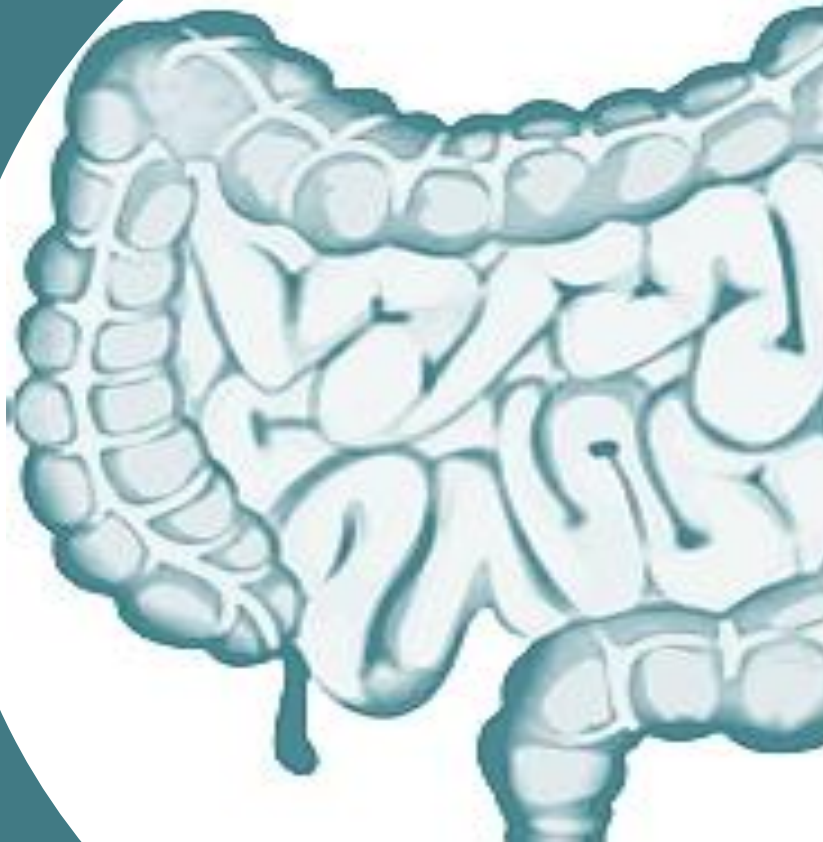
Issue 03

Disease Of the Month: June 2022

COLORECTAL CANCER



Resident Research Forum

Rawalpindi Medical University

MESSAGE FROM THE VICE CHANCELLOR

MESSAGE FROM PRESIDENT RRF

FOREWORD

Resident Research Forum's, Disease of the month publications have been conceived as a means of providing useful information to physicians, surgeons, residents, and medical students. Each issue is carefully crafted to provide a comprehensive summary of the subject after a comprehensive literature review.

For our third issue it has been our distinct pleasure to work on Colorectal Cancer which is a common source of morbidity and mortality. It's a disease process which calls out for a multidisciplinary approach based on prevention, screening and early detection.

Resident research forum aims to make up for the information deficits, uncoordinated care that residents encounter in there day to day practice. This finished product represents efforts from our residents and student associates duly reviewed by our worthy teachers, who have taken time out from there busy schedules to compile this document to bring the reader up to date with the latest advances which make a real difference to the clinical management of this disease.

I hope that you will read enjoy and reread this publication if you are a family physician, a gastroenterologist, a surgeon, an oncologist, a nurse specialist or a student who wants to develop the knowledge base to support your patients at every step of their care pathway.

The team DoTM is thankful to the Executive council of RRF for its full support and recognition of efforts and contributions of the DoTM team. I hope that RRF and DoTM will grow and flourish for many years to come.

All keen and aspiring medical writers are invited for DoTM's future and subsequent issues.

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Introduction & Epidemiology

Dr. Mudassar Abbas Siddique

Colorectal cancer, synonymous with Colorectal Adenocarcinoma, is considered as third leading cause of mortality worldwide. Its histological origin suggests that itoriginates from the glandular epithelial cells of large intestine via genetic or epigenetic mutations.(1)

While talking about the normal anatomy, primary function of the colon is the re-absorption of water and other minerals and contents in the chyme. The colonic flora is designed to break these and other proteinaceous and starchy contents. Intestinal crypts are organized to absorb these contents.

Intestinal crypts also are home to the intestinal stem cells.(2)After differentiation into specialized cells they propped up and out of the crypt as enterocytes, enteroendocrine, paneth and goblet cells. At about 14th day after propping up at the villi these cells undergo apoptosis and leave the body along with fecal matter through anus.(3)WNT, BMP and TGF-B are the signaling proteins responsible for its regulation.(4)

Mutation is the main culprit causing more and more varieties of the colorectal carcinoma and due to this diverse collection it is becoming impossible to devise one therapy for management and more strategies are being devised to cope up with each variant.(5)

Surgery is considered as a primary mode of treatment. But due to enhanced knowledge regarding disease pathology, and late presentation of this disease, surgery is considered of no value in almost 25% of the diagnosed cases.(6)

The need of time is to develop newer strategies to cure colorectal cancer based on environmental and genetic factors. Molecular level advancements are needed to fight with the variants and to stop further spread. This is the only way left behind and by which next generation including researchers and physicians will be able to give benefit to the people by this molecular and genetic advancement to cope with this fatal neoplastic disease.

HISTORICAL AND CULTURAL ASPECT

Egyptian record and treatment shows the true evidence of the existence of cancerous pathologies and they were considered as Father of 'Pharmacology' and some of their remedies were mentioned as 'magical' therapeutic remedies.(7)They left the evidence for future researchers,according to the old Egyptian culture, preserved in the form of mummification of the dead.(8)

Zimmerman showed in his article for the first time about histological confirmation of cancer in Egyptian mummy anciently. He reported that the first ever rectal cancer was diagnosed in an unnamed mummy who was a resident of Dakhleh Oasis during Ptolemaic Period ($_{CE}$200-400).(8)

First surgical removal of the tumor has been reported in papyri deciphered from

around 1500_{BC}. Deep seated tumors were treated with prescribed animal remnants as ointments and enemas etc.(7)

It is considered that in older times not enough and adequate techniques and variants were identified and published due to which information regarding variants is lacking. But here in our modern society 'Carcinogens' are known to cause cancer.(9)

Concept of screening originated after an article was published by Lockhart and Dukes in 1927 which stated that CRC's don't arise de novo rather these patients have a history of having adenomatous polyps. Multiple options for possible screening or early detection were proposed in subsequent years. The greatest paradigm shift came with introduction of colonoscopy and colonoscopicpolypectomy (1890's – 1980's)(10)

Chemotherapy with folic acid and nitrogen mustard was introduced in early 1940's as a possible means of treatment.(7) More recently, surgical resection and radiotherapy have been introduced, which caused significant miracle in reducing the mortality rate after compliant treatment by the affected individuals.

However in most developing countries incidence rates are still higher than desired with most patients diagnosed at advanced stages. This can be attributed to poor health education amongst the target population regarding CRC and its screening and also the structural barriers for screening.(11) High risk population needs to be imparted proper education regarding CRC and its screening to remove any misconceptions and social stigmas.This will enable early detection of CRC and better therapeutic outcomes.

EPIDEMIOLOGY

According to the World Health Organization GLOBOCAN database, CRC is the third most commonly diagnosed neoplasm worldwide, being more common in males than in females.

Incidence in both sexes worldwide it shows that Asia has got 52.3% incidence and Europe 26.9% incidence, while Africa, LAC And North America showed demographic incidence of about 3.4%, 7% and 9.3%.(12)

MORTALITY

The incidence of deaths in both genders and all age groups shown by GLOBOCAN for year 2020 was9.4% out of total mortalities with other tumors of closely related regions.(12)

Region wise mortality data shows that mortality in Asian subcontinent is 54.2%, Europe 26.2%, 7.4% in LAC, 6.8% in N. America and 4.6% in Africa.(12)

The geographic differences can be attributed to the regional differences in environmetnal and dietary factors, the socioeconic statuses and variable rates of CRC screening over a backdrop of basic genetic susceptibilty.(13)

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Pathophysiology

DrSania

Colorectal Cancer is the cancer affecting caecum, colon and rectum. Anal canal and Appendix are not considered in the definition, and are treated as a separate entities. The incidence of colorectal cancer varies between and within the countries suggesting environmental factors. The peak incidence appear in the seventh decades of life. The ratio between male & female is almost equal. Life style play very important role in etiology of cancers.

ETIOLOGY :

The exact cause/s of the colorectal cancer is unknown.

Risk Factors :

1. Age :
   Colorectal cancer is more likely to occur as people get older. This disease is more common in people over the age of 50. However, colorectal cancer can occur at younger ages, even, in rare cases, in teens.
2. Diet :
   Colorectal cancer seems to be associated with diets that are high in fat and calories and low in fiber, diet low in indigestible fibers, high in animal fat.
3. Polyps :
   Polyps are benign growths on the inner wall of the colon and rectum. They are fairly common in people over age 50. Some types of polyps increase a person's risk of developing colorectal cancer. Colonic polyp is well known cause of colorectal cancer. The risk of malignant change in benign polyp depend on many factors including:
   - size, number of polyp
   - histological type : the risk of cancer development is more common in villous type of adenomas than in tubular type.
   - also presence of epithelial dysplasia increase the risk of cancer.
4. Personal Medical History :
   Research shows that women with a history of cancer of the ovary, uterus, or breast have a somewhat increased chance of developing colorectal cancer. Also, a person who has already had colorectal cancer may develop this disease a second time.
5. Family Medical History :
   First-degree relatives (parents, siblings, children) of a person who has had colorectal cancer are more likely to develop this type of cancer themselves, especially if the relative had the cancer at a young age.
6. Genetic Factors :
   Play small but very important role in etiology of Colonic cancer.
   The familial syndromes with increased risk of colorectal carcinoma includes:
   - Familial Adenomatous Polyposis
   - HNPCC - Lynch syndrome I & ii

- Turcot,s syndrome
- Peutz-jeghers syndrome
- ***FAP***

Familial adenomatous polyposis (FAP) accounts for 1% of colorectal cancer cases. People with FAP typically develop hundreds to thousands of colon polyps; the polyps are initially benign, but there is nearly a 100% chance that the polyps will develop into cancer if left untreated. Colorectal cancer usually occurs by age 40 in people with FAP. Mutations in the APC gene cause FAP; genetic testing is available.

- ***HNPCC***

Hereditary non-polyposis colorectal cancer (HNPCC), sometimes called Lynch syndrome, accounts for approximately 5% to 10% of all colorectal cancer cases. The risk of colorectal cancer in families with HNPCC is 70% to 90%, which is several times the risk of the general population .People with HNPCC are diagnosed with colorectal cancer at an average age of 45. Genetic testing for the most common HNPCC is available.

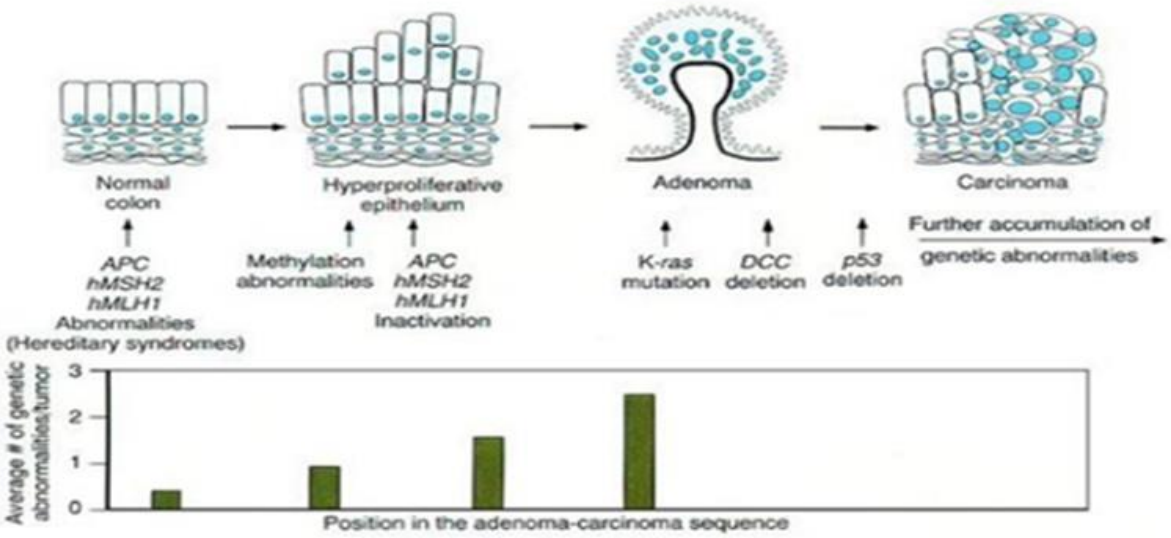
7. Inflammatory bowel disease:
    - Ulcerative colitis: Patient with extensive colitis and for long duration are at high risk of developing colorectal cancer.
    - Crohns disease is also associated with increased risk of is also associated with increased risk of cancer.
8. Irradiation &Immunosuppresion:
    - Irradiation is well known carcinogenic.
    - Patient on immunosuppression drugs or disease are at increased risk of developing colorectal cancer.

PATHOPHYSIOLOGY

- Colorectal cancers arise from dysplastic adenomatous polyps in the majority of cases. There is a multistep process involving the inactivation of a variety of tumour-suppressor and DNA repair genes, along with simultaneous activation of oncogenes. This confers a selective growth advantage to the colonic epithelial cell and drives the transformation from normal colonic epithelium to adenomatous polyp to invasive colorectal cancer. Germline mutations underlie the well-described inherited colon cancer syndromes, whereas sporadic cancers arise from a step-wise accumulation of somatic genetic mutations. A single germline mutation in the adenomatous polyposis coli (APC) tumour suppressor gene is responsible for the dominantly inherited syndrome that bears the same name. Clinical expression of the disease is seen when the inherited mutation of one APC allele is followed by a second hit mutation or deletion of the second allele. Ulcerative colitis and Crohn's colitis are associated with an increased risk of colorectal cancer with an interim step of dysplastic epithelium.
- Spread of colorectal cancer is to local lymph nodes and via the vasculature to liver and lungs and, less commonly, to bone and brain. However, as survival improves with systemic chemotherapy,

bone and brain metastases have been increasingly reported.

- ***Genetic Changes in CRC :***
- Activation of oncogenes (K-ras).
- Loss of tumour suppressor gene activity (APC, DCC).



- Abnormalities in DNA repair genes (hMSH2, hMLH1), especially HNPCC syndromes.

MECHANISM :The mutational activation of an oncogene followed by and coupled with the loss of genes that normally suppress tumorigenesis.

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Clinical Features & Diagnosis

Dr Noor us Sabah, JawadBasit, Mohammad EbadurRehman

CLINICAL FEATURES:

Colorectal carcinomas are known to develop insidiously and usually remain undetected until the late stages of the disease. The clinical presentation differs based on the location of invasion of the carcinoma. The initial signs of right-sided colorectal carcinoma include fatigue and weakness mostly secondary to undiagnosed iron deficiency anemia. Alternatively, left-sided adenocarcinomas usually present with changes in bowel habits or cramping in the left lower quadrant of the abdomen. Different clinical features of CRC are enumerated below.

- RECTAL BLEED:

  Around 37% of the patients of CRC have some degree of rectal bleeding (1). Hematochezia refers to the passage of fresh blood par rectal. It indicates a lower gastrointestinal bleed. The differentials associated with hematochezia include arteriovenous malformation, diverticulitis or a bleeding adenocarcinoma of the colon. Melena is defined as the passage of fresh tarry stool par rectal. Though not associated with prognosis or mortality, melena is a symptom of CRC in 2.9% of the population having this disease (2)

- IRON DEFICIENCY ANEMIA:

  The prevalence of iron deficiency anemia in the population having CA of the colon is around 57%(1) Most patients having colorectal carcinoma have underlying bleeding either in the form of fecal occult blood or hemorrhagic lower gastrointestinal bleed. High suspicion of colorectal carcinoma should be raised if a male patient who is 50+ years presents with iron deficiency anemia (3)

- ABDOMINAL PAIN:

  Initially, colon cancer presents with a mild dull ache in the abdomen that is difficult to localize the pain. The pain may or may not be accompanied by abdominal tenderness. Abdominal pain is more often experienced in left-sided cancers than the right-sided ones with the frequency of the population depicting abdominal pain as a symptom proportionally increasing with the staging of the cancer and node-positive changes. (2)Abdominal pain has been established as a predictor of advanced colorectal carcinoma (ACRC) (4) indicating a poor prognosis.

