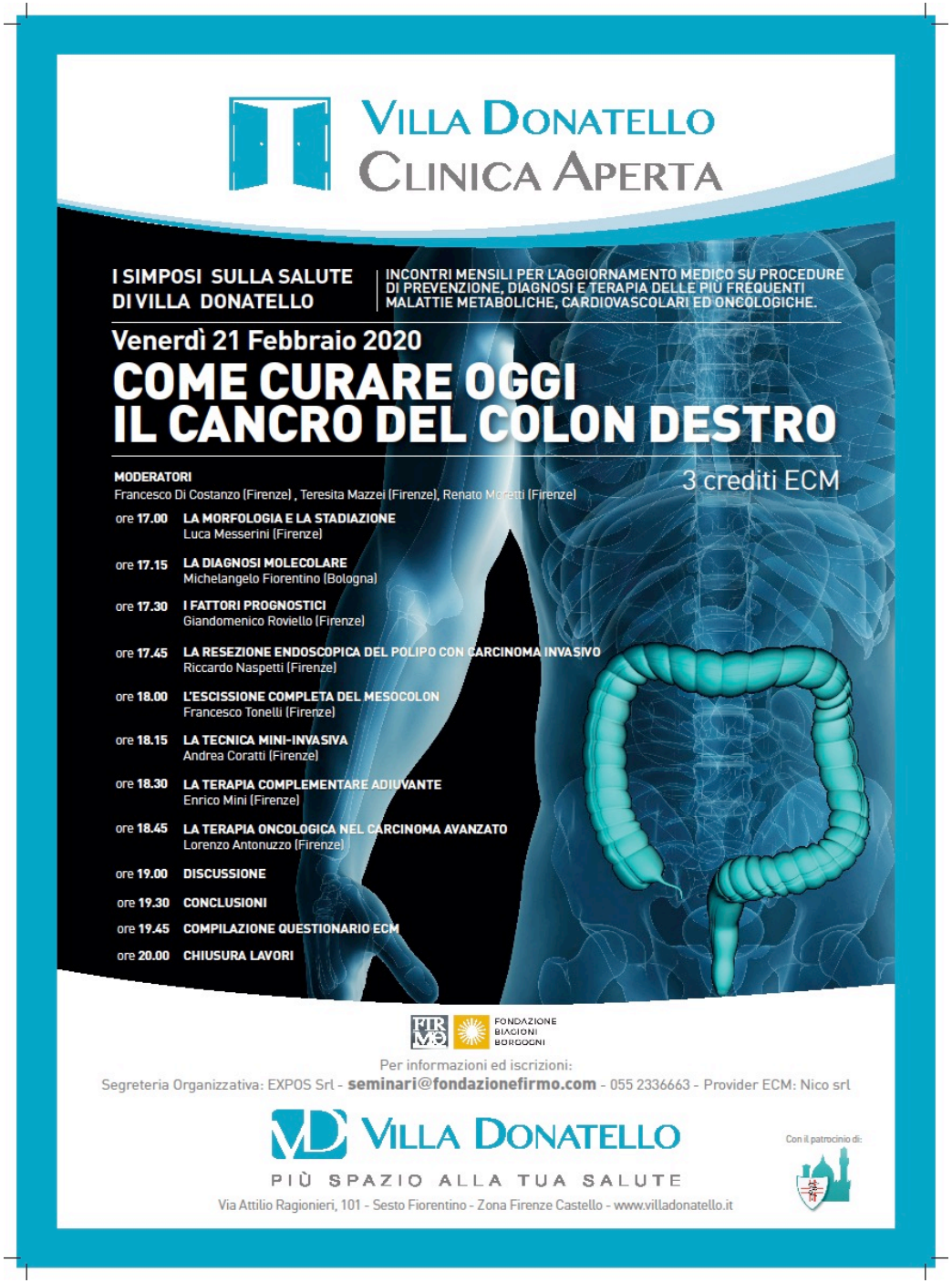

La morfologia e la stadiazione

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Sezione di Chirurgie Specialistiche
e di Diagnostica Istopatologica e Molecolare
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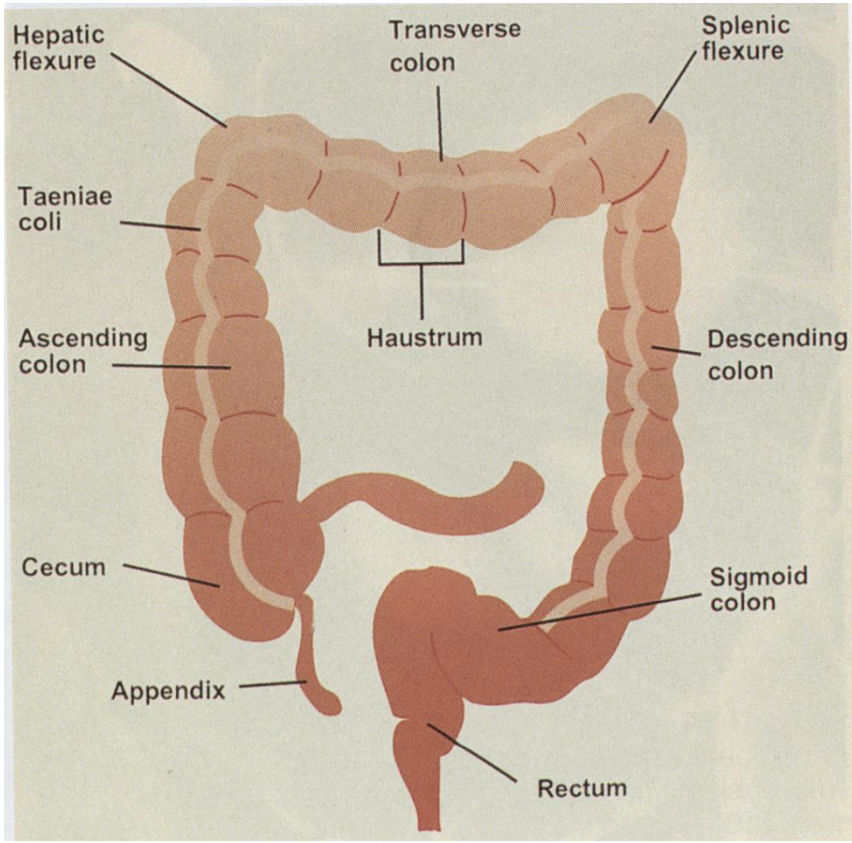


Embriology

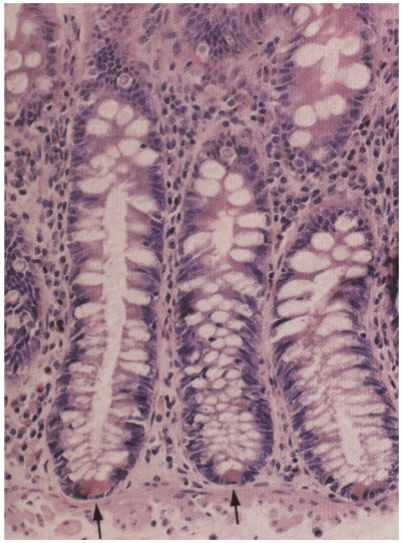
Midgut: duodenum (2nd portion), jejunum, ileum, appendix, ascending colon, proximal 2/3 of the transverse colon.

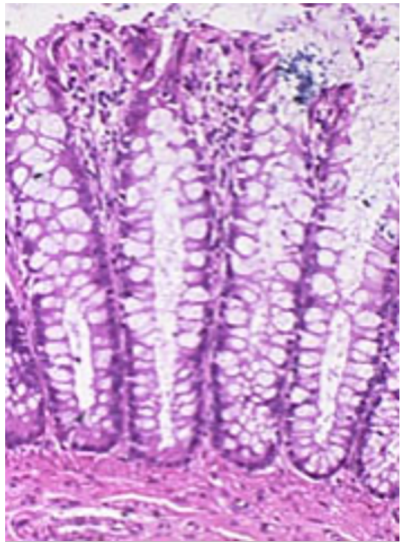
Hindgut: distal 1/3 of the transverse colon, splenic flexure, descending colon, rectum.

Histology

Proximal location: Paneth cells, goblet cells

Distal location: no Paneth cells, >goblet cells





WHO 2018

For pratical purposes colorectal carcinomas are divided into three groups by location:

-Right-sided colon carcinoma
(including those in the caecum, ascending colon, hepatic flexure and transverse colon)

-Left-sided colon carcinoma
(located anywhere from the splenic flexure up to the sigmoid)

-Rectal carcinomas

Classification of colorectal carcinoma WHO 2018

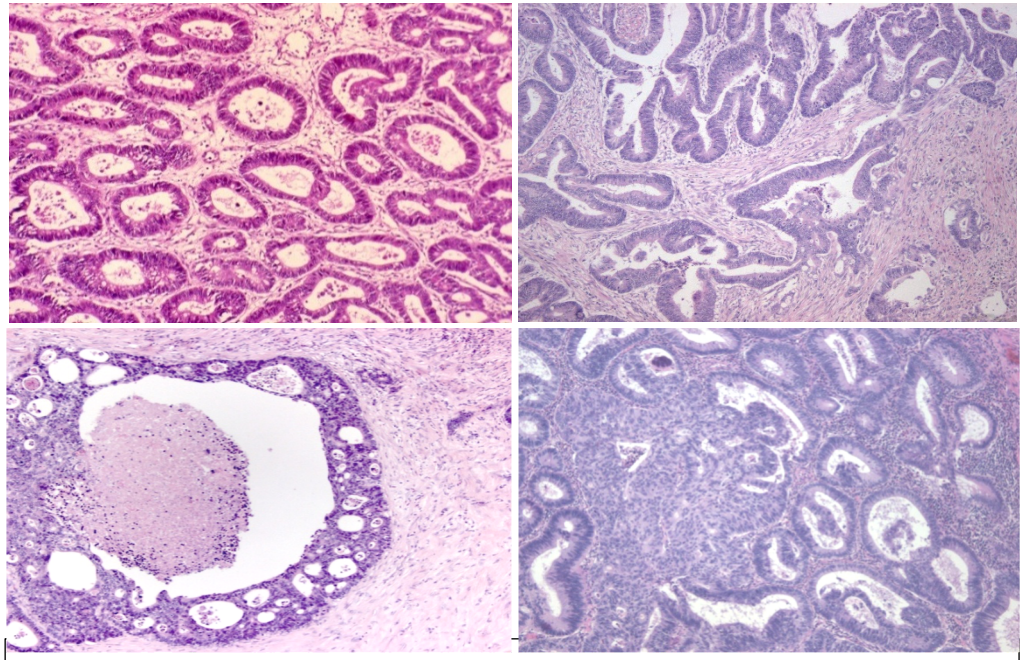
- Adenocarcinoma NOS
- Serrated adenocarcinoma
- Adenoma-like adenocarcinoma
- Micropapillary carcinoma
- Medullary carcinoma
- Mucinous adenocarcinoma
- Signet-ring cell carcinoma
- Undifferentiated carcinoma
- Others

