COST-UTILITY ANALYSIS OF ADJUVANT CHEMOTHERAPY IN PATIENTS WITH STAGE III COLON CANCER IN THAILAND

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COST-UTILITY ANALYSIS OF ADJUVANT CHEMOTHERAPY IN PATIENTS WITH STAGE III COLON CANCER IN THAILAND

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ABSTRACT

The objective of this study was to compare the cost-utility of each chemotherapy treatment compared with first-line 5-fluorouracil/leucovorin (5-FU/LV) plus second-line capecitabine in patients with stage III colon cancer after resection in Thailand based on societal and governmental perspectives using an economic evaluation model. Cost utility analysis was used to compare adjuvant chemotherapy treatments for stage III colon cancer patients after resection. A Markov model was used to estimate the relevant costs and health outcomes during the patient's lifetime horizon based on societal and governmental perspectives. Direct medical costs, direct non-medical costs, and indirect costs were included and health outcomes were Life Years (LYs) and Quality Adjusted Life Years (QALYs). The results were presented as the Incremental Cost Effectiveness Ratio (ICER) in Thai baht (THB) per LY or QALY gained. One-way sensitivity and probabilistic sensitivity analyses (PSA) were conducted to investigate the effects of model variable uncertainties.

The results of this study suggested that providing first-line 5-FU/LV and second-line capecitabine would be the most cost-effective chemotherapy. first-line FOLFOX and second-line FOLFIRI, the next best intervention, seemed to be the choice of treatment for stage III colon cancer patients, since its ICER value yielded the lowest ICER value with 474,000 and 398,000 THB per QALY gained based on societal and governmental perspectives, respectively. Threshold sensitivity analysis was conducted and if both prices of FOLFOX and FOLFIRI were decreased by 40% (i.e., FOLFOX4 = 179,025 THB, FOLFIRI = 527,015 THB), first-line FOLFOX and second-line FOLFIRI would be cost-effective with the ICER of 299,365 THB per QALYs gained based on a societal perspective. Thus, first-line 5-FU/LV and second-line capecitabine would be the most cost-effective chemotherapy and should be still included in the NLED while oxaliplatin was not cost-effective at a WTP threshold in the Thai context.

KEY WORDS: HEALTH TECHNOLOGY ASSESSMENT / ECONOMIC EVALUATION / STAGE III COLON CANCER / ADJUVANT CHEMOTHERAPY

99 pages

การประเมินความคุ้มค่าทางการแพทย์ของการรักษาเสริมโดยใช้ยาเคมีบำบัดในผู้ป่วยโรคมะเร็งลำไส้ใหญ่ระยะที่ 3 ในประเทศไทย

COST-UTILITY ANALYSIS OF ADJUVANT CHEMOTHERAPY IN PATIENTS WITH STAGE III COLON CANCER IN THAILAND

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บทคัดย่อ

วัตถุประสงค์ของการศึกษานี้เพื่อประเมินต้นทุนอรรถประโยชน์เปรียบเทียบระหว่างทางเลือกในการรักษาด้วยยาเคมีบำบัดสูตรต่างๆ เปรียบเทียบกับการรักษาด้วยยาสูตรมาตรฐานที่ใช้ในการรักษาเสริมคือยา (5-FU/LV) และสูตรการรักษาเมื่อมีการกลับเป็นซ้ำของโรคคือยา Capecitabine การวิเคราะห์ด้วยวิธีต้นทุนอรรถประโยชน์ถูกนำมาใช้เปรียบเทียบสูตรยารักษาผู้ป่วยโรคมะเร็งลำไส้ใหญ่ระยะที่สาม แบบจำลองมาร์คอฟถูกนำมาใช้ในการวิเคราะห์ต้นทุนและผลลัพธ์ของการรักษาที่เกิดขึ้นตลอดชีวิตโดยใช้มุมมองของสังคมและรัฐบาล ต้นทุนที่ศึกษาเป็นต้นทุนทางตรงทางการแพทย์ ต้นทุนทางตรงที่ไม่เกี่ยวกับทางการแพทย์และต้นทุนทางอ้อม ผลลัพธ์ทางสุขภาพคือปีชีวิตและปีสุขภาวะของผู้ป่วย ผลการศึกษานำเสนอโดยใช้อัตราส่วนต้นทุนและประสิทธิผลส่วนเพิ่ม การประเมินผลกระทบของความไม่แน่นอนของตัวแปรที่ใช้ในแบบจำลองโดยวิธีการวิเคราะห์ความไวแบบทีละตัวแปรและแบบความน่าจะเป็น

ผลการศึกษาเสนอแนะว่ายาสูตรมาตรฐานที่ใช้ในการรักษาเสริมคือยา 5-FU/LV และสูตรการรักษาเมื่อมีการกลับเป็นซ้ำของโรคคือยา Capecitabine ยังคงเป็นทางเลือกแรกที่คุ้มค่าที่สุด และยา Oxaliplatin ไม่มีความคุ้มค่าในการรักษาโรคมะเร็งลำไส้ใหญ่ในการรักษาเสริมตามบริบทของประเทศไทย โดยหากพิจารณายาที่มีความคุ้มค่ารองจากสูตรมาตรฐานแล้วพบว่ายารักษาเสริมสูตร FOLFOX และสูตรการรักษาเมื่อมีการกลับมาเป็นซ้ำของโรคคือ FOLFIRI มีอัตราส่วนต้นทุนประสิทธิผลเท่ากับ 474,000 และ 398,000 บาทต่อปีสุขภาวะที่เพิ่มขึ้นตามมุมมองของสังคมและรัฐบาลตามลำดับ ซึ่งหากมีการลดราคายาของยาสูตรดังกล่าวร้อยละ 40 โดยมีราคายาสูตร FOLFOX และ FOLFIRI เท่ากับ 179,025 และ 527,015 ยารักษาเสริมสูตร FOLFOX และสูตรการรักษาเมื่อมีการกลับมาเป็นซ้ำของโรคคือ FOLFIRI จะมีอัตราส่วนต้นทุนประสิทธิผลส่วนเพิ่มเท่ากับ 299,365 บาทต่อปีสุขภาวะที่เพิ่มขึ้นตามมุมมองสังคม

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LIST OF ABBREVIATIONS

AJCC	American Joint Committee on Cancer
APC	Adenomatous polyposis coli
ASR	Age-standardized incidence rates
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CI	Credible Interval
CMA	Cost-minimization analysis
CPI	Consumer price index
CSMBS	Civil Servants' Medical Benefit Scheme
CUA	Cost-utility analysis
CUC	Chronic Ulcerative Colitis
DFS	Disease-free survival
EQ-5D	EuroQol
FACT-C	The Functional Assessment of Cancer Therapy Scales for Colorectal Cancer
FAP	Familial adenomatous polyposis
5-FU/LV	5- Fluorouracil/Leucovorin/
FOLFOX/FLOX	Fluorouracil/Leucovorin/Oxaliplatin
HRQOL	Health related quality of life
HNPCC	Hereditary nonpolyposis colorectal cancer
HUI	Health Utilities Index
ICD-10	Principal diagnosis code
ICER	Incremental cost–effectiveness ratio
NCI	National Cancer Institue
NHSO	National Health Security Office
NMB	Net monetary benefit

LIST OF ABBREVIATIONS (cont.)

NLED	National List of Essensial Drug
OR	Odd Ratio
OS	Overall survival
PSA	Probabilistic sensitivity analysis
PSA	Probabilistic sensitivity analysis
QALYs	Quality adjusted life years
QoL	Quality of life
RCT	Randomized controlled trials
SA	Sensitivity analysis
SE	Standard Error
SEER	Surveillance Epidemiology and End Results
SG	Standard Gamble
SSO	Social Security Office
THB	Thai Baht
TTO	Time trade off
UC	Universal Coverage
WTP	Willingness to pay
XELOX/CAPOX	Capecitabine/oxaliplatin

CHAPTER I
INTRODUCTION

Colorectal cancer is a major public health issue. It is the third most common cancer with one million new cases worldwide and the fourth leading cause of death due to cancer in 2004 (1). In Thailand, colorectal cancer is the third most frequent malignancy in males and the fifth in females with age-standardized incidence rates of 11.3 and 7.9 per 100,000 for males and females during 2001-2003, respectively (2).

Surgical resection is the mainstay initial treatment for stage III colon cancer and almost 50% of patients who undergo potentially curative surgery alone finally relapse and death as microscopic metastases present but are undetected at the time of surgery (3). The role of chemotherapy for colon cancer after curative resection has been used as adjuvant chemotherapy which has antitumor activity by decreasing relapse and death. The benefit of adjuvant chemotherapy (i.e., 5-FU combined with leucovorin) reduces relapse rates and improves overall survival by about 33% in patients with node-positive colon cancer (stage III or Dukes' stage C). These advantages were not observed in stage II or Dukes' stage B(4-5).

At present, 5-Fluorouracil and leucovorin (5-FU/LV) based has been the standard treatment of care which established for 6 months (6). Several schedules regimens of 5-FU/LV exist and lead to a difference in toxicity. Besides, the benefits of capecitabine and oxaliplatin (in combination with 5-FU/LV) have been evaluated in the adjuvant treatment of patients with stage III colon cancer. Capecitabine is an oral dosage form chemotherapy with convenience, favorable safety and better-tolerated toxicity (7) and currently in the National List of Essential Drugs (NLED). However, oxaliplatin is another drug shown to have synergistic activity with 5-FU in colon cancer (8). The addition of oxaliplatin to the 5-FU/leucovorin combination has demonstrated significant improvement in disease-free survival and overall survival in the adjuvant setting (9-10).

Currently, oxaliplain has been still expensive and not yet included in NLED. The price of oxaliplatin 50 mg per 10 mg is ranged from 9,000 to 14,000 baht (11). In Thailand, there has been no economic evaluation study of adjuvant chemotherapy for stage III colon cancer patients after resection. Therefore, the NLED committees requested economic evaluation information of adjuvant chemotherapy regimen, particularly oxaliplatin added regimen in stage III colon cancer to consider whether oxaliplatin should be included in the NLED. This study was conducted in order to provide the information for policy decision making.

Conceptual framework

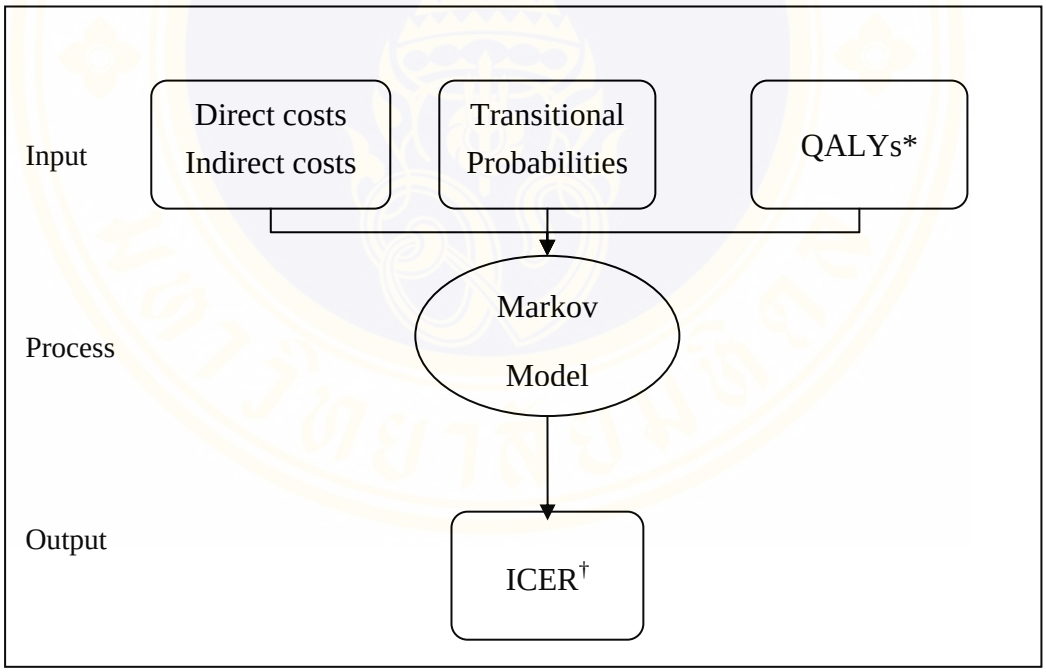

Figure 1.1 The conceptual framework of the cost-utility analysis

*****QALYs=quality adjusted life years

† ICER=Incremental cost-effectiveness ratio

Objectives

General objectives

To compare the cost-utility of each chemotherapy treatment compared with the first-line 5-fluorouracil/leucovorin (5-FU/LV) plus the second-line capecitabine in patients with stage III colon cancer after resection in Thailand based on the societal and governmental perspectives.

Specific objectives

1. To estimate cost and utility of between chemotherapy regimen in patients with stage III colon cancer
2. To estimate incremental cost-effectiveness ratio (ICER) for each compared intervention.

Expected outcomes and Benefits

This study provided the information on the cost-utility of adjuvant chemotherapy for patients with stage III colon cancer after resection based on the societal and governmental perspectives. The expected outcomes and benefits from this study were as follows.

1. The cost-utility analysis of adjuvant chemotherapy could be used to provide the information for policy makers or to determine which regimen should be given to patients with stage III colon cancer after resection.
2. The results from this study could be used to provide the information for policy decision making whether oxaliplatin should be included in the National List of Essential Drugs (NLED)

Definition of terms

Remission state

Remission state is the state that patients' sign and symptoms of cancer disappear.

Recurrence or relapse state

Recurrence state is the state that the patients have cancer again either local or distant organs usually after a period of time when the cancer could not be detected.

Metastases

The development of cancers from one part of the body to another part

Adjuvant chemotherapy

Chemotherapy is given after surgery to eliminate any remaining cancer cells in order to reduce the risk of recurrence of the cancer, either local or distant metastases, to patients in higher risk categories.

Palliative chemotherapy

Chemotherapy administered to control cancer-related symptoms for improving the quality of life of patients and prolong survival. The goal of palliative care is to prevent or treat, not to cure.

Disease-free survival

The time from randomization to first time of recurrence/new occurrence of colon cancer or death.

Overall survival

Time from trial randomization to death but not necessarily free of colon cancer.

Age-standardized incidence rates (ASR)

The ASR is the rate that a population will have if there is a standard age structure. It is calculated by approximating the age-specific incidence rates and applying these rates to the standard population using the world standard population that is used to express per 100,000 population.

Incremental cost

Incremental cost is the added cost with the alternative.

Incremental effectiveness

Incremental effectiveness is the added effectiveness with the alternative.

Incremental cost-effectiveness ratio (ICER)

Incremental cost-effectiveness ratio (ICER) is the ratio that the alternatives are compared on the basis of the increments in costs and effectiveness and calculated by being divided incremental cost by incremental effectiveness**.**

ICER = $(C_I-C_N)/(E_I-E_N)$

Where,

C_I = Alternative cost

C_N= Standard cost

E_I = Alternative effectiveness

E_N = Standard effectiveness

CHAPTER II
LITERATURE REVIEW

The literature review was divided into four parts as follows.

Part I Description of colon cancer

Part II Clinical effectiveness of adjuvant chemotherapy

Part III Economic evaluation methods in healthcare

Part IV Economic evaluation of oxaliplatin for stage III colon cancer patients

Part I Description of colon cancer

1.1 Pathophysiology of colon cancer

Colon cancer is carcinoma presenting in the colon as a result of mutations after invasion of at least the submucosa (12). The mutations result from accumulation of genetic alterations in certain genes because of gene mutations by themselves or exposure to risk factors such as environmental exposures, advancing age, dietary, etc. The genetic alterations are frequently involved with progression from premalignant lesion (adenoma) to invasive adenocarcinoma. The role of genetic factors which are Familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) are obviously mentioned. FAP is the most common inherited syndromes of colon cancer characterized by mutations of adenomatous polyposis coli (APC) gene (13) and HNPCC is an autosomal inherited condition with mutations in one of five mismatch repair (MMR) gene (14-15).

1.2 Classification of colon cancer

A stage is a method to describe the extent of a cancer. The most common staging system is the TMN system staging classification in the 6th edition of the American Joint Committee on Cancer's AJCC Cancer Staging Manual (16). The other older staging systems for colon cancer are Duke's classification and MAC. The TMN

system for describing the anatomical extent of disease is based on the assessment of three categories. T denotes the degree of invasion of intestine wall. N is the absence or presence and extent of lymphatic node involvement and M represents the degree of metastases. The details of these systems are shown in Table 2.1

Table 2.1 American Joint Committee on cancer (AJCC) TMN staging system for colorectal cancer

Stage	TNM Stage			Dukes	MAC
Stage 0	Tis	N0	M0	-	-
Stage I	T1	N0	M0	A	A
Stage II-A	T3	N0	M0	B	B2
Stage II-B	T4	N0	M0	B	B3
Stage III-A	T1-2	N1	M0	C	C1
Stage III-B	T3-4	N1	M0	C	C2/C3
Stage III-C	any T	N2	M0	C	C1/C2/C3
Stage IV	any T	any N	M1	-	D

The following general definitions are used as follows:

Primary Tumor

TX: Primary Tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma *in situ:* intraepithelial or invasion of lamina propia

T1: Tumor invades submucosa.

T2: Tumor invades muscularis propria.

T3: Tumor invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues.

T4: Tumor directly invades other organs or structures, and/or perforates visceral peritoneum.

Regional Lymph Node

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis.

N1: Metastasis in 1 to 3 regional lymph nodes.

N2: Metastasis in 4 or more regional lymph nodes.

Metastasis

MX: Distant metastasis cannot be assessed

M0: No distant metastasis.

M1: Distant metastasis present.

The stage grouping uses the characteristics of tumor (T), nodal status (N) and metastases (M) to determine stage I to IV and prognosis. Based on the Surveillance, Epidemiology, and End Results (SEER) and United States (US) national cancer registry data of 119,363 patients from January 1st, 1991 through December 31st, 2000 (17), five-year colon cancer survival rates were 93.2% for stage I, 84.7% for stage IIA, 72.2% for stage IIB, 42%-83.4% in stage IIIA and IIIB patients with N1 disease, 27.3%-44.3% with N2 disease and 8.1% for stage IV disease according to the AJCC 6th edition staging (Table 2.2) (18).

Table 2.2 Five-year survival rate by the American Joint Committee on Cancer 6th edition system stages I–IV

Staging system	Five-year survival rate (%)
Stage I (T1-2 NO MO)	93.2[b]
Stage IIA (T3 NO MO)	84.7[b]
Stage IIB (T4 NO MO)	72.2[b]
Stage IIIA(T1-2 N1 MO)	83.4[b] -59.8[c]
Stage IIIB (T3-4 N1 MO)	64.1[b] -42.0[c]
Stage IIIC (AnyT N2 M0)	44.3[b] -27.3[c]
Stage IV (AnyT AnyN M1)	8.1 [b]

b According to SEER database(17)

c According to US National Cancer database (18)

Risk factors

1. Age, Gender

Colon cancer increases with age for both males and females. Most individuals (90%) with colon cancer are diagnosed over the age of 50. Males tend to have incidence of colon cancer higher than females (19).

2. Genetics

Genetic vulnerability to colon cancer has been obviously contributed to Familial adenomatous polyposis (FAP) or Hereditary nonpolyposis colorectal cancer (HNPCC). The mutation or loss of APC gene causes the inherited syndromes of FAP or the mismatch repair genes (MMR) is associated with HNPCC. The inherited syndromes of colon cancer is responsible for 3-5% of all colon cancers, with less than 0.5% of FAP, with 3-5% of HNPCC and less than 0.1% of the hamartomatous polyposis conditions (20).

3. Family history

Individuals with a family history of colon cancer, especially a first degree relative, are at an increased risk of colon cancer about 1.8-8 times (21).

4. Diet

i. Obesity and total caloric intake increase a twofold risk of colorectal cancer. The relation is the strongest in men for colon rather than rectal cancer (22). The proposed mechanism for the association is the relative insulin resistance resulting in hyperinsulinemia and increasing activity of IGF (insulinlike growth factor) in obese patients. IGF-1 levels are involved with cell proliferation and increase risk of colon cancer (23).

ii. Red meat

Red meat contains a lot of iron which may increase free-radical production in colon causing chronic mucosal damage or promoting carcinogens. N-nitroso compounds or heat-generated heterocyclic amines from the consumption of red meat correlates with the risk of colorectal cancer (24).

