Dysplasia and epithelial polyps in gastrointestinal tract

SALVADOR J. DIAZ-CANO

ORCID 0000-0003-1245-2859

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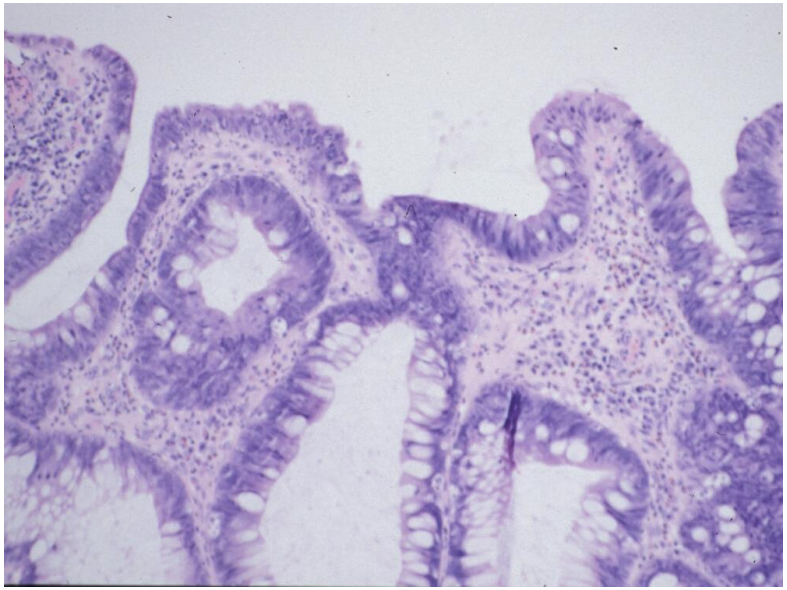
Dysplasia and Polyps of GI Tract

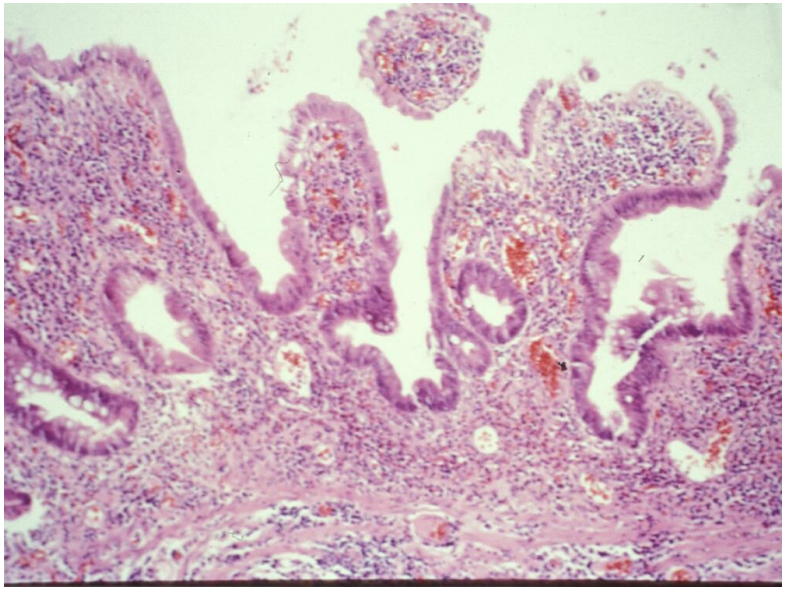
- **Dysplastic lesions, preceding invasive colonic neoplasm can present as flat or elevated lesions, are relevant due to:**
  - **High incidence in daily practice**
  - **It is an evolving area with diagnostic criteria frequently modified that result in low reproducibility**
  - **It is a key area for prevention and screening of CRC**
- **The main controversial areas are:**
  - **In the context of inflammatory bowel disease, and**
  - **Grading, subtyping, and staging of polyps**

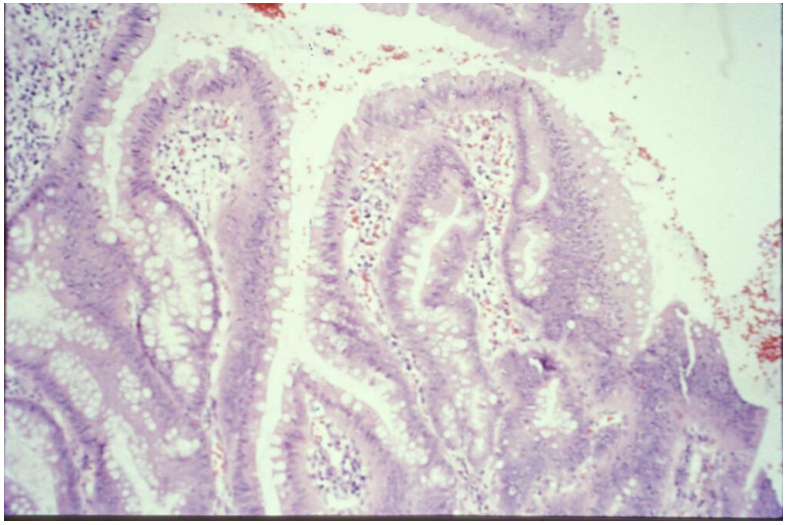
Colitis-associated dysplasia

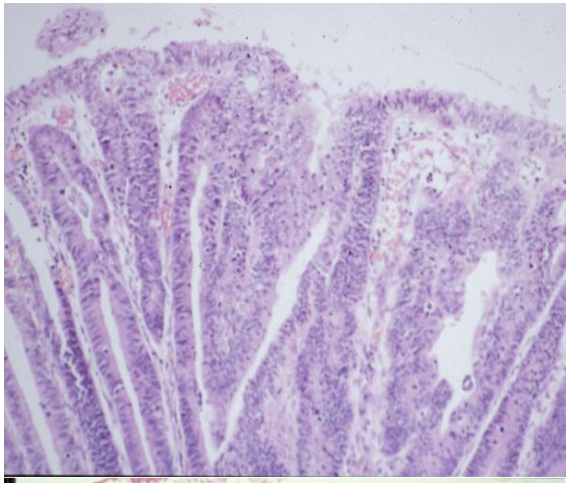
Dysplasia in IBD
Gross Features

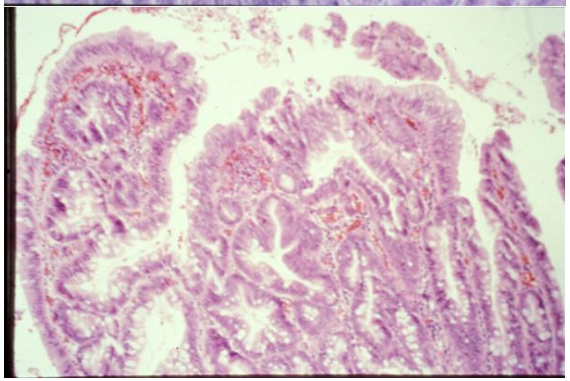
- **Flat**
- **Raised (DALM)**

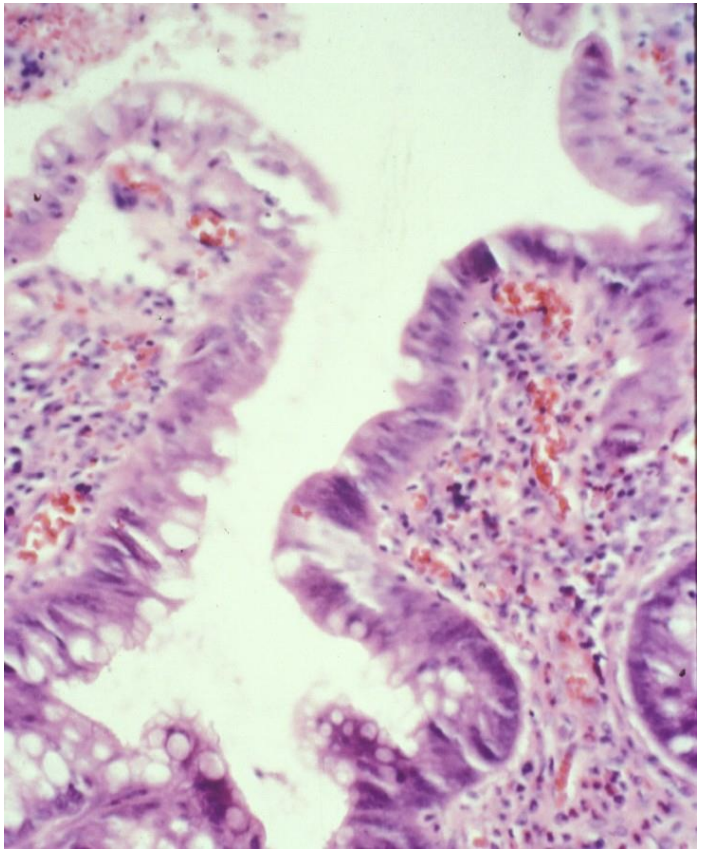


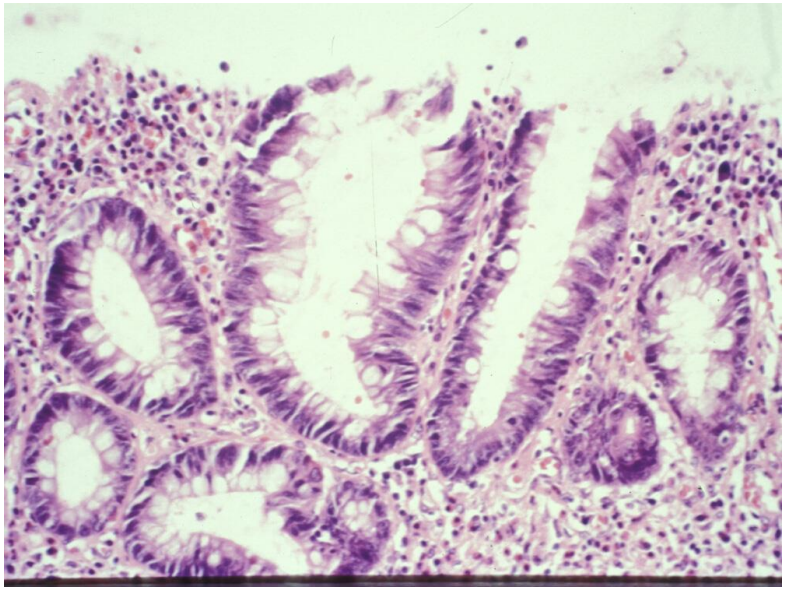


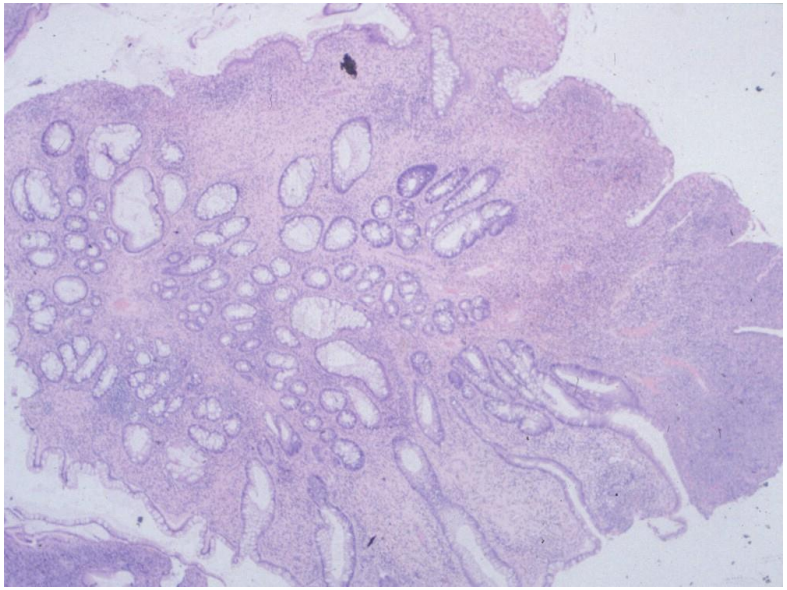


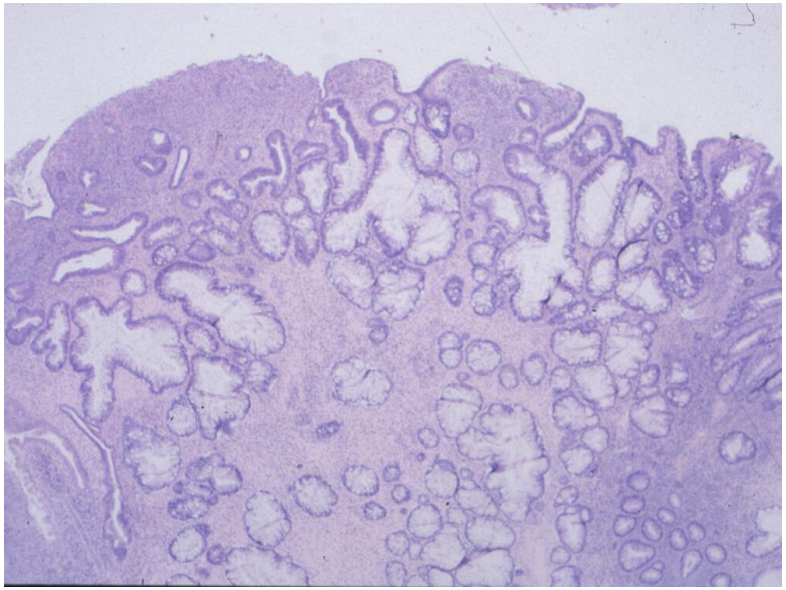


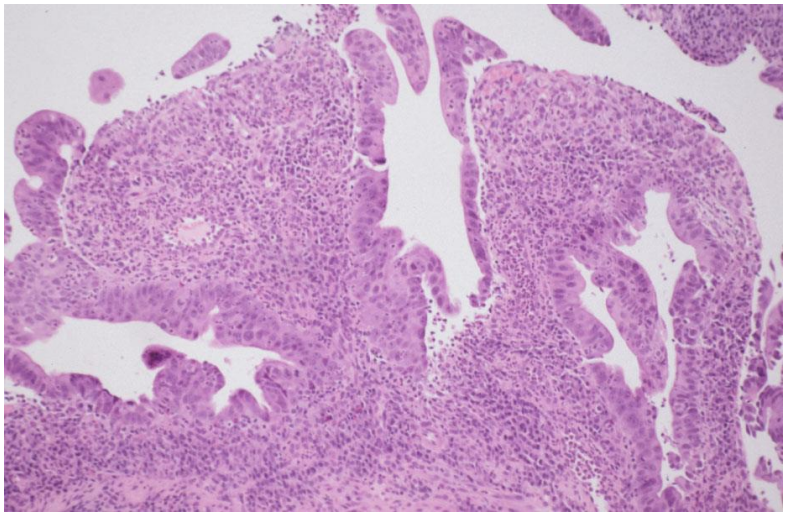


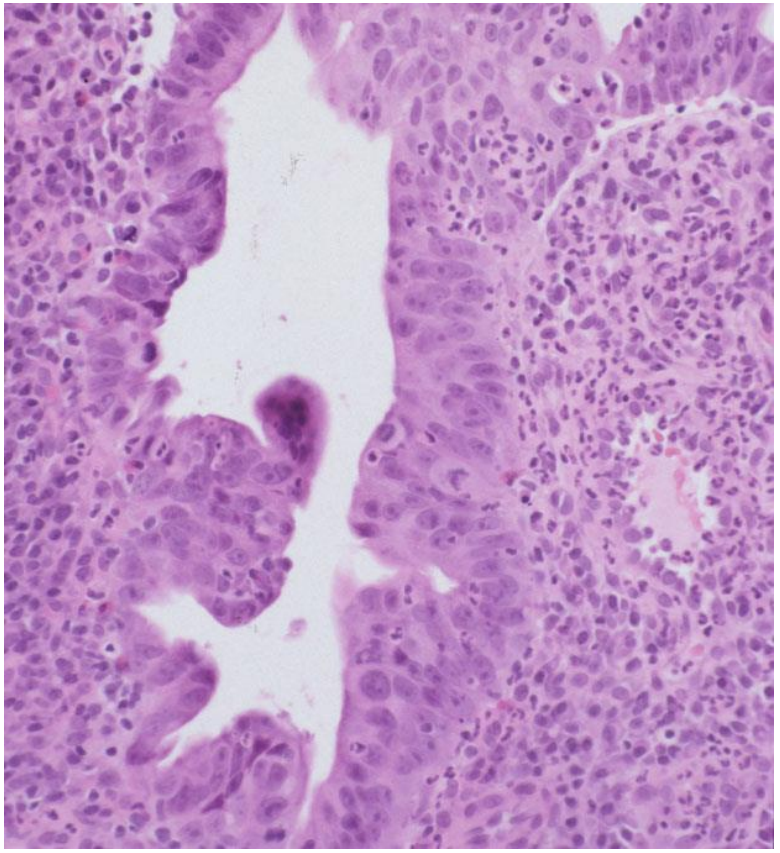


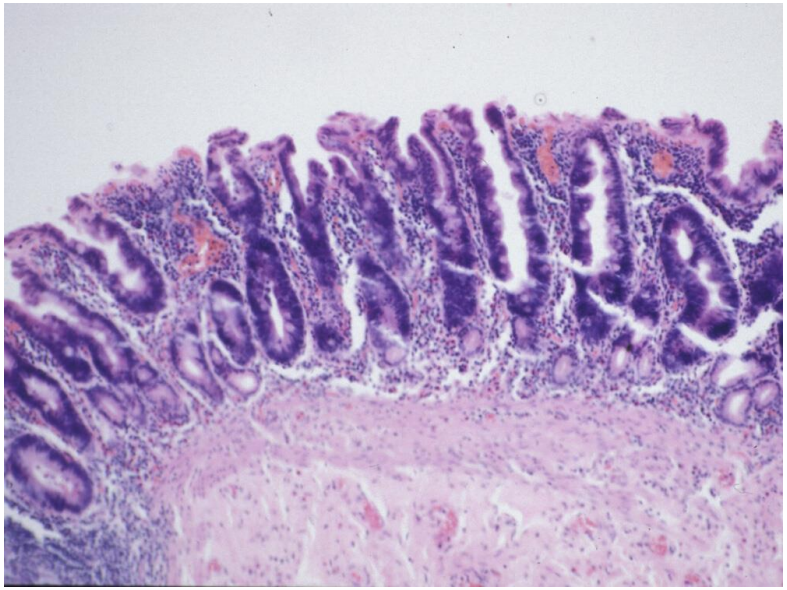


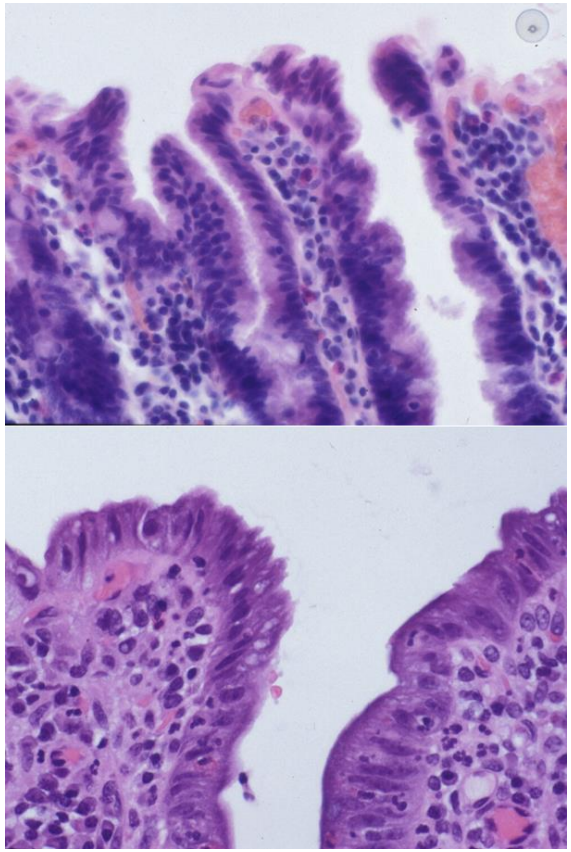


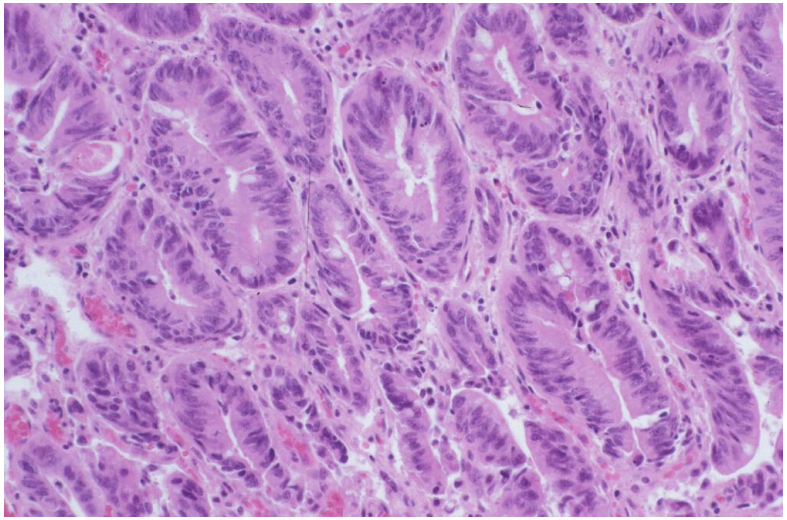


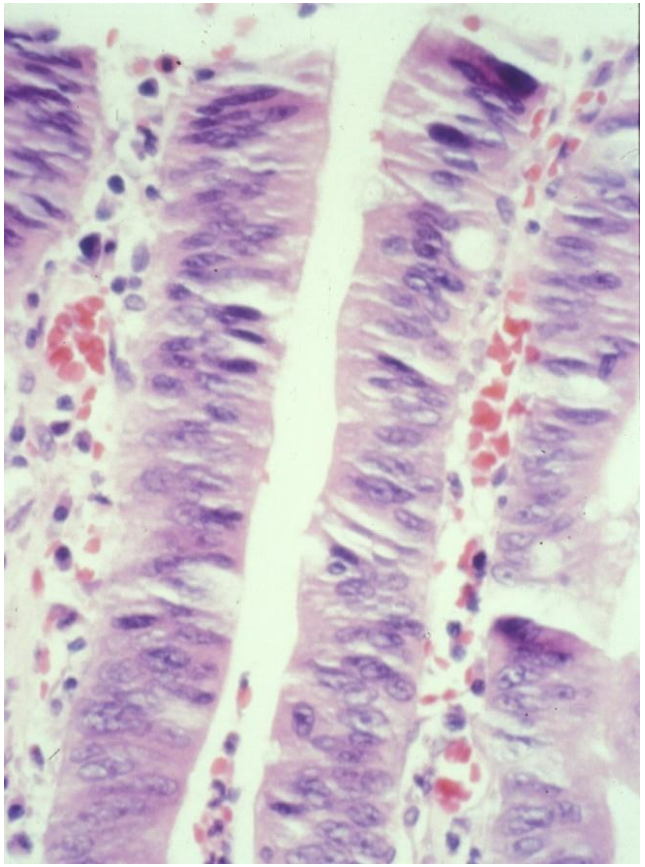


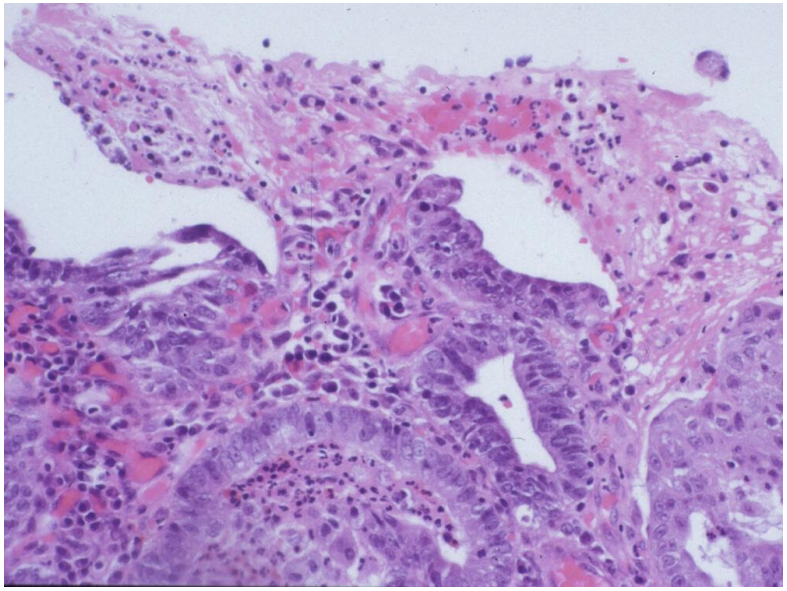


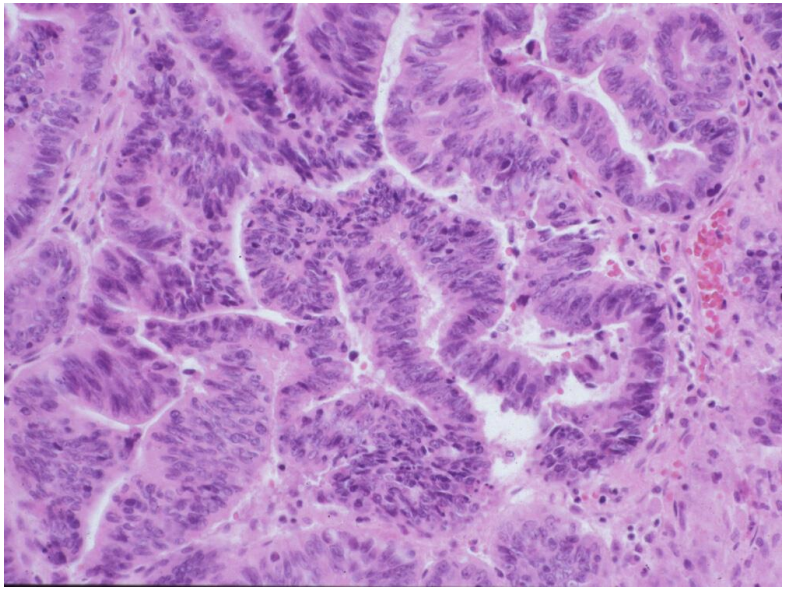












Flat Dysplasia
Natural History
(Bernstein et al, Lancet 1994;343:71)

1. **Low grade**

   - Co-existent carcinoma: 9%

   - Progression to HGD/CA: 30-54%
   (5 year predictive value)

2. **High grade**

   - Co-existent carcinoma: 40-67%

   - Progression to CA: 40-90%
   (2-5 year predictive value)

Colectomy for Low Grade Dysplasia

Author	Data
Connell 1994	LGD to HGD (54%, 5 years)
Taylor 1992	LGD in CA colectomy (34%)
Bernstein 1994	CA in LGD colectomy (19%)
Woolrich 1992	LGD to CA (18%, 6 years)

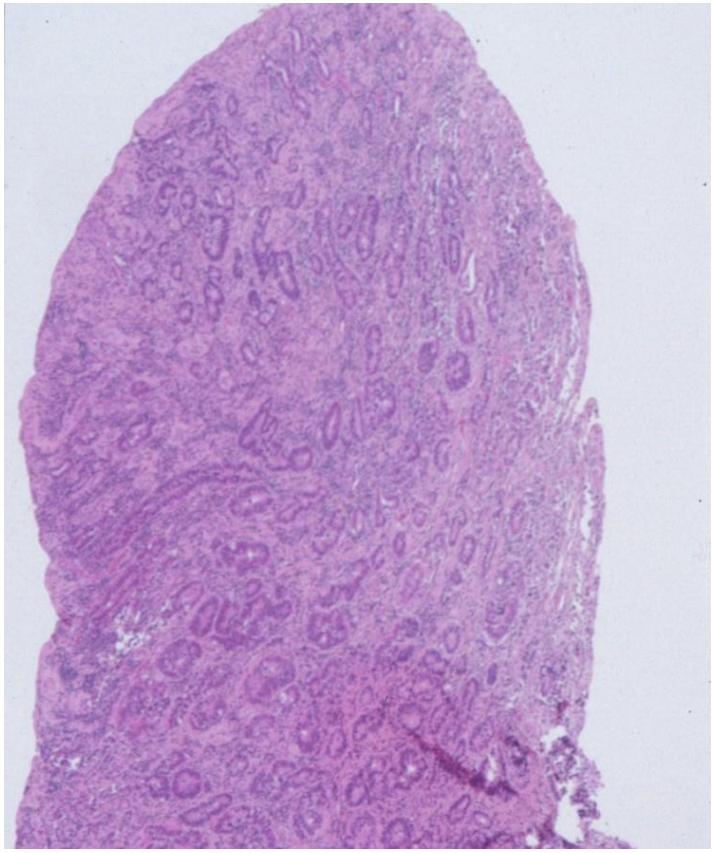
Adenoma *vs.* Polypoid Dysplasia

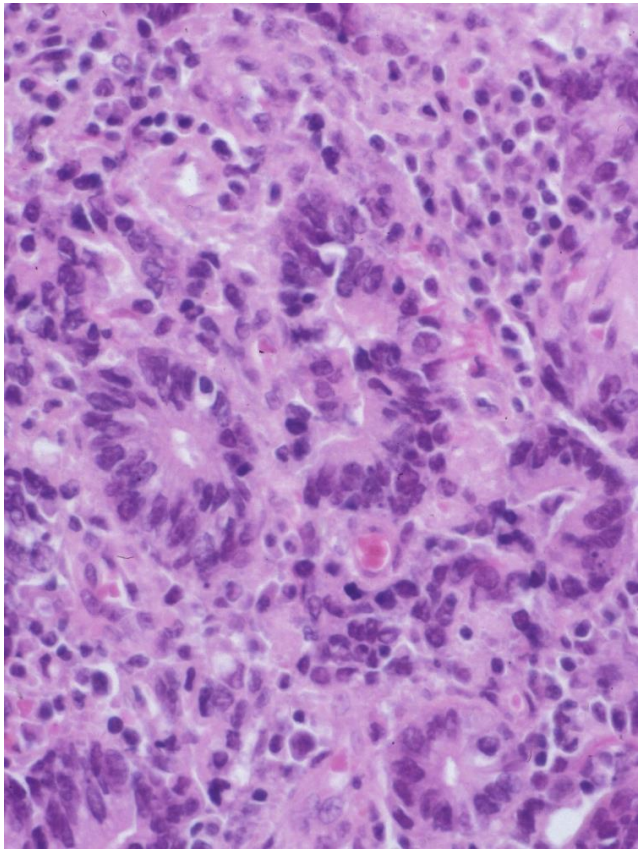
1. **Morphology**
2. **Immunohistochemistry**
3. **Molecular defects**

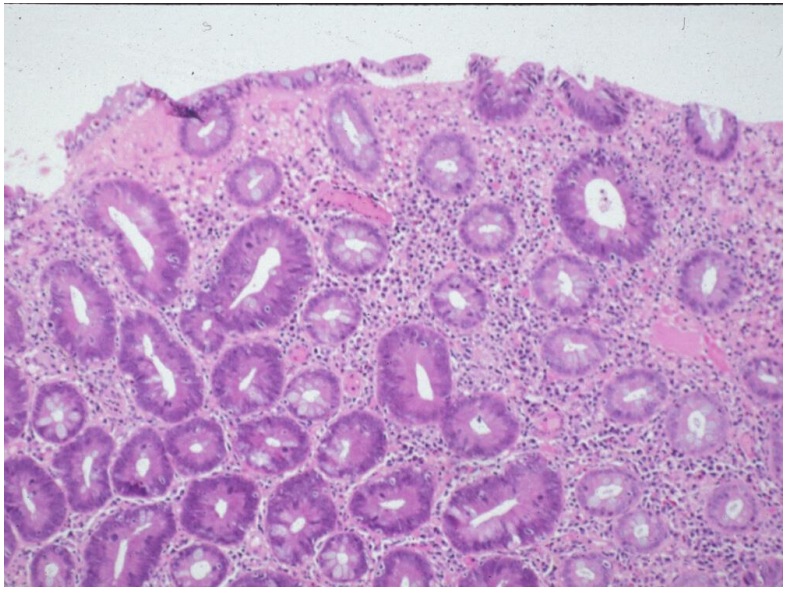
Polypoid Dysplasia and Adenomas in Inflammatory Bowl Disease

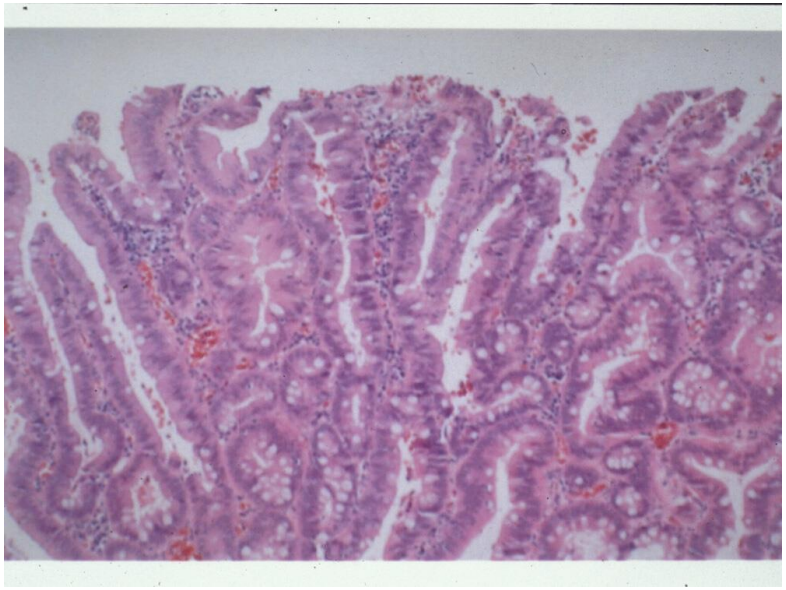
TORRES, ANTONIOLI, ODZE

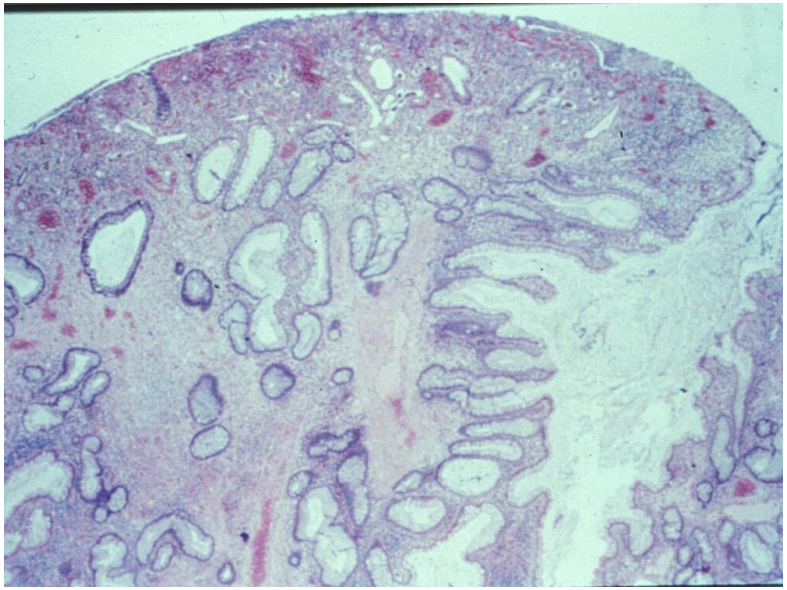
AM J SURG PATHOL 1998;22(3):275-284

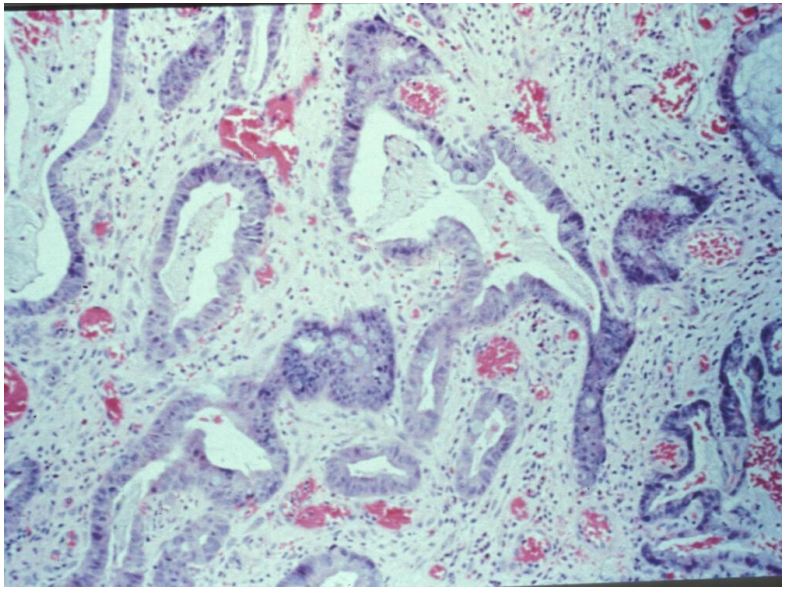












Dysplasia in Crohn's Disease

- Risk of Colon Cancer Similar to UC
- Involved (SI and colon) and uninvolved areas
- Dysplasia-carcinoma sequence
- Dysplasia morphologically similar UC
- Endoscopic surveillance controversial
- Dysplasia adjacent to Ca in 40-100%
- More common close to tumor
- 2-16% of patients without carcinoma

Dysplasia in Crohn's Disease

- **30 Cases Crohn's Adenocarcinoma**
- **27% SI, 73% colon (all involved)**
- **Dysplasia adjacent to Ca: 87%**
- **Dysplasia distant to Ca: 41% (75% in UC)**

Sigel et al, Am J Surg Pathol 23:651,1999

Dysplasia in Ulcerative Colitis

- Unequivocal neoplastic epithelium
- Marker of malignancy risk
- Present in 90% (close and distant) of carcinomas
- Any portion of colon (parallels cancer)
  - single, multiple, diffuse
- Flat or elevated (DALM)

Dysplasia in UC

- **Dysplasia in ulcerative colitis is unequivocally neoplastic epithelium with the potential to progress to carcinoma**
  - **Flat dysplasia: Low grade or High grade**
  - **Raised lesions (dysplasia-associated lesion or mass – DALM): Low grade or High grade**

Dysplasia/Ca in Ulcerative Colitis
Risk Factors

- Disease duration (> 10 years)
- Disease extent
- Primary sclerosing cholangitis
- Disease severity
- Early age of onset?
- Family history of colon cancer?
- Folate deficiency?

1. Dysplasia
   A. 5% incidence/10 years
   B. 25% incidence/20 years
2. Carcinoma
   A. 3-43% incidence 25-35 years
      A. 5-10% incidence/20 years
      B. 10-20% incidence/30 years
   B. 1-2%/year after 10 years

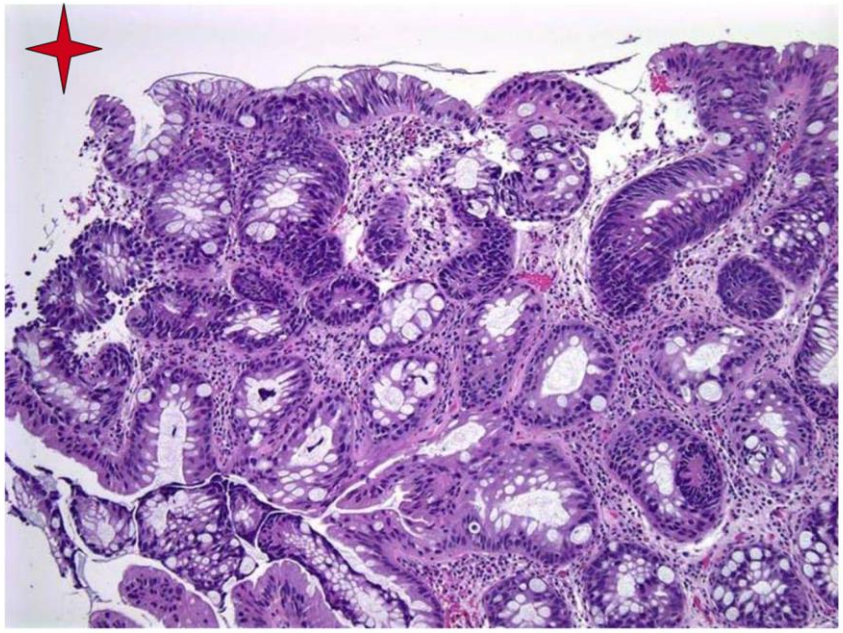
Colonic Dysplastic Lesions

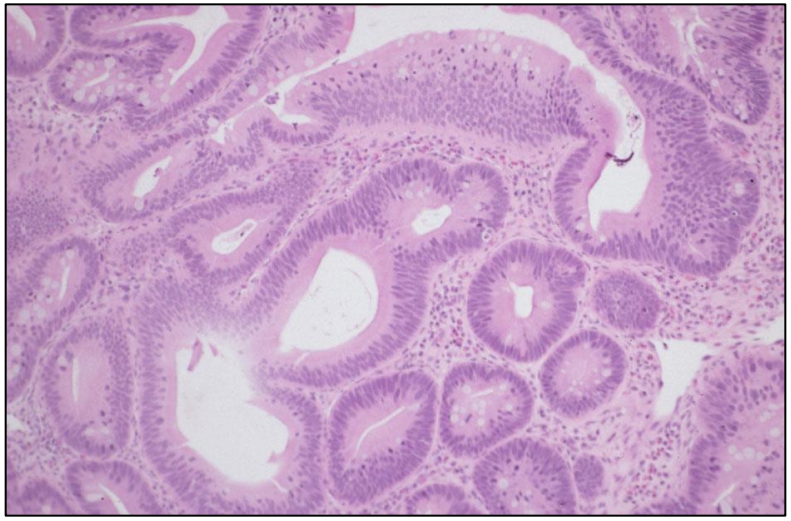
- **Sporadic adenomas in non-UC patients are managed by simple polypectomies**
- **UC patients:**
  - **Do they get sporadic adenomas?**
  - **Can we tell the sporadic adenomas from DALMs?**
  - **What happens to UC patients with adenoma-like lesions?**
- **Adenoma-like lesions in UC patients are dysplastic polyps that resemble sporadic adenomas and occur in the region of colitis**

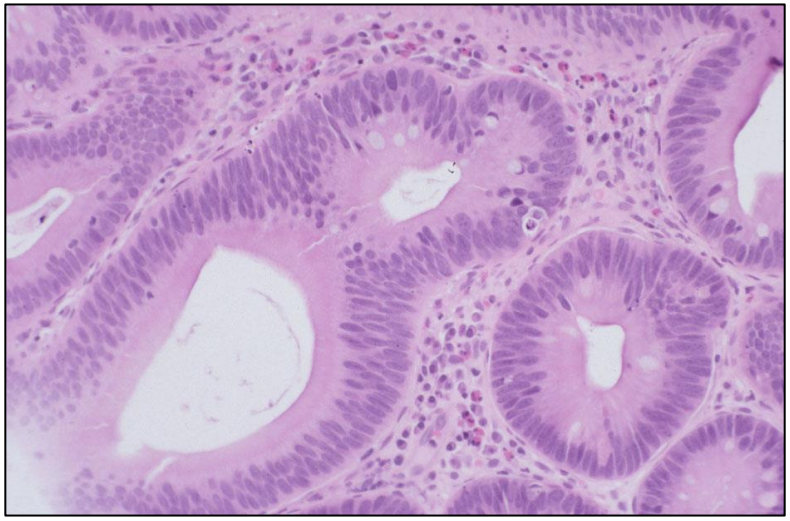
Dysplasia in IBD

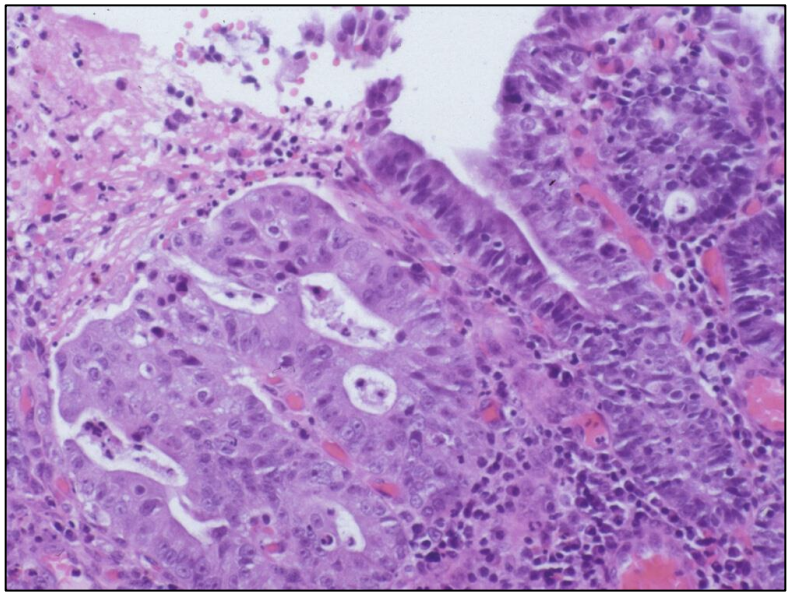
Before the notion of “adenoma-like lesion, we used these features to identify a sporadic adenoma in UC patients.

