COLO-RECTAL CANCER

GENERAL

- Incidence is higher in developed countries than in developing countries
- Colon cancer is shifting from distal colon to proximal colon

INCIDENCE

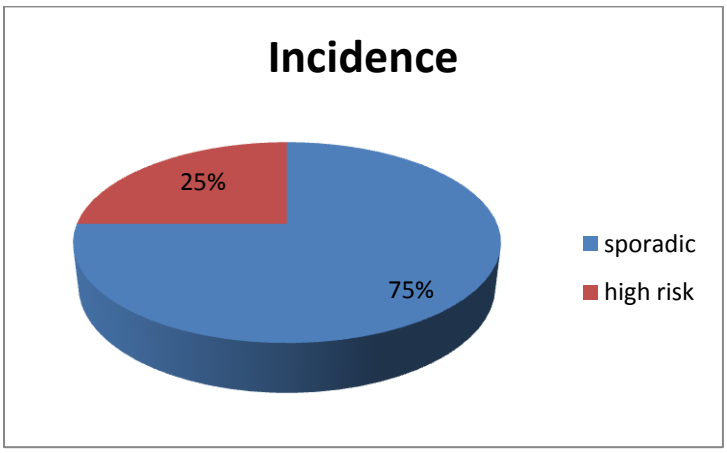
- In United states of America: 2013 American cancer society estimates
  - Colo-rectal cancer: Estimated cases 142820
  - Colon cancer: Estimated deaths 50830
  - Incidence has decreased in US in last decade
- Second leading cause of death
- The incidence of colorectal cancer increases with advancing age
- Similar among men and women until the age of 50 years, after which the incidence becomes higher in men.
- The highest incidence of disease occurs in countries of more advanced economic development
- A lifetime risk for developing colorectal cancer of approximately 1 in 18.

RISK FACTORS

Increased risk of colo-rectal cancer	
Polyposis syndromes	• Familial polyposis • Peutz-Jeghers syndrome • Juvenile polyposis
Hereditary non-polyposis colorectal cancer syndromes (HNPCC)	• Lynch type I (colorectal adenocarcinoma only) • Lynch type II (colorectal and extra colonic tumors, particularly uterine)
Other	• Inflammatory bowel disease • Prior polyps • Prior colon cancer • First degree relative with colo-rectal cancer diagnosed below age 50

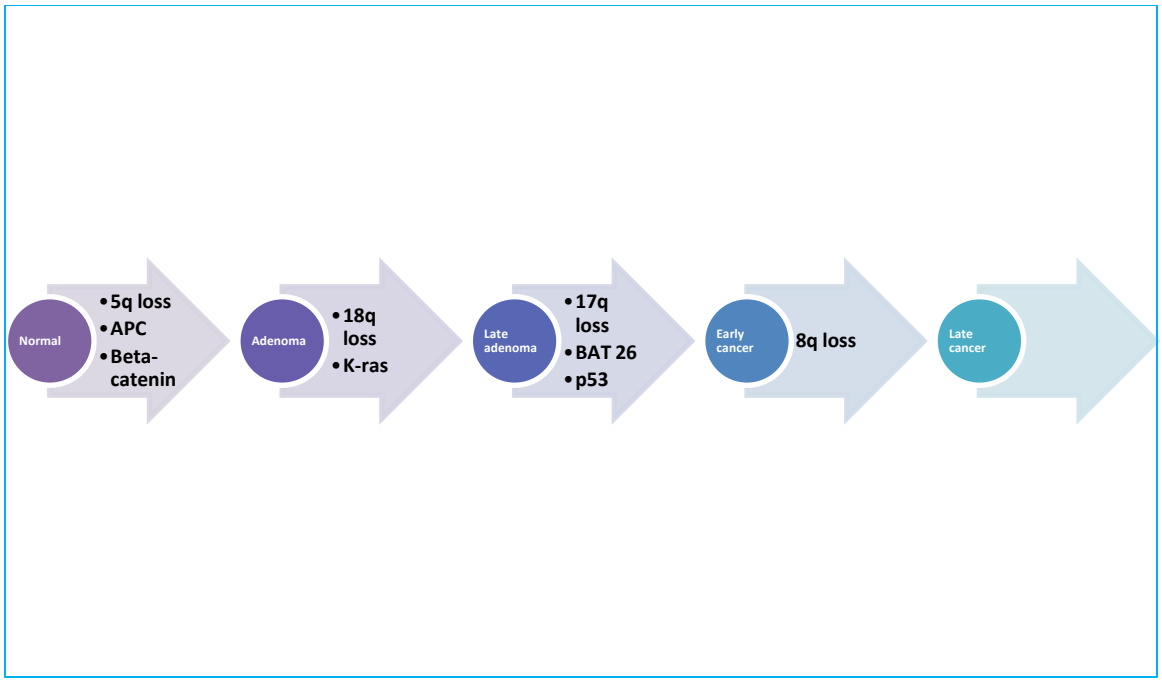
- Age: is the greatest risk factor for colorectal cancer, with 90% of cases occurring in patients older than 50 years.
- Individuals with a family history of colorectal cancer occurring in close relatives in the absence of known genetic predispositions
- In patients with familial hereditary cancer syndromes
- In those with inflammatory bowel disease.
  - Ulcerative colitis increase risk of colon cancer: 5-10% risk by 20 years of colitis, higher risk of synchronous cancers
  - Chrohn's disease also increase risk of cancer – particularly in the ileo-colic region (risk is generally not increased in absence of colonic involvement by Chrohn's disease)
- Most adenocarcinomas are thought to arise from adenomatous polyps. The risk for malignant conversion of polyps is related to polyp size, number, and histological type. (3% risk of cancer development in patient with history of polyps)
- Blacks have a greater incidence of and mortality from colorectal cancer than do whites.

