N̄O̅N ADENOMATOUS DYSPLASIA OF THE GIT

Gregory Y. Lauwers, MD

AGPS - 5th Annual Scientific Meeting – Adelaide; 25-26 of October 2019

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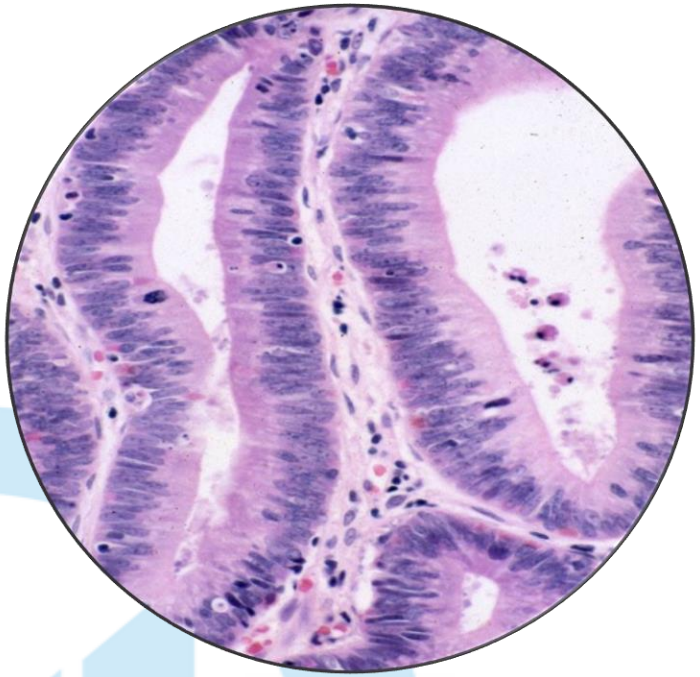
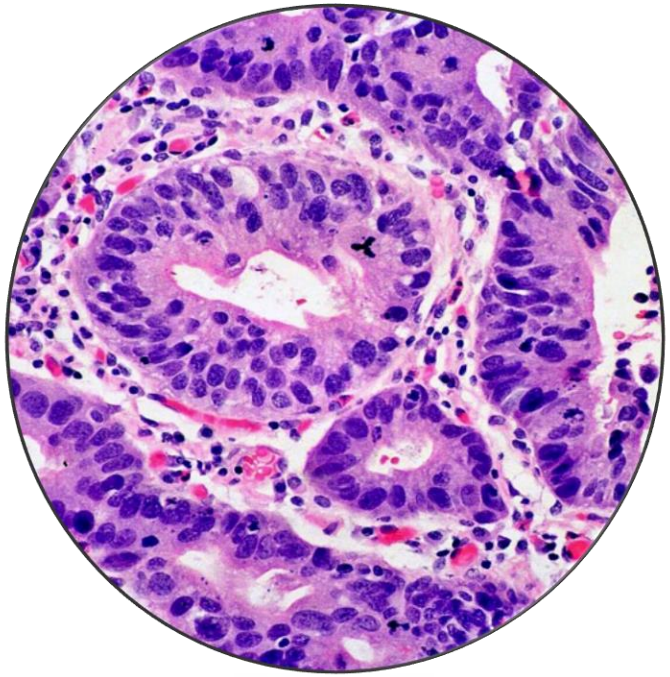
Dysplasia: unequivocal neoplastic epithelium confined to the basement membrane. Classic prototype: *adenomatous dysplasia*





Inflammation → **Dysplasia** → **Adenocarcinoma**

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ESOPHAGUS

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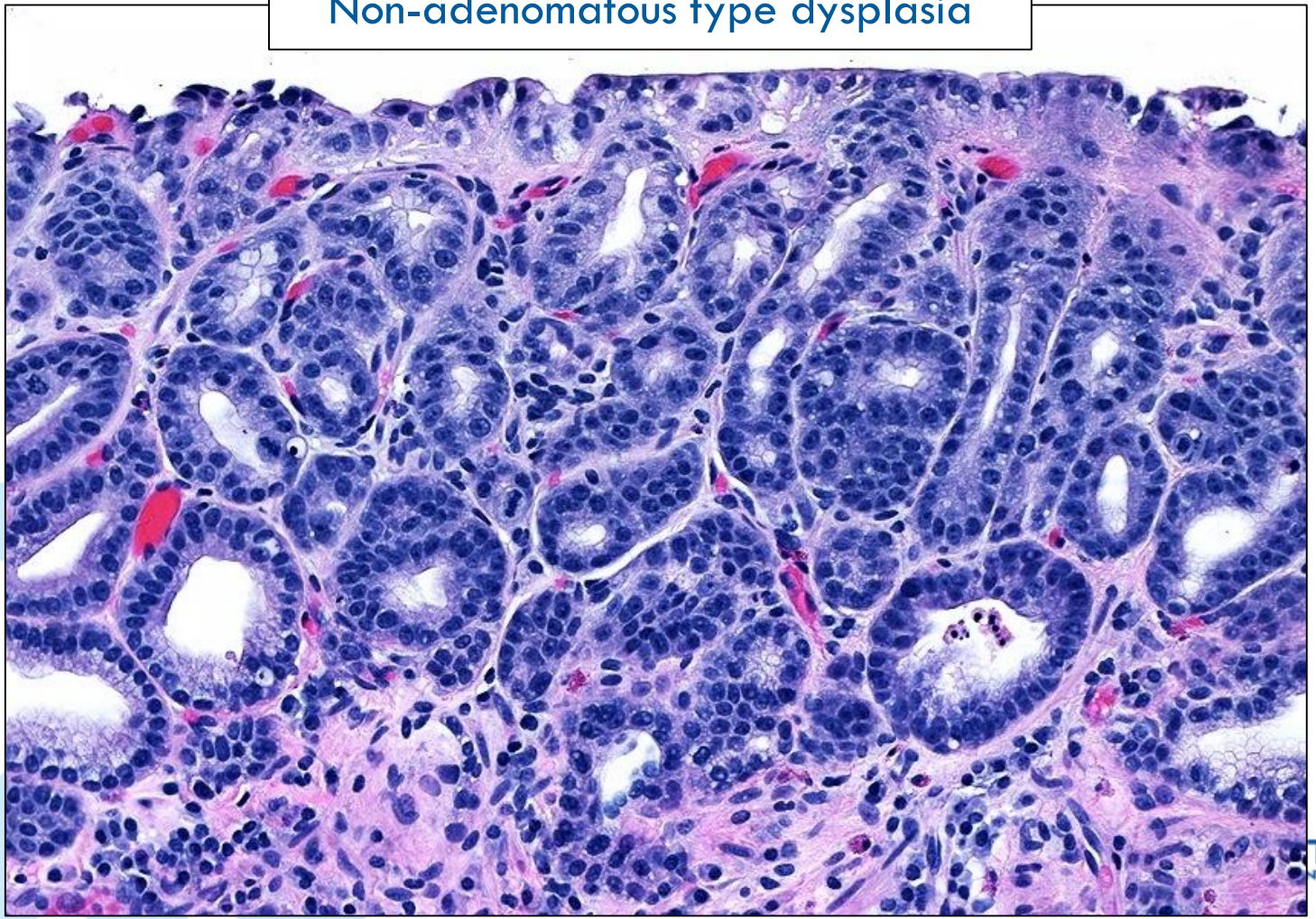
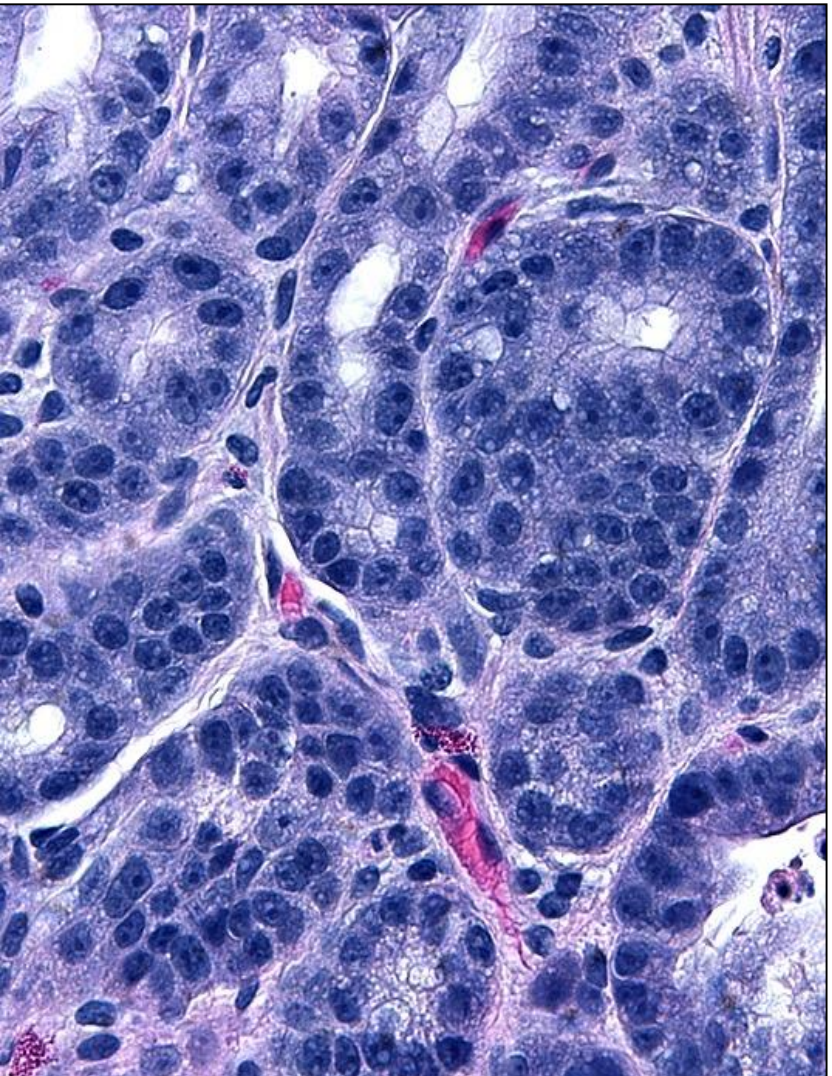
Non-adenomatous type dysplasia





- Prevalence: 6.7%
- 94% the cases are associated with typical dysplasia [**HGD**>LGD]
- High rate DNA abnormalities

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Non-adenomatous type dysplasia in BE

10 Year Follow-up

Dysplastic Variant	N	Maximum dx upon Follow-up: Low-grade	High-grade	Carcinoma
Nonadenomatous	18	0%	78%	17%
Adenomatous	24	25%	54%	21%
Low-grade	13	46%	31%	23%
High-grade	11		***82%***	***18%***

Rucker-Schmidt et al. Am J Surg Pathol 2009;33(6):886-93

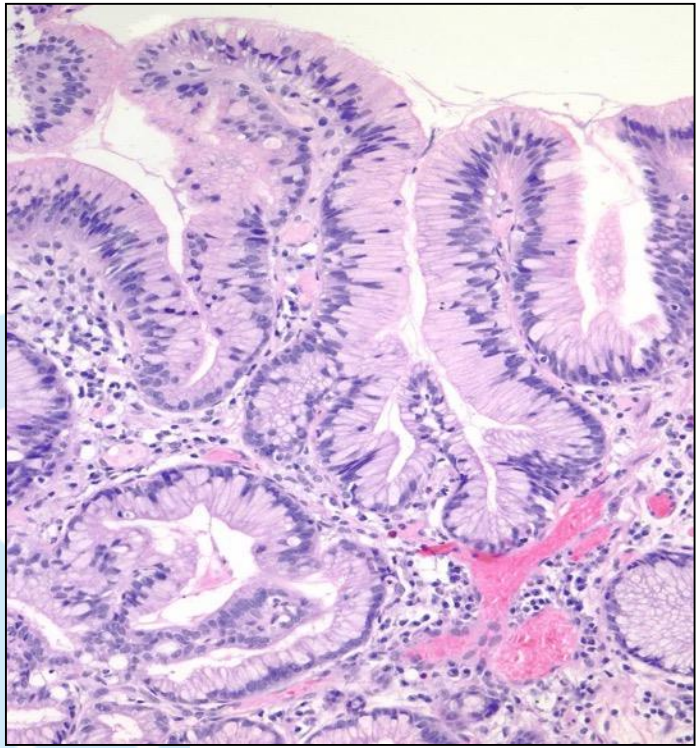
Modern Pathology; 2010-23:834-843

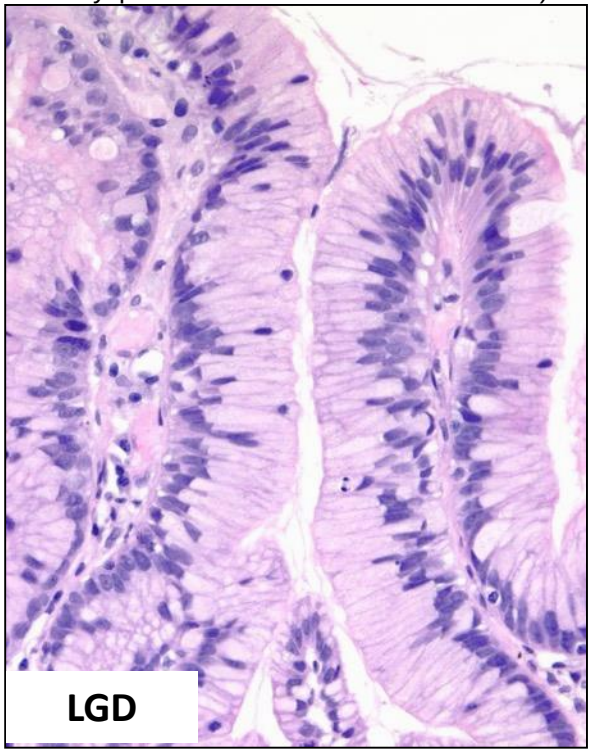
Foveolar type dysplasia in Barrett esophagus

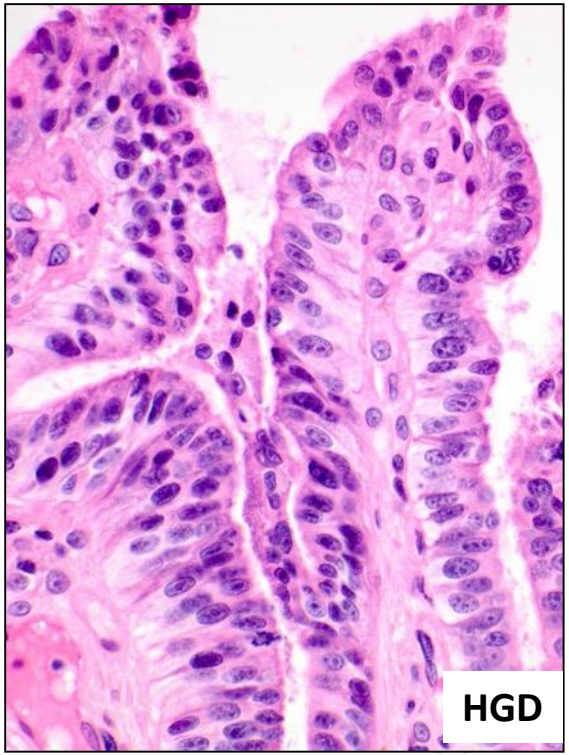
Ian S Brown[1], David C Whiteman[2,3] and Gregory Y Lauwers[4]

