MALIGNANCY IN GASTROINTESTINAL TRACTUS

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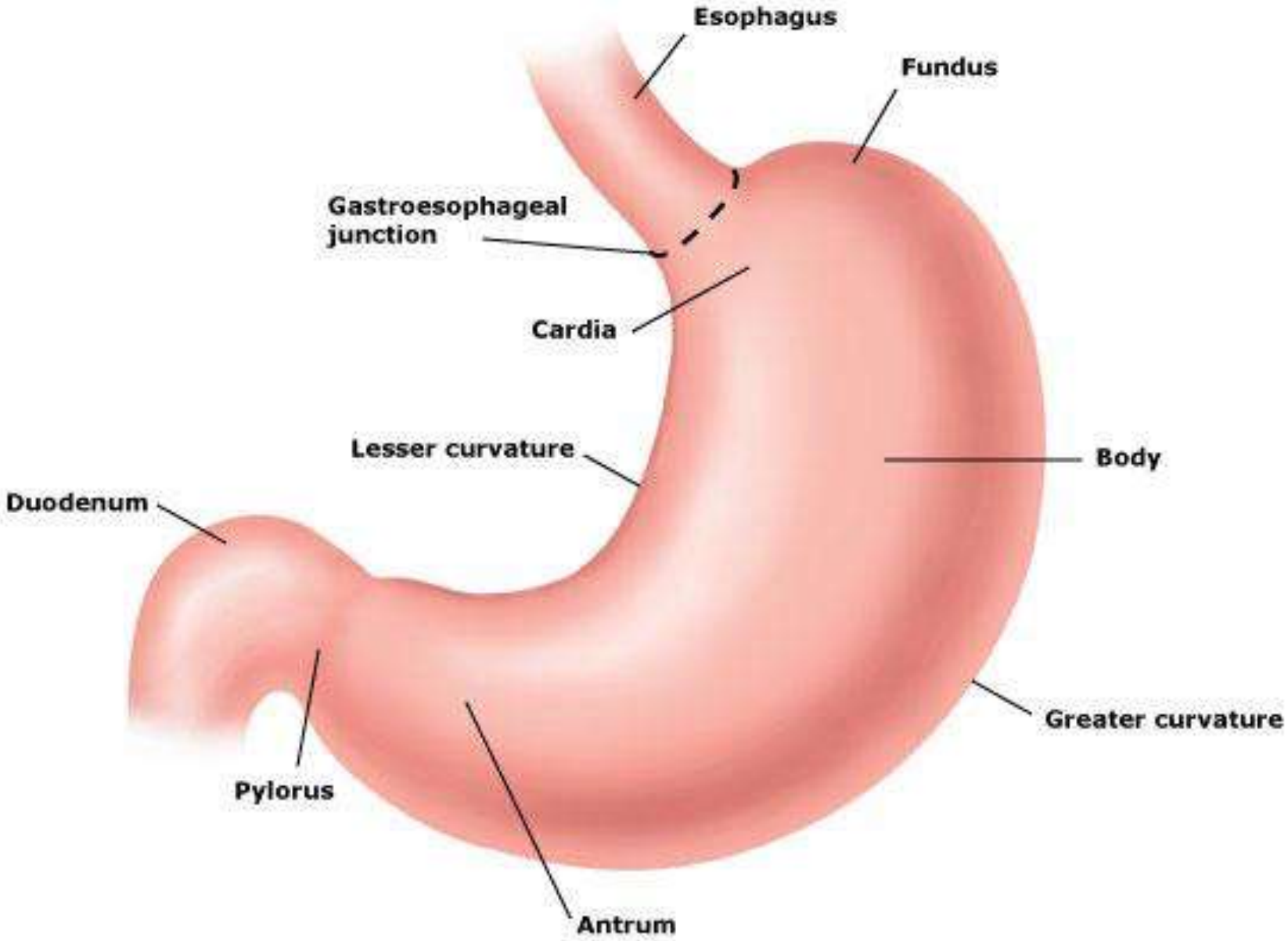
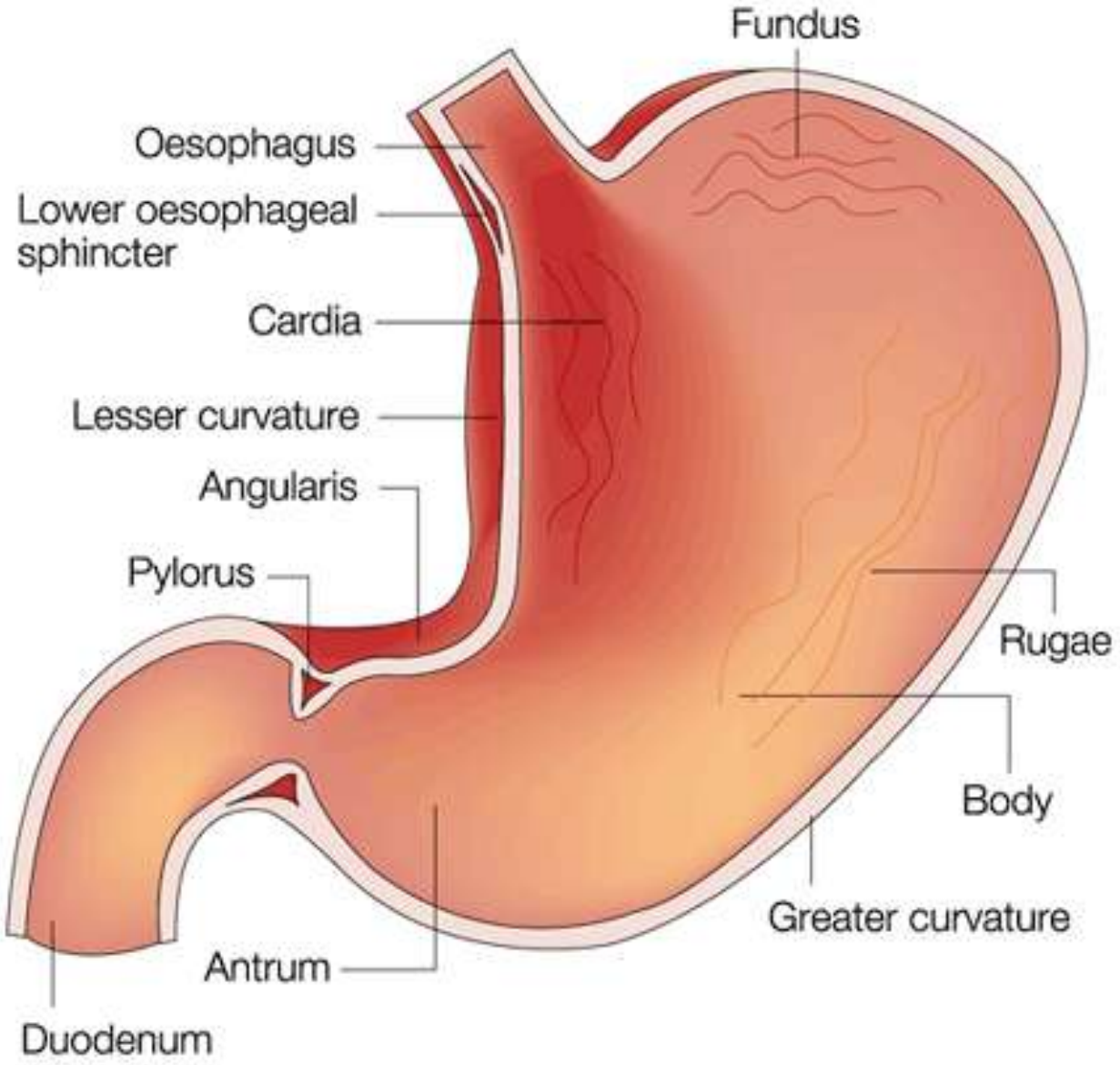

Esophagus
Fundus
Gastroesophageal junction
Cardia
Lesser curvature
Body
Duodenum
Greater curvature
Pylorus
Antrum

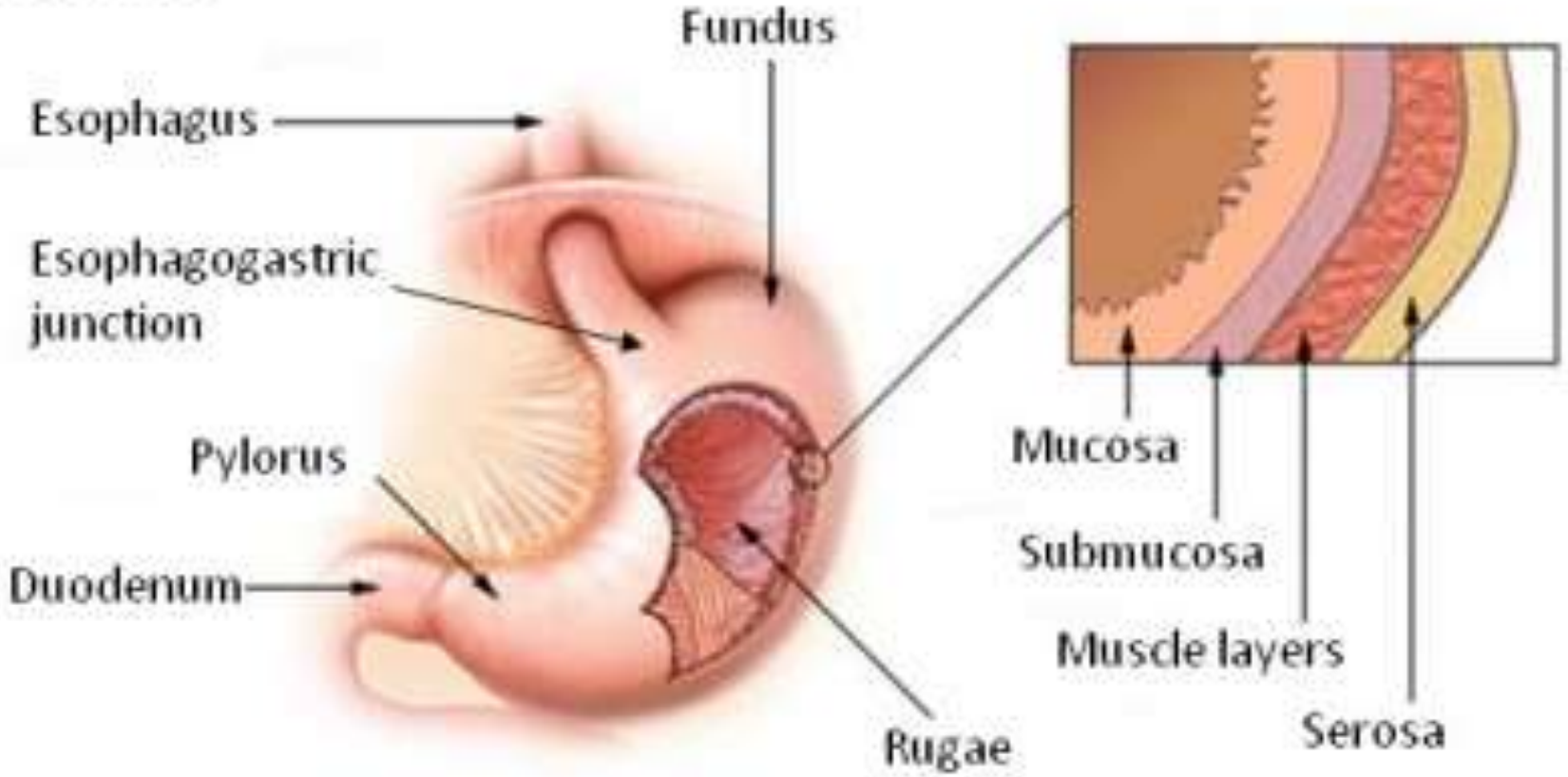
Objectives

- Describe adenocarcinoma of the stomach in terms of
  - etiology,
  - epidemiology,
  - signs and symptoms,
  - the risk factors for development of colorectal cancer.
- Outline the pathophysiologic development of colorectal cancer.
- Describe the following inheritable factors and syndromes for colorectal cancer:
  - Polyposis
  - Gardner's syndrome
  - Juvenile polyposis
- Describe the work-up and preventive measures for patients with familial polyposis.
- Discuss the clinical features and presenting signs and symptoms of colorectal cancer
- Summarize the Dukes classification of colorectal cancer and TNM classification and discuss the significance of staging.

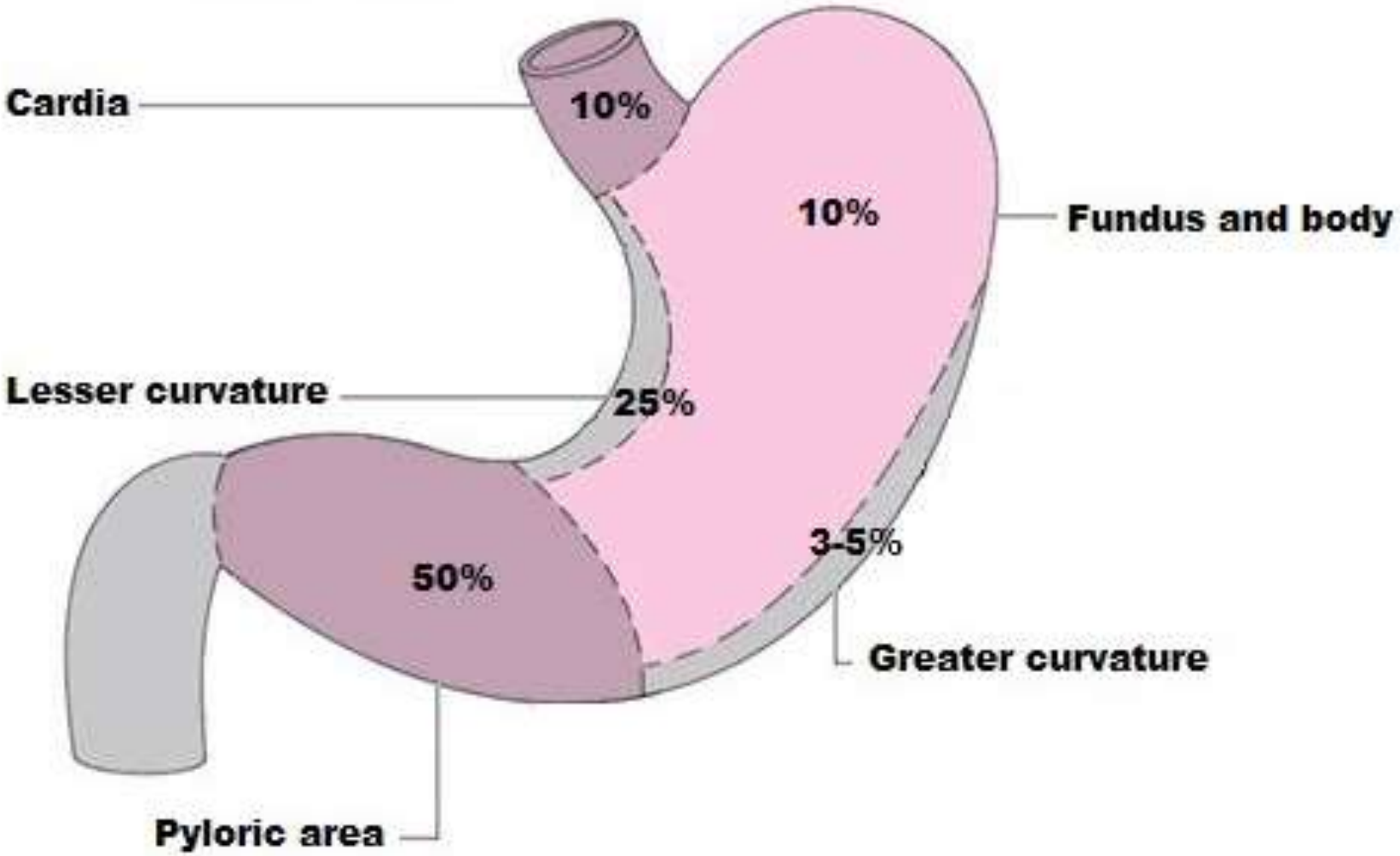
- List and describe the factors that predict a poor outcome after total surgical resection for colorectal cancer
- Discuss the treatment of other colorectal tumors.
- Identify the symptoms that may indicate small bowel tumors, and discuss appropriate diagnostic imaging techniques and treatment
- Describe the following types of small bowel tumors
  - Adenomas
  - Polypoid adenomas
  - Leiomyomas
  - Lipomas
  - Angiomas
  - Carcinoid tumors


Fundus
Oesophagus
Lower oesophageal sphincter
Cardia
Lesser curvature
Angularis
Pylorus
Rugae
Body
Greater curvature
Antrum
Duodenum

Stomach


Fundus
Esophagus
Esophagogastric junction
Pylorus
Duodenum
Rugae
Mucosa
Submucosa
Muscle layers
Serosa

Locations of Stomach Cancer by Percentage



EPIDEMIOLOGY

- Rare before the age of 40,
  - Incidence steadily climbs thereafter
  - Peaks in the seventh decade of life.
- It is estimated that
  - 876,340 cases of primary gastric cancer
  - 650,000 deaths worldwide.

- In North America
  - The lifetime probabilities of developing and dying: 1.5% and 1.0%, respectively.
- Mortality rates
  - Females: 9.9 to 4.2 per 100,000
  - Males: 21.2 to 9.1 per 100,000
- In the United States
  - 24,000 new cases and 14,000 deaths annually.
  - 65% present at an advanced stage (T3/T4), with nearly 85%: node metastasis at diagnosis.

RISK FACTORS

ETHNIC FACTOR

- Incidence:
  - Highest in Japan
    >40 per 100,000, Eastern Asia, South America, and Eastern Europe
  - Lowest in canada
    10 per 100,000, Northern Europe, Africa, United States
- Ethnicity is identified into 3 groups:
  1. High
     Koreans, Vietnamese, Japanese, Native American, Hawaiian
  2. Intermediate
     Latino, Chinese, and black
  3. Low
     Filipino and white

RISK FACTOR

DIETARY FACTOR

- Rich in salt

  Leads to atrophic gastritis ---- Alteration in the gastric environment---- Generation of carcinogenic N-nitroso compounds.
- Rich in fruits and vegetables : reduced risk of cancer.
- Raw vegetables and fruit: decreased the risk of gastric cancer
- Calcium, vitamin A, and vitamin C: protective effect on the gastric mucosa----- through the reduced formation of N-nitroso carcinogenic compounds.

BEHAVIORAL FACTORS

- Cigarette smokers: 2- 3 times increased risk of proximal gastric cancer.
- Smoked or poorly preserved foods,
- Habitual alcohol consumption.

RISK FACTOR

NON-GENETIC

- Sporadically,

GENETIC : inherited familial component

- 8% to 10%:
  - Germline mutations in p53 (Li-Fraumeni syndrome)
  - BRCA2
- In 1% to 3%
  - Germline mutations in the gene encoding the cell adhesion protein E-cadherin--- leads to an autosomal-dominant
  - Hereditary diffuse gastric cancer
  - Should prompt prophylactic gastrectomy in affected kindreds.
- Hereditary nonpolyposis colon cancer (HNPCC) syndrome
- Gastrointestinal polyposis syndromes,
  - Familial adenomatous polyposis (FAP) and Peutz-Jeghers syndrome.

RISK FACTOR

INFECTION-INFLAMATION

- *Helicobacter pylori* infection.
  - 10 or more years before the cancer diagnosis
  - Induce changes in the gastric mucosa and the gastric flora
  - Capable of adhering to the Lewis blood group antigen---important factor facilitating chronic infection--- increased cancer risk in blood group A phenotype.
- Chronic atrophic gastritis
  - Pernicious anemia

OTHERS

- Previous gastric surgery with bile reflux,
- Hypertrophic gastropathy (Metenier's disease),
- Gastric polyps,
- Obesity.