- CHANGE IN BOWEL HABITS:

  A change in bowel habits is usually the earliest sign of colorectal cancer. The symptoms are usually but are not limited to constipation, diarrhea and tenesmus. Right sided colorectal cancers might present as a patient having reduced stool caliber clinically interpreted as pencil stools. Chronic constipation has been linked to colorectal carcinoma and has been found to have a role in the carcinogenesis of the carcinoma (5) Loose stools have also been found to

increase the risk of colorectal carcinoma by three fold after adjustment for the covariates (6) Sudden onset diarrhea especially if combined with unintentional intense weight loss raises a high suspicion of colon cancer. Change in bowel habits is exhibited by 58 percent of patients diagnosed in early stages of colorectal carcinoma compared to 87 percent having advanced colorectal carcinoma (4) Change in bowel habits might be accompanied by distended abdomen and bloating. Diarrhea has been found to be associated with non-emergency presentation of colorectal carcinoma with adjusted odds ratio of 6.2 (7)

- WEIGHT LOSS

The prevalence of weight loss in patients of colorectal cancer in Dukes stage A is 18% compared to 28% in dukes stage B-D (4) Body Weight loss (BWL) is defined as loss of greater than 5 percent of body weight in a span of 6-12 months and has been associated with tumor size depth and location as well as predictor of poor outcomes (8) Diet induced weight loss, however, has been associated with improved insulin sensitivity, reduced cholesterol levels and reduced colorectal tissue expression demonstrated by reduction in the levels of Ki-67(9) Weight loss in colorectal carcinoma is due to cancer cells consuming the body's energy as well as due to additional energy required by the immune system to fight the cancer cells.

- LOCATION AND TYPE OF ADENOCARCINOMA:

The location and type of adenocarcinoma in colon cancer has been established as known prognostic factors. The most common location is proximal colon including the splenic flexure followed by rectum, distal colon and other sites respectively (10) Non-mucinous adenocarcinoma is most common, however, mucinous adenocarcinoma shows a preponderance for younger patients (11)

- ASYMPTOMATIC PATIENTS

Almost 12% of the patients with colorectal carcinoma remain asymptomatic especially those who are at an early stage of disease. Early detection reflects a better prognosis which highlights the role of screening for the detection of colorectal carcinoma.

DIAGNOSIS:

The diagnosis of colon cancer involves a systemized strategy involving clinical exams, blood tests, histopathology testing and imaging to yield a confirmed diagnosis and exclude the differentials.

- CLINICAL HISTORY:

The patient of colorectal carcinoma usually gives history of mild dull ache in the lower quadrants of abdomen that is difficult to localize. Additionally, there might be a history of chronic constipation that has been worsening or constipation unresponsive to laxatives and Over the Counter medication. Some patients give history of diarrhea unresponsive to bactericidal and luminal agents. Patients of familial colorectal carcinoma usually have a positive family history. The patient usually complains of generalized cachexia and lethargy.

PHYSICAL EXAM:

Physical exam findings in colorectal cancer are not always conspicuous and usually remain concealed until the later stages of the disease. On the general exam, the patient appears emaciated with generalized or localized pallor. In the later stages of the disease, the vital signs are usually remarkable with patient being hypotensive, febrile and tachypnic. On inspection of the abdomen, ascites maybe present especially if the cancer is presented at later stages. Discomfort or tenderness on palpation is usually present especially in the right lower quadrant or left iliac fossa. A palpable abdominal mass might also be appreciated and can give substantial clues pertaining to the location of the carcinoma. On visceral palpation, non-tender hepatomegaly maybe appreciated indicating hepatic metastasis of the carcinoma and poor prognosis. Bowel sounds maybe absent if the carcinoma has culminated into intestinal obstruction. Digital Rectal Exam is a must in every suspected patient of colorectal carcinoma. Majority of the rectal carcinomas are palpable during DRE as a hard irregular mass.

BLOOD TESTS:

Though blood tests cannot aid in a direct diagnosis of colorectal cancer, they can aid in the progression towards a confirmed diagnosis as well as in the monitoring of the disease.

- **Complete Blood Count:** Since most colorectal carcinomas bleed internally, a complete blood count is warranted to evaluate the blood hemoglobin levels. Colorectal carcinomas usually cause Iron deficiency anemia with microcytic hypochromic picture.
- **Liver Function Tests:** Since the most common site of metastasis of colorectal carcinomas is liver, so assessment of synthetic liver function tests and liver enzymes is necessary. These include Alanine transaminase (ALT), Aspartate Transaminase (AST) ,Alkaline phosphatase (ALP) , gamma-glutamyltransferase (GGT) ,prothrombin time (PT), international normalized ratio (INR) and Albumin.
- **Tumor markers:** Following tumors markers have been frequently used to screen and diagnose colorectal cancer.
    I. **Carcinoembryonic antigen (CEA):** It is the most commonly measured tumor marker for colorectal cancer and its level co-relate with the disease burden. CEA has the highest sensitivity as a single biomarker for colorectal carcinoma (12)CEA is the most accurate tumor marker for early stages of colorectal cancer. Its levels co relate the most with overall survival in patients of colorectal cancer(13)

II. **Carbohydrate antigen 19-9 (CA 19-9):** Though primarily considered a tumor marker for pancreatic cancer, levels of CA 19-9 rise in metastatic colon cancer and are indicative of advanced carcinogenesis (14)

III. **Carbohydrate Antigen 125 (CA-125):** CA-125 is a marker of peritoneal dissemination of colon cancer and has a sensitivity of 57 percent and a specificity of 92 percent, which is superior to that of CEA (15)

➢ IMAGING

- **Barium Enema with Fluoroscopy:**
  Barium Enema is the analysis of the lower gastrointestinal tract using the X rays after the rectum has been injected with barium sulfate. Multiple X ray images are taken during the procedure. Sometimes, fluoroscopy is additionally done by passing a continuous X ray beam while the barium liquid is passing through the large intestine to obtain an X ray movie in order to record the motion of barium.
- **Computed tomography Colonoscopy (CTC):**
  CT-Colonoscopy uses low radiation CT scanning to examine the inside surface of large intestine using CT images. Detailed three dimensional CT images are generated which can be used to identify the anomalies. It is also known as virtual Colonoscopy. CT-colonoscopy has a higher sensitivity than barium enema for detection of large polyps and carcinoma of the colon and is usually the assessment of choice by the patients for being non invasive(16)
- **Endorectal ultrasound**
  In this technique, the transducer is injected into the rectum to assess the degree of penetration of the rectal wall by the carcinoma as well as to look for nearby metastasis and lymphadenopathy.
- **Magnetic Resonance Imaging (MRI):**
  MRI is used to obtain images of the soft tissues of the body. MRI has been found to be more specific than other radiological investigations for rectal carcinomas.
- **Computed tomography using contrast medium:**
  CAT scan is done pre-operatively to measure the degree of metastasis of the carcinoma into lungs, liver and other sites, so that appropriate surgical plan can be devised.

➢ INVASIVE TESTING:

- **Conventional Colonoscopy:**
  It is an invasive test and is considered the gold standard for the diagnosis of colorectal carcinoma. It involves the insertion of thin flexible tube with a camera at the end into the rectum through the anal canal. The entire large intestine including the rectum, sigmoid colon, descending, transverse and ascending colon can be visualized

through this approach. Biopsy samples can be taken during this procedure. Additionally, the procedure has a therapeutic value as polypectomy of suspicious polyps can be achieved. Srnsitivity and specificity of colonoscopy to detect adenomas 6 mm or larger ranges from 75 to 93 percent (17) The accuracy of colonoscopy can be ascertained by the fact that screening with colonoscopy is associated with 74 percent reduction in CRC mortality compared to 34 percent for flexible sigmoidoscopy(18)

- **Sigmoidoscopy:**
  Though a less invasive procedure, sigmoidoscopy is limited to the visualization of anus, rectum and sigmoid colon. The entire length of the colon cannot be examined by this approach. Diagnostic sigmoidoscopy is followed by conventional colonoscopy if suspicious lesions or polyps are detected during the exam. For diagnostic purposes, Flexible sigmoidoscopy is usually preferred over rigid sigmoidoscopy as it is preferred by the patients and retrieval of biopsy samples is easier. Flexible sigmoidoscopy maybe preferred over regular colonoscopy if the risk of proximal colon cancer is negligible (19)

➢ BIOPSY AND HISTOPTHOLOGY:

- Biopsy is taken during colonoscopy, sigmoidoscopy or surgical resection. Atleast three endoscopic biopsies are usually recommended to establish a correct diagnosis (20)Histopathologically, if invasion of the colonic mucosa is appreciated, it indicates an infiltrative adenocarcinoma. Poorly differentiated carcinomas have a high metastasis rate and indicate a poor prognosis. Lymphatic, vascular or angiolymphatic invasion indicates higher odds of a metastatic carcinoma and distant spread. If a suspicious polyp is biopsied, then a villous and serrated polyp with or without dysplasia indicates higher chances of formation of a carcinoma and demand of a more stringent follow-up.
- Gene testing of the tumor cells is recommended to gauge the appropriate treatment regimen. Tumors cells extracted through biopsy are typically tested for KRAS,BRAF, NRAS,PIK3CA and TP53. Special pathology techniques maybe used to look for Microsatellite Instability (MSI) and Mismatch Repair (MMR) genes such as MLH1,MSH2 and PMS2. If MSI is found, it is mostly associated with Lynch Syndrome. Endoscopic biopsies, though much tinier than surgical resection specimens, are equally predictive for detection of genetic mutations in colon cancer(21)

➢ BRUSH CYTOLOGY:

With a positive and negative predictive value of 98.6 and 61.9 percent and sensitivity and specificity of 88.2 and 94.1

percent, the efficacy of cytology for the diagnosis of colorectal cancer is comparable to biopsy (22). Combination of these two diagnostic methods results in a definitive diagnosis of colorectal carcinoma.

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Tumor Markers & Histopathology of Colorectal Carcinoma

Dr. Hiba Khalid, NidaNisar

CRC affects almost more than one million men and women every year, and causes half a million of deaths worldwide. In the Europe in 2010, CRC was the third most common malignant cancer in both men and women. Colorectal cancer (CRC) is the second most commonly diagnosed cancer among females, and third among males worldwide. Despite the continuous progress in diagnostic and therapeutic methods, CRC still contributes to significant number of deaths.

TUMOR MARKERS

The term 'tumor marker', by some researchers, considered as a synonym of 'biomarker' refers to substances (most typically proteins and glycolipids) which can be attributed to the development of normal cells or carcinogenesis at different cell development stages e.g., tumour-associated antigens (TAAs).

The National Institute of Health (NIH) defines a biomarker as 'a biological molecule that is a sign of either normal or abnormal process or a sign of a disease found in blood, body fluids or tissues'. A definition of biomarker mostly refers to DNA, RNA, microRNA (miRNA), epigenetic changes or antibodies. Biomarkers currently play an important role in the detection and treatment of patients with colorectal cancer. Biomarkers also help us to select the diagnostic and treatment algorithms by selecting the proper chemotherapeutic drugs across a broad spectrum of patients. The basic approach of research in field of biomarkers is to locate the best ,non invasive and cost effective diagnosis alongside to look for best prognostic follow-up and to define the predictive markers for available treatments.

Tumor markers also help us for an early diagnosis, screening , monitoring of tumor progression, results of neo-adjuvant chemotherapy , radiotherapy and follow-up for recurrence.

For diagnosis of CRC we can use certain classical markers however recent studies have also included certain hematopoietic growth factors HGFs, enzymes, circulating tumor cells and tumor antigens.(1)

CLASSICAL MARKERS:

1. Carcinoembryonic antigen

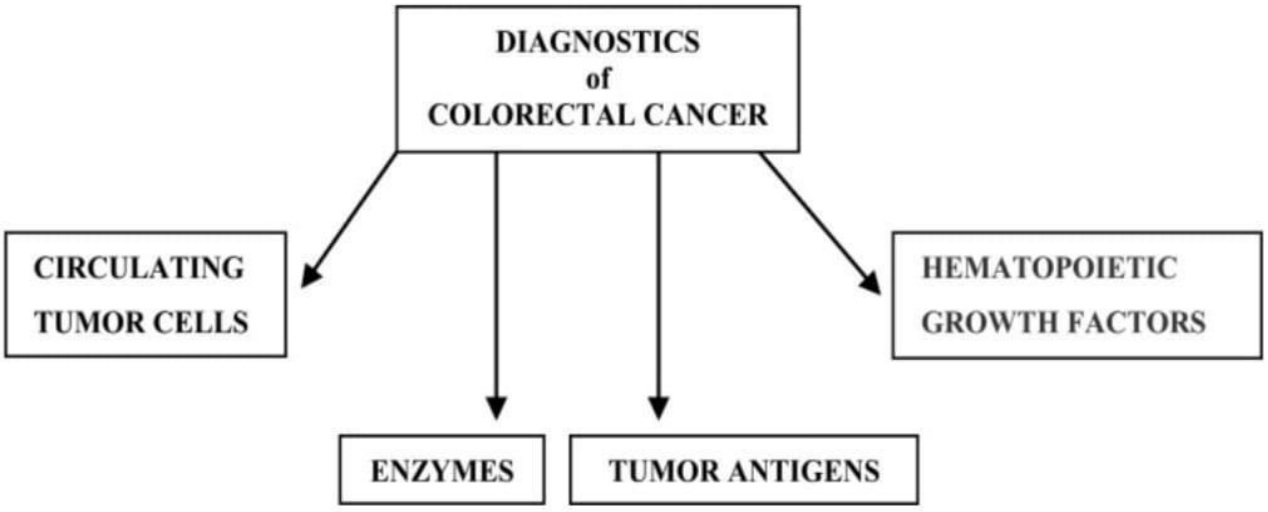


Figure 1

(CEA)

2. Carbohydrate antigen (CA 19.9)
3. Tissue polypeptide specific antigen (TPS)
4. Tumor-associated glycoprotein-72 (TAG-72).(2)

HEMATPOIETIC GROWTH FACTORS:

1. Macrophage-colony stimulating factor (M-CSF)
2. Granulocyte-macrophage-colony stimulating factor (GM-CSF)
3. Interleukin-3
4. Interleukin-6

ENZYMES:

1. Alcohol dehydrogenase
2. Lysosomalexoglycosidases

Circulating cancer cells (CTCs):

CTCs are the factors responsible for metastasis, as most of the deaths do not occur due to primary tumor but because of the tumor spread .

We can also classify tumor markers as tumor markers found in blood and markers present in tumor tissue.

TUMOR MARKERS FOUND IN BLOOD:

1. Carcinoembryonic antigen (CEA) level
2. CA 19-9
3. Chromosome 18q loss of heterozygosity (18qLOH): Often applied in patients with stage II or III colorectal cancer; can influences prognosis.(3)

TUMOR MARKERS IN TUMOR TISSUES:

1. MSI (microsatellite instability
2. K-RAS mutations:
3. BRAF mutations:

Classical Tumor Markers:

1.CEA

Carcinoembryonic antigen (CEA) is a glycoprotein onco-fetal antigen, first described by GOLD and FREEDMAN in 1965, that is expressed in many epithelial tumors. CEA is considered relatively inexpensive. (4) CEA level can be checked prior to surgery to predict prognosis, can be used during therapy to assess response to treatment or after completion of therapy to monitor for recurrence.(3)

CEA is considered a very good biomarker for diagnosis as it being elevated in 70 % patients of CRC, CEA is actually a glycoprotein that is being formed in the cells of large bowel.

CEA is considered a tumor marker, however its concentration is also seen elevated in benign states like hepatitis, pancreatitis, obstructive pulmonary disease and inflammatory bowel disease.

Tan, et al. conducted a quantitative meta-analysis of 20 studies involving 4285 patients and investigated CEA performance characteristics when used to detect recurrence of colorectal cancer.

Generally, levels upto 5ng L are considered normal levels of antigen in blood. Normal levels of CEA in patients of liver cirrhosis and ulcerative colitis can elevate up to 10 ng L.

CEA has 0.64 sensitivity and 0.90 specifity overall. [3] The positive rate of CEA is 40-60% . The study by Chen, et al. in Taiwan examined elevating CEA levels are also important in postroperative relapses. In a study of 4841 patients, 999 had elevated CEA (defined at >5 ng/mL) and a relapse. The cases of relapse which are being diagnosed by some other means also first showed increase in CEA levels. Patients treated for colorectal cancer should have CEA levels monitored every 3 months. Unfortunately, an increase in CEA concentration is only sometimes observed during the first stage of CRC. This mostly happens in the advanced

stages of cancer. An increased concentration of CEA prior to operation may correlate with an adverse prognosis.

2.CA 19.9

CA 19.9 (carbohydrate antigen) is a glycoprotein characterized by a high molecular weight which may be released to the blood. Positivity rate of CA19.9 is 30 to 35% .[4] Like CEA, its not specific for CRC, this marker is used in the diagnostics of pancreatic, colorectal and gastric cancers. Vukobrat-Bijedic, et al. showed that CA 19.9 is less sensitive than CEA. The combined assays of CEA and CA 19.9 may increase diagnostic sensitivity in colorectal cancer detection. Moreover, the determination of both of these markers is used as a postoperative prognostic factor in the evaluation of the stage of the disease and survival rate.

Nakatani, et al. in their research from 2012 provided data that colon cancer located in the region of sigmoid had extremely high concentrations of CEA and CA19.9. Both CA 19.9 concentration and sensitivity increase with higher Dukes' stage of disease, but do not correlate with the tumor location and number of positive lymph nodes. Patients with Dukes' C tumors with preoperative CA 19.9 concentrations higher than 37 U/mL had a shorter disease-free survival period.

3.Tissue polypeptide specific antigen (TPS)

TPS is considered an important tumor marker in many malignant cancers and as a response factor in monitoring chemotherapy in different advanced gastrointestinal carcinomas. It is a singular conjugated chain of polypeptide, which is produced in different phases of the molecular cycle (S or G2) and subsequently released to tissue after mitotic division. High TPS concentration is a marker of proliferation of cancer cells. TPS is a function of the cell division rate. A high level of tissue polypeptide specific antigen occurs in about 60–80% of patients with colorectal cancer, it is being estimated for early stages of CRC. The survival rate was significantly lower in patients with initially higher concentrations of TPS. In asymptomatic patients that require active treatment due to a generally poor prognosis, changes in elevated TPS levels appear to be useful in determining the length of treatment. Hence, it being considered superior to commonly used CEA.

