SURVIVAL RATE AND PROGNOSTIC FACTORS OF COLORECTAL CANCER

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Thesis
Entitled

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SURVIVAL RATE AND PROGNOSTIC FACTORS OF COLORECTAL CANCER

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ABSTRACT

This study was an ambispective cohort design to assess the survival rate and prognostic factors of colorectal cancer at the Oncology Unit, Department of Medicine, Rajavithi Hospital from January 1, 1995 to December 31, 2003 and to follow up cancer patients' current statuses until August 31, 2004 with the medical records and the Population Registration Database, Ministry of Interior. The data was collected from the medical records of 287 colorectal cancer patients.

The colorectal cancer patients who died totaled 145 cases. The median age was 61 years old. Males and females were found in similar numbers (1:1.02). The most common job description was unemployed (50.8%). The highest percentages of tumor-related factors were as follows: colon cancer (71.08%), adenocarcinoma (96.15%), well differentiated (62.06%), stage IV (35.86%), and location of recurrence of disease (stage I-III) and distant metastasis (M1) to liver were 56.27%. Seventy percent of patients were treated with surgery plus chemotherapy. Overall median survival time was 148.86 weeks and overall 3, 5, 7-year survival rates were 48.8%, 38.6%, and 37.6%, respectively. Multivariate analysis showed that factors such as age, degree of differentiation, stage, TNM, the surgery, and the chemotherapy were independent prognostic factors ($p<0.05$).

This study found age and stage were related to survival time. The patients in the early stages (stage I, II) had a longer survival time than patients in stage IV. Young and elderly patients had a higher risk of death. Thus, people at risk of the disease should be screened at the early stage. People who have family history of colorectal cancer should be screened before 30 years of age and cancer screening programs should be given to the aging group.

KEY WORDS: COLORECTAL CANCER (CRC) / SURVIVAL RATE / PROGNOSTC FACTORS

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อัตราการรอดชีพ และปัจจัยพยากรณ์โรคของผู้ป่วยมะเร็งลำไส้ใหญ่
(SURVIVAL RATE AND PROGNOSTIC FACTORS OF COLORECTAL CANCER)

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บทคัดย่อ

การศึกษานี้เป็นการศึกษาอัตราการรอดชีพและปัจจัยพยากรณ์โรคของผู้ป่วยมะเร็งลำไส้ใหญ่ ที่มารับการรักษา ณ.งานโรคมะเร็ง กลุ่มงานอายุรศาสตร์ โรงพยาบาลราชวิถี ตั้งแต่ 1 มกราคม 2538 ถึง 31 ธันวาคม 2546 จำนวน 287 ราย โดยติดตามสถานะสุดท้ายของผู้ป่วยจากเวชระเบียน และฐานข้อมูลทะเบียนราษฎร์ จนกระทั่งถึง 31 สิงหาคม 2547 เก็บข้อมูลโดยคัดลอกข้อมูลลงในแบบบันทึก

ผลการศึกษา ผู้ป่วยเสียชีวิต 145 ราย ค่ามัธยฐานของอายุคือ 61 ปี พบเพศชายและเพศหญิงใกล้เคียงกัน (1:1.02) อาชีพอยู่ในกลุ่มที่ไม่ได้ทำงาน (ร้อยละ 50.8) ผู้ป่วยส่วนใหญ่มีลักษณะโรคดังนี้ คือเป็นมะเร็งในส่วนลำไส้ใหญ่ (colon) ร้อยละ 71.08 เซลล์ชนิด adenocarcinoma ร้อยละ 96.15 และ well differentiated ร้อยละ 62.06 ผู้ป่วยระยะที่ 4 ร้อยละ 35.86 ตับเป็นอวัยวะที่มีการกลับเป็นซ้ำของโรค (ผู้ป่วยระยะที่ 1 ถึง 3) และมีการแพร่กระจายของเซลล์มะเร็งมากที่สุด (ร้อยละ 56.27) ผู้ป่วยร้อยละ 70 รับการรักษาด้วยการผ่าตัดร่วมกับเคมีบำบัด ค่ามัธยฐานของระยะเวลารอดชีพของผู้ป่วยคือ 148.86 สัปดาห์ อัตราการรอดชีพ 3 ปี 5 ปี และ 7 ปี เท่ากับ ร้อยละ 48.4, ร้อยละ 38.6 และ ร้อยละ 37.6 เมื่อวิเคราะห์ความสัมพันธ์เชิงซ้อน โดยใช้ Cox's Proportional Hazard Model พบว่าปัจจัยที่มีความสัมพันธ์กับระยะเวลารอดชีพอย่างมีนัยสำคัญทางสถิติ ($p<0.05$) ได้แก่ อายุ, degree of differentiation, stage, TNM, การรักษาด้วยการผ่าตัด และ การรักษาด้วยเคมีบำบัด

อายุ และระยะของโรคมีความสัมพันธ์กับระยะเวลารอดชีพ ผู้ป่วยระยะที่ 1 และ 2 มีระยะเวลารอดชีพมากกว่าผู้ป่วยระยะที่ 4 ผู้ป่วยอายุน้อย และอายุมากเป็นกลุ่มที่มีความเสี่ยงต่อการตายสูง ดังนั้นผู้ป่วยที่อยู่ในกลุ่มเสี่ยงต่อการเกิดโรคจึงควรได้รับการคัดกรองโรคตั้งแต่ระยะแรกของโรคซึ่งได้แก่ บุคคลที่มีคนในครอบครัวป่วยด้วยมะเร็งลำไส้ใหญ่ควรได้รับการคัดกรองก่อนอายุ 30 ปี ในการตรวจสุขภาพประจำปีของกลุ่มผู้สูงอายุควรได้รับการคัดกรองโรคมะเร็งลำไส้ใหญ่ร่วมด้วย

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CHAPTER I
INTRODUCTION

Cancer is a fatal disease. The incidence rate and the death rate have increased every year in many countries. The World Cancer Report predicts that new cases in the world will increase by fifty percent (or 15 millions) in year 2020. In year 2000, 5.3 million men and 4.7 million women developed malignant tumors, and altogether 6.2 million people died from the disease (12% of all death cases in the world) (1). In 2001, the US reported that cancer is the second cause of death, which is 22.9% (553,768). It is estimated that cancer the death rate due to cancer is 41.20% among all cases in 2004 (2).

In the past 15 years, cancer is ranked the third as the cause of death in Thailand (Heart disease and fatal accidents are the number one and two causes of death respectively). The death rate due to cancer has increased to 50.5 per 100,000 persons in 1996, comparing to 45 per 100,000 persons in 1992 (3). In 2002, cancer became the number-one cause of death, i.e. 73.3 per 100,000 persons, which is higher than the death rates from accidents, poisoning, hypertension and vascular diseases (4).

In most countries, colorectal cancer is the top five reasons among all cancerous illnesses and death cases. In the year 2000, World Health Organization (WHO) reported that the numbers of patients with colorectal cancer were 940,000 persons (9.4%) among all cancer patients and the colorectal cancer-related deaths were 500,000 persons (8%) from all cancerous death cases (1).

Lifestyle is one significant factor to colorectal cancer. People with western lifestyles such as those in the United States of America, Canada, The United Kingdom, France, Australia, and New Zealand have a high risk of colorectal cancer. The estimated cases of patients with cancer are 12.6% in men and 14.1% in women. Contrarily, low-risk countries like Eastern countries show the incidence cases are 7.7% in men and 7.9% in women (5). Globally, colorectal cancer runs the fourth rank

to cause death in both male and female. Age Adjusted Standard Rates (ASR) are 9.78 for men and 7.58 for women (6).

Morbidity rate in Western countries are higher than Eastern countries because of differences in lifestyles and types of food consumption. People in Western countries are meat lover. Hence, the incidence cases are higher as compared to Eastern countries. Surprisingly, the race is does not show any relationship to the disease. For instance, Japanese and Chinese people who migrated to the US can also be at higher risk than those who are in Japan and Chinese. (7).

In 2000, the colorectal cancer mortality rates in Japan went up to 32.4 per 100,000 males and 25.1 per 100,000 females, which were higher than the figures in 1990. Ten years ago, the mortality rates caused by colorectal cancers were 22.19 per 100,000 males and 18.23 per 100,000 females (8).

In Thailand, the morbidity rate of colorectal cancer is the fourth rank for men. It is behind liver cancer, lung cancer, and oral cancer respectively. For women, the morbidity rate of colorectal cancer is the sixth or seventh rank from 1977 to 1982 (9). However, in 1993, the rate of colorectal cancer incidence moved up to the third rank to replace the oral cancer in men, and the fifth rank in women, following cervix cancer; breast cancer; liver cancer; and lung cancer. The highest incidence case is in Bangkok with the ASR equals to 11.3, and the lowest incidence case is in Songkra with the ASR equals to 4.2 (10).

In 2002, deaths from all cancerous disease were 2.1 per 100,000 persons in both genders (4). Nonetheless, the colorectal cancer incidence has increased due to changes in lifestyle, environment, and food intake like fast foods or processed foods. Fast foods and processed foods are high in saturated fat and meat, and less in fiber. Many researches show foods in high meat and fat yield high risk for colorectal cancer.

Besides, alcohol consumption, smoking and genetics are other causes of such cancer. According to the statistics of year 2001 in Thailand, people who started smoking at the age of eleven were estimated 20.6% (11).

The survival time varies from patients to patients. It depends upon sex, age, career, localtion of primary tumor, histological type, degree of differentiation, progress of disease, treatment, number of tumor marker before and after operation, and other factors. The designs of many researches, emphasized on either comparing one by one

factor or factors from the same sample group. However, there were no indicators in Thailand, where difference characteristics of population, technology for screening and treatment exist. Based on the last study performed in 1999, a five-year survival rate was about fifty percent in Thailand (12). The value is almost the same as the value of the US from 1974 to 1976 (twenty year ago) (13). However, there is very little study on survival time of colorectal cancer patients in Thailand. Therefore, the study of prognostic factors of survival time aims to suggest the treatment of the disease.

Rajavithi Hospital was chosen to perform the study. It is the most well-known hospital for its fully-facilitated in Department of Medical Services. Also, there is a training center for extern-interns, general physicians, and sub-specialty training programs, e.g. Medicine, Surgery, Medicine Oncology, and Obstetric-Gynecology. Many walk-in patients and patients from referral system come to Rajavithi Hospital for services. From the data of Out Patient Department (OPD), the hospital provided services to approximately 781,125 patients each year, between year 2000 and 2002 (14). In 1995, cancer patients admitted under the Oncology unit were only 88 cases. After that, the numbers of cancer patients had increased to 338 in 1999 and 429 in 2003. In the past ten years, the mean of colorectal cancer patients was 13.67% from all cancer cases (the range is between 8.71% and 19.32%) (15).

Objectives

1. To study survival rate of colorectal cancer patients.
2. To study prognostic factors associated with survival time of colorectal cancer patients.

Hypothesis

Personal factors, tumor-related factors, and treatment will have effects on the survival time of colorectal cancer patients.

Limitation of study

The study is cohort study of survival rate and prognostic factors of colorectal cancer. The data was collected from patients' charts, medical records, pathology reports, and so on. In the past 10 years (1995-2004), there were many stage classifications. This study uses the last update of Modified Astler-Coller classification (MAC; 2002) by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) to classify stages. Colorectal cancer patients in Rajavithi Hospital have been treated by using standard clinical practice guideline (National Comprehensive Cancer Network (NCCN) practice guideline). The final status of the follow-up ended on August 31, 2004 using medical records, Population Registration Database, Ministry of Interior, letters, and phone calls.

Variables in study

Independent Variables

Personal Variables	age, gender
Tumor-related Variables	location of the primary tumor, histological type, degree of differentiation, clinical stage, primary tumor(T), regional lymph node (N), distant metastasis (M)

Treatment	Type of treatments (surgery, radiotherapy, chemotherapy)
Dependent Variables	Survival time
	Patient's final status

Definition

Colorectal cancer (CRC)

Cancer in cecum colon, ascending colon, transverse colon descending colon, sigmoid colon, rectosigmoid, and rectum (16).

Stage

This study uses the last update of Modified Astler-Coller classification (MAC; 2002) by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) to classify different stage of colorectal cancer.

Histological type

Types of tumorous cells that are confirmed by surgical biopsy.

Degree of differentiation

Development of tumorous cells by comparing the cells to the normal cells. It is confirm by pathology report.

Age

A patient's age is defined as the age at the time of diagnosis (in year).

Survival time

The length of time or duration from the date of diagnosis until the date of tumor-related death or the date at the end point.

5 year-survival rates

Ability to live for 5 years after being diagnosed with colorectal cancer.

Disease free interval

The duration time of after surgical tumor mass until recurrence of disease in patients with stage I to III.

Recurrence of disease

After surgery, patients with stage I to III had progression of disease or metastasis to other parts.

Censored

Patients were still alive until August 31, 2004, or who withdrew from the study for any reason or were lost for a follow up.

Event

Patients who died during the study period from colorectal cancer, or other cancer-related causes.

Lost follow up

Patients have been lost contact for 1 year or more, and were unknown status.

CHAPTER II
LITERATURE REVIEW

Reviewing of the literature is divided into 2 parts as follows:

1. Colorectal Cancer
2. Influential factors to colorectal cancer survival time

Colorectal Cancer

Anatomy (17-21)

The large bowel intestine is an organ of digestive system. It is the storage of the dross after digression, while the absorption functions at the small intestine. That is peristalsis function to absorb water and electrolyze that dross contract epithelium intestinal cell. The movement of the dross or feces to rectum is slow and fixed which helps to relieve the stool.

The length of the large bowel intestine is shorter than the length of the small intestine. It is approximately 1 to 1.5 meter (m.) long and extends from the cecum to the anus. The large intestinal can be divided into 4 parts:

1. Cecum and Appendix.

The appearance of the cecum is pouch-like, with the length of 5 to 7 centimeter (cm.). The cecum is contracted with the small intestine. The top of the cecum is located by the right iliac fossa, and is surrounded with peritoneum.

The vermiform appendix stands right below the lowest part of the cecum. It looks like a dead-end pipe (5-15 cm. long) and its function is unspecified.

2. Colon

It begins from the right of iliac fossa (end of cecum), and ends at the entry of the rectum. It is classified into 4 extents.

2.1 Ascending colon is 12 to 20 cm. long. It ends in the right flexure, which turns sharply to the left on the lower part of the right kidney posterior to the liver called hepatic flexure.

2.2 Transverse colon is the longest extent with the length of 40 to 50 cm., and is most mobile part of the colon. The transverse colon covers the area from the hepatic flexure to the splenic flexure.

2.3 Descending colon passes from the left flexure to the left iliac region. The average length is 25 to 30 cm.

2.4 Sigmoid colon extends from the end of the descending colon to the rectum, and its characteristic is s-shaped with the length of 15 to 50 cm.

3. Rectum

The rectum is 15 cm. long It is connected to the anal canal, and is separated into 3 parts:

The lower third rectum is 3 to 6 cm. apart from the anal verge. The middle third rectum is 6 to10 cm. in distance from the anal verge. The upper third rectum (distal sigmoid or rectosigmoid) extends approximately 10 to 15 cm. from the anal verge.

4. Anal canal

The anal canal is the terminal portion of the intestinal tract. It is 2.5 cm. to 3.8 cm. long, and has sphincter to control the mechanism of fecal continence.

Risk factors of colorectal cancer

Age: As people age, they are likely to develop colorectal cancer. Therefore, elder lees are at higher risk to be diagnosed with such cancers because their bodies have gradually stored up many carcinogens. Generally, colorectal cancer can occur to anyone at any age. But, over ninety percent of all the cases presents that people over the age of 50 develop colorectal cancer while people (22), who are young than forty, only represent 6-7% (23).

