بسم الله الرحمن الرحيم

Prevention of Gastrointestinal Malignancies

By

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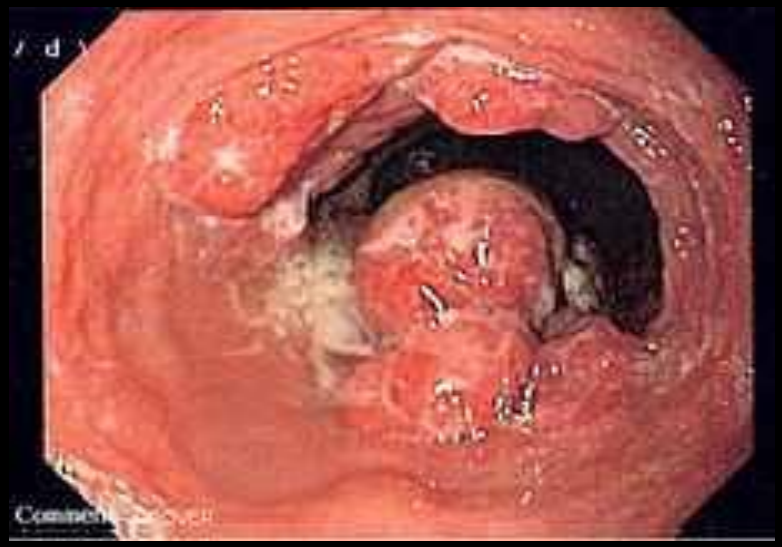
Gastrointestinal malignancies

- **G I malignancies** refers to malignant conditions of the gastrointestinal tract, including :
  - Esophageal cancer.
  - Stomach cancer.
  - liver cancer (HCC).
  - Gallbladder cancer.
  - Pancreatic cancer.
  - Colorectal cancer.



- Oesophageal and gastric cancers are most common in the non-industrialized countries, while colorectal cancer is the predominant gastrointestinal malignancy in westernized countries.

- Screening for cancer, its early detection and treatment requires medical facilities, endoscopic expertise and a major investment of national financial resources and accompanied with improved survival and prognosis.

Preventive strategies of gastrointestinal malignancies

- Screening of high risk groups.
- Encouraging protective factors
- Life style modifications.

Cancer esophagus

Risk factors:

- Age : most patients are over 55 .
- Sex : Men are affected twice as commonly as women.
- Heredity: it is more likely in people who have close relatives with cancer.
- Ethinity : ESCC is more common in African Americans than Caucasians. On the other hand, EAC appears to be more common in middle-aged Caucasian men

- Alcohol: an important risk factor (ESCC).
- Combination of alcohol and tobaco (about 90% of ESCC).
- Thermal injury as a result of drinking hot beverages.
- Obesity increases the risk of (EAC) fourfold.

Risk factors

- Gastroesophageal reflux disease (GERD).
- Barrett's esophagus.
- Human papillomavirus (HPV).
- Corrosive injury .
- Particular dietary substances, such as nitrosamines.

Risk factors

- History of head and neck cancers.
- Plummer–Vinson syndrome
- Radiation therapy in the mediastinum.
- Coeliac disease.
- Achalasia.
- Tylosis

Prevention

- The risk can be greatly reduced by:

lifestyle modification:

- Avoiding tobacco and alcohol
- Eating a healthy diet (rich in fruits and vegetables)
- Maintaining a healthy weight.

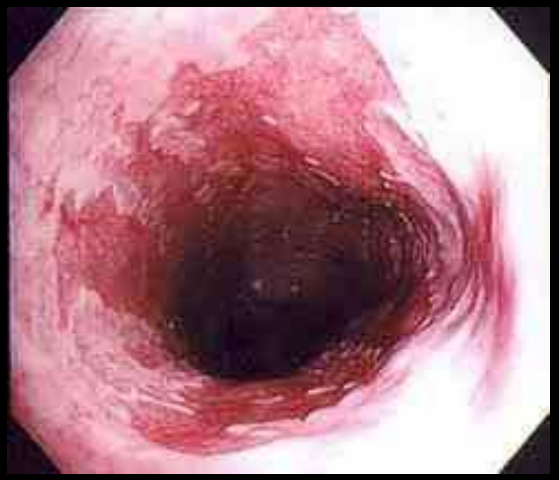
Drugs:

- Statins.
- NSAIDs &PPI.
- cyclooxygenase-2 selective inhibitors (COXIBs)

Screening of high risk groups

- There is no currently acceptable screening method for esophageal cancer in the United States. Economic models suggest Screening of high-risk individuals:
- White males , chronic reflux, age >50 years.
- Patients with Barrett's esophagus with frequent & long standing GERD (several times per week), GERD (>5 years).
- Patient with nocturnal reflux.

Screening of Barrett's esophagus



Barrett's esophagus without dysplasia:

- Repeat endoscopy should be performed within the next year. If no dysplasia is confirmed Therefore, the interval for additional surveillance has been recommended to be every 3 years

Barrett's esophagus and low grade dysplasia:

- Although an increased cancer risk has not been established, endoscopy at 6 months and yearly thereafter should be considered as long as dysplasia persists (C)

Barrett's esophagus with confirmed HGD

- Should be considered for surgery or aggressive endoscopic therapy (B). Patients with HGD who elect endoscopic surveillance should be followed-up closely (every 3 months) with extensive biopsy protocols for at least 1 year.

- If no further HGD is confirmed, then the interval between follow-up may be lengthened (every 6 months for 1 -2 years and then yearly as long as no dysplasia is reencountered.

If the presence or degree of dysplasia is indeterminate but there is evidence of acute inflammation due to GRED , repeat biopsy should be performed after 8 weeks of effective acid-suppression therapy.

- **Patients with achalasia :**

  There are insufficient data to recommend routine surveillance(C).

Patients with a severe caustic esophageal injury

Should undergo surveillance every 1 to 3 years beginning 15 to 20 years after the injury (C).

Patients with tylosis

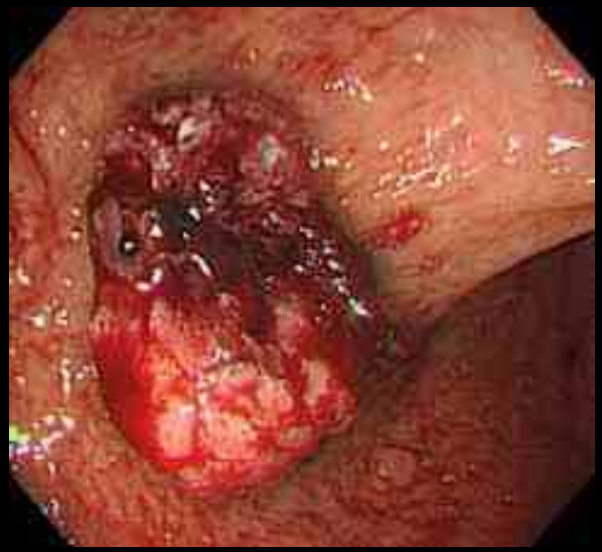
- Should undergo surveillance endoscopy every 1 to 3 years beginning at age 30 years

  (C).

Aerodigestives quamous cell cancer

- There are insufficient data to support routine endoscopic surveillance for patients with previous aerodigestives quamous cell cancer (C).

Stomach cancer



Risk factors:

- Certain medical conditions.
- Certain genetic conditions.
- Environmental causes.
- Diet.

Certain medical conditions:

- Helicobacter pylori (class I carcinogen)
- Intestinal metaplasia.
- Atrophic gastritis.
- Perinicious anemia.
- Gastric polyps.
- Previous stomach surgery

Certain genetic conditions:

- Family history of cancer stomach(mother, father, sister, or brother).
- Type A blood group.
- Familial adenomatous polyposis (FAP).
- Hereditary nonpolyposis colon cancer (HNPCC)
- Lynch syndrome.

Diet:

- low in fruits and vegetables.
- High in salted or smoked foods.
- Alcohol.
- Smoking.
- Nitrosamine?

Environmental factors:

- Being exposed to radiation.
- Working in the rubber or coal industry.
- people who come from countries where stomach cancer is common.