H.PYLORI-AUTOIMMUNE GASTRITIS

- Create an environment conducive to gastric inflammation.
  - Gastritis persists
  - Gastric atrophy------ Intestinal metaplasia--- lead to dysplasia.
- Dysplasia can arise in either
  - the native gastric or
  - “intestinalized” gastric epithelium

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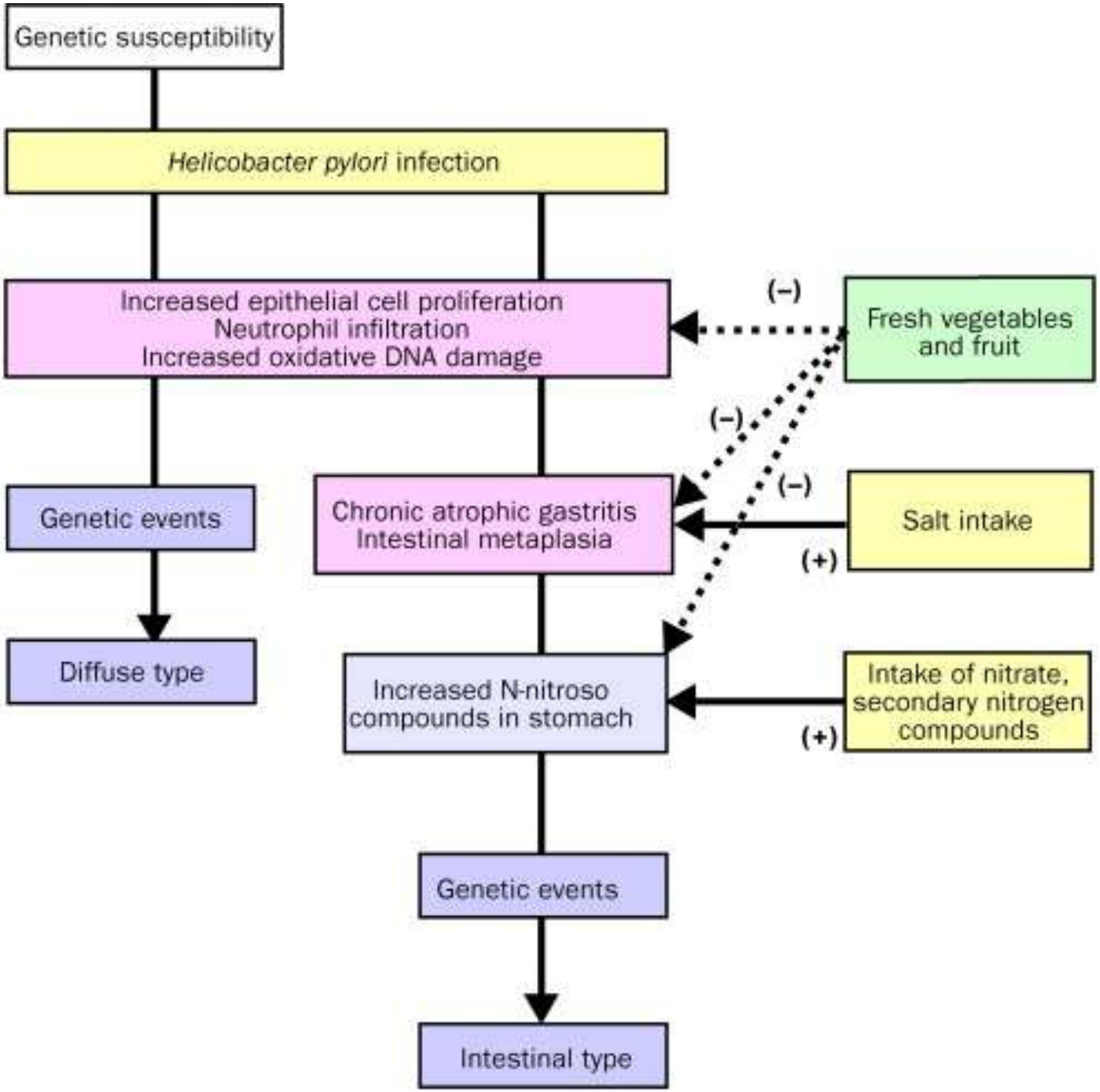

Genetic susceptibility
Helicobacter pylori infection
Increased epithelial cell proliferation
Neutrophil infiltration
Increased oxidative DNA damage
(–)
Fresh vegetables and fruit
(–)
(–)
Genetic events
Chronic atrophic gastritis
Intestinal metaplasia
Salt intake
(+)
Diffuse type
Increased N-nitroso compounds in stomach
Intake of nitrate, secondary nitrogen compounds
(+)
Genetic events
Intestinal type

CLASSIFICATION

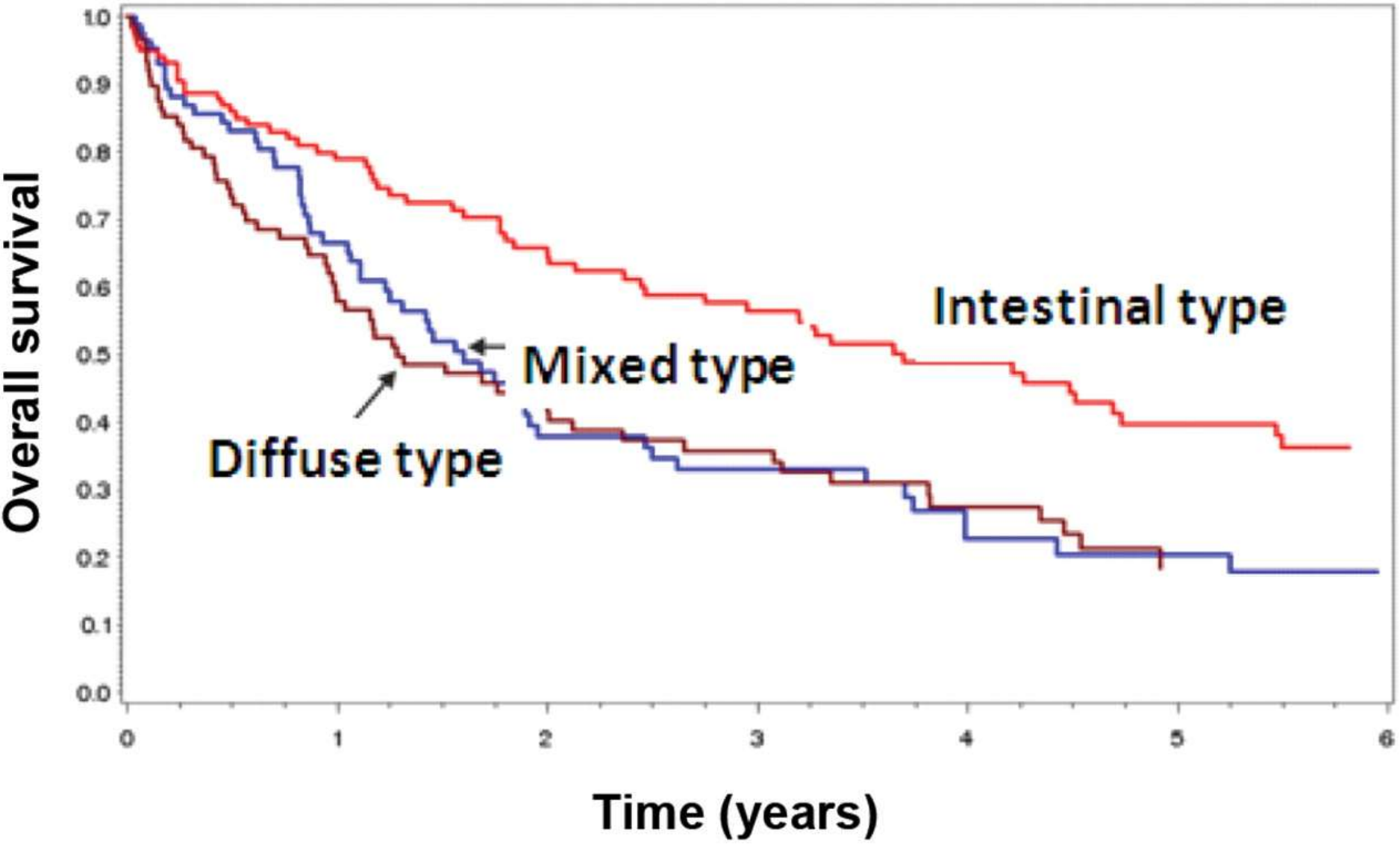
The 2 most commonly used are

1. Lauren System
2. WHO Systems

This system describes tumors on the basis of microscopic configuration and growth pattern.

LAUREN SYSTEM

- The Lauren classification divides gastric cancer into 2 major histologic types:
  1. Diffuse
  2. Intestinal
- Useful in evaluating the natural history of gastric carcinoma, especially with regard to
  - Incidence trends,
  - Clinicopathologic correlations
  - Etiologic precursors.


Overall survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
4
5
6
Time (years)
Intestinal type
Mixed type
Diffuse type

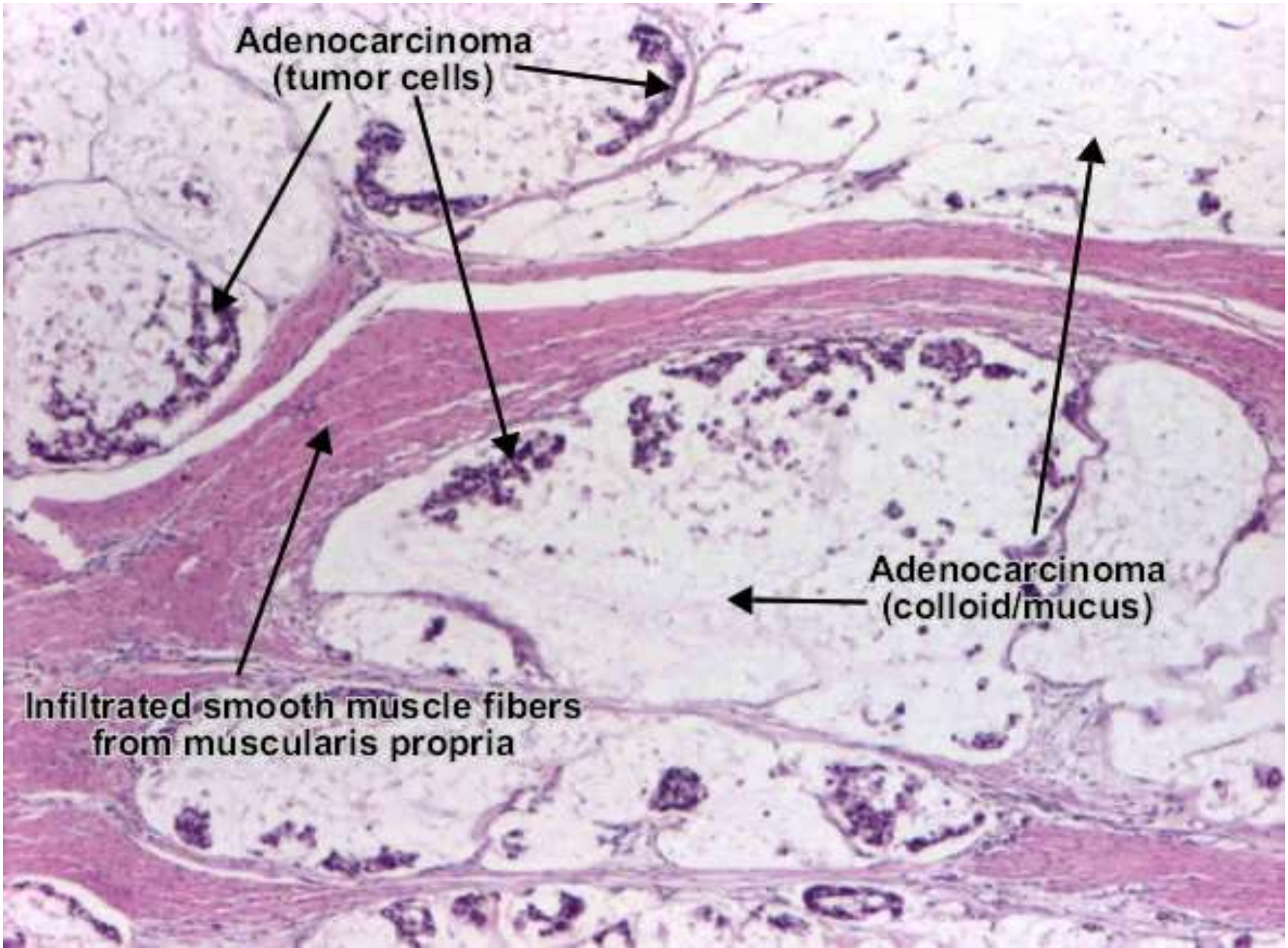
WHO SYSTEM

- Has revised the definition:

  "malignant epithelial tumors of the gastric mucosa with glandular differentiation.
- Based on the degree of resemblance to metaplastic intestinal tissue.
- Histologic patterns into 5 subtypes:
  1. Adenocarcinoma (intestinal and diffuse),
  2. Papillary
  3. Tubular
  4. Mucinous
  5. Signet-ring cell.

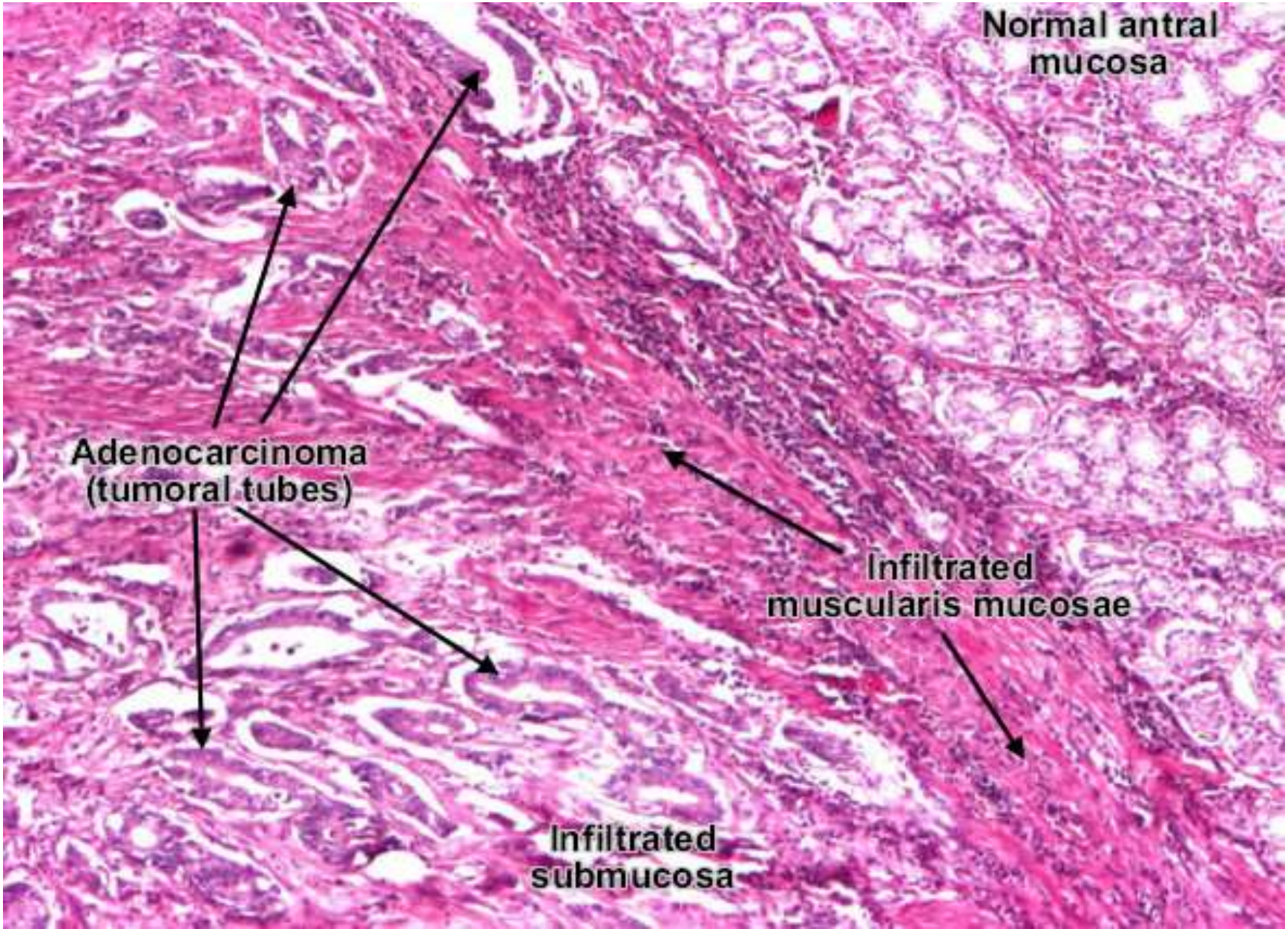
DIFFUSE-TYPE CANCER

- Noncohesive tumor cells diffusely infiltrating the stroma of the stomach
  - Deep infiltration of the stomach wall with little or no gland formation.
- Desmoplasia
- Associated inflammation
- More often in young
- Worse prognosis
- Not associated with intestinal metaplasia
- Not localized to the antrum
- Single-cell mutations within normal gastric glands--hereditary diffuse gastric carcinoma


Adenocarcinoma
(tumor cells)
Adenocarcinoma
(colloid/mucus)
Infiltrated smooth muscle fibers
from muscularis propria

INTESTINAL TYPE CANCER

- Recognizable gland formation similar in microscopic appearance to colonic mucosa.
- Glandular formation ranges from well to poorly differentiated tumors
- Grow in expanding, rather than infiltrative
- Secondary to chronic atrophic gastritis.


Normal antral mucosa
Adenocarcinoma (tumoral tubes)
Infiltrated muscularis mucosae
Infiltrated submucosa

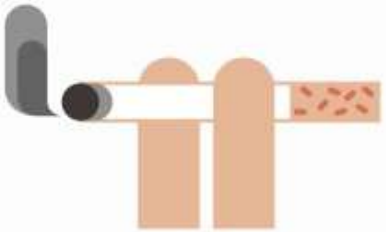
ADENOMA

- Dysplastic proliferation produces a macroscopic protruding lesion and as tubular, tubulovillous, or villous adenoma morphologically.
- In the distal stomach
- Prolonged precancerous phase---expanding growth pattern.
- Carcinoma is diagnosed when the tumor invades into the lamina propria or through the muscularis mucosae.
- Up to 80% of dysplastic lesions may progress to invasion

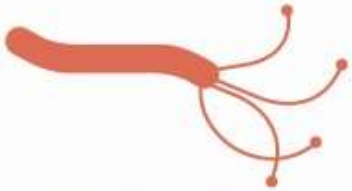
STOMACH CANCER

RISK FACTORS

LONG- TERM INFLAMMATION OF THE STOMACH



SMOKING

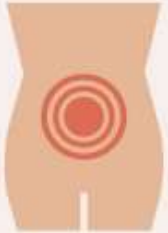


HELICOBACTER PYLORI INFECTION

FAMILY HISTORY

POOR DIET OR OBESITY

SYMPTOMS



PAIN IN THE STOMACH AREA

DIFFICULTY SWALLOWING

WEIGHTLOSS

BLOATED AFTER A SMALL MEAL

NAUSEA AND VOMITING

VOMITING BLOOD OR HAVING BLOOD IN THE STOOL

CLINICAL MANIFESTATIONS

Symptoms

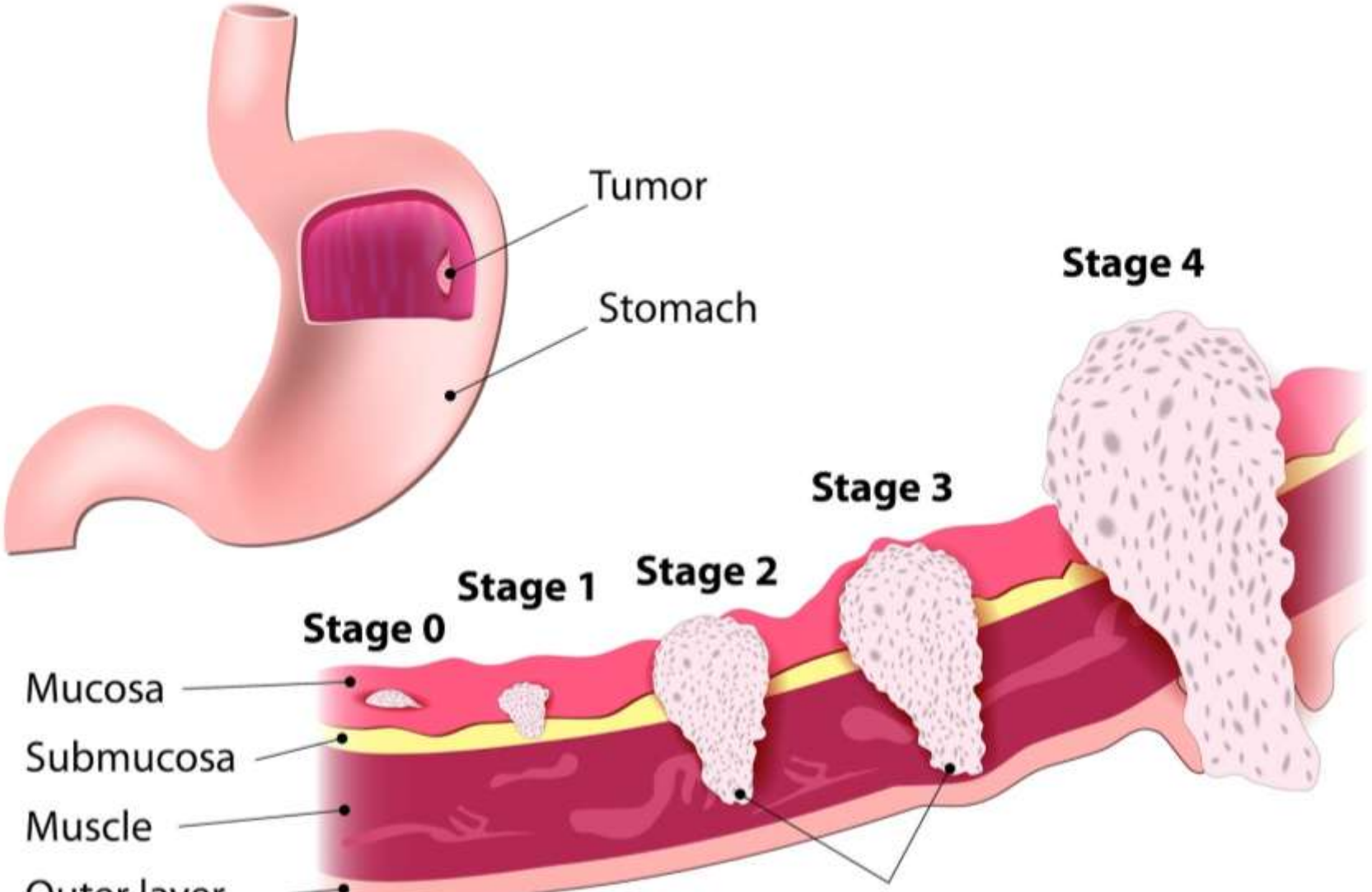
- No specific symptoms when it is superficial
  - Up to 50% of patients: Nonspecific gastrointestinal complaints-- Dyspepsia
- Often delays the diagnosis-- 80% to 90%: advanced or metastatic tumors
- Anorexia and weight loss (95%) as well as abdominal pain that is vague and insidious in nature.
- Nausea, vomiting, and early satiety
  - Occur with bulky tumors that obstruct the gastrointestinal lumen or infiltrative lesions that impair stomach distension.
- Ulcerated tumors may cause bleeding: hematemesis, melena, or massive upper gastrointestinal hemorrhage.