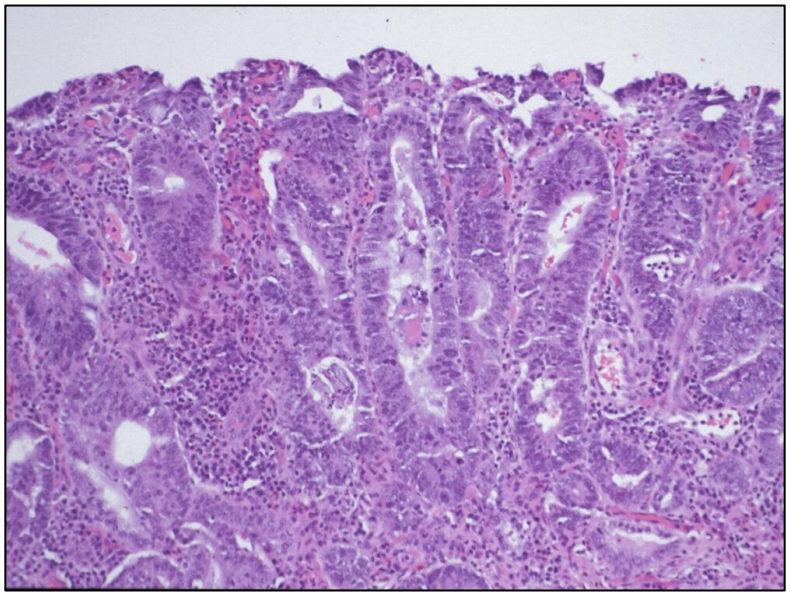
- Older patient, >60 yo
- Quiescent disease
- No flat dysplasia
- **Usually not villous**
- **No mixture of benign and dysplastic crypts at surface**
- Presence in colon proximal to extent of UC

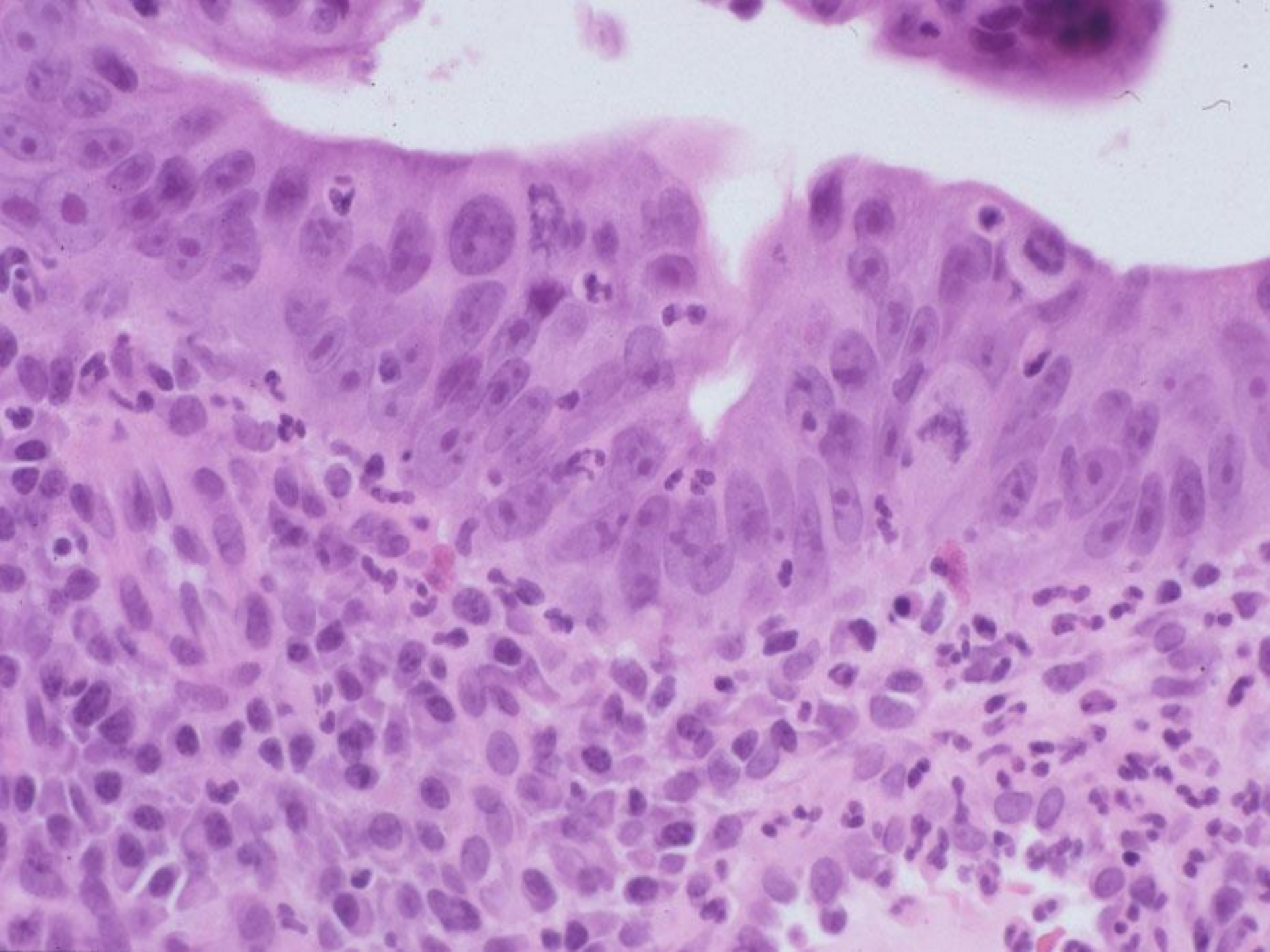








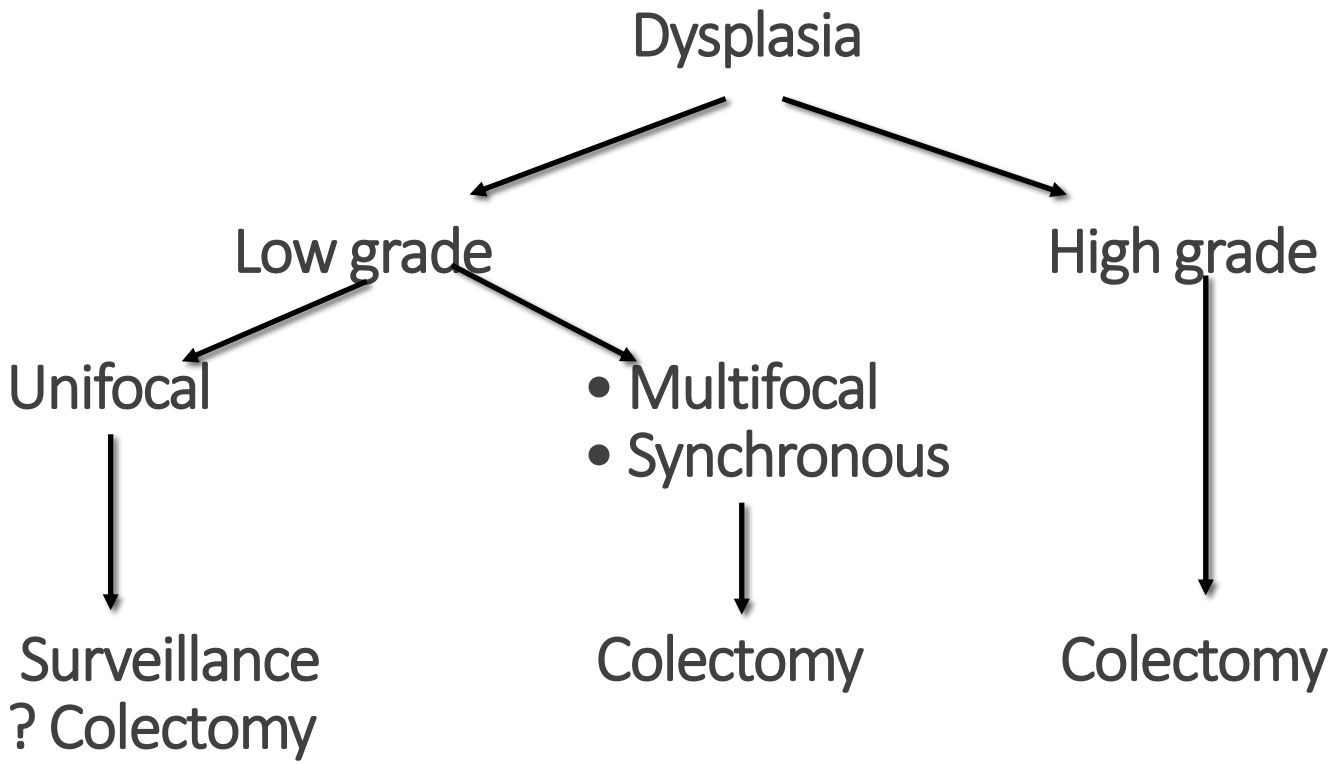




UC-Associated Dysplasia
Interobserver Variability

Author	# Specimens	#Pathologist	K value
Odze (2001)	38	4	0.4
Melville (1990)	207	5	0.2-0.5
Dixon (1988)	100	6 (pairs)	0.4

Management


Dysplasia
Low grade
High grade
Unifocal
• Multifocal
• Synchronous
Surveillance
? Colectomy
Colectomy
Colectomy

IBD vs Sporadic Neoplasia

Gene/Locus	IBD Neoplasia	Sporadic Neoplasia
KRAS	Early, frequent	Early, frequent
TP53 (17p)	Early, 44%	Late, 20%
17p LOH (*TP53*)	Early, 85%	Late, 20-30%
9p LOH (*CDKN2A*)	Early, 50%	Rare, 50%
3p LOH	Early, 50%	Rare
APC (5q)	Late 6%	Early, 75%
CDKN1A $p21^{WAF1}$	Early, 90%	Late, 30%

Adenoma vs Polypoid Dysplasia
Value of Impox

Adenoma: β catenin ↑, Bcl-2

Polypoid Dysplasia: P53 ↑

Non sensitive and non-specific

DALM

1. **Adenoma-like**
   - **Sporadic (“Adenoma”)**
   - **IBD-associated (“Polypoid dysplasia”)**
2. **Non Adenoma-like**

DALM

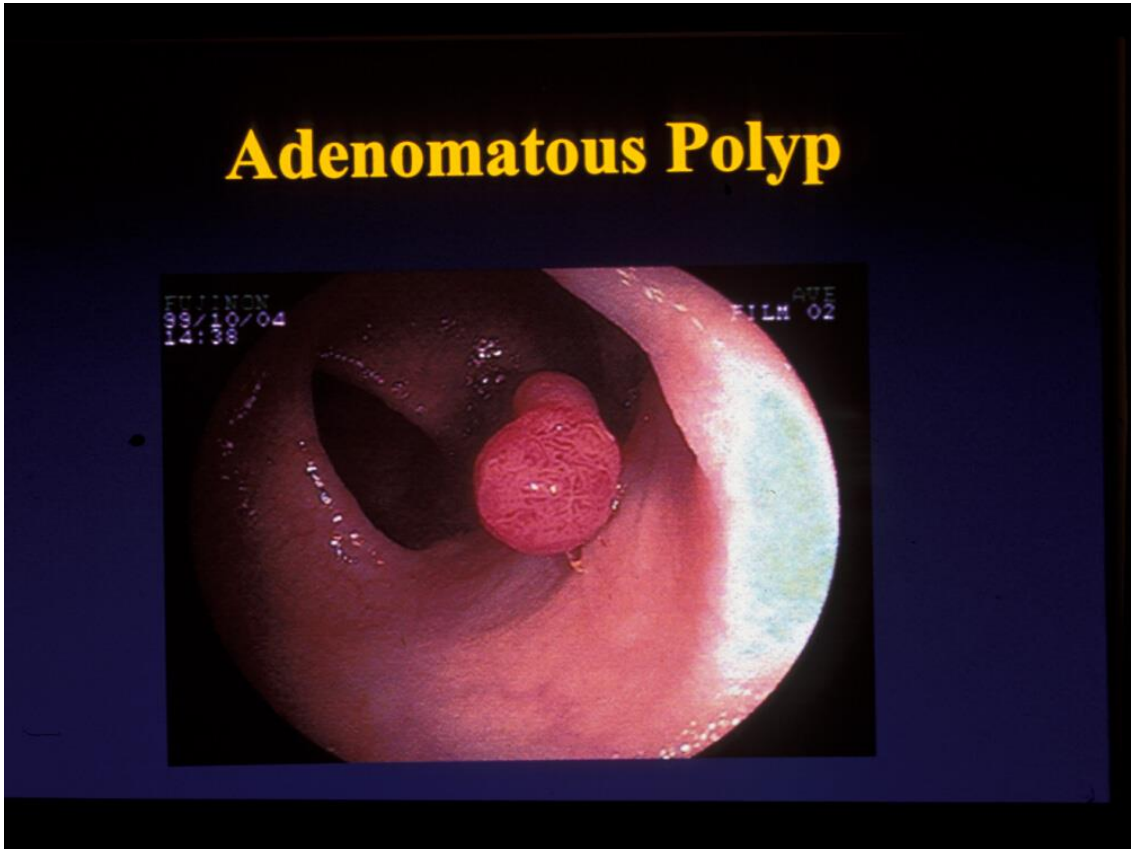
ADENOMA LIKE

- Sessile/Pedunculated
- Well circumscribed
- Smooth surface
- Visible borders
- Non-ulcerated
- No stricture or mucosal tethering

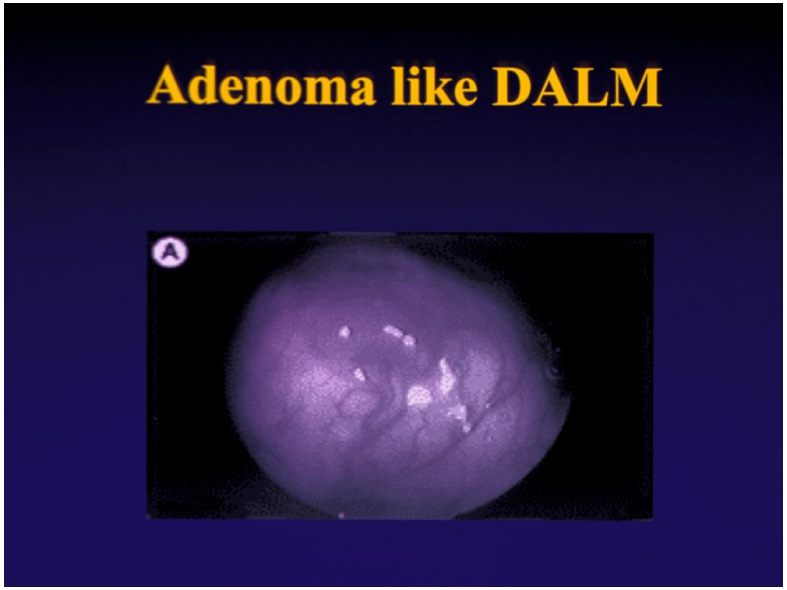
NON ADENOMA-LIKE

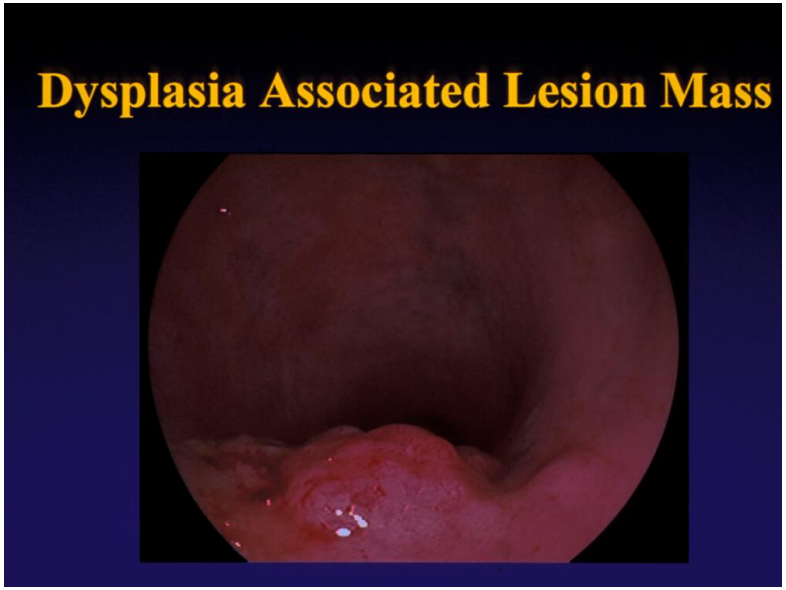
- Usually sessile
- Poorly circumscribed
- Irregular surface
- Indistinct border
- Ulceration/necrosis
- +Stricture/tethering

Adenomatous Polyp



Dysplasia in IBD





Summary of DALM Studies

Author	#Patients	% DALM	% DALM with cancer
Blackstone (1981)	112	11%	58%
Butt (1983)	62	29%	83%
Rosenstock (1985)	248	5%	38%
Len-Jones (1990)	401	1.5%	83%
Bernstein (1994) (10 studies)	1225	3.2%	43%

Genetic Alterations in Chronic ulcerative colitis-associated adenoma like DALMS are similar to non-colitic sporadic adenomas

Odze et al, Am J Surg Pathol 2000;24(9)

Adenoma-like DALMS in Ulcerative Colitis

	Non-CUC Adenoma	CUC Adenoma-like DALM (within colitis)	CUC Adenoma-like DALM (outside colitis)	CUC Non-Adenoma like DALM
	N=23	N=10	N=11	N=12
3p LOH	5%	30%	25%	50%*[1]
APC	33%	29%	38%	43%
p16	4%	0%	10%	56%*[2]

*[1]P=0.01 *[2]P = 0.003

1. It looks like a sporadic adenomatous polyp endoscopically.
2. It looks like a sporadic adenomatous polyp histologically.
3. It has been completely removed and there is no dysplasia in flat mucosa.

Are there reliable criteria to use to determine #2 above?

Is it possible to reliably differentiate adenoma from polypoid dysplasia by morphology, impox, or molecular methods?

NO

Polypectomy may be adequate treatment for adenoma-like dysplastic lesions in chronic ulcerative colitis

ENGELSQJERD, FARRAYE, ODZE (GASTROENTEROLOGY 1999;117:1288-1294)

Adenoma-like DALM in Ulcerative Colitis

Feature	CUC Adenoma-like DALM	CUC Adenoma	Non-CUC Adenoma
# patients	24	10	49
Follow-up (months)	42	41	37
Flat dysplasia	1 (4%)	0 (0%)	N/A
New polyps	58%	50%	39%
Adenocarcinoma	0%	0%	0%

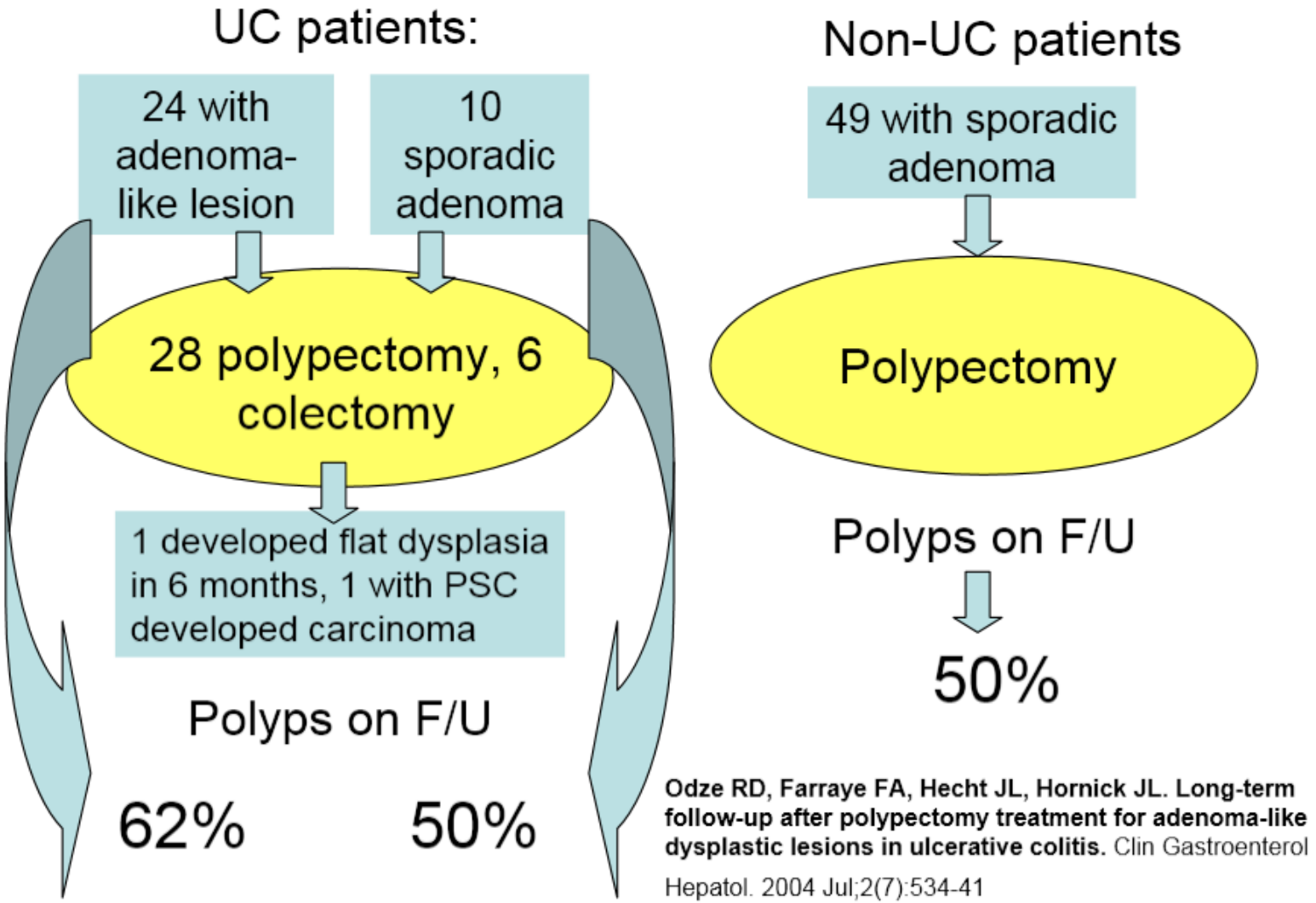
Colonoscopic polypectomy in chronic colitis: Conservative management after endoscopic resection of dysplastic polyps

RUBIN, FRIEDMAN, HARPAZ, ET AL (GASTROENTEROLOGY 1999;117:1295-1300)

Rubin et al

No further polyps	**25 (52%)**
Polyps in same vicinity	**13 (27%)**
Polyps in different location	**10 (21%)**
Dysplasia/CA in flat mucosa	**0 (0%)**

Follow up of UC patients with polypectomy for adenoma-like lesions (look like adenomas, occur in area of colitis)



Odze RD, Farraye FA, Hecht JL, Hornick JL. Long-term follow-up after polypectomy treatment for adenoma-like dysplastic lesions in ulcerative colitis. Clin Gastroenterol Hepatol. 2004 Jul;2(7):534-41

Conclusion

IF IT LOOKS LIKE AN ADENOMA
IT PROBABLY IS!

Risk of Malignancy in UC
Adjunctive Methods

Method	Abnormality
Histochemical	Mucin, sialosyn TN
Impox	Proliferation
Molecular defects, locus specific	*TP53, RB1, APC, CDKN2B, CDKN2A*
Molecular defects, generic	MSI, CIN, aneuploidy
Laser fluorescence	Dysplasia

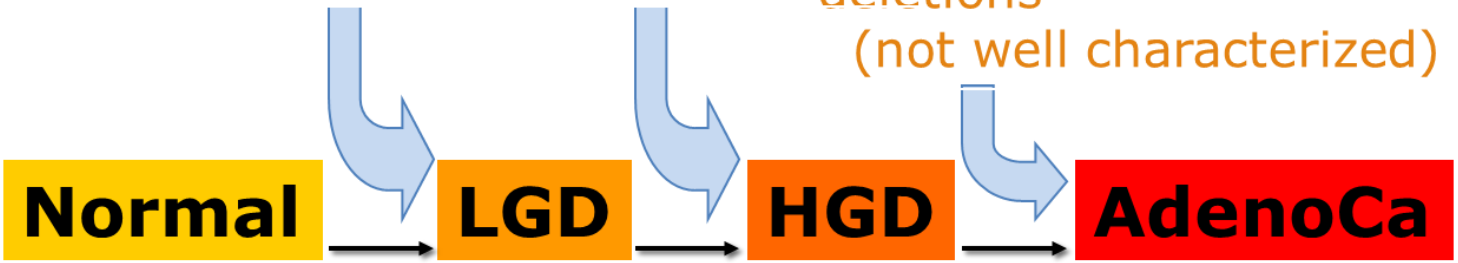
Molecular Basis of Colitis-Associated Neoplasia

- **Stepwise genetic progression**
- **Sporadic vs colitis-associated**
- **Specific factors**
  - **aneuploidy**
  - **17p deletion/p53 mutation**
  - **p16**
- **Genomic instability pathways**

Genetic Progression in Colitis-Associated Neoplasia

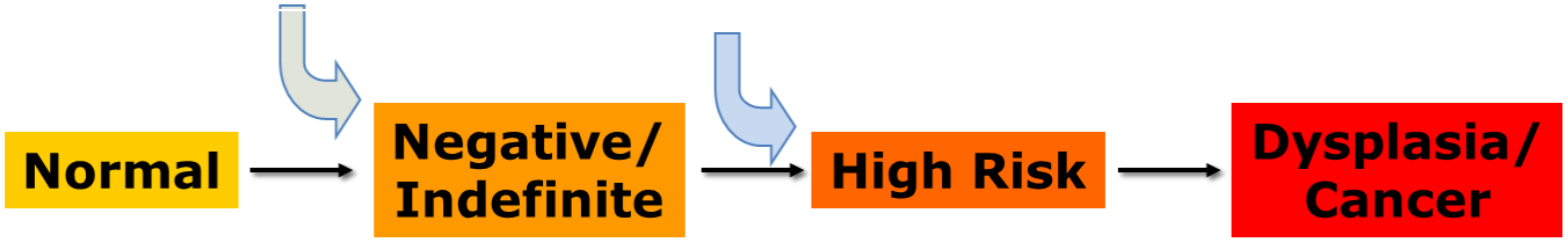
- 5q21 deletion/*APC* inactivation
- 17p13 deletion/*TP53* mutation
- 9p21 deletion/*CDKN2A* inactivation
- aneuploidy
- 13q14 deletion/*RB1* inactivation
- other chromosomal deletions
- *KRAS* mutation
- p21 overexpression
- telomere erosion

- 18q LOH
- p27 down-regulation
- other chromosomal deletions
  (not well characterized)



Genetic Progression in Colitis-Associated Neoplasia

- aneuploidy
- 17p13 deletion/*TP53* mutation
- 9p21 deletion/*CDKN2A* inactivation
- chromosomal instability



Colitis-Associated *vs.* Sporadic Neoplasia

- **Aneuploidy pre-invasion**
- **TP53 mutation pre-invasion**
- **Chromosome 3p deletion**
- **Loss of p27 expression**

- **Less bcl-2 expression**
- **Less β-catenin staining**

Aneuploidy Associations in Colitis-Associated Neoplasia

- **Associated with:**
  - **duration**
  - **extent**
  - **severity**
  - **dysplasia**
  - **other genetic alterations**

Aneuploidy Predicts Progression in Colitis-Associated Neoplasia

Histology	Ploidy	Dysplasia/Cancer Progression
Negative	diploid	0/15
	aneuploid	1/1
Indefinite	diploid	1/5
	aneuploid	4/4

Rubin et al, Gastroenterology 103:1611;1992

Aneuploidy Predicts Progression in Non-Dysplastic Colitis

Study	Ploidy	Dysplasia/Cancer Progression
Lindberg 1999	diploid	0/127
	aneuploid	4/10
Holzman 2001	diploid	1/39
	aneuploid	5/10

Aneuploidy in Colitis-Associated Neoplasia

- **Extremely common**
- **Extensively studied**

- **70-90% of dysplasia/cancers**
- **10-20% of non-dysplastic**

17p LOH in Colitis-Associated Neoplasia

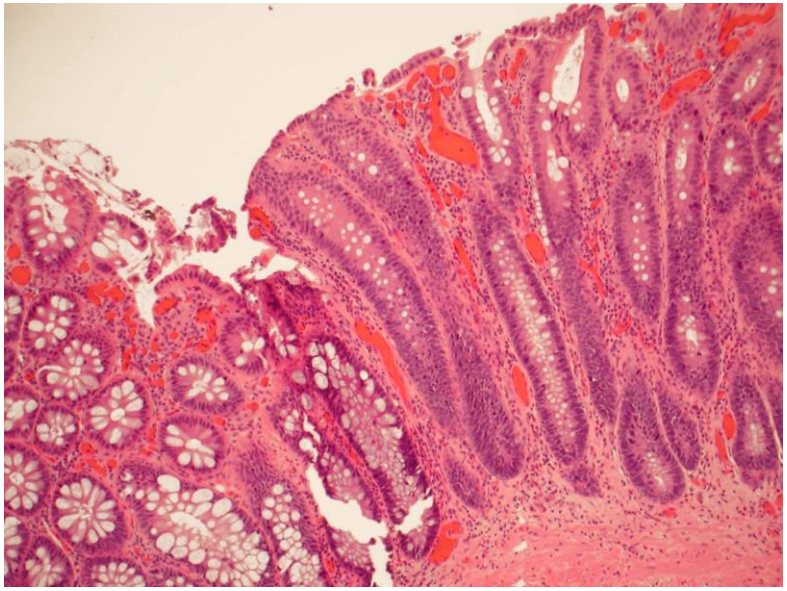
Lesion	Frequency
Carcinoma	22/26 (85%)
HGD	25/40 (63%)
LGD	7/21 (33%)
Indefinite	5/57 (9%)

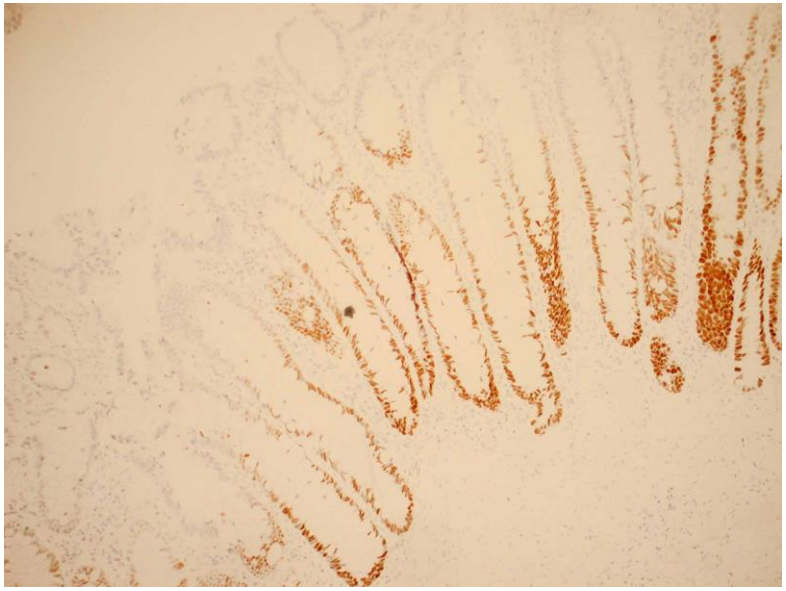
Burmer et al, Gastroenterology103:1602;1992

TP53 Mutation Predicts Progression in Colitis Neoplasia

- **Holzmann Scand J Gastroenterol 2001**
  - **83 high risk UC patients**
- **p53 mutations predict progression:**
  - **no mutation - 3/64 (5%)**
  - **yes mutation - 7/18 (39%)**
- **Less predictive than aneuploidy**

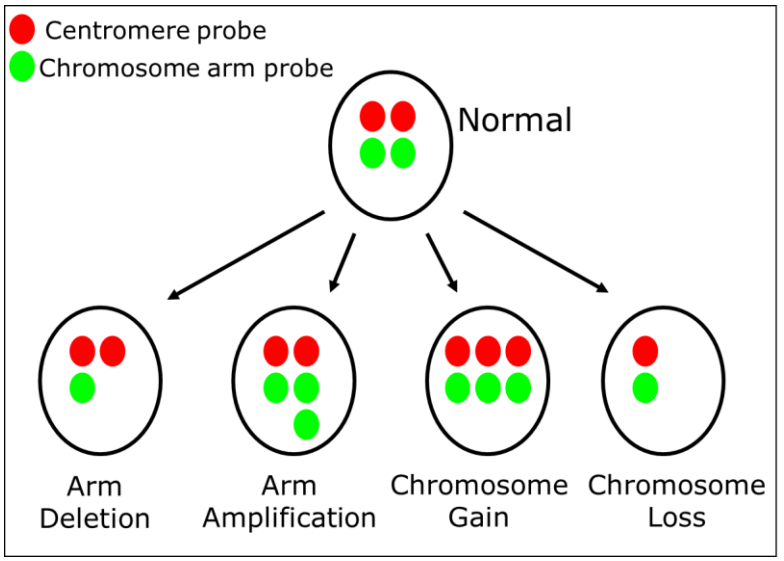
TP53 in Negative/Indefinite Mucosa





Chromosomal Instability (CIN) in Colitis-Associated Neoplasia

- **Dual color FISH chromosomes 8, 11, 17, 18**
- **Histologically negative rectal biopsies**
- **CIN present in:**
  - **10% non-IBD control cells**
  - **22% negative colitis cells (dysplasia or cancer elsewhere)**
  - **P<0.0004**



Telomere Erosion in Colitis-Associated Neoplasia

- "Cap" on ends of chromosomes
  - Maintain genome stability
  - Loss associated with senescence
- Accelerated shortening with:
  - rapid cell turnover
  - oxidative injury

Telomere Erosion in Colitis-Associated Neoplasia

- O'Sullivan et al, Nature Genetics 2002
- Determined telomere length in non-dysplastic mucosa by FISH
- Patients with and without HGD/cancer

- Telomere erosion associated with:
  - **chromosomal instability**
  - **progression to HGD/cancer)**

Other Markers in Colitis-Associated Neoplasia

- **Proliferation index (Ki67)**
- **Cyclin A**
- **E-cadherin**
- **Sialosyl-Tn antigen**
- **Metallothionein**

- **Further studies needed to validate**

Fecal DNA Mutation Testing

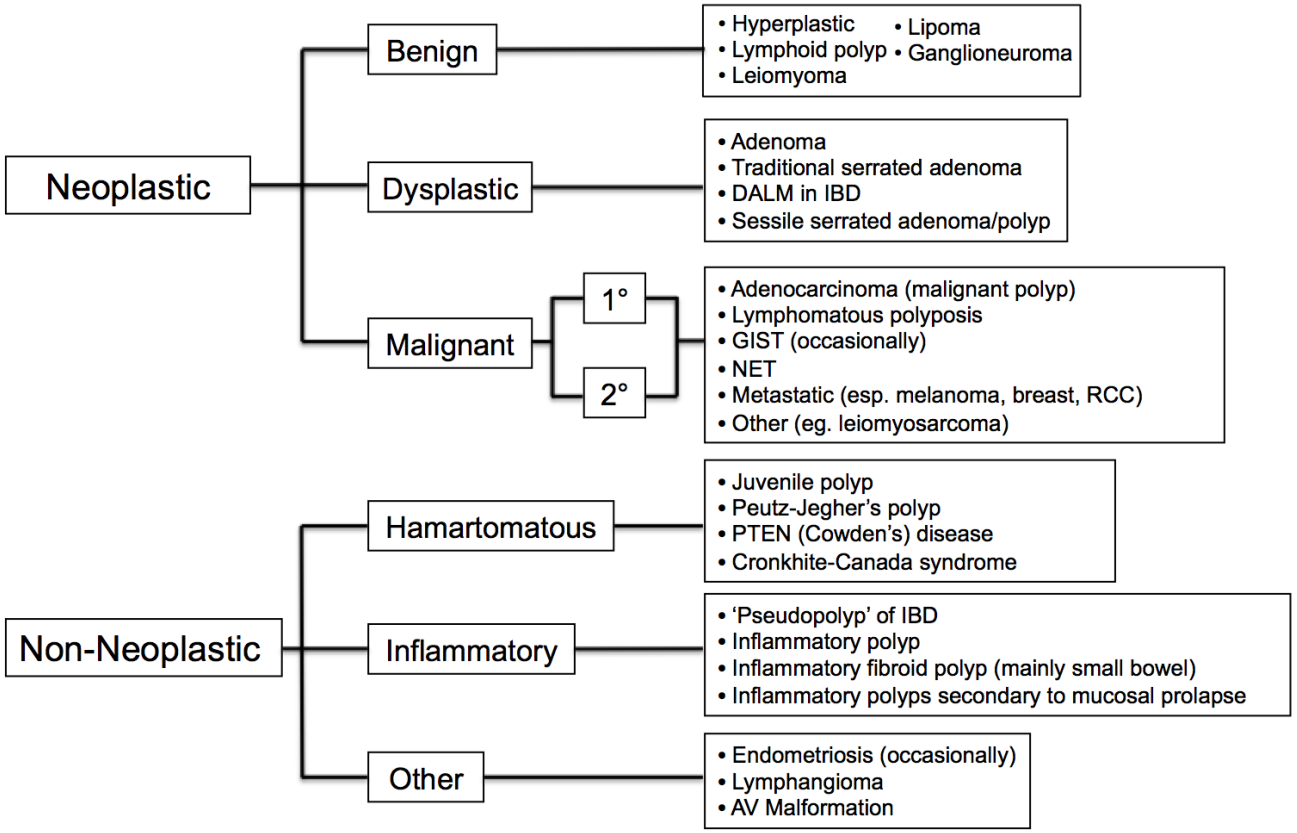
- Cells shed into lumen
- Target DNA by hybrid capture
- Test specific mutation panel
- *KRAS*
- *TP53*
- *APC*
- DNA integrity

- High sensitivity/specificity in CRC
- Adenoma validation ongoing
- Testing required on colitis
- Development of cost-effective kit

Molecular Summary of Colitis-Associated Neoplasia

- **Useful predictive factors:**
  - **Aneuploidy**
  - **17p deletion/*TP53* inactivation**
  - **Chromosomal instability**
  - **Telomere erosion**

Classification of GI polyps

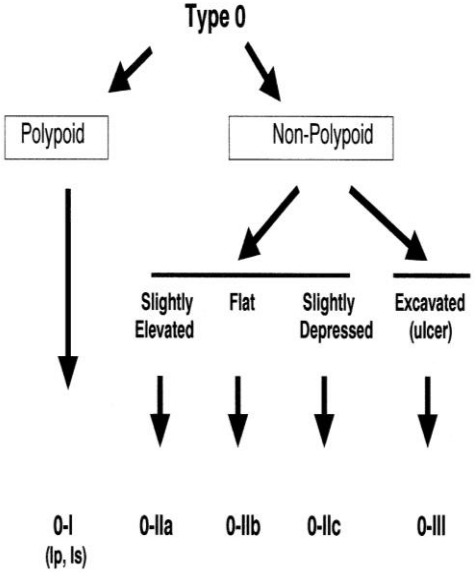


Endoscopic Classification of intestinal lesions

Paris classification:

- **Type 0 – superficial polypoid, flat/depressed or excavated lesions**
- **Type 1 – polypoid tumors, usually attached on a wide base**
- **Type 2 – ulcerated with sharply demarcated and raised margins**
- **Type 3 – nonulcerated, diffusely infiltrating carcinomas**
- **Type 4 – unclassifiable advanced carcinomas**

