Chapter I
Colorectal Cancer

Epidemiology of colorectal cancer

Colorectal carcinoma (CRC) is the third leading cause of cancer death in western world. It occurs in about eight million people and it causes five million deaths each year. More than ninety percent of cases diagnosed are in people older than fifty years age. There has been an overall decrease in the incidence and mortality rates over the past twenty years mostly due to the wide spread increased screening methods and early detection along with improvement in both medical and surgical care (Cunningham et al., 2010).

In Egypt, it is the seventh leading cause of cancer death, representing about 4% of total cancers in both sexes. However, Egypt is characterized by an even distribution among different age groups with high prevalence in young people less than twenty years (more than thirty percent compared to with two to four percent in the west) (Zeeneldin et al, 2012).

Colorectal carcinoma that arises proximal or distal to the splenic flexure exhibits embryologic, morphologic, physiologic and biochemical differences confirming the assumed two sided colon theory. Both right and left colon develops from the midgut and hindgut, respectively with different lymphovascular supply. Underlying molecular and environmental factors follow that theory in most cases of CRC. However, a considerable overlap between right- and left-sided cancers is still present in some cases (Glebov et al., 2003).
Aetiology and pathogenesis of colorectal cancer:

(A) Genetic factors:

Up to 70% of the patients have sporadic form of the disease. Of the remaining 30%, a small percentage belongs to the familial syndromes, whereas the vast majority (more than 25%) shows nonsyndromic familial susceptibility and clinically inapparent inherited mechanisms. Having a single affected first-degree relative (i.e., parent, child, sibling) doubles the risk over that of the general population suggesting a dynamic multifactorial process which occurs on many interrelated levels including genetic (germline and somatic) and environmental factors driving the initiation, Promotion and progression of the disease (Labianca et al., 2010).

Fig. (1): Types of colon cancer cases that arise in various family risk settings (Burt et al., 2000).

Recognition that histologically identical tumors may have drastically different prognosis and/or response to treatment prompted the theory that, rather than a single malignancy, CRC is a heterogenous, multifactorial disease. As a result, the focus of CRC research is shifting from a clinical perspective towards developing an understanding of the molecular basis of this malignancy, including individual
susceptibility, development, progression, response, and resistance to antitumor treatment and metastatic spread. Moreover, during the last decade, CRC incidence in the Eastern population increased from two- to four-times, whereas it progressively diminished in western countries, implying yet undefined gene environmental interactions (Curtin et al., 2011).

**Hereditary colorectal syndromes:**

It accounts for 5% to 10% of cases colorectal cancer. Heald and colleagues (2012) reported many red flags for these syndromes in the personal or family history like:

1-Early age of onset of cancer (e.g. colorectal cancer before age 50).
2-More than 10 colorectal adenomas.
3-Synchronous or metachronous primary cancers.
4-Multiple relatives in successive generations with the same or related cancers.
5-Family member with a known hereditary colorectal cancer syndrome.

They can be divided into two categories and subcategories (Heald et al., 2012):

**a-Non polyposis syndrome:**

1-Hereditary nonpolyposis colorectal cancer (Lynch syndrome).
2-Familial colorectal cancer.

**b-Polyposis syndromes: 1-With adenomatous polyps:**

a-Familial adenomatous polyposis.

b-Mut Y homolog (MYH)- associated polyposis.

**2-With serrated polyps:** Serrated polyposis syndrome.

**3-With hamartomatous polyps:**

a-Juvenile polyposis syndrome.  
b- Peutz-Jeghers syndrome.  
c-Phosphate and tensin (PTEN)-hamartoma tumor syndrome.
(1) Hereditary Non-Polyposis CRC (HNPCC or Lynch syndrome):

Autosomal dominant (AD) disorder represents only 2-3% of all CRC patients with up to 80% of diseased persons develop CRC at an early age (average 40 years) than sporadic CRC. The clinical diagnosis depends on several criteria known as Amsterdam I, modified Amsterdam II and Bethesda criteria. Traditionally, HNPCC was classified as Lynch I (without extracolonic manifestations) and Lynch II (with extracolonic manifestations) (Lynch & de la Chapelle, 2003).

Muir-Torre syndrome (MTS) is considered a variant of Lynch syndrome; it is a rare disorder characterized by the presence of at least one sebaceous gland neoplasm and at least one visceral malignancy. Sebaceous adenomas, sebaceous carcinomas, and sebaceous epitheliomas are all characteristic glandular tumors of MTS (Lynch & de la Chapelle, 2003).

The genes responsible for Lynch syndrome are the MMR genes which include seven proteins (MLH1, MLH3, MSH2, MSH3, MSH6, PMS1, PMS2) which associate and form functional heterodimers. MLH (mut L homolog), MSH (mut S homolog) and PMS (postmeiotic segregation). These genes code for proteins that are responsible for DNA mismatch repair, one of the cell proofreading mechanisms during DNA replication (Jasperson et al., 2010).

Some confusion is mentioned between severe cases of HNPCC, attenuated FAP and familial CRC because of the more subtle phenotype. Patients identified as an HNPCC family on the basis of the mentioned criteria should undergo extensive counseling including genetic testing for both the patients and all at-risk relatives (Jasperson et al., 2010).
Different criteria for clinical diagnosis of HNPCC (Heald et al., 2012):

(a) Amsterdam Criteria
1-At least three relatives with colon cancer and all of the following:
2-One affected person is a first-degree relative of the other two affected persons.
3-Two successive generations affected.
4-At least one case of colon cancer diagnosed before age 50 years.
5-Familial adenomatous polyposis excluded.

(b) Modified Amsterdam Criteria

Same as the Amsterdam criteria, except that cancer must be associated with HNPCC (colon, endometrium, small bowel, ureter, renal pelvis) instead of specifically colon cancer.

(c) Revised Bethesda guidelines
1-Colorectal cancer diagnosed in a patient less than 50 years of age.
2-Synchronous or metachronous colorectal cancer or other Lynch syndrome-associated tumors, regardless of age.
3-Colorectal cancer with a high level of microsatellite instability or undifferentiated histopathologic pattern, diagnosed in a patient who is less than 60 years of age.
4-Colorectal cancer diagnosed in one or more first-degree relatives with a Lynch syndrome-related tumor, with one of the cancers being diagnosed before age 50 years.
5-Colorectal cancer diagnosed in two or more first- or second-degree relatives with Lynch syndrome-related tumors, regardless of age.

Three approaches for genetic testing are described, the first and most important is detection of the functional loss of the mutated gene product or MSI
testing using a standardized panel of five DNA markers, is performed on normal and tumor tissue. High MSI (MSI-H), in usually up to 90%-95% of tumors, when two or more markers are involved, low MSI (MSI-L) if only one marker is involved, and MSS if none. The second test is direct gene sequencing of MMR genes starting with hMLHI and hMSH II genes (contain up to 90% of all gene mutations). The third test used to detect the presence of mutations is immunohistochemistry (IHC) of the MMR genes product. However, it may give false negative results as the mutations may involve single base and no truncated protein is produced (Brand & Church, 2010).

