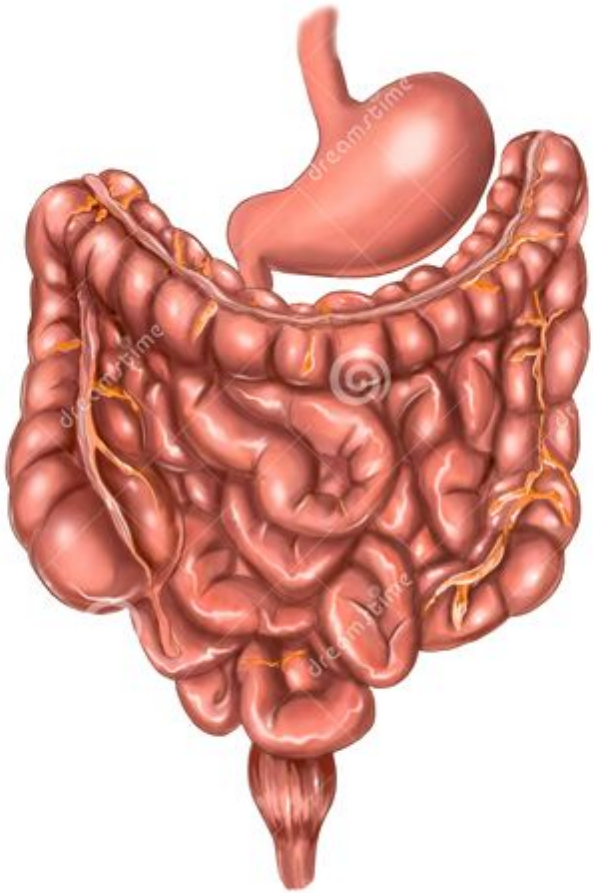
Colonic Tumors and polyps

Robbins page 592

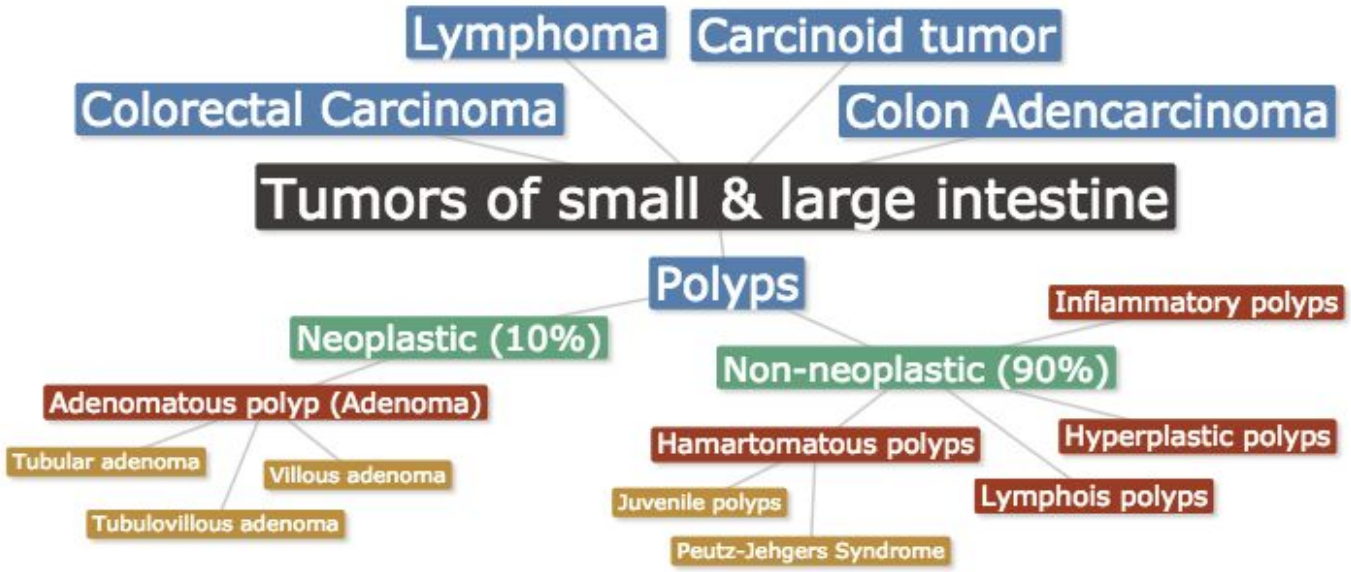


Objectives:

- Know common types of intestinal polyps.
- Differentiate between the neoplastic and non-neoplastic polyps.
- Know the clinical presentation of left and right sided colon cancer, and the environmental factors that increase its risk.
- Understand the pathogenesis of colon cancer.
- Describe the Pathological features of colon cancer.

