CHAPTER II

COLORECTAL CANCER

Colorectal cancer is a solid tumor of colon, rectal and anal. Colon is a portion of the large intestine that begins at the ileocecal valve and ends at the peritoneal reflection. Rectum is comprised of the large bowel extending from the peritoneal reflection to the anus. A tumor that is completely above the peritoneal reflection is treated as colon cancer, while a tumor that has any part below the peritoneal reflection is treated as rectal cancer.[17] In the past, colorectal cancer was a leading cause of cancer death in industrial countries. In Thailand, incidence of colorectal cancer mortality is highly increasing and became a health problem in Thai people.

Signs and symptoms of colorectal cancer are nonspecific. Patients with early stage are often asymptomatic and the most common symptoms which suggest a diagnosis of colorectal cancer are consisted of rectal bleeding of short duration, abdominal pain and bowel habits changing such as constipation, diarrhea or bloody stool. Treatment of colorectal cancer is focused on precise staging diagnosis and histopathology to choose appropriate treatment for individual patients. The stage of colorectal cancer identified by depth of tumor invasion of the bowel wall, presence or absence of involved lymph nodes and organ metastases. Fig. 1 shows different stages of colorectal cancer. [18-19]

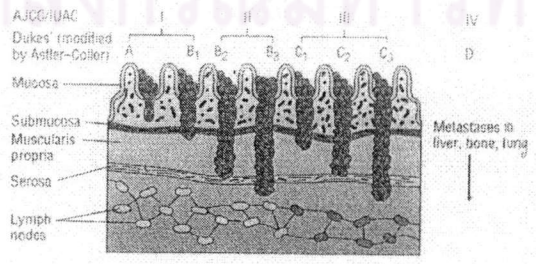

Figure 1 Staging system for colorectal cancer

Table 1 TNM Staging Classification System for Colorectal cancer[18]

Primary Tumor (T)					
TX	Primary tumor cannot be assessed				
T0	No evidence of primary tumor				
Tis	Carcinoma in situ				
T1	Tumor invades submucosa				
T2	Tumor invades muscularis propia				
T3	Tumor invades through the muscularis propia into the submucosa or into nonperitonealized pericolic or perirectal tissues				
T4	Tumors perforates the visceral peritoneum or directly invades other organ or structures				
Regional Lymph Nodes (N)					
NX	Regional lymph nodes cannot be assessed				
N0	No regional lymph node metastasis				
N1	Metastasis in one to three pericolic or perirectal lymph nodes				
N2	Metastasis in four or more pericolic or perirectal lymph nodes				
N3	Metastasis in any lymph nodes along the course of a named vascular trunk				
Distant Metastasis (M)					
MX	Presence of distance metastasis cannot be assessed				
M0	No distant metastasis				
M1	Distant metastasis				
Stage		Grouping		Dukes	Modified Astler-Clooier
Stage 0	Tis	N0	M0	A	
Stage 1A	T1	N0	M0	A	A
Stage 1B	T2	N0	M0	B	B1
Stage 2	T3	N0	M0	B	B2
	T4	N0	M0	B	B2,B3
Stage 3	Any T	N1	M0	C	C1-3
	Any T	N2	M0	C	C1-3
	Any T	N3	M0	C2	
Stage 4	Any T	Any N	M1	D	D

Treatment of Colorectal Cancer [17-19]

Surgery

Surgery remains the primary definitive treatment of choices for most patients with colorectal cancer. Patients with metastatic colorectal cancer may also require surgery for palliation of bleeding, obstruction or localized abdominal pain due to a bulky tumor mass. The surgical approach for colon cancer generally involves a complete resection of the tumor with an appropriate margin of tumor-free bowel and a regional lymphadenectomy. Surgery for rectal cancer depends on the region of tumor involvement. A low anterior resection is the procedure of choice in patients with lesions in the mild to upper rectum. Patients with lesions in the lower portion of the rectum may require an abdominalperitoneal resection if either the amount of unaffected bowel is insufficient for a resection.

Radiation

Radiation therapy (XRT) can be administered in conjunction with curative surgical resection and in the setting of advanced or metastatic disease. In patients undergoing surgery, XRT is used to reduce local tumor recurrence. Primary goal of XRT is reduced symptom for patients with advanced or metastatic disease, XRT is given prior to or following surgery and can be delivered using a variety of dosing regimens, administration schedules, and techniques that expose different amounts of body surface area.

