CECIL Essentials of MEDICINE

GASTROINTESTINAL CANCERS

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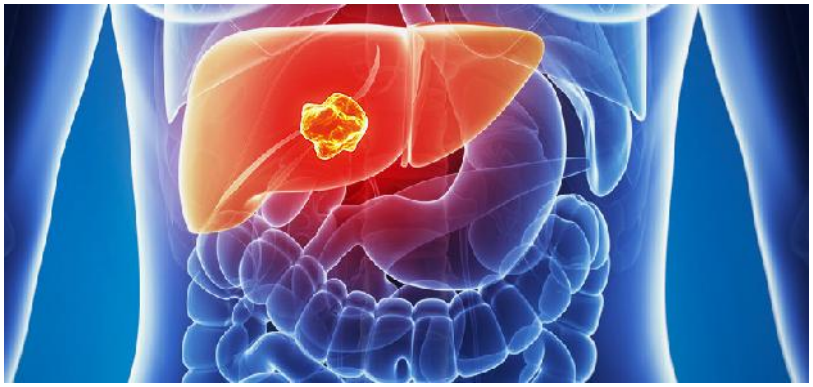
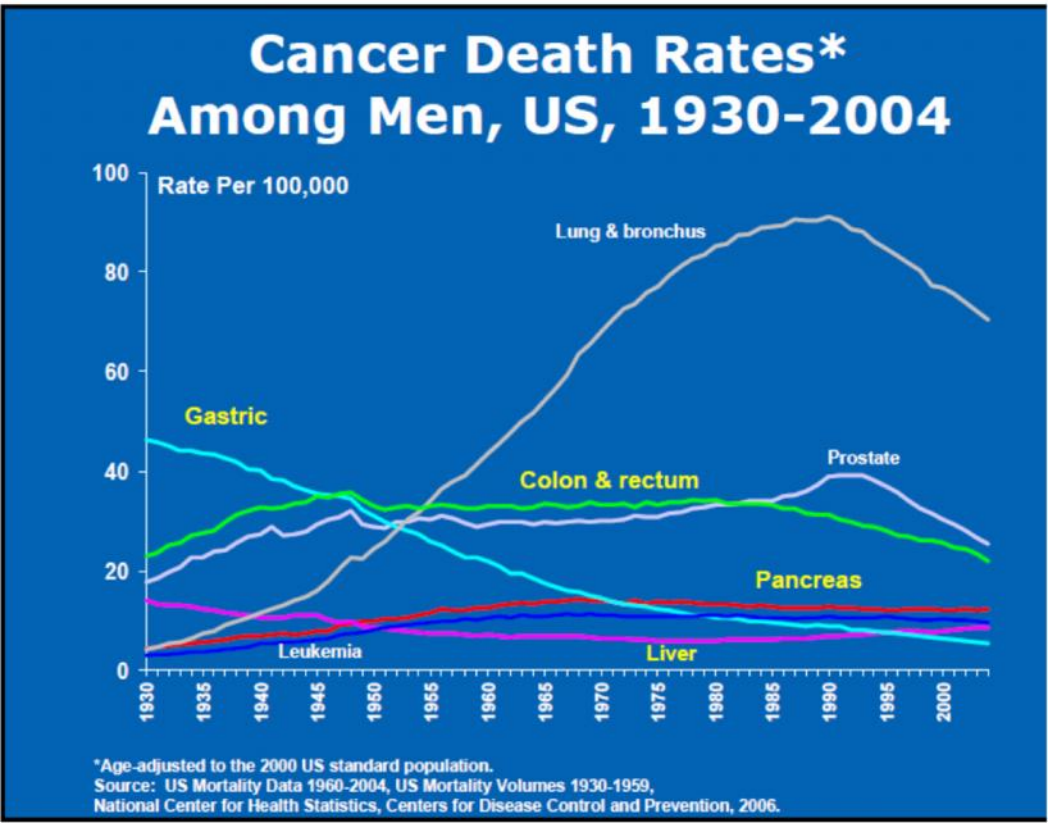
بسم الله الرحمن الرحیم



Burden of Gastrointestinal and Liver Diseases in Iran

- >**40**% of all cancer prevalence and mortality in Iran
- a major proportion of all deaths due to G.I & Liver Disease.
- Gastric cancer alone constitutes 20% of cancer mortality in Iran
- Gastrointestinal and liver malignancies along with chronic liver disease constitute the **main causes of hospitalization and deaths** in Iran


Cancer Death Rates*
Among Men, US, 1930-2004
Rate Per 100,000
100
80
60
40
20
0
Lung & bronchus
Gastric
Colon & rectum
Prostate
Pancreas
Leukemia
Liver
1930
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2004, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention, 2006.

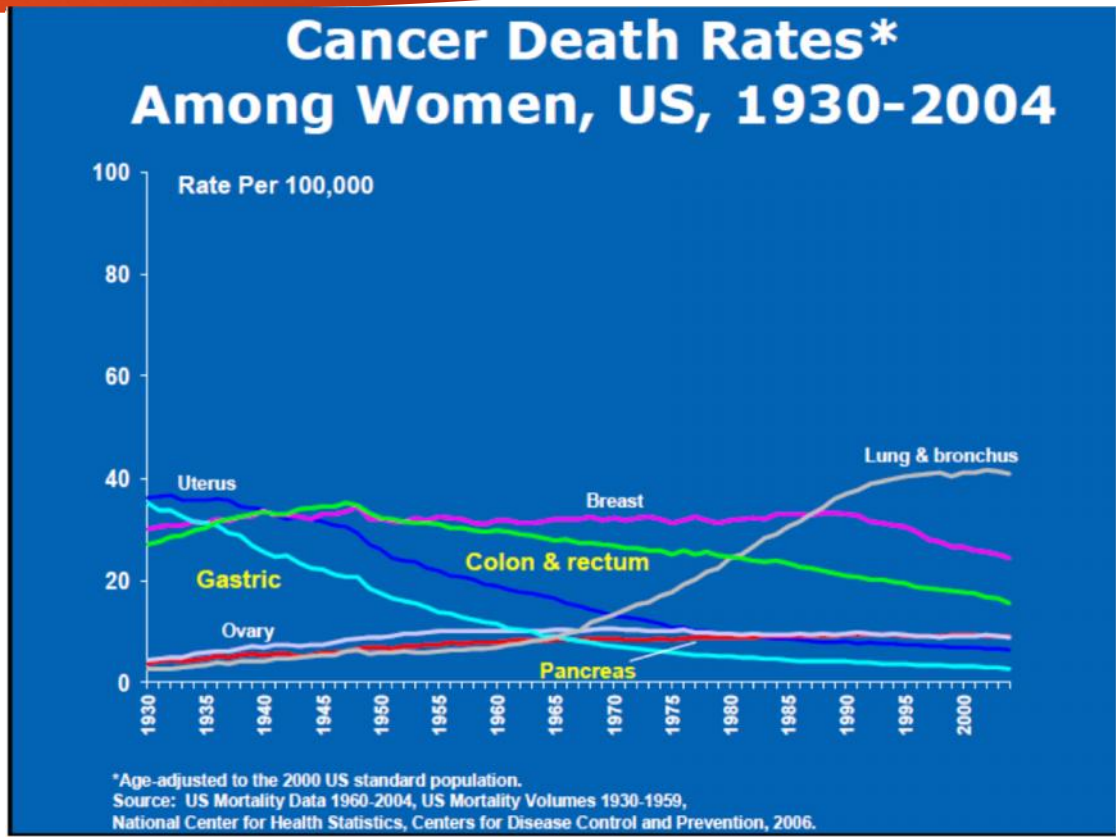
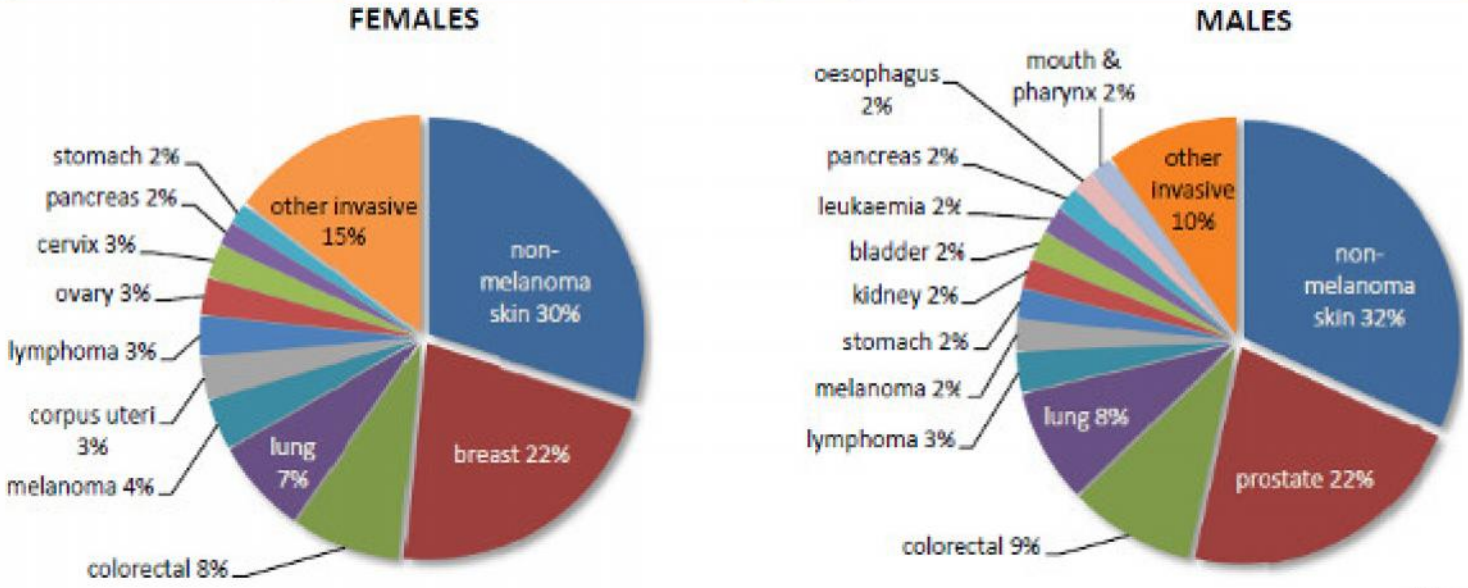
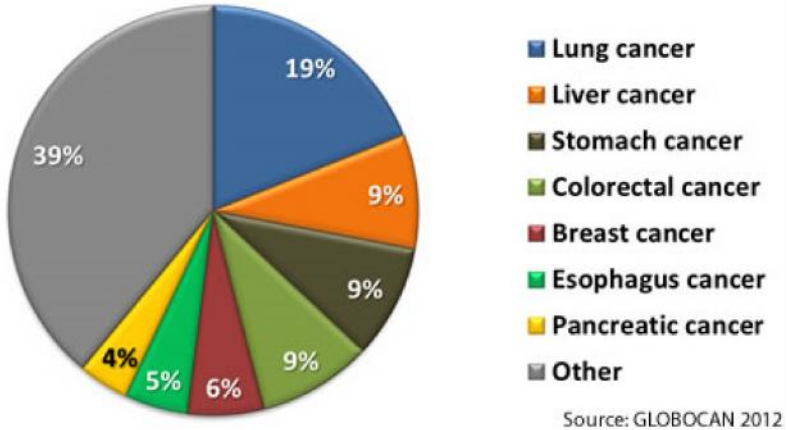