Important note: **Please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all or our work: Pathology Edit.**

Introduction



Pathoma

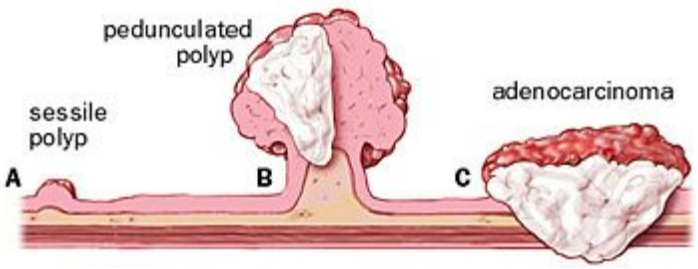
Ascending "right" colon	Descending "left" colon
- Wider than left colon so tumors tend to grow larger before causing symptoms. - Tumors tend to embed themselves within the wall and do not block the flow of feces. - Obstruction is uncommon.	- The lumen is smaller. - Tumors tend to grow directly outward into the lumen. - Obstruction is more common.

- Sigmoid colon is the most common site GI polyps, diverticula and cancer.

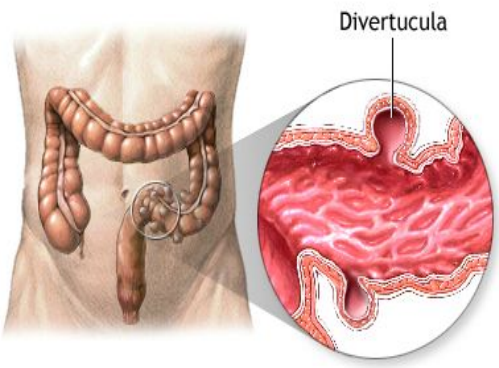
Polyps

Abnormal growth of tissue, protruding from a mucous membrane, usually benign but some can develop into **cancer.** (e.g adenomas)

- **Pedunculated polyp:** Polyp is attached to the surface by a narrow elongated *stalk*.
- **Sessile polyp:** Polyp is attached directly without a stalk.



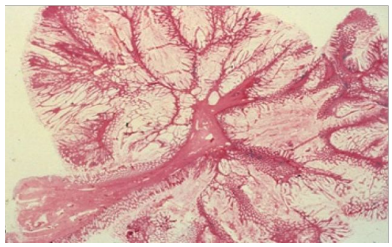
Diverticula: Small bulging of the colonic mucosa and submucosa through weaknesses of muscle layers in the colon wall. *These are more common in the sigmoid colon.*(
↑ pressure of the muscle wall "constipation" → some of the mucosa will herniate into the muscle wall → formation of diverticula.)

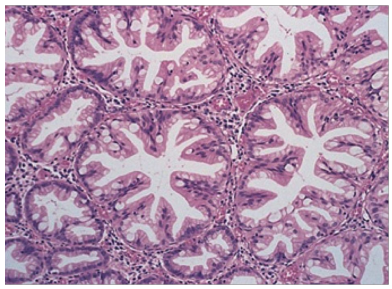


Colonic Polyps

A- Non-neoplastic polyps (90%):

Non-neoplastic colonic polyps can be further classified as:



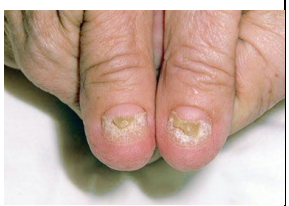
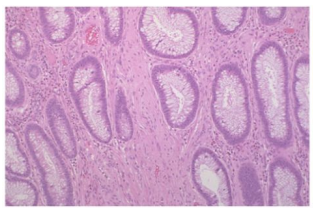
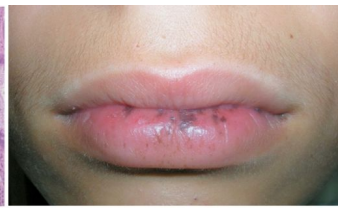


1- Hyperplastic Polyps:

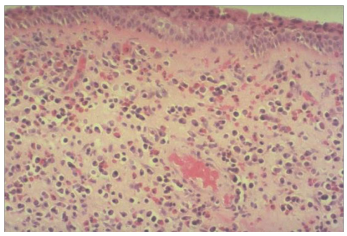
They're common epithelial proliferation that found mostly in the **left colon**
(> 50% are located in the *rectosigmoid*). They have **NO malignant potential** or polyposis syndromes (page.6). (No dysplasia, No polymorph, same lining as normal crypt but with increase in number only.)

- Asymptomatic.
- Most common type in adults.
- Sawtooth surface (مُسنن).
- Star shaped crypts. (caused by delayed shedding of these cells → crowding)
- Composed of well-formed -mature- glands and crypts lined by *differentiated* **goblet** or **absorptive cells**.

2- Hamartomatous Polyps:

Juvenile Polyps (*Retention polyp*)	Peutz-Jeghers syndrome
• Developmental malformations affecting the glands and lamina propria. - Mucus filled glands → dilation of the glands → edema with inflammatory cells in the lamina propria → rectal bleeding. • Commonly occur in **children <5 years** old in rectum. • In adult called retention polyp. • No malignant potential. • Juvenile polyposis: Autosomal dominant or non-hereditary. **Cronkhite-Canada syndrome:** - Non hereditary polyposis syndrome. - Polyps plus ectodermal abnormalities of the nails. 	• Rare, autosomal dominant. • hamartomatous polyps accompanied by mucosal and cutaneous pigmentation around the lips, oral mucosa, face and genitalia, present with red blood in stool. • Polyps tend to be large and pedunculated. • Increased risk of developing carcinoma of the pancreas, breast, lung, ovary and uterus.  

