Pathological and molecular features of colorectal cancer and precursor lesions

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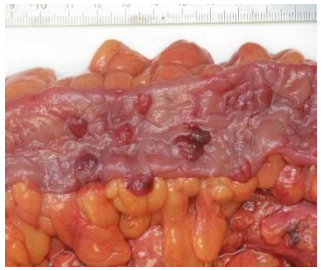
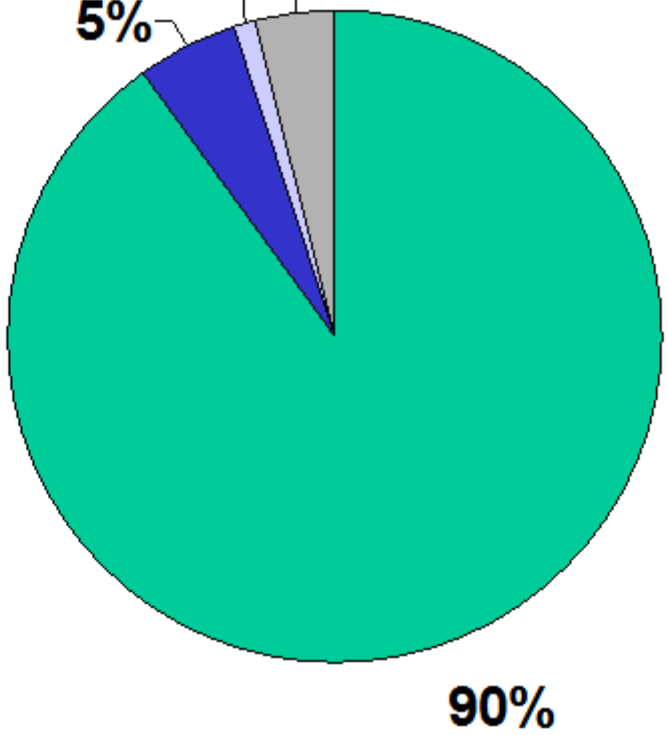
Overview

- Molecular basis of colorectal cancers (CRC)
- Precursor lesions (conventional and serrated)
- Challenges in the pathologic assessment and reporting of CRC:
  - Histologic subtypes
  - Changes of TNM8 classification (pT4a)
  - “Tumor deposits”
  - "Tumor budding”

The colorectal cancer (CRC), a frequent pathology



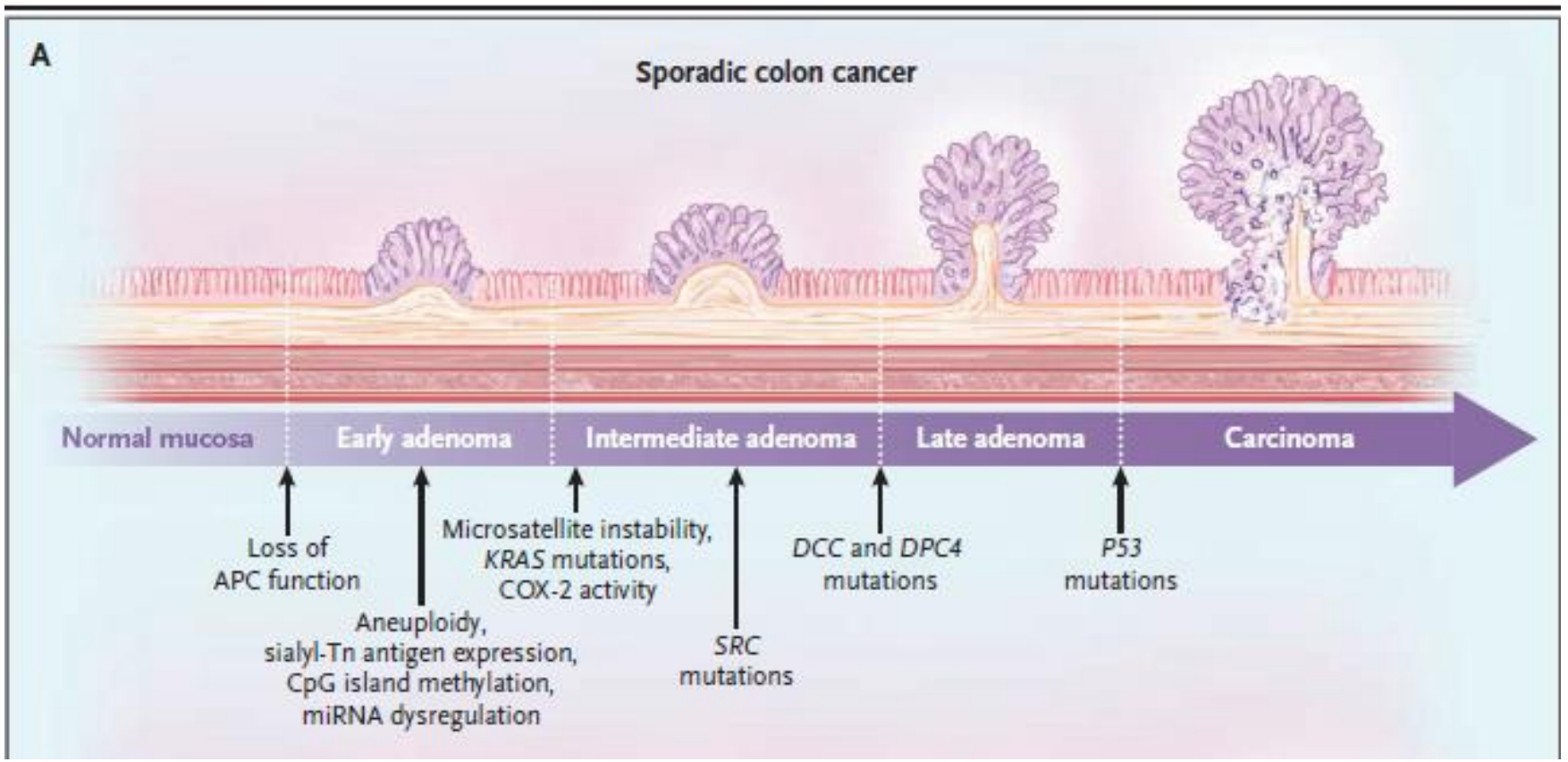


3rd most frequent cancer and 4th most frequent cause of cancer death in the world

In France, 36,000 new cases diagnosed per year; 41% survival rate at 5 years and 16,000 deaths per year.

MUTYH-associated polyposis, serrated polyposis, *Polymerase Proofreading-Associated Polyposis (POLE mutations)*

The colorectal carcinogenesis, a multi-step model



From Beaugerie et Itzkowitz, NEJM 2015

CRCs are heterogeneous from a molecular point of view

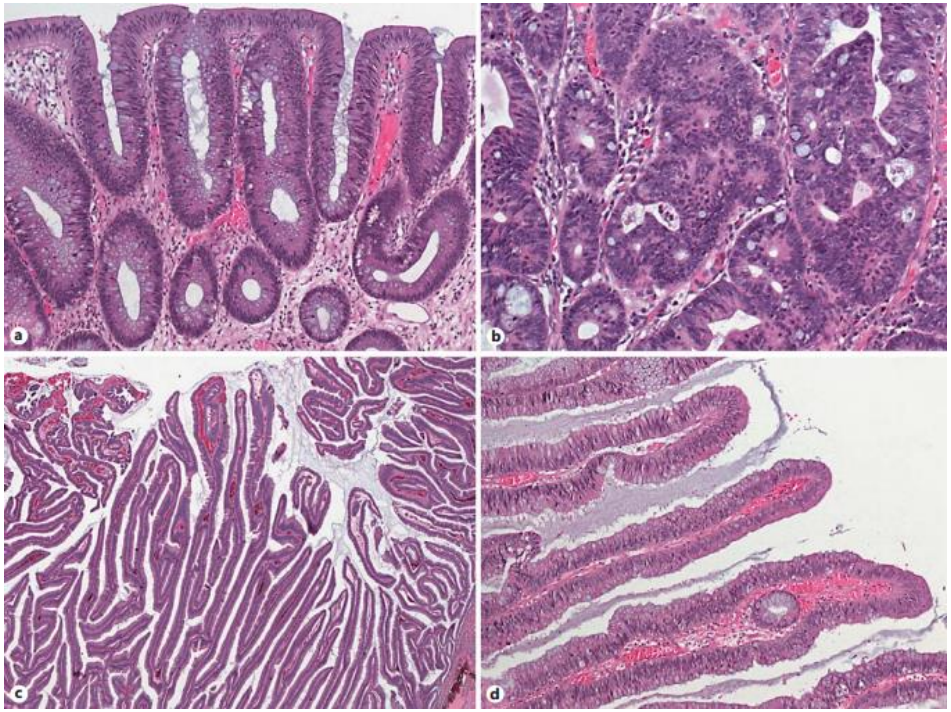
CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGFβ activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

MSI **CIN**

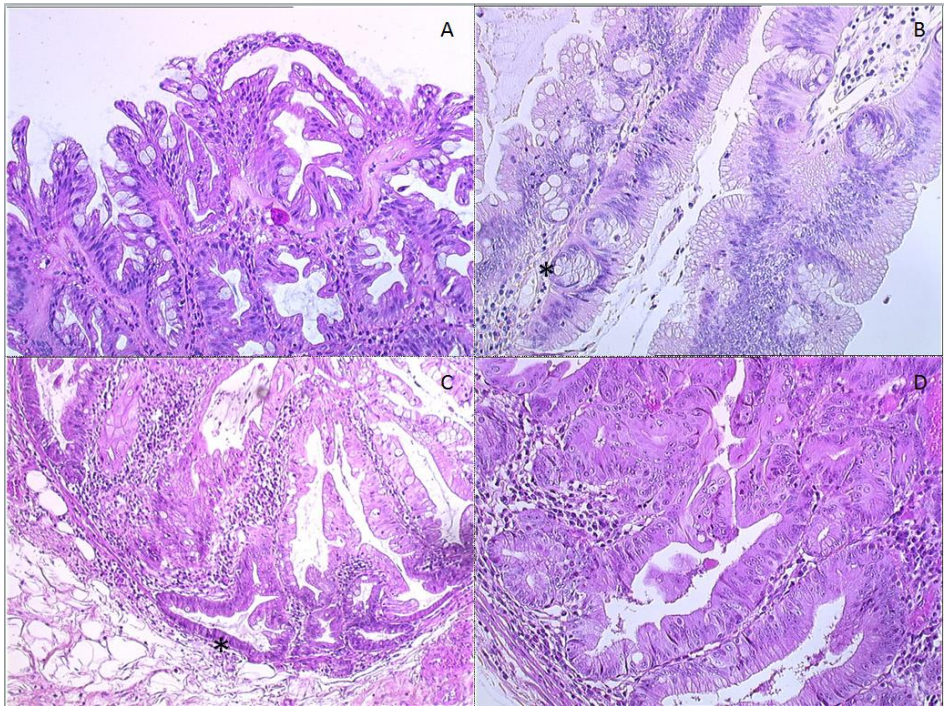
+ epigenetic alterations (CIMP)

Guinney et al., Nature Med 2015

The two main types of precursor lesions of CRC

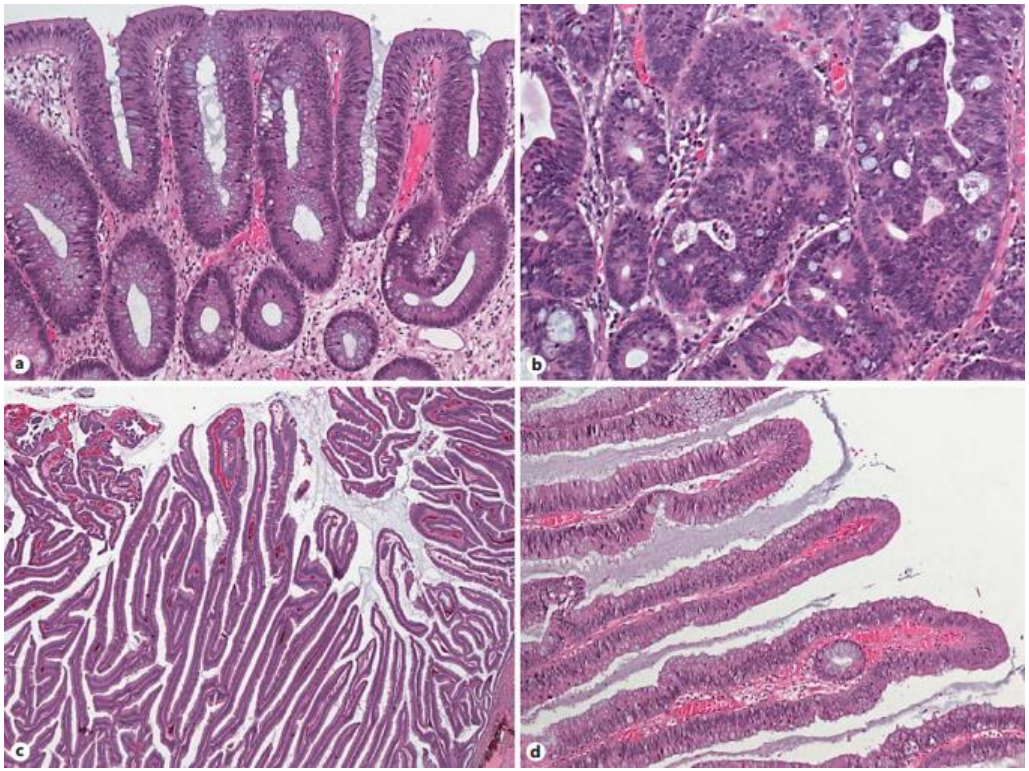


Conventionnal adenomas



Serrated lesions

Conventional colorectal adenoma



Benign, premalignant neoplasm composed of dysplastic epithelium

Conventional *versus* serrated

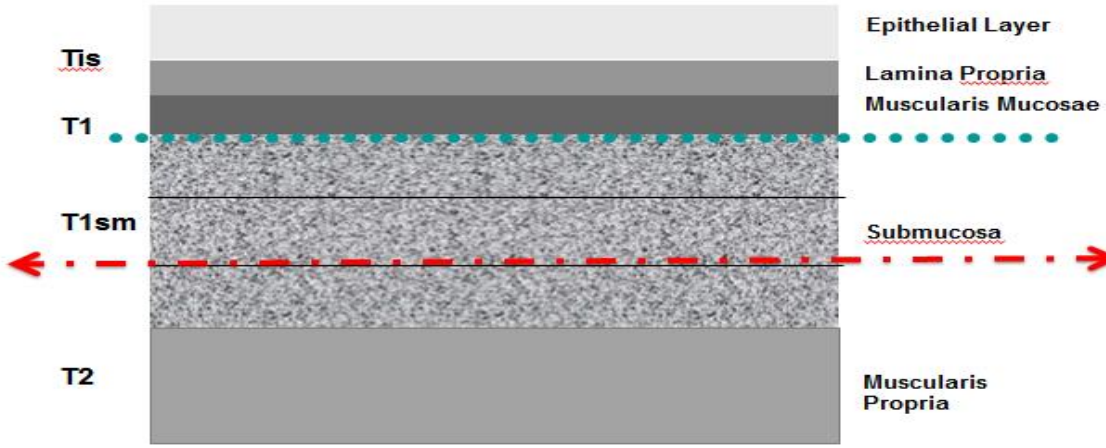
Three subtypes:
- Tubular adenoma
- Villous adenoma (>75% with a villous architecture)
- Tubulovillous adenoma (villous structures resembling small intestinal villi in >25% of the adenoma)

Low grade *versus* high grade

What is a malignant polyp?