Genetic counseling and genetic testing should be offered to at-risk relatives aged ≥18. Those whom test is negative are at the same risk as the general population. However, those identified to be an HNPCC member either aggressively and prophylactically treated or undergo clinical screening program. Clinical screening effectively reduces the CRC incidence and mortality with improved 5 year survival rate by detecting patients at an earlier stage. As these patients are at increased risk of many epithelial lined organ cancer by the age of 70 (90%, 33.5% and 10% develop CRC, endometrial carcinoma and ovarian cancer respectively). So, these 3 cancers should be regularly screened (Heald et al., 2012).

Each HNPCC adenomas patient has a more rapid growth rate (50% chance even if < 1cm size) and 70% of them develop proximal to the splenic flexure. So, colonoscopy is recommended every 1-3 years at age 20-25 years or 2-5 years before the age of the diagnosis of the youngest affected relative then annually after age 40. Females aged 25-30years underwent annual gynecological examination by transvaginal ultrasound “TVUS”, endometrial aspiration and serum CA-125) (Engel et al., 2010).
(2) Familial adenomatous polyposis (FAP):

Autosomal dominant (AD) disorder characterized by development of hundreds (sparse type) to thousands (Profuse type) visible adenomatous polyps shortly after puberty. It occurs in 1 to 8000 live birth and it is responsible for ≤1% of CRC burden usually before the age of 40 and the risk approaches 100%(without surgery) by age 50 years. Up to 25% of patients present without other affected family members and typically are diagnosed when symptoms develop from the polyps or cancer. Over 50% of these symptomatic patients have cancer at the time of diagnosis (Migliore et al., 2012).

There is a direct relationship between the site of mutation of the APC gene (located on the long arm of chromosome 5 and its protein product provides a tumor suppressor function), the phenotypic expression of the disease, age of presentation and the variability of extra colonic manifestations (Jasperson et al., 2010).

Several genotype-phenotype correlations have been identified according to the affected genetic segments (exons) and extra colonic manifestations : Gardner syndrome (desmoid tumors, epidermoid cyst, osteomas “especially in the mandible □ and proximal GIT polyps ), Turcot’s syndrome (medulloblastomas), attenuated APC (delayed onset > 15 years than classic FAP, fewer polyps < 100, usually spared splenic flexure and rectum and absent congenital hypertrophy of the retinal pigment epithelium (CHRPE) which is important landmark in up to 75% of classic FAP (Jasperson & Burt, 2011).

Most APC mutations result in a premature stop codon then a truncated (short) protein product that can be detected in up to 80% of FAP patients by the protein truncation test (PTT) on a peripheral blood sample. If PTT is negative (mutation is not found) or patient refusal, other tests like linkage analysis and direct gene sequencing should be performed. Otherwise, these families must be
evaluated by an endoscopic screening program as there are various phenotype of the disease in still unknown carrier status. The program depends on the age, site of first polyp appearance and onset of cancer development. So, it should be done annually at age 10 years (Brand & Church, 2010).

All at-risk individuals presented at a presymptomatic stage (more than 10 adenomas detected on a single colonoscopy, first-degree relatives of patients with FAP or the presence of any extra colonic manifestation prior to the onset of polyp appearance) should be tested for the same mutation usually at age 10-12 years. If positive PTT test appears, annual endoscopic surveillance should start immediately until polyps identified. However, if negative test appears, this relative has a CRC risk similar to the general population then, the genetic testing is repeated in 2-3 years, flexible sigmoidoscopy at 18, 25 and 35 years or simple dealt with as an average risk person at 50 years age (Heald et al., 2012).

Duodenal polyps affect up to 90% of FAP patients. Periampullary carcinoma represents the second most common cause of cancer death. Upper endoscopy is mandatory by age 20-25 years according to Spigelman stage (based on polyp number, size, histologic pattern and dysplasia). Patients with stage 1 or 2 are re-examined every 3 years, then every 5 years if no progression. Those with stage 3 and stage 4 are re-examined biannually and annually respectively. Large villous adenomas, severe dysplastic adenomas or duodenal cancers mandate early re-examination and if possible pancreaticoduodenectomy (Brand & Church, 2010).

(3) MYH-associated polyposis:

This is only known autosomal recessive hereditary colorectal cancer syndrome. Biallelic mutations in the MYH gene result in an adenomatous polyposis syndrome that may be indistinguishable from the attenuated or classic
forms of familial adenomatous polyposis. Synchronous CRC is seen in more than 60% of these patients. Up to 30% of patients with familial adenomatous polyposis who are APC-negative will have biallelic mutations in the MYH gene. The siblings of a patient with biallelic MYH mutations should be offered genetic counseling and testing in their late teens or early 20s. All children of an individual with MYH-associated polyposis will carry one MYH mutation and are only at risk of having the syndrome if the other parent is also a MYH carrier and passed on his or her mutation (Heald et al., 2012).

(4) Familial Colorectal Cancer:

The term familial colorectal cancer (FCC) is used to categorize CRC families that do not meet the clinical criteria for a diagnosis of known hereditary CRC syndromes. The number of affected family members and age at cancer diagnosis correlate with disease risk. A first degree relative of an affected individual diagnosed after age 50 years have a twofold to threefold increased risk of CRC. However, a first relative individual diagnosed at an age below 45 years or more than one first relative with CRC are conditions associated with a threefold to six fold increased relative risk. It is presented in some families that meet the Amsterdam I criteria but have microsatellite-stable tumors. This condition is associated with a higher risk of colorectal cancer but not the other malignancies observed in Lynch syndrome (Migliore et al., 2012).

(5) Neoplastic polyps:

Polyps can be generally classified according to Shape, Size, site, Prevalence, and being Precancerous or not into:

a- Lesions of the adenoma-carcinoma pathway:

Adenomatous polyps are thought to carry a risk of malignant transformation. The risk of invasive carcinoma is related to size, shape and
histology of the polyps. It is rare in polyps less than 1 cm and up to 35–40 % in those more than 2 cm. Flat sessile villous polyps may harbor cancer in up to 40 %, where is tubular pedunculated adenomas carry a risk of 5% only. Haggit proposed a classification for polyps containing cancers according to the depth of invasion. All sessile polyps with invasive carcinoma are level 4 by Haggit criteria. The incidence of lymphatic metastasis is higher than 15 % when the depth of invasion by cancer reaches the neck or the stalk of the pedunculated polyp and that of the head seldom metastasizes. The incidence of lymph node metastasis is approximately 8% and 15 % for pedunculated and sessile polyps respectively if one or more unfavorable criteria are present (incomplete endoscopic resection, involved resection margin, poorly differentiated histologic features, lymphatic or vascular invasion and finally evidence of invasive carcinoma) (Burkitt et al., 2012).