3- Inflammatory Polyps:

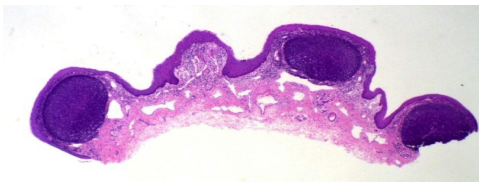


- Longstanding IBD, especially in chronic ulcerative colitis.
- Represent an exuberant -large- reparative response to longstanding mucosal injury called **pseudopolyps**.

(multiple ulceration → inflammation and protrusion of the mucosa in between → appears as a polyp. ' not actual polyp it's because the rest of the mucosa is ulcerative').

4- Lymphoid Polyps:

Mucosal or submucosal lymphoid follicles with germinal centers. Has been reported in children with common variable immunodeficiency.



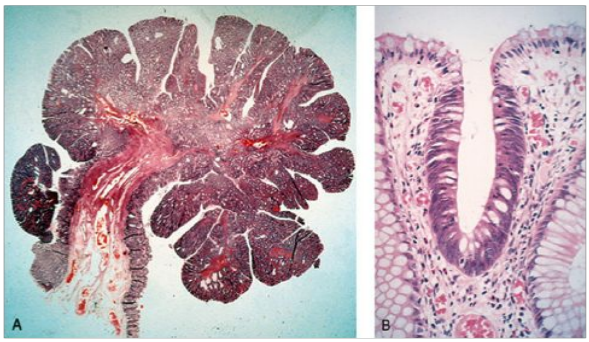
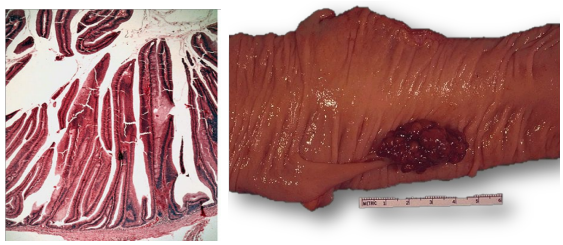
B- Neoplastic polyps 10% (Adenomatous Polyps "Adenoma")

Adenomatous polyps are neoplasms **with malignant potential**, located mainly at the level of the sigmoid and rectum.

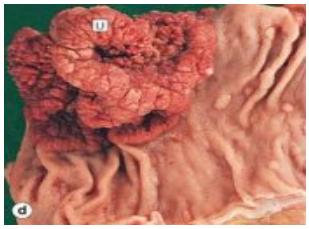
Characteristics:

1. Occur mainly in large bowel.
2. Sporadic and familial.
3. Vary from small pedunculated to large sessile.
4. Epithelium proliferation and **dysplasia.**

Divided into (according to architecture)**:**

Tubular adenoma "Villous architecture less than 25%"	**Villous adenoma** "Villous architecture over 50%"
- Represents 75% of all neoplastic polyps. - 75% occur in the distal colon and rectum. - Sigmoid colon most common site.  **Morphological changes:** ● pedunculated. ● The lining shows **dysplasia** (nuclear enlargement, pleomorphism, hyperchromatism, abnormal mitosis).	1. Most serious and most dangerous. 2. The least common, largest and most ominous -bad- of epithelial polyps. 3. **Most likely to undergo malignant transformation.** 4. **Age:** 60 to 65 years, 75% located in rectosigmoid area. 5. Present with rectal bleeding or anemia, large ones may secrete large amounts of mucoid material rich in protein and potassium leading to hypokalemia, hypoalbuminemia, dehydration, hyponatremia, and hypochloremia.  **Gross:** appearance of villous (non-stalk) adenoma.

Tubulovillous adenoma "Villous architecture between 25 and 50%":
- 20%–30% of polyps
- Intermediate in size, degree of dysplasia and malignant potential between tubular and villous adenomas.