Grading

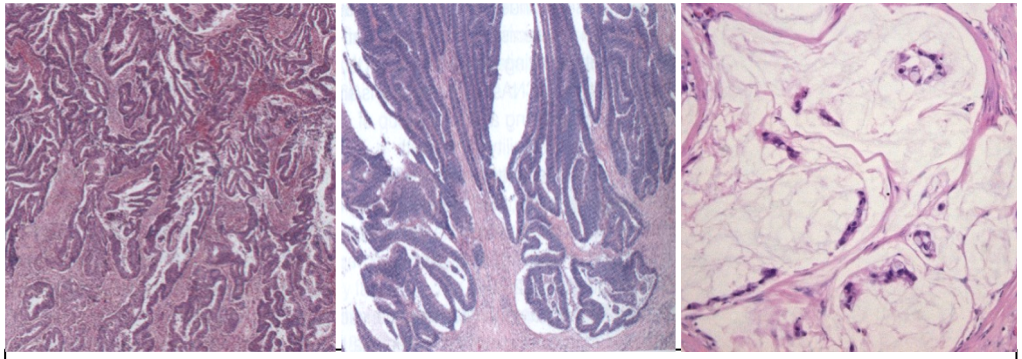
G1 >95% gland formation
G2 50-95% gland formation
G3 >0-49% gland formation

Low-grade: G1-G2
High grade: G3

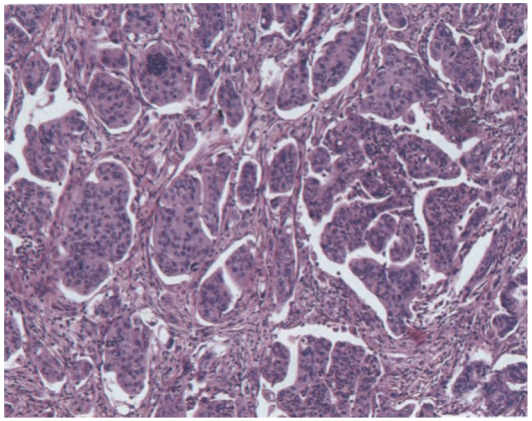
*Grading is based on the least differentiated component



Adenocarcinoma NOS



Serrated Adenoma-like Mucinous

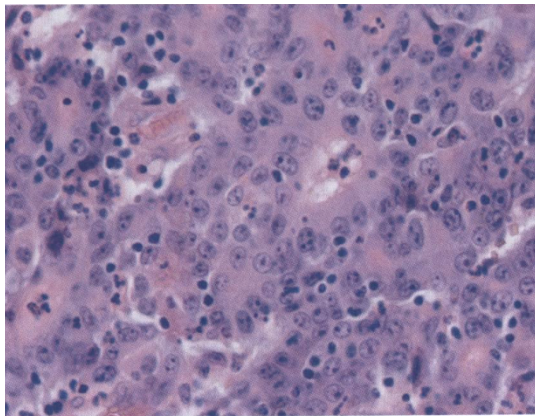


Micropapillary adenocarcinoma 5%

Small clusters of tumor cells within stromal spaces mimicking vascular channels.

Lymph-nodes metastasis, lymphatic, venous and perineural invasion are frequently present.

KRAS, p53

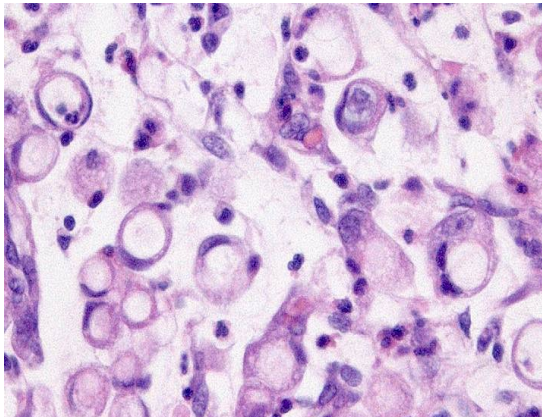


Medullary carcinoma 4%

Sheets of malignant cells with vescicular nuclei, prominent nucleoli, prominent infiltration by lymphocytes. Good prognosis.

Loss of CDX2 and of CK20.

MSI, BRAF-V600E mutation.



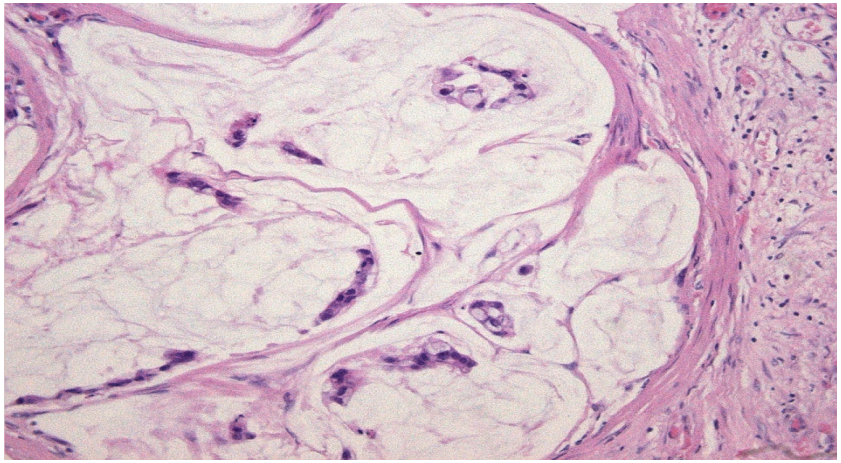
Signet-ring cell carcinoma 1%

Signet-ring cells >50% of the tumor cells.

Metastases develop rapidly.

Bad prognosis.

MSI, KRAS, BRAF-V600E mutation

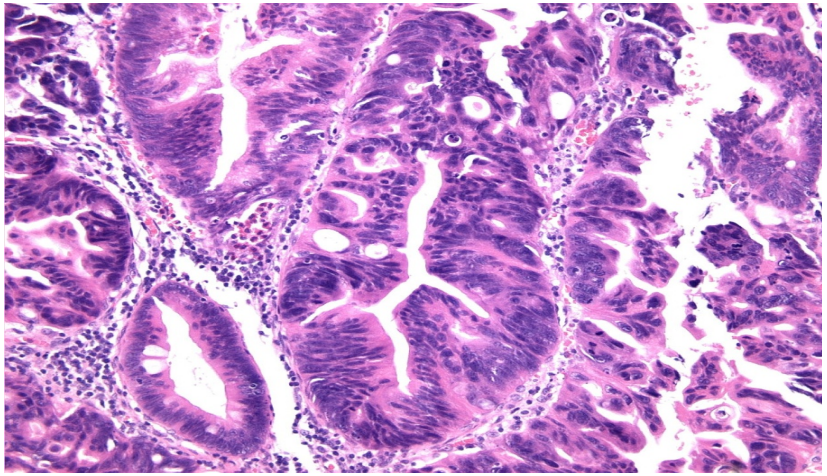


Mucinous adenocarcinoma

>50% of the lesion is composed of pools of extracellular mucin that contain malignant epithelium.

Predilection for right colon.

MSI 40%, KRAS 60%.



Serrated adenocarcinoma

This rare variant has architectural similarity to a sessile serrated polyp with glandular serration that can be accompanied by mucinous areas.

Right colon and rectum.

KRAS 35%, BRAF 45%, MSI 30%.

