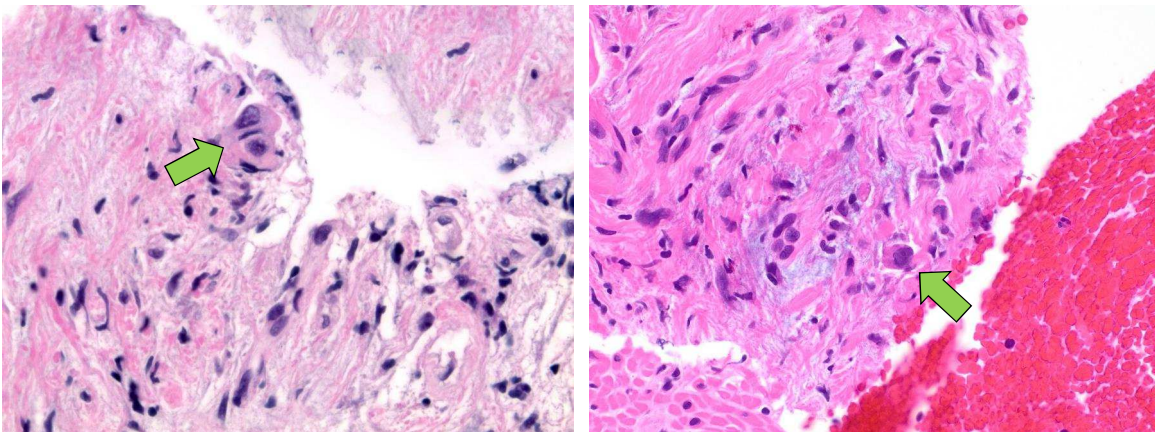
# Features of PDAC on small biopsies

Box 1
**Features supporting adenocarcinoma over chronic pancreatitis on core biopsy specimens**

Haphazard growth pattern

Incomplete lumina/luminal necrosis

Nuclear size variation greater than 4:1

Growth next to muscular vessel

Perineural invasion

Vascular invasion

Ancillary IHC: loss of immunolabeling for Smad4
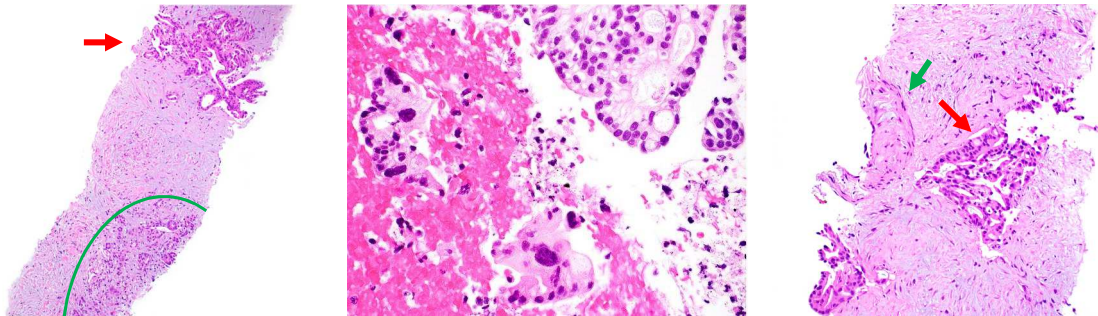


