

COLORECTAL CANCER REVIEW

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ABSTRACT

Cancer had become a common disease worldwide and cancer related death is also increasing in various parts of the world in spite of increased screening and diagnostic facilities available with effective treatment modalities and modern technologies. The prevalence of different type of cancer varies with variation in the living environment, differences in the ethnicity, diet and life style. Early detection of cancer and availability of advanced health care system makes it possible to reduce cancer related mortalities. Life style modification, sedentary life style, processed food and fast-food consumption, lack of fibre rich food in the diet, stress causes alteration in the microenvironment of the cells leading to genetic changes and mutation. Mutation in the cellular level becomes the primary reason for the development of cancer cells. Colorectal cancer prevalence, risk factors for the development of colorectal cancer, pathogenesis, diagnosis and various treatment modalities available are discussed in this article.

KEY WORDS: Cancer, colorectal cancer, chemotherapy, biological agents.

INTRODUCTION:

Cancer is defined as abnormal division of cells. Uncontrolled cell division in the region of colon or rectum it is called as colorectal cancer (CRC). The colon, rectum and anus make up the large intestine which is the final segment of the gastrointestinal system. Large intestine absorbs water and minerals and eliminates waste. The first part of the large intestine is colon which is about 1.5 meters in length and 5 cm diameter. Colon is divided into 4 regions such as ascending colon, transverse colon, descending colon and the sigmoid colon. Colorectal cancer is caused by eating low fibre and high fatty food. Study says too much consumption of alcohol, smoking and sedentary life style can increase the risk of CRC. Presentation of Inflammatory bowel disease, a family history of colorectal cancer can also be a risk factor for the development of colon cancer. A polyp is a small growth in the lining of the colon which can develop into an adenomatous (precancerous) polyps over time. Colorectal cancers begin as small precancerous polyps which grows

slowly without causing much symptoms until they become large or cancerous. Screening of these polyps at the right time can aid in the removal of them and preventing its growth into cancer. Polyps undergo various mutation in the cellular DNA and gets converted in a cancerous out growth¹.

MATERIALS AND METHODS:

Prevalence:

Colorectal cancer is the third most common type of cancer worldwide amongst men and second most common type of cancer amongst women. Almost 2 million cases were diagnosed in the year 2020. It is the second most common cause of cancer related deaths, almost 1 million deaths per year happened in the year 2020 according to WHO statistics. The burden of colorectal cancer is highest amongst Asians. More than half a million new cases and more than 280,000 deaths reported annually in China. Second highest number of deaths from colorectal cancer, almost 60,000 per year was reported by Japan¹.

Highest incidence rates have been identified in regions of North America, Europe, Australia, New Zealand, South Korea, Japan. 45% of incidence have been identified amongst low and middle-income countries [LMICs] accounting to 52% of death in these regions. Increased incidence in the number of cases and death has been observed in regions of Eastern Europe, China and South America. Decreased incidence observed in regions of South Asia and Africa. The differences observed in these regions may be due to limitation in screening or access to early detection and health care².

The incidence rates for colorectal cancer among Indian population were 4.4 per 100000 population. More than 1.4 million new cancer cases are being identified every year amongst the Indian sub-population³.

Five-year survival rate for stage 4 colorectal cancer at the time of diagnosis was less than a 10% which might be due to the ineffectiveness of current treatment regimens.

Worldwide, an estimated 1,931,590 colorectal cancer were newly identified during the year 2020. Incidence of CRC varies as much as six-times in different regions globally. Southern European region has the highest estimated rates (per 100,000 population, 40.6 in men and 24.5 in women), as compared to the lowest levels in south-central Asia (per 100,000 population, 6.6 in men and 4.4 in women).

Worldwide, CRC had caused around 935,173 deaths during the year 2020, leading to 9.4% of CRC related mortality overall. As with incidence rates, mortality rates worldwide vary six-fold, with the highest estimated mortality rates at the eastern and central Europe (14.5 / 100,000), and the lowest in the regions of south-central Asia (3.2 per 100,000 population)⁴.

