UNIVERSITA' DEGLI STUDI DI PERUGIA
DIPARTIMENTO DI MEDICINA E CHIRURGIA

CLMMC AA 2021/22

Patologia sistematica VI

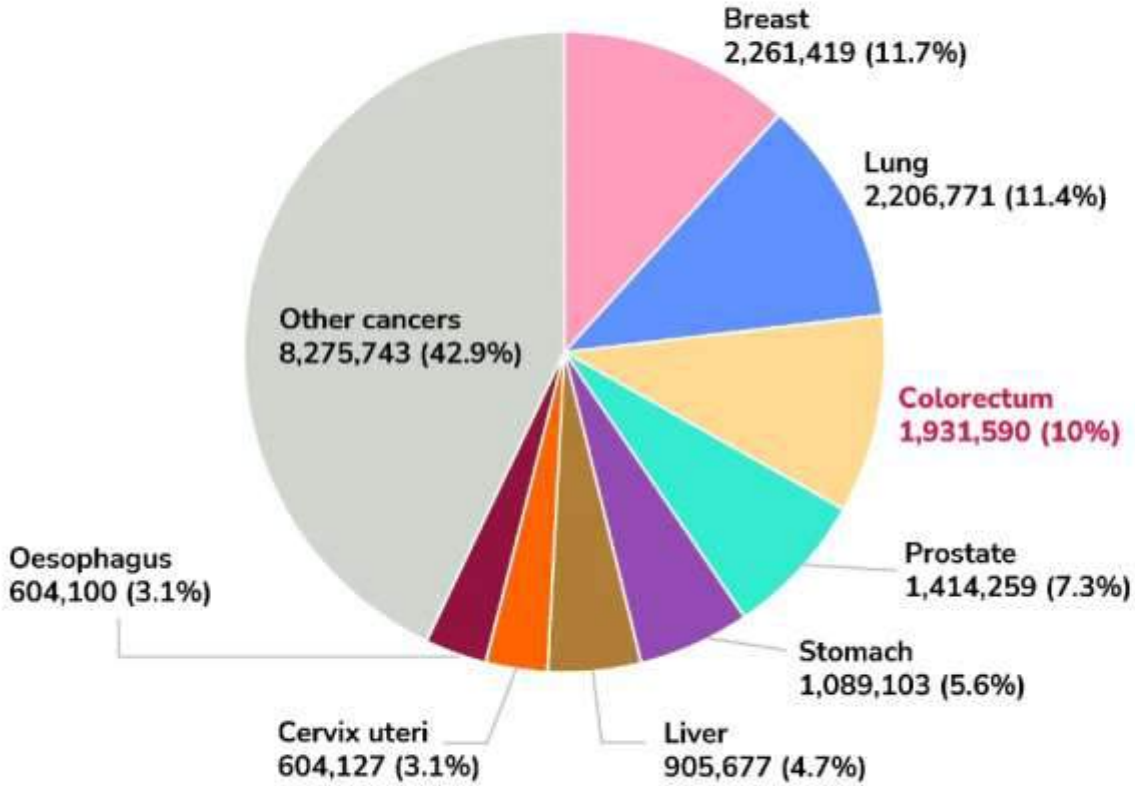
Gastroenterologia

Prof. Stefano Fiorucci

Colorectal cancer

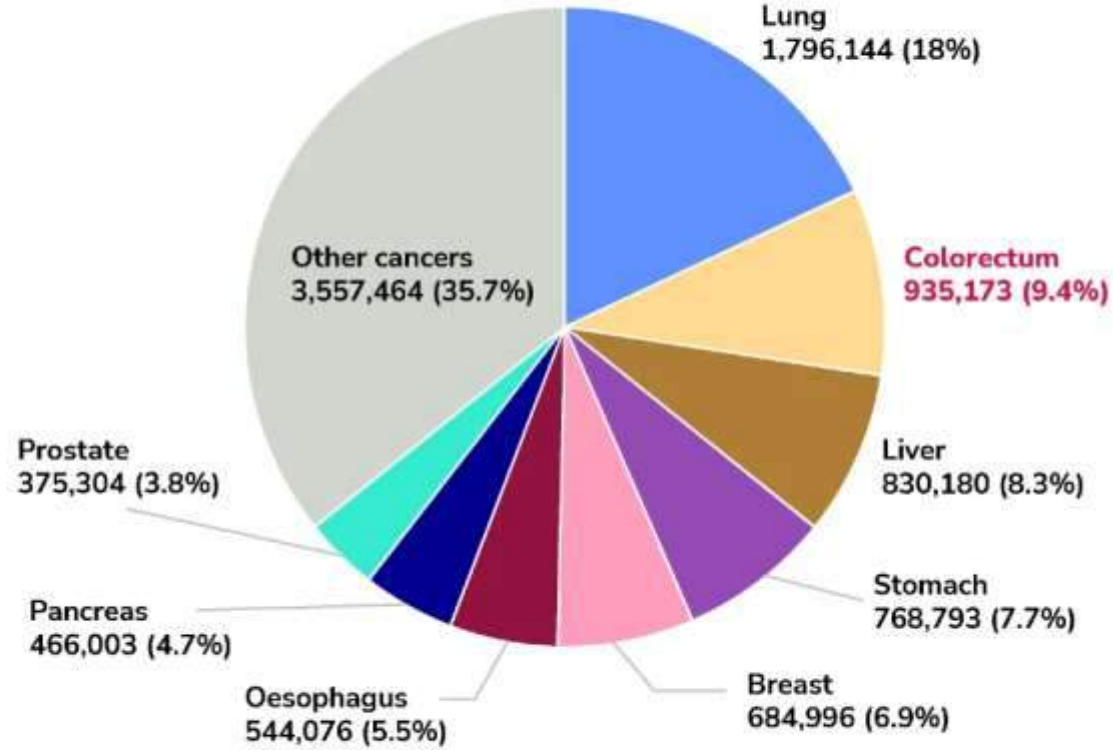
Harrison's Principles of Internal Medicine – 19-20° Ed.

Number of new cancer cases in 2020 (both sexes, all ages)

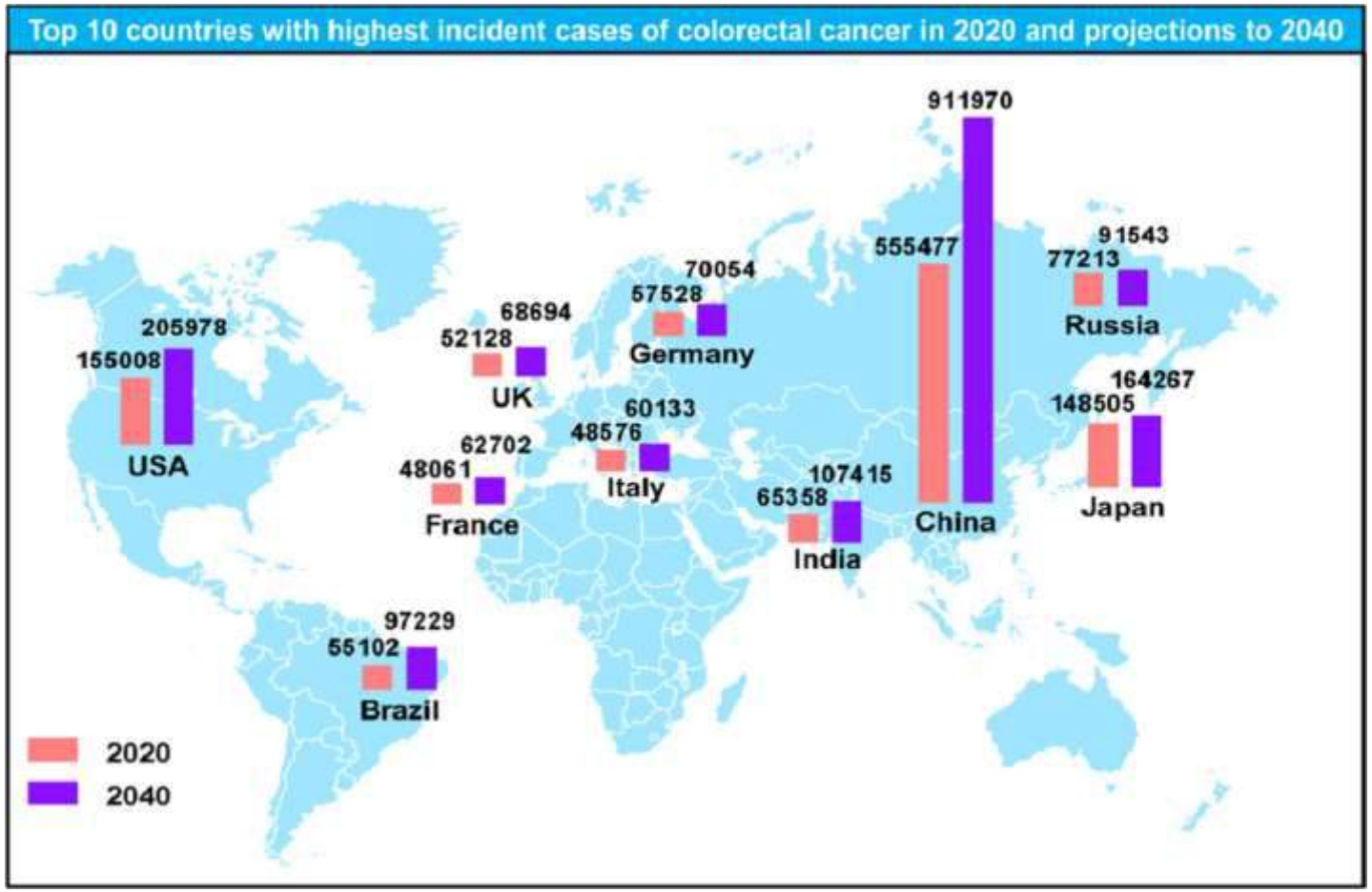


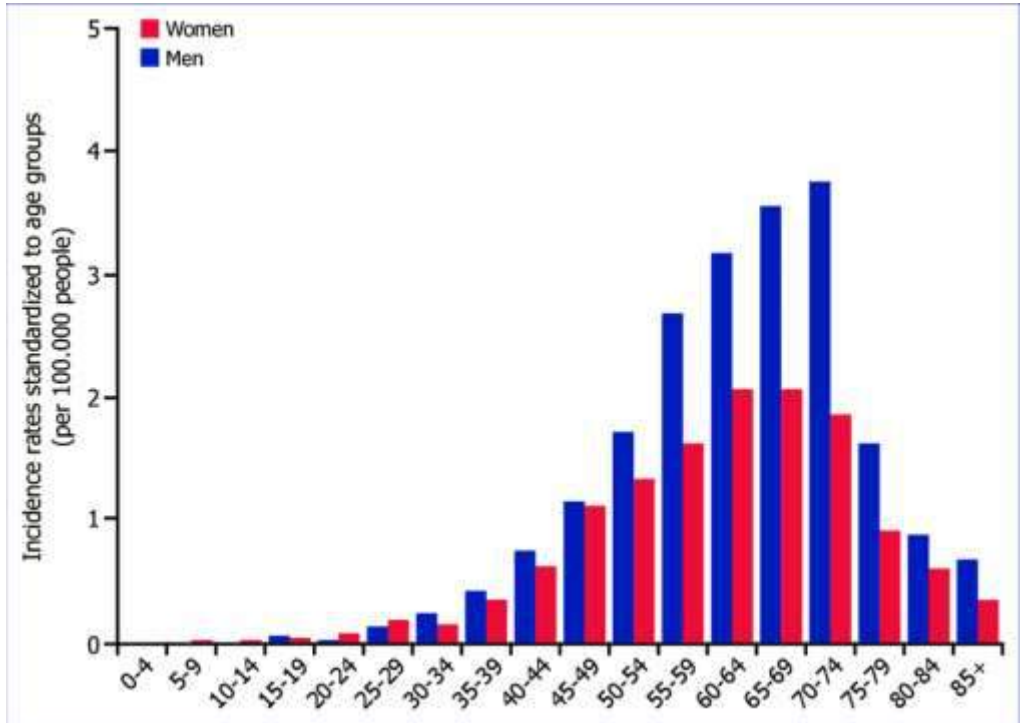
Total: 19,292,789 new cases

Number of cancer deaths in 2020 (both sexes, all ages)

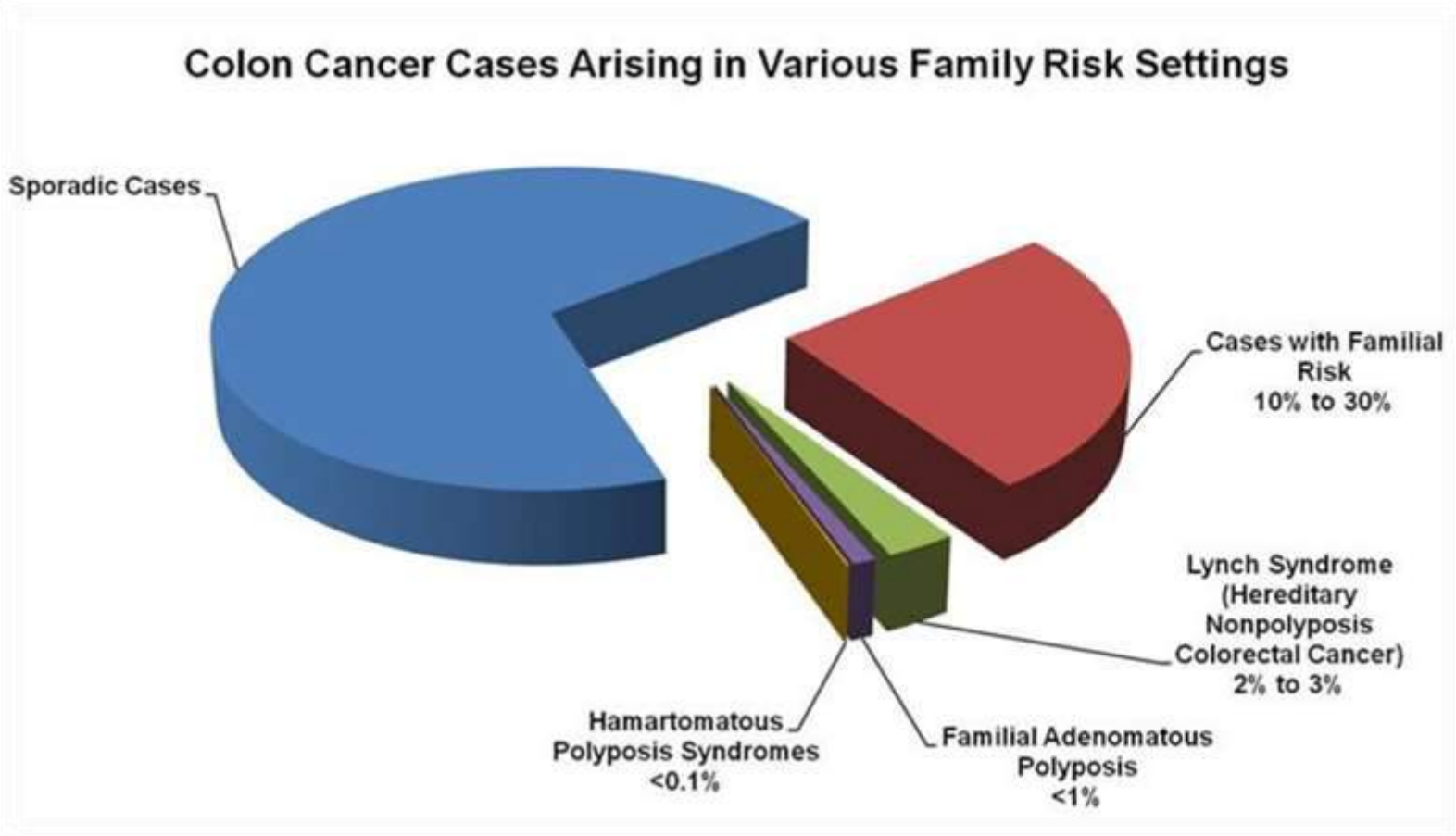


Total: 9,958,133 deaths

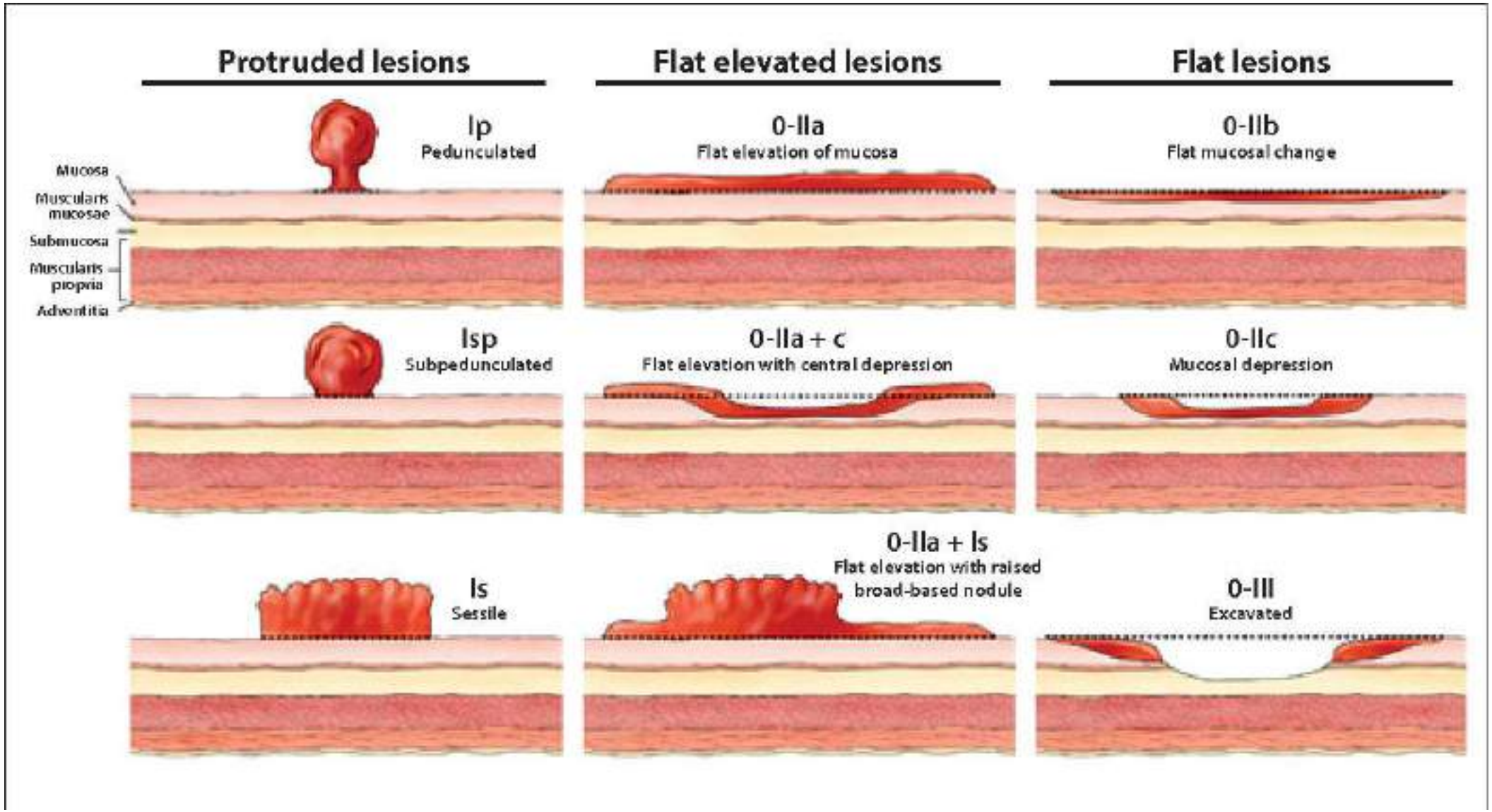

Top 10 countries with highest incident cases of colorectal cancer in 2020 and projections to 2040
911970
555477
91543
77213
Russia
70054
57528
Germany
68694
52128
UK
205978
155008
USA
60133
48576
Italy
62702
48061
France
107415
65358
India
China
164267
148505
Japan
97229
55102
Brazil
2020
2040


Women
Men
Incidence rates standardized to age groups (per 100.000 people)
0
1
2
3
4
5
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85+

Colorectal cancer



Paris Endoscopic Classification of CRC



Colorectal cancer

Most cancers arise from a polyp or mucosal lesions

This process begins with an **aberrant crypt,** evolving into a neoplastic precursor lesion (a polyp), and eventual progressing to colorectal cancer over an estimated 10–15 year period.

The cell of origin for the majority of colorectal cancers is currently assumed to be **a stem cell or stem-cell-like cell.**

These cancer stem cells are the result of progressive accumulation of genetic and epigenetic alterations that inactivate tumor-suppressor genes and activate oncogenes. Cancer stem cells reside in the base of the colonic crypts and are essential for the initiation and maintenance of a tumor.

Colorectal cancer

Globally, there are two major distinct precursor lesion pathways:

- **the traditional adenoma–carcinoma pathway** leading to 70–90% of colorectal cancers;
- **the serrated neoplasia pathway** (10–20% of colorectal cancers).

These pathways represent distinct multiple genetic and epigenetic events in a rather sequential order.

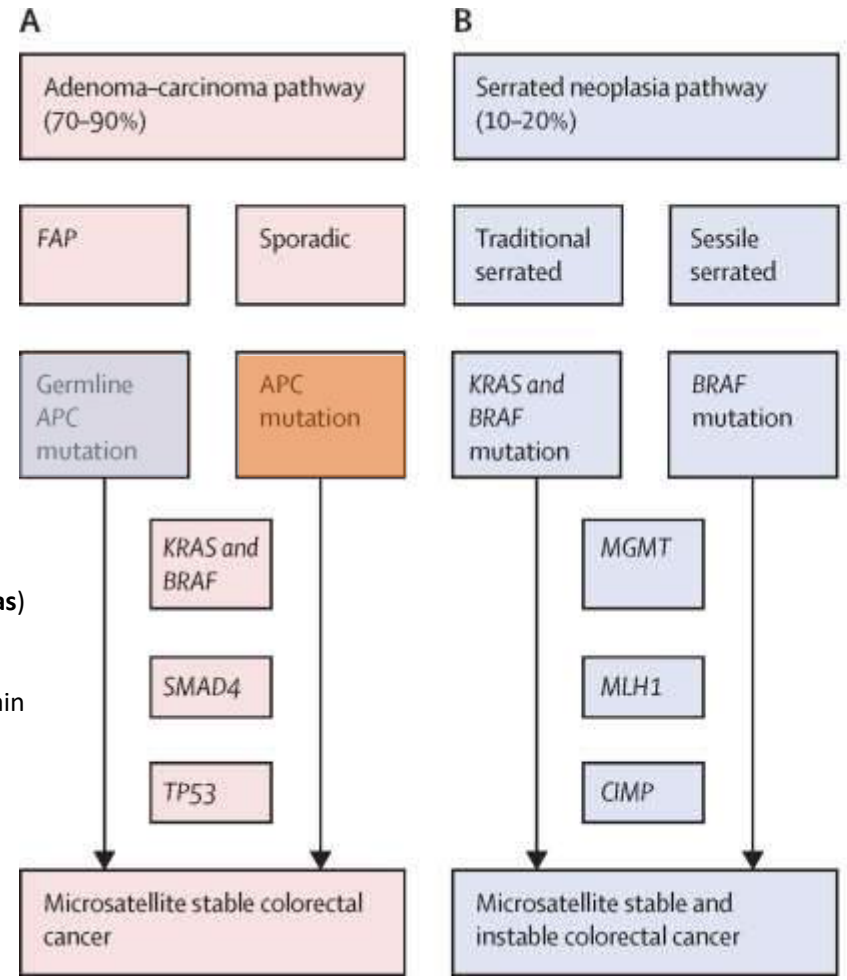
Cancer Genome Atlas Network
Comprehensive molecular characterization of human colon and rectal cancer. *Nature.* 2012; **487**: 330-337

Colorectal cancer

Familial adenomatous polyposis (**FAP**) is an autosomal dominant inherited condition

Adenomatous Polyposis Coli (**APC**) is an oncosoppressor gene

The three **Ras genes in humans (HRas, KRas, and NRas**) are the most common oncogenes in human cancer; mutations that permanently activate Ras are found in 20 to 25% of all human tumors and up to 90% in certain types of cancer (e.g., pancreatic cancer).

