

Pathologist Experience and Concordance in the Diagnosis of Dysplasia in Long-standing Inflammatory Bowel Disease

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汇报人：贾旭春

- IBD Inflammatory bowel disease 炎症性肠病
- CRC Colorectal cancer 结直肠癌
- NEG Negative for dysplasia 无异型增生
- IND Indefinite for dysplasia 不确定异型增生
- LGD Low-grade dysplasia 低级别异型增生
- HGD High-grade dysplasia 高级别异型增生
- ADC Adenocarcinoma 腺癌

- 长期IBD患者发生CRC危险性增高
- 最近研究>20年为5%
- 广泛病变可高达50%
- CRC逐步转化过程
- 慢性炎症 → LGD → HGD → CRC
- 内镜监测发现异型增生，预防癌发生

异型增生

- 癌前病变
- 细胞学和/或组织结构改变，无浸润性证据
- 恶性转化的较强预测因子
- 分类决定临床监督管理策略

Vienna

1. Negative for neoplasia/dysplasia
 2. Indefinite for neoplasia/dysplasia
 3. Non-invasive low grade neoplasia
(low grade adenoma/dysplasia)
 4. Non-invasive high grade neoplasia
 - 4.1 High grade adenoma/dysplasia
 - 4.2 Non-invasive carcinoma
(carcinoma *in situ*)
 - 4.3 Suspect for invasive carcinoma
 5. Invasive neoplasia
 - 5.1 Intramucosal adenocarcinoma
 - 5.2 Submucosal carcinoma or beyond
-

Negative for dysplasia

- Architecture normal
- Surface maturation (nuclear–cytoplasmic ratio of surface cells is lower than of deeper glands)
- Cytology normal (nuclear polarity normal, which means size not different and located basally)

Indefinite for dysplasia

- Architecture normal
- Surface maturation
- Cytology: mild alterations (nuclear membrane irregularities, increased mitoses in deeper glands, inflammation)

Low grade dysplasia

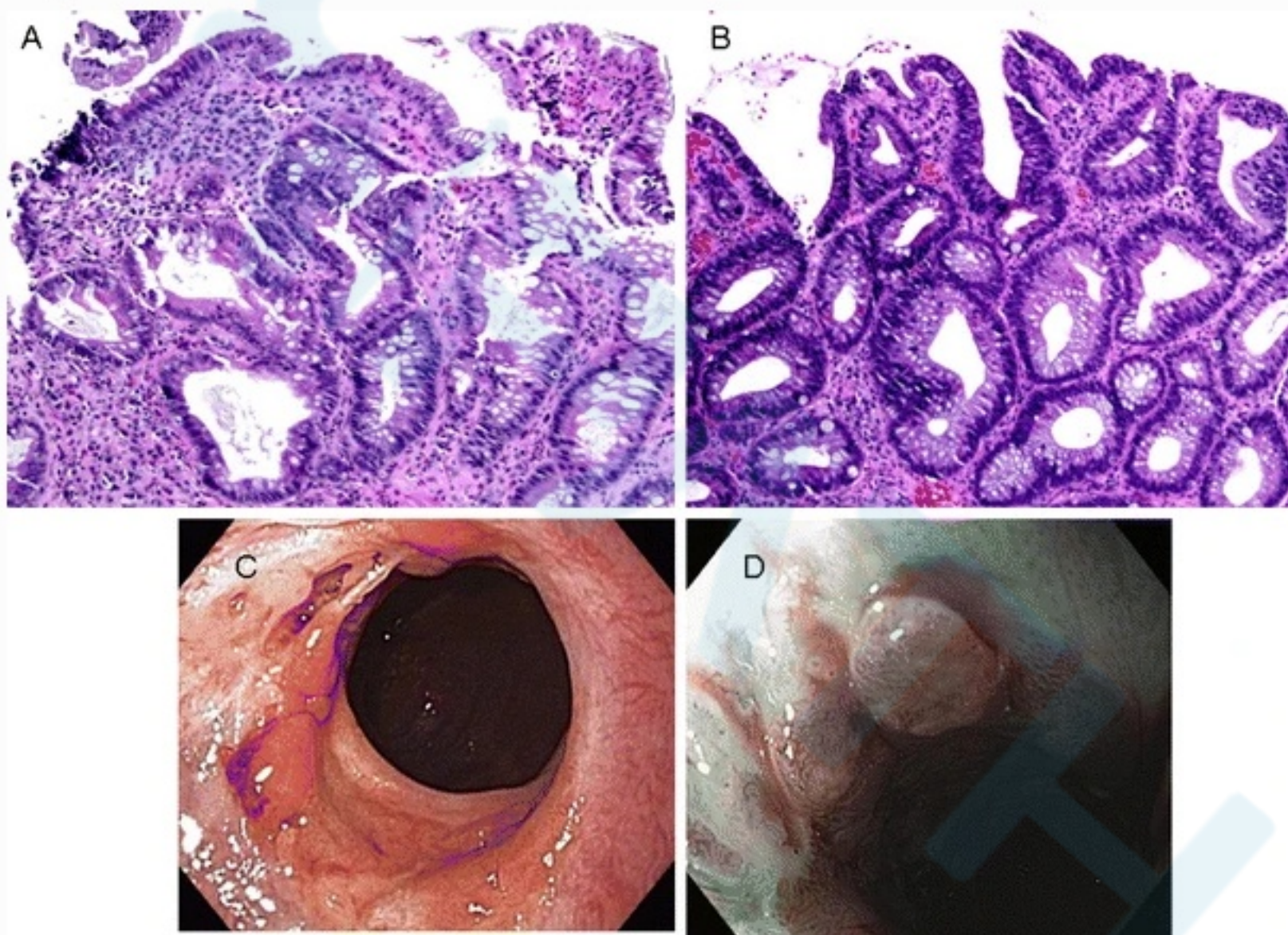
- Architecture mildly altered (glandular crowding, but identifiable lamina propria)
- Surface maturation distorted (surface similar to deeper glands)
- Cytology: mild, diffuse alterations (nuclear hyperchromasia, nuclear membrane irregularities, nuclear polarity normal)

High grade dysplasia

- Architecture markedly altered (crowding of cytologically abnormal glands)
- Surface maturation lacking
- Cytology: marked alterations (nuclear hyperchromasia, prominent irregular nucleoli with clumped chromatin, loss of nuclear polarity)

Intramucosal carcinoma

- Architecture markedly altered (lamina propria effaced, penetration through basement membrane into lamina propria, syncytial growth pattern, extensive back-to-back microglands)
 - Surface maturation lacking
 - Cytology: marked alterations
-



Clinical Significance of Indefinite for Dysplasia on Pouch Biopsy in Patients with Underlying Inflammatory Bowel Disease . [Journal of Gastrointestinal Surgery](#) 2012 Vol.16 562-571

