

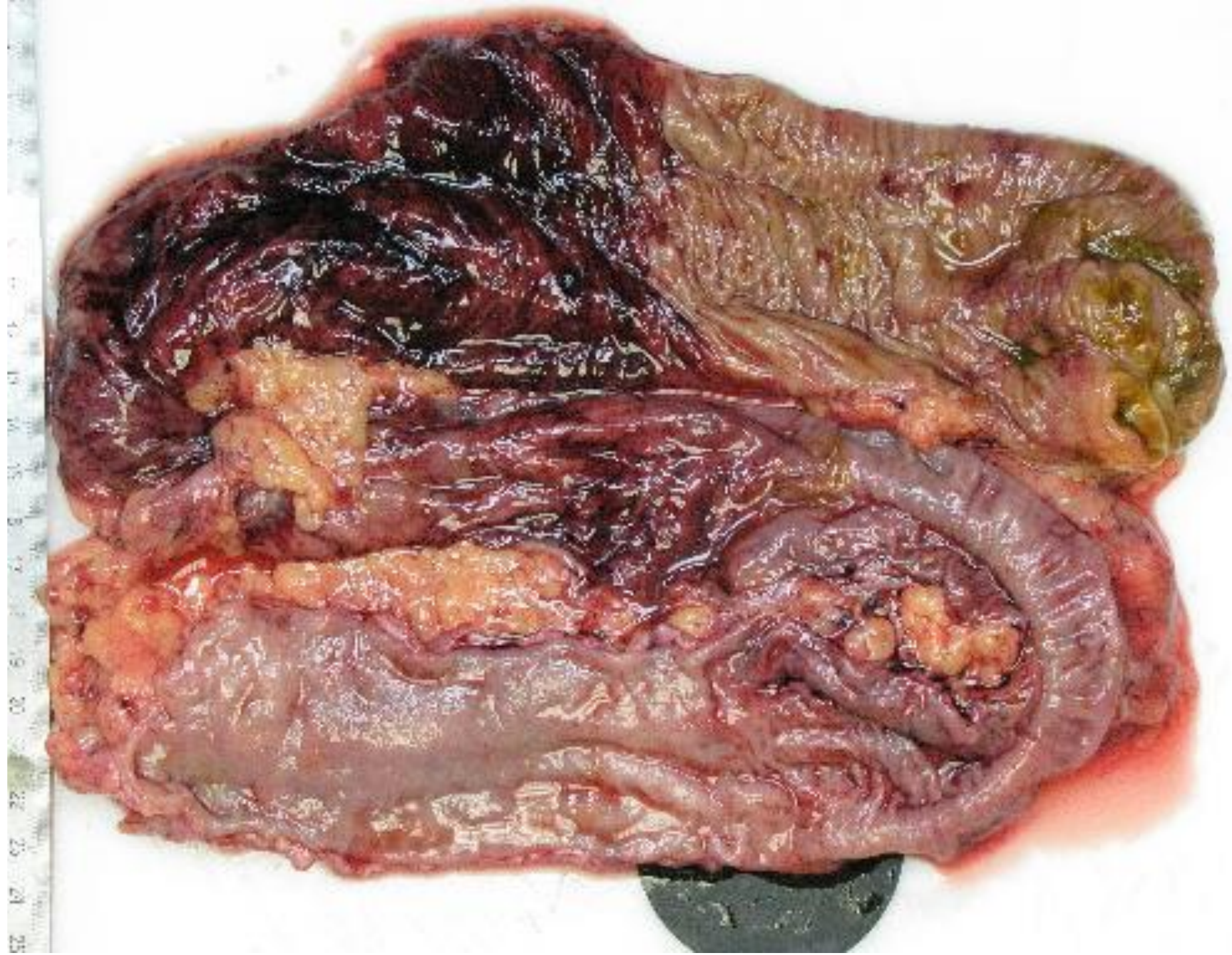
Mécanismes de la carcinogenèse colique au cours des MICI

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Department of Pathology, Paris, France

Overview

- Increased risk of developing intestinal (CRC+++) and extra-intestinal malignancies in IBD
- Role of chronic inflammation in the development of neoplasia (« field defect »)
- Dysplasia, a pre-neoplastic lesion; non-conventional types of dysplasia
- Distinct clinicopathologic and molecular features that can assist in their risk stratification
- Small intestinal carcinogenesis in CD



Increased risk of developing intestinal and extra-intestinal malignancies in patients with IBD

Table 1. Background risk of cancer in patients with IBD.¹⁻⁸

Tumour	SIR in IBD	Incidence in background population	5-year Survival
Small bowel adenocarcinoma in CD	18.7-46	0.3-0.5	±40%
Colorectal cancer in IBD	1.7-8.6	0.5-0.8	64%
Cholangiocarcinoma [* IBD with PSC]	2-160*	0.08	8% ⁴
Gastric cancer in CD	2.8	0.3-1 ⁵	31% ⁶
Leukaemia in UC [** adult age]	2	0.015	24%** -67% ⁷
Urinary tract cancer in CD	2	0.5	77% ⁸

Annese V. JCC 2020

+ Extra-intestinal malignancies (consequence of an underlying inflammatory state and immunosuppressive therapies)

Risk factors for CRC in patients with IBD

Table 1. Risk Factors for Colorectal Cancer in Patients with Inflammatory Bowel Disease.

Risk factors established in the general population

- Increasing age*
- Male sex*
- History of colorectal cancer in first-degree relatives*
- Increased body-mass index†
- Low level of physical activity†
- Cigarette smoking†
- High consumption of red meat†
- Consumption of alcohol†

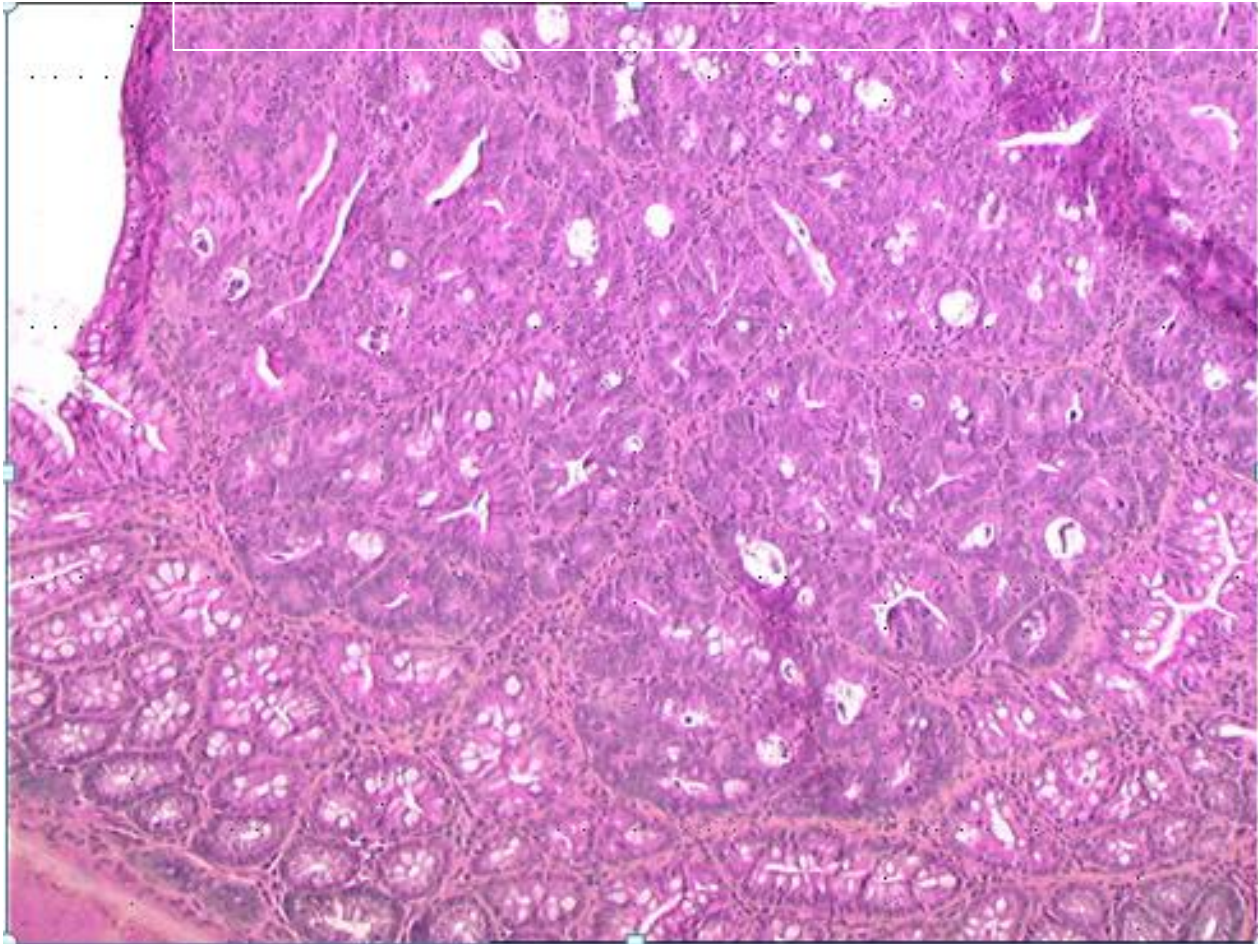
Risk factors specific to patients with inflammatory bowel disease

- Coexisting primary sclerosing cholangitis
- Increasing cumulative extent of colonic inflammatory lesions‡
- Increasing duration of inflammatory bowel disease§
- Active chronic endoscopically assessed inflammation
- Active chronic histologically assessed inflammation

Anatomical abnormalities

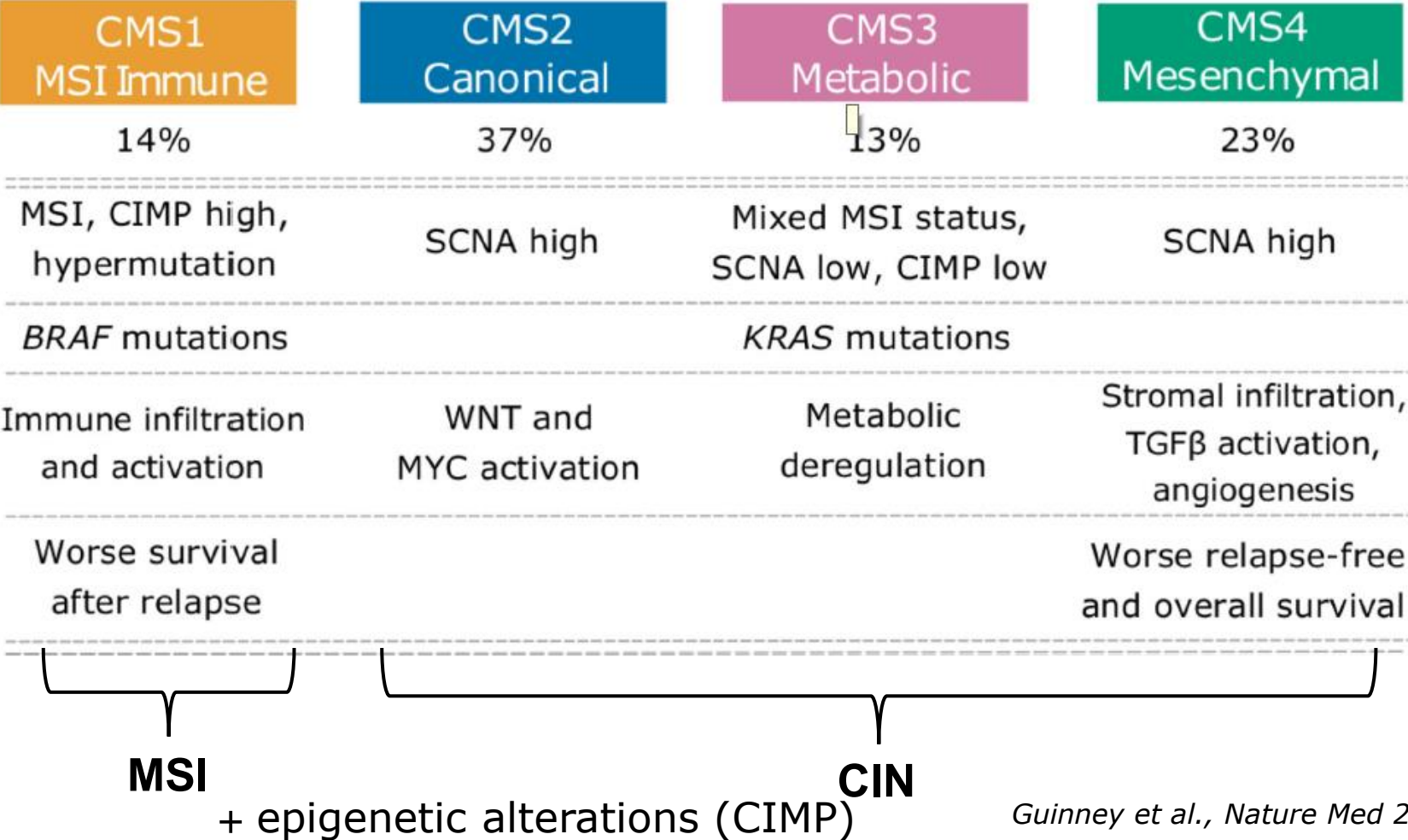
- Foreshortened colon
- Strictures
- Pseudopolyps
- Personal history of flat dysplasia

In an AOM-DSS murine model



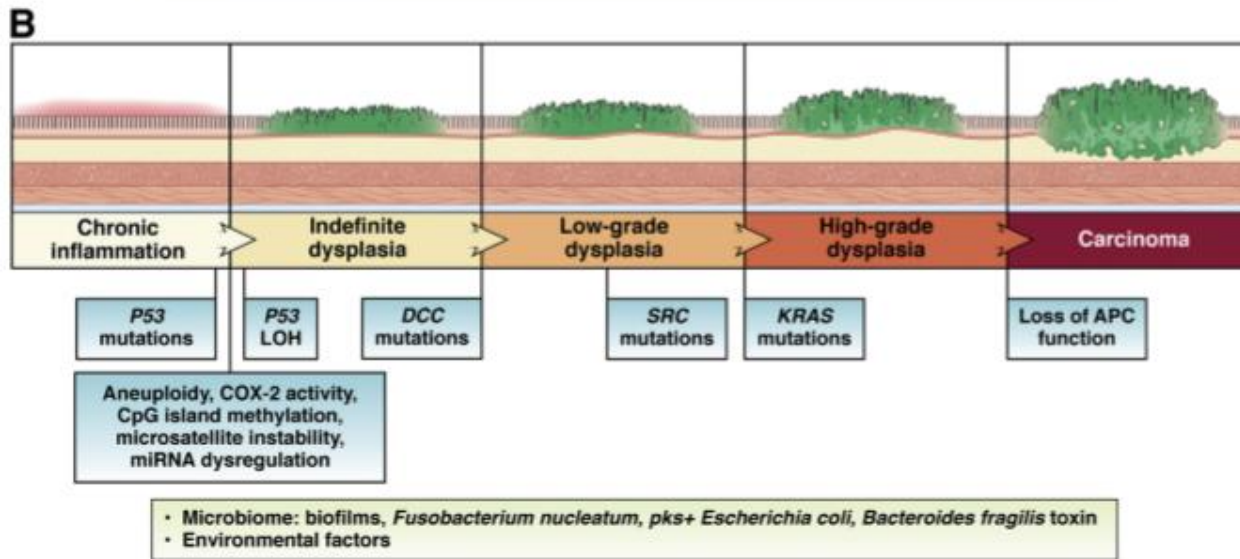
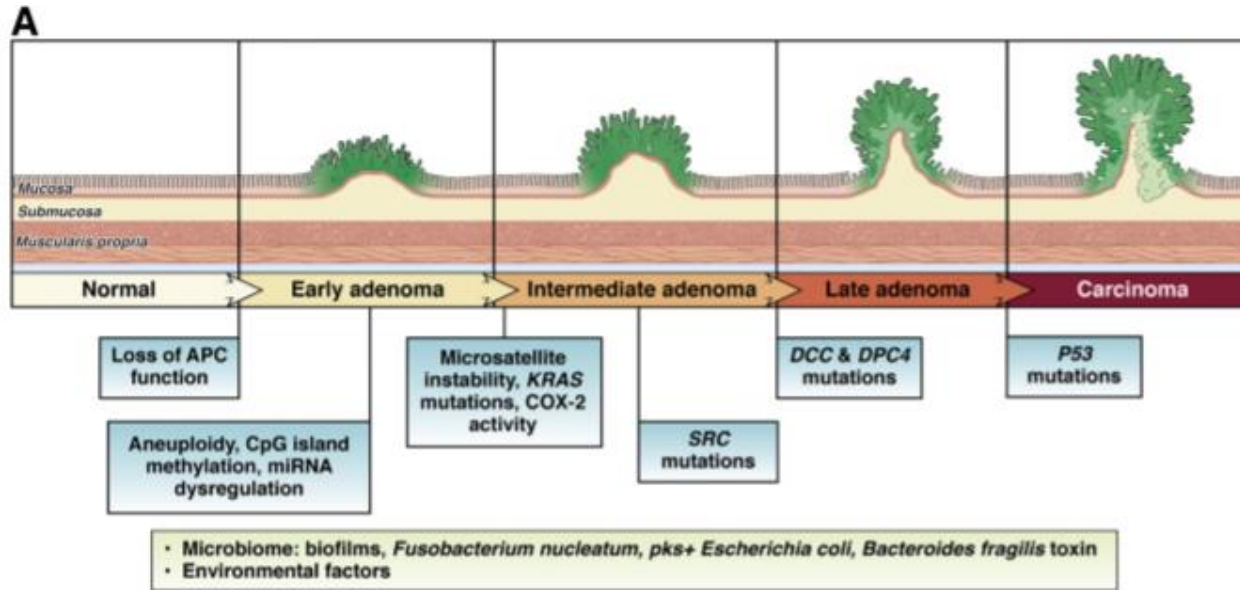
Induction of inflammation -> CRC