- Approximately 75% of colorectal cancer occurs in individuals who do not have excessive risk factors- "sporadic cancer." About 25% cases occur in high-risk populations.
- Need more confirmatory prospective data on:
  - Amount of fat (relative to fiber) in diet is believed to have effect on colo-rectal cancer
  - Fiber rich food (at least 13 grams of fiber per day) is associated with low risk of colo-rectal cancer in case controlled studies
  - Dietary and lifestyle factors, including physical inactivity, calcium deficiency, excess body weight, and excessive consumption of alcohol—likely in conjunction with a diet low in folic acid and methionine—and smoking at an early age, are associated with an increased risk for developing colorectal cancer. However data from prospective studies are unclear.
  - Non steroidal anti-inflammatory drugs (Aspirin, Celecoxib) may have a protective effect against adenomas and colo-recital cancer (but not in Lynch Syndrome related).



PATHOGENESIS

- Germline genetic mutations (mutations incorporated into every cell of the body that can be passed onto children) are the basis for inherited colorectal cancer syndromes
- Accumulation of somatic mutations in a cell (acquired genetic mutations that cannot be passed on to children) is the basis for sporadic colorectal cancer.
- APC mutation activating *wnt* pathways are seen in 80-85% of sporadic colo-rectal cancer



- **Adenoma- carcinoma sequence: Mutations that lead to colo-rectal cancer**

Inherited colorectal cancer syndromes

1. Familial adenomatous polyposis (FAP)
2. Hereditary non-polyposis colorectal cancer syndromes (HNPCC)

Familial adenomatous polyposis (FAP)

- Inherited mutation in FAP coli (APC) gene (regulator of *wnt* signaling pathway)
- Mutation in APC leads to hundreds to thousands to polyps in colon
- Malignant tumors develop at young age
- Represent only a small % - 0.5 to 1% of total number of colo-rectal cancer
- up to 80-85% sporadic cancers also carry APC gene mutations

Other polyposis syndromes

- Gardener syndrome – epidermoid cysts, desmoids tumors, osteoma, fibromas, diffuse 100's of polyps
- Turcot syndrome – brains tumors, diffuse 100's of polyps
- Flat adenoma syndrome – 1-100 right sided polyps and fundic gland polyps and peri ampullary carcinoma
- Peutz-Jeghers syndrome – diffuse 1-100 polyps, ovarian and testicular tumors

Hereditary non-polyposis colorectal cancer syndromes (HNPCC) include:

- Lynch type I (colorectal adenocarcinoma only)
- Lynch type II (colorectal and extracolonic tumors, particularly uterine)

- Muir-Torre syndrome, a familial cancer syndrome that combines at least one sebaceous neoplasm and at least one visceral malignancy, usually gastrointestinal or genitourinary carcinoma.

