Gastric Carcinoma: Criteria and Differential Diagnosis

PRESENTED BY

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USCAP 108TH ANNUAL MEETING

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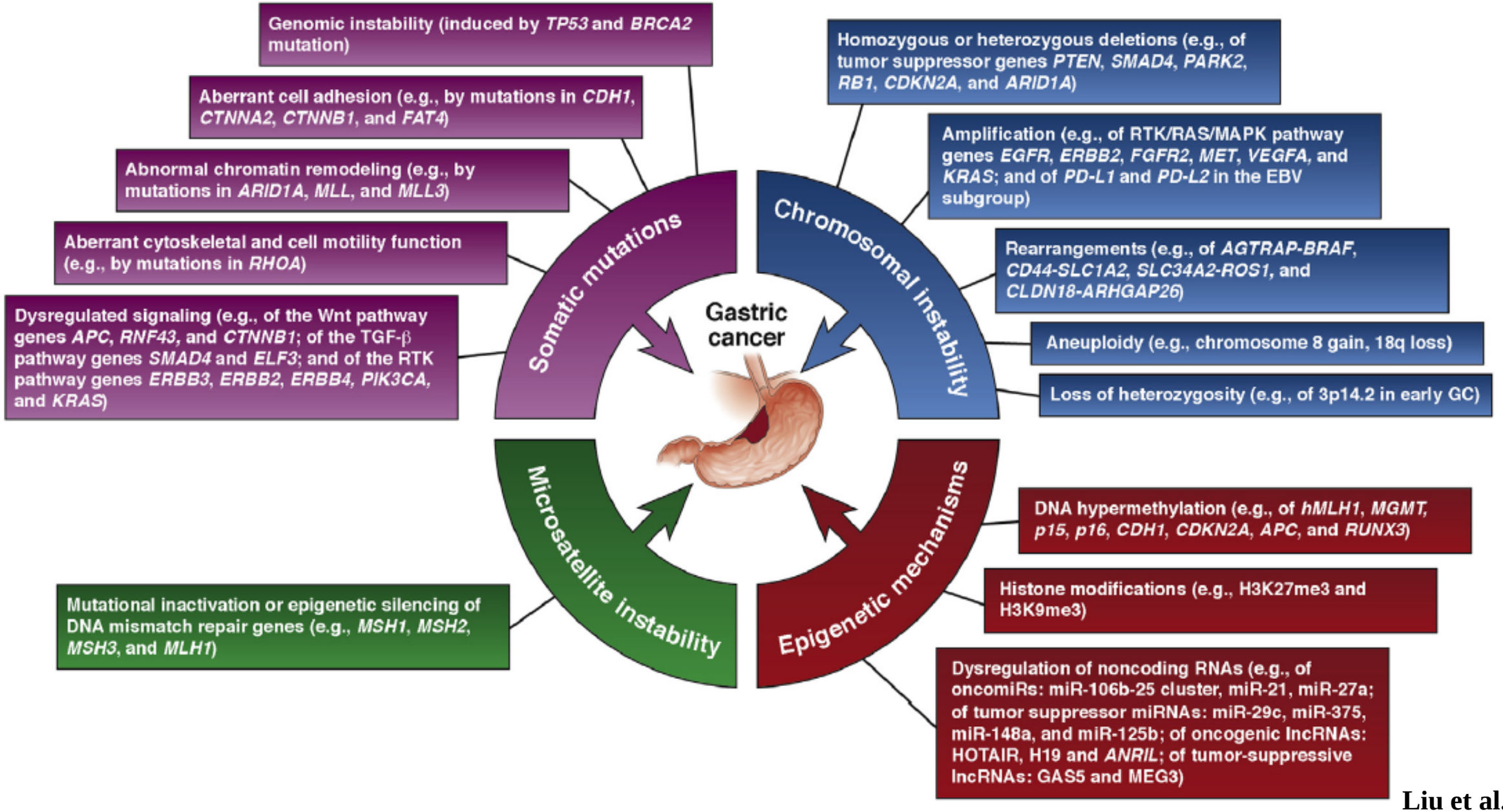
Michael Vieth reported no relevant financial relationships

PLEASE TURN OFF YOUR CELL PHONES

Genetic and epigenetic mutations in gastric cancer



Liu et al. 2017

Histopathological classification systems: gastric cancer 1965-2011

Laurén 1965	Nakamura 1968	Ming 1977	Goseki 1992	Borchard 1993	Carneiro 1995	Solcia 2009	WHO 2010	Japanese classification 2011
Intestinal	Differentiated Undifferentiated	Expanding	I. Tubular, G1, mucin poor II. Tubular, G1, mucin rich	Glandular a) gastric b) instestinal c) mixed (hybrid)	Glandular	Cohesive, ordinary Cohesive, tubular Mucinous, mucondular Mucinous, infiltrative	Papillary Tubular Mucinous	Papillary Tubular 1 (G1) Tubular 2 (G2) Mucinous
Diffuse	Undifferentiated	Infiltrative	III. Tubular, G3, mucin poor	Diffuse a) gastric b) intestestinal c) Mixed (hybrid)	Isolated cell	Diffuse, low grade, desmoplastic type Diffuse, ordinary	Poorly cohesive other cell types Poorly cohesive Signetring cell CA	Poorly differentiated, non-solid Signetring cell CA
Mixed			IV Tubular, G3, mucin rich	Glandular mixed Diffuse mixed	Mixed		Mixed	
Inderterminate	undifferentiated		III. Tubular, G3, mucin poor	(Null –type)	Solid Rare variants	Analplastic High lymphoid response	Undifferentiated Rare variants	Poorly differentiated, solid type

Why is there a problem ?

Current situation
(interobserver variation in neoplasia diagnosis):

Criteria are non validated and non accepted worldwide
Lower threshold for carcinoma diagnosis in Japan
Higher threshold for carcinoma diagnosis in US
Europe in between

Different medical systems
US: strictly outcome driven
Europe: strictly best performance for treatment option

Vienna classification
Grouping of therapeutic groups
Not assessing the real reasons for variances

Schlemper R et al. 2000 & 2001
Vieth et al. 2014 Am J Surg Pathol

Japanese Point of view

Carcinoma diagnosis based
on nuclear and structural critieria

Result:
almost no discrepancy between biopsy and resection

Critisism:
Contribution to high incidence and good prognosis?

Schlemper R et al. Lancet 2000

Western Point of view

Carcinoma diagnosis based

on break through basal membrane

and single tumor cells, desmoplasia

Result:

discrepancies between biopsy and resection

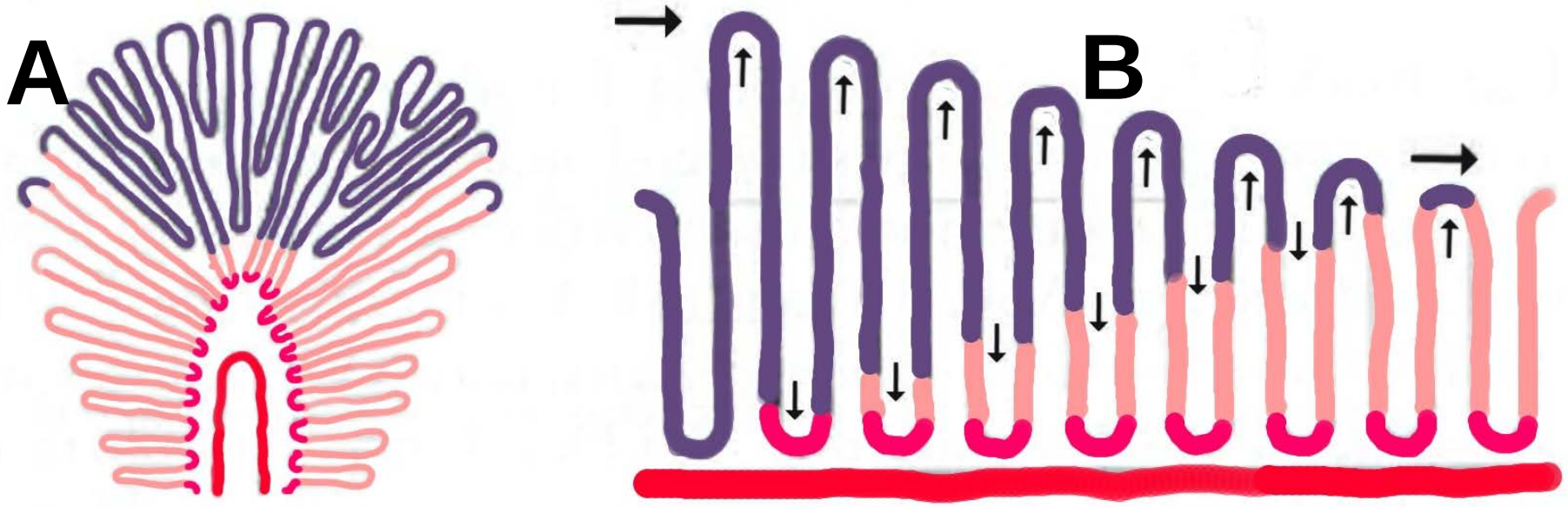
Critisism:

Contribution to lower incidence and bad prognosis?

Basal membrane production

Borchard F. Verh Dt Pathol Ges. 2000. WHO classification 2010

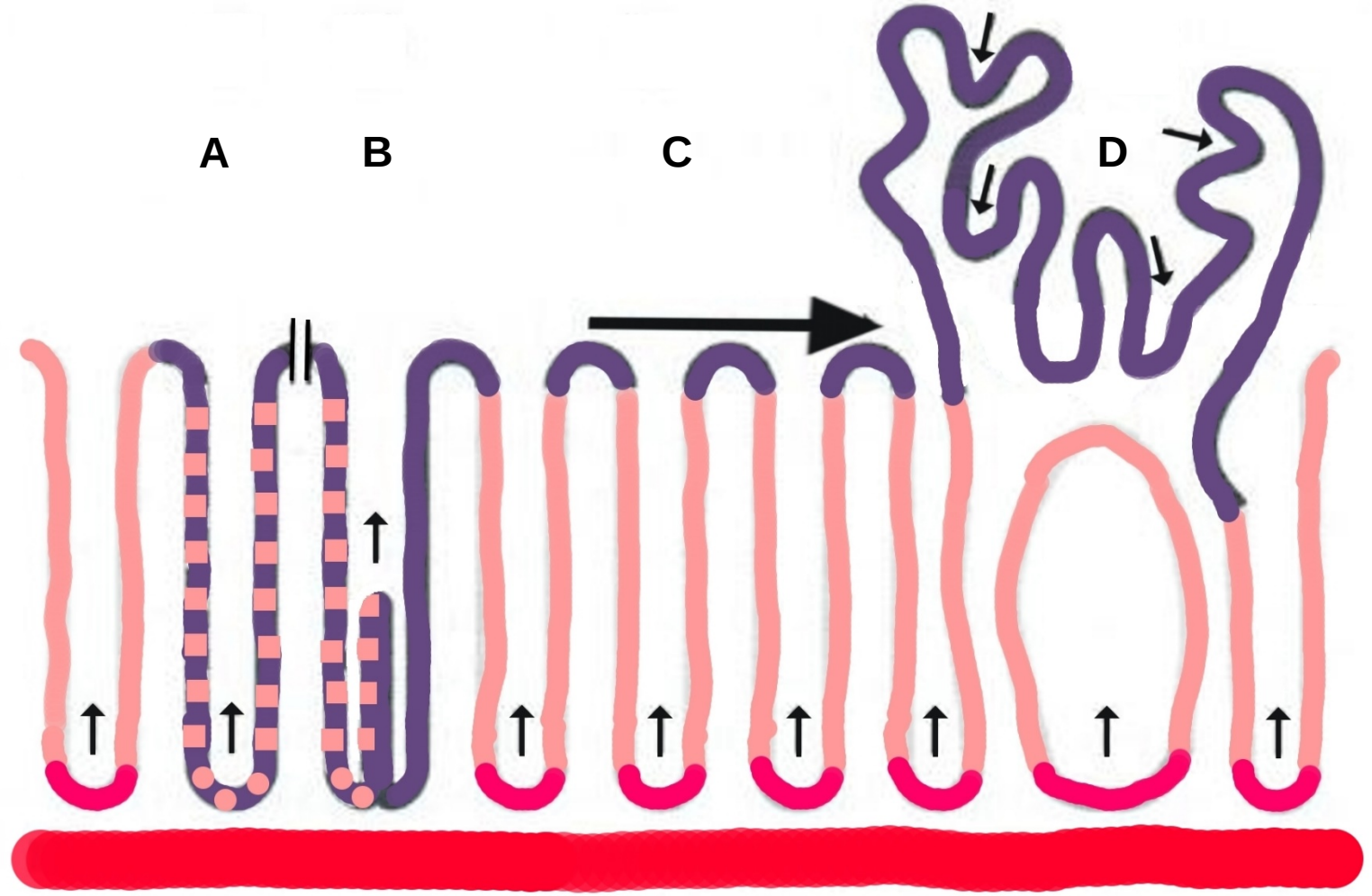
Expansion pattern of GI low grade dysplasia