5. Lifestyles

i. Alcohol may reduce folate absorption resulting in the disruption of DNA synthesis and repair and finally lead to colon cancer. Alcohol ingestion (two or more drinks per day) is associated with an increased risk of colorectal cancer (25).

ii. Smoking

Cigarette smoking demonstrates a two to threefold increased risk of adenoma compared with non-smoking (26).

iii. Physical activity

Physical inactivity is relatively consistent to an increase risk of colon cancer based on recreational, occupational, and total activity (27). However, mechanisms for this association have not been established

6. Inflammatory Bowel Disease

Chronic Ulcerative Colitis (CUC) is associated with risk of colorectal cancer (28).

1.3 Epidemiology of colon cancer

In 2004, globally colon and rectum cancer was the third leading common cancer after lung cancer and breast cancer with one million new cases. It was the twentieth most frequently diagnosed causes of any deaths worldwide with 0.6 million deaths (1.1% of total deaths). Particularly in high-income countries, 0.3 million people

died from colon and rectum cancer disease (3.3% of total deaths). Colon and rectum cancer was the fourth leading cause of cancer death among both males and females worldwide. This was also the second cause of males cancer death in high-income and females cancer death in Europe (1).

In Thailand, a total of 17,071 cases with colon and rectum cancer were diagnosed during 2001-2003. These accounted for 9,397 in males and 7,674 in females and corresponded to age-standardized incidence rate (ASR) of 11.3 and 7.9 per 100,000 for males and females, respectively. Based on the tenth leading cancer during 2001-2003 from the national cancer institute (NCI), colon and rectum cancer was ranked as the third leading cause of cancer in males after liver cancer and lung cancer and the fifth leading cause of cancer in females after the breast, cervix, liver and lung cancer. The number of cases of colorectal cancer in both genders has been increasing from 8.4 to 13.9 per 100,000 population for males and 5.7 to 10.3 per 100,000 population for females from 1990 to 2002 (29). Moreover, the data of hospital-based registry from the NCI in 2008 showed that old patients were more likely to develop colorectal cancer than young patients, with the incidence rising from 45-70 years of age. Moreover, patients with stage III colon and rectum cancer were the highest (or about 30%) among stage groupings. Of all 17,071 cases with colorectal cancer during 2001-2003, there were an estimated 11,377 cases of colon cancer and 5,694 cases of rectal cancer with age-standardized incidence rate (ASR) of 12.6 and 7.8 per 100,000, respectively.

1.4 Treatment of stage III colon cancer

1.4.1.1 Surgical treatment

Surgery is the mainstay of therapy for patients with potentially curable colon cancer and complete resection is required for curative treatment. The goal of surgery is to provide an extensive resection that the procedure involves the excision of the lymph nodes draining the tumor, obtaining tumor-free margin, and resection of any adjacent involved organ. The surgical approach is based on the anatomical location of tumors.

1.4.2.1 Adjuvant Chemotherapy

The role of chemotherapy given either before or after surgical treatment has established as adjuvant treatment. Adjuvant chemotherapy has been used after curative resection to reduce the risk of death and recurrence of the cancer, either local or distant metastases, which could result from remaining tumor cells that are not detectable. Adjuvant chemotherapy, therefore, is well established as a standard of care that improves survival about 10% - 15% for stage III disease. Table 2.3 shows the details of four adjuvant chemotherapies currently used in Thailand for stage III colon cancer with curative resection. In this study, adjuvant chemotherapy was categorized into two main groups as:

1.4.1.2.1 Fluoropyrimidines based regimens

- 5-fluorouracil based regimen (i.e.5-fluorouracil /leucovorin (5-FU/LV)
- oral fluoropyrimidines (i.e. capecitabine monotherapy)

1.4.1.2.2 Oxaliplatin based regimen

- 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX or FLOX)
- capecitabine/oxaliplatin (XELOX or CAPOX)

5-fluorouracil/leucovorin (5-FU/LV)

5-FU/LV is the standard treatment of care in adjuvant setting for many years (30) and two regimens of 5-FU/LV generally administered: 1) LV 20 mg/m2 plus bolus 5-FU 425 mg/m2 on days 1-5 repeated every 4-5 weeks for 6 months (National Cancer Institute of Canada Clinical Trials Group[NCCTG]/Mayo Clinic regimen) or 2) weekly LV 500 mg/m2 plus bolus 5-FU 500 mg/m2 during 6 weeks followed by 2 weeks of rest for 4 cycles (Roswell Park regimen). The benefits of 5-FU/LV in reducing risk of relapse or death have been evaluated with no differences between infused 5-FU/LV and bolus 5-FU/LV in the adjuvant setting (31-33). In addition, The Quick and Simple and Reliable (QUASAR) study reported that in combination with bolus 5-FU at low-dose LV(20 mg/m2) was equivalent to high

doses LV (200-500 mg/m2) (34) thus, the tolerability and safety profile of these regimens were considered for the treatment of colon cancer.

Capecitabine monotherapy (7)

The oral fluoropyrimidine capecitabine at the dose of 1,250 mg/m2 administered twice daily on days 1 to 14 every 3 weeks was also shown to be as effective as 5-FU/LV (the Mayo Clinic regimen) in stage III colon cancer. Patients receiving capecitabine had significantly lower incidences of nausea/vomiting, diarrhea, neutropenia, alopecia and stomatitis ($p<0.001$), but significantly higher hand-foot syndrome than those receiving 5-FU/LV ($p<0.001$).

Oxaliplatin based regimen

Oxaliplatin is a third generation platinum complex that gives a synergic activity with 5-FU/LV and capecitabine. The benefits of adding oxaliplatin to 5-FU/LV and capecitabine demonstrated in the MOSAIC trial, NSABPC-07 trial and XELOXA trial.

1. Oxaliplatin in combination with 5-fluorouracil/leucovorin (FOLFOX or FLOX)

In 2004, the addition oxaliplatin to infusion 5-FU/LV prolonged disease-free survival and overall survival for stage III colon cancer obviously in MOSAIC trial. The dose of FOLFOX4 was administrated by a 2-hour infusion of 85 mg/m2 oxaliplatin simultaneously with 200 mg/m2 LV followed by a 400 mg/m2 bolus of 5-FU on day 1 followed by a 22-hr protracted infusion of 600 mg/m2 5-FU days 1-2, every 14 days for 12 cycles and the dose of 5-FU/LV was administrated as the same 5-FU/LV regimen in FOLFOX4 (9). In 2007, a clinical trial (NSABPC-07) demonstrated that there was a significant improvement in 3-year disease-free survival of FLOX compared to weekly bolus 5-FU/LV(Roswell Park regimen). The dose of 5-FU/LV included 500 mg/m2 LV given as a 2-hour intravenous infusion weekly for 6 consecutive weeks (on days 1, 8, 15, 22, 29, and 36 of the treatment cycle) followed by a 2-week rest period and 5-FU 500 mg/m2 administrated weekly (on days 1, 8, 15, 22, 29, and 36 of the treatment cycle) as an intravenous bolus 1 hour after infusion LV followed by a 2-week rest period. The dose of FLOX regimen was the same 5-FU/LV described, in addition, oxaliplatin 85 mg/m2 was administrated as a 2-hour infusion before LV and 5-FU on day 1, 15, and 29 of the treatment duration of 6 months (35).

2. Capecitabine/oxaliplatin (XELOX or CAPOX) is given by a 2-hour intravenous infusion of oxaliplatin 130 mg/m2 on day 1 and oral capecitabine 1,000 mg/m2 twice a day for 14 days every 3 weeks, for a total of eight cycles (24 weeks). The XELOXA trial was carried out to compare the efficacy and safety of capecitabine plus oxaliplatin with bolus 5-FU/LV but only safety data of XELOX was available from this study. The results showed that neurotoxicity was higher in XELOX group compared to 5-FU/LV group (11% vs <1%). Hand-foot syndrome was still higher in XELOX group than 5-FU/LV group(5% vs <1%) while stomatitis and neutropenia were higher in 5-FU/LV group than XELOX group.(9% vs <1% for stomatitis, 16% vs 9% for neutropenia)(36)

Table 2.3 Summary of adjuvant chemotherapy regimens for treatment stage III colon cancer

Regimen	Chemotherapy dosing	Schedule
Fluoropyrimidines		
1.Mayo Clinic	5-FU 425 mg/m2 bolus on days 1 to 5 LV 20 mg/m2 bolus on days 1 to 5	Every 4-5 weeks
2. Roswell Park	5-FU 500 mg/m2 bolus LV 500 mg/m2 infused over 2 hours	Weekly for 6 of 8 weeks
3. Capecitabine	1,250 mg/m2 orally twice per day on days 1 to 14	Every 3 weeks
Oxaliplatin		
4. FOLFOX4	5-FU 400 mg/m2 bolus + 600 mg/m2 IVCI over 22 hours on days 1 and 2 LV 200 mg/m2 over 2 hours on days 1 and 2 Oxaliplatin 85 mg/m2 on day 1	Every 2 weeks
5. FLOX	5-FU 500 mg/m2 bolus on days 1, 8, 15, 22, 29, and 36 LV 500 mg/m2over 2 hours on days 1, 8, 15, 22, 29, and 36 Oxaliplatin 85 mg/m2 on days 1, 15, and 29	Every 8 weeks

Table 2.3 Summary of adjuvant chemotherapy regimens for treatment stage III colon cancer (cont.)

Regimen	Chemotherapy dosing	Schedule
6.XELOX	Oxaliplatin 130 mg/m2 on day 1 oral capecitabine 1,000 mg/m2 twice a day for 14 days	Every 3 weeks

Part II Clinical effectiveness of adjuvant chemotherapy

A systematic review and meta-analysis of randomized controlled trials (RCTs) of adjuvant chemotherapy for patients with stage III colon cancer were searched through the Pubmed and Cochrane databases. Searching terms were the Mesh terms of medication with generic names, colon cancer, adjuvant chemotherapy and type of articles as follows.

"Fluorouracil"[Mesh] OR "Leucovorin"[Mesh] OR
"Oxaliplatin "[Substance Name] OR " Capecitabine "[Substance Name]
AND
"Colonic Neoplasms"[Mesh]
AND
"Randomized Controlled Trial "[PublicationType] OR "Meta-Analysis "[Publication Type]

Inclusion criteria

1. The RCT or meta-analysis studies related to clinical efficacy of four adjuvant chemotherapy regimens (i.e., 5-fluorouracil/leucovorin (5-FU/LV), 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX or FLOX), capecitabine monotherapy, and capecitabine/oxaliplatin (XELOX or CAPOX)) were included.

2. The outcome was disease-free survival of patients with stage III colon cancer after resection.

Exclusion criteria

1. Studies related to interventions plus other chemotherapies
2. Studies comparing duration given interventions
3. Ongoing studies in phase II clinical trial

A total of ninety-eight abstracts were reviewed and finally five eligible studies with six pair interventions compared with 5-fluorouracil/leucovorin (5-FU/LV) were obtained and shown in Table 2.4. Five articles were evaluated by Jadad score's criteria. Four articles had Jadad score equal to 3 and one article had Jadad score equal to 2. Three pair interventions of 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX or FLOX), one pair intervention of capecitabine monotherapy and two pair interventions of capecitabine/oxaliplatin (XELOX or CAPOX) were included. Bayesian approach and WinBUGS1.4 software program (Medical Research Council and Imperial College of Science, Technology and Medicine, United Kingdom) were used to perform meta-analysis of all six pair interventions. Mixed treatment or indirect comparison meta-analysis was applied. The odds ratio (OR) and its 95% credible interval (CI) were used as the summary efficacy in terms of disease-free survival of the medication. Table 2.5 showed the meta-analysis results. When compared with 5-fluorouracil/leucovorin, the odds ratio of 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX or FLOX) was 0.76, the odds ratio of capecitabine was 0.85, and the odds ratio of capecitabine/oxaliplatin (XELOX or CAPOX) was 0.80. The results demonstrated that stage III colon cancer patients after resection receiving FOLFOX or FLOX, XELOX or CAPOX and capecitabine monotherapy had significantly lower risk of relapse and death by 24%, 20% and 15% compared to those receiving 5-fluorouracil/leucovorin, respectively. However, there was no significant difference in odds ratio when compared capecitabine with FOLFOX or capecitabine with XELOX or CAPOX and FOLFOX or FLOX with XELOX or CAPOX

Table 2.4 Summary of adjuvant chemotherapy studies

Study	Numbers randomized	Interventions	Duration of follow-up(months)	Event of outcomes	
				Disease-free survival	Overall survival
Andre T. et al.(31) (2004)	T1: 1,123 T2: 1,123	T1: oxaliplatin in combination with 5-FU/LV(FOLFOX4 regimen) T2: 5-FU/LV (de Gramont regimen)	37.9	T1: 237 T2:293	T1: 133 T2: 146
Kuebler J. et al.(10) (2007)	T1: 1,247 T2: 1,245	T1: oxaliplatin in combination with bolus 5-FU/LV(FLOX regimen) T2: 5-FU/LV(Roswell Park bolus regimen)	34	T1: 308 T2: 369	T1: 187 T2: 198
Twelves C. et al.(59) (2005)	T1: 1,004 T2: 983	T1: capecitabine monotherapy T2: 5-FU/LV (Mayo regimen)	45.6	T1: 348 T2: 380	T1: 200 T2: 227

Table 2.4 Summary of adjuvant chemotherapy studies (cont.)

Study	Numbers randomized	Interventions	Duration of follow-up(months)	Event of outcomes	
				Disease-free survival	Overall survival
Haller D.G. et al.(60) (2010)	T1: 994 T2: 942	T1: capecitabine plus oxaliplatin(XELOX regimen) T2: 5-FU/LV (Mayo regimen)	57	T1: 274 T2: 311	Not reported
Diao C et al.(61) (2008)	T1: 98 T2: 87 T3: 71	T1: 5-FU/LV T2: modified Folfox4 T3: XELOX	N/A	T1: 33 T2: 18 T3: 13	N/A

Where:

T = treatment

FOLFOX4 regimen: 2-h infusion of 200 mg/m2 intravenous LV followed by intravenous bolus 400 mg/m2 5-FU and then a 22-h infusion of 600mg/m2 5-FU on 2 consecutive days plus oxaliplatin 85 mg/m2 over 2 h on day I (given simultaneously with LV)

De Gramont regimen: 2-h infusion of 200 mg/m2 intravenous LV followed by intravenous bolus 400 mg/m2 5-FU and then a 22-h infusion of 600mg/m2 5-FU on 2 consecutive days

FLOX regimen: 5-FU 500 mg/m2 plus LV 500 mg/m2 intravenous bolus weekly for 6 weeks plus oxaliplatin 85 mg/m2 intravenous on weeks 1, 3 and 5 of each 8-week cycle in the absence of disease of disease progression or unacceptable toxicity

Roswell Park bolus regimen: 5-FU 500 mg/m2 plus LV 500 mg/m2 intravenous bolus weekly for 6 weeks

Table 2.5 The odds ratio (OR) of interventions compared to 5-FU/LV

Adjuvant chemotherapy	OR(95% CI)
oxaliplatin in combination with 5-FU/LV (FOLFOX or FLOX regimen)	0.76* (0.69-0.85)
capecitabine monotherapy	0.85* (0.72-0.98)
capecitabine/ oxaliplatin(XELOX regimen)	0.80* (0.68-0.94)

* Statistical significance

Moreover, the probability of death for relapse patients was obtained from a systematic review and meta-analysis of randomized controlled trials among stage IV colon cancer patients performed through the Pubmed and Cochrane databases using the key words as follows.

"irinotecan "[Substance Name] OR "oxaliplatin "[Substance Name] OR OR "capecitabine "[Substance Name] OR "Fluorouracil"[Mesh] OR Leucovorin"[Mesh]

AND

"Colonic Neoplasms"[Mesh]

AND

"Randomized Controlled Trial "[PublicationType] OR "Meta-Analysis "[Publication Type]

Inclusion criteria

1. The RCT or meta-analysis studies related to clinical efficacy of 5-fluorouracil/leucovorin(5-FU/LV), 5-fluorouracil/leucovorin/oxaliplatin, capecitabine monotherapy, capecitabine/oxaliplatin and irinotecan in combination with 5-FU/LV (irinotecan/5-FU/LV) without regard to dose intensity in stage IV colon cancer patients
2. The outcome was overall survival of stage IV colon cancer patients.

Exclusion criteria

1. Studies related to interventions plus other chemotherapies
2. Studies without the number of dead or alive patients reported
3. Studies comparing dose or duration of interventions
4. Ongoing studies in phase II clinical trial

Bayesian approach and WinBUGS14 (Medical Research Council and Imperial College of Science, Technology and Medicine, United Kingdom) software program were used to perform meta-analysis. Mixed treatment or indirect comparison meta-analysis was applied. Odds ratio and its 95% credible interval were used as the summary efficacy of the medication. Heterogeneity test was applied for testing the variation of study outcomes between studies.

Based on the results of systematic reviews, 241 abstracts were reviewed and 18 relevant RCTs were included in the analysis. Eighteen articles were evaluated by Jadad score's criteria. Eighteen articles had Jadad score equal or greater than 3.

There were two studies comparing capecitabine with 5-FU/LV (37-38) four studies comparing FOLFOX with 5-FU/LV (39-42), three studies comparing FOLFIRI with 5-FU/LV (43-45), four studies comparing FOLFOX with XELOX (46-49) and five studies comparing FOLFOX with FOLFIRI (50-54). Table 2.6 presented the odds ratio of death at the 1st, 2nd and 3rd year and its 95% credible interval (CI) of all treatments compared with 5-FU/LV. The results showed that there were statistical significance differences in odds ratio of death between FOLFOX and 5- FU/LV at the 1st year. However, at the 2nd and 3rd year, there was no statistical significance difference in odds ratio of death between each treatment and 5- FU/LV.

Table 2.6 The odds ratio (OR) of interventions compared to 5-FU/LV at the 1st, 2nd and 3rd year

Chemotherapy regimen	**OR (95% CI)**		
	Year 1	**Year 2**	**Year 3**
oxaliplatin in combination with 5-FU/LV	0.74* (0.58-0.93)	0.86 (0.6751-1.08)	0.61 (0.14-1.50)
capecitabine/ oxaliplatin (XELOX)	0.89 (0.59-1.28)	0.94 (0.60-1.39)	0.88 (0.09-2.62)
irirnotecan in combination with 5-FU/LV	0.91 (0.70-1.14)	0.90 (0.70-1.14)	0.71 (0.15-1.81)
capecitabine	1.19 (0.81-1.66)	0.92 (0.62-1.31)	0.63 (0.09-1.76)

* Statistical significance

According to expert opinion, the ORs of capecitabine should not be greater than 1 or higher than the ORs of 5-FU/LV. Therefore, it was assumed that the probability of death of capecitabine was equal to that of 5-FU/LV (mean ORs=0.39, Standard error; = 0.026)

In terms of quality of life (QOL), Ness et al (55) measured utilities for stage-dependent outcome of colorectal cancer using the standard gamble method. Each

state outcome was described as a state of colorectal cancer with or without resection, chemotherapy, radiation and ostomy. The HRQOL scores were higher in patients at early stage of diagnosis than those at late state. Considering the HRQOL scores for state III colon cancer, two groups were categorized. First, patients with stage III colon cancer treated with resection and chemotherapy without significant side effects had the utility score of 0.70 (0=death and 1=full health). Second, patients with stage III colon cancer treated with resection and chemotherapy with significant side effects had the utility score of 0.63 and the utility score of metastaic disease was 0.24. Nevertheless, the definition of significant side effects was not mentioned in this study.

According to Ramsey et al (56), 173 survivals of colorectal cancer who survived at least one year recruited from databases completed the two self-administered surveys: the Functional Assessment of Cancer Therapy Scales for Colorectal Cancer (FACT-C), a disease specific HRQOL instrument with a summary score ranging from 0 (worst possible) to 112 (best possible), and the Health Utilities Index (HUI) Mark III, a generic multiattribute preference-based system for valuing the utility ranging from 0–1. This survey measured utility in all colorectal cancer TNM stages at diagnosis time periods from the date of initial diagnosis: 1) 13–24 months; 2) 25–36 months; 3) 37–60 months; and 4) > 60 months. The summary measures of HRQOL revealed that the pattern of HRQOL over time differed depending on the initial stage at diagnosis and all stages except stage IV, HRQOL tended to increase over time and appeared to stabilize at a high level over 36 months. The average HUI utility score by stage III colorectal cancer and time since diagnosis were 0.82 (0=death and 1=full health) in 13–24 months, 0.95 in 25–36 months, 0.79 in 37–60 months and 0.92 for more than 60 months. Mean FACT-C scores were 106.7 in 13–24 months, 117.4 (score 0-100) in 25–36 months, 106.1 in 37–60 months, and 117.9 for more than 60 months. They also reported the utility for colorectal cancer related to interventions in last month (i.e. surgery (FACT-C = 95.4, HUI= 0.584), chemotherapy (FACT-C =105.1, HUI=0.80), radiation (FACT-C=92.9, HUI=0.68) and colostomy (FACT-C =103.2, HUI=0.85). The HRQOL scores at the last year of life were reported as HUI score of 0.85 for survivals and 0.65 for individuals who died within 1 year of being interviewed.