4.Tumor associated glycoprotein-72 (TAG-72)

TAG-72 is a glycoprotein formed in bile duct endothelial cells, gastric epithelium or renal pelvis cells. It is a mucin-like molecule. TAG-72 is found on the surface of many cancer cells, including colon, ovary, breast, and pancreatic cells. Guadagni, et al. showed that serum concentrations of TAG-72, CEA, CA 19.9 were elevated in 43%, 43% and 27% of patients with colorectal cancer, respectively. It is advisable to determine TAG-72 together with other markers, primarily, CEA. Sixty-one percent of patients had at least one marker with elevated levels when measuring these three markers.

Recently, several inflammatory markers including pre-treatment neutrophil to lymphocyte ratio (NLR) have been used as prognostic factors. Dimitriou, et al. have found that in patients with CRC, a pre-treatment NLR above 4.7 is a poor prognostic factor for disease-free survival, 5-year survival and overall survival. The poor prognostic effect of NRL is magnified in stage II CRC patients.

Sensitivity and Specificity assessment of individual and combinational examination of serum CEA, CA19-9, CA72-4 in CRC patients:

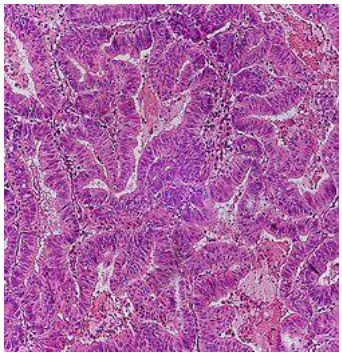
CEA has the highest sensitivity (46.59%) followed by CA72-4 (44.80%), while CA19-9,

CA125, and SF were all lower than 15%.
CA125 has the highest specificity (99%) of individual maker, followed by CA72-4, CA19-9, while CEA has the lowest specificity (80%). Combined tests of any two of the five tumor markers concludes that the highest sensitivity is the combination of CEA + CA72-4 which was significantly lower than the sum of sensitivities (91.39%) of these two markers tested individually (46.59% + 44.80% (This result suggests that there is a positive correlation of the two markers).(5)

HISTOPATHOLOGY:

The histopathology of colorectal cancer involves analysis of tissue taken from a biopsy or surgery. There is high incidence of adenocarcinoma in around 95 to
98% of all the types of colorectal carcinoma.(6) CRC is a significantly heterogeneous tumor with three major histological sub-types:

1. Adenocarcinoma
2. Mucinous adenocarcinoma
3. Signet-ring cell carcinoma



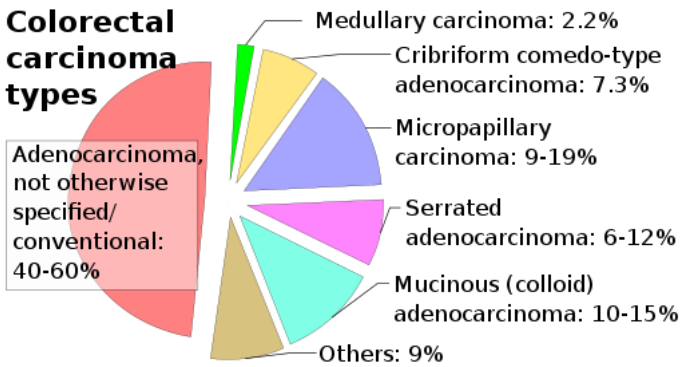


Figure 2

Adenocarcinoma is an epithelial tumor. It originates from superficial glandular epithelial cells that line the colon and rectum. It invades the wall, infiltrating the muscularis mucosae layer, the submucosa, and then the muscularispropria. Tumor cells present irregular tubular structures, harboring pluri-stratification, multiple lumens, reduced stroma ("back to back" aspect).
Sometimes, there occurs large pools of mucus as the tumor cells secret mucus that invades the interstitium and leads to mucinous adenocarcinoma, in which cells are poorly differentiated. If the mucus persists in tumor cell, it pushes the nucleus to the periphery and leads to formation of "signet-ring cell." Depending on glandular architecture, cellular pleomorphism, and mucosecretion of the predominant pattern. Adenocarcinoma may present three degrees of differentiation i.e. well ,moderately and poorly differentiated.(6)

MICROSCOPIC CRITERIA

A lesion with "high grade intramucosalneoplasia" has:

1. Severe cytologicatypia.
2. Cribriform architecture, consisting of juxtaposed gland lumens without stromainbetween, with loss of cell polarity. Rarely, they have foci of squamous differentiation(morules).

This should be distinguished from cases where piles of well-differentiated mucinproducing cells appear cribriform. In such piles, nuclei show regular polarity with apical mucin, and their nuclei are not markedly enlarged. Invasive adenocarcinoma shows

1. Varying degrees of gland formation with tall columnar cells
2. Frequent desmoplasia
3. Dirty necrosis, consisting of extensive central necrosis with granular eosinophilickaryorrhectic cell detritus. It is located within the glandular lumina,[9] or often with a garland of cribriform glands in their vicinity.

Histological findings of colorectal adenocarcinoma are also important for staging and histopathological subtyping.(7)

Serrated adenocarcinoma:

Epithelial serrations or tufts (thick blue arrow), abundant eosinophilic or clear cytoplasm, vesicular basal nuclei with preserved polarity. (Figure 3:A)

Mucinous carcinoma:

Presence of extracellular mucin (>50%) associated with ribbons or tubular structures of neoplastic epithelium.(Figure 3:B)

Signet ring carcinoma:

More than 50% of signet cells with infiltrative growth pattern or floating in large pools of mucin.(Figure 3:C)

Medullary carcinoma:

Neoplastic cells with syncytial appearance (thick yellow arrow) and eosinophilic cytoplasm associated with abundant peritumoral and intratumorallymphocytes.(Figure 3:D)

Lymphoepitelioma-like carcinoma:

Poorly differentiated cells (red arrow) arranged in solid nests, tubules and trabeculae with poorly demarcated,

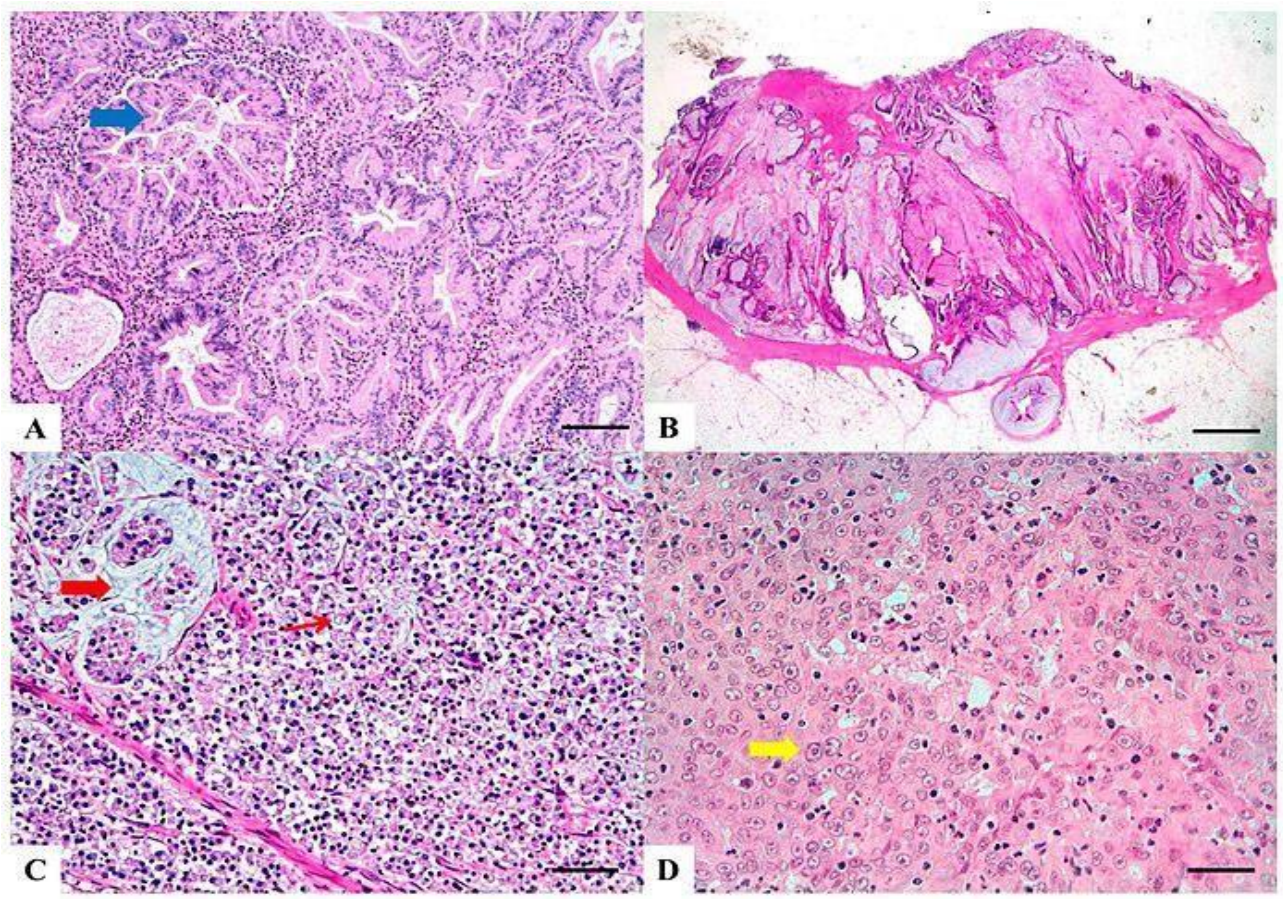


Figure 3

infiltrative margins; intratumoral lymphoid infiltrate is extremely abundant.(Figure 4:A)

Cribiformcomedo-type carcinoma:

Cribriform gland with central necrosis comedo-like.(Figure 4:B)

Micropapillary carcinoma:

Small, tight round to oval cohesive clusters of neoplastic cells (>5 cells) floating in clear spaces (double circle red-black), without endothelial lining and with no evidence of inflammatory cells.(Figure 4:C)

Low grade tubulo-glandular carcinoma:

Very well-differentiated invasive glands with uniform circular or tubular profiles (blue arrow) with bland cytologicatypia.(8)(Figure 4:D

Villous carcinoma:

Invasive carcinoma with villous features consisting of usually intraglandular papillary projections (yellow arrow) associated with an expansile growth pattern, at the deep portions of the tumor.(Figure 5A)

Squamous carcinoma: Morphologically similar to other squamous cell carcinomas occurring in other organs with possiblekeratinization.(Figur 5B)

Clear cell carcinoma:

Clear cell cytoplasm identified in polygonal cells with a central nucleus, columnar cells with an eccentric nucleus and/or round/oval cells with abundant cytoplasm and inconspicuous marginally located nucleus similar to lipocytes or lipoblasts.(Figure 5C)

Hepatoid carcinoma:

Large polygonal-shaped cells, with granular eosinophilic cytoplasm, prominent nucleoli and trabecular and pseudo-acinar growth pattern similar to hepatocarcinoma. (Figure 5D)

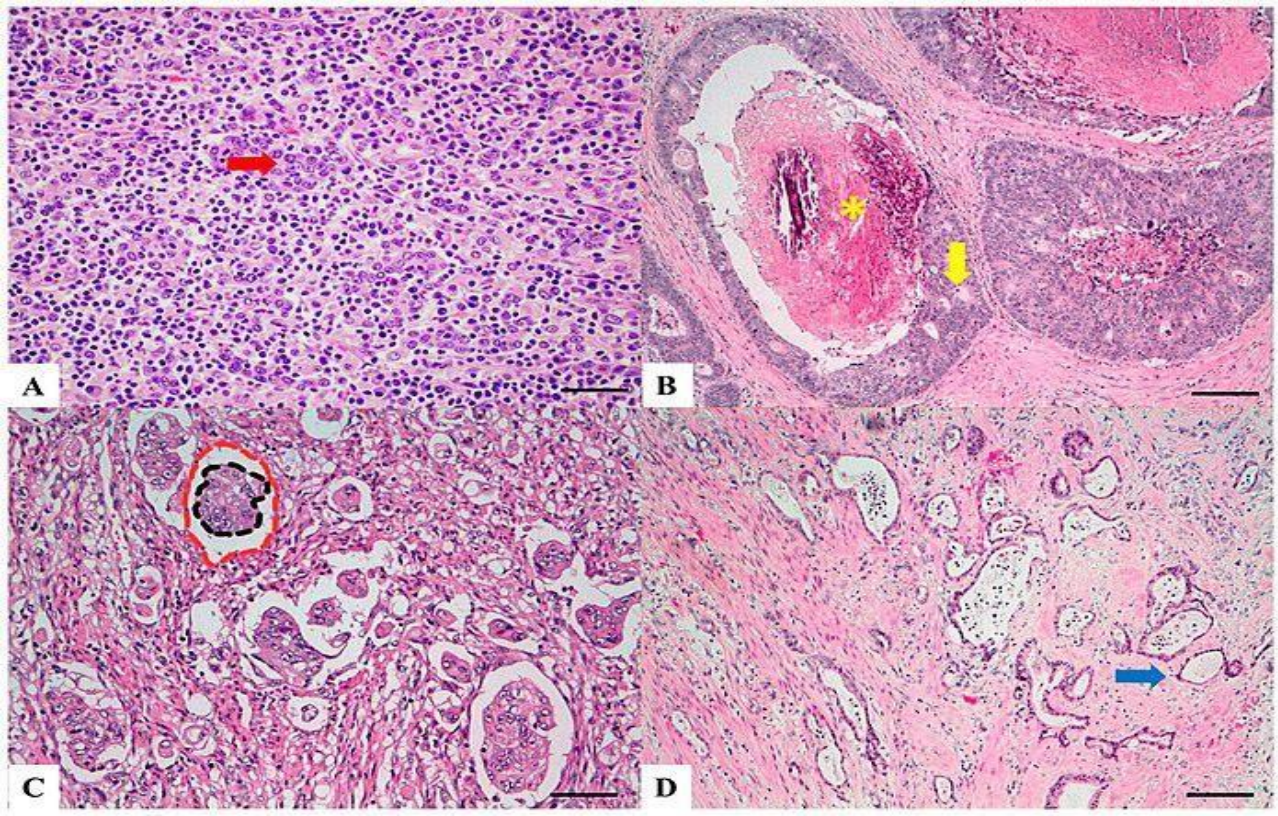


Figure 4

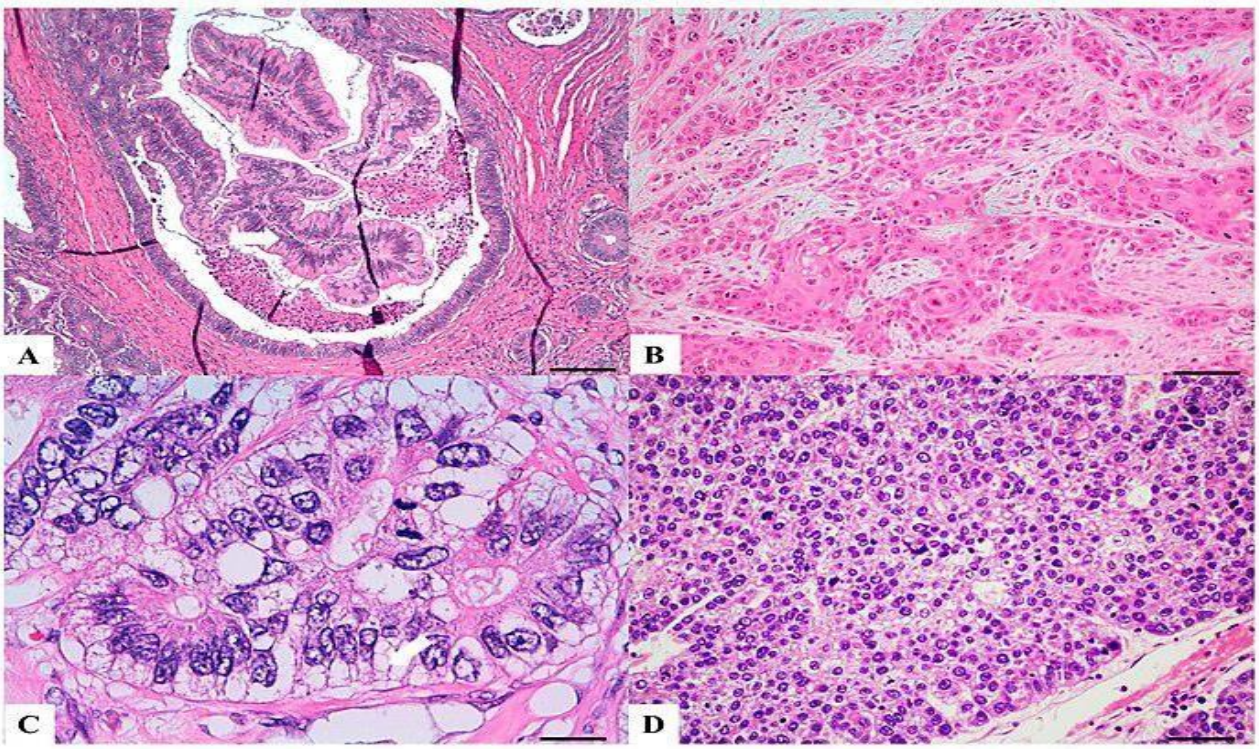


Figure 5

Colorectal choriocarcinoma:

Biphasic solid nests and trabeculae of mononucleotide cells with clear cytoplasm and pleomorphic cells with abundant vacuolated or eosinophilic cytoplasm and single or multiple vesicular nuclei with conspicuous nucleoli.(Figure 6A)

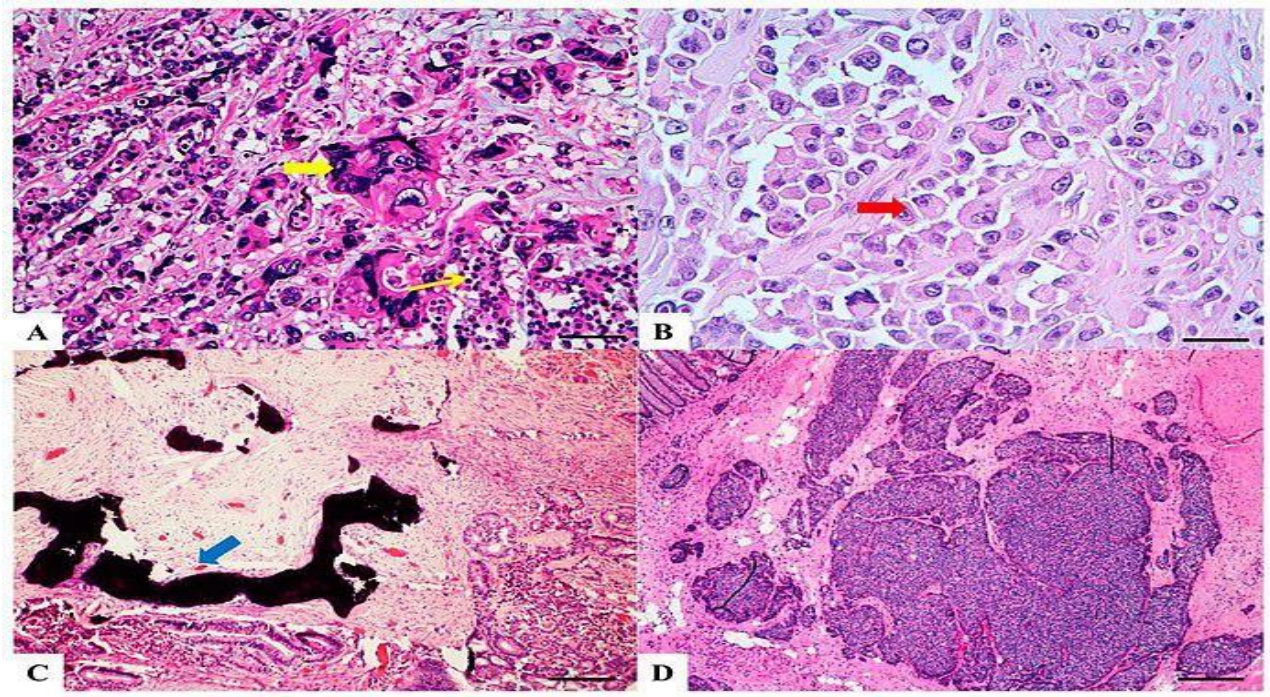


Figure 6

Rhabdoid colorectal carcinoma:

Rhabdoid cells characterized by a large, eccentrically located nuclei, prominent nucleoli and abundant eosinophilic cytoplasm.(Figure 6B)

Undifferentiated carcinoma:

Sheets of undifferentiated cells showing a variable grade of pleomorphism with no gland formation, mucin production or other line of differentiation.

Colorectal adenocarcinoma is differentiated from a colorectal adenoma (mainly tubular and ⁄or villous adenomas) mainly by invasion through the muscularis mucosae. (Figure 6C)

In carcinoma in situ (Tis), cancer cells invade into the lamina propria, and may involve but not penetrate the muscularis mucosae. This can be classified as an adenoma with "high-grade dysplasia", because prognosis and management are essentially the same. (9) (Figure 6D)

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Grading and Staging of Colorectal Carcinomas

Dr. Tayyaba Ismail, JawadBasit, SajeelSaeed

GRADING

Grading refers to the degree of similarity of the tumor cells with the normal cells when viewed under a microscope. Tissue that is in good health is likely to have a variety of cell types clustered together. It is dubbed a "differentiated" or "low-grade tumor" if the cancer appears to resemble healthy tissue and contains various of the cell groupings. A "poorly differentiated" or "high-grade tumor" is defined as a tissue that is considerably different from the normal tissue. Generally, the lower the grade of the tumor, the better the prognosis. Tumor grading is an independent prognostic factor since patients with low-grade tumors have a better prognosis than those with high-grade tumors. (1) Though conventional tumor grading is based on the extent of tumor differentiation, a new system that grades tumors based on the poorly differentiated clusters in the resected specimens has been proposed and has been found to be less subjective as a predictor of prognosis (2) The conventional grading system though subject to inter-observer bias (3) is still widely used.

STAGING

Staging is a term that is used to refer to the location of the cancer, whether or not it has spread, and if it has spread to the other parts of the body. Doctors use diagnostic tests such as Computerized tomography scan, Magnetic resonance imaging and histopathological analysis of the biopsy samples to find out the cancer's stage, consequently, staging cannot be completed until all of the tests have been performed. Staging helps forecast therapeutic decisions and predict a patient's prognosis.

Table 1 Conventional Grading system of the colorectal carcinoma

Grade	Description
Gx	The tumor grade cannot be identified
G1	Well-differentiated (high resemblance with healthy cells)
G2	Moderately differentiated cells
G3	Poorly differentiated, very low resemblance with normal cells
G4	Undifferentiated, no resemblance with normal cell

TNM classification system:

The TNM classification is currently the most used and prevalent classification system for the staging of colorectal carcinoma. It effectively describes the prognostic factors and also incorporates the other classification systems (4). The TNM classification is currently considered the gold standard for the establishment of prognosis as well as serves as the main guide for treatment modality (5). Different investigations that are usually used to stage the tumor include Computed tomography (CT) of the abdomen, pelvis, and chest as well as histopathologic analysis of the resected specimen (6)

- **Tumor T:**

The T in TNM classification stands for Tumor

and is used to measure if the tumor has invaded the wall of large intestine as well as the depth of invasion.

Table 2 Shows subclassification of Tumor in TNM staging

T	Primary tumor
T0	No primary tumor
Tis	Carcinoma in situ
T1	Tumor has invaded the submucosa of the colonic wall
T2	Invasion of the muscularispropria
T3	Subserosal invasion
T4 . T4a .T4b	Tumor has invaded nearby organs or visceral peritoneum invasion . Tumor has infiltrated the surface of visceral peritoneum . There is Direct invasion of other organs or adherence to other organs

- **Node N:**

The N stands for 'Node' is used to assess the presence and degree of involvement of the lymph nodes. The following *table 2* indicates the subclassification of the presence of nodal involvement as well as the degree of nodal involvement.

- **Metastasis M:**

The M stands for metastasis and is used to gauge the degree of nearby and distant spread of the carcinoma

Table 3 Shows subclassification of Nodal Involvement in TNM Staging

N	Regional lymph node
NX	No evaluation can be done regarding the regional lymph nodes
N0	Absence of lymph node metastasis
N1 . N1a . N1b . N1c	1-3 lymph nodes are involved . 1 lymph node involved . 2-3 lymph nodes involved . Nodules comprising of the tumor cells can be appreciated However, don't appear to be lymph nodes
N2 - N2a - N2b	>4 lymph nodes are involved . Involvement of 6 OR <6 regional lymph nodes . Involvement of >7 regional lymph nodes

Table 4 shows subclassificstion of Metastasis in TNM staging

M	Metastasis
MX	Distant metastasis cannot be gauged
MO	No distant metastasis
M1 . M1a . M1b . M1c	Distant metastasis visible . Spread of the carcinoma to atleast 1 other part beyond the large intestine . Cancer has spread to more than 1 other body part beyond the Colon and rectum . Spread of metastatic cancer to the surface of the peritoneum

Classification of the American Joint Commission on Cancer (AJCC):

The AJCC has been publishing different editions of guidelines for the staging of the colorectal cancer since 1959 (7) The status of primary tumor and nodal involvement still is the main factor to describe prognosis and guide therapeutic interventions (8)

Table 5 AJCC-7th Edition Classificationbasedon the TNM Staging

STAGE	AJCC-7TH EDITION TNM CLASSIFICATION
I	T1N0M0, T2N0M0
IIA	T3N0M0, T4AN0M0
IIB	T4AN0M0
IIC	T4BN0M0
IIIA	T1N1M0,T1N1cM0,T2N1/N1cM0,T1 N2AM0
IIIB	T3N1M0, T4bN1M0, T1N2bM0, T3N2aM0
IIIC	T4AN2aM0, T3N2bM0, T4aN2M0, T4BN2M0, T4BN1M0
IVA	Any T stage+ Any N stage + M1a
IVB	Any T stage + Any n Stage + M1b

Dukes Classification System:

This classification system was put forward by Cuthbert Dukes in 1932 for rectal cancer only. However, later on it was modified by Kirklin to stage both colonic and rectal cancers. In 1967, Turnbull re-modified the Dukes classification to include distant metastasis as well as introduced a stage for unresectable tumors. TNM staging, however, is now preferred over Duke's classification and its use in clinical practice is no more recommended (9)

- DUKES A: The carcinoma has invaded the inner lining of the colonic wall however no invasion through the colonic wall
- DUKES B: Invasion through the muscular wall however no involvement of the nearby lymph nodes
- DUKES C: Involvement of at least 1 nearby Lymph node
- DUKES D: Distant metastasis, modern day's Advanced Colorectal Carcinoma

AstlerColler Classification:

AstlerColler classification was proposed after a few modifications n were made in the original Dukes classification in 1954. AstlerColler classification has been found to be valid for the selection of those patients of colorectal carcinoma whose life expectancy can be predicted (10)

- Stage A : Tumor limited to the mucosa of the wall of the large intestine
- Stage B1: Extending into muscularispropria of the colonic wall, no penetration of muscularispropria and absence of lymph node involvement
- Stage B2: Penetrates the muscularispropria with no involvement of nearby lymph nodes
- Stage C1: the carcinoma extends into the muscularispropria however doesn't invade it. Lymph node involvement positive
- Stage C2: Penetration of the muscularispropria with nodal involvement
- Stage D: Metastatic disease, visible involvement of distant organs

PRE OPERATIVE EVALUATION:

Evaluation for diagnosis & staging:

- Digital rectal examination &proctoscopy: Performed under local anesthesia to detect lesions upto 6-8cm from anal verge. Tissue sample can also be taken using a punch biopsy forceps.
- Colonoscopy & biopsy: Performed under local anesthesia and light sedation. It is used to inspect the entire length of the large bowel. Especially important in detecting synchronous lesions. Suspesious lesions can be biopsied
- Ultrasound/ endoscopic USG: Used to detect the extent of tumor spread 'T' stage as well as lymph node metastasis 'M' stage.
- MRI pelvis: Better modality than USG in determining extent of tumor spread and lymph node metastasis
- CT virtual colonoscopy: provides reconstructed images of the colon from CT abdomen & pelvis, can detect as small as 6mm lesions
- CT scan chest abdomen, pelvis: To look for distal metastasis
- Bone scan: To detect skeletal metastasis
- Positron Emission Tomography Scan: detects tumor metastasis by calculating energy expenditure of cells

Pre-anesthesia workup:

- Baseline investigations including full blood count, clotting profile, liver, renal function tests, serum electrolyte levels
- Chest Xray
- ECG & echo cardiographty

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Surgical Management: Principles & Follow up

Dr. Noor Fatima, Mohammad Ebad Ur Rehman, JawadBasit

Surgery is the sole curative option for people with localized colon cancer (stages I-III) and maybe the only curative option for patients with minimal liver and/or lung metastatic disease (stage IV disease). Removal of the principal vascular pedicle feeding the tumor, as well as its lymphatics, achieving a tumor-free margin, and en bloc excision of any organs or structures linked to the tumor are the core surgical concepts. True mucosal recurrences in the colon are uncommon. Para-anastomotic recurrences, which may indicate a lack of lymphadenectomy, are more prevalent. To reduce the risk of an anastomotic recurrence, it is advised that at least a 5-cm margin of normal bowel be acquired on each side of the tumor.

PRE-OPERATIVE WORKUP:

• Hemoglobin blood level should be more than 10 g/100 mL and clotting factors should be corrected if they are compromised before surgery.
• It is advised to do a preoperative evaluation of symptoms, prior medical and family history, physical examination, and baseline serum carcinoembryonic antigen levels.
• If possible, confirm the diagnosis of colon cancer before elective surgical resection, as non-cancerous conditions such as diverticulitis or inflammatory bowel disease (IBD) can mimic colon cancer on endoscopic or radiographic examination.
• A computed tomography scan of the trunk is recommended before operation.

SURGICAL APPROACH:

If another pathology is not present, a resection should normally include 5- to 7-cm proximal and distal margins to guarantee sufficient removal of potentially dangerous pericolic lymph nodes. To facilitate the removal of the lymph nodes, the mesentery to the tumor-bearing segment of the intestine should be excised to the origin of the principal feeding vessel(s). This excision should be done en bloc to preserve the colonic mesentery's integrity.

A right hemicolectomy is recommended for right-sided lesions. The ileocolic, right colic and right branch of the middle colic vessels are removed during this procedure. It is critical to distinguish the right ureter from the gonadal arteries, as well as the duodenum. If the omentum is connected to the tumor, it is excised alongside the tumor. An extended right hemicolectomy may be used to treat lesions in the proximal or middle transverse colon.

Splenic flexure and left colon lesions may be treated with a left hemicolectomy. The left branch of the middle colic vessels, the inferior mesenteric vein, and the left colic vessels with their mesenteries are all included in the specimen.
A sigmoid colectomy is indicated for sigmoid colon lesions. Dissection begins at the origin of the inferior mesenteric artery and progresses toward the pelvis until appropriate margins are acquired. During dissection, the left ureter and left gonadal vessels must be preserved.

Oophorectomy should be considered in postmenopausal females. In up to 7% of

Stage C colon cancer patients, occult ovarian metastases have been recorded. Furthermore, ovarian cancer may be prevented through prophylactic oophorectomy.

Total abdominal colectomy followed by anastomosis of the ileum and rectum may be necessary for patients with Lynch syndrome, familial adenomatous polyposis, or multiple tumors in separate segments of the colon.

Recent advances have expanded our understanding of the extraluminal spread of rectal cancer. Additionally, the end-to-end anastomotic stapling device has simplified the procedure of performing a lower rectal anastomosis. On the other hand, insufficient resection and incorrect usage of these devices have resulted in a high risk of pelvic recurrence. With proper resection margins, pelvic recurrence rates of 10% or less have been recorded. Healdpopularised total mesorectal excision (TME) surgery, which is now commonly performed across the Western world. The rectum and full mesorectum are resected down to the pelvic floor, while the pelvic autonomic nerves are preserved. Although a distal margin of two centimeters is ideal, a margin of one centimeter is acceptable since the majority of rectal cancers have a distal submucosal extension of less than one centimeter. Subtotal mesorectal excision should be used to remove cancer in the upper third of the rectum. Abdominoperineal resection is used to treat tumors located near or on the sphincter mechanism; TME is a critical component of this resection.

LYMPHADENECTOMY

Because some patients with stage III colon cancer may be treated with surgery alone, the importance of doing a thorough lymphadenectomy cannot be overstated. For proper staging and selection of patients for adjuvant therapy, sufficient lymph node resection is required. It's still up for debate whether a broad or extended resection is required. Disease outside of the resection area should be recorded if at all feasible since it will affect prognosis and clinical trial eligibility. To correctly diagnose node-negative illness, at least 12 negative lymph nodes should be evaluated.

OBSTRUCTION AND PERFORATION:

Morbidity and mortality rise as a result of perforation and blockage. Both of these symptoms may result in electrolyte imbalance, dehydration, and infection, all of which can complicate an emergency surgery. Patients with obstructive cancer should, in general, be resected if at all feasible.

Obstructing malignancies are most often treated with two or three staged operations. A proximal ostomy is used to resect the obstructive lesion in the first case. A diverting stoma is done as the first step, followed by resection and stoma removal as the second and third stages, respectively. The technique must be tailored to the patient's condition, the surgeon's expertise, and any concomitant conditions. A subtotal colectomy may be recommended for patients with obstructive descending colon cancer.

Colorectal cancer perforation happens most often at the location of the tumor or in the intestine near the blockage. Localized peritonitis or widespread peritonitis might be present in these individuals. They may also be dehydrated, infected, or have electrolyte abnormalities. All of these variables contribute to the high morbidity associated with emergency surgery. Perforation may cause adhesion to nearby organs or the creation of a fistula. In individuals with blockage, concurrent perforation is not uncommon. The surgical treatment concepts

are the same as for patients with obstructive carcinomas. An effort at resection should be made if possible. However, in certain cases, the inflammatory response or the patient's state makes resection impossible, and it is thus better to redirect the patient and drain the perforation than undertake a risky surgical operation. The drainage tract must be seeded, which is a disadvantage of this method. At the moment of final resection, the tract must be removed along with the tumor.