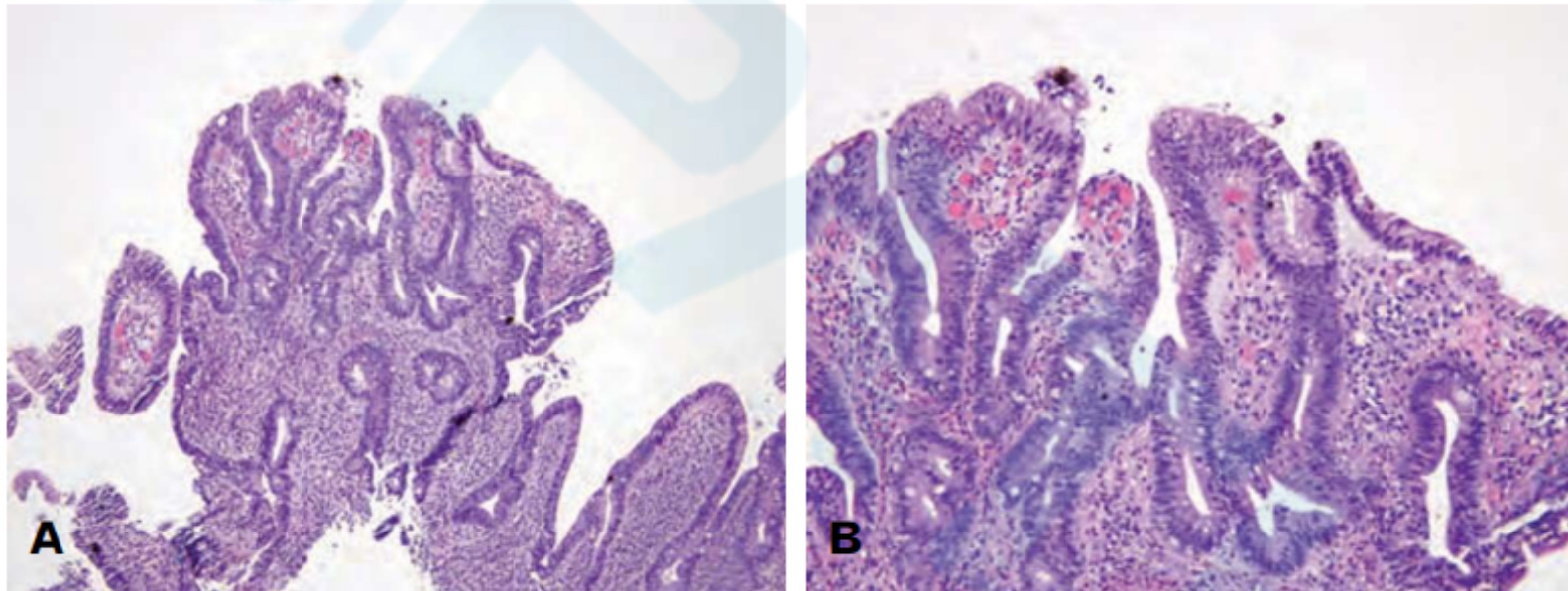


Fig. 7 (A) Low grade dysplasia in inflammatory bowel disease. The lesion shows a villiform surface. (B) There is lack of surface maturation. Nuclear stratification and atypia is seen.

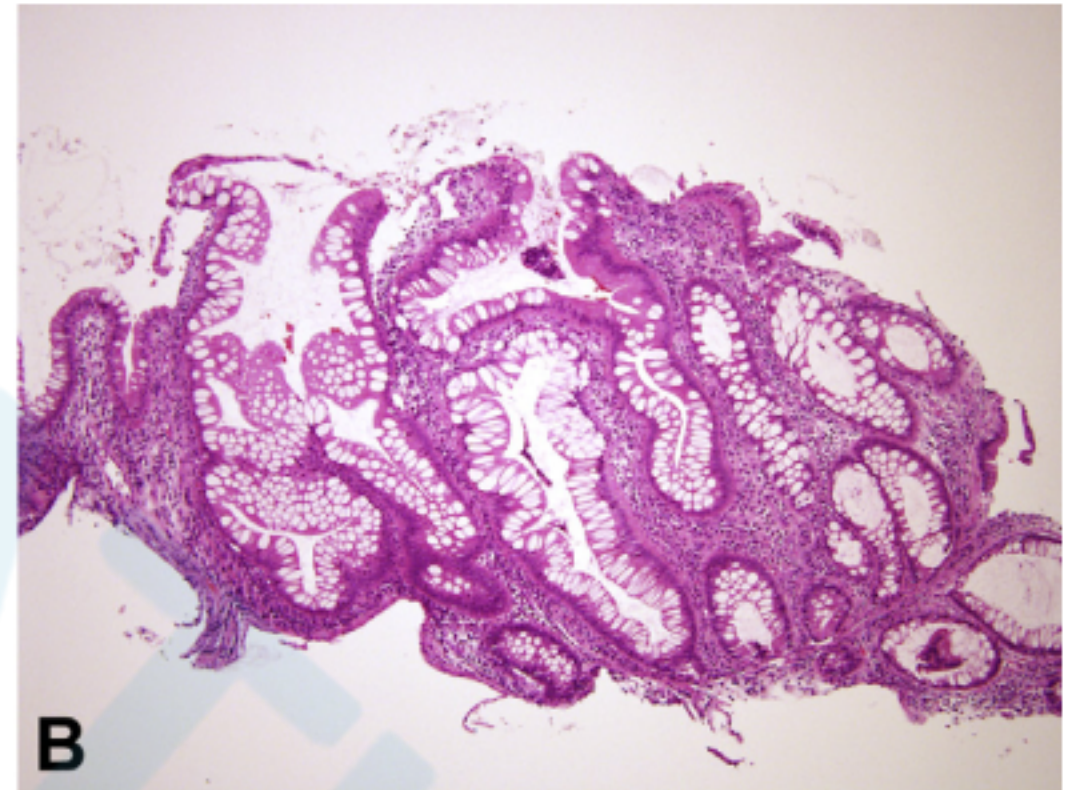
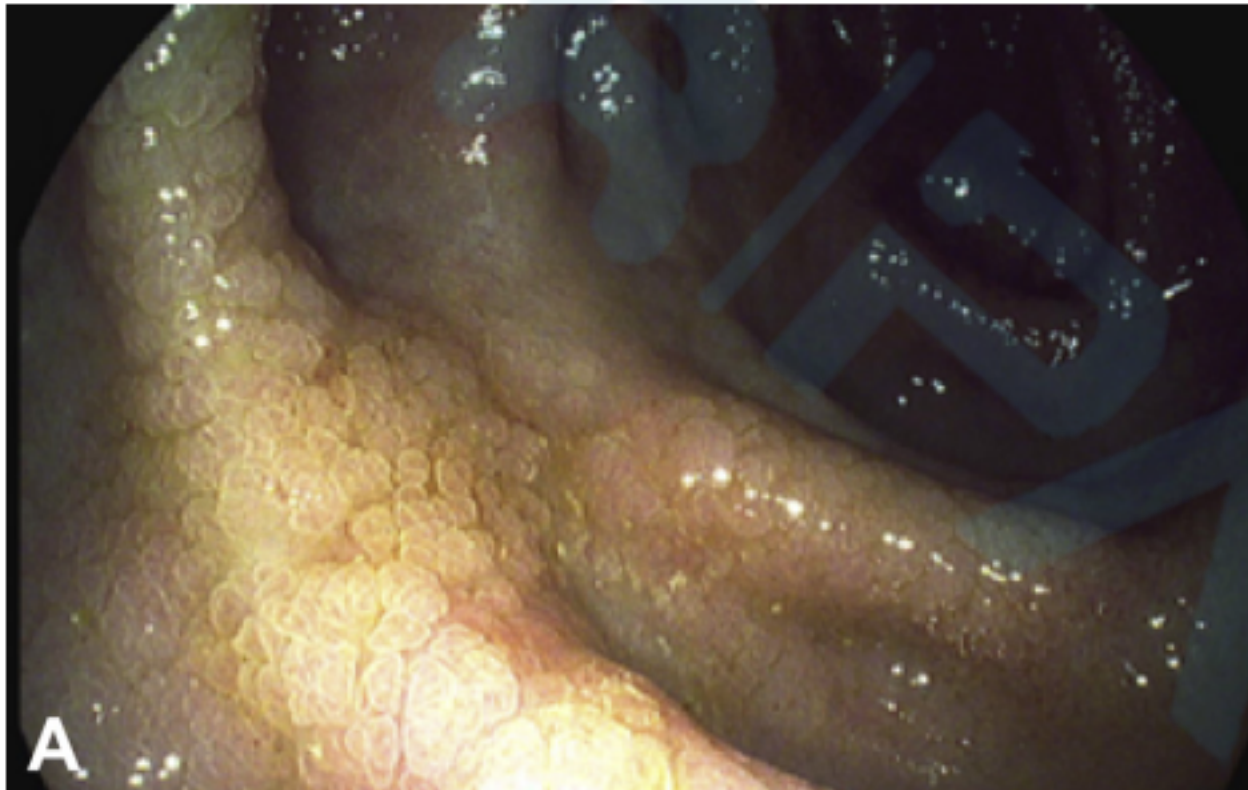


Figure 1. A, Endoscopic picture of SEC. **B,** Histologic picture of serrated epithelial change.

Association between serrated epithelial changes and colorectal dysplasia in inflammatory bowel disease. *Gastrointest Endosc* 2016;84:87-95.

