How to diagnose and measure invasion in the cervix?

Gerd JACOMEN

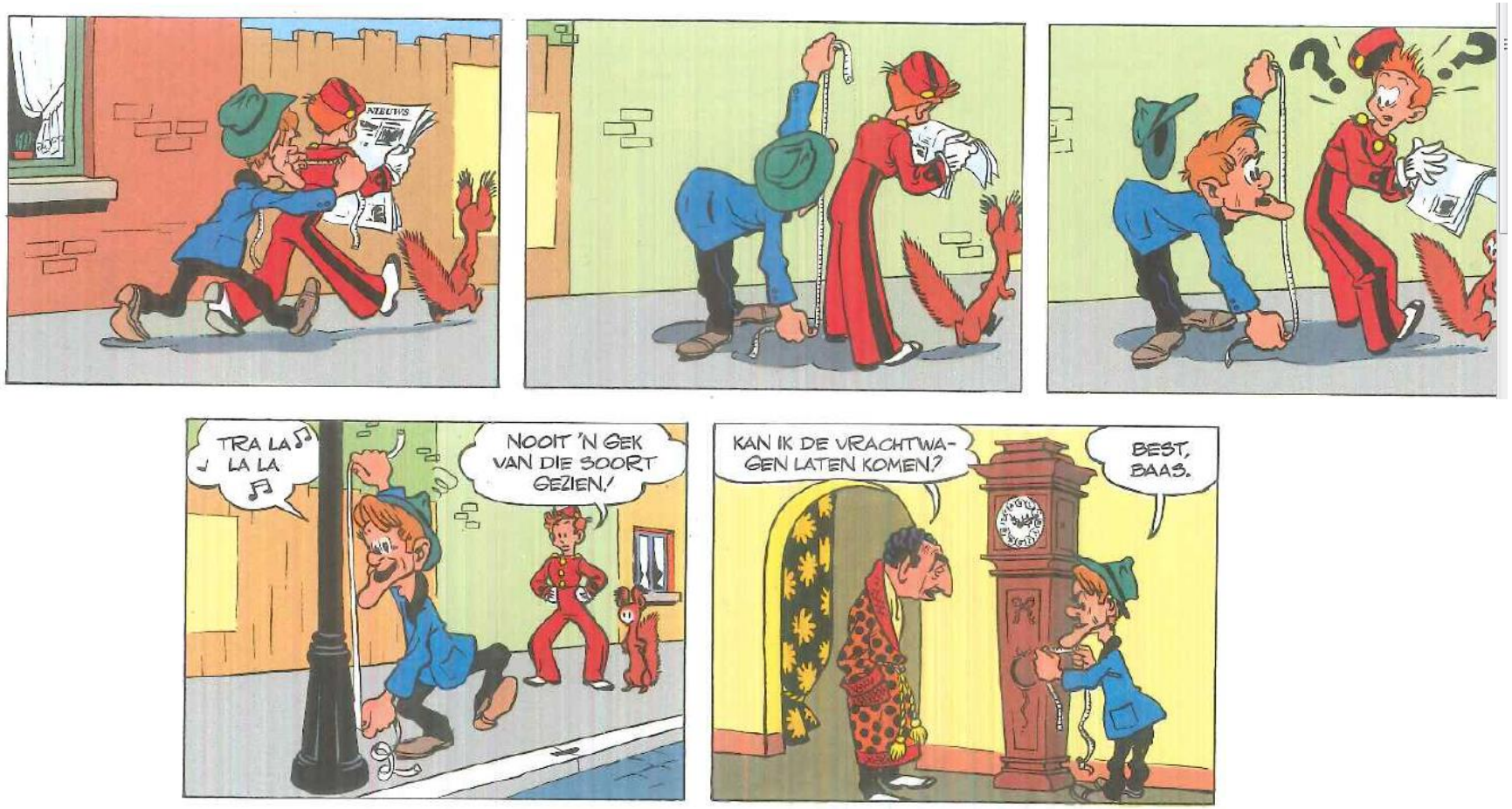
AZ St Maarten Mechelen

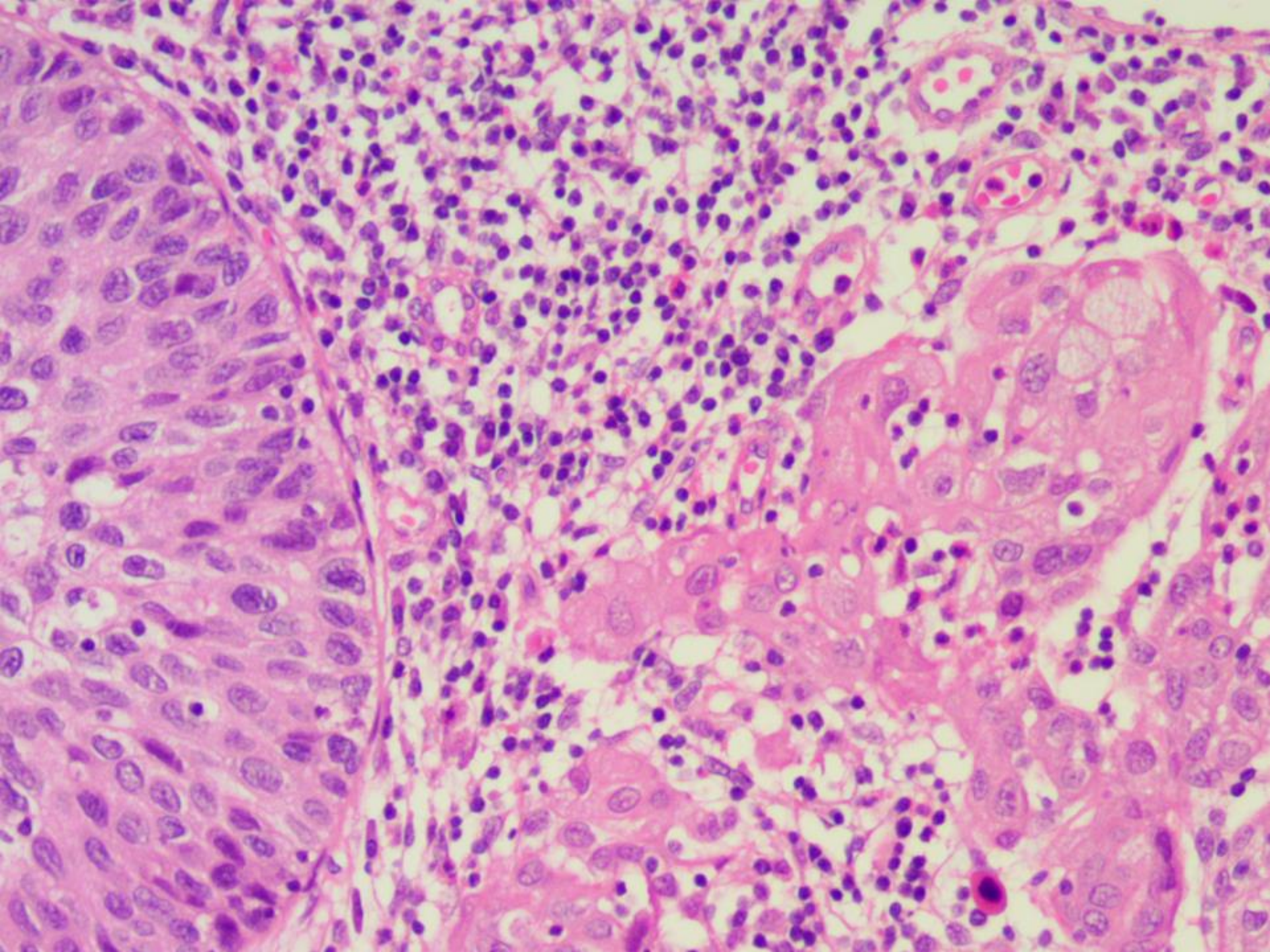
What should be in all onco reports?

- Type
- Grade
- Features that define stage
- All features that have influence on therapeutic decisions or are of prognostic relevance

Stage in early CxCa

Correct measuring requires correct recognition of invasion





Interface epithelium/stroma

- Loss of polarity of basal cells epithelium
- Blurring of the interface
- Loss of a sharply-defined basal membrane
- Irregular margins (scalloping)
- Small buds of atypical squamous cells with hypermature appearance (paradoxal maturation)

- Retraction
- Stromal reaction: desmoplasia/inflammation

Paradoxal maturation

- In situ: atypical cells are compressed by the basal membrane (BM)
- Cells that pass the BM (= invasion) are no longer compressed
- The amount of cytoplasm increases and the shape becomes irregular

Paradoxal maturation

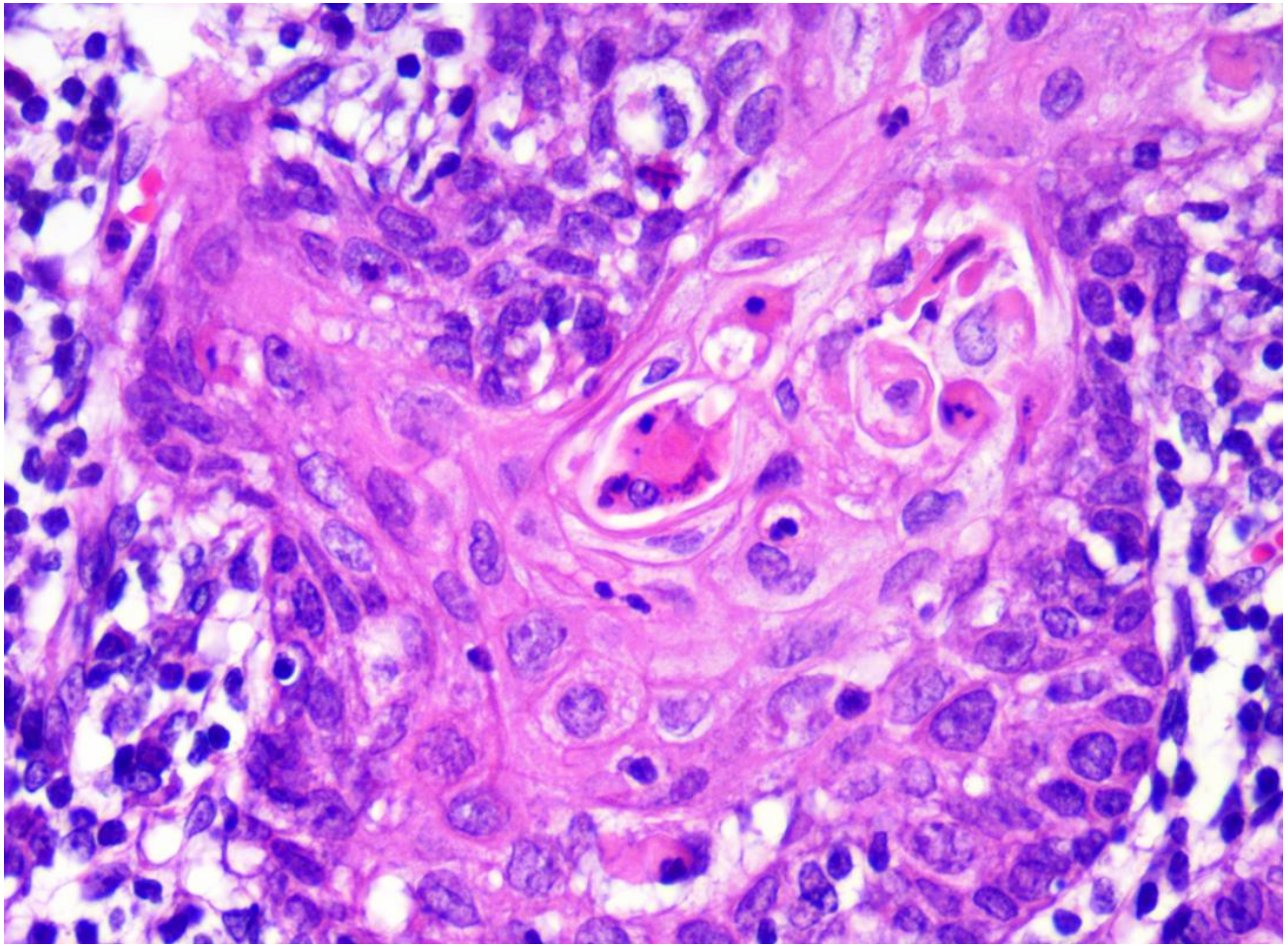
- Gaining cytoplasm = maturation
- Normally towards the surface and not under the basal layer = paradoxal maturation
- Also helpful in other organs!