Cancer Death Rates*
Among Women, US, 1930-2004
Rate Per 100,000
100
80
60
40
20
0
Uterus
Breast
Lung & bronchus
Colon & rectum
Gastric
Ovary
Pancreas
1930
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2004, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention, 2006.

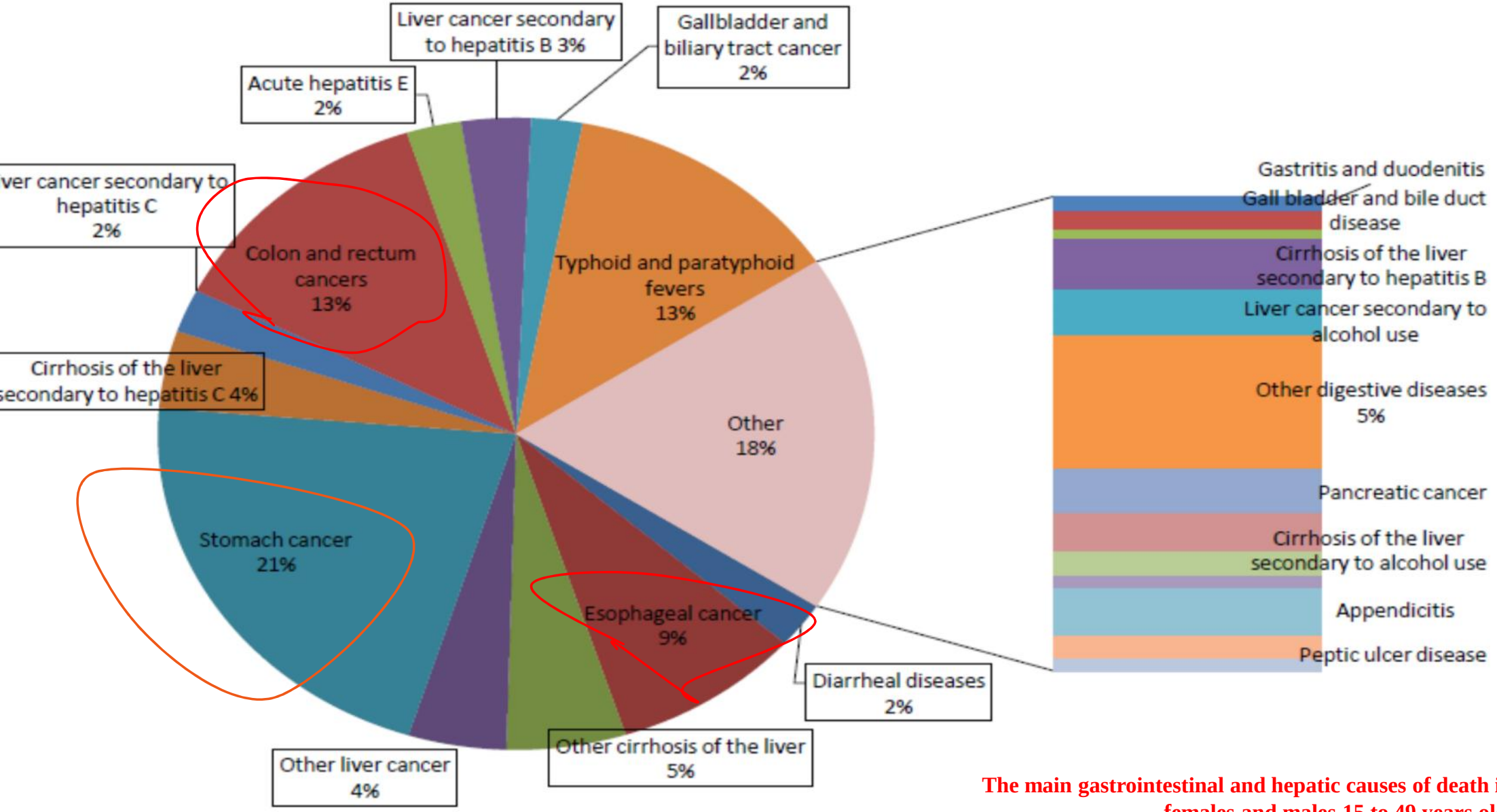
Figure 1.1 Relative frequency of the main invasive cancers diagnosed, 2009-2011



Most Common Causes of Cancer Death Worldwide in 2012



Source: GLOBOCAN 2012



The main gastrointestinal and hepatic causes of death in females and males 15 to 49 years old

men	DALY	Death
Stomach cancer	1	1
Diarrheal diseases	2	7
Esophageal cancer	3	2
Typhoid fevers	4	9
Colorectal cancer	5	3
Other digestive diseases	6	4
Cirrhosis hepatitis C	7	5
Acute hepatitis B	8	11
Liver cancer hepatitis B	9	6
Cirrhosis alcohol	10	10
Cirrhosis other	11	14
Liver cancer hepatitis C	12	8
Cirrhosis hepatitis B	13	12
Peptic ulcer	14	15
Pancreatic cancer	15	13
Liver cancer other	16	17
Acute hepatitis E	17	23
Gastrititis & duodenitis	18	19
Appendicitis	19	20
Liver cancer alcohol	20	16
Gall bladder diseases	21	21
Acute hepatitis A	22	24
Gallbladder cancer	23	18
Acute hepatitis C	24	22
Pancreatitis	25	25

women	DALY	Death
Diarrheal diseases	1	5
Stomach cancer	2	1
Esophageal cancer	3	2
Colorectal cancer	4	3
Typhoid fevers	5	8
Other digestive diseases	6	4
Cirrhosis hepatitis C	7	6
Cirrhosis other	8	13
Liver cancer hepatitis C	9	7
Liver cancer hepatitis B	10	9
Liver cancer other	11	15
Peptic ulcer	12	12
Gallbladder cancer	13	10
Pancreatic cancer	14	11
Gastrititis & duodenitis	15	22
Acute hepatitis B	16	20
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Acute hepatitis E	18	23
Cirrhosis hepatitis B	19	14
Appendicitis	20	18
Liver cancer alcohol	21	16
Acute hepatitis A	22	24
Cirrhosis alcohol	23	19
Acute hepatitis C	24	21
Pancreatitis	25	25

- Cancers of the gastrointestinal tract are among **the most common tumors**,
- >271,000 new cases occurring in 2008.
- Advances in the treatment of colorectal cancer have improved survival and quality of life for patients with these diseases. Table 57-4 outlines the common signs and symptoms, treatments, and prognosis of gastrointestinal tumors.

ESOPHAGEAL CANCER

Epidemiology and Natural History

- **squamous cell and adenocarcinoma.**
  1. *Squamous cell cancers :*
     - in the cervical and thoracic esophagus,
     - predisposing factors :smoking, caustic injury, achalasia, and alcohol intake
     - associated with other tobacco-related cancers in the upper airways and digestive tract.
  2. *Adenocarcinomas :*
     - commonly occur in the lower esophagus
     - The rate of adenocarcinoma is increasing due to **Barrett** esophagus
       - ~25% of patients with severe Barrett esophagus eventually develop esophageal adenocarcinoma
     - adenomatous metaplasia of the distal esophagus often caused by GERD
       - useful intervention is frequent **endoscopic screening and biopsy**
       - pharmacologic treatment of acid reflux disease does not prevent neoplastic transformation

ESOPHAGEAL CANCER

- Symptoms
  - most common symptom is **dysphagia**.
  - a sensation that solid food becomes "**stuck**."
    - Eventually, the patient may be unable to swallow liquids.
  - Patients commonly become **afraid to eat** because **of frequent regurgitation** at mealtime, resulting in significant **weight loss**.

ESOPHAGEAL CANCER

- Diagnosis
  1. upper gastrointestinal radiographic series or endoscopy with biopsy.
  2. The **most effective staging tool is endoscopic ultrasonography**, an accurate tool in assessing local **depth** of penetration and **lymph node metastases**.
  3. CT and positron-emission tomographic (PET) scanning
     1. for metastasized to the **chest or liver**, the two most common sites of spread.