Shiroiwa et al (57) measured health utility scores of colorectal cancer (CRC) patients from a societal perspective in Japan using standard gamble (SG) and time trade-off (TTO) methods. This study described the health state of metastatic patients treated with FOLFOX4 or XELOX concerning adverse events and health state of adjuvant chemotherapy (during or after chemotherapy) was also defined. However, the state of disease, specific chemotherapy as well as the detailed information on side effects were not mentioned. For patients with stoma, the utility scores of adjuvant chemotherapy measured by SG and TTO methods were equal to 0.54 and 0.56 during chemotherapy as well as 0.60 and 0.62 after adjuvant chemotherapy, respectively. For patients without stoma, the utility scores of adjuvant chemotherapy measured by SG and TTO methods were 0.74 and 0.69 during chemotherapy and 0.80 and 0.75 after adjuvant chemotherapy, respectively.

Recently, Best et al (58) evaluated preference value for seven health states with the effect of neuropathy from adjuvant chemotherapy in stage III colon cancer i.e. 1) remission 2) adjuvant therapy without neuropathy 3) adjuvant therapy with mild neuropathy 4) adjuvant therapy with moderate neuropathy 5) adjuvant therapy with severe neuropathy 6) metastatic stable and 7) metastatic progressive disease by using time trade-off (TTO) methods. The patients' adjusted mean TTO value for remission was 0.83. The utility values of adjuvant chemotherapy health states were ranged from 0.48 to 0.61 and the utility value of metastatic state was 0.37 for progressive and 0.40 for stable.

In fact, until recently there has been no data on health utility scores of colon cancer who underwent chemotherapy in Thailand yet. Although many studies have estimated the utility scores from foreign trials in order to calculate quality-adjusted life years (QALYs) for economic evaluation studies, the validity of estimation has not been assured due to cultural differences between Thailand and foreign countries. For this reason the utility scores were collected from patients and caregivers using EQ-5D questionnaire at National Cancer Institute (NCI).

Part III Economic evaluation (EE) in health care

Economic evaluation is relevant to identification, measurement and evaluation of at least two compared alternatives in terms of both costs and outcomes. The cost component is always measured in monetary unit, whereas the outcome component can be measured in many ways. Due to different outcome measurements, the full economic evaluation is divided into four types of analysis. There are cost-benefit analysis (CBA), cost-minimization analysis (CMA), cost-utility Analysis (CUA), and cost-effectiveness analysis (CEA)(62).

1. **Cost-Benefit Analysis (CBA)** compares costs and consequences of two or more alternatives that have different outcomes. Costs and outcomes are measured in monetary unit. The benefit from a program and all the costs of establishing a program are identified and converted into equivalent monetary unit in the year in which they occur. The purpose of cost-benefit analysis is to find the alternative with the most favorable cost- to-benefit ratio. Many outcomes such as years of life saved and quality of life are difficult to value in monetary terms, therefore these are the limitations of outcome valuation in monetary units.

2. **Cost-Minimization Analysis (CMA)** compares costs of two or more alternatives that have equivalent outcomes. The outcomes of the alternatives are assumed to be equal, only costs of each alternative have been estimated. Cost-minimization analysis shows only cost savings of one program or treatment over another.

3. **Cost-Utility Analysis (CUA)** is a type of economic evaluation to manage health care costs. It is similar to cost-effectiveness analysis, except the outcomes are measured as quality-adjusted life-years (QALYs). Cost-utility analysis is the most useful in evaluating health programs that extend life but with serious side effects such as cancer chemotherapy or arthritis.

4. **Cost-Effectiveness Analysis (CEA)** is a form of economic analysis that compares the relative costs and outcomes of two or more courses of action that achieve the most effective at the least cost. When treatment alternatives are not therapeutically equivalent, or when it is inappropriate to express benefits (outcomes) in monetary units, cost-effectiveness analysis may provide a more appropriate evaluation technique. For drug therapy, different drugs as alternatives are compared as

well as drug treatment is also compared with do nothing or non drug treatment. Cost-effectiveness analysis assesses the cost and consequences of pharmaceutical products and services, with non-equivalent therapeutic outcome. After the costs and effectiveness of the alternatives are obtained, two approaches have been used to compare them in CEA.

1) Cost-effectiveness ratio approach: the alternatives are compared on the basis of the average cost per unit of effectiveness (occasionally, average effectiveness per unit cost). Typically, the most cost-effective alternative has the lowest average cost per unit of effectiveness.

2) Incremental cost-effectiveness ratio (ICER) approach: the alternatives are compared on the basis of the increments in costs and effectiveness and lower ICER is preferable since it implies less incremental cost for a unit of effectiveness. The ICER expresses the additional costs that an alternative has over another as compared to the additional effectiveness.

Incremental cost effectiveness ratio (ICER) is calculated by incremental cost divided by incremental effectiveness

$$ICER = (C_I - C_N)/(E_I - E_N)$$

Where,

C_I = Intervention cost or current practice cost

C_N = Null cost

E_I = Intervention effectiveness or current effectiveness

E_N = Null effectiveness

Part IV Economic evaluation of oxaliplatin for stage III colon cancer patients

A systematic review of the literatures on the cost-effectiveness of oxaliplatin for the treatment of stage III colon cancer patients was searched through Pubmed and Cochrane databases until 2009 using the following keywords.

("Colon Neoplasms"[Mesh])

AND

(cost effectiv* OR cost utilit* OR cost evaluat*

OR cost benefit OR economic evaluat*)

AND

(Oxaliplatin "[Substance Name])

Studies comparing both costs and outcomes of oxaliplatin added regimens as the adjuvant chemotherapy in state III colon cancer were included. The exclusion criteria were the studies related to only cost or outcome analysis or the studies related to editorial article or expert opinion. The literatures were selected based on the inclusion and exclusion criteria as shown in Table 2.7

Table 2.7 Inclusion and exclusion criteria of economic evaluation of oxaliplatin for stage III colon cancer patients

Inclusion criteria	**Exclusion criteria**
Studies comparing both cost and outcome in term of incremental cost per quality-adjusted life-year (QALY) gained of oxaliplatin added regimens as the adjuvant chemotherapy in state III colon cancer Publication date until 2009 Only English publications	The studies considered only outcome (efficacy, effectiveness) or cost analysis The studies were editorial article or expert opinion The studies in which the methodologies were not unclear

The systematic review resulted in a total of thirty studies for potential inclusion in the review. Twenty-six studies were excluded and four studies were identified as the specified criteria. All eligible studies were extracted using data extraction forms and major key components of economic evaluation for each study were summarized as shown in Table 2.8

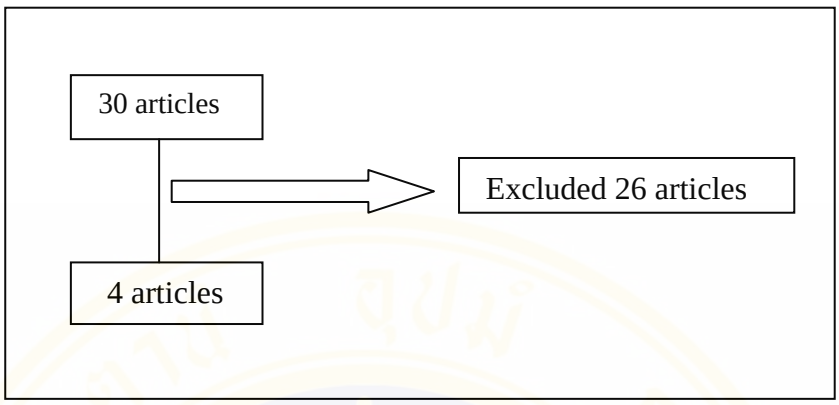

Figure 2.1 Result of systematic literature review search

The relevant studies were critically appraised using the Drummond's checklist for assessing the quality of economic evaluation (see Appendix A) The details extracted from each included study were as follows: (1) author, year, country, (2) disease and patient group, (3) objective, (4) intervention, (5) perspective, (6) source of data, (7) outcome, (8) method, (9) discounting rate, (10) sensitivity analysis, and (11) incremental cost-effectiveness result.

All four studies were conducted based on the perspective of healthcare payer which considered only direct medical costs. Outcomes were mostly measured as life year gained, disease–free years and quality-adjusted life years. The cost-utility analysis method was performed in all studies using Markov model with a lifetime horizon but only one study presented the model. Mostly, data used in the model were retrieved from systematic review, published literature and clinical trials. One-way and probabilistic sensitivity analyses were used to handle parameter uncertainty. Based on the systematic review, FOLFOX4 (oxaliplatin plus 5-fluorouracil and leucovorin, 5FU/LV) was more cost-effective in patients with colon cancer in the US and UK compared with 5FU/LV. The summary of each studies were as follows.

1. The cost-effectiveness of oxaliplatin in the U.S.

Aballea et al (63) reported the results of cost-effectiveness analysis of oxaliplatin in combination with 5-FU/LV (FOLFOX4) compared to 5-FU/LV in patients with resected stage III colon cancer in the perspective of U.S. Medicare. The

mean total lifetime disease-related costs were $56,300 with FOLFOX4 and $39,300 with 5-FU/LV. Cost of chemotherapy was the main cost component at approximately $29,000 per patient receiving FOLFOX4 as a treatment and $6,500 per patient receiving 5-FU/LV. In addition, cost associated with relapse regarding to incidence of relapse and position (local, lung, liver, other types of disseminated disease) was the most costly resource use with the average of $16,600 in the FOLFOX4 group and $23,700 in the 5-FU/LV group. The main outcomes were disease-free years (DFYs), life-year (LYs) and quality-adjusted life years (QALYs). DFYs and overall survival (OS) were extrapolated by using data from MOSAIC trial to a lifetime horizon. The predicted life expectancy of stage III colon cancer patients for stage III colon cancer on FOLFOX4 group and 5-FU/LV group was 12.34 and 11.52 years, respectively. In conclusion, FOLFOX4 was likely to be cost-effectiveness compared to 5-FU/LV in adjuvant treatment of stage III colon cancer with an incremental cost of $12,800 per DFY, $20,600 per LY gained,$22,800 per QALY gained with the probability being cost-effective of 91% at willingness to pay (WTP) of $50,000 per QALY gained.

2. The cost-effectiveness of oxaliplatin in U.K.

Eggington et al (64) and Aballea et al (65) conducted the cost-effectiveness analysis of oxaliplatin for the adjuvant treatment of stage III colon cancer. Both studies compared oxaliplatin in combination with 5-FU/LV (FOLFOX4) to 5-FU/LV based on the perspective of the NSH in the UK. The effectiveness data were obtained from MOSAIC trial and extrapolated to DFYs, life-years and overall survival (OS). Eggington et al developed a health economic Markov model to estimate the marginal cost-effectiveness of oxaliplatin. For those who relapsed, the expected survival was modelled using a parametric Weilbull survival model based on the experience of patients in FOCUS trial (66). Only direct medical cost was £26,000 and £22,000 in FOLFOX4 group and 5-FU/LV group, respectively. FOLFOX4 estimated to produce 12.15 LY gained while 5-FU/LV produce 10.80 LY gained. The incremental cost-effectiveness ratio (ICER) was equal to £2,970 per QALY. Aballea et al found that FOLFOX4 was more cost-effective than 5-FU/LV. The main outcomes measured as DFYs, LYs and QALYs. Cost of FOLFOX4 increased by £3,923 but decrease the cost of relapse by £1,026 compared to that of 5-FU/LV. Total costs of the treatment during four years after resection were higher by £3,407 in patients receiving

FOLFOX4 compared with those with 5-FU/LV. The results showed that the incremental cost was £2,600 per DFY, £4,200 per LY, and £4,805 per QALY with the probability being cost-effective of 94% at WTP of £20,000 per QALY. In conclusion, the evidences from these two studies showed that FOLFOX4 was more cost-effective at WTP of £20,000 per QALYs.

Furthermore, Koperna et al (67) assessed the cost-effectiveness of oxaliplatin in combination with 5-FU/LV compared to 5-FU/LV in patients with resected stage III colon cancer based on the perspective of the Austrian healthcare provider. Cost data in this study included cost of metastatic disease and the efficacy data on disease-free survival and overall survival for oxaliplatin in combination with 5-FU/LV were obtained from clinical trials from Stage IV colon cancer. The results were presented as the incremental cost per life-year gained (£24,952) of oxaliplatin in combination to 5-FU/LV. However, Pandor et al conducted a systematic review of clinical effectiveness and economic evaluation of oxaliplatin and capecitabine for the adjuvant treatment of stage III colon cancer and suggested that the study of Koperna et al had many methodological flaws related to cost and effectiveness data collection (68).

Based on existing cost-effectiveness studies of oxaliplatin added regimen to 5-FU/LV, effectiveness data were obtained from MOSAIC trial. Moreover, there has been no cost-effectiveness and cost-utility analysis of adjuvant chemotherapy compared to the first-line 5-FU/LV and the second- line capecitabine for stage III colon cancer patients in Thailand yet. Recently oxaliplatin has not yet included in the National List of Essential Drug (NLED). Thus, the cost-effectiveness analysis of oxaliplatin added regimen to 5-FU/LV was conducted and used effectiveness data obtained from two existing clinical trials (i.e., MOSAIC and NSABP-07). The results from this study were provided the information for policy decision making.

Table 2.8 Summary of major key components of each economic evaluation study

Study	Disease and patient group	Objective	Intervention	Perspective	Source of data	Cost	
						Direct	Indirect
1. Aballea S.et al. (2007)(US)	Patients with stage III colon cancer after surgical resection	To confirm the cost-effectiveness of oxaliplatin in combination with infusion 5-FU/LV compared with 5-FU/LV	1. oxaliplatin in combination with infusion 5-FU/LV (FOLFOX4) 2. 5-FU/LV	NHS in the UK.	Literature review, MOSAIC trial	Cost of chemotherapy, clinic attendance, Infusion pumps, Premedication adjuvant chemotherapy, Cost of routine follow up, Cost of recurrence, Cost of management serious side effect	N/A
2.Eggington S.et al (2006)(UK)	Patients with stage III colon cancer after surgical resection	To estimate the cost-effectiveness of 1.oxaliplatin plus 5-FU/LV and 2. capecitabine compared to 5-FU/LV	1. oxaliplatin in combination with infusion 5-FU/LV (FOLFOX4) 2. Infusion 5-FU/LV (de Gramont) 3. capecitabine 4.bolus 5-FU/LV	NHS in the UK. and personal social service(PSS)	Literature review, MOSAIC trial, X-act trial	Drug acquisition and administration, Pharmacy handling and dispensing infusor pumps, Examinations and tests, Hospitalization resource use for the management of toxicity	

Table 2.8 Summary of major key components of each economic evaluation study (cont.)

Study	Disease and patient group	Objective	Intervention	Perspective	Source of data	Cost	
						Direct	Indirect
3. Pandor A. et al. (2006) (UK)	Patients with stage III (Duke'C) colon cancer after surgical resection	To assess the clinical and cost-effectiveness of oxaliplatin in combination with infusion 5-FU/LV and capecitabine monotherapy as adjuvant chemotherapy	1. Oxaliplatin in combination with infusion 5-FU/LV (FOLFOX4) 2. Infusion 5-FU/LV(de Gramont)	NHS in the UK.	Systematic review	Drug acquisition and administration, Cost of hospitalization from adverse events, Medication cost of associated with the treatment of adverse events, Number of physician consultants(eg. GP visit, hospital outpatient visits, accident and emergency attendences	N/A

Table 2.8 Summary of major key components of each economic evaluation study (cont.)

Study	Disease and patient group	Objective	Intervention	Perspective	Source of data	Cost	
						Direct	Indirect
4. Aballea S. et al. (2007)(UK)		To evaluate the long- term cost-effectiveness of oxaliplatin in combination with5-FU/LV	1. oxaliplatin in combination with infusion 5-FU/LV (FOLFOX4) 2. 5-FU/LV	NHS in the UK	Literature review, MOSAIC trial	Cost of chemotherapy, Replacement chemotherapy, Outpatient visit, Laboratory tests, Adverse events and surgery, Treatment for relapse, Treatment for disease monitoring during chemotherapy and afterwards, Treatment associated with non-serious toxicities, serious side effect	N/A

Table 2.8 Summary of major key components of each economic evaluation study (cont.)

Study	Outcome	Method	Discounting	Sensitivity analysis	Results
1. Aballea S. et al. (2007)(US)	1. Disease-free years(DFY) 2. Life years gained(LYs) 3. ICER	CUA (No model presented)	3.% per year	Bootstrap method	1. The predicted life expectancy of stage III on FOLFOX4 and 5-FU/LV was 17.6 and 16.26 years 2. Mean total life time disease-related costs on FOLFOX4 and 5-FU/LV were $56,300 and $393,000 3. oxaliplatin/5FU/LU was cost effectiveness compared with 5-FU/LU (ICER=$12,900 per DFY gained, $ 20,600 per LY gained,$ 22,800 per QALY 4. FOLFOX4 was cost effective 91-96% probability (willingness to pay of $ 50,000 to $ 1000,000 per QALY gained)
2.Eggington S.et al (2006)(UK)	1.Life years gained(LYs) 2.Quality of life adjusted year gained 3.ICER	CUA (model presented)	6% per year	One way and Probabilistic sensitivity analysis	1. The incremental cost per QALY gain of capecitabine was dominant to 5-FU/LU (MAYO clinic) 2.FOLFOX4 was estimated to cost £2970 per additional QALY gained compared with 5FU/LU(de gramont)

Table 2.8 Summary of major key components of each economic evaluation study (cont.)

Study	Outcome	Method	Discounting	Sensitivity analysis	Results
3. Pandor A. et al. (2006)(UK)	1.Life years gained(LYs) 2.Quality of life adjusted year gained 3.ICER	CUA (No model presented)	6% for cost and 1.5% for QALY per year	Probabilistic sensitivity analysis	1.capecitabine and FOLFOX4 were clinically effective and cost-effective in comparison with 5-FU/LV regimens (Mayo Clinic and de Gramont schedules) 2.capecitabine was a dominating and cost-saving of £3320 per patient in comparison with the Mayo Clinic 3.FOLFOX4 in comparison with de Gramont 5-FU/LV regimens cost an additional £2970 per QALY gained
4. Aballea S. et al. (2007)(UK)	1. Disease-free years(DFY) 2. Life years gained(LYs) 3. ICER	CUA (No model presented)	3.5% per year	Bootstrap method	1. FOLFOX4 (oxaliplatin/5FU/LV) was cost effectiveness compared with 5-FU/LV (ICER = £ 4805 per QALY) 2. The probability of oxaliplatin/5-FU/LV from the cost - effectiveness acceptability curve was 94.7% at a threshold of £20,000 and 96.7% at a threshold of £ 30,000

CHAPTER III
METHODOLOGY

The methodology of this study was consisted of two parts:.

Part I: Other direct healthcare cost analysis

Part II: Economic evaluation of adjuvant chemotherapy of stage III colon cancer

Part I Other direct healthcare cost analysis

1. Data source

The data of stage III colon cancer patients receiving chemotherapy regimen from January 2005 to December 2010 were obtained from electronic database at the National Cancer Institute (NCI). Data included demographic characteristics (e.g., age, gender), principal diagnosis (i.e., ICD-10), type of health insurance (e.g., Civil Servants' Medical Benefit Scheme (CSMBS), Universal Coverage (UC), Social Security Office (SSO), out of pocket and state enterprise and total cost of treatment.

2. Selection of patients

All patients with principal diagnosis related to colon cancer (ICD-10 code=C18) receiving treatment at the NCI during from January 2005 to December 2010 were selected.

3. Data Management

First, data of patients with principal diagnosis codes of colon cancer (ICD-10) shown in Table 3.1 were retrieved from the NCI database. Then, data of these patients with stage III and IV colon cancer disease identified from the NCI database and medical chart review were selected.