Adenoma-carcinoma sequence

progressive step-wise accumulation of genetic and epigenetic events

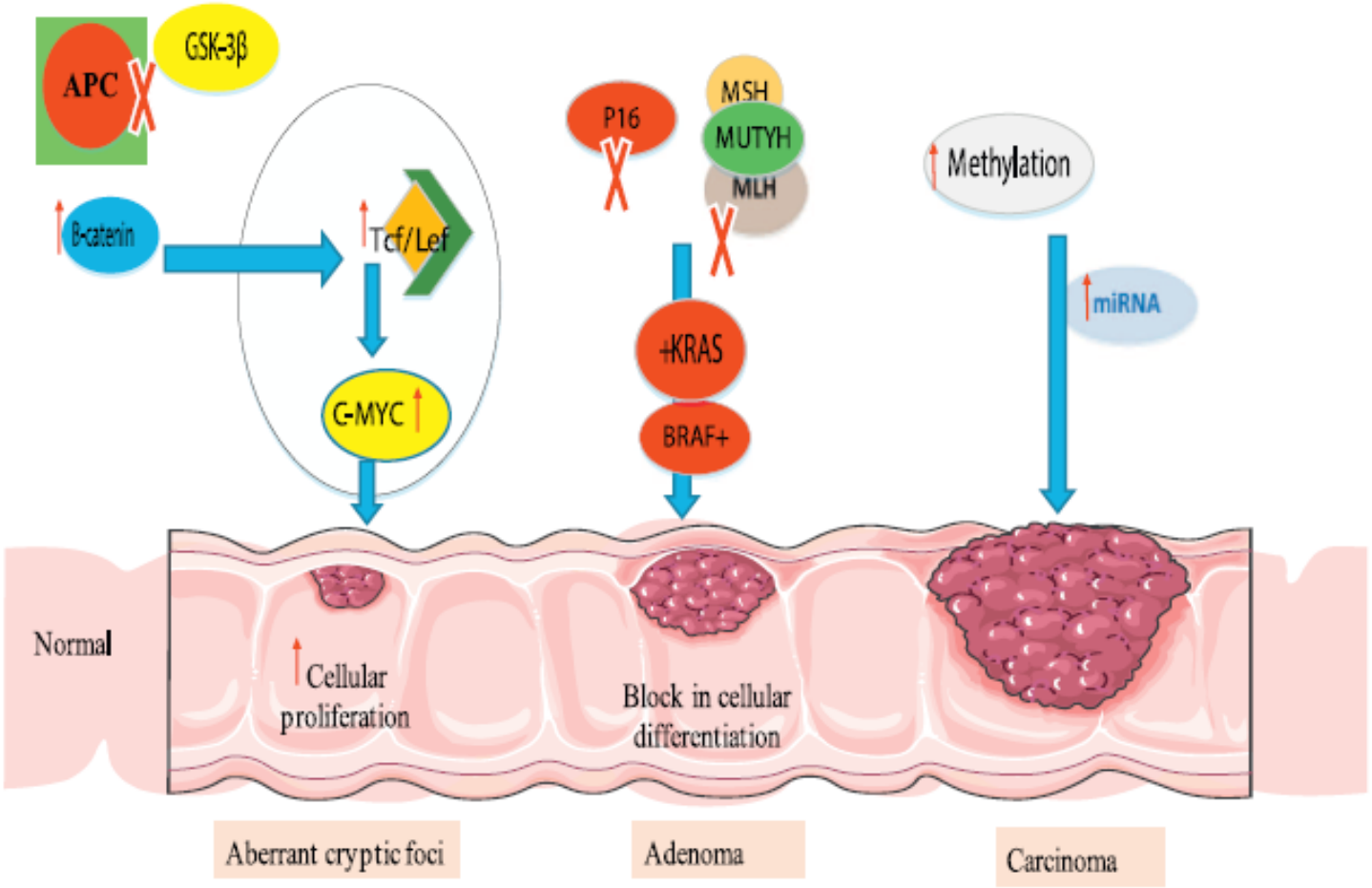
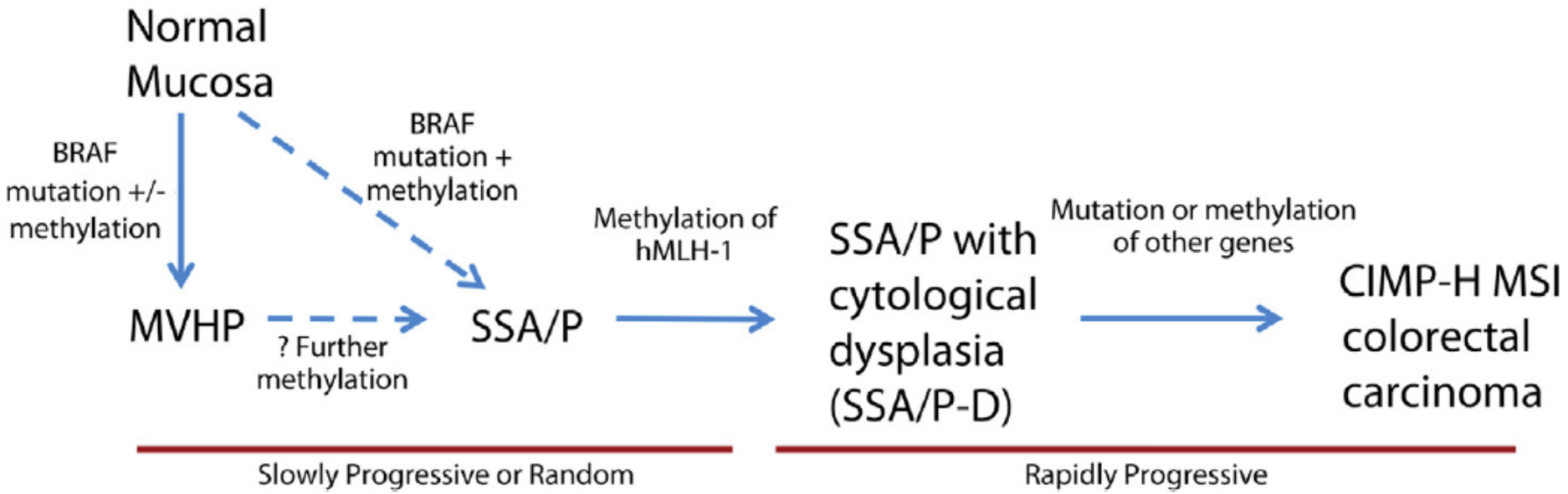
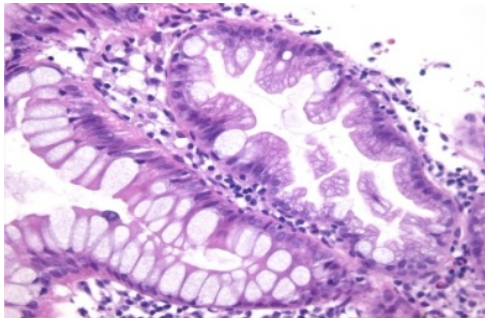


Fig. 1. Carcinogenesis pathway of CRC. The mutation in Adenomatous Polyposis Coli gene, APC, leads to accumulation of cytoplasmic β catenin, which in turn transported to the nucleus to bind Tcf/Lef complex. Then, Tcf/Lef complex activates C-myc resulting in cellular proliferation. The second hit may be caused by KRAS and BRAF gene mutations. This is catastrophic to the cell especially when repair system genes such as MSH, MLH and MUTYH are nonfunctional. Besides, the epigenetic methylation of critical genes such as P53 and PTEN genes drives tumorigenesis. As well, degradation of mRNA by defective miRNAs is also involved in CRC carcinogenesis.

Serrated pathway





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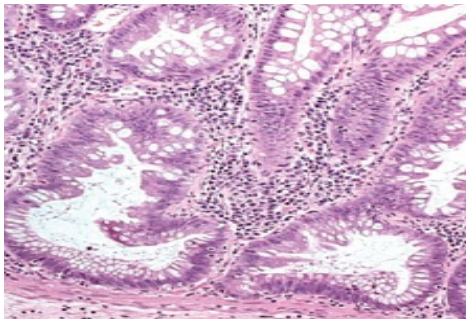
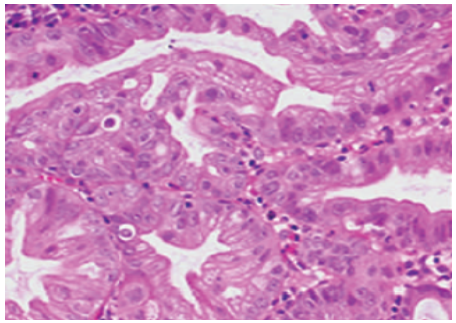
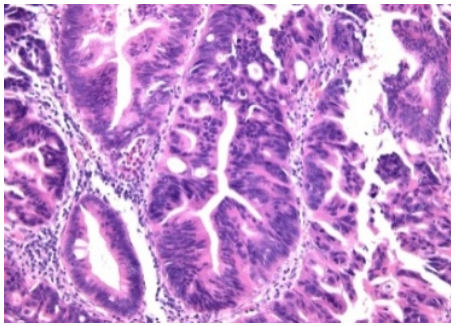
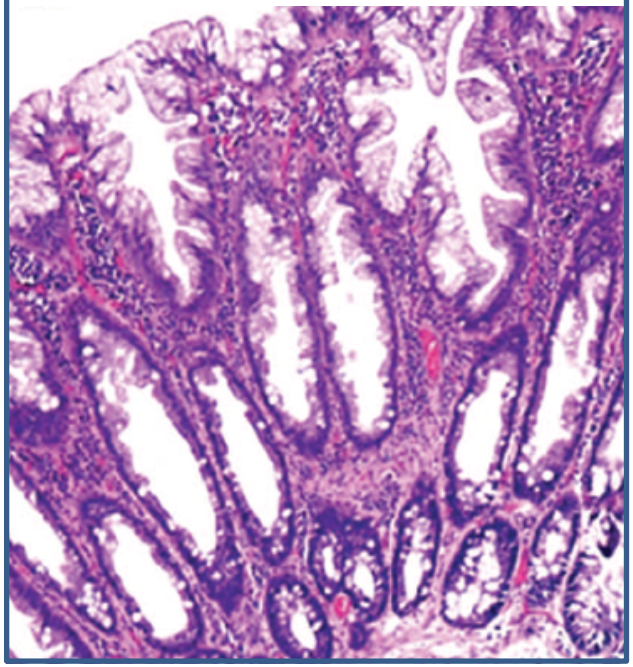