CRCs are heterogeneous from a molecular point of view



Guinney et al., Nature Med 2015

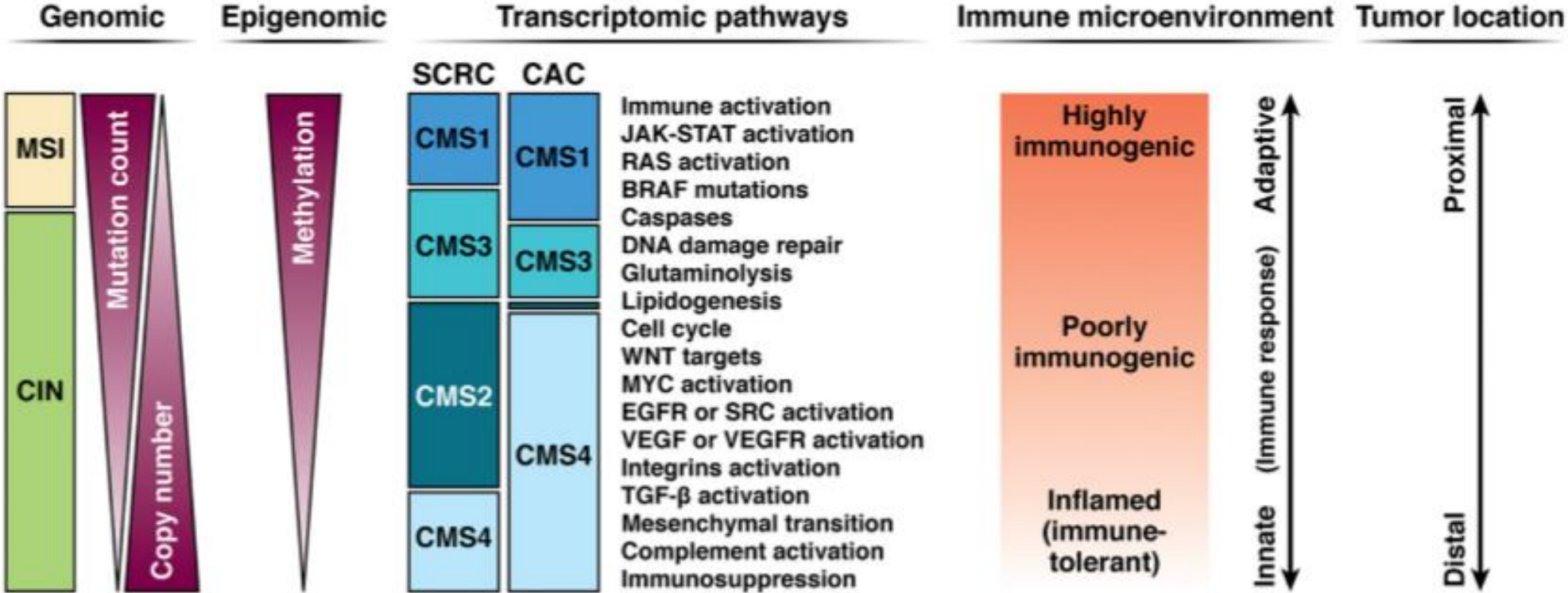
Pathogenesis of colitis-associated CRC



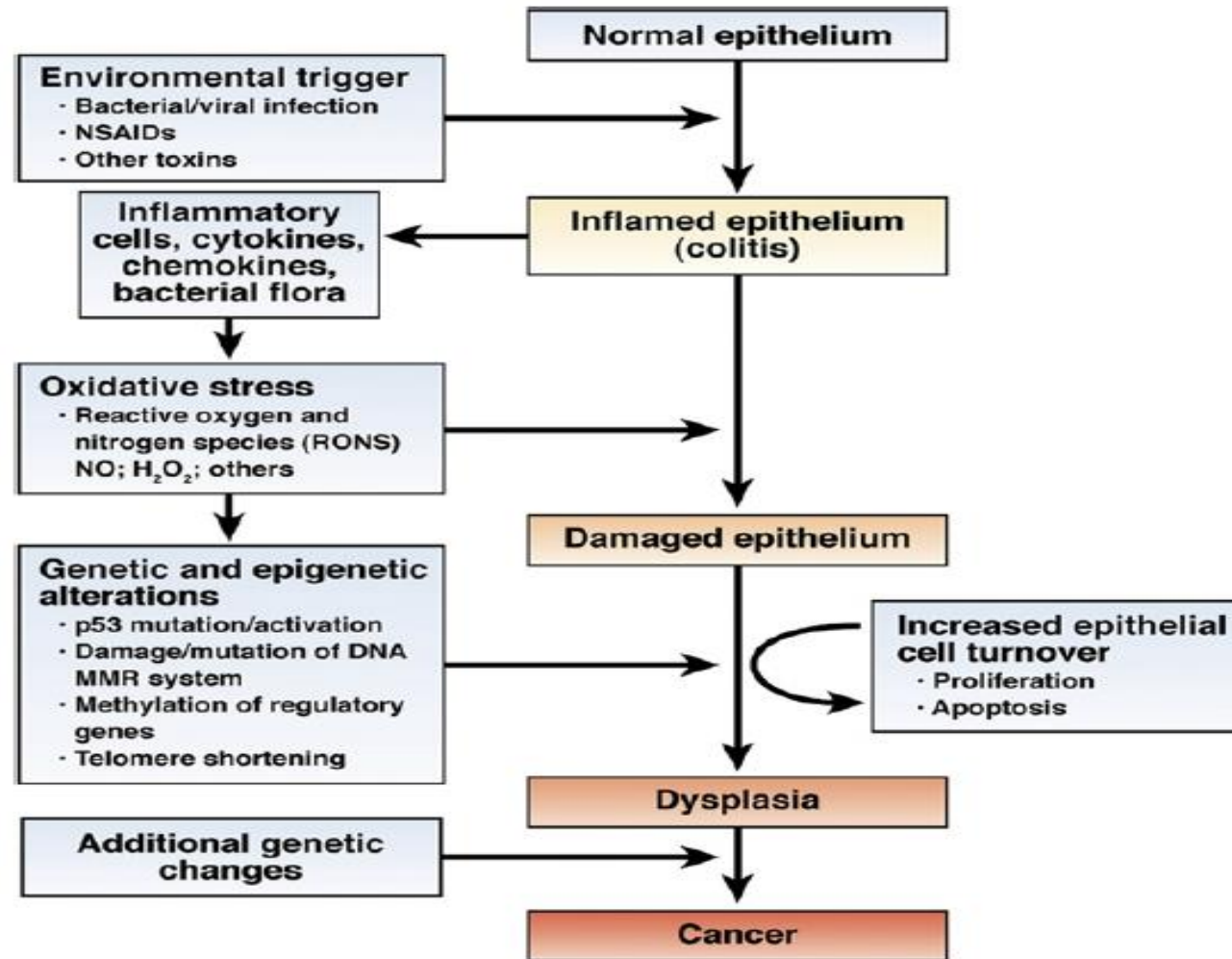
85% CIN
15% MSI



Molecular and immunologic classification of IBD-associated CRCs



Pathogenesis of IBD-associated colorectal tumours



Role of the innate and adaptative immune systems

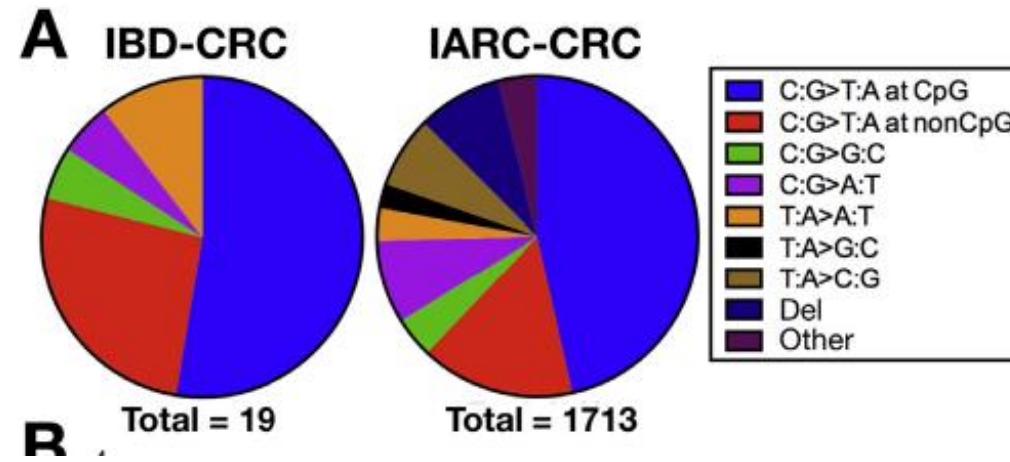
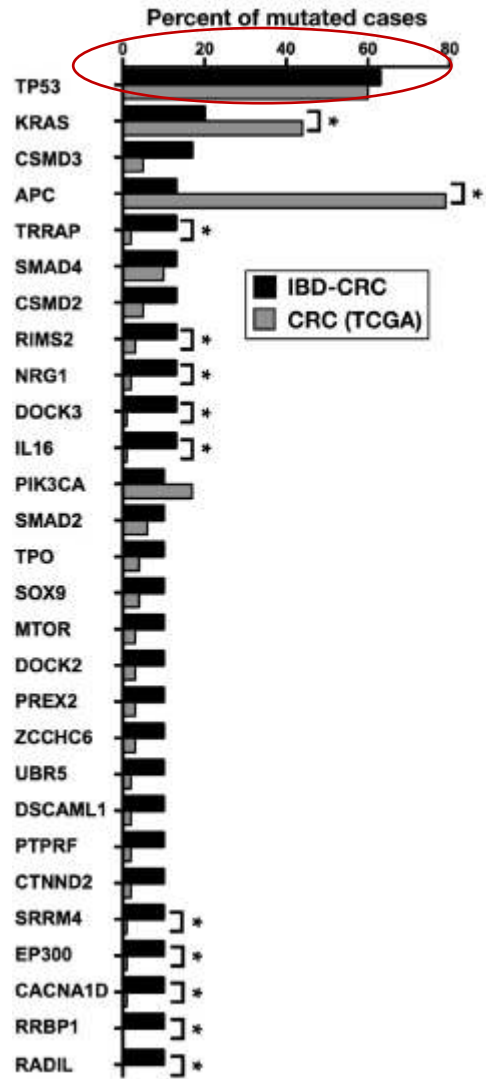
Role of gastrointestinal microflora

Field cancerization
(Galandiuk S et al, Gastroenterology 2012)

