Carcinogénesis en enfermedad inflamatoria intestinal idiopática (EIII)

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Enfermedad inflamatoria intestinal idiopática

Enfermedad inflamatoria, de curso crónico, con afección exclusiva o predominantemente intestinal, de etiología desconocida

Enfermedad inflamatoria intestinal idiopática

- Colitis ulcerosa crónica idiopática (CUCI)
- Enfermedad de Crohn (EC)
- Colitis indeterminada (CI)

Enfermedad inflamatoria intestinal idiopática

- **Colitis ulcerosa crónica idiopática (CUCI) “NO” inespecífica**
- **Enfermedad de Crohn (EC)**
- **Colitis indeterminada (CI)**

Enfermedad inflamatoria intestinal idiopática

- **Colitis ulcerosa crónica idiopática**: es una condición inflamatoria crónica que causa inflamación continua de la mucosa colónica sin granulomas en la biopsia, que afecta al recto y en extensión variable al colon contiguo, que se caracteriza por tener un curso con recaídas y remisiones
- **Enfermedad de Crohn**: es un proceso inflamatorio crónico del tracto intestinal principalmente. Aunque puede afectar cualquier parte del tracto digestivo desde la boca hasta el ano, más comúnmente afecta la porción más baja del intestino delgado (íleon) o el intestino grueso (colon y recto)
- **Colitis indeterminada**: es un término reservado para que los patólogos describan una muestra de colectomía que tiene características tanto de CUCI como de enfermedad de Crohn
- ***EIII no clasificada** es el término más conveniente para la minoría de los casos donde no puede hacerse una distinción definitiva entre CUCI, enfermedad de Crohn u otra causa de colitis después de que se han tomado en cuenta los antecedentes, los hallazgos endoscópicos, la histopatología de múltiples biopsias de la mucosa y la radiología adecuada

Dignass A, Eliakim R, Magro F, Maaser C, Chowers Y, Geboes K, Mantzaris G, Reinisch W, Colombel JF, Vermeire S, Travis S, Lindsay JO, van Assche G. [Second European evidence-based Consensus on the diagnosis and management of ulcerative colitis Part 1: Definitions and diagnosis (Spanish version)]. Rev Gastroenterol Mex. 2014 Oct-Dec;79(4):263-89.

Diagnóstico de EIII
CUCI vs EC / CI vs EIII no clasificada

- **Información clínica**
- **Estudio endoscópico**
- **Exámenes de laboratorio**
- **Estudios radiológicos**
- **Características macro y microscópicas**

Dignass A, Eliakim R, Magro F, Maaser C, Chowers Y, Geboes K, Mantzaris G, Reinisch W, Colombel JF, Vermeire S, Travis S, Lindsay JO, van Assche G. [Second European evidence-based Consensus on the diagnosis and management of ulcerative colitis Part 1: Definitions and diagnosis (Spanish version)]. Rev Gastroenterol Mex. 2014 Oct-Dec;79(4):263-89.

Journal of Crohn's and Colitis (2013) 7, 827–851

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CONSENSUS/GUIDELINES

European consensus on the histopathology of inflammatory bowel disease ☆

F. Magro[a,*,1], C. Langner[b,1], A. Driessen[c], A. Ensari[d], K. Geboes[e], G.J. Mantzaris[f], V. Villanacci[g], G. Becheanu[h], P. Borralho Nunes[i], G. Cathomas[j], W. Fries[k], A. Jouret-Mourin[l], C. Mescoli[m], G. de Petris[n], C.A. Rubio[o], N.A. Shepherd[p], M. Vieth[q], R. Eliakim[r] on behalf of the European Society of Pathology (ESP) and the European Crohn's and Colitis Organisation (ECCO)[2]

ECCO-ESP statement 1

For a reliable diagnosis of inflammatory bowel disease, ileocolonoscopy rather than rectoscopy should be performed. A minimum of two biopsies from at least five sites along the colon, including the rectum, and the terminal ileum should be obtained [EL 1]. In patients with fulminant colitis, two samples from at least one site should be obtained [EL5]. The biopsies should be collected in separate vials, as localization of the biopsies gives important diagnostic information

ECCO-ESP statement 2

All tissue samples should be fixed immediately by immersion in buffered formalin or an equivalent solution prior to transport [EL5]. Since lesions may be focal, it is recommended that multiple sections from each sample are examined [EL2]

ECCO-ESP statement 3

The biopsy samples should be accompanied by clinical information including endoscopic findings as well as the age of the patient, duration of disease, duration and type of treatment, comorbidities and travel history [EL 5]

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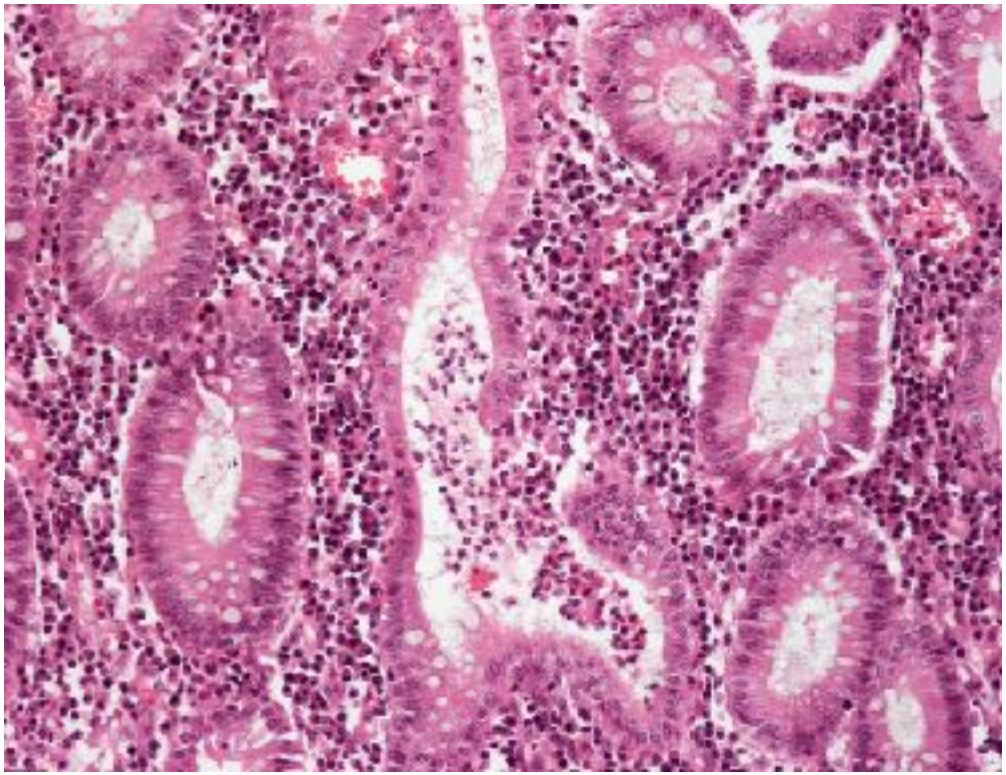
ECCO-ESP statement 4

A surgical sample needs complete gross examination, carried out in an orderly and systematic manner, including photographic documentation, preferably at the time when the specimen is removed [EL5]

ECCO-ESP statement 9

Microscopic diagnosis of ulcerative colitis is based on widespread crypt architectural distortion, a diffuse transmucosal inflammatory infiltrate with basal plasmacytosis, eventually associated with an active component, causing cryptitis and crypt abscesses. Mucin depletion is less specific, but a helpful diagnostic feature [EL 1]



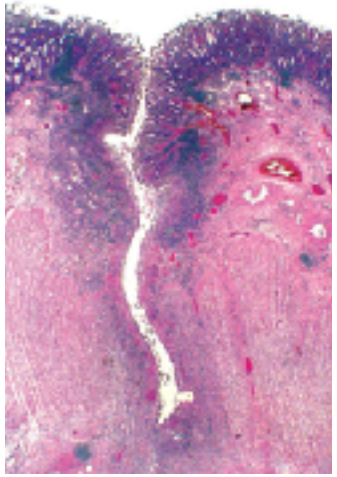
Enfermedad de Crohn

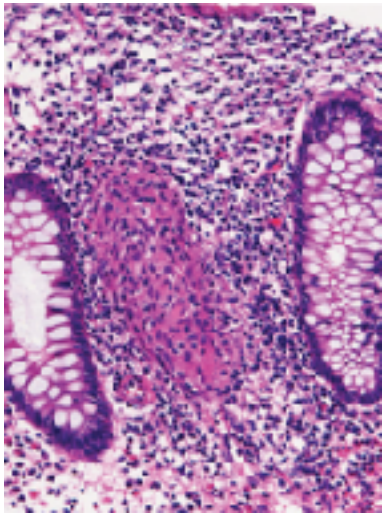
ECCO-ESP statement 22

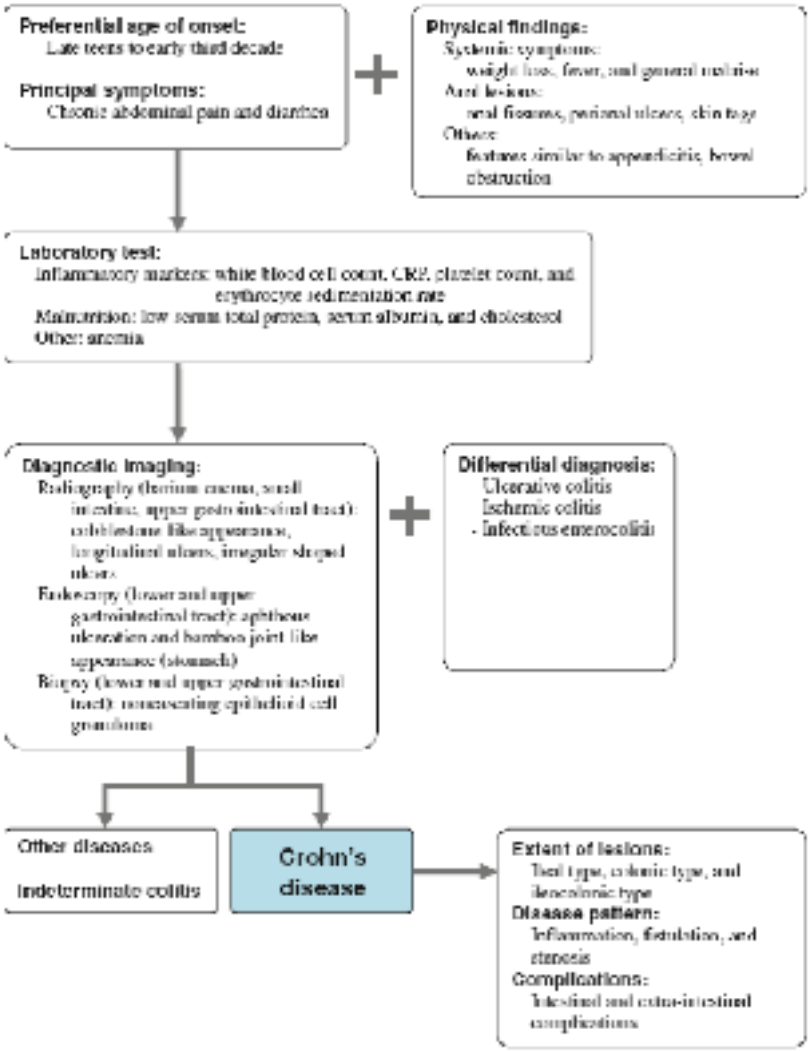
Focal (discontinuous) chronic inflammation, focal crypt irregularity (discontinuous crypt distortion) and granulomas (not related to crypt injury) are the generally accepted microscopic features which allow a diagnosis of CD in the colon (on endoscopic biopsies) [EL 2]. The same features and, in addition, an irregular villous architecture, can be used for analysis of endoscopic biopsy samples from the ileum. If the ileitis is in continuity with colitis, the diagnostic value of this feature should be used with caution [EL 2]

ECCO-ESP statement 23

Despite detailed histologic criteria used to differentiate Crohn's colitis from ulcerative colitis in colonoscopic biopsies, accurate discrimination between the two diseases is not yet optimal among expert gastrointestinal pathologists [EL 2]







II-7. Histopathological examination

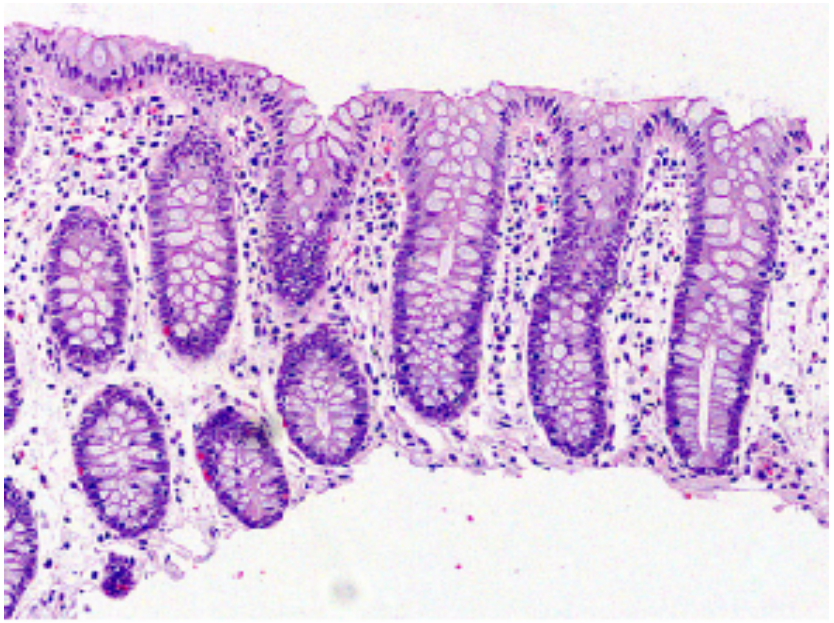
CQ14: What pathological findings are characteristic of CD? [52, 54]

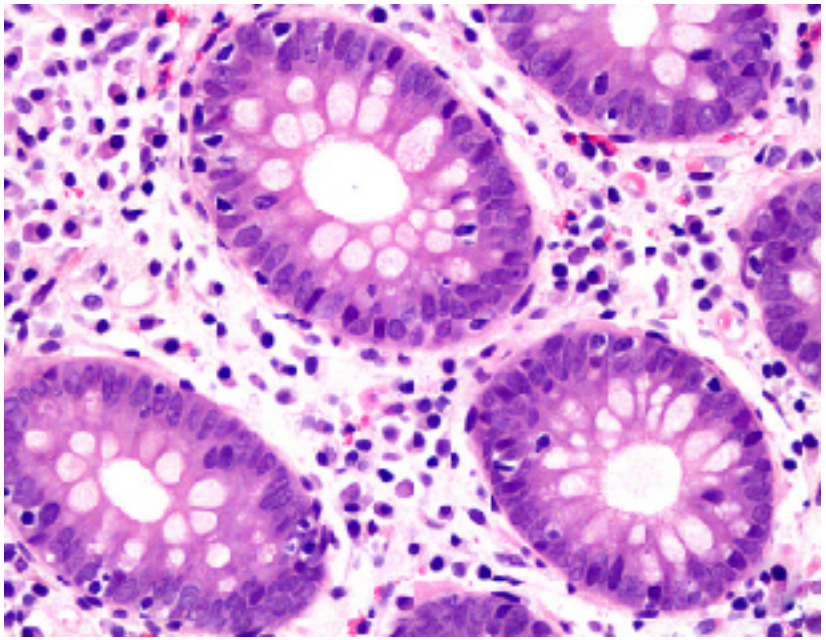
- Findings for a definitive diagnosis of CD include: (1) noncaseating epithelioid cell granuloma, (2) transmural inflammation, (3) fissure, and (4) ulcers. C1 (Japan VI, overseas VI; 8).

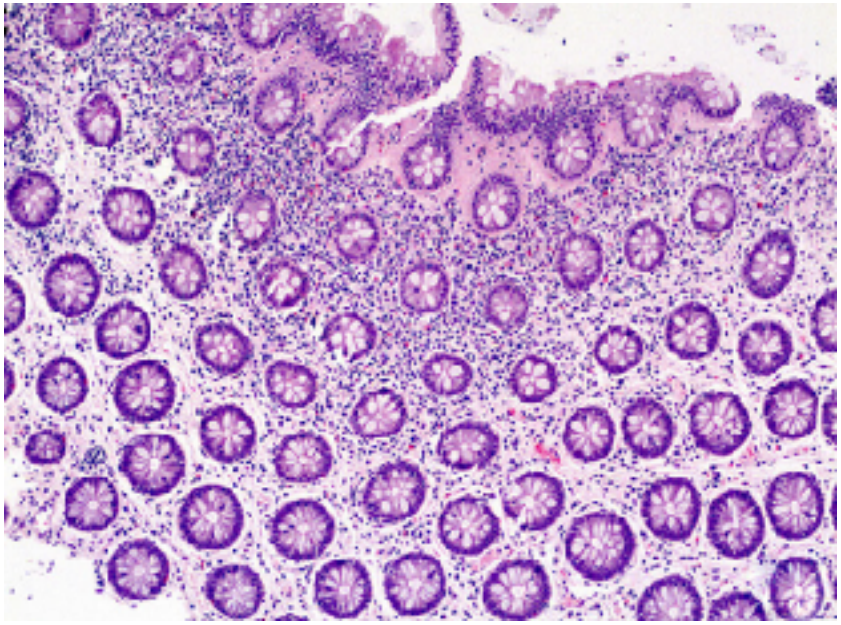
Granulomas
Bx: 15-36%
Qx: 40-60%

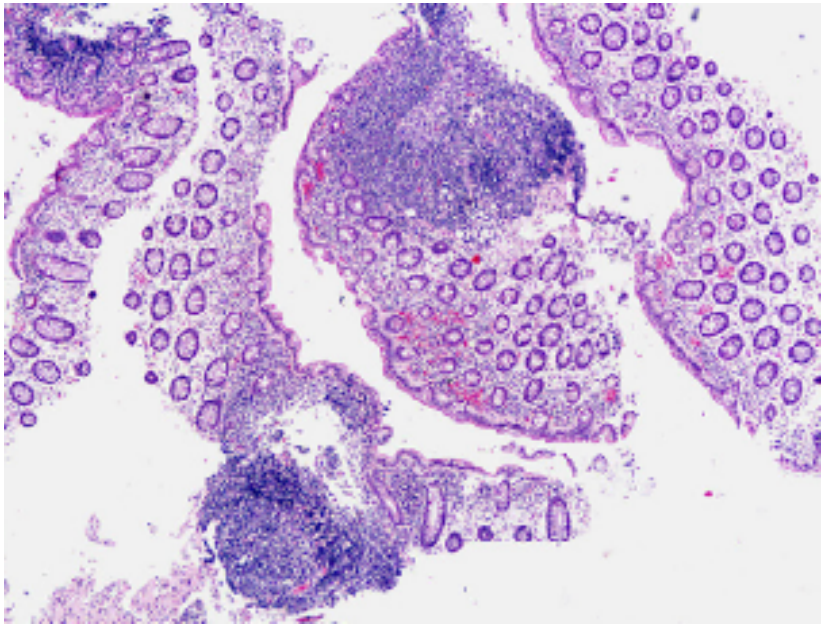
Evidence-based clinical practice guidelines for Crohn's disease, integrated with formal consensus of experts in Japan

J Gastroenterol (2013) 48:31–72

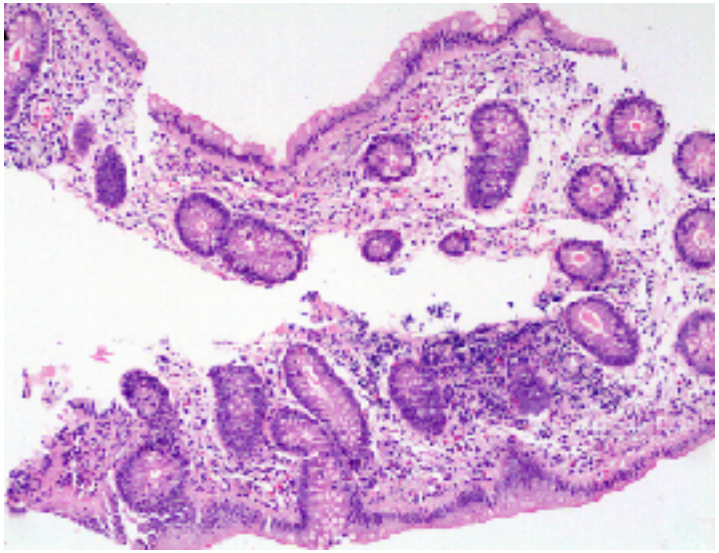


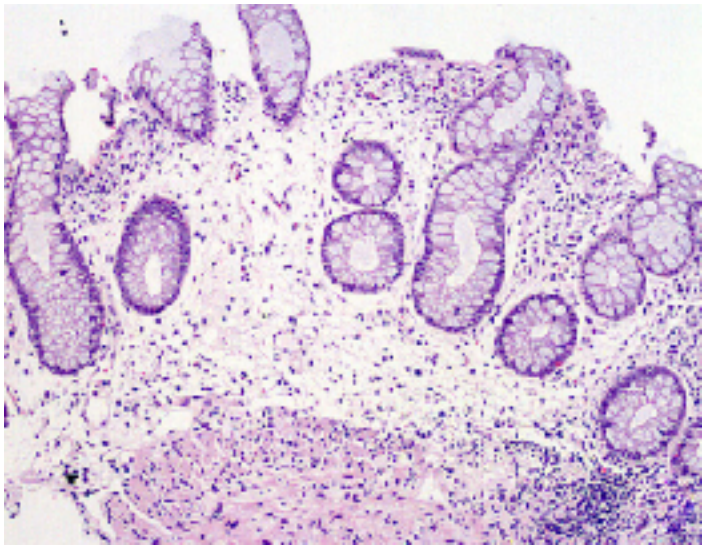


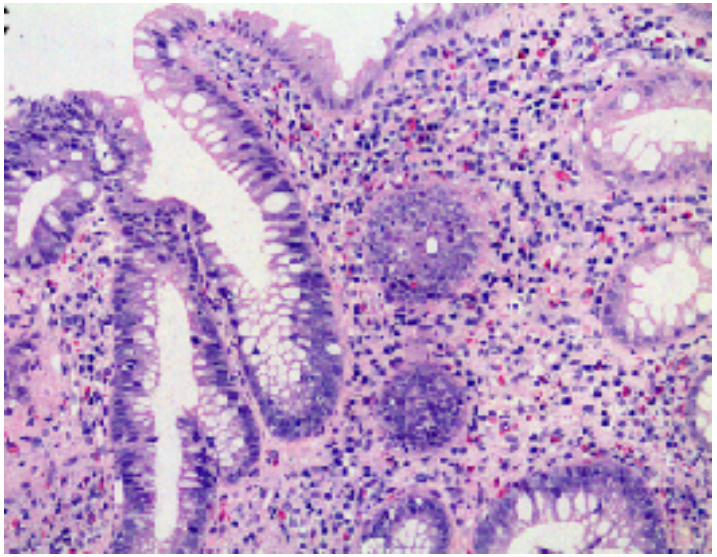


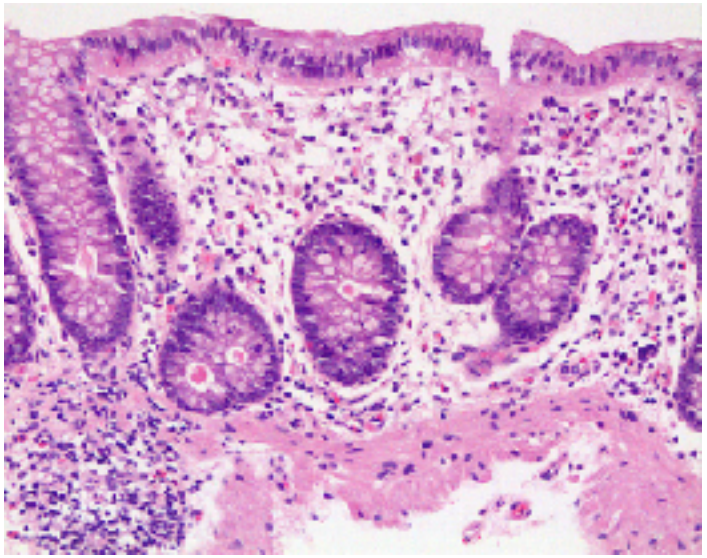


Estructura glándulas / criptas (CUCI)









