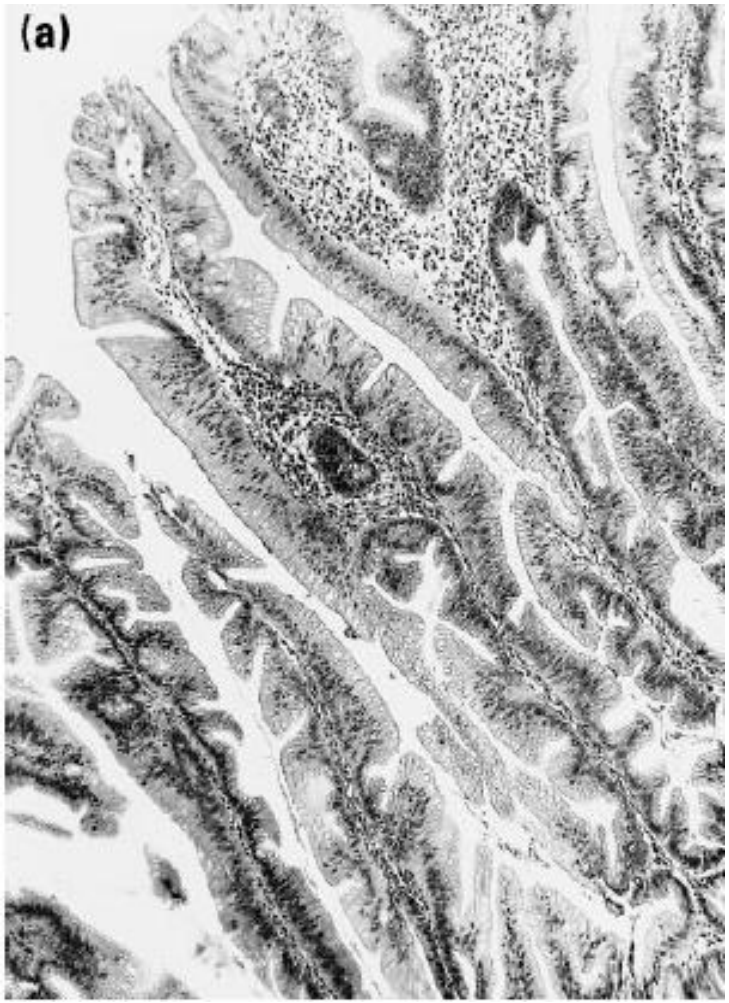
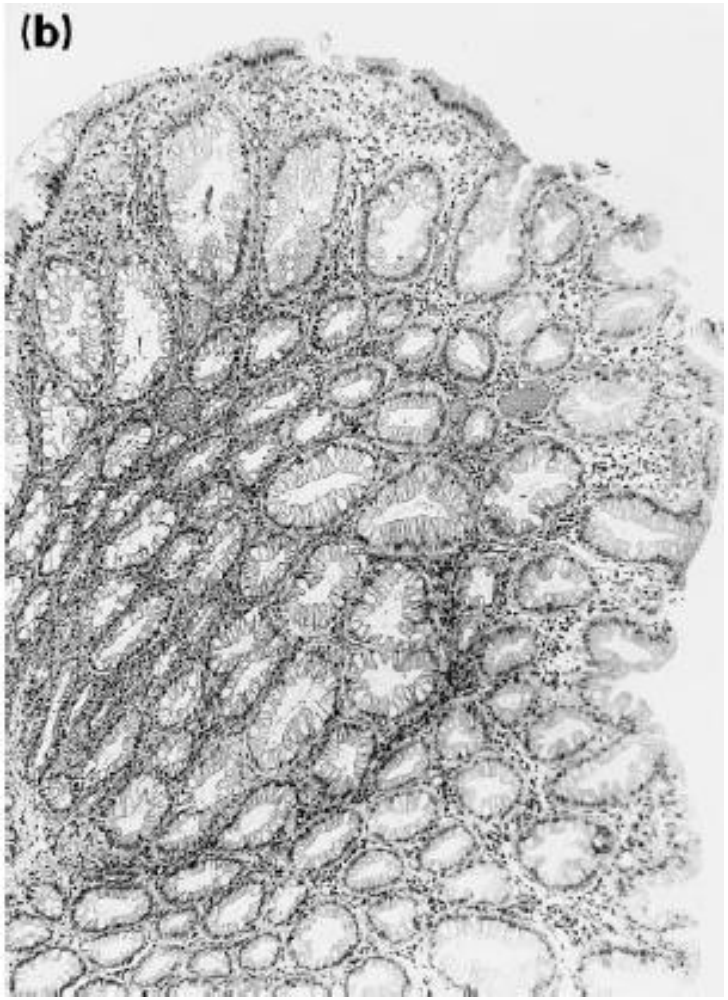
An update on Serrated Polyps

Elizabeth Montgomery, Baltimore
Arzu Ensari, Ankara

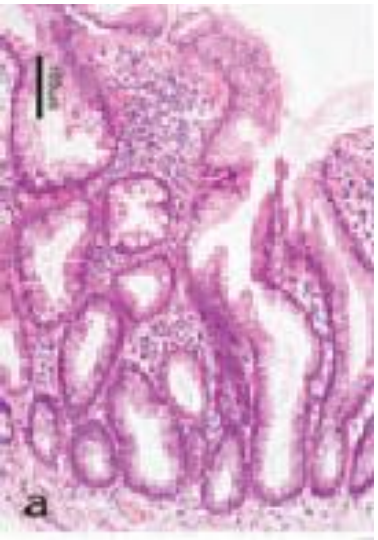


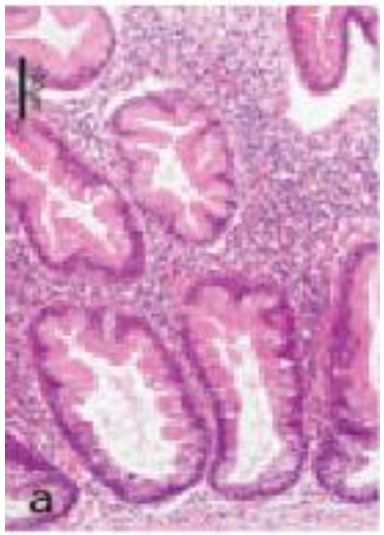
Serrated adenoma

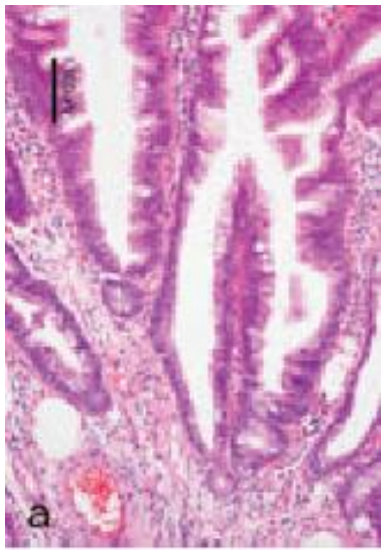


Hyperplastic polyp

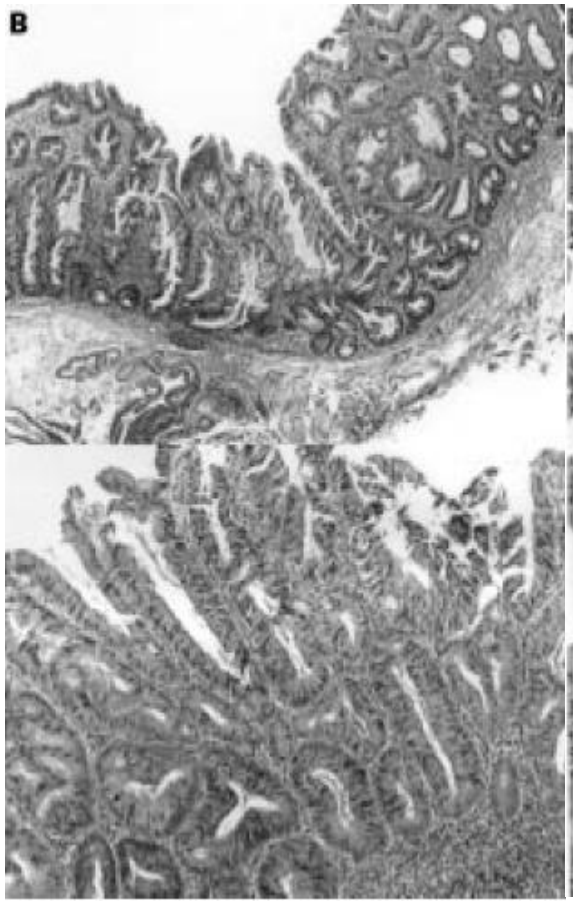
Yao, 1999



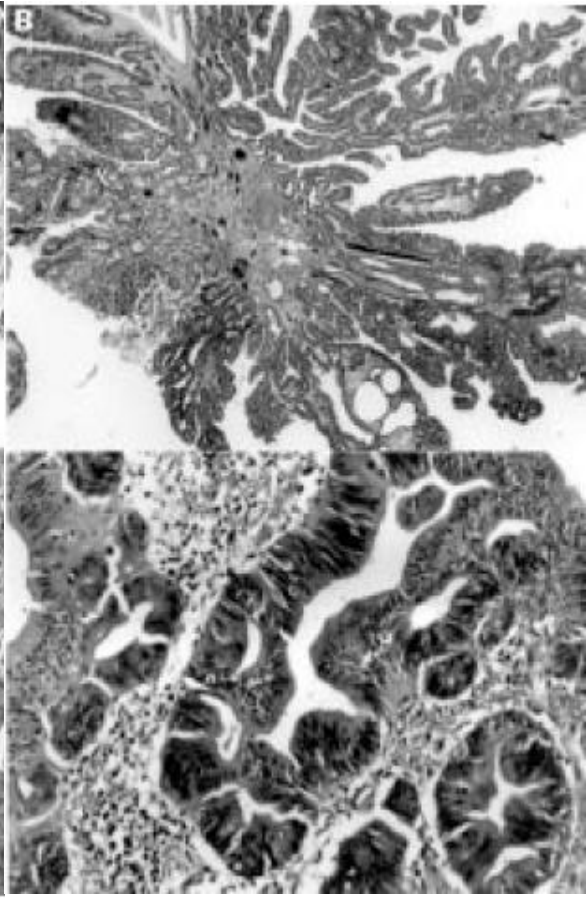




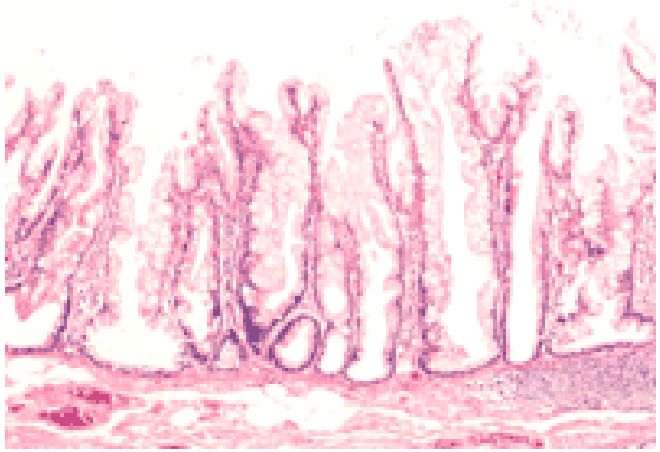
Serrated adenoma
Hirono, 2004

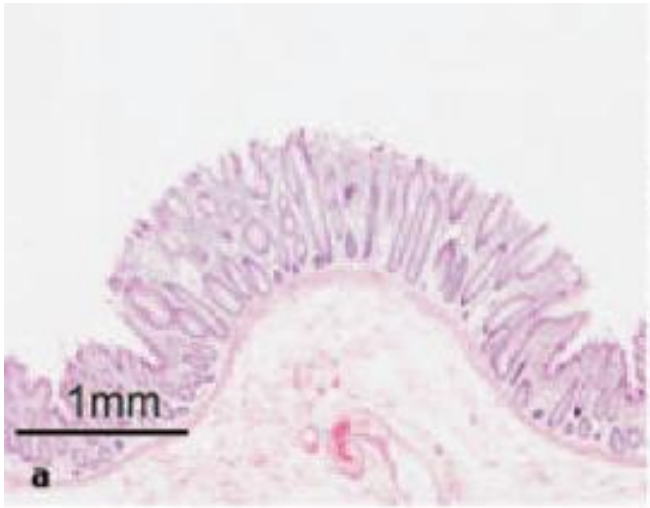


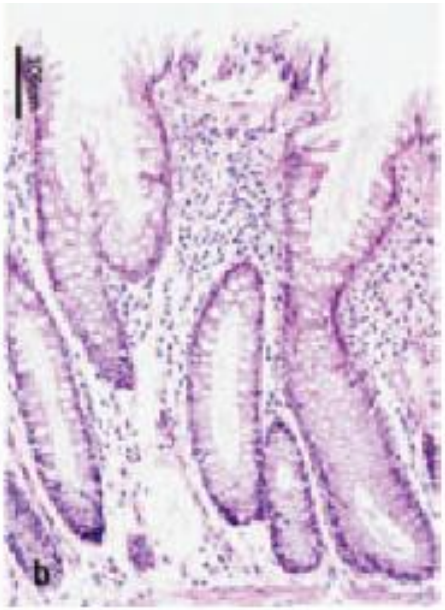
Sessile serrated adenoma
Matsumoto, 1999



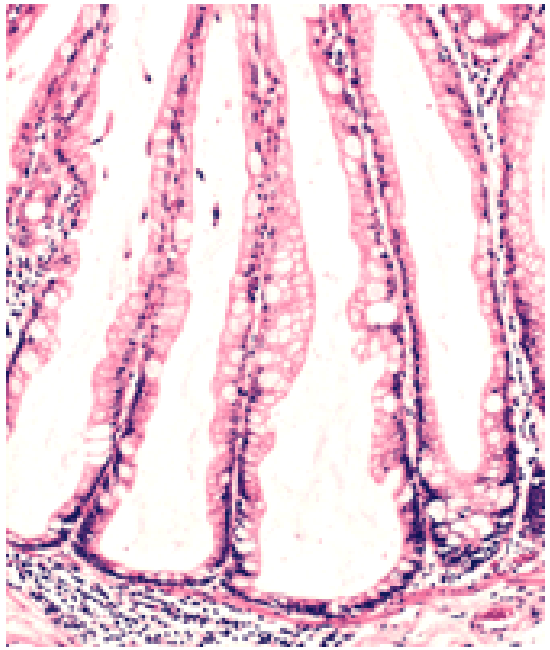
Pedunculated serrated adenoma
Matsumoto, 1999



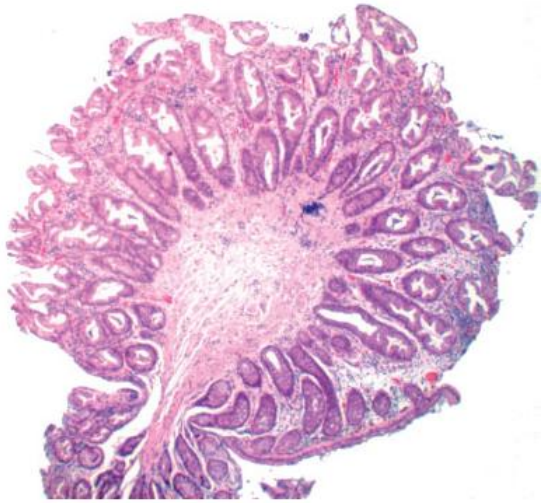




Hyperplastic polyp
Hirono, 2004



Variant Hyperplastic polyp
Jass, 2004



LG dysplastic serrated adenoma
Goldstein, 2008

Management of Serrated Adenomas and Hyperplastic Polyps

Valerie P. Bauer, M.D.[1] and Harry T. Papaconstantinou, M.D.[2]

CLINICS IN COLON AND RECTAL SURGERY/VOLUME 21, NUMBER

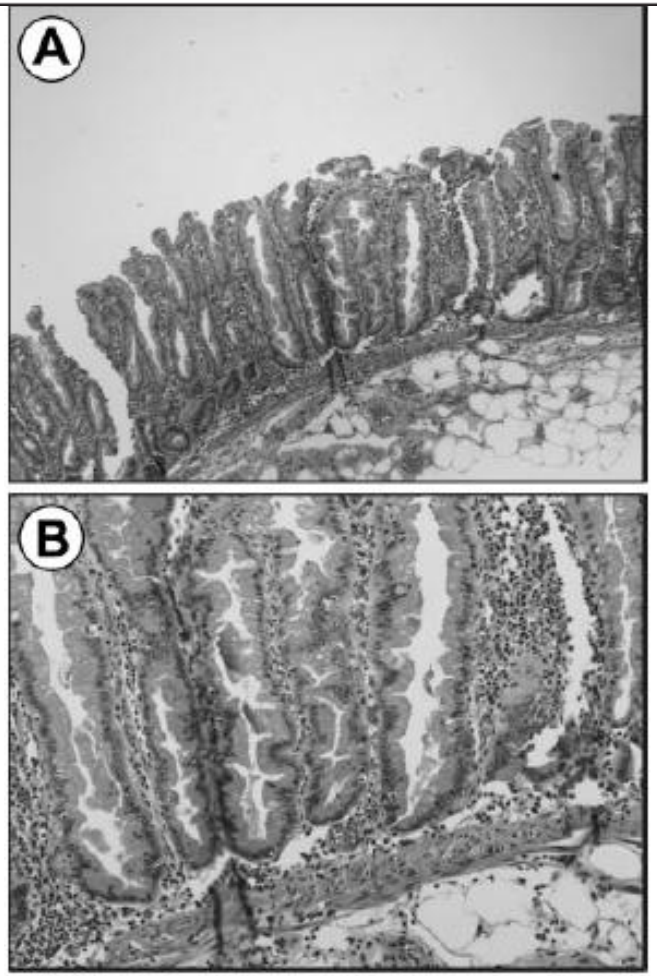


Figure 2 The architectural features of sessile serrated adenoma are shown here in (A) low power field and (B) high power field illustrating the branching dilated crypts at the lower base parallel to the muscularis mucosa creating an inverted T or L shape.

Serrated polyps of the colon

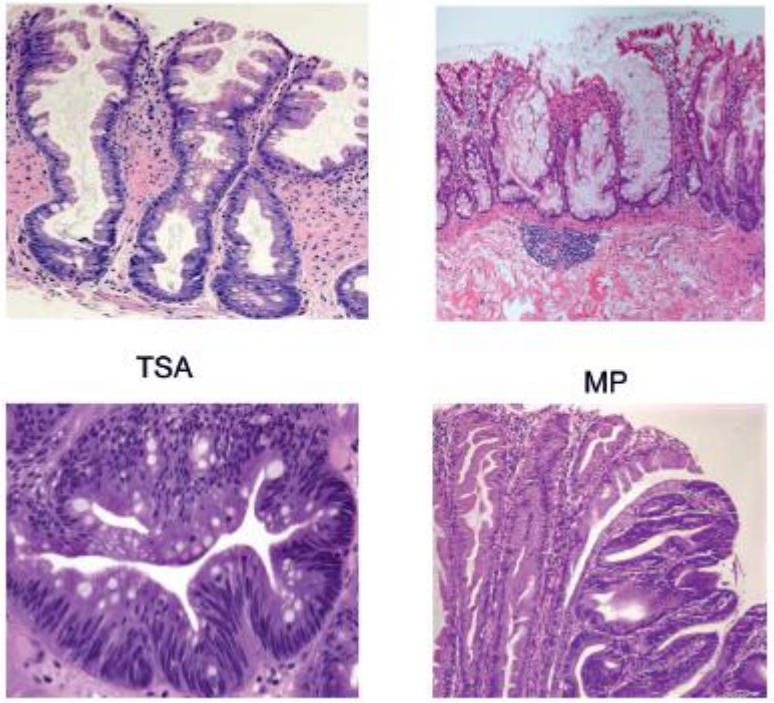
Aravind Sugumar and Frank A Sinicrope*

Address: Division of Gastroenterology & Hepatology and Division of Oncology, Mayo Clinic and Mayo College of Medicine, 200 First Street SW, Rochester, MN 55905, USA

* Corresponding author: Frank A Sinicrope (sinicrope.frank@mayo.edu)

F1000 Medicine Reports 2010, 2:89 (doi:10.3410/M2-89)

Figure 2. Types of serrated polyp



- "overlaps" in serrated polyps
- variations in terminology and diagnostic criteria
- unreliable molecular data

We need consensus criteria!

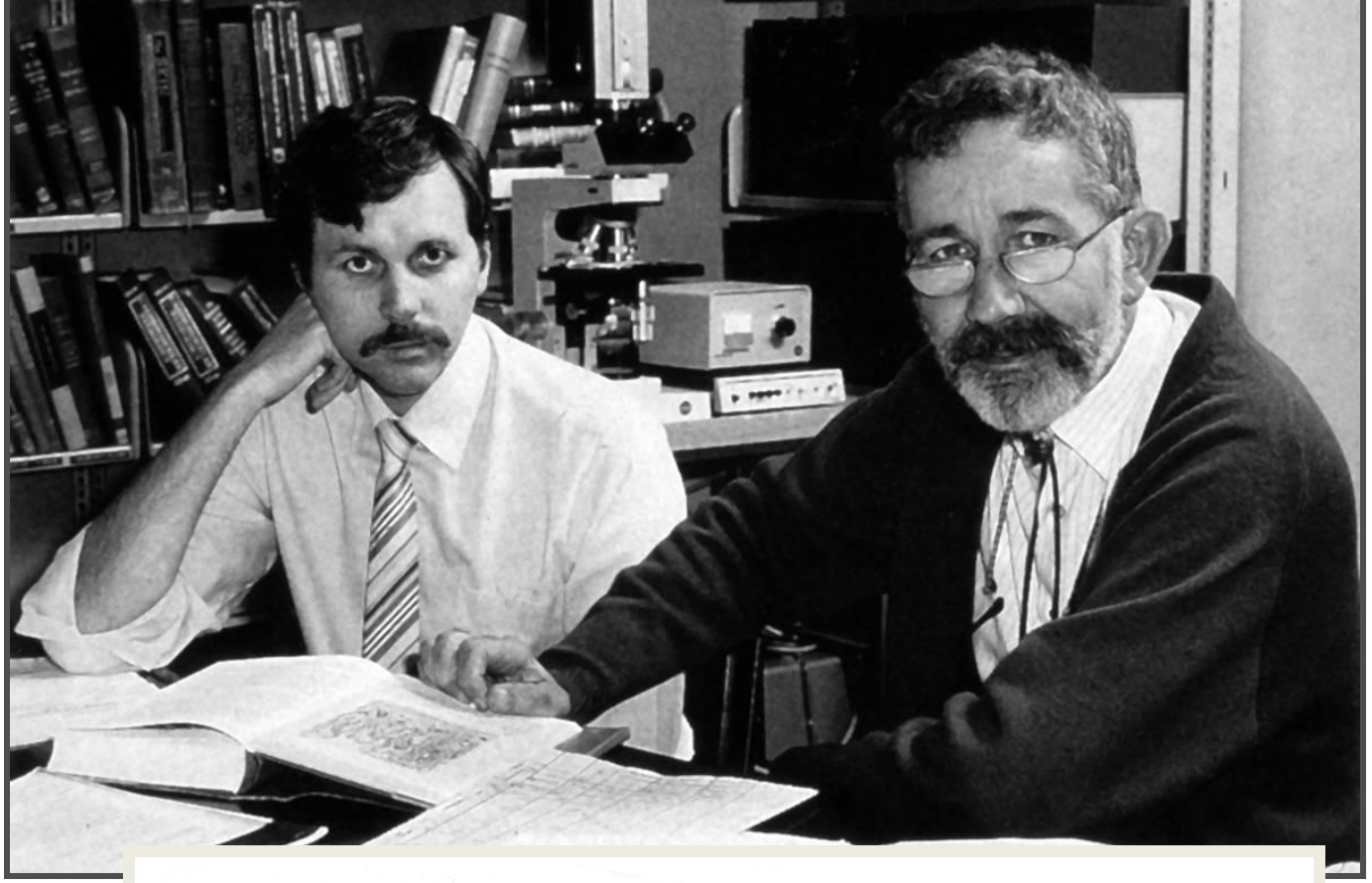
LET’S GO BACK IN TIME A BIT…

Dr Castleman – Harvard

- In 1951 Dr. Benjamin Castleman succeeded Dr. Mallory as Chief of Pathology and Editor of the Case Records of the Massachusetts General Hospital in NEJM.
- **Castleman's disease of lymph nodes**.
- Armed Forces Institute of Pathology fascicles on tumors of the thymus and parathyroid glands.
- Dr. Castleman's former residents created the Benjamin Castleman Award, which is presented annually at the meeting of the United-States-Canadian Academy of Pathology to a young pathologist who has performed outstanding research.

NEJM 1962; 267: 469-475

- Castleman re-evaluated polyps that had been believed to contain cancer from another study. Essentially no follow-up.
- Concluded "The overwhelming majority of cancers in the colon arise as cancer *de novo* or in villous adenomas, not in adenomatous polyps. The adenomatous polyp is a lesion of negligible malignant potential."



UNIDENTIFIED CURVED BACILLI IN THE STOMACH OF PATIENTS WITH GASTRITIS AND PEPTIC ULCERATION*

BARRY J. MARSHALL J. ROBIN WARREN

Departments of Gastroenterology and Pathology, Royal Perth Hospital, Perth, Western Australia

Two Australians win Nobel Prize in Medicine

Awarded for work on peptic ulcer disease

Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD, Schapiro M, Bond JH, Panish JF, et al.
Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med. 1993 Dec 30;329(27):1977-81.

NEJM, Cont

- 1418 patients had a complete colonoscopy during which one or more adenomas of the colon or rectum were removed.
- Follow-up colonoscopy [average 5.9 years]
- Colorectal cancer [CRC] incidence compared with that in 3 reference groups; 2 cohorts in which colonic polyps were not removed and one general-population registry adjusted for sex, age, polyp size.

Cont

- 5 asymptomatic early-stage CRC (malignant polyps) detected by colonoscopy (3 at 3 years, one at 6 years, and one at 7 years). No symptomatic cancers were detected.
- The numbers of CRC expected on the basis of the rates in the three reference groups were 48.3, 43.4, and 20.7, for reductions in the incidence of colorectal cancer of 90, 88, and 76 percent, respectively ($P < 0.001$).

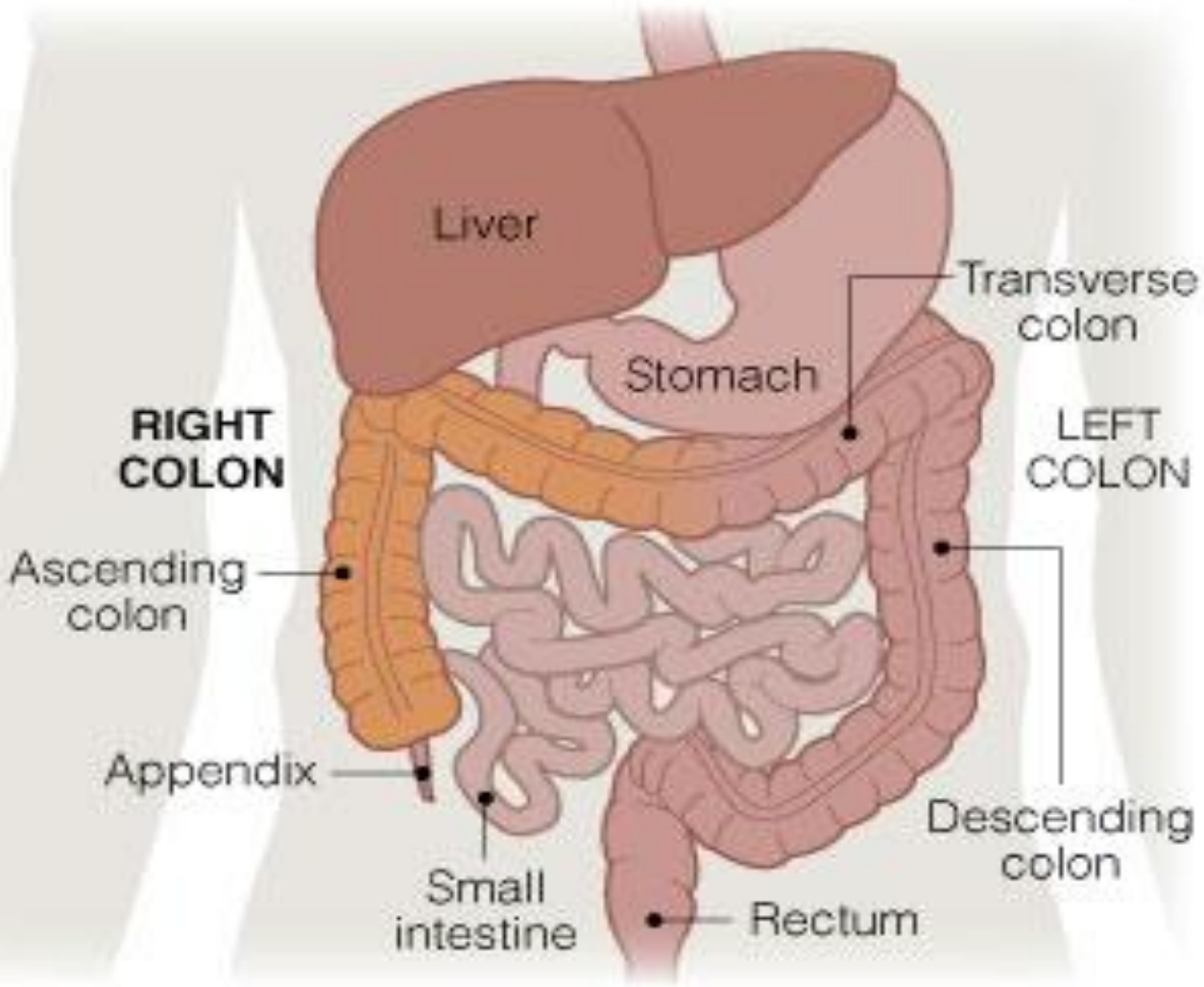
Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of Colonoscopy and Death From Colorectal Cancer: A Population-Based, Case-Control Study. Ann Intern Med. 2008 Dec 15. [Epub ahead of print]

Imperfect Test For a Cancer

A Canadian study found that colonoscopies miss more cancers than previously thought.

Colonoscopies missed nearly all cancers in the right colon, where cancers are harder to detect, and roughly a third of cancers arising in the left colon.

Source: Annals of Internal Medicine



THE NEW YORK TIMES

Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of Colonoscopy and Death From Colorectal Cancer: A Population-Based, Case-Control Study. Ann Intern Med. 2008 Dec 15. [Epub ahead of print]

- Case control study of patients diagnosed with colorectal cancer between 1996-2001 and died by 2003
- 0f 10,292 cases [people who were ***DEAD*** of colorectal cancer], 7% had previous colonoscopy
- Among 51,460 controls, 9.8% had previous colonoscopy
- Colonoscopies performed between 1/1/1992 and 6 m prior to dx of CRC

Canadian Study

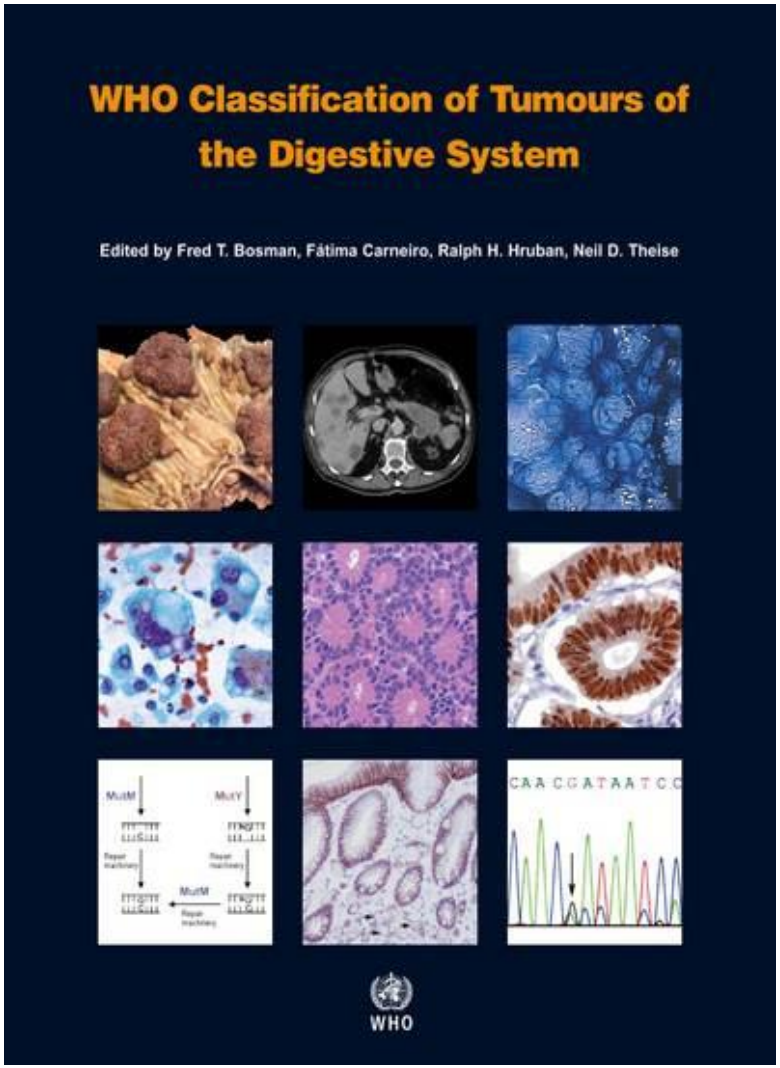
- Odds ration for association between complete colonoscopy and CRC reduction was ***0.33 for left-sided lesions***
- *0.99 for right sided lesions*

Why???

- Colonoscopy was performed by non gastroenterologists 69% of the time
- ***NO ONE KNEW HOW TO RECOGNIZE RIGHT SIDED PRECURSORS ENDOSCOPICALLY OR HISTOLOGICALLY***
- The hope – we will do better in a few more years [although this study is different from prospective method]

Another problem

- Many women simply do not have colons – some do not even have a GI tract at all.



Serrated Polyps

- Hyperplastic polyp (>75%)
- Sessile serrated adenoma/polyp (15-25%)
- (Traditional) serrated adenoma (<10%)

- (Ad)Mixed polyp
- Sessile serrated adenoma/polyp with dysplasia

- Hyperplastic polyposis
- Serrated polyposis

WHO 2010

WHO Classification of Tumours of the Digestive System
Consensus and Editorial meeting
IARC, Lyon, 10-12 December 2009

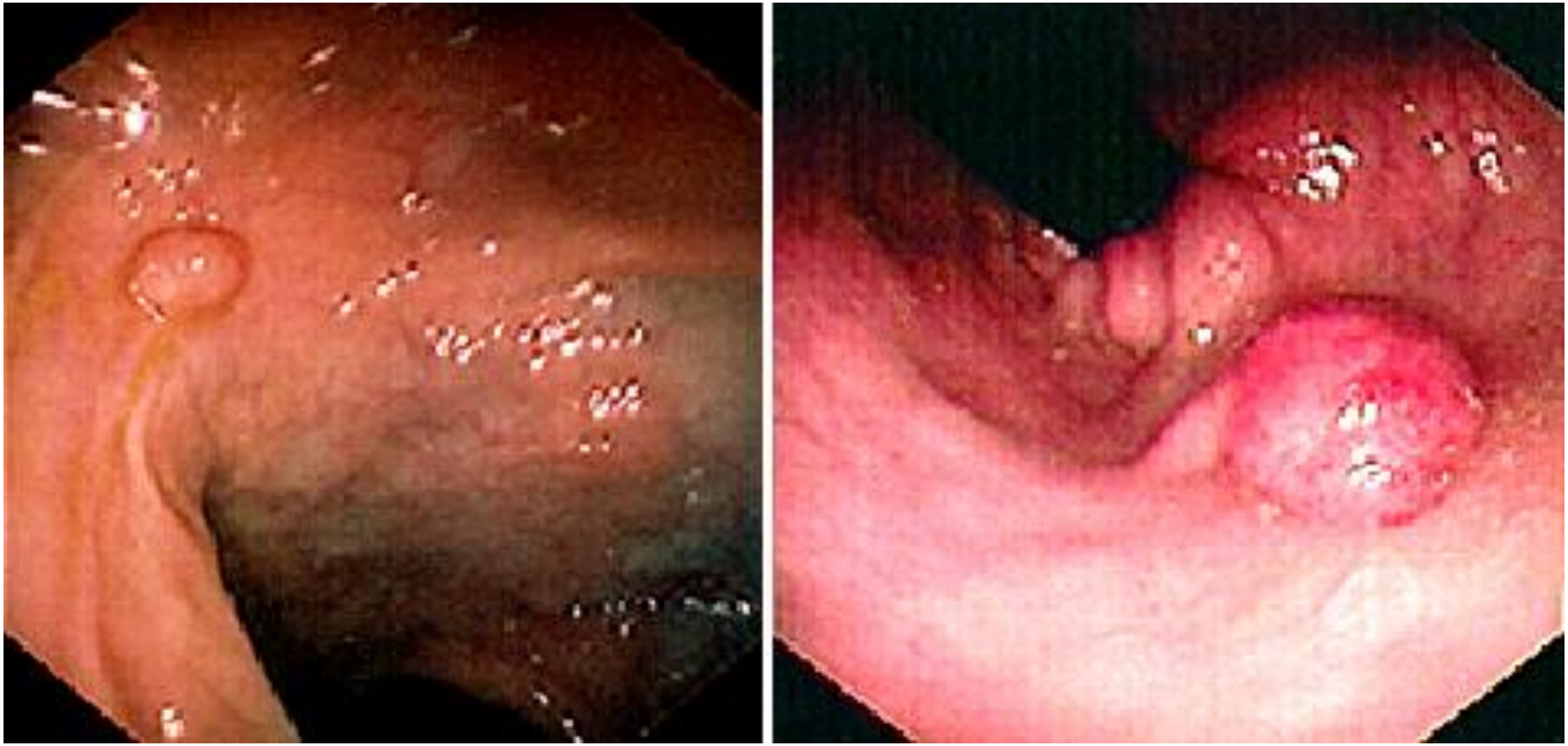
Serrated lesions WHO 2010

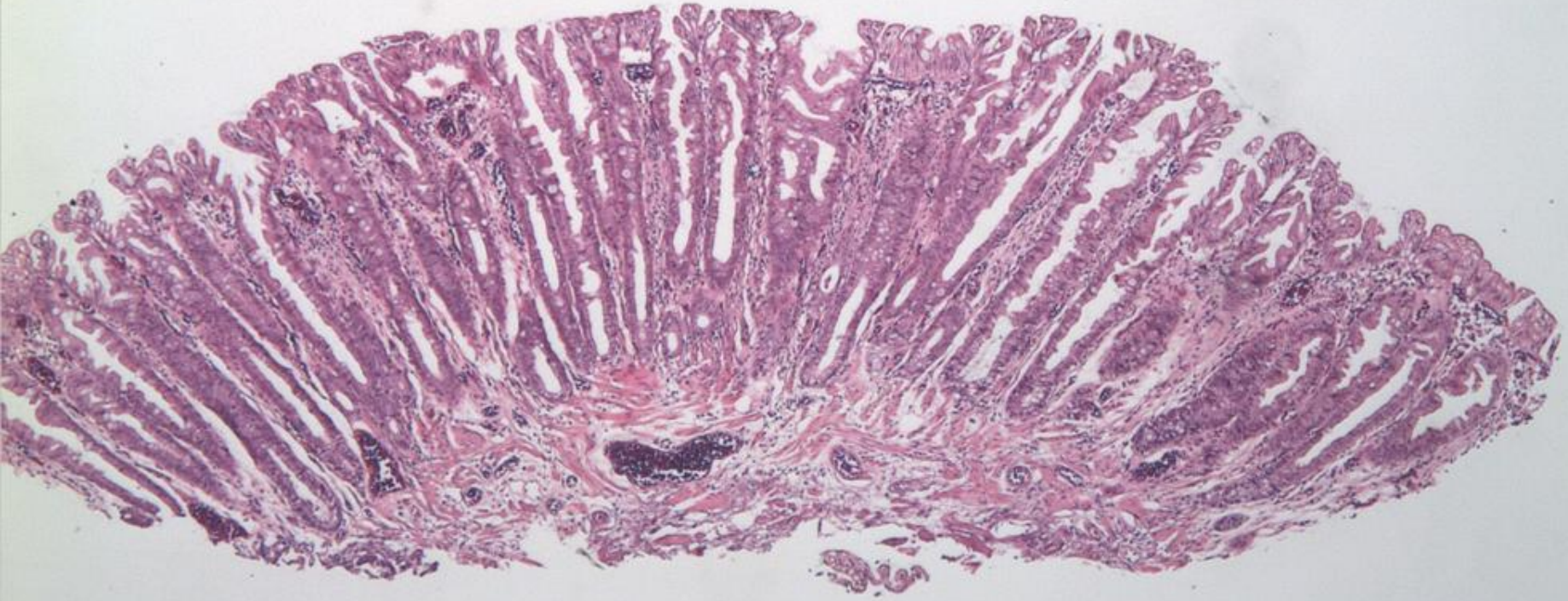
Type	Synonyms	Histological features[a]				Genetic features[b]			
		Crypts	Proliferation	Cytological dysplasia	Mucin type	*BRAF* mutation	*KRAS* mutation	CIMP	*MLH1* methylation
MVHP	Hyperplastic polyp; metaplastic polyp	Straight with serrations toward lumen	Located uniformly in basal portion of crypts	No	Microvesicular or mixed goblet cell & microvesicular	+++	–	+	–
GCHP	Hyperplastic polyp; metaplastic polyp	Straight, serrations may be minimal	Located uniformly in the basal portion of crypts	No	Pure goblet cells	–	+++	U	–
MP/HP	Hyperplastic polyp; metaplastic polyp	Straight, serration toward lumen	Located uniformly in the basal portion of crypts	Atypia present but appears reactive	None	U	U	U	U
SSA/P	Serrated polyp with abnormal proliferation; giant hyperplastic polyp; variant hyperplastic polyp	Crypts distorted, often dilated near base, excess serration near base	Proliferation abnormally located often away from the base of the crypts, variable from crypt to crypt	No	Usually microvesicular, sometimes with goblet cells or gastric foveolar differentiation	+++	–	+++	–
SSA/P with cytological dysplasia	Mixed hyperplastic-adenomatous polyp; advanced SSA/P	As for SSA/P	As for SSA/P but with more proliferation in cytologically dysplastic areas	Present	As for SSA/P	+++	–	+++	++
TSA	Serrated adenoma; filiform serrated adenoma	Hyperserrated in part owing to formation of ectopic crypts	Proliferation present at base of ectopic crypts	May be present, usually in the form of cells with eosinophilic cytoplasm	None or goblet cells	+[c]	+[c]	++	–
Serrated polyposis	Hyperplastic polyposis; giant hyperplastic polyposis	Mostly SSA/P with some MVHP	As per polyp subtype	Present as disease advances	As per polyp subtype	++[c]	+[c]	+++	+

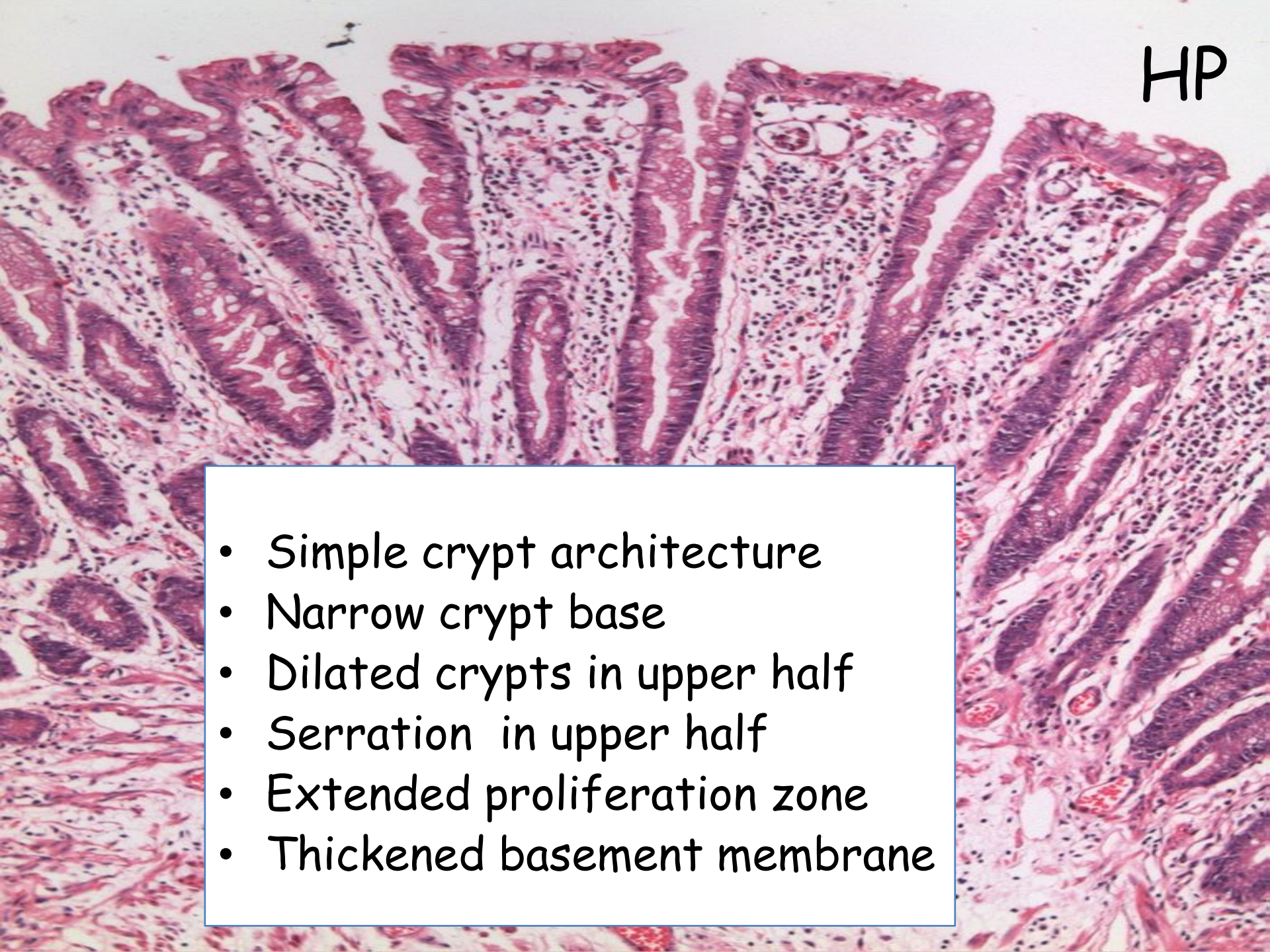
CIMP, CpG island methylator phenotype; GCHP, goblet cell-rich hyperplastic polyp; MPHP, mucin-poor hyperplastic polyp; MVHP, microvesicular hyperplastic polyp; SSA/P, Sessile serrated adenoma/polyp; TSA, traditional serrated adenoma.

