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RISK FACTORS, SURVEILLANCE AND SCREENING OF COLORECTAL CANCER

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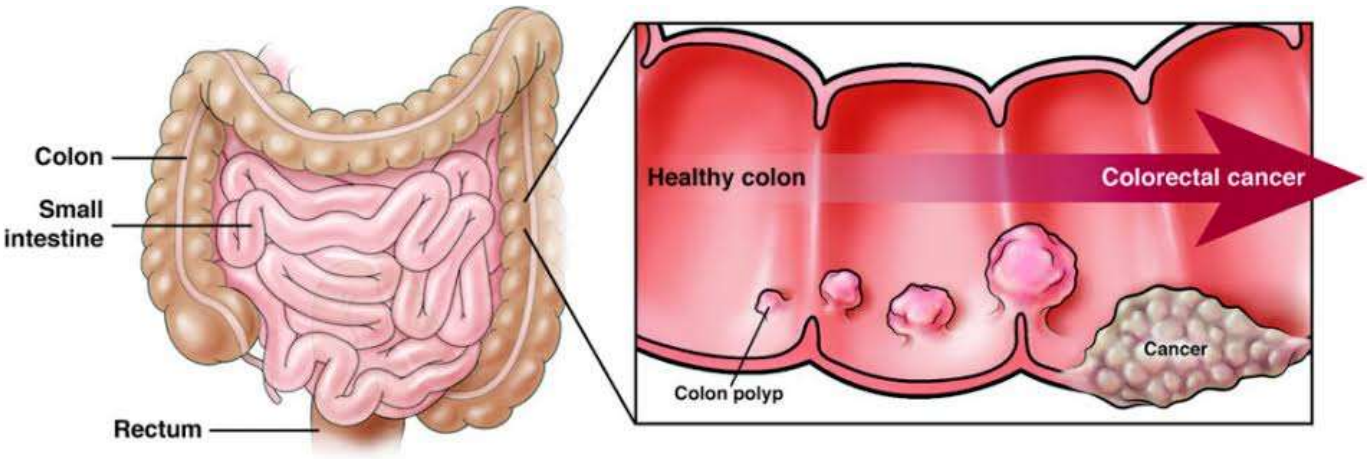
Introduction:-

The term colorectal cancer refers to a slowly developing cancer that begins as a tumor or tissue growth on the inner lining of the rectum or colon. If this abnormal growth, known as (a polyp), eventually becomes cancerous, it can form a tumor on the wall of the rectum or colon, and subsequently grow into blood vessels or lymph vessels, increasing the chance of metastasis to other anatomical sites. the cancers that begin in the colorectal region, the vast majority (over 95%) are classified as adenocarcinomas.These begin in the mucus-making glands lining the colon and rectum . Other less common cancers of the colorectal region include carcinoid tumors (which begin in hormone-producing intestinal cells), gastrointestinal stromal tumors (which form in specialized colonic cells known as interstitial cells of Cajal), lymphomas (immune system cancers that form in the colon or rectum), and sarcomas (which typically begin in blood vessels but occasionally form in colorectal walls)



Incidence:-

●The commonest lower G.I.T carcinoma.
●Usually occurs above 50 years but not rare before this age.
●Peak incidence is at 60s.
●It's more in males above 50 years & more in black race.
●Rectal carcinoma may occur in young age, around 30 years
●Carcinoma of right colon(cecum) is more in females

