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Colorectal Cancer: New Perspectives

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Abstract Colorectal cancer is one of the gastrointestinal malignant tumors that carries relatively poor prognosis. It represents one of the most common cancers in males and the third commonest cancer among females worldwide. Various factors may contribute to the pathogenesis of colorectal cancer such as adenomatous polyps and personal history of chronic inflammatory bowel disease. Early colorectal carcinoma is usually asymptomatic. Bleeding from the rectum is the most common presenting symptom. Intestinal obstruction and distant metastasis are life threatening complications of colorectal carcinoma. Accurate diagnosis is achieved by sampling of areas of the colon suspicious for possible tumor development during colonoscopy or sigmoidoscopy. Lines of treatment include surgery, chemotherapy, radiotherapy and biologic treatment. This review sheds light on colorectal carcinoma regarding its prevalence, etiology, clinical presentation, diagnosis and possible lines of management.

Keywords: *colorectal, cancer, perspectives, etiology, diagnosis, management*

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1. Introduction

Colorectal carcinoma (CRC) is abnormal growth in the colon or the rectum, also known as bowel cancer [1]. The abnormal growth of cells may invade or spread to other parts of the body [2]. Symptoms may include blood in the stool, change in intestinal motility, weight loss, and feeling tired all the time [3].

Globally, CRC is the third most commonly diagnosed cancer in males and the second in females, with 1.4 million new cases and almost 694,000 deaths estimated to have occurred in 2012 [4]. Rates are substantially higher in males than in females. Global, country-specific incidence and mortality rates are available in the World Health Organization. In the United States, both the incidence and mortality have been slowly but steadily decreasing [5]. Annually, approximately 134,490 new cases of large bowel cancer are diagnosed, of which 95,270 are colon and the remainder rectal cancers [6]. Approximately 5%, or 1 in 20, Americans will be diagnosed with cancer of the colon or rectum in their lifetime [7]. Incidence and death rates for colorectal cancer increase with age [8]. There are about 56,000 deaths each year in the USA only [9].

Colorectal cancer has been the most common cancer among men and the third commonest among women since 2002 in Saudi Arabia. In the capital, Riyadh, where it reached 14.5/100000 in 2010. Median age at presentation has been stable at around 60 years (95% confidence Interval (CI): 57-61 years) for men and 55 years (95% CI: 53-58 years) for women. Distant metastasis was diagnosed in 28.4% of patients at the time of presentation and rectal cancer represented 41% of all colorectal cancers diagnosed in 2010. The overall 5-years survival rate was 44.6% for the period 1994-2004 [10,11].

2. Classification of Colorectal Carcinoma

The most common staging system is the TNM (for tumors/nodes/metastases) system, from the American Joint Committee on Cancer (AJCC). The TNM system assigns a number based on three categories. "T" denotes the degree of invasion of the intestinal wall, "N" the degree of lymphatic node involvement, and "M" the degree of metastasis [12]. Stage I means that the disease involves tumor invasion of the submucosa (T1) or muscularispropria (T2) and negative lymph nodes. Stage II means that the disease involves tumor invasion through the muscularispropria into per colorectal tissues (T3),or penetration to surface of the visceral peritoneum(T4a),or directly invade or adherent to other organs or structure (T4B). Stage III means that the disease includes T1-4 AND positive regional lymph nodes. Stage IV means that the disease includes any T, any N, and distant metastasis.

Other classifications are present such as Dukes' classification which classifies the tumor as follows: Dukes' A means invasion into but not through the bowel wall; Dukes' B means invasion through the bowel wall penetrating the muscle layer but not involving lymph

nodes; Dukes' C means involvement of lymph nodes; and Dukes' D means widespread metastases [13]. Also, Astler-Coller classification divides cases of colorectal carcinoma to stage A: Limited to mucosa; stage B1: Extending into muscularispropria but not penetrating through it and nodes not involved; stage B2: Penetrating through muscularispropria and nodes not involved; stage C1: Extending into muscularispropria but not penetrating through it and nodes involved; stage C2: Penetrating through muscularispropria and involvement of lymph nodes; and stage D that means distant metastatic spread [14].