ESOPHAGEAL CANCER
Treatment

- surgery
  - The most common treatment of esophageal cancer is **surgery**. (wide margin)
  - The stomach is then **pulled up** to join the remainder of the esophagus. Or part of the intestine may be **transposed**
  - **~ 10% to 30%** of patients with stage II disease who are treated by surgical resection alone are **alive** and free of cancer 5 years after diagnosis.
- neoadjuvant chemoradiotherapy
  - chemoradiotherapy before surgical resection may offer survival benefit over surgery alone.
  - If surgical treatment is not possible, standard of care for these patients is to provide chemotherapy and radiation.
    - This approach may cure 20% to 30% of patients.
  - Whether the outcomes of combined chemotherapy and radiation are as favorable as surgical resection alone is not clear.
- **metastatic** esophageal cancer,
  - systemic chemotherapy using **platinum-based combination** regimens are effective in palliation and extending survival.
  - patients with **severe dysphagia that does not resolve with radiation or surgery**,
    - endoscopic placement of a metal or plastic stent

Table 57-4 Gastrointestinal Cancers

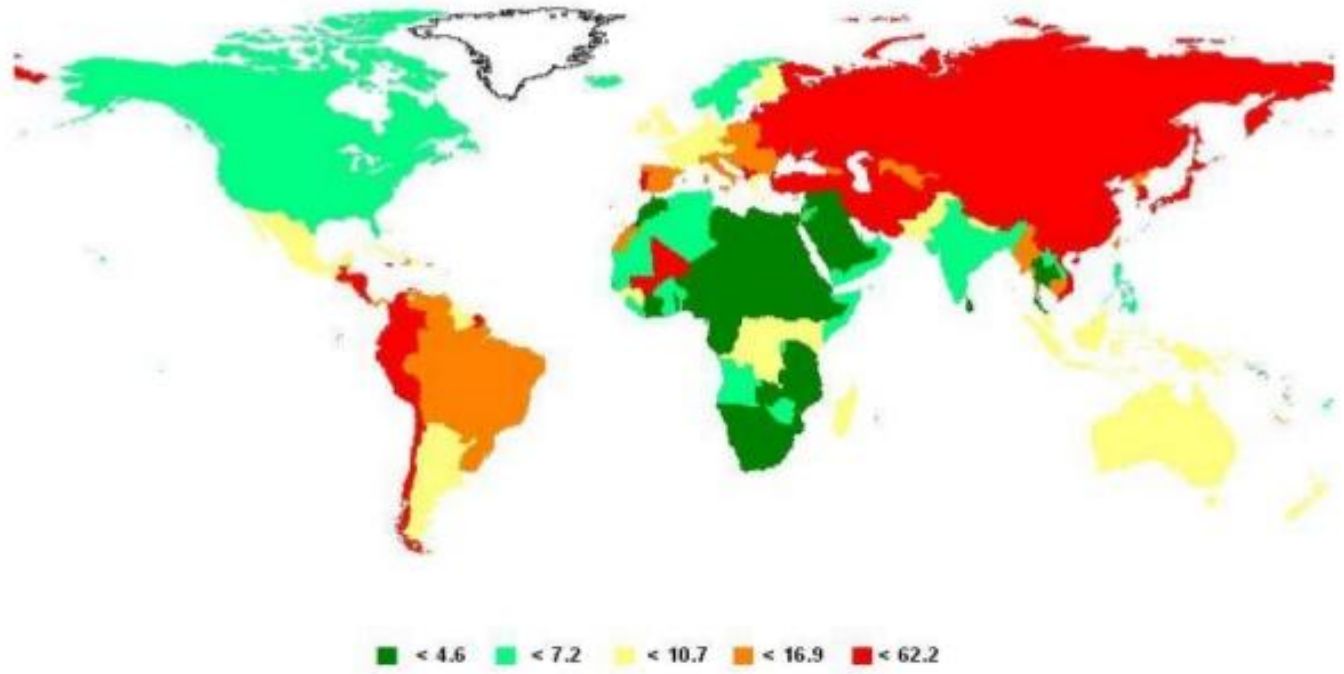
Tumor Site	Common Findings	Standard Treatments	Expected Outcome
Esophageal	Dysphagia, chest pain, weight loss	Early stage: neoadjuvant chemoradiotherapy and surgery Later stages: combination chemotherapy and radiation therapy and/or surgery	Stage II/III stage: about 30% 5-yr survival Average survival for metastatic disease is <9 mo
Gastric	Pain, supraclavicular adenopathy, vomiting, melena	Stage I: surgery alone Stage II and III: surgery if possible, followed by chemotherapy and/or radiation Metastatic disease: chemotherapy alone	Early stage: >90% 5-yr survival Positive nodal involvement: 20%-75% 5-yr survival for tumors <2 cm
Hepatocellular	Elevated α-fetoprotein; pain or change in liver function test	Resection for early lesions Unresectable: chemoembolization or tyrosine kinase inhibitor therapy for palliation	Always fatal in later stages of disease

Pancreas	Weight loss, boring midline pain through back, jaundice	Early stage: Whipple procedure and/or radiation therapy Late stage: chemotherapy with radiation or chemotherapy alone	Resectable: median survival 10-20 mo Radical surgery: 25% with negative nodal involvement and 10% with positive nodal involvement may be cured by surgery Unresectable: median survival 4-6 mo
Colon, rectal	Abdominal pain, occult or overt bleeding in stool, change in bowel habits	Early stage: resection alone If nodal involvement, add chemotherapy Chemotherapy and radiation therapy before and after surgery for patients with rectal cancers	Early stage: >70% at 5 yr Nodal involvement: 50%-70% at 5 yr Metastatic: median 14-24 mo
Anal	Constipation, bleeding, rectal pain and urgency	Early stage: chemotherapy with radiation therapy Later stage: abdominoperineal resection	Localized: 70% at 5 yr

Gastric cancer-

Epidemiology of gastric cancer

Incidence rate /year per 100.000 inhabitants

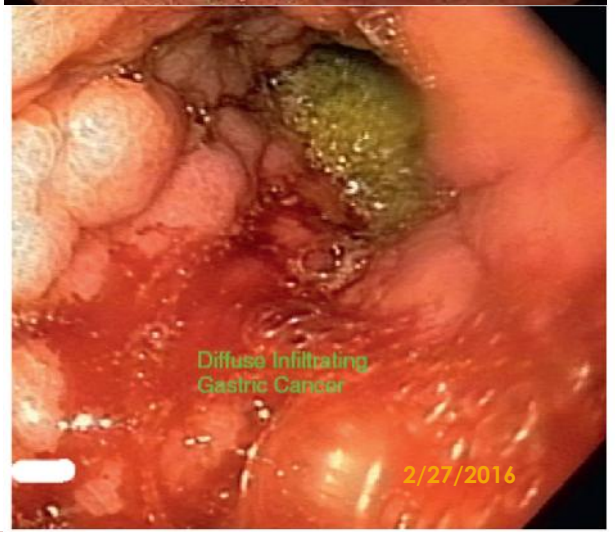


Ferlay et al., IARC Globcan 2008

GASTRIC CANCER

Epidemiology and Natural History

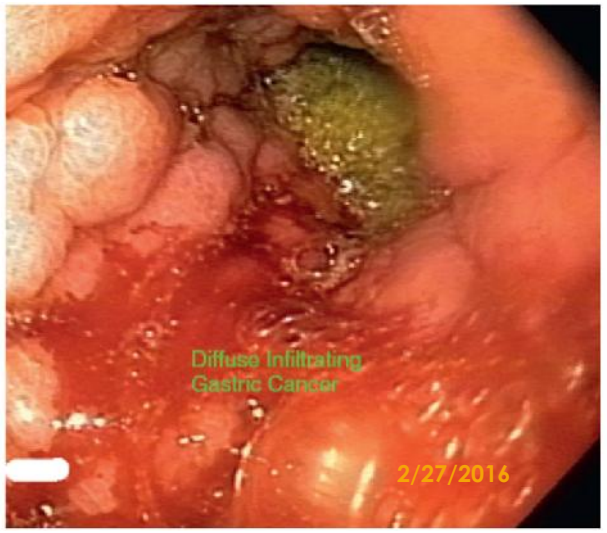
- Gastric cancer rates are **highest** in **developing countries** that use smoked meats and meats high in **nitrates**.
- Risk factors: pernicious anemia, achlorhydria, gastric ulcers, and prior gastric surgery.
- gastric cancer rates have decreased in the United States (21,500 new cases occurring in 2008), Except for cancers of the gastroesophageal junction,



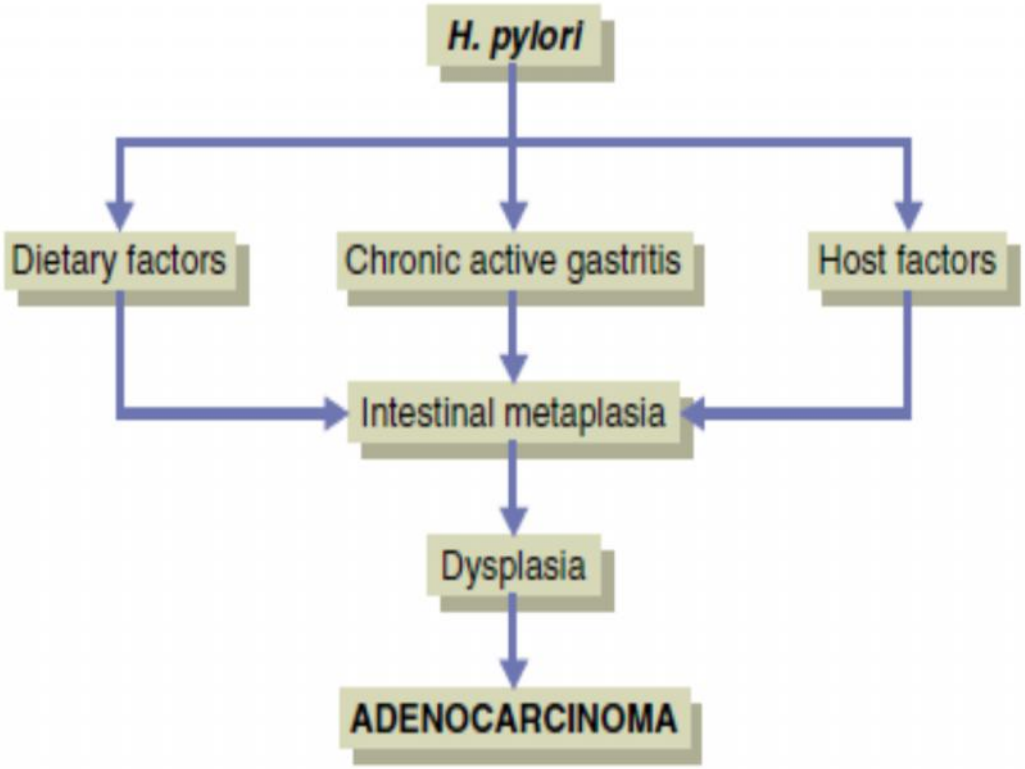
GASTRIC CANCER

Epidemiology and Natural History

- A recognized risk factor for gastric cancer is infection with ***Helicobacter pylori***.
- **Whether early treatment of *H. pylori* infection**
  - **changes the rate of cancer in infected populations is <u>not clear</u>.**