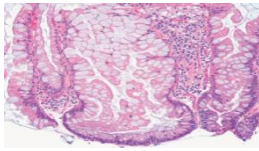
AJCC/UICC TNM 2017, 8th edition:
pTis: carcinoma *in situ,* intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)

pT1: tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)

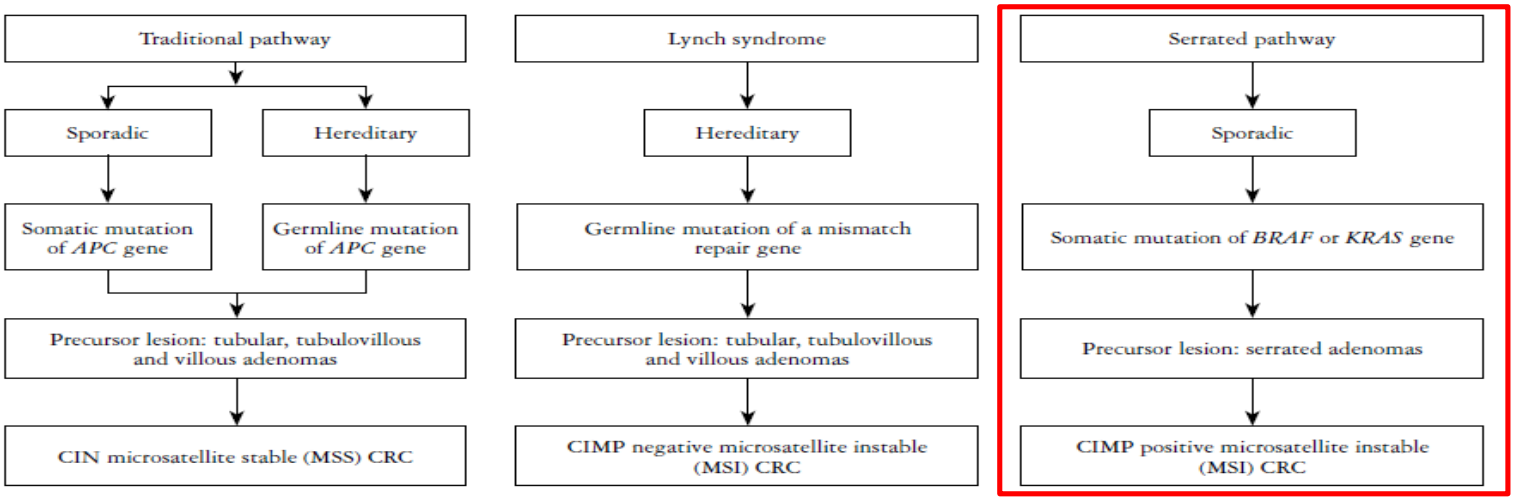


0.75% to 5.6% of large bowel polyps removed in general diagnostic colonoscopy practice (Haggitt et al., Gastroenterology 1985)

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

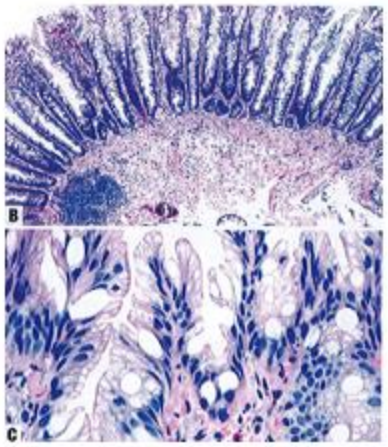
Hyperplastic polyp

- > 75% of serrated polyps
- Distal colon and rectum
- Sessile, 1 à 5 mm
- Often multiple in the rectum

- Histological features:

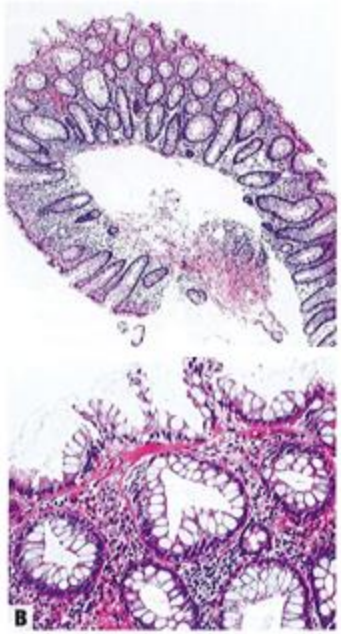
Microvesicular type:

- Funnel-shaped crypts with serrations limited to upper two thirds
- With proliferative zone confined to crypt bases
- Diagnosis by exclusion
- The epithelium matures early, and it is composed of microvesicular epithelial cells (with abundant cytoplasm containing fine apical vacuoles) and a variable number of goblet cells



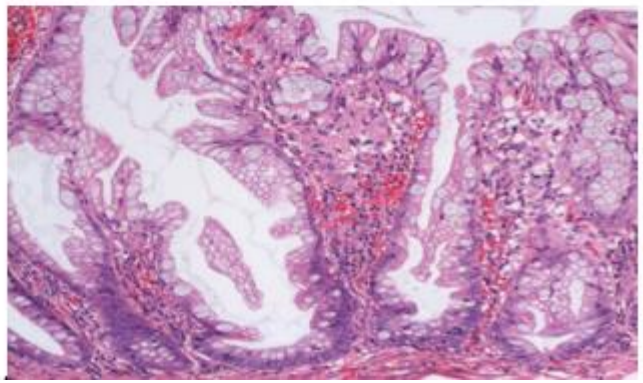
Goblet cell-rich type :

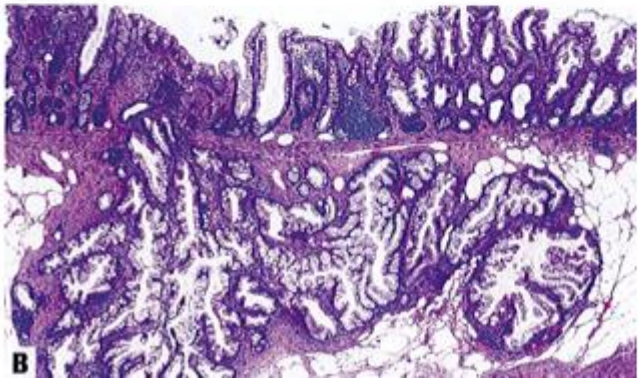
- Elongated crypts that resemble enlarged normal crypts; little to no serration
- Slight serration that is confined to the surface epithelium and crypt orifices
- Most of the cells of the surface and crypt epithelium are goblet cells.



Sessile serrated lesions (the ex « sessile serrated adenoma/polyp »)

- Proximal colon, > 10 mm, flat lesion (difficult to detect at endoscopy+++)
- The distinguishing feature: an overall distortion of the normal crypt architecture (alterations of the proliferative zone)
- Horizontal growth along the muscularis mucosae, dilatation of the crypt base (basal third of the crypt), and/or serrations extending into the crypt base
- The presence of ≥1 unequivocal architecturally distorded serrated crypt is sufficient for a diagnosis of SSL (Bettington et al, *Am J Surg Pathol* 2014)

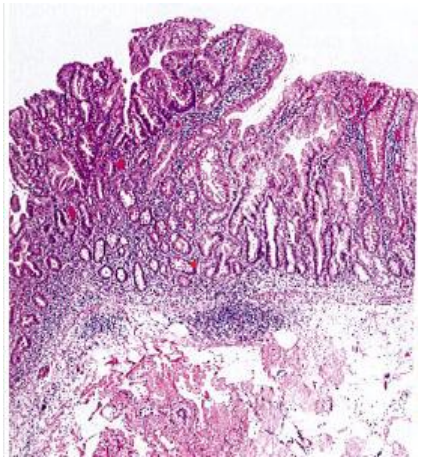


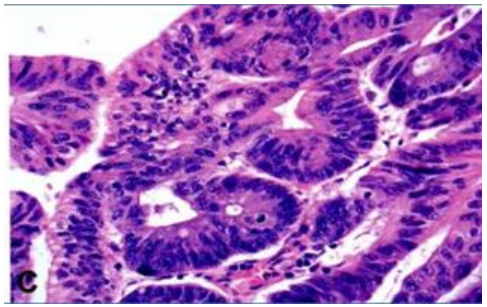


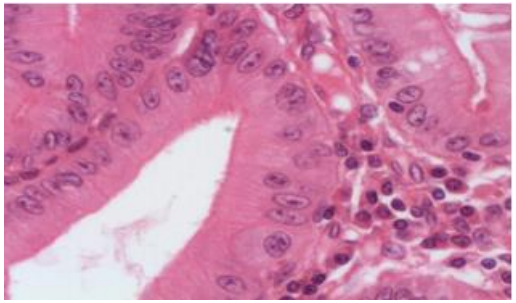
Sessile serrated lesions (the ex « sessile serrated adenoma/polyp ») with dysplasia

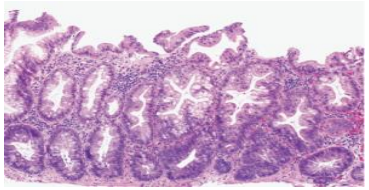
- Dysplasia may develop in some SSL (transient step during progression to carcinoma)

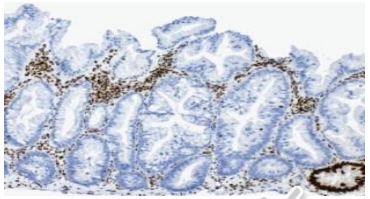
- The dysplastic component :
  - Sharply demarcated from the SSL
  - Greater morphological heterogeneity (complex architecture with crypt crowding, complex branching, cribriforming, villous architecture)
  - Intestinal dysplasia or serrated dysplasia (multiple patterns+++);
  - Stratification of dysplasia into low-grade versus high-grade is not recommended.









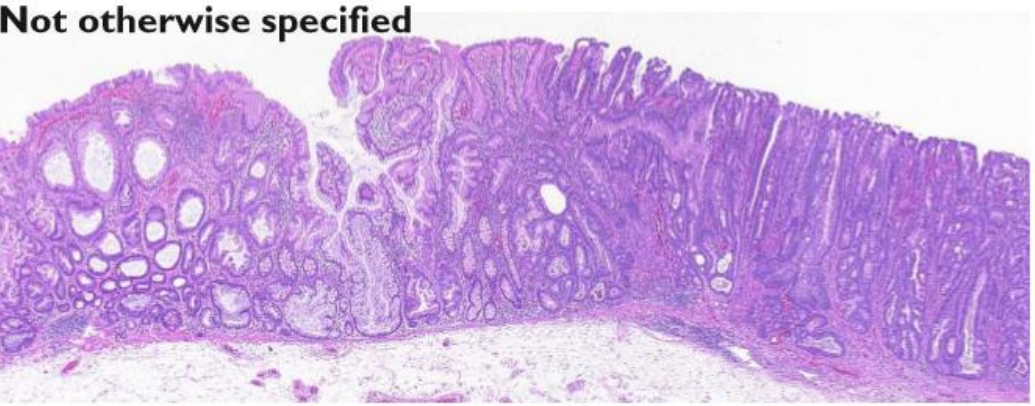


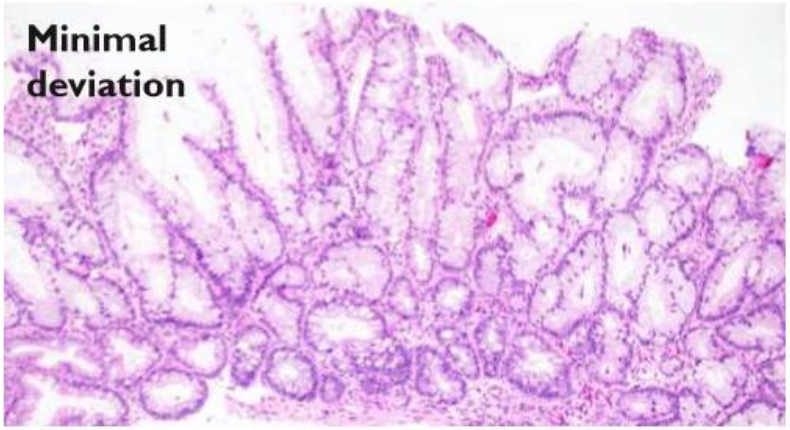
Morphologic patterns of SSLD

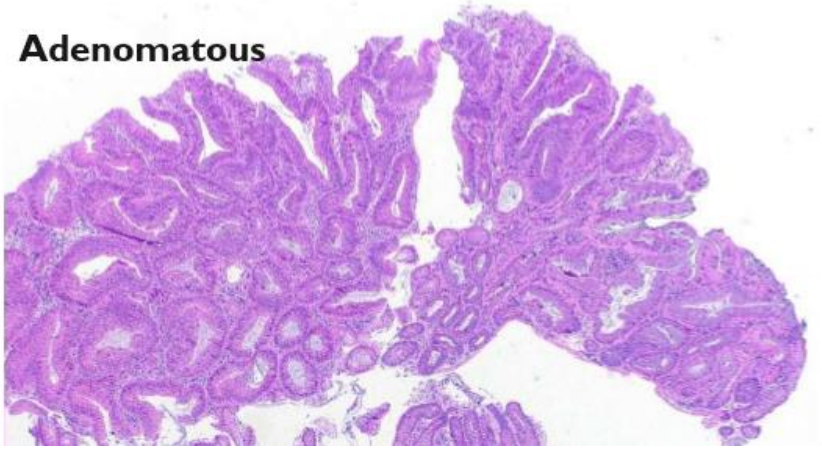
Patterns	Architectural changes	Cytologic features	MLH1 loss	Frequency[a]
Dysplasia not otherwise specified	Easily identifiable and varied in appearance: crypt elongation, crowding, complex branching, change in serration	Obvious atypia with amphophilic or eosinophilic cytoplasm, hyperchromatic nuclei with pseudostratification, frequent mitotic figures and loss of polarity	Frequent (>80%)	79%
Minimal deviation	Subtle changes with crypt crowding, change in crypt branching pattern and often reduced serration	Cells with hypermucinous cytoplasm or slightly eosinophilic with gastric phenotype, basally located nuclei showing mild hyperchromasia and mitotic figures not restricted to the lower part of the crypts.	Required for the diagnosis	19%
Serrated dysplasia	Closely packed small glands with reduced serration and cribriforming	Cuboidal cells with eosinophilic cytoplasm, frequent mitotic figures, marked nuclear atypia with vesicular nuclei and prominent nucleoli	Rare	12%
Adenomatous dysplasia	Absence of crypt serration, same appearance as conventional adenomas; dysplastic component on the upper part of the lesion	Cells with amphophilic or basophilic cytoplasm, elongated hyperchromatic nuclei and variable amount of goblet cell differentiation resembling cells from conventional adenomas	Rare	8%