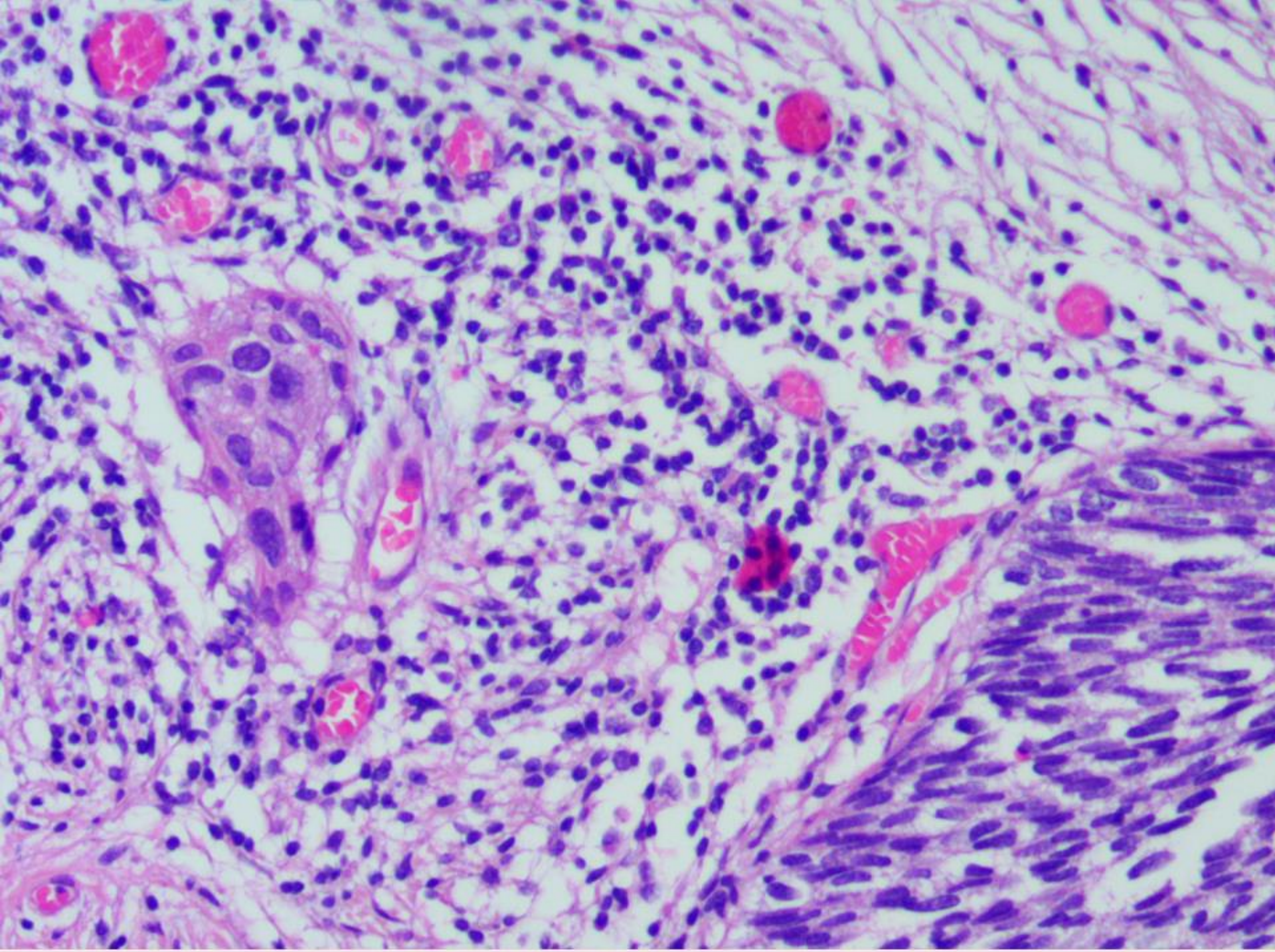
Retraction

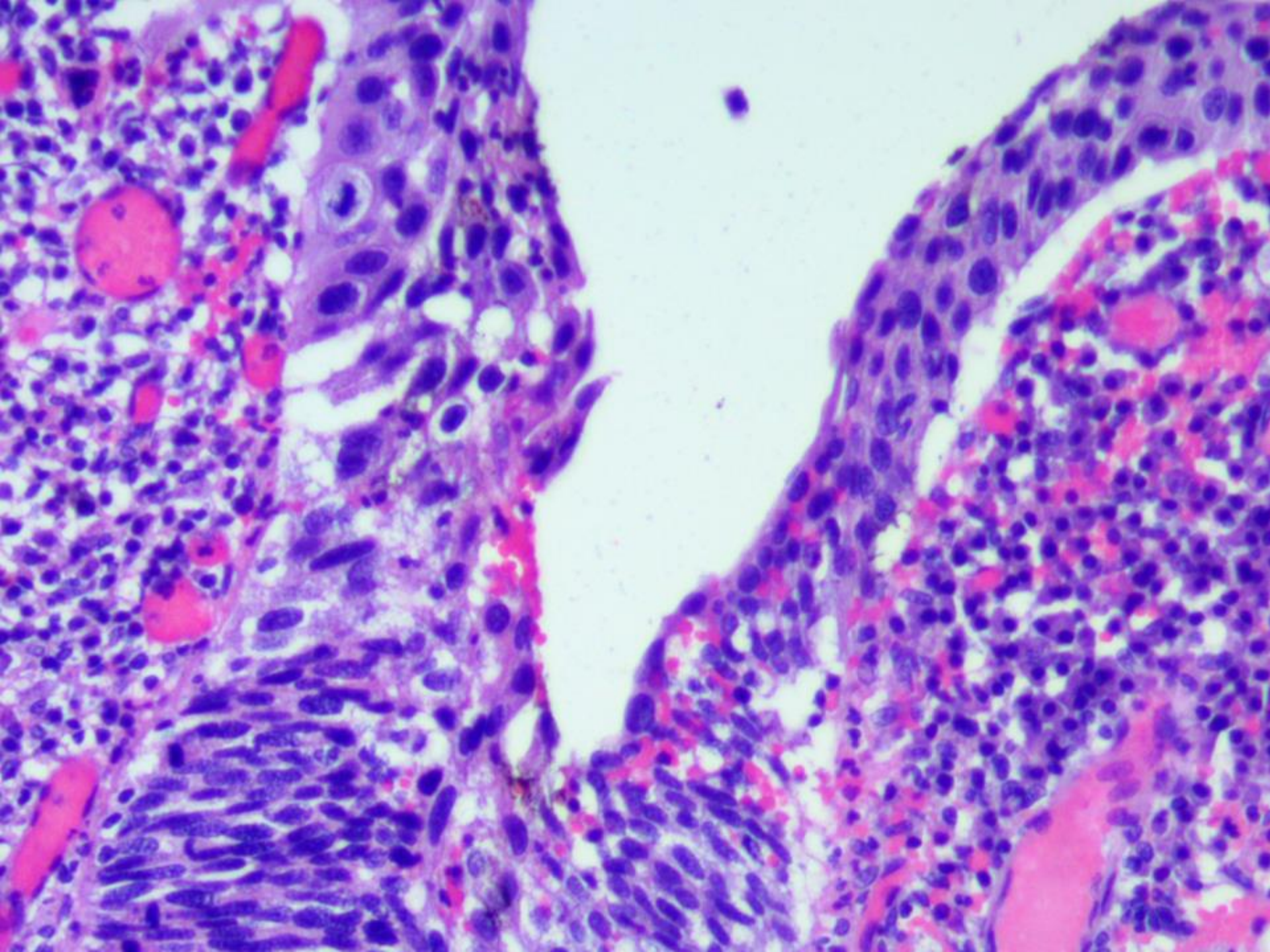
- During processing of paraffin blocks, tissue is dehydrated
- Dehydratation causes shrinking
- Amount of water is much higher in stroma compared to epithelium
- More shrinking in stroma compared to epithelium

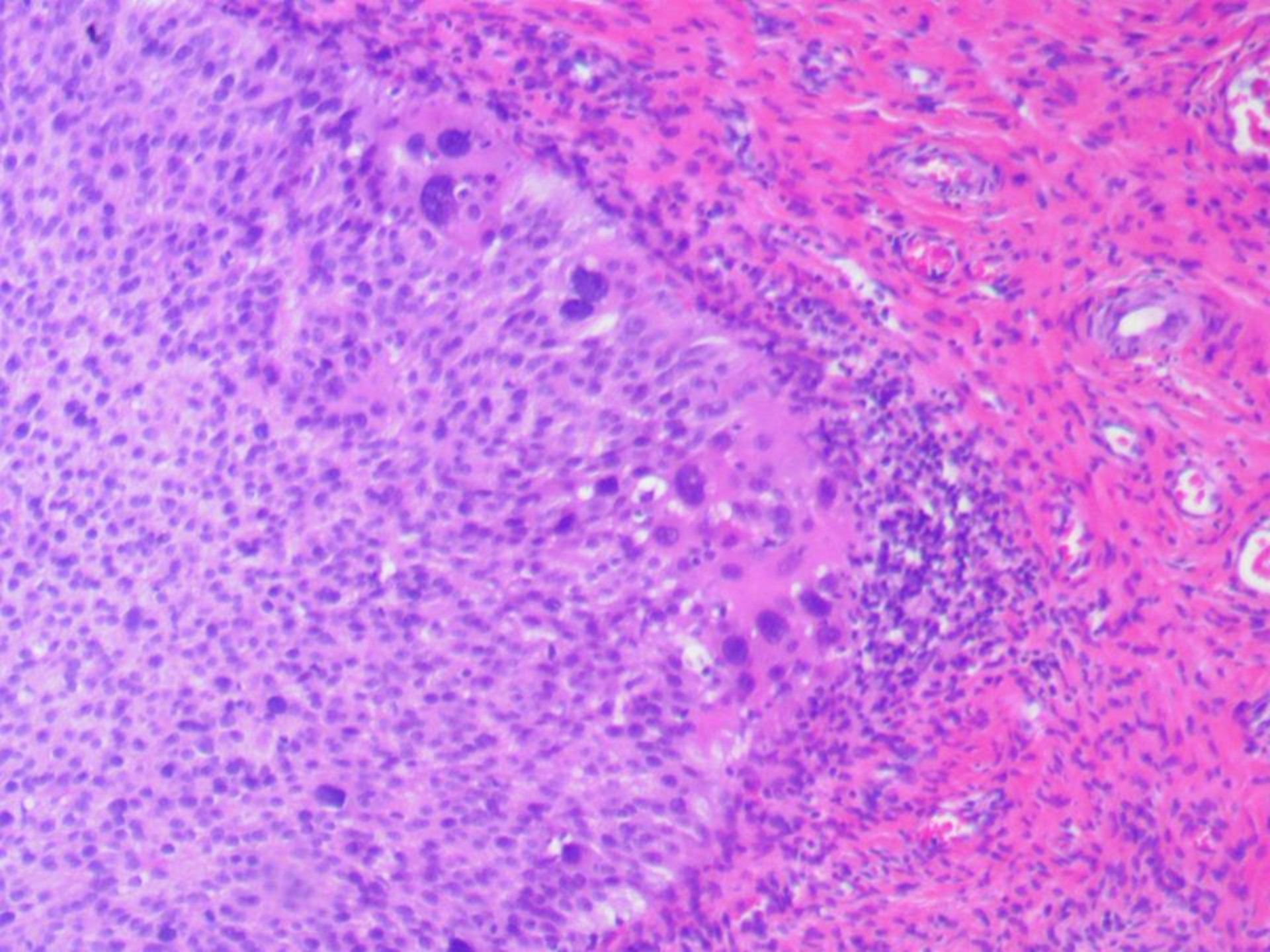
Retraction

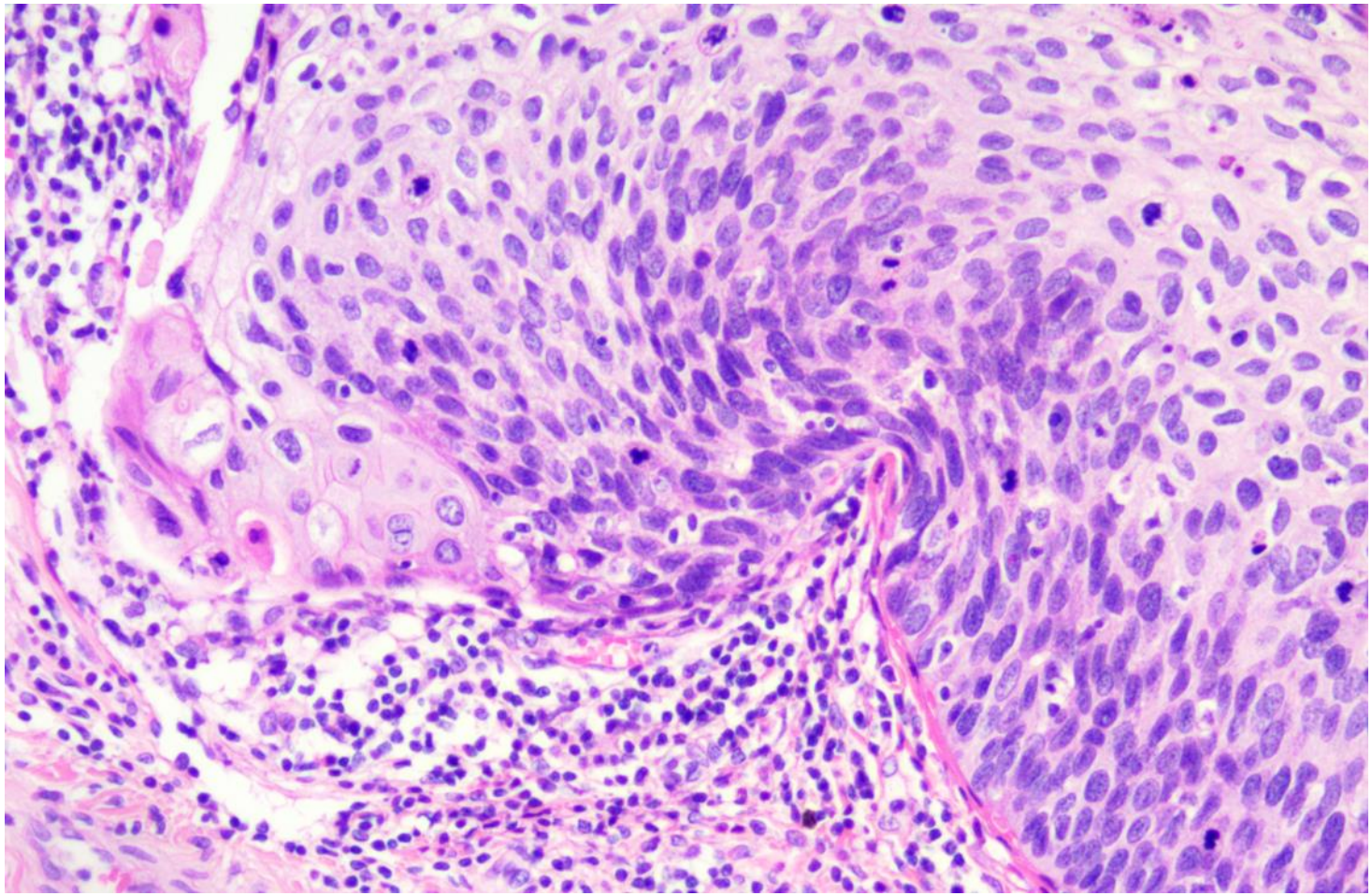
- In situ: stroma and epithelium are tightly connected by basal membrane: no separation
- Invasion: no basal membrane, so no tight connection
- Differential shrinking causes separation of stroma and epithelium









