Adenocarcinoma classification should be easy

Los Angeles Society Of Pathologists
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OUTLINE

- IASLC/ATS/ERS classification of lung adenocarcinomas

- Practical issues
  - Invasion
  - Histological subtyping

- Subtyping on cytology specimens

WHO 2004
classification of lung adenocarcinomas

- Mixed subtype
- Bronchioloalveolar carcinomas (in situ)
- Acinar
- Papillary
- Solid
- Fetal
- Mucinous (colloid)
- Mucinous cystadenocarcinoma
- Signet ring
- Clear cell

IASLC/ATS/ERS classification of lung adenocarcinoma

- **<u>Obsolete terms</u>**
  - **Bronchioloalveolar carcinoma (BAC)**
    - **terms AIS (adenocarcinoma in situ) and minimally invasive adenocarcinoma (MIS) introduced**
  - **Mixed subtype adenocarcinoma**
    - **comprehensive histologic subtyping and classification by the predominant subtype**

- **Provides <u>guidelines</u> for resection and small biopsies/cytology specimens**

IASLC/ATS/ERS classification of lung adenocarcinoma *for resection specimens*

- **PREINVASIVE LESIONS**
  - Atypical adenomatous hyperplasia
  - Adenocarcinoma in situ (AIS) (formerly BAC)
    - Non-mucinous; mucinous

- **MINIMALLY INVASIVE ADENOCARCINOMA (MIA)**
  - A lepidic predominant tumor with ≤ 5 mm invasion
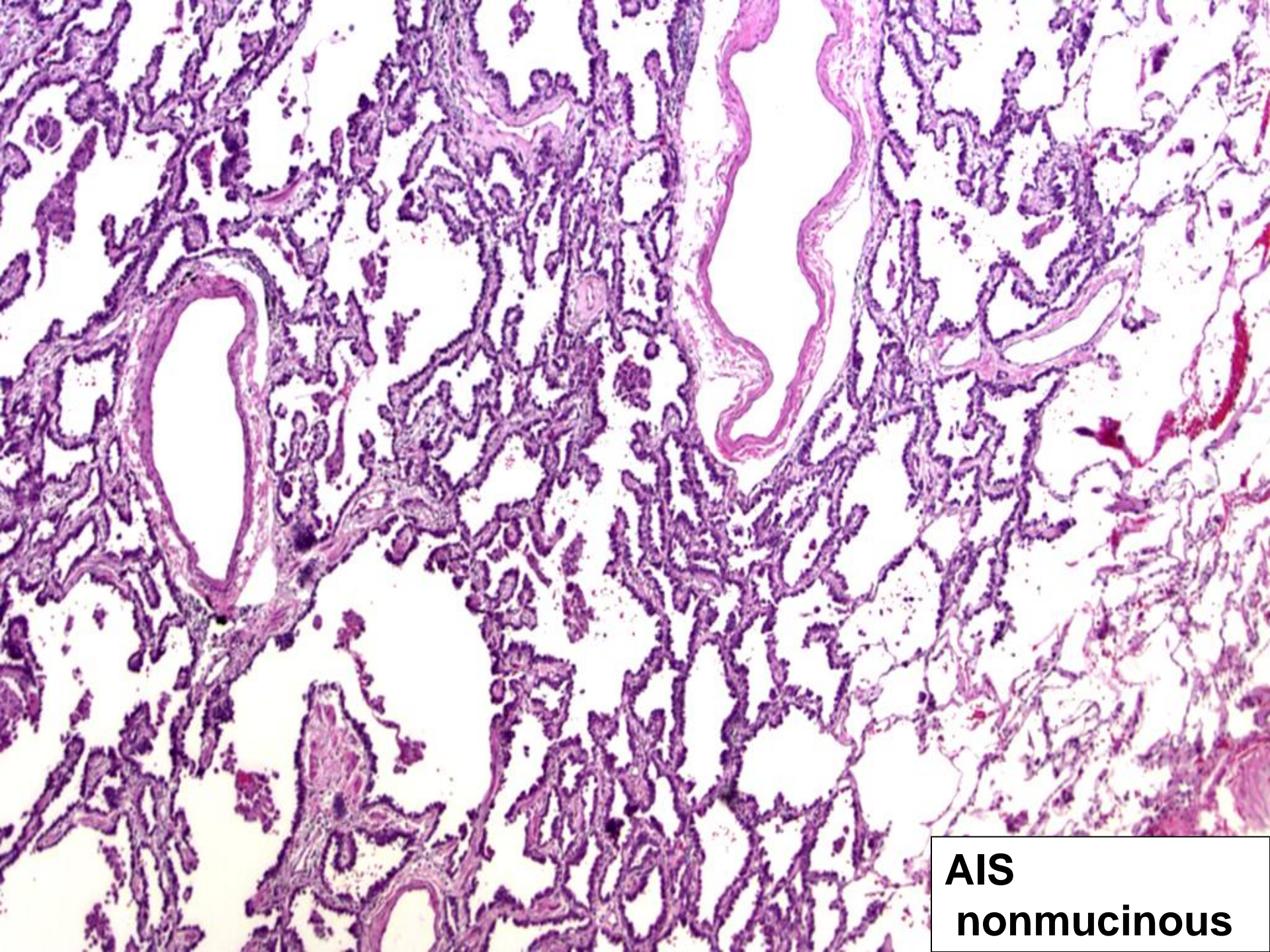   - Non-mucinous; mucinous

- **INVASIVE ADENOCARCINOMA**

Travis WD et al. JTO 2011; 6(2):244-285.

PROBLEM 1

How to separate AIS from minimally invasive adenocarcinoma (MIA) ?

Adenocarcinoma in situ (AIS) (formerly known as BAC)

Definition:

- A localized small (≤ 3.0 cm) adenocarcinoma with growth restricted to neoplastic cells along pre-existing alveolar structures (lepidic growth) lacking stromal, vascular or pleural invasion

- 100% disease-free specific survival if completely resected

Travis WD et al. JTO 2011; 6(2):244-285.

AIS nonmucinous
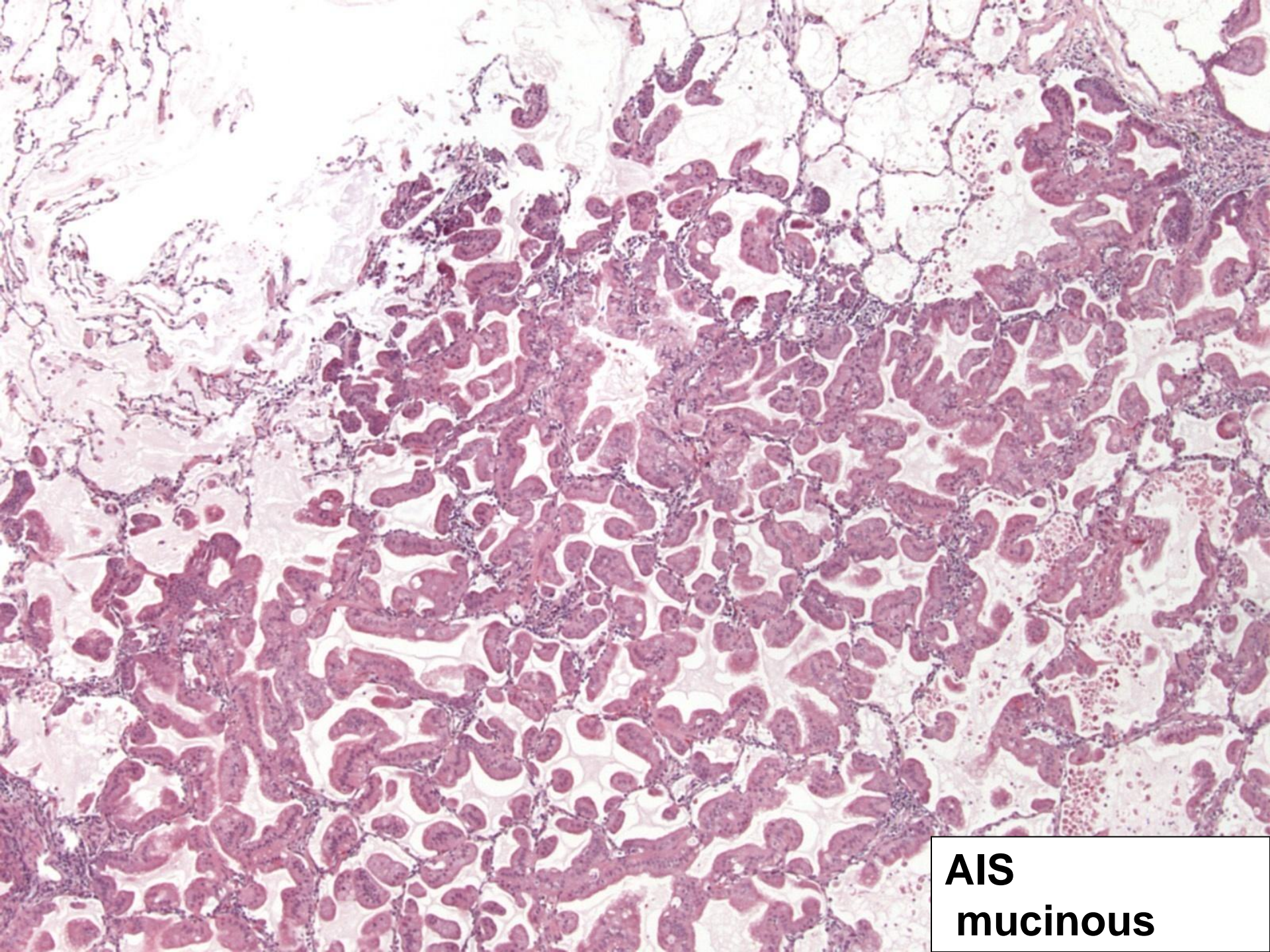
AIS
mucinous

Minimally invasive adenocarcinoma (MIA)

Definition

- Solitary and discrete, ≤ 3.0 cm with a predominantly lepidic pattern and ≤ 5 mm invasion in <u>any one focus</u>

- 100% disease-free specific survival if completely resected

Travis WD et al. JTO 2011; 6(2):244-285.

DEFINITION OF INVASIVE COMPONENT

- Histologic subtypes other than a lepidic pattern
- Desmoplastic reaction
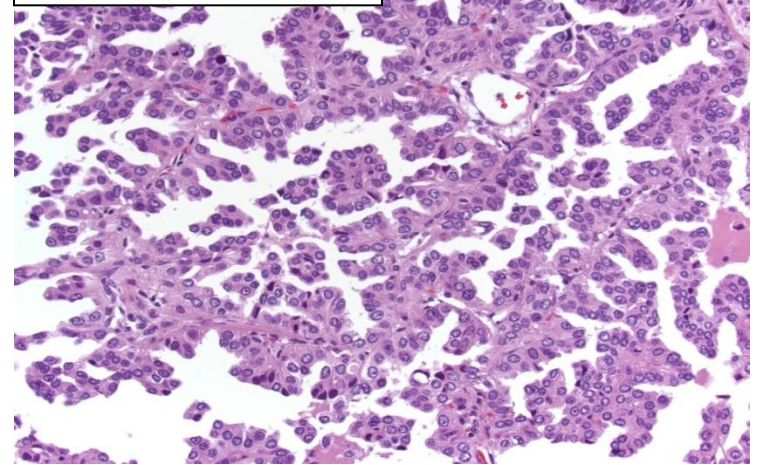- MIA is excluded if the tumor shows
  - AL invasion
  - Pleural invasion
  - Tumor necrosis
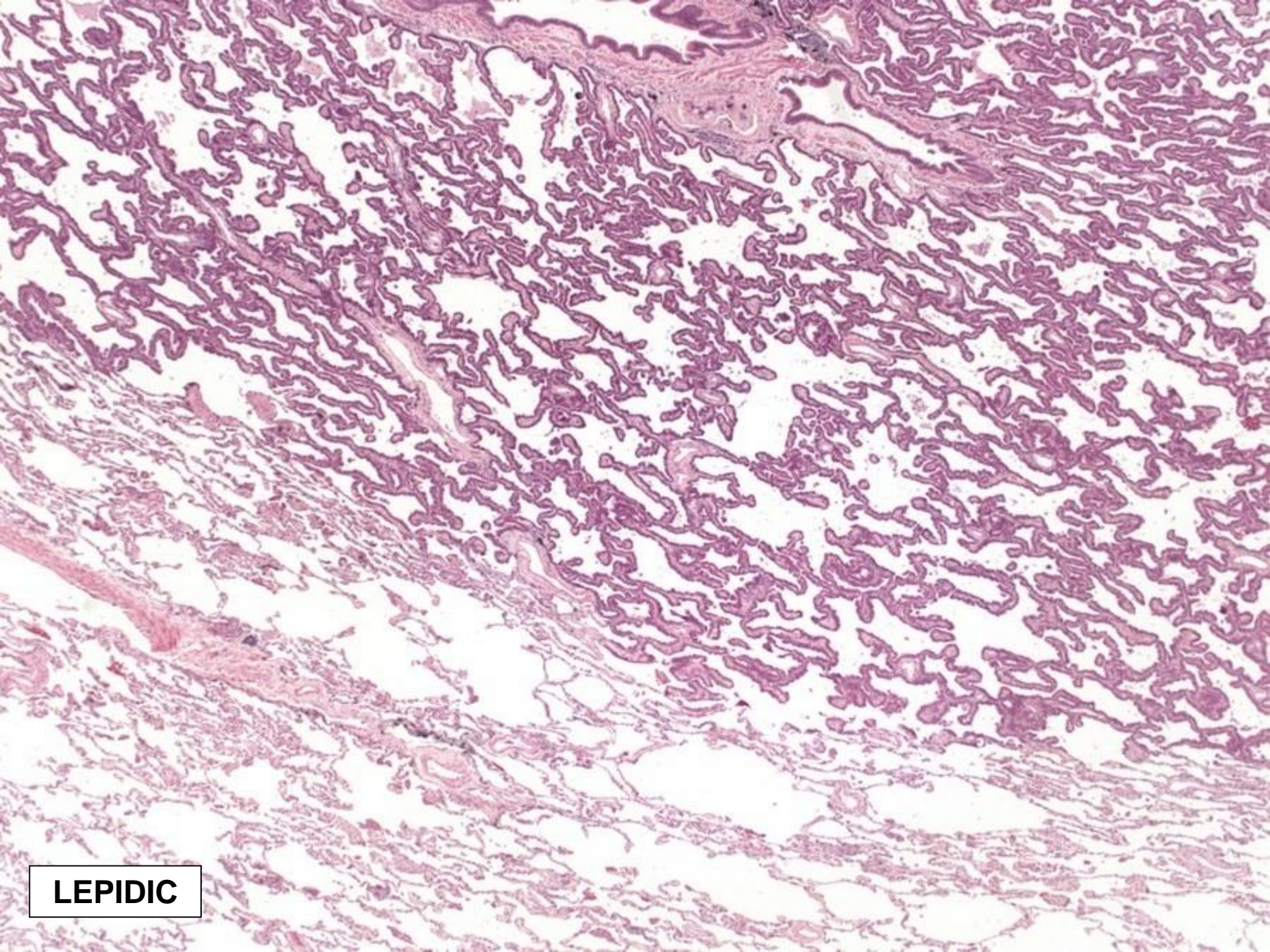
LEPIDIC

HISTOLOGIC SUBTYPES SUPPORTING INVASION

ACINAR
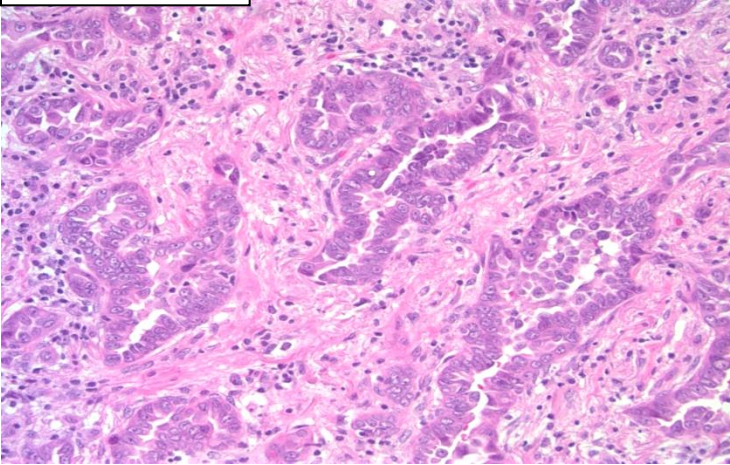
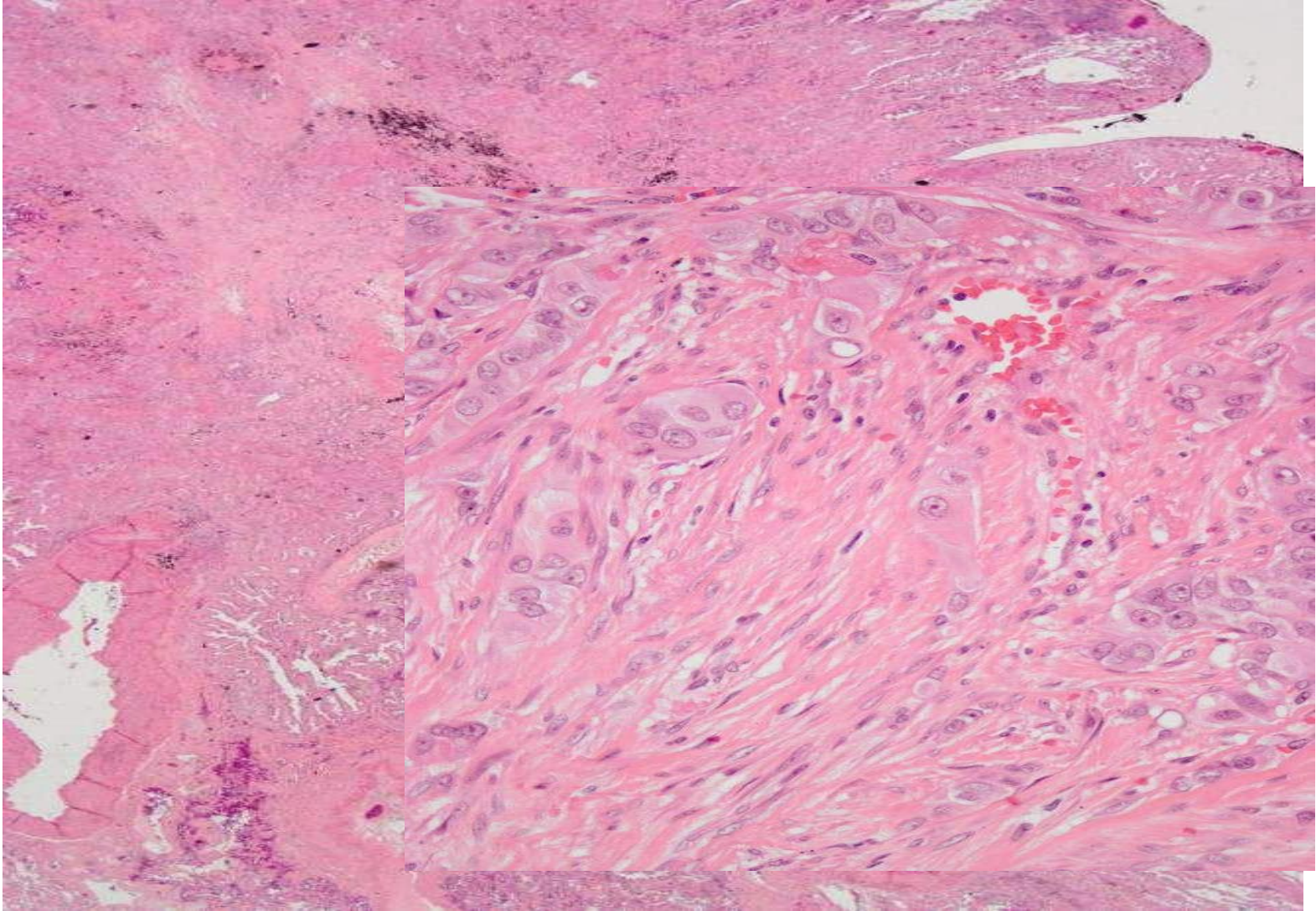**PAPILLARY**