Stomach Cancer Prevention

- Avoiding risk factors.
- Screening of high risk patients.
- Increasing protective factors .
- Stop smoking.
- Treatment of H. pylori infection.

prevention

- Diet :eating fruits and vegetables that are high in vitamin C and beta carotene may lower the risk of stomach cancer.
- Studies also show that whole-grain cereals, carotenoids, green tea, and substances found in garlic may lower the risk of stomach cancer.

Prevention of cancer stomach

Screening

- Gastric epithelial polyps:
  - Adenomatous polyps are at increased risk for malignant transformation.
  - Hyperplastic polyps have a rare malignant potential.
  - Polyps should be endoscopically excised wherever feasible and clinically appropriate.

- If endoscopic polypectomy is not possible, a biopsy of the polyp should be performed
- If adenomatous or dysplastic tissue is detected, referral for surgical resection should be considered in (B)
- If the polyp is non dysplastic, no further intervention is necessary(B).

- Surveillance endoscopy 1 year after removing adenomatous gastric polyps is reasonable to assess recurrence, new or previously missed polyps, and/or supervening early carcinoma(B)

- If the results of this examination are negative ,surveillance endoscopy should be repeated at 3- to 5-year intervals (B).

Endoscopic surveillance for gastric intestinal metaplasia

- Has not been extensively studied in the U.S. and therefore cannot be routinely recommended (C).
- High-risk patients due to ethnic background or family history may benefit from surveillance (B).
- Patients with confirmed gastric high-grade dysplasia should be considered for gastrectomy or local resection because of the high incidence of prevalent carcinoma (B).

Patients with pernicious anemia

May be considered for a single screening endoscopy, particularly if symptomatic, but there are insufficient data to recommend ongoing surveillance (C).

Previous partial gastrectomy for PUD

- There are insufficient data to support routine endoscopic surveillance in these patients (C).
- If surveillance is considered, it should be initiated after an interval of 15 to 20 years.

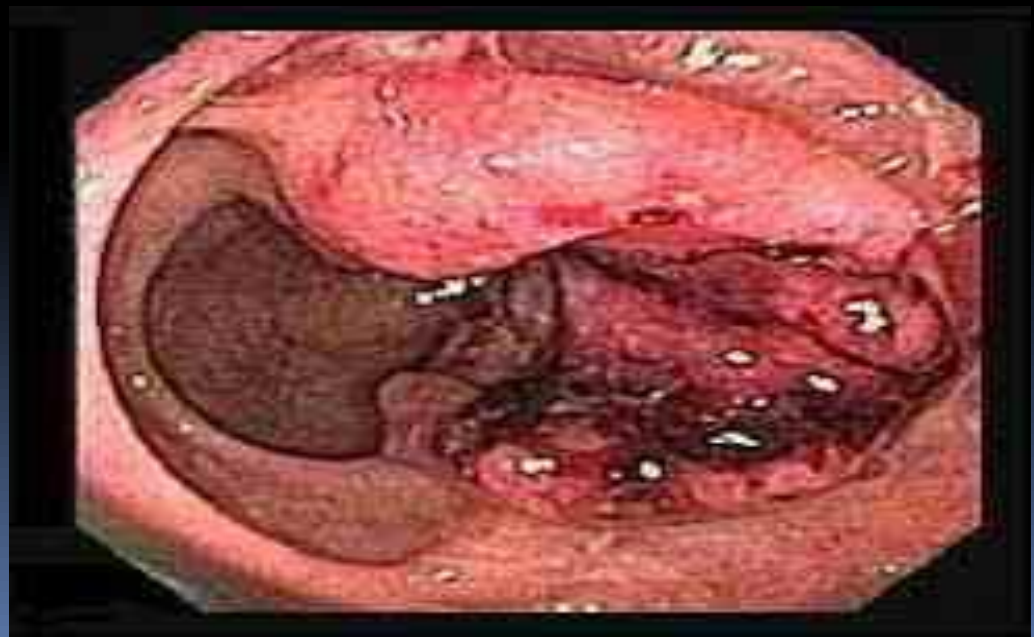
Patients with FAP

should undergo regular surveillance endoscopy starting around the time of colectomy or after age 30 years (B).

