DIAGNOSIS AND TREATMENT OF COLORECTAL CANCER: A REVIEW

1,2 Agrawal Dilip*, 1 Ranawat MS, 2 Khinci Mahaveer P, 2 Gupta MK, 2 Sharma Natasha, 2 Avlani Gunjan

1 B.N.P.G. College of Pharmacy, Udaipur-303101, Rajasthan, India
2 Kota College of Pharmacy, Kota-324005, Rajasthan, India

*Corresponding Author: Dilip Agrawal, (Ph.D. Scholar), B.N.P.G. College of Pharmacy, Udaipur, (Raj.), Email id.: dilip.kcp@gmail.com

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ABSTRACT
Colorectal cancer (CRC) is a worldwide problem, with an annual incidence of approximately 1 million cases and an annual mortality of more than 50,000. CRC is the second most common cause of cancer mortality among men and women. Most CRCs arise from sporadic adenomas, and a few from genetic polyposis syndromes or inflammatory bowel diseases. Screening of CRC can be done by Computerized Tomography (CT) Colonoscopy, Sigmoidoscopy, virtual colonoscopy, Fecal Immuno-histochemical Test (FIT), Fecal Occult Blood Testing (FOBT) are used for diagnosis and Capestitbine Adrucil Bevacizumab, Camptosar, Cetuximab are the drugs used in the colon cancer. Adrucil (Fluorouracil), Efudex, Erbitux (Cetuximab), Fluoroplex (Fluorouracil), Irinotecan Hydrochloride etc. drugs are used in rectal cancer.

INTRODUCTION
Colorectal cancer, commonly known as bowel cancer, is a cancer caused by uncontrolled cell growth (neoplasia), in the colon, rectum, or vermiform appendix. Colorectal cancer is clinically distinct from anal cancer, which affects the anus. Invasive cancers that are confined within the wall of the colon (TNM stages I and II) are often curable with surgery. For example, in England and Wales over 90% of patients diagnosed at this stage will survive the disease beyond 5 years. However, if left untreated, the cancer can spread to regional lymph nodes (stage III) around 48% of patients diagnosed at this stage survive the disease beyond five years. Cancer that has spread widely around the body (stage IV) is usually not curable approximately 7% of patients diagnosed at this stage survive beyond five years.1 Colorectal cancer is the third most commonly diagnosed cancer in the world, but it is more common in developed countries. More than half of the people who die of colorectal cancer live in a developed region of the world. GLOBOCAN estimated that, in 2008, 1.23 million new cases of colorectal cancer were clinically diagnosed, and that this type of cancer killed more than 600,000 people.2

Estimated new cases and deaths from colon and rectal cancer in the United States in 2011 are- New cases: 101,340 (colon); 39,870 (rectal) Deaths: 49,380 (colon and rectal combined).3

SYMPTOMS
Local symptoms are more likely if the tumor is located closer to the anus. There may be a change in bowel habit (such as unusual and unexplained constipation or diarrhea), and a feeling of incomplete defecation (rectal tenesmus). Lower gastrointestinal bleeding, including the passage of bright red blood in the stool, may indicate colorectal cancer, as may the increased presence of mucus. Melena, black stool with a tarry appearance, normally occurs in upper gastrointestinal bleeding (such as from a duodenal ulcer), but is sometimes encountered in colorectal cancer when the disease is located in the beginning of the large bowel.

A tumor that is large enough to fill the entire lumen of the bowel may cause bowel obstruction. This situation is characterized by constipation, abdominal pain, and abdominal distension and vomiting. This occasionally lead to the obstructed and distended bowel perforating and causing peritonitis. A large left colonic tumor may compress the left ureter and cause hydronephrosis.4

Certain local effects of colorectal cancer occur when the disease has become more advanced. A large tumor is more likely to be noticed on feeling the abdomen, and it may be noticed by a doctor on physical examination. The disease may invade other organs, and may cause blood or air in the urine (invasion of the bladder) or vaginal discharge (invasion of the female reproductive tract.)

Risk factors
The lifetime risk of developing colon cancer in the United States is about 7%. Certain factors increase a person’s risk of developing the disease these includes:

- Age: The risk of developing colorectal cancer increases with age. Most cases occur in the 60s and 70s.
- Polyps of the colon, particularly adenomatous polyps, are a risk factor for colon cancer. The removal of colon polyps at the time of colonoscopy reduces the subsequent risk of colon cancer.
- Heredity:
Family history of colon cancer, especially in a close relative before the age of 55 or multiple relatives.