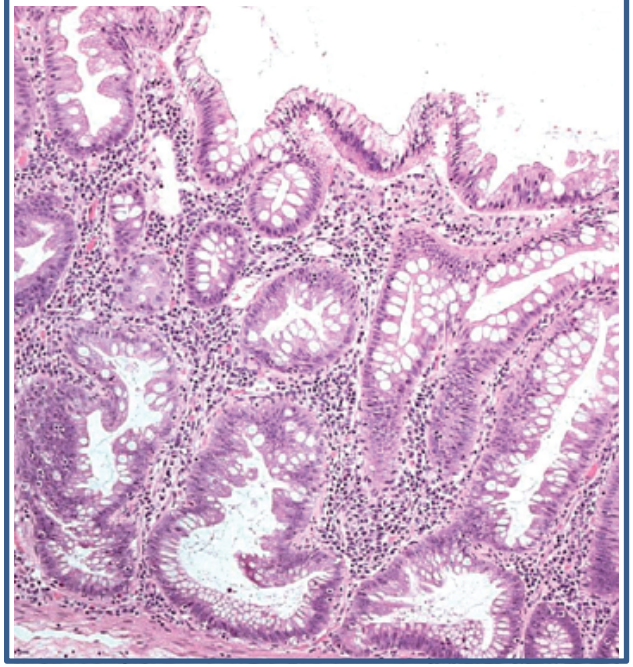




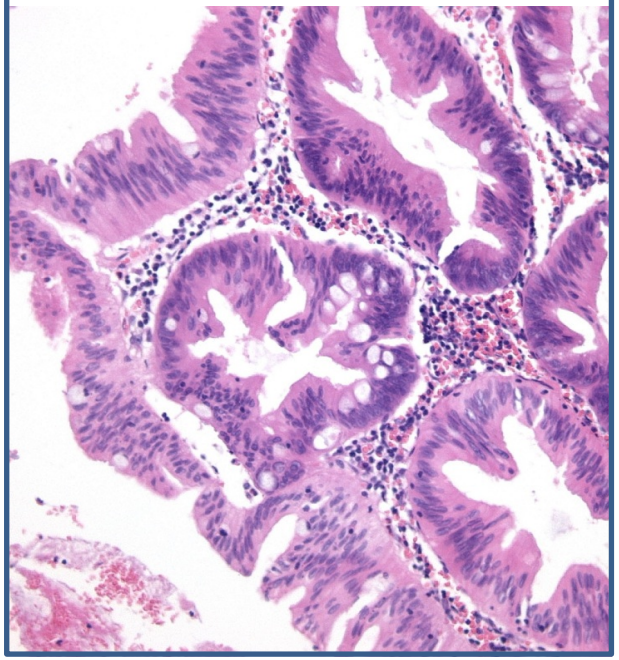
Polipo iperplastico



Adenoma «serrato» sessile



Adenoma «serrato» tradizionale

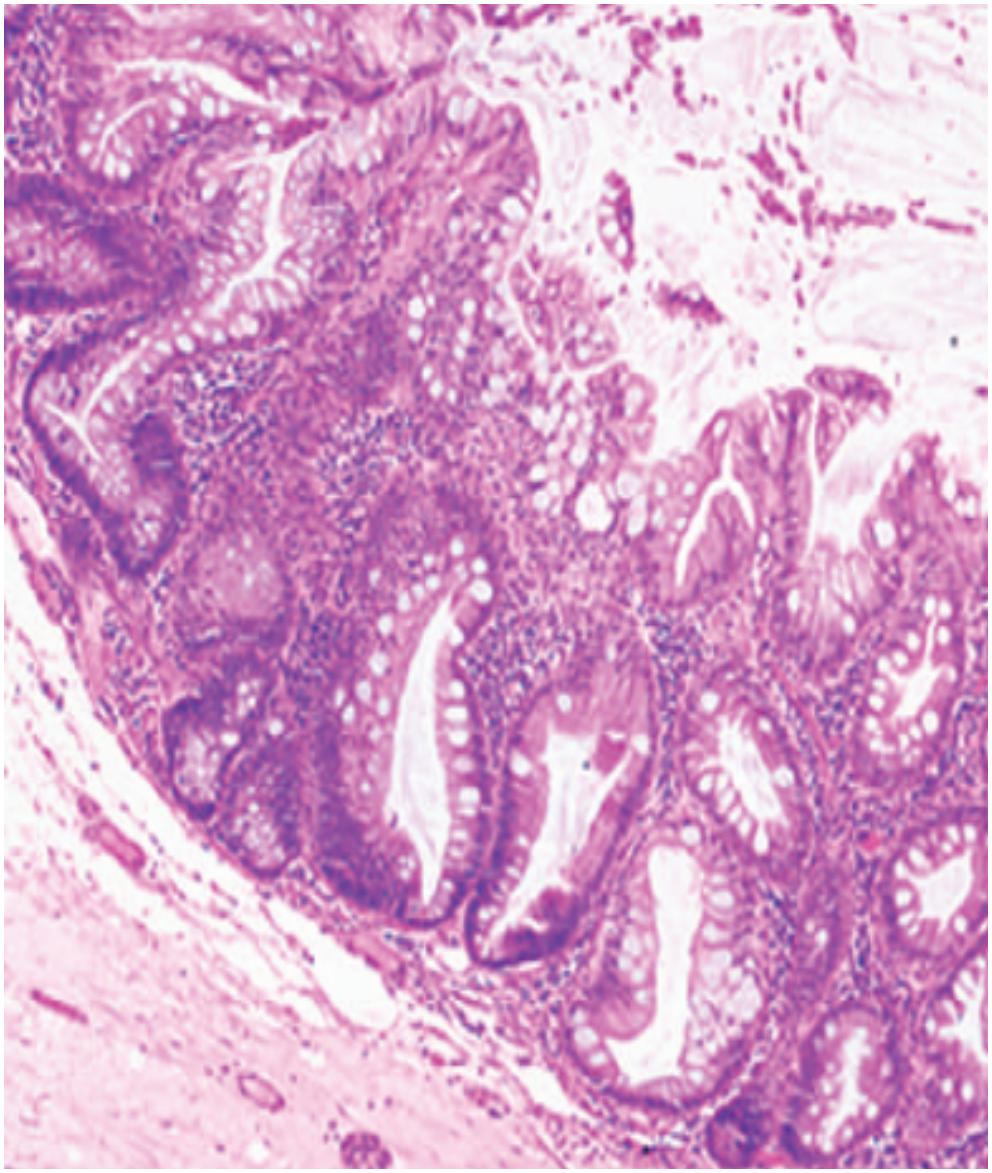


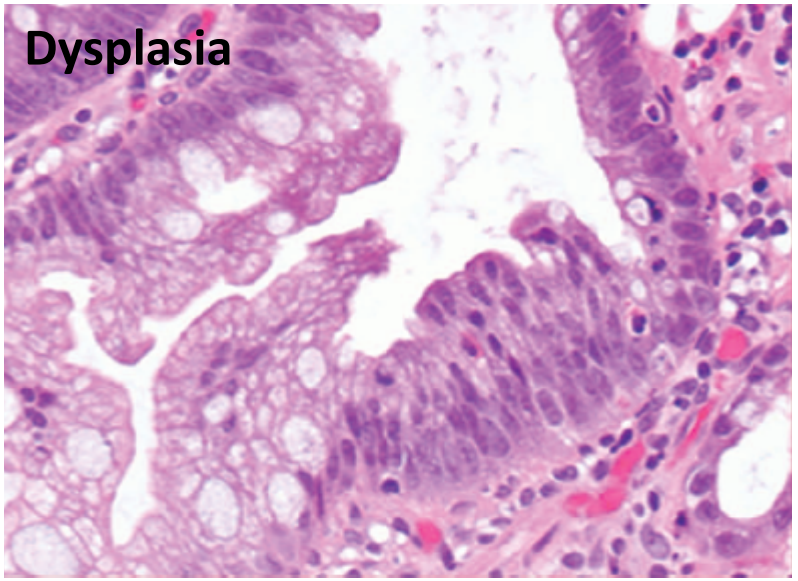
Serrated polyps of the colon and rectum WHO 2010

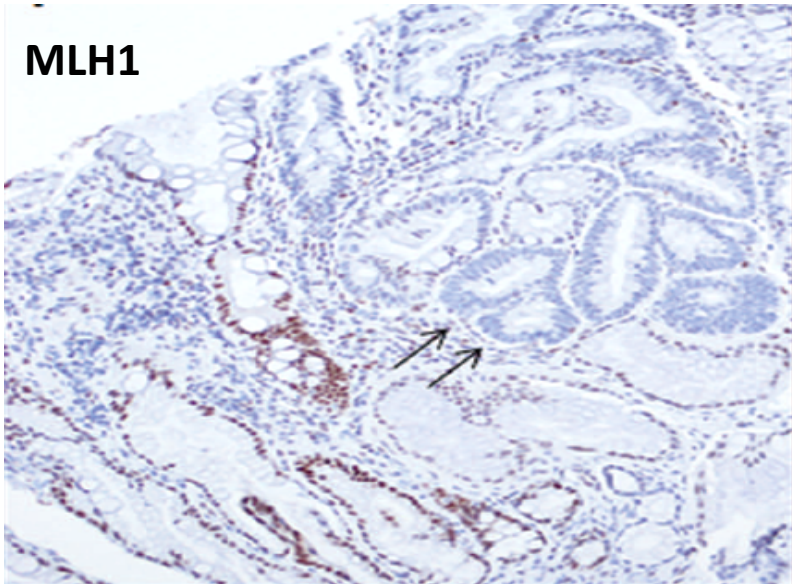
Hyperplastic polyps	**75% of all serrated polyps**
Sessile serrated adenomas/polyps	**15-25% of all serrated polyps**
Traditional serrated adenoma	**<1% of all polyps**

«The SSA/P was identified as a subgroup that comprised about 20% of what had previously been called HPPs.» KP Batts 2015

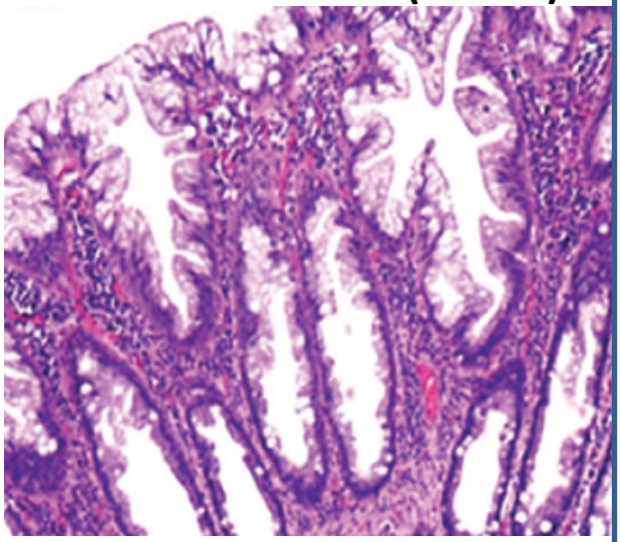
Sessile serrated adenoma/polyp



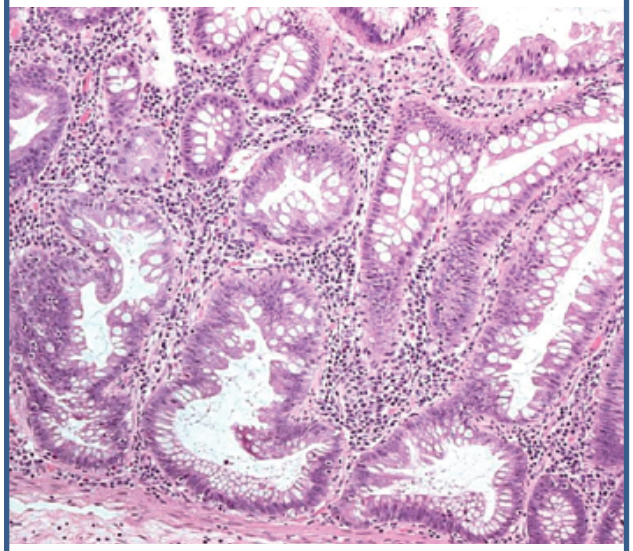




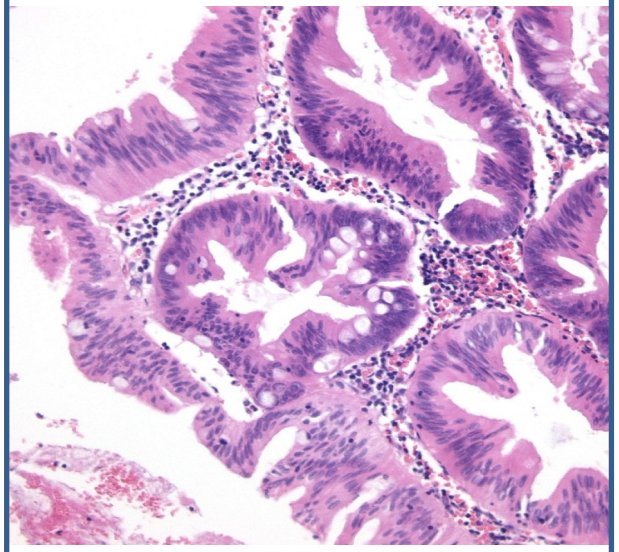
Microvesicular HP(MVHP)

