GASTROINTESTINAL CANCER

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ESOPHAGUS

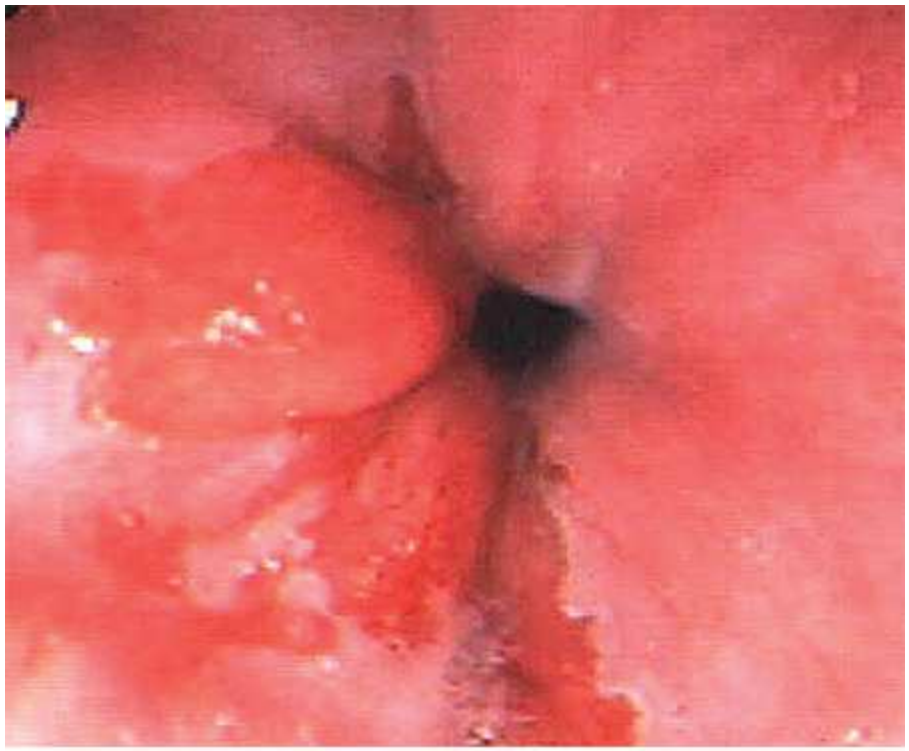
Barrett esophagus

- 40-50 years of age.
- A complication of long-standing gastro-esophageal reflux.
- Resistant to proton pump therapy.
- Up to 10% of patients with symptomatic gastro-esophageal reflux disease (GERD).
- Red, velvety appearance on endoscopy.
- This metaplastic mucosa of distal esophagous alternates with residual smooth, pale squamous (esophageal) mucosa and interfaces with light-brown columnar (gastric) mucosa distally
- May reflect abnormality in stem cell maturation.

Barrett esophagus

- It is the single most important risk factor for development of esophageal adenocarcinoma.
- Divided into short (<3cm) and long (>3cm) segment disease depending upon length of mucosal abnormality.
- Risk related to extent of disease.
- Multifocal dysplasia treated as if it were intramucosal carcinoma.
- Intramucosal carcinoma is characterized by invasion of the lamina propria.

Barrett's esophagous



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Endoscopic view. Metaplastic change.

(Courtesy of Klaus Monkemuller, MD, UAB, Birmingham, AL)

Fig. 14-16
Accessed 04/01/2010

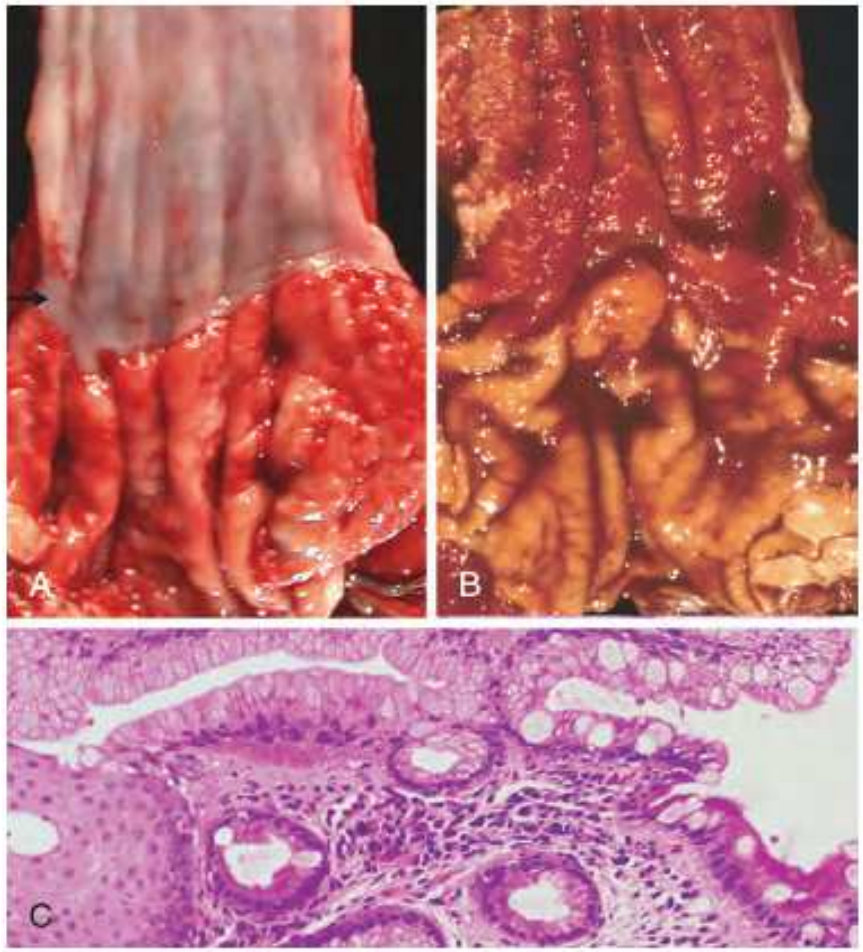


Figure 17-7 Barrett esophagus. **A,** Normal gastroesophageal junction. **B,** Barrett esophagus. Note the small islands of residual pale squamous mucosa within the Barrett mucosa. **C,** Histologic appearance of the gastroesophageal junction in Barrett esophagus. Note the transition between esophageal squamous mucosa (left) and Barrett metaplasia, with abundant metaplastic goblet cells (right).

Barrett esophagus

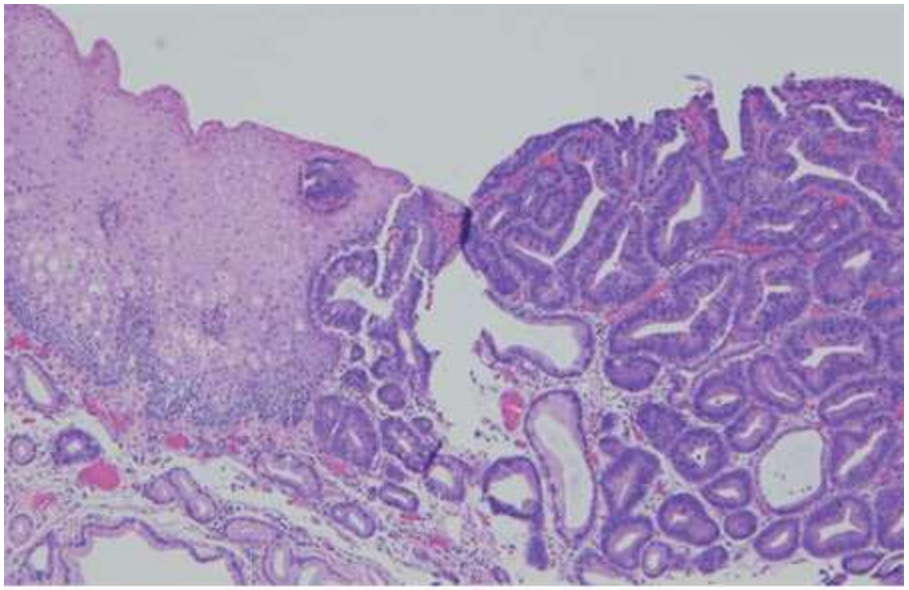


Fig.14-17 Accessed 04/01/2010

Microscopically, intestinal-type metaplasia is seen as replacement of the squamous esophageal epithelium with goblet cells. These are diagnostic of Barrett esophagus, and have distinct mucous vacuoles that stain pale blue by H&E and impart the shape of a wine goblet to the remaining cytoplasm. Non-goblet columnar cells, such as gastric type foveolar cells, may also be present.

(*Courtesy of Dr. Stephen May, MD, and Dr. Asif Rashid, MD, UTMDACC, Department of Pathology, Houston, TX*)

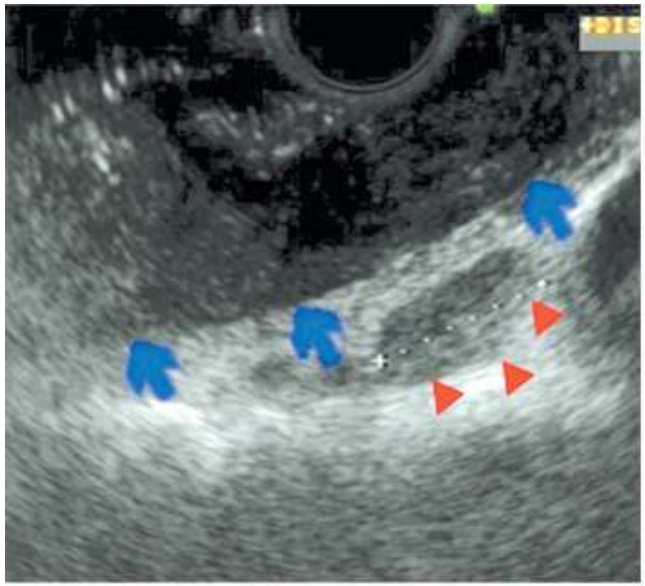
Benign esophageal tumor

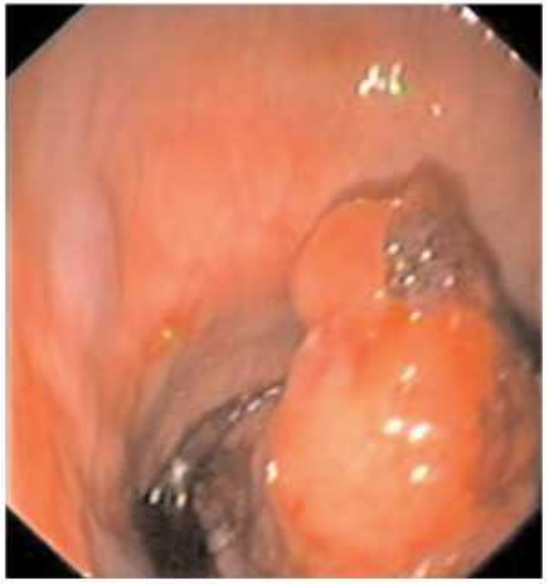
- Leiomyoma (tumor of smooth muscle) is the most common benign tumor of the esophagus.
- May interfere with swallowing.
- Resect

Esophageal cancer

- Endoscopy with biopsy is the primary test for the diagnosis of esophageal cancer.
- Endoscopic ultrasound (EUS) is important in the initial local staging.
- CT of the chest and abdomen is recommended for staging and assessing tumor resectability.
- MRI provides better assessment of vascular structures than does CT.

Esophageal cancer

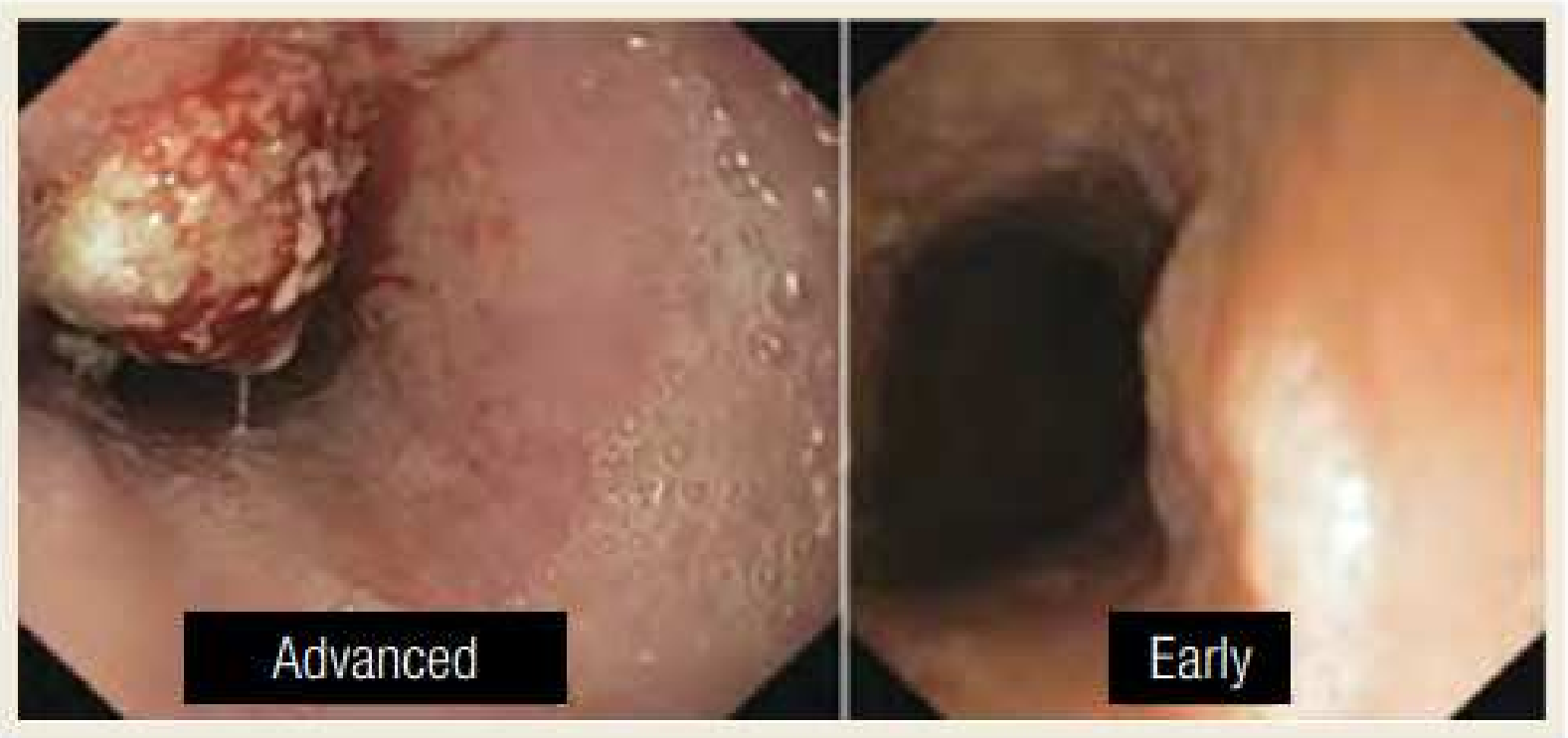


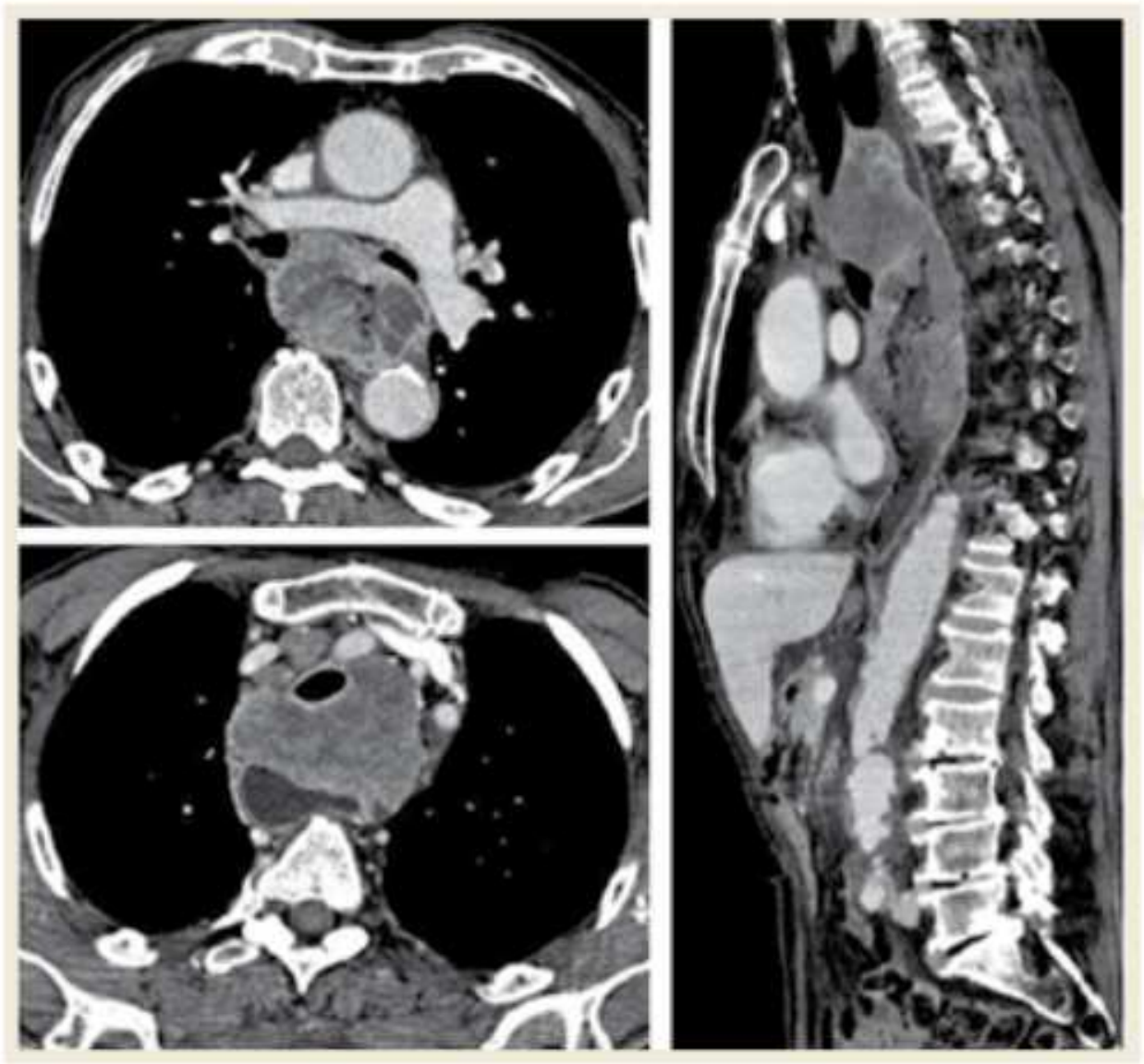


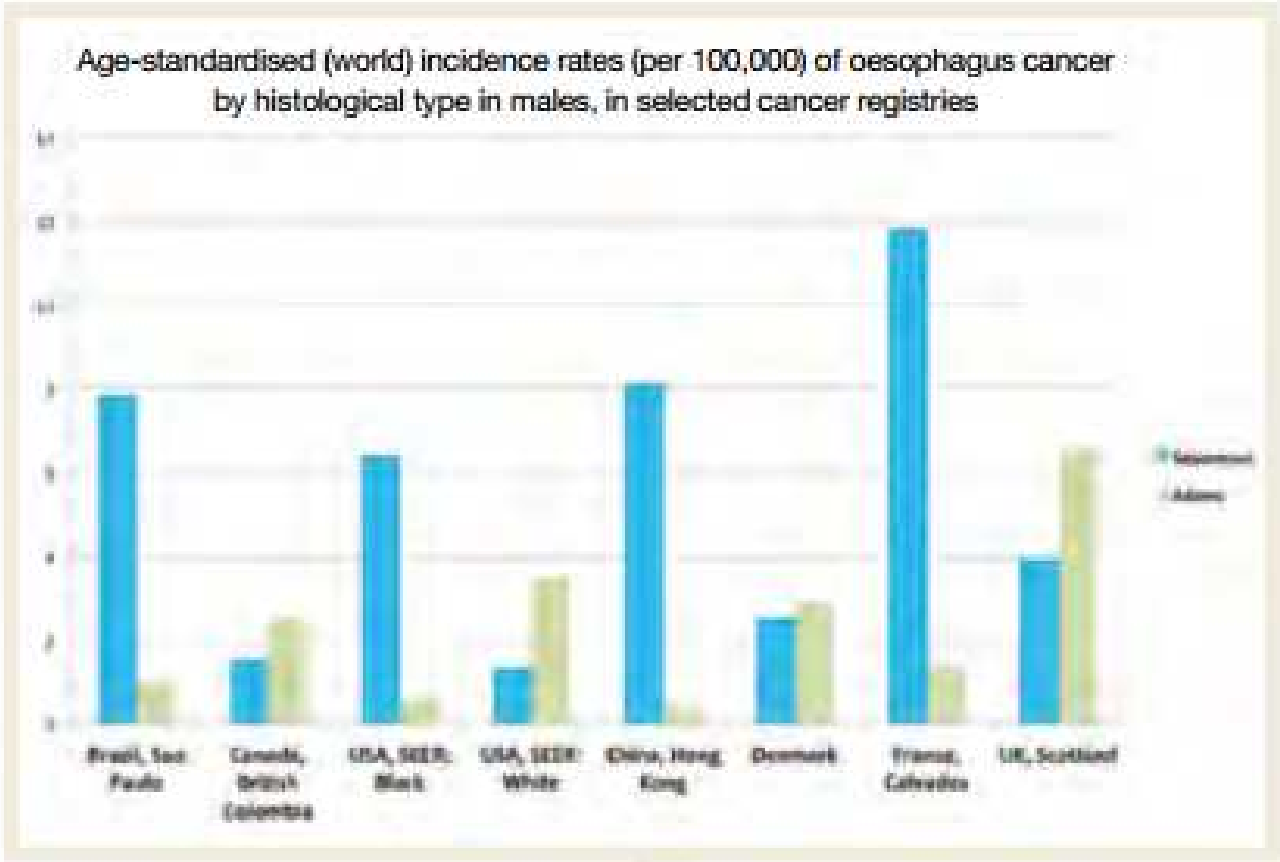
Endoscopic ultrasound and endoscopic view demonstrating polypoid mass.

(*Courtesy of Adrian Saftiou, MD, University of Medicine and Pharmacy Craiova, Romania.*)

Fig. 14-20 Accessed 04/01/2010


Advanced
Early




Age-standardised (world) incidence rates (per 100,000) of oesophagus cancer by histological type in males, in selected cancer registries

FACTORS	OSCC	OAC	
	INCREASES RISK	DECREASES RISK	INCREASES RISK
Tobacco	Smoking (mainly in Western population)		Smoking
Dietary factors	Low fruit intake Low vegetable intake High alcohol intake (mainly in Western population) High intake of processed meat		Low fruit intake Low vegetable intake Low vitamin C intake Low carotene intake High intake of processed meat
Infectious agents		*H. pylori* infection	
Hot beverages	Coffee, tea, mate		Coffee, tea, mate
Body mass index			Obesity
Other	Tooth loss and poor oral hygiene (in Asian populations)		Gastro-oesophageal reflux disease Barrett's oesophagus Some drugs (beta-blockers, aminophyllines, anticholinergics) that relax the sphincter

OAC, Oesophageal adenocarcinoma; OSCC, oesophageal squamous cell carcinoma.

Adenocarcinoma

- Adenocarcinoma now represents up to half of all esophageal cancers reported in the United States.
- The majority of cases arise from the Barrett mucosa.
- Occur in the distal third of the esophagus.
- May invade adjacent gastric cardia.
- Tobacco use also a risk factor.
- In rare instances, adenocarcinoma originates from heterotopic gastric mucosa or submucosal glands.

Adenocarcinoma

- Morphologic patterns
- Barrett esophagus is frequently present adjacent to the tumor.
- Tumors most commonly resemble mucin producing colon adenocarcinoma
- Less frequently, resemble diffusively infiltrative adenocarcinoma (with signet ring cells) as in the stomach
- Rarely, resemble poorly differentiated small cell carcinoma as in the lung.

Adenocarcinoma

- The more common genetic and epigenetic alteration is the inactivation of CDKN2A (p16/INK4a)
- Bi-allelic loss or hypermethylation of CDKN2A
- Patients with LOH in TP53 are 16 times more likely to progress to adenocarcinoma
- Overexpression of p53
- Predominantly G:C to A:T transitions at CpG dinucleotides
- These changes are seen both in Barrett's as well as in adenocarcinoma of the cardia

Adenocarcinoma

- In high-grade dysplasia, chromosome 4 amplification is generally present.
- When the dysplastic epithelium develops into adenocarcinoma, additional genetic changes, including nuclear translocation of β-catenin and amplification of *c*-ERB-B2*,* are present.
- MET as well as Cyclin D1 and E amplifications are also noted.
- TNF as well as NF-kB upregulated.

Molecular relationships

- Esophageal squamous cell carcinoma resembles squamous cell carcinoma of other organs
- Esophageal adenocarcinoma strongly resembles the chromosomally unstable variant of gastric adenocarcinoma:
- The EAC-like group
- High copy number amplification and increased protein expression of ERBB2 and EGFR
- The gastric adenocarcinoma located at the fundus or body of the stomach–like group
- Activated phosphoinositide 3-kinase–AKT signaling with decreased expression of ERBB2.

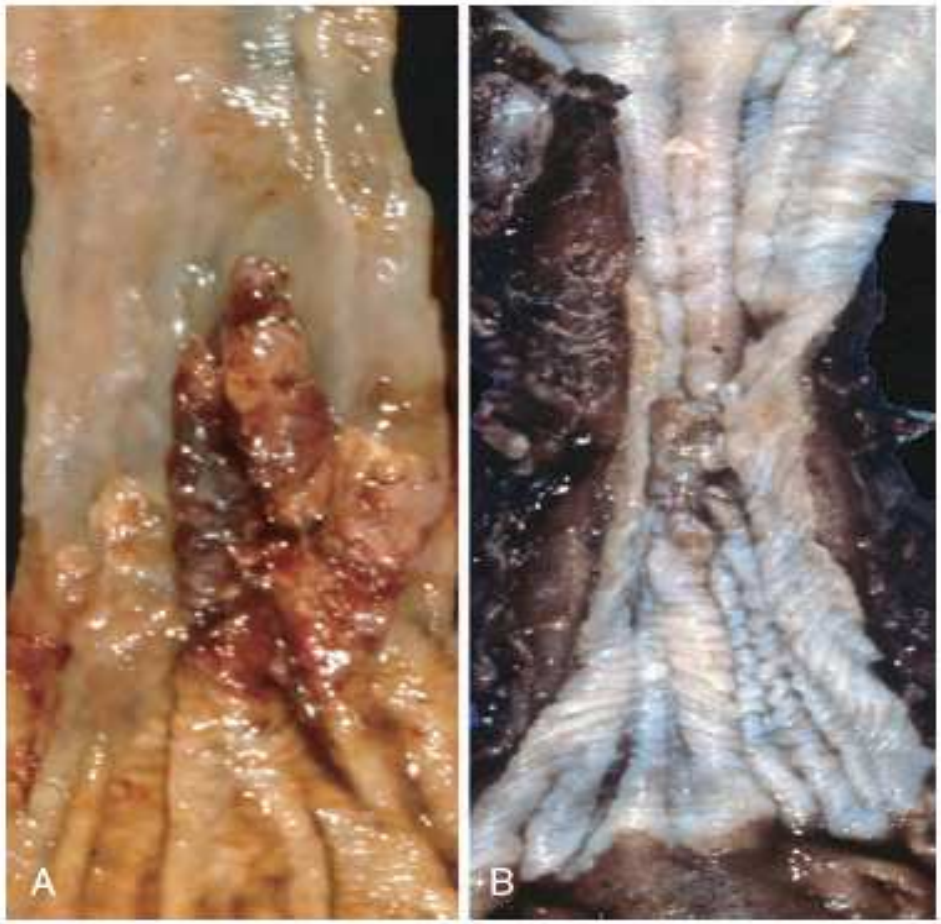


Figure 17-9 Esophageal cancer. **A,** Adenocarcinoma usually occurs distally and, as in this case, often involves the gastric cardia. **B,** Squamous cell carcinoma is most frequently found in the mid-esophagus, where it commonly causes strictures.

Squamous cell carcinoma

- Dysphagia and pain on swallowing are the usual presenting symptoms
- Most squamous cell carcinomas occur in adults over age 50.
- Iran, central China, Hong Kong, Brazil, South Africa are regions of highest incidence
- More common in rural and undeveloped areas
- Those of African descent in the US are at significantly higher risk for squamous cell carcinoma
- Likelier in males.
- This may reflect tobacco and alcohol use.

Squamous cell carcinoma

- Other risk factors
- Polycyclic hydrocarbon exposure
- Nitrosamines in food
- Nutritional deficiencies
- Aflatoxin
- HPV
- Associated with consumption of a fermented acetaldehyde containing milk (mursik) in Western Kenya

Squamous cell carcinoma

- Generally occur in middle-third of esophagous
- May either be polypoid or exophytic and protrude into esophageal lumen
- May be diffusely infiltrative in submucosa and wall
- May extend to surrounding structures such as aorta, lung, mediastinum, or pericardium

Squamous cell carcinoma

- Lymph node involvement for cancers in the upper-third of the esophagous are cervical;
- For the middle-third of the esophagous, mediastinal, paratracheal, or tracheobronchial;
- For the lower-third of the esophagous, gastric and celiac nodes

Squamous cell carcinoma

- GWAS studies in Asian populations showed a significant increase of squamous cell carcinoma risk associated with:
- 2q33 (CASP8, ALS2CR12, TRAK2
- ALDH2 and ADH1B locus in alcohol drinkers
- 10q23 (PLCE1, C20orf54)
- 5q31.2 (TMEM173)
- 17p13.1 (ATP1B2).

Esophageal squamous carcinoma

- Loss of function early change in squamous cancer.
- Transversion G:C to T:A occurred preferentially at known sites of adduct formation on DNA.
- A spectrum of p53 point mutations are present in over half of squamous cell esophageal cancers.
- Mutations common in area that affects adduct formation.

Squamous cell carcinoma

- Other genetic alterations, such as mutations in p16INK4, and amplification of Cyclin D1, C-MYC, and epithelial growth factor receptor (EGFR), are prevalent in these cancers as well.
- Notably rare in esophageal squamous cell carcinomas are KRAS and APC mutations

Treatment strategy for cancer

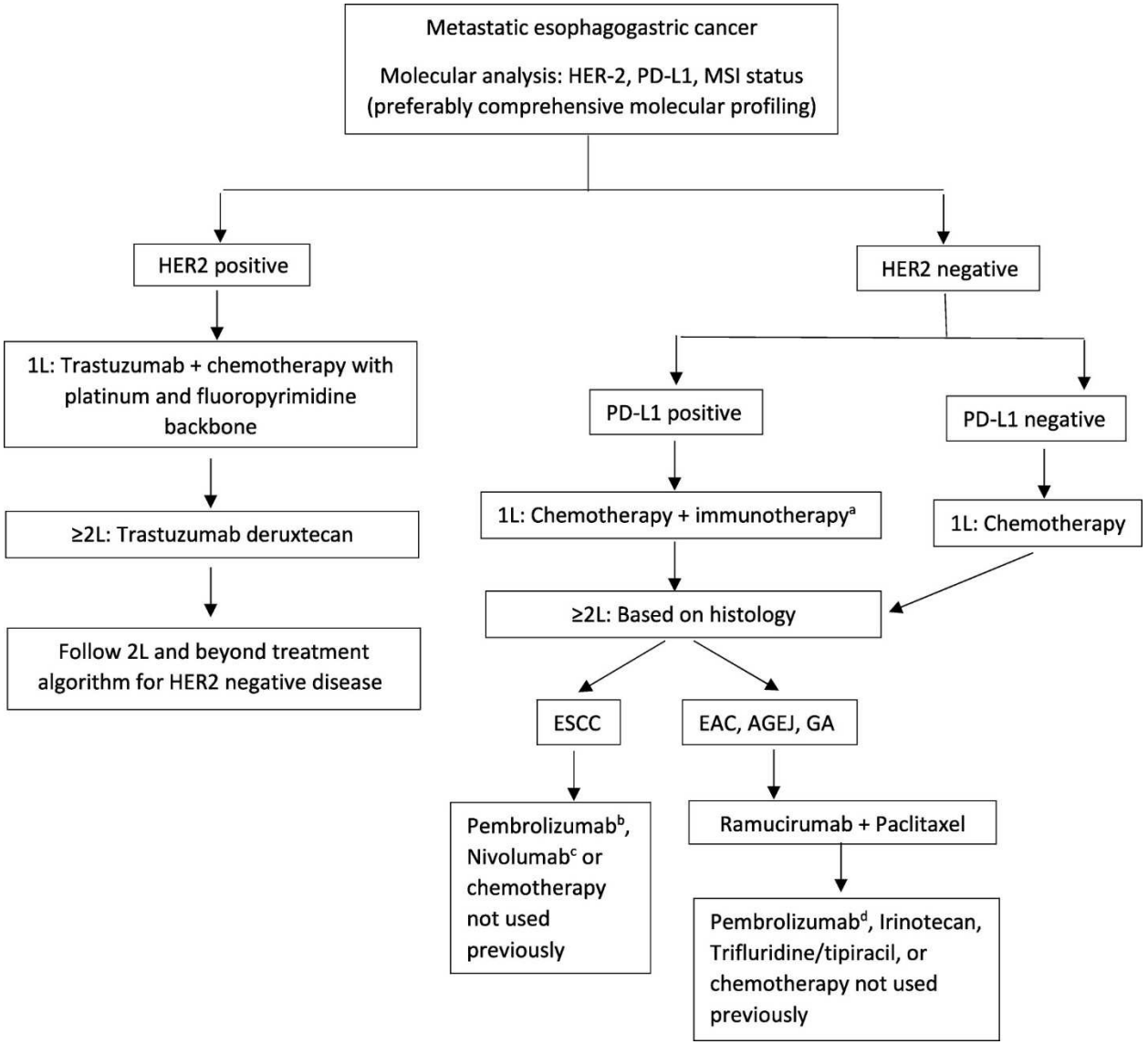
- Endoscopic ultrasound is the optimal technique for local regional staging.
- MRI provides better assessment of vascular structures than does CT.
- Thoracic esophageal tumors above the aortic arch as well as T4 or N1 tumors are not resectable.

Treatment strategy for cancer

- Tis and T1a tumors are potentially curable with endoscopic mucosal resection.
- Stage I and II cancers are treated with en bloc resection of the esophagus and lymphadenectomy of the cervical and superior mediastinum in Japan
- OR
- By transhiatal esophagectomy with cervical anastamosis (avoiding thoracotomy).

Treatment strategy

- Much longer survival (40% vs 27% at 5 years) but much higher morbidity is noted with the Japanese approach.
- Chemotherapy with cisplatin and 5FU and Pembrizolumab (PDL-1 target) is administered as definitive therapy in stage III esophageal cancer, irrespective of HER2 status.
- Trastuzumab induces antibody dependent cellular phagocytosis, allowing uptake of tumor by antigen processing cells. May also be used if HER2+.
- Stents may be placed in advanced lesions.



Mamdani, H, and Jalal, SL, "Where to Start and What to Do Next: The Sequencing of Treatments in Metastatic Esophagogastric Cancer," American Society of Clinical Oncology Educational Book 41 (March 25, 2021) 170-185. DOI: 10.1200/EDBK_321243 Figure 1

STOMACH

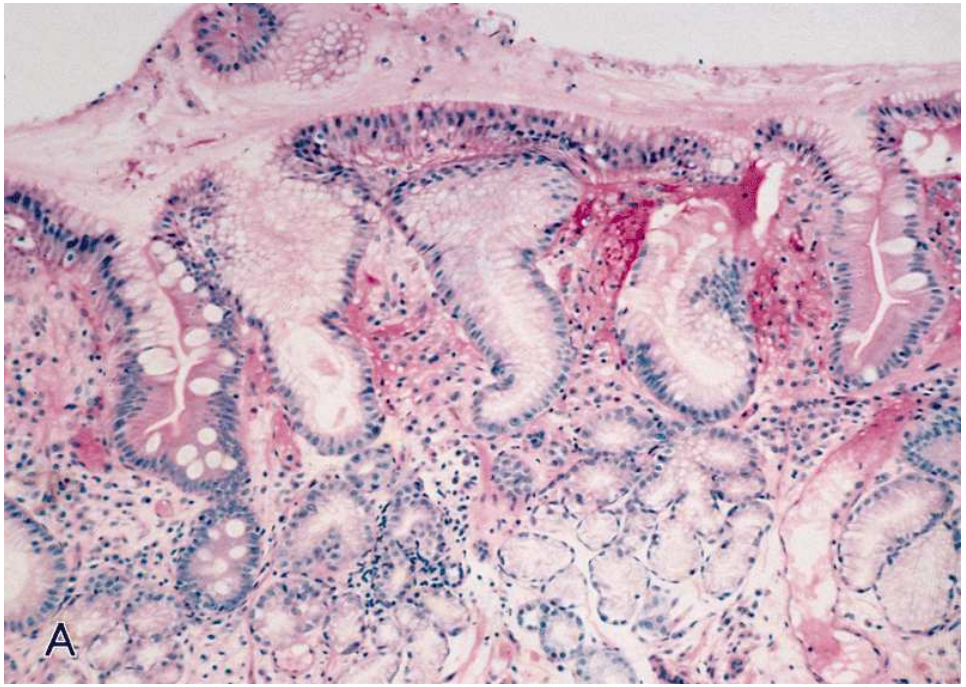
Gastric mucosal dysplasia

- There are two separate types of dysplastic epithelial changes identified.
- Both may be found.
- The most common is the intestinal type.
- This epithelium is indistinguishable from that which occurs in colonic adenomas.
- Composed of altered intestinal epithelial cells, including the dominant undifferentiated or primitive cell, along with a group of differentiated cells such as goblet cells, Paneth cells, possibly absorptive cells, and endocrine cells.

Mucosal dysplasia

- The second type is the gastric type.
- Composed of dysplastic cells resembling gastric foveolar and surface cells with apical neutral mucin vacuoles.

Intestinal metaplasia

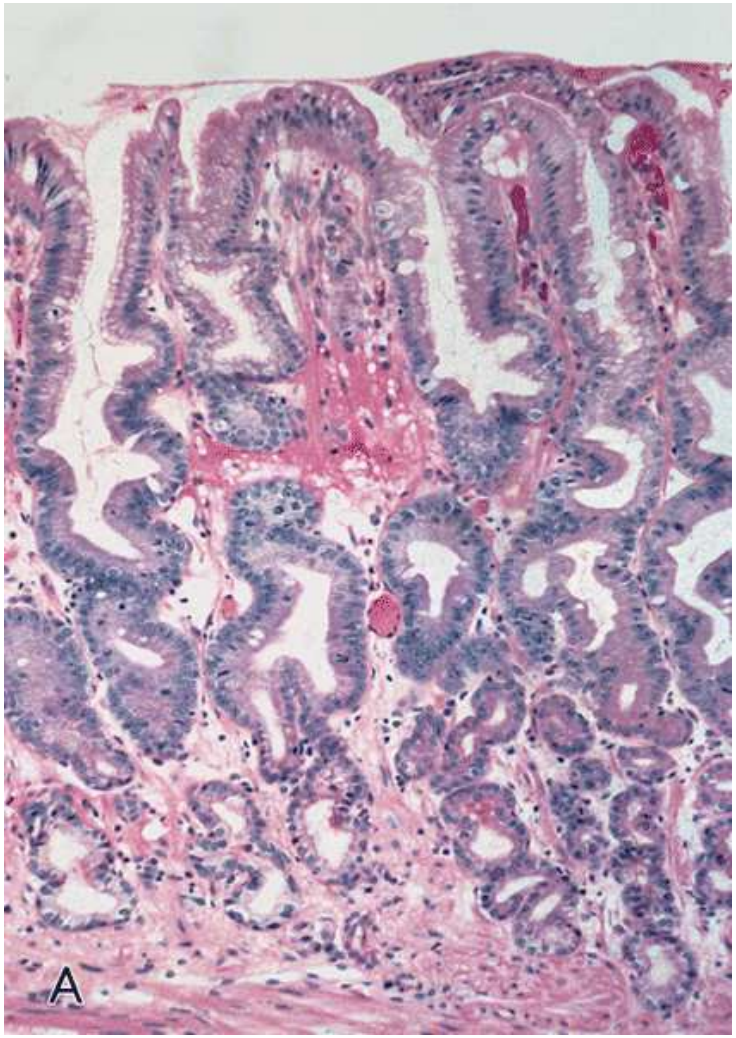


This epithelium is identical to that in many colorectal adenomas. The cells are elongated, as are their nuclei. The nuclei are stratified, but the stratification is mostly confined to the basal half of the cells. There is no nuclear pleomorphism. Small mucus vacuoles within dysplastic goblet cells are present in the luminal cytoplasm of many cells.

Fig. 11-1A

Lewin, KJ, Appelman, HD., “Tumors of the esophagus and stomach.” Atlas of Tumor Pathology, Third Series, Fascicle 18. Armed Forces Institute of Pathology, Washington, DC. 1996.

Foveolar metaplasia



The cells are columnar. Many cells contain apical mucin vacuoles that stain red with periodic acid- Schiff, but not with Alcian blue. The nuclei are oval to round, and many have small nuclei. Nuclear stratification is limited to the basal half of the epithelium. (Hematoxylin and eosin stain)

Fig. 11-2A

Lewin, KJ, Appelman, HD., "Tumors of the esophagus and stomach." Atlas of Tumor Pathology, Third Series, Fascicle 18. Armed Forces Institute of Pathology, Washington, DC. 1996.

Gastric polyps

- 75% of gastric polyps are inflammatory or hyperplastic. Usually associated with chronic gastritis. Foveolar hyperplasia.
- Commonly present between 50-60 years of age
- May regress with H. pylori therapy.
- Fundic gland polyp prevalence has increased with use of proton pump inhibitors. Women more likely affected.
- Single or multiple and composed of cystically dilated, irregular glands lined by flattened parietal and chief cells. No inflammation.

Gastric adenoma

- Gastric adenomas account for 10% of polyps.
- Men.
- Present between 50-60 years of age.
- Intestinal-type columnar epithelium comprise the adenoma.
- A background of chronic gastritis is present.
- Dysplastic change noted.
- May be present in those with familial adenomatous hyperplasia.
- >2cm size usually associated with malignancy.

Environmental, dietary and lifestyle factors that are or may be associated with gastric cancer risk		
FACTORS	DECREASES RISK	INCREASES RISK
Infectious factors		*H. pylori* (non-cardia) (virulence factors: *CagA, VacA s1, VacA m1, babA2, CagA Epiya-C*)
Tobacco		Smoking
Dietary factors	Green-yellow vegetables Allium vegetables Fruits and citrus fruits Flavonoid Green tea	Salt and salty foods Smoked foods Pickled foods Nitrosamines and nitroso-compounds Alcohol (heavy intake) Red and processed meat Haem iron (from red meat)
Body mass index		Obesity (cardia)
Hormones	Oestrogens	
Anti-inflammatory drugs	Aspirin use	

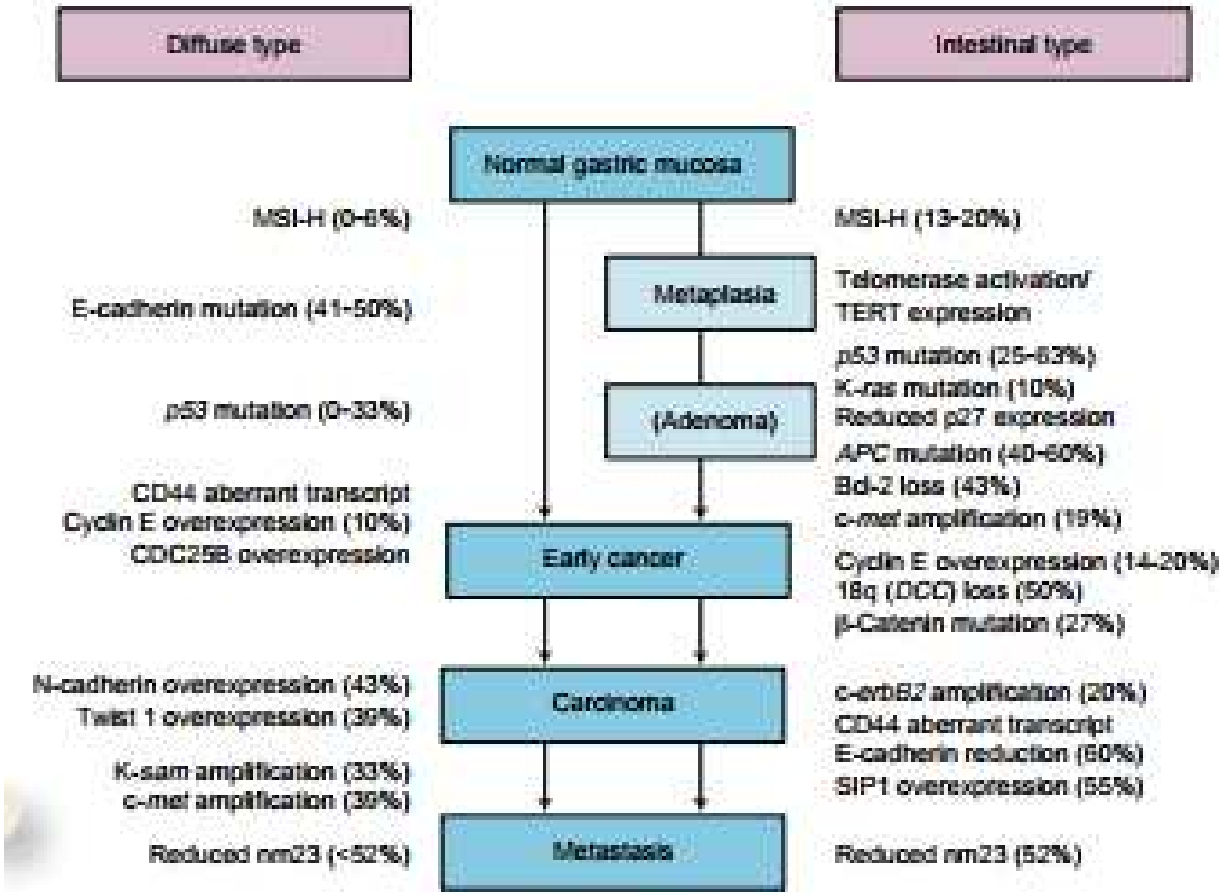
Gastric cancer

- The majority of gastric cancers are adenocarcinomas.
- Most gastric cancers are associated with infectious agents, including Helicobacter pylori and Epstein–Barr virus (EBV).
- A minority are associated with germline mutation in E-cadherin (CDH1) or MMR genes
- Sporadic MMR-deficient gastric cancers have epigenetic silencing of MLH1 in the context of CIMP.
- Mutations in the ubiquitin ligases RNF43 and ZNRF3 or fusions of RSPO2/3 genes are alterations that activate WNT/β-catenin oncogenic signaling.