A: stalked tubular adenoma with cuneiform expansion by crypt fission, lateral-superficial and predominant intertubular-vertical expansion and very little intratubular expansion
B: villous adenoma with predominant lateral-superficial, luminal and intratubular expansion

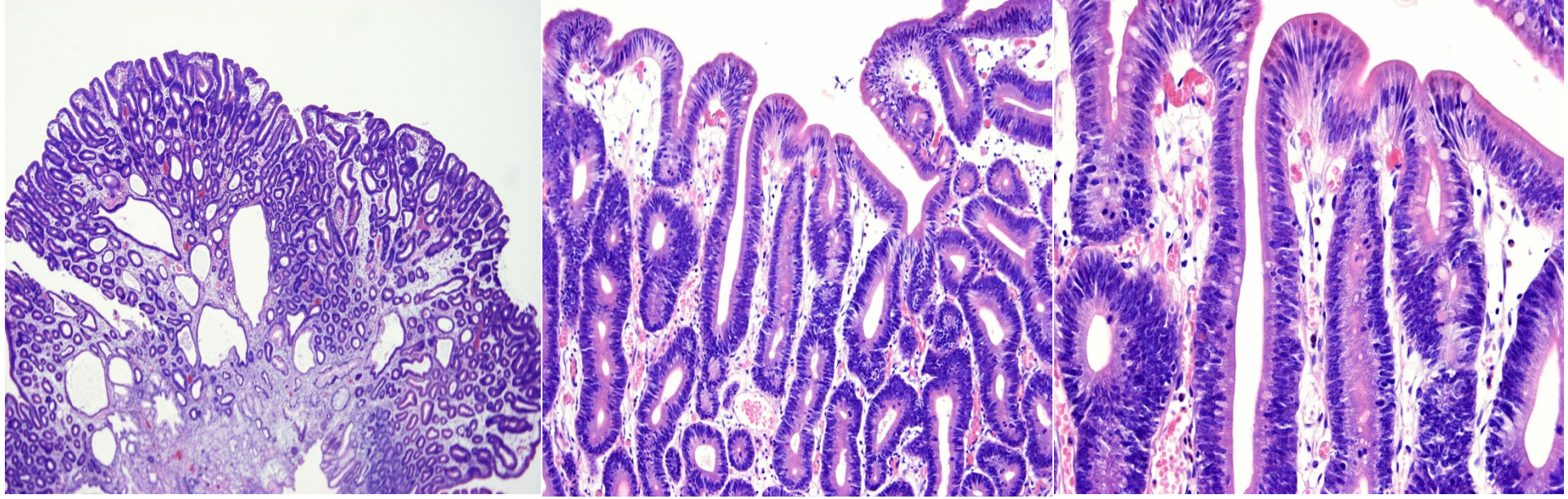
modified after Borchard F Verh Dtsch Ges Path 2000

Expansion in low grade dysplasia

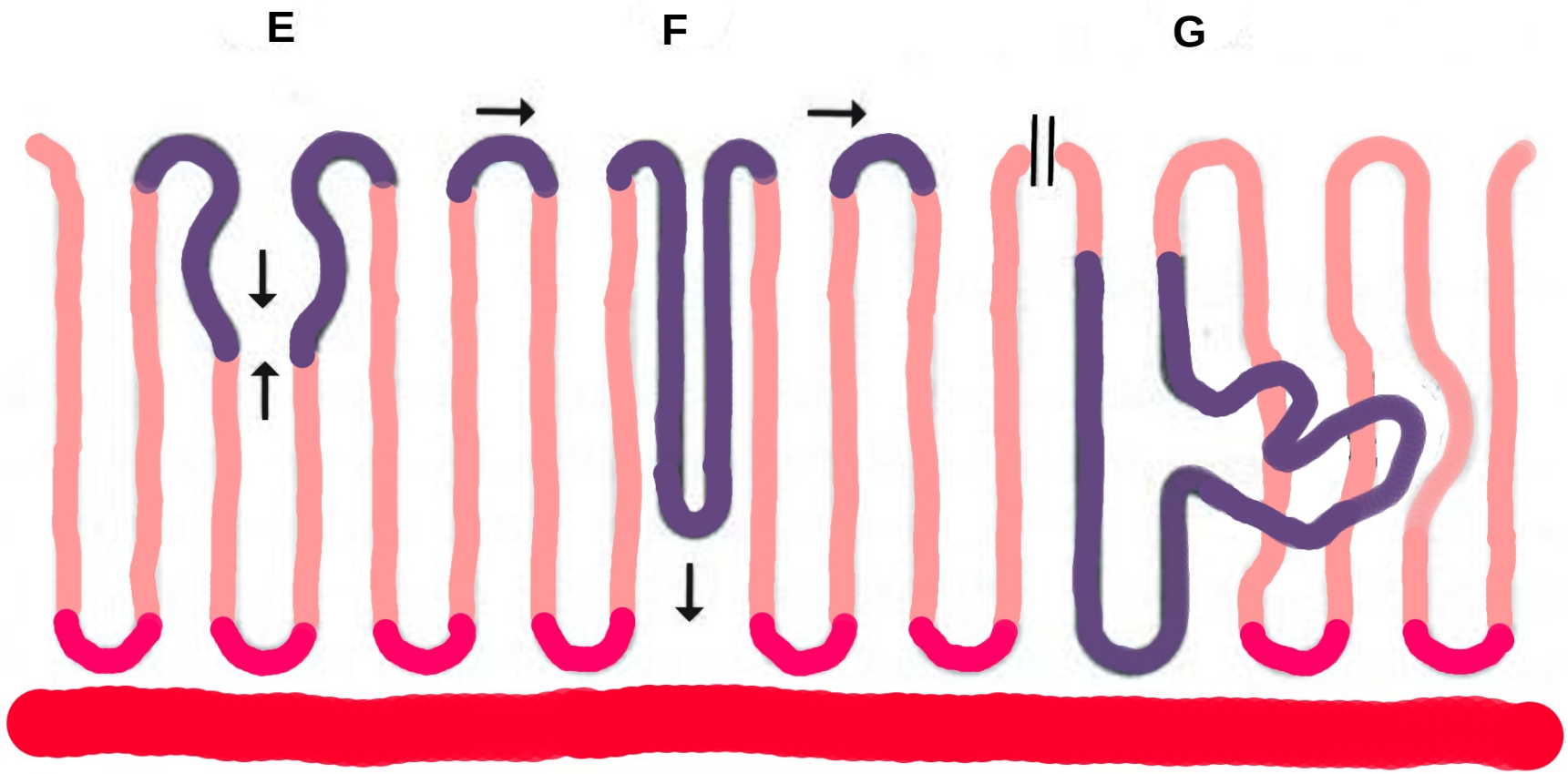


A: first neoplastic gland with some non neoplastic cells still present
B: crypt fission with irregular distribtution of mutated and normal cells
C: lateral, superficial expansion
D: luminal expansion with overgrowth of basal normal glands and retention cysts