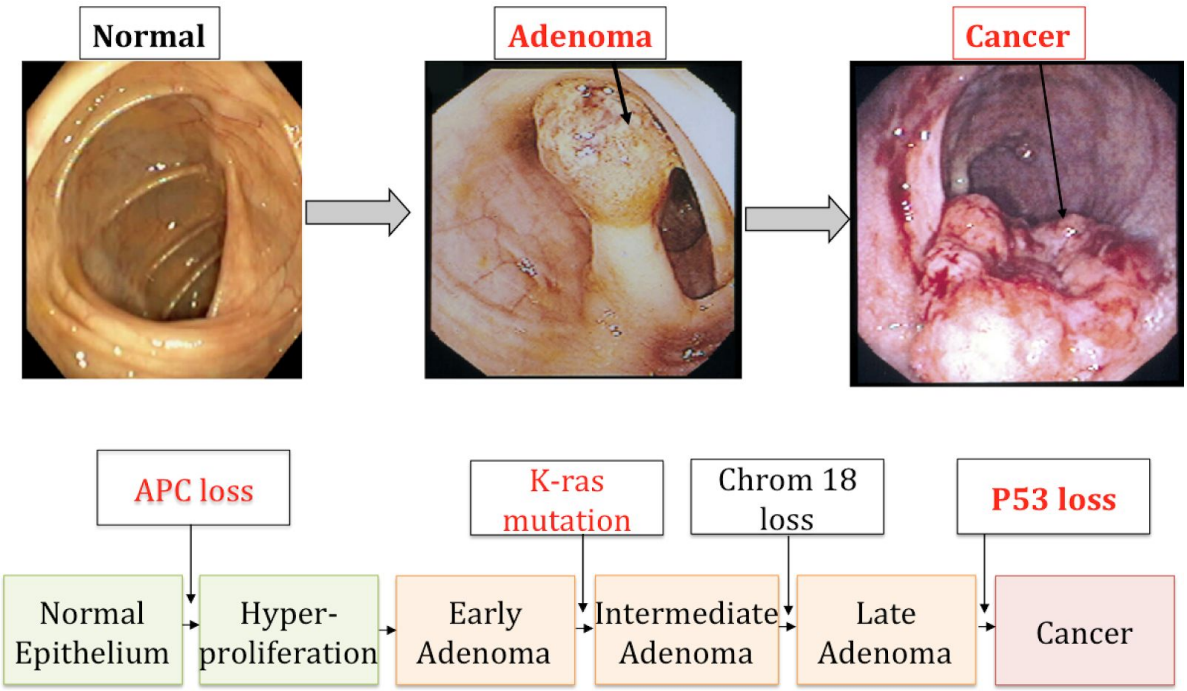


Relationships of Neoplastic Polyps to Carcinoma:

Adenoma to carcinoma sequence is documented by several genetic alterations. The probability of carcinoma occurring in a neoplastic polyp is related to:

1. **The size of the polyp.**
2. The relative proportion of its villous features.
3. The presence of significant cytologic atypia (**dysplasia**) in the neoplastic cells.
4. Multiple polyps.
5. Accumulation of genetic mutation.

Adenoma to Carcinoma Pathway[1]:



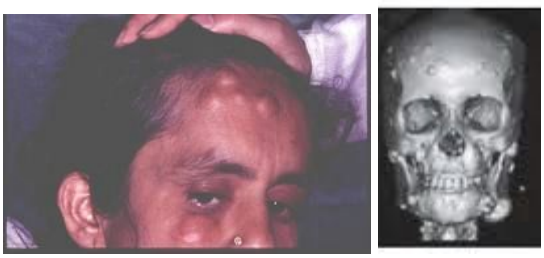
- **APC[2] (Adenomatous polyposis coli) gene mutation** → increased risk for formation of polyp.
- **K-ras mutation** → formation of polyp.
- **P53 mutation** → progression to carcinoma.

[1] The molecular progression from normal colonic mucosa to adenomatous polyp to carcinoma.
[2] Located on chromosome 5

Familial Polyposis[3] Syndrome.

Patients have genetic tendencies to develop neoplastic polyps. In contrast with hereditary non-polyposis colon cancer.

Familial polyposis coli (FPC)[4]		
Types	**Gardner's Syndrome**	**Turcot Syndrome**
Genetic defect	**Adenomatous polyposis coli gene** (APC), which is located on the long arm of **chromosome 5** (5q21).	
Gross features of the polyps	- Innumerable (500 to 2500). - Diffused in all of the alimentary tract.	
What characterize it other than the polyps??	Fibromatosis (fibrous overgrowths of dermal and subcutaneous connective tissue.)	
	- Multiple osteomas[5] (Bone) - Epidermal cysts[6] (Skin)	Glioma[7] (Brain tumor)
Prognosis	The risk of colorectal cancer is 100% by midlife. So Polyp removal leads to colorectal cancer prevention.	



Multiple osteomas

[3] Multiple polyps
[4] Also known as Familial Adenomatous Polyposis or FAP.
[5] Benign tumor composed of bone tissue.
[6] Benign cyst usually found on the skin.
[7] Malignant tumor of the glial tissue of the nervous system.

Tumors of Large Intestine

Adenocarcinoma

- **Adenocarcinoma of the colon is the** most common malignancy of the GI tract.
- Major cause of morbidity and mortality worldwide.
- Constitutes 98% of all cancers in the large intestine.
- Incidence peaks at 60 to 70 years of age.

Predisposing factors:

1. IBD, adenomas (mostly Villous), polyposis syndrome.
2. Diet appears to play an important role in the risk for colon cancer:
   - Low fiber diet.
   - High fat content.
   - Alcohol
   - Reduced intake of Vit. A, C & E

- Reduced fiber content → decreased stool bulk (constipation) → prolonged exposure of intestinal mucosa to residual and undigested food → altered composition of the intestinal microbiota → increase synthesis of potentially toxic oxidative by-products of bacterial metabolism.
- High fat intake also enhances hepatic synthesis of cholesterol and bile acids, which can be converted into carcinogens by intestinal bacteria.

Epidemiologic Studies: suggest that aspirin or other NSAIDs have a protective effect. This is consistent with studies showing that some NSAIDs cause polyp regression in FAP patients in whom the rectum was left in place after colectomy.