Prevalence:46%.(HGD:58%) (adjacent IM: 53%)

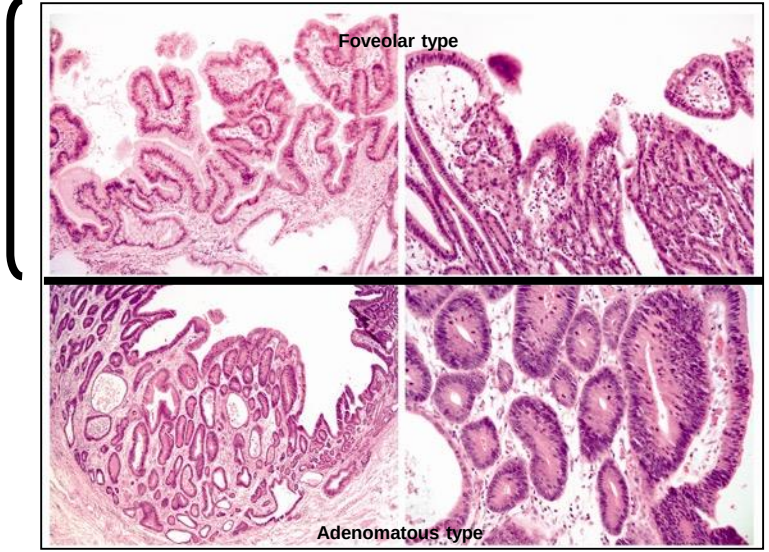
(41 resections w/ dysplasia w or w/o associated inv. ACA)





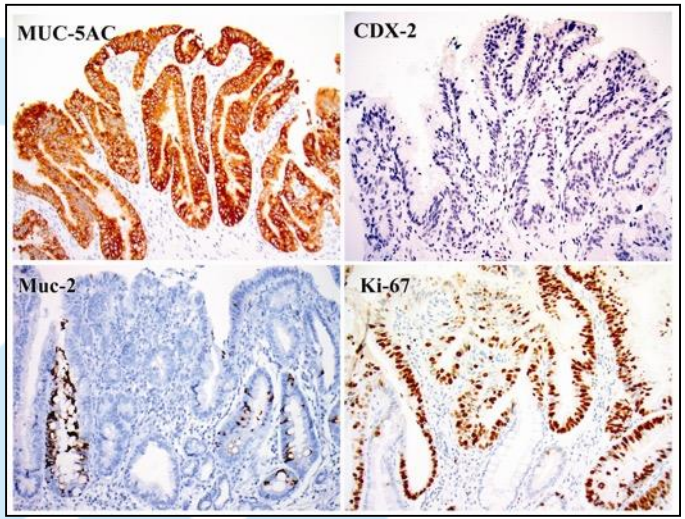


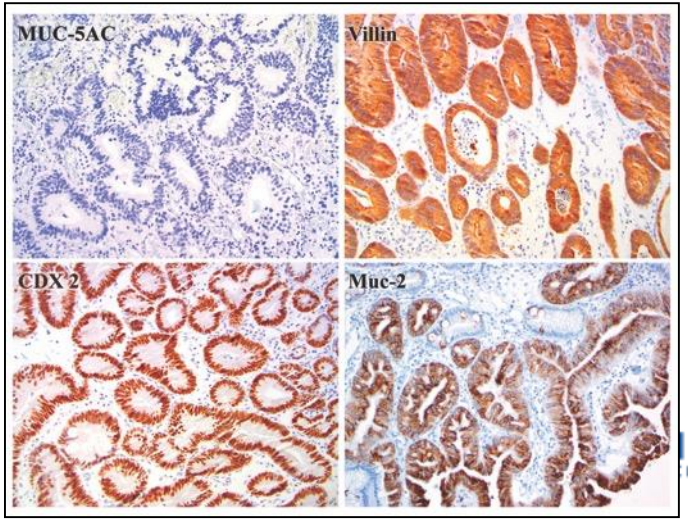
Adenomatous & Hybrid Dysplasia: Prevalence:27%.(HGD:91%;100%) (adjacent IM: 100%/82%%)



Foveolar type

Adenomatous type





Foveolar dysplasia: progression to cancer

Dysplasia	Association with		Progression to cancer
	Conventional LGD	Conventional HGD	
Conventional LGD (N=22)			1 (5%)
Conventional HGD (N=16)			**12 (75%)**
Foveolar Dysplasia (N=17)	**4(24%)**	**13(76%)**	**8 (47%)**

Srivastava et al, USCAP 2010

214 patients

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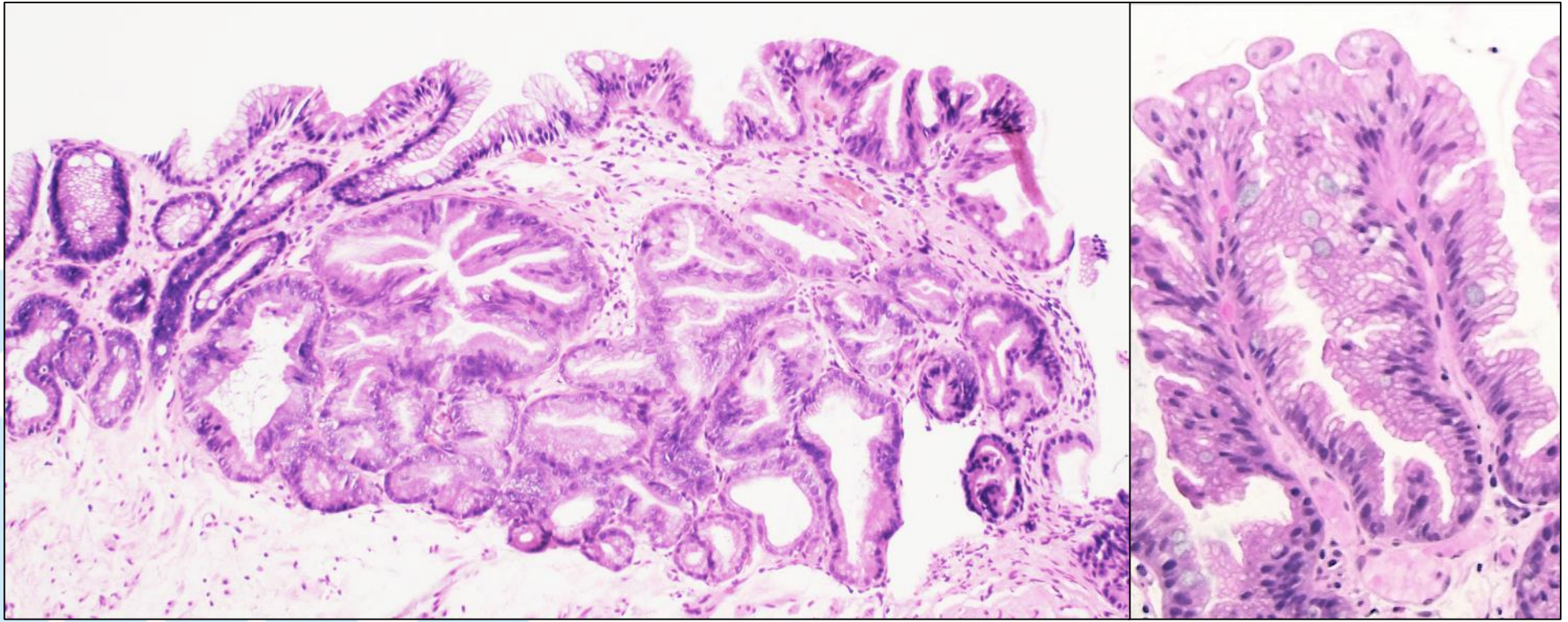
Serrated dysplasia



Serrated dysplasia: Progression to cancer

Dysplasia	Association with		Progression to cancer
	Conventional LGD	Conventional HGD	
Conventional LGD (N=22)			1 (5%)
Conventional HGD (N=16)			**12 (75%)**
Serrated Dysplasia (N=6)	**3(50%)**	**3(50%)**	**3 (50%)**

Srivastava et al, USCAP 2010

214 patients

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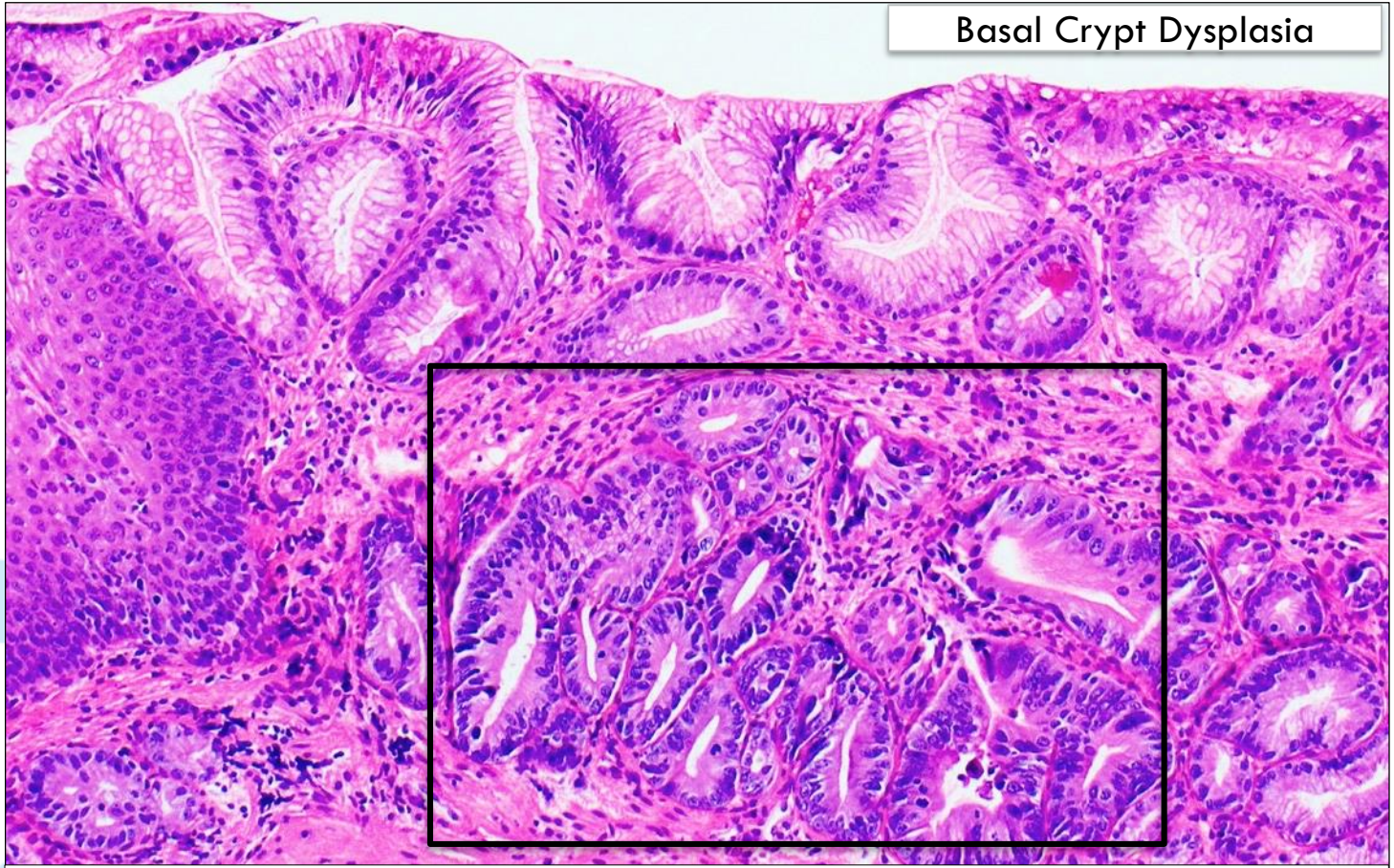
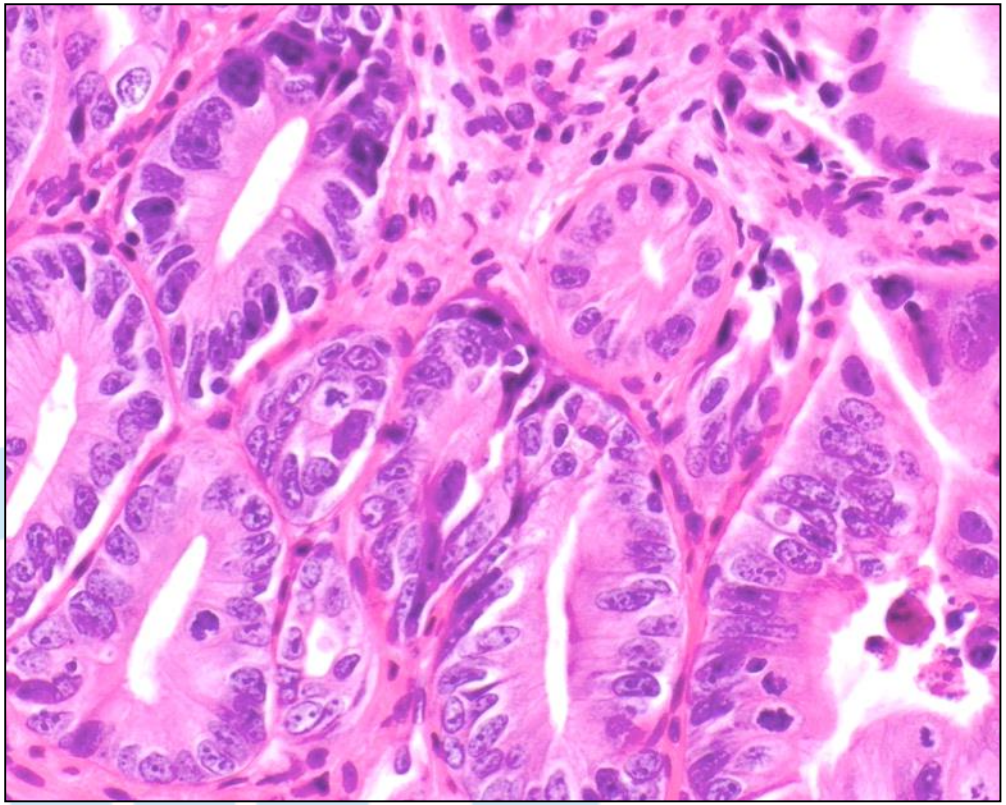
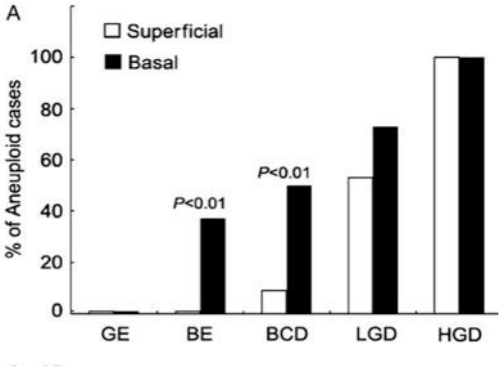


- Prevalence:7.3%
- 87% have prior or concurrent dysplasia or CA
- Association particularly significant w/ regard to the assoc. w/ HGD (P=0.004).