Sex: In the United States, the lifetime risk of developing colorectal cancer was 1 per 17 in males and 1 per 18 in females (13). In Australia, the lifetime risk of developing colorectal cancer was 1 per 18 in males and 1 per 28 in females (24).

Race: In the United States, the American-Africans are more potential to colorectal cancer than Caucasian Americans and Asians (13). However, in Africa, the Africans have low risk to develop colorectal cancer. On average, twenty-seven people are found to be diagnosed with colorectal cancer yearly in Gana (25). The study

established in Japan found Japanese refugees in Hawaii have higher risk of developing colorectal cancer than the Japanese in Japan (Age standardize incidence per 100,000 = 53.48 and 50.99 respectively) (5). Hence, the findings above demonstrate that people, who live in a developed country live USA, tend to be at risk of developing colorectal cancer.

Family history: Most colorectal cancers are sporadic whereas approximately ten percent represents familial syndromes. If a person has a first-degree relative (i.e. parent, brother, sister, or sibling) who has had colorectal cancer or adenomatous polyp (Herditary non polyposis colorectal cancer; HNPCC and Familial adenomatous polysis colitis; FAP) the risk for developing the disease of the person is increased (26-28). As the study shows, the risk of a person who has a family history of colorectal cancer is about 2.5 times the risk of normal people with no family history of colorectal cancer (29). Statistically, forty percent of all colorectal cancer patients with the age of less than forty years old indicate family history of colorectal cancer (30), and of all colorectal cancer patients, fifteen to twenty percent has family history of the disease (31).

Chronic inflammation: Patient who has chronic ulcerative colitis and Crohn's disease will have high risk of cancer (32, 33) because cancerous cell develop patterns from the chronic inflammation had incidence of colorectal cancer about 2%, 9%, and 19% at 10, 20, and 30 years, respectively (34). In addition, eighteen percent of rectal cancer patients are also Crohn's disease patients (35).

Bile acid: Patient who has been pancreactomy will have high risk of colorectal cancer. This is because the colon bowel irritates bile acid for 24 hours, or the bile acid secretes high lithocholic acid acting toxic more than normal from the high fat and high protein food consumption. It damages DNA, which affects cell growths, and abnormally transform to cancerous cells (36). In the other study, cholecystectomy increases cancer risk at the right colon (37).

Food: High fat, high protein and little fiber food will increase risk of colorectal cancer. Percentage of having colorectal cancer is likely high to occur with patients who love to eat high fat and high cholesterol foods (38, 39). The high heat baking red meat will produce heterocyclic amine. Thus, eating red meat for a long period of time will cause irritation to the bowel intestine, which affects normal cells, and eventually

changes to cancerous cells (39). Instead, high fiber foods such as vegetables and fruits will reduce the risk of colorectal cancer because fiber will clean food residue to prolong carcinogen in the bowel colon (40, 41).

Physical activity: Exercises help to decrease the risk of colorectal cancer for both male and female. It will help the bowel intestine to excrete faster and reduce contraction of dross with cells (42). The modulated physical activity to a high level is decreasing of colorectal cancer (43). According to the previous study defined, obesity relates to increase risk for normal body mass index (BMI) of the colon cancer by about 1.93 times (95% CI, 1.61-2.31) and of the rectum cancer by about 1.65 times (95% CI, 1.36-2.00) (44).

Smoking: Smoking is relatively risky to cause colorectal polyp which will develop to colorectal cancer. According to many studies, smoking habit of more than 20-30 years and the quantity of cigarettes will affect morbidity and mortality of colorectal cancer (45-47). Also, smoking affects the recurrence of colorectal cancer. However, the risk of colorectal cancer for thoes who stop smoking is reduced or low (48).

Alcohol consumption: Alcohol consumption is both direct and indirect cause of carcinogen in colorectal cancer development. Alcohol beverages may act to stimulate cell proliferation or suppress immunization (45). In addition, alcohol causes bile acid solution to become carcinogen in liver (35). Non-smoking drinkers who eat high quantities of vegetables and fruits will have low risk of colorectal cancer compared to those who both drink and smoke (45, 49).

Signs and Symptoms

The right side of the colon cancer is not associated with the change of bowel habit or obstruction because the size of the large bowel intestine is large and the feces is still liquid. Also, the patient has signs and symptoms of abdominal pain. The stool has mucous bloody. Other signs and symptoms are weakness, anemia, and weigh loss. The fined mass in abdominal estimate of colorectal cancer is about 10%.

The left side of colon is associated with the change of bowel habit and obstruction from the scar lesion. The obvious signs and symptoms are flatulence, constipation,

lack of fart, weakness, loss of appetite, and weigh loss. Also, there may be anaemia from hemafecia mixing blood loss.

The rectum colon is often associated with altered bowel. The patient may have diarrhea alternating with constipation, feces of narrow site, anal pain and irregular excrement of the stool.

The signs and symptums of colorectal cancer depend on the location of primary tumor and the stage. The major signs are hemafecia, constipation, abdominal pain, and feces of narrow site. Colonic obstruction in the senile of colorectal cancer disease is about 15%.

Pathology

Pathology of disease is defined by physical examination and the resection examination. These are location of primary tumor, histological type, degree of differentiation and regional lymph node distanted or in another organ. The data are used for diagnosis and treatments.

Location of primary tumor

Colorectal cancer is the cancer of cecum colon, ascending colon, transverse colon descending colon, sigmoid colon, rectosigmoid and rectum. It has two major parts: colon and rectum. Nationality is another factor to indicate the site of colorectal cancer disease (Table 1).

Table 1 Percentage of sites of colorectal cancer disease (12, 50).

Location	USA.*	Europe*	Thailand**
Colon			
- Right (Cecum Colon, Ascending colon) hepatic flexure	37	26	20
- Transverse colon splenic flexure	6	5	7
- Left (Descending colon, Sigmoid colon)	30	24	24
Rectum			
- Rectosigmoid	10	7	9
- Rectum	18	31	40

* 1985-1989 Gatta G, Cicolallo L, Cappocaccia R, Coleman MP, Hakulinen T, Møller H, et al. Differences in colorectal cancer survival between European and US populations: the importance of sub-site and morphology. *Eur J Cancer* 2003; 39: 2214-22.

** 1998 สุกัญญา จงถาวรสถิตย์. การรอดชีพของผู้ป่วยมะเร็งลำไส้ใหญ่ในประเทศไทย [วิทยานิพนธ์ปริญญาวิทยาศาสตร์มหาบัณฑิต สาขาโรคติดเชื้อและวิทยาการระบาด]. กรุงเทพฯ: บัณฑิตวิทยาลัย มหาวิทยาลัยมหิดล; 2541.

Histological Type

The majority types of colorectal cancer are classified by surgical biopsy. It indicated into three types as shown in Table 2.

Table 2 The histological type and percentage of colorectal cancer (12, 17, 20).

Type	Characteristic of present	Percentage	% in Thai*
Adenocarcinoma	Culumnar or cuboids overlapping become to the glandular cell	80-95	90.2
Mucionus carcinoma	Same as adenocarcinoma but has many the mucin	10-17	6.6
Signet ring cell carcinoma	The mucin producing tumor but the mucin stable in intracellular	1-2	1.6

** สุกัญญา จงถาวรสถิตย์. การรอดชีพของผู้ป่วยมะเร็งลำไส้ใหญ่ในประเทศไทย [วิทยานิพนธ์ปริญญาวิทยาศาสตร์มหาบัณฑิต สาขาโรคติดเชื้อและวิทยาการระบาด]. กรุงเทพฯ: บัณฑิตวิทยาลัย มหาวิทยาลัยมหิดล; 2541.

Definitions of Degree of differentiation (Broders, 1925) (51)

(By biopsy from the surgical biopsy)

- Well differentiated means 75-100% of cells have the same characteristic as normal cells and cell type can simply be identified. Glandular and nuclear polarity can be clearly detected.

- Moderately differentiated is a critical stage. However, the ability to tell cell type is reduced to 50-75%. This is tubular irregular complex and partially seen nuclear polarity.

- Poorly differentiated is a much more critical stage, and the ability to cell type is about 25-50%. These are irregular glandular structure and nuclear polarity is not completely seen.

- Undifferentiating cannot be defined.

Classification of Stage (16, 51-53)

After physicians know the pathology of cancer, they classify the stage that cancer invades in other segment or metastasis. The benefits of knowing the stage of disease are as follow:

- Know prognostic factors
- Use to define treatment
- Understand tumor biology of patients.
- Use to standardize the change of clinical information of cancer in all stages.
- Use to compare the progress of disease after treatment.
- Use all clinical information that is obtained from the surgical exploration by biopsy laparotomy for surgical evaluative stage.
- Use all data available at the time of surgery, which is based upon histological examination of all tissues removed during surgical treatment for post surgical pathologic stage.
- Provide retreatment staging when restaging is necessary for additional or secondary definitive treatment after a disease-free interval following the first treatment.

The most widely used and universally recommended staging system is the TNM method of the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC).

" T " refers to characteristics of the primary tumour in term of size, skin involvement, ulceration, or other changes.

" N " refers to characteristics of regional lymph node and localization of those that are involved.

" M " refers to distant metastases.

Thus, the staging system used is the TNM method used with Dukes' classification. After that, it is further developed with a complete method called "MAC (Modifine Aslter-Coller)" as shown in table 3.

Table 3 Classification of stage from colorectal cancer by AJCC, Dukes', and Aslter-Coller (16, 53)

AJCC Stage	T	N	M	Dukes'	MAC
0	Tis	N0	M0	-	-
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
II	T3	N0	M0	B	B2
	T4	N0	M0	B	B3
III	T1-T2	N1	M0	C	C1
	T3-T4	N2	M0	C	C2/C3
	Any T	N2	M0	C	C1/C2/C3
IV	Any T	Any N	M1	-	D

Definitions of TNM

Primary tumor (T)

Tx Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ interepithelial or invasion of lamina propria*

T1 Tumor invades submucosa

T2 Tumor invades muscularis propria

T3 Tumor invades through muscularis propria into subserosa, or into nonperitonealized pericolic or perirectal tissues

T4 Tumor directly invades other organs or structures, and/or perforates visceral peritoneum**'***

*note: Tis includes cancer cell confined within the glandular basement member (intraepithelial) or lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.

**note: Direct invasion in T4 includes invasion of other segments of the colorectalby way of serosa; for example, invasion of sigmoid colon by a carcinoma of the cecum.

***note: Tumor that is adherent to other organs or structures, macroscopically, is classified T4. However. If no tumor is present in the adhesion, microscopically, the classification should be pT3. The V and L substaging should be used to identify the presence or absence of vascular or lymphatic invasion

Regional lymph node (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph nodes metastasis

N1 Metastasis begin in 1 to 3 regional lymph node

N2 Metastasis in 4 or more regional lymph node

Distant metastases (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

Treatments

Surgical treatment is the most widely used treatment with four staging patients of colorectal cancer. It is commonly used and universally recommended for diagnostic and specific treatment. The process is to directly cut cancerous cells and tumor mass. The treatment can reduce pain from obstructive massive cancer that effects abdominal pain, which causes constipation.

Radiotherapy is commonly used before and after the surgery to limit the spreading of cancerous cells, and to reduce its' size for rectum cancer. It can also reduce pain and bleeding.

Chemotherapy, which is divided into 3 types

1. Neoadjuvant Chemotherapy is the first choice of chemotherapy treatment for control tumour size of atrophy and distribution. It is used after, with the pre-operative radiotherapy for rectal carcinoma patients (chemo radiotherapy).

2. Adjuvant Chemotherapy is chemotherapy treatment after surgery. The objective is to damage remaining tumors. The treatment is mostly used with all Duck's C patient and some Dusk's B2 in a high risk group.

3. Palliative Chemotherapy is chemotherapy treatment to be used for patients with stage IV or Dukes' D who have tumor metastasis to other organs or recurring disease. The aim of this treatment is to palliate symptoms and prolong survival time but not curative.

The most common chemotherapy used is 5-Fluorouracil (5-FU). It can be used alone or in combination with other drugs (e.g. Leucovorin (LV), Capecitabine, Irinotecan, Oxaliplatin and et.al.). However, the common side effects are diarrhea and mucositis.

Influential factors of colorectal cancer survival rate.

Gender

Colorectal cancer is a common malignancy in both sexes for different survival times. According to the previous study by Ronald C, et al (54), the 5-year survival rates (5Y-SR) of patients with positive lymph node in female showed higher than in male (45%, and 37%, respectively: p=0.053). The same study by Angell AE, et al(55), in Norway found the 5Y-SR in male and female were about 56% (95 % CI, 54.6-58.0) and 60% (95 % CI, 57.9-61.2), respectively, and the relative risk (RR adj.) for female was 0.88 (95 % CI, 0.86-0.90). In another study, the death rate of male was about 2% higher than the death rate of female. Also, in the group of same age, the death rate of male was still higher than that of female (male's age over 65 years, female's age between 60-69 years) (56). However, in the young patient group, the survival time both sexes is not significantly different (33).

Age

Colorectal cancer is generally found in the group of people with age over 50 years. However, a significant proportion of patients with age under 40 years also has the disease. The 5-year survival rates of patients with age over 75 years were less possible than patients with age under 75 years (28 %, and 44 %, respectively) (54). Mortality rate of patients over 60 years old is twice or three times higher than that of those who are under 60 years old in both male and female (56). This is due to patients lose the function of immune response system which deteriorates by aging and depression from tumor treatment through chemotherapy and radiotherapy. In other study, patients under the age of 45 have poor prognosis because they usually come for treatment in the last stage (31, 57). In addition, young patients had worse grade tumors (moderately and poorly differentiated). Their histological types were signet-ring and they had more mucinous carcinoma than elder patients (31, 32, 57). Although both young and older patients had poor prognosis, the survival rate of young patients was higher than the survival rate of older patients whose the overall 5Y-SR was 30 to 60% (31, 58-60)

Location of primary tumor

Site of tumor is another factor that influence on the survival time. The 5-year survival rates of patients with colon cancer was higher than patient with rectal cancer. The reason for high 5Y-SR is that the muscle of the rectum was more flexible so it hides the sign of the disease until it is developed to an advanced and critical stage. In addition, the rectum is located inside the pelvic whose cavity makes it difficult for treatment, and the risk of complication can increase. However, the 5-year survival rates of patients with rectal cancer showed higher survival rate in the first year of a follow-up, which is possibly due to earlier diagnosis for site of tumor, is more accessible for clinical examination. In Italy, the 5-year survival rates of colon cancer and of rectum cancer were about 34% and 28%, respectively (61). In US and England, the 5-year survival rates of colon cancer were 62% and 43%, respectively, and the 5Y-SR of rectal cancer were 60% with 39%, respectively (50).

Histological type

About 90-95% of histological type was adenocarcinoma. The rest was found in other types such as young-aged patients with poor prognosis. In Australia, 5-year survival rates of patients with mucinous carcinoma was 31%, and that with adenocarcinoma was 40%. O'Conell JB, et al (23), had reviewed the study of colorectal cancer in young patients. They found the 5Y-SR of patients with mucinous adenocarcinoma was 24.7 % (range 11.3%-41.6%).