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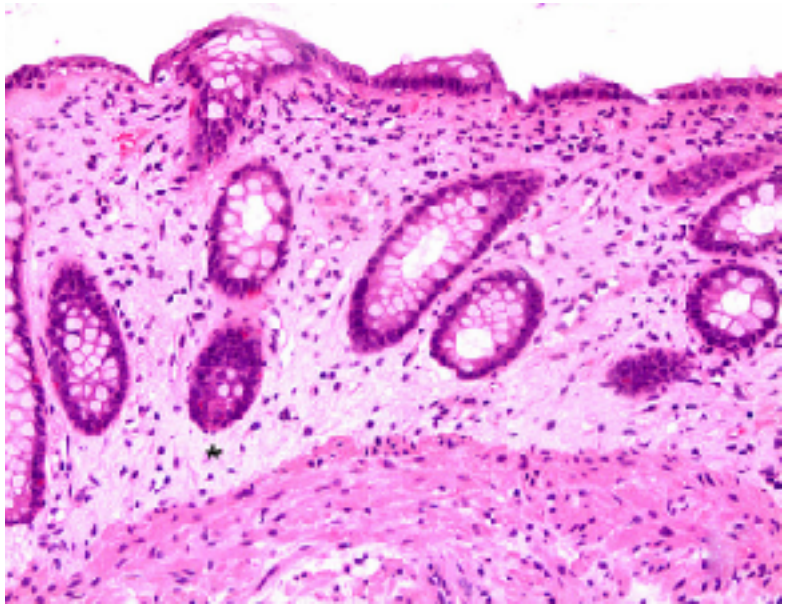
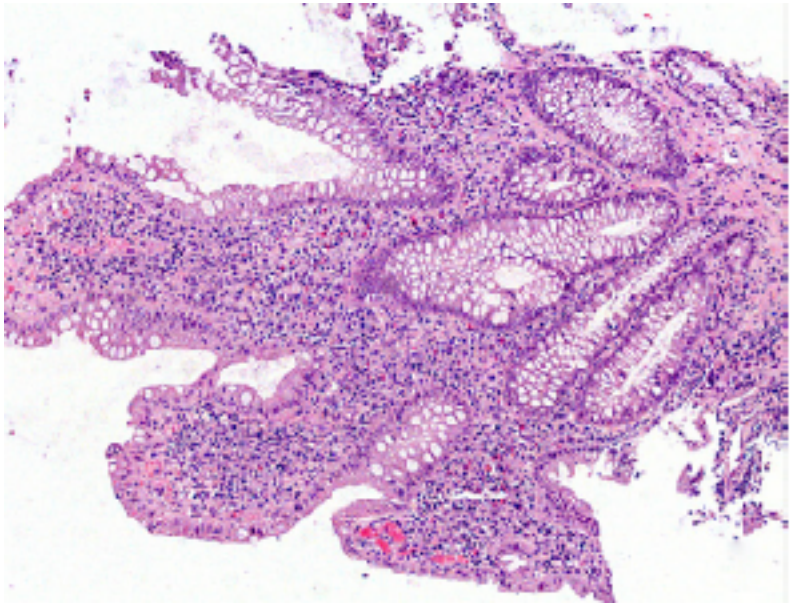
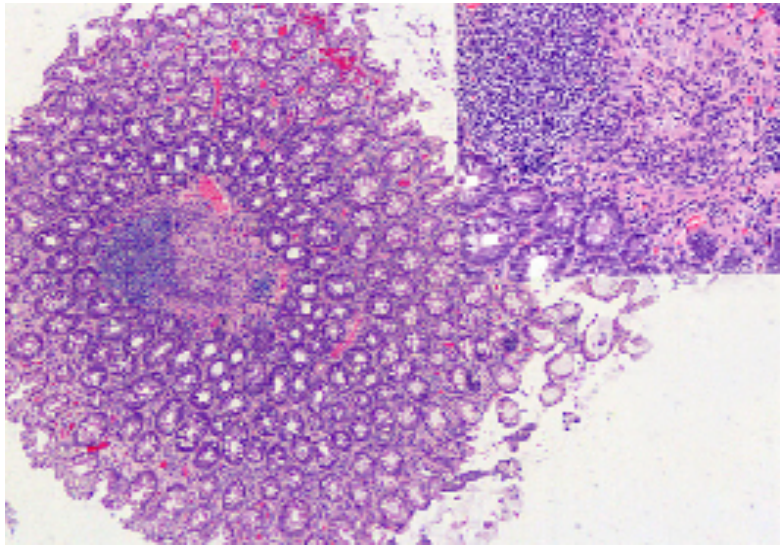
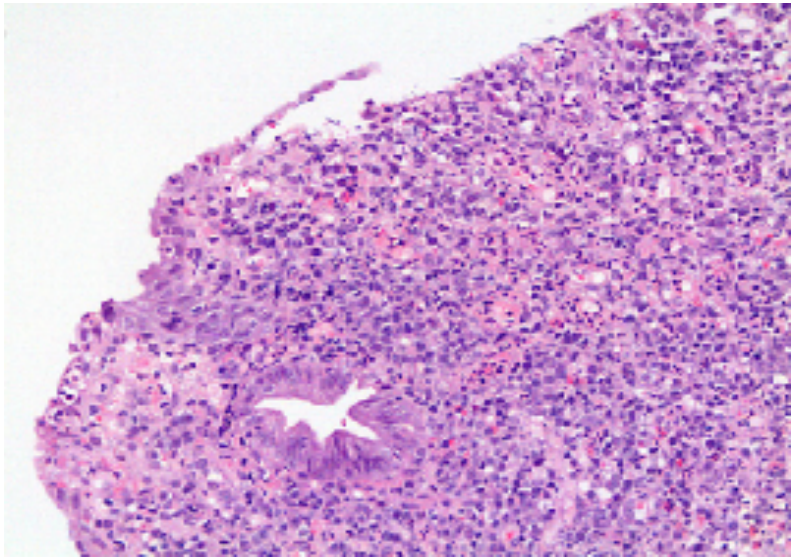
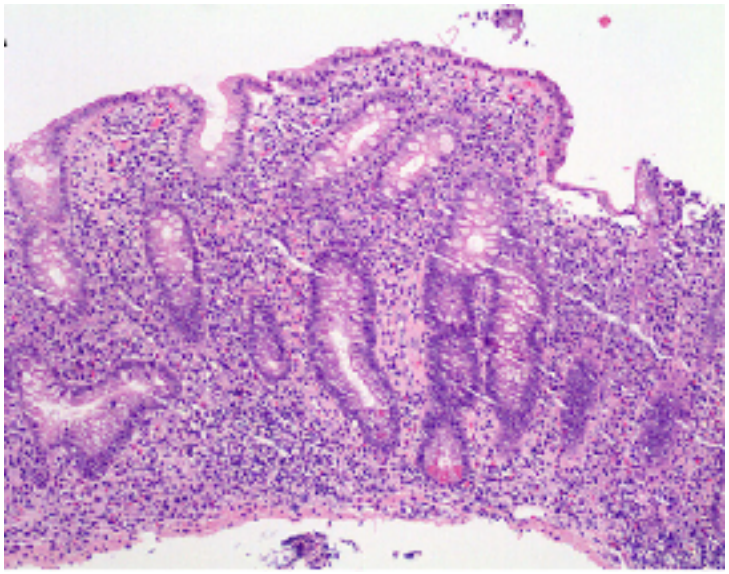


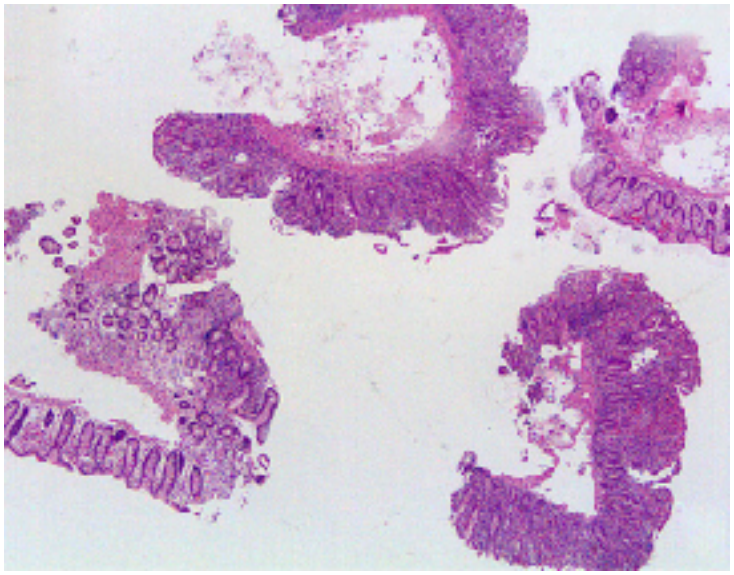


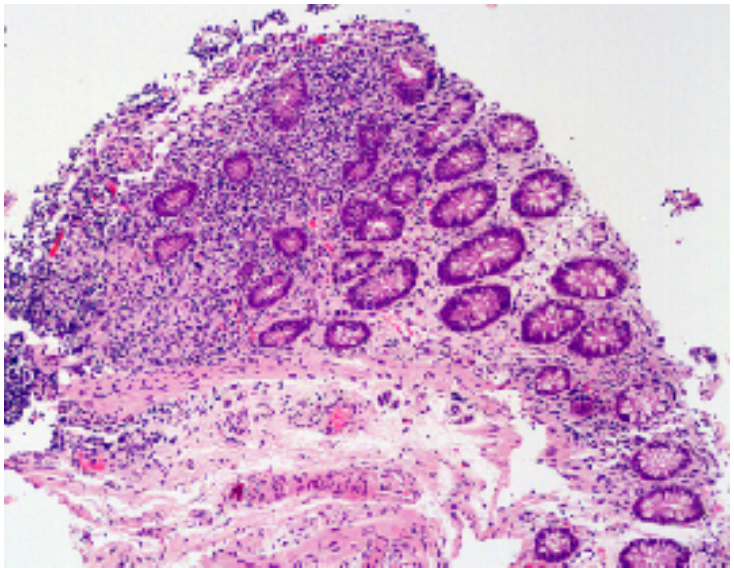


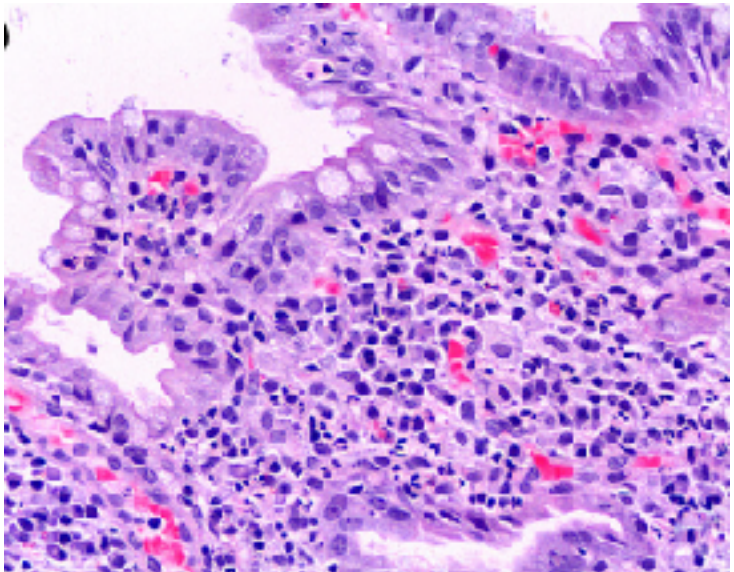


Estructura glándulas / criptas (EC)

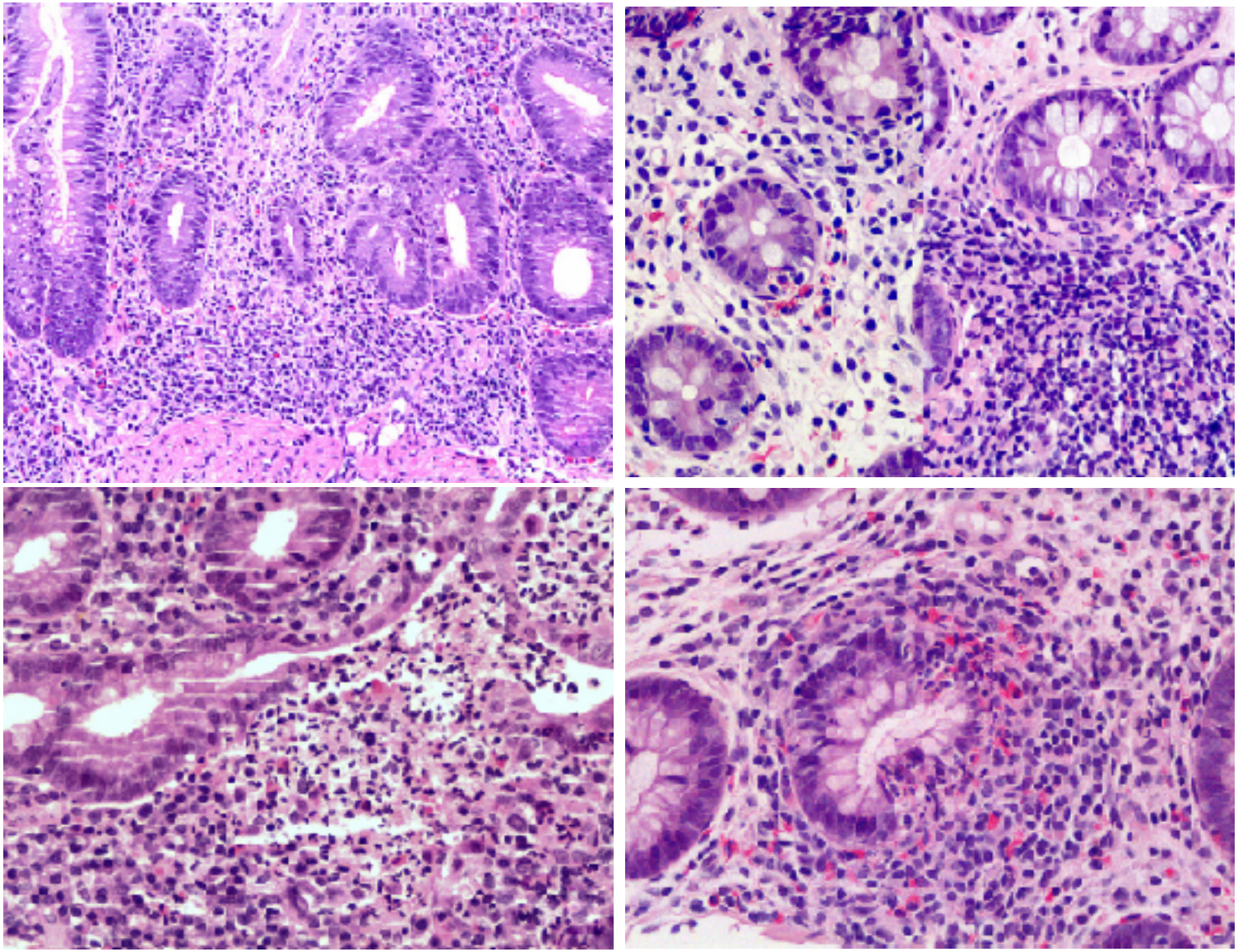




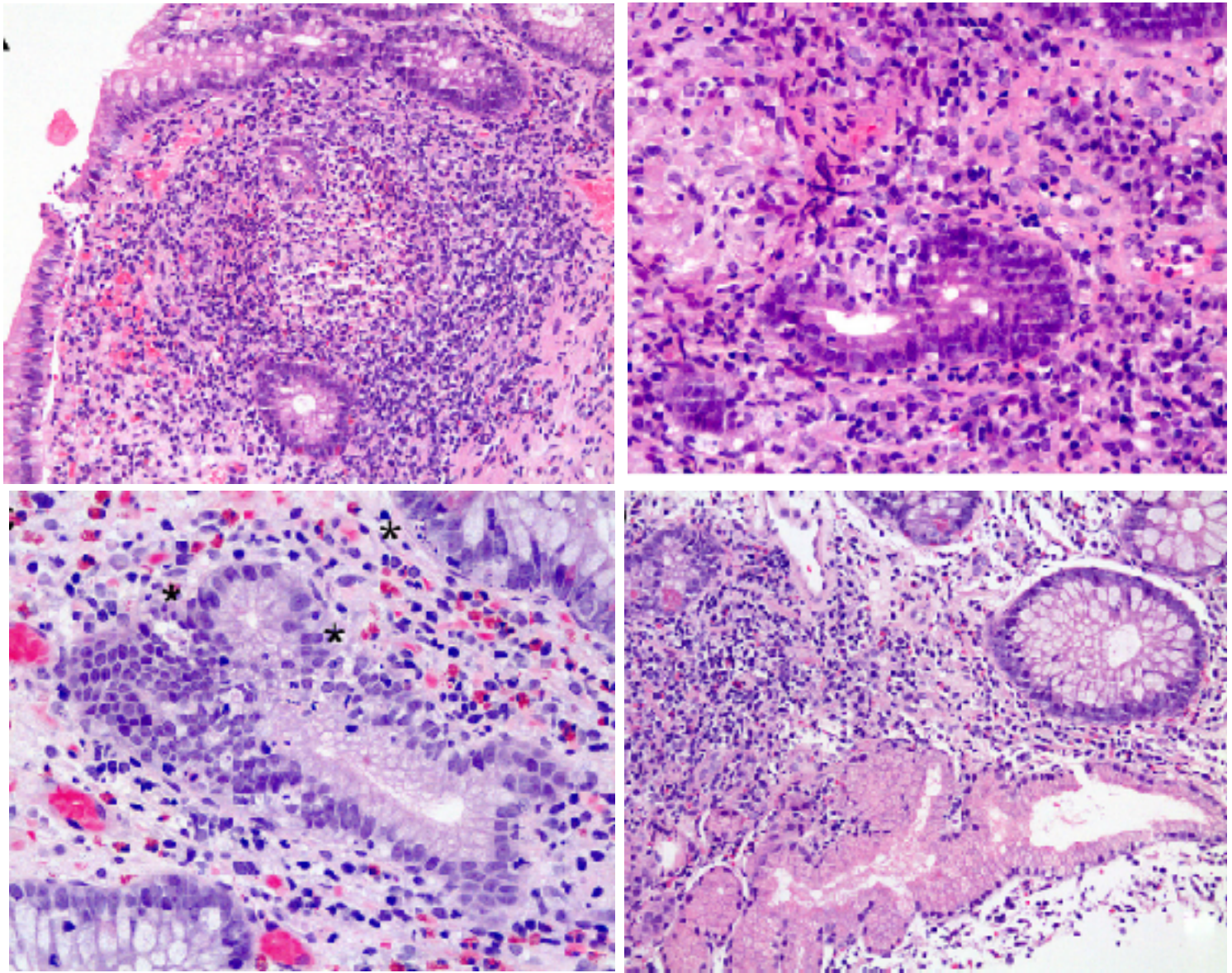




Infiltrado inflamatorio (CUCI)

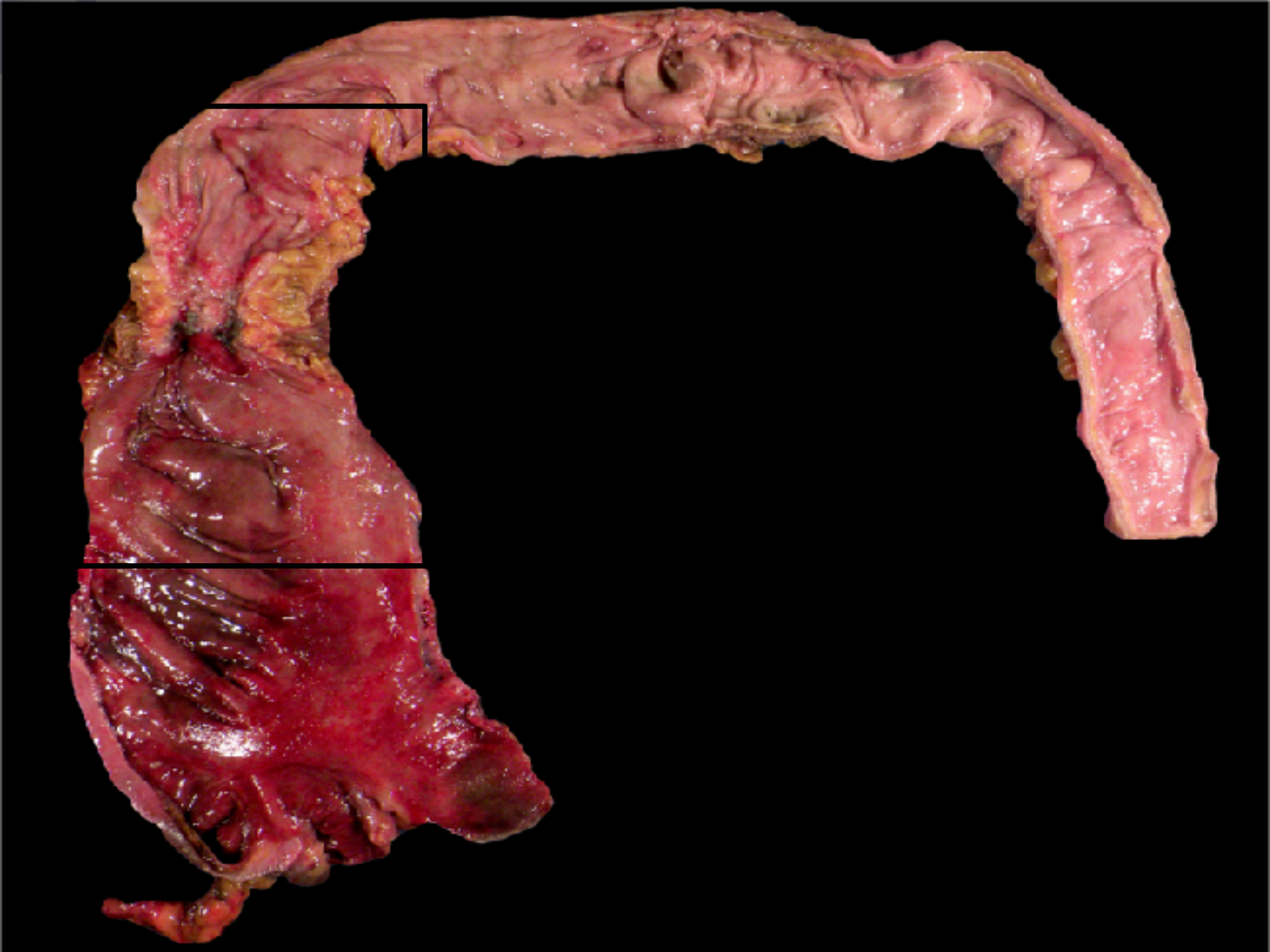


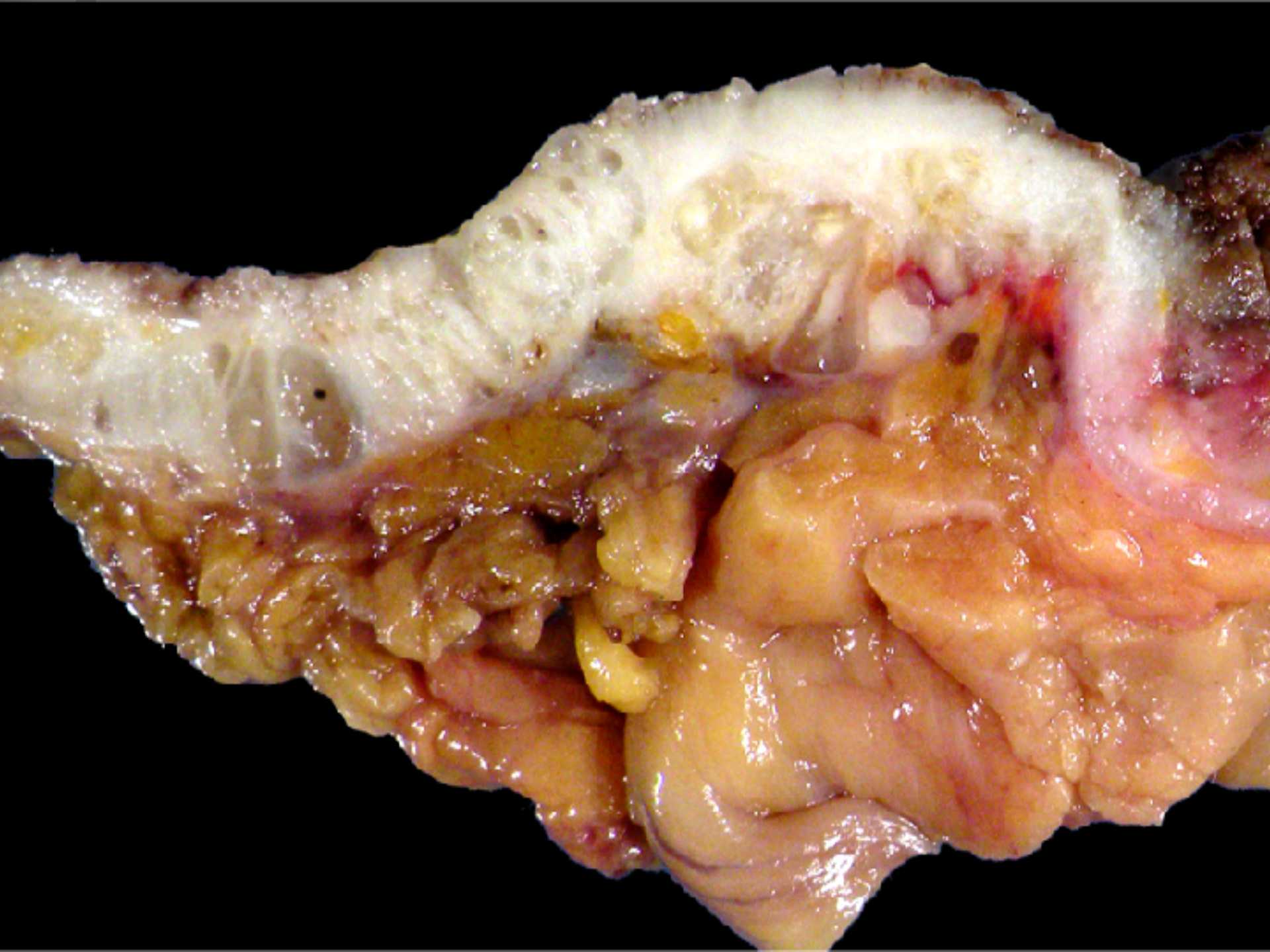
Infiltrado inflamatorio (EC)