Patients with HNPCC

Have an increased risk of gastric and small-bowel cancer (B). Surveillance should be strongly considered (C).

PREVENTION OF COLORECTAL CANCER



Introduction

Colorectal cancer (CRC) is a common and lethal disease .

Worldwide, it is the second most commonly diagnosed cancer in women and third most common in men.

In the United States (US) ,CRC is the second leading cause of cancer death and accounts for approximately 9 % of cancer deaths overall .

Incidence

Globally, the incidence of CRC varies over 10-fold. The highest incidence rates are in Australia and New Zealand, Europe and North America, and the lowest rates are found in Africa and South-Central Asia .

- These geographic differences appear to be attributable to differences in dietary and environmental exposures that are imposed upon a background of genetically determined susceptibility.

EPIDEMIOLOGY

- CRC incidence and mortality rates vary markedly around the world. with over 1.2 million new cases and 608,700 deaths estimated to have occurred in 2008 . Rates are substantially higher in males than in females.

- CRC is infrequent before age 40; the incidence rises progressively thereafter to 3.7/1000 per year by age 80. The lifetime incidence for patients at average risk is 5 percent , with 90 percent of cases occurring after age 50.

- Given the finding that adenomatous polyps are precursors to cancer and that polyps and early cancers are usually asymptomatic, there is a strong rationale to support screening asymptomatic individuals for early cancer detection and prevention.

- Both the incidence of and mortality rates from CRC have been declining in the US . The onset of the decline some what predates:
  - Widespread screening.
  - Changes in behavioral risk factors.
  - Removal of colonic polyps.
  - Detection of CRCs at an earlier stage.
  - More effective treatments especially adjuvant treatment.

Risk factors

- Approximately 30% of individuals harbor risk factors for CRC and the other 70% are considered average risk.
- Factors confer a sufficiently high risk to alter recommendations for CRC screening.
- Factors that may influence screening recommendations.
- Risk factors that do not alter screening recommendations

Factors that currently influence screening recommendations

Hereditary colon cancer:

- **FAP and its variant:**
  - Gardner's syndrome.
  - Turcot's syndrome.
  - Attenuated adenomatous polyposis(AAPC)
- **MUTYH-associated polyposis coli .**
- **Lynch syndrome .**
- **Inflammatory bowel disease.**
- **Family history of CRC.**

Factors that may influence screening recommendations

- Race/ethnicity .
- Gender.
- Acromegaly.
- Renal transplantation

- **Risk factors that do not alter screening recommendations:**
  - Diabetes mellitus and insulin resistance.
  - Chronic insulin therapy .
  - Serum levels of C-peptide.
  - Cholecystectomy.
  - Alcohol .
  - Obesity.

Other risk factors

- Coronary heart disease.
- Cigarette smoking.
- Ureterocolic anastomoses.
- Diet : red meat.
- Coffe and tea.

Other risk factors

- History of radiation therapy for prostate .
- Barrett's esophagus.
- Several bacterial and viral agents :
  - Streptococcus bovis (S. bovis).
  - H. pylori.
  - Human papilloma virus) .
  - HIV-positive patients .
  - Prior treatment for Hodgkin lymphoma.

Familial adenomatous polyposis(APC)

- Caused by germline mutations in the (APC) gene located on chromosome 5 .
- Account for less than 1% of colorectal cancers.
- In typical FAP, numerous colonic adenomas appear during childhood.
- Symptoms appear at an average age of approximately 16 years .
- colonic cancer occurs in 90% of untreated individuals by age 45.

MUTYH-associated polyposis

- Caused by biallelic germline mutations in the base excision repair gene (MYH or MUTYH).
- These mutations predispose patients to autosomal recessive inheritance of multiple colonic adenomas that can present with a polyposis phenotype, frequently referred to as MUTYH-associated polyposis (MAP)

Lynch syndrome

- Often called hereditary nonpolyposis colorectal cancer (HNPCC).
- It is an autosomal dominant syndrome.
- More common than FAP
- Accounts for approximately 3 to 5 % of all colonic adenocarcinomas.