MICROPAPILLARY
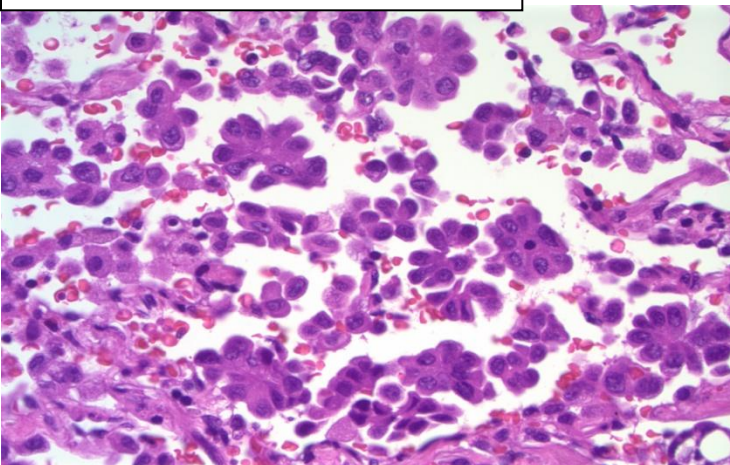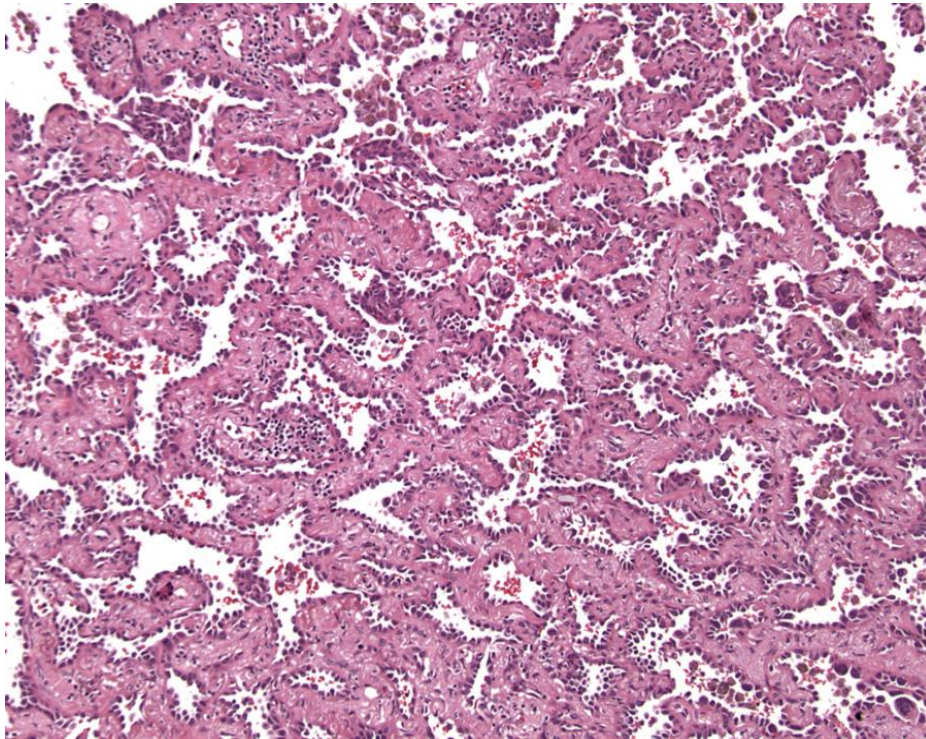

SOLID

DESMOPLASTIC REACTION

14
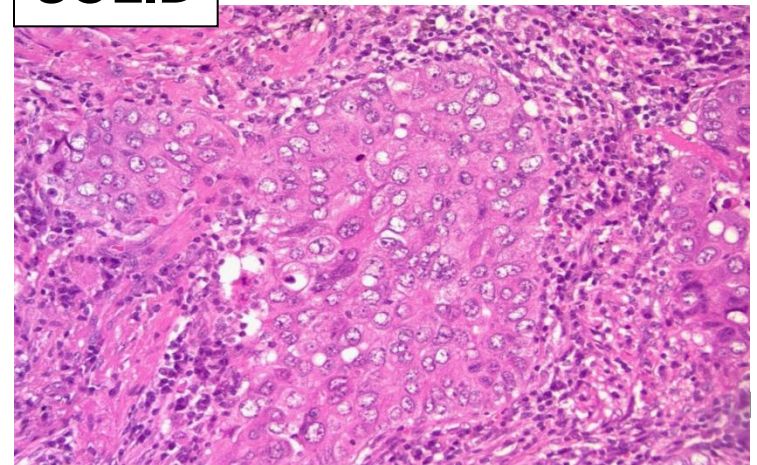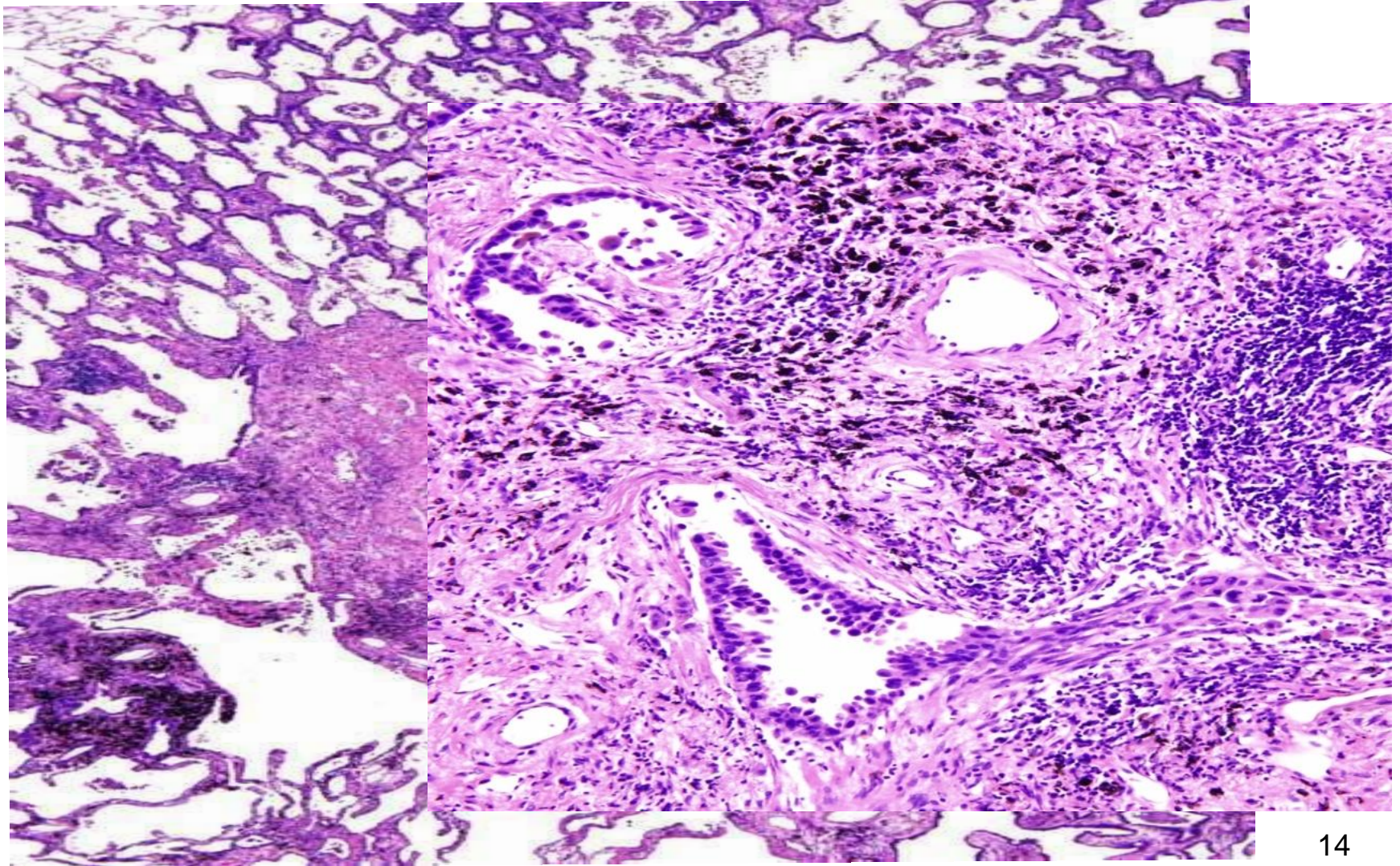
DESMOPLASTIC REACTION

COLLAPSE OR INVASION

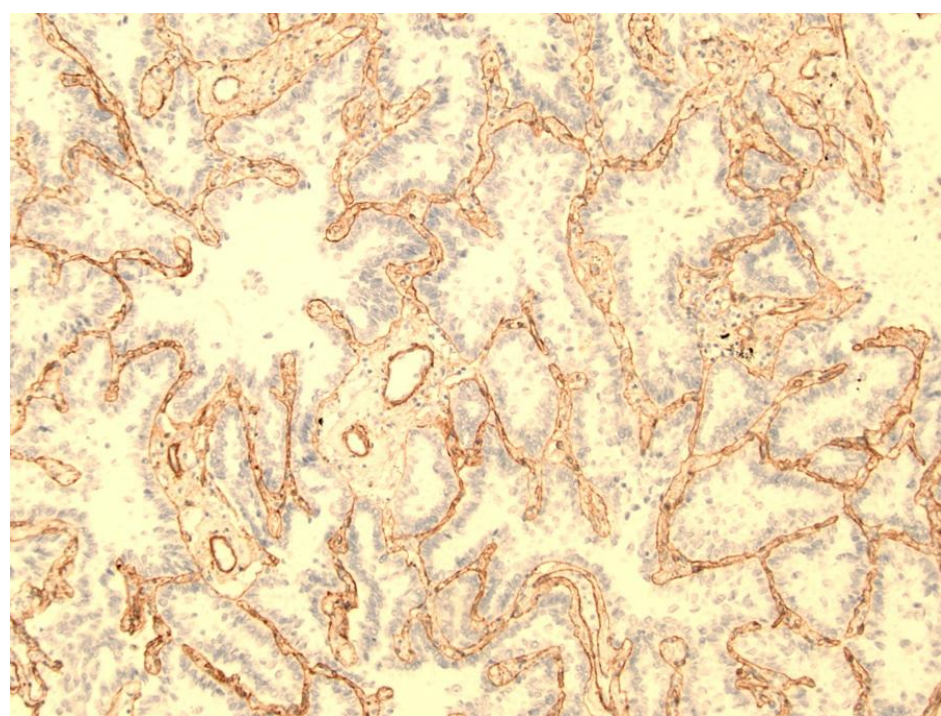# Invasion vs. stromal collapse/central sclerosis
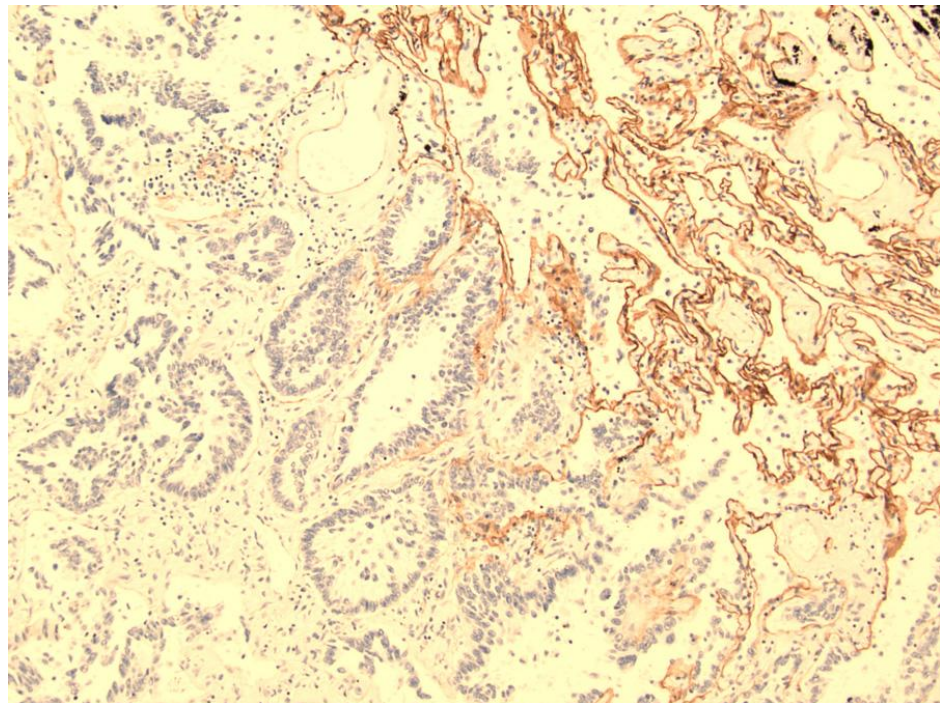

COLLAPSE
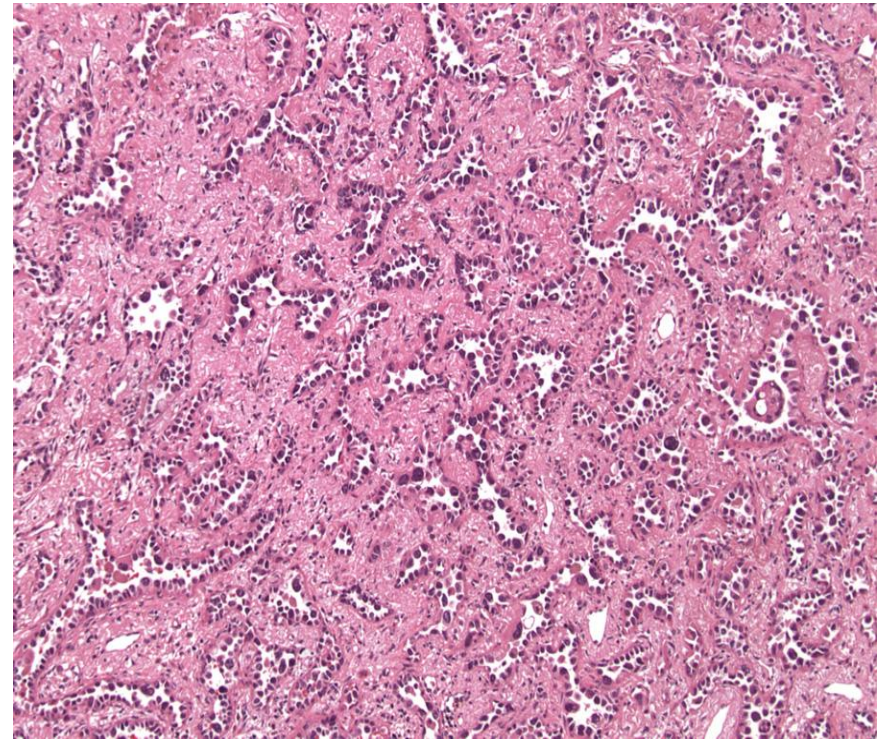
INVASION

Basement membrane stains

COLLAPSE
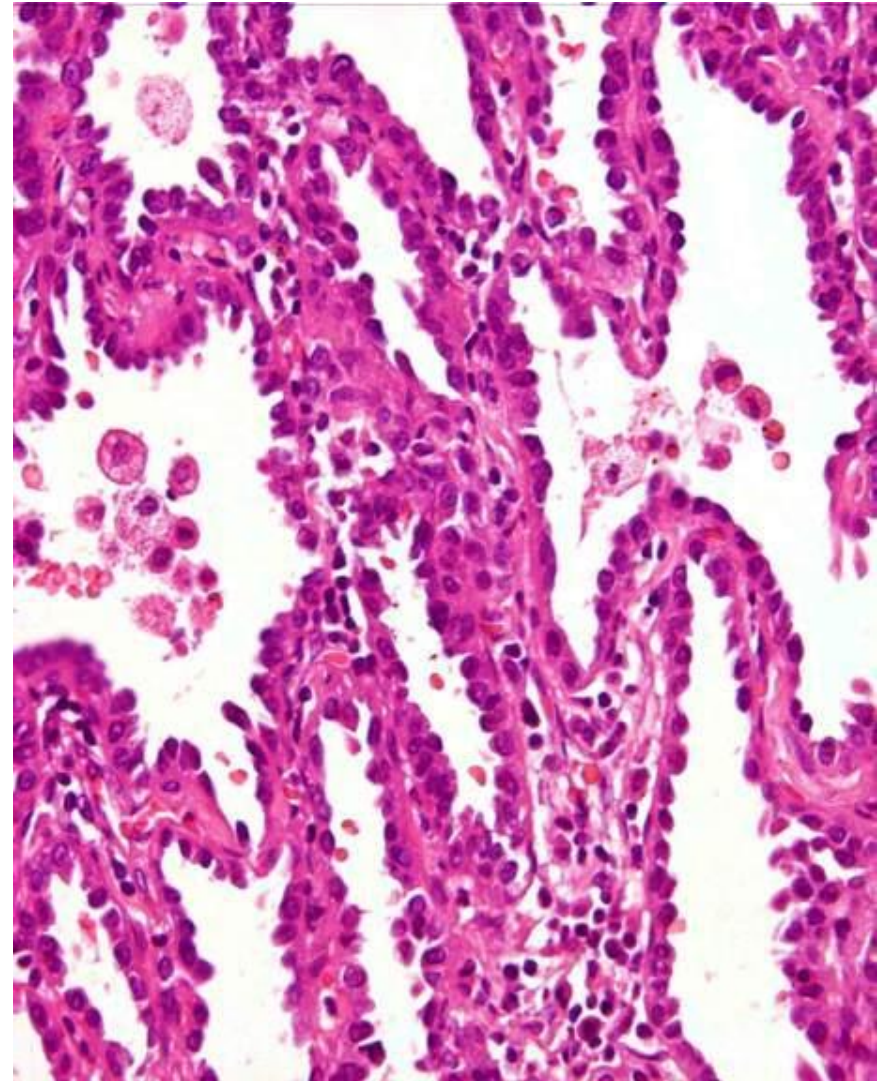
INVASION

How to separate AIS from MIA ?

- The diagnosis of AIS cannot be established with certainty on cytology or small biopsy specimens

- Small tumors (3 cm or less) and tumors with a dominant lepidic growth should be entirely submitted