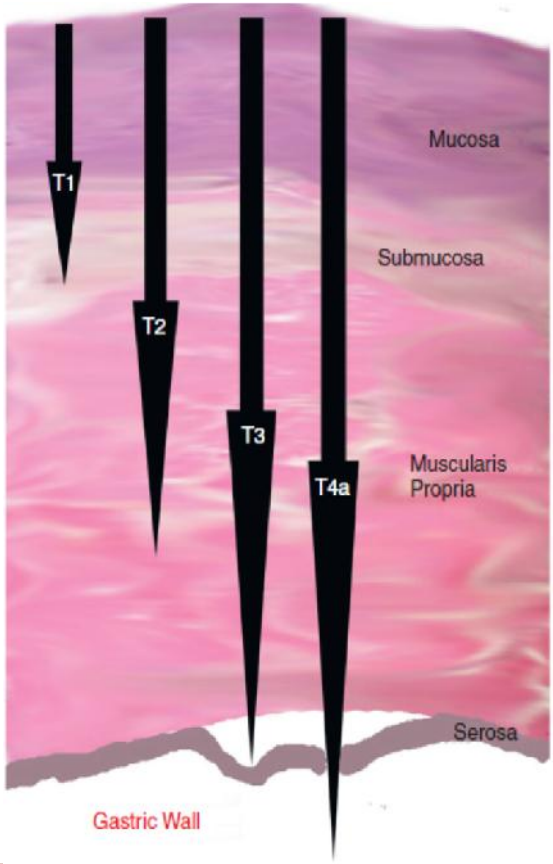
GASTRIC CANCER



GASTRIC CANCER

Diagnosis

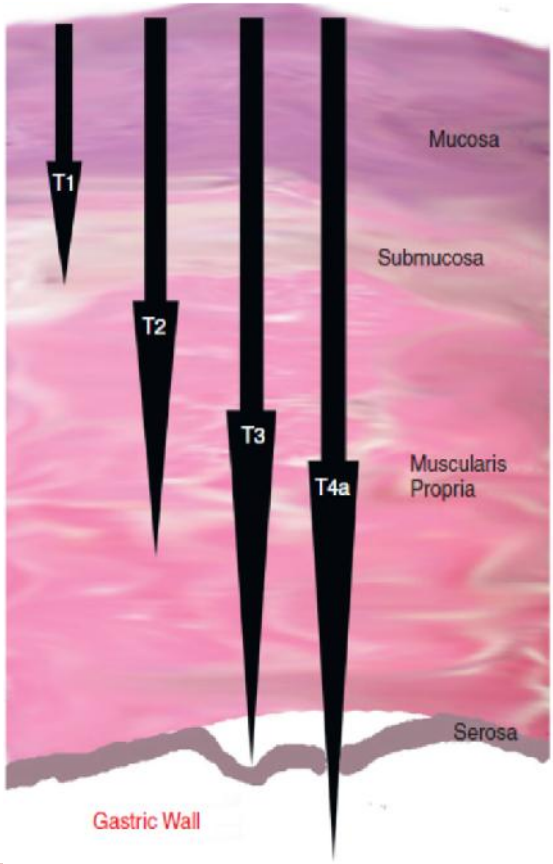
- commonly experience
  - abdominal pain, early satiety, anemia, hematemesis, weakness, and weight loss.
  - Frequently, local lymph nodes is involved
- Physical examination may
  - gastric mass, an umbilical node (Sister Mary Joseph node), or a left supraclavicular node (Virchow node).
- Pathologic analysis shows



GASTRIC CANCER

Diagnosis

- adenocarcinoma that can be localized or spread throughout the gastric lining *(linitis plastica)*.
- Required staging :
  - CT scan
  - upper gastrointestinal endoscopy,
  - endoscopic ultrasonography
  - biopsy abnormal lymph nodes.

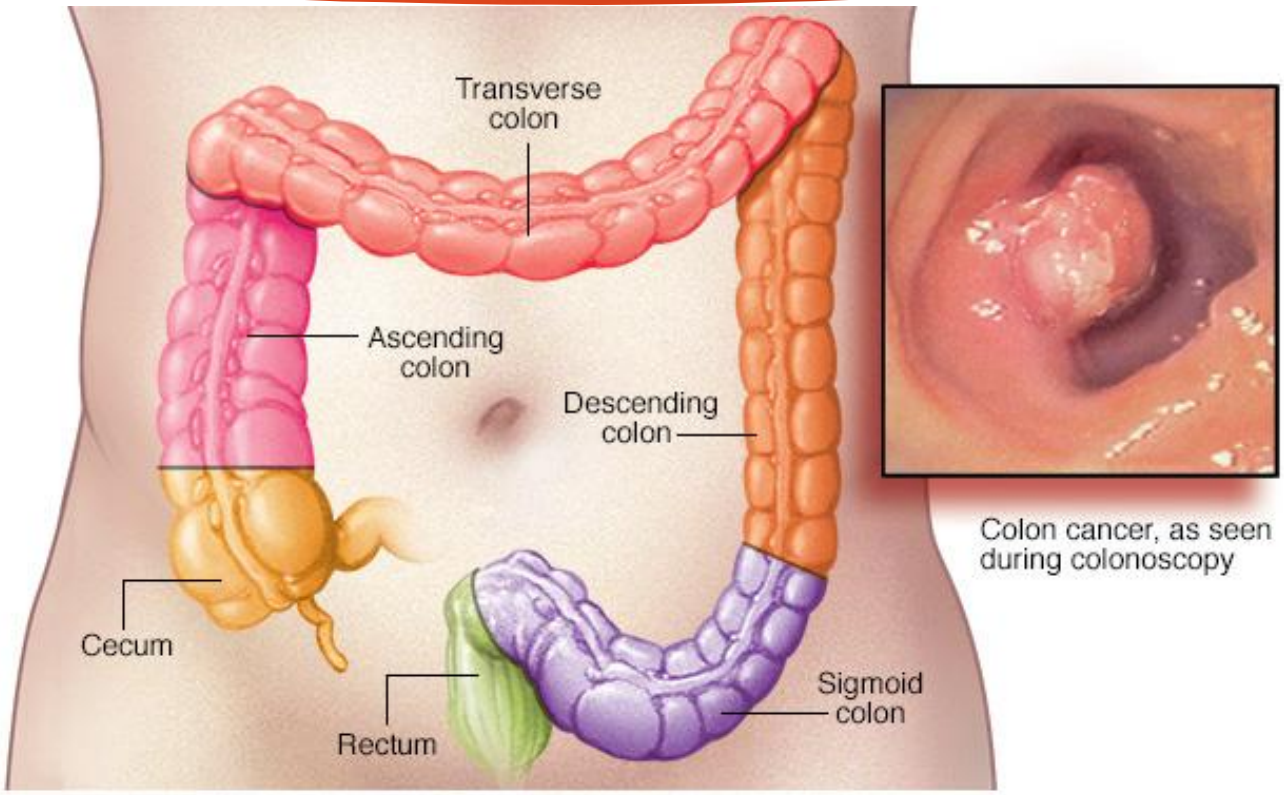


GASTRIC CANCER

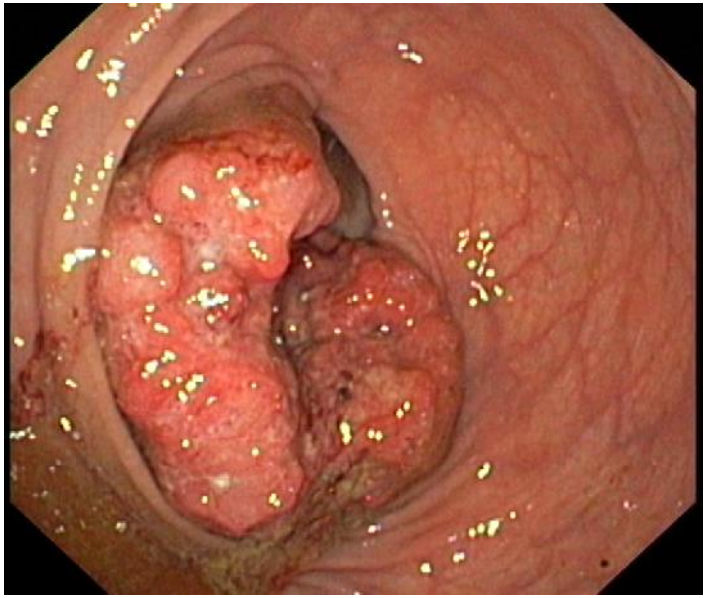
Treatment

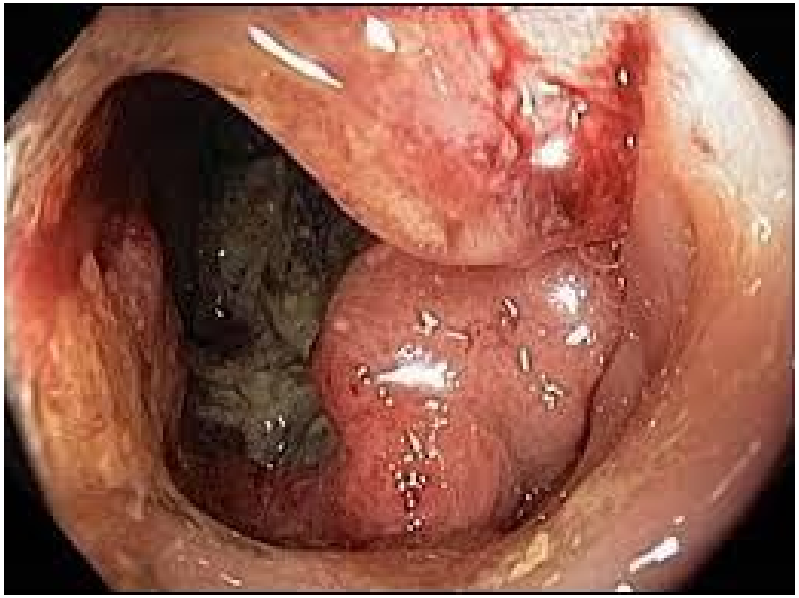
- Gastric cancer is most often treated **surgically**.
  - By **complete removal**,
    - patients have a 20% to 60% chance of a 5-year survival, depending on the pathologic stage.
- If gastric cancer recurs,
  - the most common sites are **local extension** or **hematogenous** spread through the **portal vein to the liver**.
  - 5-fluorouracil (5-FU) and leucovorin chemotherapy and postoperative radiation therapy.
    - median survival increased by about 15 months.
- For **metastatic** gastric cancer
  - may elect **chemotherapy** to palliate symptoms.
  - platinum compounds, fluoropyrimidines, anthracyclines, taxanes, and irinotecan.
  - **Combination chemotherapy** provides a 20% to 40% response rate and **may extend survival**.