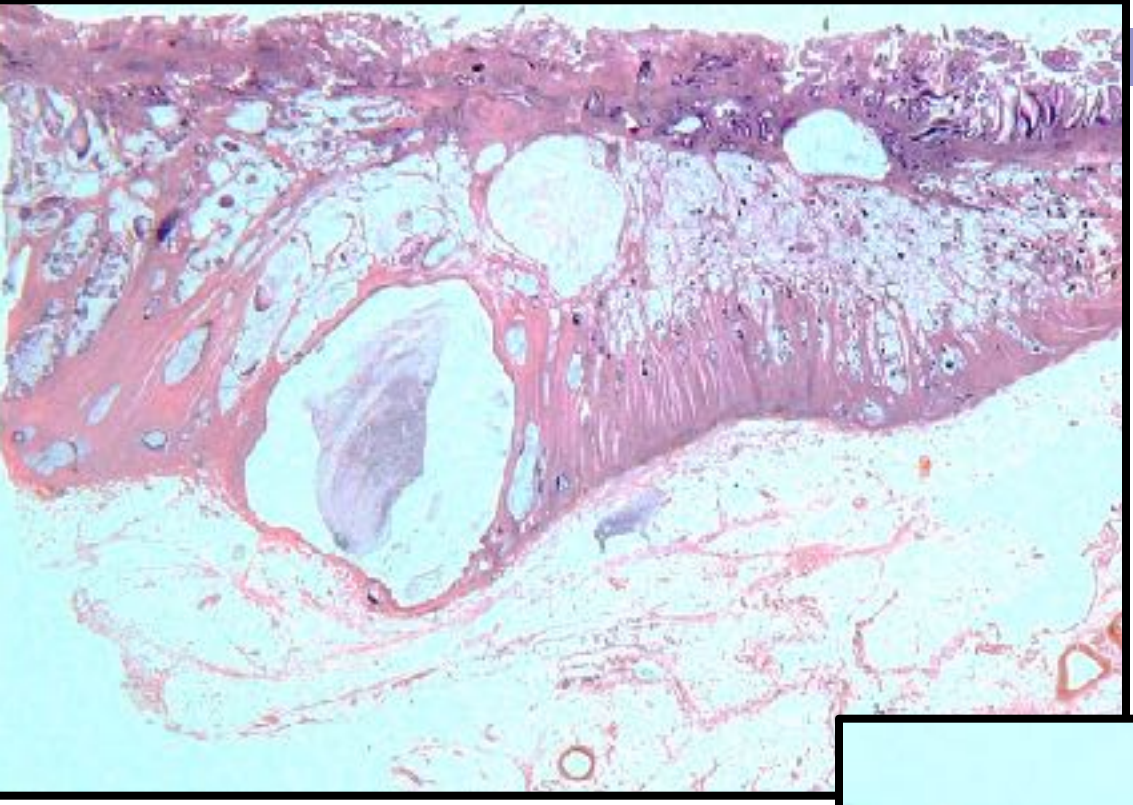


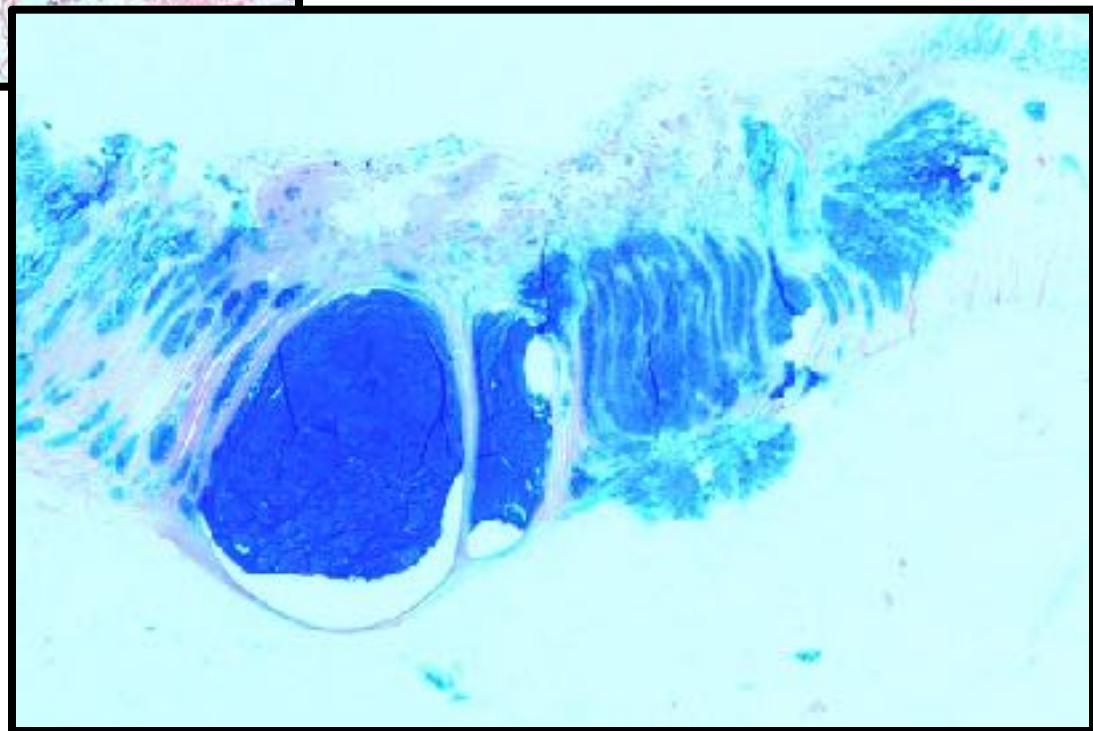
Caso interesante

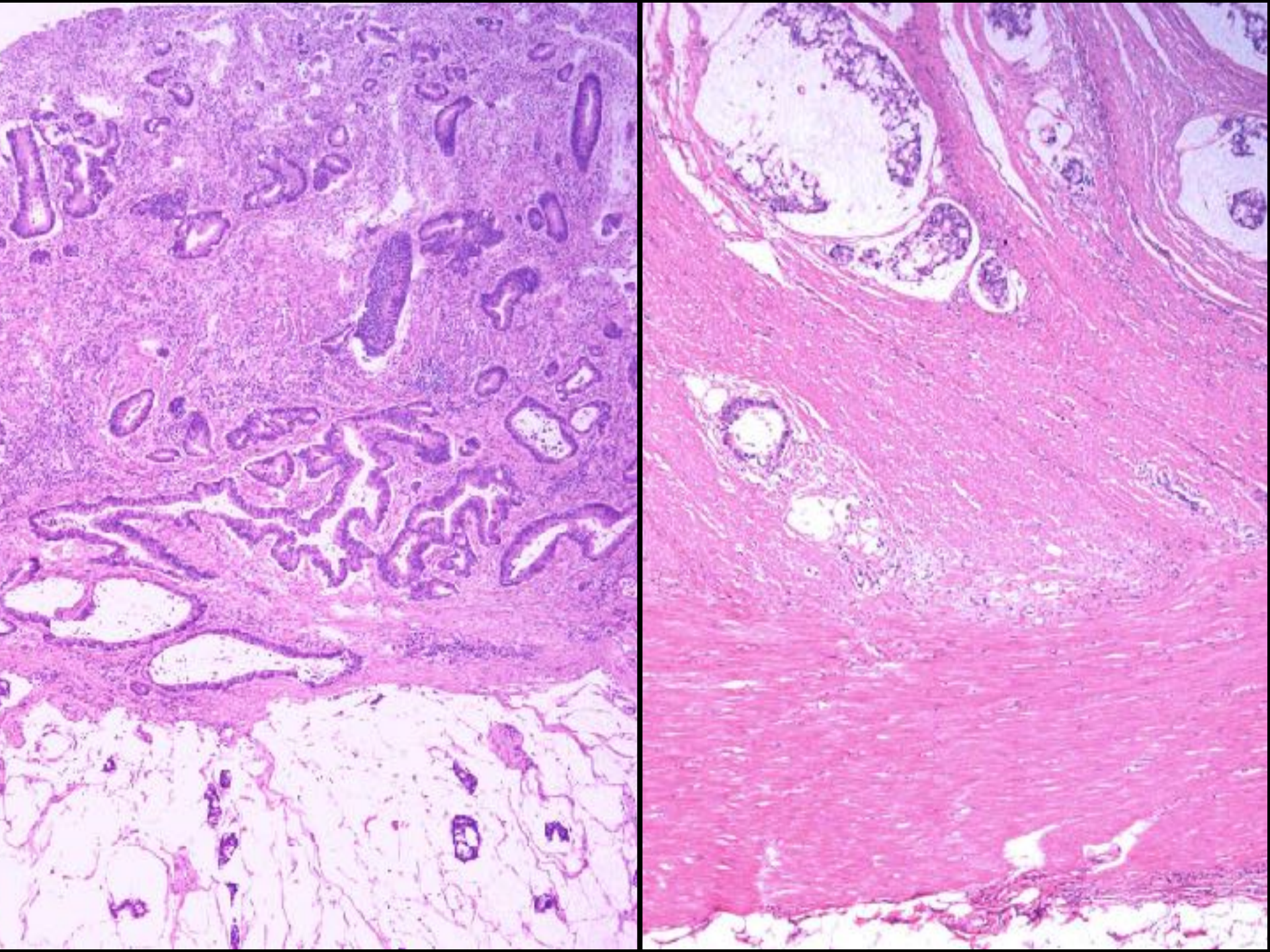
- Hombre de **57 años**
- **CUCI** (1998), en tratamiento irregular con mesalazina vía oral
- La última ***colonoscopía*** de control hace 12 años, sin alteraciones
- 2010 cuadro clínico compatible con obstrucción intestinal de 48 hrs de evolución

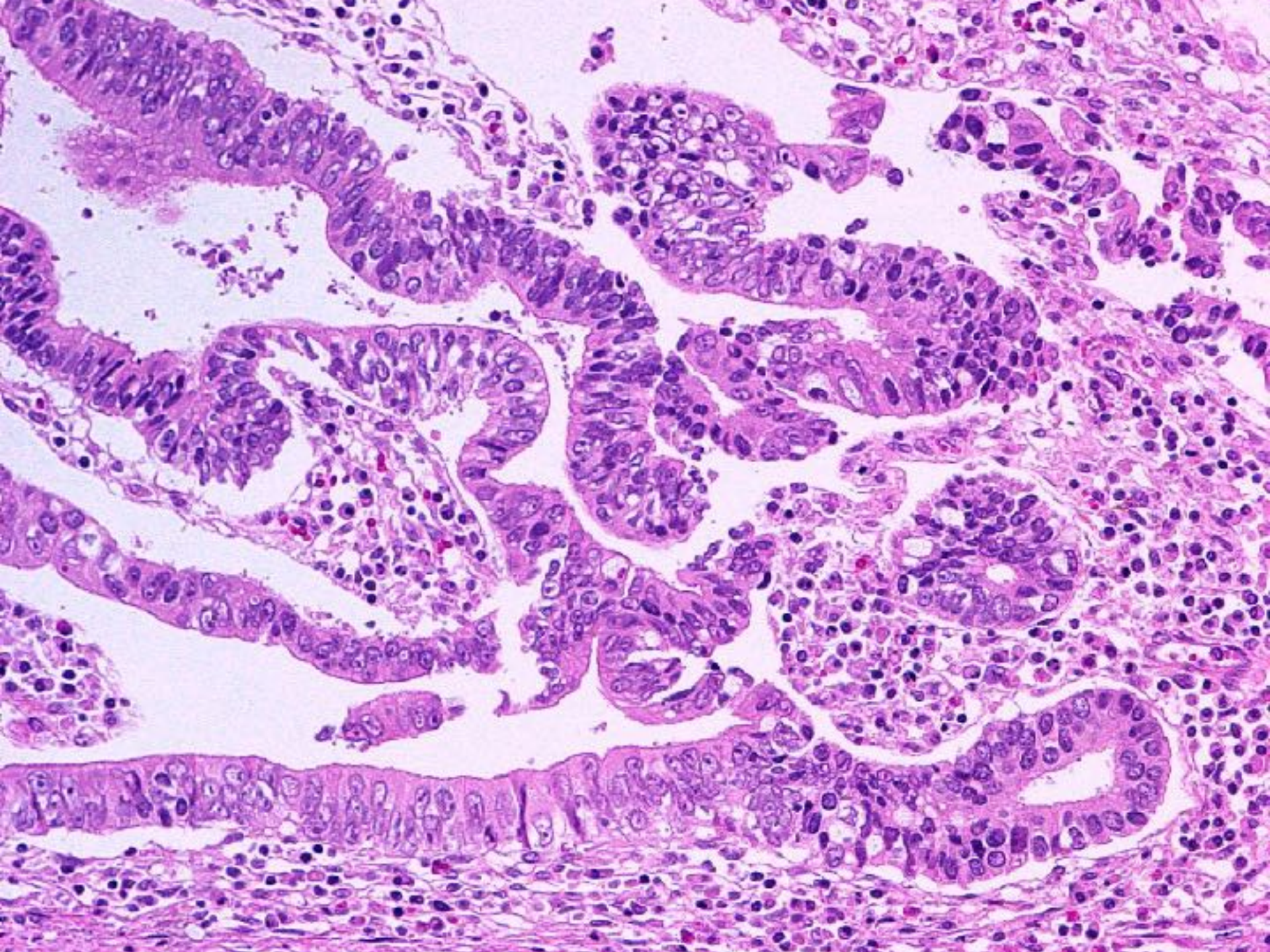


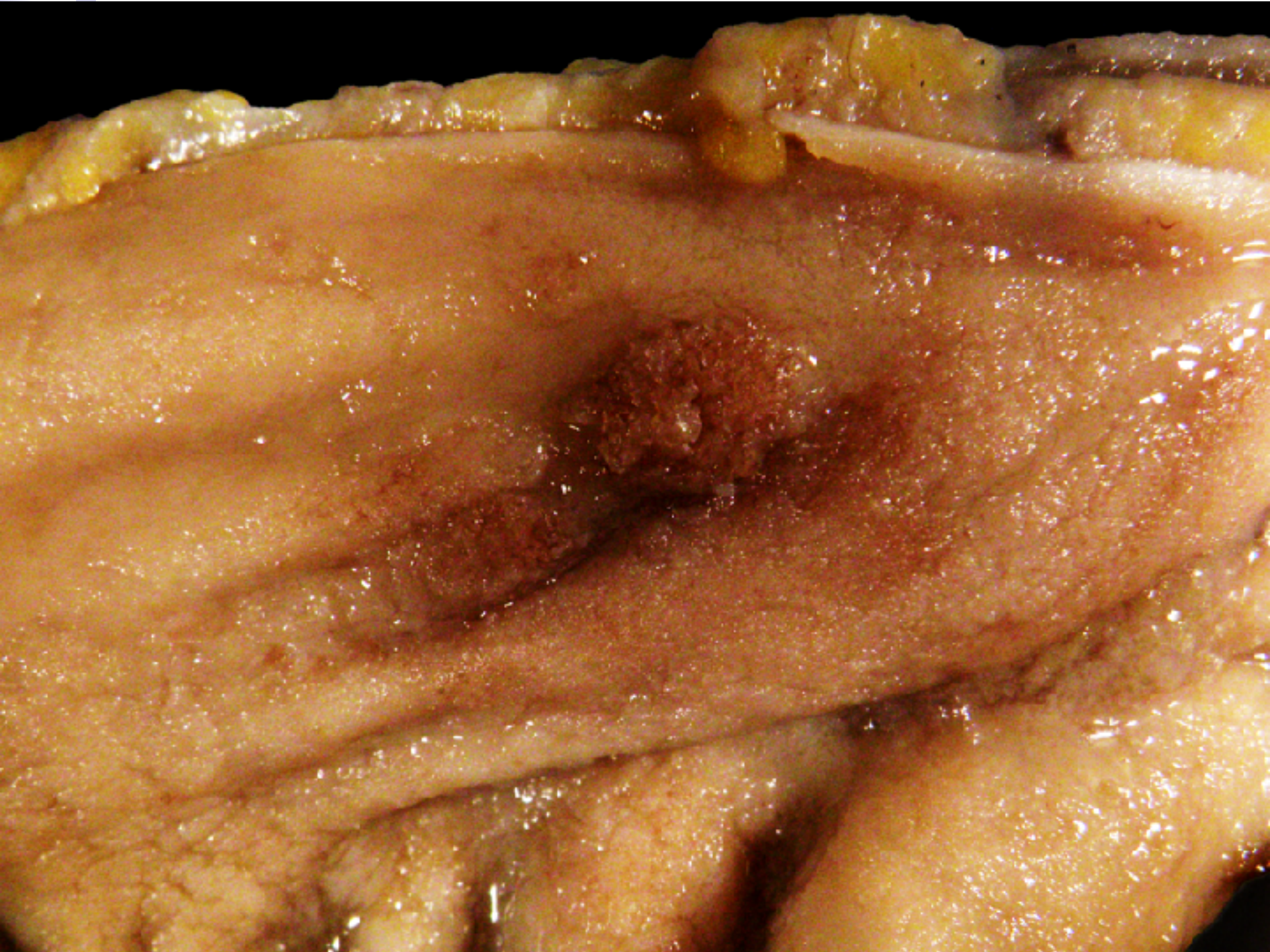


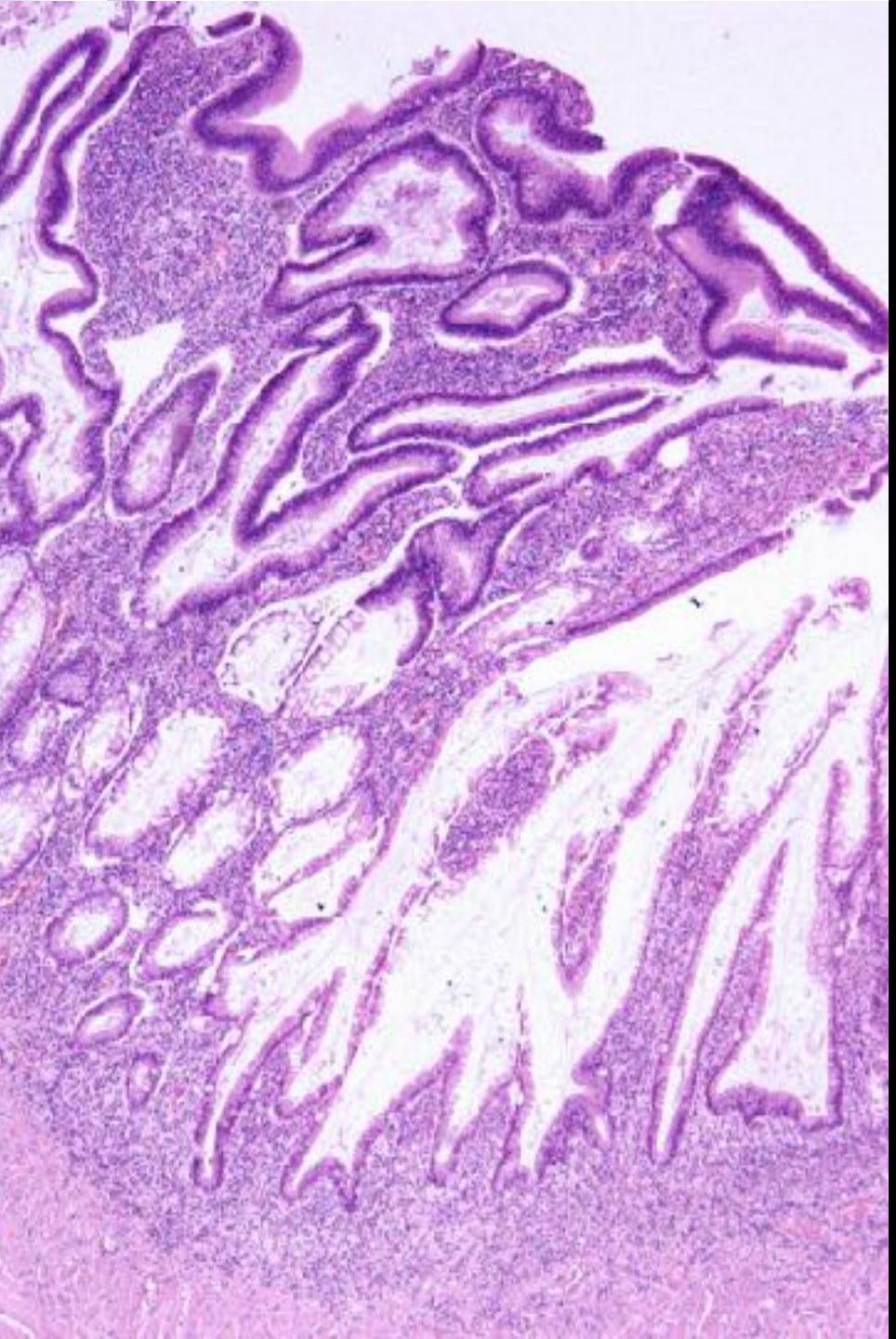


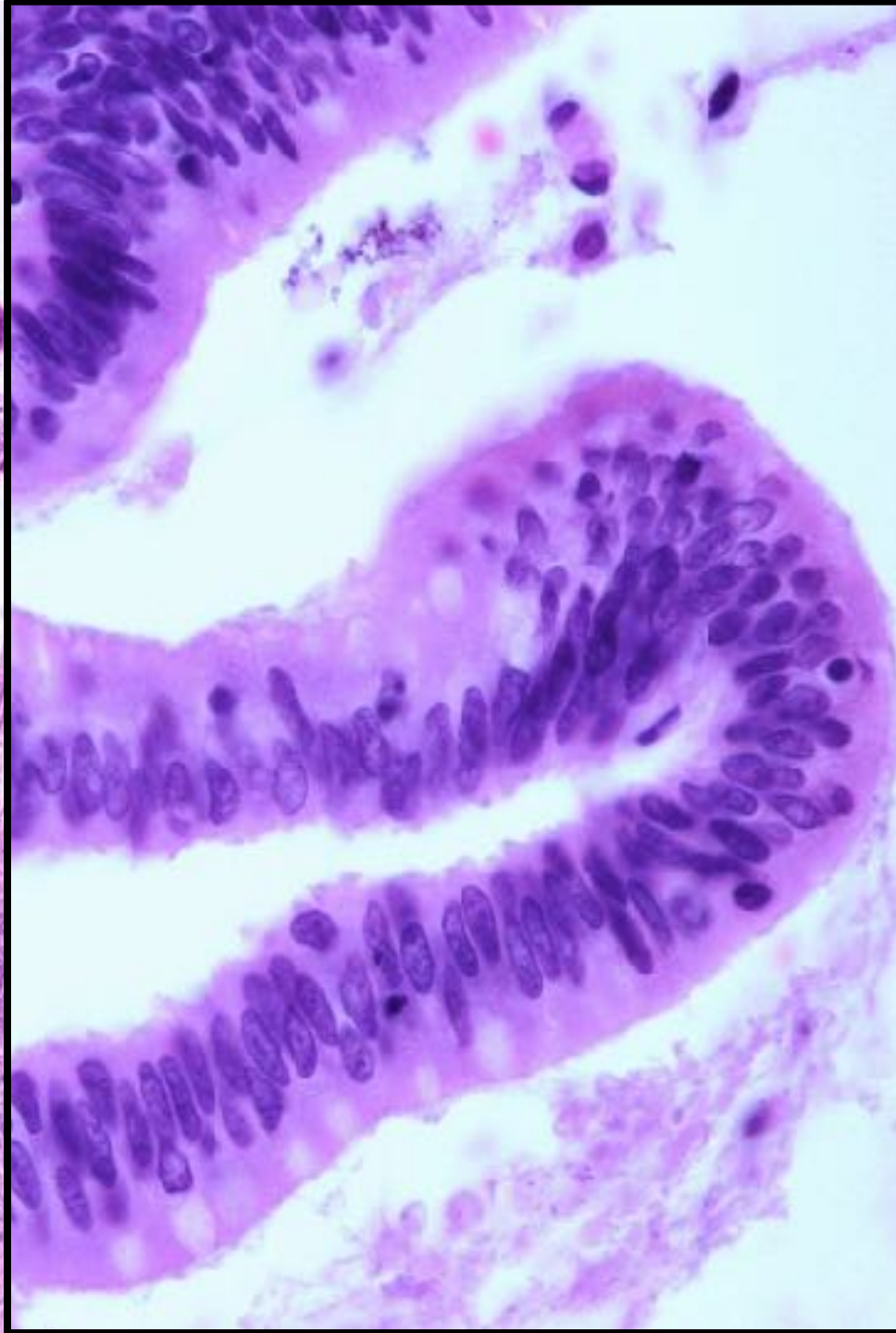












Diagnóstico

COLECTOMÍA SUBTOTAL:

- Adenocarcinoma mucinoso con invasión a tejido adiposo pericolónico
- Colitis ulcerosa crónica idiopática con actividad leve, atrofia extensa y displasia de bajo y alto grado multifocal
- Displasia de alto grado en mucosa polipoide

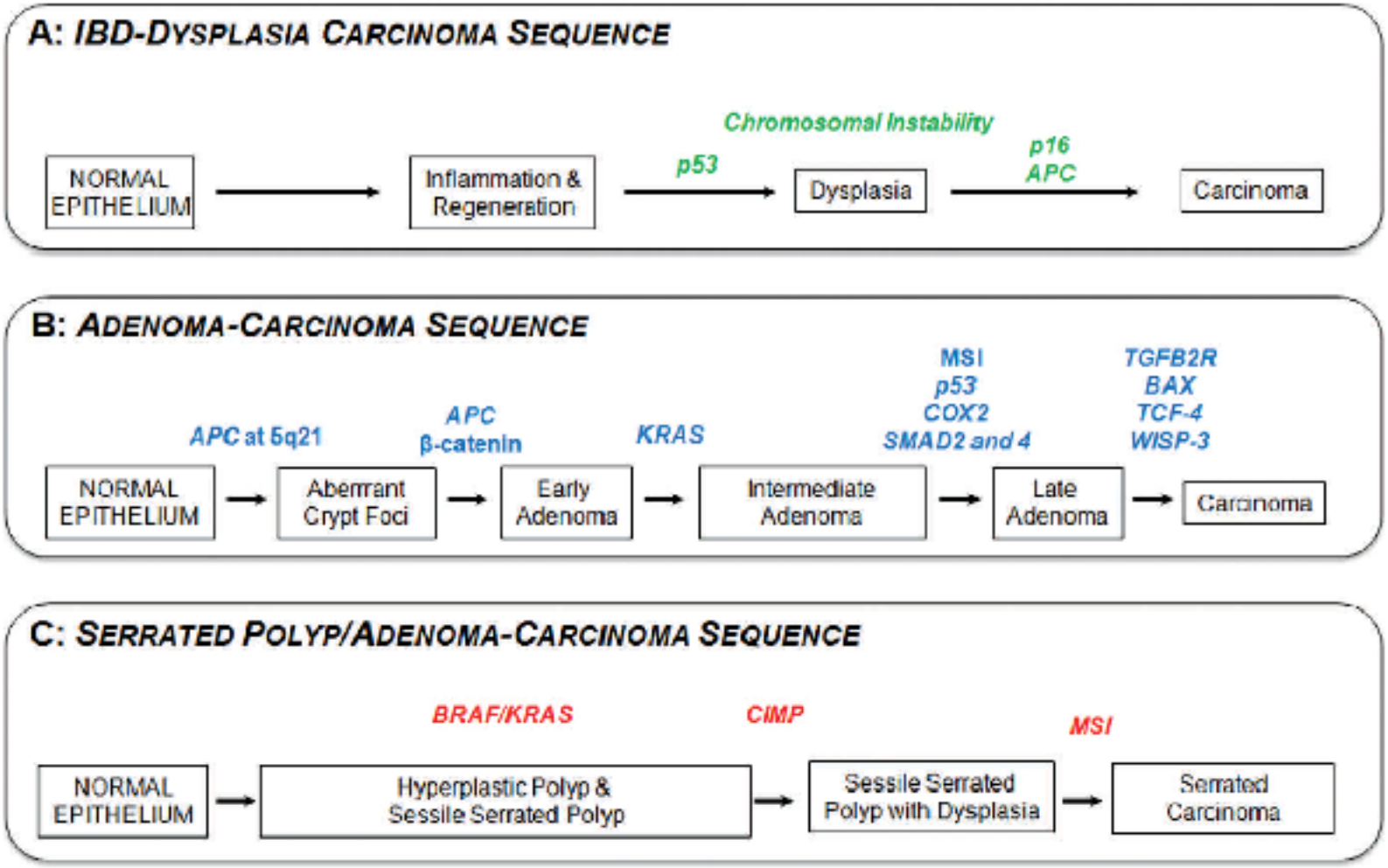
ECCO-ESP statement 19

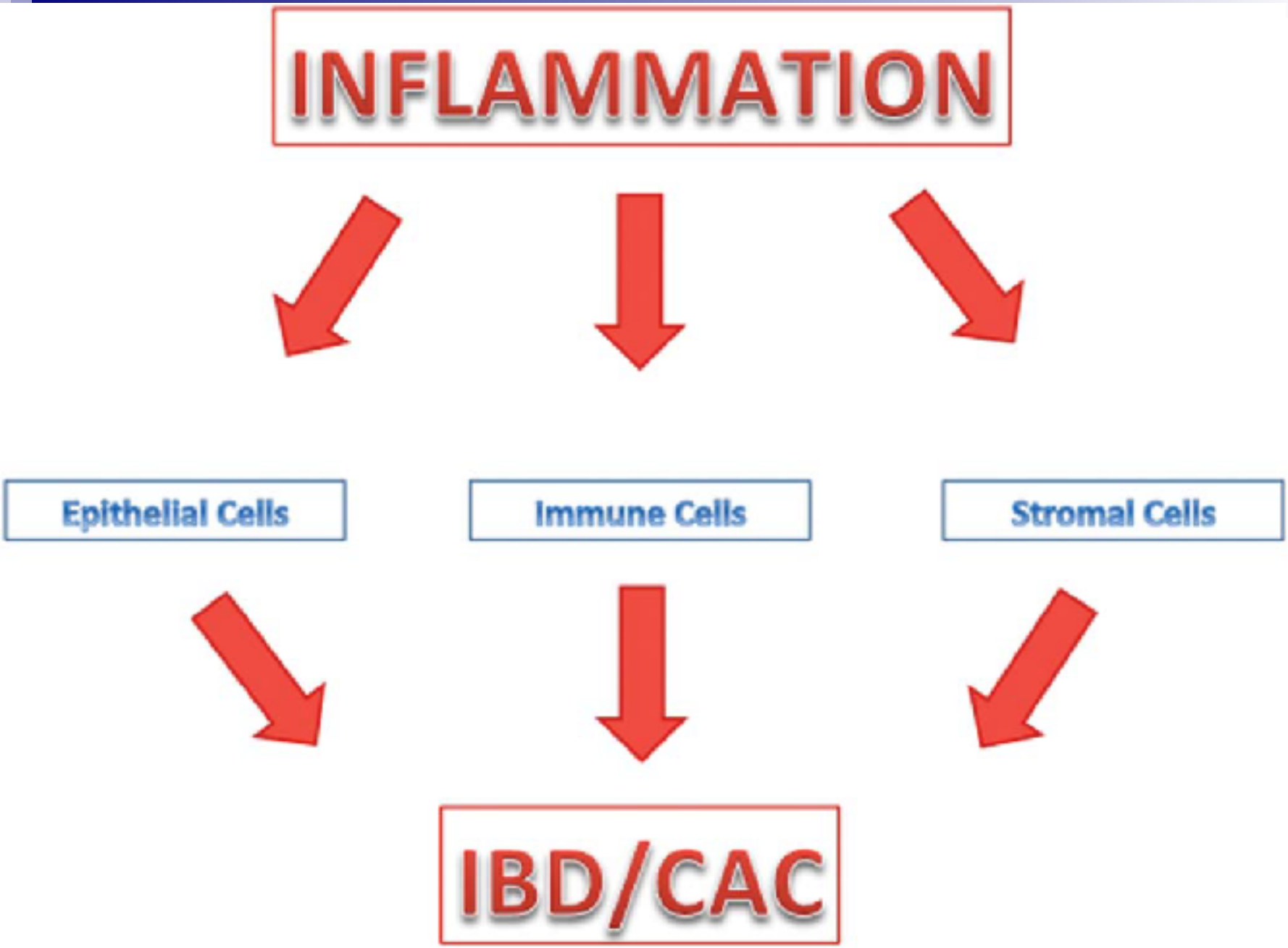
For surveillance 4 biopsy specimens should be taken from every 10 cm of the entire colon in addition to biopsies from macroscopically visible atypical lesions [EL 2]