Carcinogenesis:

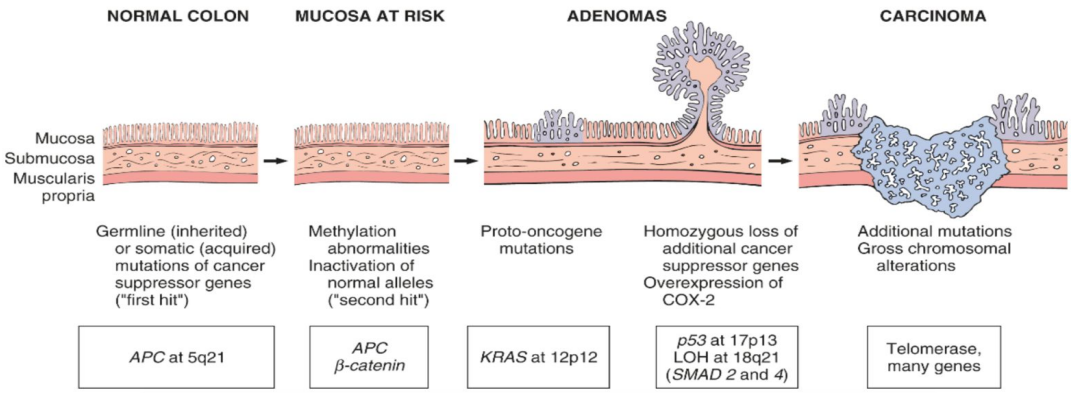
Two pathogenetically distinct pathways for the development of colon cancer, both seem to result from accumulation of multiple mutations: (starts with single small mutations, progress with time to multiple large gene mutations including p53 which it is called the guardian of the genome).

1- The APC/ β -*catenin pathway (85 %)*

Chromosomal instability that results in stepwise **accumulation of mutations** in a series of oncogenes (induction) and tumor suppressor genes (inhibition).

β **-catenin:** protein that stimulate the transcription and cell proliferation. so the APC holds on to that protein therefore decrease the rate of cell proliferation.

Adenoma-carcinoma sequence



REMEMBER:
APC mutation → Early.
p53 mutation → Late.

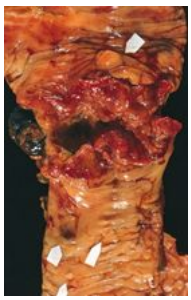
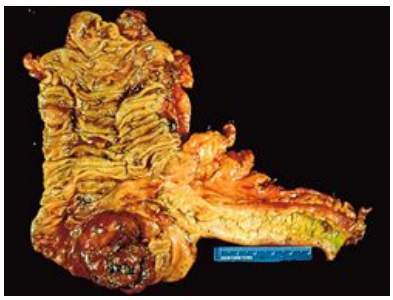
2- The DNA mismatch repair genes pathway:

- Give rise to the **hereditary non-polyposis colon carcinoma** (HNPCC) syndrome.
- These are referred to as MSI (microsatellite instability) high, or MSI-H tumors.
- 10% to 15% of sporadic cases.
- There is accumulation of mutations (as in the APC/B-catenin schema).
- Five DNA mismatch repair genes **(MSH2, MSH6, MLH1, PMS1, AND PMS2).**

Colorectal Carcinoma

Morphology:

- 70% are in the **rectum**, **rectosigmoid** and **sigmoid colon**.
- Adenocarcinoma.
- Mucinous adenocarcinoma secret abundant mucin that may dissect through cleavage planes in the wall.

Left-sided carcinomas	Right-sided carcinomas
	
- Tend to be annular. - Encircling lesions. - Early symptoms of **obstruction**. - Usually detected later and could present with bowel obstruction.	- Tend to grow as polypoid fungating masses. - More likely to bleed (occult fecal). - **Obstruction is uncommon** - Associated with **unexpected finding** which is **iron deficiency anemia.**

Signs and Symptoms:

- If located close to the **anus**: change in bowel habit, feeling of incomplete defecation, Per Rectal bleeding (fresh blood).
- A tumor that is large enough to **fill the entire lumen** of the bowel may cause bowel **obstruction.**

Tumor markers:

Is a substance found in the blood, urine or body tissues that can be elevated in cancer, among other tissue types.

1. Carcinoembryonic antigen (CEA) → related to tumor size and extent of spread.

- **CEA levels may also be raised in:** some non-neoplastic conditions like (ulcerative colitis pancreatitis, cirrhosis COPD, Crohn's disease , smokers).
- They are helpful in monitoring for recurrence of tumor after resection 'not used for diagnosis'.

2. Carbohydrate antigen (CA19-9)→ Useful to assess disease recurrence 'not used for diagnosis'.

- **CA19-9 are raised in in patients with** (colon cancer and pancreatic cancer, esophageal cancer and hepatocellular carcinoma)**.**
- Apart from cancer, elevated levels may also occur in pancreatitis and cirrhosis**.**

3. Tissue inhibitor of metalloproteinases 1 (TIMP1) → Early as well as late stage disease.

Staging of Colon Cancer:

1. **TNM[8]:**

- **T** → Depth of invasion.
- **N** → Spread to regional lymph nodes.
- **M** → Distant spread.

2. **Duke classification is used for staging:**

- The Dukes' staging system is divided into 4 groups - A, B, C and D. Dukes' A is an early bowel cancer and Dukes' D is advanced.

Prognostic Factors: The two most important prognostic factors are

- Depth of invasion.
- The presence or absence of lymph node metastases.

[8] Tumor-Node-Metastasis.