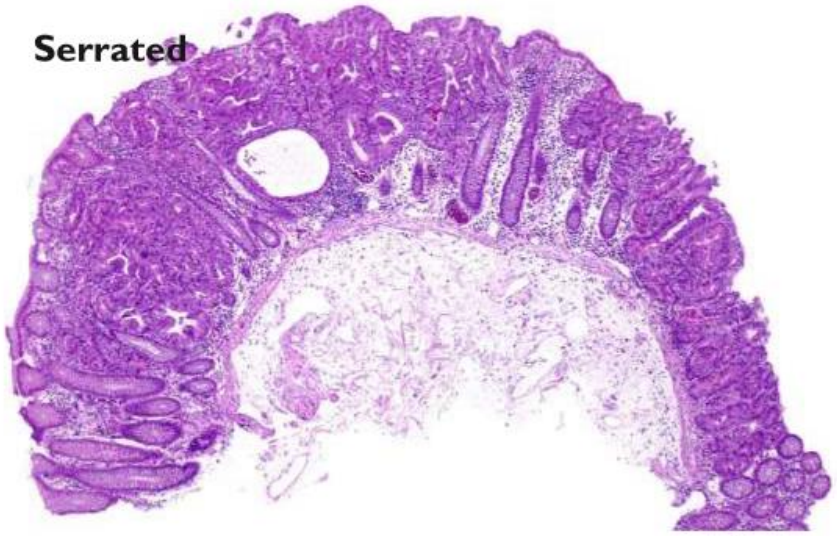
Liu et al. Mod Pathol 2017;30:1728-1738
Pai RK et al. Mod Pathol. 2019;32:1390-1415

Morphologic patterns of SSLD









Classification is not required or recommended

With the courtesy Dr Ian Brown

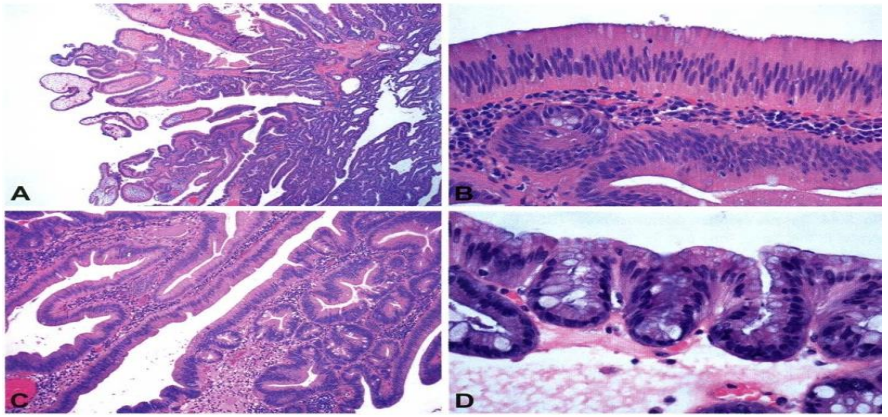
Traditional serrated adenoma

- 5 % of serrated polyps

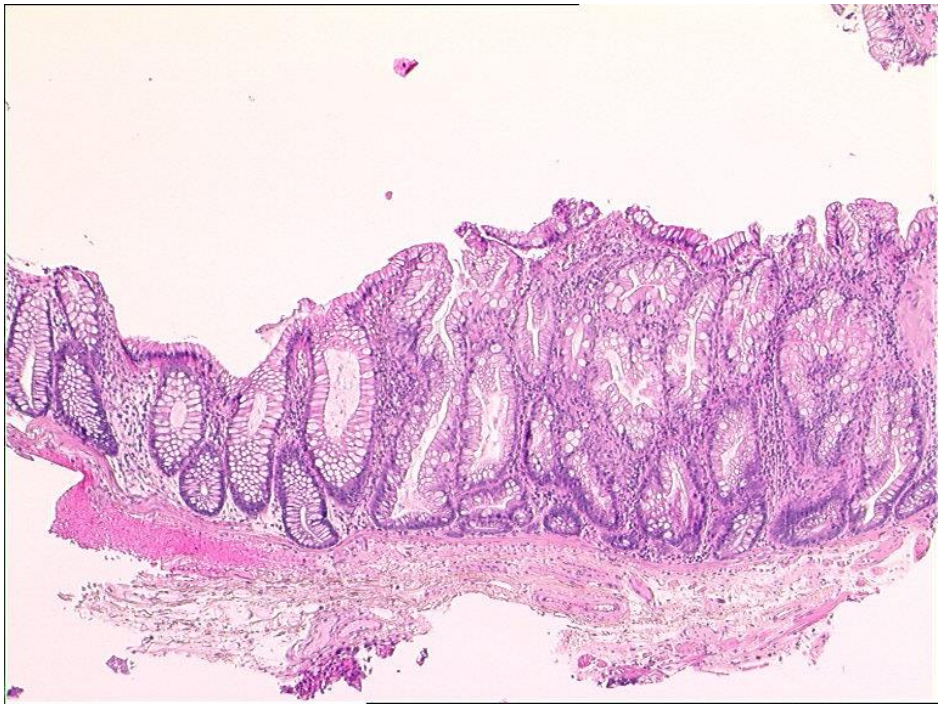
- Large protuberant polyps (distal colorectum++) or flat lesions (proximal colon)

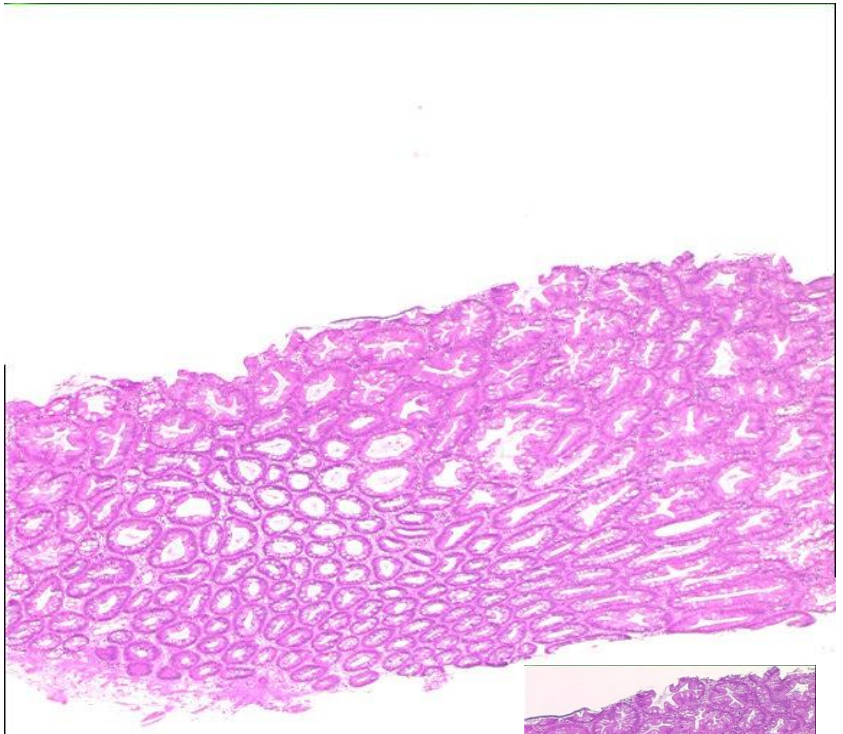
- The two most distinctive features:
  - Slit-like serration
  - Tall columnar cells with intensely eosinophilic cytoplasm and pencillate nuclei stratification
  - Ectopic crypt formations along the sides of the villous projections of protuberant TSA (but rarely present in flat TSA)

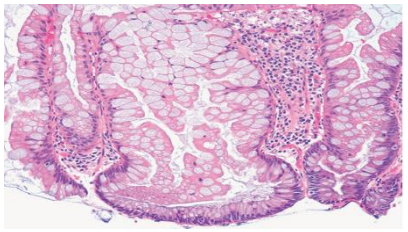
- Areas of overt dysplasia (either intestinal or serrated type).

