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Colorectal Cancer Management: An Overview

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ABSTRACT

Background: Colorectal cancer is the third most common cancer worldwide with a high mortality rate at the advanced stages. However, colorectal cancer is not a single type of tumor; its pathogenesis depends on the anatomical location of the tumor and differs between right side and left side of the colon. Tumors in the proximal colon (right side) and distal colon (left side) exhibit different molecular characteristics and histology. In the right-sided tumors, mutations in the DNA mismatch repair pathway are commonly observed; and these tumors generally have a flat histology. In the left-sided tumors, chromosomal instability pathway-related mutations, such as *KRAS, APC, PIK3CA, p53* mutations are observed and these tumors demonstrate polypoid-like morphology. Therapy responses are totally different between these tumor entities. Left-sided colorectal cancer (LCRC) patients benefit more from adjuvant chemotherapies such as 5-fluorouracil (5-FU)-based regimes, and targeted therapies such as anti- epidermal growth factor receptor (EGFR) therapy, and have a better prognosis. Right-sided colorectal cancer (RCRC) patients do not respond well to conventional chemotherapies, but demonstrate more promising results with immunotherapies because these tumors have high antigenic load. For the development of effective therapy regimes and better treatment options, it is essential to evaluate right-sided and left-sided tumors as separate entities, and design the therapy regime considering the differences between these tumors.

Key words: Colorectal cancer, Right side, Left side, Epidemiology, Molecular mechanism, Adjuvant chemotherapies, Targeted therapies, Immunotherapies.

Epidemiology:

Worldwide, an estimated 1,849,518 new cases of colorectal cancer occurred in 2018 (10.2% of all cancers). Geographically, the incidence varies as much as 10-fold. The highest estimated rates are in Australia/New Zealand, and the lowest in South-Central Asia.Colorectal cancer causes approximately 694,000 deaths annually, accounting for 8.5% of cancer mortality overall. More deaths (52%) occur in the less-developed regions of the world, reflecting a poorer survival in these regions **(1).**

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Since 1989, colorectal cancer incidence rates have been higher for blacks than for whites in both men and women. Currently, incidence rates of colorectal cancer are 24% higher in black men and 19% higher in black women compared with white men and women, respectively **(2).**
Colorectal mortality rates are 47% higher in black men and 34% higher in black women compared with whites. However, from 2007 to 2016, colorectal cancer death rates declined faster in blacks than in whites, narrowing the racial disparity in both men and women **(2).**

Clinical risk factors:

A- Genetic factors:

Mutations may cause activation of oncogenes (K-ras) and/or inactivation of tumor-suppressor genes (APC, DCC [deleted in colorectal carcinoma], p 53). Colorectal carcinoma is thought to develop from adenomatous polyps by accumulation of these mutations **(3).**

► The Adenoma-Carcinoma Model (Fig. 9):

Defects in the APC gene were first described in patients with FAP. By investigating these families, characteristic mutations in the APC gene were identified. They are now known to be present in 80% of sporadic colorectal cancers as well **(4).**