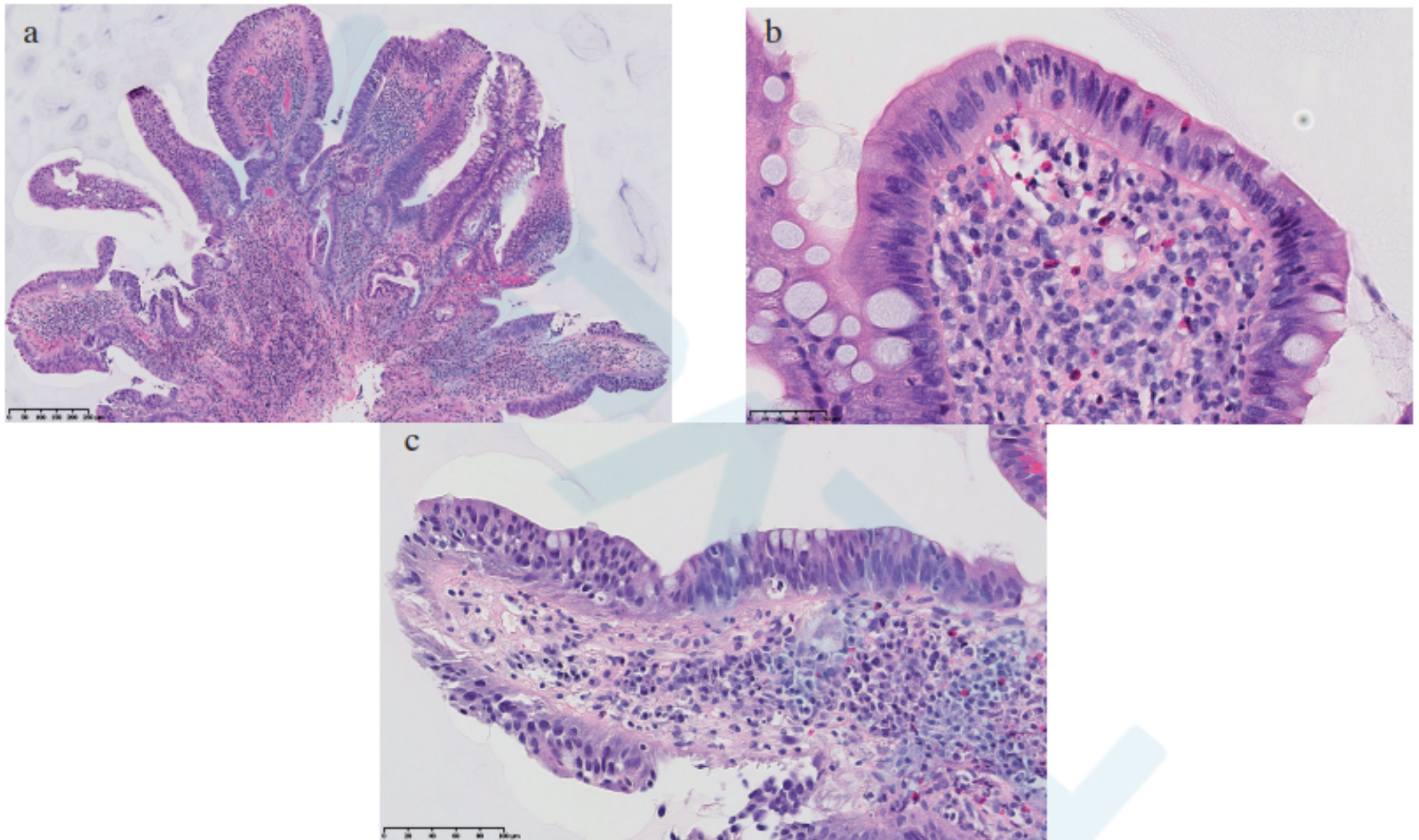
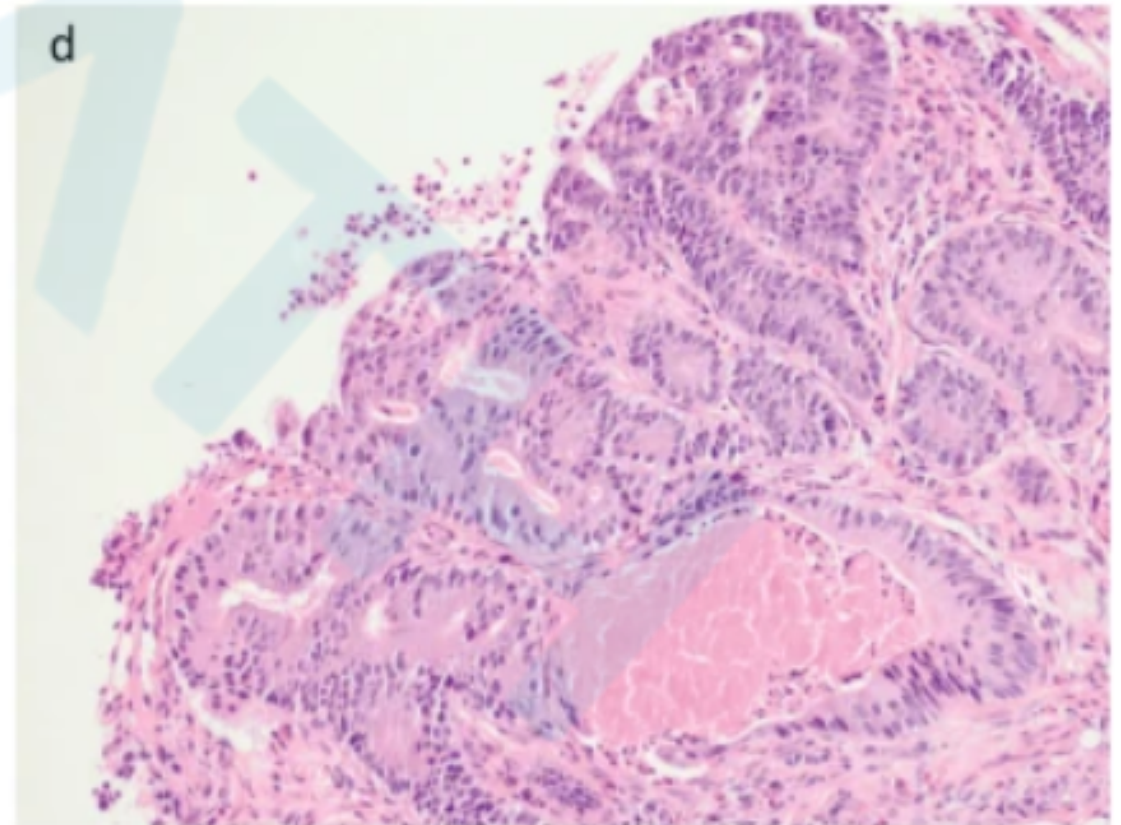
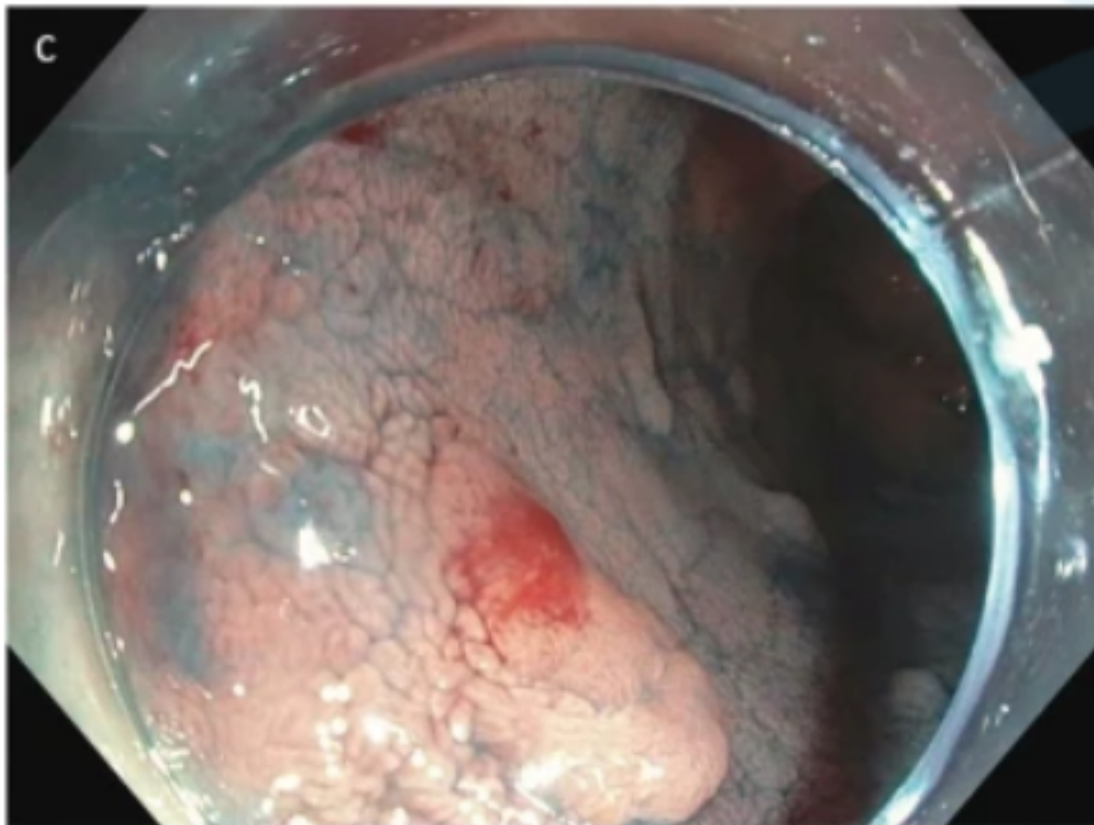