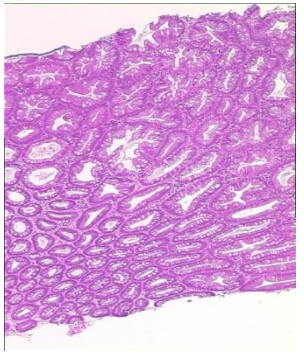


Importance of the orientation for the diagnosis of serrated lesions

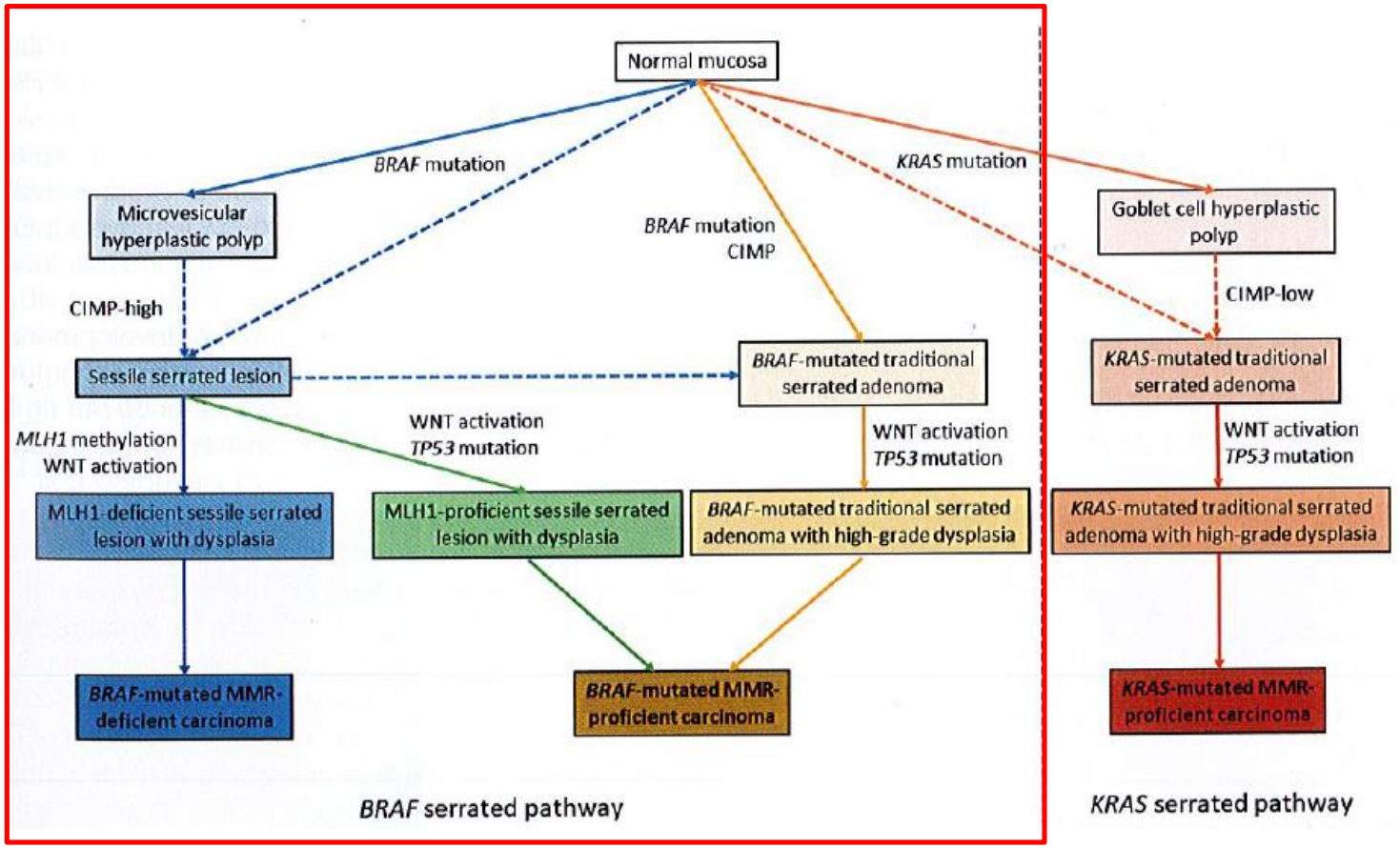






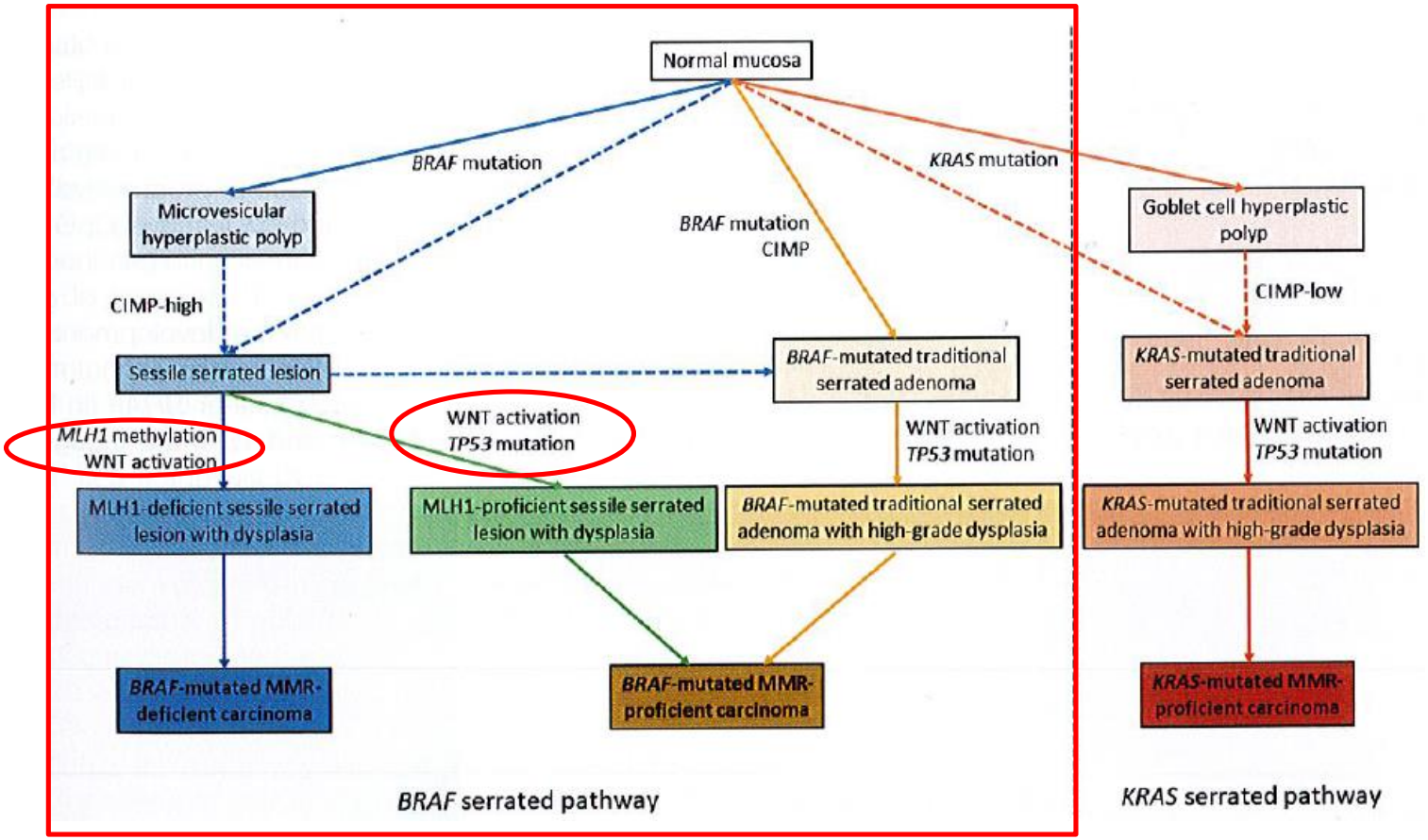


The serrated pathway



WHO 2019 classification of digestive system tumours

The serrated pathway



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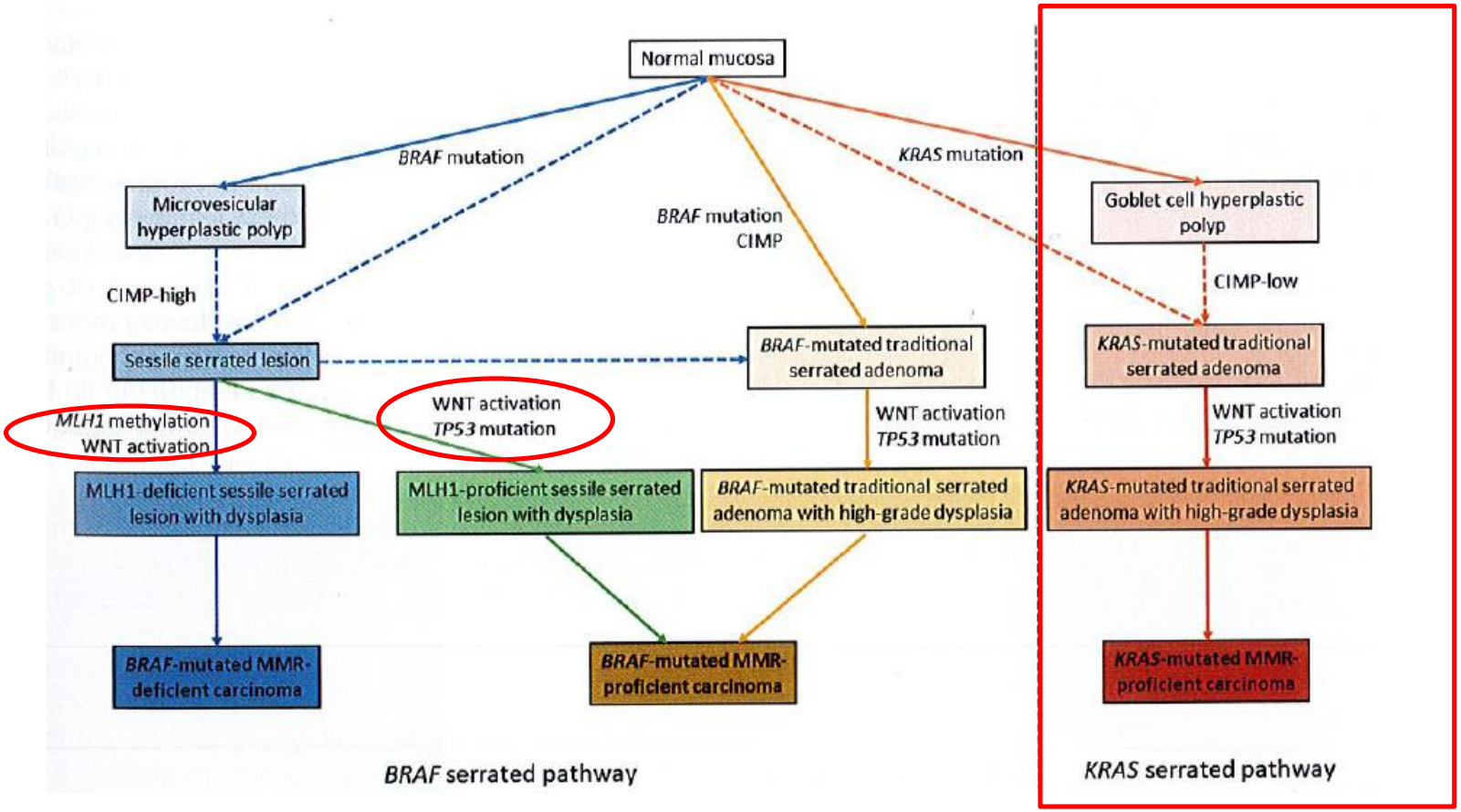

WHO 2019 classification of digestive system tumours

Pathology report of CRC after surgical resection: the example of Saint-Antoine hospital's standardized report

- Type histologique :
  - Adénocarcinome [ ]
  - Composante colloïde muqueuse % (si >50% cocher adénocarcinome mucineux)
  - Grade de différenciation : bas grade (bien ou moyennement différencié) [ ]
    haut grade (peu différencié ou indifférencié) [ ]
  - [ ] Adénocarcinome mucineux
  - [ ] Carcinome à cellules indépendantes en bague à châton
  - [ ] Carcinome médullaire
  - [ ] Autre carcinome (donner la dénomination suivant la classification OMS)
  - [ ] Autre type histologique :

- Envahissement en profondeur (Stade T, TNM 8ème édition) :
  - [ ] Pas de tumeur retrouvée (T0)
  - [ ] Carcinome intra-muqueux (Tis)
  - [ ] Sous-muqueuse (T1) (preciser sm1, sm2 ou sm3)
  - [ ] Musculeuse (T2)
  - [ ] Sous-séreuse (ou graisse péri-rectale) (T3)
  - [ ] Envahissement de la séreuse (revêtement mésothélial) (T4a)
  - [ ] Envahissement des organes ou structures adjacents (T4b) (préciser le(s)quel(s)

- Résection chirurgicale :
  - Limite proximale : non envahie [ ] envahie [ ] non précisée [ ]
  - Limite distale : non envahie [ ] envahie [ ] non précisée [ ]
  - Marge mésentérique : non envahie [ ] envahie [ ] non précisée [ ]
  - Pour les cancers du rectum, marge circonférentielle en mm :
    par rapport au contingent infiltrant : mm
    par rapport à un ganglion métastatique (si présent et si marge <10 mm) : mm

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Different types of adenocarcinoma

Term	ICD-O code
Adenocarcinoma NOS	8140/3
• Serrated adenocarcinoma	8213/39
• Mucinous adenocarcinoma	8480/3
• Adenoma-like adenocarcinoma	8262/39
• Micropapillary adenocarcinoma	8265/39
• Poorly cohesive carcinoma	8490/39
• Signet ring cell carcinoma	8490/39
• Medullary adenocarcinoma	8510/39
Adenosquamous carcinoma	8560/39
Carcinoma, undifferentiated, NOS	8020/34
Carcinoma with sarcomatoid component	8033/34

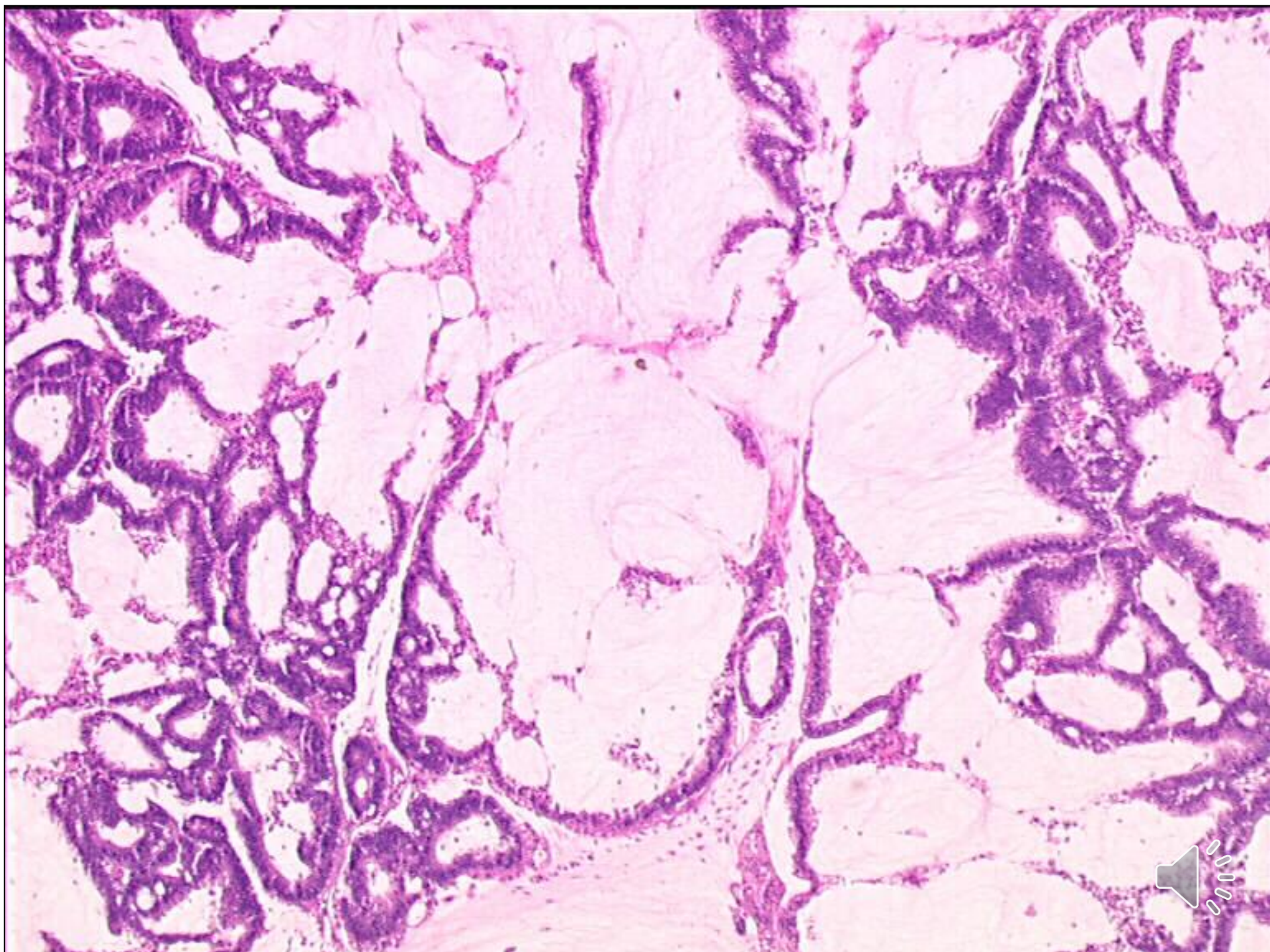
x Cancelled: Cribriform comedo-type adenocarcinoma

Some definitions in tumour pathology (OMS 2000)

- **Mucinous adenocarcinoma**: an adenocarcinoma containing extracellular mucin comprising more than 50% of the tumour. Note that « mucin producing » is not synonymous with mucinous in this context; grading

- **Signet-ring cell carcinoma:** an adenocarcinoma in which the predominant component (more than 50%) is composed of isolated malignant cells containing intracytoplasmic mucin.

- **Medullary carcinoma:** a malignant epithelial tumour in which the cells form solid sheets and have abundant eosinophilic cytoplasm and large, vesicular nuclei with prominent nucleoli. An intraepithelial infiltrate of lymphocytes is characteristic.