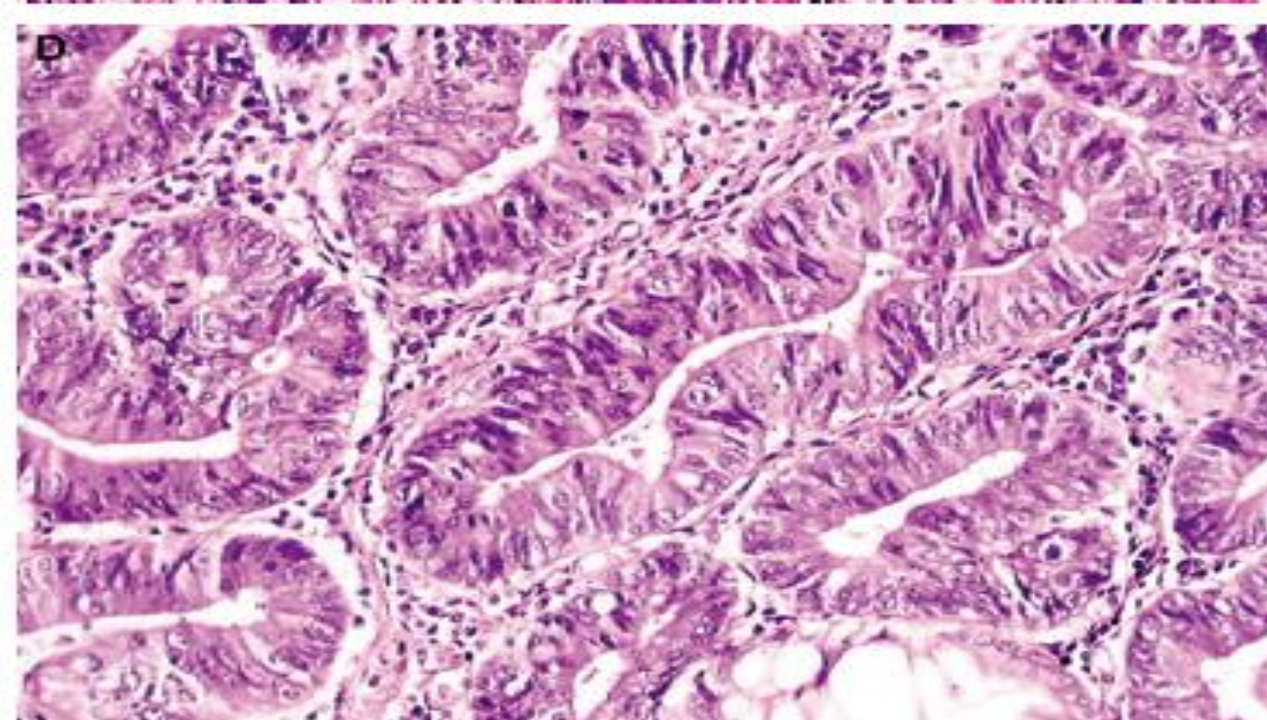
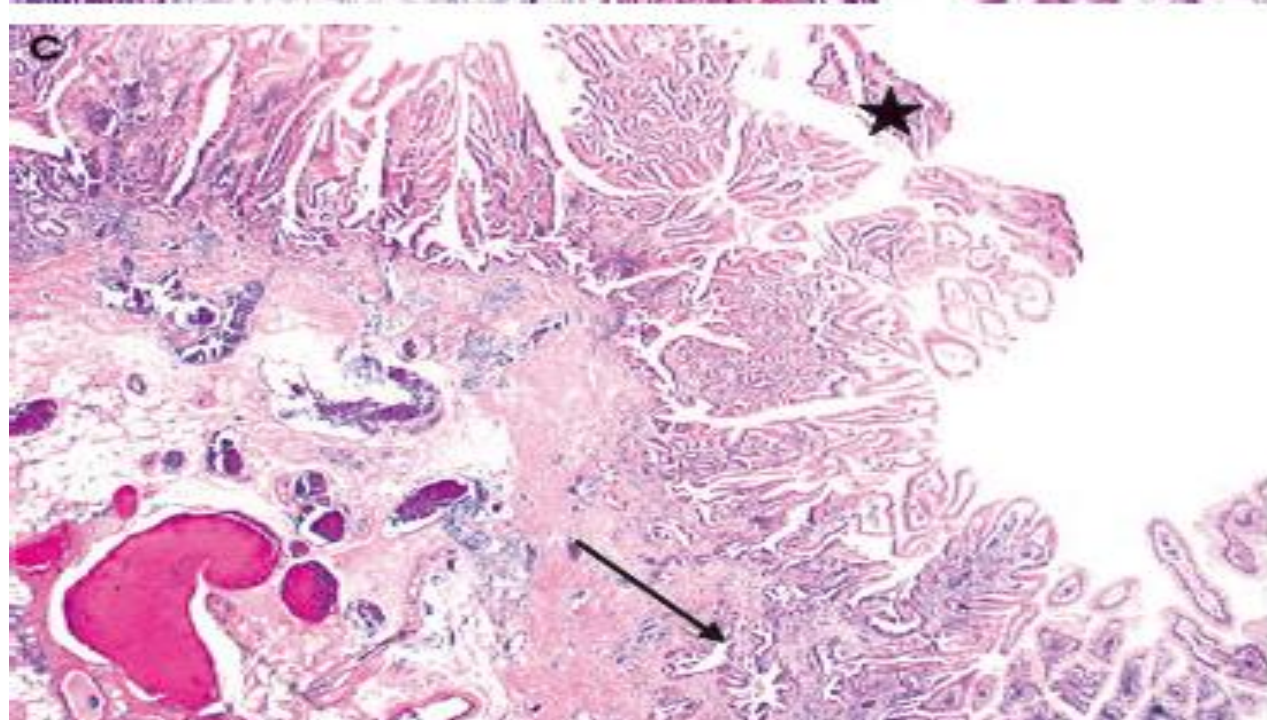
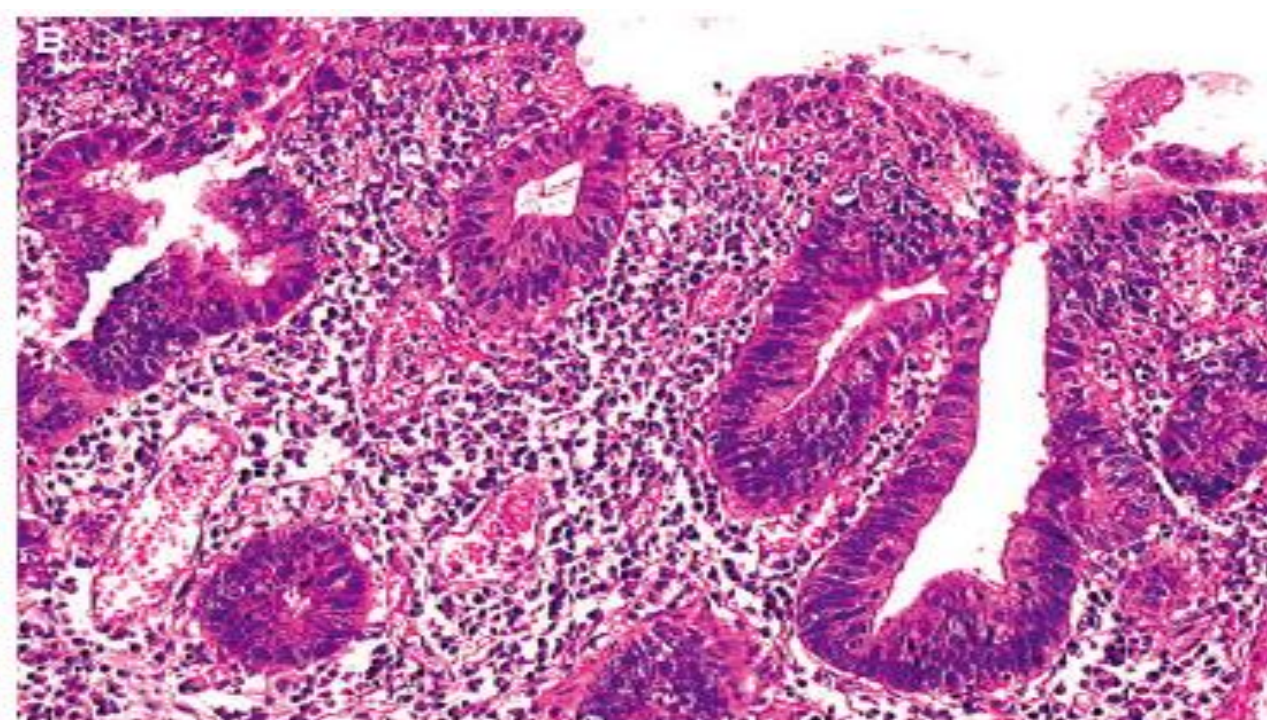
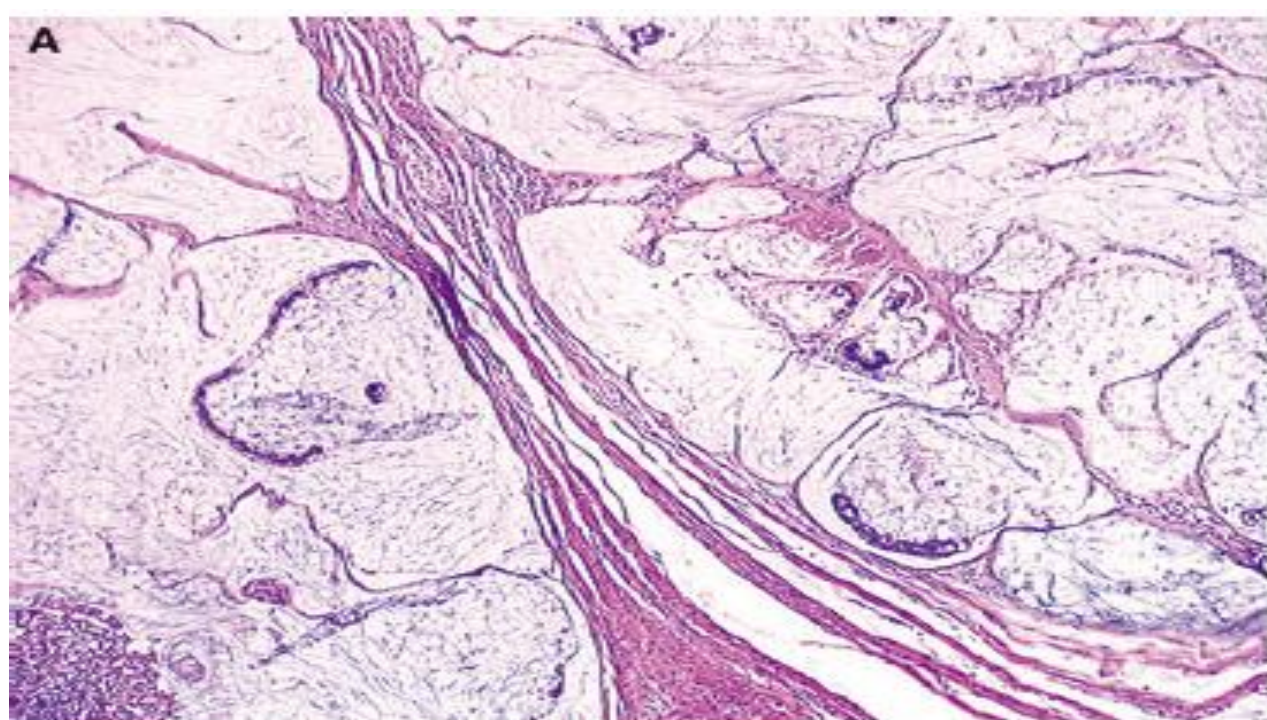
Clinico-pathological specificities of CRC complicating IBD

	Sporadic CRC	Colitis-associated CRC
Dysplasia	Polypoid adenoma, in general unique	Polymorphous dysplastic lesions, raised or flat, often multifocal
Median age of occurrence	70 years	50 years
Number of tumours	Unique	High rate of synchronous tumours
Histological type		
Lack of tumor necrosis	++	+++
Crohn like reaction	Rare	+++
Presence of mucin	+	+++
Tumor heterogeneity	Rare	++
Signet ring cell	Rare	+
Well differentiated tumour	Rare	++
Pathogenesis	No role of inflammation	Role of chronic inflammation (RONS)
Main molecular abnormalities		
- <i>APC</i> loss of function	Early and frequent event	Late and less frequent event
- <i>P53</i> mutation	Late event (the defining event that drives the adenoma to carcinoma)	Frequent (the most frequent mutated gene) and early event (detected in nondysplastic mucosa)
- <i>KRAS</i>	+++	+
- <i>SOX9</i> and <i>EP300</i>	-	+++
- <i>IL-16</i>	-	+++

The spectrum of P53 mutations observed in IBD is different from that observed in a sporadic setting.







Morphologic and molecular characterization and classification of dysplastic lesions

Dysplasia (or intra-epithelial neoplasia), a pre-neoplastic lesion in IBD



Dysplasia: «Unequivocal neoplasia of the epithelium confined to the basement membrane, without invasion into the lamina propria» (Riddell, Inflammatory Bowel Disease-Dysplasia Morphology Study group, 1983).

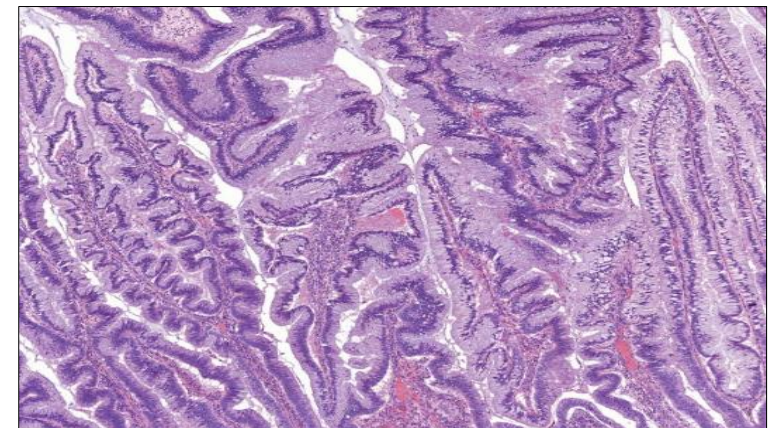
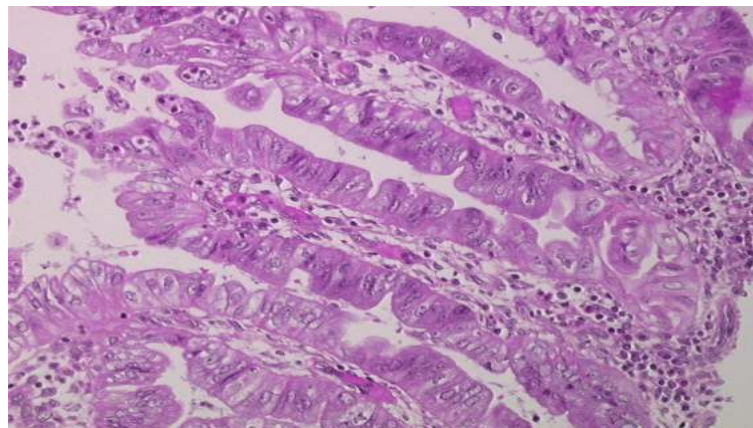
No molecular markers routinely used to stratify IBD patients into groups at low or high risk for developing colorectal neoplasia.

Dysplasia : best marker for the increased risk of CRC in IBD (Goldman, Cancer 1996)

Dysplasia in IBD

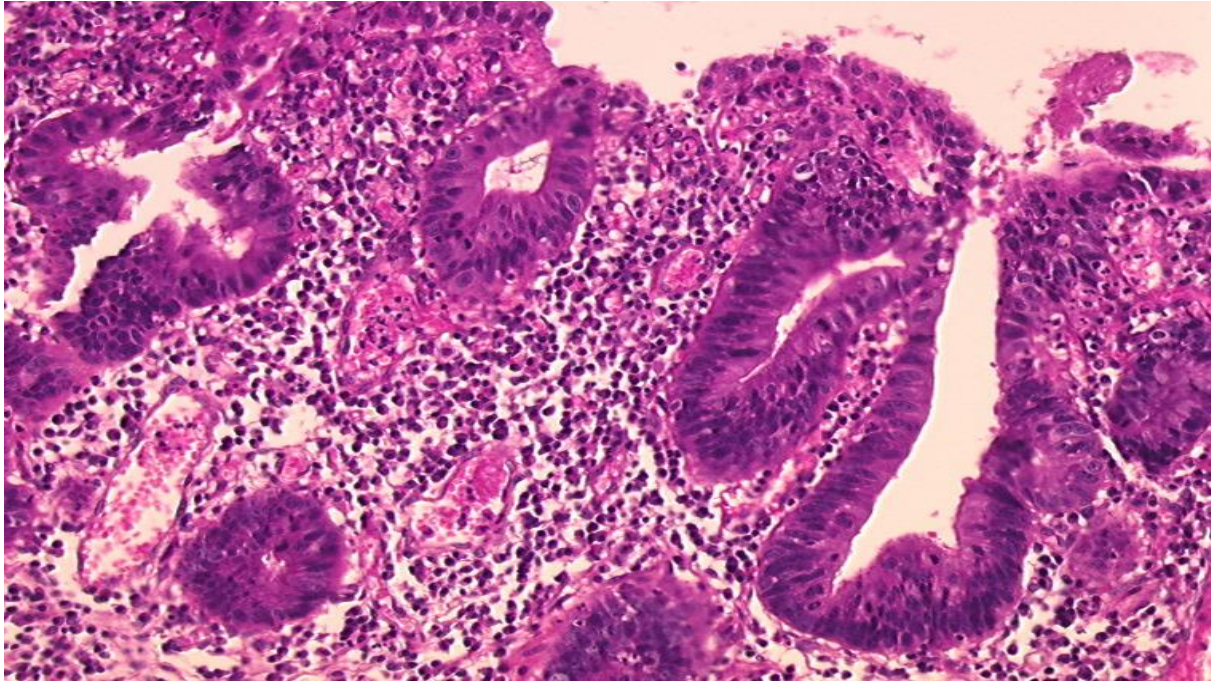
- (i) Intestinal (or conventional) dysplasia
- (ii) Hypermucinous/villous dysplasia
- (iii) Serrated dysplasia