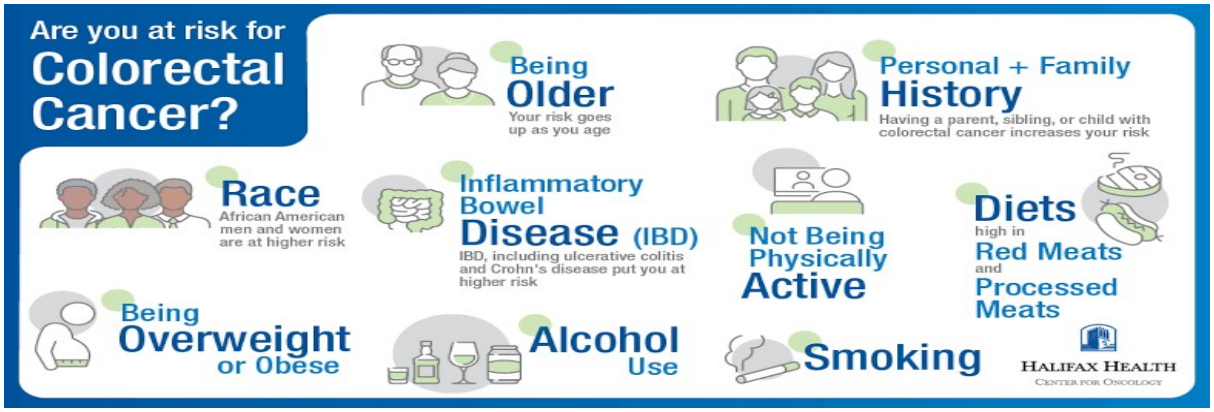
Epidemiology:-

In the United States, colorectal cancer is the third deadliest of all cancers. In 2016 there were an estimated 134,490 new colorectal cancer cases (70,820 in males and 63,670 in females) along with 49,190 colorectal cancer deaths (26,020 and 23,170 in males and females, respectively). Colorectal cancer ranks third, only behind prostate cancer and lung cancer, for new cases in males (8% of all new cancer cases), and behind breast cancer and lung cancer for new cases in females (8% of all new cancer cases however, the U.S national statistics have revealed reductions in both incidence rates and death rates. Although the highest colorectal cancer incidence rates can still be found in North America, Europe and Australia

New Zealand and other countries with historically low rates are now experiencing increased risk. For example, Japan and Thailand are suffering rapid increases in colorectal cancer incidence, and incidence has been steadily increasing in Iran for the past 30 years. The rates have more than doubled in Saudi Arabia since 1994, about the same time that rates started to increase in the Philippines. Elsewhere in the East, colorectal cancer incidence rates have also been slowly increasing, for example, in Jordan, as well as China, South Korea, and Singapore, all regions where cancers of the stomach and liver have typically caused the greatest concern. Another observable difference between incidence of colorectal cancer in the East and West can be seen in the average age of diagnosis. In the United States and European Union, only about 2-8% of cases occur in individuals under 40 years of age, whereas Egypt, Saudi Arabia, Philippines, and Iran show rates of 38%, 21%, 17%, and 15-35%, respectively for this same age group...

Risk factors for colorectal cancer (CRC):-

Individuals with risk factors are more likely to harbor cancer so precursors screening programs should be targeted toward this population....



Risk factors for CRC have been identified in epidemiologic studies. These include, amongst others, physical inactivity, genetic factors, family history, smoking and nutritional habits....

21.70 Dietary risk factors for colorectal cancer

Risk factor	Comments
Increased risk	
Red meat*	High saturated fat and protein content Carcinogenic amines formed during cooking
Saturated animal fat*	High faecal bile acid and fatty acid levels May affect colonic prostaglandin turnover
Decreased risk	
Dietary fibre*	Effects vary with fibre type; shortened transit time, binding of bile acids and effects on bacterial flora proposed
Fruit and vegetables	Green vegetables contain anticarcinogens, such as flavonoids Little evidence for protection from vitamins A, C and E
Calcium	Binds and precipitates faecal bile acids
Folic acid	Reverses DNA hypomethylation
Omega-3 fatty acids	May be of modest benefit

*Evidence is inconsistent and a clear relationship is unproven.

21.71 Non-dietary risk factors for colorectal cancer

Medical conditions

- Colorectal adenomas (p. 827)
- Long-standing extensive ulcerative colitis or Crohn's colitis (p. 813), especially if associated with primary sclerosing cholangitis
- Ureterosigmoidostomy
- Acromegaly
- Pelvic radiotherapy

Others

- Obesity and sedentary lifestyle – may be related to diet
- Smoking (relative risk 1.5–3.0)
- Alcohol (weak association)
- Cholecystectomy (effect of bile acids in right colon)
- Type 2 diabetes (hyperinsulinaemia)
- Use of aspirin or NSAIDs (COX-2 inhibition) and perhaps statins associated with *reduced* risk

(COX-2 = cyclo-oxygenase 2; NSAIDs = non-steroidal anti-inflammatory drugs)

(Genetics):

Most colorectal cancers develop as a result of progression from normal mucosa to adenoma to invasive cancer. This progression is controlled by the accumulation of abnormalities in a number of critical growth-regulating genes and can be divided into three main pathways:

1• Chromosomal instability (CIN). CIN is the most common cause of conventional adenomas throughout the colon. This pathway involves the sequential accumulation of genetic mutations in tumor suppressor genes, usually initiated by a mutation in the gene encoding adenomatous polyposis coli (APC).