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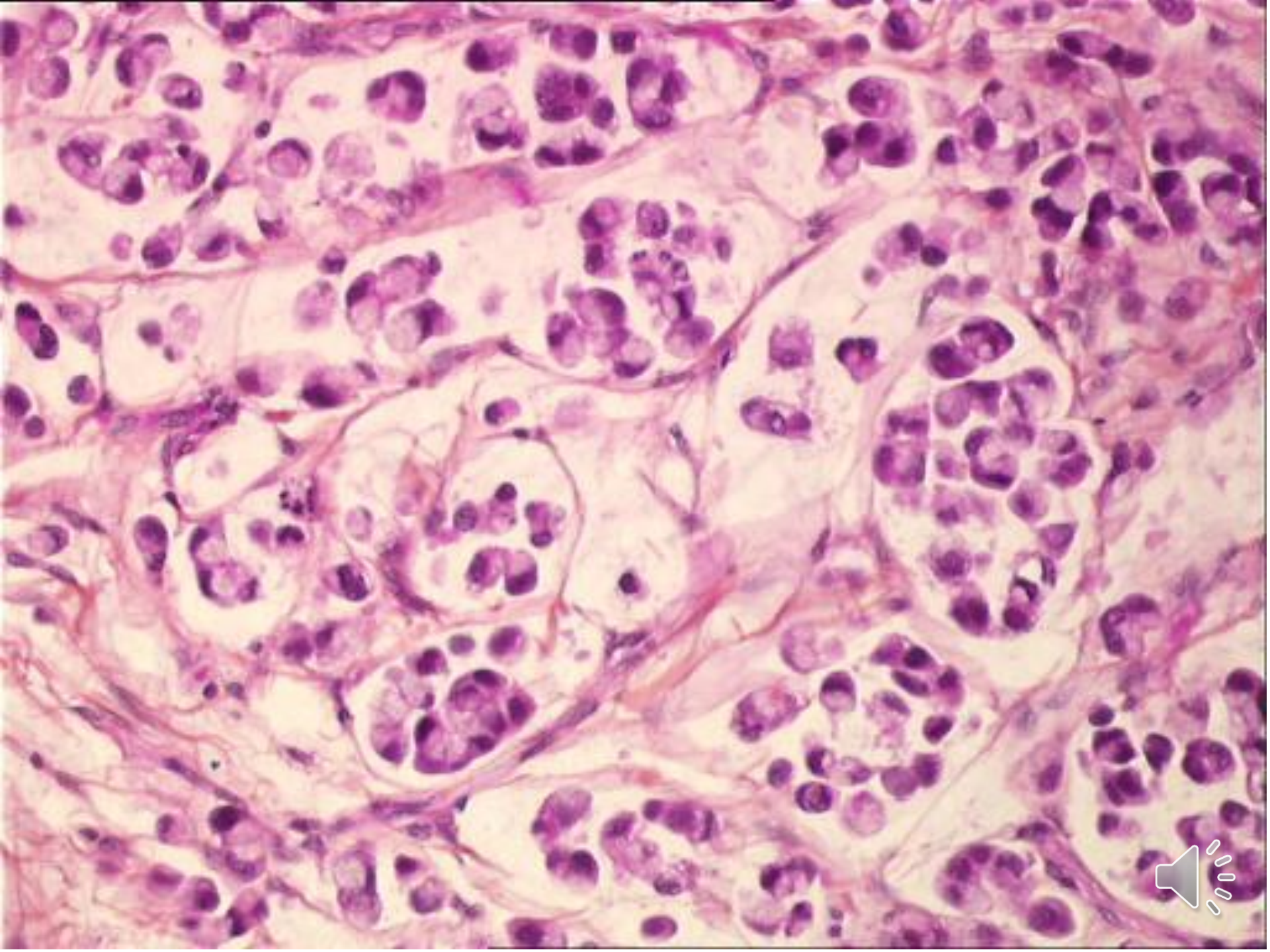

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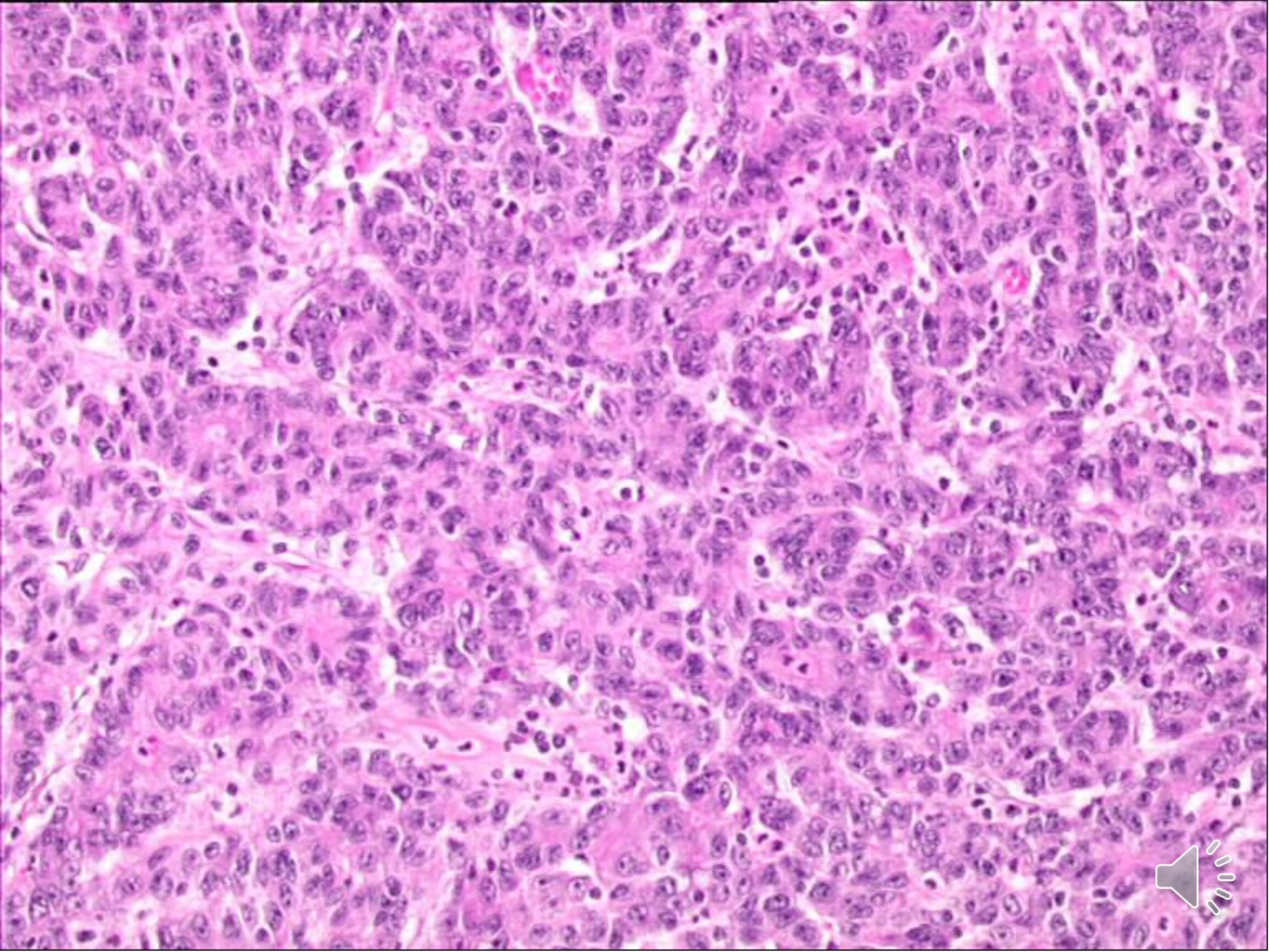
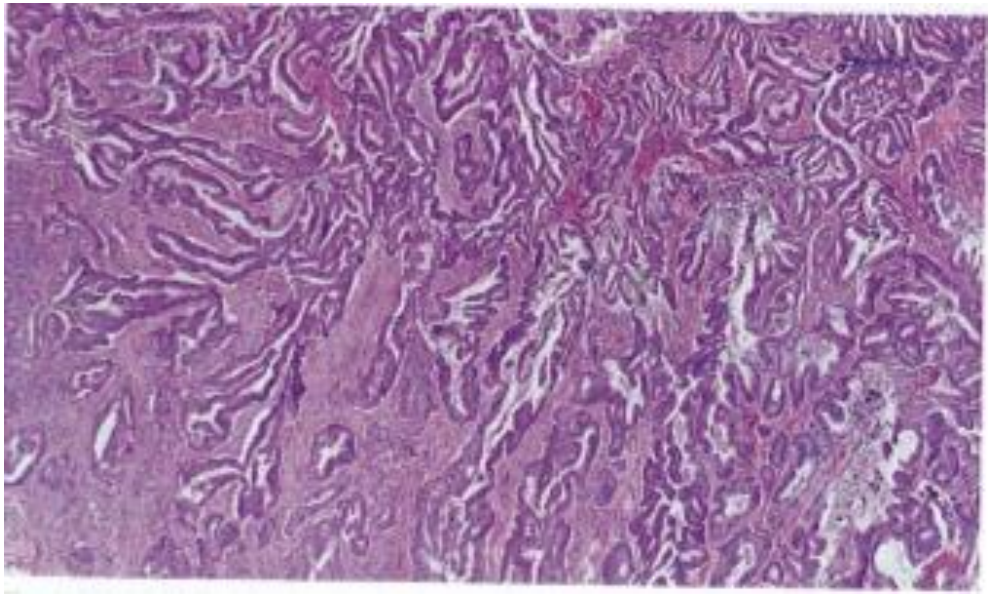


A new subtype of colorectal adenocarcinoma, the « adenoma-like adenocarcinoma



WHO 2019 classification of digestive system tumours

Previously described as « villous adenocarcinoma » and « invasive papillary adenocarcinoma »

Invasive adenocarcinoma in which ≥50% of the invasive areas have an adenoma-like aspect with villous structures, with low-grade aspect Minimal desmoplastic reaction; pushing growth pattern;

Incidence: 3 to 9%

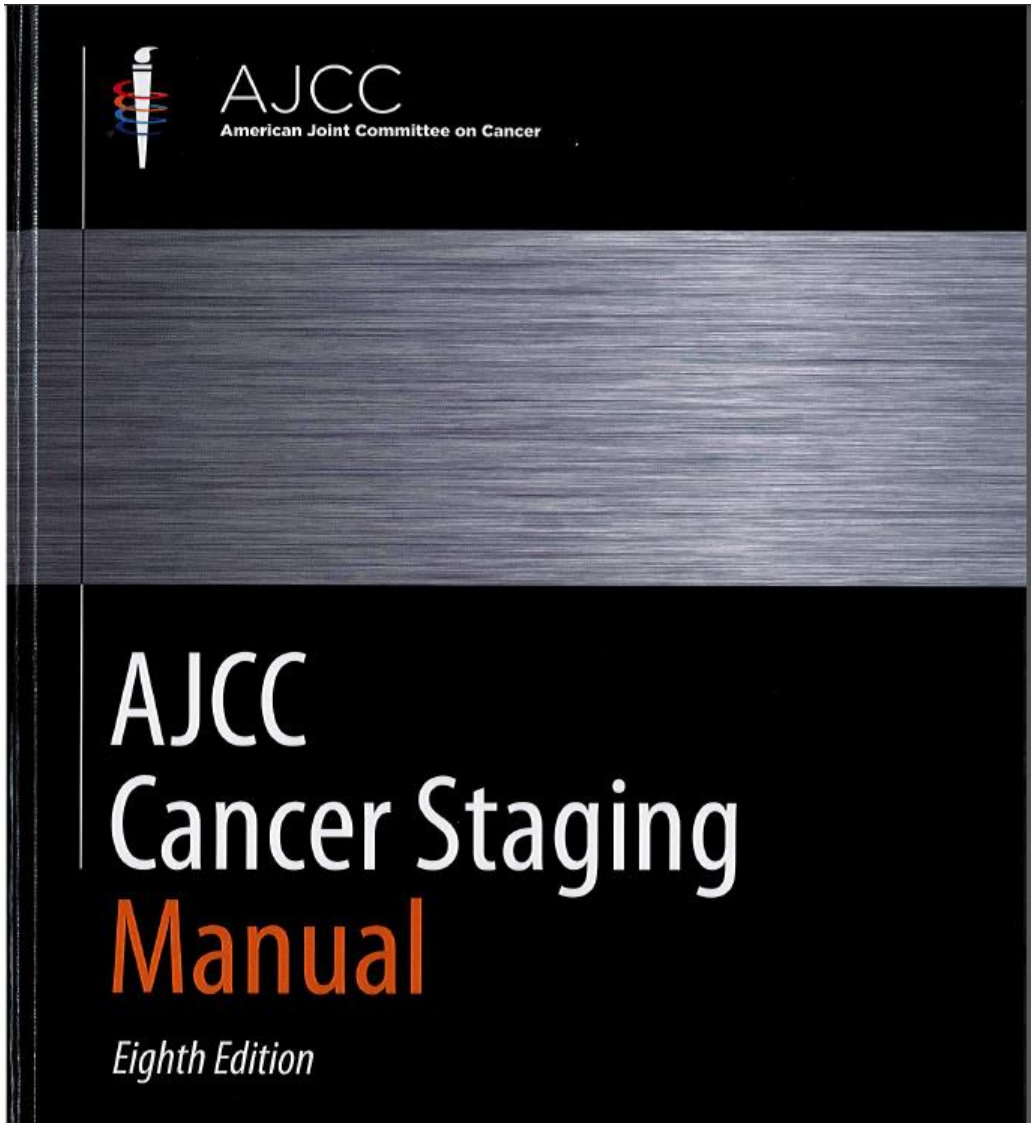
Difficulties in establishing a diagnosis of the invasive comonent on biopsies, high KRAS mutation rate and favourable diagnosis

Pathology report of CRC after surgical resection: the example of Saint-Antoine hospital's standardized report

- Type histologique :
  - Adénocarcinome [ ]
  - Composante colloïde muqueuse % (si >50% cocher adénocarcinome mucineux)
  - Grade de différenciation : bas grade (bien ou moyennement différencié) [ ]
    haut grade (peu différencié ou indifférencié) [ ]
  - [ ] Adénocarcinome mucineux
  - [ ] Carcinome à cellules indépendantes en bague à châton
  - [ ] Carcinome médullaire
  - [ ] Autre carcinome (donner la dénomination suivant la classification OMS)
  - [ ] Autre type histologique :

- Envahissement en profondeur (Stade T, TNM 8ème édition) :
  - [ ] Pas de tumeur retrouvée (T0)
  - [ ] Carcinome intra-muqueux (Tis)
  - [ ] Sous-muqueuse (T1) (preciser sm1, sm2 ou sm3)
  - [ ] Musculeuse (T2)
  - [ ] Sous-séreuse (ou graisse péri-rectale) (T3)
  - [ ] Envahissement de la séreuse (revêtement mésothélial) (T4a)
  - [ ] Envahissement des organes ou structures adjacents (T4b) (préciser le(s)quel(s)