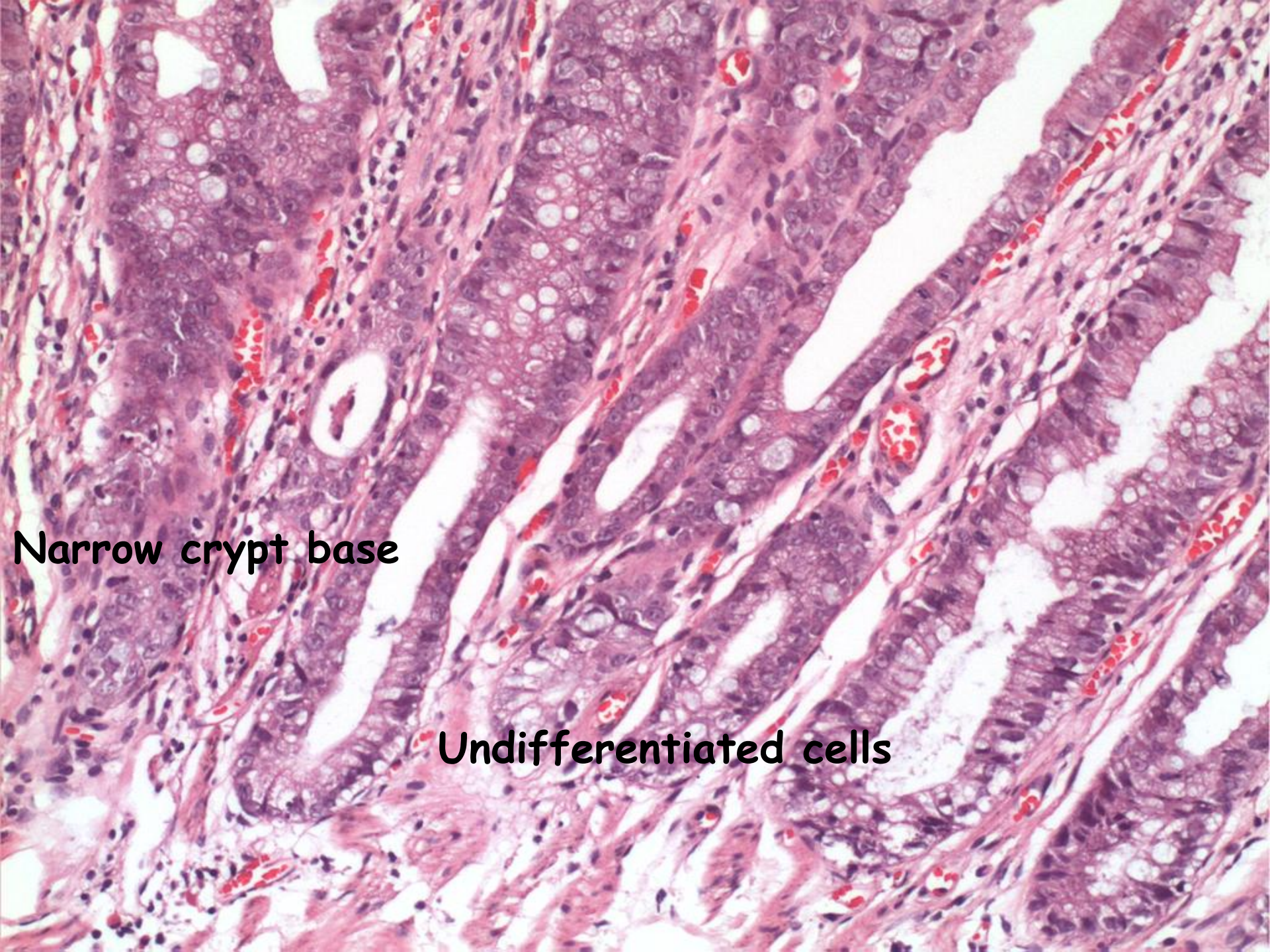
[a] Please see text for details of histology. [b] –, not present; +, present often to a limited extent or in some cases; ++ and +++, present extensively; U, unknown. [c] *KRAS* and *BRAF* mutations are mutually exclusive. Individuals only carry a mutation in one of these two genes.

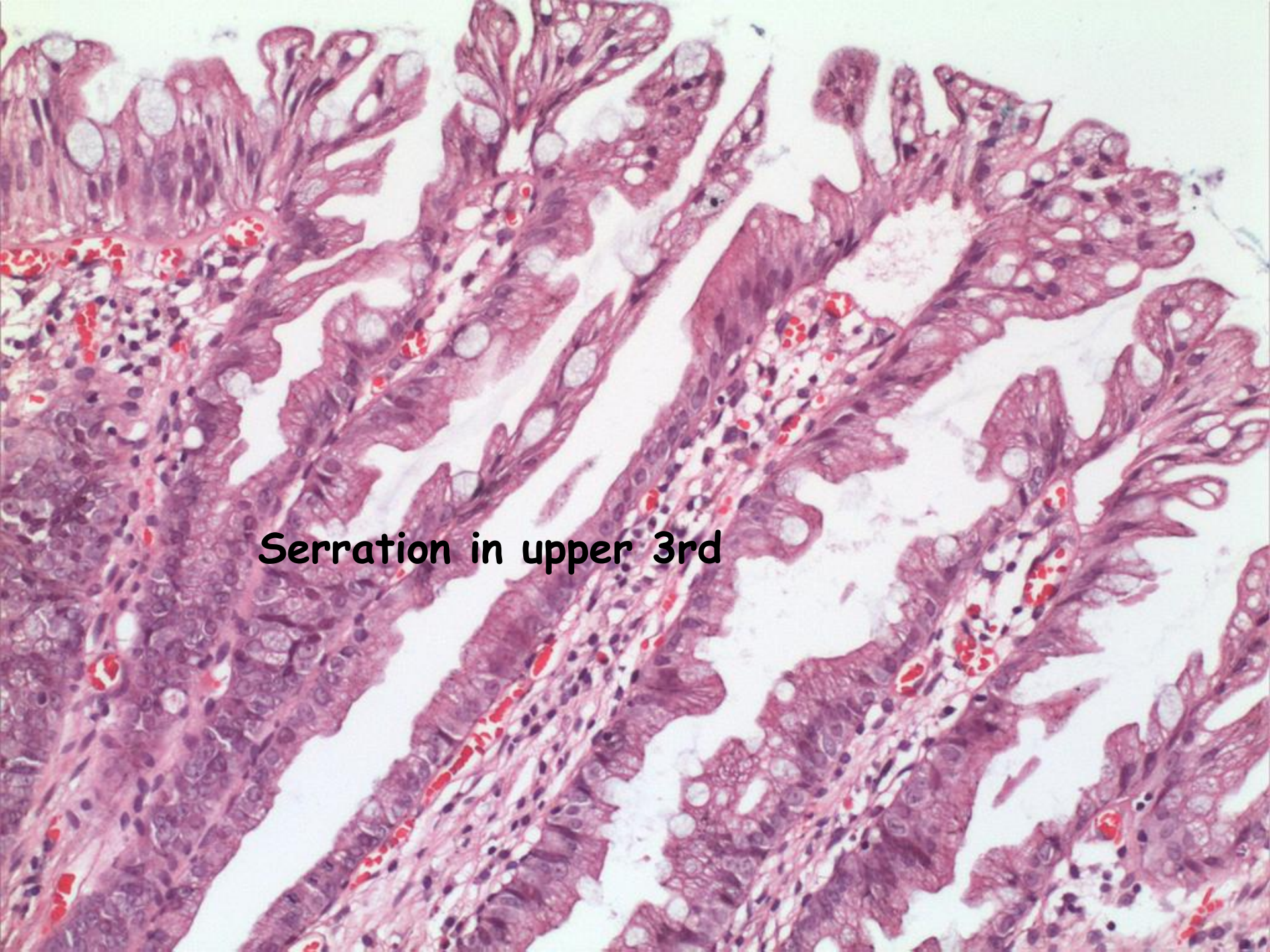
Hyperplastic Polyp

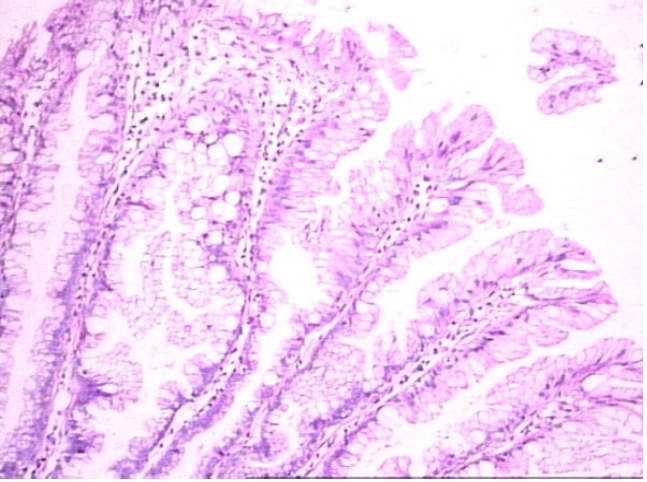


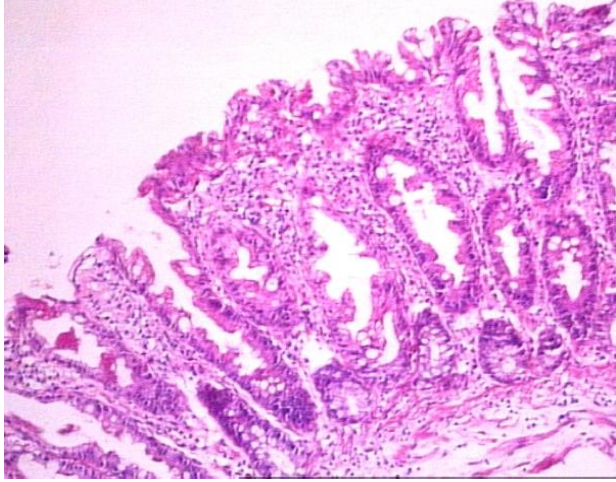
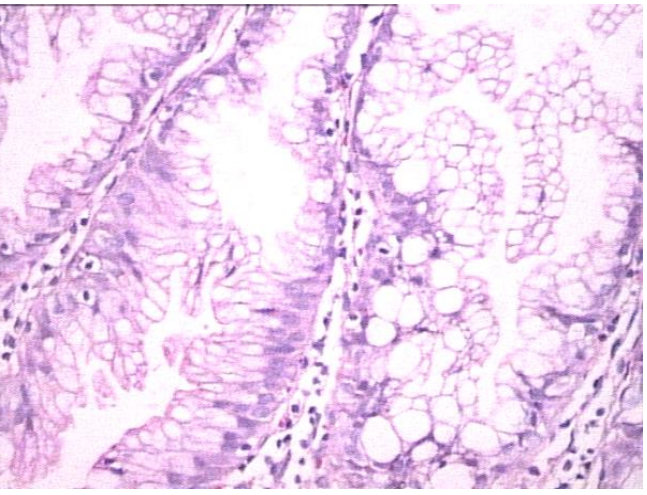
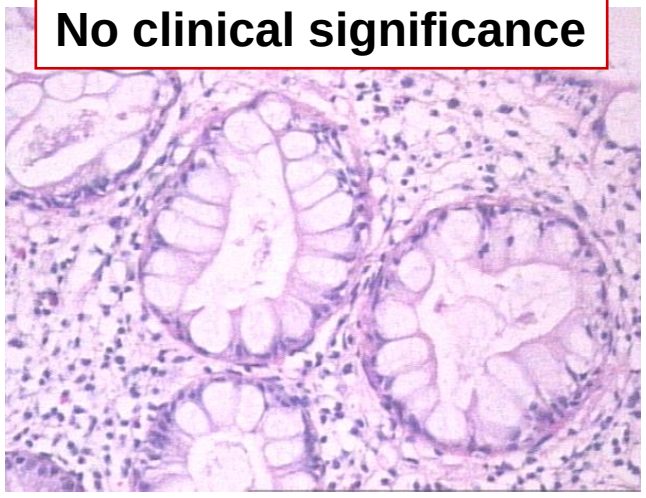
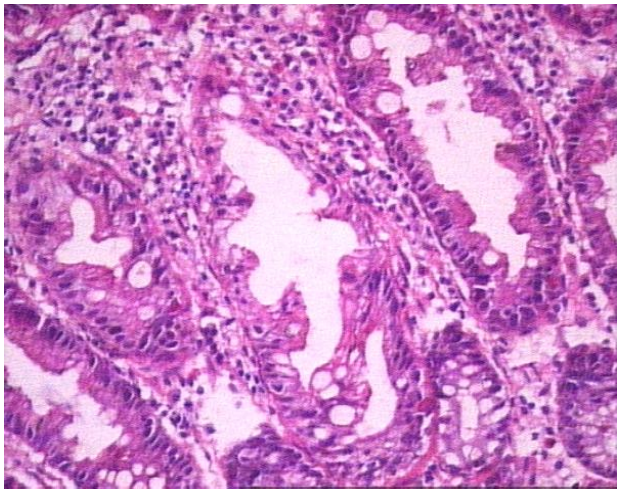



HP
• Simple crypt architecture
• Narrow crypt base
• Dilated crypts in upper half
• Serration in upper half
• Extended proliferation zone
• Thickened basement membrane


Narrow crypt base
Undifferentiated cells


Serration in upper 3rd



Not used in routine
No clinical significance

Microvesicular (MVHP)
- Commonest HP
- Entire colon
- "Serration" prominent
- Microvacuolation
- Precursor of SSA/P ?

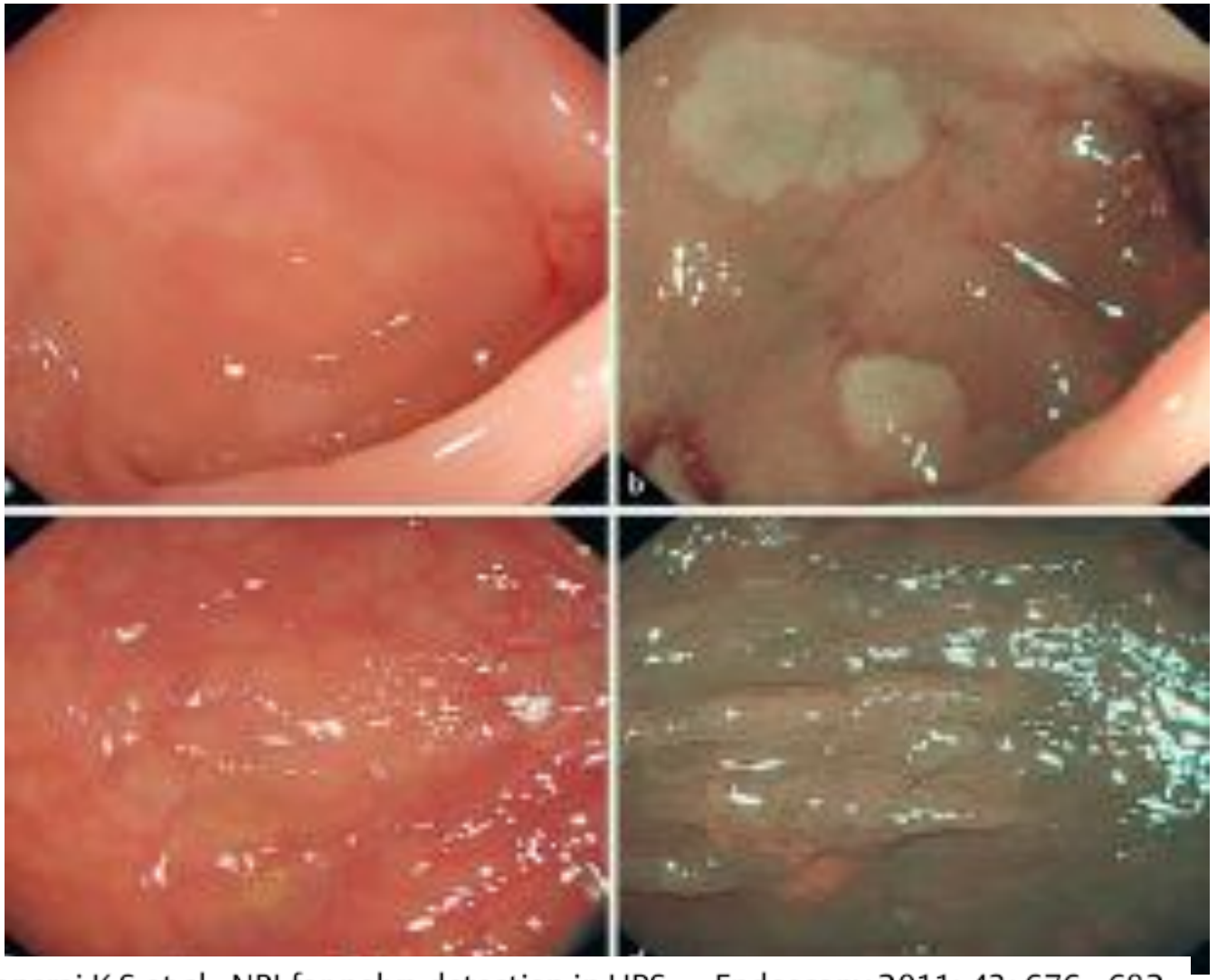
Goblet cell (GCHP)
- Second common
- Left colon
- Hyperplastic goblet cells
- "Serration" subtle

Mucin-poor (MPHP)
- Very rare
- "Serration" prominent
- Nuclear atypia present

Type	Synonyms	Histological features[a]				Genetic features[b]			
		Crypts	Proliferation	Cytological dysplasia	Mucin type	BRAF mutation	KRAS mutation	CIMP	MLH1 methylation
MVHP	Hyperplastic polyp; metaplastic polyp	Straight with serrations toward lumen	Located uniformly in basal portion of crypts	No	Microvesicular or mixed goblet cell & microvesicular	+++	–	+	–
GCHP	Hyperplastic polyp; metaplastic polyp	Straight, serrations may be minimal	Located uniformly in the basal portion of crypts	No	Pure goblet cells	–	+++	U	–
MP/HP	Hyperplastic polyp; metaplastic polyp	Straight, serration toward lumen	Located uniformly in the basal portion of crypts	Atypia present but appears reactive	None	U	U	U	U

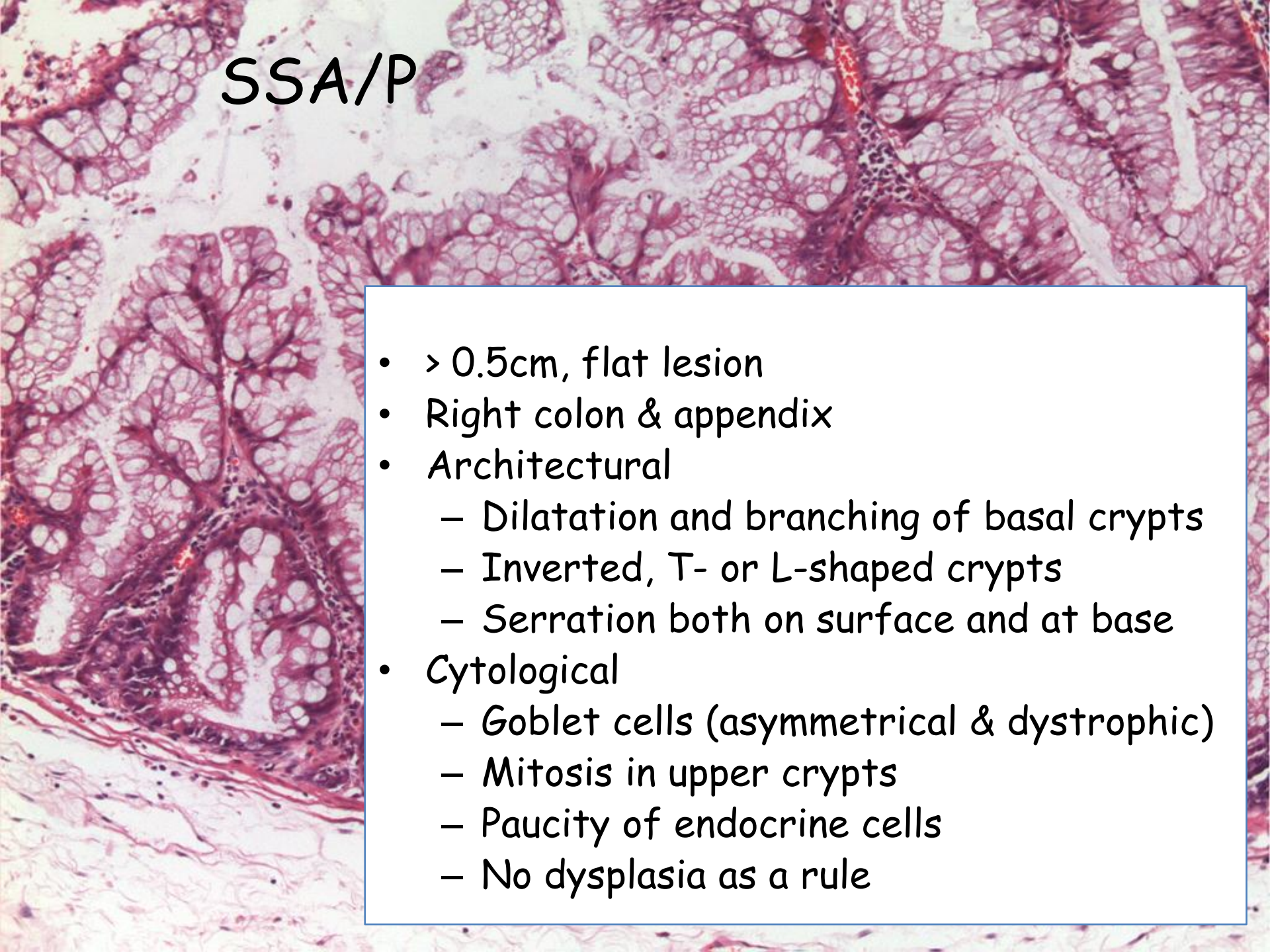
WHO 2010

Sessile Serrated Adenoma/Polyp

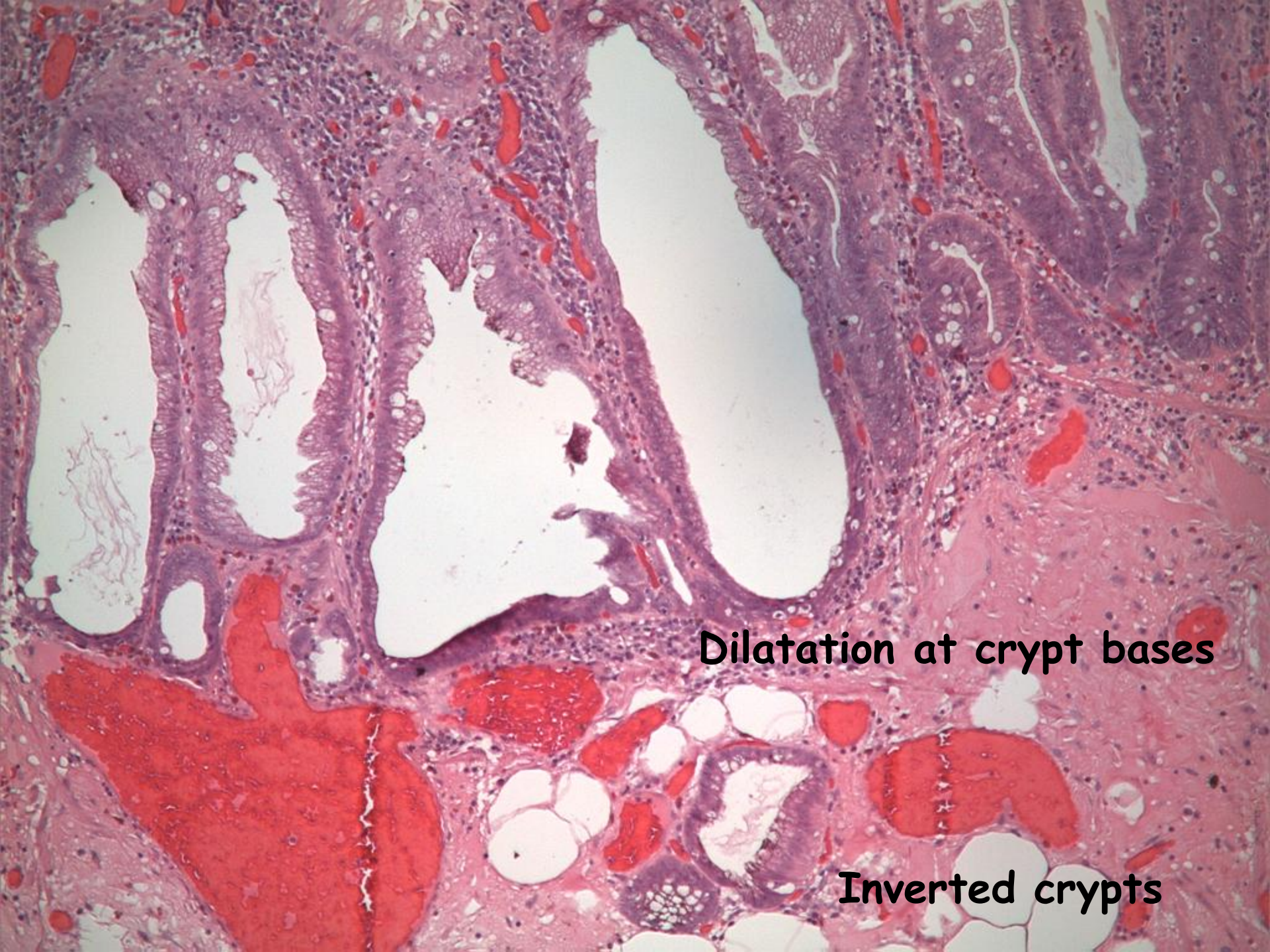


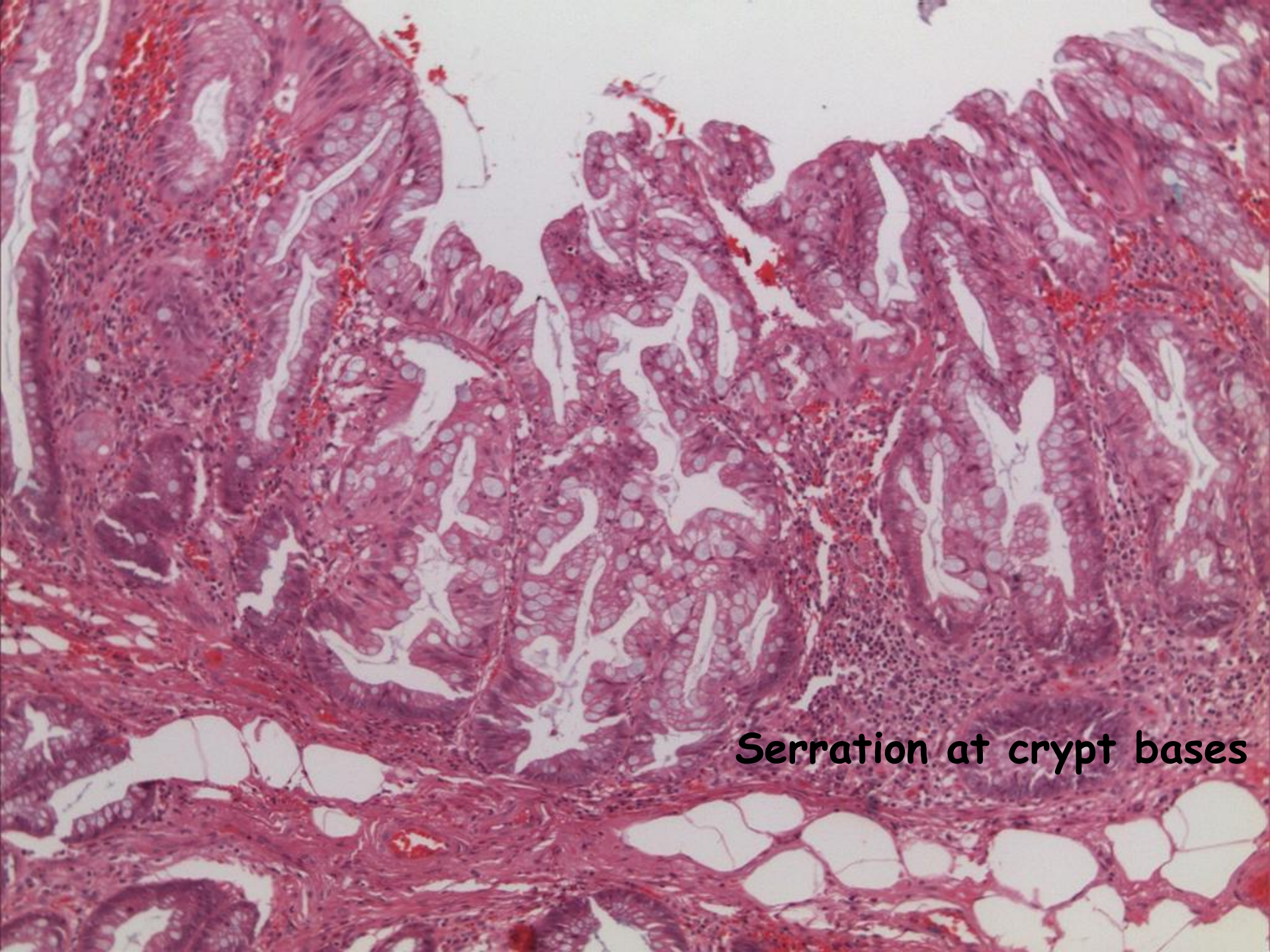
Boparai K S et al. NBI for polyp detection in HPS … Endoscopy 2011; 43: 676 – 682

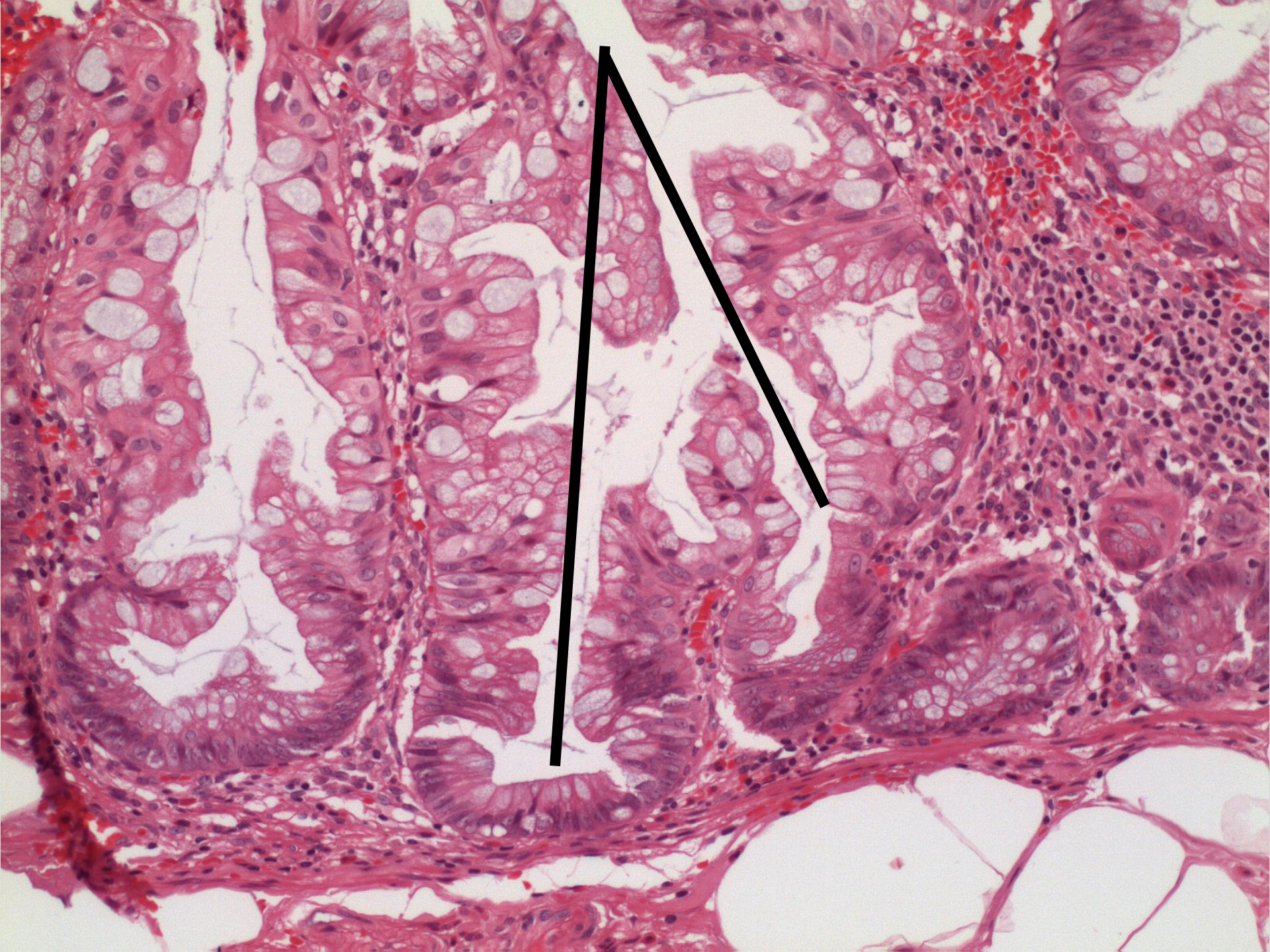
SSA/P

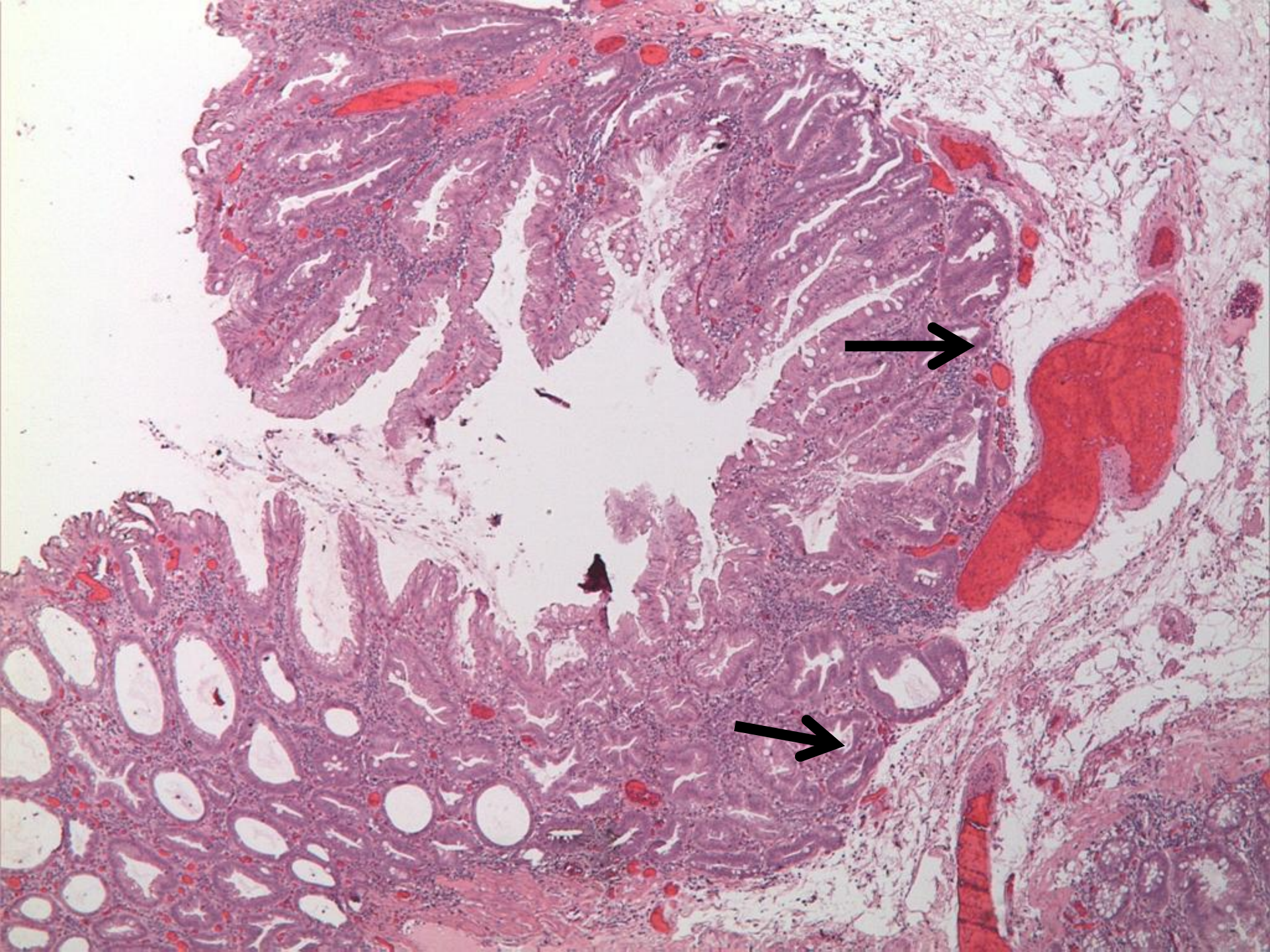


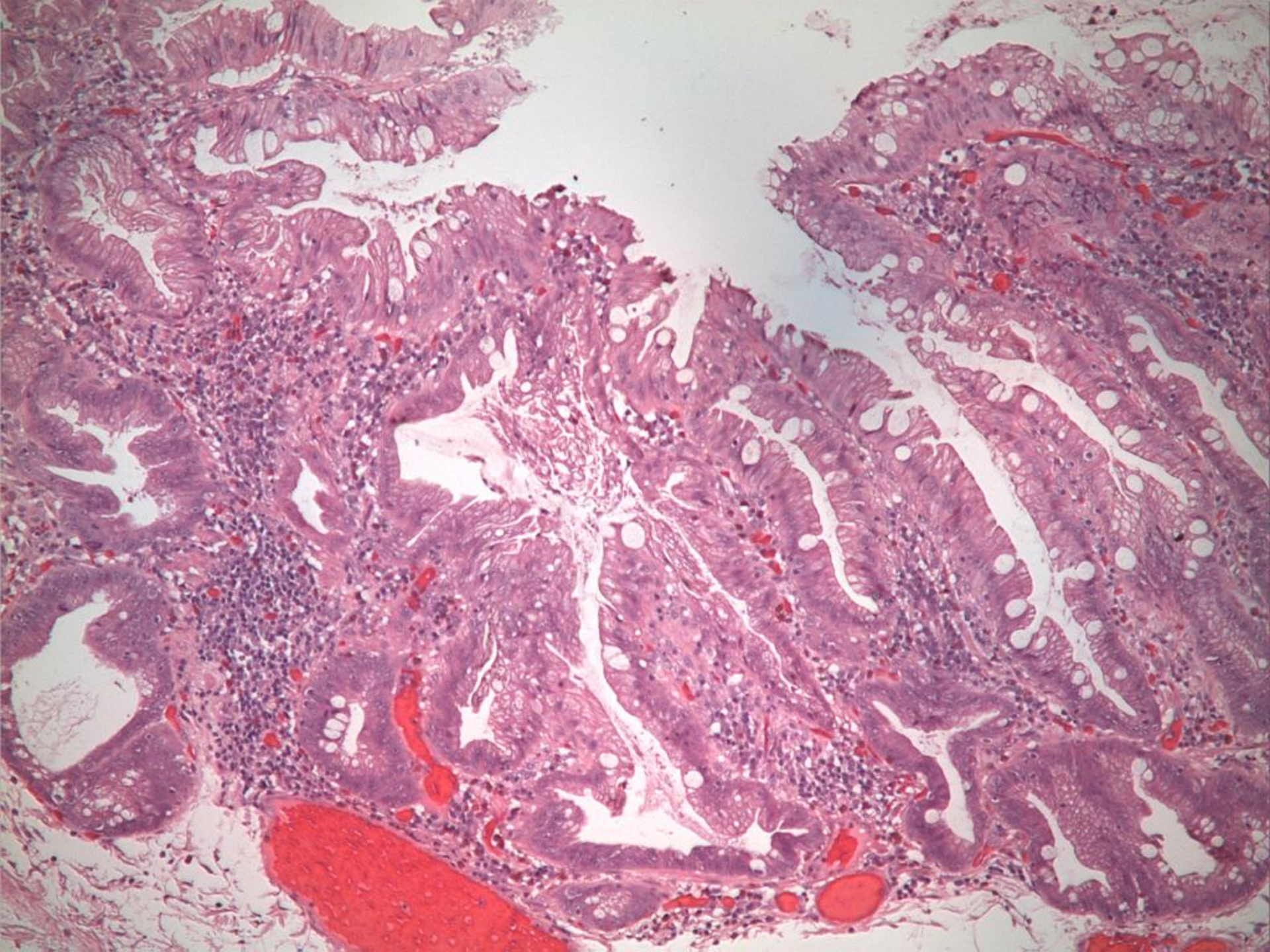
- > 0.5cm, flat lesion
- Right colon & appendix
- Architectural
  - Dilatation and branching of basal crypts
  - Inverted, T- or L-shaped crypts
  - Serration both on surface and at base
- Cytological
  - Goblet cells (asymmetrical & dystrophic)
  - Mitosis in upper crypts
  - Paucity of endocrine cells
  - No dysplasia as a rule