- More aggressive search for stromal, vascular and pleural invasion (e.g. ancillary studies as a routine work up)
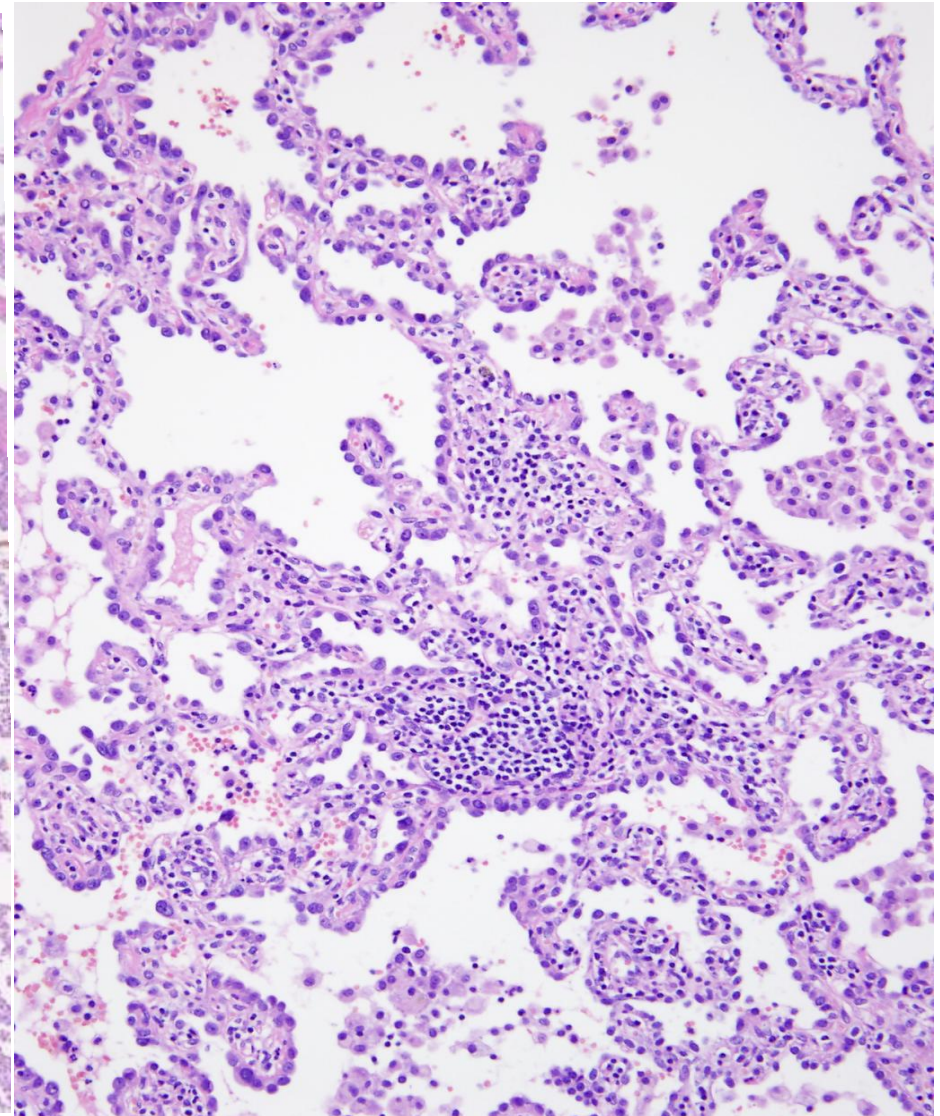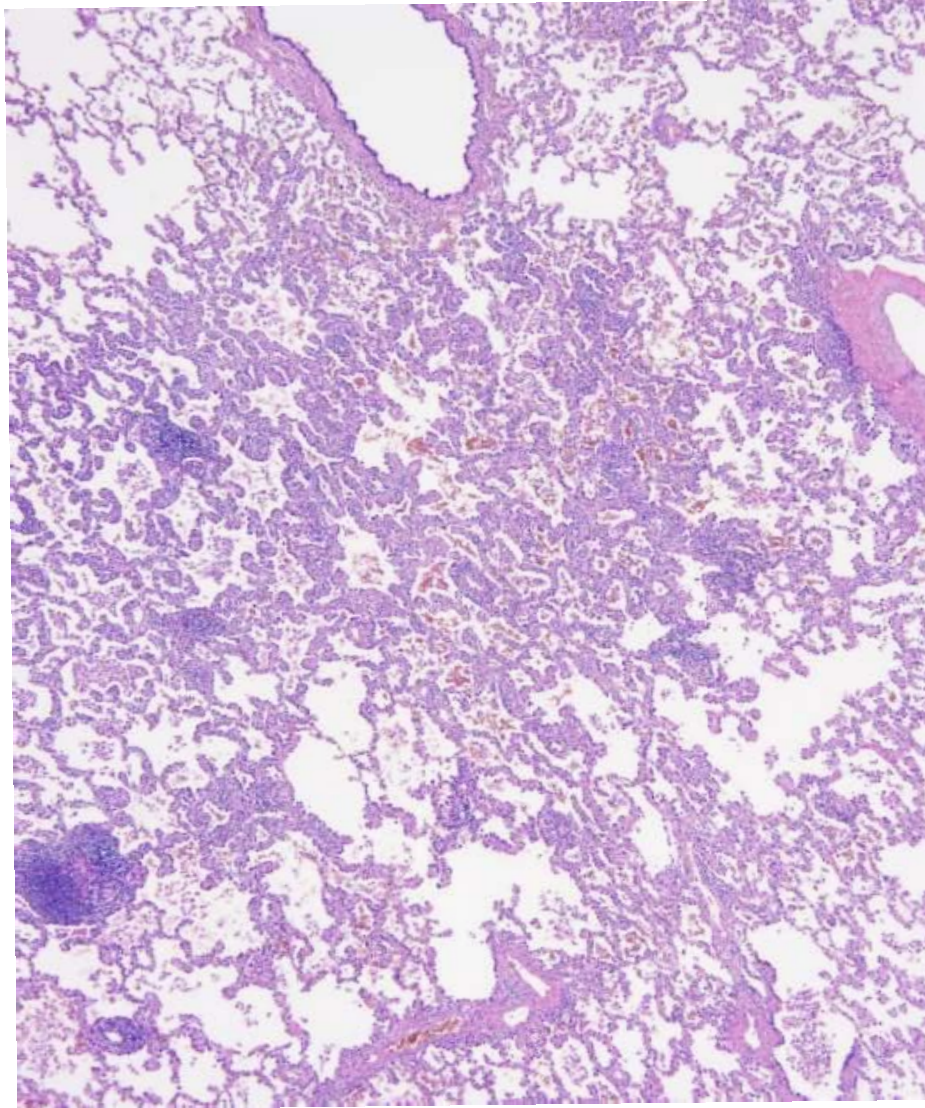
PROBLEM 2

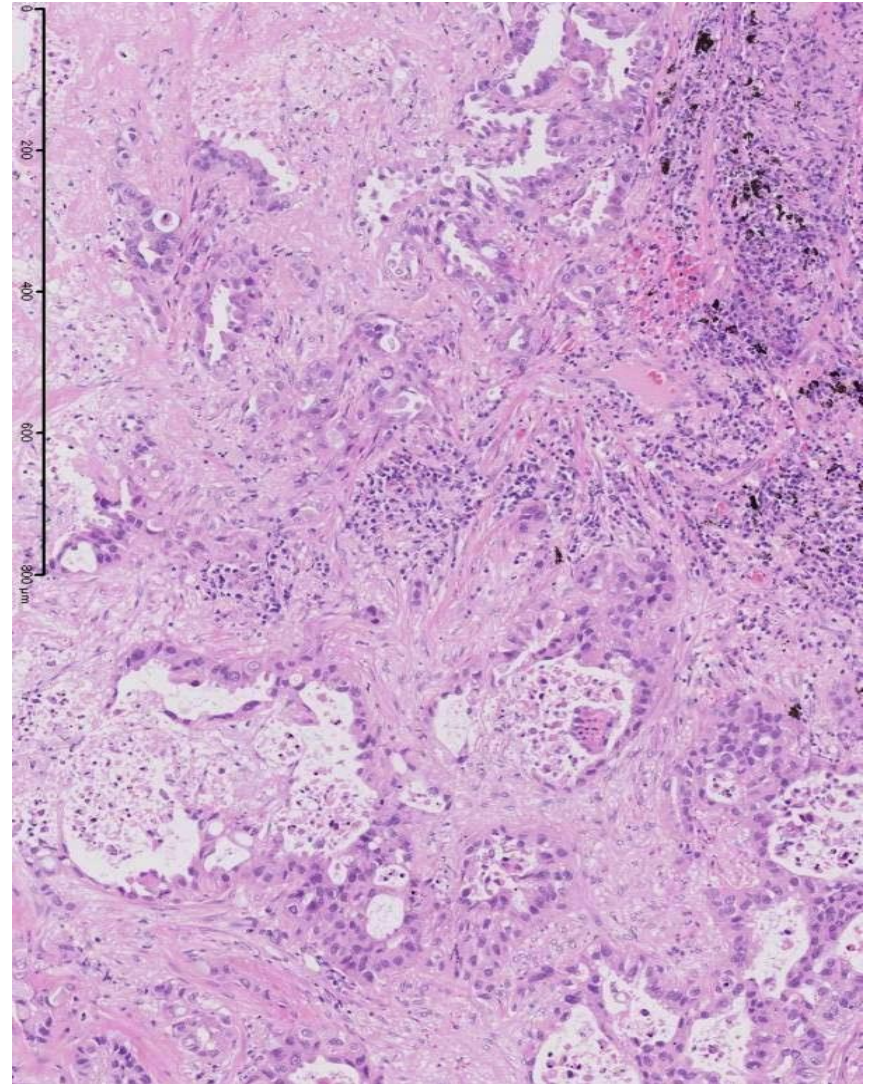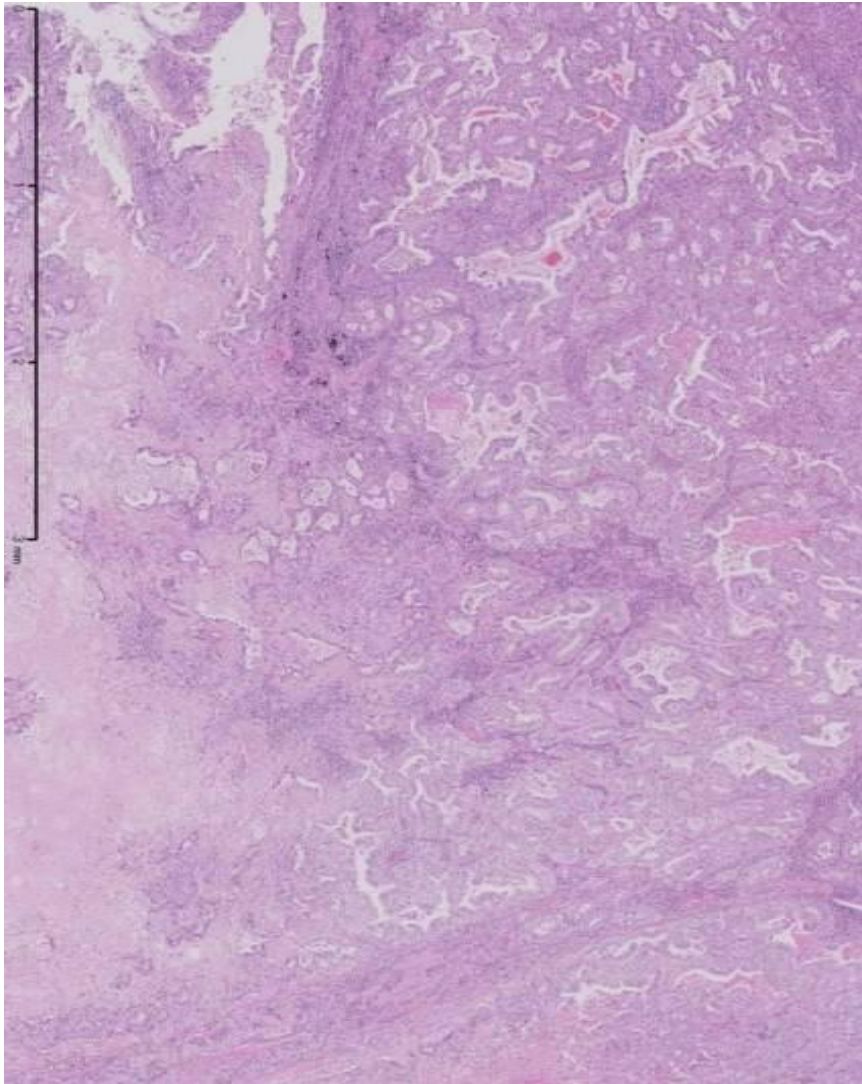# What is the reproducibility of invasion criteria?

- Typical (easy) cases

UNANIMOUS NON-INVASIVE

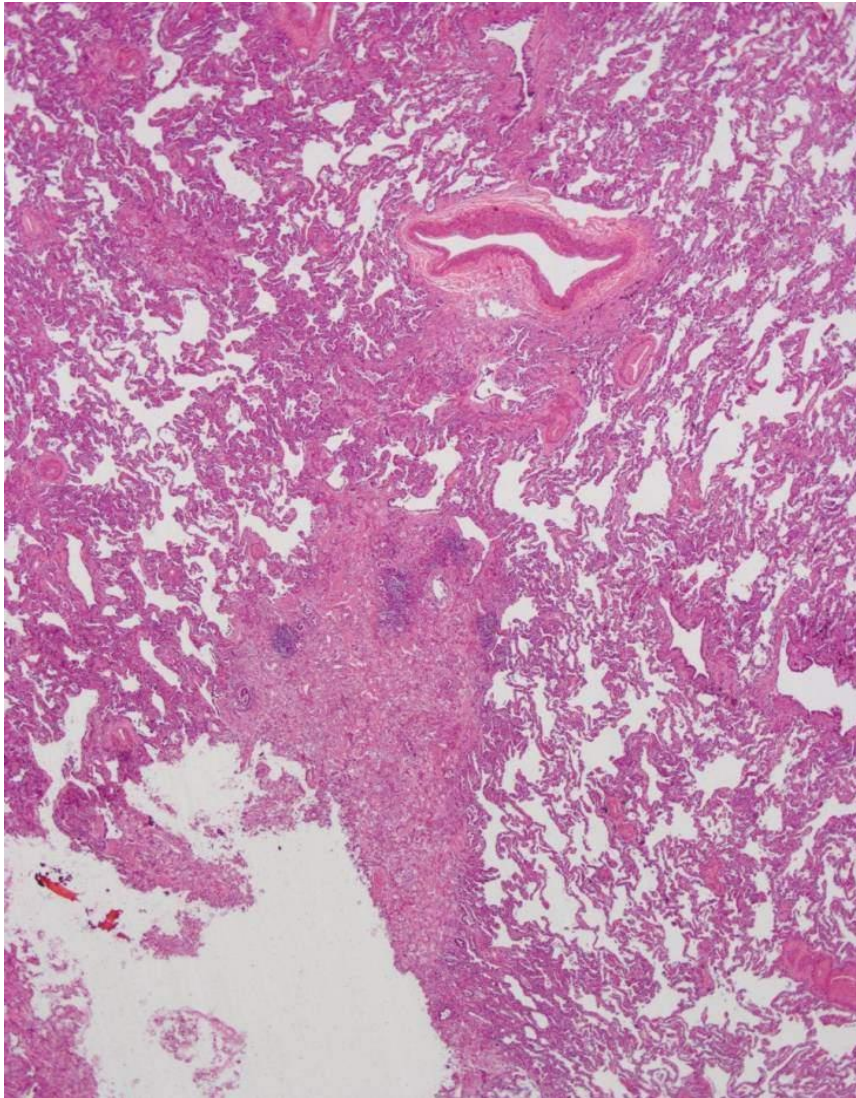*IASLC Pathology Committee, October 2010;*   *Thunissen E. et al. Mod Pathol 2012; 25:1574-83.*

UNANIMOUS NON-INVASIVE

UNANIMOUS INVASION

IASLC Pathology Committee, October 2010

Thunissen E. et al. Mod Pathol 2012; 25:1574-83.

__UNANIMOUS INVASION__

IASLC Pathology Committee, October 2010

Thunissen E. et al. Mod Pathol 2012; 25:1574-83.
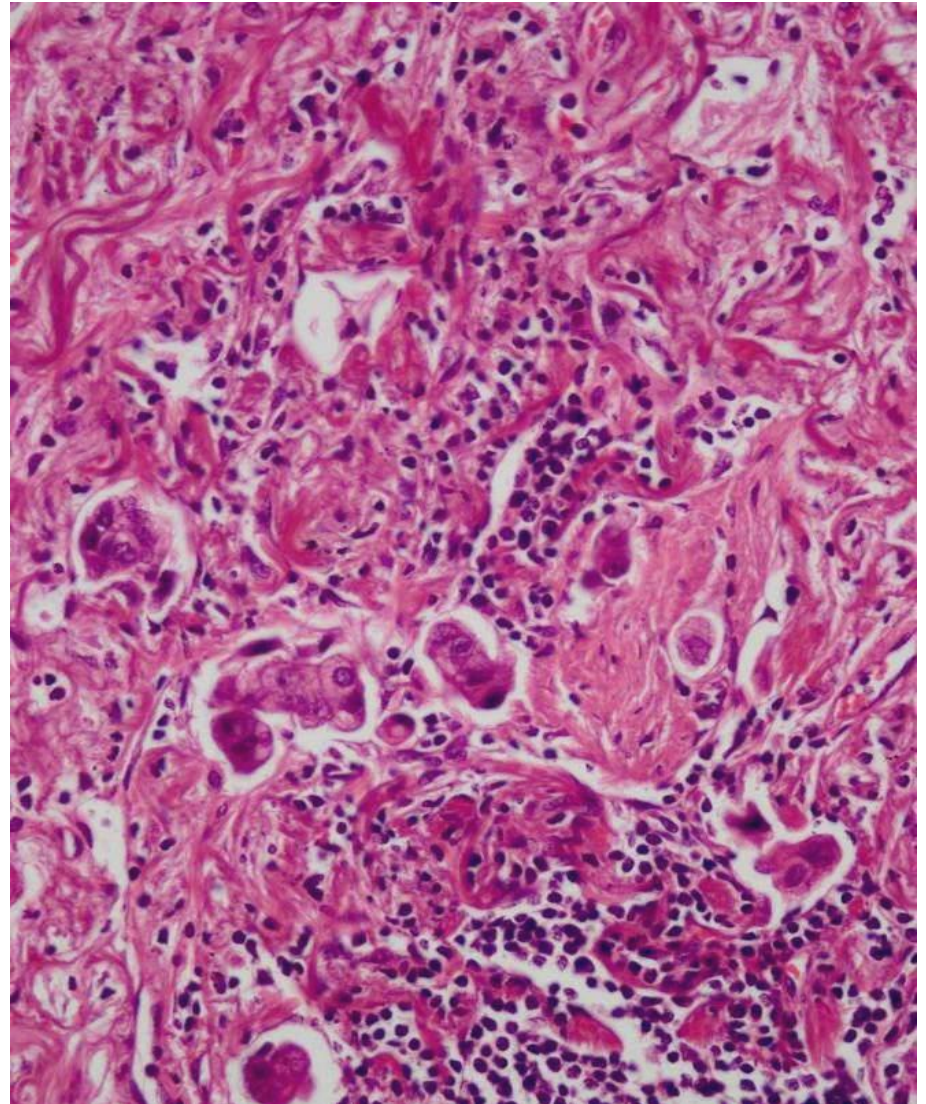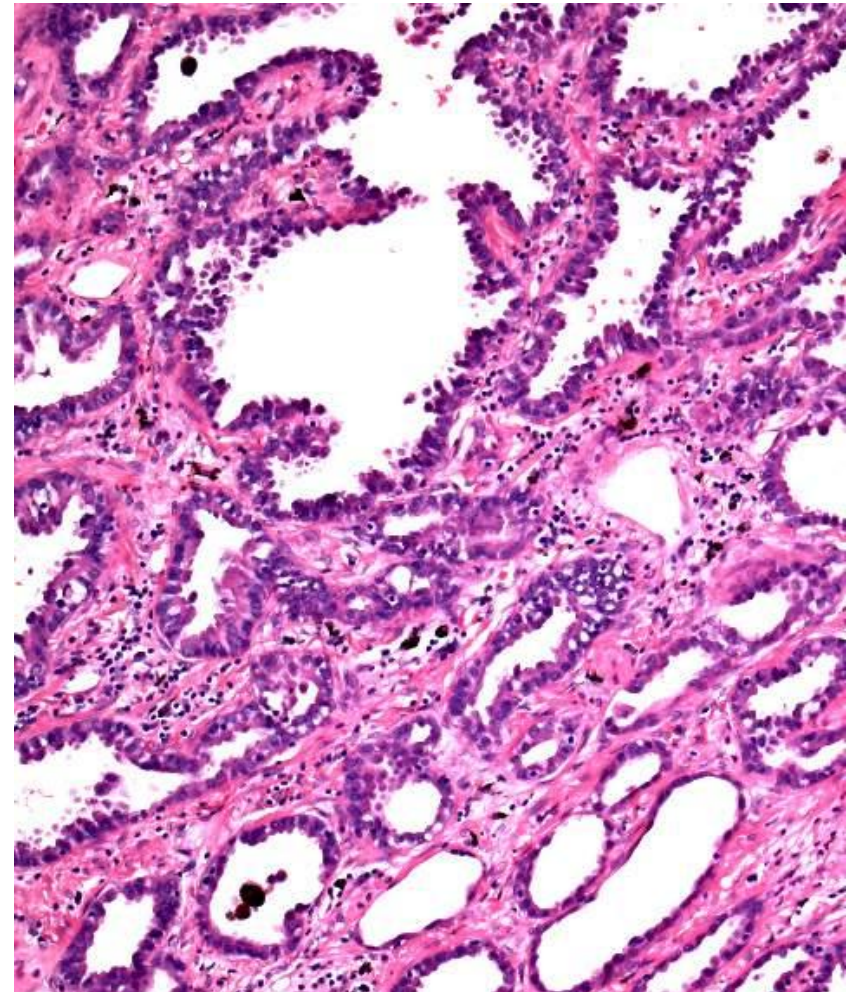
- **Difficult cases**

≥10 for invasion and ≥ 10 for non-invasion

IASLC Pathology Committee, October 2010   *Thunissen E. et al. Mod Pathol 2012; 25:1574-83.*