Lynch syndrome

The CRC that develop in patients with Lynch syndrome are characterized by:

- Early age of onset (mean age is 48 years).
- Some patients presenting in their 20s.
- Predominance of right-sided lesions:

  (nearly 70 % arise proximal to the splenic flexure)
- Approximately 10 % will have synchronous or metachronous cancers .

Lynch syndrome

Extracolonic cancers are very common

Particularly endometrial carcinoma 60%.

Other sites at increased risk of neoplasm formation include:

(ovary, stomach, small bowel, hepatobiliary system, brain and renal pelvis or ureter).

Risk factors

Personal history:

- Resection of a single CRC , metachronous primary cancers develop in 1.5 to 3 percent of patients in the first five years postoperatively.

- large (>1 cm) adenomatous polyps and polyps with villous or tubulovillous histology particularly if multiple . The relative risk (3.5 - 6.5)
- One or two small (<1 cm) tubular adenomas do not appear to be at substantially increased risk of metachronous CRC

Risk factors

Family history:

- Having a single affected first-degree relative increases the risk about 2 fold over that of the general population.
- Risk is further increased if two first-degree relatives have colon cancer or if the index case is diagnosed below 50 to 60 years of age.
- A family history of a large (>1 cm) or histologically advanced colonic adenoma carry about the same significance as a positive family history of CRC .

Inflammatory bowel disease

- Ulcerative colitis : The extent, duration, and activity of disease being the primary determinants of CRC .
  - Pancolitis confers a 5- to 15-fold increase in risk.
  - Left side colitis is associated with about a 3 fold relative risk.
  - The risk does not appear to be significantly increased with proctitis or proctosigmoiditis alone .

Ulcerative colitis

The co-occurrence of ulcerative colitis and primary sclerosing cholangitis identifies a subset of patients with an even greater risk.

The increase in risk of colon cancer begins about 8 to 10 years after the initial diagnosis of Pancolitis and 15 to 20 years for colitis limited to the left colon.

Ulcerative colitis

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- The probability of developing cancer then increases with disease duration, and by the fourth decade of disease, it reaches as high as 30 percent in patients with pancolitis.

Crohn's disease•

- **CD** associated with a similar relative risk of colon malignancy as extensive ulcerative colitis, although the data are less consistent.
- Recommendations from expert groups vary for **Crohn's** disease where there is less colonic involvement, but most guidelines recommend surveillance when one-third or more of the colonic mucosa is involved.

Factors that may influence screening recommendations

- **Race/ethnicity and gender:**
  - African Americans have the highest CRC rates of all ethnic groups in the US. CRC mortality is about 20 percent higher in African Americans than it is in whites .
  - CRC mortality is about 25 percent higher in men than in women, and both colonic adenomas and CRCs appear to have a more proximal distribution in women particularly in postmenopausal women.

- **Acromegaly :**
  - Patients with acromegaly are more likely to have multiple adenomatous polyps.
- **Renal transplantation:**
  - Renal transplantation, in association with long-term immunosuppression, has been linked with increased CRC risk .
- **Renal transplant recipients**

  Are screened for colorectal cancer starting at age 40 or five years after transplant.

Risk factors that do not alter screening recommendations

- There are a large number of clinical environmental and lifestyle factors that are associated with a small and/or uncertain increased risk of CRC. Although many of these associations have been seen consistently in observational studies, the causal relationship of these associations is largely unproven.

DM and insulin resistance

- Increasing evidence suggests that DM is associated with an elevated risk of CRC.

- A meta-analysis of 15 studies (six case-control and nine cohort) estimated that the risk of CRC among diabetics was approximately 30 percent higher than non diabetics.

- A similar relationship between serum levels of C-peptide and CRC risk was reported.
- Chronic insulin therapy may also be associated with an increased risk of CRC in diabetics, although the data are conflicting

Use of androgen deprivation therapy

- Men who received treatment with a gonadotropin-releasing hormone (GnRH) agonist or orchidectomy had a higher risk of developing CRC, and the risk increased with longer duration of ADT.