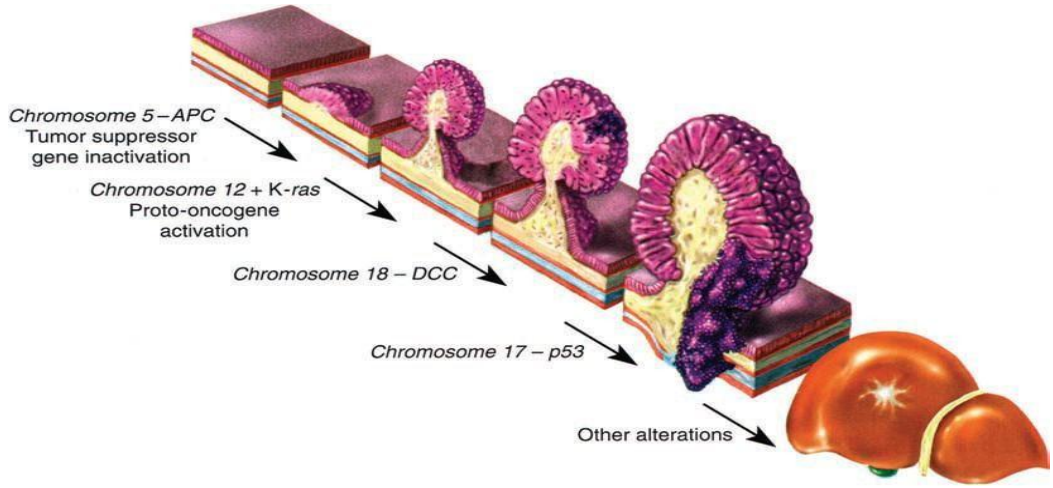

Fig. (1): Adenoma-Carcinoma Sequence**.**

The APC gene is a tumor-suppressor gene. Mutations in both alleles are necessary to initiate polyp formation**(5).**
APC inactivation alone does not result in a carcinoma. Instead, this mutation sets the stage for the accumulation of genetic damage that results in malignancy via mutations accumulated in the loss of heterozygosity (LOH) pathway. Additional mutations involved in this pathway include activation of the K-ras oncogene, and loss of the tumor suppressor genes DCC and p53**(6).**

K-ras is classified as a proto-oncogene because mutation of only one allele will perturb the cell cycle**(7).**DCC is a tumor-suppressor gene and loss of both alleles is required for malignant degeneration. The role of the DCC gene product is poorly understood, but it might be involved in cellular differentiation. DCC mutations are present in more than 70% of colorectal carcinomas and may negatively impact prognosis **(7).**

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The tumor-suppressor gene p53 has been well characterized in a number of malignancies. The p53 protein appears to be crucial for initiating apoptosis in cells with irreparable genetic damage. Mutations in p53 are present in 75% of colorectal cancers **(8).**

► Pathological features of colorectal cancer:

Size alone is not a reliable predictor of outcome from colon cancer because of the predominance of biologic behavior in predicting outcome. Tumors of the right colon often are fungating masses that grow into the lumen and for which the symptom is occult bleeding rather than obstruction; they often present with a palpable mass. Adenocarcinoma represents 90% to 95% of all colonic tumors. Tumors can be further classified by grade and histologic subtypes **(9).**

► Spread of colorectal cancer:

The capability of a tumor to invade and metastasize is not on the most visible hallmark of cancer but also the leading cause of death in cancer patients, colorectal cancers can spread locally or distantly via the lymphatic and venous systems**(9).**

A) Local spread:

Colorectal cancers usually grow preferentially in the transverse direction rather than in the horizontal direction. The long axis of the ulcerating tumor was always transverse, with the lesion tending to involve the bowel circularly rather than longitudinally. Therefore, the tumors tended to narrow and constrict the bowel wall**(10).**

B) Lymphatic spread:

The lymphatic drainage starts with lymphatic follicles in the colonic submucosa, drains through the colonic muscle wall into the epicolic nodes, and continues to the paracolic lymph nodes that follow the blood vessels to the bowel, along the major arteries to the principal lymph nodes at the level of the arterial runoff from the aorta**(11).**

C) Hematogenous spread:

Approximately 10% to 15% of colorectal cancer patients have evidence of distant metastasis at the time of the initial diagnosis. The liver is the most commonly involved organ**(9).**

► Staging of colon cancer:

Table (1): TNM staging of colorectal cancer According to 7th edition of AJCC (12).

Tumor Stage (T)	
Tx	**Cannot be assessed**
T0	**No evidence of cancer**
Tis	**Carcinoma in situ**
T1	**Tumor invades submucosa**
T2	**Tumor invades muscularis propria**
T3	**Tumor invades throughmuscularis propriainto subserosaor into nonperitonealized pericolic or perirectal tissues**
T4a	**Tumor penetrates to the surface of the visceral peritoneum**

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T4b	**Tumor directly invades or is adherent to other organs or structures**
Nodal Stage (N)	
NX	**Regional lymph nodes cannot be assessed**
N0	**No lymph node metastasis**
N1	**Metastasis to one to three pericolic or perirectal lymph nodes**
N1a	**Metastasis in one regional lymph node**
N1b	**Metastasis in 2–3 regional lymph nodes**
N1c	**umor deposit(s) in the subserosa, mesentery,ornonperitonealized pericolic perirectal tissues without regional nodal metastasis**
N2	**Metastasis to four or more pericolic or perirectal lymph nodes**
N2a	**Metastasis in 4–6 regional lymph nodes**
N2b	**Metastasis in 7 or more regional lymph nodes**
Distant Metastasis (M)	
MX	**Presence of distant metastasis cannot be assessed**
M0	**No distant metastasis**
M1a	**stasis confined to one organ or site (for example, liver, lung, ovary, non-re node)**
M1b	**Metastases in more than one organ/site or the peritoneum**

► Clinical Symptoms:

Symptoms are common and prominent late in colon cancer when the prognosis is poor but are less common and less obvious early in the disease.the classic warning signs include loss of appetite, loss of weight, worsening constipation, alternating bowel habits, blood in the stool, decrease in stool caliber, and nausea or vomiting **(13).**