≥10 for invasion and ≥ 10 for non-invasion

IASLC Pathology Committee, October 2010
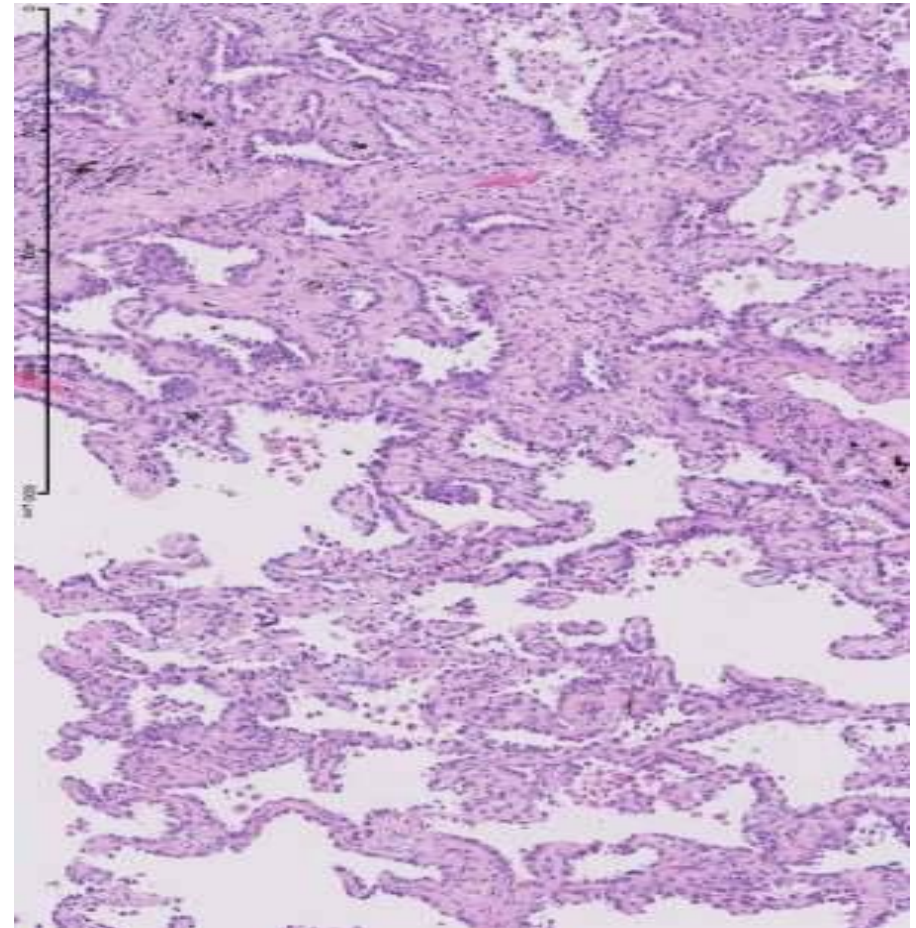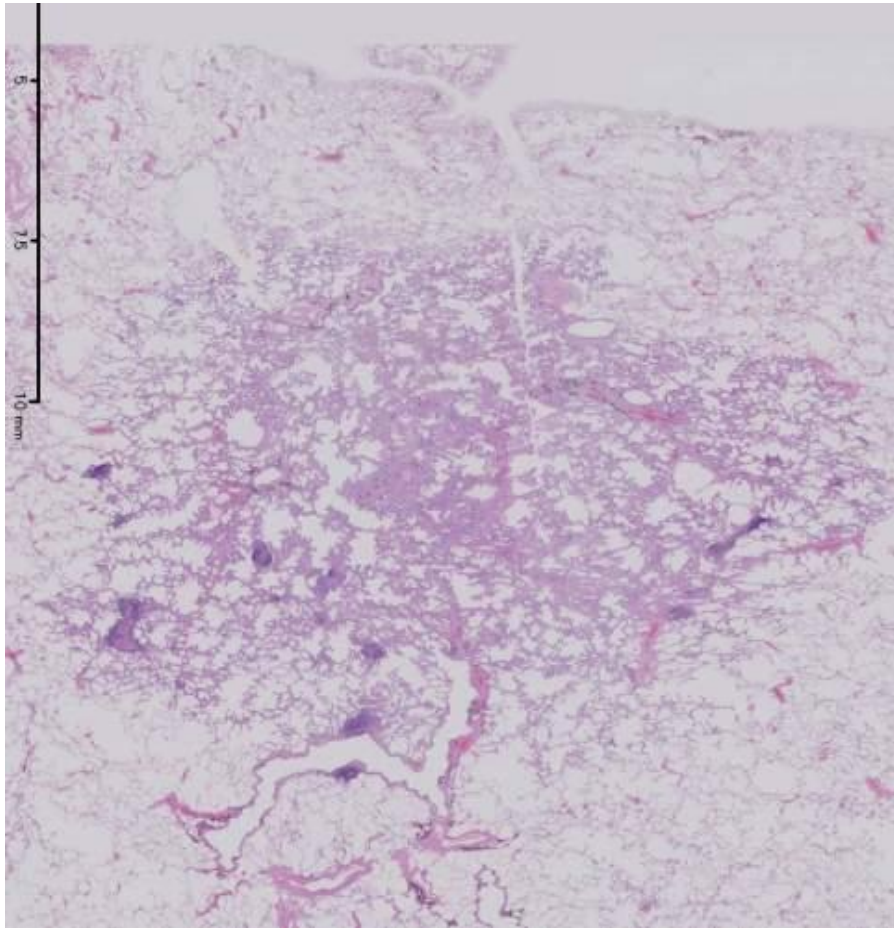
Thunissen E. et al. Mod Pathol 2012; 25:1574-83.
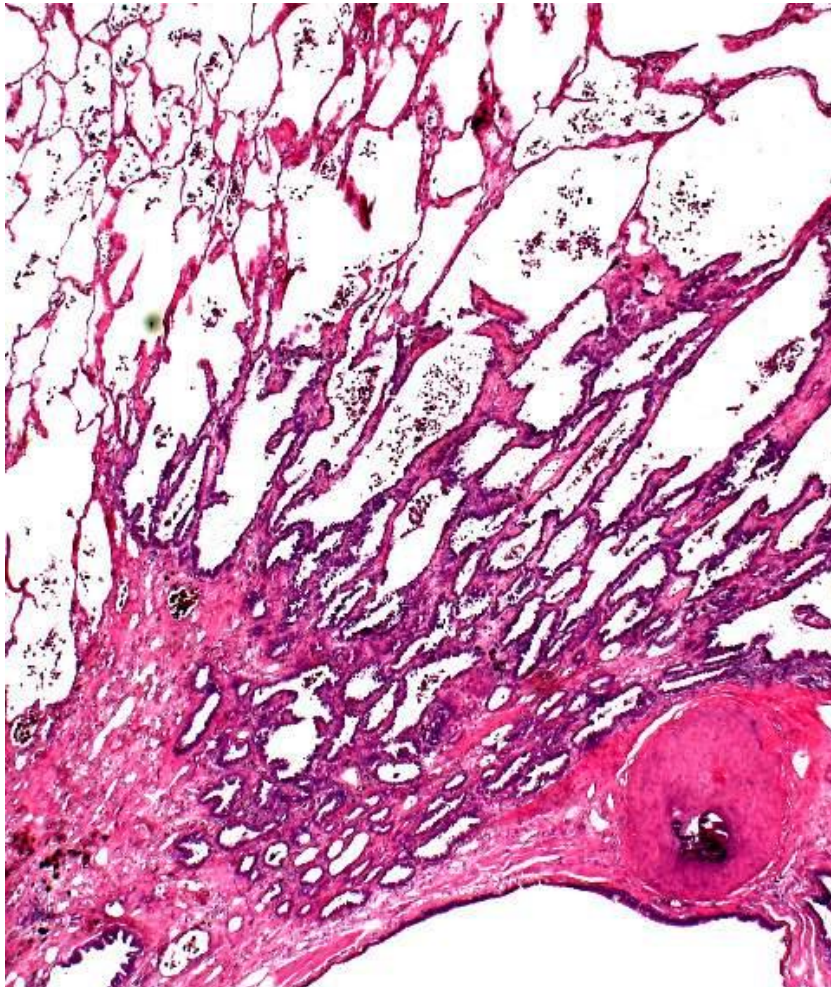
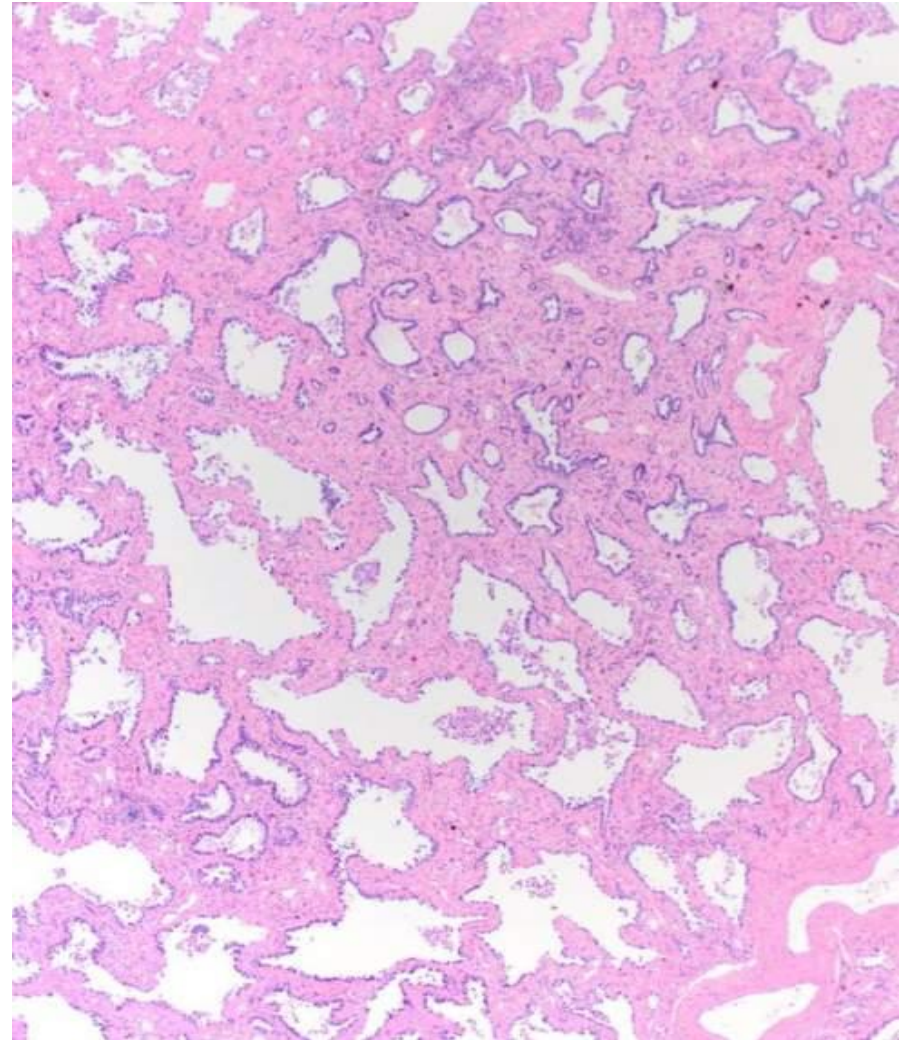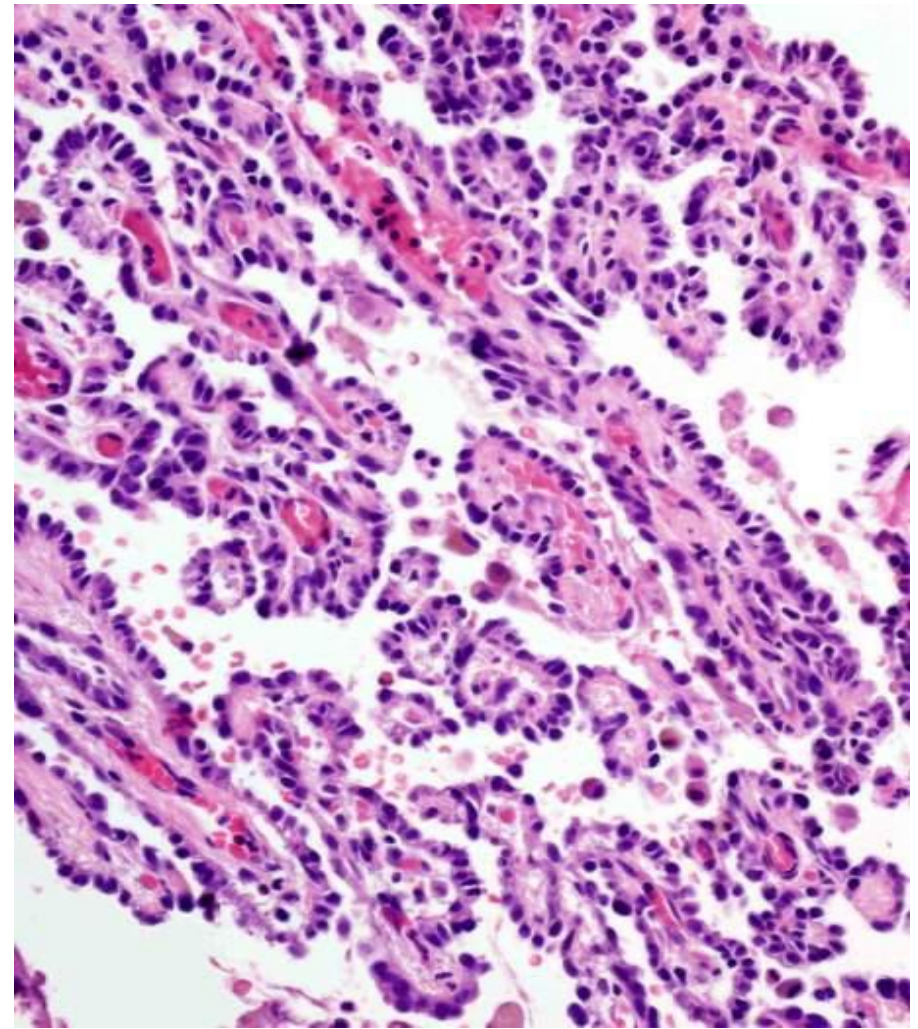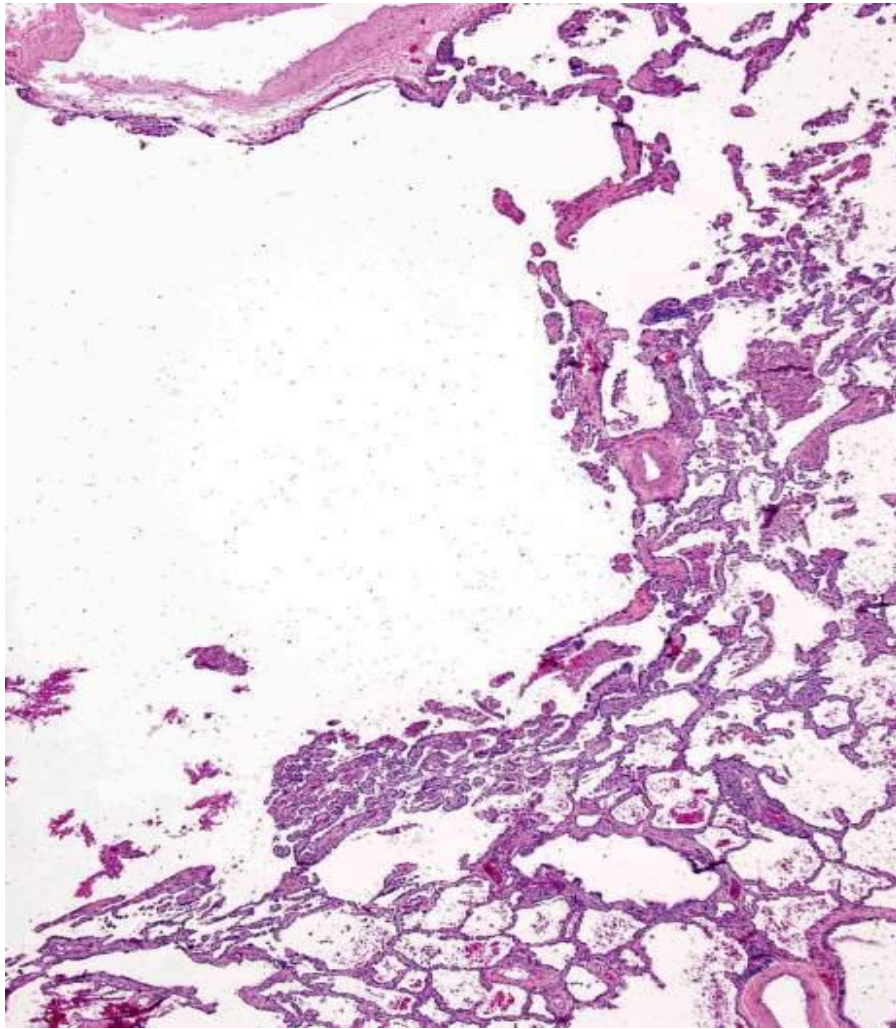# Stroma can be an issue…
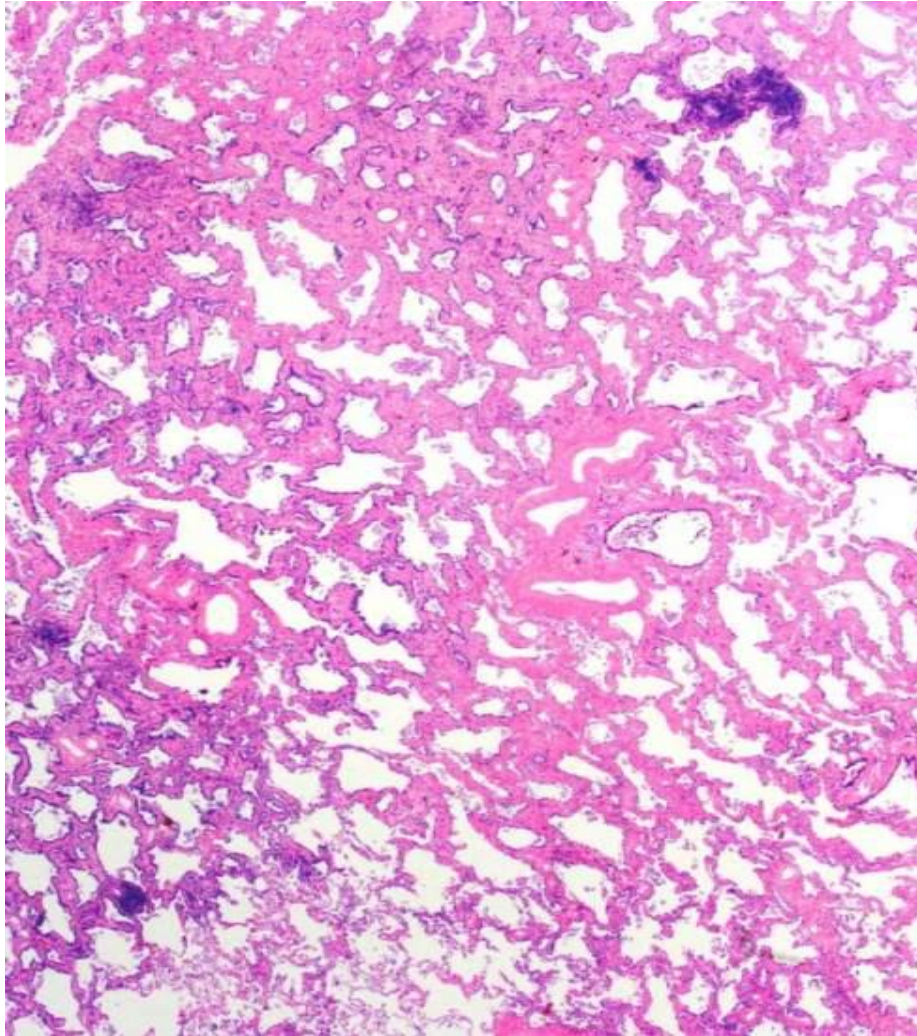
Thunissen E. et al. Mod Pathol 2012; 25:1574-83.

Thunissen E. et al. Mod Pathol 2012; 25:1574-83.