Thompson ED, Zhang ML, VandenBussche CJ. Surg Pathol Clin 2022.
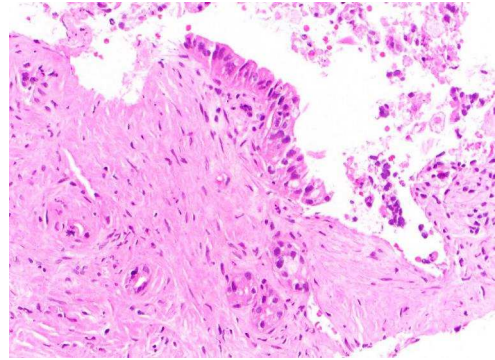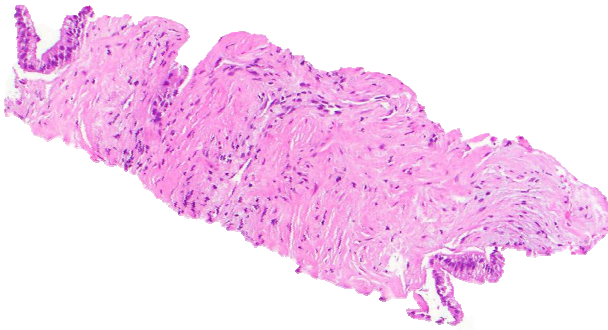
---

# Features of PDAC on small biopsies

- Detached epithelial strips (floating tumor)
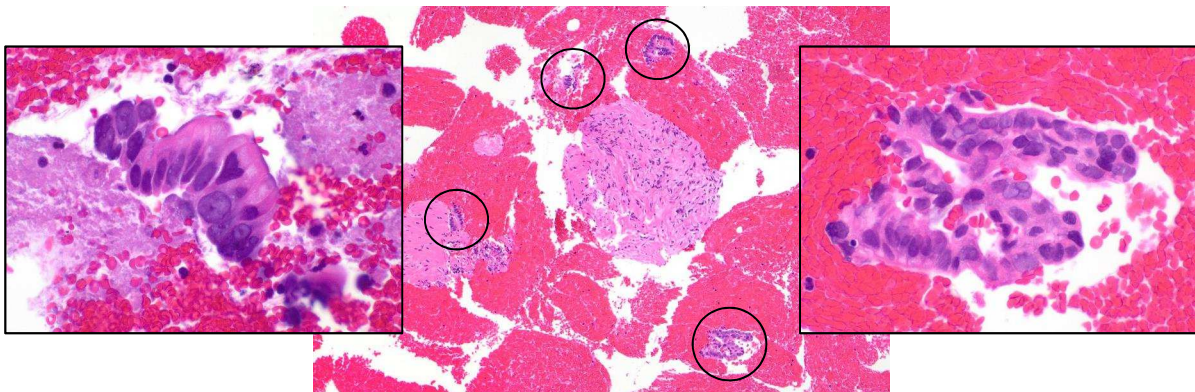
# Features of PDAC on small biopsies

- Tumor strips at tissue fragment ends (tumor breakage)
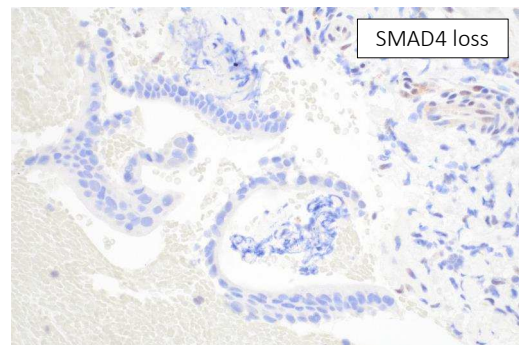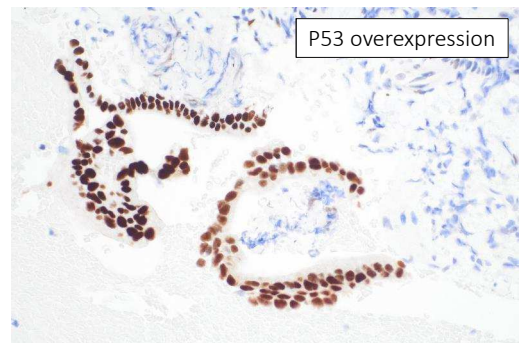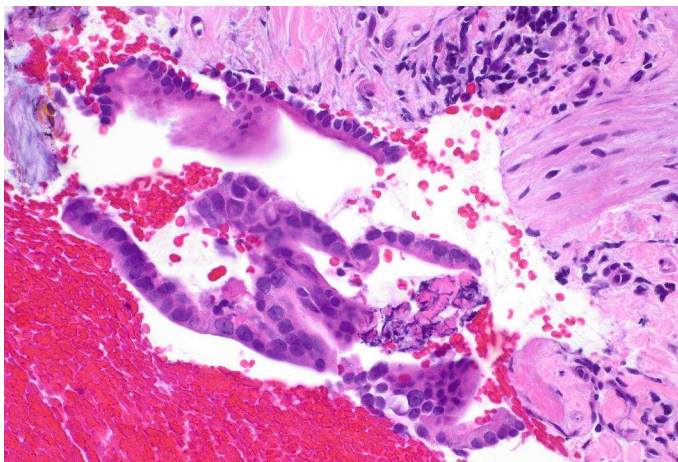