- Résection chirurgicale :
  - Limite proximale : non envahie [ ] envahie [ ] non précisée [ ]
  - Limite distale : non envahie [ ] envahie [ ] non précisée [ ]
  - Marge mésentérique : non envahie [ ] envahie [ ] non précisée [ ]
  - Pour les cancers du rectum, marge circonférentielle en mm :
    - par rapport au contingent infiltrant : mm
    - par rapport à un ganglion métastatique (si présent et si marge <10 mm) : mm



Publication of TNM8 at the end of 2016

Used since January 2018

The main changes of TNM8: better definition of the pT4a subcategory

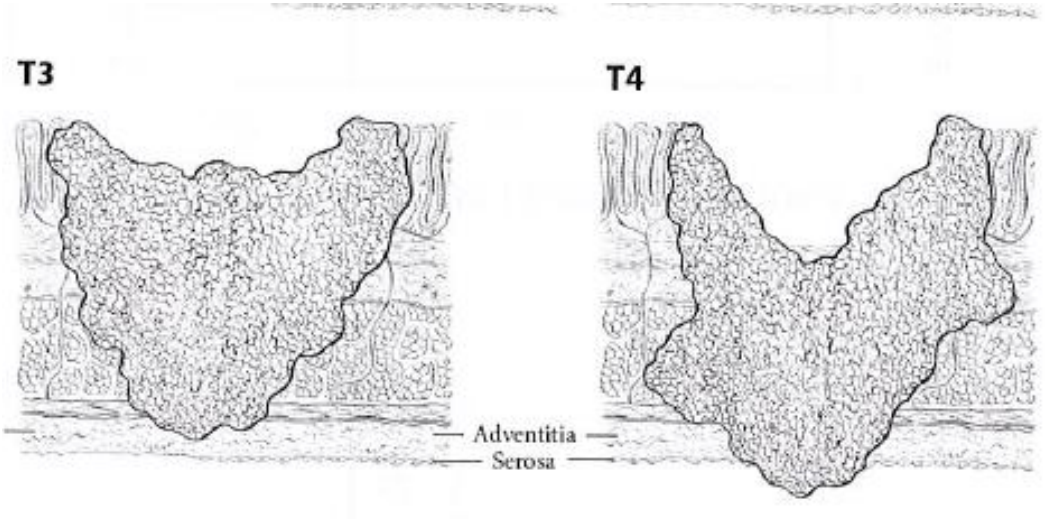
- TNM7: Subdivision of pT4 into 2 categories:
  - (i) pT4a (« tumor penetrates the surface of the visceral peritoneum »)
  - (ii) pT4b (« tumor directly invades or is histologically adherent to other organs or structures »),

  based on different outcomes shown in expanded datasets

- Tumor with perforation?

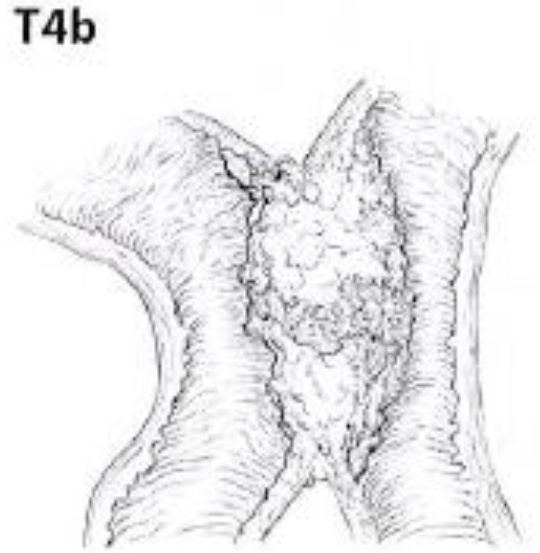
Clarification on the definition of pT4a

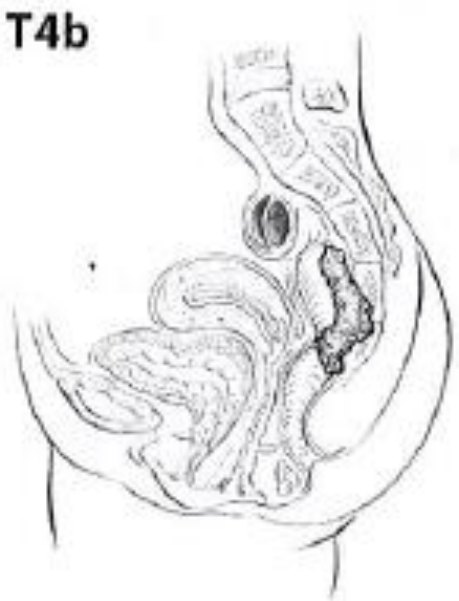
T Category	T Criteria
T4	Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure
T4a	Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades or adheres to adjacent organs or structures

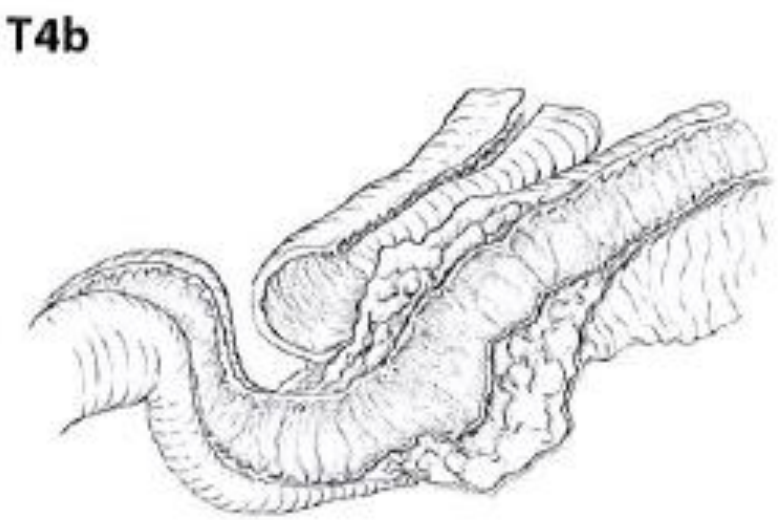


pT4b

Direct invasion or adhesion to adjacent structures or organs by the tumor







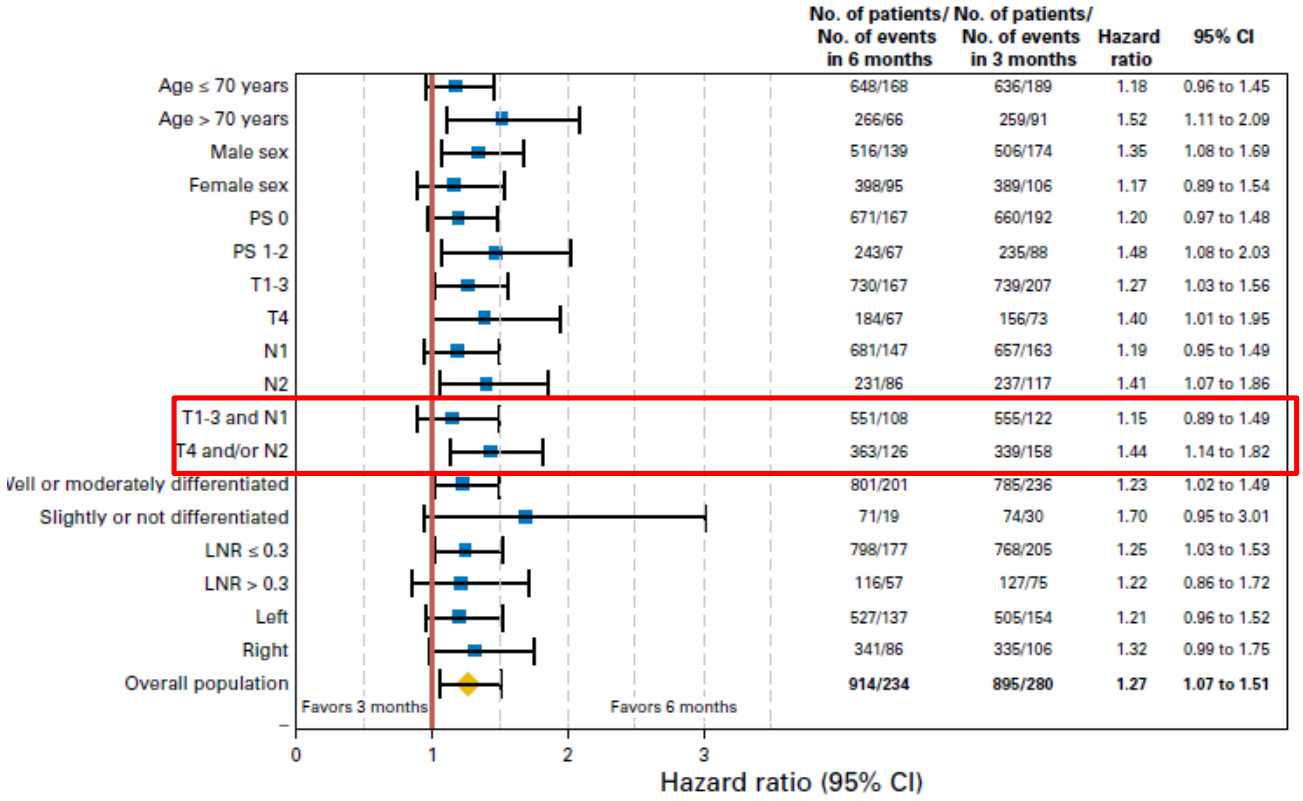
Stratification of type and duration of adjuvant chemotherapy in stage III colon cancer according to TNM classification

VOLUME 36 · NUMBER 15 · MAY 20, 2018

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Three Versus 6 Months of Oxaliplatin-Based Adjuvant Chemotherapy for Patients With Stage III Colon Cancer: Disease-Free Survival Results From a Randomized, Open-Label, International Duration Evaluation of Adjuvant (IDEA) France, Phase III Trial

Thierry André, Dewi Vernerey, Laurent Mineur, Jaafar Bennouna, Jérôme Desrame, Roger Faroux, Serge Fratte, Marine Hug de Larauze, Sophie Paget-Bailly, Benoist Chibaudel, Jeremie Bez, Jérôme Dauba, Christophe Louvet, Céline Lepere, Olivier Dupuis, Yves Becouarn, May Mabro, Joëlle Egreteau, Olivier Bouche, Gaël Deplanque, Marc Ychou, Marie Pierre Galais, François Ghiringhelli, Louis Marie Dourthe, Jean-Baptiste Bachet, Ahmed Khalil, Franck Bonnetain†, Aimery de Gramont, and Julien Taieb for PRODIGE investigators, GERCOR, Fédération Française de Cancérologie Digestive, and UNICANCER



Superiority of 6 months of adjuvant chemotherapy, compared to 3 months, particularly in subgroups p**T4 et/ou pN2.**

Interobserver, intraobserver, and interlaboratory variability in reporting pT4a colon cancer

Virchows Archiv

Charlotte E. L. Klaver[1] · Nicole Bulkmans[2] · Paul Drillenburg[3] · Heike I. Grabsch[4] · Nicole C. T. van Grieken[5] · Arend Karrenbeld[6] · Lianne Koens[7] · Ineke van Lijnschoten[8] · Jos Meijer[9] · Iris D. Nagtegaal[10] · Xavier Sagaert[11] · Kees Seldenrijk[12] · M. F. van Velthuysen[13] · Annette H. Bruggink[14] · Pieter J. Tanis[1] · Petur Snaebjornsson[15]

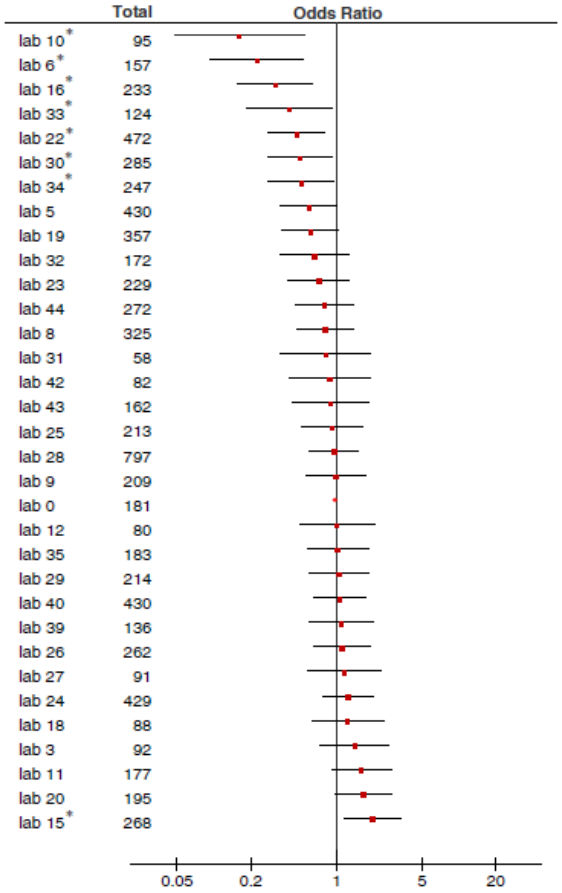
Twelve experienced Deutch and Belgian GI pathologists, working at university or non-university hospitals classified 66 preselected scanned Hematoxylin (1 slide per case).

Results:

Interobserver variability among 12 pathologists was 0.50 (95%CI 0.41–0.60; moderate agreement).