Table (1): Haggit classification for polyps (Bernard, 2004):

<table>
<thead>
<tr>
<th>Level</th>
<th>Depth</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level 0</strong></td>
<td>Carcinoma does not invade the muscularis mucosa (carcinoma in situ).</td>
</tr>
<tr>
<td><strong>Level 1</strong></td>
<td>Carcinoma invades through the muscularis mucosa into the submucosa but is limited to the head of the polyp.</td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
<td>Carcinoma invades the level of the neck of the polyp.</td>
</tr>
<tr>
<td><strong>Level 3</strong></td>
<td>Carcinoma invades any part of the stalk.</td>
</tr>
<tr>
<td><strong>Level 4</strong></td>
<td>Carcinoma invades into the submucosa of the bowel wall below the stalk but above the muscularis propria.</td>
</tr>
</tbody>
</table>
b-Lesions of the serrated neoplasia pathway (Makkar et al., 2012):

i. **Hyperplastic polyps**: It includes 2 types:
   1. Goblet cell-rich type (GCHP).
   2. Microvesicular type (MVHP):

ii. Sessile serrated adenoma (SSA).

iii. Traditional serrated adenoma (TSA).

iv. Mixed serrated polyp (MP).

6-Hamartomatous Polyposis Conditions: Peutz-Jeghers, Juvenile Polyposis and Cowden syndromes:

Peutz-Jeghers syndrome (PJS) is an inherited, AD disorder distinguished by hamartomatous polyps in the gastrointestinal tract and pigmented mucocutaneous lesions, typically presenting in childhood on the lips, buccal mucosa, and perioral region. Juvenile polyposis syndrome (JPS) is a rare, AD early-onset disease, characterized by the presence of hamartomatous polyps throughout the gastrointestinal tract. The lifetime CRC risk in JPS individuals is estimated to be 39%. Cowden syndrome (CS) is another rare AD hamartomatous polyposis condition. 27%–43% of CS patients have been shown to have hamartomatous polyps in the gastrointestinal tract; however, CS seems to confer little, if any, CRC risk (Migliore et al., 2012).

**B) Dietary Factors:**

A diet rich in saturated or poly unsaturated animal fats increases the risk of CRC while a diet rich in oleic acid ( olive oil, coconut and fish oil ) does not increase it. A diet rich in vegetable fibers (the whole grain cereals, cellulose and bran) appears protective in comparison with red meat. These factors act by factors either a direct toxic effect on the mucosa or indirectly by forming stool bulk which stimulates the motility and decreases the exposure to the mutagenic effect of many.
heterocyclic amines and bile acids on the mucosa. Calcium, selenium, vitamins A, C and E, and carotenoids decrease the risk of CRC (O’Hagan 2013).

C) Hormonal factors:

Elevated growth and insulin hormones increase the risk but post-menopausal hormonal is protective up to 5 years after stoppage of the treatment (Niemin en et al., 2012).

D) Inflammatory bowel disease (IBD):

The duration and extent of inflammatory bowel disease (IBD) correlate with the risk of developing CRC especially in the presence of primary sclerosing cholangitis and family history of CRC. Screening colonoscopy is recommended with multiple random mucosal biopsies (Cuschieri & Robert, 2013).

E) Alcohol & smoking:

Daily alcohol intake has been associated with two fold increase in CRC. Cigarette smoking is associated with increased risk of CRC especially after more than 35 years of intake. Both tea and coffee has been suggested as protective measures (Niemin en et al., 2012).

F) Drugs:

Regular use of aspirin and NSAIDS has been suggested to decrease the risk of CRC mostly due to its COX-II enzyme isoform inhibitory effect (O’Hagan 2013).

G) Other risk factors:

They include pelvic irradiation (either a direct effect or damage effect), non-cancer surgery including cholecystectomy and ureterosigmoidostomy after more than 20 years from primary surgery with unclear explanation (Niemin en et al., 2012).
Histopathology of Colorectal cancer:

The distribution of the cancers in the colorectum is as follows: caecum & ascending colon 22%; transverse colon 11%; descending colon 6%; rectosigmoid colon 55%; and other sites 6%. Ninety-nine percent of carcinomas occur singly, but when multiple carcinomas are present, they are often at widely disparate sites in the colon (Chen & James, 2010).

A-Gross appearance (El-Bolkainy, 2013):

1) **Fungating polypoid carcinoma:** This form tends to be more common in the right colon. It is frequently a very large, soft, friable growth. Ulceration and hemorrhage are common, leading to anemia. Generally, polypoid cancer has a better prognosis than other lesions.

2) **Annular carcinoma:** This is the commonest type of growth and is typical of those neoplasms at the rectosigmoid junction. The tumor is actually a malignant ulcer that progresses to stenosis and then obstruction.

3) **Diffuse carcinoma:** This type produces a condition similar to that seen in the "leather-bottle" or linitis plastica of the stomach.

4) **Ulcerative carcinoma:** This type predominates on the left colon as atypical malignant ulcer and presents mainly with bleeding per rectum

**Fig. (2):** Gross picture: a- Annular lesion. b- Polypoid lesion.

**Fig.2(a&b)**(Singh et al., 2011).
B- Microscopic appearance (Singh et al., 2011):

(1) Colorectal cancer:

World Health Organization (WHO) classification of colorectal carcinoma:

1- Adenocarcinoma
2- Adenosquamous carcinoma.
3- Mucinous (colloid) adenocarcinoma
4- Signet ring cell carcinoma.
5- Small cell carcinoma (oat cell).
6- Squamous cell carcinoma.
7- Undifferentiated carcinoma.
8- Medullary carcinoma.

![Microscopic picture: a- Mucinous type. b- Undifferentiated type.](image)

Fig. (3): Microscopic picture: a- Mucinous type. b- Undifferentiated type.

Fig 3(a&b)(Singh et al., 2011)

(2) Neoplastic polyps (Makkar et al., 2012):

a) Traditional tubulovillous adenoma: characterized by round, straight crypts lined with epithelial cells with elongated and pseudostratified nuclei.

b) Hyperplastic polyps: Typically small (≤ 5 mm) polyps in the distal (rectosigmoid) bowel with normal architecture and proliferation. This is only non precancerous type. It includes 2 types:

1) **Goblet cell-rich type** (GCHP): have abundance of mature goblet cells in the upper crypt.

2) **Microvesicular type** (MVHP): have mostly enlarged microvacuolated columnar cells in the upper crypt.
c) **Sessile serrated adenoma (SSA):** Distinction from hyperplastic polyps based mainly on abnormal architectural features including branching crypts, dilated crypt bases, and lateral growth of crypts parallel to the muscularis mucosa, resembling a letter \( t \) or \( L \). It is \( \geq 10 \) mm and more prevalent in proximal colon. It does not usually demonstrate cytological dysplasia; if an area of dysplasia is present, this should be clearly specified and the polyp could be included in the mixed polyp category.

d) **Traditional serrated adenoma (TSA):** This category does not include sessile serrated adenomas with conventional dysplasia; rather, these polyps are defined by an overall protuberant growth pattern with viliform projections, \(< 10 \) mm, more in the distal colon and contain cytologically dysplastic cells with elongated nuclei and eosinophilic cytoplasm. They have abundant ectopic crypts (budding crypts) in the long, slender villi.

e) **Mixed serrated polyp (MP):** Individual components should be listed from different previous types.
Fig. (4a): Hyperplastic polyps.

Fig. (4b): Tubular adenoma.

Fig. (4c): Sessile serrated polyps.  Fig. (4d): Traditional serrated adenomas.