Table 3.1 Principal Diagnosis code (ICD-10) of colon cancer

C18	Malignant neoplasm of colon
C180	Caecum malignant neoplasm
C181	Appendix malignant neoplasm
C182	Ascending colon malignant neoplasm
C183	Hepatic flexure malignant neoplasm
C184	Transverse colon malignant neoplasm
C185	Splenic flexure malignant neoplasm
C186	Descending colon malignant neoplasm
C187	Sigmoid colon malignant neoplasm
C188	Overlapping lesion of colon malignant neoplasm
C189	Colon malignant neoplasm unspecified

Demographic characteristics of 114 patients based on patient selection criteria were summarized in Table 3.2. Mean age of patients was 60 years. Fifty one percent of patients were female. Forty two percents of patients were under CSMBS, while those under UC, SSO, state enterprise and out of pocket were 39%, 12%, 6% and 2%, respectively. The number of stage III colon cancer patients receiving adjuvant chemotherapy (61%) was higher than that of stage IV colon cancer patients (39%). All patients with colon cancer received chemotherapy regimens which were FOLFOX (63%), XELODA (23%), 5-FU/LV (18%), XELOX (6%) and FOLFIRI (4%).

Table 3.2 Characteristics of stage III colon cancer patients receiving chemotherapy

Demographic characteristics	Statistical Values
1. Age	Mean ± SD
	61 ± 12
2. Gender	No. of patients (%)
female	58 (51)
male	56 (49)
3. Type of health insurance	
CSMBS	44(42)
UC	39(38)
SSO	12(12)
State enterprise	6(6)
Out of pocket	2(2)
4. Stage of disease	
Stage III	69(61)
Stage IV	45(39)
5. Chemotherapy	
5-FU/LV	18(16)
FOLFIRI	4(4)
FOLFOX	63(55)
XELODA	23(20)
XELOX	6(5)

4. Data analysis

Direct medical costs covered all treatment costs (i.e., chemotherapy cost and other healthcare costs) at the NCI. Other healthcare costs included the cost of other medications without chemotherapy, cost of pre-treatment medications, cost of management of adverse events and toxicities, cost of laboratory and diagnostic tests, cost of procedures, cost of outpatient visits and cost of hospitalizations (IPD admission). All other healthcare costs excluded chemotherapy costs of these patients during January 2005 to December 2010 were included and analyzed. For patients with

state III colon cancer, the annual average direct healthcare costs at the first year and subsequent years of the treatment were calculated. It was assumed that average direct healthcare costs per year per patient were the same for all treatment regimens. For those with stage IV colon cancer, the annual average direct healthcare costs were calculated at the first year which was assumed to be equal to the subsequent years and to be the same for all treatment regimens.

To calculate the annual average direct healthcare costs at the first year, patients receiving the treatment less than six months were excluded from the analysis. It was assumed that those receiving the treatment for more than six months were more likely to receive complete chemotherapy regimens. Moreover, the annual average direct healthcare costs at the subsequent years were calculated by total direct healthcare costs from the second year to the end of the treatment divided by the total number of years of the treatment excluded the first year. Univariate statistical analysis was applied using the SPSS software program.

For the first year, the mean direct healthcare costs of state III colon cancer patients receiving the treatment (49,844 THB) were higher than subsequent years (28,228 THB), whereas the average direct healthcare costs of stage IV colon cancer patients were 70,133 THB at the first year and subsequent years.

Part II Economic Evaluation of Adjuvant Chemotherapy of Stage III Colon Cancer

1. Study design

This study performed the cost-utility analysis based on economic model to compare all chemotherapy regimens with the first line 5FU/LV and the second line capecitabine in patients with stage III colon cancer patients after resection. A Markov model was used to estimate the relevant costs and health outcomes during lifetime horizon with one year cycle length**.**

2. Perspective

Cost-utility analysis was performed based on the societal and governmental perspective.

3. Study population

Study population was the patients who had undergone complete resection of histological stage III colon cancer receiving the first-line adjuvant chemotherapy currently used in Thailand which were 1)5-FU/LV 2) capecitabine monotherapy 3) fluorouracil/leucovorin/oxaliplatin FOLFOXorFLOX) and 4) capecitabine/ oxaliplatin (XELOX or CAPOX) and the second-line chemotherapy as 1) irinotecan in combination with 5-FU/LV (FOLFIRI) 2) capecitabine monotherapy 3) fluorouracil/leucovorin/oxaliplatin (FOLFOXorFLOX) and 4)capecitabine/ oxaliplatin (XELOX or CAPOX).

4. Intervention

All available adjuvant chemotherapies were given to stage III colon cancer as the first-line treatment which were 1)5-FU/LV 2) capecitabine monotherapy 3) fluorouracil/leucovorin/oxaliplatin (FOLFOXorFLOX) and 4) capecitabine/ oxaliplatin (XELOX or CAPOX)

In addition, based on the current clinical practice guidelines for disease recurrence, the second-line chemotherapy regimens which were 1)capecitabine monotherapy 2)fluorouracil/leucovorin/oxaliplatin(FOLFOXorFLOX) 3) capecitabine/ oxaliplatin (XELOXorCAPOX) and 4) irinotecan in combination with 5- FU/LV (FOLFIRI) were considered for patients with recurrence. Thus, the set of nine interventions was studied depended upon when chemotherapy regimens were given for the management of patients who developed metastases as follows (Table 3.3).

1) For those receiving the first-line 5-FU/LV, the second-line capecitabine, FOLFOX, XELOX, or irinotecan in combination with 5- FU/LV (FOLFIRI) was given (4 interventions). It was noted that first-line 5-FU/LV followed by the second-line capecitabine was used as a comparator in this study.

2) For those receiving the first-line capecitabine, the second-line FOLFOX, XELOX, or irinotecan in combination with 5- FU/LV (FOLFIRI) was provided (3 interventions).

3) For those receiving the first-line FOLFOX or XELOX, the second-line irinotecan in combination with 5- FU/LV (FOLFIRI) was given (2 interventions).

Table 3.3 All compared interventions in this study

First-line regimen	Second-line regimen
5-FU/LV	Capecitabine
5-FU/LV	FOLFOX
5-FU/LV	XELOX
5-FU/LV	Irinotecan plus 5- FU/LV (FOLFIRI)
Capecitabine	FOLFOX
Capecitabine	XELOX
Capecitabine	Irinotecan plus 5- FU/LV (FOLFIRI)
FOLFOX	Irinotecan plus 5- FU/LV (FOLFIRI)
XELOX	Irinotecan plus 5- FU/LV (FOLFIRI)

5. Economic evaluations

5.1 Model structure

Figure 3.1 illustrated a Markov model structure that was used to estimate the relevant costs and health outcomes during life time horizon with one year cycle length. The study compared eight mutually exclusive treatment options as stated above with the first-line 5-FU/LV followed by the second-line capecitabine.

The health states of stage III colon cancer patients after resection consisted of three states: 1) alive without relapse or pre-relapse 2) alive with relapse and 3) death. All stage III colon cancer patients after resection who required the treatment based on the mentioned criteria above would start at alive without relapse state. For the patients receiving adjuvant chemotherapy, if cancer were detected again either local or distant metastasis, the patients would move to alive with relapse and needed to change chemotherapy regimens. Patients in all states could stay at the same state and could move to death state. An arrow represents the probability of moving from one state to another known as transitional probability. Adverse events of each treatment were included in health state of patients receiving chemotherapy. The model simulation was used to estimate the costs and health outcomes over a 99-year period to cover the maximum expected lifetime horizon.

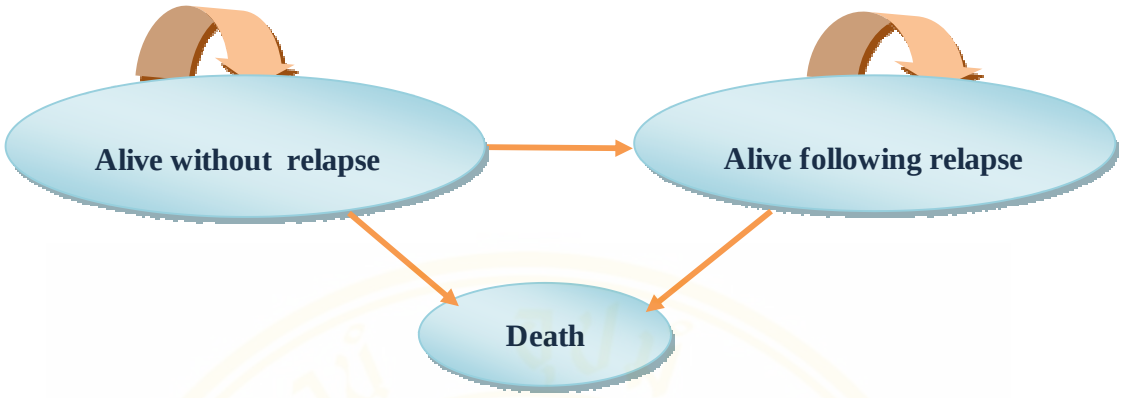

Figure 3.1 Schematic diagram of the Markov model

5.2 Model assumptions

Based on clinical information and practice, the assumptions of analytical model were addressed. First, patients completing resection of histological stage III colon cancer were treated by adjuvant chemotherapy for six months. Second, all recurrences were assumed to occur within five years after resection of primary tumor. Third, the survival of patients with relapse was equal to that of patients diagnosed with stage IV colon cancer depended on the efficacy of chemotherapy regimen given over lifetime. Fourth, the survival of alive patients with disease- free was estimated from overall survival of stage III colon cancer depended on the efficacy of adjuvant chemotherapy regimen given. Last, it was assumed that utility scores of patients receiving intravenous chemotherapy regimens (i.e., 5-FU, FOLFOX, XELOX, and FOLFIRI) were the same but different from those receiving oral chemotherapy (i.e., capecitabine).

5.3 Transitional probabilities

Transitional probabilities used in this study were as follows (Table 3.4).

1. The transition from alive without relapse to alive with relapse
2. The transition from alive without relapse to death
3. The transition from alive with relapse to death

First, the transitional probability that alive patients without relapse moved to alive with relapse state was estimated from disease-free survival data obtained from

the mixed treatment or indirect comparison meta-analysis of clinical efficacy studies using a Bayesian fix effect model in stage III colon cancer patients receiving adjuvant chemotherapy. Second, the transitional probability that alive patients without relapse moved to death was estimated from overall survival curves of stage III colon cancer patients receiving adjuvant chemotherapy. The transitional probability that alive patients with relapse moved to death was obtained from a systematic review and meta-analysis of clinical trials in patients with metastatic disease. In addition, mortality rates of Thai general population at each age were also used in the analysis.

6. Ethical concern

This study was applied for ethical approval and was approved by the Committee on Human Rights Related to Research Involving Human Subjects, Mahidol University Institutional Review Board (MU-IRB), Mahidol University and National Cancer Institute, Thailand.

7. Time Horizon

The study estimated the costs and health outcomes over a 99-year period to cover the expected life time horizon.

8. Cost measurement

The cost analysis was performed based on societal and governmental perspectives. Since this study adopted the societal perspective, both direct (i.e., medical and non-medical) and indirect costs were collected.

8.1 Direct medical costs

Direct medical costs covered all treatment costs (i.e., chemotherapy cost and other healthcare costs) at the hospital and were obtained from two data sources (Table 3.4). Costs of chemotherapy were calculated from chemotherapy dosage based on body surface area (BSA) defined as 1.60 m^2 multiplied by the price per dosage retrieved from the reference price database of the Drugs and Medical Supplies Information Center (DMSIC), the Ministry of Public Health (see Appendix B). Other healthcare costs except chemotherapy cost of stage III colon cancer patients receiving chemotherapy were retrieved from the hospital database at

the National Cancer Institute during 2005 through 2010. The charges per patient per year were adjusted to costs using the cost-to-charge ratio of 0.8 (69). All costs were converted and reported value in 2010 THB using the consumer price index (CPI) (70-71). Direct medical costs were classified into two states (i.e., alive patients without relapse and alive patients with relapse).

8.1.1 Direct medical costs of alive patients without relapse

At the first year, direct medical costs of alive patients without relapse included chemotherapy costs and other healthcare costs without chemotherapy. Direct medical costs at the first year were higher than those at the subsequent years due to the cost of chemotherapy regimens given for six months. The average chemotherapy costs of patients receiving XELOX were 344,094 THB (Standard error, SE=344,094) followed by FOLFOX (298,375 THB, SE=298,375), capecitabine monotherapy (124,146 THB, SE=124,146) and 5-FU/LV (10,680 THB, SE=10,680) at the first year.

In addition, other healthcare costs included the cost of other medications without chemotherapy, cost of pre-treatment medications, cost of management of adverse events and toxicities, cost of laboratory and diagnostic tests, cost of procedures, cost of outpatient visits and cost of hospitalizations (IPD admission). The average other healthcare costs of patients receiving FOLFOX, XELOX, capecitabine and 5-FU/LV were estimated to the same at the first year (27,597 THB, SE=26,666).

Direct medical costs of alive patients without relapse in subsequent years were the costs of follow up and other medication occurred after the first year of chemotherapy. The average costs per year were estimated to be 28,228 THB (SE=28,228).

8.1.2 Direct medical costs of alive patients with relapse

Direct medical costs of patients with relapse at the first year were estimated from the cost of treatment for stage III colon cancer patients with disease recurrence and patients diagnosed with stage IV colon cancer. The annual costs of chemotherapy at the first were the same as those in subsequent years, since it

was assumed that patients with relapse would receive chemotherapy regimen over lifetime period. The average chemotherapy costs of patients with relapse receiving FOLFOX, XELOX, capecitabine and FOLFIRI were estimated to be 596,749 THB (SE=596,749), 688,188 THB (SE=688,188), 248,293 THB (SE=248,293) and 878,359 THB (SE=878,359), respectively.

Moreover, other healthcare costs of patients with relapse at the first year and subsequent years included the cost of other medications without chemotherapy drug, cost of laboratory and diagnostic tests, cost of pre-treatment medications, and cost of management of adverse events and toxicities. The average other healthcare costs of patients with relapse treated with FOLFOX, XELOX, capecitabine and FOLFIRI were the same and estimated to be 70,133 THB (SE=70,133),

8.2 Direct non-medical and indirect costs

Based on the societal perspective, direct non-medical as well as indirect costs were collected. Direct non-medical cost such as food, accommodation, transportation, time lost due to receiving treatment and direct medical costs incurred outside hospitals (e.g., at private clinics, drug store, and traditional medicine suppliers, etc) and indirect cost (i.e., productivity loss due to sick leave and informal care) were included, while mortality costs were excluded.

In this study, annual direct non-medical and indirect costs were collected from interviewing stage III colon cancer patients without relapse and with relapse or stage IV colon cancer patients receiving chemotherapy regimen as well as their caregivers at the National Cancer Institute, Thailand. Twenty four patients without relapse and twenty four patients with relapse or stage IV colon cancer were interviewed using the developed questionnaire (see Appendix C). Mean age was 60 years (Range=37-84 years). Pre-relapse patients received chemotherapy for six months at the first year. Therefore, direct non-medical costs, direct medical costs incurred outside hospitals and indirect costs at the first year were higher than those in subsequent years. For the patients with relapsed disease or stage IV colon cancer, it was assumed that patients would receive chemotherapy over lifetime period. Thus, direct non-medical costs, direct medical costs incurred outside hospitals and indirect

costs in subsequent years were assumed to be equal to those at the first year. Resource cost parameters are presented in Table 3.4

9. Health outcomes

The health outcome were life years (LYs) gained and quality-adjusted life year (QALY), the multiplication of utility weight and life years, of the patients with stage III colon cancer receiving adjuvant chemotherapy and those with recurrence state receiving palliative chemotherapy.

The quality of life in term of utility scores were derived from data collected from the patients receiving chemotherapy and caregivers using EQ-5D questionnaire at the NCI (72-73). A total of sample size was forty eight stage III colon cancer patients without relapse as well as patients with relapsed disease or stage IV colon cancer patients. The utility scores were collected according to the health states as follows: 1) alive without relapse state and 2) alive with relapse state. For stage III colon cancer patients without relapse, the utility scores were collected from two groups (i.e., twelve patients receiving the first-line oral capecitabine monotherapy and twelve patients receiving the first-line intravenous chemotherapy such as 5- FU/LV, FOLFOX and XELOX. For relapsed patient, the utility scores were collected from twelve patients receiving the second-line capecitabine and twelve patients receiving the second-line intravenous chemotherapy such as FOLFOX, XELOX and FOLFIRI. Mean utility score of alive patients without relapse was 0.85 (SE= 0.1) (56) (Table 3.4).

10. Discounting

Cost and health outcome were discounted at 3% per year due to time horizon more than one year (74). Sensitivity analysis was performed at the discount rate of 0% and 6%.

11. Sensitivity analysis

One way sensitivity analysis and probabilistic sensitivity analysis (PSA) were undertaken to address uncertainty of parameters in the model. One-way sensitivity analysis was conducted to examine the uncertainty surrounding each parameter individually and presented the results as a tornado diagram. In this study,

one way sensitivity analysis was performed to investigate model parameter uncertainties of the most cost-effective option (i.e., the first line FOLFOX and the second line FOLFIRI). The PSA was carried out in order to simultaneously examine the effect of all parameter uncertainties using a second order Monte Carlo simulation. Microsoft Office Excel 2007 (Microsoft Corp., Redmond, WA) with macro function were used to simulate by sampling from the distribution of each variable with 1,000 iterations. The probability distributions were assigned to all parameters such as beta-distribution for all probability and utility parameters, gamma distribution for all cost parameters and a log-normal distribution for survival parameters such as constant and coefficient for baseline hazard, and ancillary parameter (gamma) of death and failure events (75). Eventually, these provided the feasible results in average and expressed in the term of probabilistic values of total costs, LYs, and QALYs as well as incremental cost–effectiveness ratio (ICER) in baht per LY and QALY gained.

ICER is calculated by incremental cost divided by incremental effectiveness.

$$\mathbf{ICER = (C_H - C_F)/(E_H - E_F)}$$

Where,

C_H = Alternative chemotherapy cost

C_F = The first-line 5-FU/LV and the second-line capecitabine cost

E_H = Alternative chemotherapy effectiveness

E_F = The first-line 5-FU/LV and the second-line capecitabine cost effectiveness

Moreover, a net monetary benefit (NMB) was performed to determine the maximum expected NMB of the most cost-effective option (i.e., the first line FOLFOX and the second line FOLFIRI) for each value of ceiling ratio (i.e., the value society would be willingness to pay (WTP) for the intervention giving one QALY gained). In Thailand, the WTP per a QALY gained for implementing health technology and intervention for policy decision makers (i.e., the Subcommittee for Development of the National List of Essential Drugs and the Subcommittee for Development of the Benefit Packages) is between 100,000 THB and 300,000 THB per QALY gained or one to three times the gross domestic product (GDP) per capita (76-77). The results of the PSA were presented as cost-effectiveness acceptability curves.

Table 3.4 Input parameters used in economic model

Parameter	Distribution	Mean	SE	Reference
Yearly discount rate (%)				
Costs (range)		3(0-6)		(74)
Outcomes (range)		3(0-6)		(74)
Transitional probability parameters				
Probability of pre-relapse to relapse treated with FOLFOX	Beta	0.133	0.0092	Meta-analysis
Probability of pre-relapse to relapse treated with XELOX	Beta	0.140	0.0097	Meta-analysis
Probability of pre-relapse to relapse treated with capecitabine	Beta	0.149	0.0102	Meta-analysis
Probability of pre-relapse to relapse treated with 5-FU/LV	Beta	0.175	0.0121	(59)
Mortality rate pre-relapse patients treated with FOLFOX at the 1st year	Beta	0.040	0.0076	(9)
Mortality rate pre-relapse patients treated with FOLFOX at the 2nd year	Beta	0.063	0.0095	(9)
Mortality rate pre-relapse patients treated with FOLFOX at the 3rd year	Beta	0.056	0.0093	(9)
Mortality rate pre-relapse patients treated with FOLFOX in subsequent years	Beta	0.035	0.0077	(9)
Mortality rate pre-relapse patients treated with XELOX at the 1st year	Beta	0.030	0.0054	(78)
Mortality rate pre-relapse patients treated with XELOX at the 2nd year	Beta	0.072	0.0083	(78)
Mortality rate pre-relapse patients treated with XELOX at the 3rd year	Beta	0.044	0.0069	(78)

FOLFOX; oxaliplatin/5-fluorouracil/leucovorin; XELOX = capecitabine/oxaliplatin; 5-FU/LV = 5-fluorouracil/leucovorin; SE=Standard error; DMISC=Drugs and Medical Supplies Information Center; NCI=National Cancer Institute

Table 3.4 Input parameters used in economic model (cont.)