- Cholecystectomy:
  - **A relationship between cholecystectomy and right-sided colon cancer has been described in some reports.**

Obesity

Two large prospective cohort studies have shown that being obese confers an approximately 1.5-fold increased risk of developing CRC relative to being normal weight (body mass index 18.5 to 24.9 kg/m2).

Furthermore, obesity also increases the likelihood of dying from CRC .

Other risk factors

- **Cigarette smoking :**
  - Has been associated with increased incidence and mortality from CRC.
  - The association was stronger for cancer of the rectum than the colon .
  - Risk factor for all types of colonic polyps.
  - May increase for the risk of CRC in patients with Lynch syndrome.

Diet

- long-term consumption of red meat or processed meats may be associated with an increased risk of CRC, particularly left sided tumors .
- High temperature cooking (barbecuing) has been implicated, probably through the production of polyaromatic hydrocarbons and other carcinogens produced from proteins in the charring process.
- Lean red meat may be associated with less risk

- **Alcohol** :
  - Increased risk of CRC has been observed in several studies. The risk may be related to interference of folate absorption by alcohol and decreased folate intake

Caffeine:

- The evidence linking caffeine (coffee, tea) consumption and CRC is inconsistent.
- Although a link between high rates of coffee and a reduced risk of CRC was reported in a meta analysis of case control studies.

Other risk factors

- Radiation therapy for prostate cancer.
- Barrett's esophagus.
- Uretero-colic anastomoses after extensive bladder surgery.
- HIV-positive patients.

PROTECTIVE FACTORS

Physical activity:

- Substantial observational data suggest that regular physical activity, either occupational or leisure time, appears to be associated with protection from colorectal cancer.

- In a meta-analysis of 52 studies, there was a significant 24 % reduced risk of colon cancer when comparing the most versus the least active individuals across all studies (relative risk [RR] 0.76, 95% CI 0.72 to 0.81)]. R

protective factors

Diet:

- A diet high in fruits and vegetables.
- Low in red meat, animal fat and/or cholesterol.

Folic acid and folate :

- folate inhibits pathogenesis of cancer in a number of tissues including the colon .
- Its role in prevention of colorectal cancer is unclear.
- By contrast, the possibility that folic acid supplementation increases the risk of colon cancer has also been raised.

- **Vitamin B6 (pyridoxine):** The available data suggest a modest association between higher vitamin B6 intake and decreased colorectal cancer risk.

- **Calcium:** Another possible protective factor is increased intake of dietary or supplemental calcium and has been recommended for the primary or secondary prevention of colonic adenomas by the ACG.

- **Magnesium:** A population based study from Sweden found an inverse association between magnesium intake and the risk of colorectal cancer in women .

- **Garlic:** Consumption has also been consistently associated with a reduced risk of colonic adenomas in observational studies of patients with colorectal cancer and in laboratory studies.

- **Fish consumption:**

  Consumption of omega 3 fatty acids (mainly as fish oil) has been associated with a reduced incidence of colorectal cancer in observational studies. A meta-analysis of prospective cohort studies found an overall lower incidence of colorectal cancer among individuals with the highest compared with the lowest fish consumption (relative risk 0.88, 95% CI 0.78-1.00).

Drugs

Aspirin and NSAIDs:

- protect against the development of colonic adenomas and cancer.
- Regular use of aspirin and other NSAIDs are associated with a 20 to 40 percent reduction in the risk of colonic adenomas and colorectal cancer in individuals at average risk.

- Sulindac and celecoxib have been shown to cause regression of adenomas in familial adenomatous polyposis (FAP), and celecoxib was approved for a time as an adjunct to surgery for the treatment of this condition

Postmenopausal hormone therapy:

- Postmenopausal hormone therapy has been linked to a reduced risk of colorectal cancer.

Statins:

- Some observational data suggest that statins are associated with a protective effect against several cancers, including colon cancer, but overall, the data are conflicting

Fiber

- The degree to which dietary fiber protects against the development of adenomas or CRC is uncertain since the results of epidemiologic studies and at least two randomized trials are discordant.

