Introduction

The liver is a frequent site of metastatic colorectal disease. Colorectal cancer (CRC) is the third most commonly diagnosed malignancy accounting for 11% of cancers in men and women and also is the third leading cause of cancer mortality each year in USA. Hepatic metastases are present at one point or another in about 50% of patients with colorectal cancer, with 20–25% of these presenting with synchronous liver metastases. About a one-third of the patients of colorectal cancer are presented with metachronous liver metastases, usually within the first 2 years following resection of the primary tumor. In these patients, the extent of liver disease is the main determinant of survival **(Jemal et al., 2011).**

In 30% to 40% of colorectal cancer (CRC) patients, metastases are confined to the liver when they are initially found. One quarter to one third of patients who are able to undergo resection of liver metastases will live 5 years or longer; median survival after resection is between 24 and 40 months. This high rate of liver metastases has transformed treatment and evaluation in an effort to improve cure rates. The outcome for patients with untreated hepatic metastases is poor, with a median survival time of only 5-12 months **(Voest et al., 2011).**

Over the past 2 decades, improvements in systemic chemotherapy and surgical techniques have improved the survival of patients with hepatic metastases. Hepatectomy is the only potentially curative therapy for colorectal liver metastases (CLM), but when traditional criteria for resectability were used, only 10-20% of patients were candidates for surgical resection **(Folprecht et al., 2010).**

Long-term survival following liver resection for colorectal liver metastasis (CRLM) has improved considerably through lower operative mortality, better patient selection aided by better diagnostic investigations and more frequent use of perioperative chemotherapy and biologic therapy. The 5-year survival rate after resection of CLM has improved from a historical rate of 25% to rang from 40% to 58% at major centers **(Wong et al., 2011).**

Generally, CRLM can be categorized into three subjects: clearly resectable, potentially resectable, or definitely un resectable. It is estimated that 80%-90% of CRLMs are considered unresectable at diagnosis .Due to the development of new chemotherapy agents and targeted therapeutic agents, a bout 5-15% of initially unresectable CRLM tur into resectable disease. Intensified chemotherapy such as irinotecan, oxaliplatin, and 5-fluorouracil/leucovorin has been shown to have high response. In recent years, the addition of targeted agents (anti- epidermal growth factor receptor (anti-EGFR)

agents) such as cetuximab and paitumumab and vascular growth factor receptor (VEGF) agents such as bevacizumab to traditional chemotherapy in patients with unresectable metastatic colorectal cancer has shown to further improve the survival benefit **(Peeters et al., 2010).**

Close cooperation of surgeons and medical oncologists with consideration of the timing and sequence of chemotherapy and surgery, as well as the roles of cryoablation, radiofrequency ablation, has produced significant increases in survival for patients with liver metastases **(Montagnani et al., 2011).**

Aim of the Work

- To give an overview on colorectal cancer, and its liver metastases.
- To demonstrate new trends of management of liver metastases from colorectal cancer.

Overview of Colorectal Cancer

Epidemiology:

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy accounting for 11% of cancers in men and women and also is the third leading cause of cancer mortality each year in USA. with an estimated 1.24 million cases worldwide in 2008 .The incidence rate declined by 2.9% annually from 1998 to 2001. The decline in incidence may have been due, in part, to increased screening and polyp removal **(Jemal et al., 2011).**

In 30% to 40% of CRC patients, metastases are confined to the liver. By the time of diagnosis, about 25% of patients have liver metastases (synchronous metastases); another 25%-30% will present hepatic lesions in the following 2-3 years (metachronous metastases). The estimated 5-year survival rates are less than 10% for patients who have unresectable or metastatic disease. One quarter to one third of patients who are able to undergo resection of liver metastases will live 5 years or longer; median survival after resection is between 24 and 40 months **(Voest et al., 2011)**.