Parameter	Distribution	Mean	SE	Reference
Mortality rate pre-relapse patients treated with XELOX in subsequent years	Beta	0.047	0.0072	(78)
Mortality rate pre-relapse patients treated with capecitabine at the 1st year	Beta	0.020	0.0044	(59)
Mortality rate pre-relapse patients treated with capecitabine at the 2nd year	Beta	0.082	0.0087	(59)
Mortality rate pre-relapse patients treated with capecitabine at the 3rd year	Beta	0.100	0.0099	(59)
Mortality rate pre-relapse patients treated with capecitabine in subsequent years	Beta	0.074	0.0092	(59)
Mortality rate pre-relapse patients treated with 5-FU/LV at the 1st year	Beta	0.020	0.0045	(59)
Mortality rate pre-relapse patients treated with 5-FU/LV at the 2nd year	Beta	0.112	0.010	(59)
Mortality rate pre-relapse patients treated with 5-FU/LV at the 3rd year	Beta	0.103	0.0104	(59)
Mortality rate pre-relapse patients treated with 5-FU/LV in subsequent years	Beta	0.090	0.0103	(59)
Mortality rate relapse patients treated with FOLFOX at the 1st year	Beta	0.287	0.0189	Meta-analysis
Mortality rate relapse patients treated with FOLFOX at the 2nd year	Beta	0.489	0.0277	Meta-analysis
Mortality rate relapse patients treated with FOLFOX - in subsequent years	Beta	0.490	0.0343	Meta-analysis
Mortality rate relapse patients treated with XELOX at the 1st year	Beta	0.344	0.0228	Meta-analysis
Mortality rate relapse patients treated with XELOX at the 2nd year	Beta	0.538	0.0305	Meta-analysis
Mortality rate relapse patients treated with XELOX in subsequent years	Beta	0.705	0.0493	Meta-analysis
Mortality rate relapse patients treated with capecitabine at the 1st year	Beta	0.386	0.0256	Meta-analysis

FOLFOX; oxaliplatin/5-fluorouracil/leucovorin; XELOX = capecitabine/oxaliplatin; 5-FU/LV = 5-fluorouracil/leucovorin; SE=Standard error; DMISC=Drugs and Medical Supplies Information Center; NCI=National Cancer Institute

Table 3.4 Input parameters used in economic model (cont.)

Parameter	Distribution	Mean	SE	Reference
Mortality rate relapse patients treated with capecitabine at the 2nd year	Beta	0.571	0.0324	Meta-analysis
Mortality rate relapse patients treated with capecitabine in subsequent years	Beta	0.800	0.0560	Meta-analysis
Mortality rate relapse patients treated with FOLFIRI at the 1st year	Beta	0.350	0.0232	Meta-analysis
Mortality rate relapse patients treated with FOLFIRI at the 2nd year	Beta	0.515	0.0292	Meta-analysis
Mortality rate relapse patients treated with FOLFIRI in subsequent years	Beta	0.573	0.0401	Meta-analysis
Mortality rate relapse patients treated with 5-FU/LV at the 1st year	Beta	0.386	0.0256	(39)
Mortality rate relapse patients treated with 5-FU/LV at the 2nd year	Beta	0.571	0.0323	(39)
Mortality rate relapse patients treated with 5-FU/LV in subsequent years	Beta	0.800	0.0560	(41)
Annual direct medical cost				
Cost of FOLFOX at pre-relapse state	Gamma	298,375	298,375	DMSIC
Cost of XELOX at pre-relapse state	Gamma	344,094	344,094	DMSIC
Cost of capecitabine at pre-relapse state	Gamma	124,146	124,146	DMSIC
Cost of 5-FU/LV at pre-relapse state	Gamma	10,680	10,680	DMSIC
Cost of other healthcare without FOLFOX at the 1st year of pre-relapse state	Gamma	49,844	49,844	NCI
Cost of other healthcare without XELOX at the1st year of pre-relapse state	Gamma	49,844	49,844	NCI
Cost of other healthcare without capecitabine at the1st year of pre-relapse state	Gamma	49,844	49,844	NCI

FOLFOX; oxaliplatin/5-fluorouracil/leucovorin; XELOX = capecitabine/oxaliplatin; 5-FU/LV = 5-fluorouracil/leucovorin; SE=Standard error; DMISC=Drugs and Medical Supplies Information Center; NCI=National Cancer Institute

Table 3.4 Input parameters used in economic model (cont.)

Parameter	Distribution	Mean	SE	Reference
Cost of other healthcare without 5-FU/LV at the 1st year of pre-relapse state	Gamma	49,844	49,844	NCI
Cost of follow-up in the following years at pre-relapse state	Gamma	28,228	28,228	NCI
Cost of FOLFOX at relapse state	Gamma	596,749	596,749	DMSIC
Cost of XELOX at relapse state	Gamma	688,188	688,188	DMSIC
Cost of capecitabine at relapse state	Gamma	248,293	248,293	DMSIC
Cost of FOLFIRI at relapse state	Gamma	878,359	878,359	DMSIC
Cost of other healthcare without FOLFOX at the 1st year and subsequent years of relapse state	Gamma	70,133	70,133	NCI
Cost of other healthcare without XELOX at the 1st year and subsequent years of relapse state	Gamma	70,133	70,133	NCI
Cost of other healthcare without capecitabine at the 1st year and subsequent years of relapse state	Gamma	70,133	70,133	NCI
Cost of other healthcare without FOLFIRI at the 1st year and subsequent years of relapse state	Gamma	70,133	70,133	NCI
Annual direct non-medical cost				

FOLFOX; oxaliplatin/5-fluorouracil/leucovorin; XELOX = capecitabine/oxaliplatin; 5-FU/LV = 5-fluorouracil/leucovorin; SE=Standard error; DMISC=Drugs and Medical Supplies Information Center; NCI=National Cancer Institute

Table 3.4 Input parameters used in economic model (cont.)

Parameter	Distribution	Mean	SE	Reference
Out of pocket medical cost for pre-relapse patients treated with FOLFOX at the 1st year	Gamma	68,006	33,973	Survey
Out of pocket medical cost for pre-relapse patients treated with XELOX at the 1st year	Gamma	188,000	188,000	Survey
Out of pocket medical cost for pre-relapse patients treated with capecitabine at the 1st year	Gamma	53,991	22,466	Survey
Out of pocket medical cost for pre-relapse patients treated with 5-FU/LV at the 1st year	Gamma	5,220	4,187	Survey
Out of pocket medical cost for pre-relapse patients in the following years	Gamma	15,418	9,954	Survey
Out of pocket medical cost for relapse patients treated with FOLFOX	Gamma	98,246	58,337	Survey
Out of pocket medical cost for relapse patients treated with XELOX	Gamma	364,000	364,000	Survey
Out of pocket medical cost for relapse patients treated with capecitabine	Gamma	68,181	27,340	Survey
Out of pocket medical cost for relapse patients treated with FOLFIRI	Gamma	70,362	69,639	Survey
Other non-medical costs for pre-relapse patients treated with FOLFOX at the 1st year	Gamma	17,264	4,566	Survey

FOLFOX; oxaliplatin/5-fluorouracil/leucovorin; XELOX = capecitabine/oxaliplatin; 5-FU/LV = 5-fluorouracil/leucovorin; SE=Standard error; DMISC=Drugs and Medical Supplies Information Center; NCI=National Cancer Institute

Table 3.4 Input parameters used in economic model (cont.)

Parameter	Distribution	Mean	SE	Reference
Annual direct non-medical cost				
Other non-medical costs for pre-relapse patients treated with XELOX at the 1st year	Gamma	8,736	1,494	Survey
Other non-medical costs for pre-relapse patients treated with capecitabine in the 1st year	Gamma	8,736	1,494	Survey
Other non-medical costs for pre-relapse patients treated with 5-FU/LV in the 1st year	Gamma	27,956	4,779	Survey
Other non-medical costs for pre-relapse patients during follow-up in the following years	Gamma	3,495	597	Survey
Other non-medical costs for relapse patients treated with FOLFOX	Gamma	29,596	7,828	Survey
Other non-medical costs for relapse patients treated with XELOX	Gamma	13,978	2,390	Survey
Other non-medical costs for relapse patients treated with capecitabine	Gamma	13,978	2,390	Survey
Other non-medical costs for relapse patients treated with FOLFIRI	Gamma	29,596	7,828	Survey
Annual indirect cost				
Indirect cost of pre-relapse patients treated with FOLFOX in the 1st year	Gamma	18,215	3,582	Survey

FOLFOX; oxaliplatin/5-fluorouracil/leucovorin; XELOX = capecitabine/oxaliplatin; 5-FU/LV = 5-fluorouracil/leucovorin; SE=Standard error; DMISC=Drugs and Medical Supplies Information Center; NCI=National Cancer Institute

Table 3.4 Input parameters used in economic model (cont.)

Parameter	Distribution	Mean	SE	Reference
Indirect cost of pre-relapse patients treated with XELOX at the 1st year	Gamma	4,625	4,625	Survey
Indirect cost of pre-relapse patients treated with capecitabine at the 1st year	Gamma	13,840	8,096	Survey
Indirect cost of pre-relapse patients treated with 5-FU/LV at the 1st year	Gamma	10,255	1,776	Survey
Indirect cost of relapse patients treated with FOLFOX at the 1st year	Gamma	62,550	13,113	Survey
Indirect cost of relapse patients treated with XELOX at the 1st year	Gamma	6,845	6,845	Survey
Indirect cost of relapse patients treated with capecitabine at the 1st year	Gamma	16,092	8,091	Survey
Indirect cost of relapse patients treated with FOLFIRI at the 1st year	Gamma	70,613	8,852	Survey
Indirect cost of pre-relapse patients in the following years	Gamma	1,755	80	Survey
Utility parameters				
Utility of pre-relapse patients receiving capecitabine	Beta	0.651	0.0473	Survey
Utility of pre-relapse patients receiving intravenous chemotherapy	Beta	0.60	0.0633	Survey
Utility of relapsed patients receiving capecitabine	Beta	0.624	0.0429	Survey
Utility of relapse patients receiving intravenous chemotherapy	Beta	0.56	0.1010	Survey
Utility of stage III colon patients without chemotherapy	Beta	0.85	0.1	(56)

FOLFOX; oxaliplatin/5-fluorouracil/leucovorin; XELOX = capecitabine/oxaliplatin; 5-FU/LV = 5-fluorouracil/leucovorin; SE=Standard error; DMISC=Drugs and Medical Supplies Information Center; NCI=National Cancer Institute

CHAPTER IV
RESULTS

The results of this study were divided into two parts as follows:

Part I Cost utility analysis

Part II Sensitivity analysis

Part I Cost-utility analysis

The cost-utility analysis based on societal perspective and governmental perspectives estimated lifetime costs and health outcome (i.e., QALYs) of each treatment option for stage III colon cancer patients. In general, the risk of developing colon cancer increased when average age started at 50 years. Total costs, LYs and QALYs of all treatments compared with the first-line 5-FU/LV and the second-line capecitabine in patients aged 50 year based on societal and governmental perspectives are shown in Table 4.1 and 4.2, respectively. For societal perspective, direct (i.e., medical and non-medical) and indirect costs were included. Based on societal and governmental perspectives, the total cost of the first-line 5-FU/LV and the second-line capecitabine was the lowest and (586,000 THB and 388,000 THB), while that of the first-line XELOX and the second-line FOLFIRI was the highest (1,762,000 THB and 1,279,000 THB), respectively. In this study, all interventions had higher cost and yielded more LYs than the first-line 5-FU/LV and the second-line capecitabine. Based on societal and governmental perspectives, patients receiving first-line 5-FU/LV and the second line XELOX had more LYs (4.16 and 4.10) but less QALYs (3.10 and 3.09) compared to those receiving the first-line 5-FU/LV and the second-line capecitabine (LYs=4.09 and 4.10 and QALYs=3.11 and 3.10), respectively. In addition, patients receiving the first-line FOLFOX, then the second-line FOLFIRI had the highest LYs (6.69 and 6.13) and QALYs (5.27 and 4.75) based on societal and governmental perspectives, respectively.

Table 4.1 Total costs, LYs and QALYs of all interventions for stage III colon cancer patients aged 50 years based on a societal perspective

Intervention		Total cost (THB) †*	Lys	QALYs
1st line	2nd line			
5-FU/LV	capecitabine	586,000	4.09	3.11
5-FU/LV	FOLFOX	1,182,000	4.37	3.23
5-FU/LV	XELOX	1,211,000	4.16	3.10
capecitabine	FOLFOX	1,278,000	5.11	3.92
capecitabine	XELOX	1,301,000	4.91	3.81
5-FU/LV	FOLFIRI	1,311,000	4.25	3.16
capecitabine	FOLFIRI	1,377,000	5.01	3.86
FOLFOX	FOLFIRI	1,610,000	6.69	5.27
XELOX	FOLFIRI	1,762,000	6.12	4.78

† **Total costs are calculated in 2010 THB**

*** Costs are rounded up to nearest 1,000 THB**

Table 4.2 Total costs, LYs and QALYs of all interventions for stage III colon cancer patients aged 50 years based on a governmental perspective

Intervention		Total cost (THB) †*	Lys	QALYs
1st line	2nd line			
5-FU/LV	capecitabine	388,000	4.10	3.10
5-FU/LV	XELOX	811,000	4.16	3.09
5-FU/LV	FOLFOX	858,000	4.37	3.21
capecitabine	XELOX	886,000	4.91	3.77
capecitabine	FOLFOX	932,000	5.10	3.88
5-FU/LV	FOLFIRI	989,000	4.26	3.14
capecitabine	FOLFIRI	1,047000	5.00	3.82
FOLFOX	FOLFIRI	1,217,000	6.64	5.19
XELOX	FOLFIRI	1,729,000	6.13	4.75

†**Total costs are calculated in 2010 THB**

*** Costs are rounded up to nearest 1,000 THB**

Cost-utility analysis was performed to compare all medications in the treatment of stage III colon cancer patients. The results were presented as the incremental cost effectiveness ratio (ICER) in THB per LY gained (Table 4.3 and 4.4) and QALY gained (Table 4.5 and 4.6) when compared with the first-line 5-FU/LV and the second-line capecitabine. Of all interventions, patients with stage III colon cancer receiving the first-line FOLFOX and the second-line FOLFIRI had the lowest ICER value with 394,000 and 326,000 THB per LY gained based on societal and governmental perspectives, whereas those receiving the first-line 5-FU/LV and the second-line XELOX had the highest with 9,485,000 and 6,342,000 THB per LY gained, respectively.

Table 4.3 Incremental cost, incremental LYs gained and incremental cost-effectiveness ratio of all interventions compared with the first-line 5-FU/LV and the second-line capecitabine for stage III colon cancer patients aged 50 years based on a societal perspective

Interventions		**Incremental cost (THB)**	**Incremental LYs**	**ICER per LY gained**
1st line	**2nd line**			
FOLFOX	FOLFIRI	1,024,000	2.60	394,000
XELOX	FOLFIRI	1,176,000	2.03	580,000
capecitabine	FOLFOX	691,000	1.02	677,000
capecitabine	FOLFIRI	791,000	0.92	862,000
capecitabine,	XELOX	715,000	0.82	867,000
5-FU/LV	FOLFOX	595,000	0.28	2,137,000
5-FU/LV	FOLFIRI	725,000	0.16	4,406,000
5-FU/LV	XELOX	625,000	0.07	9,485,000

†ICERs are rounded up to nearest 1,000 THB

Table 4.4 Incremental cost, incremental LYs gained and incremental cost-effectiveness ratio of all interventions compared with the first-line 5-FU/LV and the second-line capecitabine for stage III colon cancer patients aged 50 years based on a governmental perspective

Interventions		**Incremental cost (THB)**	**Incremental LYs**	**ICER per LY gained**
1st line	**2nd line**			
FOLFOX	FOLFIRI	829,000	2.54	326,000
XELOX	FOLFIRI	891,000	2.04	437,000
capecitabine	FOLFOX	544,000	1.01	540,000
capecitabine	XELOX	498,000	0.81	613,000
capecitabine,	FOLFIRI	659,000	0.90	730,000
5-FU/LV	FOLFOX	470,000	0.28	1,699,000
5-FU/LV	FOLFIRI	601,000	0.16	3,690,000
5-FU/LV	XELOX	423,000	0.07	6,342,000

†ICERs are rounded up to nearest 1,000 THB

Table 4.5 Incremental cost, incremental QALYs and incremental cost-effectiveness ratio of all interventions compared with the first-line 5-FU/LV and the second-line capecitabine for stage III colon cancer patients aged 50 years based on a societal perspective

Interventions		**Incremental cost (THB)**	**Incremental QALYs**	**ICER per QALY gained**
1st line	**2nd line**			
5-FU/LV	XELOX	625,000	-0.01	-111,238,000
FOLFOX	FOLFIRI	1,024,000	2.16	474,000
XELOX	FOLFIRI	1,176,,0000	1.66	707,000
capecitabine	FOLFOX	691,000	0.81	855,000
capecitabine	XELOX	715,000	0.70	1,025,000
capecitabine	FOLFIRI	791,000	0.75	1,055,000
5-FU/LV	FOLFOX	595,000	0.11	5,205,000
5-FU/LV	FOLFIRI	725,000	0.05	14,567,000

†ICERs are rounded up to nearest 1,000 THB

Table 4.6 Incremental cost, incremental QALYs and incremental cost-effectiveness ratio of all interventions compared with the first-line 5-FU/LV and the second-line capecitabine for stage III colon cancer patients aged 50 years based on a governmental perspective

Interventions		Incremental cost (THB)	Incremental QALYs	ICER per QALY gained
1st line	2nd line			
5-FU/LV	XELOX	423,000	-0.01	-30,927,000
FOLFOX	FOLFIRI	829,000	2.08	398,000
XELOX	FOLFIRI	891,000	1.65	540,000
capecitabine	FOLFOX	544,000	0.78	698,000
capecitabine	XELOX	498,000	0.67	743,000
capecitabine	FOLFIRI	659,000	0.72	914,000
5-FU/LV	FOLFOX	470,000	0.10	4,529,000
5-FU/LV	FOLFIRI	601,000	0.04	14,956,000

†ICERs are rounded up to nearest 1,000 THB

According to the Thai Subcommittee for Development of the National List of Essential Drugs, the willingness to pay (WTP) threshold for a QALY gained for the adoption of health technologies and interventions is between one and three times the Thai GDP (i.e., approximately 100,000 to 300,000 THB (79). In this study, the ICER values in THB per QALY gained of all interventions exceeded the WTP threshold for a QALY in Thai context. It was indicated that all interventions might not be cost-effective compared with the first-line 5-FU/LV and the second-line capecitabine based on societal and governmental perspectives. However, of all interventions, the first-line FOLFOX and the second-line FOLFIRI had the lowest positive ICER value (474,000 and 398,000 THB per QALY gained), while the first-line 5-FU/LV and the second-line FOLFIRI had the highest (14,567,000 and 14,956,000 THB per QALY gained) on the view point of societal and governmental perspectives, respectively. Moreover, the first-line 5-FU/LV and the second-line XELOX had the negative ICER value due to higher cost but less QALY gained indicating that it was inferior to the first-line 5-FU/LV and the second-line capecitabine.

In addition, the ICER results of all interventions among stage III colon cancer patients aged 50 years are presented as the cost-effectiveness planes which Y-axes illustrated incremental cost and X-axes represented incremental effectiveness (i.e., LYs (Figure 4.1 and 4.2) and QALYs (Figure 4.3 and 4.4) when compared with the first-line 5-FU/LV and the second-line capecitabine. Almost all interventions were located on the upper right-hand quadrant of the plane in Figure 4.1, 4.2, 4.3 and 4.4 meaning that most interventions had higher effectiveness and higher costs compared to the first-line 5-FU/LV and the second-line capecitabine. However, Figure 4.3 and 4.4 shows that the first-line 5-FU/LV and the second-line XELOX was the only intervention located on the upper left-hand quadrant of the plane indicating that the second-line XELOX yielded less QALYs gained and higher costs compared to the second-line capecitabine. Of all interventions, the next best intervention subsequent to the first-line 5-FU/LV and the second-line capecitabine would be the first-line FOLFOX and the second-line FOLFIRI. Nevertheless, the incremental cost of 1,024,000 and 829,000 THB would be needed in order to yield QALYs gained of 2.16 and 2.08 compared to the first-line 5-FU/LV and the second-line capecitabine based on societal and governmental perspectives, respectively.