3. Etiology of Colorectal Carcinoma

There are many known factors that increase or decrease the risk of colorectal cancer some of these factors are modifiable while others are not. Non modifiable risk factors include a personal or family history of colorectal cancer or adenomatous polyps and a personal history of chronic inflammatory bowel disease. People with inflammatory bowel disease are at increased risk of colon cancer [15]. The most common of these is hereditary nonpolyposis colorectal cancer(HNPCC or Lynch syndrome) which is present in about 3% of people with colorectal cancer [16]. Other syndromes that are strongly associated with colorectal cancer include Gardner syndrome [17]. Familial adenomatous polyposis (FAP) is the second most common predisposing genetic syndrome, and is characterized by the development of hundreds to thousands of colorectal polyps in affected individuals [18]. Risk factors include older age, male gender, high intake of fat , alcohol, red meat, processed meats, obesity, smoking, and a lack of physical exercise[19,20].

4. Clinical Presentation

Early colorectal cancer often has no symptoms, which is why screening is so important. As a tumor grows, it may bleed or obstruct the intestine. Bleeding from the rectum, aark or black stools, a change in the shape of the stool (e.g., more narrow than usual), cramping or discomfort in the lower abdomen and an urge to have a bowel movement when the bowel is empty are common complaints. Constipation or diarrhea that lasts for more than few days may occur. In some cases, blood loss from the cancer leads to anemia, causing symptoms such as weakness and excessive fatigue [21,22].

5. Complications of Colorectal Carcinoma

Blockage of the colon, causing bowel obstruction, cancer spreading to other organs or tissues (metastasis) anddevelopment of a second primary colorectal cancer may complicate cases of advanced colorectal carcinoma. Complications from chemotherapy and biotherapy depend on the agents used, but may include nausea, vomiting, diarrhea, inability to fight infection and allergic reactions. Radiation therapy may cause skin reactions or burns, mechanical blockages (strictures), bleeding and radio necrosis (tissue destruction due to the radiation energy) [23].

6. Diagnosis of Colorectal Carcinoma

Diagnosis of colorectal cancer is performed by sampling of areas of the colon suspicious for possible tumor development, typically during colonoscopy or sigmoidoscopy, depending on the location of the lesion. Disease extent is usually determined by a CT scan of the chest, abdomen and pelvis. Other potential imaging tests such as PET and MRI may be used in certain cases. Colon cancer staging is done next, based on the TNM system which considers how much the initial tumor has spread, if and where lymph nodes are involved and the extent of metastasis [24].

6.1. Structural *Examination* of the Colon

6.1.1. Flexible Sigmoidoscopy

A slender, flexible, hollow, lighted tube is inserted through the rectum into the colon by a trained examiner. The sigmoidoscope is about 2 feet long (60 cm) and provides a visual examination of the rectum and lower one-third of the colon (sigmoid colon) [23].

6.1.2. Colonoscopy

Like sigmoidoscopy, this procedure allows for direct visual examination of the colon and rectum. A colonoscope is similar to a sigmoidoscope, but is a much longer, more complex instrument, allowing visualization of the entire colon and removal of polyps [21].

6.1.3. Barium Enema with Air Contrast

The use of this procedure, which is also called double-contrast barium enema (DCBE), has become very uncommon due to the increased availability of colonoscopy, changing patient and physician preferences, a limited number of radiologists adequately trained to perform the procedure, and lower insurance reimbursement (21).

6.1.4. Computed Tomographic Colonography (CTC)

It is also referred to as virtual colonoscopy.This imaging procedure was introduced in the 1990s and results in detailed, cross-sectional, 2- or 3-dimensional views of the entire colon and rectum with the use of a special x-ray machine linked to a computer [23].

6.2. Stool Tests

6.2.1. Fecal Occult Blood Test (FOBT)

Cancerous tumors and some large polyps bleed intermittently into the intestine. This blood can be detected in stool by the FOBT kit, which is obtained from a health care provider for use at home. Bleeding from colorectal cancer may be intermittent or undetectable, so accurate test results require annual testing that consists of collecting 1 to 3 samples (depending on the product) from consecutive bowel movements [21].