modified after Borchard F Verh Dtsch Ges Path 2000

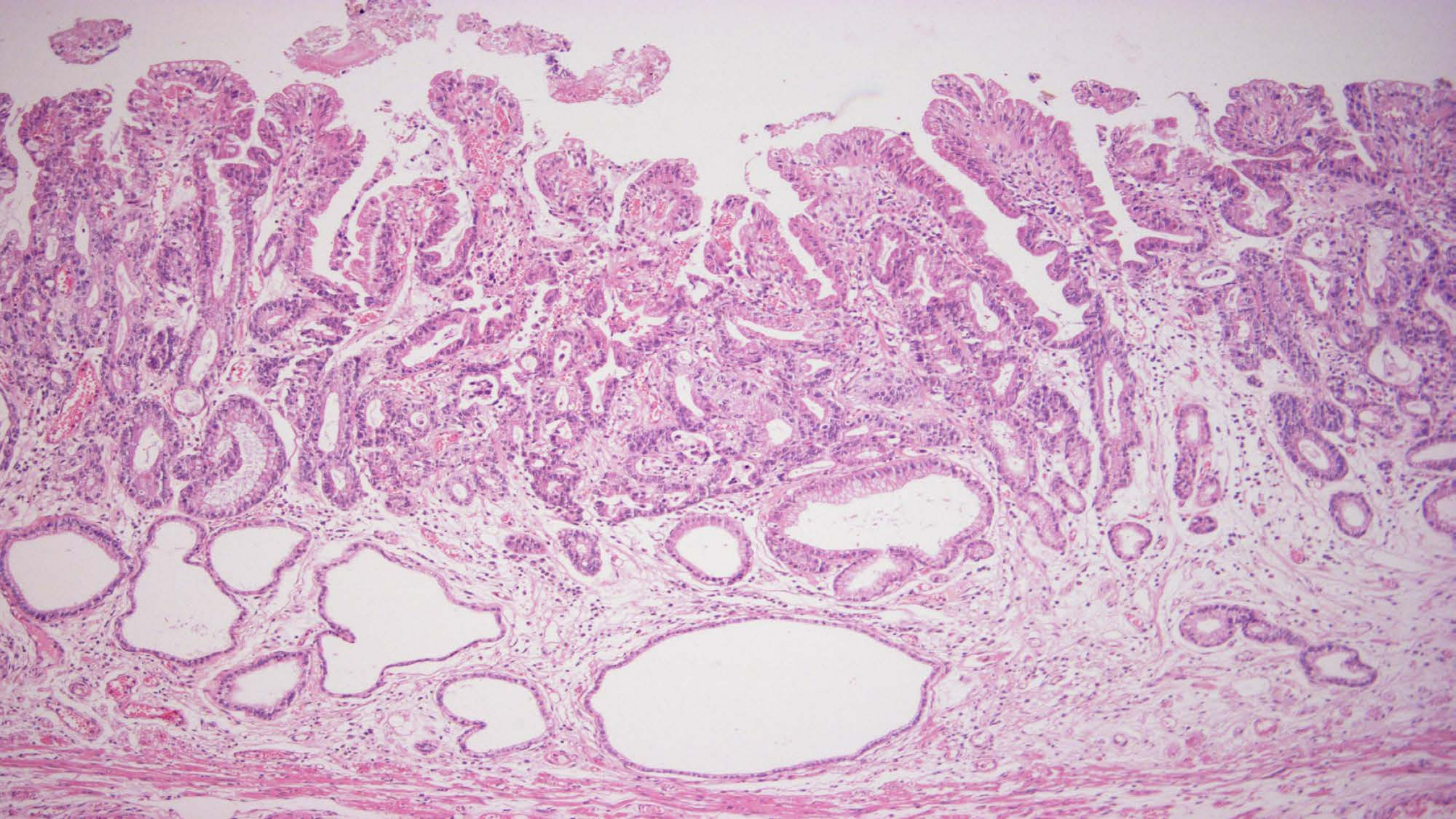


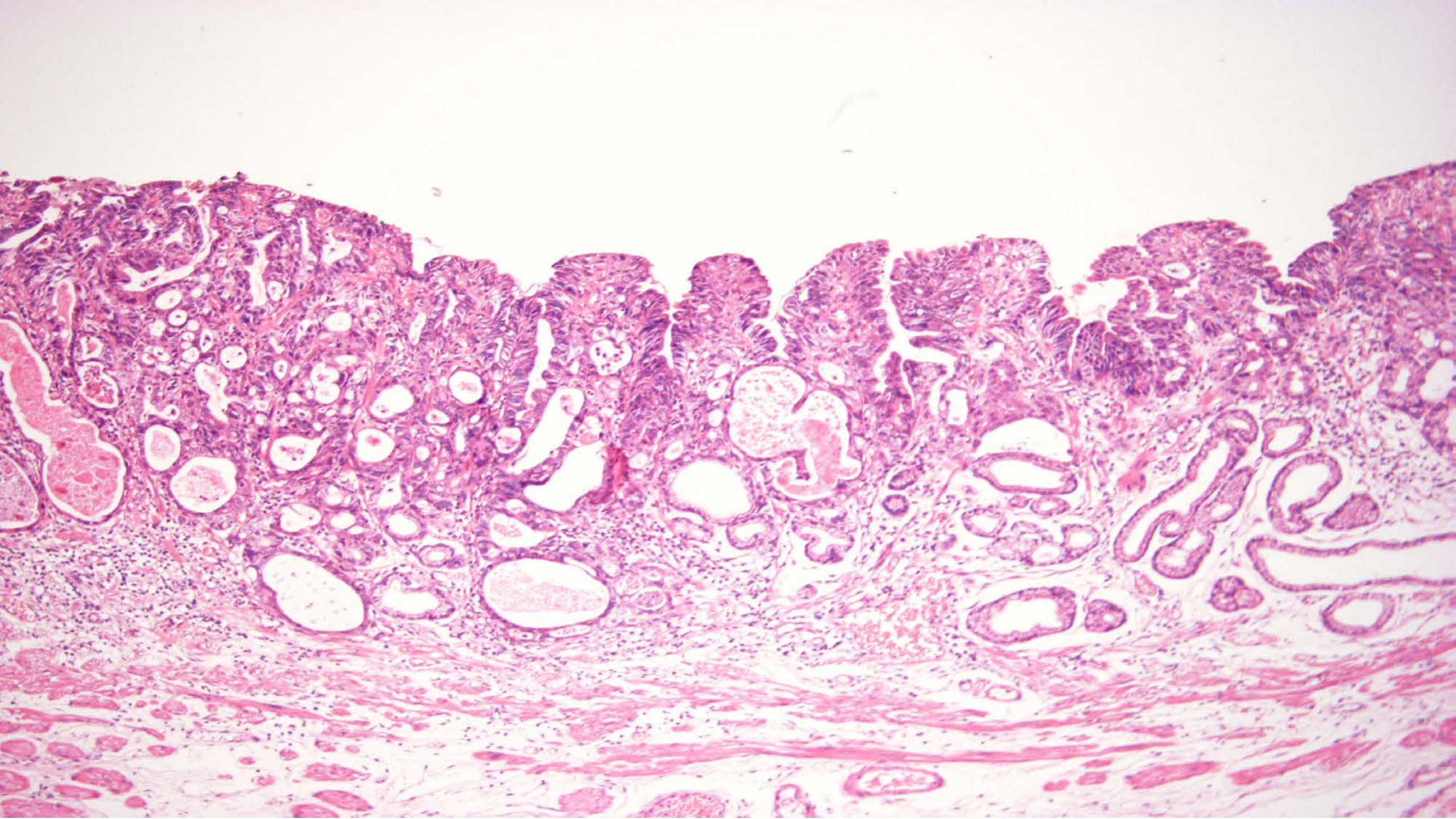
Expansion in low grade dysplasia (E-F) and early carcinoma (G)

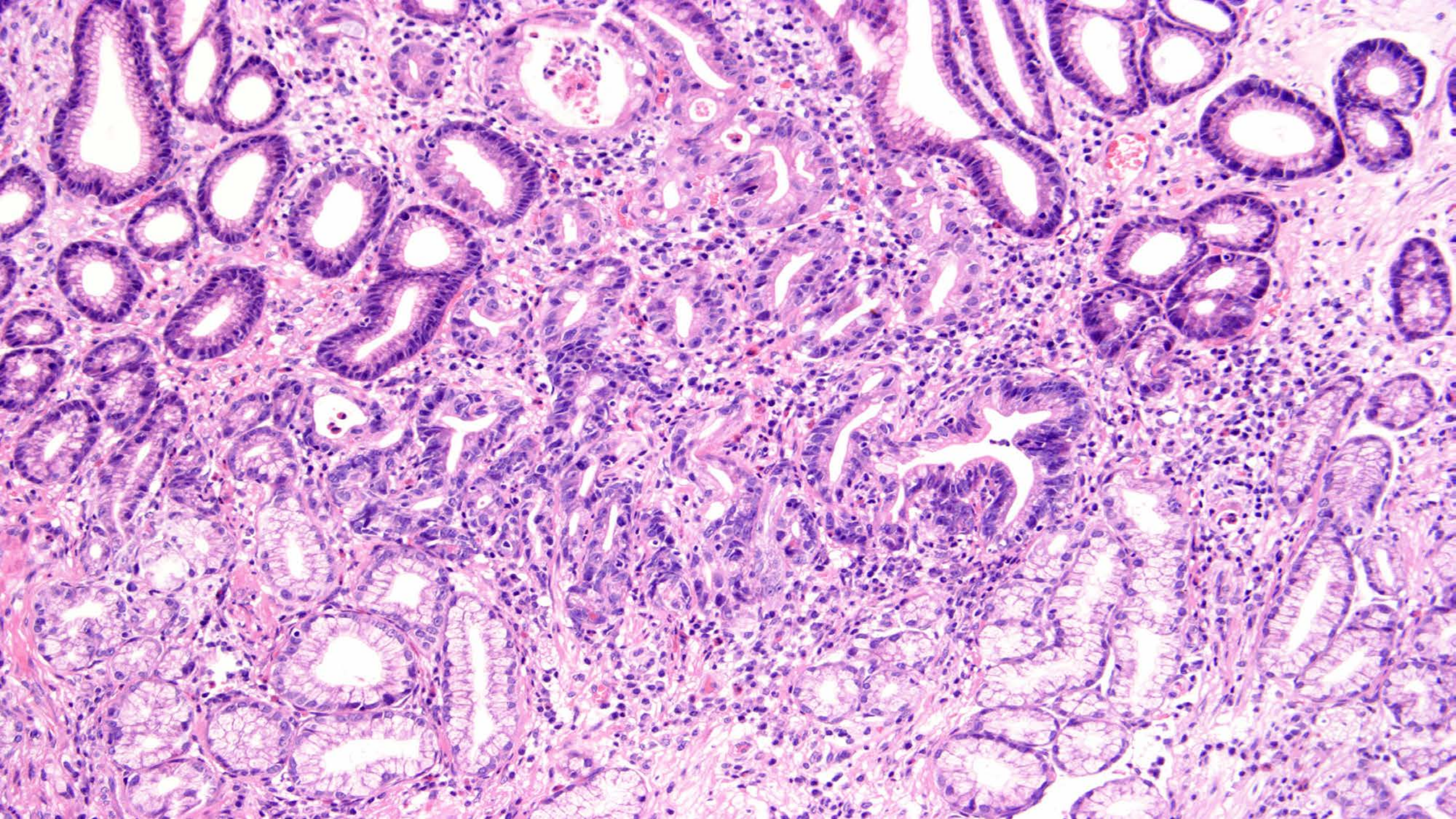


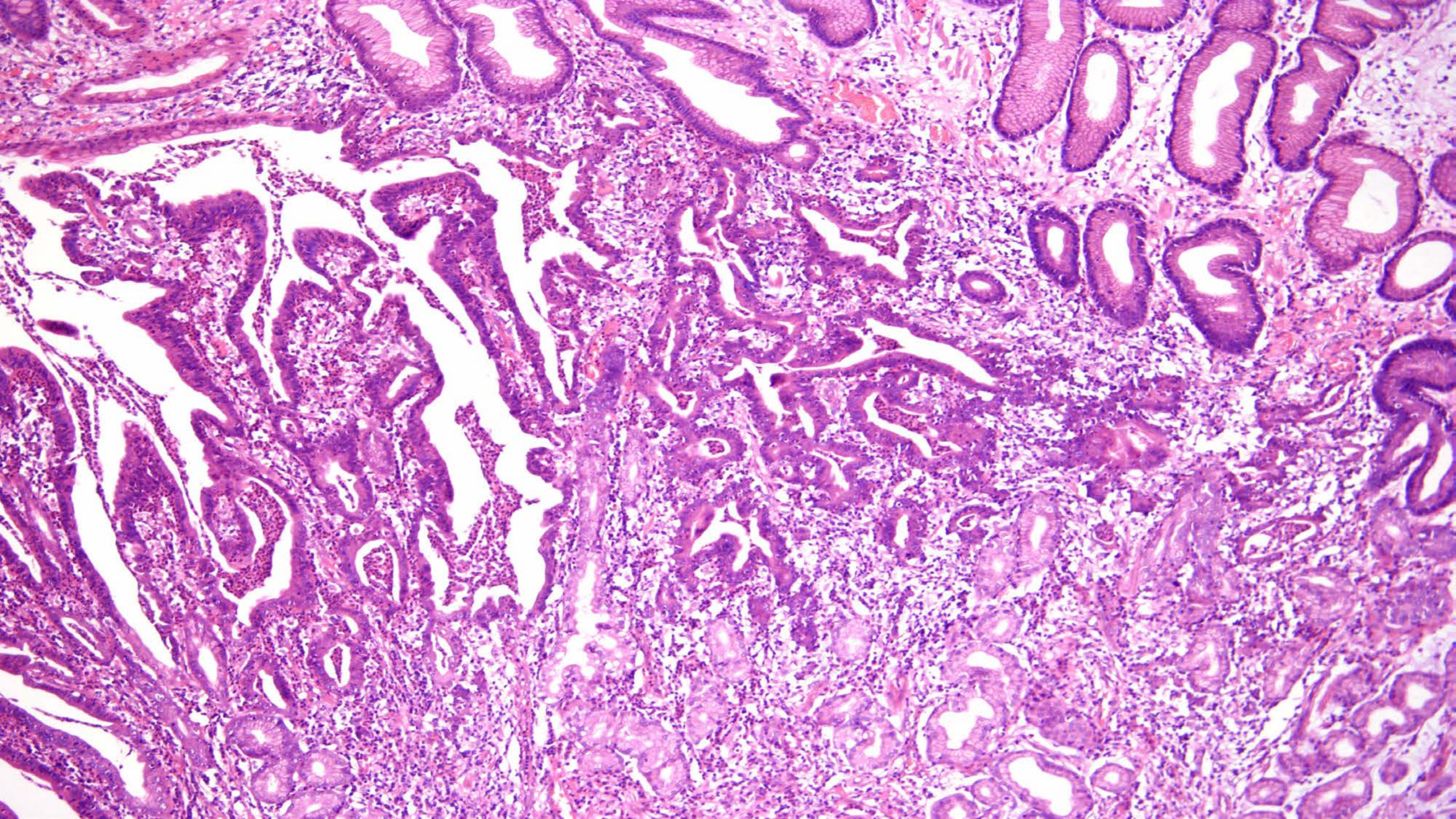
E: Retrograde intratubular Expansion
F: (orderly) retrograde vertical-intertubular Expansion
G: (disordered) retrograde vertical-intertubular Expansion in carcinomas