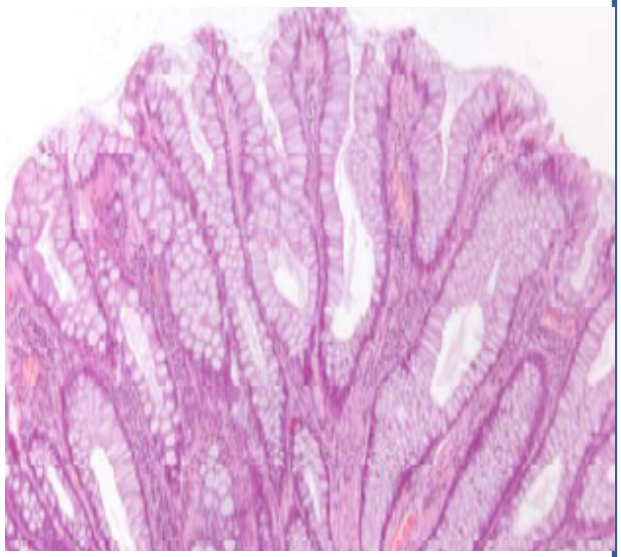


Sessile Serrated Lesion

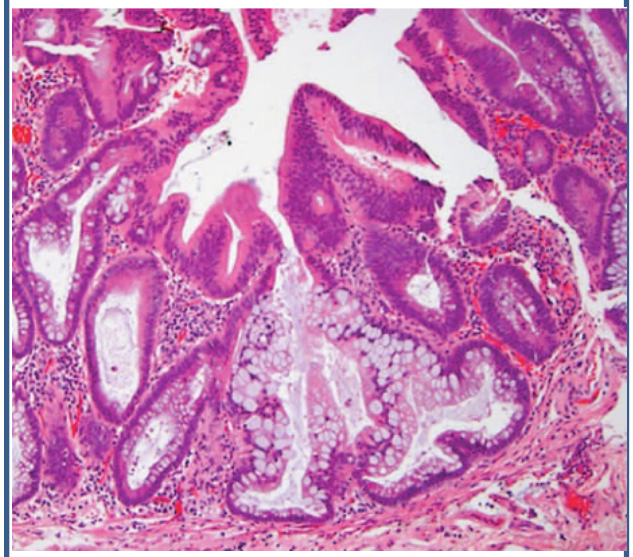


Traditional serrated adenoma

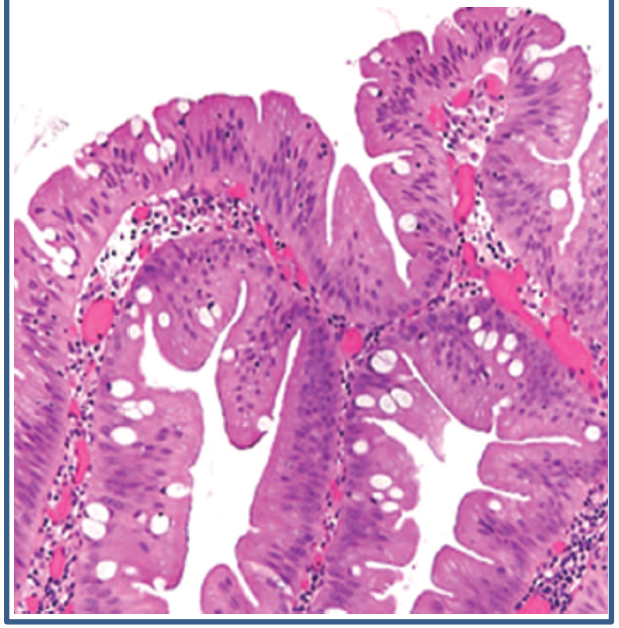




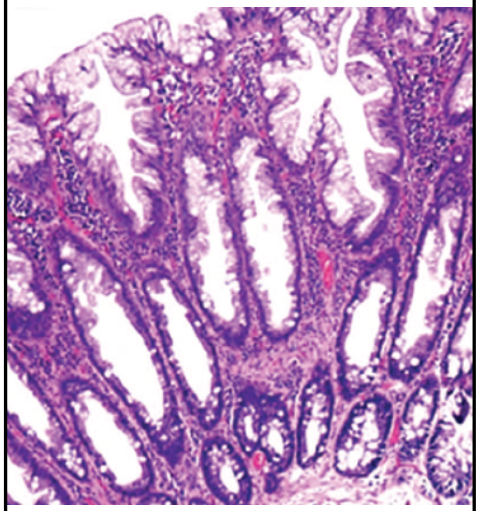
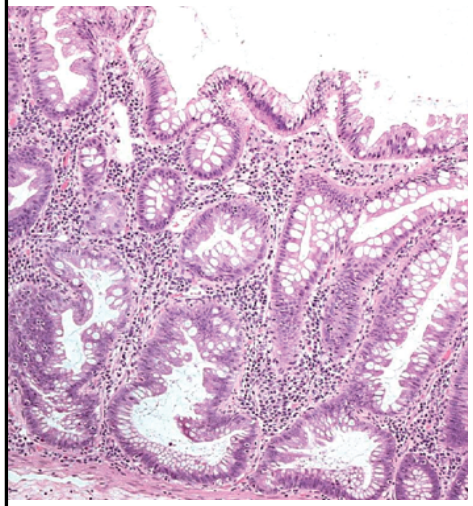
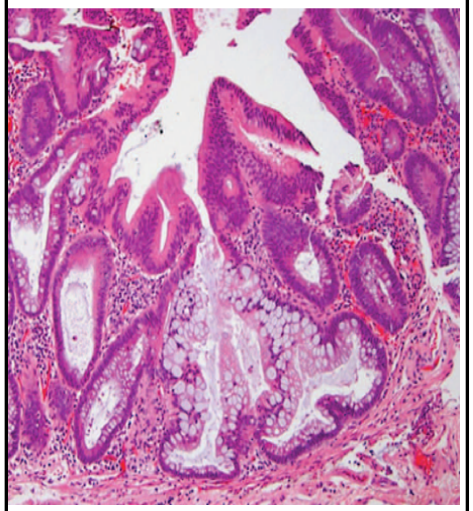
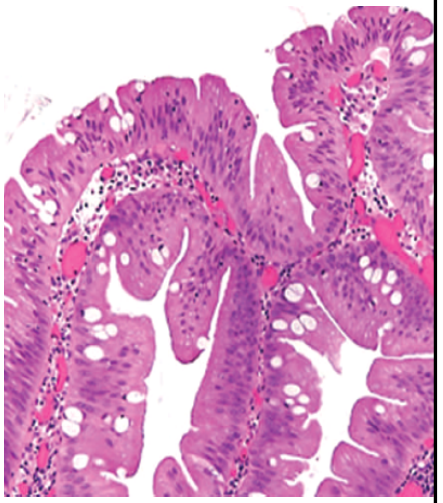
Goblet-cell rich HP (GCHP)



SSL with dysplasia



Serrated lesions and polyps of the colon and rectum WHO 2018

Polipo iperplastico	Lesione serrata sessile	LSS con displasia	Adenoma serrato tradizionale
			
< 5mm.	5-10 mm.	5-12 mm.	10-15mm
Prossimale 20%	Prossimale 85%	Prossimale 85%	Prossimale 10%
Distale 80%	Distale 15%	Distale 15%	Distale 90%
BRAF (MVHP) 60%	BRAF 90%	BRAF 90%	BRAF mut+
KRAS (GCHP) mut+	KRAS mut-	KRAS mut-	KRAS mut +
CIMP +/-	CIMP 90%	CIMP 90%	CIMP ++
MLH1- NO	MLH1- NO	MLH1- 75%	MLH1- NO

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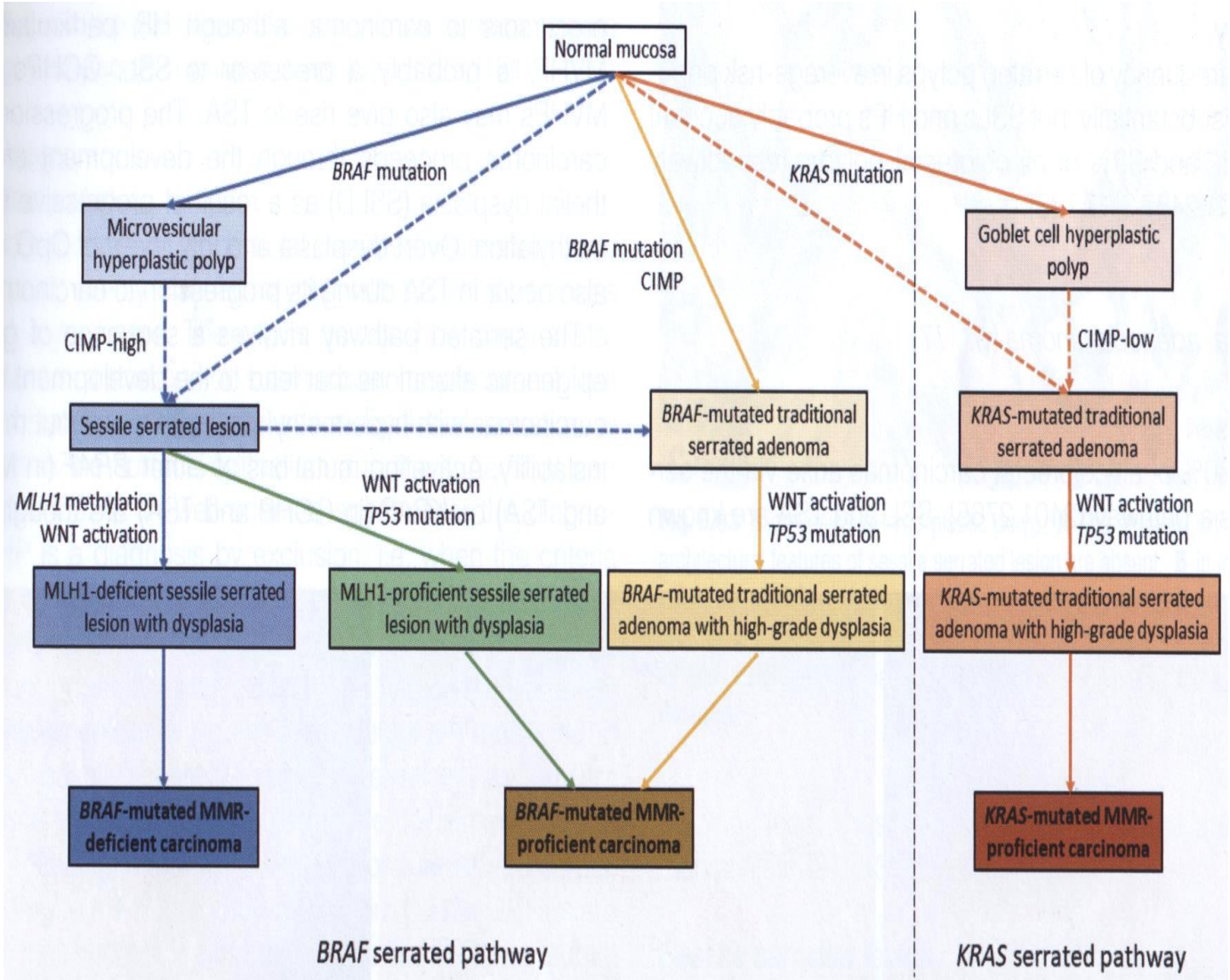