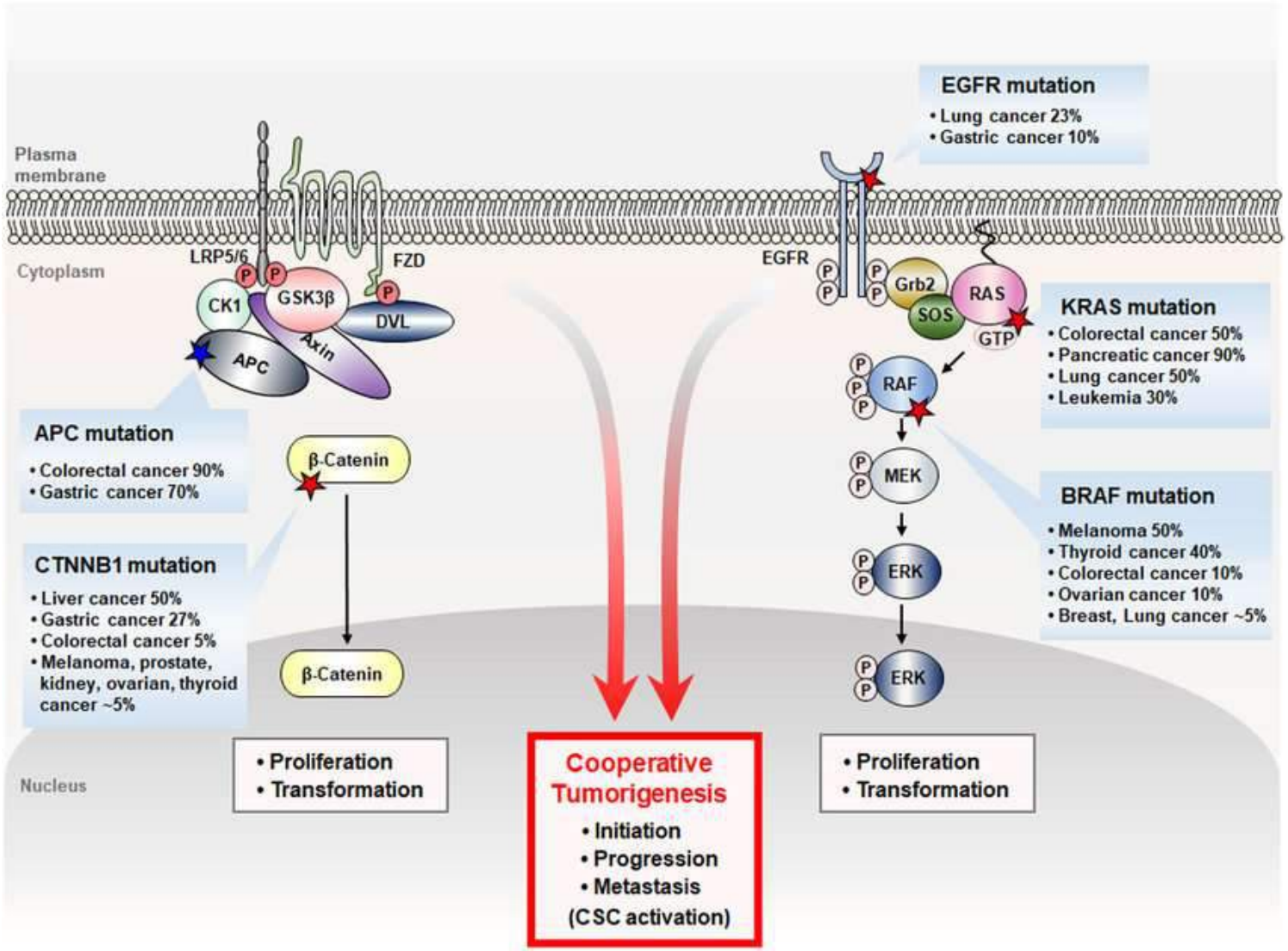


DNA **mismatch repair** (MMR) is a highly conserved biological pathway that plays a key role in maintaining genomic stability.

Chromosomal instability phenotypes typically develop following genomic events initiated by an *APC* mutation, followed by *RAS* activation or function loss of *TP53*.

Conversely, the serrated neoplasia pathway is associated with *RAS* and *RAF* mutations, and epigenetic instability, characterised by the CpG island methylation phenotype, leading to microsatellite stable and instable cancers. Further genome-wide studies have also identified newer markers and phenotypic subtypes on the basis of mutations present (eg, presence of polymerase-ε or POLE mutations or mismatch repair deficiency [dMMR]) leading to a hypermutated phenotype.

APC and RAS


EGFR mutation
• Lung cancer 23%
• Gastric cancer 10%
Plasma membrane
Cytoplasm
LRP5/6
FZD
CK1
GSK3β
DVL
Axin
APC
EGFR
Grb2
SOS
RAS
GTP
RAF
MEK
ERK
ERK
KRAS mutation
• Colorectal cancer 50%
• Pancreatic cancer 90%
• Lung cancer 50%
• Leukemia 30%
APC mutation
• Colorectal cancer 90%
• Gastric cancer 70%
β-Catenin
β-Catenin
CTNNB1 mutation
• Liver cancer 50%
• Gastric cancer 27%
• Colorectal cancer 5%
• Melanoma, prostate, kidney, ovarian, thyroid cancer ~5%
BRAF mutation
• Melanoma 50%
• Thyroid cancer 40%
• Colorectal cancer 10%
• Ovarian cancer 10%
• Breast, Lung cancer ~5%
Nucleus
• Proliferation
• Transformation
Cooperative Tumorigenesis
• Initiation
• Progression
• Metastasis
(CSC activation)
• Proliferation
• Transformation

Colorectal cancer

Consensus molecular subtypes

In 2014, on the basis of gene expression, colorectal cancer was classified into four molecular subtypes (consensus molecular subtypes [CMS])

The genes or pathways implicated are unique to each CMS

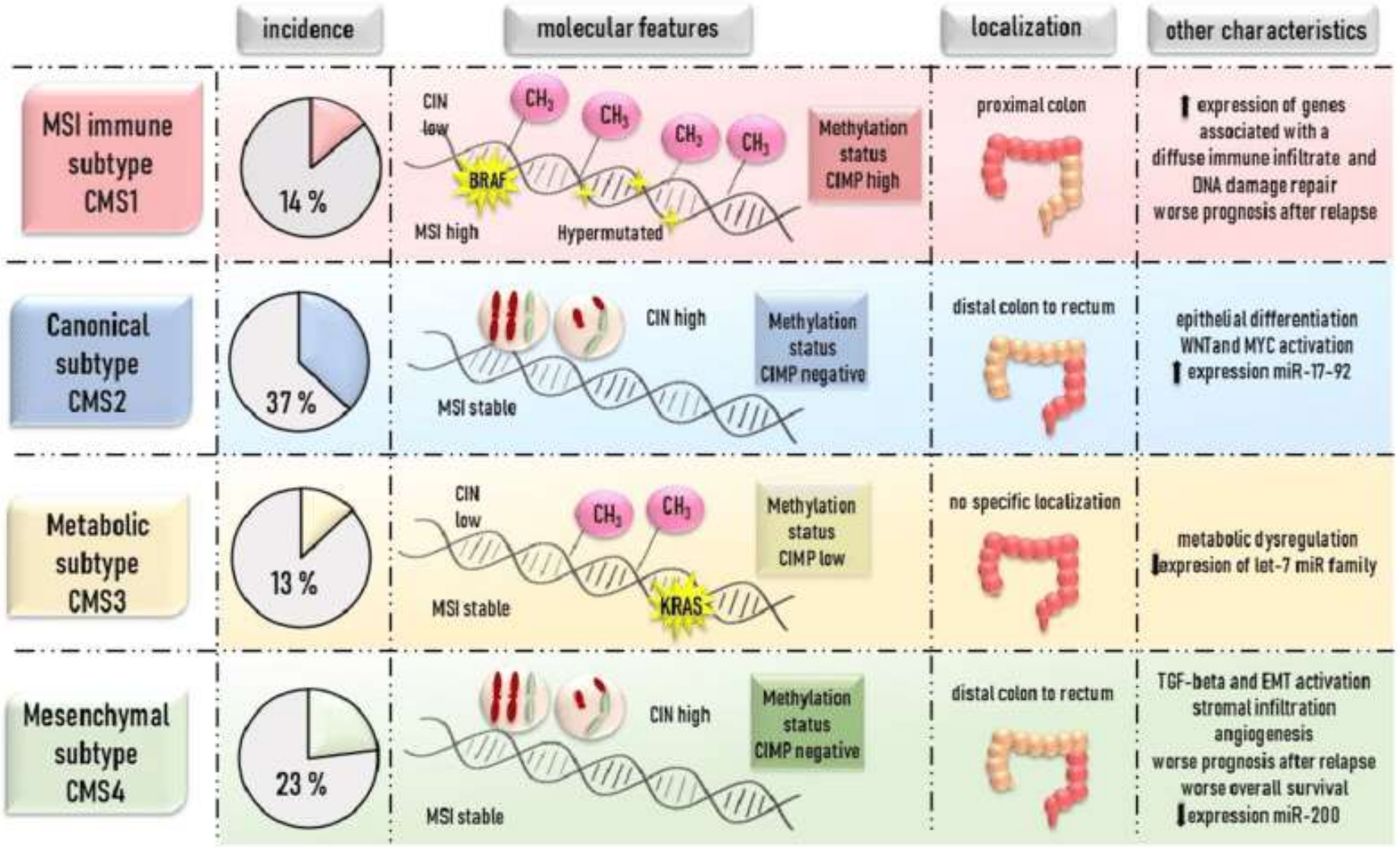
- **MSI immune [CMS1]**
- **canonical [CMS2]**
- **metabolic [CMS3]**
- **mesenchymal [CMS4]**

Right-sided colorectal cancers are more often **MSI-immune and metabolic tumours**.

Although the **sidedness and mutation status (*RAS* or *RAF*) of tumors are factors** that help to choose systemic treatments, the CMS classification is being explored in clinical trials as a prognostic or predictive marker.

The consensus molecular subtypes of colorectal cancer. *Nat Med.* 2015; **21**: 1350-1356

Colorectal cancer: CMS classidfication



Although the sidedness and mutation status (RAS or RAF) of tumors are factors that help to choose systemic treatments, the CMS classification is still being explored in clinical trials as a prognostic or predictive marker.

Colorectal cancer

Left-sided versus right-sided disease

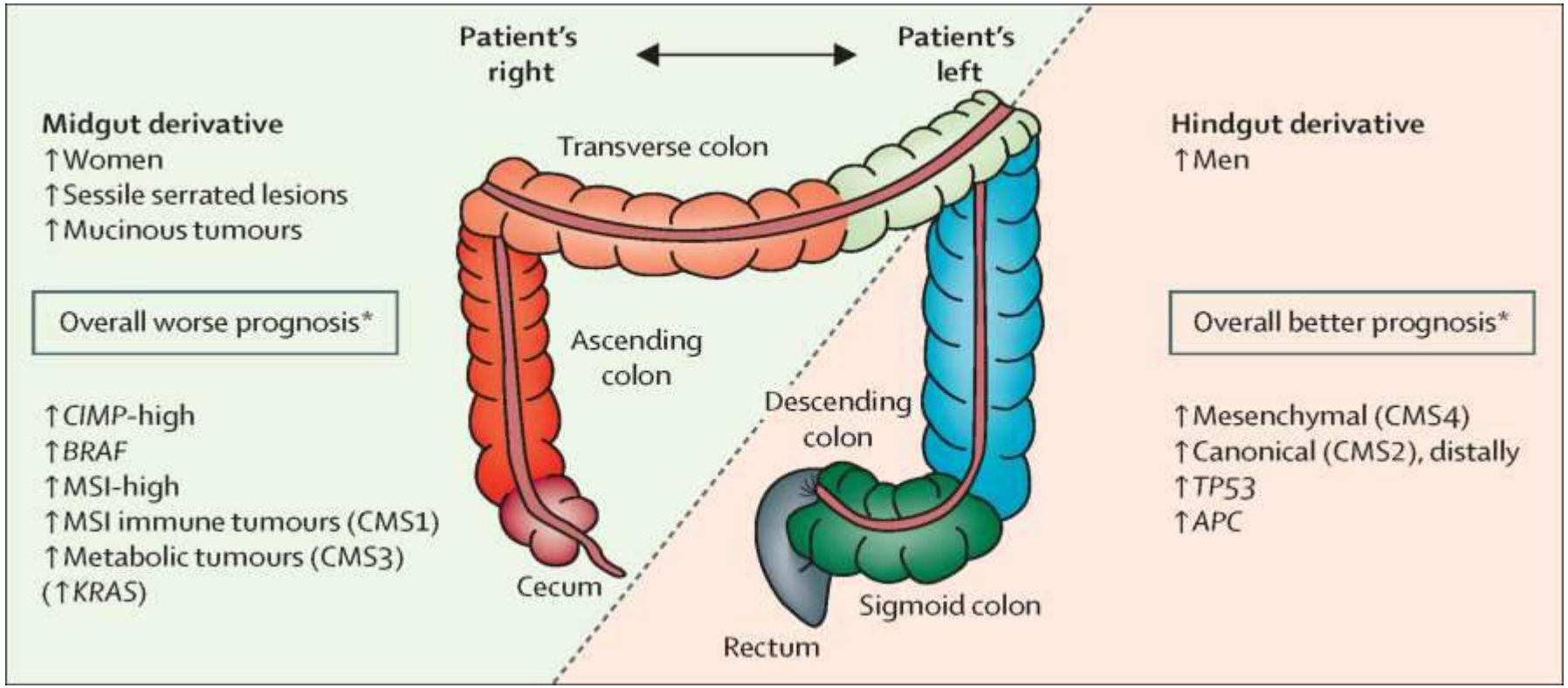
Molecular features of **right-sided (proximal)** colon cancers **are different** when compared **with left-sided (distal)** colon cancers and rectal cancers.

Right-sided colorectal cancers are more often **MSI-immune and metabolic tumours (CMS1 and CMS3**)

Colorectal cancer

Left-sided versus right-sided disease

Apart from molecular differences, embryological, biological, and anatomical differences exist between left-sided and right-sided colorectal cancer.
Sidedness has a key role, particularly **in the metastatic setting and is increasingly being recognized as a predictive marker of response to anti-EGFR drugs.**

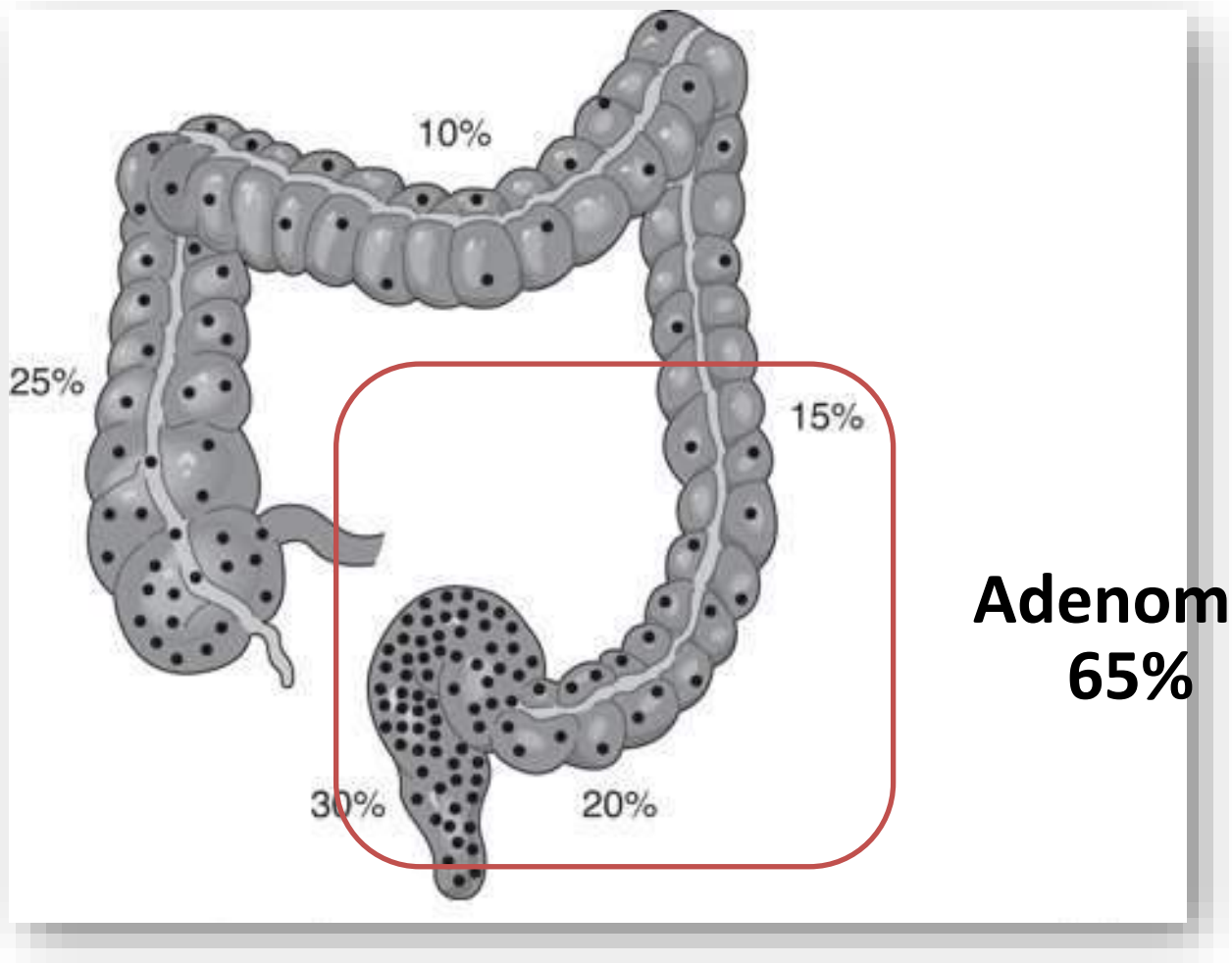


CRC and colon polyps

- Most colorectal cancers, regardless of etiology, arise from **adenomatous polyps**.
- A polyp is a grossly **visible protrusion** from the mucosal surface and may be classified pathologically as a **non-neoplastic hamartoma** (*juvenile polyp and others*), a hyperplastic mucosal proliferation (**serrated polyps**), or an **adenomatous polyp**.
- **Only adenomas** are clearly premalignant, and only a minority of such lesions becomes cancer.
- **Adenomatous polyps** may be found in the colons **of ~30% of middle-aged and ~50% of elderly people;** however, <1% of polyps ever become malignant. Most polyps produce no symptoms and remain clinically undetected.

CRC and colon polyps

10% Sessile Serrated Adenomas (SSA)



Adenoma 65%

Colon polyps: pathology classification

Polypoid lesions of the colon

Non neoplastic

Hamartomatous

Neoplastic

Adenomas:

Tubular 

Tubulovillous

Villous 

Serrated polyps:

Hyperplastic polyps (HP)

Sessile serrated adenomas (SSA)

Traditional serrated adenomas (TSA).

Colon polyps histopathology (1)
Non neoplastic

Hamartomatous polyp

They are growths, like tumours found in organs as a result of **faulty development**. They are normally made up of a mixture of tissues, **containing mucus-filled glands, with retention cysts, abundant connective tissue, and a chronic cellular infiltration of eosinophils**.

- **Hamartomatous polyps** are often found by chance; occurring in syndromes such as Peutz-Jegher Syndrome or Juvenile Polyposis Syndrome.
- **Peutz-Jeghers syndrome** is associated with polyps of the GI tract and also increased pigmentation around the lips, genitalia, buccal mucosa feet and hands. People are often diagnosed with Peutz-Jegher after presenting at around the age of 9 with an intussusception. The polyps themselves carry little malignant potential but because of potential coexisting adenomas there is a 15% chance of colonic malignancy.
- ***Juvenile polyps*** are hamartomatous polyps which often become evident before twenty years of age, but can also be seen in adults. They are usually solitary polyps found in the rectum which most commonly present with rectal bleeding. Juvenile polypoids characterised by the presence of more than five polyps in the colon or rectum, or numerous juvenile polyps throughout the gastrointestinal or any number of juvenile polyps in any person with a family history of juvenile polyposis. People with juvenile polyposis have an increased risk of colon cancer.
- **Inflammatory polyp**

  These are polyps which are associated with inflammatory conditions such as UC and CD

Colon polyps histopathology : adenomas (2)

Benign neoplastic polyps: Adenomas

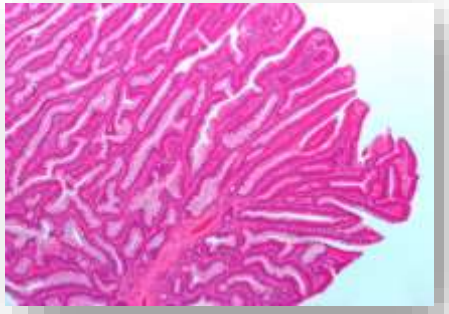
Tubular adenoma

An adenoma is tumor glandular tissue, that has not (yet) gained the properties of a cancer. The common adenomas of the colon are the: **tubular, tubulovillous, villous.**

The villous subdivision are associated with the highest malignant potential because they generally have the largest surface area.

This is because the villi are projections into the lumen and hence have a bigger surface area).

However, **villous adenomas are no more likely than tubular or tubulovillous adenomas to become cancerous if their sizes are all the same.**

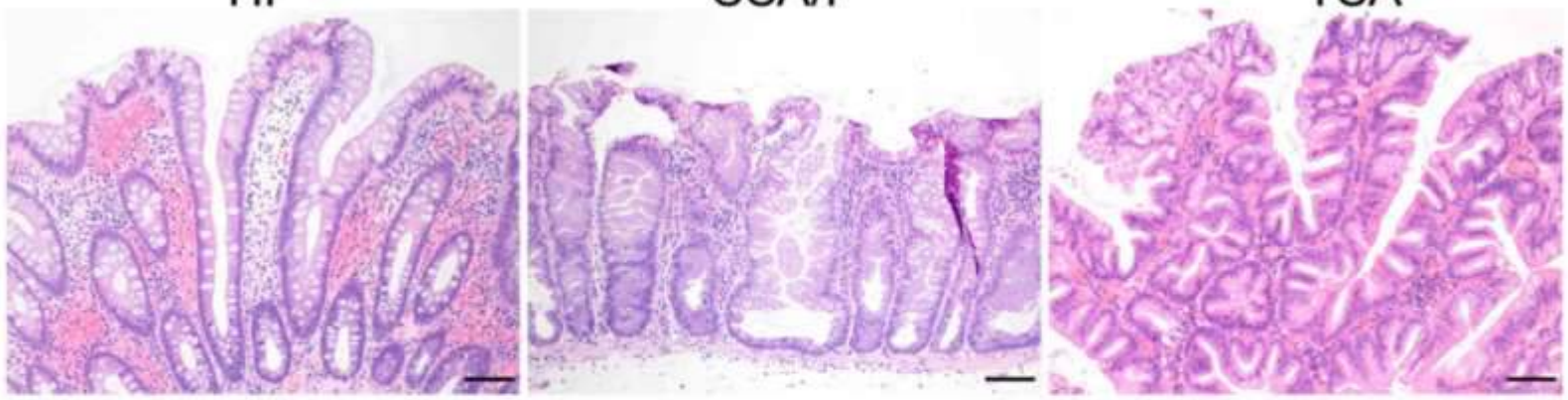


Villous adenoma

Colon polyps histopathology (3)

Serrated polyps of the large intestine **consist of those that display a lumen with a serrated or stellate architecture. The serrated polyps family includes: the hyperplastic polyps (HP),** the **sessile serrated adenomas** (**SSA**) and the **traditional serrated adenomas (TSA).**

A



B

Diagnostic criteria of SSA/P from WHO classification (2010)
1. Crypt dilation
2. Irregular branching crypts (inverted T- and/or L-shaped crypts)
3. Excess serration at the base of crypts
If straight crypt (HP-like) account for less than half of the lesion and more than two of three contiguous crypts demonstrate feature of SSA/P (1-3 in upper list), the lesion should be classified as SSA/P.

