

A LINEAR PERSPECTIVE REVIEW ON COLORECTAL CANCER: A DEADLIEST DISEASEMahendra Dwivedi^{1*}, Suraj Mandal² and Sanjeev Kumar³^{1,2,3}Pt. Rajendra Prasad Smarak College of Pharmacy, Campus- Kajri Niranjanpur, Khutar Road, Puranpur, Pilibhit, Uttar Pradesh, India, 262122.***Corresponding Author: Mahendra Dwivedi**

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ABSTRACT

Colorectal cancer (CRC) is the third most common cancer in the world. In India rank of colon cancer is 8th and rectal cancer has 9th rank among men. In 2018 Hungary had the highest rate of colorectal cancer. This is a deadliest disease. CRC can occur in younger and teenager also but old age person and women have higher risk. Exact cause of colorectal cancer is still unknown but obesity, smoking, old age, less physical activity, genetic, ethnicity are the most common risk factors for this disease. CRC have various diagnostic method including Colonoscopy, Biopsy, molecular testing of the tumor, blood test, CT scan and MRI. This is a preventive disease and in the early stage it can be prevented. Surgery, drug therapy, radiation therapy, immunotherapy etc. are the various treatment options for the treatment of colorectal cancer. In this review paper introduction, stages, cause, sign & symptoms, cause, pathogenesis, diagnosis & treatment of colorectal cancer has been mentioned.

KEYWORDS: Colorectal Cancer, Inflammatory bowel disease, Genetics, Polyps, Chemotherapy, Immunotherapy.**INTRODUCTION**

Cancer could be a cluster of over one hundred totally different and distinctive illness. It involves abnormal growth of cells which tend to proliferate in an uncontrolled way.^[1] Cancer is one of the most dangerous diseases in today's world that kills millions of people every year. It has no boundary and can affect any organ of people from any place.^[2] Possible signs and symptoms include lump, abnormal bleeding, prolonged cough, weight loss, and a change in bowel movements.^[3] Cancer is a group of disease it has various variety and this variety is a major challenge in diagnosis and efficacy of treatment. Prostate, lung and bronchus, colorectal, and urinary bladder cancer etc. are major types of cancer that occurs in male. In women, mostly cancer occurs in breast, lung and bronchus, colon and rectum, uterine corpus and thyroid, respectively. Where prostate and breast cancer constitute a major portion of cancer in men and women, respectively. For children, the highest percentage types of cancer disease are blood cancer, brain cancer and cancer related to lymph nodes, respectively.^[4] There are many approaches for the treatment of cancer but each of them has their limitations and side effects. The types of treatment that you receive will depend on the type of cancer you have. It includes surgery, radiation therapy, chemotherapy, Immunotherapy, targeted therapy, hormone therapy,

stem cell transplant, precision medicine and biomarker testing for cancer treatment.^[5]

Colorectal cancer is the third most common type of cancer. This is a malignant cancer and is second most common cause of death related to cancer in men and women worldwide. It is common in those aged 65-74 and has higher chance in women. Obesity, sedentarism, bad nutritional habits (high in fats and proteins), smoking, and the progressive aging of the population are the risk factor for Colorectal cancer.^[6] Common symptoms of colorectal cancer may include changes in bowel movements, cramping in your rectum, bleeding from rectum, blood in or on stool, belly discomfort or bloating, fatigueness, appetite and weight loss, excessive gas, pelvic pain, anemia (occurs because of bleeding in intestine).^[7]

Stages of Colorectal cancer^{[8],[9]}

Doctors use diagnostic test to determine the stage of the cancer which help in treatment planning and predict the chance of recovery. Colorectal cancer has following stages

Stage 0: This stage of cancer is highly curable. In this stage abnormal cell are only in the inner lining of the colon or rectum and have not spread nearby the tissue.

Stage 1: This is called as early-stage cancer. This stage is usually a small cancer or tumour and has penetrated

the lining or mucosa of the colon or rectum and may have grown into the muscle layer, but it hasn't spread to nearby lymph nodes or to other parts of the body.

Stage 2: In this stage cancer has become larger and spread to the walls of the colon or rectum or through the

walls to nearby tissues, but has not affected the wall of lymph nodes.

Stage 3: In this stage cancer affect to lymph nodes but not to the other part of the body.

Stage 4: This is last stage of cancer. In this stage cancer spray to the other part of the body such as liver or lungs.