INVOLVEMENT OF CONTIGUOUS ORGANS:

Colorectal cancers that have attached to nearby organs are not uncommon. This widespread involvement might be the outcome of the tumor's bulky local growth or adhesions caused by a local perforation and/or fistula development. Adherence may affect any intraabdominal structure. Adhesions to the abdominal wall, duodenum, stomach, small intestine, ureters, urinary bladder, uterus, and ovaries are the most prevalent sites for colon cancer adhesions. The uterus and vagina, urinary bladder, and sacrum or coccyx are the most prevalent sites for rectal cancer. The surgery for these tumors must be meticulously planned to resect the tumors in their entirety while preserving the adhesions. In more than 40% of instances, the adhesions are cancerous. Recurrence and survival will be jeopardized if en bloc resection is not done in these individuals.

LAPAROSCOPIC SURGERY:

In terms of survival and recurrence rates, several recent clinical investigations and meta-analyses have revealed that laparoscopy is comparable to open surgery. In addition, laparoscopic surgery provides several immediate advantages, including a shorter hospital stay, fewer painkiller prescriptions, and a faster return to normal intestinal function. However, there are certain disadvantages to this approach, such as a longer surgical time, a larger probability of positive circumferential resection margins (CRM), and a steeper learning curve. Laparoscopic resection is a difficult operation that involves numerous segments of surgery, ligation of major arteries, intestinal transection, and reanastomosis. As the surgeon must understand a three-dimensional environment on a two-dimensional screen, a high degree of skill is necessary. Furthermore, as reported in the literature, this method is technically challenging for obese patients in the late stages of cancer and following neoadjuvant therapy. Despite this, laparoscopic resection is becoming more common. The widespread use of laparoscopy by trained surgeons, as well as the advancement of surgical equipment and technology, promise to improve clinical and pathological outcomes even further.

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Oncological Management of Colorectal Cancer

Dr. Sayyam Fatima

Approximately 75% colorectal carcinoma patients present with a surgically resected disease.[1] The mortality rate associated with metastatic disease is still high, despite the high resectability rate in stage III CRC patients. Such patients are candidates for adjuvant local or systemic therapies, primarily because of residual disease.[2]

Oncological treatment of Colon Cancer

Adjuvant chemotherapy

The overall survival benefit related to use of chemotherapy in resected stage II colon cancer patients is uncertain. Several factors should be considered, such as number of resected lymph nodes, poor prognostic features, MSI (microsatellite instability) status, comorbid conditions, and life expectancy.[2]

The choice of adjuvant therapy in resected, non-metastatic colon cancer is dependent upon the disease stage.[3]

- No adjuvant therapy is required in stage I disease and MSI-high stage II disease.
- Patients with low risk, microsatellite stable (MSS) stage II disease can be observed without any adjuvant treatment or considered for capecitabine or 5-FU/Leucovorin.
- Patients with stage II disease that is microsatellite stable (MSS) and at high risk for systemic recurrence, can be given adjuvant chemotherapy for 6 months with 5-FU/Leucovorin, capecitabine or FOLFOX (infusional 5-FU, leucovorin, and oxaliplatin). The alternative option is 3 months of therapy with CAPEOX (capecitabine and oxaliplatin).
- For low risk (T1-3, N1) stage III disease, preferred options include 3 months of CAPEOX or 3 to 6 months of FOLFOX. Patients who are intolerant to oxaliplatin therapy can be considered for 6 months of singe agent capecitabine or 5-FU/Leucovorin.
- Patients who present with high risk (T4, N1-2 or any T, N2) stage III disease are candidates for 6 months of FOLFOX therapy or 3 to 6 months of CAPEOX. Patients who are intolerant to oxaliplatin therapy can be considered for 6 months of singe agent capecitabine or 5-FU/Leucovorin.

Literature suggested that patients with resected colon cancer treated with adjuvant treatment do have a survival benefit over those who didn't receive adjuvant therapy. A phase III European MOSAIC trial for resected stages II and III colon cancer patients showed that the use of FOLFOX is associated with a higher 5-year disease-free survival rate as compared with the same infusional regimen without oxaliplatin (66.4% vs 58.9%, P = 0.005).[4] Multiple phase III trials failed to demonstrate any benefit of additional targeted therapy to FOLFOX.

Results of systematic reviews and meta-analysis showed that each 4-week delay in adjuvant chemotherapy is associated with a 14% decline in overall survival, emphasizing that adjuvant therapy should be started as soon as the patient is able medically.[5]

Neoadjuvant therapy for Resectable colon cancer

For patients with clinically evident T4b or bulky nodal disease, neoadjuvant radiation therapy with concurrent FOLFOX or CAPEOX may be considered to aid resectability. A trial in 2012 showed that preoperative therapy is associated with significant downstaging as compared to postoperative treatment (P = 0.04).[6] Another trial in 2019 showed that neoadjuvant therapy resulted in marked histologic regression as well as lower rate of incomplete resections, when compared to adjuvant therapy (5% vs 10%, P = 0.001).[7]

Oncological treatment of Rectal Cancer

Up to 50% of rectal carcinoma patients present with either local recurrence alone or in combination with distant metastases.[1] Major factors for locoregional failure include nodal disease and deep bowel wall penetration. In the absence of nodal metastases, the rate of local recurrence may be as low as 5% to 10% for stage I rectal cancer and 15% to 30% for stage II tumors. In stage III disease, the incidence of pelvic failure increases to 50% or more.[2]

Neoadjuvant/ adjuvant treatment for stage II or Stage III rectal carcinoma includes locoregional therapy for reducing recurrence. In contrast, oncological treatment for colon cancer is done to prevent distant metastasis, as risk of local recurrence is low.

Combined modality therapy consisting of surgery, concurrent fluoropyrimidine-based chemotherapy with radiation to pelvis and chemotherapy is recommended for patients with stage II/III rectal cancer.[8]

Preoperative or postoperative radiation therapy

Radiation therapy is implicated to decrease the incidence of locoregional recurrence in rectal tumors. Neoadjuvant radiotherapy has shown reduced local tumour recurrence, even in patients undergoing TME surgery. A German Rectal Cancer Study group showed a significant reduction in local recurrence (6% vs 13%, P = 0.006) and treatment associated toxicity (27% vs 40%, P = 0.001) in patients who received preoperative radiotherapy.[9] The overall survival remained the same in both groups. The prime reason for performing preoperative radiotherapy is to reduce the radiation toxicity to surgically created rectum/ pouch. This leads to better life quality, decreased pain and bowel movements and improved continence.

Concurrent chemotherapy with radiation

Multiple RCTs have evaluated the role of adding concurrent chemotherapy to radiotherapy either preoperatively or in the postoperative setting. The possible advantages of this modality include local RT sensitization and systemic control of micro metastasis. This also increased the rates of pathologic complete response and sphincter preservation. A trial showed that patients who receive chemoRT were more likely to exhibit a complete response (11.4 vs 3.6%, P < 0.05) as compared to those who receive RT alone.[10]

Radiation doses of 45 to 55 Gy are recommended in combination with 5-FU–based chemotherapy.[2]

Adjuvant chemotherapy for resectable rectal cancer

Postoperative chemotherapy is recommended for all patients with stage II/III rectal cancer following neoadjuvantchemoRT and surgery if they did not receive neoadjuvant chemotherapy. The therapy should be started as soon as the patient is fit

medically because each 4-week delay in chemotherapy results in a 14% decrease in overall survival.[11]The therapy is recommended for a period of 6 months.

The choice of adjuvant therapy in resected, non-metastatic rectal cancer is dependent upon the disease stage.[11]

- Patients with stage 1 disease require no adjuvant treatment.
- Patients with stage II disease should be given adjuvant treatment with FOLFOX or CAPEOX, followed by infusional 5-FU with RT or Capecitabine with RT.
- Patients with stage III disease should be considered for adjuvant treatment with FOLFOX or CAPEOX, followed by infusional 5-FU with RT or Capecitabine with RT.

Neoadjuvant therapy

Preoperative chemoradiotherapy significantly reduces the size of most rectal tumors, making sphincter-preserving surgery possible for rectal cancers approaching the anal sphincter. Preoperative chemoRT is important for patients with locally advanced, unresectable rectal cancer, as the disease will become resectable following chemoRT.[2]

Treatment of Advanced Colon Cancer

Local recurrences from colon cancers usually occur at the site of anastomosis, in the resection bed, or in the contiguous and retroperitoneal (para-aortic, paracaval) lymph nodes. Anastomotic recurrences diagnosed during surveillance in asymptomatic patients are the most curable, followed by local soft tissue recurrences. Regional and retroperitoneal lymph node recurrences portend a poor prognosis and systemic disease. Although 5-FU remains the backbone of most regimens, the new agent's irinotecan and oxaliplatin have become an important part of front-line treatment.[1, 2]

Treatment of Advanced Rectal Cancer

Radiation therapy

Radiation therapy is moderately effective in palliating the symptoms of advanced rectal cancer. Pain is decreased in 80% of irradiated patients, although only 20% report complete relief. Bleeding can be controlled in more than 70% of patients. Obstruction cannot be reliably relieved by irradiation, and diverting colostomy is recommended. Only 15% of patients with recurrent rectal cancers achieve local disease control with irradiation, and median survival is less than 2 years.[1, 2] Radiation therapy may be used for retreatment of recurrent rectal cancer; however, the best chances of local control and long-term survival are achieved when complete surgical extirpation can be accomplished.[11]

Chemoradiation therapy.

Chemoradiation therapy may be useful to convert fixed unresectable lesions into resectable lesions. These regimens have generally used protracted infusions of 5-FU (200 to 250 $mg/m^2/d$) delivered via a portable infusion pump during pelvic radiation therapy (4,500 cGy over 5 weeks) or capecitabine.[2, 8]

Intraoperative radiotherapy

Localized irradiation given to the tumor or tumor bed at the time of resection is under active investigation in advanced and locoregionally recurrent rectal cancers.[1]

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Management of Colorectal Cancer: Summary

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Clinical staging helps determine the best course of therapy for colorectal cancer. For patients with localized disease (stage II or lower), surgical colon resection is used to achieve complete remission. For individuals with stage III illness, adjuvant chemotherapy is the gold standard of treatment. Although its use in stage II illness is debatable, current recommendations advocate treatment for selected patients with high risk of recurrence. Radiation therapy is currently used only for specific metastatic sites, such as the bones or brain. Chemotherapy has been the mainstay of care for individuals with metastatic disease, rather than surgery. Biologic therapies have become more effective for the management of advanced cancer, with selection increasingly driven by tumour gene analysis.

SURGICAL MANAGEMENT

All resection procedures follow the same fundamental principles, which involve the excision of the main tumour with sufficient margins, including regions of lymphatic drainage. The surgical approach is guided by the stage and location of the lesion.

PRE-OPERATIVE WORKUP

• Hemoglobin blood level should be more than 10 g/100 mL and clotting factors should be corrected if they are compromised prior to surgery.

• It is advised to do a preoperative evaluation of symptoms, prior medical and family history, physical examination, and baseline serum carcinoembryonic antigen levels.

• If possible, confirm the diagnosis of colon cancer prior to elective surgical resection, as non-cancerous conditions such as diverticulitis or inflammatory bowel disease (IBD) can mimic colon cancer on endoscopic or radiographic examination.

• A computed tomography scan of the trunk is recommended prior to operation.

OPEN SURGERY:

If another pathology is not present, a resection should normally include 5- to 7-cm proximal and distal margins to guarantee sufficient removal of potentially dangerous pericolic lymph nodes. To facilitate removal of the lymph nodes, the mesentery to the tumor-bearing segment of intestine should be excised to the origin of the principal feeding vessel(s). This excision should be done en bloc to preserve the colonic mesentery's integrity.

A right hemicolectomy is recommended for right sided lesions. The ileocolic, right colic, and right branch of the middle colic vessels are removed during this procedure. It is critical to distinguish the right ureter from the gonadal arteries, as well as the duodenum. If the omentum is connected to the tumour, it is excised alongside the tumor. An extended right hemicolectomy may be used to treat lesions in the proximal or middle transverse colon.

A left hemicolectomy is suitable for lesions of the splenic flexure and left colon. The specimen includes the left branch of the middle colic vessels, the inferior mesenteric vein, and the left colic vessels with their mesenteries.

A sigmoid colectomy is indicated for sigmoid

colon lesions. Dissection begins at the origin of the inferior mesenteric artery and progresses toward the pelvis until appropriate margins are acquired. During dissection, the left ureter and left gonadal vessels must be preserved.

Total abdominal colectomy followed by anastomosis of ileum and rectum may be necessary in patients with Lynch syndrome, familial adenomatous polyposis or multiple tumors in separate segments of the colon.

LAPROSCOPIC SURGERY:

A number of recent clinical studies and meta-analyses have shown that laparoscopy is not inferior to open surgery in terms of survival and recurrence rates. Additionally, laparoscopic surgery has many immediate benefits, including a reduced hospital stay, less painkiller usage, and a quicker restoration of intestinal function. This method, however, has certain drawbacks, including a longer surgical duration, a higher chance of positive circumferential resection margins (CRM), and a steeper learning curve. Laparoscopic resection is a complicated procedure; it entails surgery in multiple segments, ligation of large vessels, transection of the bowel, and reanastomosis. A high level of competence is thus required as the surgeon must interpret a three-dimensional environment on a two-dimensional screen. Additionally, as indicated in the literature, this strategy remains technically problematic for obese patients, in advanced tumour stages and after neoadjuvant treatment. Nonetheless, laproscopic resection has grown in popularity. The widespread use of laparoscopy by skilled surgeons and the development of more advanced surgical instruments and technology promise to enhance clinical and pathological results further.

ONCOLOGICAL MANAGEMENT

ROLE OF ADJUVANT THERAPY

Adjuvant chemotherapy may be beneficial for individuals with resected stage III and high-risk stage II colorectal cancer, according to international recommendations. It is meant to combat unresectedmicrometastases that may result in recurrence. Recurrence occurs in 15-50% of patients with stage III cancer. Fluorouracil based chemotherapy significantly lowers the risk of recurrence by 40%. The combination of oxaliplatin and fluorouracil enhances this benefit and is the standard of care for these patients during adjuvant chemotherapy, increasing survival by 10-20%. Typically, six months of adjuvant chemotherapy is administered. Newer medications and combination therapies are being investigated in order to shorten the time of chemotherapy. Due to the decreased likelihood of recurrence in stage II disease, the advantages of adjuvant chemotherapy are limited. The therapy is reserved for patients with high risk of recurrence. Patients must be informed of the potential side effects and consequences of various chemotherapy regimens during their appointment with the oncologist. Chemotherapy often causes exhaustion, nausea, vomiting, diarrhoea, myelosuppression, and peripheral neuritis.

ROLE OF NEOADJUVANT THERAPY

Neoadjuvant (preoperative) radiation is advised for rectal tumours that have progressed (at least T3 and/or at least N1). Radiotherapy is useful both for preventing recurrence and to reduce size of tumor preoperatively. Radiotherapy may be administered alone ("short course" radiotherapy administered for five days) or in

combination with 5-flurouracil, most typically in the form of oral capecitabine ("long course" chemoradiotherapy administered over five weeks). Two large multicenter randomised controlled trials (RCTs) comparing short and long course radiotherapy found no difference in overall survival. Current international recommendations advocate either course unless the tumour is T4 or there is suspicion of mesorectal fascia involvement, in which case a lengthy course of chemoradiotherapy followed by surgery at 2-3 months is indicated for tumour size reduction. Side effects include urinary tract infection and skin rash.

TREATMENT OF METASTATIC COLORECTAL CANCER

Nearly 50% of patients develop metastases. The mainstay of treatment is chemotherapy. The therapeutic objectives can be divided into four groups, based on the extent of metastasis.

1. In easily resectable disease, upfront resection is advised. Perioperative chemotherapy (FOLFOX or CAPOX) is essential in patients with an uncertain or worse prognosis. Additionally, adjuvant chemotherapy with FOLFOX or CAPOX is suggested in individuals who have not previously had systemic chemotherapy.
2. Some patients may be potentially curable by resection if tumor shrinkage can be achieved by rigorous chemotherapy. Prior to initiating therapy, it is critical to examine the patient's molecular profile (RAS and BRAF status). For individuals with left-sided RAS wild type illness, the therapy of choice should be a two-drug chemotherapy (FOLFOX or FOLFIRI) with an anti-EGFR antibody. Three-drug chemotherapeutic regimens alongside bevacizumab should be the treatment of choice for individuals with right-sided RAS wild-type cancer, although cytotoxic doublet with anti-EGFR therapy may be an alternative. For individuals with RAS- or BRAF-mutant disease, cytotoxic doublet+bevacizumabis the preferable alternative. Following the initiation of these 'conversion treatments,' patients must be examined every 2-3 months for a maximum of six months to ensure the greatest response and prevent overtreatment. Complete excision of liver metastases is achievable, preserving at least 30% of the liver remaining; 5-year OS rates range from 25% to 58 percent in retrospective investigations. R0 resection may be curative in patients with pulmonary metastases, if tumor-free margins are obtained.
3. Some individuals have minimal metastases (up to three sites, with >5 lesions). This is termed as 'oligometastatic disease'. The treatment plan is centred on the prospect of completely ablating all tumour masses utilising R0 either initially or after systemic therapy induction.
4. In patients with unresectable metastases, the therapeutic aim is disease control, and extensive procedures are not indicated. In this context, a two-drug chemotherapy regimen combined with a biologic drug is the gold standard of treatment, depending on the molecular profile of the tumour and its 'sideness.' Cytotoxic doublet with

anti-EGFR antibody should be the therapy of choice for individuals with left-sided RAS wild-type illness. Cytotoxic doublet+bevacizumabis the favoured treatment for patients with right-sided RAS wild-type disease or RAS mutations. Triplet chemotherapy is warranted only when symptomatic illness exists or when BRAF-mutant tumours have a poor prognosis.