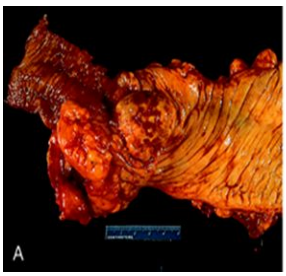
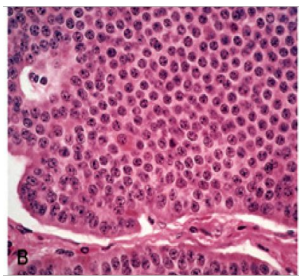
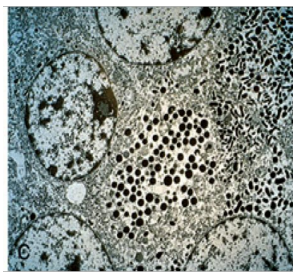
Malignant Small Intestinal Neoplasms

In order "more frequent": Carcinoid > Adenocarcinoma > Lymphomas > Leiomyosarcomas.

1- Carcinoid Tumors.

- Neoplasms arising from endocrine cells[9] found along the length of GIT mucosa.
- The peak incidence: sixth decade, but they may appear at any age.
- They compose less than 2% of colorectal malignancies.
- 60 to 80% appendix and terminal ileum & 10 to 20% rectum.

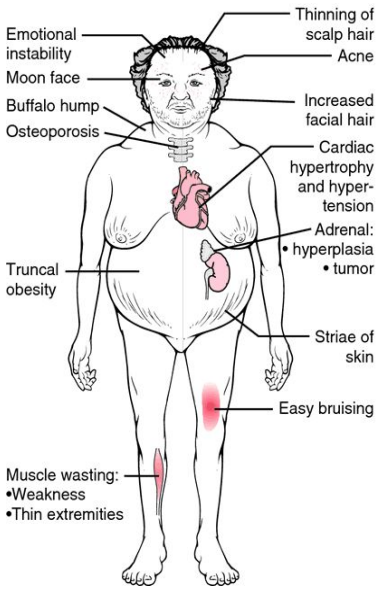
Morphology:

Gross	Microscopic	
		
A solid, yellow-tan appearance.	The cells are monotonously similar, having a scant, pink granular cytoplasm and a round-to-oval stippled nucleus.	Ultrastructural features: **neurosecretory electron dense bodies** in the cytoplasm.

Behavior of Carcinoid Tumors:

Aggressive behavior correlates with:

1. **Site of origin:**
   - Appendiceal and rectal carcinoids infrequently metastasize, even though they may show extensive local spread.
   - 90% of ileal, gastric, and colonic carcinoids that have penetrated halfway through the muscle wall have **spread to lymph nodes** and distant sites at the time of diagnosis, especially those larger than 2 cm in diameter.
2. **Depth of local penetration.**
3. **Size of the tumor.**



Clinical Features:

- ➔ Asymptomatic.
- ➔ May cause obstruction, intussusception[10] or bleeding.
- ➔ May elaborate hormones: Zollinger-Ellison, Cushing's[11] carcinoid or other syndromes.

[9] Secreting internally, most commonly into the systemic circulation; or pertaining to such secretion.
[10] Part of the intestine slides into an adjacent part of the intestine.
[11] Caused by any condition that produces an elevation in glucocorticoid levels.

2- Carcinoid Syndrome.

- 1% of carcinoid tumor and in 20% of those of widespread **metastasis**.
- The principal chemical mediator is **serotonin.**
- the syndrome is classically associated with **ileal carcinoids with hepatic metastases**.

Clinical Findings:

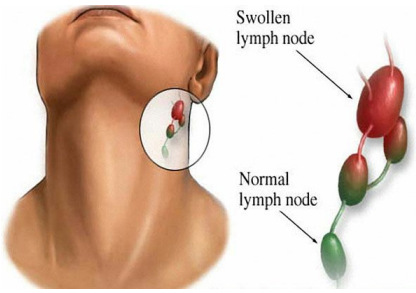
- Paroxysmal flushing (due to serotonin, histamine, bradykinin).
- Episodes of asthma-like wheezing.
- Right-sided heart failure (Serotonin increases collagen production in the valves).
- Attacks of watery diarrhea (Due to vasodilation)
- Abdominal pain.

Serotonin and Diarrhea:

Patients with carcinoid syndrome often suffer from diarrhea, which has both a **secretory** and a **motor** component. The **secretory component of carcinoid diarrhea is attributable to** excessive serotonergic stimulation of submucosal secretomotor neurons; the **motor component includes faster small bowel and colon transit and an exaggerated tonic response of the colon to ingestion of a meal.**

3- Lymphoma.

- Most often **low-grade lymphomas** arising in **mucosal-associated lymphoid tissue** (MALT) lymphoma or **high-grade non-Hodgkin's** lymphomas of B cell type.
- May occur in any part of the intestine.
- The ileocecal region is a favored site for Burkitt's[12] lymphoma.



Non-Hodgkin's lymphoma, is cancer that originates in the lymphatic system, the disease-fighting network spread throughout your body. In non-Hodgkin's lymphoma, tumors develop from lymphocytes.

[12] High grade non-Hodgkin's lymphomas, mostly seen in children.

Summary.