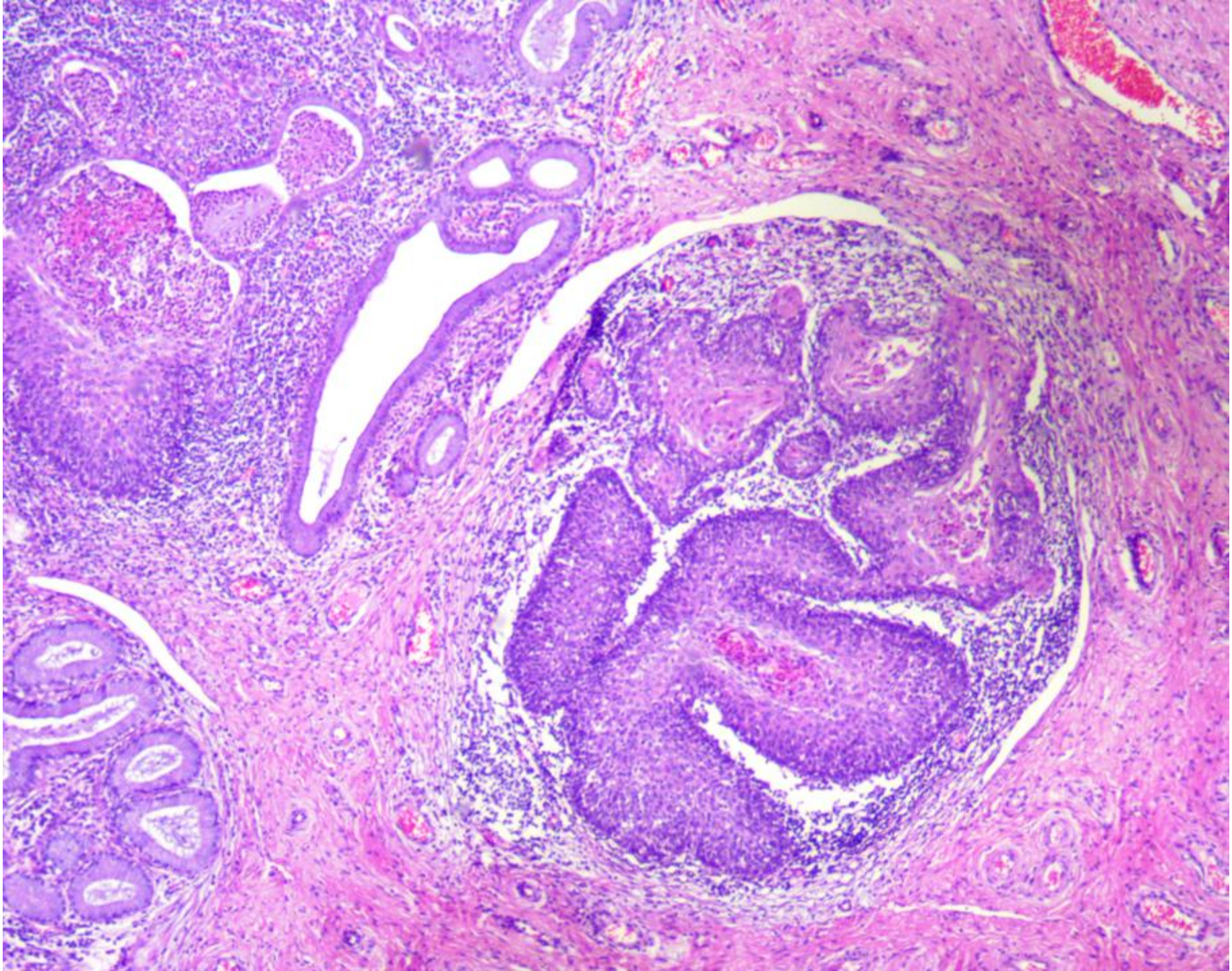


Architectural clues

- Pseudocrypt involvement
- Complex anastomosing and interlacing growth

Pseudocrypt involvement

- DD colonisation of glandular crypt by squamous in situ Ca
- Look for:
  - Luminal glandular cells
  - Central necrosis
  - Loss of polarity
  - Multiple or single?
  - Retraction
  - Desmoplasia/inflammation



Complex growth

- Look for:
  - Central vascular structures in sheets of epithelium

Early invasive adenoCa

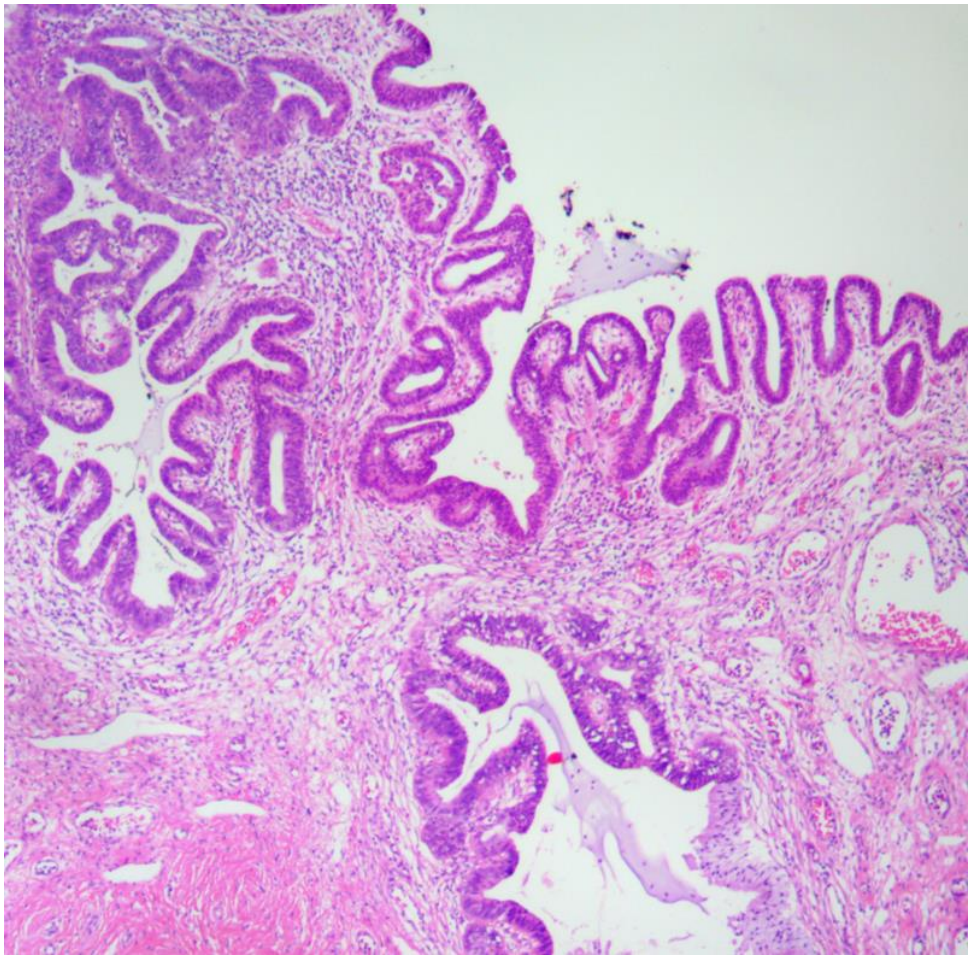
- More difficult to diagnose than squamous invasion
- AIS: preservation of lobular architecture, but this might be accentuated