Partial obstruction occasionally paradoxically produces intermittent diarrhea as stool moves beyond the obstruction. proximal cancers rarely produce bleeding because the blood becomes mixed with stool and chemically degraded during colonic transit **(14).**

► Signs:

A palpable abdominal mass is a rare finding that suggests advanced disease. Hypoactive or high-pitched bowel sounds suggest gastrointestinal obstruction. Rectal examination, including fecal occult blood testing (FOBT), is important in the evaluation of possible colon cancer. Other physical findings, including peripheral lymphadenopathy, especially a Virchow's node in the left supraclavicular space; hepatomegaly from hepatic metastases; and temporal or intercostal muscle wasting from cancer cachexia. Very rare findings with colon cancer include a Sister Mary Joseph node caused by metastases to a periumbilical node, and a Blumer's shelf caused by perirectal extension of the primary tumor **(15).**

► Laboratory abnormalities:

a) Carcinoembryonic antigen (CEA):

Since its initial description in 1965 by Gold and Freedman, CEA has been the most extensively investigated tumor marker for colon cancer. CEA is present in normal adult tissues in addition to malignant tissues, but very low levels normally are seen in the blood from healthy individuals with normal concentrations of 2.5 to 5.0 ng/ml. Although 80% or more of patients with advanced

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colonic adenocarcinoma have circulating CEA, the CEA assay should not be used as the sole diagnostic test for suspected carcinoma.

B)Tests that detect adenomatous polyps and cancer:(16).

- Flexible sigmoidoscopy every 5 years.
- Colonoscopy every 10 years.
- Double-contrast barium enema (DCBE) every 5 years, or
- Computed tomographic colonography (CTC) every 5 years.

C)Tests that primarily detect cancer: *(*16).

- Annual guaiac-based fecal occult blood test (FOBT) with high test sensitivity for cancer, or
- Annual fecal immunochemical test (FIT) with high test sensitivity for cancer, or
- Stool DNA (sDNA) test with high sensitivity for cancer, interval uncertain.

Treatment:

Treatment options for colon cancer depend on the stage of the tumor that is, how far it has spread or how deeply it is affecting the intestinal wall and other tissues. In general, patients with colon cancer receive post-operative chemotherapy if the lymph nodes are positive. Treatment is also determined by the patient's age, medical history, overall health, and tolerance for specific medications and therapies **(17).**

1) Non-surgical treatment:

a) Systemic Chemotherapy*:*

5-Fluorouracil remains the backbone of chemotherapy regimens for colon cancer, both in the adjuvant and metastatic setting. In the past years, it was established that combination regimens provide improved efficacy and prolonged progression-free survival in patients with metastatic colon cancer. In addition to 5-fluorouracil, oral fluoropyrimidines such as capecitabine (Xeloda) and tegafur are increasingly used as monotherapy or in combination with oxaliplatin (Eloxatin) and irinotecan (Camptosar). Some of the standard combination regimens employ prolonged continuous infusion of fluorouracil (FOLFIRI, FOLFOX) or capecitabine (CAPOX, XELOX, XELIRI) ***(18).***

b) Radiotherapy*:*

While radiation therapy remains a standard modality for patients with rectal cancer, the role of radiation therapy is limited in colon cancer. It does not have a role in the adjuvant setting, and in metastatic settings, it is limited to palliative therapy for selected metastatic sites such as bone or brain metastases. More selective ways of administering radiation therapy such as stereotactic radiotherapy (CyberKnife) and tomotherapy extend indications for radiotherapy in further management of colon cancer**(19).**

2) Surgical treatment:

Surgery is the only curative modality for localized colon cancer (stage I-III) and potentially provides the only curative option for patients with limited metastatic disease in liver and/or lung (stage IV disease). The general principles for all operations include removal of the primary tumor with adequate margins including areas of vascular and lymphatic drainage **(17).**

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a) Open Colectomy:

An open colectomy is the most common surgical procedure employed when treating colon cancers. The surgery is performed through a laparotomy incision where a part of the colon with the cancer and a small segment of normal colon on either side of the cancer are removed. Usually, approximately one fourth to one third of the colon is removed but is subject to the exact size and location of the cancer. Nearby lymph nodes are removed at this time. Removing as many lymph nodes as possible for examination is important to determine proper staging and post-operative treatment of the disease**(17).**

b) Laparoscopic Colectomy:

This minimally invasive technique is an approach to resect a part of the colon and nearby lymph nodes and may be an option for some earlier stage cancers. Instead of making one long incision in the abdomen, the surgeon makes several smaller incisions **(20).**