modified after Borchard F Verh Dtsch Ges Path 2000

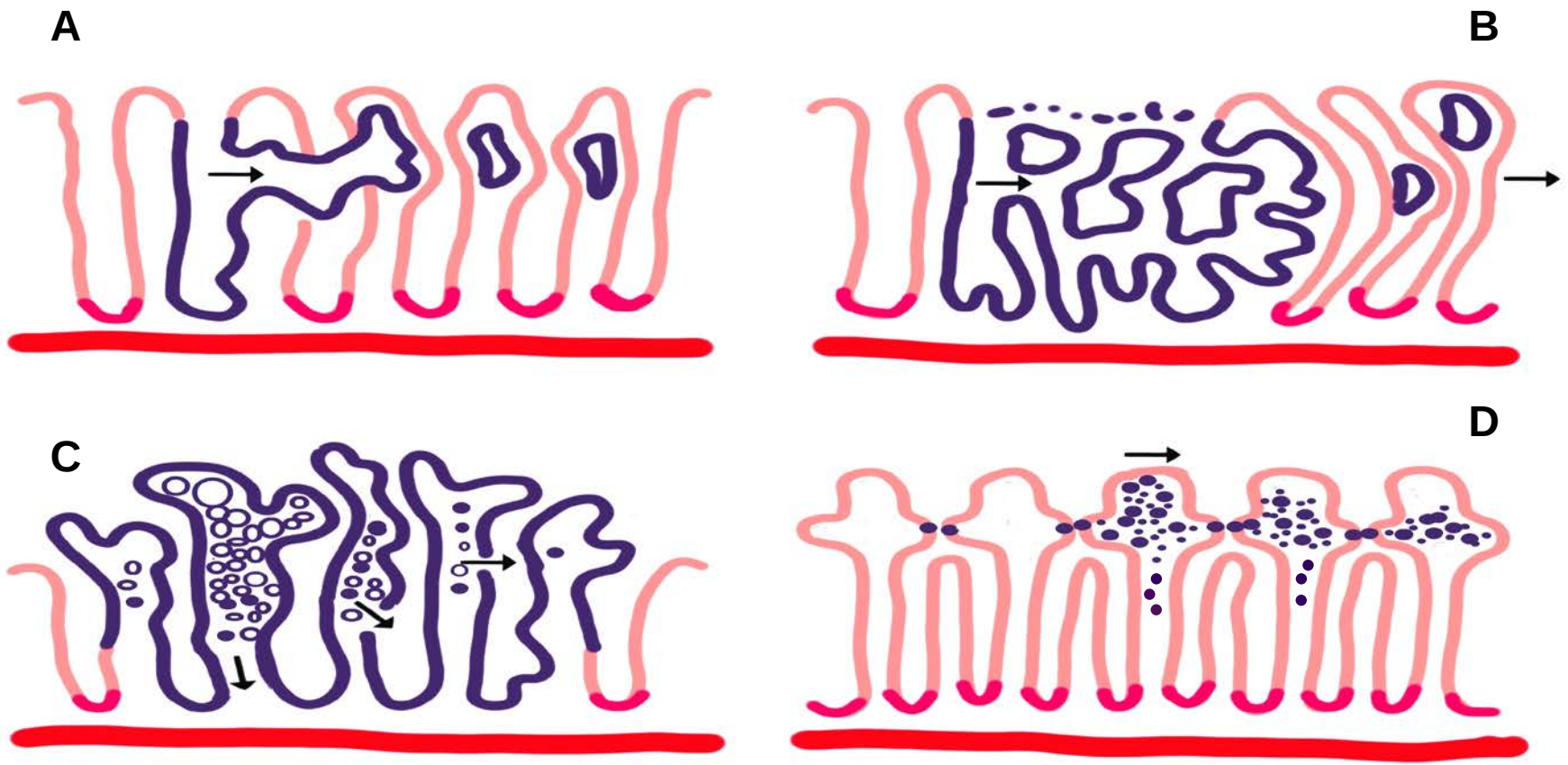






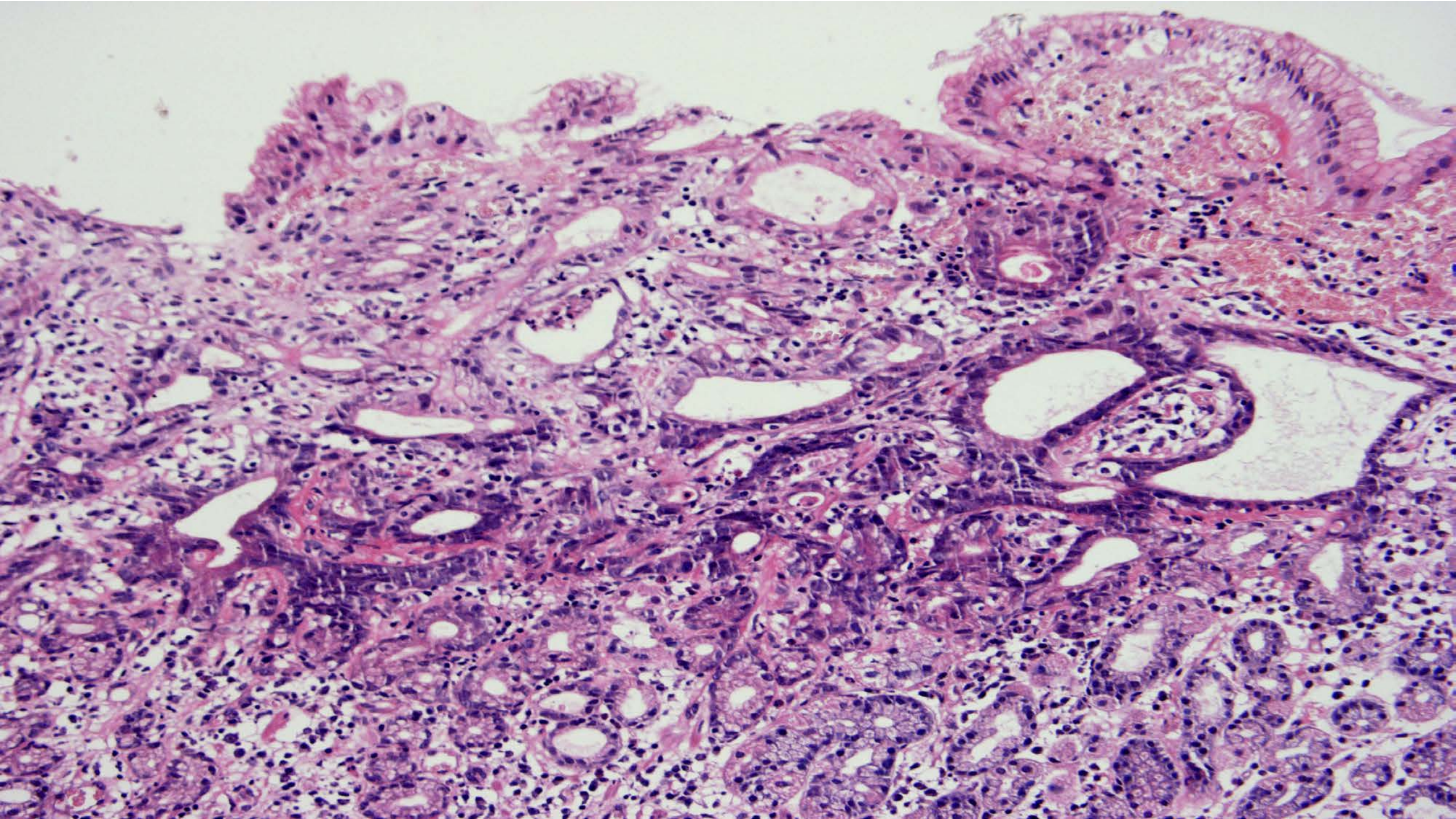


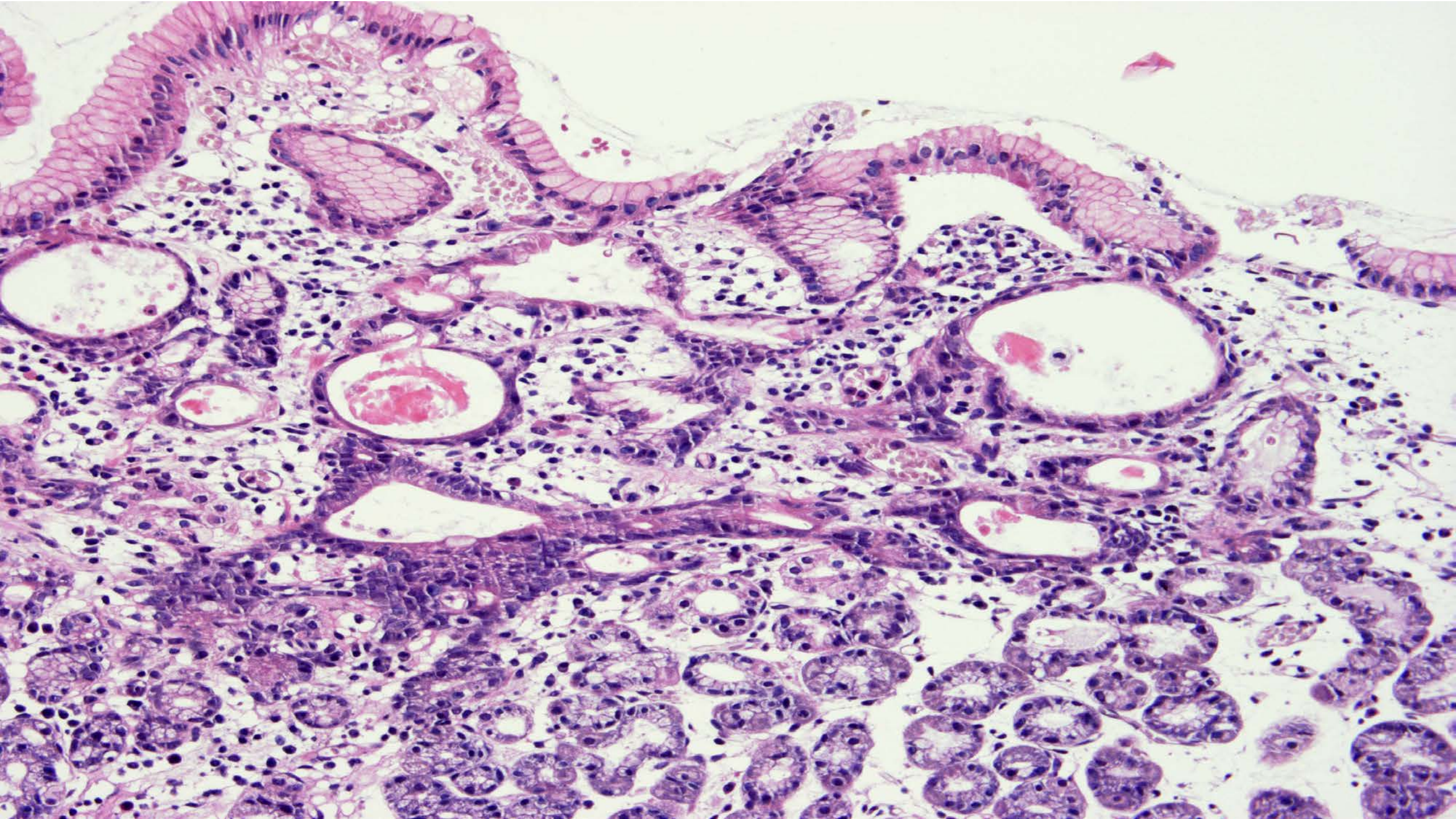
Expansion pattern in early GI

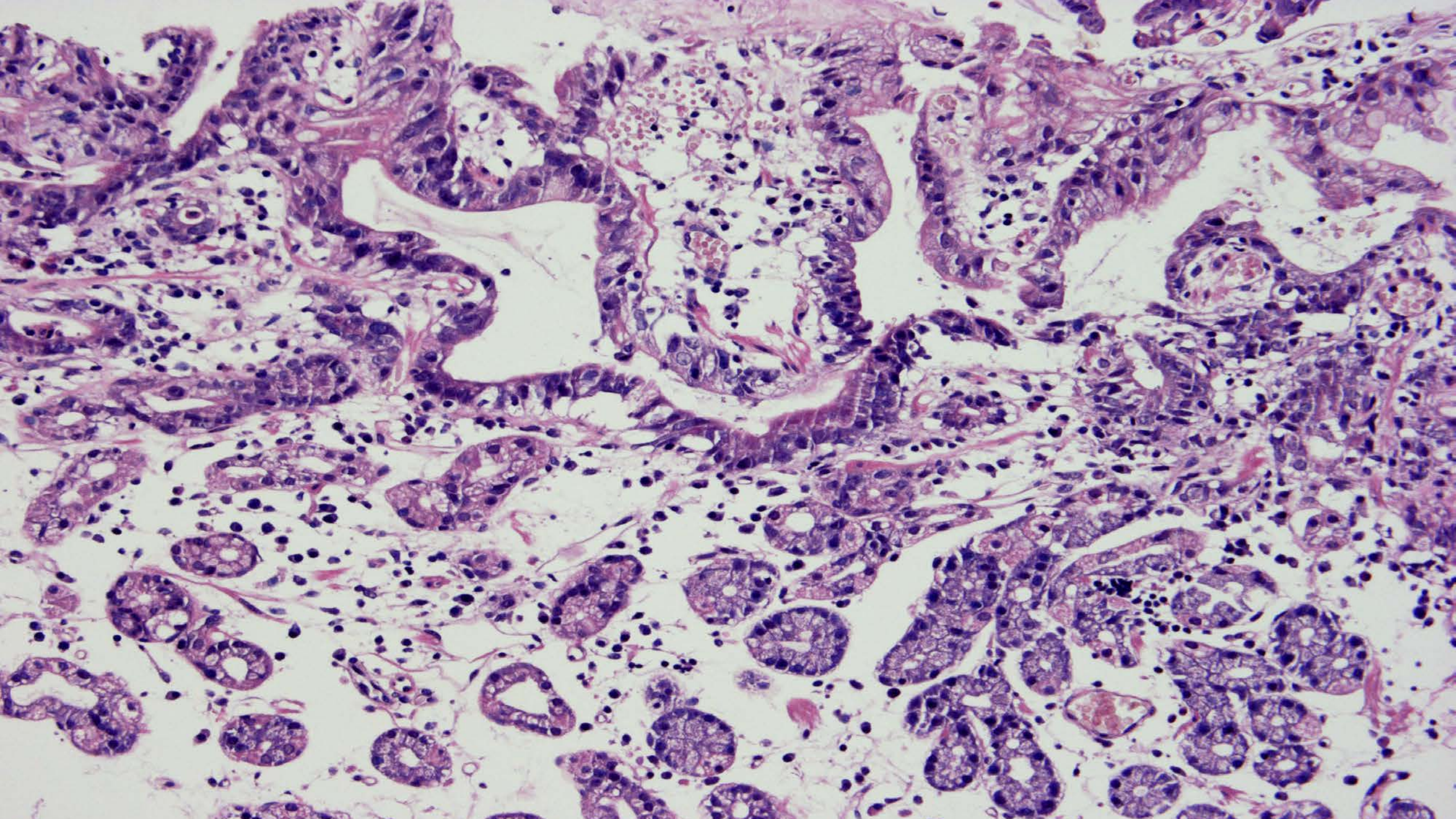


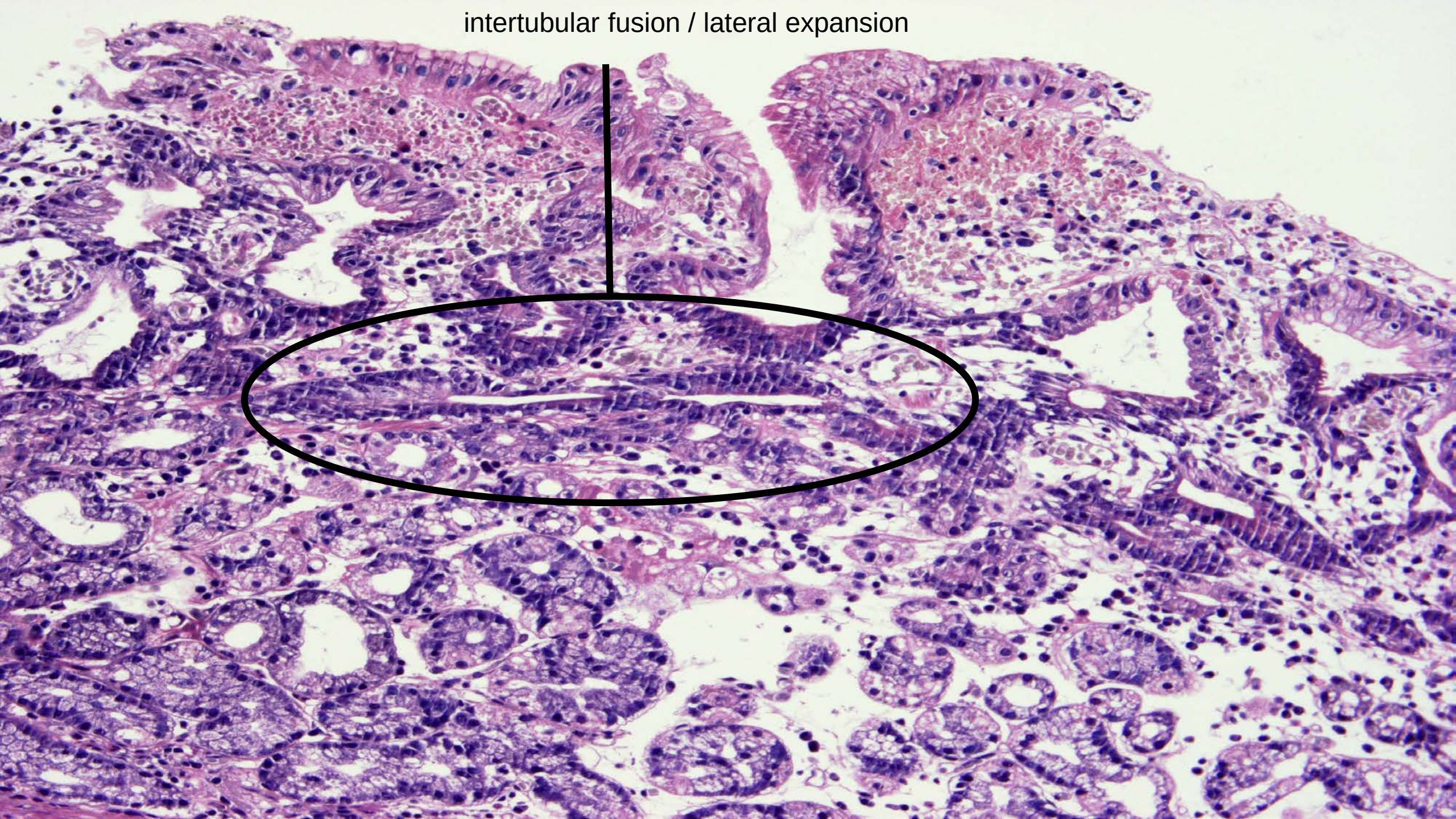
A & B: **mid-mucosal-intertubular-lateral expansion** with initial discontinous expansion with secondary intertubular merging and abnormal branching. Growth underneath, parallel to the surface, compression of preexisting glands and capillaries. **Additional erosion and destruction of adjacent mucosa**
C: Adenoma-Carcinoma-Sequence
D: (de novo) carcinogenesis of diffuse type of gastric carcinoma by drop seeding of mutated stem cells into the stromal tissuse

modified after Borchard F Verh Dtsch Ges Path 2000

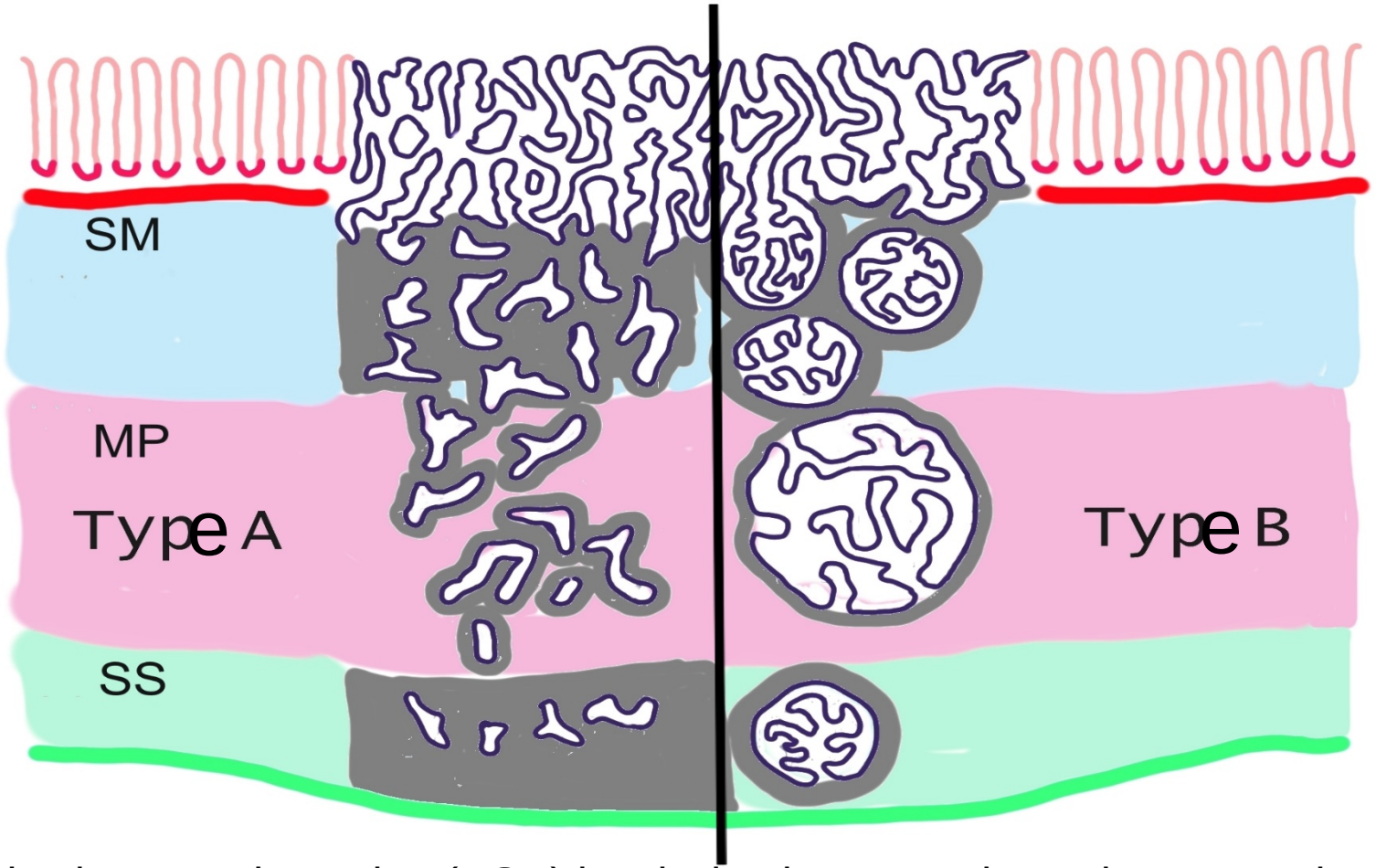







intertubular fusion / lateral expansion

Desmoplastic stromal reaction



Desmoplastic stromal reaction (DSR) is missing in mucosal neoplasms, markedly in submucosal and subserosal tissue but less marked within the muscularis propria
A: infiltrative tubular adenocarcinoma: more pronounced DSR
B: expansive papillary – (cystic) adenocarcinoma: less pronounced DSR

modified after Borchard F Verh Dtsch Ges Path 2000

Cytological and structural criteria of high grade intraepithelial neoplasia and invasive adenocarinoma