Screening of CRC

Average-risk individuals

- Beginning at age 50 years:

Preferred modality

- Colonoscopy every 10 y

Alternatives

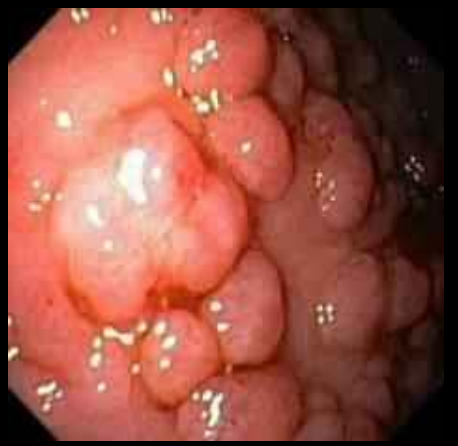
- FOBT yearly
- Flexible sigmoidoscopy every 5 y
- FOBT yearly and flexible sigmoidoscopy every 5 y.

Recommendations:

- Single digital rectal examination FOBT has a poor sensitivity for CRC and should not be performed as a primary screening method (A).

- Studies evaluating virtual colonoscopy and fecal DNA testing for CRC screening have yielded conflicting results and therefore cannot be recommended (A).

Screening of high risk groups



FAP

- Individuals with a diagnosis of FAP have an almost 100% risk for development CRC by age 40 to 50 years.
- Genetic testing along with counseling is recommended for individuals with hereditary forms of CRC, including FAP and HNPCC (C).

Individuals at risk for FAP should undergo screening flexible sigmoidoscopy yearly starting at age 10 to 12 years. The development of multiple, diffuse adenomas in the colon is an indication for total colectomy (B).

Individuals at risk for HNPCC should undergo colonoscopy every 1 to 2 years starting at age 20 to 25 years or 10 years younger than the age of the earliest diagnosis of cancer in the family, whichever is earlier (B).

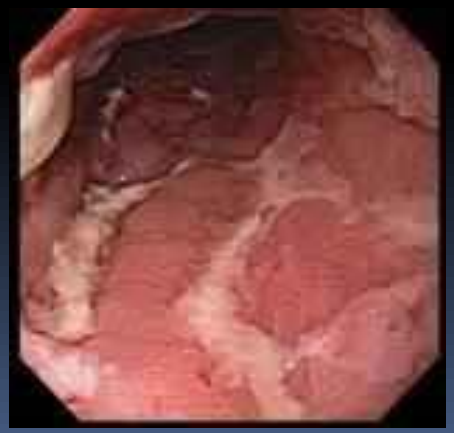
- **Individuals with a family history** of 1 or more first degree relatives with sporadic CRC regardless of age should have a colonoscopy beginning at age 40 years or 10 years younger than the affected relative. If the index colonoscopy has normal results, repeat colonoscopy should be performed on the basis of the age of the affected relative (B).

- Individuals with a first-degree relative age ≥60 years with adenomatous polyps should undergo colonoscopy beginning at age 40 years or 10 years younger than the affected relative. If the index examination is normal, recommend repeat colonoscopy every 5 years (B).

- **The risk of rectal cancer recurrence** is dependent on stage, surgical management, and the administration of radiation therapy.
- Patients who did not receive pelvic radiation for locally advanced disease or those who underwent non mesorectal resection should undergo sigmoidoscopy every 6 months for the first 2 years postoperatively (B).

Extensive UC and Crohn's colitis:

- Surveillance colonoscopy with multiple biopsy specimens should be performed every 1 to 2 years beginning after 8 to 10 years of disease (B).



A complete colonoscopy:

- Should be performed in all patients diagnosed with CRC to rule out synchronous cancers or adenomatous lesions. If a complete examination cannot be performed at the time of CRC diagnosis, a colonoscopy should be performed within 6 months after surgical resection (B).

Adenomatous polyps:

- Patients with a personal history of adenomatous polyps should undergo surveillance colonoscopy, the timing of which should be individualized depending on the number, size, and pathologic diagnosis of the adenomatous polyps removed, as well as the quality and completeness of the examination (B). When feasible, all polyps ≥0.5cm should be removed (B).

THANK YOU