CHAPTER III

COLORECTAL CANCER

The human body looks like a large energy factory, many mechanisms of which operate from the trillion of cells. Moreover, the working cells from hundreds of different tissue are collaborating to make goods for whole organism. An organism cell has a unique function for example some cells have a function to convert food into energy, some transport oxygen or nutrients throughout the human body, some resist infections, and some shuttle the heredity organism's gene into descendant. Cancer is derived from a rebellious single cell acquiring the ability to reproduce and spread to other tissue without control. Cancer cells are growing and multiplying, colonizing on organ of the body where it does not belong to. It interferes normal function of the body system, destroys the organ and ultimately kills the organism. As cancers spread, it can cause a problem to eradicate because cancer cells come from the body itself. The ability of immune system is decreased–what cells should fight or destroy, how to distinguish cancer cell from normal ones. The physicians try to introduce the new modalities for cancer treatment among the cancerous diversity. Nowadays, there are at least 200 cancer types. The type of cancer depends upon—where cancer arises and colonizes in the human body. The name of cancer follows the site where cancer cell starts. For example, brain cancer starts in the brain; lung cancer starts in the lung. Cancer is a disease that probably affects people of all nationalities, gender and age groups. The cancer diversity challenges on physicians to understand an aberration of molecule that can derive cancer.

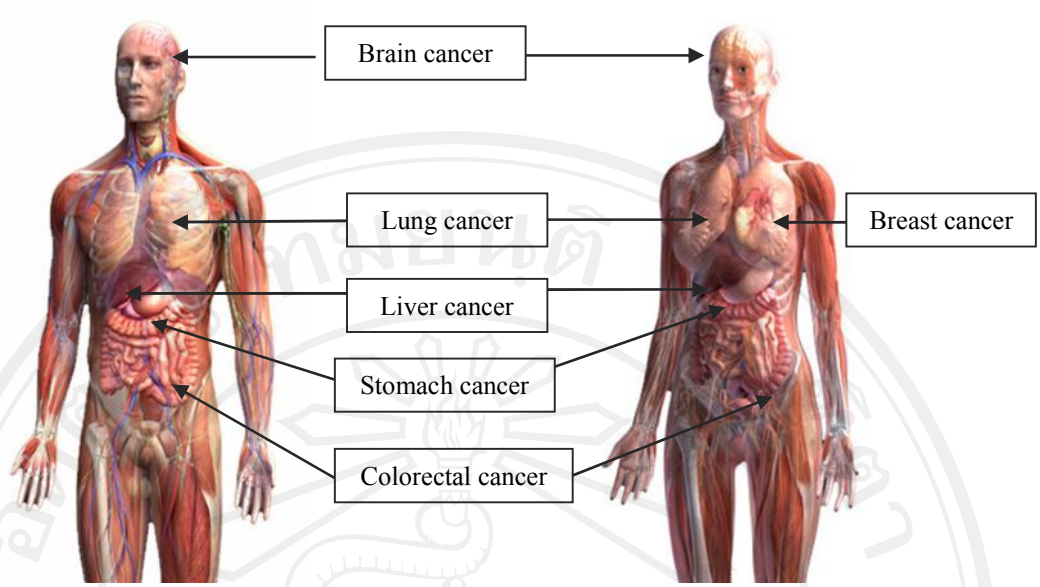

Figure 3.1 The diversity of cancer (39).

3.1 Epidemiology

Colorectal cancer (CRC) is the third common malignancy worldwide, around one-two- million new cases each year (40). It trends to increase in developed countries such as United States. In Thailand, cancer is a leading cause of death followed by accidents and heart disease. Moreover, it has become the first common cause of death in the northern part of Thailand, and colorectal cancer is ranked the third among different fatalities in this region. Epidemiological studies with the incidence of colorectal cancer on populations migrating from low to high-risk associated with the geographical area. CRC risk is principally involved dietary and environmental factor. Risk factors also includes advanced age, sex- men tend to get colorectal disease more than women, positive familial history of adenomatous polyps, high alcohol consumption, red and processed meat, low physical activity (40).

3.2 Biologic characteristics and pathology

CRC is the cancer that begins in the digestive system and/or the excretory system. Tumor begins in the inner lining of the colon and rectum, passageway connect the colon and the anus. Sometimes tumor occurs in colon intestine or bowel, it is so-called colon cancer. But, if cancerous cell originates in rectum it usually called rectal cancer. Both man and woman can get the colorectal cancer. It is often found in people aged 50 and older because cancer risk is increasing with age and people who have a familial history of this disease are the high risk group.