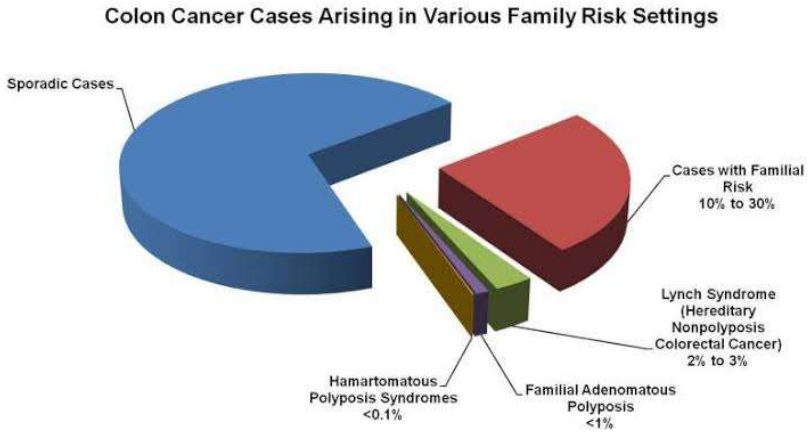
2• CpG island methylator phenotype. CpG island methylator phenotype (CIMP) tumors arise via the serrated neoplasia pathway and have a marked predilection for the proximal colon. Following an initiating genetic mutation in the genes encoding BRAF or KRAS, these lesions progress via epigenetic silencing of tumor suppressor and mismatch repair (MMR) genes by promoter methylation. This pathway is epitomized by the serrated polyposis syndrome.

3• Microsatellite instability. Microsatellite instability (MSI) tumors are also more commonly located in the proximal colon. They arise from defective DNA repair through inactivation of mismatch repair genes, epitomized by the germline mutation of MMR genes seen in Lynch syndrome (HNPCC).

This molecular classification can help to distinguish clinical characteristics, such as patient demographics, tumor distribution, response to therapy and prognosis.

(Cancer families):

A family history of CRC confers an increased risk to relatives. Family history, next to age is the most common risk factor for CRC. FAP is the best-recognized syndrome predisposing to CRC but represents less than 1% of all colorectal cancers. Lynch syndrome (HNPCC) accounts for 3–10% of familial cancer. Additionally, some colon cancers arise, at least in part, from an inherited predisposition, so called familial risk (Box below). Estimates of their frequency range from 10% to 30% of all CRC but the genes involved have yet to be identified. The risk of CRC can be estimated from a family history matched with empirical risk tables, so that appropriate advice regarding screening can be offered.



●Life time risk of colorectal cancer (CRC) in first-degree relatives of a CRC patient

Individuals affected	Risk
Population risk	1 in 50
One first-degree relative affected (any age)	1 in 17
One first-degree and one second-degree relative affected	1 in 12
One first-degree relative affected (age <45)	1 in 10
Two first-degree relatives affected	1 in 6
Autosomal dominant pedigree	1 in 2

●Most CRCs are, however, sporadic and occur in individuals without a strong family history. Their distribution is shown in:

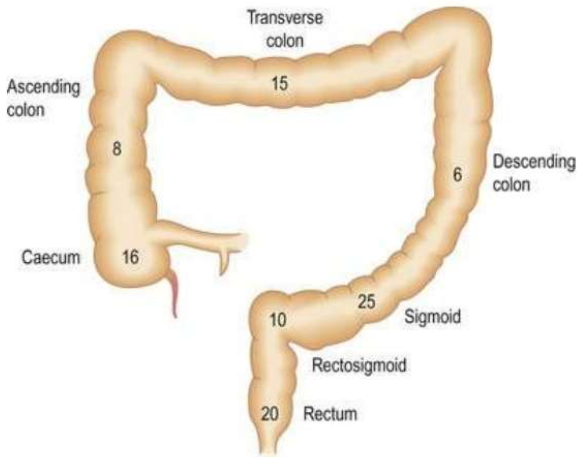


FIGURE 13.54 Distribution of sporadic colorectal cancer. Only 60%are in the range of flexible sigmoidoscopy.