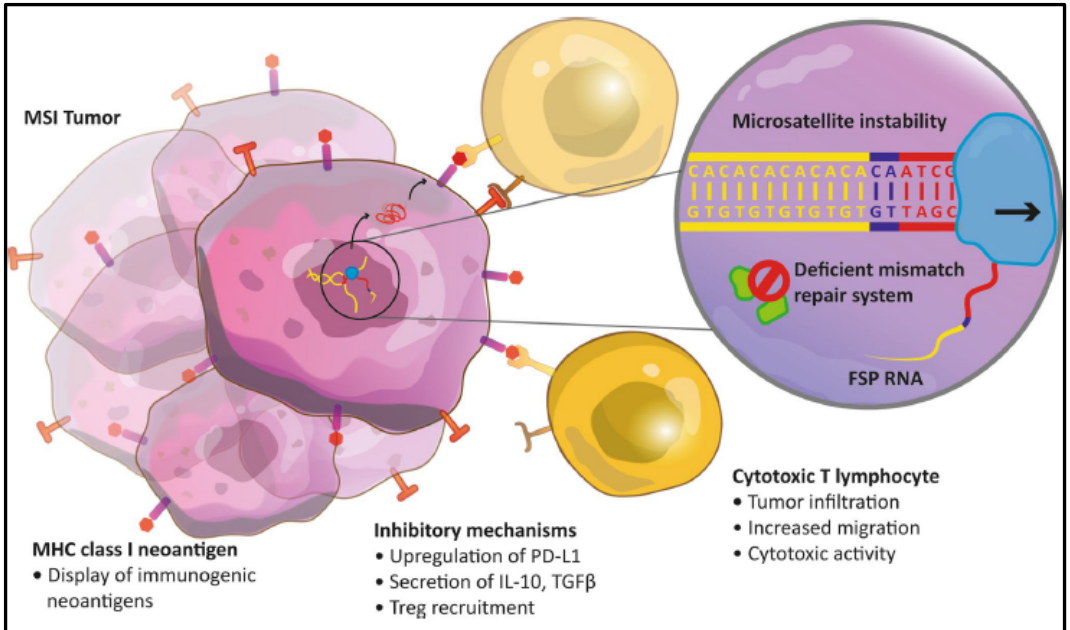
ematic representation of the serrated neoplasia pathway. Sessile serrated lesions (SSLs) have *BRAF* mutation and can develop de novo or pos
cular hyperplastic polyps (HPs). A key molecular event thought to precipitate the progression of SSL to malignancy is either *MLH1* methylati
pG island methylator phenotype (CIMP), progressing to mismatch repair (MMR)-deficient colorectal carcinoma, or *TP53* mutation progressing t
noma. Traditional serrated adenomas (TSAs) may develop de novo, possibly from SSL or from goblet cell HP (dotted lines). TSAs progress via th
-grade dysplasia and MMR-proficient colorectal carcinoma. WNT signalling pathway activation occurs in all pathways through different mechani

Opportunities for immunotherapy in microsatellite instable colorectal cancer

Harm Westdorp[1,2] · Felix L. Fennemann[1] · Robbert D. A. Weren[3] · Tanya M. Bisseling[4] · Marjolijn J. L. Ligtenberg[3,5] · Carl G. Figdor[1] · Gerty Schreibelt[1] · Nicoline Hoogerbrugge[3] · Florian Wimmers[1] · I. Jolanda M. de Vries[1,2]

Pathologic features of MSI CRCs

- Mucinous differentiation
- Crohn's like peritumoral reaction
- Tumor-infiltrating CD8 lymphocytes
- High yeld of lymph-nodes in resected specimens
- Right-sided

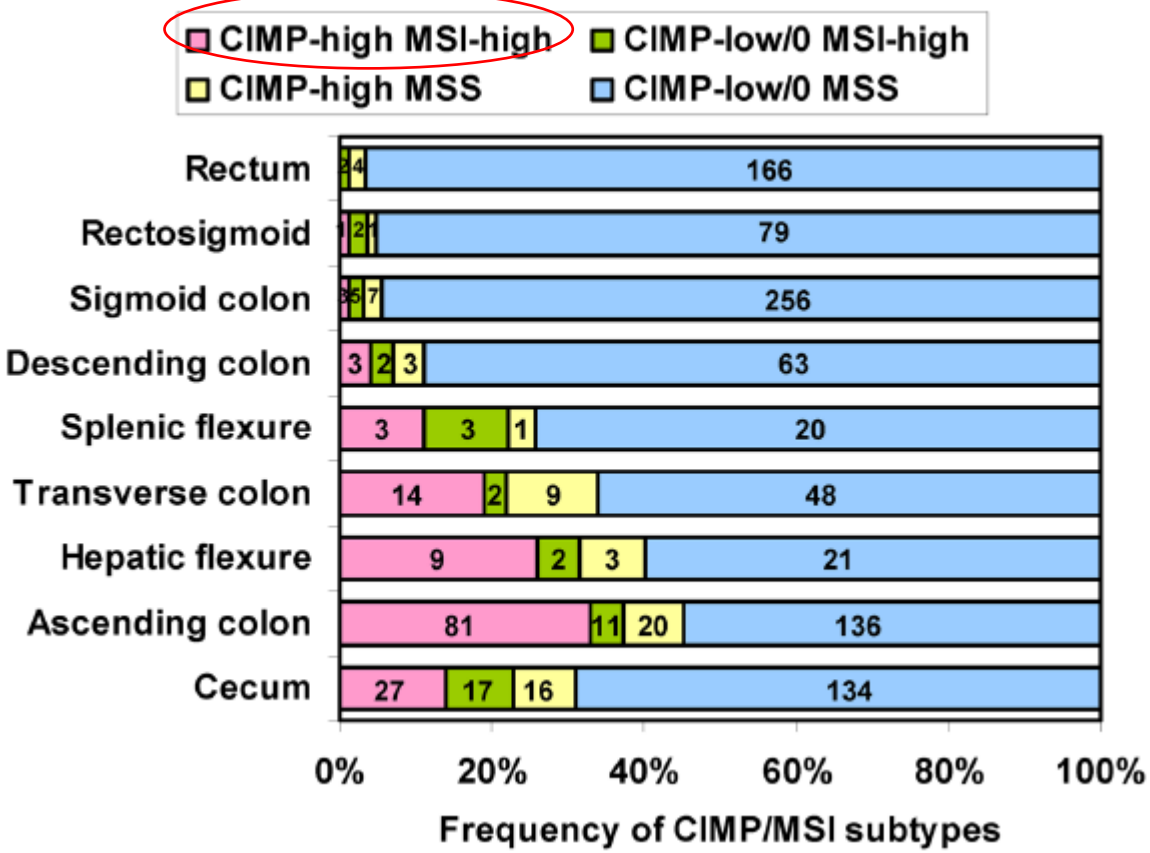


Molecular and immunological features of a MSI CRC harboring a frameshift mutation.

Cancer Immunol Immunother
DOI 10.1007/s00262-016-1832-7

Assessment of Colorectal Cancer Molecular Features along Bowel Subsites Challenges the Conception of Distinct Dichotomy of Proximal vs. Distal Colorectum

Mai Yamauchi[1], Teppei Morikawa[1], Aya Kuchiba[1], Yu Imamura[1], Zhi Rong Qian[1], Reiko Nishihara[1], Xiaoyun Liao[1], Levi Waldron[2,3], Yujin Hoshida[4], Curtis Huttenhower[2], Andrew T. Chan[5,6], Edward Giovannucci[6,7], Charles S. Fuchs[1,6], and Shuji Ogino[1,8]



Frequencies of CIMP/MSI subtypes of colorectal cancer along bowel subsites. The frequency of CIMP-high MSI-high tumors increased gradually from rectum to ascending colon, while that of CIMP-low/0 MSS tumors decreased gradually from rectum to ascending colon.

CIMP, CpG island methylator phenotype; MSI, microsatellite instability; MSS, microsatellite stable.

Gut. 2012 June ; 61(6): 847–854

Colorectal Cancer

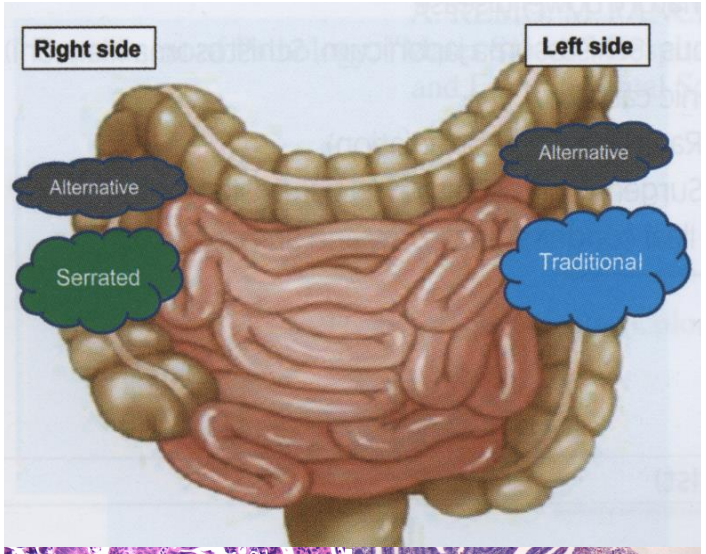
Microsatellite instability (15%-20%)

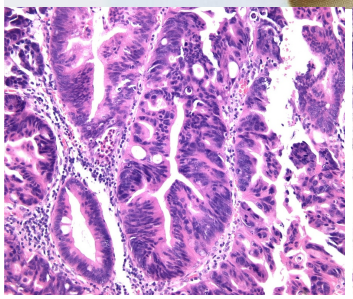
-**HNPCC** (Lynch syndrome)
germline mutations MMR