Gastric cancer

- Gastric carcinomas of the pylorus and antrum account for 50-60% of cases
- Cardia, 25%
- With the remainder divided equally between the body and fundus.
- The lesser curvature is involved in about 40%
- The greater curvature, in 12%.
- Metastases are often detected at time of diagnosis.

Genetic alterations in gastric cancer



Genetic variation and gastric cancer risk in GWAS studies	
GENES	GASTRIC SUBGROUPS
MUC1 rs2070803 (1q22)	*Diffuse carcinoma*
MTX1 rs2075570 (1q22)	*Diffuse carcinoma*
PSCA rs2294008 (8q24.2)	*Non-cardia*
PRKAA1 rs13361707 (5p13)	*Non-cardia*
PLCE1 rs2274223 (10q23)	*Cardia*
TGFBR2 rs3087465 (3p22)	*Asian*
PKLR rs3762272 (1q22)	*Diffuse*
PSCA rs297392 (8q24.2)	*Intestinal*
GSTP1 rs1695 (11q13)	*Asian*
CASP8 rs3834129 (2q33)	*Mixed*
TNF (rs1799724 (6p21.3)	*Mixed*

GWAS, Genome wide association studies.

Single nucleotide polymorphisms (SNPs) in a wide variety of genes may modify the effect of environmental exposure, and this could explain the high variation in GC incidence worldwide

A germline mutation in CDH1 causes the rare familial form of diffuse gastric carcinoma

Gastric cancer

- <u>There are four molecular subtypes</u>
- (1) Tumors positive for Epstein–Barr virus
- EBV-positive tumors display CDKN2A ($p16^{INK4A}$) promoter hypermethylation
- No MLH1 hypermethylation
- >80% have PIK3CA mutations
- 55% have ARID1A mutations (helicase and ATPase functions)
- Amplification of JAK2, PD-L1 and PD-L2

Gastric cancer

- (2) Microsatellite unstable tumors
- Elevated mutation rates
- MLH1 hypermethylation characteristic
- TP53, KRAS, ARID1A, PIK3CA, ERBB3, PTEN and HLA-B commonly mutated
- HLA-B mutation associated with diminished presentation of tumor antigen
- More common in distal stomach

Gastric cancer

- (3) Genomically stable tumours
- The diffuse histological variant
- Mutations of RHOA or fusions involving RHO-family GTPase-activating proteins
- Actin-myosin dependent cell contractility and cell motility
- STAT kinase
- ARID1A mutations common
- 50%, loss-of-function mutations in CDH1 in sporadic diffuse gastric tumors
- E-cadherin expression is drastically decreased
- Hyper-methylation and silencing of the CDH1 promoter.

Gastric cancer

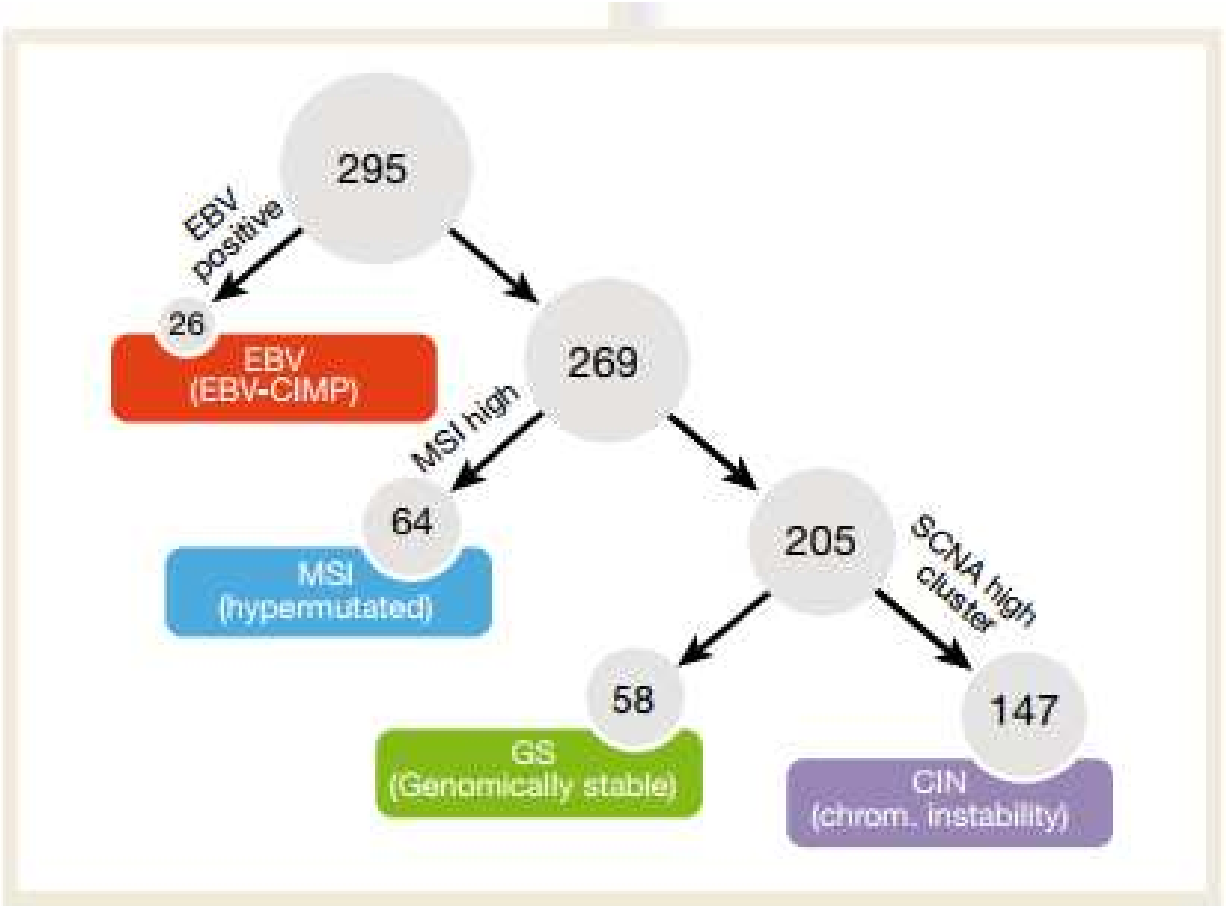
- (4) Tumors with chromosomal instability, which show marked aneuploidy and focal amplification of receptor tyrosine kinases.
- EGFR amplified or mutated
- 32%, gastroesophageal junction
- 26%, distal stomach
- CDH1/TP53 are the most frequent driver mutations
- Elevated expression of p53

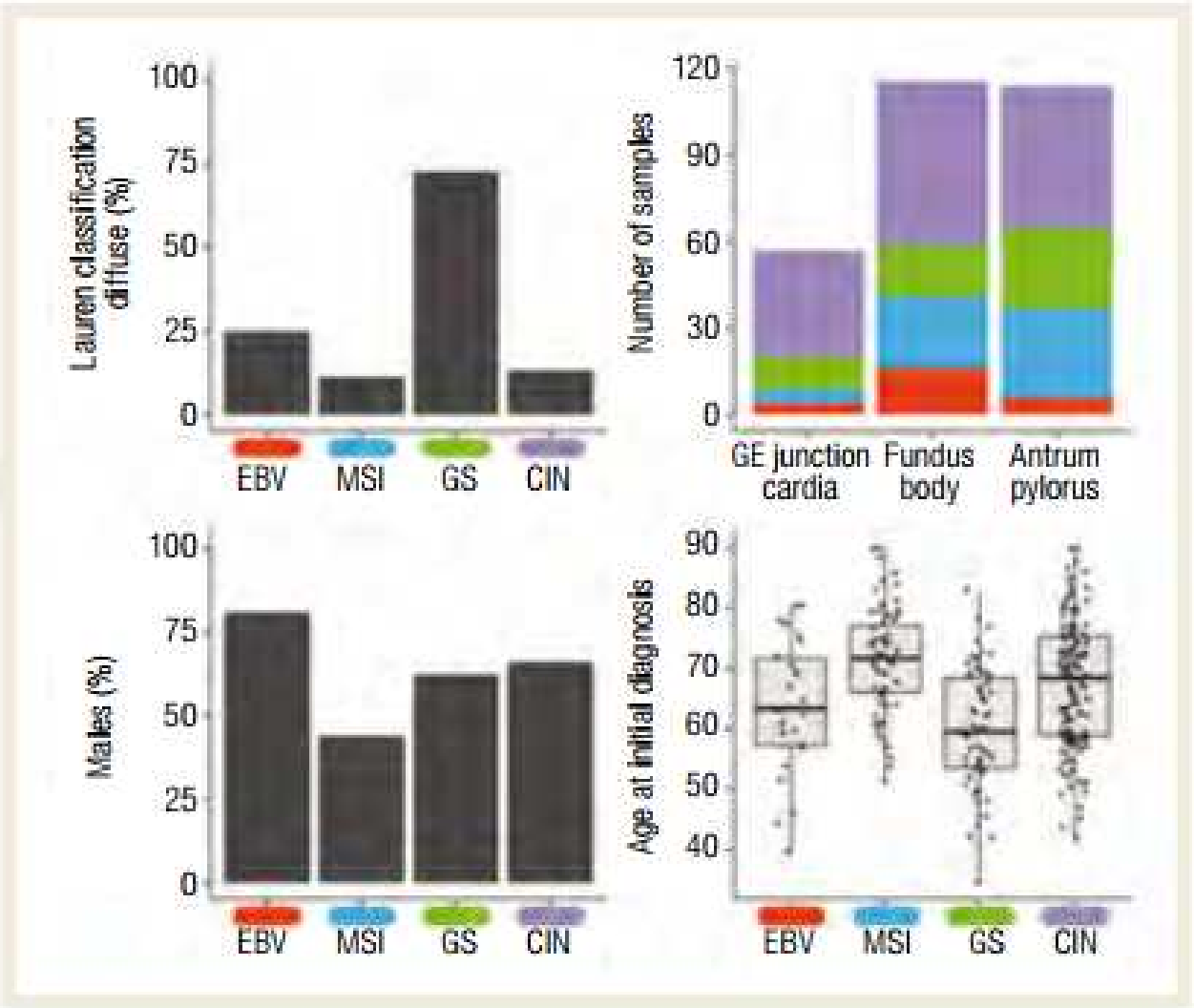
Gastric cancer

- The intestinal and diffuse histologic sub-types appear to have a different pathogenetic basis.
- The intestinal type predominates in high-risk areas, and develops from precursor lesions.
- The intestinal type exhibits a mean age of incidence of 55 years and predominantly involves men.
- FAP gene abnormality.
- CIMP associated with poor response, young age.

Gastric cancer

- The incidence of the diffuse type is relatively constant, and the tumors have no identifiable precursor lesions.
- Diffuse gastric cancer occurs at a mean age of 48 years with no sex predominance.
- Undifferentiated signet-ring histology.
- Associated with Helicobacter pylori infection but no mechanism of carcinogenesis proposed.
- Involve the body 25% of the time; cardia and fundus, each 35%.


295
EBV positive
26
EBV
(EBV-CIMP)
269
MSI high
64
MSI
(hypermutated)
205
SCNA high cluster
58
GS
(Genomically stable)
147
CIN
(chrom. instability)


Lauren classification diffuse (%)
100
75
50
25
0
EBV
MSI
GS
CIN
Number of samples
120
90
60
30
0
GE junction cardia
Fundus body
Antrum pylorus
Males (%)
100
75
50
25
0
EBV
MSI
GS
CIN
Age at initial diagnosis
90
80
70
60
50
40
EBV
MSI
GS
CIN

Gastric cancer

- The intestinal and diffuse histologic sub-types appear to have a different pathogenetic basis.
- The intestinal type predominates in high-risk areas, and develops from precursor lesions.
- The intestinal type exhibits a mean age of incidence of 55 years and predominantly involves men.
- 40% occur in the body of the stomach.
- Bulky.

Gastric cancer

- Associated with H. pylori.
- Loss of function mutations in the APC gene as well as gain of function mutation in β-catenin (binds to E-cadherin and APC)
- CIMP associated with poor response, young age.

Gastric cancer

- The incidence of the diffuse type is relatively constant, and the tumors have no identifiable precursor lesions.
- Diffuse gastric cancer occurs at a mean age of 48 years with no sex predominance.
- No peristalsis.
- Tumor cells infiltrate stomach wall. Marked desmoplastic reaction. (Linitis plastica)
- Undifferentiated signet-ring histology.
- Chemotherapy resistant

Gastric cancer

- BRCA2 mutations predispose
- Associated with Helicobacter pylori infection but no mechanism of carcinogenesis proposed.
- Involve the body 25% of the time
- Cardia and fundus, each 35%.

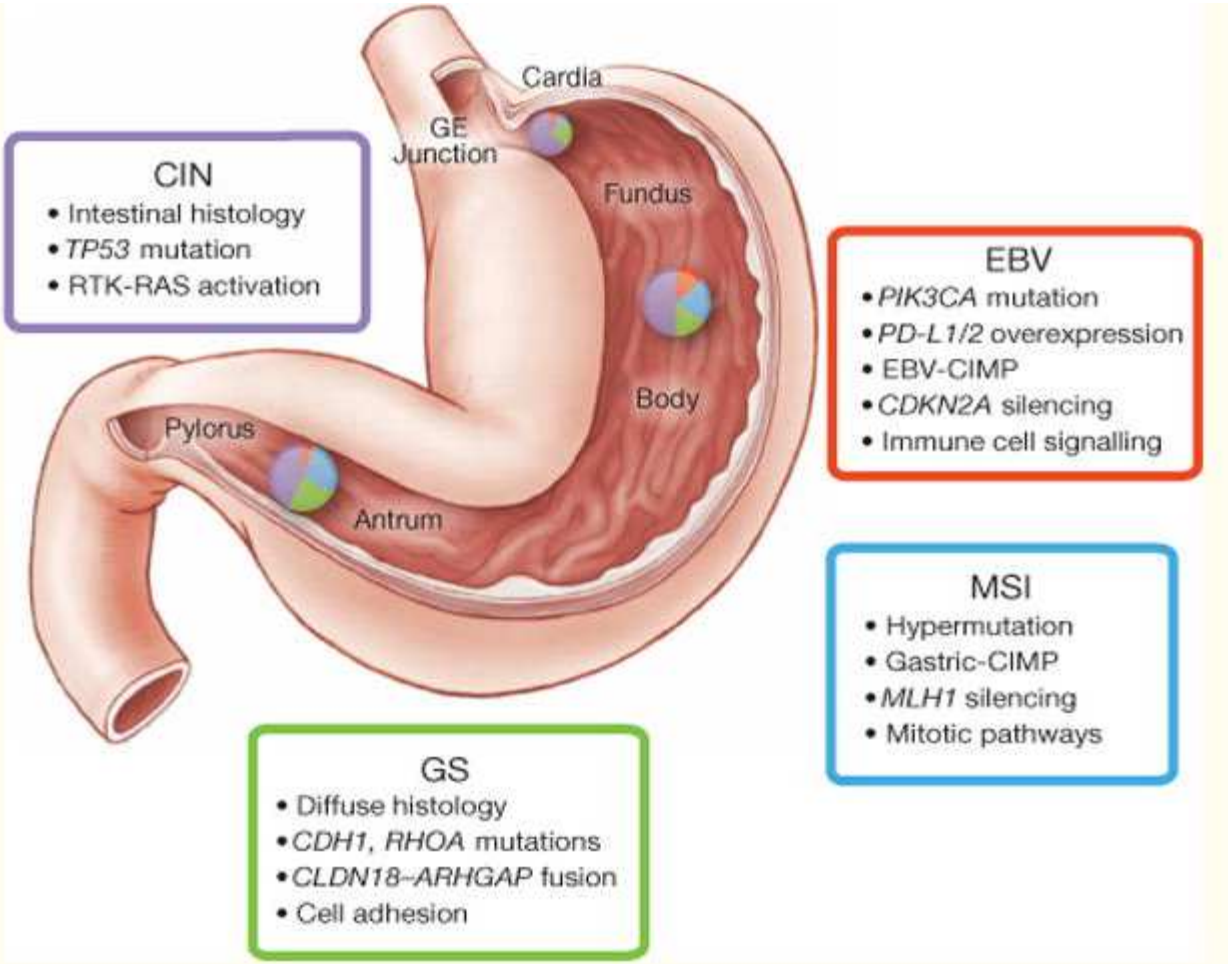


Figure 6

Key features of gastric cancer subtypes

This schematic lists some of the salient features associated with each of the four molecular subtypes of gastric cancer. Distribution of molecular subtypes in tumours obtained from distinct regions of the stomach is represented by inset charts.

doi: 10.1038/nature13480

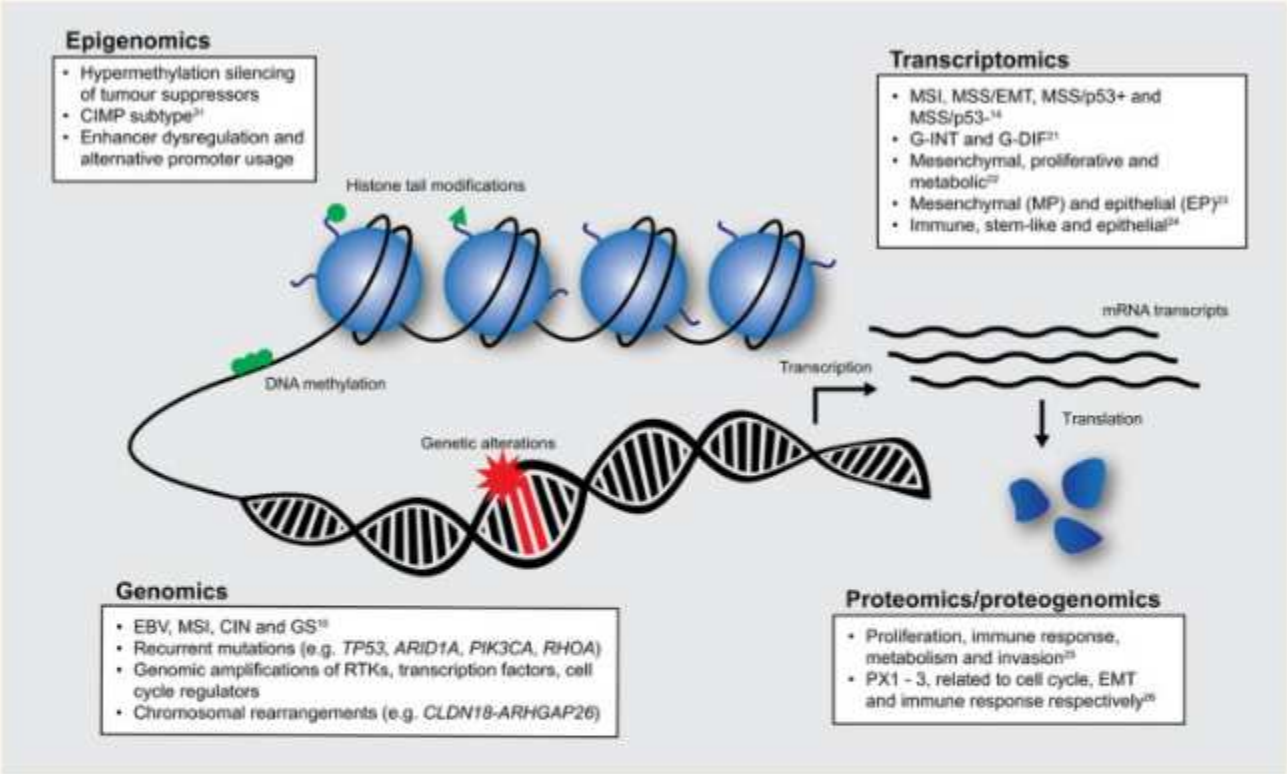


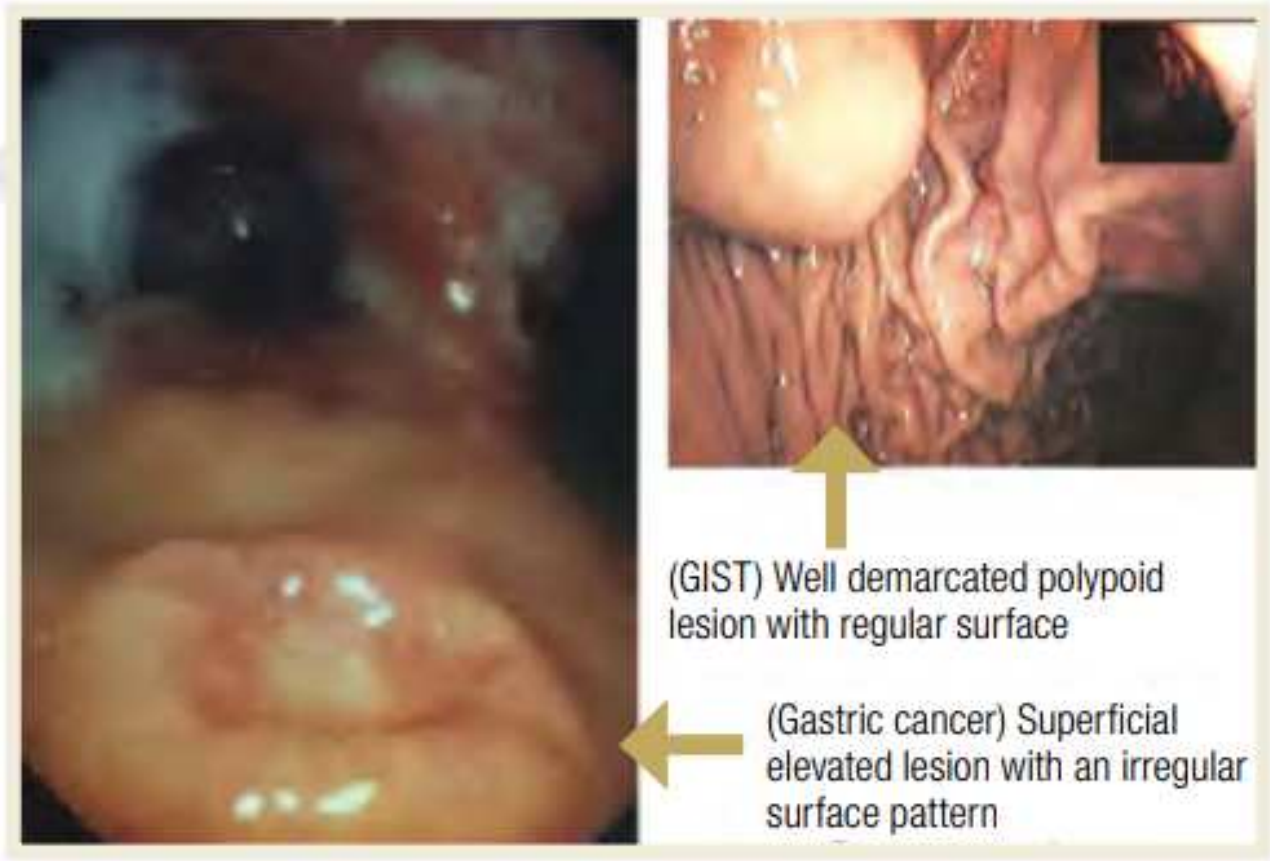
Figure 1

Overview of current molecular classifications in gastric cancer including epigenomic, genomic, transcriptomic and proteomic alterations. Key relevant papers are referenced. CIMP, CpG island methylator phenotype; CIN, chromosomal instability; EBV, Epstein-Barr virus; EMT, epithelial-mesenchymal transition; G-DIF, genomic diffuse; G-INT, genomic intestinal; GS, genomically stable; MSI, microsatellite instability; MSS/EMT, microsatellite stable with EMT phenotype; RTK, receptor tyrosine kinase

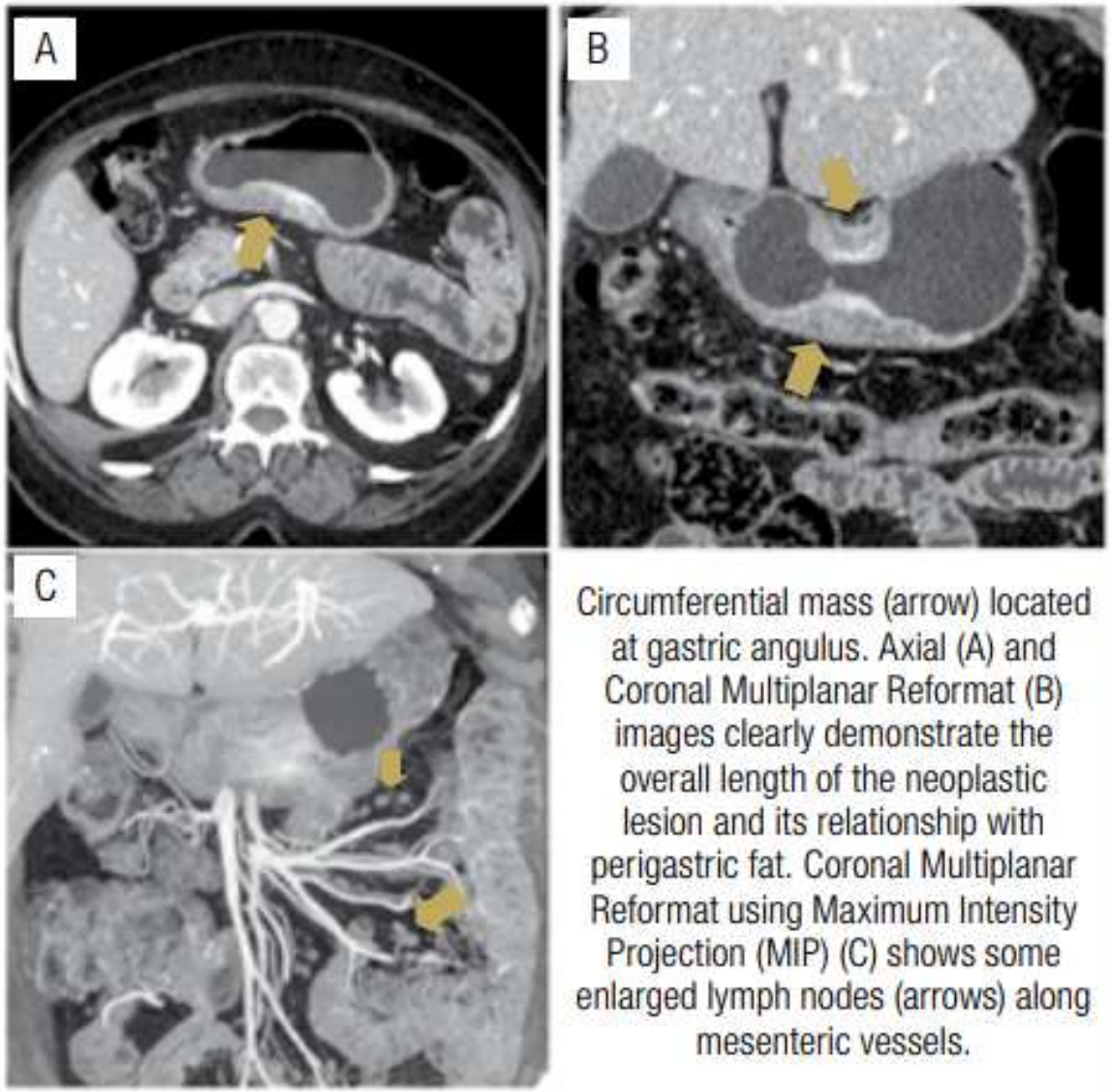
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6825006/

Gastric cancer

- Endoscopy with biopsy is the most sensitive and specific test to detect gastric cancer.
- EUS is important in the initial staging
- Pneumo/hydro-CT has proved to be a useful, safe and accurate technique to identify gastric wall thickening and to stage gastric cancer.
- In diffuse or mucinous tumours, 18 FDG-PET/CT can be inconclusive.

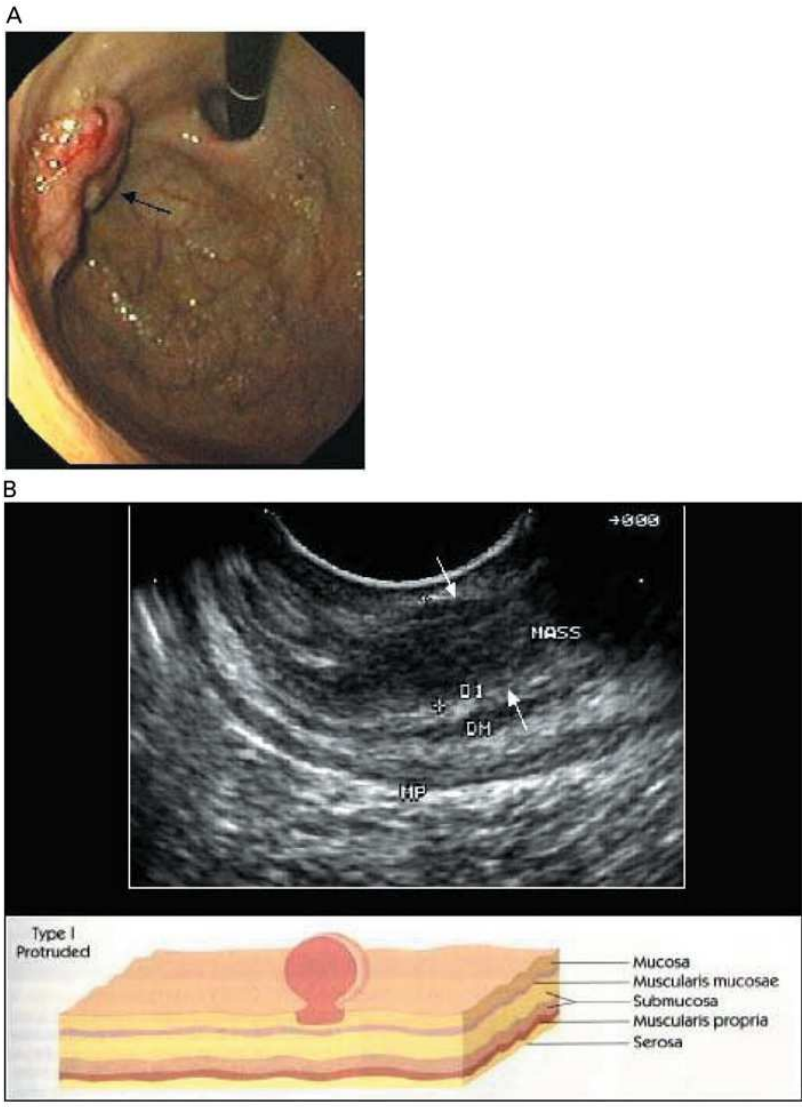


GIST, Gastrointestinal stromal tumour.



Circumferential mass (arrow) located at gastric angulus. Axial (A) and Coronal Multiplanar Reformat (B) images clearly demonstrate the overall length of the neoplastic lesion and its relationship with perigastric fat. Coronal Multiplanar Reformat using Maximum Intensity Projection (MIP) (C) shows some enlarged lymph nodes (arrows) along mesenteric vessels.

Gastric cancer

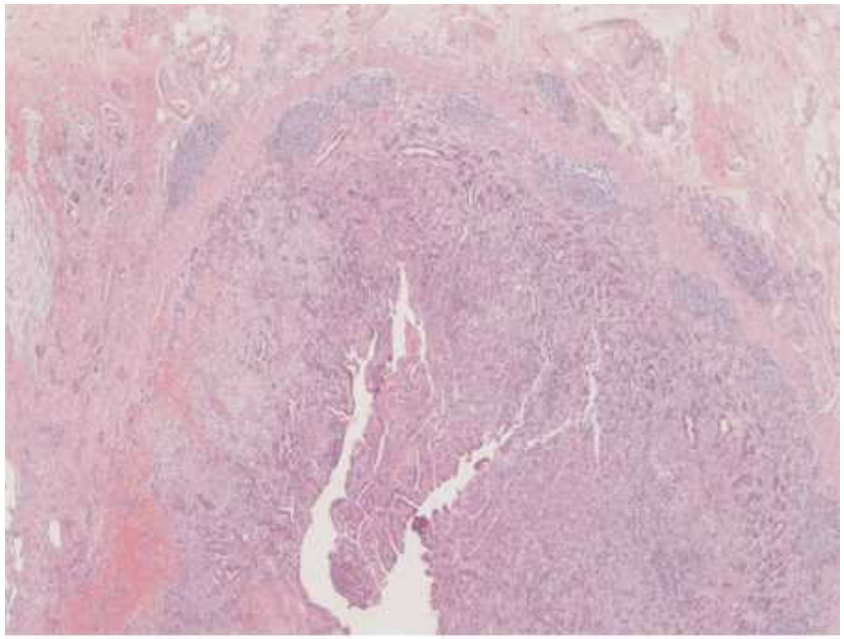


T1 lesion.
A. Endoscopic view.
B. Ultrasound.

(*Reproduced with permission from* http://www.massgeneral.org/gastro/endo_homepage.htm .)

Fig.14-10 Accessed 04/01/2010

Gastric adenocarcinoma



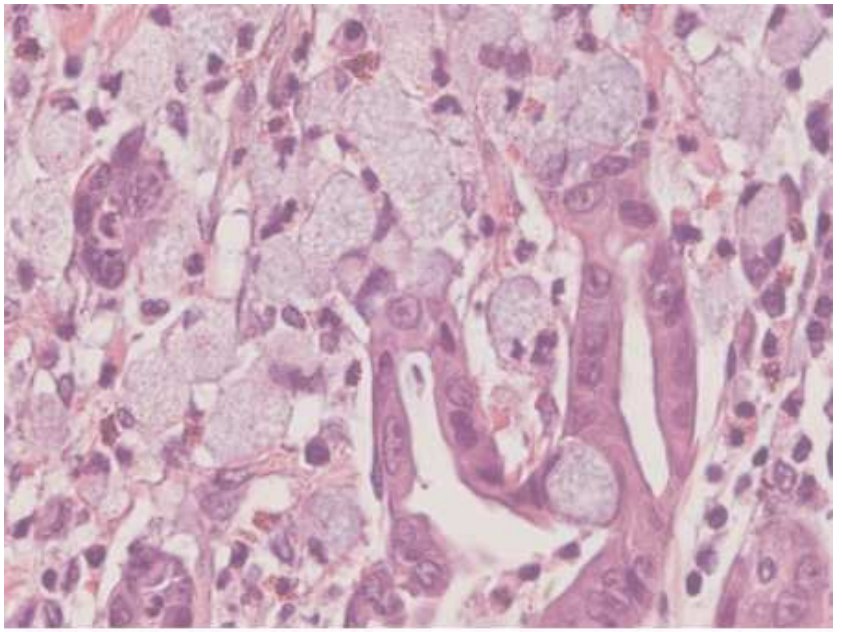
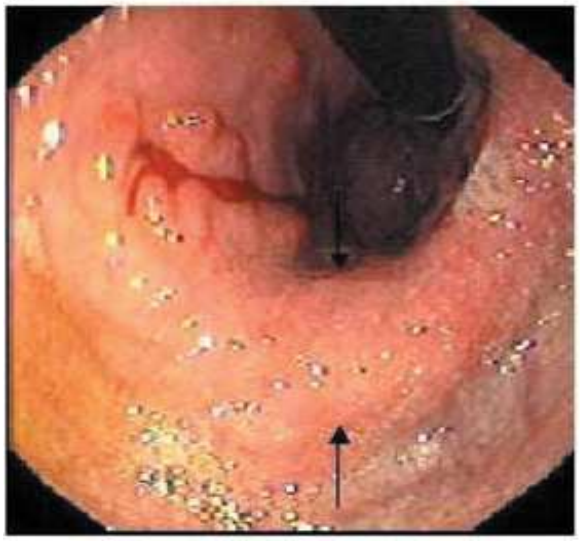


Fig. 14-5 10x and Fig14-8 40x (*Courtesy of Dr. Stephen May and Dr. Asif Rashid, UTMDACC, Houston, TX*)
Accessed 04/10/2010

Linitis plastica

A



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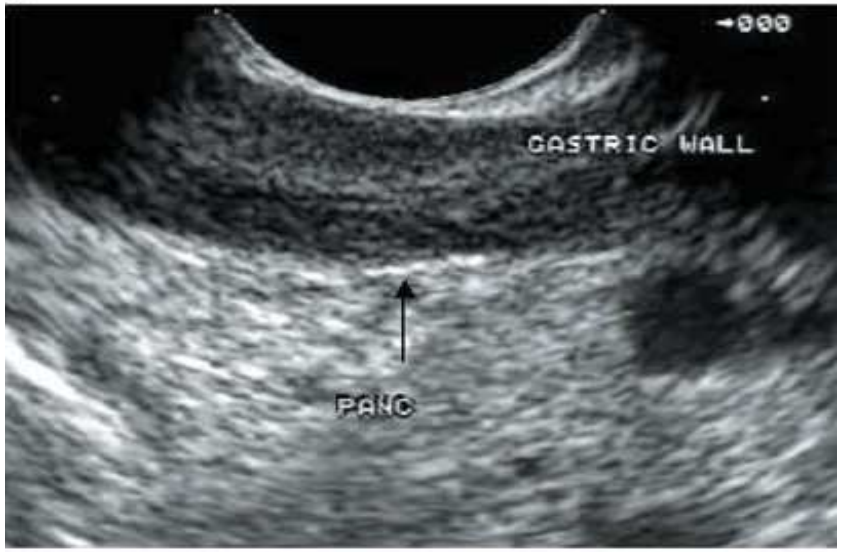


Diffuse submucosal infiltration by cancer.

Fig.14-12 Accessed 04/01/2010

Gastric cancer

- Local invasion of gastric carcinoma into the duodenum, pancreas, and retroperitoneum.
- At the time of death, widespread peritoneal seeding and metastases to the liver and lungs are common.
- Sister Mary Joseph nodule. Metastasis to the periumbilical region to form a subcutaneous nodule.
- Virchow node (left supraclavicular node).
- A notable site of visceral metastasis is to one or both ovaries. Although uncommon, metastatic adenocarcinoma to the ovaries (from stomach, breast, pancreas, and even gallbladder) is so distinctive as to be called Krukenberg tumor.

Treatment strategy

- Resection is indicated in patients with stage I-III disease with minimal lymph node involvement.
- Subtotal gastrectomy in the case of proximal cardia or distal lesions provided the fundus or gastroesophageal junction is not involved.
- Total gastrectomy in the case of diffuse tumors arising in the body and extending to within 6cm of the cardia.
- Pre-operative chemotherapy associated with poorer outcomes.

Treatment strategy

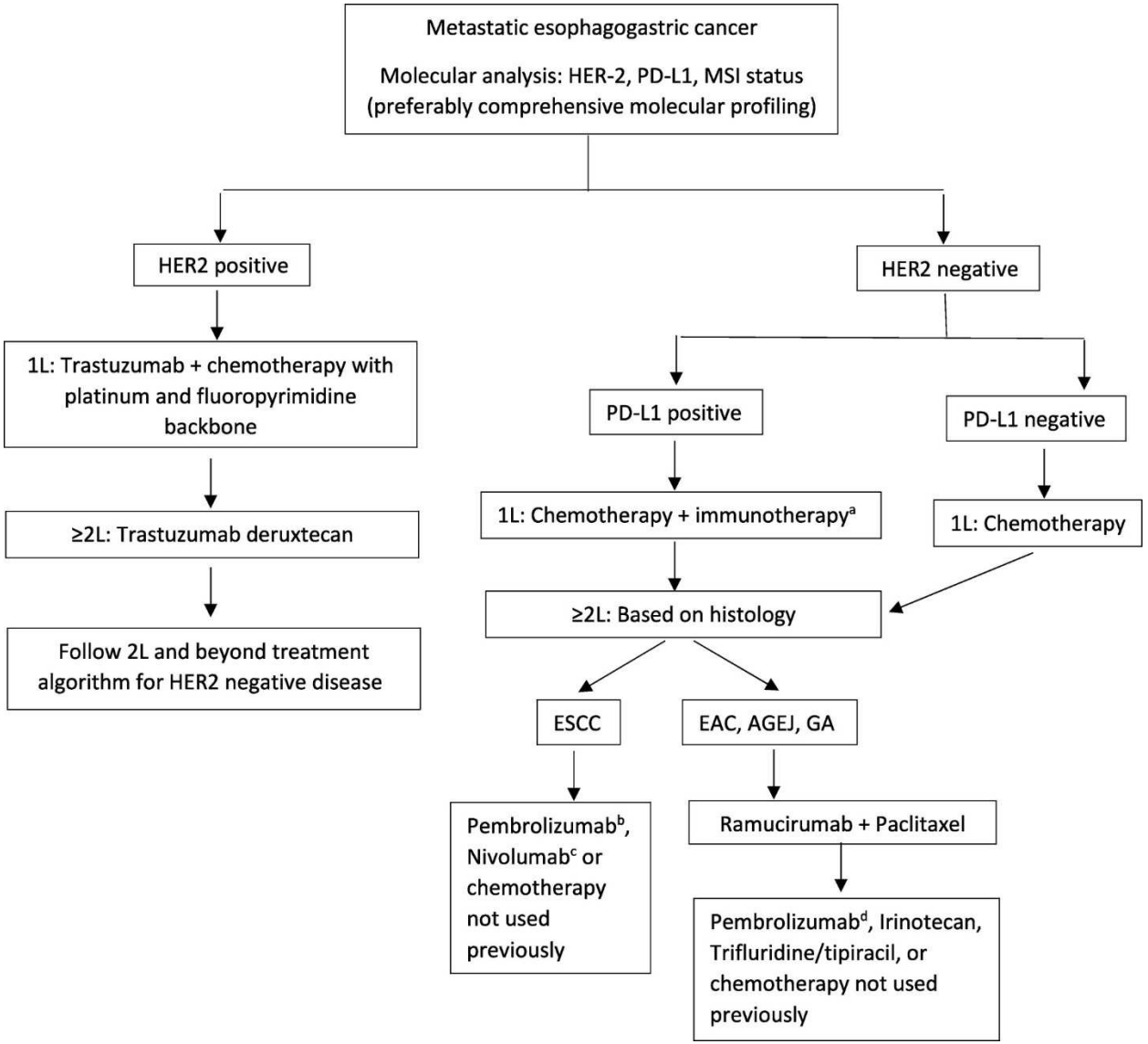
- Lymphadenectomy of perigastric, left gastric, common hepatic, splenic, and celiac axis nodes (D2) may be curative
- No need for adjuvant radiation therapy
- 50% recur locally or intraperitoneally if less than D2 resection.
- Chemotherapy recommendations similar both for tumors arising at gastro-esophageal junction as well as in stomach itself

Treatment strategy

- Nivolumab or pembromizulab (PDL1 target) and FOLFOX chemotherapy if EBV positive or MSI high or dMMR mutation or squamous carcinoma or HER2 negative tumors
- Oxaliplatin induces immunogenic death of tumor cells, which activates antigen processing cells via calreticulin 1, HMGB 1, and other damage associated molecular patterns.
- In HER2 positive tumors, trastuzumab is added to FOLFOX chemotherapy; tucatinib (TKI inhibitor) also employed

Treatment strategy

- Percutaneous gastrostomy/jejunostomy and endoscopic placement of self-expandable metallic stents are safe, effective and minimally invasive palliative treatments for patients with luminal obstruction.



Mamdani, H, and Jalal, SL, "Where to Start and What to Do Next: The Sequencing of Treatments in Metastatic Esophagogastric Cancer," American Society of Clinical Oncology Educational Book 41 (March 25, 2021) 170-185. DOI: 10.1200/EDBK_321243 Figure 1

MALT lymphoma

- Extranodal marginal zone (MALT) lymphoma.
- Stomach is most common extranodal site.
- 5% of gastric tumors
- 50% of gastric lymphomas.
- Associated with H. pylori infection.
- In the stomach, MALT is induced, typically as a result of chronic gastritis.