Colon polyps histopathology:serrated pathway

Non neoplastic

Hyperplastic polyps

Most hyperplastic polyps are found in the distal colon and rectum. They have no malignant potential, which means that they are no more likely than normal tissue to eventually become a cancer.

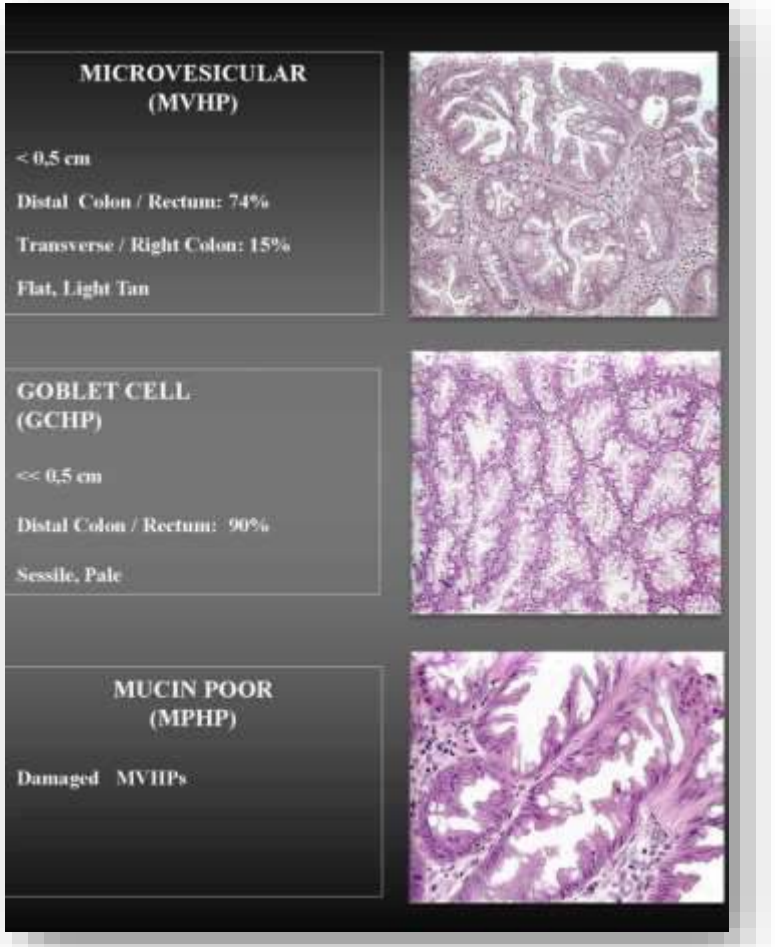
Hyperplastic polyps are serrated polyps.

Hyperplastic polyps have three histologic patterns patterns of growth:

- **microvesicular**
- **goblet cell**
- **mucin poor**

Athough thought to exhibit no malignant potential it has been shown that hyperplastic polyps on the right side of the colon do exhibit a malignant potential.

This occurs through multiple mutations which effect the DNA-mismatch-repair pathways. As such DNA mutations during replication are not repaired. This leads to microsatellite instability which can eventually lead to malignant transformation in polyps on the right side of the colon.

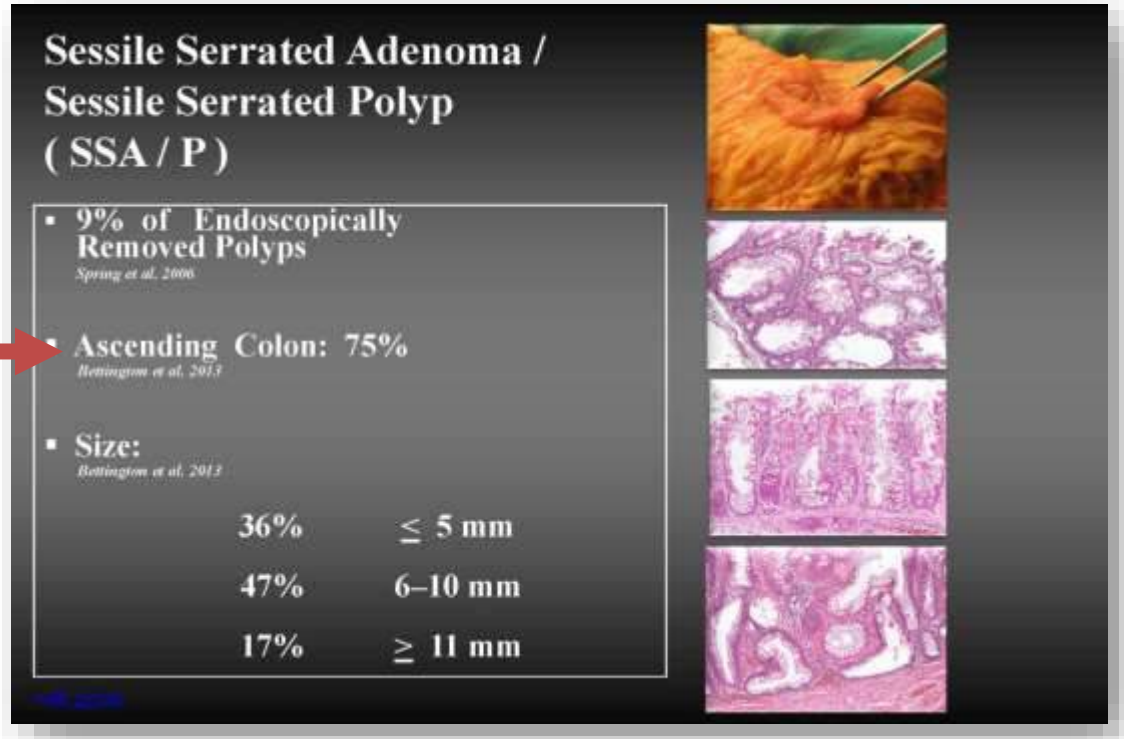


Serrated polyposis syndrome according to the definition proposed by the World Health Organization.

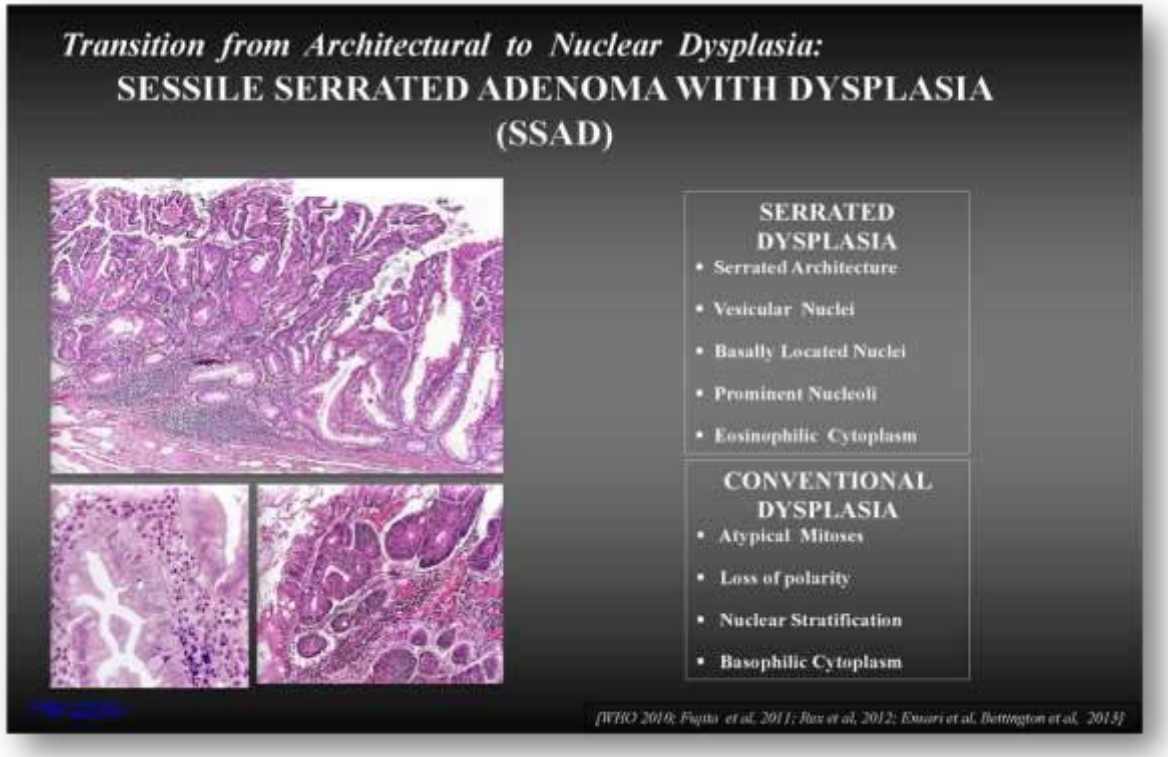
- ≥ Five serrated polyps proximal to the sigmoid colon, of which two are ≥10 mm in size
- Any number of serrated polyps proximal to the sigmoid colon in an individual who has a first degree relative with serrated polyposis syndrome
- ≥ 20 Serrated polyps distributed throughout the colon, regardless of size

Colon polyps histopathology: serrated pathway

Sessile serrated adenoma (SSA)

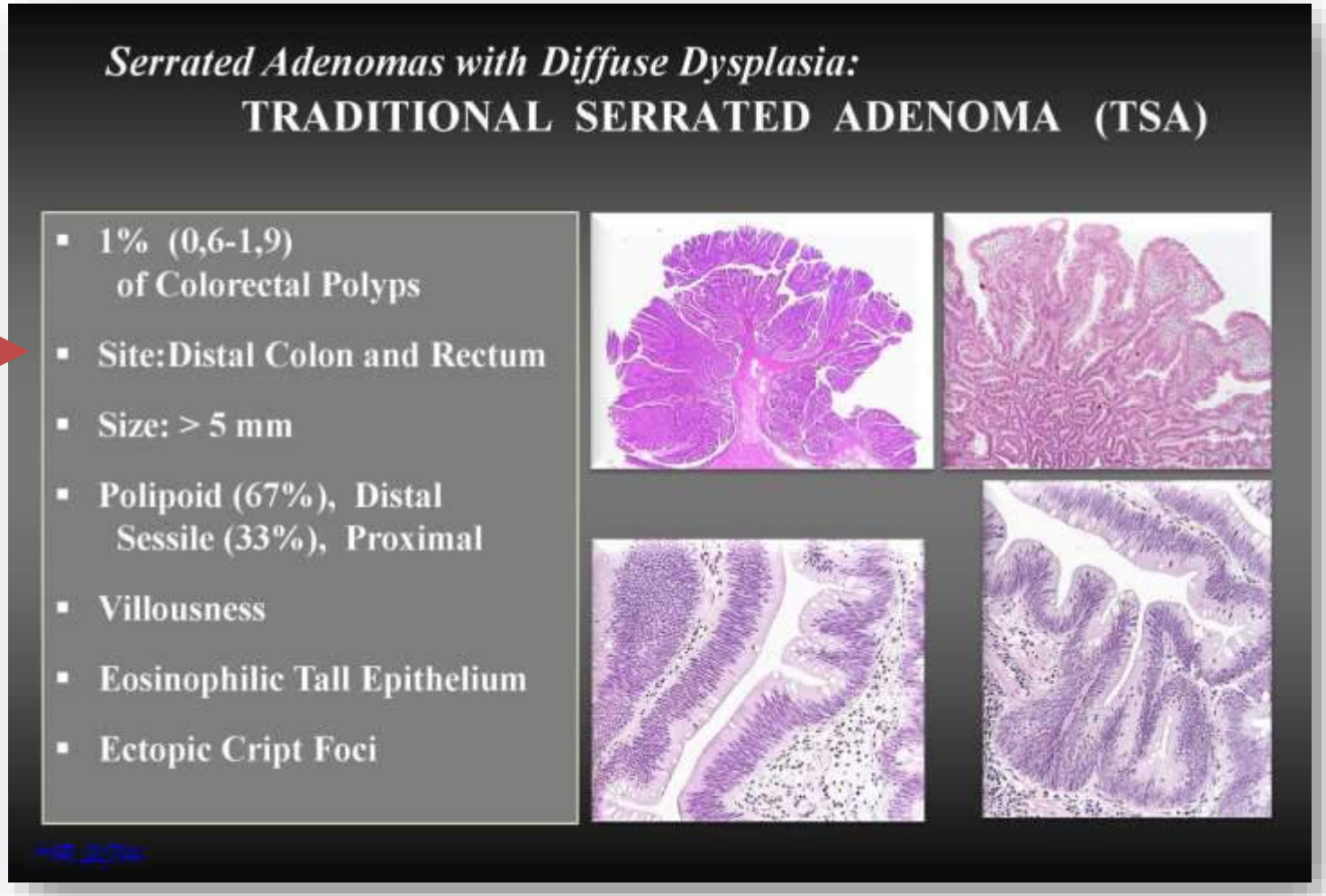


SSA with dysplasia



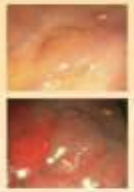
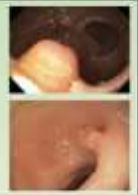
Colon polyps histopathology: serrated pathway

Traditional serrated adenoma (TSA)

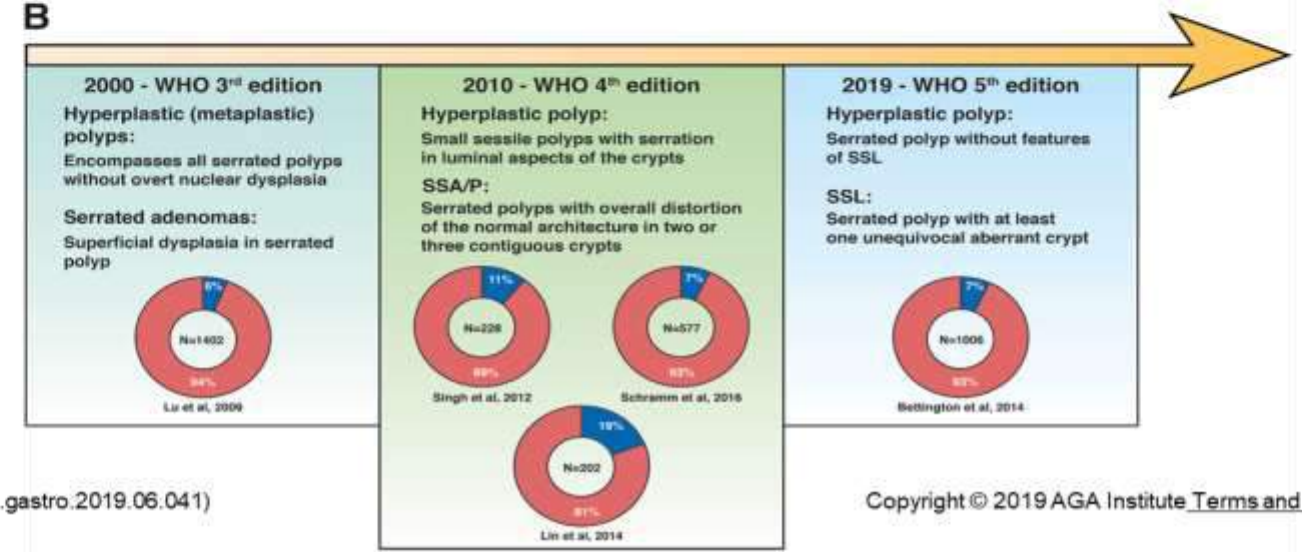


Colon polyps histopathology: Serrated pathway

A

Features	Hyperplastic polyps (HPs)	Sessile serrated lesions (SSLs)	Traditional serrated adenomas (TSAs)
Clinical characteristics	• Prevalence: 20%–30% • Size: Usually small or diminutive (≤ 5mm) • Morphology: Flat or sessile	• Prevalence: 5%–15% • Size: Usually larger than HPs, mean diameter= 5–7mm • Morphology: Flat (45%) or sessile	• Prevalence: <1% • Size: Usually larger than SSLs • Morphology: Polypoid or pedunculated
Location	 70%–80% distal	 75%–90% proximal	 Mostly distal
Endoscopic appearance	White light: • Pale or same color as surrounding mucosa • Round or oval shape • Flatten with insufflation • Absent or fine, lacy vessels Narrow band imaging: • NICE type 1 • Uniform dark or white spots 	White light: • Mucus cap • Ring of debris • Cloud-like surface • Irregular shape Narrow band imaging: • NICE type 1 • WASP criteria • Dark spots in crypts 	White light: • Erythematous • Multilobulated • "Pine cone" appearance • Type IV-S pit pattern Narrow band imaging characterisitics not well defined 
Histopathology	Microvesicular HP (MVHP): • Narrow, uniform basal crypt • Serrated upper crypt • Eosinophilic mucin droplets in cytoplasm  Goblet cell rich HP (GCHP): • Goblet cells predominate epithelium • Less serrated than MVHP 	• Serration extending to base of crypts • Dilated and inverted "T" or boot shaped crypts • Crypt branching 	• Pseudostratification • Villous pattern with stretched or penciliate nuclei • Eosinophilic predominant • Ectopic crypts 

B



Gastroenterology 2019 157949-966.e4DOI: (10.1053/j.gastro.2019.06.041)

Colon polyps: risk for CRC

Malignant potential is associated with degree of dysplasia and lesion size

Type of polyp (e.g. vilous adenoma):

Tubular Adenoma: 5% risk of cancer
Tubulovillous adenoma: 20% risk of cancer
Villous adenoma: 40% risk of cancer
Serrated*

Size of polyp and number

<1 cm =<2% risk of cancer
1 cm=10%risk of cancer
2 cm=15%risk of cancer

A polyp which is greater than 0.5 cm needs to be treated

Colon polyps: risk for CRC

TABLE 126-1 Histologic Types of Adenomas and Their Features

Type of Adenoma	Size of Adenoma* (%)			Degree of Dysplasia† (%)		
	<1 cm	1-2 cm	>2 cm	Mild	Moderate	Severe
Tubular	77	20	4	88	8	4
Tubulovillous	25	47	29	58	26	16
Villous	14	26	60	41	38	21

*Adapted from Muto T, Bussey HJR, Morson BC. The evolution of cancer of the colon and rectum. Cancer 1975; 36:2251-70.
†Adapted from Konishi F, Morson BC. Pathology of colorectal adenomas: A colonoscopic survey. J Clin Pathol 1989; 35:830-41.

TABLE 126-3 Relation of Adenoma, Histology, and Degree of Dysplasia to the Incidence of Invasive Carcinoma, by Adenoma Size

Adenoma Size (cm)	Histology (% with Invasive Carcinoma)			Degree of Dysplasia (% with Invasive Carcinoma)		
	Tubular	Tubulovillous	Villous	Mild	Moderate	Severe
<1	1	4	10	0.3	2	27
1-2	10	7	10	3	14	24
>2	35	46	53	42	50	48

Adapted from Muto T, Bussey HJR, Morson BC. The evolution of cancer of the colon and rectum. Cancer 1975; 36:2251-70.

Colon polyps symptoms

In the large majority of cases colon polyps **cause no symptoms**.
Sometimes, however, there may be signs and symptoms
such as:

- Rectal bleeding
- Occult bleeding (anemia)
- Changes in the bowel habit (constipation, diarrhea or narrowing of the stool).
- Pain or obstruction (rare)

Colon polyps diagnosis

Nearly all colon cancers develop from polyps, but the polyps grow slowly, usually over a period of years.

Screening tests play a key role in detecting polyps before they become cancerous.

These tests can also help find colorectal cancer in its early stages, when you have a good chance of recovery.

- **Fecal Fecal blood test (immunochemical quantitative).**
- **Colonoscopy (flexible sigmoidoscopy)**
- Barium enema.
- Computerized tomographic colonography (virtual colonoscopy).
- Stool DNA testing.
- Genetic testing.