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Palliation and Stoma Care

DrAmeena

Palliative Care

Palliative care has been defined by the American Academy of Hospice and Palliative Medicine as providing care 'focused on alleviating suffering and promoting quality of life.(1)

From the surgeon's standpoint, therapy is considered palliative when resection of all known tumor sites is no longer possible or advisable. Since a cure, as commonly defined, is not possible, the goal of treatment and eventually the success of therapy becomes judged by the control of symptoms and alleviation of suffering. Importance of optimal palliative care has been realized in recent years and achieving it is a complex and challenging process.(2)

Palliation should be accomplished by a multidisciplinary approach. Palliative care is reserved for the remaining patients considered to have unresectable cancer, disseminated metastatic cancer or patients unwilling to undergo extirpative surgery.

Utmost priorities are pain and symptom management, information sharing and advance care planning, psychological and spiritual support, and coordination of care . About 20-25 percent patients with colorecral carcinoma present with stage 4 disease then the surgeon has to decide among them which can be treated aggressively to surgically resect metastasis.(3) A clear survival benefit has been shown when isolated hepatic and/or pulmonary metastases are resected. Patients who have unresectable metastatic disease are treated in a different fashion and their aim of treatment is to improve quality of life.

Designing a treatment plan for these patients should begin with a frank discussion with the patient and family regarding the situation. Ideally, goals for treatment, clearly understood by both the surgeon and family, should emerge from these discussions with the family. These goals should be tailored to each patient. The surgeon plays a unique role in what is ideally a multi-disciplinary effort to provide the best palliative care

Since the cure is not possible, therapy will be considered successful when patient is symptom free and their suffering has alleviated. Palliation can be done in various ways starting from non invasive management to surgical palliation.

Nonsurgical Methods of Palliation

Previously patients presenting with acute symptoms such as obstruction were treated by surgical techniques and usually ending with a stoma but with the increasing awareness and knowledge such problems can be managed with non surgical methods of palliation. The currently available methods are discussed below.

1) Endorectal Metallic Stent Placement

First case report dated back in 1991 after which it has been increasingly used. (4) Success rate of endorectal metallic stents is greater than 80% proved in recent studies with most complications being fairly minor. (5,6) They can be placed under both fluoroscopic and endoscopic guidance depending on the expertise. Complications that have been reported include perforation,

migration, tenesmus, rectal bleeding and stent overgrowth. Most commonly encountered complication is migration.(7)

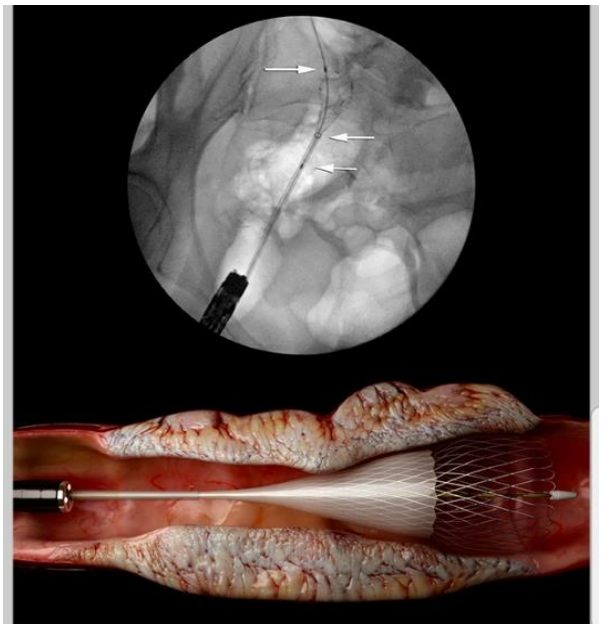

Figure 7 Fluoroscopic Control of Stent Placement

2) Laser Recanalization

Modern laser therapy including endoscopic neodymium:yttrium aluminum garnet (Nd:YAG) or a CO_2 laser have been shown to be effective in the control of obstructive symptoms and bleeding. It frequently involves multiple treatment sessions over a period of weeks. It has been shown to be more successful in controlling bleeding with fewer sessions rather than in managing obstruction.(8)

The best current indications for endoscopic laser therapy are to treat bleeding and tenesmus in rectal cancer patients with the most advanced disease and shortest life expectancy.(9)

3) Radiation Therapy

Radiation therapy is an integral part of treatment. It may be useful both for patients presenting initially with advanced disease as well as in those patients with recurrent disease, even for those who may have been treated with prior pelvic radiation. One chief advantage of radiation therapy is pain relief which is likely caused by pelvic nerve invasion by tumor.

Palliative chemotherapy may need to be reduced by up to 25% in order to accommodate the additional toxicity involved with combined radiation and chemotherapy. Therefore, this approach does palliate local symptoms at the expense of optimal systemic palliation, and is probably best suited for patients with the most local symptoms.(10)

4) Chemotherapy

Treating systemic disease with chemotherapy may double the survival of patients with metastatic disease when compared to those who are not treated.(11) Input from medical oncologists should be considered when planning the treatment sequence and coordinating interventions for palliation.

The standard treatment continues to remain 5-FU based, although there are several emerging chemotherapeutic modalities available for palliation. Several trials have shown this to provide a significant improvement in survival of patients with metastatic disease when these new medications like oxaliplatin are added to a 5-FU regimen.(12)

5) Pain Management

It is an imperative part of palliative therapy. The proper and adequate control of pain is an outcome that is increasingly expected by both patients and families. Patients with metastatic cancer commonly suffer from pelvic pain related to the primary tumor or from symptoms of metastases.

The first-line treatment is usually oral opioids being effective for majority patients. When pain is not relieved with opioids, one may add oral medications such as amitriptyline or gabapentin for neuropathic pain. Epidural

catheter placement in selective patients and Neuroablative techniques in refractory pain may be considered.(13)

Surgical Palliation

Surgical palliation remains an integral part of management ranging from tumor excision and tailoring to minimal invasive palliative methods. Following are the options available.

Management of the Primary Tumor

There is currently no consensus in the literature concerning the management of the primary tumor when treating patients with incurable colon and rectal cancer.

Younger patients with less widespread disease and very symptomatic tumors may be offered aggressive resection as a palliative option while the majority of older patients with more advanced disease may avoid routine laparotomy and be more effectively treated with immediate chemotherapy.

1) Palliative Open Resection

There are different options of surgical procedures which can be used for open resection of tumor as a palliation. The most commonly performed open operations for palliation include abdominoperineal resection (APR), pelvic exenteration, Hartman's procedure and low anterior resection (LAR).

The most radical surgical option used in the palliation of colorectal cancer is pelvic exenteration used when tumor has invaded other pelvic organs. it is reserved for the most fit patients as it is associated with significant morbidity.(14)

2) Local Excision

Local excision of tumor is a minimally invasive modality that may be used on patients with significant comorbidities that are not fit to undergo open surgery, using urologic resectoscope or cryosurgery.(15,16)

In contrast to stent placement and laser recanalization which provide palliation of symptoms but generally leave the tumor relatively intact, these methods allow local control of the tumor to be achieved.

3) Laparoscopic Palliation

Use of laparoscopy for attempted curative resection is initially limited due to risk of port site recurrence but this is not the concern in surgeries done for palliation. The development of laparoscopy has also increased surgical options for palliation in advanced colorectal cancer. Laparoscopy may be used to effectively provide diversion with either colostomy or ileostomy formation. It is a best alternative to open surgery being significantly less invasive.

Conclusion

Providing optimal palliative care for the patient with advanced colorectal cancer is a complex and challenging process. The best palliative care will likely come from a multidisciplinary team that individualizes the treatment plan in accordance with the patient's wishes, allowing symptoms to be maximally treated, lifespan to be optimized and hospital stay (particularly the ratio number of inpatient days to number of days of remaining survival) to be minimized.

Stoma care(17)

1) Protecting the skin around the stoma

The skin around stoma should always look the same as skin anywhere else on abdomen. But stoma output can make this skin tender or sore. Following are some ways to help keep skin healthy:

- **Use the right size pouch and skin barrier opening**. An opening that's too small can cut or injure the stoma and may cause it to swell. If the opening is too large, output could get to and irritate the skin. In both cases, change the

pouch or skin barrier and replace it with one that fits well.

- **Change the pouching system regularly**. To avoid leaks and skin irritation. It's important to have a regular schedule for changing your pouch. Don't wait for leaks or other signs of problems, such as itching and burning.
- **Be careful when pulling the pouching system away from the skin and don't remove it more than once a day unless there's a problem**. Remove the skin arrier gently by pushing your skin away from the sticky barrier rather than pulling the barrier away from the skin.
- **Clean the skin around the stoma with water**. Dry the skin completely before putting on the skin barrier or pouch.
- **Watch for sensitivities and allergies** to the adhesive, skin barrier, paste, tape, or pouch material. They can develop after weeks, months, or even years of using a product because you can become sensitized over time. If your skin is irritated only where the plastic pouch touches it, you might try a pouch cover or a different brand of pouch.

2) Emptying and changing the pouching system

One should be taught how to change and empty pouching system before leaving the hospital. One doesn't have to use sterile supplies. For instance, facial tissue, toilet paper, or paper towels can be used to clean around the stoma instead of sterile gauze pads.

i) How to empty the pouch

Empty the stoma pouch when it is about 1/3 to 1/2 full to keep it from bulging and leaking. Follow these steps:

- Sit as far back on the toilet as one can or on a chair facing the toilet.
- Place a small strip of toilet paper in the toilet to decrease splashing.
- Hold the bottom of the pouch up and open the clip on the end or tail of the pouch.
- Slowly unroll the tail over the toilet.
- Gently empty the contents and one may put some toilet paper in the toilet first to help avoid splashing if needed.
- Clean the outside and inside of the pouch tail with toilet paper.
- Roll up the end of the pouch and clip.

ii) When to change the pouching system

- It's best to have a regular changing schedule so problems don't develop. Different pouching systems are made to last different lengths of time. It depends on the type of pouch one use.
- There may be less bowel activity at certain times in the day. It's easiest to change the pouching system during these times. Empty stomach is best or allow at least 1 hour after a meal, when digestive movement has slowed down.

❖ Factors that affect the pouching system seal

The pouching system must stick to your skin. Here are some other things that may affect how long a pouch sticks:

- Sweating will shorten the number of days you can wear the pouching

system.
- Moist, oily skin may reduce wearing time.
- Weight changes will affect how long you can wear a pouch. Weight gained or lost after surgery can change the shape of abdomen. One may need an entirely different system.
- Diet may affect your seal. Foods that cause watery output are more likely to break a seal than a thicker discharge.
- Physical activities may affect wearing time. Swimming, very strenuous sports, or anything that makes one sweat may shorten wear time.

3) Bathing

- Water will not harm stoma. If one uses soap, be sure to rinse skin well.
- On shower time, removing pouch is not necessary and not usually recommended. One big reason not to remove pouch is to avoid the risk of fecal output happening.

4) Spots of blood on the stoma

- Spots of blood are not a cause for alarm.
- Cleaning around the stoma as one changes the pouch or skin barrier may cause slight bleeding. The bleeding will usually stop quickly. If it doesn't, one should call stoma nurse or doctor.

5) Shaving hair under the pouch

- Having a lot of hair around the stoma can make it hard to get the skin barrier to stick well and may cause pain while removing it. Shaving with a razor or trimming hair with scissors is helpful.
- After shaving, rinse well and dry the skin well before applying your pouch.

6) What to wear when you have a colostomy

- One does not need special clothes for everyday wear. Stoma pouches are fairly flat and hard to see under most clothing. The pressure of elastic undergarments won't harm the stoma or prevent bowel function.
- Snug undergarments such as cotton stretch underpants, t-shirts, or camisoles may give you extra support, security, and help conceal pouches. A simple pouch cover adds comfort by absorbing body sweat and keeps the plastic pouch from resting against your skin.

7) Managing colostomy problems

i) Severe skin problems

- Large areas of skin that are red, sore, and weeping (always wet) will keep you from getting a good seal around stoma. Consult the doctor and get immediate treatment.
- For deep pressure ulcers caused by a very tight stoma belt, loosen or remove the belt and see a doctor.

ii) Blockage (obstruction)

- If stoma is not active for 4 to 6 hours

and one have cramps, pain, and nausea, the intestine could be obstructed. Call your doctor or stoma nurse right away if this happens.

These are some things that can be done for stoma output

- Watch for swelling of the stoma and adjust the opening of the wafer as needed until the swelling goes down.
- Take a warm bath to relax abdominal muscles.
- Fluids can be taken if there is some stool output: solid foods should be avoided
- Sometimes changing your position, such as drawing your knees up to your chest, may help move along the food in gut.
- Do **NOT** take a laxative.

If one keep having pain and cramping with no output from stoma for more than 2 hours, and can't reach doctor or stoma nurse, go to the emergency room. Take all stoma supplies along.

iii) Diarrhea

- Diarrhea is defined as frequent loose or watery bowel movements in greater amounts than usual. It can cause body to lose a lot of fluids and electrolytes and these must quickly be replaced.
- Consult doctor or stoma nurse if one have ongoing diarrhea. Discuss eating schedule and any medicines one might be taking. Remember, no matter what, one needs a well-balanced diet and good fluid intake to have a good output.

iv) Electrolyte imbalance

- Keeping electrolytes balanced is important. When the colon is removed, there is greater risk for electrolyte imbalance. Diarrhea, vomiting, and a lot of sweating can increase this risk.
- Dehydration is also a serious concern. To avoid dehydration, one should try to drink 8 to 10 eight-ounce glasses of fluid a day. If having diarrhea, one may need more especially drinks like Pedialytethat contains potassium and sodium.
- Dehydration, low sodium, and low potassium can all be dangerous and should be treated right away.

v) Short bowel syndrome

- This condition happens when surgery is done to remove a large part of the small intestine. The shorter the small intestine, the more watery the discharge will be.
- This may reduce the time a pouch can be worn because the skin barrier breaks down more rapidly.
- One should be strictly seen by a doctor in order to monitor required caloric intake and essential nutrients.

❖ When one should call the doctor

One should call the doctor or stoma nurse if having one of these symptoms:

- Cramps lasting more than 2 or 3 hours
- Continuous nausea and vomiting
- No stoma output for 4 to 6 hours with cramping and nausea
- Severe watery discharge lasting more than 5 or 6 hours
- Bad odor lasting more than a week (may be a sign of infection)
- A cut in the stoma
- Injury to the stoma
- Bad skin irritation or deep sores

(ulcers)

- A lot of bleeding from the stoma opening
- Continuous bleeding where the stoma meets the skin
- Unusual change in your stoma size or color
- Anything unusual going on with stoma

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Surveillance and Prevention Of Colorectal Carcinoma

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Colorectal carcinoma which was previously thought to be an exclusive disease of the western hemisphere is equally devastating in Asian countries in terms of incidence and mortality [(1)], Eastern Asian countries like China, Japan, South Korea, and Singapore have experienced a two-to four-fold increase in incidence in recent decades, whereas in countries of middle east increase in incidence and mortalities have also been reported, in Iran younger age groups have been more affected, but countries like ours, India, and other selective middle eastern countries due to lack of national registry for CRC the true analysis of the trends in demographic data, anatomical and histological features of CRC prevalent in this region is a hard challenge[(1)]. Colorectal cancer in its early stages does not usually cause symptoms. It starts as a benign polyp. Colon polyps can be both pre-cancerous and non-pre-cancerous. If detected at an early stage can be removed, thus preventing the development of colorectal cancer.90% of such cases can be cured with the help of surgery in early stages. Once colorectal cancer causes bleeding, change in bowel habits, or abdominal pain, it has usually progressed to a more advanced stage where less than 50% of patients are cured. [(2)]Thus screening and surveillance are major requirements to prevent the development of and death from colorectal cancer (CRC).