MALT lymphoma

- Low grade tumors that do not regress with treatment of Helicobacter pylori usually contain genetic abnormalities
- t(11,18)(q21;q21)
- t(1;14)(p22;q32)
- t(14;18)(q23;q21)
- Trisomy 3
- t(11,18) brings together the API2 (apoptosis-inhibitor 2) gene on chromosome 11 with the MLT (mutated in MALT lymphoma) gene on chromosome 18.
- The fusion protein is thought to inhibit apoptosis.

MALT lymphoma

- t(1;14) and t(14;18) translocations increase expression of BCL10 and MLT proteins respectively.
- Antigen dependent activation of NF-κB in normal lymphocytes requires BCL10 and MLT.
- Constitutively expressed in t(1;14) and t(14;18) lesions.
- p53 and p16 mutations may lead to transformation to diffuse large B-cell lymphoma.

MALT lymphoma

- The neoplastic lymphocytes infiltrate the gastric glands focally to create lymphoepithelial lesions.
- This is diagnostic.
- Reactive-appearing B-cell follicles may be present, and, in about 40% of tumors, plasmacytic differentiation is observed.
- At other sites GI lymphomas may disseminate as discrete small nodules or infiltrate the wall diffusely.
- Like other tumors of mature B cells, MALTomas express the B-cell markers CD19 and CD20.
- They do not express CD5 or CD10, but are positive for CD43 in about 25% of cases

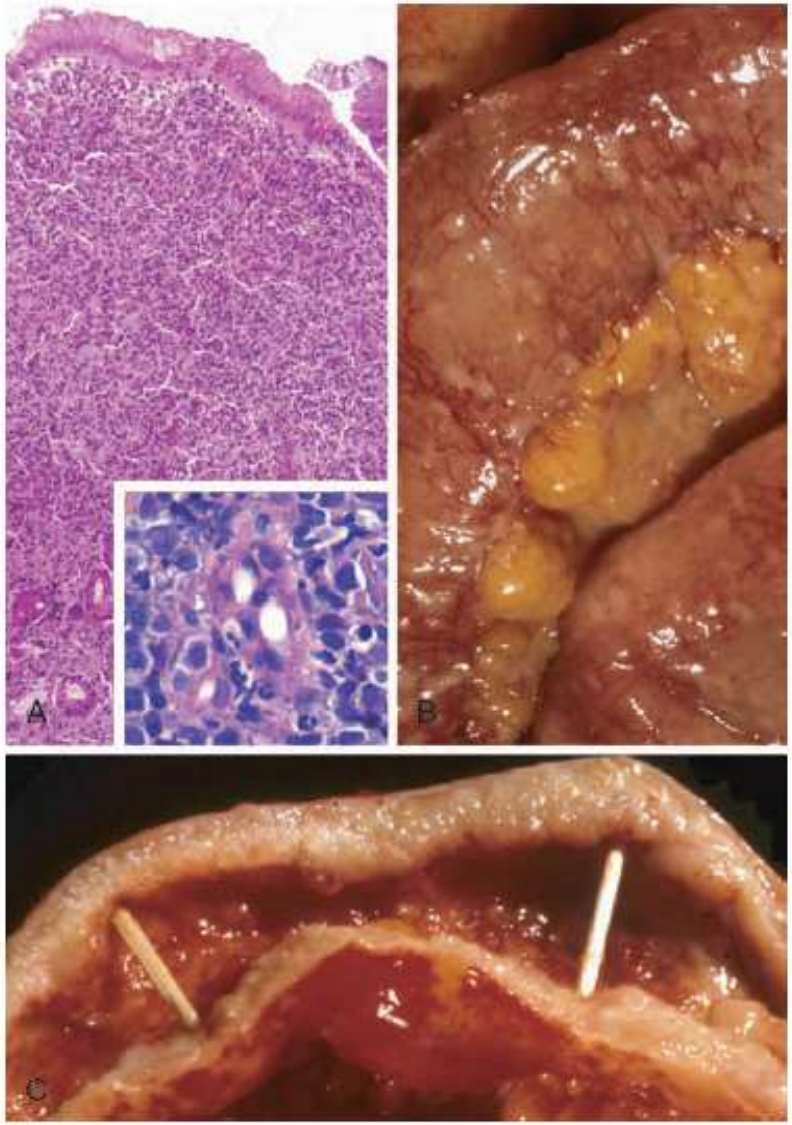
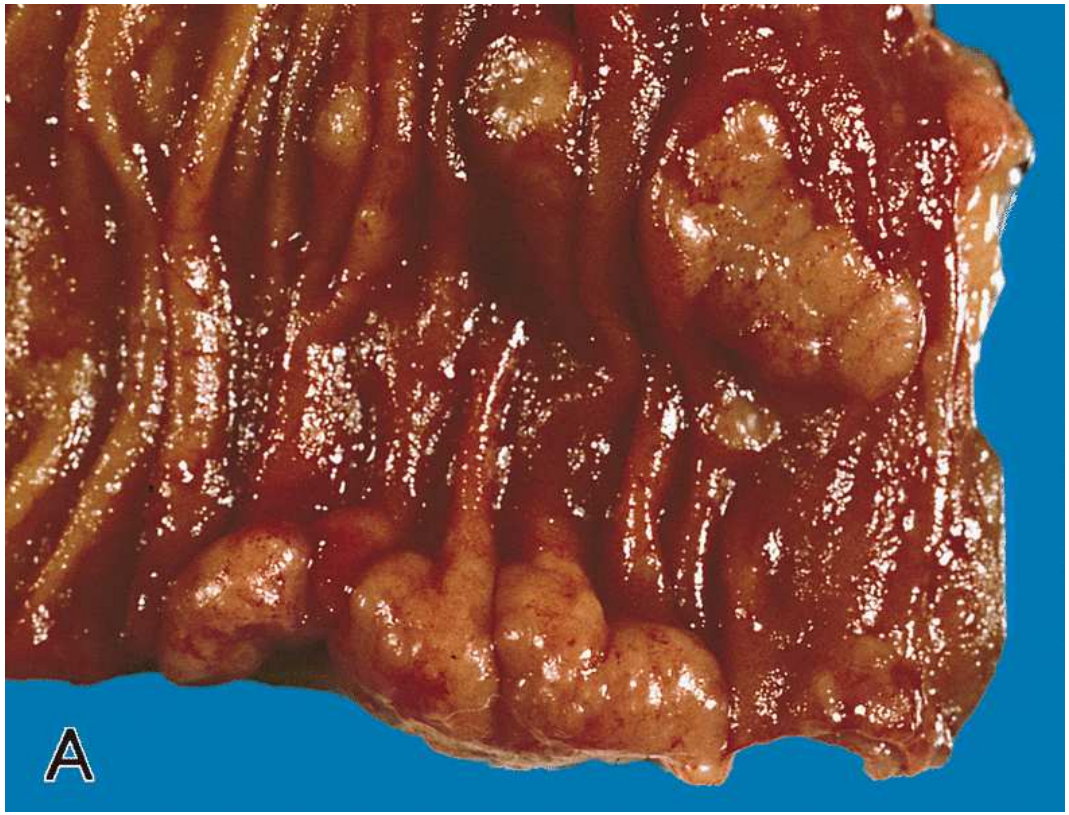


Figure 17-19 Lymphoma. **A,** Gastric MALT lymphoma replacing much of the gastric epithelium. Inset shows lymphoepithelial lesions with neoplastic lymphocytes surrounding and infiltrating gastric glands. **B,** Disseminated lymphoma within the small intestine with numerous small serosal nodules. **C,** Large B-cell lymphoma infiltrating the small intestinal wall and producing diffuse thickening.

MALT lymphoma

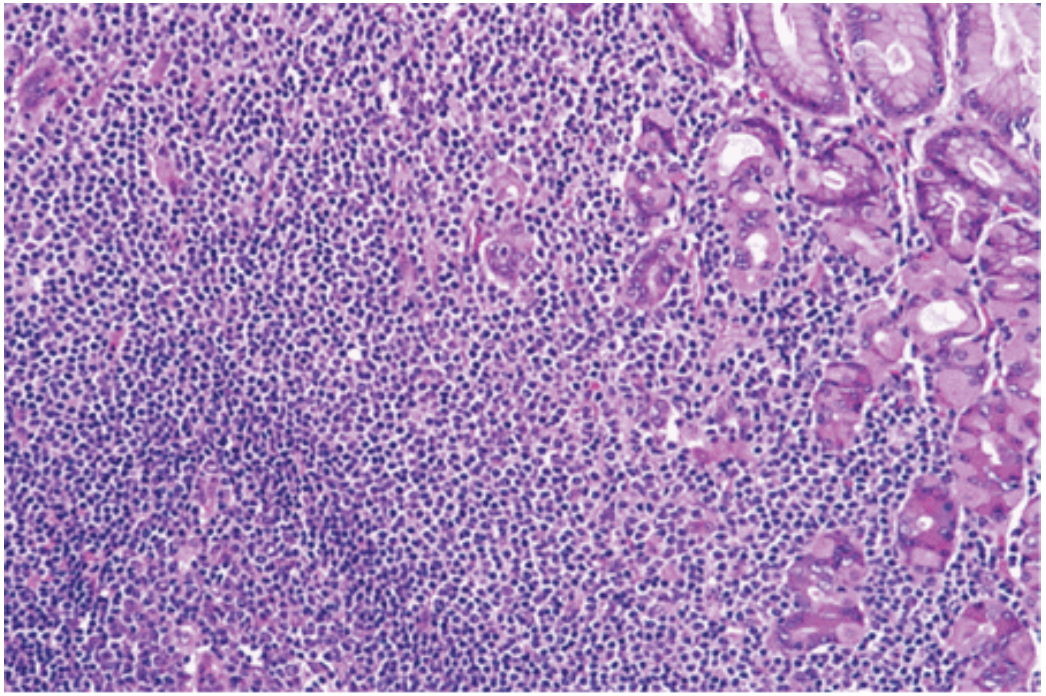


Numerous lymphomatous polyps vary from small expansions of the folds to larger nodules.

Fig. 8-7A

Riddell, RH, Petras, RE, Williams, GT, Sobin, LH., "Tumors of the intestines." Atlas of Tumor Pathology, Third Series, Fascicle 32. Armed Forces Institute of Pathology, Washington, D.C. 2003.

MALT lymphoma



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Fig. 5-7 Accessed 04/27/2010

The neoplasm partially replaces gastric mucosa and infiltrates epithelium. A reactive follicle is present at the bottom left of the field.

CD19 +, CD20+, CD5-, CD10-.

25% CD43+; aids in diagnosis.

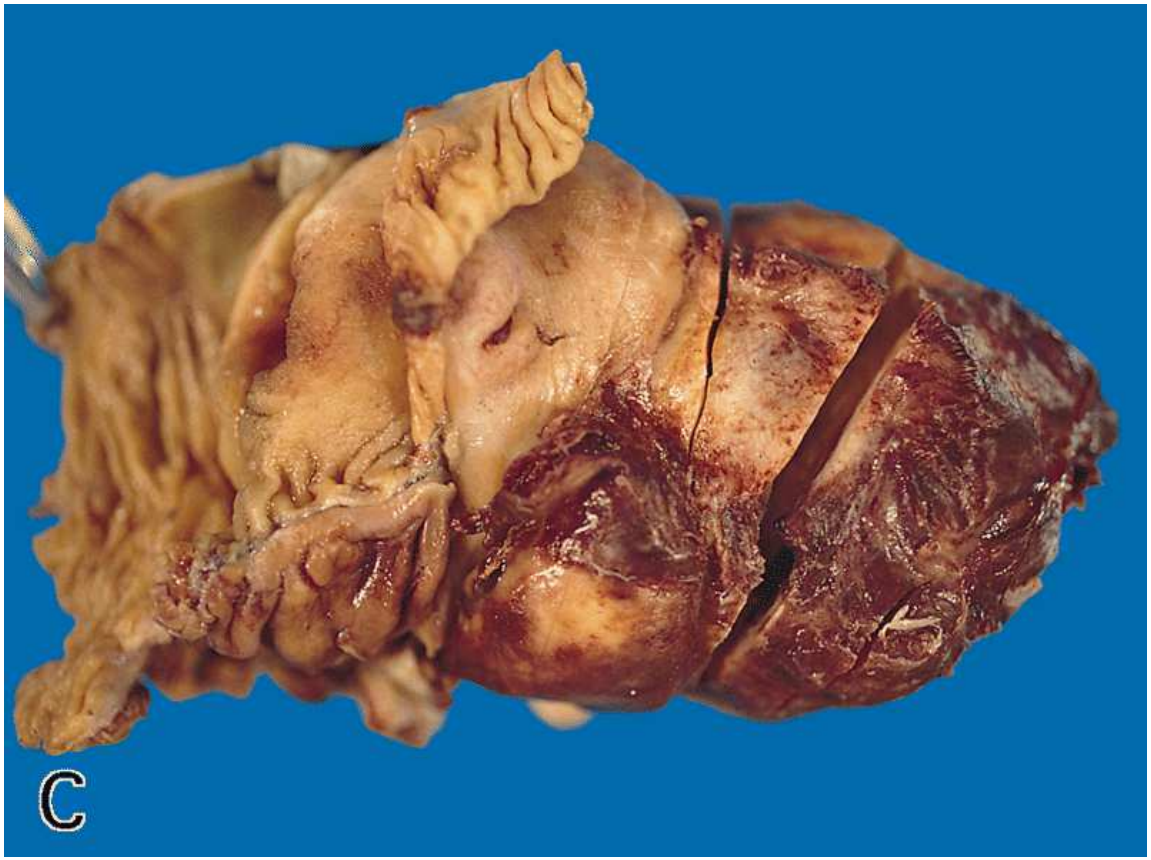
Treatment of MALT not responsive to H. pylori therapy

- Cyclophosphamide, doxorubicin, vinblastine, prednisone, etoposide regimen followed by antibody to CD-20 is the treatment regimen for high grade lymphoma.

Burkitt's lymphoma

- Found principally in children (40-50% of lymphomas).
- Endemic form involves mandible, then kidneys, ovaries, adrenal glands.
- Sporadic form involves mass at the ileocecum and in the peritoneum.
- Mature B-cells of germinal center origin.
- Endemic form demonstrates EBV transcripts.
- Progression free survival 92% at 2 years following therapy with cyclophosphamide, vincristine, doxorubicin, high dose methotrexate/ifosfamide, etoposide, and high dose cytosine arabinoside.

Burkitt's lymphoma

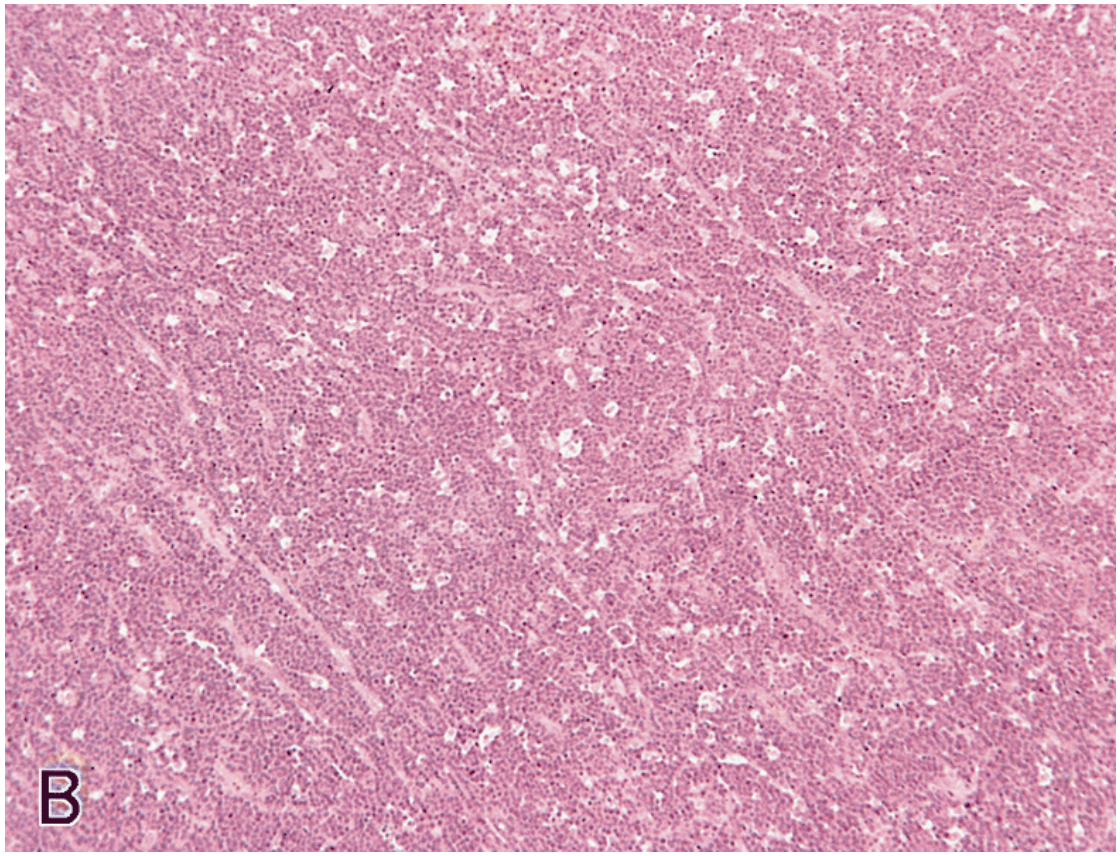


Extensive tumor is pushing into the lumen of the bowel, causing obstructive symptoms, but with a large amount of extramural tumor.

Fig. 8-8C

Riddell, RH, Petras, RE, Williams, GT, Sobin, LH., "Tumors of the intestines." Atlas of Tumor Pathology, Third Series, Fascicle 32. Armed Forces Institute of Pathology, Washington, D.C. 2003.

Burkitt's lymphoma

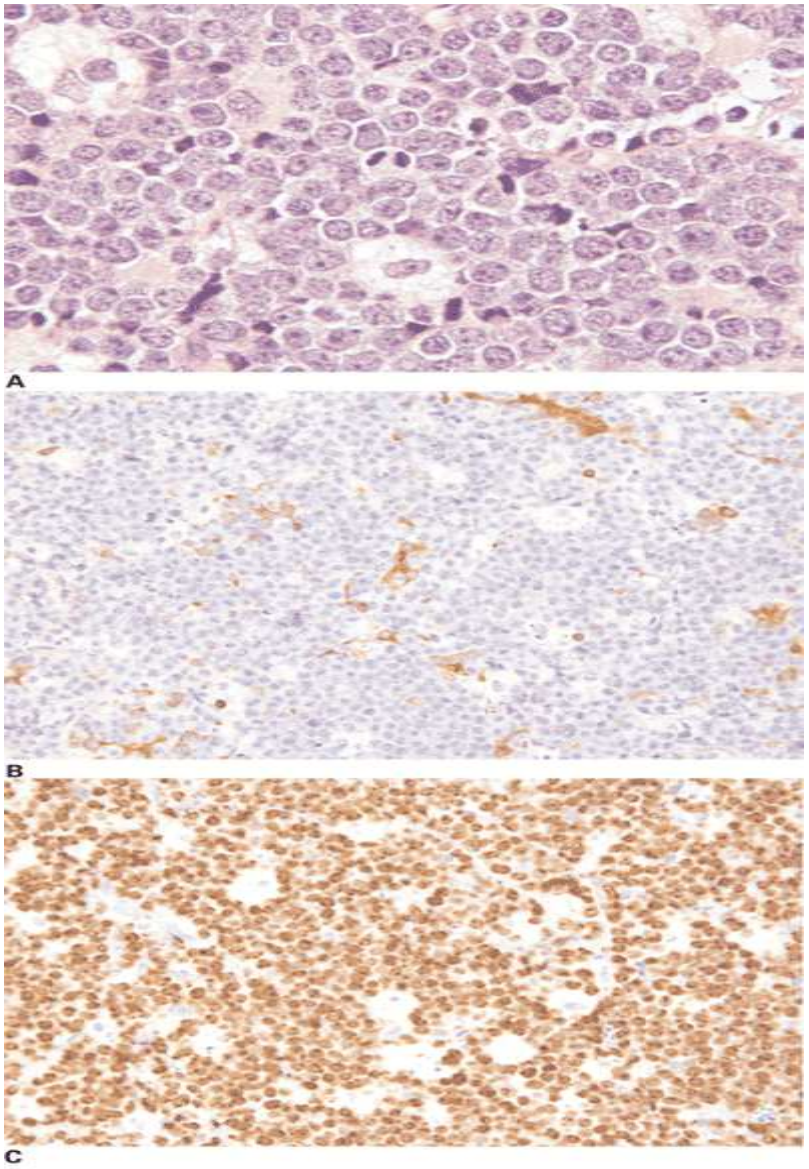


A "starry sky" pattern is evident.

Fig. 8-9B

Riddell, RH, Petras, RE, Williams, GT, Sobin, LH., "Tumors of the intestines." Atlas of Tumor Pathology, Third Series, Fascicle 32. Armed Forces Institute of Pathology, Washington, D.C. 2003.

Burkitt's lymphoma



The neoplastic cells are intermediate in size, similar to that of benign histiocyte nuclei, with multiple small nucleoli. A starry-sky pattern is also seen in this field. B,C. The neoplastic cells are negative for BCL-2 (B), and are >99% positive for Ki-67 (C). (A, hematoxylin-eosin, 1000x; B,C, immunohistochemistry, 400x.)

Fig. 6-22 Accessed 04/27/2010

Carcinoid tumor

- Gastric carcinoid tumors may be associated with endocrine cell hyperplasia, autoimmune chronic atrophic gastritis, MEN-I, and Zollinger-Ellison syndrome.
- Grossly, carcinoids are intramural or submucosal masses that create small polypoid lesions.
- In the stomach they typically arise within oxyntic mucosa.
- The overlying mucosa may be intact or ulcerated
- Carcinoids tend to be yellow or tan in color and are very firm as a consequence of an intense desmoplastic reaction.

Carcinoid tumor

- Histologically, carcinoids are composed of islands, trabeculae, strands, glands, or sheets of uniform cells with scant, pink granular cytoplasm and a round to oval stippled nucleus.
- There is minimal pleomorphism.

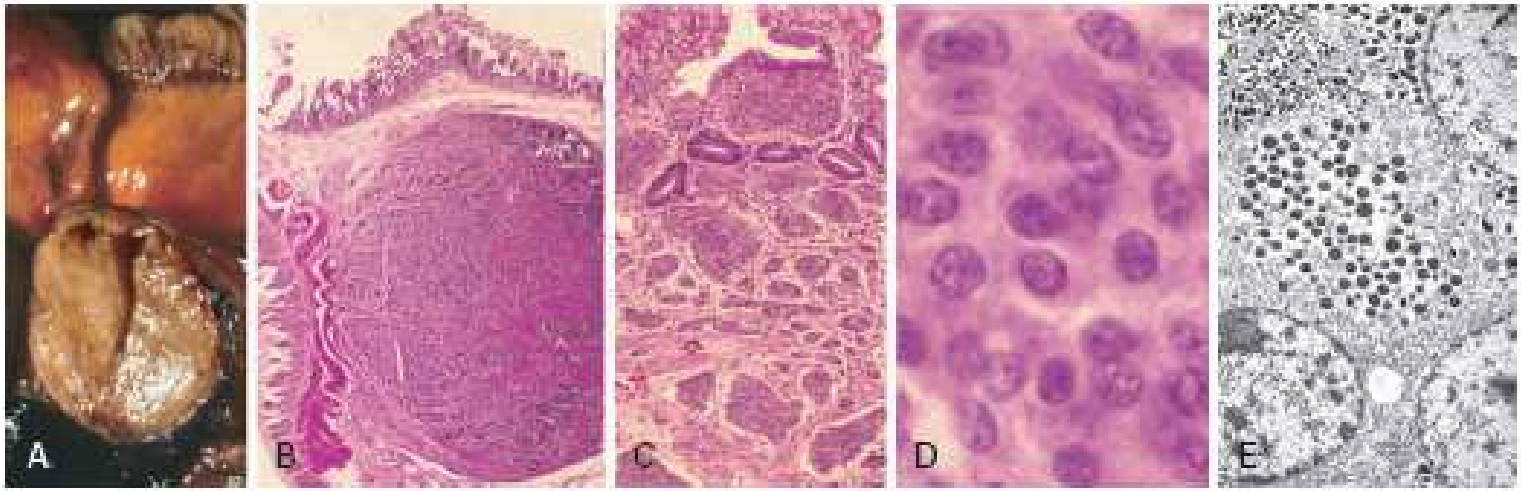


Figure 17-20 GI carcinoid tumor (neuroendocrine carcinoma). **A,** Gross cross-section of a submucosal tumor nodule. **B,** Microscopically the nodule is composed of tumor cells embedded in dense fibrous tissue. **C,** In other areas, the tumor has spread extensively within mucosal lymphatic channels. **D,** High magnification shows the bland cytology of carcinoid tumors. The chromatin texture, with fine and coarse clumps, is frequently described as a "salt and pepper" pattern. Despite their innocuous appearance, carcinoids can be clinically aggressive. **E,** Electron microscopy reveals cytoplasmic dense core neurosecretory granules.

Gastrointestinal stromal tumor

- Most common mesenchymal tumor in gastrointestinal tract
- Stomach (60%) and jejunum and ileum (30%)
- Arise from interstitial cells of Cajal.
- 25% metastasize (gastric)
- 35-40% metastasize (small intestine)
- Mean age 60-65 years old
- Smooth muscle is commonly found in esophagus and rectum (CD34+ and SMA+).
- Tumors arising from striated muscle are CD34+ but SMA-.

Gastrointestinal stromal cell tumor

- Familial:
- Germline mutations in C-KIT or PDGFRα
- Autosomal dominant
- Immunopositive for SDHB
- Neurofibromatosis:
- 7% of patients with NF1 develop one or more GIST, usually in small bowel
- Both C-KIT (75% of cases) and PDGFR (10% of cases) mutations lead to constitutive phosphorylation of tyrosine kinases (75% of cases)
- C-KIT and PDGFR mutations are mutually exclusive

Gastrointestinal stromal tumor

- Succinate dehydrogenase (SDH) deficient
- Young adults (before age 40)
- 1 - 2% of all GIST in pediatric patients
- Female preponderance (> 2:1)
- Almost exclusively in stomach (predilection for distal stomach and antrum)
- Minimal nuclear pleomorphism

Gastrointestinal stromal tumor

- Succinate dehydrogenase (SDH) deficient:
- Carney triad:
- GIST, pulmonary chondroma, paraganglioma
- Nonhereditary
- SDHC promoter hypermethylation
- Small percentage have germline SDH mutations
- Carney-Stratakis syndrome:
- GIST and paraganglioma
- Autosomal dominant
- Germline mutations in SDHB, SDHC or SDHD subunit

Gastrointestinal stromal cell tumor

- GIST is CD117+
- 82% of gastric tumors are CD34+, but only 40% of small intestinal tumors
- SMA+ in 18% of gastric tumors, but 34% of small intestinal tumors
- Tumors that show features of enteric plexus (spindle cell) differentiation are often classified among GISTs.
- Gastrointestinal autonomic tumor (GIST)
- Vimentin, S100, and NSE+.

Gastrointestinal stromal cell tumor

- Well circumscribed, intramural lesion, centered within the muscularis propria
- Fleshy, tan-pink cut surfaces, which may show hemorrhage or cystic degeneration
- Size >5cm associated with poor prognosis
- 3 morphologic types:
- Spindle (70%),
- Epithelioid (20%)
- Mixed (10%)

Gastrointestinal stromal cell tumor

- Epithelioid:
- Round cells with clear to eosinophilic cytoplasm in sheets or nests; increased tendency for pleomorphism versus spindle type
- Subtypes: sclerosing, discohesive, hypercellular, sarcomatous with significant atypia and mitotic activity
- Mixed:
- Tumor is composed of cells with spindle and epithelioid morphology

Gastrointestinal stromal cell tumor

- Spindle:
- Bland spindle cells with faintly eosinophilic cytoplasm in a syncytial pattern; elongated nuclei with inconspicuous nucleoli;
- Subtypes: sclerosing, palisaded, vacuolated, diffuse hypercellular, sarcomatoid features with significant nuclear atypia and mitotic activity

Gastrointestinal stromal tumor

- Dedifferentiated:
- Anaplastic appearance with an unusual phenotype (may lose expression of KIT or may aberrantly express other markers such as cytokeratin)

Gastrointestinal stromal l tumor

- C-kit and PDGFR mutations critical to tumor function
- 85% of GISTs have C-KIT mutations (receptor for stem cell factor) and 35% of GISTs with normal C-KIT contain PDGFRA mutations (platelet-derived growth factor receptor).
- Both C-KIT and PDGFRA have cytoplasmic tyrosine kinases that activate RAS and PI3K/AKT pathways.
- KIT leads to activation of PI3K and activation of mTOR and S6K with nuclear transcription.

Gastrointestinal stromal tumor

- PDGFR activation leads to activation of RAS/RAF/MEK/ERKpathway.
- No C-KIT mutation associated with poor prognosis; exon 9 deletion, intermediate prognosis; exon 11 mutation, good prognosis
- C-KIT and PDGFRA mutations are mutually exclusive in sporadic tumors.
- Metastasis outside the abdomen is uncommon.

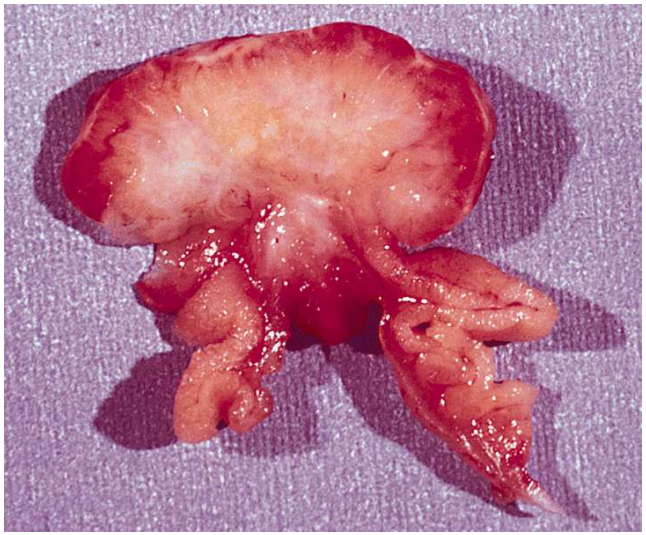
Gastrointestinal stromal tumor

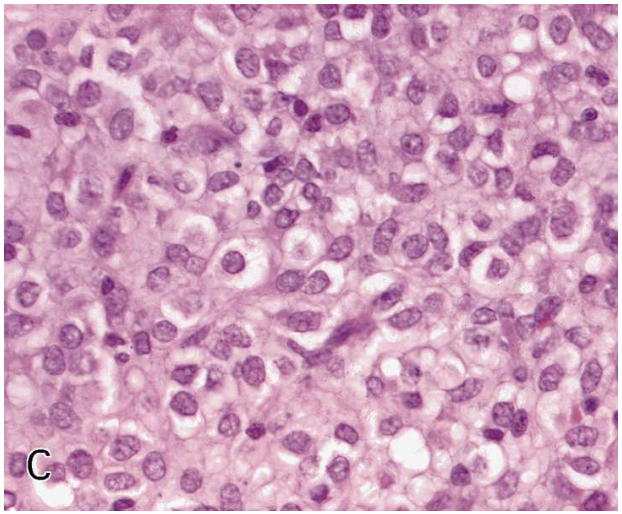
- Imatinib not indicated for low-risk (completely resected) patients.
- Imanitib blocks C-KIT, leading to tumor regression.
- Dysuria, edema, nausea common.
- PDGFR D842V mutation not responsive to imatinib (tyrosine kinase inhibitor) .
- All others receive imatinib.

Gastrointestinal stromal tumor

- 3 years imatinib improves survival for high risk patients.
- High-risk includes incomplete resection as well as tumor rupture.
- May add mTOR inhibitor.
- Regorafenib is a multiple tyrosine kinase inhibitor used as third line therapy.

Gastrointestinal stromal tumor





Gross appearance of primarily submucosal tumor. Typical central nuclei and partially retracted cytoplasm are seen. Tumors vary in cellularity: those that are the most cellular tend to have smaller cells and larger nuclei. These are the areas where mitoses are most likely to be found.

Figs. 7-01R and 07-08C

Riddell, RH, Petras, RE, Williams, GT, Sobin, LH., "Tumors of the intestines." Atlas of Tumor Pathology, Third Series, Fascicle 32. Armed Forces Institute of Pathology, Washington, D.C. 2003.

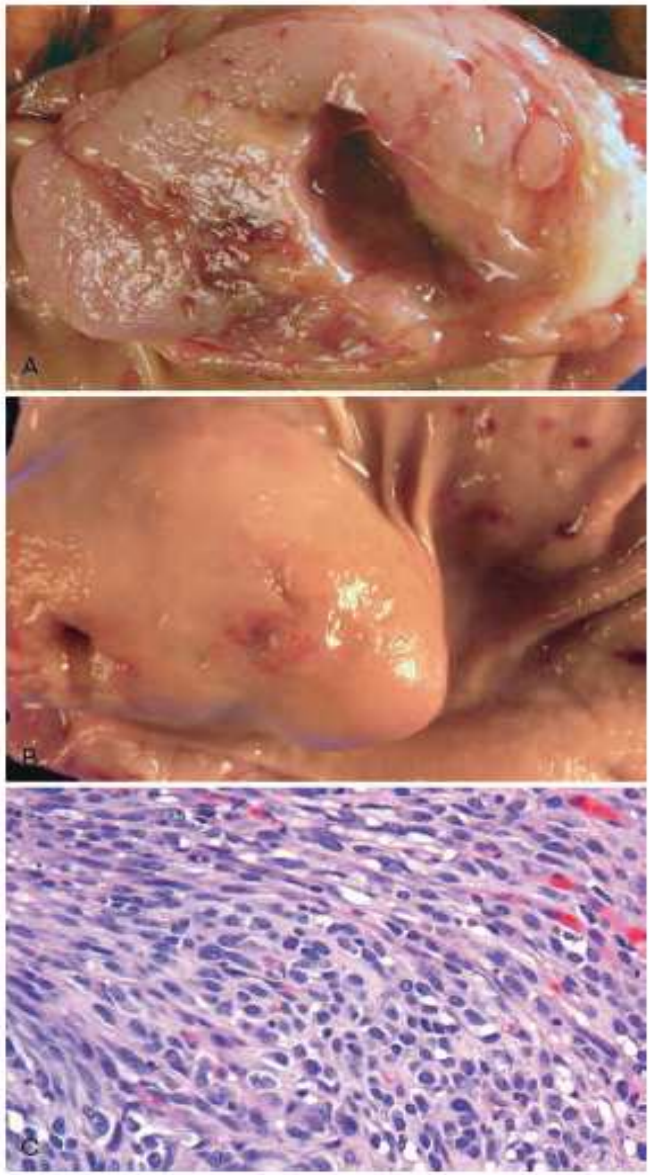
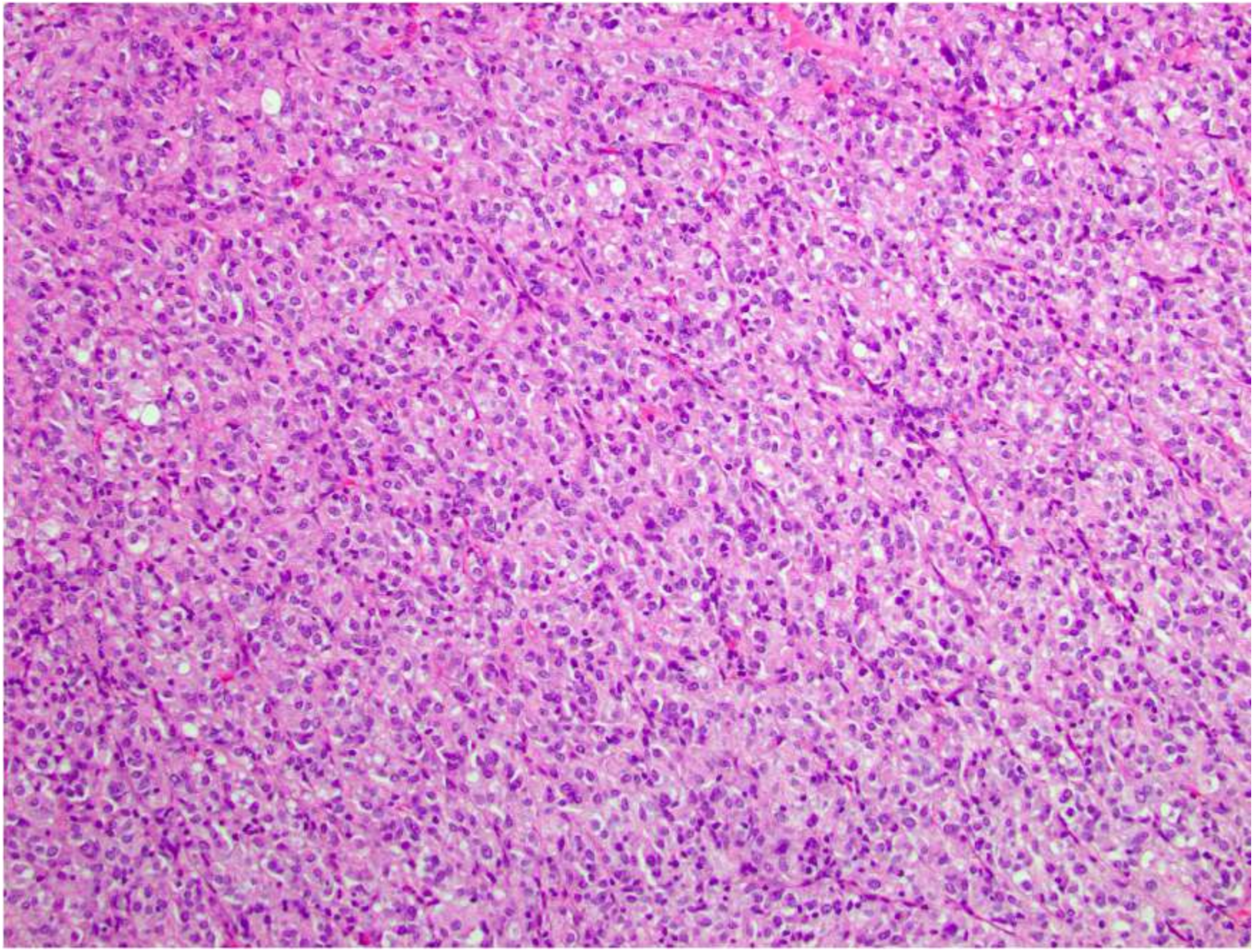
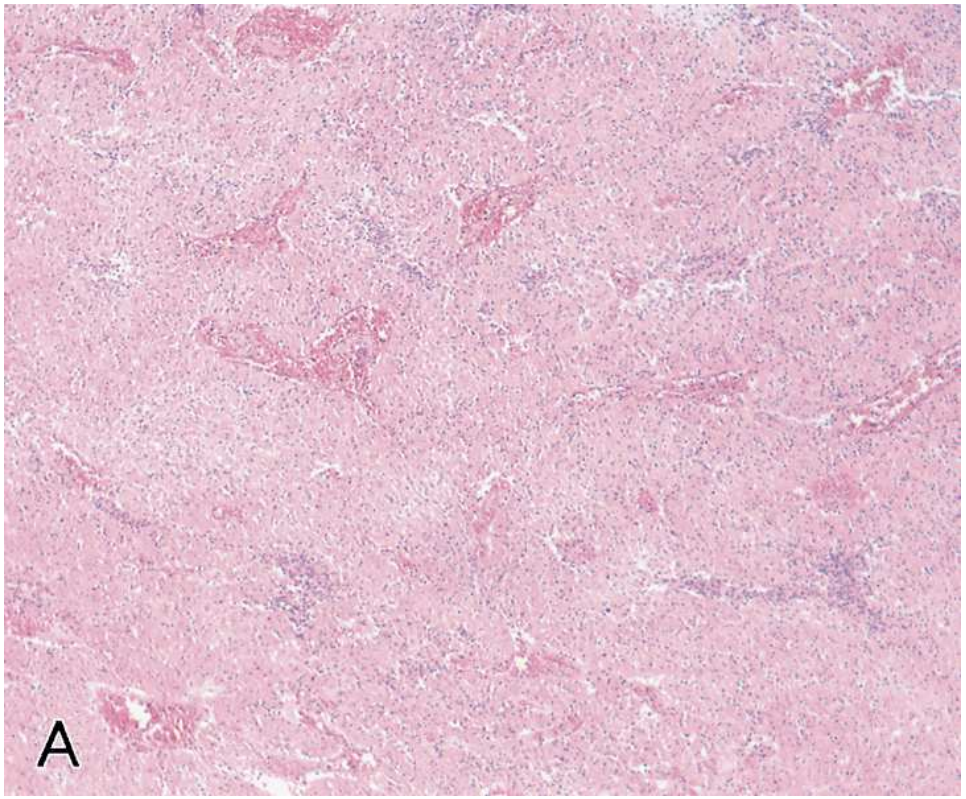


Figure 17-21 GI stromal tumor. **A,** On cross-section a whorled texture is evident within the white, fleshy tumor. **B,** The mass is covered by intact mucosa. **C,** Histologically the tumor is primarily composed of bundles, or fascicles, of spindle-shaped tumor cells. (Courtesy Dr. Christopher Weber, The University of Chicago, Chicago, Ill.)



Gastrointestinal stromal tumor



The more intact parts of the tumor are composed of uniform eosinophilic cells in which are seen occasional lymphoid aggregates. Resemble enteric plexus.

Fig. 7-11A

Riddell, RH, Petras, RE, Williams, GT, Sobin, LH., "Tumors of the intestines." Atlas of Tumor Pathology, Third Series, Fascicle 32. Armed Forces Institute of Pathology, Washington, D.C. 2003.

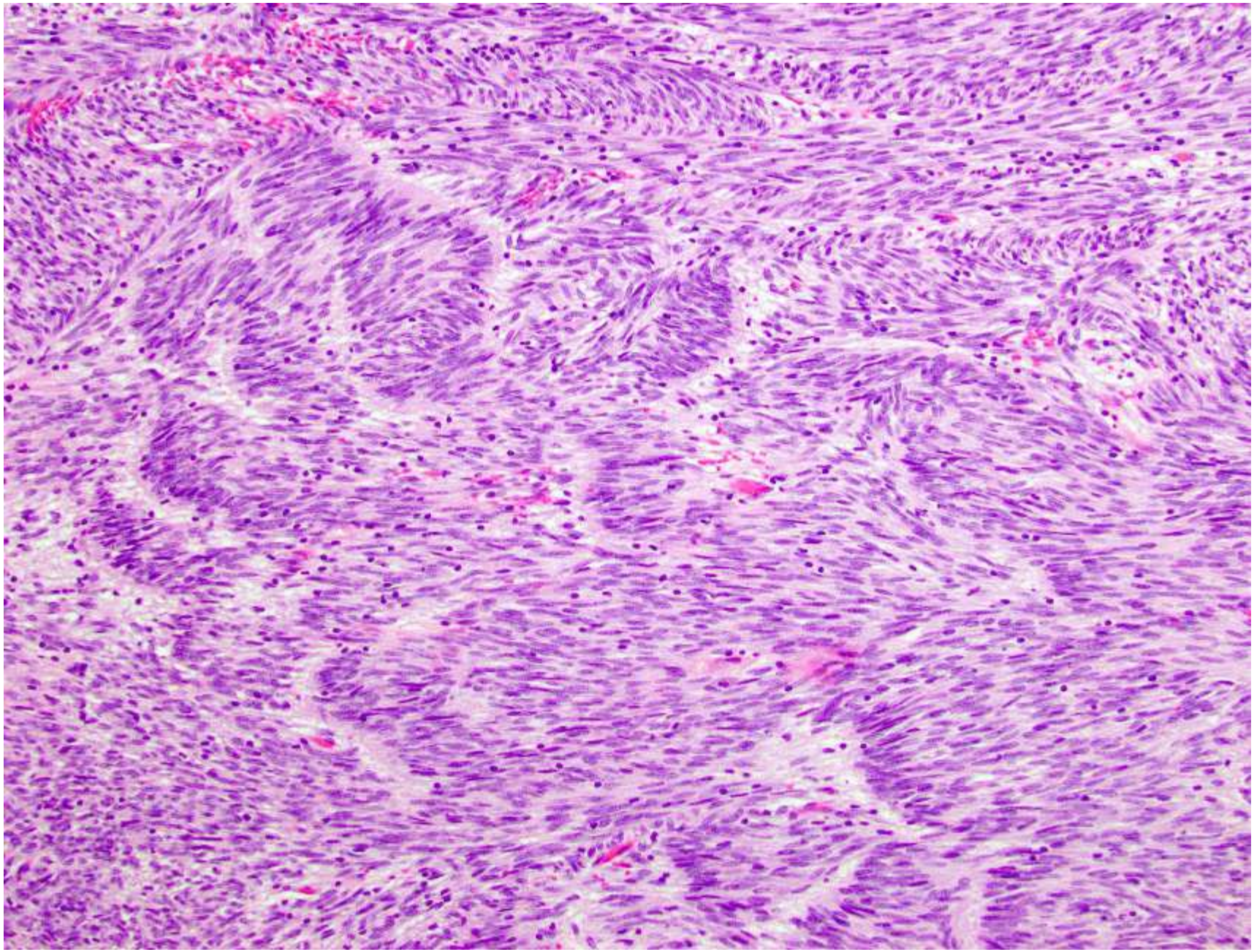


Table 17-6 Features of Gastrointestinal Carcinoid Tumors

Feature	Esophagus	Stomach	Proximal Duodenum	Jejunum and Ileum	Appendix	Colorectum
Fraction of GI carcinoids	<1%	<10%	<10%	>40%	<25%	<25%
Mean patient age (yr)	Rare	55	50	65	All ages	60
Location	Distal	Body and fundus	Proximal third, peri-ampullary	Throughout	Tip	Rectum > cecum
Size	Limited data	1-2 cm, multiple; >2 cm, solitary	0.5-2 cm	<3.5 cm	0.2-1 cm	>5 cm (cecum); <1 cm (rectum)
Secretory product(s)	Limited data	Histamine, somatostatin, serotonin	Gastrin, somatostatin, cholecystokinin	Serotonin, substance P, polypeptide YY	Serotonin, polypeptide YY	Serotonin, polypeptide YY
Symptoms	Dysphagia, weight loss, reflux	Gastritis, ulcer, incidental	Peptic ulcer, biliary obstruction, abdominal pain	Asymptomatic, obstruction, metastatic disease	Asymptomatic, incidental	Abdominal pain, weight loss, incidental
Behavior	Limited data	Variable	Variable	Aggressive	Benign	Variable
Disease associations	None	Atrophic gastritis, MEN-I	Zollinger-Ellison syndrome, NF-1, sporadic	None	None	None

MEN-I, Multiple endocrine neoplasia type I; NF-1, neurofibromatosis type I.