Colon polyps diagnosis

Colorectal Cancer Screening Recommendations

Risk level	Action	Age	Strength of recommendation	Evidence grade
Average risk	Start screening	45 years	Conditional	Very low
	Screen	50 to 75 years	Strong	Moderate
	Stop screening	> 75 years	Conditional	Very low
One or more first-degree relatives with colon cancer or advanced polyps	Start screening	40 years or 10 years before age of youngest relative at time of diagnosis	Conditional	Very low

Colon polyps endoscopic glossary

Colon polyps endoscopic classification

Terms	
Diminutive	Lesion size ≤5 mm
Small	Lesion size 6–9 mm
Large	Lesion size ≥20 mm
Polypoid	Lesion protrudes from mucosa into lumen, includes pedunculated and sessile
Pedunculated (0-Ip)	Lesion attached to mucosa by stalk; the base of lesion is narrow
Sessile (0-Is)	Lesion not attached to mucosa by stalk; the base and top of the lesion have the same diameter
Non-polypoid	Lesion has little to no protrusion above the mucosa. Includes superficial elevated, flat, and depressed.
Superficial elevated (0-IIa)	Lesion height <2.5 mm above normal mucosa; sometimes defined as height less than one-half of the lesion diameter
Flat (0-IIb)	Lesion without any protrusion above mucosa
Depressed (0-IIc)	Lesion with base that is lower than the normal mucosa
Laterally spreading tumor (LST)	Laterally growing superficial neoplasm (instead of upward or downward growth) ≥10 mm in size
LST-granular-homogenous (LST-G-H)	LST polypoid type that corresponds to Paris subtype 0-IIa
LST-granular-nodular mixed (LST-G-NM)	LST type that corresponds to combination of Paris subtype 0-IIa and 0-Is
LST-non-granular-flat elevated (LST-NG-FE)	LST non-polypoid type corresponds to Paris subtype 0-IIa
LST-non-granular-pseudodepressed (LST-NG-PD)	LST non-polypoid type corresponds to combination of Paris subtype 0-IIa and 0-IIc
NICE type 1	Serrated class includes hyperplastic and sessile serrated lesions
NICE type 2	Adenomas
NICE type 3	Lesions with deep (>1000 μm) submucosal invasion
Cold snare polypectomy	Snare polypectomy without use of electrocautery

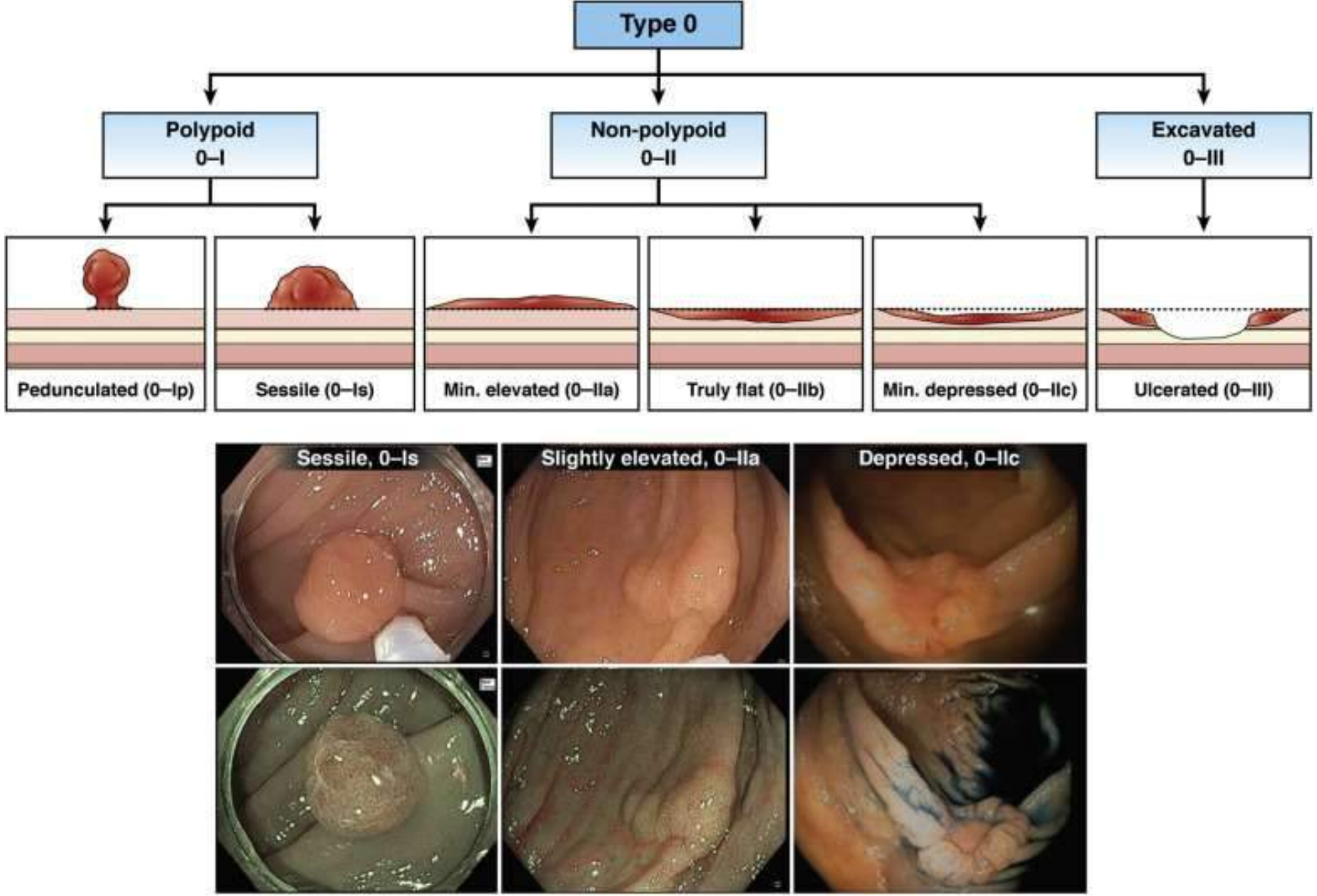


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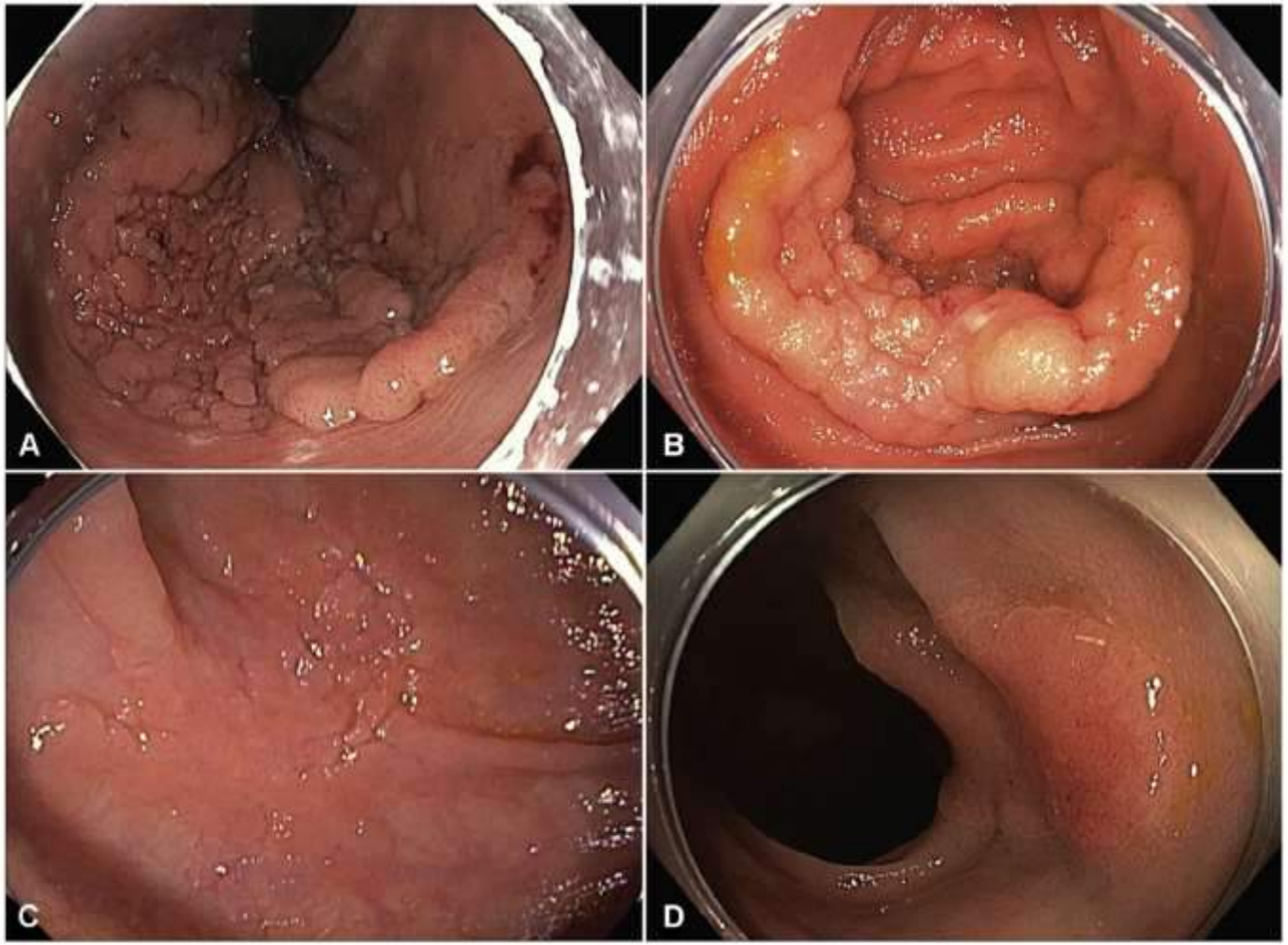
Figure 1. Paris Endoscopic Classification 2005 of superficial neoplastic lesions in the colon and rectum.

Lateral spreading tumors (LTS)

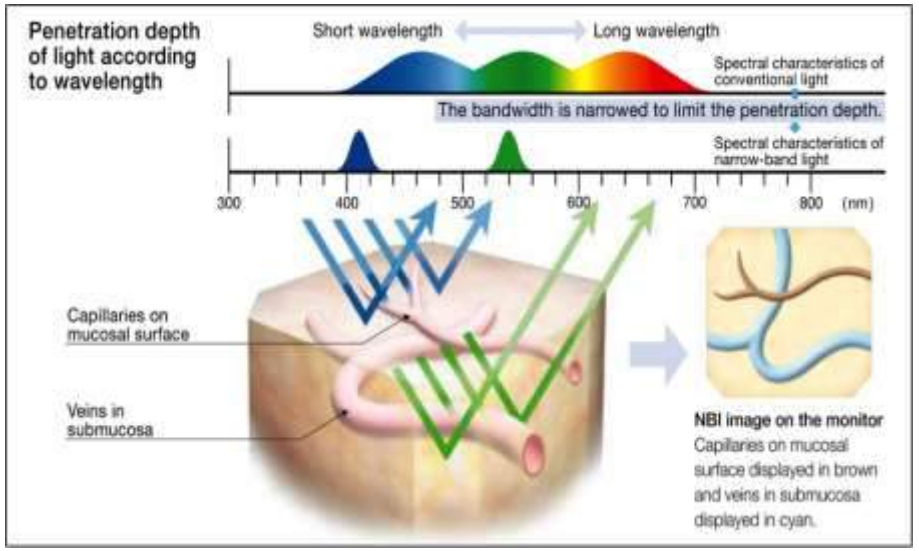


GASTROINTESTINAL ENDOSCOPY Volume 91, No. 3 : 2020

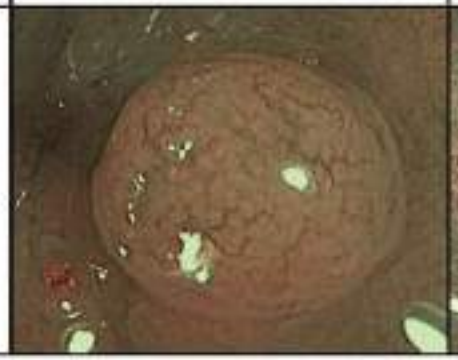
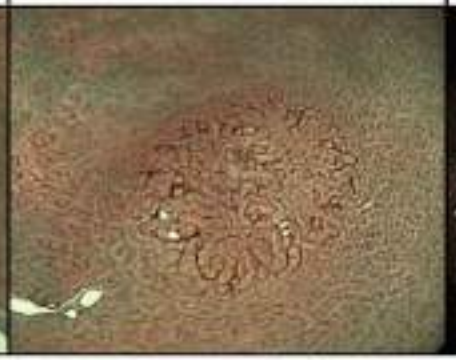
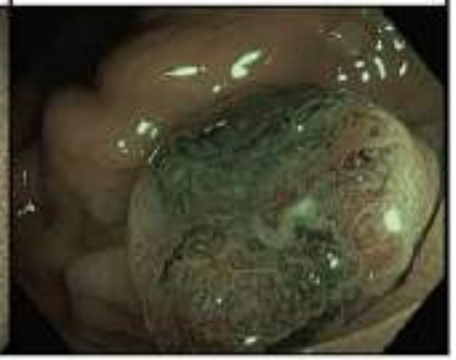
Lateral spreading lesions. Non-polypoid lesions 10 mm in diameter are referred to as laterally spreading tumors (LSTs). They have a low vertical axis and extend laterally along the luminal wall. LSTs are morphologically subclassified into granular type (LST-G) (A, B), which have a nodular surface, and non-granular type (LST-NG), which have a smooth surface (C, D)

Narrow band imaging (NBI)

La luce bianca viene sottoposta ad un filtro che seleziona esclusivamente due lunghezze d'onda (415 e 540 nm) corrispondenti alla luce blu ed alla luce verde. La luce così filtrata ha una particolare affinità ed un picco di assorbimento specifico per l'emoglobina, garantendo l'enfatizzazione dei vasi sanguigni che appaiono blu scuro se localizzati a livello epiteliale o verdi se localizzati a livello sottomucoso. La tecnologia NBI è stata ulteriormente ottimizzata in termini di qualità delle immagini accoppiandola al sistema dell'High Definition Television (HDTV).



Colon polyps: narrow band imaging (NBI)

	Type 1	Type 2	Type 3
Color	Same or lighter than background	Browner relative to background (verify color arises from vessels)	Brown to dark brown relative to background; sometimes patchy whiter areas
Vessels	None, or isolated lacy vessels may be present coursing across the lesion	Brown vessels surrounding white structures**	Has area(s) of disrupted or missing vessels
Surface pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular, or branched white structures** surrounded by brown vessels	Amorphous or absent surface pattern
Most likely pathology	Hyperplastic and sessile serrated lesions***	Adenoma****	Deep submucosal invasive cancer
			

Optical diagnosis of colorectal lesions, NICE classification. The diagnostic criteria for colorectal lesions using NBI as recommended in the NICE

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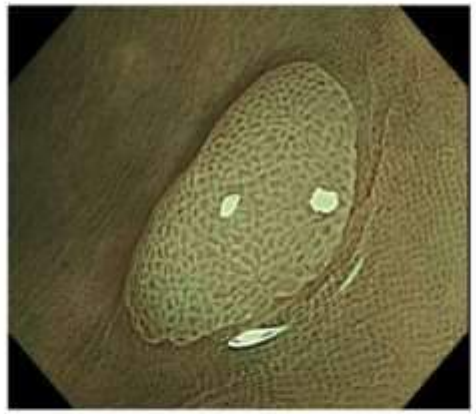
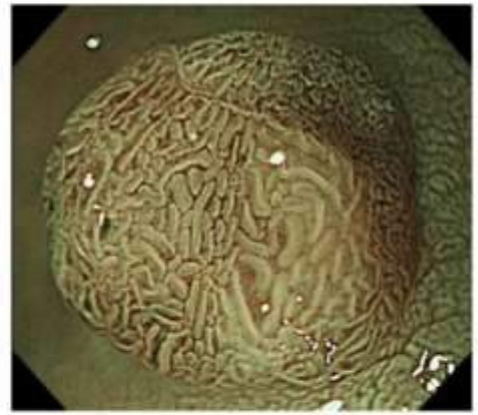
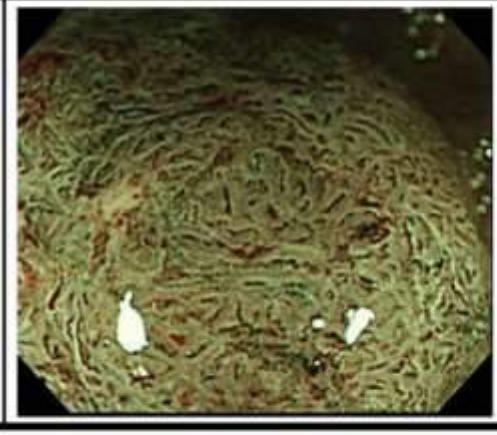
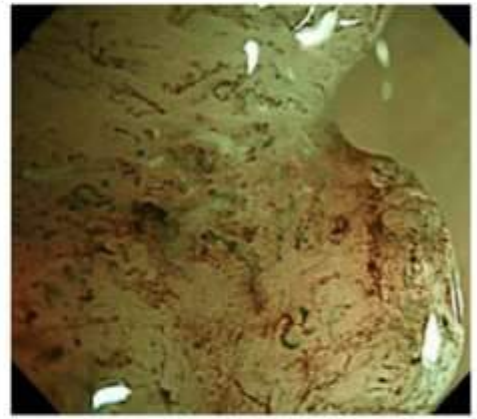
	Type 1	Type 2A	Type 2B	Type 3
Vessel pattern	・Invisible※1	・Regular caliber ・Regular distribution (meshed/spiral pattern)※2	・Variable caliber ・Irregular distribution	・Loose vessel areas ・Interruption of thick vessels
Surface pattern	・Regular dark or white spots ・Similar to surrounding normal mucosa	・Regular (tubular/branched/papillary)	・Irregular or obscure	・Amorphous areas
Most likely histology	Hyperplastic polyp/ Sessile serrated polyp	Low grade intramucosal neoplasia	High grade intramucosal neoplasia/ Shallow submucosal invasive cancer※3	Deep submucosal invasive cancer
Endoscopic image				

*1. If visible, the caliber in the lesion is similar to surrounding normal mucosa.

*2. Microvessels are often distributed in a punctate pattern and well-ordered reticular or spiral vessels may not be observed in depressed lesions.

*3. Deep submucosal invasive cancer may be included.

Endoscopic removal of colon polyps

- **Standard polipectomy**
  (Polipectomia endoscopica)

- **Endoscopic Mucosal Resection**
  (Mucosectomia Endoscopica)

- **Endoscopic Submucosal Dissection**
  (Dissezione sottomucosa endoscopica)

Endoscopic removal of colon polyps: terminology

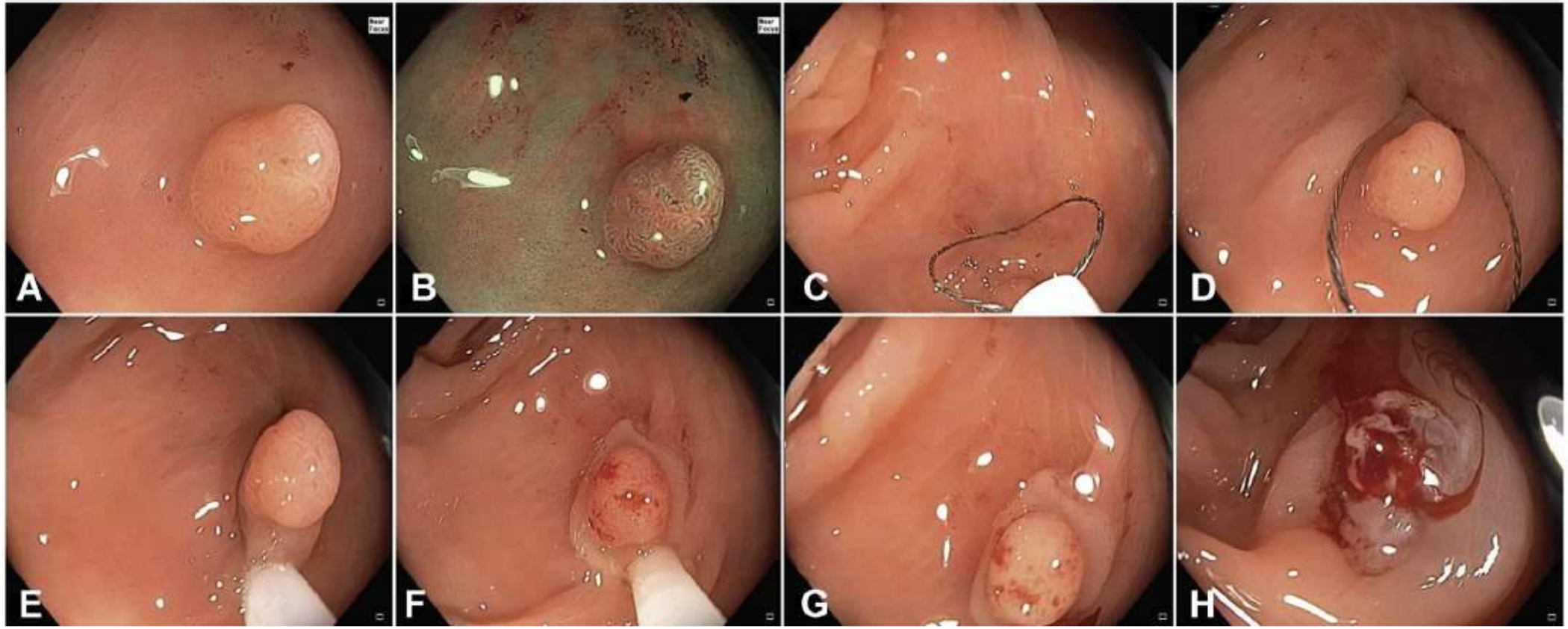
- **Endoscopic mucosal resection (ESR)** - Technique involving injecting solution into submucosal space to separate mucosal lesion from underlying muscularis propria; lesion can then be removed by snare

- **Endoscopic submucosal dissection (ESD)-** Technique involving lifting by submucosal injectant and using ESD knife to create incision around lesion's perimeter and to dissect through expanded submucosal layer for **en bloc resection**
- Hybrid ESD - Partial submucosal dissection followed by en bloc snare resection
- Endoscopic full thickness resection - Technique involving the use of a full-thickness resection device for lesions <30 mm

- **Cold or hot avulsion** - Variant of biopsy technique for resection of fibrous residual or recurrent tissue that is non-lifting ordifficult to capture with a snare. The hot avulsion technique uses endocut current (not coagulation current) and pulls the tissue away in the forceps as the current is applied.

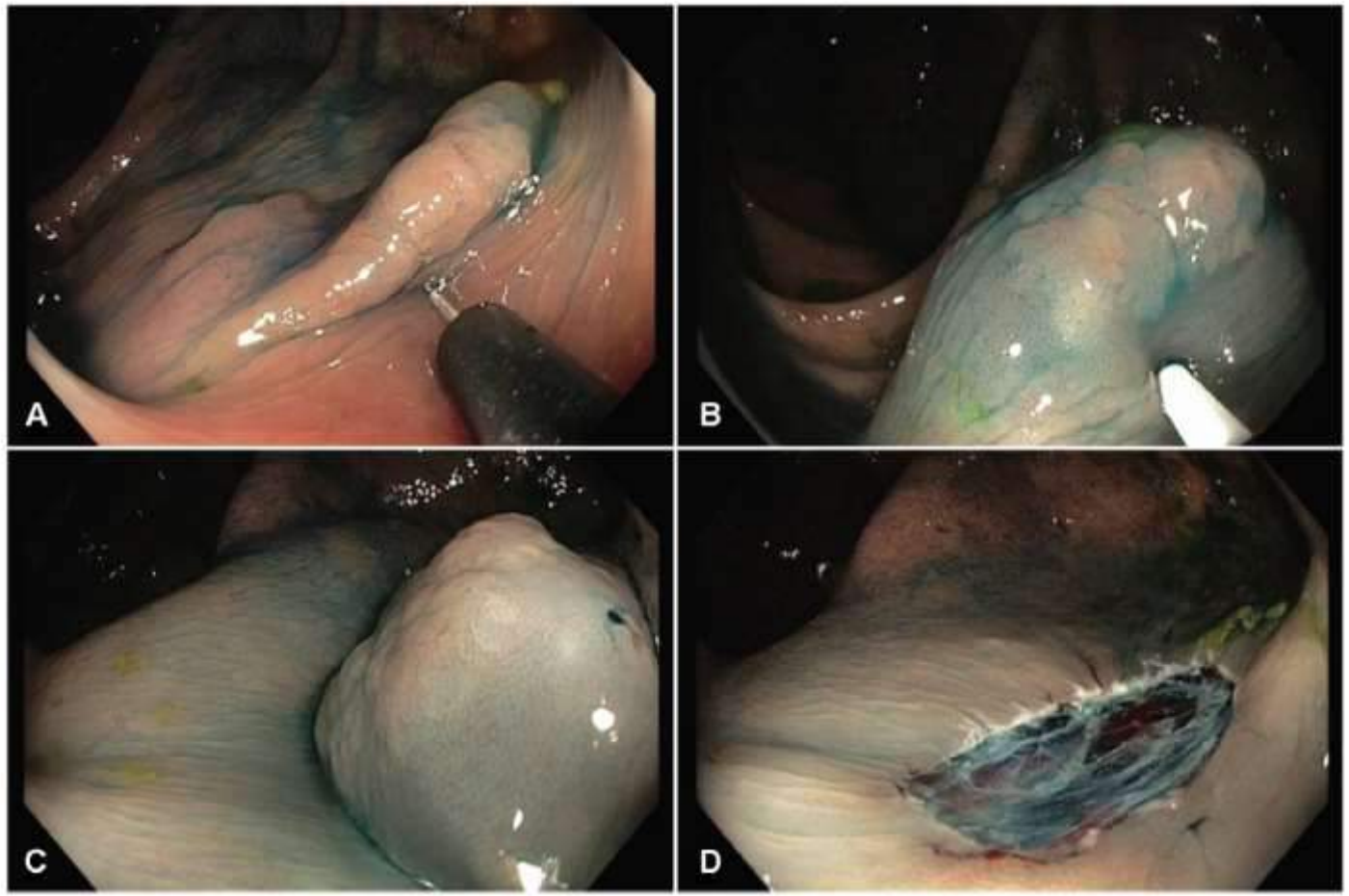
- **Argon plasma coagulatio**n - Ablative technique requiring use of ionization of argon gas by electrocautery to prevent deep
- tissue injury
- Snare tip soft coagulation - Ablative technique requiring use of a microprocessor-controlled generator capable of delivering fixed low-voltage output, which is capped at 19 volts to prevent deep tissue injury
- **Chromoendoscopy**- Application of dye to the colon mucosa or in the submucosal injectant for contrast enhancement to improve visualization of epithelial surface detail and resection plane

Standard polypectomy



Cold polypectomy technique. (A) Diminutive colon lesion in white light. (B) Lesion characterization as a diminutive colon adenoma with type 2 NICE features using NBI.