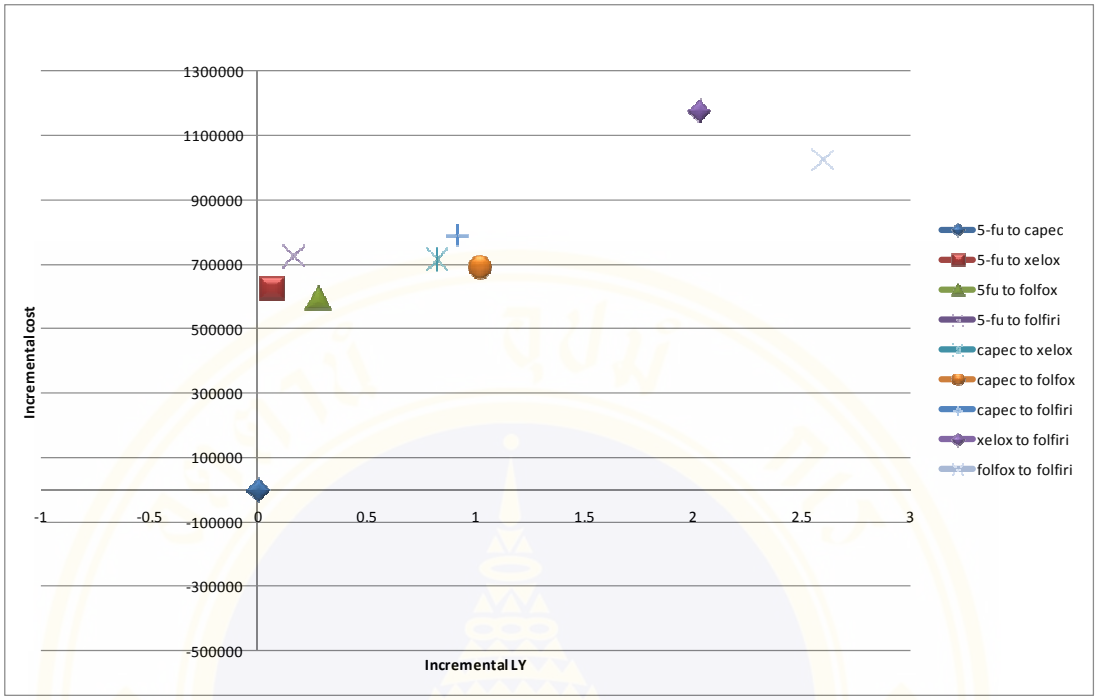

Figure 4.1 Cost-effectiveness planes of all interventions compared with the first-line 5-FU/LV and the second-line capecitabine for stage III colon cancer patients aged 50 years (THB per LY gained) based on a societal perspective

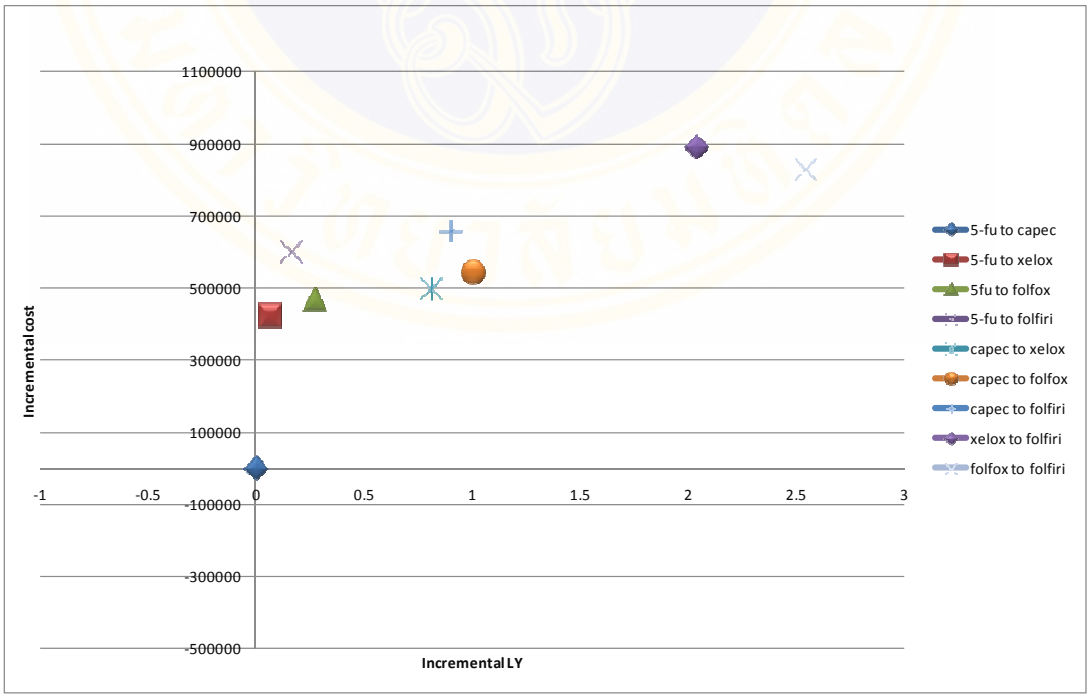

Figure 4.2 Cost-effectiveness planes of all interventions compared with the first-line 5-FU/LV and the second-line capecitabine for stage III colon cancer patients aged 50 years (THB per LY gained) based on a governmental perspective

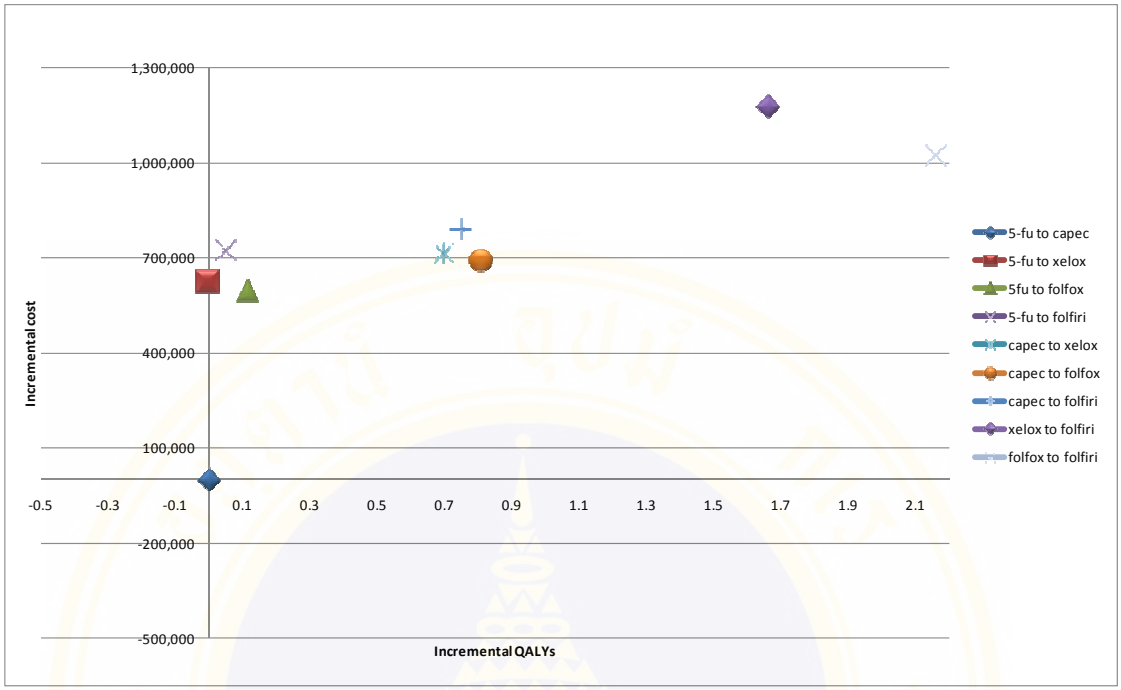

Figure 4.3 Cost-effectiveness planes of all interventions compared with the first-line 5-FU/LV and the second-line capecitabine for stage III colon cancer patients aged 50 years (THB per QALY gained) based on a societal perspective

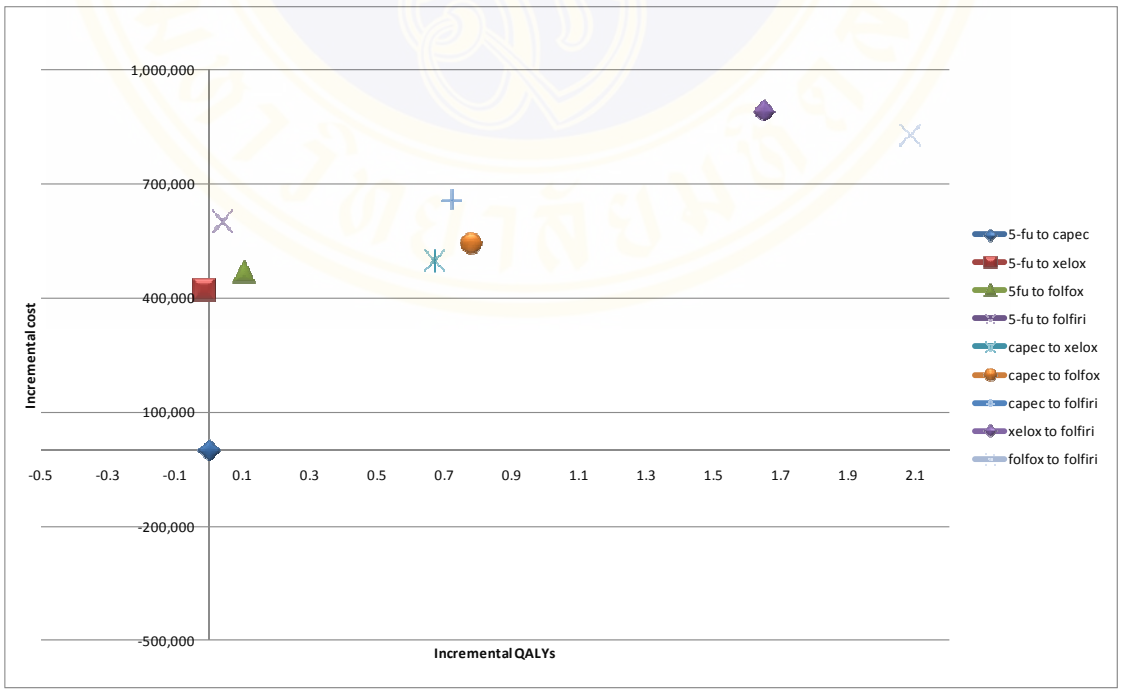

Figure 4.4 Cost-effectiveness planes of all interventions compared with the first-line 5-FU/LV and the second-line capecitabine for stage III colon cancer patients aged 50 years (THB per QALY gained) based on a governmental perspective

Part II Sensitivity analysis

2.1 One way sensitivity analysis

Figure 4.5 and Figure 4.6 showed a tornado diagram presenting the results of one-way sensitivity analysis in patients receiving the first-line FOLFOX and the second-line FOLFIRI (i.e., the intervention with the lowest ICER value in this study). One-way sensitivity analysis was carried out in order to investigate the uncertainty of only important parameters.

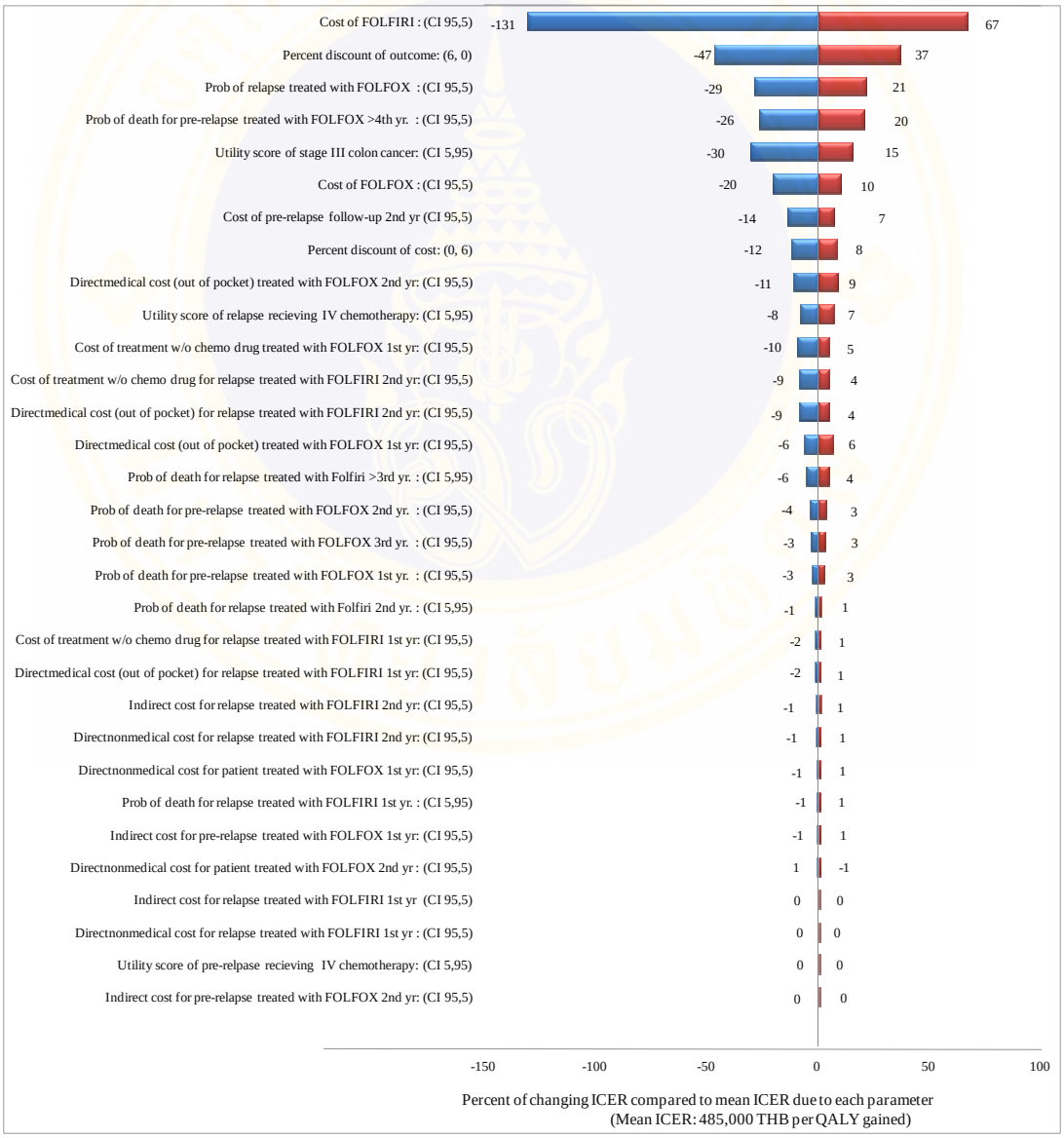

Figure 4.5 One-way sensitivity analysis results presenting as a tornado diagram of patients receiving the first-line FOLFOX and the second-line FOLFIRI based on a societal perspective

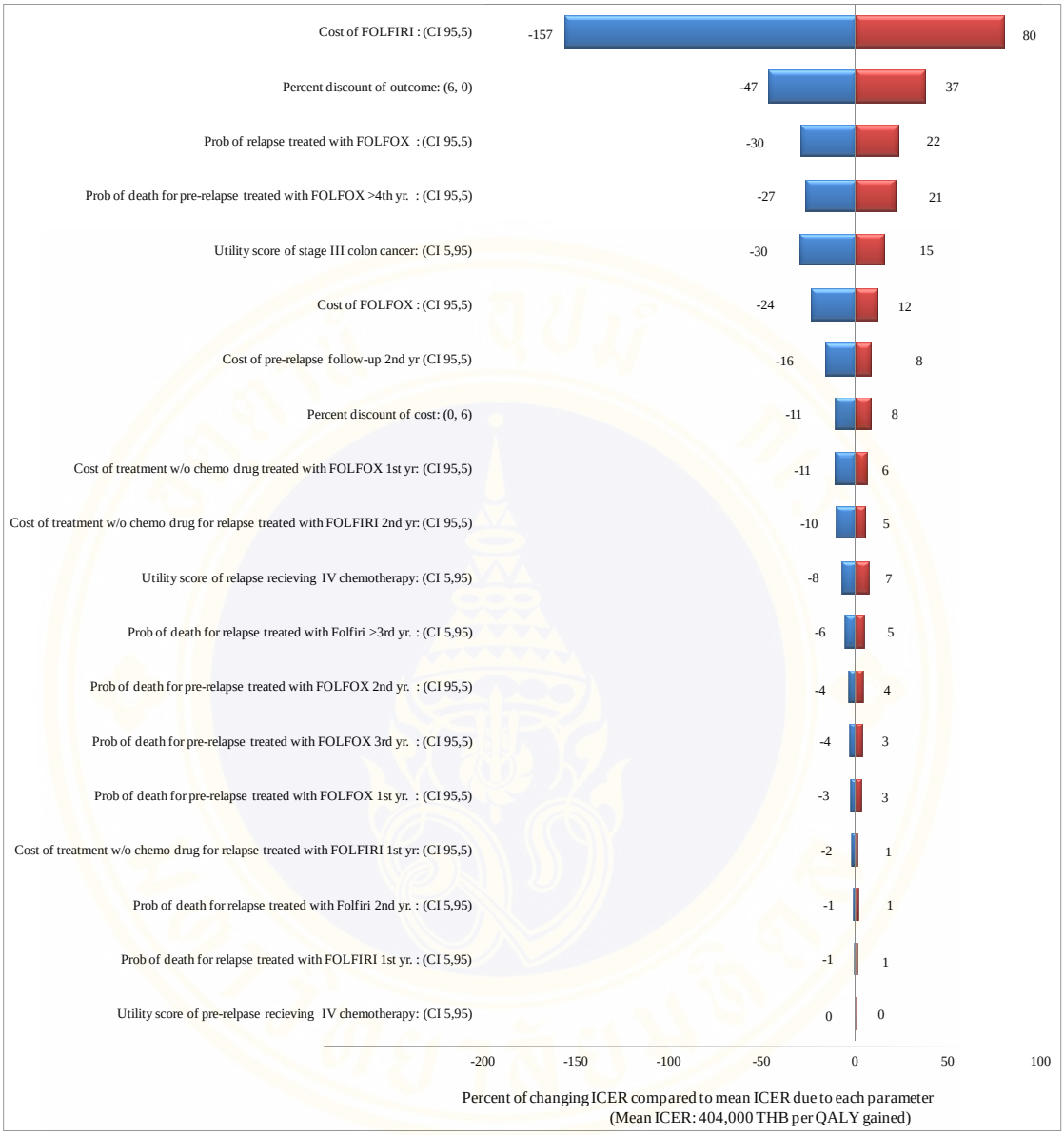

Figure 4.6 One-way sensitivity analysis results presenting as a tornado diagram of patients receiving the first-line FOLFOX and the second-line FOLFIRI based on a governmental perspective

Discount rate of 0% and 6%, the 95% confidence interval of transitional probabilities, utility scores and the minimum and maximum cost of FOLFOX (i.e. 197,000 and 507,000 THB) were applied. It was found that when altering the value of each parameter, the ICER per QALY gained was the most sensitive to the changes in the price of FOLFIRI regimen, the discount rate of outcome, the probability of relapse when treated with FOLFOX, the probability of death when treated with FOLFOX at

the 4th year or longer at pre-relapse state and the utility score of stage III colon cancer patients based on the societal and governmental perspectives, respectively

2.2 Probabilistic sensitivity analysis (PSA)

Based on the societal and governmental perspectives, the PSA was conducted to determine the impact of the input parameter uncertainties of which distributions were defined and shown in Table 3.4. According to the Thai Subcommittee for Development of the National List of Essential Drugs, the willingness to pay (WTP) threshold for a QALY gained for the adoption of health technologies and interventions is between one and three times the Thai GDP (i.e., approximately 100,000 to 300,000 THB as shown by the vertical dashed lines in Figures 4.7 and 4.8.

Figure 4.7 and 4.8 showed the cost-effectiveness acceptability curves based on the PSA results among stage III colon cancer patients who received treatment intervention. Based on a societal perspective, at the WTP threshold of 100,000 and 300,000 THB per QALY gained, the probabilities of providing the first-line 5-FU/LV and the second-line capecitabine being cost-effective were 68% and 50%, respectively. Moreover, the probabilities of providing the first-line FOLFOX and the second-line FOLFIRI being cost-effective were 5% and 28% at the WTP threshold of 100,000 and 300,000 THB per QALY gained, respectively. Moreover, based on a governmental perspective, the probabilities of providing the first-line 5-FU/LV and the second-line capecitabine being cost-effective were 45% and 20%, respectively whereas the probabilities of providing the first-line FOLFOX and the second-line FOLFIRI being cost-effective were 10% and 30% at the WTP threshold of 100,000 and 300,000 THB per QALY gained, respectively. When the WTP threshold increased, the probabilities of providing the first-line 5-FU/LV and the second-line capecitabine being cost-effective would be decreased, while those of all other interventions would be increased. For example, as the WTP based on a societal perspective increased to 1,350,000 THB per QALY gained, the probabilities that providing the first-line 5-FU/LV and the second-line capecitabine would be decreased to 1%, whereas providing the first-line FOLFOX and the second-line FOLFIRI or other remainder interventions being cost-effective would be increased to 80% or less than 15%, respectively.