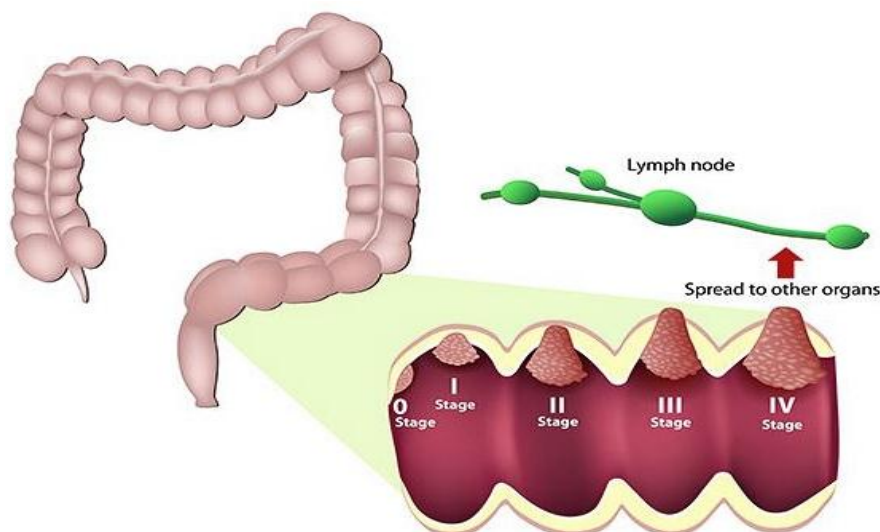


Fig. 1: Stages of Colorectal cancer.^[10]

Cause and risk factors of Colorectal cancer

Exact cause of colorectal cancer is still unknown. But it is believed that colorectal cancer may be caused by genetic factors or may be associated with inflammatory bowel disease.^[11]

Possible risk factors of colorectal cancer may include

- Smoking
- Obesity
- High alcohol consumption
- Older age
- Intake of less fibers from diet
- Less physical activity
- Presence of polyps in colon or rectum^[12]
- Genetics: Around 18% cases on colorectal cancer are associated with a family history. They have higher risk of this type cancer than other people
- IBD (Inflammatory bowel disease): This is also a risky factor for the colorectal cancer.^{[11],[12]}
- Ethnicity: African Americans in US and Jews of Eastern European descent are more prone to develop CRC than other member of any other ethnic group.^[13]

Pathogenesis

Colorectal cancer (CRC) is a disease derives from the epithelial cells lining the colon or rectum of the gastrointestinal tract (GIT), the term pathogenesis defined as the mechanism underlying the progress of a disease condition like other types of neoplasia, colorectal cancer is currently figured out to be a genetic disorder. The term “genetic” is not synonymous with the term

“hereditary,” but implies that the modification of an ordinary cell to an uncontrolled growth, malignant cell (cancerous cell) is achieved through the step-by-step accumulation of genetic alterations.^{[14][15]} The conventionally mutated gene in all colorectal cancer is the adenomatous polyposis coli (APC) gene, which produces the APC protein acts as a tumour suppressor or as antagonist. The APC protein stop the agglomeration of β -catenin protein (multifunctional protein) without APC, β -catenin accumulates to high levels and moves into the nucleus, binds to the DNA, and activates the transcription of proto-oncogenes.^{[16][17]} While APC gene is mutated in most colon cancers, and in the cases of some cancers have increased β -catenin because of mutations in β -catenin (CTNNB1) that block its own malfunction, or have mutations in other genes with outcome similar to APC such as AXIN1, AXIN2 (protein coding gene) TCF7L2, or NKD1 is a human gene that encodes the protein.^{[16][17]}

Sign and symptoms of colorectal cancer

CRC has no symptoms in its early stage. It has non-specific symptoms and varies according to cancer's size and location of tumor in large intestine. Possible symptoms may include fatigue, shortness of breath, loss of appetite, constipation, excessive gas, pelvic pain, weakness, blood in stool, narrow stools, diarrhea, iron deficiency anemia (due to slow loss of blood over a longer period of time).^[18] If the cancer spreads to a new location in the body, such as the liver, it will show some additional symptoms.^[19]

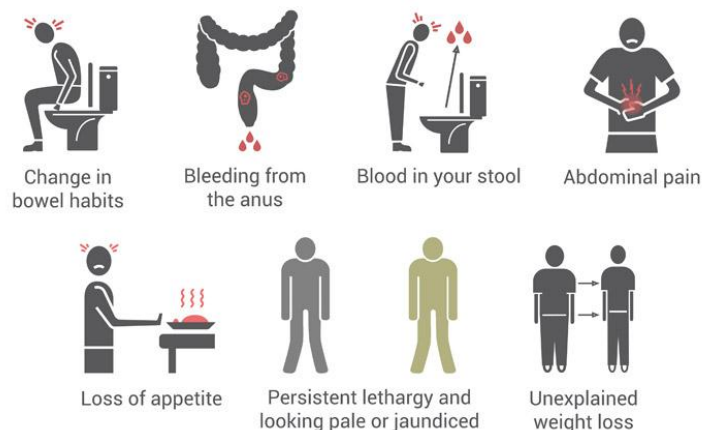


Fig. 2: Sign and symptoms of colorectal cancer.^[20]