Anatomy:

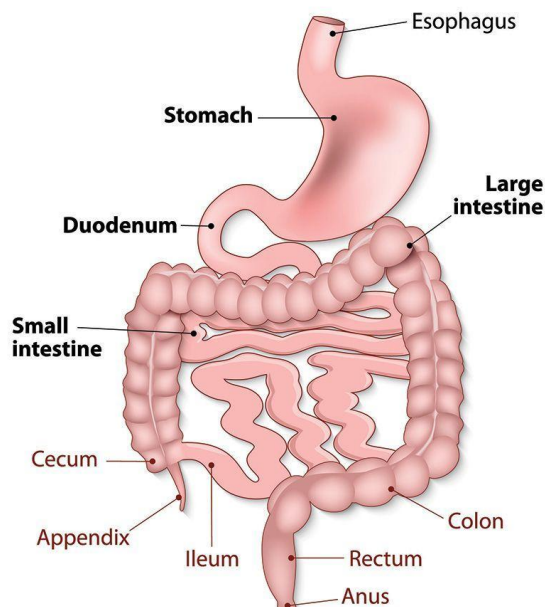


Fig 1: Gastrointestinal tract

Risk factors:

Some of the major risk factor for the development of colorectal cancer are: having a family history of colorectal cancer among the first-degree relative, increase in age. A personal history of colorectal adenomas, ovarian cancer. Hereditary conditions like familial adenomatous polyposis and Lynch syndrome. History of chronic ulcerative colitis or Crohn's disease. Excessive alcohol consumption, cigarette smoking, obesity, being an African-American can have a risk for the development of CRC⁵.

Etiology:

AGE: Majority of CRC occurs in people above the age of 50, though it is found amongst younger adults also. The incidence had declined in older adults due

to early detection and screening. But the incidence has increased in younger adults below 50 for unknown reasons.

Genetics: Mutation of APC gene results in Familial Adenomatous Polyposis (FAP) which can develop into CRC and have a 100% risk. Hereditary non-polyposis colon cancer syndrome (HNPCC) has 40% risk of development for CRC.

Race: Black people have a higher risk and incidence in US and also increased death rate.

Gender: Men have higher in the incidence rate than women.

Family History: About 6% have an association with inherited genetic mutation.

Rare Inherited Conditions: Lynch syndrome, Familial adenomatous Polyposis, attenuated familial adenomatous polyposis, Gardner syndrome, Juvenile polyposis syndrome, Muir-Torre syndrome, MYH associated polyposis, Peutz-Jeghers syndrome, Turcot syndrome.

Adenomatous Polyyps: Presentation of adenoma in the colon has high risk of developing into a CRC⁶.

Diet: Diet rich in animal fat, red meat is linked with the development of CRC. Also diet with low fibre, low fruits and vegetable intake can also progress to CRC.

Life Style: Obesity, smoking, consumption of alcohol, excessive consumption of sweetened beverages, sedentary life style has increased the risk of development of CRC.

Inflammatory Digestive Tract: Presentation of IBD like Ulcerative colitis, Crohn's disease increases the risk of CRC.

Signs and symptoms:

Iron-deficiency anaemia, rectal bleeding, abdominal pain, change in bowel habits, intestinal obstruction or perforation.

Physical findings:

Early Disease: Fatigue, weight loss.

Advanced Disease: Abdominal tenderness, macroscopic rectal bleeding, palpable abdominal mass, hepatomegaly, ascites.

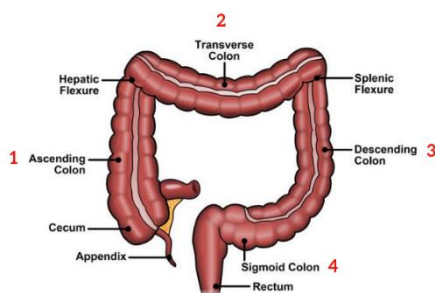
Diagnosis: Diagnosis of CRC can be done by performing a complete blood count test, liver function tests, serum carcinoembryonic antigen.

Imaging Studies: Imaging studies include chest radiography, chest computed tomography, abdominal barium study, abdominal/pelvic CT, contrast ultrasonography of the abdomen and liver, abdominal/pelvic MRI, Positron emission tomography, including fusion PET-CT scan.

Other Procedures: Other procedures which can help in providing conclusive evidence for the presentation of CRC are Colonoscopy, Sigmoidoscopy, Biopsy of suspicious lesions, Double-contrast barium enema⁷.

Pathophysiology: Molecular Pathway for Colorectal Cancer

The colon is divided into four sections



Conventional Pathway: More than 80% CRC cases are caused due to chromosomal instability pathway, which is initiated by APC mutation, followed by mutations in KRAS, PIK3CA and SMAD4, loss of heterozygosity of chromosome 18 (LOH 18q) and TP53 mutation. Colorectal cancer progression through conventional chromosomal instability pathway is associated with high levels of CIN (CIN+++), microsatellite stability (MSS) and very low levels of the CpG island methylation pathway (CIMP-).