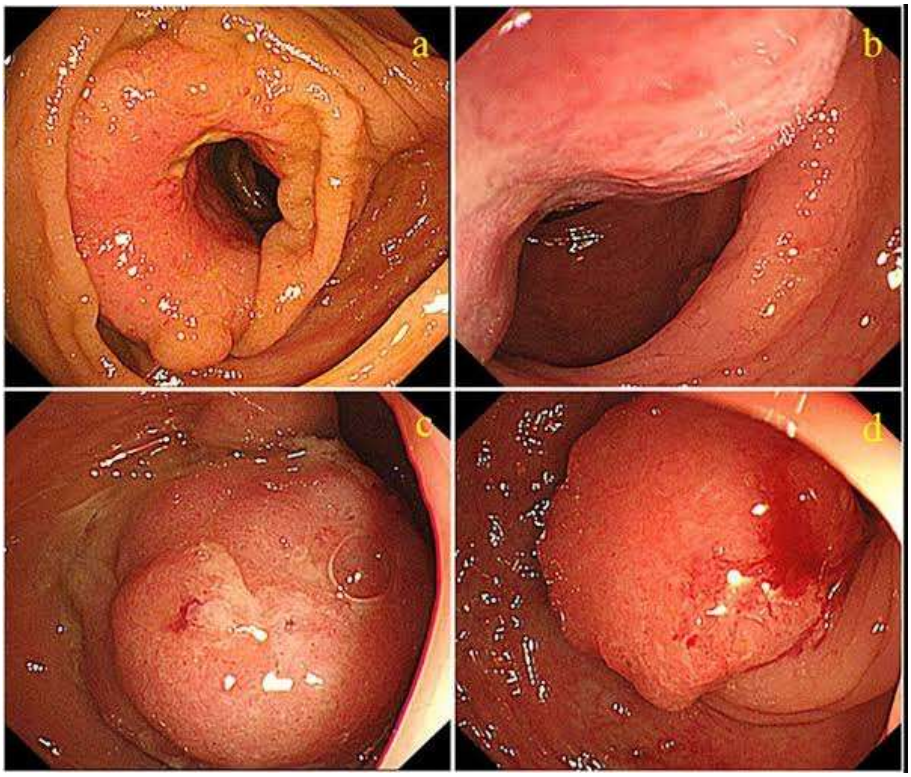
Pathology:-

CRC, which usually takes the form of a polypoid mass with ulceration, spreads by direct infiltration through the bowel wall. It involves lymphatics and blood vessels with subsequent spread, most commonly to the liver and lung. Synchronous cancers are present in 2% of cases. Histology is adenocarcinoma with variably differentiated glandular epithelium and mucin production. 'Signet ring' cells, in which mucin displaces the nucleus to the side of the cell, are relatively uncommon and generally have a poor prognosis.

I) Site:
- 2/3 of CRC in rectum & sigmoid colon
- In caecum 10%.
- Multifocal tumor occurs in 5%

II) Gross picture: It may be one of the following forms:

a. Proliferative type: commonest in the right colon & ampulla of rectum. It forms a bulky fungating cauliflower mass with ulceration, necrosis, hge & infection
b. Ulcerative type: commonest in the right colon & ampulla of rectum. the ulcer show features of malignancy.
c. Annular stricture type: commonest type in upper part of rectum & sigmoid colon
d. Colloid type: the wall of the colon is infiltrated by malignant tissue containing gelatinous substance.