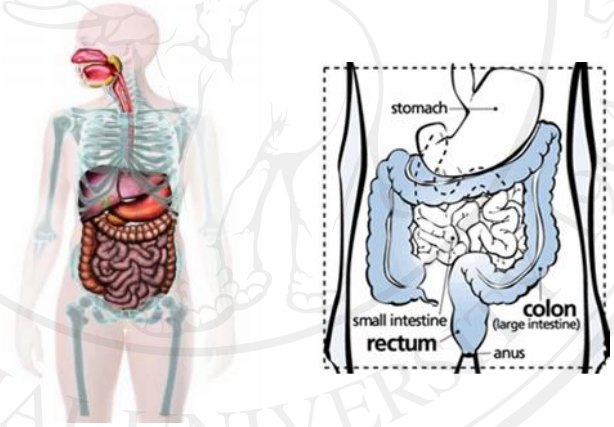

Figure 3.2 The anatomy of colon and rectum (41).

Colorectal cancer usually begins as a small mass tumor so-called polyp in a colon or rectum. Polyp is noncancerous that grows or develops inside mucosa of colon or rectum, this incidence increases as people get older. If a polyp is not treated and removed, it can become a cancer overtime. The benign form is adenomas polyp. The important prognostic factor for colorectal is tumor extent; extension through the bowel wall, nodal spread and the presence of metastasis disease.

Colorectal tumorigenesis involves multistep process of genetic, including gene mutations, gene amplification, epigenetic silencing of gene transcription through promoter (40). A genetic model for colorectal cancer tumorigenesis describes how normal epithelial cells become adenocarcinomas follow by multi-step progression of transformation into malignant carcinomas. The progression of adenocarcinoma derived from generic changes, and subsequently the series of genetic change is shown in Figure 3.3. The occurrence of gene mutation is presented during the progression (40).

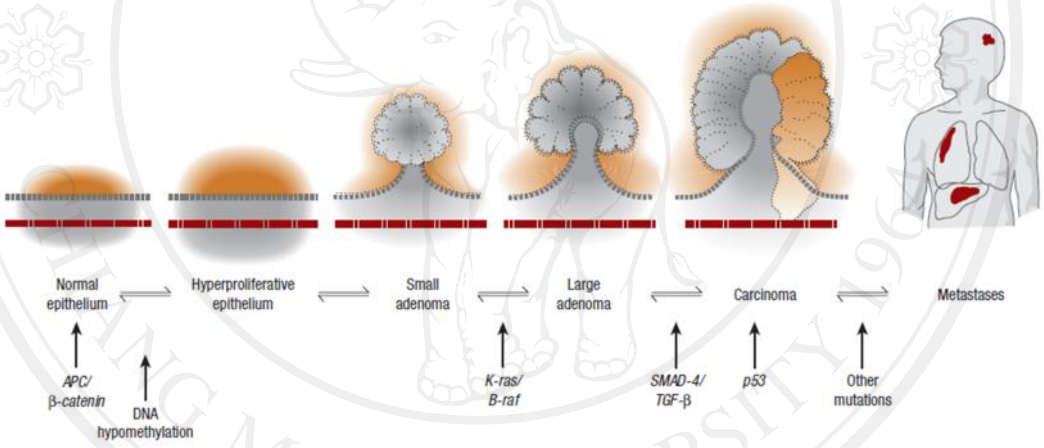

Figure 3.3 The sequence of genetic change in the progression of colorectal cancer (40).

The underlying genetic changes during the progression of normal to colorectal cancer have been implicated with a molecular pathway known as the Wnt signaling pathway. The Wnt signaling pathway involves the control processes including cellular division, cell adhesion (40, 42). Colorectal tumorigenesis usually starts with a mutation that inactivates tumor-suppressor gene *APC*. Loss of the *APC* gene, localized on chromosome 5q21 lead subsequently detected a small benign polyp.

APC gene encodes for a protein that binds to α and β-catenin. β-catenin associated with Wnt signaling pathway that can be alerted and lead the abnormal epithelium division and proliferation difference from other cells. Moreover it is involved in cell-cell adhesion when combines to the cytoplasmic domain of E-cadherin (40). Benign polyp is developed into adenomas by mutations in genes that contribute to colorectal progression. For example the mutation in Ras gene results in uncontrolled cell division and malignant transformation. Mutational inactivation of tumor suppressor genes p53 can affect apoptosis program. Finally, more additional gene changes as shown in Figure 3.3 permit the tumor to become invasive and spread to other tissues (40).