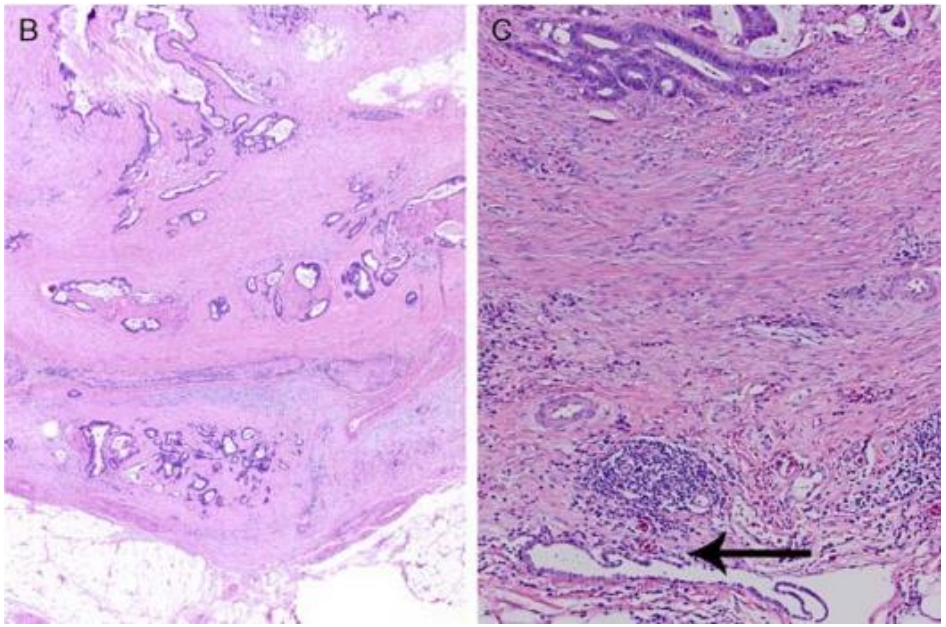
Intraobserver variability (8 pathologists) was 0.71 (substantial agreement

For interlaboratory analysis, after adjustment for case mix, 8 labs diagnosed pT4a significantly less or more frequently than the median lab.



Diagnosis of pT4a stage appears to be challenging. There is a need for standardizing assessment of this pathological entity (both with regard to sampling and microscopic assessment).

Significance of tumors that are <1 mm from the serosal surface and accompanied by serosal reaction?



Multiple-level sections and/or additional tissue blocks of the tumor should be examined to detect serosal surface involvement

Important to individualize this type of pT3 tumor

	pT3 Cases >1 mm From Serosa (n = 39)	pT3 Cases ≤1 mm From Serosa (n = 28)	pT4 Cases (n = 33)
Alive without disease	36 (92)	20 (71)	16 (48)
Alive with disease	1 (3)	3 (11)	10 (30)
Recurrence in peritoneum	1 (3)	1 (4)	4 (12)
Recurrence in solid organs	0 (0)	2 (8)	6 (18)
Dead of disease	0 (0)	3 (11)	2 (6)
Recurrence in peritoneum	0 (0)	2 (8)	2 (6)
Recurrence in solid organs	0 (0)	1 (4)	0 (0)
Dead of other cause	0 (0)	0 (0)	1 (3)
No follow-up data available	2 (5)	2 (7)	3 (9)

Panarelli et al., Am J Surg Pathol 2013

STADE DE LA TUMEUR

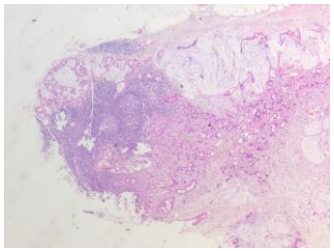
- Stade pTNM (TNM 2017, 8ème édition) :

- Si applicable : [ ] m (tumeurs multiples), [ ] r (récidive), [ ] y (post-traitement)

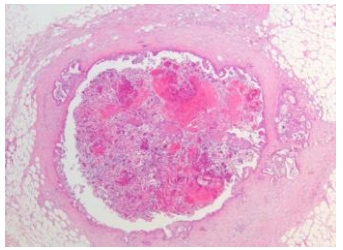
- Tumeur primitive (pT)
  - [ ] Pas de tumeur retrouvée (T0)
  - [ ] Carcinome intra-muqueux (Tis)
  - [ ] Sous-muqueuse (T1) sm1 sm2 sm3
  - [ ] Musculeuse (T2)
  - [ ] Sous-séreuse ou graisse périrectale (T3)
  - [ ] Envahissement de la séreuse (revêtement mésothélial) (T4a)
  - [ ] Envahissement organes de voisinage (T4b)

- Ganglions régionaux (pN)
  - [ ] Nx
  - [ ] N0
  - [ ] N1a (métastase dans 1 ganglion lymphatique régional) ;
  - [ ] N1b (métastase dans 2-3 ganglions lymphatiques régionaux) ;
  - [ ] N1c (dépôts tumoraux dans la sous-séreuse ou dans la graisse péri-rectale, sans métastase ganglionnaire régionale)
  - [ ] N2a (métastase dans 4-6 ganglions lymphatiques régionaux)
  - [ ] N2b ((métastase dans 7 ganglions lymphatiques régionaux ou plus)

- Métastases à distance (pM)
  - [ ] M1a : métastase à un organe ou à un site unique, sans atteinte du péritoine
  - [ ] M1b : métastase à plus d'un organe/site, sans atteinte du péritoine
  - [ ] M1c : métastase au péritoine seul ou associée à d'autres organes/sites



Tumor deposits (TD)



- Tumor deposits (TD) in the pericolonic and perirectal adipose tissue of CC were first described in 1935

"[…] we have found deposits of carcinoma cells at a distance from the primary growth although the lymphatic glands themselves have been free"

Gabriel WB, Dukes C, Bussey HJR, Br. J. Surg., 1935

- TD were first introduced in the 5th edition of AJCC/TNM staging in 1997:
  - if > 3 mm diameter, TD classified as regional LN metastasis
  - Si < 3 mm, tumour classified as pT3

- In the 6th edition (2002), definition according to criterion on their contours:
  - TD being defined as positive LNs when they have the firm and smooth contour of LN,
  - while irregular TD remained in the pT category

Tumor deposits in the 7th edition

- “Isolated tumor foci in the pericolic, perirectal, or mesocolic fat, away from the leading edge of the tumor, within the lymph drainage area of the primary carcinoma, without residual LN tissue »

- TD occur in approximately 20% of patients with colon cancer and are associated with poor outcome

- In AJCC TNM 7 (and 8): separate entity to LNM; TD-positive tumors are classified pN1c in the absence of lymph node metastases (LNM)

- TD are not taken into account in the presence of a LNM

- Addition of TD to the LNM count (Nagtegaal et al., JCO 2016)?

Prognostic value of tumor deposits (TD) for disease free survival (DFS) in patients with stage III colon cancer: a post hoc analysis of IDEA France phase III trial (PRODIGE-GERCOR)

Delattre et al., J Clin Oncol 2020

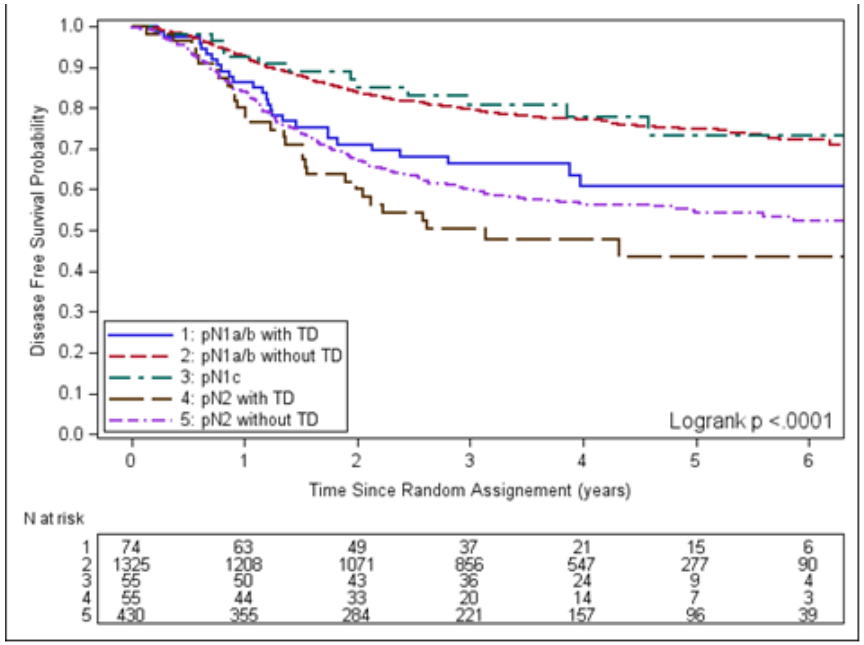
Background

In the TNM7 CC staging, the presence of TD is only considered in the absence of LNM.
In the era of personalized duration of histopathological criteria-based adjuvant therapy, this could potential lead to a loss of the prognosis prediction accuracy.

Methods

- A post hoc analysis of all pathological reports of patients included in IDEA France phase III trial (André et al., JCO 2018) regarding the presence and the number of tumor deposits
- Analysis of:
  - Disease-free survival (DFS) according to the presence or absence of TD, evaluated using Kaplan-Meier estimator
  - Association between TD and other histopathological features (perineural and vascular invasion)
  - Multivariable Cox model analysis to evaluate the association between main prognostic predictors, including TD, and DFS
  - Restadification of pN stage by adding TD to the LNM count

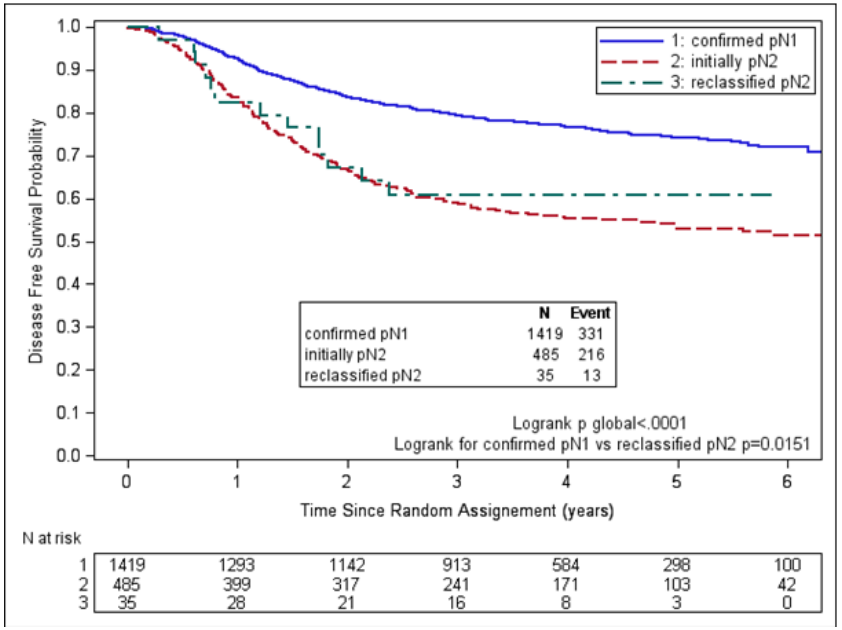
Of 1942 patients, 184 (9.5%) had TD.



Negative prognostic impact of the presence of TD across all pN groups (qualitative variable)

Prognostic value of tumor deposits (TD) for disease free survival (DFS) in patients with stage III colon cancer: a post hoc analysis of IDEA France phase III trial (PRODIGE-GERCOR)

		Restadification		
		Non restadified	**Restadified N2**	Total
		n	n	n
Initial N stage	N0*	3	0	3
	N1 (a-b)	1367	32	1399
	N1c	52	3	55
	total	1422	**35**	1457



A total of 35 patients were restadified from pN1 to pN2 by adding TD to the LNM count

pN2-restaged patients had similar DFS than those initially classified as pN2

TD are a major prognostic factor, both qualitatively and quantitatively.
The addition of TD to LNM may help to better define the duration of adjuvant therapy.

Pathology report of CRC after surgical resection: the example of Saint-Antoine hospital's standardized report

- Extension :
  - Nombre de ganglions prélevés :
  - Nombre de ganglions métastatiques :
  - Nombre de ganglions avec ilôts de cellules tumorales isolées :
  - Nodules adventiciels sans tissu lymphoïde résiduel (ou « dépôts tumoraux ») :
  - Emboles vasculaires :
    - emboles lymphatiques : présents [ ] non identifiés [ ] ;
      si présents, intra-muraux [ ] extra-muraux [ ]
    - emboles veineux : présents [ ] non identifiés [ ]
      si présents, intra-muraux [ ] extra-muraux [ ]
  - Engainements péri-nerveux : présents [ ] non identifiés [ ]
  - Autres :

- Bourgeonnement tumoral (ou « Tumor budding ») :
  - Nombre de bourgeons tumoraux (1 champ objectif x200, hotspot) :

  [ ] Bd1 : 0-4 bourgeons (bourgeonnement faible)
  [ ] Bd2 : 5-9 bourgeons (bourgeonnement intermédiaire)
  [ ] Bd3 : 10 bourgeons et plus (bourgeonnement élevé)

MODERN PATHOLOGY (2017), 1–13

Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016

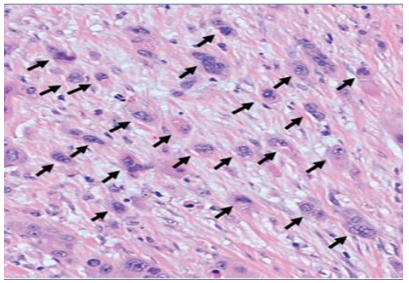
Alessandro Lugli[1,22], Richard Kirsch[2,22], Yoichi Ajioka[3], Fred Bosman[4], Gieri Cathomas[5], Heather Dawson[1], Hala El Zimaity[6], Jean-François Fléjou[7], Tine Plato Hansen[8], Arndt Hartmann[9], Sanjay Kakar[10], Cord Langner[11], Iris Nagtegaal[12], Giacomo Puppa[13], Robert Riddell[2], Ari Ristimäki[14], Kieran Sheahan[15], Thomas Smyrk[16], Kenichi Sugihara[17], Benoît Terris[18], Hideki Ueno[19], Michael Vieth[20], Inti Zlobec[1] and Phil Quirke[21]

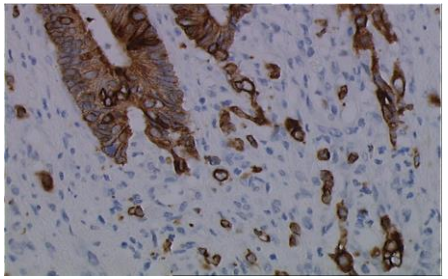
Tumor budding is defined as a single tumor cell or a cell cluster consisting of four tumor cells or less

Assessment in one hotspot (in a field measuring 0.785 mm2) at the invasive front

Bd1 (low):	0-4 buds	per 0.785 mm²
Bd2 (intermediate):	5-9 buds	
Bd3 (high):	≥10 buds	

Bd2 and Bd3: independent predictor of LNM in pT1 CRC
(Lugli et al., Modern Pathology 2017)





Tumor budding should be incorporated into CRC guidelines/protocols and staging systems.