Fig. (4a, b, c, d): Different types of polyps (Makkar et al., 2012).
Modes of Spread of CRC (Danciu et al., 2002):
Carcinoma of the colon may spread in different ways:

1- **Direct spread:** This is more important in the rectum as it is located in the true pelvis with close relationship to the adjacent organs and the mesorectum with its enveloped fascia forms a barrier against invasion.

2- **Intramural spread:** Malignant cells shed from the surface of the tumor can be swept along in the fecal current. Implantation more distally on intact mucosa occurs rarely, if ever, but viable exfoliated cells presumably can be trapped in an anastomotic suture or staple line during operation.

3- **Lymphatic spread:** This is the most common form of tumor spread. Lymph nodes draining the colon are grouped as follow:
   - N1–nodes in the immediate vicinity of bowel wall.
   - N2–nodes arranged along the ileocolic, right colic, middle colic and left colic arteries.
   - N3–the apical nodes around the superior and inferior mesenteric vessels where they arise from the abdominal aorta.
   - Involvement of the lymph nodes by the tumor progresses in a gradual manner from those closest to the growth along the course of the lymphatic vessels to those placed centrally. Retrograde lymphatic spread into the internal iliac and inguinal lymph nodes may occur in some cases.

4- **Haematogenous spread:** This accounts for a large proportion (30-40 percent) of late deaths. Metastases are carried to the liver via the portal system sometimes at an early stage before clinical or operative evidence is detected (occult hepatic metastases). The liver is the most common site of haematogenous spread of colorectal cancer; liver metastasis occurs in about half of all cases. The lung is the second most common site of metastasis for colorectal tumors. Tumor involvement of other sites in the absence of liver and lung metastases is unusual. In certain
circumstances, isolated bone metastases to the sacrum or vertebral bodies can arise from tumor embolism by portal–vertebral venous communications known as the Batson plexus.

5- Transcelomic spread: It follows penetration to the serosal surface and causes ascites. Cells may also be implanted on the ovaries. Surprisingly transperitoneal dissemination of colorectal cancer is relatively unusual. When it occurs however, it is associated with a grave prognosis. Mucinous cancers are most prone to spread in this manner.

Staging of CRC (Choti, 2011):

Many staging systems have been devised to help predict the patient prognosis and select additional therapies to compare the outcome of various treatments for patients with a similar expected outcome. Different prognostic staging systems are shown in table (3).

Table (2): CRC different staging systems in relation to local recurrence and 5-year survival (Choti, 2011):

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>Dukes’</th>
<th>Modified Astler-Coller</th>
<th>Local recurrence(%)</th>
<th>5-year Survival%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis N0 M0</td>
<td>A</td>
<td>A</td>
<td>&lt;5</td>
<td>93</td>
</tr>
<tr>
<td>I</td>
<td>T1-2 N0 M0</td>
<td>A-B1</td>
<td>B2</td>
<td>8</td>
<td>85</td>
</tr>
<tr>
<td>IIA</td>
<td>T3 N0M0</td>
<td>B</td>
<td>B3</td>
<td>15</td>
<td>72</td>
</tr>
<tr>
<td>IIB</td>
<td>T4 N0M0</td>
<td>B</td>
<td>C2-C3</td>
<td>10</td>
<td>64</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-2 N1M0</td>
<td>C</td>
<td>C1</td>
<td>6</td>
<td>83</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3-4 N1M0</td>
<td>C</td>
<td>C1-2-3</td>
<td>18</td>
<td>44</td>
</tr>
<tr>
<td>IIIIC</td>
<td>Any T N2M0</td>
<td>C</td>
<td>D</td>
<td>-</td>
<td>0-16</td>
</tr>
<tr>
<td>IV</td>
<td>Any T, any N M1</td>
<td>D</td>
<td>-</td>
<td>-</td>
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</table>

T: Tumour, N: node, M:metastasis.

Tumor remaining in the patient after primary surgical resection (e.g., corresponding to a proximal, distal, or circumferential resection margin that is shown to be involved by tumor on pathologic examination) is categorized by a
system known as R classification, which is as following (Alberts & Richard, 2011):
RX: Presence of residual tumor cannot be assessed.
R0: No residual tumor.
R1: Microscopic residual tumor.
R2: Macroscopic residual tumor.

In contrast to residual disease, tumor that is locally recurrent after a documented disease-free interval after surgical resection should be classified according to the TNM categories and modified with the prefix "r" (e.g., rpT1). By convention, the recurrent tumor is topographically assigned to the proximal segment of the anastomosis unless the proximal segment is small intestine (Alberts & Richard, 2011).

In terms of staging, identification of distant metastatic disease is more important than T-and N-staging in colon cancer as it may justify up front systemic chemotherapy rather than an initial tumor resection. For rectal cancer, accurate T- and N-staging is essential for the extent of mesorectal resection and to determine whether neoadjuvant therapy and a sphincter-salvage procedure can be performed (Chang & Feig, 2011).

**Screening and surveillance:**

The rationale for screening for CRC comes from the fact that most cases progress through an adenoma- carcinoma sequence, a process that may take up to 10 years. The goal of screening is to prevent cancer development by identification and removal of premalignant lesions. In addition many cancers are asymptomatic and screening may detect these tumors at an early curable stage reducing cancer-related mortality. The life time risk of developing CRC increases with a family history of the disease being 6% in average risk population but rises to 12% and 35% if one first degree relative and two first degree relatives are affected
respectively. Screening of average risk individuals is recommended at age 50 but those at high risk (two folds as normal) should be screened earlier at age 40 and more frequently (Chang et al., 2011).

Surveillance after polypectomy and previous colon resection is recommended after 3 years interval (at risk of metachronous and recurrent original cancer) choosing the procedure should be suitable to the normal anatomic distortion and adhesions. Patients at risk for hereditary syndromes should be screened earlier and more frequently with genetic counseling and testing and consider prophylactic surgery in some selected cases. The age to stop screening and surveillance depends on many factors which are variable between the population and their clinicians. Advantages and disadvantages of different methods are shown in table (3) (Levin et al., 2008).

Table (3): Advantages and disadvantages of different modalities for asymptomatic individuals (Levin et al., 2012):

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fecal occult blood testing</td>
<td>Ease of use and noninvasive, low cost and good sensitivity with repeat testing.</td>
<td>May not detect most polyps, low specificity, poor compliance with serial testing and colonoscopy required for positive result. Cannot be used in Egypt due to parasitic infestations.</td>
</tr>
<tr>
<td>Procedure</td>
<td>Description</td>
<td>Advantages</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Sigmoidoscopy</strong></td>
<td>Examines colon most at risk, does not require full bowel preparation (enemas only) and very sensitive for polyp detection in left colon.</td>
<td>Invasive, uncomfortable, slight risk of perforation or bleeding, may miss proximal lesions and colonoscopy is required if polyp identified.</td>
</tr>
<tr>
<td><strong>Colonoscopy</strong></td>
<td>Examines entire colon, Highly sensitive and specific and therapeutic.</td>
<td>The most invasive, costly, uncomfortable and requires sedation, requires bowel preparation and high risk of perforation or bleeding.</td>
</tr>
<tr>
<td><strong>Double-contrast barium enema</strong></td>
<td>Examines entire colon and good sensitivity for polyps &gt;1 cm.</td>
<td>Requires bowel preparation, less sensitivity for polyps &lt;1 cm, may miss lesions in the sigmoid colon and colonoscopy is required for positive result.</td>
</tr>
<tr>
<td><strong>Computed tomographic colonography (virtual colonoscopy)</strong></td>
<td>Examines entire colon, Noninvasive, Sensitivity may be as good as colonoscopy.</td>
<td>Costly, Requires bowel preparation, minimal experience and data, Insensitive for small polyps and in positive result colonoscopy is recommended.</td>
</tr>
</tbody>
</table>
1- Fecal occult blood test (FOBT):