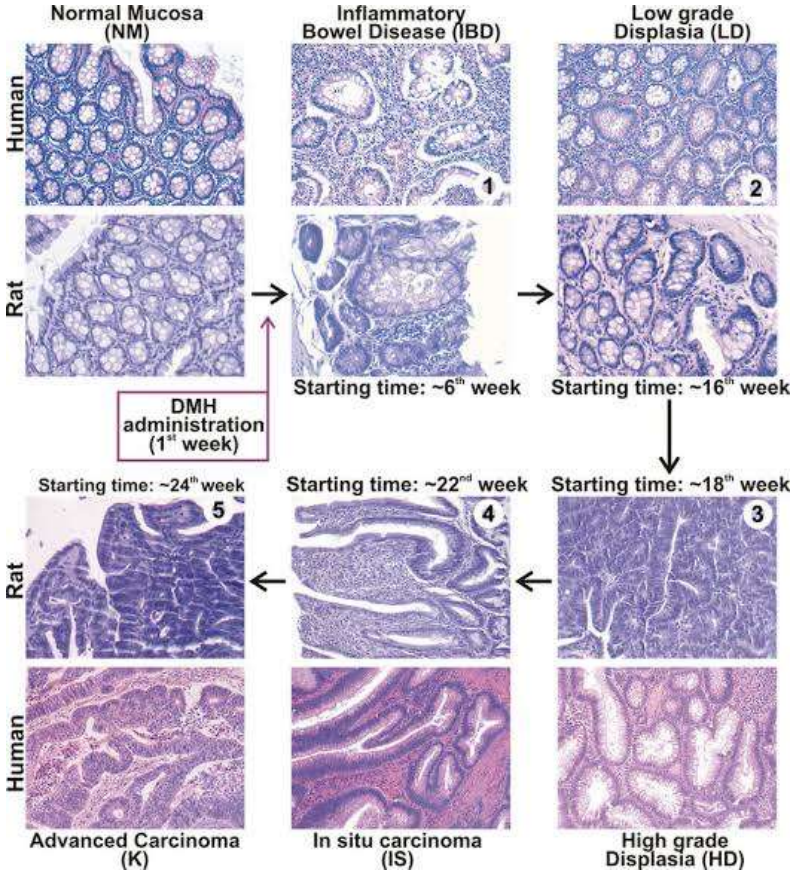
Colonoscopy images showing four tumors. (a) One cauliflower-like tumor with lumen stenosis is located in the ascending colon. (b) Another cauliflower-like tumor is located in the descending colon. The third (c) and fourth (d) tumors are located in the sigmoid colon.

III. Microscopic picture:

A-Adenocarcinoma: 95% of cases with colorectal carcinoma. It is one of the followings types:

a. Columnar cell adenocarcinoma: malignant cells are arranged in complete or incomplete irregular acini.
b. Spheroidal cell carcinoma: groups of spheroidal cells are separated by variable amount of fibrous tissue.
c. Colloid or mucoid carcinoma: it is an adenocarcinoma with excess mucin in the cells, acini and tissue spaces.

B-Squamous cell carcinoma: 5%, usually in the lower 1/3 of the rectum. It may be spread from carcinoma of the lower 1/2 of anal canal or due to squamous metaplasia.