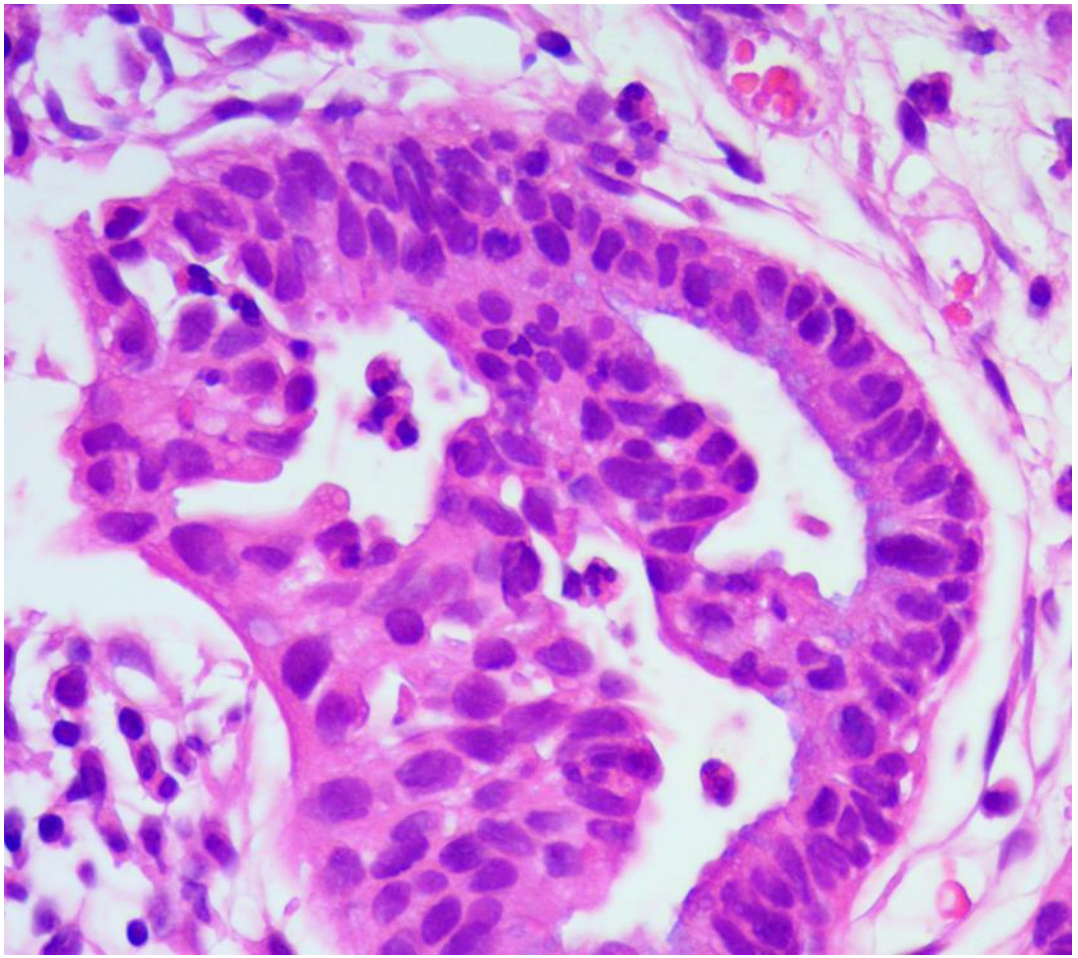
- Oedema, inflammation, desmoplasia

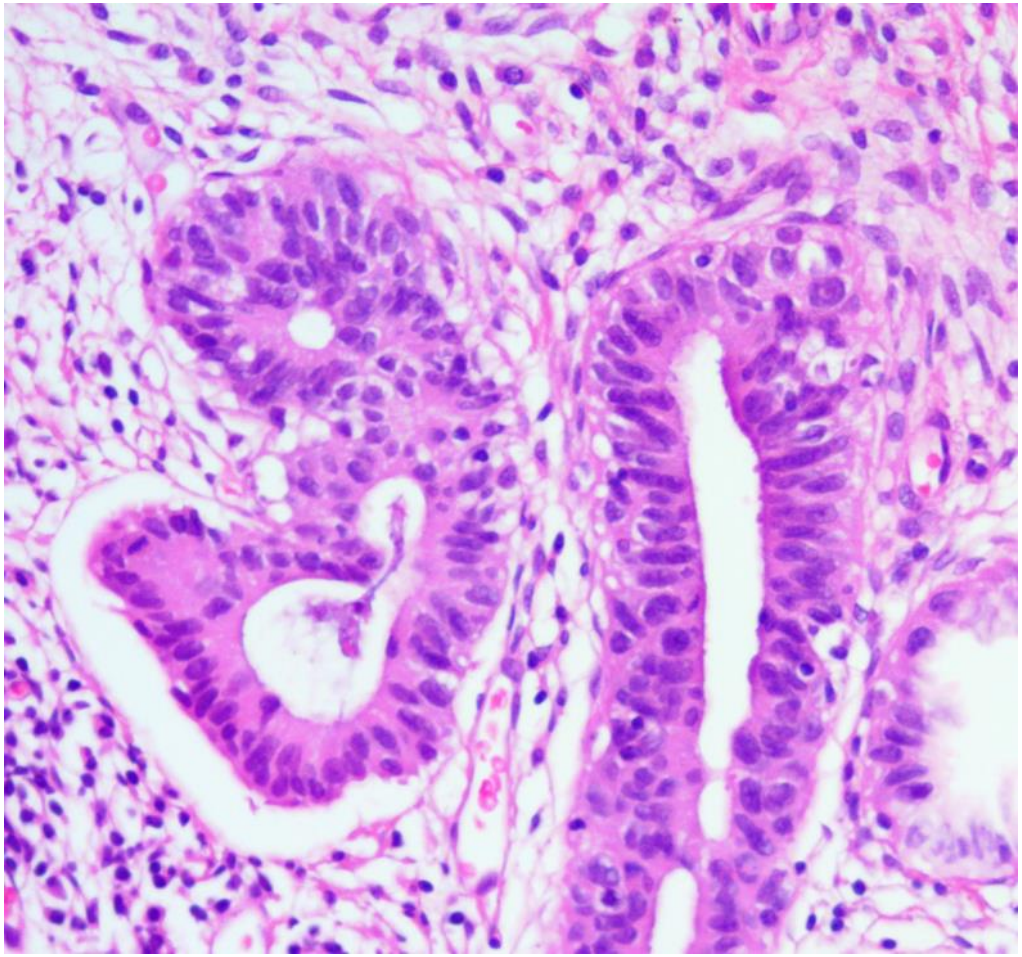
Invasion in glandular lesions (1)

- Look carefully at the perifery of the glands for:
  - Budding
  - Irregular contour of glands: angulation
  - Squamoid features

AIS

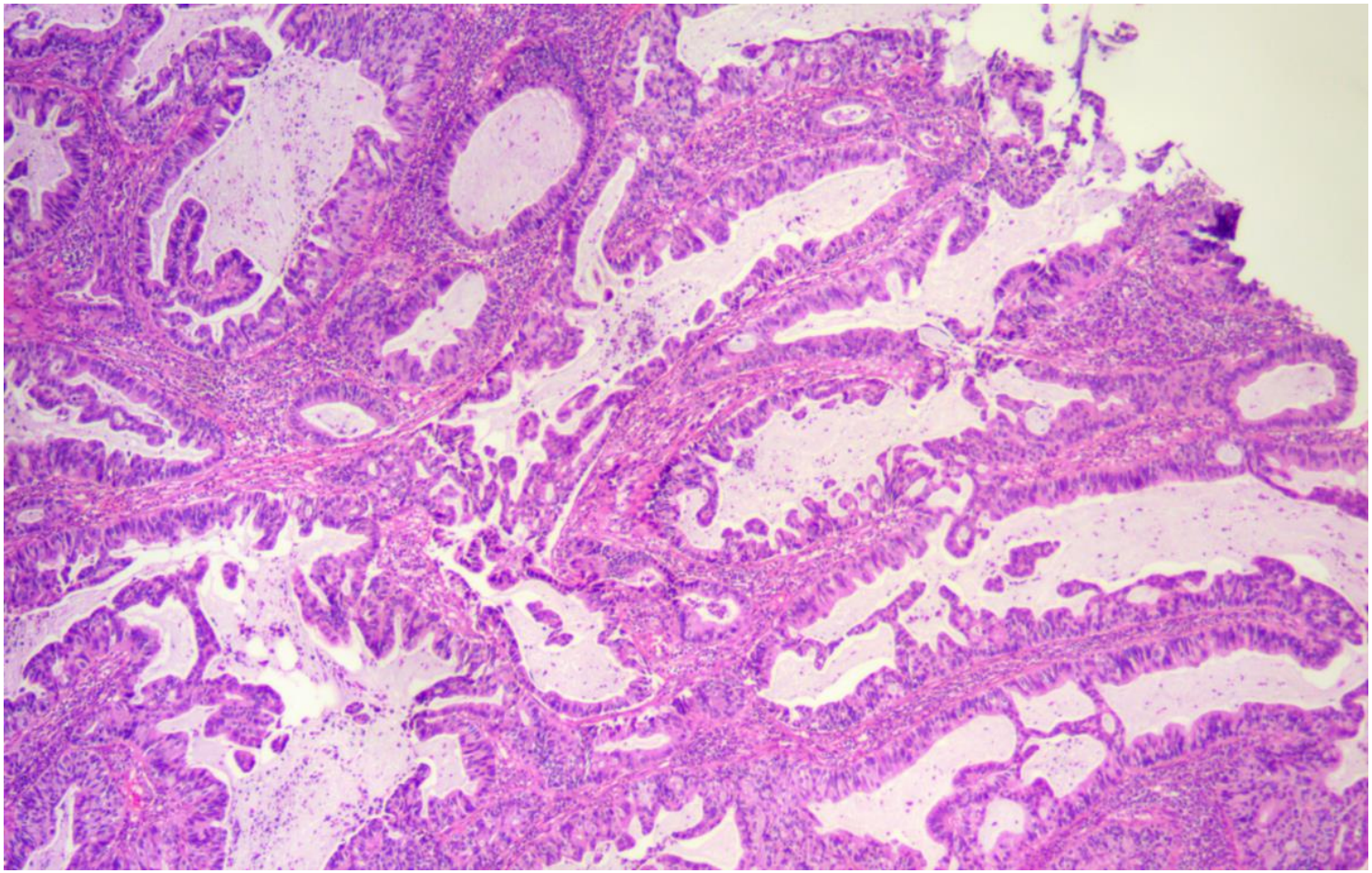


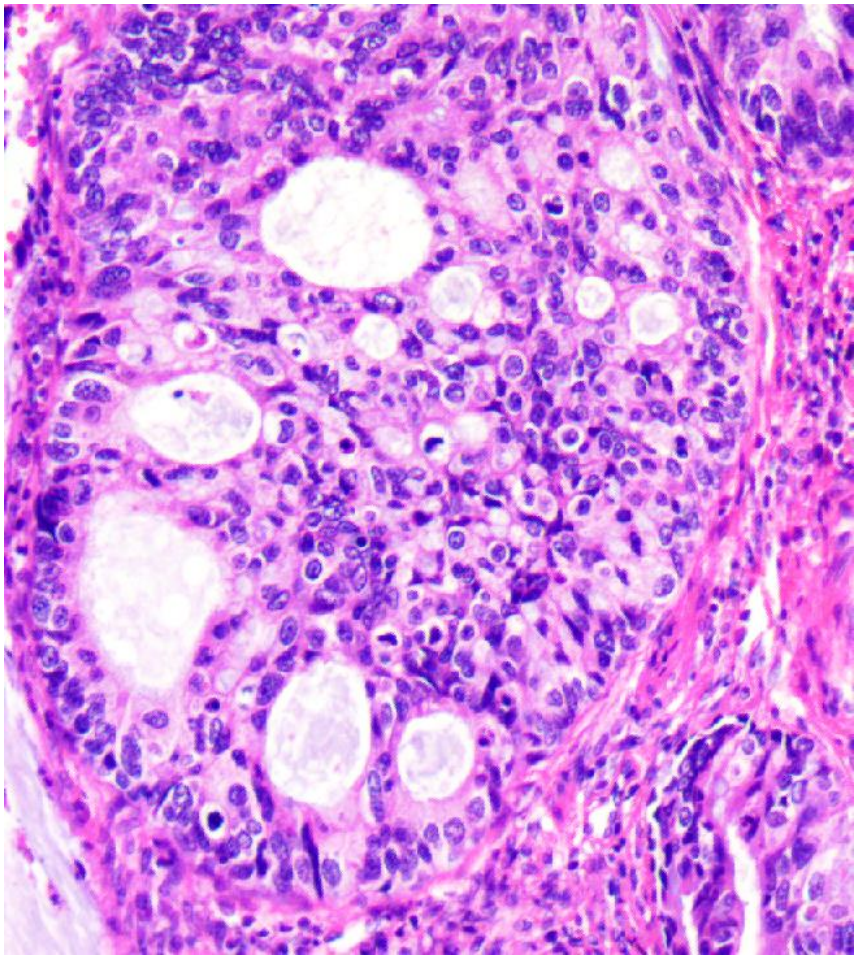


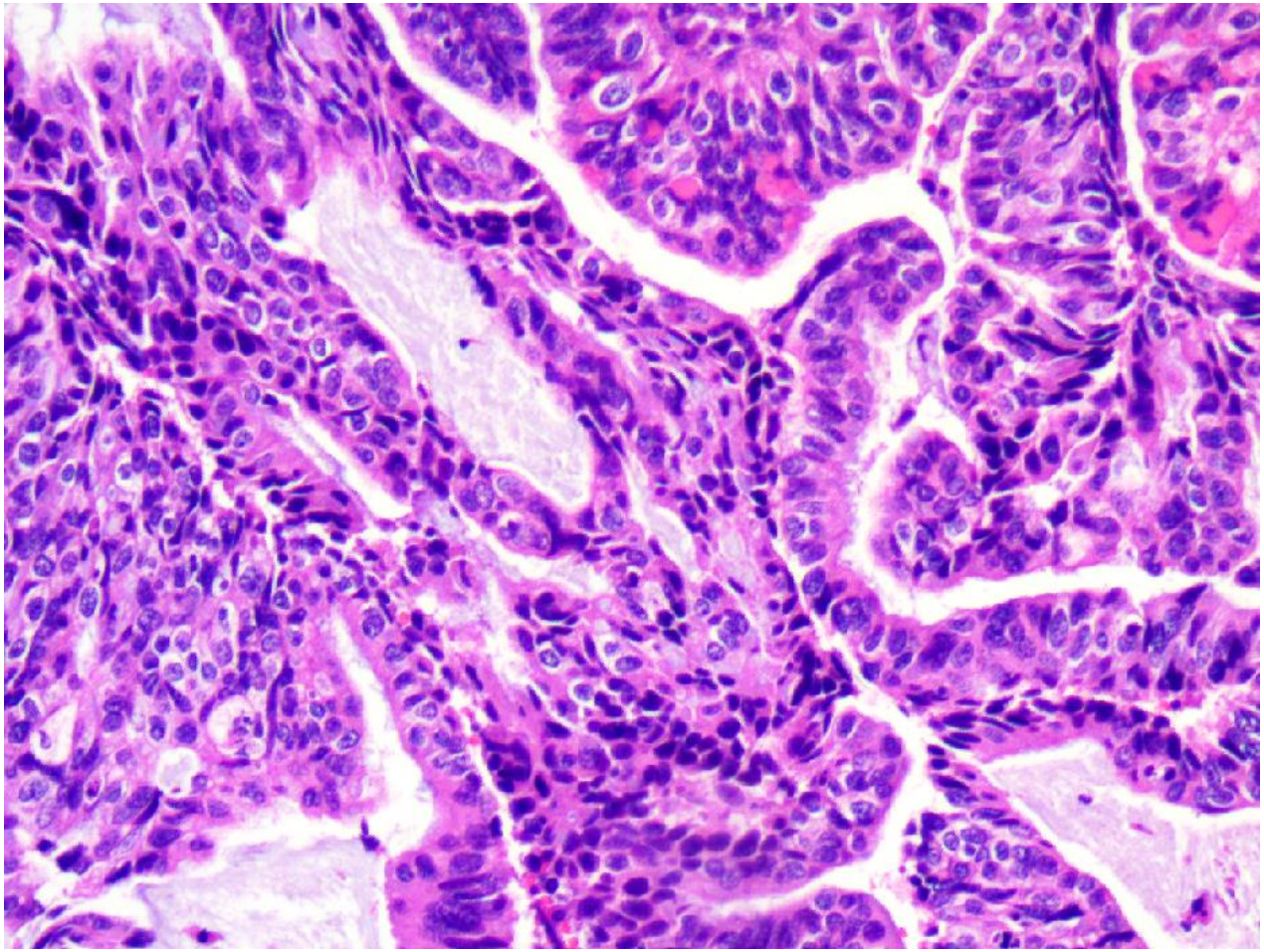


Invasion in glandular lesions (2)

- Architecture that becomes too complex
- Cribriform, papillary, solid, labyrinth growth
- Glands lying too deep