From WHO Classification of Tumours of the Digestive System, 2010

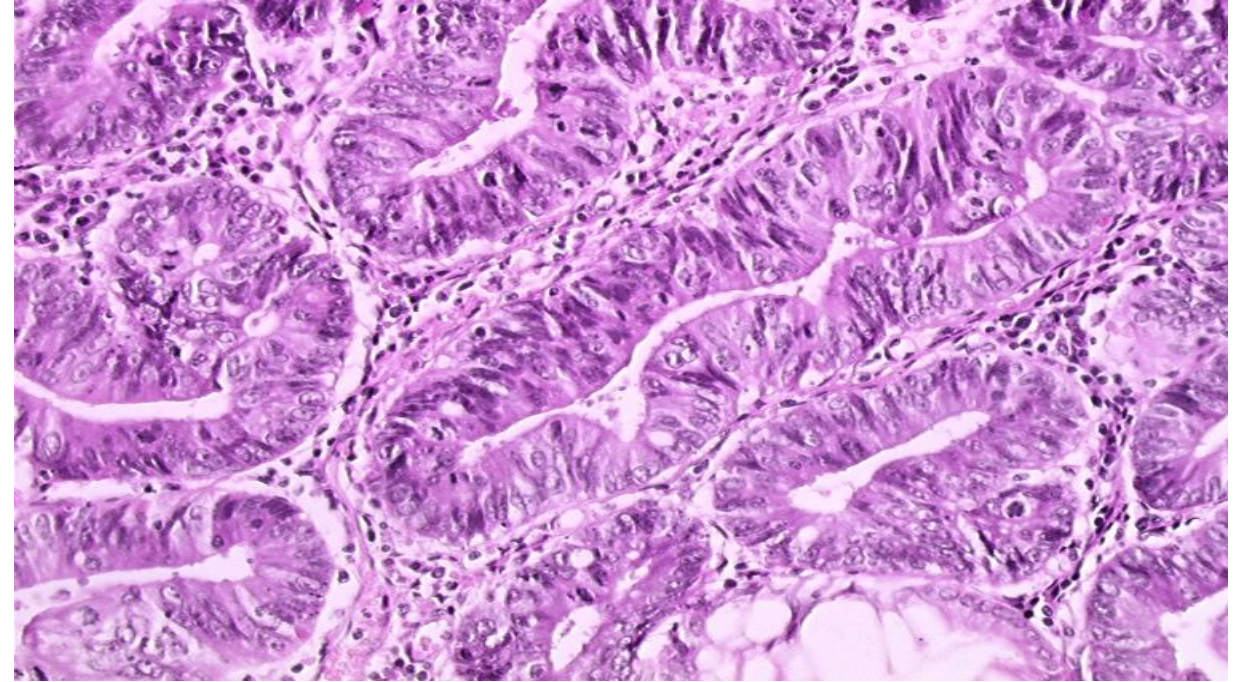


Different types of dysplasia

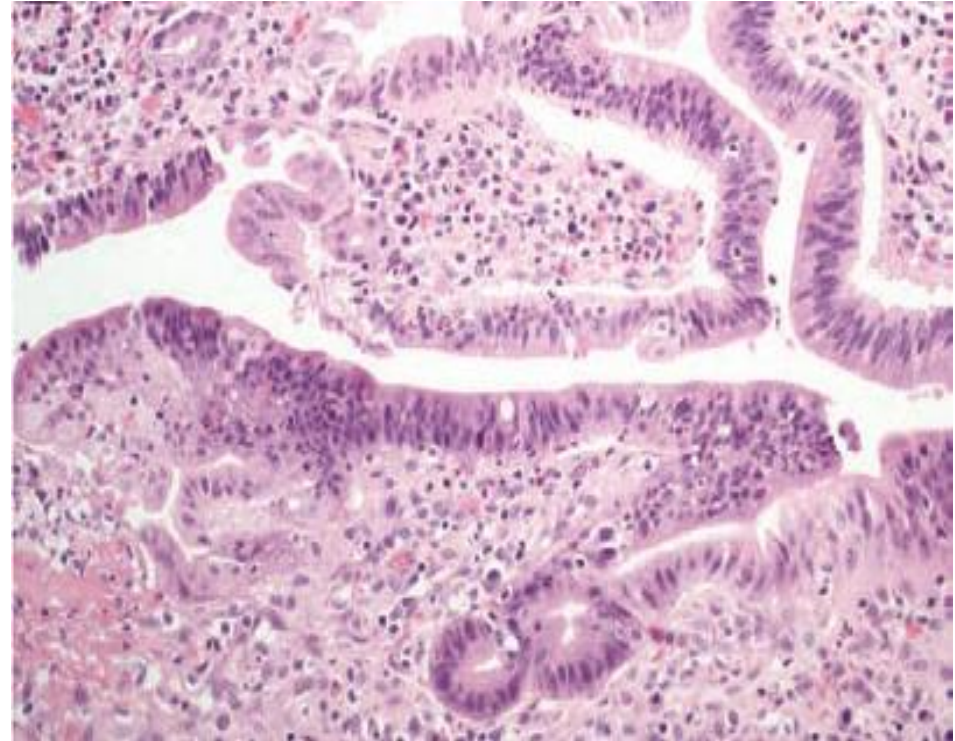
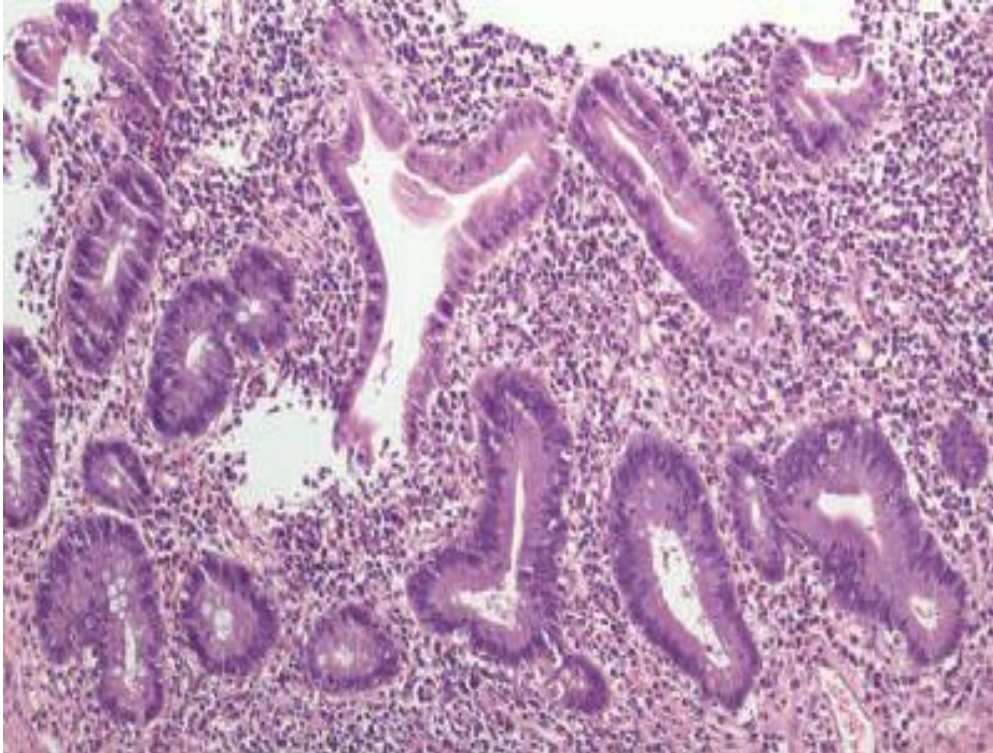
Low grade



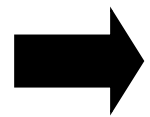
High grade



Indefinite for dysplasia



Biopsies probablement négatives et probablement positives pour des lésions de dysplasie

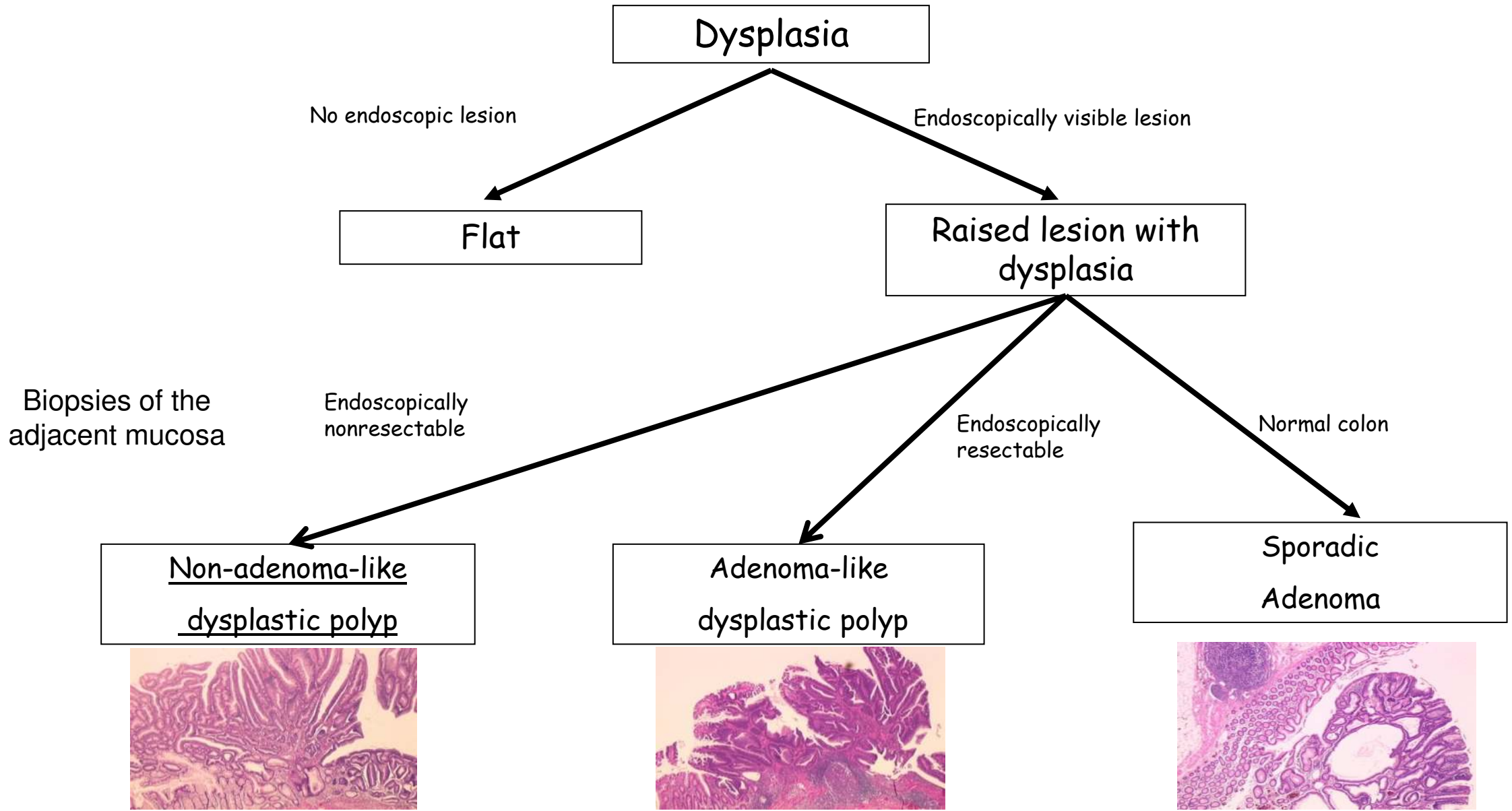


Biopsies de contrôle, après renforcement du traitement anti-inflammatoire

It is important to distinguish low-grade and high-grade dysplasia

- Consequences for the management of patients
- Important inter and intra-observer variability (poor agreement for low-grade and indefinite for dysplasia)
- Confirmation of dysplasia by an independent GI pathologist is recommended (ECCO-ESP statement 17).

Macroscopic classification of dysplasia in IBD



SCENIC International Consensus Statement on Surveillance and Management of Dysplasia in Inflammatory Bowel Disease

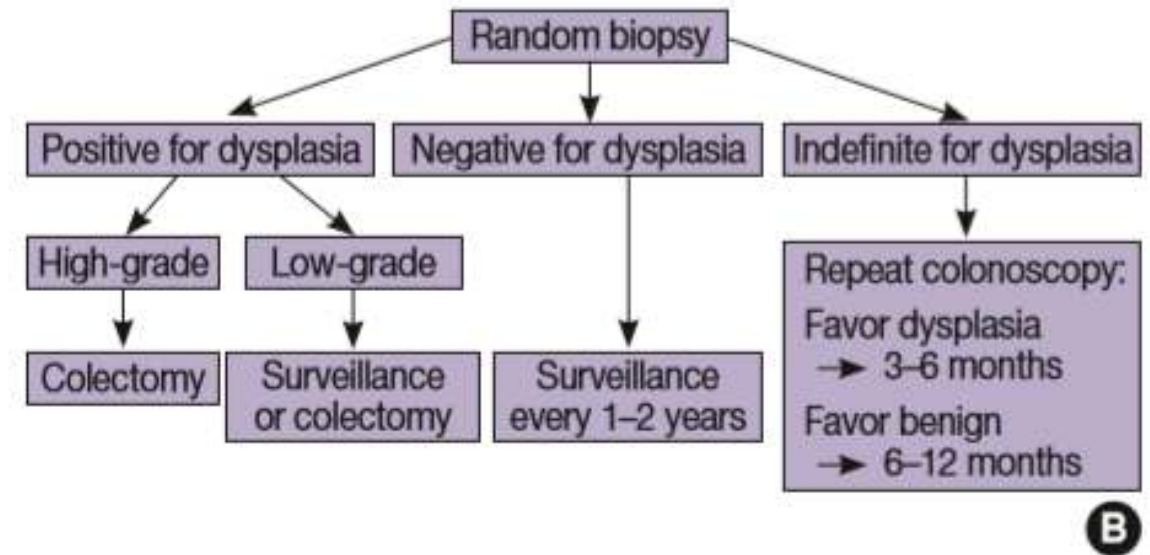
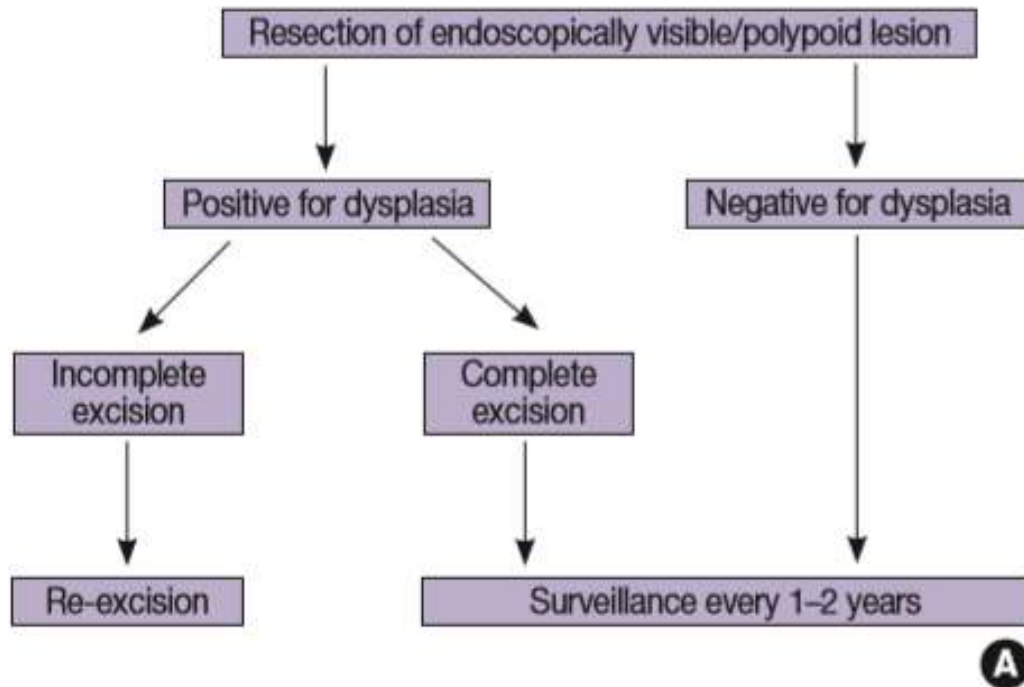


Loren Laine,^{1,2} Tonya Kaltenbach,³ Alan Barkun,⁴ Kenneth R. McQuaid,⁵
Venkataraman Subramanian,⁶ and Roy Soetikno,³ for the SCENIC Guideline Development Panel

Table 2. The SCENIC consensus statement on morphologic terminology for reporting findings on colonoscopic surveillance of patients with inflammatory bowel disease .