Adjuvant Chemotherapy

Resectable cancers of colon and rectum are treated with adjuvant chemotherapy to improve the chance that an operation will be truly curative. It is important to recognize that the portion of the tumor that is removed by surgery is not a treatment. It is the potential for microscopic tumor to be outside of the resected field that creates the need for additional treatment. Adjuvant chemotherapy is therefore used to attempt to cure those patients who are rendered surgically free of disease. Because such clinical relapse into

significant recurrent disease would be due to undetected microscopic disease present at the time of surgery. Another reason is the early use of adjuvant chemotherapy in asymptomatic patients can prolong both symptom-free survival and overall survival.

Thymidylate synthase Inhibitors

Fluorouracil

5-FU is used for standard treatment of colorectal cancer, increasing disease-free and overall survival in patient. Detail in pharmacokinetics and mechanism of action of 5-FU are described in chapter III.

Raltitrexed

Raltritrexed is a specific thymidylate synthase (TS) inhibitor. It binds to folate receptor and is actively transported across cell membrane. It undergoes polyglutamation and is retained in the cell leading to prolong TS inhibition. Dose limiting toxicity of raltitrexed is myelosuppression while elevation of hepatic transminase enzyme, anemia and diarrhea are also common. In phase III trial of raltitrexed monotherapy compare with rapid IV infusion 5-FU and LV showed equal response rate but not significant (18.1% vs 18.6%,p = 0.90) and superior time to progression in 5-FU plus LV group (5.1 vs 3.9 months, $p< 0.05$)[20] Treatment-related deaths from diarrhea and infection and impaired quality of life occurred in raltitrexed arm was the reason that the Pan-European Trials in Adjuvant Colon Cancer (PETACC I) trial discontinued prematurely.[21-22]

Oral Fluoropyrimidine

Oral Flouoropyrimidine have been developed to provide prolong exposure without high peak concentration mimicking pharmacokinetic profiles of injection regimens.

UFT

UFT is composed of uracil and tegafur in a fixed molar ratio 4:1. Uracil is a competitive inhibitor of DPD enzyme while tegafur is a prodrug of 5-FU that is rapidly and completely absorbed after oral administration and converted to 5-FU by cytochrome P-450 in liver. UFT activity is improved with the addition of folinic acid.[10,21-22] Two randomized trials enrolling patients with metastasis colorectal cancer showed equal efficacy (12 and 11% in UFT plus LV vs 15 and 9% in 5-FU plus LV arm) and less toxicity in UFT plus LV arm compared with bolus 5-FU plus LV regimen.[23-24]

Capecitabine

Capecitabine is an oral 5-FU prodrug with three-step enzymatic conversion to 5-FU. It is finally converted by enzyme thymidine phosphorylase (TP) at the tumor site to the acive moiety. Ishigawa et al. found tumor selectivity of capecitabine in ratios of tumor to non-tumor tissues of 22-127:1.[25] Consequently, capecitabine is resulting in preferential accumulation of 5-FU level 3.2 times higher in tumor tissue than in normal tissue. Side effects of capecitabine is similar to 5-FU with less toxicity on diarrhea, stomatitis, nausea, alopecia, neutropenia and sepsis but high toxicity on hand-foot syndrome. Occurrence of bowel toxicity is disappointing because capecitabine is not metabolite in the intestinal mucosa.[10,20-21,25] In randomized trial showed significant higher hand-foot syndrome and superior in remission rated (25.7% vs 16.7%,$p<0.0002$) of capecitabine arm compared with 5-FU plus LV bolus regimen.[27]

Eniluracil

Eniluracil is a potent uracil analogue. It is a potent inactivator of DPD by irreversible competitive inhibitor to increase oral bioavailability of 5-FU. However the complete inhibition of DPD is decreased therapeutic index of 5-FU, resulting it has high rates of toxic effects. Therefore clinical development of eniluraci is not ensured.[10,21,28]

Irinotecan

Irinotecan is a semisynthetic derivative of campothecan, a natural alkaloid that inhibit topoisomerase I enzyme which is the nuclear enzyme necessary for the potential for the positional control of DNA strand breaks. Irinotecan is a prodrug which requires activation by carboxylesterase enzymes which are variably expressed in liver, blood and tumor deposits and also entero-hepatic recirculation related to gastrointestinal bacterial beta-glucoronidase. These factors produce interpatient variability in pharmacokinetics and unpredictable patient toxicities.[21-22] Phase III trials, irinotecan monotherapy had equal effective in remission rate, time to progression and overall survival but more toxic than 5-FU plus LV in Mayo regimen while irinotecan combined with bolus 5-FU and LV showed significant higher in overall survival both in bolus injection and continuous infusion regimen.[29-30]