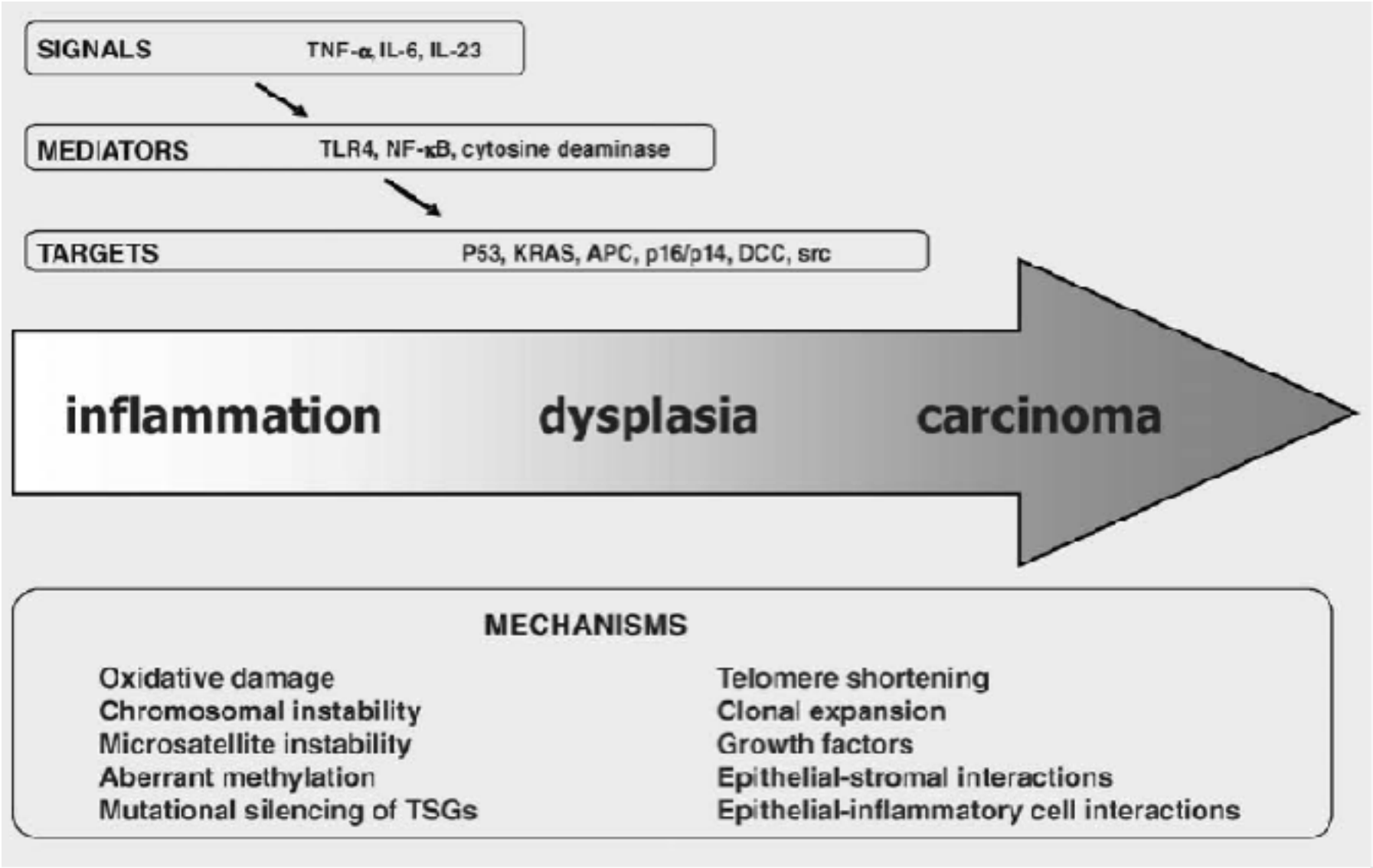
ECCO-ESP statement 20

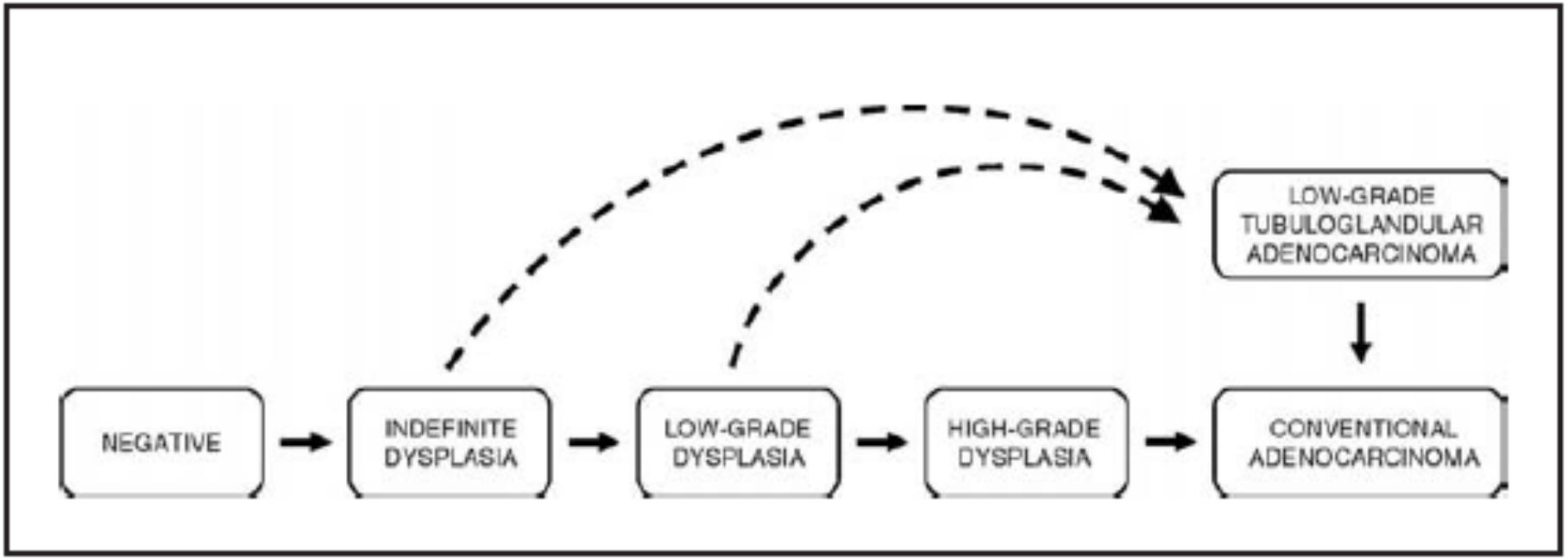
Adenoma-like lesions (sporadic adenomas) may be difficult to distinguish from colitis-associated dysplasia. The distinction is however important, because the management of sporadic adenomas differs from that of colitis-associated dysplasia. The patient's age, the site and morphology (endoscopic appearance, microscopy) of the lesion, along with biopsies of flat surrounding mucosa, may be helpful in this distinction [EL2]

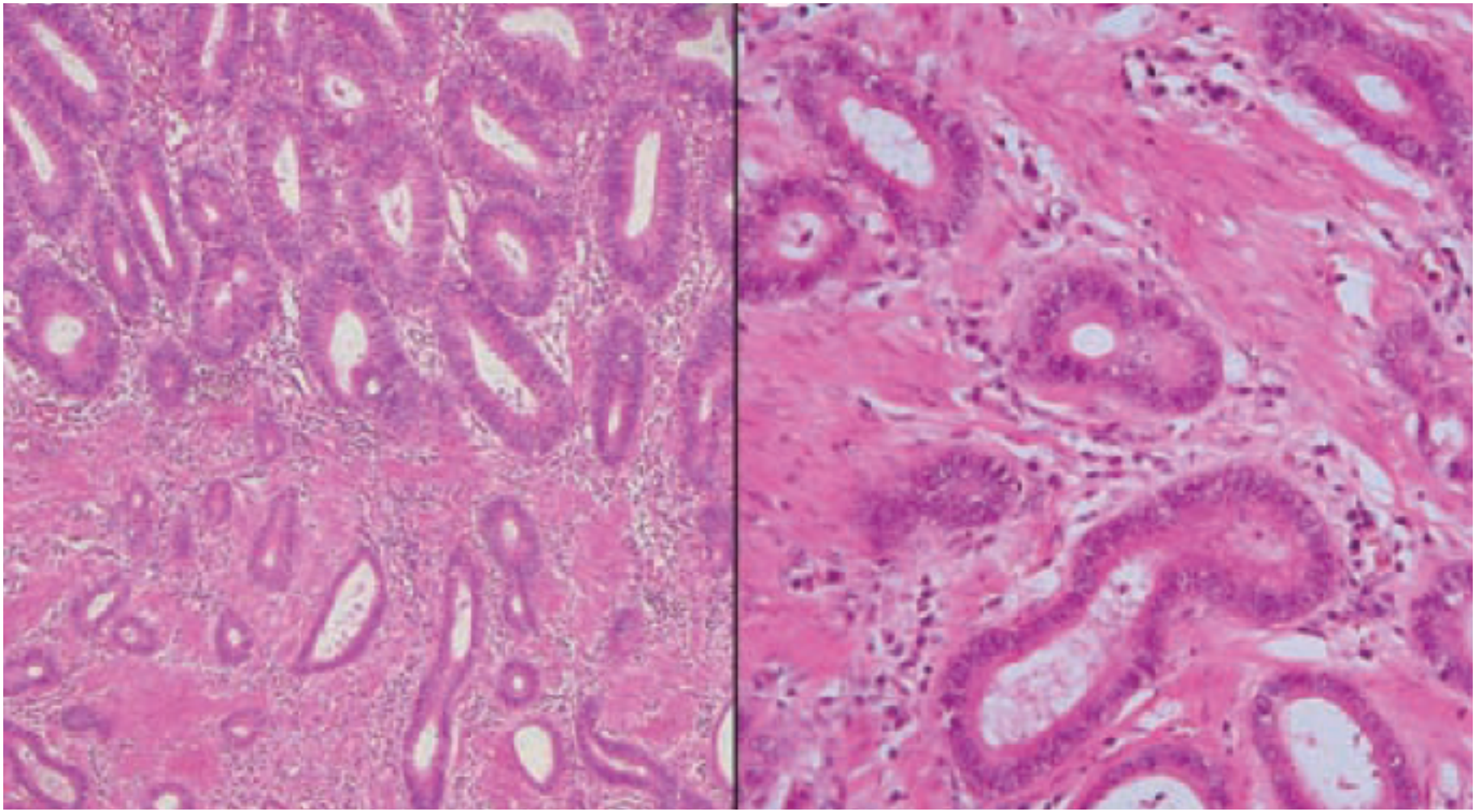
Carcinoma colorectal y CUCI

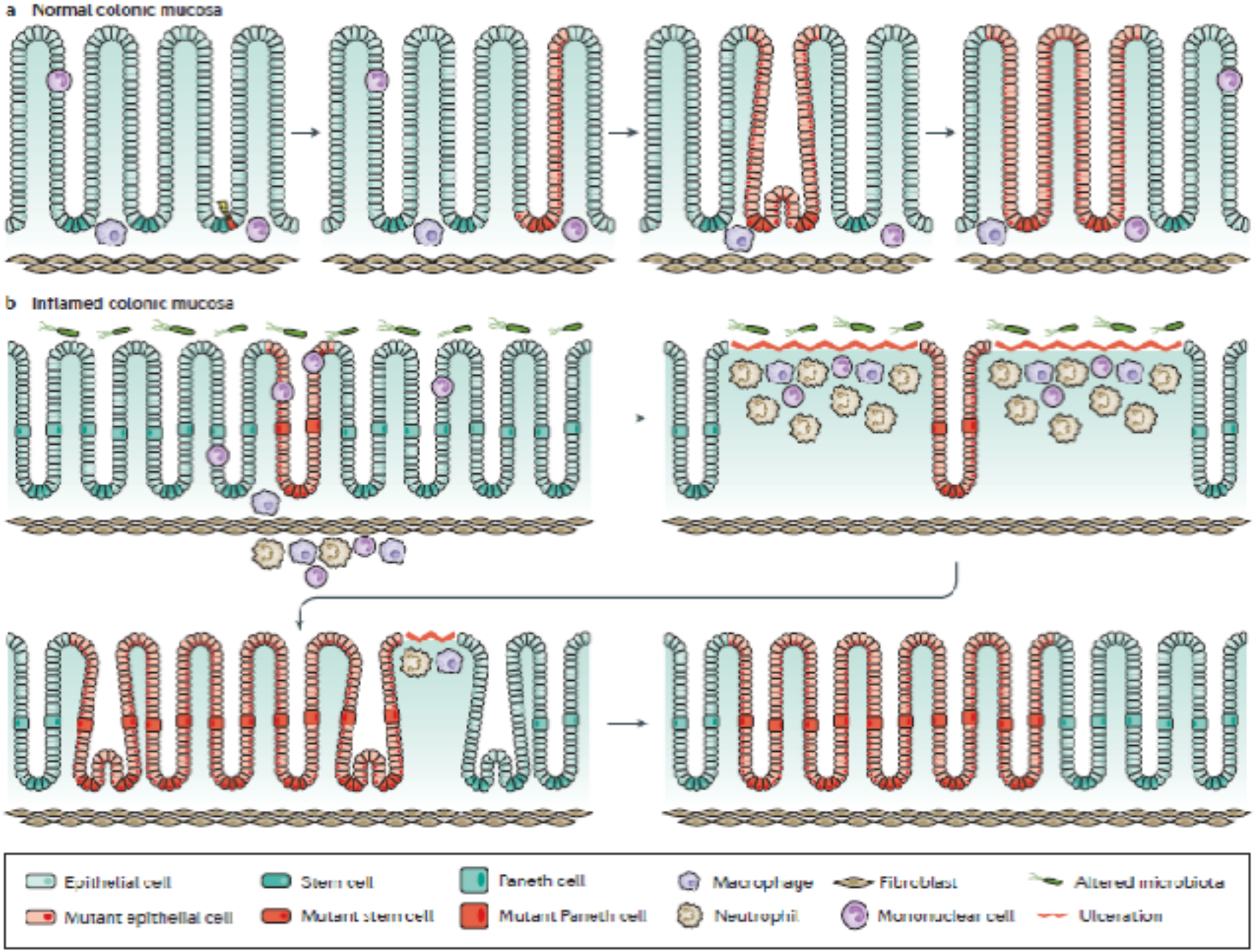


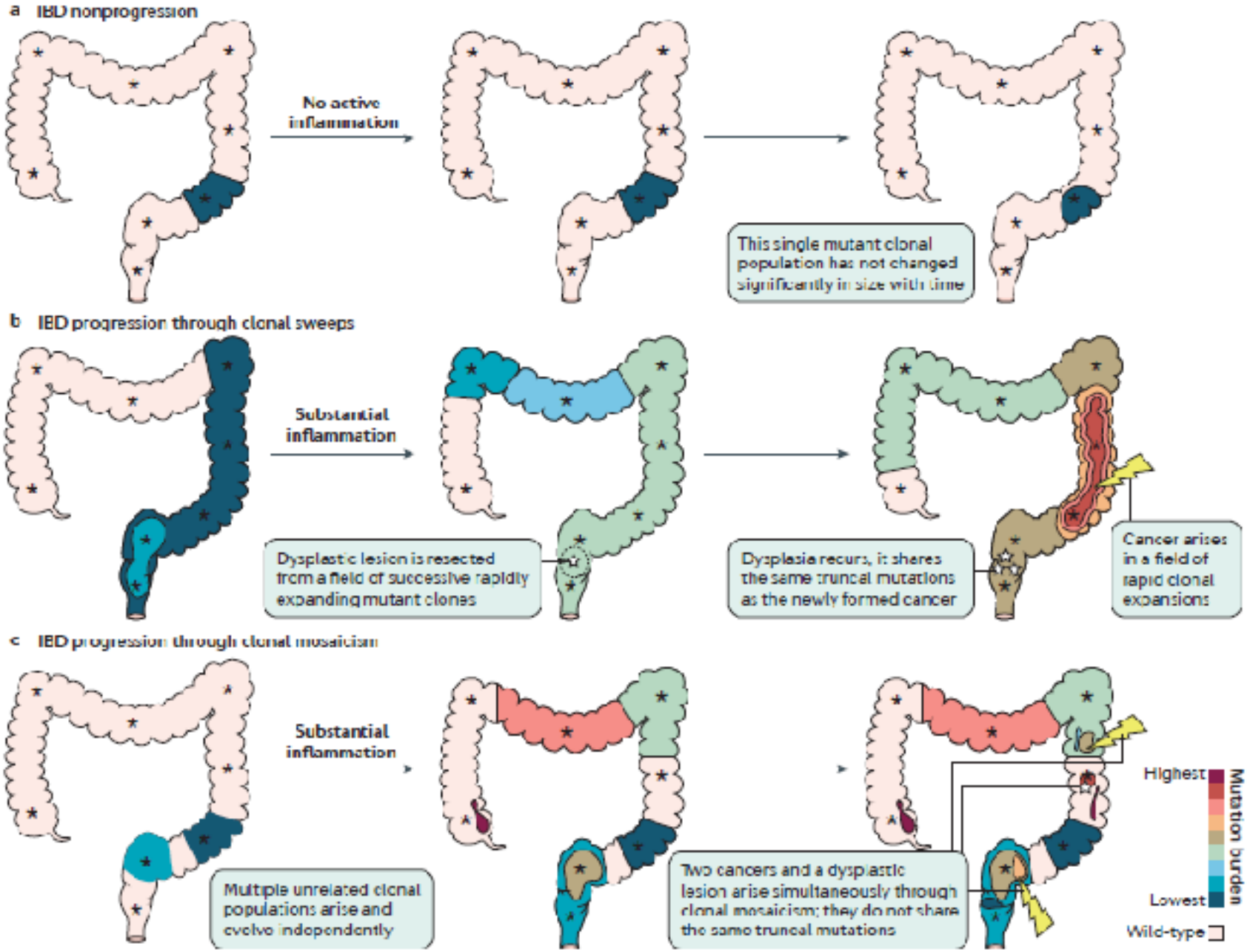

INFLAMMATION
Epithelial Cells
Immune Cells
Stromal Cells
IBD/CAC

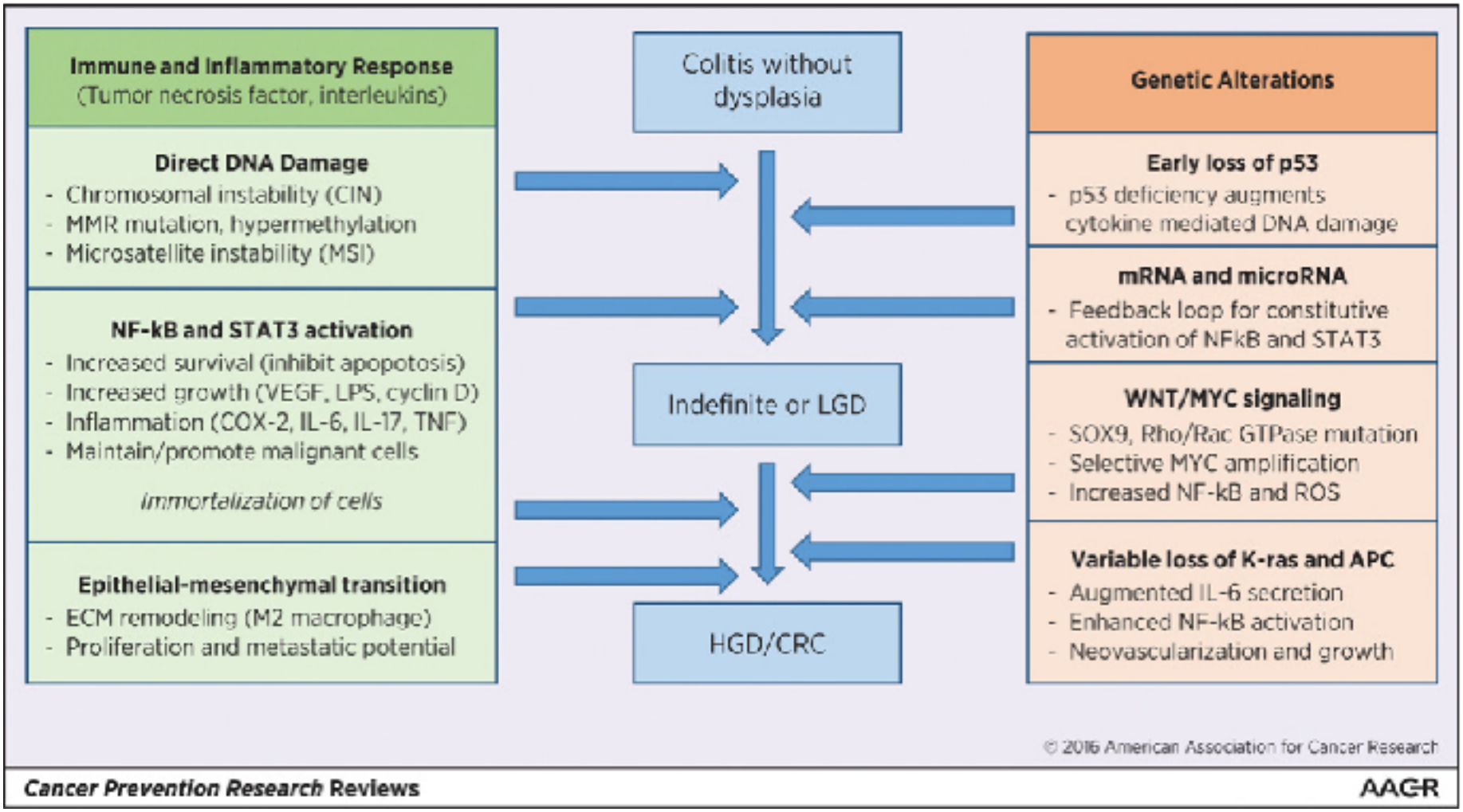

SIGNALS
TNF-α, IL-6, IL-23
MEDIATORS
TLR4, NF-κB, cytosine deaminase
TARGETS
P53, KRAS, APC, p16/p14, DCC, src
inflammation
dysplasia
carcinoma
MECHANISMS
Oxidative damage
Chromosomal instability
Microsatellite instability
Aberrant methylation
Mutational silencing of TSGs
Telomere shortening
Clonal expansion
Growth factors
Epithelial-stromal interactions
Epithelial-inflammatory cell interactions

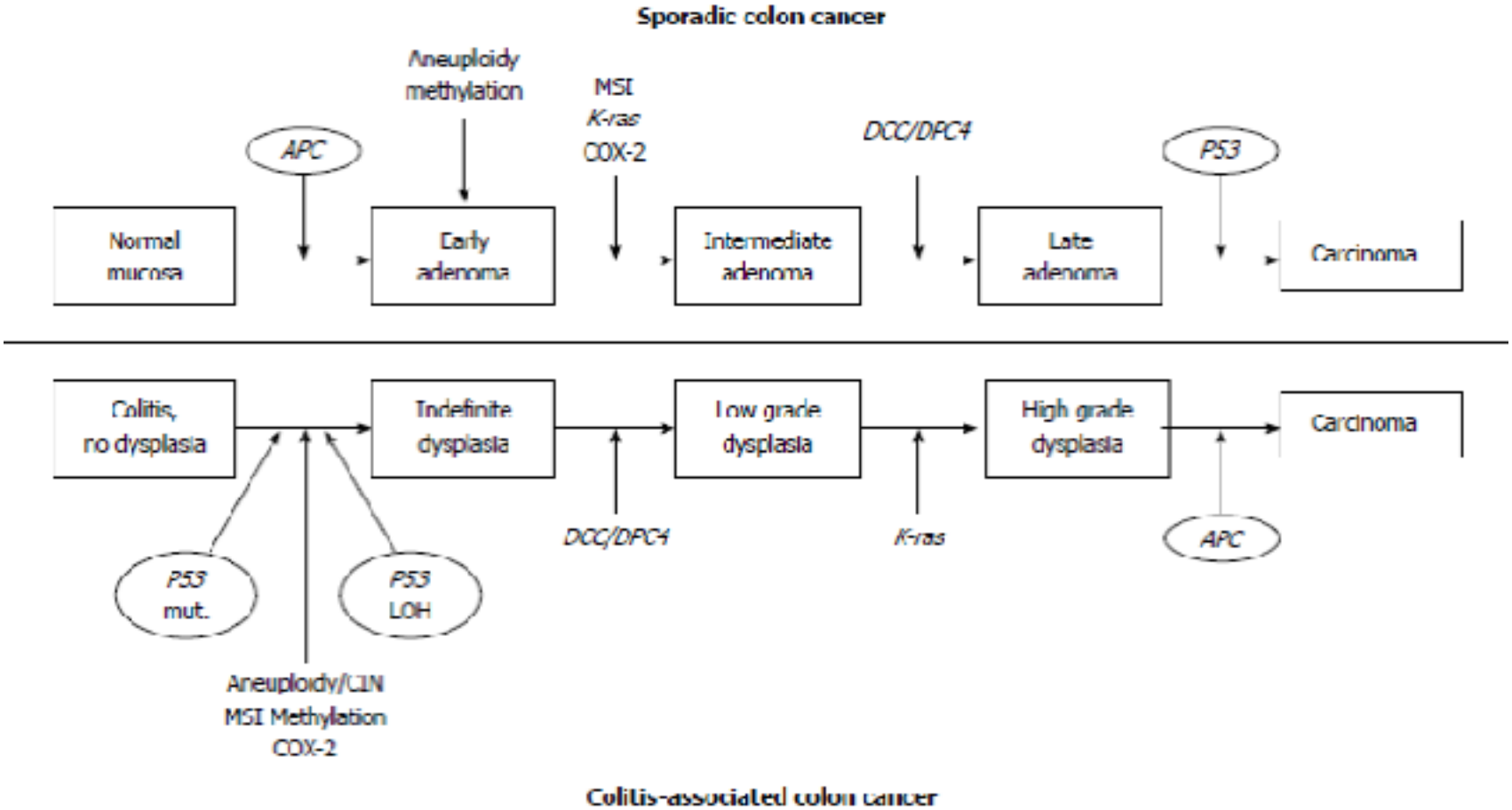

NEGATIVE
INDEFINITE DYSPLASIA
LOW-GRADE DYSPLASIA
HIGH-GRADE DYSPLASIA
CONVENTIONAL ADENOCARCINOMA
LOW-GRADE TUBULOGLANDULAR ADENOCARCINOMA