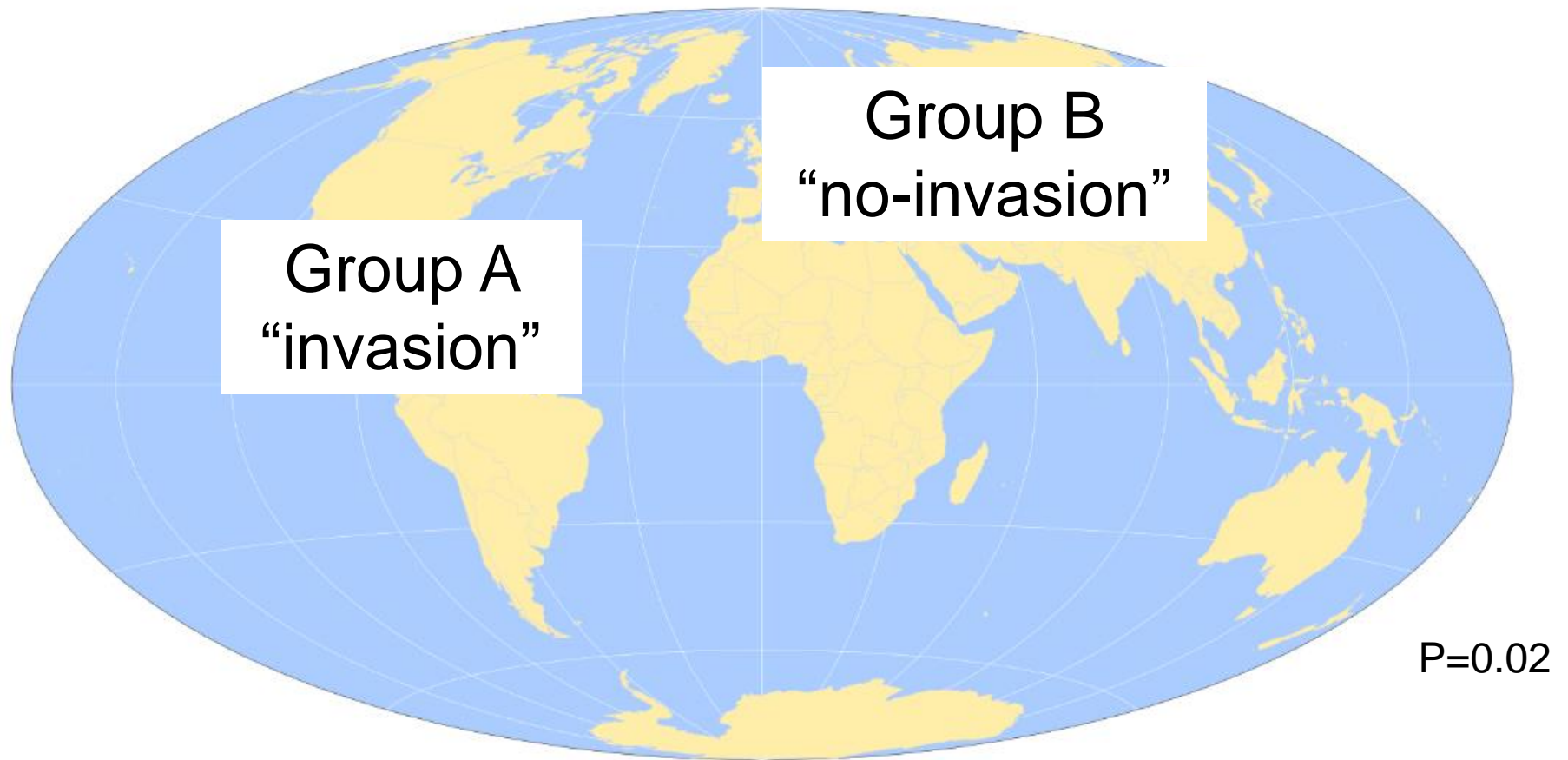# Pre-existing lung architectural changes

Thunissen E. et al. Mod Pathol 2012; 25:1574-83.

REPRODUCIBILITY OF INVASION

- "typical" cases
  - κ=0.55±0.06

- "difficult" cases
  - κ=0.08±0.02

Thunissen E. et al. Mod Pathol 2012; 25:1574-83.

PATHOLOGISTS CAN BE DIVIDED....

Group B
"no-invasion"

Group A
"invasion"

P=0.02

Thunissen E. et al. Mod Pathol 2012; 25:1574-83.

INVASIVE ADENOCARCINOMA

- The term "predominant" is appended to all categories of invasive adenocarcinoma

- Recording the percentages of the various histologic types in 5% increments (not just the most predominant type)

- No established histologic or cytologic grading criteria exists for lung adenocarcinoma

# IASLC/ATS/ERS classification of lung adenocarcinoma

- **<u>SUBTYPES</u>**
- Lepidic predominant (formerly non-mucinous BAC pattern)
- Acinar predominant
- Papillary predominant
- Micropapillary predominant
- Solid predominant

- **<u>VARIANTS</u>**
- Mucinous adenocarcinoma (formerly mucinous BAC)
- Colloid
- Fetal (low and high grade)
- Enteric

IASLC/ATS/ERS classification and survival

IASLC/ATS/ERS Classification subtypes	Number (%)	Disease-free survival at 5 years
Low Grade		
Adenocarcinoma in situ	1 (0.2%)	100%
Minimally invasive adenocarcinoma, non-mucinous	7 (1%)	100%
Minimally invasive adenocarcinoma, mixed mucinous and non-mucinous	1 (0.2%)	100%
Intermediate Grade		
Lepidic predominant	29 (6%)	90%
Acinar predominant	232 (45%)	84%
Papillary predominant	143 (28%)	83%
High Grade		
Micropapillary predominant	12 (2%)	67%
Solid predominant	67 (13%)	70%
Colloid predominant	9 (2%)	71%
Invasive mucinous adenocarcinoma, mixed mucinous/non-mucinous	13 (3%)	76%

Yoshizava A et al. Mod Pathol 2011;24(5):653-64
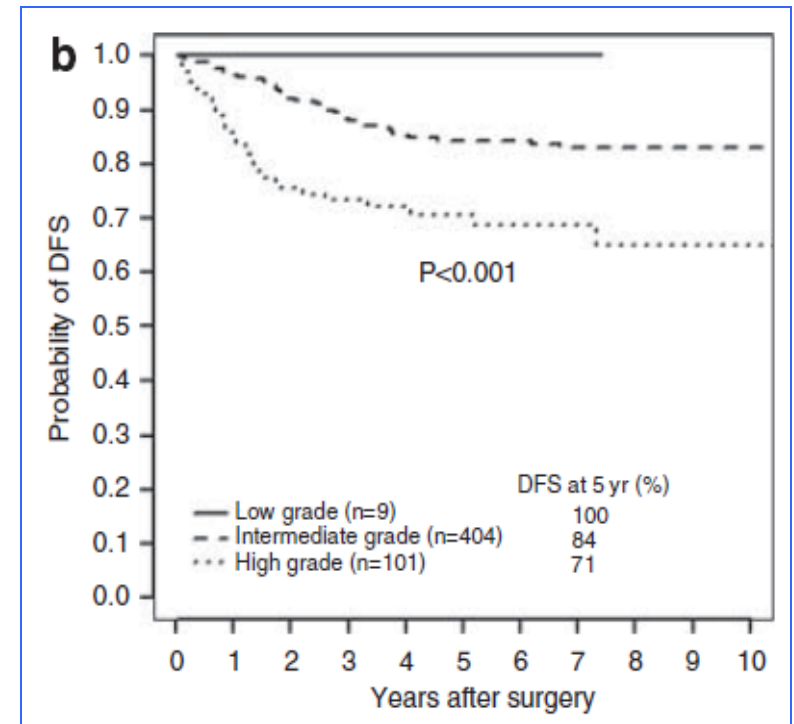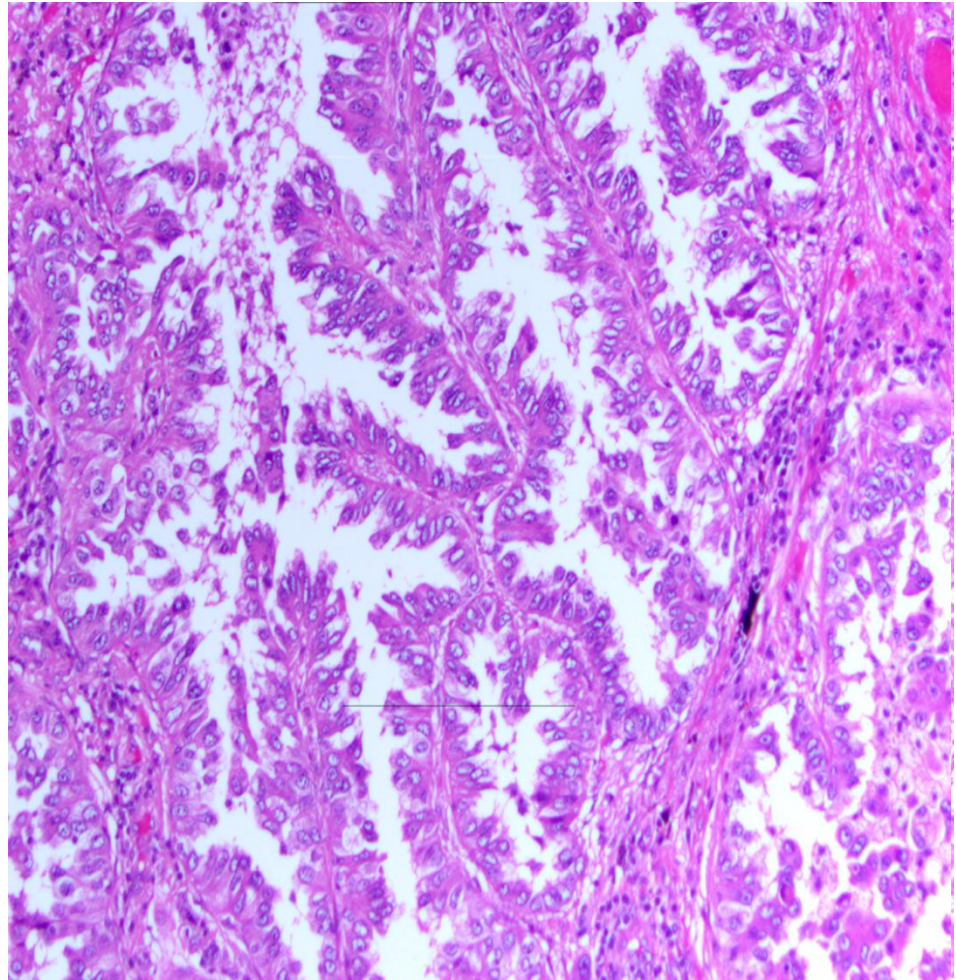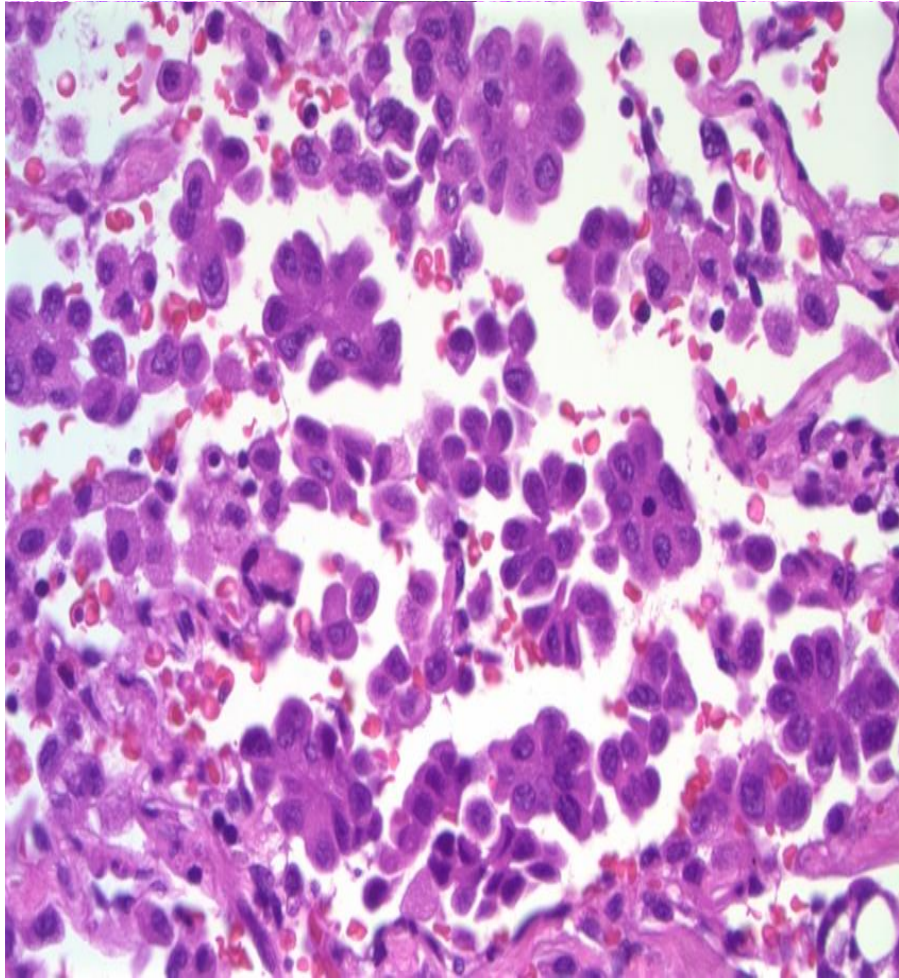
PROBLEM 3

What is the reproducibility of histological subtyping of lung adenocarcinoma?
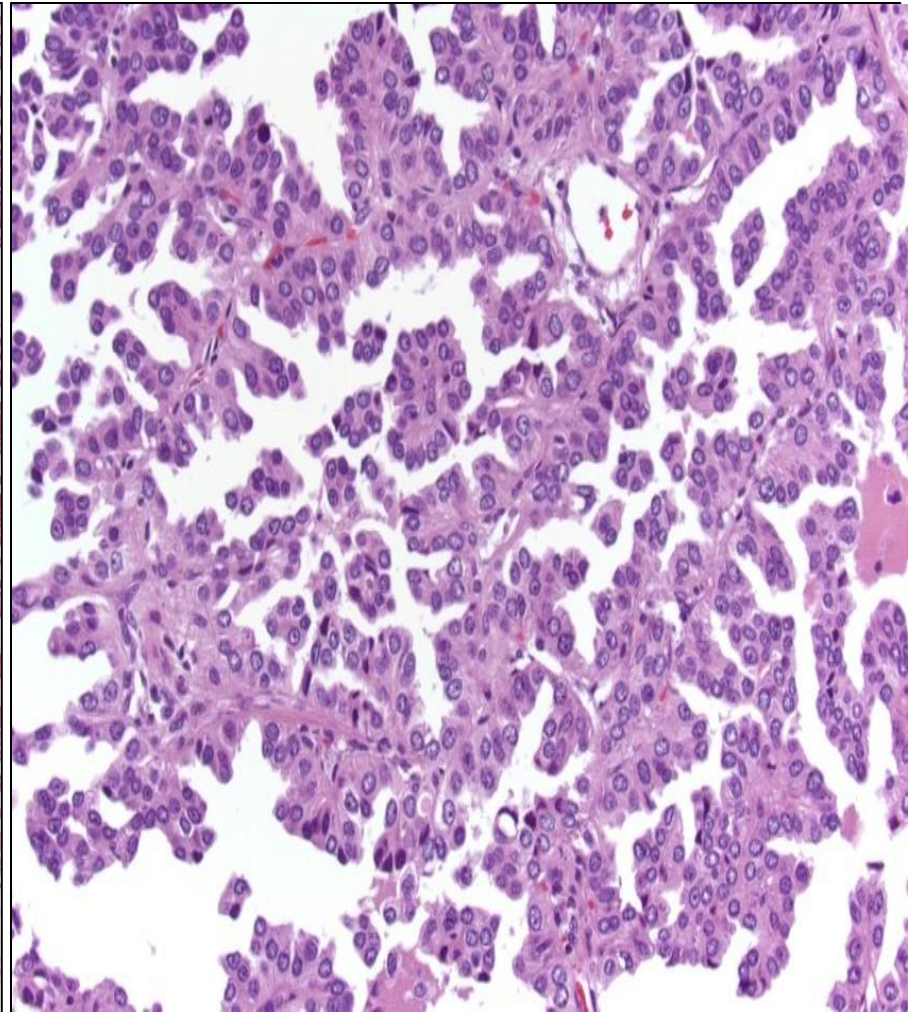
REPRODUCIBILITY OF HISTOLOGICAL SUBTYPING

Submitted pattern	Single pattern (%)	Predominant pattern (%)
Acinar (n=20)	17/26 (65)	25/26 (96)
Lepidic (n=19)	11/26 (42)	24/26 (92)
Micropapillary (n=16)	3/26 (12)	16/26 (62)
Papillary (n=19)	5/26 (19)	25/26 (96)
Solid (n=20)	17/26 (65)	26/26 (100)

"typical" cases	$\kappa=0.77\pm0.06$
"difficult" cases	$\kappa=0.38\pm0.14$

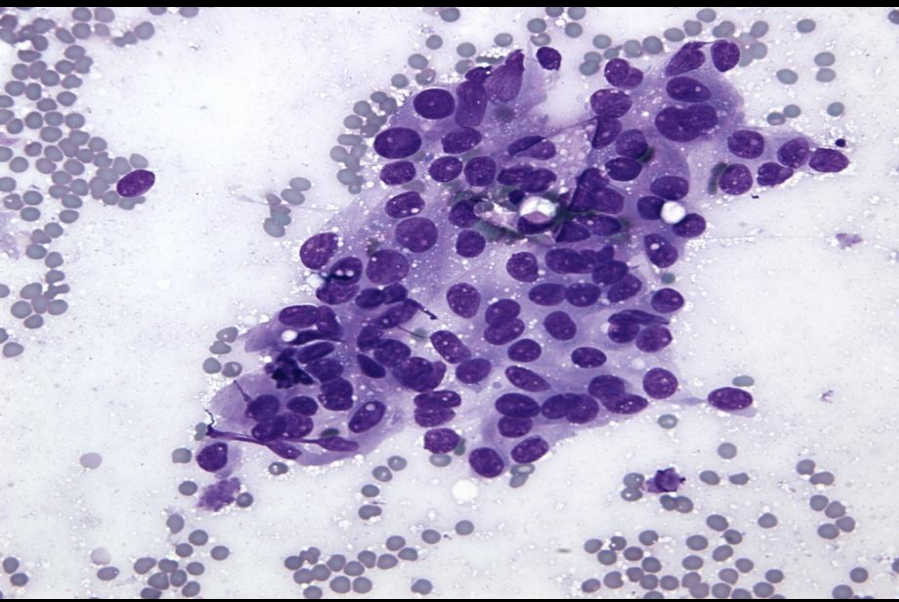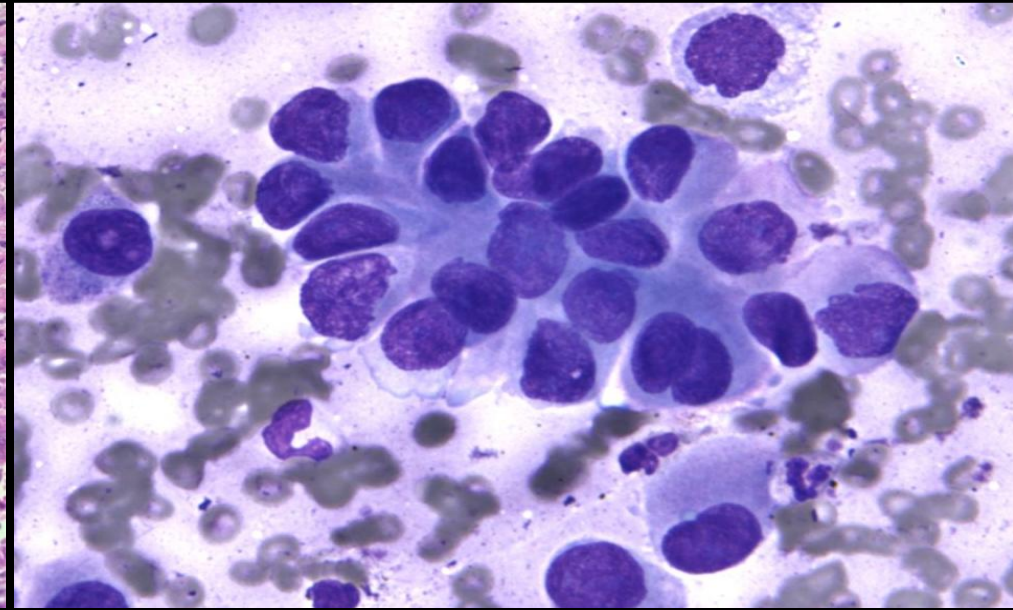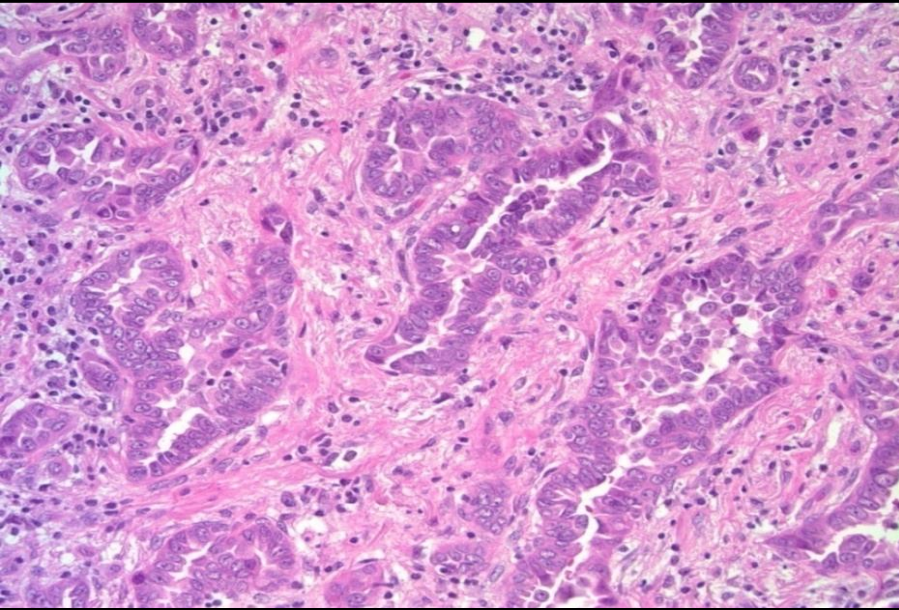# MICROPAPILLARY vs. PAPILLARY