Diagnosis of colorectal cancer

Diagnosis of colorectal cancer in its early stage gives best chance to cure it.^[8] There are many tests which are performed by the doctor for diagnosis of CRC. Imaging tests are used in metastasis condition. In metastasis cancer spread to other body parts from where it started. Biopsy is another test which is used to ensure that which part of body have cancer. In laboratory biopsy is performed by taking a small sample of tissue. There are following factors that are considered during selection of test method –

- Age of the patient
- Sign and symptoms
- Medical condition
- Family history etc.
- Result of previous test^{[21],[22]}

Following test are performed for diagnosis of colorectal cancer –

1. Colonoscopy: Colonoscopy is the screening technique that provides diagnostic as well as therapeutic effect. It has high accuracy for diagnosis of CRC.^[23] During the test the doctor uses a colonoscope, a long, flexible, cannular instrument regarding 1/2-inch in diameter that transmits a picture of the liner of the colon therefore the doctor will examine it for any abnormalities. The colonoscope is inserted through the rectum and advanced to the opposite finish of the large bowel.^[24] By using this technique doctor look inside the entire rectum and colon while a patient is sedated.^[21]



Fig. 3: Colonoscopy technique.^[25]

2. Biopsy: In colon biopsy tissue sample from colon is removed and under a microscope sample is examined. This is used to make definite diagnosis of colorectal cancer.^[26] A biopsy is performed during colonoscopy, or it may be performed on any tissue i.e., removed during surgery. Biopsy is associates with cancer but just because your doctor says for your biopsy, it doesn't mean you are a cancer patient. Biopsy is done by the doctors to check that the problem in your body is caused by cancer or by other reasons. Biopsy is confirmatory test for cancer, other tests like CT scans and X-rays are also used in cancer diagnosis but they can't differentiate to cancerous and noncancerous cells.^[27]

Three type's biopsies are used in diagnosis of colorectal cancer

- **Endoscopic biopsy:** In colorectal cancer diagnosis this is most commonly used biopsy which is done during colonoscopy or sigmoidoscopy. Endoscopy biopsy is performed by using equipment that is called endoscope. Endoscope is used for the screening and diagnostic tests to look at the colon. For the biopsy of colon a equipment is used that is called colonoscope. And by using sigmoidoscope, sigmoidoscopy is performed.^{[27][28]}



Fig. 4: Colonoscope.^[29]

- **Needle biopsy:** In needle biopsy, by using a syringe a piece of tissue is pulling out from the tumor.

Before biopsy a local anesthetic is used to numb your skin. Needle biopsy also has two types –

- A) Fine needle biopsy: In this biopsy a very fine needle and syringe are used to pull out the tissue.
- B) Core needle biopsy: In this biopsy a slightly larger needle are used to perform the biopsy.^{[29],[30]}
 - **Surgical biopsy:** Most biopsy is performed by using endoscopic and needle biopsy. But in the condition of large polyp, surgical biopsy is used. In the condition of surgical biopsy, patient will be given general anaesthesia which make loss of sensation in entire body.^[28]
3. **Molecular testing of tumour:** Molecular testing is the laboratory test that is used to check some proteins, genes or other molecules in a tissue and body fluid sample. This test is also used to check the changes in gene or chromosomes that may cause cancer.

CRC have 3 molecular pathway of carcinogenesis –

- The Conventional Suppressor Pathway (Chromosomal Instability Pathway)
- Hereditary MSI Pathway (Lynch Syndrome)
- Serrated Pathway

The main aim of molecular testing in colorectal cancer is to detect lynch syndrome and forecasting response to anti-epidermal growth factor receptor (EGFR) therapies.^{[31][32]}