Prospective Multicenter Study on the Prognostic and Predictive Impact of Tumor Budding in Stage II Colon Cancer: Results From the SACURA Trial

Ueno et al., JCO 2019

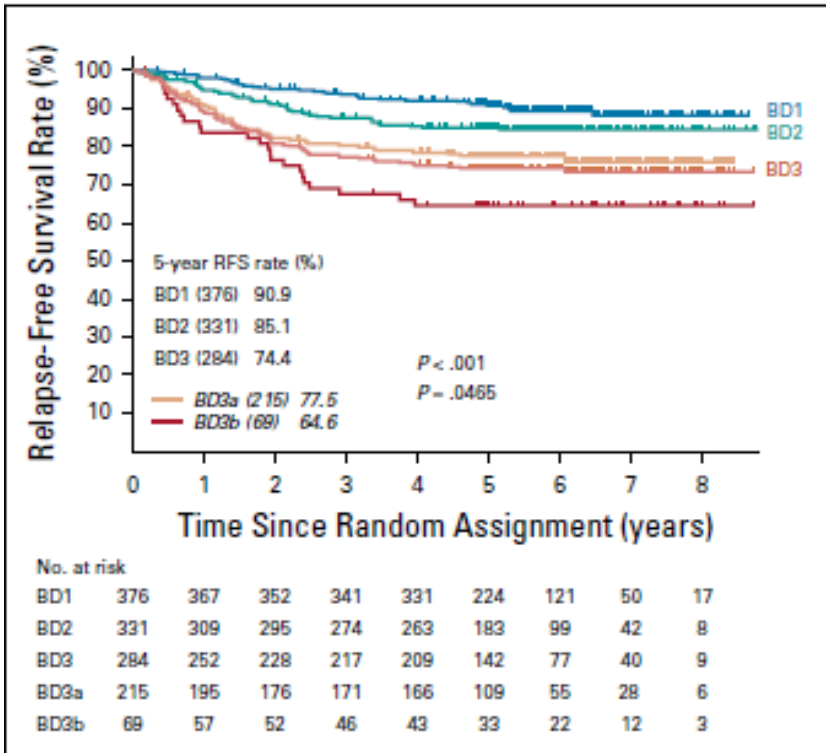


TABLE 3. Univariable and Multivariable Analyses of Relapse-Free Survival Using Cox Proportional Hazards Regression Model

		Univariable		Multivariable*	
Parameter	**No.**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
No. of LNs examined					
≥ 12	749	1		1	
< 12	242	1.26 (0.90 to 1.78)	.1799	1.22 (0.85 to 1.74)	.2880
Tumor differentiation					
G1	420	1		1	
G2	526	1.25 (0.91 to 1.72)	.1734	1.16 (0.84 to 1.62)	.3741
G3	45	0.45 (0.14 to 1.44)	.1808	0.60 (0.18 to 2.01)	.4056
T stage					
T3	823	1		1	
T4	168	2.76 (1.98 to 3.84)	< .001	2.53 (1.79 to 3.58)	< .001
Lymphatic invasion					
Negative	416	1		1	
Positive	575	1.10 (0.80 to 1.51)	.5682	0.93 (0.67 to 1.31)	.6859
Venous invasion					
Negative	386	1		1	
Positive	605	1.29 (0.93 to 1.79)	.1293	1.12 (0.79 to 1.59)	.5182
MSI					
MSI-low, MSS	892	1		1	
MSI-high	69	0.33 (0.12 to 0.90)	.0296	0.41 (0.15 to 1.17)	.0944
Treatment arm					
Surgery alone	501	1		1	
UFT	490	0.85 (0.62 to 1.16)	.3099	0.85 (0.61 to 1.16)	.3007
Tumor budding					
BD1	376	1		1	
BD2	331	1.58 (1.03 to 2.42)	.0352	1.51 (0.97 to 2.34)	.0692
BD3	284	2.93 (1.97 to 4.36)	< .001	2.57 (1.69 to 3.91)	< .001

Validation of the clinical value of the definition and grading system for tumor budding in a prospective study for stage II CC

Tumor budding, an important prognostic factor in stage III colon cancer patients treated with oxaliplatin-based chemotherapy: a post-hoc analysis of the IDEA France Prodige-GERCOR study

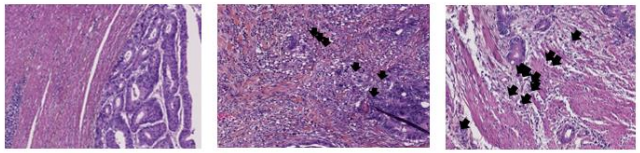
Basile et al., Annals Oncology 2022

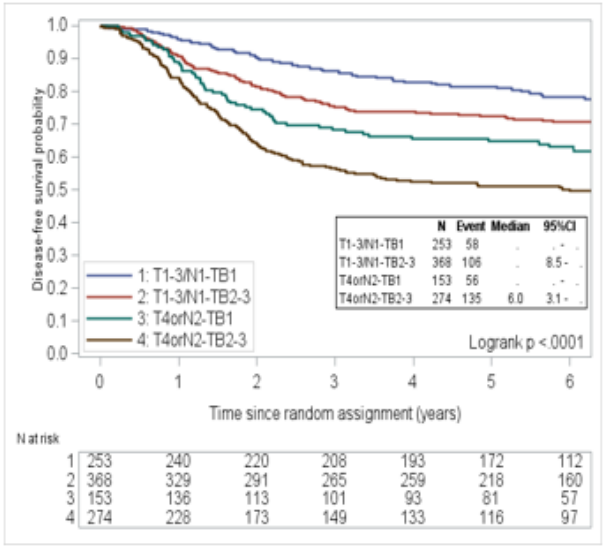
Materials and Methods

Post-hoc analysis of IDEA-France phase III trial: a randomized, open-label phase III trial enrolling 2000 stage III CC patients, candidate to receive adjuvant oxaliplatin-based chemotherapy (3 vs 6 months)

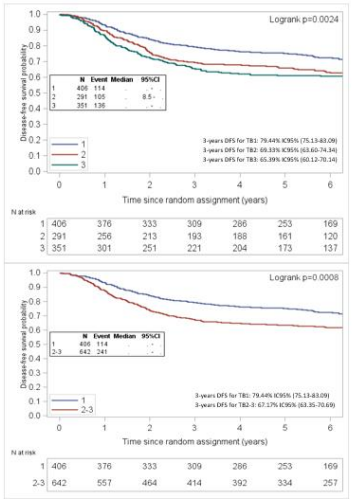
- Tumor buds were counted per 0.785 mm2 in the hotspot at the invasive front according ITBCC2016 criteria, by 2 independent physicians. Controversial cases were analyzed by a third pathologist.

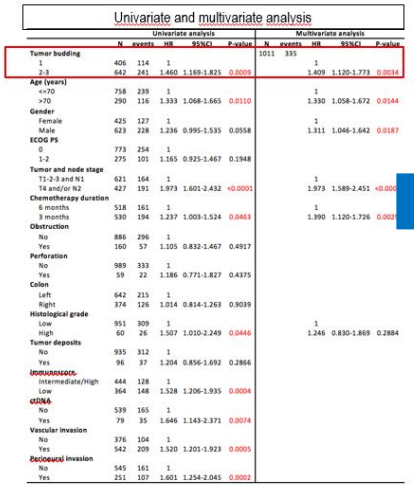
TB1 (0-4: low) **TB2 (5-9: intermediate)** **TB3 (≥10: high)**





- ***Disease-free survival***





Strong association of Bd2 and Bd3 categories with poor DFS (and OS)

When combined with pTN stage, Bd significantly improved disease prognostication

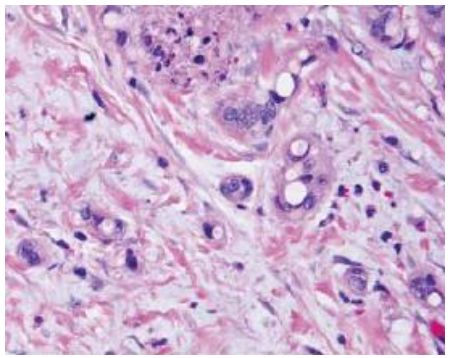
Bd per the ITBCC 2016 should be mandatory in every pathology report in stage III CC patients.

Am J Surg Pathol • Volume 42, Number 6, June 2018

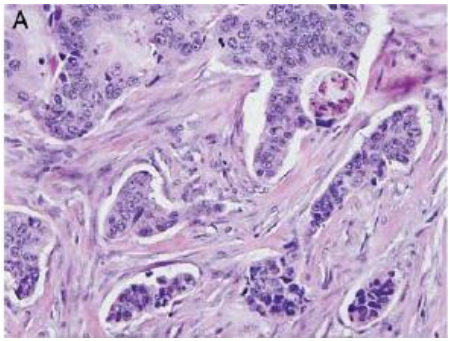
Poorly Differentiated Clusters Predict Colon Cancer Recurrence

An In-Depth Comparative Analysis of Invasive-Front Prognostic Markers

Tsuyoshi Konishi, MD,*† Yoshifumi Shimada, MD,*‡ Lik Hang Lee, MD,§ Marcela S. Cavalcanti, MD,§ Meier Hsu, MS,‖ Jesse Joshua Smith, MD, PhD,* Garrett M. Nash, MD,* Larissa K. Temple, MD,* José G. Guillem, MD,* Philip B. Paty, MD,* Julio Garcia-Aguilar, MD, PhD,* Efsevia Vakiani, MD, PhD,§ Mithat Gonen, PhD,‖ Jinru Shia, MD,§ and Martin R. Weiser, MD*



Tumor budding: single cancer cells or clusters comprising<5 cancer cells



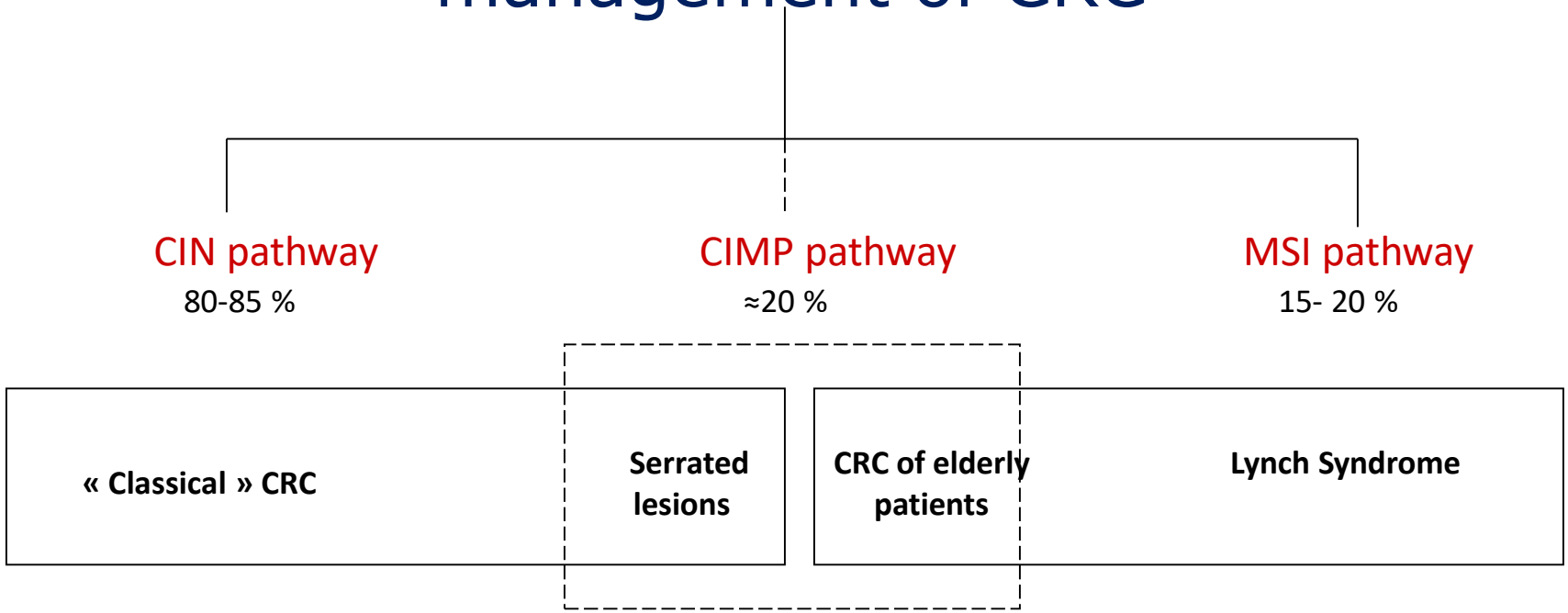
Poorly differentiated clusters: clusters of ≥5 cancer cells that lacked gland-like structures

Poorly differentiated clusters (PDC):

Recently identified as a novel risk factor for LNM

Validation is warranted.

Pathologist's role for the therapeutic management of CRC



RAS and NRAS mutations

Anti-EGFR resistance (predictive factor)

BRAF mutation

Prognostic factor (MSS)

MSI

- Diagnosis of LS
- Predictive factor for the lack of efficay of 5-FU
- Efficacy of ICKi (stage 4)

If therapeutic failure: *NTRK* (notably if MSI KRAS and BRAF WT), HER2 (IHC +/- ISH)

Universal screening of all newly diagnosed CRC

- Histological subtype
- Differentiation grade: Low/high
- Invasion depth: According to TNM, specify if invasion in other organs (pT4) or tumour perforation
- Presence of (lympho)vascular invasion: Intramural vascular invasion, extramural vascular invasion, lymphatic invasion
- Perineural growth: Present/absent
- Resection margin status (proximal, distal, circumferential): Positive, negative, distance in cm
- Diameter of the tumour
- Site/localization of the tumour
- Quality of the resection specimen
- Number of investigated lymph nodes
- Number of positive lymph nodes
- Presence of treatment response: Yes/no; if yes, partial or complete response
- Microsatellite status / presence of DNA mismatch repair proteins (MLH1, MSH2, MSH6, PMS2): Microsatellite-stable or -instable, staining for mismatch repair proteins present or absent
- Tumour budding status
- Immune response
- Presence or absence of relevant mutations