Molecular anomalies & natural history of basal crypt dysplasia



DNA abnormalities in basal crypt cells



Compared w/ BE, BCD shows:

↑ prevalence rate of p53 positivity (60% vs.13%, P<0.02)

↑ total & basal crypt Ki-67 proliferation rate (P<0.001) *(similar to LGD or HGD*)

Clonal identity (*CDKN2A* mutations)

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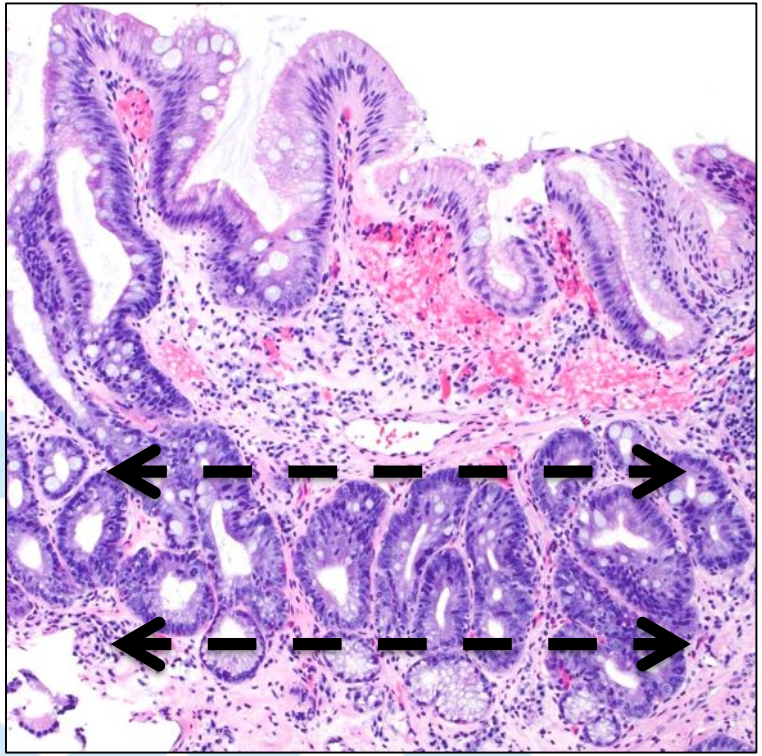
Zhang X Am J Surg Pathol ' 08; Lomo LC Am J Surg Pathol ' 06; Khan S. J. Pathol 2013;231; Srivastava A. USCAP 2011

Can we-reliably-recognize BCD?



Metaplastic atypia

- 40 bx: 10 BE,9 BCD,10 LGD,9 HGD,2 IMCa [selected by index pathologist]
  - *K* for IOV for entire cohort :0.44 (moderate)
    - [IMC (K=0.65)-LGD (K=0.31)]

- No differences in reproducibility of Basal Crypt Dysplasia (K=0.44)-LGD (K=0.31) or HGD (K=0.46)

- When disagreement w/ index diagnosis of BCD (n=17/45 readings), most diagnosed either LGD or HGD rather than BE without dysplasia.

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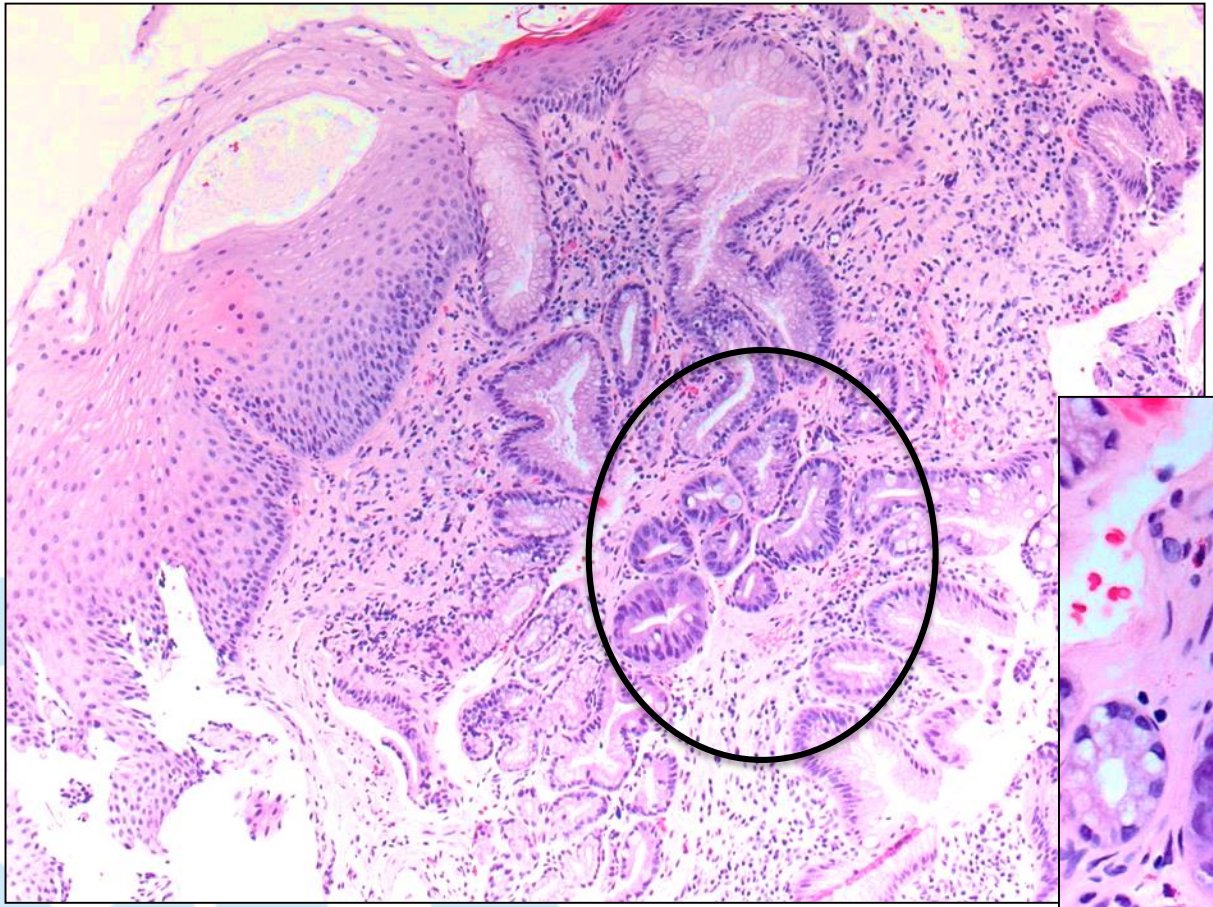
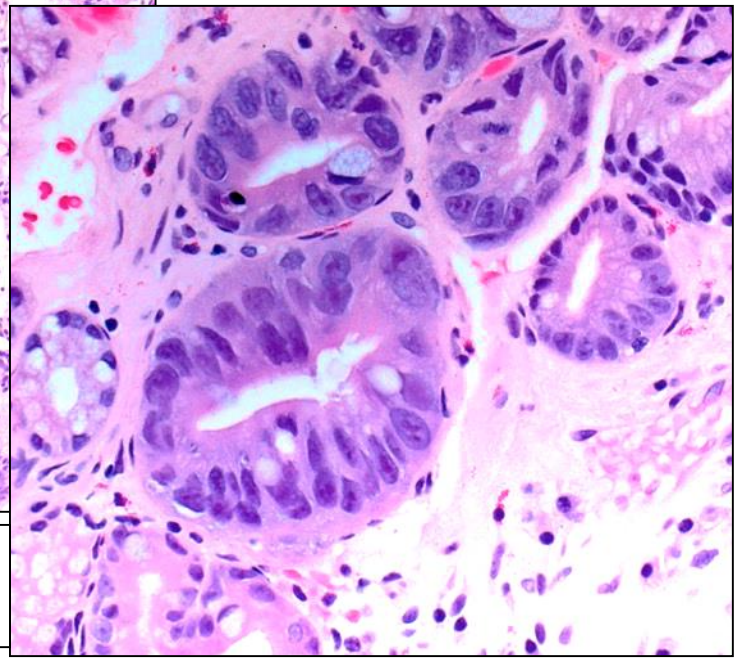
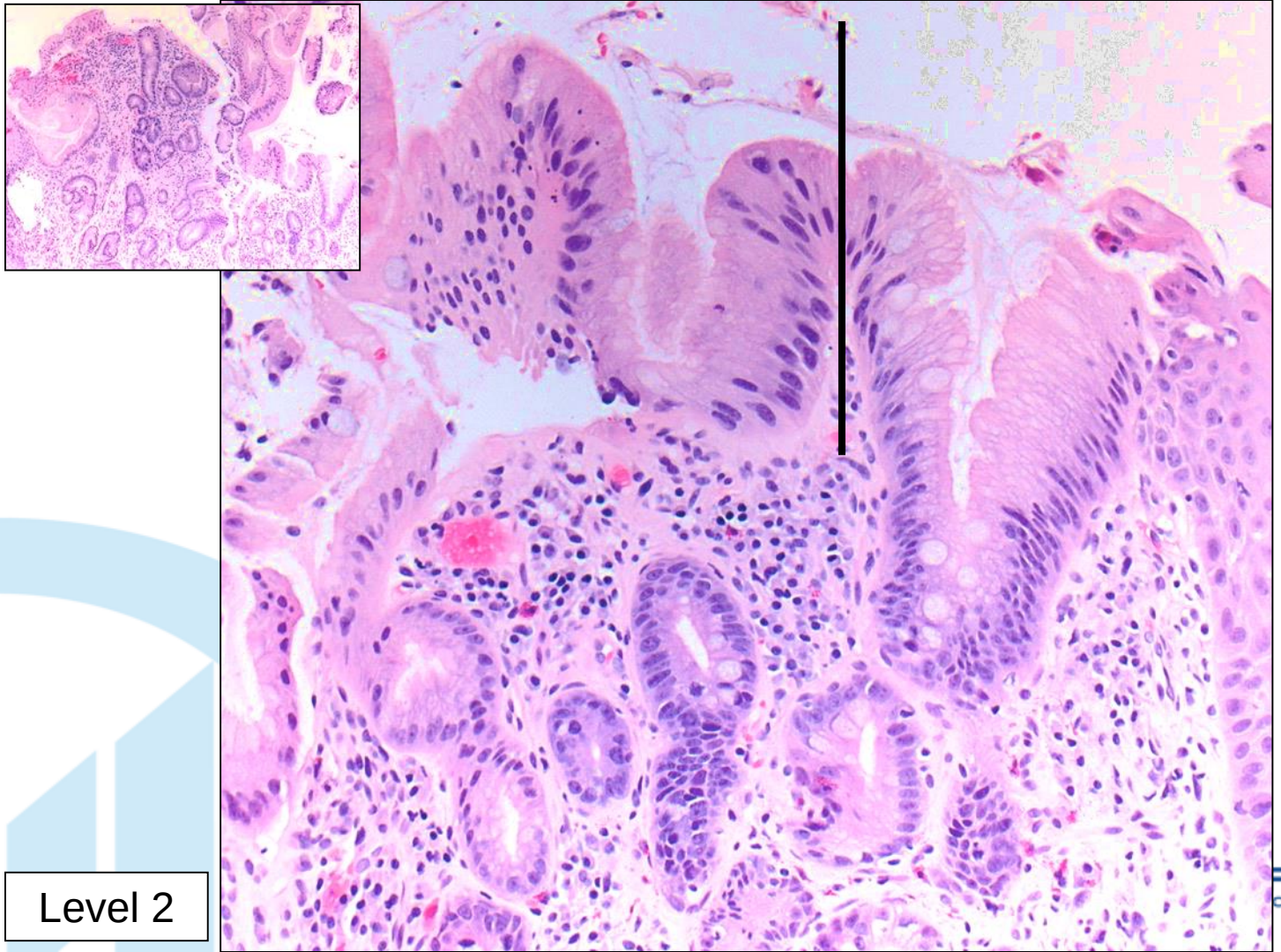
Coco et al, 2011 Am J Surg Pathol





Recurring issue w/ basal crypt dysplasia



Level 2

STOMACH

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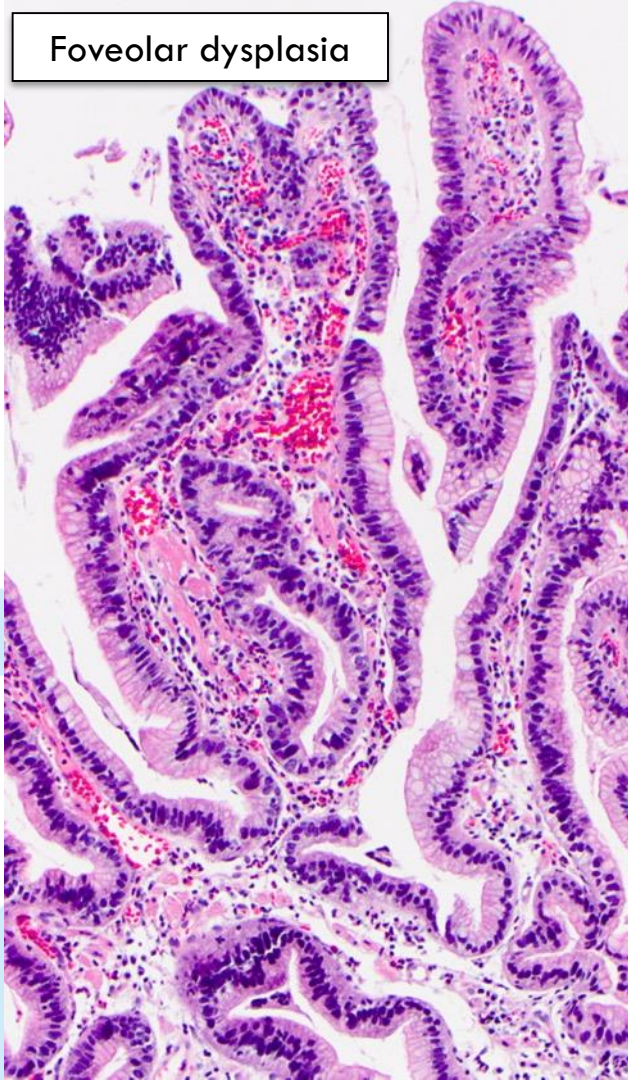
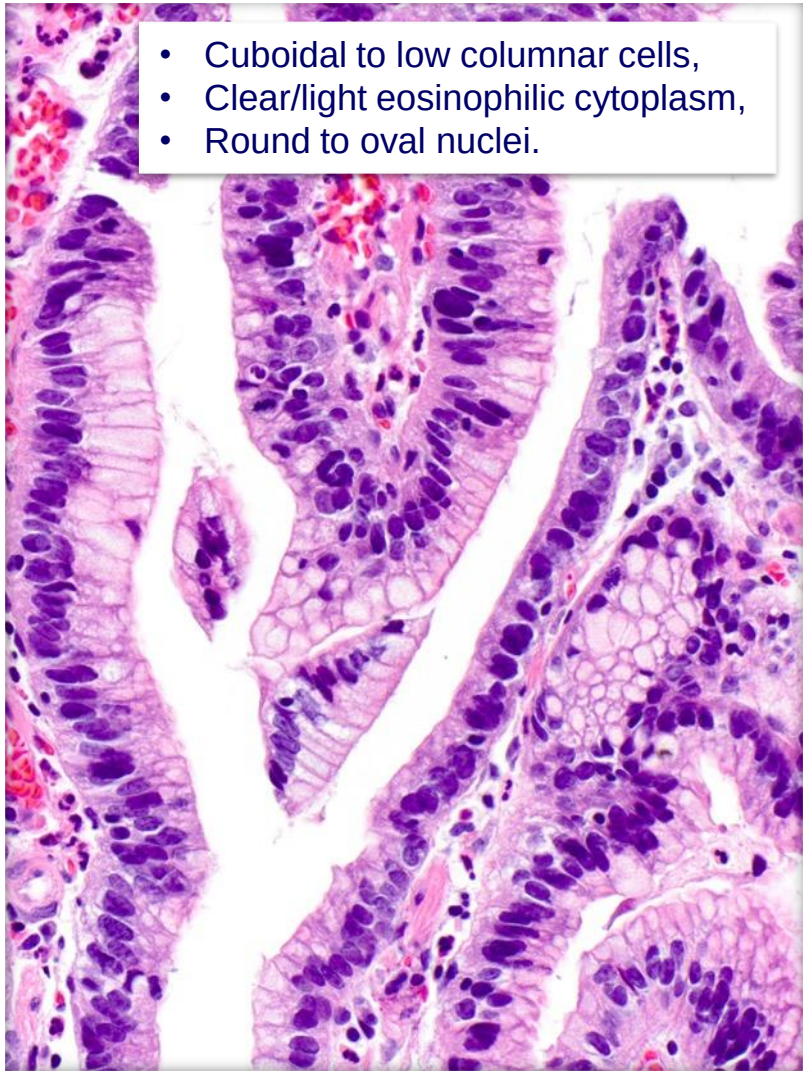
Foveolar dysplasia