4. **Blood tests:** In cancerous condition bleeding start from rectum, and people may become anemic. Counting of RBC in blood can indicate bleeding may be occurring. A blood test can't confirm you that you have colorectal cancer, but if your report is positive then you should have Colonoscopy.^[33]
5. **Computed tomography (CT) scan:** CT scan colonography is a most popular diagnostic method for diagnosis of colorectal cancer because it has good clinical performance, cost effectiveness and safety. By using x-rays taken from different angles, CT scan takes pictures of the inside of the body. This is used to check the size of the tumor. CT scan is also used to check the spread of cancer to the other body parts such as lungs, liver and other organs.^[34]
6. **Magnet resonance imaging (MRI):** MRI produces detailed image of the body by using magnetic field. Size of the tumour is measured by using MRI. To create a clear picture a special dye called a contrast medium is given before the scanning. This dye can be injected into patient's vein or can be given orally as a pill or liquid. MRI is the best imaging test that can find cancer has grown. Complete MRI of colon I take one hour or more and patient may be asked to fast for 4-6 hours before scanning. Metallic objects are not allowed in MRI room. Items such as mobile phone, watch, rings, jewelry, eyeglass, pen should not carry in MRI room.^{[21],[35]}

Ultrasound, chest x-ray, positron emission tomography (PET) are other diagnostic method used in colorectal cancer diagnosis.^[21]

Prevention of colorectal cancer^{[36], [37]}

There are some tips, by following them colorectal can be prevented

1. Regular screening: - Regular screening is the best way to protect you from colorectal cancer. This can detect colorectal cancer in its early stage, when it is most treatable. This screening test can find the polyps. Polyps are not a cancer but cancer can start in polyps.

2. by controlling over weight: - Over weight can increase the risk of colorectal cancer. Not only colorectal cancer there is many cancers which are directly linked to over weight and obesity. Regular exercise can help you to maintain body weight.

3. Don't smoke: -Smoking is a major cause of 14 type cancer including colorectal cancer. Smokers have higher chances of getting and dying from colorectal cancer.

4. Regular exercise: -Regular exercise provides a healthy body maintain body weight and decreases the chances of colorectal cancer.

5. Follow vegetarian diet: -A vegetarian diet that includes vegetables, fruits and grains decreases the chances of colorectal cancer. On the other hand, red meat (steak, pork, lamb) and processed meat (bacon, bologna etc) increase the chances of colorectal cancer.

6. Avoid alcohol: -There are many types of cancer including colorectal cancer which are caused by alcohol. If you are a non alcoholic then you have less chance to get cancer. But if you do, then you should drink it moderately (upto two drink per day for men and one drink per day for women).

Treatment of colorectal cancer

For the treatment of colorectal cancer (CRC) depends on various factors, including the person's health as well as the stage of the tumor also. Surgery and adjuvant chemotherapy is standard for patients with stage (I-III) disease.

1. Surgery

In the present time surgery is frequently used for the treatment for early-stage colon cancers. The type of surgery in the CRC used depends on the stage (extent) of the cancer, where it is in the colon, and the goal of the surgery.

2. Drug Therapy

Different types of drugs used for the treatment of colon cancer as

- Drugs Approved for Colon Cancer
- Drug Combinations Used in Colon Cancer
- Drugs Approved for Rectal Cancer
- Drug Combinations Used in Rectal Cancer
- Drugs Approved for Gastroenteropancreatic Neuroendocrine Tumors
- Drugs Approved for Colon Cancer

- **Drugs Approved for Colon Cancer**

Avastin, Bevacizumab, Camptosar (Irinotecan Hydrochloride), Capecitabine, Cetuximab, Cyramza (Ramucirumab), Eloxatin (Oxaliplatin), Erbitux (Cetuximab), 5-FU (Fluorouracil Injection), Fluorouracil Injection, Ipilimumab, Irinotecan Hydrochloride, Keytruda (Pembrolizumab), Leucovorin Calcium, Lonsurf (Trifluridine and Tipiracil Hydrochloride), Mvasi (Bevacizumab), Nivolumab, Opdivo (Nivolumab), Oxaliplatin, Panitumumab, Pembrolizumab, Ramucirumab, Regorafenib, Stivarga (Regorafenib), Trifluridine and Tipiracil Hydrochloride, Vectibix (Panitumumab), Xeloda (Capecitabine), Yervoy (Ipilimumab), Zaltrap (Ziv-Aflibercept), Zirabev, Ziv-Aflibercept

- **Drug Combinations Used in Colon Cancer**

Capox, Folfiri, Folfiri-Bevacizumab, Folfiri-Cetuximab, Folfax, FU-LV, Xeliri, Xelox