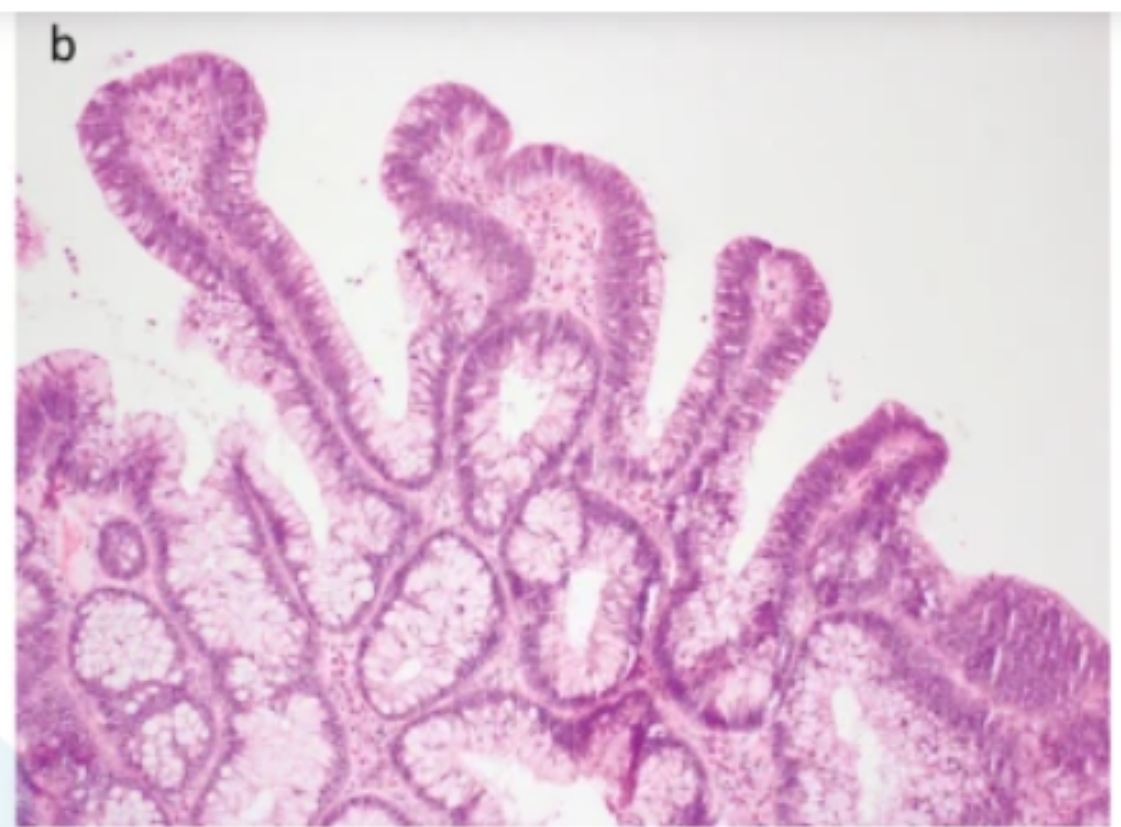
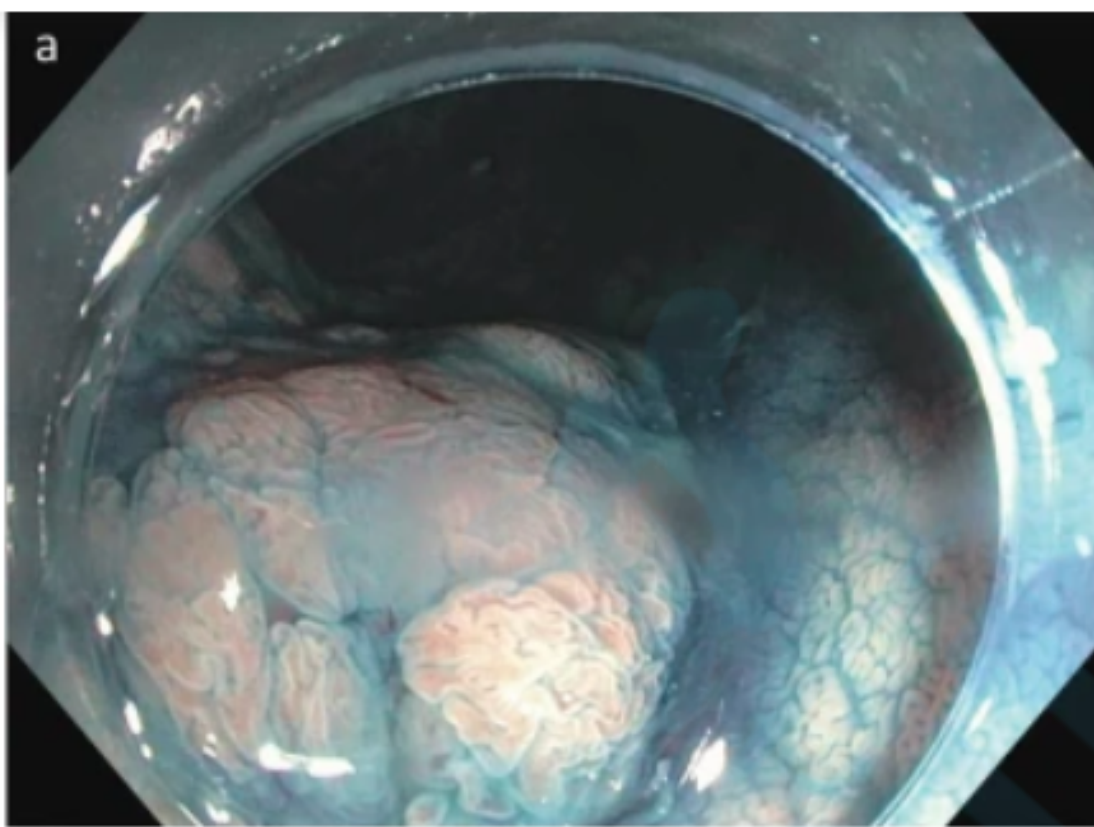