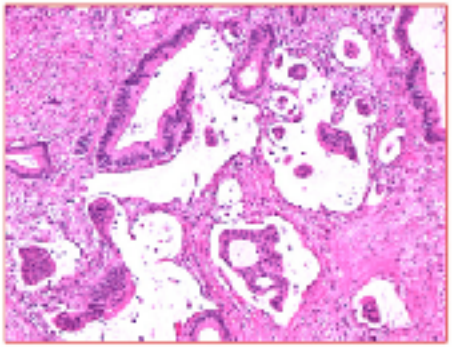
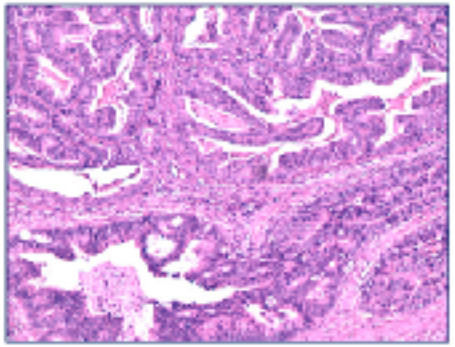



a Normal colonic mucosa
b Inflamed colonic mucosa
Epithelial cell
Mutant epithelial cell
Stem cell
Mutant stem cell
Paneth cell
Mutant Paneth cell
Macrophage
Neutrophil
Fibroblast
Mononuclear cell
Altered microbiota
Ulceration


a IBD nonprogression
No active inflammation
This single mutant clonal population has not changed significantly in size with time
b IBD progression through clonal sweeps
Substantial inflammation
Dysplastic lesion is resected from a field of successive rapidly expanding mutant clones
Dysplasia recurs, it shares the same truncal mutations as the newly formed cancer
Cancer arises in a field of rapid clonal expansions
c IBD progression through clonal mosaicism
Substantial inflammation
Multiple unrelated clonal populations arise and evolve independently
Two cancers and a dysplastic lesion arise simultaneously through clonal mosaicism; they do not share the same truncal mutations
Highest
Mutation burden
Lowest
Wild-type


Immune and Inflammatory Response
(Tumor necrosis factor, interleukins)
Direct DNA Damage
- Chromosomal instability (CIN)
- MMR mutation, hypermethylation
- Microsatellite instability (MSI)
NF-kB and STAT3 activation
- Increased survival (inhibit apopotosis)
- Increased growth (VEGF, LPS, cyclin D)
- Inflammation (COX-2, IL-6, IL-17, TNF)
- Maintain/promote malignant cells
immortalization of cells
Epithelial-mesenchymal transition
- ECM remodeling (M2 macrophage)
- Proliferation and metastatic potential
Colitis without dysplasia
Indefinite or LGD
HGD/CRC
Genetic Alterations
Early loss of p53
- p53 deficiency augments cytokine mediated DNA damage
mRNA and microRNA
- Feedback loop for constitutive activation of NFkB and STAT3
WNT/MYC signaling
- SOX9, Rho/Rac GTPase mutation
- Selective MYC amplification
- Increased NF-kB and ROS
Variable loss of K-ras and APC
- Augmented IL-6 secretion
- Enhanced NF-kB activation
- Neovascularization and growth
© 2016 American Association for Cancer Research


Sporadic colon cancer
Aneuploidy
methylation
MSI
K-ras
COX-2
APC
DCC/DPC4
P53
Normal
mucosa
Early
adenoma
Intermediate
adenoma
Late
adenoma
Carcinoma
Colitis,
no dysplasia
Indefinite
dysplasia
Low grade
dysplasia
High grade
dysplasia
Carcinoma
DCC/DPC4
K-ras
APC
P53
mut.
P53
LOH
Aneuploidy/CIN
MSI Methylation
COX-2
Colitis-associated colon cancer

	IBD-related	Sporadic
		
Phenotypic	Multiple lesions ↑ Mucinous ↑ Signet ring cells component High grade	Single lesion ↓ Mucinous ↓ Signet ring cells component Most moderate-differentiated
Molecular	TNF-α, IL-6, IFN-γ, NF-κB Reactive oxygen species Early *TP53* dysregulation Late *APC* dysregulation Infrequent *KRAS* mutations Non-canonical Wnt signaling	Early *APC* dysregulation Late *TP53* dysregulation Frequent *KRAS* mutations Canonical Wnt signaling
	Chromosomal instability (CIN) Microsatellite instability (MSI) Telomere shortening CpG island methylator phenotype (CIMP)	

Displasia en CUCI

- Displasia: 5% después de 5a, 25% después de 20a
- Adenocarcinoma: 5 - 10% de casos con CUCI

- Pancolitis
- Inicio en la infancia
- Más de 10 años de duración

- A partir de los 10 años de evolución, el riesgo de cáncer se incrementa 2% por año

Carcinoma colorectal y CUCI

- Incrementa el riesgo global de CCR de 2.7 a 5.7 veces
- Incidencia anual de 0.06% a 0.16%, riesgo relativo de 1.0 a 2.75
- Reducción en la frecuencia:
  - Tratamiento con mesalazina
  - Fármacos inmunosupresores
  - Tratamiento quirúrgico

Carcinoma colorectal y CUCI

Factores de riesgo:

a) Duración de la enfermedad
b) Extensión de la colitis
c) Intensidad del daño inflamatorio
d) Historia familiar de CCR
e) Colangitis esclerosante primaria

Carcinoma colorectal y CUCI

Duración de la enfermedad

Riesgo acumulado

- 2.5% (20 a)
- 7.6% (30 a)
- 10.8% (40 a)

- 2% (10 a)
- 8% (20 a)
- 18% (30 a)

Gastroenterology. 2006;130:1030–1038

Gut. 2001;48:526–535

Carcinoma colorectal y CUCI

Extensión de la colitis

Riesgo

- 14.8 (pancolitis)
- 2.8 (colitis izquierda)
- 1.7 (proctitis)

Carcinoma colorectal y CUCI

Evidencia de daño inflamatorio intenso

Constricciones (61% son malignas después de la 2a. década)

Pseudopólipos (2.5)

Historia familiar (RA:2-5)

Colangitis esclerosante primaria (RA:4.8)

Inflamm Bowel Dis 2010

Table 2: Summary of the characteristics of the studies evaluating the risk factors for CRC in IBD patients

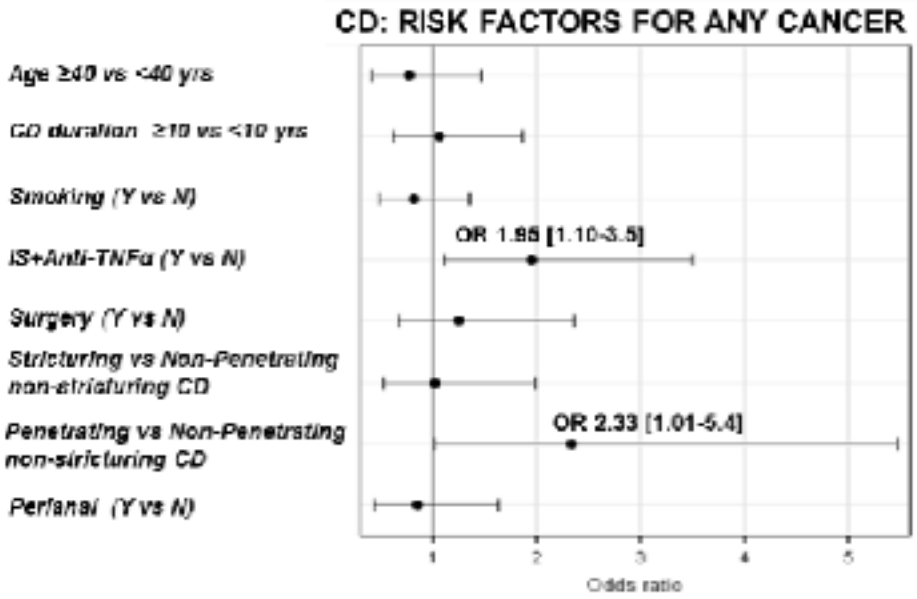
Study (Author, year)	Study design	Prognostic factors for recurrence or progression of dysplasia or cancer	Frequency of surveillance	Population
Laden *et al.* (2001)	Meta-analysis of 116 studies	Duration of disease Extent of disease	-	24,470 people with ulcerative colitis 1698 with CRC
Jess *et al.* (2005)	Meta-analysis of 6 studies	Gender Extent of disease	-	6538 people with Crohn's disease 55 with CRC
Soetikno *et al.* (2002)	Meta-analysis of 11 studies	PSC	-	16,844 people with ulcerative colitis 564 with ulcerative colitis and PSC 560 with CRC, including 30 with ulcerative colitis and PSC
Thomas *et al.* (2007)	Meta-analysis of 20 studies	Displasia at diagnosis	-	Over 2677 people with ulcerative colitis 508 with LGD 31 with CRC
Askling *et al.* (2001)	Retrospective (assumed) cohort, with nested case– control	Extent of disease Family history	-	19,876 people with ulcerative colitis or Crohn's disease 143 with CRC
Brentnall *et al.* (1996)	Prospective cohort	Age at diagnosis Duration of disease PSC	-	45 people with ulcerative colitis 20 with PSC 13 with dysplasia

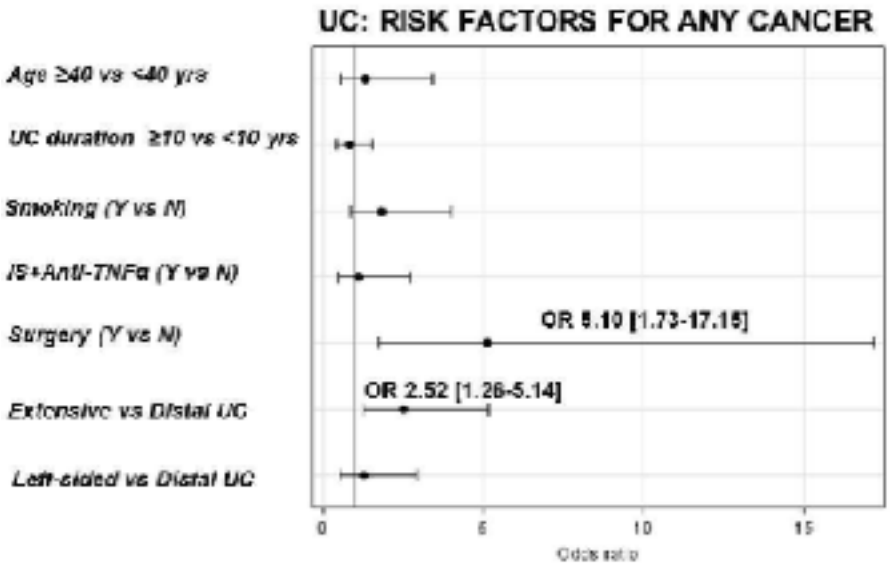
Table 2. Characterization of incident cancers in **Inflammatory Bowel Disease patients.**

Cancer	Crohn's Disease n=99	Ulcerative Colitis n=75
Digestive system (n=64)		
CRC	19	24
SBC	7	1 (pouch)
Anal carcinoma	2	0
Cholangiocarcinoma	1	2
GIST	1	0
Carcinoid	3	0
Gastric	1	0
Pancreatic	1	0
HCC	0	1
Esophageal	0	1
Skin (n=23)		
NMSC	7	2
Melanoma	6	5
Kaposi	0	2
Keratoacanthoma	1	0
Urinary tract (n=21)		
Renal	4	4
Prostatic	5	6
Bladder	0	2
Lung (n=15)	7	8
Breast (n=14)	7	7
Genital (n=12)		
Ovary	1	1
Uterine	5	2
Testis	2	1
Thyroid (n=8)	6	2
Lymphoma (n=6)	6	0

Accepted Manuscript

INFLAMMATORY BOWEL DISEASE PHENOTYPE AS RISK FACTOR FOR CANCER IN A PROSPECTIVE MULTICENTER NESTED CASE-CONTROL IG-IBD STUDY





INFLAMMATORY BOWEL DISEASE PHENOTYPE AS RISK FACTOR FOR CANCER IN A PROSPECTIVE MULTICENTER NESTED CASE-CONTROL IG-IBD STUDY

Figure 4c

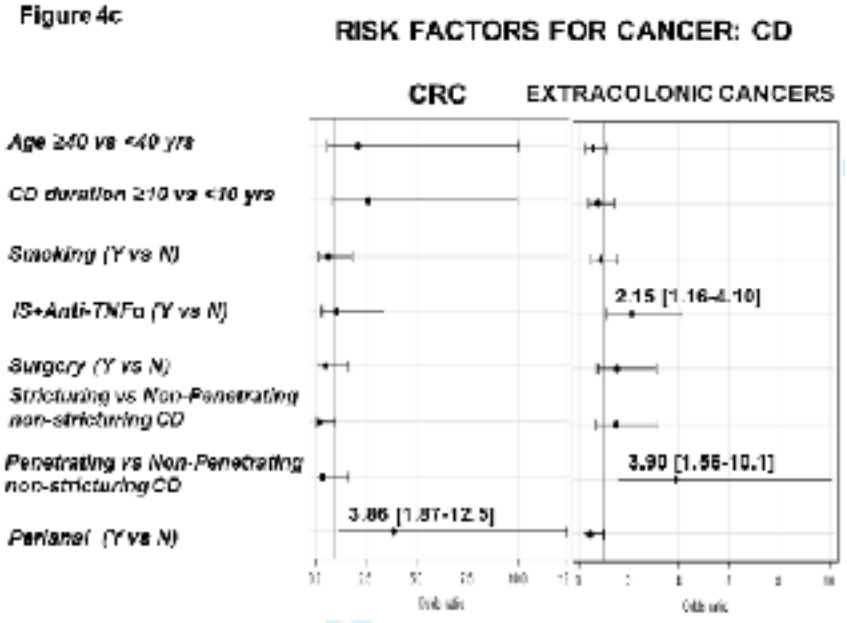
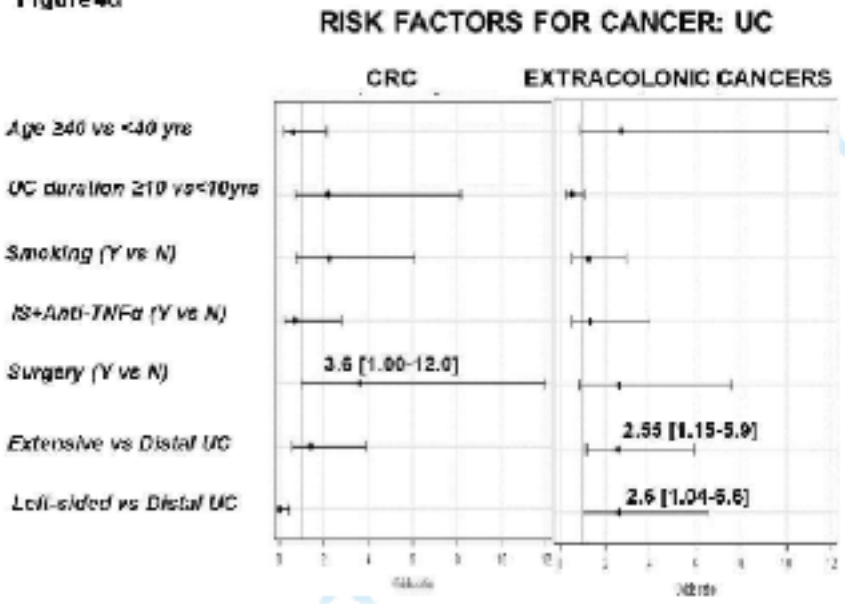