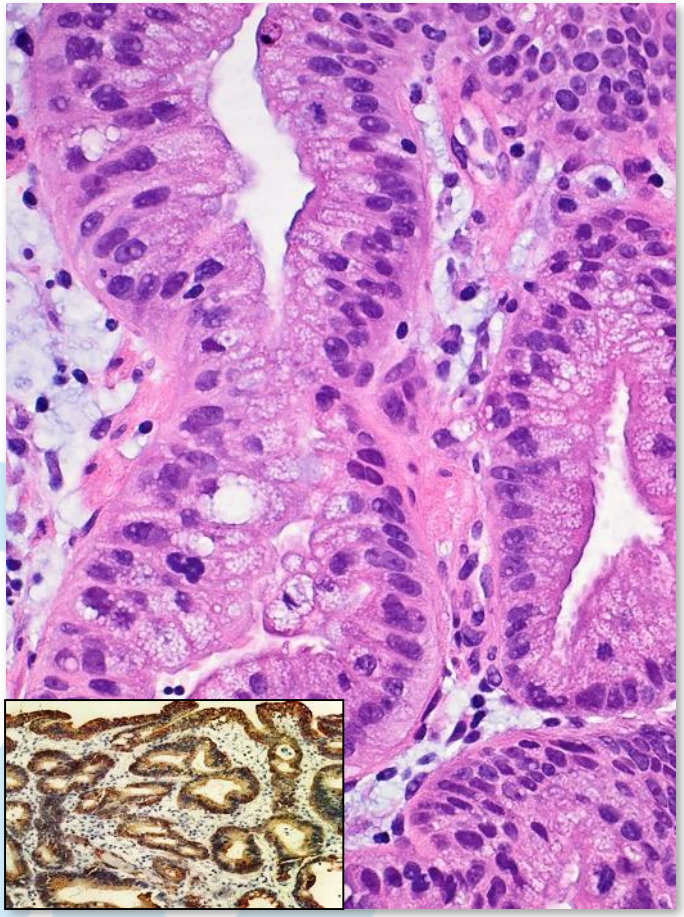




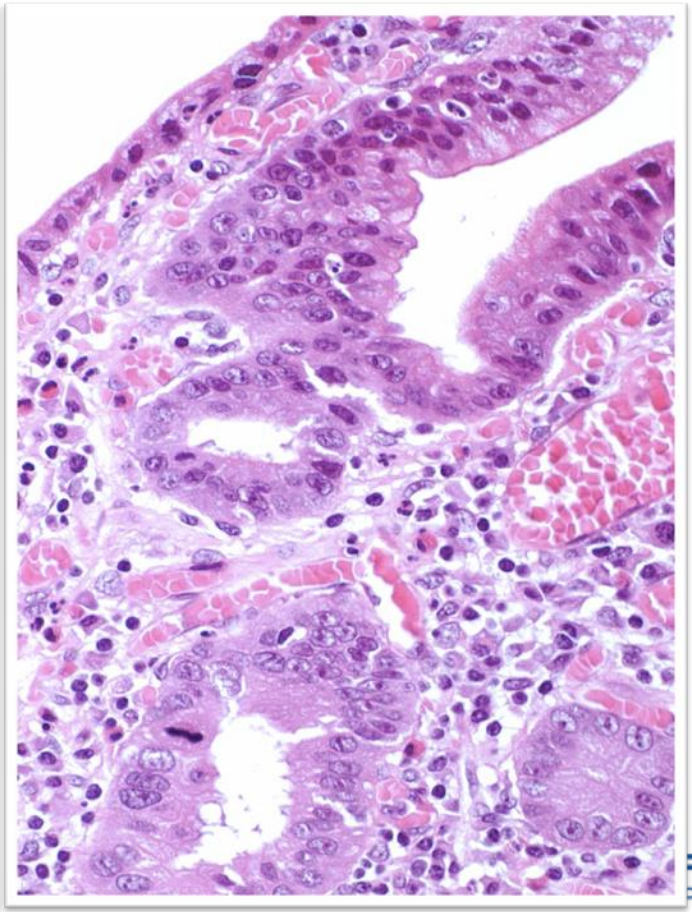
- Cuboidal to low columnar cells,
- Clear/light eosinophilic cytoplasm,
- Round to oval nuclei.

Foveolar type dysplasia-low grade

Foveolar type dysplasia-high grade

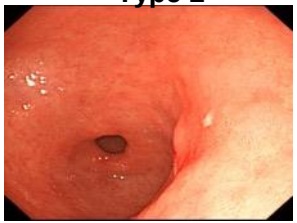


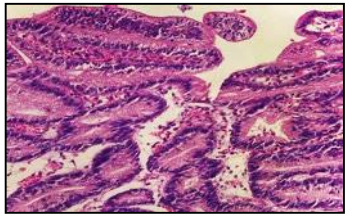
MUC5AC



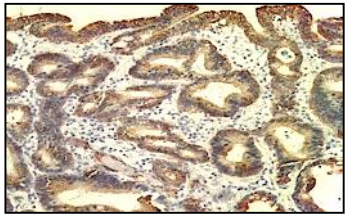
Prevalence of foveolar GED: 22% (Adenomatous: 45%, hybrid 33%) (n=69)

Type 2





Muc5AC



- Foveolar GED is often depressed/flat and associated w/ HGD (p= 0.046).
- HGD associated w/ MUC5AC expression regardless of the type (p=0.026).

Grade	Immunophenotype			p value
	Foveolar (n=24)	Intestinal (n=22)	Hybrid (n=14)	
HGD (n=25)	15* (63%)	4 (18%)	6 (43%)	
Low grade (n=35)	9 (37%)	18 (82%)	8 (57%)	0.010

* coexistent intramucosal carcinoma in 8 cases

Foveolar differentiation is associated w/ HGD & coexistence of IMC

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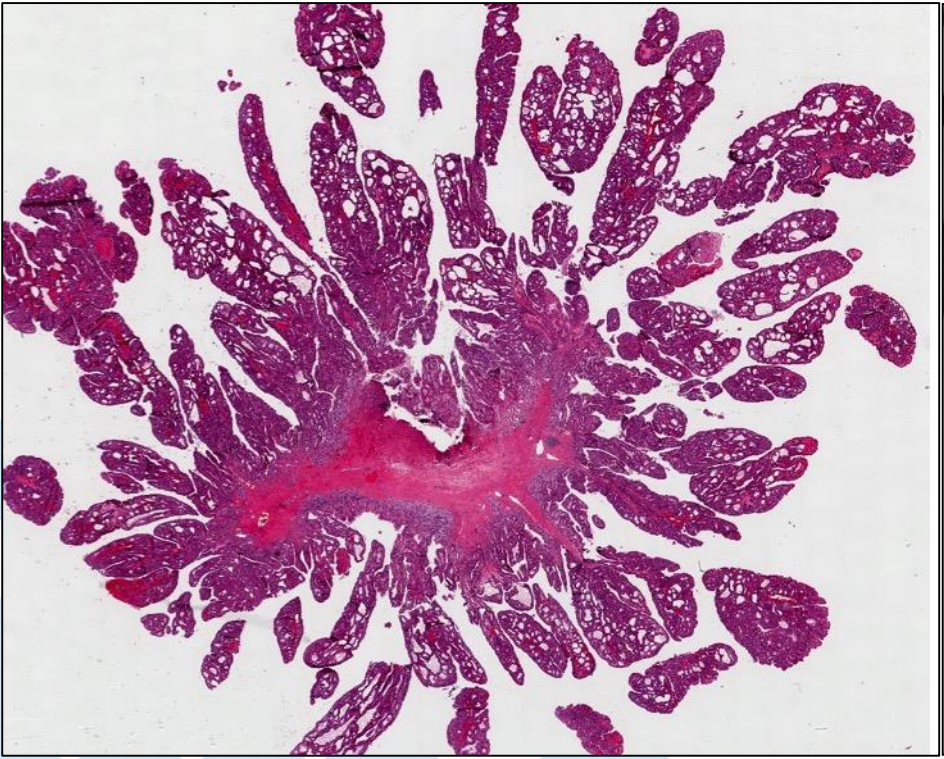
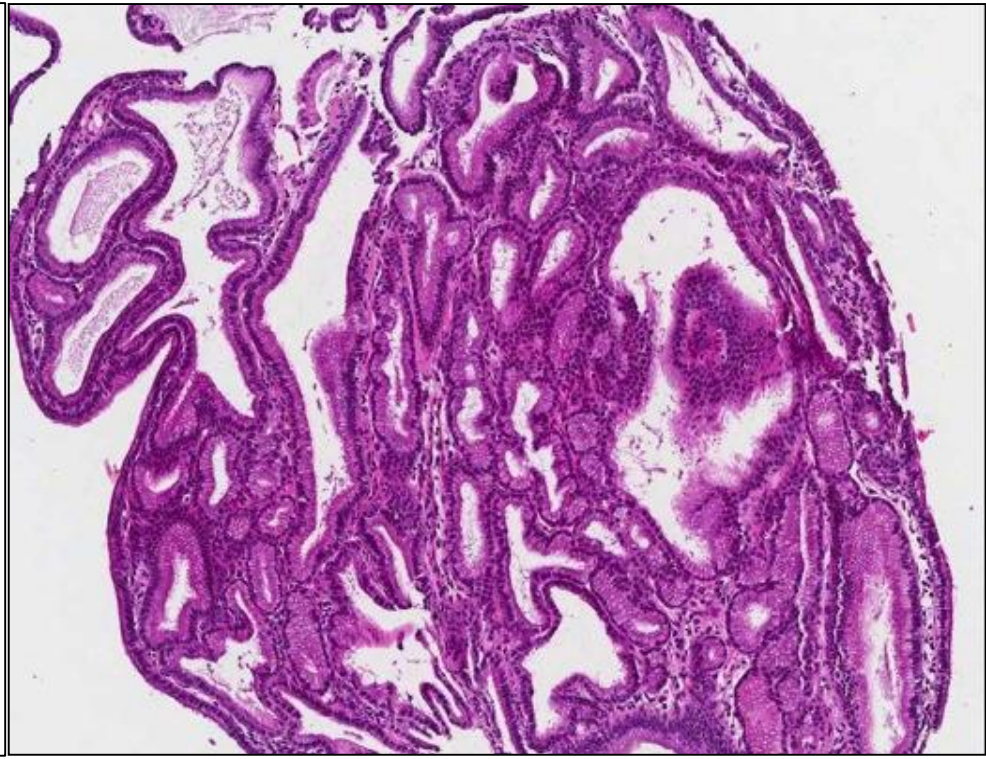
Valente P; Gastric Cancer 2014

Pyloric Gland Adenoma (<3% of all polyps)

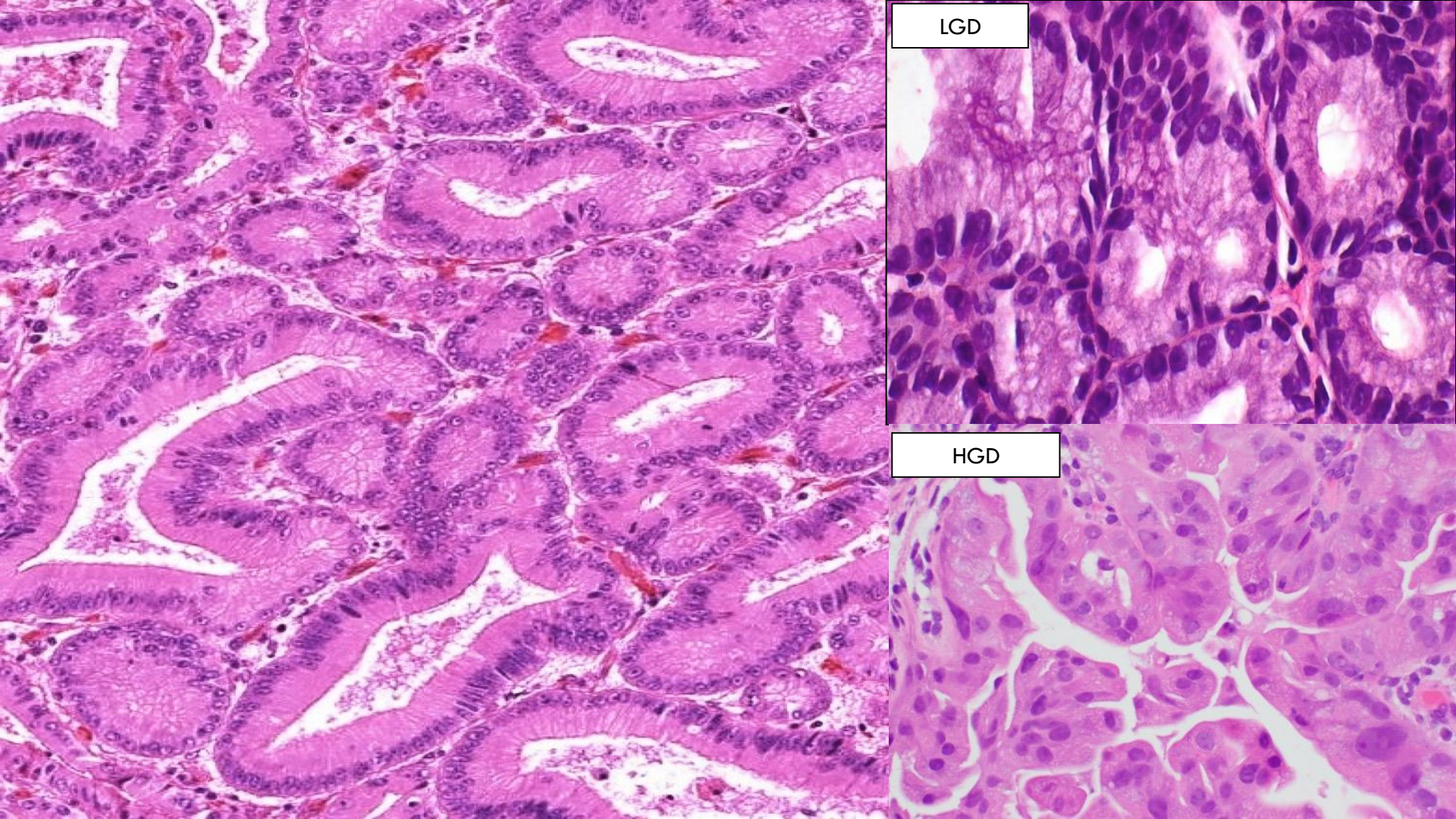
Oberhuber G. Virchows Archiv; 2000; 437:581-90