CLINICAL MANIFESTATIONS

Physical examination

- Usually uninformative (in early)
- Advanced tumors may present with
  - Palpable abdominal mass
  - Cachexia,
  - Bowel obstruction
  - Ascites
  - Hepatomegaly
  - Lower extremity edema
- Peritoneal seeding may cause involvement of
  - Ovaries (Krukenberg tumor)
  - Pelvic cul de sac (Blumer's shelf) detectable on rectal examination
- Metastasis may manifest as
  - Enlarged supraclavicular lymph node (Virchow's node),
  - Left axillary lymph node (Irish's node), or
  - Periumbilical lymph node (Sister Mary-Joseph's node)

STAGES OF STOMACH CANCER



Gastric Cancer Survival by stage

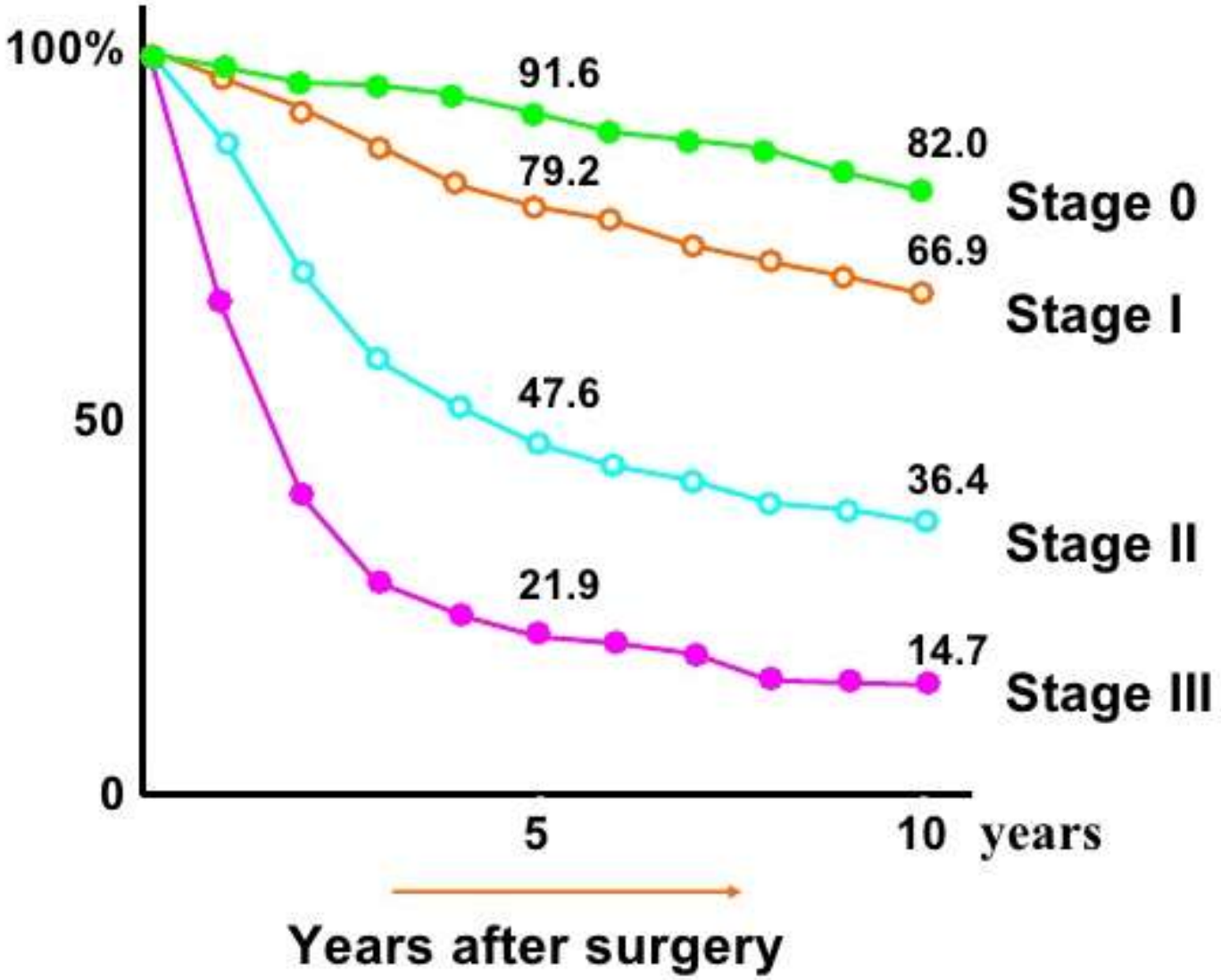


TABLE 1. Japanese Classification for Gastric Carcinoma (JCGC)

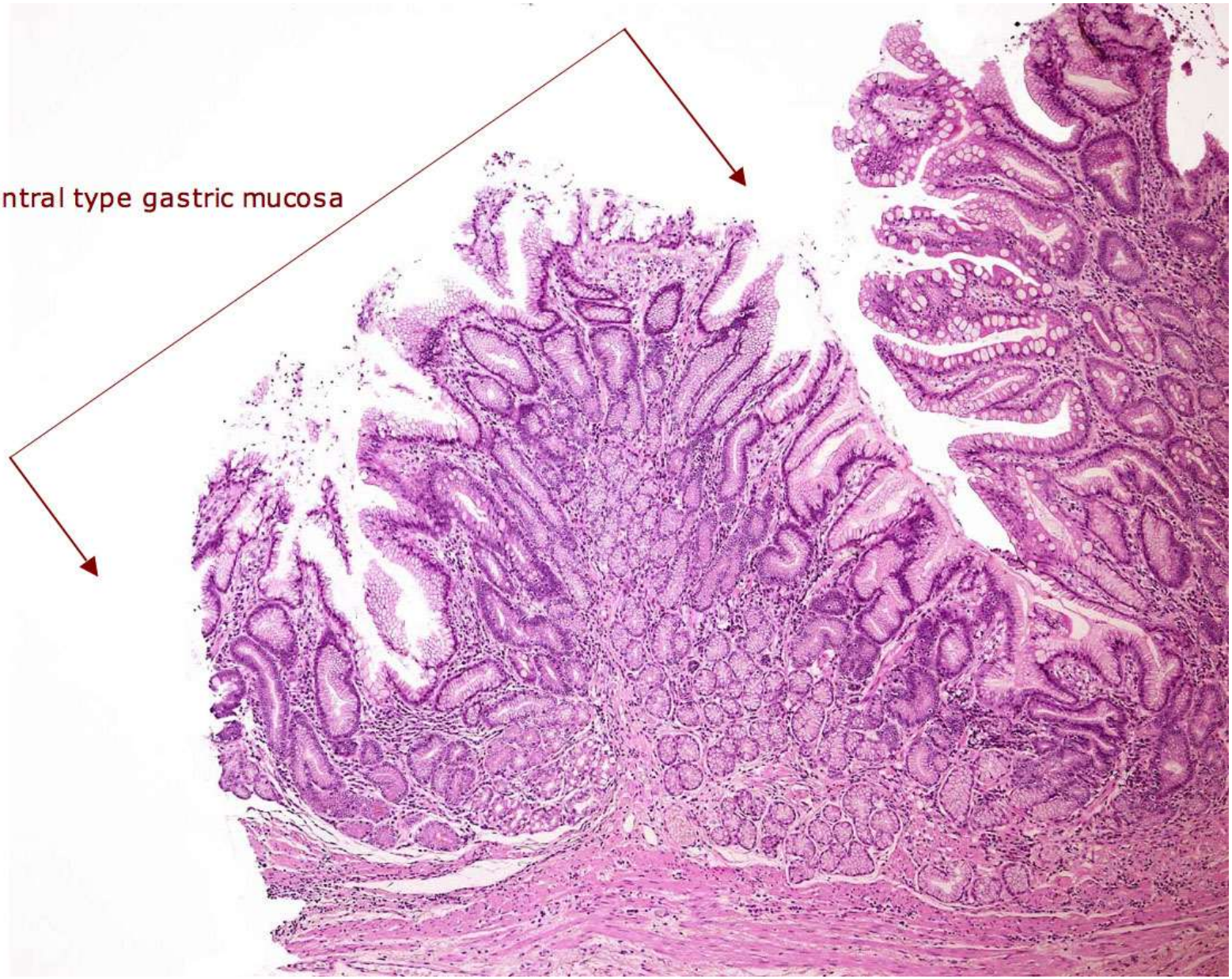
Lymph Node Group	Anatomic Location	D Categor
Group 1	Left cardiac, right cardiac, greater and lesser curvature supra- and infrapyloric	D1
Group 2	Left gastric, common hepatic, splenic artery, splenic hilum hepatic proper, celiac	D2
Group 3	Lepatoduodenal, posterior pancreas, root of mesentery, paraesophageal, diaphragmatic	D3

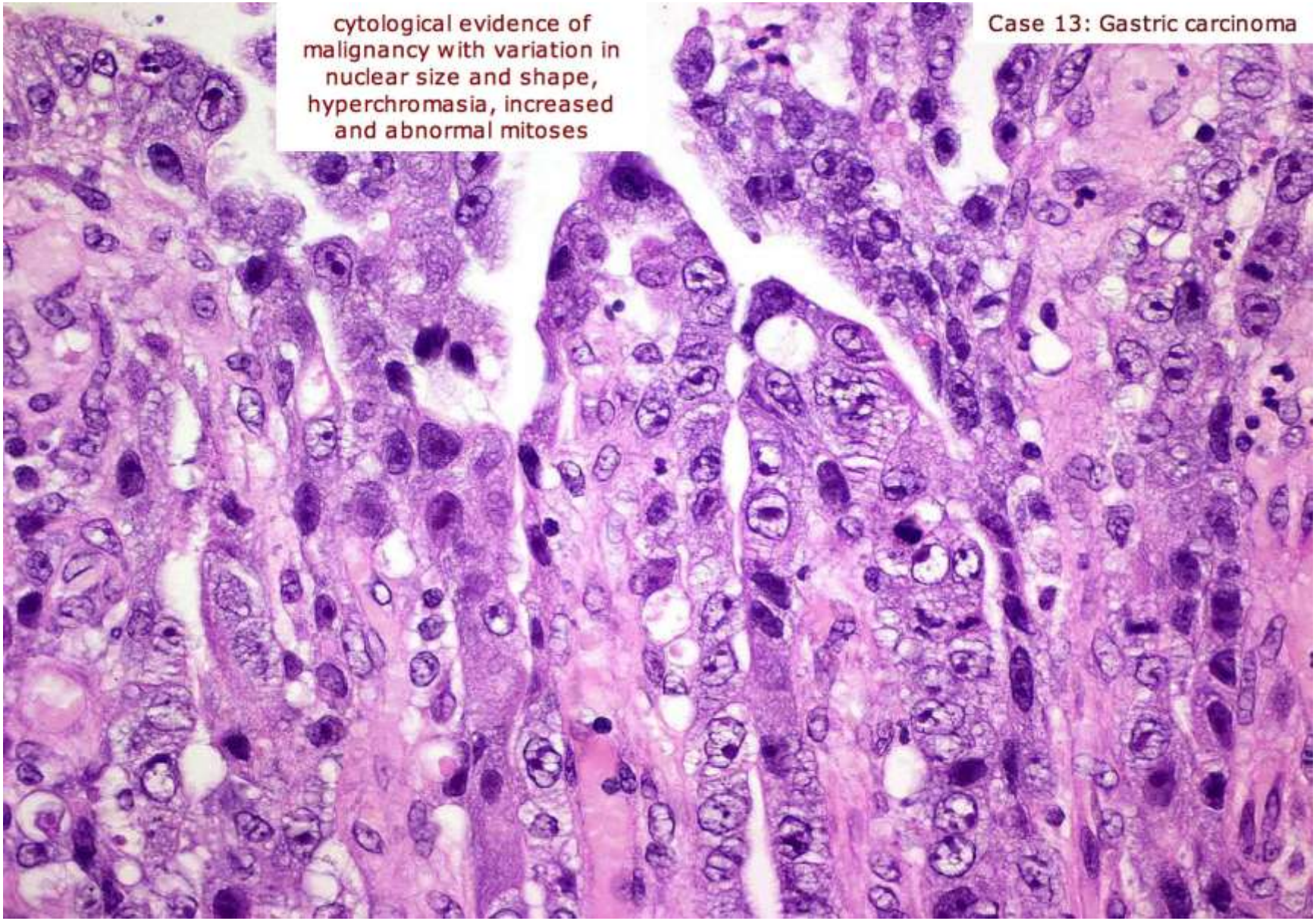
D indicates extent of surgical resection according to Western nomencla ture; D1, group 1; D2, groups 1 + 2; D3, groups 1+ 2 + 3 + paraaorti dissection.

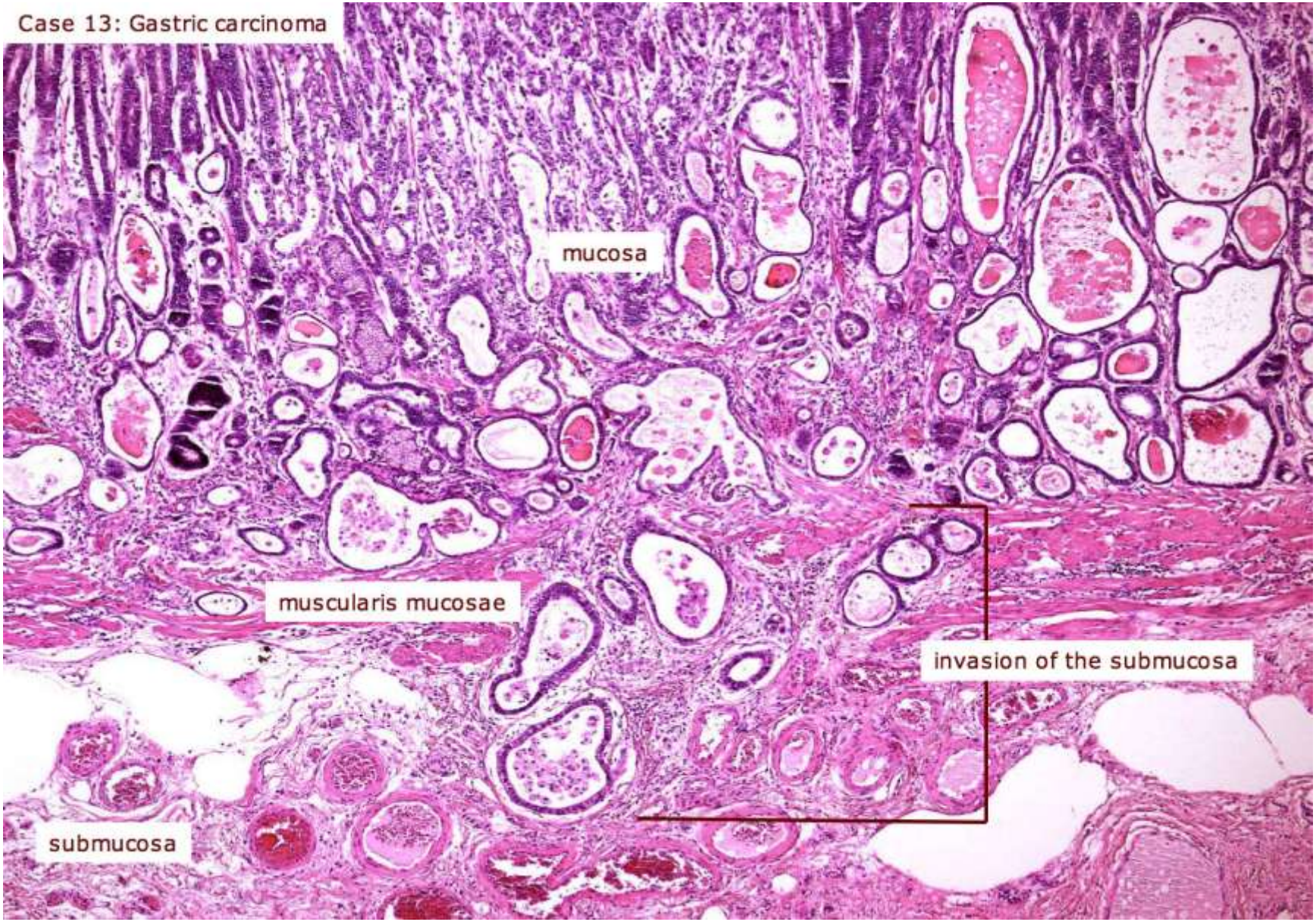
Reprinted from Karpeh MS, et al. *Ann Surg.* 2000;232:362–371.

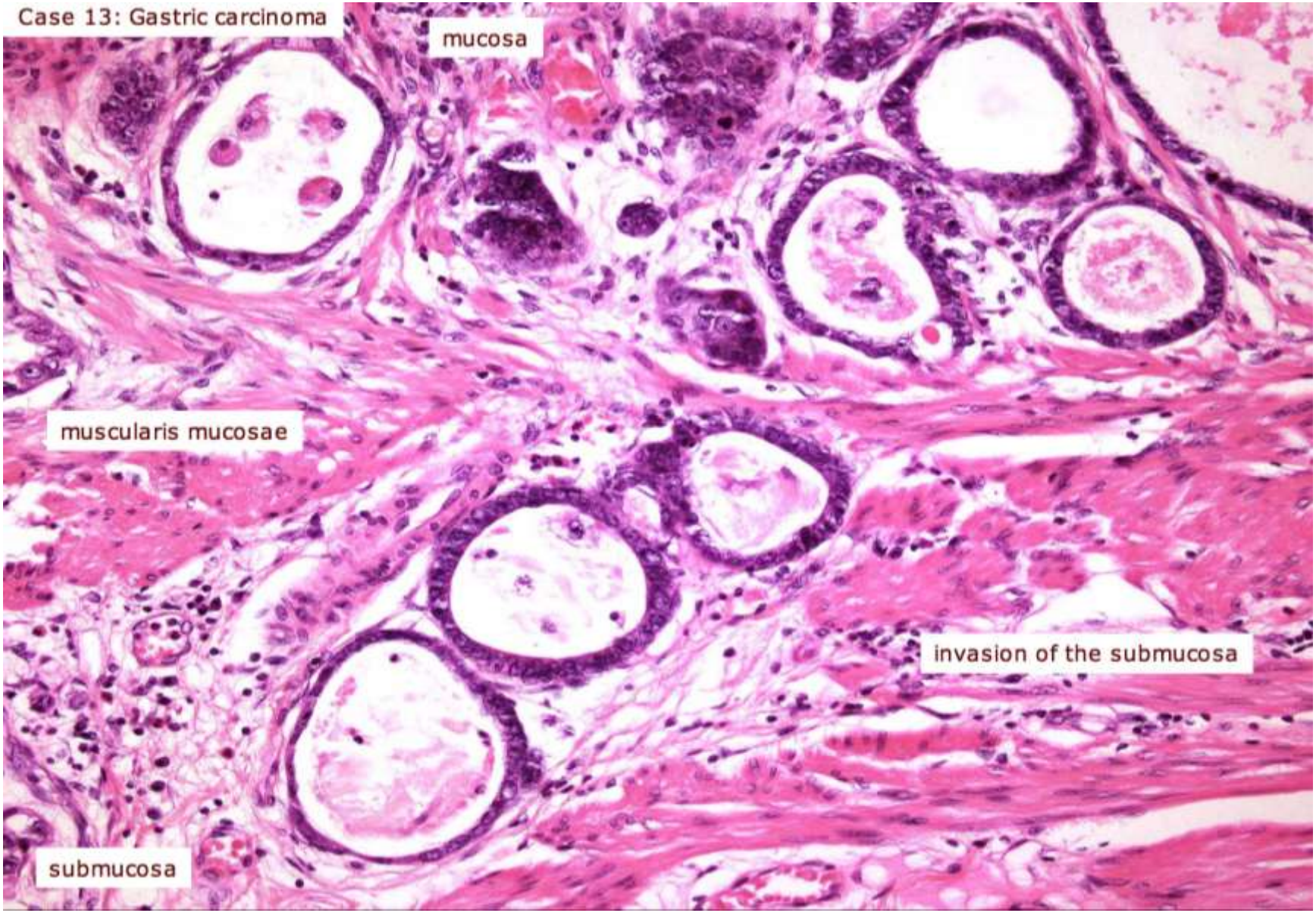
TABLE 2. American Joint Committee on Cancer (AJCC) Classification of Gastric Cancer (5th Edition)

T = Primary Tumor			
Tx	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Invades lamina propria/submucosa		
T2	Invades muscularis propria/subserosa		
T3	Penetrates serosa		
T4	Invades adjacent structures		
N = Lymph Node Status			
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph nodes involved		
N1	Metastasis in 1–6 regional lymph nodes		
N2	Metastasis in 7–15 regional lymph nodes		
N3	Metastasis in more than 15 regional lymph nodes		
M = Distant Metastasis			
Mx	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage Grouping			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T1	N1	M0
	T2	N0	M0
Stage II	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
Stage IIIA	T2	N2	M0
	T3	N1	M0
	T4	N0	M0
Stage IIIB	T3	N2	M0
Stage IV	T4	N1, N2, N3	M0
	T1, T2, T3	N3	M0
	Any T	Any N	M1