Figure 4d



CUCI y carcinoma

Displasia de bajo grado

↓

Displasia de alto grado o carcinoma in situ

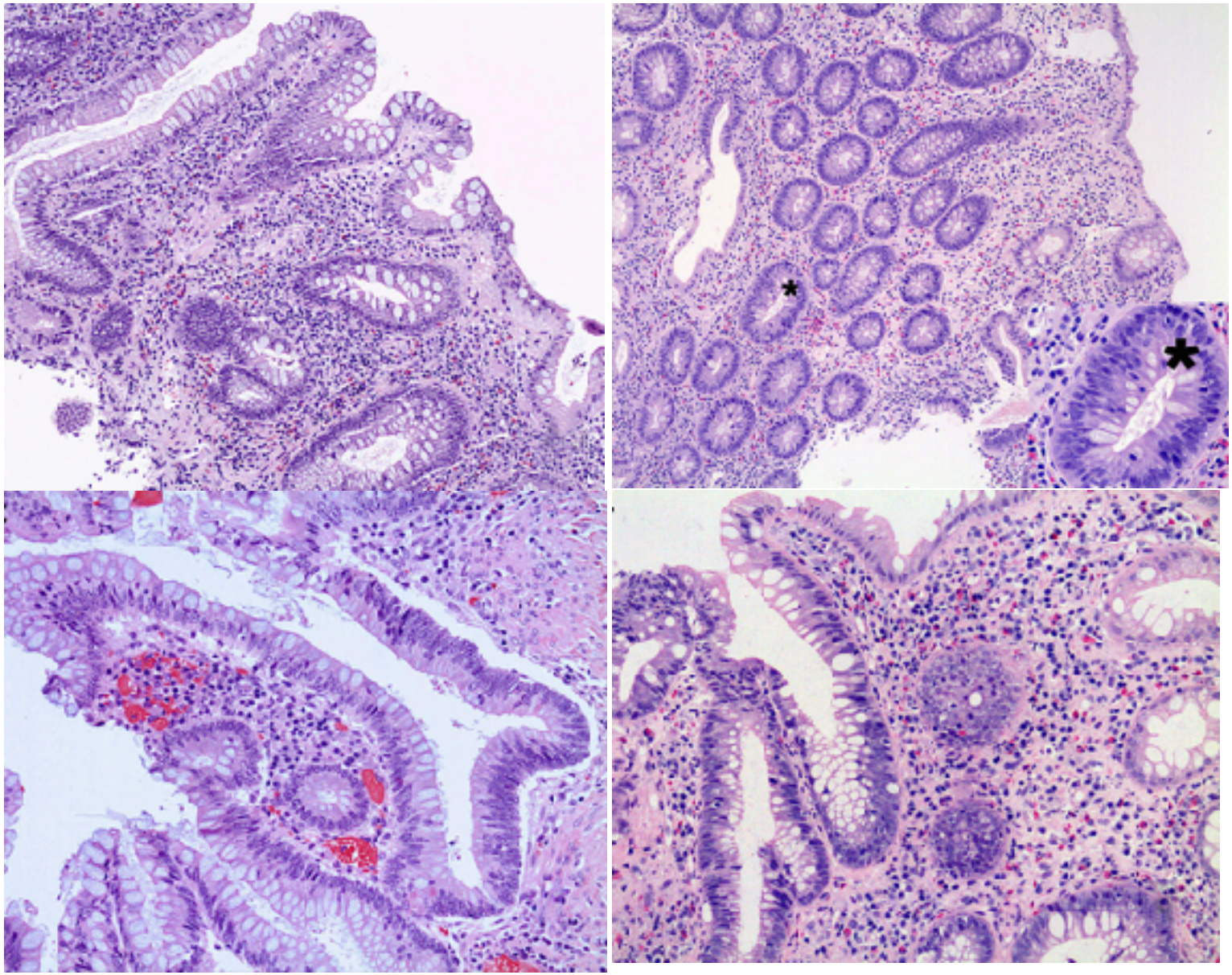
↓

Carcinoma intramucoso

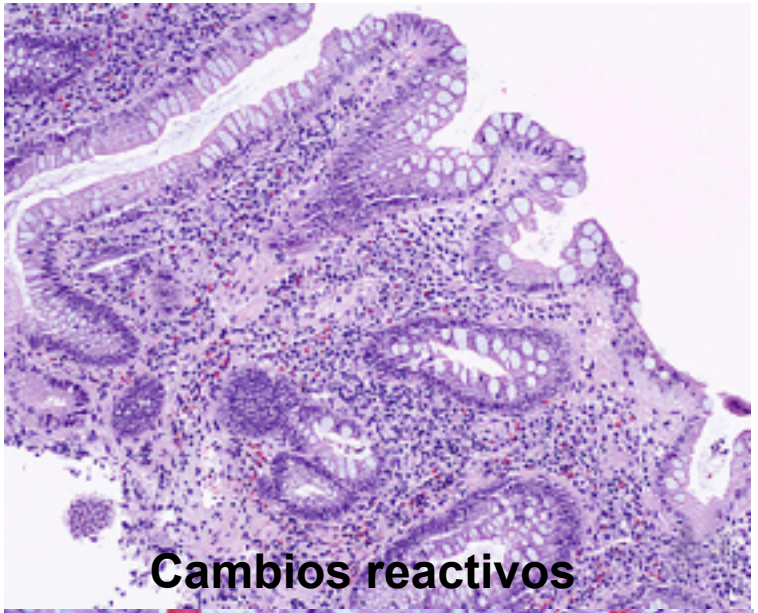
↓

Carcinoma invasor

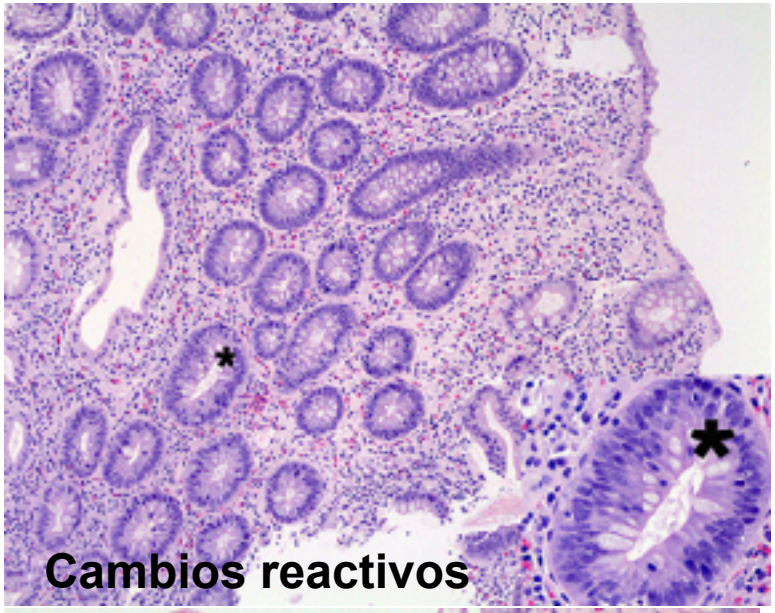
Cambios epiteliales



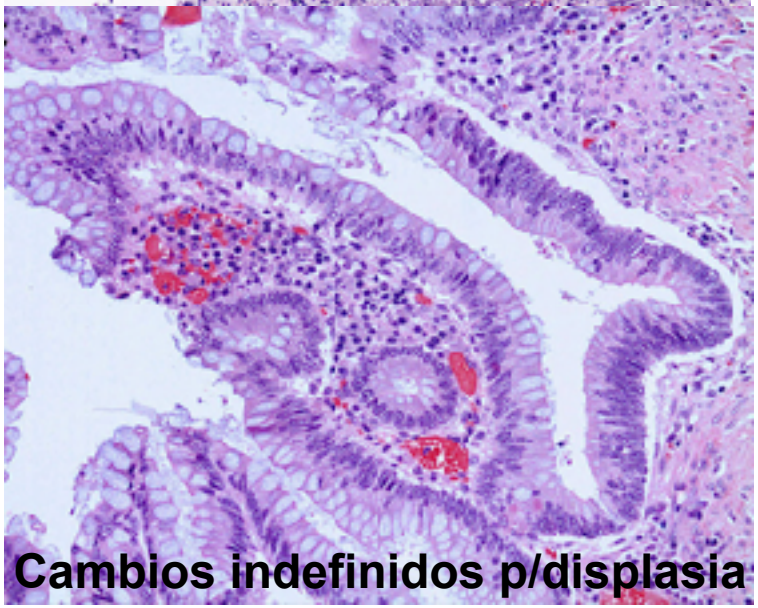
Cambios epiteliales



Cambios reactivos

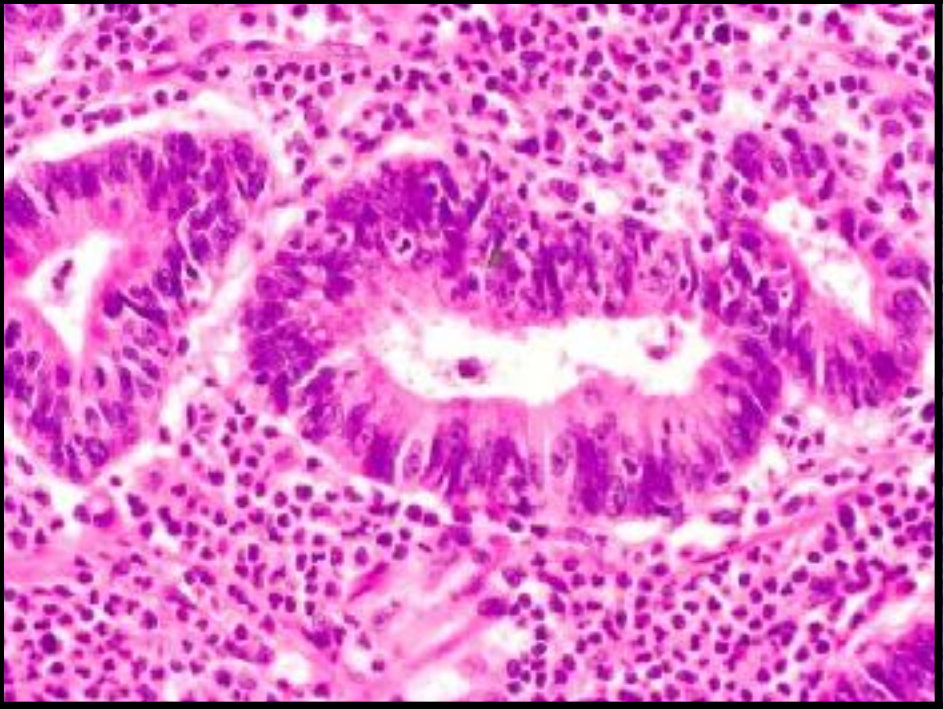


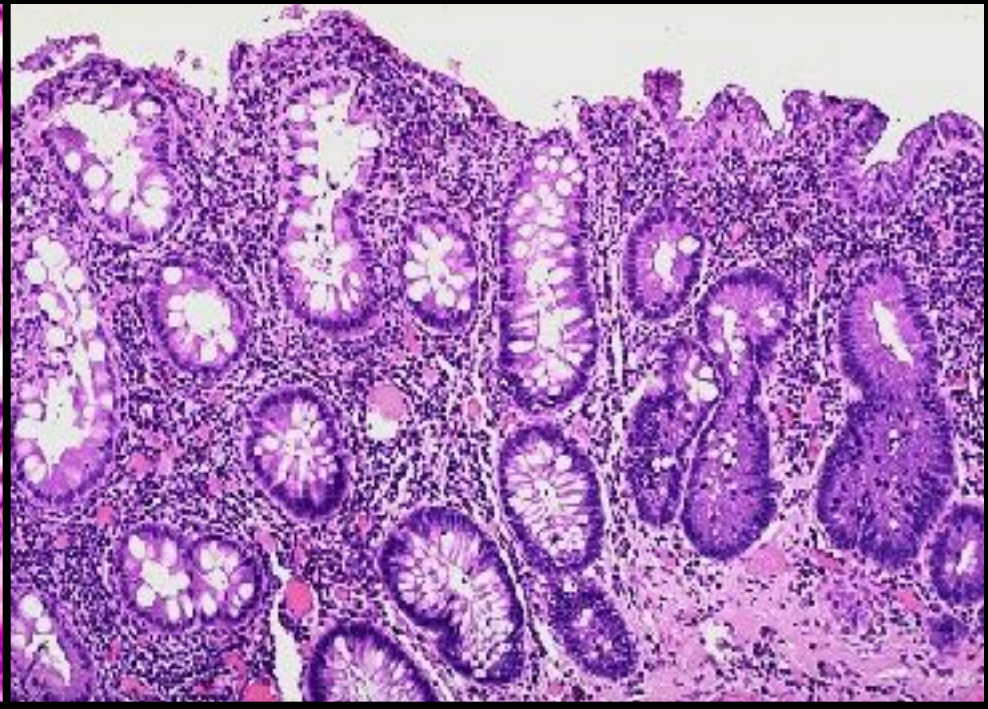
Cambios reactivos

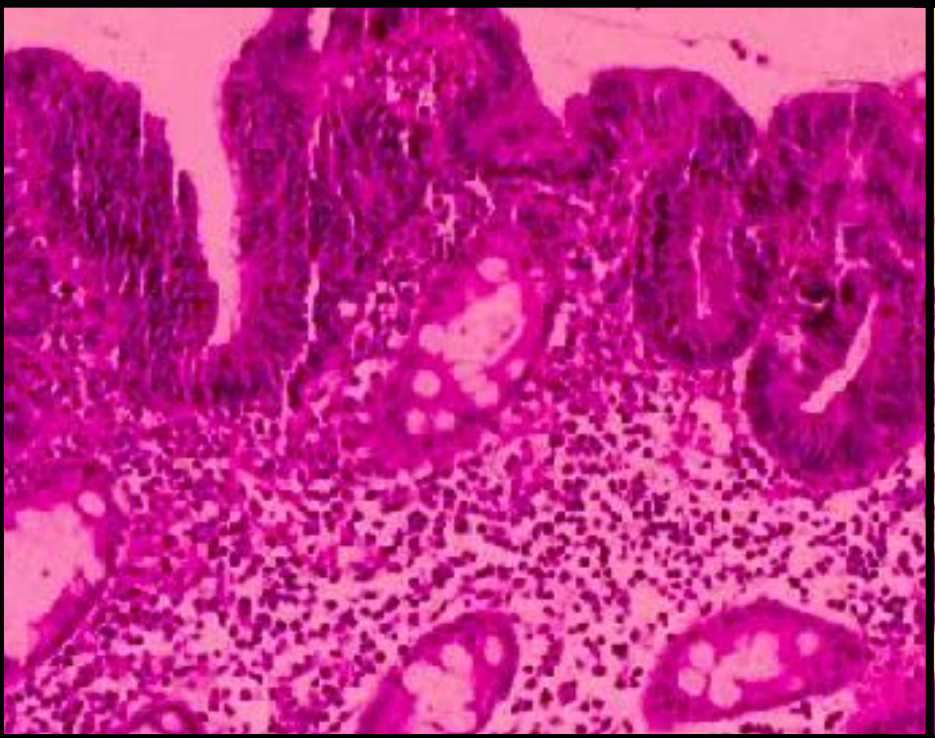


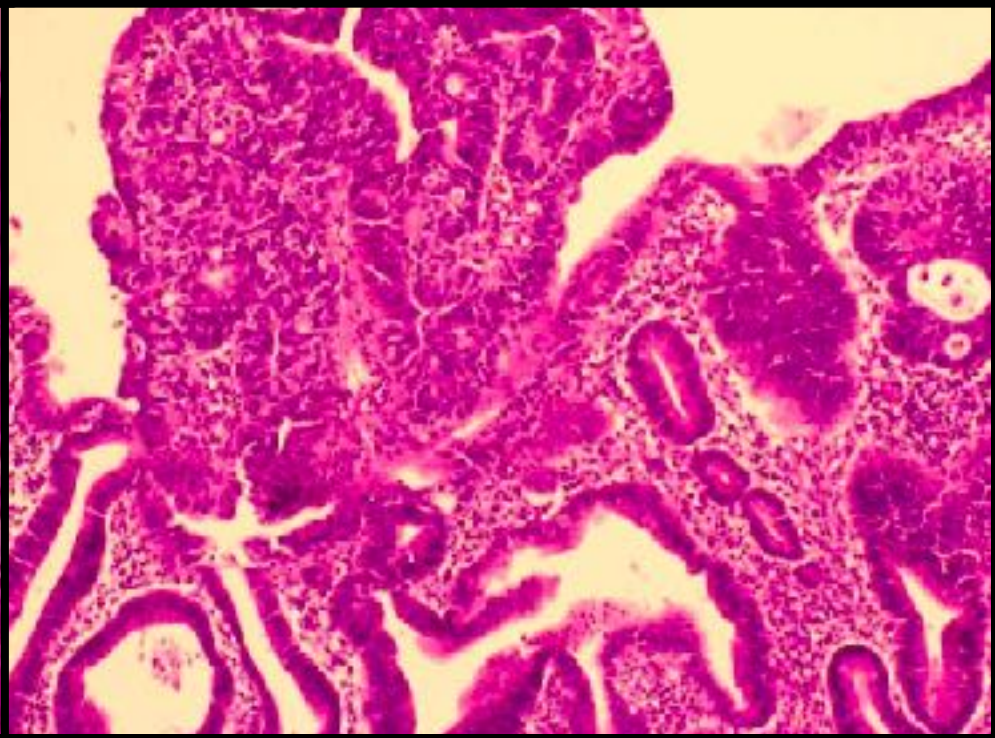
Cambios indefinidos p/displasia

Cambios indefinidos p/displasia



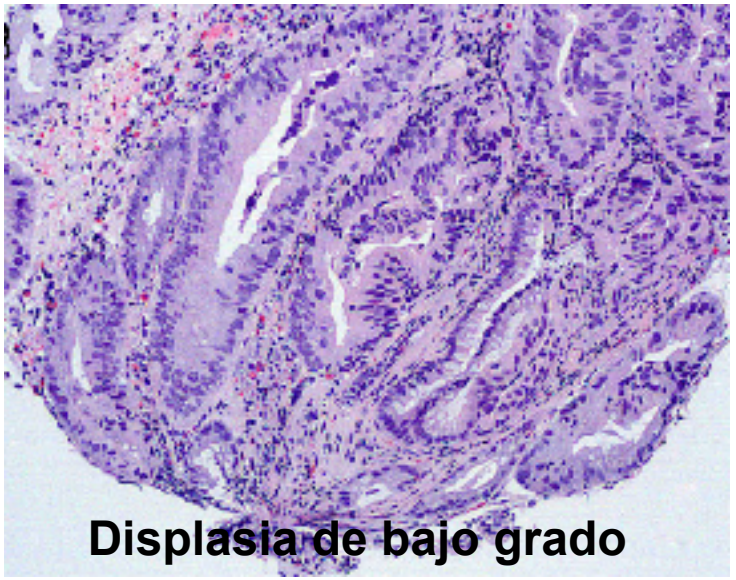




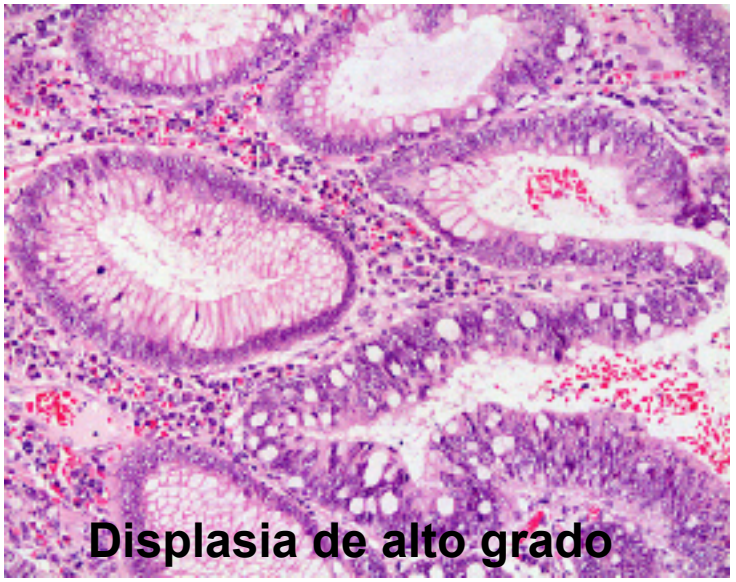


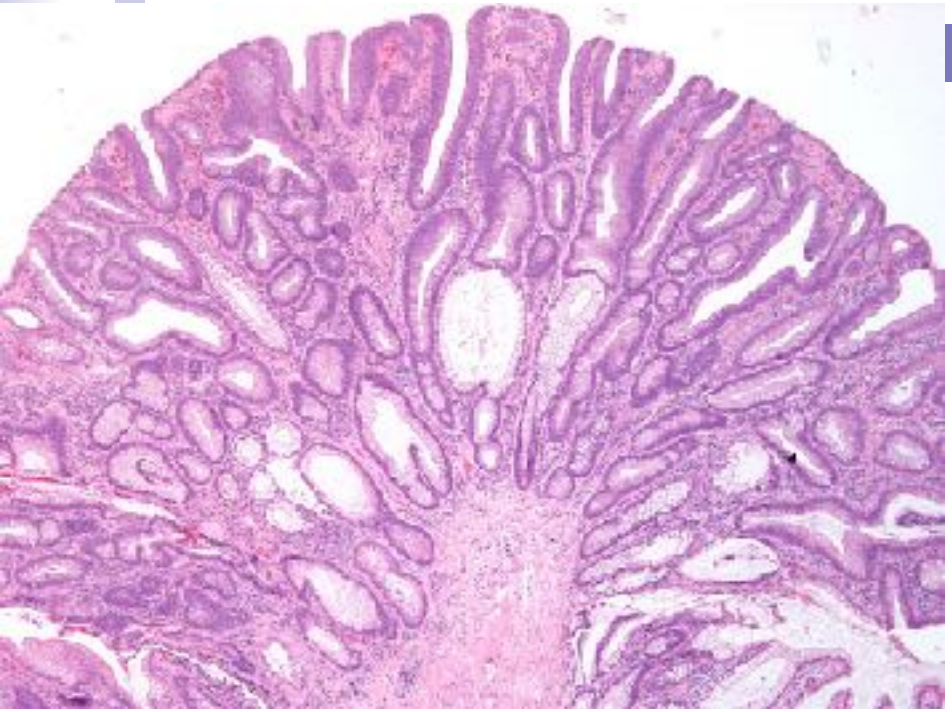
Cambios epiteliales

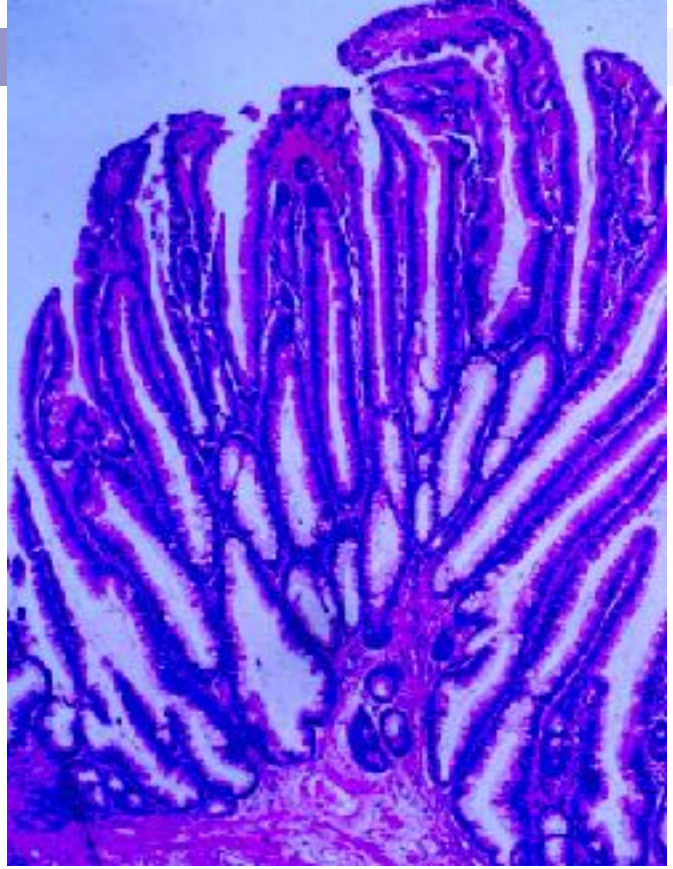
Displasia de bajo grado

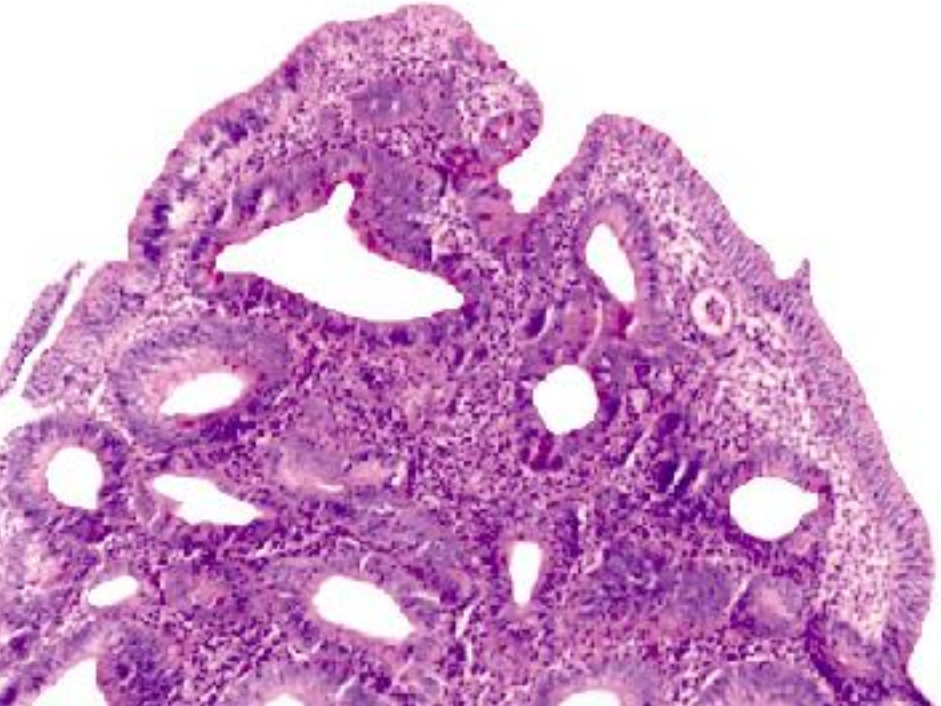

Displasia de bajo grado

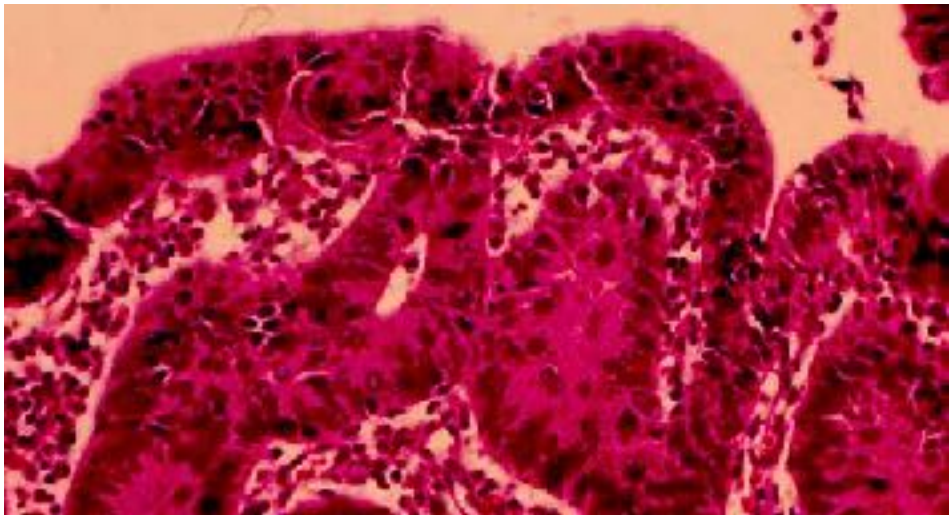
Displasia de alto grado


Displasia de alto grado

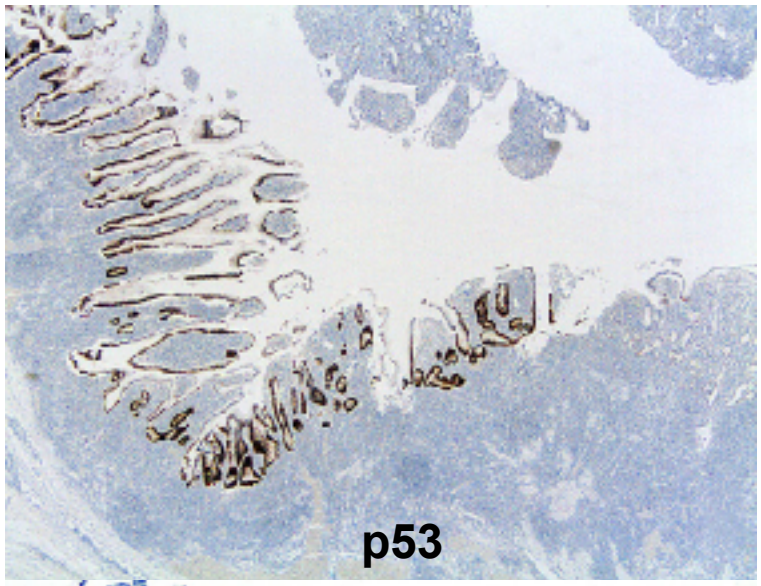


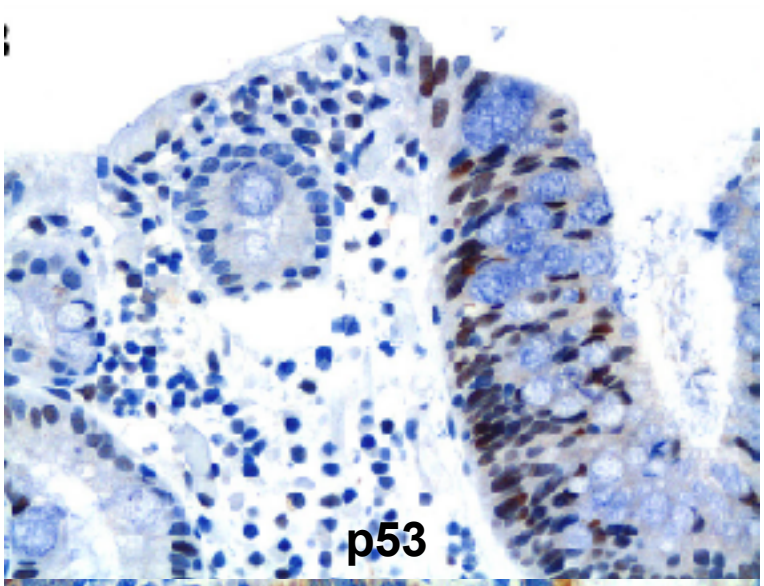


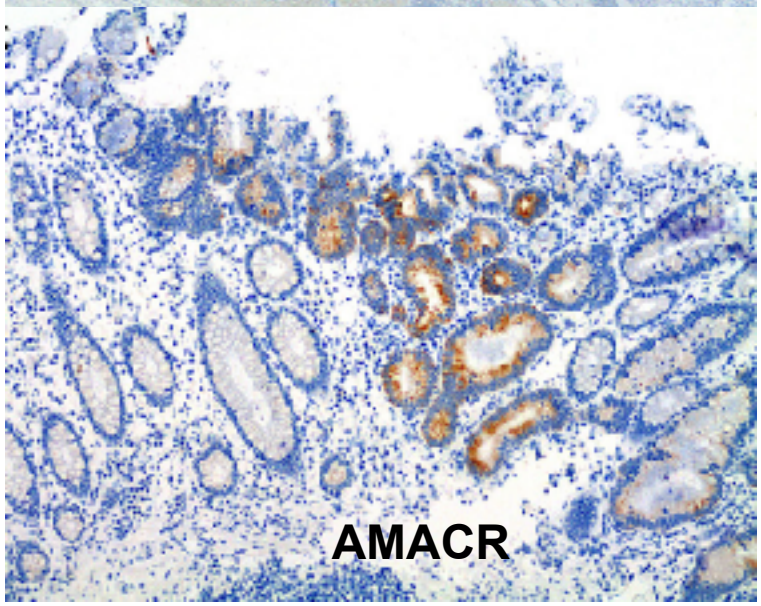


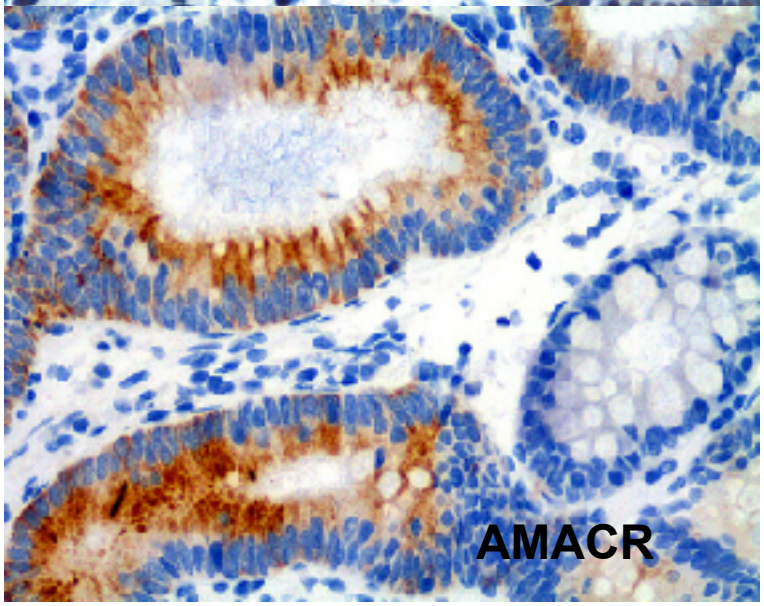


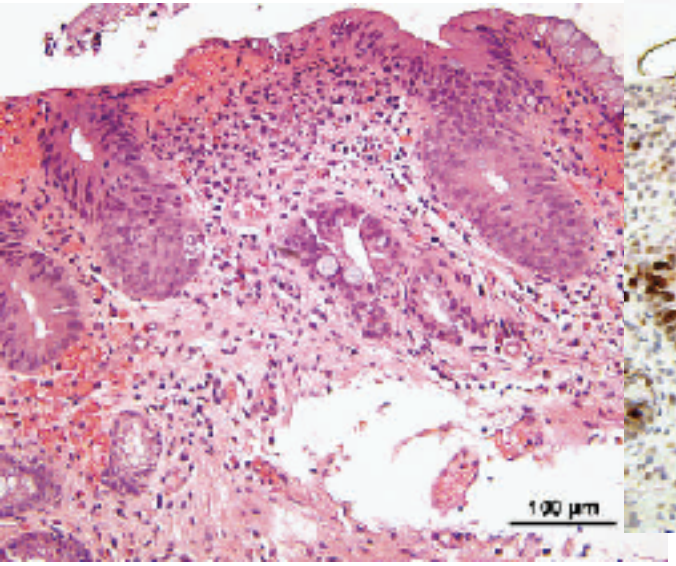
Inmunohistoquímica en displasia

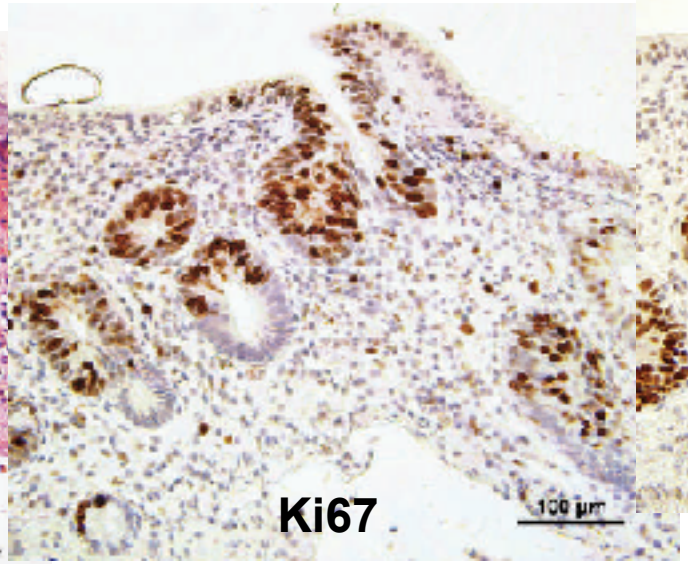


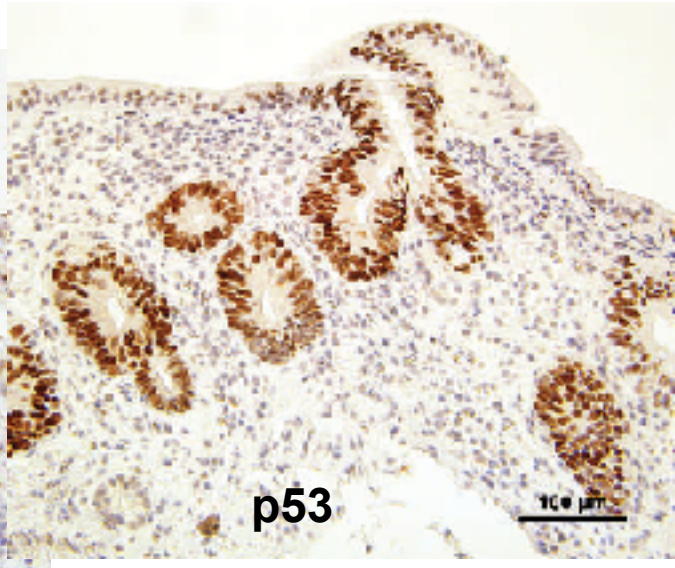







100 µm


Ki67
100 µm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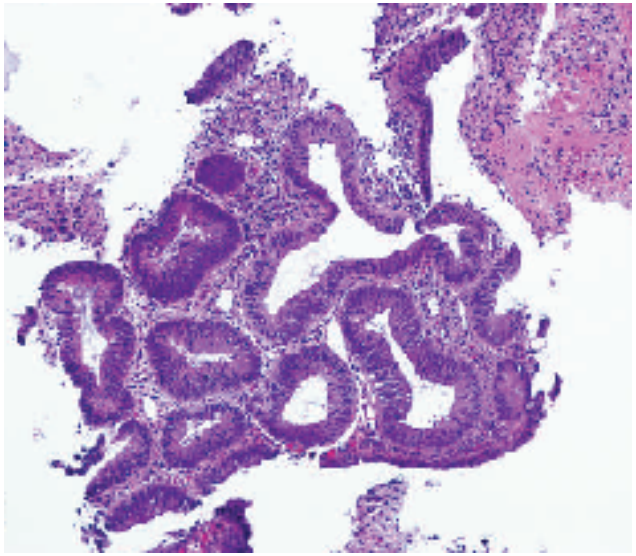