Tubulo-villous Pyloric gland adenoma

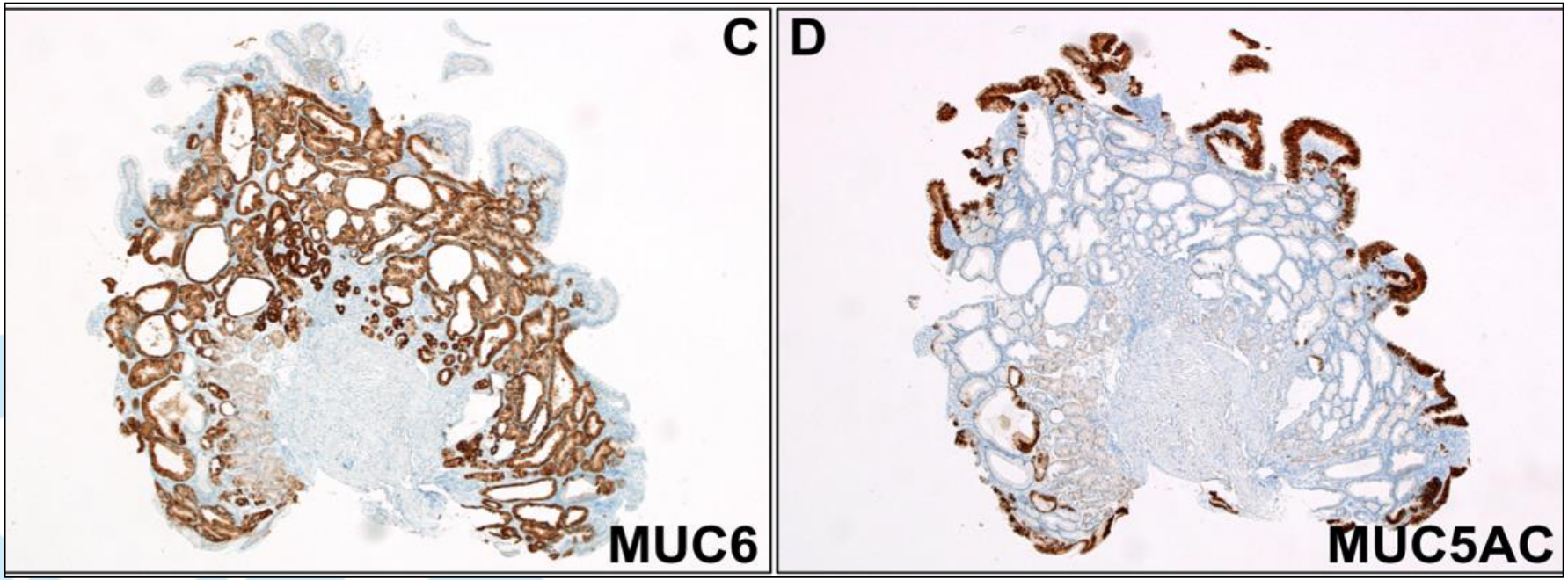


Tubular Pyloric gland adenoma


LGD
HGD

Classic immunophenotype of pyloric gland adenoma

51% co-expressed MUC5AC in an intermixed pattern



TFF2 is also diffusely expressed [MST1 and pepsinogen can be focally expressed]

Choi WT. Histopathology 2018;

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Gastric pyloric gland adenoma

Older pts (mean age: 70 yrs)		
Females > males (3:1)		
Oxyntic mucosa	Antrum (6%),	pylorus (3%)
73% not associated with AIG	36% in normal mucosa	
Cases associated with FAP; Lynch Sd.		

55% LGD [avg:1.7 cm]; 37% HGD [avg:3.4 cm]	*Previously reported 53% w/ HGD*
TVA more commonly asso.ted w/ in HGD (52%) than LGD	
7% w/ recurrence at 1year	

Vieth . J Clin Pathol 2014;38:784-792 Choi WT. Histopathology 2018;

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DUODENUM

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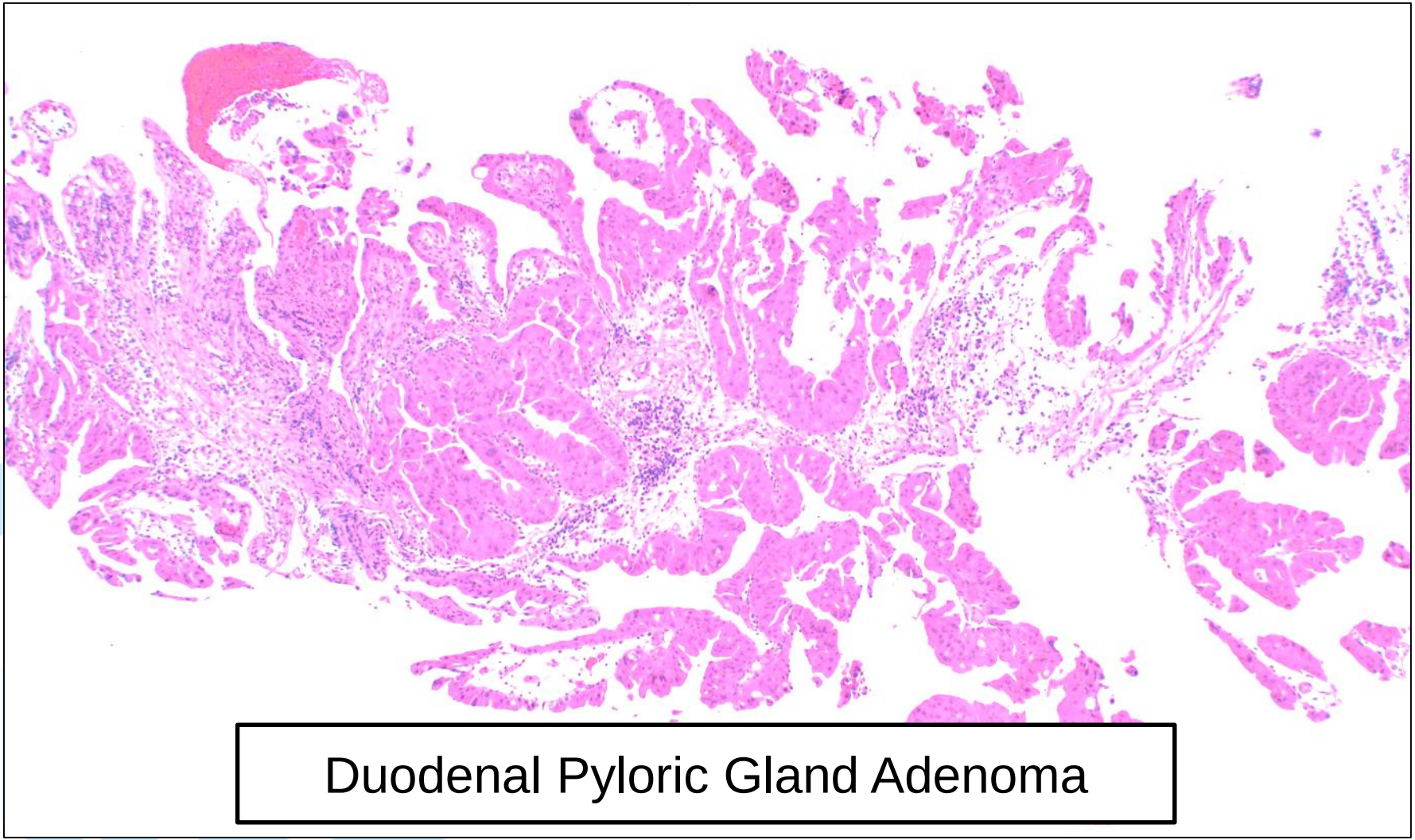

Duodenal Pyloric Gland Adenoma

Duodenal Pyloric Gland Adenoma [n=42]

		LGD (n=25)	HGD (n=17)
Age, (range)		73.4 (54-85)	69.8 (51-77)
Sex, male (%)		13 (52)	9 (56.5)
Location	**D1**	9	10
	D2	4	6
	D3	1	1
	Unknown	11	0
Size, mm (range)		9.5 (2-37)	19.6 (7-60)

P:0.008

Miller G et al. *in print*

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Duodenal Pyloric Gland Adenoma [n=42]

		LGD (n=25)	HGD (n=17)
Gastric heterotopia (%)		4 (16)	4 (23.5)
Architecture	**Tubular (%)**	17 (68)	7(37.5)
	Tubulovillous (%)	8 (32)	10 (62.5)
MUC staining pattern	**Pyloric (%)**	5 (21.7)	4 (28.6)
	Mixed (%)	18 (78.3)	10 (71.4)
Recurrence		1	1
Associated carcinoma		0	4

Miller G et al. *in print.*

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COLON

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Novel Classification of Dysplasia in IBD

Noam Harpaz, John Goldblum, Neil Shepherd, Robert Riddell, Carlos Rubio, Michael Vieth, Robert Odze

Icahn School of Medicine at Mount Sinai, New York, NY; Cleveland Clinic, Cleveland, OH; Gloucestershire Cellular Pathology Laboratory, Gloucester, United Kingdom; Mount Sinai Hospital, Toronto, Canada; Karolinska Institutet, Stockholm, Sweden; Institute of Pathology, Bayreuth Clinic, Bayreuth, Germany and Brigham and Women's Hospital and Harvard Medical School , Boston, MA

BACKGROUND

The classification system for diagnosis and grading of dysplasia in IBD, originally proposed in 1983 by Riddell et al. (Hum Pathol. 1983;14:931-68), has been widely adopted as the standard for clinical and research purposes, but there has been little subsequent effort to address the recently recognized morphological and biological diversity of dysplasia in IBD. The aims of this study were to determine the morphological spectrum of dysplasia in IBD and to develop a reproducible and consistent classification system in order to facilitate future studies on their biology and natural history.

Seven GI pathologists, a
of 200 electronic images
(N.H. and R.O.) collated
distinct morphologic cat
features. After this was
illustrative images of eac
a written description of it
a guide for evaluating a
and R.O.
Each participant also rec
cases and was asked (1
criteria, (2) to indicate w
routine IBD practice, and
possible.
Any image graded negat
from the study. Thus, the

Seven categories of dys
Type 1: conventional adenoma-like dysplasia
Type 2: hypermucinous dysplasia
Type 3: sessile serrated polyp/adenoma-like dysplasia
Type 4: traditional serrated adenoma-like dysplasia
Type 5: dysplasia with "terminal epithelial differentiation"
Type 6: goblet cell-deficient dysplasia
Type 7: serrated dysplasia NOS

The overall diagnostic agreement for dysplasia was excellent Twenty-nine test cases (83%) were diagnosed as definite dysplasia by ≥6 participants and 32 cases (91%) by ≥5 participants.

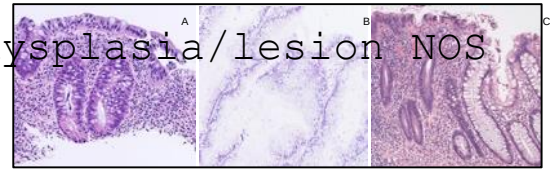
In response to the question as to whether the case was considered familiar based on the participant's routine IBD practice, an affirmative response was given by all 7 participants for 32 (94%) cases and by 6 of 7 for 34 (100%) cases.

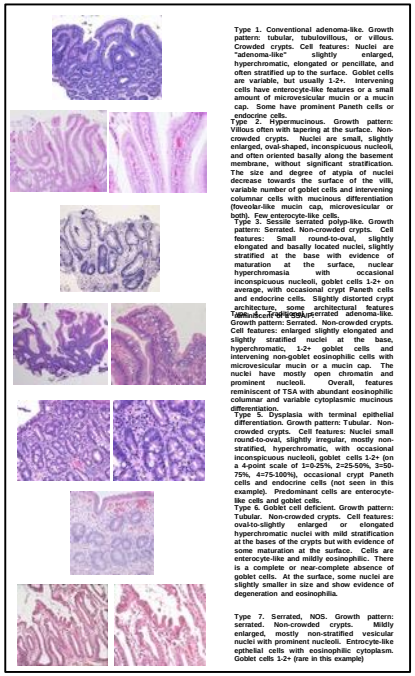
RESULTS (cont.)

Diagnostic agreement for each dysplasia category was also excellent. At least 4 participants were in agreement in 25/35 cases (71%), and ≥5 participants were in agreement in 18 cases (51%). Diagnostic agreement was highest for Types 2, 5 and 6 (Fig. 2), with mean agreement by 6, 4.7 and 4.7 participants (86%, 67%, 67%), respectively (Table).

Dysplasia types 5 and 6 have not been formally described hitherto. They are characterized by non-polypoid growth pattern, non-crowded, evenly distributed crypts, and cytoplasmic features that either simulate the repertoire of normal colonic epithelial cells (Type 5) or are devoid of goblet cells (Type 6).