Hereditary nonpolyposis colorectal cancer syndromes - Lynch type I and Lynch type II:

- Autosomal-dominant with high penetrance
- Malignant tumors develop at young age, proximal location (right side), mucinous pathology, higher grade
- Accounts for 5% to 10% of cases of colorectal cancer.
- Amsterdam criteria and Bethesda criteria are used to determine likelihood of HNPCC
- General prognosis is better for HNPCC colon cancer compared to sporadic colon cancer

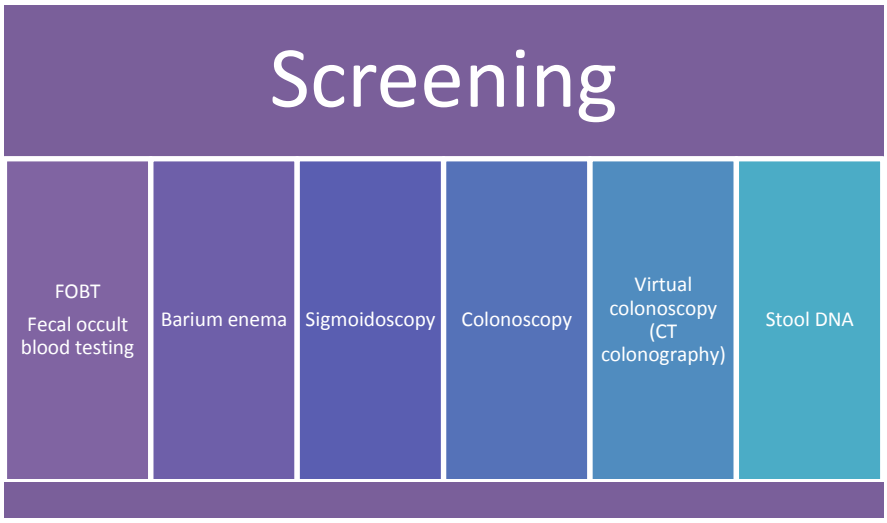
Microsatellite instability (MSI high)	Microsatellite stable (MSI low)
Common in HNPCC cancers	
Caused by mutations in DNA mismatch repair genes	
Mismatch repair defect allows genetic mutations to accumulate in colonic mucosa	
Reduced or absent DNA repair activity	
10-15% sporadic cancers also carry these mutations	
Tumors may develop quickly from normal mucosa without polyps phase (screening must be different for HNPCC)	
Better prognosis	Worse prognosis
Low sensitivity to FU based therapy	Better response to FU based therapy

PREVENTION STRATEGY

- Although the precise pathologic mechanisms of colorectal cancer have not been identified,
- Aspirin and nonsteroidal anti-inflammatory drug use has been associated with decreased colorectal cancer mortality rates in patients with rheumatologic disorders.

SCREENING

- Screening can reduce mortality from colo-rectal cancer
- Genetic screening for colorectal cancer should be reserved for those patients with an elevated risk.
- Customary screening protocols should be used for the rest of the population.
- Fewer than 30% cases go though screening.
- Guidelines for screening vary among different organizations.
- Common recommendation: Average risk
    - Start colonoscopy at age 50 - every 5-10 years
- Common recommendation: High risk
    - HNPCC: Colonoscopy every 1-3 years, start at age 20-25 (more right sided, may not be precede by polyps)
    - FAP: Start colonoscopy at as early as age 10



- FOBT + Sigmoidoscopy: Shown to be effective in reducing mortality from cancer but will miss proximal cancers
- Colonoscopy advantages
  - Screens entire bowel
  - Immediate biopsy is possible
  - Allows removal of polyps

SYMPTOMS / SIGNS

Symptoms depend on the site of the primary tumor:

- Change in bowel habits, diarrhea, constipation, a feeling that the bowel does not empty completely
- Bright-red blood in the stool or melanotic stools
- Stools that are narrower in caliber than usual.
- General abdominal discomfort (frequent gas pains, bloating, fullness, or cramps)
- Weight loss for no known reason, anorexia, fatigue.
- Documentation of symptoms, risk factors, and family history in all patients

Physical examination

- A digital rectal examination and fecal occult blood testing.
- Sings of metastatic disease – liver, abdomen, nodes, lungs etc.