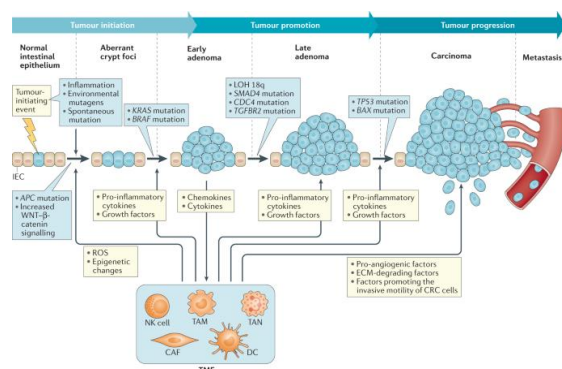


Fig 2: Large Intestine

Fig 3: Tumour pathogenesis

Serrated Pathway: Around 20% of CRC cases develop cancer through the serrated pathway. Serrated pathway can be divided into CIMP^{low} MSS tumours (KRAS mutations), BRAF-mutant CIMP^{high} MSS tumours or BRAF mutant CIMP^{high} microsatellite instability (MSI) tumours. Serrated

tumours are mostly associated with silencing of *MGMT*, *CDKN2A* or *MLH1*.

MSI pathway: CRC cases are development due to dysfunctional DNA mismatch repair genes⁸.

Premalignant Adenoma: Premalignant adenoma undergoes genetic transformation and results in adenocarcinoma which can be invasive. Mutation takes place in the adenomatous polyposis gene (APC), activating oncogene c-MYC and cyclin D1 resulting in the progression towards malignancy.

KRAS mutation: KRAS (Kirsten rat sarcoma viral oncogene), belongs to the RAS family genes associated with tumour. KRAS binds to guanosine 5'-triphosphate (GTP), and gets activated and is involved in the process of cell signal transduction for the regulation of cell proliferation and differentiation.

When mutations happen in the KRAS gene, the responsiveness to GAPs gets altered. Mutation results in rapid exchange for GTP, uncontrolled cell division, growth, transformation and metastasis. This also results in the development of resistance to chemotherapy and EGRF targeted therapy. KRAS mutations lead to unusual signal activation of the RAS/RAF/MEK/ERK signalling pathway and promotes liver metastasis. KRAS mutation enhances angiogenesis by activating Vascular endothelial growth factor. KRAS mutation also affects the tumour microenvironment by increasing the glucose uptake of the tumour cells, alter glutamine metabolism and elevate autophagy. KRAS mutations causes elevated levels of glycolysis and protein expressions and metabolic alterations⁹.

DNA mismatch repair: Deficient DNA mismatch repair results in the development of CRC. Mutations of MSH2, MLH1, and PMS2 gene results in high frequency microsatellite instability resulting in the development of hereditary nonpolyposis colon cancer syndrome.

Epigenetics: Abnormalities in the tumour suppressor genes or activation of oncogenes results due to abnormal DNA methylation, this can compromise the genetic balance of the cell and results in malignant transformation.

Staging:

Stage 0 is the very early stage of cancer, this is followed by stage I, II, III, IV. Lower the number in the stage, lesser the cancer spread.

The American Joint Committee on Cancer (AJCC): TNM system of cancer staging: TNM

system staging of cancer is based on the size and spread of the cancer cells.

Size of tumour (T): Growth of the cancer cells in the region of the colon or rectum. This includes different layers like mucosa, muscular mucosa, submucosa, muscularis propria, subserosa and serosa.

Spread to lymph nodes (N): The growth and spread of cancer cells to the nearby lymph nodes.

Distant metastasis (M): Cancer cells travel along the lymph nodes and reach distant organs like liver, lungs, kidney, brain and cause cancer in those organs, this is called as distant metastasis¹⁰.

MANAGEMENT:

Localized cancers can be completely removed by surgical procedures. Name of the surgical procedure varies based on the location of the lesion in the colon region like: right hemicolectomy (cecum, right colon), extended right hemicolectomy (proximal or middle transverse colon), left hemicolectomy (splenic flexure and left colon), sigmoid colectomy (sigmoid colon lesions), total abdominal colectomy with ileorectal anastomosis.