- **Drugs Approved for Rectal Cancer**

Avastin (Bevacizumab), Bevacizumab, Camptosar (Irinotecan Hydrochloride), Capecitabine, Cetuximab, Cyramza (Ramucirumab), Eloxatin (Oxaliplatin), Erbitux (Cetuximab), 5-FU (Fluorouracil Injection), Fluorouracil Injection, Ipilimumab, Irinotecan Hydrochloride, Keytruda (Pembrolizumab), Leucovorin Calcium, Lonsurf (Trifluridine and Tipiracil Hydrochloride), Mvasi, Nivolumab, Opdivo (Nivolumab), Oxaliplatin, Panitumumab, Pembrolizumab, Ramucirumab, Regorafenib, Stivarga (Regorafenib), Trifluridine and Tipiracil Hydrochloride, Vectibix (Panitumumab), Xeloda (Capecitabine), Yervoy (Ipilimumab), Zaltrap (Ziv-Aflibercept), Zirabev, Ziv-Aflibercept

- **Drug Combinations Used in Rectal Cancer**

Capox, Folfiri, Folfiri-Bevacizumab, Folfiri-Cetuximab, Folfax, FU-LV, Xeliri, Xelox

- **Drugs Approved for Gastroenteropancreatic Neuroendocrine Tumors**

Afinitor (Everolimus), Everolimus, Lanreotide Acetate, Somatuline Depot (Lanreotide Acetate)

3. Radiation therapy

It is seen that a combination of radiation and chemotherapy can be very beneficial for rectal cancer,^[38] in this case, some people need treatment and they also have benefits, but there are some problems with chemo. Radiotherapy may increase acute treatment-related toxicity, which is fatal, and has a worse effect on life, and has not been shown to improve survival rates compared to radiotherapy alone, although it is associated with lower local recurrence of this has been seen.^[39] The use of radiotherapy to treat stomach cancer is not routine due to its highly reactivity to electromagnetic radiation because it also has very fatal consequences.^[40] As chemotherapy, radiotherapy can be used today as a newly adjuvant procedure for rectal cancer for clinical stages T3 and T4 which is proving beneficial.^[40] This

results in the downsizing or down staging of the tumor, is prepared for surgical laser, and the procedure also reduces the local recurrence rate.

4. Immunotherapy

Immunotherapy with immune checkpoint inhibitors has been found to be useful for mismatched cancer deficiency and microsatellite instability in this entire process. Most people who make improvements, however, still get worse after months or years.^[41] By 2017, other types of colorectal cancer are being studied and, in this case, various experiments are being done to save the patient.^{[41][42]}

5. Palliative care

In this entire process, palliative care is recommended for anyone who has advanced colon cancer or who has significant symptoms who may have succumbed to the disease.^{[43] [44]} Incorporating palliative care to improve the quality of life can be beneficial for both the individual and his family by preventing symptoms, anxiety, and hospital admissions, and it is also rapidly working. And better results are coming out.^[43] In people with incurable colorectal cancer, palliative care may involve procedures that relieve symptoms or complications from the cancer but do not attempt to cure the prime cancer, thereby improving quality of life. Some cancers exclude tissue, intestinal tract or stent placement. These procedures can be considered to improve symptoms and reduce complications such as tumor bleeding, abdominal pain, and intestinal obstruction, which is a very important good result.

6. Follow-up

The objectives of follow-up are, at the earliest possible stage, any metastasis or tumors that develop later, but do not originate from the original cancer (metachronous lesions). The US National Comprehensive Cancer Network and the American Society of Clinical Oncology provide. Guidelines for the follow-up of colon cancer.^[45] A medical history and physical examination is recommended every 3 to 6 months for 2 years, then every 6 months for 5 years. Carcinoembryonic antigen blood level measurements follow at the same time, but are only recommended for people with T2 or greater lesions who are candidates for intervention.

7. Exercise

Physical activity in the case of colorectal cancer can prevent about 15–16% of two weeks of moderate exercise after completing their first aid. Oxidative balance may be another possible mechanism for the observed benefits. In this process, a significant change in the urine of people undergoing 2 weeks of moderate exercise after first aid was seen as a reduction of 8-oxo-DG. Other possible mechanisms may include metabolic hormones and sex-steroid hormones, although these pathways may be involved in other types of cancer.^[46]

Epidemiology

According to many research and review data colorectal cancer (CRC) is the third most death causing disease and fourth most commonly diagnosed cancer in the world. According to American Cancer Society (ACS) estimation for new cases and deaths for 2020 based on earlier report.

CONCLUSION

Colorectal cancer is a malignant cancer and is a deadliest disease. But it can be prevented by regular screening of colon, avoiding smoking, controlling by weight, regular exercise. It has been seen vegetarian have less chances of colorectal cancer as comparison to non-vegetarians. According to the stages of cancer doctors can prefer to surgery, drug therapy, radiation therapy or immunotherapy or two of them. Alcohol should be avoided because it enhances the cancer chances including colorectal cancer also.

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Conflict of Interest

The authors declare that the review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

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Ethical Approval

Not required.

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