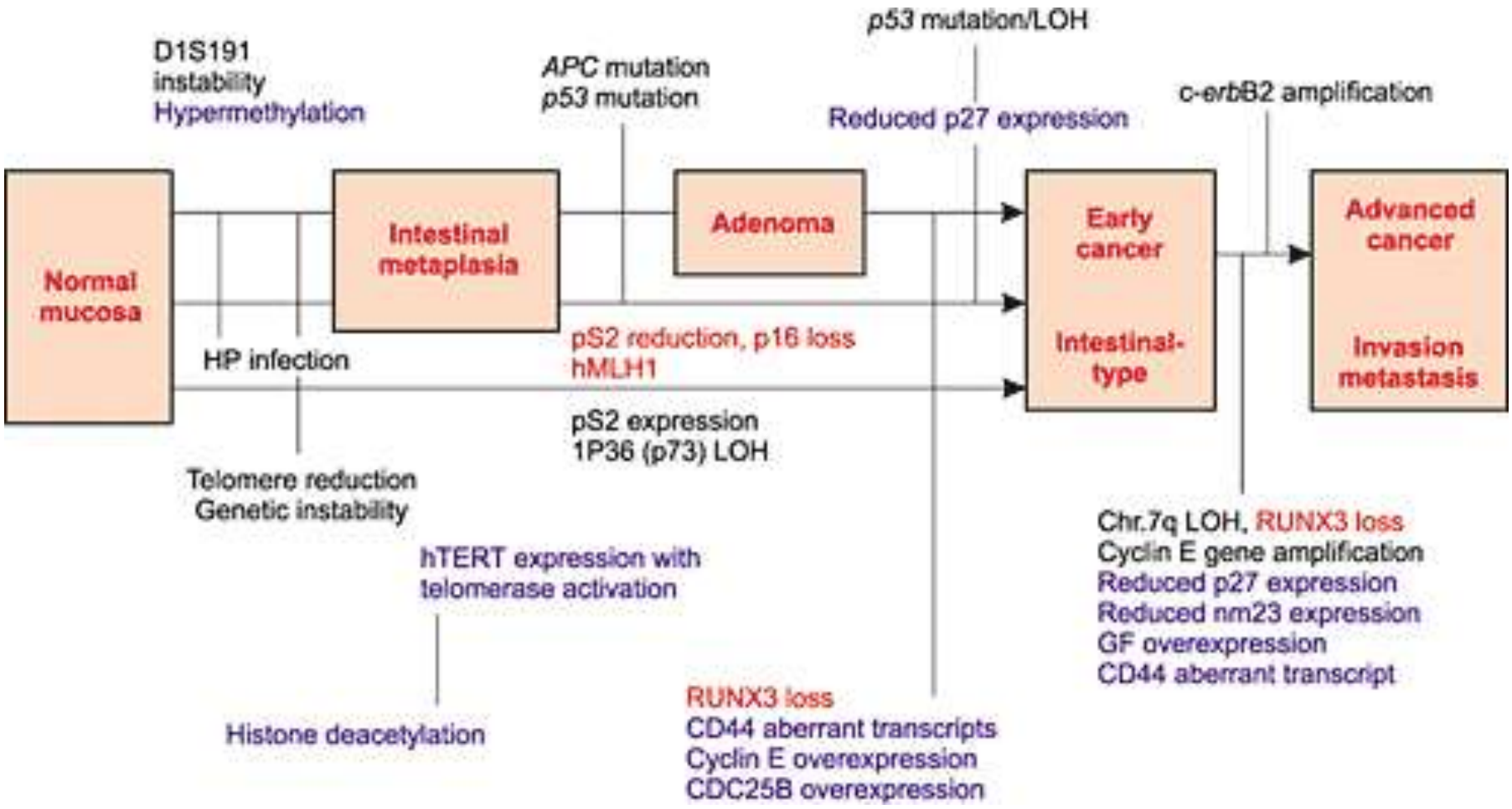

normal antral type gastric mucosa

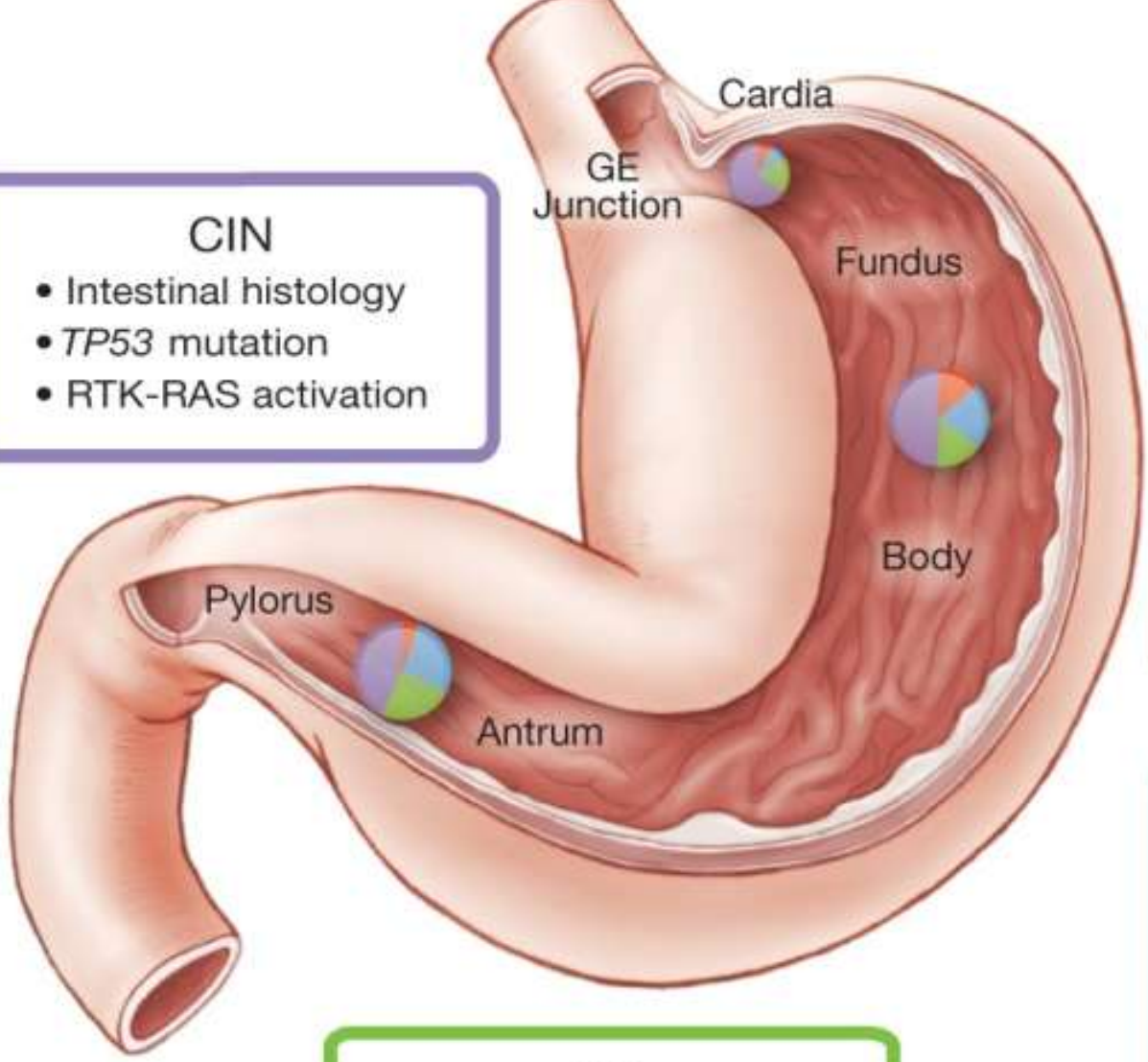

cytological evidence of malignancy with variation in nuclear size and shape, hyperchromasia, increased and abnormal mitoses
Case 13: Gastric carcinoma


Case 13: Gastric carcinoma
mucosa
muscularis mucosae
invasion of the submucosa
submucosa


Case 13: Gastric carcinoma
mucosa
muscularis mucosae
invasion of the submucosa
submucosa

MOLECULER OF CANCER





CIN

- Intestinal histology
- *TP53* mutation
- RTK-RAS activation

EBV

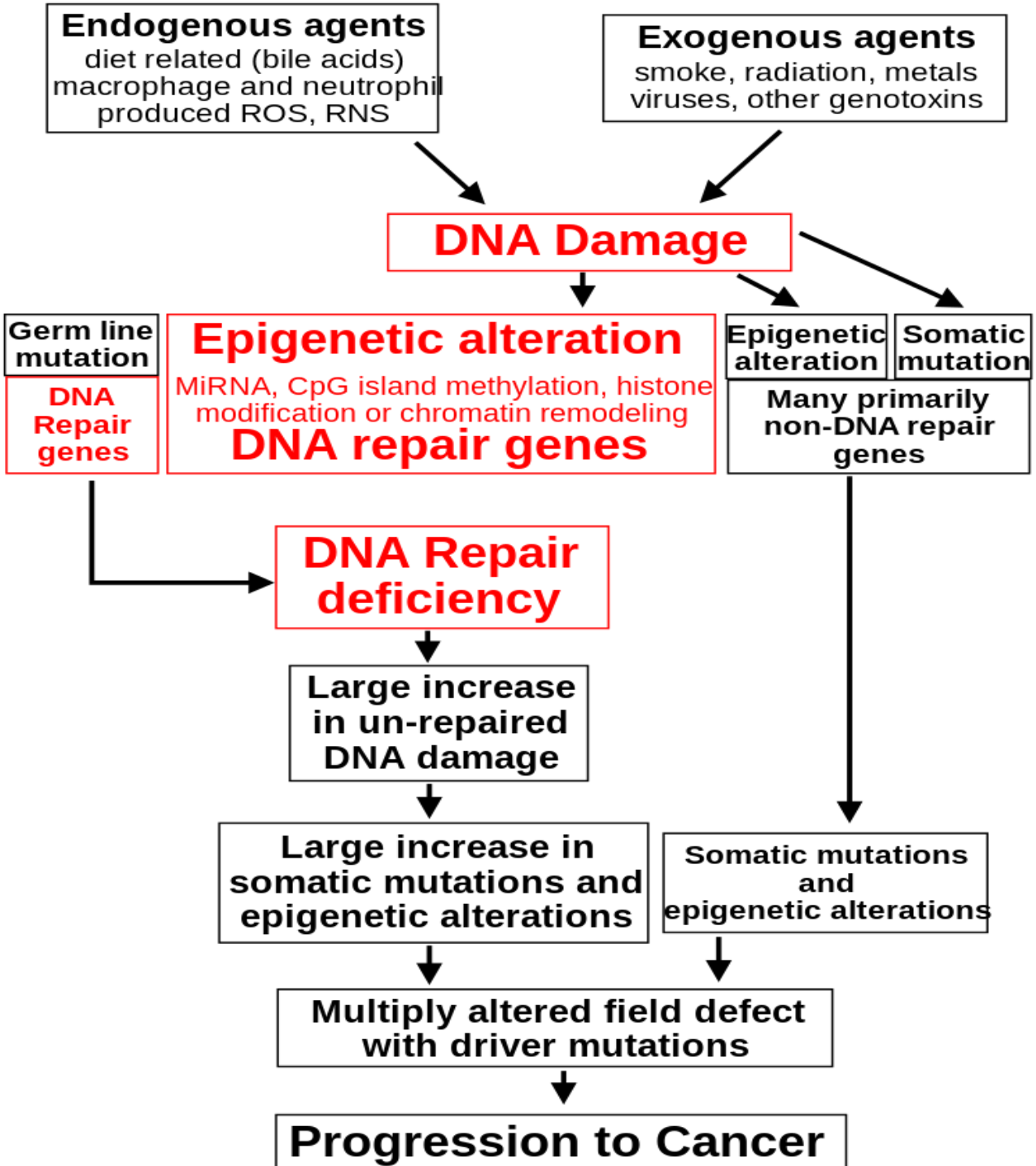
- *PIK3CA* mutation
- *PD-L1/2* overexpression
- EBV-CIMP
- *CDKN2A* silencing
- Immune cell signalling

MSI

- Hypermutation
- Gastric-CIMP
- *MLH1* silencing
- Mitotic pathways

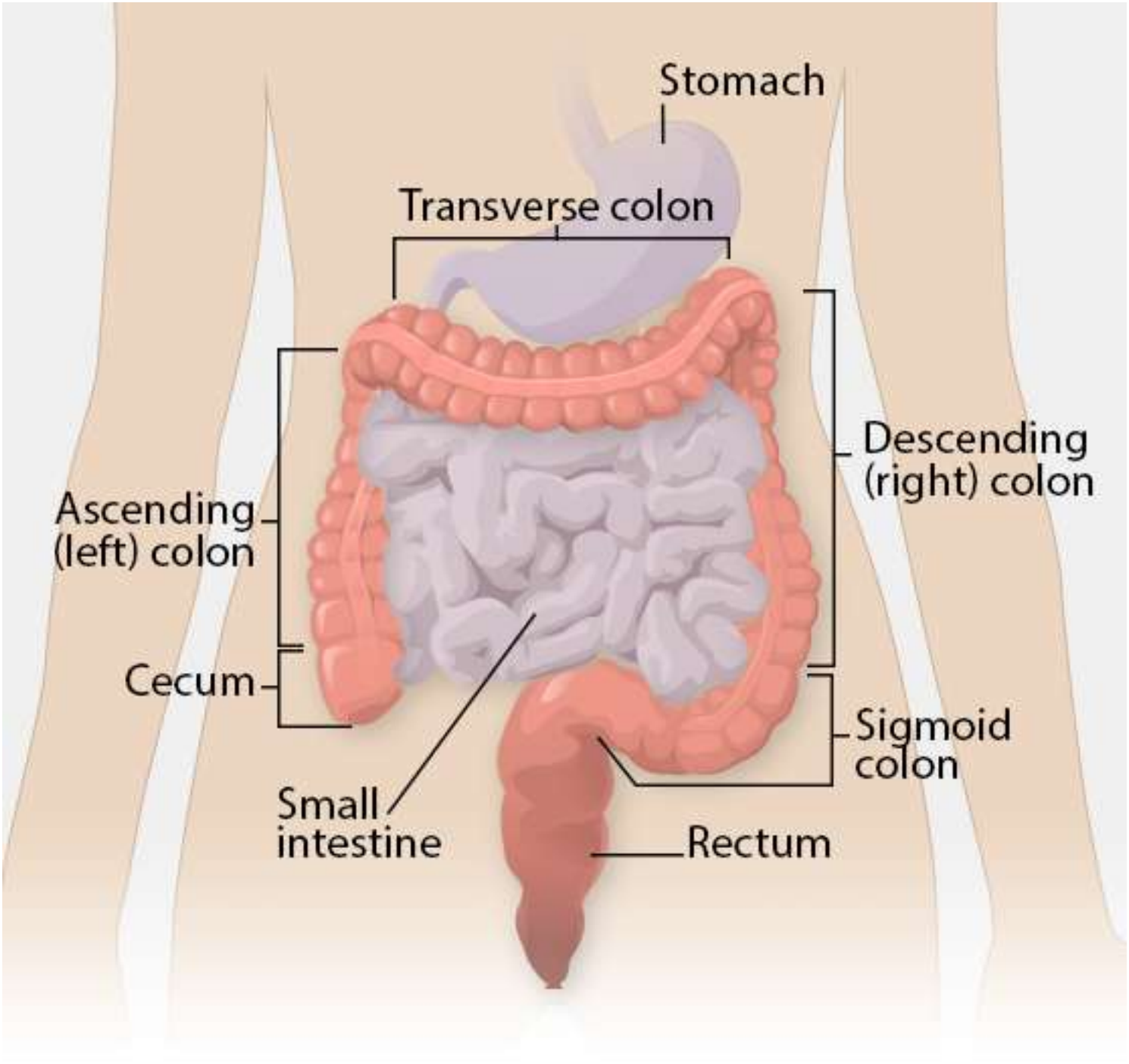
GS

- Diffuse histology
- *CDH1*, *RHOA* mutations
- *CLDN18–ARHGAP* fusion
- Cell adhesion


Endogenous agents
diet related (bile acids)
macrophage and neutrophil
produced ROS, RNS
Exogenous agents
smoke, radiation, metals
viruses, other genotoxins
DNA Damage
Germ line mutation
DNA Repair genes
Epigenetic alteration
MiRNA, CpG island methylation, histone modification or chromatin remodeling
DNA repair genes
Epigenetic alteration
Somatic mutation
Many primarily non-DNA repair genes
DNA Repair deficiency
Large increase in un-repaired DNA damage
Large increase in somatic mutations and epigenetic alterations
Somatic mutations and epigenetic alterations
Multiply altered field defect with driver mutations
Progression to Cancer

COLORECTAL CANCER

- Cancer that starts in the colon or the rectum.
- Colon cancer or rectal cancer, depending on where they start.
- Grouped together because they have many features in common.
- Most colorectal cancers begin as a growth on the inner lining of the colon or rectum called a *polyp*.
- Some types of polyps can change into cancer over the course of several years, but not all polyps become cancer.
- The chance of changing into a cancer depends on the kind of polyp.

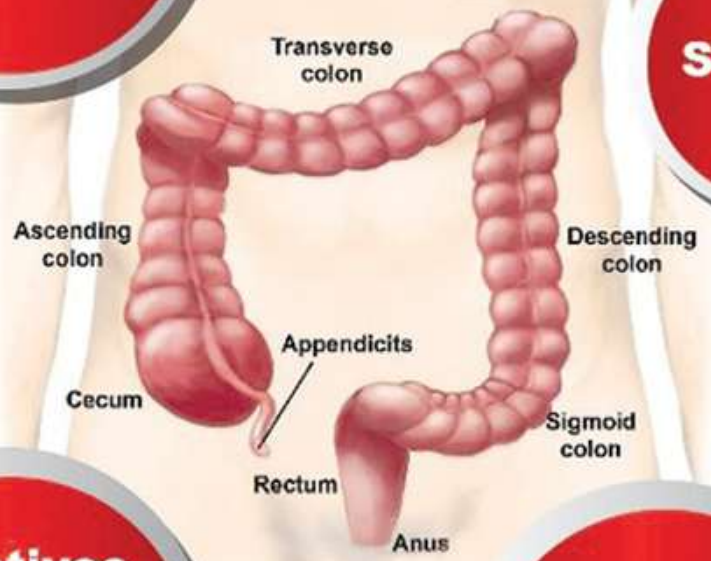

Stomach
Transverse colon
Descending (right) colon
Ascending (left) colon
Cecum
Sigmoid colon
Small intestine
Rectum

YOU ARE AT RISK IF :-

Diet high in red meat and low fiber

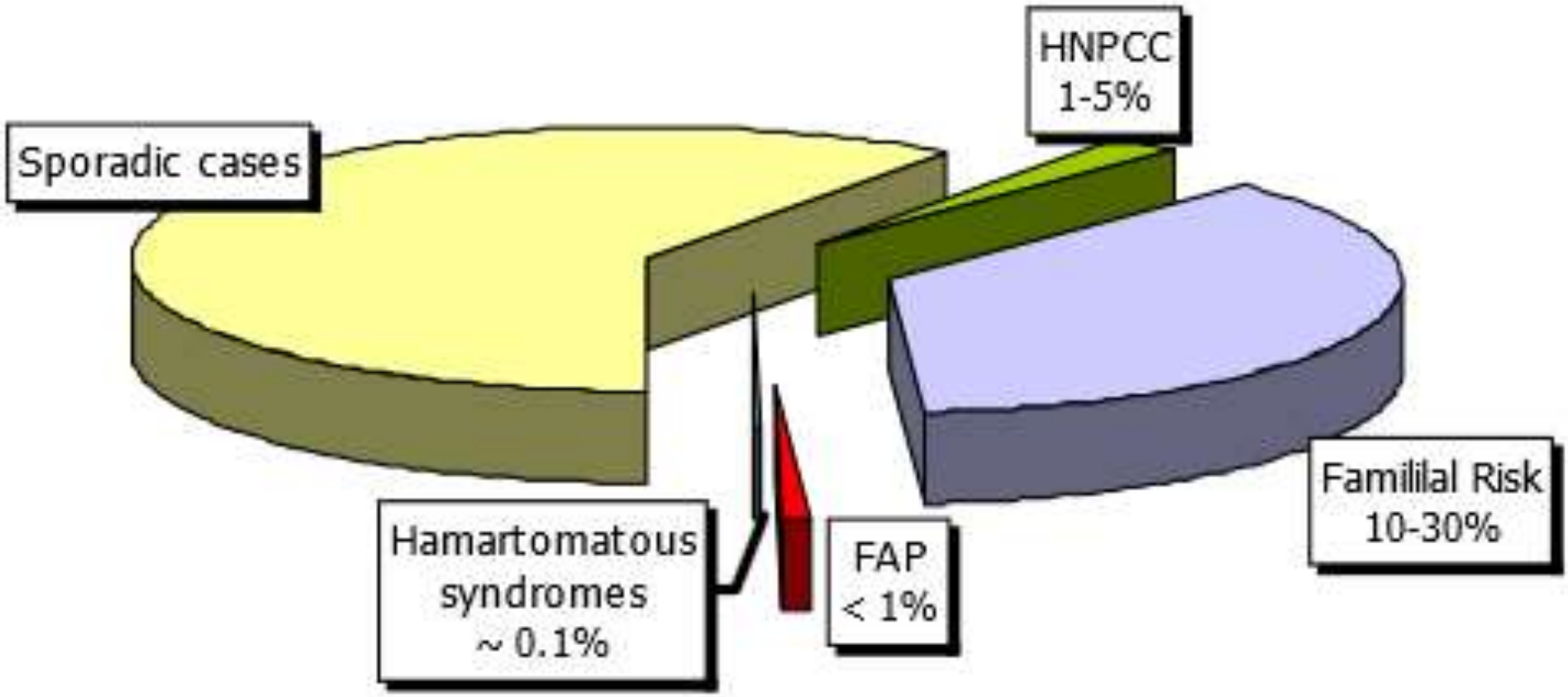
Over weight

Smoking

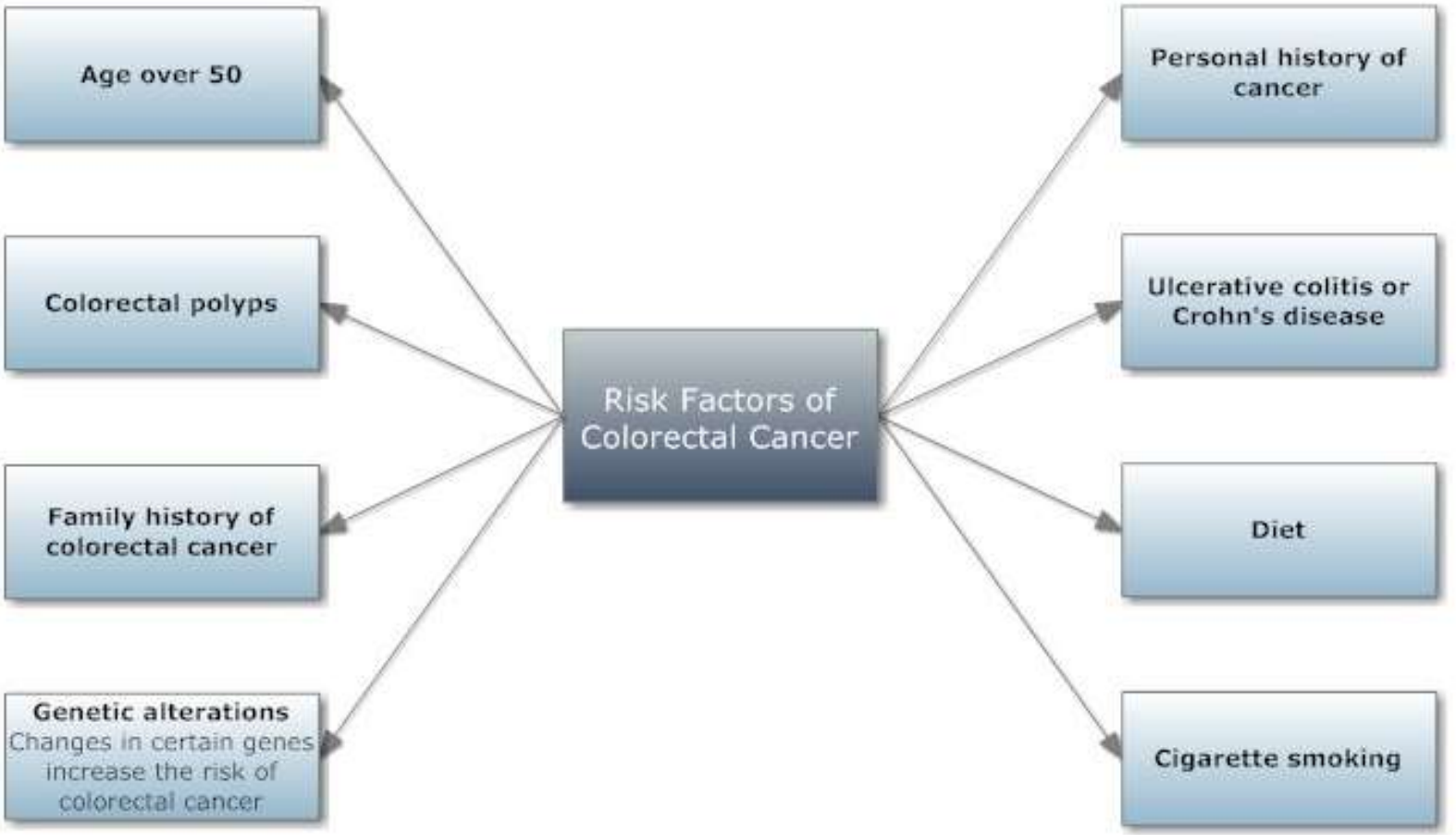


Relatives with colon cancer and polyps

Above 50 years of age


HNPCC
1-5%
Sporadic cases
Famililal Risk
10-30%
Hamartomatous
syndromes
~ 0.1%
FAP
< 1%