DIAGNOSIS

- Lab: Iron-deficiency anemia may reflect prolonged bleeding from the tumor
- Abnormal liver chemistry studies may indicate hepatic metastases.
- An elevated (>5 ng/mL) preoperative carcinoembryonic antigen (CEA) level may be associated with poorer prognosis.
- Biopsy:
- A colonoscopy or lower endoscopy with biopsy
- Biopsy of metastatic site

HISTOLOGY

- Adenocarcinoma – most common

STAGING SYSTEM

- **AJCC staging**

STAGING WORK UP

- Preoperative studies.
  - A chest radiograph
  - A CT scan, or MRI of the abdomen and pelvis
  - A complete evaluation of the entire colon, preoperatively when possible, to determine the presence of additional polyps or synchronous multiple primary cancer.
  - CEA level
  - Rectal primary tumors: An endoscopic ultrasonography evaluation for accurate tumor stage and perirectal lymph node involvement.

PROGNOSTIC FACTORS

- Stage
- Local invasion T4
- Undifferentiated histology. mucinous features, signet ring type
- Lympho-vascular invasion
- Number of sampled nodes (minimum 12 needed for adequate sampling)
- Number of positive nodes
- Elevated CEA level
- Molecular markers and genetic signatures are being evaluated

TREATMENT

- Treatment depends on stage of cancer
  - Surgery
  - Chemotherapy
  - Radiation
  - Palliation

Table

Colon cancer				
TNM stage	Stage I	Stage II	Stage III	Stage IV
Incidence	T1-2N0M0	T3-4N0M0	TanyN1M0	TanyNanyM1
Treatment	15%	25%	35%	25%
	Surgery alone	Surgery	Surgery	Chemotherapy
	--	± ? chemotherapy	+ chemotherapy	± ? surgery

MANAGEMENT OF RESECTABLE TUMORS

Primary surgical management

- Open versus laparoscopic surgery: Same overall survival and recurrence.

Colon cancer surgery:

- Resection of the tumor-containing bowel segment, the adjacent mesentery, and the regional lymph nodes (generally hemi-colectomy).
- Patients whose tumors extend through the bowel wall to involve adjacent structures have no worse prognosis than patients with similarly staged disease without such invasion, provided that clear resection margins can be achieved.
- Table

Surgery alone for early stage colon cancer	
Stage	Cure rate
I	>85%
II	70-75%
III	30-50%

Rectal cancer surgery:

- In patients who undergo total mesorectal excision (that is, excision of the fatty tissue directly adjacent to the rectum that contains blood vessels and lymph nodes) for low or middle rectal tumors, or mesorectal excision to at least 5 cm below the tumor for high rectal primary tumors, local recurrence rates of less than 10% are achievable.
- Wide surgical resection and anastomosis with low anterior resection is performed when there is sufficient distal rectum to allow for conventional anastomosis or coloanal anastomosis.
- For lesions too distal to permit low anterior resection (usually tumors within 6 cm of the anal verge), wide surgical resection with abdominoperineal resection (removing the anus and sphincter muscle) and permanent colostomy, is performed.
- Surgery alone with either type of resection has been associated with local recurrence rates of 25%; postoperative radiation therapy administered alone or with chemotherapy has reduced local recurrence rates to approximately 15% and 10%, respectively.
- Pre-operative (Neoadjuvant therapy) for rectal cancer:
    - For rectal tumors near the anal sphincter, preoperative combination of chemotherapy and radiation therapy is effective in reducing tumor size to facilitate sphincter-preserving surgery. In patients who present with locally advanced unresectable rectal cancer (T4 tumors that directly invade other organs or structures), preoperative chemotherapy and radiation therapy may render the disease resectable.
    - The addition of 5-fluorouracil–based chemotherapy to radiation therapy is associated with an increased response and resection rate and improvement in local control postoperatively**.** To achieve optimal disease down-staging, full-dose radiation therapy (≥45 Gy) is recommended, with a 4- to 6-week delay between completion of radiation therapy and surgery. Although the value of additional postoperative chemotherapy in patients who have had preoperative chemotherapy and radiation therapy has not been established, many oncologists recommend additional chemotherapy with 5-fluorouracil and leucovorin or FOLFOX postoperatively.
    - Neo-adjuvant therapy with chemo-RT followed by surgery is considered standard of care in stage II and III rectal cancer. Oral Capecitabine or infusional FU are used concurrently with RT.