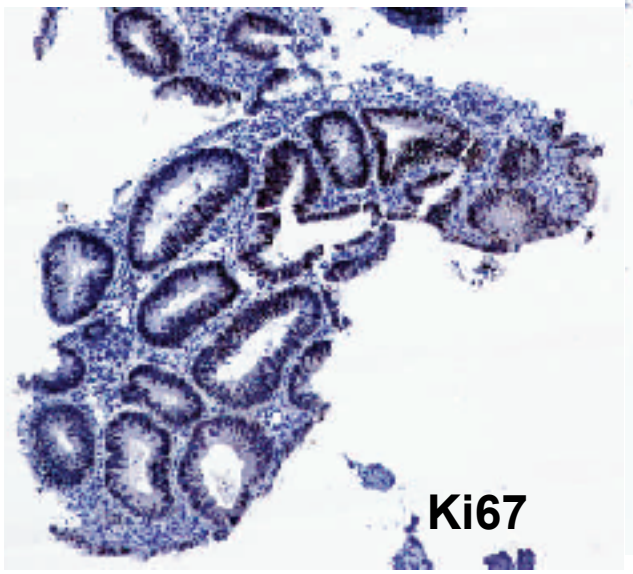
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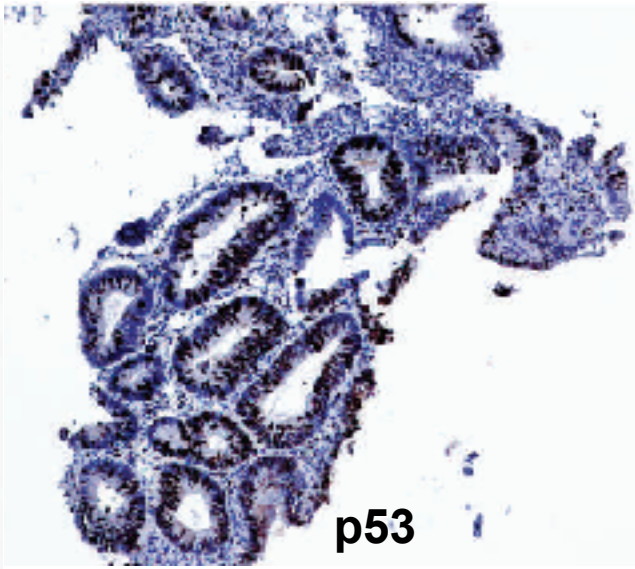
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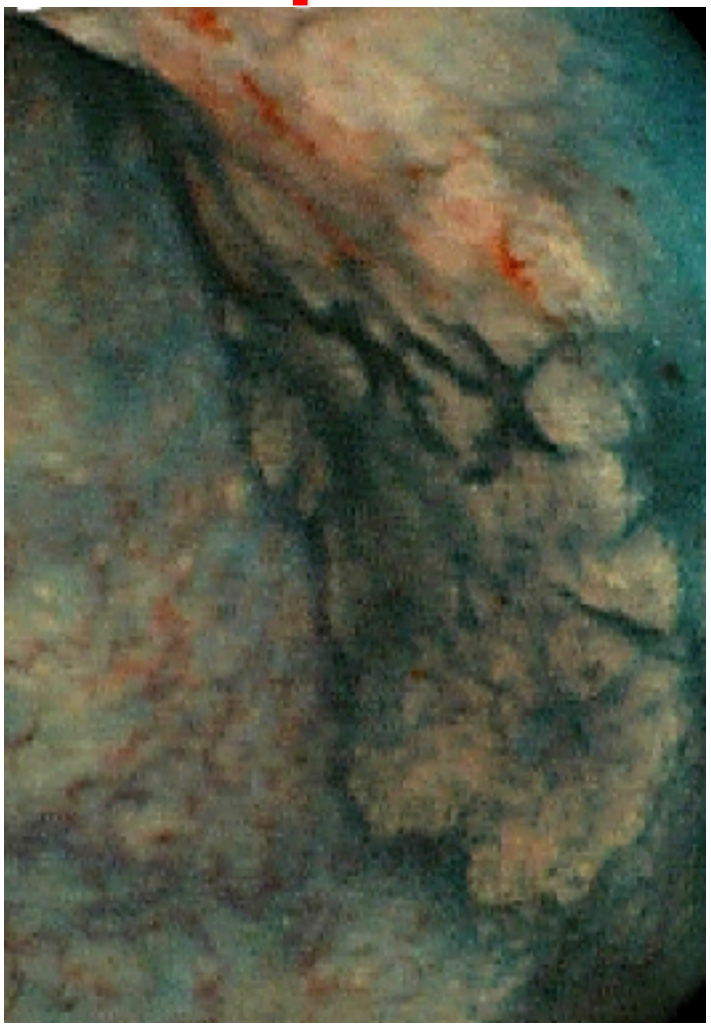
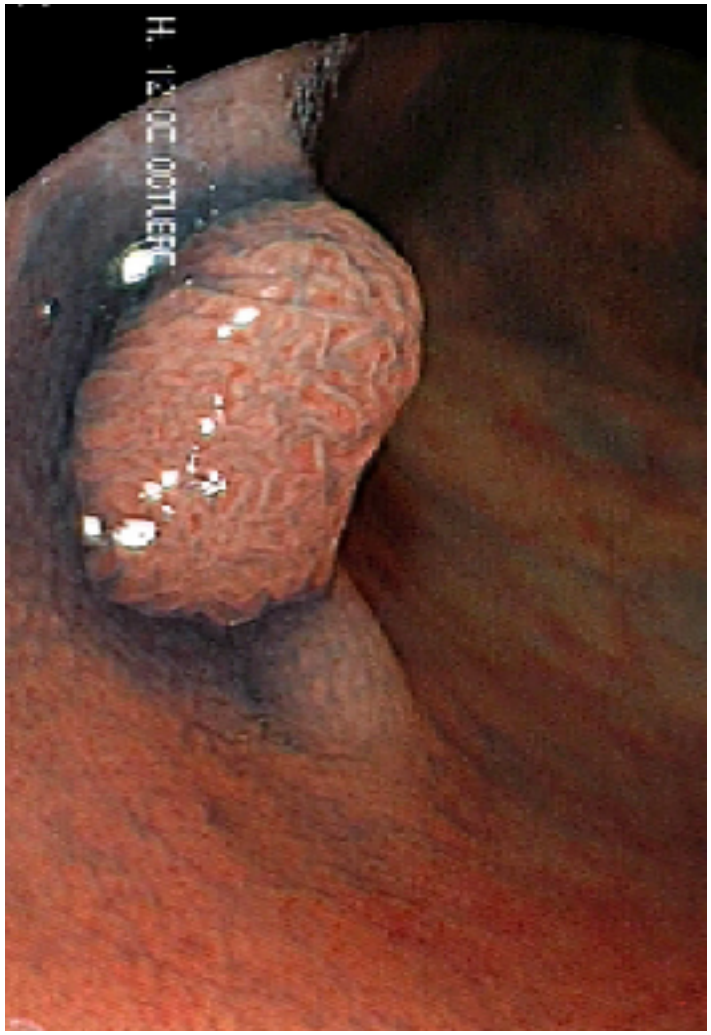
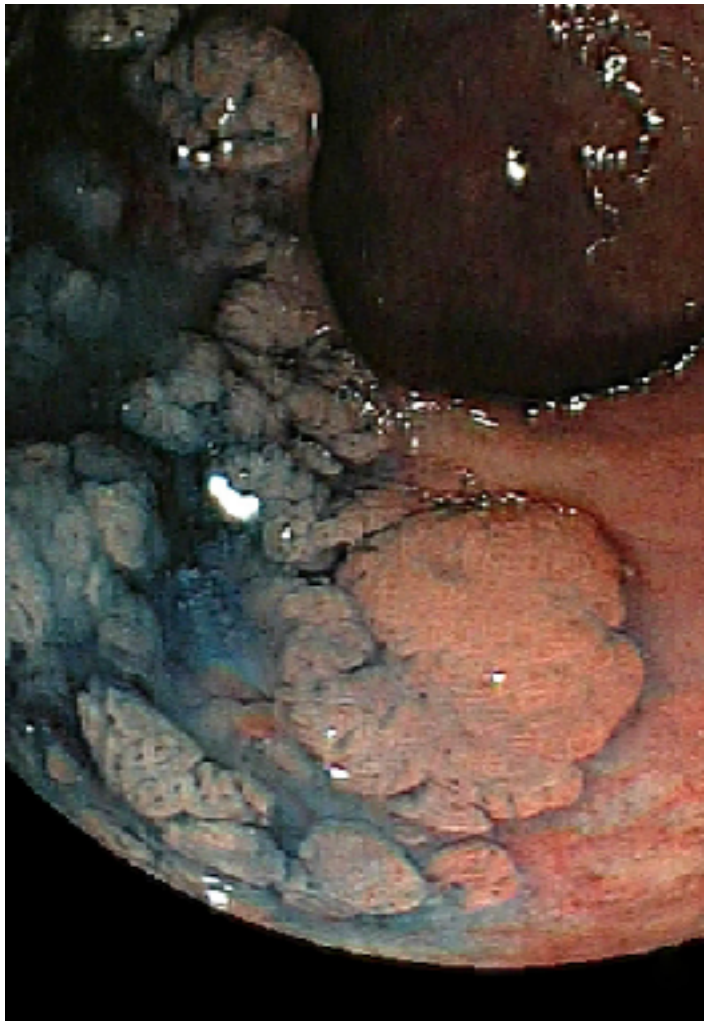
Displasia en mucosa plana



Displasia en mucosa elevada





Ten year follow up of ulcerative colitis patients with and without low grade dysplasia

C H Lim, M F Dixon, A Vail, D Forman, D A F Lynch, A T R Axon

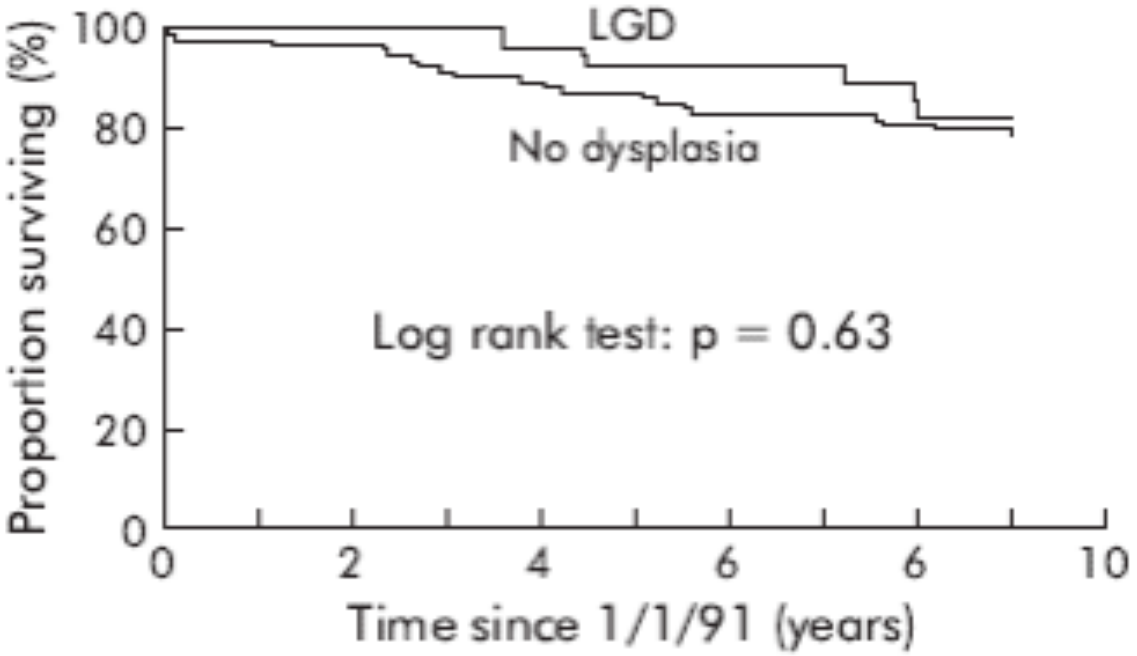


Figure 3 Comparison of time to colectomy or death between the low grade dysplasia (LGD) and control (no dysplasia) groups.

Gut 2003;**52**:1127–1132

Ten year follow up of ulcerative colitis patients with and without low grade dysplasia

C H Lim, M F Dixon, A Vail, D Forman, D A F Lynch, A T R Axon

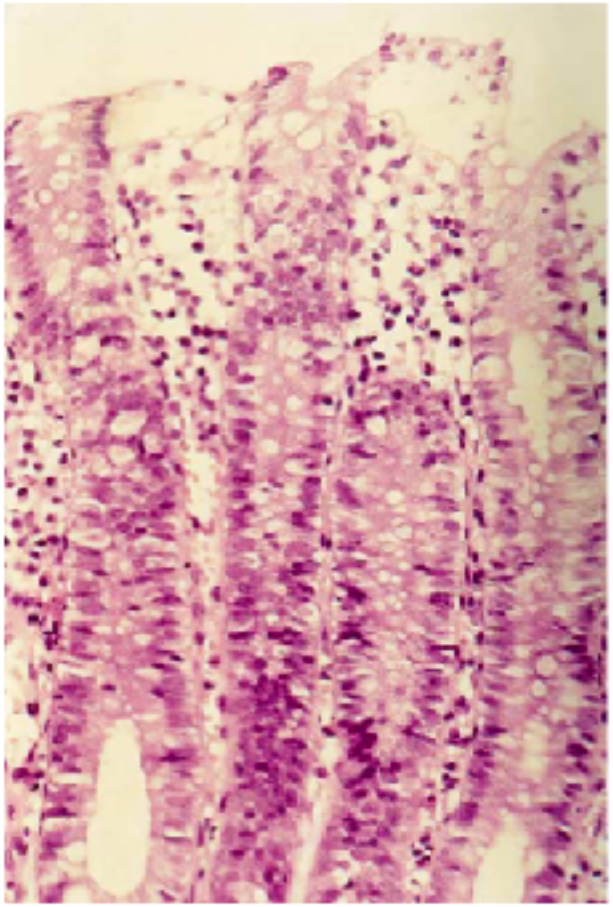


Figure 4 Low grade dysplasia by majority diagnosis.

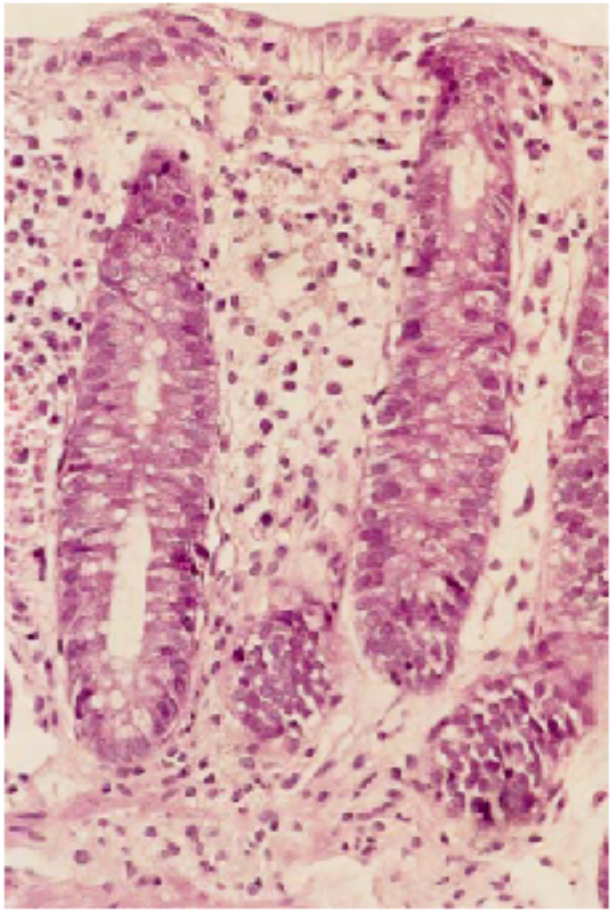
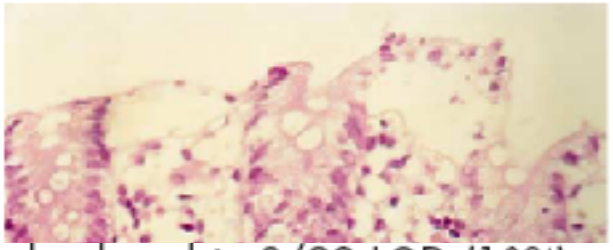


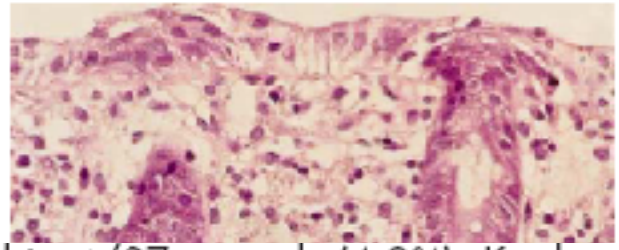
Figure 5 No dysplasia by majority diagnosis.

Gut 2003;**52**:1127–1132

Ten year follow up of ulcerative colitis patients with and without low grade dysplasia

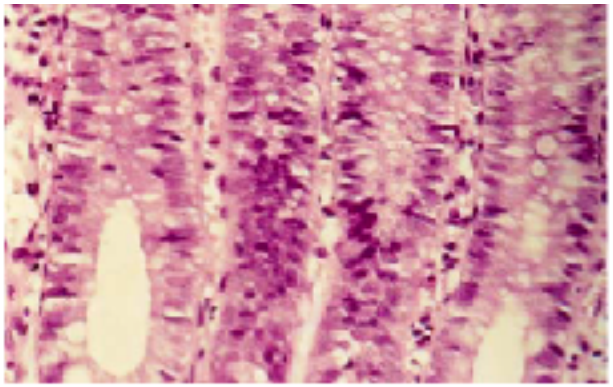
C H Lim, M F Dixon, A Vail, D Forman, D A F Lynch, A T R Axon





(HGD) or CRC developed in 3/29 LGD (10%) and in 4/97 controls (4.0%). Kaplan-Meier analysis from 1991 to death or colectomy did not show a statistically significant difference between the two groups (log rank test p=0.63). Histopathological review demonstrated the unreliability of LGD diagnosis. Agreement between pathologists was uniformly poor: kappa <0.4 for all comparisons.

Conclusion: LGD diagnosis is not sufficiently reliable to justify prophylactic colectomy. Conservative management of established LGD cases should not be ruled out.



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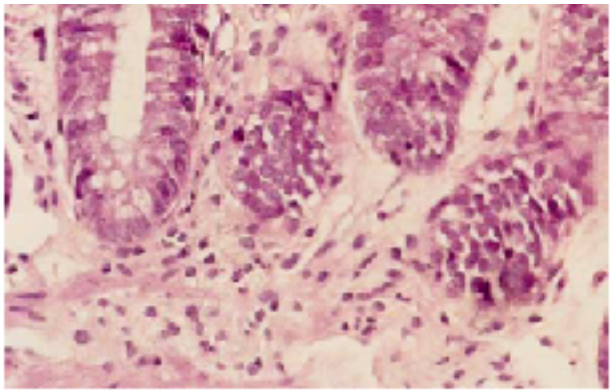

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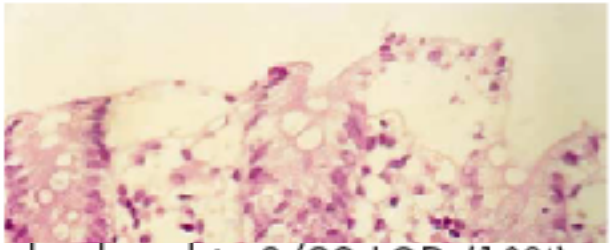

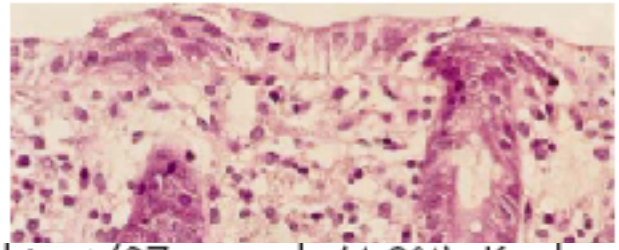

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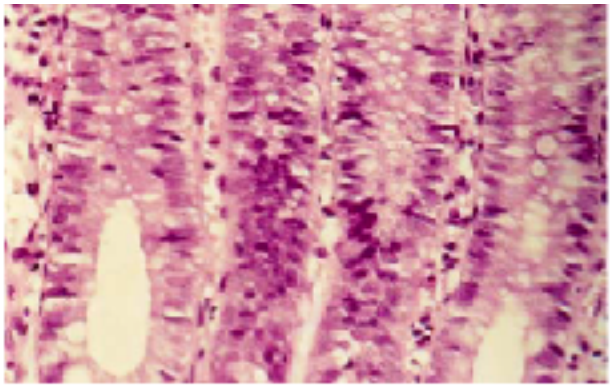

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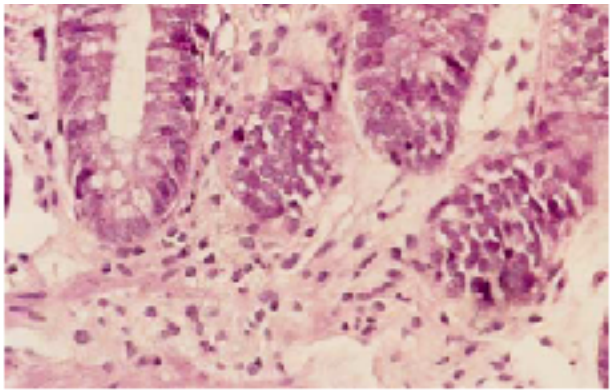

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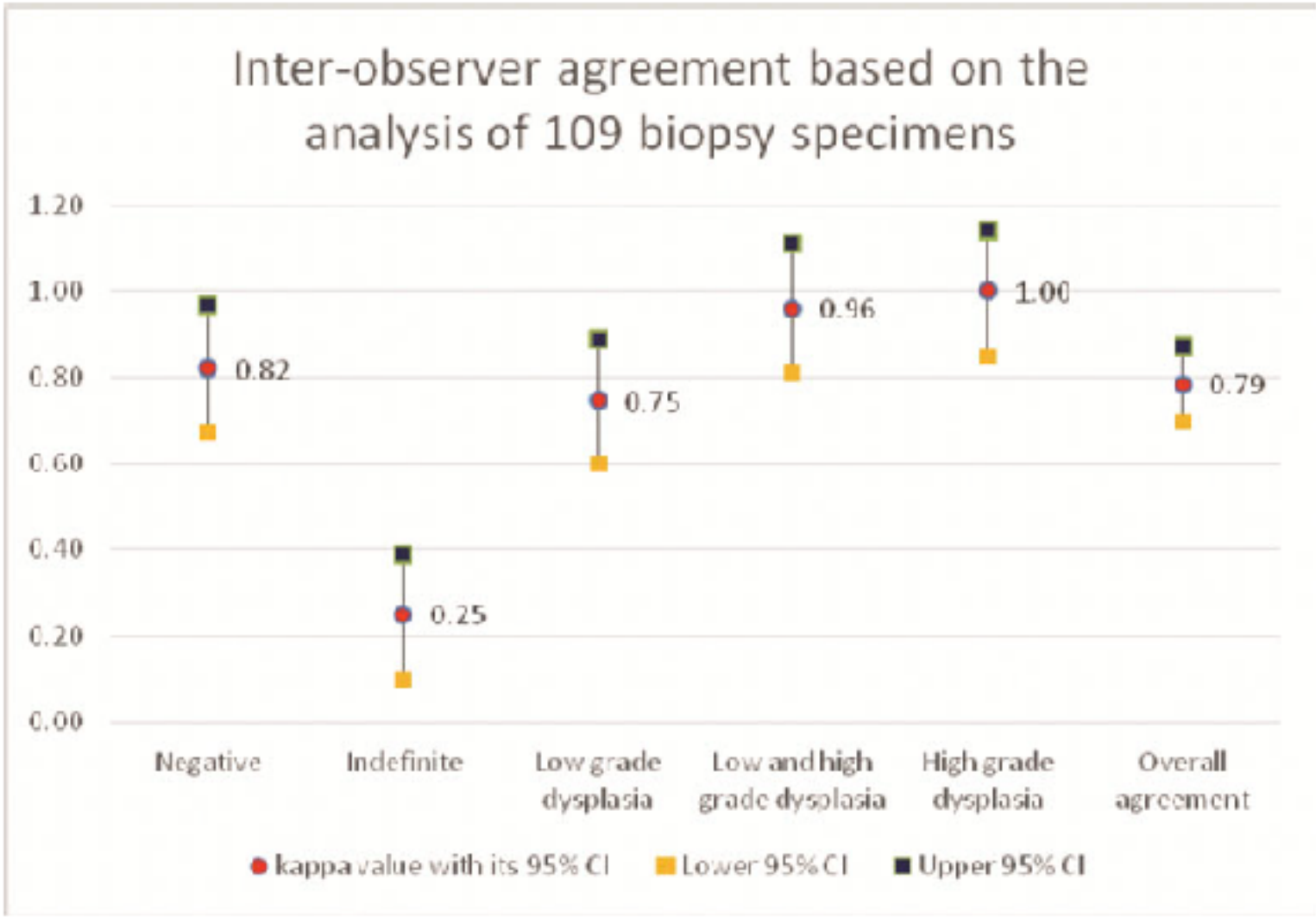
Inter-observer agreement based on the analysis of 109 biopsy specimens
1.20
1.00
0.80
0.60
0.40
0.20
0.00
0.82
0.25
0.75
0.96
1.00
0.79
Negative
Indefinite
Low grade dysplasia
Low and high grade dysplasia
High grade dysplasia
Overall agreement
kappa value with its 95% CI
Lower 95% CI
Upper 95% CI

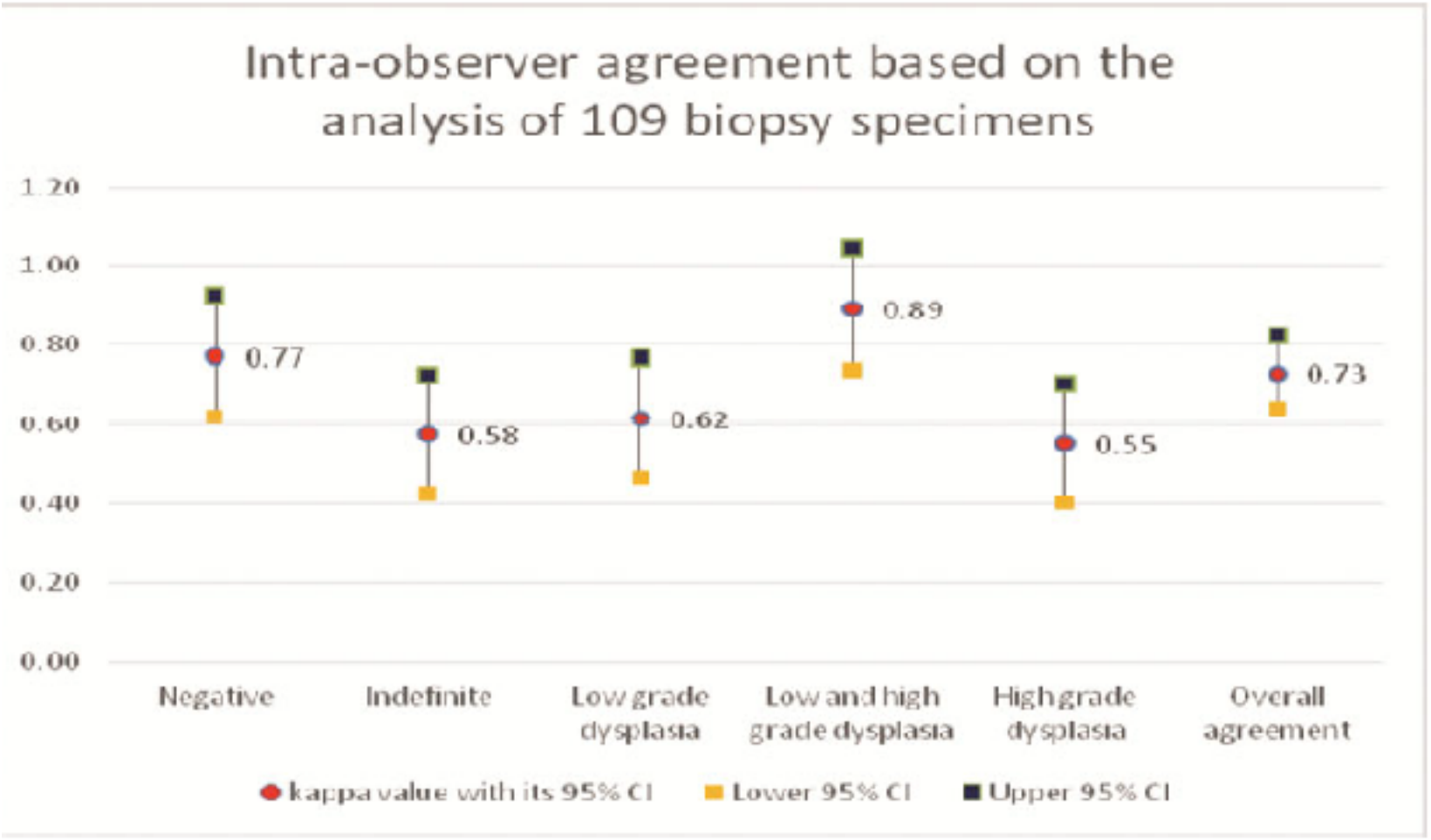
Intra-observer agreement based on the analysis of 109 biopsy specimens
1.20
1.00
0.80
0.60
0.40
0.20
0.00
0.77
0.58
0.62
0.89
0.55
0.73
Negative
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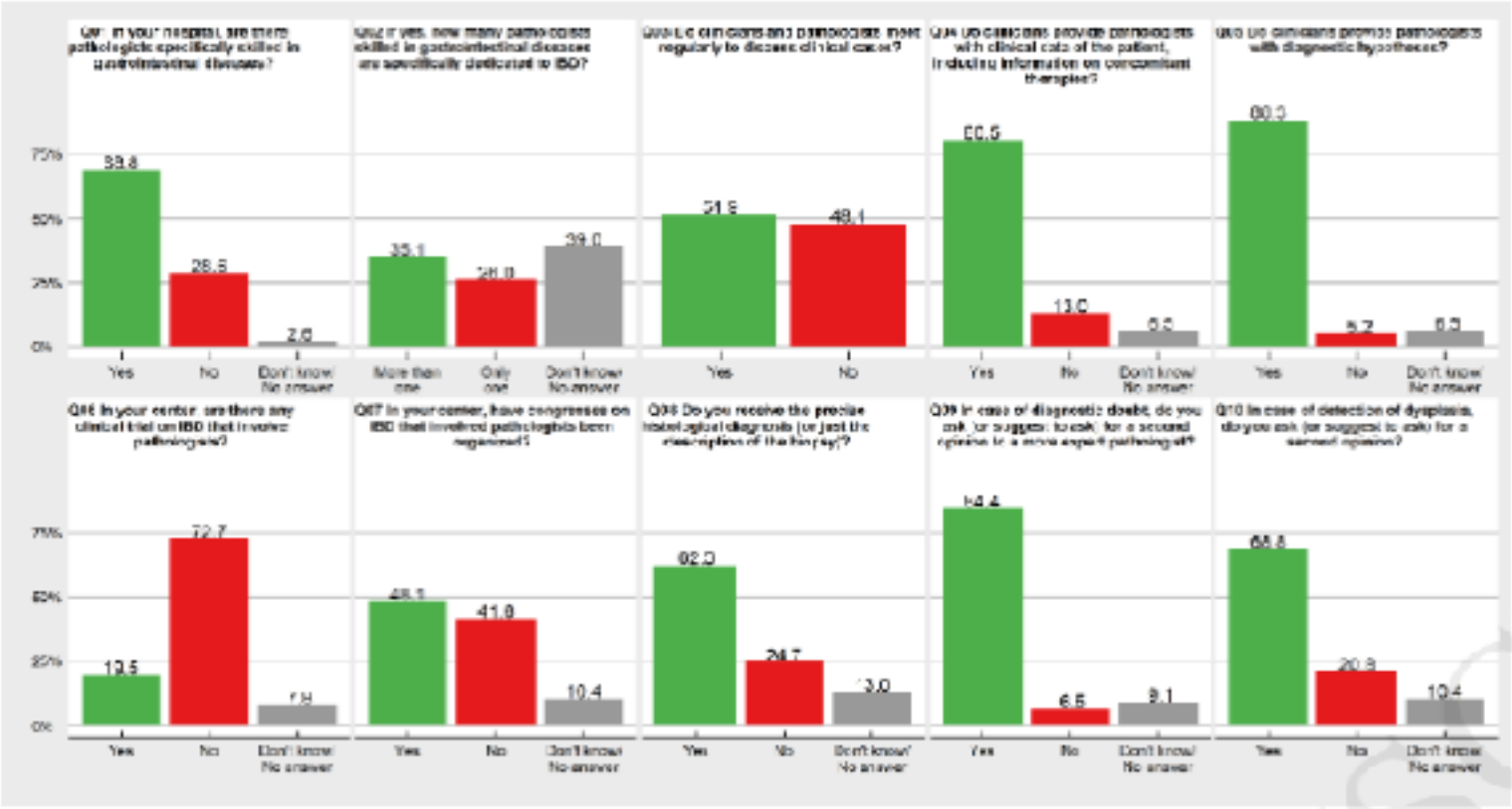
Figure 1. Set of questions 1: the interplay between clinicians and pathologists.