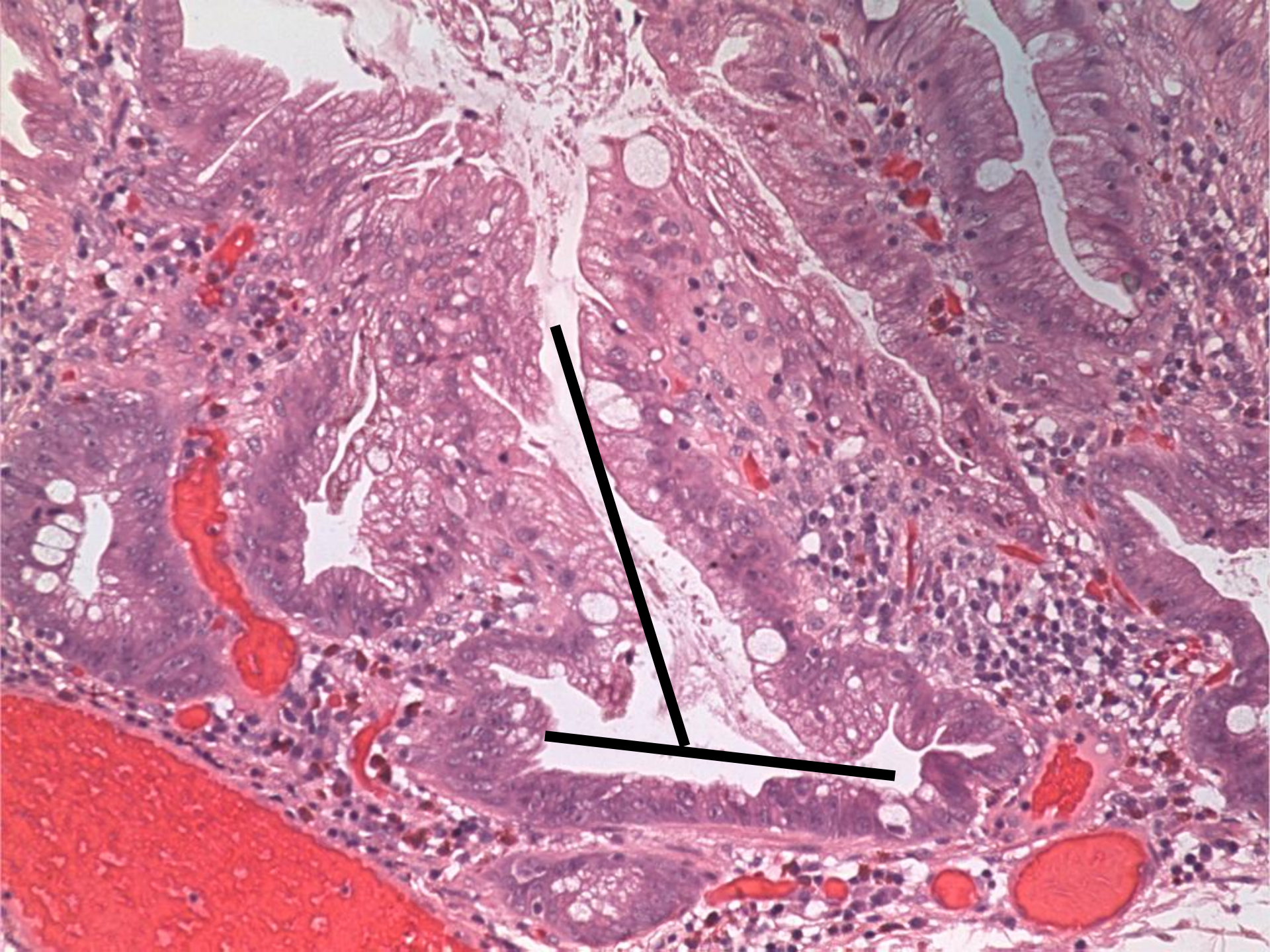

Dilatation at crypt bases
Inverted crypts

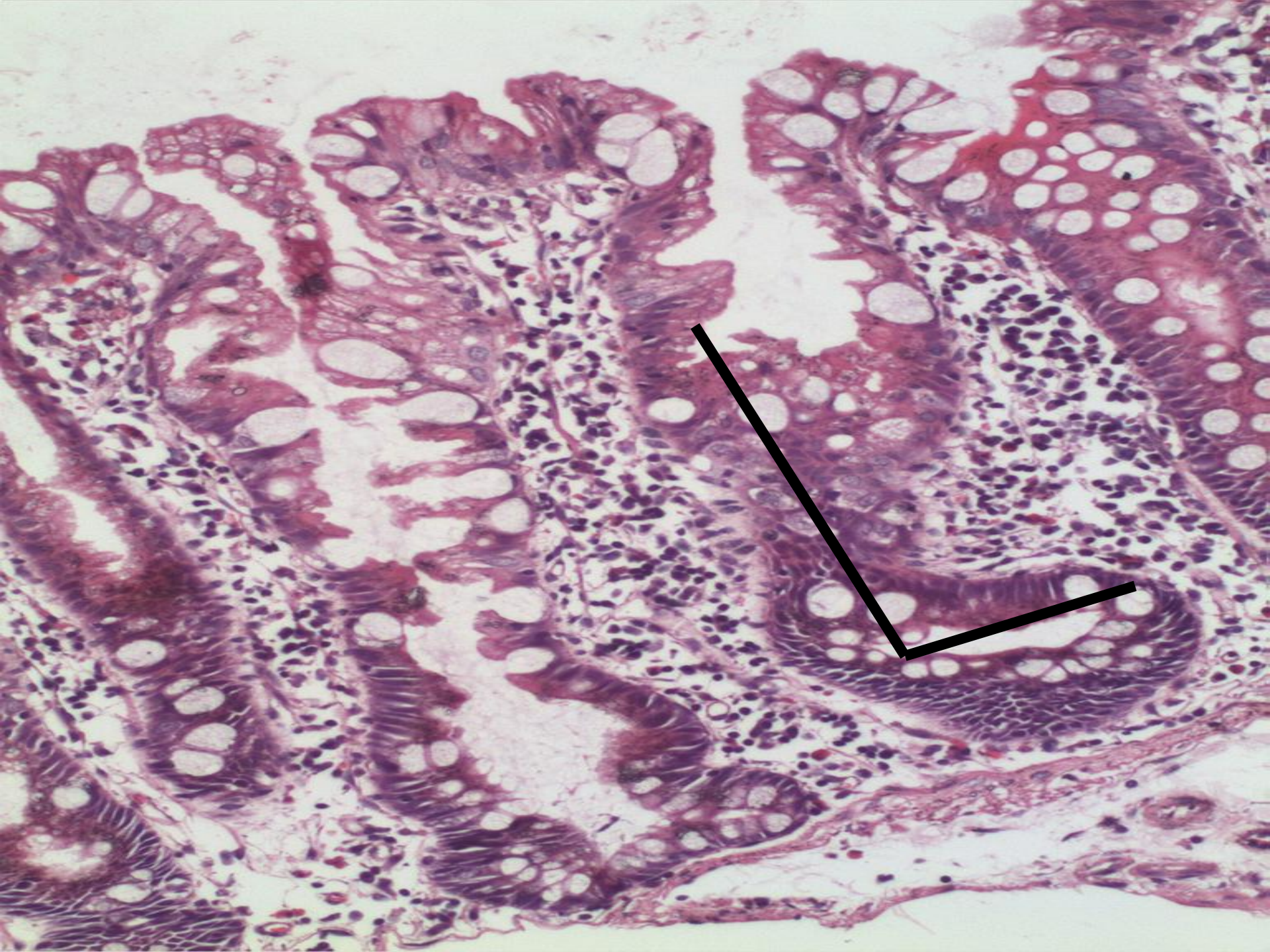

Serration at crypt bases

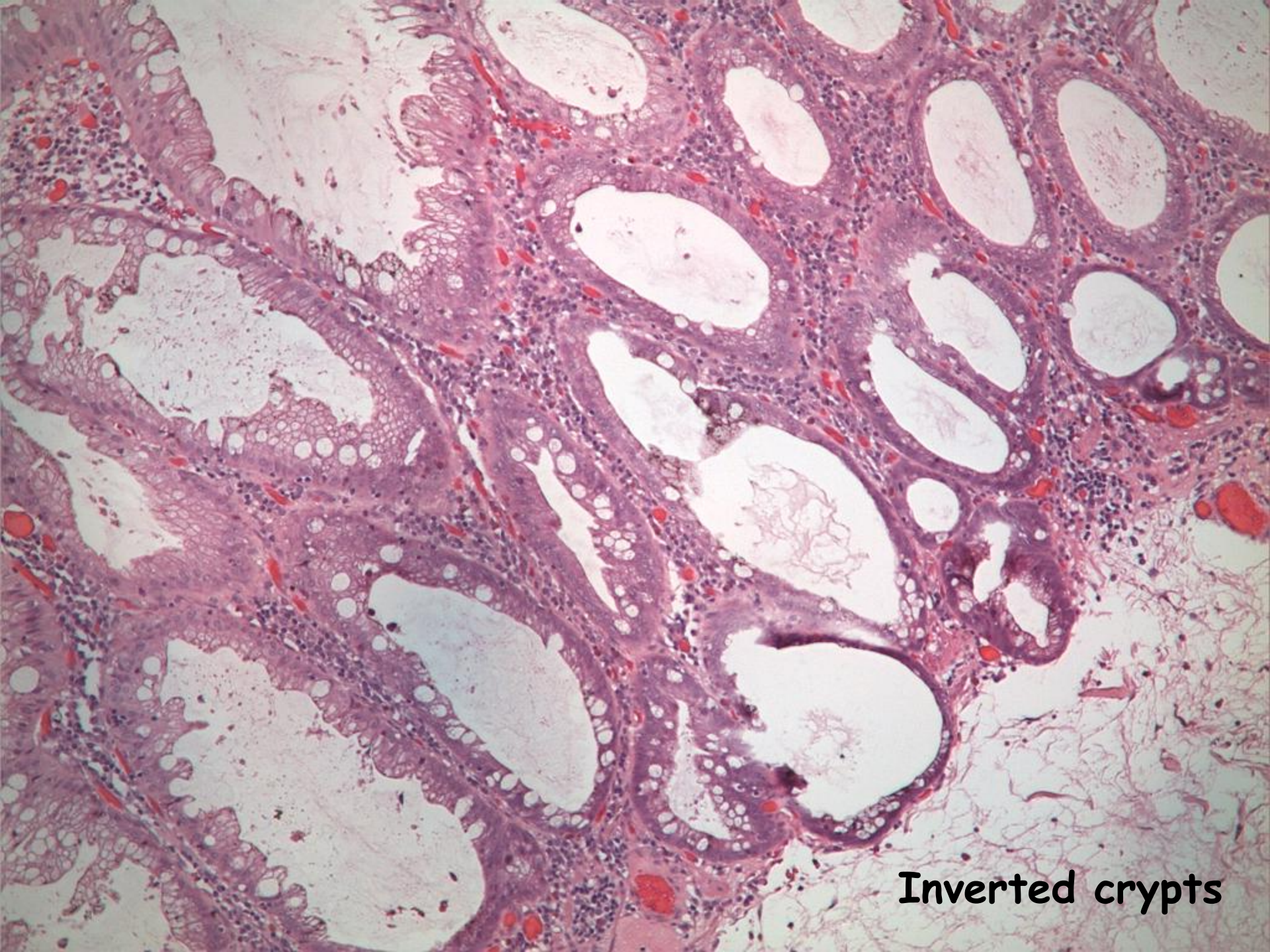


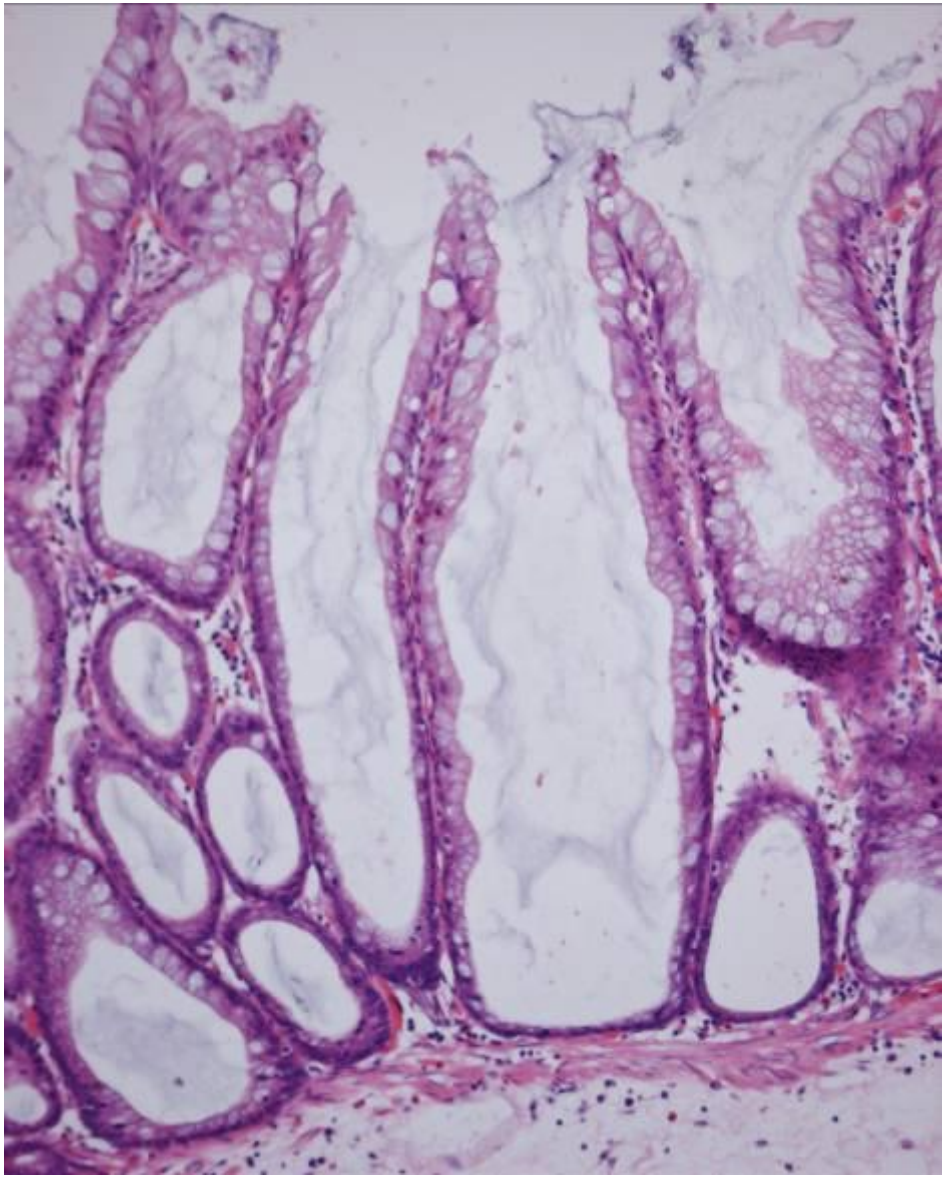


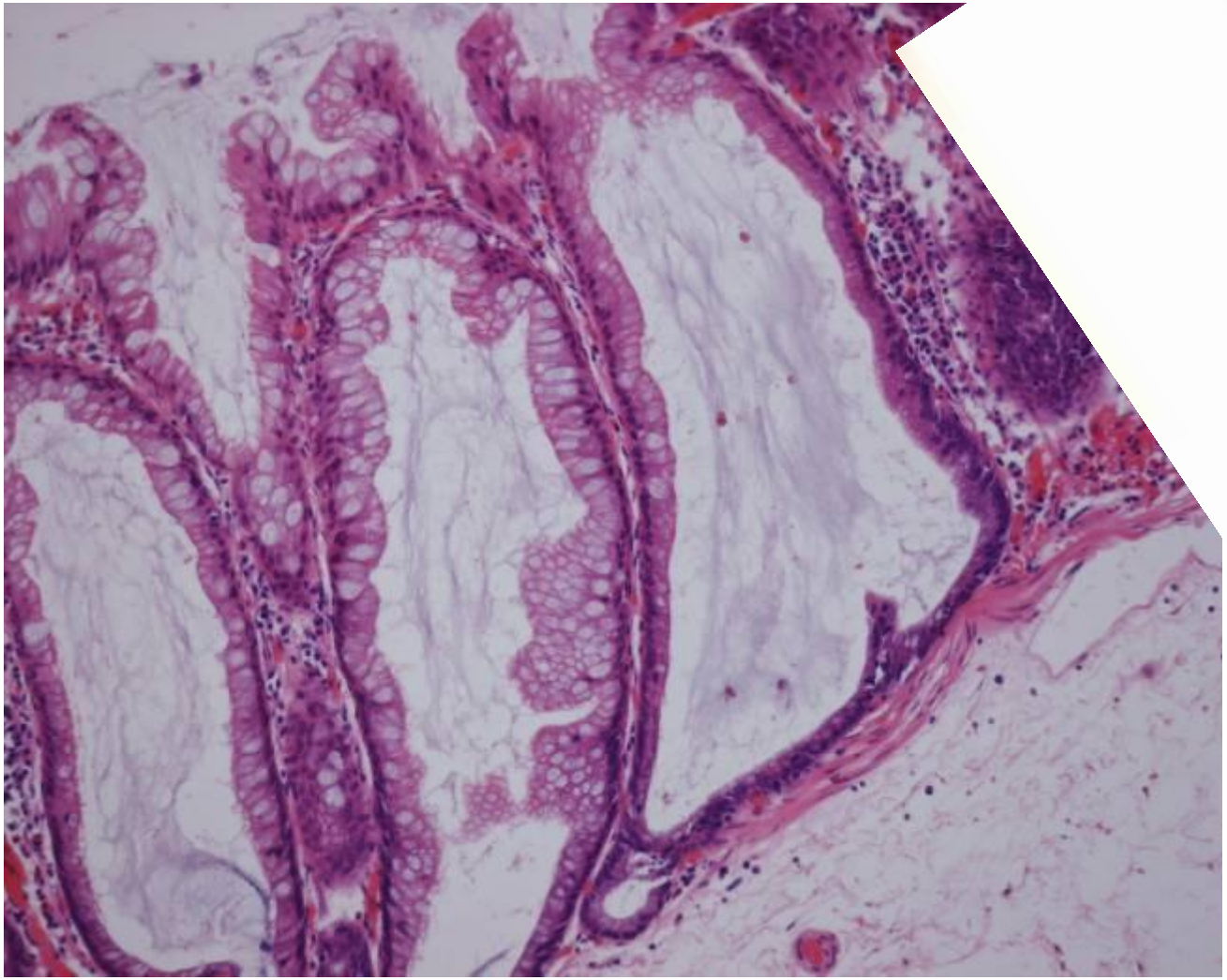




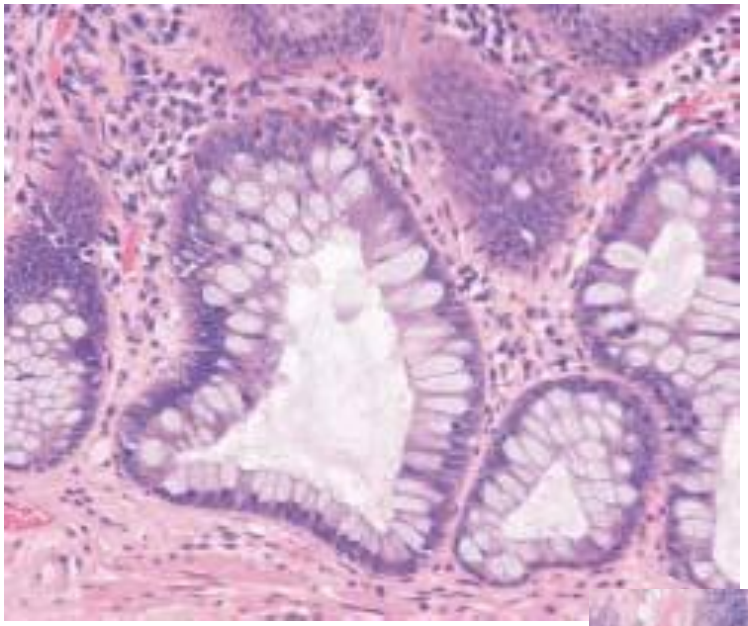


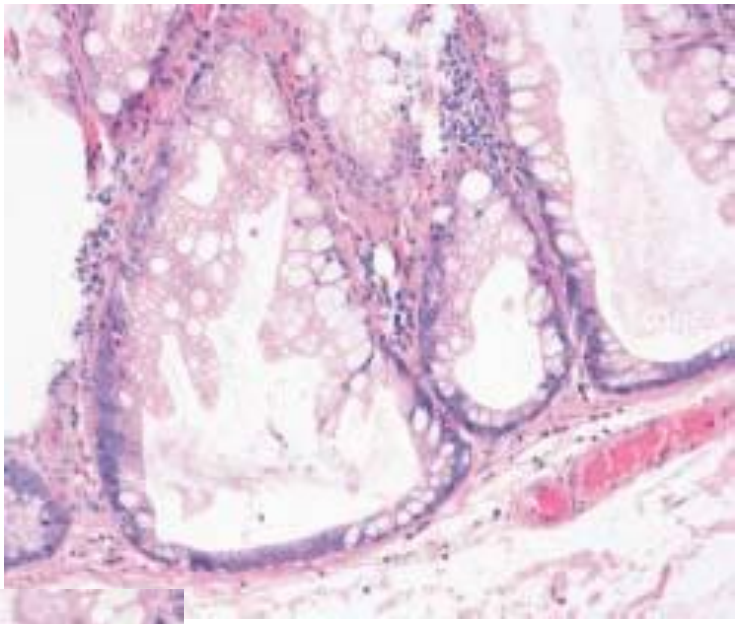

Inverted crypts

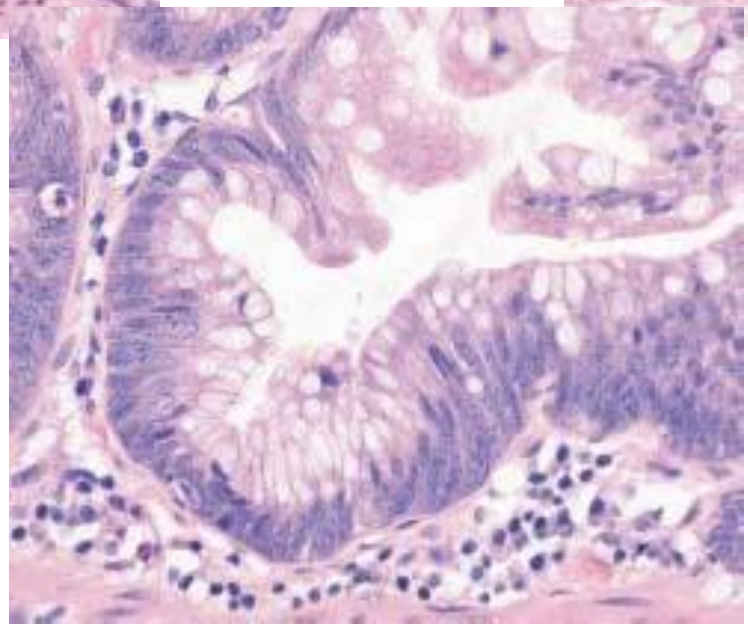




SSA/P – cell types



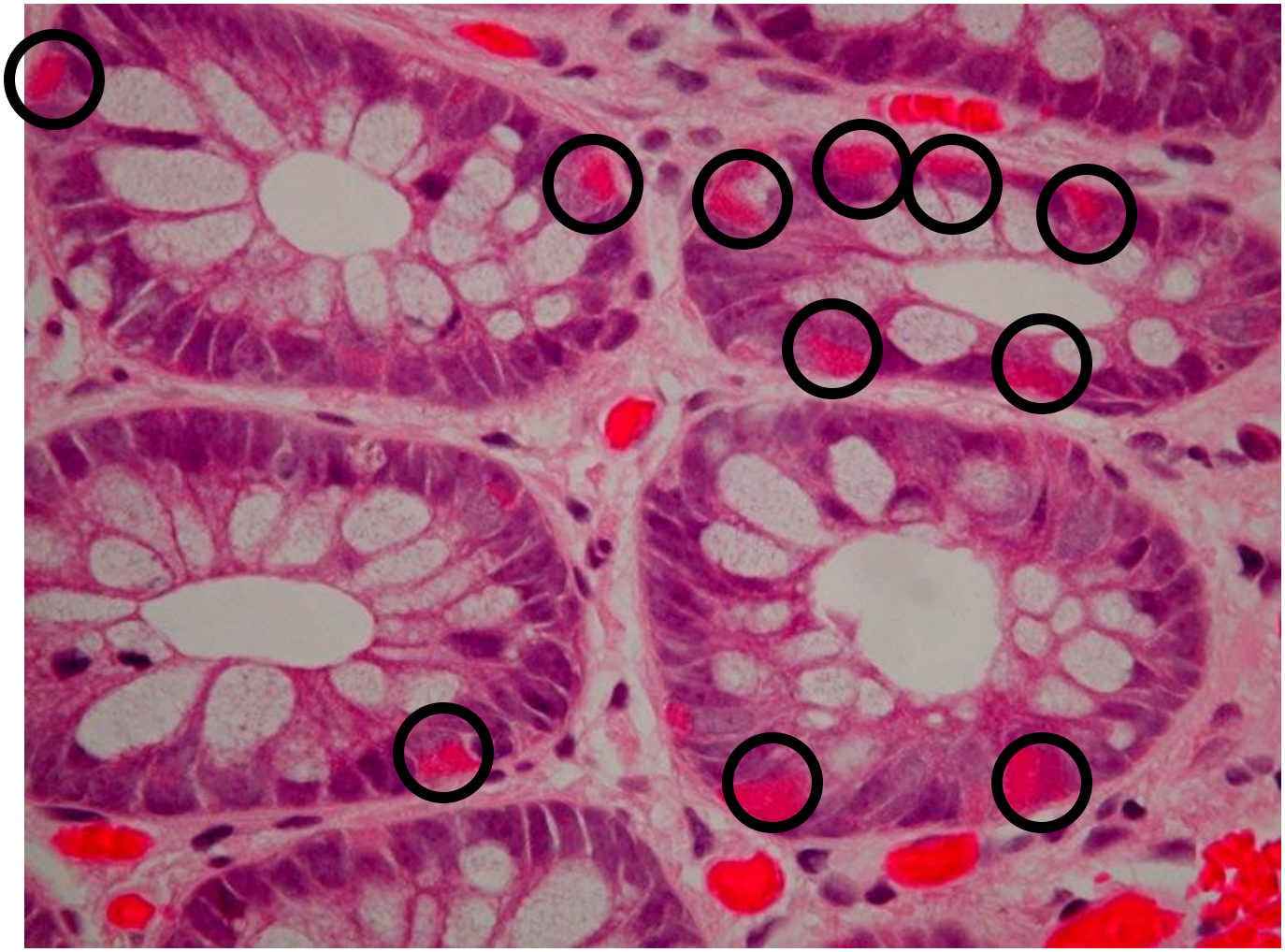




- crypt base cells (undifferentiated)
- goblet cells
- foveolar-type cells

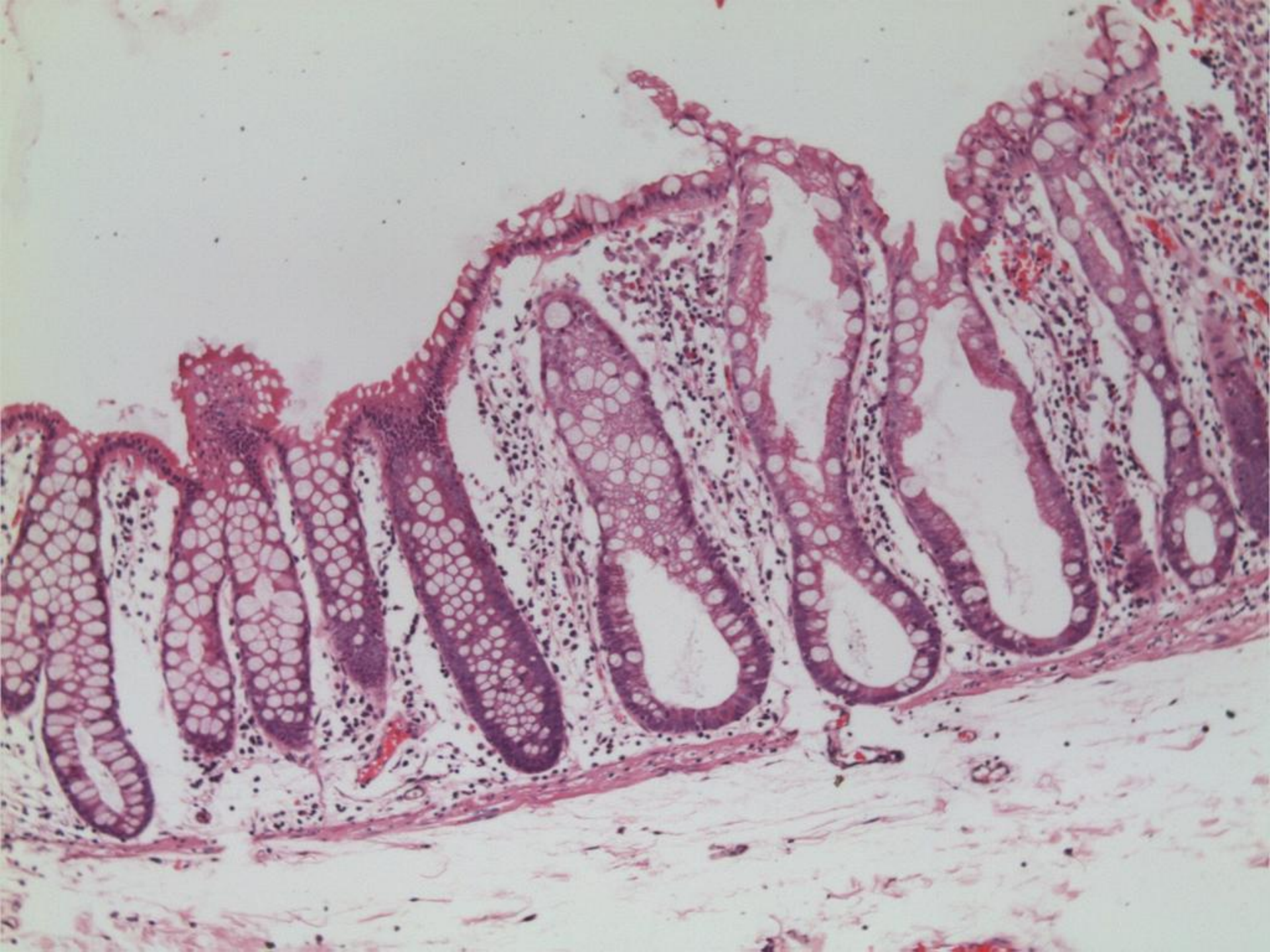
Torlakavic and Snover – "SSA"

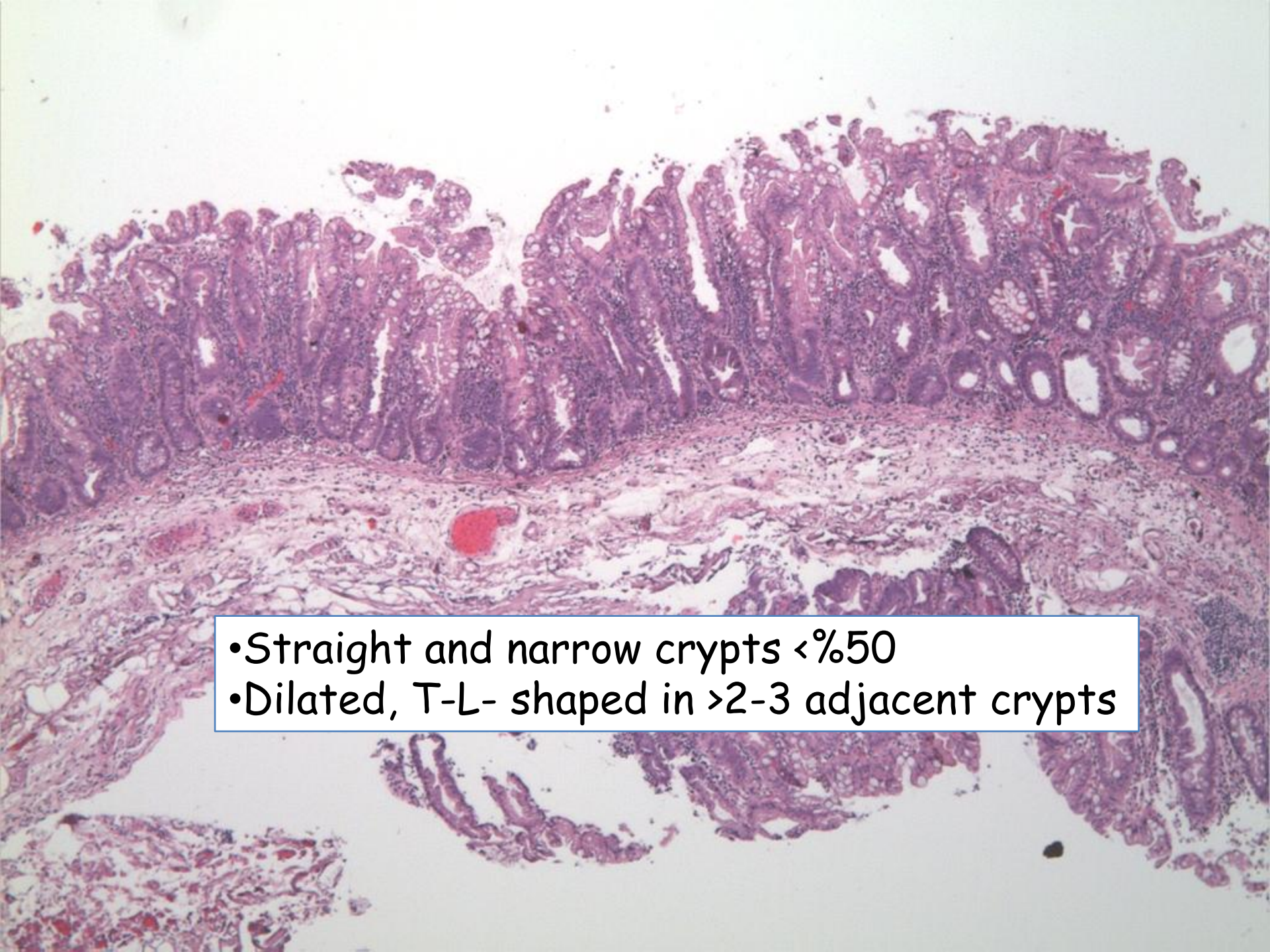
Decreased Endocrine Cells

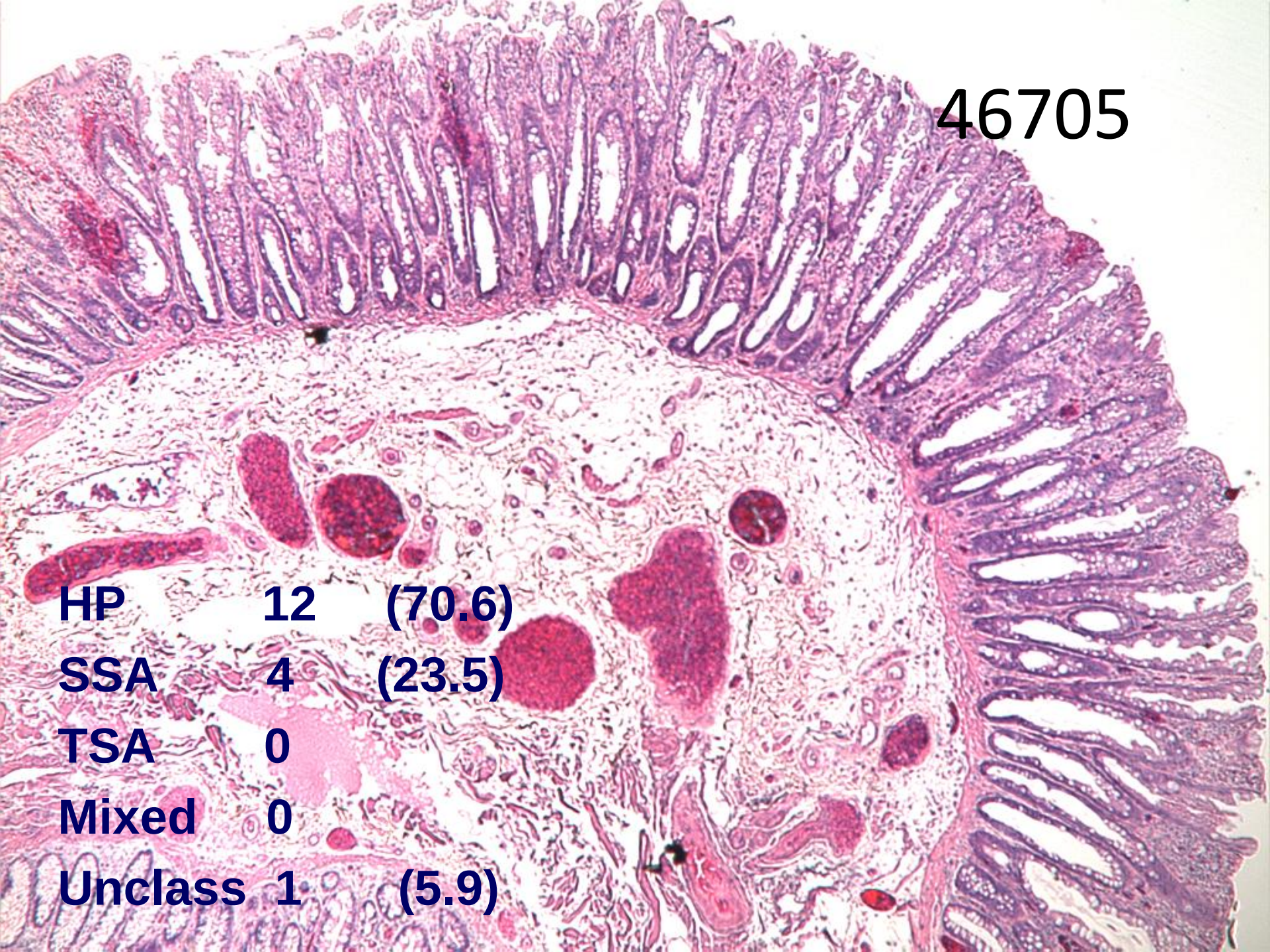


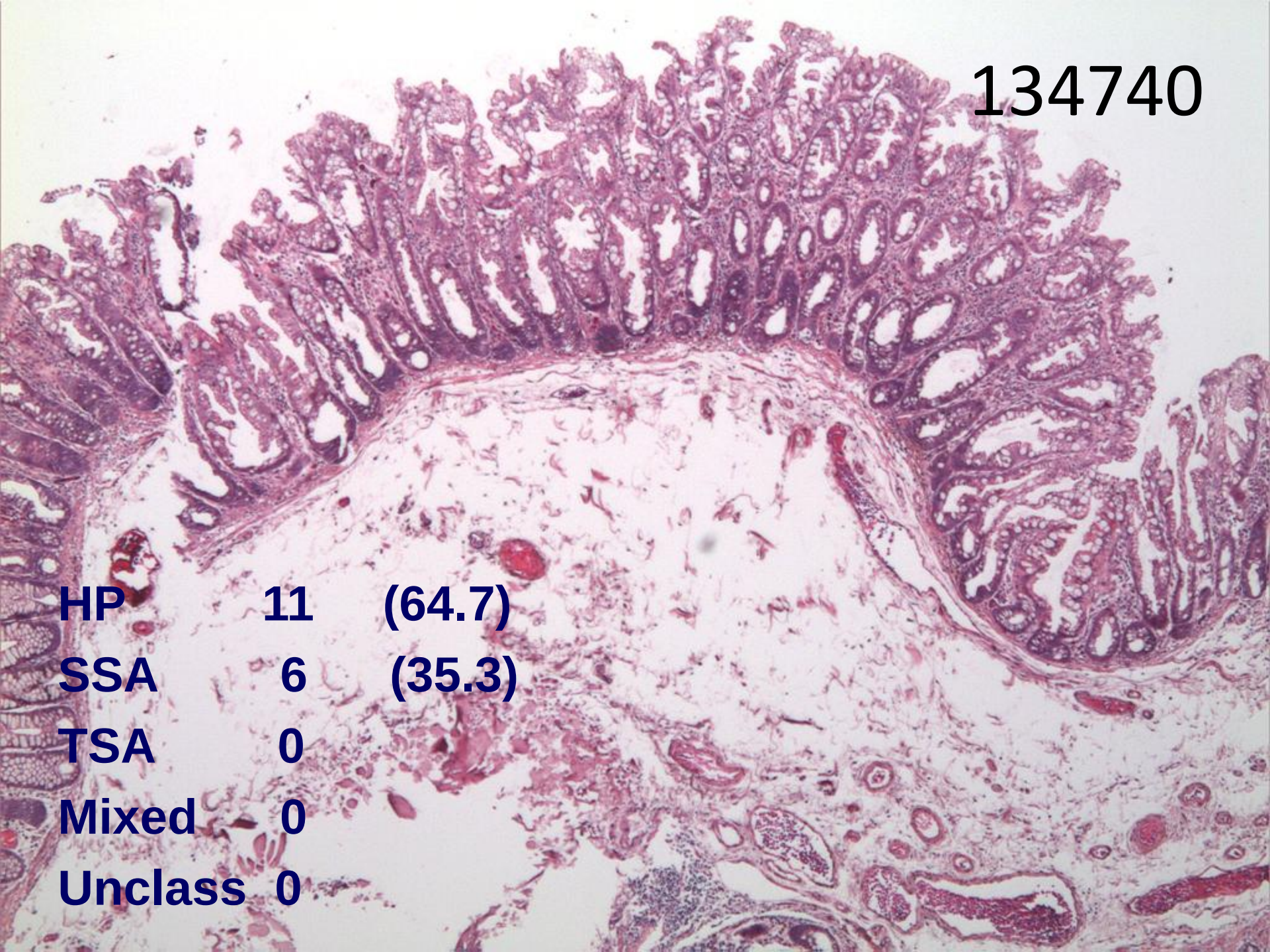
This is from a "usual" HPP with increased endocrine cells