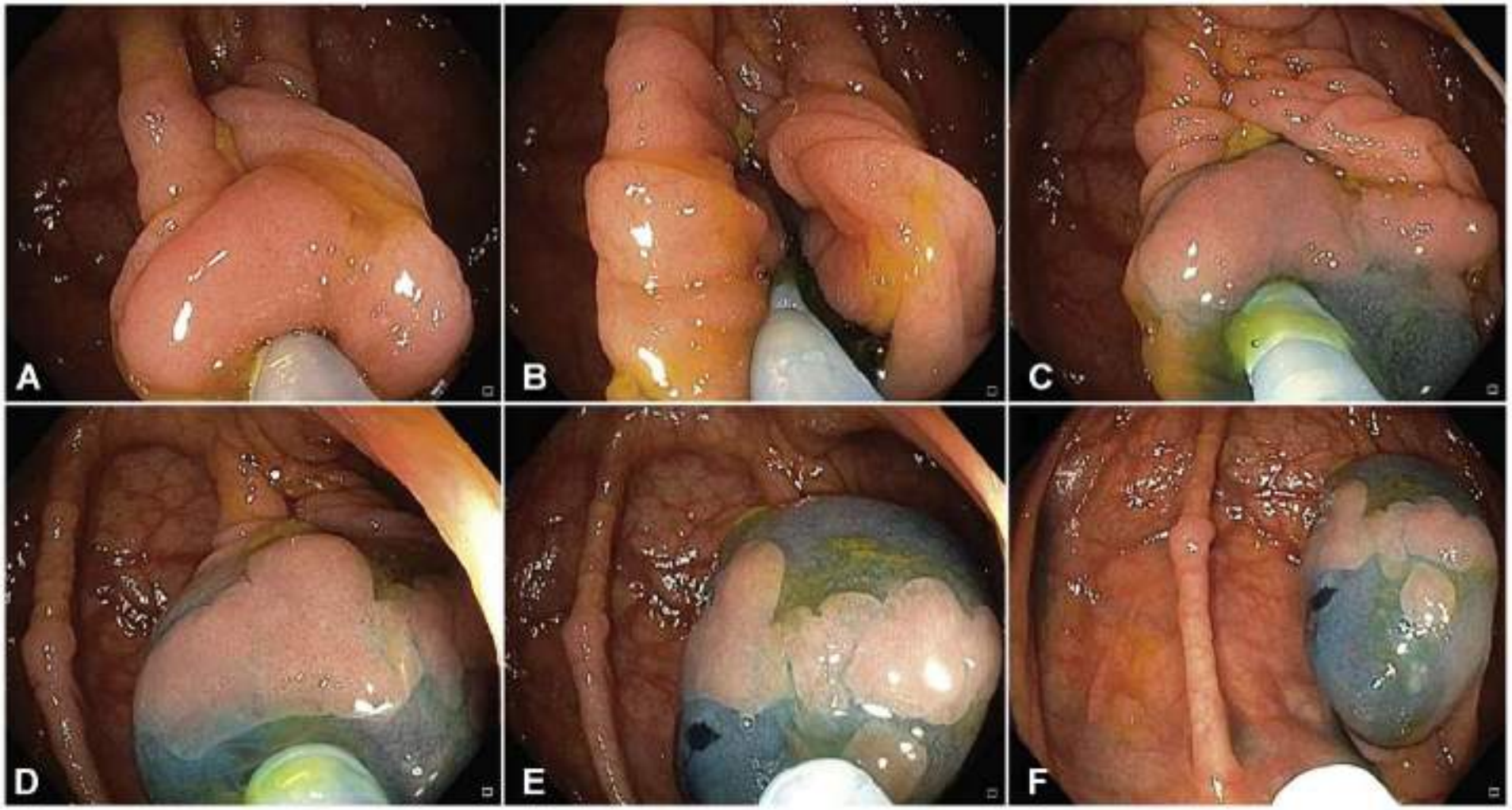
Endoscopic mucosal resection (ESR)



opic Submucosal Resection (ESR) part 1.mp4

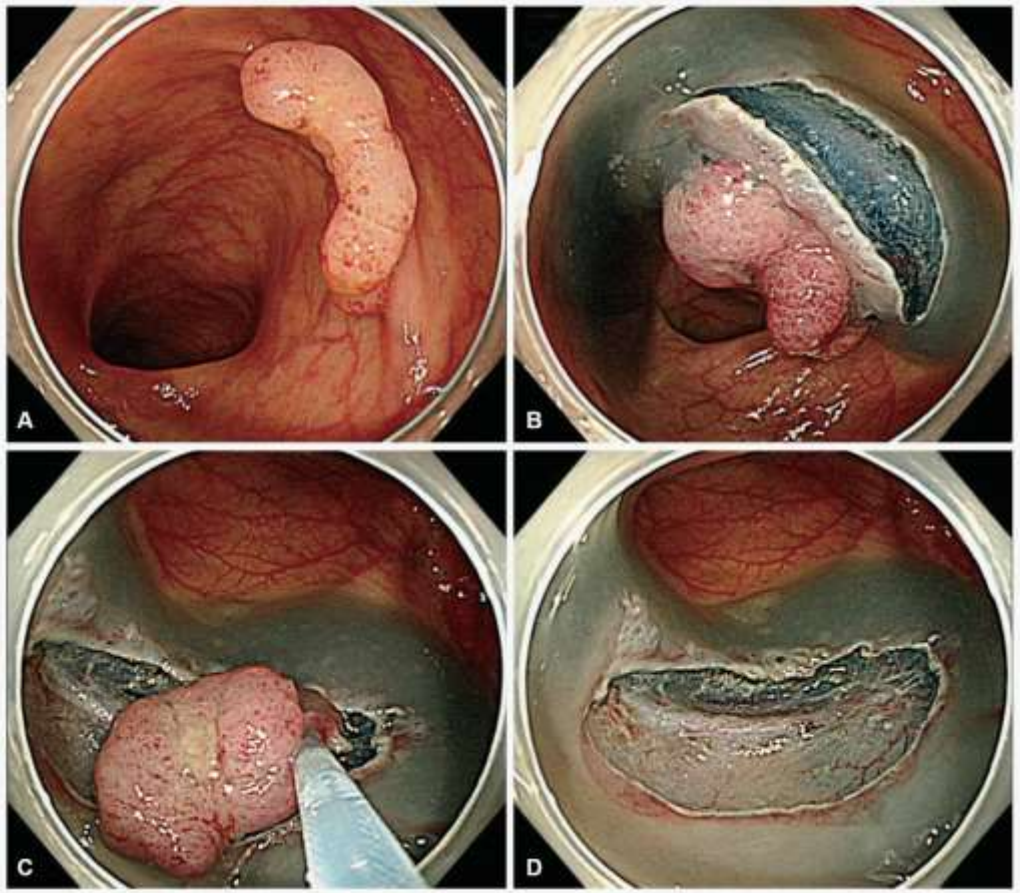
Inject-and-cut EMR. (A) A15-mm superficially elevated serrated–appearing lesion under white light with diluted indigo carmine solution. In preparation for resection, we ensure the targeted lesion to the 5–6 o'clock

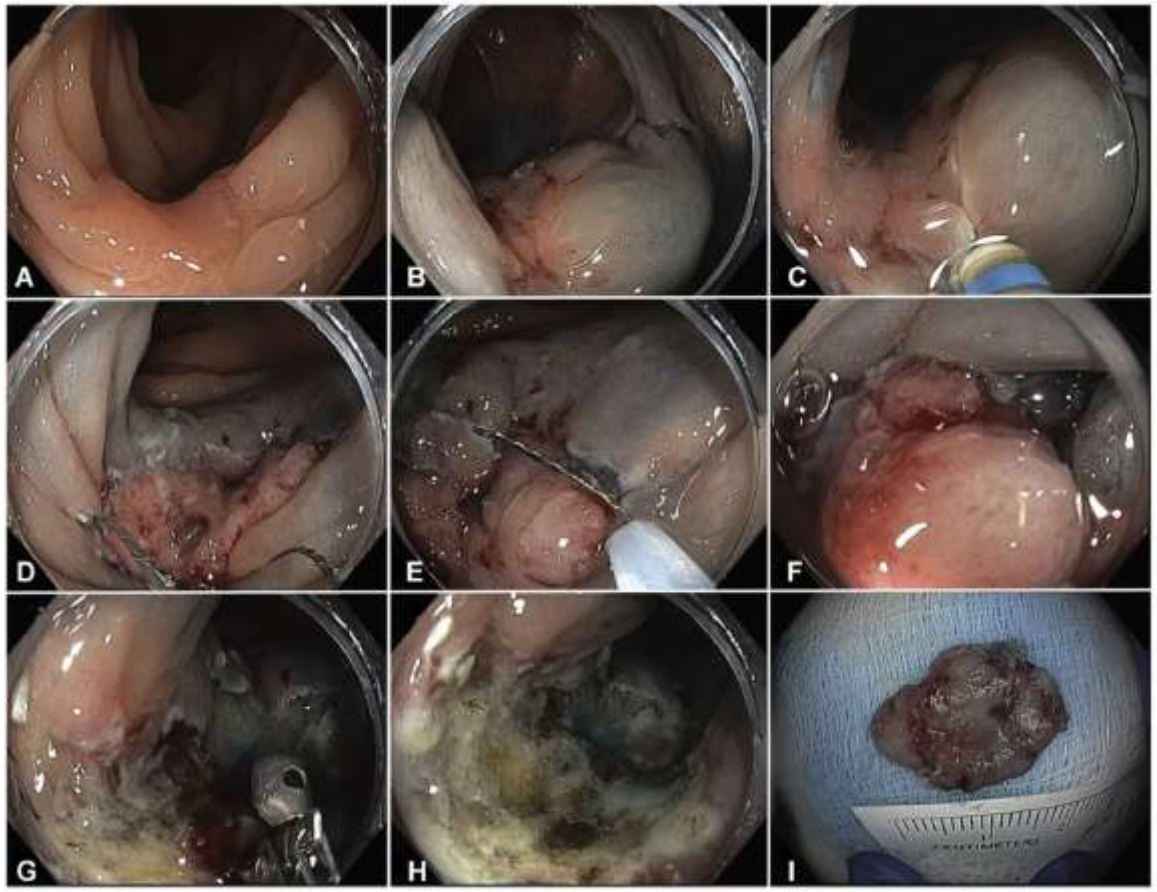
Endoscopic mucosal resection (ESR)



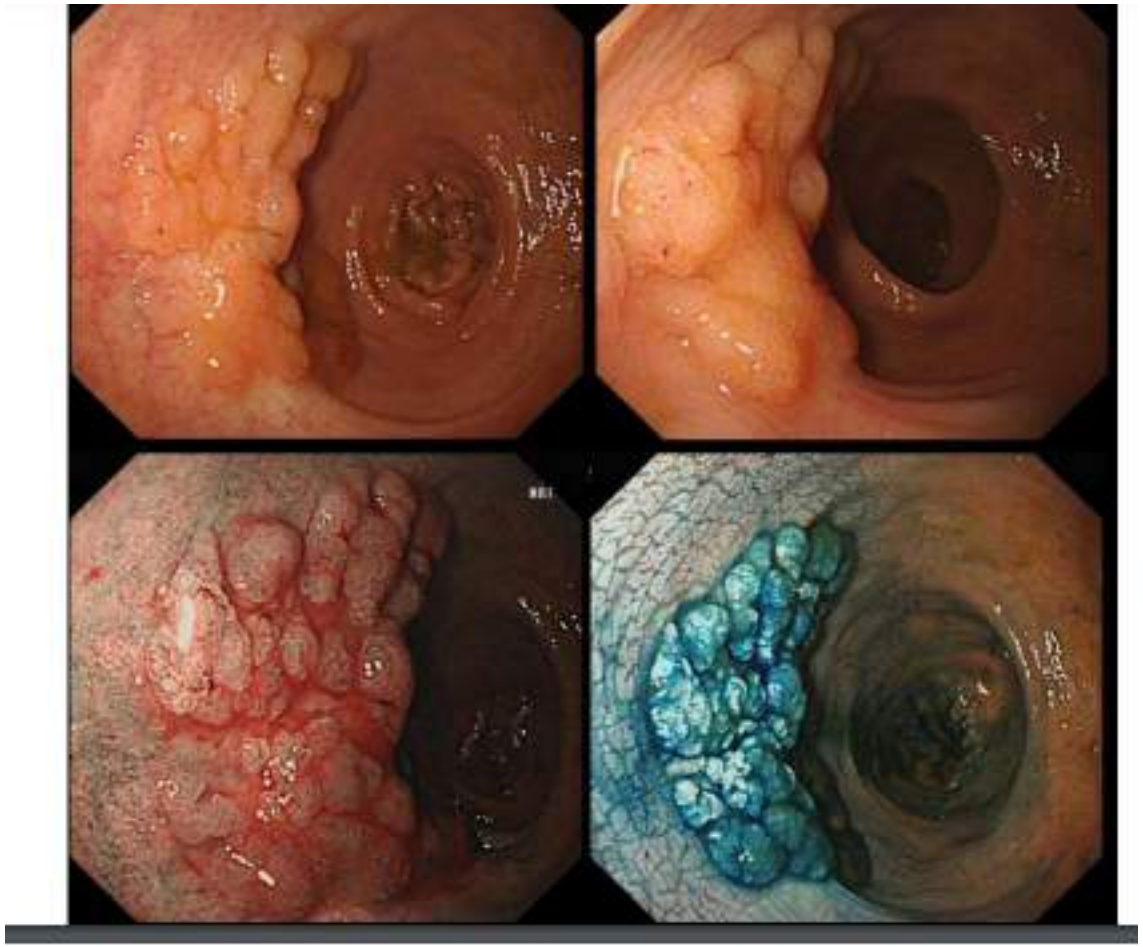
Inject-and-cut EMR. (A) A15-mm superficially elevated serrated–appearing lesion under white light with diluted indigo carmine solution. In preparation for resection, we ensure the targeted lesion to the 5–6 o'clock

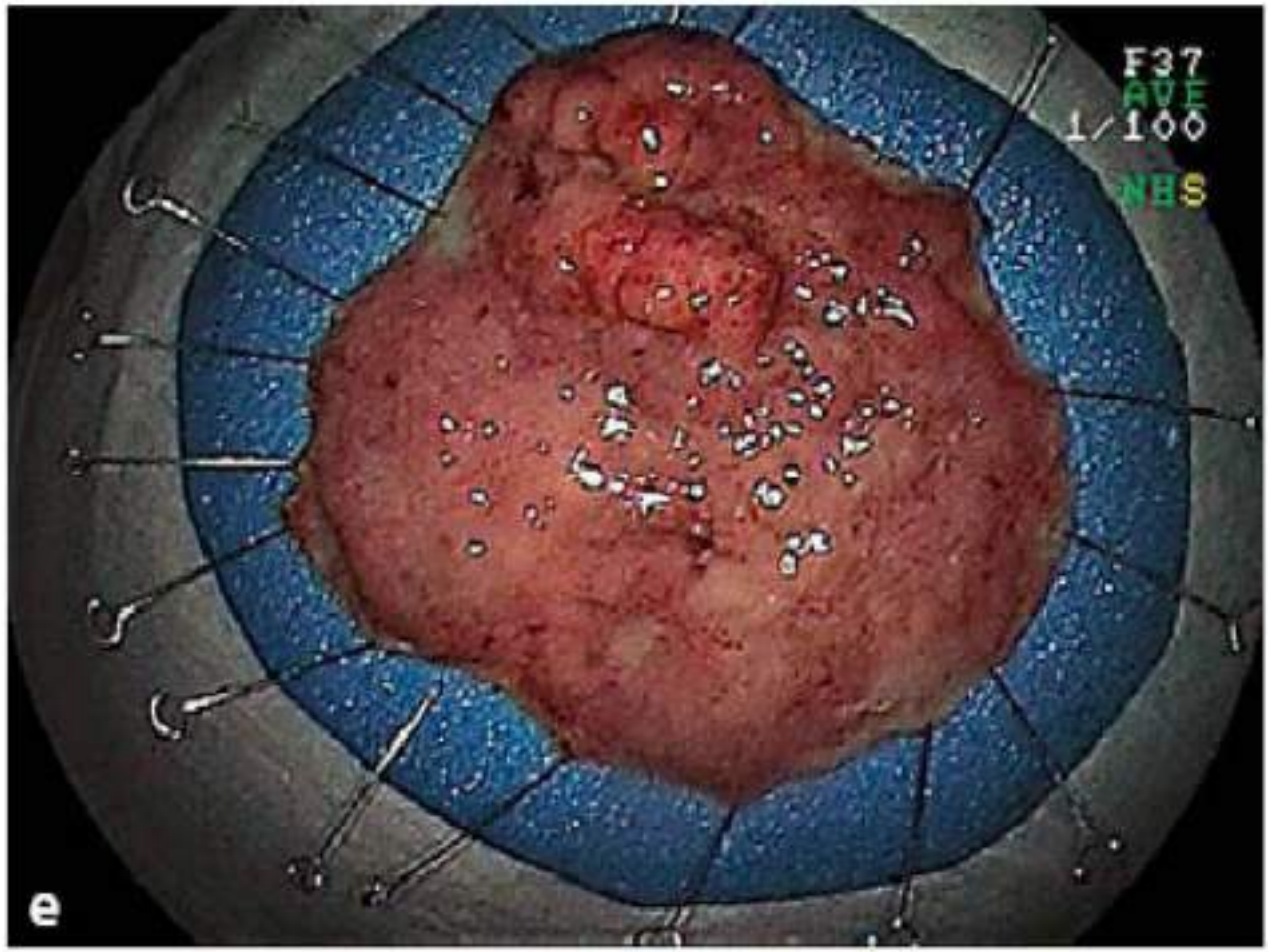
Endoscopic submucosal dissection (ESD)



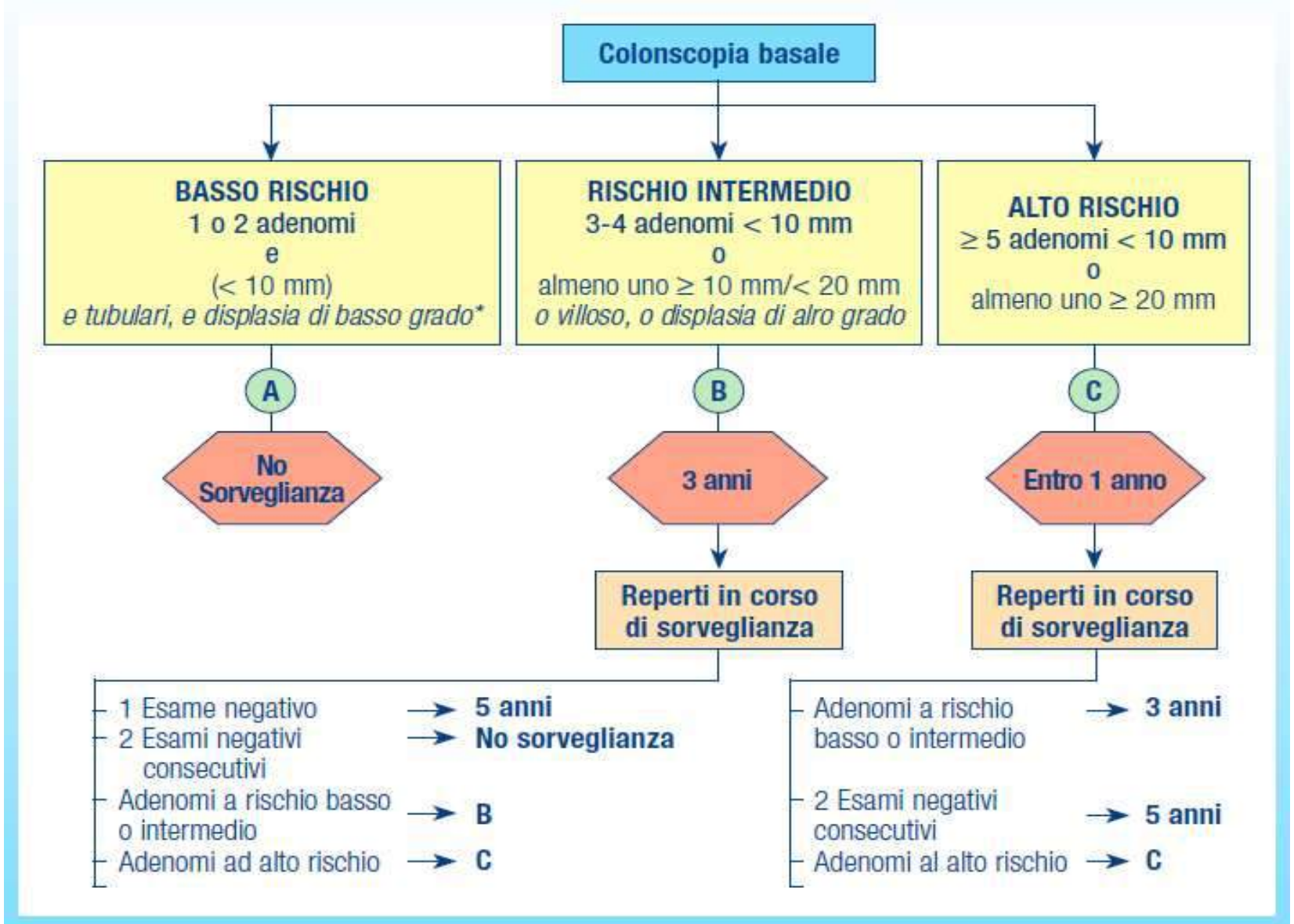


En bloc resection

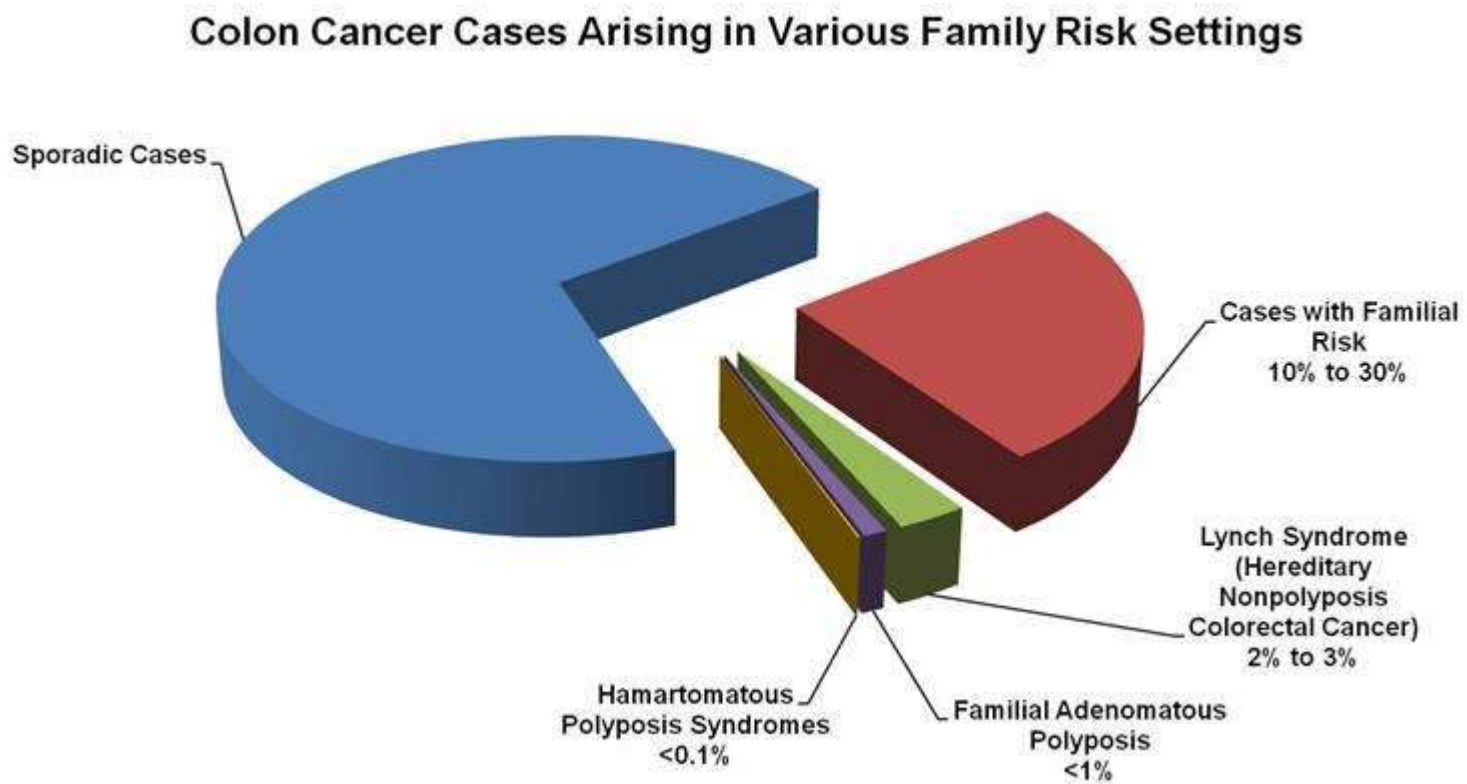




Follow up of patients with colon polyps



Colorectal cancer



Heritable (autosomal dominant) gastrointestinal polyposis syndromes

TABLE 126-11 Adenomatous Polyposis Syndromes

Syndrome	Gene Mutation	Polyps	Extraintestinal Abnormalities
Classic FAP	*APC* (usually truncated protein)	Colonic adenomas (thousands) Duodenal, periampullary adenomas Gastric fundic gland polyps Jejunal and ileal adenomas Ileal lymphoid polyps	Mandibular osteomas Dental abnormalities
Gardner variant of FAP	*APC*	Same as FAP	Osteomas (mandible, skull, long bones) CHRPE Desmoid tumors Epidermoid and sebaceous cysts Fibromas, lipomas Thyroid, adrenal tumors
Turcot variant of FAP	*APC* DNA MMR*	Colonic adenomas (sometimes fewer than in classic FAP)	Medulloblastoma Glioblastoma multiforme CHRPE
Attenuated FAP	*APC* 5′ and 3′ regions	Colonic adenomas (<100; proximal colon) Duodenal, periampullary adenomas Gastric fundic gland polyps	Mandibular osteomas (rare)
Familial tooth agenesis	*Axin2* (APC pathway)	Colonic adenomas Hyperplastic polyps	Agenesis of teeth
Bloom's syndrome	*BLM*	Colonic adenomas	Small stature Facial erythema/telangiectasia Male sterility Adenocarcinomas, leukemia, lymphoma
MUTYH polyposis	*MUTYH (MYH)*	Colonic adenomas (5-100) Duodenal polyposis Gastric cancer	CHRPE Osteomas