Term	Definition
Visible dysplasia	Dysplasia identified on targeted biopsies from a lesion visualized at colonoscopy
Polypoid	Lesion protruding from the mucosa into the lumen ≥ 2.5 mm
Pedunculated	Lesion attached to the mucosa by a stalk
Sessile	Lesion not attached to the mucosa by a stalk; entire base is contiguous with the mucosa
Nonpolypoid	Lesion with little (< 2.5 mm) or no protrusion above the mucosa
Superficial elevated	Lesion with protrusion but < 2.5 mm above the lumen (less than the height of the closed cup of a biopsy forceps)
Flat	Lesion without protrusion above the mucosa
Depressed	Lesion with at least a portion depressed below the level of the mucosa
General descriptors	
Ulcerated	Ulceration (fibrinous-appearing base with depth) within the lesion
Border	
Distinct border	Lesion's border is discrete and can be distinguished from surrounding mucosa
Indistinct border	Lesion's border is not discrete and cannot be distinguished from surrounding mucosa
Invisible dysplasia	Dysplasia identified on random (non-targeted) biopsies of colon mucosa without a visible lesion

Algorithms for management of endoscopically visible/polypoid dysplasia versus invisible/flat dysplasia in IBD patients

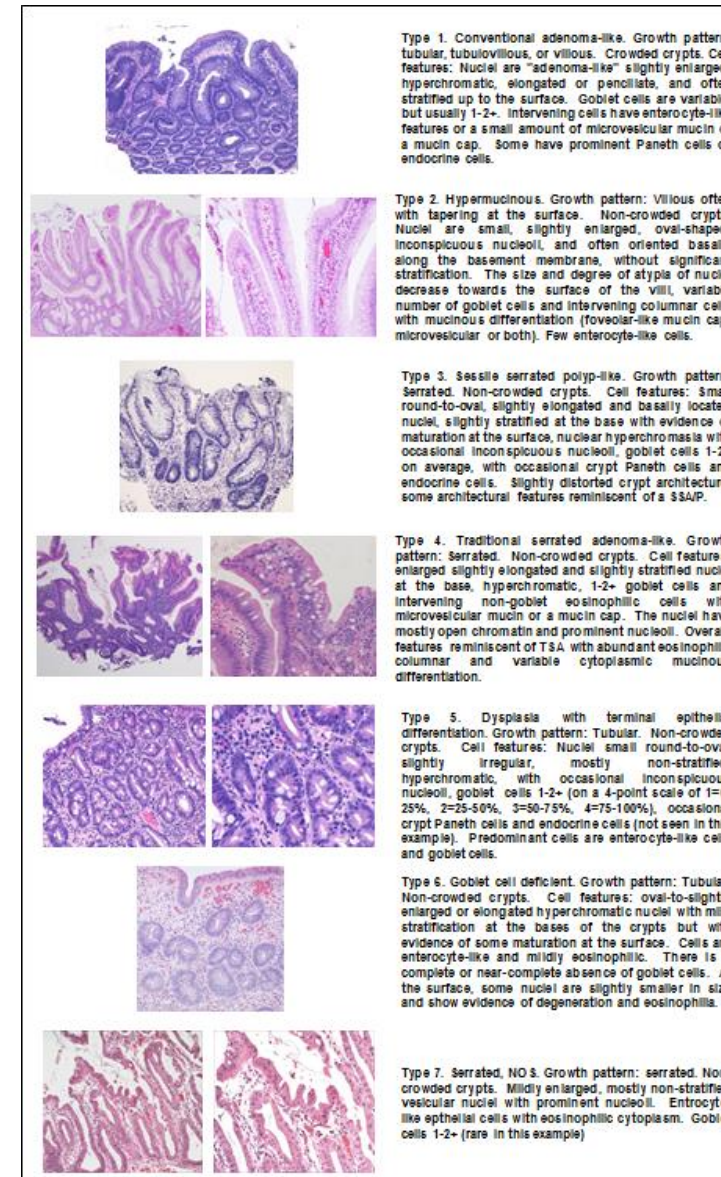


Non-conventional dysplastic subtypes in IBD

1. Hypermucinous dysplasia
2. Goblet cell deficient dysplasia
3. Crypt cell dysplasia (or dysplasia with terminal epithelial differentiation)
4. Dysplasia with increased Paneth cell differentiation
5. Sessile serrated lesion-like dysplasia
6. Traditional serrated adenoma-like dysplasia
7. Serrated dysplasia, not other specified

Excellent diagnostic agreement for each dysplasia category (by expert GI pathologist)

Highest diagnostic agreement for types 1, 2 and 3

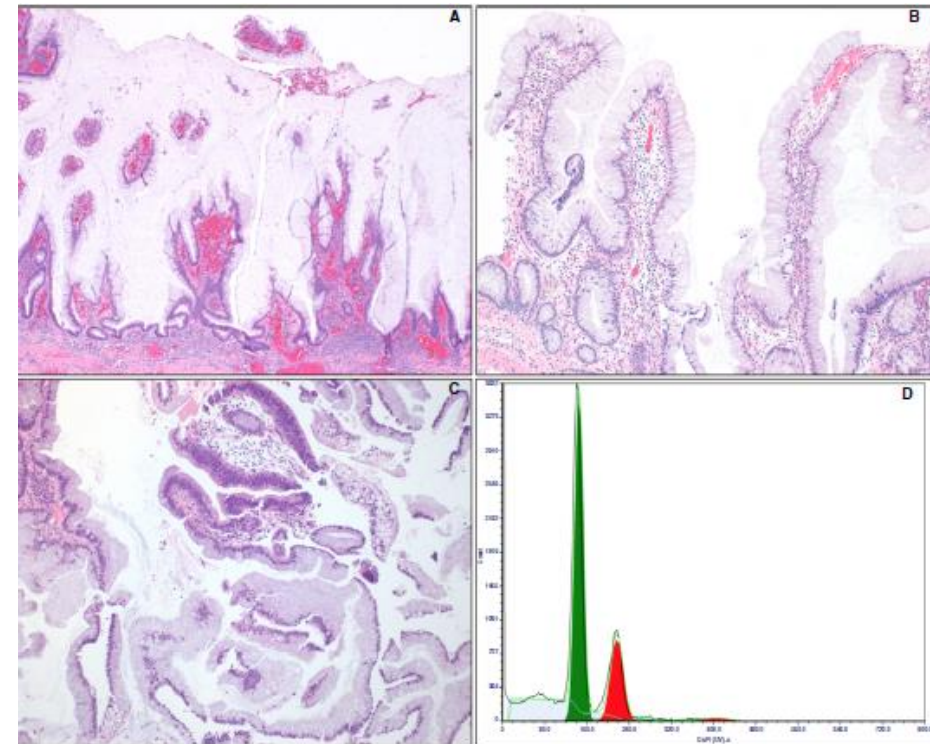


Towards a better knowledge of nonconventional dysplasia in patients with IBD

-Flat/invisible lesion+++

-Higher risk of harboring advanced neoplasia in patients with nonconventional dysplasia than in those with IBD-related conventional dysplasia (crypt cell, hypermucinous, and goblet cell deficient dysplasias++)

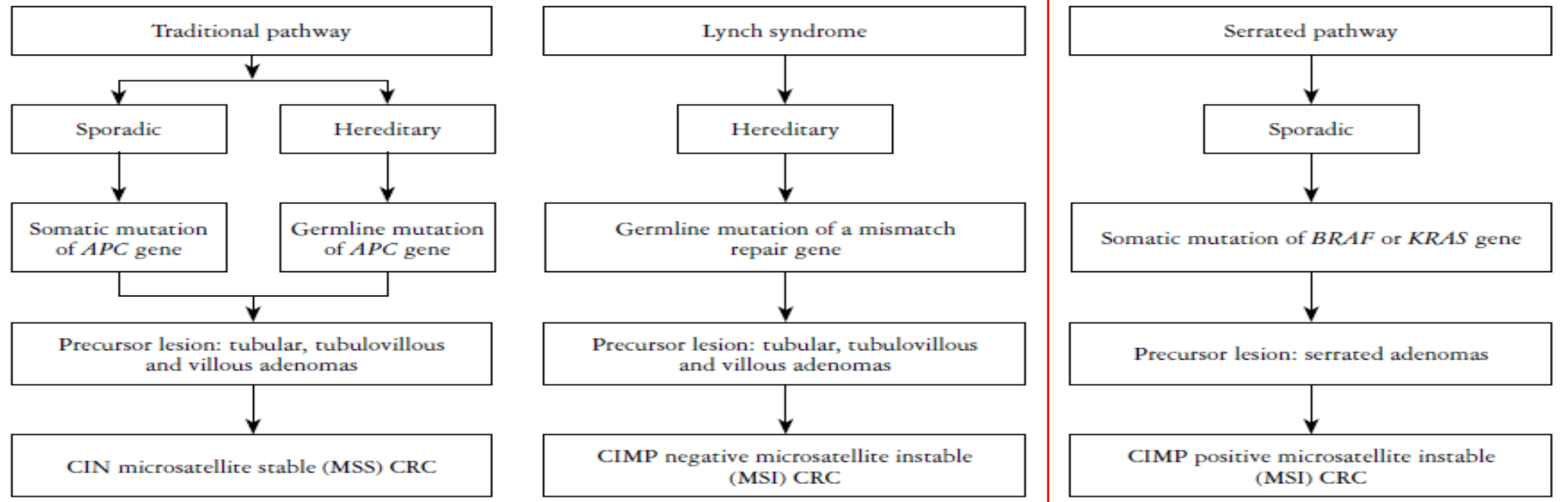
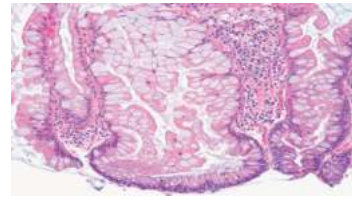
-Higher rate of aneuploidy in low-grade non-conventional dysplasia (crypt cell, hypermucinous, and goblet cell deficient dysplasias++)



Serrated lesions in IBD

The serrated pathway, an alternative pathway

30% of CRC



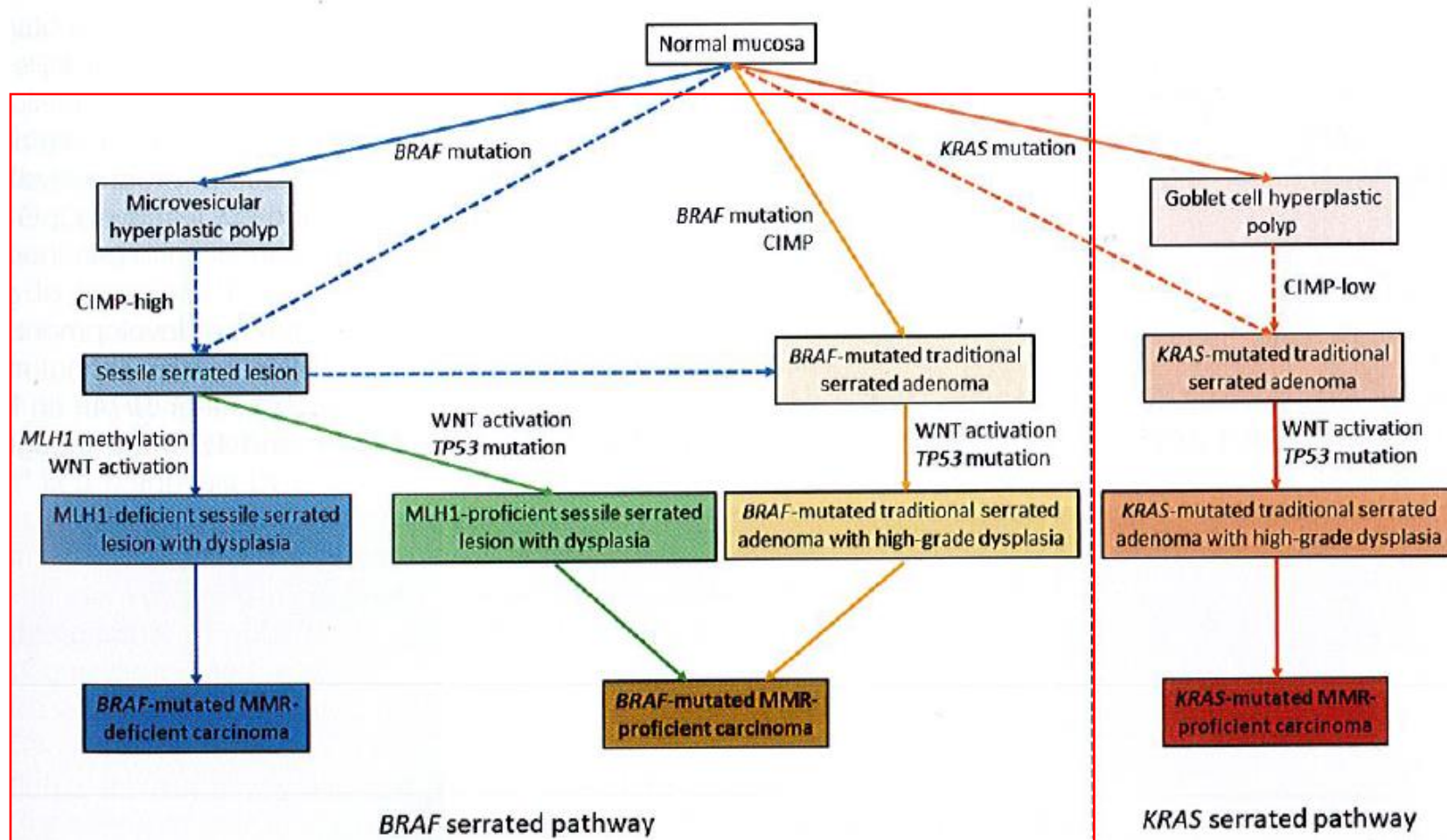
Setaffy et al, 2015

Colorectal serrated lesions and polyps are characterized morphologically by a serrated (sawtooth or stellate) architecture of the epithelium

- Hyperplastic polyp (HP) (microvesicular type and goblet cell-rich type)
- Sessile serrated lesion (ex « sessile serrated adenoma/polyp ») with or without dysplasia (SSL)
- Traditional serrated adenoma (TSA)
- Unclassified serrated adenoma