Staging:-

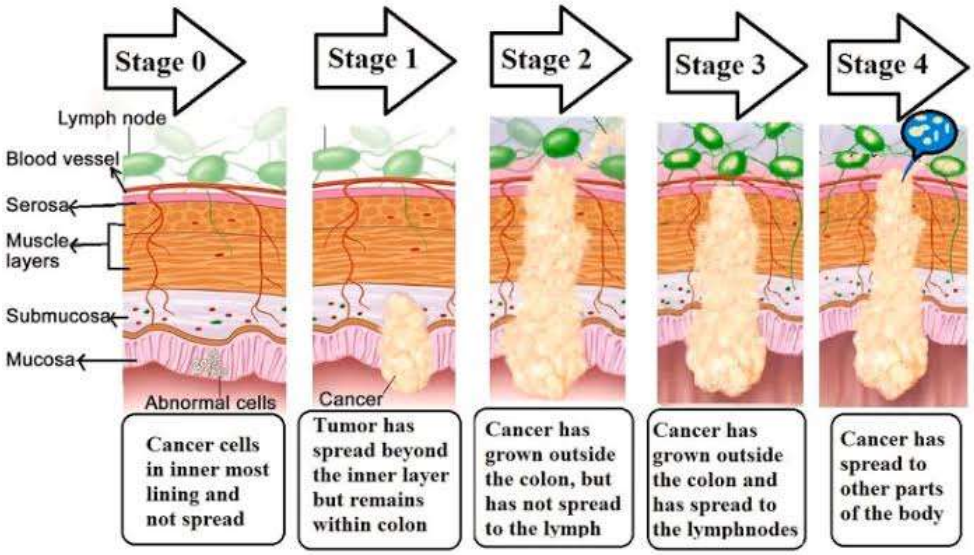
STAGING

1- T.N.M STAGING

T = Tumor	N = Nodes	M = Metastases
T_1 = invades into **submucosa**	N_0 = **No** nodes are involved	M_0 = **No** metastases.
T_2= invades into **musculosa**	N_1 = **1 - 2** nodes are involved	M_1 = distant metastases.
T_3 = invades into **serosa**	N_2 = **3 or more** nodes are involved	
T_4= invades into **another organ**		

2- DUKE'S STAGING

A =	The growth is **limited** to the bowel wall
B =	The growth extends **outside** the bowel wall **but NO L.Ns**
C =	**There are L.Ns** **C_1**= Para-rectal or Para-colic L.Ns **C_2**= Superior or Inferior mesenteric L.Ns
D =	**Distant metastasis**



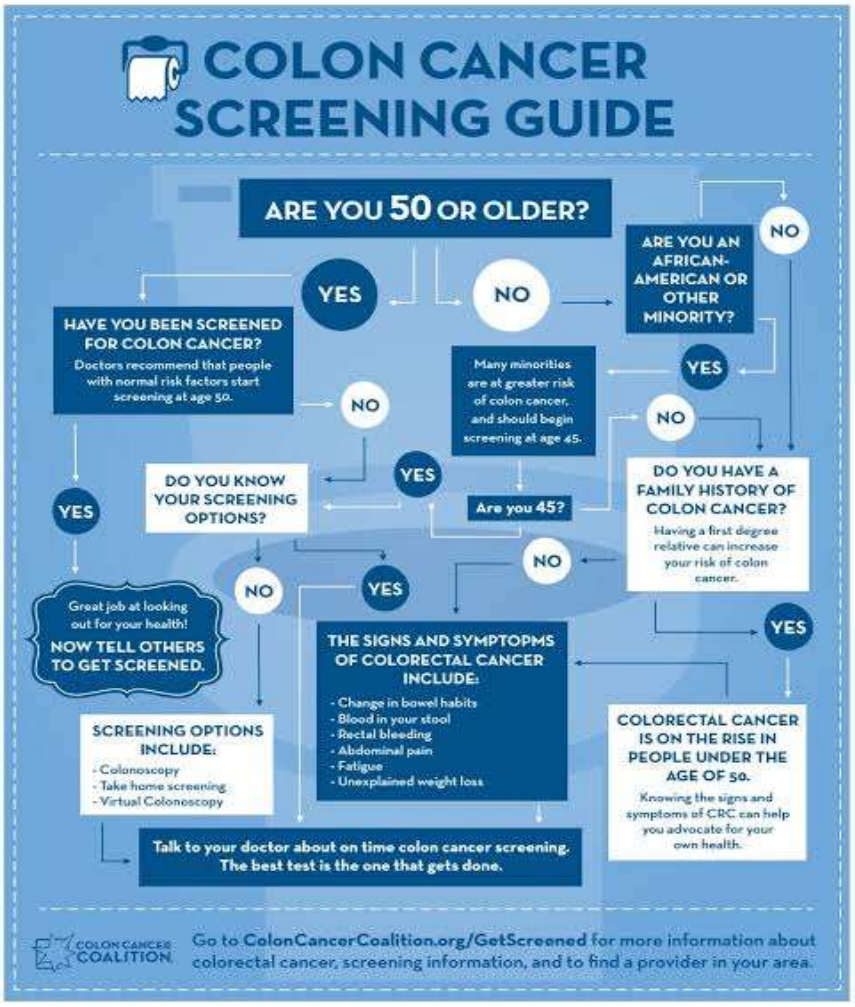
Clinical features:-

Symptoms suggestive of colorectal cancer include change in bowel habit with looser and more frequent stools, rectal bleeding, tenesmus and symptoms of anemia. A rectal or abdominal mass may be palpable. Cancers arising in the caecum and right colon are often asymptomatic until they present as an iron deficiency anemia. also, may present with intestinal obstruction. Patients aged over 35–40 years presenting with new large bowel symptoms should be investigated.....