Torlakavic and Snover, Gastroenterology 1996;110:748-755



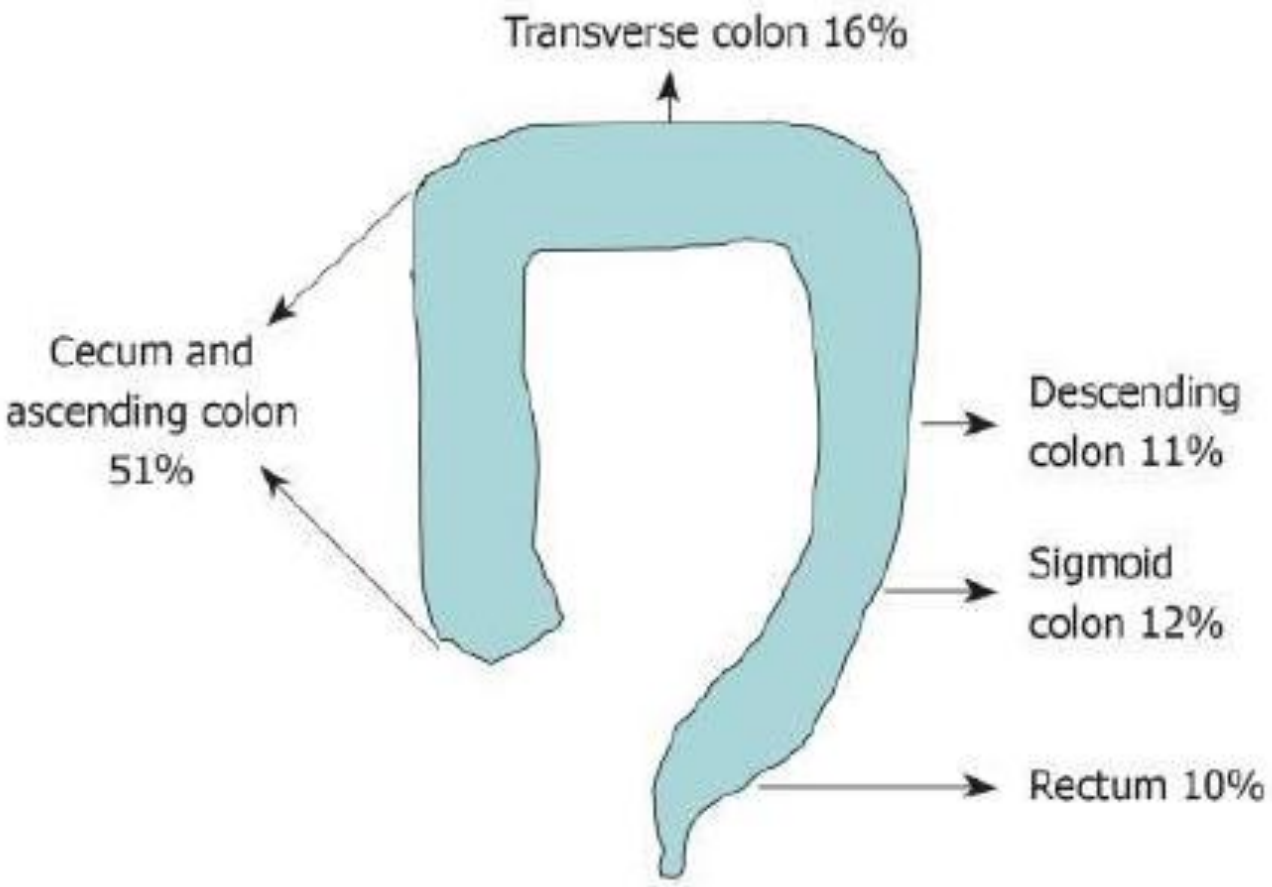

•Straight and narrow crypts <%50
•Dilated, T-L- shaped in >2-3 adjacent crypts


46705
HP 12 (70.6)
SSA 4 (23.5)
TSA 0
Mixed 0
Unclass 1 (5.9)


134740
HP 11 (64.7)
SSA 6 (35.3)
TSA 0
Mixed 0
Unclass 0

Topographical distribution of SSA/P

Gurudu et al. WGL 2010;16:3402

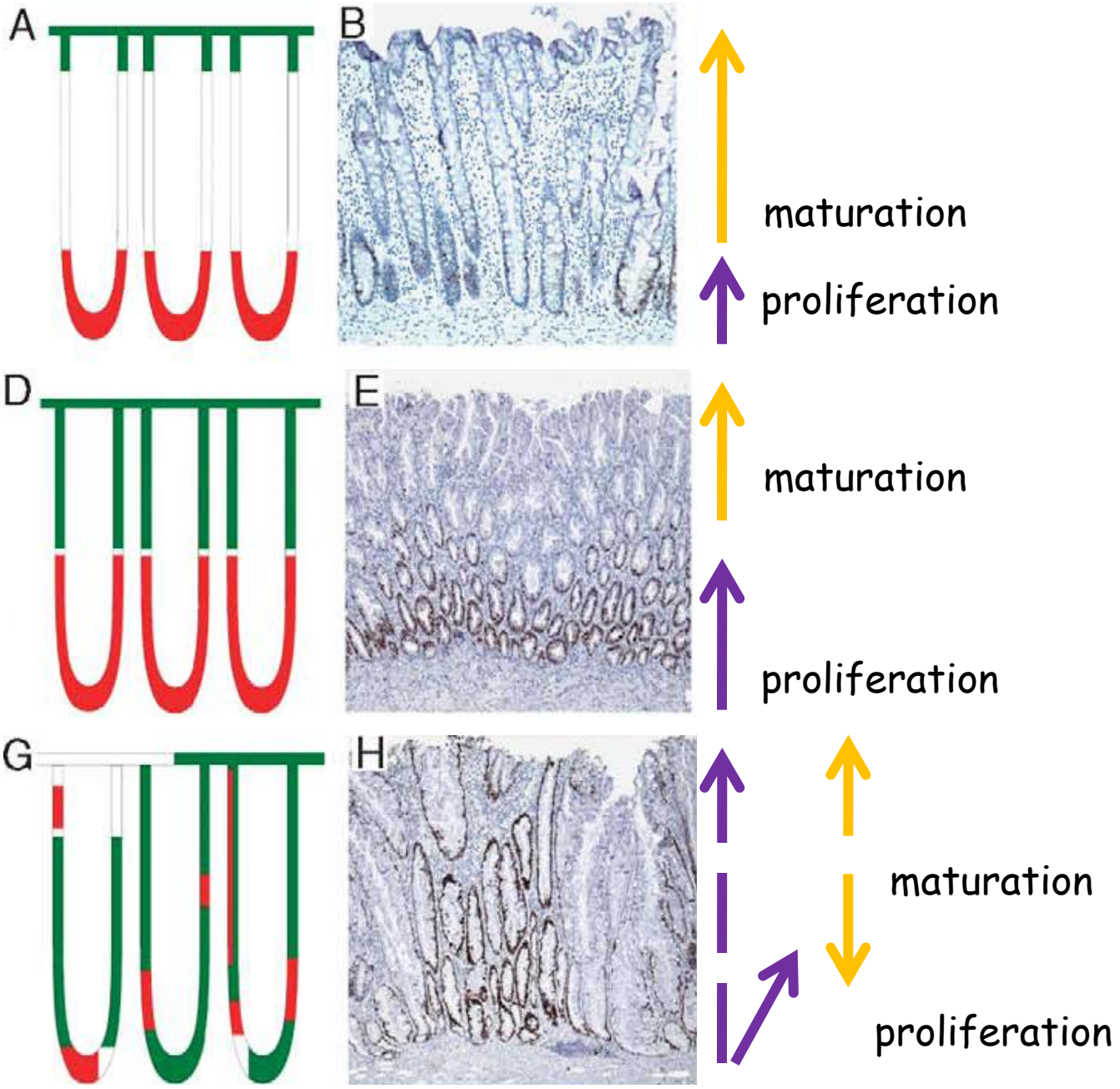


Ki 67

Normal

HP

SSA/P



Torlakovic, 2008

Snover, 2010

Morphological characteristics of serrated lesions		
	SSA/P	**HP**
Location	Right colon	Rectosigmoid
Shape	Flat	Flat, protuberant
Size	> 5mm	< 5mm
Dysplasia	Typically absent, can be present	Absent
Subepithelial collagen band	Absent	Present
Surface maturation	Present	Present
Basal crypt dilation	Present	Absent
Horizontal crypts	Present	Absent
Branched crypts	Present	Absent
Basal crypt serration	Present	Absent
Nuclear shape	Round to oval	Flat to low columnar
Cytoplasmic eosinophilia	Present	Inconspicuous

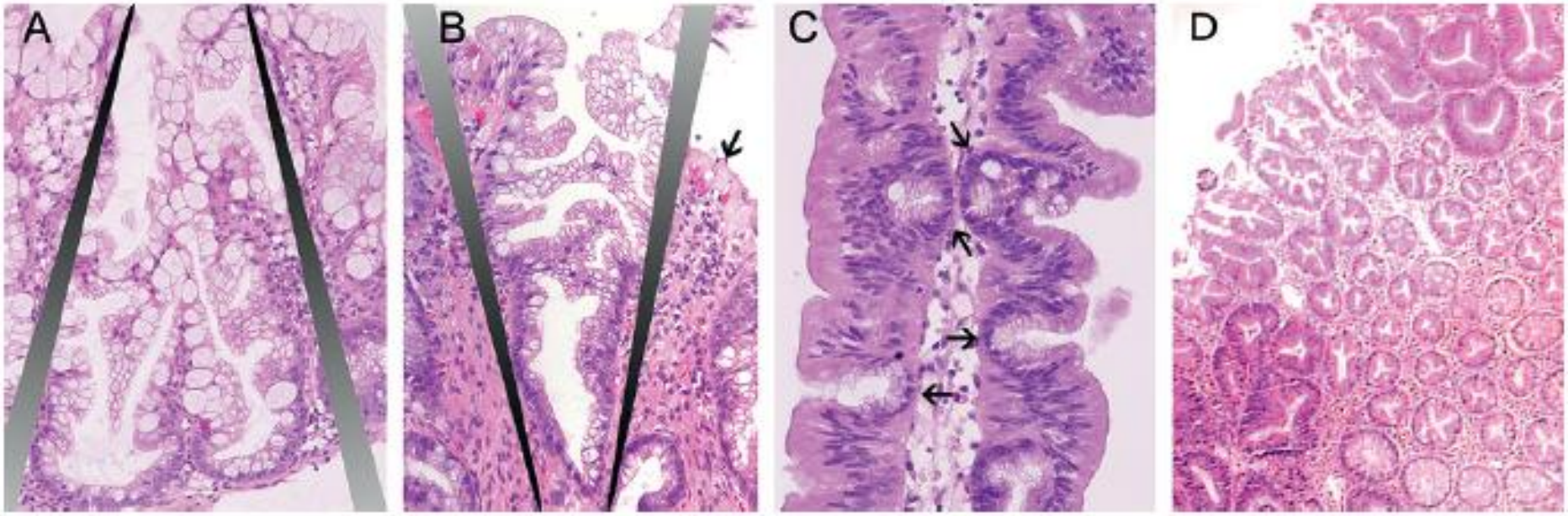
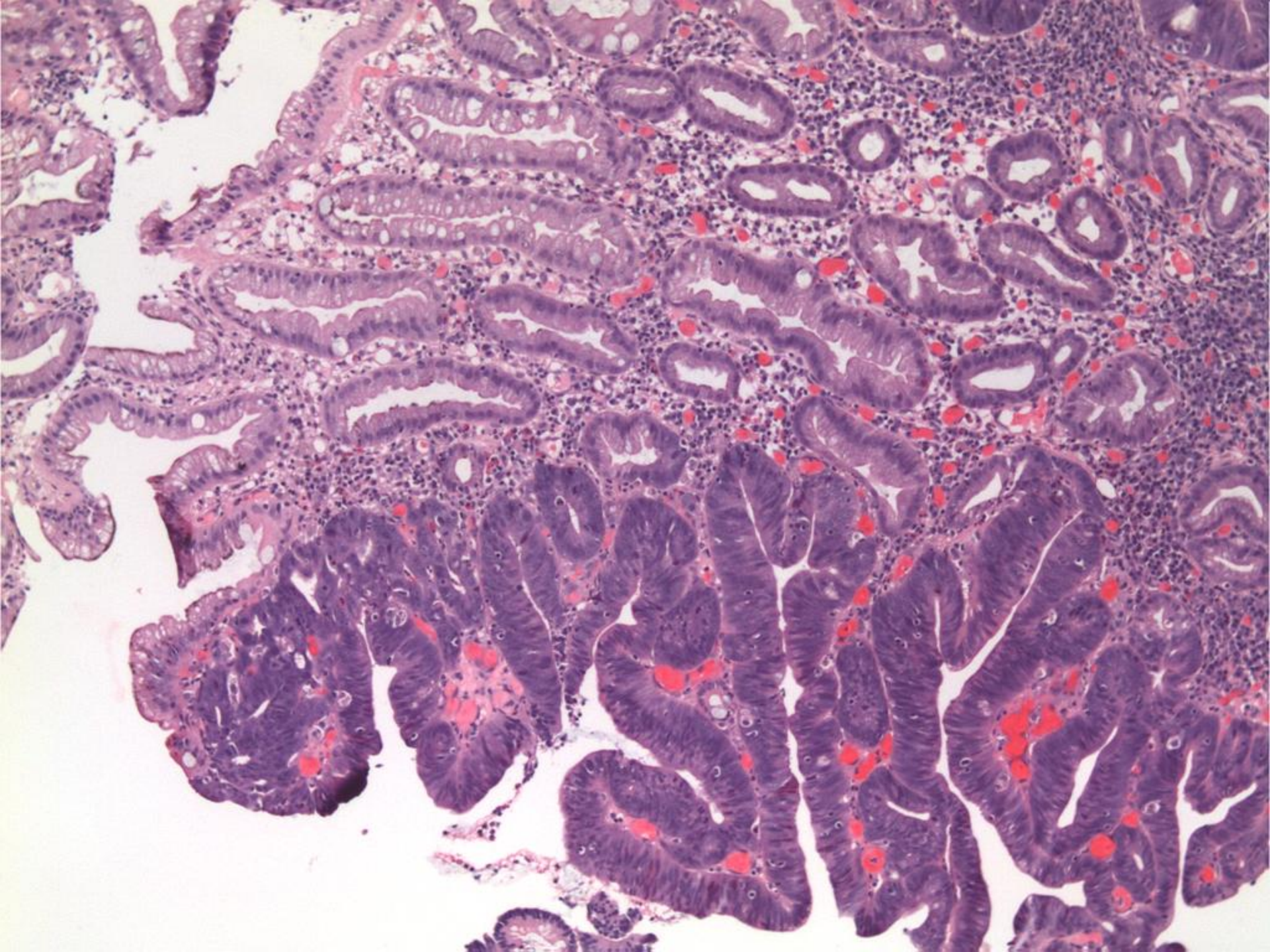


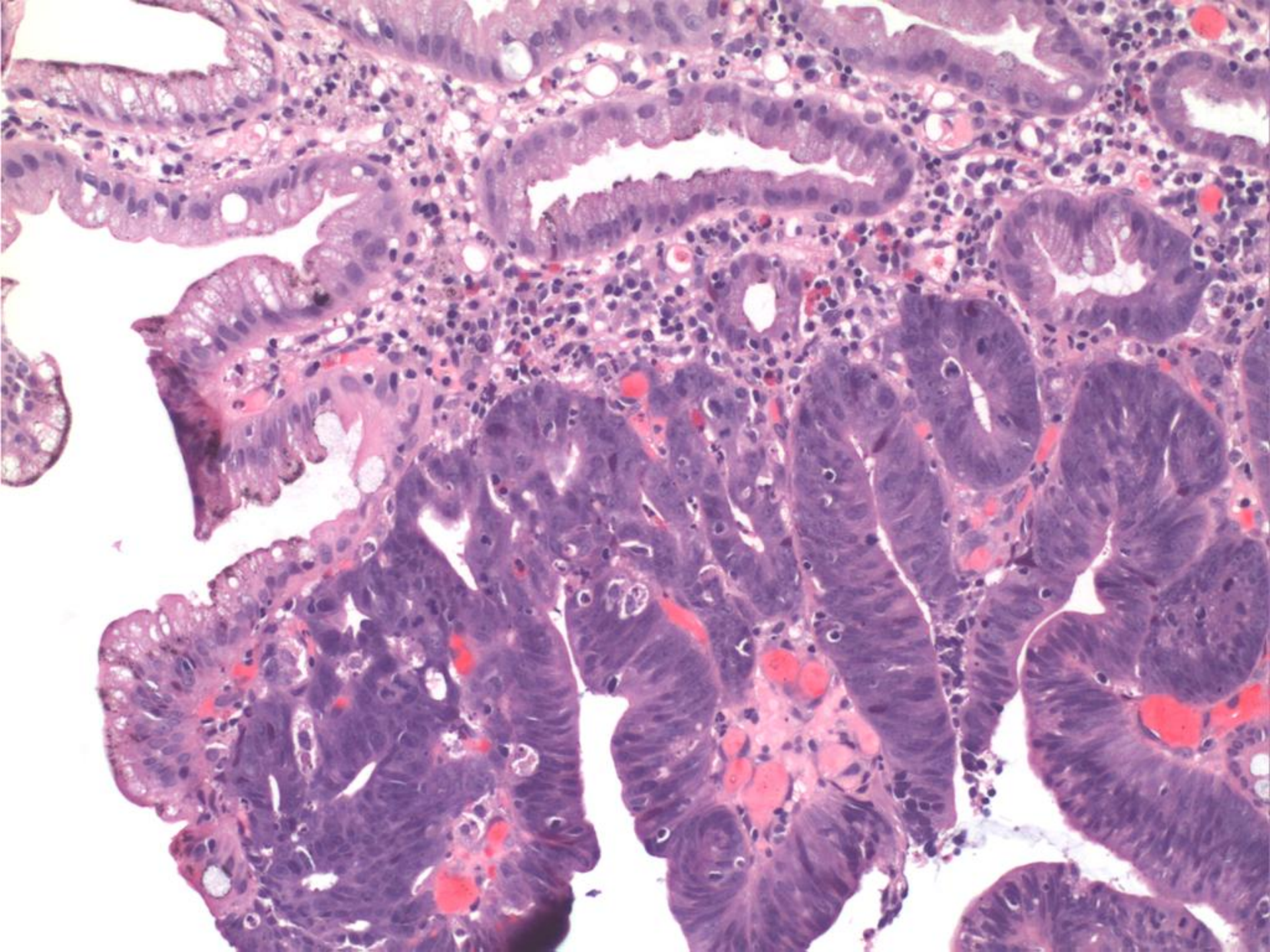
Figure 1 (A) Crypts showing basal dilation and serration in a 'crescendo' fashion in sessile serrated adenomas/polyps (H&E, ×200). (B) Hyperplastic polyp with crypt showing epithelial serration and dilatation in the upper part (ie, 'decrescendo' pattern) (H&E, ×200). Note broad basement membrane (arrow). (C) Ectopic crypts (arrows) in traditional serrated adenoma (H&E, ×200). (D) Admixed polyp with areas of hyperplastic polyp and tubular adenoma (H&E, ×100).

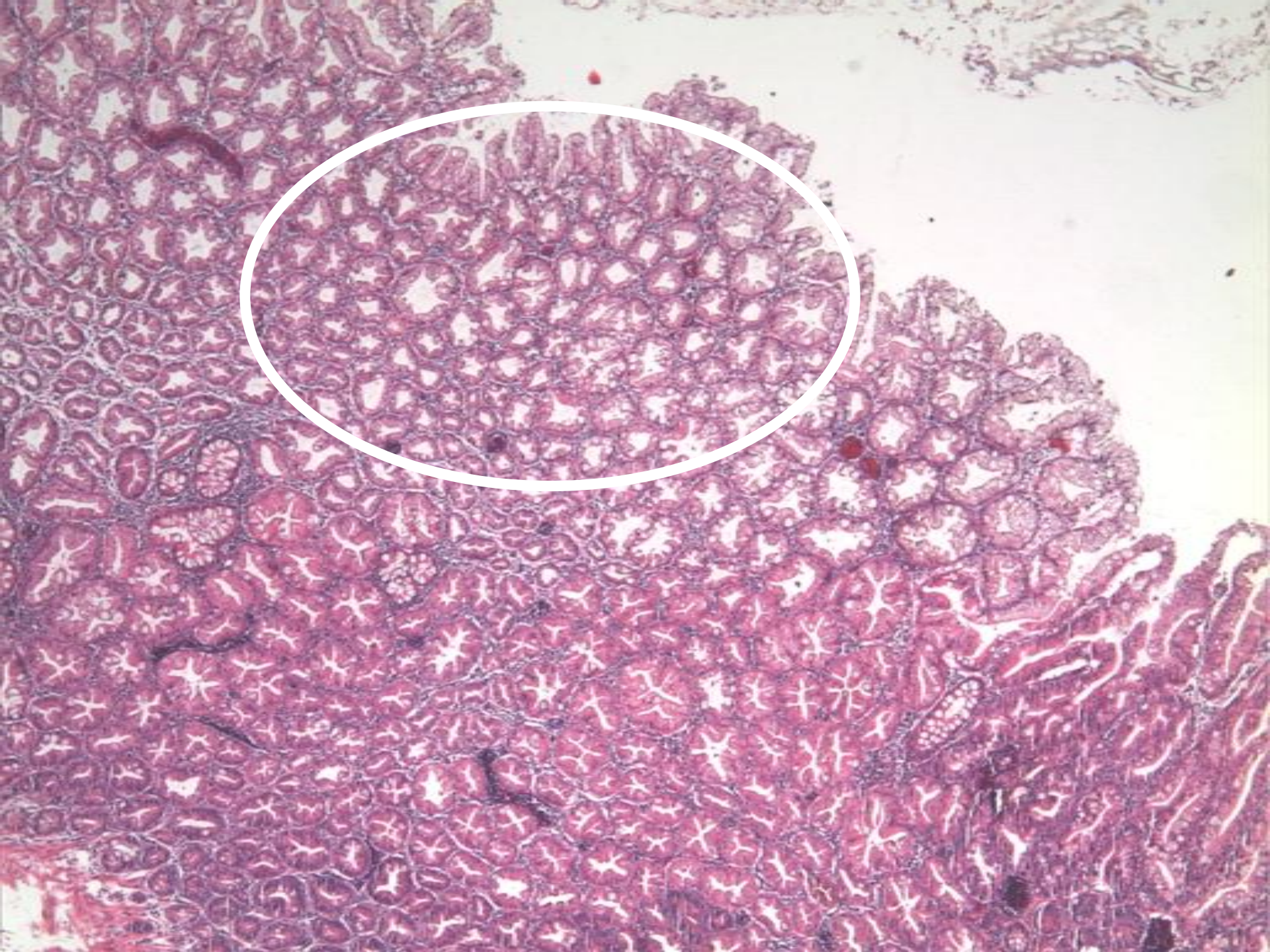
Ensari A et al. J Clin Pathol 2010;63:665-668

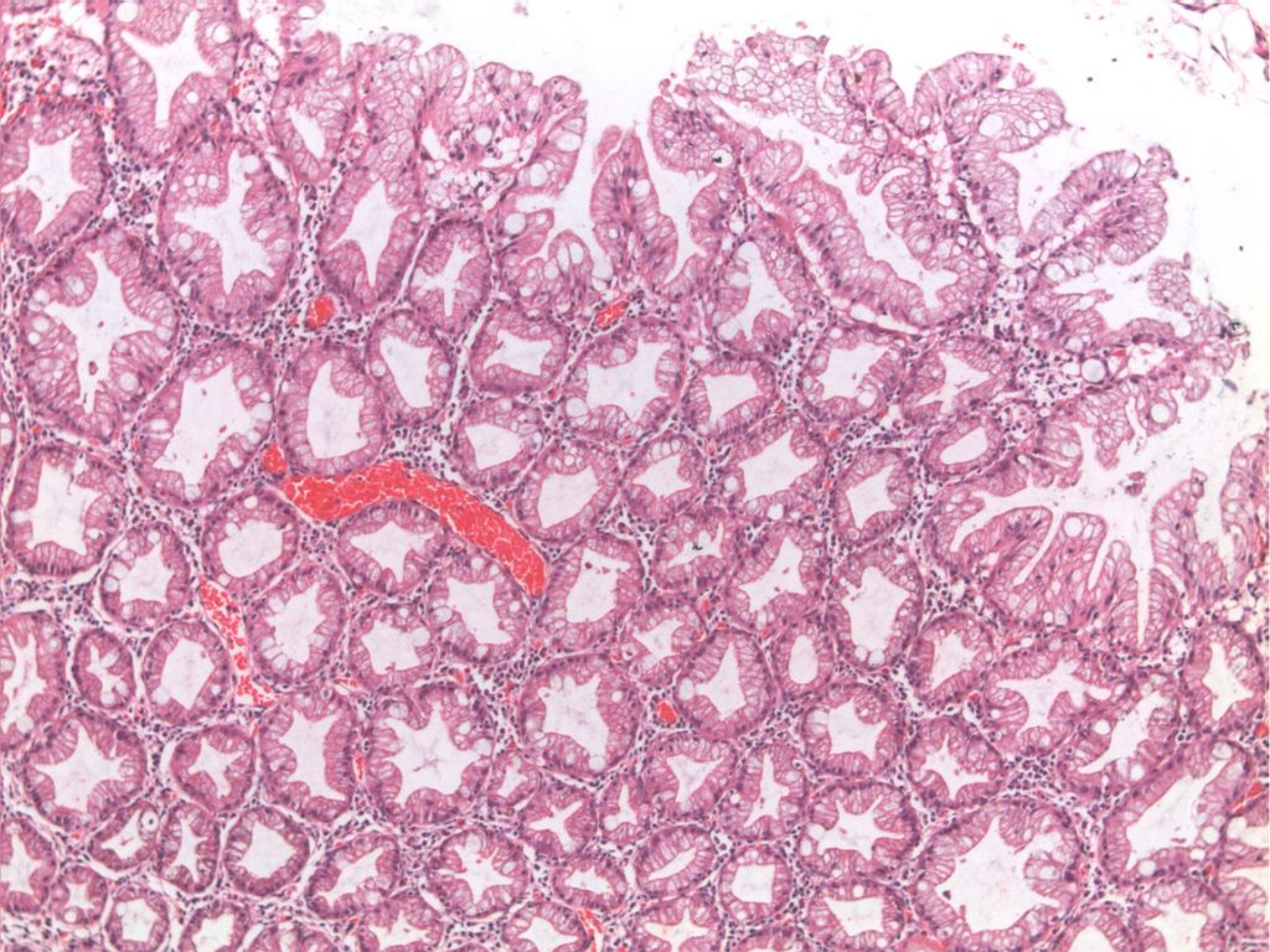
Dysplasia in serrated polyps

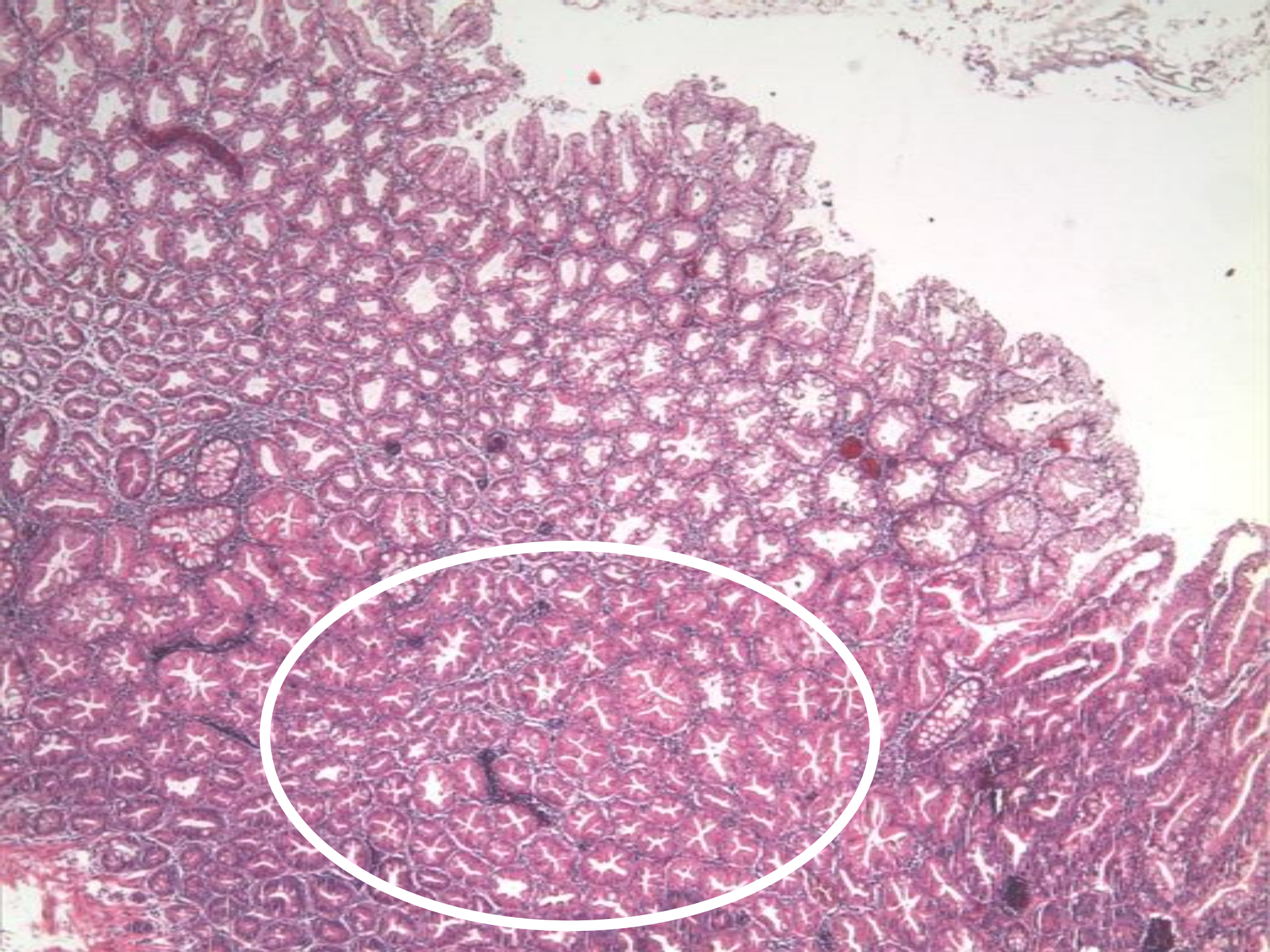
- Premalignant lesion
- LG and HG dysplasia can occur
- SSA/P with dysplasia-replaces "mixed polyp"
- Traditional -adenomatous- dysplasia
- Serrated dysplasia (Goldstein, 2008)
  - enlarged round nuclei
  - irregular nuclear membrane
  - prominent nucleoli
  - coarse chromatin