► Advantages and Disadvantages of Laparoscopic Colon Surgery:

Conventional open surgery is associated with significant morbidity and long convalescence. The advantages of laparoscopic colon surgery (LCS) in comparison with open surgery have been suggested with respect to decreased morbidity, decreased pain, faster recovery, shorter hospital stay and possibly reduced immunosuppression **(Table 3)(21).**

Table (2): Advantages and disadvantages of LCS**(21).**

Advantages	Disadvantages
Limited abdominal wall trauma	Expensive equipment and high cost of surgery
Reduced postoperative pain	Increased surgical time
Possible more rapid return of bowel function	Surgeon's experience
Possible reduced length of hospital stay	Significant learning curve
Possible hastened postoperative recovery	Inability of some patients to tolerate pneumoperitoneum
Similar staging opportunities compared with open procedures	
Short-term outcomes similar to traditional procedures	
Possible protection of immune function	

One of the important advantages of LCS is the decreased intensity and duration of pain sensation. In the Clinical Outcomes of Surgical Therapy (COST) study grouptrial, patients in the laparoscopic arm required parental and oral analgesics for a shorter period of time **(22).** In another randomized control trial (RCT), significantly less morphine was used in the laparoscopic groups only on the first postoperative day. It has been demonstrated that well managed pain control supports respiratory function and lowers the risk of complications ***(*23).**

In colorectal surgery the major modalities of postoperative pain control are patient- controlled analgesia, opioids, non-steroidal anti-inflammatory drugs, and epidural analgesia. Some studies show that pain control, patient satisfaction and bowel function are improved after abdominal surgery under epidural analgesia **(24).**

A major advantage of laparoscopic surgery lies in the magnification that is offered by the endoscopic camera which enables greater surgical precision and better identification of tissue

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structures. This important issue may potentially lead to greater standardization of the surgical approach and technique **(25).**

The major disadvantage of laparoscopic colectomy is increased operative time. As opposed to most other laparoscopic procedures, laparoscopic colorectal surgery requires dissection in more than one quadrant and there is need for intraoperative repositioning of instruments, ports, and personnel. The colonic mesentery includes numerous large vessels and vascular control requires considerable time and quite often much more cost than do other procedures **(26)**.

Complications of Laparoscopic Colorectal surgery approach:

1) Intra-operative complications

a) Anesthesia related complications:

The use of a steep Trendelenburg position and the distension of the abdomen may both reduce excursion of the diaphragm. Carbon dioxide (CO_2) can be absorbed particularly during prolonged operations. Monitoring by pulse oximetry, the use of endotracheal intubation and positive pressure assisted ventilation reduce the risk of hypercapnia to a minimum **(27).**Brachial plexus injury attributed to the Trendelenburg position during prolonged laparoscopic procedures has been reported **(28).**

b) Trocar complications:

Abdominal access carries a definite risk of vascular and visceral injury. many techniques used to create a pneumoperitoneum: blind Verrus needle, direct trocar insertion, optical trocar insertion and open laparoscopy. The described overall complication rates in these techniques are below 1%. Some studies revealed a higher rate of visceral injuries, in the open-entry technique **(29,30).**

Direct insertion of trocar without prior pneumoperitoneum is associated with less insufflation-related complications such as gas embolism, is faster to perform and is a safe alternative. The visual entry cannula system may provide advantages over the traditional techniques but has to be fully' explored in the future**(31).**

c) Bowel Injury*:*

There is limited data regarding iatrogenic injuries in colorectal surgery. The main fears of the surgeon are vessel injury, damage to the spleen during colorectal surgery (incidence of 0.006%), or intestinal perforation and ureteric injuries (incidence < 0.01%)**(32).**

d) Ureteric and Bladder Injuries:

One of the hazards of colorectal surgery is ureteric injury. The incidence of ureteric injuries during laparoscopic resections is estimated to be about 0.66%, Injuries to the ureters or the bladder occur mainly in patients undergoing oncologic resections, and those with difficult anatomic exposure, owing to previous operation, recurrent tumor or radiation therapy. Most of the injuries can be repaired by primary suture. Placement of ureteric catheterization preoperatively can reduce the incidence of this complication **(33).**

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2) Postoperative Complications:

a) Surgical Site Infection

Colorectal surgery is associated with a high rate of surgical site infection (SSI), with overall infection rates reported to be as high as 26%**(34).** There is increasing awareness of the need to reduce SSI given that development of this complication adversely affects length of hospitalization, quality of life, other post-operative outcomes and costs **(35).**