Table 2. Neoplastic lesions with "superficial" morphology



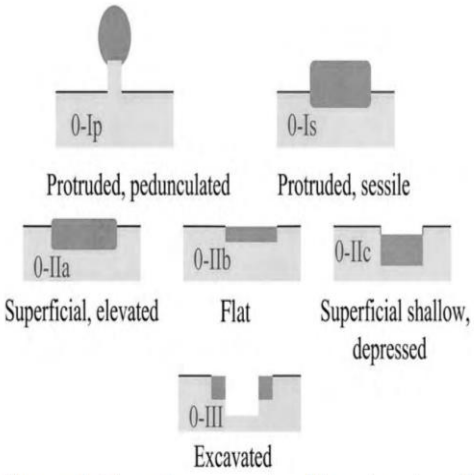
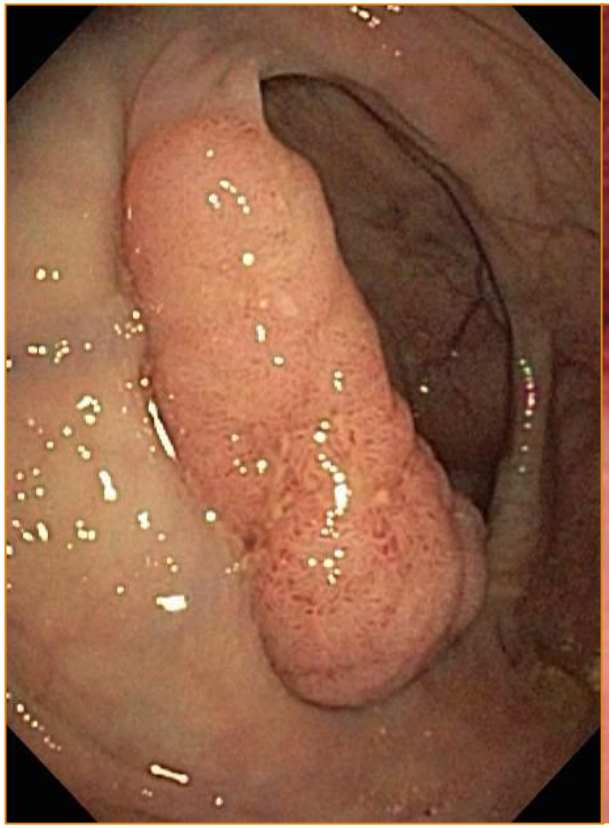
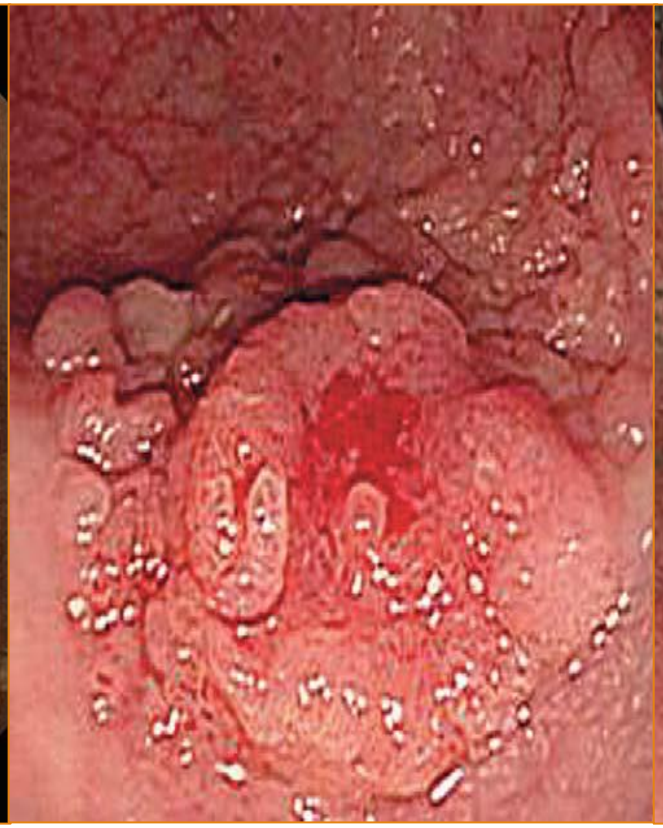


Diagram 1. Schematic representation of the major variants of *type 0* neoplastic lesions of the digestive tract: polypoid *(Ip and Is)*, non-polypoid *(IIa, IIb, and II c)*, non-polypoid and excavated *(III)*. Terminology as proposed in a consensus macroscopic description of superficial neoplastic lesions.[15]

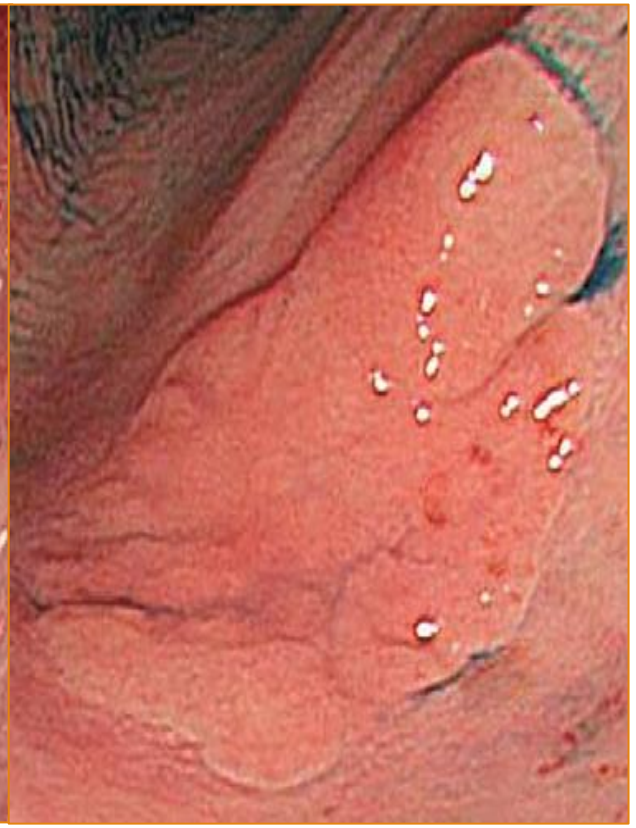
Paris Classification – Examples



Type 0-Is
Protruded sessile



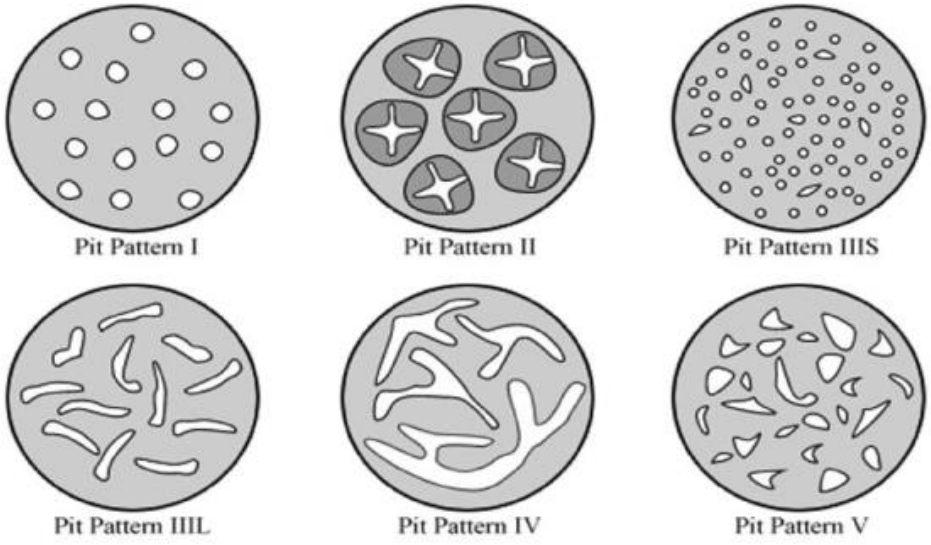
Type 0-IIa
Superficial elevated



Type 0-IIb
Flat

Kudo Classification – Pit Pattern Assessment

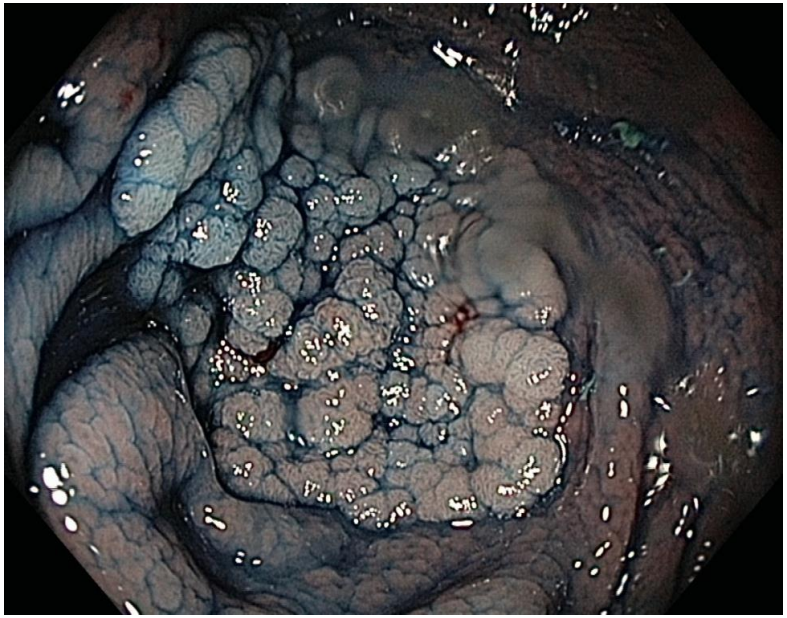
Pit pattern type	Characteristics
I	roundish pits
II	stellar or papillary pits
III S	small roundish or tubular pits (smaller than type I pits)
III L	large roundish or tubular pits (larger than type I pits)
IV	branch-like or gyrus-like pits
V	non-structured pits



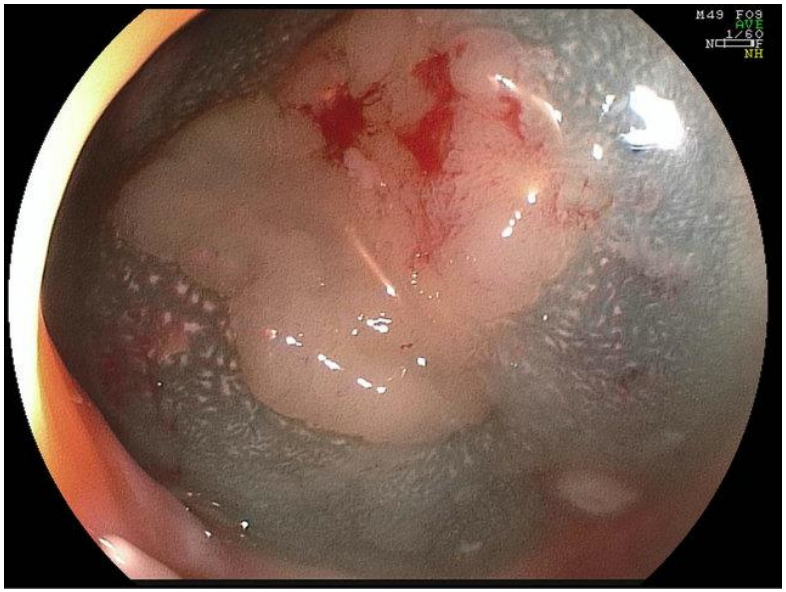
Kudo S. J Clin Pathol 1994;47:880-885

Pit Pattern Assessment

GRANULAR



NON-GRANULAR



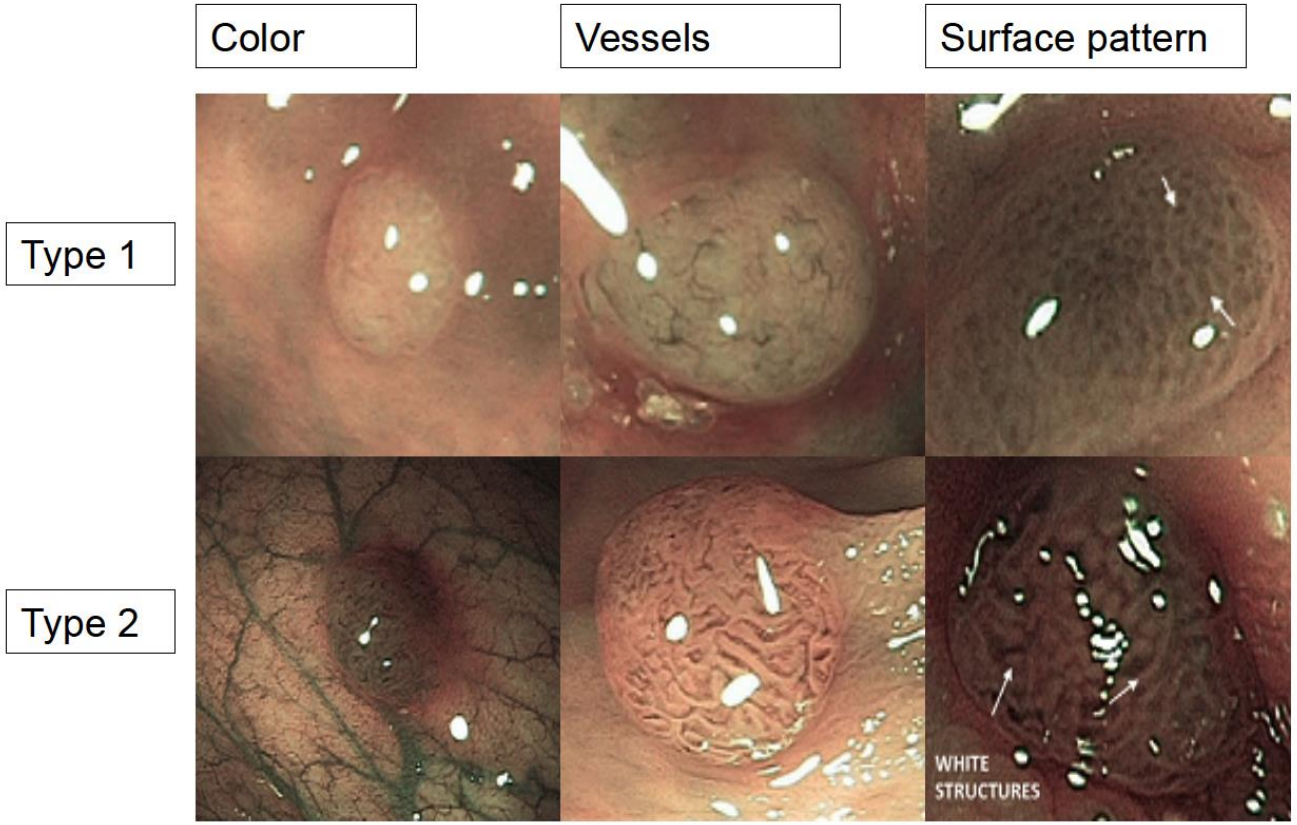
Risk of invasive malignancy based on morphology

Multiple risk factors increase the risk of SMIC:

- 1% in 0–IIa granular lesion
- 46% in 0–IIa nongranular lesions
- 56% in 0–IIa nongranular lesions with type V pits

	n	% of total cohort	n (%) with SMI	*P* value
Paris classification				
Is	146	30.5	11 (7.5)	.001
IIa	222	46.3	9 (4.1)	
IIb	9	1.9	1 (11.1)	
IIc or IIa+c	22	4.6	7 (31.8)	
Is + IIa	80	16.7	5 (6.3)	
III	0	0	0 (0)	
Surface morphology				
Granular	311	64.9	10 (3.2)	<.001
Nongranular	98	20.5	15 (15.3)	
Mixed granular and nongranular	30	6.3	3 (10)	
Unable to classify	40	8.4	5 (12.5)	
Kudo pit pattern				
Pit pattern I	7	1.5	0 (0)	<.001
Pit pattern II	41	8.6	0 (0)	
Pit pattern III	182	38.0	8 (4.4)	
Pit pattern IV	202	42.2	10 (5.0)	
Pit pattern V	25	5.2	14 (56.0)	
Unable to classify	22	4.6	1 (4.5)	

Narrow band Imaging (NBI) International Colorectal Endoscopic (NICE) classification

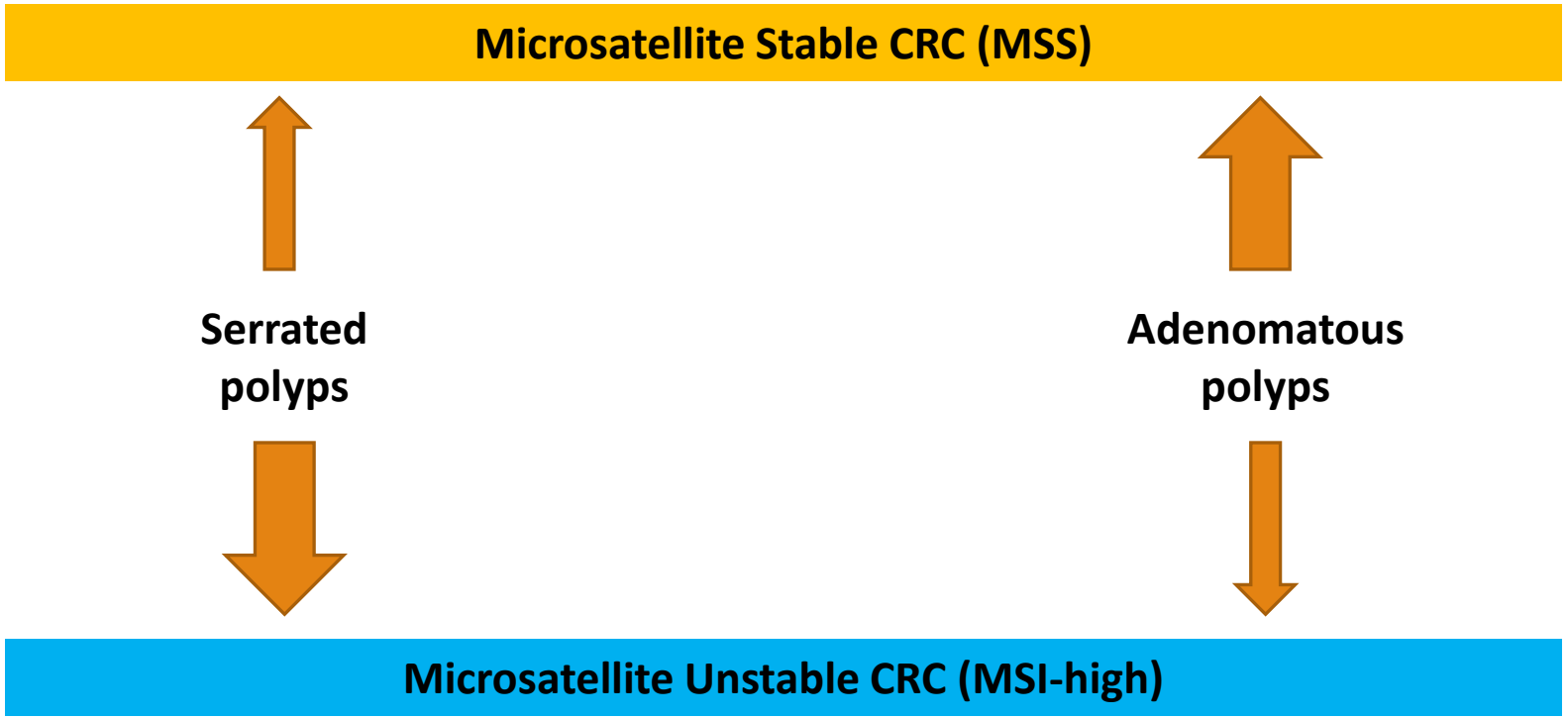


Hewett DG, Kaltenbach T et al. Gastroenterology 2012;143:599-607.

Serrated Polyp Pathway

MORPHOLOGY AND MECHANISMS

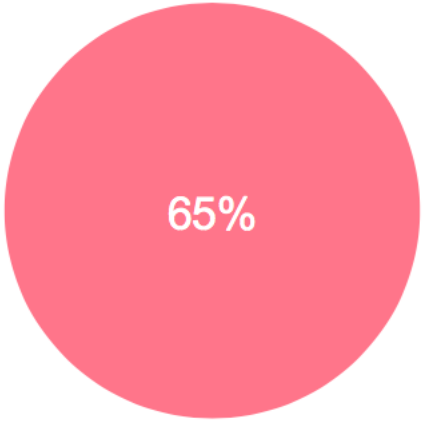
Why should we care about serrated polyps?



Evidence to support serrated pathway

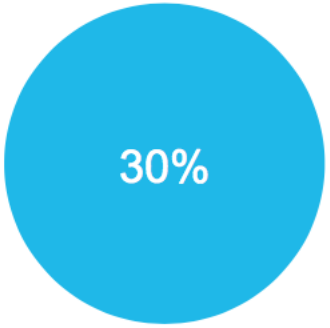
- **Patients with numerous serrated polyps are at increased risk of colorectal carcinoma (CRC)**
- **Large serrated polyps are associated with synchronous advanced polyps and CRC**
- **Serrated polyps are present in areas that subsequently developed MSI-H CRC**
- **Patients with MSI-H CRC often have serrated polyps elsewhere in the colon**
- **Serrated polyps can develop dysplasia and are seen adjacent to some CRC**
- **Serrated polyps have molecular features similar to MSI-H CRC**

Types of Serrated Polyps



Hyperplastic polyp (HP)

Microvesicular (MVHP)
Goblet cell rich (GCHP)

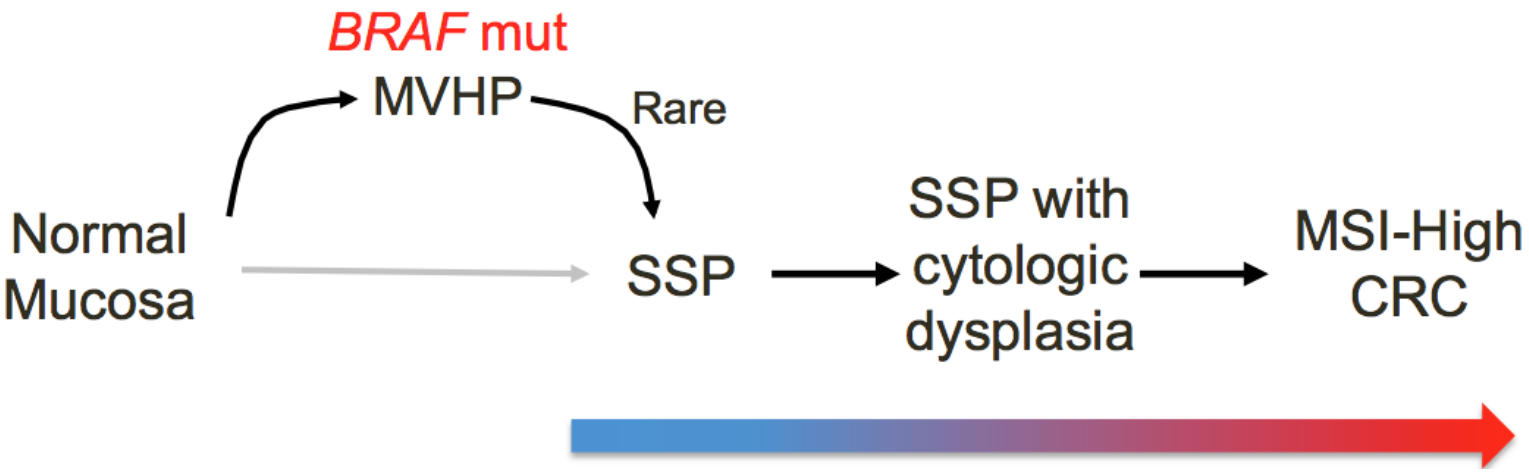


Sessile Serrated polyp (SSP)

(also knows as SSA)

Traditional Serrated Adenoma (TSA)

Simplified View of Serrated Pathway



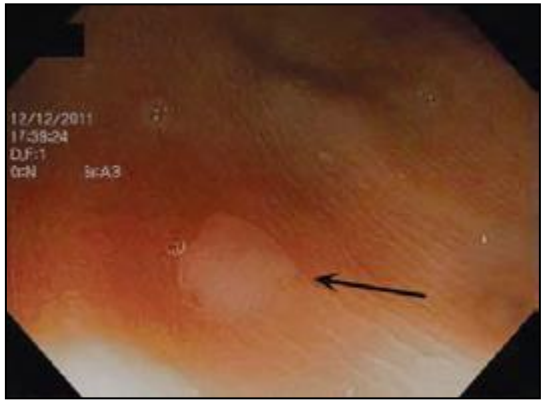
Important points

- **SSPs probably develop from MVHPs: MVHPs aren't completely innocuous but transformation to SSP is likely a rare event (occurs more commonly in the right colon)**
- **Serrated pathway is characterized by hypermethylation of CpG islands (CIMP-high) and BRAF mutations**

Hyperplastic Polyp (Microvesicular)

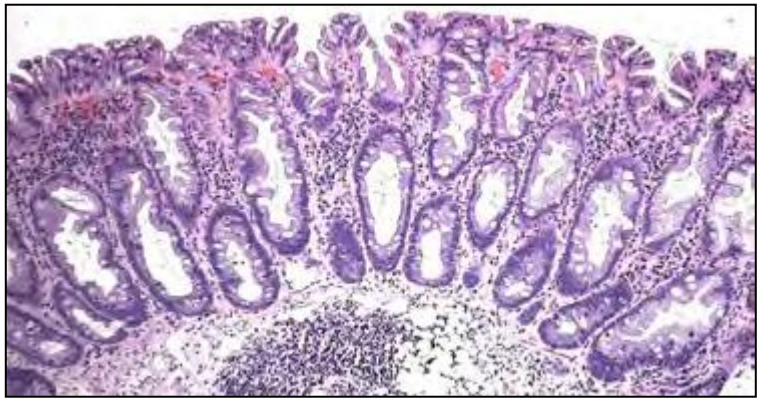
CLINICAL/ENDOSCOPIC FEATURES

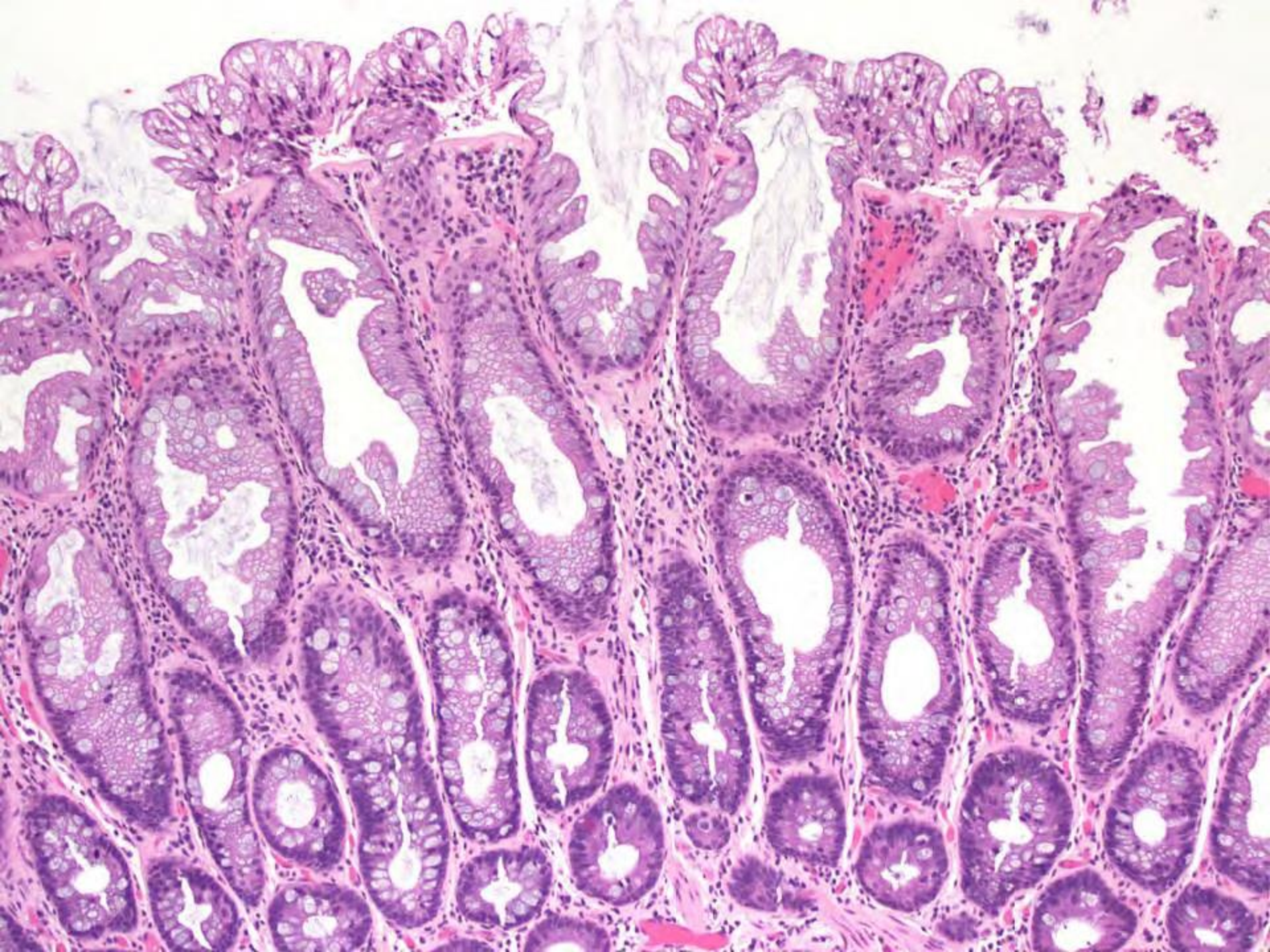
- 65% of serrated polyps
- Small
- Distal>>Proximal

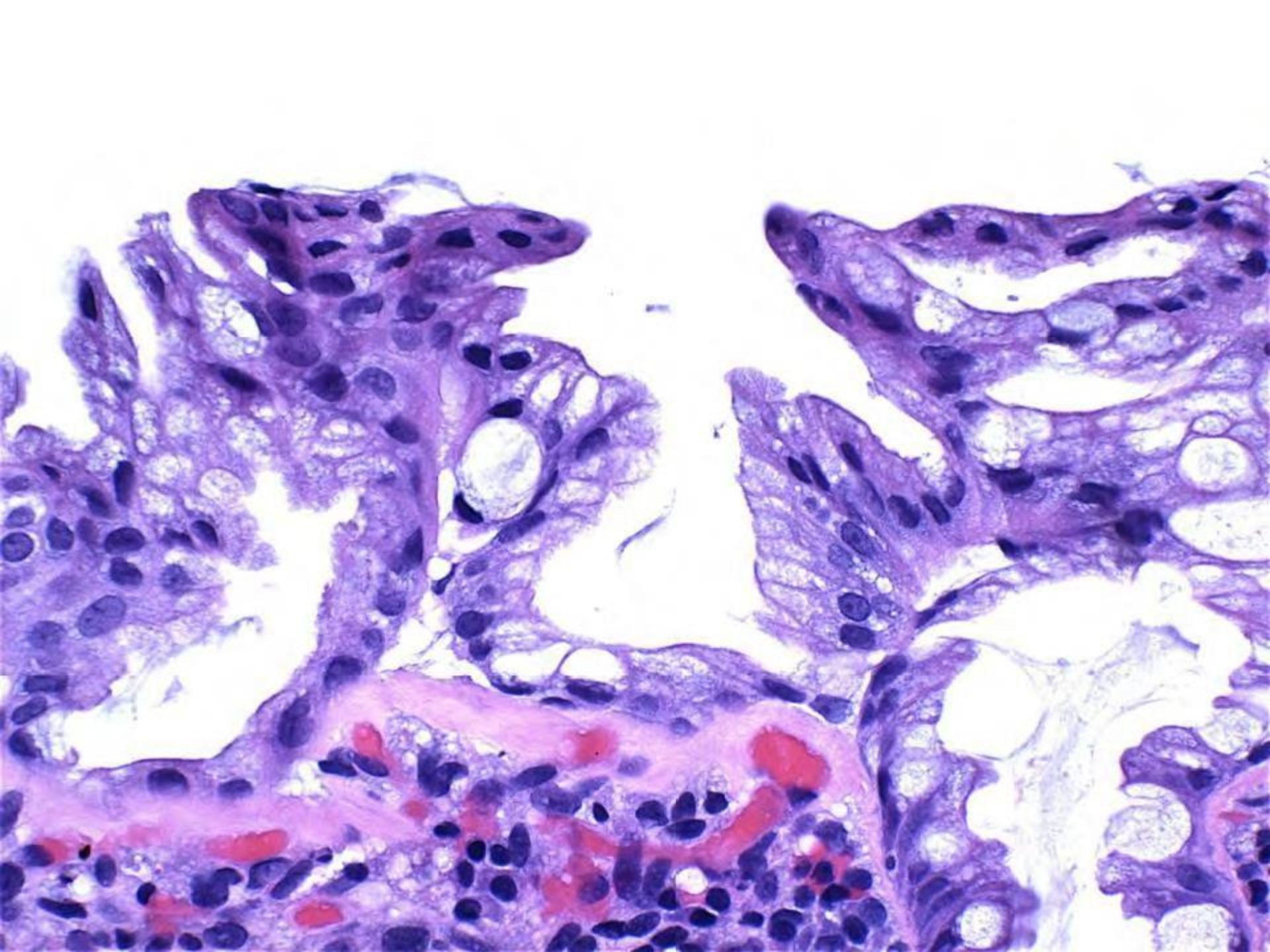


PATHOLOGIC FEATURES

- Serrated crypts: serrations are limited to the upper 2/3 of crypts
- Crypts are elongated and straight
- Base of crypts are uniform
- No cytologic dysplasia
- Microvesicular mucin droplets



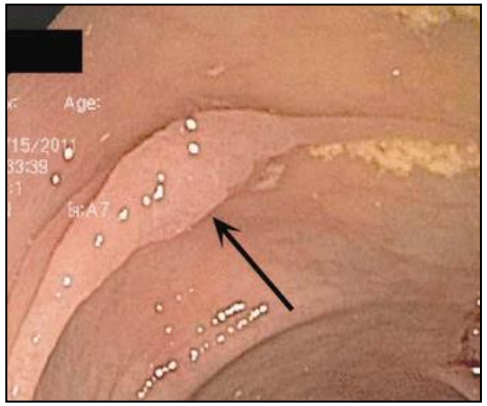




Sessile Serrated Polyp

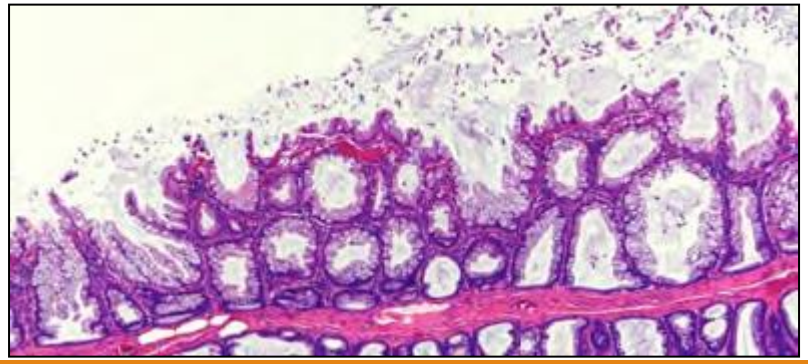
CLINICAL/ENDOSCOPIC FEATURES

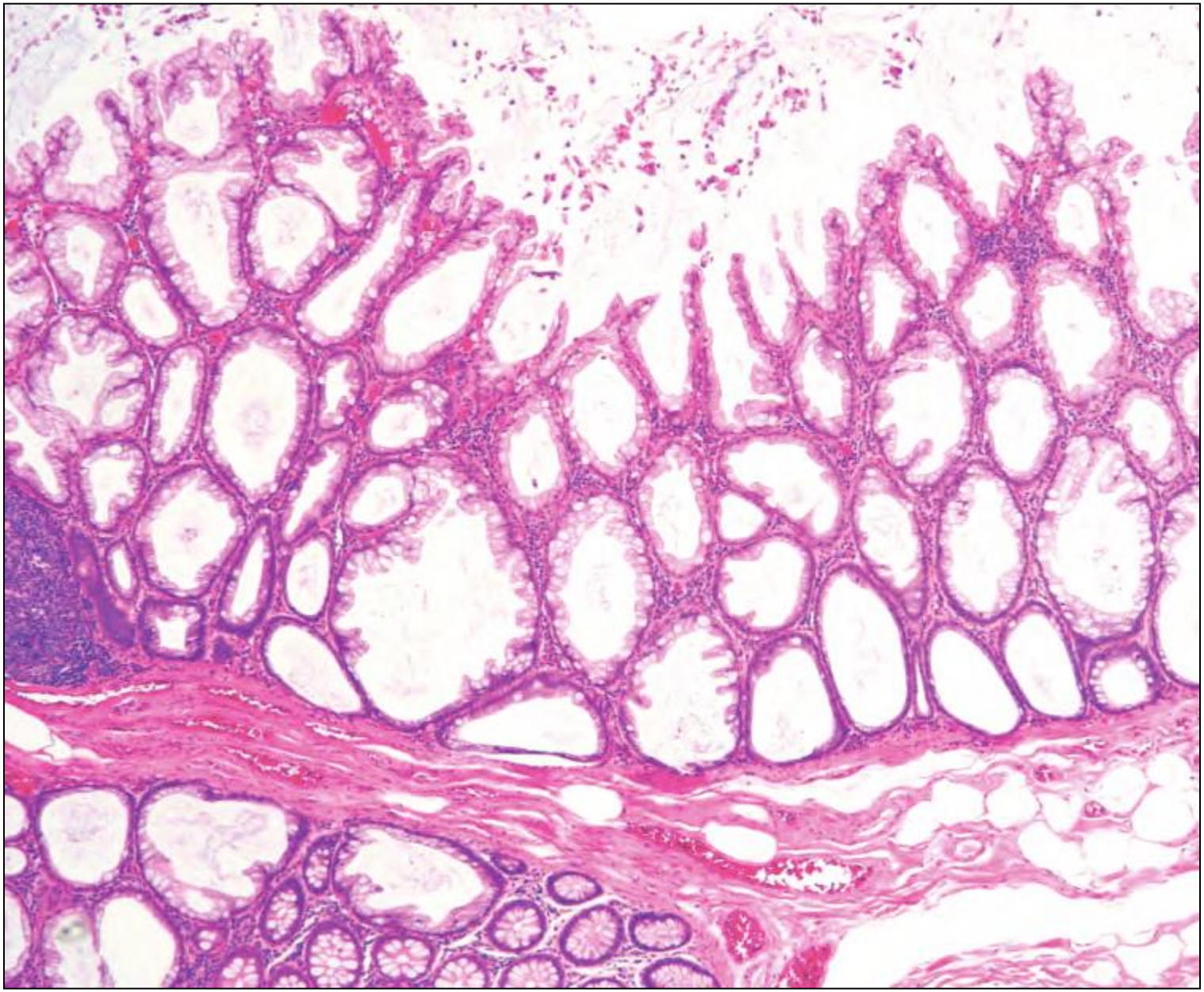
- 35% of all serrated polyps
- Larger than hyperplastic polyps
- Prominent mucosal fold with mucin cap
- Rim of debris/bubbles
- Proximal>>Distal

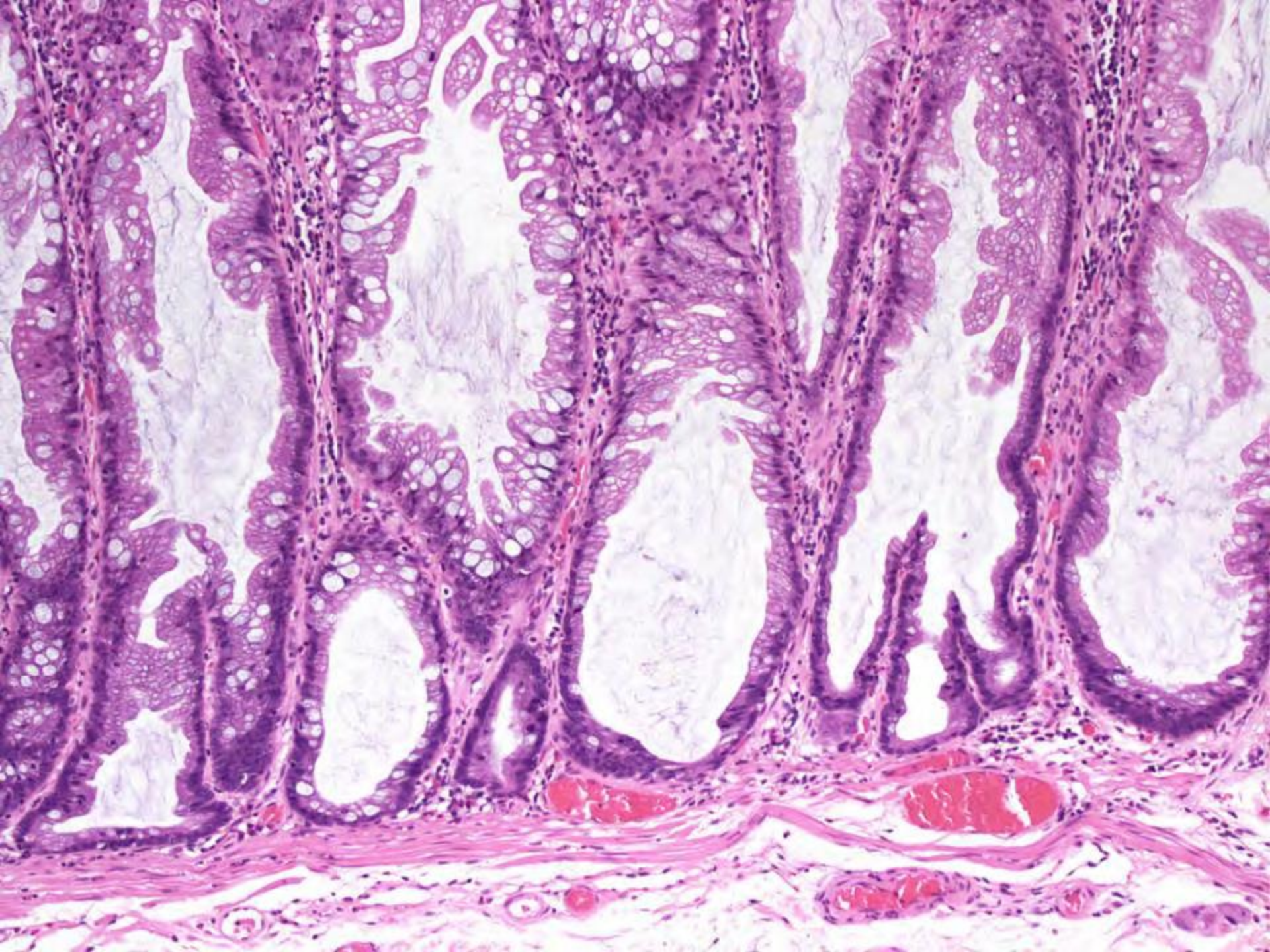


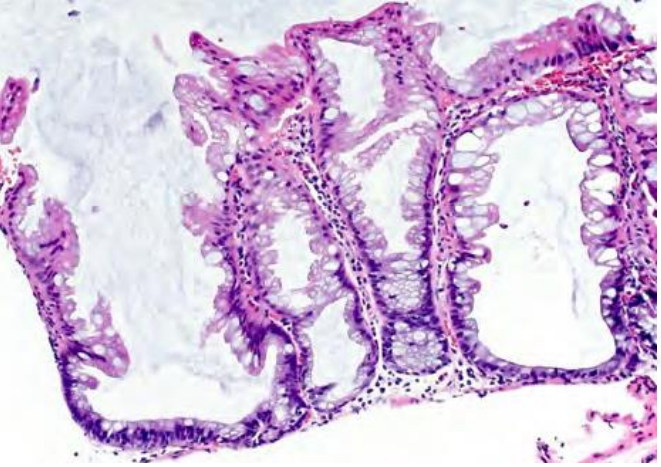
PATHOLOGIC FEATURES

- Resemble hyperplastic polyps
  - Serrated crypts
  - No cytologic dysplasia
  - Cells with microvesicular mucin
- BUT **Architectural** differences:
  - Serrations are present along the entire length of **some** crypts
  - The base of **some** crypts are dilated, irregular, and extend laterally