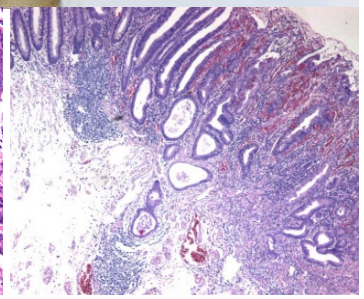
-Sporadic CRC
hypermethylation MLH1
BRAF mutations

- Midgut
- Exophityc
- Mucinous
- Worse prognosis

➢ **Serrated pathway**







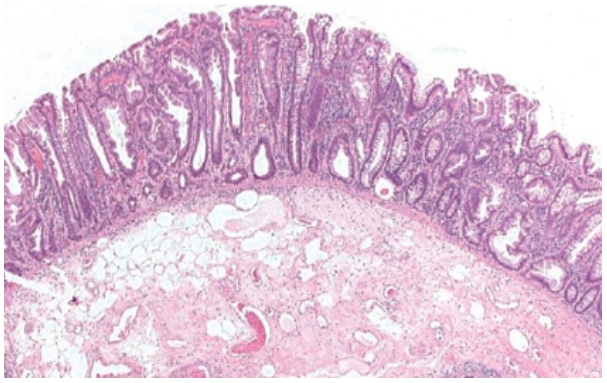
Chromosomal instability (80%-85%)

-FAP
germline mutations APC

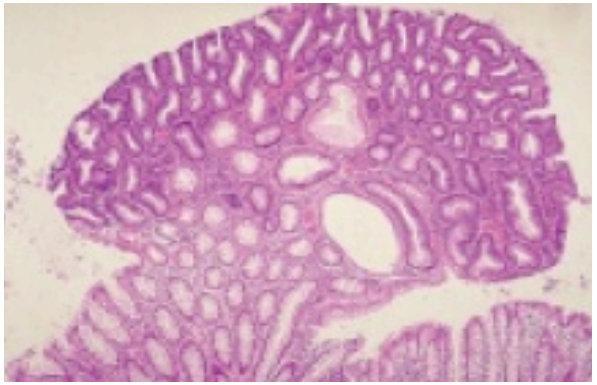
-Sporadic CRC
acquired mutations
APC, KRAS, p53...

- Hindgut
- Infiltrating
- Non-mucinous
- Better prognosis

➢ **Adenoma pathway**



Proximal colon	30-35%
Distal colon	25-30%
Rectum	30-35%



Right-sided colorectal cancer

- Predominantly occur in female
- Occur in older age
- Serrated pathway (MSI)
- Mucinous, Signet- ring cells, G3
- High T cell infiltration
- Metastases in peritoneal region
- Responde well to immunotherapy
- Better prognosis in stage I-II
- Worse prognosis in stage III and IV

Baran B et al. Gastroenterol Res 2018

Stadiazione del carcinoma del colon-retto
AJCC 2017 (TNM)

TX	Tumore primitivo non valutabile
T0	Tumore primitivo non evidente
Tis	Carcinoma in situ (intraepiteliale o intramucoso)
T1	Tumore che infiltra la sottomucosa
T2	Tumore che infiltra la muscolare propria
T3	Tumore che supera la muscolare propria e infiltra la sottosierosa o i tessuti pericolici o perirettali non rivestiti da sierosa
T4a	Tumore che invade e perfora il peritoneo viscerale
T4b	Tumore invade direttamente organi adiacenti

NX	non valutabili
N0	assenza di metastasi
N1 N1a N1b N1c	1-3 linfonodi regionali 1 linfonodo regionale 2-3 linfonodi regionali depositi tumorali in N0 (sottosierosa, mesentere, mesoretto)
N2 N2a N2b	≥ 4 linfonodi regionali 5-6 linfonodi regionali ≥ 7 linfonodi regionali
M0	metastasi assenti (categoria clinica)
M1 M1a M1b M1c	≥ 1organi distanti o peritoneo 1 organo distante ≥ 1 organo distante peritoneo con o senza coinvolgimento di organi distanti

STADIO: **I** T1-T2 N0M0, **II** T3-T4 N0 M0, **III** N+ o N1c, **IV** M+

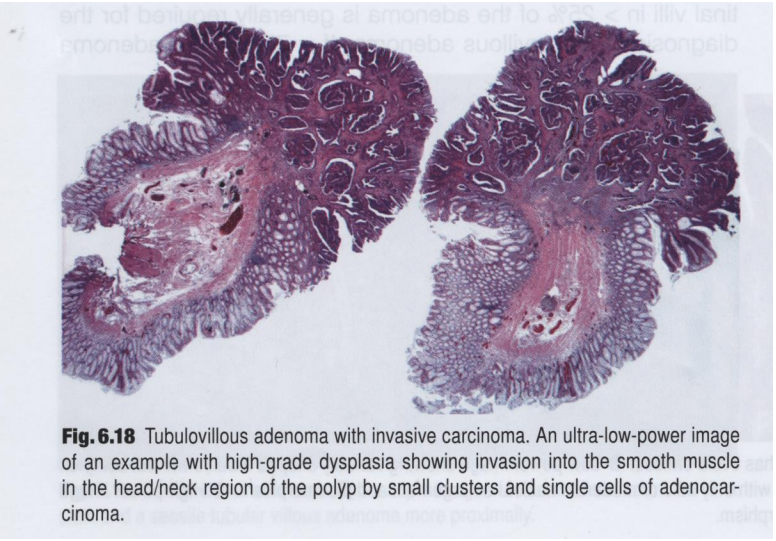


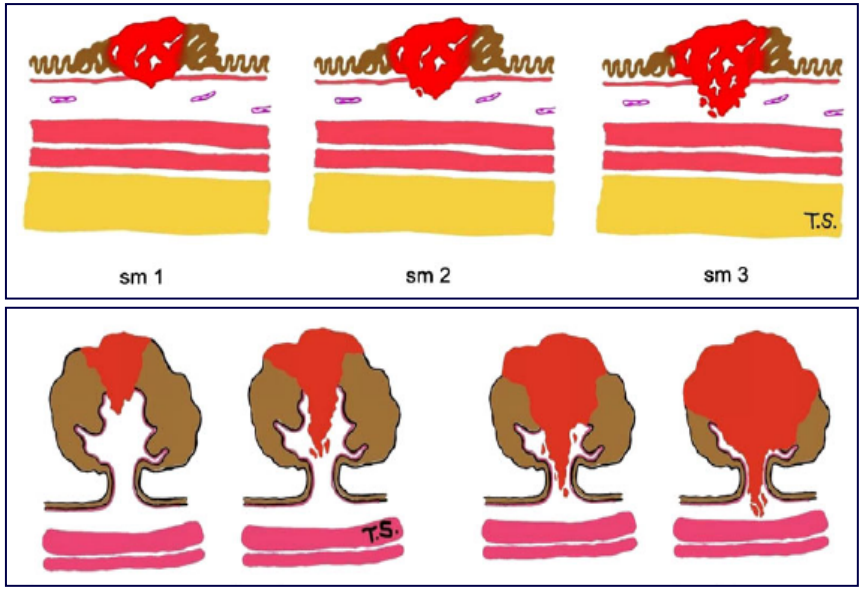
Fig. 6.18 Tubulovillous adenoma with invasive carcinoma. An ultra-low-power image of an example with high-grade dysplasia showing invasion into the smooth muscle in the head/neck region of the polyp by small clusters and single cells of adenocarcinoma.

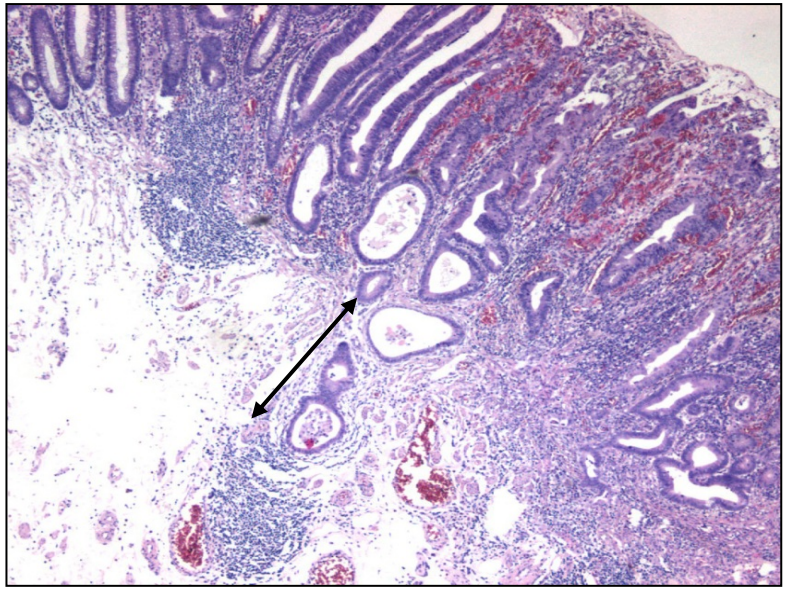
pT1 Colorectal cancer

(cancerized adenoma)

Histologic risk factors

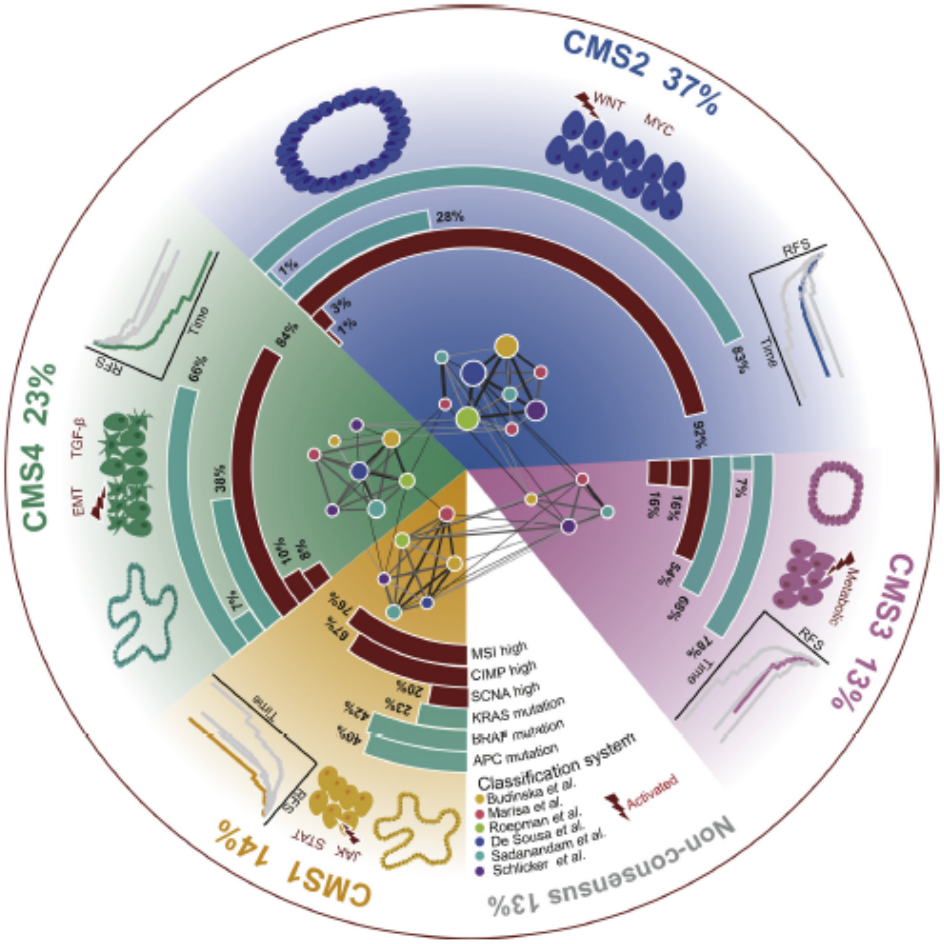
Grading	G1,G2	G3,G4
Vascular invasion	no	yes
Resection margin	negative	positive
Budding	absent/low	high