Fig. 3. — Colitis-associated dysplasia: Polypoid dysplasia (a, HE, 8.3X) with an adenomatous type of dysplasia, consisting of areas of low grade dysplasia, showing a pseudostratified epithelium with mild cytologic atypia (b, HE, 40X) and high grade dysplasia, characterized by a pseudostratified epithelium with nuclear polymorphisms (c, HE, 31X), in stead of original text.



DALM, rest in peace: a pathologist's perspective on dysplasia in inflammatory bowel disease
 In the post-DALM era. [Modern Pathology](#) volume 31, 1180–1190(2018)

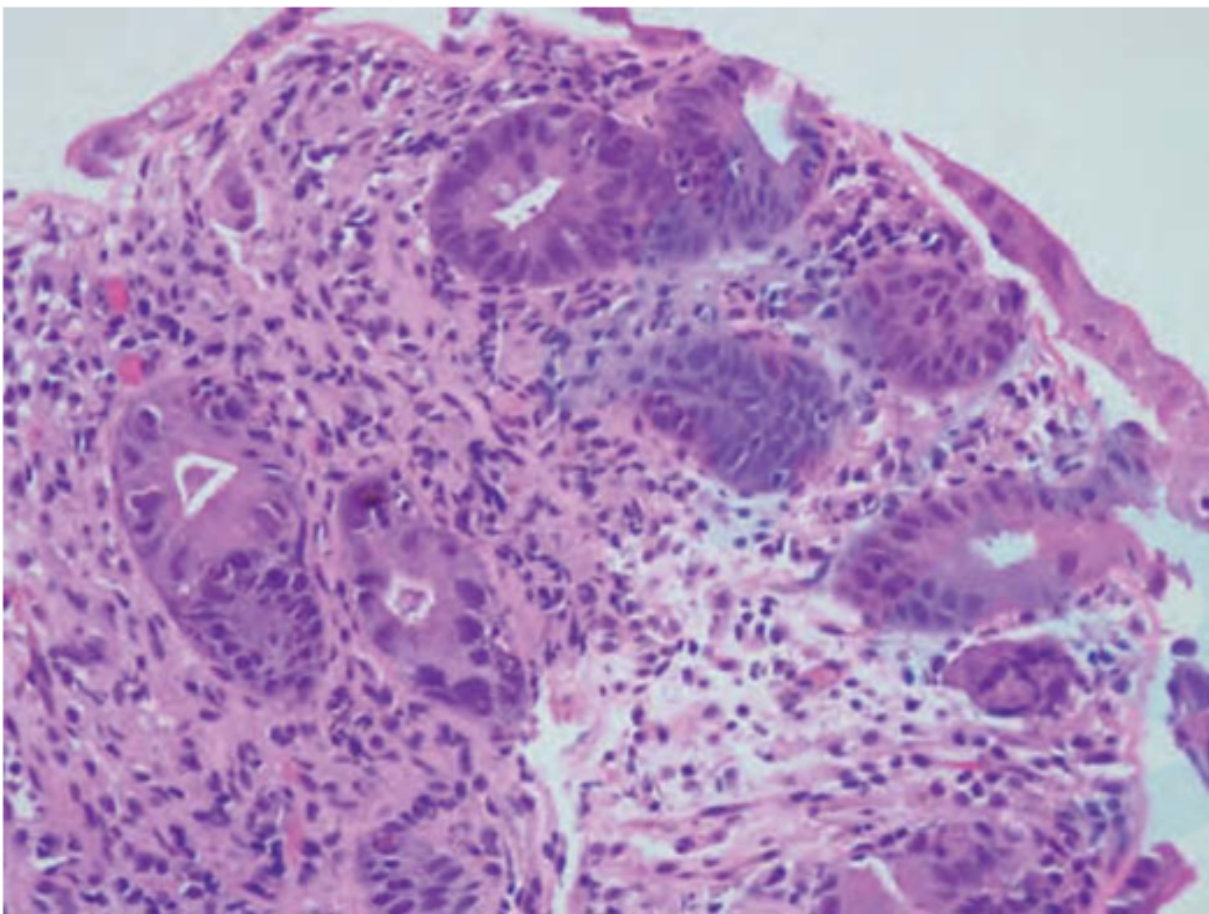


Fig. 8 High grade dysplasia in inflammatory bowel disease. The lesion shows marked nuclear atypia.