It has been demonstrated that; despite the presence of predisposing factors such as ASA > III, obesity, smoking, diabetes, inflammatory conditions as indication for surgery, operative time > 180 minutes and anastomosis involving the rectum; LAP approach is associated with decreased rate of SSI **(36).**

b) Anastomotic leak

Anastomotic leaks occur in approximately 3 to 15 percent of patients having undergone colon and rectal surgery and can lead to significant morbidity and mortality.The most important risk factor is the level of the anastomosis; low rectal anastomoses have a much higher leak rate compared with intra peritoneal colonic anastomosis. Technical considerations most often relate to tension and inadequate blood supply **(37,38).**

The anastomotic leak rate from intracorporeal laparoscopic anastomosis (2.5-12%) is not greater than that for open surgery or laparoscopic surgery with extra-corporeal anastomosis (1.3- 18%) **(39).**

c) Port Site Metastasis:

Port-site metastasis is defined as cancer recurrence at a trocar insertion site without evidence of recurrence anywhere else **(40)**.

Although the etiology of port-site metastasis is still unclear, the likely mechanism involves direct tumor cell contact and implantation. The initial enthusiastic application of laparoscopic techniques in colorectal surgical procedures was tempered in the early 1990s by reports of tumor implants in the laparoscopic incisions. Substantial evidence has accumulated to support that laparoscopic resection results in oncologic outcomes similar to open resection, when performed by well-trained experienced surgeons **(41).**

Abdominal wall recurrence after open colectomy was considered to be rare about 0.7% according to a retrospective study **(42).**However, abdominal wall recurrence was reported in 2.5% of patients after open resection of colon cancer **(43)**.

According to the consensus of the European association of endoscopic surgery (E.A.E.S.) the incidence of port site metastasis after laparoscopic colectomy is <1%. Proper surgical technique and practice reduce the likelihood of port site metastasis**(44).**

3) Conversion:

Laparoscopic colectomy is converted to open surgery in 14% (0- 42%) of cases. The most common causes of conversion are tumor invasion of adjacent structures or bulky tumor, adhesions, and technical failure **(44).**

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Conversion from laparoscopy to laparotomy can be expected in a variable percentage of surgeries. Patients who experience conversion to a laparotomy may have a worse outcome than those who have a successfully completed laparoscopic procedure. In a study aimed to compare the outcomes of converted cases based on whether the case was a reactive conversion (RC) due to an intra-operative complication such as bleeding or bowel injury or a preemptive conversion (PC) due to a lack of progression or unclear anatomy, preemptive conversion is associated with a better outcome than reactive conversion. Based on this finding, it appears preferable for the surgeon to have a low threshold for performing PC rather than awaiting the need for an RC ***(43).***

Laparoscopic CME with CVL

Laparoscopic CME with CVL is based on resection of the colon within its intact and inviolate mesocolon with high tie ligation, so to improve the quality of the resection specimen produced; anatomo-embryological concepts were developed, focusing on the latest studies of the mesenteric organ, its dissection by mesofascial and retrofascial cleavage planes, and questioning the need for a new terminology in colonic resections. Laparoscopic CME with CVL demonstrated better quality of the surgical specimen produced and significant survival advantage when compared to *standard* non-mesocolic resections, stressing the importance of meso-resectional surgery, especially when performed with minimally invasive techniques: higher surgical quality, faster recovery and better immunological response may in fact contribute to better long term oncologic outcome **(45).**

The concept of complete excision of the involved organ along with its primitive mesentery, associated to central ligation of the blood vessels, is progressively gaining acceptance as the next step towards a modern surgical oncology; surgical resection of the primitive embryological mesenterium is in fact pivotal for optimal local clearance. Furthermore, CVL allows for an extensive lymph node dissection along the feeding vessels, with significant effect on regional recurrence and systemic dissemination, as shown by improved survival cancers treated with enhanced lymph node harvesting **(45).**

There are three essential components of CME with CVL:

1) Development of a mesofascial or retrofascial plane to mobilize an intact and inviolate mesocolon as an intact package.
2) CVL with high tie to maximize the vertical lymph node dissection (central spread).
3) Adequate length of bowel to remove pericolic lymph nodes, maximizing the longitudinal lymph node harvesting (longitudinal spread).

CVL is essential in obtaining an adequate regional control and impact onsurvival. The latest 2010 Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines recommends D2 dissection for clinically early stages colorectal cancers and D3 dissection for more advanced disease. Impressive results in terms of local recurrence and patient's survival have been reported **(45).**

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