- Dysplasia with terminal epithelial differentiation
- Hypermucinous dysplasia
- Goblet cell deficient dysplasia
- Sessile serrated polyp/adenoma-like dysplasia
- Traditional serrated adenoma-like dysplasia
- Serrated dysplasia/lesion NOS





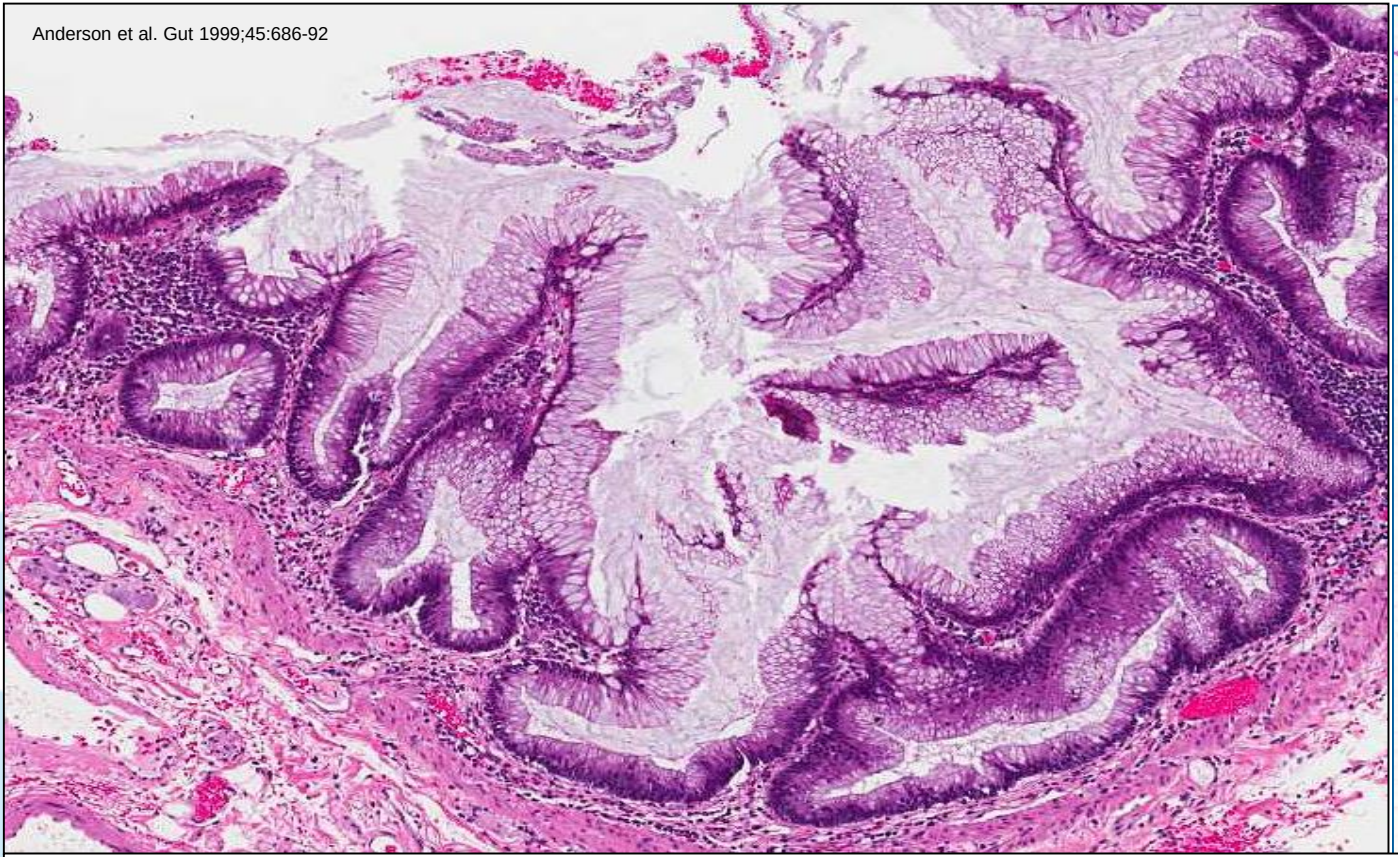
Type 1. Conventional adenoma-like. Growth pattern: tubular, tubulovillous, or villous. Crowded crypts. Cell features: Nuclei are "adenoma-like" slightly enlarged, hyperchromatic, elongated or pencillate, and often stratified up to the surface. Goblet cells are variable, but usually 1-2+. Intervening cells have enterocyte-like features or a small amount of microvesicular mucin or a mucin cap. Some have prominent Paneth cells or endocrine cells.
Type 2. Hypermucinous. Growth pattern: Villous often with tapering at the surface. Non-crowded crypts. Nuclei are small, slightly enlarged, oval-shaped, inconspicuous nucleoli, and often oriented basally along the basement membrane, without significant stratification. The size and degree of atypia of nuclei decrease towards the surface of the villi, variable number of goblet cells and intervening columnar cells with mucinous differentiation (lovesiar-like mucin cap, microvesicular or both). Few enterocyte-like cells.
Type 3. Sessile Serrated polyp-like. Growth pattern: Serrated. Non-crowded crypts. Cell features: Small round-to-oval, slightly elongated and basally located nuclei, slightly stratified at the base with evidence of maturation at the surface, nuclear hyperchromasia with occasional inconspicuous nucleoli, goblet cells 1-2+ on average, with occasional crypt Paneth cells and endocrine cells. Slightly distorted crypt architecture, some architectural features
Type 4. Traditional serrated adenoma-like. Growth pattern: Serrated. Non-crowded crypts. Cell features: enlarged slightly elongated and slightly stratified nuclei at the base, hyperchromatic, 1-2+ goblet cells and intervening non-goblet eosinophilic cells with microvesicular mucin or a mucin cap. The nuclei have mostly open chromatin and prominent nucleoli. Overall, features reminiscent of TSA with abundant eosinophilic columnar and variable cytoplasmic mucinous differentiation.
Type 5. Dysplasia with terminal epithelial differentiation. Growth pattern: Tubular. Non-crowded crypts. Cell features: Nuclei small round-to-oval, slightly irregular, mostly non-stratified, hyperchromatic, with occasional inconspicuous nucleoli, goblet cells 1-2+ (on a 4-point scale of 1=0-25%, 2=25-50%, 3=50-75%, 4=75-100%), occasional crypt Paneth cells and endocrine cells (not seen in this example). Predominant cells are enterocyte-like cells and goblet cells.
Type 6. Goblet cell deficient. Growth pattern: Tubular. Non-crowded crypts. Cell features: ovalto-slightly enlarged or elongated hyperchromatic nuclei with mild stratification at the bases of the crypts but with evidence of some maturation at the surface. Cells are enterocyte-like and mildly eosinophilic. There is a complete or near-complete absence of goblet cells. At the surface, some nuclei are slightly smaller in size and show evidence of degeneration and eosinophilia.
Type 7. Serrated, NOS. Growth pattern: serrated. Non-crowded crypts. Mildly enlarged, mostly non-stratified vesicular nuclei with prominent nucleoli. Entrocyte-like epithelial cells with eosinophilic cytoplasm. Goblet cells 1-2+ (rare in this example)

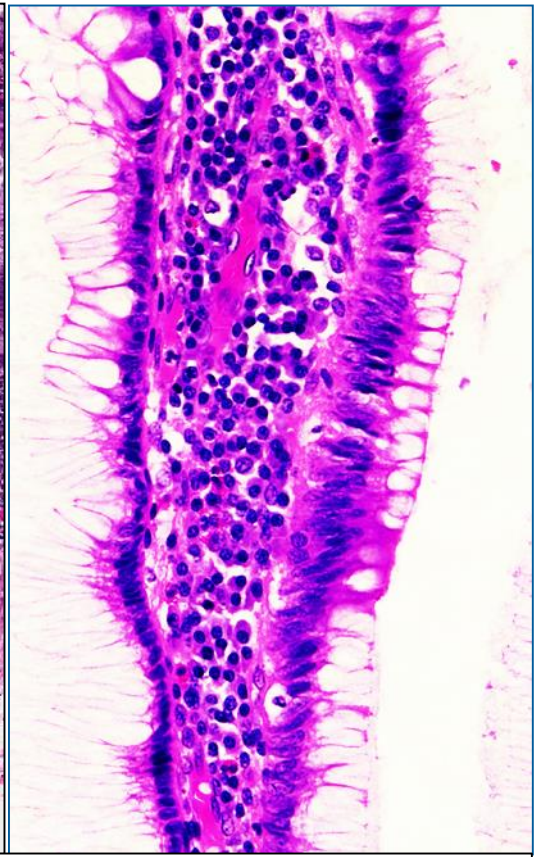
Fig. 1. Morphologic dysplasia categories. Each participant was initially provided these images with a written description of their salient morphological features.

Fig. 2. Examples of test cases provided to participants for classification. These categories yielded the highest degrees of agreement among the participants. A. Dysplasia with terminal epithelial differentiation. B. Hypermucinous dysplasia. C. Goblet cell-deficient dysplasia.

	HYPERMUCINOUS	INTESTINAL TYPE		CRYPT CELL TYPE	SERRATED TYPE		
	Hypermucinous	**Dysplasia with increased Paneth cell differentiation**	**Goblet cell deficient**	**Crypt Cell Dyspl./ Terminal epithelial diff.**	**TSA-like**	**SSL-like**	**Serrated lesion NOS**
Architecture	Tubulovillous/villous	Tubular	Tubular	Flat	Tubulovillous/ villous with serration	Tubular w/ serration	Tubular with serration
Defining features	Tall mucinous cells with elongated, hyperchromatic nuclei, minimal nuclear atypia Hypermucinous > 50% of the lesion	Intestinal type cells with elongated, hyperchromatic nuclei Increased Paneth cell differentiation involving at least 2 contiguous crypts in 2 different foci (beyond what is present in background mucosa)	Intestinal type cells w/ elongated hyperchromatic nuclei Complete or near-complete absence of goblet cells	Mostly round-to-oval, non-stratified nuclei Atypia can be limited to the crypt base without surface involvement	Columnar cells with mostly elongated nuclei, intensely eosinophilic cytoplasm, and ectopic crypts TSA-like represent > 50% of the lesion	Prominent serration & dilation at crypt base and surface, including dilated L- or inverted T-shaped crypts at the interface wi/ muscularis mucosa SSL-like component should represent > 50% of the lesion	Often complex serration but without definite features of TSA or SSL Serrated lesion NOS component should represent > 50% of the lesion
Other features	Degree of atypia tends to decrease from the crypts to the surface of the villi	Some loss of goblet cells allowed, but no complete or near-complete absence of goblet cells	Scattered Paneth cells allowed, but not in multiple clusters of dysplastic crypts as seen in DPD	Some loss of goblet cells allowed, but no complete or near-complete absence of goblet cells		Dysplasia, can be confined to the lower portion or involve the entire thickness of the mucosa	Dysplasia, which can be confined to the lower portion or involve the entire thickness of the mucosa

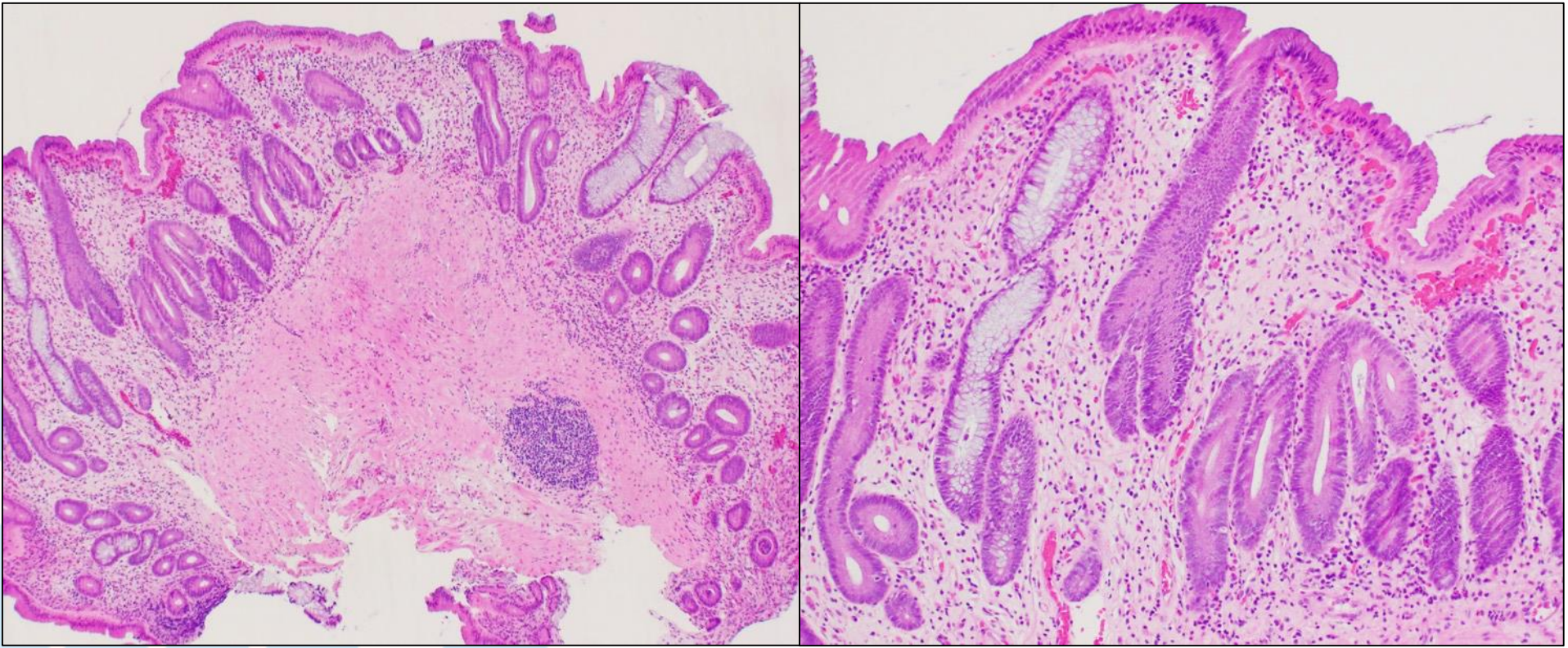
Villiform hypermucinous dysplasia





Variable # of goblet cells & columnar cells with mucinous differentiation. Few enterocyte-like cells. Small nuclei, slightly enlarged, oval-shaped, and often oriented basally w/o significant stratification