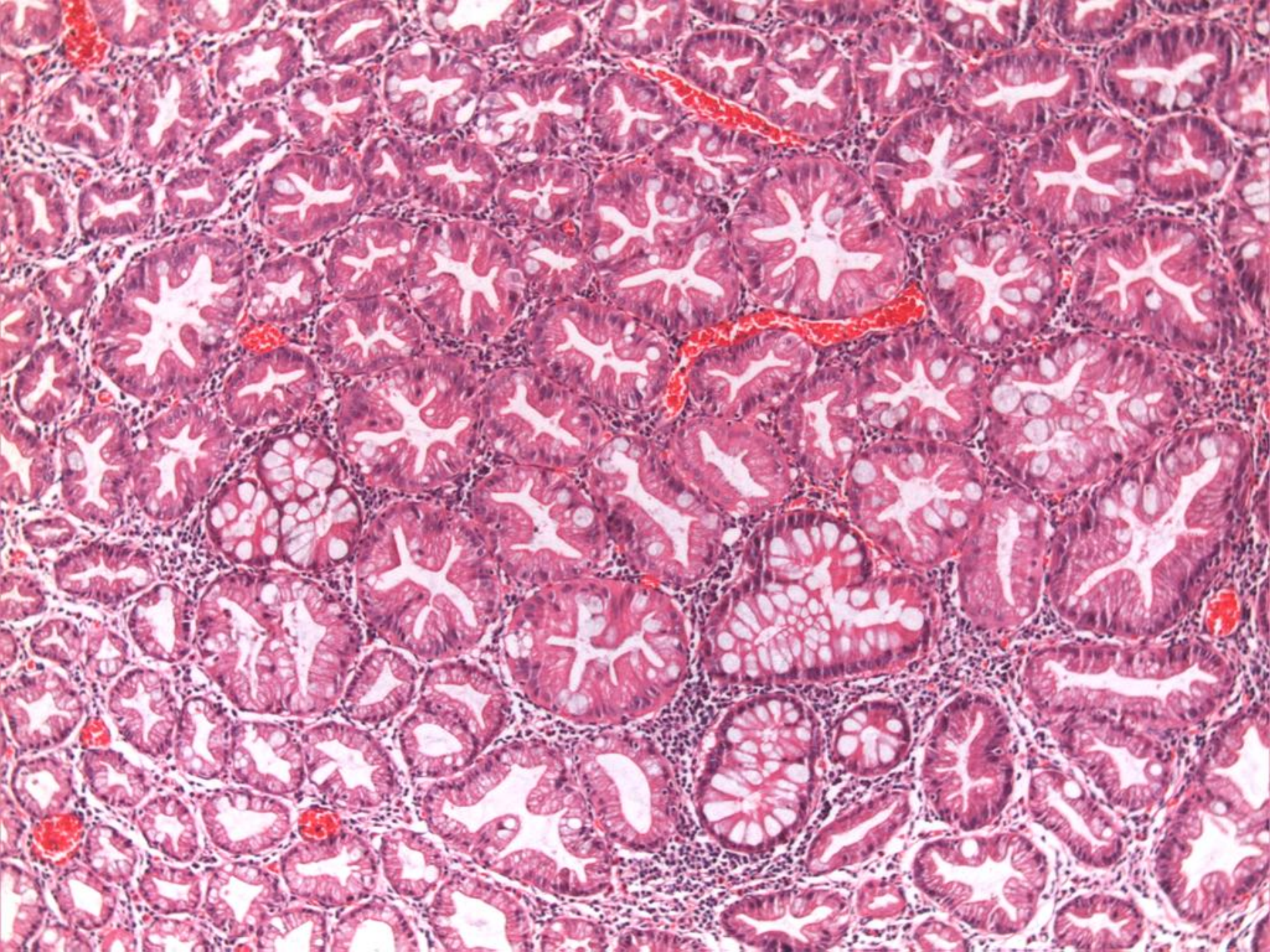


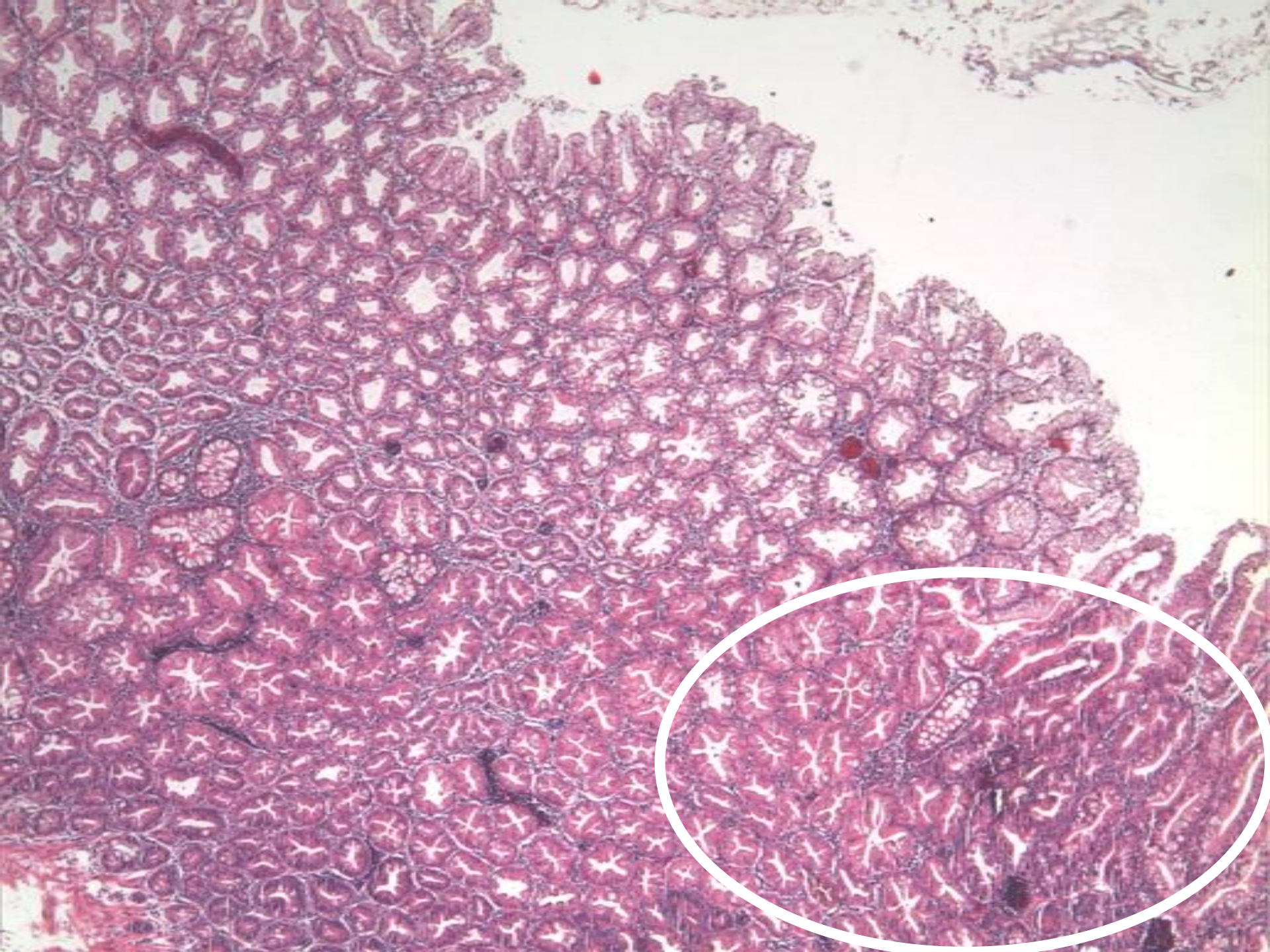


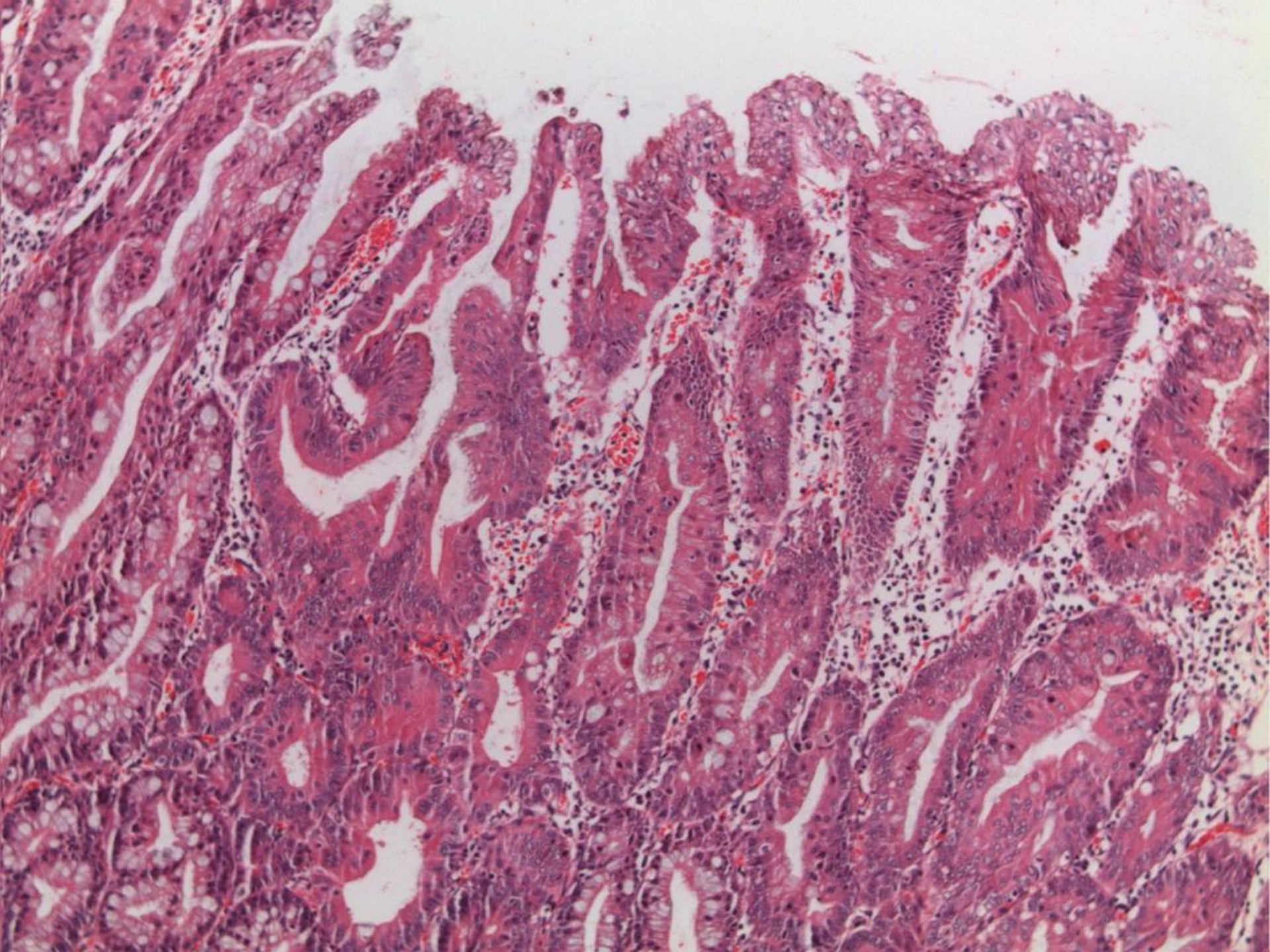


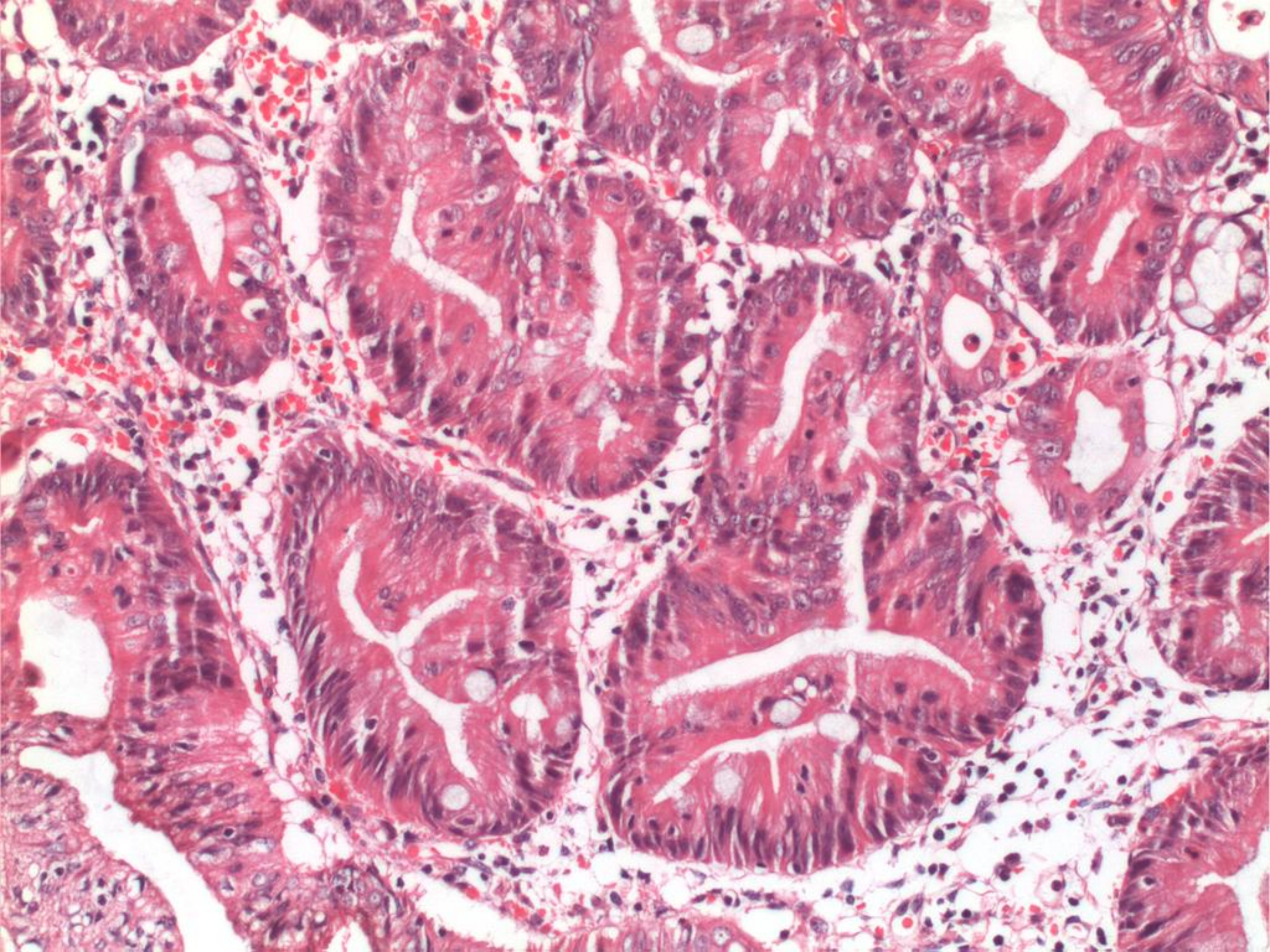


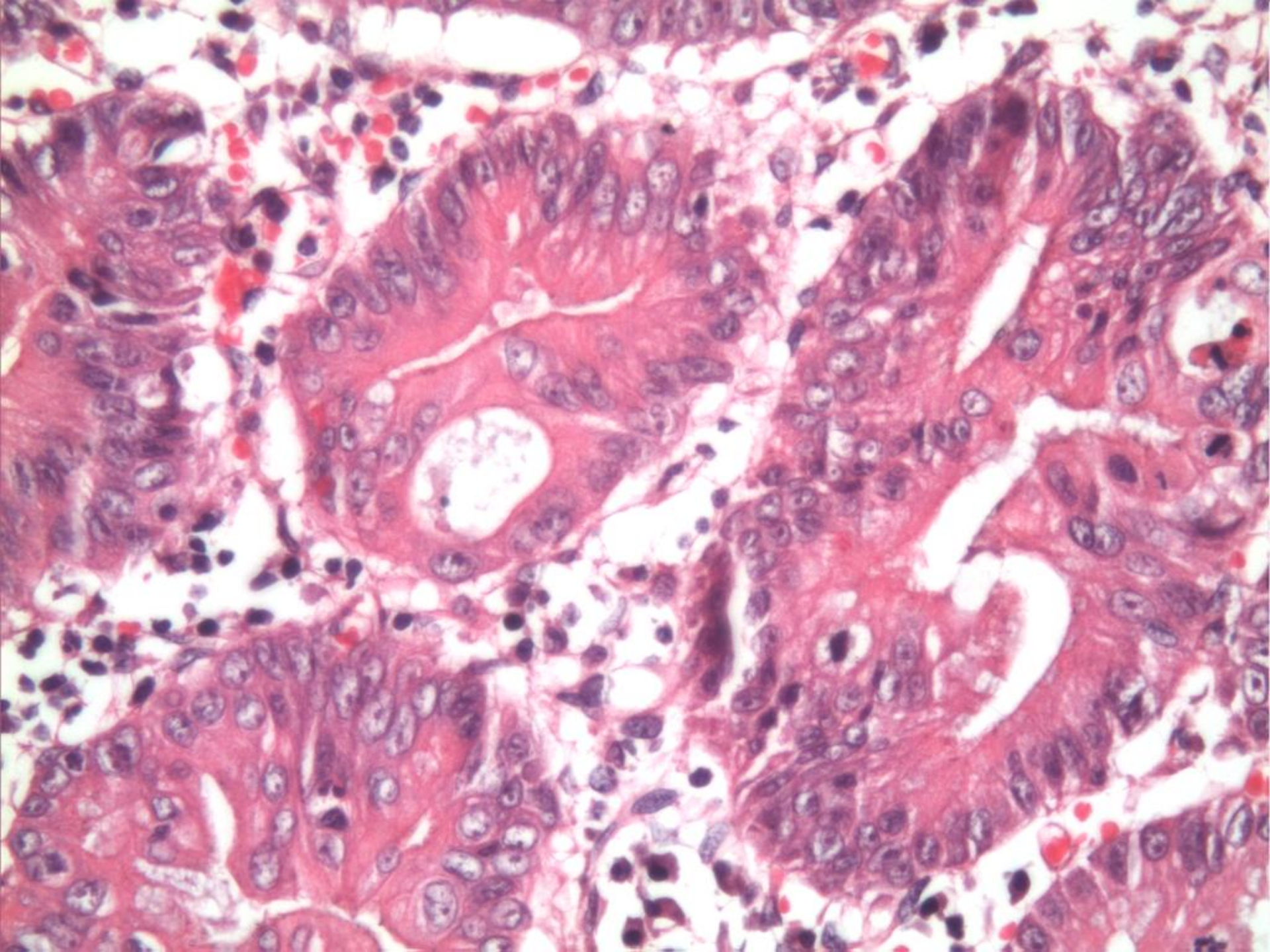


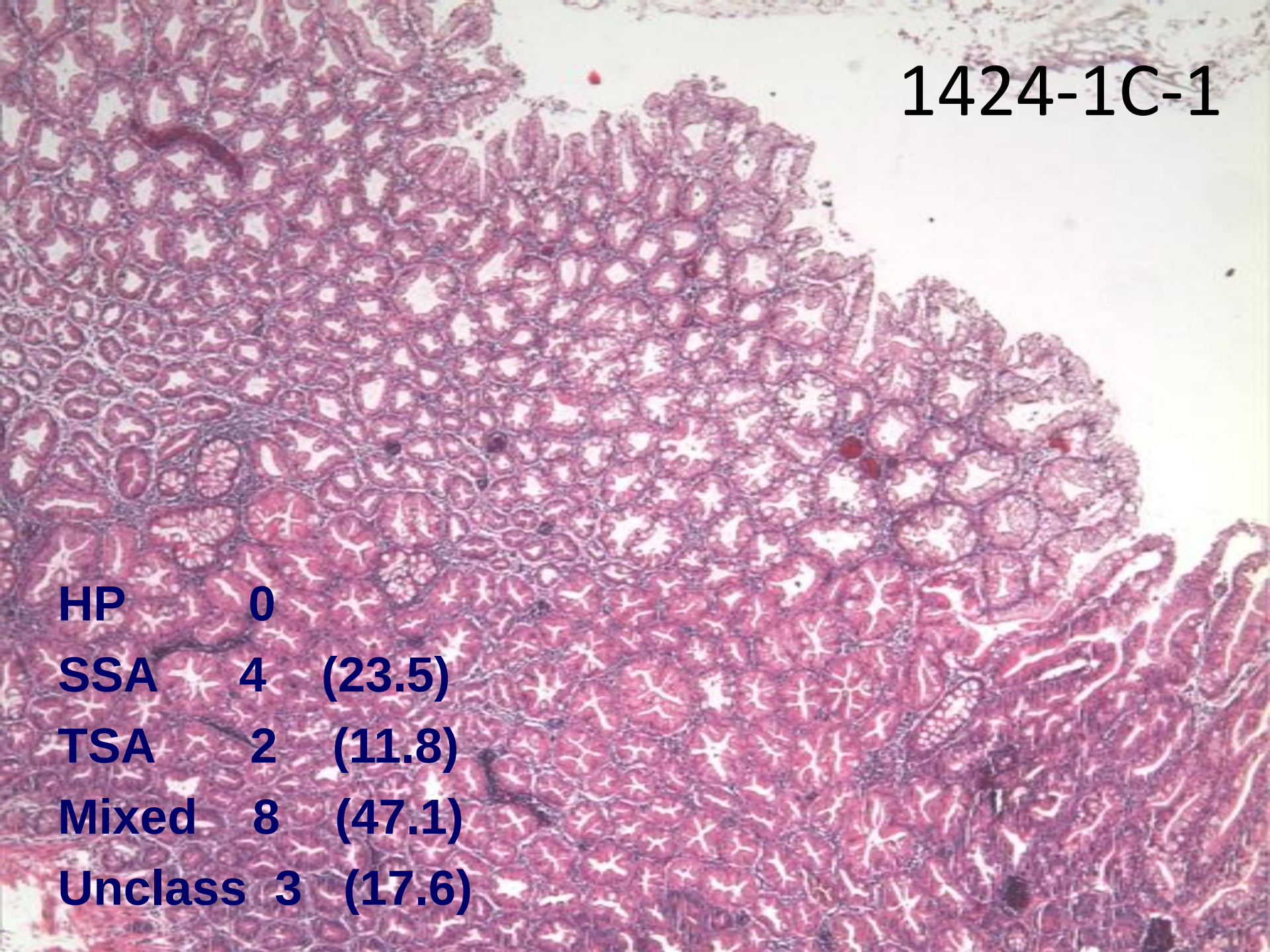


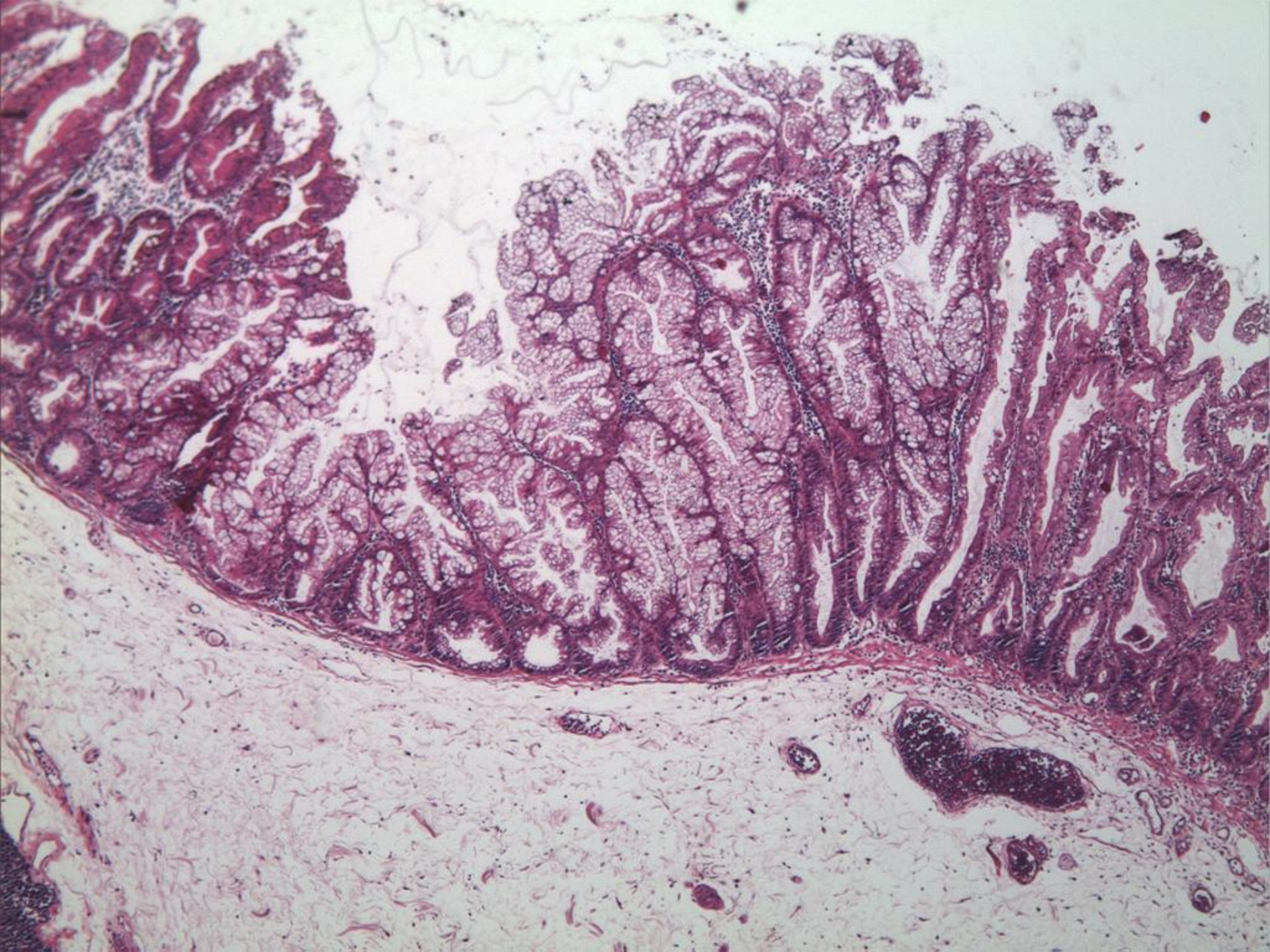


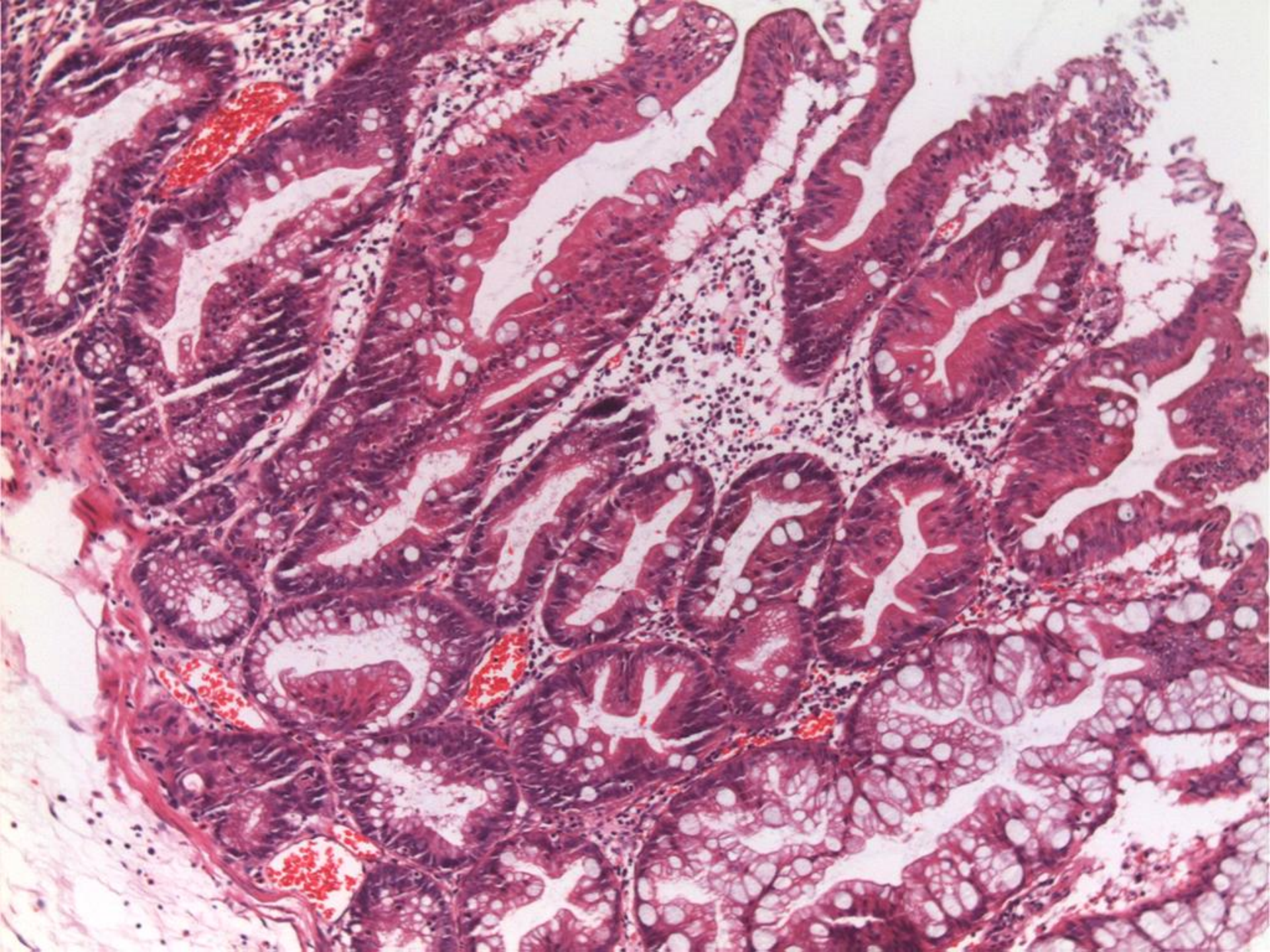


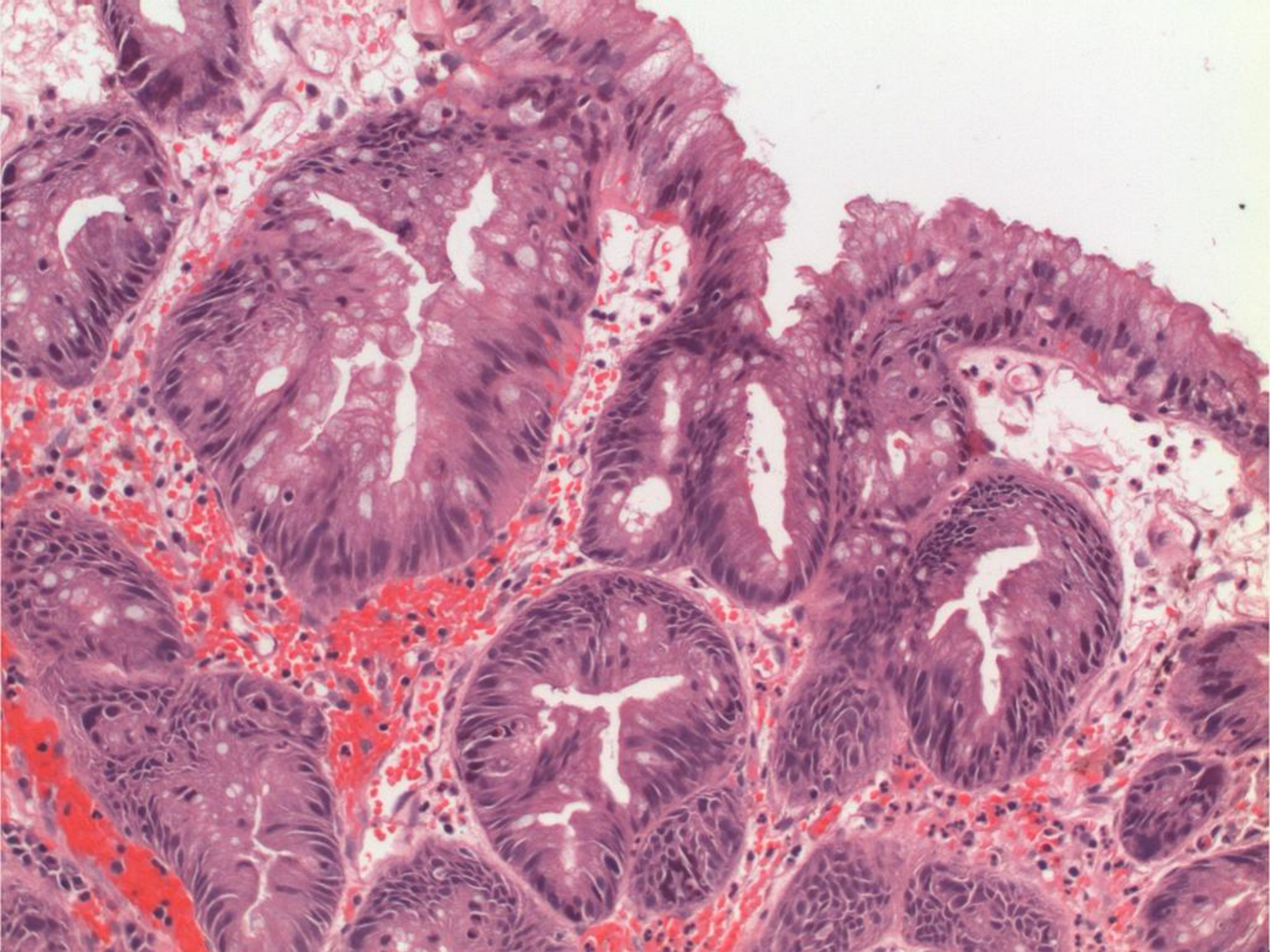


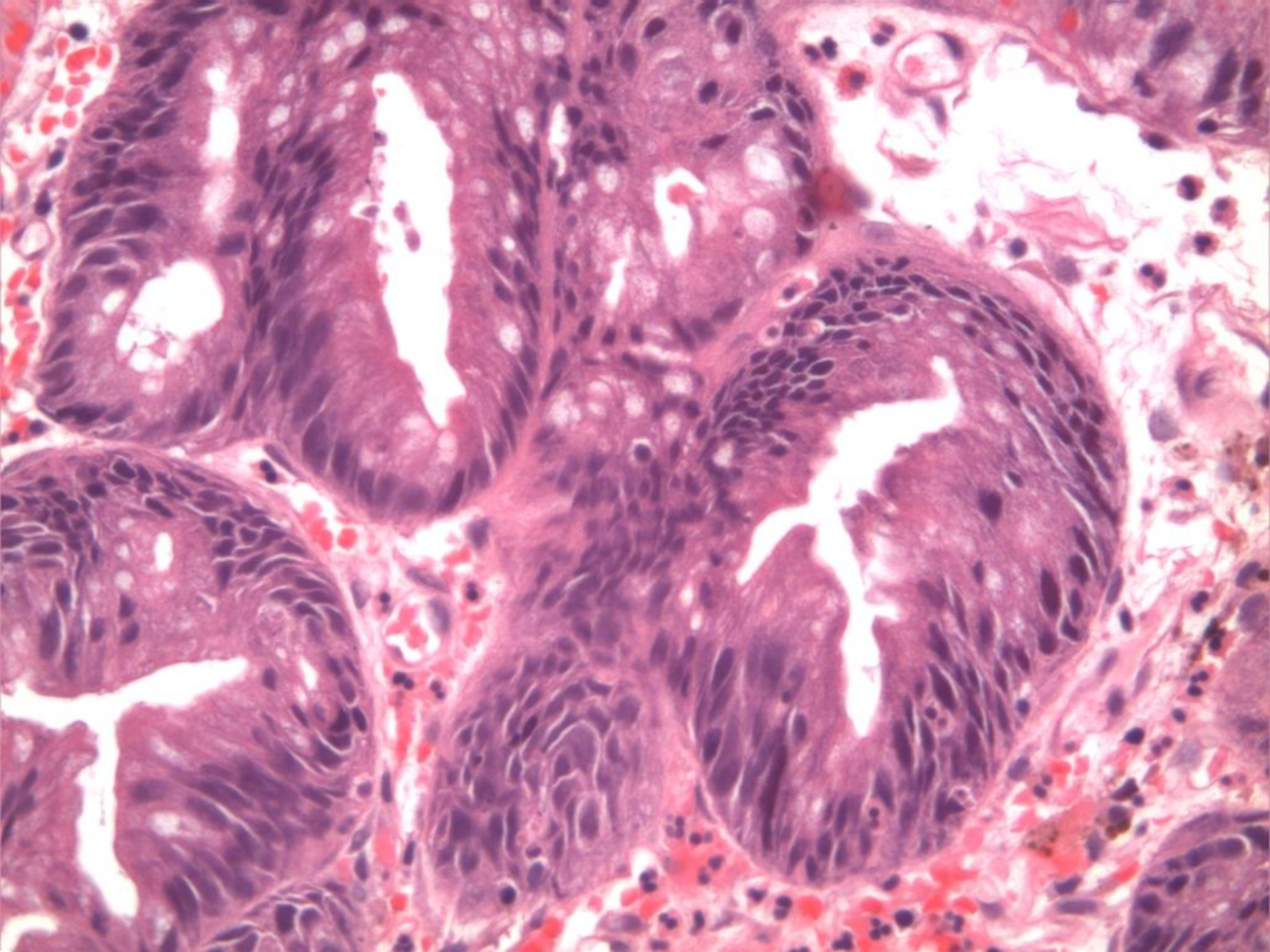


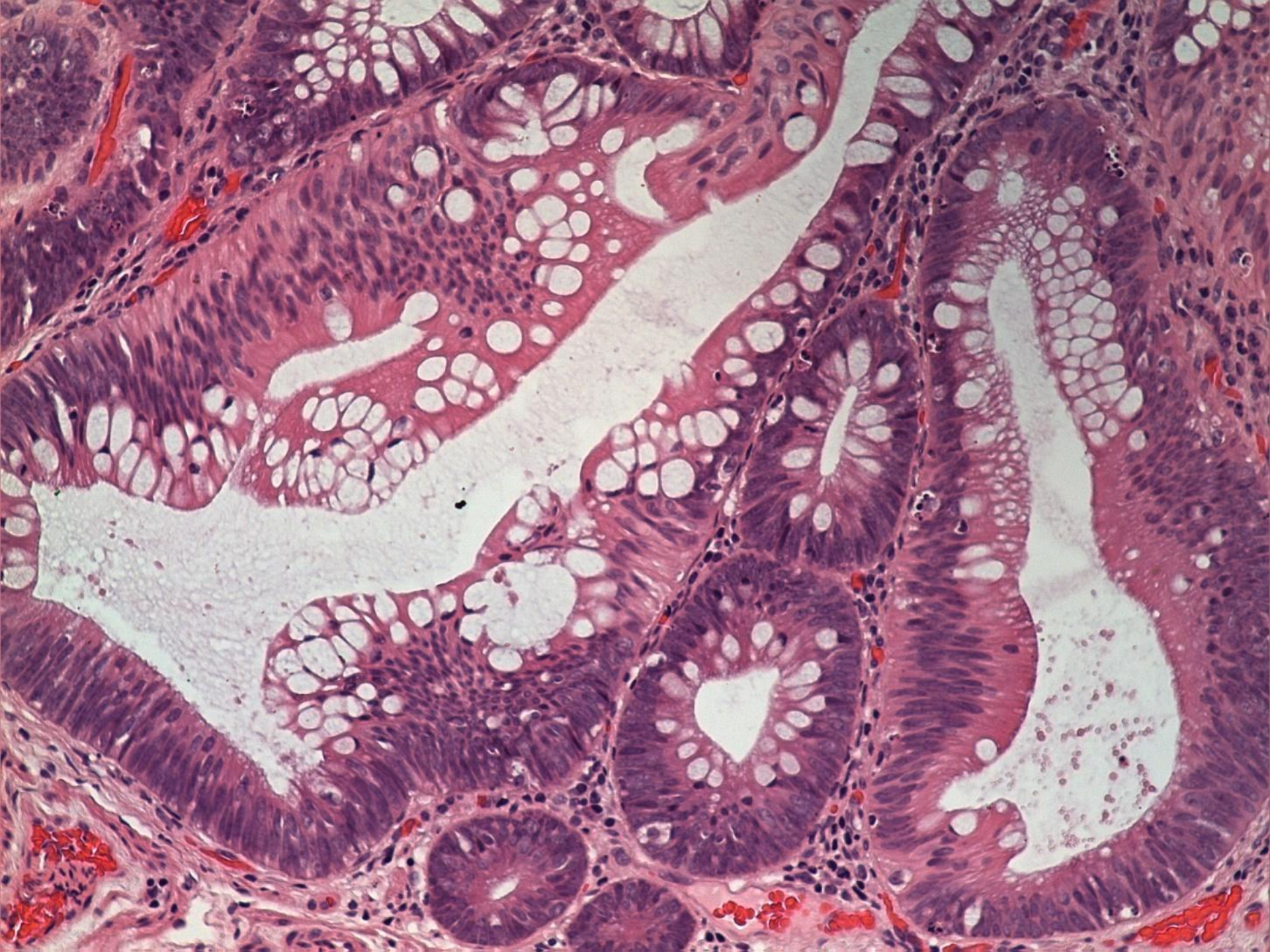

1424-1C-1
HP 0
SSA 4 (23.5)
TSA 2 (11.8)
Mixed 8 (47.1)
Unclass 3 (17.6)