Degree of differentiation

The degree of differentiation which affected the survival rate is associated with primary tumor (T) and regional lymph (N) (62). Patients with different degrees of differentiation have different probabilities of positive lymph node metastasis. For example, patients with well differentiated was 25% chance of lymph node metastasis. For example, patients with moderately and poorly differentiated were 50% and 40% chance of lymph node metastasis, respectively. As a result, the 5Y-SR of each differentiation was 80%, 60%, and 25%, respectively. Many studies reported the survival rate of well differentiated is higher than moderate and poorly differentiated (56, 59, 60). Further, T1-3 N0M1 of rectal cancer patients with different degree of

differentiation also have different survival rate. The well differentiated patients will have a high percentage to live up to five years, i.e. 75 to 76.86%. Those with moderately differentiated will have 54.75 to 64% chance to live up to five years while those with poorly differentiation will have only 18.75 to 25% 5Y-SR (63, 64).

Clinical stage

The clinical stage is the most common factor to predict survival time of cancer patients. The early the stage is known, the higher is the curability rate. After surgery, more than 80%, 70%, and 40% (Dukes' A, B, and C, respectively) can expect to live longer than 5 years. About 1 in 3 (30%) of patients with Dukes' D would live for at least 2 years after palliative surgery (65). Some study found the 5Y-SR, according of the Dukes' classification were 93.4%, 84.5%, and 74% (Dukes' A, B, and C, respectively) for colon cancer and 93.9%, 79.8%, and 64.7%, respectively, for rectal cancer (66). In USA, American Cancer Society reported that, the 5Y-SR of patients with localized stage (T1-4N0M0) was 90%; of patients with the regional stage (T1-4N1-2M0) was 65%; and of patients with distant stage was 19% (13). A similar study in Norway, found the 5Y-SR of patients with stage I-II were 84% for male and 87% for female while the 5Y-SR of patients in stage III was 64% for male and 65% for female. Those in stage IV were 15% and 22% for male and female, respectively. In addition, the risk of death of patients with M1 was 8.66 times (55).

Treatment

Although surgery is still the only way to cure, it is the best way to palliate patients with colorectal cancer regardless of patient's age. But, the combination of radiotherapy and/or chemotherapy may provide palliation, and improve the quality of life and/or survival. In Japan, the 5Y-SR of patients with surgery treatment alone was 79.5% and 60.2% in colon and rectal cancer, respectively (67). The National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol C-01 found that the 5Y-SR of patients who had surgery plus chemotherapy was 60% compared to 58% for surgery alone ($p=0.05$) (68). According to a similar study in China, the 5Y-SR of patients treated with surgery plus chemotherapy would have higher rate compare with patients who underwent surgery alone (60.72% and 55.01%, respectively) (69). In addition, the

disease-free survival was higher for patients who received surgery plus chemotherapy. The survival rate of patients who unresection was lower (3Y-SR, 7%) and the 3Y-SR of patients who received resection was about 57% (70). In rectal cancer, the survival rate of patients with pre-operative radiotherapy-chemotherapy (5-FU) was higher than patients with chemotherapy alone (71). Radiotherapy can reduce the number of local recurrences and increase the survival time. Paris V, et al (72) found after a three-year follow-up, patients who responded to pre-operative radiotherapy had no recurrences (0%). Conversely, patients who did not respond to pre-operative radiotherapy showed 7% recurrences and patients who were not treated with operative radiotherapy had 41% recurrences. Chemotherapy would be helpful to increase the survival time for patient at stage III and IV (73).

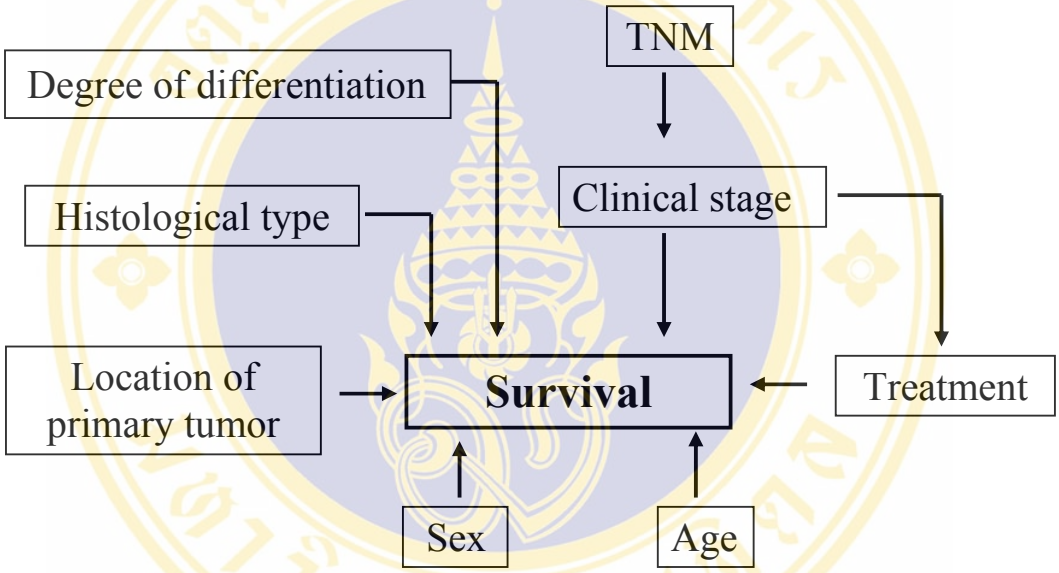


Figure 1 Conceptual framework

CHAPTER III
MATERIALS AND METHODS

Study design

This study was an ambispective cohort at the Oncology Unit, Rajavithi Hospital. The data was collected from the medical records of colorectal cancer patients for retroactive nine years from January 1, 1995 to December 31, 2003; and followed up patient's status until August 31, 2004, from medical records and the Population Registration Database, Ministry of Interior.

Study site

Oncology Unit, Department of Medicine, Rajavithi Hospital.

Study population

This study included all cases of colorectal cancer diagnosed by pathologic examination with treatment at Oncology Unit, Department of Medicine, Rajavithi Hospital from January 1, 1995 until to December 31, 2003.

Inclusion criteria

1. Patients had been diagnosed with colorectal cancer (location of primary tumor is colorectal).
2. Patient has Thai nationality.

Exclusion criteria

1. Since patients were after referred to Oncology Unit, they had neither been treated for cancer at Oncology Unit, Department of Medicine, Rajavithi Hospital, nor attended Oncology Unit continuously, and nor received appropriate treatment due to their losses to follow up for at least 3 months (except stage IV disease who received supportive treatments).

2. Patients had cancer history in different location (excuse Tix), and were not cured for this disease, or were completely cured for less than 3 years.

Sample size

No sample size estimation. All patients who stratified the criteria were included in the study.

Research tools

Using information record model, which was created by researchers, the model has been approved by the oncology specialist. The information record breaks the records into four parts:

Part 1 Personal factors: age, gender, occupation and address.

Part 2 Tumor-related factors: date of diagnosis, sign and symptom, location of the primary tumor, histological type, degree of differentiation, clinical stage (MAC stage), primary tumor (T), regional lymph node (N), distant metastasis (M), site of metastasis, carcinoembrynic antigen level (CEA).

Part 3 Data of treatment: date of first operation, start date of adjuvant chemotherapy or palliative chemotherapy, date of recurrence, type of treatments, response to treatment.

Part 4 Patients' final status: date of death, cause of death.

Data collection

The information was collected and recorded from medical records, pathology reports, operative records, radiology reports (CT, x-ray), summary sheets, etc. It was done by using Information Record Model. The information included test density after the information was approved for the correctness and use of data code. Then, there are data analysis and correction analysis by computer software.

Data analysis

Standard software was used for data analysis. The variables in this study were classified into 2 groups.

Independent factors: age, gender, location of the primary tumor**,** histological type, degree of differentiation, clinical stage (MAC stage), primary tumor (T), regional lymph node (N), distant metastasis (M), and type of treatments.

Dependent factors: Survival time, Patients' final status.

Analytic statistics

1. Descriptive statistic was used to explain personal factors, tumor-related factors, and treatment of population study sample. They are expressed by using table, frequency, percent, mean and standard deviation.

2. Descriptive statistic for survival study

Kaplan-Meier was used to estimate the median survival time of independent factors. The log-rang test was to test difference between subgroup of independent factors at 95 percent confident interval. Cox's Proportional Hazard Model with unadjusted was used to determine the relationship between independent factors and survival time at 90 percent confident interval.

3. Analytic statistic for survival study

Cox's Proportional Hazard Model was used to determine the factors that have influence on the survival time and estimate hazard ratio (HR) of subgroup at 95 percent confident interval.

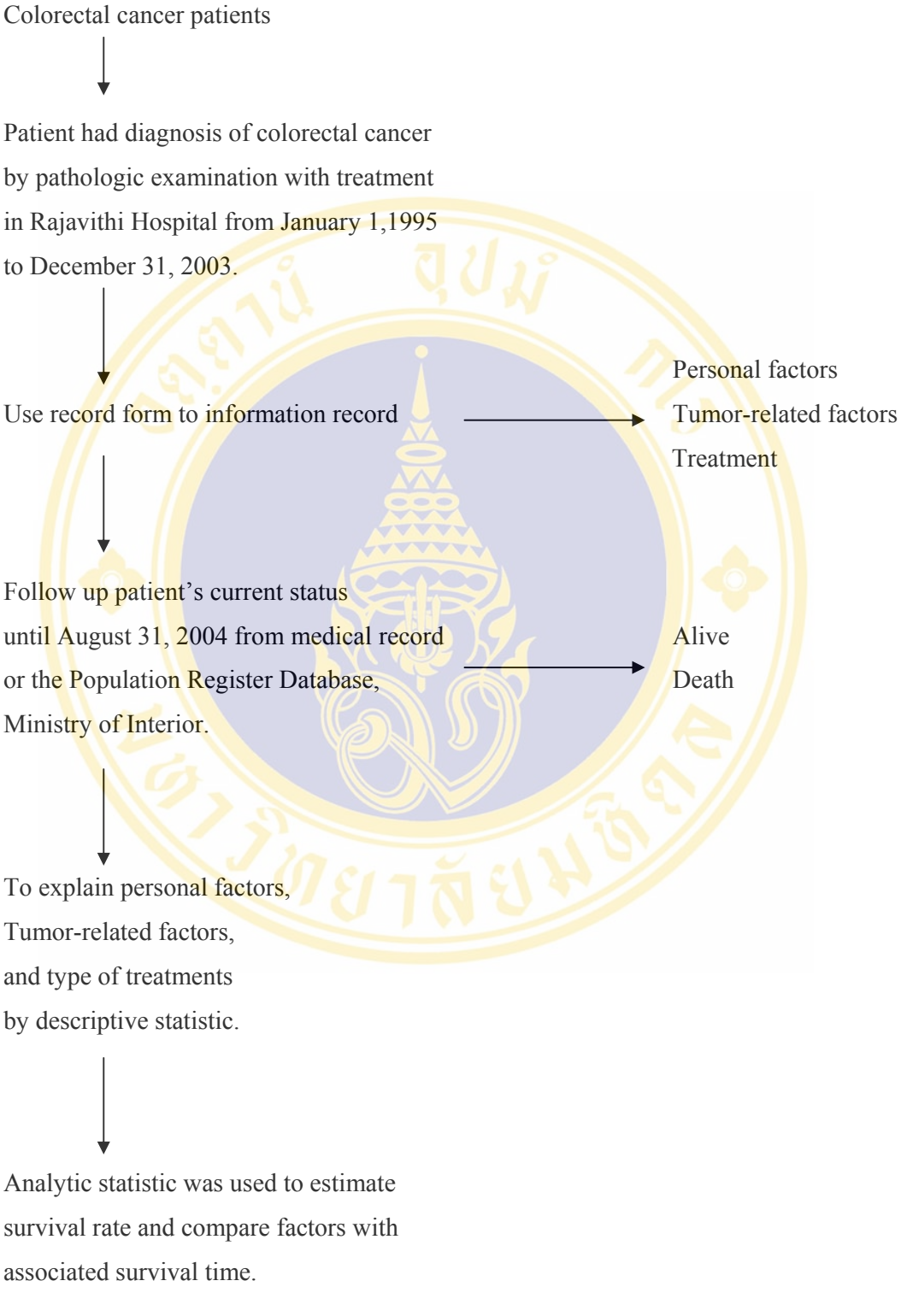


Figure 2 Study design

CHAPTER IV
RESULT

This study defined the survival rates and prognostic factors of the colorectal cancer patients at the Oncology Unit, Rajavithi Hospital. The data was collected from the medical records of patients for retroactive nine years from January 1, 1995 to December 31, 2003. Totally, 430 cases were included 287 cases were with the follow-up of last status until August 31, 2003; 242 cases were from the medical records and the Population Registration Database, Ministry of Interior; 39 cases were letters and telephones, and 6 cases could not be found for follow-up of the last status. The results were divided into 4 parts, as follow:

Part 1: The general characteristics of the colorectal cancer (CRC) patients.

Part 2: The comparative differences of the survival time for determining the survival time in subgroup of personal factors, tumor-related factors and type of treatments by using univariate analysis method by Kaplan-Meier and log-rank test.

Part 3: Analysis of the relationships between personal factors, tumor-related factors, type of treatments and the survival time by Cox's Proportional Hazard Model (unadjusted).

Part 4: The multivariate analysis of the relationship between personal factors, tumor-related factors, type of treatments and survival time by Cox's Proportional Hazard Model.

Part 1 The general characteristics of the colorectal cancer patients.

Personal factors

About 58.54% of CRC patients lived in Bangkok and suburban. The percentage of female was 50.52%. The median age was 61 years (range 19–91, SD=13.37). High percentage rate were found in the age group of 61–70 years, 51– 60 years, and 71– 80 years (28.57%, 24.40%, and 18.47 %, respectively). The most common occupation

was unemployment group (50.87%, such as retired government officials and housewives or unemployed). Detail is shown in Table 4.

Table 4 Number and percentage of personal factors of CRC patients.

Variables	No. of observation	
	number	percent
Site		
Bangkok, suburban	168	58.54
Province	117	40.77
Unknown	2	0.69
Sex		
Male	142	49.48
Female	145	50.52
Age at diagnosis (years)		
<41	36	12.54
41-50	36	12.54
51-60	70	24.40
61-70	82	28.57
71-80	53	18.47
>80	10	3.48
Median = 61, SD = 13.37		
Career		
Housewife or unemployed	120	41.81
Employee	57	19.86
Merchant	31	10.80
Retired government official	26	9.06
Agriculture	21	7.32
Government official	18	6.27
Other	7	2.44
Unknown	7	2.44

Tumor-related factors

The patients with sign of intestinal obstruction were 86 cases and 3 cases had intestinal perforation.

The location of primary tumor (site of tumor) found in colon was 71.08% (such as right colon 19.51%, transverse colon 9.41%, and left colon 42.16%, respectively) and in rectum was 28.92%.

The adenocarcinoma was the most common of histological type (95.82%) and 4.18% of other type (such as mucinous adenocarcinoma, signet ring cell carcinoma, and unknown).

The degrees of differentiation were well differentiated, 60.98%; moderately differentiated, 32.40%; and poorly differentiated 4.88%, respectively.

Patients with lymphatic invasion were 13 cases and 6 cases of blood vessel invasion.

There were four stage of disease found, stage IV has the highest cases, followed by stage III, and stage II (35.86%, 31.71% and 29.96%, respectively).

Primary tumor (T), T4 was the most commonly found followed by T3, T2, and Tx (69.34%, 23.00%, 3.83%, 3.48%, respectively). In the case of the regional lymph node (N), the most common incidence was N0 (40.77%), follow by N1 (30.66%) and N2 (25.44%). The distant metastases (M) showed that 64.11% was M0.

Recurrence was found 34.78% in stage I, II, and III. Patients at stage II and III had recurrence of disease about 25.58 and 46.15%, respectively.