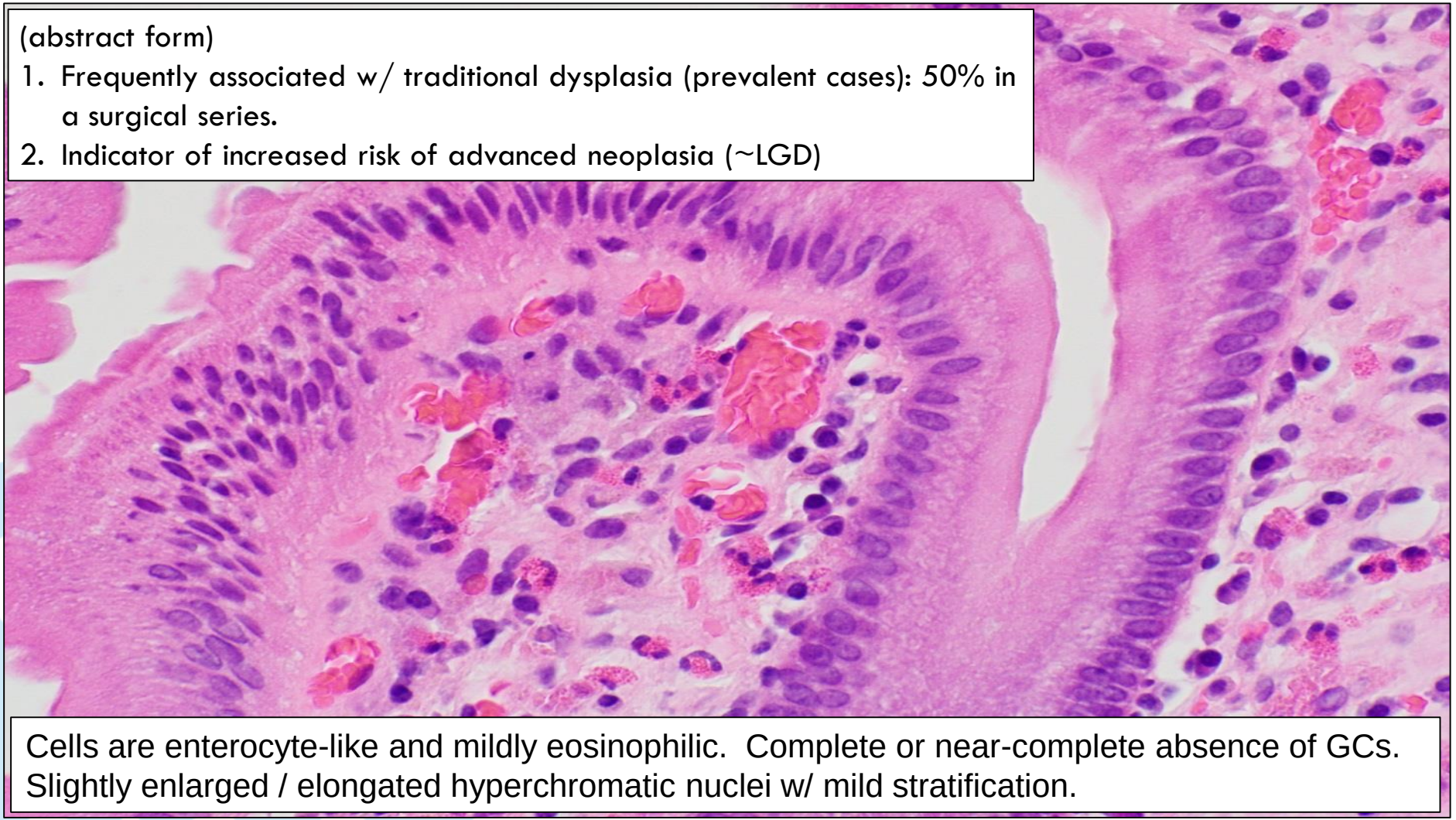
“Goblet cell deficient” type dysplasia



Tubular growth pattern; Non-crowded crypts. Mildly eosinophilic enterocyte-like cells

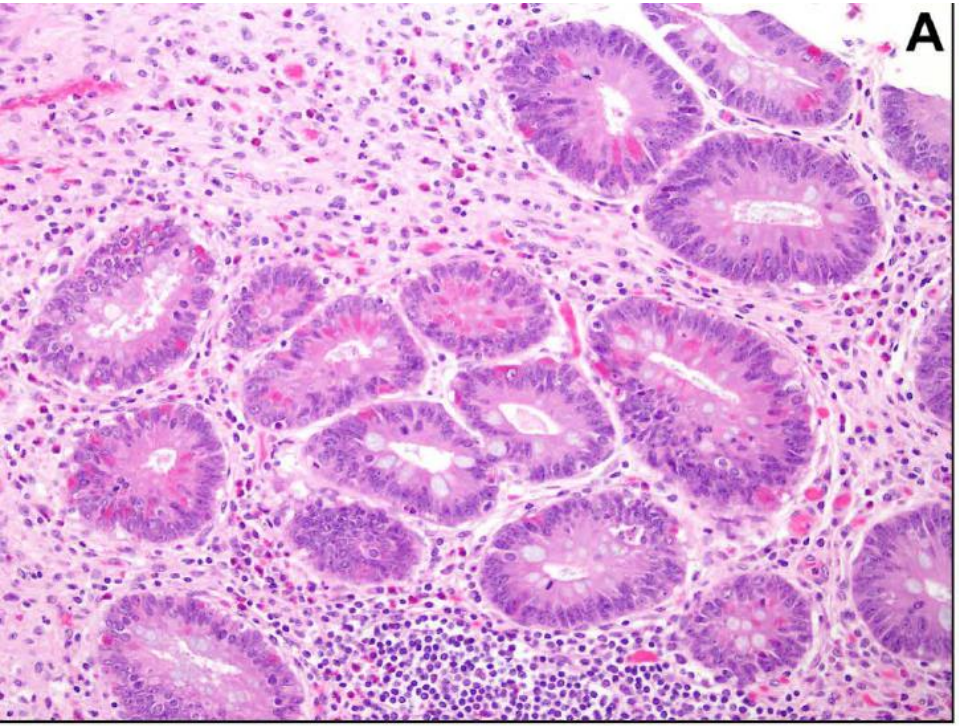
(abstract form)

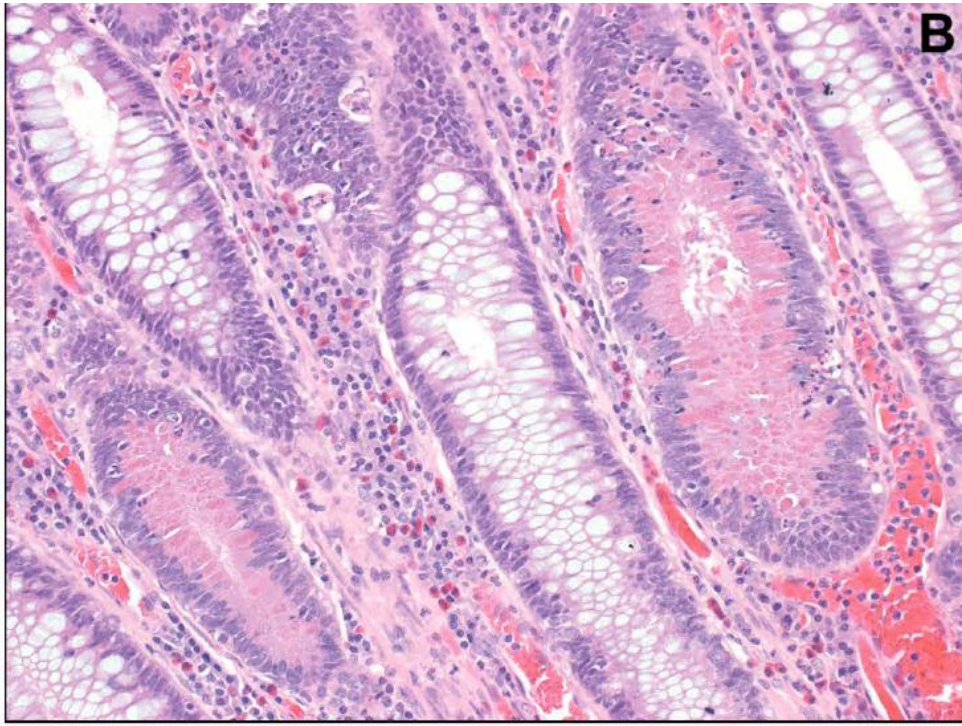
1. Frequently associated w/ traditional dysplasia (prevalent cases): 50% in a surgical series.
2. Indicator of increased risk of advanced neoplasia (~LGD)



Cells are enterocyte-like and mildly eosinophilic. Complete or near-complete absence of GCs. Slightly enlarged / elongated hyperchromatic nuclei w/ mild stratification.

Dysplasia with increased Paneth cell differentiation





Elongated, hyperchromatic nuclei and increased Paneth cell differentiation present in clusters of crypts. Despite some loss, goblet cells are easily identified.

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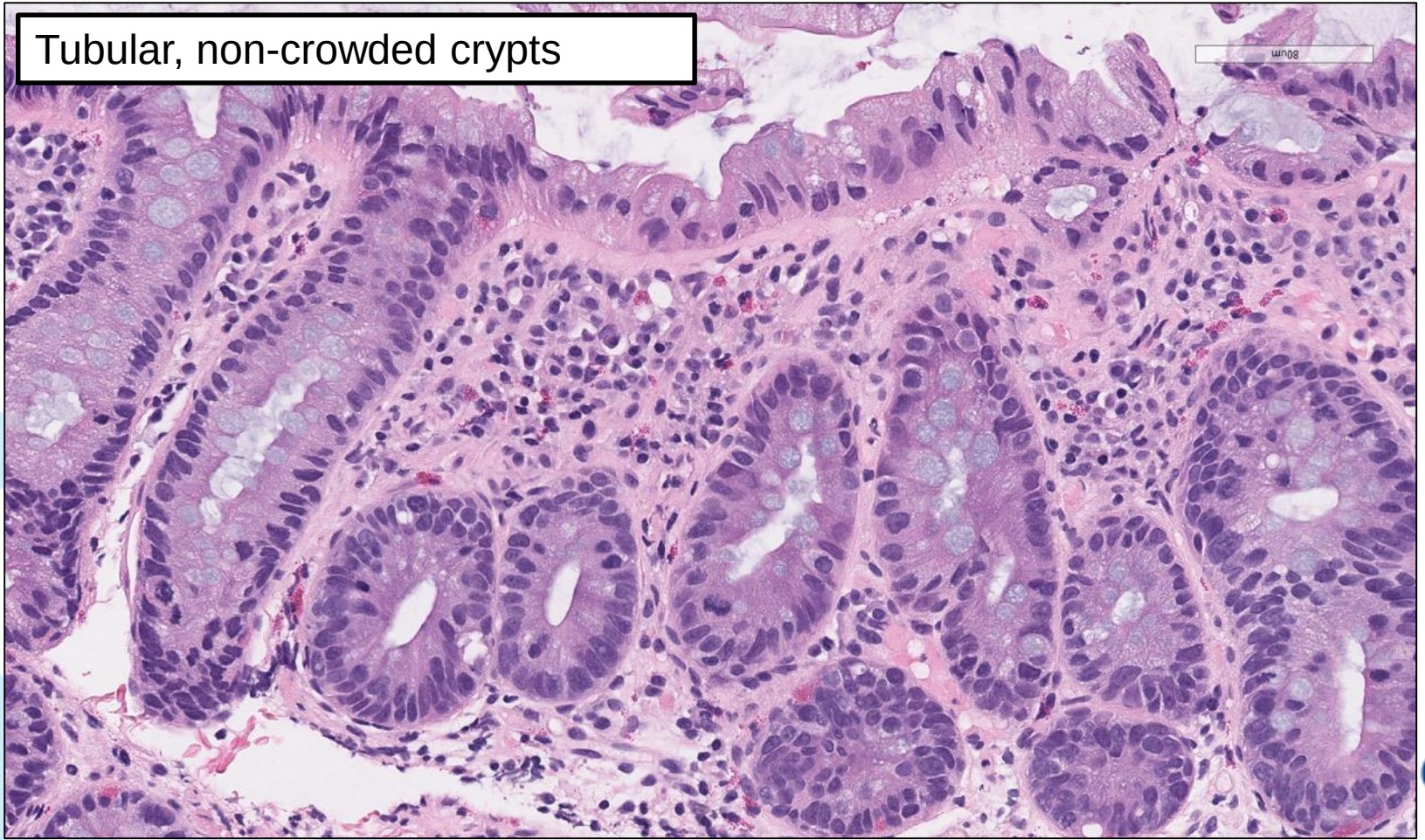
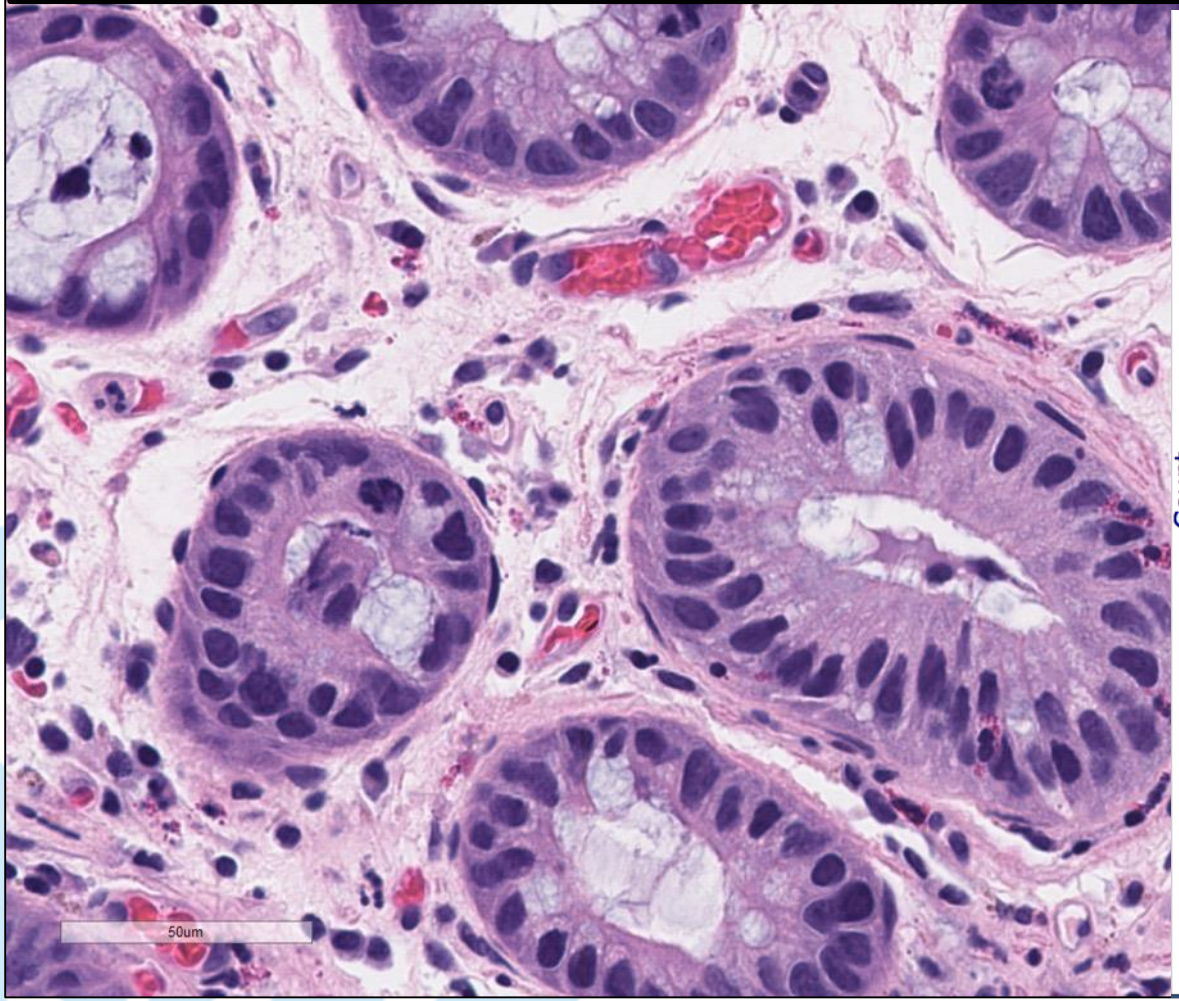
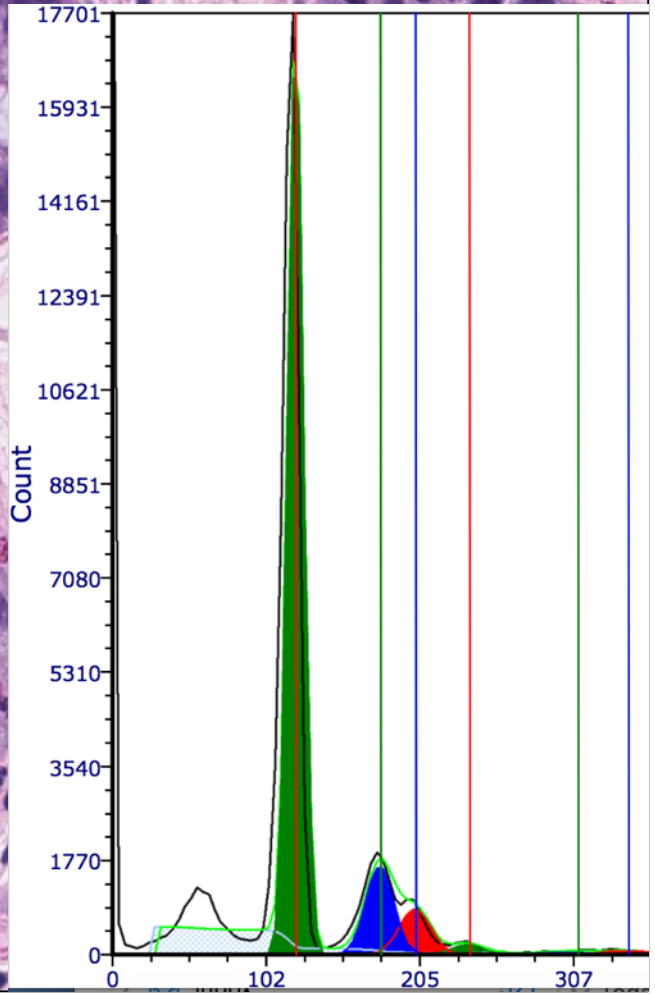
Crypt cell dysplasia /Dysplasia w/ terminal epithelial differentiation