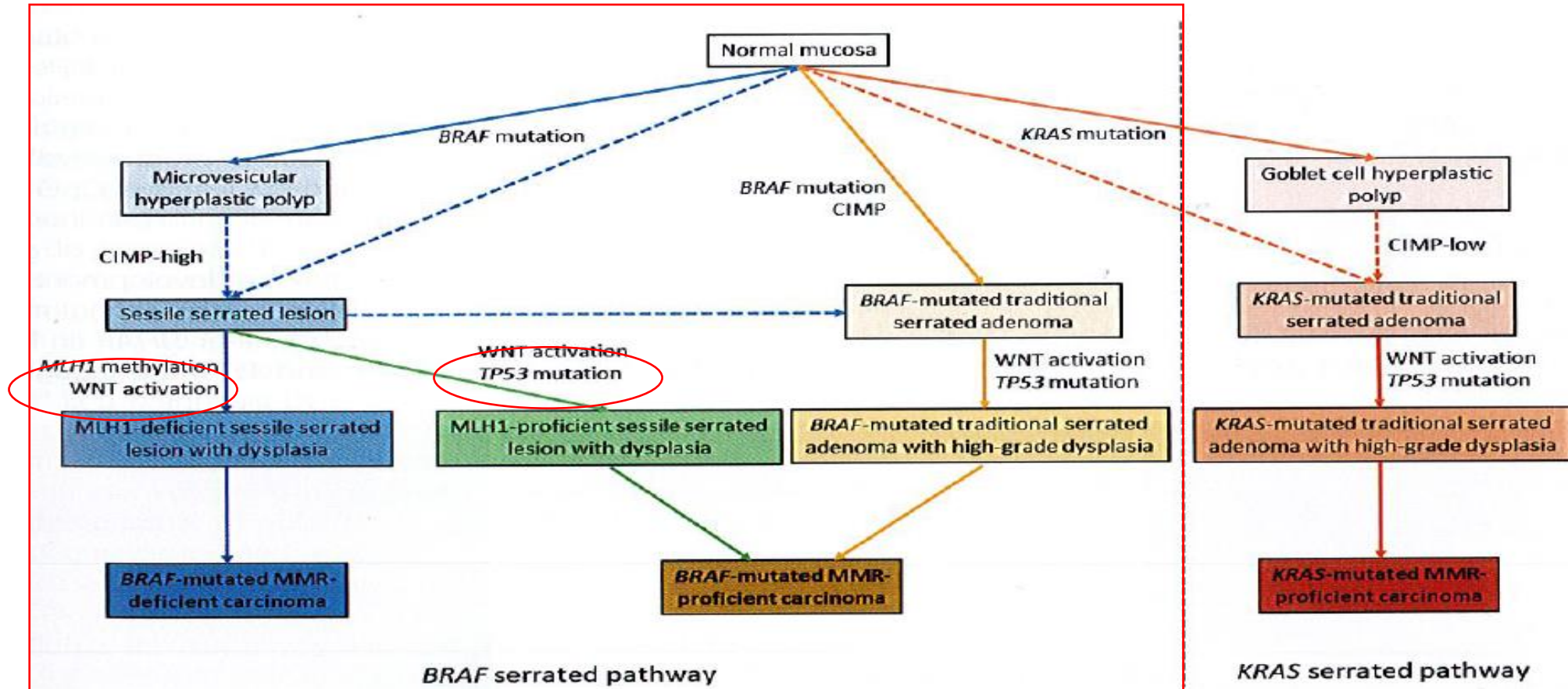
WHO 2019 classification of digestive system tumours

The serrated pathway



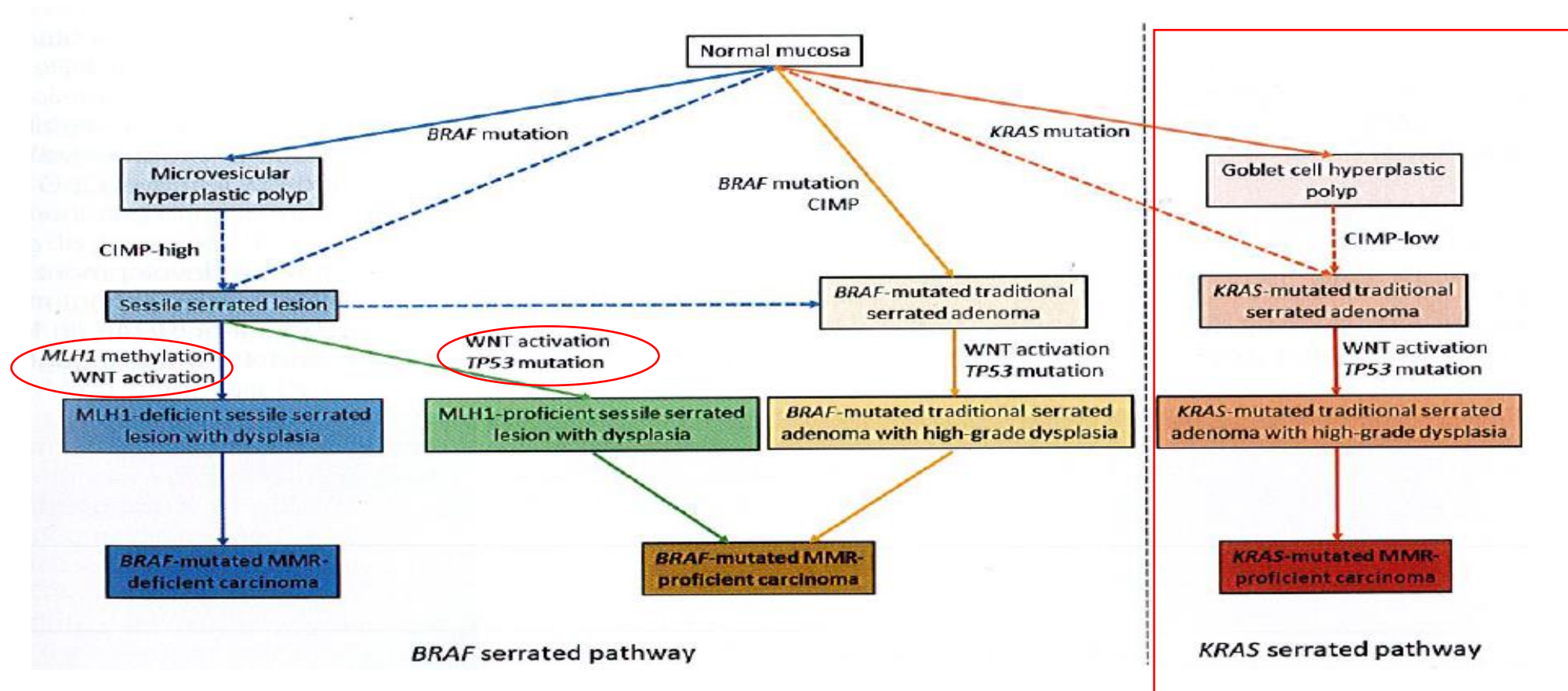
**WHO 2019 classification
of digestive system tumours**

The serrated pathway



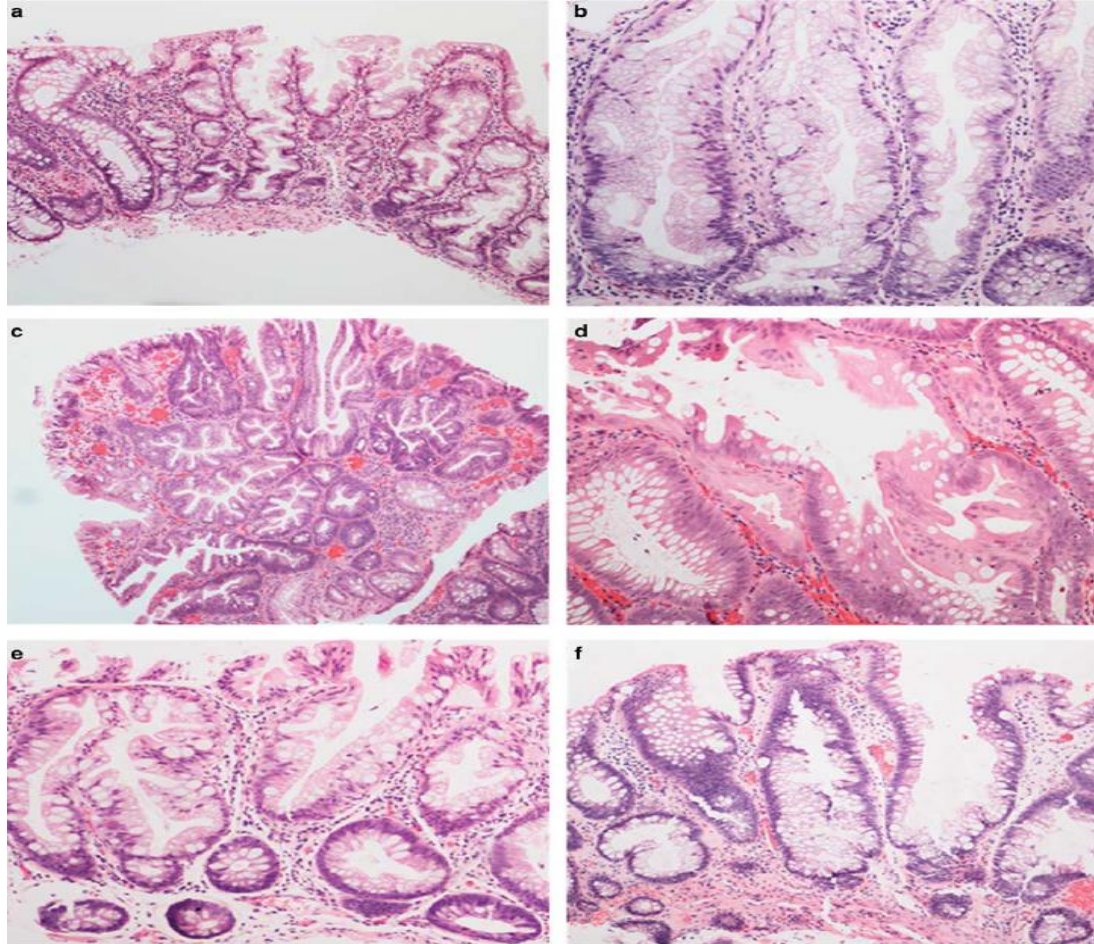
**WHO 2019 classification
of digestive system tumours**

The serrated pathway



**WHO 2019 classification
of digestive system tumours**

The serrated pathway in IBD-associated neoplasia



Ko et al., Modern pathol 2015

Hyperplastic/Serrated Polyposis in Inflammatory Bowel Disease

A Case Series of a Previously Undescribed Entity

Amitabh Srivastava, MD,* Mark Redston, MD,† Francis A. Farraye, MD, MSc,‡
Rhonda K. Yantiss, MD,§ and Robert D. Odze, MD, FRCP(C)†

Am J Surg Pathol 2008

A rare case series of concomitant inflammatory bowel disease, sporadic adenomas, and serrated polyposis syndrome ☆



J.D. Feuerstein ^{a,b,*}, S.N. Flier ^b, E.U. Yee ^c, D. Pleskow ^b, A.S. Cheifetz ^b

JCC 2015

Original contribution

Clinical, pathologic, and outcome study of hyperplastic and sessile serrated polyps in inflammatory bowel disease ☆



Jeanne Shen MD ^{a,1}, Joanna A. Gibson MD, PhD ^b, Stephanie Schulte MD ^c,
Hema Khurana MD ^d, Francis A. Farraye MD, MSc ^e, Jonathan Levine MD ^a,
Robert Burakoff MD, MPH ^a, Sandra Cerda MD ^e, Taha Qazi MD ^e,
Matthew Hamilton MD ^a, Amitabh Srivastava MD ^a, Robert D. Odze MD, FRCP ^{a,*}

Human Pathol 2015

Serrated colorectal polyps in inflammatory bowel disease

Huaibin M Ko ^{1,4}, Noam Harpaz ^{1,2,4}, Russell B McBride ^{1,3}, Miao Cui ¹, Fei Ye ¹, David Zhang ¹,
Thomas A Ullman ² and Alexandros D Polydorides ^{1,2}

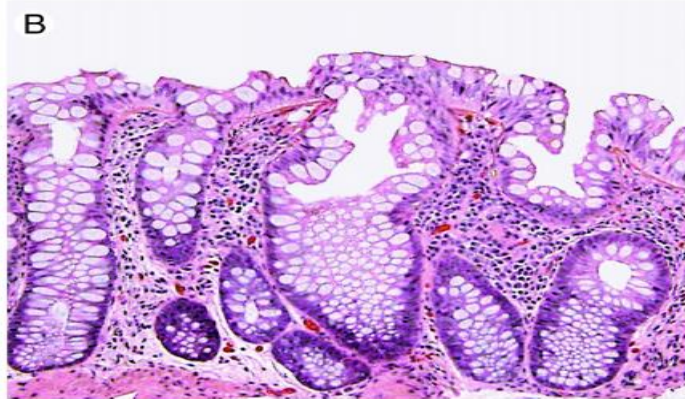
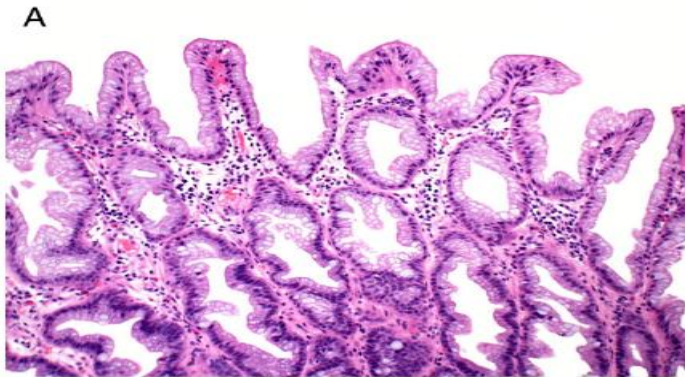
Modern Pathol 2015

Large serrated polyp with KRAS mutation in inflammatory bowel disease: a “nondysplastic dysplasia-associated lesion or mass (DALM)”?

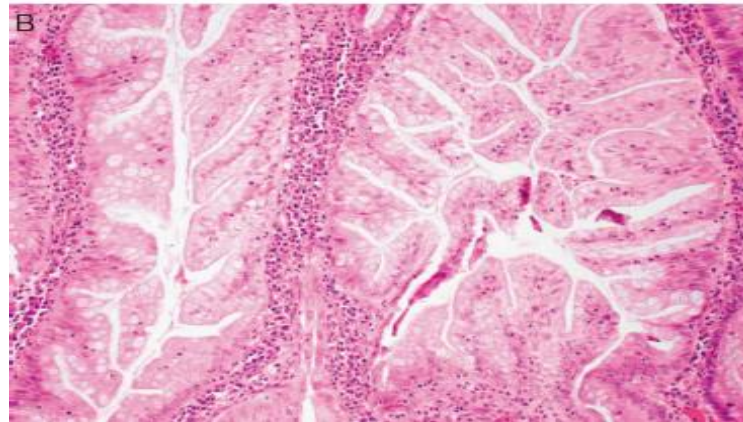
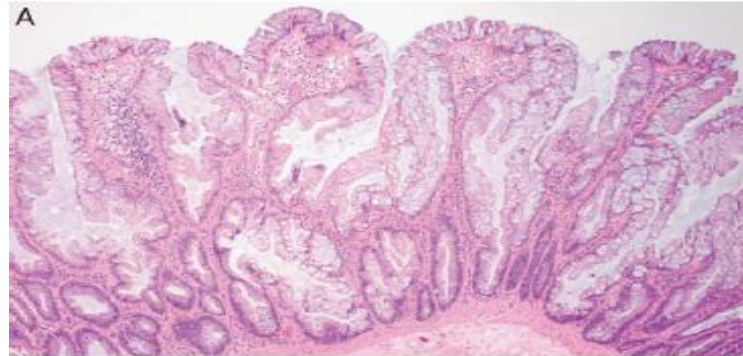
Langner et al., Endoscopy 2013

Morphological aspect of serrated lesions in IBD

3 types of lesions are described: HP, SSL (with or without dysplasia), and TSA



Shen et al, Human Pathol 2015



Srivastava et al, Am J Surg Pathol 2008

- HP+++ (96% Shen's series)
- SSL+
- TSA are exceptional

Left colon and rectum+++ (Shen et al, 2015)

More than 50% are detected endoscopically

(Shen et al)

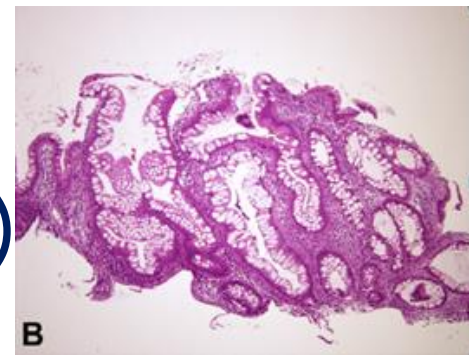
Very low incidence (1.2%) (Ko et al., Modern Pathol 2015)