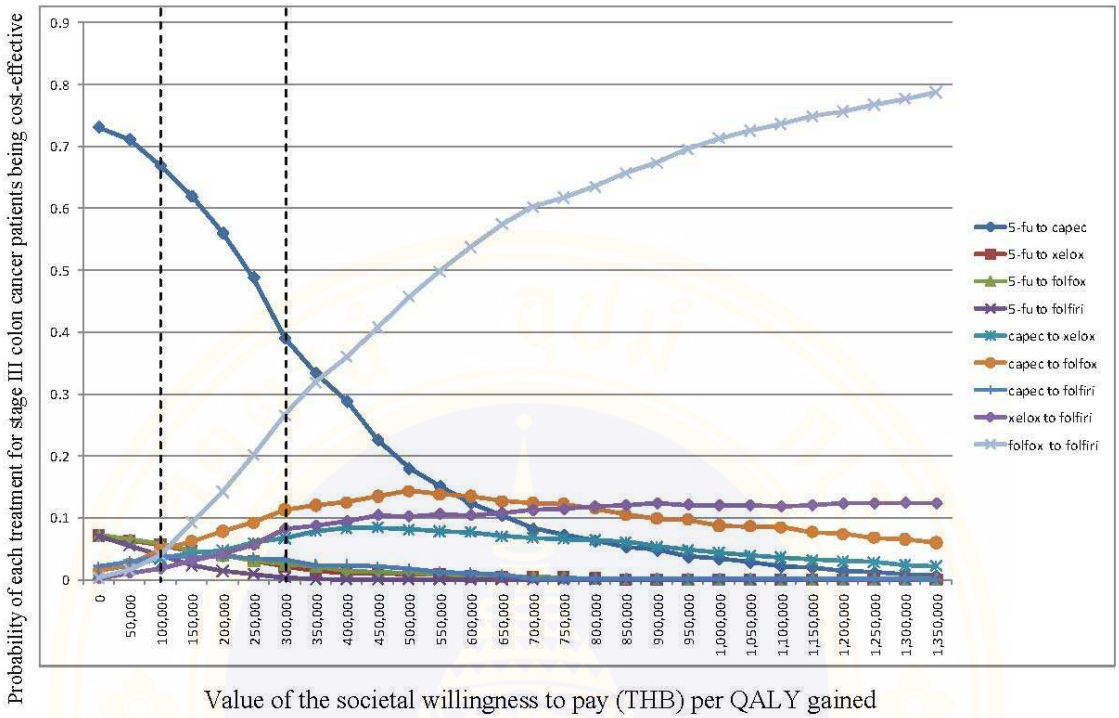

Figure 4.7 Cost-effectiveness acceptability curve of treatment intervention for stage III colon cancer patients based on a societal perspective

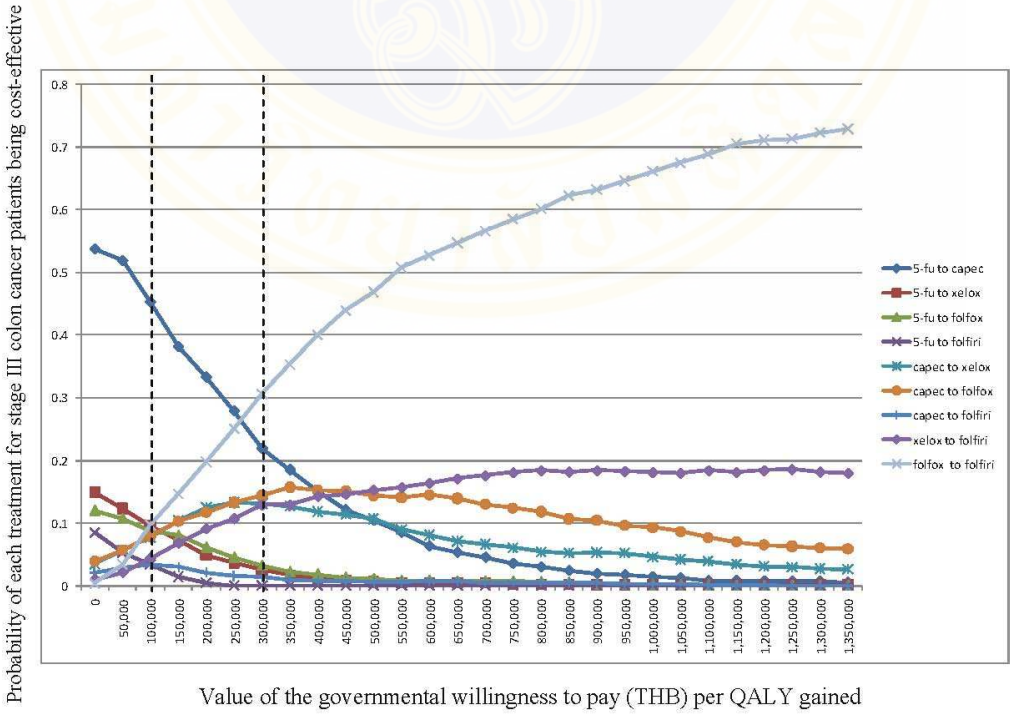

Figure 4.8 Cost-effectiveness acceptability curve of treatment intervention for stage III colon cancer patients based on a governmental perspective

CHAPTER V
DISCUSSION

The discussion of this study was divided in to two parts as follows:

Part I Cost-utility analysis

Part II Limitations of the study

Part I Cost-utility analysis

The economic evaluation information in this study requested by the National Health Security Office (NHSO) would be used to consider whether oxaliplatin should be included in the NLED for the treatment of stage III colon cancer. However, to date there has been no such data yet. Therefore, this study was the first to compare the cost-utility of all available treatments with the first-line 5-FU/LV and the second-line capecitabine in patients with stage III colon cancer based on societal and governmental perspectives in Thai context.

Based on the results of this study, it was found that all interventions would not be cost-effective compared with the first-line 5-FU/LV and the second-line capecitabine in Thai context since their ICER values were greater than the WTP threshold of one to three times the gross domestic product (GDP) per capita (i.e., 100,000 to 300,000 THB per QALY gained) recommended by the Thai Subcommittee for Development of the National List of Essential Drugs (NLED) and the Subcommittee of the Development of Benefit Package and Service System, NHSO. The first-line 5-FU/LV and the second-line capecitabine would be the most cost-effective chemotherapy and has already been included in the NLED. Thus, 5-FU/LV should be considered to be the first drug for the treatment of stage III colon patients and capecitabine should be given for all patients who relapsed and required the treatment base on the criteria.

When considering the next best intervention to the first-line 5-FU/LV and the second-line capecitabine based on societal and governmental perspectives, the first-line FOLFOX and the second-line FOLFIRI seemed to be the choice of treatment for stage III colon cancer patients, since its ICER value yielded the lowest (474,000 and 398,000 THB per QALY gained) compared to all other interventions, respectively. Therefore, threshold sensitivity analysis was conducted to calculate the optimal price of FOLFOX and FOLFIRI which could make this intervention be cost-effective at the WTP threshold of one to three times the GDP per capita (i.e., 100,000 to 300,000 THB per QALY gained) when adopted FOLFOX as the first-line adjuvant chemotherapy and FOLFIRI as the second-line chemotherapy. It was found that if both prices of FOLFOX and FOLFIRI were decreased by 40% (i.e., FOLFOX= 179,025 THB, FOLFIRI= 527,015 THB), the first-line FOLFOX and the second-line FOLFIRI would be cost-effective with the ICER of 299,365 THB per QALYs gained. Moreover, threshold sensitivity analysis was also conducted to calculate the optimal price of the first-line capecitabine and the second-line FOLFOX. We found that even though both prices of capecitabine and FOLFOX were reduced by 90%, the first-line capecitabine and the second-line FOLFOX would not be cost-effective with ICER of 565,000 THB per QALYs gained.

In addition, our results suggested that the first-line 5-FU/LV and the second-line capecitabine would be the most cost-effective option. If the first-line 5-FU/LV was given, the second-line FOLFOX would also be the next best intervention in addition to providing the second-line capecitabine in patients with relapse. The second-line FOLFOX could yield higher cost (595,000 THB) and QALYs (0.11) gained compared to the second-line capecitabine. Based on the threshold sensitivity analysis, the price of FOLFOX (i.e., 5-FU/LV plus oxaliplatin) in relapse disease would be decreased to 75,943 THB per year in order to make FOLFOX be cost-effective at the WTP threshold of 300,000 THB per QALY gained. This price did not seem possible because the price of only 5-FU/LV not included oxaliplatin would be 117,000 THB per year which was much higher than the price the cost-effectiveness threshold. The results from this study showed that oxaliplatin with the mean price of 147 THB per mg would not be cost-effective in Thai context.

Threshold sensitivity analysis was also conducted to calculate the optimal price of FOLFOX and FOLFIRI based on a governmental perspective. If both prices of FOLFOX and FOLFIRI were decreased by 25% (i.e., FOLFOX= 224,000 THB, FOLFIRI= 659,000 THB), the first-line FOLFOX and the second-line FOLFIRI would be cost-effective with the ICER of 288,000 THB per QALYs gained. Moreover, threshold sensitivity analysis was also conducted to calculate the optimal price of the first-line capecitabine and the second-line FOLFOX. It was found that if both prices of capecitabine and FOLFOX were reduced by 60% (i.e. capecitabine= 49,658, THB, FOLFIRI=239,000 THB, the first-line capecitabine and the second-line FOLFOX would be cost-effective with the ICER of 282,000 THB per QALYs gained. Furthermore, the threshold sensitivity analysis was performed to calculate the price of FOLFOX in the first-line 5-FU/LV and the second-line FOLFOX regimen for relapse disease. At the WTP threshold of 300,000 THB per QALY gained, FOLFOX would be decreased to 194,000 THB per year in order to make FOLFOX be cost-effective. It was indicated that the mean price of oxaliplatin should be reduced to 24 THB per mg. Because the first-line 5-FU/LV and the second-line capecitabine would be the most cost-effective option compared to all interventions and have been already included in the NLED, the budget impact analysis would not be required in this study.

However, our study results were not in accordance with other previous published studies. Based on the systematic reviews, most studies (3 studies) indicated that oxaliplatin was more cost-effective compared to 5-FU/LV. It could be explained that our study considered the set of eight interventions including both the first-line and second-line chemotherapy regimens compared to the first-line 5-FU/LV and the second-line capecitabine which imitate the real current clinical practice, while previous studies (63, 65) compared only the first-line 5-FU/LV with the first-line FOLFOX in stage III colon cancer. Moreover, a previous study (64) developed a model which expected survival following relapse was assumed to be independent from the efficacy of adjuvant treatment received. The expected survival of relapsed patients after receiving FOLFOX was assumed to be the same as that of relapsed patients after receiving 5-FU/LV, while expected survival data in this study were obtained from the meta-analysis of the RCTs studies related to clinical efficacy of each chemotherapy

regimen among patients after relapse. Nevertheless, the LYs and QALYs in this study were quite similar to those obtained from previous study

Part II Limitations of study

This study had some limitations as follows:

1. The direct medical costs used in this study were obtained from the data available during 2005-2010 due to an incomplete computer-based information system before 2005 in one tertiary care hospital in Bangkok. In addition, direct non-medical and indirect costs as well as utility data were collected from interviewing stage III colon cancer patients without and with relapse or stage IV patients receiving chemotherapy regimens and their caregivers at the same hospital. Therefore, it might not be a representative of general Thai populations.

2. The utility score of follow-up patients were obtained from published articles in foreign countries so that it might be different from that obtained from Thai people due to differences in culture and healthcare infrastructure.

CHAPTER VI
CONCLUSIONS

The conclusions of this study were divided into two parts as follows:

Part I Recommendations for policy decision making

Part II Recommendations for further study

Part I Recommendations for policy decision making

In 2008, the NHSO requested the study on economic evaluation of oxaliplatin as adjuvant chemotherapy for stage III colon cancer patients for the development of health benefit package under universal health care coverage scheme. Thus, the results of this study could be used to inform the Subcommittee of the Benefit package Design that the first line 5-FU/LV and the second line capecitabine should be still included in the NLED.

The results of this study suggested that oxaliplatin was not cost-effective at a WTP threshold in Thai context. Even though 5-FU/LV and capecitabine have already been contained in the NLED, these chemotherapy regimens were very expensive. The price of chemotherapy should be reduced to enhance the feasibility to receive chemotherapy regimen. Moreover, the strategies of prevention should be adopted to reduce risk of colon cancer disease. Due to nonspecific symptoms of colon cancer, the most common presenting are constipation, abdominal pain, weakness, weight loss, bleeding, altered bowel habit, and obstructive symptom. Colon cancer can be well developed before they are detected. Screening identifies cancers earlier and normally cause to cancer prevention when it leads to removal of adenomas. Therefore, the Ministry of Public Health (MOPH) should provide the interventions such as screening people in order to reduce the risk of colorectal cancer and increase the

access to the treatment for colon cancer patients. Thus, healthcare provides as well as policymakers under health insurance schemes should accelerate patients' awareness to get an access to colorectal cancer screening and treatment.

Recently screening to diagnose colon cancer can be performed in community hospitals, while treatment and monitoring are usually done in teaching hospitals. There have been very few oncologists who can manage colon cancer and most of them are at university and regional hospitals. Therefore, the MOPH should enhance the ability of general hospitals to increase the number of oncologists who could treat and monitor colon cancer patients. Moreover, the MOPH should develop a good referral system of the community hospitals and encourage the development of national guidelines for the treatment of colon cancer disease.

Part II Recommendations for the further study

1. Utility parameter, one of the important parameters that were sensitive to the changes in ICER values, should be derived from Thai data and collected for each chemotherapy regimen (i.e. FOLFOX, XELOX, 5-FU/LV).
2. There have been a few oncologists and laboratory facilities for stage III colon cancer treatment and monitoring in Thailand. The feasibility of stage III colon cancer treatment and monitoring provision system should be further investigated.
3. As this study compared all treatments for stage III colon cancer patients, further study for rectum cancer patients should be conducted.
4. Cost data and expenses should be obtained from a standard costing reference or collected in multicentre setting

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APPENDICES

APPENDIX A

Table A: Paper extraction according to Drummond checklists

Study	Aballea S (US,2007)	Eggington S (UK,2006)	Pandor A. (UK,2006)	Aballea S (UK,2007)
1. Was a well-defined question posed in an answerable form?	+	+	+	+
2. Was a comprehensive description of the competing alternatives given?	+	+	+	+
3. Was there evidence that the programme's effectiveness had been established?	+	+	+	+
4. Were all the important and relevant outcomes and costs for each alternative identified?	+	+	+	+
5. Were outcomes and costs measured accurately in appropriate units?	+	+	+	+
6. Were the outcomes and costs valued credibly?	+	+	+	+
7. Were outcomes and costs adjusted for different times at which they occurred?	+	+	+	+
8. Was an incremental analysis of the outcomes and costs of alternatives performed?	+	+	+	+
9. Was a sensitivity analysis performed?	+	+	+	+
10. Did the presentation and discussion of the results include all, or enough, of the issues that are of concern to purchasers?	+	+	+	+
11. Were the conclusions of the evaluation justified by the evidence presented?	+	+	+	+
12. Can the results be applied to the local population?	+	+	+	+

APPENDIX B

COST OF CHEMOTHERAPY DOSING CALCULATION

Regimen	Chemotherapy dosing	Schedule	Total 6 month Quantity(Mg)	Total 6 month Pricing (THB)
5-FU /LV	5-FU 425 mg/m2 bolus on day 1 to 5 LV 20 mg/m2 bolus on day 1 to 5	Every 4 weeks	5-FU = 20,400 LV =960	10,680
Capecitabine	1,250 mg/m2 orally twice per day on day 1 to 14	Every 3 weeks	Capecitabine = 896 tablets	124,146
FOLFOX4	5-FU 400 mg/m2 bolus + 600mg/m2 IVCI over 22 hrs on days 1 and 2 LV 200 mg/m2 over 2 hrs on days 1 and 2 Oxaliplatin 85 mg/m2 on day 1	Every 2 weeks	5-FU = 38,400 LV = 7,680 Oxaliplatin = 1,632	298,374
XELOX	Oxaliplatin 130 mg/m2 on day 1 oral capecitabine 1,000 mg/m2 twice a day for 14 days	Every 3 weeks	Oxaliplatin = 1,664 Capecitabine = 716.8 tablets	344,093
FOLFIRI	Irinotecan 180 mg/m2 in 2 hrs day 1, LV 100 mg/m2 in 2 hrs day 1, 5-FU 1,000 mg/m2 bolus day 1-2	Every 2 weeks	Irinotecan = 3,456 5-FU =38,400 LV =3,840	439,179

SCHEDULE OF CALCULATION CHEMOTHERAPY DOSING

Drug Name	Price(mean)THB	Price(mean) (THB/mg)	Company
1. CALCIUM FOLINATE VIAL 100 MG/10ML (10 ML)	480.00	4.80	PHARMACHEMIE B.V.
1.1 CALCIUM FOLINATE VIAL 300 MG (30 ML)	1,605.00	5.35	ABIC ISRAEL
1.1 CALCIUM FOLINATE VIAL 300 MG/30ML(30 ML)	2,500.00	8.33	HOSPIRA
1.3 CALCIUM FOLINATE VIAL 300 MG/30ML (30 ML)	1,695.98	5.65	PHARMACHEMIE B.V.
1.4 CALCIUM FOLINATE VIAL 50 MG/5ML (5 ML)	385.74	7.71	ABIC ISRAEL
1.5 CALCIUM FOLINATE VIAL 50 MG/5ML (5 ML)	246.67	4.93	BIOCHEM GES.M B H
1.6 CALCIUM FOLINATE VIAL 50 MG/5ML (5 ML)	475.00	9.50	HOSPIRA
1.7 CALCIUM FOLINATE VIAL 50 MG/5ML (5 ML)	264.91	5.30	PHARMACHEMIE B.V.
1.8 CALCIUM FOLINATE VIAL DRY 15	181.82	12.12	PHARMACHEMIE B.V.