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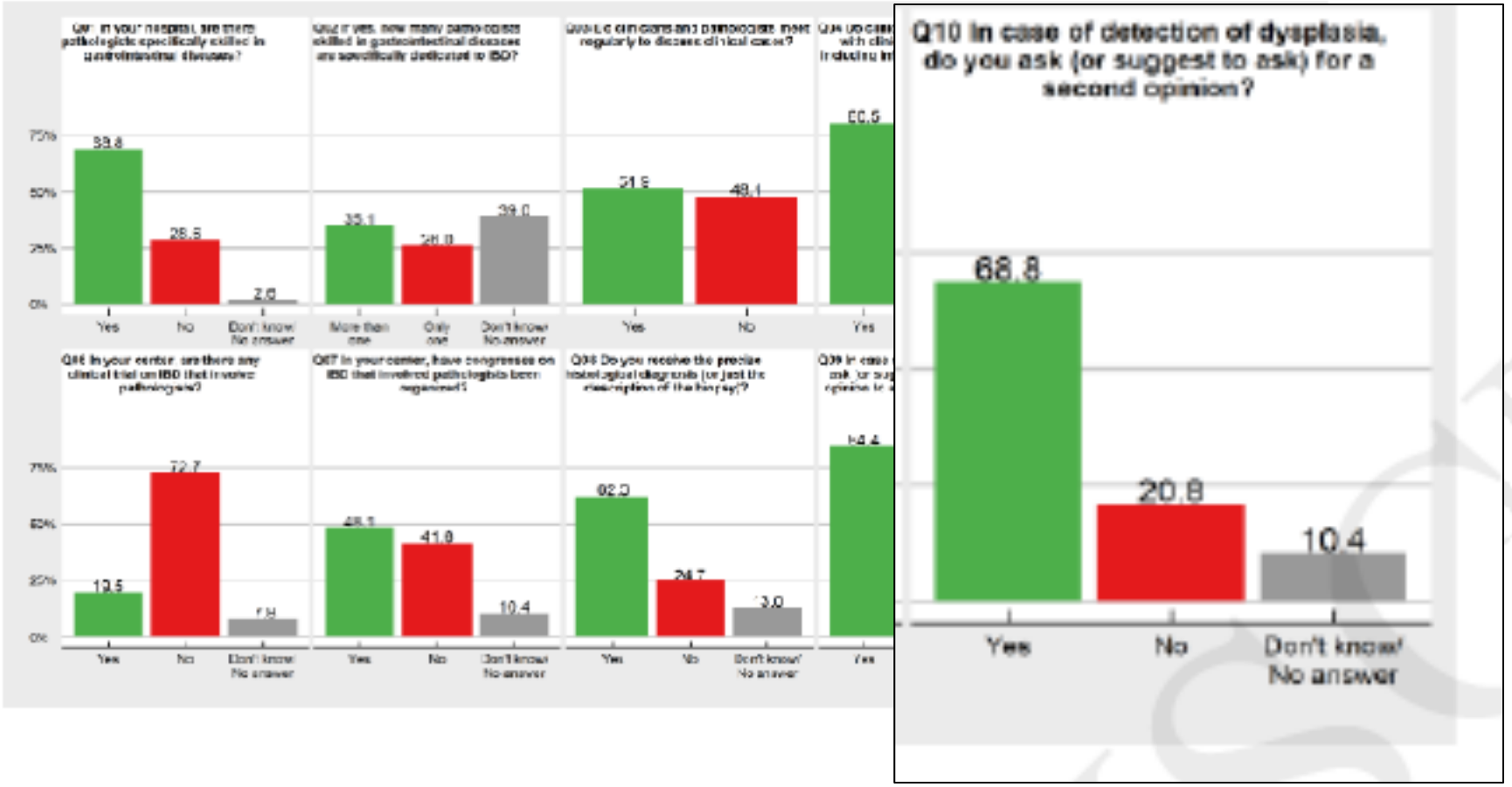


Carcinoma colorectal y CUCI

Recomendaciones:

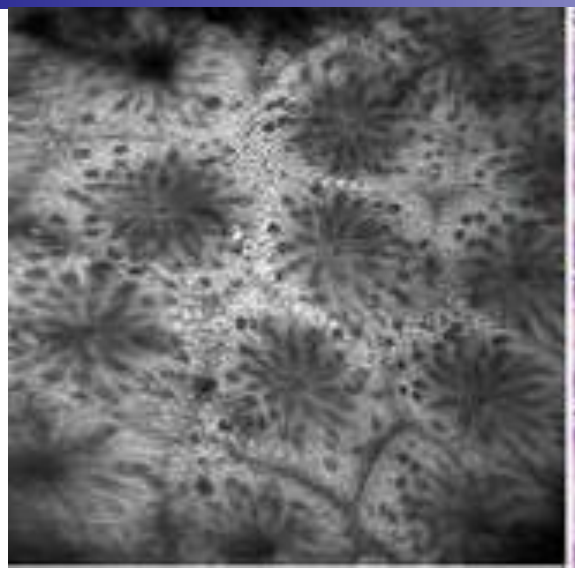
- Iniciar después de 8-10 años
- Realizar colonoscopia cada 1-3 años dependiendo del riesgo (cromoendoscopia, magnificación)
- Obtener 4 biopsias aleatorias por cada 10 cm de colon

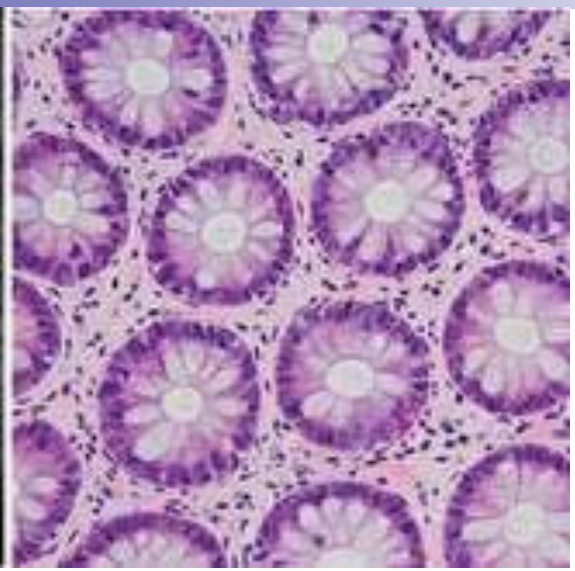
Carcinoma colorectal (CC-R) y CUCI

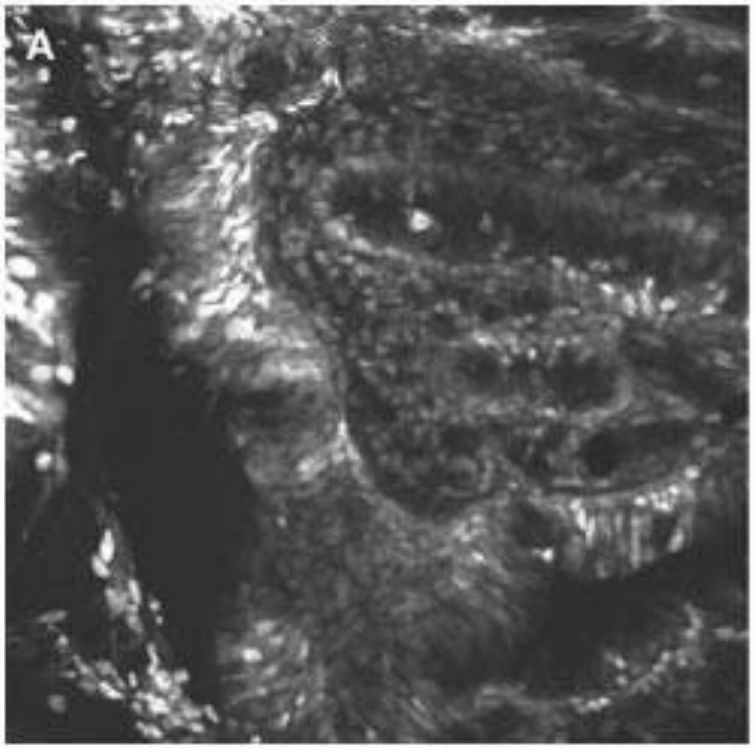
Nuevas técnicas endoscópicas:

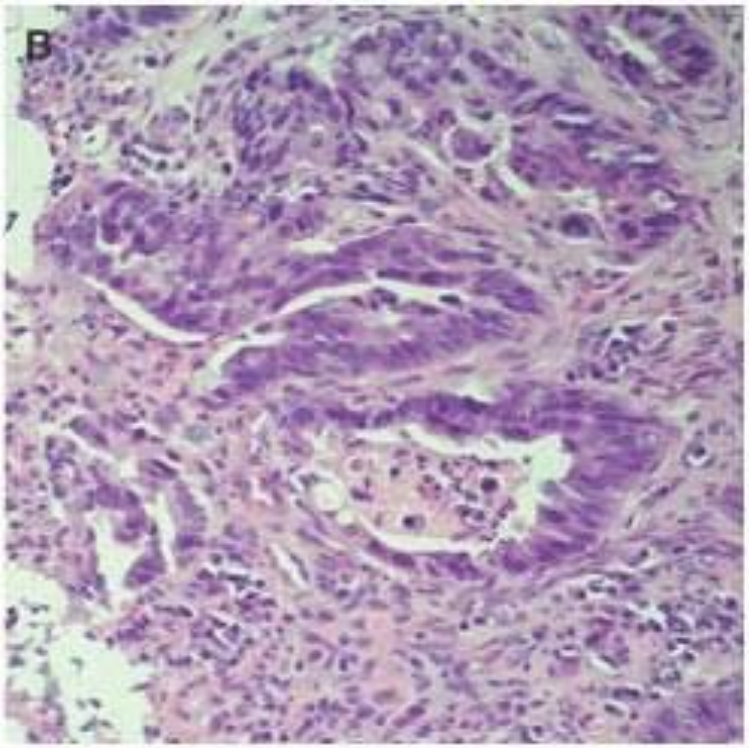
- Cromoendoscopia: detecta de 2.5 - 5.7 veces más displasia
- Imagen de banda estrecha (NBI), autofluorescencia, colonoscopia de magnificación, endomicroscopía confocal.

Inflamm Bowel Dis 2010






A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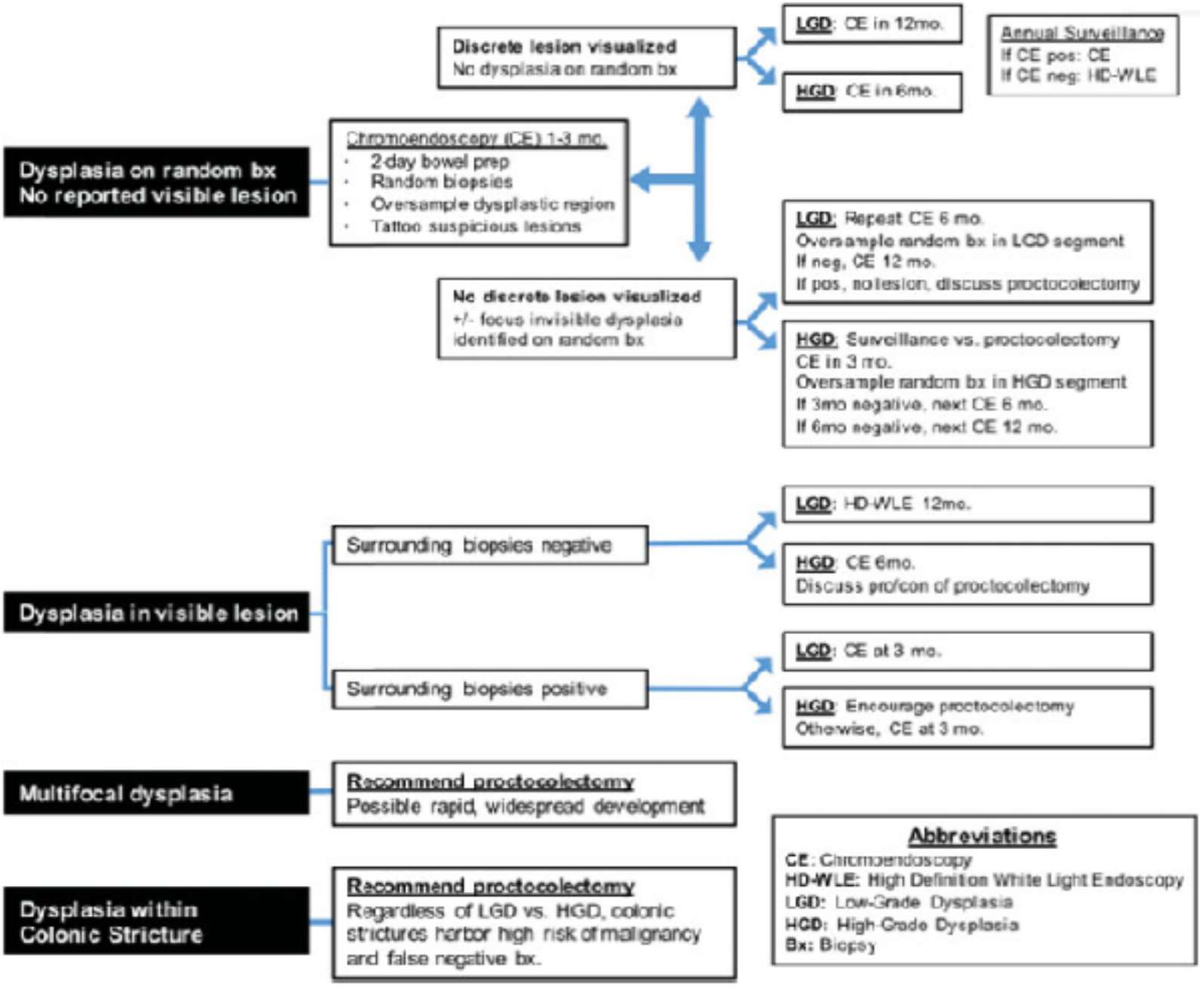
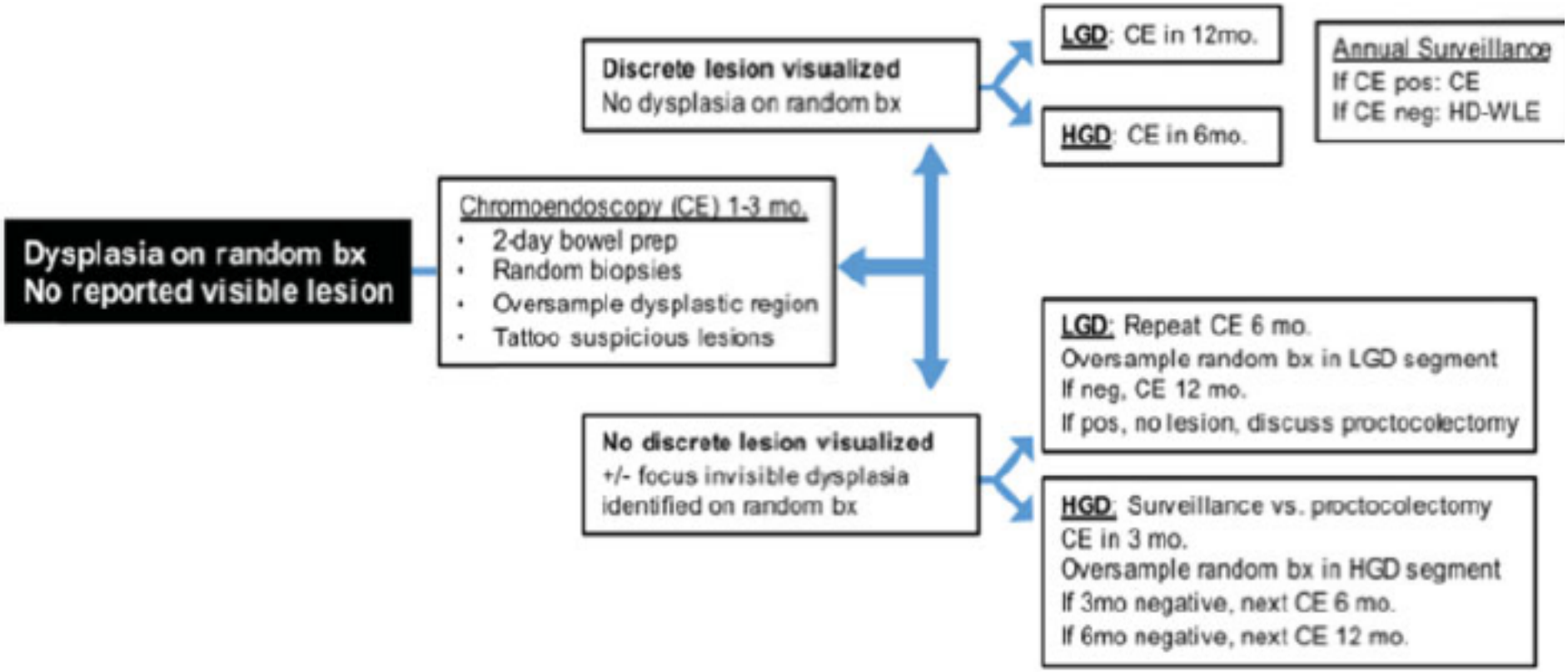

Dysplasia on random bx
No reported visible lesion
Chromoendoscopy (CE) 1-3 mo.
2-day bowel prep
Random biopsies
Oversample dysplastic region
Tattoo suspicious lesions
Discrete lesion visualized
No dysplasia on random bx
LGD: CE in 12mo.
HGD: CE in 6mo.
Annual Surveillance
If CE pos: CE
If CE neg: HD-WLE
No discrete lesion visualized
+/- focus invisible dysplasia identified on random bx
LGD: Repeat CE 6 mo.
Oversample random bx in LCD segment
If neg, CE 12 mo.
If pos, no lesion, discuss proctocolectomy
HGD: Surveillance vs. proctocolectomy
CE in 3 mo.
Oversample random bx in HGD segment
If 3mo negative, next CE 6 mo.
If 6mo negative, next CE 12 mo.
Dysplasia in visible lesion
Surrounding biopsies negative
LGD: HD-WLE 12mo.
HGD: CE 6mo.
Discuss pro/con of proctocolectomy
Surrounding biopsies positive
LGD: CE at 3 mo.
HGD: Encourage proctocolectomy
Otherwise, CE at 3 mo.
Multifocal dysplasia
Recommend proctocolectomy
Possible rapid, widespread development
Dysplasia within Colonic Stricture
Recommend proctocolectomy
Regardless of LGD vs. HGD, colonic strictures harbor high risk of malignancy and false negative bx.
Abbreviations
CE: Chromoendoscopy
HD-WLE: High Definition White Light Endoscopy
LGD: Low-Grade Dysplasia
HGD: High-Grade Dysplasia
Bx: Biopsy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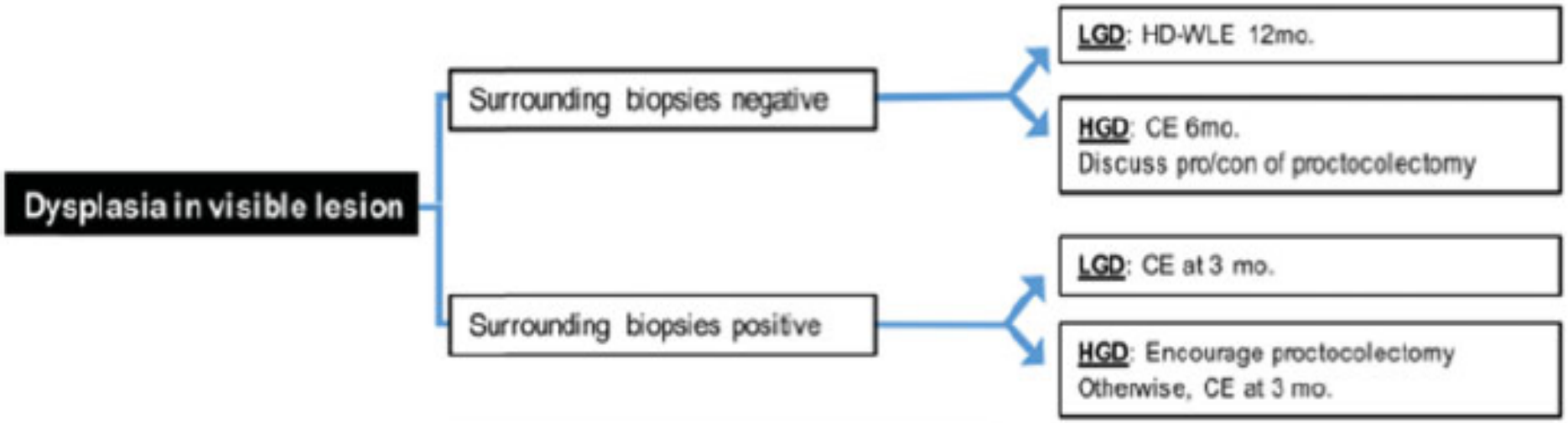
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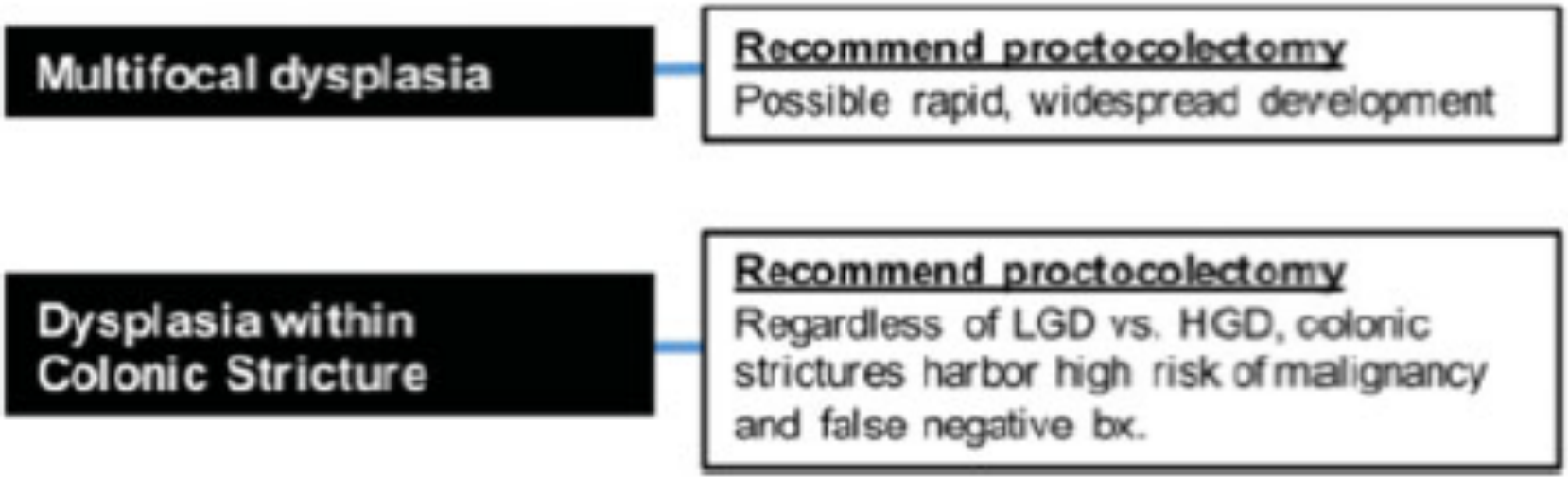
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Problemas en el dx de EIII (lesiones preneoplásicas)

- Tiene problemas en el diagnóstico de displasia (baja concordancia)
- No puede discriminar entre displasia y atipia reactiva (indefinido para displasia)
- No puede separar displasia en adenoma de displasia propia del CUCI
- No solicita la opinión de otro patólogo cuando diagnostica displasia