Can be multiple
(« Hyperplastic/serrated polyposis syndrome ») (Srivastava et al, 2008, Feuerstein et al, 2014)

Serrated lesions in IBD: a challenge

- Two considerations:
 - (i) serrated lesions that occur in the population may also occur in IBD patients.
 - (ii) IBD-associated dysplastic lesions may show serration
- Similar clinical and molecular features of IBD-associated serrated lesions with their sporadic counterpart
- The gross or endoscopic appearance (large irregular ill-defined area vs polyp/lesion), size and histology may be helpful to distinguish sporadic SL from serrated IBD-associated dysplasia

Serrated epithelial changes (SEC)



- SEC (serrated epithelial changes) is a histologic finding in longstanding colitis.
- SEC: synonymous with hyperplastic-like mucosal change and flat serrated change
- Histologically: glands with distorted architecture and by crypts which are no longer perpendicular to the muscularis mucosae and which do not necessarily reach the muscularis mucosae. Serration of the epithelium and enlarged goblet cells both extend to the base of the crypts.
- SEC is not a widely recognized histopathologic finding and does not have WHO criteria
- Unclear clinical significance in the development of dysplasia in IBD patients

Non-conventional mucosal lesions (serrated epithelial change, villous hypermucinous change) are frequent in patients with inflammatory bowel disease—results of molecular and immunohistochemical single institutional study

Surgical specimens and/or endoscopical biopsy samples of IBD patients during a 10-year period

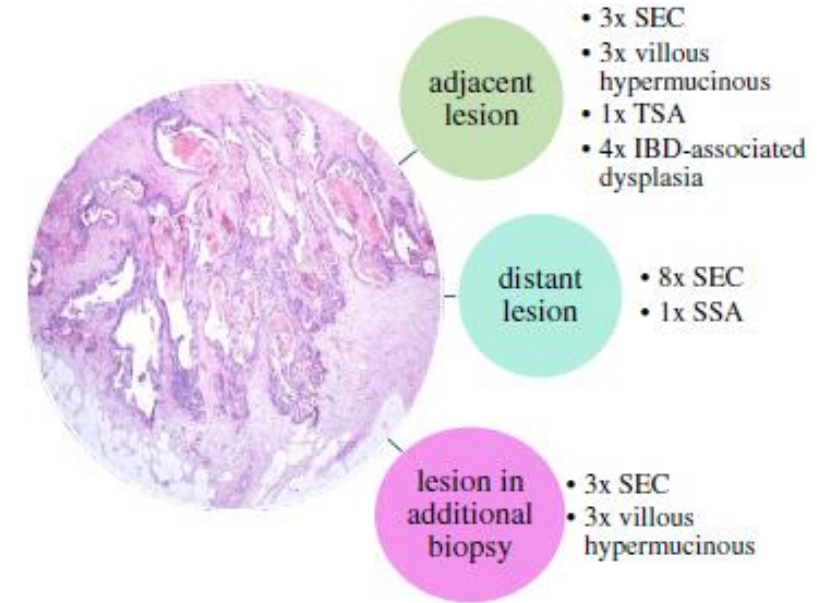
Table 3 Immunohistochemical and molecular characteristics of lesions from all groups (groups 1–3)

	Serrated epithelial change <i>N</i> = 41 (100%, \$)	Villous hypermucinous change <i>N</i> = 6 (100%, \$)	Combined serrated and villous lesions <i>N</i> = 5 (100%, \$)	HP-like lesions <i>N</i> = 4 (100%, \$)	All PPLs <i>N</i> = 56 (\$ 100%)	Hyperplastic poly <i>N</i> = 6 (100%)	Sessile serrated adenoma <i>N</i> = 7 (100%)	Traditional serrated adenoma <i>N</i> = 2 (100%)	IBD-associated dysplasia <i>N</i> = 6 (100%)	IBD-associated CRC <i>N</i> = 11 (100%)
IHC results										
MGMT loss	17 (41%, \$ 30%)	4 (67%, \$ 7.1%)	2 (40%, \$ 3.6%)	2 (50%, \$ 3.5%)	25 (\$ 44.6%)	2 (33.3%)	7 (100%)	2 (100%)	2 (33.3%)	6 (54.5%)
p53 aberrant expression (complex and basal)	14 (26.9%, \$ 19.7%)	2 (33.3%, \$ 3.6%)	1 (20%, \$ 1.8%)	1 (25%, \$ 1.8%)	18 (\$ 32.1%)	1 (16.6%)	1 (14.2%)	2 (100%)	3 (50%)	6 (54.5%)
MLH1 loss	0	1 (16.6%, \$ 1.8%)	0	0	1	0	0	0	0	0
Molecular results										
<i>KRAS/NRAS</i> mutated	17 (41.5%, \$ 30.6%)	2 (33.3%, \$ 3.6%)	4 (80%, \$ 7.1%)	1 (25%, \$ 1.8%)	24 (\$ 42.9%)	3 (50%)	4 (57.1%)	2 (100%)	4 (66.6%)	8 (72.7%)
<i>BRAF</i> mutated*	6 (15%, \$ 10.7%)	2 (33.3%, \$ 3.6%)	0	1 (25%, \$ 1.8%)	9 (16.4%, \$ 16.1-%)*	4 (66.6%)	4 (57.1%)	0	0	1 (9.1%)
Concurrent <i>KRAS(NRAS)</i> and <i>BRAF</i> mutation	3 (7.3%, \$ 5.3%)	0	0	0	3 (\$ 5.3%)	2 (33.3%)	2 (28.6%)	0	0	0

CRC, colorectal carcinoma; IBD, inflammatory bowel disease; HP, hyperplastic polyp; IHC, immunohistochemistry; PPLs, putative precursor lesions

\$Percentage of cases counted from all PPLs

**p* = 0.017 comparing difference between *KRAS* and *BRAF* mutations in PPLs



SEC: 46.6% of cases (most common non-conventional mucosal lesion)
 SEC: loss of MGMT expression (41%), aberrant P53 expression and *KRAS* mutation (41.5%)
 Association with invasive carcinoma (with same *KRAS* or *BRAF* mutation)

Possible neoplastic potential?

Small bowel adenocarcinoma complicating Crohn's disease

Increased risk of developing intestinal and extra-intestinal malignancies in patients with IBD

Table 1. Background risk of cancer in patients with IBD.¹⁻⁸

Tumour	SIR in IBD	Incidence in background population	5-year Survival
Small bowel adenocarcinoma in CD	18.7-46	0.3-0.5	±40%
Colorectal cancer in IBD	1.7-8.6	0.5-0.8	64%
Cholangiocarcinoma [* IBD with PSC]	2-160*	0.08	8% ⁴
Gastric cancer in CD	2.8	0.3-1 ⁵	31% ⁶
Leukaemia in UC [** adult age]	2	0.015	24%** -67% ⁷
Urinary tract cancer in CD	2	0.5	77% ⁸

Annese V. JCC 2020

+ Among patients with UC, the relative risk of incident small bowel cancer was highest for those with extensive colitis and PSC (Axelrad et al., Gut 2021)

Risk factors for SBA in CD patients

Long disease duration+++

Childhood-onset+++

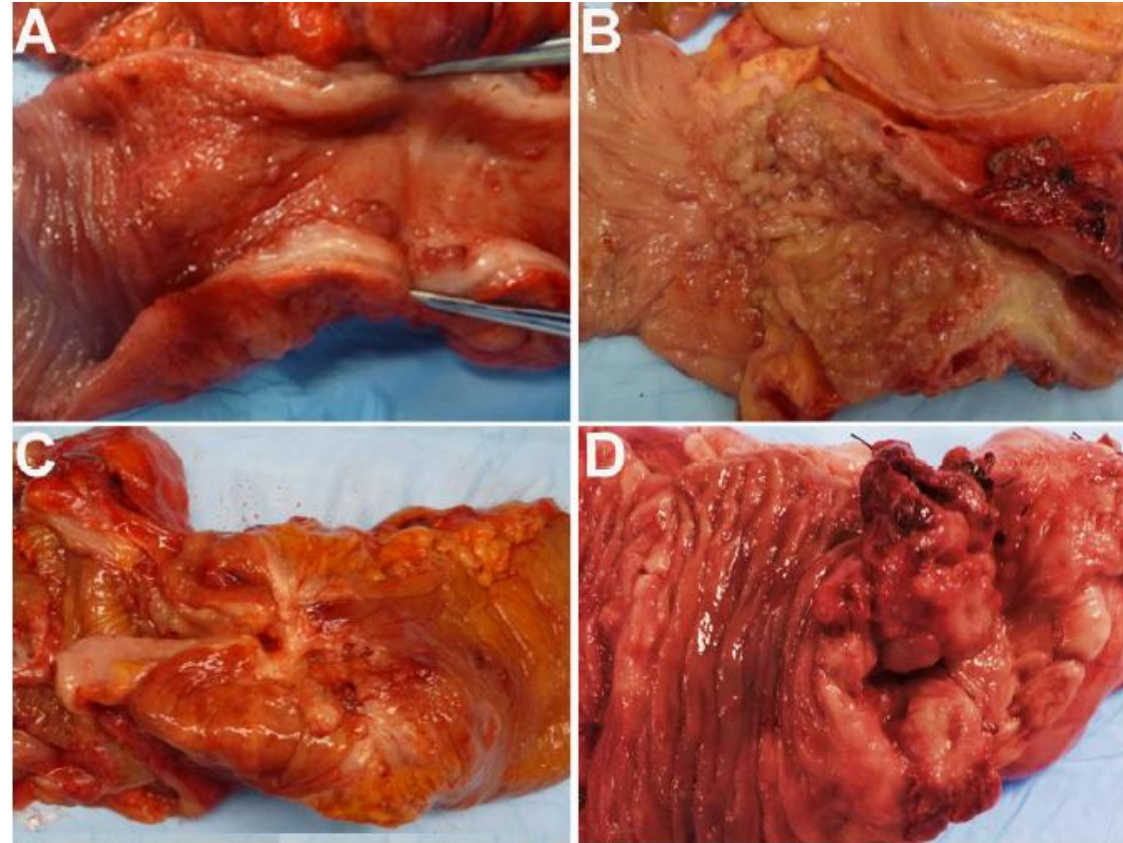
Male sex

Distal jejunal/ileal localization

Strictures+++ and chronic penetrating disease

Small-bowel bypass loops

Use of steroids and immunomodulators



Lower incidence of SBA:

Small-bowel resection

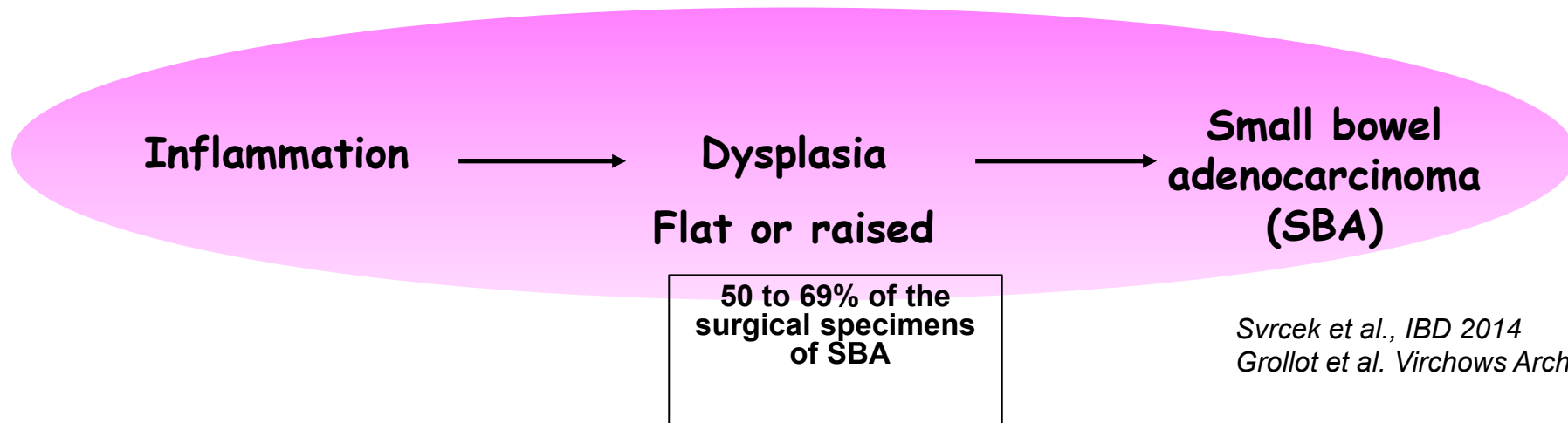
Use of aminosalicylates for >2 years

(Piton et al., Am J Gastroenterol 2008)

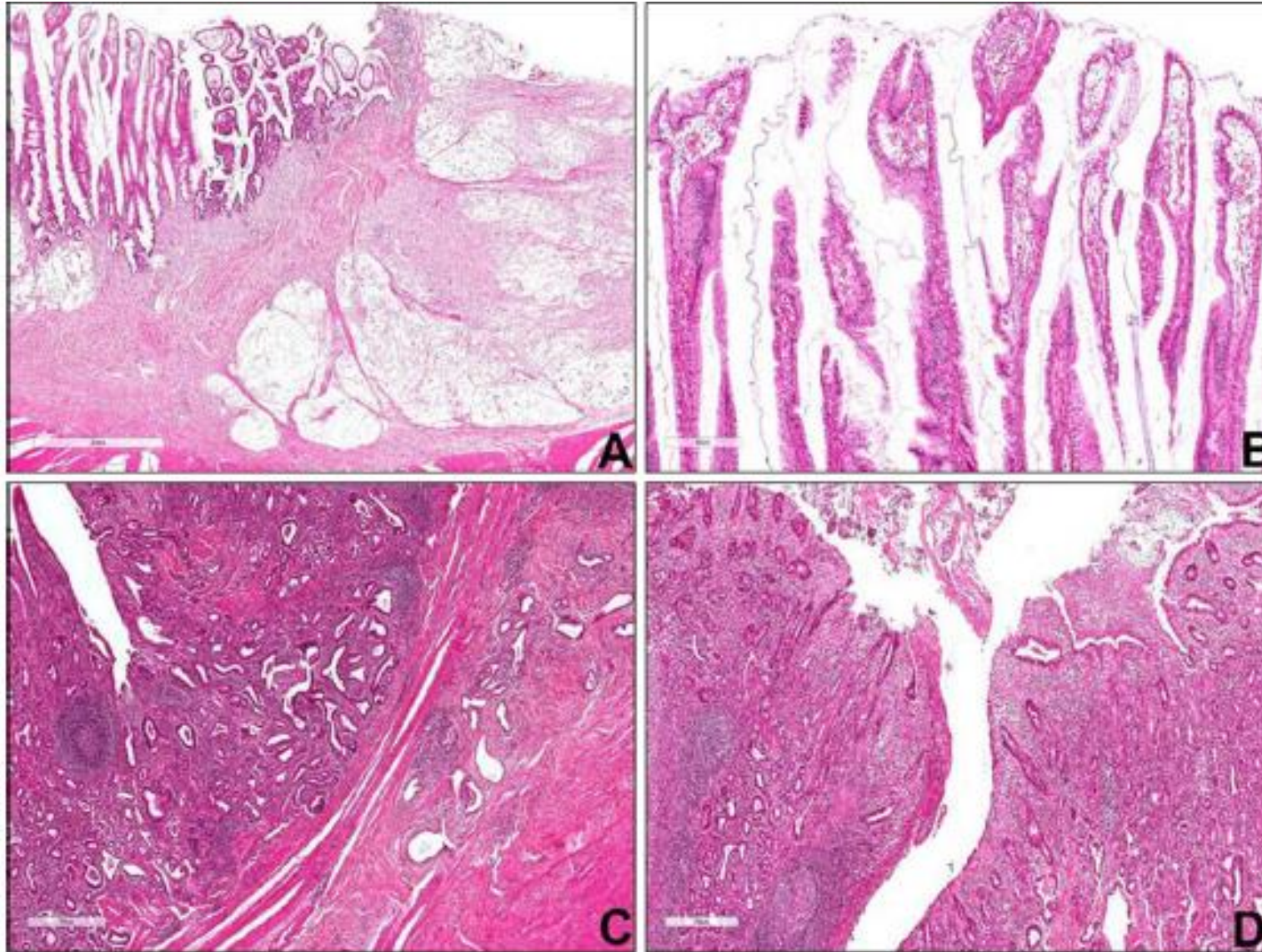
Liao et al., JCC 2019

*Annese et al, JCC 2015
Laukoetter et al., J Gastrointest Surg 2011
Annese V. JCC 2020
Axelrad et al. Gut 2021*