A guaiac based test for peroxidase activity performed on 6 samples, 2 samples from each of 3 consecutive stools. Positive test is detected if a blue color appears on adding hydrogen peroxide to the rehydrated samples. Colonoscopy is recommended if any of the 6 samples is positive as there is 50% chance of cancer or large adenoma > 1cm (Levin et al., 2003). False positive results are common in Egypt due to endemic parasitic infestation with ascaris and ancylostoma even if the stool was negative for ova or adult parasitic organisms (Hassan et al. 2012). An immunologic test for occult blood in stool that detects human haemoglobin is recently available, although specific as no need to avoid eating meat or using 3 consecutive samples, shows low sensitivity at detecting adenomas and CRC (Tsang AHF et al., 2014).

2- Flexible sigmoidoscopy:

Sigmoidoscopy (60 cm) is introduced 1-2 hours after single or double saline laxative or phosphor soda enemas without sedation or analgesia. A positive result means the presence of any polyp > 1 cm in diameter, small polyps with high risk synchronous or metachronous lesion (≥ 3 in number, villous type and severe dysplasia) mandate full colonoscopy (Atkin, 2002).

3- Double contrast (air-contrast) barium enema (DCBE):

It has been used as a back-up examination if colonoscopy is incomplete. It improves mucosal details of the whole colon in 90-95% of cases but with limited accuracy in rectosigmoid region. So, it should be combined with sigmoidoscopy (Cuschieri & Robert, 2013).

4- Colonoscopy:

The most sensitive for identifying small polyps < 1 cm and allows biopsy of the polyp to detect whether it is adenomatous or not and safe endoscopic removal. Chromoendoscopy and other high-definition magnification techniques
improve detection of serrated polyps by approximately 2 fold. New endoscopic technologies might prove to be useful and perhaps more time-efficient than chromoendoscopy in detecting serrated polyps (Burkitt et al., 2012).

5- Genetic testing:

About 80% of affected individuals of the families of the familial syndromes are carriers of the known gene mutation. If the blood is available from a clinically affected relative and a genetic mutation has been identified, it is possible to determine if other members are carriers because the genetic mutation is constant. A negative test of an individual from a family that has affected member with a positive test essentially rule out the disease. However, a negative test in the absence of a positive test in the family does not rule out the disease (Migliore et al., 2012).

6- DNA-based stool test:

The amount of epithelial DNA derived from cells shed from neoplastic lesions and extracted from the stool by polymerase chain reaction (PCR) is increased by less efficient degradation by apoptotic cells in comparison with fully differentiated cells (Ahlquist et al., 2000).

Table (4): Colorectal cancer screening and surveillance guidelines in average risk and increased risk population (Levin et al., 2012).

<table>
<thead>
<tr>
<th>Population</th>
<th>Initial Age</th>
<th>Recommended Screening Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average risk</td>
<td>50 y.</td>
<td>Annual FOBT or Flexible sigmoidoscopy every 5 y or Annual FOBT and flexible sigmoidoscopy every 5 y or Air-contrast barium enema every 5 y or Colonoscopy every 10 y.</td>
</tr>
<tr>
<td>Condition</td>
<td>Frequency</td>
<td>Protocol Description</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Neoplastic polyps</td>
<td>50 y.</td>
<td>Colonoscopy at first detection, colonoscopy in 3y, If no Further polyps found then colonoscopy done every 5 y, If polyps found, colonoscopy is done every 3 y. Annual colonoscopy for &gt;5 adenomas. Colonoscopy every 1–2 years with the aim of removing all polyps &gt; 5 mm in size (serrated polyps).</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>At diagnosis.</td>
<td>Pretreatment colonoscopy; then at 1 year after curative resection; then colonoscopy after 3 y; then colonoscopy every 5 y if no new lesions.</td>
</tr>
<tr>
<td>Ulcerative colitis, Crohn's colitis</td>
<td>At diagnosis; then after 8 y for pancolitis, after 15 y for left-sided colitis.</td>
<td>Colonoscopy with multiple biopsies every 1–2 y.</td>
</tr>
<tr>
<td>Attenuated FAP</td>
<td>20 y.</td>
<td>As FAP.</td>
</tr>
<tr>
<td>HNPCC</td>
<td>20–25 y or 10 y before the age of the youngest affected relative then annually after age 40 y.</td>
<td>Colonoscopy every 1–2 y Endometrial aspiration biopsy every 1–2 y.</td>
</tr>
<tr>
<td>Familial colorectal cancer (FDRs)</td>
<td></td>
<td>Colonoscopy every 5 y then Increase frequency if many family members are affected, especially before 50 y.</td>
</tr>
</tbody>
</table>
Diagnosis and preoperative evaluation:

Symptoms of CRC are non-specific and generally developed when the cancer is locally advanced. Complete history (including a detailed family history) and physical examination is necessary to also assess any comorbid conditions. Patients may be diagnosed in three different pictures: colorectal cancer outside a screening program, interval cancer within a screening program and an early age of onset due to evaluation of symptoms or finding on examination (Mortensen & Ashraf, 2013).

Different bowel caliber, tumor growth pattern and stool character often dictate the type of symptoms in both right-sided tumors (anemia, poor appetite and loss of weight) and left-sided tumors (change in bowel habits with progressive constipation and bleeding per rectum). Colon cancer may present with acute symptoms in the form of obstruction, perforation or localized abscess. However, rectal cancer rarely presents as an emergency but usually present with sense of incomplete evacuation and spurious morning tenesmus. Pain is usually late due to sacral plexus and adjacent organ infiltration (Browse et al., 2012).

Digital rectal examination (DRE):

It is accurate in up to 80% of cases in experienced hands. It gives idea about the tumor site, size, mobility, extent of circumferential envolvement (1/4 of the wall circumference is invaded every 6 months) and finally the relationship to the anorectal ring rather than the distance of the mass from the anal verge which is a variable non-dependent landmark (Cuschieri & Robert, 2013).

Computed tomography (CT) of the chest and abdomen:

It helps identifying advanced metastatic disease, as up to 20% of colon cancer patients have metastatic disease at the time of presentation, which may limit the extent of surgery to minimize morbidity. However, if it is resectable and potentially curable it may allow more intraoperative ultrasonographic assessment
for possible combined surgical approach. CT is reliable for confirming rather than excluding spread of advanced tumors through the bowel wall. CT rule (especially Coronal views) is more established in rectal than colonic cancer especially in staging of locally advanced disease or if CEA is elevated  5 ng /ml and cases of pre- and postoperative tumor-related complications (obstruction, perforation and fistula formation) (Feig, 2012).