# Features of PDAC on small biopsies

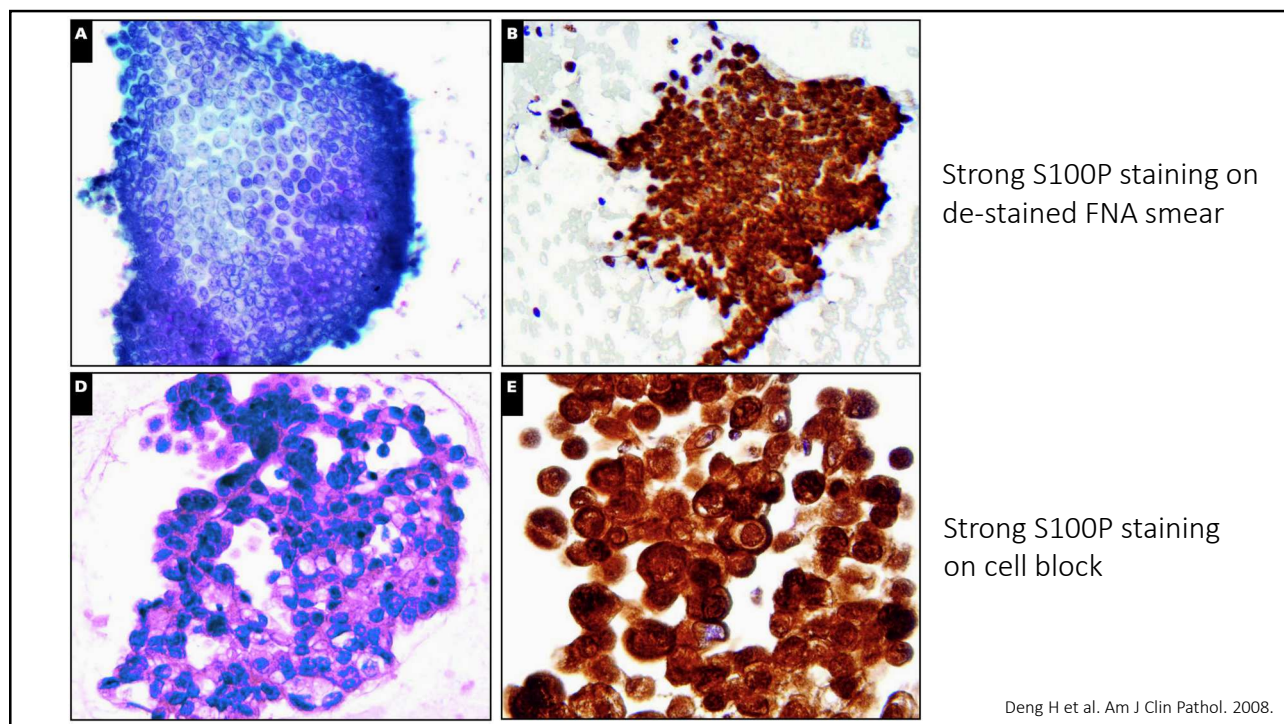- Epithelial strips at tissue fragment ends (tumor breakage)



WHO Reporting System for Pancreaticobiliary Cytopathology 2022.