Oxaliplatin

Oxaliplatin is a third generation platinum derivative which mechanism of action is similar to platinum with formation of platinum-DNA linkages. Recognition by the DNA mis-match repair pathway is less inhibited than with the parent platinum compounds. Dose limiting toxicity of oxaliplatin in phase I study is peripheral sensory neuropathy at dose more than 100 mg/m^2/cycle. Nausea and diarrhea are also common while nephrotoxicity and myelosuppression are uncommon. Oxaliplatin combined with 5-FU and LV in continuous infusion (de Gramont regimen) showed significant in response rate (50.7% vs 22.3%, $p = 0.0001$) and progression free survival (9.0 vs 6.2 m0nths, $p < 0.0001$).[22,31]

Adjuvant Therapy in Colon Cancer

Adjuvant therapy in colon cancer is almost based on chemotherapy. The aim of therapy is destroyed micrometastatic disease and preventing death from metastatic cancer. Trials of adjuvant chemotherapy in colon cancer have been performed over 30 years. Before the widespread use of 5-FU in colon cancer adjuvant therapy, the first trial

that showed slightly statistical significant effective was reported by the National Surgical Adjuvant Breast and Bowel Project C-01 (NSABP C-01).[32] This trial randomized patients to receive semustine plus vincristine plus 5-FU (MOF regimen) or BCG or no treatment group. In 1990, Moertel CG, Fleming TR, Macdonald JS et al was reported significant on clinical investigation and standard of care of 5-FU and levamisole (LEV) regimen compared with LEV alone or surgery alone group. 5-FU and LEV group showed significant superior in disease free survival in stage III colon cancer group to LEV alone or surgery alone group but no significant in stage II group relatively from small number of patients.[33-35] Biomodulation of 5-FU by LEV was replaced by leucovorin (LV) from early report of 5-FU and high dose LV which reported by IMPACT and NSABP C-03 trial.[36-37] The results of these clinical trials demonstrated significant improvement in disease free and overall survival for 5-FU plus LV compared with surgery alone in IMPACT and MOF regimen in NSABP C-03 trial. In 1998, INT-0089 tiral[38] randomized patients to receive either 5-FU plus LEV for 12 months or 5-FU plus high dose LV for 32 weeks or 5-FU plus low dose LV or 5-FU plus low dose LV plus LEV for 6 months. The results showed 5-FU plus LEV plus LV arm was statistically superior to 5-FU plus LEV arm but was not superior to the two 5-FU arms. From this result has no different between either high or low dose LV. Several other important trials comparing the role of LEV and LV in the adjuvant therapy of colon cancer has been reported. In 1999, NSABP C-04 trial[39] assigned patients to receive 5-FU plus high dose LV for 1 year or 5-FU plus high dose LV plus oral LEV or 5-FU plus LEV arm for 1 year therapy. The five years overall survival and disease free survival in 5-FU plus LV arm was superior to 5-FU plus LEV arm while 5-FU plus LEV plus LV arm was not significant different in efficacy from the other two regimens.

Furthermore, NCCTG trial[40] compared time of treatment by 5-FU plus LEV for 6 or 12 months and 5-FU plus LEV plus LV for 6 or 12 months. The results indicated 6 months of treatment was not inferior to 12 months of treatment. Another large study from QUASAR[41] group studied for patients received 5-FU plus high dose or low dose l –LV in weekly or monthly regimen plus LEV or placebo. There was no survival differences which ruled out any benefit or the LEV addition and no benefit of high dose LV compared to low dose LV neither in the weekly nor monthly regimen.[42] In conclusion, 5-FU plus LV for six

months has been the most widely accept standard treatment in colon cancer. Although the benefit from adjuvant treatment by 5-FU plus LV has been clearly established in stage III colon cancer patients, the role of 5-FU plus LV in stage II colon cancer is still questioned likely in elderly patients. The early trials of stage II colon cancer patients showed no significant increased in disease free or overall survival. Most trials had underpowered to demonstrate the significant because stage II patients has lower event rate referring to insufficient number of patients with stage II disease. In NSABP C-02, C-03, C-04 showed significant reduction in mortality rate, recurrence or disease free survival event rates in stage II and III patients between treatment groups that patients received either PVI 5-FU plus heparin or MOF regimen of 5-FU plus LV and control group that received either operation alone or 5-FU plus LV or 5-FU plus LEV in C-02, C-03, C-04 trials. Due to the limit number of patients in each trial, In 1999 Manoumas E, Wiend S, Wolmark N, et al [43] compared only two groups of stage II colon cancer in either adjuvant therapy regimen or no adjuvant therapy from C-01-C-04 trials. These four trials had overall 41% of stage II patients and similar eligibly criteria. Reduction in mortality, recurrence or disease free survival event rate is significant improvement in C-02 trial for stage II patients and both stage II and III in C-03 trial.[43-45] But adjuvant treatment in stage II colon is now conflicted from IMPACT B2 trial[46], the meta-analysis include 1025 patients received 5-FU 370-425 mg/m^2/day plus LV 20-200 mg/m^2/day which well balance to compare control group that has no treatment. The result in terms of five years disease free survival and difference in overall survival was slightly advantage but no statistical significant. This trial does not support the routine use of 5-FU plus LV in all stage II patients. However, the value of adjuvant therapy in stage II cannot be definitively answered. A sufficient number of prospective randomized control trials with a control group can prove the efficacy of adjuvant therapy in stage II patients.