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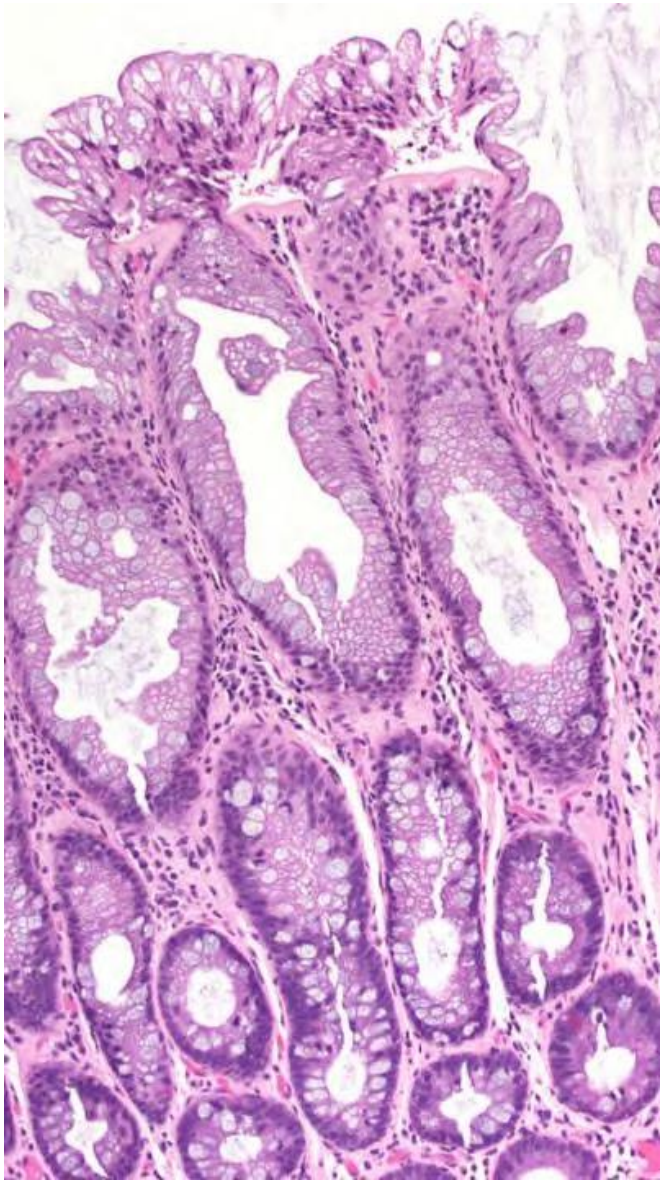
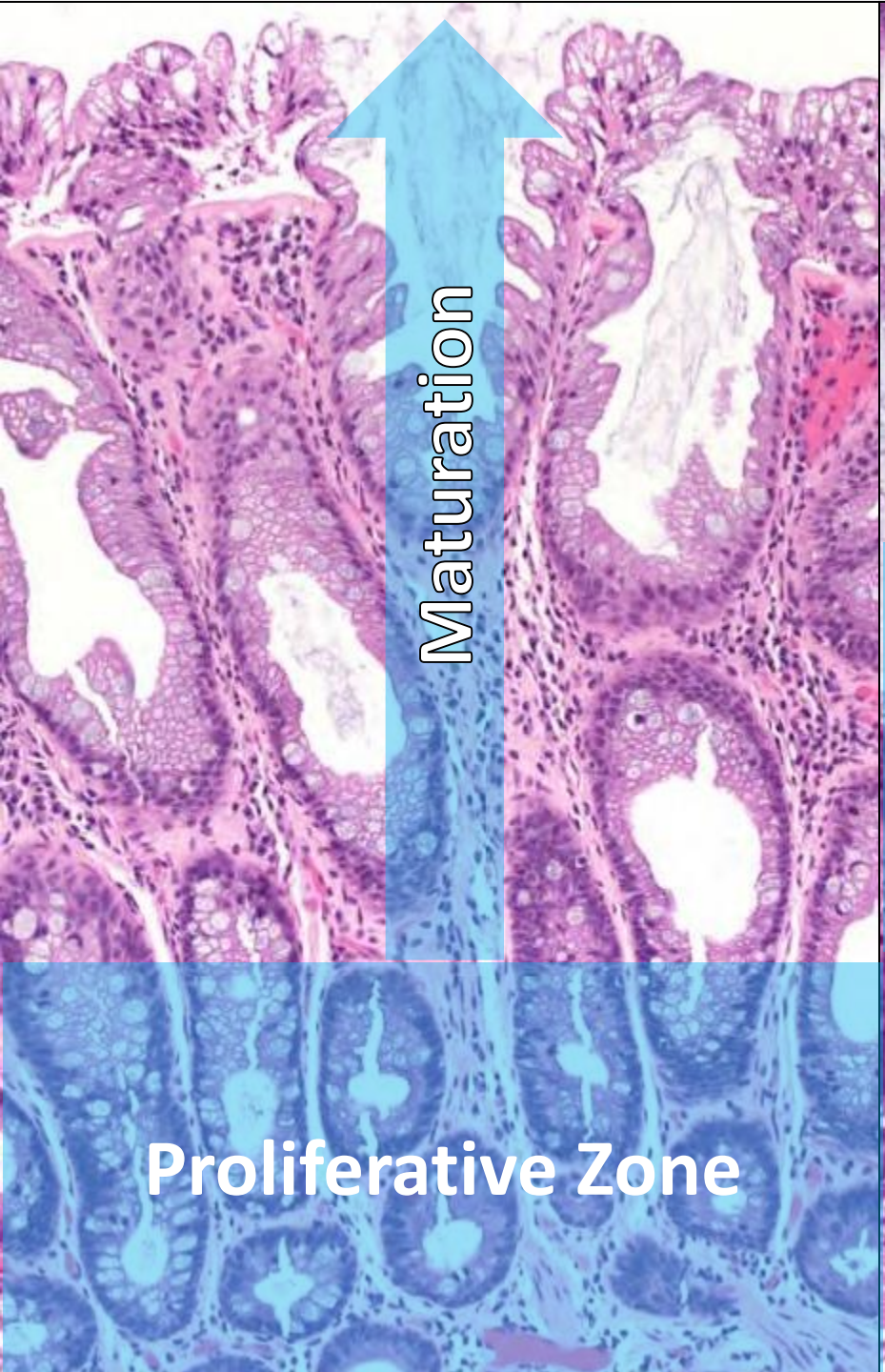
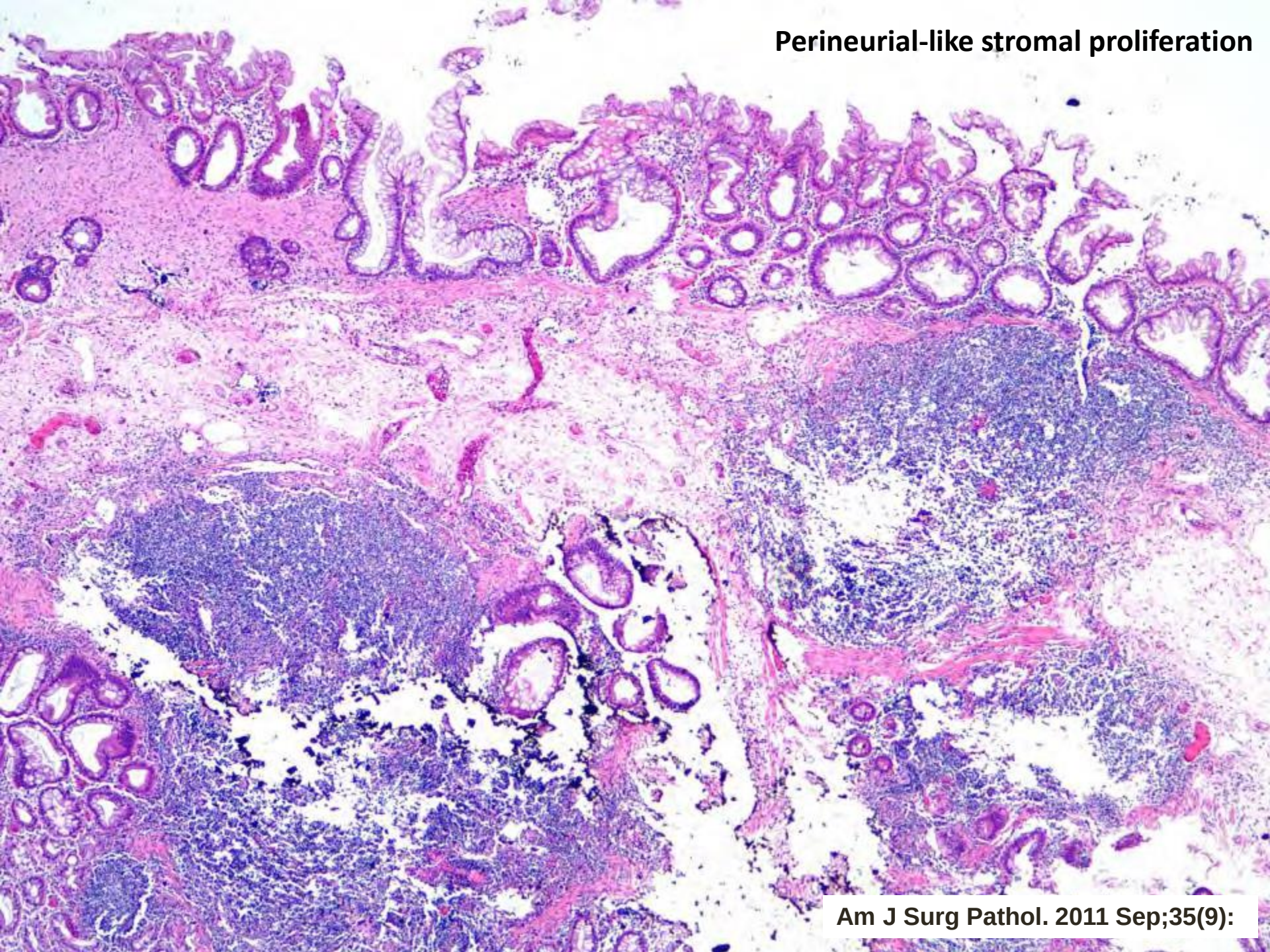
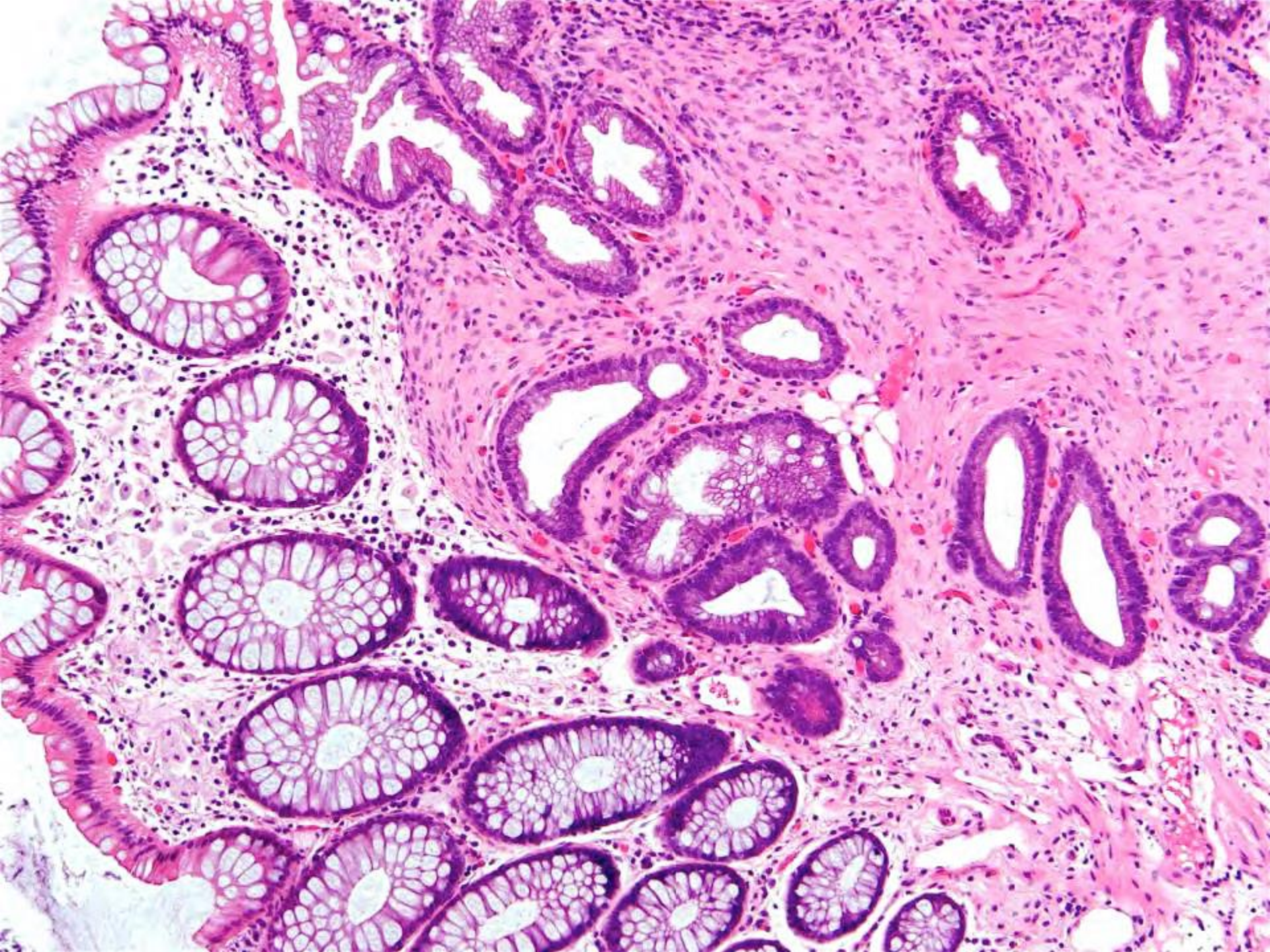
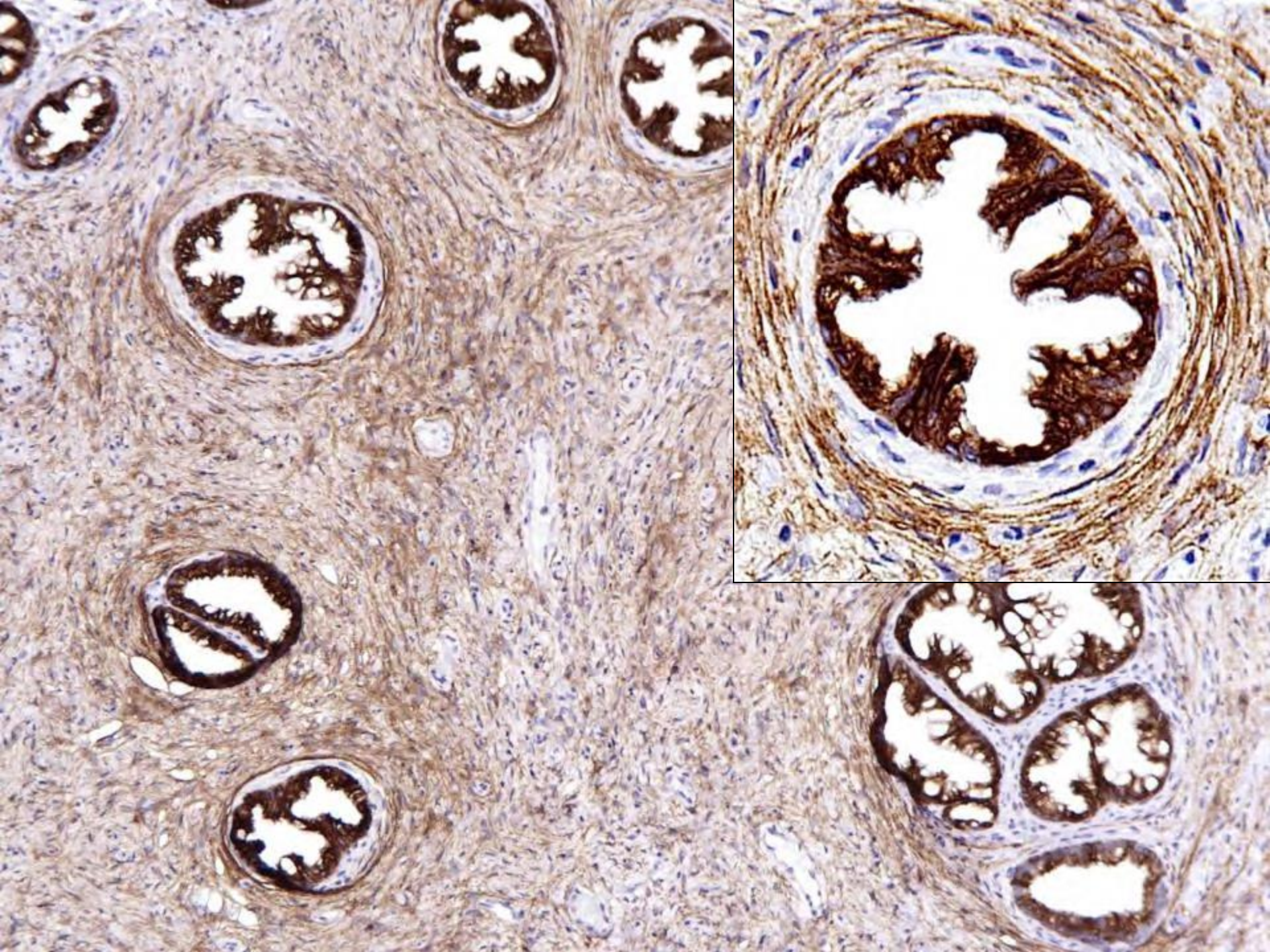


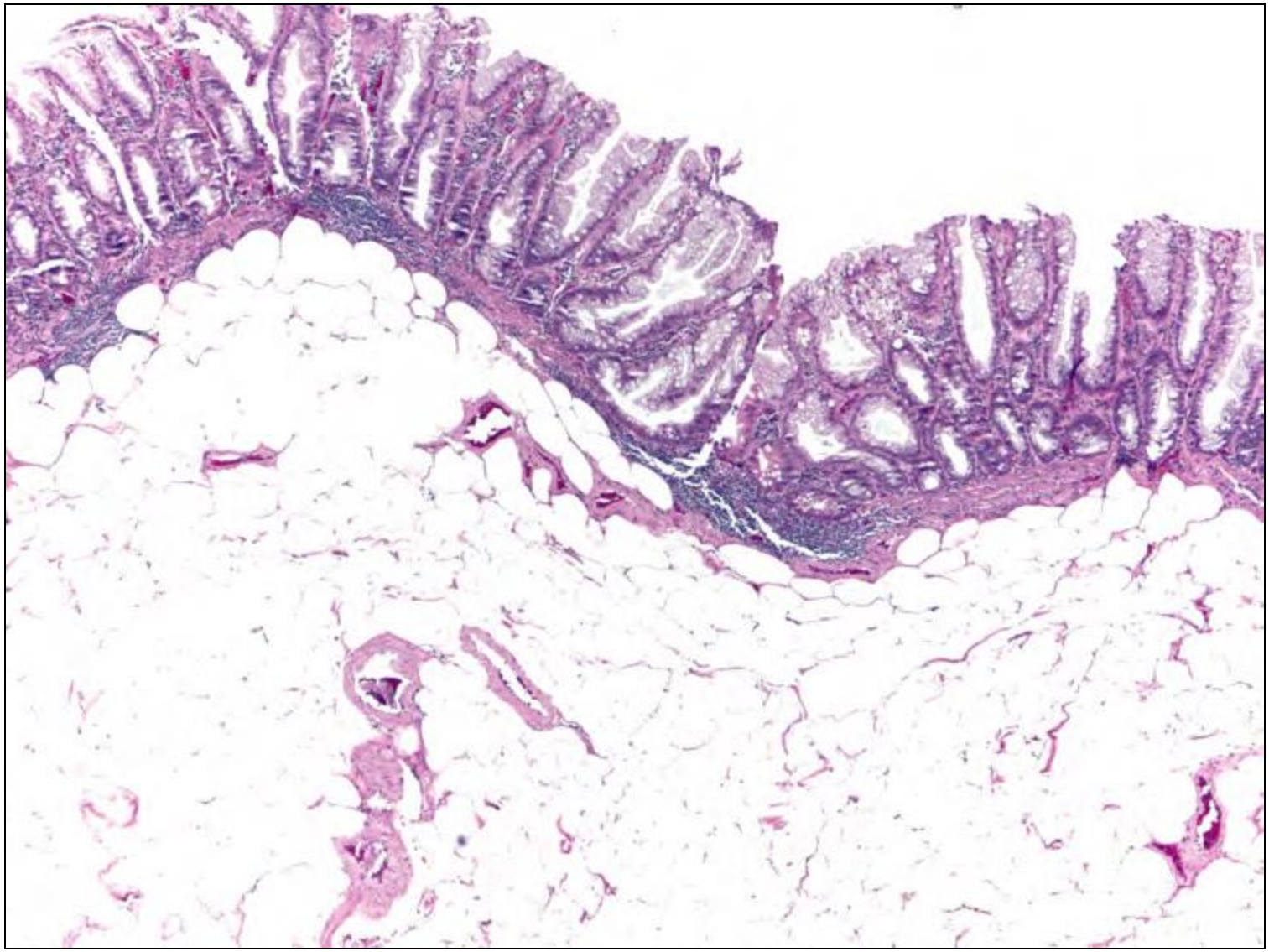

Maturation
Proliferative Zone


Maturation
Proliferative Zone
Maturation

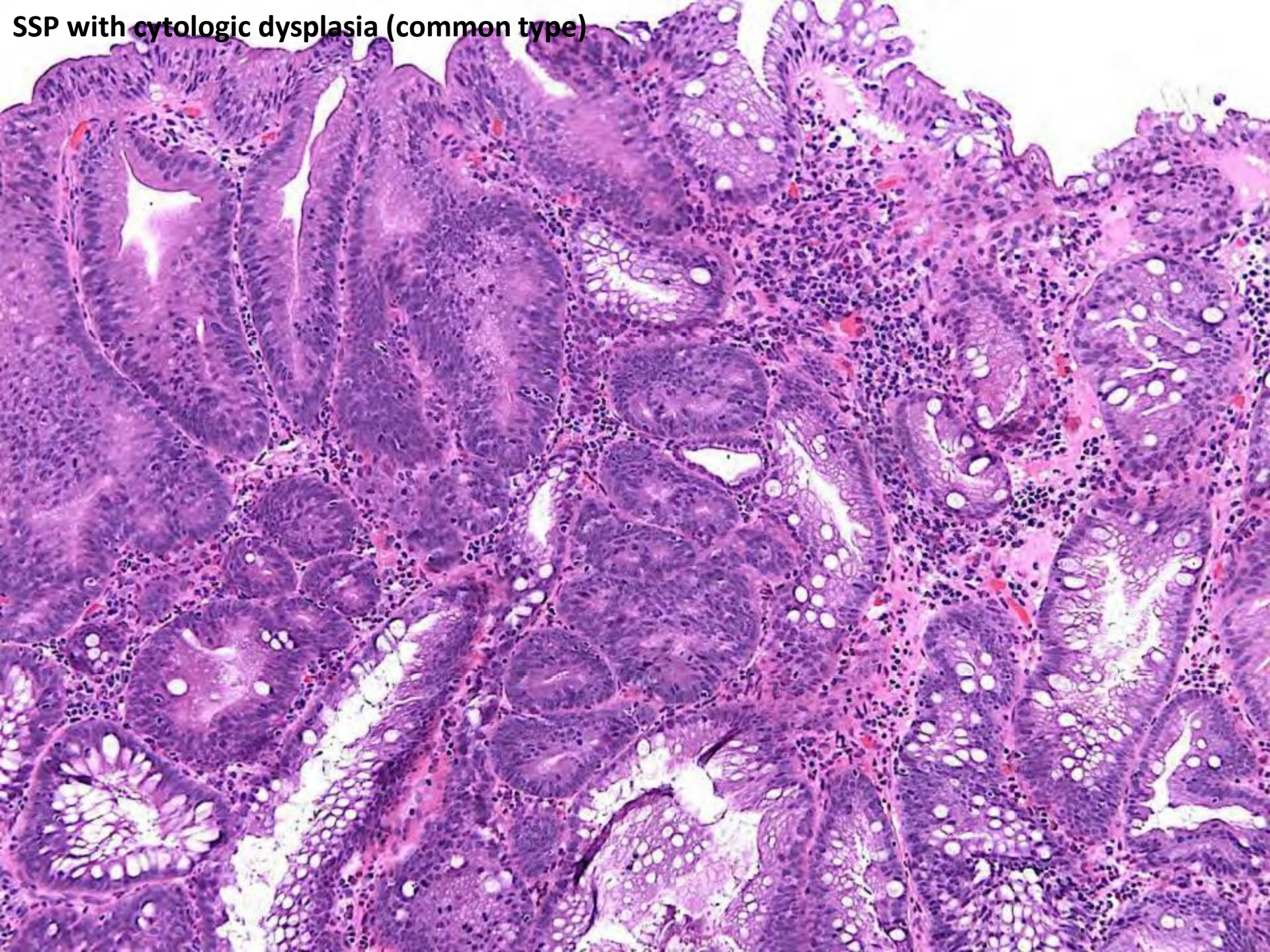

Perineurial-like stromal proliferation
Am J Surg Pathol. 2011 Sep;35(9):



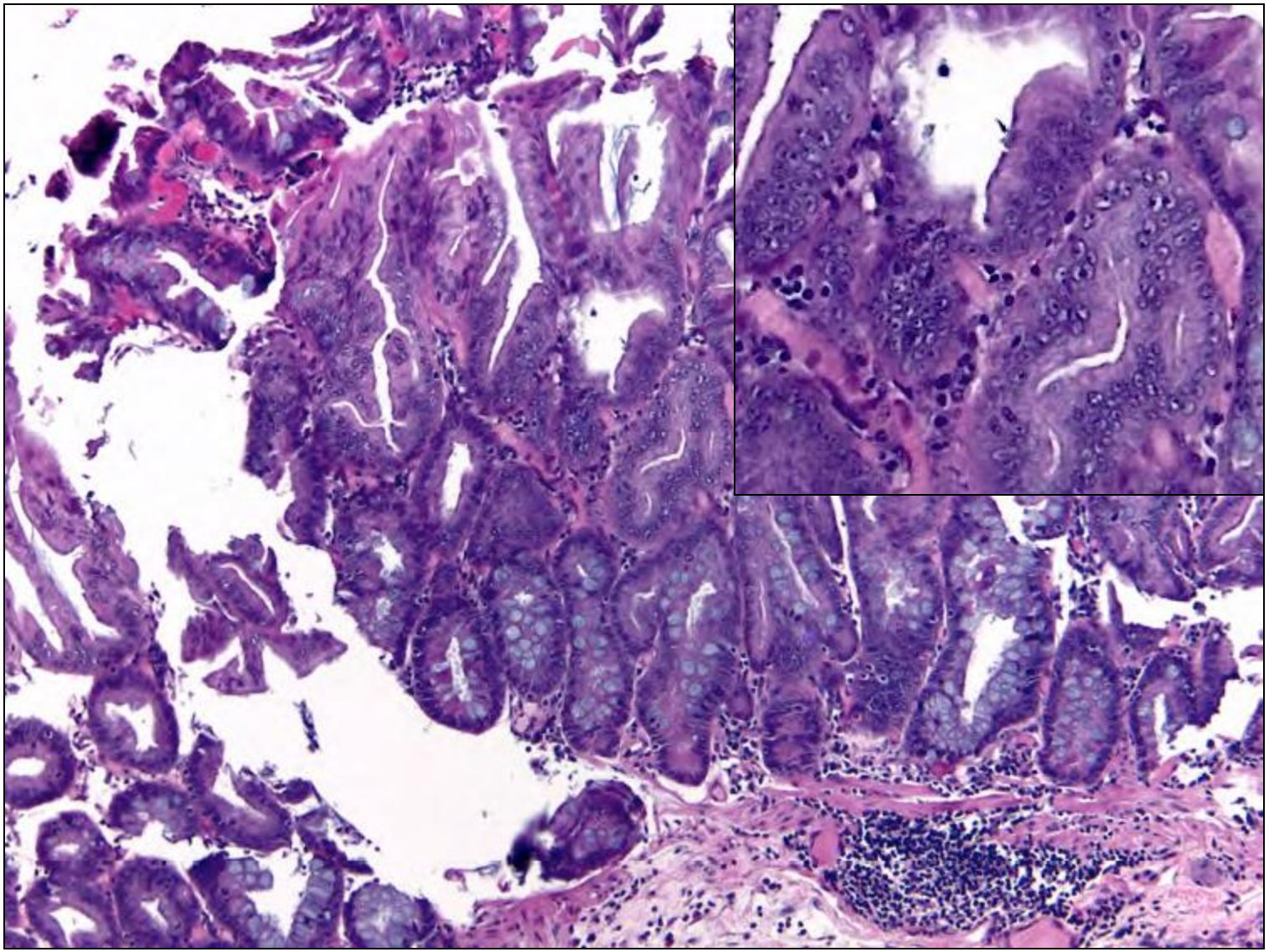




SSP with cytologic dysplasia (common type)



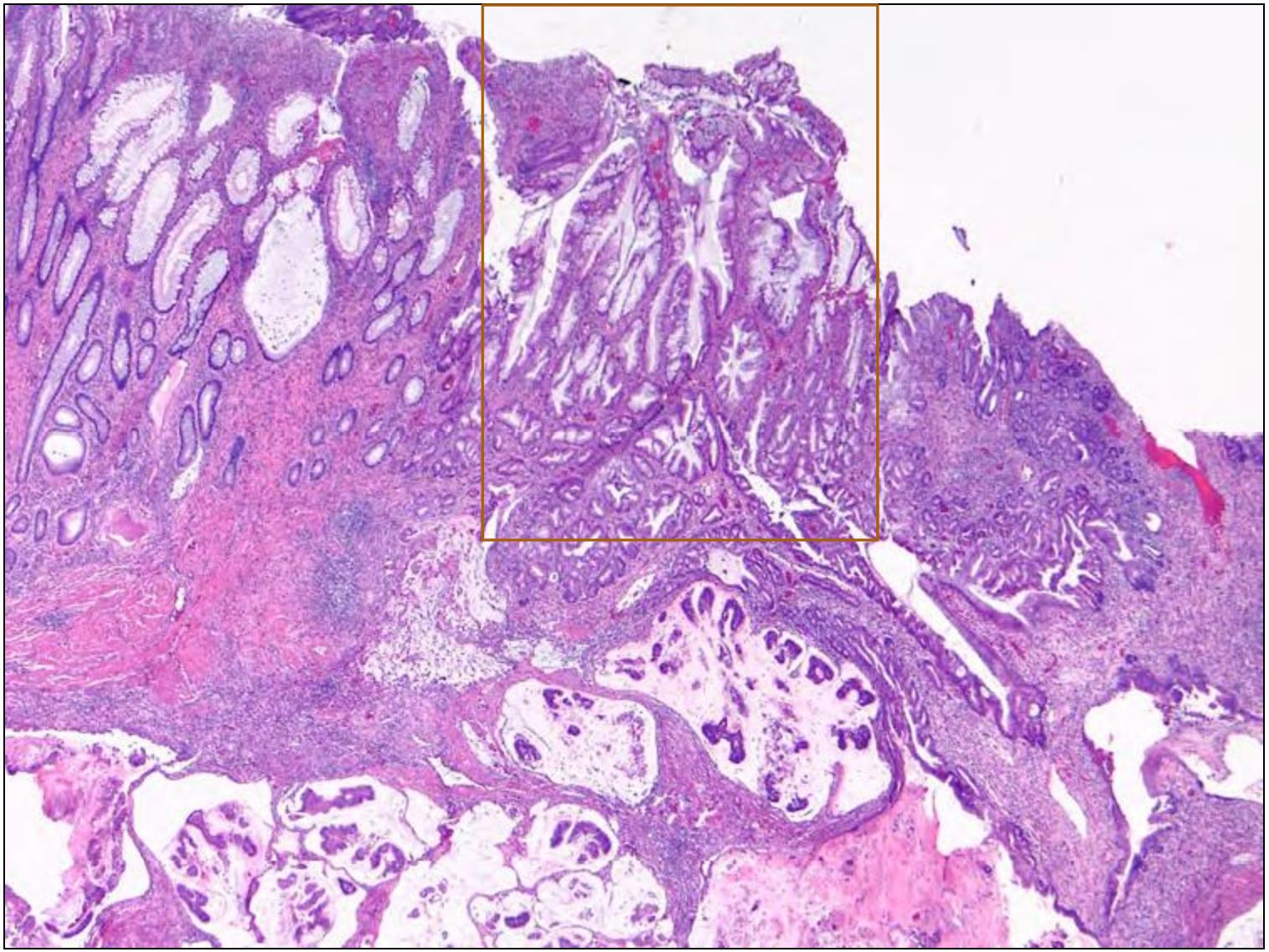
“Serrated dysplasia” within SSP



Sessile Serrated Polyps with cytologic dysplasia

- **Prevalence**
  - **About 5% of SSPs in one large study harbor dysplasia**
- **WHO does not require to separate into high- and low-grade; however, I try to do so**
  - **Diagnosis: Sessile serrated polyp with cytologic dysplasia (low-grade)**
- **Morphologic variants are being described**
  - **Abtract at USCAP: Common NOS, serrated, adenomatous, and "minimal deviation"**
  - **Not required to morphologic subtype**

SSP Precursor



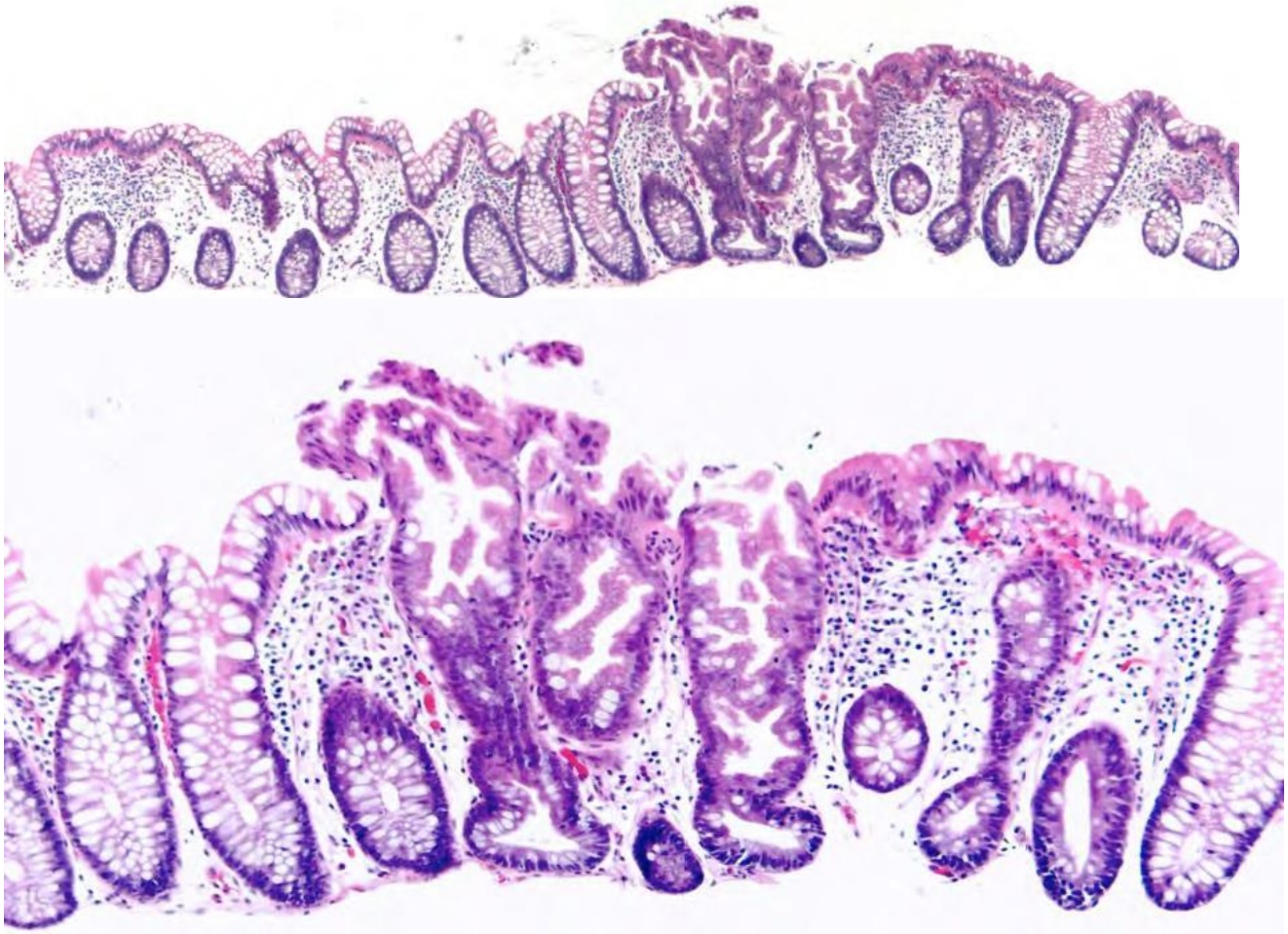
- **Danish CRC study: 2,060 CRC cases, 8,237 controls**
- **Determined what polyps at index colonoscopy increase risk of CRC**
- **Reviewed all serrated polyps (4 GI pathologists)**

Polyp type	**Cases %**	**Controls**	**Adjusted OR**
No polyp	56.5	74.2	1.00 (reference)
SSA/P no cytologic dysplasia	2.9	1.4	2.75
SSA/P with cytologic dysplasia	1.0	0.3	4.76
Conventional adenoma	37	21	2.51
Hyperplastic polyp	2.7	2.9	1.30

Baseline colonoscopy: most advanced finding(s)	Recommended surveillance interval (y)	Quality of evidence supporting the recommendation	New evidence stronger than 2006
Serrated lesions			
Sessile serrated polyp(s)			
<10 mm with no dysplasia	5	**Low**	NA
Sessile serrated polyp(s) ≥10 mm	3	**Low**	NA
Sessile serrated polyp with dysplasia	3	**Low**	NA
Traditional serrated adenoma	3	**Low**	NA
Serrated polyposis syndrome	1	**Moderate**	NA

Questions

1. What about patients with multiple SSPs?
2. Is there any difference in proximal versus distal SSP?
3. What about HPs? Particularly proximal HPs?



WHO 2010 – At least 2 adjacent crypts or 3 individual crypts with abnormal architecture
Rex et al – At least one unequivocal architecturally distorted, dilated, and/or horizontally branched crypt

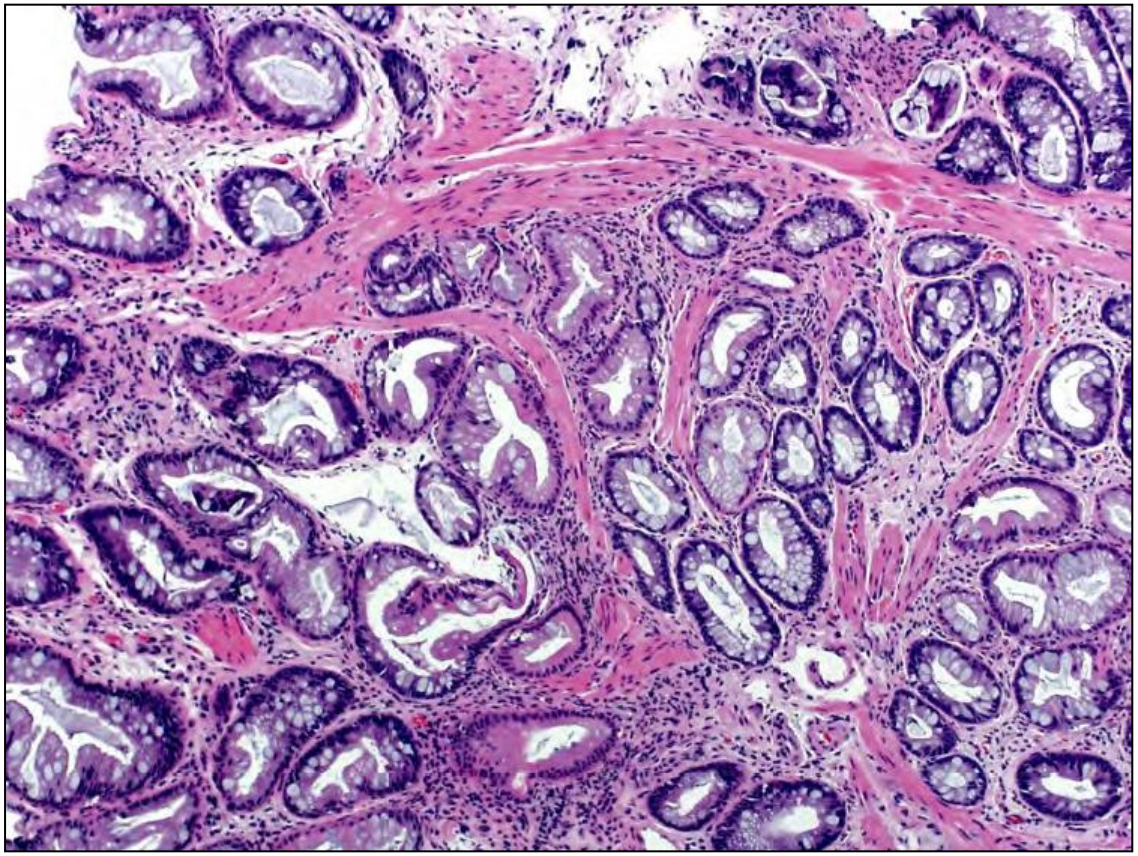
How to make the diagnosis of SSP?