Polyps	Incidence	Region	Features	Prognosis
Non-neoplastic polyps 90%				
Hyperplastic polyps	**Adults.**	**rectosigmoid**	- Sawtooth surface. - Star shaped crypts. - Well-formed glands and crypts.	No malignant potential.
Hamartomatous polyps (Juvenile)	**Children** under 5.	**rectum**	Affects the glands and lamina propria	
Hamartomatous polyps (Peutz-Jeghers polyps)	Rare, autosomal dominant.	-	- large and pedunculated hamartomatous polyps. - Mucosal and cutaneous pigmentation.	Carcinoma of the pancreas, breast, lung, ovary and uterus.
Inflammatory polyps	Longstanding IBD, especially in chronic ulcerative colitis.	-	Pseudopolyps	-
Neoplastic polyps Adenomatous Polyp(adenoma) 10% **Epithelium proliferation and dysplasia**				
Tubular adenoma	75% of all neoplastic polyps.	Sigmoid colon	Villous architecture less than 25%.	-
Tubulovillous adenoma	20%–30% of polyps	-	- Intermediate in size. - between tubular and villous adenomas.	-
Villous adenoma	The least common. Age: 60 to 65 years.	rectosigmoid area	● Villous architecture over 50%. 1. rectal bleeding 2. anemia 3. hypokalemia 4. hypoalbuminemia	Malignant transformation.

Tumor	Incidence	Features	Classification
Tumors of the large intestines			
Adenocarcinoma of the colon	most common (98%) peaks at 60 to 70 years of age	**Predisposing factors:** - IBD, adenomas , polyposis syndrome. - Low fibre diet. - High fat content. - Alcohol. - Reduced intake of vit A, C & E.	**2 pathways:** 1. The APC/B-catenin pathway (85 %) 2. The DNA mismatch repair genes pathway:
Colorectal Carcinoma	70% are in the rectum, rectosigmoid and sigmoid colon.	**If located closer to the anus:** change in bowel habit, feeling of incomplete defecation, PR bleeding	Left-sided carcinomas: obstruction. Right-sided carcinomas: obstruction is uncommon.
Tumors of the small intestines **Carcinoid > adenocarcinomas > lymphomas > leiomyosarcomas**			
Tumor	**Incidence**	**features**	
Carcinoid Tumors	From endocrine cells of the GIT mucosa.	Neurosecretory electron dense bodies in the cytoplasm **Clinical features:** - Asymptomatic. - May cause obstruction, intussusception or bleeding. - May elaborate hormones: Zollinger-Ellison, Cushing's carcinoid or other syndromes.	
Carcinoid syndrome		- Paroxysmal flushing. - Asthma-like wheezing, right-sided heart failure, attacks of watery diarrhea, abdominal pain. - The principal chemical mediator is **serotonin.**	
Lymphoma	In any part of the intestine	Low-grade lymphomas arising in (MALT) lymphoma or high-grade non-Hodgkin's lymphomas of B cell type.	

MCQ's.

1. **A 45-year-old woman presents with sudden attacks of wheezing, shortness of breath, and episodic hot flashes. She also reports abdominal cramps and diarrhea. Physical examination shows facial redness, pitting edema of the lower legs, and a murmur of tricuspid regurgitation. Which of the following is the most likely diagnosis?**
   A. Carcinoid tumor.
   B. Mediterranean intestinal lymphoma.
   C. Mucosa-associated lymphoid tissue (MALT) lymphoma.
   D. Peutz-Jeghers syndrome

2. **A 59-year-old man complains of progressive weakness. His friends have noticed that he has become pale, and he reports that his stools are tinged with blood. On abdominal palpation, there is fullness in the right lower quadrant. Laboratory studies show iron-deficiency anemia, Stool specimens are positive for occult blood. Colonoscopy reveals an elevated and centrally ulcerated lesion of the sigmoid colon. Which of the following is the most likely diagnosis?**
   A. Adenocarcinoma.
   B. Carcinoid tumor.
   C. Gastrointestinal stromal tumor.
   D. Lymphoma.

3. **A gastroenterologist performs a colonoscopy on a patient with family history of gastric and colon cancer and discovers multiple polyps. Biopsy of one lesion reveals a benign hamartoma. On physical examination the patient is noted to have dark pigmentation of the buccal mucosa and lips. What is the most likely diagnosis?**
   A. Adenomatous polyposis coli.
   B. Gardner syndrome.
   C. Peutz-Jeghers (PJ) syndrome.
   D. Turcot syndrome.

4. **A 25-year-old man is discovered to have colon cancer. It is noted that several members of his family also developed colon cancer at relatively young ages. Which of the following genes is most likely to be involved?**
   A. Hereditary nonpolyposis colorectal cancer gene.
   B. Mismatch repair gene.
   C. p53 gene.
   D. K-ras oncogene.

5. **Routine screening colonoscopy is performed on an asymptomatic 50-year-old man and finds a 5-mm lesion in the sigmoid colon. The lesion is removed and histologic examination reveals a polyp composed of dysplastic stratified epithelial cells having hyperchromatic nuclei and decreased mucin production. Fingerlike villous projections are not seen. Which of the following is the most likely diagnosis?**
   A. Hyperplastic polyp.
   B. Inflammatory polyp.
   C. Retention polyp.
   D. Tubular adenoma.
   E. Villous adenoma

Answers: 1-A, 2-A, 3-C, 4-A, 5-D

SAQ's.