Digital examination (PR) of the rectum is essential and examination of the colon should be performed in all cases.

Colorectal cancer screening and surveillance:-

Guidelines have been updated for screening for colorectal cancer. The original guidelines were prepared by a panel convened by the U.S. Agency for Health Care Policy and Research and published in 1997 under the sponsorship of a consortium of gastroenterology societies. Since then, much has changed, both in the research rature and in the clinical context. The present report summarizes new developments in this field and suggests how they should change practice. As with the previous version, these guidelines offer screening options and encourage the physician and patient to decide together which is the best approach for them. The guidelines also take into account not only the effectiveness of screening but also the risks, inconvenience, and cost of the various approaches. These guidelines differ from those published in 1997 in several ways: we recommend against rehydrating fecal occult blood tests; the screening interval for double contrast barium enema has been shortened to 5 years; (colonoscopy)is the preferred test for the diagnostic investigation of patients with findings on screening and for screening patients with a family history of hereditary nonpolyposis colorectal cancer; recommendations for people with a family history of colorectal cancer make greater use of risk stratification; and guidelines for genetic testing are included. Guidelines for surveillance are also included. Follow-up of postpolypectomy patients relies now on colonoscopy, and the first follow-up examination has been lengthened from 3 to 5 years for low-risk patients....



(Endoscopic and Radiologic procedures used for screening and investigations of colorectal cancer)

●Colonoscopy: is the 'gold standard' technique for examination of the colon and rectum and allows biopsy for histology. Biopsy of the tumor usually is mandatory at endoscopy...
It's the investigation of choice for high-risk patients. Universal screening strategies have been implemented in the UK for subjects between 60 and 69 years who have a positive FOB. Cancer has been detected in 8–12% of patients, 75% of which was located in the left colon; 72% of detected cancers are at an 'early' stage (10% polyp cancer, 32% stage I and 30% stage II).

●CT colonography: ('virtual colonoscopy') is increasingly being used.

●Double-contrast barium enema: although double-contrast barium enema (DCBE) offers the evaluation of the entire colon, its diagnostic sensitivity and specificity is inferior to colonoscopy and computed tomographic colonography (CTC). Even for large polyps and cancers, DCBE offers substantially less sensitivity (48%) than colonoscopy, and DCBE is more likely than colonoscopy to yield false positives (artefacts diagnosed as polyps). Patients with an abnormal barium enema need a subsequent colonoscopy. However, DCBE is widely.

●Endoanal and pelvic ultrasound.

●Chest, abdominal and pelvic CT scanning: evaluate tumor size, local spread, and liver and lung metastases, contributing to tumor staging.

●PET scanning: is useful for detecting occult metastases and for evaluation of suspicious lesions found on CT or MRI.

●MRI: is also useful for evaluating suspicious lesions found on CT or ultrasound, especially in the liver.

●Serum carcinoembryonic antigen (CEA): is of little use for primary diagnosis and should not be performed as a screening test. It is useful for follow-up, rising levels suggest recurrence.

●Fecal occult blood (FOB): tests are used for mass population screening.

Management:-

Management should be undertaken by multidisciplinary teams working in specialist units. About 80% of patients with CRC undergo surgery (often laparoscopically). The operative procedure depends on the *cancer site*...

Long-term survival relates to the stage of the primary tumor and the presence of metastatic disease. There has been a gradual move from using Dukes' classification to the TNM classification system. Long-term survival is only likely when the cancer is completely removed by surgery with adequate clearance margins and regional lymph node clearance.

1•Total mesorectal excision (TME): is required for rectal cancers and removes the entire package of mesorectal tissue surrounding the cancer. A low rectal anastomosis is then performed Abdomino-perineal excision, which requires a permanent colostomy, is reserved for very low tumors within 5 cm of the anal margin. TME combined with preoperative radiotherapy reduces local recurrence rates in rectal cancer to around 8% and improves survival. Pre- or postoperative chemotherapy reduces local recurrence rates but had no effect on survival in a recent study.