Table 5 Numbers and percentage of tumor-relate factors of CRC patients.

Variables	No. of observation	
	number	percent
Obstruction		
No	194	67.60
Yes	86	29.96
Unknown	7	2.44
Perforation		
No	277	96.52
Yes	3	1.04
Unknown	7	2.44
Site of tumor		
Colon* Right colon	56	19.51
Transverse colon	27	9.41
Left colon	121	42.16
Rectum**	83	28.92
Histological type		
Adenocarcinoma	275	95.82
Mucinous Adenocarcinoma	10	3.48
Signet ring cell carcinoma	1	0.35
Unknown	1	0.35
Degree of differentiation		
Well differentiated	175	60.98
Moderately differentiated	93	32.40
Poorly differentiated	14	4.88
Unknown	5	1.74
Lymphatic invasion		
No	260	90.59
Yes	13	4.53
Unknown	14	4.88

* right colon = ascending and hepatic flexure; transverse colon = transverse and splenic flexure; left colon = descending and sigmoid.
**rectum = rectosigmoid and rectum.

Table 5 Numbers and percentage of tumor-relate factors of CRC patients (continued).

Variables	No. of observation	
	number	percent
Blood vessel invasion		
No	267	93.03
Yes	6	2.09
Unknown	14	4.88
Stage		
I	7	2.44
II	86	29.96
III	91	31.71
IV	103	35.89
TNM		
T		
T1	1	0.35
T2	11	3.83
T3	66	23.00
T4	199	69.34
Tx	10	3.48
N		
N0	117	40.77
N1	88	30.66
N2	73	25.44
Nx	9	3.13
M		
M0	184	64.11
M1	103	35.89
Recurrent (Stage I,II,III)(n = 184)		
No	120	65.22
Yes	64	34.78
Stage II (n = 86)	22	25.58
Stage III (n = 91)	42	46.15

Site of metastasis

Liver was the most common site of metastasis in recurrence and stage IV patients. The next common sites were intra abdominal organ and intra abdominal lymph node. The median number of metastasis site was 1 (range1- 6 sites) (Detail is shown in Table 6).

Table 6 Numbers and percentage of site of metastasis by location of primary tumor.

Site of metastasis	colon		rectum	
	number	percent	number	percent
Stage II and III with recurrence	n = 48		n = 16	
Lung	9	18.75	3	18.75
Liver	14	29.17	7	43.75
Bone	2	4.17	1	6.25
Intra abdominal lymph node	12	25.00	3	18.75
Other lymph node	1	2.08	0	0.00
Intra abdominal organs*	24	50.00	6	37.50
Other organs**	1	2.08	1	6.25
Unspecified	5	10.42	1	6.25
Stage IV	n = 64		n = 39	
Lung	7	10.94	7	17.95
Liver	41	64.06	32	82.05
Bone	0	0.00	1	2.56
Intra abdominal lymph node	9	14.06	6	15.38
Other lymph node	3	4.69	2	5.13
Intra abdominal organs*	23	35.94	11	28.20
Other organs**	0	0.00	4	10.26

* Intra abdominal organs: small bowel, stomach, abdominal, peritoneum, bladder, omentum, pancreas, gall bladder, kidney, pelvis, uterus, ovary, ureter, colon, and rectum.
** Other organs: anus, perineum, vaginal, and seminal tube.

Treatment

The percentage of patients who had been treated by surgical therapy with chemotherapy was 70.73%. About 14.98% of patients had been treated with three treatments (surgery combined with chemotherapy and radiotherapy). Surgery alone was 9.76%, and chemotherapy alone was 4.18%. Detail is shown in Table 7, 7.1, 7.2, 7.3, and 7.4.

Table 7 Numbers and percentage of treatments of CRC patients.

Variables	No. of observation	
	number	percent
Treatment (n=287)		
Surgery only	28	9.76
S+CT	201	70.03
S+RT	1	0.35
S+CT+RT	43	14.98
Chemotherapy only	12	4.18
CT+RT	1	0.35
Supportive	1	0.35

S: Surgery, CT: Chemotherapy, and RT: Radiotherapy

Table 7.1 Numbers and percentage of treatments of CRC stage I - III.

Variables	No. of observation	
	number	percent
Stage I (n = 7)		
Surgery only	6	85.71
S+CT+RT	1	14.29
Stage II (n = 86)		
Surgery only	7	8.14
S+CT	68	79.07
S+CT+RT	11	12.79
Stage III (n = 91)		
Surgery only	7	7.69
S+CT	62	68.13
S+CT+RT	22	24.18

S: Surgery, CT: Chemotherapy, and RT: Radiotherapy

Table 7.2 Numbers and percentage of treatment of CRC stage IV.

Variables	No. of observation	
	number	percent
Stage IV (n = 103)		
Surgery only	8	7.77
S+CT	71	68.93
S+RT	1	0.97
S+CT+RT	9	8.74
Chemotherapy only	12	11.65
CT+RT	1	0.97
Supportive	1	0.97

Stage IV, surgery is means palliative surgery.
S: Surgery, CT: Chemotherapy, and RT: Radiotherapy

Table 7.3 Numbers and percentage of type of surgery by stage.

Stage	number	Curative surgery (%)	Palliative surgery (%)*
I	7	7 (100.0)	-
II	86	86 (100.0)	6 (7.0)
III	91	90 (98.9)	9 (9.9)
Total	184	183 (99.5)	15 (8.1)

* Palliative surgery was done when disease recurrence

Table 7.4 Numbers and percentage of type of chemotherapy by stage.

Stage	number	Neoadjuvant CT (%)	Adjuvant CT (%)	Palliative CT (%)*
I	7	-	1 (14.3)	-
II	86	2 (2.3)	77 (89.5)	11 (12.8)
III	91	1 (1.1)	79 (86.8)	24 (26.4)
IV	103	1 (0.9)	-	93 (90.3)
Total	287	4 (1.4)	157 (54.7)	128 (44.6)

* Palliative chemotherapy was done when disease recurrence

Part 2 To analyze comparative differences of the survival time of the colorectal cancer patients with personal factors, tumor-related factors, and type of treatments by using the Kaplan-Meier and the log-rank test.

Overall

Of two hundred eighty-seven cases, 145 cases died. One hundred forty-two cases (49.48%) were alive at the time of study period, or could not be found for follow-up of the last status. The incidence density was 3.58 per 1,000 persons-week and the median survival time was about 148.86 weeks. The overall 3, 5, and 7-years survival rates were about 48.4%, 38.6%, and 37.6%, respectively.

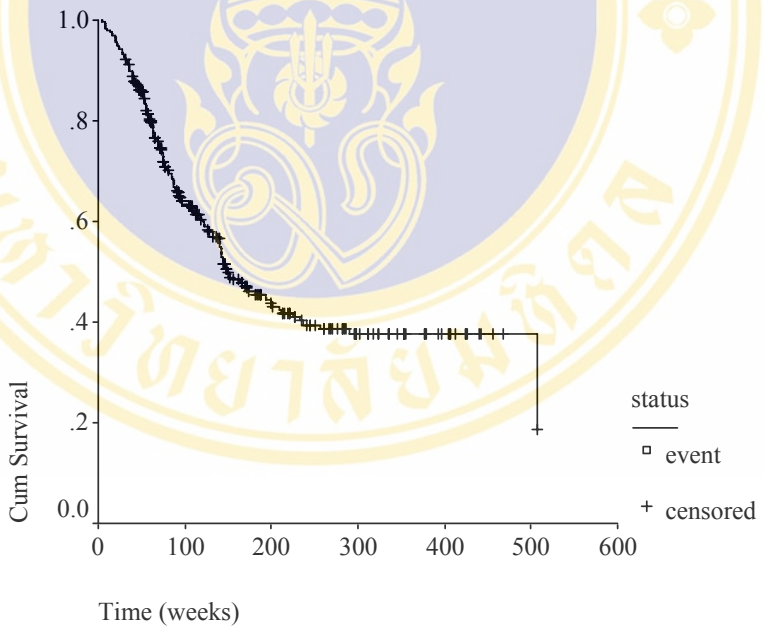


Figure 3 The overall survival curves of the CRC patients.

The factors were not significantly different with the survival time including gender (p=0.825), the site of tumor (p=0.093), and histological type (p=0.983)

The factors such as age, degree of differentiation, stage, the primary tumor (T), regional lymph node (N), distant metastasis (M), and treatment were significantly different with the survival time.

Age

Patients with age over 80 years had the highest incidence density, 7.5 per 1,000 persons-week and the median survival time of 109.71 weeks. The other age groups of less than 41 years, 41–50 years, 51–60 years, 61–70 years, and 71–80 years had lower amounts of incidence density were 2.42, 2.16, 3.10, 4.85, and 3.99 per 1,000 persons-week, respectively, and the median survival times were >146.57, >256, 192.57, 139.71, and 123.29 weeks, respectively.

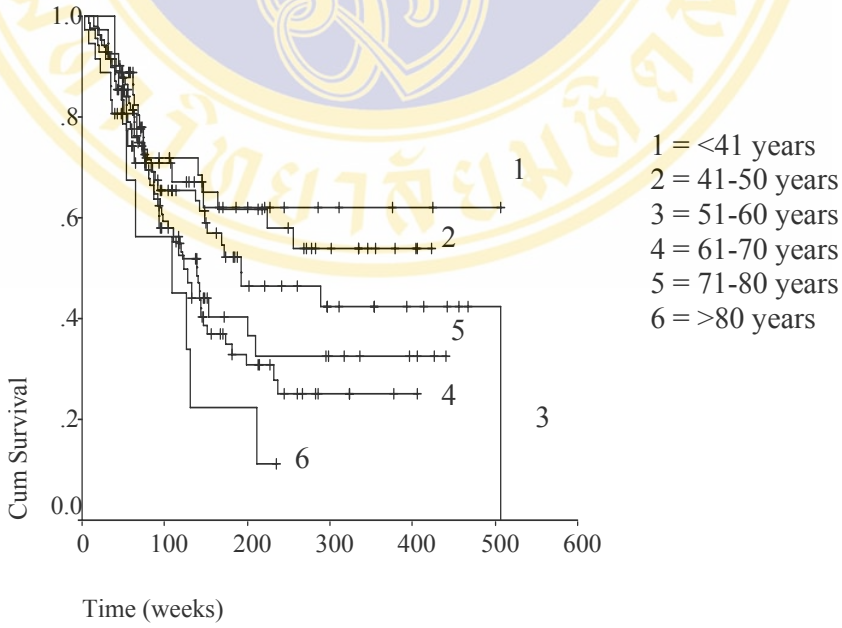


Figure 4 Comparison of survival curves of patients by age group (p=0.044)

Degree of differentiation

Patients with well, moderately, and poorly differentiated had incidence density of 3.22, 3.69 and 9.54 per 1000 persons-week, respectively. The median survival times were 171.86, 141.43, and 55.86 weeks, respectively

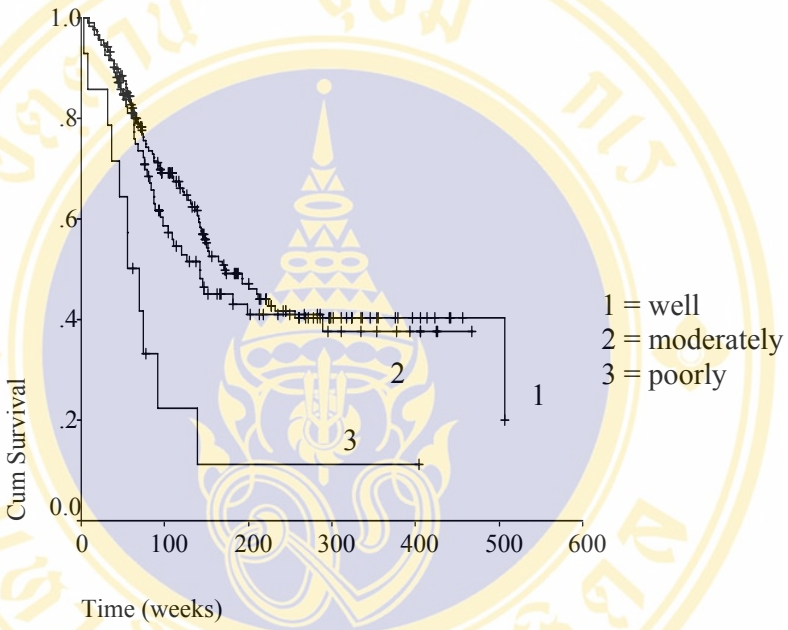


Figure 5 Comparison of survival curves of patients among degree of differentiation (p=0.002)

Stage

Patients with stage I plus II, III and IV had incidence density of 1.02, 3.07, and 10.41 per 1000 persons-week, respectively. The median survival times were 256.00, 201.14, and 68.57 weeks, respectively.

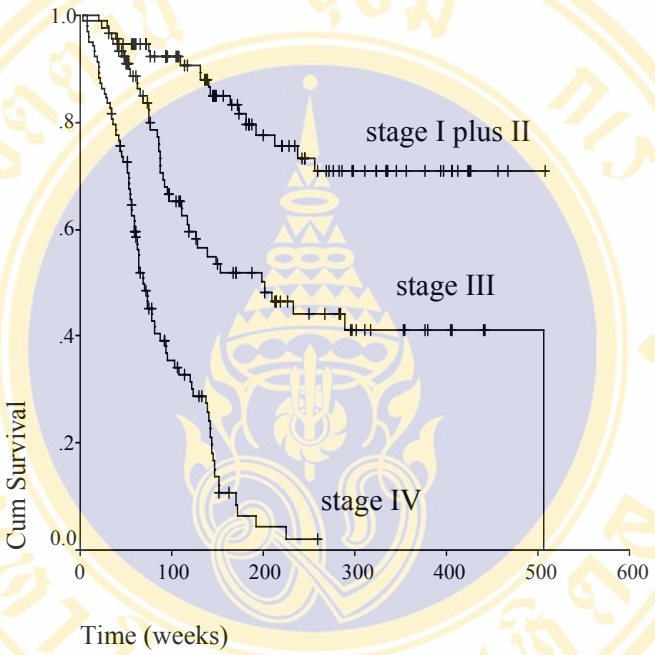


Figure 6 Comparison of survival curves of patients among stages (p=0.002)

Primary tumor (T)

Patients with T1 plus T2, T3, T4, and Tx had incidence density of 0.41, 3.49, 3.62, and 13.65 per 1000 persons-week, respectively. The median survival times were >53.57, 143.86, 148.86, and 44 weeks, respectively.

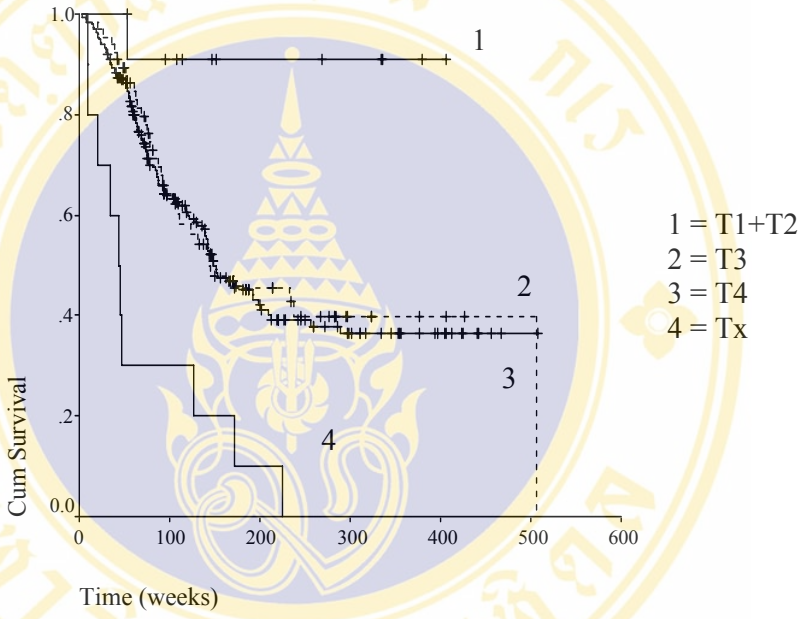


Figure 7 Comparison of survival curves of patients among T (primary tumor) involvement ($p<0.001$)

Regional lymph node (N)

Patients with N0, N1, N2, and Nx had incidence density of 1.88, 3.74, 7.24, and 15.99 per 1000 persons-week, respectively. The median survival times were >256, 139.71, 78.43, and 34.29 weeks, respectively.