Familial adenomatous polyposis (FAP) carries a near 100% risk of developing colorectal cancer by the age of 40 if untreated.

Hereditary nonpolyposis colorectal cancer (HNPPC) or Lynch syndrome.

Gardner syndrome.

Smoking: Smokers are more likely to die of colorectal cancer than nonsmokers. An American Cancer Society study found. Male smokers had more than a 30% increase in risk of dying from the disease compared to men who never had smoked.

Diet: Studies show that a diet high in red meat and low in fresh fruit, vegetables, poultry and fish increases the risk of colorectal cancer. In June 2005, a study by the European Prospective Investigation into Cancer and Nutrition suggested that diets high in red and processed meat, as well as those low in fiber, are associated with an increased risk of colorectal cancer. Individuals who frequently eat fish showed a decreased risk. However, other studies have cast doubt on the claim that diets high in fiber decrease the risk of colorectal cancer; rather, low-fiber diets was associated with other risk factors, leading to confounding. The nature of the relationship between dietary fiber and risk of colorectal cancer remains controversial.

Lithocholic acid: Lithocholic acid is a bile acid that acts as a detergent to solubilize fats for absorption. It is made from chenodeoxycholic acid by bacterial action in the colon. It has been implicated in human and experimental animal carcinogenesis.

Viruses: Exposure to some viruses (such as particular strains of human papilloma virus) may be associated with colorectal cancer.

Primary sclerosing cholangitis offers a risk independent to ulcerative colitis.

Low levels of selenium.

Inflammatory bowel disease: About one percent of colorectal cancer patients have a history of chronic ulcerative colitis. Patients with colorectal Crohn's disease have a more than average risk of colorectal cancer, but less than that of patients with ulcerative colitis.

Environmental factors. Industrialized countries are at a relatively increased risk compared to less developed countries that traditionally had high-fiber/low-fat diets. Studies of migrant populations have revealed a role for environmental factors, particularly dietary, in the etiology of colorectal cancers.

Exogenous hormones. The differences in the time trends in colorectal cancer in males and females could be explained by cohort effects in exposure to some gender-specific risk factor; one possibility that has been suggested is exposure to estrogens. In contrast, there is evidence that exogenous estrogens such as hormone replacement therapy (HRT). Tamoxifen or oral contraceptives might be associated with colorectal tumors.

Alcohol: Drinking, especially heavily, may be a risk factor.

Vitamin B6 intake lowers the risk of colorectal cancer.

Globally, cancer of the colon and rectum is the third leading cause of cancer in males and the fourth leading cause of cancer in females. The frequency of colorectal cancer varies around the world. It is common in the Western world and is rare in Asia and Africa. In countries where the people have adopted western diets, the incidence of colorectal cancer is increasing.

RECTAL CANCER:
Rectal cancer occurs when cancerous cells develop in the tissue of the rectum. The rectum is the last part of the large intestine and leads to the anus, which is the opening to the outside of the body. Body waste is stored in the rectum until it is eliminated from the body through the anus.

Although rectal cancer is a life-threatening disease, it is a highly curable form of cancer if found early. Therefore, regular check-ups and screenings are very important.

SIGN AND SYMPTOMS:
Common signs and symptoms of rectal cancer include:

- A change in bowel habits
- Diarrhea, constipation, or feeling that the bowel does not empty completely
- Blood, either bright red or very dark in the stool
- Stools that are narrower than usual
- General abdominal discomfort such as frequent gas pains, bloating, fullness or cramps
- Weight loss with no known reason
- Constant tiredness
- Vomiting

WHAT IS CANCER OF THE COLON AND RECTUM?

The colon is the part of the digestive system where the waste material is stored. The rectum is the end of the colon adjacent to the anus. Together, they form a long, muscular tube called the large intestine (also known as the large bowel). Tumors of the colon and rectum are growths arising from the inner wall of the large intestine. Benign tumors of the large intestine are called polyps. Malignant tumors of the large intestine are called cancers. Benign polyps do not invade nearby tissue or spread to other parts of the body. Benign polyps can be easily removed during colonoscopy and are not life-threatening. If benign polyps are not removed from the large intestine, they can become malignant (cancerous) over time. Most of the cancers of the large intestine are believed to have developed from polyps. Cancer of the colon and rectum (also referred to
as colorectal cancer) can invade and damage adjacent tissues and organs. Cancer cells can also break away and spread to other parts of the body (such as liver and lung) where new tumors form. The spread of colon cancer to distant organs is called metastasis of the colon cancer. Once metastasis has occurred in colorectal cancer, a complete cure of the cancer is unlikely.