Criterion	high grade intraepithelial neoplasia	invasive carcinoma
Architecture	irregular	branching, anastomoses
		rare: single tumour cells
Proliferation zone	whole gland	whole gland
Epithelial expansion	surface epithelium	also underneath surface ep.
Epithelial differentiation	none	none
Foveolar epithelium	none	none
Nuclear layer in rows	2-5	changing within one gland
Size of nucleus	enlarged	vesicular
Nucleoli	some	prominent, possible: >1

Vieth et al. in: Diversity of gastric cancer 2005 Springer Tokyo

Who is wrong ?
Who is right ?

Final proof :

Metastasis
Vessel permeation

LGD
- Structural features:
  - Shape and size of the glands are regular.
  - Glands are slightly crowded.
- Nuclear features:
  - Spindle-shaped nuclei.
  - Basally oriented.
  - Mildly hyperchromatic.

HGD
- Structural features:
  - Glands with variable size and shape.
  - Branching, tortuous glands.
- Nuclear features:
  - Spindle-shaped nuclei.
  - Moderately hyperchromatic.
  - Moderate stratification.

Carcinoma
- Invasion into the lamina propria forming single cells, micronests, trabecular growth, or budding is seen.
- Invasion into the muscularis mucosae.

Critisism:
not present even in clear cut invasive carcinoma

Question

What answer is most comprehensive ?

What are the earliest signs of invasion ?