LEPIDIC VS. PAPILLARY

PROBLEM 4

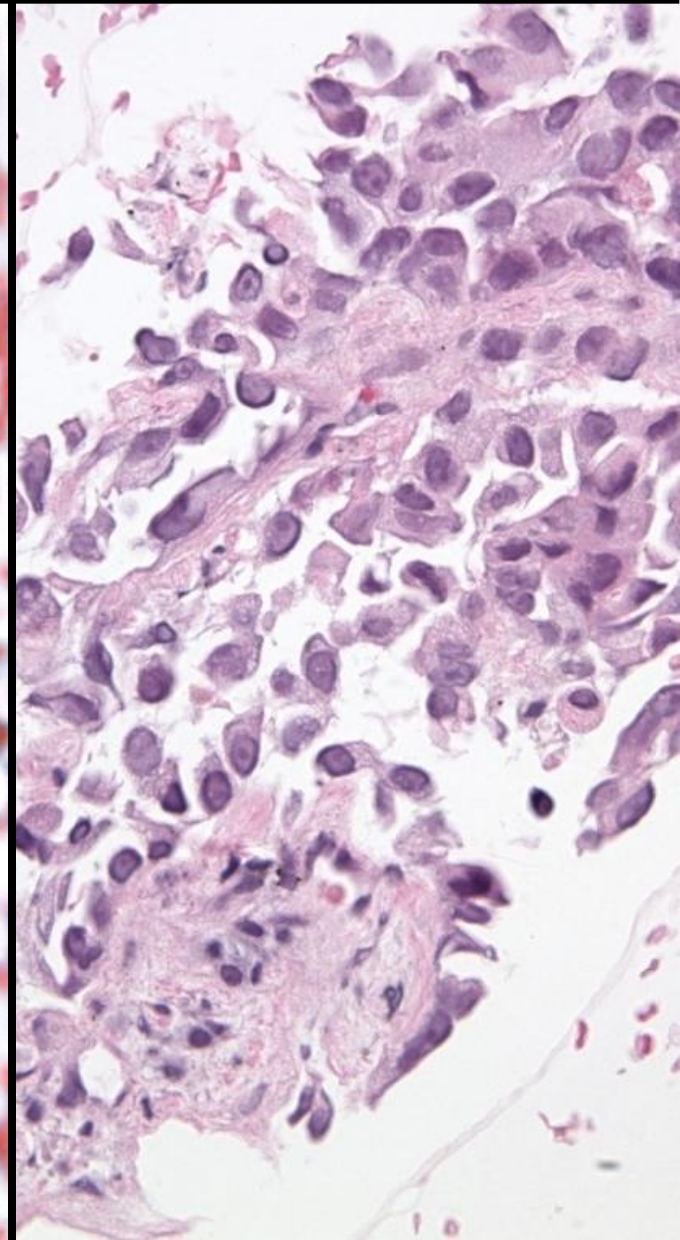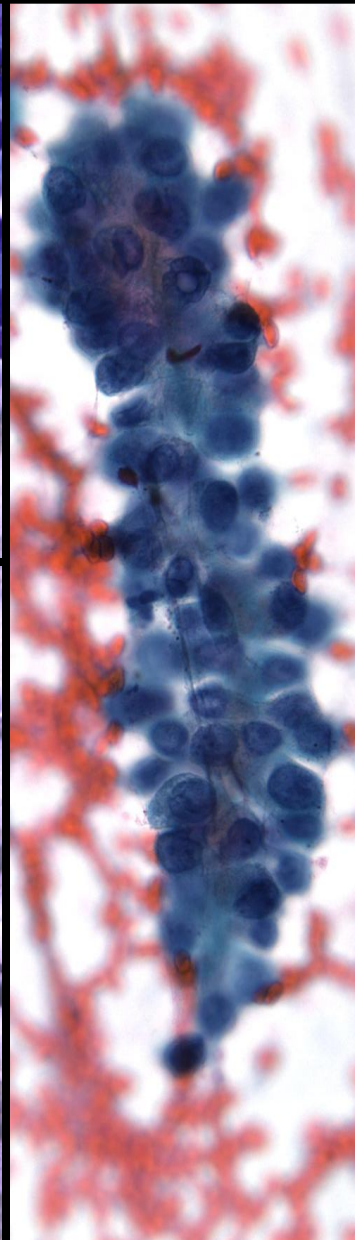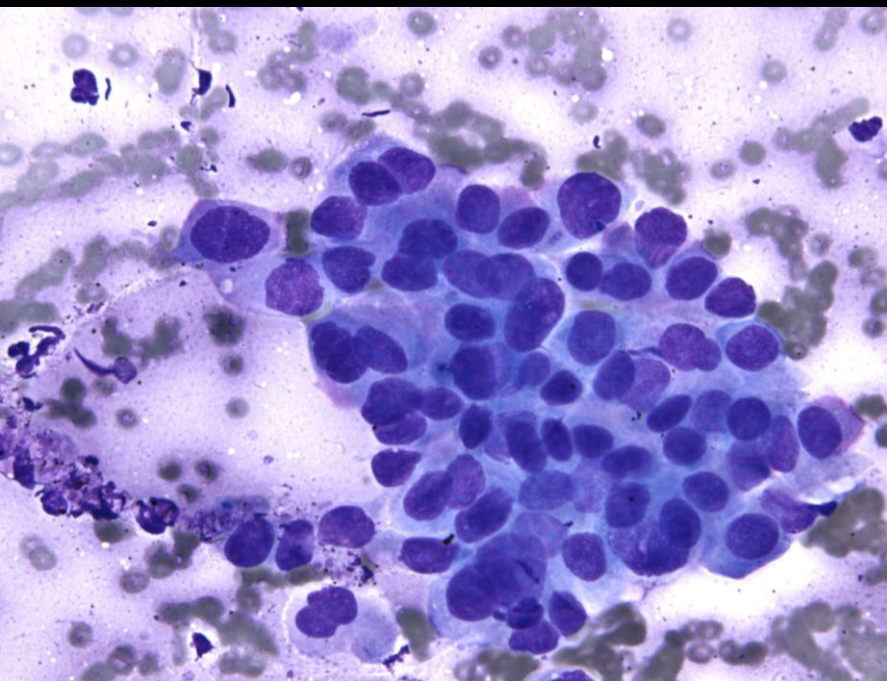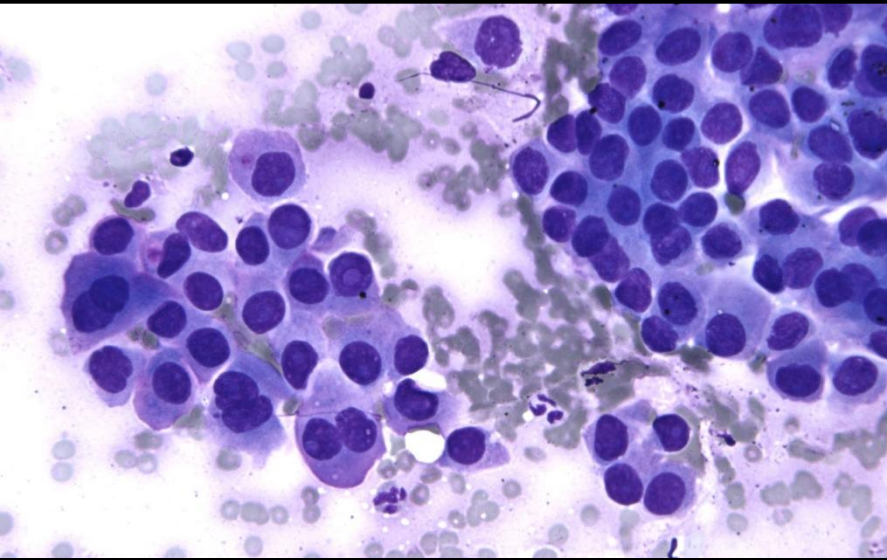**Can morphological subtyping be applied to small cytology/biopsy specimens?**

MORPHOLOGIC ADENOCARCINOMA PATTERNS CLEARLY PRESENT

- Adenocarcinoma, describe identifiable patterns present

ADENOCARCINOMA, ACINAR PATTERN

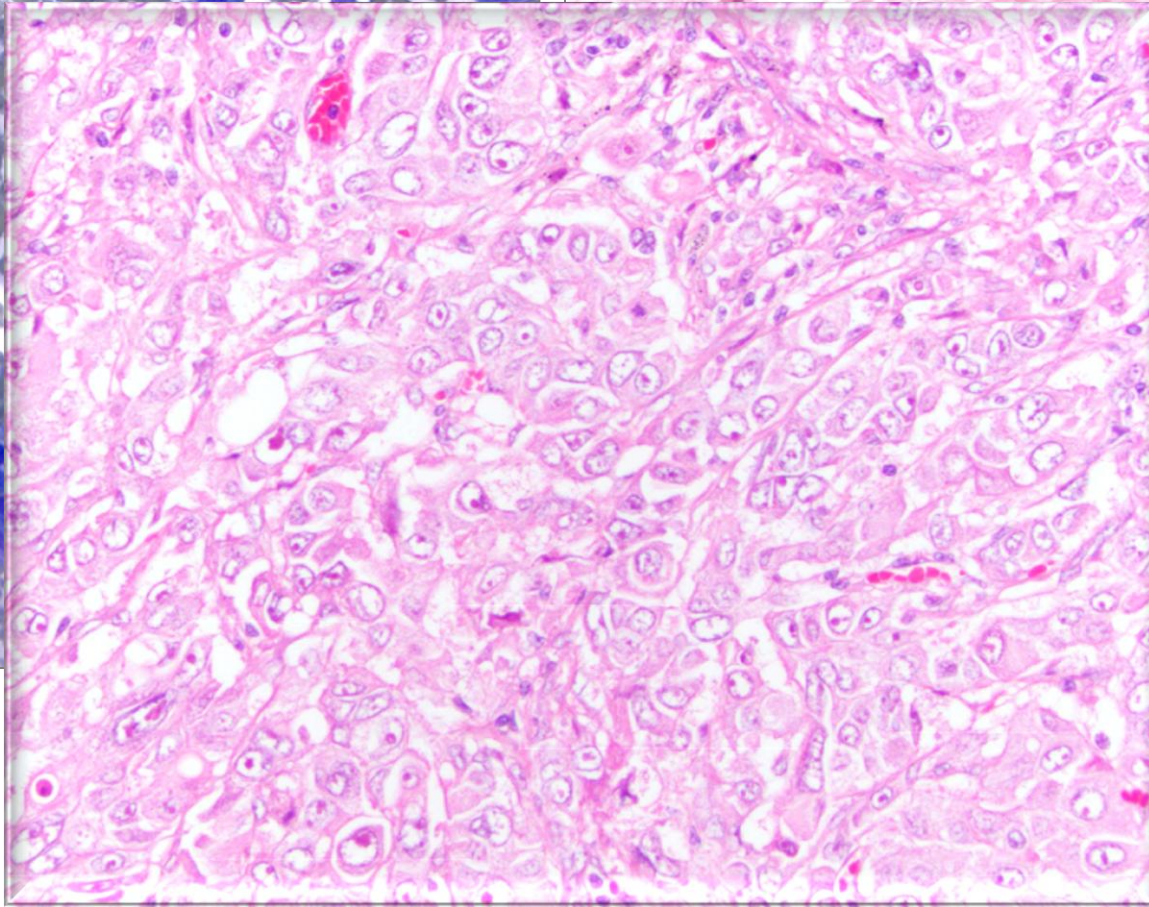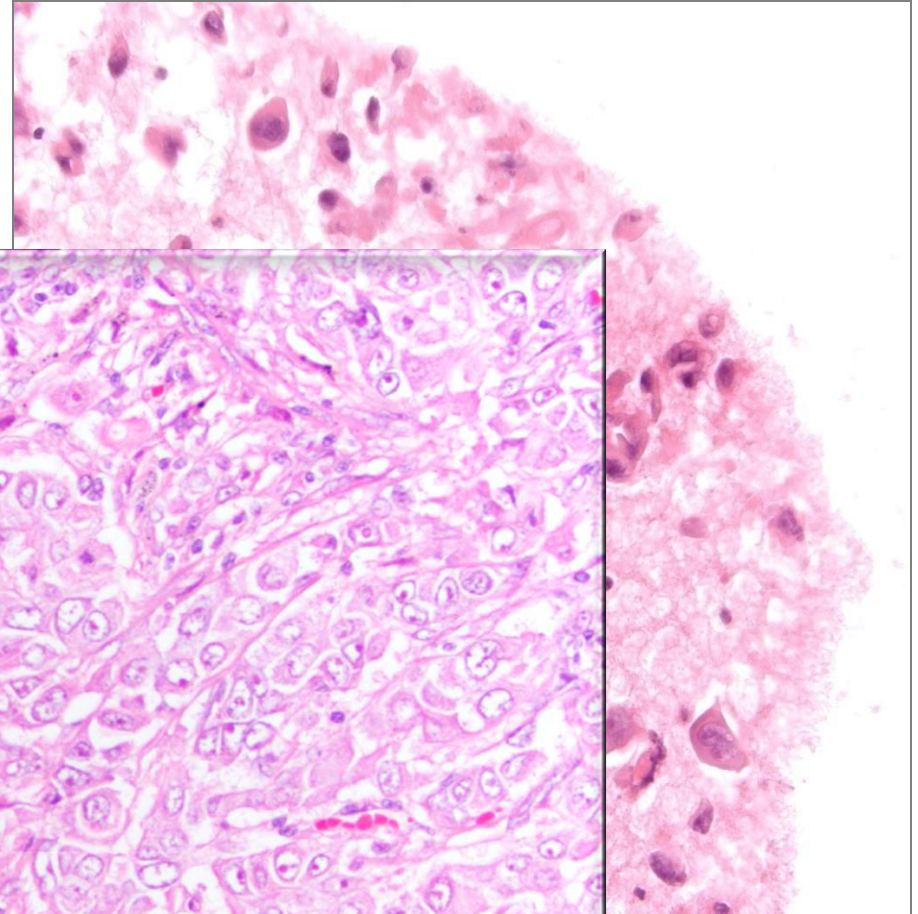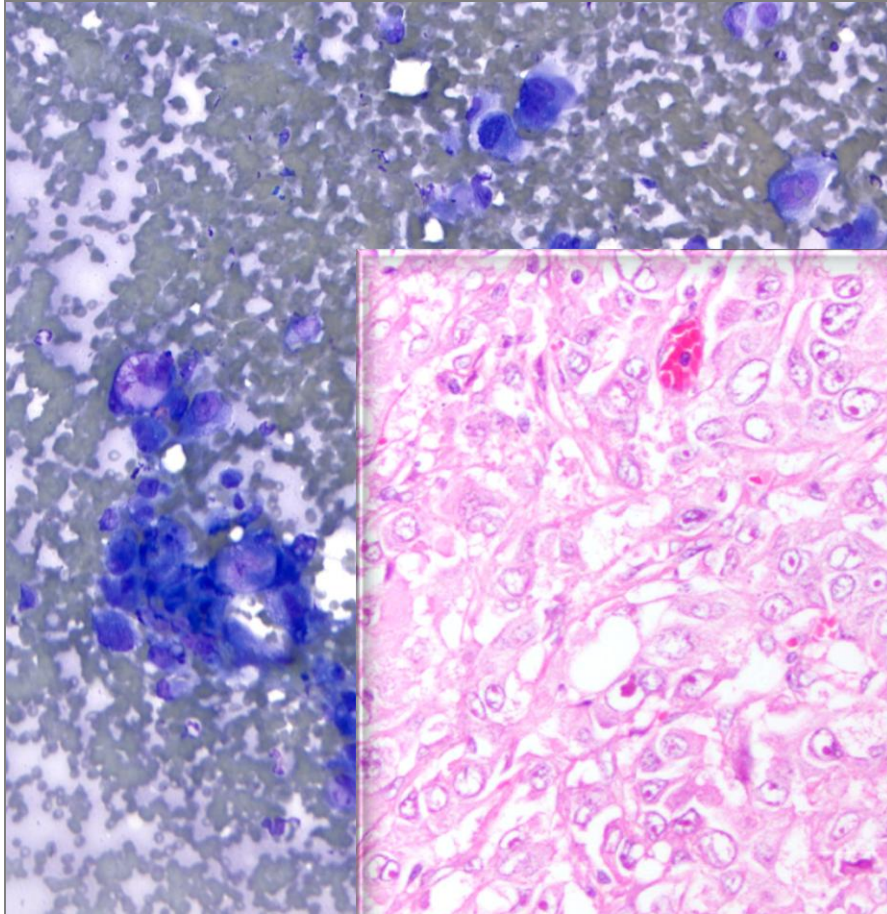*Cytology images courtesy of Dr. Sara Monaco, UPMC*
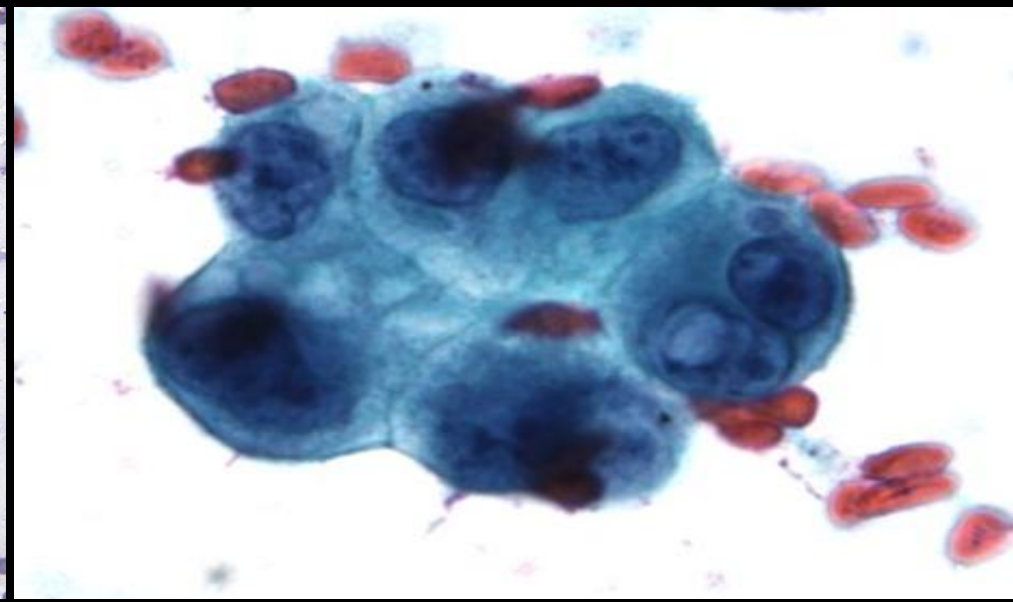
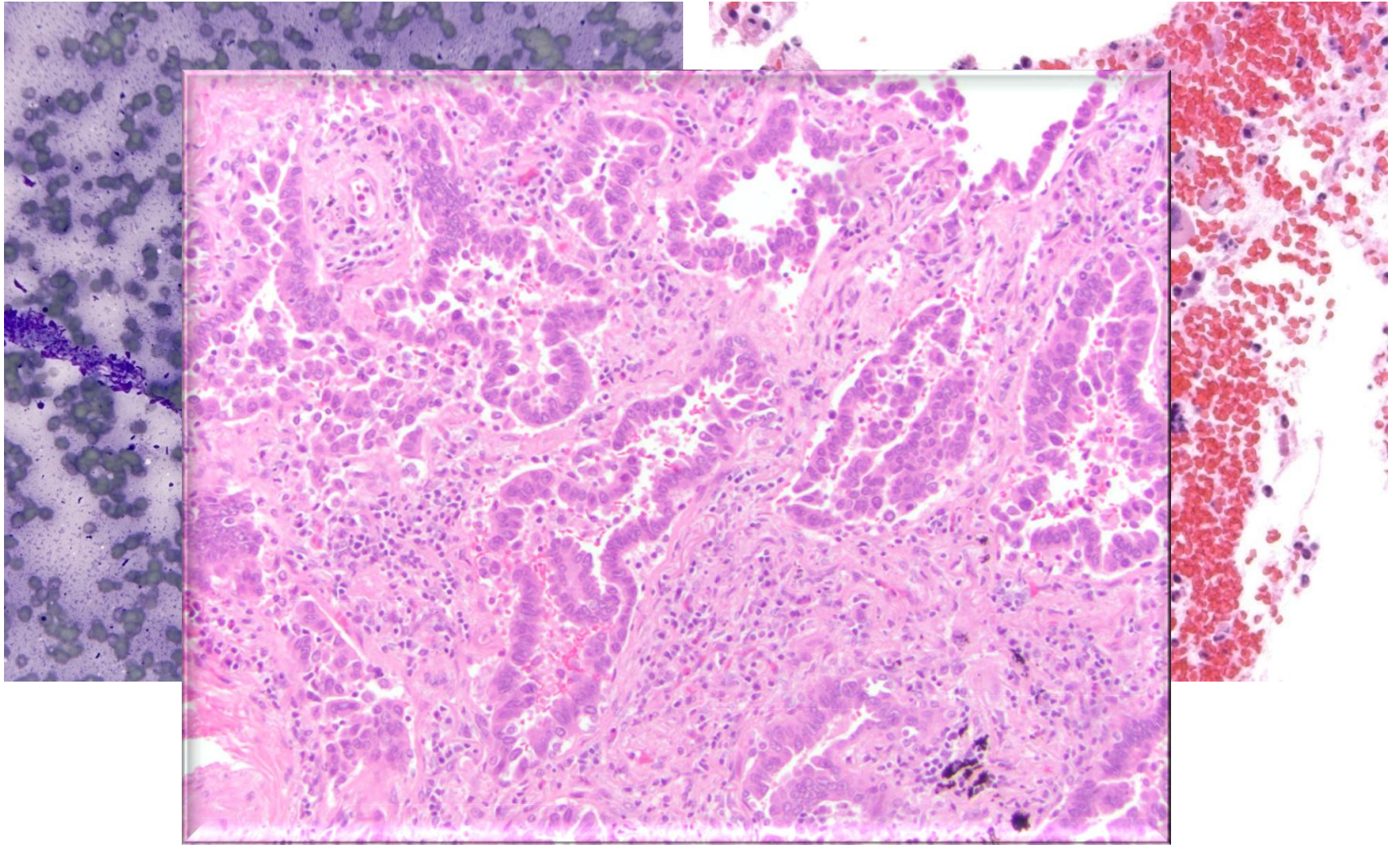# ADENOCARCINOMA, PAPILLARY PATTERN