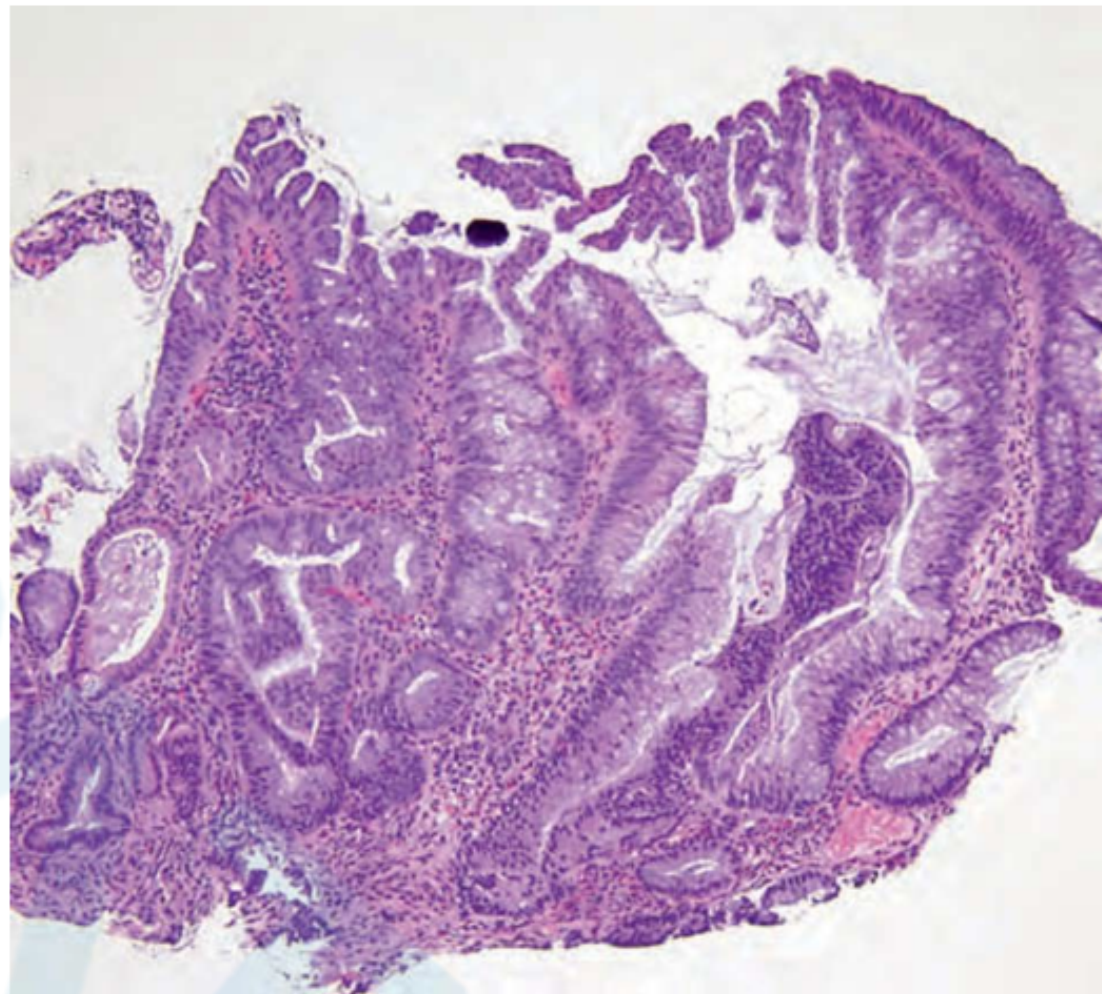
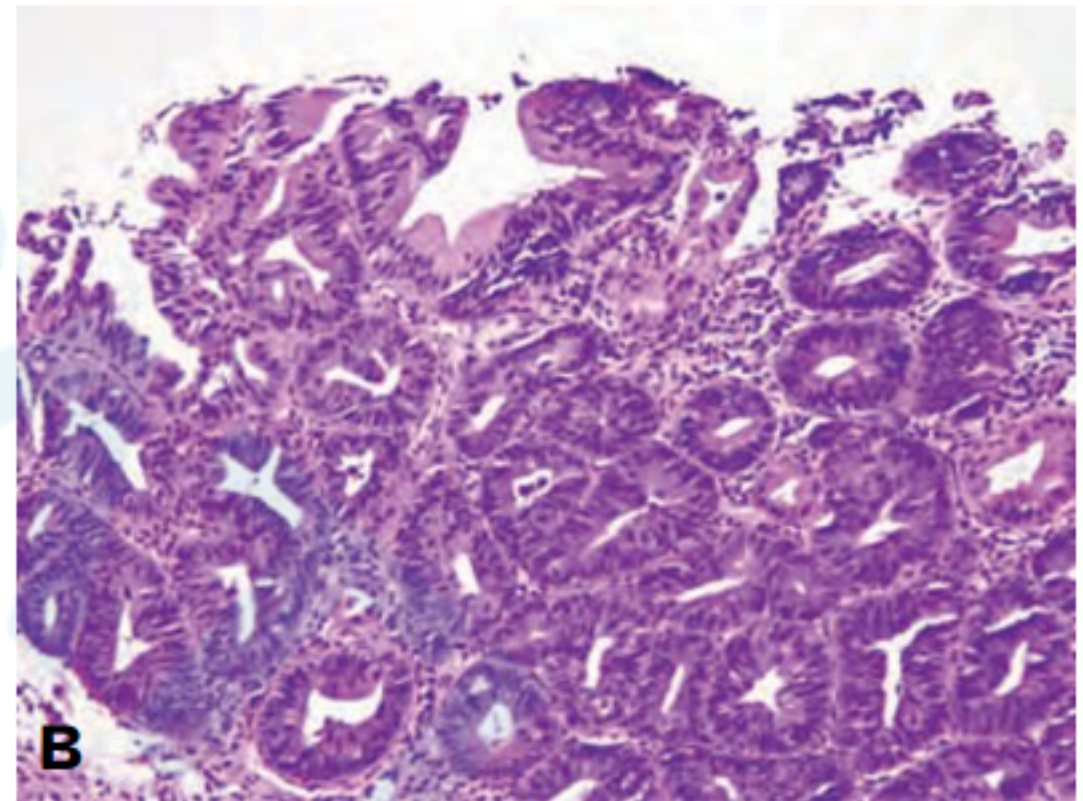
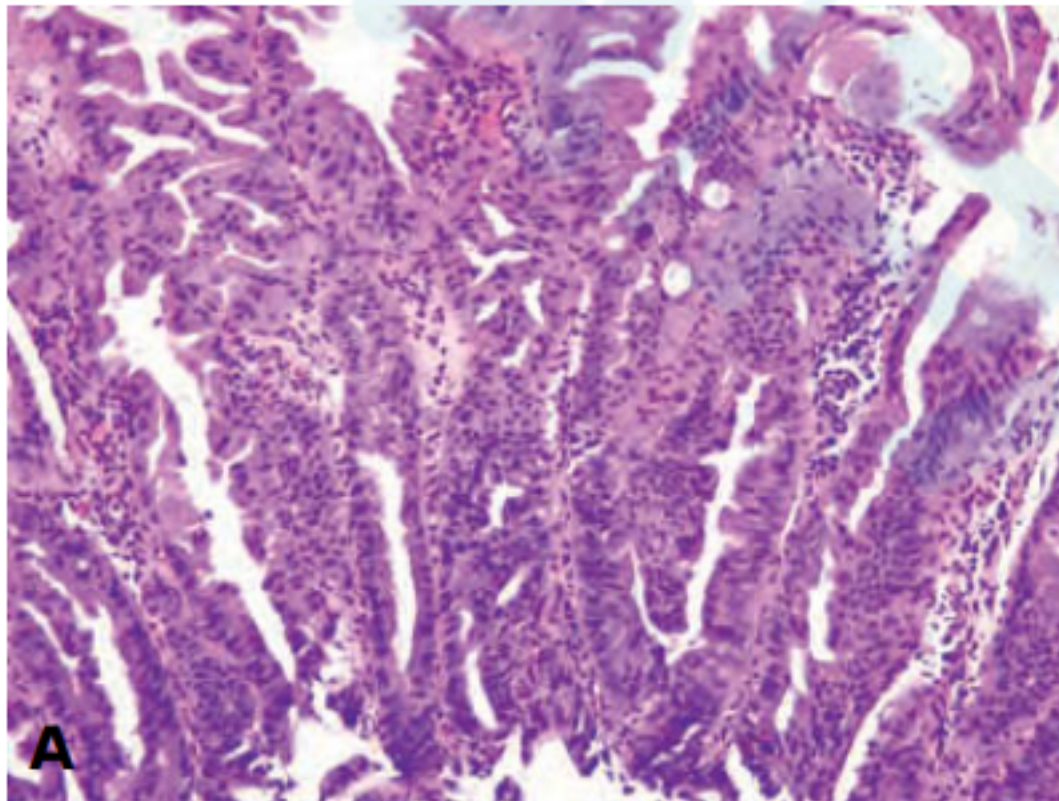
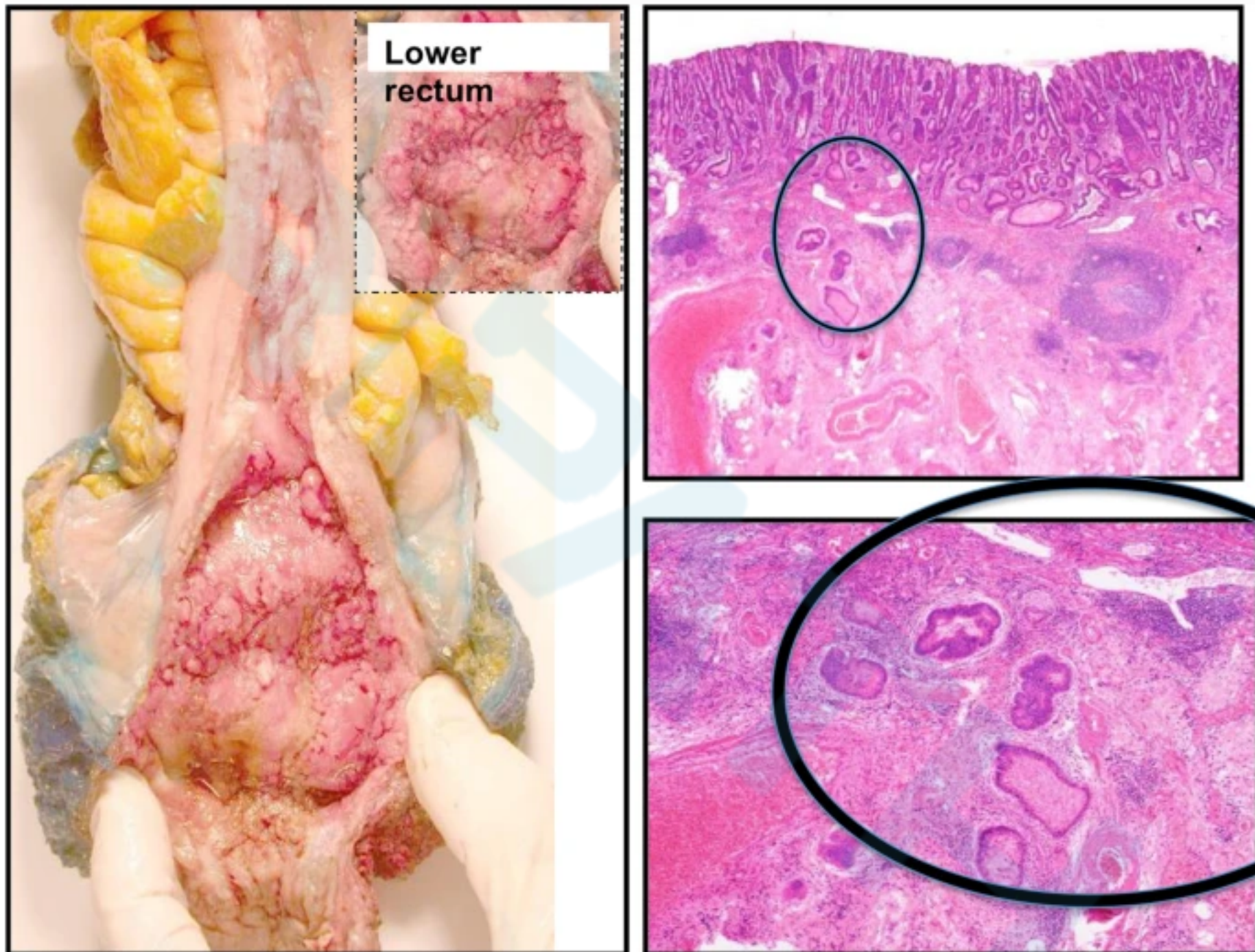


Fig. 9 Serrated low grade dysplasia in inflammatory bowel disease. The lesion shows serrated surface and crypt epithelium mimicking hyperplastic polyp.