Doctors are certain that colorectal cancer is not contagious (a person cannot catch the disease from a cancer patient). Some people are more likely to develop colorectal cancer than others. Factors that increase a person's risk of colorectal cancer include high fat intake, a family history of colorectal cancer and polyps, the presence of polyps in the large intestine, and chronic ulcerative colitis.

**Diet and colon cancer**

Diets high in fat are believed to predispose humans to colorectal cancer. In countries with high colorectal cancer rates, the fat intake by the population is much higher than in countries with low cancer rates. It is believed that the breakdown products of fat metabolites lead to the formation of cancer-causing chemicals (carcinogens). Diets high in vegetables and high-fiber foods such as whole-grain breads and cereals may rid the bowel of these carcinogens and help reduce the risk of cancer.

**Colon polyps and colon cancer**

Doctors believe that most colon cancers develop in colon polyps. Therefore, removing benign colon polyps can prevent colorectal cancer. Colon polyps develop when chromosome damage occurs in cells of the inner lining of the colon. Chromosomes contain genetic information inherited from each parent. Normally, healthy chromosomes control the growth of cells in an orderly manner. When chromosomes are damaged, cell growth becomes uncontrolled, resulting in masses of extra tissue (polyps). Colon polyps are initially benign. Over years, benign colon polyps can acquire additional chromosome damage to become cancerous.

**Ulcereative colitis and colon cancer**

Chronic ulcerative colitis causes inflammation of the inner lining of the colon. For further information, please read the Ulcerative Colitis article. Colon cancer is a recognized complication of chronic ulcerative colitis. The risk for cancer begins to rise after eight to 10 years of colitis. The risk of developing colon cancer in a patient with ulcerative colitis also is related to the location and the extent of his or her disease.

Current estimates of the cumulative incidence of colon cancer associated with ulcerative colitis are 2.5% at 10 years, 7.6% at 30 years, and 10.8% at 50 years. Patients at higher risk of cancer are those with a family history of colon cancer, a long duration of colitis, extensive colon involvement, and those with primary sclerosing cholangitis (PSC).

**Genetics and colon cancer**

A person's genetic background is an important factor in colon cancer risk. Among first-degree relatives of colon cancer patients, the lifetime risk of developing colon cancer is 18% (a threefold increase over the general population in the United States).

Even though family history of colon cancer is an important risk factor, majority (80%) of colon cancers occur sporadically in patients with no family history of colon cancer. Approximately 20% of cancers are associated with a family history of colon cancer. And 5% of colon cancers are due to hereditary colon cancer syndromes. Hereditary colon cancer syndromes are disorders where affected family members have inherited cancer-causing genetic defects from one or both of the parents.

Chromosomes contain genetic information, and chromosome damages cause genetic defects that lead to the formation of colon polyps and later colon cancer. In sporadic polyps and cancers (polyps and cancers that develop in the absence of family history), the chromosome damages are acquired (develop in a cell during adult life). The damaged chromosomes can only be found in the polyps and the cancers that develop from that cell. But in hereditary colon cancer syndromes, the chromosome defects are inherited at birth and are present in every cell in the body. Patients who have inherited the hereditary colon cancer syndrome genes are at risk of developing large number of colon polyps, usually at young ages, and are at very high risk of developing colon cancer early in life, and also are at risk of developing cancers in other organs.

HNPCC (hereditary nonpolyposis colon cancer) is a hereditary colon cancer syndrome where affected family members can develop colon polyps and cancers, usually in the right colon, in their 30s to 40s. Certain HNPCC patients are also at risk of developing uterine cancer, stomach cancer, ovarian cancer, and cancers of the ureters (the tubes that connect the kidneys to the bladder), and the biliary tract (the ducts that drain bile from the liver to the intestines).