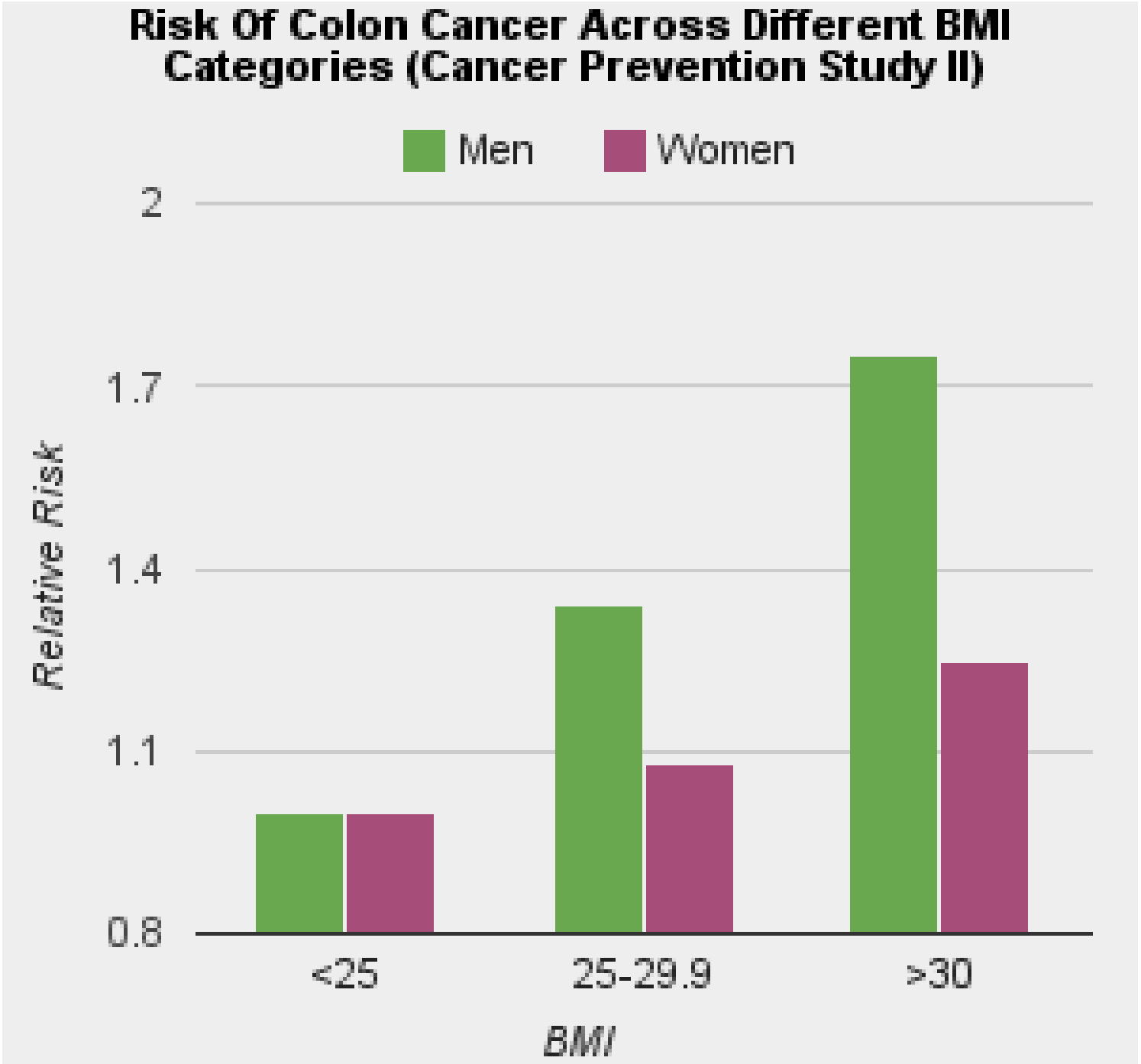
Risk Factors of Colorectal Cancer



Source: National Cancer Institute, U.S. National Institutes of Health. www.cancer.gov

Colon Cancer:

- Age (over 50)
- Personal history of colorectal cancer or polyps
- Personal history of Inflammatory Bowel Disease (IBD)
- Family history of colorectal cancer or polyps
- Inherited syndromes
- Racial & Ethnic Backgrounds: African-Americans & Jewish persons of Eastern European descent
- Type 2 Diabetes


Risk Of Colon Cancer Across Different BMI Categories (Cancer Prevention Study II)
Men
Women
2
1.7
1.4
1.1
0.8
Relative Risk
<25
25-29.9
>30
BMI

Colorectal Cancer:
Risk Factors

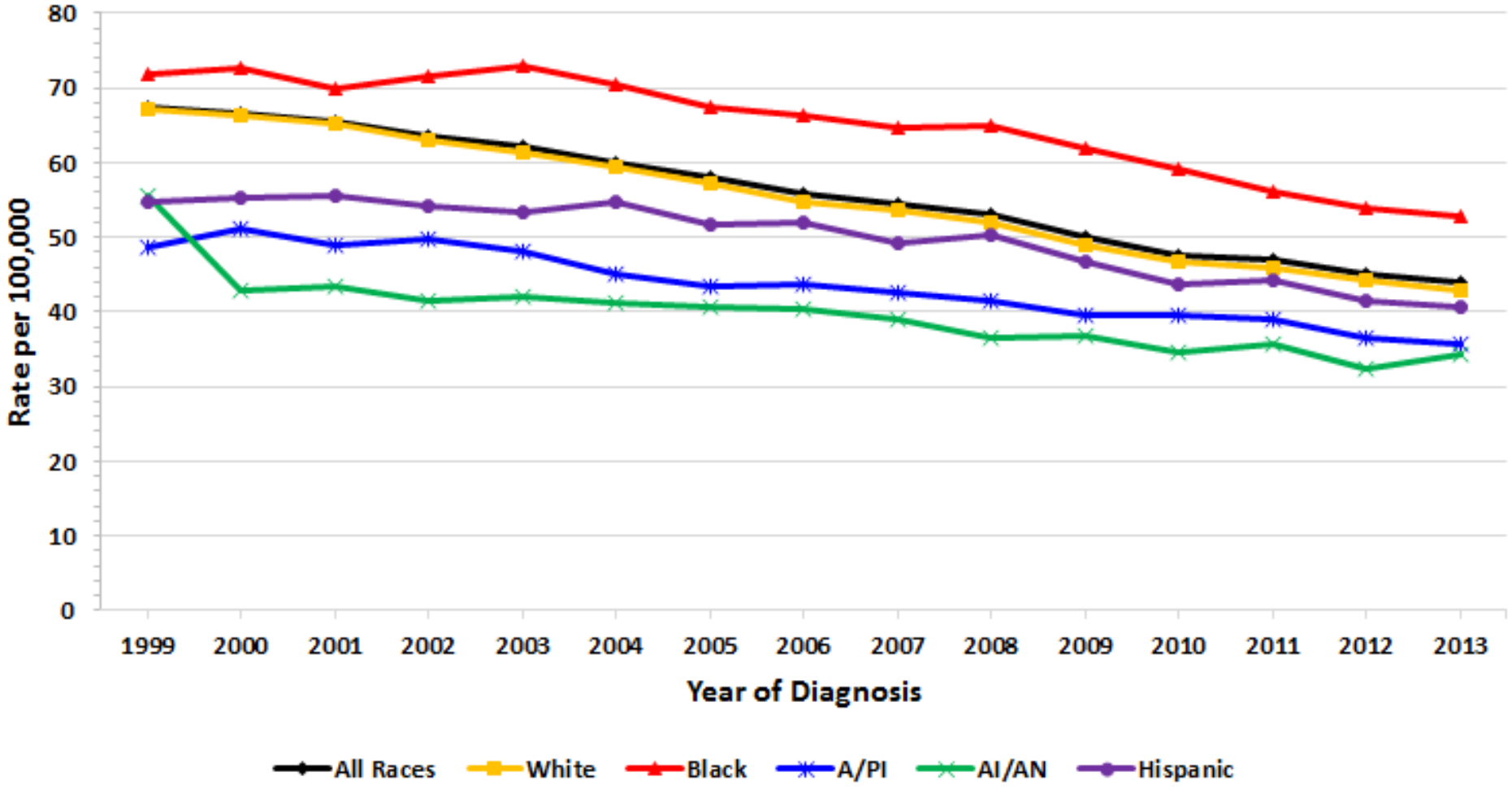
Non Modifiable

- Age
- Personal History
- Family History
- Race

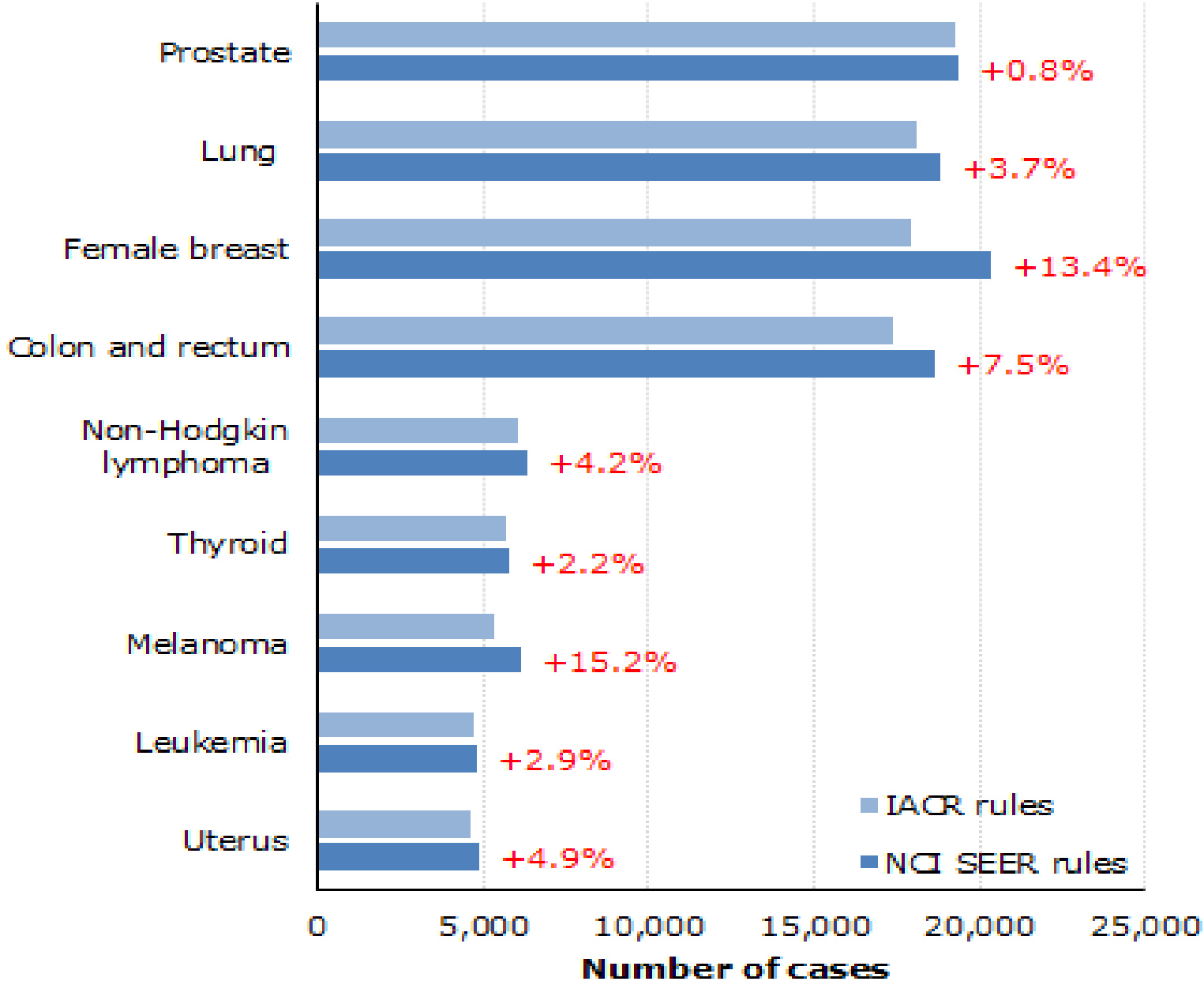
Modifiable

- Diet
- Physical Activity
- Obesity
- Smoking
- Alcohol Use

Colorectal Cancer
Incidence Rates* by Race and Ethnicity,† Male, United States, 1999–2013¶§



Number of new cancer cases for most common cancers, IACR vs. NCI SEER rules, Ontario, 2010–2011



Source: Ontario Cancer Registry, 2015 (Cancer Care Ontario)

Genetic alterations and bowel cancer

Inherited (<10%)

- HNPCC
- FAP
- Unknown genes

Non inherited (90%)