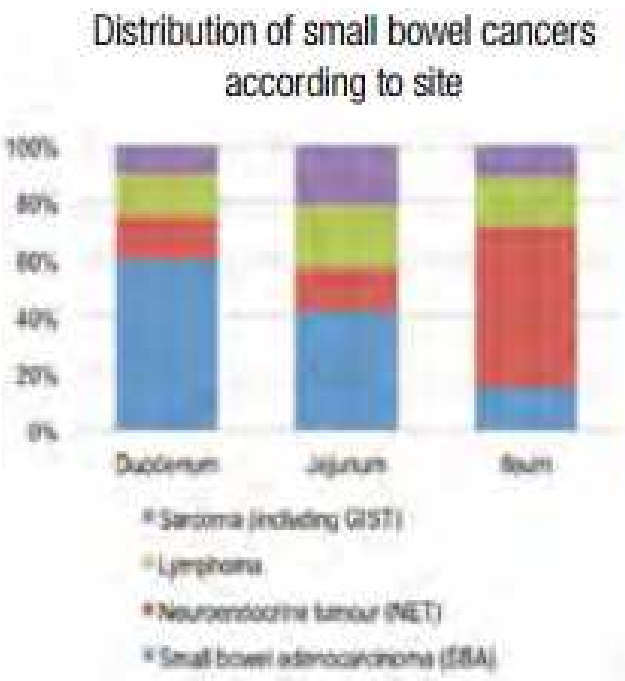
SMALL INTESTINE

Benign tumors of the small intestine

- Adenomas are 25% of benign small intestinal tumors.
- Benign mesenchymal tumors (especially leiomyomas), lipomas, and neuromatous lesions follow adenomas in frequency.
- Most adenomas occur in the region of the ampulla of Vater
- The usual presentation is that of a 30- to 60-year-old patient with occult blood loss
- Rarely present with obstruction or intussusception
- Some are discovered incidentally during radiographic investigation.

Benign tumors of the small intestine

- Patients with familial polyposis coli are particularly prone to developing periampullary adenomas.
- Macroscopically, the ampulla of Vater is enlarged and exhibits a velvety surface.



Conditions and genetic syndromes	Risk of SBA
Inflammatory disorders	Relative risk
Coeliac disease	*34 x*
Crohn's disease	*27-60 x*
Polyposis syndromes	Life-time risk
FAP	*7-13%*
HNPCC	*2-8%*
Peutz-Jeghers	*13%*
Other	
Cystic fibrosis	
Ileal urinary diversion	
Von Recklinghausen	
MEN-2	

FAP, Familial adenomatous polyposis; HNPCC, hereditary non-polyposis colorectal cancer; SBA, small bowel adenocarcinoma.

Small intestinal tumors

- 40% are adenocarcinomas.
- The large majority occur in the duodenum, usually in 40- to 70-year-old patients.
- These tumors grow in a napkin-ring encircling pattern or as polypoid exophytic masses.
- Increased risk conferred by Crohn's disease, familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer.
- Dysphagia, weight loss, abdominal pain, nausea, vomiting, fatigue, gastric outlet syndrome and bleeding as presenting symptoms

Small intestinal tumors

- 40% of tumors are carcinoids.
- 15% are gastrointestinal stromal tumors.
- May affect the whole small bowel and it appears as a demarcated mass with exophytic extension.
- Lymphoma usually affects the terminal ileum and it produces an aneurysmatic dilatation of the bowel loop.

Small intestinal tumors

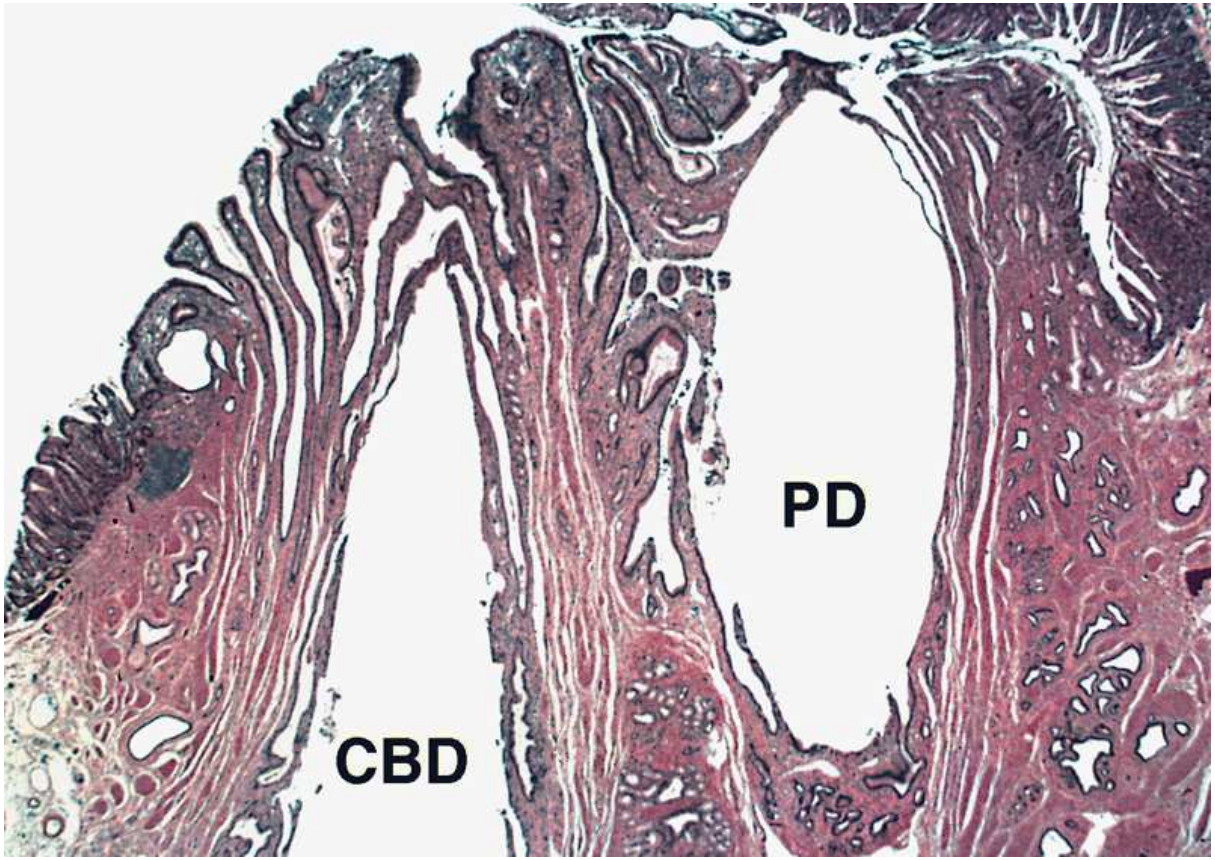
- A good evaluation of the small bowel requires luminal distension
- Administration of enteric contrast agent either orally (enterography) or through a naso-jejunal tube (enteroclysis).
- The use of an intravenous contrast medium with CT or MRI is mandatory to assess the bowel wall, lesion enhancement and mesenteric vessels.
- PET/CT has a primary role for the evaluation of small bowel lymphoma.

Performance and drawbacks of imaging modalities in the diagnosis of small bowel pathology

Imaging technique	Performance	Disadvantages
Conventional small bowel follow-through	Pick-up rates rather limited (20%-54%)	Radiation
Abdominal CT + CT enteroclysis	High sensitivity (100%) and specificity (95%)	Radiation
Abdominal MR + MR enteroclysis	High sensitivity (86%) and specificity (98%)	Not available in all centres
Video capsule endoscopy	Low false-positive rate (2%), 19% false-negative rate	Capsule retention due to stenosis
Double balloon enteroscopy	Direct visualisation and possibility to biopsy; probably the best technique	Time consuming and expert technique

CT, Computed tomography; MR, magnetic resonance.

Normal ampulla of Vater



In this low- power view, the larger terminal common bile duct (CBD) and the smaller pancreatic duct (PD) drain separately into the duodenum.

Fig. 1-15

Albores-Saavedra, J, Henson DE, Klimstra ,DS, “Tumors of the extrahepatic bile ducts, and ampulla of Vater.” Atlas of Tumor Pathology, Third Series, Fascicle 27. Armed Forces Institute of Pathology, Washington, D.C. 2000.

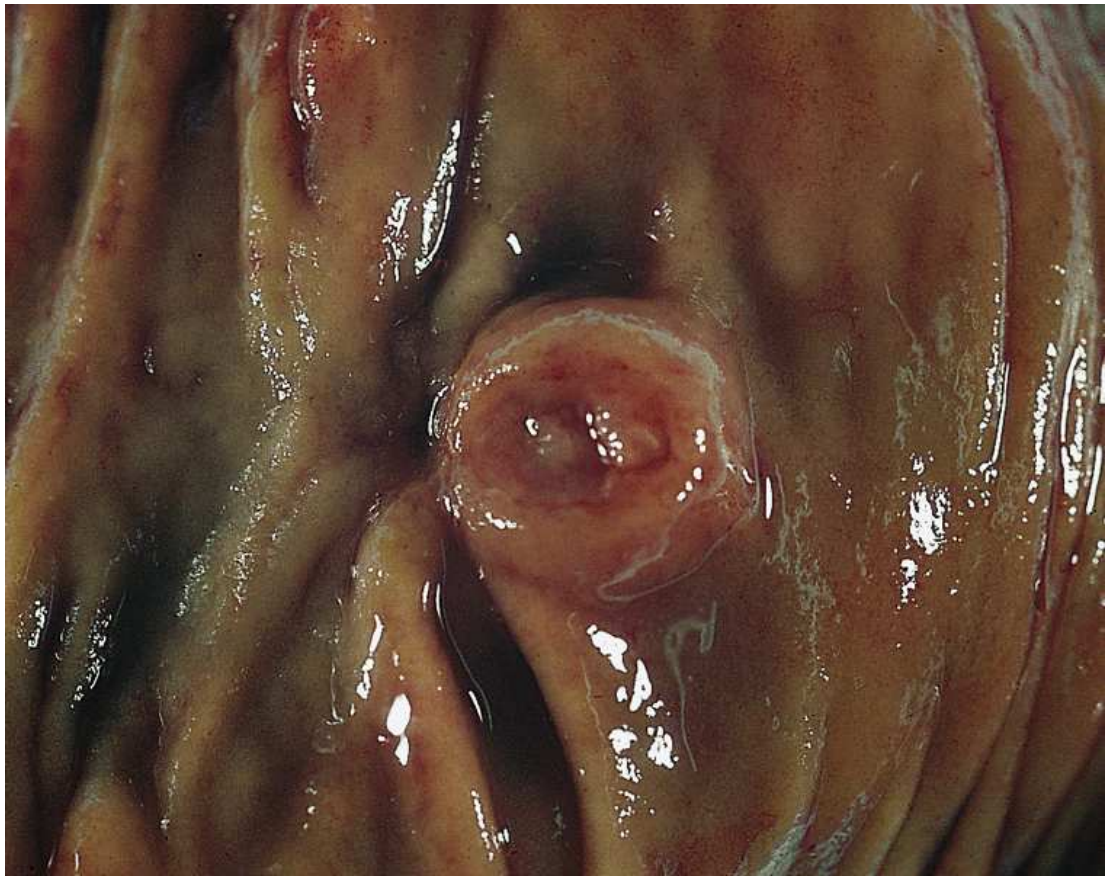
Adenocarcinoma of the small intestine

- The large majority occur in the duodenum, usually in 40- to 70-year-old patients.
- These tumors grow in a napkin-ring encircling pattern or as polypoid exophytic masses.
- Fatigue from occult blood loss may be the only sign.

Adenocarcinoma of the small intestine

- Tumors in the duodenum, particularly those involving the ampulla of Vater, may cause obstructive jaundice early in their course.
- More typically, intestinal obstruction is the presenting event.
- Rarely, the tumor mass is a lead point for intussusception.

Amupllary adenocarcinoma

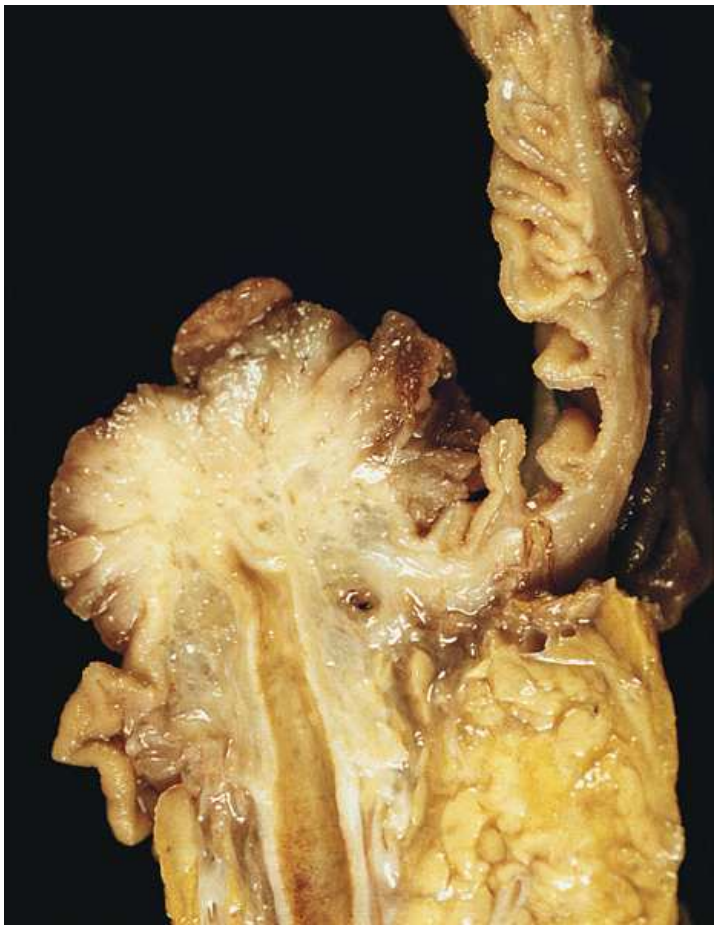


This intra- ampullary carcinoma is small, producing only slight prominence to the ampulla from the luminal aspect. Minimal tumor is visible through the ampullary orifice.

Fig. 20-4L

Albores-Saavedra, J, Henson DE, Klimstra ,DS, “Tumors of the extrahepatic bile ducts, and ampulla of Vater.” Atlas of Tumor Pathology, Third Series, Fascicle 27. Armed Forces Institute of Pathology, Washington, D.C. 2000.

Ampullary adenocarcinoma



This exophytic mucinous carcinoma involves the ampulla and duodenal mucosa but also extends into the common bile duct.

Fig. 20-7

Albores-Saavedra, J, Henson DE, Klimstra ,DS, “Tumors of the extrahepatic bile ducts, and ampulla of Vater.” Atlas of Tumor Pathology, Third Series, Fascicle 27. Armed Forces Institute of Pathology, Washington, D.C. 2000.

Adenocarcinoma of the small intestine

- Surgical resection necessary.
- In limited series, chemoradiation (with infusional 5FU) of adenocarcinomas has shown improved survival.

APPENDIX

Tumors of the appendix

- There are five main histopathologic subtypes of appendiceal neoplasms:
- Neuroendocrine neoplasms (NENs)
- Epithelial neoplasms
- Mucinous neoplasms
- Goblet cell adenocarcinomas (GCAs)
- Colonic-type (non-mucinous) adenocarcinomas
- Signet ring cell adenocarcinomas

Neuroendocrine tumors

- The appendix is the most common site of gut carcinoid tumors
- Followed by the small intestine (primarily ileum), rectum, stomach, and colon.
- However, the rectal tumors may represent up to half of tumors that come to clinical attention.
- Those that arise in the stomach and ileum are frequently multicentric, but the remainder tend to be solitary lesions.

Neuroendocrine tumors

- In the appendix, carcinoids appear as bulbous swellings of the tip, which frequently obliterate the lumen.
- Elsewhere in the gut, they appear as intramural or submucosal masses that create small, polypoid or plateau-like elevations.

Carcinoid

- 40% of gut carcinoid tumors occur in the appendix
- Small intestine (primarily terminal ileum, 20%), rectum, stomach, and colon are other sites
- Those that arise in the stomach and ileum are frequently multicentric, but the remainder tend to be solitary lesions.
- In the appendix they appear as bulbous swellings of the tip, which frequently obliterate the lumen.
- Elsewhere in the gut, they appear as intramural or submucosal masses that create small, polypoid or plateau-like elevations.

Carcinoid syndrome

- Fewer than 10% manifest carcinoid syndrome.
- Tricuspid insufficiency, vasomotor signs, diarrhea, and wheezing are the syndrome.
- Niacin deficiency may be seen as it is required for tryptophan conversion to serotonin (5-HT).
- 5-HT produced by gastrointesinal carcinoid tumors is degraded to functionally inactive 5-HIAA in the liver.
- Carcinoids also may secrete histamine, bradykinin, kallikrein, and prostaglandins.

Carcinoid syndrome

- Hepatic metastases are usually present for the development of the syndrome from gastrointestinal carcinoids.
- Rectal tumors may represent up to half of tumors that come to clinical attention, presenting with carcinoid syndrome.
- Hepatic metastases are usually not required for the production of a carcinoid syndrome by extraintestinal or rectal carcinoids
- Venous drainage from the ovary as well as the rectum is directly into the vena cava and bypass the portal circulation to the liver.

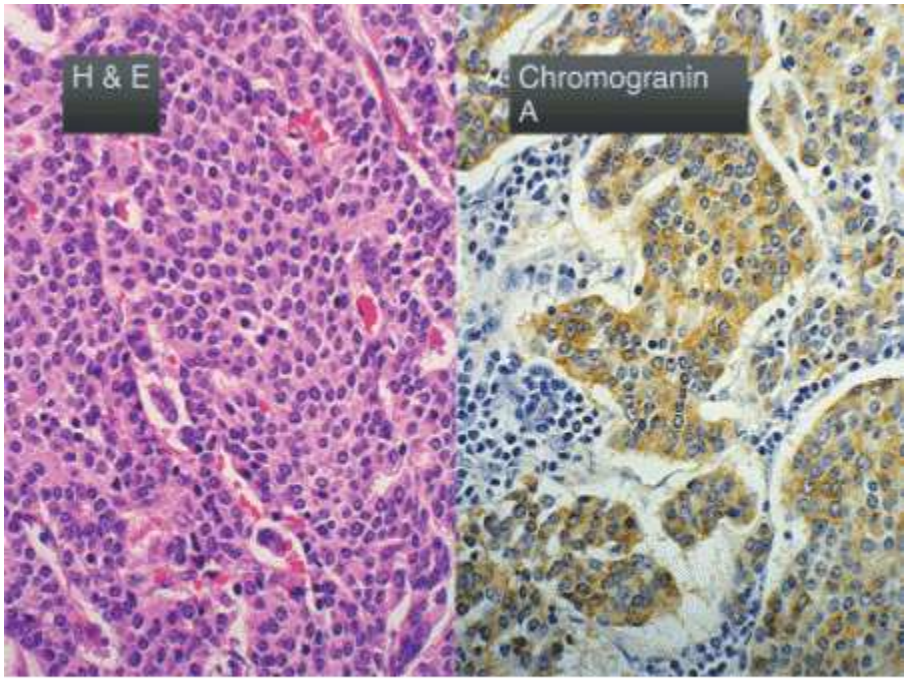
Carcinoid

- Foregut tumors rarely metastasize and are generally cured by resection.
- Midgut carcinoid tumors are often multiple and aggressive.
- Hindgut carcinoid tumors arising in the appendix are generally benign.
- Those arising in the rectum rarely metastasize.
- Those arising in the proximal colon may grow to large size and metastasize.

Carcinoid

- Histologically:
- The neoplastic cells may form discrete islands, trabeculae, stands, glands, or undifferentiated sheets.
- The tumor cells are monotonously similar, having a scant, pink granular cytoplasm and a round to oval stippled nucleus. In most tumors there is minimal variation in cell and nuclear size and mitoses are infrequent or absent.

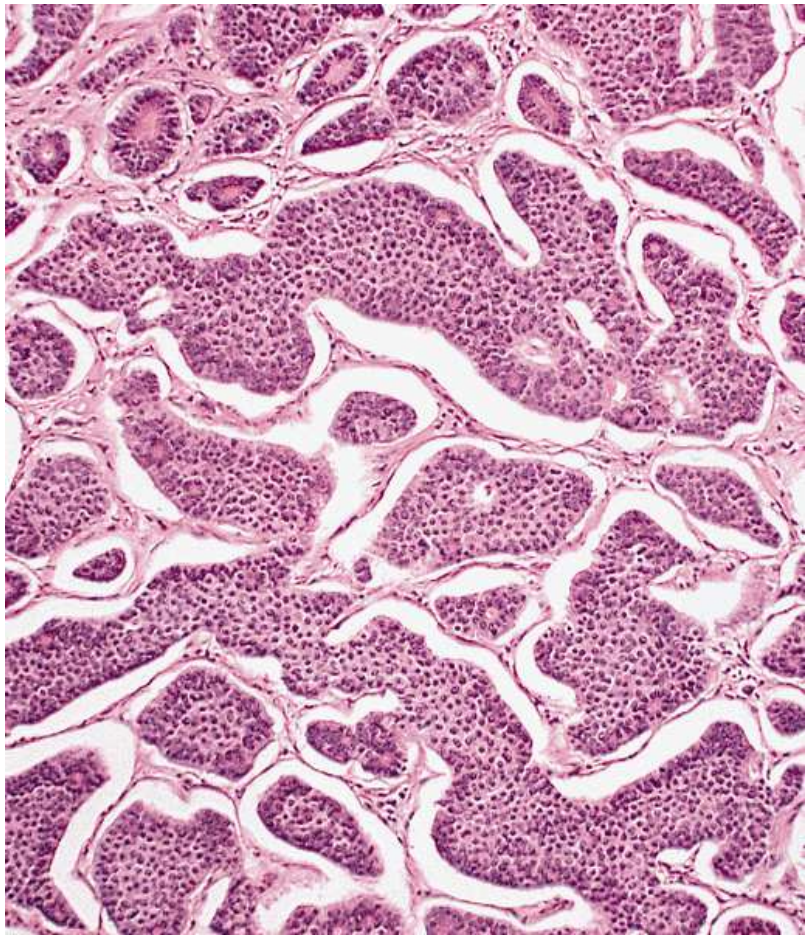
Carcinoid



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Fig. 18-4 Accessed 04/01/2010

Enterochromaffin cell tumor of ileum



The classic insular growth pattern shows irregular but well-demarcated islands of uniform tumor cells with a suggestion of peripheral palisading. Marked tumor retraction from the surrounding fibrotic stroma may give a false impression of lymphovascular invasion.

Fig. 6-17

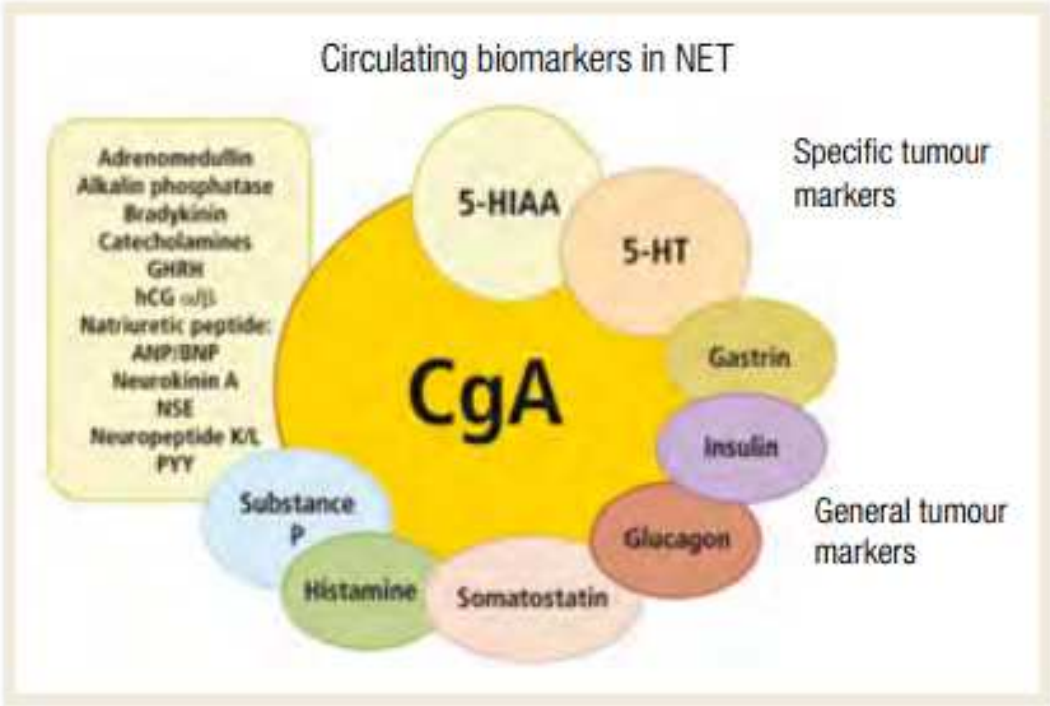
Riddell, RH, Petras, RE, Williams, GT, Sobin, LH., "Tumors of the intestines." Atlas of Tumor Pathology, Third Series, Fascicle 32. Armed Forces Institute of Pathology, Washington, D.C. 2003.

Prognosis

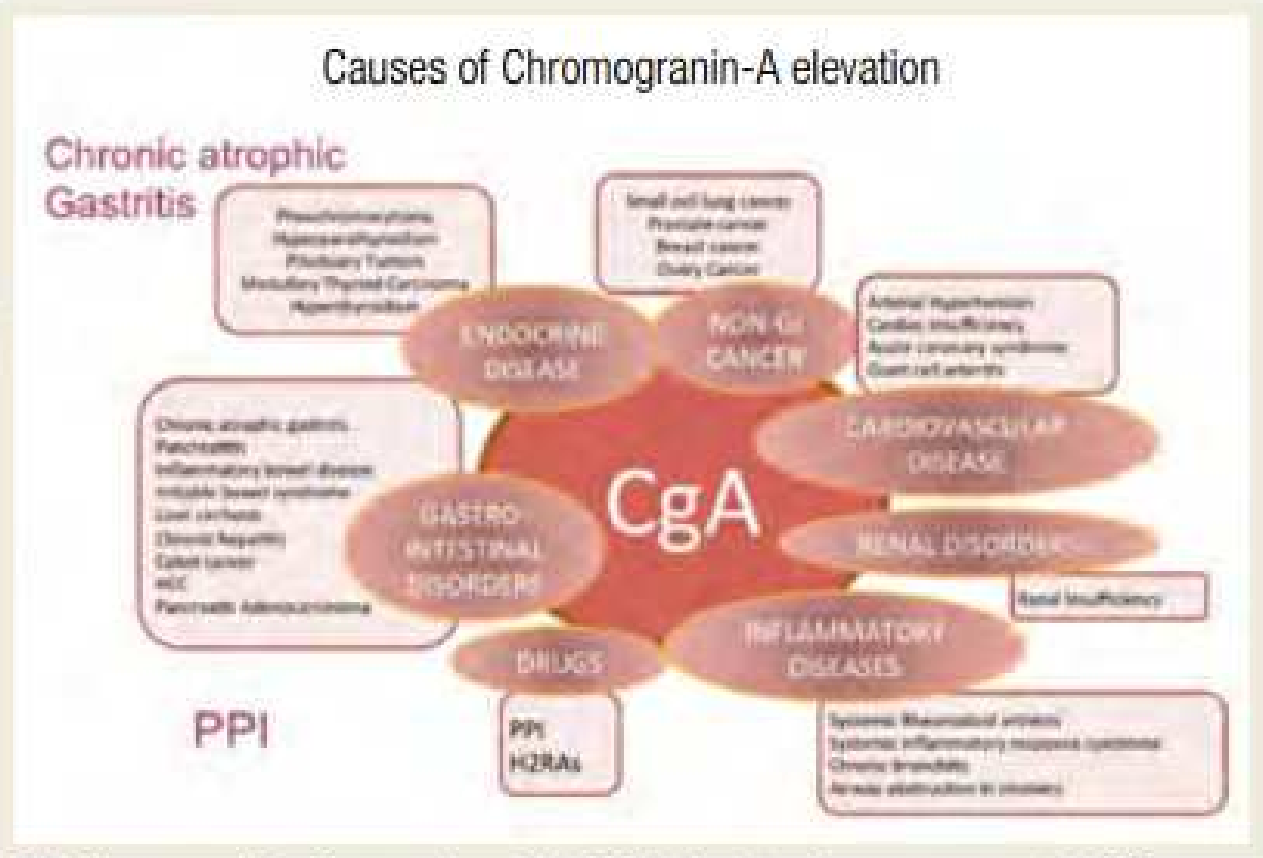
- Lymph node involvement in 15% of appendiceal NENs 1 cm or smaller
- 47% of NENs between 1 and 2 cm
- 86% of NENs larger than 2 cm.
- The corresponding 10-year survival rates for patients with nonmetastatic node-positive disease in these groups were 100%, 92%, and 91%, respectively.

WHO Classifications of Neuroendocrine Neoplasms of the GEP System	
WHO 2000	**WHO 2010**
Well-differentiated endocrine tumour (WDET) Well-differentiated endocrine carcinoma (WDEC)	Neuroendocrine tumours Grade 1 Grade 2
Poorly-differentiated endocrine carcinoma/small-cell carcinoma (PDEC)	Neuroendocrine carcinoma Grade 3
Mixed exocrine–endocrine carcinoma (MEEC)	Mixed adenoneuroendocrine carcinoma (MANEC)
Tumour-like lesions (TLL)	Hyperplastic and preneoplastic lesions

GEP, Gastroenteropancreatic; WHO, World Health Organisation.



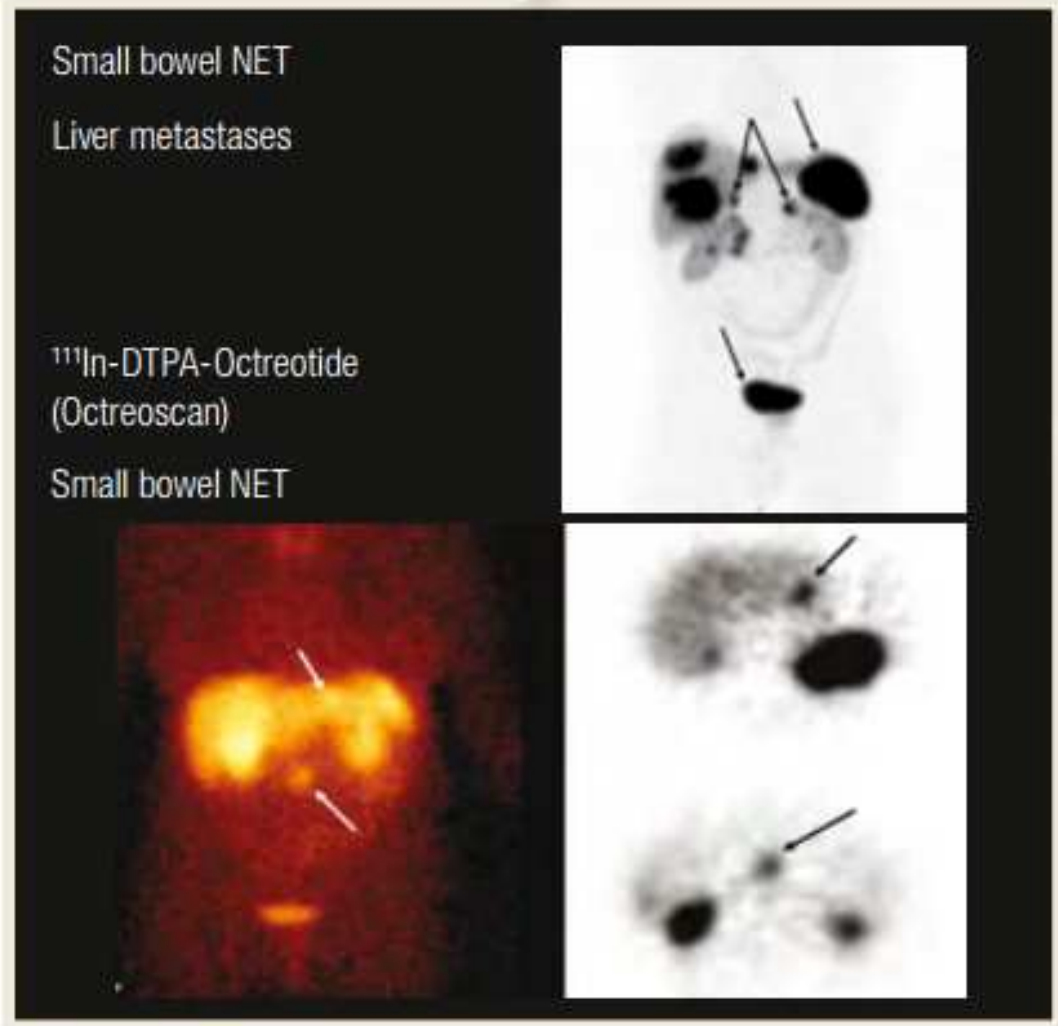
5-HIAA, 5-Hydroxy-3-indoleacetic acid; 5-HT, serotonin; ANP/BNP, atrial natriuretic peptide and brain/ventricular natriuretic peptide; GHRH, gonadotropin hormone releasing hormone; hCG, human chorionic gonadotropin; NSE, neurone-specific enolase; PYY, peptide YY.



CgA, Chromogranin-A; GI, gastrointestinal; H2RA, histamine-2 receptor antagonist; HCC, hepatocellular carcinoma; PPI, proton pump inhibitor.

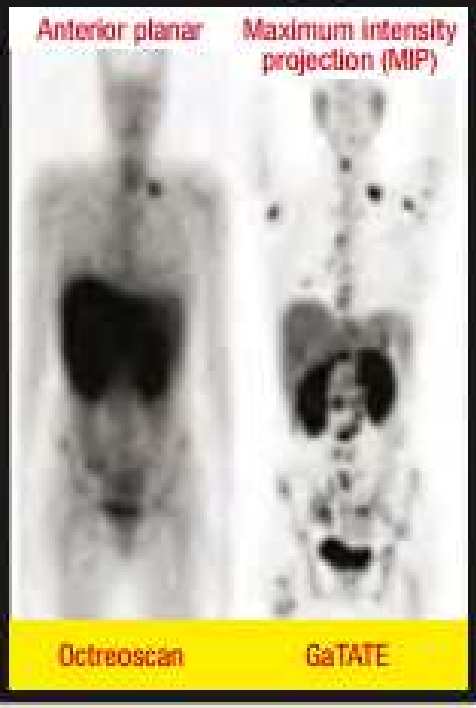
Imaging of Neuroendocrine Tumours: Techniques	
Morphological	**Functional**
Ultrasound Computed tomography (CT) Magnetic resonance imaging Endoscopic ultrasound	Diffusion-weighted magnetic resonance Somatostatin receptor scintigraphy ^{68}Ga-DOTA-TATE/TOC/CT ^{11}C-5-HTP, ^{18}F-DOPA/CT ^{18}F-FDG/CT
At diagnosis, CT abdomen and thorax, including a dynamic contrast enhancement of pancreas and liver + somatostatin receptor imaging	

DOPA, Dihydroxyphenylalanine; FDG, fluorodeoxyglucose; HTP, hydroxytryptophan.



NET, Neuroendocrine tumour.

Imaging of Neuroendocrine Tumours



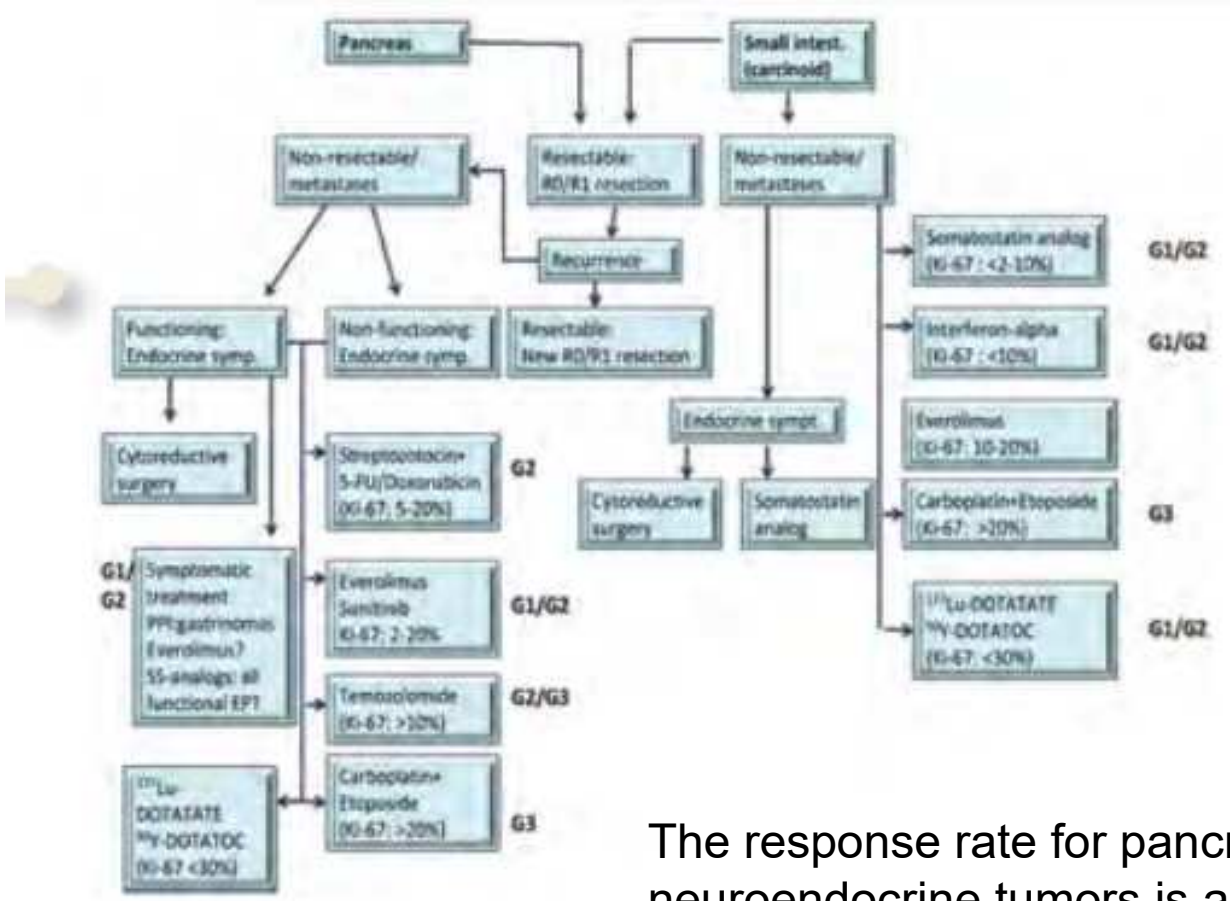
^{68}Ga-DOTATATE PET scan vs SRS

- Increased sensitivity and specificity
- Tomographic
- Exact CT co-registration
- Faster imaging 60–90 min vs 24–72 h
- Quantitative
- Lower radiation
- Onsite production

CT, Computed tomography; SRS, somatostatin receptor scintigraphy; PET, positron emission tomography.

Treatment

- In patients with intestinal neuroendocrine tumors, chemotherapy has no significant benefit (10%–15% objective responses and less than 2 years' median survival).
- Somatostatin analogues are considered to be first-line treatment for low-proliferating tumors with a Ki-67 proliferation index of up to 10%.
- ^{177}Lu-DOTATATE for patients with advanced/metastatic gastrointestinal NETs that are somatostatin receptor–positive on imaging



The response rate for pancreatic neuroendocrine tumors is about 40% (median survival 40 months).

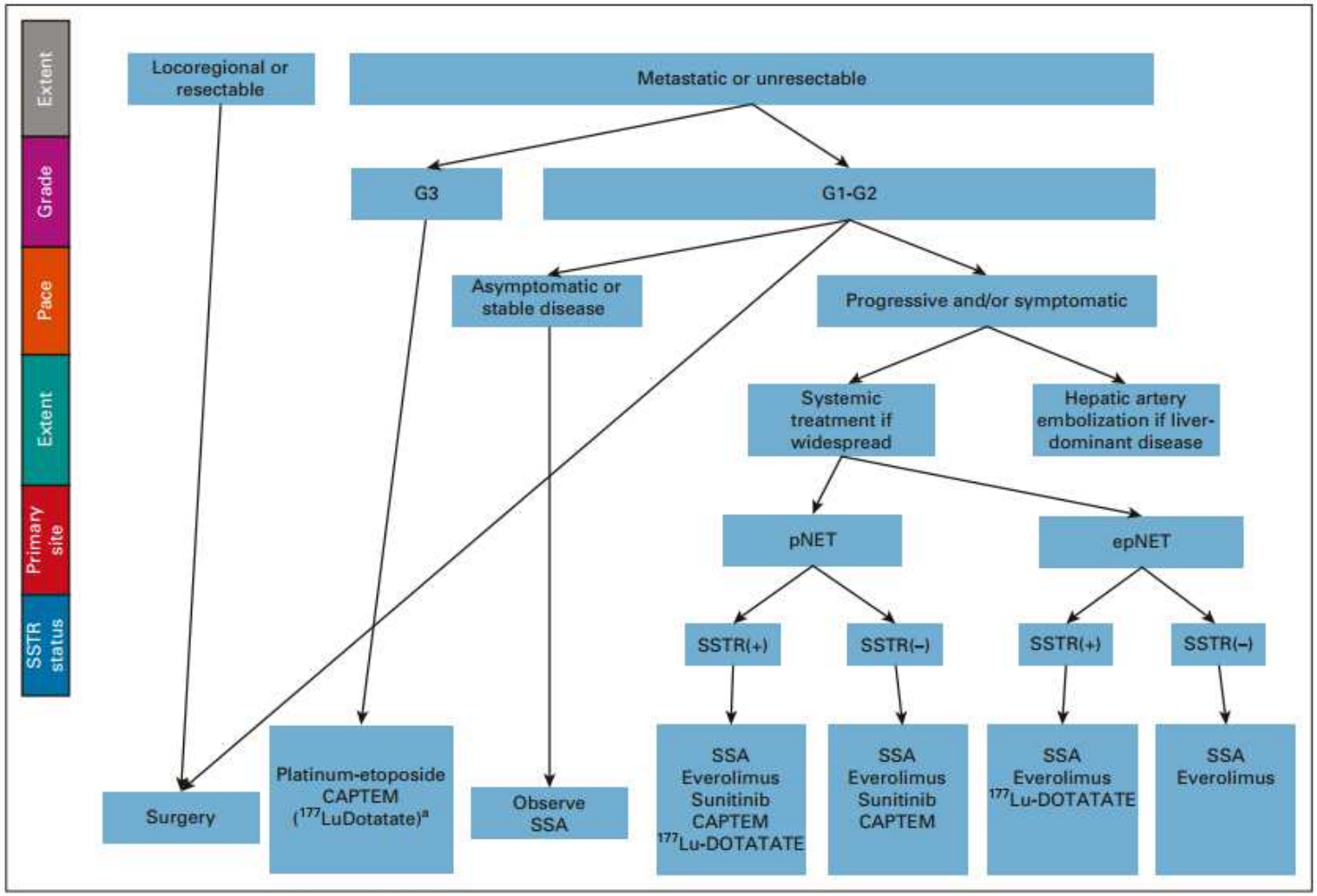


FIG 1. [a]For select cases. Schema for management of well-differentiated neuroendocrine tumors according to patient and tumor characteristics. CAPTEM, temozolomide plus capecitabine; epNET, extrapancreatic neuroendocrine tumor; pNET, pancreatic neuroendocrine tumor; SSA, somatostatin analog; SSTR, somatostatin receptor.