Colorectal cancer



COLORECTAL CANCER (CRC)





COLORECTAL CANCER

Epidemiology and Natural History

- ~1 in 20 people in the United States will be diagnosed with colon cancer (lifetime risk is 6%).
  - An estimated 148,700 new cases were diagnosed in 2008,
  - in the same year, nearly 50,000 deaths occurred.
- Known predisposing factors are a
  - history of **ulcerative colitis**
  - **strong family history** of colon cancer.
- Several **mutations**, whether **inherited** or **spontaneous**,.

Age ≥ 50 yr
Personal history of adenomatous polyps or colorectal cancer
Familial adenomatous polyposis or Gardner syndrome
MYH-associated adenomatous polyposis
Hereditary nonpolyposis colon cancer
Ulcerative colitis or Crohn colitis
First-degree relative with colon cancer or adenomatous polyps diagnosed before age 60 yr
Hamartomatous polyposis syndrome (Peutz-Jeghers syndrome, juvenile polyposis)

COLORECTAL CANCER

mutations

1. **<u>familial polyposis</u>** is autosomal dominant manner.
    1. Individuals have mutations in the ***APC* gene**,
    2. **periampullary** and **thyroid** cancers or **osteomas**, **sebaceous** cysts, and **gastric polyps**.
2. **Hereditary nonpolyposis** colorectal cancer (HNPCC) is a more common autosomal disorder associated with **microsatellite instability** and **mutations in h*MSH-2*, h*MLH-1*, *PMS-1*, *PMS-2*, and h*MSH-6***.

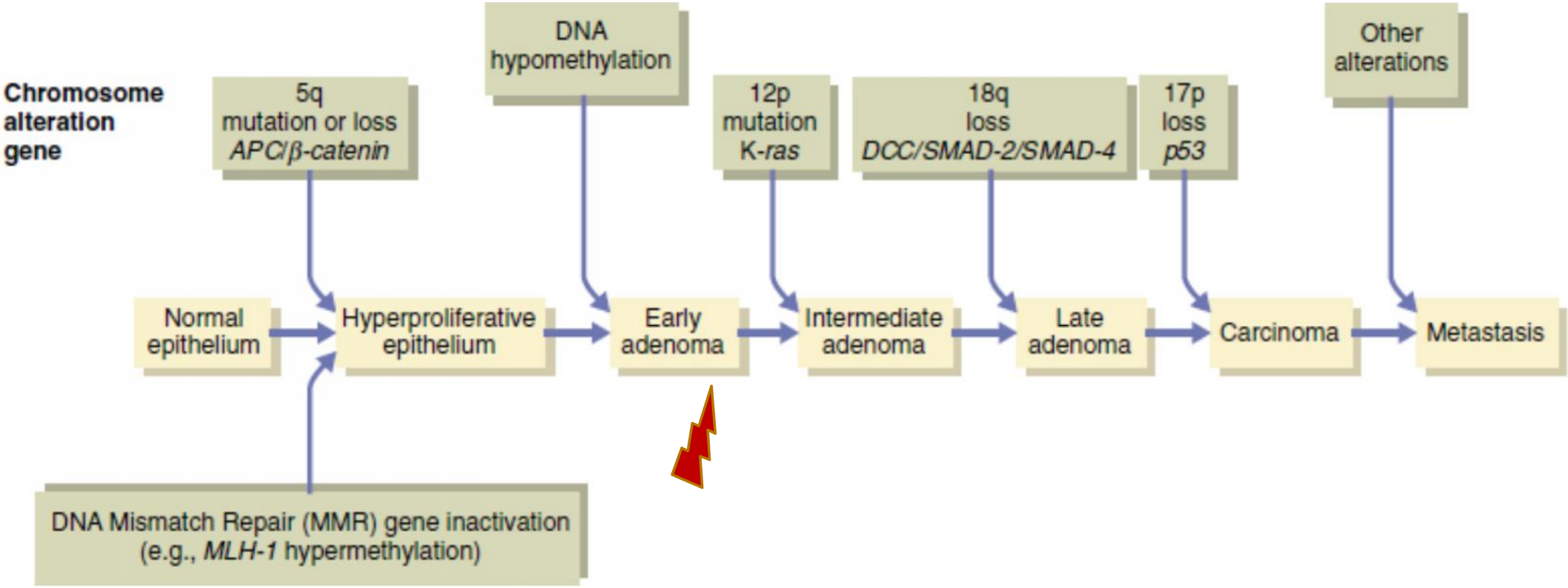
COLORECTAL CANCER

mutations

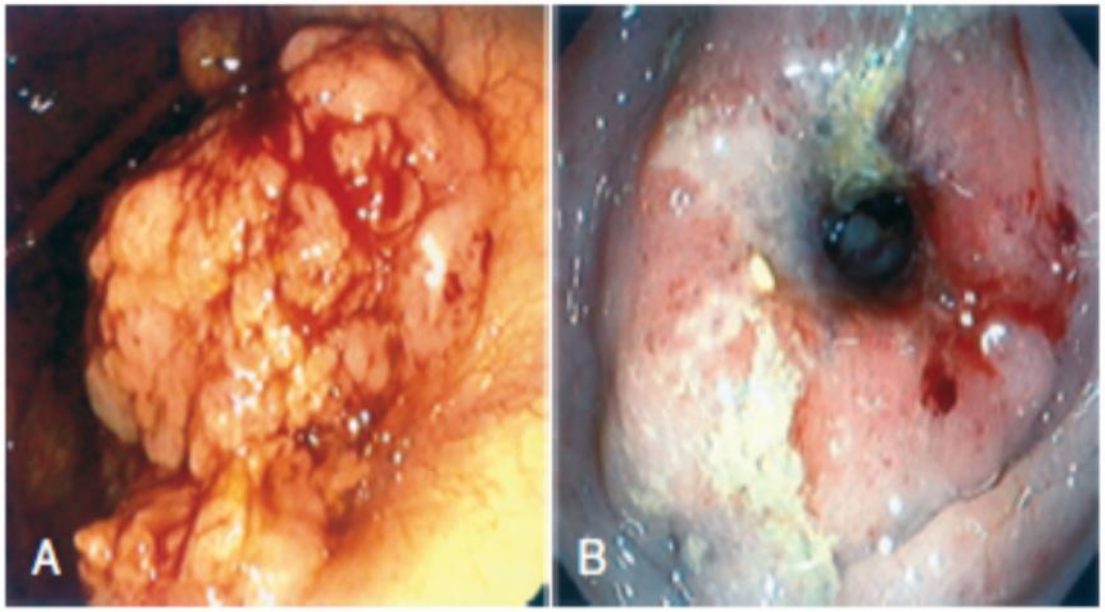
1. HNPCC usually have **colon** or **endometrial** cancer when
    1. younger than **50** years and
    2. have **first-degree** relatives with colon cancer or other HNPCC-related cancers
        - from the stomach, ovary, small bowel, biliary tract, ureter, or renal pelvis.

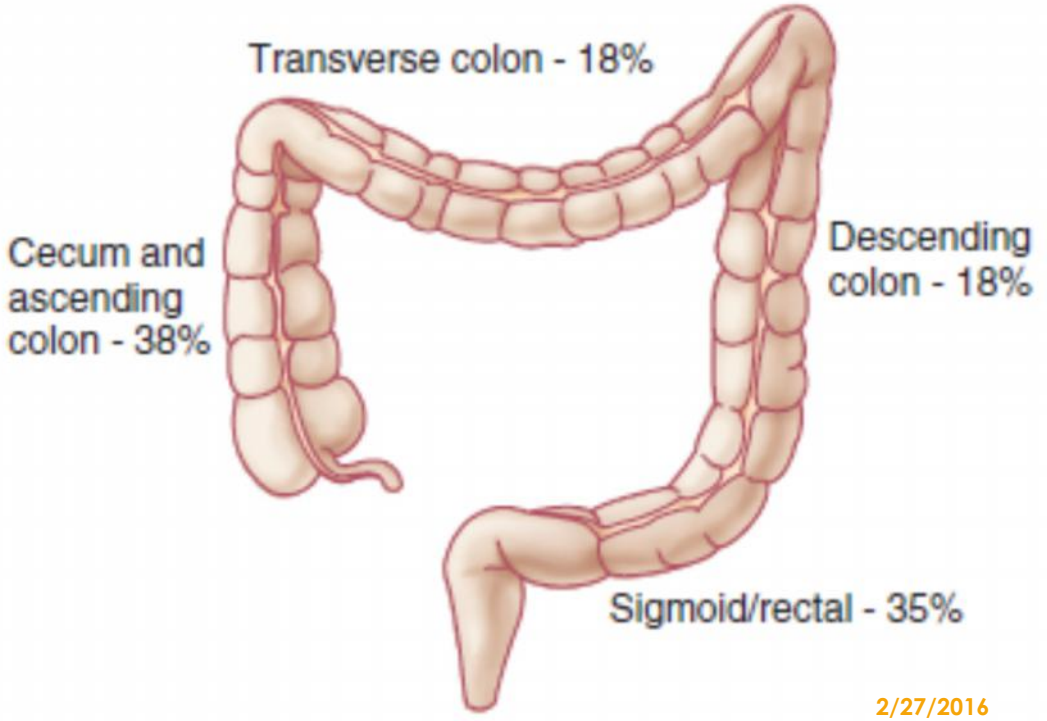
COLORECTAL CANCER

mutations



COLORECTAL CANCER





COLORECTAL CANCER

prevention

- **adenomatous polyps and the later development of colon cancer**
- the **most reliable** way to reduce colon and rectal cancer mortality is to perform regular **screening**.
- **Colonoscopy** is the **most commonly used screening test**.
- Studies using sigmoidoscopy and regular fecal occult blood testing also show reductions in the incidence and mortality of colorectal cancer.