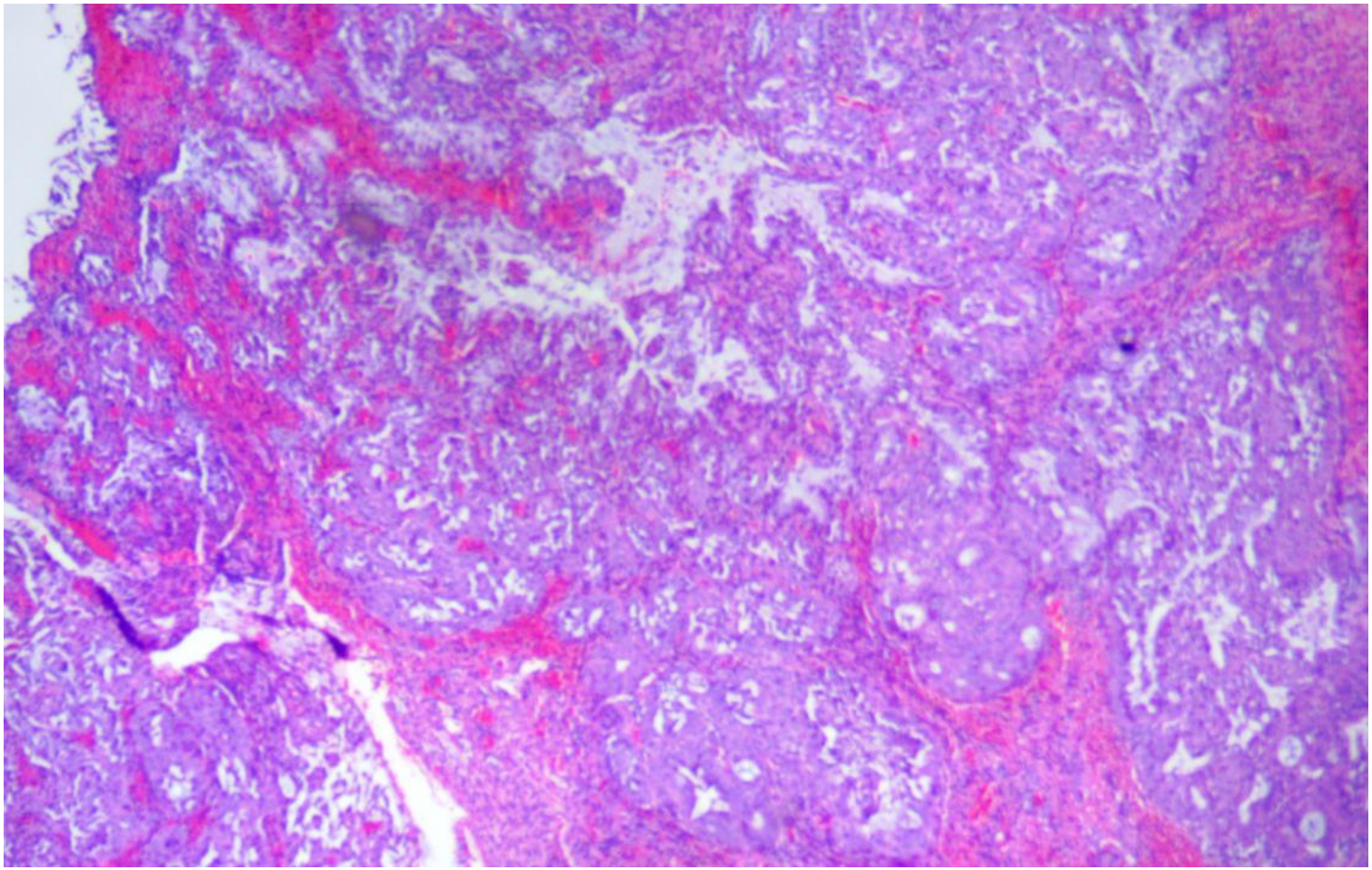


Too complex glandular lesions

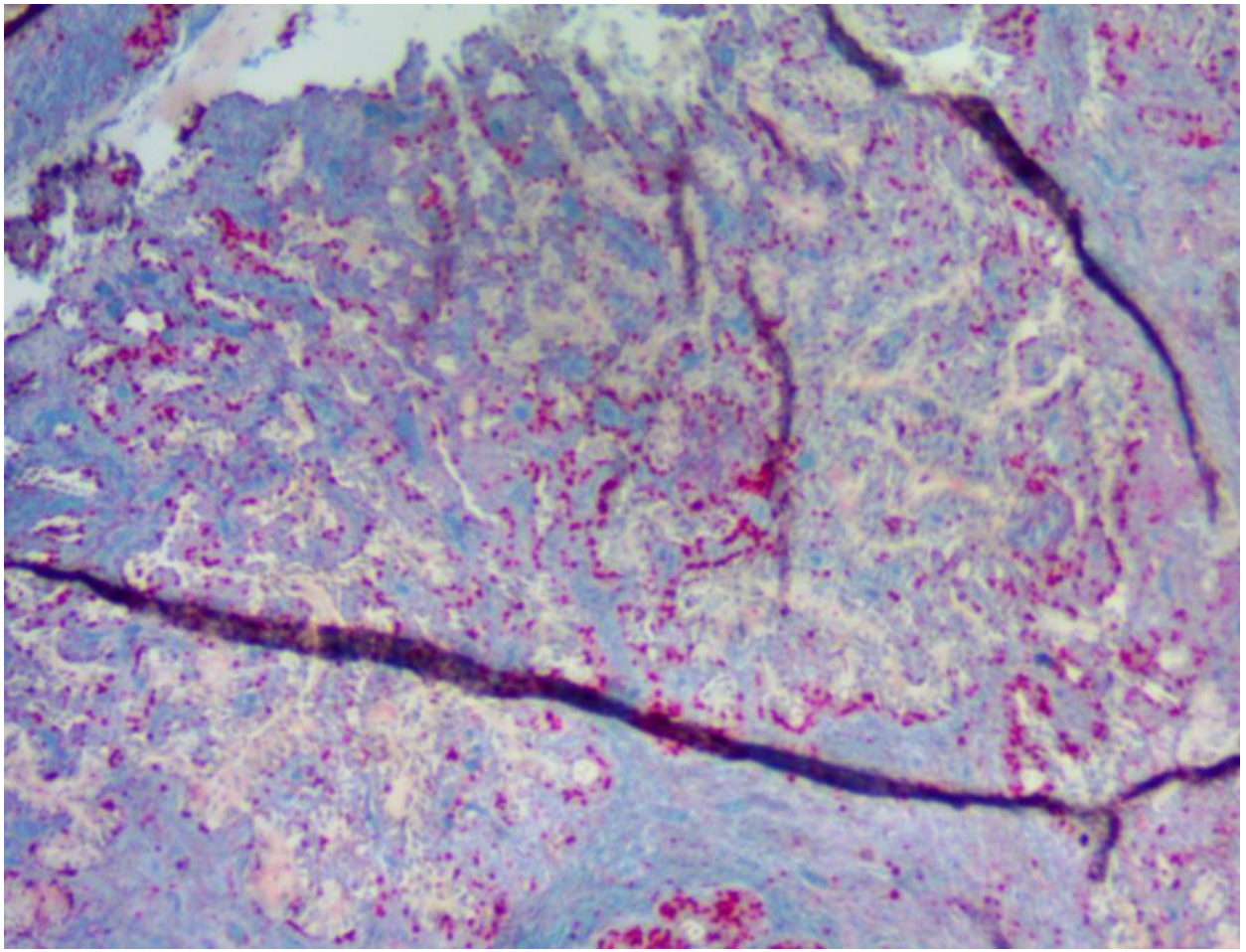
- Compare to subjacent benign glands

- Rare: involvement of pre-existing complex benign lesion by AIS/SquamIS

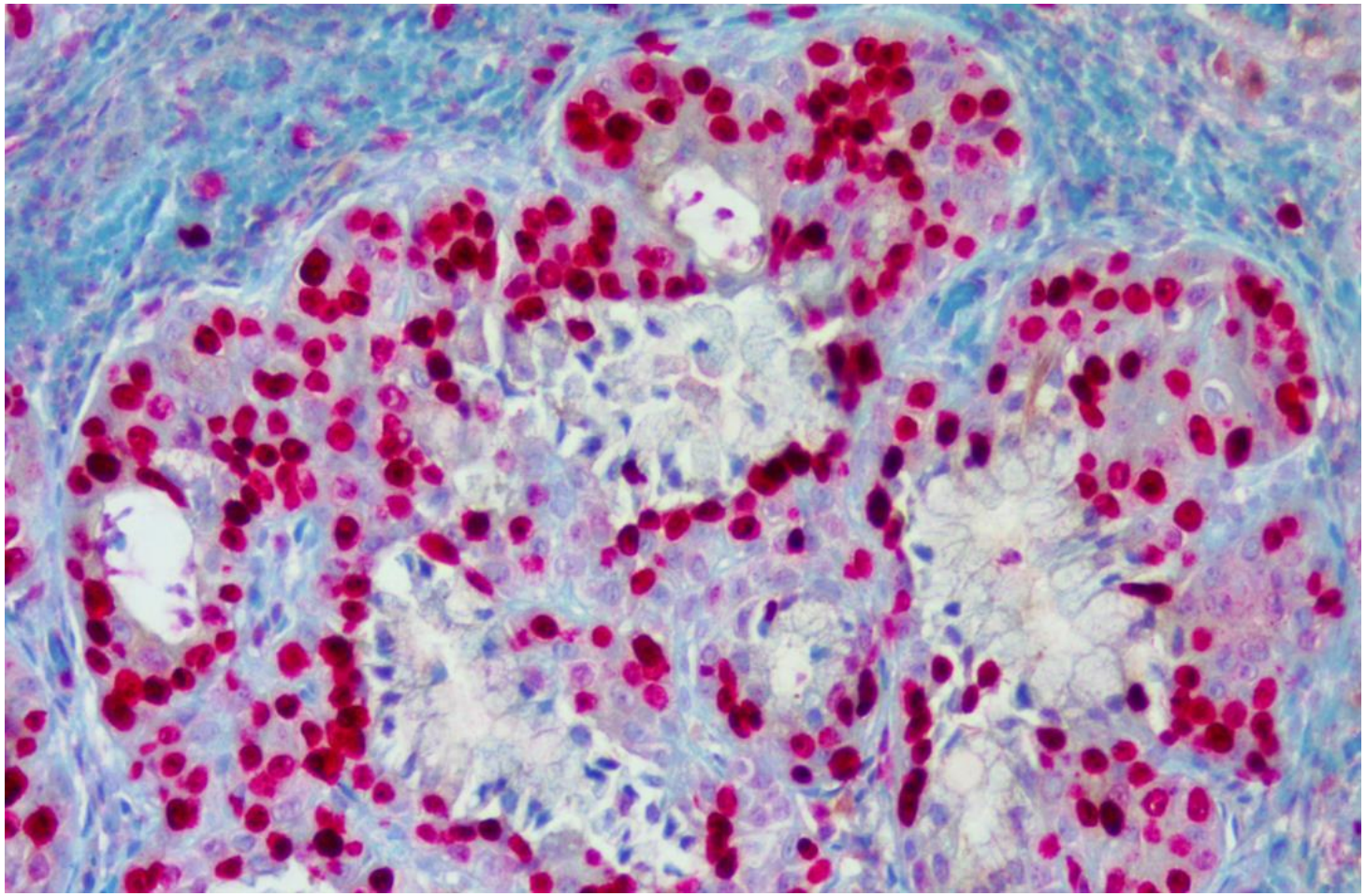
Complex glandular proliferation in pt with HSIL