- **Which criteria should we use?**
  - **Bettington et al analyzed 6340 polyps (AJSP. 2014. 38(2):158-66)**
    - **WHO criteria: 12.1% were SSPs**
    - **Using Rex criteria: 14.7% were SSPs**
    - **Found that serrated polyps with any SSP-like crypts (Rex criteria) had clinical features more like SSPs than HPs (more proximal, larger, etc.)**
  - **They conclude that only 1 abnormal crypt is necessary for the diagnosis independent of size and location**
- **Kolb et al found that using the Rex criteria resulted in improved interobserver agreement and a ~7% increase in the diagnosis of SSA/P compared to WHO criteria (J Clin Gastroenterol 2015, PMID: 26501882)**

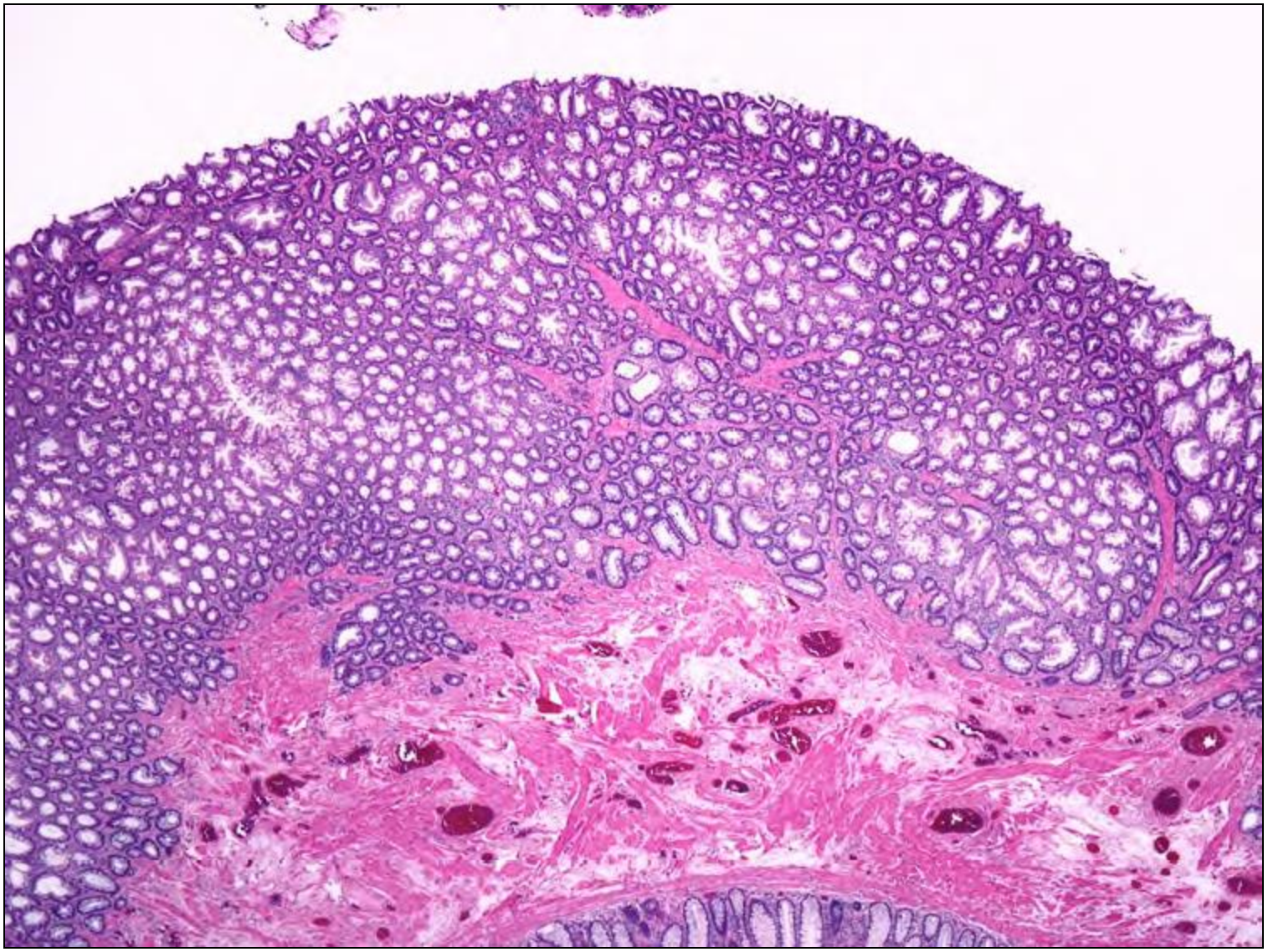
Mucosal Prolapse (left sided HPs)

- **Pai et al (Histopathology 2010)**
  - **276 serrated polyps, independent review by 2 pathologists**
  - **30 polyps lacked consensus, 11/30 had features of mucosal prolapse**
- **Huang et al reanalyzed 78 rectal polyps diagnosed as SSP (Human Path 2013)**
  - **Mucosal prolapse was common in these "SSPs" and 31/78 were felt to be better classified as HPs with prolapse**

Prolapsed HP

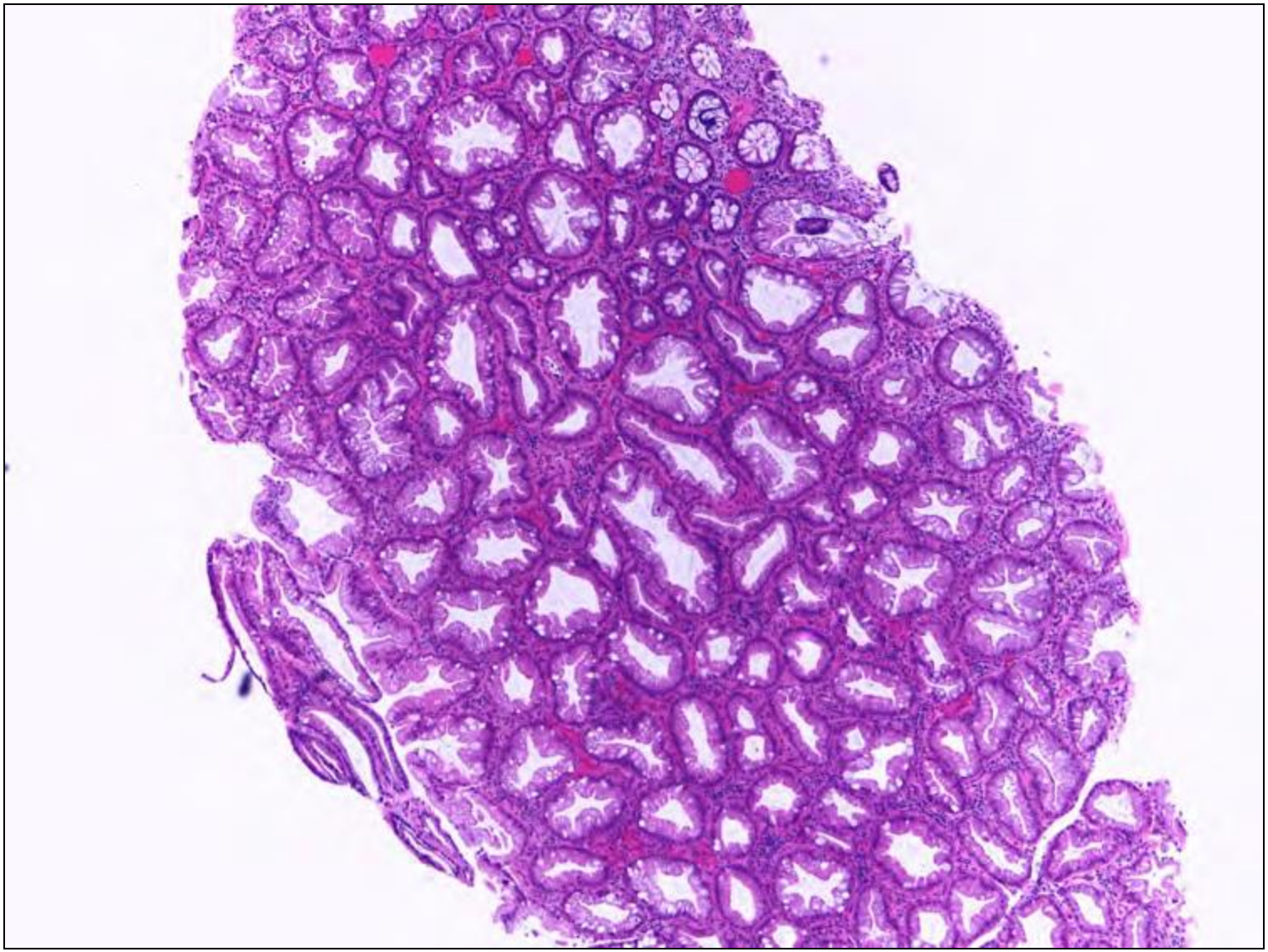


Prolapsed HP vs. SSP?



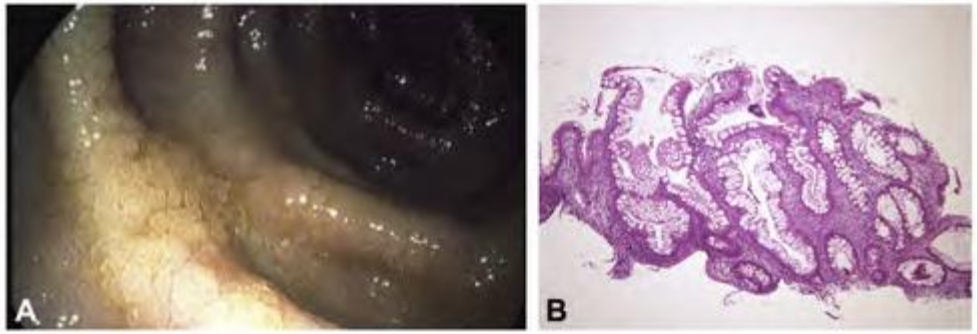
Poorly orientated biopsy fragments

- **As architecture is the most important determining feature of SSP, poorly oriented fragments are difficult to interpret**
- **Morales et al placed suspicious polyps in a paper envelope and flattened them before placing in formalin to help with embedding. (Endoscopy 2013 45(11):906)**
- **This improved the interobserver agreement between pathologists and increased the % of polyps diagnosed as SSPs**



Serrated polyps in IBD

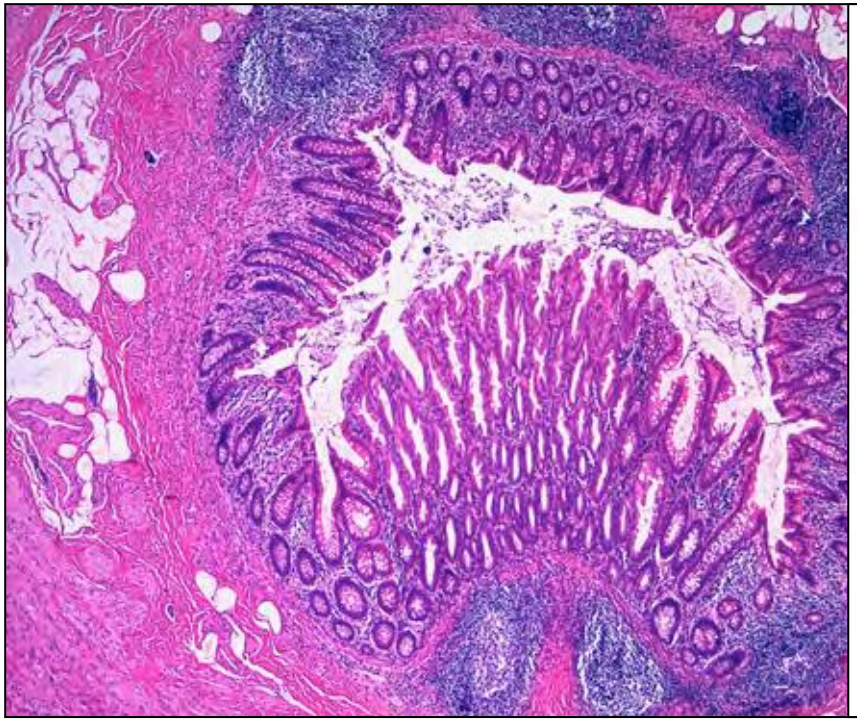
- Scenario 1: It looks like an HP – call it an HP
- Scenario 2: It looks like an SSP – call it an SSP
- Scenario 3: Flat mucosa with surface hyperplasia – I call it hyperplastic change, negative for dysplasia
- Scenario 4: Serrated changes in a background of inflammation and distorted architecture: call it serrated epithelial change
  - May be associated with metachronous and synchronous dysplasia



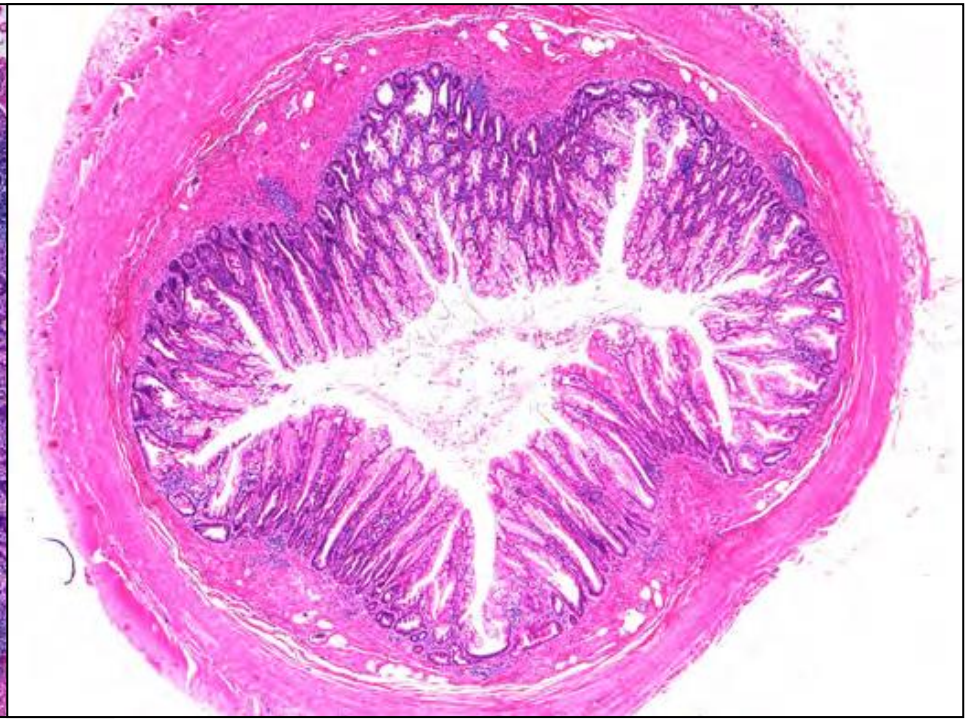
Appendiceal serrated polyps

- **Morphologically similar to colon counterparts, but molecularly distinct**
  - **Most serrated lesions of the appendix (even those that resemble colonic HPs and SSPs) primarily have *KRAS* and not *BRAF* mutations**
- **Recommendation is to simply diagnose as "appendiceal serrated polyp". Also mention if there is cytologic dysplasia**

Appendiceal Serrated Polyp without Dysplasia



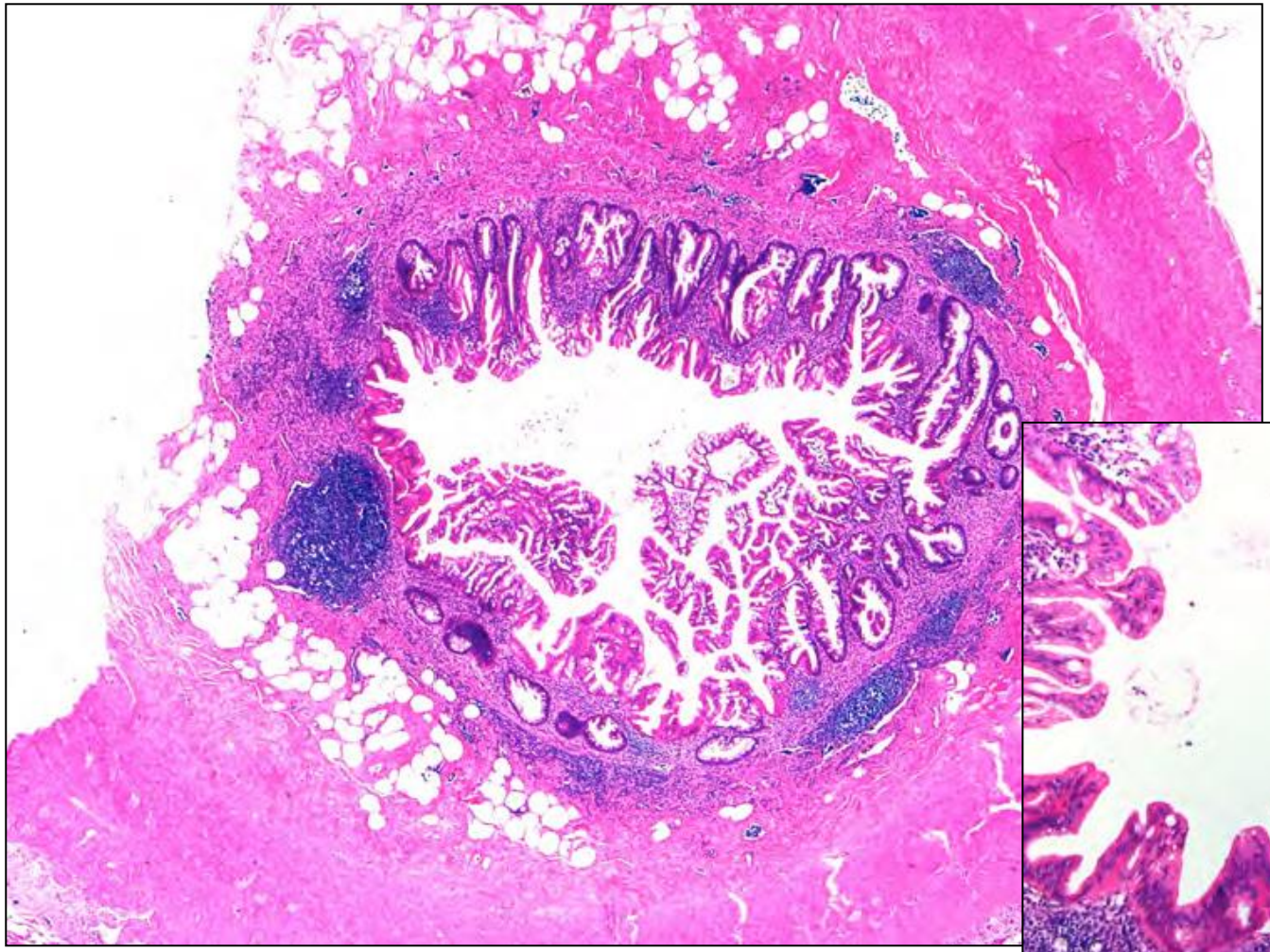
Resembles a colonic HP

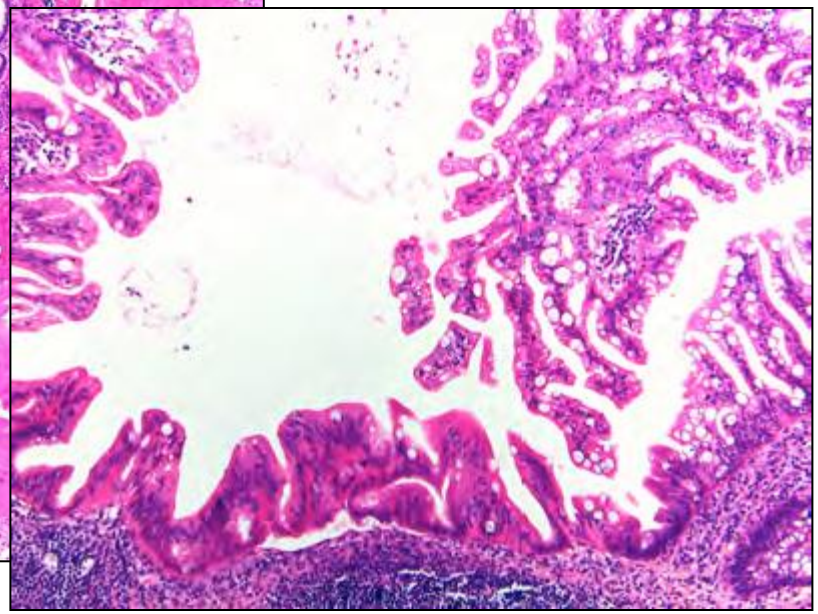


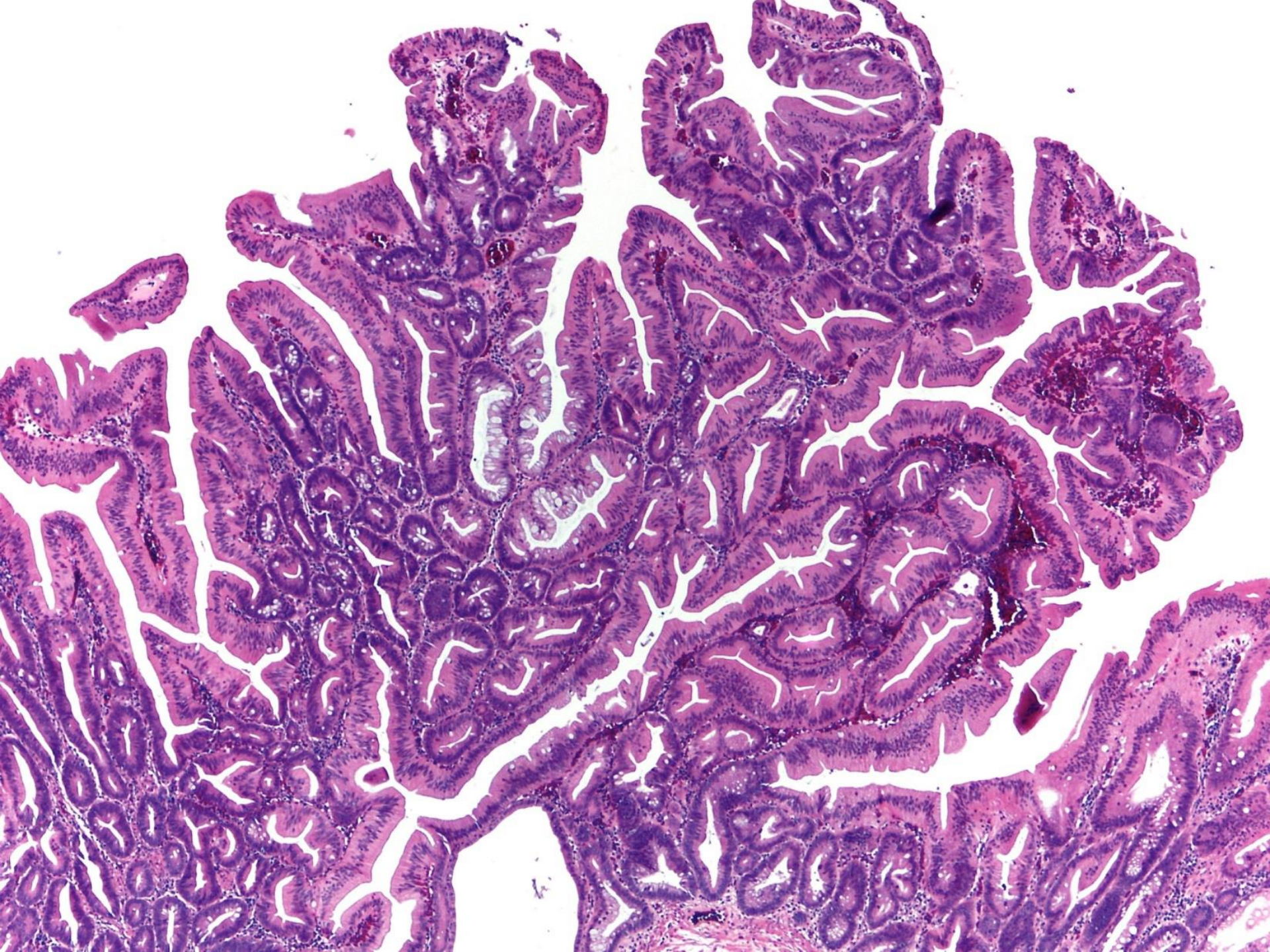
Resembles a colonic SSP

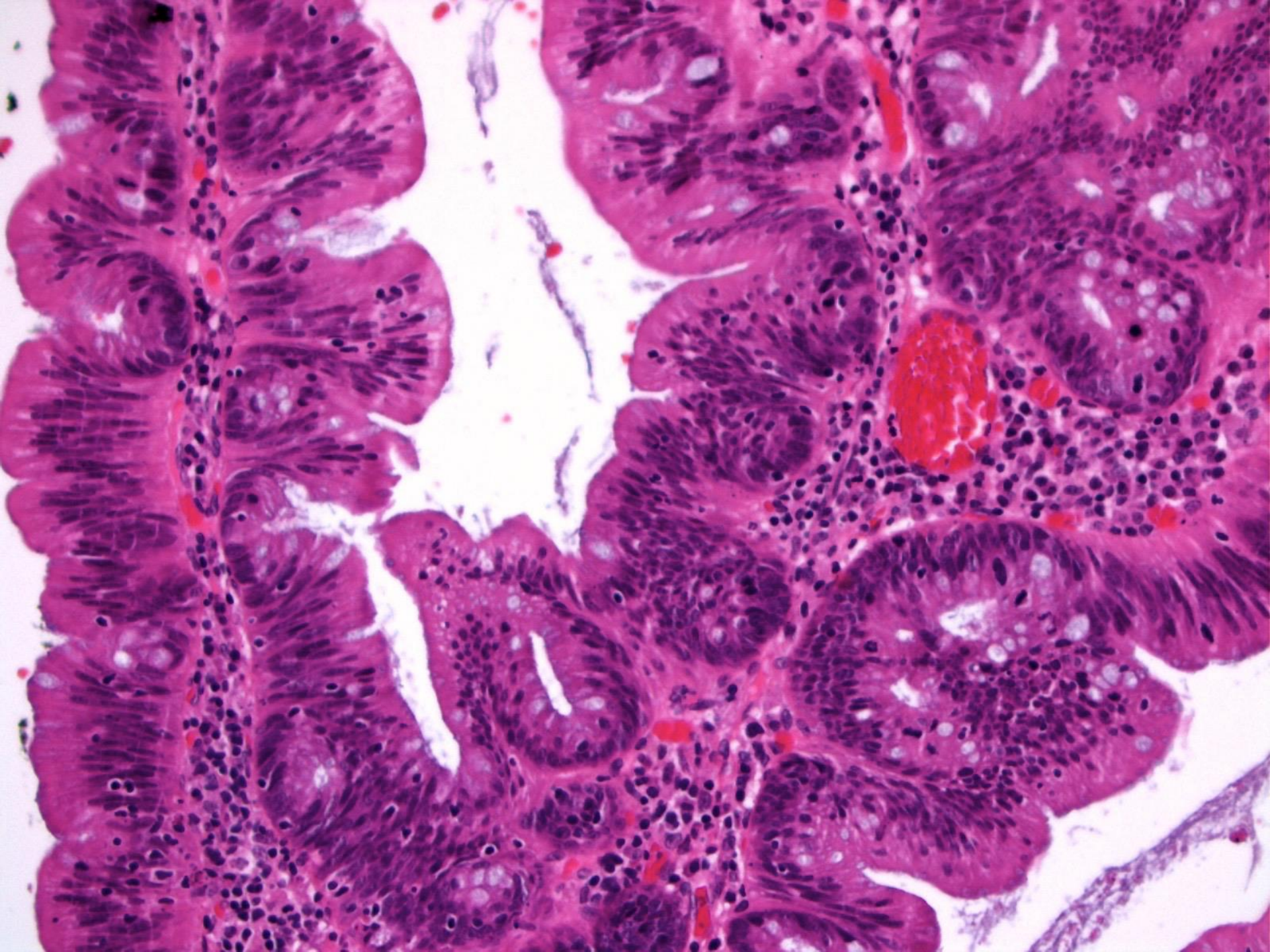
Pai RK, et al. Hum Pathol. 2014 Feb;45(2):227-35.

Appendiceal Serrated Polyp with cytologic dysplasia (low-grade)



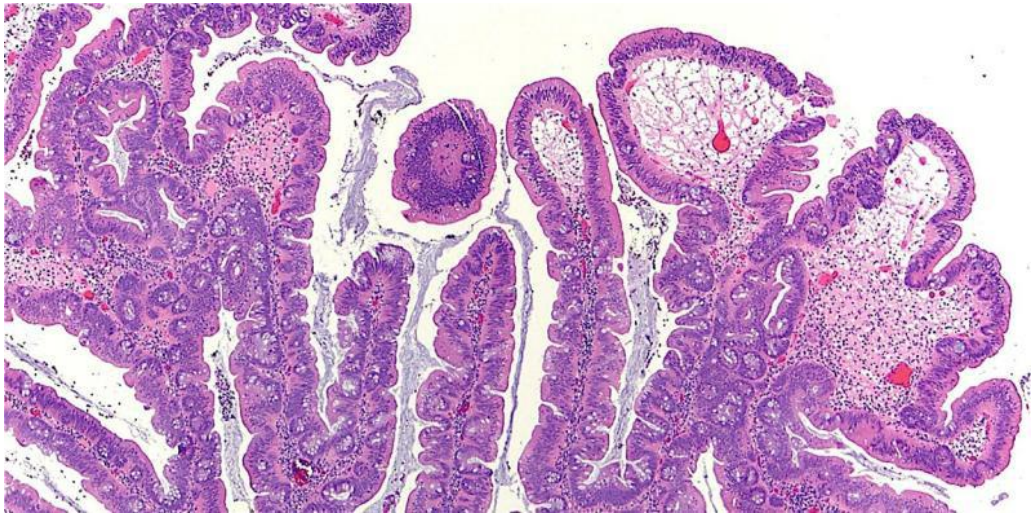


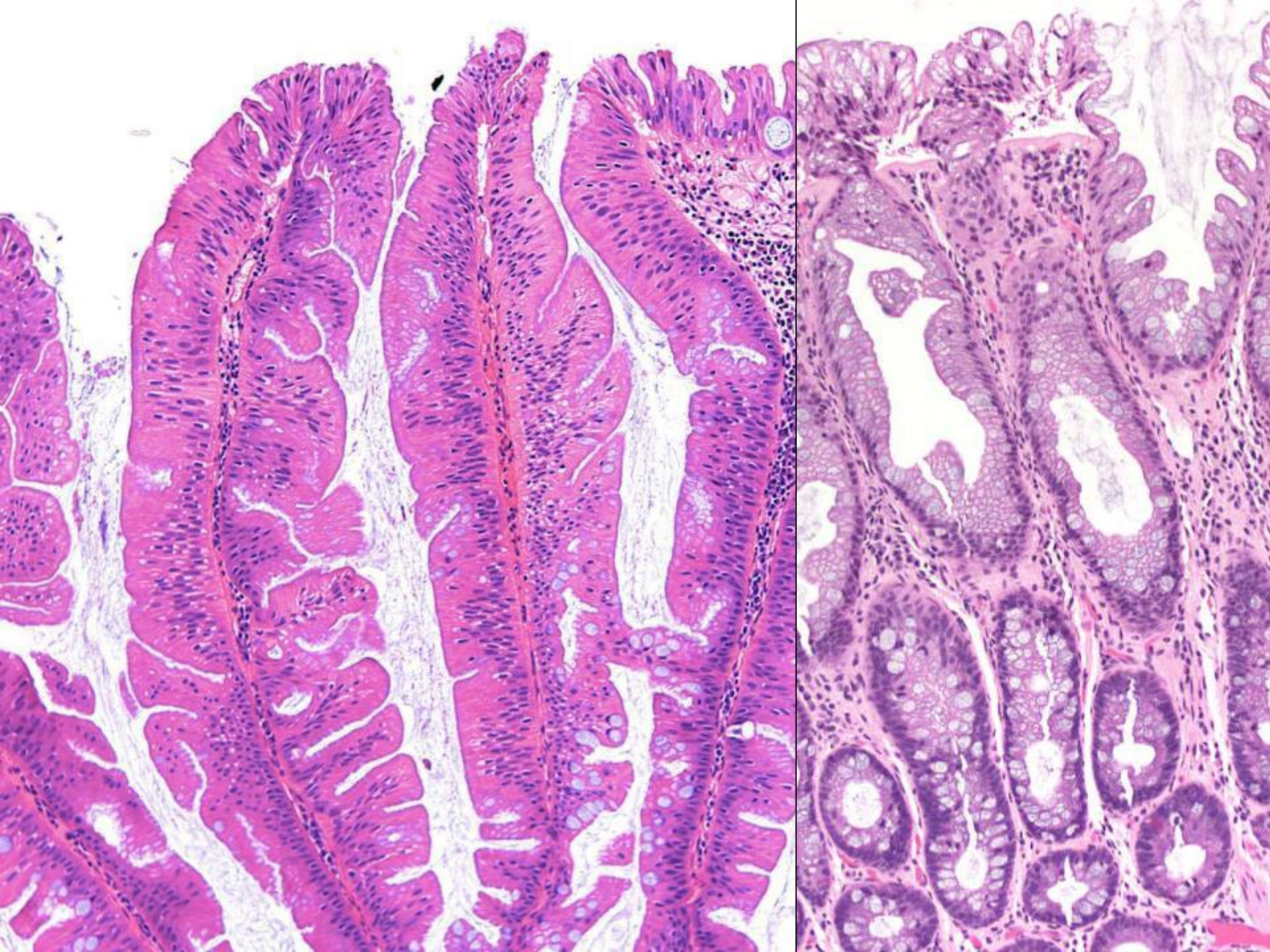


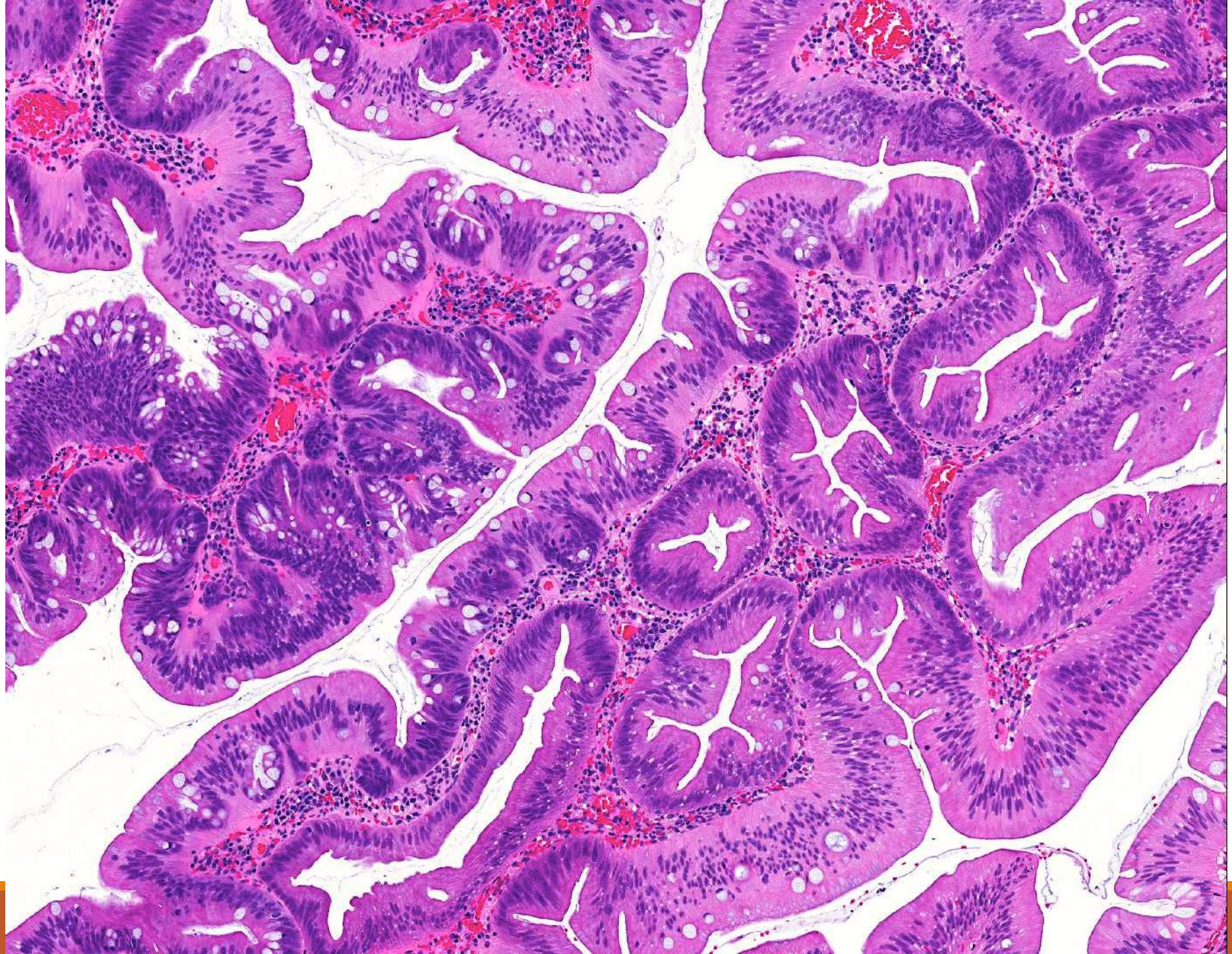


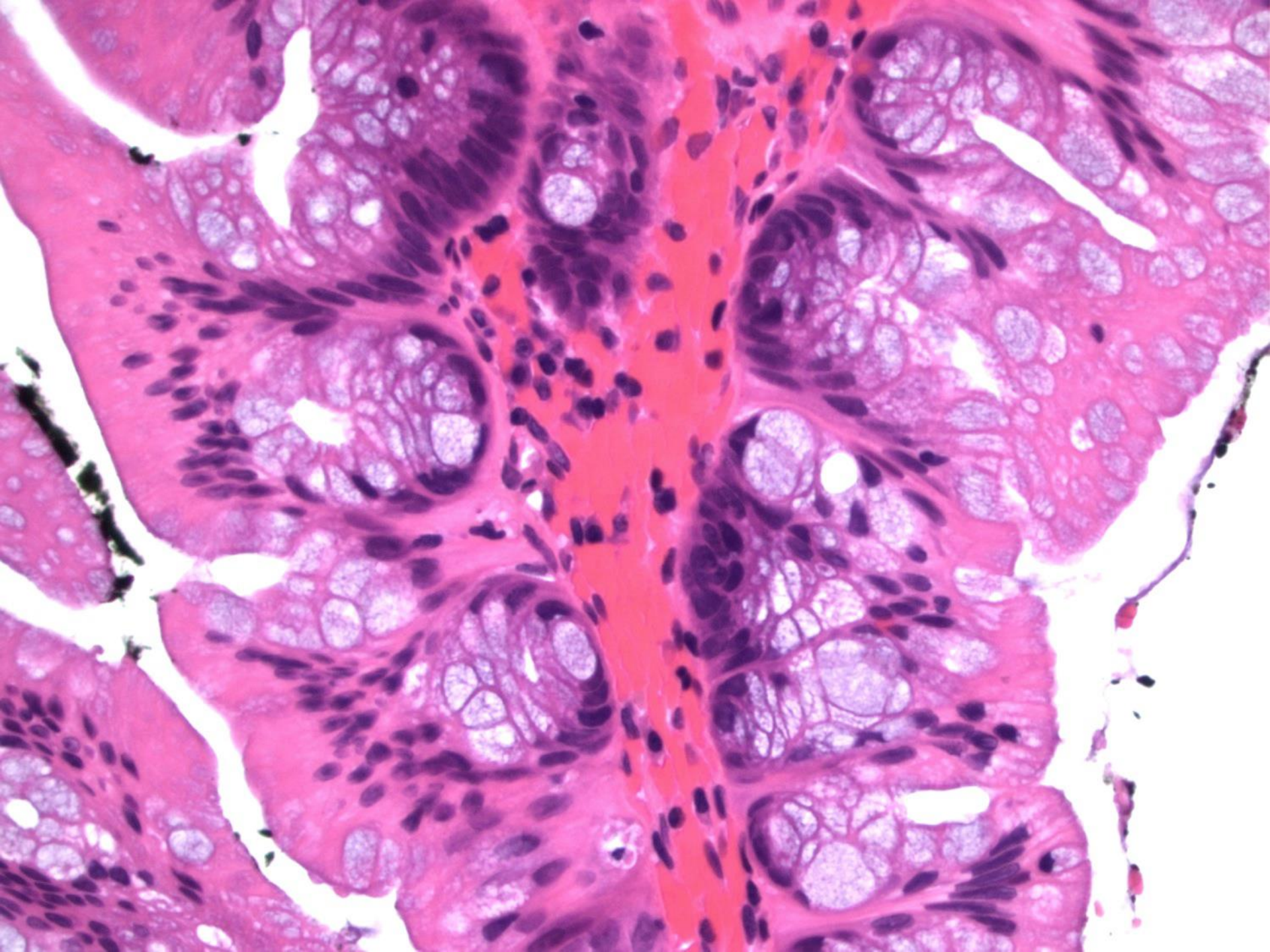
Serrated Adenomatous Polyp

- 2-5% of serrated polyps
- Large
- Protuberant, exophytic
- Distal>>Proximal
- Villiform
- Serrated crypts
- Pseudostratified pencillate nuclei
- Abundant eosinophilic cytoplasm