COLORECTAL CANCER

prevention

- begin colonoscopy **earlier** than suggested for the general population.
  1. Patients with a proven mutation (Gardner syndrome, HNPCC) or a strong family history (familial adenomatous polyposis),
  2. those who acquire other diseases associated with colorectal cancer, such as ulcerative colitis,
- For patients with **familial adenomatous polyposis**, screening should start in the **teenage** years.
- For patients with **HNPCC**, should start 10 years before the age of diagnosis in the youngest family member with colorectal cancer

COLORECTAL CANCER

prevention

- Research efforts are underway in the primary prevention of colorectal cancers using interventions such as diet, daily aspirin, cyclo-oxygenase-2 inhibitors, calcium and vitamin D supplementation, and other chemopreventive agents to reduce cancer incidence.
- Enthusiasm for promoting a high fiber diet to reduce the risk for colon cancer has waned.
- Lifestyle changes are still considered important—fresh fruits and vegetables, regular exercise, fewer than two red meat servings per week—based on epidemiologic association

COLORECTAL CANCER

Symptoms

- **Rectal bleeding** commonly occurs with colon and rectal cancers.
  - left-sided colon lesions often complain of a change in stool color or caliber or pelvic pain and transient bloating.
  - Right-sided lesions result in occult bleeding.
  - Occasionally, patients with colon and rectal cancers are asymptomatic until the tumor totally obstructs the bowel or perforates the peritoneal cavity.
- Colon and rectal cancers tend to spread hematogenously to the lungs and liver.
- **Rectal** cancer more **recurs locally**

  more difficult to get a wide margin of normal tissue and lymph nodes

COLORECTAL CANCER

Diagnosis

- The work-up for colon
  1. serum carcinoembryonic antigen (CEA)
  2. abdominalpelvic CT scan
  3. chest radiograph
  4. endoscopic imaging of the colon to ensure that all polyps and cancers are removed near the time of the primary operation
- Table 57-5 describes the staging system for colon and rectal cancers.

COLORECTAL CANCER

staging system

Table 57-5 Staging for Colon and Rectal Cancer

Stage	Tumor Size	Nodal Status	Metastases
0	In situ	No	No
I	Invades mucosa only	No	No
II	May invade muscularis or through serosa	No	No
III	Any size tumor or any level of invasion	Yes	No
IV	Any size or depth	Positive nodal involvement present or absent	Yes

COLORECTAL CANCER

Treatment

- colon cancer:
  1. In patients with stages I, II, and III colon cancer,
     - surgical resection of the primary carcinoma along with any regional lymph node metastases is routinely performed
  2. all patients with stage III cancer & for selected high-risk individuals with stage II cancer
     - multiagent, adjuvant chemotherapy is recommended (which reduces the rate of recurrence by about 40%)
- rectal cancer:
  1. primary **resection** (which may require colostomy) **or neoadjuvant** chemoradiotherapy is performed.
  2. any lesion that invades the muscle or lymph nodes is also treated with **radiation** therapy (if not given before surgery**) and adjuvant** chemotherapy.
  3. **surgical resection** of the primary lesion in patients with advanced (stage **IV**)
     1. to palliate or avoid symptoms of obstruction, bleeding, and pain.

Survival and Comparison of Dukes and TNM Staging in Colorectal Carcinoma

Dukes	TNM Stage	5-Year Survival Rate (%)
A	I	93
B	II	72-85
C	III	44-83
D	IV	8

COLORECTAL CANCER

chemotherapy protocols:

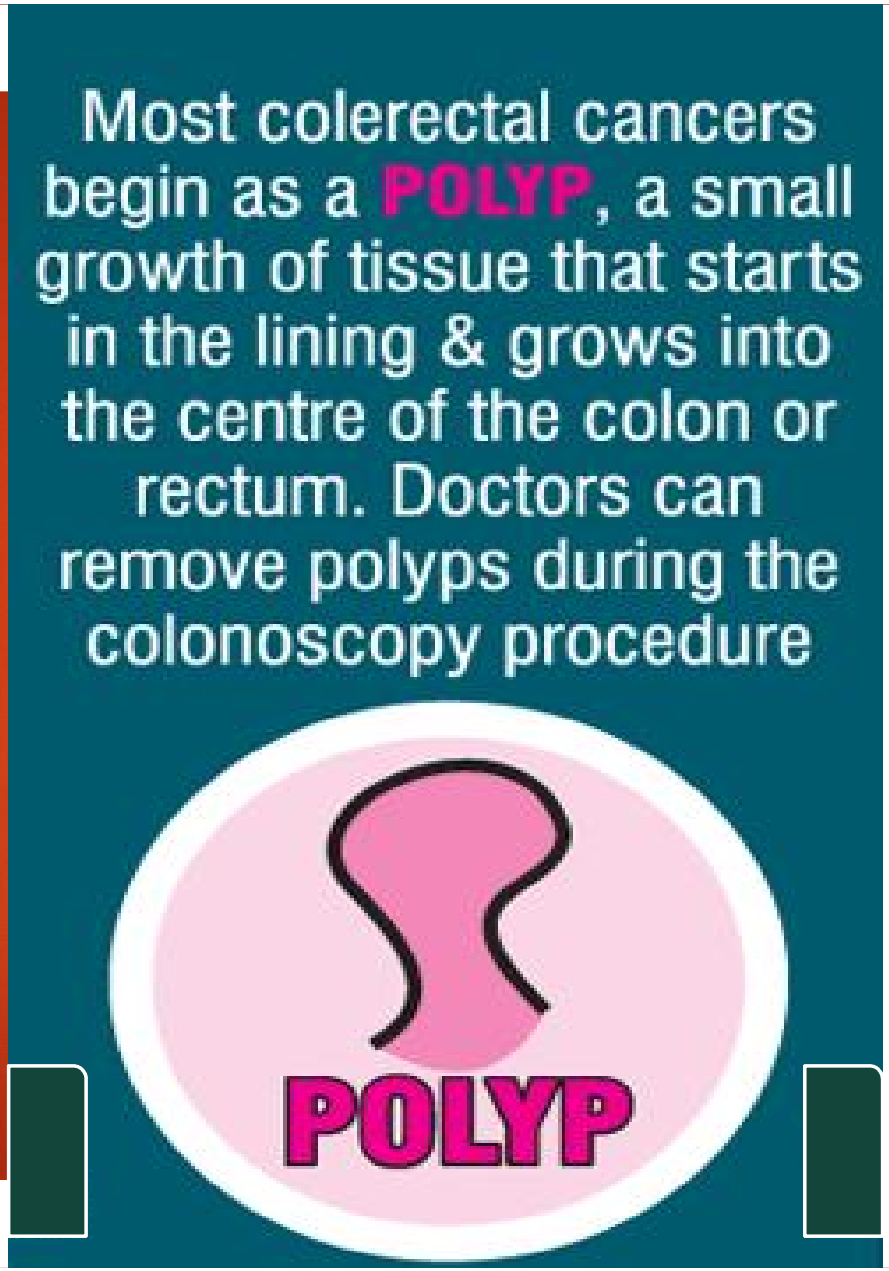
- chemotherapy for colorectal cancer:
  - Regimens proved successful in prolonging survival for colon cancer include **5-FU with leucovorin** or its oral analogue, **capecitabine**, alone.
  - The addition of **oxiliplatin to 5-FU–based adjuvant therapy** has recently been shown to further improve survival after surgery.
- metastatic cancer:
  - infusions of chemotherapy with FOLFOX (5-FU, leucovorin, oxiliplatin), or FOLFIRI (5-FU, leucovorin, irinotecan) with
    1. antibodies targeting the vascular endothelial growth factor (VEGF; bevacizumab) or
    2. the epidermal growth factor receptor (cetuximab)
  - prolong median survival beyond 20 months, almost twice the survival expected in the early 1990s.
  - But **metastatic** colon and rectal cancers are **incurable** unless the metastatic lesions can be surgically resected.

Colorectal Cancer (CRC)

Screening and Surveillance Recommendations

Indication	Recommendations
Average risk	Beginning at age 50 yr: Colonoscopy every 10 yr Computed tomographic colonography every 5 yr Flexible sigmoidoscopy every 5 yr Double-contrast barium enema every 5 yr (Stool blood testing annually or stool DNA testing acceptable but not preferred)
One or two first-degree relatives with CRC at any age or adenoma at age < 60 yr	Colonoscopy every 5 yr beginning at age 40 yr, or 10 yr younger than earliest diagnosis, whichever comes first
Hereditary nonpolyposis colorectal cancer	Genetic counseling and screening[†] Colonoscopy every 1 to 2 years beginning at age 25 yr and then yearly after age 40 yr[‡]
Familial adenomatous polyposis and variants	Genetic counseling and testing[†] Flexible sigmoidoscopy yearly beginning at puberty[‡]
Personal history of CRC	Colonoscopy within 1 yr of curative resection; repeat at 3 yr and then every 5 yr if normal
Personal history of colorectal adenoma	Colonoscopy every 3 to 5 yr after removal of all index polyps
Inflammatory bowel disease	Colonoscopy every 1 to 2 yr beginning after 8 yr of pancolitis or after 15 yr if only left-sided disease

PATIENT EDUCATION



COLORECTAL CANCER

SIGNS & SYMPTOMS

(many people experience no symptoms)

- Change in bowel habits, including diarrhoea/ constipation
- Rectal bleeding or blood in stools
- Persistent abdominal discomfort (cramps, gas or pain)
- A feeling that the bowel doesn't empty completely
- Weakness or fatigue
- Unexplained weight loss

RISK FOR COLON CANCER INCREASES WITH AGE (50+)