Epithelial neoplasms

- Low-grade mucinous adenocarcinomas neoplasms (MANs) are characterized by low-grade cytology without evidence of infiltrative (destructive) invasion
- Lymph node involvement is quite rare.
- High-grade (MANs) have high-grade cytologic features but without evidence of infiltrative (destructive) invasion.
- Lymph node involvement noted in 17% of grade 2; 72%, grade 3 lesions

Epithelial neoplasms

- Tumors that demonstrate infiltrative invasion of the appendiceal wall are considered mucinous appendiceal adenocarcinomas (AAs) and carry an increased risk for lymph node metastasis.
- 56% KRAS mutations
- 25% GNAS mutations
- 23% TP53 mutations
- 2% APC mutations
- 2% PIK3CA mutations
- 2-3% high TMB (high MSI status)
- <u>AAs are not genetically identical to colon cancer.</u>

Benign mucinous cystadenoma of the appendix

- Replaces the appendiceal mucosa.
- The cyst is lined by a single cell layer of benign mucin producing columnar epithelium.
- Luminal dilation is associated with appendiceal perforation in 20% of instances, producing localized collections of mucus attached to the serosa of the appendix or lying free within the peritoneal cavity.

Malignant mucinous cystadenocarcinoma of the appendix

- 20% as common as cystadenomas.
- Macroscopically they produce mucin-filled cystic dilatation of the appendix indistinguishable from that seen with benign cystadenomas.
- Penetration of the appendiceal wall by invasive cells and spread beyond the appendix in the form of localized or disseminated peritoneal implants, however, is frequently present.

Malignant mucinous cystadenocarcinoma of the appendix

- Continued cellular proliferation and mucin secretion fills the abdomen with tenacious, semisolid mucin (pseudomyxoma peritoneii**)**.
- Anaplastic adenocarcinomatous cells can be found, distinguishing this process from mucinous spillage.
- Instances in which pseudomyxoma peritoneii is accompanied by both appendiceal and ovarian mucinous adenocarcinomas are usually ascribed to spread of an appendiceal primary lesion.

Epithelial neoplasms

- Goblet cell adenocarcinomas are characterized by the degree of high-grade histologic features observed (infiltrating tumor cells, complex tubules, cribriform masses, loss of tubular or clustered growth, high-grade cytology, and necrosis):
- Grade 1 <25% high-grade pattern
- Grade 2 25% - 50% high-grade pattern
- Grade 3 >50% high-grade pattern
- Signet ring cell carcinomas have the worst outcome
- Epithelial neoplasms are treated with right hemicolectomy; 5FU if stage III-IV

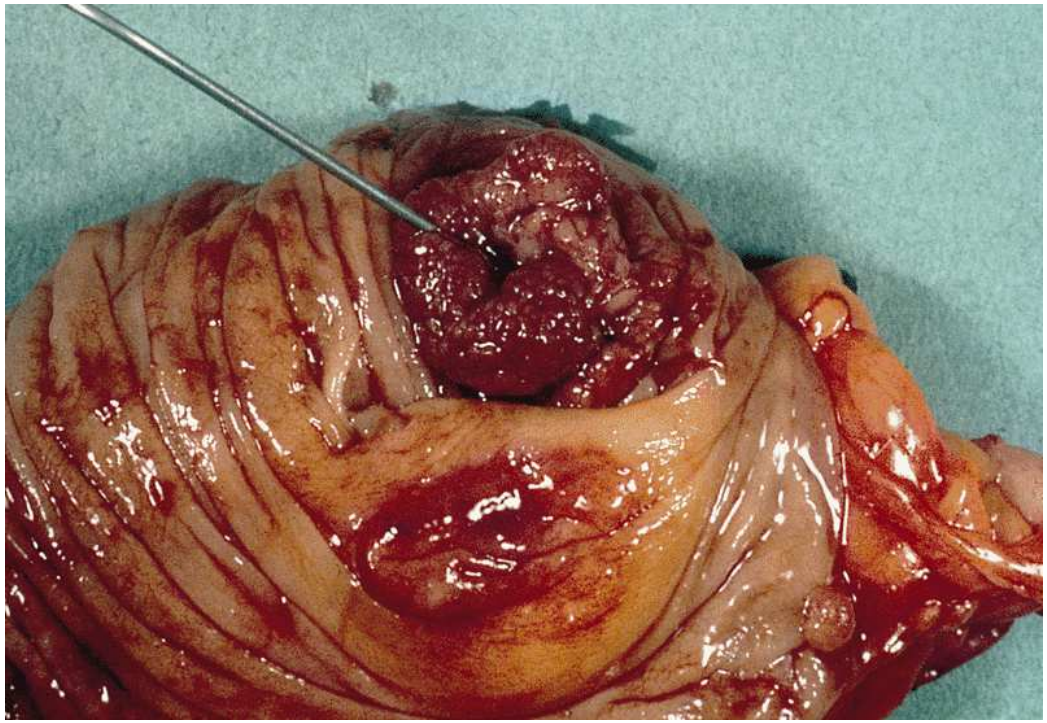
Treatment

- Epithelial neoplasms are treated with right hemicolectomy
- 5FU if stage III-IV
- If extension to serosa and peritoneum, hyperthermic intraperitoneal chemotherapy following cytoreductive surgery

Molecular alterations

- 80-100% of MANs have KRAS hotspot mutations.
- GNAS hotspot mutations are also more commonly enriched in low-grade MANs and are frequently seen in mucinous neoplasms across various organs.
- TP53 mutations are infrequent in low-grade MANs
- 10% of GCAs have KRAS and 6% have GNAS hotspot mutations

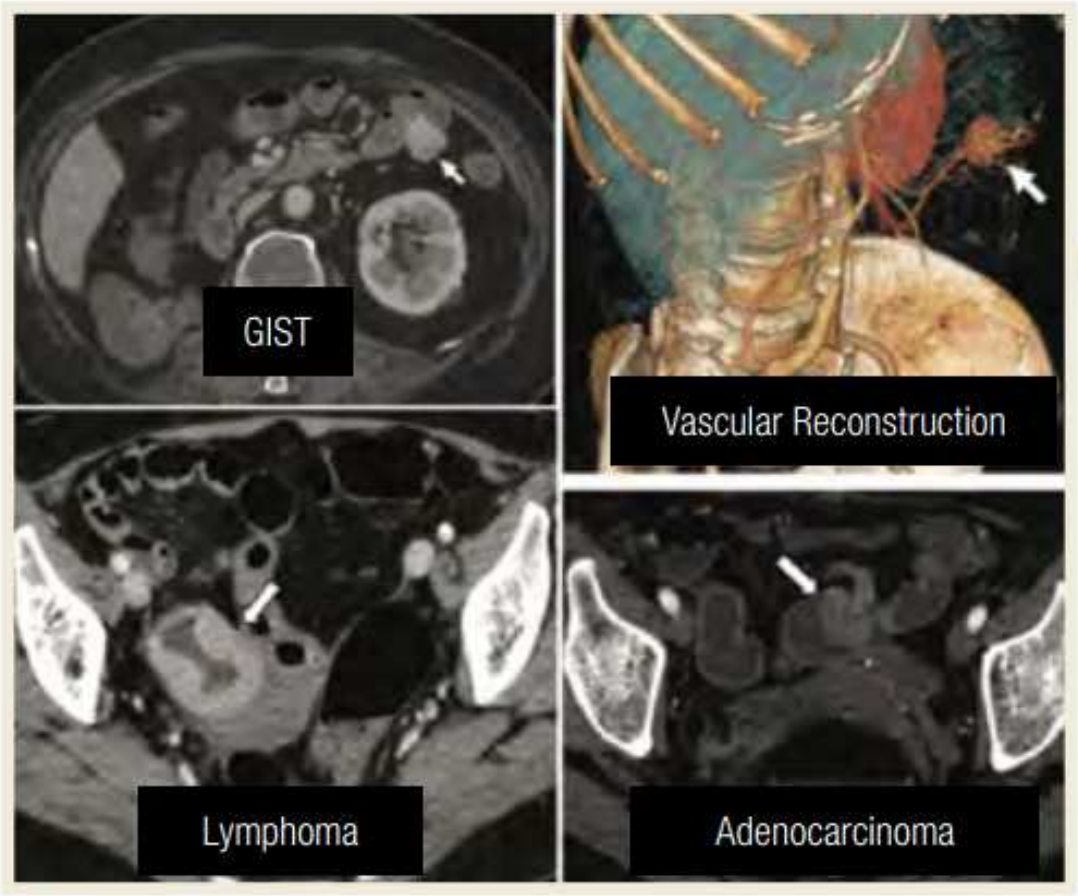
Adenocarcinoma of the appendix



A solid, noncystic lesion is less common than a cystic adenocarcinoma in the appendix.

Fig. 4-8

Riddell, RH, Petras, RE, Williams, GT, Sobin, LH., "Tumors of the intestines." Atlas of Tumor Pathology, Third Series, Fascicle 32. Armed Forces Institute of Pathology, Washington, D.C. 2003.



GIST, Gastrointestinal stromal tumour.

LARGE INTESTINE

Screening for colon cancer

- Screen all asymptomatic patients >50yo.
- Screen earlier if first degree relative with colon cancer or polyps before age 50.
- Amsterdam criteria:
- Consider gene study if three or more family members have been diagnosed with hereditary non-polyposis colon cancer and one is a first degree relative of the others
- Or, if colon cancers have occurred in two successive generations
- And, there is no history of familial adenomatous polyposis

Screening for colon cancer

- Although screenign sigmoidoscopy alone is associated with improved outcomes,
- Currently recommended:
- Immunochromatographic fecal occult blood test annually AND Flexible Sigmoidoscopy
- Six common fecal occult blood tests annually may be sufficient if the imunochromatographic method is not available.
- Methylated septin 9 as screen only if colonoscopy or barium enema refused by patient.
- Or, Double Contrast Barium Enema every 5 years
- Or, Virtual Colonoscopy every 5 years

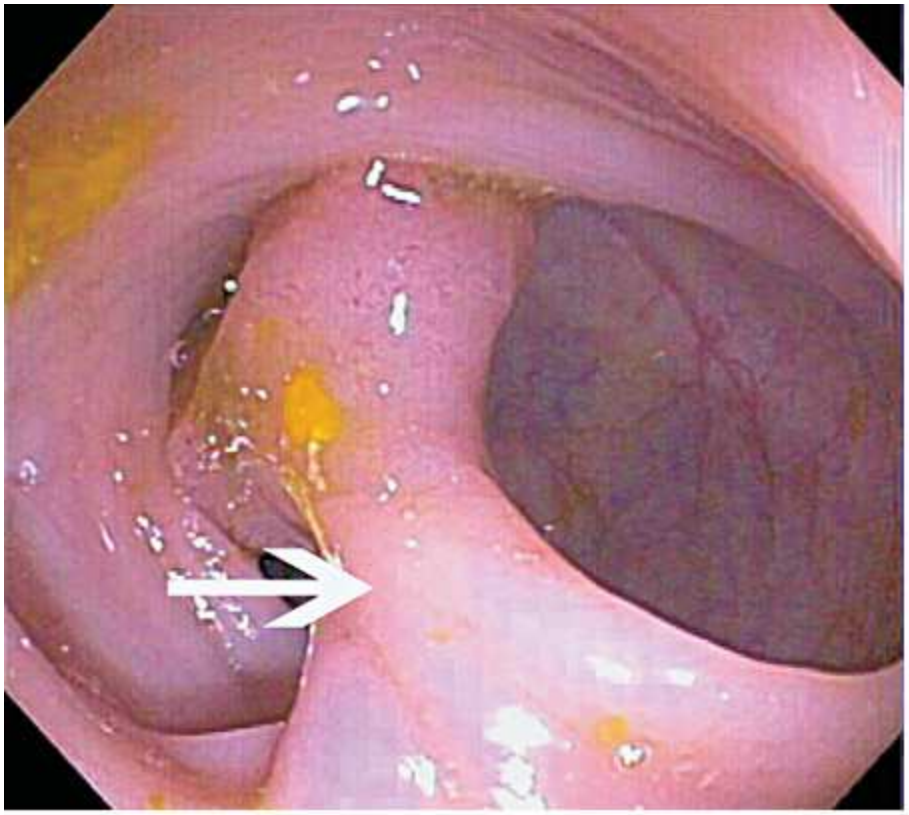
Screening for colon cancer

- Virtual colonoscopy recommended for the elderly as well as for those with a high risk of perforation if instrumentation employed.
- Colonoscopy only for positive screens
- Repeat every 10 years if negative or if low grade adenomas completely resected.
- If higher grade lesions identified, repeat every 3 years

Hyperplastic polyps

- Sporadic.
- Increase in frequency with age.
- 90% of all epithelial polyps in the large intestine.
- Often found incidentally in the sixth and seventh decades.
- They are found in more than half of all persons age 60 and older.
- Decreased epithelial cell turnover and accumulation of mature cells on the surface.
- Architecture preserved.

Hyperplastic polyp

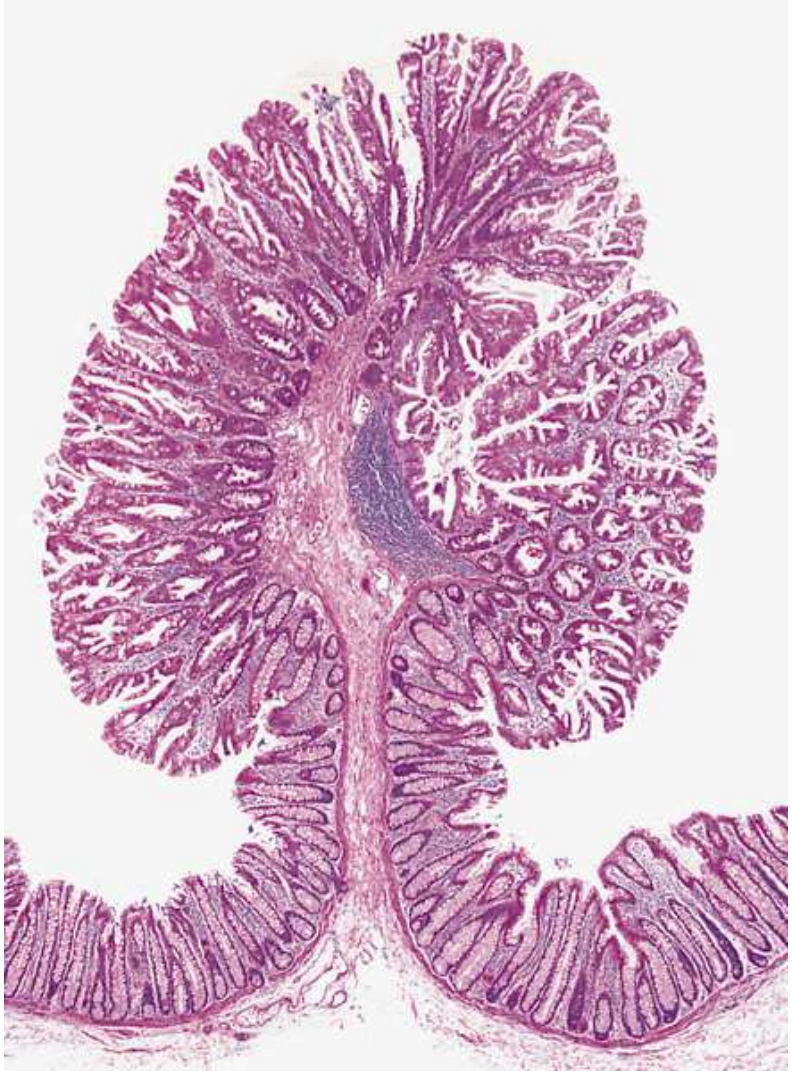


A

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Fig. e25-5A
Accessed 03/01/2010

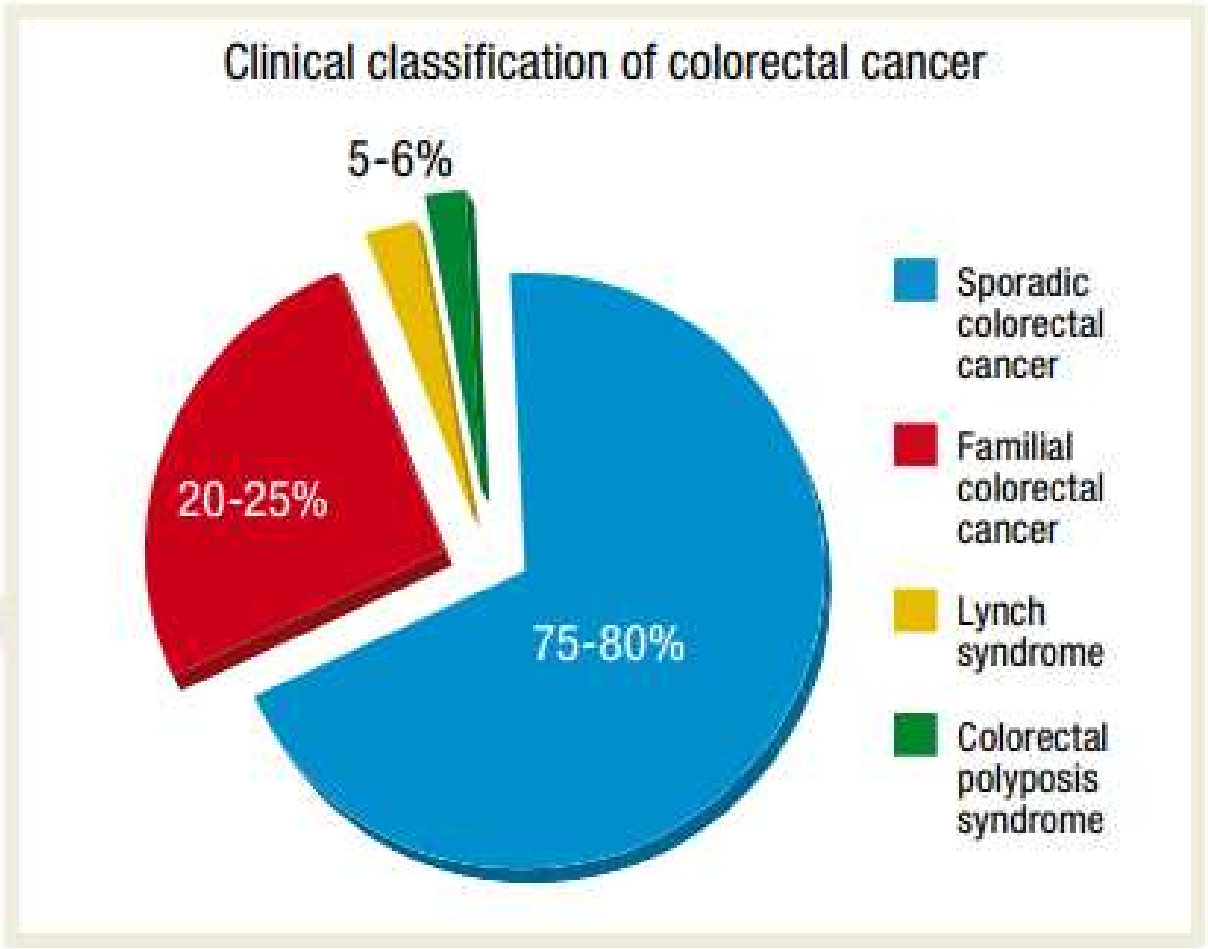
Hyperplastic polyp

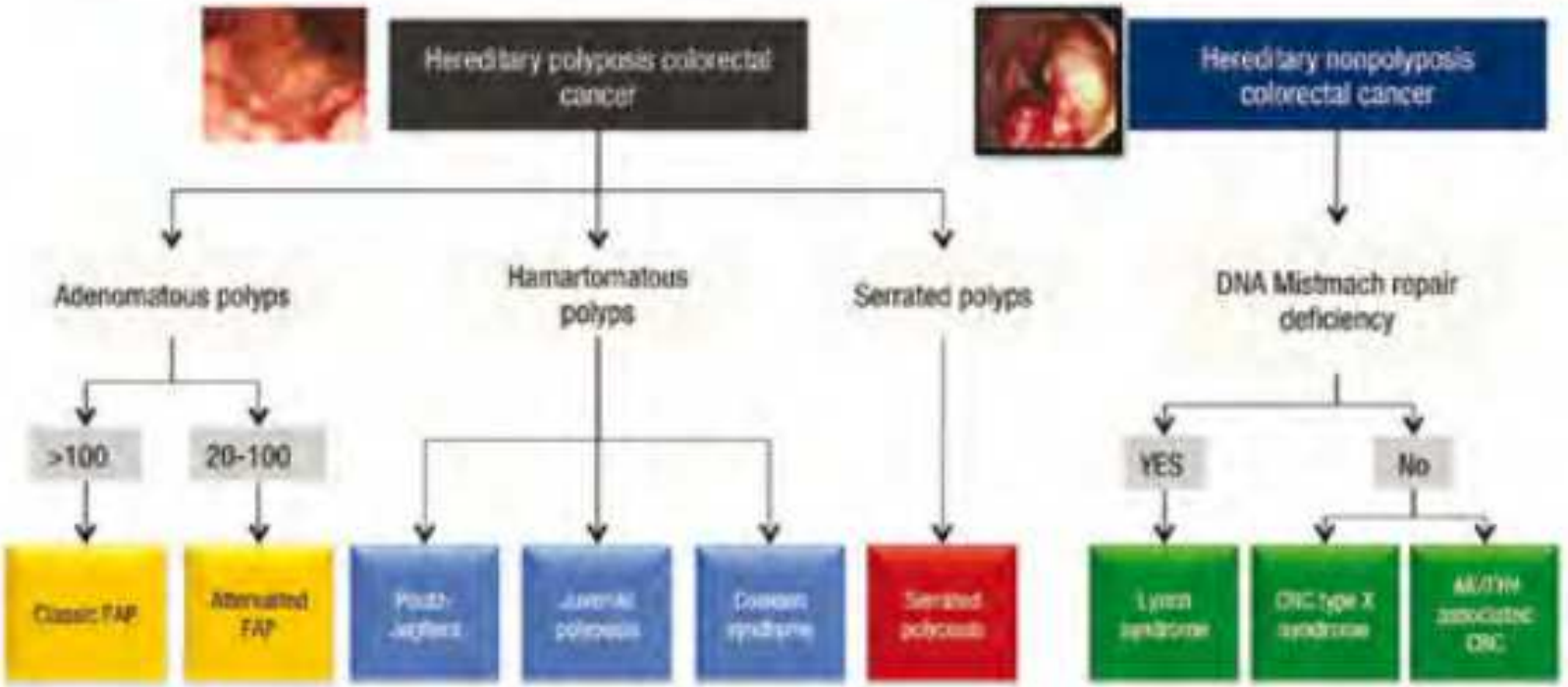


This pedunculated polyp has complex glandular structures focally.

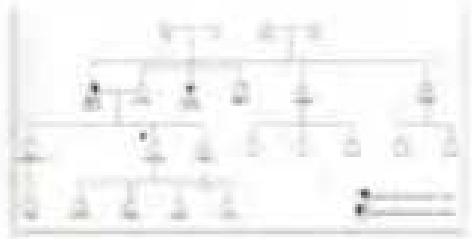
Fig. 2-002

Riddell, RH, Petras, RE, Williams, GT, Sobin, LH., "Tumors of the intestines." Atlas of Tumor Pathology, Third Series, Fascicle 32. Armed Forces Institute of Pathology, Washington, D.C. 2003.


Clinical classification of colorectal cancer
5-6%
20-25%
75-80%
Sporadic colorectal cancer
Familial colorectal cancer
Lynch syndrome
Colorectal polyposis syndrome



CRC, Colorectal cancer; FAP, familial adenomatous polyposis.



Lynch syndrome	Autosomal dominant	80-10%
APC-Familial adenomatous polyposis	Autosomal dominant	100%
MUTYH associated polyposis	Autosomal recessive	80%
Peutz-Jeghers syndrome	Autosomal dominant	50%
Juvenile polyposis	Autosomal dominant	40-60%
Cowden syndrome	Autosomal dominant	10%
Serrated polyposis	Unknown	50%

Hamartomatous polyps

- Hamartomatous polyps generally have very low malignant potential.
- Malformations of the glands and the stroma.
- Juvenile polyposis syndrome usually autosomal dominant but may be nonhereditary.
- <5 years of age
- Rectum
- Mutations in the SMAD4/DPC4 gene at 18q21.2 (which encodes signaling intermediate that binds to DNA) or BMPRIA at 10q23.2 (TGF-β superfamily kinase) account for fewer than 50% of juvenile polyposis syndrome.

Hamartomatous polyps

- Typically pedunculated, smooth-surfaced, reddish lesions with characteristic cystic spaces apparent after sectioning.
- Microscopic examination shows these cysts to be dilated glands filled with mucin and inflammatory debris
- The remainder of the polyp is composed of lamina propria expanded by mixed inflammatory infiltrates.
- The muscularis mucosae may be normal or attenuated.

Hamartomatous polyps

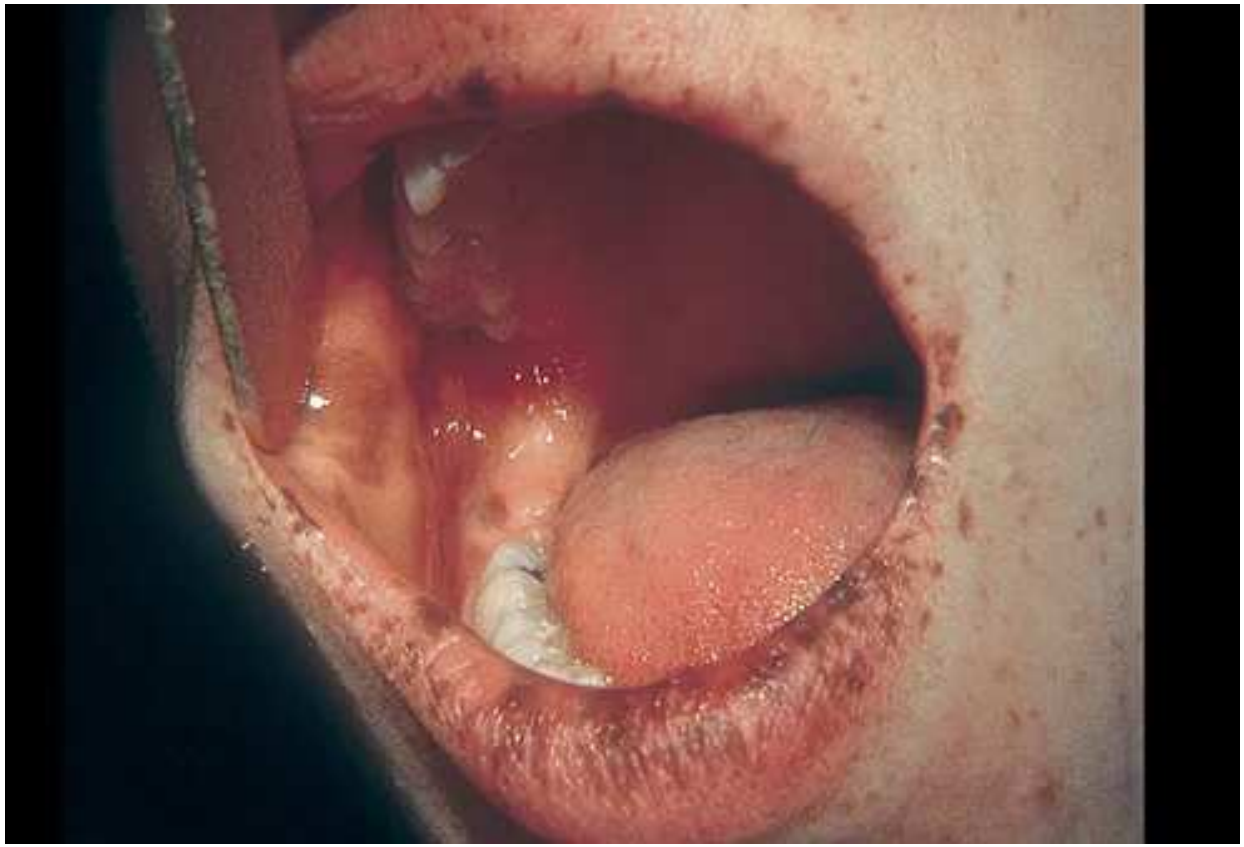
- Cronkhite-Canada syndrome is non-hereditary.
- Presents in those over 50 years of age
- Nail atrophy
- Areas of skin hyperpigmentation and hypopigmentation.

Peutz-Jeghers syndrome

- Hamartomatous polyps predominate in small bowel but may also be found in colon and stomach.
- Can initiate intussusception
- Mucosal pigmentation of buccal mucosa, lips.
- Germline mutation of the gene STK11 (LKB1) at 19p.13.3
- The gene encodes a protein with serine/threonine kinase activity that regulates cell polarization and growth.
- Autosomal dominant.

Peutz-Jeghers syndrome

- An arborizing network of connective tissue, smooth muscle, lamina propria, and normal appearing intestinal epithelium characterize the polyp.
- The presence of lamina propria differentiates Peutz-Jeghers syndrome polyps from juvenile polyps.
- 50% increased risk for colorectal, breast, gynecologic cancers



https://www.medicinenet.com/image-collection/peutz-jeghers_syndrome_picture/picture.htm

Peutz-Jeghers polyp

Delicate arborizing muscular infrastructure forms lobules of colonic mucosa in a 5-year-old boy (Masson trichrome stain).

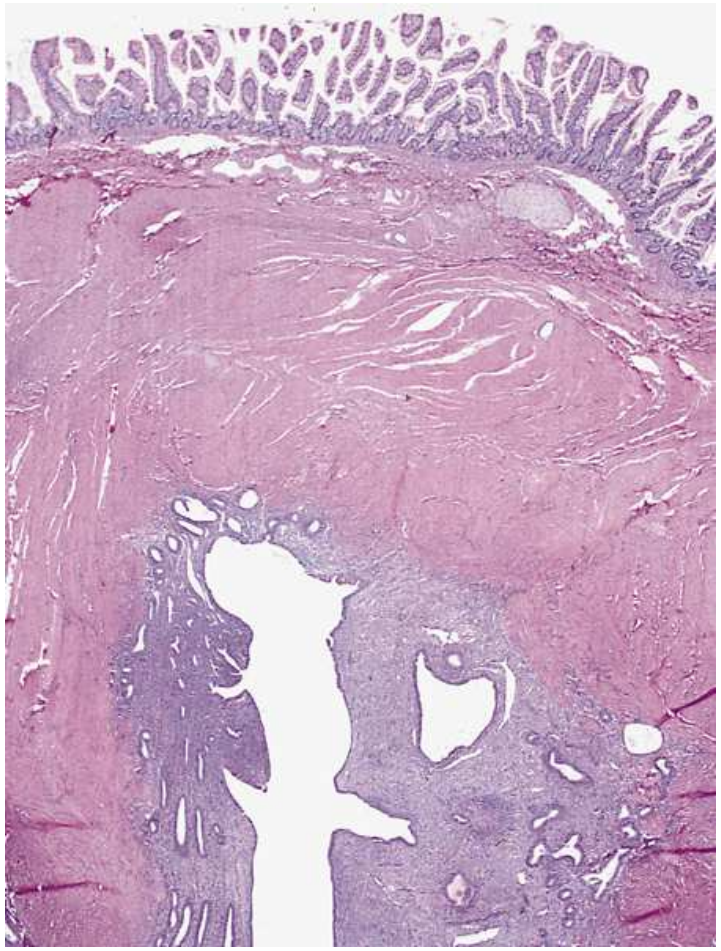
Fig. 2-23L

Riddell, RH, Petras, RE, Williams, GT, Sobin, LH., "Tumors of the intestines." Atlas of Tumor Pathology, Third Series, Fascicle 32. Armed Forces Institute of Pathology, Washington, D.C. 2003.

Cowden syndrome

- Intestinal hamartomatous polyps
- Hamartomatous polyps in skin and oral as well as nasal mucosa
- Macrocephaly
- Trichilemmoma.
- Males may have pigmented macules on the glans penis.
- Autosomal dominant.
- Increased risk of breast, endometrial, thyroid cancers
- Loss of function mutations in PTEN gene at 10p23.21 (inhibitor of $P1_3K$/AKT signaling pathway)

Endometriosis



The large endometrial deposit has a prominent muscular component resembling myometrium. Lesions are usually found on the serosal surface.

Fig. 2-92

Riddell, RH, Petras, RE, Williams, GT, Sobin, LH., "Tumors of the intestines." Atlas of Tumor Pathology, Third Series, Fascicle 32. Armed Forces Institute of Pathology, Washington, D.C. 2003.

Adenomatous polyp

- All adenomatous lesions arise as the result of epithelial proliferative dysplasia
- Histologically, the hallmark of epithelial dysplasia is nuclear hyperchromasia, elongation, and stratification
- These changes are most easily appreciated at the surface of the adenoma and are often accompanied by prominent nucleoli, eosinophilic cytoplasm, and a reduction in the number of goblet cells.
- Notably, epithelial cells fail to mature as they migrate from crypt to surface.

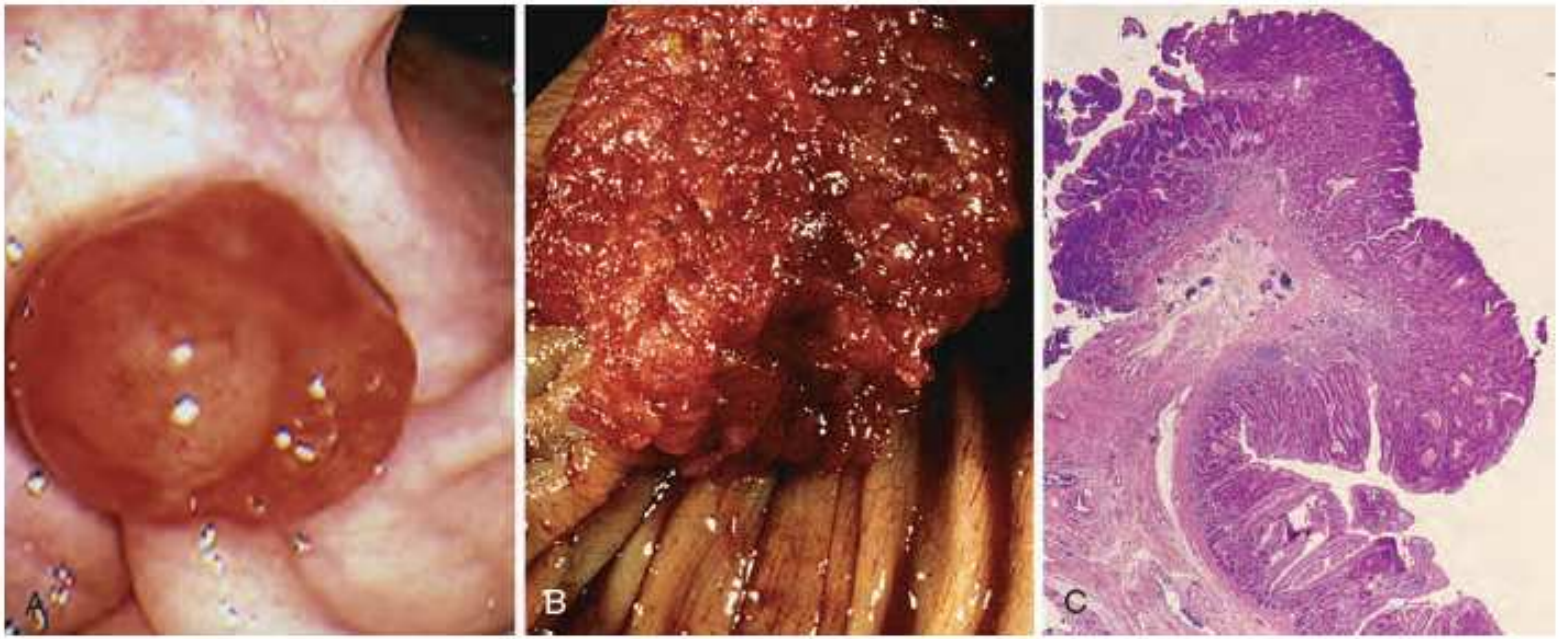


Figure 17-45 Colonic adenomas. **A,** Pedunculated adenoma (endoscopic view). **B,** Adenoma with a velvety surface. **C,** Low-magnification photomicrograph of a pedunculated tubular adenoma.

Adenomatous polyps

- Tubular adenoma most common (60% of polyps).
- Most tubular adenomas are small and pedunculated; conversely, most pedunculated polyps are tubular.
- Pedunculated adenomas have slender fibromuscular stalks
- Sigmoid colon most common site.
- Cancer is rare in tubular adenomas smaller than 1 cm in diameter.
- Tubulovillous adenoma are 20-30% of polyps.

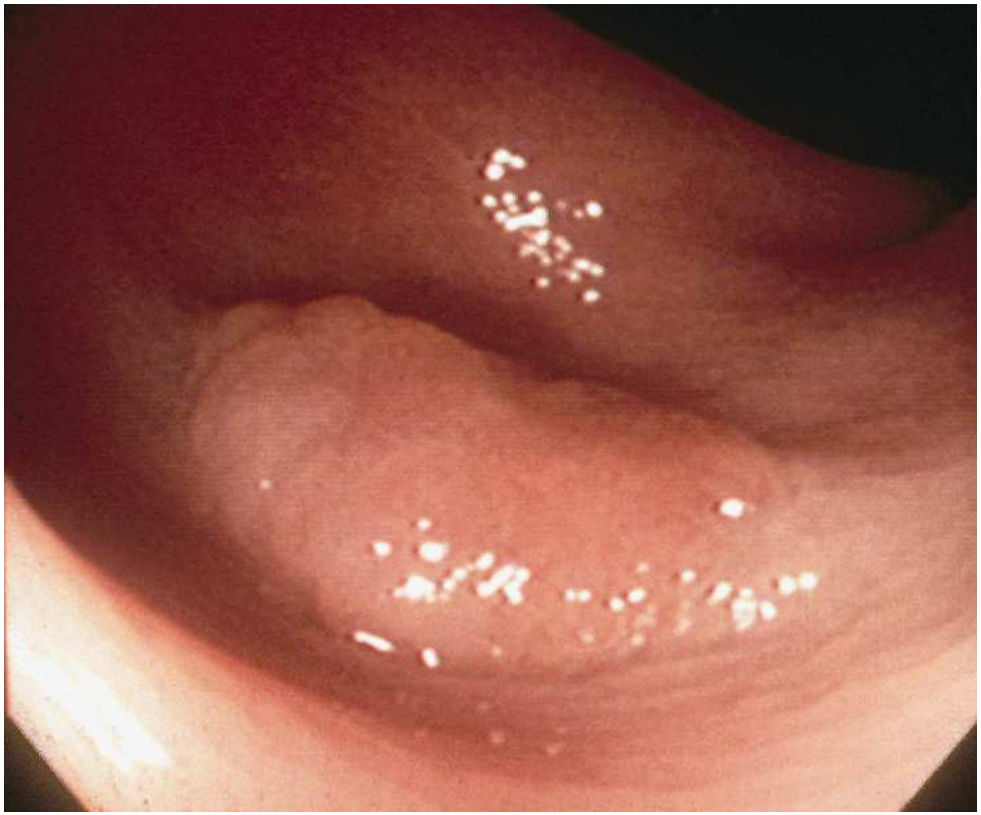
Adenomatous polyps

- Villous adenomas are 10% of polyps
- Tend to be large and sessile, and sessile polyps usually exhibit villous features.
- Rectosigmoid
- Secrete protein and K^+ rich mucus (prostaglandin E).
- May manifest as diarrhea.
- The risk of cancer is high (approaching 40%) in sessile villous adenomas more than 4 cm in diameter.
- Severe dysplasia, when present, is often found in villous areas.

Sessile serrated polyps

- Histologic criteria for these lesions include serrated architecture throughout the full length of the glands, including the crypt base, crypt dilation, and lateral growth
- Commonly display CpG island methylator promoter (CIMP) and V600E BRAF mutations, which are correlated with CIMP.
- CIMP mutations are associated with microsatellite instability.
- CIMP adenocarcinomas arises from a stem-like cell that is different than the stem-like cell of origin that gives rise to those cancers developing from tubular adenomas.

Villous adenoma



Endoscopic view. There is no way that an underlying infiltrating component can be excluded until examined in toto microscopically.

Fig. 3-15 R

Riddell, RH, Petras, RE, Williams, GT, Sobin, LH., “Tumors of the intestines.” Atlas of Tumor Pathology, Third Series, Fascicle 32. Armed Forces Institute of Pathology, Washington, D.C. 2003.

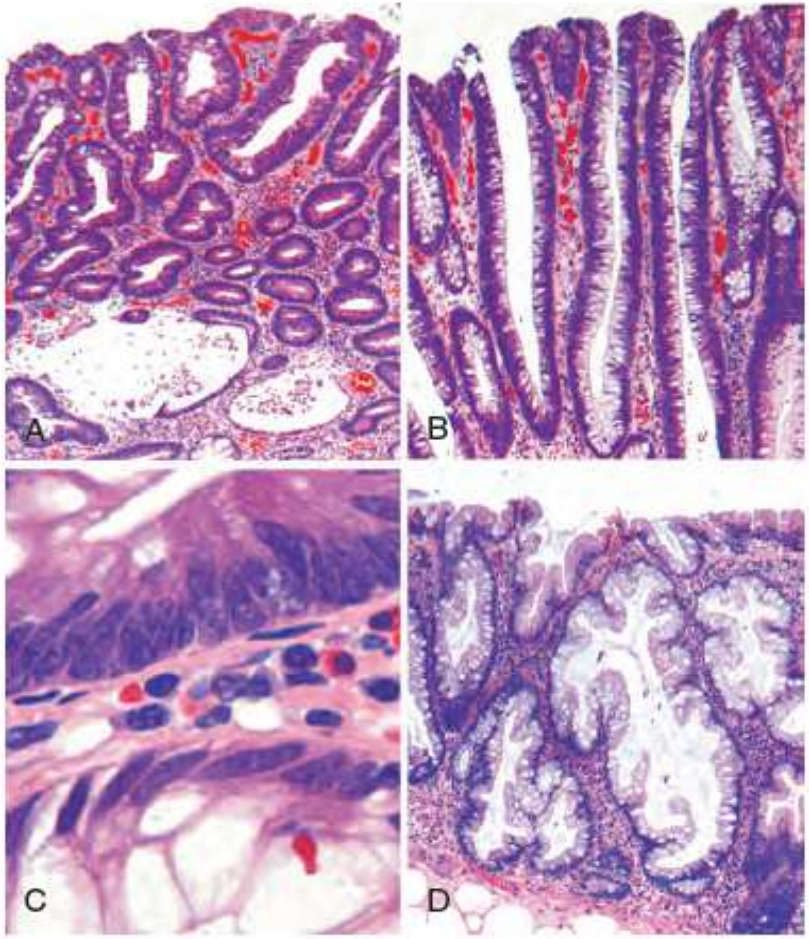
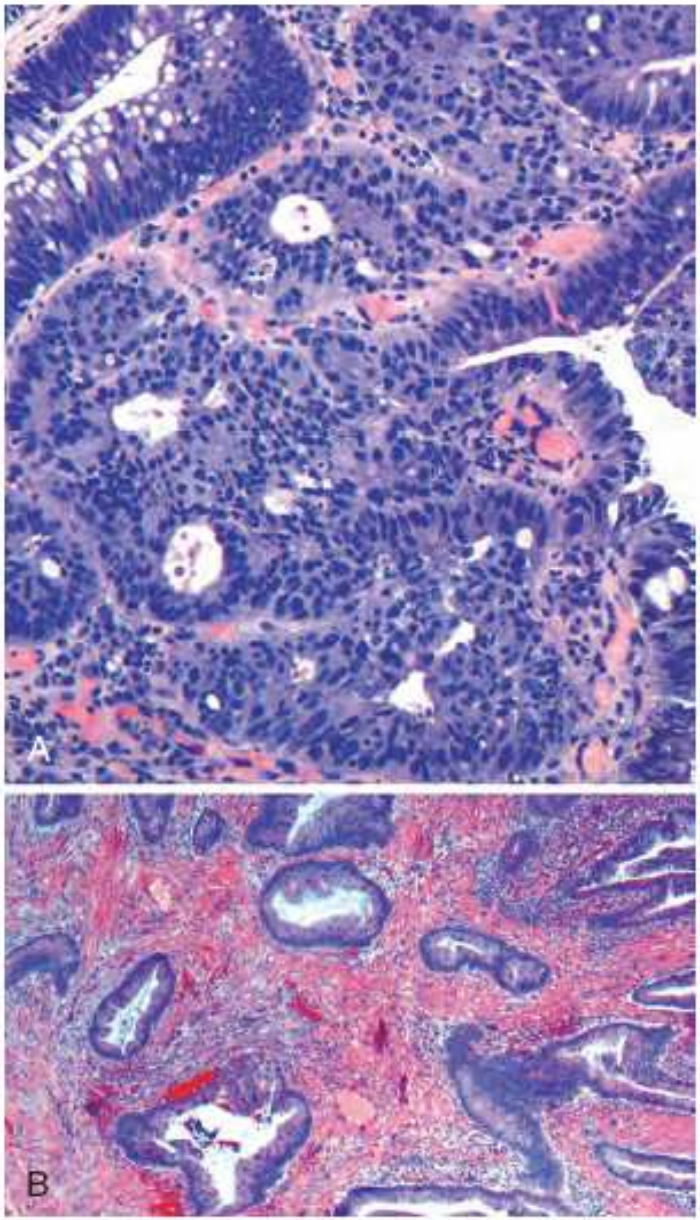


Figure 17-46 Histologic appearance of colonic adenomas. **A,** Tubular adenoma with a smooth surface and rounded glands. Active inflammation is occasionally present in adenomas, in this case, crypt dilation and rupture can be seen at the bottom of the field. **B,** Villous adenoma with long, slender projections that are reminiscent of small intestinal villi. **C,** Dysplastic epithelial cells (top) with an increased nuclear-to-cytoplasmic ratio, hyperchromatic and elongated nuclei, and nuclear pseudostratification. Compare to the non-dysplastic epithelium below. **D,** Sessile serrated adenoma lined by goblet cells without cytologic features of dysplasia. This lesion is distinguished from a hyperplastic polyp by extension of the neoplastic process to the crypts, resulting in lateral growth. Compare to the hyperplastic polyp in Figure 17-44A.