Many genes unidentified

Colon Polyps

Normal

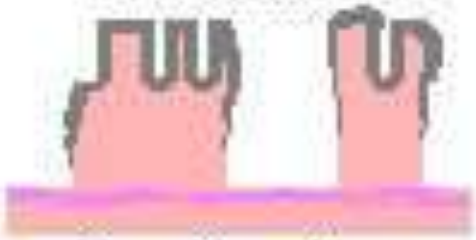
Hyperplastic polyp/
serrated adenoma

Juvenile hamartoma

Peutz-Jeghers hamartoma

Pedunculated
tubular adenoma

Sessile villous
adenoma

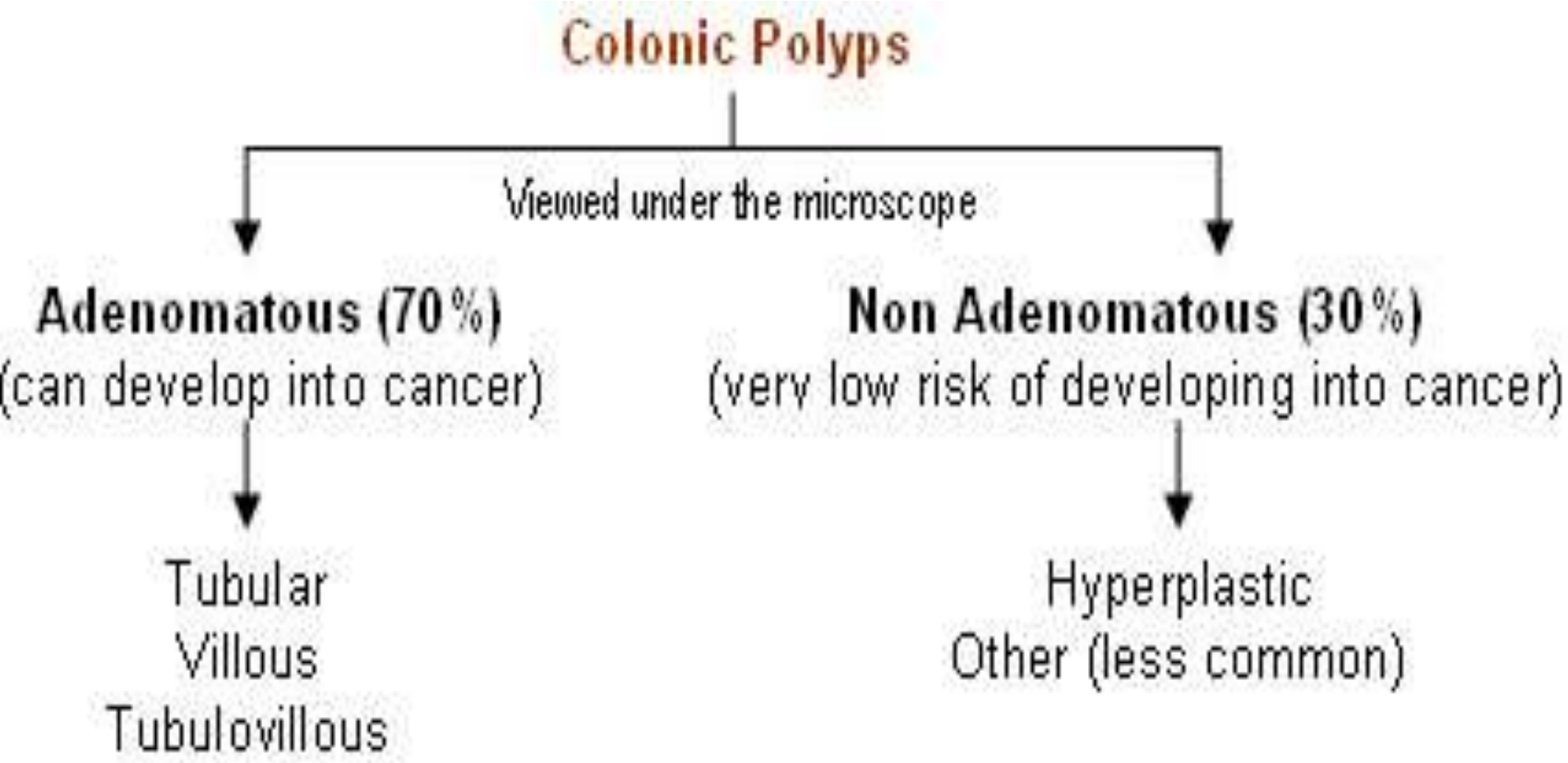


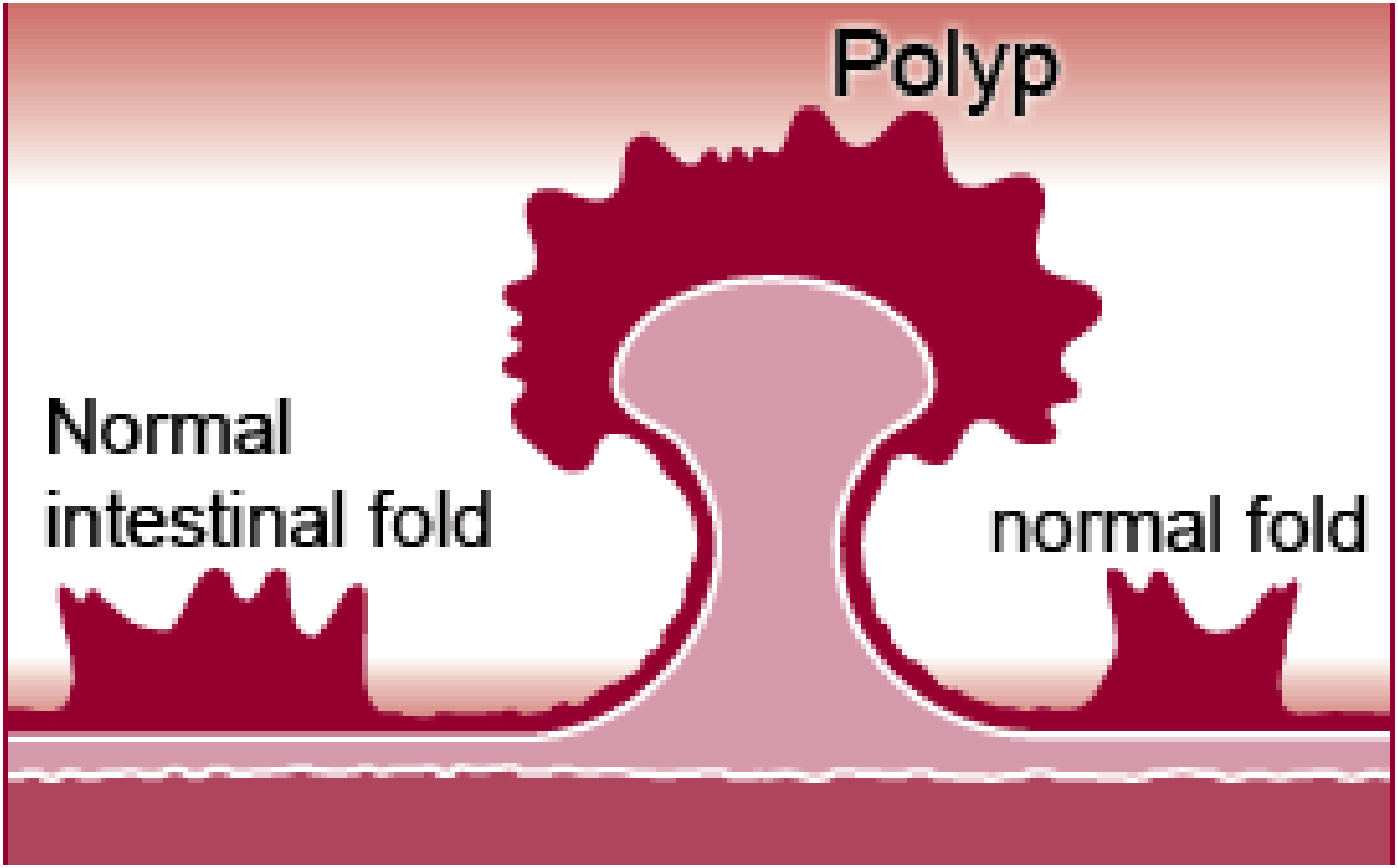
Pseudopolyps

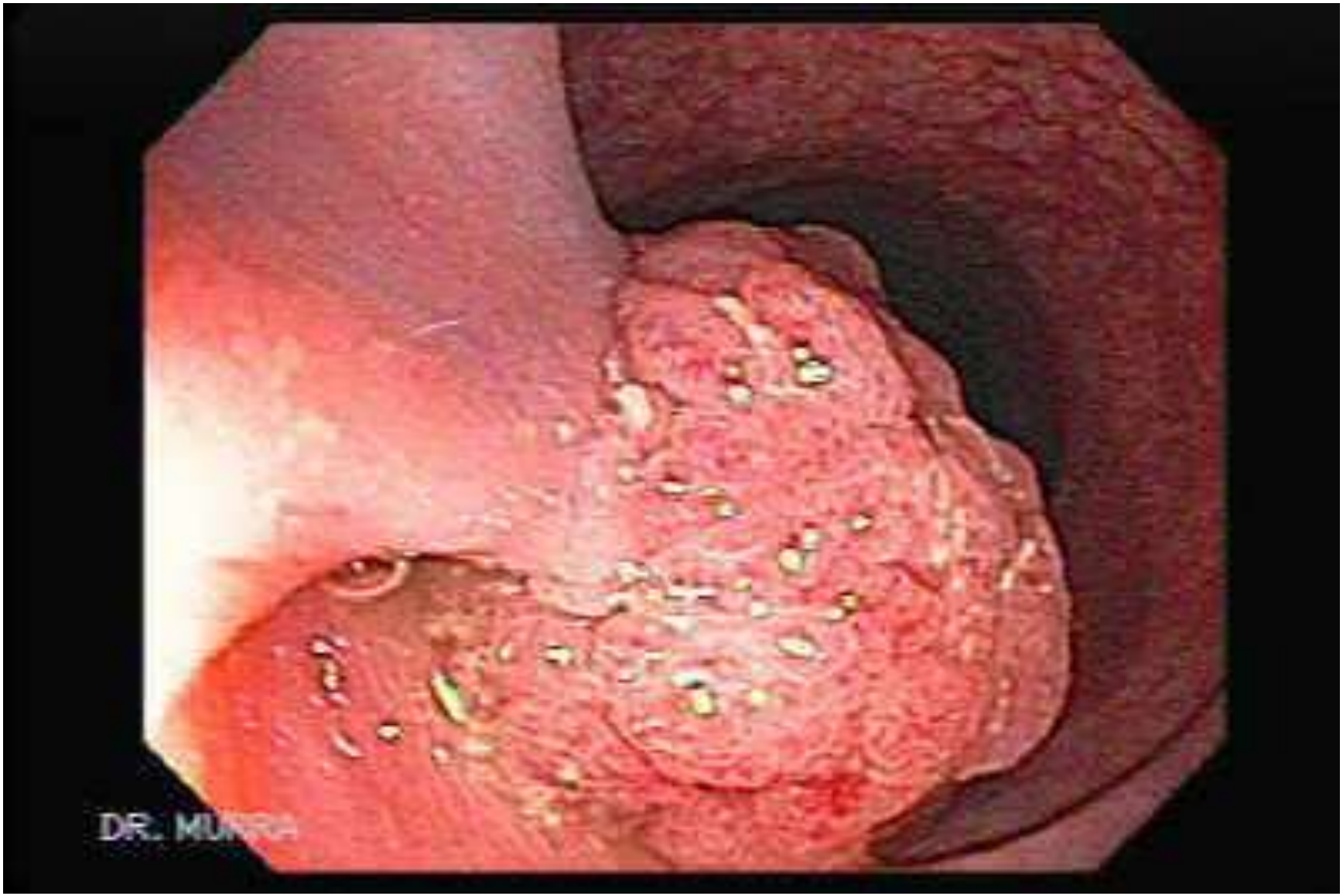
Adenocarcinoma

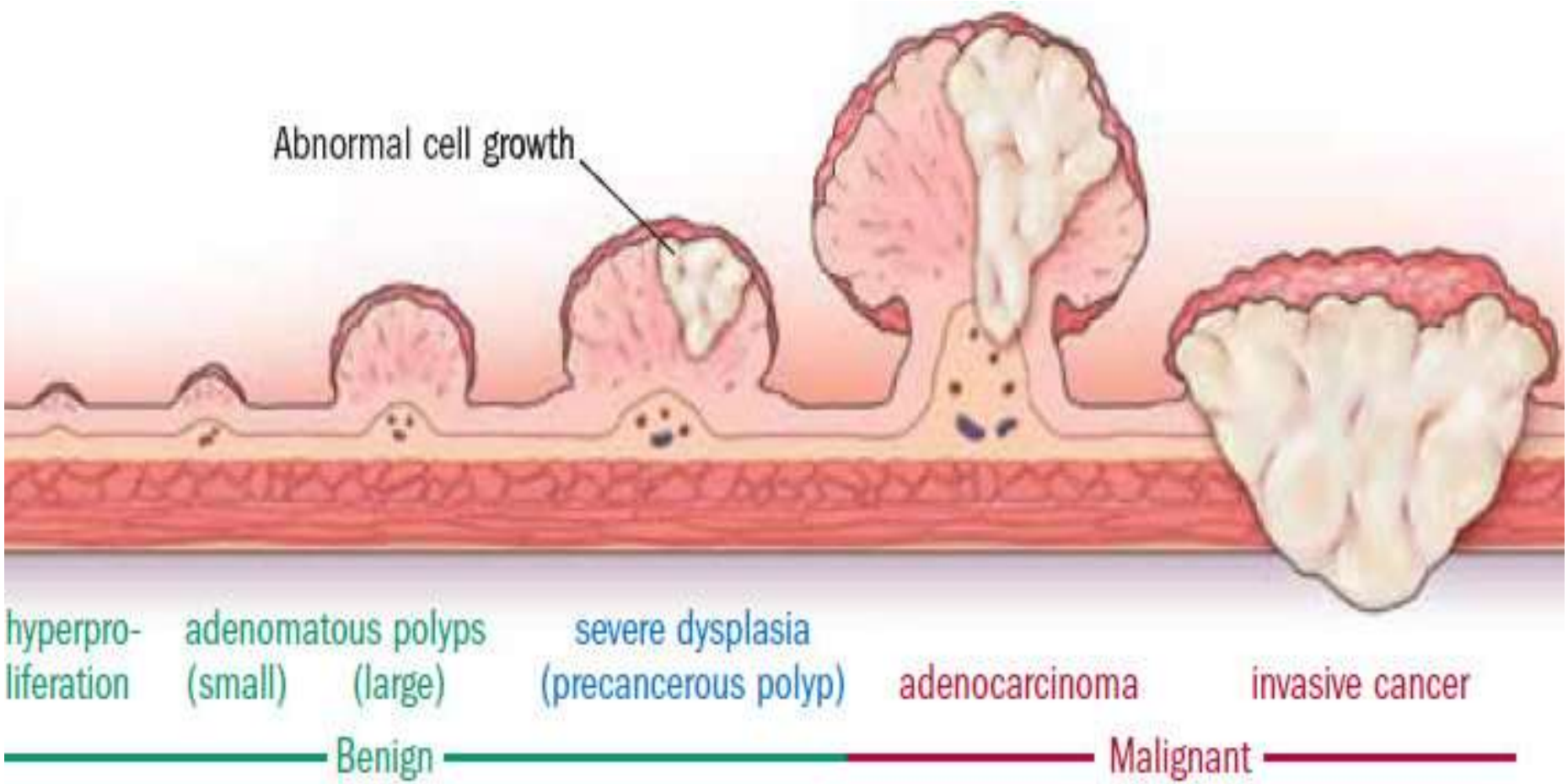
HISTOLOGIC CLASSIFICATION OF POLYPS

- Adenomas are one histologic subtype of colorectal polyps.
- Other histologic subtypes include mucosal polyps, hyperplastic/ serrated polyps, juvenile polyps, and inflammatory polyps.
- In addition, certain types of polyps can arise from layers deeper than the mucosa, including lipomas, carcinoid tumors, gastrointestinal stromal tumors (GIST), and serosal lesions.


Colonic Polyps
Viewed under the microscope
Adenomatous (70%)
(can develop into cancer)
Non Adenomatous (30%)
(very low risk of developing into cancer)
Tubular
Villous
Tubulovillous
Hyperplastic
Other (less common)


Polyp
Normal
intestinal fold
normal fold


DR. MURRA

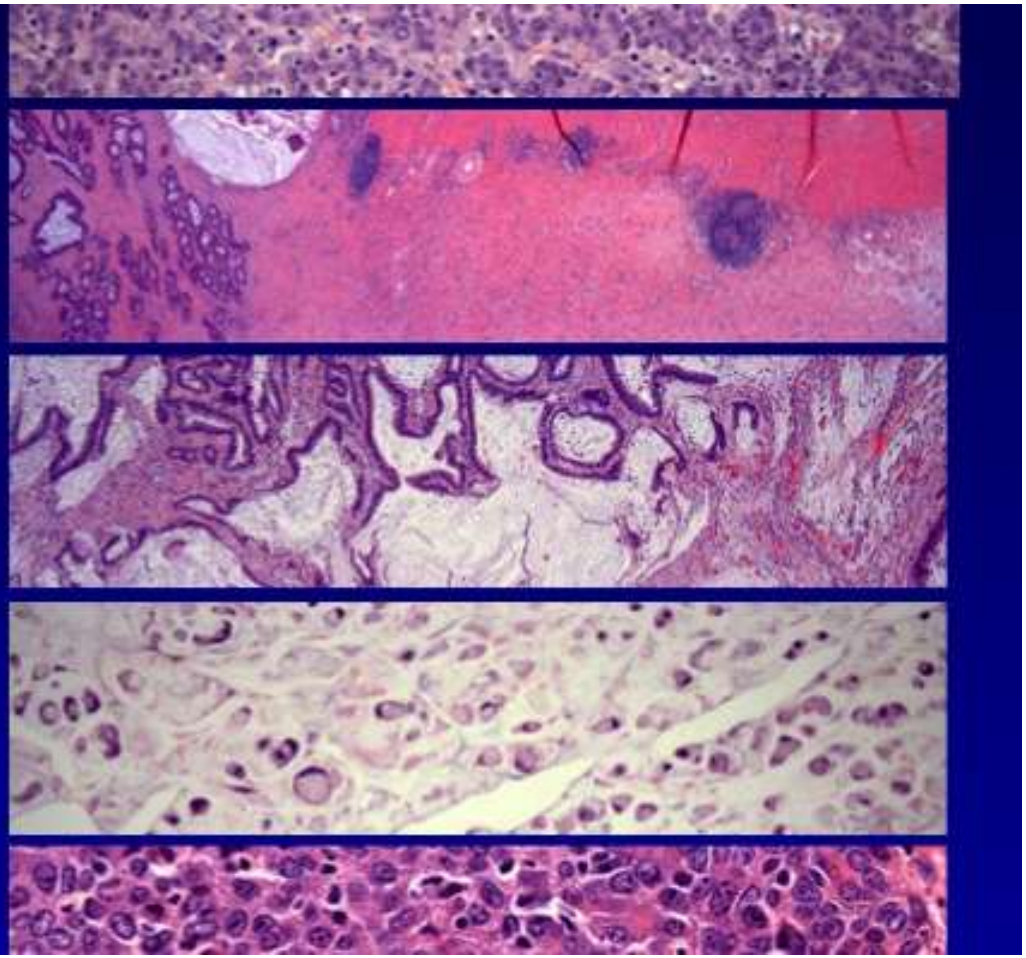

Abnormal cell growth
hyperpro-
liferation
adenomatous polyps
(small)
(large)
severe dysplasia
(precancerous polyp)
adenocarcinoma
invasive cancer
Benign
Malignant

Crohn's-like reaction

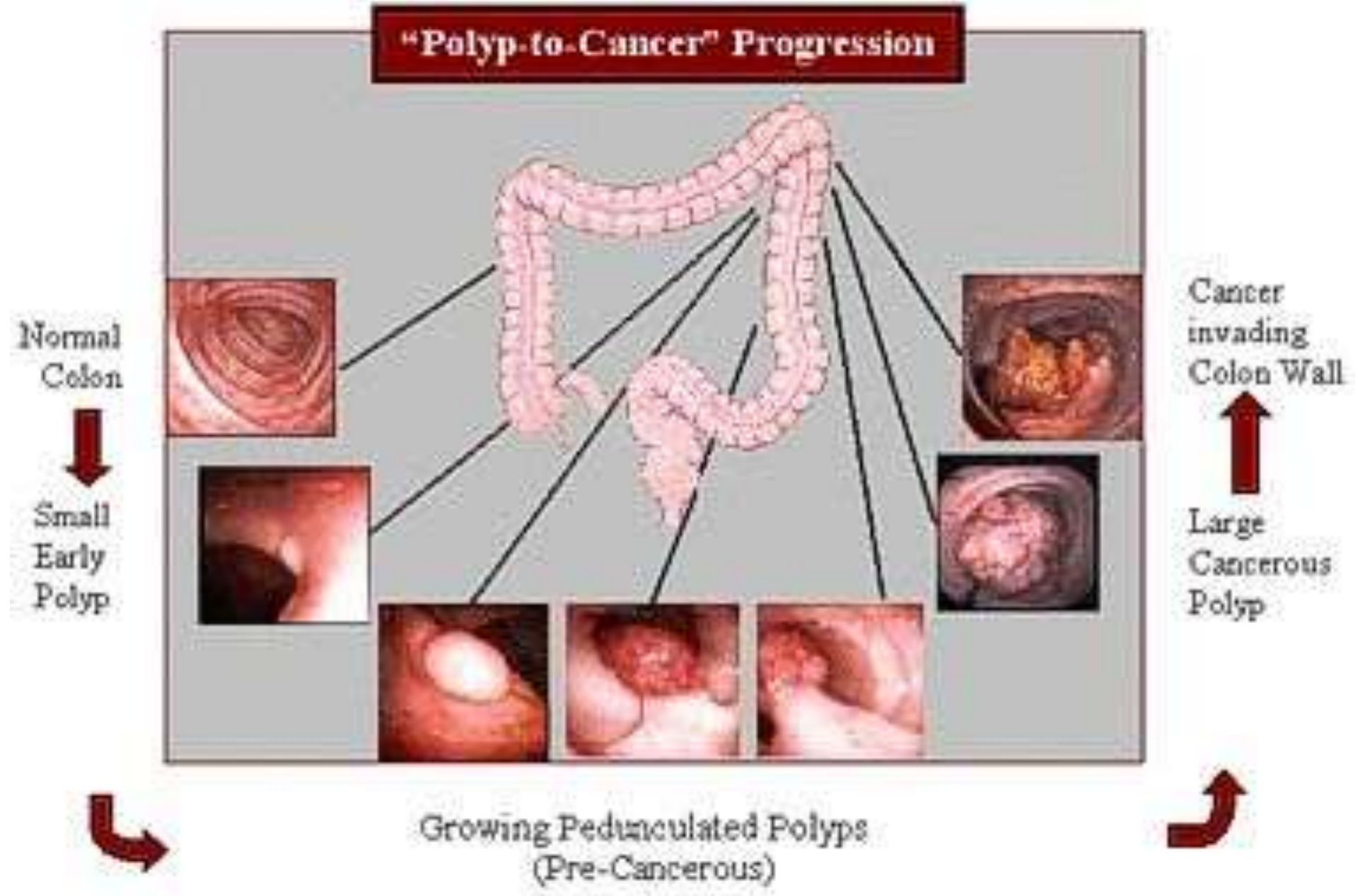
Mucinous

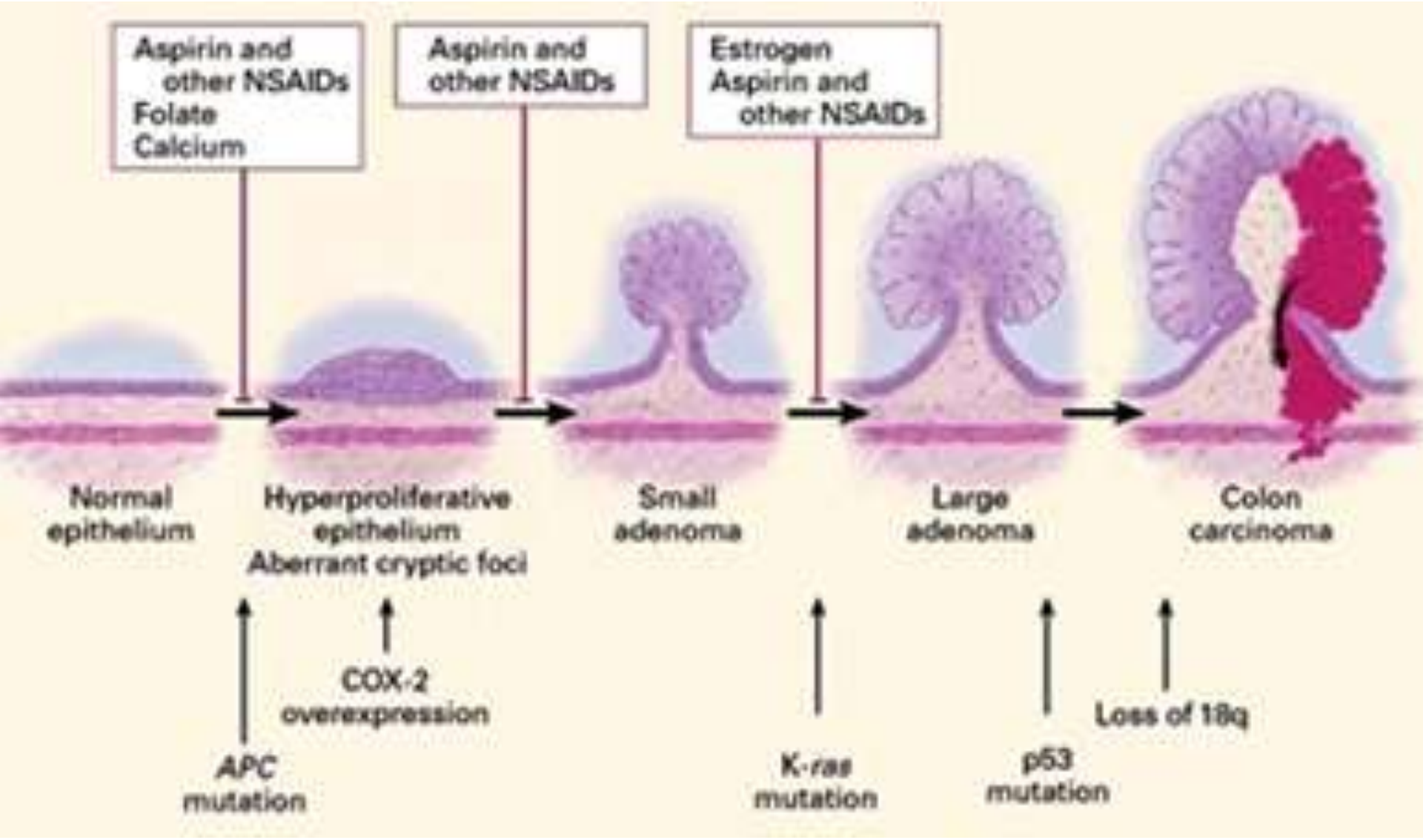
Signet Ring

Medullary pattern

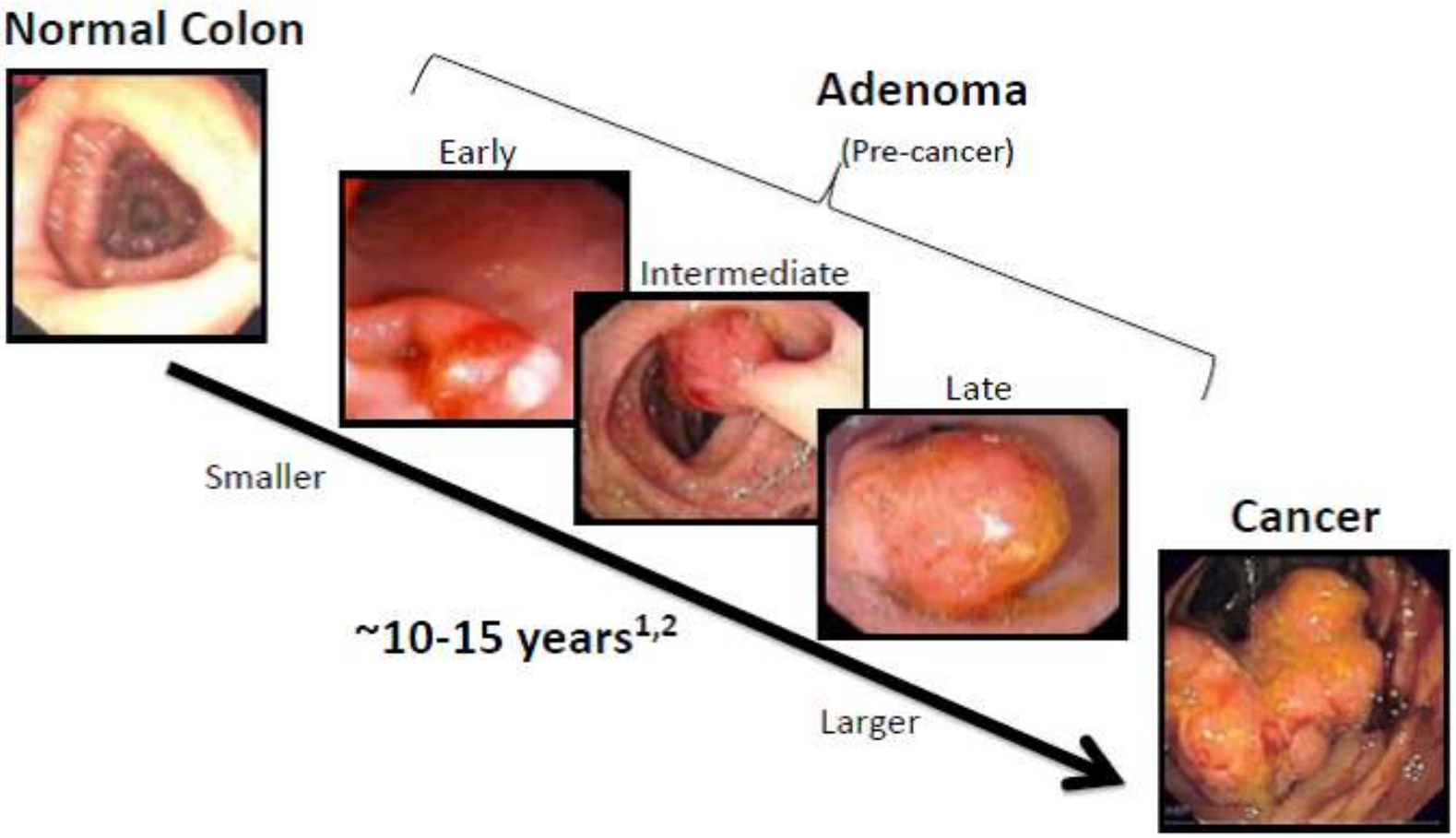


Neoplastic polyps	Nonneoplastic (tumorlike) polyps
▶ adenoma ▶ polypoid carcinoma ▶ carcinoid tumor ▶ nonepithelial tumors (lipoma, leiomyoma, hemangioma, lymphangioma, etc.)	▶ Peutz–Jeghers polyp ▶ juvenile polyp ▶ hyperplastic polyp ▶ benign lymphoid polyp ▶ inflammatory polyp