EARLY DETECTION IS KEY

The risk for 30% of cancers can be reduced by changing your diet and lifestyle

- Go for regular colon screening tests such as a colonoscopy as from age 50 - every 10 years
- Some CANSA Care Centres & Mobile Health Clinics countrywide offer faecal occult blood tests (sample of stool collected on end of an applicator to help detect small quantities of blood). Although not always an indication of cancer, positive results require a referral to a doctor

Lifestyle factors that contribute to increase the risk of colorectal cancer:


Lack of regular exercise


Low fruit/ vegetable intake


Low-fibre & high-fat diet


Being overweight (obesity)


Alcohol consumption


Insufficient intake of clean safe water

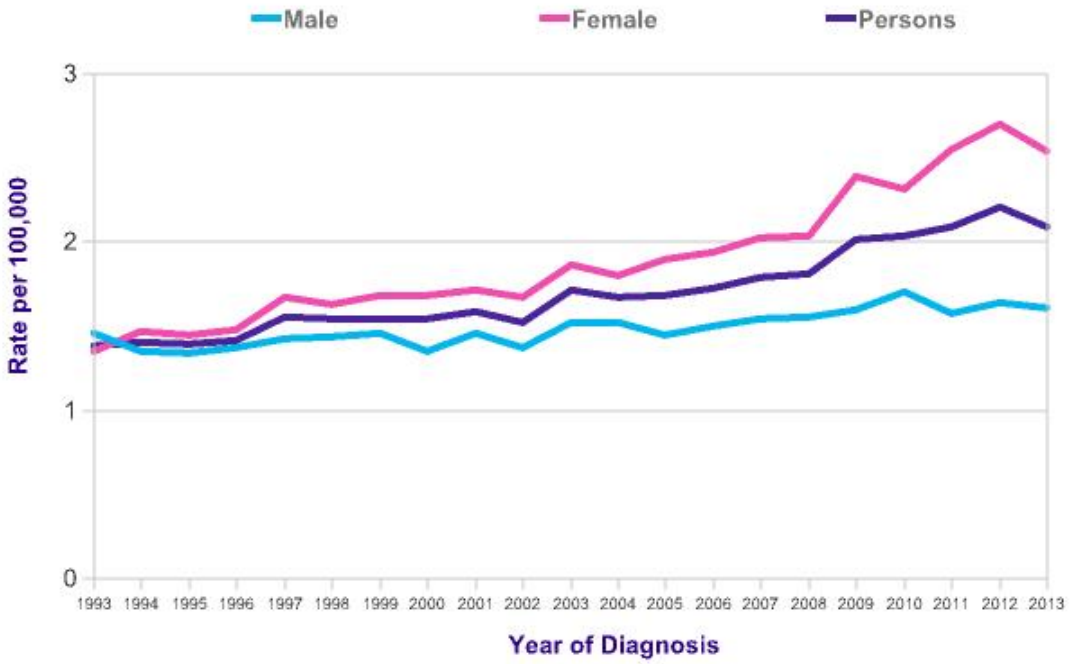

Tobacco use

Other risk factors:

- Inflammatory bowel disease
- Personal or family history of:
  - Colorectal polyps
  - Colorectal cancer

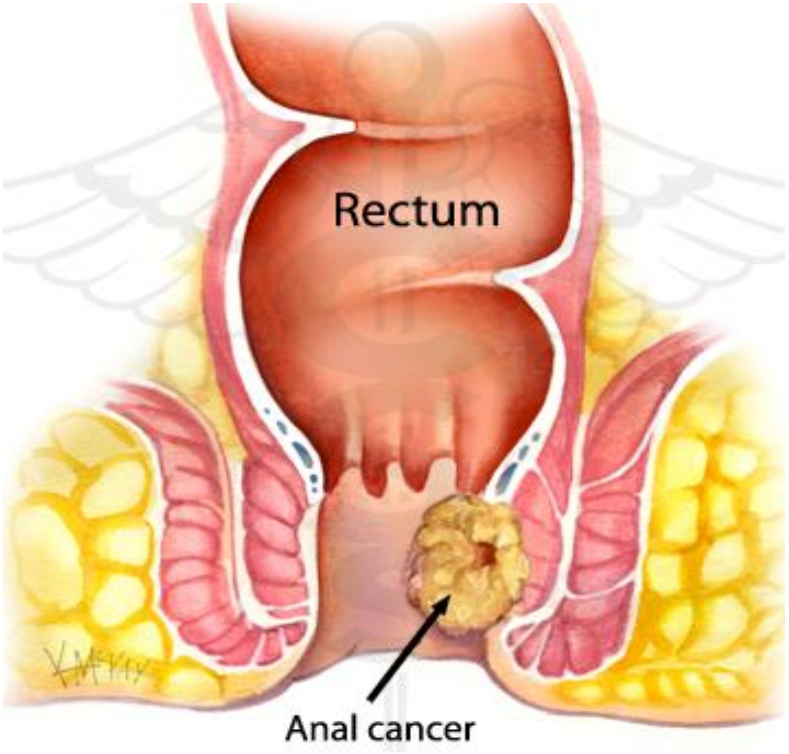
ANAL CARCINOMA

- Anal cancers are **increasing** in frequency
  - Persons infected with HPV and HIV are more likely to develop anal cancer.
  - Patients with anal cancer usually experience rectal bleeding or complain of rectal fullness.



ANAL CARCINOMA

- **Combined chemotherapy** with 5-FU and mitomycin **and radiation** therapy
  - make up the standard approach to a patient with localized anal cancer.
  - Results with combined therapy **are superior to those with surgery**, with the additional benefit of sparing the anal sphincter.
  - Abdominoperineal resection is reserved for patients in whom chemoradiotherapy fails.

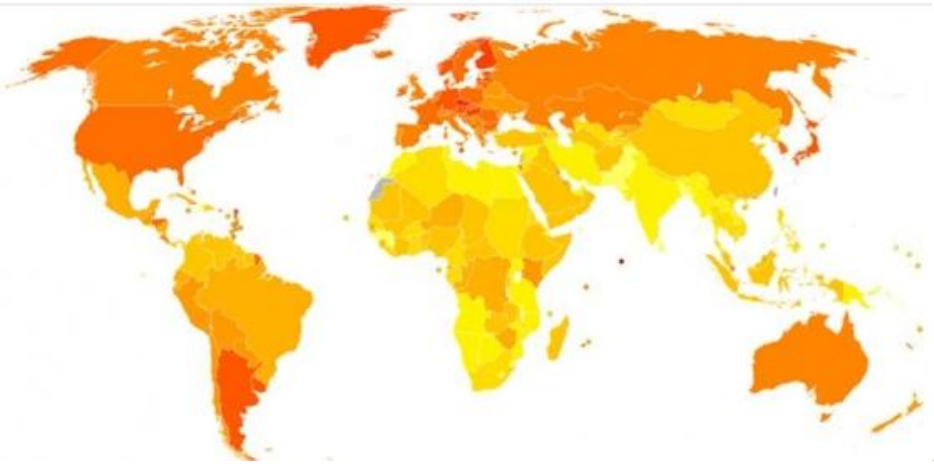


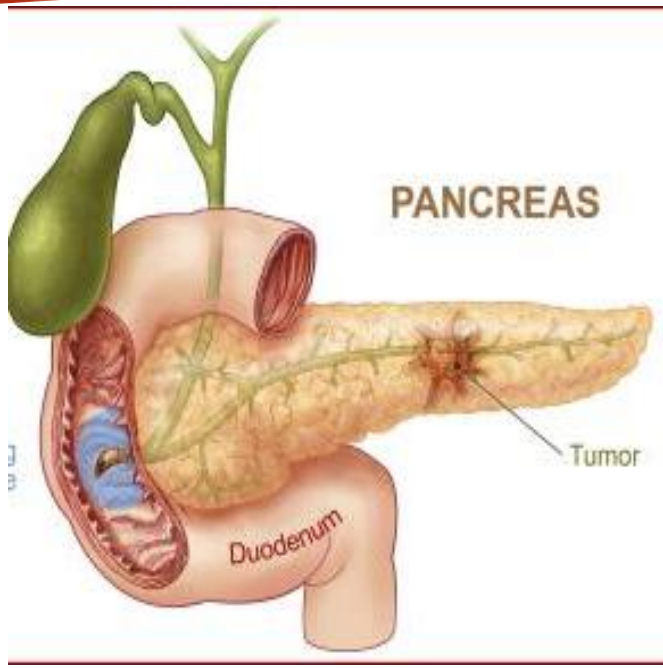
PANCREATIC CANCER

Epidemiology and Natural History

- Pancreatic cancer, which is diagnosed in more than 37,000 people living in the U.S. each year,
- is strongly associated with cigarette smoking.

World Map of Pancreatic Cancer





PANCREATIC CANCER

Epidemiology and Natural History

- A small proportion of pancreatic cancers are inherited from mutations in the *p16* and *BRCA-2* genes.
- Epithelial pancreatic cancer is an adenocarcinoma with an extremely high mortality rate because it is usually diagnosed when the tumor is beyond the capability of surgical resection.
- A less common type of pancreatic cancer, islet cell carcinoma, originates in the endocrine cells. Symptoms related to secretion of peptides such as gastrin, vasointestinal polypeptide, and insulin characterize these tumors.

Pancreatic Cancer

Epidemiology & Pathophysiology

- 4th leading cause of cancer death in U.S.*
- All stages, 5 year survival** < 5%
- Stage IIB, resected, 5 year survival** <8%

Annual Incidence in Major Markets			
Total	U.S.*	Europe	Japan
117,000	43,000	45,000	29,000

- Resection rate 20-25% U.S.*
- Post resection standard of care
  - Chemotherapy +/- Radiotherapy
  - Gemcitabine +/- 5FU Concurrent Radiotherapy

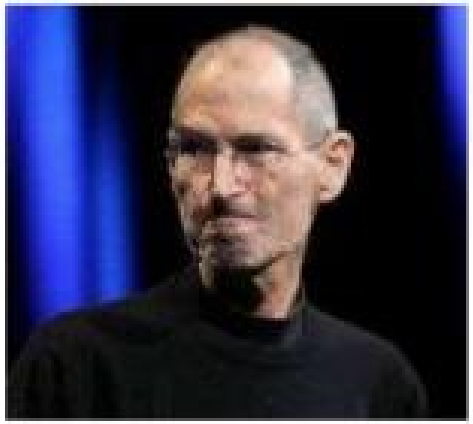
*2013 Cancer Facts & Figures
**Bilimoria et al., Cancer; August 15, 2007: Volume 110, Number 4: 738-744

NewLink GENETICS

PANCREATIC CANCER

Symptoms

- The most common presentation
  - is abdominal pain accompanied by rapid weight loss.
  - the pain is located in the periumbilical region and pierces or stabs through to the back.
    - The pain is often explained by the frequent invasion of the celiac plexus deep in the retroperitoneum.