In the Ain Shams university hospitals, clinical oncology and nuclear medicine department, in Cairo between January 2013 and December 2013; there were 91 new cases of

colorectal cancer and rectosigmoid cancer. These cases accounted for 5.2% of all 1732 newly diagnosed cases.26 cases of them presented with liver metastases, which accounts 28% of all cases of colorectal cancer (**Ain Shams University Hospital, Cairo, 2013).**

The incidence of colorectal cancer is higher in well developed countries and this may be attributed to consumption of a high-fat and high red meat diet and lack of physical activity with resulting obesity **(Berenson et al., 2006).**

For both men and women, the incidence of CRC begins to rise around the age of 40 years. Incidence sharply increases at age 50 years; 92% of CRCs are diagnosed in persons aged 50 years or older. People in their 80s clearly continue to be at risk for CRC, with 12.5% of cases diagnosed after age 85. Men tend to develop colorectal cancer slightly more often than women **(Jemal et al., 2011).** In Egypt, the age distribution of colorectal cancer shows that a high proportion occurs in children and adults under 40 years of age **(Soliman et al., 2000)**.

Etiology and risk factors:

Colon cancer has many proven environmental and demographic risk factors. The most important risk factors include:

1. Polyps. The main importance of polyps is the well-recognized potential of a subset to evolve into colorectal cancer.

The evolution to cancer is a multistage process that proceeds through mucosal cell hyperplasia, adenoma formation, and growth and dysplasia, to malignant transformation and invasive cancer **(Ferlay et al., 2008).**

Environmental carcinogens may result in the development of cancer regardless of a patient's genetic background, but patients with genetically susceptible mucosa inherit a predisposition to abnormal cellular proliferation. Oncogene activation and chromosomal deletion lead to adenoma formation, growth with increasing dysplasia, and invasive carcinoma **(Ahnen et al., 2011).**

2. Diet. Populations with high intake of fat, higher caloric intakes, and low intake of fiber (fruits, vegetables, and grains) tend to have increased risk for colorectal cancer in most but not all studies. Higher calcium intake, calcium supplementation, and regular aspirin use are associated with a lower risk for colorectal cancer in some studies. Increased intake of vitamins C and E and beta-carotene do not appear to decrease the risk for polyp formation. The higher incidence of rectal and sigmoid cancer in men may be related to their greater consumption of alcohol. Postmenopausal women who have taken estrogen replacement therapy appear to have a lower risk for colorectal cancer than those who have not **(Reedy et al., 2008).**

3. Inflammatory bowel disease: Patients with IBD colitis are 6 times more likely to develop colorectal cancer than the general population and have a higher frequency of multiple synchronous colorectal cancers **(Lennard_jones et al., 1983).**

a. Ulcerative colitis is a clear risk factor for colon cancer. About 1% of colorectal cancer patients have a history of chronic ulcerative colitis. The risk for the development of cancer in these patients varies inversely with the age of onset of the colitis and directly with the extent of colonic involvement and duration of active disease. The cumulative risk is 3% at 15 years, 5% at 20 years, and 9% at 25 years **(Munkholm et al., 2003).**

The recommended approach to the increased risk for colorectal cancer in ulcerative colitis has been annual colonoscopy to determine the need for total proctocolectomy in patients with extensive colitis of more than 8 years' duration. This strategy is based on the assumption that dysplastic lesions can be detected before invasive cancer has developed. An analysis of prospective studies concluded that immediate colectomy is essential for all patients diagnosed with dysplasia (high grade or low grade). Most important, the analysis demonstrated that the diagnosis of dysplasia does not preclude the presence of invasive cancer. The diagnosis of dysplasia has inherent problems with sampling of specimens and with

variation in agreement among observers (as low as 60%, even with experts in the field) **(Biancone et al., 2008).**

b. Crohn's disease: Patients with colorectal Crohn's disease are at increased risk for colorectal cancer, but the risk is less than that of those with ulcerative colitis. The risk is increased about 1.5 to 2 times 4 **(Freeman et al., 2001).**

4.Genetic factors:

a. Family history: may signify either a genetic abnormality or shared environmental factors or a combination of these factors. About 15% of all colorectal cancers occur in patients with a history of colorectal cancer in first-degree relatives **(Woolf et al., 2000).**

b. Gene changes: Specific inherited (adenomatous polyposis coli [APC] gene) and acquired genetic abnormalities (ras gene point mutation; c-myc gene amplification; allele deletion at specific sites of chromosomes 5, 17, and 18) appear to be capable of mediating steps in the progression from normal to malignant colonic mucosa. About half of all carcinomas and large adenomas have associated point mutations, most often in the K-ras gene. Such mutations are rarely present in adenomas smaller than 1 cm. Allelic deletions of 17p– are demonstrated in three-quarters of all colorectal carcinomas, and deletions of 5q– are demonstrated

in more than one-third of colonic carcinoma and large adenomas **(Vogelstein et al., 2001).**