*May be more appropriately classified under hereditary nonpolyposis colon cancer (HNPCC) (see Chapter 127).
APC, adenomatous polyposis coli; CHRPE, congenital hypertrophy of the retinal pigment epithelium; FAP, familial adenomatous polyposis; MMR, mismatch repair; *MUTYH* (mutY homolog [*E. coli*]).

Heritable (autosomal dominant) gastrointestinal polyposis syndromes

TABLE 126-14 Familial Hamartomatous Polyposis Syndromes

Syndrome	Mutated Gene	Polyps	Location of GI Polyps	Other Features
Peutz-Jeghers syndrome	*STK11/LKB1*	Hamartomas with bands of smooth muscle in the lamina propria	Small intestine Stomach Colon	Pigmented lesions (mouth, hands, feet) Ovarian sex cord tumors Sertoli tumors of the testes Airway polyps Pancreatic cancer Breast cancer Colon and esophageal cancer
Juvenile polyposis	*MADH4, BMPR1A, ENG*	Juvenile polyps; also adenomas and hyperplastic polyps	Colon Small intestine Stomach	Colon cancer in some families Congenital abnormalities
Cowden's disease	*PTEN*	Hamartomas with disorganized muscularis mucosae	Stomach Colon	Trichilemmomas and papillomas Other hamartomas Benign and malignant breast disease Benign and malignant thyroid disease
Bannayan-Ruvalcaba-Riley syndrome	*PTEN*	Juvenile polyps	Colon	Macroencephaly; developmental delay
Neurofibromatosis	*NF1* *RET*	Neurofibromas	Small intestine Stomach Colon	von Recklinghausen's disease MEN IIB

MUTYH (**mutY DNA glycosylase**, earlier **mutY Homolog (E. coli)**) is a gene encoding a DNA glycosylase, MUTYH glycosylase, involved in oxidative DNA damage repair

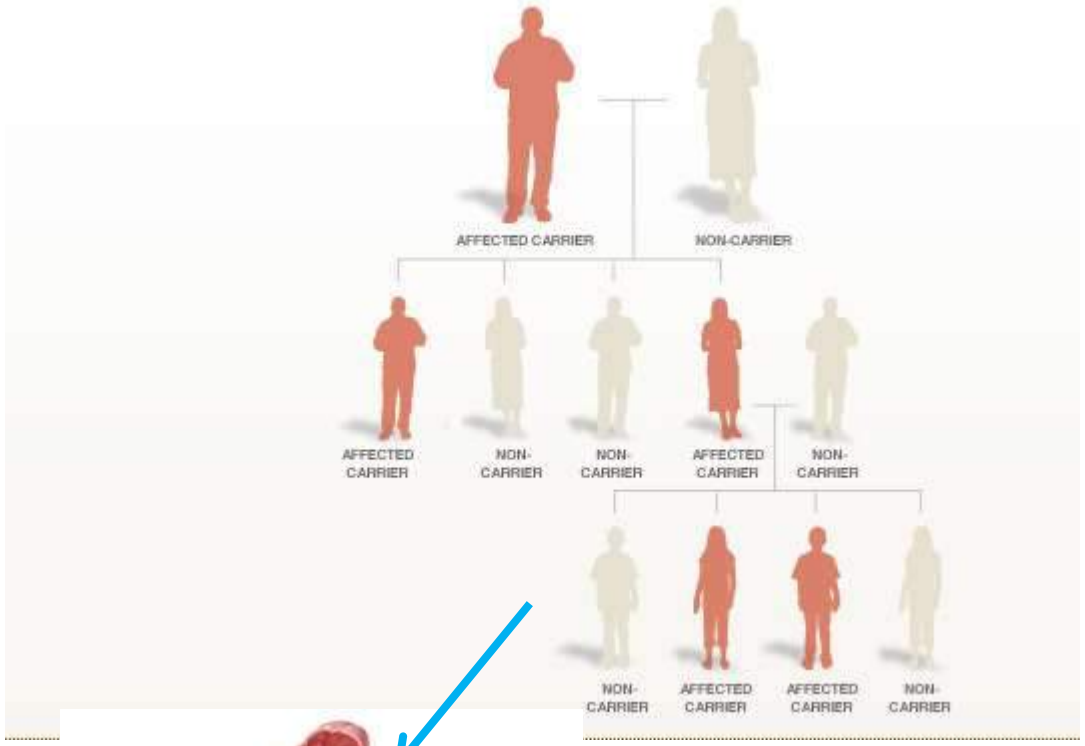
Heritable (autosomal dominant) gastrointestinal polyposis syndromes

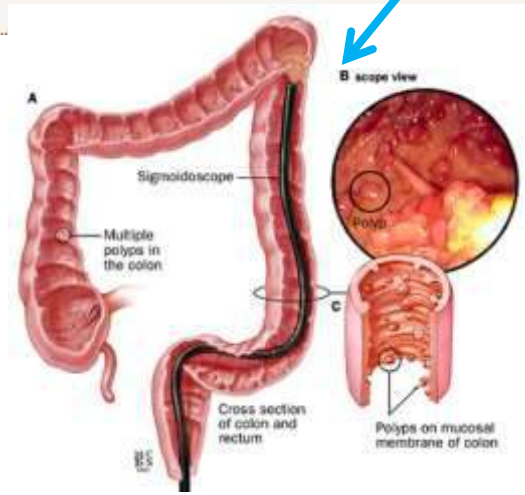
ESTIMATED RISK FOR COLON CANCER BY SYNDROME

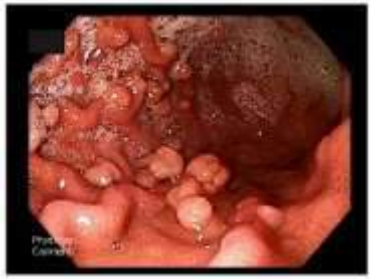
Syndrome	Gene(s)	Risk
FAP (familial adenomatous polyposis)	*APC*	90% by age 45
Attenuated FAP	*APC*	69% by age 80
Lynch (HNPCC)	*MLH1, MSH2, MSH6 PMS2, EPCAM*	40% to 80% by age 75
MUTYH-associated polyposis	*MUTYH*	35% to 53%
Peutz-Jeghers	*STK11*	39% by age 70
Juvenile polyposis	*BMPR1A, SMAD4*	17% to 68% by age 60

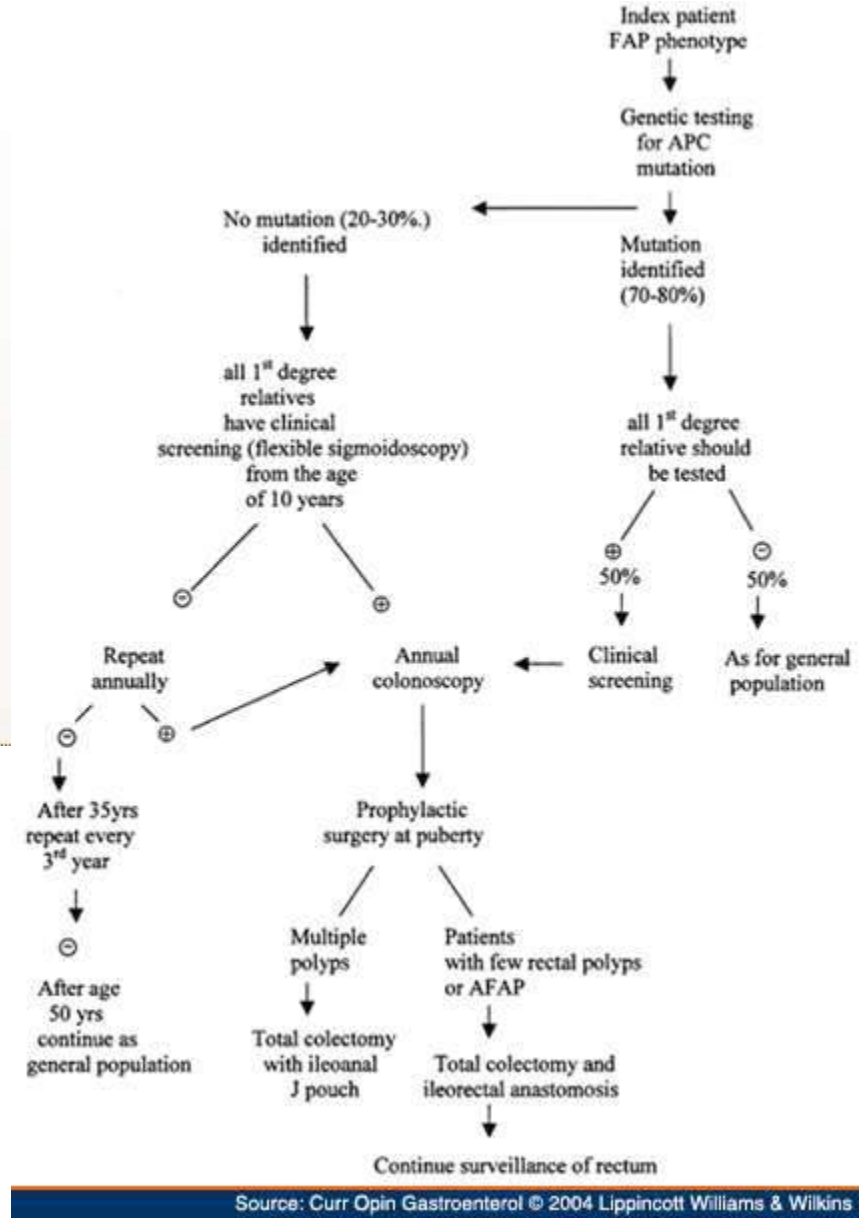
MUTYH (**mutY DNA glycosylase**, earlier **mutY Homolog (E. coli)**) is a gene encoding a DNA glycosylase, MUTYH glycosylase, involved in oxidative DNA damage repair

FAP autosomal dominant

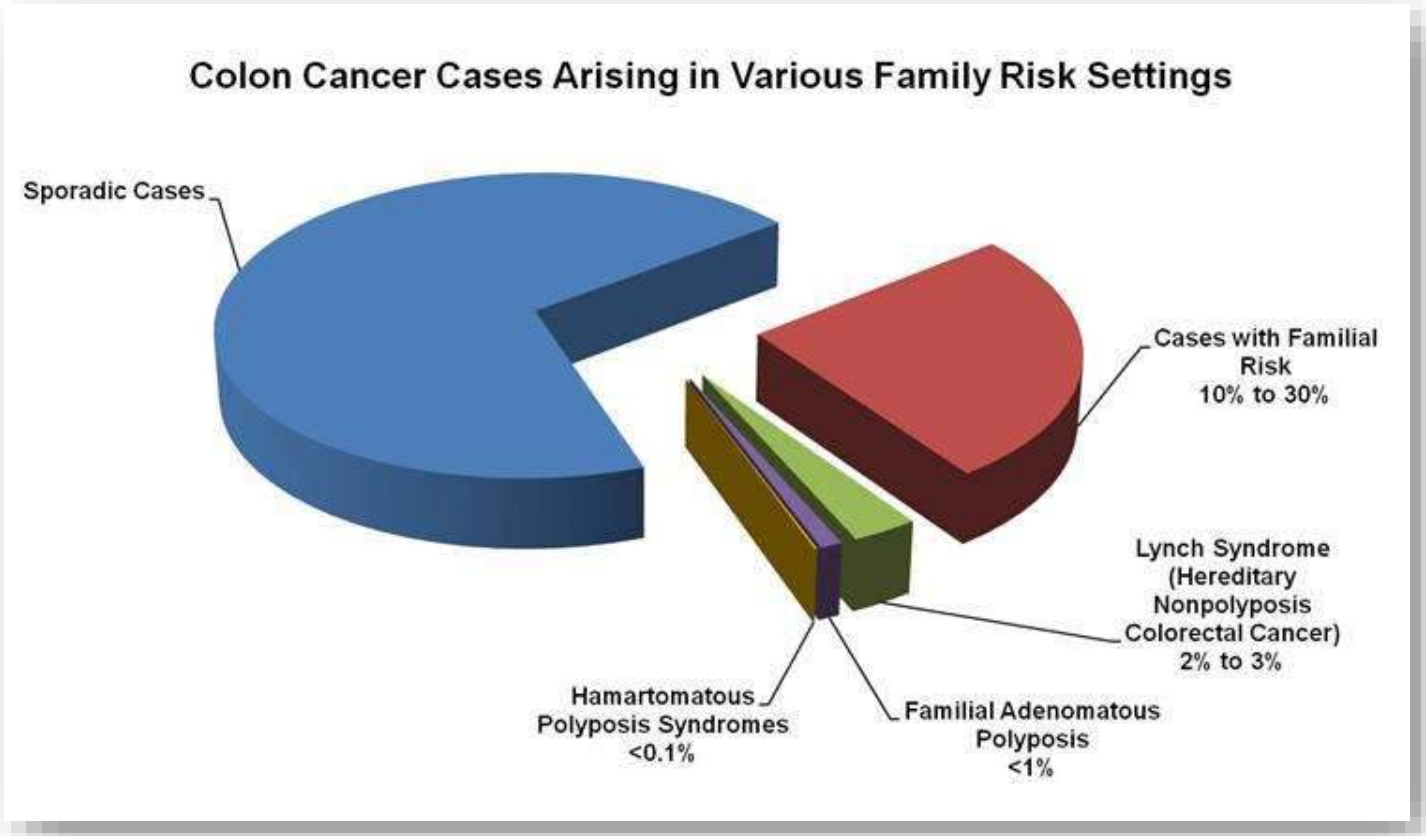








Sporadic cases of CRC



CRC risk factors

Factor		Relative Risk
Heredity and medical history		
Family history		
1 first-degree relative		2.2
> 1 first-degree relative		4
Relative with diagnosis before age 45		3.9
Inflammatory bowel disease		
Crohn's disease	colon	2.6
Ulcerative colitis	colon	2.8
Ulcerative colitis	rectum	1.9
Others		
Obesity (per 5-unit increase in BMI)		
Men	colon	1.3
	rectum	1.1
Women	colon	1.1
Alcohol consumption		1.1
Red meat consumption		1.3
Diabetes		1.3
Processed meat consumption		1.2

Source: Colorectal Cancer Facts and Figures, 2008–2010. Atlanta, American Cancer Society

BMI = body mass index

CRC screening

Programmi di screening del cancro del colon-retto

Rischio normale medio (età >50 anni, assenza di altri fattori di rischio)
ricerca sangue occulto annuale, rettosigmoidoscopia con strumento flessibile o
Colonscopia ogni 10 anni

Rischio moderato
- Storia di adenoma: colonscopia
- parenti di primo grado con CRC: **colonscopia all'età di 40 anni, o 10 anni prima se familiari hanno presentato il tumore in giovane età**
- parenti di primo grado con adenoma prima di 60 anni: **colonscopia all'età di 40 anni**

Rischio elevato
- poliposi familiare: **colonscopia a dieci anni di età e valutazione genetica**
- cancro in poliposi non familiare: **colonscopia a 20 anni e valutazione ogni 2 anni; dopo 40 anni, colonscopia ogni anno; valutazione genetica**

- malattie infiammatorie del colon: **colonscopia ogni 2 anni in RCU o Crohn-colite estese a tutto il colon**, della durata 8 anni; se colite ulcerosa o Crohn-colite sono limitate al colon sinistro, dopo 12 anni

CRC presenting symptoms

Symptoms depend on the anatomic location

- **Cancer in right colon** usually become larger than cancer in the left colon and synptoms are less specific **(fatigue, anemia, weight loss, intermittent bleeding)**

- **Cancer in the left co**lon **are more commonly linked to stool obstruction, abdominal pain & rectal bleeding**

- **Cancer from rectosigmoidal location** might have hematochezia, tenesmus, narrowing of stool caliber. **Anemia is less frequent. Rectal bleeding is common.**

CRC presenting symptoms

Symptoms depend on the anatomic location

- In general **abdominal pain** is seen in 44% of patients, change in bowel habits in 43%, blood in the stools or dark stools in 40%, weakness in about 20%, Iron deficiency anemia in 10% and weight loss in about 5%.

- **Symptoms can be of gradual onset or sudden such as when the tumor causes intestinal obstruction or perforation (a hole in the bowel wall).**

- About 20% of patients will have disease already spread to the liver at the time of diagnosis.

Common causes of rectal bleeding

Table 1. Causes of Acute Lower Gastrointestinal Bleeding in Adults.*

Cause	Percentage of Cases
Diverticulosis	30–65
Ischemic colitis	5–20
Hemorrhoids	5–20
Colorectal polyps or neoplasms	2–15
Angioectasias	5–10
Postpolypectomy bleeding	2–7
Inflammatory bowel disease	3–5
Infectious colitis	2–5
Stercoral ulceration	0–5
Colorectal varices	0–3
Radiation proctopathy	0–2
NSAID-induced colopathy	0–2
Dieulafoy's lesion	Rare

Colorectal cancer staging

CRC diagnosis and staging

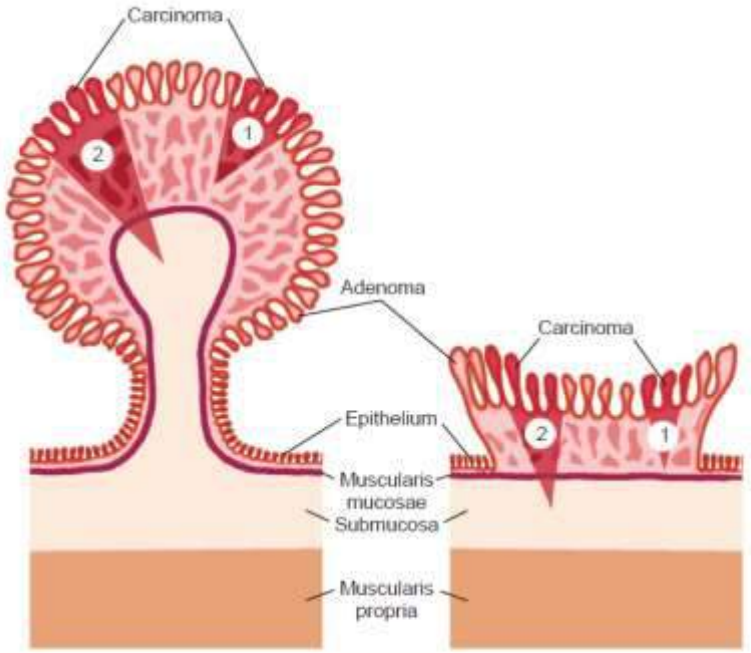
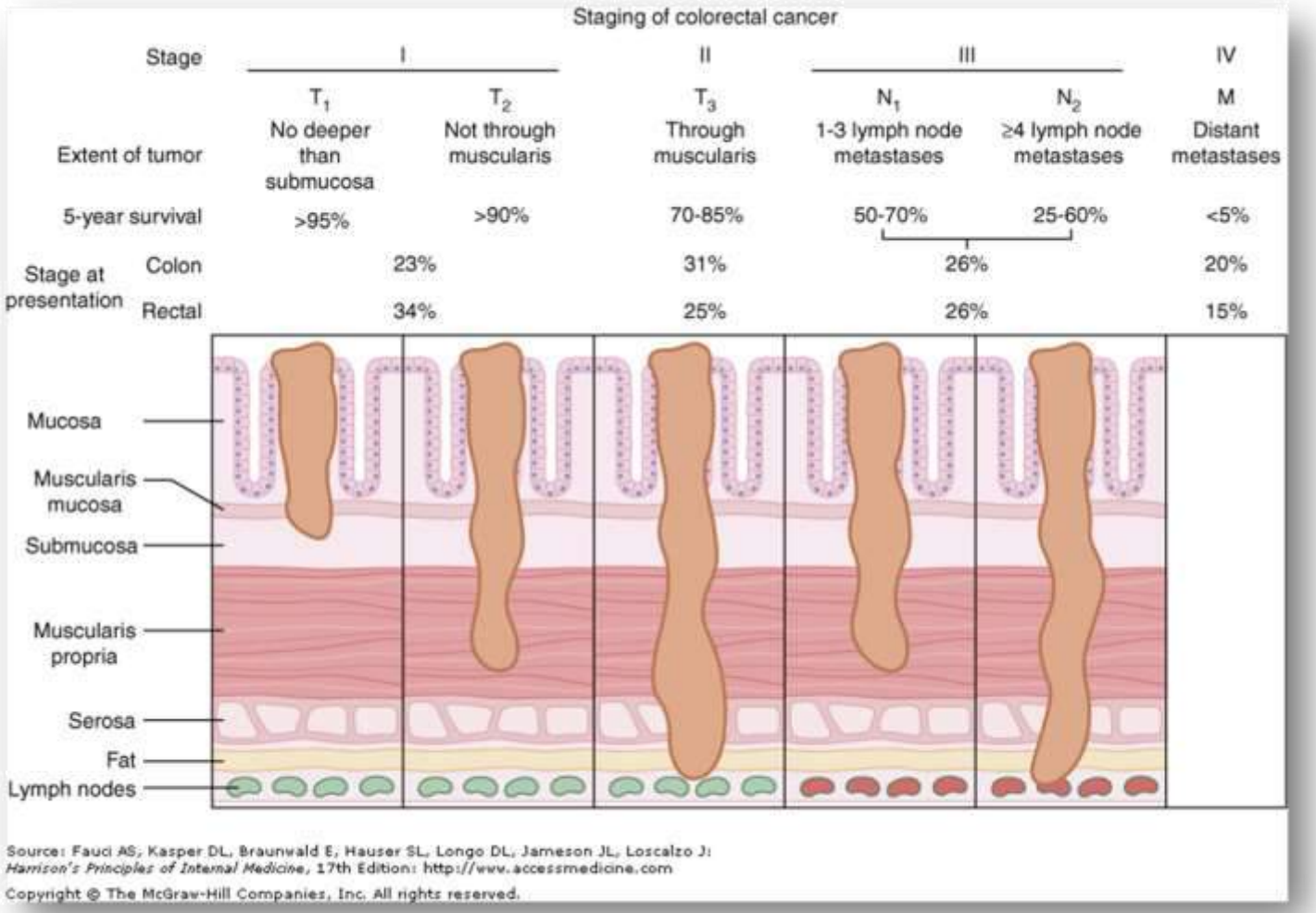


FIGURE 126-6. Comparison of carcinoma in situ and invasive cancer. Carcinoma is considered intramucosal or carcinoma in situ, as indicated by the area labeled "1," either in a pedunculated adenoma *(left)* or in a sessile adenoma *(right)* when there is not a breach of the muscularis mucosae. This lesion, as a rule, does not metastasize. Carcinoma in an adenomatous polyp is considered invasive when it breaches the muscularis mucosae, as indicated by the areas labeled "2." Invasive cancer in a pedunculated polyp *(left)* is unlikely to metastasize, and it is managed differently from invasive cancer in a sessile polyp *(right)*, which often requires surgical resection.