Rectal moderately differentiated adenocarcinoma in a Crohn's disease patient. Gross specimen, moderate, and high power histopathology views

- 内镜明显病变**LGD**—加强肠镜监督
- 随机活检**LGD**—推荐外科手术
- **NEG**—定期复查
- **IND**—加强肠镜监督

- 病理诊断异型增生非常重要
- 诊断具有挑战性
- 近十年相关诊断一致性评估研究
- 研究结果差异性较大（K0.06差—K0.79好）

- 研究病理医生经验水平可能性是减少不同的关键
- 专家/水平-广泛运用-无明确定义
- 准确性与工作量及专门研究比兴趣及年限更相关

目的

- 病理诊断**IBD**相关异型增生
- 评估观察者之间及观察者之内的一致性

材料及方法

- 多中心参与，前瞻性研究（**CROMO**）
- 2年所有病人先前临床及组织学诊断IBD
- 参选标准：
 - ✓ **CD至少1/3结肠累及，UC近端包括直肠**
 - ✓ **长期至少8年或任何时间合并PSC**
 - ✓ **无临床活动：UC Mayo评分<6**
CD活动指数<150

排除标准

- CRC病史
- 局部或全部外科切除
- 凝血障碍
- 拒绝分享研究
- 近6月肠镜

- 详细内镜全结肠检查
- 取材：病变、周围黏膜、随机2处
- 选择125例从420例活检350患者
- 70NEG、13IND、42LGD
- 无HGD及ADC

- 二次分析简化诊断分类
- 避免倾向性：**NEG**高发
- 排除**NEG**---变为**51**例

- 8位病理医生参与研究
- 详细问卷调查、个人GI兴趣、专业年限等

TABLE 1. Initial Questionnaire

A	Birth date							
B	Trainee ending date							
C	Training hospital							
D	GI pathology specialized diagnosis practice (y)							
E	Where this activity was carried out?							
F	Total biopsy number diagnosed in 2014							
G	Endoscopic GI biopsies/total biopsies diagnosed in 2014							
H	Is there a screening program to detect IBD dysplasia in your working center?							
I	If you answered YES, how many endoscopies of this type are performed every month?							
J	Number of specific training activities last year							
	Observer 1	Observer 2	Observer 3	Observer 4	Observer 5	Observer 6	Observer 7	Observer 8
A	1977	1959	1974	1972	1971	1964	1964	1976
B	2008	1993	2004	2001	2000	1994	1994	2005
C	AH	AH	AH	AH	AH	AH	AH	AH
D	4 (2012 to date)	4 (2012 to date)	4 (2012 to date)	4 (2012 to date)	10 (2006 to date)	11 (2005 to date)	0 (—)	3 (2005 to 2007)
E	AH	AH	AH	AH	AH	AH	CH	CH
F	1580	250	1580	1580	2200	1890	985	450
G	79%	80%	66%	71%	90%	75%	30%	20%
H	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
I	20	20	20	20	12	12	4	8
J	8	8	8	8	0	0	0	0

Observers' characteristics.

Data retrieved on November 2015.

Experience by years: > 15 years of practice and at least the last 4 years of specialized diagnosis in GI. Observers who meet these criteria: 2,5,6; observers who do not meet these criteria: 1,3,4,7,8. Experience by volume: > 1500 GI biopsies diagnosed in the last year. Observers who meet these criteria: 1,3,4,5,6; observers who do not meet these criteria: 2,7,8. Years of practice and volume of biopsies were selected as the most important criteria for the creation of subgroups. Other secondary characteristics are, however, consistent with the formation of these groups.

AH indicates academic hospital; CH, community hospital.

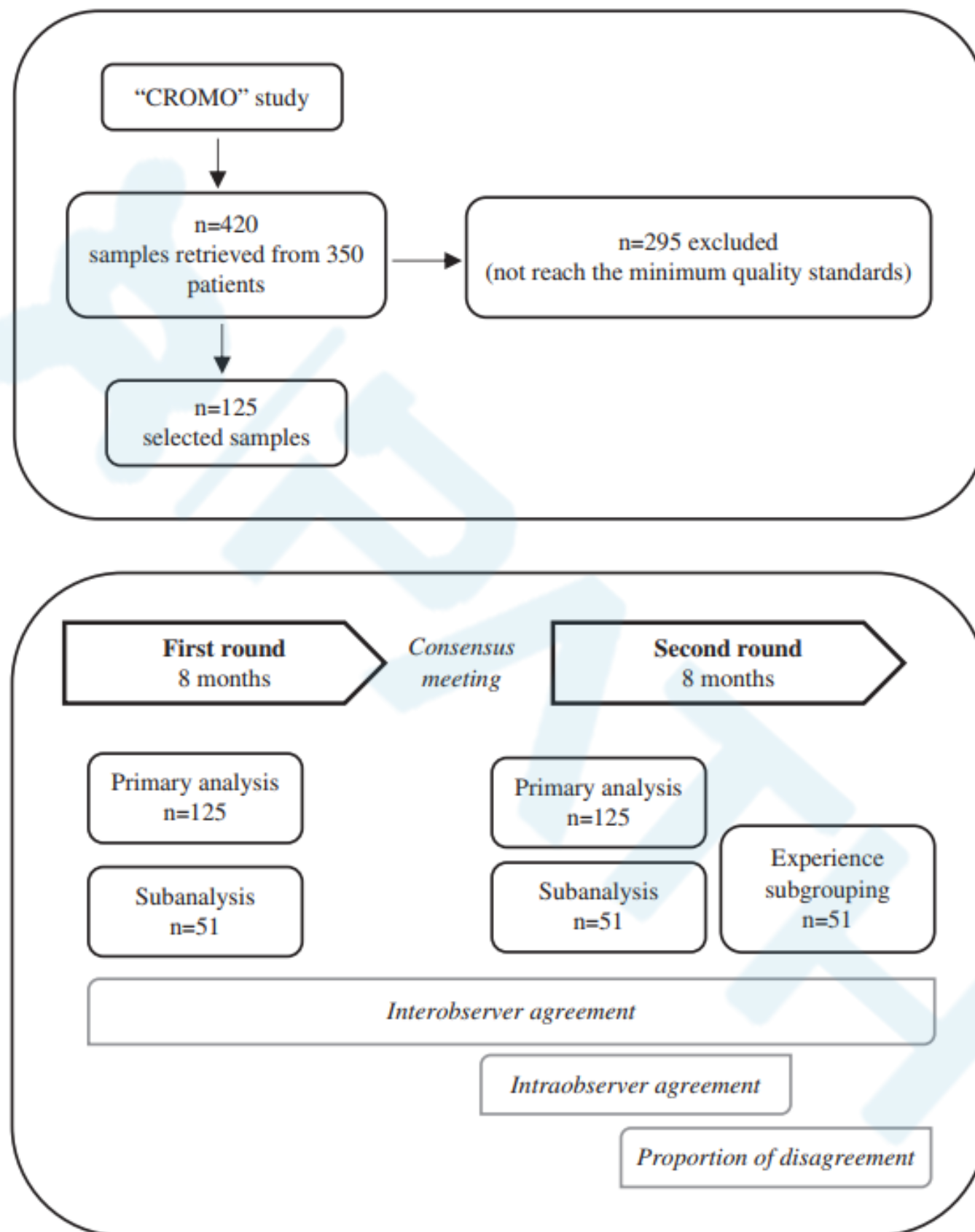


FIGURE 1. Samples and study flowcharts.

统计分析

- SPSS, version 24 (SPSS Inc. Chicago, IL) 软件
 - Fleiss' and Cohen K统计
-
- ✓ **K值0-0.2** 一致性差
 - ✓ **0.21-0.4** 一致性一般
 - ✓ **0.41-0.6** 一致性中等
 - ✓ **0.61-0.8** 一致性好
 - ✓ **0.81-1.0** 一致性很好

结果

- 观察者之间一致性
- 初步分析一致性好，配对K值中-很好
- 二次分析中度一致性，配对K值一般-好

TABLE 2. Interobserver Agreement

	Overall First Round	Overall Second Round	Range of Paired Values
125 cases	0.73 (0.70-0.76)	0.72 (0.69-0.75)	0.49-0.86 ^a
51 cases*	0.48 (0.43-0.52)	0.50 (0.46-0.54)	0.22-0.72 ^b

Overview of κ values with 95% confidence intervals in parentheses.