Post operative adjuvant therapy:

- *Colon cancer adjuvant therapy:*
  - Stage I:
    - Patients with stage I colon cancer have an excellent prognosis with surgery alone (90% or better survival at 5 years)
    - No adjuvant therapy is indicated.
  - Stage 2:
    - Patients with stage II disease who have surgery alone have a 5-year survival of approximately 75%.
    - Adjuvant chemotherapy remains controversial for patients with stage II disease, with an absolute treatment benefit of approximately 5%.
    - Not all stage II patients should get chemotherapy.
    - A discussion should be held with stage II patients about risk benefit ratio.
    - Some tools to help decide adjuvant chemotherapy candidates in stage II
      - Mayo clinic calculator or adjuvant online prognostic calculator
      - High risk features: T4, undifferentiated histology, perforation, obstruction, angio-lymphatic invasion or less than 10 nodes sampled)
      - Molecular markers: MSI (MSI high – good prognosis and do not need chemotherapy), LOH 18q etc.
  - Stage 3:
    - For patients with lymph node–positive colon cancer (stage III), the overall 5-year survival rate with surgery alone is approximately 50%.
    - Adjuvant chemotherapy is indicated and results in an approximately 30% reduction in disease recurrence and mortality.
    - Regimens of 5-fluorouracil and calcium leucovorin or oxaliplatin with 5-fluorouracil and calcium leucovorin (FOLFOX) are acceptable.
    - FOLFOX is better than FU-LV (HR 0.76 means 24% improvement in relative risk and 8-10% absolute risk reduction) – benefit may be limited to patient under age 70. Careful risk benefit analysis is needed before using adjuvant FOLFOX over FU-LV in patients over age 70 years.
    - FOLFOX is now considered standard of care in US.
    - Do not use Irinotecan based regimen in adjuvant setting.
    - Do not use Bevacizumab or Cetuximab type antibodies in adjuvant setting (as of 2013 data)
- *Rectal cancer adjuvant therapy:*
  - Patients with rectal cancer have local recurrences at a higher rate than do patients with colon cancer. The combination of adjuvant chemotherapy and radiation therapy is the standard treatment in the United States for patients with stage II and III rectal cancer.

Summary table: Post operative adjuvant therapy

Stage	**Colon cancer**	**Rectal cancer**
I	**--**	**--**
II	**Controversial**	**Chemo + RT**
III	**Chemotherapy**	**Chemo + RT**

Management of Patients with Metastatic Disease (Stage 4 cancer)