3.3 Type of colorectal cancer

Hereditary genetic of colorectal cancer broadly classify into two categories usually based on presences or absences of colorectal polyps including Hereditary Nonpolyposis Colorectal Cancer (HNPCC) and Familial adenomatous polyposis (FAP) (43). HNPCC, also known as Lynch syndrome, is the most common form of hereditary colorectal, accounting for approximately 3-5% under detected in colorectal patients (43). HNPCC is inherited in an autosomal dominant, however, the other genes mutation corresponding to HNPCC was not found in all members of the family who had developed the disease. Gene mutation responding for HNPCC disease are included in the group of DNA mismatch repair (MMR) genes, and subsequently five HNPCC genes have been discovered: MSH2 on chromosome 2, MLH1 on chromosome 3, PMS2 on chromosome 7, MSH6 on chromosome 2 and PMS1 on

chromosome 2 (44). Mutations in MSH2 and MLH1 are the most common mutations that cause HNPCC that founded around 90% among genes in MMR groups (43, 45). Familial adenomatous polyposis (FAP) is rare with the incidence approximately 0.5-1% of colorectal cancer patients (43). Mutation of APC gene is responsible for FAP syndrome. FAP is an autosomal dominant disease, strong inherited cancer genetic array into descendent (42, 43).

3.4 Cancer staging

The evolution of cancer takes place by growth and spread process. The leading cause of cancer is gene mutation (40). The gene mutation associates to the cancer type, in addition it is complicate such as cancer-promoting mutation does not occur on one gene. Both endogenous and exogenous sources such as chemical agent can stimulate these gene mutations which effect the other genes to become new gene mutation. At each stage, the kind of gene-promoting is essential for driving cancer genetic processing (growth advantage crop up and damage neighbor cells or tissues). Cancer staging describes the expanding of cancer cells in human body. It is used to determine how far the cancer spread though out or nearby the original site. Indeed, cancer can spread into lymph node and interfere the distant organ such as liver, lung and brain. Therefore, cancer staging is important to determine the prognosis of patients and treatment decision. The information for staging are based on location of primary tumor, tumor size, number of tumor and cancer metastasis. The staging involves physical exams, imaging test-for example x-ray, CT scans, MRI scans, laboratory test including studies of blood and urine, tissue biopsies and pathology reports. The American Joint Committee on Cancer (AJCC) and the International

Union Against Cancer developed TNM staging system, a standardized program for classification the severity of cancer. The clinical utility of TNM staging is to help clinicians decide an appropriate treatment modality. The term of TNM is abbreviation of tumor size, lymph node involvement and metastasis (presence or absence metastases) (Figure 3.4). The three categories have subdivision in more details by providing a number to indicated criteria for each category. The number 1 through 4 indicates the increasing severity and x is used when cannot be assessed or information is not available (45). Table 3.1 is shown the definition of TNM staging colorectal cancer that according to AJCC.

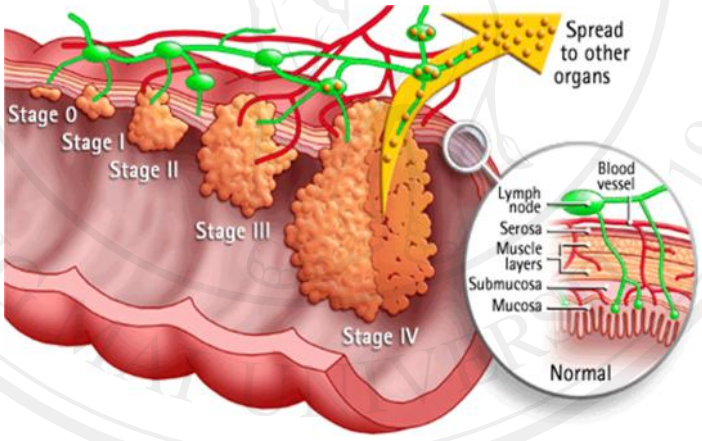

Figure 3.4 Colorectal cancer staging (46).

Table 3.1 TNM staging definition for colorectal cancer (45).

Criteria	Classification	Definitions
Primary Tumor (T)	TX	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria[1]
	T1	Tumor invades submucosa
	T2	Tumor invades muscularis propria
	T3	Tumor invades through the muscularis propria into pericolorectal tissues
	T4a	Tumor penetrates to the surface of the visceral peritoneum[2]
	T4b	Tumor directly invades or is adherent to other organs or structures[2,3]
Regional Lymph	Nx	Regional lymph nodes cannot be assessed
Nodes (N)	N0	No regional lymph node metastasis
	N1	Metastasis in 1–3 regional lymph nodes
	N1a	Metastasis in one regional lymph node
	N1b	Metastasis in 2–3 regional lymph nodes
	N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
	N2	Metastasis in 4 or more regional lymph nodes
	N2a	Metastasis in 4–6 regional lymph nodes
	N2b	Metastasis in 7 or more regional lymph nodes
Distant Metastasis (M)	M0	No distant metastasis
	M1	Distant metastasis
	M1a	Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
	M1b	Metastases in more than one organ/site or the peritoneum

Notes of Table 3.1

[1]Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or mucosal lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.

[2] Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (that is, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina).

[3]Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion, whereas the PN site-specific factor should be used for perineural invasion.