# Immunohistochemistry (1st tier panel)

- **SMAD4/DPC4**: complete loss of expression in 50-55% of PDAC
  - Also lost in variety of other primary carcinomas (not as helpful for metastases)
- **P53**: mutant expression in 50-75% of PDAC (overexpression > loss)
  - >90% reported concordance between P53 IHC and mutation status
- **S100P**: strong diffuse nuclear+cytoplasmic expression in >90% of PDAC
  - Strong expression in gastric epithelium
  - Rare false positives (patchy or cytoplasmic only) in benign reactive ductal epithelium

Sweeney J et al. J Am Soc Cytopathol. 2018.
Hutchings D et al. Am J Surg Pathol. 2018.
Lin F, Chen ZE, Wang HL. Arch Pathol Lab Med. 2015.

P53 overexpression

SMAD4 loss

Strong S100P staining on de-stained FNA smear

Strong S100P staining on cell block

Deng H et al. Am J Clin Pathol. 2008.

---

# Outline

- Background
- Normal pancreas elements
- Conventional pancreatic ductal adenocarcinoma (PDAC)
  - Differential diagnosis
  - Challenging scenarios
  - Immunohistochemistry
- PDAC variants

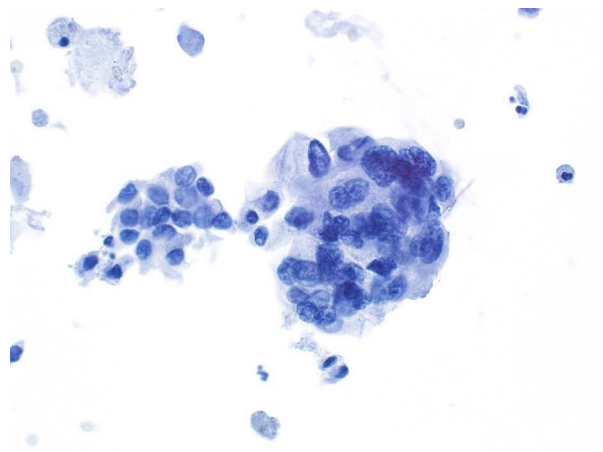# Morphologic patterns vs. Histologic subtypes

- Morphologic patterns
  - Large duct pattern
  - Cystic papillary pattern
  - Foamy gland pattern
  - Clear cell pattern

- Histologic subtypes
  - Adenosquamous
  - Colloid
  - Hepatoid
  - Medullary
  - Invasive micropapillary
  - Signet-ring cell
  - Undifferentiated
    - Anaplastic
    - Sarcomatoid
    - Carcinosarcoma
    - Osteoclast-like giant cells

---

# Cystic PDAC

- Scenario 1: Not arising in mucinous cyst
  - Secondarily cystic due to necrosis
  - Large duct or cystic papillary patterns (mimic IPMN)
- Scenario 2: Arising in mucinous cyst (IPMN or MCN)
- Similar cytomorphologic features as usual solid PDAC
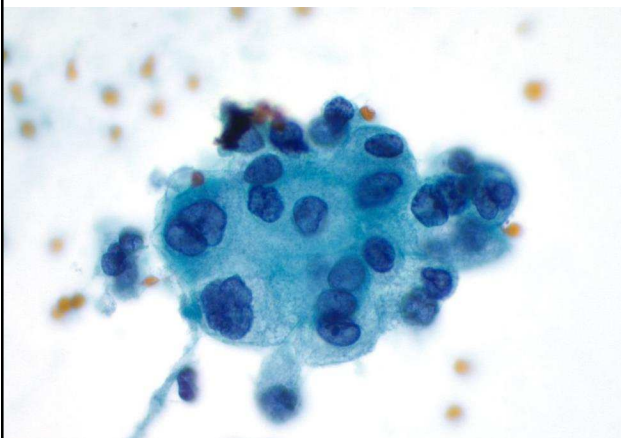
# Foamy gland pattern