*Cases resulting from excluding those with all responses NEG.

Worst and best paired values: ^aobservers 4 and 7, observers 1 and 2; ^bobservers 4 and 7, observers 5 and 6.

结果

二次分析病理医生进行分组：

- 按经验年限分组
 - ✓ 专家组：15年GI经验，至少4年专科GI
 - ✓ 非专家组
- 按GI活检量分组
 - ✓ 高量组：1年>1500例
 - ✓ 低量组

结果

- 专家组及高量组均达到中度一致（高量组稍高）
- 低量组一致性最低：一般一致（0.36）
- K值显著低于非专家组

TABLE 3. Overall Grouped Interobserver Agreement
(51 Cases)

	First Round	Second Round
Experience by years		
Expert group ^a	0.59 (0.46-0.72)	0.60 (0.48-0.71)
Nonexpert group ^b	0.43 (0.36-0.50)	0.44 (0.37-0.51)
Experience by volume		
High-volume group ^c	0.60 (0.53-0.68)	0.61 (0.54-0.67)
Low-volume group ^d	0.36 (0.25-0.48)	0.41 (0.28-0.54)

Overview of κ values with 95% confidence intervals in parentheses.

^aObservers 2, 5, 6; ^bobservers 1, 3, 4, 7, 8; ^cobservers 1, 3, 4, 5, 6; ^dobservers 2, 7, 8 (see Table 1).

结果

工作量组内计算不一致性比例

- 高量组：1/3病例不一致
- 低量组：1/2不一致
- 大部为NEG/LGD
- 也有LGD/HGD，尤其低量组
- 总体不一致性低量组内更高

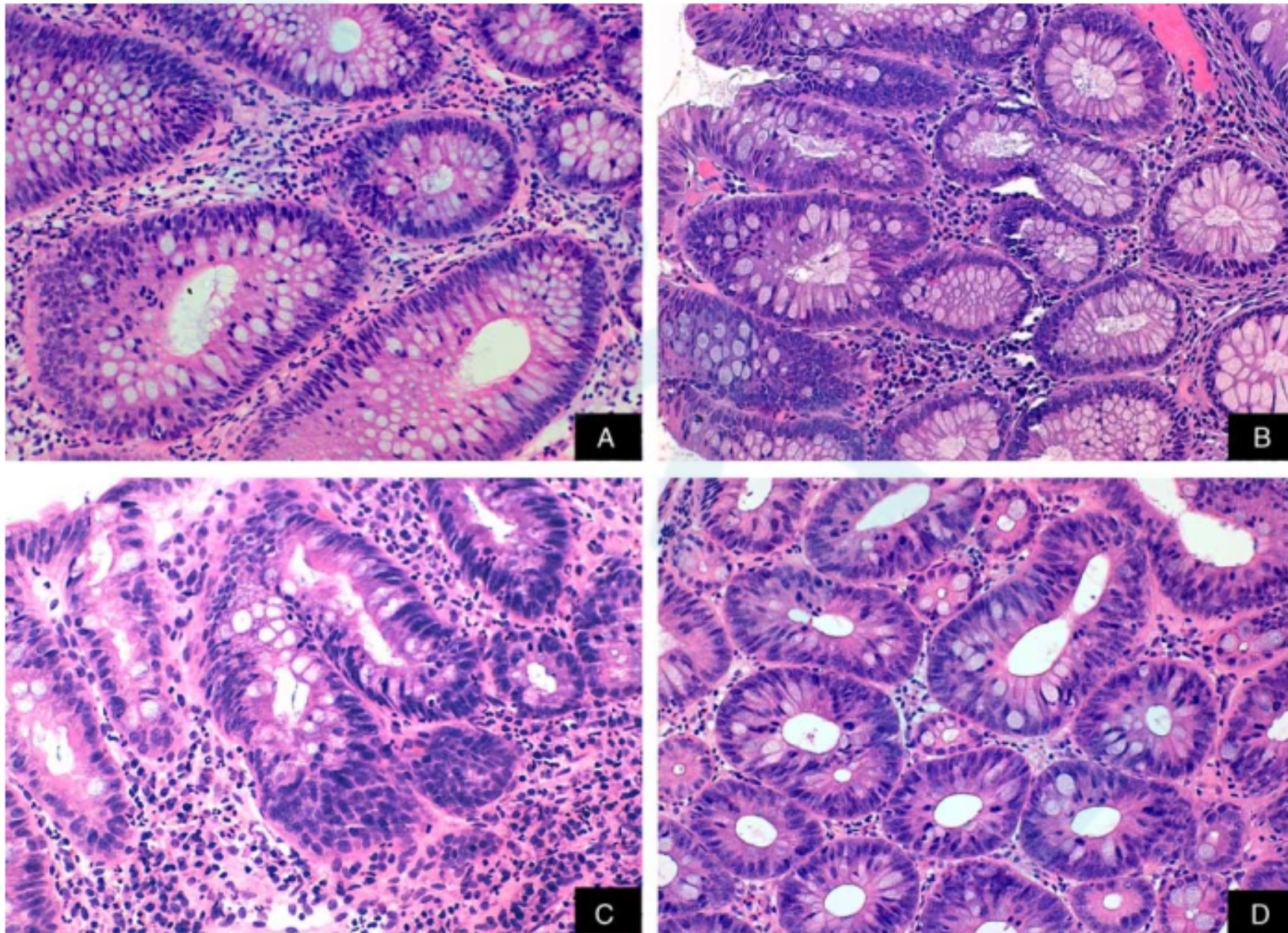


FIGURE 2. A, Case with diagnostic discordance in both low-volume and high-volume groups between NEG and LGD (hematoxylin and eosin). B, Case with a diagnostic trend for NEG in the low-volume group, while total agreement was achieved for LGD diagnosis among the high-volume group (hematoxylin and eosin). C, Case in which some of the responses were IND (hematoxylin and eosin). D, Case with overall diagnosis agreement of LGD in both rounds (hematoxylin and eosin).

结果

- 观察者内一致性
- 中-很好一致性
- 只有1人一般一致（非专家、低量组）

TABLE 4. Intraobserver Agreement

	Observer 1	Observer 2	Observer 3	Observer 4	Observer 5	Observer 6	Observer 7	Observer 8
125 cases	0.85 (0.68-1.0)	0.81 (0.65-0.97)	0.77 (0.61-0.93)	0.82 (0.67-0.97)	0.81 (0.65-0.96)	0.85 (0.69-1.0)	0.44 (0.30-0.56)	0.70 (0.54-0.86)
51 cases*	0.67 (0.43-0.91)	0.65 (0.42-0.88)	0.54 (0.31-0.77)	0.60 (0.39-0.80)	0.59 (0.36-0.80)	0.68 (0.45-0.91)	0.23 (0.01-0.38)	0.52 (0.27-0.77)

Overview of κ values with 95% confidence intervals in parentheses.

*Cases resulting from excluding those with all responses NEG.

讨论

- 首个研究关于**IBD**相关异型增生病理诊断稳定性
- 结果令人振奋—之前一致性低估
- 有些研究设计不合理、没有运用K检验、分组过少、倾向性病例

讨论

结果可靠

- 避免评估偏见，不提供诊断及临床信息
- 均为活检标本，按照临床**CRC**监督程序
- 阅片其间不进行特殊培训、讨论

结果可靠

- 二次分析排除多发病例**NEG**，避免统计学倾向
- 参与者按经验及工作量分组较客观、量化
- 参与观察者较多

讨论

临床活检影响评估，可能导致致癌作用

- 进一步研究5年随访
- 50-80%的IND出现了同段LGD
- 以前报道类似，密切随访内镜出现IND患者
- 大部有异型增生的同段重新出现
- 2/3LGD出现LGD，一例出现HGD
- 有1例升结肠LGD，出现直肠癌

结论

- 一致性之前被低估
- 观察者之间及内一致性均好
- 大量活检病例诊断是提高一致性关键
- 强调诊断共识及临床监管的重要性
- 确保可靠、稳定的诊断，提供适应的临床管理

谢谢!

A Dreamy World

A man's dreams are an index to his greatness.