Adenomatous polyps

- High-grade dysplasia (carcinoma in situ) has not yet acquired the ability to metastasize and is still a clinically benign lesion.
- Because lymphatic channels are largely absent in the colonic mucosa, intramucosal carcinoma with lamina propria invasion only is regarded also as having little or no metastatic potential.
- If the intramucosal carcinoma penetrates through the muscularis mucosa into the submucosal space, the resultant invasive adenocarcinoma is a malignant tumor with metastatic potential.



ure 17-47 Adenoma with intramucosal carcinoma. **A,** Cribriform glands rface directly with the lamina propria without an intervening basement mbrane. **B,** Invasive adenocarcinoma (left) beneath a villous adenoma ht). Note the desmoplastic response to the invasive components.

Polyps of the large intestine

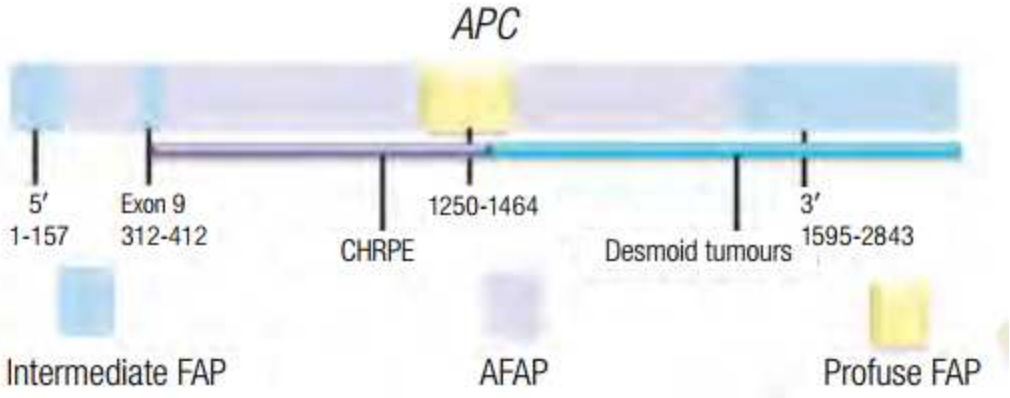
- The only adequate treatment for a pedunculated or sessile adenoma is complete resection.
- If adenomatous epithelium remains behind the patient still has a premalignant lesion or may even be harboring invasive carcinoma in the residual lesion.
- Size correlates with malignant potential
- KRAS/BRAF, 18qLOH mutations in high risk adenoma.

Familial adenomatous polyposis

- >100 polyps are necessary for diagnosis of FAP.
- 50% have polyps by age 15; 95% by age 35.
- Extracolonic manifestations:
- Gastric and duodenal polyps
- Congenital hypertrophy of the retinal pigmented epithelium (CHRPE)
- Desmoid tumours (10%–15%)
- thyroid cancer (2%–3%)
- Medulloblastoma (<1%)
- Hepatoblastoma (1%)
- Supernumerary teeth, osteomas, epidermoid cysts.

Familial adenomatous polyposis

- Begin to screen at age 10.
- Autosomal dominant.
- APC germline mutation
- APC is negative regulator of WNT/β-catenin signaling involved in controlling cell proliferation. E-cadherin is lost.
- Morphologically indistinguishable from adenoma.
- There is an attenuated form with <100 adenomas
- Cancer penetrance is incomplete



AFAP; Attenuated FAP; CHRPE, congenital hypertrophy of the retinal pigmented epithelium; FAP, familial adenomatous polyposis.

Familial adenomatous polyposis

- COX 2 gene is cytokine induced and downstream from EGFR.
- COX 2 inhibitor binds to cis-recognition site of PPAR 8.
- Progression on COX- 2 inhibitor is poor prognostic sign.
- Total colectomy prevents colorectal cancer.
- However, patient remains at risk for carcinoma at the ampulla of Vater or stomach.

Familial adenomatous polyposis

- Gardner's syndrome is associated with desmoid tumors of abdominal wall as well.
- Autosomal dominant.
- Turcot's syndrome is associated with astrocytoma and medulloblastoma as well.
- Autosomal recessive
- Total colectomy prevents colorectal cancer. However, patient remains at risk for carcinoma at the ampulla of Vater or stomach.

Familial adenomatous polyposis

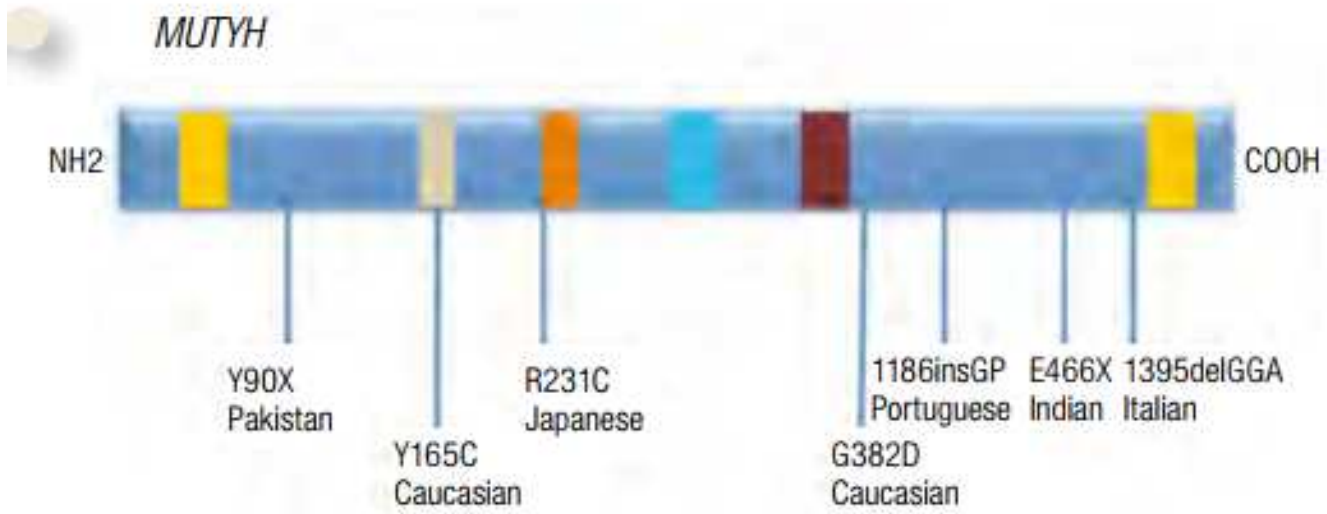
Myriad well-formed polypoid adenomas.

Fig. 3-31A

Riddell, RH, Petras, RE, Williams, GT, Sobin, LH., "Tumors of the intestines." Atlas of Tumor Pathology, Third Series, Fascicle 32. Armed Forces Institute of Pathology, Washington, D.C. 2003.

MYH-associated polyposis

- Fewer extracolonic mutations
- If no germline APC mutation, there is bi-allelic loss of the base excision repair gene MUTYH (MYH).
- In the Caucasian population, G396D or Y179C missense variants account for >80% of mutations
- Autosomal recessive
- Morphologically indistinguishable from adenoma.
- K-RAS mutated serrated adenoma may be found in these patients
- Polyposis managed with surveillance colonoscopy and polypectomy


MUTYH
NH2
COOH
Y90X
Pakistan
Y165C
Caucasian
R231C
Japanese
G382D
Caucasian
1186insGP
Portuguese
E466X
Indian
1395delGGA
Italian

Adenocarcinoma

- 90% occur in those over 50 years of age.
- Colon cancer is more common in women; rectal cancer, in men.
- High fiber, low animal-fat diets decrease risk. Smoking is an identifiable risk factor.
- Left sided lesions tend to be annular, produce "napkin-ring" constrictions and luminal narrowing leading to obstruction
- Right sided lesions tend to be polypoid, silent.
- Diarrhea related to COX-2 overexpression (Ca^{2+} transport).

Adenocarcinoma

- Cancers in the colorectum are found in the:
- Cecum/ascending colon, 22%
- Transverse colon, 11%
- Descending colon, 6%
- Rectosigmoid colon, 55%
- and other sites, 6%.

Adenocarcinoma

- Most tumors are composed of dysplastic tall columnar cells.
- Tumors may also be composed of signet-ring cells
- Some poorly differentiated tumors form few glands
- May display neuroendocrine differentiation.
- Others may produce abundant mucin that accumulate in the bowel wall.
- Mucin, released into system, has a procoagulant effect

Adenocarcinoma

- The invasive component of these tumors elicits a strong stromal desmoplastic response, which is responsible for their characteristic firm consistency.
- The two most important prognostic factors are depth of invasion and the presence of lymph node metastases
- Liver is the principal site of metastasis

Table 17-11 Common Patterns of Sporadic and Familial Colorectal Neoplasia

Etiology	Molecular Defect	Target Gene(s)	Transmission	Predominant Site(s)	Histology
Familial adenomatous polyposis	APC/WNT pathway	*APC*	Autosomal dominant	None	Tubular, villous; typical adenocarcinoma
MYH-associated polyposis	DNA mismatch repair	*MYH*	Autosomal recessive	None	Sessile serrated adenoma; mucinous adenocarcinoma
Hereditary nonpolyposis colorectal cancer	DNA mismatch repair	*MSH2, MLH1*	Autosomal dominant	Right side	Sessile serrated adenoma; mucinous adenocarcinoma
Sporadic colon cancer (70%-80%)	APC/WNT pathway	*APC*	None	Left side	Tubular, villous; typical adenocarcinoma
Sporadic colon cancer (10%-15%)	DNA mismatch repair	*MSH2, MLH1*	None	Right side	Sessile serrated adenoma; mucinous adenocarcinoma
Sporadic colon cancer (5%-10%)	Hypermethylation	*MLH1, BRAF*	None	Right side	Sessile serrated adenoma; mucinous adenocarcinoma

Environmental and lifestyle factors associated with colorectal cancer risk		
FACTORS	INCREASES RISK	DECREASES RISK
Tobacco smoking	About 40% increased risk for 40 cigarettes/day	
Anthropometry	Body fatness, abdominal fatness, adult attained height	
Physical activity		11% decrease for 30 min/day of recreational activity; mostly colon
Dietary factors		
convincing evidence:	Red meat, processed meat, alcoholic drinks (mainly men)	
convincing evidence:		Foods containing dietary fibre
probable evidence:		Garlic, milk, calcium
limited evidence:	Foods containing iron, sugars, abdominal fats, cheese	Non-starchy vegetables, fruits, foods containing vitamin D
Other diseases	Inflammatory bowel disease (Crohn's disease, ulcerative colitis)	
Medication		Non-steroidal anti-inflammatory drugs, postmenopausal women, hormone replacement therapy

Genetic model of cancer

- The process of colorectal tumorigenesis has been termed the polyp-carcinoma sequence, and it generally takes place over an 8- to 11-year time frame.
- There appears to be acceleration of this process in familial adenomatous polyposis (APC gene) and hereditary nonpolyposis colorectal cancer (MMR, mismatch repair genes).
- Defective DNA repair caused by inactivation of DNA mismatch repair genes is the fundamental and the most likely initiating event in colorectal cancers

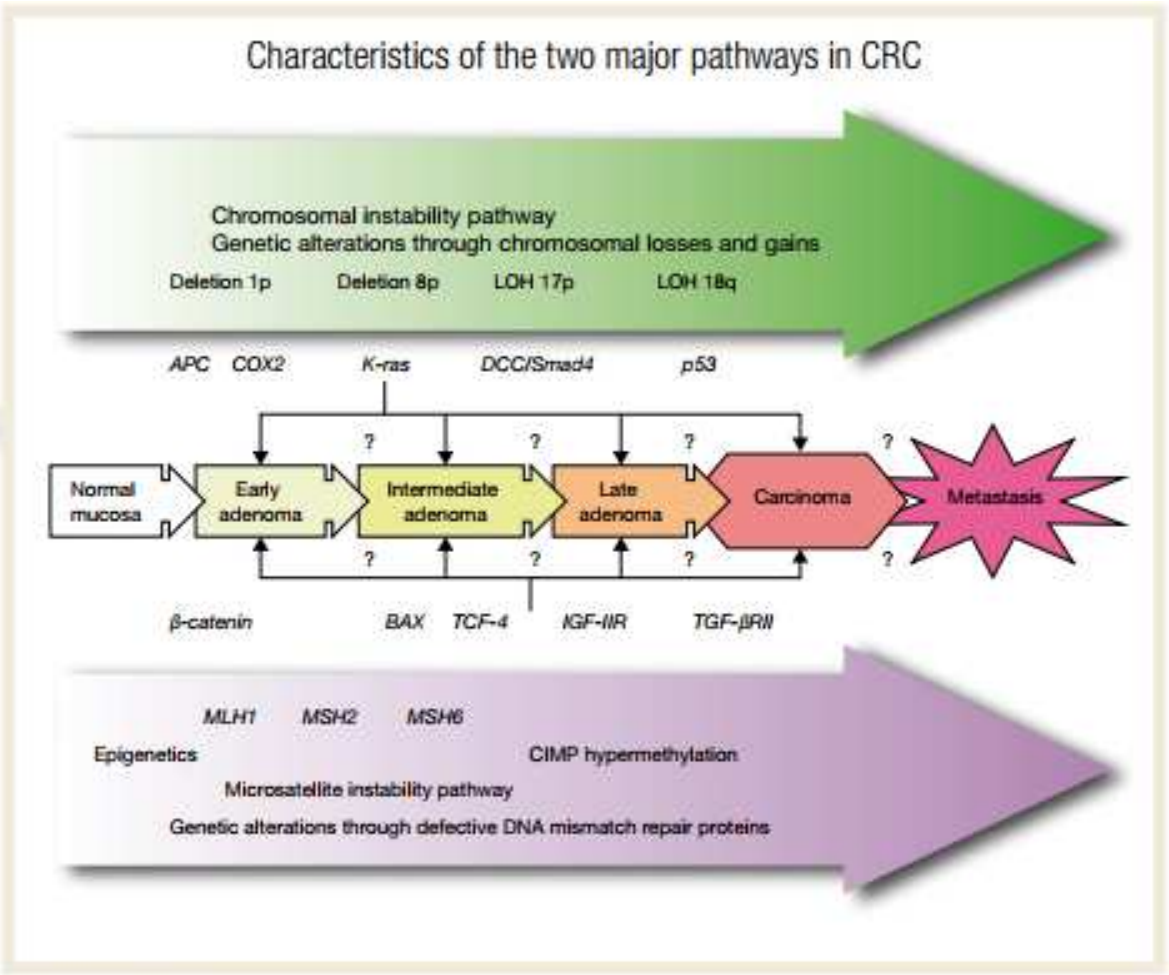
Genetic model of cancer

- Colon cancer can be divided at the molecular level into at least two distinct molecular categories based on the types of mutations observed.
- The chromosome instability (CIN) group is characterized by the presence of aneuploidy, chromosome translocations, and chromosomal gains and losses
- The microsatellite instability (MSI) group is characterized by the presence of frameshift mutations in repetitive elements of DNA called microsatellite repeats.

Adenocarcinoma of colon

Table 1 Features of CRCs based on CIMP status

Features	Non-CIMP	CIMP-low	CIMP-high
Tumour location	Distal > proximal	—	Proximal > distal
Gender bias	Male=female	Male>female	Male < female
BRAF mutation status	Wild type	Wild type	Mutant
KRAS mutation status	Wild type	Mutant	Wild type
Genomic instability status	CIN	Similar to non-CIMP	MSI is common



CRC, Colorectal cancer.

Adenoma-carcinoma sequence

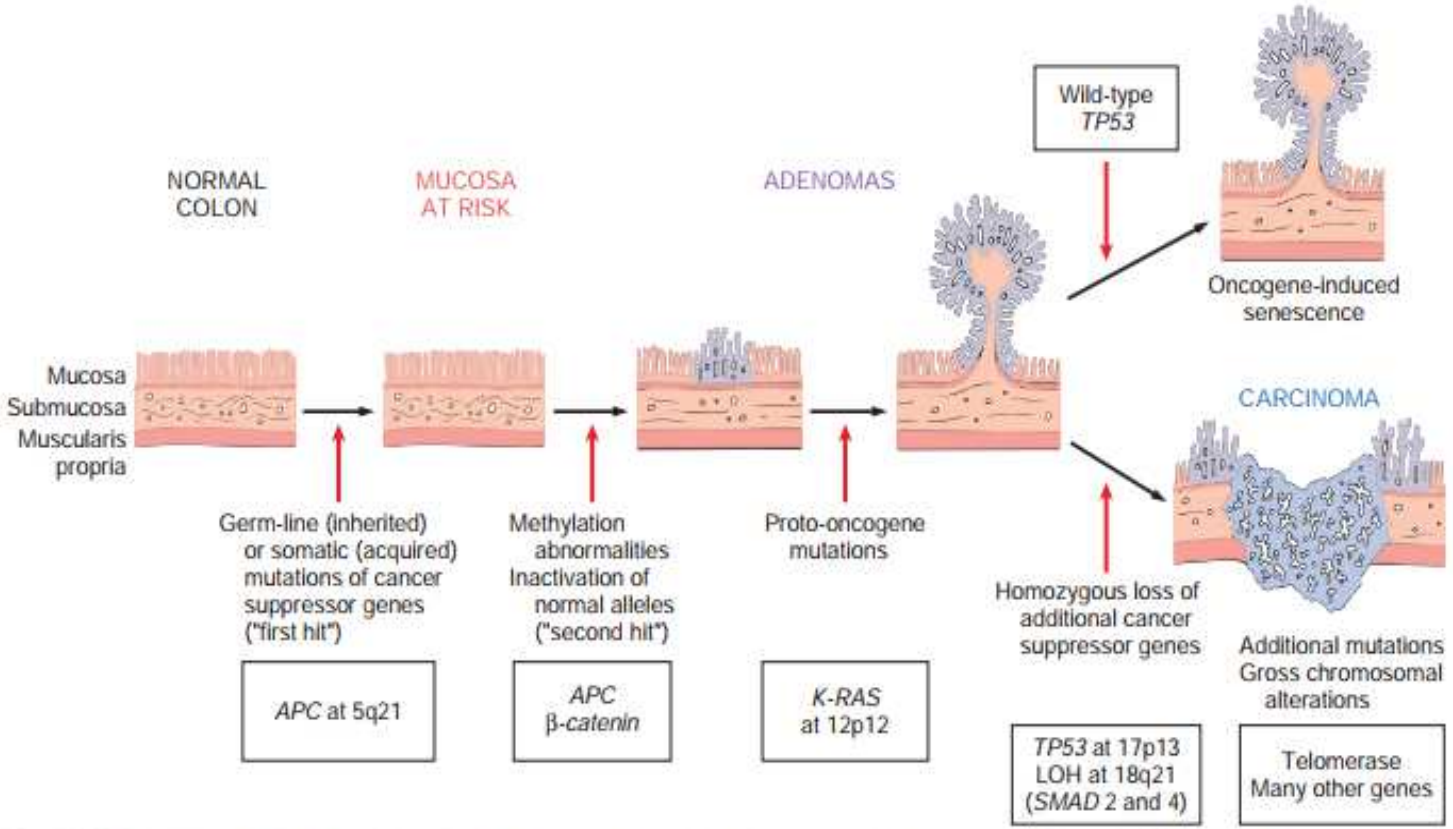


Figure 7-42 Molecular model for the evolution of colorectal cancers through the adenoma-carcinoma sequence. Although *APC* mutation is an early event and loss of *TP53* occurs late in the process of tumorigenesis, the timing for the other changes may be variable. Note also that individual tumors may not have all of the changes listed. *Top right*, cells that gain oncogene signaling without loss of *TP53* eventually enter oncogene-induced senescence. LOH, loss-of-heterozygosity.

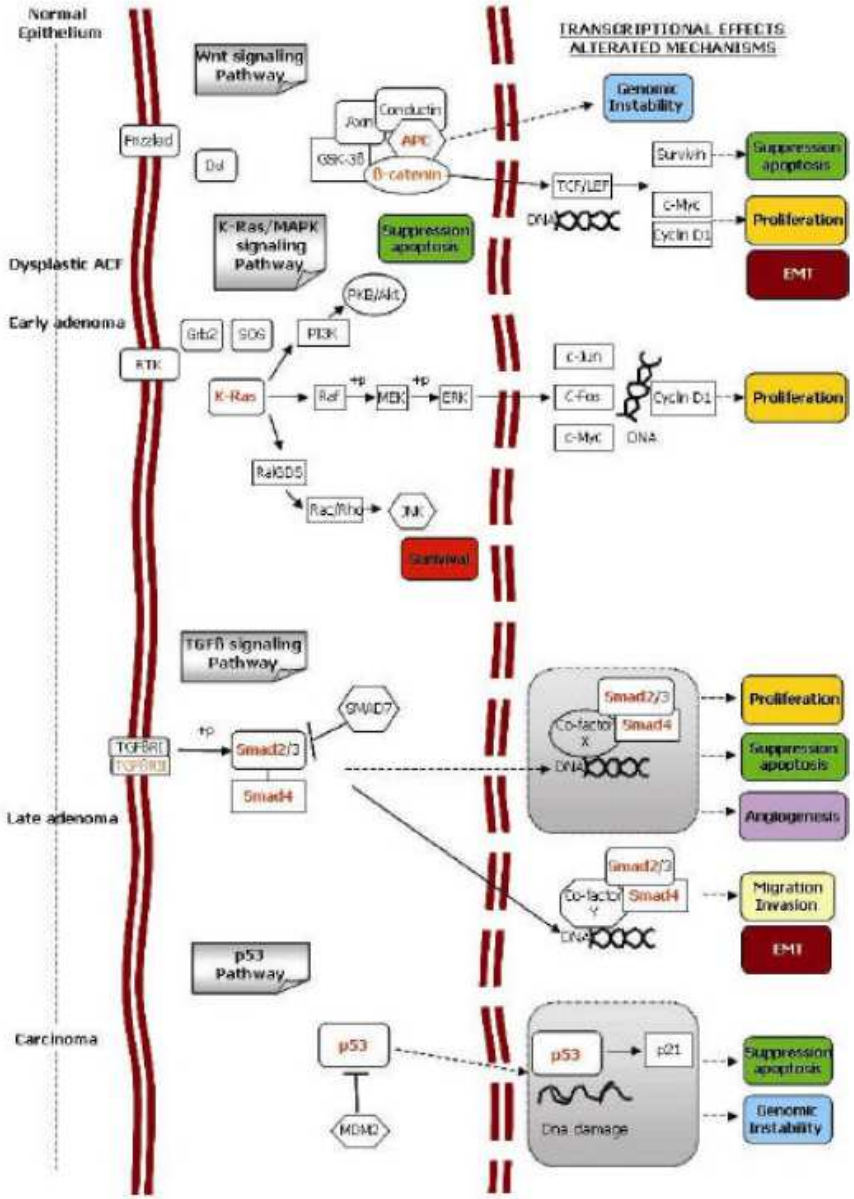


Figure 2. Schematic representation of the accumulation of alterations in different pathways along the adenoma-carcinoma sequence. In red are shown the genes frequently mutated in CRC. The different cellular alterations resulting from the accumulations of these signaling defects are listed in the right column.

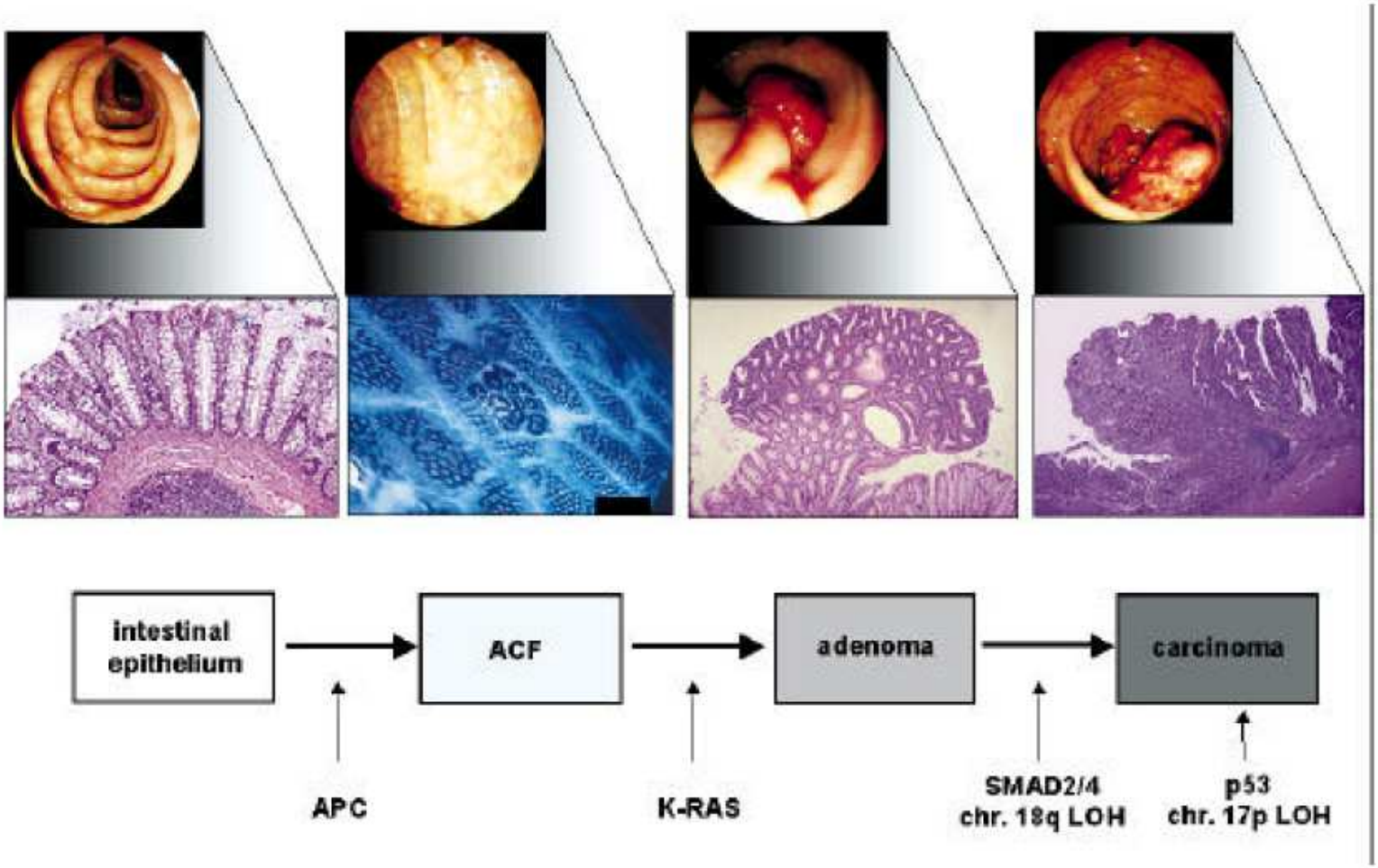


Figure 1. The adenoma-carcinoma sequence: a stepwise progression from normal epithelium to carcinoma due to a series of genetic changes. Macro- and microscopical representations of the progression changes are depicted. See text

Adenocarcinoma

- APC/ β-catenin mutation is first step to dysplastic epithelium.
- More than 80% of colorectal carcinomas have inactivated APC, and 50% of cancers without APC mutations have β-catenin mutations.
- APC is a negative regulator of WNT as it binds to β-catenin
- β-catenin is a member of the cadherin-based cell adhesive complex, consisting of APC, Axin, GSK-3β, and β-catenin, which also acts as a transcription factor if the protein is translocated to the nucleus.

Adenocarcinoma

- Bind to a family of transcription factors called T-cell factor or lymphoid enhancer factor (TCF or LEF) proteins.
- The TCF contributes a DNA-binding domain and β-catenin contributes a trans-activation domain.
- Genes activated by the β-catenin-TCF complex are thought to include those regulating cell proliferation and apoptosis, such as c-MYC and cyclin D1.
- LOH 18q (SMAD2 and SMAD4) mutations lead to loss of TGF-β signaling and unrestrained cell growth.

Mis-match carcinogenesis

- 90% of the mutations of “caretaker genes” involve MSH2 and MLH1.
- Mutations in the mismatch repair genes lead to microsatellite instability.
- CpG rich zones or CpG islands (5’ region that frequently includes promoter and transcriptional start sites) may be silenced by methylation (CIMP gene)
- BRAF is a serine-threonine protein kinase that acts as downstream effector of KRAS signaling.
- KRAS in the absence of BRAF

Adenocarcinoma

- KRAS codes a GTP/GDP binding protein facilitating ligand binding tyrosine kinase growth factor signaling.
- KRAS activates the RAF-MEK-ERK pathway.
- p53 mutation occurs late in adenoma carcinoma transition.

Mis-match repair carcinogenesis

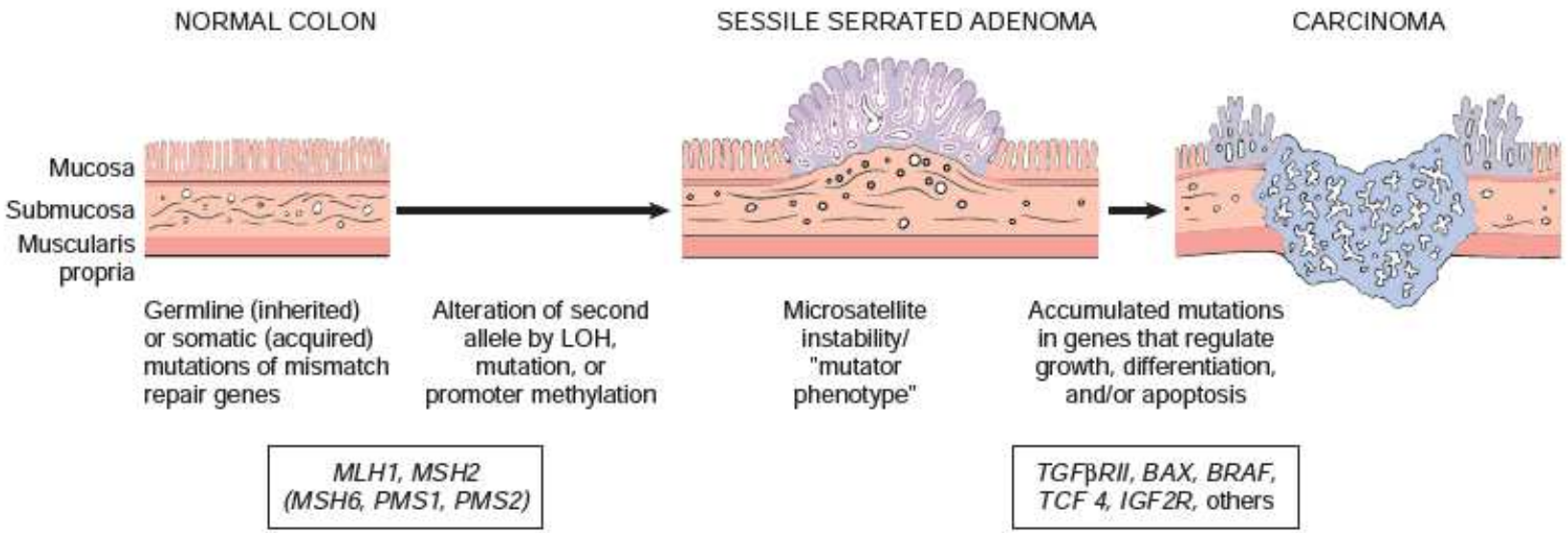


Figure 17-50 Morphologic and molecular changes in the mismatch repair pathway of colon carcinogenesis. Defects in mismatch repair genes result in microsatellite instability and permit accumulation of mutations in numerous genes. If these mutations affect genes involved in cell survival and proliferation, cancer may develop.

Adenocarcinoma

- RAS mutation associated with poor prognosis
- BRAF V600E mutation associated with poor prognosis.
- Notch 1 over-expression associated with poor prognosis (T3/T4 common) as is Notch 2 under-expression.
- RNF43 mutation associated with poor prognosis.
- Stem cell ligase that negatively regulates WNT signaling
- Deletion associated with adenoma formation

Adenocarcinoma

- KRAS mutations are found in 42.6% of whites and 56.8% of blacks. The differences are significant.
- DDR mutations are found in 12.9% of Asians and 21.7% of whites. The differences are significant.
- RNF43 mutation more common in blacks.

Adenocarcinoma

- p53 and EGFR over-expression more common in left sided lesions (favorable sign).
- Those with left sided lesions with DNA mismatch repair mutations have better prognosis than those with right sided lesions and the same mutations in Stage II or III disease.
- LRBP mutation (10% of colon cancers) generally left sided lesions.
- No benefit to use of cetuximab or bevicuzumab
- Respond to immunomodulators

Adenocarcinoma

- Diarrhea related to COX-2 overexpression (Ca^{2+} transport).
- p53 and EGFR over-expression more common in left sided lesions (favorable sign).
- Those with left sided lesions with DNA mismatch repair mutations have better prognosis than those with right sided lesions and the same mutations in Stage II or III disease.

Lynch syndrome

- Hereditary non-polyposis colon cancer (HPNCC)
- 2% of all colon cancers
- Most common syndromic form
- Two-thirds of the cancers occur in the proximal colon.
- Often tumors show mucinous change.
- Average age of diagnosis is mid-forties.
- 80% lifetime risk of colon cancer
- AND, for women, endometrial cancer as well
- Endometrial cancer may present first in women.

Lynch syndrome

- Associated with ovarian cancer
- Presents in the thirties
- For those presenting in the fifties
- May also see gastric cancer of intestinal type
- Small bowel adenocarcinoma
- Transitional cell cancers in the genitourinary tract
- Glioblastoma

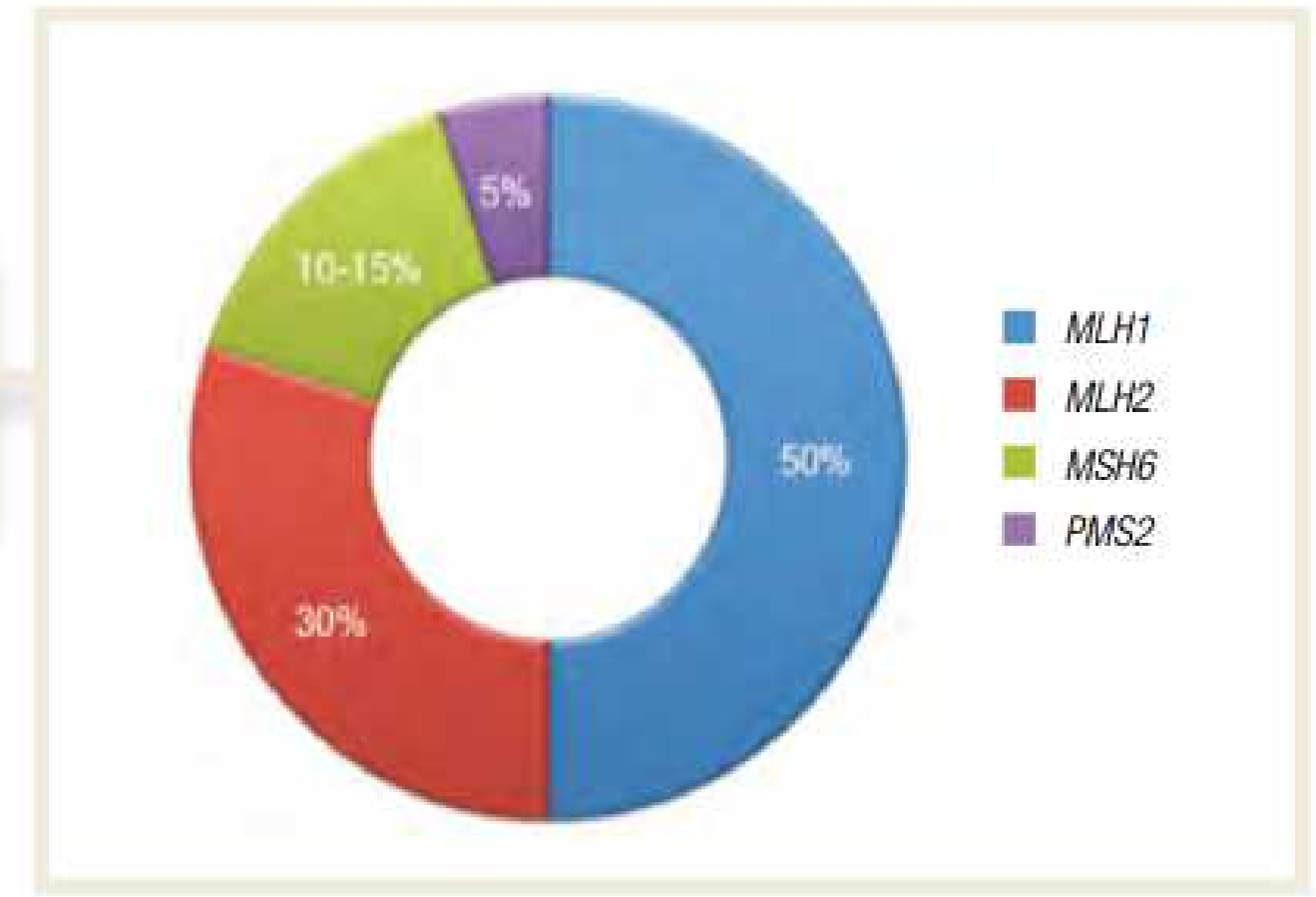
Lynch syndrome

- Inherited mutations (germ-line mutations) in any of five genes that are involved in involved in genetic "proofreading" during DNA replication:
- hMSH2 (2p22), hMLH1 (3p21), MSH6 (2p21), hPMS1 (2q31-33), and hPMS2 (7p22)
- Carcinogenesis is promoted when mismatches occur within the coding region of tumor suppressor genes (TGF-BRII, BAX, IGF2R, PTEN, CASP5).

Lynch syndrome

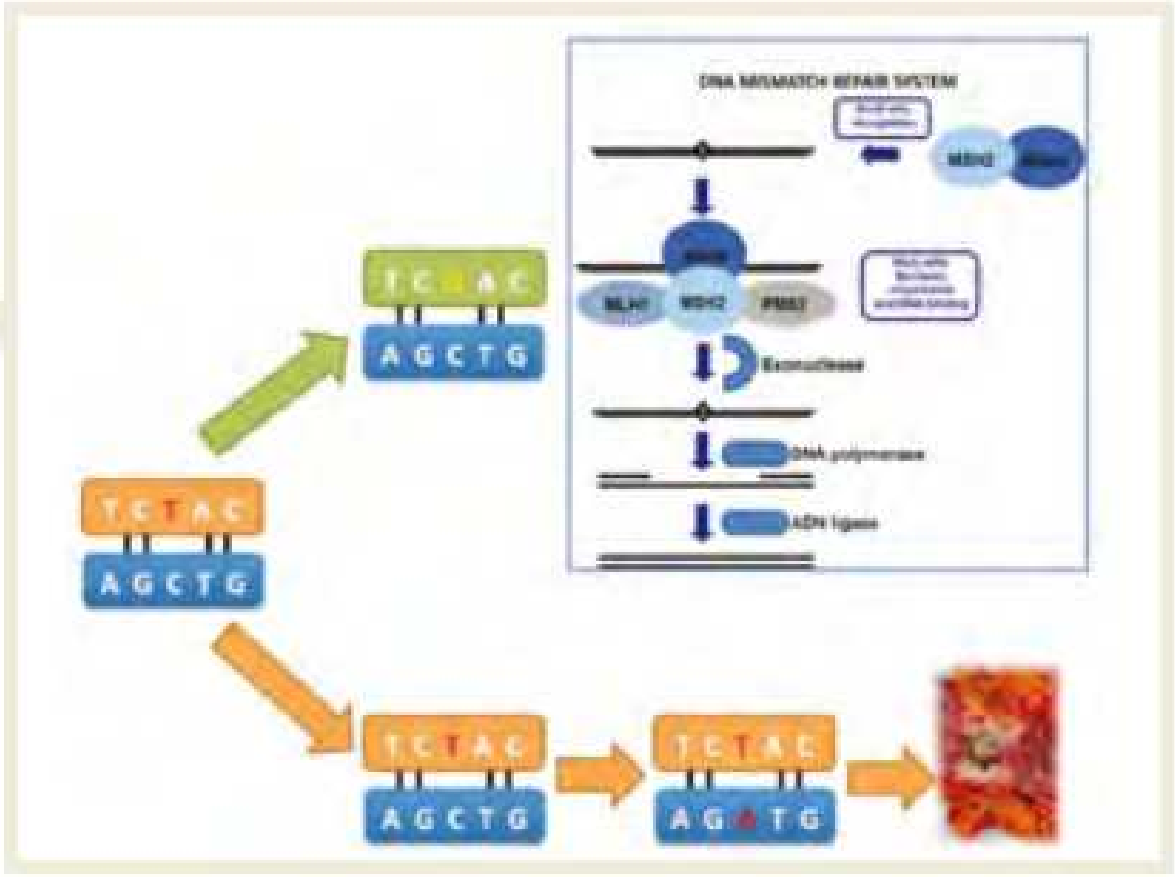
- Germline 3'EPCAM deletions also cause Lynch syndrome by epigenetic silencing of MSH2 by hypermethylation of its promoter region.
- TGFβRII mutation leads to unrestrained epithelial cell proliferation.
- BAX mutation permits cell to escape apoptosis.
- Microsatellite instability (MSI) is a marker for the presence of mismatch proteins as is the presence of tumor infiltrating lymphocytes.

Mismatch mutation frequency

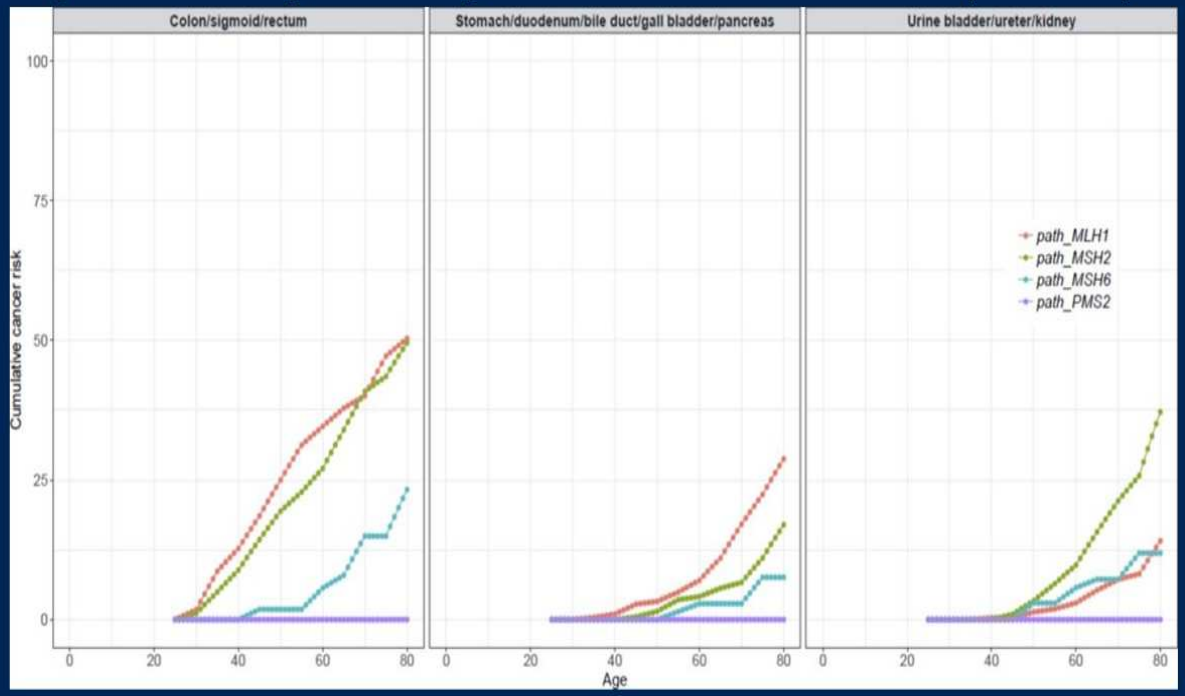


Lynch syndrome

- Any cancer with MSI abnormality suggests Lynch Syndrome
- MSH2 abnormality associated with rare tumor presentations in the syndrome
- PMS2 abnormality is most common abnormality in general population but of low penetration
- Up to 15% of all CRCs show MLH1/PMS2 protein loss due to somatic MLH1 promoter hypermethylation, usually associated with somatic BRAF mutations.