- Morphologic pattern, not histologic subtype – not prognostically distinct from conventional PDAC
- Important to recognize because deceptively bland morphology
- Large cell size
- Low N/C ratio
- Abundant foamy, lacy, microvesicular cytoplasm
- Basally-oriented hyperchromatic nuclei
  - Relatively bland, rasinoid
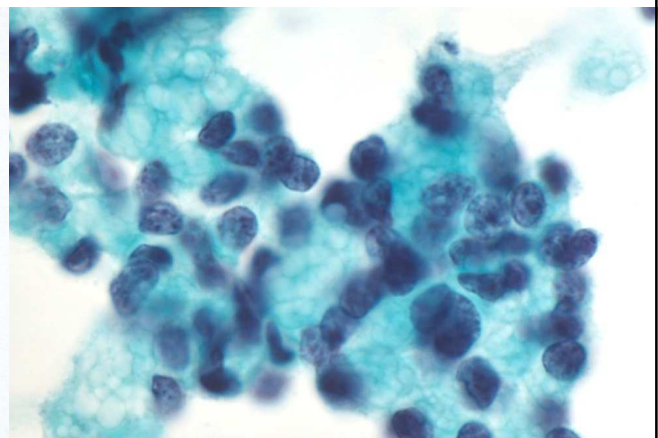- Some PDACs have mixture of foamy and more conventional tumor cells
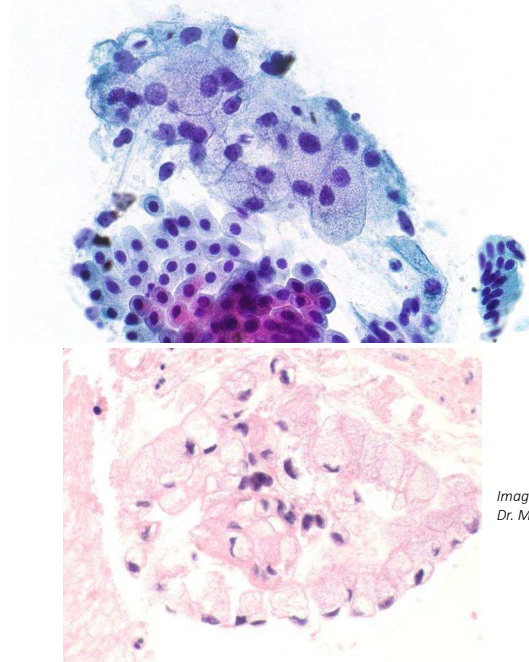


*Images courtesy of Dr. Martha Pitman*

Adsay V et al. Am J Surg Pathol. 2000.

---

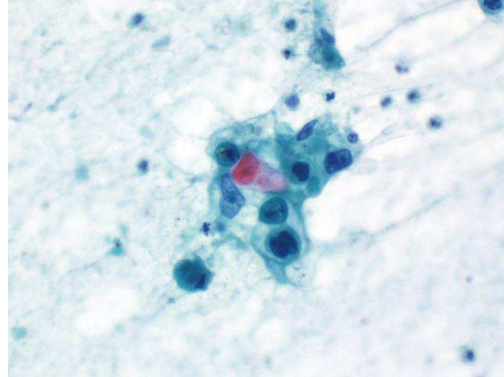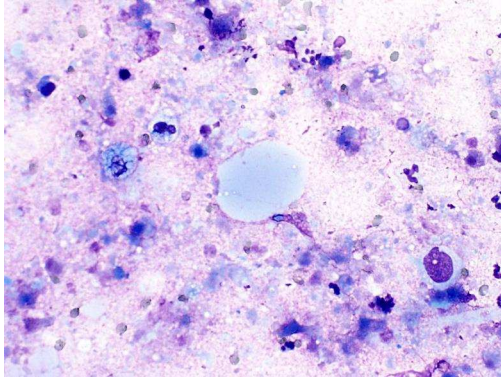| Metastatic renal cell carcinoma | PanNET, lipid-rich variant |
|---|---|