Cytology images courtesy of Dr. Sara Monaco, UPMC

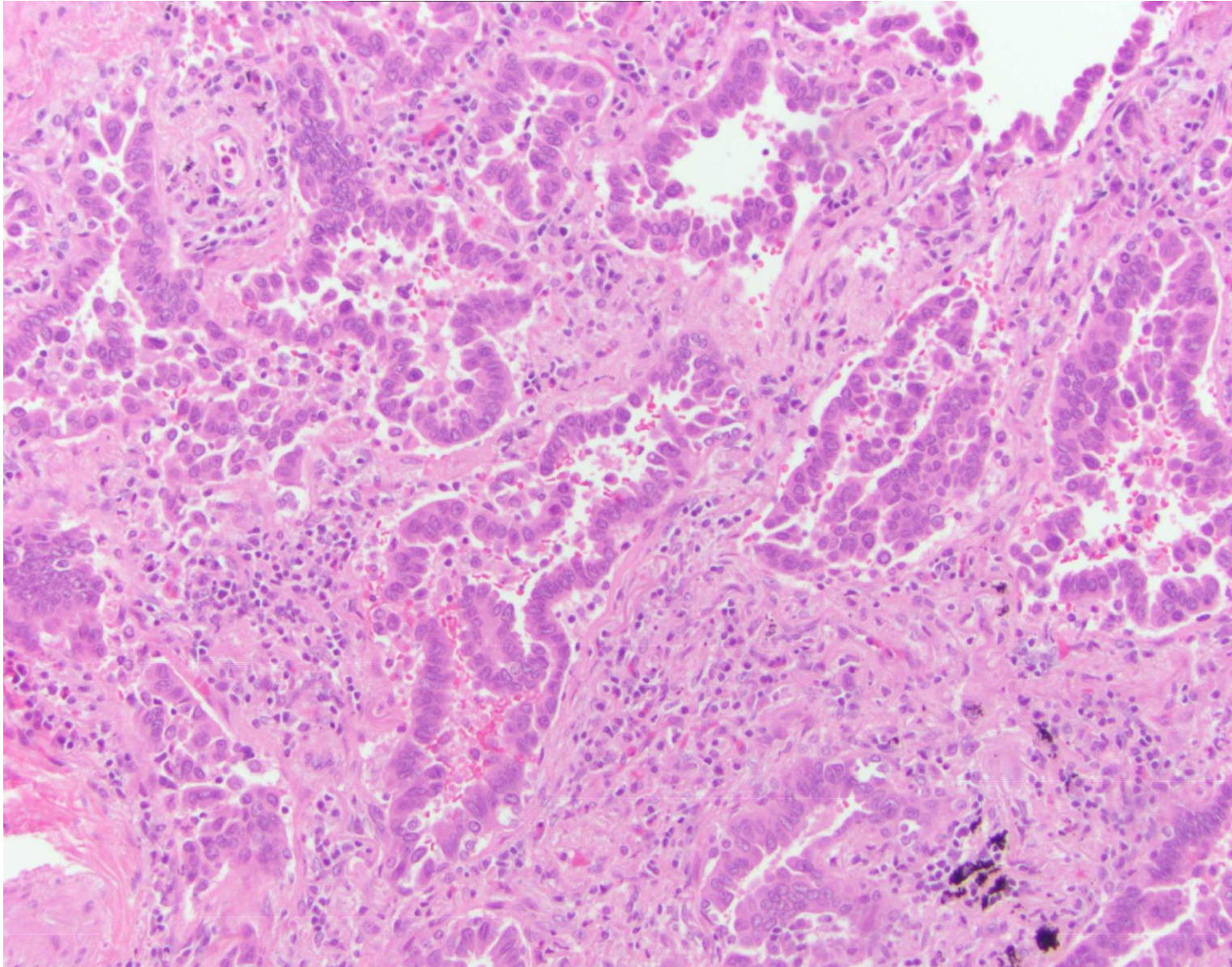# How accurate is subtyping on the cytology/small biopsy specimens?
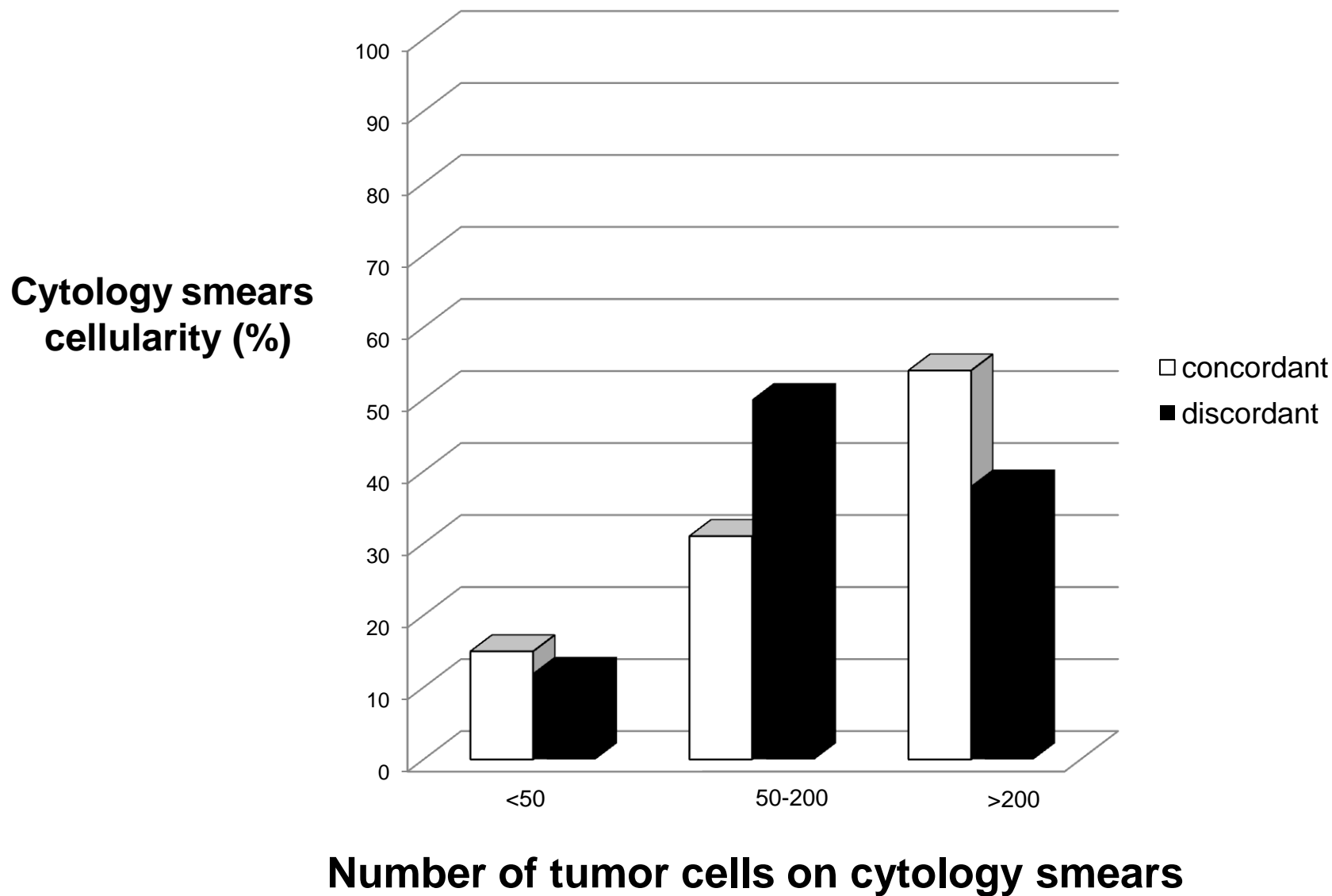
WHAT DO YOU THINK?

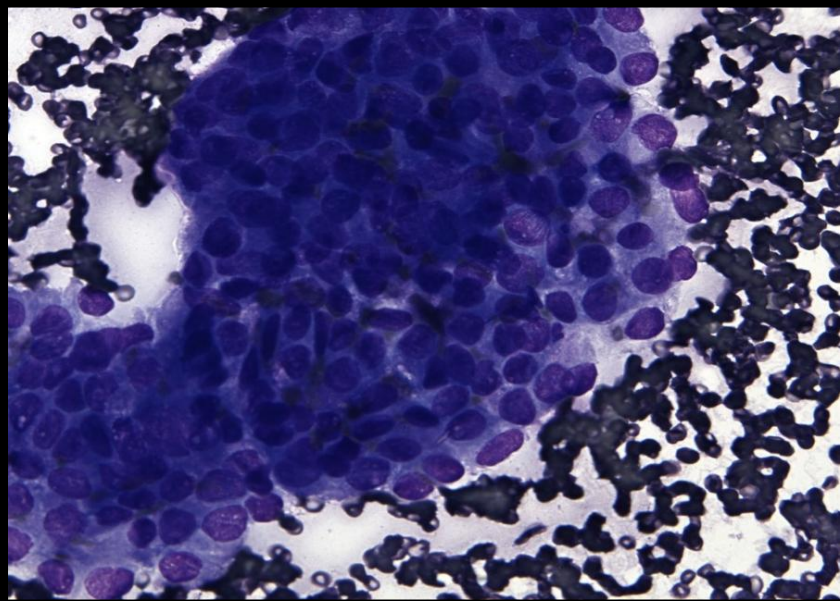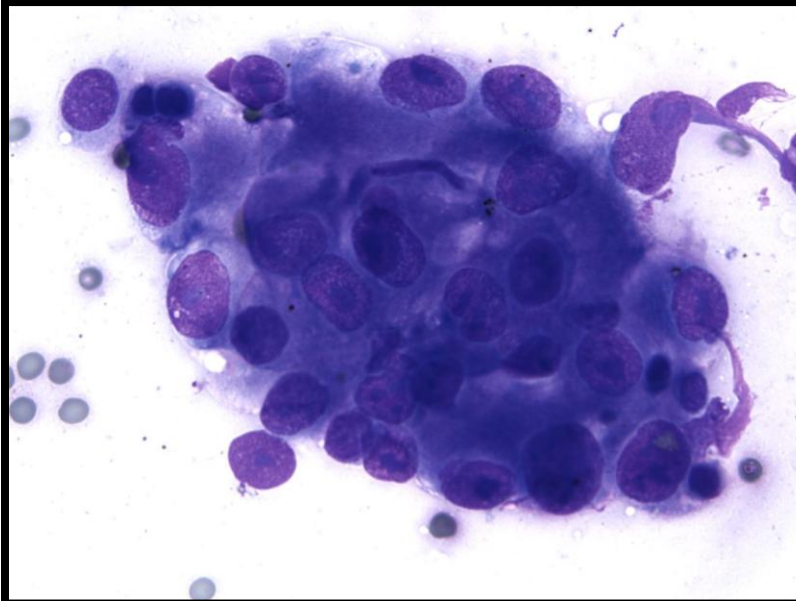# WHAT DO YOU THINK?

ACINAR PATTERN

Histologic-cytologic correlation

Histologic pattern	Concordant (N=26)	Discordant (N=32)	Cytologic classification in discordant cases (N)
Solid	6 (23%)	8 (25%)	Acinar (7); papillary (1)
Acinar	18 (69%)	6 (19%)	Solid (5); papillary (1)
Papillary	1 (4%)	6 (19%)	Acinar (5); mucinous (1)
Lepidic	0	7 (22%)	Acinar (5); solid (1); papillary (1)
Mucinous	1 (4%)	4 (12%)	Acinar (2); solid (1); lepidic (1)
Clear cell	0	1 (3%)	Acinar (1)

Rodriguez E. et al. Cancer Cytopath 2013 August

SPECIMEN CELLULARITY AND SUBTYPING

Cytology smears cellularity (%)

Number of tumor cells on cytology smears

concordant
discordant

NON-SMALL CELL CARCINOMA, FAVOR ADENOCARCINOMA

0

Cytology images courtesy of Dr. Sara Monaco, UPMC

ANCILLARY STUDIES

IHC
1 SQC/1 ADC
and/or mucin

ADC
IHC + or mucin+
SQC
IHC -

SQC
IHC +
ADC
IHC - or mucin-

SQC
IHC +
ADC
IHC + or mucin+

IHC-
mucin -

**NSCLC,
favor ADC**

**NSCLC,
favor SQC**

NSCLC,NOS
possible
adenosquamous
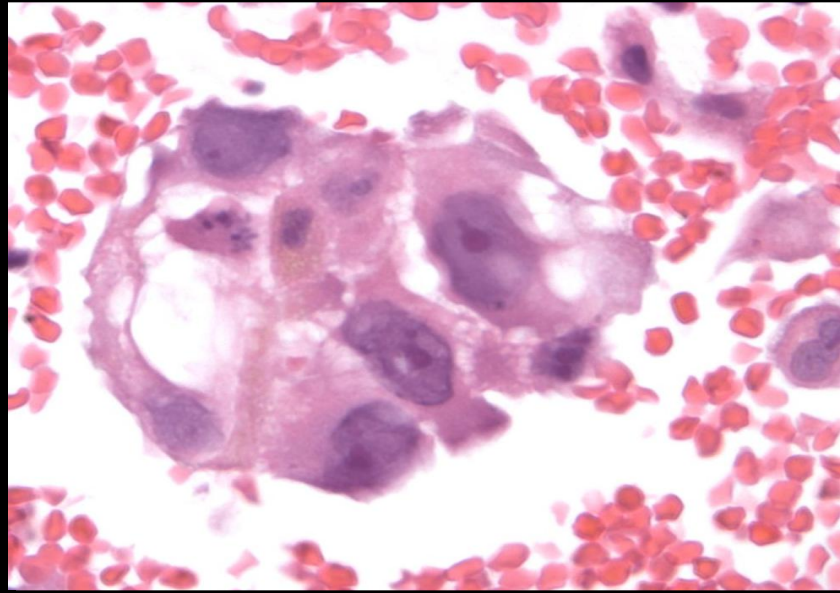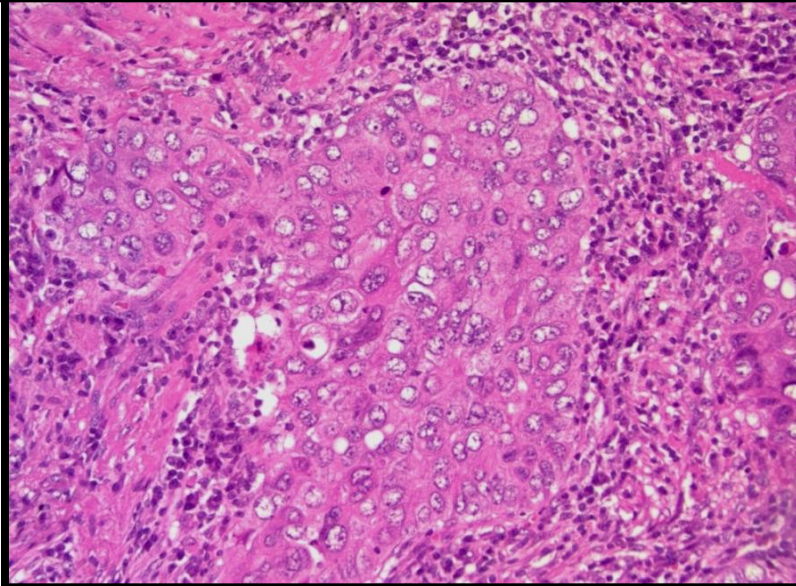
NSCLC,NOS
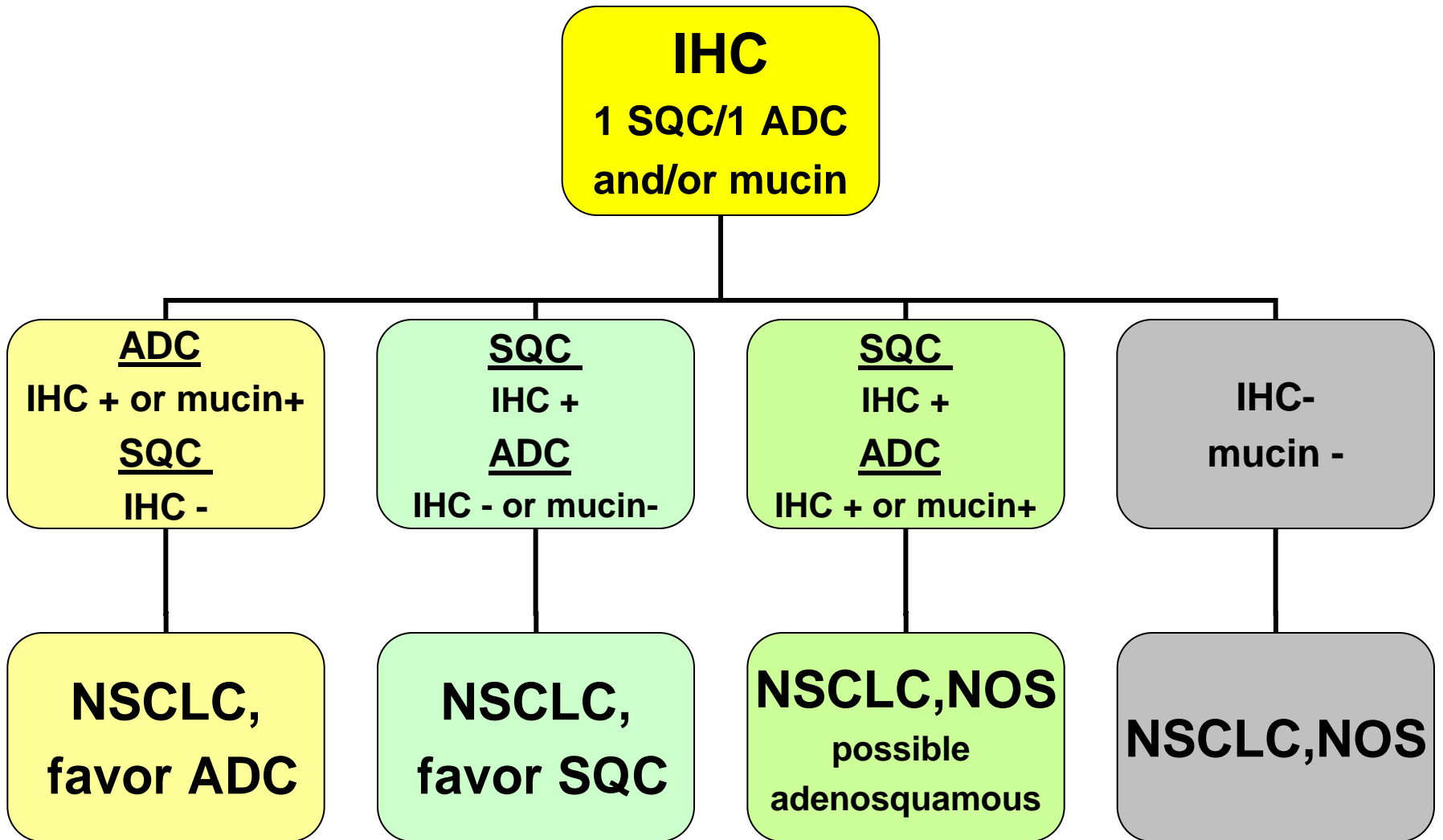
FREQUENCY OF ANCILLARY STUDIES