Neither the Kikuchi (for sessile lesions) nor Haggitt (for polypoid tumors) are easy to use in practice. The depth and the width of invasion provides a more objective measure.

Molecular subtyping of colorectal cancer: Recent progress, new challenges and emerging opportunities



Non-consensus 13%

- CMS1-MSI immune subtype (~14%): characterized by MSI, CIMP high, diffuse immune infiltrate and BRAF V600E mutations; associated with worse survival after relapse.
- CMS2-canonical subtype (~37%): characterized by epithelial features, CIN, activated WNT and MYC signaling pathways;
- CMS3-metabolic subtype (~13%): characterized by deregulation of metabolic pathways, KRAS mutations, low level of CIMP and CIN, and mixed MSI status.
- CMS4-mesenchymal subtype (~23%): characterized by upregulation of EMT, TGF-β activation, angiogenesis, stromal infiltration; associated with worse relapse-free and overall survival.

Wang, W., Seminars in Cancer Biology (2018), https://doi.org/10.1016/j.semcancer.2018.05.002

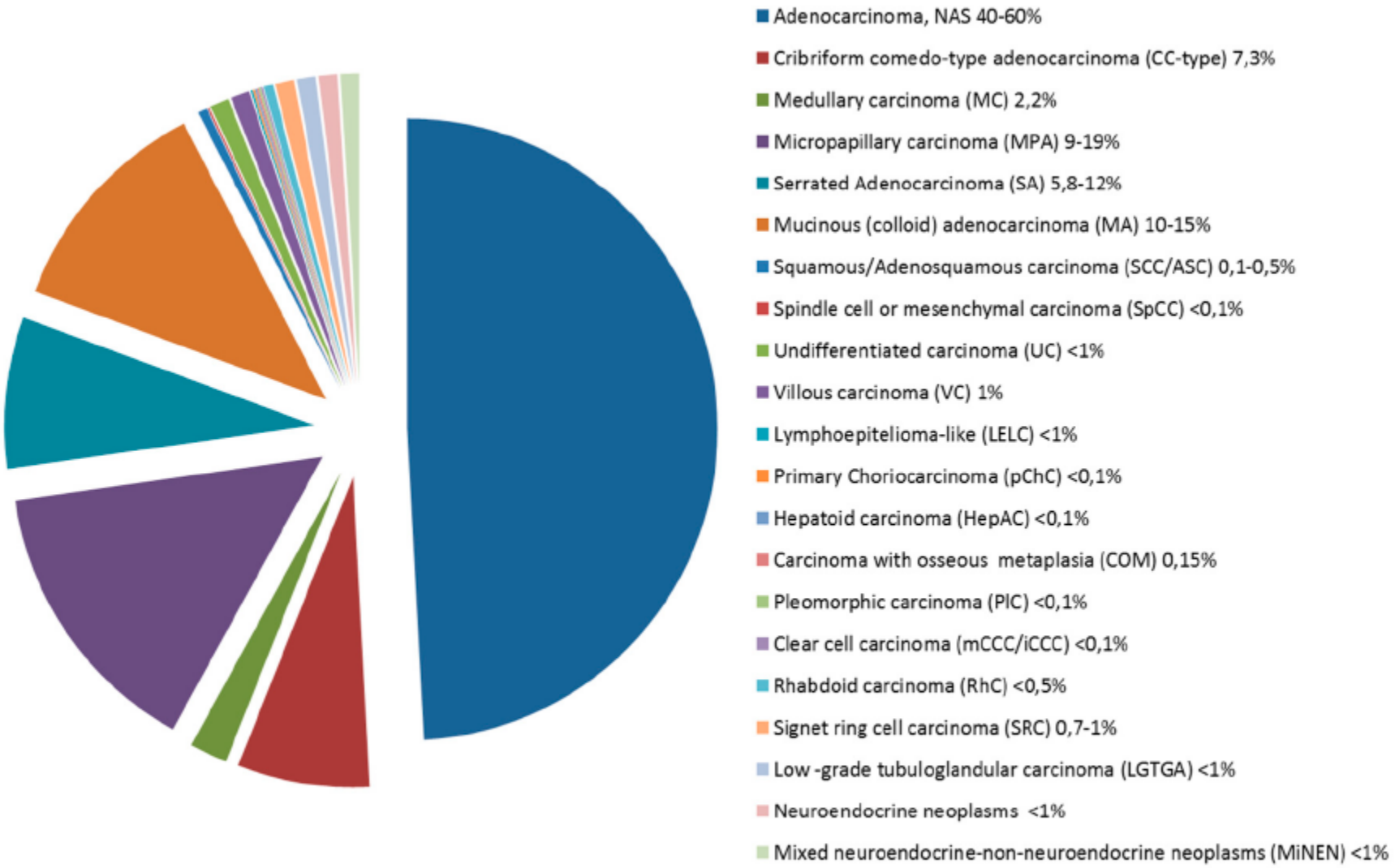


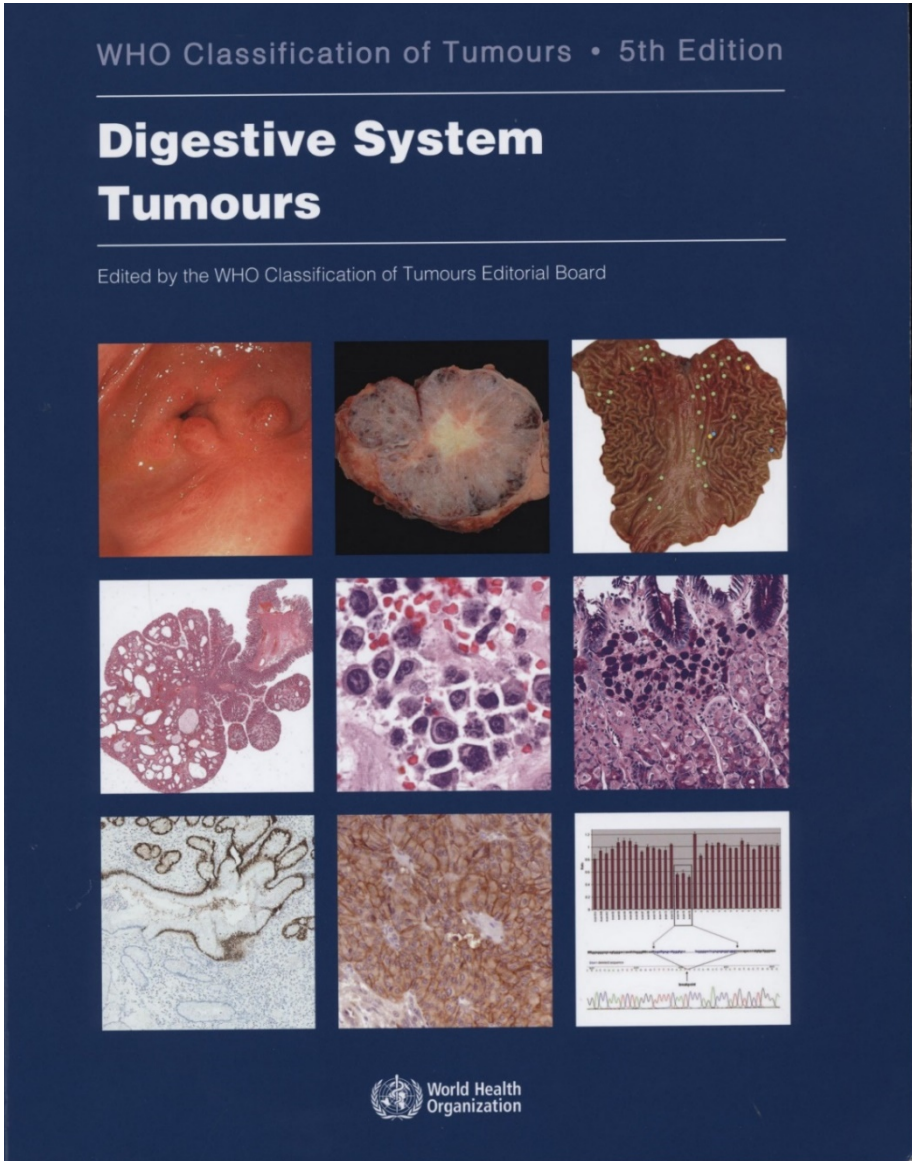
Figure 1. Pie chart showing the frequency of colorectal carcinomas by histologic type.

Risk assessment models

(AJCC 2017, WHO 2018)

Twenty-nine prognostication tools for colorectale cancer were identified

- Age,sex, race, BMI, performance status
- Surgical procedure, treatment group
- Location of tumor
- Stage
- T category
- Number of lymp-nodes evaluated
- Number of lymp-nodes positive
- Lymph-nodes ratio
- Total mesorectal excison
- Complete mesocolon excision
- Grading
- Budding
- Lymphovascular invasion
- Perineural invasion
- Tumor Regression Grade
- Immune response
- MSI, KRAS, NRAS, BRAF


WHO Classification of Tumours • 5th Edition
Digestive System Tumours
Edited by the WHO Classification of Tumours Editorial Board
World Health Organization


Serrated (sawtooth or stellate) pathway