*Images courtesy of Dr. Martha Pitman*

# Adenosquamous carcinoma

- Histologic diagnosis requiring ≥30% of each component, but can suggest based on cytology
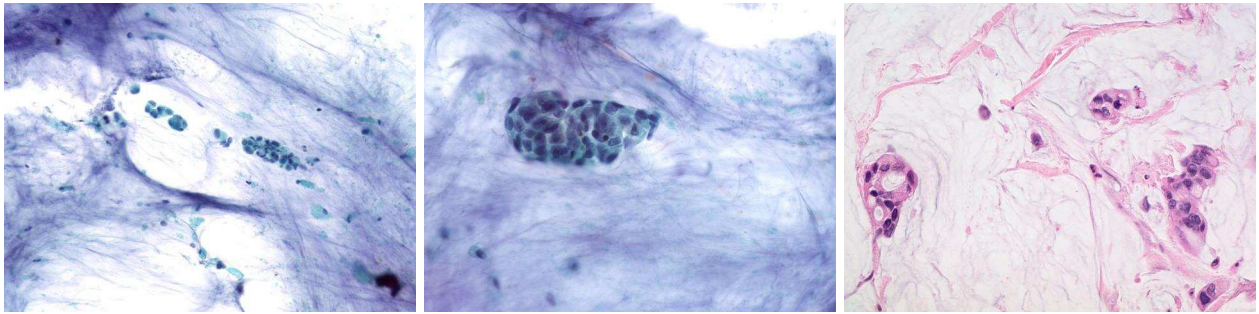- Worse prognosis than conventional PDAC



# Example report

- Carcinoma with squamous differentiation (see note).

- Note: The differential includes adenocarcinoma with squamous differentiation, primary adenosquamous carcinoma, or metastatic carcinoma.

# Colloid carcinoma

- Histologic diagnosis requiring ≥80% of neoplastic epithelium to be suspended in extracellular mucin pools
- Better prognosis than conventional PDAC
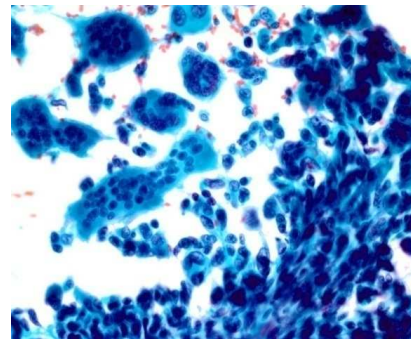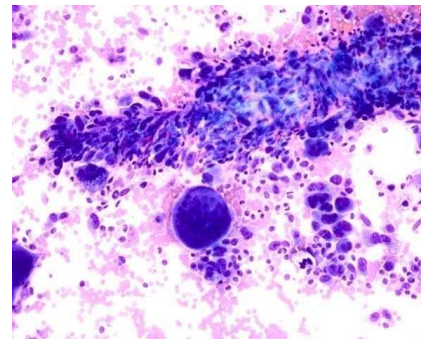