**Dynamic contrast enhanced subtraction (DCES) multiplanar MRI with gadolinium:**

It is more accurate in adjacent soft tissue invasion and it often complements CT findings. Positive criteria include asymmetric thickening of bowel wall especially if 6 mm, obliteration of perianastomotic fascial or fat planes, presacral or lateral side wall mass or enlarged lymph nodes. It is highly efficient in recurrent cases especially if done 2-4 months after completion of adjuvant therapy (Ahuja, 2011).

**Endorectal ultrasound (ERUS):**

It is superior to CT and MRI for locoregional staging. The accuracy of ERUS in determining both the depth of invasion (T stage) and nodal status (N stage) is 80-95% and 65-75% compared with 65-75% and 55-65% for CT and 75-85% and 60-65% for MRI respectively. ERUS visualize the gut wall as a 5 multilayer structure, the first, third and fifth are hyperechoic but the second and fourth are hypoechoic. The peri-rectal fat has a mixed appearance as the fat itself is hypoechoic but the metastatic peri-rectal lymph node appears oval echo-poor lesions. Staging according to the depth of invasion is shown in table (6) (Chang et al., 2011).

Other advantages of ERUS is to detect pre-symptomatic local recurrence at an early stage especially if combined with color Doppler (to distinguish viable tumor from fibrosis) and allow ultrasound guided fine needle aspiration of
suspected tissue and positive lymph nodes especially if < 5mm that improves the accuracy of staging (Maor et al., 2006).

**Table (5): Endorectal ultrasound staging of CRC (Chang et al., 2011).**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Depth of invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tu1</td>
<td>Lesion confined to submucosa with intact bright middle hyperechoic layer</td>
</tr>
<tr>
<td>Tu2</td>
<td>Lesion invading the muscularis propria with no disruption of the peri-rectal fat or serosa</td>
</tr>
<tr>
<td>Tu3</td>
<td>Lesion penetrates through the peri-rectal fat. The tumor edge is irregular with saw tooth projection</td>
</tr>
<tr>
<td>Tu4</td>
<td>Lesion invades an adjacent structure</td>
</tr>
</tbody>
</table>

**Figure (6):** Endoscopic ultrasound image of a T2 rectal cancer invading through submucosa and extending into superficial muscularis propria (arrow) (Maor et al., 2006).
Limitations to ERUS is being operator dependent and need more learning curve. Over staging especially with early stage disease (T2) is due to desmoplastic inflammatory reaction, hypervascularity and hemorrhage from biopsy site, tangential rather than perpendicular scanning and difficult resolution by the rectal anatomy. Under staging is overlapped by the three dimensional ERUS, high frequency many probes, contrast enhancement with microbubbles and color Doppler imaging (Garcia-Aguliar et al., 2002).

**Virtual colonoscopy:**

It is a relatively new radiologic technique using helical CT and 3D reconstruction to detect intraluminal colonic lesions. Oral bowel preparation, stool tagging with both oral and rectal high density and diluted solid (diluted barium) and liquid (iodinated contrast) to distinguish small stool particles from polyps combined with colon insufflation (colon relaxation then rectal tube insufflation by air using either 1-2 L room air or carbon dioxide 3-4 L and the later is better as well tolerated and absorbed). The image starts on left lateral decubitus then supine and prone position to ensure adequate colonic distention and shifting of the residual stool away from the wall. It is helpful non co-operative frail patients but it may miss small flat lesions (Levin et al., 2003).

**Fluorine 18-labeled–deoxy glucose positron emission tomography (18F- FDG-PET):**

It is a functional imaging technique by visualizing metabolic active cells through its uptake for the glucose analogue. Giving the expense of it, its limited accuracy for detecting small lesions < 1cm, primary and recurrent mucinous cancer and false positive results with inflammatory lesions, it does not qualify as a screening modality in its present form. PET-CT gives more anatomical details and is useful in suspected occult unresectable recurrence in an asymptomatic and potentially
curable stage especially with unexpected CEA levels and equivocal or non conclusive other imaging (Leibold et al., 2011).

Figure (7): Colorectal cancer showing metastatic disease to the liver on FDG PET imaging. The heart shows the most FDG uptake (normal). Two foci of increased FDG uptake showing cancer in the liver (left). Rectal cancer on PET/CT imaging (right) (Ahuja, 2011).

Treatment of Colorectal cancer

(A) Principles of surgical treatment:

The aim of surgical therapy with curative intent is to achieve complete removal of the primary tumor with adequate tumor-free margin, an anatomically complete lymphadenectomy along with its lymphovascular supply and enblock resection of any involved adjacent organs. Otherwise, all other therapy is either adjunctive or palliative. The best operative approach and resection for each patient depends on many factors including age, body habitus, medical co-morbidities, extent of tumor burden and feasibility of laparoscopic surgery. However, all operations with curative aim must include a detailed exploration to exclude metastasis in the liver, omentum, peritoneal surfaces, ovaries and Douglas pouch, para-aortic lymph nodes and locally advanced disease (Cuschieri & Robert, 2013).
Any suspicious lesion is biopsied to provide a tissue diagnosis for disseminated metastases. The presence of synchronous cancers, adenomas or a strong family history means that the entire colon is at risk for carcinoma (often called a field defect) and subtotal or total colectomy should be considered. Metachronous tumors (a second primary colon cancer) identified during follow up should be treated similarly giving attention to the previous ligated vessel at the initial colectomy (Mortensen & Ashraf, 2013).

Colorectal cancer can spread through transmural submucosal lymphatics (more important distally) and vascular channels (more important proximally). So, the proximal and distal resection margins up to 5 cm are adequate, but a 2 cm measured fresh with the use of full thickness is the minimally accepted distal margin for sphincter preservation in rectal cancer with the same survival and local control. High vascular ligation allows more radical LN dissection especially the apical ones (Feig, 2012).

At least 12 lymph nodes should be removed and pathologically assessed specially with fat clearance in order to accurately determine the N stage of CRC tumors to ensure adequate adjuvant therapy and to achieve a good prognostic value. Less than 40% of patients receive adequate lymph node evaluation. Examination of fewer nodes is associated with the risk of under staging and inaccurate diagnosis of node-negative disease along with inaccurate 5-year survival and so, inappropriate deprivation of beneficial chemotherapy as in some cases of stage II cancers (Saclarides, 2010).

The “no-touch” isolation technique begins with medial to lateral lymphovascular ligation, proximal and distal bowel division and then mobilization of the colon and tumor-bearing segment from its attachments to avoid intravascular and intraluminal tumor dissemination. Whether this technique results in a decreased incidence of metastasis, improved 5-year survival and local control
remains controversial. However, this technique is more reasonable in locally advanced disease where early mobilization is associated with high incidence of bleeding, tumor perforation and adjacent organ injury (Chang & Morris, 2011).