Two major syndromes and several variants of these syndromes of inherited predisposition to colorectal cancer have been characterized. The two syndromes, which predispose to colorectal cancer by different mechanisms, are FAP (familial adenomatous polyposis) and hereditary nonpolyposis colorectal cancer syndrome (HNPCC or lynch syndrome**) (Kinzler et al., 2002).**

1. **FAP** (familial adenomatous polyposis)**:** The genes responsible for FAP, APC (adenopolyposis coli) genes, are located in the 5q21 chromosome region. Inheritance of defective APC tumor-suppressor gene leads to a virtually 100% likelihood of developing colon cancer by 55 years of age. Screening for polyps should begin during early teenage years. The FAP syndrome is associated with the development of gastric and ampullary polyps, desmoid tumors, osteomas, abnormal dentition, and abnormal retinal pigmentation. Variants of FAP include Gardner's and Turcot's syndromes **(Tamandl et al., 2011).**

2. **HNPCC.** The autosomal-dominant pattern of HNPCC includes Lynch's syndromes I and II, both of which are associated with an increased incidence of predominantly right-sided colon cancer. This genetic abnormality in the

mismatch repair mechanism leads to defective excision of abnormal repeating sequences of DNA known as microsatellites ("microsatellite instability"). Retention of these sequences leads to expression of a mutator phenotype characterized by frequent DNA replication errors (RER+ phenotype), which predispose affected people to a multitude of primary malignancies, including endometrial, gastric, ovarian, bladder, and ureteral cancers and biliary tract cancers. Specific mutated genes on chromosomes 2 and 3, known as hMSH2, hMLH1, hPMS1, and hPMS2, have been linked to HNPCC **(Adam et al., 2010).**

Patients with HNPCC have a tendency to develop colon cancer at an early age, and screening should begin by 20 years of age for relatives of HNPCC patients. The median age of HNPCC patients with colon cancer at diagnosis was 44 years, versus 68 years for control patients in one study. The prognosis for HNPCC patients appears to be better than for those patients with sporadic colon cancer; the death rate from colon cancer for HNPCC patients is two thirds that for sporadic cases over 10 years **(Miyaki et al., 2000).**

3. **Smoking.** Men and women smoking during the previous 20 years have three times the relative risk for small adenomas (less than 1 cm) but not for larger ones. Smoking for more than 20 years was associated with a 2.5 relative risk for larger adenomas (**Winkels et al., 2012).**

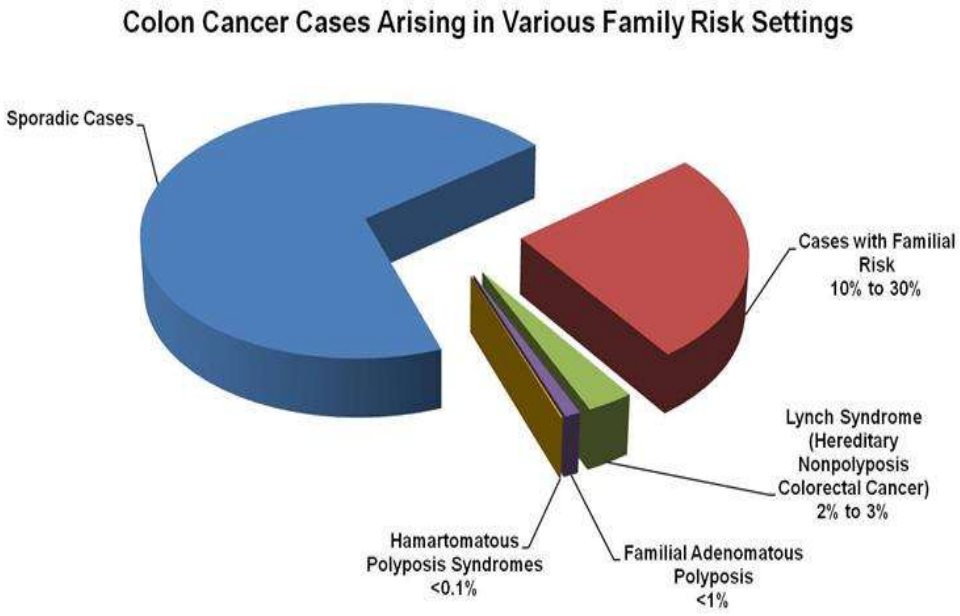

Figure (1): The fractions of colon cancer cases that arise in various family risk settings **(Randal et al., 2000).**