**MYH polyposis syndrome** is a recently discovered hereditary colon cancer syndrome. Affected members typically develop 10-100 polyps occurring at around 40 years of age, and are at high risk of developing colon cancer early in life, and also are at risk of developing cancers in other organs.

**SCREENING FOR COLORECTAL CANCER:**

Colorectal cancer (CRC) is preventable by removing pre-cancerous lesions or adenomatous polyps long before invasive cancer develops. For the general population, screening is advised starting at age 50.

**Table.1. Stratification of CRC Risk Groups**

<table>
<thead>
<tr>
<th>Risk Rating</th>
<th>Risk Criteria</th>
</tr>
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<tbody>
<tr>
<td>Average Risk</td>
<td>Age ≥ 50, No personal history of adenoma, CRC or Inflammatory bowel disease Negative family history</td>
</tr>
<tr>
<td>Increased Risk</td>
<td>Personal history of adenomas/sessile serrated polyps, CRC or inflammatory bowel disease Positive family history of CRC or advanced Adenomas</td>
</tr>
<tr>
<td>High Risk</td>
<td>Family history of Lynch Syndrome Personal or family history of polyposis Syndromes</td>
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</table>
In this population, it is estimated that the risk of developing a colorectal adenoma is approximately 19% and that 2%-5% of sporadic polyps will develop into an invasive carcinoma. 1 5% to 15% of individuals have a genetic predisposition for development of CRC, thus cancer can develop for these patients at an earlier age. Given that the risk of CRC is variant in individuals based on high or average risk factors, recommendations for CRC screening are made accordingly.25

TESTS FOR CRC SCREENING:

There are several options for CRC screening

1. Fecal Occult Blood Testing (FOBT) detects blood loss in the stool. This test is performed on a fecal sample which has been placed on a guaiac-impregnated card. Through addition of a hydrogen peroxide developer, a positive test is reflected in the appearance of a blue color. This test should be performed on 3 separate bowel movements. Dietary substances like rare red meat, turnips or horseradish can result in a false positive or vitamin C can result in a false negative. Restrictions of these substances have not been shown to reduce this false positivity rate rather they may inhibit compliance with the testing. Additionally, it is recommended that non-steroidal anti-inflammatory drugs be avoided 7 days prior to testing as they can cause bleeding which can result in a false positive.27

2. Fecal Immunohistochemical Test (FIT) was approved by the Food and Drug administration in 2001. It can detect hidden blood in the stool. It reacts to part of the human hemoglobin protein found in red blood cells. No dietary restrictions are required prior to this test and it only requires one specimen.

3. Stool DNA Test looks for certain abnormal sections of DNA. For this test an entire bowel movement is collected and examined in the lab for cancer cells. Time intervals for this test are not yet known.28

4. Sigmoidoscopy is an invasive procedure using a 60 cm flexible lighted tube inserted into the rectum and can visualize the lower part of the colon. A video camera is at the end of the scope and images are visualized on a display monitor. Polyps can be biopsied and removed through the scope. This procedure can be done without sedation.29 The greatest limitation of this procedure is that it can identify premalignant and malignant lesions in only half of the colon. Abnormal findings will result in the patient needing to undergo a colonoscopy.

5. Colonoscopy is an invasive procedure through which the entire length of the colon is visualized through a colonoscope. Similar to the sigmoidoscopy, it has a video camera on the end which allows the endoscopist to closely view the colon on a display screen. Biopsy and removal of suspicious findings can be done during the procedure. Patients typically receive anesthesia for this procedure.

6. Double-Contrast Barium Enema (DCBE) or lower gastrointestinal series. This procedure done in the radiology department entails the insertion of a small flexible tube into the rectum through which barium is injected. Air is injected following the barium to assist in expansion. DCBE is insensitive to detecting small or flat adenomas and is only recommended when a total colonoscopy cannot be completed.

7. Computerized Tomography (CT) Colonoscopy or virtual colonoscopy uses 3-dimensional imaging. During this test the patient will lie on a table and a small flexible tube is inserted into the rectum through which air is pumped in to expand the colon for better visualization. Positive findings on this test will require follow-up with a colonoscopy. 3 Individuals ≥ 50-years-old with no personal history of adenoma, CRC or inflammatory bowel disease or a family history of CRC are considered at average risk for developing colorectal cancer. Their lifetime risk for developing CRC is about 1 in 19 (5.2%).