"Polyp-to-Cancer" Progression
Normal Colon
Small Early Polyp
Cancer invading Colon Wall
Large Cancerous Polyp
Growing Pedunculated Polyps
(Pre-Cancerous)

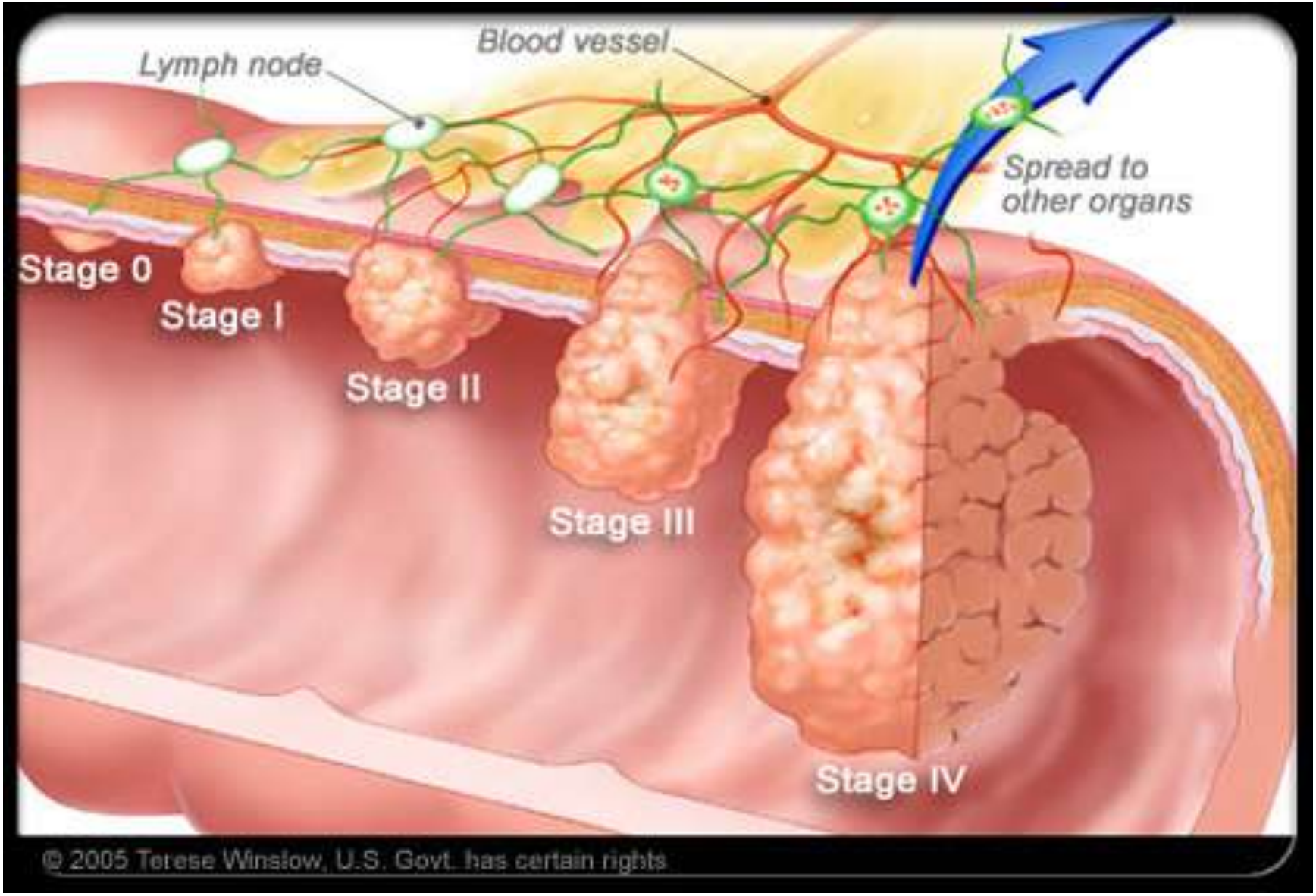

Aspirin and other NSAIDs Folate Calcium
Aspirin and other NSAIDs
Estrogen Aspirin and other NSAIDs
Normal epithelium
Hyperproliferative epithelium Aberrant cryptic foci
Small adenoma
Large adenoma
Colon carcinoma
APC mutation
COX-2 overexpression
K-ras mutation
p53 mutation
Loss of 18q

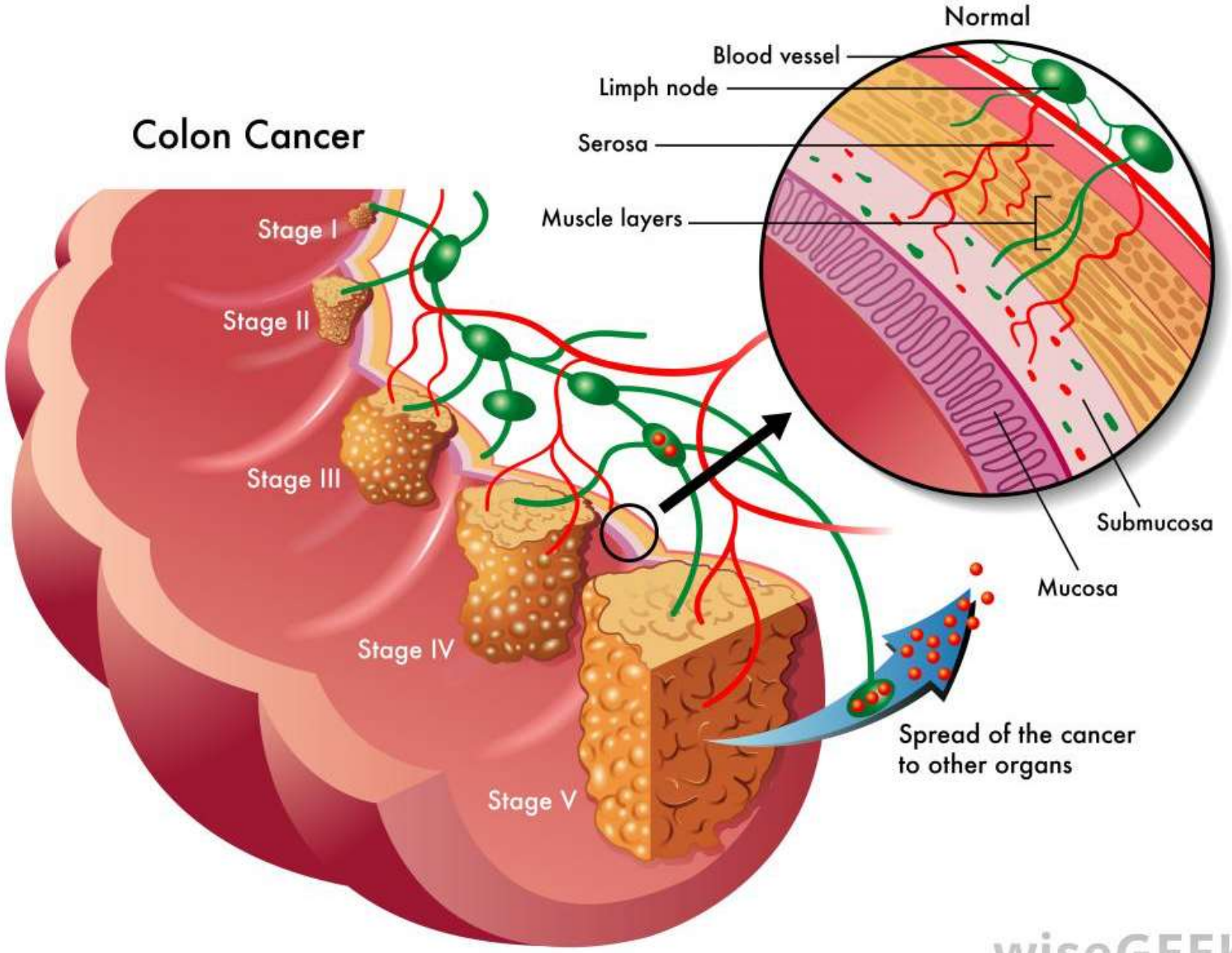
Natural History of Colorectal Neoplasia

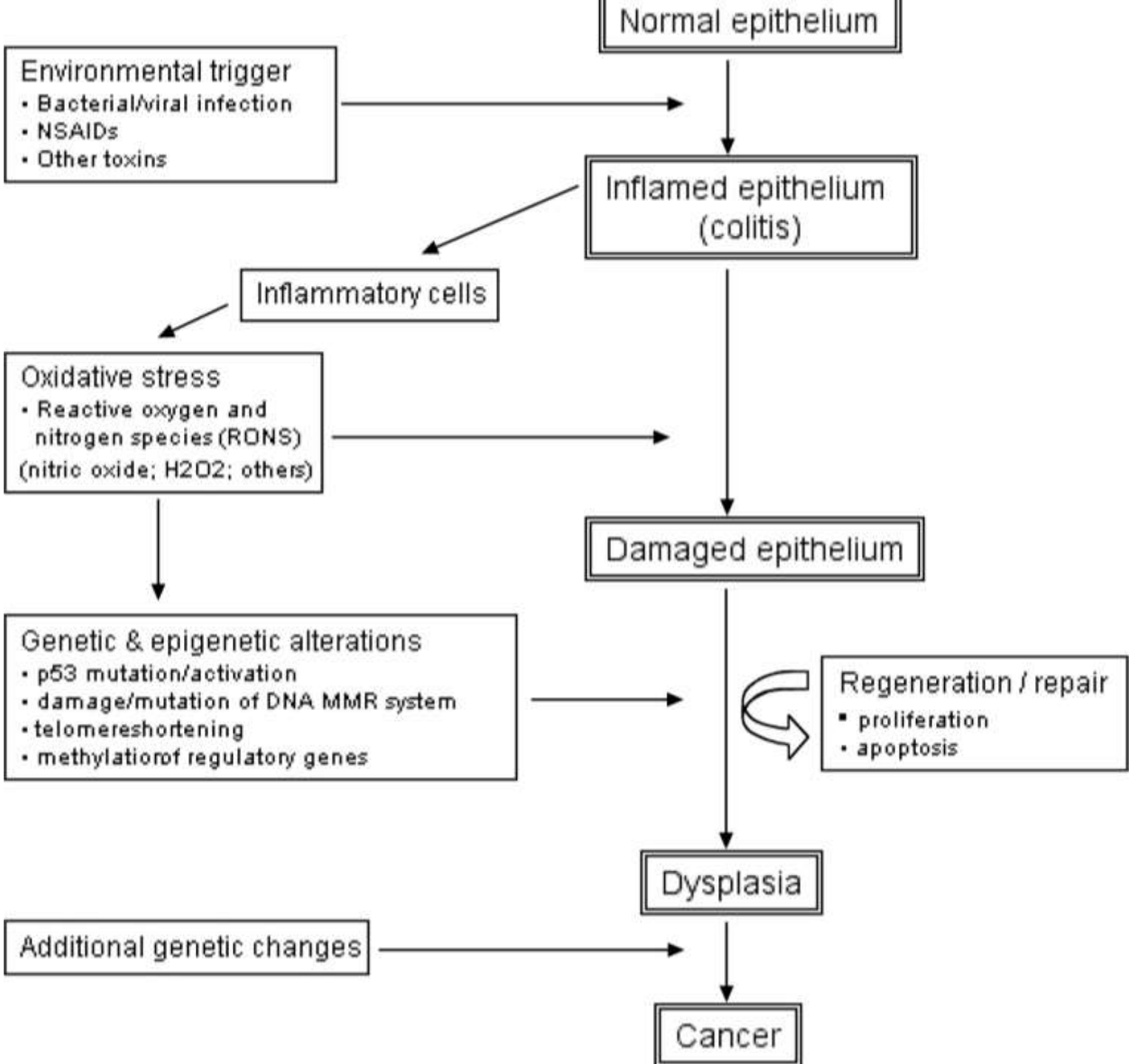


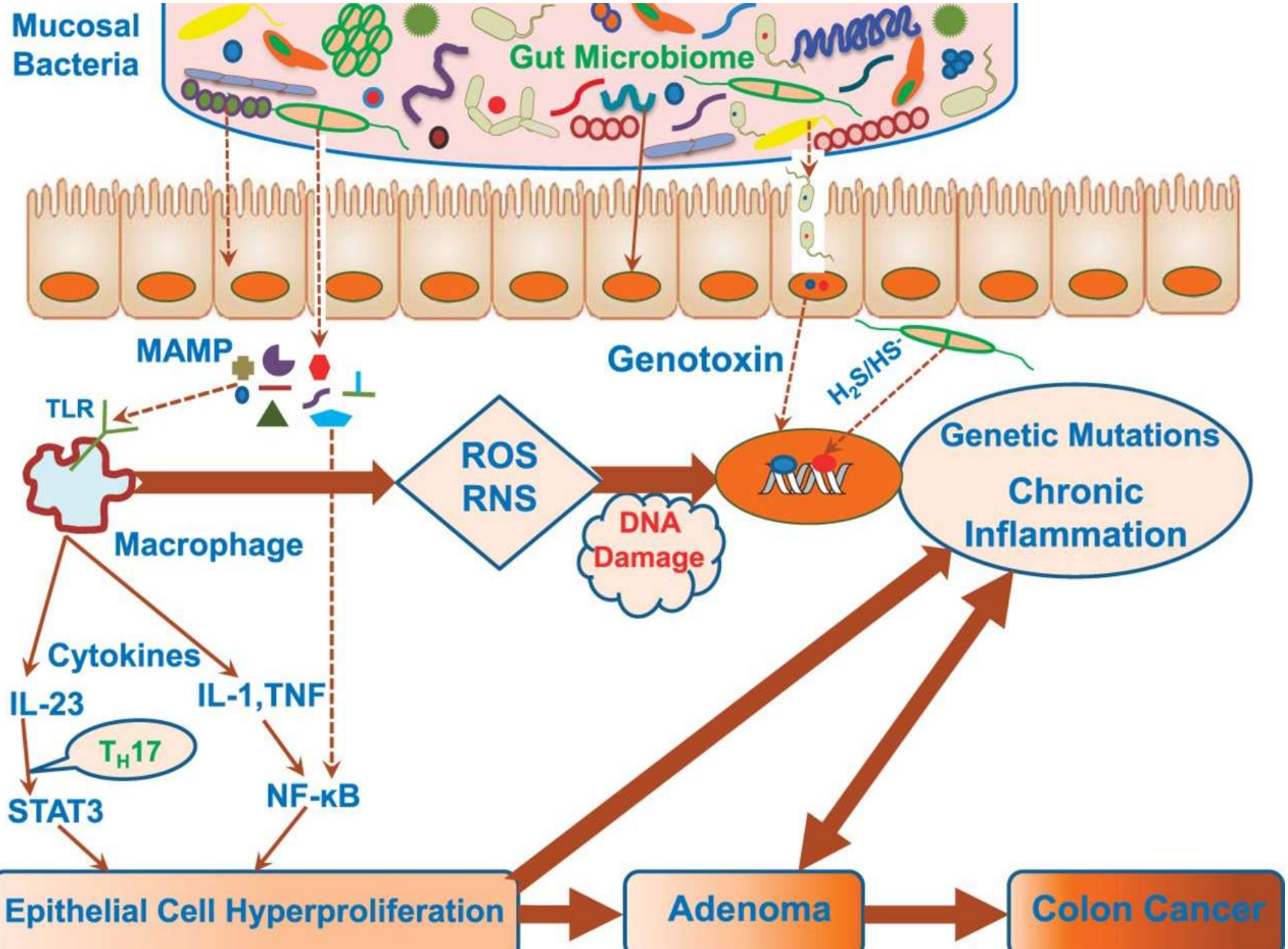
[1]Amersi et. al., Clin Colon Rectal Surg (2005)
[2]Zauber et. al., New Eng J Med (2012)
Photo source: Rozen, Young, Levin, Spann, *Colorectal Cancer in Clinical Practice* (2002)

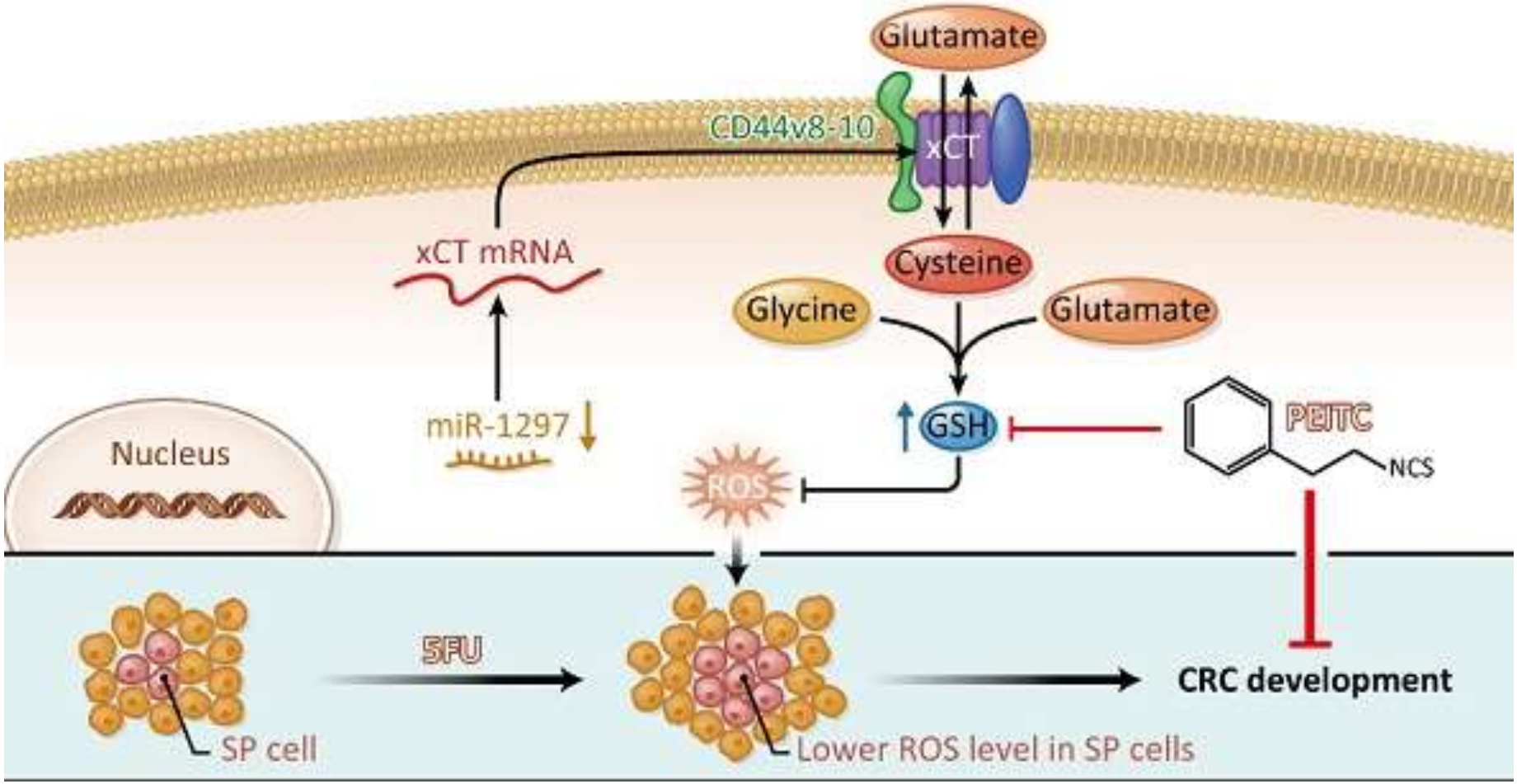
exact sciences

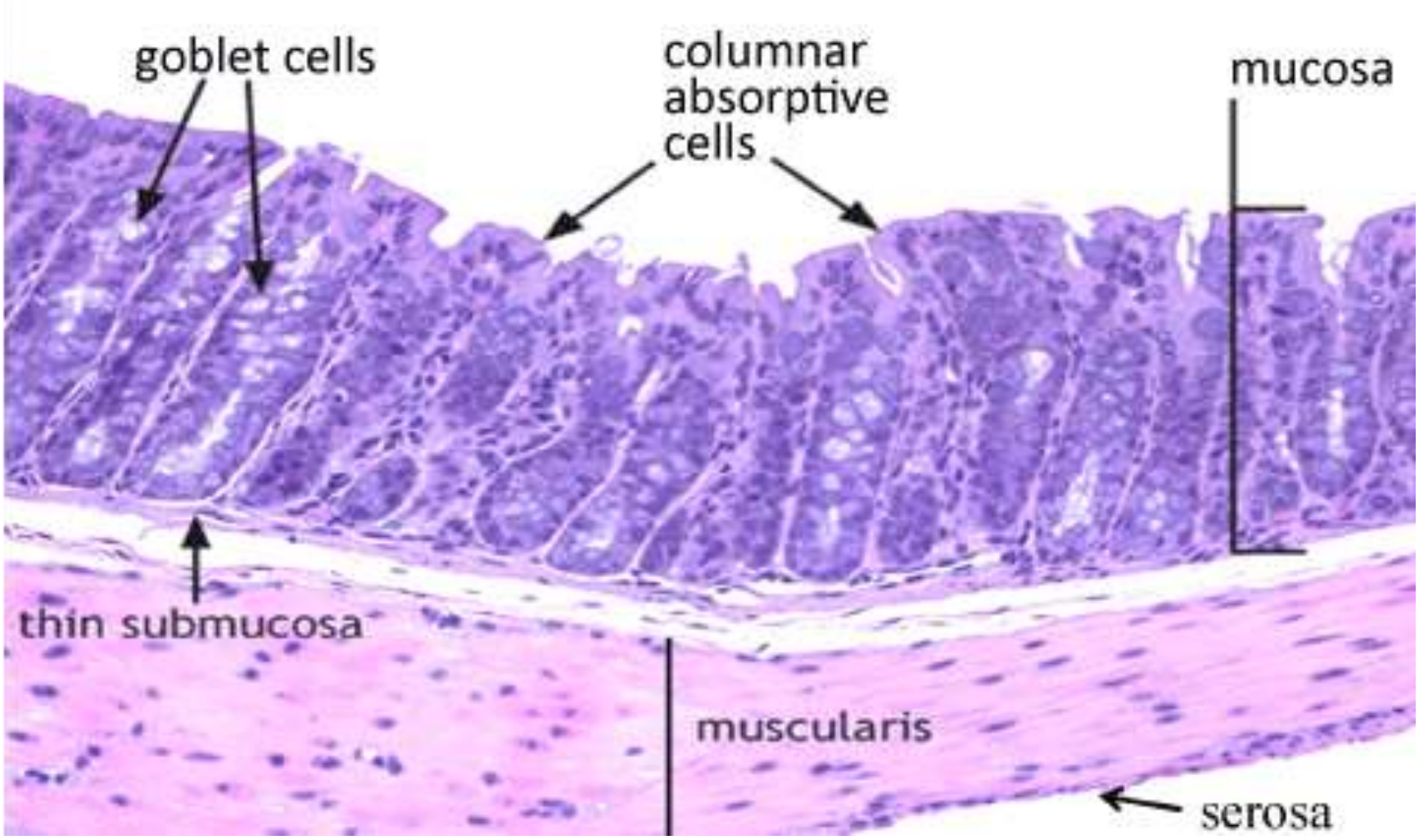

Lymph node
Blood vessel
Spread to other organs
Stage 0
Stage I
Stage II
Stage III
Stage IV
© 2005 Terese Winslow, U.S. Govt. has certain rights