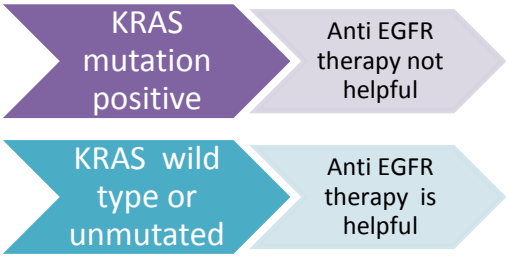
- Prognosis without treatment is poor for stage 4 disease – median survival is about 5-6 months.
- Most patients with metastatic disease have incurable disease and therapy is palliative.
- Goal: Extend life, improve quality of life.
- In patients with stage IV disease and in those with recurrent colon cancer, palliative chemotherapy is used.
- **Standard of care in US:** Combinations of 5-fluororacil + Leucovorin + Irinotecan (FOLFIRI) or 5-fluororacil and Leucovorin with Oxaliplatin (FOLFOX) with or without antibody are considered standard therapy in these patients. Combinations have significantly improved outcome in stage 4 disease.
- **Targeted agents:** Bevacizumab and Cetuximab and Panitumumab were approved for the treatment of advanced colorectal cancer. They are antibodies targeted to a protein that is more frequently found in colon cancer cells than in normal cells. These agents may not result in the usual side effects associated with use of conventional chemotherapeutic drugs. They do have different set of side effects.
- **Single agent:** Capecitabine is an orally administered prodrug of fluorouracil that has been shown to produce equivalent results compared with bolus-administration 5-fluorouracil/leucovorin as first-line therapy for patients with metastatic colorectal cancer.
- **Best supportive care:** Patients with poor performance status (that is, those who cannot perform activities of daily living because of cancer-related symptoms, such as fatigue, pain, and cachexia) are unlikely to benefit from systemic chemotherapy and are more likely to have considerable toxicity that may diminish the quality of life. Best supportive care with attention to symptom management is the most appropriate option in these patients.
- **Historical data:** Data have been obtained from several randomized prospective trials comparing a 5-fluorouracil–based chemotherapeutic regimen initiated at the time of diagnosis of metastatic disease with best supportive care in patients with good performance status. These data indicate that early institution of chemotherapy relieves anxiety, prolongs the time before symptoms appear, and increases survival.
- Oxaliplatin alone as single agent has very poor activity in stage 4 disease –Oxaliplatin alone is generally not used.
- Bevacizumab alone as single agent has very poor activity in stage 4 disease – Bevacizumab alone is generally not used.
- **Second-line:** For patients whose disease has progressed during or within the 6 months of front-line chemotherapy, second-line chemotherapy has been shown to be superior to best supportive care in patients with good performance status.
- Regorafenib is a novel targeted therapy approved as salvage treatment

Systemic agents used for stage 4 colo-rectal cancer		
Conventional cytotoxic drugs	Targeted therapy	Common regimens
Fluoropyrimidines (FU, oral Capecitabine)	Bevacizumab	FOLFOX ± antibody
Oxaliplatin	Cetuximab	FOLFIRI ± Antibody
Irinotecan	Panitumumab	Capecitabine + Oxaliplatin
	Regorafenib	Capecitabine + Irinotecan
	Ziv-aflibercept	FU-LV + Bevacizumab
		Others

Molecular markers and selection of antibody:

- K-RAS mutation positive colo-rectal cancers: Do not benefit from anti EGFR therapy (Cetuximab or Panitumumab).
- BRAF mutation positive colo-rectal cancers: Do not benefit from anti EGFR therapy (Cetuximab or Panitumumab).
- KRAS and BRAF are generally mutually exclusive mutations.

EGFR therapy based on KRAS mutation status



Liver directed therapy:

- Most patients with metastatic disease are not candidates for liver resection because of the presence of multiple hepatic lesions or extra hepatic involvement.
- Metastatectomy has not been proved in randomized clinical trials. However, tumor resection in patients with three or fewer hepatic metastases has been associated with 5-year survival rates of 20% to 25% - even up to 30% in highly selected patients. Selection of relatively healthy patients with a minimal burden of systemic disease may explain some or all of these favorable outcomes.
- Patients with limited pulmonary metastases may also be considered for surgical resection, with 5-year disease-free survival possible in highly selected patients.
- Historical data: Not used much now. Data from randomized clinical trials indicate a benefit in time to recurrence for patients who received a combined hepatic arterial infusion of fluorodeoxyuridine and intravenous 5-fluorouracil–based therapy after metastatectomy but not in overall survival. It is unclear how this therapy compares with newer systemic chemotherapeutic regimens that result in higher response rates and improved survival.
- Used sometimes in US: Other local ablative techniques include cryosurgery, chemoembolization, and radiofrequency ablation. Cryosurgical ablation in patients with hepatic metastases that are deemed unresectable because of their location, distribution, or excessive number may be associated with long-term disease control. Prognostic variables that predict a favorable outcome in patients who undergo cryotherapy are similar to those in patients who undergo hepatic resection.