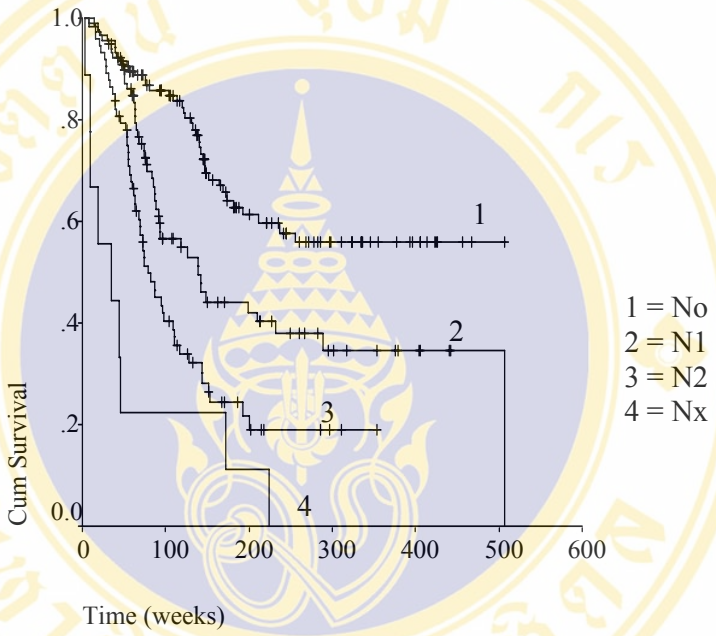


Figure 8 Comparison of survival curves of patients among N (regional lymph node) involvement ($p<0.001$)

Distant metastasis (M)

The incidence density of patients with M0 (no metastases) was 1.9 per 1000 persons-week and 10.41 per 1000 persons-week for patients with M1 (metastases). The median survival times were 506.71 and 68.51 weeks, respectively.

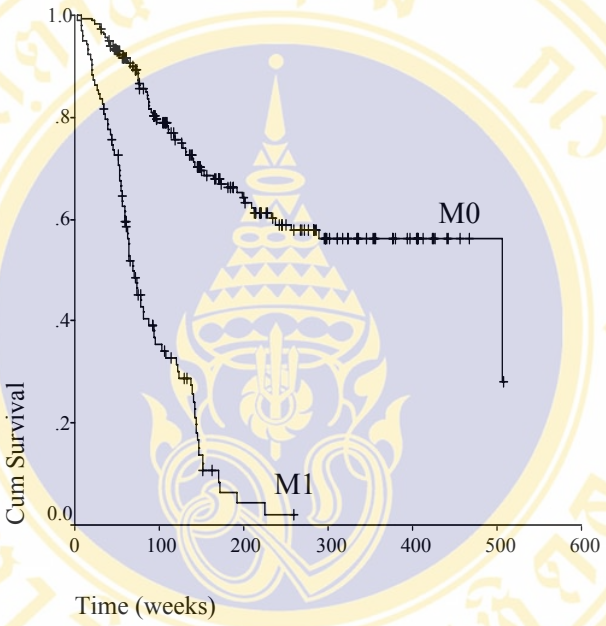


Figure 9 Comparison of survival curves of patients according to metastatic status ($p<0.001$)

Treatment

The patients received any combination of treatments: surgery (S) combine with radiotherapy (RT) and chemotherapy (CT), surgery plus chemotherapy, radiotherapy plus chemotherapy or surgery, surgery alone, chemotherapy alone and supportive treatment had incidence density about 2.99, 3.10, 5.40, 6.84, 15.27, and 101.42 per 1000 persons-week, respectively. The median survival times were 192.57, 198.71, 93.29, 74.71, 46.00, and 9.86 weeks, respectively.

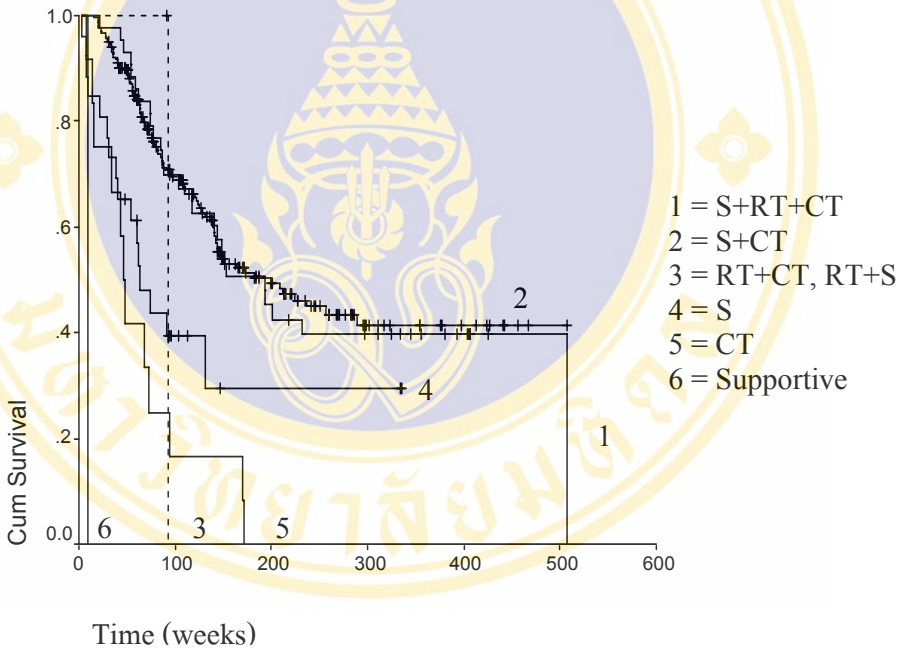


Figure 10 Comparison of survival curves of patients by type of treatments ($p<0.001$)

Type of treatment in individual clinical stage

Stage I plus II

There was not a significant difference with survival times among patients who received different treatments in patients stage I plus II (p=0.101). The incidence density of surgery combine with radiotherapy and chemotherapy, surgery plus chemotherapy, and surgery alone were 0.27, 1.07, and 2.23 per 1000 persons-week, respectively. The median survival times were >192.57, >256.00, and >131.71 weeks, respectively. (Detail is shown in Table 8)

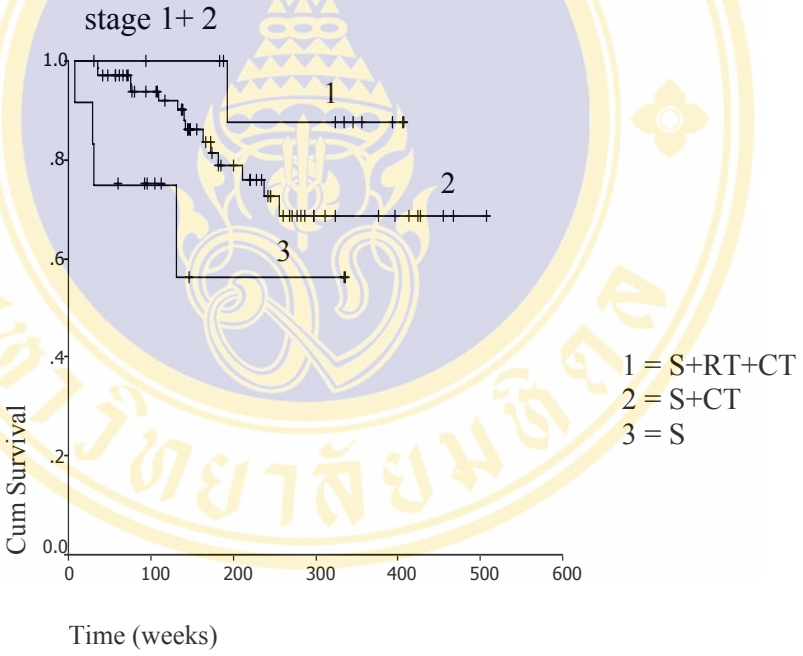


Figure 11 Comparison of survival curves of treatment received in patients with stage I add II

Stage III

Stage III patients receiving surgery and chemotherapy had significantly higher survival when compared with surgery combined with radiotherapy and chemotherapy, and surgery alone (p=0.002). The incidence density of patients received surgery combines with radiotherapy and chemotherapy, surgery plus chemotherapy, and surgery alone were 3.9, 2.33, and 10.53 per 1000 persons-week, respectively. The median survival times were 118.29, 289.43, and 74.71 weeks, respectively. (Detail is shown in Table 8)

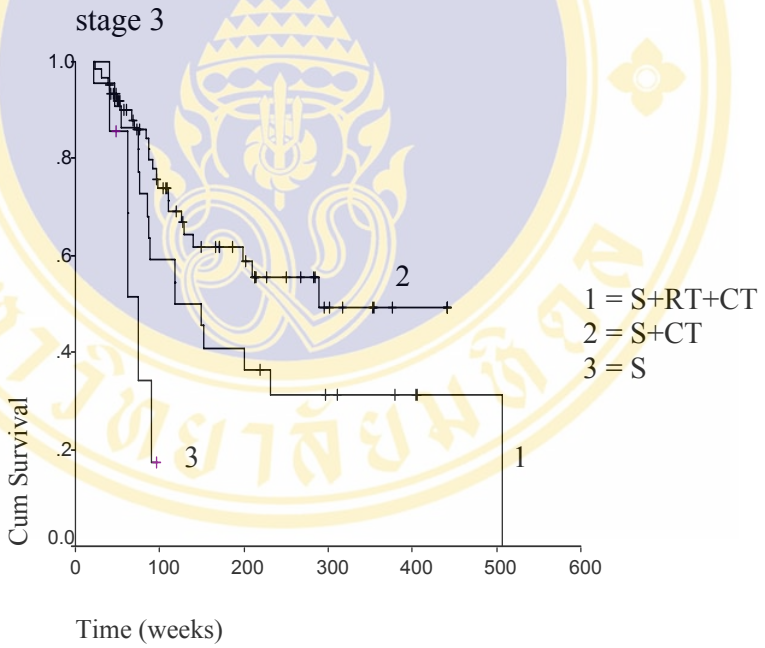


Figure 12 Comparison of survival curves of treatment received in patients with stage III

Stage IV

There was a significantly different with survival times among patients who received treatment in stage IV ($p<0.001$). Surgery combined with radiotherapy and chemotherapy, surgery plus chemotherapy, radiotherapy plus chemotherapy or surgery, surgery alone, chemotherapy alone and supportive treatment had incidence density were 9.46, 8.93, 5.40, 37.33, 15.27, and 101.42 per 1000 persons-week, respectively. The median survival times were 103.43, 78.14, 93.29, 19.57, 46.00, and 9.6 weeks, respectively. (Detail is show in Table 8)

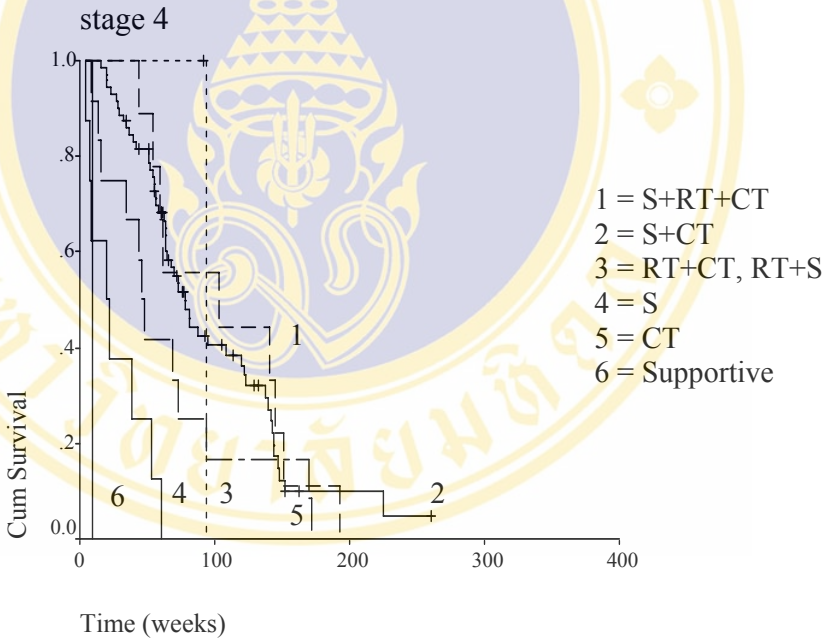


Figure 13 Comparison of survival curves of treatment received in patients with stage IV

The survival rate of colorectal cancer (Detail is shown in Table 8)

The overall 3-years survival rates were about 48.4%. The 5-year survival rates showed the similar rate as the 7-year survival rates

The 3-year survival rates (3Y-SR)

Age

The 3-year survival rates of patients with age under 41 years were 61.9%. The patients with age 41-50 years, 51-60 years, 61-70 years, 71-80 years and age over 80 year were 65.2%, 56.9%, 37.0%, 44.2%, and 22.5%, respectively.

Degree of differentiation

The 3-year survival rates of patients with well, moderately, and poorly differentiated were 52.6%, 45.0%, and 11.1%, respectively.

Stage

The 3-year survival rates of patients with stage I plus II, stage III, and stage IV were 85%, 51.9%, and 10.6%, respectively..

Primary tumor (T)

The 3-year survival rates of patients were 90.9% for T1 plus T2, 47.7% for T3, 47.6% for T4, and 20.0 % for Tx.

Regional lymph node (N)

The 3-year survival rates of patients were 68.3% for N0, 41.2% for N1, 24.4% for N2, and 22.2 % for Nx, respectively.

Distant metastasis (M)

The 3-year survival rates of patients with M0 and M1 were 68.7% and 10.6%, respectively.

Type of Treatments

The 3-year survival rates of patients who received surgery combined with radiotherapy and chemotherapy were 50.5%. The 3-year survival rates for surgery plus chemotherapy, surgery alone, and chemotherapy alone were 53.1%, 32%, and 16.7%, respectively. However, patients who received radiotherapy plus chemotherapy or surgery and supportive treatment did not have 3Y-SR.

The 5-year survival rate (5Y-SR)

Age

The 5-year survival rates of patients with age under 41 years were 61.9% (same as 3Y-SR). The patients with age 41-50 years, 51-60 years, 61-70 years, 71-80 years and age over 80 year were 53.7%, 46.3%, 25.1%, 32.4%, and 11.3%, respectively.

Degree of differentiation

The 5-year survival rates of patients with well and moderately differentiated were 40.3% and 41.0 %, respectively. The 5-year survival rates of patients with poorly differentiated was the same as the 3Y-SR (11.1%).

Stage

The 5-year survival rates of patients with stage I plus II, stage III and stage IV were 70.8%, 44.1%, and 2.1%, respectively.

Primary tumor (T)

The 5-year survival rates of patients were 39.9% for T3, 37.9% for T4. T1 plus T2 show the 5Y-SR same as the 3Y-SR (90.0%). Tx did not have the 5Y-SR.