About 20% of CRC presents as an emergency, mainly obstruction, perforation and less commonly lower gastrointestinal bleeding (LGIB). The surgical options for managing obstructed colon cancer are the same as those for colonic obstruction in general, but the former is usually an advanced case with bad prognosis. These options include proximal diversion with delayed resection (3 stage operation), segmental resection without anastomosis, segmental resection with intraoperative colonic lavage and primary anastomosis (single stage operation), subtotal colectomy with ileorectal anastomosis, bypassing the obstructed segment and finally stenting whenever possible followed by single stage operation in acute obstruction (Brand, 2010).

All these options depend on the site of obstruction, the stage of the cancer, the surgeon experience and the degree of acute and chronic illness of the patient. Proximal diversion is indicated only in unresectable cancer (smaller risk of permanent colostomy) or prohibitive operative risk. Both single stage operation and subtotal colectomy with ileorectal anastomosis, although considered the operation of choice by many surgeons, have the same mortality and complication rate regarding the anastomotic leak rate (5% and 9% respectively). However, colectomy is reserved for synchronous cancers, caecal ischemia, perforation or massive colonic dilatation, younger age less than 60 years, absence of fecal peritonitis, completely obstructed sigmoid cancers and predominantly right sided cancer (e.g. HNPCC) (Choti, 2011).

Unlike colon cancer, in addition to curative resection, local control and restoration of intestinal continuity; preservation of genitourinary and anorectal sphincteric functions is mandatory whenever possible in rectal cancer. Selection of
the proper surgical options involves multiple factors including the T stage, the N stage, the size of the tumor, degree of circumferential involvement of the tumor, tumor site in relation to the anorectal ring and patients’ body habitus (Ahuja, 2011).

The anatomy of the pelvis and proximity of other structures makes rectal resection more challenging and more associated with high local recurrence rate. However, the relative paucity of small bowel makes radiotherapy easier in treatment. Upper rectal lesions (10-15 cm from the anal verge) are treated similarly to sigmoid cancer as it is rarely fixed to surrounding structures. So, no need for preoperative radio- or chemo-therapy. Biologically, upper rectal lesions have a recurrence rate comparable to those of sigmoid colon, but is generally lower than that reported from mid- (5-10 cm from the anal verge) and distal (< 5 cm from the anal verge) rectal cancers (Saclarides, 2010).

Any mid- or distal rectal lesion confined to the mucosa and submucosa (Tu1) can be treated by trans-anal, transphincteric or trans-sacral excision, unless having high risk features, with great care to achieve full thickness excision and avoid peritoneal violation specially in upper rectal lesions. These high risk features include poorly differentiated lesions, lymphovascular or perineural invasion, tumor > 3cm, mucinous tumors and unclear histopathological margins (Bullard & Rothenberger, 2007).

Transanal endoscopic microsurgery (TEM) overcomes the limitations of the conventional instruments in selected upper rectal lesions. This procedure uses a 40 mm diameter rectoscope available in lengths 12 and 20 cm, and long shafted instruments that are operated and inserted in parallel through the face piece of the scope. CO₂ insufflation, suction and saline irrigation are regulated so that the intrarectal pressure is maintained at about 15 cm water. After trans-anal excision, if the lesion is proved to be a pathological T2 lesion (penetrate the muscularis propria
or beyond it) then low anterior resection (LAR) is the standard therapy. Otherwise, recurrence rate up to 30% could be expected (Saclarides, 2010).

Endocavitary radiation (high-dose radiation given in multiple sessions at total dose 12000 cGY with 6mm depth of penetration) and fulguration (repeated tumor debulking by electrical current) are usually used as a palliative therapy in high risk patients or medically unfit for major surgery. However, it may be used, combined with external beam irradiation, as a curative method in small (< 3cm), accessible and superficial lesions. The exact depth of invasion and accurate pathological analysis are usually missed in the previous methods. Postoperative irradiation and chemotherapy is considered in rectal lesions proposed to be Tu2, N0 (preoperatively) that has been proven to be pathologically T3 or higher or N1 disease (Chang & Feig, 2011).

Mid-and distal rectal ≥ T3 or (N1) cases, preoperative neoadjuvant chemoradiation followed by total mesorectal excision (TME) and coloanal anastomosis whenever sphincteric preservation is possible with or without reservoir and diverting stoma for 3 months. Conventional surgery with blunt pelvic dissection violates the mesorectal circumference leaving residual mesorectum with positive radial margin in 20-33% of patients despite negative proximal and distal resection margins. Of these cases, 80-85% has been shown to develop local recurrence within 2 years (Saclarides, 2010).

Total mesorectal excision (TME) is a technique that uses sharp dissection in the avascular loose areolar tissue between the visceral fascia covering the mesorectum and the parietal fascia enveloping the pelvic wall structure to ensure complete resection with less blood loss, improved long-term survival rates and preserved genitourinary function. This technique passes along the inner space leaving the pelvic nerve plexus on both lateral sides. This allows complete clearance of lymphatics passing up to the origin of the inferior mesenteric artery
(IMA), thus suitable for rectal cancers > 5cm above the dentate line. However, in low rectal cancers (< 5cm from the dentate line), dissection of the intermediate and outer spaces around the internal iliac artery (IIA) is mandatory to remove the obturator (lateral) nodes with preservation of the obturator nerve. Concerns about TME especially in upper rectal lesions include potentially higher anastomotic leak rate from devascularization, worsening postoperative bowel function and ineffectiveness of this procedure to deal with positive lateral margins (Farquharson & Moran, 2005).

Thirty five years ago, abdominoperineal resection (APR) with permanent colostomy was the standard operation for about two thirds of patients with rectal cancer. However, the recognition that a 2 cm distal safety resection margin is adequate, the availability of stapling devices and the appreciation that complete rectal mobilization is necessary before deciding whether a sphincter saving procedure is possible, led to the increased rate of LAR and decreased rate of APR to be accepted for only about 20% of cases (Heald, 2007).

Laparoscopic colorectal surgery by skilled experienced surgeon is comparable to open surgery but still technically more challenging. Theoretical advantages of laparoscopic surgery are achieved. However, concerns about difficult localization of small lesions (can be overcome by intraoperative colonoscopy and preoperative tattooing) and some risk of trocar site tumor implantation are still discussed (Janjan et al., 2005).

(B) Treatment of locally recurrent CRC:

About 30-50% of patients will develop local recurrence within the first 2 years after curative resection of the primary CRC. The postoperative follow up aims at early detection of these patients. So, the likelihood of potential curative resection is increased. After the diagnosis of recurrence is confirmed by both IV and oral contrast CT chest-abdomen-pelvis to exclude distant metastatic disease.
DCES MRI with gadolinium and PET CT may be more accurate in differentiating fibrosis from pelvic recurrence. The strategy of management is based on the presence of extrapelvic (disseminated) disease, local resectability and symptoms related to affected invaded structures (Feig, 2012).

Local recurrence can be anatomically classified into axial (perianastomotic in sphincter saving procedure, mesorectal in LAR and perineal in abdominoperineal resection (APR), anterior (genitourinary tract), posterior (sacrum) and lateral (pelvic side wall). Pelvic exentration with or without partial resection of ureters, major vessels including iliac ones is a technically challenging and potentially morbid procedure specially if combined with sacrectomy which carries high risk of significant bleeding and sacral nerve root damage. Therefore, it should not be attempted unless an R0 resection is anticipated in the presence of bilateral ureteric stents whenever possible especially if bladder involvement is suspected (Chang et al., 2011).