Summary for stage 4 disease:

- FOLFOX or FOLFIRI are current best first line regimens for patients with good performance status. Antibody added to FOLFOX or FOLFIRI adds further benefit.
- Sequential treatment is possible for patients in good health.
- A small number of patients with surgical resectable metastases might have prolonged survival. Chemotherapy is necessary part of overall management of this group.

SPECIAL SITUATIONS

- Colon cancer or dysplasia in inflammatory bowel disease: Consider near total or subtotal colectomy (high risk of synchronous and metachronus cancers)
- HNPCC type II: Consider hysterectomy and oophorectomy in women beyond child bearing age.
- Stage 0 cancer (carcinoma in situ or intra mucosal disease if detected); generally treated with endoscopic resection, however nodes are not assessed and make sure that invasive disease is not missed.

- A small number of patients with stage 4 disease with a very limited and resectable lung or liver metastases might have chance of cure if complete surgical resection or metastatic sites is feasible.

FOLLOW UP

Postresection Colorectal Cancer Surveillance

- In patients with colorectal cancer who have undergone a complete resection, most have recurrences within 5 years, usually within 3 years of surgery.
- Local recurrences from a colonic primary tumor most commonly develop at the site of anastomosis, in the resection bed, or in the contiguous, para-aortic, and paracaval lymph nodes. Anastomotic recurrences that produce local symptoms are the most curable, followed by local soft-tissue recurrences.
- Regional and retroperitoneal lymph node recurrences portend systemic disease and a poor prognosis.
- The liver is the most frequent site of metastasis in patients with colon cancer, whereas rectal cancers may spread through paravertebral venous and lymphatic channels to the lungs, without liver involvement.

Recommendations by the American Society of Clinical Oncology for postresection surveillance of colorectal cancer are shown below.

- Because empiric evidence for better outcomes is weak, these recommendations are derived from panel consensus rather than evidence-based data.
- Data from a large surveillance study indicated that approximately 80% of colorectal cancer recurrences were indicated by serum CEA measurement, with only 20% detected by routine history-taking and physical examination performed during the same period.
- Therefore, monitoring of CEA concentrations is often performed in patients who would be candidates for surgical resection. However, the benefit of postoperative CEA measurement has not been found to improve survival.
- Approximately one third of colorectal cancer recurrences are associated with normal serum concentrations of CEA, particularly for poorly differentiated tumors.
- CEA concentrations that were normal in patients before colorectal cancer resection may increase with disease recurrence.
- Patients should undergo postresection colonoscopy to document a cancer- and polyp-free colon, with repeated colonoscopy every 3 to 5 years to detect new cancers and polyps, in accordance with the World Health Organization's recommendations for patients with adenomatous polyps.

Colo-rectal cancer surveillance: Follow up care: 2005 American Society of Clinical Oncology recommendations:

Follow up	Year 1	Year 2	Year 3	Years 4-5
Doctor's visit	Every 3-6 months	Every 3-6 months	Every 3-6 months	**Every 6 months**
CEA test	Every 3 months	Every 3 months	Every 3 months	**As determined by doctor**
CT chest and abdomen	Every year if recommended by doctor	Every year if recommended by doctor	Every year if recommended by doctor	
CT pelvis for rectal cancer	Every year if recommended by doctor	Every year if recommended by doctor	Every year if recommended by doctor	

Colonoscopy	Once		At 3 years	
Procto-sigmoidoscopy for rectal cancer only: Every six months for five years (for patient who did not have radiation treatment).				
After five years, the need for future test sand visits are decided by the patient and doctor.				

- Any additional imaging or testing can be done based on new symptoms. Report any new symptoms promptly.
- Please note that individual patient recommendations may vary based on individual case scenarios.

PROGNOSIS

- See above.

SAMPLE QUESTIONS