A) High grade nuclear atypia and atypical mitoses

B) High grade nuclear atypia and desmoplastic stromal reaction

C) High grade nuclear atypia and lateral expansion

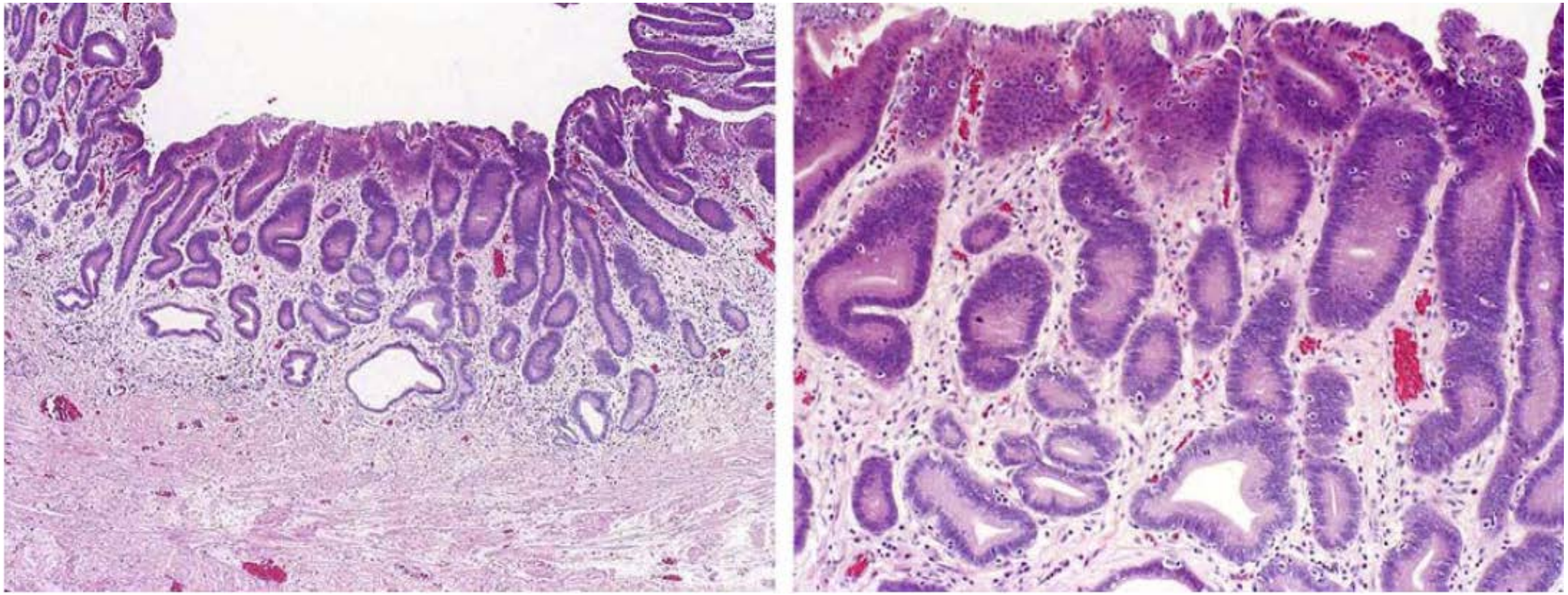
D) Atypical mitoses and submucosal invasion

E) Atypical mitoses and desmoplastic stromal reaction

Borchard et al. 1999 and 2000

Vieth et al. in: Diversity of gastric cancer 2005 Springer Tokyo

Easy :

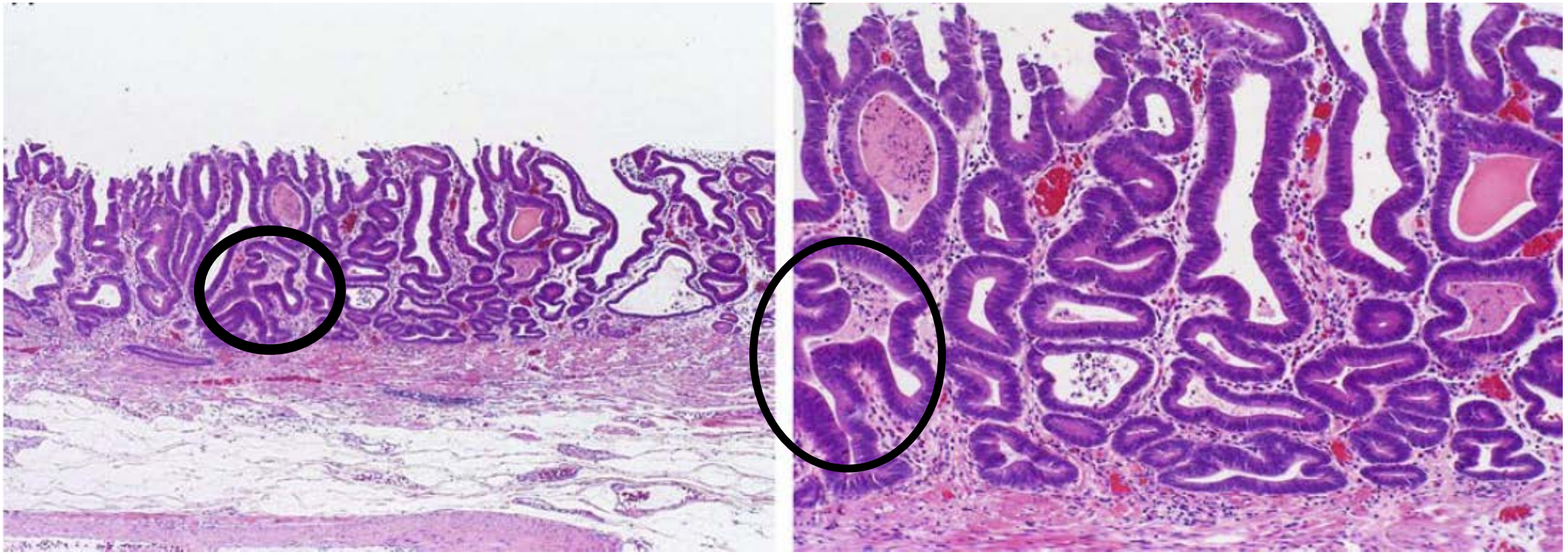


LGD !

The glands are slightly crowded and maintain a regular overall shape and size. Nuclei are elongated and palisading and mildly hyperchromatic.

Sakurai U et al. Am J Surg Pathol 2014

Easy ?

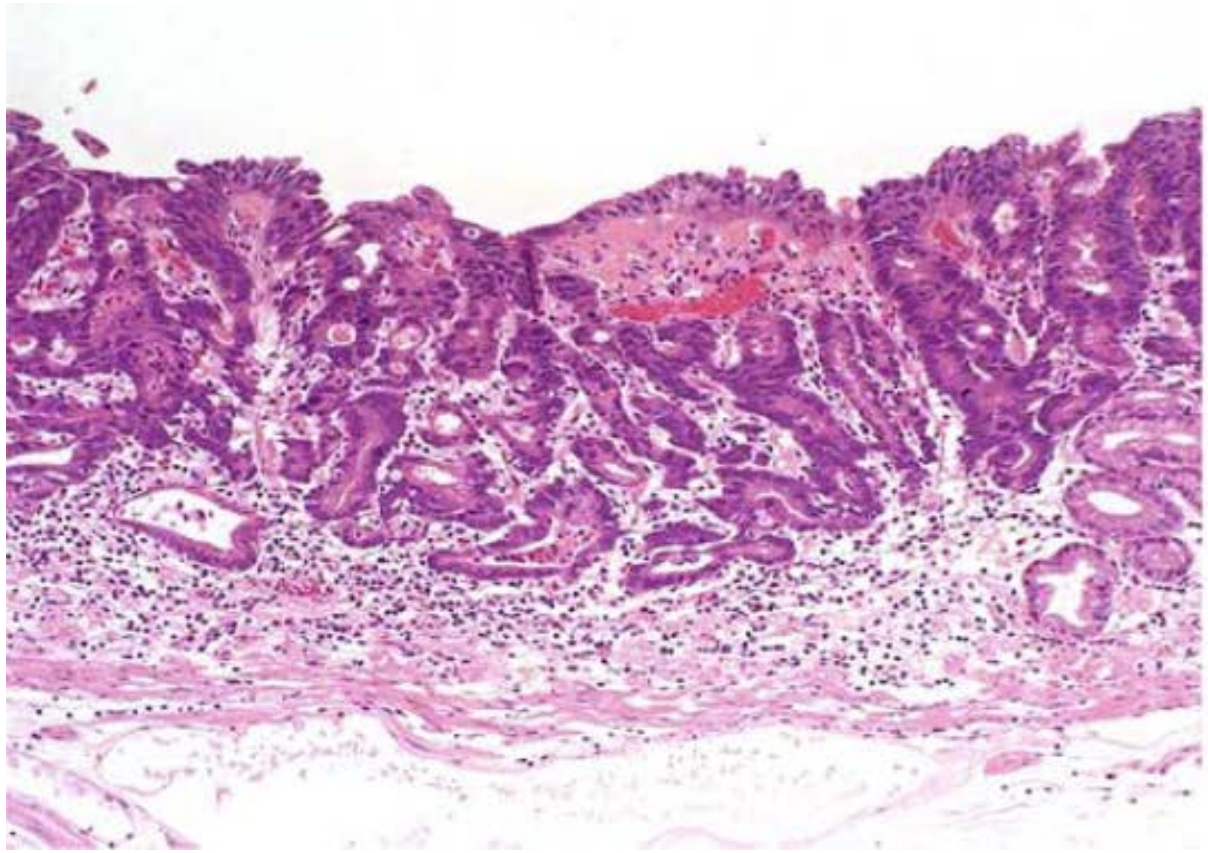


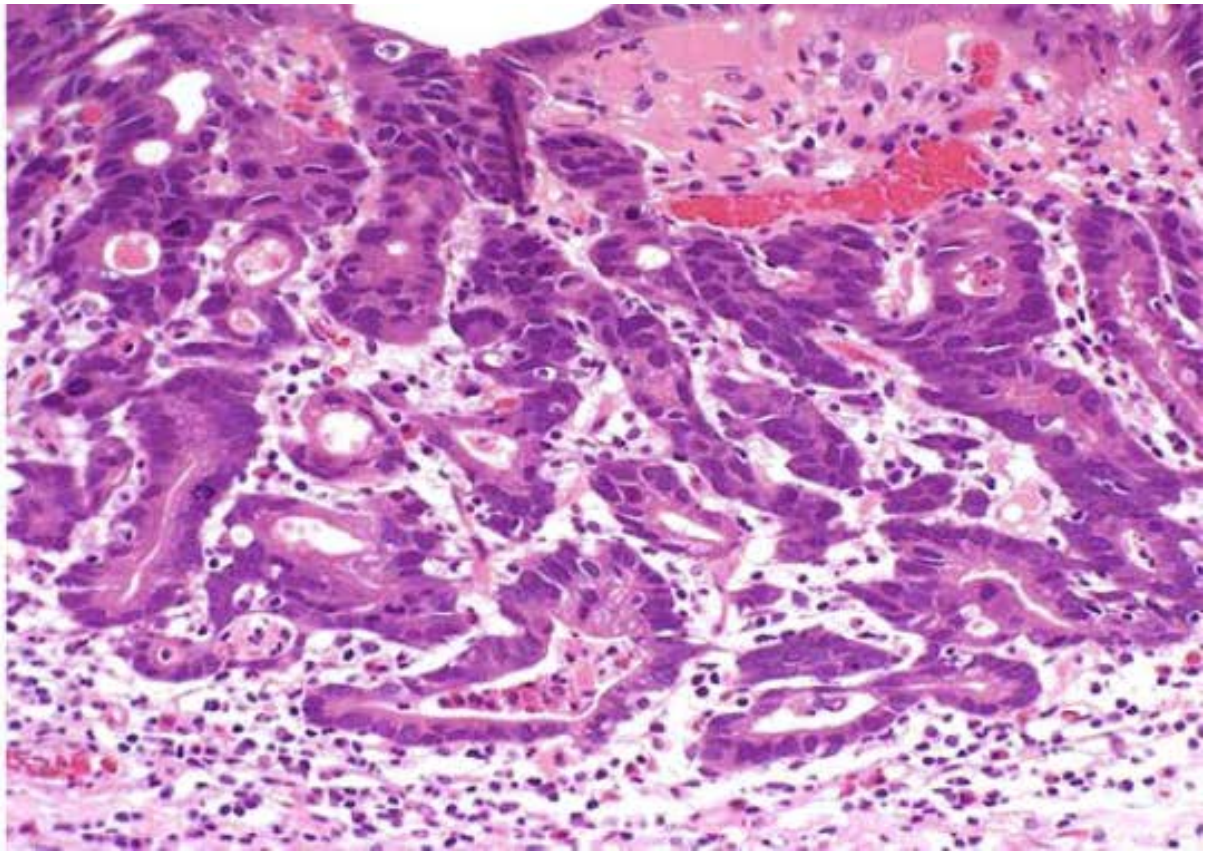
HGD ?

The glands are tortuous with branching varying in shape and size.
Nuclei irregular in shape and size and have prominent nucleoli.