Other therapeutic options:

Cryotherapy involves application of extreme cold or freezing of the cancer tissue, causing death of the cells. Radiofrequency ablation is a technique by which high frequency radiation are passed on the affected tissue and causes destruction of the cells, hepatic arterial infusion of chemotherapeutic agents directly to liver cells for colorectal liver metastasis. Adjuvant therapy is used in selected patients who are at high risk for recurrence of tumour cells.

Systemic chemotherapy:

5-fluorouracil (5-FU) is an antimetabolite drug widely used in the treatment of colorectal cancer. 5-FU exerts its anticancer effects through inhibition of thymidylate synthase (TS) and incorporation of its metabolites into RNA and DNA¹¹. Topoisomerase inhibitors are chemotherapeutic agents interfering with the [topoisomerase](#) enzymes I and II, which regulates the change in the structure of the [DNA](#). Topoisomerase inhibitors block the [ligation](#) step of the cell cycle, which generates DNA single and double-strand breaks, leading to apoptotic [cell death](#)¹². The platinum-containing agent [oxaliplatin](#), and the 5-FU [prodrug capecitabine](#) are the first line drugs in the treatment of colorectal cancer¹³. The combination therapies, using FU/leucovorin and oxaliplatin and 5-FU/leucovorin and irinotecan, have become established as efficacious cytotoxic regimens for the treatment of [metastatic CRC](#),

resulting in overall survival times of approximately 2 years¹⁴.

Biologic agents:

Biological agents are substances made from living organisms used in the treatment of cancer. Biological agents like Bevacizumab, a humanized monoclonal antibody that targets vascular endothelial growth factor. Cetuximab, Panitumumab, monoclonal antibodies against the epidermal growth factor. Ipilimumab a CTLA-4 immune checkpoint inhibitor. Cytotoxic T lymphocyte-associated antigen (CTLA-4) is a coinhibitory transmembrane protein which binds to the B-71 and B7-2 ligands on [antigen presenting cells](#)¹⁵. Nivolumab is a human immunoglobulin (Ig) G4 anti-PD-1 monoclonal antibody. By binding to PD-1, an inhibitory co-receptor expressed on antigen-activated T cells, thus preventing interaction with PD-L1, resulting in the loss of inhibitory signals in T cells, and tumour recognition by cytotoxic T cells and thus restoring T-cell function¹⁶. Pembrolizumab is also an anti-PD-1 antibody which stimulates the body to act against the cancer cells. Ramucirumab is a monoclonal antibody against VEGFR2, it has antiangiogenic activity preventing formation of new blood vessels. It also has an inhibitory effect on the cell cycle progression¹⁷.

CONCLUSIONS:

A family history of colorectal cancer in the first degree relative has a highest risk factor for the development of colorectal cancer with the increase in age. 80% CRC cases are caused due to chromosomal instability pathway, which is initiated by APC mutation. If cancer is localized, it can be completely removed by surgical procedures. To stop the growth and progression of the tumour cells, chemotherapeutic agents are used. Treatment option becomes more advanced with the introduction and utilization of biological agents which acts on various growth factor and interrupts the growth cycle. Targeted drug delivery system has gained more importance in recent times which has an effective means of drug delivery making the treatment more precise and limiting the toxicity.

LIST OF ABBREVIATIONS:

CRC: Colorectal cancer
CT: Computerized Tomography
MRI: Magnetic resonance imaging
PET: Positron emission tomography,
PET-CT: positron emission tomography-computed tomography
FAP: Familial Adenomatous Polyposis.
HNPCC: Hereditary non-polyposis colon cancer syndrome
WHO: World Health Organization

MSS: Microsatellite Stability
 CIMP: CpG island methylation pathway
 5-FU: 5-Fluorouracil
 DNA: Deoxyribonucleic acid
 RNA: Ribonucleic Acid
 LMICs: Low and Middle-Income Countries
 IBD: Inflammatory Bowel Disease
 AJCC: The American Joint Committee on Cancer
 KRAS: Kirsten rat sarcoma viral oncogene
 EGRF: Epidermal Growth Factor Receptor
 TNM: Tumour, Nodes and Metastases
 Ig: Immunoglobulin
 TS: Thymidylate Synthase
 APC: Adenomatous Polyposis Gene
 CTLA-4: Cytotoxic T lymphocyte-associated antigen
 VEGFR2: Vascular endothelial growth factor receptor 2
 PD-1: Programmed cell death protein 1
 GTP: Guanosine 5' -Triphosphate

CONFLICT OF INTEREST:

The author has no conflicts of interest in this review.

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