Regional lymph node (N)

The 5-year survival rates of patients with N0, N1, and N2 were 55.8 %, 37.8%, and 19%, respectively. Patients with Nx did not have the 5Y-SR.

Distant metastasis (M)

The 5-year survival rates of patients with M0 were 57.7% and 2.1% for patients with M1.

Type of treatment

The 5-year survival rates of patients who received surgery combined with radiotherapy and chemotherapy were of 39.7%, while 43.3% for patients who received surgery plus chemotherapy. Patients who received radiotherapy plus chemotherapy or surgery, chemotherapy alone and supportive treatment did not have the 5Y-SR. In addition, the 5Y-SR of patients who underwent surgery alone would have the same rate as 3Y-SR (32%).

The 7-year survival rates (7Y-SR)

Age

The 7-year survival rates of patients with age 51–60 year were 42.5% and the other age groups showed the same rates as the 5Y-SR.(age under 41 years 61.9%, age 41-50 years 53.7%, 61-70 years 25.1%, 71-80 years 32.4%, and age over 80 year 11.3%)

Degree of differentiation

The 7-year survival rates of patients with moderately differentiated were 37.5%. But, the 5-year survival rates of patients with well and poorly differentiated was the same rates as the 5Y-SR. (well differentiated 40.3%, and poorly differentiated 11.1%)

Stage

The 7-year survival rates of patients with stage III were 41.2%. The other stages showed the same rate as 5Y-SR (stage I plus II 70.8% and stage IV 2.1%).

Primary tumor (T)

The 7-year survival rates of patients with T4 were 36.4%, and other primary tumor showed the same rate as 5Y-SR (T1 plus T2 90.9%, T3 39.9%, and Tx 0.0% respectively).

Regional lymph node (N)

The 7-year survival rates of patients with N1 were 34.7%, and other regional lymph node showed the same rate as 5Y-SR (N0 55.8%, N2 19.0%, and Nx 0.0%, respectively).

Distant metastasis (M)

The 7-year survival rates of patients with M0 were about 55.8%, but M1 gave the same rate as the 5Y-SR (2.1%).

Type of treatment

The 7-year survival rates of patients who underwent surgery plus chemotherapy were about 41.4% and patients who received other type of treatments had the same rate as 5Y-SR (S+RT+CT 39.7%, RT+CT or RT+S 0.0%, Surgery alone 32.0%, CT alone 0.0%, and supportive 0.0%, respectively).

Table 8 Univariate analysis of survival time of colorectal cancer patients followed their personal factors, tumor-related factors and type of treatments by Kaplan Meier and log-rank test.

Variables	n	3Y-SR %	5Y-SR %	7Y-SR %	Median survival (weeks)	Cumulative Survival (%)	Incidence density*	*P***
Overall	287	48.4	38.6	37.6	148.86	18.8	3.58	
Sex								0.825
Male	142	48.8	40.5	38.7	151.14	19.3	3.41	
Female	145	48.0	37.0	37.0	148.86	37.0	3.76	
Age								**0.044**
<41	36	61.9	61.9	61.9	>146.57	61.9	2.42	
41 – 50	36	65.2	53.7	53.7	>256.00	53.7	2.16	
51 – 60	70	56.9	46.3	42.5	192.57	0.0	3.10	
61 – 70	82	37.0	25.1	25.1	139.71	25.1	4.85	
71 – 80	53	44.2	32.4	32.4	123.29	32.4	3.99	
>80	10	22.5	11.3	11.3	109.71	11.3	7.50	
Site of tumor								0.093
Colon	204	52.1	41.4	39.4	173.14	39.4	3.34	
Rectum	83	40.1	31.6	31.6	118.29	0.0	4.12	
Histological type								0.983
Adenocarcinoma	275	48.3	39.1	38.0	148.86	19.0	3.56	
Other	11	43.0	43.0	43.0	140.29	43.0	3.89	
Degree of differentiation								**0.002**
Well	175	52.6	40.3	40.3	171.86	20.2	3.22	
Moderately	93	45.0	41.0	37.5	141.43	37.5	3.69	
Poorly	14	11.1	11.1	11.1	55.86	11.1	9.54	
Stage								**<0.001**
I+II	93	85.0	70.8	70.8	>256.00	70.8	1.02	
III	91	51.9	44.1	41.2	201.14	0.0	3.07	
IV	103	10.6	2.1	2.1	68.57	2.1	10.41	
T								**<0.001**
T1+T2	12	90.9	90.9	90.9	>53.57	90.9	0.41	
T3	66	47.7	39.9	39.9	143.86	0.0	3.49	
T4	199	47.6	37.9	36.4	148.86	36.4	3.62	
Tx	10	20.0	0.0	0.0	44.00	0.0	13.65	

Table 8 Univariate analysis of survival time of colorectal cancer patients followed their personal factors, tumor-related factors and type of treatments by Kaplan Meier and log-rank test (continued).

Variables	n	3Y-SR %	5Y-SR %	7Y-SR %	Median survival (weeks)	Cumulative Survival %	Incidence density*	*P***
N								**<0.001**
N0	117	68.3	55.8	55.8	>256.00	55.8	1.88	
N1	88	41.2	37.8	34.7	139.71	0.0	3.74	
N2	73	24.4	19.0	19.0	78.43	19.0	7.24	
Nx	9	22.2	0.0	0.0	34.29	0.0	15.99	
M								**<0.001**
M0	184	68.7	57.7	56.1	506.71	28.1	1.90	
M1	103	10.6	2.1	2.1	68.57	2.1	10.41	
Treatment								**<0.001**
S+RT+CT	43	50.5	39.7	39.7	192.57	0.0	2.99	
S+CT	201	53.1	43.3	41.2	198.71	41.2	3.10	
RT+CT or RT+S	2	0.0	0.0	0.0	93.29	0.0	5.40	
Surgery only	28	32.0	32.0	32.0	74.71	32.0	6.84	
CT only	12	16.7	0.0	0.0	46.00	0.0	15.27	
Supportive	1	0.0	0.0	0.0	9.86	0.0	101.42	
Treatment by stage								
Stage I+II								0.101
S+RT+CT	12	100.0	88.9	88.9	>192.57	88.9	0.27	
S+CT	68	86.0	68.1	68.1	>256.00	68.1	1.07	
Surgery only	13	60.9	60.9	60.9	>131.71	56.2	2.23	
Stage III								**0.002**
S+RT+CT	22	40.9	31.2	31.2	118.29	0.0	3.90	
S+CT	62	61.8	55.4	49.3	289.43	49.3	2.33	
Surgery only	7	17.4	17.4	17.4	74.71	17.4	10.53	
Stage IV								**<0.001**
S+RT+CT	9	11.1	0.0	0.0	103.43	0.0	9.46	
S+CT	71	9.9	4.9	4.9	78.14	4.9	8.93	
RT+CT or RT+S	2	0.0	0.0	0.0	93.29	0.0	5.40	
Surgery only	8	0.0	0.0	0.0	19.57	0.0	37.33	
CT only	12	16.7	0.0	0.0	46.00	0.0	15.27	
Supportive	1	0.0	0.0	0.0	9.86	0.0	101.42	

3-year survival = 156 weeks, 5-year survival = 260 weeks, 7-year survival = 364 weeks
Incidence density* = mortality rate per 1000 persons-week
*p*** = log-rang test (p-value)

Part 3 To analyze relationship between personal factors, tumor-related factors, treatment, and the survival time by Cox's Proportional Hazard Model (unadjusted). (Detail is shown in Table 9)

Personal factors

Gender

The gender was not significantly associated with survival time (p=0.825)**.**

Age

The age was significantly associated with survival time (p=0.044). The risk of death of patients with age over 80 years was about 2.83 times. There was significantly different (p=0.933). But, in the other age groups were not significantly different (p.0.05).

Tumor-related factors

Location of primary tumor (site of tumor)

The site of tumor was not significantly associated with survival time (p=0.093).

Histological type

The histological type was not significantly associated with survival time (p=0.983).

Degree of differentiation

The degree of differentiation was significantly associated with survival time (p=0.002). The risk of death of patients with moderately differentiated was higher than patients with well differentiated, but it was not significantly different (p=0.355). The risk of death of patients with poorly differentiated was 3.23 times (95%CI, 1.738–5.127, p<0.001) of patients with well differentiated.

Stage

The stage was significantly associated with survival time ($p<0.001$). The risk of death of stage III patients was 2.98 times (95%CI, 1.738-5.127, $p<0.001$) and stage IV patients was 10.36 times (95%CI, 6.171-17.411, $p<0.001$) when compared with stage I plus II patients.

Primary tumor (T)

The primary tumor was significantly associated with survival time ($p<0.001$). The risk of death of patients with T3, T4, and Tx were 7.67 times (95%CI, 1.050-56.090, $p=0.045$), 8.06 times (95%CI, 1.123 -57.806, $p=0.038$), and 28.83 times (95%CI, 3.685–225.560, $p=0.001$) of T1 plus T2 patients, respectively.

Regional lymph node (N)

The regional lymph node was significantly associated with survival time ($p<0.001$). The risk of death of patients with N1, N2, and Nx were 1.99 (95%CI, 1.297-3.068, $p=0.002$), 3.54 (95%CI, 2.322-5.382, $p=0.01$), and 8.13 times (95%CI, 3.922-16.832, $p<0.001$) of patients with N0, respectively.

Distant metastasis (M)

The distant metastasis was significantly associated with poor survival time ($p<0.001$).The risk of death of patients with M1 was 5.5 times (95%CI, 3.638-7.317, $p<0.001$) of patients with M0.

Treatment

The risk of death of patients who received chemotherapy was 0.45 times (95%CI, 0.121-0.373, $p<0.001$) of patients who did not received chemotherapy. In addition, the risk of death of patients who received surgery was 0.21 times (95%CI, 0.271-0.746, $p=0.002$) of patients who did not received surgery. However, radiotherapy did not significantly affect survival time ($p=0.983$).

Table 9 The relationship between other factors and survival time by Cox's Proportional Hazard Model (unadjusted).

Variables	n	HR	95% CI Of HR	p-value
Sex				0.825
Male	142	1.00		
Female	145	1.04	0.748 – 1.439	
Age				**0.044**
<41	36	1.00		
41-50	36	0.97	0.451 - 2.076	0.933
51-60	70	1.32	0.679 - 2.567	0.412
61-70	82	1.87	0.990 - 3.523	0.054
71-80	53	1.65	0.834 - 3.256	0.150
>80	10	2.83	1.153 - 6.957	0.023
Site of tumor				0.093
Colon	204	1.00		
Rectum	83	1.34	0.951 – 1.889	
Histological type				0.983
Other	11	1.00		
Adenocarcinoma	275	1.09	0.445 - 2.658	0.865
Unknown	1	1.16	0.136 - 10.00	0.889
Degree of differentiation				**0.002**
Well	175	1.00		
Moderately	93	1.18	0.827 - 1.698	0.355
Poorly	14	3.23	1.711 - 6.081	<0.001
Unknown	5	1.59	0.504 - 5.049	0.427
Stage				**<0.001**
I+II	93	1.00		
III	91	2.98	1.738 - 5.127	<0.001
IV	103	10.36	6.171 - 17.411	<0.001

Table 9 The relationship between other factors and survival time by Cox's Proportional Hazard Model (unadjusted) (continued).

Variables	n	HR	95% CI Of HR	p-value
T				**<0.001**
T1+T2	12	1.00		
T3	66	7.67	1.050 - 56.090	0.045
T4	199	8.06	1.124 - 57.806	0.038
Tx	10	28.83	3.685 - 225.560	0.001
N				**<0.001**
N0	117	1.00		
N1	88	1.99	1.297 - 3.068	0.002
N2	73	3.54	2.322 - 5.382	<0.001
Nx	9	8.13	3.922 - 16.832	<0.001
M				**<0.001**
M0	184	1.00		
M1	103	5.51	3.868 - 7.860	
Treatment				
Supportive		1.00		
Surgery	273	0.21	0.121 - 0.374	**<0.001**
Radiotherapy	45	0.99	0.651 - 1.523	0.983
Chemotherapy	257	0.45	0.271 - 0.746	**0.002**

Part 4 Multivariate analyses of the relationships between independent factors and survival time by Cox's Proportional Hazard Model.
(Detail is shown in Table 10)

From the study, the factors were significantly associated with survival time at 95 percent confidence interval including age, degree of differentiation, stage, primary of tumor (T), regional lymph node (N), distant metastases (M), and treatment. The result was the same as Kaplan-Meier that the factors were significantly different with survival time ($p<0.05$). However, there was no control of the confounding factors. Thus, significant factor with 90 percent confidence interval was used for multivariate analysis, which was the site of tumor.

The factors were significantly associated with survival time ($p<0.05$) base on multivariate analysis of age, degree of differentiation, stage, TNM, surgical and chemotherapy treatment.

Age

The risk of death of patients at the age group of 61-70 and over 80 years was high significantly different when compared with patients at the age group 51-60 (61-70 years; HR 1.88, 95%CI, 1.159–3.056, p=0.011, and over 80 years; HR 3.96, 95%CI, 1.677–9.339, p=0.002). The risk of death in the other age groups was not significantly different.

Degree of differentiation

The risk of death of patients with moderately differentiated was 1.27 times, but not significantly different (95%CI, 0.899–1.979, p=0.222). The risk of death of patients with poorly differentiated was 3.39 times of patients with well differentiated and was significantly different (95%CI, 1.616–6.388, p=0.001).

Stage

The risk of death of stage III patients was 3.58 times (95%CI, 2.045-6.278, $p<0.001$) and stage IV was 12.26 times (95%CI, 6.970-21.58, $p<0.001$) of stage I plus II patients.

Primary tumor (T)

The risk of death of patients with T3, T4, and Tx were 19.7 times (95%CI, 2.557–151.845, p=0.004), 21.99 times (95%CI, 2.914-165.99, p=0.008), and 18.2 times (95%CI, 1.377–381.118, p=0.029) of patients with T1 plus T2, respectively.

Regional lymph node

The risk of death of patients with N1, N2, and Nx were 1.49 times (95%CI, 0.937–2.358, p=0.092), 2.78 times (95%CI, 1.754–4.418, p<0.001), and 2.30 times (95%CI, 0.283– 8.762, p=0.436) of patients with N0, respectively.

Distant Metastasis

The risk of death of patients with M1 was 4.72 times (95%CI, 3.121–7.134, p=0.001) of patients with M0.

Surgical

The risk of death of patients who underwent surgery was lower risk when compared with patients who did not receive surgery (HR 0.44, p<0.02)

Chemotherapy

The risk of death of patients who received chemotherapy was lower risk when compared with patients who did not receive chemotherapy (HR 0.15, p<0.001).

Table 10 Multivariate analysis of the relationship between other factors and survival time by Cox's Proportional Hazard Model.

Variables	HR	95% CI Of HR	p-value
Age			
<41	1.06	0.516 – 2.163	0.088
41-50	1.23	0.628 – 2.425	0.542
51-60	1.00		
61-70	1.88	1.159 – 3.056	**0.011**
71-80	1.61	0.925 – 2.801	0.092
>80	3.96	1.677 – 9.339	**0.002**
Site of tumor			
Colon	1.00		
Rectum	1.04	0.714 – 1.512	0.742
Degree of differentiation			
Well differentiated	1.00		
Moderately differentiated	1.27	0.899 – 1.979	0.222
Poorly differentiated	3.39	1.616 – 6.388	**0.001**
Stage			
I+II	1.00		
III	3.58	2.045 – 6.278	**< 0.001**
IV	12.26	6.970 – 21.576	**< 0.001**

Table 10 Multivariate analysis of the relationship between other factors and survival time by Cox's Proportional Hazard Model (continued).