Sakurai U et al. Am J Surg Pathol 2014

Easy :



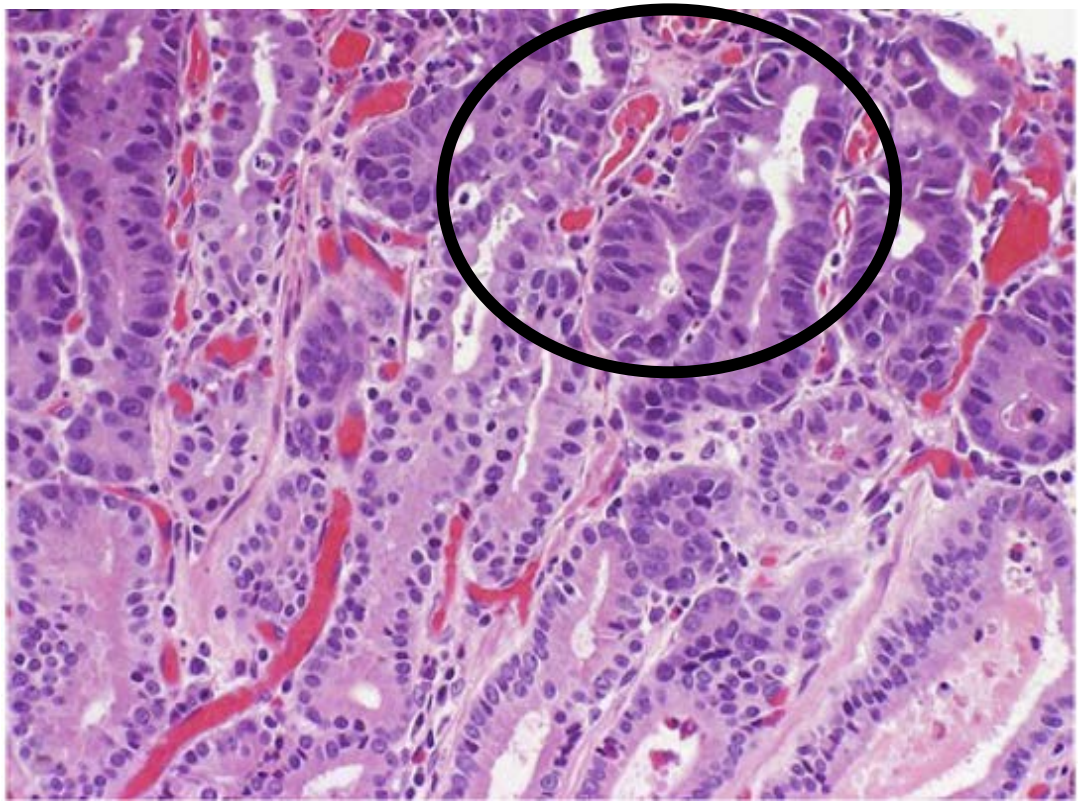


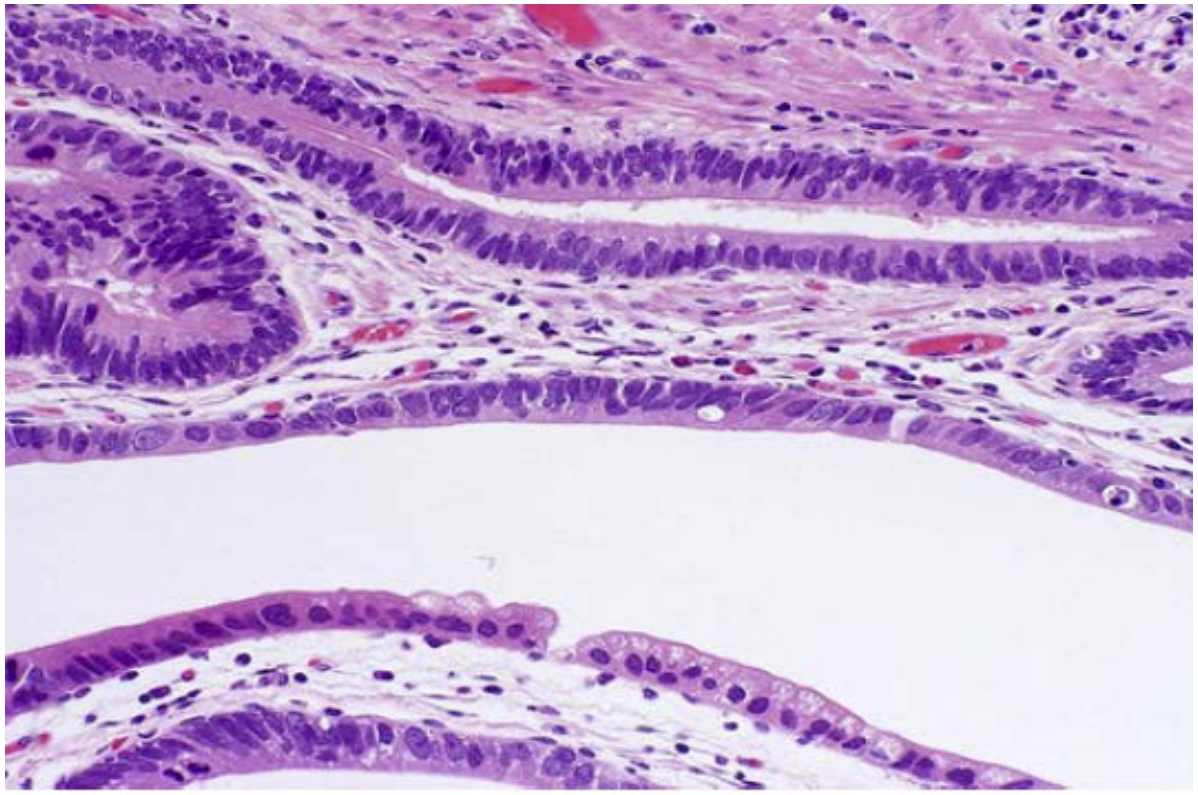
Carcinoma !

The glands show irregular anastomosis and complex branching. No desmoplasia. Nuclei are irregular in shape and size with prominent nucleoli.

Sakurai U et al. Am J Surg Pathol 2014

Easy ?





HGD ?

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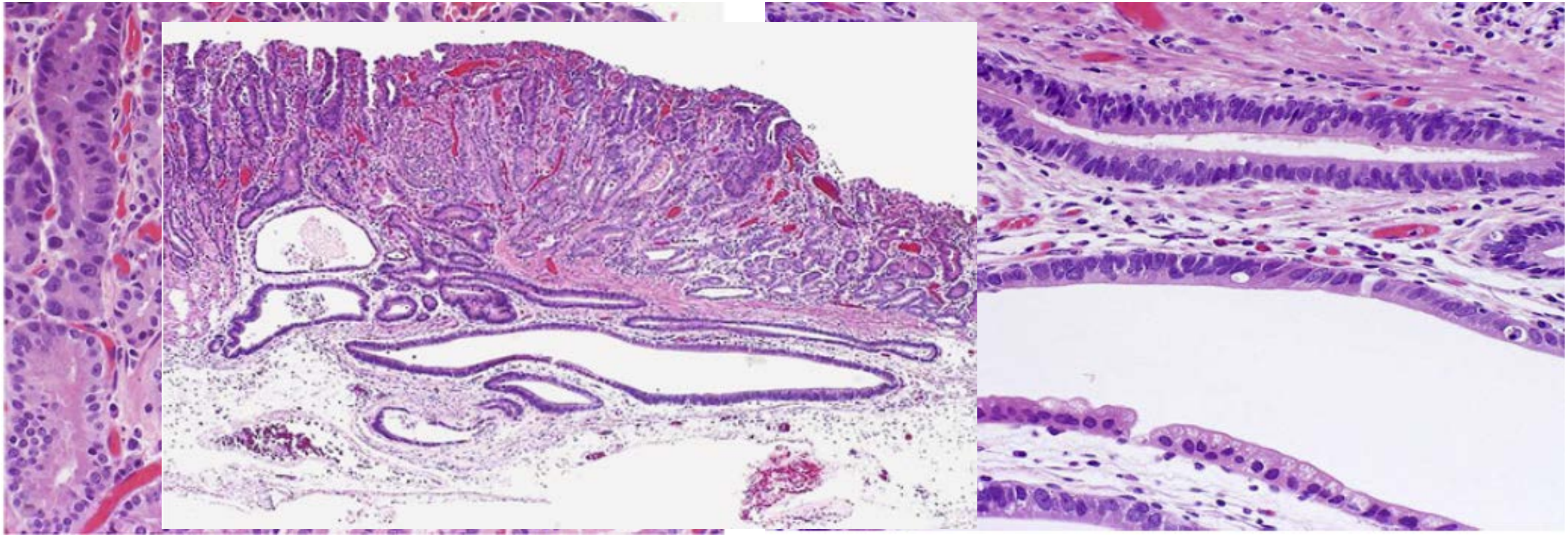
Sakurai U et al. Am J Surg Pathol 2014

Easy ?



HGD ? = Ca !!!!

The glands are tortuous with branching varying in shape and size.
Nuclei irregular in shape and size and have prominent nucleoli.

Sakurai U et al. Am J Surg Pathol 2014

Even worse :

Histology (WHO)	No. cases	sm invasion ; n (%)	venous invasion in sm; n (%)	Lymphatic invasion in sm; n (%)
LGD	4	0 (0)	0 (0)	0 (0)
HGD	78	**3 (3.8)**	**1 (1.3)**	0 (0)
HGD + Ca	4	3 (75)	3 (75)	1 (25)
Carcinoma	35	4 (11.4)	0 (0)	1 (2.9)
Total	121	10 (8.3)	4 (3.3)	2 (1.7)

HGD with sm and/or venous invasion ?????

Sakurai U et al. Am J Surg Pathol 2014

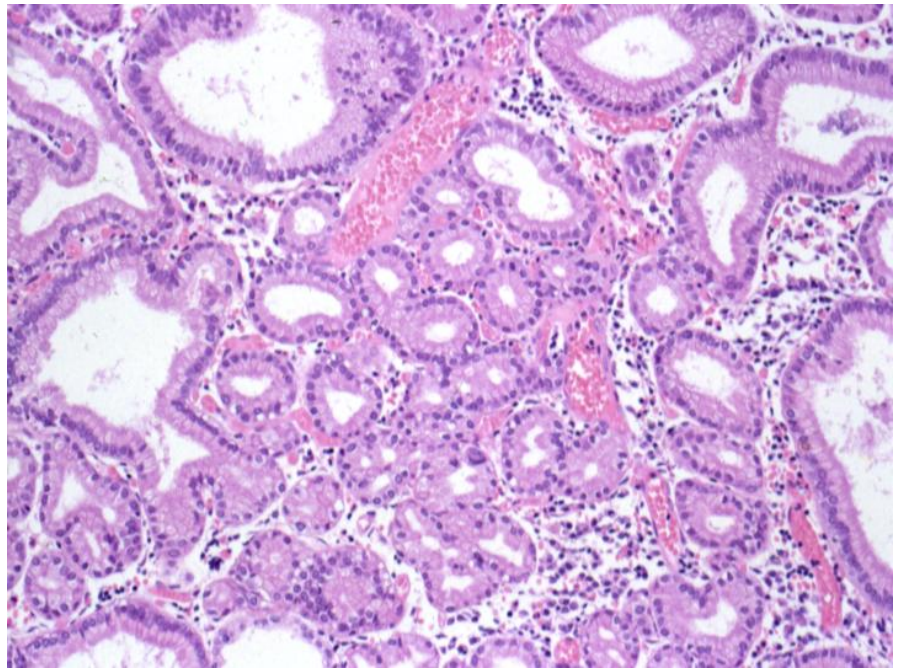
Question your criteria now !

esp. in biopsies !