Dysplasia (or intra-epithelial neoplasia), a pre-neoplastic lesion in IBD



Small intestinal dysplasia in CD

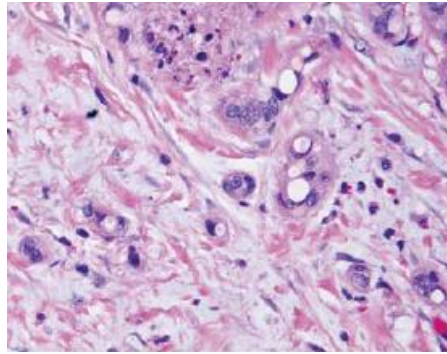


Adenomatous
dysplasia

Hypermucinous
dysplasia

SBA complicating CD, a distinct clinical, pathological and molecular entity

- Younger age (62 *versus* 65, $p < 0.001$) (Fields et al., JCC 2020)
- Microscopically,
 - Heterogeneity (with at least 3 distinct growth pattern)
 - Higher rates of low-grade tubuloglandular adenocarcinoma, mucinous/signet ring cell histology, poorly differentiated and undifferentiated tumours (Grolleau et al., Virchows Archiv 2017, Liao et al., JCC 2019, Fields et al., JCC 2020)
 - Peritumoral Crohn's like reaction
- MMR proficient >>> MMR deficient
- Similar profiles of frequently mutated genes as sporadic SBA (*TP53*, *PIK3CA*), except *IDH1* and *SMAD4* (Liao et al, JCC 2019, Aparicio et al., Int J Cancer 2021)



Prognostic of SBA complicating CD

- **Factors associated with improved survival**

- Glandular histology
- High density of TIL
- Stage I/II
- Receipt of chemotherapy
- Tumor budding and poorly differentiated clusters

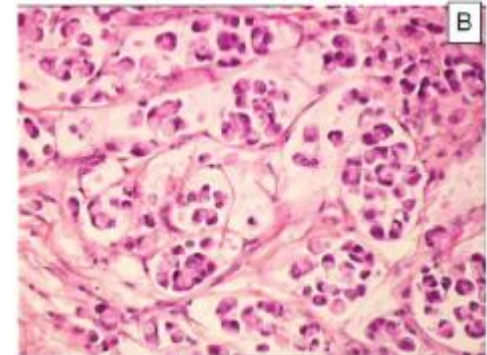
- **Factors associated with poor survival**

- Non-glandular histology
- Older age
- Higher tumour grade (excluding signet ring cell carcinoma)
- Positive surgical margins
- Stage III/IV

Similar overall survival of CD patients compared to patients with sporadic SBA (Fields et al., JCC 2020)

SBA complicating CD: a diagnostic challenge

- Non specific symptoms (abdominal pain, obstruction, nausea, and emesis), closely mimicking that of CD flares
- Low-sensitivity and specificity of non-invasive imaging techniques, notably at early stages
- Poor results of endoscopic screening secondary to impassable strictures and incomplete visualisation of the small bowel
- SBA: a diagnosis rarely made preoperatively and often an incidental finding made by the surgeon or the pathologist
- Careful investigation with frozen section and/or resection in case of any suspicious finding at the time of surgery in a patient with chronic CD





Aberrant p53 protein expression is associated with an increased risk of neoplastic progression in patients with Barrett's oesophagus

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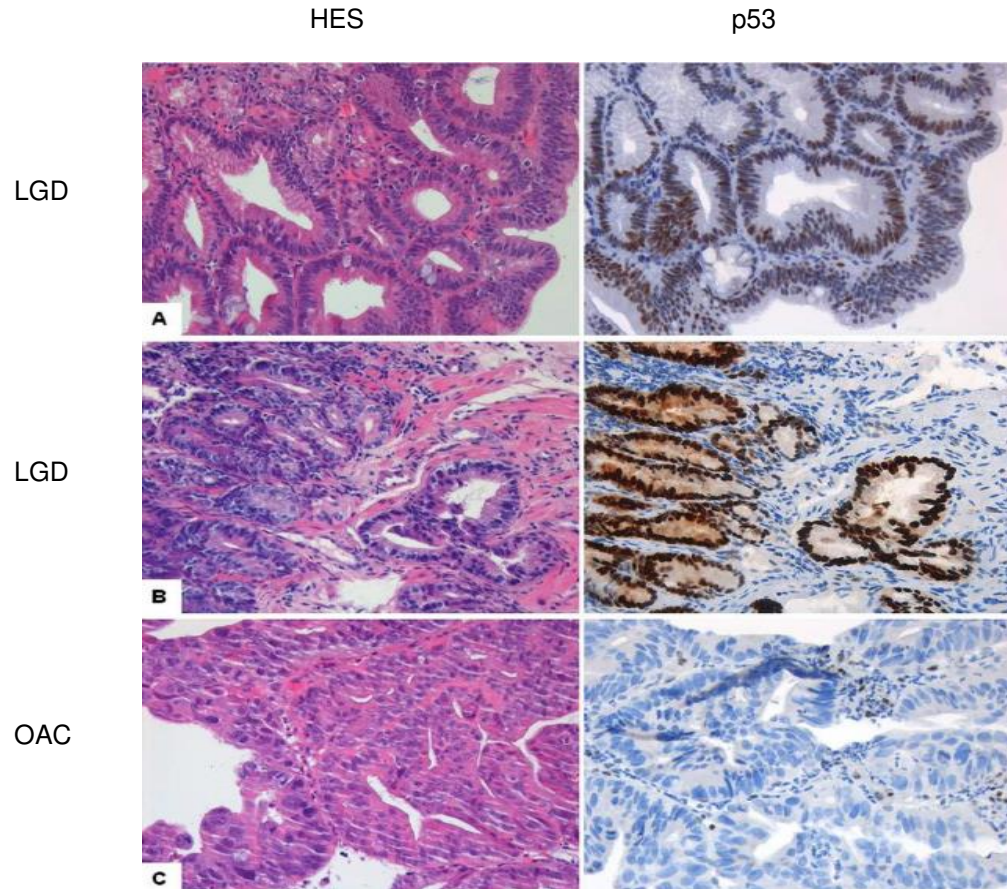
- Etude cas-témoin au sein d'une cohorte prospective de 720 patients présentant un endobrachyoœsophage

Table 2 Histology and p53 immunohistochemistry in biopsy series of cases and controls

	Controls n=1300	Cases n=132	RR (95% CI)	RR* (95% CI)
Histology				
ND	1011 (78%)	74 (56%)	Reference	Reference
LGD	289 (22%)	58 (44%)	4.2 (2.4 to 7.3)	4.0 (2.3 to 7.0)
P53 immunohistochemistry				
Normal p53 expression	1115 (86%)	67 (51%)	Reference	Reference
Aberrant p53 expression	185 (14%)	65 (49%)	6.2 (3.6 to 10.9)	6.4 (3.6 to 11.3)
P53 overexpression	169 (13%)	58 (44%)	5.5 (3.1 to 10.0)	5.6 (3.1 to 10.3)
Loss of p53 expression	16 (1%)	7 (5%)	13.4 (5.1 to 35.3)	14.0 (5.3 to 37.2)
Histology and p53 immunohistochemistry				
ND and normal p53 expression	918 (71%)	50 (38%)	Reference	Reference
LGD and normal p53 expression	197 (15%)	17 (13%)	2.4 (0.9 to 6.0)	2.2 (0.8 to 5.5)
ND and aberrant p53 expression	93 (7%)	24 (18%)	4.5 (2.0 to 10.0)	4.3 (1.9 to 9.8)
LGD and aberrant p53 expression	92 (7%)	41 (31%)	11.2 (5.7 to 22.0)	12.2 (6.1 to 24.5)

*Adjusted for age, gender, Barrett length and oesophagitis.
The highest degree of abnormality was reported for each endoscopy after examining all biopsies.
Loglinear regression models were used to calculate relative risks (RRs) and CIs for neoplastic progression.
LGD, low-grade dysplasia; ND, no dysplasia.

**Association du « pattern absent »
avec un risque augmenté de
progression néoplasique chez les
patients avec endobrachyoesophage**



Bonne reproductibilité inter-observateur dans l'interprétation de l'expression de p53

Table 3 Interobserver agreement for p53 expression between two expert pathologists

P53 expression	Normal expression	Overexpression	Loss of expression	κ
Normal expression	1126 (76%)	56 (4%)	7 (0%)	0.793
Overexpression	24 (2%)	234 (16%)	—	
Loss of expression	14 (1%)	—	19 (1%)	

The highest degree of abnormality was reported for each endoscopy after examining all biopsies.
Cohen κ statistics were used to determine interobserver agreement.

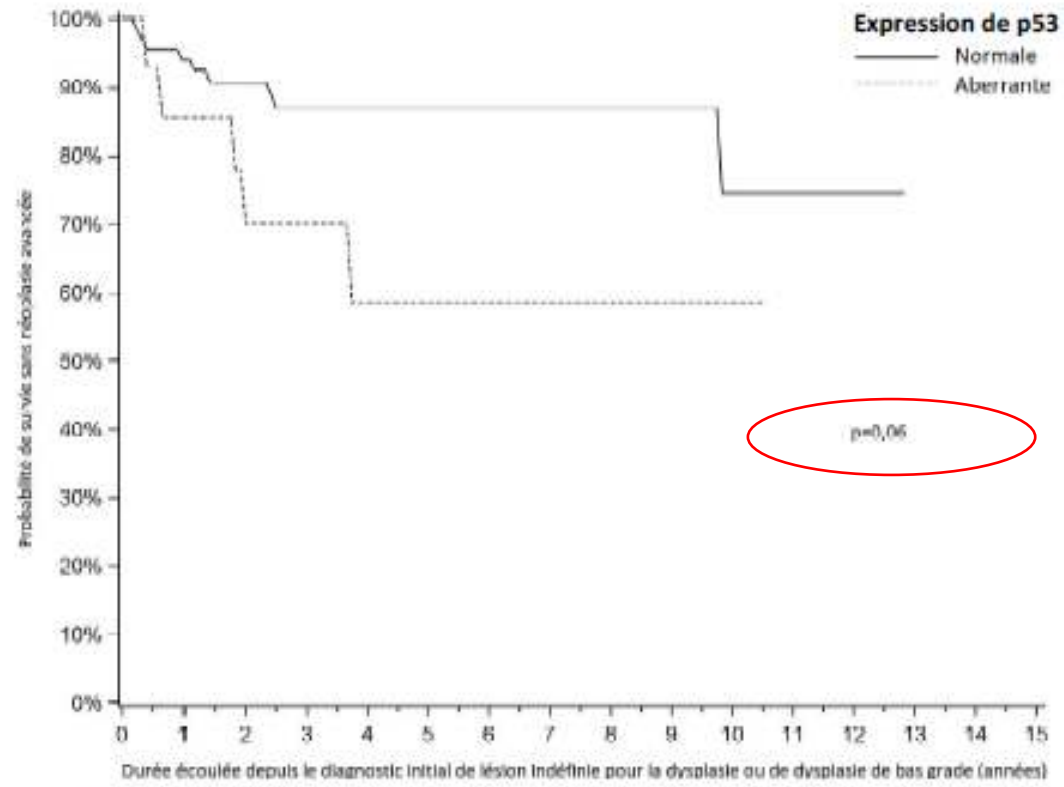
➔ L'immunomarquage anti-p53 pourrait être un test discriminant utile pour améliorer la stratification du risque et ainsi le rapport "coût-efficacité" des programmes de surveillance dans l'oesophage de Barrett.

L'expression anormale de P53 pourrait être un marqueur prédictif de la survenue de néoplasies avancées dans les MICI

86 patients
14 events
Follow-up: 13 years

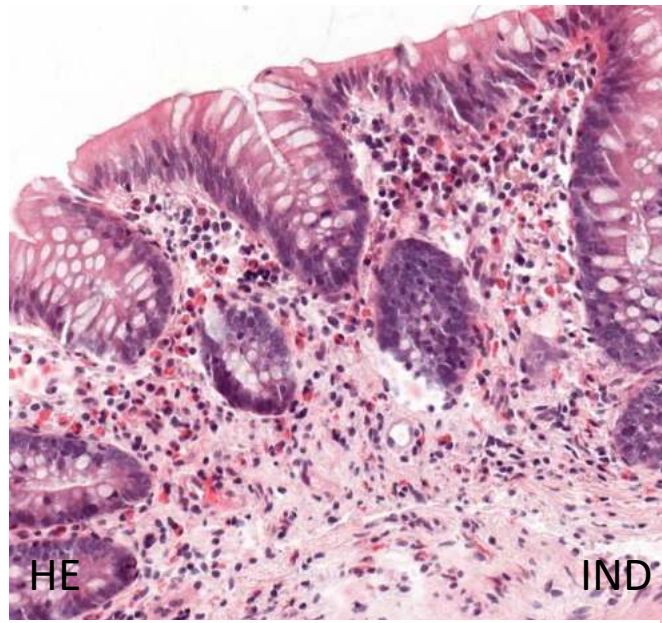
R

Follow-up of patients with indefinite and/or low grade dysplasia

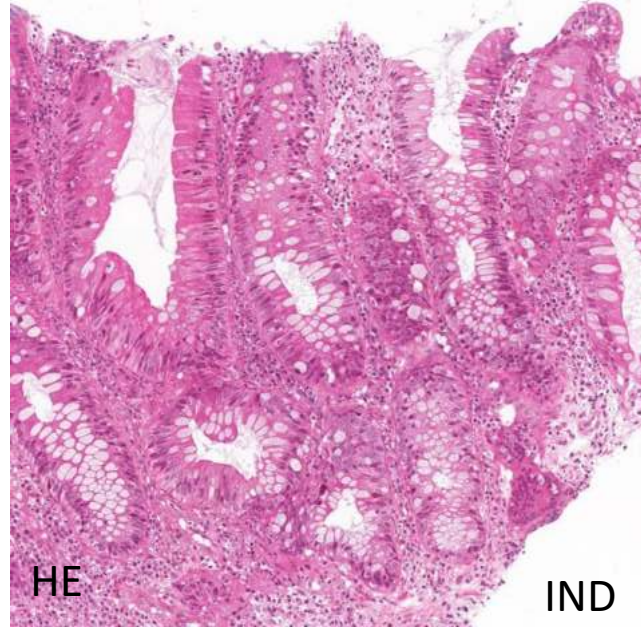


Test = normal		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Nb de patients à risque		70	60	50	42	33	29	25	20	14	9	6	2	1	0		
Événements		0	4	6	8	8	8	8	8	8	8	9	9	9	9		
Test = aberrant		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Nb de patients à risque		16	11	9	8	5	4	4	3	2	2	1	0	0	0		
Événements		0	2	4	4	5	5	5	5	5	5	5	5	5	5		

Normal expression of p53



Overexpression



Complete loss of expression