DNA MISMATCH REPAIR SYSTEM
MSH2
MLH1
MSH2
PMS2
Exonuclease
DNA polymerase
ADN ligase
TCTAC
AGCTG
TCTAC
AGCTG
TCTAC
AGCTG
TCTAC
AGATG

Gene- and age-specific considerations – Prospective Lynch Syndrome Database (PLSD)



Møller P, et al. *Gut* 2018;67:1306-16

Gene-, age-, and sex-specific considerations – Prospective Lynch Syndrome Database (PLSD)

MLH1 associated Lynch syndrome

- High-penetrance
  - Lifetime risk of *any* Lynch cancer: 71% males, 81% females
- High risk of GI cancers, esp for males
  - Lifetime risk colorectal cancer: 57% males, 48% females
  - Lifetime risk upper GI cancer: 22% males, 11% females

Dominguez-Valentin M, et al. *Genet Med* 2020;22:15-25

Gene-, age-, and sex-specific considerations – Prospective Lynch Syndrome Database (PLSD)

MSH2 associated Lynch syndrome

- High-penetrance
  - Lifetime risk of *any* Lynch cancer: 75% males, 84% females
- Particularly high risk of urinary tract cancers, esp for males (15-20%)
- Widest spectrum of increased risk
  - GI, Gyn, urinary, sebaceous neoplasia, sarcomas

Dominguez-Valentin M, et al. *Genet Med* 2020;22:15-25

Gene-, age-, and sex-specific considerations – Prospective Lynch Syndrome Database (PLSD)

MSH6 associated Lynch syndrome

- High-penetrance for Gyn cancers
  - Lifetime risk : 41% endometrial cancer, 11% ovarian cancer (comparable to *MLH1* and *MSH2*)
- Moderate-penetrance for GI and other Lynch cancers
  - Lifetime risk colorectal cancer: 18% males, 20% females

Dominguez-Valentin M, et al. *Genet Med* 2020;22:15-25

Gene-, age-, and sex-specific considerations – Prospective Lynch Syndrome Database (PLSD)

PMS2 associated Lynch syndrome

- Low-penetrance
  - Lifetime risk of *any* Lynch cancer: 34% males & females
- May only confer increased risks of colorectal and endometrial cancers
- Recent data showing *no increased risk* of ovarian, upper GI, or urinary tract cancers

Dominguez-Valentin M, et al. *Genet Med* 2020;22:15-25
ten Broeke SW, et al. J Clin Oncol 2018;36:2961-8

Gene-, age-, and sex-specific considerations – Prospective Lynch Syndrome Database (PLSD)

EPCAM associated Lynch syndrome

- Minimal data
- Likely high lifetime risks of colorectal cancer
- Presumed to have phenotypic overlap with *MSH2*-associated Lynch syndrome

Lynch syndrome

- Screen every 1-2 years by colonoscopy beginning at age 25 (30 if MSH6 or PMS2 mutations).
- The risk of metachronous colorectal cancer is 16% at 10 years and 41% at 20 years.
- Screen women with endometrial biopsy beginning at age 30.
- Transvaginal ultrasound and CA125 have not been useful screening tools in ovarian cancer.

Familial colorectal cancer type X

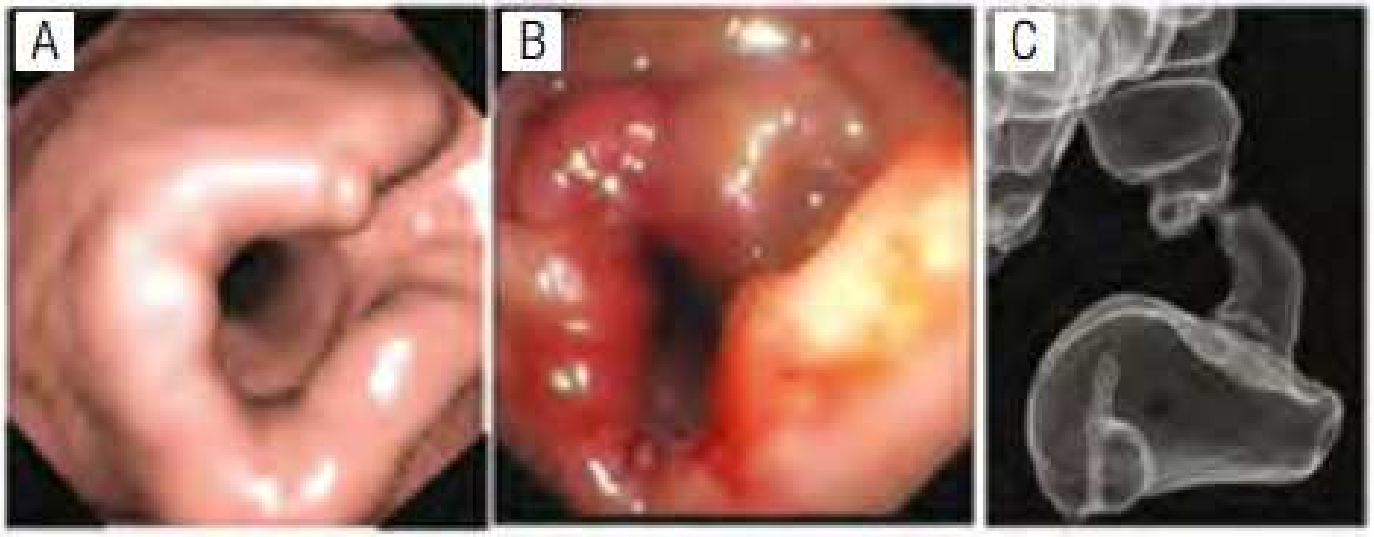
- 40% of those who fulfill the Amsterdam criteria for diagnosis of Lynch syndrome do not have a mismatch repair abnormality.
- Adenocarcinoma without polyposis
- Genetic basis has not been identified. However, in some cases, germline mutations have been identified
- BMPR1A, BMP4, GALNT12
- Cancer risk is lower than in Lynch syndrome

Familial colorectal cancer MUTYH associated

- Up to 30% of biallelic mutation carriers display adenocarcinoma without polyposis.
- MUTYH encodes a member of the base excision repair system which contributes to protect cells against the mutagenic effects of aerobic metabolism.

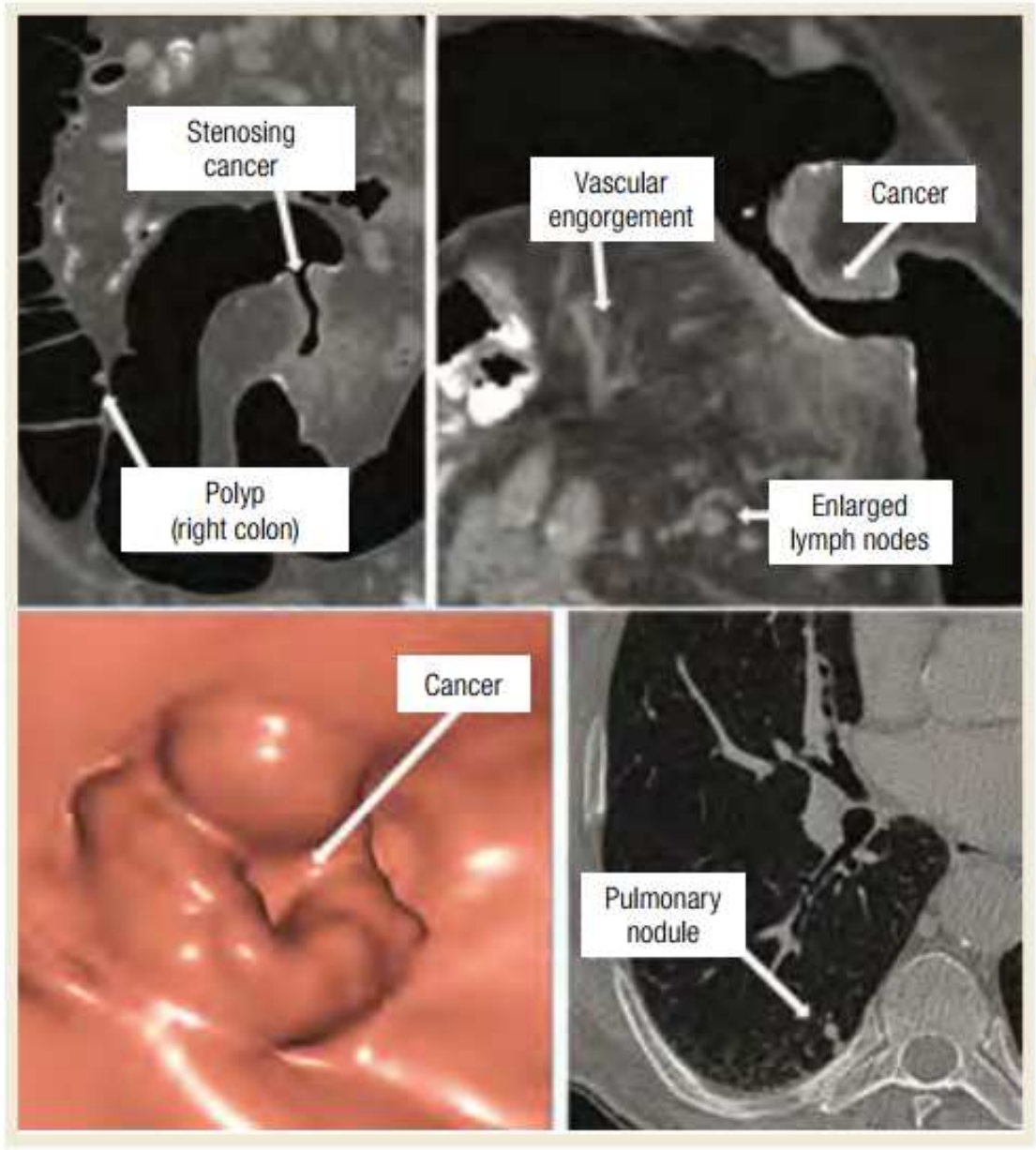
Adenocarcinoma of the large intestine

- Diagnosis of colon cancer is obtained with colonoscopy and biopsy.
- CT colonography (CTC) as an alternative.
- CT of the chest, abdomen and pelvis is appropriate to detect distant metastasis.
- If initial colonoscopy is incomplete (also due to the presence of a stenosing cancer), the adjunct of CTC to CT can be used to detect synchronous colonic lesions.
- Contrast-enhanced MRI is suggested if CT is contraindicated or if liver lesions require further characterization.



Stenosing Colon Cancer: (A) 3D endoluminal image from CTC, (B) optical colonoscopy and (C) double-contrast barium enema reconstruction from CTC.

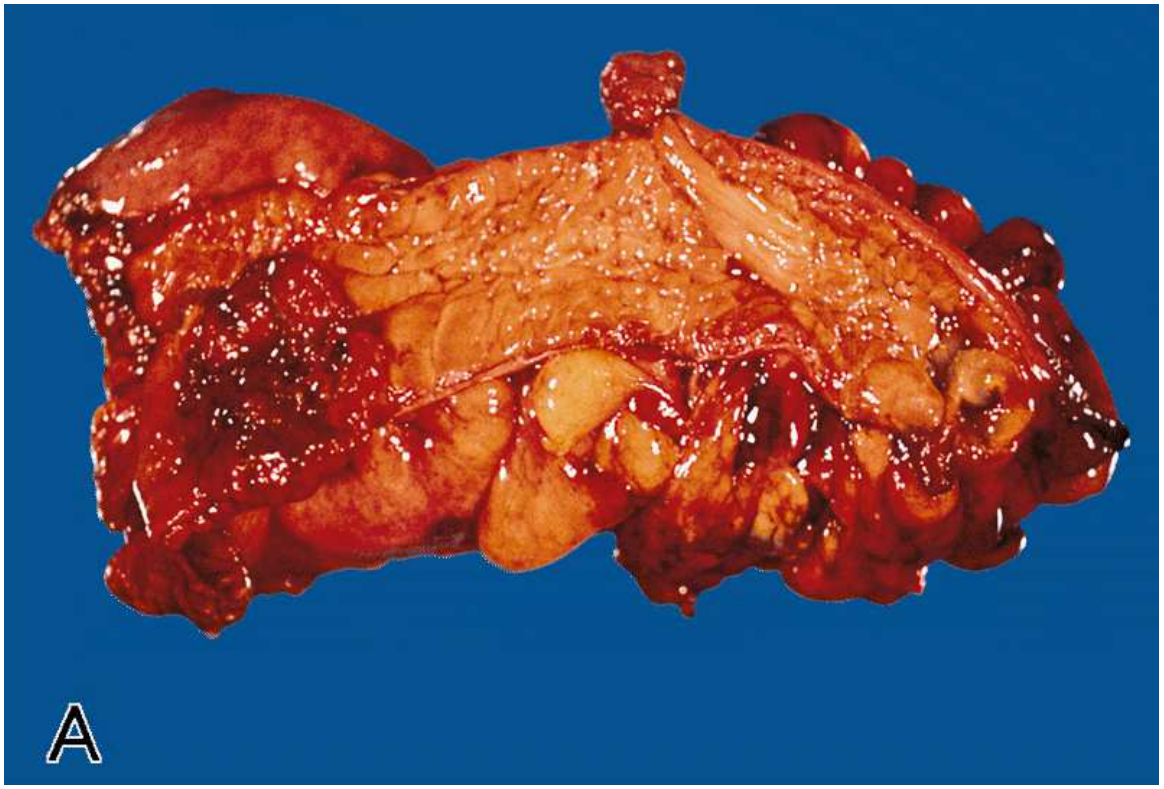
CTC, Computed tomography colonography.


Stenosing cancer
Polyp (right colon)
Vascular engorgement
Cancer
Enlarged lymph nodes
Cancer
Pulmonary nodule

Adenocarcinoma

- When the rare multiple carcinomas are present, they are often at widely disparate sites in the colon.
- 1% to 3% of colorectal carcinomas occur in patients with familial syndromes or inflammatory bowel disease.
- 98% of all cancers in the large intestine are adenocarcinomas.
- Carcinomas arising in the anorectal canal constitute a distinct subgroup of tumors, dominated by squamous cell carcinoma.

Adenocarcinoma of the large intestine

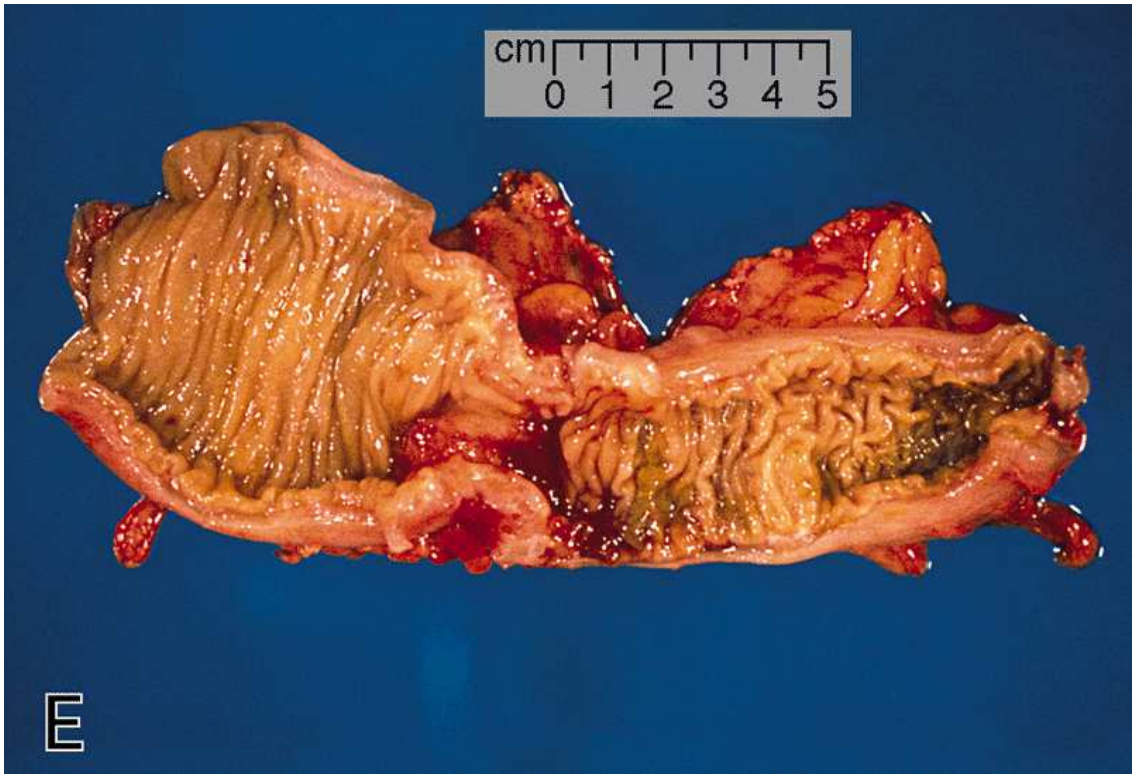


Typical tumor with central depression and raised, rolled, everted edges.

Fig. 3-45A

Riddell, RH, Petras, RE, Williams, GT, Sobin, LH., "Tumors of the intestines." Atlas of Tumor Pathology, Third Series, Fascicle 32. Armed Forces Institute of Pathology, Washington, D.C. 2003.

Adenocarcinoma of the large intestine



Annular stenosing carcinoma of sigmoid colon associated with diverticular disease.

Fig. 3-45E

Riddell, RH, Petras, RE, Williams, GT, Sobin, LH., "Tumors of the intestines." Atlas of Tumor Pathology, Third Series, Fascicle 32. Armed Forces Institute of Pathology, Washington, D.C. 2003.

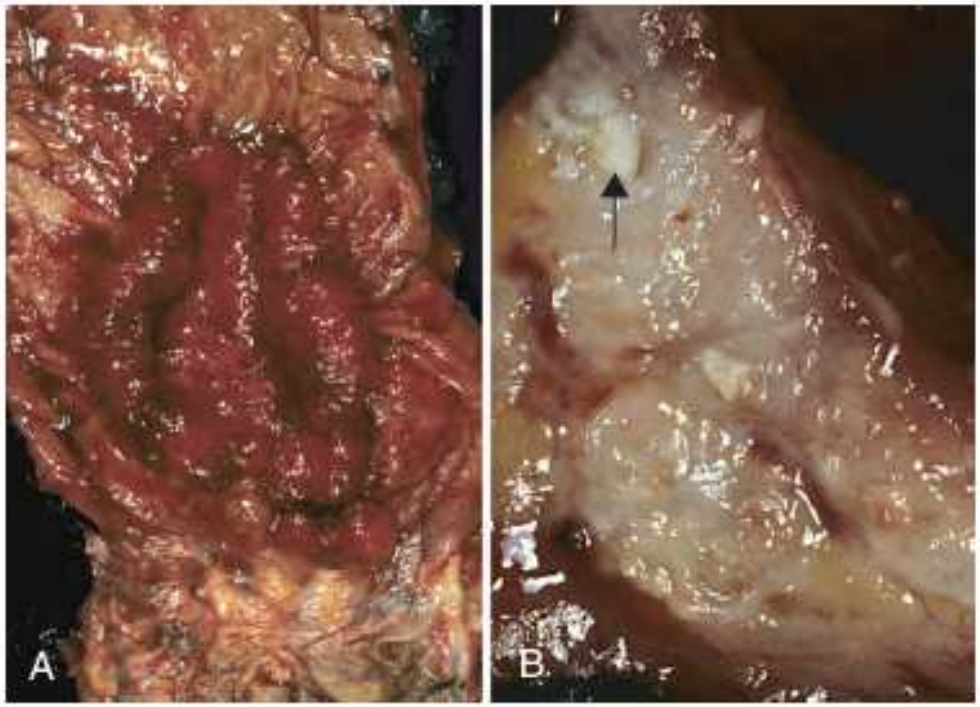


Figure 17-51 Colorectal carcinoma. **A,** Circumferential, ulcerated rectal cancer. Note the anal mucosa at the bottom of the image. **B,** Cancer of the sigmoid colon that has invaded through the muscularis propria and is present within subserosal adipose tissue (left). Areas of chalky necrosis are present within the colon wall *(arrow)*.

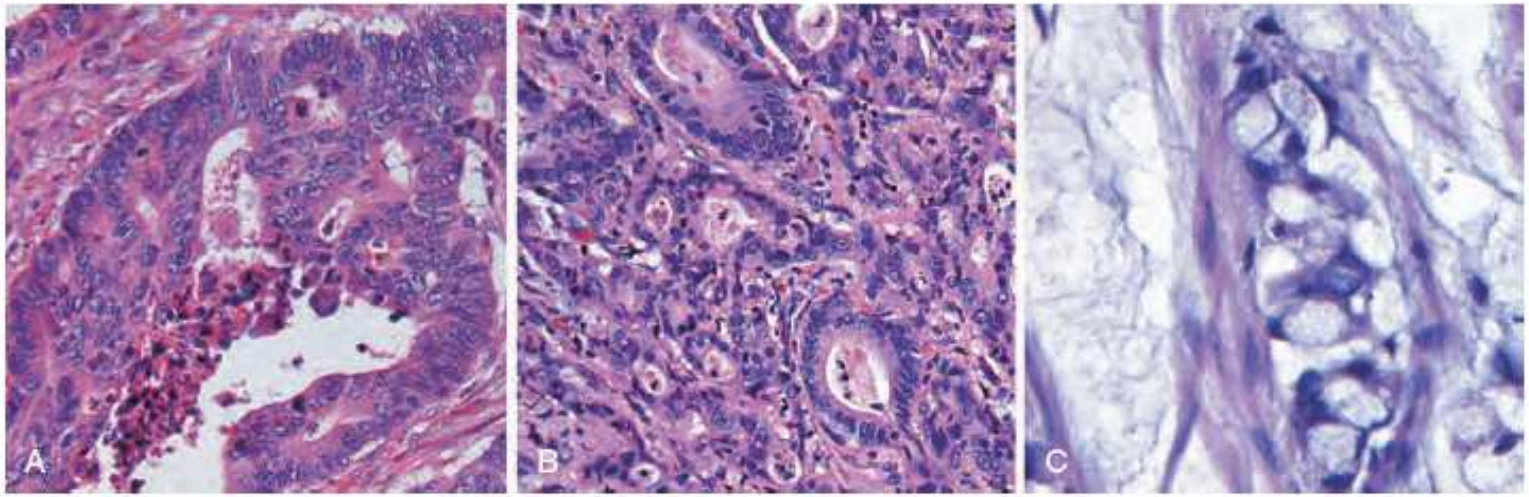
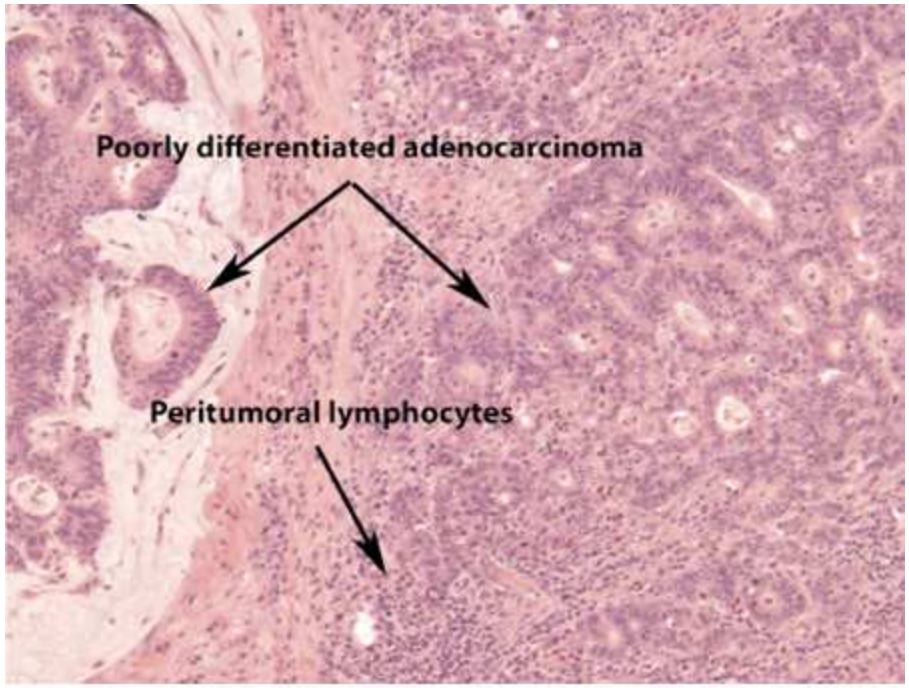


Figure 17-52 Histologic appearance of colorectal carcinoma. **A,** Well-differentiated adenocarcinoma. Note the elongated, hyperchromatic nuclei. Necrotic debris, present in the gland lumen, is typical. **B,** Poorly differentiated adenocarcinoma forms a few glands but is largely composed of infiltrating nests of tumor cells. **C,** Mucinous adenocarcinoma with signet-ring cells and extracellular mucin pools.

Adenocarcinoma of the large intestine



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Photomicrograph of a tumor with microsatellite instability. Upper arrows point to poorly differentiated malignant cells with some glandular differentiation and mucin. Lower arrow shows peritumoral lymphocytes clustering near areas of malignant cells and permeating the local stroma.

Fig. 16-1 Accessed 03/01/2010

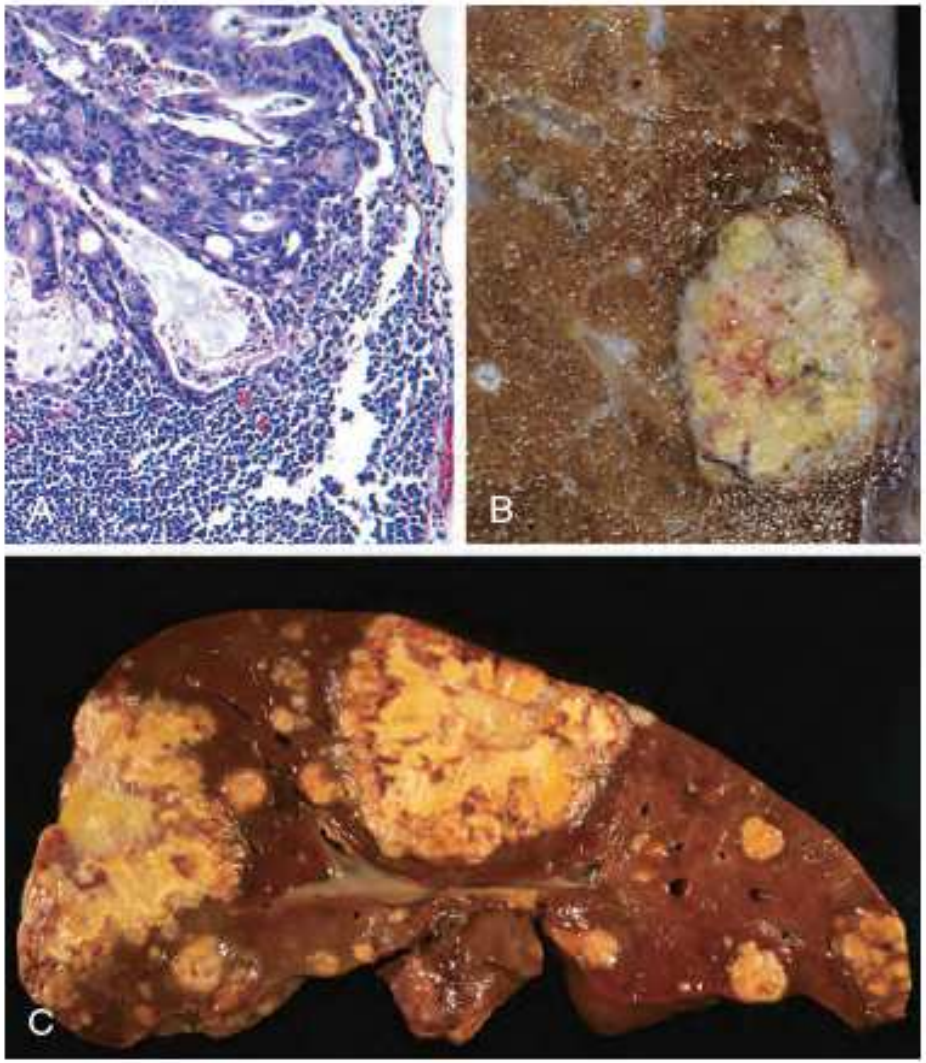


Figure 17-53 Metastatic colorectal carcinoma. **A,** Lymph node metastasis. Note the glandular structures within the subcapsular sinus. **B,** Solitary subpleural nodule of colorectal carcinoma metastatic to the lung. **C,** Liver containing two large and many smaller metastases. Note the central necrosis within metastases.

Table 17-12 American Joint Committee on Cancer (AJCC) TNM Classification of Colorectal Carcinoma

TNM	
Tumor	
Tis	In situ dysplasia or intramucosal carcinoma
T1	Tumor invades submucosa
T2	Tumor invades into, but not through, muscularis propria
T3	Tumor invades through muscularis propria
T3a	Invasion < 0.1 cm beyond muscularis propria
T3b	Invasion 0.1 to 0.5 cm beyond muscularis propria
T3c	Invasion > 0.5 to 1.5 cm beyond muscularis propria
T3d	Invasion > 1.5 cm beyond muscularis propria
T4	Tumor penetrates visceral peritoneum or invades adjacent organs
T4a	Penetration into visceral peritoneum
T4b	Invasion into other organs or structures
Regional Lymph Nodes	
NX	Lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N1a	Metastasis in one regional lymph nodes
N1b	Metastasis in two or three regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in four or more regional lymph nodes
N2a	Metastasis in four to six regional lymph nodes
N2b	Metastasis in seven or more regional lymph nodes
Distant Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site
M1b	Metastases in more than one organ/site or the peritoneum

Table 17-13 Colorectal Cancer Staging Systems

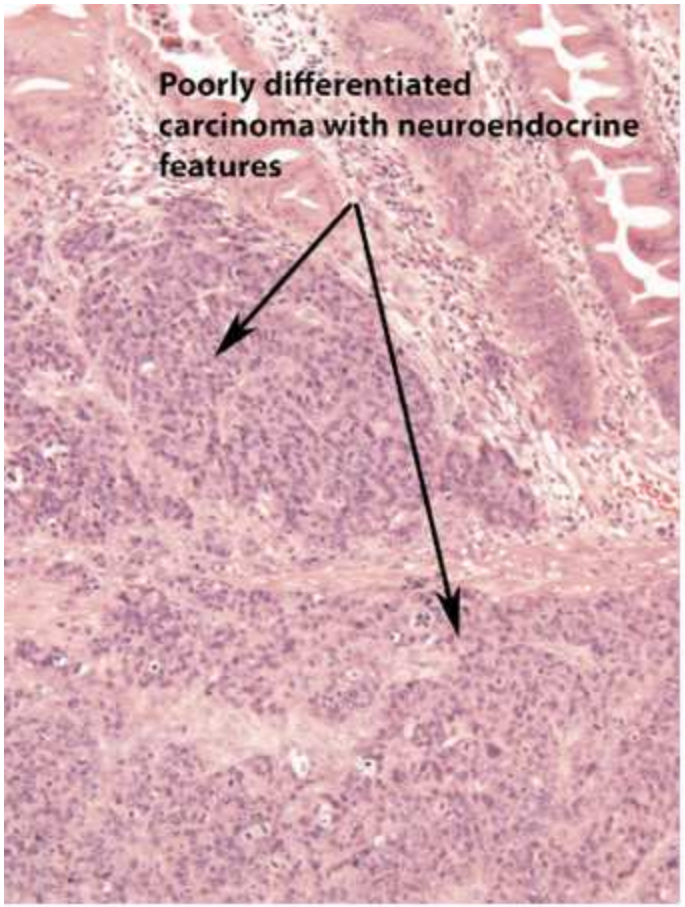
American Joint Committee on Cancer (AJCC) Stage				Astler-Coller Modification of Dukes Classification
	T	N	M	
I	T1	N0	M0	A
	T2	N0	M0	B1
IIA	T3	N0	M0	B2
IIB	T4a	N0	M0	B2
IIC	T4b	N0	M0	B3
IIIA	T1-T2	N1/N1c	M0	C1
	T1	N2a	M0	C1
IIIB	T3, T4a	N1 (any)	M0	C2
	T2, T3	N2a	M0	C1/C2
	T1, T2	N2b	M0	C1
IIIC	T4a	N2a	M0	C2
	T3, T4a	N2b	M0	C2
	T4b	N1, N2	M0	C3
IVA	Any T	Any N	M1a	D*
IVB	Any T	Any N	M1b	D*

*Stages not included in original Dukes classification; added later for comparison with AJCC staging.

Adenocarcinoma

- Foci of endocrine differentiation may be found in about 10% of colorectal carcinomas.
- The small-cell undifferentiated carcinoma appears to arise from endocrine cells per se and elaborates a variety of bioactive secretory products.
- In some cancers the cells take on a signet-ring appearance.
- Some cancers, particularly in the distal colon, have foci of squamous cell differentiation and are therefore referred to as adeno-squamous carcinomas.

Neuroendocrine change



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Photomicrograph of a poorly differentiated carcinoma of the colon with neuroendocrine features. Tumor appears in sheets of fairly monotonous cells without glandular or mucinous characteristics.

Fig. 16-2 Accessed 03/01/2010

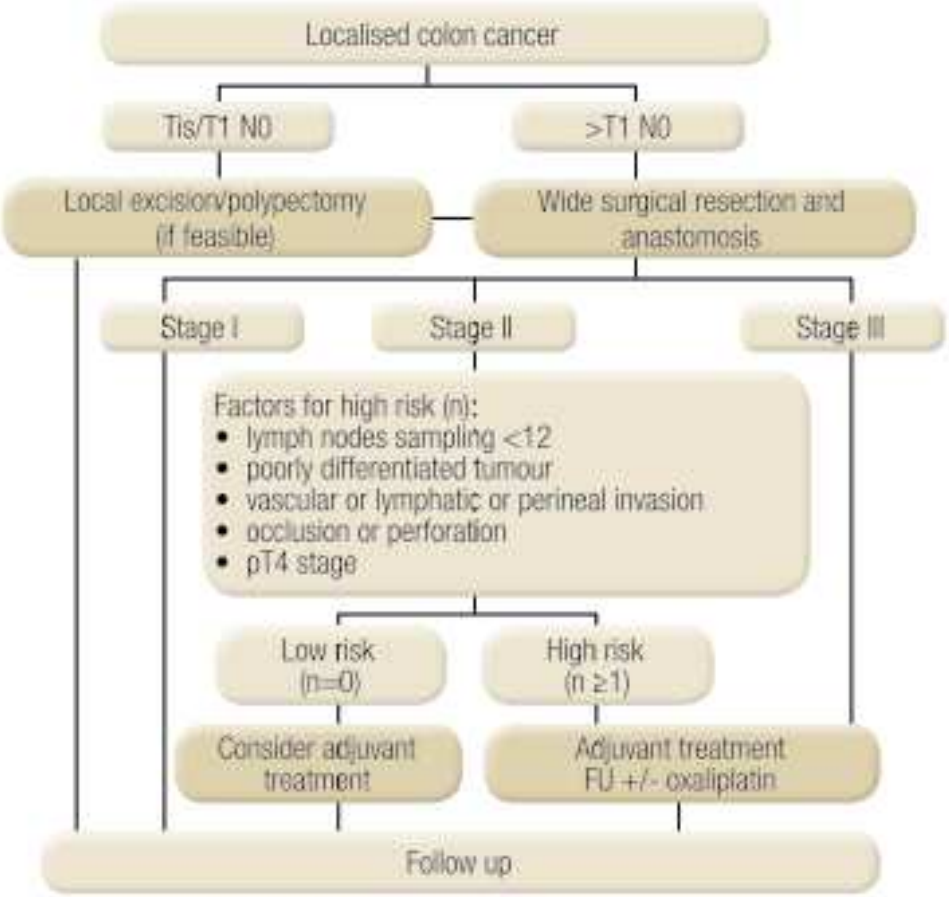
Adenocarcinoma of the large intestine

- Increased levels of NK and CD8+ cells in right sided lesions.
- Increase in Homeobox transcription factor 1 in right sided lesions
- Increased number of mutations in right sided lesions
- Increase in Homeobox transcription factor 2 in left sided lesions

Adenocarcinoma of the large intestine

- p53 and EFGR over-expression more common in left sided lesions (favorable sign).
- Those with left sided lesions with DNA mismatch repair mutations have better prognosis than those with right sided lesions and the same mutations in Stage II or III disease.
- RAS and BRAF mutations are associated with adverse outcome.

Treatment algorithm for early colon cancer



FU, Fluorouracil; N, node; T, tumour; Tis, carcinoma in situ.

Treatment strategy

- En block extirpation of the involved bowel segment along with mesentery as well as pericolic and intermediate lymphadenectomy is primary modality.
- No colostomy required.
- 5FU by infusion, oxaliplatin, and leucovorin (FOLFOX) is recommended adjuvant regimen following resection of stage III disease (colon).
- CAPOX (capecitabine with oxaliplatin) as alternative
- Survival advantage for those <70 years of age

Treatment strategy

- FOLFOX preferred if RAS mutation and no multisatellite mutations.
- PD1 inhibitor preferred over chemotherapy if mismatch gene mutations
- 5FU plus panitumumab in ROS mutated, wild type BRAF disease
- Capecitabine maintenance therapy associated with better progression free survival
- Left primary with PI3K mutation, no PTEN loss, no EFGR inhibitor did best

Treatment strategy

- Patients with loss of MMR (mismatch repair genes) do not benefit from 5FU.
- Benefit from check point inhibitors
- KRAS wild type lesion may respond to cetuximab (anti- EGFR).
- KRAS codon mutations 12 (40%), 13 (20%), or both (20%) associated with poor response to cetuximab.
- BRAF mutation testing if KRAS wt.
- Right sided EGFR+, KRAS- lesions respond to bevacizumab but not cetuximab
- Left sided EGFR+, KRAS- lesions respond to cetuximab as well as bevacizumab

Treatment strategy

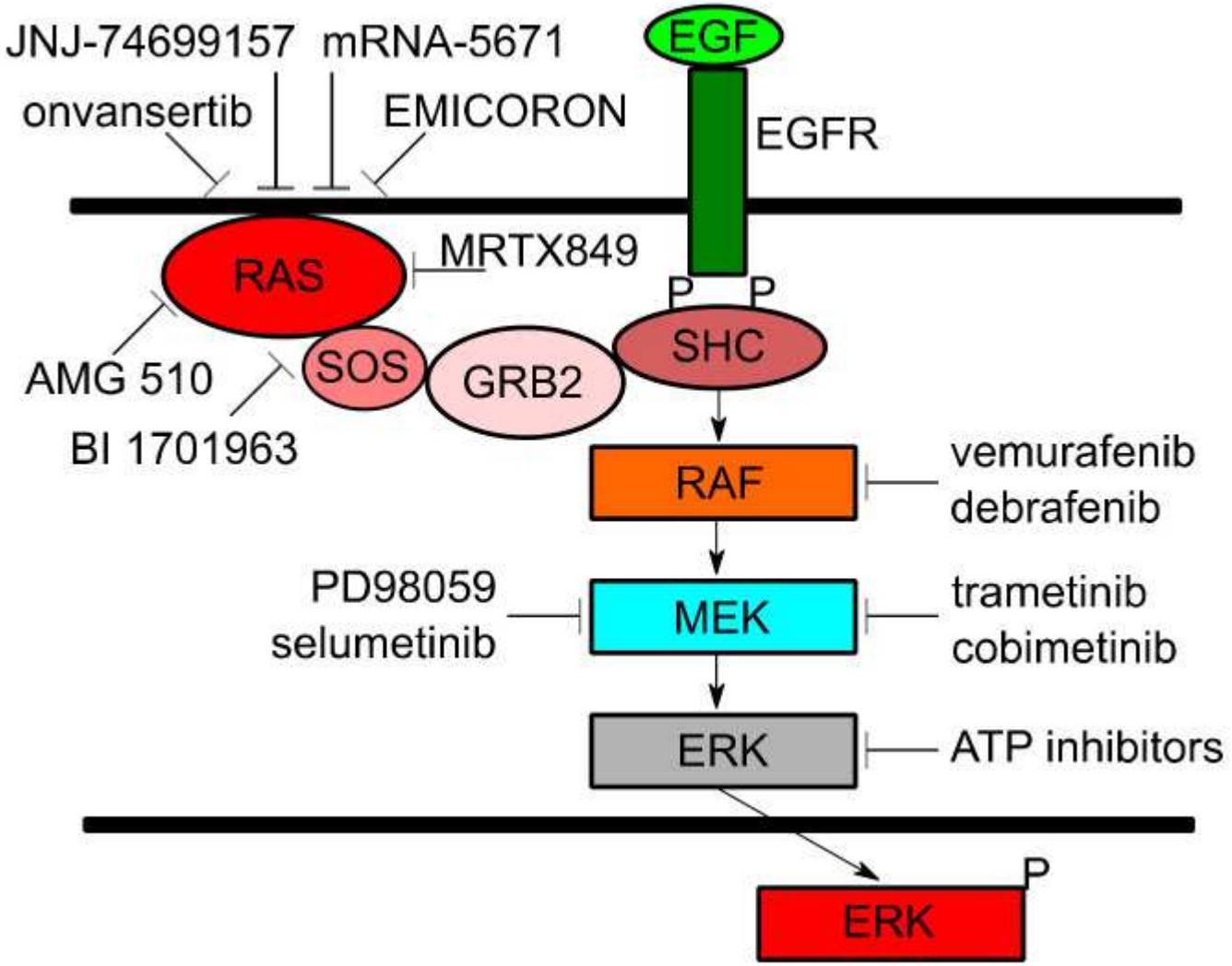
- RAS wild type lesion may respond to cetuximab (anti-EGFR).
- If HER2+, tratuzumab with tucatinib as option
- KRAS codon mutations 12 (40%), 13 (20%), or both (20%) associated with poor response to cetuximab.
- KRAS G12C mutation associated with poor response to fluropyrimidines
- Common in tobacco use
- Sotorasib (AMG 510) binds to cysteine residue, holding protein in inactive form
- If fail first line therapy

Treatment strategy

- Encrafenib and cetuximab if BRAF and Notch mutations is another alternative
- Hypomagnesemia surrogate marker for cetuximab success.

Treatment strategy

- Asymptomatic primary lesions with (synchronous) metastases may not require resection but solely treatment with chemotherapy (FOLFOX) and bevacizumab, an anti-VEGF agent
- Bleeding common.
- Better response if hypertension ensues.
- Median survival is 2 years.