Patients with symptomatic local recurrence will be assessed for resectability. Diagnostic laparoscopy may help identify unresectable masses (25-50% of cases), involvement of peritoneum, omentum, liver (occult small metastasis) and periaortic lymph nodes. Moreover, laparoscopically directed intraoperative ultrasonoraphy (IOUS) will exclude any occult liver metastases. If unresectable extrapelvic or locally recurrent disease is detected and confirmed by frozen section, a laparoscopically assisted loop colostomy or ileostomy is an option in cases with proximal impending obstruction (Kaiser et al., 2011).

Other options for lesions within 10-12cm include; radiation, fulguration, stenting, CT-guided radiofrequency ablation(if the tumor more than 4cm)or bypass are done for symptomatic cases(pain, bleeding, neurologic and pressure symptoms) until chemoradiation produces an effect unless there is entrapment of small bowel in the pelvis following the initial resection or progression to complete
obstruction by the effect of edema specially after radiotherapy (a lumen of at least 1 cm should be maintained). In patients with asymptomatic local recurrence and resectable distant disease, treatment should be offered judiciously. Selected cases will get benefit from resection of 2 isolated sites (e.g. pelvis with liver or lung) (Chang et al., 2011).

(C) Treatment of high risk premalignant conditions:

1- Hereditary Non-Polyposis CRC (HNPCC):

Patients with HNPCC presented with a polyp should be biopsied or removed endoscopically unless unfavourable features are present (poorly differentiated, involved margins or lymphovascular invasion). Otherwise, subtotal colectomy with ileorectal anastomosis is better than segmental resection as the former reduces the risk of metachronous lesions (40% after 10 years if segmentally resected in young age) and makes subsequent follow up of the remaining bowel much easier (Brand & Church, 2010).

Total proctocolectomy with ileal pouch anal anastomosis (TPC/IPAA) is better than coloanal anastomosis or ileostomy in young patients as sphincter, bowel continuity preservation and elimination of the risk of metachronous lesion are mandatory. Construction of ileal pouch is delayed if postoperative radiotherapy is recommended. Total abdominal hysterectomy and bilateral salpingo-ophrectomy (TAH/BSO) should be considered in postmenopausal females or those who have completed their child bearing (Church, 2011).

2- Familial adenomatous polyposis (FAP):

Prompt surgical intervention is mandatory in FAP patients with CRC, suspicious polyp carrying cancer but not proven histologically (may be false negative by sampling error) and symptomatic patients (65% rate of cancer at the initial site) as it is both curative (the surgeon assumes that an occult cancer is
present) and prophylactic (significant durable reduction in cancer incidence without excess operative or functional morbidity) (Jasperson et al., 2010).

Total proctocolectomy with end ileostomy can be devastating to young patients undergoing prophylactic procedure unless there is low rectal cancer or poor operative sphincteric function as it has significant morbidity with permanent ileostomy and genitorurinary dysfunction. Both TPC/IPA and total abdominal colectomy with ileorectal anastomosis (TAC/IRA) require follow up at relatively short intervals (3 months) until the risky areas, the rectum (in the latter), the anal transition zone and the ileal pouch are free from polyps for 2 successive examinations then after 6 months then annually (Jasperson & Burt, 2011).

Total proctocolectomy with ileal pouch anal anastomosis is often reserved for high risk patients like severe polyposis ≥ 1000, large rectal polyp and synchronous colon cancer, when it is not wise to retain the rectum but still continence, several motions per day and multiple anastomotic lines are potentially dangerous. Severe or advanced FAP i.e. large polyp ≥ 1cm, phenotypic (≥ 1000 polyp), genotypic (mutation in exon 15G) has twice times cancer risk than mild FAP patients. So, early surgical intervention is recommended. Mild cases can be followed up by annual colonoscopy to delay surgery especially in young patients till improved psychosocial and physical development unless the mild form has been progressed to a severe one. Sulindac is the most chemopreventive agent for polyp formation but still in its infancy and not replacing the close endoscopic surveillance programs (Brand & Church, 2010).

3-Neoplastic polyps:

Total colectomy with ileorectal anastomosis should be considered in patients, without significant comorbidity, in case harboring invasive cancer, numerous large > 5mm especially if they cannot do frequent colonoscopies. If there is significant comorbidity or the patient declines surgery and all polyps > 5 mm
cannot be removed endoscopically, colonoscopy with biopsy and/or removal of the largest and most adenomatous-appearing lesions is reasonable, but patients must understand there is a significant risk of cancer that may not be detected at an early stage (Leggett & Whitehall, 2010).

**D- Adjuvant therapy in CRC**

It is the treatment given in a phase either immediately before (neoadjuvant) or after the primary surgery in order to eradicate micrometastases, reduce the incidence of both local and systemic recurrence and improve the overall survival. The addition of this treatment depends on many risk factors including the TNM stage, site (Rt/Lt sided colon or rectum), pathological factors (grade, lymphovascular, perineural invasion, biomarkers (preoperative CEA level) and molecular actors (involved genes either mutated or hypermethylated). It is highly recommended in any LN positive colon cancer described also in stage B (T4N0MO) specially if there is risk factors. It is of little benefit in stage A and of palliative value in stage IV (Choti, 2011).

The most widely used agent is i.v. 5-Fluouracil (5-FU), a fluropyrimidine used either weekly, biweekly or monthly for 6 months. The addition of leucovorin (LV) or levamisole decreases the toxicity of 5-FU but with the same survival. The use of 2 oral 5-FU prodrugs (Capecitabine and Uracil/Tegafur) became more popular and avoids the risk of i.v. infusion. Addition of oxaliplatin or irinotecan doubles the response rate to around 50% (Cuschieri & Robert, 2013).

Combined modality therapy i.e. surgery with radiochemotherapy in the form of 6 months 5-FU i.v. infusion based chemotherapy combined with pelvic irradiation course (50 GY) is highly recommended in locally advanced rectal cancer i.e. T3/T4, N1/N2&M0 to control locoregional recurrence and both disease free and overall survival. Owing to the natural history, different anatomy and biology of the rectum, T2 and selected T1 tumors with high risk factors that was
treated with local therapy should receive a concurrent radiochemotherapy (Chang & Feig, 2011).

Neoadjuvant therapy is highly recommended in large distal rectal tumors as a primary or induction treatment to increase the chance of sphincter preservation and improving the R0 resectability avoiding the need of APR after downstaging in about 75% of cases. New trends in adjuvant treatment include intraoperative radiotherapy (IORT) by electron beams in high risk residual or recurrent tumors with or without neoadjuvant therapy, 3-D conformal-radiotherapy, portal vein infusion in liver metastases ≤ 5 mm in diameter, intraperitoneal chemotherapy and immunotherapy with monoclonal antibodies like bevacizumab, antivascular endothelial growth factor (VEGF) and cetuximab, antiepidermal growth factor(EGF) (Ahuja, 2011).