Variables	HR	95% CI Of HR	p-value
T			
T1+T2	1.00		
T3	19.70	2.557 - 151.845	**0.004**
T4	21.99	2.914 - 165.993	**0.003**
Tx	22.91	1.377 - 381.118	**0.029**
N			
N0	1.00		
N1	1.49	0.830 - 2.146	0.234
N2	2.78	1.411 - 3.661	**0.001**
Nx	3.55	0.494 - 25.563	0.208
M			
No	1.00		
M1	4.72	3.121 - 7.134	**<0.001**
Surgery			
No	1.00		
Yes	0.44	0.223 - 0.879	**0.002**
Chemotherapy			
No	1.00		
Yes	0.15	0.081 - 0.267	**<0.001**

CHAPTER V
DISCUSSION

Colorectal cancer was the most common carcinoma in Western countries. Recently, in Eastern countries like Japan, China, Singapore, and Thailand, the trend of the incidence of colorectal cancer has increased. In Thailand, the study of colorectal cancer is less than other countries. Many studies on the prognostic factors of colorectal cancer were done to identify the independent prognostic factor in order to improve patients' survival time. Interestingly, of all cancer type, the morbidity rate and mortality rate of colorectal cancer are the top five in the world. In Thailand, according to the recent study done in 2001, the 5-year survival rates of patients with colon cancer were 51% and 45% for patient with rectal cancer (12). In the same study, some factors in relation to survival time were also discovered.

In this study including the ten factors such as gender, age, location of primary tumor, histological type, degree of differentiation, stage, primary of tumor (T), regional lymph node (N), distant metastases (M) and type of treatments were studied. Three factors that had no significant influence on survival ($p>0.05$), were gender, location of primary tumor, and histological type.

The risk of death of patients with age under 50 years and over 60 years were higher than patients in 51-60 aged group because there were higher numbers of stage IV patients in both groups. According to other study, young-aged and old-aged groups were also worse prognostic factors (31, 56, 57). In the young-aged group, patients were often found with aggressive pathology, and were present with the late-stage cancer (23, 30, 31, 57, 58, 74). In the old-aged group, the risk of death was high because of their other risk of death. However, between these two groups, the young patients had the lower risk of death than the older patients (60). On the other hand, another study on the survival time between young and older-aged groups in relation to various stages showed a mixed result. Young patients in stage I or II had better survival time than older patients with similar stages. However, the study showed

young patients diagnosed with stage III or IV lesion had the same or worse survival time than older patients (59).

Degree of differentiation was another factor that was significantly associated with survival time ($p<0.05$). In this study, the result indicated that poorly differentiated was a poor prognostic factor just like the results of many studies (57, 62-64, 75, 76). The risk of death of patients with moderately differentiated was about 1.27 times of patients with well differentiated, but this number was not statistically significant ($p=0.222$). Other previous studies found the degree of differentiation was related to primary tumor (T), regional lymph node (N), and the recurrence of disease, which all affected patient's survival time (15, 62, 77). Moreover, the study found all cases of poorly differentiated groups were T3 and T4 patient groups, 71.43% of patients in this group had recurrence of the disease, and 57.14% of the patients were over 60 years old. But, some study reported the degree of differentiation did not affect the survival time (78).

Stage of disease was also an important factor to predict the probabilities of survival time, same as in other studies (53-55, 64, 67, 79). The risk of death of patients with stage III and IV were higher risk and the 5Y-SR were 44.1% and 2.1%, respectively. Patients with stage III had the same survival rate as other studies while patients with stage IV had survival rate lower than other studies. The study found the 5Y-SR of patients with stage III were 40-70% of III and 9-15% for stage IV patients (13, 65, 80, 81). The main reason for such result was that most patients with stage IV in our study had poor prognostic factors. Half of them were over 60 years (51.46%), and their pathology was poorly differentiated unlike those of patients with stage I plus II. Additionally, treatment was another factor to determine the survival time of patients. Although the chance of the 5Y-SR was lower than the range for stage IV patients in this study. A study also found no patient survivable more than 5 years and the 2Y-SR was 30% (65).

As in many studies, TNM was highly significant factor (12, 64, 77, 82). The indicators of T3, T4, N2 and M1 correspond to a high risk of death ($p<0.05$). In the previous study, the subgroups of T and N will have independent effects on the incidence recurrence and distant metastases (77, 83). For example, in the study of patients with negative lymph node, patients with T4 had highest risk of recurrent of

disease (77). In reverse, of patients with N1, 26.14% was between 51 and 60 years old- an age group that has the lowest risk of death according to this study. Therefore, N1 is not statistically significant different (p=0.234). However, Kaplan Meier analysis showed the 5Y-SR between N1 and N0 significantly differs. The 5-year survival rates of N1 are less than the survival rate of N0 by about 1 time (55.8% N0, and 32.8% for N1). Among distant metastasis (M), the risk of death of patients with M1 was higher than patients with M0.

Cox's Proportional Hazard Model (unadjusted) the risk of death could be reduce by surgery and chemotherapy ($p<0.001$ and $p=0.002$, respectively). However, this study showed the radiotherapy was not significantly associated with prolonged survival time because the number of patients who received radiotherapy was small (45 cases) and radiotherapy was used in most treatment for rectal cancer (84.4%). Therefore, radiotherapy was not included in multivariate analysis. The surgery and chemotherapy, in fact, reduced risk of death. On the other hand, surgery plus chemotherapy could effectively reduce the risk of death than surgery alone or chemotherapy alone (HR, 0.07) For instance, in other studies, adjuvant chemotherapy can increase the survival time by about 10-15% (84).

Gender, location of primary tumor and histological type were not associated with survival time as found in other studies (55, 60, 75, 77, 78, 85). However, some studies found they were significantly associated with survival time (54, 61, 65, 75, 79, 86).

The overall 5-year survival rates of this study were 38.6%. It was lower than other studies which found the overall 5Y-SR of 45-76% (13, 75, 87). In addition, the 5-year survival rates of each subgroup were also lower than other studies. The cause of the difference might be due to four reasons. One reason is the majority characteristics of patients. In this study, the majority of characteristic with patients were age over 60 years (50.52%), stage IV (35.89%), T4 (69.34%) and lymph node positive (56.1%). These were the worse factors. The majority of patients in this study were in stage IV because the study was done at the site of Oncology Unit where patients with stage IV were sent to receive chemotherapy. The second reason is that the numbers of cases in some groups were less. In the group with histological type, non-adenocarcinoma was only found in 11 cases that made the survival time in this group different from other groups studies. The third reason is that one-half of all patients in the study died

(50.52%) which made the median survival time in same subgroup of factors undetermined even though the overall median survival time can be estimated. Finally, the skills, the knowledge of surgeon, surgical techniques and the experiences of surgeons had influences on the recurrence of disease and the survival time (88-91). Patients in this study may receive surgery from surgical oncologist or general surgeon who had different experience.

Study issue

This study was ambispective study and the data was secondary data which might be incomplete for some cases. However, the researcher gathered the data with the best attempt, particularly for the data of independent factors. In addition, this study used the last update of Modified Astler-Coller classification (2002) by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) to classify all cases to decrease bias on the definitions of classifications.

The date of the first diagnosis means the date of the admission to the study (Time 0). But, 19 patients in recurrence cases who did not have some data (e.g. date of first diagnosis, pathology report, and data before disease recurrent). So, those patients were added into stage IV and we used the date of recurrence for analysis. The follow up process for the last status of patients ended when the patient died or at the end of the study period. Finally, of 281 cases, whose last statuses were known, 145 died, and 6 cases were unknown of last status. For those with unknown statuses, we used the date of the last contact as the date of the end of study for follow-up result. The problem of following up the patient's final status was that some patients did not have personal identification numbers available at the Ministry of Interior, which were important data for the follow-up of final status from the Population Registration Database. An alternative was to send letter or make phone calls to follow up final status for those who lost contacts.

All cases of cancer in the Rajavithi Hospital were not referred to the Oncology Unit, Department of Medicine. Only patients who were referred to receive chemotherapy were sent here. So, there were 430 cases of colorectal patient in the unit. Because some patients had incomplete data, only 287 cases of colorectal patients were enrolled in this study.

CHAPTER VI
CONCLUSION AND RECOMMENDATION

Colorectal cancer patients (287 cases) at the Oncology Unit, Department of Medicine in Rajavithi Hospital were the target group of the study, which was collected between January 1, 1995 and December 31, 2003, and whose follow-up on the last status ended on August 31, 2004. One hundred forty-five cases died with the median follow up time of 104.43 weeks (range 3.71-507.57 weeks). The median age was 61 years (SD = 13.36), for both male and female with similar ratio (1:1.02). Most patients lived in Bangkok and suburban (58.54%). They were unemployed 50.87%. The majority of tumor-related factors, the site of cancer were found in colon (71.08%) than in rectum, the histological type found was adenocarcinoma and degree of differentiation was well differentiated. Most patients were at stage IV (35.89%), and more than 40% of the patients were under 41 years old and between 61-70 years. The patients with stage I to III had about 34.78% chance of recurrence of disease. The most common sites of distant metastasis and recurrences were in liver (56.29%) and intra abdominal organ (38.32%). In addition, the study found that the overall median survival time was about 148.86 weeks. The overall 3, 5, and 7-year survival rates were 48.4%, 38.6%, and 37.6%, respectively.

Univariate analysis by Kaplan-Meier and log-rank test show that the median survival time between genders were not significantly different ($p=0.825$). The median survival time for male was higher than female. The age was also significantly different with survival time ($p=0.044$). Generally, patients at older age had low median survival time. However, the 5-year survival rates of patients in the age group of 71-80 years were higher than those in the age of 61-70 years (32.4% and 25.1%, respectively). Colon cancer patients had higher median survival time than rectal cancer patients, but there was not significant difference ($p=0.093$). Histological type was not significantly different ($p<0.983$). Among the degree of differentiated, well differentiated showed the highest median survival time as well as the highest 5-year survival rates when

compared with moderately or poorly differentiated. The significance of well differentiated was also high (p=0.002). Patients with stage IV had lower survival time and had lower the 5-year survival rates which are about 2.1%. Patients with stage I plus II and III had median survival time about >256.00 and 201.14 weeks, respectively. TMN were high significantly different. The analysis of T4 showed higher median survival time than T3 (148.86, and 143.86 weeks), but T3 had better 5-year survival rates than T4 (37.9%, and 39.9%). The median survival time of N2 was less than that of N1, nearly 2 times. The median survival time of M1 was about 68.57% compared with M0 median survival time, i.e. 506.71 weeks. Patients who received surgery plus chemotherapy had the highest median survival time and the highest 5-year survival rates (198.71 weeks, and 43.3%)

According to Cox's Proportional Hazard Model with unadjusted factors, the factors such as, the age, location of primary tumor, degree of differentiation, stage, primary of tumor (T), regional lymph node (N), distant metastases (M), and type of treatment were significantly associated with survival time at 90% CI.

In multivariate analysis by Cox's Proportional Hazard Model, the risk of death of patients with age over 80 years was higher than other age groups (p=0.002). Similarly, the risk of death in patients with age under 51 years was higher than patients in the age group of 51-60 years, but it was not significantly different (p>0.1). The risk of death between site of tumor in colon and in rectum were not significantly different (p=0.842). Among the degree of differentiation, the risk of death of patients with poorly differentiated were 3.39 times of patients with well differentiated (p=0.001), and about 1.27 times for patients with moderately differentiated, but there was not significant difference (p=0.222). Among stages, there was significant different (p<0.001). The risk of death of patients with stage III and IV were about 3.58 and 12.26 times of patients with stage I plus II, respectively. For primary tumor (T), the risk of death of patients with T3 and T4 were higher than patients with T1 plus T2, and that there was a high significant difference. For regional lymph node (N), the risk of death of patients with N2 was higher than the other N (p<0.001). While the risk of death of patients with N1 and Nx were higher than N0, but there were not significance. The risk of death of patients with M1 was 4.72 times of patients with M0. Patients

who received surgery and chemotherapy had a lower death risk, and there was significantly different ($p<0.05$).

Recommendation for the results of application

1. This study found age and stage related to survival time. The patients with early stage (stage I, II) had higher survival time than patients in stage IV. The risk of death in young and elderly patients was higher. So, the risk group should be screened in early stage. The persons with family history of colorectal cancer should be screened in age before 30 years and add cancer screening program in aging group.

Screening Guidelines for the Early Detection of Colorectal Cancer, American Cancer Society 2003(2)

Beginning at age 50, men and women should follow one of the following examination schedules:

- A fecal occult blood test (FOBT) every year
- A flexible sigmoidoscopy (FSIG) every five years
- Annual fecal occult blood test and flexible sigmoidoscopy every five years*
- A double-contrast barium enema every five years
- A colonoscopy every ten years

*Combined testing is preferred over either annual FOBT, or FSIG every 5 years alone.

- People who are at moderate or high risk for colorectal cancer should talk with a doctor about a different testing schedule

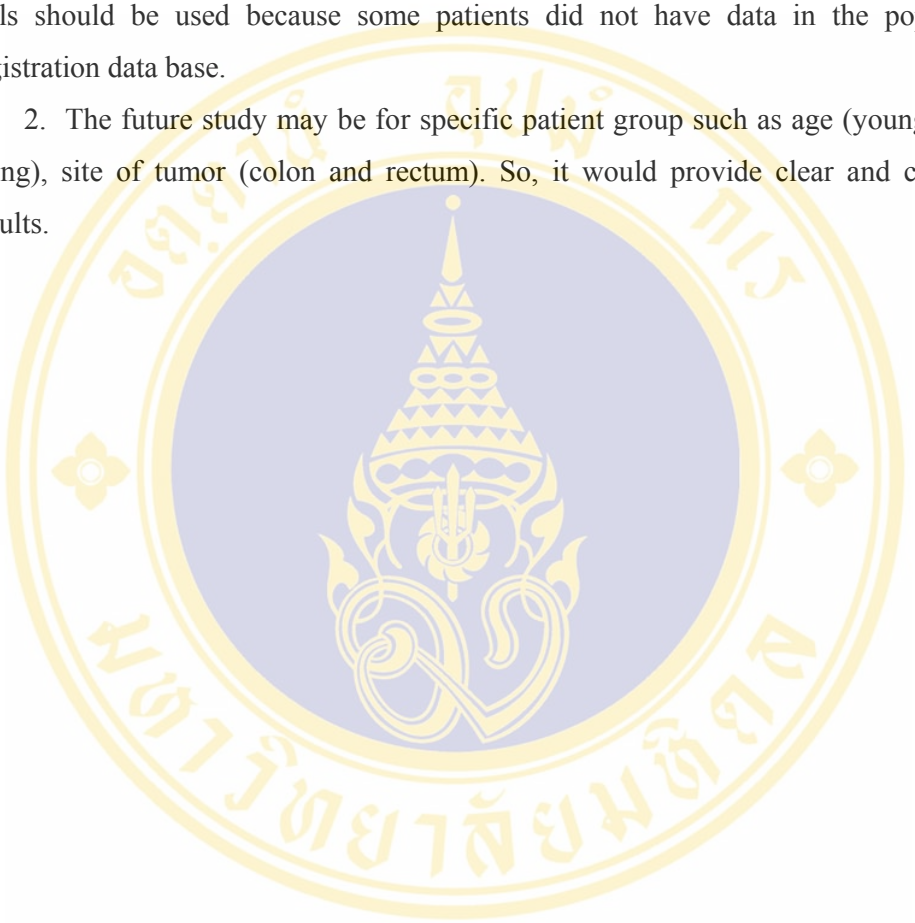
2. Chemotherapy was important treatment because the patients who received it had lower risk of death than the untreated group. Therefore, health system should provide the supportive care to help patients to receive complete treatment course and the hospital has to have good management. Also, a good follow-up must be done in order for patients to continue receiving complete treatment.