Primary tumor (T)

Tx – Primary tumor cannot be assessed
T*is* – Carcinoma *in situ*
T1 – Tumor invades submucosa (inner most lining of colon)
T2 – Tumor invades muscularis propria (into the muscle)
T3 – Tumor invades through the muscularis propria into the subserosa (gets outside the colon)
T4- Tumor invades other organs or structures, or perforates

CRC diagnosis and staging



Primary tumor (T)

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T3 – Tumor invades through the muscularis propria into the subserosa (gets outside the colon)

T4- Tumor invades other organs or structures, or perforates

Colon cancer survival rate

GETTING SCREENED CAN MAKE ALL THE DIFFERENCE

If found early, colon cancer is highly treatable[1]:

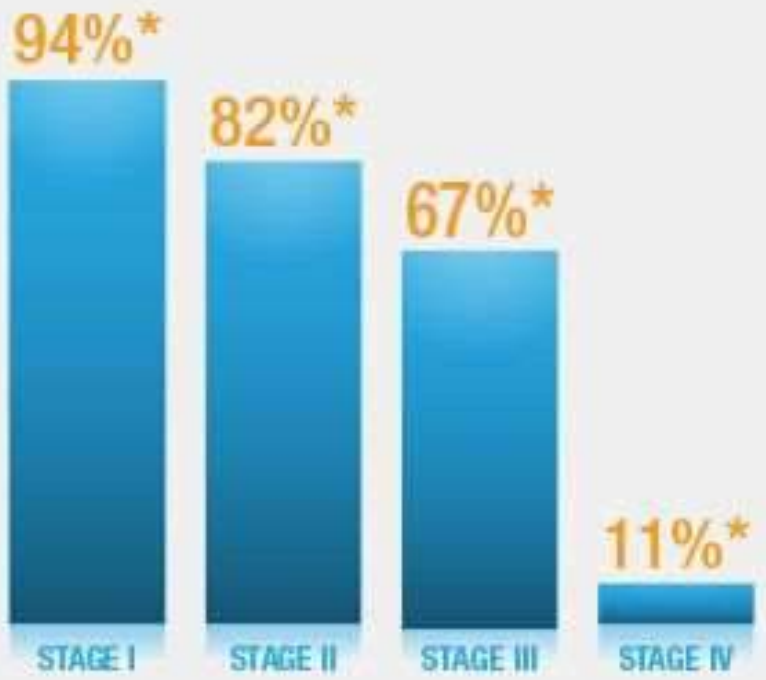
Stage I = 94%* survival rate

Stage II = 82%* survival rate

Stage III = 67%* survival rate

Stage IV = 11%* survival rate

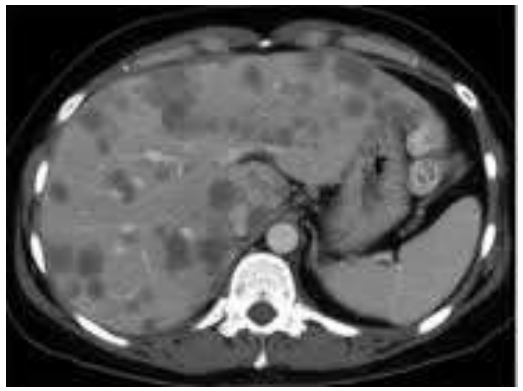
*Based on 5-year survival rate.

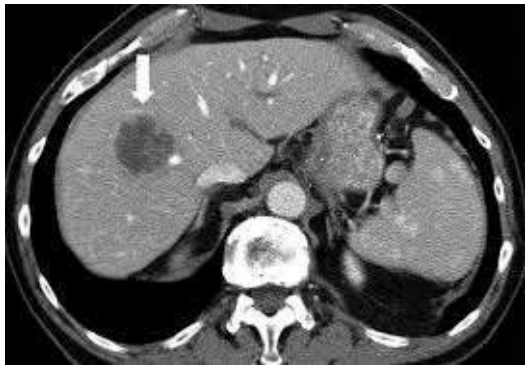


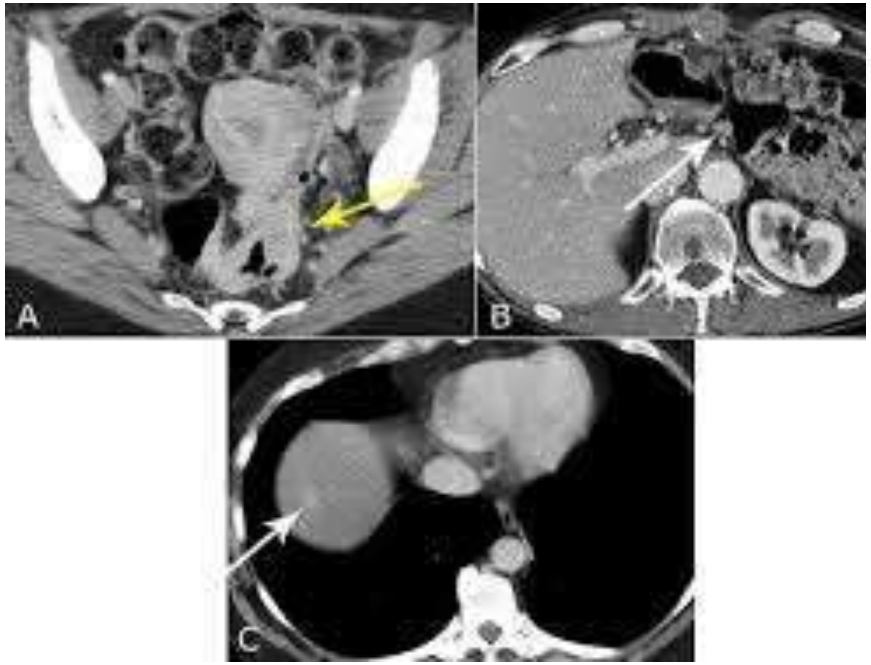
1. Lansdorp-Vogelaar I, van Ballegooijen M, Zauber A, Habbema J, Kulpers E. Effect of rising chemotherapy costs on the cost savings of colorectal cancer screening. *J Natl Cancer Inst.* 2009;101:1412-1422.

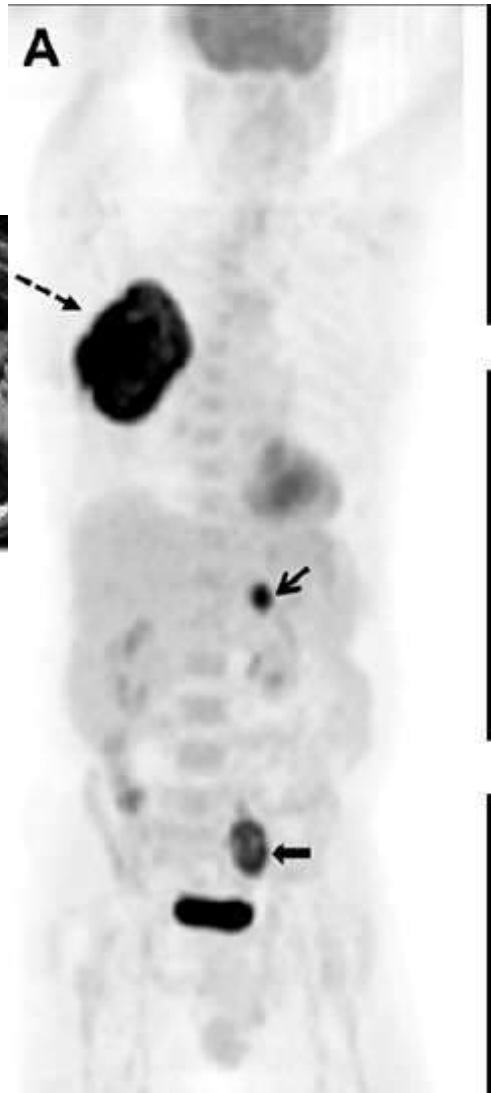
BeSeenGetScreened.com

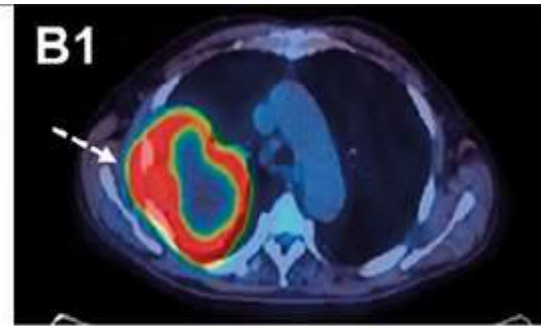
CRC staging: TC and PET

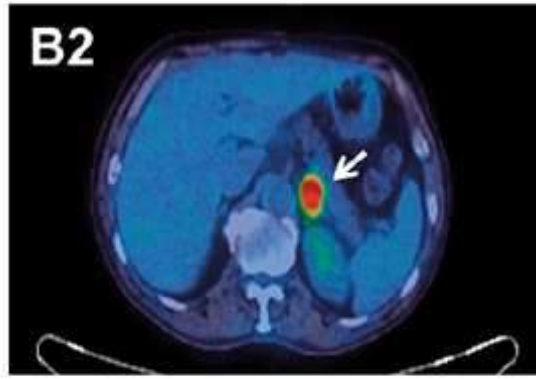


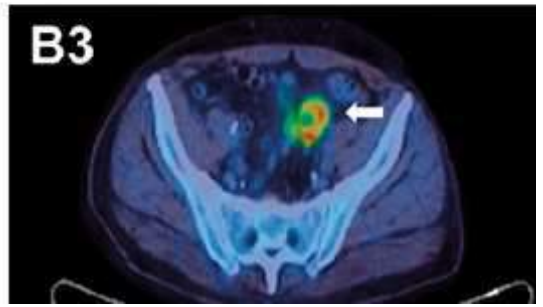


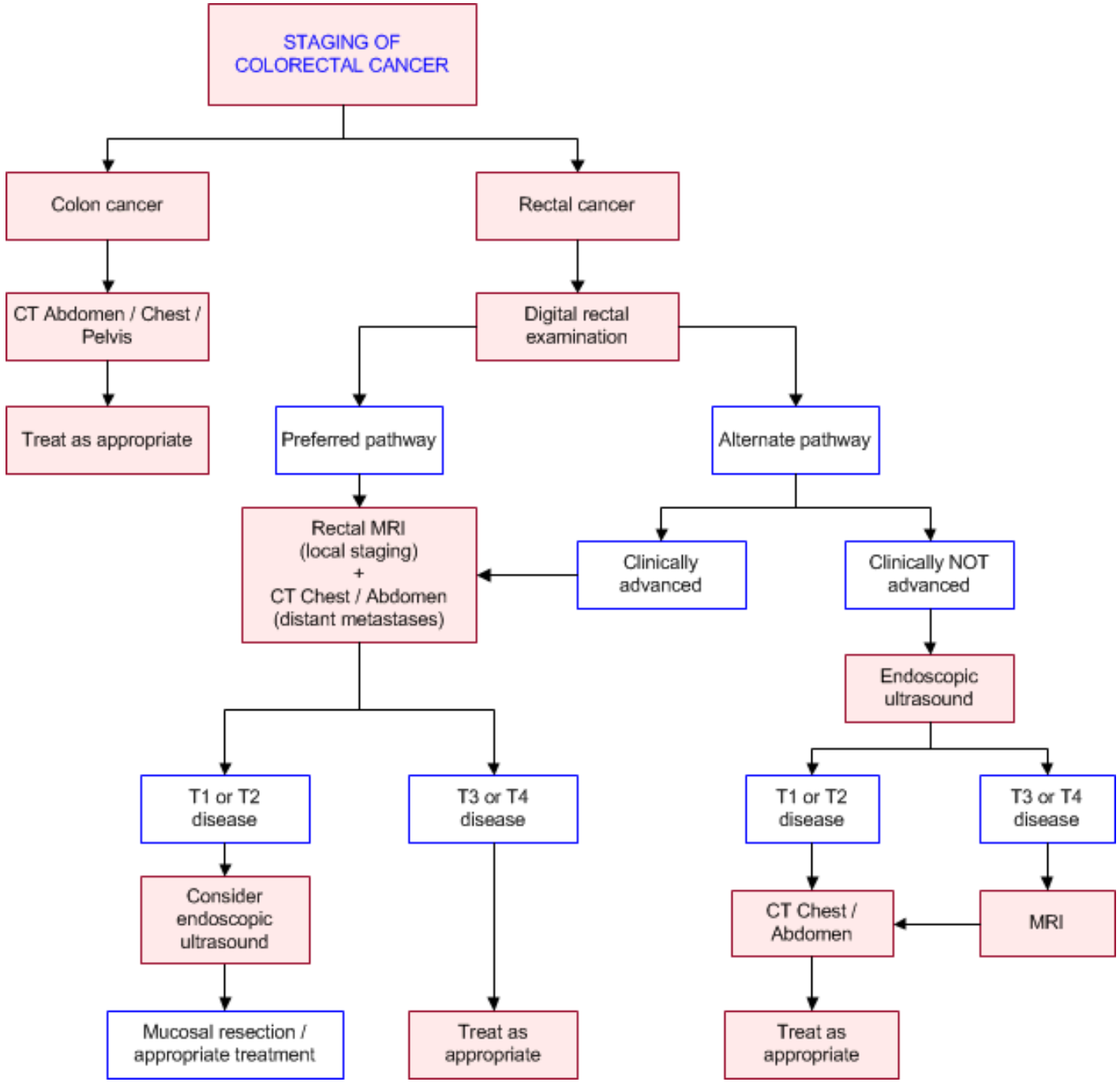






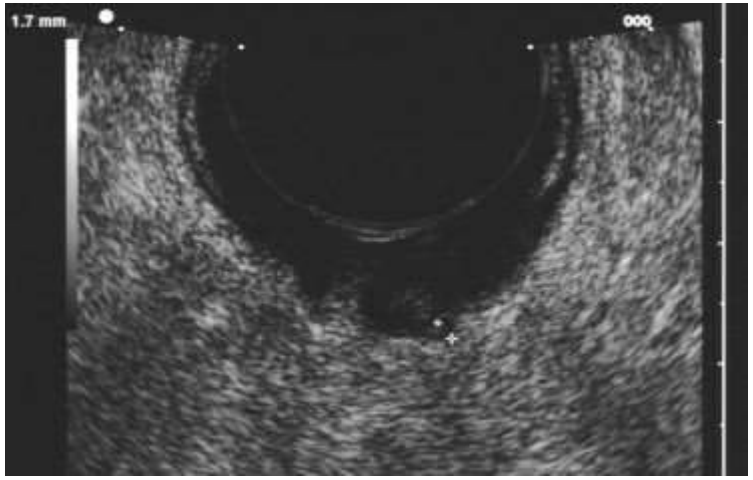




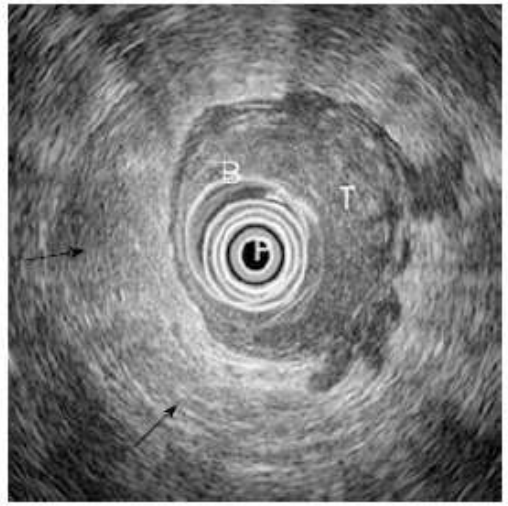

STAGING OF COLORECTAL CANCER
Colon cancer
Rectal cancer
CT Abdomen / Chest / Pelvis
Digital rectal examination
Treat as appropriate
Preferred pathway
Alternate pathway
Rectal MRI (local staging) + CT Chest / Abdomen (distant metastases)
Clinically advanced
Clinically NOT advanced
Endoscopic ultrasound
T1 or T2 disease
T3 or T4 disease
T1 or T2 disease
T3 or T4 disease
Consider endoscopic ultrasound
CT Chest / Abdomen
MRI
Mucosal resection / appropriate treatment
Treat as appropriate
Treat as appropriate

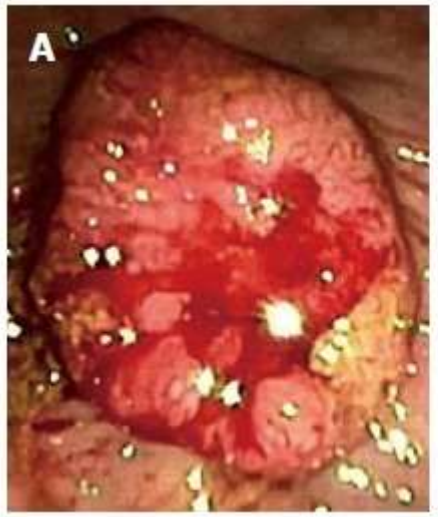
Rectal cancer: eco-endoscopy

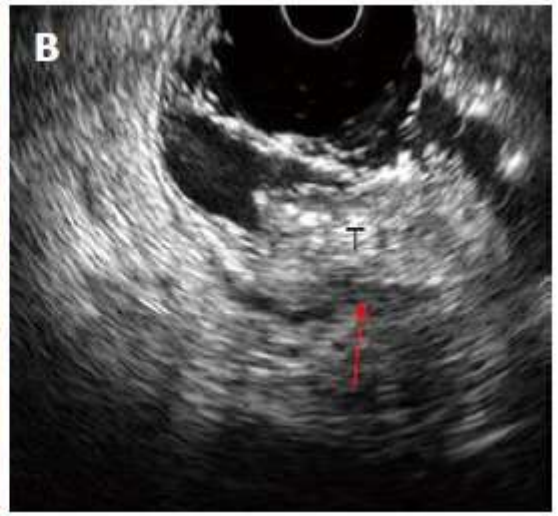
T3

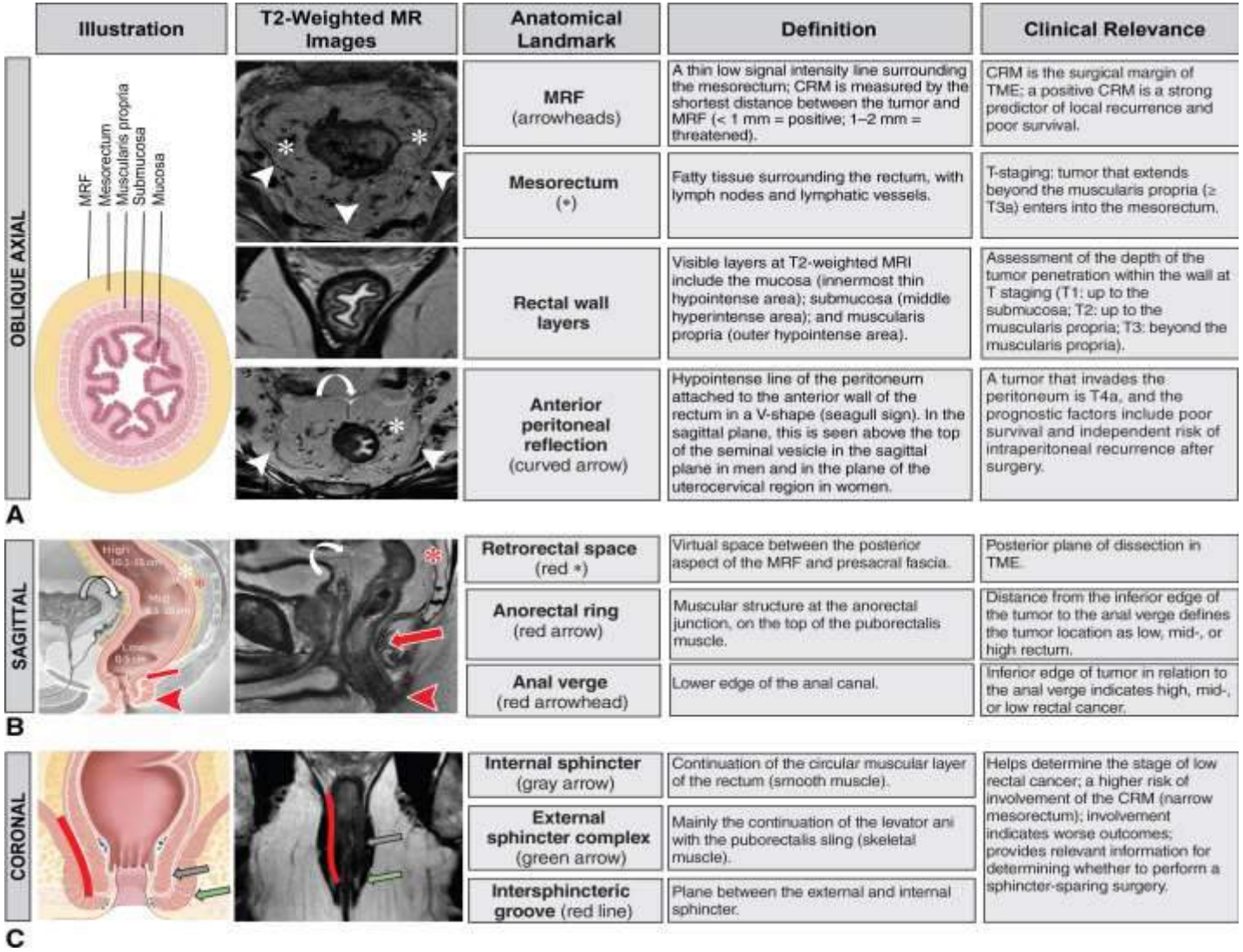


T4









. Chart shows the anatomic landmarks of the rectum, describes their clinical relevance, and summarizes their imaging appearance. *A*, Illustration and MR images in the oblique axial view best depict the MRF, mesorectum, rectal wall layers, and anterior peritoneal reflection. *B*, Illustration and MR image in the sagittal view best depict the retrorectal space, anorectal ring, and anal verge. Curved arrows = anterior peritoneal reflection, white * = mesorectum. *C*, Illustration and MR image in the coronal view best depict the internal sphincter, external sphincter complex, and intersphincteric space. (Illustrations adapted and reprinted, under a CC BY-ND 4.0 license, from Memorial Sloan Kettering Cancer Center.)