High Ki67

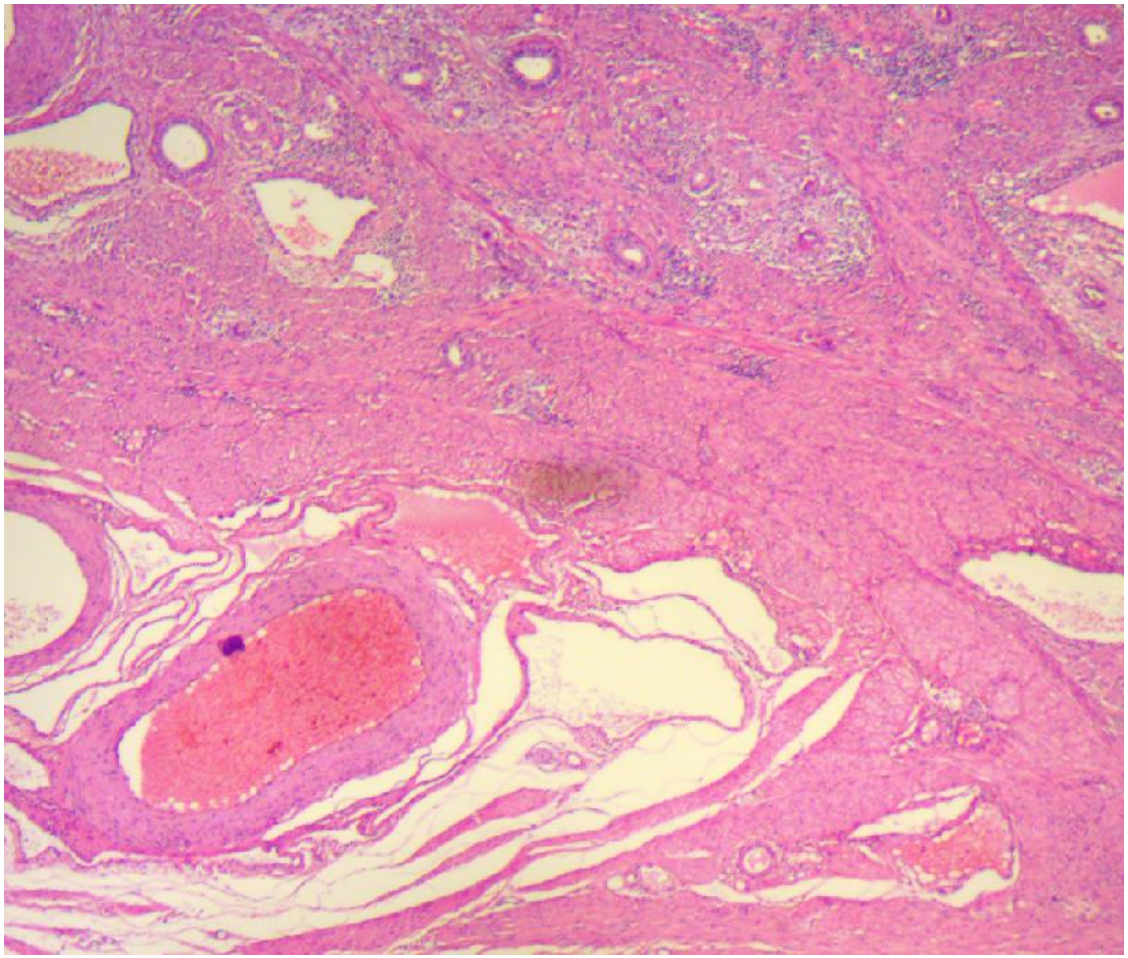


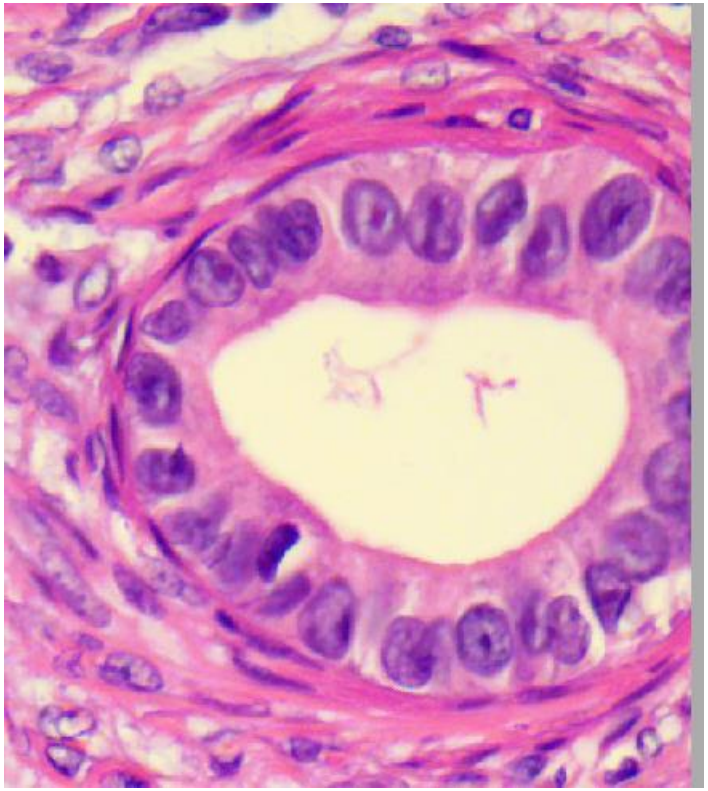
Ki67 low in luminal glandular cells



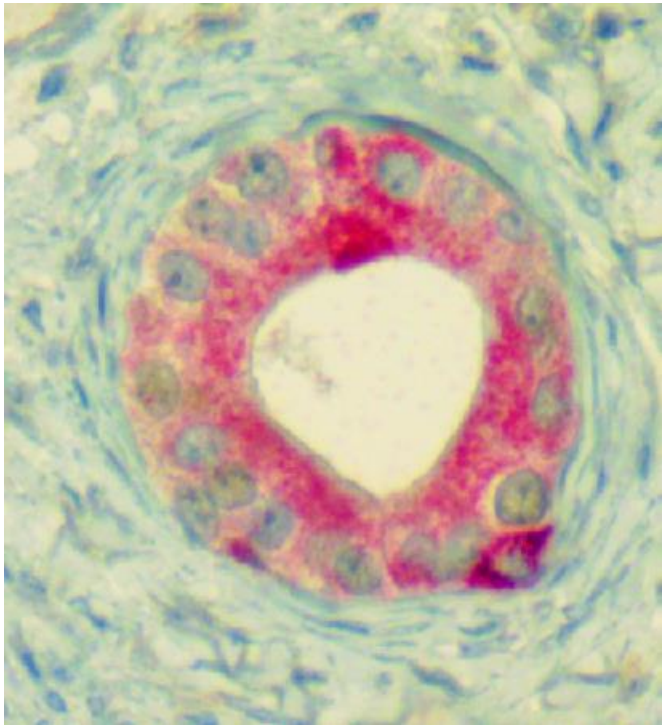
Glands lying too deep

- Minimal deviation Ca
  - Always look for at least focal atypia
  - MUC6/p53





MUC6+, p53 WT

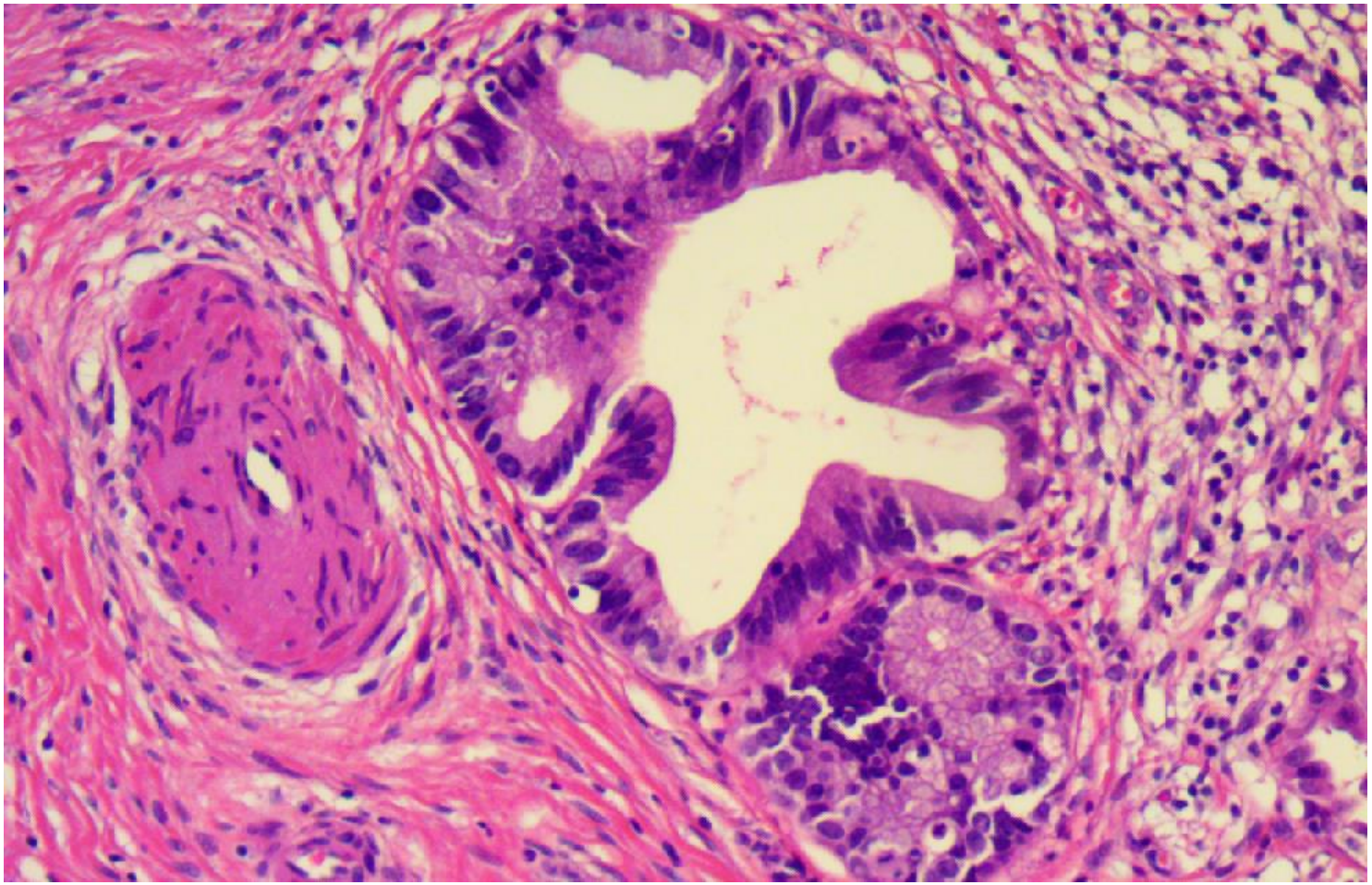


Glands close to thick-walled vessels

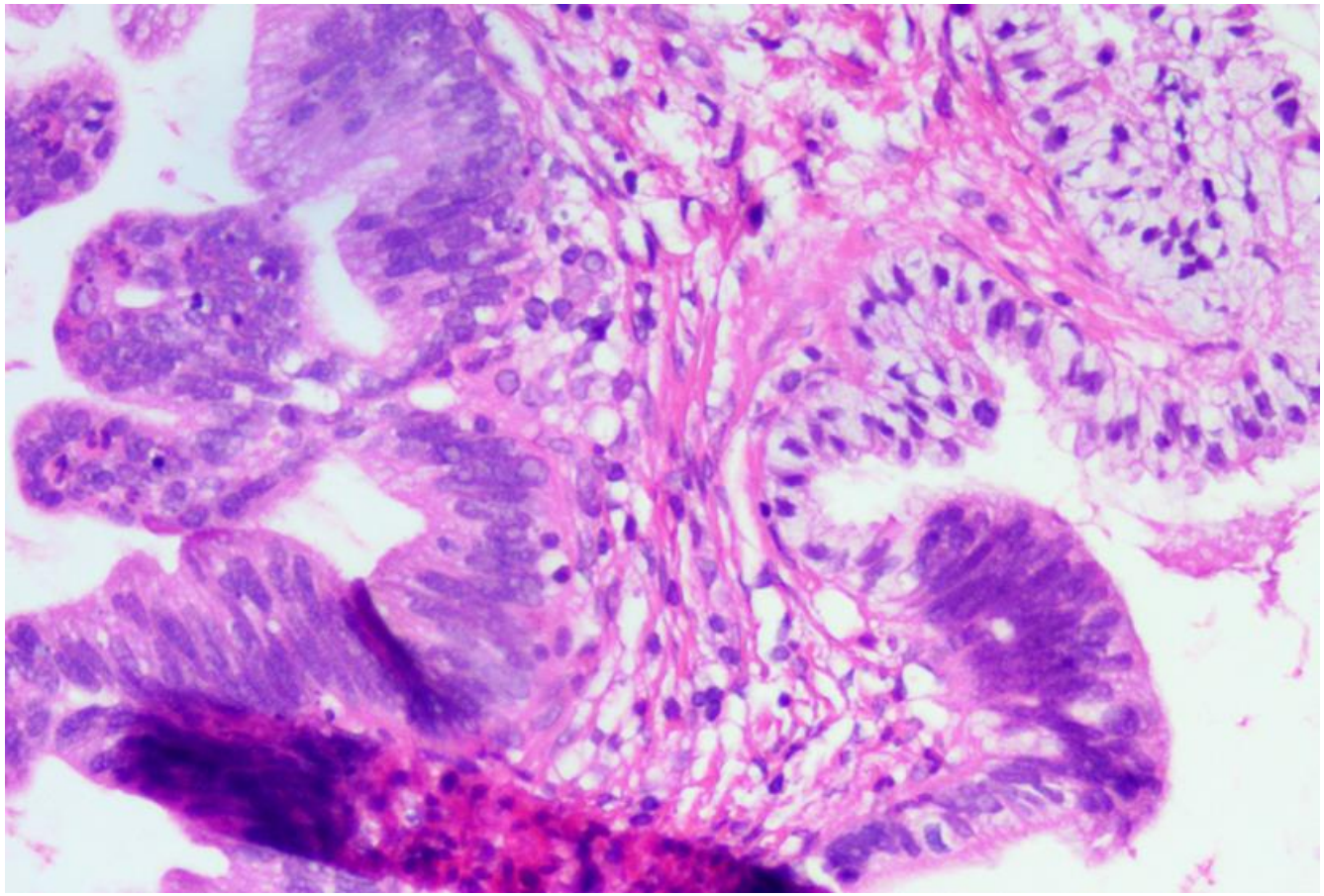
Rule of thumb:

If distance between gland and thick-walled vessel < thickness of that vessel wall:

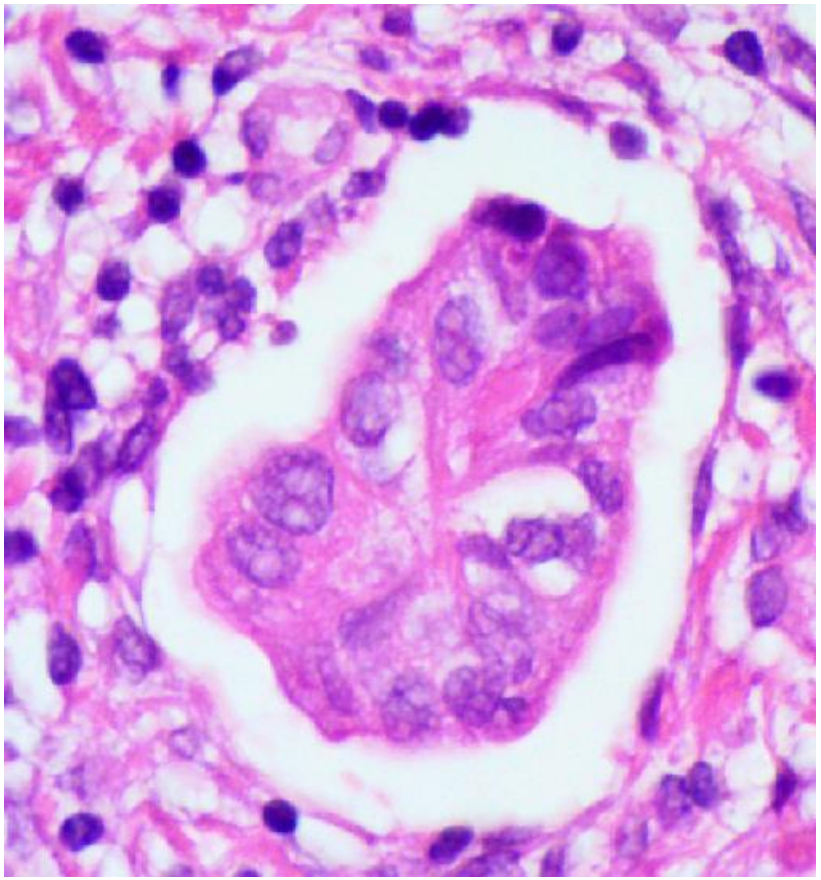
cave invasion



AIS but no clear invasion



pL+ as only sign of invasion (sampling)



Measuring should be performed using strict criteria

- Excellent description in the ICCR data set paper by McCluggage et al

International Journal of Gynecological Pathology
37:205–228, Lippincott Williams & Wilkins, Baltimore

Original Article

Data Set for the Reporting of Carcinomas of the Cervix: Recommendations From the International Collaboration on Cancer Reporting (ICCR)

W. Glenn McCluggage, F.R.C.Path., Meagan J. Judge, M.D., Isabel Alvarado-Cabrero, M.D., Máire A. Duggan, M.D., Lars-Christian Horn, M.D., Pei Hui, M.D., Jaume Ordi, M.D., Christopher N. Otis, M.D., Kay J. Park, M.D., Marie Plante, M.D., Colin J.R. Stewart, M.D., Edwin K. Wiredu, M.D., Brian Rous, F.R.C.Path., and Lynn Hirschowitz, F.R.C.Path.

Looks easier than we think…

Histopathology. 2019 Apr 25. doi: 10.1111/his.13883. [Epub ahead of print]

Measuring the depth of invasion in vulvar squamous cell carcinoma: interobserver agreement and pitfalls.

Pouwer AW[1], Bult P[2], Otte I[2], van den Brand M[2], van der Horst J[3], Harterink LJV[2], van de Vijver KK[4], Guerra E[5], Aliredjo RP[3], Bosch SL[6], Grefte JMM[7], Zomer S[8], Hollema H[9], de Heus B[9], Satumalaij S[9], Ewing-Graham PC[10], IntHout J[11], de Hullu JA[1], Bulten J[2].

- Vulvar Ca, not Cx
- 10 experts and 4 trainees
- Level of agreement was moderate (κ 0,57)

Measuring should be in 3 dimensions

- Report should included 3 dimensions
- “Microinvasive Ca”: NEVER USE IT

- Larger tumors: measure grossly
- Small tumors: on the microscope

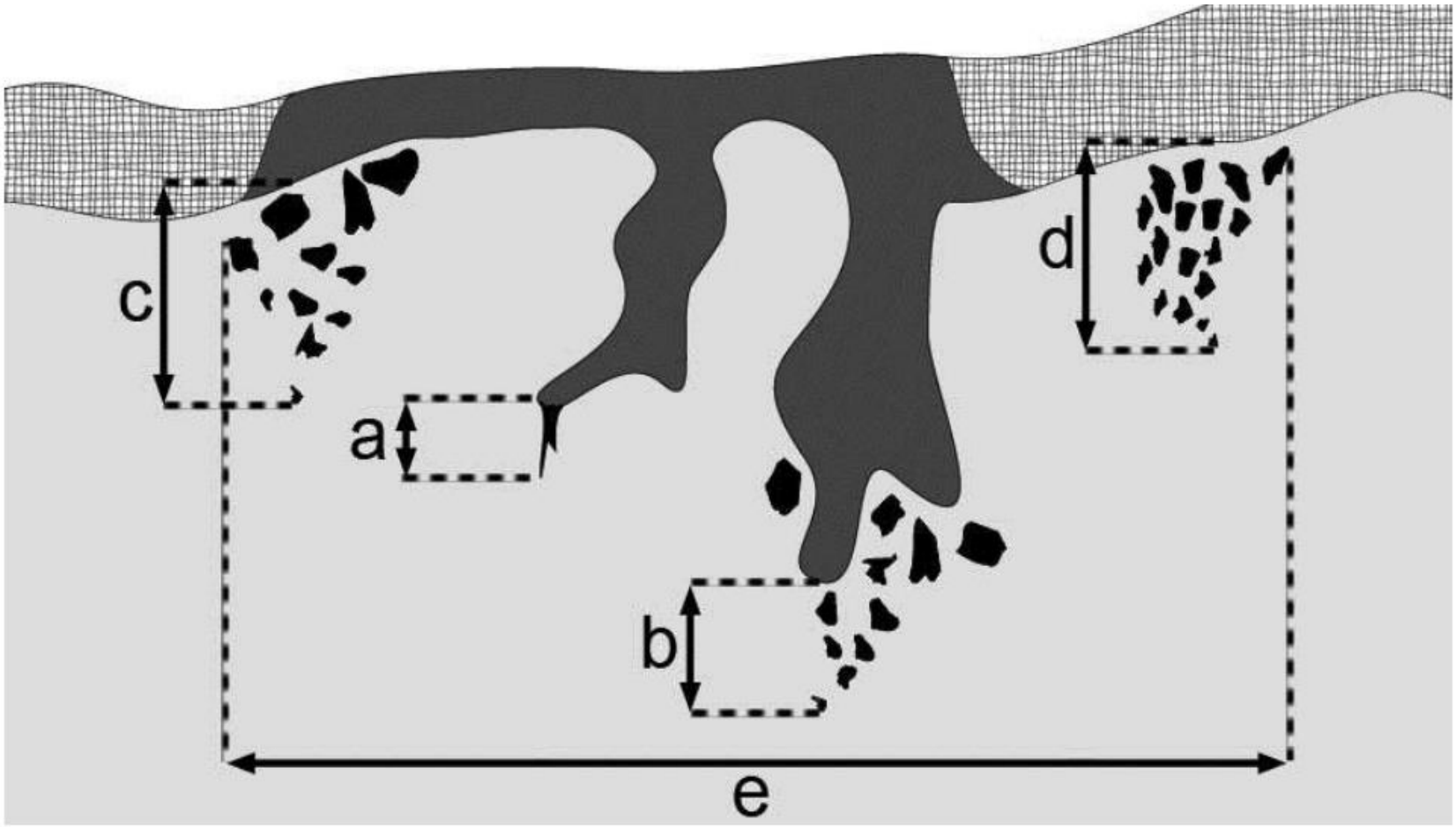
3 dimensions

- Depth of invasion: measured on slide

- Horizontal extension
  - Measured on slide
  - By reconstruction

Depth of invasion

“from the base of the epithelium (surface or crypt) from which the carcinoma arises to the deepest point of invasion”


c
a
b
d
e

Tumor thickness

- In situations where depth of invasion cannot be measured

- In report:
  - Depth of invasion cann't be measured due to…
  - Tumor thickness measured on slide 2: 4 mm

When is tumor thickness used? (1)

- AdenoCa: difficult to establish where invasion begins

-> thickness from epithelial **surface** to deepest point of invasion

add to report: “This thickness is likely to **over**estimated depth of invasion.”

When is tumor thickness used? (2)

- Ulcerated tumors without overlying epithelium

-> thickness from the **surface** to the deepest point of invasion

Add to report: “This thickness is likely to **under**estimated the depth of invasion”

When is tumor thickness used? (3)

- Polypoid tumors with exophytic growth pattern

-> tumor lies above the surface of the cervix

-> thickness from **surface** of tumor to deepest point

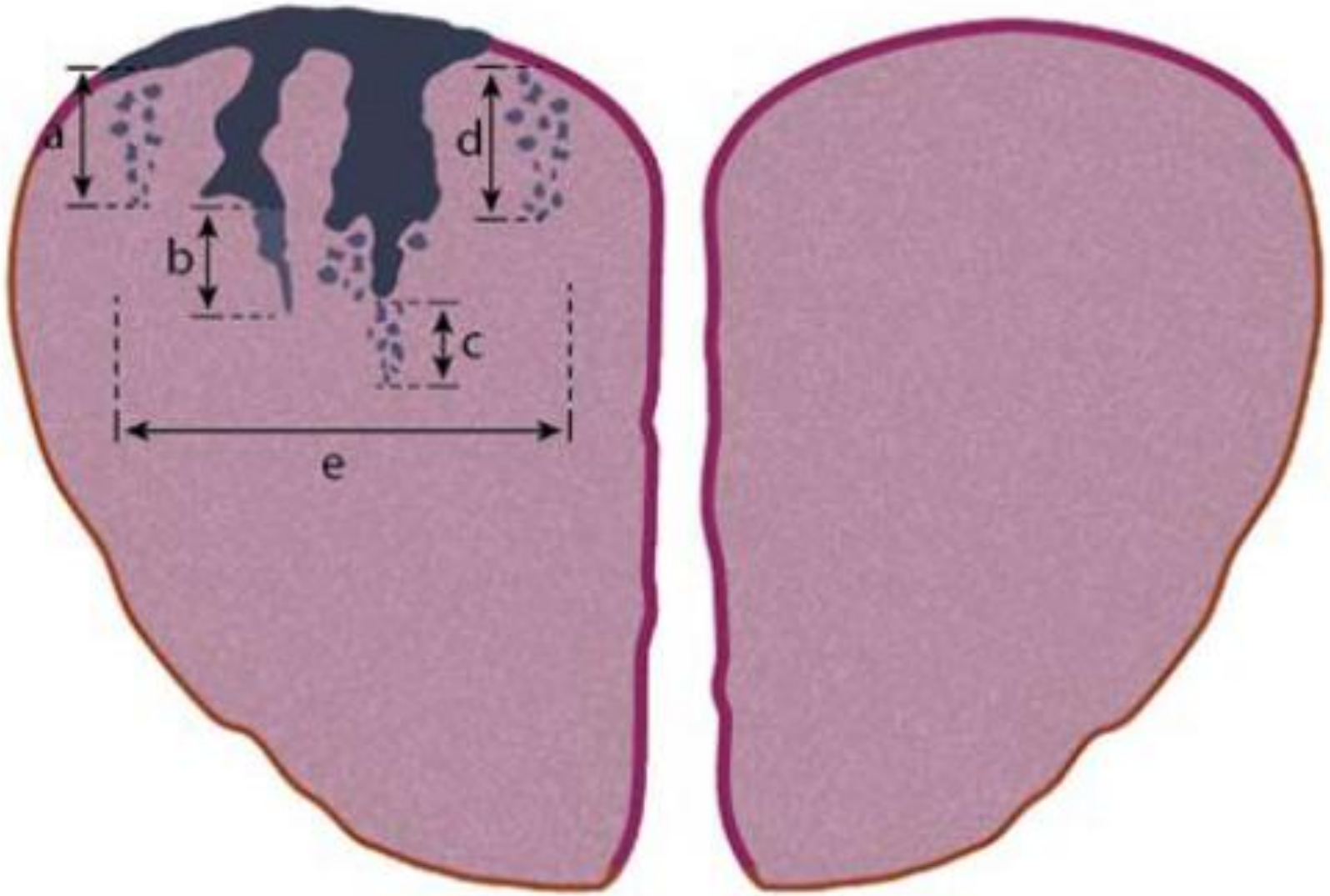
Depth of invasion might **under**estimate the biologic behaviour (in situ) and should not be reported