3. Patients with poor prognostic factors are poorly differentiated, stage III, IV, T4 and N2. They should receive highly potent chemotherapy which has efficacy higher than standard 5FU plus leucovorin eg. oxaliplatin and irinotecan.

Recommendation for the further studies

1. The study design should use retrospective cohort because some patients lived more than 7 years. Patients should be contacted routinely by post or telephone calls if they did not attend the clinic. For the follow-up of patient's status, letters or telephone calls should be used because some patients did not have data in the population registration data base.

2. The future study may be for specific patient group such as age (young age or aging), site of tumor (colon and rectum). So, it would provide clear and complete results.



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APPENDIX A
INFORMATION FORM

Id No._____

Prognostic factors in Colorectal Cancer
Oncology unit, Rajavithi Hospital

Name_____Lastname_____
HN. _____Oncology No._____
Address (province)
_____
_____

☐ 1. Bangkok, Samutprakarn, Nonthaburi, Pratumtanee

☐ 2. Other_____

Id No._____

1. Sex ☐ 1. Male ☐ 2. Female

2. Age_____ years

3. Occupation

☐ 1. Government official ☐ 2. Employee

☐ 3. Merchant ☐ 4. Housewife

☐ 5. Agriculture ☐ 6. Business

☐ 7. Others_____ ☐ 8.Unknown

4. Date diagnosis _____

5. Date attend to Oncology unit _____

6. Date of treatment

6.1 Date of first operation _____

6.2 Date start neoadjuvant Chemotherapy _____

6.3 Date start adjuvant Chemotherapy _____

6.4 Date start palliative Chemotherapy _____

7. Symptoms

7.1 Intestinal obstruction ☐ 0.No ☐ 1.Yes

7.2 Intestinal perforation ☐ 0.No ☐ 1.Yes

8. Location of the primary tumor

☐ 1. Right (cecum, ascending colon, hepatic flexure)

☐ 2. Transverse (transverse, splenic flexure)

☐ 3. Left (descending colon, sigmoid colon)

☐ 4. Rectosigmoid ☐ 5. Rectum

9. Histology Type

☐ 1. Adenocarcinoma ☐ 2. Medullary carcinoma

☐ 3. Mucinous Adenocarcinoma ☐ 4. Signet ring cell carcinoma

☐ 5. Adenosquamous carcinoma ☐ 6. Squamous cell carcinoma

☐ 7. Undifferentiated ☐ 8. Other_____

10. Degree of differentiation

☐ 1. Well differentiated ☐ 2. Moderately differentiated

☐ 3. Poorly differentiated ☐ 4. Undifferentiated

11. Lymphatic invasion ☐ 0.No ☐ 1.Yes

12. Blood vessel invasion ☐ 0.No ☐ 1.Yes

13. Clinical stage (MAC stage)

Stage 1 ☐ 1. Dukes' A ☐ 2. Dukes' B1

Stage 2 ☐ 3. Dukes' B2 ☐ 4. Dukes' B3

Stage 3 ☐ 5. Dukes' C1 ☐ 6. Dukes' C2 ☐ 7.Dukes' C3

Stage 4 ☐ 8. Dukes' D (at present) ☐ 9. Dukes' D (recurrent case)

14. TMN stage

14.1 Primary tumor

☐ 1. Tx ☐ 2. T0 ☐ 3. Tis ☐ 4. T1

☐ 5. T2 ☐ 6. T3 ☐ 7. T4

14.2 Regional lymph node

☐ 1. Nx ☐ 2. N0 ☐ 3. N1 ☐ 4. N2

14.3 Distant metastasis

☐ 1. Mx ☐ 2. M0 ☐ 3. M1

15. Site of metastasis (stage 4 or recurrent)

15.1 Lung ☐ 0.No ☐ 1.Yes

15.2 Liver ☐ 0.No ☐ 1.Yes

15.3 Lymph nodes ☐ 0.No ☐ 1.Yes

15.4 Stomach ☐ 0.No ☐ 1.Yes

15.5 Bladder ☐ 0.No ☐ 1.Yes

15.6 Bone ☐ 0.No ☐ 1.Yes

15.7 Peritoneal involvement ☐ 0.No ☐ 1.Yes

15.8 Others_____ ☐ 0.No ☐ 1.Yes

16. CEA (Preoperative) _____ng/ml

17. Surgery ☐ 0.No ☐ 1.Yes

17.1 Curative Surgery ☐ 0.No ☐ 1.Yes

17.2 Palliative Surgery ☐ 0.No ☐ 1.Yes

18. Radiotherapy ☐ 0.No ☐ 1.Yes

18.1 Neoadjuvant Radiotherapy ☐ 0.No ☐ 1.Yes

18.2 Adjuvant Radiotherapy ☐ 0.No ☐ 1.Yes

18.3 Palliative Radiotherapy ☐ 0.No ☐ 1.Yes

19. Neoadjuvant & Adjuvant Chemotherapy

19.1 Neoadjuvant Chemotherapy

☐ 0. No ☐ 1. Low dose 5FU + Leucovorin

☐ 2. Others_____

19.2 Number of courses of Neoadjuvant Chemotherapy _____

19.3 Adjuvant Chemotherapy

☐ 0. No ☐ 1. Low dose 5FU + Leucovorin

☐ 2. High dose 5FU + Leucovorin ☐ 3. Oral UFT + Leucovorin

☐ 4. Capecitabine (Xeloda) based ☐ 5. Irinotecan based

☐ 6. Oxaliplatin based ☐ 7. Others _____

19.4 Number of courses of Adjuvant Chemotherapy_____

19.5 Response to Adjuvant Chemotherapy: Recurrence

☐ 0. No ☐ 1. Yes ☐ 2. Don't assess ☐ 3. Not assessable

19.6 Date of disease recurrence_____

20. Palliative Chemotherapy

20.1 Palliative Chemotherapy (First line)

☐ 0. No ☐ 1. Low dose 5FU + Leucovorin

☐ 2. High dose 5FU + Leucovorin ☐ 3. Oral UFT + Leucovorin

☐ 4. Capecitabine (Xeloda) based ☐ 5. Irinotecan based

☐ 6. Oxaliplatin based ☐ 7. Others _____

20.2 Number of courses of first line Palliative Chemotherapy_____

20.3 Response to first line Palliative Chemotherapy

☐ 1.CR ☐ 2. PR ☐ 3.SD

☐ 4. PD ☐ 5. Don't assess ☐ 6. Not assessable

20.4 Date of disease Progression (First line) _____

20.5 Palliative Chemotherapy (Second line)

☐ 0. No ☐ 1. Low dose 5FU + Leucovorin

☐ 2. High dose 5FU + Leucovorin ☐ 3. Oral UFT + Leucovorin

☐ 4. Capecitabine (Xeloda) based ☐ 5. Irinotecan based

☐ 6. Oxaliplatin based ☐ 7. Others _____

20.6 Number of courses of second line Palliative Chemotherapy_____

20.7 Response to second line Palliative Chemotherapy

☐ 1.CR ☐ 2. PR ☐ 3. SD

☐ 4. PD ☐ 5. Don't assess ☐ 6. Not assessable

20.8 Date of disease Progression (Second line)_____

20.9 Palliative Chemotherapy (Third line)

☐ 0. No ☐ 1. Low dose 5FU + Leucovorin

☐ 2. High dose 5FU + Leucovorin ☐ 3. Oral UFT + Leucovorin

☐ 4. Capecitabine (Xeloda) based ☐ 5. Irinotecan based

☐ 6. Oxaliplatin based ☐ 7. Others _____

20.10 Number of courses of third line Palliative Chemotherapy_____

20.11 Response to third line Palliative Chemotherapy

☐ 1.CR ☐ 2. PR ☐ 3.SD

☐ 4. PD ☐ 5. Don't assess ☐ 6. Not assessable

20.12 Date of disease Progression (Third line) _____

20.13 Number of regimens of Palliative Chemotherapy

☐ 0. 0 ☐ 1. 1 ☐ 2. 2 ☐ 3. 3 ☐ 4. > 3

21. Patient status

☐ 0. alive

☐ 1. death Date of death_____

☐ 2. loss F/U Date of last contract_____

22. Cause of death

☐ 1. Cancer related specify_____

☐ 2. Treatment related specify _____

☐ 3. Non cancer or treatment related specify _____

APPENDIX B
TABLE

Table 11 Number and percentage of characteristics of colorectal cancer patients.

Characteristics	number	percentage
Year of diagnosis		
38	12	4.1
39	24	8.3
40	24	8.3
41	34	11.9
42	23	8.0
43	30	10.4
44	42	14.6
45	40	13.9
46	59	20.5
Site of tumor		
Colon		
cecum	21	7.3
ascending	22	7.7
hepatic flexure	12	4.2
transverse	18	6.3
splenic flexure	9	3.1
descending	14	4.9
sigmoid	105	36.6
unknown	3	1.0
Rectum		
retrosigmoid	30	10.4
rectum	53	18.5
Stage		
I (n=7)		
Duke ‘s A	1	0.3
Duke ‘s B1	6	2.1
II (n=85)		
Duke ‘s B2	20	7.0
Duke ‘s B3	66	23.0
III (n=91)		
Duke ‘s C1	3	1.0
Duke ‘s C2	22	7.7
Duke ‘s C3	65	22.6
Unknown	1	0.3
IV (n=104)		
Duke ‘s D (at present)	84	29.3
Recurrent case	19	6.6

Table 12 Number of patients characteristics among site of tumor.

characteristic	Colon	Rectum
Sex		
Male	101	41
Female	103	42
Age (years)		
<41	31	5
41-50	23	13
51-60	42	28
61-70	60	22
71-80	40	13
>80	8	2
Intestinal Obstruction		
No	127	67
Yes	74	12
Unknown	3	4
Intestinal Perforation		
No	198	79
Yes	3	0
Unknown	3	4
Histological Type		
Adenocarcinoma	194	81
Mucinous Adenocarcinoma	8	2
Signet ring cell carcinoma	1	0
Unknown	1	0
Degree of differentiation		
Well differentiated	125	50
Moderately differentiated	67	26
Poorly differentiated	7	7
Unknown	5	0
Lymphatic invasion		
No	183	77
Yes	11	2
Unknown	10	4
Blood vessel invasion		
No	192	75
Yes	2	4
Unknown	10	4

Table 12 Number of patients characteristics among site of tumor (continued).

characteristics	Colon	Rectum
Stage		
I	5	2
II	7	15
III	64	27
IV	64	39
TNM		
T		
T1	1	0
T2	6	5
T3	43	23
T4	145	54
Tx	9	1
N		
N0	94	23
N1	60	28
N2	43	30
Nx	7	2
M		
M0	140	44
M1	64	39
Recurrence of disease*		
No	92	28
Yes	48	16
Surgery		
No	8	6
Yes	196	77
Radiotherapy		
No	197	45
Yes	7	38
Chemotherapy		
No	24	6
Yes	180	77

*Recurrence of disease in patient stage I-III (n=184 case)

Table 13 Number of patients characteristics by age groups.

characteristics	<41	41-50	51-60	61-70	71-80	>80
Sex						
Male	12	19	35	45	24	7
Female	24	17	35	37	29	3
Intestinal obstruction						
No	24	27	49	55	34	5
Yes	12	8	20	24	17	5
Unknown	0	1	1	3	2	0
Intestinal perforation						
No	36	35	67	78	51	10
Yes	0	0	2	1	0	0
Unknown	0	1	1	3	2	0
Histological Type						
Adenocarcinoma	33	34	69	77	52	10
Mucinous Adenocarcinoma	2	2	1	4	1	0
Signet ring cell carcinoma	1	0	0	0	0	0
Unknown	0	0	0	1	0	0
Degree of differentiation						
Well	22	23	47	45	34	4
Moderately	10	10	21	30	16	6
Poorly	2	3	1	5	3	0
Unknown	2	0	1	2	0	0
Lymphatic invasion						
No	32	34	61	76	47	10
Yes	1	0	4	3	5	0
Unknown	3	2	5	3	1	0
Blood vessel invasion						
No	32	34	64	77	50	10
Yes	1	0	1	2	2	0
Unknown	3	2	5	3	1	0
Stage						
I	0	2	0	2	3	0
II	12	14	20	22	14	4
III	9	11	24	22	21	4
IV	15	9	26	36	15	2

Table 13 Number of patients characteristics by age groups (continued).

characteristics	<41	41-50	51-60	61-70	71-80	>80
TNM						
T						
T1	0	0	0	0	1	0
T2	1	3	1	2	3	1
T3	3	7	14	23	17	2
T4	31	21	52	55	32	6
Tx	1	3	3	2	0	1
N						
N0	17	19	24	34	19	4
N1	7	12	23	22	20	4
N2	10	3	20	24	14	2
Nx	2	2	3	2	0	0
M						
M0	21	27	44	46	38	8
M1	15	9	26	36	15	2
Recurrence of disease*						
No	19	15	27	30	25	4
Yes	2	12	17	16	13	4
Surgery						
No	2	1	3	3	5	0
Yes	34	35	67	79	48	10
Radiotherapy						
No	34	26	55	72	45	10
Yes	2	10	15	10	8	0
Chemotherapy						
No	2	2	6	4	13	3
Yes	34	34	64	78	40	7

*Recurrence of disease in patient stage I-III (n=184 case)

Table 14 Number of patients characteristics by stage.

Characteristics	Stage I	Stage II	Stage III	Stage IV
Sex				
Male	3	44	41	54
Female	4	42	50	49
Intestinal obstruction				
No	7	57	57	73
Yes	0	29	32	25
Unknown	0	0	25	7
Intestinal perforation				
No	7	86	87	97
Yes	0	0	2	1
Unknown	0	0	2	5
Site of tumor				
Right colon	0	22	17	17
Transverse colon	2	8	9	8
Left colon	3	41	38	39
Rectum	2	15	27	39
Histological type				
Adenocarcinoma	6	83	85	101
Mucinous Adenocarcinoma	1	2	5	2
Signet ring cell carcinoma	0	0	1	0
Unknown	0	1	0	0
Degree of differentiation				
Well differentiated	7	56	52	60
Moderately differentiated	0	26	33	34
Poorly differentiated	0	2	5	7
Unknown	0	2	1	2
Lymphatic invasion				
No	7	83	84	86
Yes	0	2	6	5
Unknown	0	1	1	12
Blood vessel invasion				
No	7	83	88	89
Yes	0	2	2	2
Unknown	0	1	1	12

Table 15 Number of patients characteristics by degree of differentiation.

Characteristics	Well	Moderately	Poorly
TNM			
T			
T1	1	0	0
T2	9	2	0
T3	41	21	2
T4	118	67	12
Tx	6	2	0
N			
N0	78	33	3
N1	53	29	6
N2	38	30	4
Nx	6	1	1
M			
M0	115	59	7
M1	60	34	7
Recurrence of disease*			
No	77	39	2
Yes	38	20	5

*Recurrence of disease in patient stage I-III (n=184 case)

BIOGRAPHY

NAME	Parapat Techatanol
DATE OF BIRTH	4 May 1977
PLACE OF BIRTH	Ubonratchatanee, Thailand
INSTITUTIONS ATTENDED	Thai Red Cross College of Nursing, Bangkok, 1995-1998 Bachelor of Science in Nursing Mahidol University, 2003-2005 Master of Science (Public Health)
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