Adjuvant therapy data on risks and benefits in elderly is also limited like in stage II colon cancer. More than half of colon cancer patients are over 70 years old but elderly usually has been excluded from study design. It has no evidence that elderly has decrease in elimination rate of 5-FU. Young et al.[4] found no association between hepatic dysfunction and drug clearance following continuous infusion but there are reports of

increased AUC and half life for 5-FU in patients with impaired liver function. This is may be a reason to exclude elderly from the study because decreased liver function in old age may possible effect to the elimination of 5-FU. However a pooled analysis study in elderly patients from 7 trials (5 trials for 5-FU plus LV and 2 trials for 5-FU plus LEV) have shown overall survival, time to recurrence and five years recurrence free in patient treated with 5-FU was significantly longer than the patients who did not received treatment.[47] ($p < 0.0001$) But the limitation of this study was patients who enter trials are patients with good performance status and cognition and no coexisting conditions.

Future Treatment in Colon Cancer

Several new agents have demonstrated significant activity in metastatic colorectal cancer treatment. These agents have also entered to adjuvant trials. Efficacy and toxicity data are not yet completely available, and until the results of these trials have shown, 5-FU plus LV is still be recommend for standard use in adjuvant treatment of colon cancer.

Adjuvant therapy in Rectal cancer

Adjuvant therapy in rectal cancer has focused on stage II and III patients. Based on clinical trials in USA shown significant decreasing in local recurrence and improving survival from postoperation combine therapy (chemotherapy plus radiation) and NSABP R-01 trial in 1988 shown superior survival in chemotherapy over radiotherapy and control group.[48-49] However, in NSABP R-01 did not include combine modality treatment arm. In 1991, A National Cancer Institute Consensus Conference concluded that combine modality therapy with 5-FU based chemotherapy was standard treatment for postoperation patients with stage II and III rectal cancer.[50]

NCCTG trial by Krook JE, Moertel EG, Mayer RJ, et al.[51] shown the significant benefit in survival advantage for combined modality treatment over radiation alone but this study didn't have control arm by chemotherapy alone, however combined therapy is increased in acute toxicity. While combine modality treatment is a standard treatment for

rectal cancer patients, schedule and optimal dosage for chemotherapy and radiotherapy has been discussed. The study consisted of different schedules 5-FU plus postoperation radiotherapy and 5-FU plus or minus methyl-CCNU before and after radiotherapy. The result shown lower distant relapse in continuous infusion 5-FU compare to bolus 5-FU injection during radiotherapy and no better treatment outcome in patients received methyl-CCNU than patients received only 5-FU.[52-53] A trial by Intergroup 0114 studied irradiation in four protocols arms and compared different chemotherapy protocols shown no significant for any experiment arms (5-FU, LEV, LV plus radiotherapy) compared with control arm (irradiation plus concurrent bolus 5-FU injection).[54] Recent clinical trial was NSABP R-02 study compared chemotherapy arm (MOF or 5-FU plus LV) with chemotherapy plus radiation. There were no different in disease free and overall survival between two arms but chemotherapy plus radiation arm showed small but significant reduction in local recurrence rate. However, this trial didn't have a control arm.[55] While recent meta-analysis showed that postoperation radiotherapy improved survival in patient with resectable rectal cancer but only combined chemotherapy and radiotherapy has shown efficacy in decrease incidence of pelvic recurrence and increased in disease free and overall survival.[56] Randomized trial NSABP R-03 comparing pre- and postoperative conventional irradiation plus concurrent chemotherapy in respectable T_3 stage are now ongoing but a preliminary report showed that patient without evidence of disease in preoperation arm was higher than postoperation arm.

From available data has shown that adjuvant chemotherapy plus radiotherapy in resectable rectal cancer yields superior survival compared with chemotherapy alone, a reduction in local recurrence rate might be an important benefit.