STAGE GROUPING

TNM STAGING SYSTEM

The TNM Classification of Malignant Tumors (TNM) is a cancer staging system that describes the extent of cancer in a patient’s body.

- T describes the size of the tumors and whether it has invaded nearby tissue,
- N describes regional lymph node that are involved,
- M describes distant metastasis (spread of cancer from one body part to another).

The TNM staging system for all solid tumors was devised by Pierre Denoix between 1943 and 1952, using the size and extension of the primary tumor, its lymphatic involvement, and the presence of metastases to classify the progression of cancer.

TNM is developed and maintained by the International Union against Cancer (UICC) to achieve consensus on one globally recognized standard for classifying the extent of spread of cancer. The TNM classification is also used by the American Joint Committee on Cancer (AJCC) and the International Federation of Gynecology and Obstetrics (FIGO).31

Most of the common tumors have their own TNM classification. Not all tumors have TNM classifications, e.g., there is no TNM classification for brain tumors.

The general outline for the TNM classification is below. The values in parentheses give a range of what can be used for all cancer types, but not all cancers use this full range.32

Mandatory parameters ("T", "N", and "M")

- T: size or direct extent of the primary tumor
  - Tx: tumor cannot be evaluated
  - Tis: carcinoma in situ
  - T0: no signs of tumor
  - T1, T2, T3, T4: size and/or extension of the primary tumor
- N: degree of spread to regional lymph nodes
  - Nx: lymph nodes cannot be evaluated

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Stage 0
Tis, N0, M0: The cancer is in the earliest stage. It has not grown beyond the inner layer (mucosa) of the colon or rectum. This stage is also known as carcinoma in situ or intramucosal carcinoma.

Stage I
T1-T2, N0, and M0: The cancer has grown through the muscularis mucosa into the submucosa (T1) or it may also have grown into the muscularis propria (T2). It has not spread to nearby lymph nodes or distant sites.

Stage II
T3, N0, M0: The cancer has grown into the outermost layers of the colon or rectum but has not reached nearby organs (T3). It has not yet spread to the nearby lymph nodes or distant sites.

Stage III
T4a, N0, and M0: The cancer has grown through the wall of the colon or rectum but has not grown into other nearby tissues or organs (T4a). It has not yet spread to the nearby lymph nodes or distant sites.

Stage IV
Any T, Any N, and M1a: The cancer may or may not have grown through the wall of the colon or rectum, but it may or may not have spread to nearby lymph nodes. It has spread to 1 distant organ (such as the liver or lung) or set of lymph nodes (M1a).

Stage IVA
Any T, Any N, and M1b: The cancer may or may not have grown through the wall of the colon or rectum, and it may or
may not have spread to nearby lymph nodes. It has spread to more than 1 distant organ (such as the liver or lung) or set of lymph nodes, or it has spread to distant parts of the peritoneum (the lining of the abdominal cavity) (M1b).

**Prevention:**

Most colorectal cancers should be preventable, through increased surveillance, improved lifestyle, and, probably, the use of dietary chemo preventative agents.

**TREATMENT**

Treatment for rectal cancer may include surgery, chemotherapy or radiation therapy, or a combination of these approaches. Surgery is the main treatment for all stages of rectal cancer, although radiation, chemotherapy, or both are often recommended in combination. Some patients who undergo surgery for rectal cancer require a permanent colostomy (the surgically created opening in the abdominal wall through which waste is excreted). 36

**THERAPIES FOR COLON AND RECTAL CANCER**

**Combining Targeted Drugs Is Worse in Colorectal Cancer**

A clinical trial testing chemotherapy combined with bevacizumab (Avastin) and cetuximab (Erbitux), and comparing this with chemotherapy and bevacizumab alone, found that the addition of cetuximab was actually worse for patients, according to the Feb. 5, 2009, New England Journal of Medicine.

**5-FU-Based Chemotherapy Cures Some Patients With Colon Cancer**

Researchers from the Adjuvant Colon Colon Endpoints (ACCENT) Group used individual patient data from 18 phase III trials of adjuvant 5-FU-based chemotherapy for colon cancer to show that the regimens provide their survival benefit primarily by reducing the high risk of recurrence within the first two years after surgery, according to a study published online January 5, 2009, in the Journal of Clinical Oncology. 37

**Colorectal Cancer Trials Support Gene Testing for Two Drugs**

A trio of 2008 studies adds to the growing evidence that patients with colorectal cancer should have their tumors tested for genetic mutations prior to starting therapy with cetuximab (Erbitux®) or panitumumab (Vectibix®).