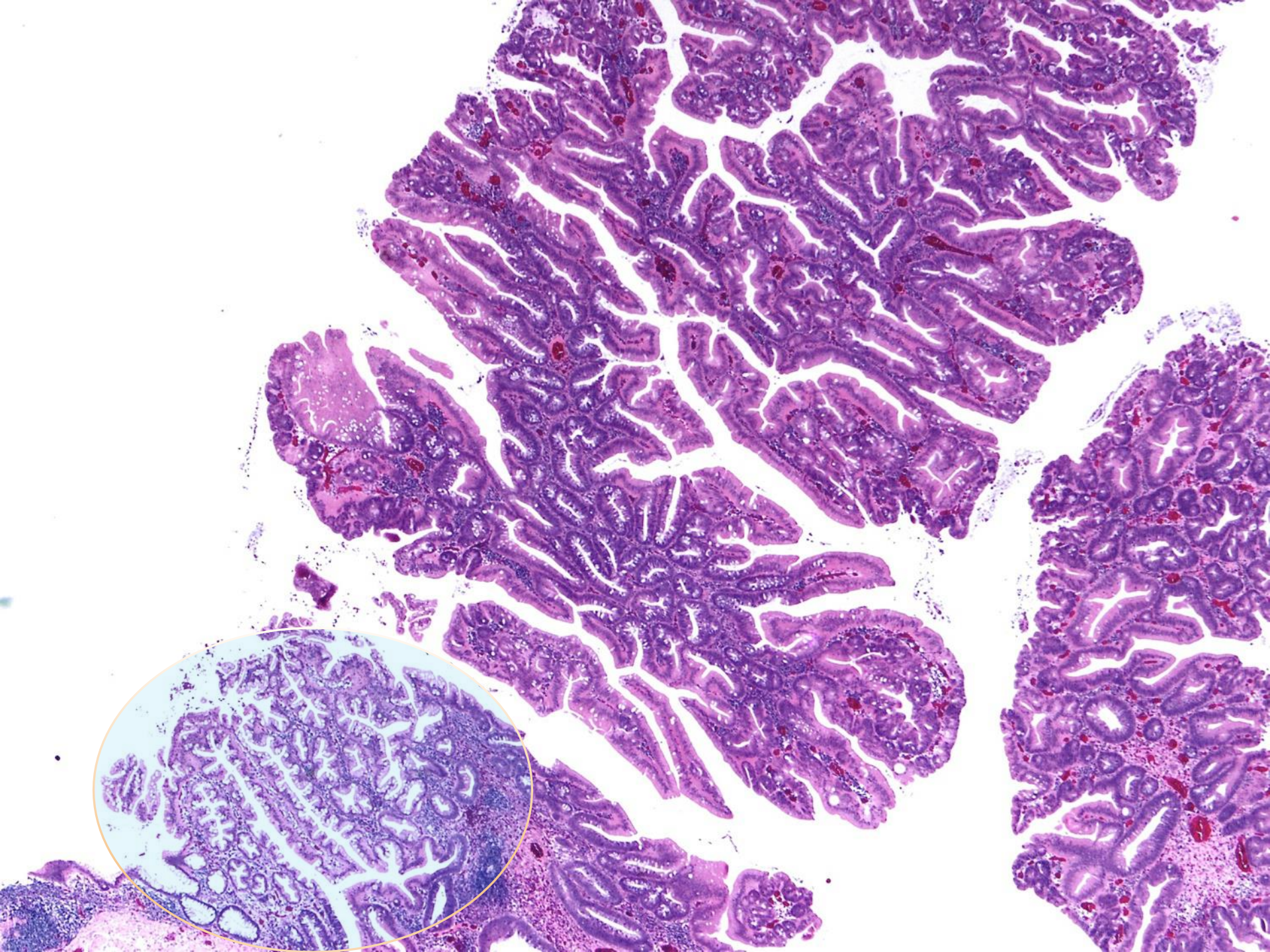




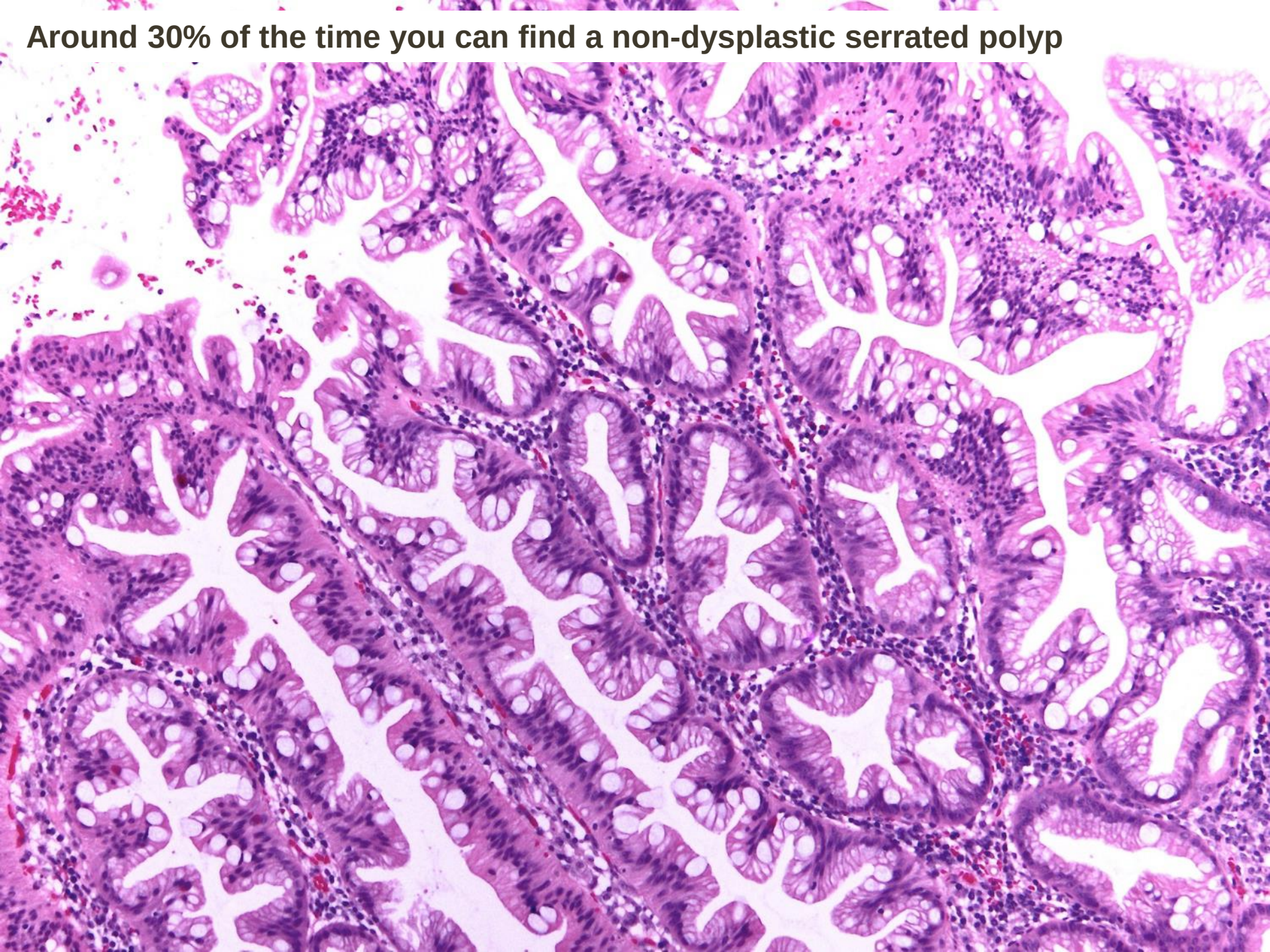


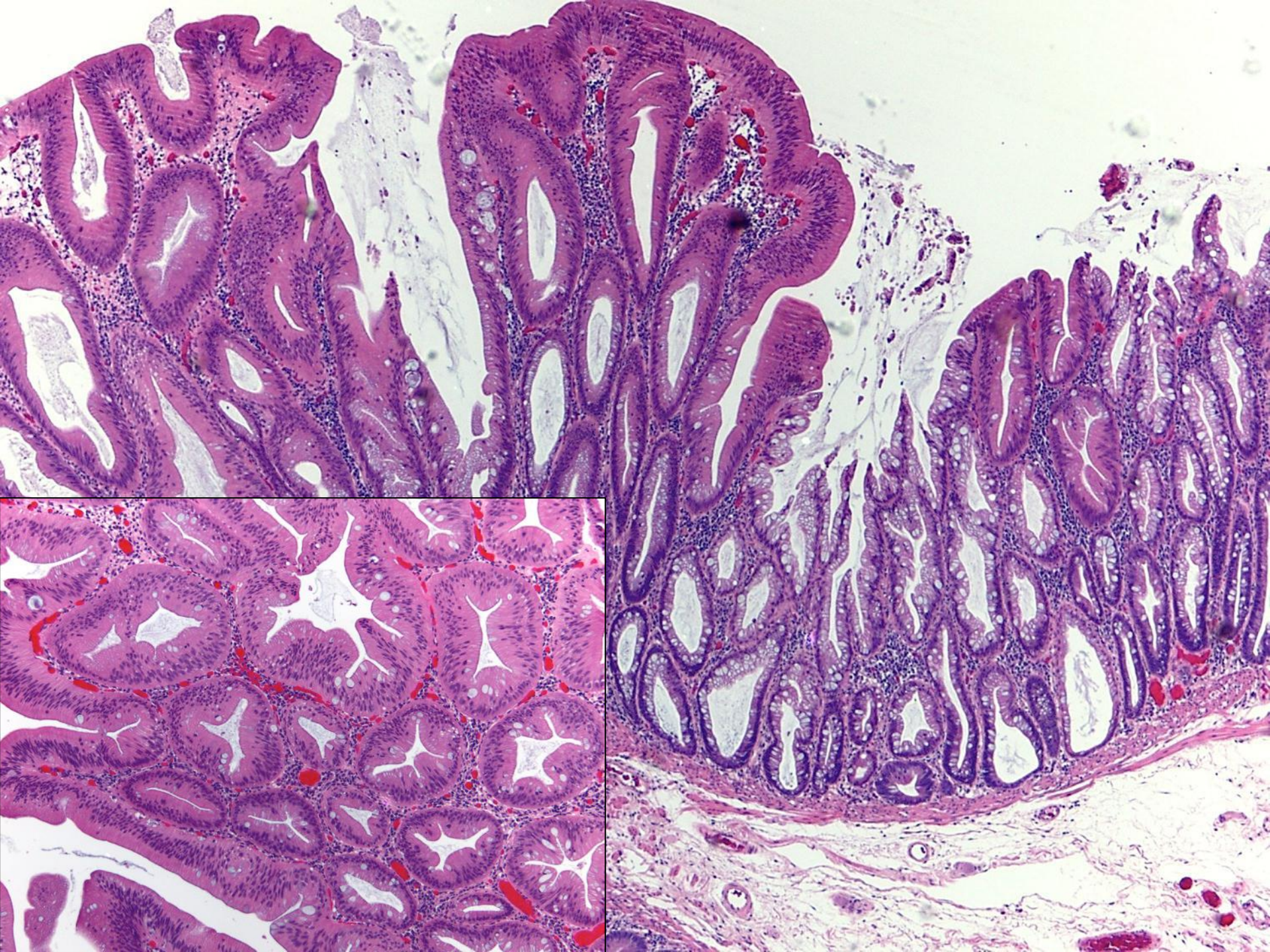
Serrated Architecture in Polyps

- **What is the relationship between SAPs, SSA/Ps and HPs?**
- **Is it important to recognize this polyp? Screening guidelines?**
  - • **Is it an aggressive polyp?**
- **What are the defining pathologic features for this polyp?**
  - **Ectopic crypt foci?**
- **How do SAPs fit in the serrated pathway?**
  - **Molecular changes?**



Around 30% of the time you can find a non-dysplastic serrated polyp





Serrated Adenomatous Polyp

- **SAPs likely come from a non-dysplastic serrated polyp (either HP or SSA/P)**
  - **If this is true, why not call these SSA/Ps with cytologic dysplasia?**
- **Calling these SSA/Ps with cytologic dysplasia doesn't really tell the whole story – these are polyps with unique clinical, histologic, and molecular features.**
- **Basically, SAPs are a specific form of serrated colorectal dysplasia**

High-risk metachronous polyps are more frequent in patients with traditional serrated adenomas than in patients with conventional adenomas: a multicenter prospective study

Jin Young Yoon, MD,[*,1] Hyung Tae Kim, MD,[*,2] Sung Pil Hong, MD, PhD,[1] Hyun Gun Kim, MD,[3] Jin-Oh Kim, MD,[3] Dong-Hoon Yang, MD,[4] Dong Il Park, MD,[2] Seun Ja Park, MD,[5] Hyun-Soo Kim, MD,[6] Bora Keum, MD,[7] Cheol Hee Park, MD,[8] Chang Soo Eun, MD,[9] Suck-Ho Lee, MD,[3] Il Hyun Baek, MD,[8] Dong Kyung Chang, MD, PhD,[2] Tae Il Kim, MD, PhD[1]

Seoul, Pusan, Wonju, Pyeongchon, Cheonan, Guri, Korea

- From a prior study 717 polyps diagnosed as SAP

- 6 GI pathologists reclassified the serrated polyps according to WHO classification
  - Only 420 of the original 717 were felt to be SAP

- Of these, only 186 patients with SAPs had clinical, endoscopic, and follow-up data

- Compared these 186 patients with SAPs to 372 age and sex-matched patients with only conventional adenomas

Risk of developing an advanced adenoma:

- Baseline SAP vs conventional adenoma: OR 2.37

- Baseline SAP vs advanced adenoma: OR 2.19

TABLE 4. High-risk polyp incidence on surveillance colonoscopies in traditional serrated adenoma, conventional adenoma, and high-risk conventional adenoma patients

	Traditional serrated adenomas (n = 186)	Conventional adenomas (n = 372)	High-risk conventional adenomas (n = 290)	*P* value
High-risk polyp				<.001,* .007†
Yes	88 (47.3%)	119 (32.0%)	101 (32.0%)	
No	98 (52.7%)	253 (68.0%)	189 (68.0%)	

Screening Guidelines

- Screening guidelines from Rex DK, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol. 2012 Sep;107(9):1315-29

Polyp	Location	Surveillance
SAP <10mm, <3 in number	Any	5
SAP ≥10mm, 1 in number	Any	3
SAP <10 mm, ≥3 in number	Any	3

Potentially screening interval for a diagnosis of SAP should be minimum 3 years, potentially 1-3

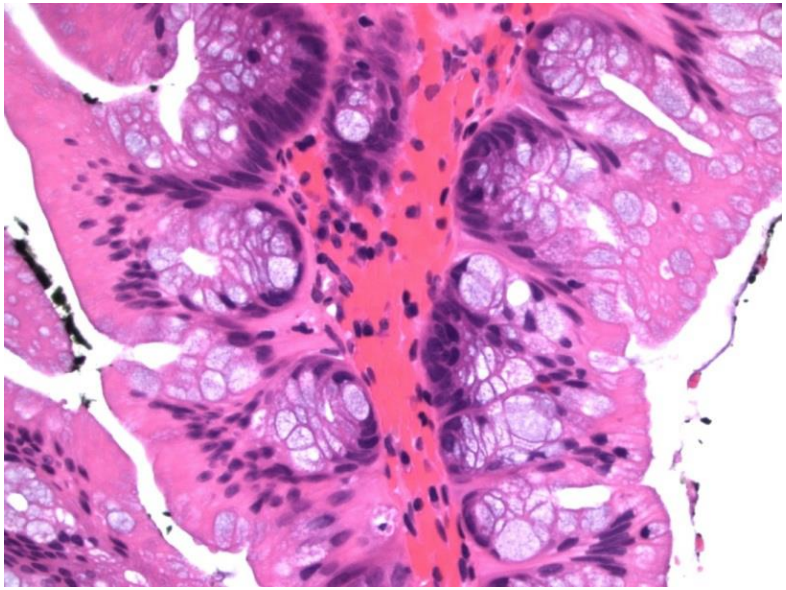
Sessile Serrated Adenoma (SSA) vs. Traditional Serrated Adenoma (TSA)

Emina Emilia Torlakovic, MD, PhD, Jose D. Gomez, MD,†*
*David K. Driman, MBChB, FRCPC,‡ Jeremy R. Parfitt, MD,‡ Chang Wang, MD,**
Tama Benerjee, MD, and Dale C. Snover, MD§*

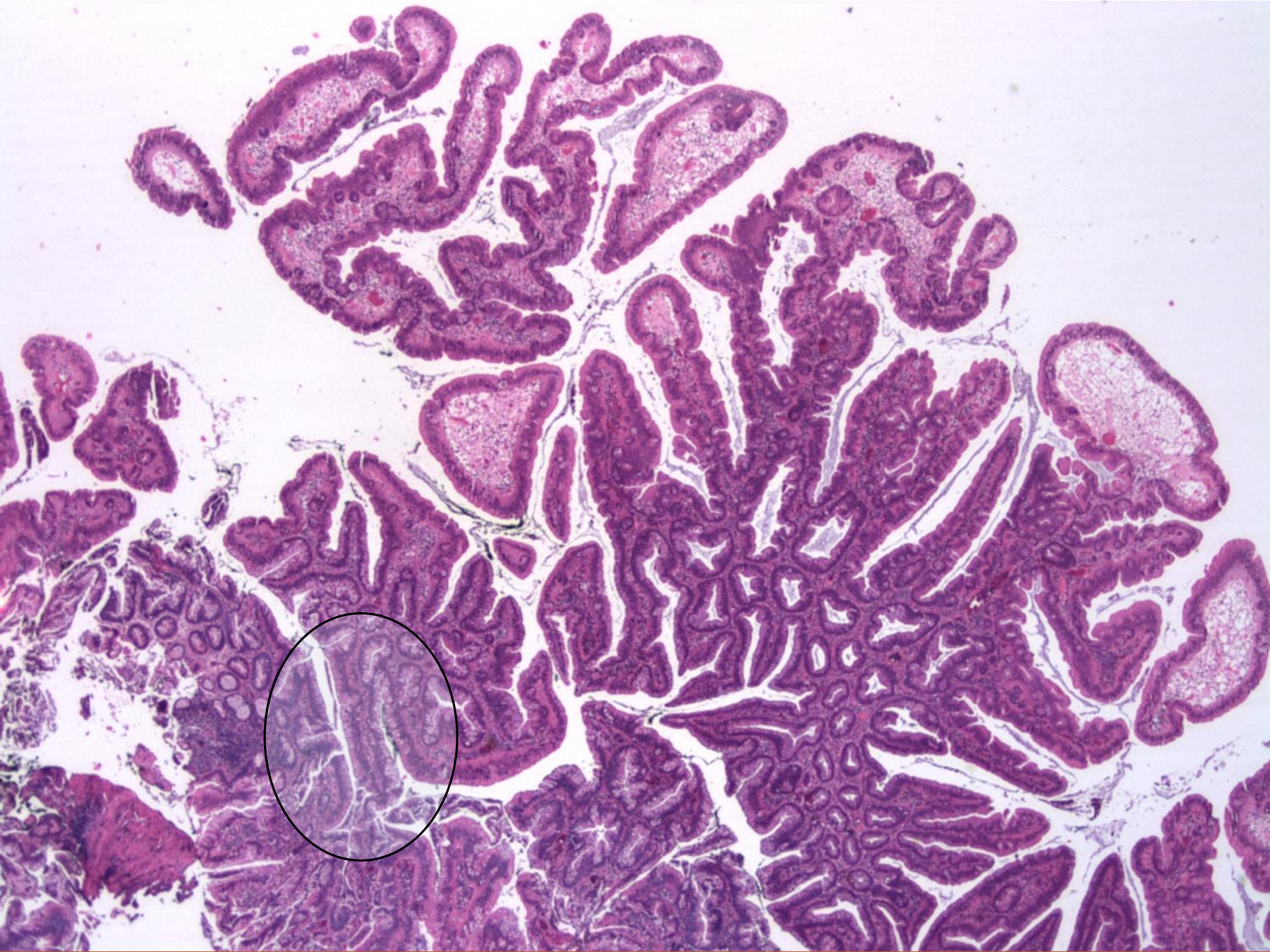
- **Distinction between SSA and TSA difficult**
- **Evaluated 66 serrated polyps for shape, architectural features of crypts, eosinophilic cytoplasm, and distribution of proliferative zones**
- **Features of SAP**
  - **Ectopic crypt foci**
  - **Eosinophilic cytoplasm**
  - **Left sided location**

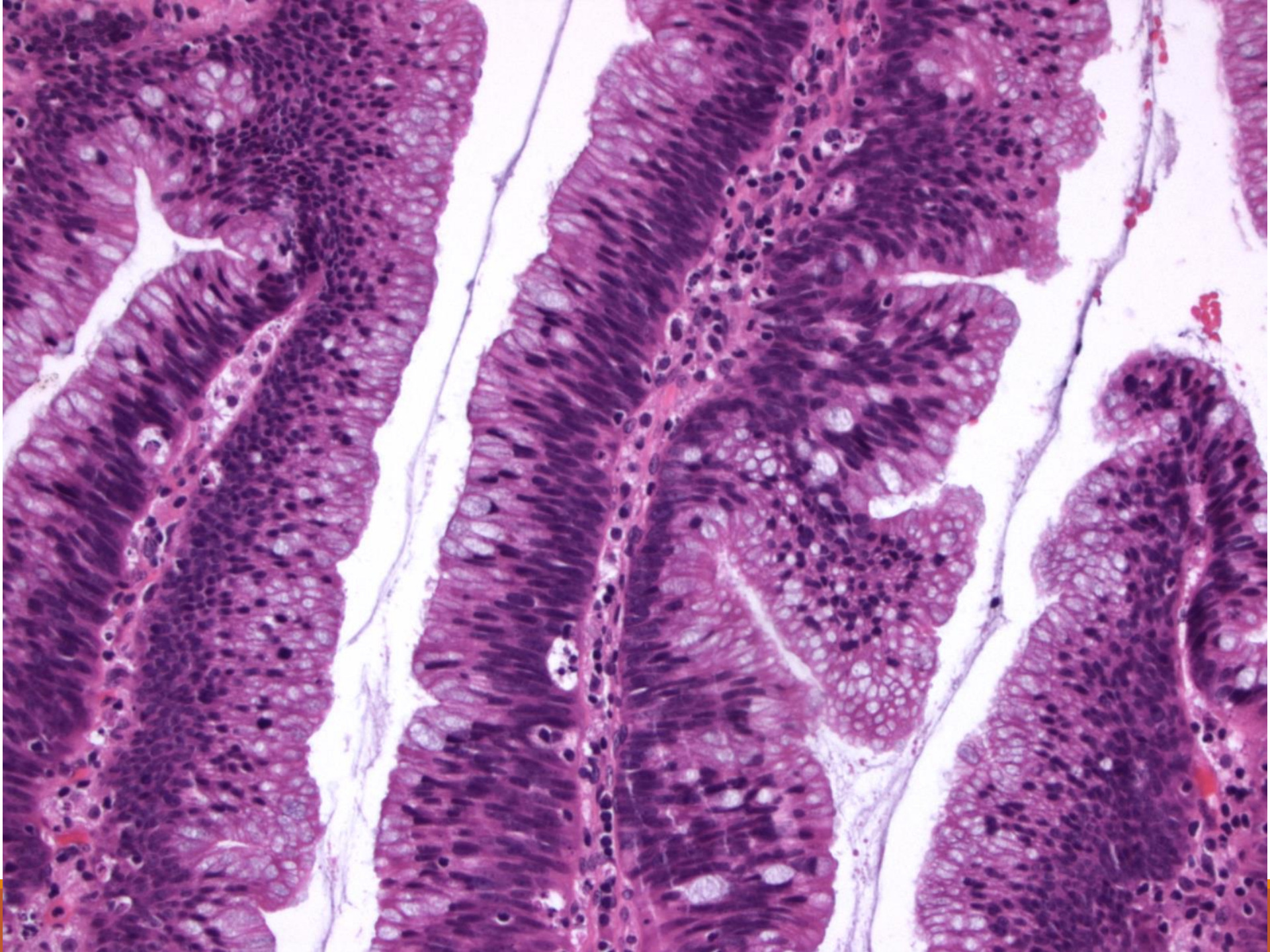
Morphologic Criteria

- **Torlakovic and Snover proposed that ectopic crypt foci be a defining feature of SAP**
- **However, ectopic crypt foci are not associated with any specific molecular alteration in SAPs**
- **In a series of SAPs diagnosed by 5 GI pathologists, ectopic crypt foci were only present in 60% of SAPs**



Wiland HO 4th, et al. Am J Surg Pathol. 2014 Sep;38(9):1290-7.



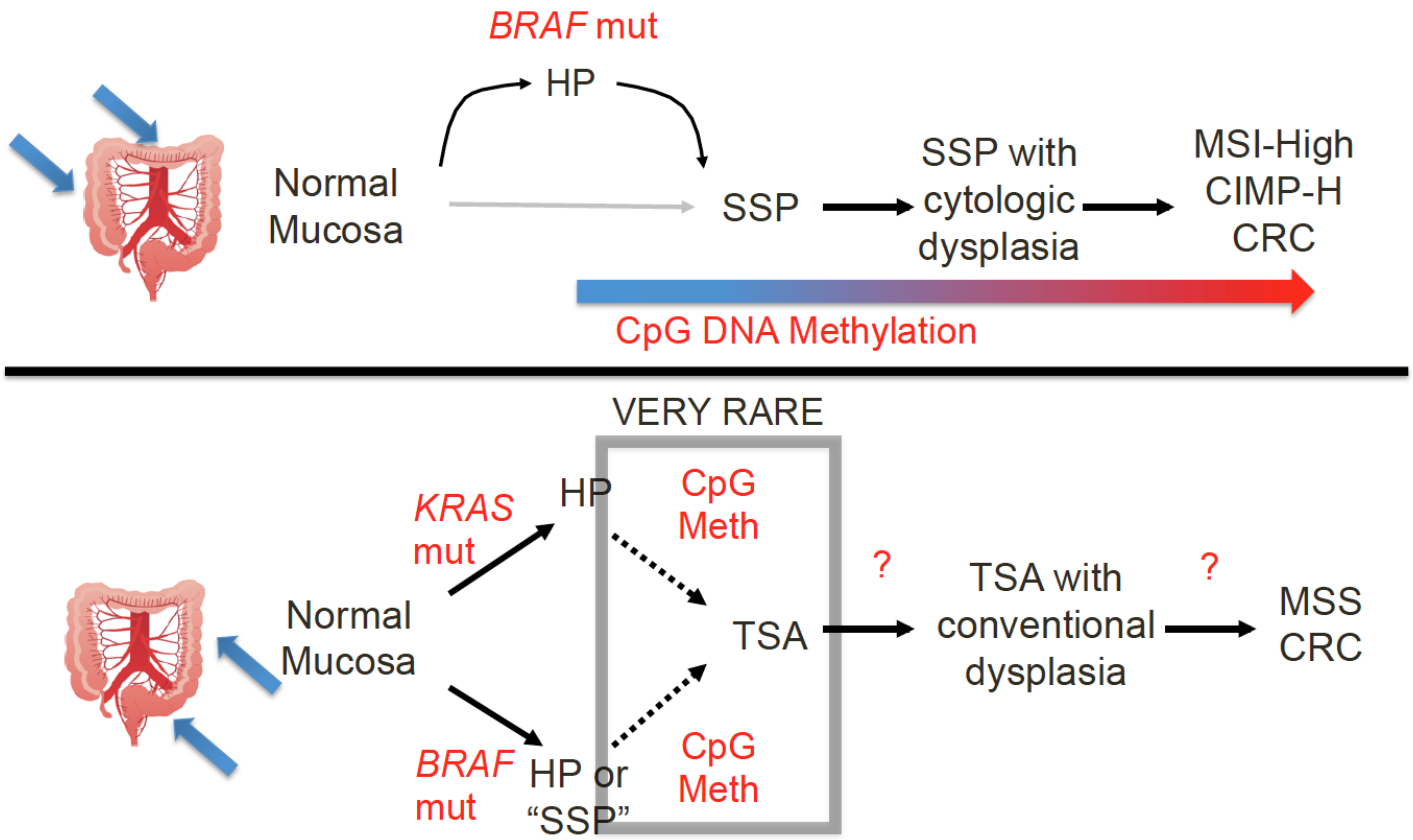


Molecular Features of SAPs

Molecular Abnormalities	No. (%)
BRAF mutant	25 (47)
KRAS mutant	23 (43)
BRAF & KRAS wild-type	5 (9)
CpG island methylation (5-marker panel)	
High (≥3)	7 (21)
Low (1 to 2)	12 (39)
Negative (0)	12 (39)

Wiland HO 4th, et al. Am J Surg Pathol. 2014 Sep;38(9):1290-7.

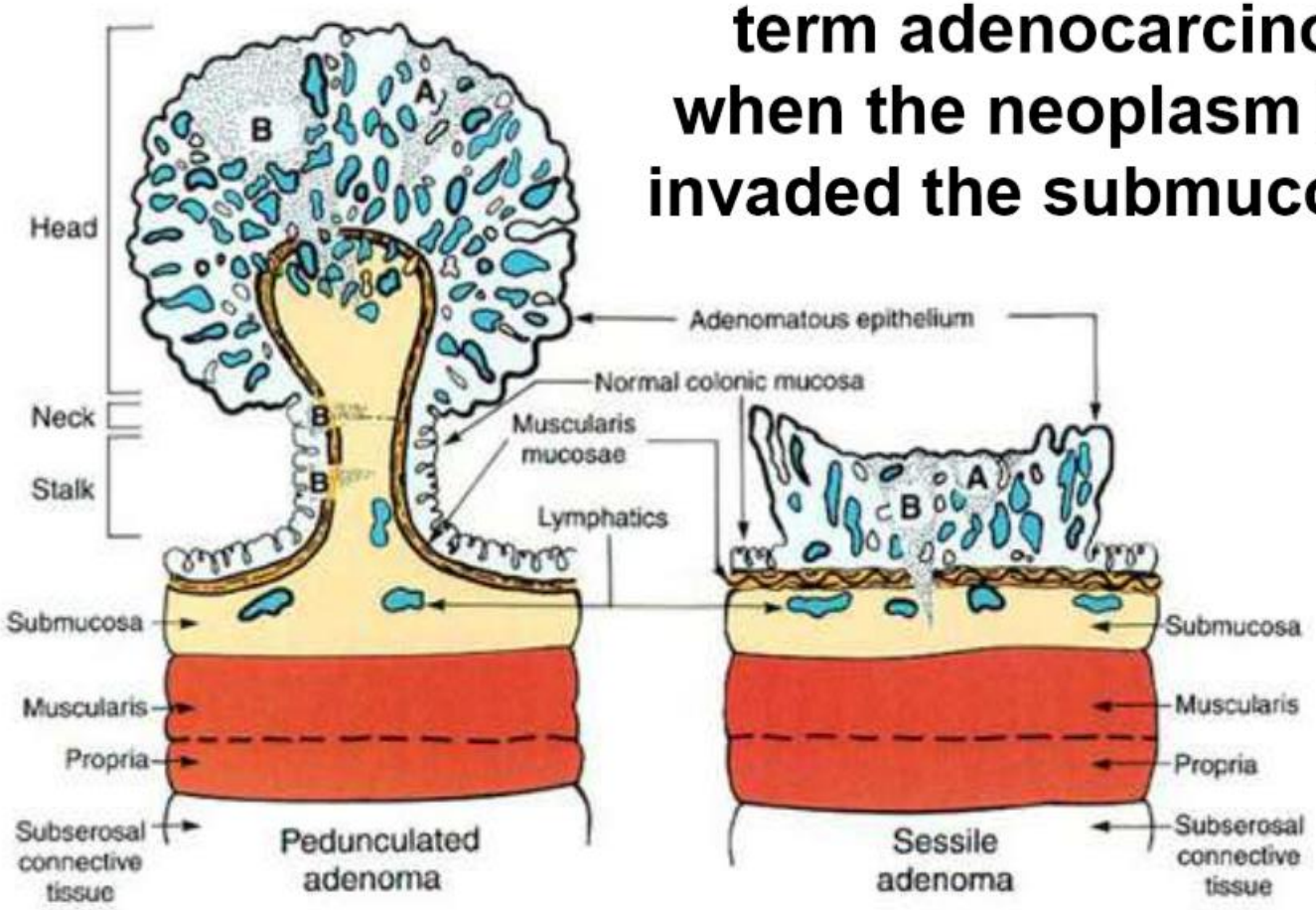
Serrated Neoplasia



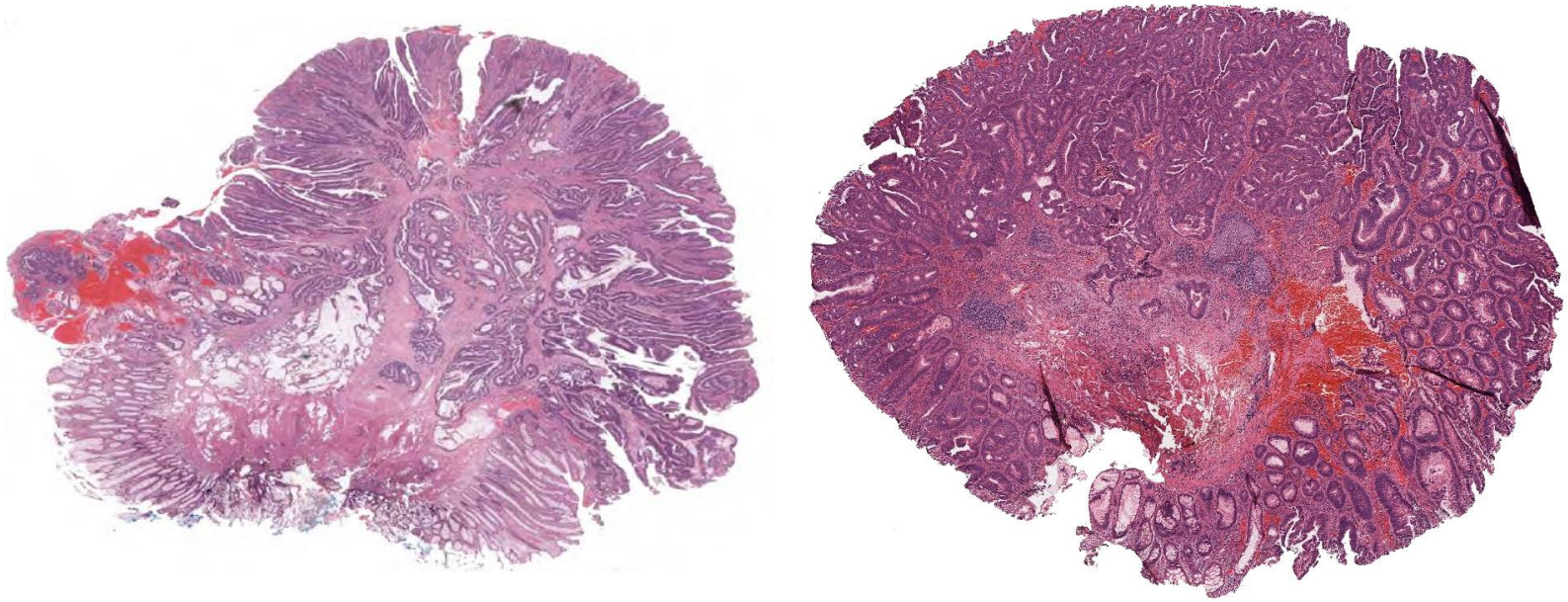
- Distal location, protuberant/villiform
- Tall columnar cells with abundant eosinophilic cytoplasm, pseudostratified nuclei
- Ectopic crypts are often present but are not required for the diagnosis
- ~50% BRAF, ~40% KRAS, ~10% WT/WT
- ~25% may have a non-dysplastic serrated precursor
- Can develop conventional adenomatous dysplasia and give rise to colon cancer likely with low levels of CpG methylation

Malignancy in Polyps

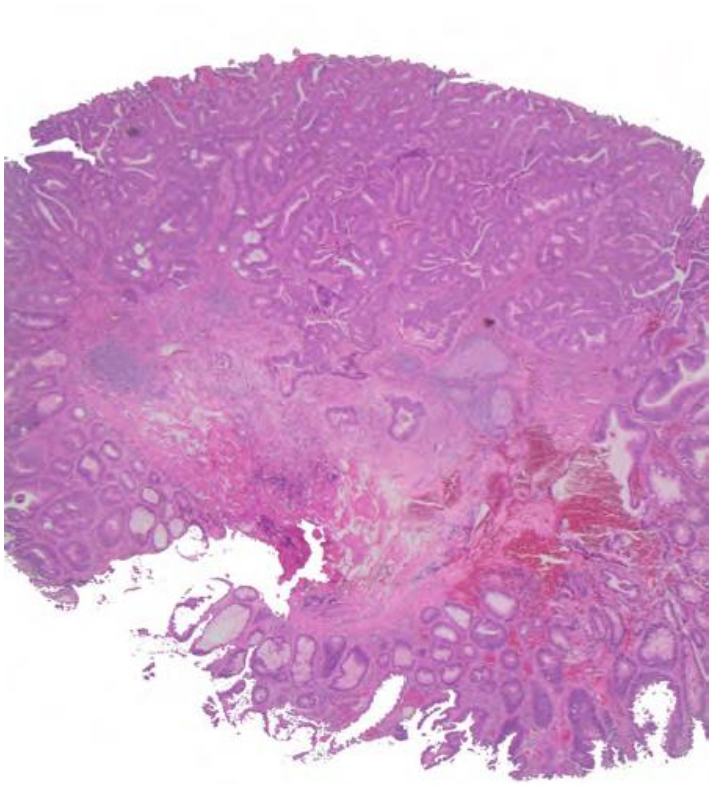
In the colon, we use the term adenocarcinoma when the neoplasm has invaded the submucosa.