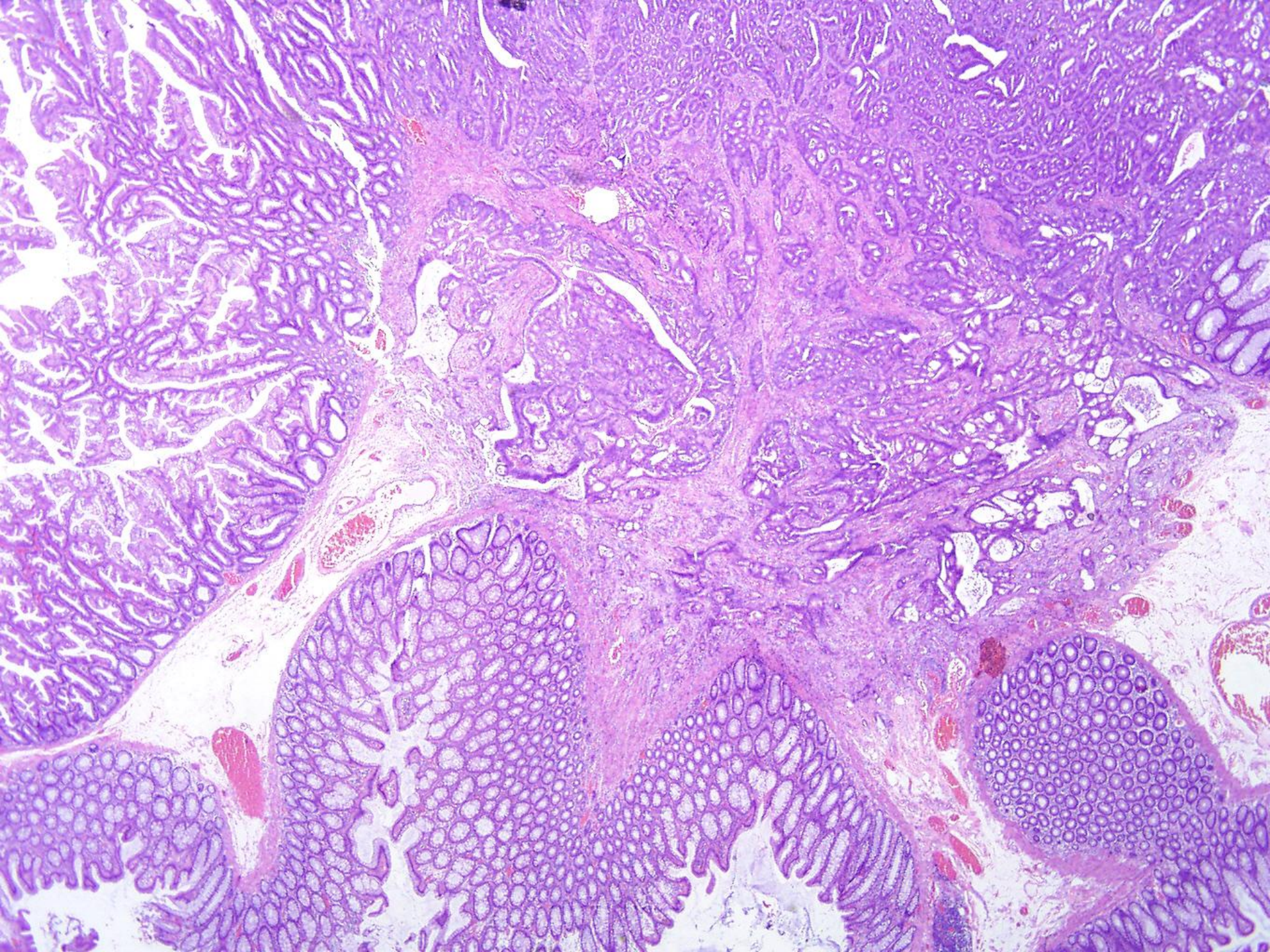


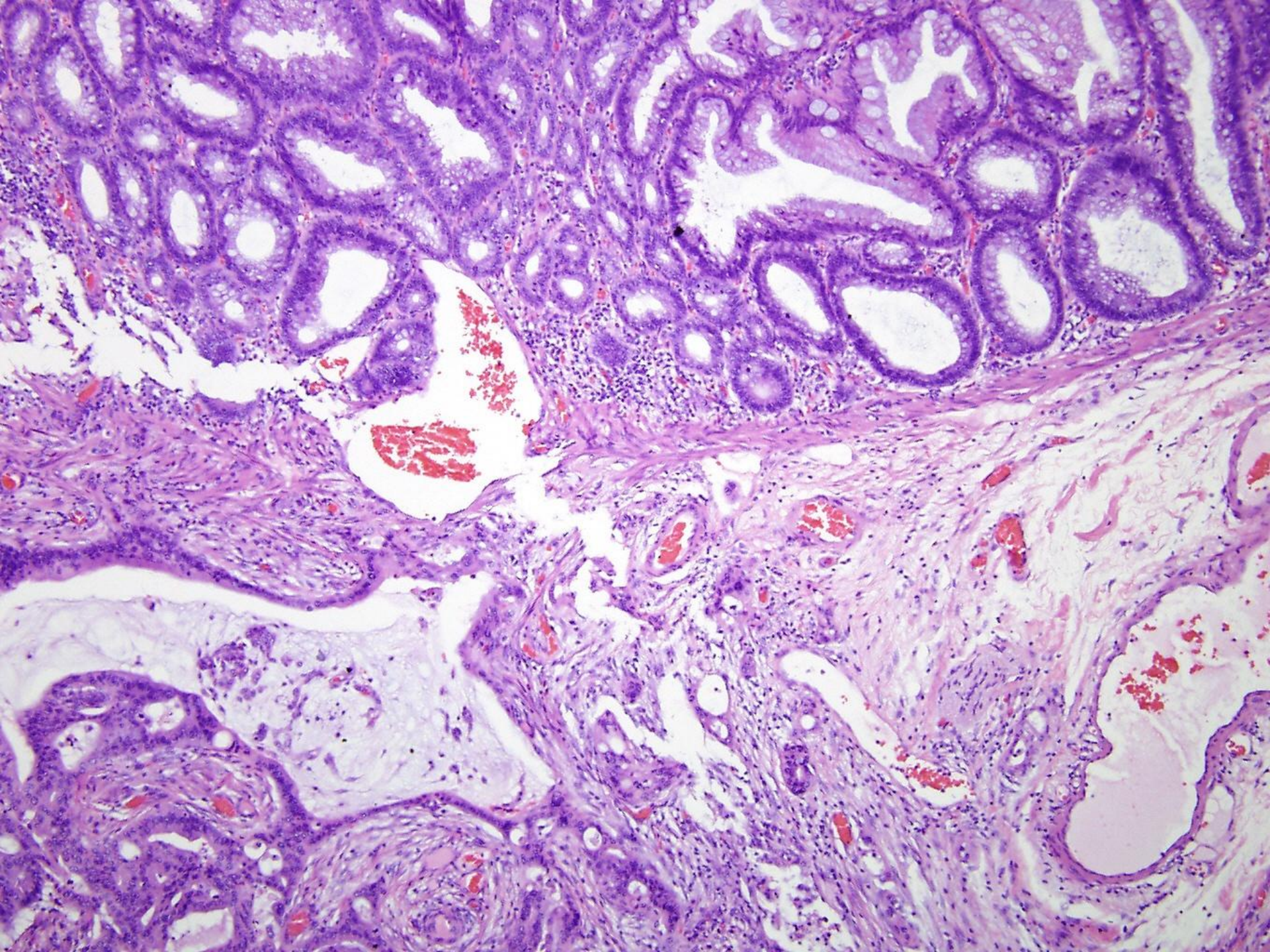


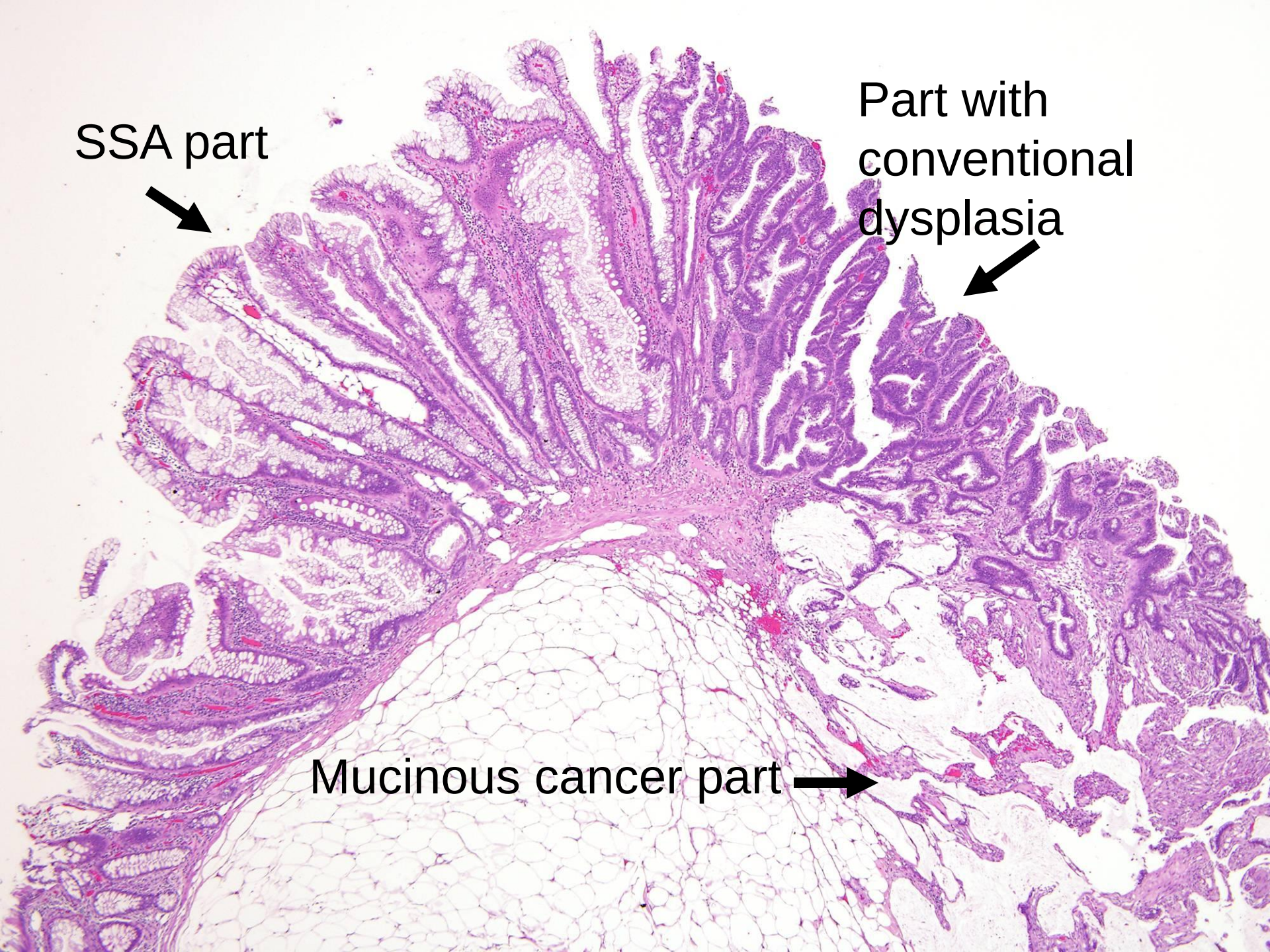


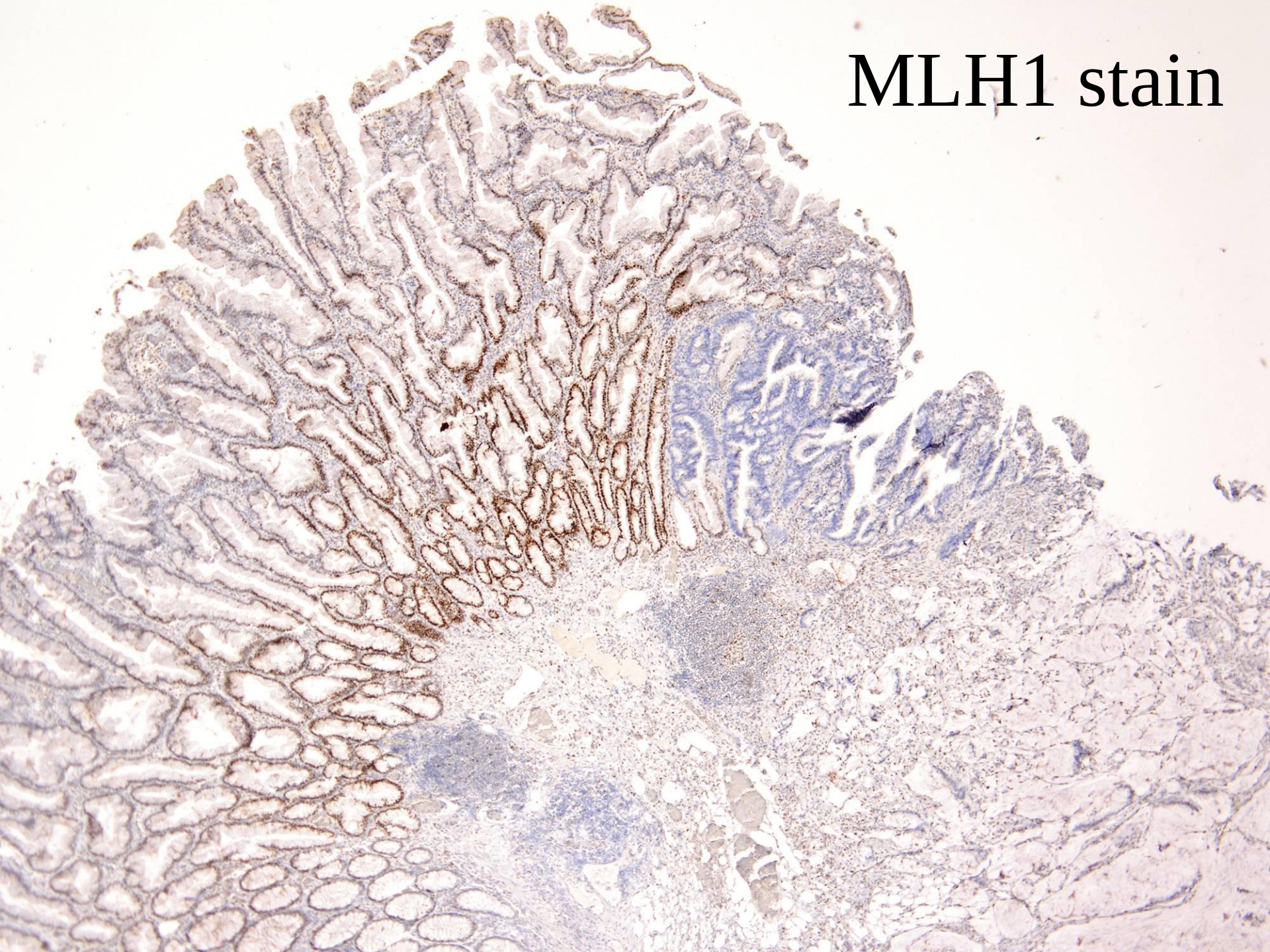
Type	Synonyms	Histological features[a]				Genetic features[b]			
		Crypts	Proliferation	Cytological dysplasia	Mucin type	BRAF mutation	KRAS mutation	CIMP	MLH1 methylation
SSA/P	Serrated polyp with abnormal proliferation; giant hyperplastic polyp; variant hyperplastic polyp	Crypts distorted, often dilated near base, excess serration near base	Proliferation abnormally located often away from the base of the crypts, variable from crypt to crypt	No	Usually microvesicular, sometimes with goblet cells or gastric foveolar differentiation	+++	–	+++	–
SSA/P with cytological dysplasia	Mixed hyperplastic-adenomatous polyp; advanced SSA/P	As for SSA/P	As for SSA/P but with more proliferation in cytologically dysplastic areas	Present	As for SSA/P	+++	–	+++	++

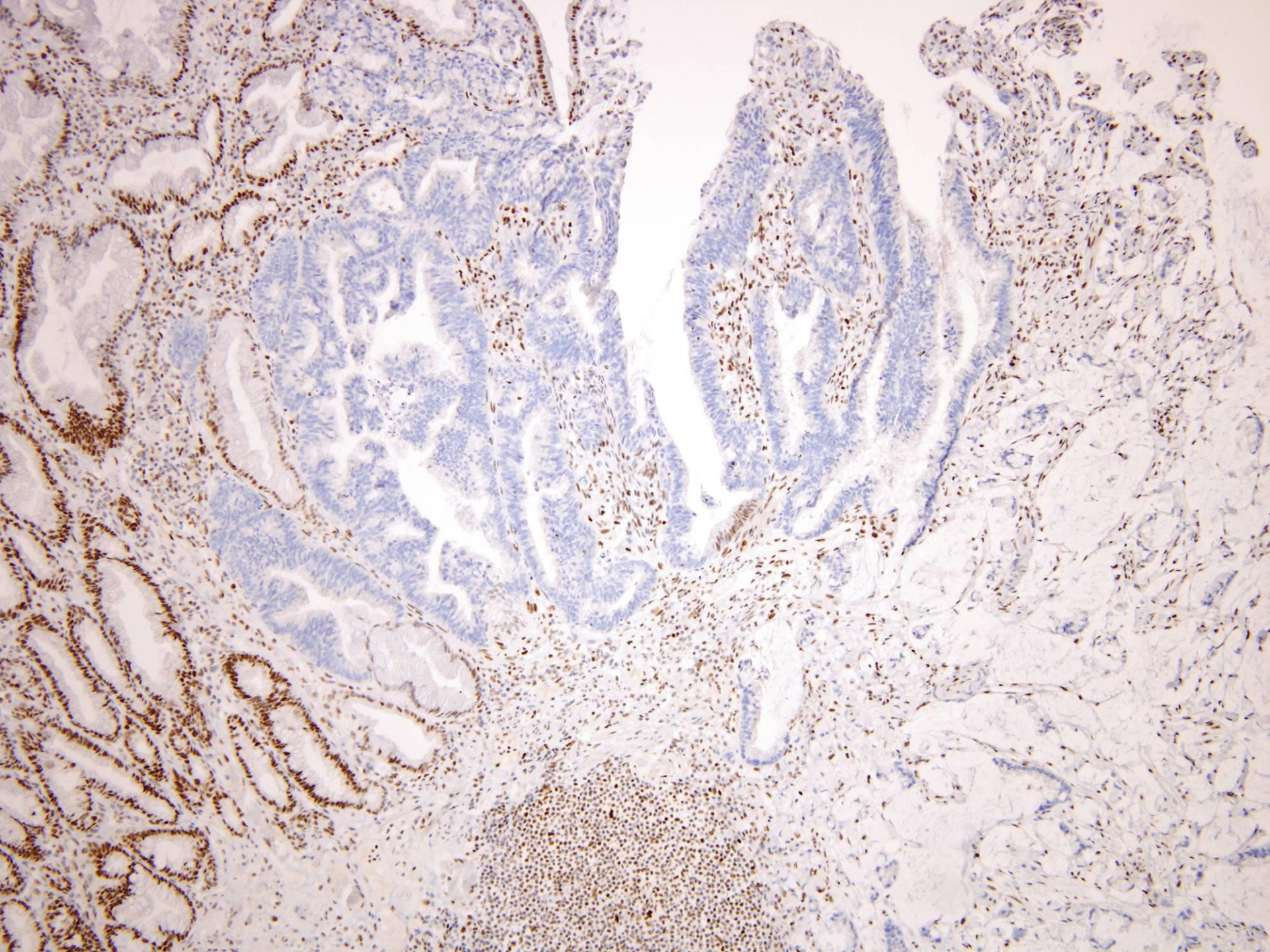
WHO 2010

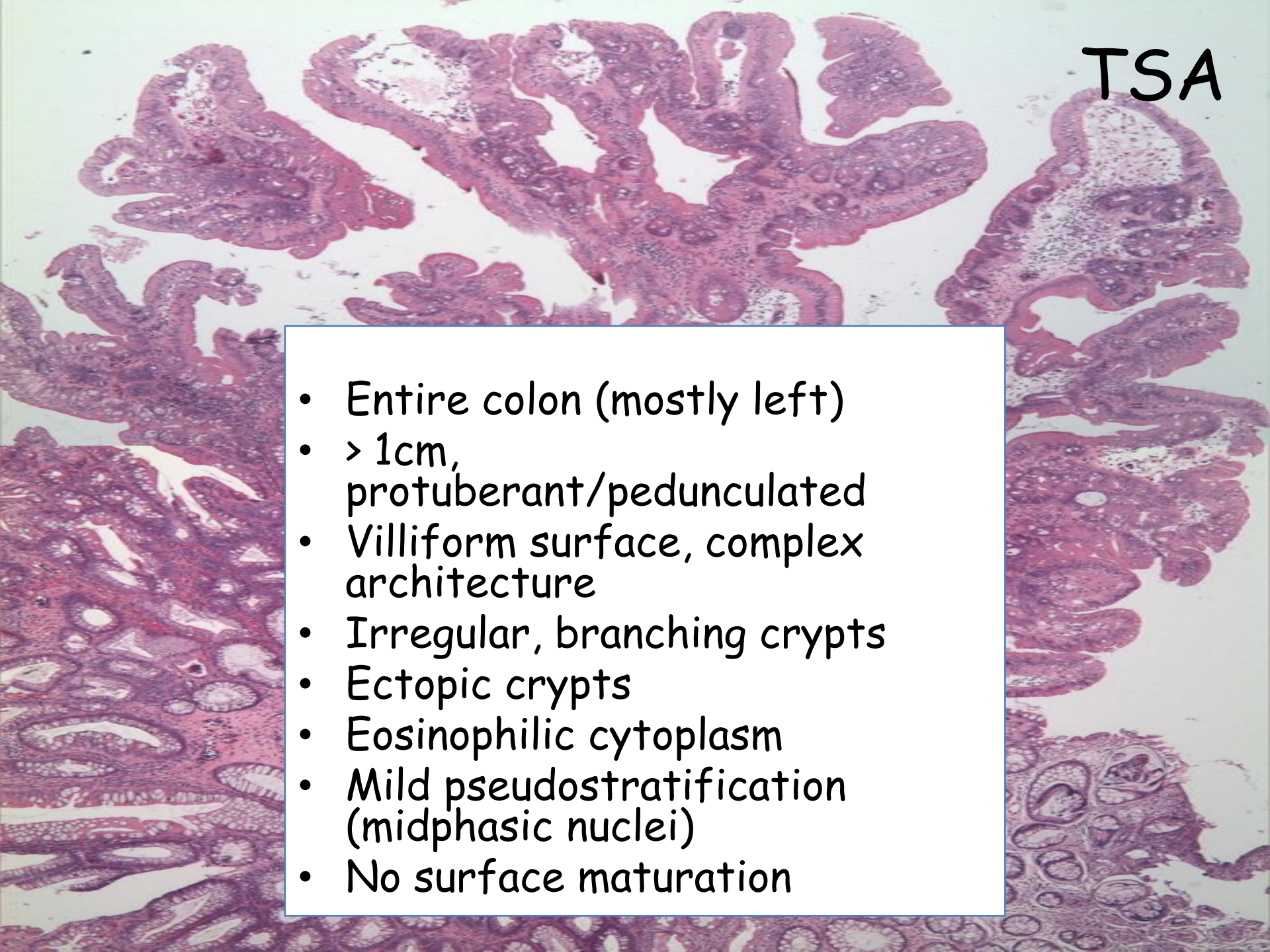





SSA part
Part with conventional dysplasia
Mucinous cancer part

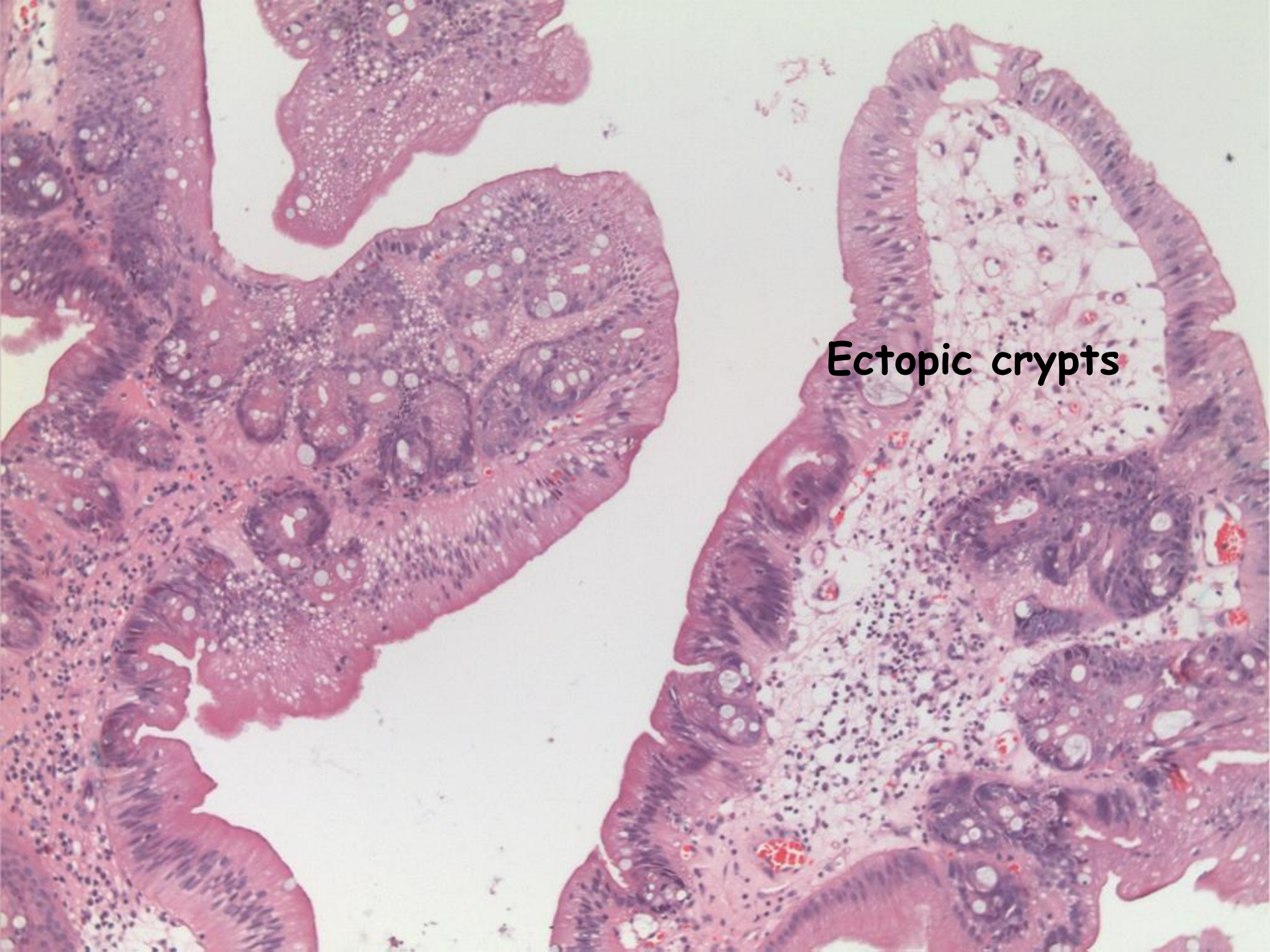

MLH1 stain

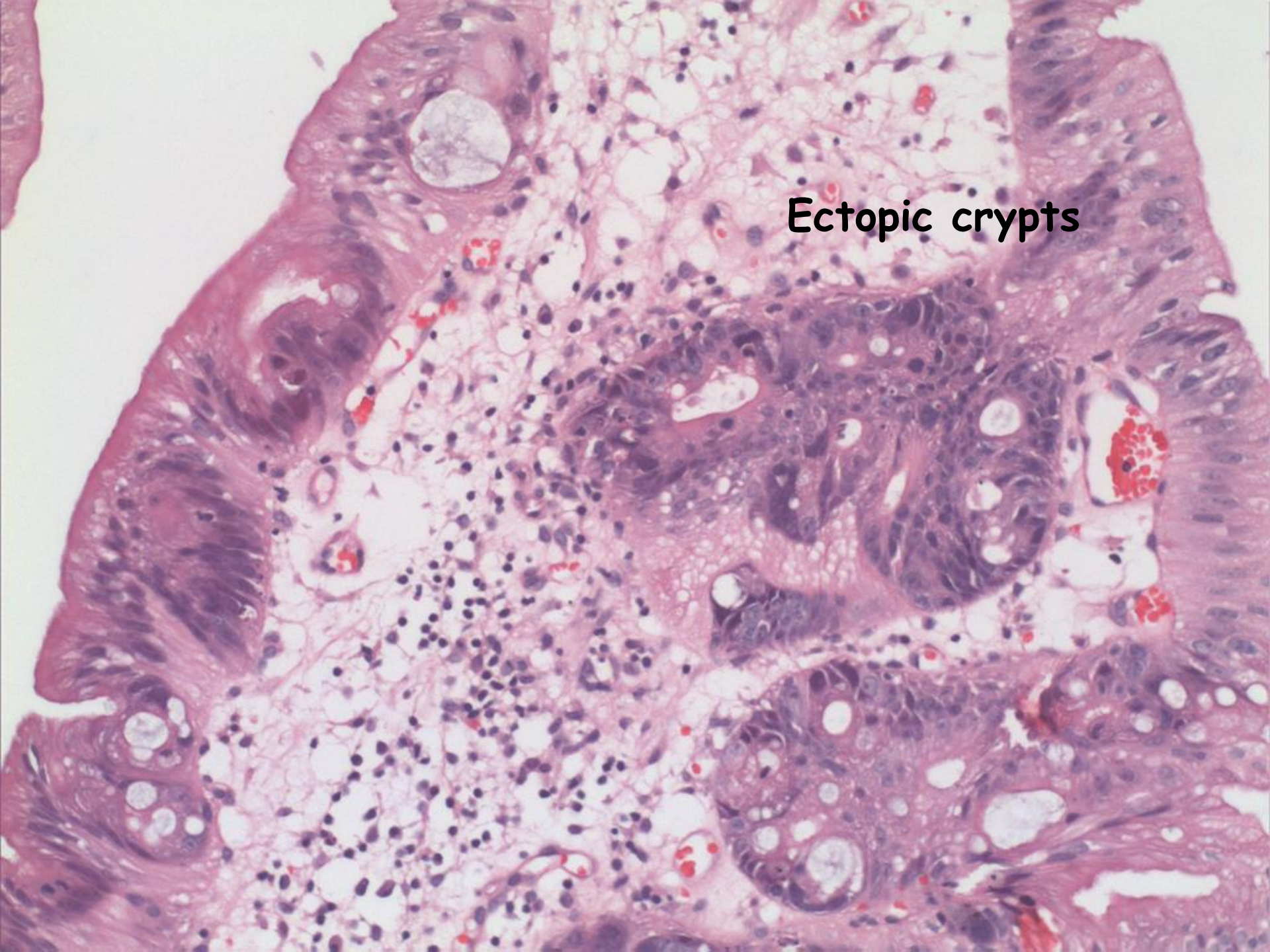


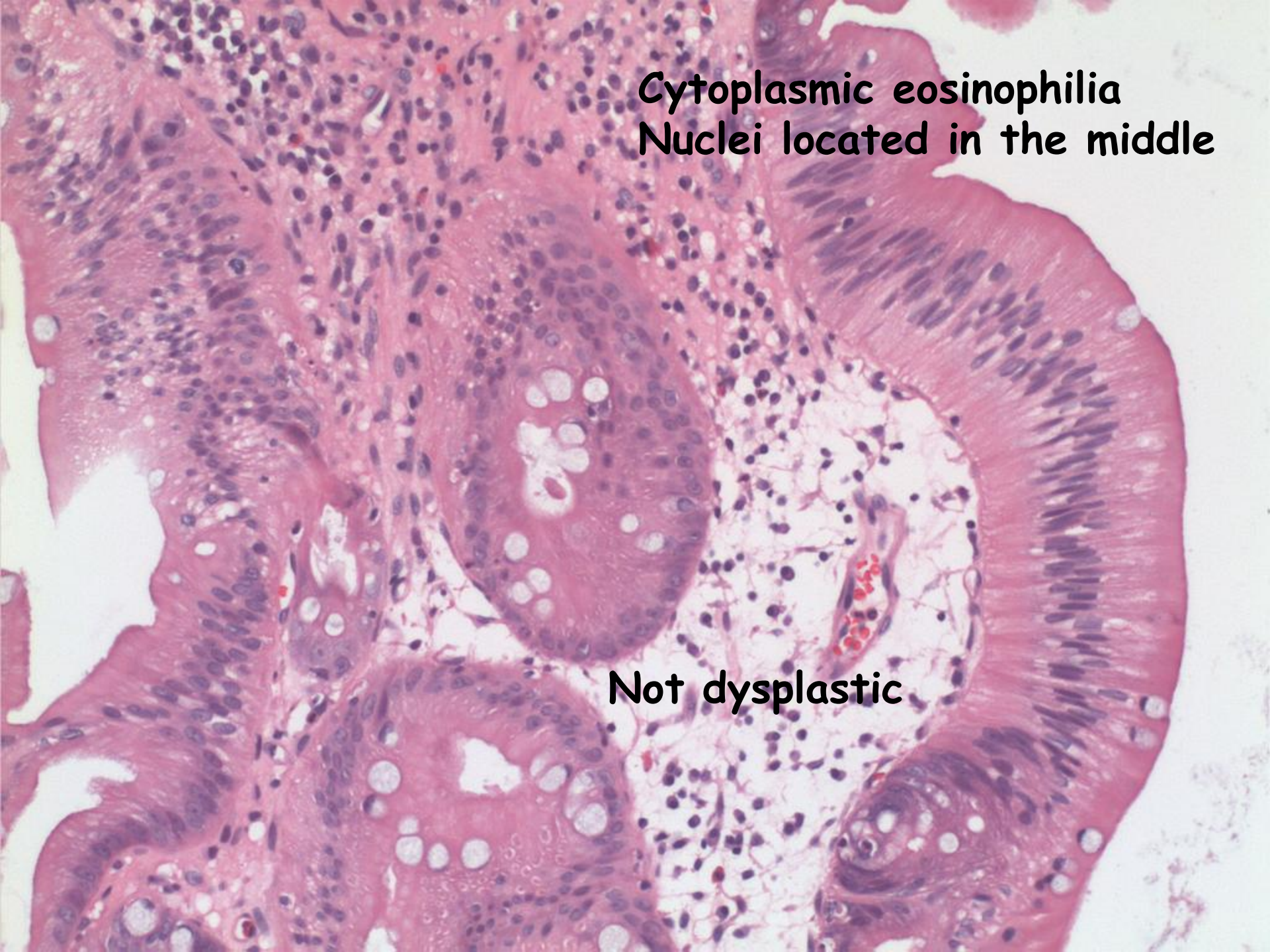


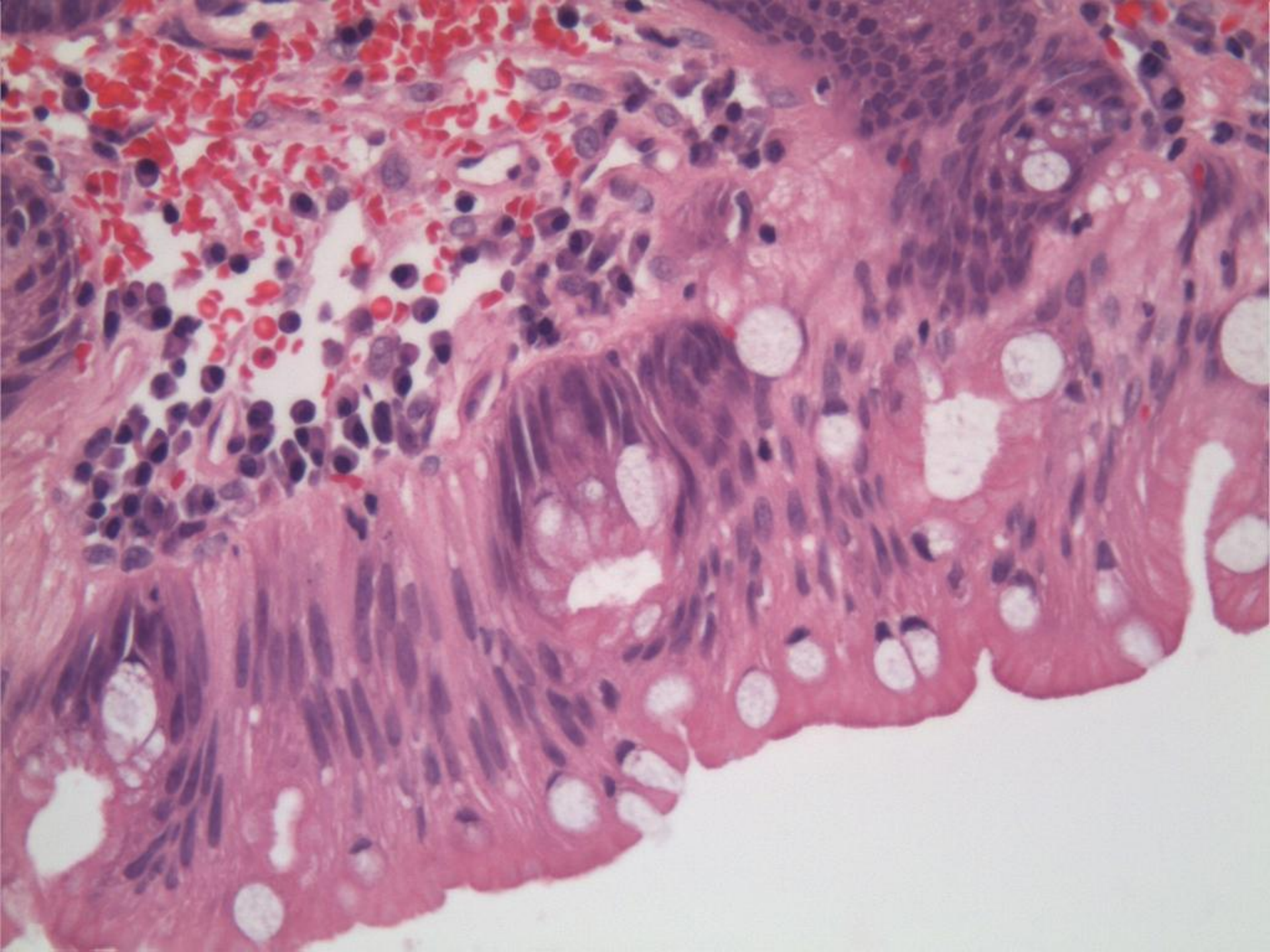
TSA

- Entire colon (mostly left)
- > 1cm, protuberant/pedunculated
- Villiform surface, complex architecture
- Irregular, branching crypts
- Ectopic crypts
- Eosinophilic cytoplasm
- Mild pseudostratification (midphasic nuclei)
- No surface maturation

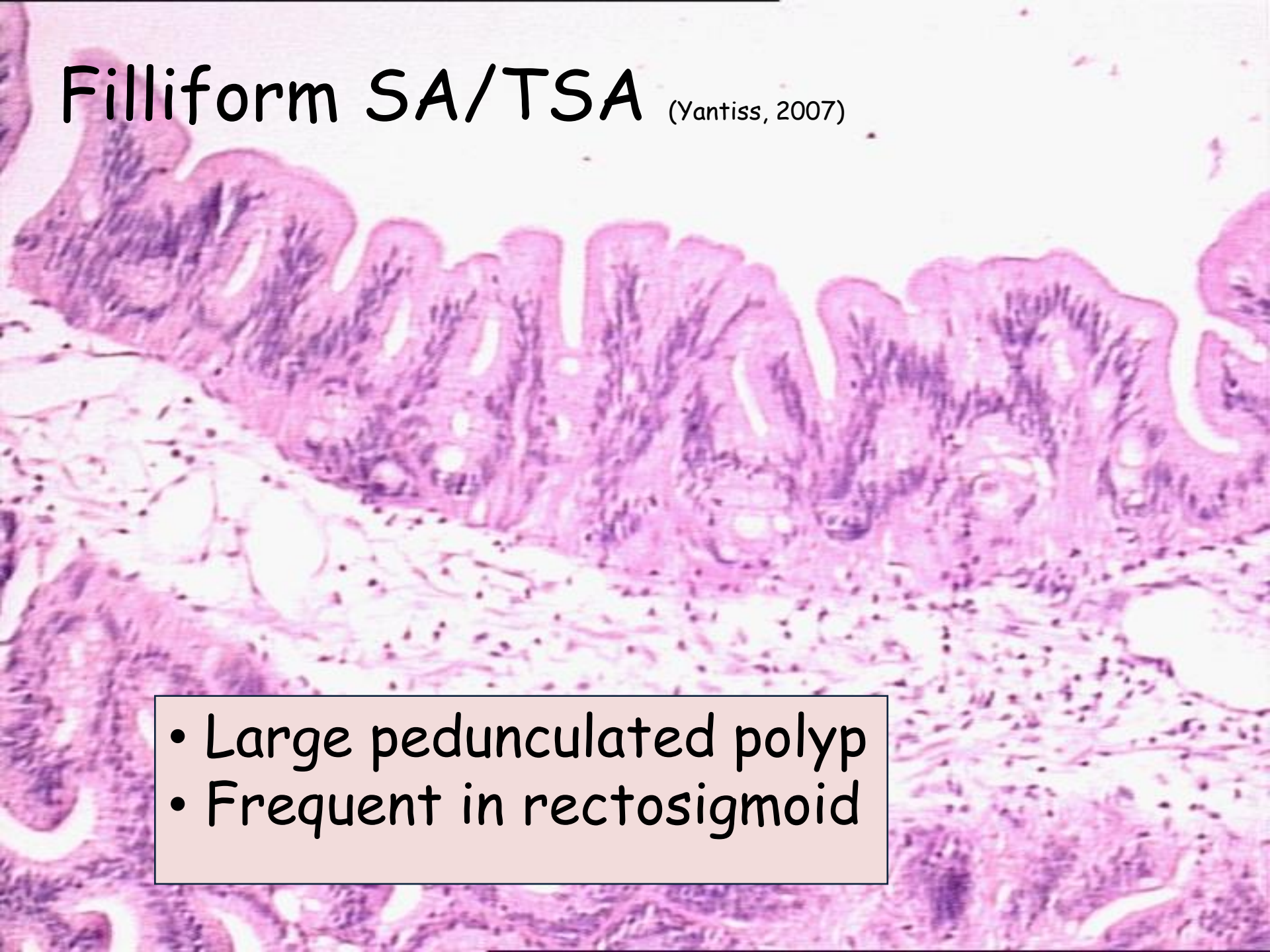

Ectopic crypts


Ectopic crypts

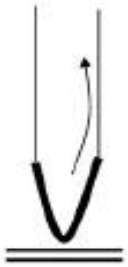

Cytoplasmic eosinophilia
Nuclei located in the middle
Not dysplastic



Filliform SA/TSA (Yantiss, 2007)

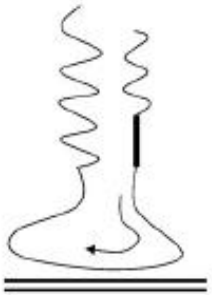


- Large pedunculated polyp
- Frequent in rectosigmoid

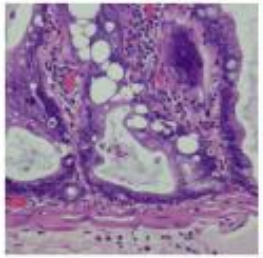


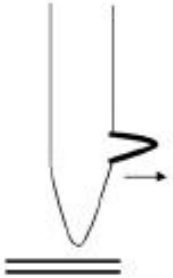
Normal crypt. Proliferation occurs at the base of the crypts and cells mature toward the lumen (arrow)

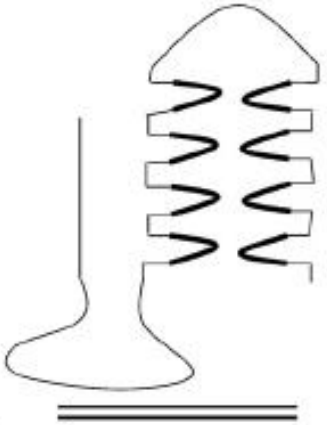
Normal crypt



Early stage with mover proliferativ side of cry arrow) and bidirectiona maturation arrow)







Normal crypt

Early stage of TSA with proliferative zone on side of crypt. Outward growth creates ectopic crypt (arrow)

Fully developed TSA with multiple ectopic crypts lining villi

Type	Synonyms	Histological features[a]				Genetic features[b]			
		Crypts	Proliferation	Cytological dysplasia	Mucin type	BRAF mutation	KRAS mutation	CIMP	MLH1 methylation
TSA	Serrated adenoma; filiform serrated adenoma	Hyperserrated in part owing to formation of ectopic crypts	Proliferation present at base of ectopic crypts	May be present, usually in the form of cells with eosinophilic cytoplasm	None or goblet cells	+[c]	+[c]	++	–
Serrated polyposis	Hyperplastic polyposis; giant hyperplastic polyposis	Mostly SSA/P with some MVHP	As per polyp subtype	Present as disease advances	As per polyp subtype	++[c]	+[c]	+++	+

WHO 2010

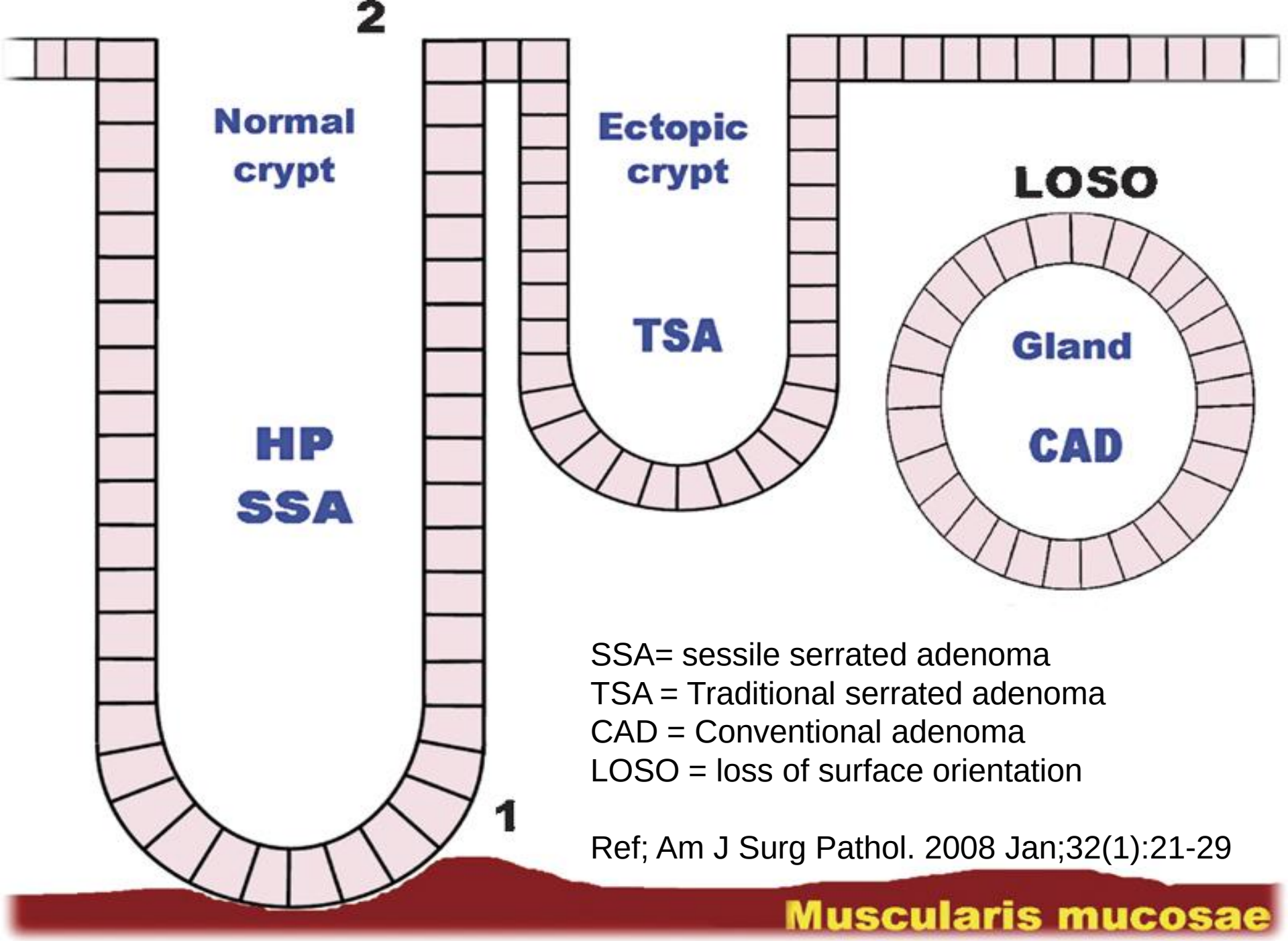
Morphological characteristics of tubal gut adenomas			
	SSA/P	**TSA**	**TA**
Location	Right colon	Throughout, 60% left	Throughout, 60% left
Shape	Flat	Mostly pedunculated	Mostly pedunculated
Dysplasia	Absent or minimal	Present	Present
Surface maturation	Present	Absent	Absent
Serration	Present	Present	Absent
Basal crypt dilation	Present	Absent	Can be present
Horizontal crypts	Present	Absent	Can be present
Branched crypts	Present	Absent	Can be present
Basal crypt serration	Present	Absent	Absent
Nuclear shape	Round to oval	Tall columnar	Tall columnar
Cytoplasm	Eosinophilic	Eosinophilic	Basophilic

What is the difference between a sessile serrated adenoma and a traditional serrated adenoma?