**Related Treatment Information:**

**Angiogenesis Inhibitors Therapy**

A fact sheet that describes the process of eliminating the blood supply to tumors. Lists the cancers in which this approach is being tested.

**Biological Therapies for Cancer**

A fact sheet that provides an overview of how the immune system functions and describes the actions of biological therapies.

**Radiation Therapy for Cancer**

A fact sheet that defines the different types of radiation therapy and discusses scientific advances that improve the effectiveness of this treatment.

**Targeted Cancer Therapies**

This NCI fact sheet describes targeted cancer therapies, which are drugs that block the growth and spread of cancer by interfering with specific molecules involved in carcinogenesis (the process by which normal cells are transformed into cancer cells) and tumor growth.

**Chemotherapy**

Chemotherapy is used to reduce the likelihood of metastasis developing, shrink tumor size, or slow tumor growth. Chemotherapy is often applied after surgery (adjuvant), before surgery (neoadjuvant), or as the primary therapy (palliative). The treatments listed here have been shown in clinical trials to improve survival and/or reduce mortality rate, and have been approved for use by the US Food and Drug Administration. In colon cancer, chemotherapy after surgery is usually only given if the cancer has spread to the lymph nodes (Stage III).

- **Adjuvant (after surgery) chemotherapy**
  - 5-Fluorouracil (5-FU) or Capecitabine (Xeloda)
  - Leucovorine (LV, folic Acid)

- **Chemotherapy for metastatic disease.** Commonly used first line regimens involve the combination of infusional 5-fluorouracil, leucovorine and oxaliplatin Oxaliplatin (FOLFOX) with bevacizumab or infusional 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) with bevacizumab or the same chemotherapy drug combinations with cetuximab in KRAS wild type tumors. 38
  - 5-fluorouracil (5-FU)
  - capecitabine (Xeloda)
  - UFT or Tegafur-uracil
  - Leucovorin (LV, folic Acid)
  - Irinotecan (Camptosar)
  - Oxaliplatin (Eloxatin)
  - Gemcitabine (Gemzar)
  - Bevacizumab (Avastin)
  - Cetuximab (Erbitux)
  - Panitumumab (Vectibix)

- **In clinical trials for treated/untreated metastatic disease.** 39
  - Bortezomib (Velcade)
  - Oblimersen (Genasense, G3139)
  - Gefitinib and erlotinib (Tarceva)
  - Topotecan (Hycamtin)

At the 2008 annual meeting of the American Society of Clinical Oncology, researchers announced that colorectal cancer patients that have a mutation in the KRAS gene do not respond to certain therapies, those that inhibit the epidermal growth factor receptor (EGFR)—namely Erbitux (cetuximab) and Vectibix (panitumumab). 40 Following recommendations by ASCO, patients should now be tested for the KRAS gene mutation before being offered these EGFR-inhibiting drugs. In July 2009, the US Food and Drug Administration (FDA) updated the labels of two anti-EGFR monoclonal antibody drugs (panitumumab (Vectibix) and cetuximab (Erbitux)) indicated for treatment of metastatic colorectal cancer to include information about KRAS mutations. 41
CONCLUSION

We can conclude the matter given in this review as colorectal cancer (CRC) is a second largest type of cancer in developed countries, as data of 2011, 49,380 death and approx 1,40,000 patients were reported as new case of colorectal cancer in America. CRC is start with a tumor in lower part of colon or in rectum part initially it change the bowel habits. Factors affecting CRC are age (60-70 years), heredity, smoking, diet alcohol etc. it can be prevent by removing pre-cancerous lesions or adenomatous polyps before invasive cancer develops, screening of crc can be done by some test like FBOT, FIT, STOOL DNA, colonoscopy, DCBE, CT etc. Stage of cancer can be identify by TNM staging system and it can be treat by surgery, chemotheraphy or radiation therapy, or a combination of these approaches. Chemotherapy is often applied after surgery (adjuvant), and before surgery (neoadjuvant), or as the primary therapy (palliative). 5-fluorouracil (5-FU), capecitabine (Xeloda) etc are the drugs used for chemotherapy of CRC.

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