6.2.2. Stool DNA (sDNA) Test

The stool DNA test approved for colorectal cancer screening in 2008 is no longer commercially available. A new test has undergone extensive study and may be evaluated for inclusion as a recommended testing option in the future. This method of screening is the result of increasing knowledge about the molecular properties of cancer. Cancerous tumors and large polyps shed cells into the large bowel that contain altered DNA that can be detected in stool samples. Patients with a positive test result would be referred for a colonoscopy [21].

7. Management of Colorectal Carcinoma

Most people with colon cancer will have some type of surgery to remove the tumor. Adjuvant therapy (additional treatments after surgery) may also be used. Treatment decisions are made by patients with their physicians after considering the best options available for the stage and location of the cancer, as well as the risks and benefits associated with each [23].

Complete surgical resection of the primary tumor with regional lymphadenectomy is a curative approach for patients with operable CRC. Adjuvant radiation therapy (RT) has a limited role in colon cancer because most recurrences are extrapelvic and occur in the abdomen. Adjuvant chemotherapy includes the following [25]:

- *FOLFOX4*:Oxaliplatin 85 mg/m^2 IV day 1 Leucovorin 200 mg/m^2 per day IV over 2 hours days 1 and 2 Fluorouracil 400 mg/m^2 IV bolus, after leucovorin, then 600 mg/m^2 CIV over 22 hours days 1 and 2 Repeat every 14 days.
- *mFOLFOX6*: Oxaliplatin 85 mg/m^2 IV on day 1 Leucovorin 400 mg/m^2 IV on day 1 Fluorouracil 400 mg/m^2 IV bolus, after leucovorin on day 1, then 1200 mg/m^2 / day × 2 days CIV (total 2,400 mg/m^2 over 46-48 hours) Repeat every 14 days.
- *FLOX*: Oxaliplatin 85 mg/m^2 IV administered on weeks 1, 3, and 5 Fluorouracil 500 mg/m^2 IV bolus weekly × 6 Folinic acid 500 mg/m^2 IV weekly × 6 Each cycle lasts 8 weeks and is repeated for 3 cycles.
- *Capecitabine*: Capecitabine 1250 mg/m^2 PO twice daily on days 1 through 14 Each cycle lasts 14 days and is repeated every 21 days.
- *CapOx*: Oxaliplatin 130 mg/m^2 IV day 1 Capecitabine 850-1000 mg/m^2 twice daily orally for 14 days Each cycle lasts 14 days and is repeated every 21 days.
- *Fluorouracil-Based Regimens:*such as Roswell Park regimen which includes Fluorouracil 600 mg/m^2 IV day 1 Leucovorin 500 mg/m^2 IV day 1 over 2 hours Repeat weekly for 6 of 8 weeks.

Patients with metastatic colorectal cancer (MCRC) are considered to have resectable, potentially resectable, or unresectable metastatic disease. Multimodality therapy is indicated for resectable or potentially resectable metastases. Chemotherapy is for disseminated disease and the primary treatment modality for unresectable MCRC. Determine mutation status with tumor KRAS genotyping at diagnosis. Epidermal growth factor receptor (EGFR) inhibitors should be considered only in patients with tumors with wild-type KRAS [24]. The selection of second-line chemotherapy is primarily based on the type of prior therapy received, as well as the response to prior treatments, site and extent of disease. This include soxaliplatin-based regimens and irinotecan-based regimens [25].

8. Prognosis

Stage at diagnosis is the most important independent prognostic factor for survival and disease recurrence. Five-year relative survival is approximately 91% for those with localized tumor as compared with 12% for those with metastatic disease. Poor prognostic clinical factors at diagnosis include bowel obstruction or perforation, high preoperative CEA level, distant metastases, and location of the primary tumor in the rectum or rectosigmoid area. Molecular markers, particularly MSI, 18q/DCC mutation or LOH, BRAF V600E mutation, and KRAS mutations are also associated with CRC prognosis [25,26].

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