SSA V TSA

- Looks like HP
- Lacks conventional dysplasia

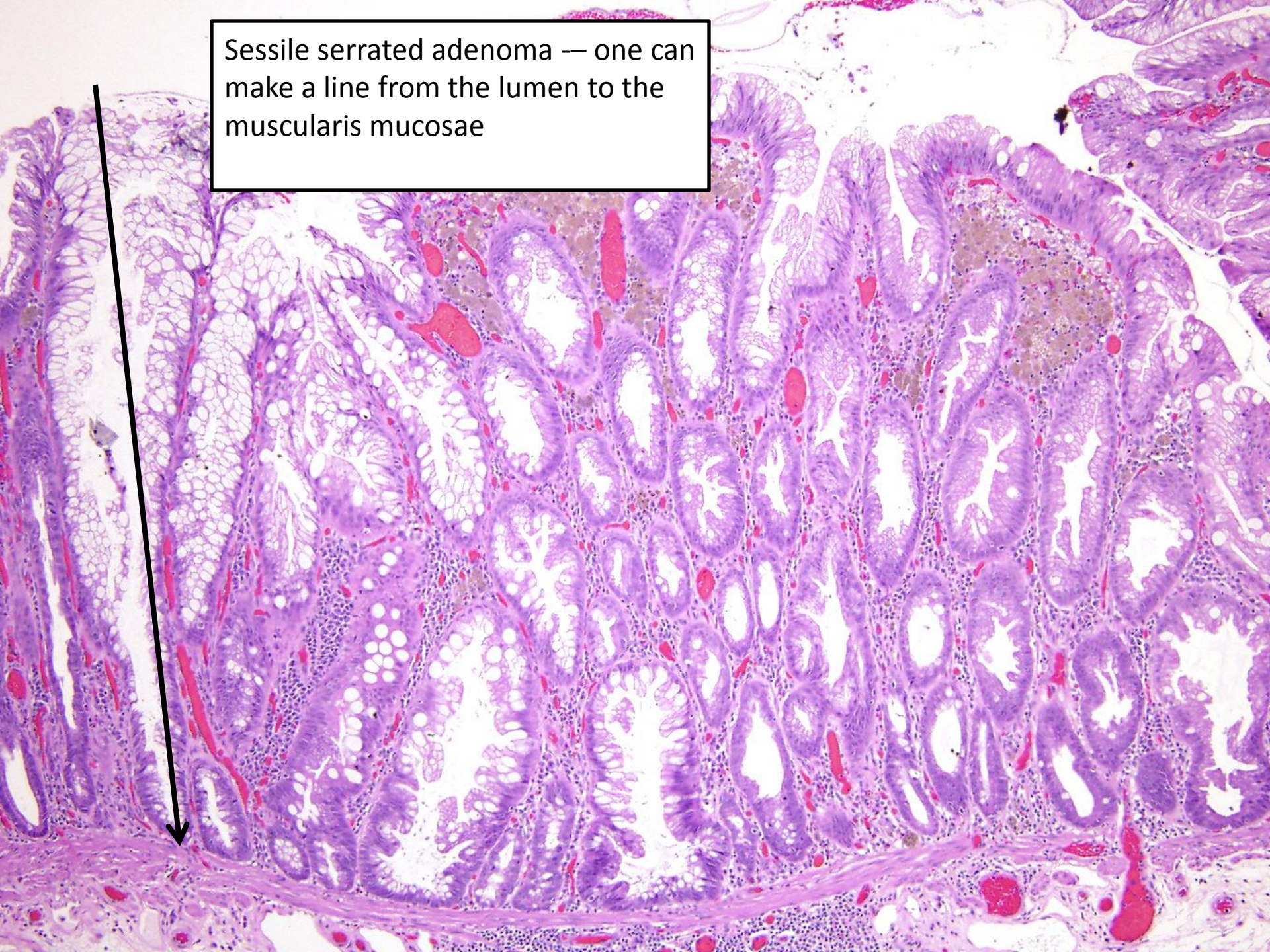
- Has pink cytoplasm and serration
- Has “pencillate” nuclei like conventional adenomas

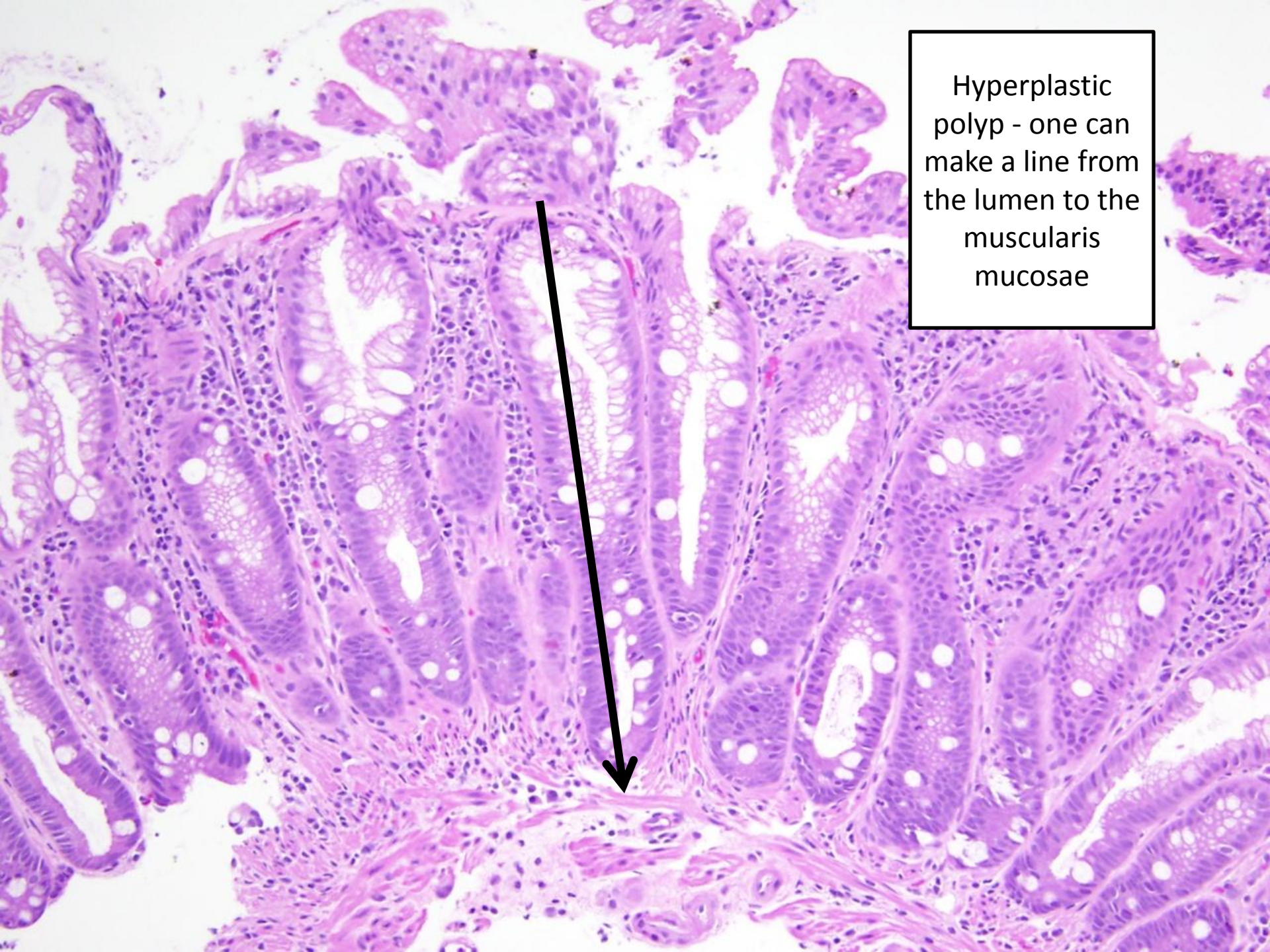


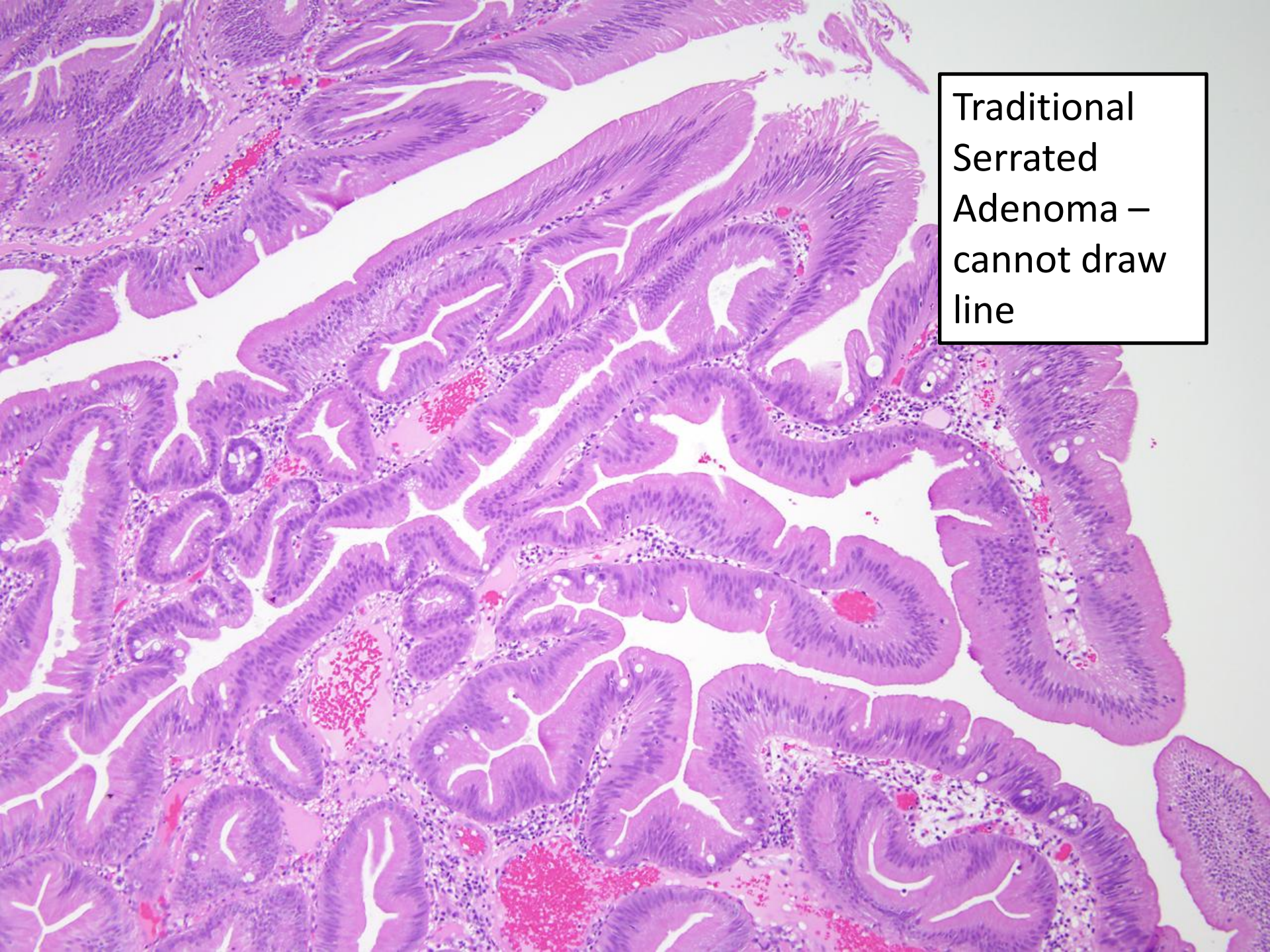
SSA= sessile serrated adenoma
TSA = Traditional serrated adenoma
CAD = Conventional adenoma
LOSO = loss of surface orientation

Ref; Am J Surg Pathol. 2008 Jan;32(1):21-29


Sessile serrated adenoma – one can make a line from the lumen to the muscularis mucosae


Sessile serrated adenoma -– one can make a line from the lumen to the muscularis mucosae

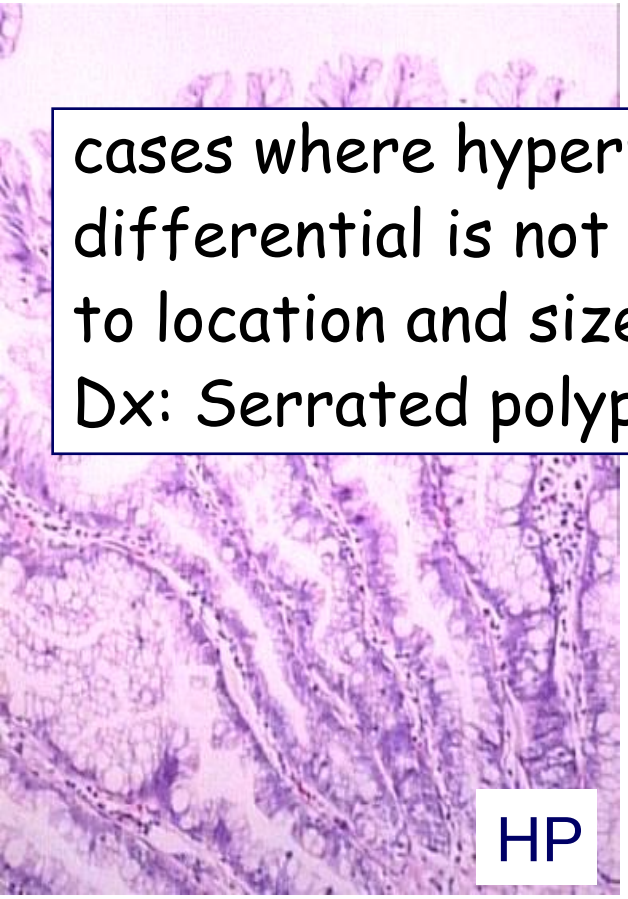

Hyperplastic polyp - one can make a line from the lumen to the muscularis mucosae

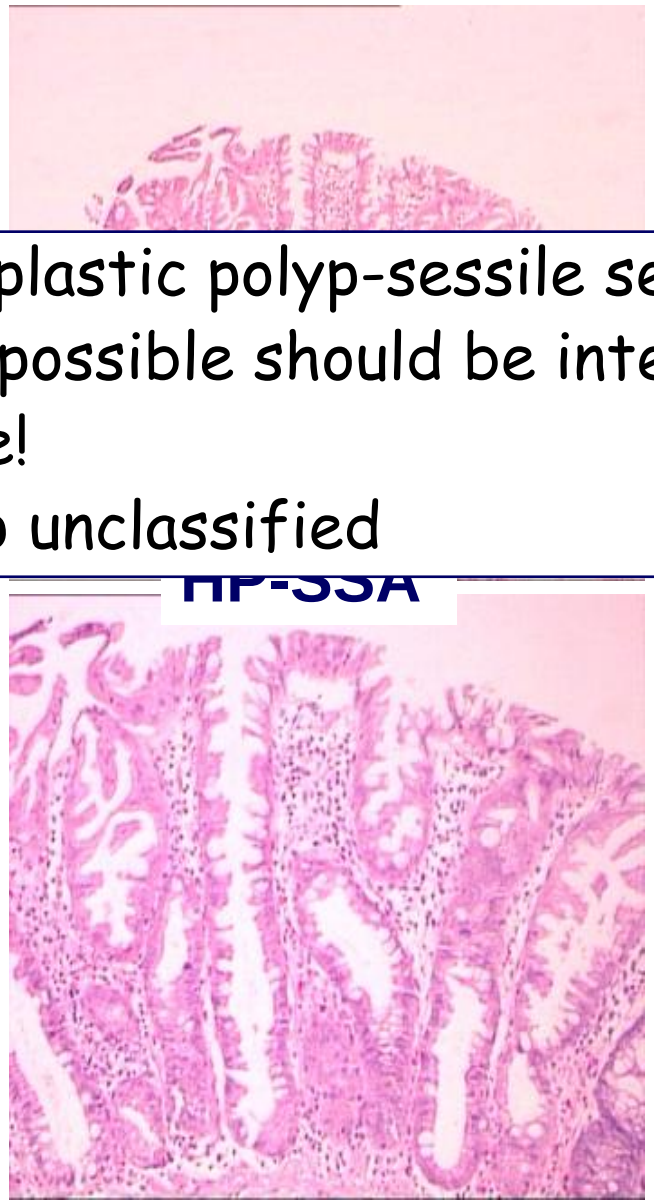

Traditional
Serrated
Adenoma –
cannot draw
line

Reproducibility?

- Insufficiently sharp criteria?
- Progression towards SSA/P of a subgroup of HPs or towards TSA of a subgroup of SSA/Ps?

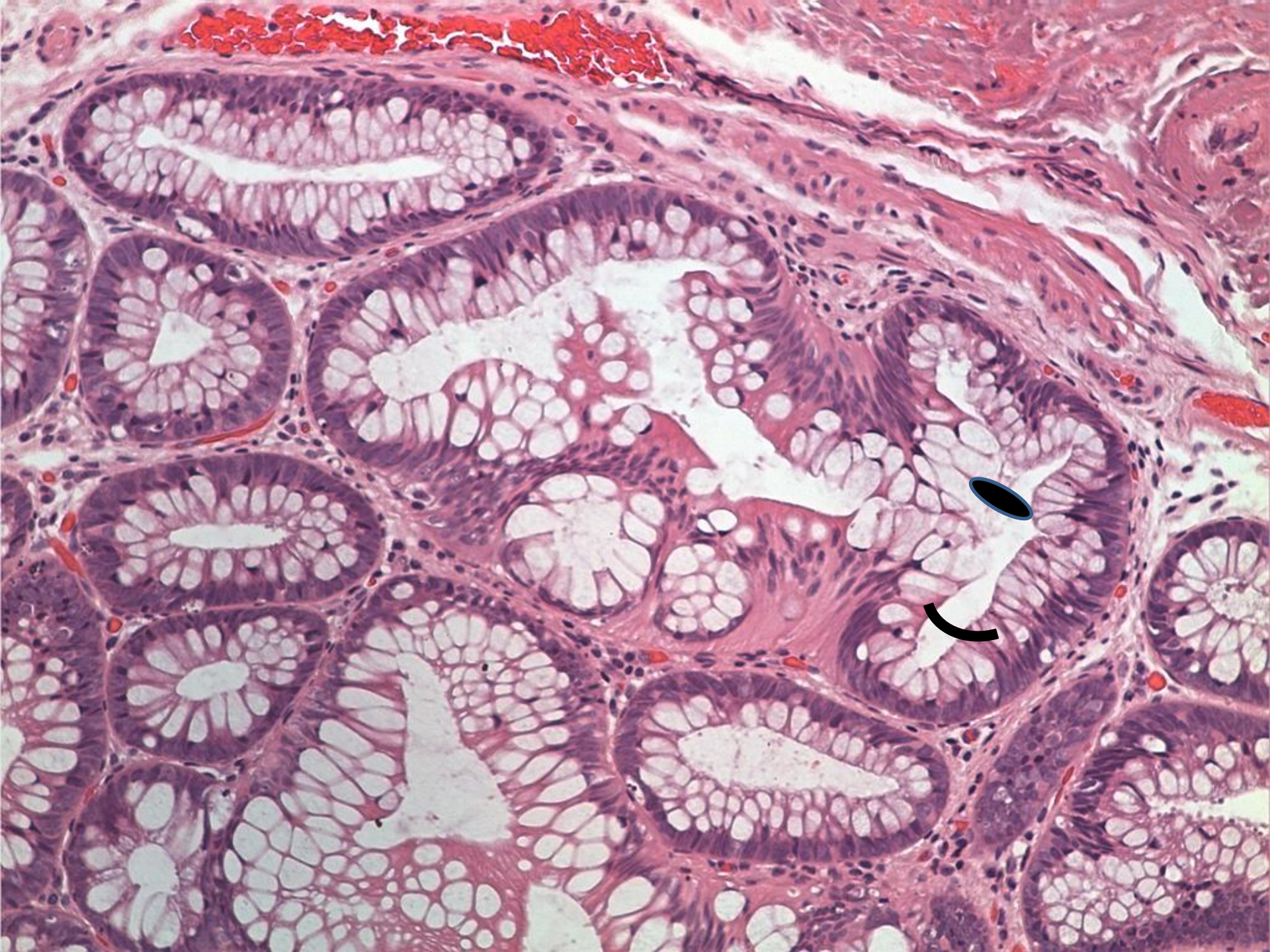
Intermediate forms





cases where hyperplastic polyp-sessile serrated adenoma differential is not possible should be interpreted according to location and size!

Dx: Serrated polyp unclassified



Farris, 2008	185 SPs - 5 observers	0.55
Bariol, 2003	380 (SPs + Adenomas) - 2 observers	No kappa
Bustamante-Balen, 2009	195 SPs - 2 observers	0.14
Glatz, 2007	20 SPs - 168 participants (internet quiz)	No kappa High interobserver variation in SSA
Sandmeier, 2007	102 SPs	No kappa
Wong, 2009	60 polyps - 4 observers	0.49
Khalid, 2009	40 SPs - 3 observers	0.16
Gunia S, 2011	49 SPs - 3 observers (trainee)	0.224-0.654
Denis B, 2009	14 SPs - 2 observers	0.41
Ensari A, 2011	70 SPs – 20 observers	0.306 (0.20-0.58)

Overall agreement for the first & second rounds

Rounds	1st group (n=15)	2nd group (n=55)	Total (n=70)
1st Round **kappa value** **CI lower-CI upper** **p value**	0.202 0.147- 0.256 p<0.001	0.349 0.320 - 0.377 p<0.001	0.318 0.293 - 0.343 p<0.001
2nd Round **kappa value** **CI lower-CI upper** **p value**	0.587 0.543 - 0.632 p<0.001	0.330 0.304 - 0.356 p<0.001	0.306 0.281 – 0.332 p<0.001

Overall agreement for diagnostic categories

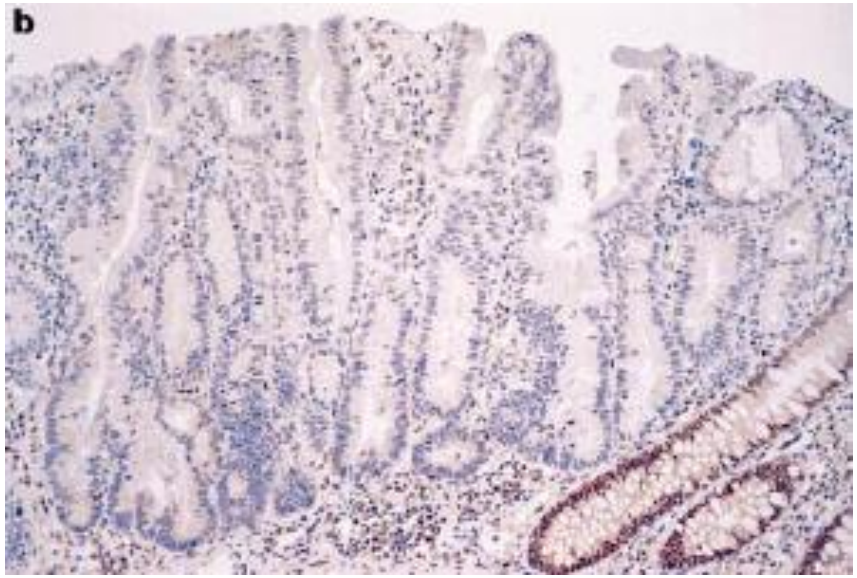
1st Round	HP	SSA	TSA	MP	UCP
1st group (n=15)	0.315 p<0.001	0.223 p<0.001	0.181 NS	0.107 NS	0.021 NS
2nd group (n=55)	0.443 p<0.001	0.323 p<0.001	0.512 p<0.001	0.235 p=0.01	0.009 NS
Total (n=70)	0.415 p<0.001	0.301 p<0.001	0.433 p<0. 001	0.221 p=0.014	0.013 NS
2nd Round	HP	SSA	TSA	MP	UCP
1st group (n=15)	0.897 p<0.001	0.997 p<0.001	0.545 NS	0.072 NS	0.016 NS
2nd group (n=55)	0.900 p<0.001	0.990 p<0.001	0.455 p<0.001	0.211 p=0.013	0.040 NS
Total (n=70)	1.00 p<0.001	1.00 p<0.001	1.00 p<0.001	1.00 p=0.014	0.017 NS

Can molecular typing help?

- Immunohistochemistry
  - Ki67
  - MUC6
  - Beta-catenin
  - p53
- Genome analysis
  - MMR
  - BRAF/KRAS
  - CIMP

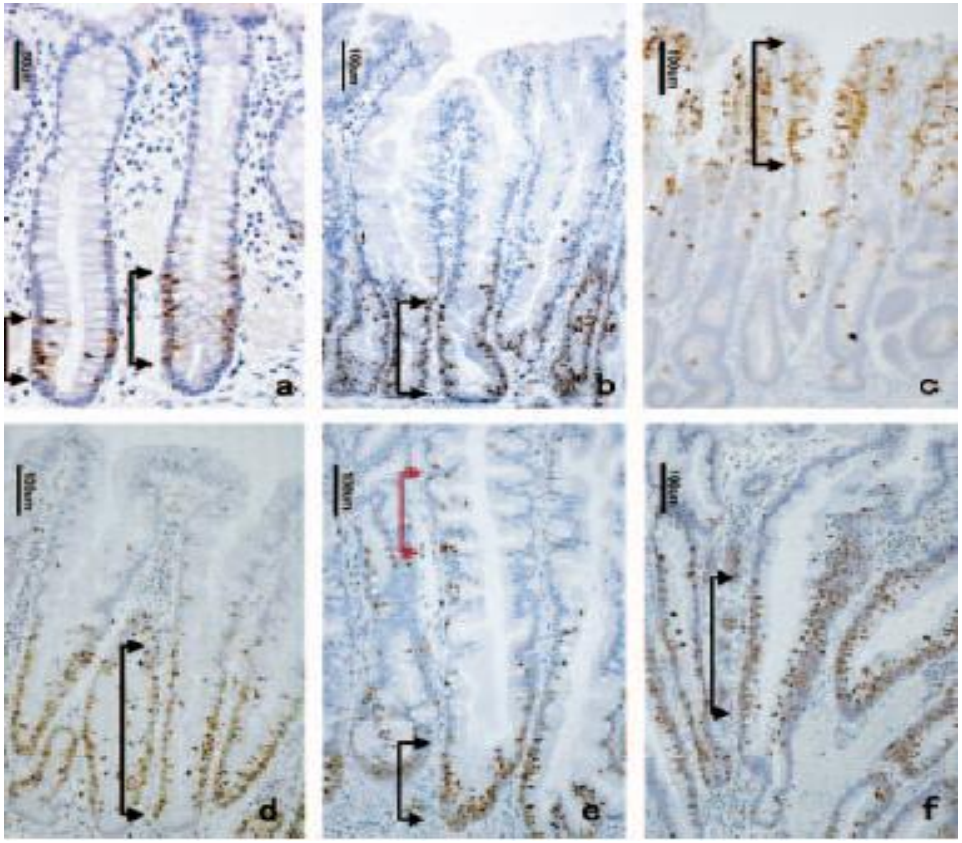
IHC

hHML-1
Focal loss



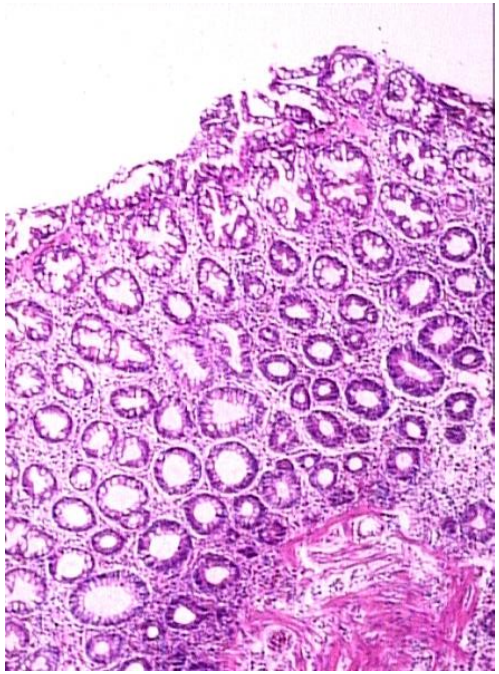
Jass, 2000

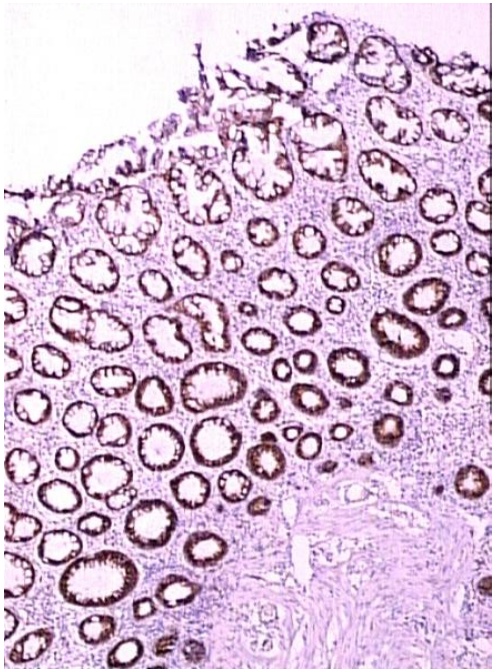
Ki-67
Abnormal proliferation



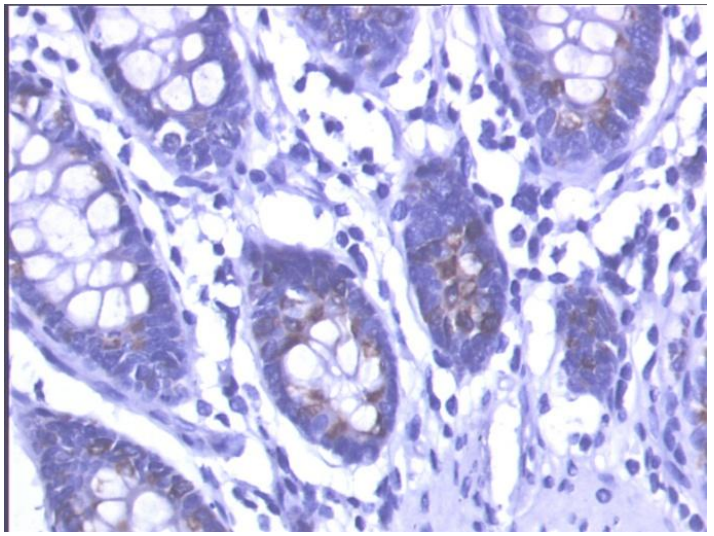
Koike, 2003

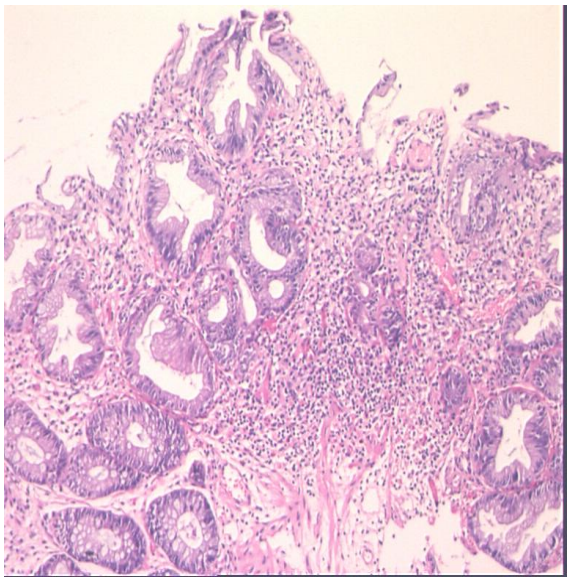
MUC 5AC

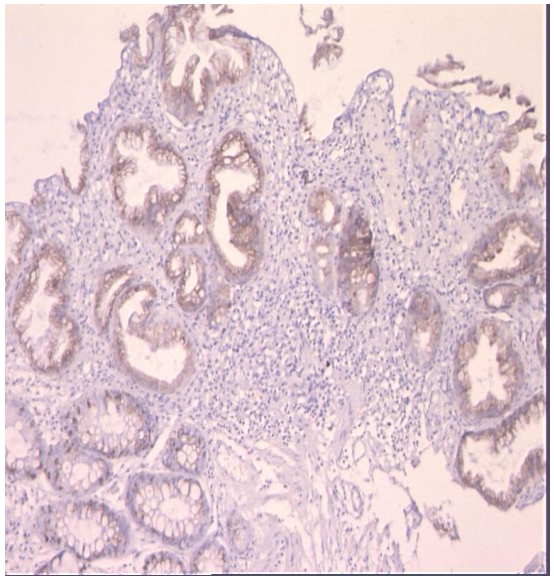


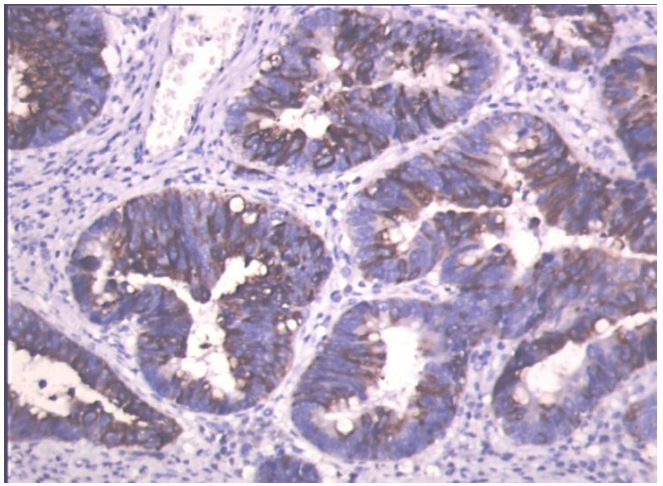


MUC6









Perçinel, 2007

Fujita, 2011 - Genome

TABLE 3. Immunohistochemical Features of HPs, SSAs, and SSANs

	HP (n = 66)	SSA (n = 53)	SSAN (n = 12)
p53	0 (0%)	0 (0%)	5 (41.7%)*
β-Catenin			
Loss of membrane expression	7 (10.6%)	11 (20.8%)	1 (8.3%)
Nuclear expression	0 (0%)	0 (0%)	6 (50%)*

*$P < 0.01$ vs. all other groups.

HP indicates hyperplastic polyps; SSA, sessile serrated adenoma; SSAN, sessile serrated adenoma with neoplastic progression.

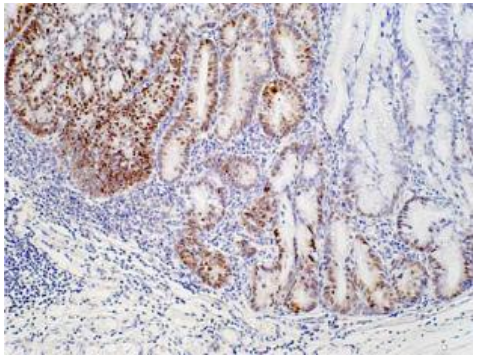
TABLE 4. Molecular Features of HPs, SSAs, and SSANs

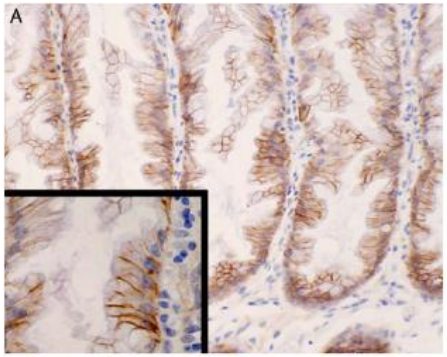
	HP (n = 24)	SSA (n = 23)	SSAN (n = 11)
BRAF mutation	11 (45.8%)	14 (60.9%)	7 (63.6%)
KRAS mutation	1 (4.2%)*	1 (4.4%)†	0 (0%)
PIK3CA mutation	0 (0%)	0 (0%)	0 (0%)

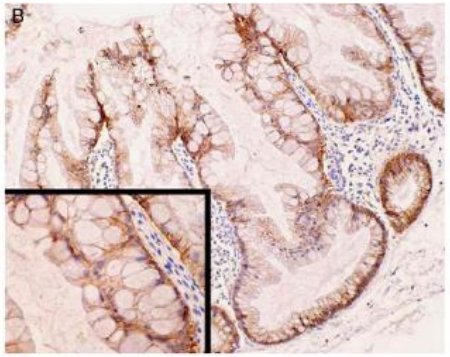
*G12S (GGT→AGT).

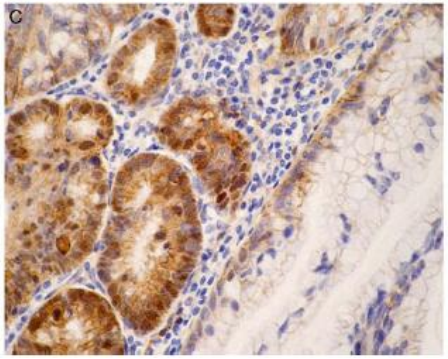
†G13D (GGC→GAC).

HP indicates hyperplastic polyps; SSA, sessile serrated adenoma; SSAN, sessile serrated adenoma with neoplastic progression.



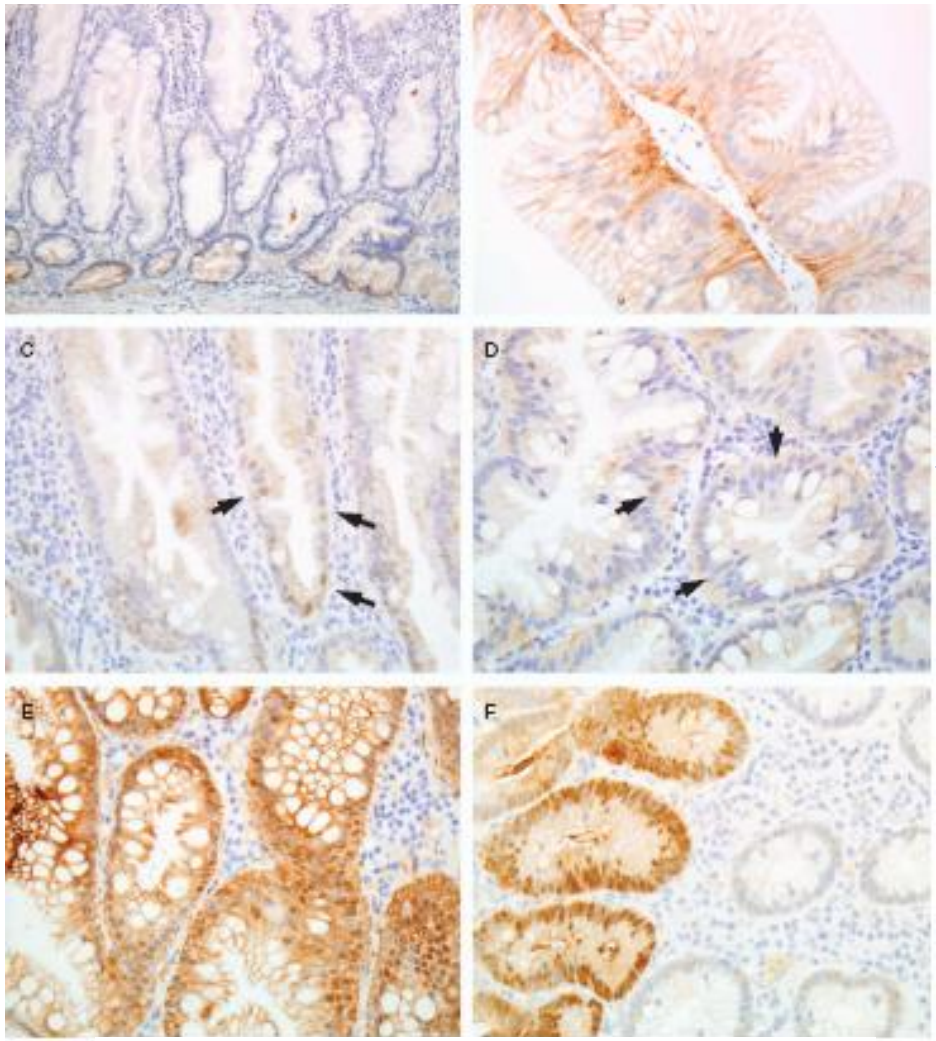






Beta-catenin Nuclear Labeling is a Common Feature of Sessile Serrated Adenomas and Correlates With Early Neoplastic Progression After *BRAF* Activation

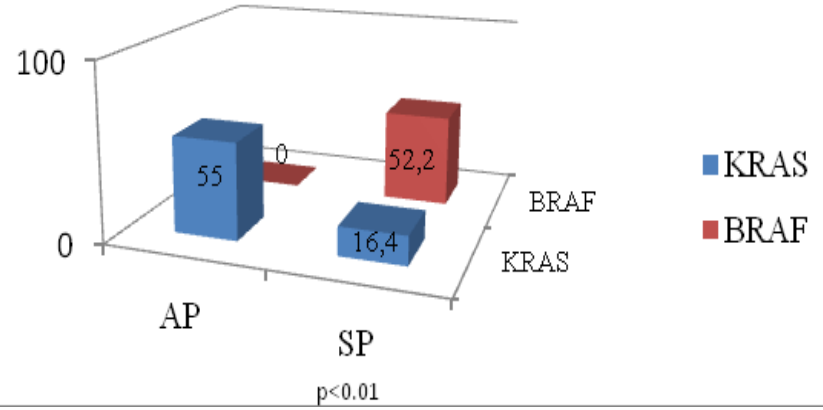
Shinichi Yachida, MD, PhD, Shiyama Mudali, MD,* Sherri A. Martin, BS,*†*
Elizabeth A. Montgomery, MD, and Christine A. Iacobuzio-Donahue, MD, PhD*‡*



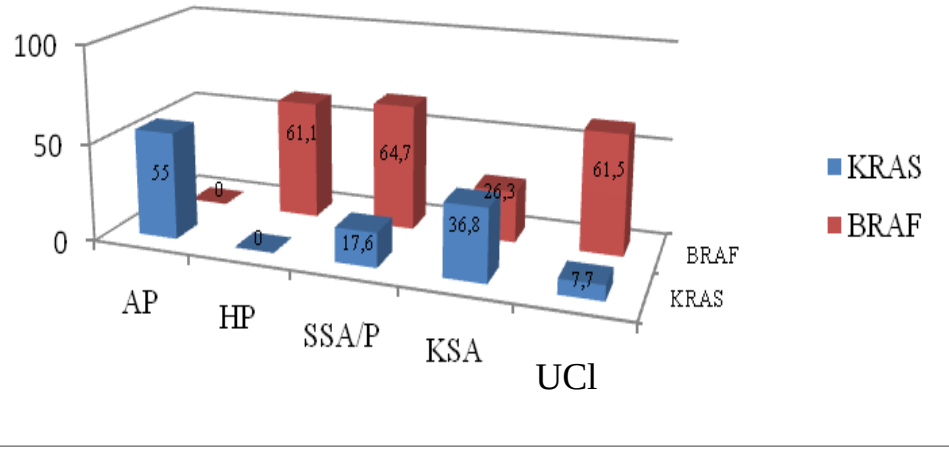
All BRAF Mutated !