Horizontal extension measured on slide

- Greatest horizontal extent on 1 single slide should be recorded

Some guidelines

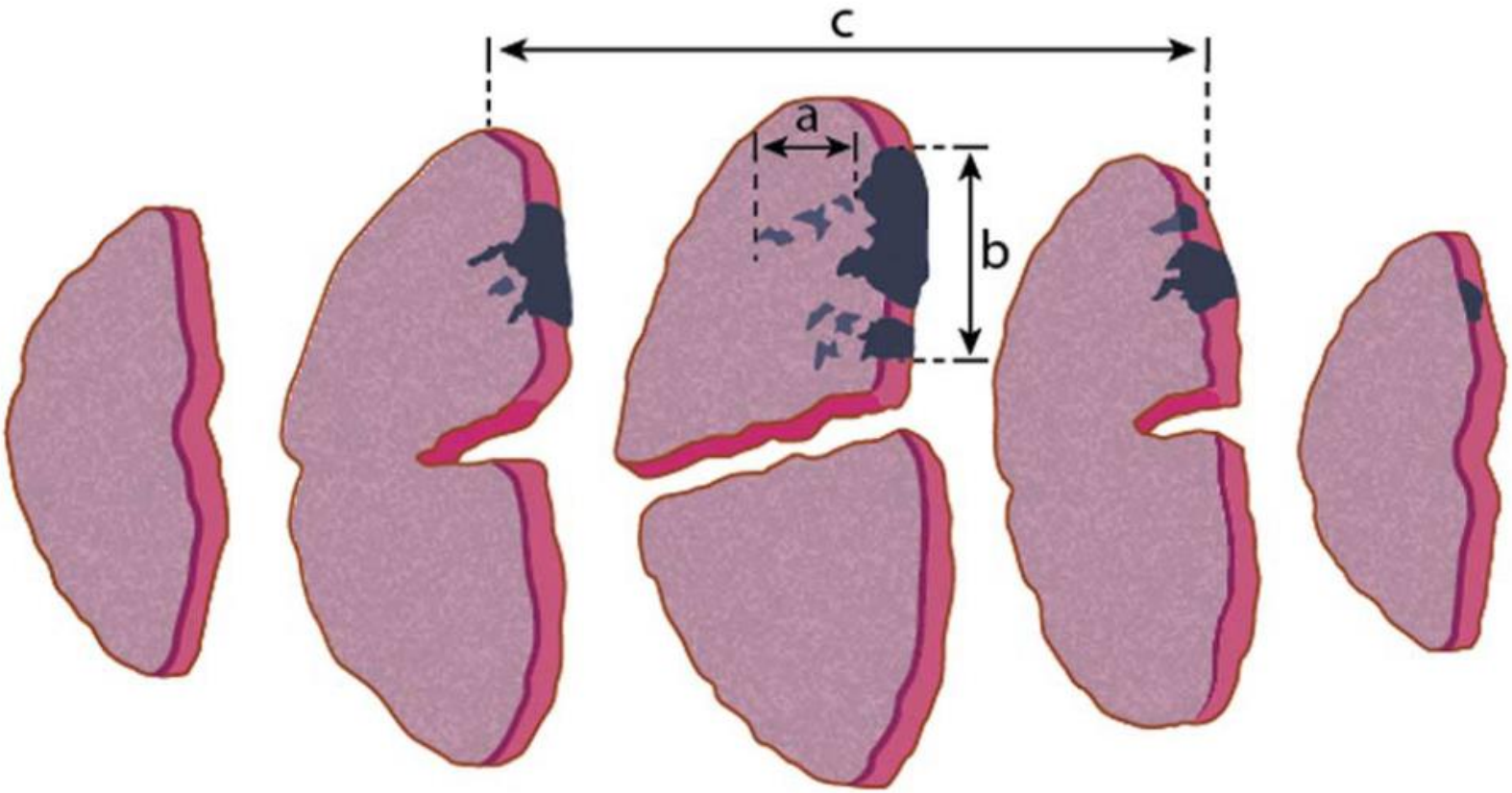
- 1 tongue of invasion: maximum width of the tongue
- Cluster of small invasive foci lying close together: from 1 outer edge of the cluster to the other
- If foci are separated by non-involved stroma but rules for multifocality are not met: the intervening stroma without invasion is included in measurement


a
b
c
d
e

Horizontal extension by reconstruction (3th dimension)

- Count sequential slices in which invasion is found
- Multiply the number by thickness of the slices

- If only in 1 slices: 3th dimension is thickness of that slice (2,5-3 mm)


c
a
b

The problems with multifocality

- Is it important?
- Is it frequent?
- When should we diagnose it?
- How to measure and stage?

Is multifocality important?

Multifocal FIGO Stage IA1 Squamous Carcinoma of the Cervix: Criteria for Identification, Staging, and its Good Clinical Outcome

Day, Elizabeth M.B., B.Chir., Ph.D.; Duffy, Siobhan B.Sc., M.B.Ch.B.; Bryson, Gareth B.Sc., M.B.Ch.B., F.R.C.Path.; Syed, Sheeba M.B.B.S., M.D., M.R.C.Path.; Shanbhag, Smruta M.B.B.S., M.R.C.O.G.; Burton, Kevin M.B.C.H.B., M.D., M.R.C.O.G.; Lindsay, Rhona B.Sc., M.B.Ch.B., M.R.C.O.G.; Siddiqui, Nadeem F.R.C.O.G., Ph.D.; Millan, David B.Sc., M.B., Ch.B., F.R.C.Path.

International Journal of Gynecological Pathology: September 2016 - Volume 35 - Issue 5 - p 467–474

Multifocal FIGO Stage 1A1 Cervical Squamous Carcinomas have an Extremely Good Prognosis Equivalent to Unifocal Lesions

McIlwaine, Patrick M.D.; Nagar, Hans F.R.C.O.G.; McCluggage, W. Glenn F.R.C.Path.

International Journal of Gynecological Pathology: May 2014 - Volume 33 - Issue 3 - p 213–217

What is the frequency?

- 12-25% of Stage IA1 tumors
- Less common in larger tumors
- Squamous > adenoCa

When to diagnose multifocality?

- Separate blocks of uninvolved cervical tissue
  - Multiple levels are required
- Ca on separate lips with discontinous growth
  - Curvature of the canal is not involved
- In same section if far apart
  - “far apart” is not defined
  - Arbitrarly, 2 mm is used in trials
  - Multiple levels are required

How to measure and stage multifocal Ca?

- Each focus should be measured in 3 dimensions
- Stage is determined by the largest focus
  - Adding the size of multiple foci would upstage the tumor
  - Biological potential would be overestimated
- Report should make clear that it is a multifocal tumor

Consequences for the patient

- More conservative surgical treatment
  - Cone/LEEP biopsy
- Cases should be discussed at multidisciplinary tumor board
- Expert opinion might be a good idea

Revised FIGO staging 2018

FIGO CANCER REPORT 2018

WILEY GYNECOLOGY OBSTETRICS FIGO

Cancer of the cervix uteri

Neerja Bhatla[1,*] | Daisuke Aoki[2] | Daya Nand Sharma[3] | Rengaswamy Sankaranarayanan[4]

Int J Gynecol Obstet 2018; 143 (Suppl. 2): 22–36

- First presented at FIGO XXII World Congress of Gynecology and Obstetrics, Rio de Janeiro Brazil, Oct 2018

Stage IA

	2009	2018
Depth	≤ 5,0 mm	< 5,0 mm
Horizontal	≤ 7,0 mm	/

Stage IA1

	2009	2018
Depth	≤ 3,0 mm	< 3,0 mm
Horizontal	≤ 7,0 mm	/

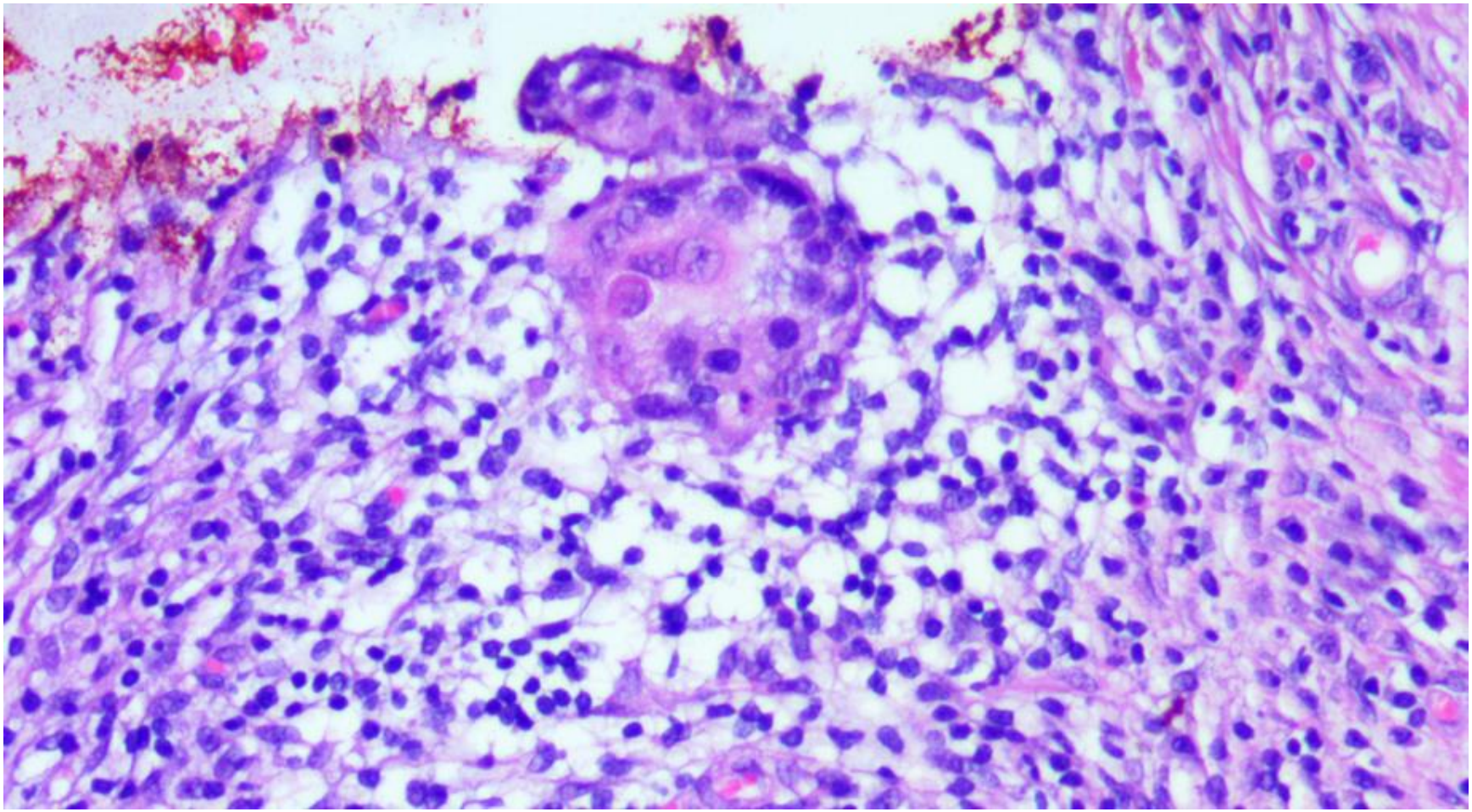
Stage IA2

	2009	2018
Depth	> 3,0 mm; ≤ 5,0 mm	≥ 3,0mm; < 5,0 mm
Horizontal	≤ 7,0 mm	/

Involved margins on LOOP

- Even if lesion is small: involved margins allocates tumor to stage IB1

Ink on tumor = Stage IB1



Stage IB

IB: Clinically visible lesions limited to the cervix or pre-clinical cancers greater than stage IA	***IB: Invasive carcinoma with measured deepest invasion >/= 5 mm (greater than Stage IA), lesion limited to the cervix uteri***
IB1: Clinically visible lesion </= 4.0cm in greatest dimension	IB1: Invasive carcinoma >/= 5 mm depth of stromal invasion, and <2 cm in greatest dimension
	IB2: Invasive carcinoma >/= 2 cm and < 4 cm in greatest dimension
IB2: Invasive carcinoma > 4 cm in greatest dimension	IB3: Invasive carcinoma >/= 4 cm in greatest dimension

THE BRITISH ASSOCIATION OF GYNAECOLOGICAL PATHOLOGISTS

Stage I (2018): Carcinoma strictly confined to the cervix (extension to the uterine corpus should be disregarded)		
2009 FIGO stage: Description	**2018 FIGO stage: Description**	**Comment**
IA: Invasive carcinoma diagnosed only by microscopy, with maximum depth of invasion </= 5mm and largest extension </= 7 mm	***IA: Invasive carcinoma diagnosed only by microscopy, with maximum depth of invasion <5mm***	**-Lateral extent of the carcinoma is no longer considered in distinguishing between FIGO Stage IA and IB carcinomas - If margins of loop are involved patient is allocated to Stage IB1.**
IA1: Measured stromal invasion <3 mm in depth and extension </= 7 mm	IA1: Measured stromal invasion <3 mm in depth	
IA2: Measured stromal invasion >/=3 mm and <5 mm in depth and extension </= 7 mm	IA2: Measured stromal invasion >/=3 mm and <5 mm in depth	
IB: Clinically visible lesions limited to the cervix or pre-clinical cancers greater than stage IA	***IB: Invasive carcinoma with measured deepest invasion >/= 5 mm (greater than Stage IA), lesion limited to the cervix uteri***	**-See above -LVSI must be commented upon, although does not affect FIGO stage.**
IB1: Clinically visible lesion </= 4.0cm in greatest dimension	IB1: Invasive carcinoma >/= 5 mm depth of stromal invasion, and <2 cm in greatest dimension	**-New stage category**
	IB2: Invasive carcinoma >/= 2 cm and < 4 cm in greatest dimension	**-New stage category**
IB2: Invasive carcinoma > 4 cm in greatest dimension	IB3: Invasive carcinoma >/= 4 cm in greatest dimension	**-New stage category**

Good news/Bad news

- We will not need to measure as much as we were used to

- Belgian Cancer Registry requires TNM
- TNM is still unchanged

Take home messages

- Recognition of invasion is important to know what you have to measure
- Measurements using strict criteria (ICCR paper)
- Multifocality
- New FIGO staging 2018