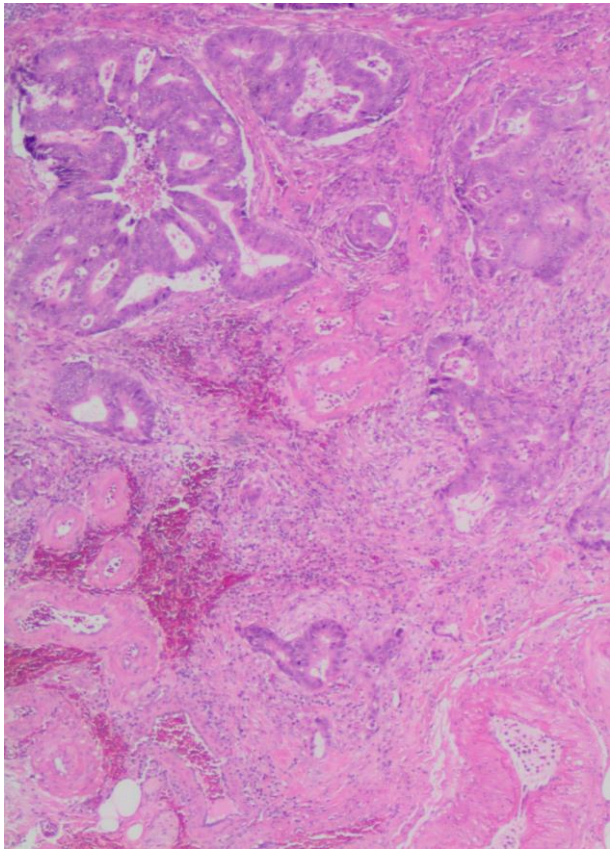


Adenocarcinoma in Polyp

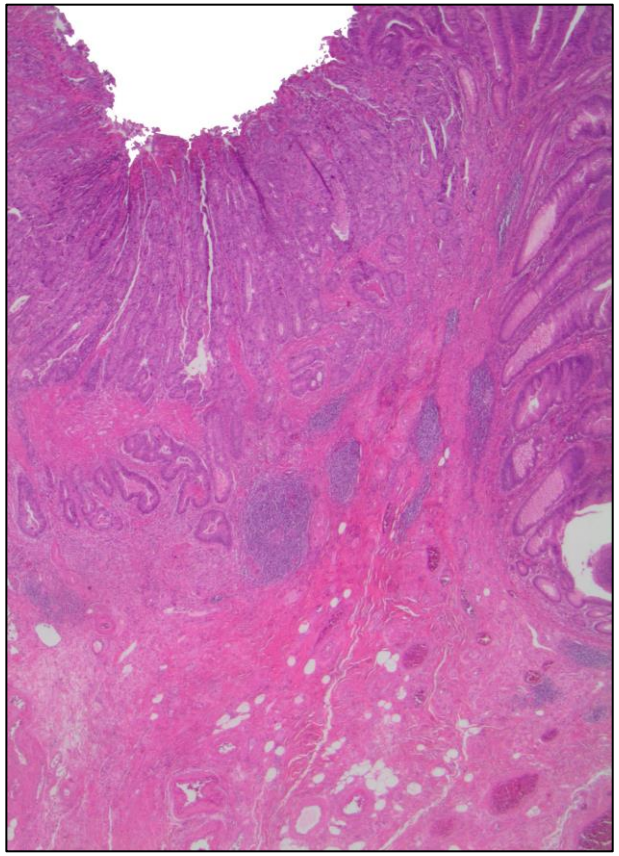


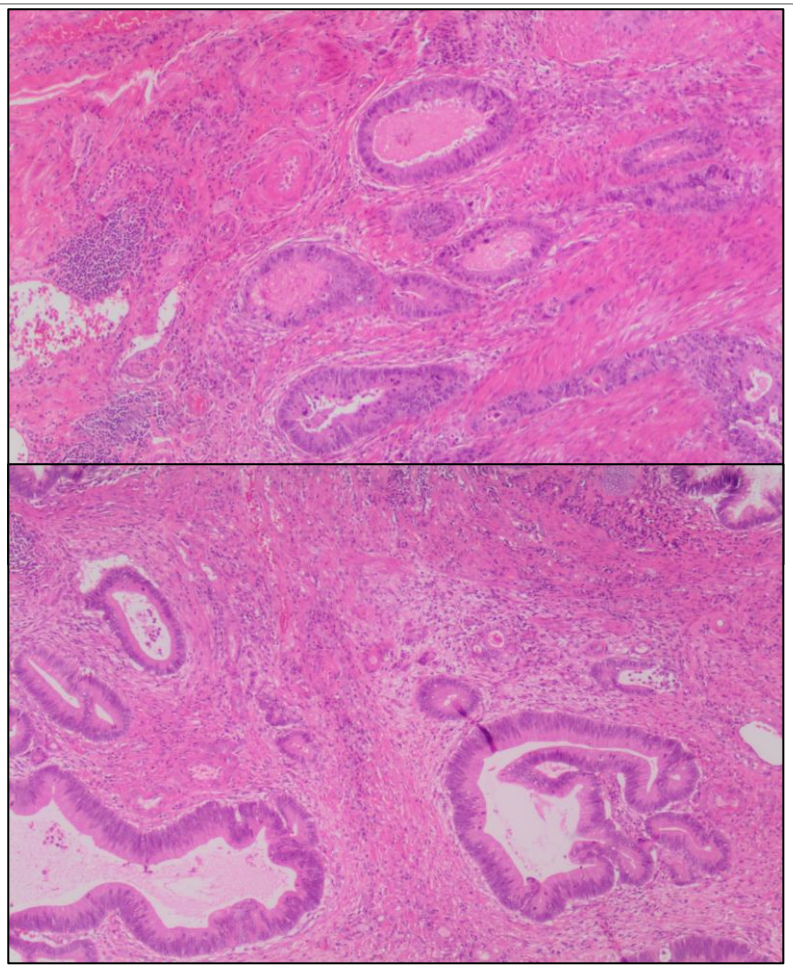
Adenocarcinoma in Polyp



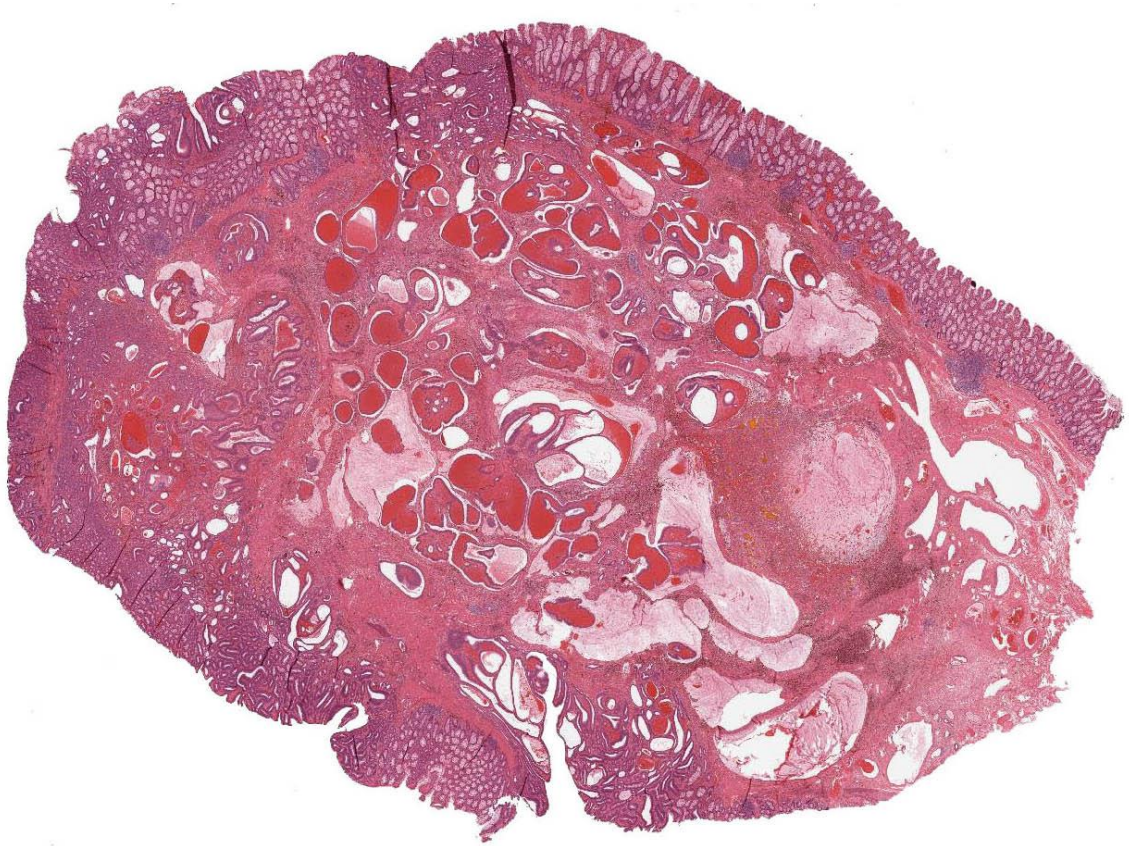


Muscularis mucosa, submucosal blood vessels, and desmoplasia

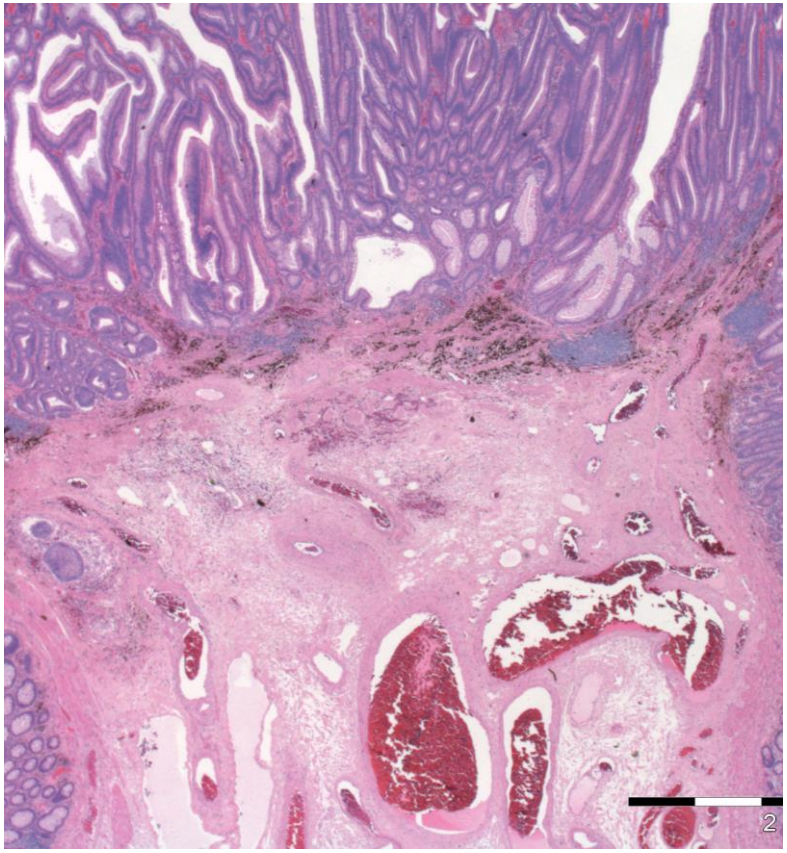


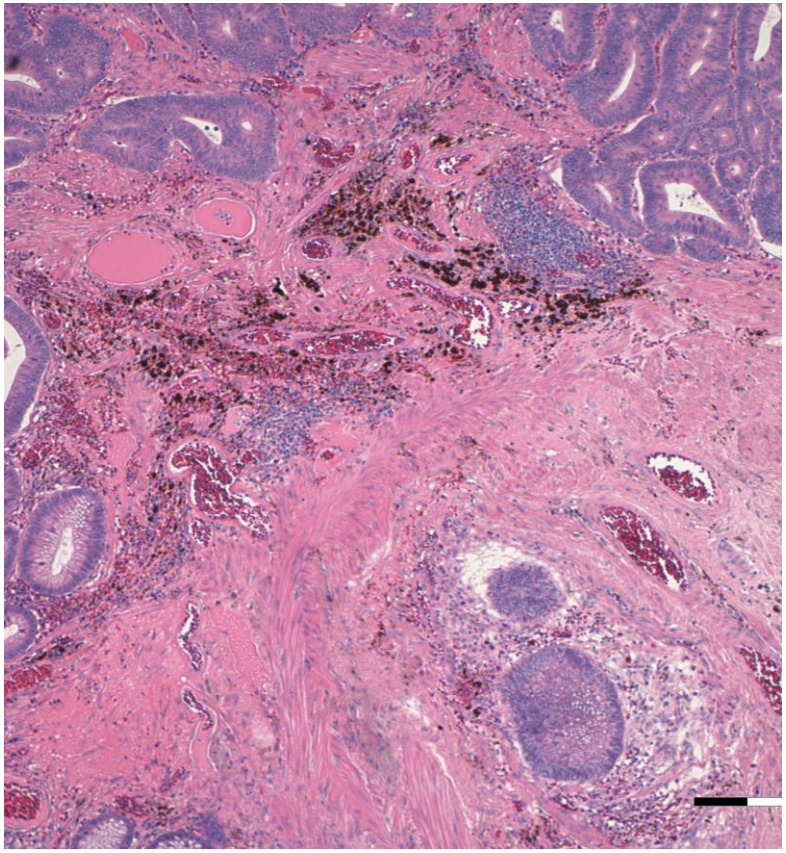


Epithelial misplacement

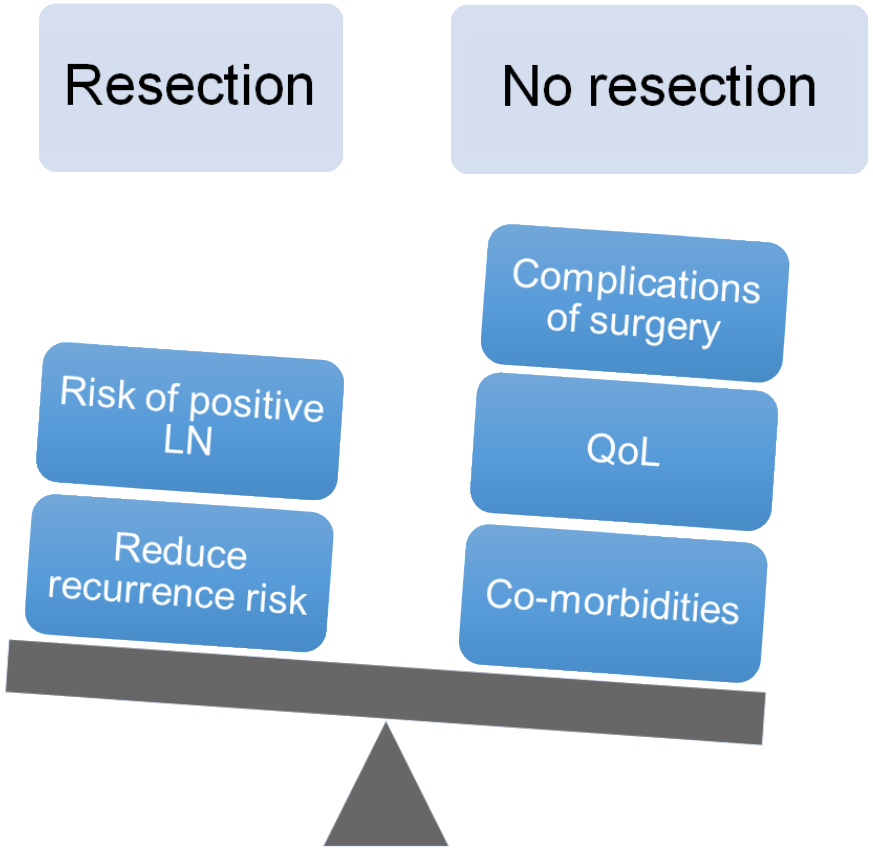


Epithelial misplacement



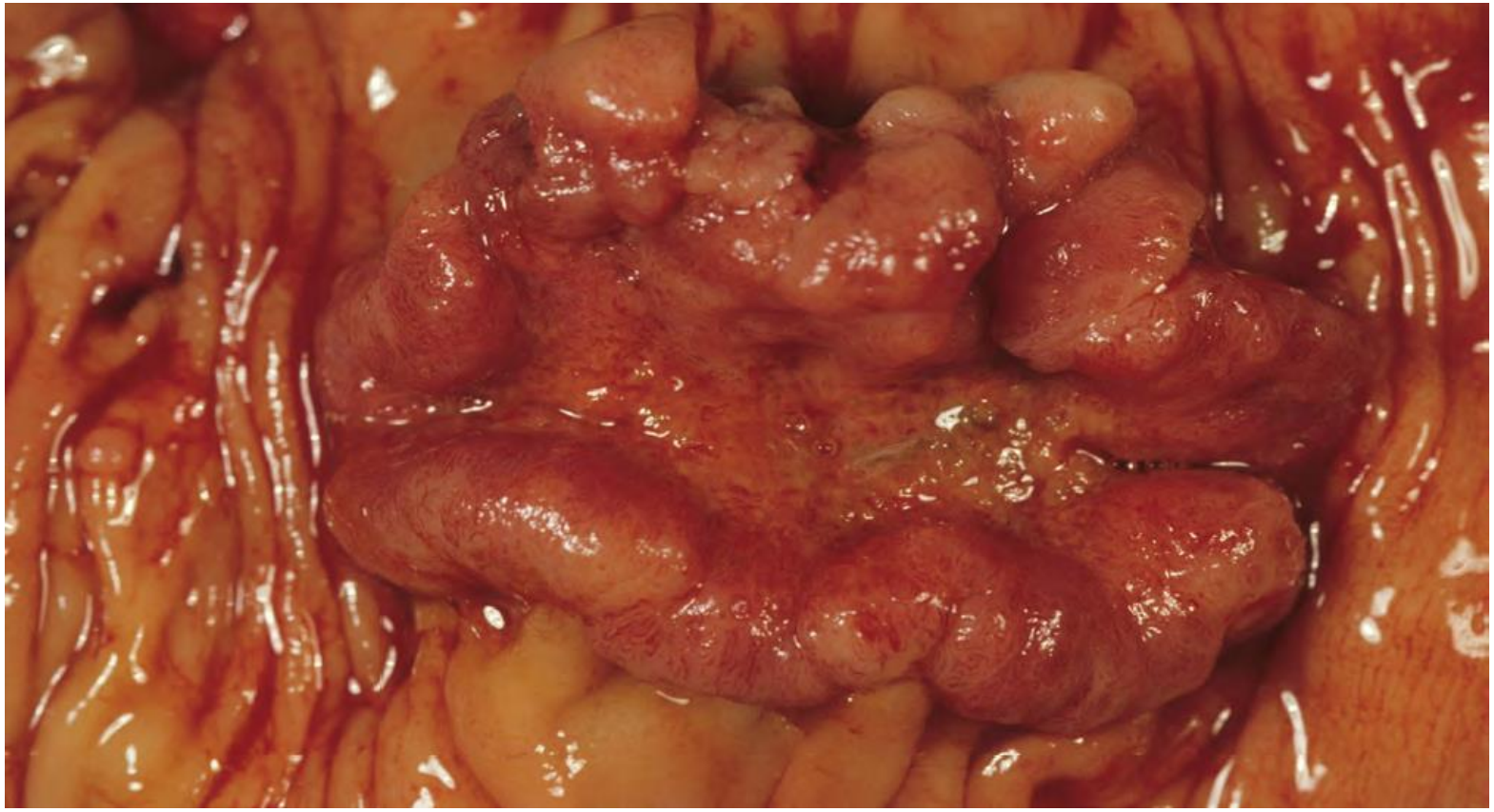


Malignant polyps: Resect or not resect



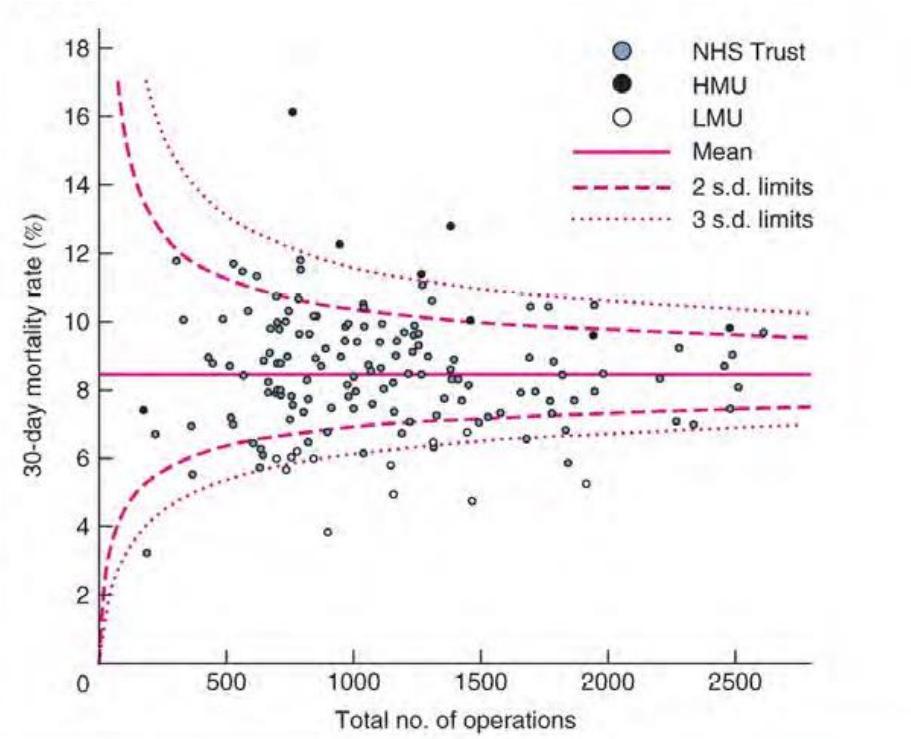
Does the risk of surgery outweigh the risk of metastatic disease?

Resect or not resect ?



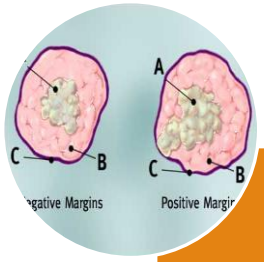
56 yr man, pT1 pN1a **0.8 cm**

30-day mortality rate of elective hemicolectomy



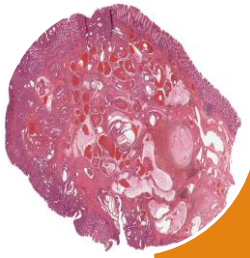
Byrne BE et al. Br J Surg. 2013 Dec; 100(13): 1810–1817

If invasive carcinoma is found, REPORT IT, along with: status of the margin, grading (presence of poorly differentiated component), and lymphovascular invasion.



Resection margins

- Lobular architecture
- Presence of normal tissue components (lamina propria, smooth muscle)
- Hemorrhage
- Mucin without cells



Pseudoinvasion vs. Invasion

If the conclusion is pseudoinvasion:
Best to leave it out of your report

- Adenomas with high incidence of trauma:
  - Large
  - Left-sided
  - Pedunculated

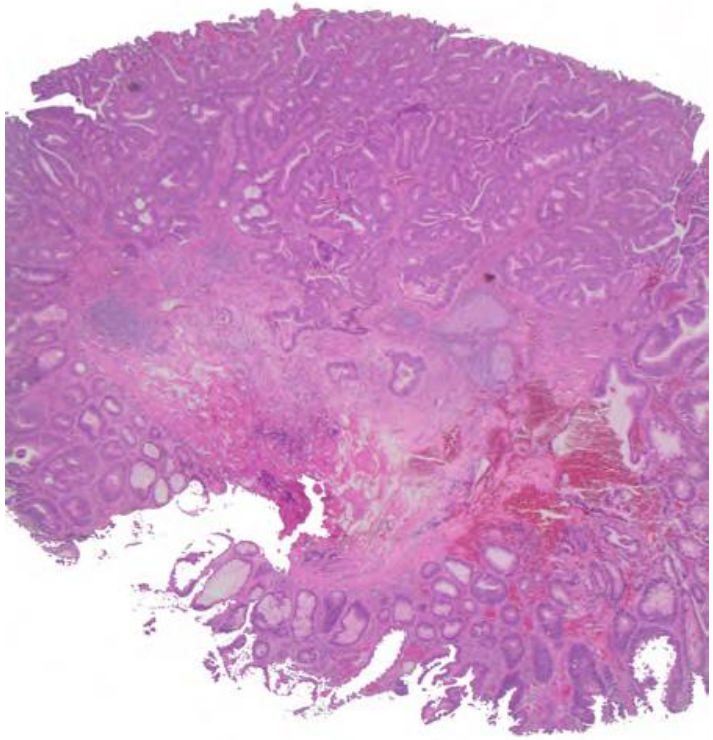
Challenging areas in malignant polyps

- **Is the depth of invasion important?**
- **What about the width of the tumor at the invasive front?**
- **Shall I always stain for lymphovascular invasion?**
- **How do I report completeness of excision?**
- **Tumor budding – is that here to stay?**
  - **• How many fields does one have to count?**
  - **• What is the difference between budding and poorly differentiated carcinoma?**
- **How do I write the report/comment?**

Depth of invasion

Mentioned in several European and Japanese guidelines:

- **Is this criterion alone sufficient for subsequent resection?**
- **Where does one measure from?**
- **The tumor often obscures the MM as a starting point.**
- **Is deeper worse?**



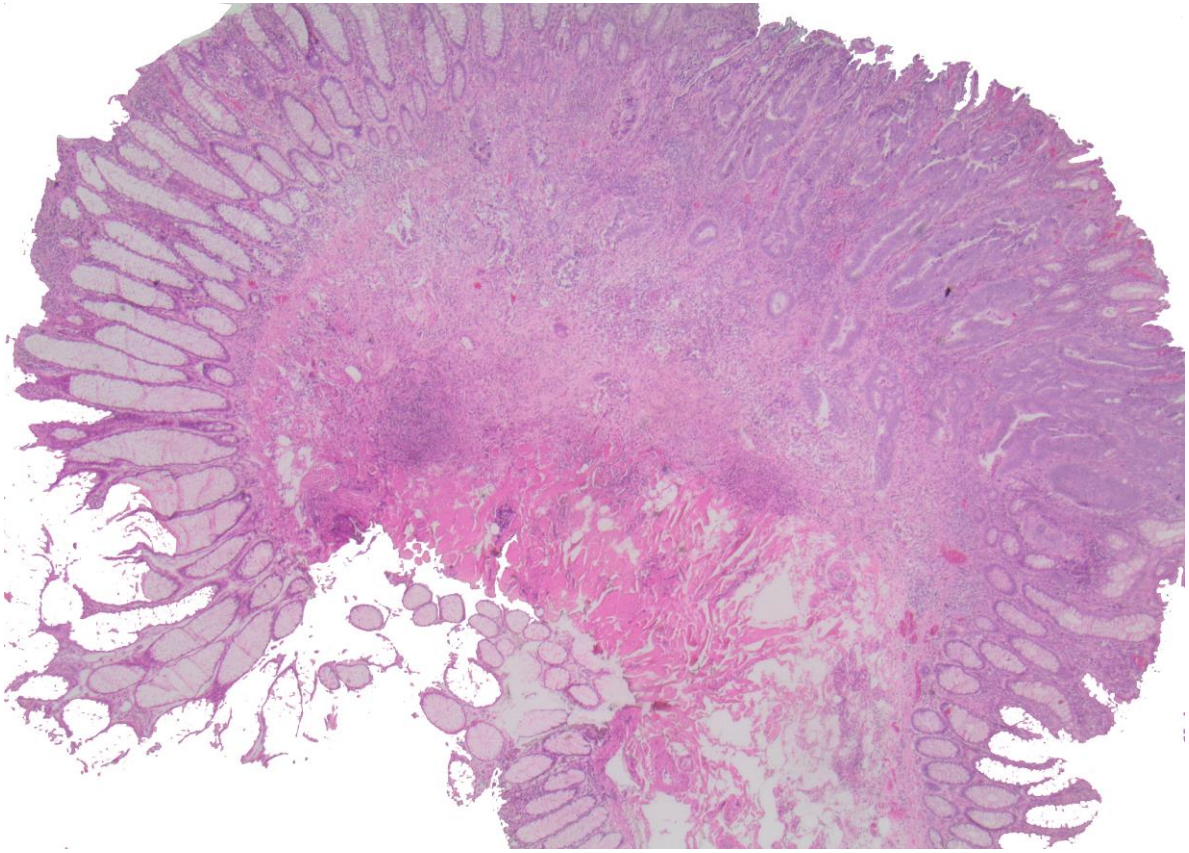
Depth of invasion and LN mets

Depth of submucosal invasion	# of cases	Nodal involvement
< 500 µm	23	0
500 – 1000 µm	15	1 (7%)
1000 – 2000 µm	38	2 (5%)
2000 – 3000 µm	61	11 (18%)
3000 – 4000 µm	45	5 (11%)
4000 – 5000 µm	31	6 (19%)
> 5000 µm	38	8 (21%)

The odds ratio of regional nodal involvement was 5.0 (range 1.5-17.0) at a threshold of 2 mm for tumor depth.

Ueno et al. Gastroenterology 2004 127:385-394

Width of invasive component



Width of invasion and LN mets

Width of submucosal invasion	# of cases	Nodal involvement
< 2000 µm	35	0
2000 ≤ X < 3000 µm	22	1 (4.5%)
3000 ≤ X < 4000 µm	24	1 (4.2%)
4000 ≤ X < 5000 µm	19	4 (21.1%)
5000 ≤ X < 6000 µm	23	4 (17.4%)
6000 ≤ X < 7000 µm	10	2 (20%)
7000 ≤ X < 8000 µm	26	4 (15.4%)
> 8000 µm	92	17 (18.5%)

The odds ratio of regional nodal involvement was 5.0 (range 4.5-21.1) at a threshold of 4 mm for tumor width.

Ueno et al. Gastroenterology 2004 127:385-394

Cooper HS. Pathologic issues in the treatment of endoscopically removed malignant colorectal polyps. J Natl Compr Canc Netw. 2007 Oct;5(9):991-6.

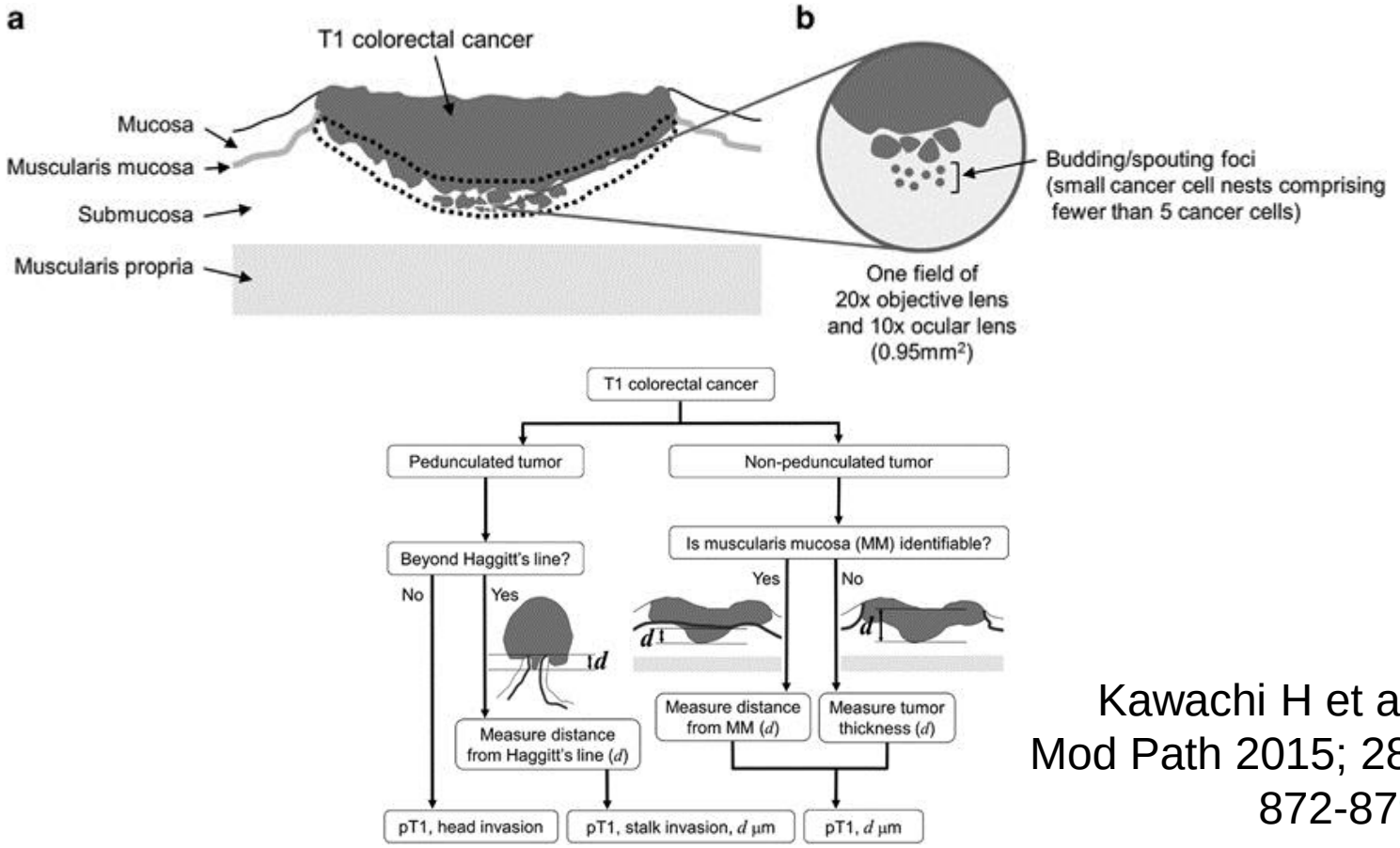
Lists the same indications for conservative management, but introduces the issue of tumor budding as an indication for surgical management.

Geboes K et al. Pathology of early lower GI cancer. Best Pract Res Clin Gastroenterol 2005 Dec;19(6):963-78.

Whenever a favourable tumour grade is found, without vascular invasion and tumour budding, there seems to be a low risk for adverse outcome and laparotomy may thus be avoided.

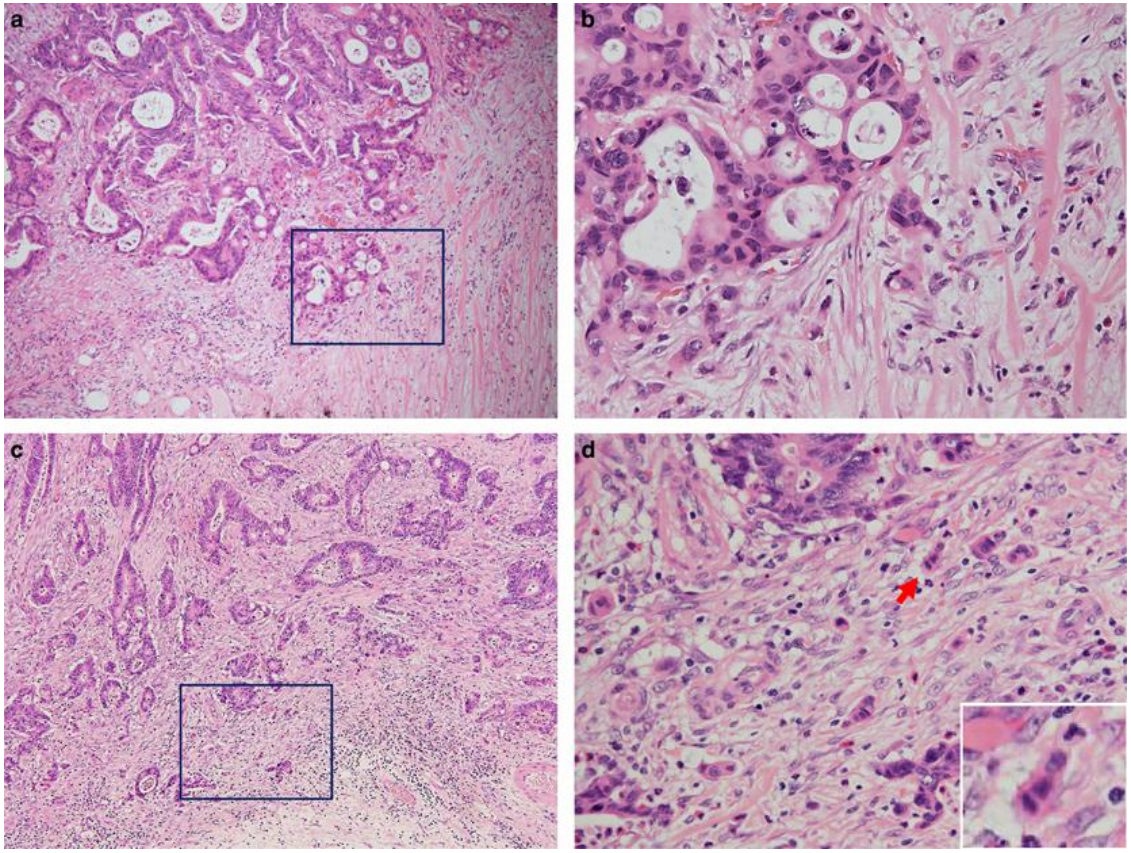
Ueno H, et al. Risk factors for an adverse outcome in early invasive colorectal carcinoma. Gastroenterology. 2004 Aug;127(2):385-94.

Tumor Budding



Kawachi H et al.
Mod Path 2015; 28:
872-879

Tumor Budding



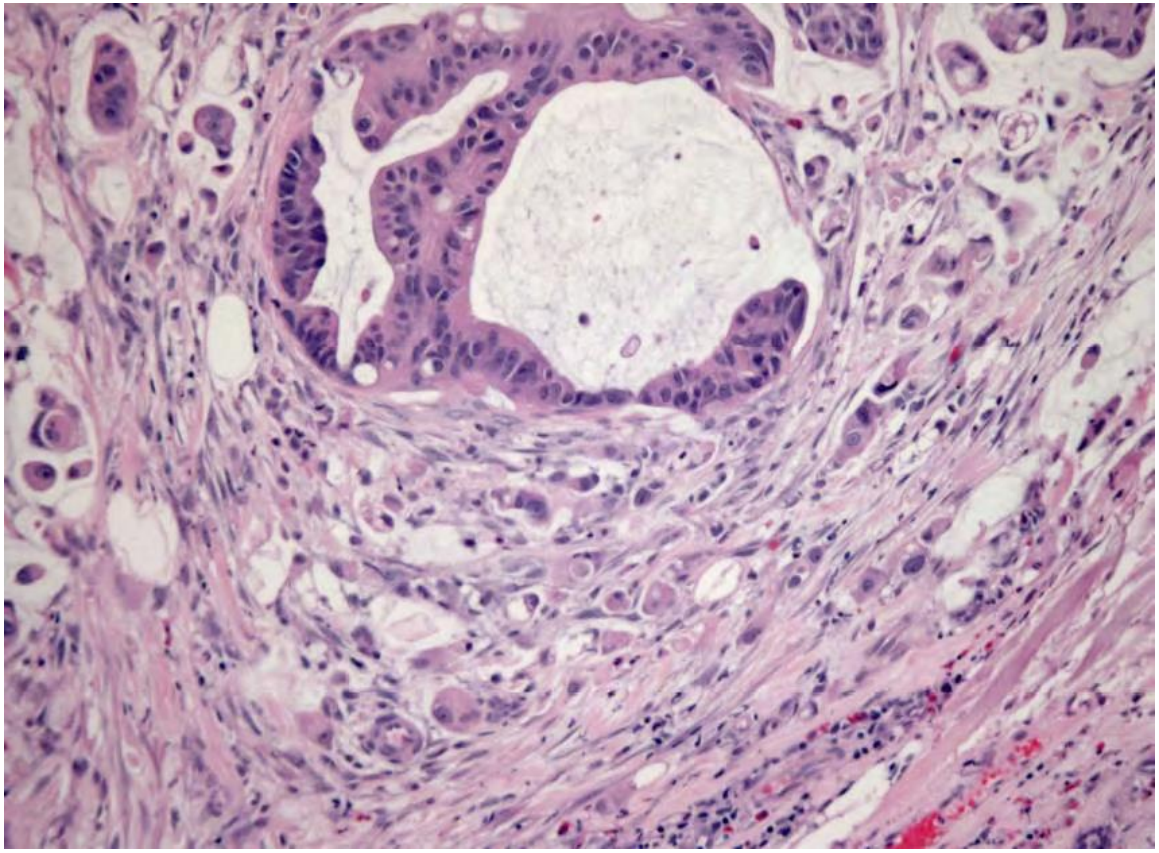
Kawachi H et al. Mod Path 2015; 28: 872-879

Tumor Budding

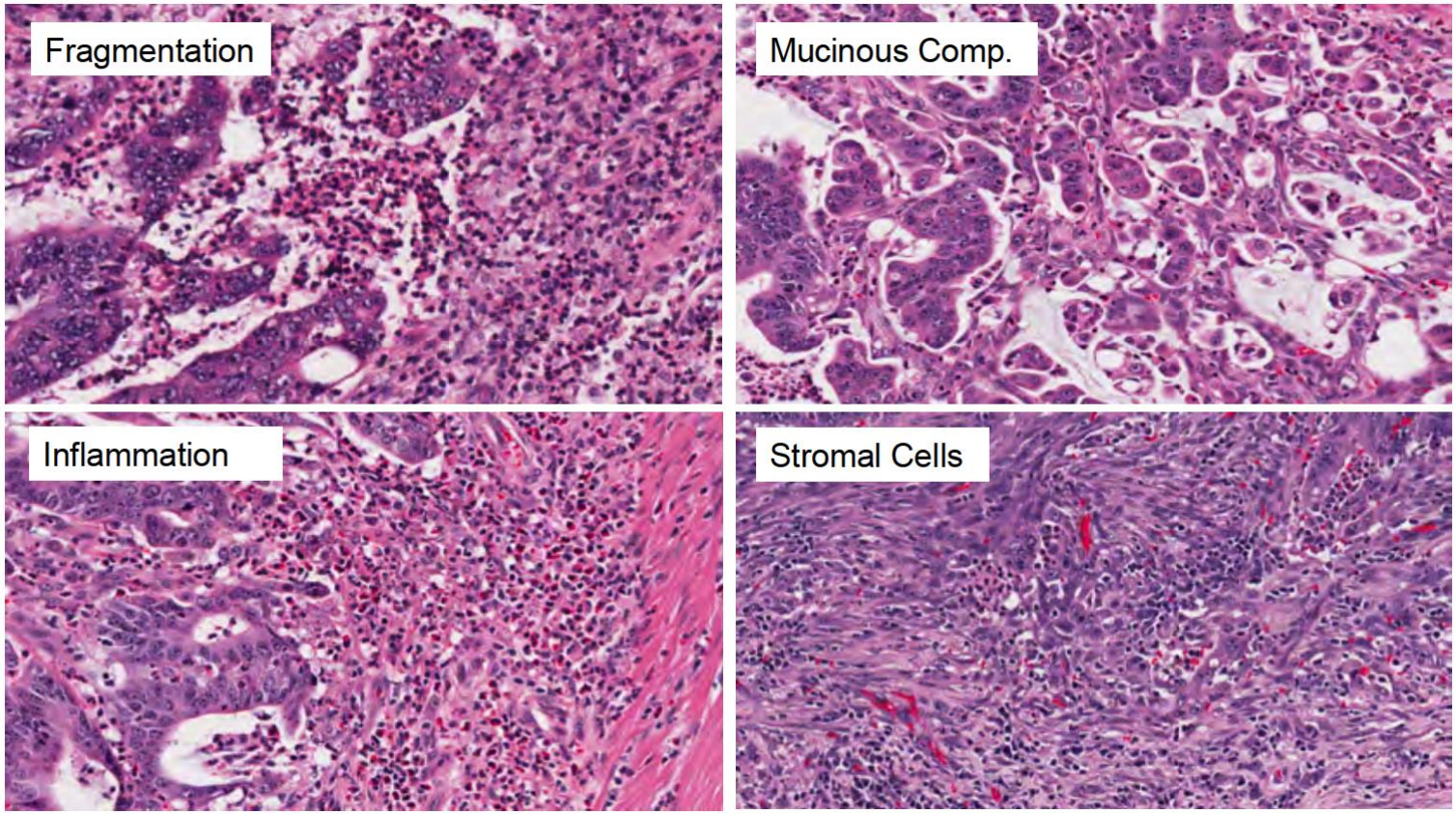
Histologic parameters	*Odds ratio*	*(95% confidence interval)*	P-*value*
Depth of submucosal invasion ≥1000 *μ*m	5.56	(2.14–19.10)	<0.0001
High-grade budding/sprouting (grade 2 or 3)	3.14	(1.91–5.21)	<0.0001
High histologic grade	1.88	(0.63–5.09)	0.25
Positive lymphatic invasion	1.53	(0.94–2.50)	0.09
Nonpedunculated type	1.49	(0.64–4.11)	0.37
Positive venous invasion	1.08	(0.67–1.74)	0.75

Kawachi H et al. Mod Path 2015; 28: 872-879

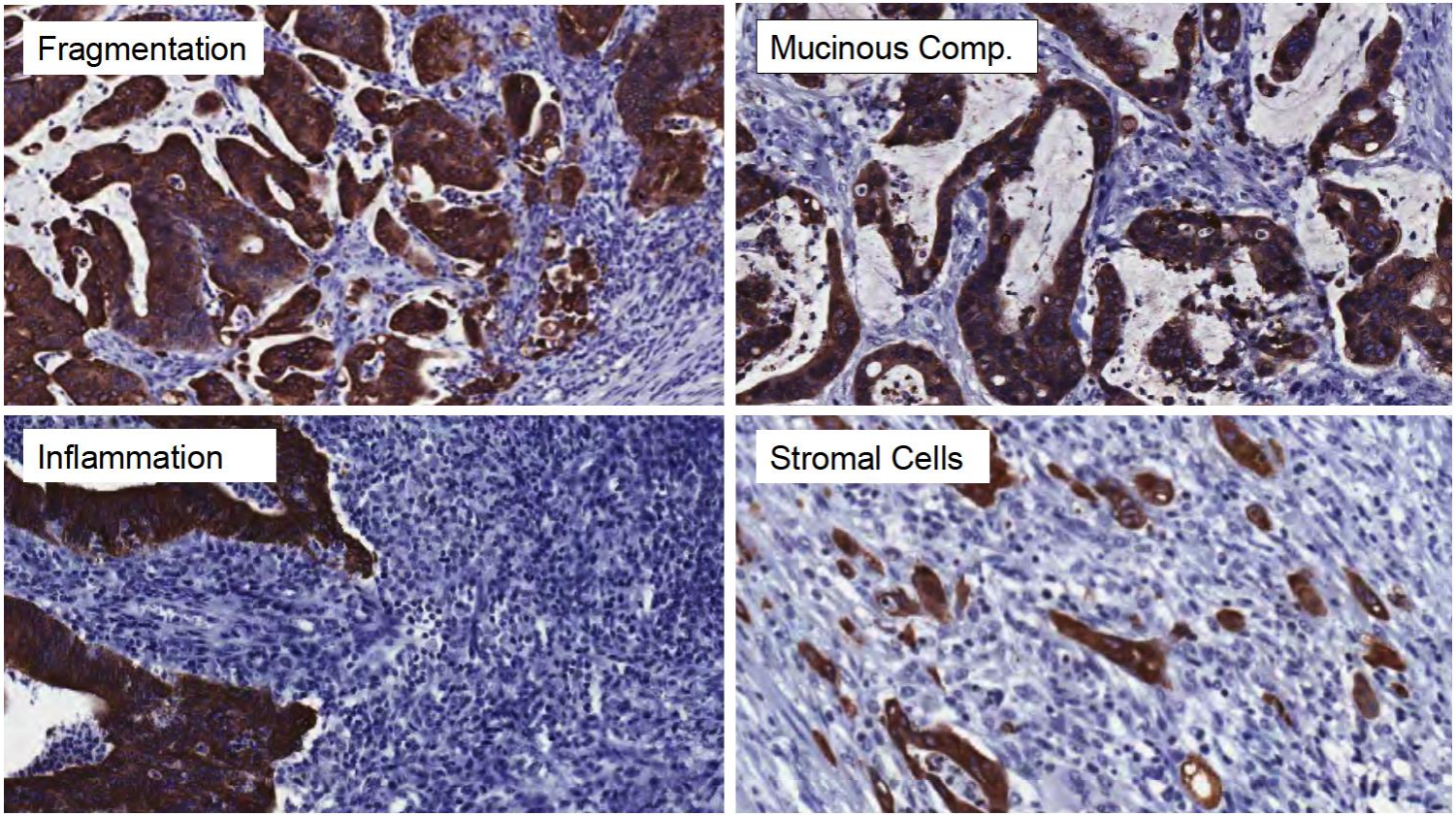
Tumor Budding



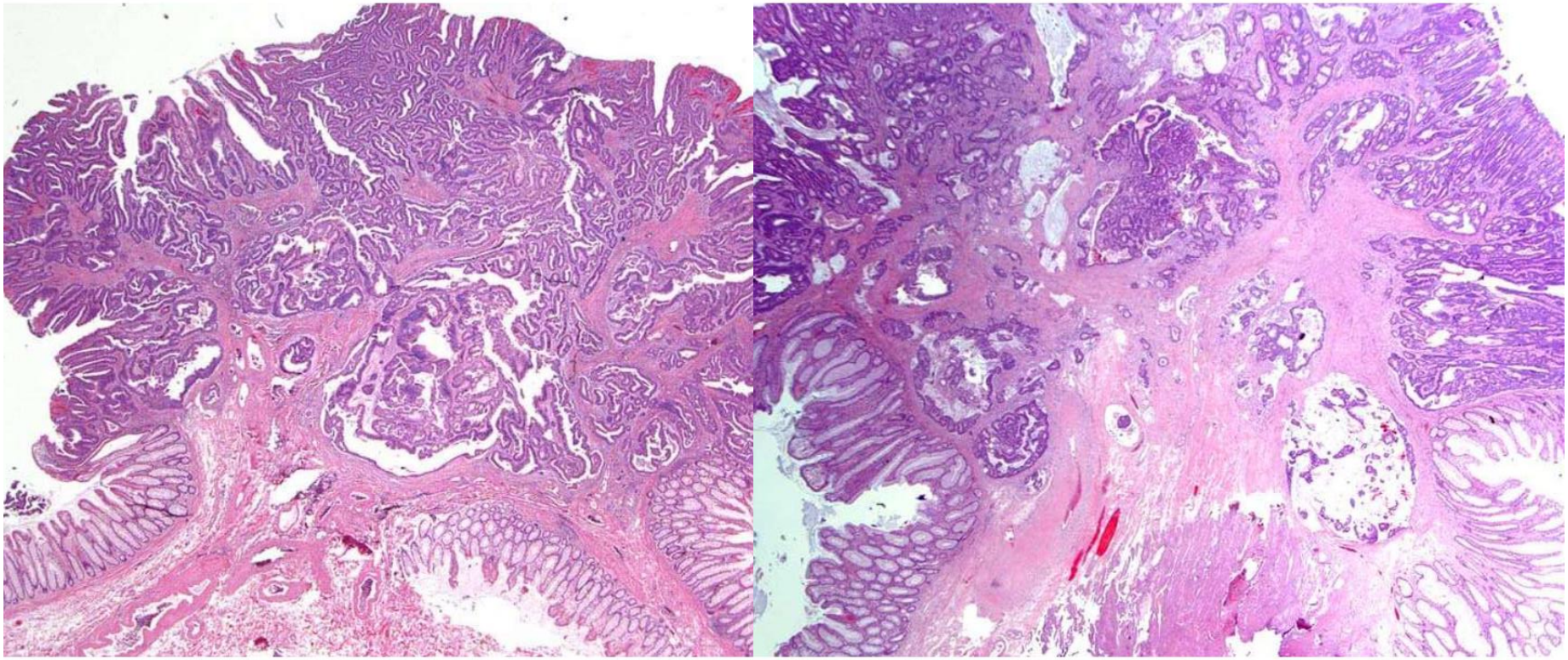
Tumor Budding - Difficulties



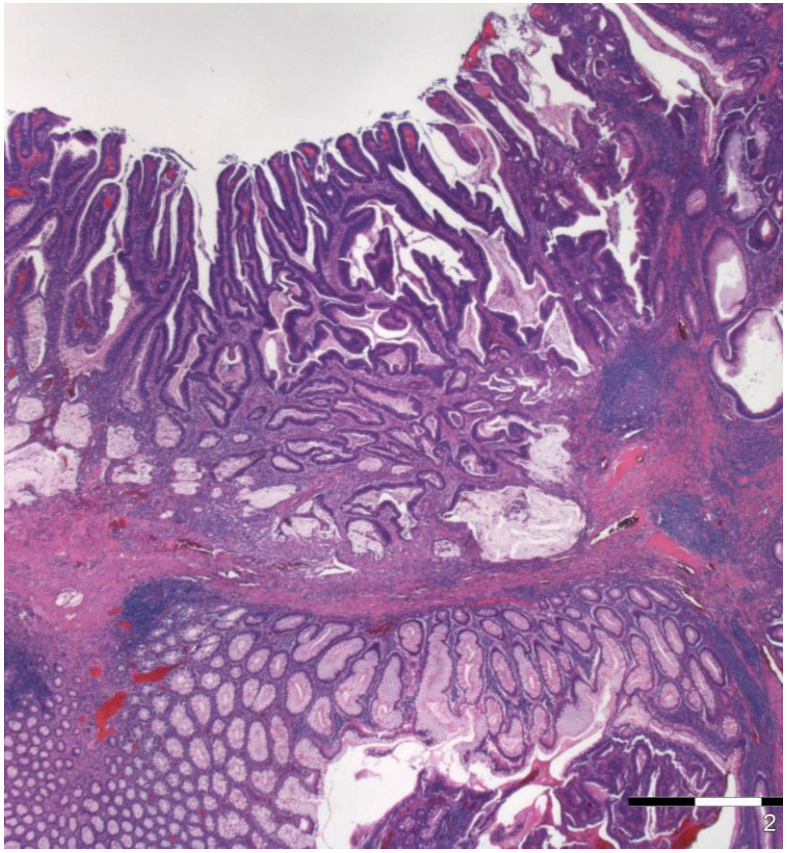
Pancytokeratin for the Selection of the Area to Screen