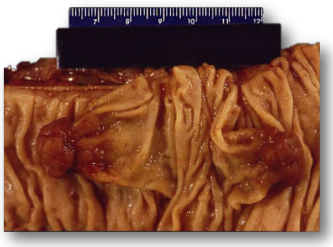
A 45-year-old man with a family history of colon cancer undergoes a screening colonoscopy. No invasive carcinomas are identified, but two small pedunculated tubular adenomas are removed and one villous adenoma measuring 5 mm in diameter is biopsied.

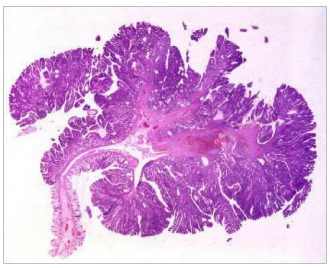
1. **What is the most likely diagnosis?**
- Hyperplastic polyps or tubular adenomas.

2. **What are the syndromes that could predispose this individual to colon cancer?**
- Familial adenomatous polyposis (FAP) and hereditary nonpolyposis colon cancer (HNPCC) are two common inherited colon cancer syndromes.

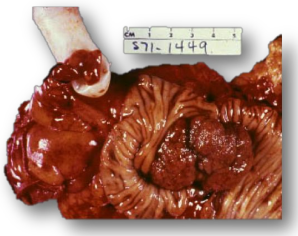
3. **What other dietary factors could play a role in the development of colon cancer?**
- Dietary factors that play a role in the development of colon cancer: Diets rich in fat and red meat and low in fiber may contribute to the development of colon cancer.

Colon, pedunculated adenomatous polyp:





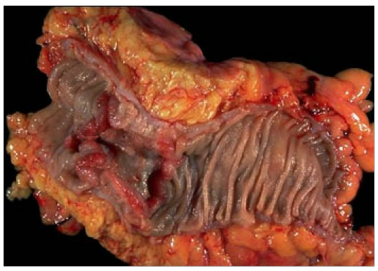
1. **Did this patient have familial polyposis syndrome?**
- No. there are two isolated polyps. Patients with familial adenomatous polyposis syndrome have at least 100 polyps.
2. **Can isolated polyps like the ones illustrated develop into colonic cancer?**
- Yes. Although all polyps do not progress to carcinoma, it is thought that most colonic carcinomas start as polyps.
3. **Are all polyps neoplastic?**
- No. Polyps can result from focal hyperplasia of the mucosa. Hyperplastic polyps do not have malignant potential
4. **What variables determine the likelihood of malignant change in a polyp?**
- Three interrelated features determine the risk of cancerous transformation: **polyp size**, histologic architecture, and severity of dysplasia.



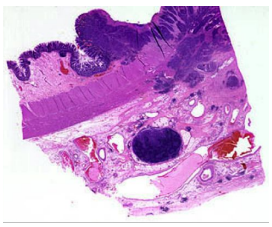
What types of mutations are likely to be present in such a lesion?
There is progressive accumulation of mutations during the conversion of adenomas to carcinomas. In this large sessile villous adenoma, it is likely that the *APC, LOH 18q*, and *RAS* genes have been affected.

Left colon, carcinoma - Gross, mucosal surface:

- This specimen from the left colon shows an annular, encircling, and constricting cancer.
- The margins of the cancer are heaped-up and firm, and the mid-region is ulcerated.
- Left-sided colon cancers come to attention by producing occult bleeding and changes in bowel habits (i.e., constipation and cramping in the left lower quadrant).
- The carcinoma is composed of irregular glands infiltrating the muscularis propria, serosa, and mesentery.



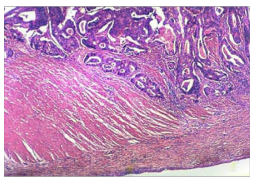
Assuming this patient did not have lymph node metastasis, what stage is this carcinoma?



The TNM stage for the current case would be T3N0MX.

- T3—extends through the muscularis propria
- N0—no lymph node involvement
- MX—extent of metastatic involvement unknown.

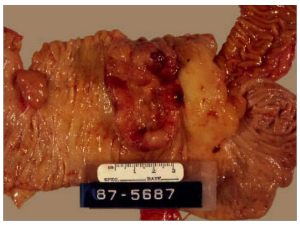
Malignant glands of an adenocarcinoma of the colon infiltrating the muscularis propria.



What is the mode of spread of this cancer?

Colonic carcinomas spread by local extension to adjacent structures. The favored sites of metastases are regional lymph nodes, liver, lungs, and bones.

Cecal adenocarcinoma



Tumors in the proximal colon tend to grow as polypoid, fungating, ulcerating masses. Obstruction is uncommon. About 25% of colon

Cecal and right colon cancers most often come to clinical attention by the appearance of fatigue, weakness, and **iron-deficiency anemia.**

For any suggestions or questions please don't hesitate to contact us on: Pathology434@gmail.com

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Ask us: www.ask.fm/Pathology434

GOOD LUCK !!

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اسماء الرصيص
أمل افراح
نورة الهلالي
فتون المطيري
رغد العتيبي
مها الربيعة