PANCREATIC CANCER

Symptoms

- Other symptoms of pancreatic cancer are
  - the recent onset of diabetes,
  - intestinal angina reflecting encasement of the superior mesenteric artery,
  - palpable gallbladder (Courvoisier sign),
  - jaundice from blockage of the distal common bile duct.
  - Migrating thrombophlebitis (Trousseau sign) is a paraneoplastic complication of pancreatic adenocarcinoma.
  - The tumor marker CA-19-9 is elevated in up to 75% of patients with pancreatic cancer.

PANCREATIC CANCER

Treatment

- The only curative treatment for pancreatic cancer is **pancreaticoduodenectomy** (Whipple procedure),
  1. With high mortality rate
  2. The 5-year survival for surgically treated patients with localized pancreatic cancer is 25% for node-negative cancer but only 10% when lymph nodes are involved.
  3. to offer adjuvant chemoradiotherapy or gemcitabine chemotherapy alone, which may provide a survival advantage.
- Patients with unresectable disease may benefit from:

PANCREATIC CANCER

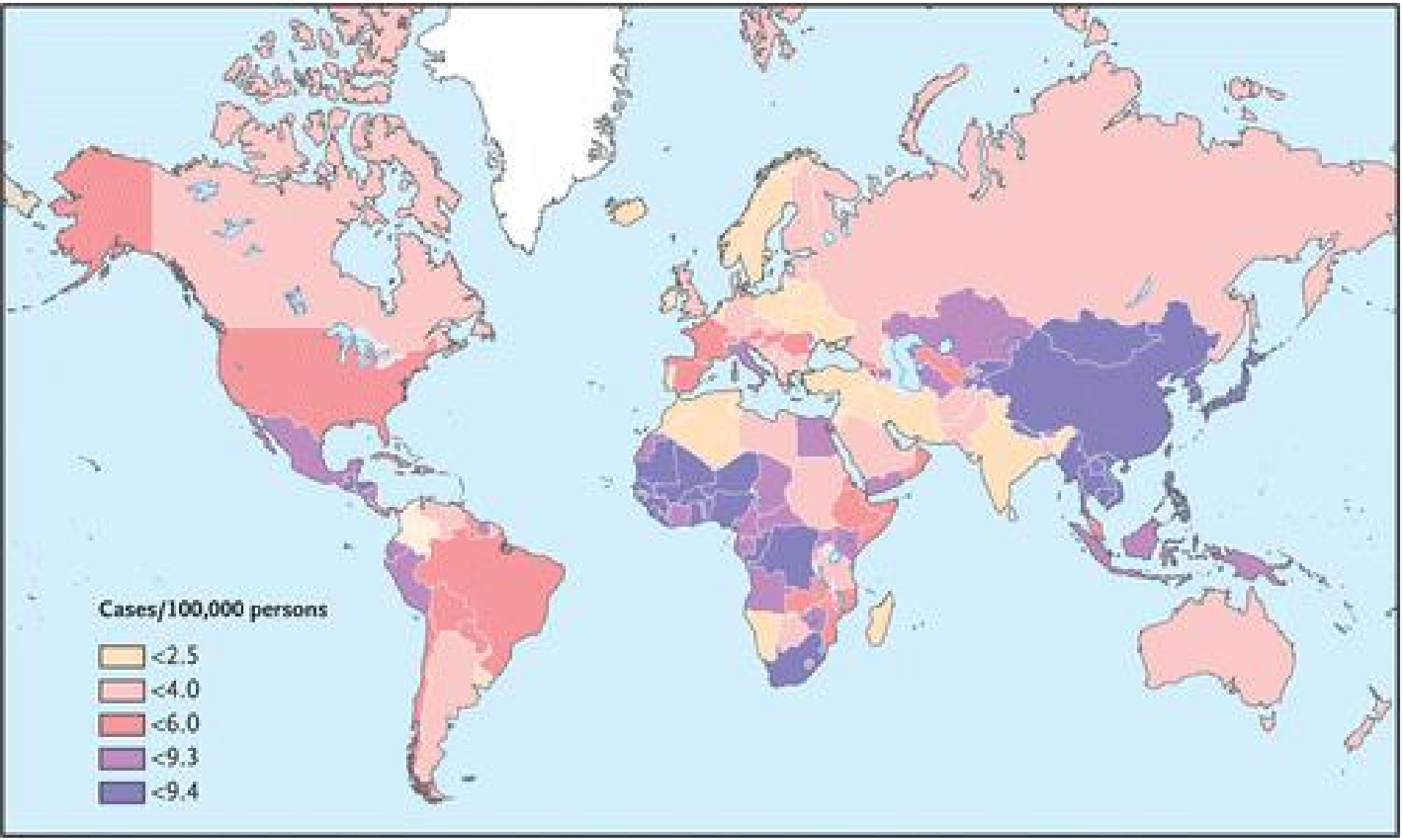
Treatment

- local radiation therapy with concurrent 5-FU;
  - more than 30% of patients treated with this combination have some improvement in their symptoms.
- Alternatively, gemcitabine-based chemotherapy alone may have palliative benefit.

- When patients have progressive or metastatic disease,
  - the use of palliative chemotherapy with weekly gemcitabine has been shown to improve quality of life and survival to a small degree

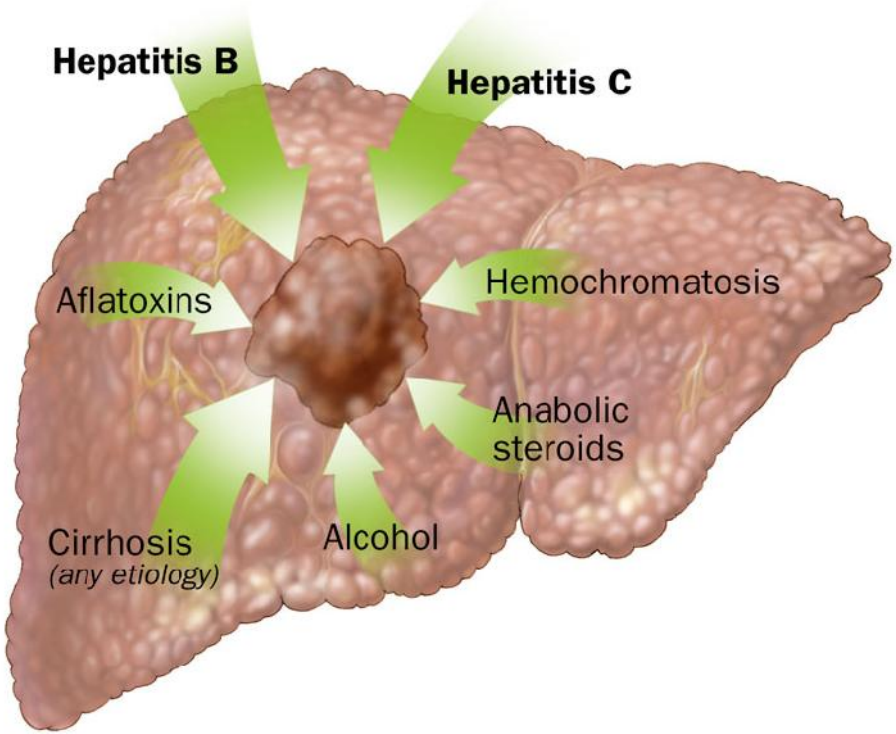
HEPATOCELLULAR CARCINOMA

- Although uncommon in the United States (about 21,000 new cases per year),
- hepatocellular carcinoma (HCC) is one of the **most common cancers** throughout the **world**;
- more than 1 million cases are diagnosed each year.
  - The common causes of HCC are chronic viral hepatitis (both B and C) and cirrhosis related to alcohol use or hemochromatosis.


Cases/100,000 persons
<2.5
<4.0
<6.0
<9.3
<9.4

HEPATOCELLULAR CARCINOMA

- Although this approach is unproved, considerable interest exists in screening patients who are at extremely high risk with serial measurement for a-fetoprotein (AFP) levels.
- AFP levels are commonly elevated even in early-stage HCC.



HEPATOCELLULAR CARCINOMA

- Treatment of early-stage HCC is surgery.
- Cure rates are more than 75% for patients with tumors smaller than 2 cm.
- Patients with severe cirrhosis and who have small liver cancers may benefit from liver transplantation.
- Chemoembolization may provide palliative benefit for patients with unresectable tumors, but conventional cytotoxic chemotherapy is generally ineffective.
- recent findings suggest that molecularly targeted tyrosine kinase inhibitors such as sorafenib offer a survival advantage over supportive care

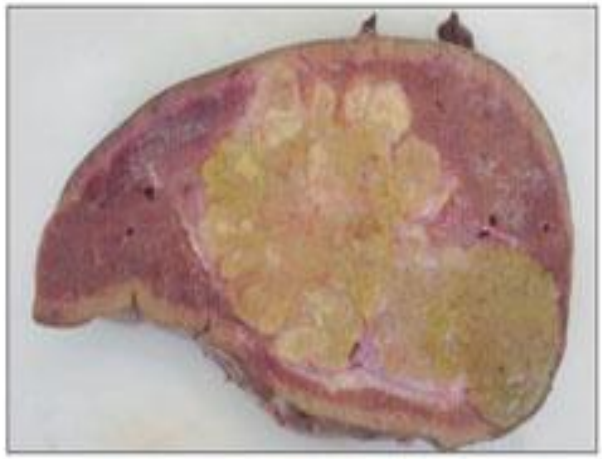


Fig. 3a. A 140×85×130 mm fibrolamellar carcinoma replacing the right hepatic lobe (patient 6, Table II).