2•Segmental resection and restorative anastomosis: with removal of the draining lymph nodes as far as the root of the mesentery, is used for cancer elsewhere in the colon. Surgery in patients with obstruction carries greater morbidity and mortality. Where technically possible, preoperative decompression by endoscopic stenting with a mesh-metal stent relieves obstruction, so surgery can be elective rather than emergency, and is probably associated with a decrease in morbidity and mortality.

3•Local trans-anal surgery: is very occasionally used for early superficial rectal cancers.

4•Surgical or ablative treatment of liver and lung metastases: prolongs life where treatment is technically feasible and the patient is fit enough to undergo the treatment.

5•Radiotherapy: is not helpful for colonic cancers proximal to the rectum because of difficulties in delivering a sufficient dose to the tumor without excess toxicity to adjacent structures, particularly the small bowel.

6•Adjuvant postoperative chemotherapy: improves disease-free survival and overall survival in stage III colon cancer. Those with stage II tumors and advanced features such as vascular invasion may also benefit.

(Management of advanced colorectal cancer)

Advanced colorectal cancer is successfully palliated with little toxicity by 5-FU and folinic acid regimens or oral capecitabine in approximately 30% of patients for a median of 12–14 months. The addition of irinotecan or oxaliplatin increases the proportion who benefit to 55%, and extends median survival to 18 months but with increased toxicity. Anti-EGFR and VEGFR agents, increase the response rate with chemotherapy, such as 5-FU/folinic acid with oxaliplatin or irinotecan (FolFOX or FolFIRI), to 68% and the median survival from 19 to 24 months. Toxicity of the anti-VEGFR agents commonly leads to hypertension, proteinuria, arterial thrombus, mucosal bleeding and perforation, and delayed wound healing. The antiEGFR agents cause acneiform rash, hypomagnesaemia, and hypersensitivity reactions. Treatment can be intermittent or may comprise an intensive induction phase followed by maintenance with 5-FU and a relevant targeted agent which prolongs the progression-free survival but not the overall survival...
Liver and lung metastases are a common problem with colorectal cancers. With appropriate selection of patients who have a good performance status and in whom MRI and PET-CT scans do not demonstrate disease elsewhere, local treatment can prolong good-quality survival. This includes a variety of methods from surgical resection to gamma-knife irradiation, radiofrequency, cryo-ablation or hepatic artery embolization. Small lesions can be ablated, but larger lesions are best managed by partial hepatectomy or a combination approach, so that embolization is followed by hepatic regeneration before final resection. Patient selection is critical; long-term survival without recurrence is reported in up to "20% of patients at 5 years with a single <4-cm lesion amenable to resection presenting more than a year from initial diagnosis. More patients can be rendered suitable with perioperative chemotherapy, such as FolFOX or FolFIRI with cetuximab if RAS is wild-type....

(Follow-up)

All patients who have surgery should have a total colonoscopy performed before surgery to look for additional lesions. If total colonoscopy cannot be achieved before surgery, a second ‘clearance’ colonoscopy within 6 months of surgery is essential. Patients with stage II or III disease should be followed up with regular colonoscopy and CEA measurements; rising levels of CEA suggest recurrence. Annual CT scanning of the chest and abdomen to detect operable liver metastases should be performed for up to 3 years post-surgery.

Staging and survival of colorectal cancers

TNM classification	Description	Notation	Modified Dukes' classification	5-year survival (%)
Stage I (N0, M0)	Tumours invade submucosa	T1	A	90
	Tumours invade muscularis propria	T2		
Stage IIA (N0, M0)	Tumours invade into subserosa	T3	B	70
Stage IIB	Tumours invade directly into other organs	T4		65
Stage III (M0)	T1, T2 + 1–3 regional lymph nodes involved	N1	C	60
Stage IIIB	T3, T4 + 1–3 regional lymph nodes involved	N1		35
Stage IIIC	Any T + 4 or more regional lymph nodes	N2		25
Stage IV	Any T, any N + distant metastases	M1	D	7

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