Horvat N. February 15, 2019 https://doi.org/10.1148/rg.2019180114

Table 14. Treatment algorithm for early colon cancer

Stage	TNM	Treatment Surgery	Pathology report	Clinical risk	Additional surgery	Age (years)	Postoperative (6 months)
0/I	Tis/T1 N0	Local excision	<G3, L0, R0	• Low (LN mets in 4%)	–		–
			>G2, L1, V1, invasion of sub-mucosa	• High	Wide resection		–
I	>T1	Wide surgical resection and anastomosis		–	–		–
II	T3/4 N0	Hemicolectomy and lymph node resection		• Low	–		(FU)
				• High: at least one of <12 LN examined, L1, V1, PN1, >G2, pT4, occlusion, perforation	–	<70	FU(+oxaliplatin)
					–	>70	FU (+ oxaliplatin for younger biological age)
III	N+				–	<70	FU + oxaliplatin
						>70	FU (+ oxaliplatin for younger biological age)

TNM, tumour–node–metastasis.

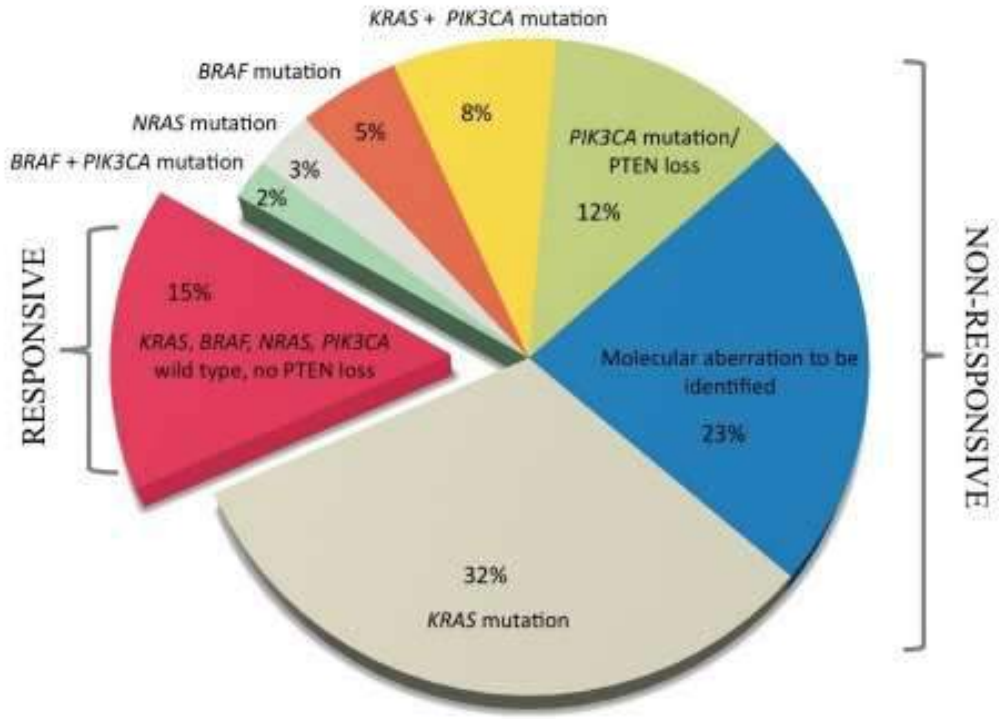
Anti EGFR and VEGF

TABLE 2. Key Study Findings With Targeted Therapies for Colon Cancer[3-8]

Targeted Therapy Drug	Results
Bevacizumab (Avastin)	• OS of bevacizumab plus IFL compared with IFL alone (20.3 vs 15.6 months; $P<.001$). • PFS of bevacizumab plus IFL compared with IFL alone (10.6 vs 6.2 months; $P<.001$)
Cetuximab (Erbitux)	• Median time to disease progression comparing cetuximab plus an irinotecan-based regimen with cetuximab alone (4.1 vs 1.5 months; $P<.001$).
Panitumumab (Vectibix)	• 46% reduction in the relative risk of progression was observed in patients receiving panitumumab compared with those receiving best supportive care (HR, 0.54; 95% CI, 0.44-0.66).
Ramucirumab (Cyramza)	• For patients receiving ramucirumab plus FOLFIRI, median OS duration was 13.3 months, while patients receiving FOLFIRI alone had a median OS duration of 11.7 months ($P=.0219$).
Ziv-aflibercept (Zaltrap)	• OS was longer in patients receiving ziv-aflibercept plus FOLFIRI compared with patients receiving placebo plus FOLFIRI (13.80 vs 11.93 months; $P=.0008$). • The difference in median PFS also favored the ziv-aflibercept plus FOLFIRI compared with placebo plus FOLFIRI (6.80 vs 4.53 months; $P<.0001$).
Regorafenib (Stivarga)	• OS was longer in the regorafenib arm than in the placebo arm (6.4 vs 5.0 months; $P=.0052$). • PFS was also longer in the regorafenib arm: 1.9 months versus 1.7 months in the placebo arm ($P<.0001$).

HR indicates hazard ratio; IFL, irinotecan/fluorouracil/levoleucovorin regimen; OS, overall survival; PFS, progression-free survival.

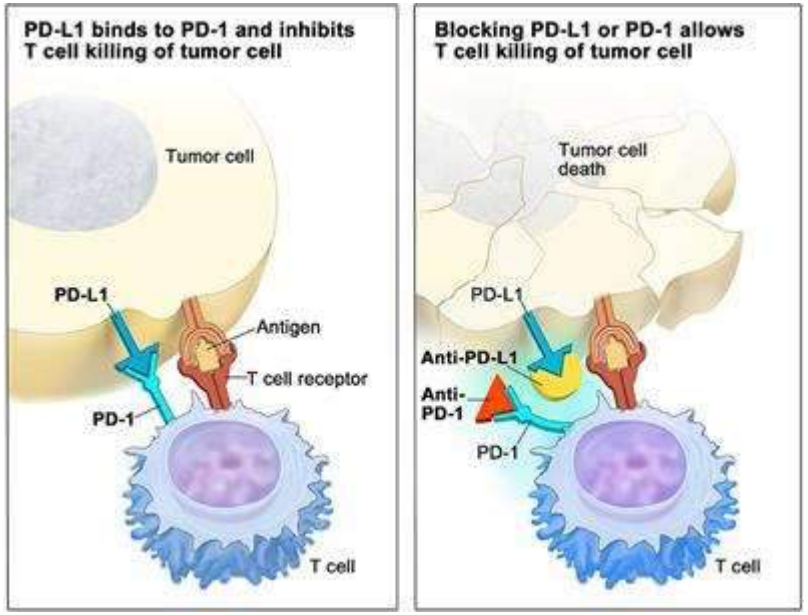
CRC therapy:
the role of molecular signature

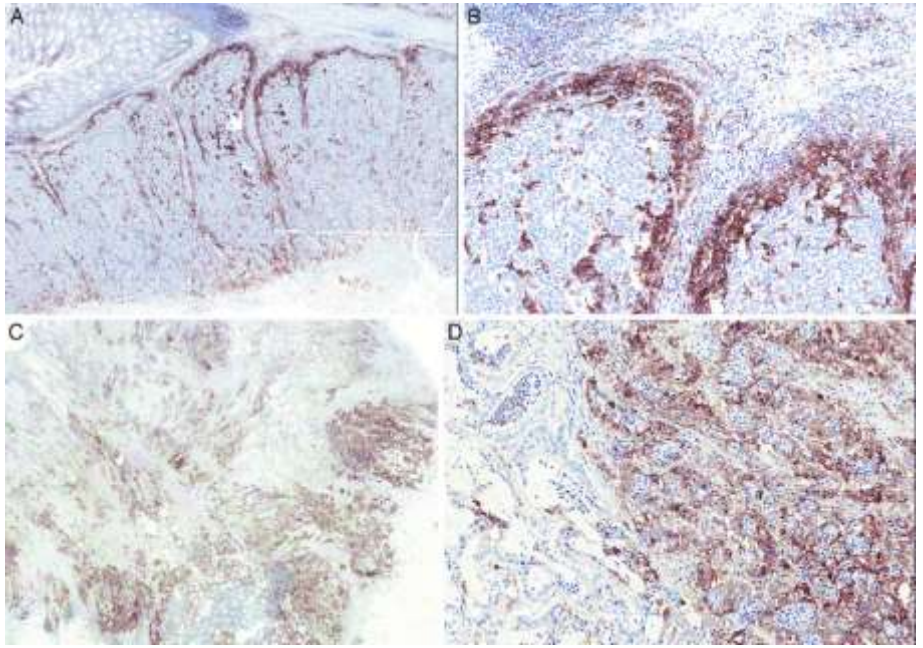


Data derived from multiple trials have indicated that ***KRAS*** mutations can be considered a **highly specific negative biomarker of response to anti-EGFR** monoclonal antibodies (MoAb). In the first-line setting, retrospective analysis of phase II and III trials comparing standard 5-fluorouracil-based chemotherapy and oxaliplatin or irinotecan with the addition of **bevacizumab, cetuximab or panitumumab confirmed that the benefit of the MoAb was restricted to patients with *KRAS* wild-type tumors.**

CRC and PD1/PDL1

There is a growing body of literature that recognizes the importance of anti-PD-1 therapy for **MSI (Microsatellite instability)** tumors among CRC subtypes.





PDL1 in MSI CRC

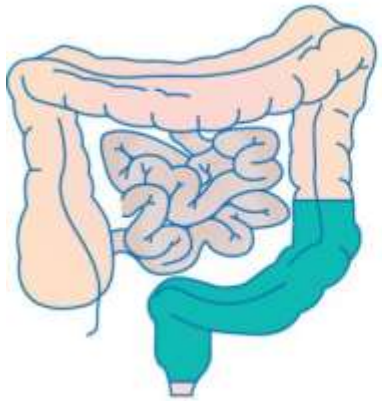
CRC and PD1/PDL1

Study/ClinicalTrials.gov Identifier	Drug(s)	N	Patient population	(iO)RR	Phase	Primary endpoint	12m OS
Le et al. (13), NEJM 2015 NCT01876511	Pembrolizumab	41 (32 CRC)	dMMR:11 pMMR 21	dMMR 40% pMMR 0%	II	irPFS	–
Lee et al. (27), JCO 2017 NCT02260440	Pembrolizumab + azacitidine	31	30 pts with MSS mCRC	3%	II	ORR	–
Shahda et al. (28), JCO 2017 NCT02375672	Pembrolizumab + mFOLFOX6	30 (3 MSI-H)	1st line mCRC	53%	II	mPFS	–
O'Neil et al. (23), BH 2017 NCT02054806	Pembrolizumab	137 (23 enrolled)	PD-L1 positive refractory mCRC	4%	Ib	ORR	29,8%
Le Dung et al. (24), KEYNOTE-164 NCT02460198	Pembrolizumab	63	MSI-H mCRC treated with ≥1 prior line	32%	II	ORR	76%
NCT02788279	Atezolizumab +- Cobimetinib	363 (1.7% MSI-H)	MSS/MSI-L mCRC	2,7%	III	OS	–
NCT01633970	Atezolizumab + FOLFOX + Bevacizumab	23	Refractory mCRC	52%	Ib	Safety	–
Brahmer et al. (10), NEJM 2012 NCT00729664	Nivolumab	19	mCRC MSI unknown	0%	I (multi tumors)	Safety	–
CheckMate142 NCT02060188	Nivolumab	74	dMMR/MSI-H mCRC	31,1%	II	ORR	85%
CheckMate142 NCT02060188	Nivolumab + Ipilimumab (4 doses)	119	dMMR/MSI-H refractory mCRC	55%	II	ORR	85%
CheckMate142 NCT02060188	Nivolumab + Ipilimumab (1mg/kg) Q6W	45	dMMR/MSI-H First-line mCRC	60%	II	ORR	83%
NCT02298946	CTX + AMP-224 + SBRT	17	mCRC	0%	I	Safety	–

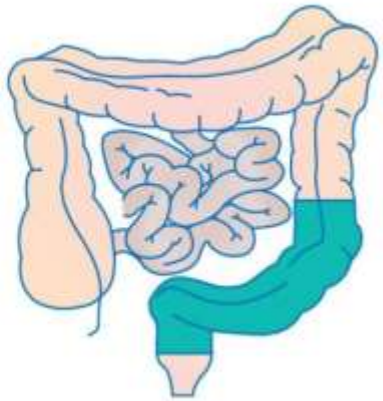
CTX, cyclophosphamide; SBRT, stereotactic body radiation therapy; mCRC, metastatic colorectal cancer; MSI, microsatellite instability; H, high; MSS, microsatellite stability; pMMR, mismatch repair proficient; ORR, objective response rate; irORR, immune-related ORR; PFS, progression-Free Survival; OS, overall survival; RR, response rate; BRR, best RR. Details available at: www.clinicaltrials.gov.

CRC surgery

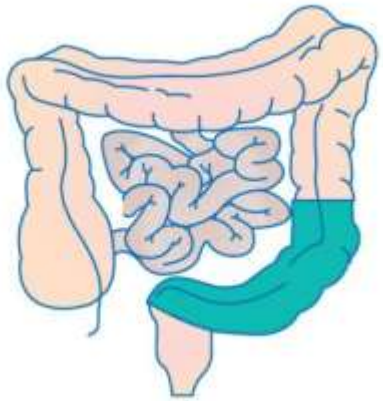
Low anterior resection



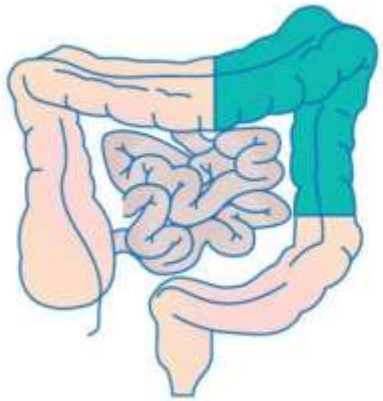
High anterior resection



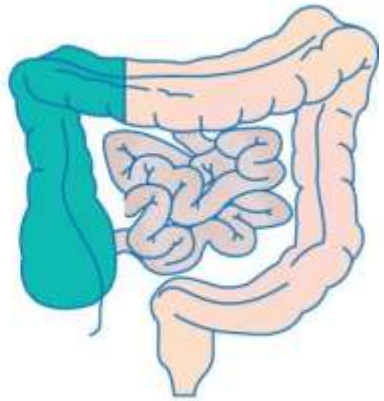
Sigmoid colectomy



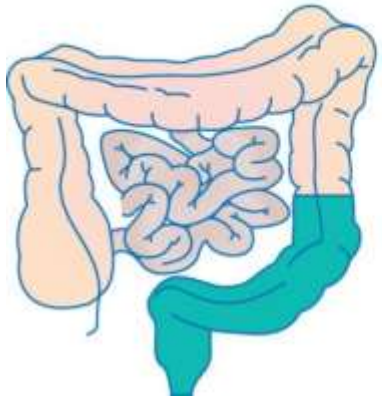
Left hemicolectomy



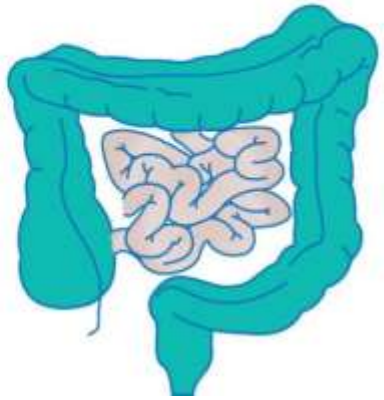
Right hemicolectomy



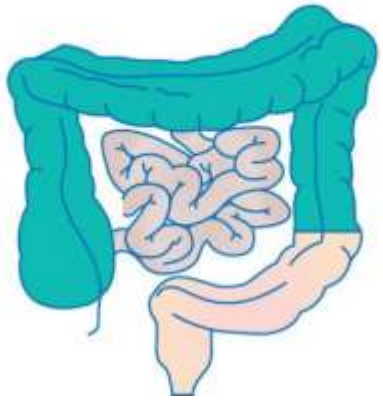
Abdomino-perineal resection



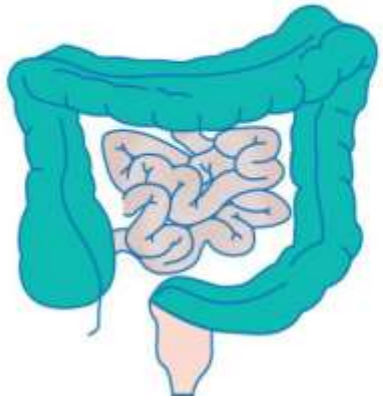
Total proctocolectomy



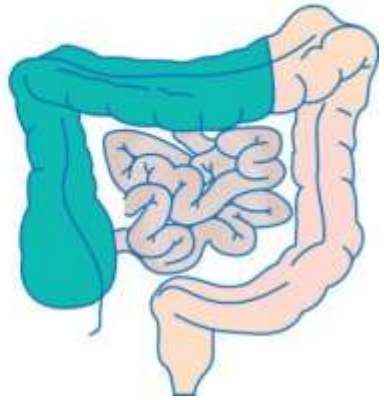
Subtotal colectomy



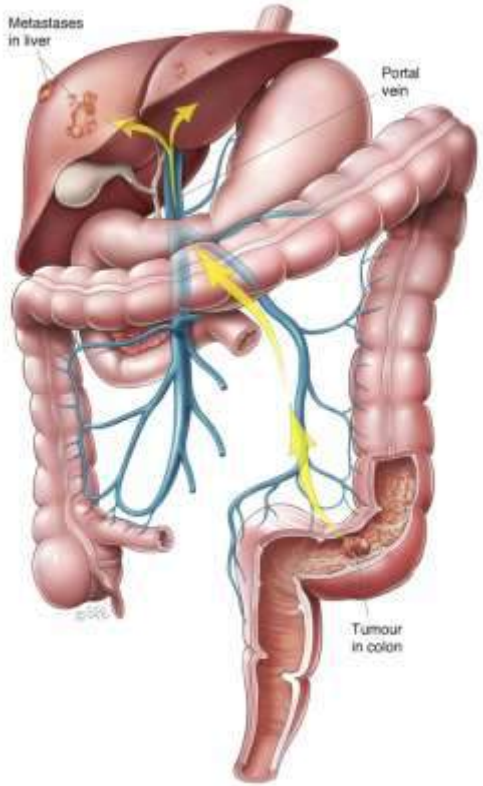
Total abdominal colectomy

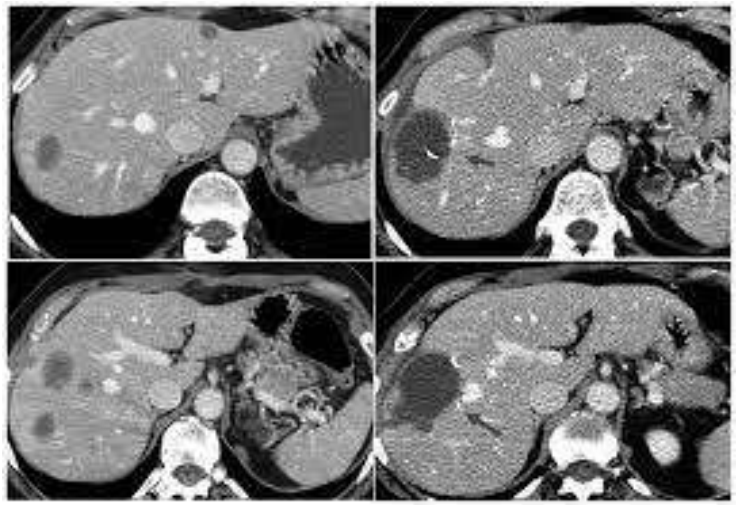


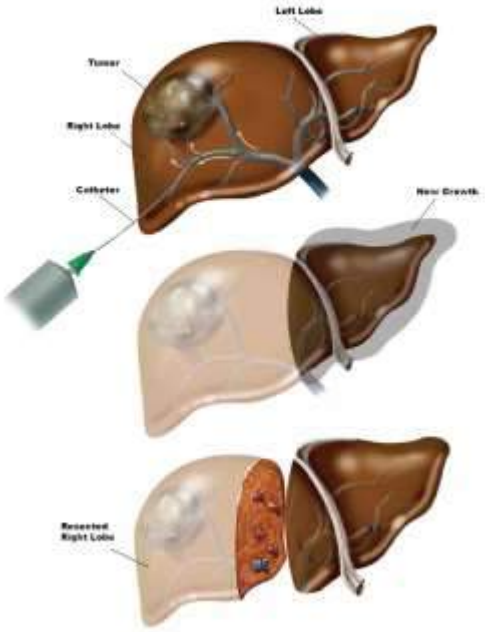
Extended right hemicolectomy



CRC metastatic disease







CRC adjuvant chemotherapy

TABLE 7: Adjuvant chemotherapy regimens for colorectal adenocarcinoma (nonmetastatic)

Drug/combination	Dose and schedule
Oxaliplatin/fluorouracil/leucovorin (FOLFOX4)	
Oxaliplatin	85 mg/m² IV piggyback over 2 hours on day 1 only
Leucovorin	200 mg/m²/d over 2 hours on day 1 given simultaneously with oxaliplatin
Fluorouracil	400 mg/m² IV bolus over 2 to 4 minutes on days 1 and 2
Fluorouracil	600 mg/m² continuous infusion over 22 hours on days 1 and 2 every 14 days for 12 cycles
Andre T, Boni C, Mounedji-Boudiaf L, et al: N Engl J Med 350:2343–2351, 2004.	
Oxaliplatin/fluorouracil/leucovorin (Modified FOLFOX6)	
Oxaliplatin	85 mg/m² IV piggyback over 2 hours on day 1 only
Leucovorin	400 mg/m²/d over 2 hours on day 1 given simultaneously with oxaliplatin
Fluorouracil	400 mg/m² IV bolus over 2 to 4 minutes on day 1
Fluorouracil	2400 mg/m² continuous infusion over 46 hours on day 1 every 14 days for 12 cycles
Allegra CJ, Yothers G, O'Connell MJ, et al: J Clin Oncol 29:11–16, 2011.	
FLOX	
Fluorouracil	500 mg/m² IV bolus weekly for 6 weeks
Leucovorin	500 mg/m² IV weekly for 6 weeks each 8-week cycle x 3
Oxaliplatin	85 mg/m² IV administered on weeks 1, 3, and 5 of each 8-week cycle x 3
Kuebler JP, Weiand HS, O'Connell MJ, et al: J Clin Oncol 25:2198–2204, 2007.	
Capecitabine and Oxaliplatin (XELOX)	
Oxaliplatin	130 mg/m² IV piggyback over 2 hours on day 1 only
Capecitabine	1,000 mg/m² twice daily on days 1–14 every 3 weeks for 8 cycles
Haller DG, Tabernero J, Maroun J, et al: J Clin Oncol 29:1465–1471, 2011.	
Capecitabine	
Capecitabine	1,250 mg/m² twice daily on days 1–14 every 3 weeks for 8 cycles
Twelves C, Wong A, Nowacki MP, et al: N Engl J Med 352:2696–2704, 2005.	