Small round-to-oval nuclei, slightly irregular, mostly non-stratified, hyperchromatic





Crypt cell dysplasia -Dysplasia w/ terminal differentiation

- 14 foci from 7 UC pts (M:F=5:2; mean age 53 years)
- Mean IBD duration:15 years
- NONE *except one*, had a previous dx of dysplasia
- Flat lesions (n = 12) or normal appearing mucosa (n = 2).
- *Aneuploidy* was detected in all 14 cases.
- Follow up on 6 pts (mean: 25 months)
  - Five (71%) developed HGD (n = 4) or ACA (n = 1)
  - One patient: multiple follow-up bx w/o a definite dx of dysplasia.

Wen KW, Histopathology 2019;75:578-588.

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Serrated changes / dysplasia in IBD

- (Hyperplastic polyp)
- *Sessile Serrated Polyp/Adenoma - like*
- *Traditional Serrated Adenoma - like*
- *Serrated dysplasia unclassified*
- Serrated epithelial changes, *NOS*

  - Prevalence:1.2 % to 1.9 % Aliment Pharmacol Ther 2014;39:1408-17; / Ko. HM Mod Pathol 2015

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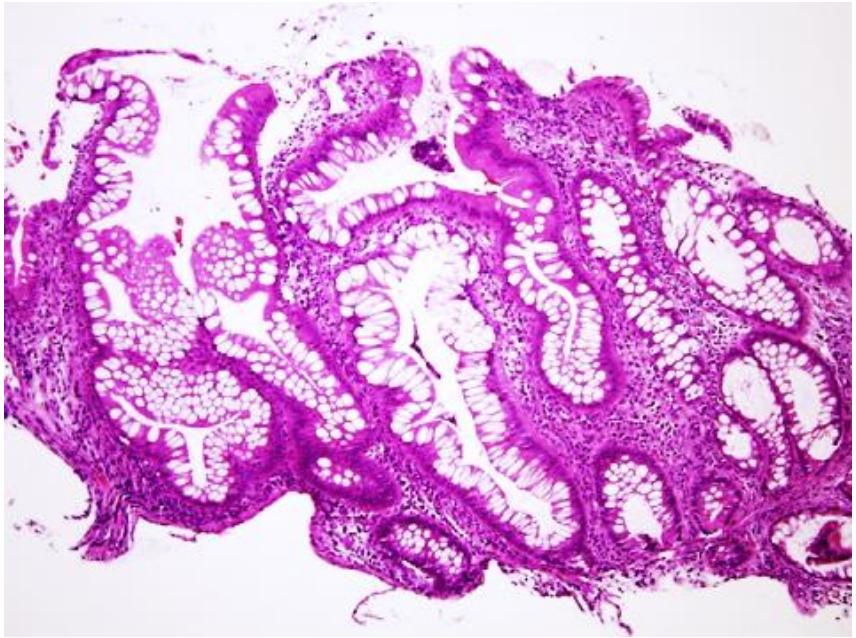
Serrated epithelial change (SEC) in IBD

1 Hyperplastic- like mucosal changes

2 Flat serrated changes

and

3 ≠ SSA/P



- *Not consistently recognized endoscopically with only 22% seen on targeted bx*

Parian A. GIE 2016;84:87

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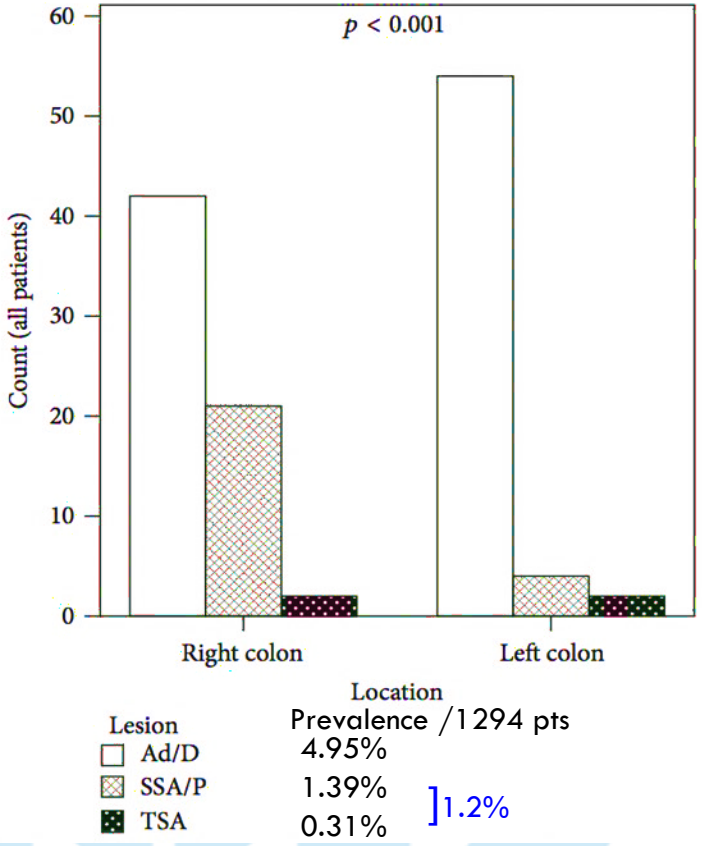
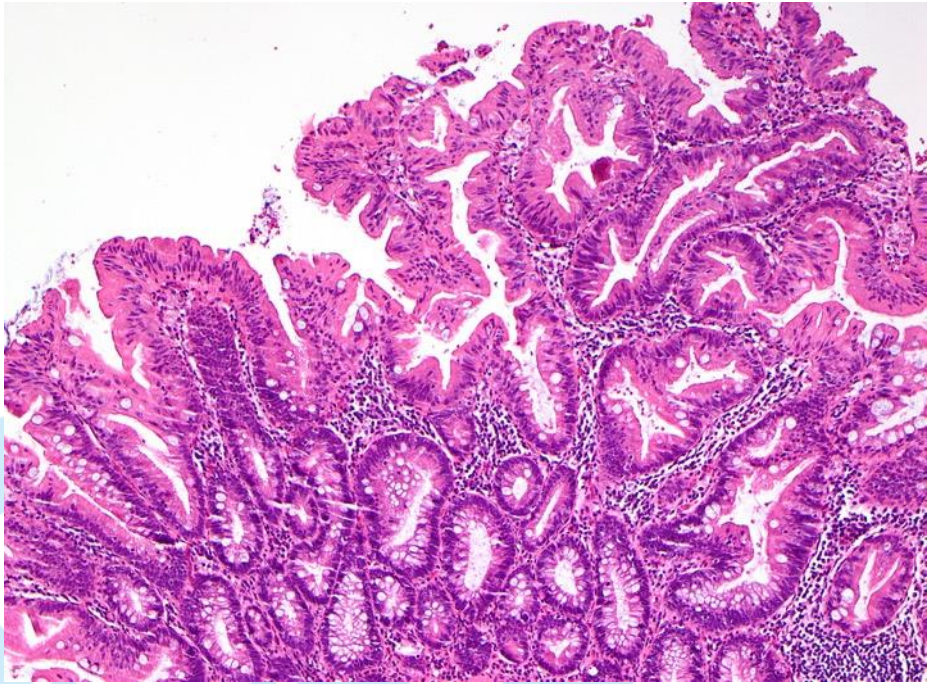
Serrated changes / dysplasia in IBD

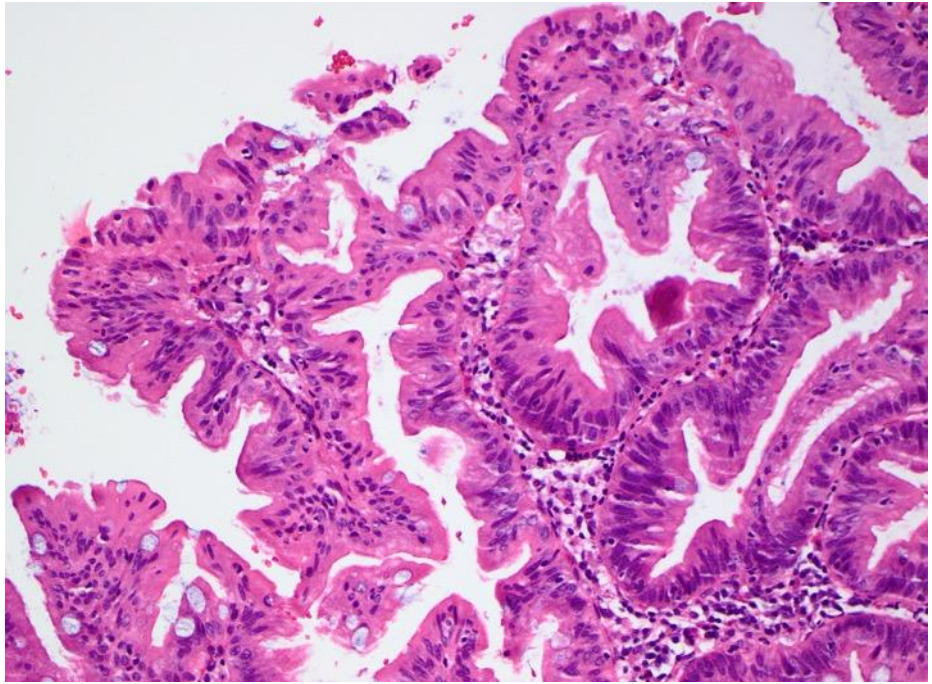


- SSA/SSP like lesions
  - F > M
  - Prox. Colon w/ BRAF mutations.
- TSA like lesions
  - M> F
  - Distal colon w/ KRAS mutations.
- Serrated polyps indef. for dysplasia
  - Morphologically heterogeneous
  - Similar TSA like lesions: M predominance, Distal location, and KRAS mutation rates.

Lee LH. Can J Gastroentetrol Hepatol 2017 / Ko. HM Mod Pathol 2015

Serrated dysplasia





Serrated dysplasia in 12-29% vs 6% in non-UC patients

.(Rubio CA. J Gastroenterol-Hepatol 2007)

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Characteristics of non conventional IBD dysplasia

Cohort of 58 IBD pts with CRC w/ mean duration of 17 years

- 36 foci of NCD in 26 pts [45%]
- 70 foci of traditional dysplasia foci in 46 pts [78%]
- 12 of the 26 pts (46%) had only NCD --remaining 14 pts had NCD+ conventional dysplasias [same colonic segment in all but 3 (79%)]
- ***Hypermucinous dysplasia (42%)***
  - 'pure' (14%) or 'mixed type' (28%), w/ either traditional dysplasia or another type of NCD.
- ***Serrated 'changes' (42%)***
  - TSA-like (28%), SSA-like (3%), and serrated NOS (11%).
- ***Dysplastic lesions w/ increased Paneth cell differentiation (11%)***
- ***Goblet Cell Deficient (5%)***

Submitted to Modern Pathology.

NCD: Non conventional dysplasia

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Characteristics of non conventional IBD dysplasia

Cohort of 58 IBD pts with CRC w/ mean duration of 17 years

- When alone, NCD is predominantly found in the left colon (81%, p= 0.006) as a raised lesion (75%, p = < 0.001) compared to when it occurs simultaneously w/ conventional dysplasia (35% & 50%, respectively).

- NCD commonly detected in the same segment as CRC or immediately adjacent to CRC at a rate (85%) similar to conventional dysplasia (96%).

- CRCs associated w/ NCD showed:
  - No difference in age/sex, type/duration of IBD or in size, pT stage or location
  - ***but*** *CRC occurring in pts w/ only NCD were more likely to be poorly differentiated (36%) than those associated w conventional dysplasia (10%) (p = 0.026).*

Submitted to Modern Pathology.

NCD: Non conventional dysplasia

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Evolving Concepts in Dysplasia in Gut

Evolving Concepts in Detection

Advances in Endoscopy

- *Standard WLE*
- *High Def.*
- *Chromoendoscopy*
- *NBI*
- *(in vivo microscopy)*

Evolving Concepts in Management

- Endoscopic management
- Surveillance
- Surgery

Evolving Concepts in Histopathologic Interpretation

- Recognition of new ‘dysplastic’patterns

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	NCD only (n= 16, 12 pts)	CD only (n=51, 32 pts)	NCD (n = 20) + CD (n = 19) (14 pts)	P-values
Non-conventional dysplasia				
Hypermucinous	7 (44%)		8 (21%)	
Dyspl.w/ Paneth Cell Differentiation			1 (3%)	
Goblet Cell Deficient	0 (0%)		2 (5%)	
TSA-like	3 (19%)		7 (18%)	
SSL-like	1 (6%)		0 (0%)	
Serrated lesion,NOS	2 (13%)		2 (5%)	
Conventional dysplasia				
TA-like		37 (73%)	14 (36%)	
TVA-like		12 (24%)	4 (10%)	
VA-like		2 (4%)	1 (3%)	
Grade of dysplasia (%)	14 LGD (88%)	20 LGD (39%)	21 LGD (54%)	0.003
Location of dysplasia (%)				0.006
Left colon	13 (81%)	30 (59%)	14 (36%)	
Transverse colon	0 (0%)	8 (16%)	9 (23%)	
Right colon	2 (13%)	13 (25%)	15 (38%)	
Entire colon	0 (0%)	0 (0%)	1 (3%)	
Unknown	1 (6%)	0 (0%)	0 (0%)	
Endoscopic appearance (%)	12 Polypoid/raised (75%)	46 Polypoid/raised (90%)	18 Polypoid/raised (46%)	< 0.001