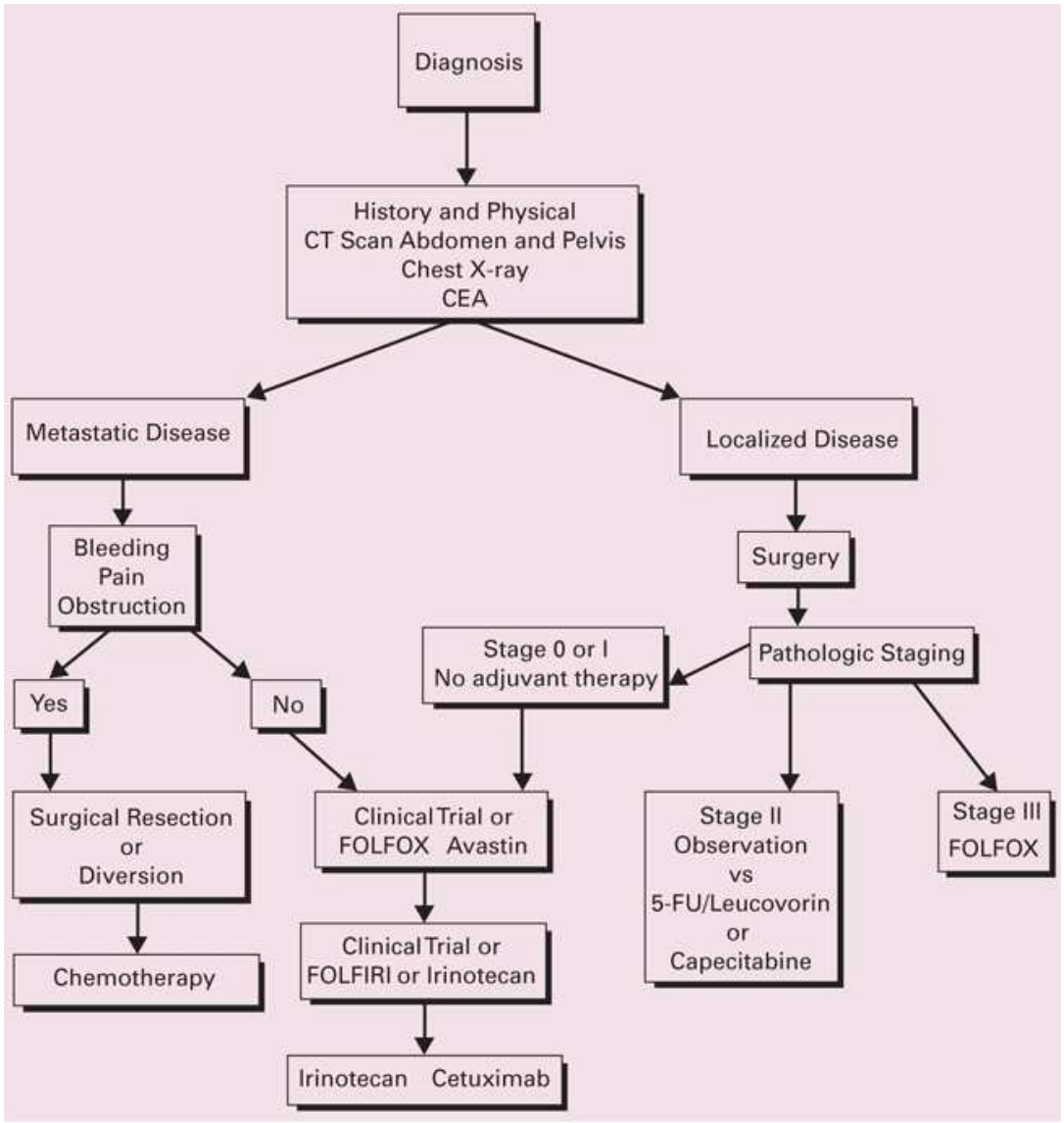


Mustachio LM, Chelariu-Raicu A, Szekvolgyi L, Roszik J. Targeting KRAS in Cancer: Promising Therapeutic Strategies. Cancers (Basel). 2021;13(6):1204. Fig. 1 Published 2021 Mar 10. doi:10.3390/cancers13061204

Treatment strategy

- >20% of patients have metastases confined to the liver
- Resection, ablation, and embolization of feeding blood vessels as effective means of local control if metachronous metastases (develop sequentially)
- Isolated pulmonary or peritoneal metastases may be resected
- >40% of patients will survive 5 years

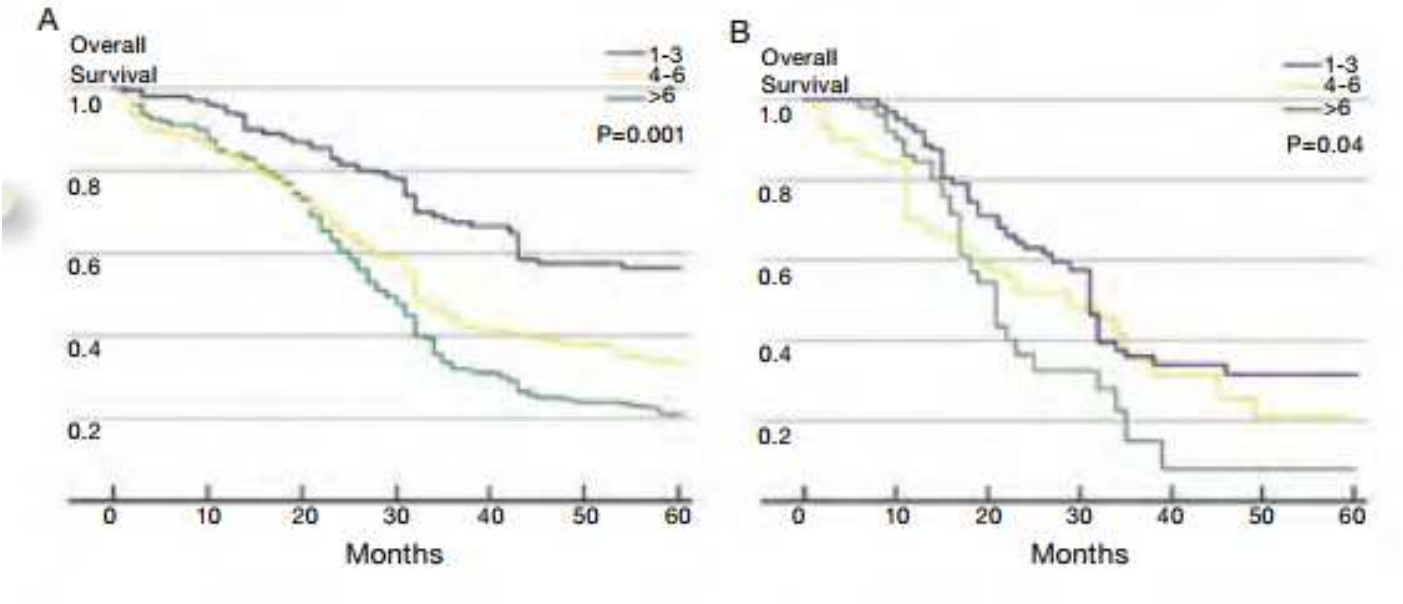
Colon cancer



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Fig. 16-4 Accessed 04/01/2010

A: Overall survival among patients with isolated colorectal liver metastases (CLM) stratified by the number of resected metastases. B: Overall survival among patients with CLM + extrahepatic disease stratified by the number of resected metastases



Evaluating anti-EGFR therapy

- IHC staining for HER2 (3+)
- >5 positive cells adjacent to each other in biopsy
- >10% positive cells in resected specimen
- In breast, circumferential staining
- In gastric cancer, basolateral or parallel staining
- >50% cells 3+ staining
- FISH (if IHC 2+ staining)
- HER2/CEP >2.2
- If in 50% of metastatic colorectal cancer

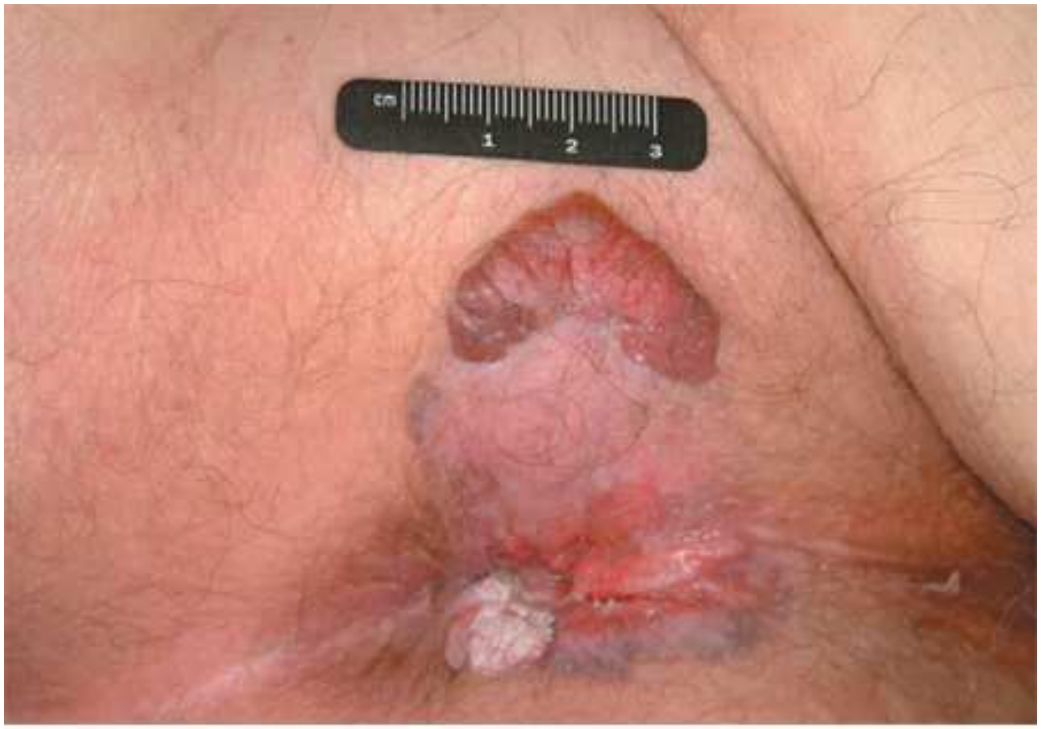
Evaluating anti-EGFR therapy

- If 2+ staining:
- First line therapy if not candidate for standard therapy in those with left sided colon lesion with KRAS exon 2 and ROS/RAF wild type
- If 3+ staining:
- Resistant to cetuximab in colorectal cancer
- Resistant to trastuzuman in gastroesophageal cancer
- Resistance to TKIs

Treatment strategy

- Asymptomatic primary lesions with metastases may not require resection but solely treatment with chemotherapy (FOLFOX) and bevacizumab, an anti-VEGF agent
- Bleeding common
- Better response if hypertension ensues
- Median survival is 2 years.
- Hypomagnesemia surrogate marker for cetuximab success.

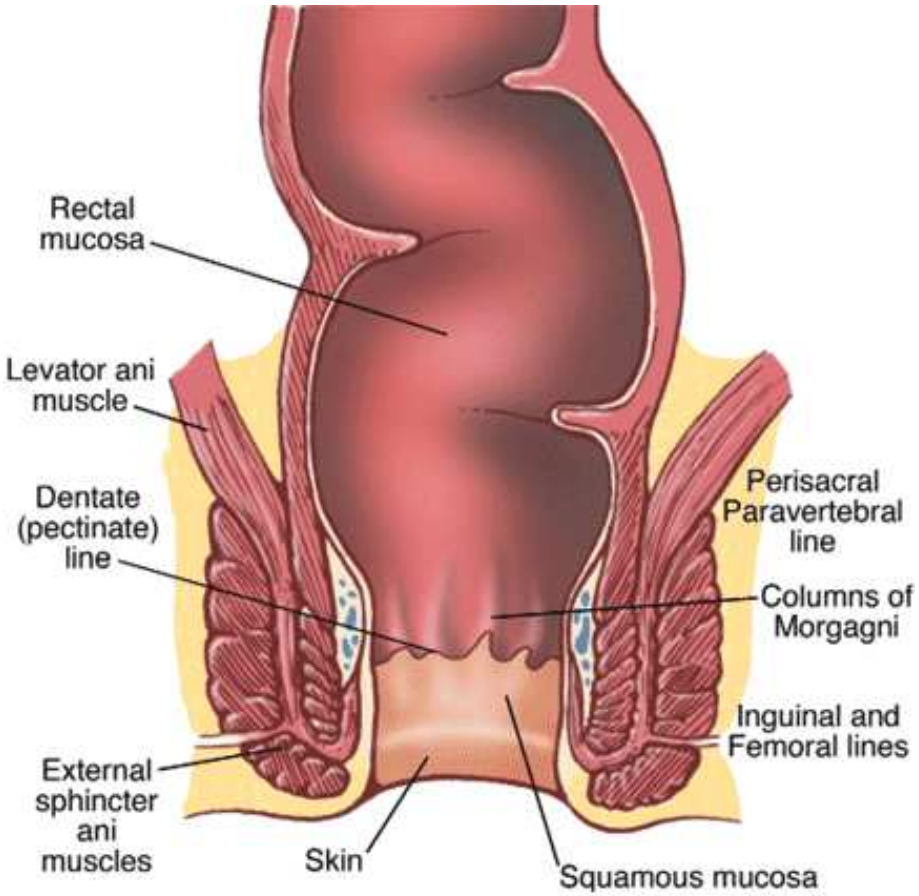
Perianal mass



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Fig.17-6 Accessed 04/01/2010

Ano-rectal junction



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Fig. 17-1 Accessed 04/01/2010

Rectal carcinoma

- 4% of lower intestinal tract cancers.
- HPV infection often precedes.
- >50 years of age
- Bleeding and pain are most common symptoms.
- May be obstructing mass.
- Pruritis more commonly noted with perianal lesions
- Squamous carcinoma and basaloid (cloacogenic) carcinomas comprise more than 85% of tumors.
- Melanoma accounts for 4%.

Rectal carcinoma

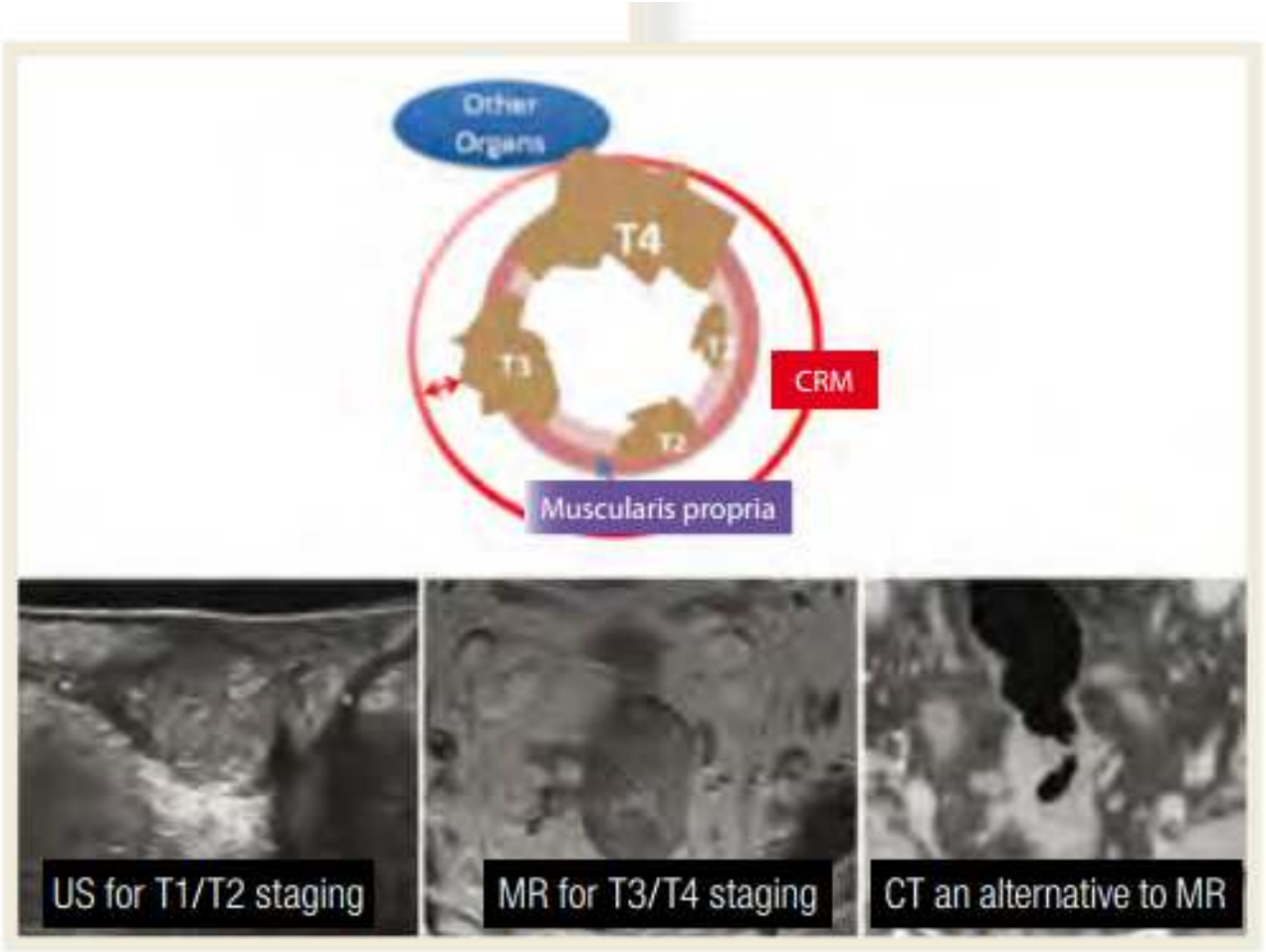
- Risk factors include:
- Low fiber diet
- Obesity
- Smoking
- Alcohol
- Adenomatous polyps
- Inflammatory bowel disease

Rectal carcinoma

- Diagnosis of rectal cancer is based on digital rectal examination and proctoscopy with biopsy.
- Tumors with distal extension ≤15 cm from the anal margin are classified as rectal.
- EUS is able to differentiate T1 and T2 tumors, selecting patients for local excision.
- Limited in stenotic tumors or those located in the upper third of the rectum.

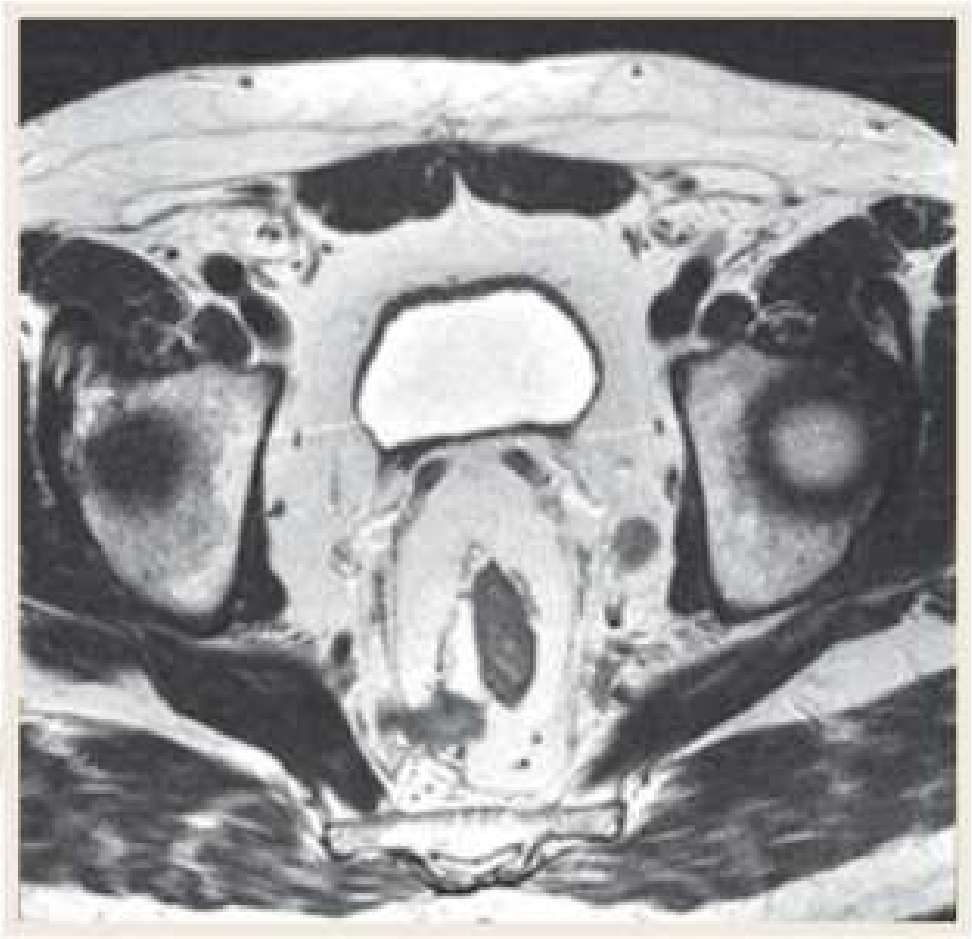
Rectal carcinoma

- MRI is the recommended technique for staging invasive cancer (≥T3).
- Magnetic resonance imaging (MRI) is best for determining involvement of the mesorectal fascia (MRF).
- May define peritoneal involvement, extramural spread >5 mm, extramural venous invasion and invasion of adjacent structures.
- It has lower sensitivity for or mesorectal/ extra-mesorectal nodal involvement
- Local staging with CT can be an alternative to MRI in advanced tumors located in the mid-high rectum.

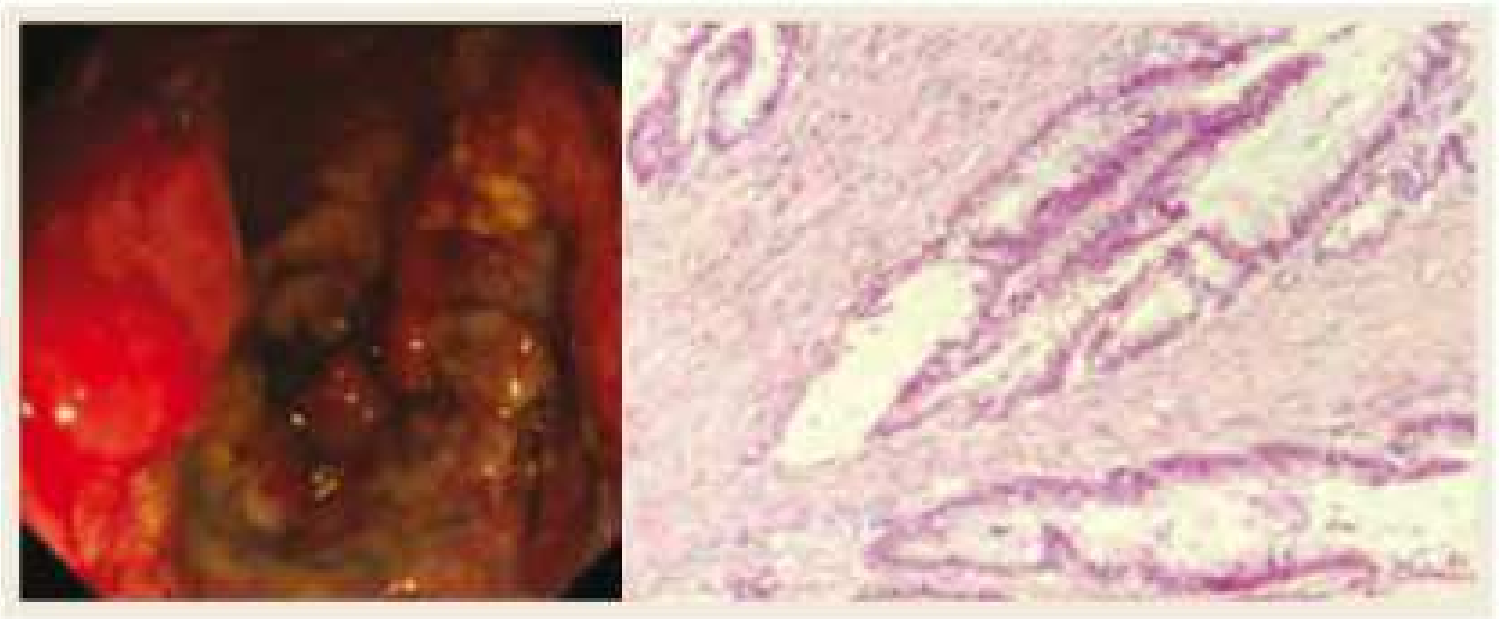


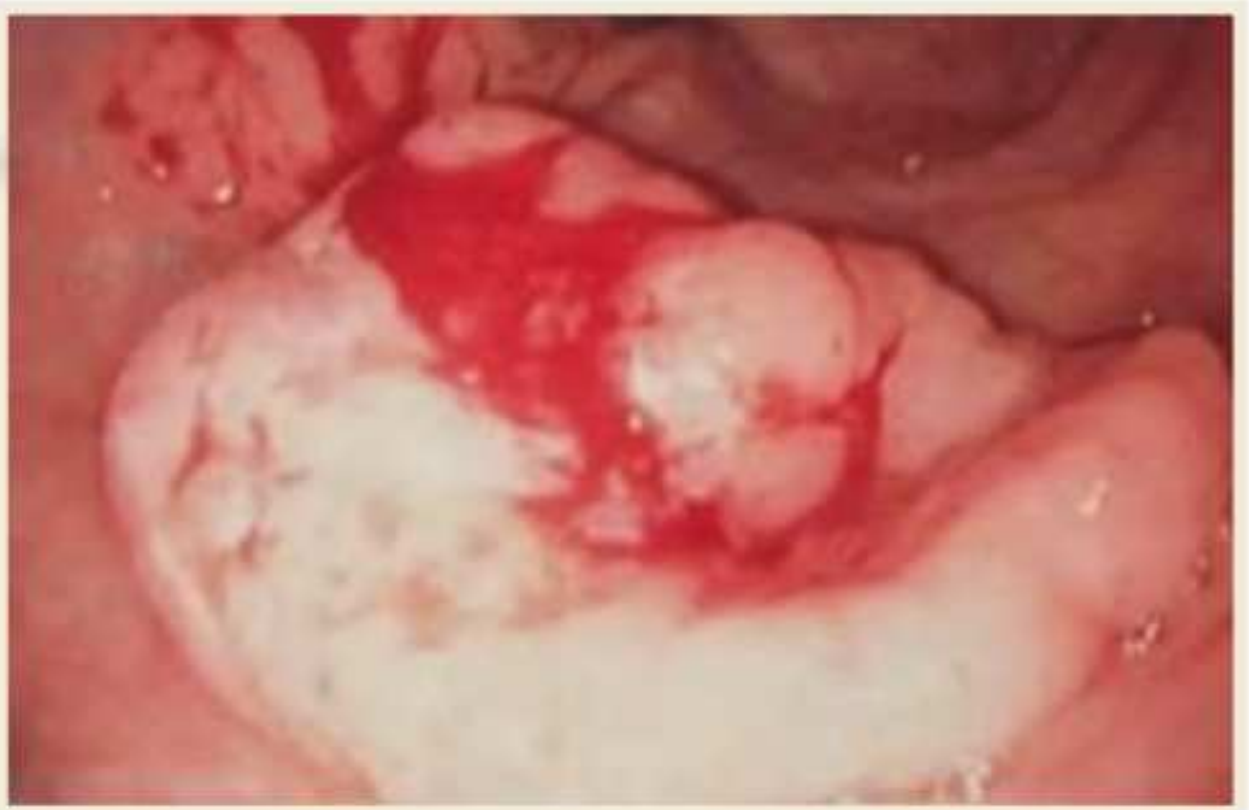
CRM, Circumferential resection margins; CT, computed tomography; MR, magnetic resonance; US, ultrasound.

Pelvic MRI of a rectal cancer with mesorectal fascia invasion and extramesorectal lymph nodes

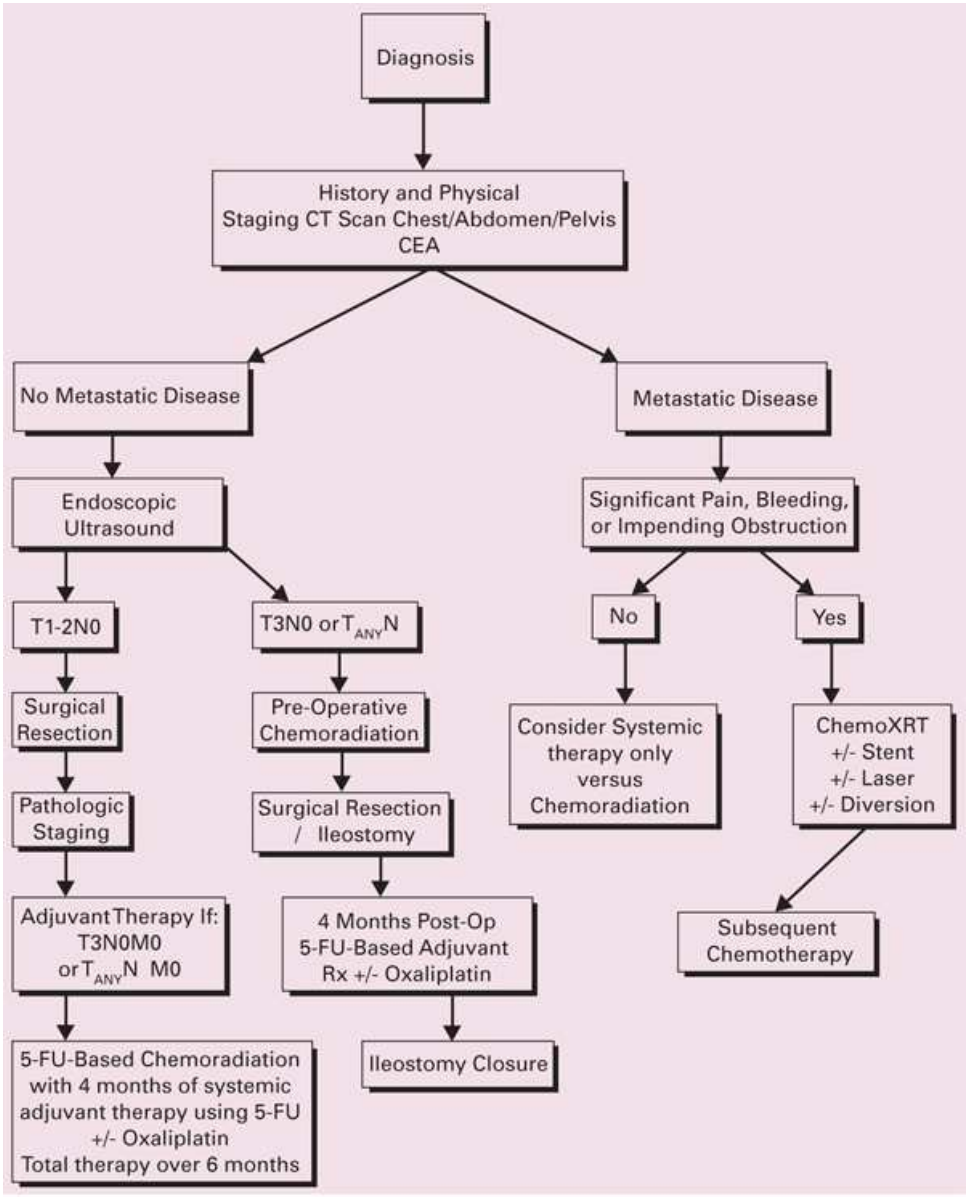


Endoscopy and biopsy of rectal cancer





Rectal cancer



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Fig. 16-5 Accessed 04/01/2010

Risk-based groups in localised rectal cancer: Locally agreed treatment policy for rectal cancer within the MDT		
Treatment group	**MRI features**	**Treatment strategy**
1	T1-T2/T3 <5 mm, N0/N1, predicted CRM -ve	Surgery alone (TME)
2	T3 ≥5 mm/T4, N2, predicted CRM -ve	Preoperative CRT
3	Predicted CRM +ve	Preoperative CRT

CRM, Circumferential resection margin; CRT, chemoradiotherapy; MDT, multidisciplinary team; MRI, magnetic resonance imaging.

Treatment strategy

- Localized, with no risk factors:
- Surgery alone.
- Early tumors with no adverse pathological factors:
- Local therapy such as mucosectomy or transanal endoscopic microsurgery (TEM).
- If muscular layer is involved by tumor (T2)
- The risk of positive lymph nodes is 15%–20%
- Local excision alone is inappropriate.

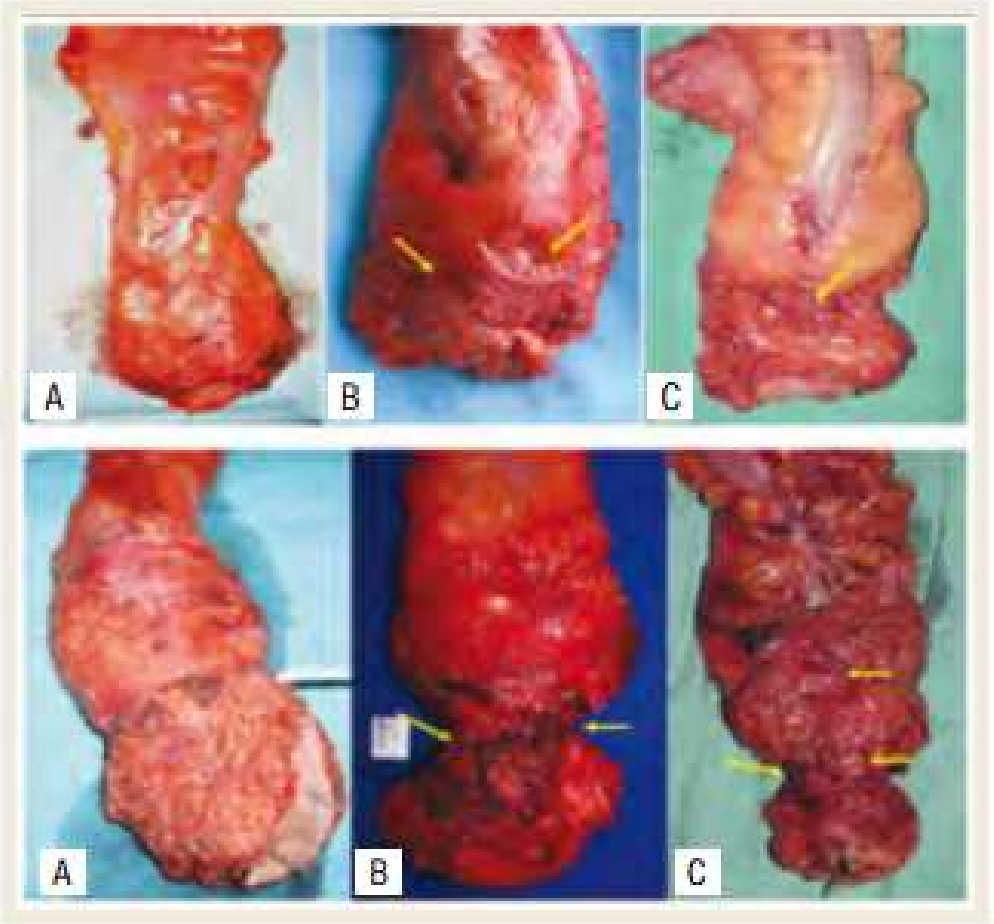
Treatment strategy

- Middle and lower third rectal cancers:
- Complete excision of visceral mesorectal tissue to the level of the levators (TME, total mesorectal excision)
- If lower third, TME with abdominal perineal resection following mesorectal fascia to sphincters
- Dissection from below, outside sphincter plane, may avoid perforation as well as circumferential margin involvement (and, later, “coning” or narrowing of the bowel lumen)

Treatment strategy

- Intermediate stage but resectable lesions may benefit from preoperative radiation.
- Unresectable disease
- Radiation with concomitant 5FU or capecetabine therapy may downstage lesion to permit an RO resection
- Addition of oxaliplatin is toxic
- Concomitant presentation of local disease and metastases limited to liver or lungs
- If local symptoms are prominent, radiotherapy may downstage to permit RO resection
- Else, chemotherapy

Surgical specimens of total mesorectal excision, anterior resection or abdominoperineal amputation according to the surgical planes: mesorectal (A), intramesorectal (B) and muscularis propria (C).



Treatment strategy

- 10-18% failure rate after curative resection (TME) for rectal cancer.
- MRI crucial in determining depth of invasion (>5mm has poor prognosis).
- Adjuvant chemotherapy with radiation therapy recommended for stage II and III disease.
- Avoid chemotherapy free intervals in metastatic disease.
- Daily low-dose aspirin (but not a COX-2 inhibitor) associated with improved survival in those with PIK3CA mutations and tumor expression of HLA I antigens.

Stage	5-year Survival Rate
I (T1N0)	71%
II (T2-T3, N0)	64%
IIIA (T1-3, N1; T4N0)	48%
IIIB (T4N1; T1-4, N2-3)	43%
IV (metastases)	21%

ANAL CANAL CARCINOMA

Anal canal carcinoma

- Carcinomas of the anal canal may have typical glandular or squamous patterns of differentiation, recapitulating the normal epithelium of the upper and lower thirds, respectively.
- An additional differentiation pattern, termed basaloid, is present in tumors populated by Immature cells
- All are considered variants of anal canal carcinoma
- Pure squamous cell carcinoma is associated with HPV

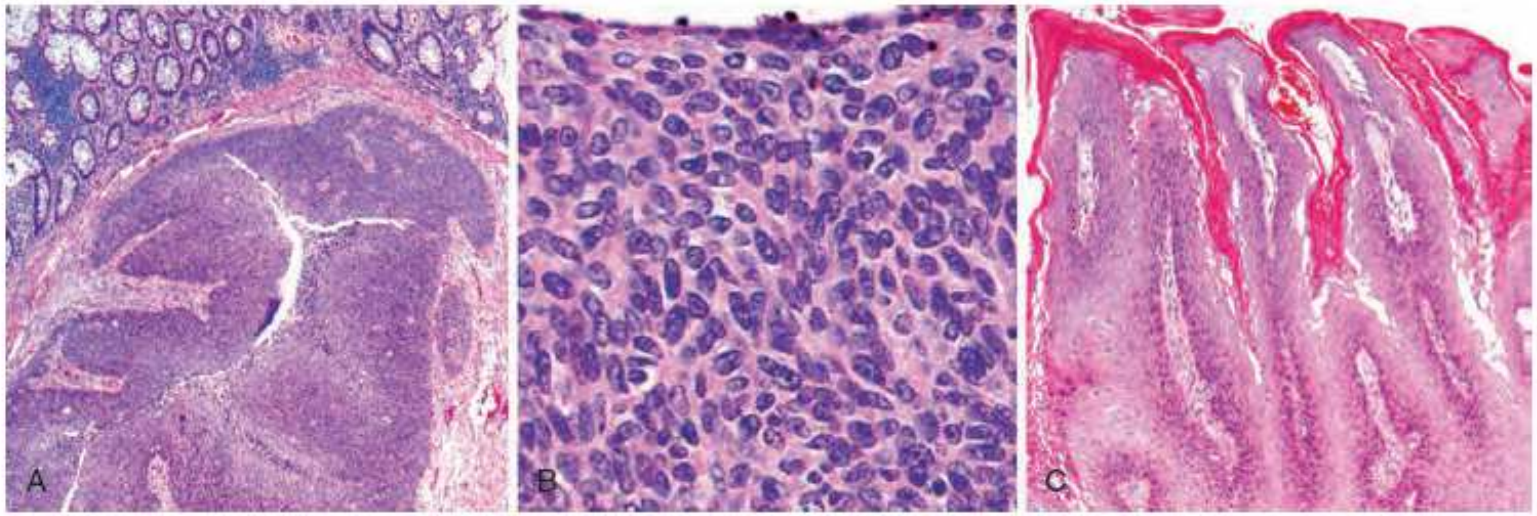


Figure 17-54 Anal tumors. **A,** This anal transition zone carcinoma demonstrates a multilayered organization reminiscent of benign squamous mucosa. The adjacent rectal mucosa is intact. **B,** This basaloid anal transition zone tumor is composed of hyperchromatic cells that resemble the basal layer of normal squamous mucosa. **C,** Condyloma acuminatum with verrucous architecture.

Non-keratinizing squamous carcinoma

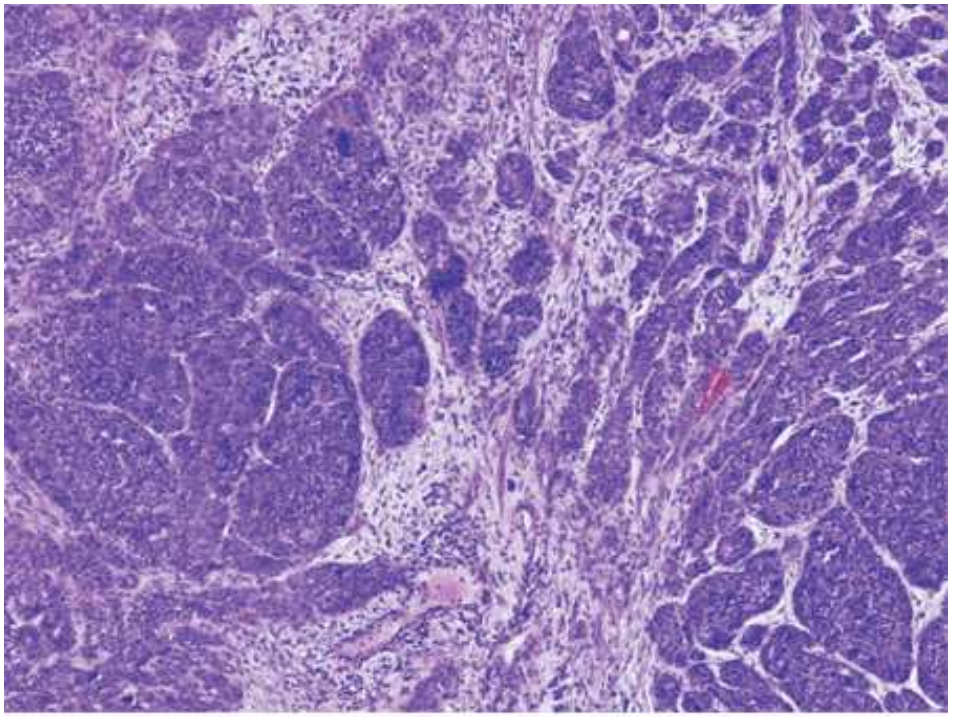


Fig. 17-2 Accessed 04/01/2010

Keratinizing squamous carcinoma

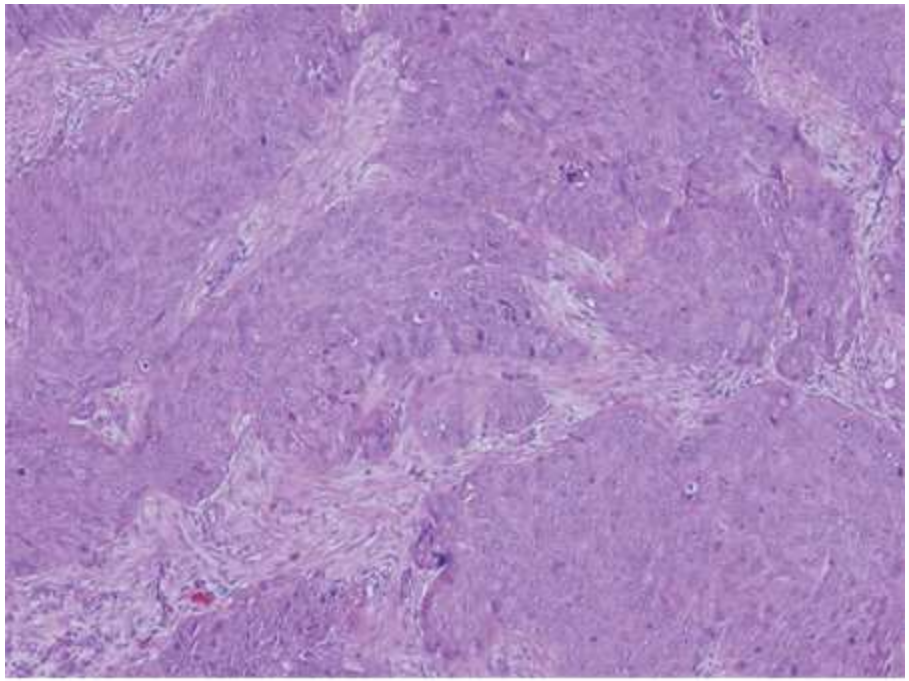
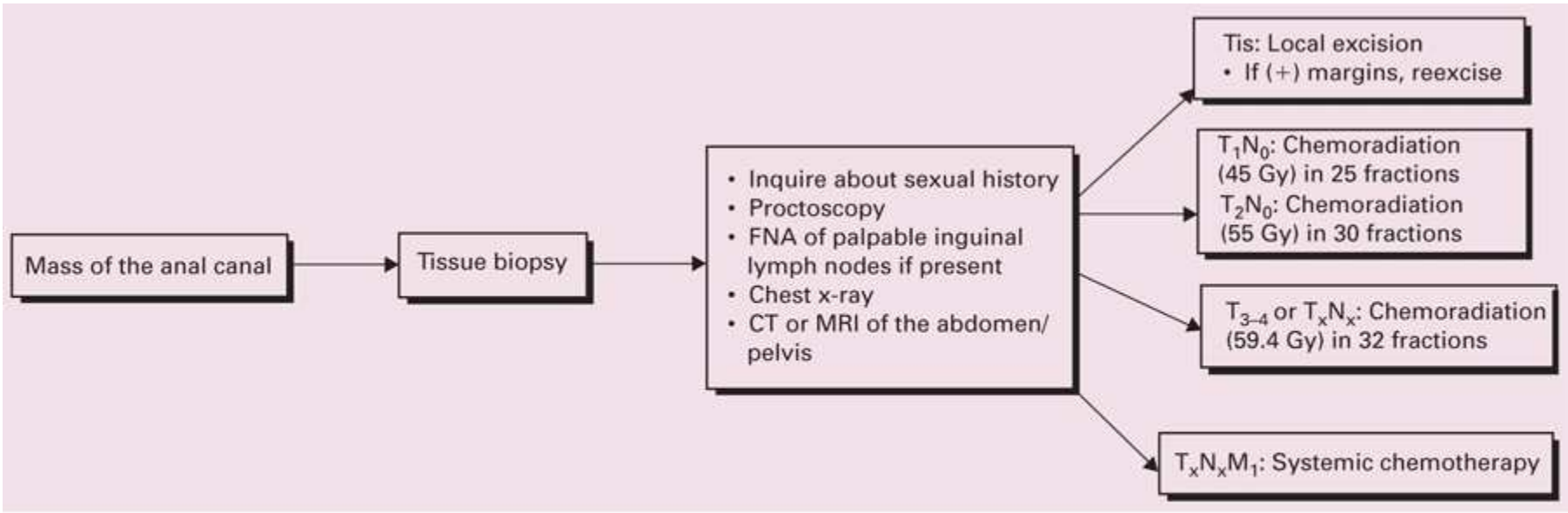


Fig. 17-4 Accessed 04/01/2010

Anal cancer



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Fig. 17-8 Accessed 04/01/2010

Treatment of anal carcinoma

- Incisional biopsy preferred for diagnosis.
- Cancers of the anal margin (area distal to the anal canal) can be treated with wide local excision without need for colostomy.
- Cancers of the anal canal are first treated with radiation therapy combined with 5FU and mitomycin C or cisplatin chemotherapy.
- If clinical examination post treatment demonstrates residual tumor, total mesorectal excision is performed as a salvage procedure.
- Anal function is preserved.
- No colostomy.

Treatment of anal carcinoma

- Inguinal lymph node metastases are poor prognostic sign.
- May require radiation boost.