SCHEDULE OF CALCULATION CHEMOTHERAPY DOSING

Drug Name	Price(mean) THB	Price(mean) (THB/mg)	Company
1.9 CALCIUM FOLINATE VIAL DRY30 MG (3 ML)	313.33	10.44	EBEWE ARZNEIMITTEL
1.10 CALCIUM FOLINATE VIAL DRY300 MG (30 ML)	1,172.17	3.91	EBEWEARZNEIMITTEL
1.11 CALCIUM FOLINATE VIAL DRY50 MG (5 ML)	238.08	4.76	FRESENIUS
AVERAGE CALCIUM FOLINATE		**6.50**	
2.0 CAPECITABINEFILM-COAT TB 500 MG	16,626.73	138.56	ROCHE
AVERAGE CAPECITABINE		**138.56**	
3.0 FLUOROURACIL AMP.250 MG/5ML (5 ML)	107.00	0.43	ABIC ISRAEL
3.1 FLUOROURACIL AMP.500 MG/10ML (10 ML)	53.75	0.11	BORYUNG
3.2 FLUOROURACIL VIAL 1000 MG (20 ML)	149.80	0.15	ABIC ISRAEL

SCHEDULE OF CALCULATION CHEMOTHERAPY DOSING

Drug Name	Price(mean) THB	Price(mean) (THB/mg)	Company
3.3 LUOROURACIL VIAL 1000 MG/20ML (20 ML)	121.03	0.12	EBEWE ARZNEIMITTEL
3.4 FLUOROURACIL VIAL 250 MG/5ML (20 ML)	150.00	0.60	BIOCHEM GES.M B H
3.5 FLUOROURACIL VIAL 250 MG/5ML (5 ML)	29.77	0.12	BIOCHEM GES.M B H
3.6 FLUOROURACIL VIAL 500 MG (10 ML)	105.25	0.21	ABIC ISRAEL
3.7 FLUOROURACIL VIAL 500 MG (10 ML)	55.00	0.11	KYOWA HAKKO KOGYO
3.8 FLUOROURACIL VIAL 500 MG/10 ML (10 ML)	55.50	0.11	BIOCHEM GES.M B H
AVERAGE FLUOROURACIL		**0.22**	
4.0 OXALIPATIN VIAL 100 MG/50 ML (50 ML)	14,000.00	140.00	FRESENIUS
4.1 OXALIPATIN VIAL 100 MG/50 ML (50 ML)	9,150.00	91.50	VENUS REMEDIES

SCHEDULE OF CALCULATION CHEMOTHERAPY DOSING

Drug Name	Price(mean) THB	Price(mean) (THB/mg)	Company
4.2 OXALIPATIN VIAL 200 MG (40 ML)	53,524.74	267.62	SANOFI AVENTIS
4.3 OXALIPATIN VIAL 50 MG (10 ML)	13,910.00	278.20	SANOFI AVENTIS
4.5 OXALIPATIN VIAL 50 MG/25 ML (25 ML)	6,474.32	129.49	FRESENIUS
4.6 OXALIPATIN VIAL 50 MG/25 ML (25 ML)	5,000.00	100.00	VENUS REMEDIES
4.7 OXALIPATIN VIAL DRY 100 MG	8,000.00	80.00	HOSPIRA
4.8 OXALIPATIN VIAL DRY 50 MG	4,500.00	90.00	HOSPIRA
AVERAGE OXALIPATIN		**147.10**	
5.0 IRINOTECAN INFUSION 100 MG/5ML	15,411.15	154.11	PFIZER INTER CORP
5.1 IRINOTECAN INFUSION 300 MG/15ML	37,045.78	123.49	PFIZER INTER CORP

SCHEDULE OF CALCULATION CHEMOTHERAPY DOSING

Drug Name	Price(mean) THB	Price(mean) (THB/mg)	Company
5.2 IRINOTECAN INFUSION 40 MG/2ML	6,069.58	151.74	PFIZER INTER CORP
5.1 IRINOTECAN VIAL100 MG/5ML	7,758.33	77.58	FRESENIUS
5.2 IRINOTECAN VIAL 40 MG/2ML	3,210.00	80.25	FRESENIUS
AVERAGE IRINOTECAN		**117.43**	

APPENDIX C

Questionnaire for collecting data for direct non-medical costs, indirect costs, and direct medical costs incurred outsides hospitals of stage III colon cancer patients and caregivers

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แบบสอบถามต้นทุนในผู้ป่วยมะเร็งลำไส้ใหญ่ระยะที่ 3 ที่ได้รับยาเคมีบำบัดในการรักษาเสริม
ชื่อโครงการ "การประเมินความคุ้มค่าของการรักษาเสริมโดยใช้ยาเคมีบำบัดในผู้ป่วยโรคมะเร็งลำไส้ใหญ่ ระยะที่ 3 ในประเทศไทย"

ผู้สัมภาษณ์: อธิบายวัตถุประสงค์ของการศึกษาวิจัยแก่ผู้ถูกสัมภาษณ์
ชื่อผู้สัมภาษณ์ .....
วัน เดือน ปี (พ.ศ.) ที่สัมภาษณ์ □□/ □□/ □□□□
รหัสแทนผู้ป่วย..... เบอร์ติดต่อ.....
ผู้ให้ข้อมูล □ 1. ผู้ป่วย □ 2. ญาติ มีความสัมพันธ์กับผู้ป่วยโดยเป็น ..... ของผู้ป่วย

ส่วนที่ 1: ข้อมูลทั่วไปของผู้ป่วย

1. เพศ □ 1.หญิง □ 2.ชาย อายุ.....ปี

2. สถานภาพสมรส □ 1.โสด □ 2.สมรส □ 3.หย่า/หม้าย □4.แยกกันอยู่

3. อาชีพหลัก
□ 1.ข้าราชการ/ลูกจ้างหน่วยงานรัฐ □ 2.พนักงานรัฐวิสาหกิจ □ 3.พนักงานบริษัท/ลูกจ้างเอกชน
□ 4.ค้าขาย/เจ้าของกิจการ □ 5.เกษตรกรรม / ประมง □ 6.แม่บ้าน/พ่อบ้าน
□ 7.เกษียณ □ 8.ผู้ใช้แรงงาน/รับจ้างทั่วไป □ 9.ไม่ได้ประกอบอาชีพ
□ 10.อื่นๆ ระบุ .....

4. ปัจจุบันที่อยู่อาศัยของผู้ป่วยอยู่บริเวณใด
□ 1.อยู่ในเขตกรุงเทพฯ
□ 2. ต่างจังหวัด ระบุ.....ในเขตเทศบาล
□ 3.ต่างจังหวัด ระบุ.....อยู่นอกเขตเทศบาล
□ 4. ต่างประเทศ ระบุ …….....

5. ระดับการศึกษาสูงสุด
□ 1.ไม่ได้เรียนหนังสือ □ 2.ประถมศึกษา □ 3.มัธยมศึกษาหรือเทียบเท่า
□ 4.อนุปริญญา/ประกาศนียบัตร □ 5.ปริญญาตรีหรือเทียบเท่า □ 6.ปริญญาโทหรือเทียบเท่า
□ 7.อื่นๆ ระบุ .....
…….....

6. สิทธิการรักษา

☐ 1.ประกันสุขภาพถ้วนหน้า ☐ 2.ประกันสังคม ☐ 3.ข้าราชการ/รัฐวิสาหกิจ

☐ 4.ทหารผ่านศึก ☐ 5.ประกันสุขภาพบริษัทเอกชน/ประกันชีวิต

☐ 6.ชำระค่าใช้จ่ายเอง ☐ 7.อื่นๆ ระบุ .....

7. วันที่เริ่มวินิจฉัยว่าเป็นโรคมะเร็งลำไส้ใหญ่ วัน เดือน ปี (พ.ศ.)……/……/……

8. ผู้ป่วยได้รับการผ่าตัดก้อนมะเร็งลำไส้ใหญ่ออกแล้วเป็นจำนวน…… ครั้ง

วันที่ได้รับการผ่าตัดครั้งที่ 1 วัน เดือน ปี (พศ.) ……/……/……

วันที่ได้รับการผ่าตัดครั้งที่ 2 วัน เดือน ปี (พศ.) ……/……/……

9. นอกจากโรคมะเร็งลำไส้ใหญ่แล้ว ผู้ป่วยมีโรคประจำตัวใดอีกบ้าง (ตอบได้มากกว่า 1 ข้อ)

☐ 1.ไม่มี ☐ 2.โรคความดันโลหิตสูง ☐ 3.โรคหัวใจ

☐ 4.โรคตับอักเสบ ☐ 5.โรคหอบหืด ☐ 6.โรคปอด

☐ 7.โรคลมชัก ☐8.โรคเบาหวาน ☐ 9. อื่นๆ ระบุ .....

10. สูตรการรักษาที่ได้รับครั้งที่ 1 ระบุวัน เดือน ปี (พศ.) ……/……/……

☐ 1. 5-fluorouracil/leucovorin regimen

☐ 2. capecitabine monotherapy

☐ 3. capecitabine/oxaliplatin (XELOX Regimen)

☐ 4. 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX Regimen)

11. สูตรการรักษาที่ได้รับการกลับเป็นซ้ำของโรค หรือมีการเปลี่ยนยาเนื่องจากผลข้างเคียงของการใช้ยาระบุวัน เดือน ปี (พ.ศ.) ……/……/……

☐ 1. capecitabine monotherapy

☐ 2. capecitabine/oxaliplatin (XELOX Regimen)

☐ 3. 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX Regimen)

☐ 4. 5-fluorouracil/leucovorin/irrinotecan (FOLFIRI)

ส่วนที่ 2: ข้อมูลด้านต้นทุนของผู้ป่วย

2.1 ต้นทุนของผู้ป่วยนอก

12. หลังจากการผ่าตัดครั้งที่ 1 ในช่วงระยะเวลา 1 เดือนที่ผ่านมา ผู้ป่วยต้องมารับการรักษาโรคที่โรงพยาบาลโดยได้รับยาเคมีบำบัดเป็นจำนวน ..... ครั้ง

13. ระยะเวลาที่ใช้ในการมารับการรักษาโรคในครั้งนี้ (เช่น 3 ชั่วโมง 1 วัน).....ชม.....วัน

14. การมารับการรักษาโรคในครั้งนี้ ผู้ป่วยเสียค่าใช้จ่ายด้านที่พักหรือไม่

☐ 1.ไม่เสียค่าใช้จ่าย ☐ 2. มีค่าที่พักคิดรวมเป็นจำนวนเฉลี่ย ..... บาท

15. ค่าใช้จ่ายในการเดินทางไป-กลับของผู้ป่วย ระหว่างที่พักและโรงพยาบาลเพื่อมารับการรักษาโรคในครั้งนี้เป็นจำนวนเฉลี่ย ..... บาท

16. ค่าอาหารที่เพิ่มขึ้นจากชีวิตปกติในการมาโรงพยาบาลของผู้ป่วยเพื่อมารับการรักษาโรคในครั้งนี้ เป็นจำนวนเฉลี่ย ..... บาท

17. ค่ารักษาพยาบาลที่ต้องจ่ายเพิ่มเติมจากสิทธิการรักษาในครั้งนี้เป็นจำนวนเฉลี่ย.....บาท

18. การมารับการรักษาโรคในครั้งนี้ ผู้ป่วยต้องมีญาติเพื่อพามารับการรักษาที่โรงพยาบาลหรือไม่

☐ 1.ไม่มี (ข้ามไปทำข้อ 19) ☐ 2. มี จำนวน ..... คน โปรดระบุรายละเอียดค่าใช้จ่าย

	จำนวน (ในครั้งนี้)		
	คนที่ 1	คนที่ 2	คนที่ 3
อายุ			
เพศ			
ระยะเวลาที่ใช้ทั้งหมดเพื่อพาผู้ป่วยมารับการรักษา เช่น 2 ชั่วโมง			
ค่าที่พัก			
ค่าเดินทางไป-กลับ			
ค่าอาหาร(ที่เพิ่มขึ้น)			
อื่นๆ ระบุ.....			

19. ในช่วงเวลาระยะเวลา 1 เดือน ตั้งแต่เริ่มได้รับการรักษาด้วยยาเคมีบำบัด นอกเหนือจากผู้ป่วยมารับการรักษาโรคที่โรงพยาบาลนี้แล้วได้ไปรับการรักษาจากสถานที่อื่นที่หรือไม่

☐ 1. ไม่ ☐ 2. ใช่……..โปรดระบุรายละเอียด

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สถานที่	จำนวนครั้ง	จำนวนเงินเฉลี่ยที่จ่ายต่อครั้ง
☐ โรงพยาบาลอื่นๆ ระบุ		
☐ คลินิก		
☐ ศูนย์บริการสาธารณสุข		
☐ อื่นๆ ระบุ		

20. ในช่วงเวลาระยะเวลา 1 เดือน ตั้งแต่เริ่มได้รับการรักษาด้วยยาเคมีบำบัด ผู้ป่วยได้ซื้อยาหรือผลิตภัณฑ์เสริมอาหารเองเพื่อการรักษา หรือบรรเทาอาการที่เกิดจากโรคเองหรือไม่

☐ 1.ไม่ ☐ 2. ใช่ โปรดระบุรายละเอียด

รายการ	ชื่อหรือชนิดของยาหรือผลิตภัณฑ์เสริมอาหาร	ระยะเวลาที่ใช้ยาหรือผลิตภัณฑ์เสริมอาหาร	ราคา
1			
2			
3			
4			

21. ในช่วงเวลาระยะเวลา 1 เดือน ตั้งแต่เริ่มได้รับการรักษาด้วยยาเคมีบำบัด ผู้ป่วยต้องอาศัยญาติในการทำกิจกรรมการดูแลอย่างไม่เป็นทางการ เช่น ล้างจาน รีดผ้า ทำความสะอาด กินข้าว อาบน้ำ การทำธุระต่างๆการเงิน การเตรียมยาให้ผู้ป่วยหรือไม่

☐ 1.ไม่ (ข้ามไปทำข้อ 25) ☐ 2.ใช่ โปรดระบุรายละเอียด

	จำนวน		
	คนที่ 1	คนที่ 2	คนที่ 3
อายุ/เพศ			
ความถี่ของการช่วยเหลือ (เช่น ทุกวัน สัปดาห์ละ … ครั้ง)			

ระยะเวลาต่อครั้ง(เช่น 2 ชั่วโมง)			
เป็นระยะเวลาต่อเนื่องนานเท่าใด (เช่น 1 สัปดาห์)			

22. จากข้อ 21. ญาติของผู้ป่วยพักอยู่บ้านเดียวกับผู้ป่วยหรือไม่

☐ 1. ใช่

☐ 2. ไม่ และต้องเสียค่าใช้จ่ายในการเดินทางไป-กลับเป็นจำนวนเฉลี่ย..... บาทต่อการมาบ้านผู้ป่วย 1 ครั้ง

2.2 ต้นทุนของผู้ป่วยใน

23. ในช่วงระยะเวลา 1 ปี ตั้งแต่เริ่มได้รับการรักษาด้วยยาเคมีบำบัด ผู้ป่วยต้องมาพักรักษาตัวในโรงพยาบาลนี้เป็นจำนวนเฉลี่ย..... ครั้ง

24. ผู้ป่วยต้องพักรักษาตัวในโรงพยาบาลในแต่ละครั้งเป็นจำนวนเฉลี่ย.....วัน

25. ค่ารักษาพยาบาลที่ต้องจ่ายเพิ่มเติมจากสิทธิการรักษาเป็นจำนวนเฉลี่ย.....บาท

26. ในการเข้ารับการรักษาตัวในโรงพยาบาล ผู้ป่วยต้องมีญาติเพื่อมาดูแลระหว่างนอนโรงพยาบาลหรือไม่

☐ 1. ไม่มี (ข้ามไปทำข้อ 28) ☐ 2. มี จำนวน..... คน โปรดระบุรายละเอียดค่าใช้จ่าย

	จำนวน		
	คนที่ 1	คนที่ 2	คนที่ 3
อายุ/ เพศ			
ความถี่ของการช่วยเหลือ(เช่น ทุกวัน สัปดาห์ละ ……ครั้ง)			
ระยะเวลาต่อครั้ง (เช่น 2 ชั่วโมง)			
ค่าที่พัก			
ค่าเดินทางไป-กลับ			
ค่าอาหาร (ที่เพิ่มขึ้น)			
อื่นๆ (ระบุ)			

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27. ในช่วง 1 ปี นับตั้งแต่ได้รับยาเคมีบำบัด ท่านเคยมีอาการป่วย จนต้องได้รับการดูแลเป็นพิเศษที่บ้านหรือหยุดงานเพื่อพักรักษาตัวที่บ้านหรือไม่

☐ 1.ไม่เคย (ข้ามไปทำข้อ 29) ☐ 2.เคย จำนวน .....วัน ในรอบ 6 เดือน โดยที่

☐ 1. มีคนคอยดูแลทุกวัน ☐ 2. ไม่ได้มีคนคอยดูแลทุกวัน จำนวนวันที่มีคนคอยดูแล .....วัน

28. ตั้งแต่ผู้ป่วยเกิดโรค ผู้ป่วยหรือญาติจัดหาสิ่งต่อไปนี้หรือไม่ โปรดระบุรายละเอียด

☐ 1.ไม่ ☐2. ใช่ โปรดระบุรายละเอียด

รายการ	**จำนวนเงิน**
☐ผู้ดูแลผู้ป่วย (ระบุอัตราจ้างต่อเดือน)	
☐ผู้ดูแลทำงานบ้านหรือคนรับใช้ เนื่องจากการเจ็บป่วยของผู้ป่วยทำให้ไม่ สามารถทำเองได้ (ระบุอัตราจ้างต่อเดือน)	
☐ผู้ดูแลบุตรหรือบุพการีของผู้ป่วยเนื่องจากการเจ็บป่วยของผู้ป่วยทำให้ไม่สามารถทำเองได้ (ระบุอัตราจ้างต่อเดือน)	
อื่นๆ (เช่น รถเข็น วิกผม) ระบุ ……	

29. ในปัจจุบันผู้ป่วยได้รับเงินช่วยเหลือ จากการเจ็บป่วย หรือไม่

☐ 1.ไม่ได้

☐ 2.ได้ โปรดระบุแหล่งที่มา.....

จำนวน …….....บาทต่อเดือน

ข้อคิดเห็น……

……

……

……

…….

แบบสอบถามคุณภาพชีวิตผู้ป่วยมะเร็งลำไส้ใหญ่ระยะที่ 3 ที่ได้รับยาเคมีบำบัดในการรักษาเสริม

ส่วนที่ 3: ข้อมูลเกี่ยวกับคุณภาพชีวิต

ในคำถามแต่ละข้อ กรุณาเลือกข้อที่ตรงกับสภาวะสุขภาพของท่านในวันนี้มากที่สุด

30. การเคลื่อนไหว

ข้าพเจ้าไม่มีปัญหาในการเดิน ❑
ข้าพเจ้ามีปัญหาในการเดินบ้าง ❑
ข้าพเจ้าไม่สามารถไปไหนได้ และจำเป็นต้องอยู่บนเตียง ❑

31. การดูแลตนเอง

ข้าพเจ้าไม่มีปัญหาในการดูแลตนเอง ❑
ข้าพเจ้ามีปัญหาในการอาบน้ำหรือการแต่งตัวบ้าง ❑
ข้าพเจ้าไม่สามารถอาบน้ำหรือแต่งตัวด้วยตนเองได้ ❑

32. กิจกรรมที่ทำเป็นประจำ *(เช่น การทำงาน, การเรียนหนังสือ, การทำงานบ้าน, การทำกิจกรรมในครอบครัว หรือการทำกิจกรรมยามว่าง)*

ข้าพเจ้าไม่มีปัญหาในการทำกิจกรรมที่ทำเป็นประจำ ❑
ข้าพเจ้ามีปัญหาในการทำกิจกรรมที่ทำเป็นประจำอยู่บ้าง ❑
ข้าพเจ้าไม่สามารถทำกิจกรรมที่ทำเป็นประจำได้ ❑

33. ความเจ็บปวด/ความไม่สุขสบาย

ข้าพเจ้าไม่มีอาการเจ็บปวดหรืออาการไม่สุขสบาย ❑
ข้าพเจ้ามีอาการเจ็บปวดหรืออาการไม่สุขสบายปานกลาง ❑
ข้าพเจ้ามีอาการเจ็บปวดหรืออาการไม่สุขสบายมากที่สุด ❑

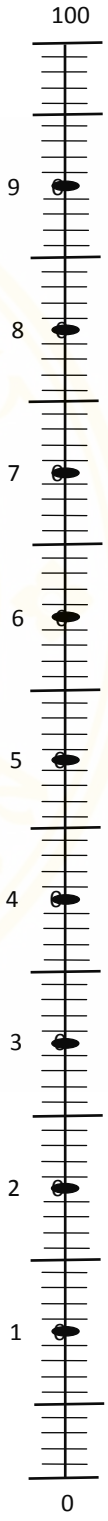
34. ความวิตกกังวล/ ความซึมเศร้า

ข้าพเจ้าไม่รู้สึกวิตกกังวลหรือซึมเศร้า ❑
ข้าพเจ้ารู้สึกวิตกกังวลหรือซึมเศร้าปานกลาง ❑
ข้าพเจ้ารู้สึกวิตกกังวลหรือซึมเศร้ามากที่สุด ❑

เพื่อช่วยในการประเมินภาวะสุขภาพของท่าน ทางเราได้จัดทำสเกลวัดระดับสุขภาพขึ้น เริ่มตั้งแต่ระดับ 0 ถึง 100 โดยที่ 100 หมายถึง ภาวะสุขภาพที่ดีที่สุด และ 0 หมายถึง ภาวะสุขภาพที่แย่ที่สุด ตามความคิดของท่าน กรุณาประเมินภาวะสุขภาพของท่านในวันนี้ว่าดีหรือไม่ดีเพียงไร โดยการลากเส้นจากช่องสี่เหลี่ยมข้างล่างนี้ไปยังจุดบนสเกลวัดระดับสุขภาพที่ตรงกับภาวะสุขภาพของท่านในวันนี้

ภาวะสุขภาพของท่านในวันนี้

ภาวะสุขภาพที่ท่านรู้สึกว่า ดีที่สุด



ภาวะสุขภาพที่ท่านรู้สึกว่าแย่ที่สุด

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2. A Systematic Review on Economic Evaluation of Oxaliplatin Added Regimens as the Adjuvant Chemotherapy in Stage III Colorectal Cancer, The 1st UKM-MU Joint Scientific Conference, Universiti Kebangsaan Malaysia, Malaysia, 12-13 October 2010