*Images courtesy of Dr. Martha Pitman*

---

# Signet-ring cell carcinoma

- Histologic diagnosis requiring ≥80% poorly cohesive signet ring cells
- Worse prognosis than conventional PDAC
- Rule out metastatic stomach or breast carcinoma
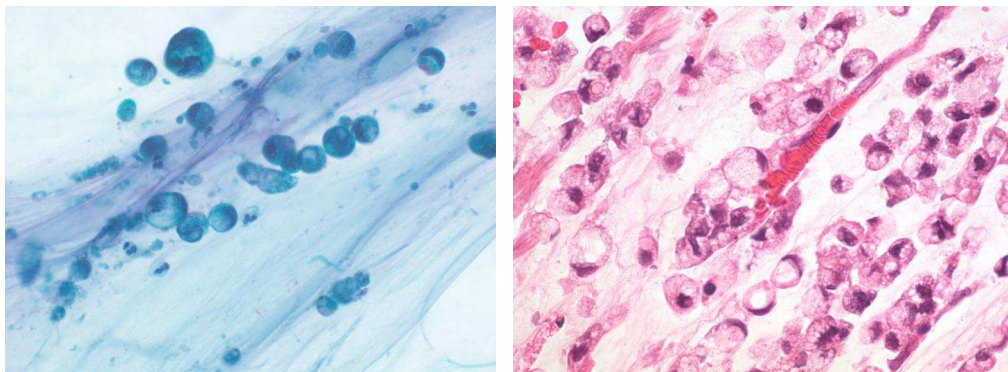
# Undifferentiated carcinoma with osteoclast-type giant cells



- Mean age: 62 years (32-93 years)
- Distinctive components
  - Non-neoplastic osteoclast-like giant cells (histiocytic)
  - Neoplastic mononuclear cells
- 40% associated with gland-forming epithelial component (conventional PDAC, IPMN, MCN)
- Many patients have relatively favorable prognosis



*Images courtesy of Dr. Martha Pitman*

# Undifferentiated carcinoma with osteoclast-type giant cells



CD68

PanCK
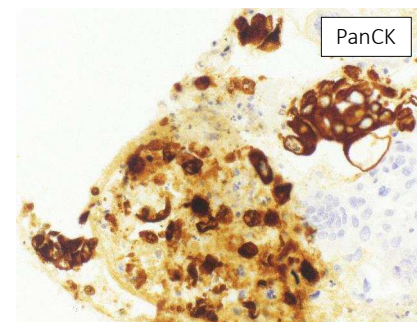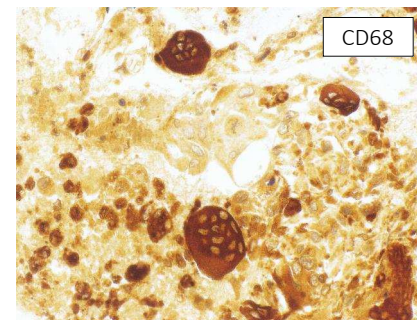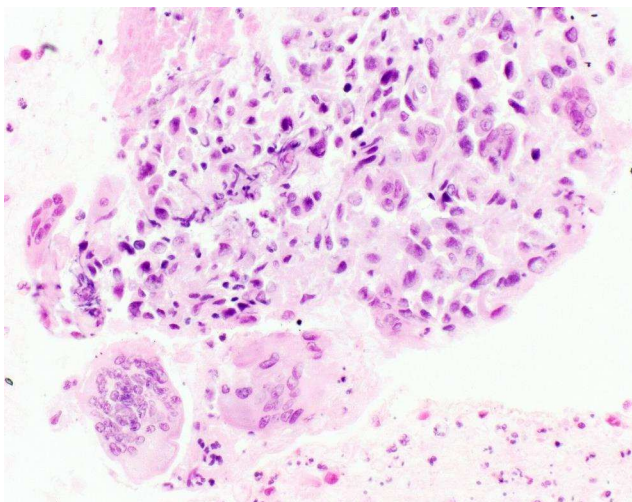
WHO Reporting System for Pancreaticobiliary Cytopathology 2022.

## Summary

- EUS-FNA is commonly used for the initial evaluation of pancreatic lesions (cytology + core biopsy)
- By far the most common pancreatic lesion is PDAC (>90%)
- Distinguishing well-differentiated PDAC from reactive atypia can be challenging, particularly at rapid on-site evaluation
- Ancillary studies (SMAD4, P53, S100P) can be helpful on core biopsies
- Be aware of the histologic subtypes and morphologic variants of PDAC

# Thank you!