Ocque R. et al . AJCP 2011; 136 (1):81-7

Adenocarcinoma classification on cytology specimens

Ocque R. et al . AJCP 2011; 136 (1):81-7
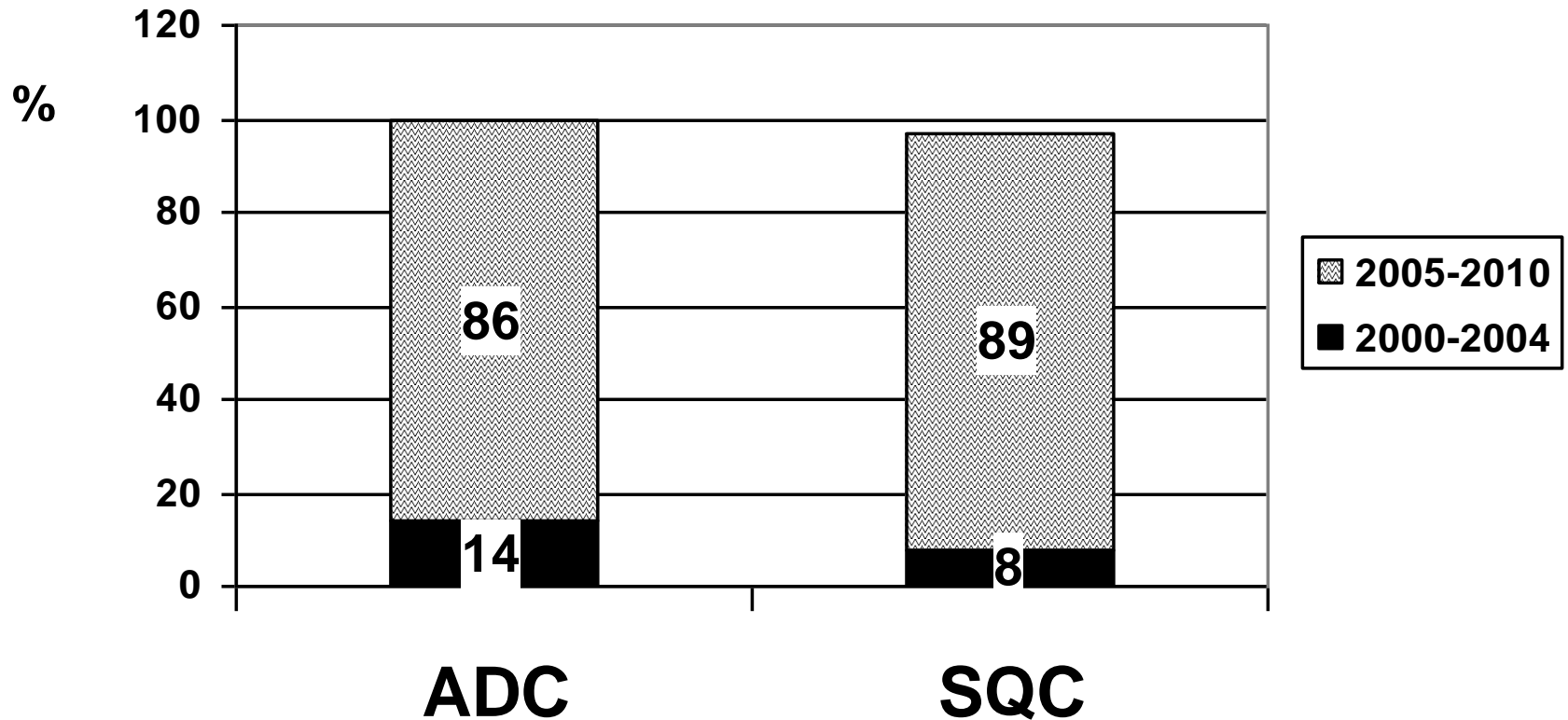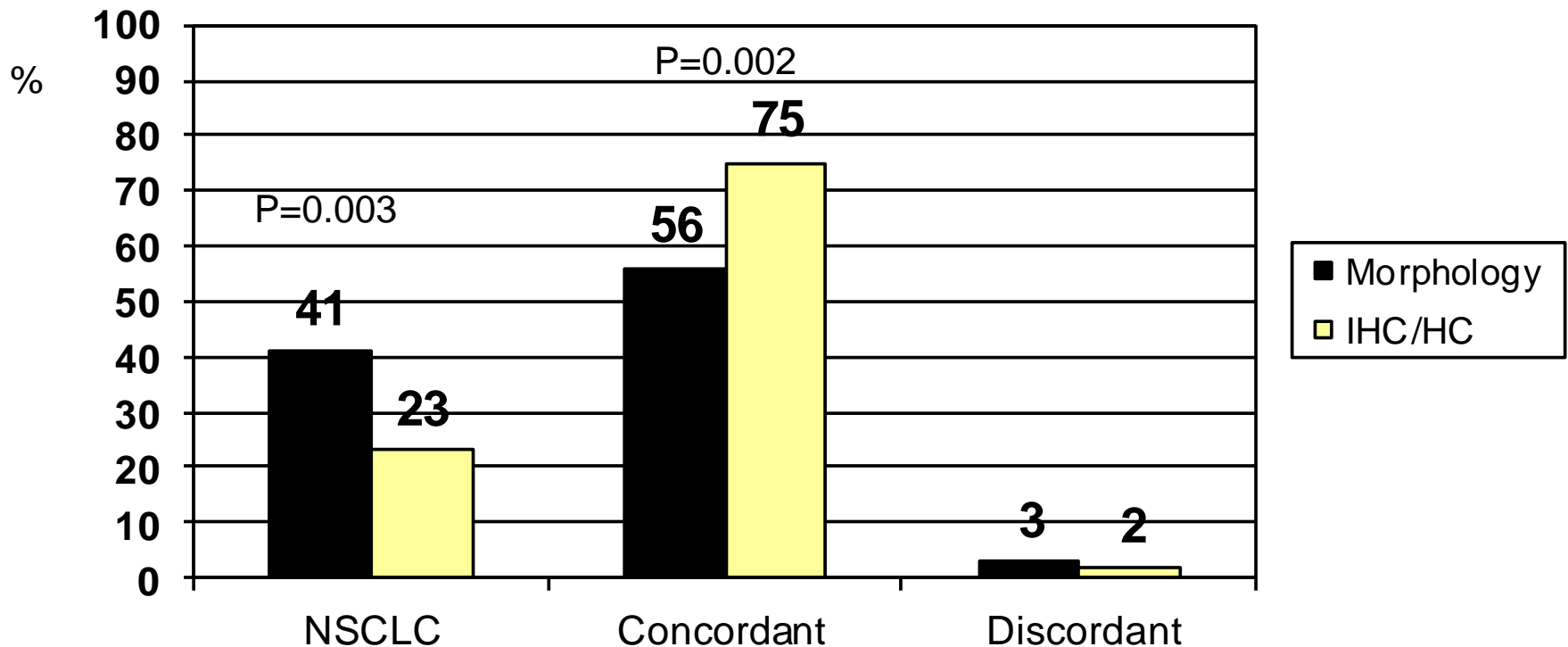
Squamous cell carcinoma classification on cytology specimens

Ocque R. et al . AJCP 2011; 136 (1):81-7

p40

TTF1
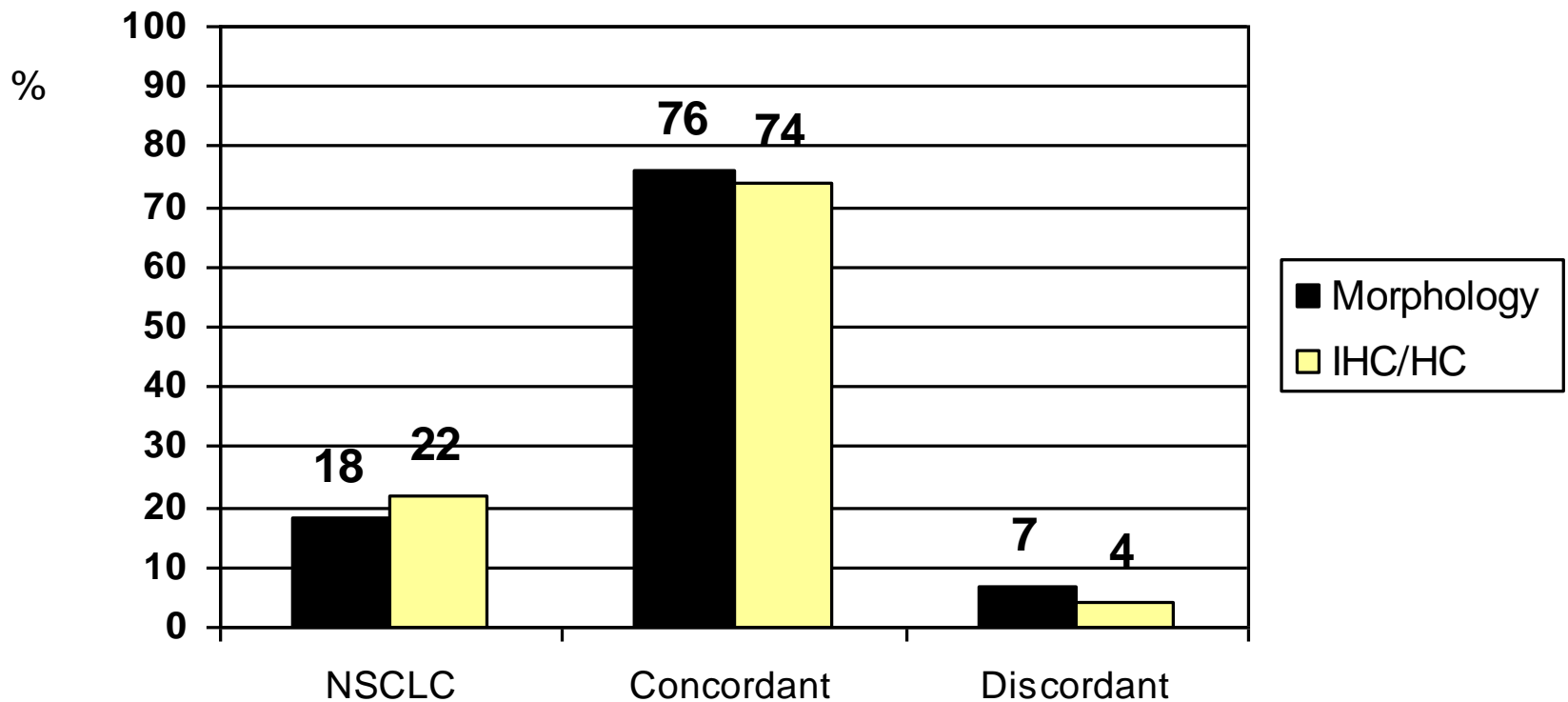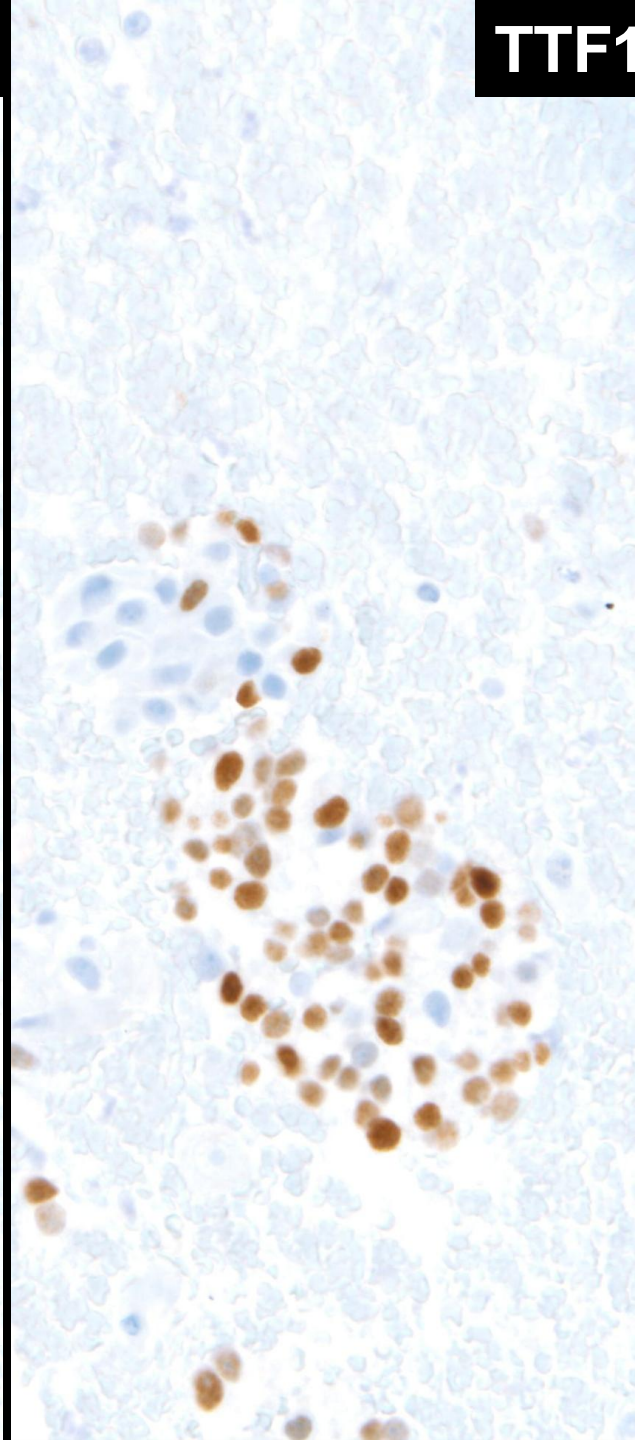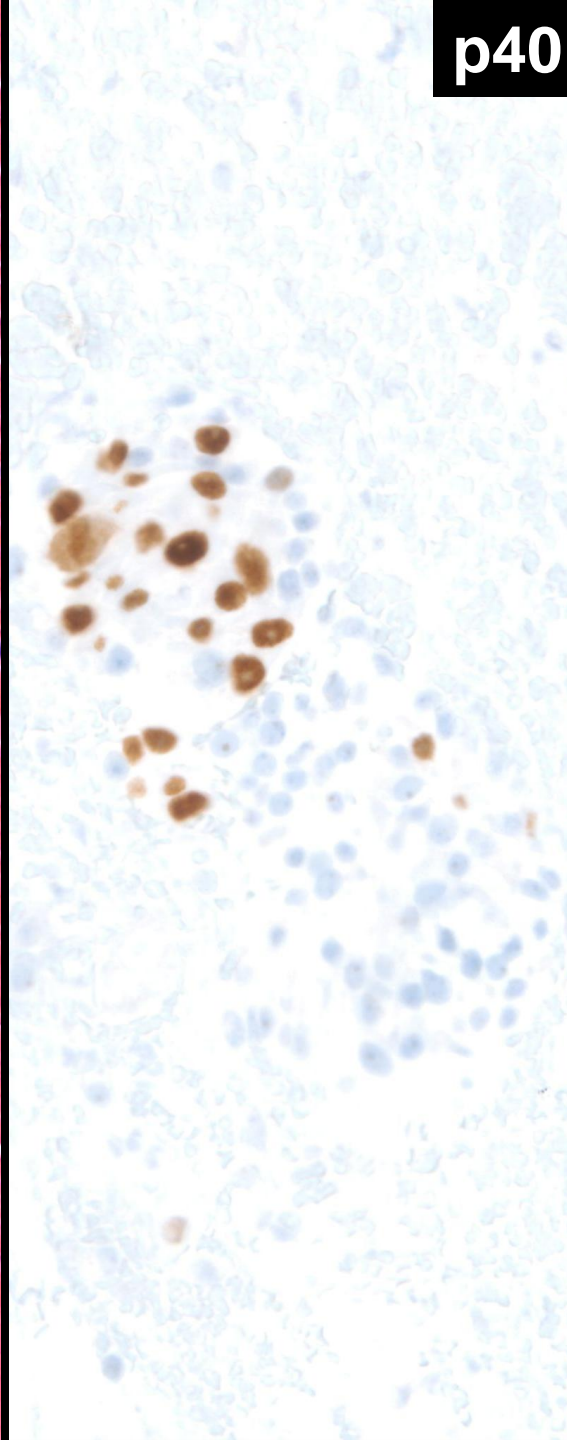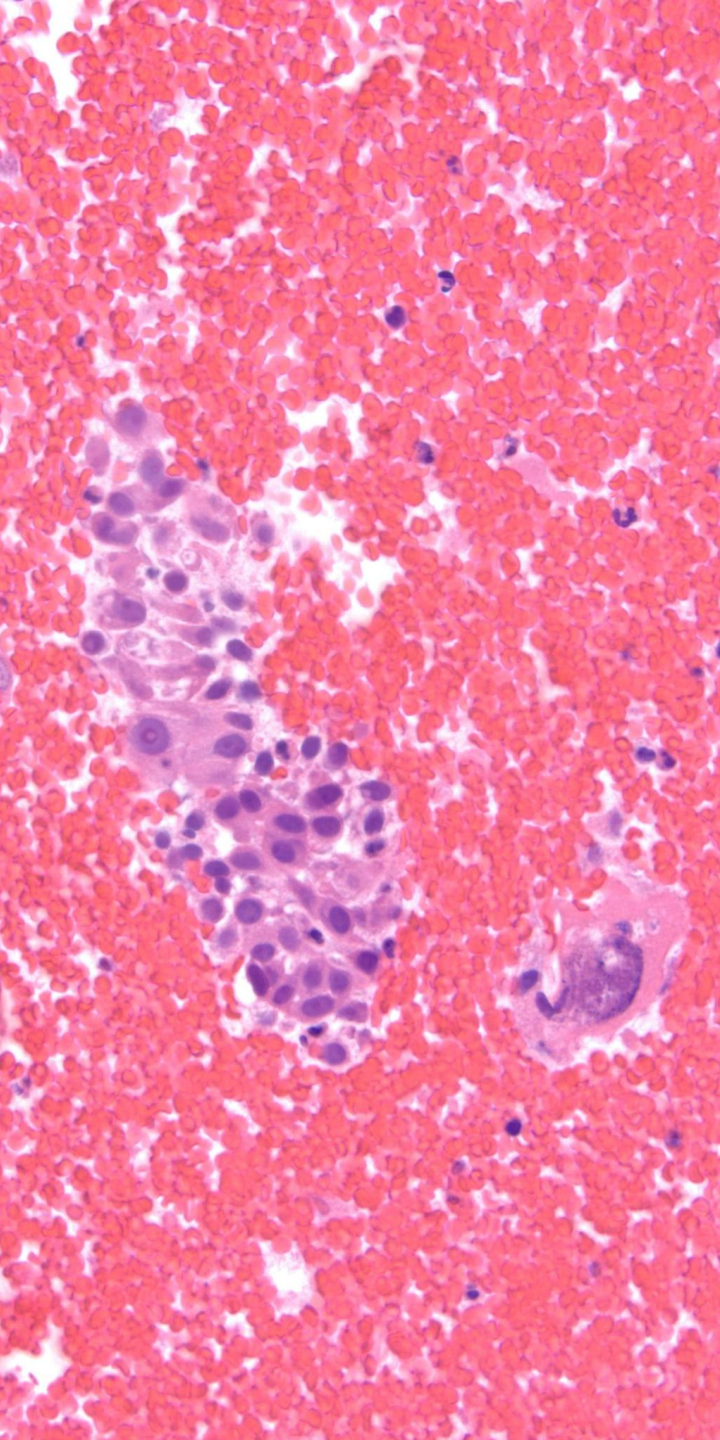
TWO SCENARIOS WHEN COMMENT SHOULD BE MADE

Morphology SQC and ADC present	IHC favor both ADC and SQC component

↓ ↓

NSCLC, NOS
Comment: tumor may represent adenosquamous carcinoma

OTHER SUGGESTIONS FOR GOOD PRACTICE

- The term large cell carcinoma should not be used for diagnosis in small biopsy or cytology specimens

- The term non-squamous cell carcinoma should not be used by pathologists in diagnostic reports

- Tumors with sarcomatoid features should be regarded as ADC or SQC; or "poorly differentiated NSCLC with giant and/or spindle cell features"

- NE markers should be used only if NE morphology is suspected

SUMMARY

- Histological subtyping of invasive adenocarcinoma has prognostic significance

- Reproducibility of subtyping on resection and cytology/small specimens is poor

- IHC should be used only when morphological classification is difficult