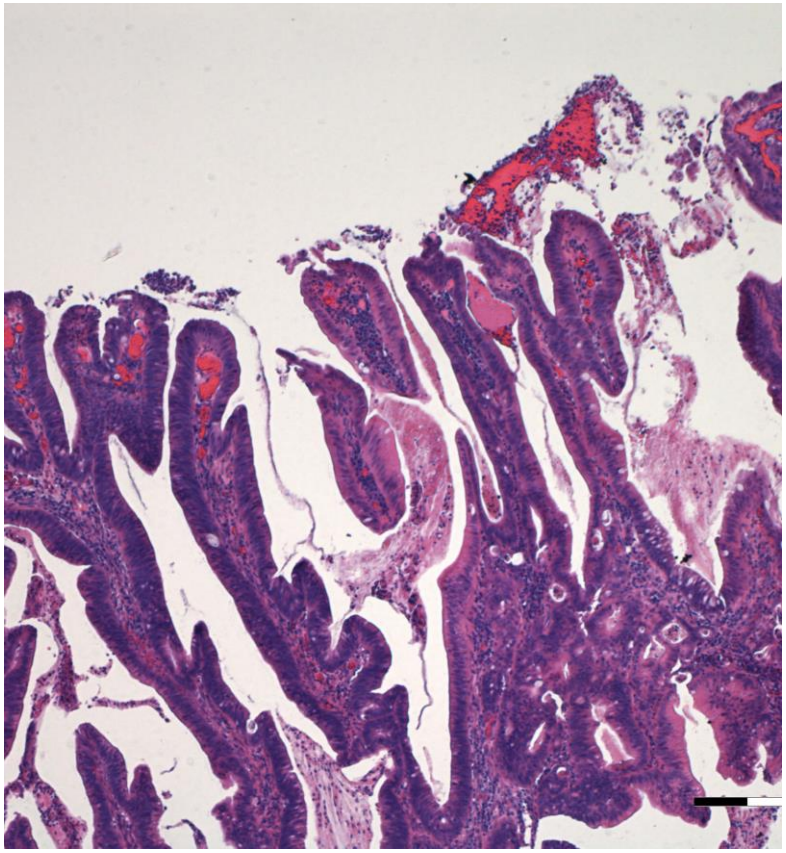


Malignancy in Polyps

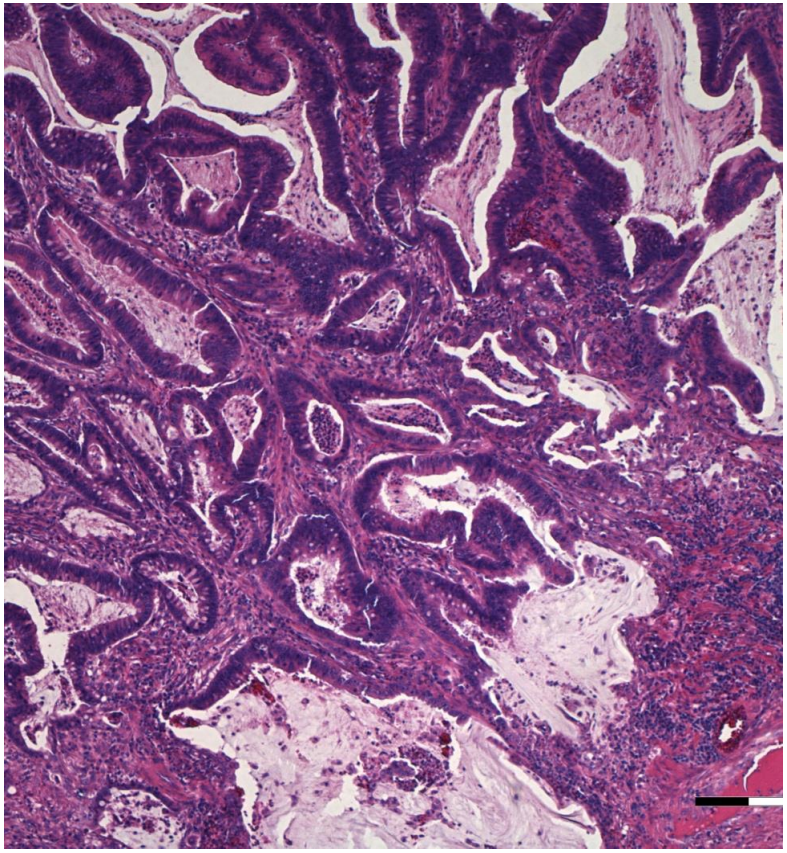


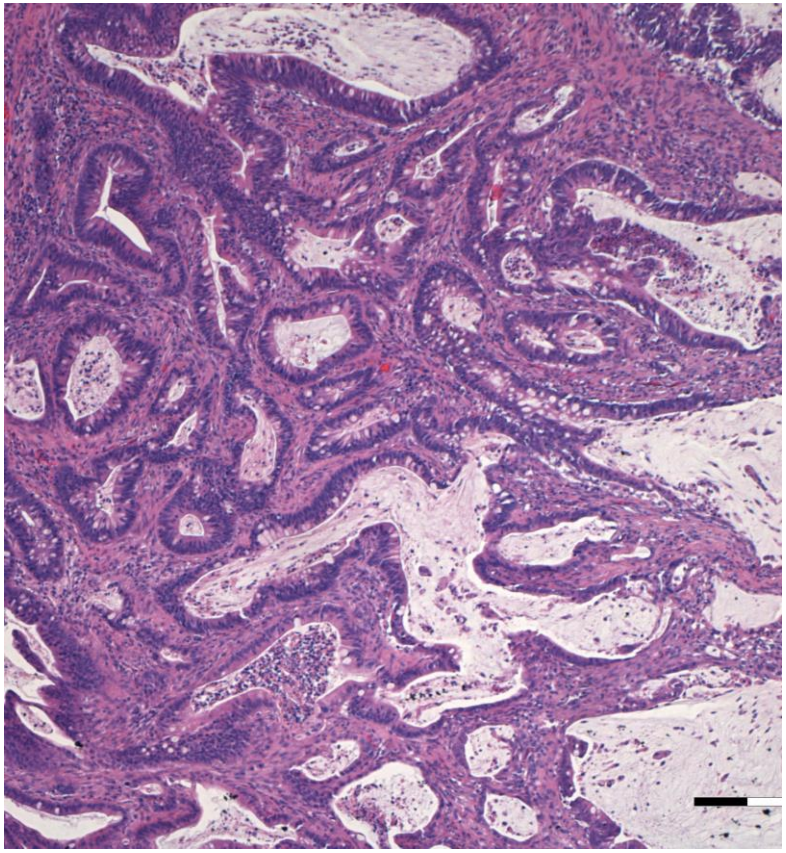
Malignancy in Polyps



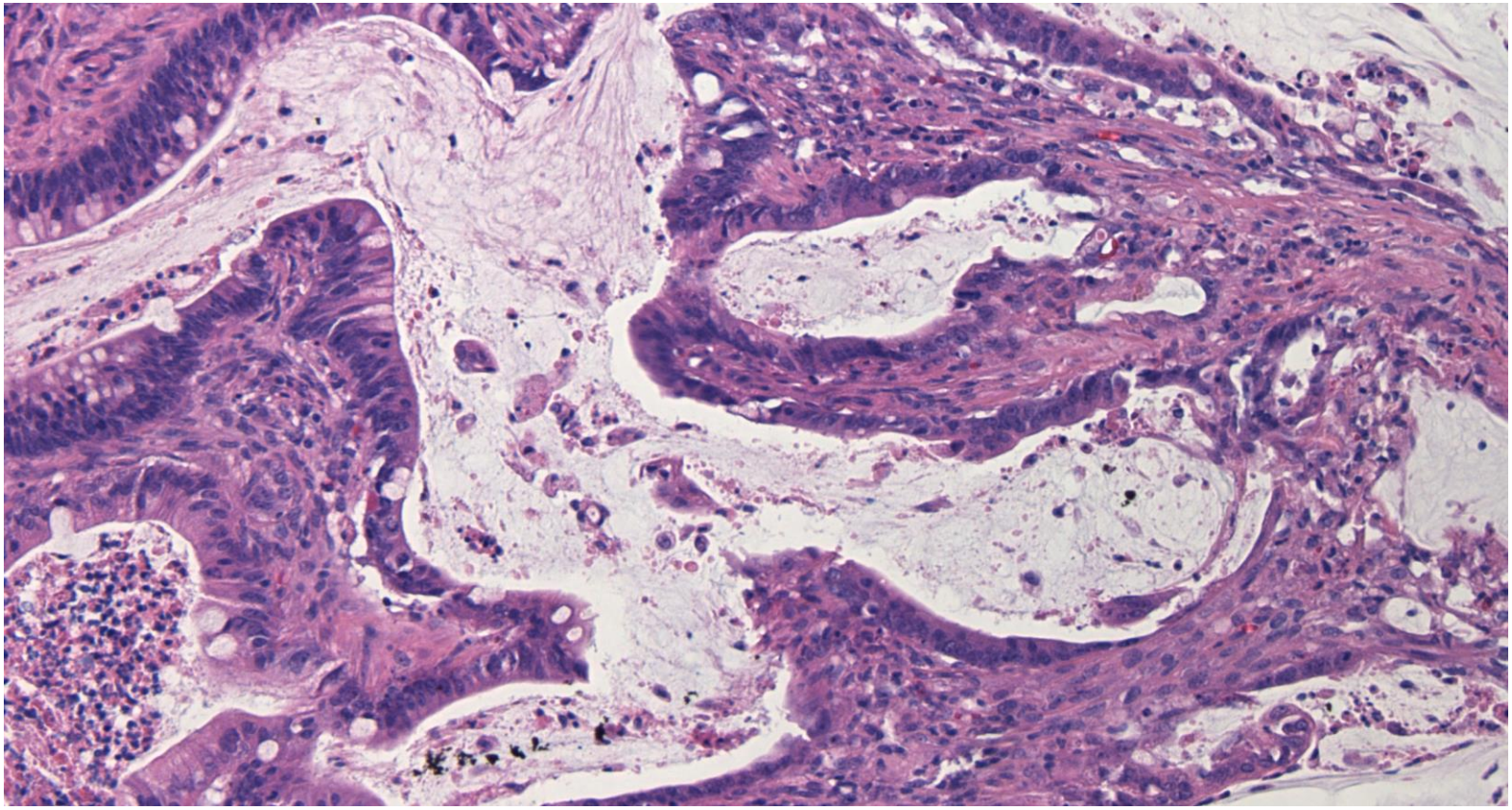


Malignancy in Polyps

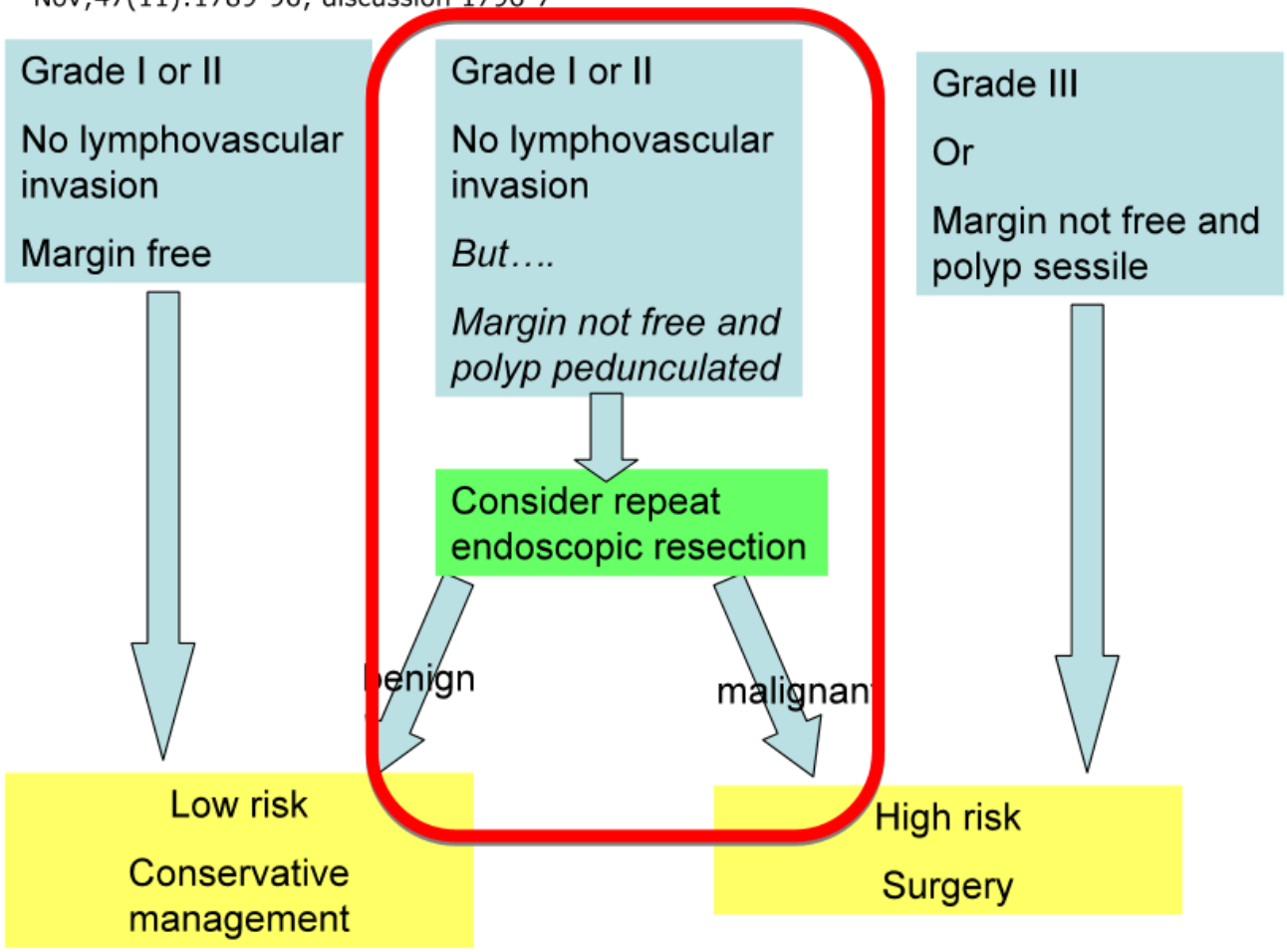


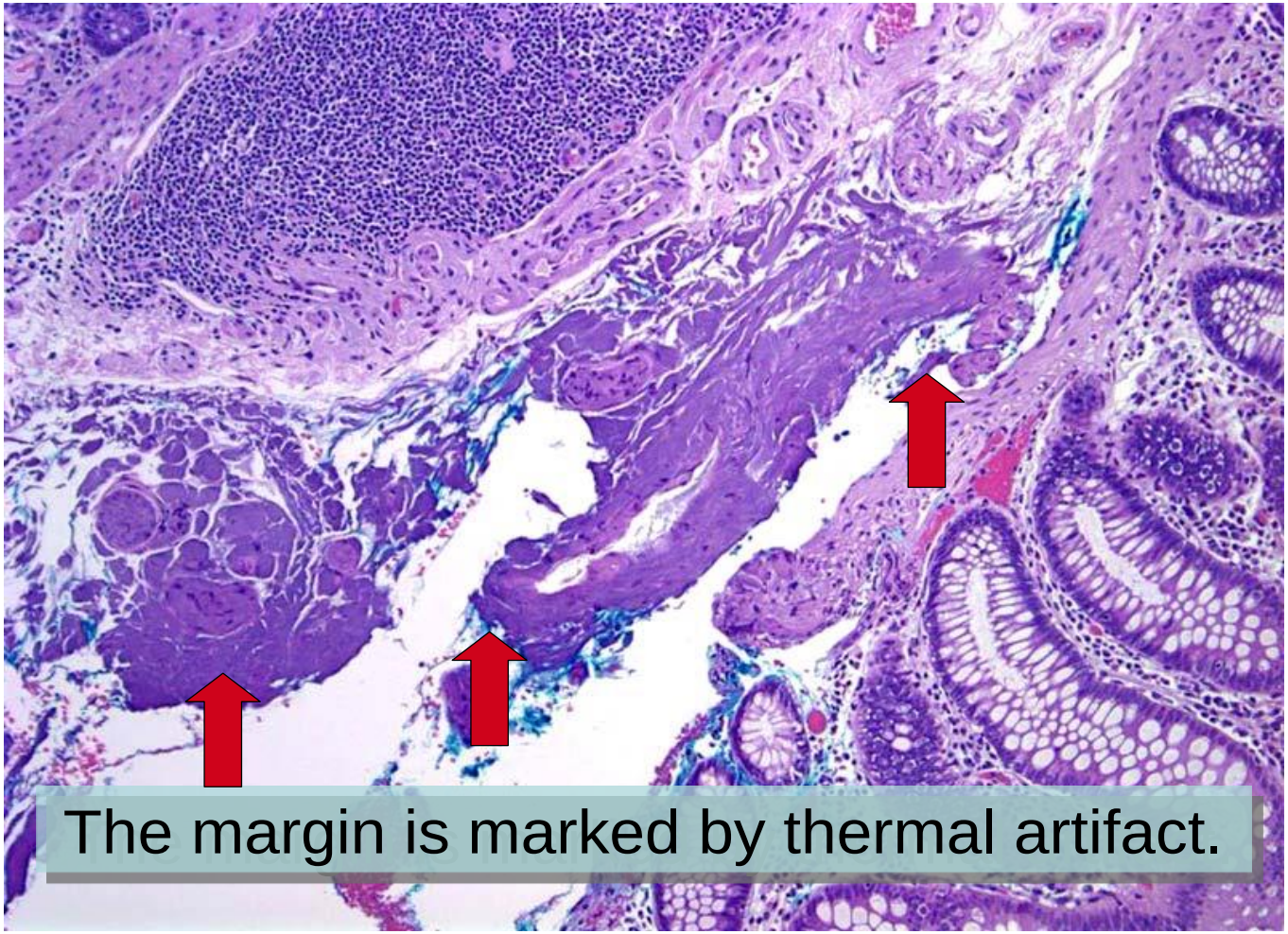


Malignancy in Polyps

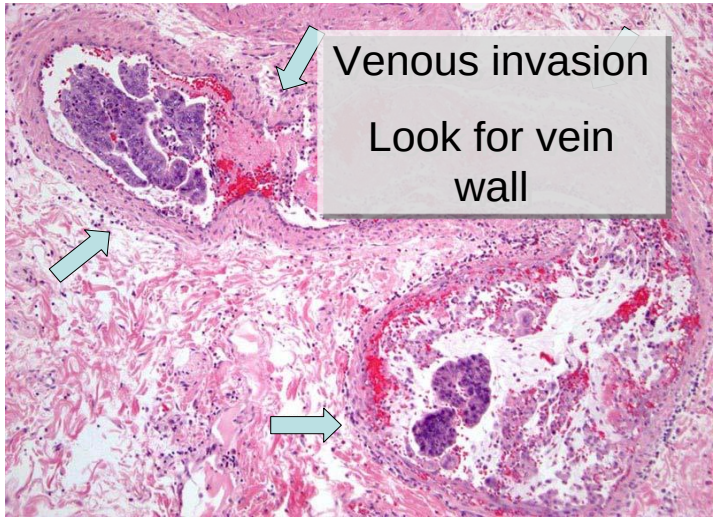


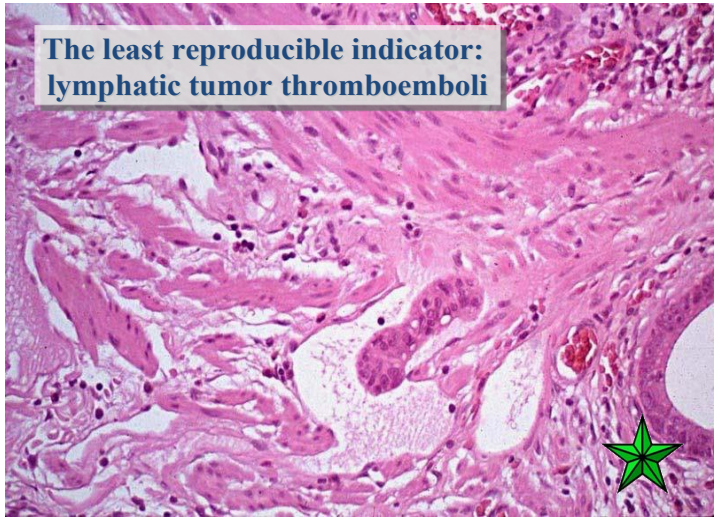
Seitz et al. Is Endoscopic Polypectomy an Adequate Therapy for Malignant Colorectal Adenomas? Presentation of 114 Patients and Review of the Literature. Dis Colon Rectum. 2004 Nov;47(11):1789-96; discussion 1796-7




The margin is marked by thermal artifact.

What is high grade carcinoma or venous invasion?





”Advanced” Adenoma

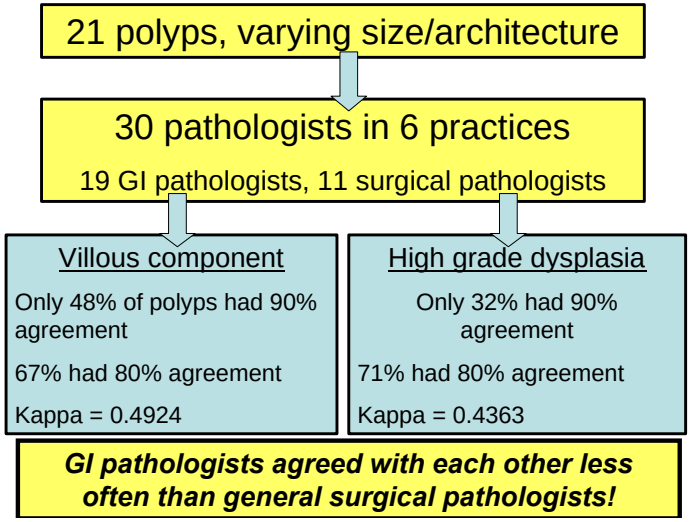
An “advanced adenoma” is one with villous histology or high grade dysplasia.

How much villous is enough?

How much high grade is enough?

The guidelines provide NO definitions.

What is the chance we will all diagnose “advanced adenomas” the same way?



Villous Architecture and Dysplasia

- **Identification of villous architecture and high-grade dysplasia in adenomatous polyps has poor reproducibility among pathologists, whether they are GI pathologists or general surgical pathologists.**

However, at the present time, the published guidelines include these histological features.

Adenomas with Carcinoma

- **Polyp is considered to be completely removed by endoscopist and submitted in one piece to pathologist**
- **Polyp is fixed and sectioned to be able to determined depth of invasion, degree of differentiation and resection margin**
- **Carcinoma is not poorly differentiated**
- **There is no lymphatic or vascular invasion**
- **The polypectomy margin is clear**

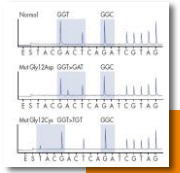
Key Elements

- **A big adenoma is at risk to contain carcinoma**
  - **If it is on the left side and pedunculated, it is also at risk to contain pseudoinvasion**
  - **Pseudoinvasion is clinically meaningless**
  - **Invasive carcinoma is important if it extends to the margins, is poorly differentiated, and perhaps has other features like vascular invasion**

CIMP-high vs. CIMP-low vs. CIMP-0

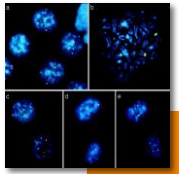
CIMP-high

- *BRAF*+
- Old age
- Female
- Proximal
- Inactive WNT



CIMP-low

- *KRAS*+



CIMP-0

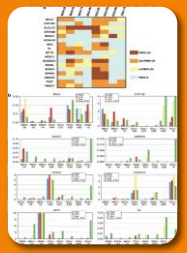
- *KRAS/BRAF* WT
- Distal
- Genome-wide hypo-CH_3
- CIN

CIMP in CRC

CpG island methylator phenotype (CIMP-high)

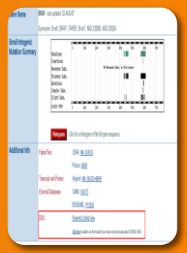
- **Non-random methylation pattern (links to *BRAF mutation)***
- ***inversely associated with genome-wide hypomethylation***
- ***DNMT3B may contribute to CIMP-high***

KRAS+ is associated with random methylation pattern (= CIMP-low)



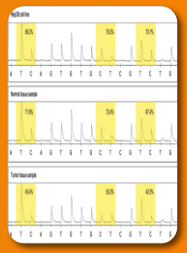
CIMP-high

- **Good prognosis**



BRAF+

- **Bad prognosis**



LINE-1 hypomethylation

- **Bad prognosis**

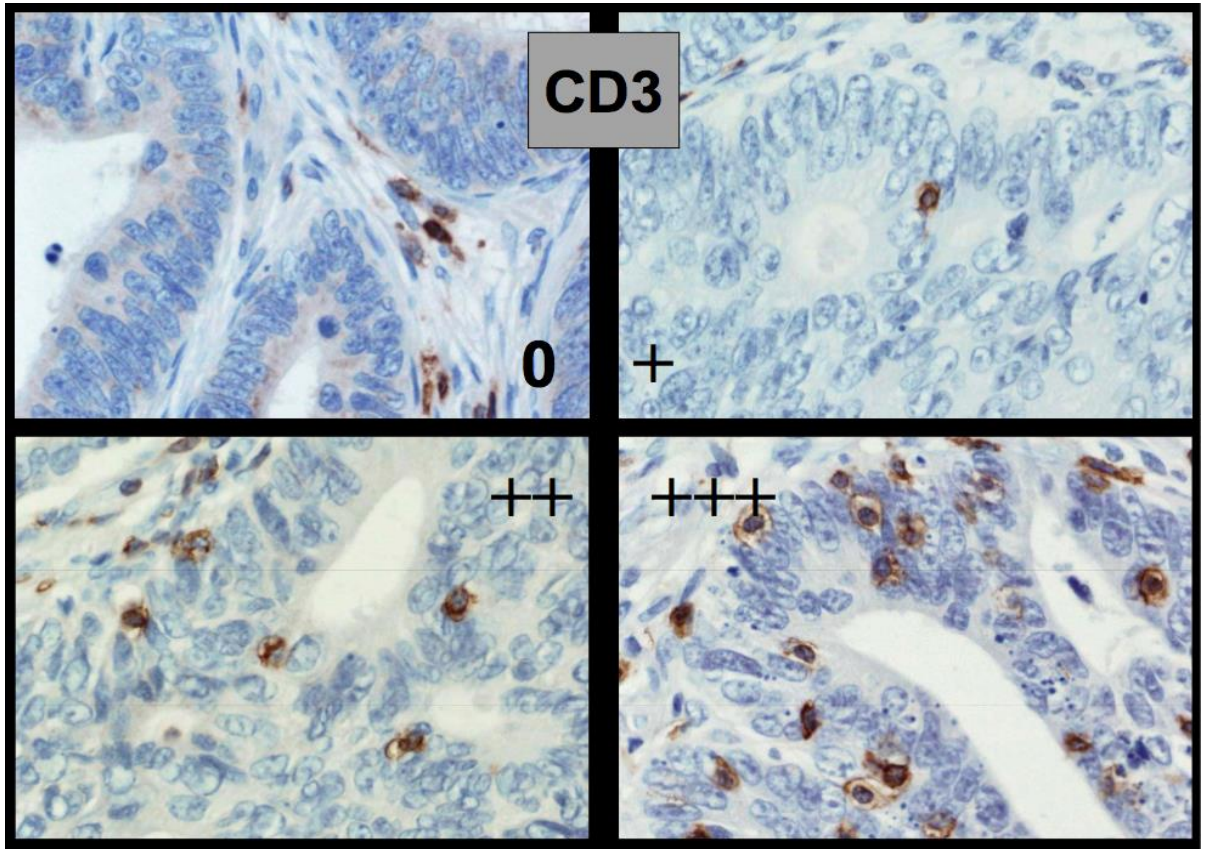
Molecular Classification of CRC

	Meth(+)	Meth(-)
MSI	Mol Class 2 (15%)	Mol Class 4 (5%)
MSS	Mol Class 3 (10%)	Mol Class 1 (70%)

Molecular Classification of CRC

	Mol Class 2	Mol Class 3	Mol Class 1
Ploidy	**Diploid**		**Aneuploid**
MS Profile	**MSI**	**MSS**	
Methylation	**Meth(+)**		**Meth(-)**

TILs in CRC



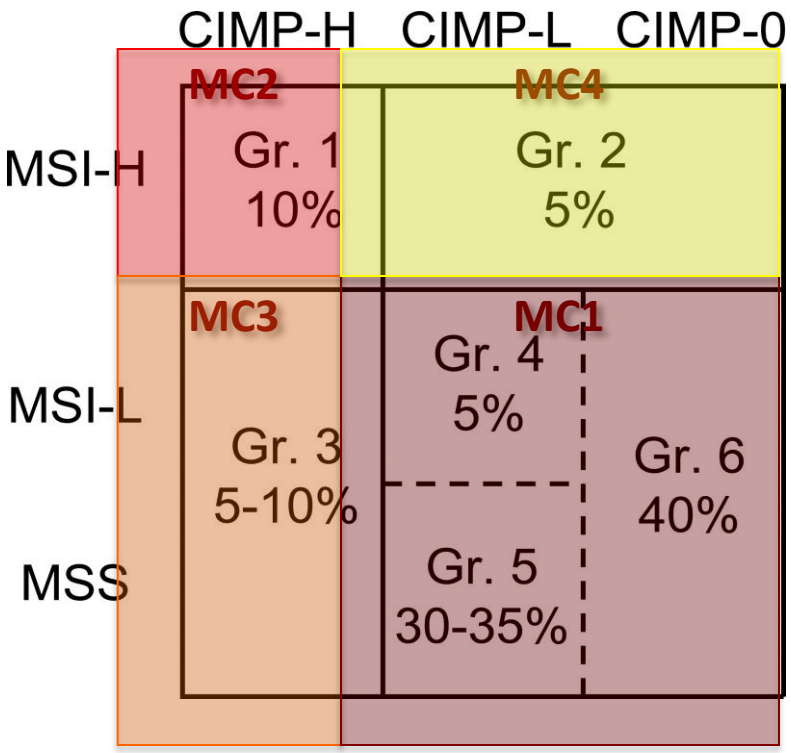
TIL counts in H&E sections

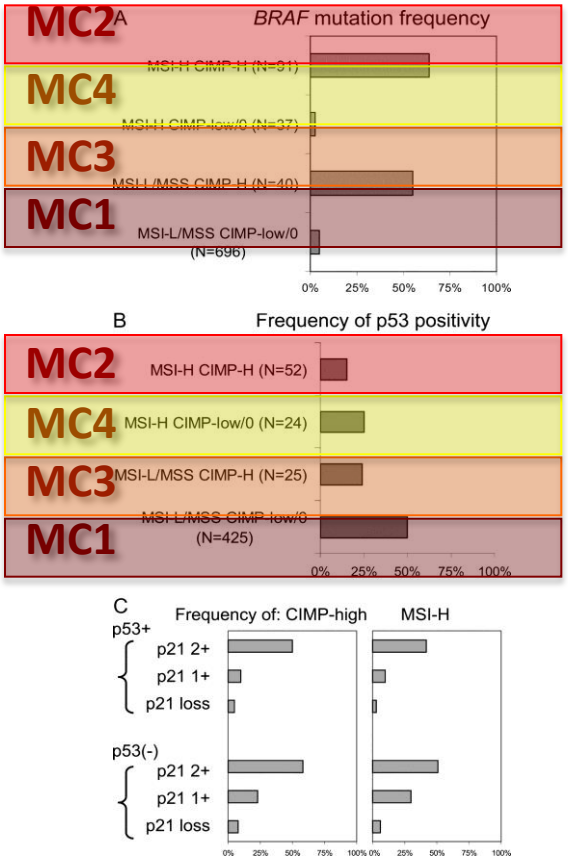
	Sensitivity	Specificity
3.5/5 HPF *	88%	75%
>10/5 HPF **	90%	77%

* *Smyrk et al, 2001*

** *Greenson et al, 2003*

CRC Molecular Classification: Microsatellites and Methylation

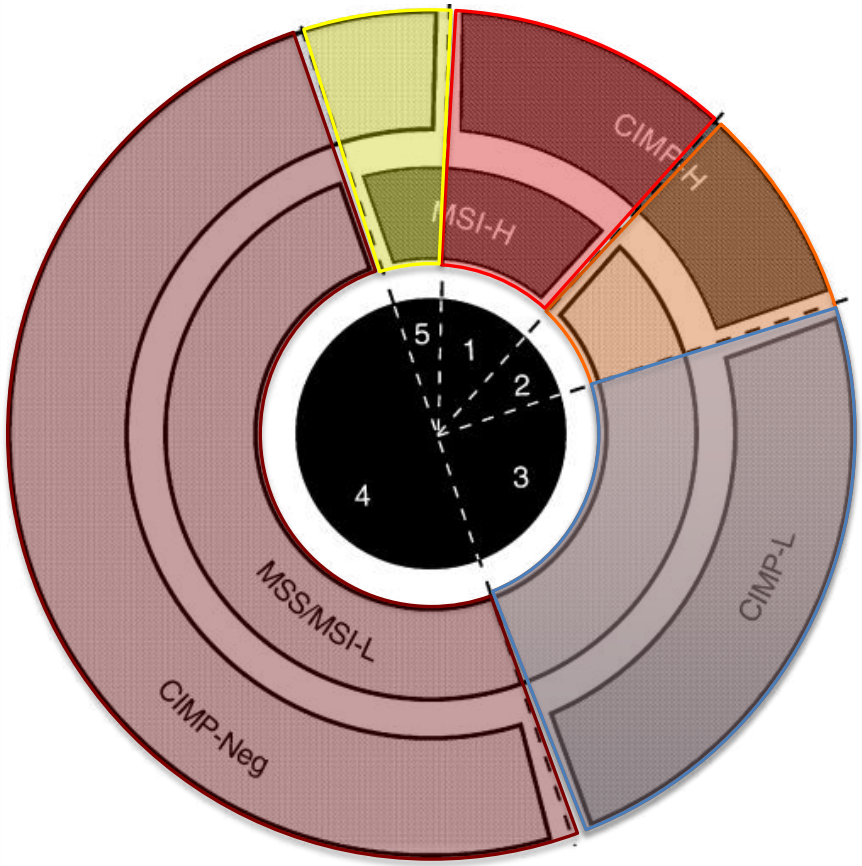




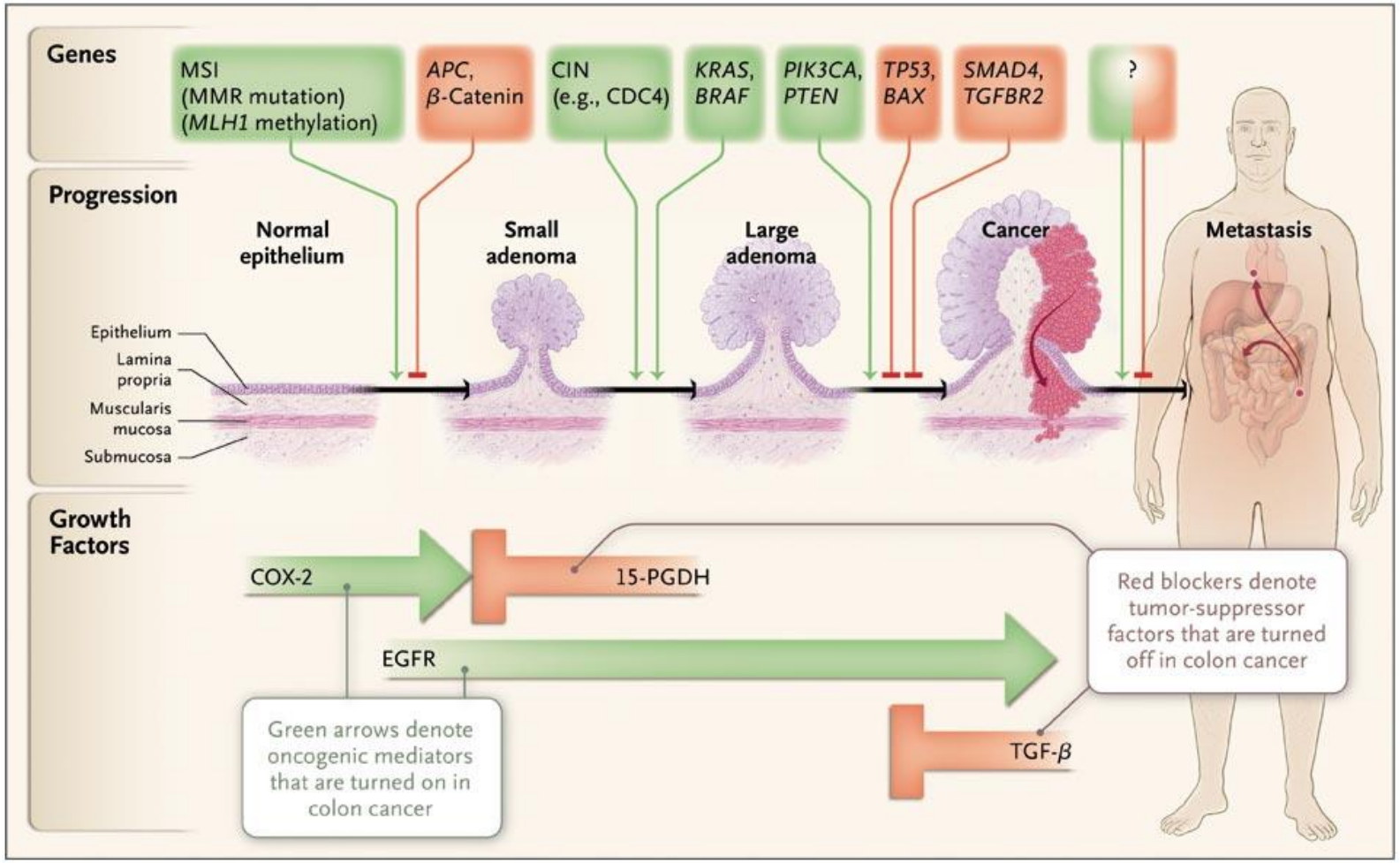
Molecular Classification of CRC

1. **Main pathways: Adenomatous (*APC* ± *KRAS*, hypo-CH_3) and serrated (*BRAF*, CIMP-high)**
2. **Microsatellite profiles further subclassify each group.**
3. **CIMP-low represents a new epigenomic subtype (*KRAS*)**

Feature	MC2	MC3		MC1	MC4
	Group 1	Group 2	Group 3	Group 4	Group 5
MSI	H	S/L	S/L	S	H
Methylation	+++	+++	++	±	±
Ploidy	**D** > A	D > A	D < A	D < A	D > A
APC	±	±	+	+++	++
KRAS	-	+	+++	++	++
BRAF	+++	++	-	-	-
TP53	-	+	++	+++	+
Precursor	SP	SP	SP/AD	AD	AD
Serration	+++	+++	+	±	±
Mucinous	+++	+++	+	+	++
Dirty necrosis	+	+	?	+++	+
Poor diff	+++	+++	+	+	++
Circumscr	+++	+	?	++	++
Tum budding	±	+	?	+++	+
TIL	+++	+	?	+	+++
Location	R > L	R > L	R < L	R < L	R > L
Gender	F > M	F > M	F < M	F < M	F < M



Genes and Growth Factor Pathways That Drive the Progression of Colorectal Cancer



Markowitz S, Bertagnolli M. N Engl J Med 2009;361:2449-2460

Dysplasia and Polyps of GI Tract

- **Dysplastic lesions in IBD should be evaluated in the clinical context (extension, severity, and duration), gross appearances (flat or elevated), and histological subtypes (adenomatous/non-adenomatous)**
- **Epithelial polyps need careful evaluation on:**
  - **Grading (advanced concept not yet defined)**
  - **Staging (definition of malignancy, extension, and resection margins)**
  - **Pathways of transformation (adenomatous *vs.* serrated)**