Screening

Early screening for colorectal carcinoma (CRC) plays an important role in combating and controlling the growth of CRC morbidity and mortality worldwide. Clinical screening for CRC involves: Colonoscopy, Flexible sigmoidoscopy, Computed tomography colon imaging, FOBT, and fecal immunochemical tests, Screening for biomarkers, Carcinoembryonic antigen, Circulating tumor cells, Circulating tumor DNA/RNA, Abnormal DNA methylation. Out of these Colonoscopy is considered to be a gold standard screening technique as it has reduced the incidence of CRC by 76% and mortality by 65%. [(3)]The standard recommendation for colonoscopy screening based on risk factors is given in table 1.1[(4)]. Even though colonoscopy or sigmoidoscopy are useful but they are highly inadequate because of their high costs and long procedures. Our country Pakistan a developing country does not have the resources to do such mass level screening because of decreased resources and staff constraints[(5).] People are reluctant to such screening methods reason being high cost, fatalistic views about the procedure, embarrassment, the importance of privacy, especially for women, moral obligations, and culture-specific concerns[(6)]. Therefore Asia has opted for easier and more cost-effective procedures that help do mass level screening and are also effective in reducing the burden of disease:

1. Based on the risk factors identified in Asian populations, the Asia-Pacific Working Group on CRC has developed a scoring system, the Asia-Pacific Colorectal Screening (APCS) score, which works by risk stratification of asymptomatic subjects. It categorizes subjects into three groups low risk (LR), Medium risk (MR), and High Risk (HR). The risk factors considered are

age, sex, CRC history in first-degree relatives, previous exposure to

Risk Factor	*Age to Initiate Screening*	*Interval If Normal (years)*
Single first degree relative with colorectal cancer or an advanced adenoma diagnosed at ≥ 60 years of age	*50 years*	*10*
Single first degree relative with colorectal cancer or an advanced adenoma diagnosed at < 60 years of age	*40 years or 10 years younger than affected relative's age when diagnosed, whichever is earlier*	*5*
Two first degree relatives with colorectal cancer or an advanced adenoma diagnosed at any age	*40 years or 10 years younger than the youngest affected relative's age when diagnosed, whichever is earlier*	*5*
NOTE: An advanced adenoma is defined as an adenoma that is 10mm or larger has villous elements, or has high grade dysplasia		

Table 1 Colonoscopy Screening Recommendations based on Risk Factor

colonoscopy or sigmoidoscopy, dietary habits, life habits (alcohol intake, cigarette smoking, use of aspirin and other NSAIDs, current vigorous leisure-time activity, and estrogen status as assessed by menopausal status and use of hormone-replacement therapy), and BMI to predict patients' risk for CRC. According to this score, low and medium risk groups are first subjected to fecal immunochemical testing (FIT) and if positive then undergo colonoscopy whereas high-risk patients directly undergo colonoscopy. Because subjects classified with LR and MR were tested by FIT, this APCS-based algorithm can significantly reduce the colonoscopy workload by approximately 50%[5].

2. An unconventional method of testing by blood biomarkers has emerged as the firsthand technique for screening followed by colonoscopy. This method attracts people because of its noninvasive approach. Some of these tumor markers like APC, VEGF, Septin9, and other DNA in feces, blood, and other biological fluids can be used as the primary detection and prognostic indicator. Also, protein markers such as IMP3 and COX-2, have attracted much attention in CRC screening[3]. Other blood biomarkers that are indicative of CRC are C3a anaphylatoxin and colon cancer-specific antigenCCSA-3 and CCSA-4[7].

SURVEILLANCE:

Surveillance is an important aspect of care in patients with colorectal cancer. The primary objectives of surveillance following surgical resection for rectal cancer are to detect

disease recurrence (local and metastatic) and to screen for metachronous colorectal lesions and primary cancers in other organ systems. Between 60 to 80% of rectal cancer recurrences occur within 24 months following primary treatment, and 90% occur within 4 years[8]. Components of intensive postoperative surveillance are:[9]

1. History and physical examination: A visit to the doctor is advised every 3 to 6 months for the first 3 years and then 6 monthly for the next 2 years. Any history of recent alteration in bowel habits, bleeding per rectum, pain abdomen, and perineal pain in rectal cancers is indicative of recurrence. Also, physical examination for ascites, hepatomegaly, and supraclavicular lymphadenopathy is important.
2. Carcinoma Embryonic Antigen (CEA): It is an oncofetal protein and it correlates with disease burden. It should return to normal who have undergone a curative procedure. Sixty percent to 90% of patients with relapse have an elevated CEA. CEA detects recurrent disease 2 to 5 months before detection by any other means.
3. CT scan: CT scan combined with CEA gives maximum survival rates. Ct scan of the abdomen and chest in the first 3 years is the standard protocol.

Organization	History/ Physical	CEA	CT Scan	Endoscopy
ASCO 2013 (Stage II-III)	*Every 3-6 mo for 5 yrs*	*Every 3-6 mo for 5 yrs*	*Chest/ abdomen +/- pelvis (if rectal) annually for 3-5 yrs*	*Colonoscopy at 1 yr; if negative, every 5 yr. Rectal cancer: proctosigmoidoscopy every 6 mo for 2-5 yrs if no pelvic RT*
ESMO Colon 2013 (Stage I, II, III)	*Every 3-6 mo for 3 yrs, then every 6-12 mo for 2 yrs*	*Every 3-6 mo for 3 yrs, then every 6-12 mo for 2 yrs*	*Chest adomen every 6-12 month for 3yr; transabdominal US can be used instead of CT abdomen*	*Colonoscopy at 1yr; if negative every 3-5 yr subsequently*
ESMO rectal 2013 (Stage II, III)	*Every 6 mo for 2yr*	*Ever 6 mo for 3 yr*	*At least 2 chest/abdomen/ pelvis in the first 3 yr*	*Colonoscopy every 5 yrupto age of 75 years*
NCCN 2018 (Stage II, III, resected IV)	*Every 3-6 mo for 2 yr, then every 6 mo for 3 yr*	*Every 3 – 6 mo for 2 yr for≥ T2 disease, then every 6 mo for 3 yr (upto 5 if resected metastatic)*	*Colon: Chest/abdomen/pelvis every 6-12 mo for upto 5 yr. For rectal cancer. CT Chest/abdomen and pelvis every 3-6 mo for 2yr, then every 6-12 mo for upto 5 yr*	*Colonoscopy at 1 yr; if negative repeat at 3 yr, then every 5 yr subsequently. If adenoma found repeat at 1 yr*
USMSTF 2016 (only for endoscopic surveillance)				*Colonoscopy at 1 yr; if negative repeat at 3 yr, then every 5 yr.. For rectal cancer flexible sigmoidoscopy or EUS every 3-6 mo for first 2-3 yrs after surgery for patients at high risk for local recurrence*

ASCO: American society for clinical oncology, ESMO: European Society for medical oncology, NCCN: National Comprehensive Cancer Network, USMSTF: United States Multi Society Task force

Table 2 Summary of postoperative surveillance recommendations for colorectal cancer by different societies(

4. Endoscopy: Endoscopic evaluation of the colon for synchronous lesions needs to be performed before surgical resection of rectal cancer. If this is not possible, a colonic evaluation should be performed within 6 months following surgery. As the risk of metachronous cancer is 1.5 to 3 times greater in patients with an established history of colorectal cancer, lifelong endoscopic surveillance is mandatory. Flexible sigmoidoscopy, which can be performed with minimal preparation in an office setting, is a useful method for visualizing rectal anastomoses for evidence of recurrence.

Other Preventive Measures:

A rising trend has been seen in the incidence of colorectal carcinoma in Asian countries. This rise is attributed to a westernized dietary lifestyle, increasing population aging, smoking, physical inactivity, and other risk factors(11). Therefore it is important to highlight the preventive measures so that we can nip the evil in the bud before this problem escalates any further. Colorectal Carcinoma can be prevented by avoiding risk factors and increasing the protective factors. The modifiable risk factors for CRC that can be avoided are Alcohol, Cigarette smoking, and Obesity. It is observed from some studies that aspirin use, hormone replacement therapy (HRT) that includes both estrogen and progestin lowers the risk of invasive colorectal cancer in postmenopausal women, NSAIDs and calcium supplementation have reduced CRC incidence; even though their use has been associated with many other problems so they are not advised way to reduce cancer. (12)

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Recurrent Colorectal Cancer

Dr Irfan Baloch, Zainab Idrees

DIAGNOSTIC METHODS FOR RECURRENT COLORECTAL CANCER

NCCN guidelines for diagnosis indicate CEA and abdominal CT along with colonoscopy for surveillance of colorectal cancer but do not include PET-CT for follow-up.

The disadvantage of these modalities is the inability to differentiate recurrence from post-operative and post-radiotherapy changes.

MRI is less sensitive than PET-CT having sensitivity values of 65.4% and 92.6% respectively. [1]

CEA LEVELS:

After undergoing curative surgery for CRC patients are followed up for 5 years with regular CEA antigen tests to detect recurrence.

The analysis explains that determining trends in levels of CEA provides improved diagnostic accuracy.

Patients free from recurrence have stable CEA levels. But patients with recurrence have a variable trend.

If the rise is 7ug/l or more above baseline the GP is advised to refer the patient for further investigation.

But it can cause false alarms in current smokers and non-smokers as well.

Moreover, recurrence is missed in patients who experience a gradual rise in levels so a trend in a series of results over time should be considered. [2]

ROLE OF PET-CT IN DIAGNOSIS

PET-CT is superior to the CEA measurements and is a reliable imaging tool to detect

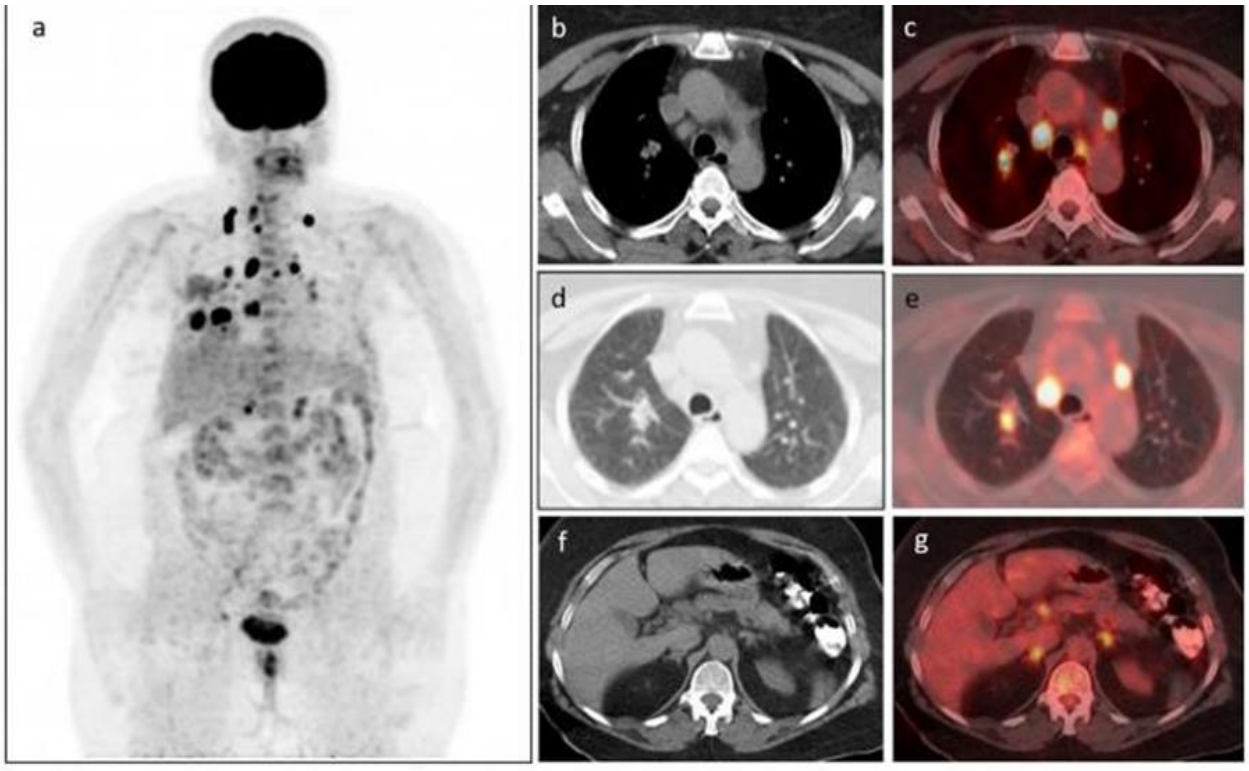

Fig. 5 60 year old, female patient. She had multiple mediastinal lymph node (**b**, **c**) and lung metastases (**d**, **e**) and also bilateral adrenal metastases (**f**, **g**) on FDG PET-CT scan (**a**). The simultaneous CEA value was 3,7 ng/ml. She died 1 month after the FDG PET-CT scan

recurrence after curative surgery. Moreover, it is independent of CEA levels. In CEA-normal patients, PET positivity leads to a less favorable survival time in comparison with PET negative patients.

In a follow-up to CRC, the primary goal is the earliest detection. FDG PET-CT can detect recurrence with a sensitivity of 92.6%. So it has the potential to become the imaging modality of choice for suspicion of recurrent CRC.

In patients with normal conventional imaging but elevated CEA levels, PET-SCAN successfully revealed recurrence in 88%. [1]

RECURRENCE AFTER RADICAL COLON SURGERY; ROLE OF ADJUVANT THERAPY:

Evidence suggests that adjuvant therapy reduces the risk of recurrence and improves overall survival. After primary treatment adjuvant therapy is administered since it kills residual tumor cells that can proliferate and be fatal. It is a routine therapy in stage 2 and in stage 3 of disease in colon surgery whereas it is less practiced in rectal carcinoma.

Side-by-side investigation of nodes in TN staging also correlates with better outcomes. However, reduction risk is not solely ascribed to the use of adjuvant therapy. Recurrence rates have also decreased due to improvement in care, better staging, improved surgical techniques, and detection of smaller metastasis. [3]

ROLE OF CSCs:

The main culprits involved in therapy resistance and recurrence are cancer stem cells (CSCs). Since these are quiescent and poorly differentiated they can easily survive chemotherapeutic insults with activation of Wnt/B-catenin, Notch, Hedgehog, and Hippo/YAP pathways. This facilitates excessive self-renewal and therapy resistance in CSCs. CSCs increase the expression of anti-apoptotic proteins and

Figure 1. The features represent special characteristics, crucial signalling pathways and associated miRNAs of cancer stem cells (CSCs) in causing therapy resistance in colorectal carcinoma.

develop drug efflux pumps. This CSCs confer resistance to radiotherapy by the excessive activation of DNA damage checkpoints. When in an experiment non-CSCs and CSCs were targeted for death, CSCs survived. This CSCs can re-populate the area and cause significant relapse in patients after successful treatment. [4]

RISK FACTORS

ROLE OF INTESTINAL MICROBIOME:

CRC is the result of multiple mutations in genes that drive normal cells towards carcinogenesis. The intestinal microbiome has an important role in it as evident by recent advances in research. The ecosystem of our gut plays a significant role in precipitating the disease. The models called "alpha-bug hypothesis" and "Bacterial-driver passenger hypothesis" well explain the role of gut microbiota in carcinogenesis. Patients with late-stage cancer had an abundance of *Fusobacterium, Corynebacterium, Neisseria, and Schlegellela*but lower levels of *Lactobacillus* and *Clostridiales.* Surgery for the cure of the primary tumor also influences the composition of the intestinal microbiome, particularly at anastomotic sites. Collagenase-producing organisms activate critical components of ECM like MMP and the urokinase-plasminogen system. Complex host-microbiome interactions are involved in recurrence. Bacterial communities can drive shed epithelial cells towards aggressive phenotypes that cause postoperative recurrence. Secondly, bacteria can interact with the primary tumor to cause micro-metastasis at the time of surgery. About one-third of the patients undergoing neoadjuvant therapy get recurrence due to alteration of the microbiome by radiation and chemotherapeutic drugs. [5]

MLC9 AND CNN1:

One of the obstacles to the successful

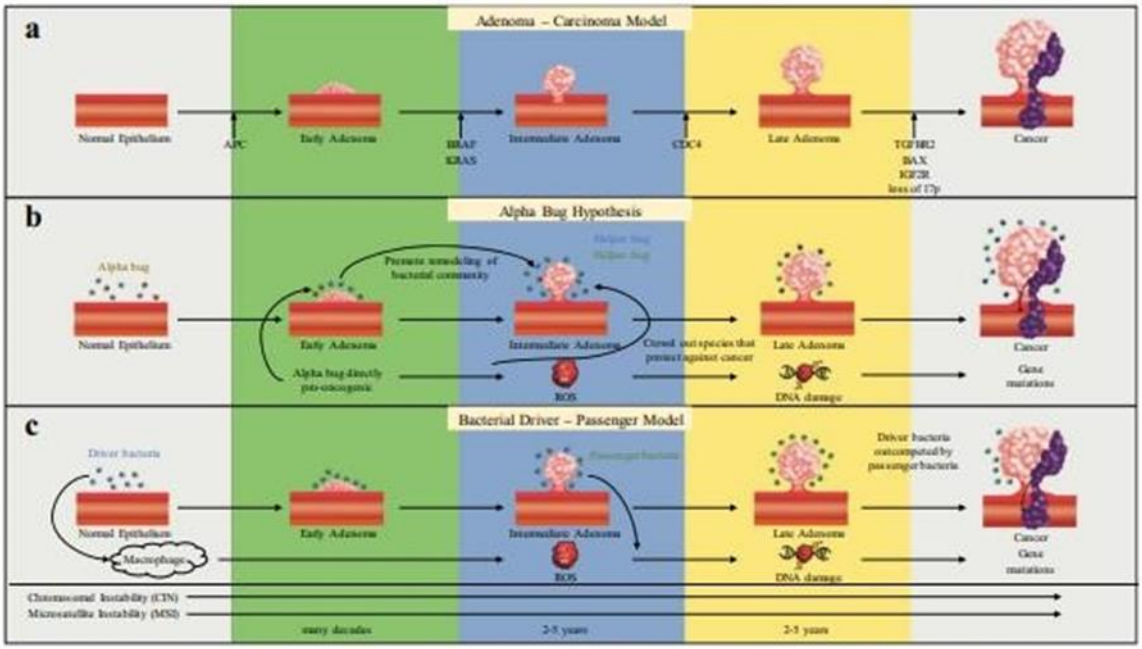

Fig. 1 **a** In the classic "*adenoma-carcinoma model*," disease progresses with serial accumulation of genetic mutations. **b** In the "*alpha-bug hypothesis*," specific microbe members, termed alpha bug, are not only directly pro-oncogenic but also capable of remodeling the entire bacterial community to enhance and promote alpha bug changes by employing helper bugs to crowd out the species that protects against cancer. **c** In the "*bacteria-driver hypothesis*," the disease progression causes the change in microbiome that favors proliferation of opportunistic bacteria (passenger bacterium) with tumor-promoting properties

treatment of colorectal carcinoma is the recurrence associated with it. By constructing weighted gene co-expression network analysis (WGCNA), we can identify hub genes involved in recurrence. WGCNA has been widely used to identify tumor markers in various cancers. It is found that MLC9 and CNNI are involved in various pathways in cancer. MLC9 participates in the migration of cells and its low levels are associated with a better survival rate. CNN1 is demonstrated to be expressed at higher levels in normal colon tissue. Various survival analyses show that higher levels of MLC9 and CNN1 are associated with poor prognosis. MLC9 and CNN1 work as tumor suppressor genes in the human body. These hub genes may be captured by tumor cells during the progression of CRC and turned into harmful genes. Hence, their major role becomes to protect tumor cells. In short, these genes are related to decreasing RFS time in patients with CRC. [6]

ARE POSTOPERATIVE COMPLICATIONS ASSOCIATED WITH RECURRENCE?