6. **Other factors.** Personal or family history of cancer in other anatomic sites (such as breast, endometrium, and ovary) is associated with increased risk for colorectal cancer. Exposure to asbestos (e.g., in brake mechanics) increases the incidence of colorectal cancer to 1.5 to 2 times that of the average population. Other than this association, there appears to be little relationship between occupational exposures and the incidence of colon cancer **(Ullrich et al., 2005).**

HPV infection of the columnar mucosa of the colon may cause benign and malignant neoplasia **(Lee et al., 2001).**

Epidemiological factors as old age due to acquired colonocyte mutations accumulating with age. Obesity is an important risk factor for colon not rectal cancer. Alcohol may promote cell proliferation and inhibit DNA repair **(Pedersen et al., 2003).**

Ureterosigmoidostomy due to carcinogens excreted in urine or colonic mucosa causing proliferation during repair after urine-induced mucosal injury. Acromegaly due to excessive growth hormone promoting proliferation of preexisting colonic adenomas and cancers **(Hawk et al., 2005).**

A sedentary life style may account for an increased colorectal cancer risk, although the mechanism is unclear. **(Boyle et al., 2012)**

Pathophysiology and molecular genetics:

Most colon cancers arise from adenomas (adenoma-to-carcinoma sequence) as demonstrated by epidemiologic, clinical, pathologic, and molecular genetic findings. Operative specimens containing colon cancer frequently contain one or more synchronous adenomas. The risk for colon cancer increases markedly with increasing number of adenomatous polyps within the colon. Adenomatous tissue frequently is

found contiguous to frank carcinoma. patients who have familial adenomatous polyposis (FAP) (a syndrome is inherited as a classic single autosomal dominant gene as a result of germline mutation of the APC gene located on chromosome 5q, who have hundreds or thousands of adenomatous colonic polyps, inevitably develop colon cancer if colectomy is not performed . Also, patients who have adenomatous polyps larger than 1 cm diagnosed by barium enema who do not undergo colonoscopic polypectomy develop colon cancer at a rate of 1% to 1.5% per year **(Cappell et al., 2005).**

Colon cancer is believed to be the result of a cascade of genetic mutations leading to progressively disordered local DNA replication and accelerated colonocyte mitosis. Progressive accumulation of multiple genetic mutations results in the transition from normal mucosa to benign adenoma to severe dysplasia to frank carcinoma. Malfunction of the mismatch repair genes may account for approximately 15% of sporadic colon cancers. In the HNPCC syndrome, the mismatch repair genes malfunction because of genetic mutation. The "serrated neoplastic pathway" describes the progression of serrated polyps, including sessile serrated adenomas (SSA) and traditional serrated adenomas, to colorectal cancer. Hyperplastic polyposis syndrome (HPS) is a relatively rare condition characterized by numerous hyperplastic polyps present in a

pancolonic distribution; some of these polyps can be ›1 cm in diameter **(Winawer et al., 2000).**

They differ from typical hyperplastic polyps, which are usually small lesions in the distal colon and rectum **(O'Brien et al., 2007)**. Colorectal cancer arising in up to 50% patients with HPS. The characteristic feature of all serrated polyps is the "saw-toothed" infolding of the crypt epithelium. Some SSAs have areas of conventional dysplasia, which are likely to indicate a more aggressive behavior, Two important discoveries were that the CpG island methylator phenotype (CIMP) and mutation of the oncogene BRAF can be traced from cancers to their serrated precursors **(Rajagopalan et al., 2002)**. Two kinds of methylation events were recognized: type A methylation, which accumulated with increasing age, and type C methylation, which was more specific to cancers hypermethylation was observed in approximately 20%–30% of all colorectal cancers **(Hyman et al., 2004)**.

In sporadic serrated adenomas, the mismatch repair gene MLH1 often malfunctions because of DNA hypermethylation. APC mutation is believed to account for approximately 80% to 85% of sporadic colon cancers. Colon cancer may arise in inflammatory bowel disease from a different but so far uncharacterized pathway. **The k-ras gene** encodes for a protein involved in signal transduction from the cell membrane to the nucleus. Specific mutations of this gene activate this signal