Am J Surg Pathol • Volume 33, Number 12, December 2009

KRAS & BRAF mutations in APs and SPs



KRAS & BRAF mutations in SP subtypes



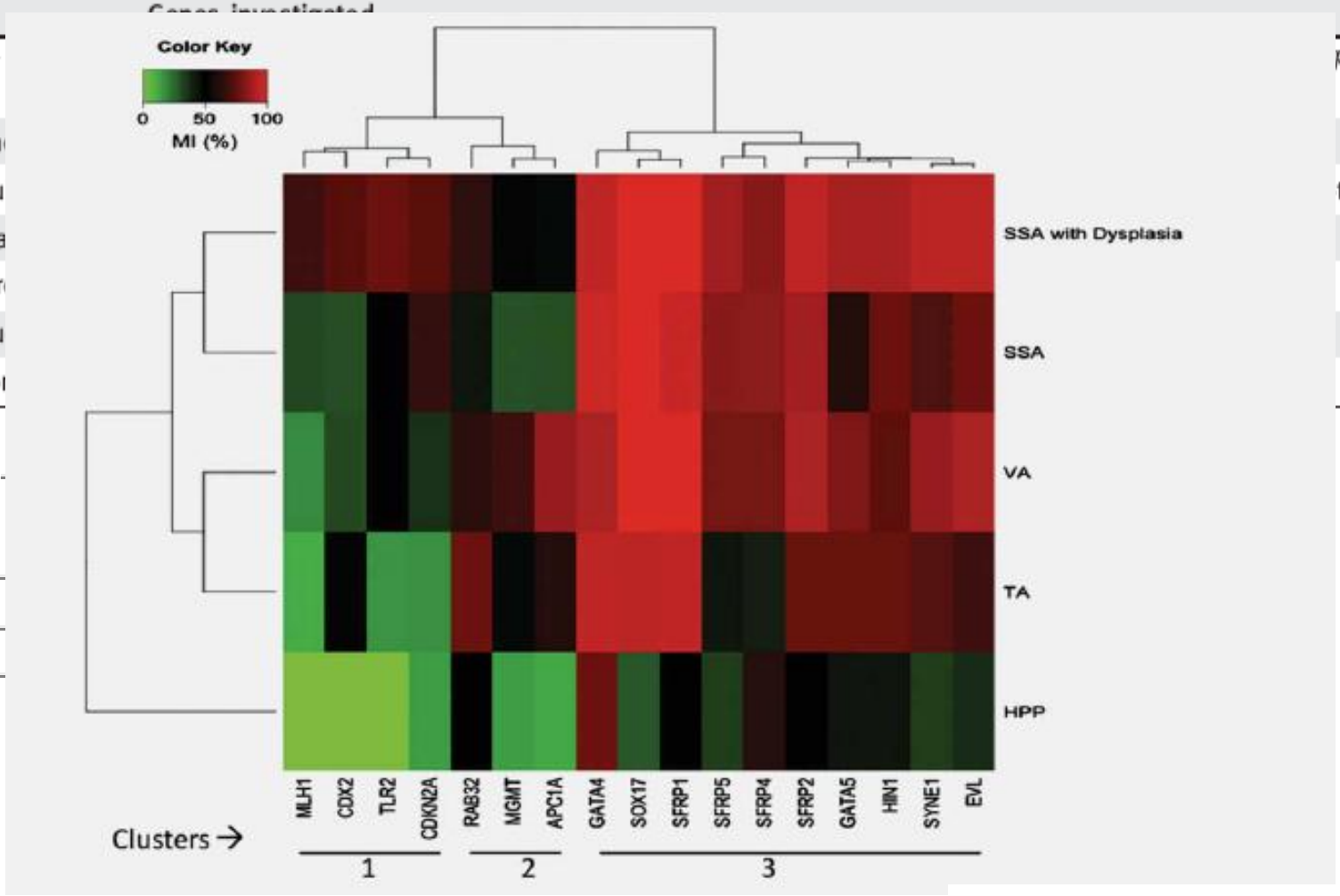
Erdoğan, 2011

Sessile serrated adenomas and classical adenomas: an epigenetic perspective on premalignant neoplastic lesions of the gastrointestinal tract

Mashaal Dhir[1], Shinichi Yachida[2], Leander Van Neste[3], Sabine C. Glöckner[4], Jana Jeschke[1], Emmanouil P. Pappou[1], Elizabeth A. Montgomery[2,5], James G. Herman[5], Stephen B. Baylin[5], Christine Iacobuzio-Donahue[2,5] and Nita Ahuja[1,5]

Table 1. Summary of gene names and pathways

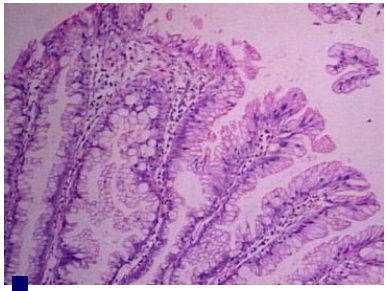
Pathways	Genes investigated
WNT signaling	*RP5, SOX17*
Gut embyogen	
Cell cycle regu	tein rab32)
Mismatch repa	
DNA damage r	
Signal transdu	
Cytoskeletal pr	



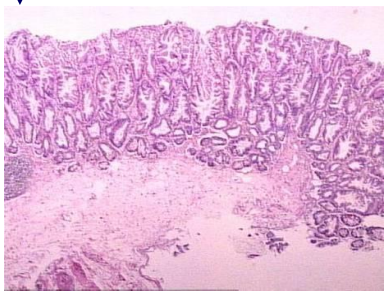
Panel 1 –
SFRP5
Panel 2 –
Panel 3 –
Panel 4 –

Int. J. Cancer: **129**, 1889–1898 (2011)

MVHP

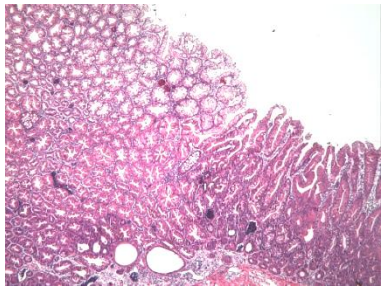


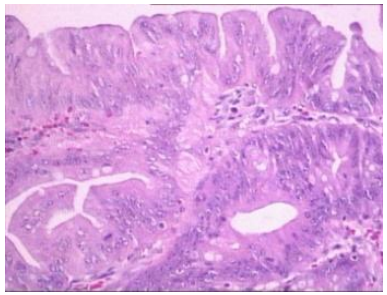
Promoter methylation



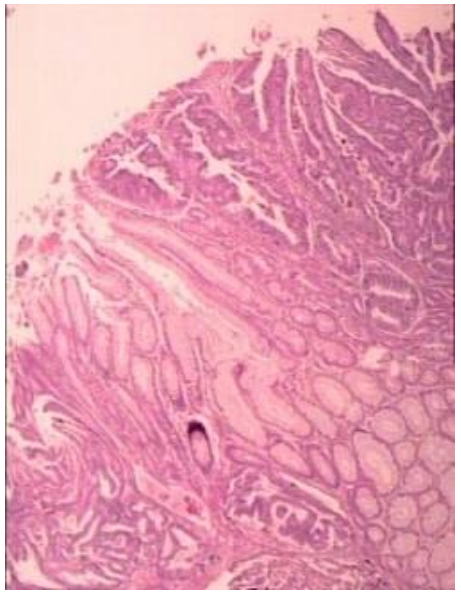
SSA/P

Dysplastic SSA/P





Adenocarcinoma



BRAF mutation (inhibition of apoptosis)

Methylation in MLH1 dysplasia

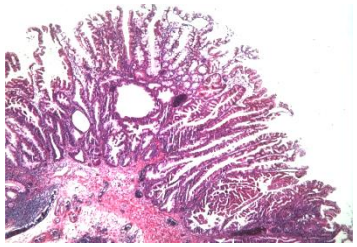
Mutations in oncogenes & tm suppressor genes

MSI –H CA

Variable rate of progression

Rapid rate of progression

TSA



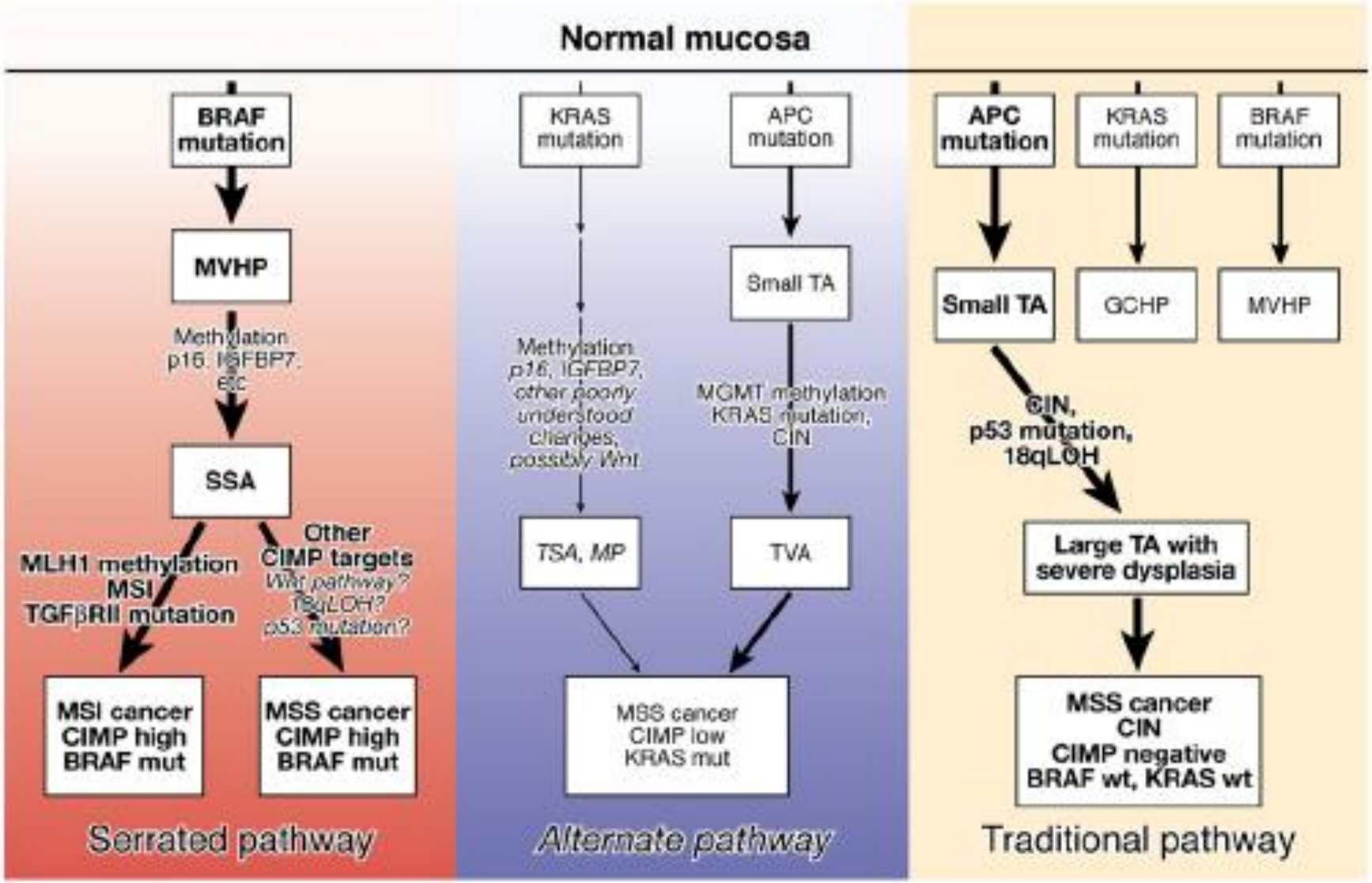
?

CIMP-H MSS CA

KRAS

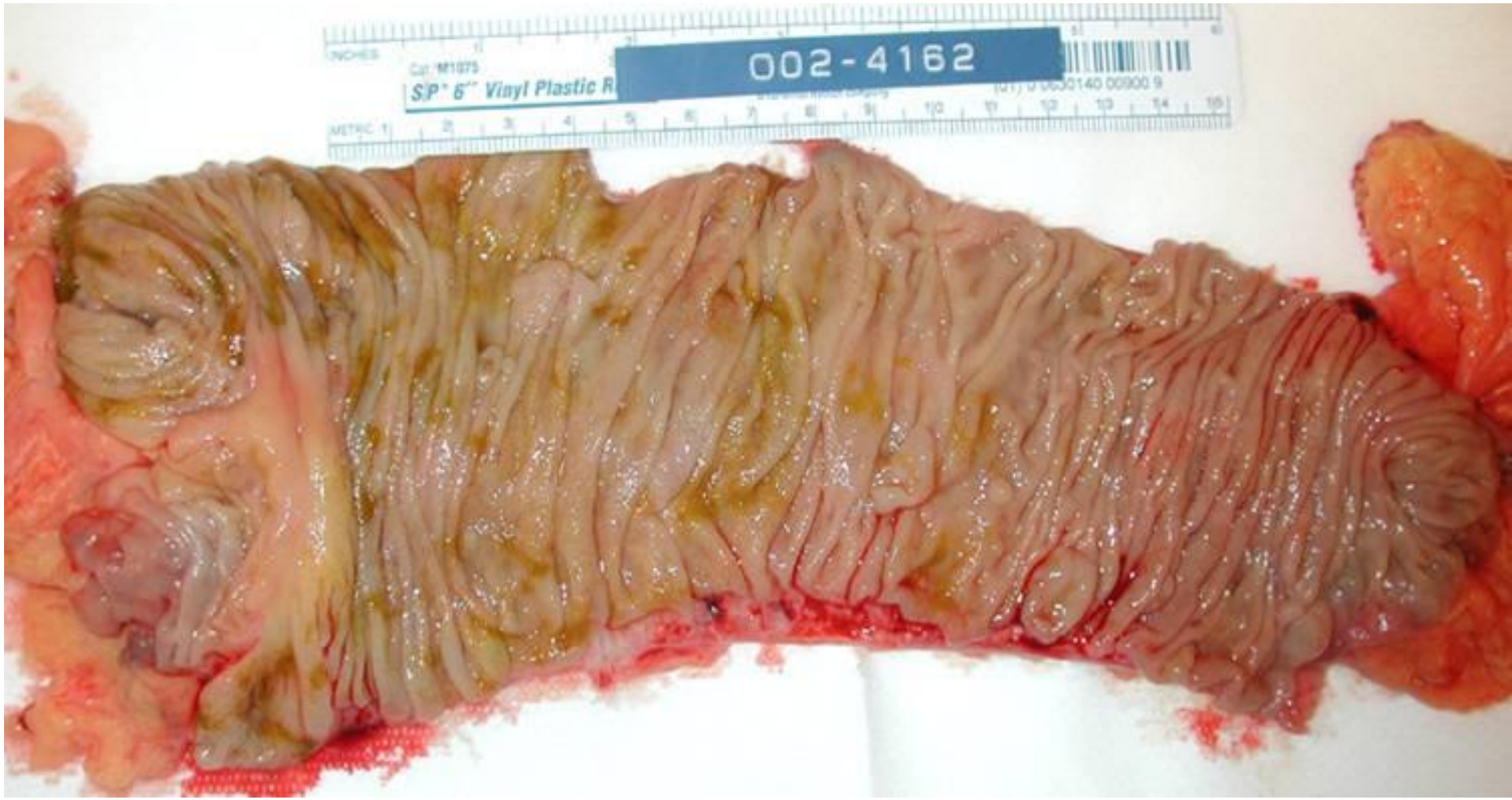
? MGMT methylation

? MSI-L CA
MSS CA



Leggett & Whitehall, 2010

SERRATED POLYPOSIS

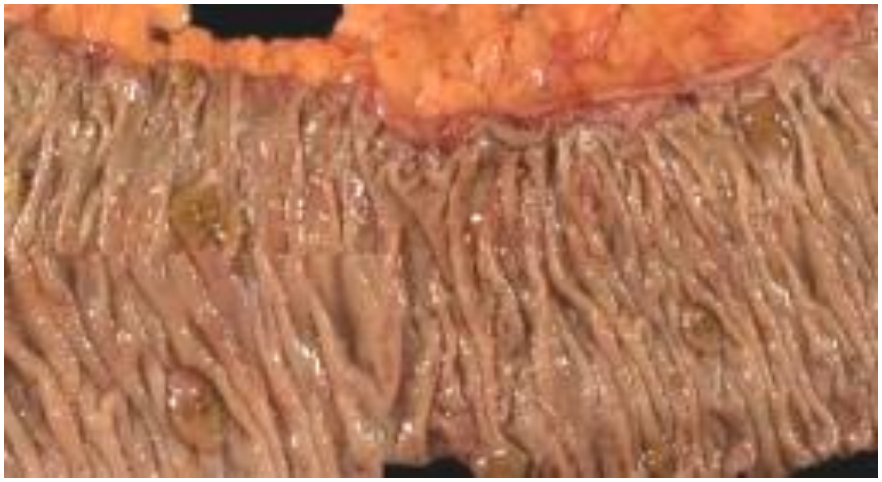


Serrated polyposis

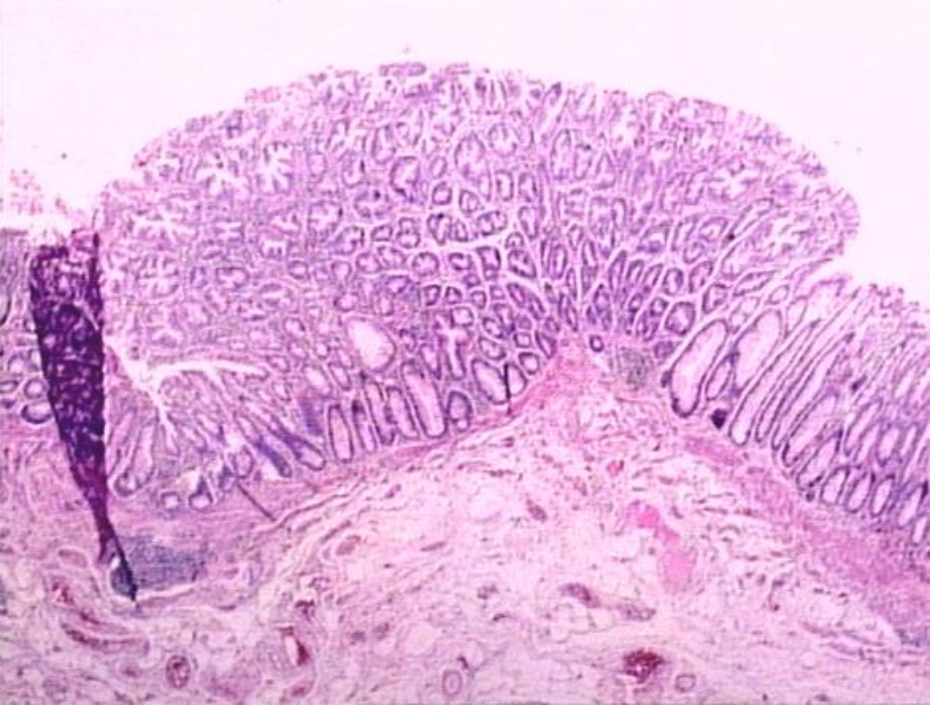
- At least 5 serrated polyps proximal to sigmoid colon,
  2 > 10mm

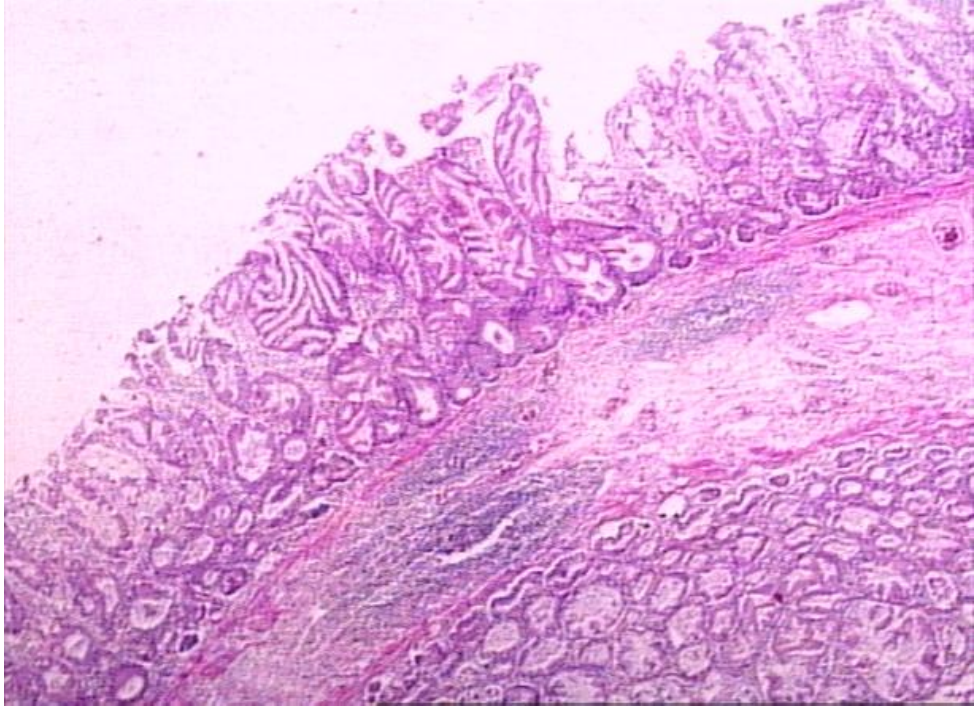
- Any number of serrated polyps proximal to sigmoid colon in a person with 1st degree relative with SPS

- >20 serrated polyps of any size throughout colon



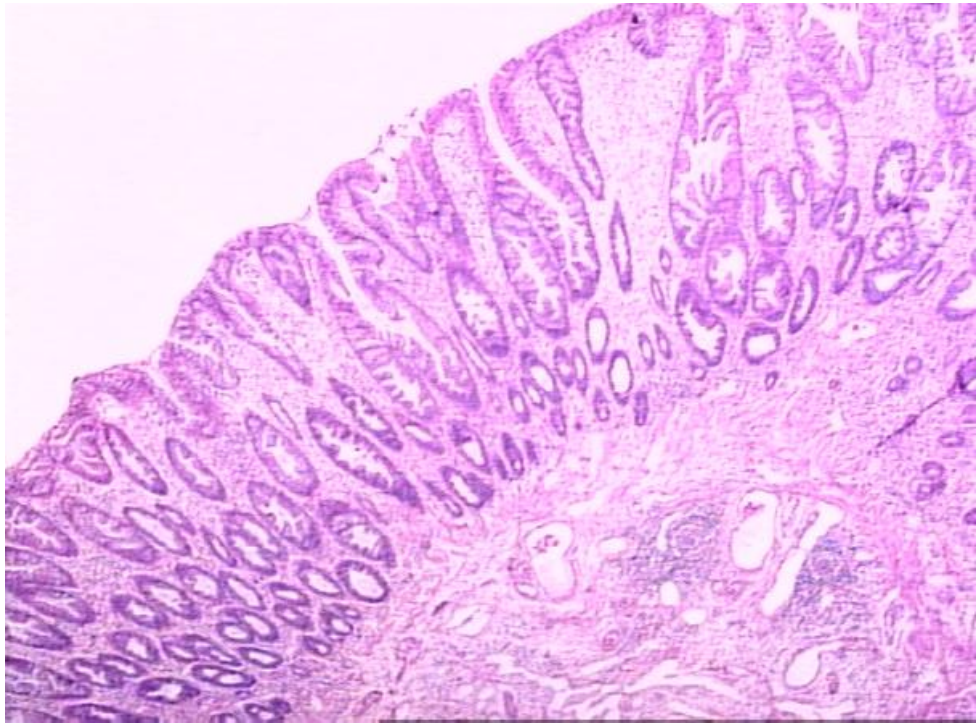
WHO, 2010

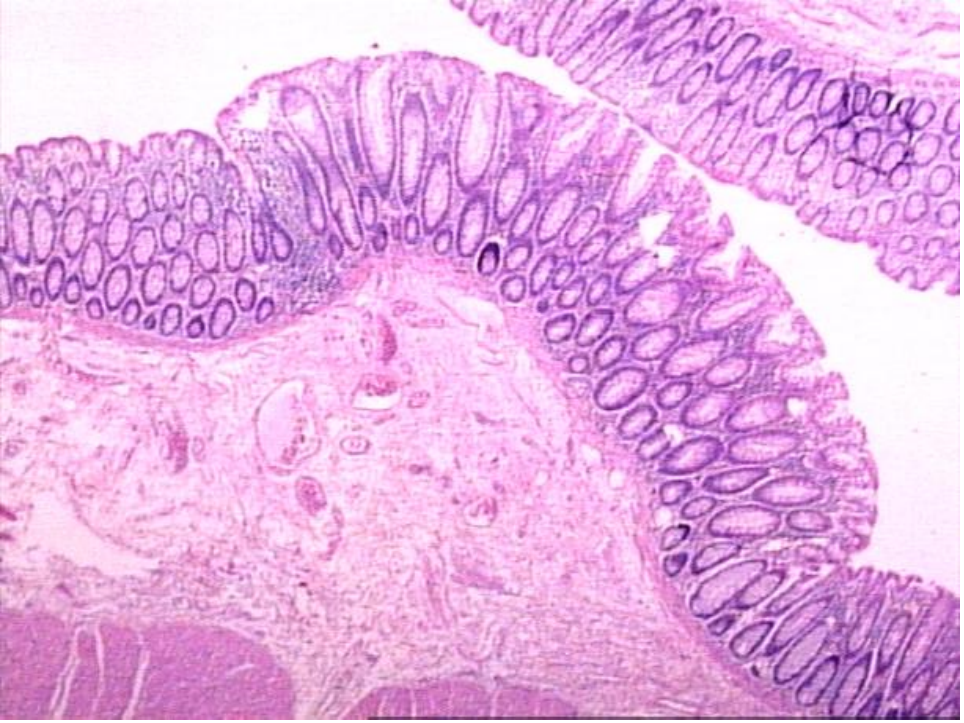


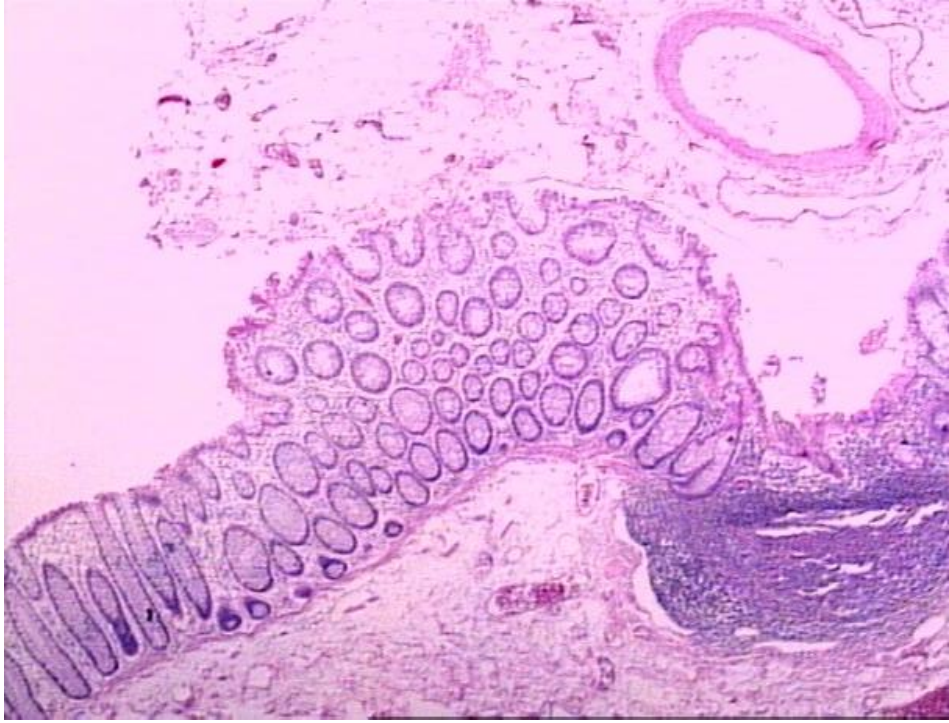


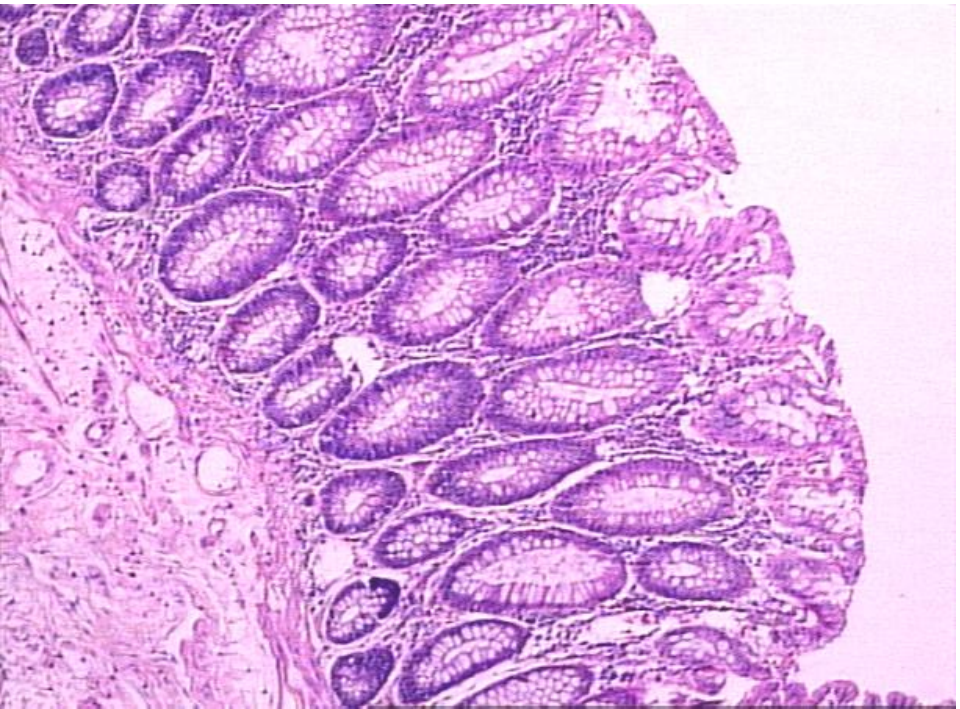
Type 1 SPS

- Multiple SSA/P
- Large polyps
- Proximal colon
- Ca risk ↑
- BRAF mutations









Type 2 SPS

- Numerous <5mm HP
- Entire colon
- Ca risk Ø
- KRAS mutations

Dealing with These "New" Polyps

- How common are they?
- How often do they progress to cancer?
- What should we all be doing about them?

How Common?

- Published UK survey [J Clin Pathol **2004**; 47: 682] – **2%** [31/1436] – not recognized yet
- **2006** figure from Australia – **9%** [Gastroenterology 2006; 131: 1400-1407]; endoscopists and pathologists were “in the know”

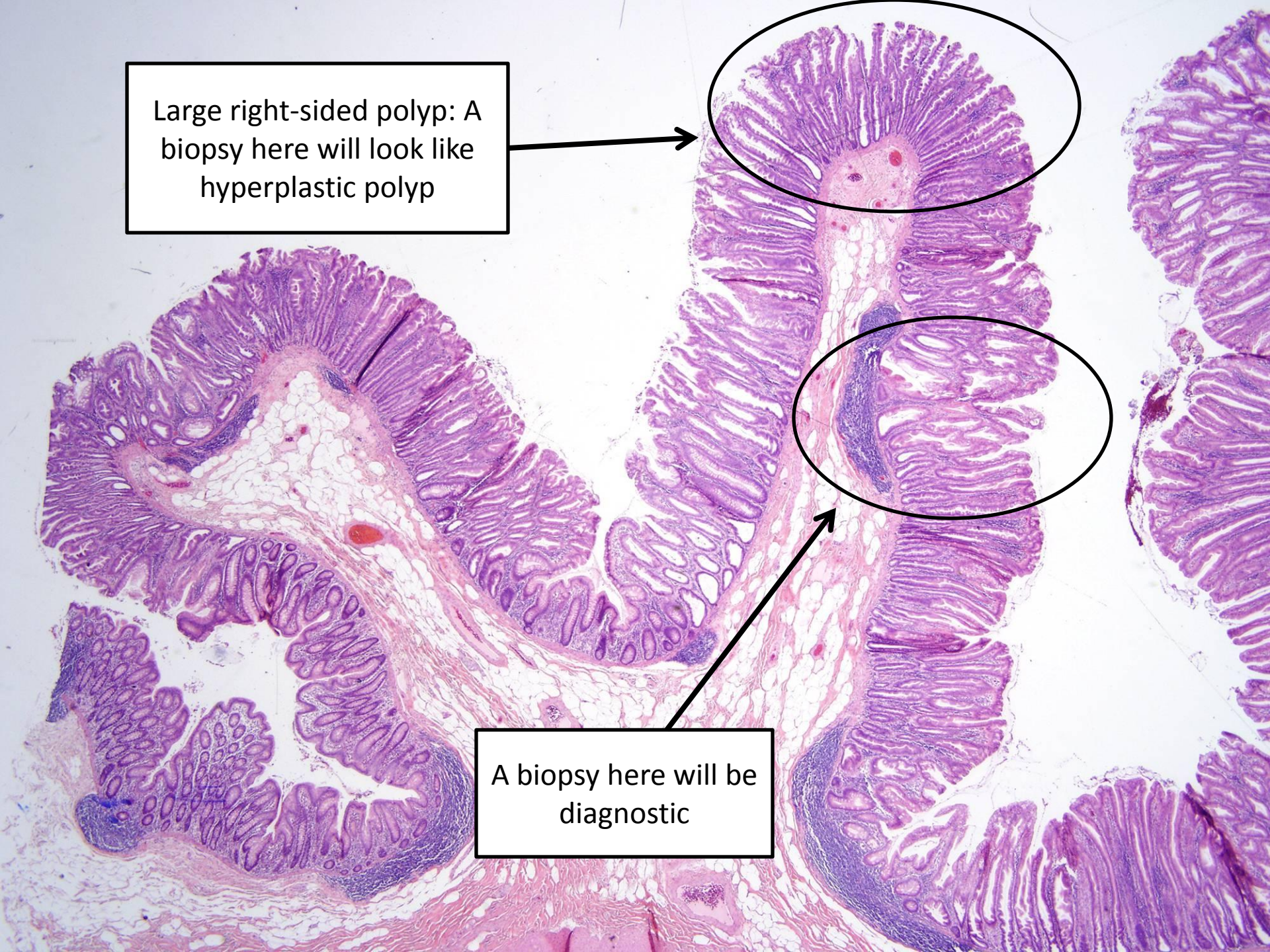
Cancer Progression Rate?

- Anecdotally a few per cent –Published estimate of 1/25 of such polyps of R colon
- In one small series of patients with hyperplastic polyposis, 7/12 developed cancers [a bit less than in adenomatous polyposis but these patients have far fewer polyps than those with FAP]

Cancer Risk and Rate of Growth

- 5 cancers in follow-up
  - 2/38 (5%) sessile serrated adenomas
  - 1/119 (0.8%) tubular adenomas
    - Statistically significant higher risk
  - 2/17 (12%) TVA
- Rate of growth (two endoscopies, divided size of polyp by time between two endoscopies)
  - HP (42): 1.36 mm/yr
  - SSA (26): 3.76 mm/yr
  - TA (50): 2.79 mm/yr

Lazarus et al. Am J Clin Pathol 2005;123:349-59


Large right-sided polyp: A biopsy here will look like hyperplastic polyp
A biopsy here will be diagnostic

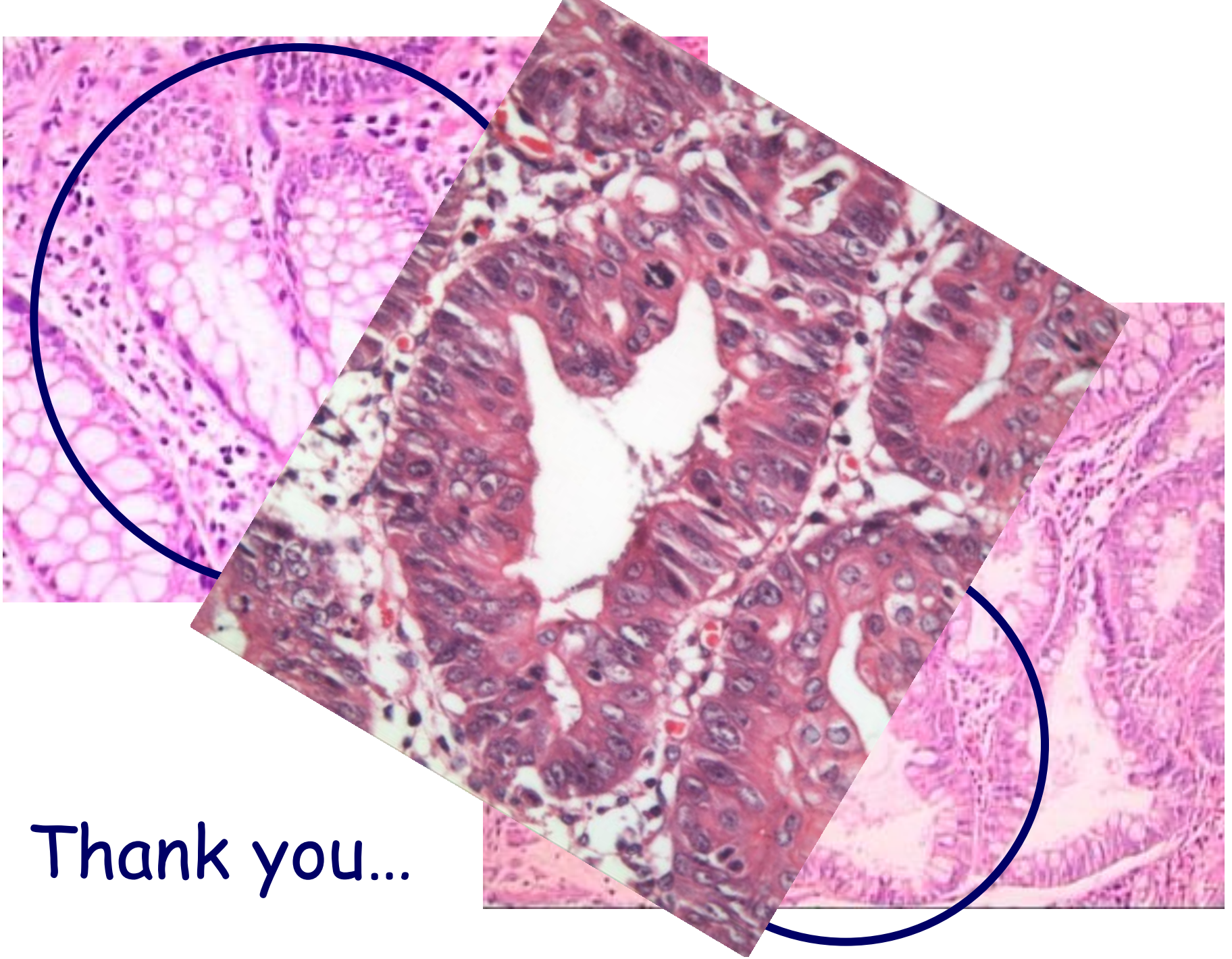
..in the future…

- Pathologists and endoscopists need to learn to better recognize this group of polyps - new endoscopic tecniques
- Consensus criteria will improve & standardize pathologic diagnosis
- Molecular data will become reliable
- Follow up data will provide information for better guidelines

..in real life?

- All polyps should be excised (except <5mm, distal, multiple HPs)
- >1cm polyps should be completely excised
- Few small polyps - 5 year interval
- Large polyps - 3 year interval
- Dysplastic SSA/P control in 1 year, then 3 year interval

WHO 2010



Thank you…