Proven by meta-analysis post-operative quality management in colorectal carcinoma is associated with better results and increased RFS.

Speaking in terms of CDC classification, the most frequent complications associated with CDC grades 1, 2, 3, and 4 are urinary bladder dysfunction, UTIs and CVC infections, anastomotic leaks, and pulmonary complications respectively.

A short-term quality indicator in rectal carcinoma is anastomotic leaks as shown by Merkel in 2001. It is also a frequent complication of CDC type 3 tumors and is associated with local recurrence and poor overall survival.

Worst and life-threatening complications are associated with CDC grade 4. These patients have the worst overall survival rate. Hence post-operative complications are an inverse prognostic factor and have a strong relationship with the Clavien-Dindo classification. [7]

IMPACT OF POSTOPERATIVE INFLAMMATION ON RECURRENCE:

SIRS is strongly linked with poor prognosis, worst outcome, and decreased RFS time. A study was conducted in Japan to know about the impact of post-operatively elevated CRP levels on recurrence. Initially, it was known that cytokines are important in the progression and prognosis of carcinoma. Cytokines enhance cancer cell growth and epithelial to mesenchymal transformation in vivo and in vitro.

The study showed that there exists a positive correlation between CRP and cytokine levels. After surgery cancer cells might persist in peripheral blood and peritoneum. This study showed that elevated CRP levels are strongly linked with poor RFS and peritoneal metastasis. The patient-related independent prognostic factor for elevated CRP levels after curative surgery was right-sided colon cancer. [8]

PROGNOSTIC MARKERS:

PREOPERATIVE LYMPHOCYTE LEVEL:

Exact diagnostic markers for recurrence of CRC have not been established yet, however, a study showed the hemogram of peripheral blood as a useful diagnostic marker.

The lymphocyte count, the systemic inflammation score (SIS), the lymphocyte and monocyte ratio (LMR), the neutrophil and lymphocyte ratio (NLR), the platelet to

lymphocyte ratio (PLR), and the platelet distribution width (PDW) have been reported to be correlated with disease-free survival (DFS) and overall survival (OS) in patients with CRC.

The relation between recurrence and lymphocyte count has been established as early as 1970. Patients having more advanced colorectal carcinoma had lower lymphocyte counts. But now it is known that the combination of the lymphocyte count and the PPLR appears to be a potential marker for predicting recurrence of stage II colon cancer. Further study is needed to establish a direct relation between lymphocyte counts and stage III colon cancer recurrence.

There is a possibility that patients who naturally have LLCs more readily develop CRC. [9]

Role of microRNAs:

The miRNAs are short RNAs involved in the post-translational regulation of gene expression by affecting the stability and translation of mRNAs. Their dysregulation is associated with carcinogenesis. Cancer-related mic RNAs are emerging as promising and non-invasive biomarkers for CRC.

Postoperative changes in miR21-5 levels at POM1 and POM6 are independent prognostic factors and their level can be used to evaluate the histopathological features of CRC. In the recurrence group, the plasma miR21-5 shows a significant rise after surgical resection at POM1 and POM6.

In conclusion, it has the potential to be a predictable and non-invasive biomarker for treatment efficacy. [10]

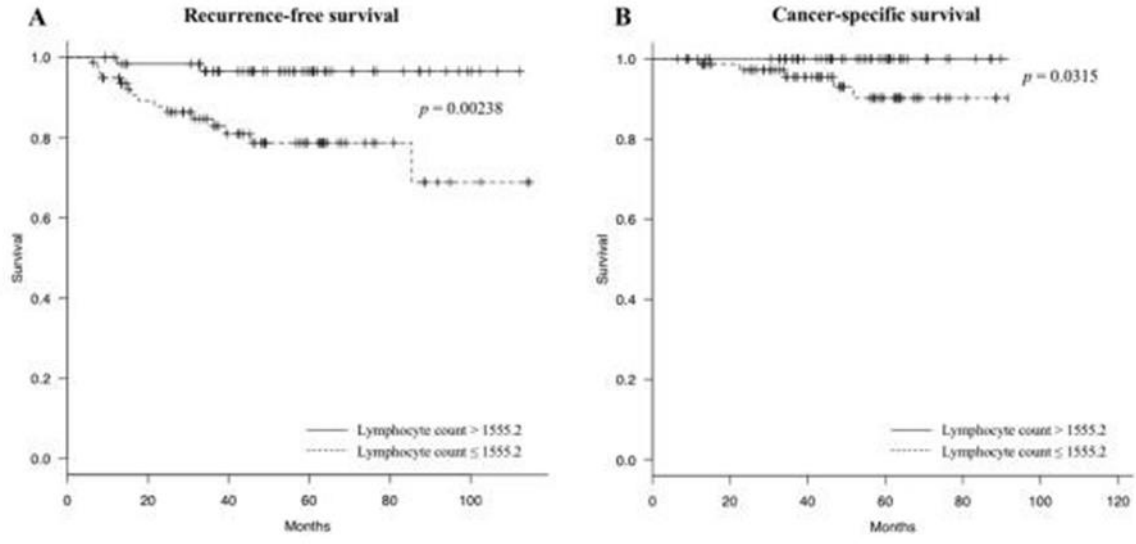

Figure 3: Recurrence-free survival (RFS) and cancer-specific survival (CSS) curves grouped by lymphatic cell count **(A)** Patients with a low lymphocyte count ≤1555.2/µl (dotted line) have a significantly worse RFS compared to patients with a high lymphocyte count (> 1555.2/µl) (solid line) (log-rank $p = 0.00238$); **(B)** Patients with a low lymphocyte count ≤1555.2/µl (dotted line) have a significantly worse CSS than patients with a high lymphocyte count (> 1555.2/µl) (solid line) (log-rank $p = 0.0315$).

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9. Combined use of preoperative lymphocyte counts and the post/ preoperative lymphocyte count ratio as a prognostic marker of recurrence after curative resection of stage II colon cancer Seiichi Shinji1, Yoshibumi Ueda2,3, Takeshi Yamada1, Michihiro Koizumi1, Yasuyuki Yokoyama1, Goro Takahashi1, Masahiro Hotta1, Takuma Iwai1, Keisuke Hara1, Kohki Takeda1, Mikihiro Okusa1, Hayato Kan1 and Eiji Uchida1

10. Postoperative changes in plasma miR21-5p as a novel biomarker for colorectal cancer recurrence: A prospective study Masahiro Fukada1 | Nobuhisa Matsuhashi1 | Takao Takahashi1 | Nobuhiko Sugito2 | Kazuki Heishima2 | Kazuhiro Yoshida1 | Yukihiro Akao2

Recent Advances and Future Aspects in the Management of Colorectal Carcinoma

Dr. Tayyaba Ismail, Fiza Farooq

Medical field is a continously expanding relam, where new and improved strategies for diagnosis and treatment of various diseases are constantly tested and added to the literature. This guides patient management and also paves way for further research into the subject. A lot of such advances have been made in the management of colorectal cancer.

ADVANCES IN SCREENING, DIAGNOSIS AND STAGING

- **Cologuard:**

Stool testing for occult blood and human DNA has since been used for the screening of Colorectal CA by health professionals. Now a home based screening test for colorectal CA/polyp, has recently been approved by FDA. It works on the same principles of detecting DNA and blood in stool. (1)

- **Testing liquid biopsies:**

Another method evolved for the screening of colorectal CA avoids the unpleasant experience of colonoscopies. A simple blood or urine test detects DNA (circulating tumor DNA ctDNA) and other substances shed from tumor in blood and urine samples. (1)

- **Tumor associated antigens:**

Tumor-associated antigens (TAAs) are produced by tumor cells and are displayed on the surface of cancer cells. Small peptides, derived from these TAAs, bind to human leukocyte antigen (HLA). The bound peptides can be identified by T lymphocytes and initiate the anticancer response.

A recent study found that 5 of these TAAs (Imp1, p62, Koc, p53, and c-myc full-length recombinant proteins) when combined with carcino embryonic antigen, increase diagnostic sensitivity from 60.9 to 82.6%. (2)

- **Lymph Node Mapping:**

Sentinal lymph mode biopsy has since been used to determine primary lymph nodes draining the tumor. However, SLE is limited in that it cannot identify whether the draining lymph nodes carry mets from the tumor or not.

A possible new tool for determining colorectal lymph node metastasis is CEA-targeted flouresent imaging using SGM - 101. This would specifically test LN for metastases from colorectal CA. (3)

ADVANCES IN CHEMO AND IMMUNOTHERAPY

- **Monocolonal Antibodies (MAbs):**

MAbs have revolutionized the therapeutic results and patient survival particularly in inflammatory and neoplastic conditions.

MAbs are produced from a single B cell clone and bind to a specific single epitope on the antigen. Hybridoma method for the production of MAbs was introduced by Kohler and Milstein. (4)

Impaired function of Epidermal Growth Factor Receptor activates MAP Kinase pathway which plays an important role in the advancement of metastatic CRC. Anti EGFR antibodies which include Cetuximab and Pantimumab block the MAPK pathway and thus help in treatment of metastatic CRC. Primary resistance to these MAbs is due to mutations in downstream signaling proteins. However, mixtures which target different

epitopes could prevent the emergence of resistance.
In addition some MAbs also act on immune cells to manipulate the immune system to attack the cancer cells. (5)
MAbs are generated by recombinant DNA technology. These MAbs are formed in mammalian cells by transient or stable transduction. During early stages of drug evolution transient transfection provides rapid manufacture of small amount of product. However, large scale industrial processing requires stably transfected cell lines.

- **Bi- Specific Antibodies:**

Bispecific antibodies are used to overcome the deficiency of MAbs therapy since they have the ability of binding to two different antigens at a time. Moreover, BsAbs can bring about change in cell signaling by targeting two different receptors on the same cell.
BsAbs have two forms; IgG-like and non-IgG-like
IgG-like (e.g, Catumaxomab) BsAbs are characterized by longer half-lives and Fc mediated effector functions.
Non-IgG-like (e.g, Blinatumomab) BsAbs have short serum half-lives due to lack of Fc region.
BsAbs are not only employed for CRC treatment but for other diseases like hemophilia, Alzheimer's disease and autoimmune disorders.
Quadroma technology produces BsAbs which are more stable and soluble than normal antibodies and have longer half-lives but the demerit lies in its low efficiency due to production of non-functional antibodies.
BsAbs produced by Knobs-into-holes technology are also highly stable. In this technique, CH3 domain of antibody is used to improve Fc hetero dimerization.
Other techniques including CrossMAB technology and protein engineering are also used for generation of BsAbs. (4)

- **Immune Checkpoint Receptors:**

Immune checkpoint receptors prevent autoimmunity and help T cells to release cytokines.
T-lymphocyte-Associated Protein 4 (CTLA-4) when expressed, inhibits normal functioning of T cells. It causes enhanced activation of T cells but on the other hand reduced immune response against cancer cells.
Programmed Cell Death-1 (PD-1) is the checkpoint expressed on T and B lymphocytes.
Immune checkpoint targeted therapy is meant to increase immune surveillance and suppression against cancer. This is achieved by blocking the tumor's ability to escape from T cell detection. (5)
A putative strategy for cancer treatment involves combined use of CTLA-4 and PD-1 inhibitors. Currently, various blocking agents have been generated to target CTLA-4 (ipilimumab) and PD-1 (nivolumab). Weber et al.to achieved good results of this combination therapy for treatment of melanoma and now it is suggested to improve therapeutic activity in CRC treatment. (4)

- **Targeted Nano-particles for Colorectal CA:**

Although chemotherapy is highly potent in CRC therapy yet it is associated with various side effects (e.g, loss of hair). Thus, monoclonal antibodies should be used along with chemotherapeutic agents. Unfortunately, this combination therapy is liable to drug resistance. Hence, researchers now use nanoparticles as carriers of their pharmaceutical drugs. These nanoparticles would decrease the side effects of cytotoxic

drugs and bring about improvement in their potency, solubility, pharmacokinetics and biodistribution.

Liposome-based nano products (CPX-1, LE-SN38, ThermoDox), first to be approved by US, are used in treatment of CRC. These nanoparticles can be made more specific for cancer therapy by conjugating them with antibodies or their fragments.

Gold nanoparticles are less cytotoxic, more biocompatible, easily functioning and most stable.

The surface of nanoparticles can be functionally modified thus allowing them to have specific drug targeting and controlled release. Lastly, nanoparticles can also inhibit cell proliferation and induced apoptosis in CRC cells. (4)

- **Theraputic Gene Vaccine:**

To date, many studies are being carried out to develop vaccines for CRC therapy or to prevent its recurrence after treatment. Cancer vaccines are required to have both cellular and the humoral immune response.

A new strategy in immunogenicity is the use of nucleic acid vaccines based on DNA (MYB, pcDNA-hNIS) or RNA (DC-CEA, mRNA 4157). Particularly important in immunotherapy are DNA vaccines since they are capable to stimulate the production of CD8 cells. Despite all the information gathered from in vitro and in vivo studies, the efficacy of DNA and RNA vaccines has not been thoroughly studied in clinical trials. (4)

ADVANCS IN SURGICAL MANAGEMENT

- **Robotic Surgery:**

First robot assisted colon surgery (colectomy) was performed in the US in 2002. Since then many improvements have been made. Studies have shown that robot assisted laparoscopic total mesorectal excision (TME) and transanal minimally Invasive TME improve mid rectal and distal rectal outcomes. (6,7)

This is because robotic surgery comes with the advantages of tremor removal, ability to scale motion, stereoscopic vision, and use of wristed instruments. This greatly improves a surgeon's dexterity and allows precise resection and anastamosis. Also precise dissection allows for preservation of sorrounding structures and minimizing damage to pelvic autonomic and genitourinary function.

However, prolonged operating time, cost, and steeper learning curve pose a challenge that requires further development.

- **Navigation Surgery:**

Navigation techniques include use of flourence with intra operative arterial injection of dyes such as Indocyanin Green (ICG) in the tissue to be reconstructed. This allows the surgeon to assess perfusion of the bowel segment to be anastamosed and hence reduces the chances of anastamotic leakage. (8)

ADVANCES IN MANAGEMENT OF METASTATIC CA

- **Cytoreductive Surgery and Hyperthermic Intra-peritoneal Chemotherapy (CTS & HIPEC):**

CTS in combination with HIPEC has been used in the treatment of peritoneal tumors (like Pseudomyxomaperitoni) as well as peritoneal Mets from abdomino pelvic organs like ovary and appendix. Recently it's effectiveness in the management of colorectal CA with peritoneal metastasis (PM) has been explored.

Two prospective case-control studies have been done to evaluate the feasibility and utility of HIPEC in reducing PM in high-risk

CRC patients. Both reported improved 5-year overall survival rates in the patients who received prophylactic HIPEC at the time of primary surgery. (9,10)
Studies have reported 5 year survival rates of 40-51% with complete cytoreduction and HIPEC. (11). However, it's effectiveness depends on the extent of disease, degree of cytoreduction and type of chemotherapy. Trials are underway to determine the best chemotherapeutic combination for HIPEC in colorectal CA. (12)

- **Hepatic artery infusion chemotherapy:**

This technique has been devised for the treatment of liver metastasis. A pump or port (similar to a port for IV chemo but larger) is implanted close to the hepatic artery, which is the blood vessel feeding most cancers in the liver. Drugs with high 1st bypass hepatic extraction are delivered directly into this port. This allows delivery of near full doses of the drug to the liver without causing systemic toxicity
When augmented with systemic therapy, HAIC augments response rate upto 85% in patients with initially unresectable colorectal liver metastasis. (13)
A meta-analysis compared HAIC with standard chemotherapy and found that there was a significantly higher Overall Survival Rate in the HAIC as palliative treatment group (HR, 0.17; 95% CI, 0.08–0.26; P = 0.000) and HAIC as adjuvant treatment group compared with SC group (HR, 0.63; 95% CI, 0.38–0.87; P = 0.000)
The complete and partial tumor Response Rates were also increased significantly in the HAIC as palliative treatment group (RR = 2.09; 95% CI, 1.36–3.22; P = 0.001) and as adjuvant treatment group compared with SC group (RR = 2.14; 95% CI, 1.40–3.26; P = 0.000) (14)

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