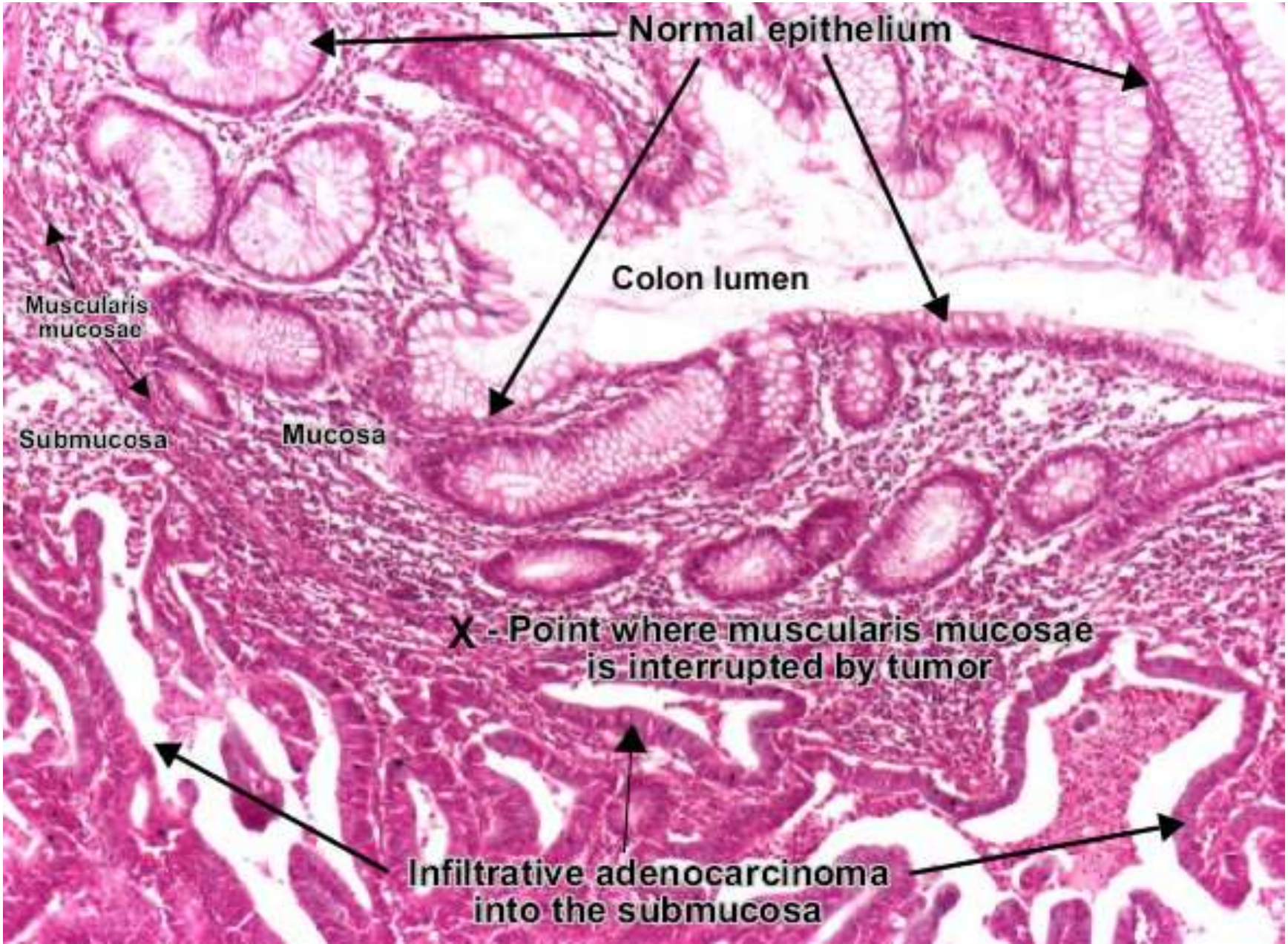

Colon Cancer
Normal
Blood vessel
Limph node
Serosa
Muscle layers
Stage I
Stage II
Stage III
Stage IV
Stage V
Submucosa
Mucosa
Spread of the cancer
to other organs


Normal epithelium
Environmental trigger
• Bacterial/viral infection
• NSAIDs
• Other toxins
Inflamed epithelium (colitis)
Inflammatory cells
Oxidative stress
• Reactive oxygen and nitrogen species (RONS)
(nitric oxide; H2O2; others)
Damaged epithelium
Genetic & epigenetic alterations
• p53 mutation/activation
• damage/mutation of DNA MMR system
• telomereshortening
• methylationof regulatory genes
Regeneration / repair
• proliferation
• apoptosis
Dysplasia
Additional genetic changes
Cancer

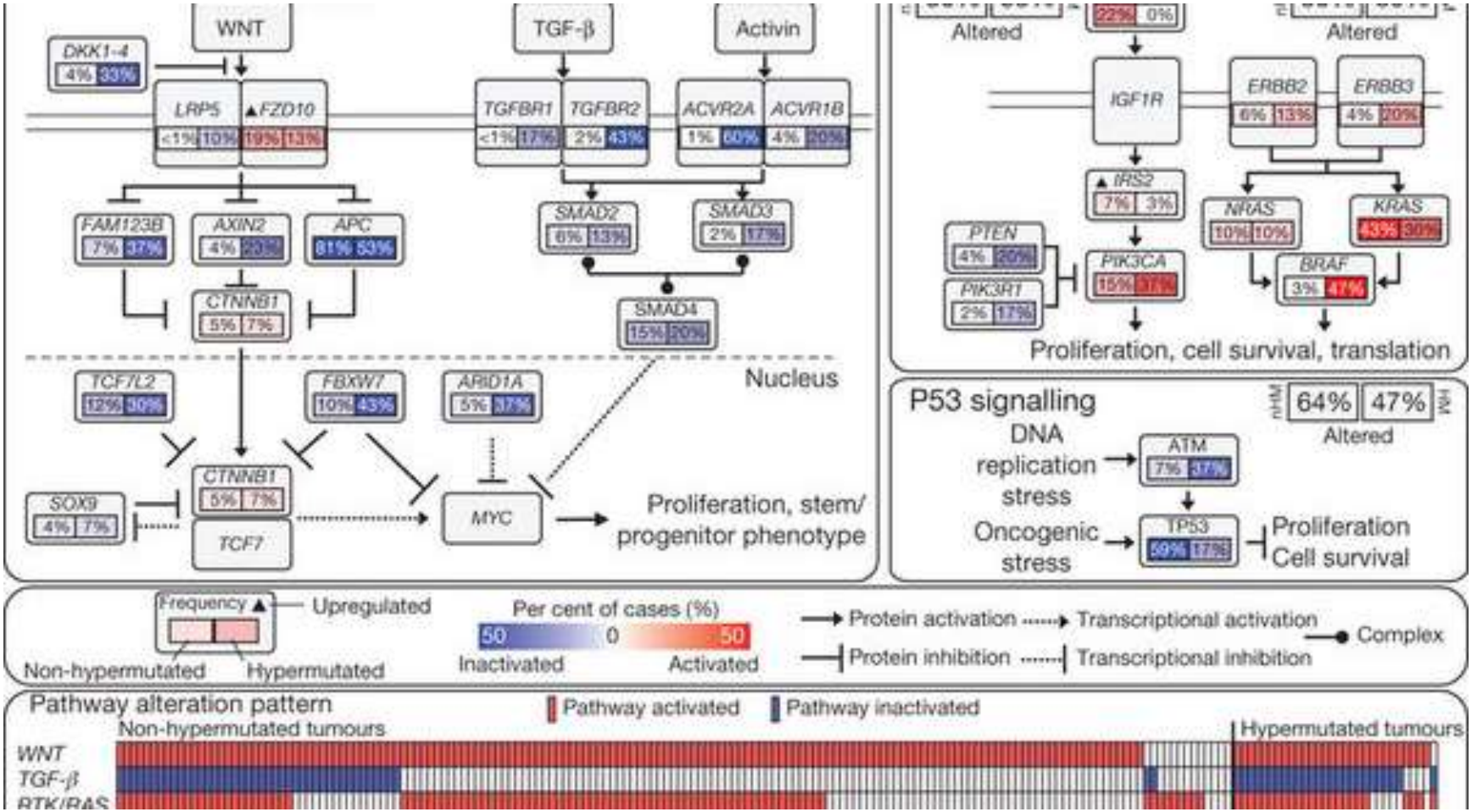

Mucosal Bacteria
Gut Microbiome
MAMP
TLR
Macrophage
Genotoxin
H_2S/HS^-
ROS
RNS
DNA Damage
Genetic Mutations
Chronic Inflammation
Cytokines
IL-23
IL-1,TNF
T_H17
STAT3
NF-κB
Epithelial Cell Hyperproliferation
Adenoma
Colon Cancer

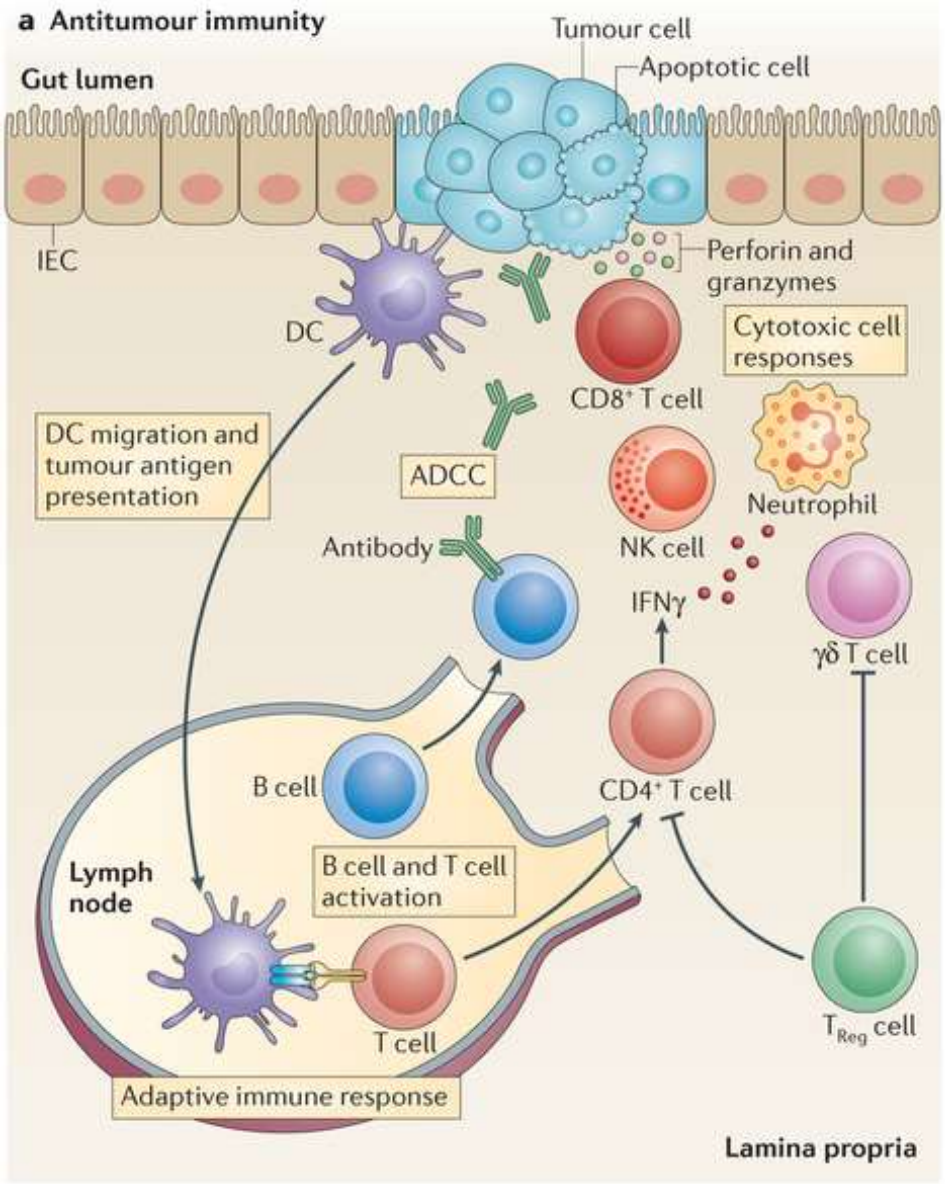

Glutamate
CD44v8-10
xCT
xCT mRNA
Cysteine
Glycine
Glutamate
miR-1297
GSH
PEITC
NCS
Nucleus
ROS
5FU
CRC development
SP cell
Lower ROS level in SP cells

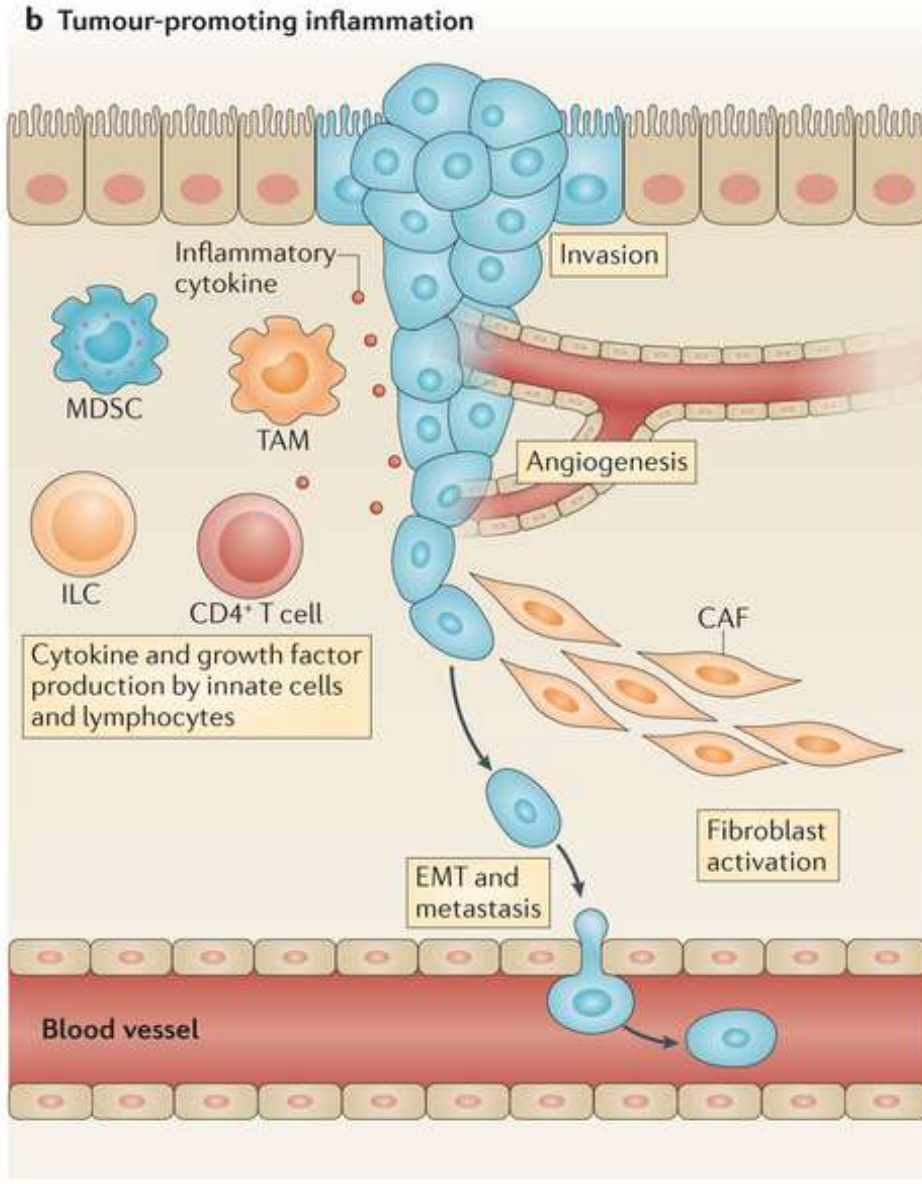

goblet cells
columnar absorptive cells
mucosa
thin submucosa
muscularis
serosa


Normal epithelium
Colon lumen
Muscularis mucosae
Submucosa
Mucosa
X - Point where muscularis mucosae is interrupted by tumor
Infiltrative adenocarcinoma into the submucosa

AJCC/Dukes' stage	Anatomical extent of disease	5-year overall survival
I/A	Confined to mucosa (T1) or muscularis propria (T2) No nodal involvement No distant metastases	93.2%
II/B	Tumour penetrates muscularis (T3) or invades adjacent organs or structures (T4) No nodal involvement No distant metastases	82.5%
III/C	Any tumour stage Nodal metastases No distant metastases	59.5%
IV/D	Any tumour stage	8.1%


WNT
TGF-β
Activin
DKK1-4
4% 33%
LRP5
FZD10
<1% 10% 19% 13%
TGFBR1
TGFBR2
<1% 17% 2% 43%
ACVR2A
ACVR1B
1% 60% 4% 20%
FAM123B
7% 37%
AXIN2
4% 20%
APC
81% 53%
SMAD2
6% 13%
SMAD3
2% 17%
CTNNB1
5% 7%
SMAD4
15% 20%
Nucleus
TCF7L2
12% 30%
FBXW7
10% 43%
ARID1A
5% 37%
CTNNB1
5% 7%
SOX9
4% 7%
TCF7
MYC
Proliferation, stem/
progenitor phenotype
Altered
22% 0%
Altered
IGF1R
ERBB2
6% 13%
ERBB3
4% 20%
IRS2
7% 3%
NRAS
10% 10%
KRAS
43% 30%
PTEN
4% 20%
PIK3R1
2% 17%
PIK3CA
15% 37%
BRAF
3% 47%
Proliferation, cell survival, translation
P53 signalling
nHM
64%
47%
wH
Altered
DNA
replication
stress
Oncogenic
stress
ATM
7% 37%
TP53
59% 17%
Proliferation
Cell survival
Frequency
Upregulated
Non-hypermutated
Hypermutated
Per cent of cases (%)
50
0
50
Inactivated
Activated
Protein activation
Transcriptional activation
Protein inhibition
Transcriptional inhibition
Complex
Pathway alteration pattern
Pathway activated
Pathway inactivated
Non-hypermutated tumours
Hypermutated tumours
WNT
TGF-β
RTK/RAS


a Antitumour immunity
Tumour cell
Apoptotic cell
Gut lumen
IEC
Perforin and granzymes
DC
Cytotoxic cell responses
CD8+ T cell
DC migration and tumour antigen presentation
ADCC
Neutrophil
NK cell
Antibody
IFNγ
γδ T cell
B cell
CD4+ T cell
Lymph node
B cell and T cell activation
T cell
TReg cell
Adaptive immune response
Lamina propria


b Tumour-promoting inflammation
Inflammatory cytokine
Invasion
MDSC
TAM
Angiogenesis
ILC
CD4+ T cell
CAF
Cytokine and growth factor production by innate cells and lymphocytes
Fibroblast activation
EMT and metastasis
Blood vessel