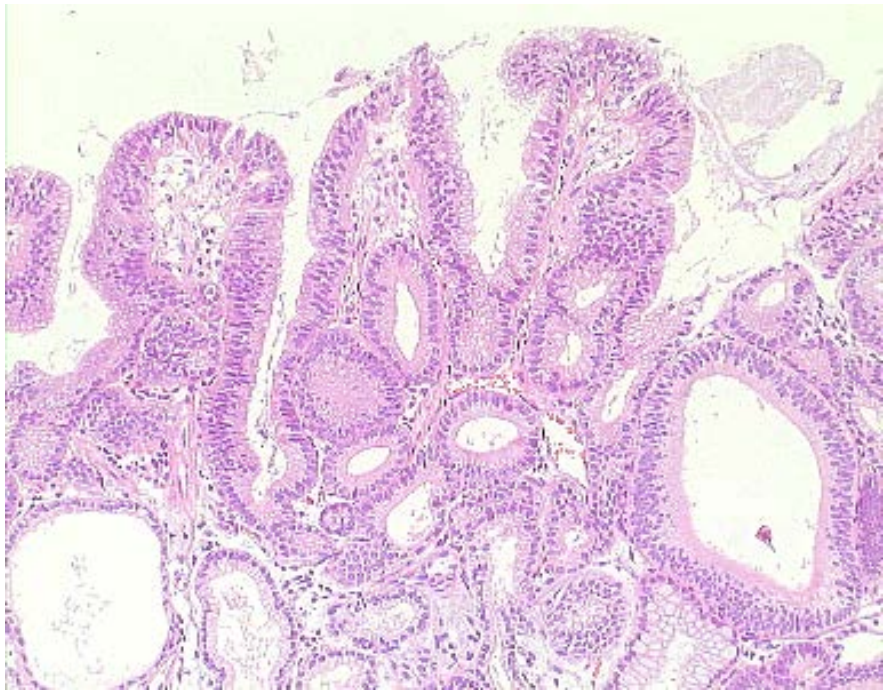
Challenges

Gastric differentiated neoplasms:

a) Pyloric gland adenoma



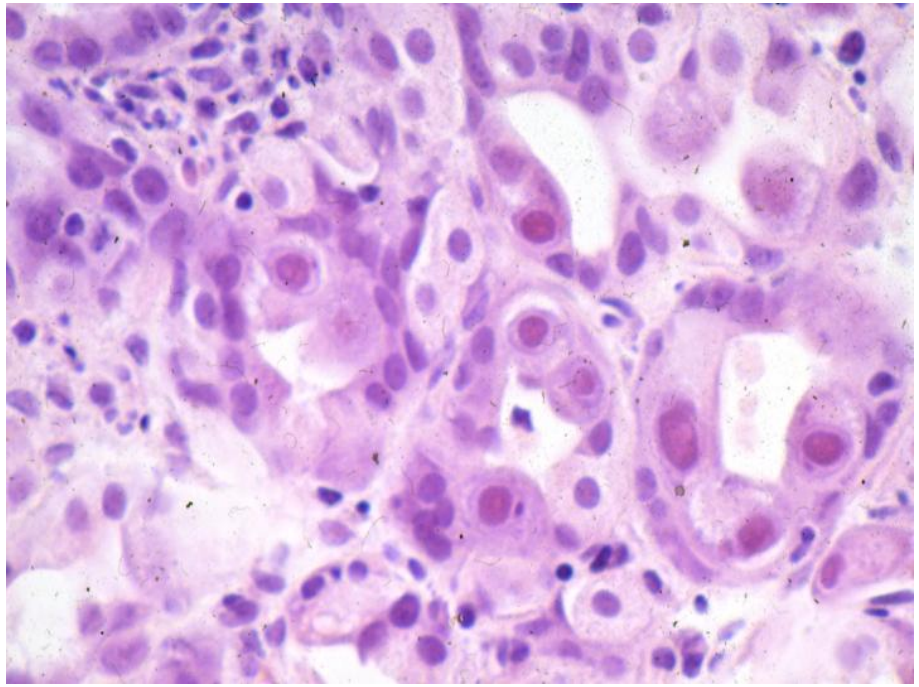
b) Foveolar adenoma



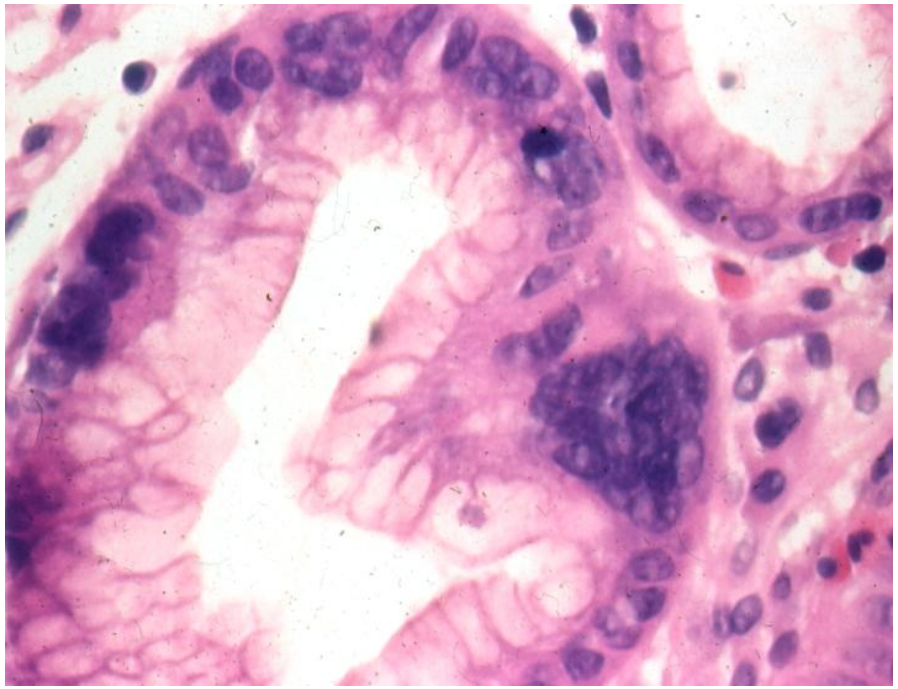
Challenges

Viral infections:

a) CMV

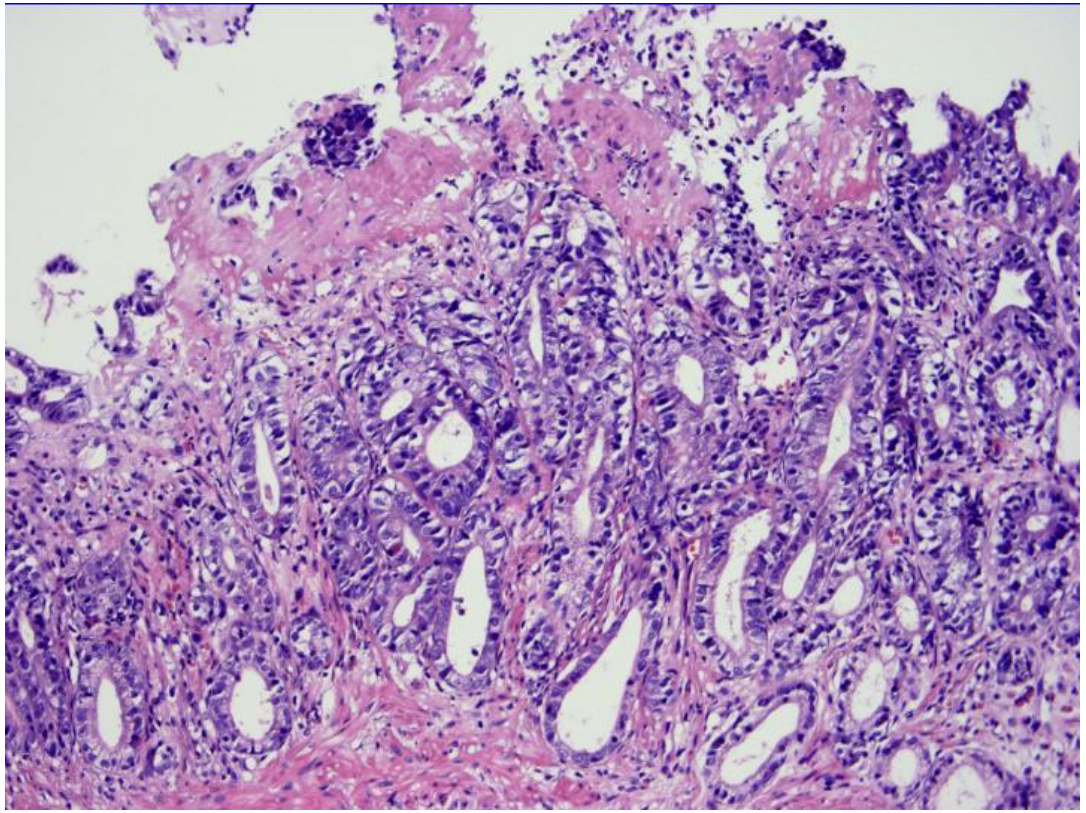


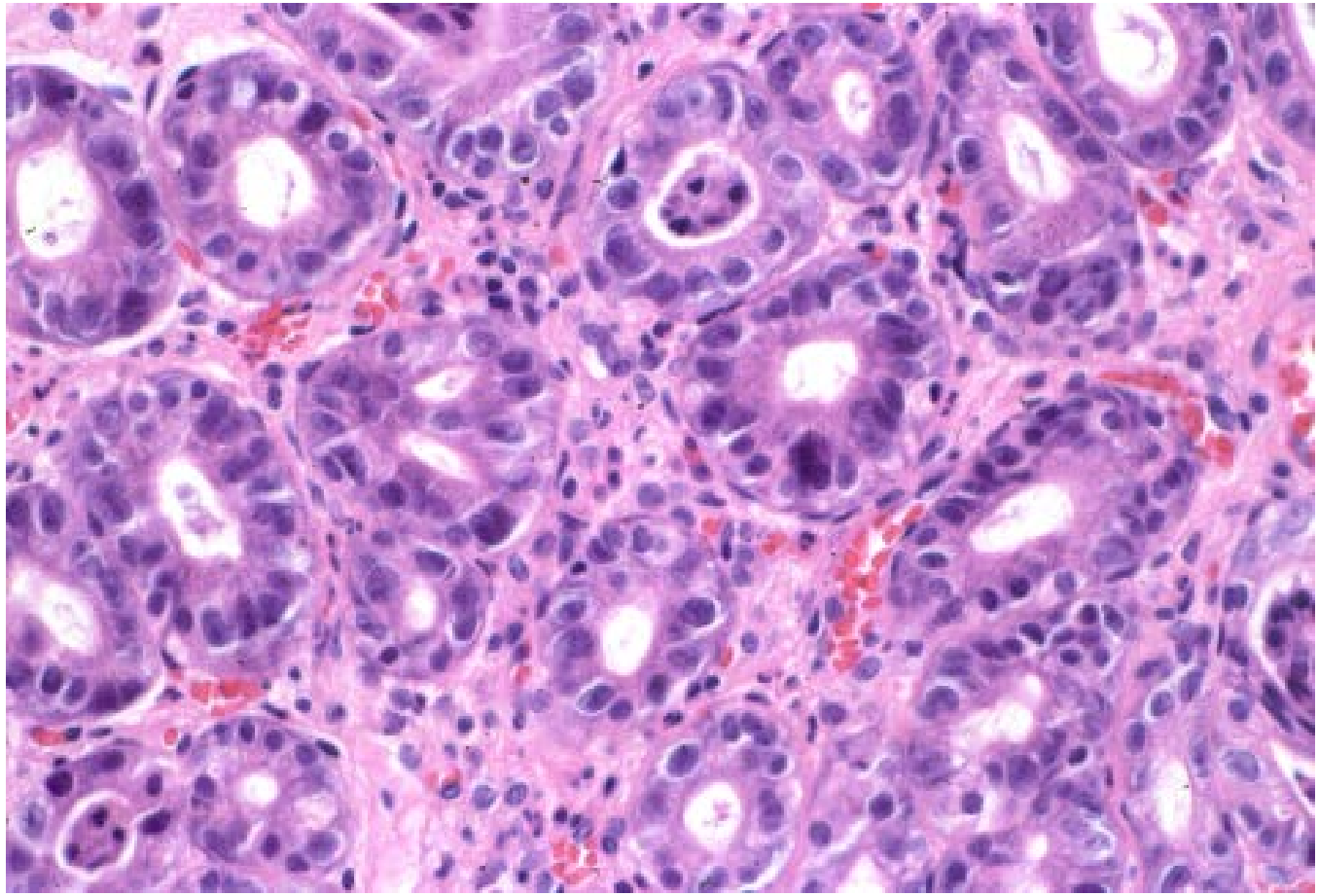
b) Measles



Challenges

NSAID/ASA lesions





Gastritis status may be helpful !

Conclusion

HGD and carcinoma can be differentiated even in biopsies

WHO classification is incomplete
(missing or non working criteria)

G1 carcinomas can build up their own basement membrane

Challenges are:
gastric differentiation, viruses, drug-induced lesions


THANK YOU