Long-term Oncologic Outcomes After Curative Surgery in Stage I–III Thai Colorectal Cancer Patients

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ABSTRACT

Objective: The survival rate for colorectal cancer varies and there are limited reports regarding the long-term outcomes after curative treatment in Thai patients. This study aimed to determine the long-term oncologic results in non-metastatic Thai colorectal cancer patients after curative surgery.

Materials and Methods: We performed a retrospective review of a prospectively collected colorectal cancer registry. Short-term and long-term outcomes were analyzed.

Results: 626 patients were included in the study, 51.9% colon cancer and 48.1% rectal cancer patients. The mean age was 63.6 ± 12.7 years. The median follow-up time was 5.4 years [IQR: 2.1–7.4]. The 5-year local recurrence was 6.4%; 3.3% in colon cancer and 9.9% in rectal cancer. The 5-year overall survival (5-yr OS) in the colon cancer patients was 76.3%; 94.6% in stage I, 80.8% in stage II, and 65.3% in stage III. The 5-yr OS in the rectal cancer patients was 65.1%; 84.7% in stage I, 75% in stage II, and 51% in stage III. The 5-year disease-free survival (5-yr DFS) in the colon cancer patients was 76.5%; 91.4% in stage I, 81.3% in stage II, and 66.4% in stage III. The 5-yr DFS in the rectal cancer patients was 63.8%; 81.5% in stage I, 75.1% in stage II, and 50.1% in stage III.

Conclusion: The long-term oncologic outcomes after curative treatments in this study were acceptable. The prognosis of treatment depends on the disease stage. Comparing stage by stage, colon cancer has a better prognosis than rectal cancer.

Keywords: Colorectal cancer; long-term outcomes; overall survival; disease-free survival; Asian; Thai (Siriraj Med J 2022; 74: 739-746)

INTRODUCTION

Colorectal cancer is one of the most common public health problems. According to the International Agency for Research on Cancer and the World Health Organization, colorectal cancer is the third-most common cancer in men and the second-most common in women worldwide.[1] When diagnosing the disease, most patients would like to know their stage of disease and prognosis. The survival rate of colorectal cancer can vary based on a variety of factors, particularly the stage of the disease. The mortality rate from colorectal cancer has declined from the past because surgeons can now diagnose it earlier and as the treatments have improved. Most of the data regarding long-term survival are reported from Western countries. While there are some publications regarding treatment in colorectal cancer reported from Asian countries, data on the long-term outcomes after curative treatment in stage I–III colorectal cancer, particularly in Thailand, are limited. We, therefore, conducted this study to determine the long-term oncologic results in stage I–III colorectal cancer patients after curative surgery.

MATERIALS AND METHODS

After approval by the Siriraj Institute Review Board (Si 581/2015), we performed a retrospective review of the prospectively collected colorectal cancer registry in the Colorectal Surgery Unit, Department of Surgery, Faculty of Medicine Siriraj Hospital. We retrieved data including stage I–III colorectal cancer patients who underwent curative surgery between 2007 and 2011. Patients' information was abstracted from the registry, such as patients' demographic data (age, gender, co-morbidities), preoperative carcinoembryonic antigen (CEA), location of the tumor, type of surgery, short-term outcomes (postoperative complications and mortality), pathological staging, date of the last visit, current survival, and recurrence. The 5-year local recurrence rate (5-yr LR), 5-year overall survival (5-yr OS), and 5-year disease-free survival (5-yr DFS) were analyzed.

The exclusion criteria were 1) patients who had synchronous or a history of other primary cancers or who had developed other primary cancers during the study period, 2) histology other than adenocarcinoma, 3) stage IV disease, 4) patients who did not receive curative-intent surgery, 5) hereditary colorectal cancer syndrome, such as Lynch syndrome and familial adenomatous polyposis (FAP), and 6) either synchronous or metachronous colorectal adenocarcinoma.

Statistical analysis

We exported the retrieved data to SPSS version 23 statistical software for performing all the statistical analysis. We examined the baseline characteristics of the enrolled patients using descriptive statistics. We report the categorical data by number and percentage, while continuous data, such as age, preoperative CEA level, and follow-up time, were reported by the mean and standard deviation or median and interquartile range depending on the skewness of the data. We estimated the distribution of overall survival and disease-free survival through Kaplan–Meier survival analysis.

RESULTS

Study population

We retrieve the data related to 1,010 colorectal cancer patients who underwent surgery in our unit during the study period, but then excluded 384 patients according to our exclusion criteria. Therefore, the data of 626 stage I-III colorectal adenocarcinoma patients were analyzed comprising 325 colon cancer patients and 301 rectal cancer patients. The median follow-up time was 5.4 years [IQR: 2.1-7.4].

Patient characteristics

The mean age ± standard deviation of the patients was 63.6 ±12.7 years old. There were 335 (53.5%) male and 291 (46.5%) female patients. The most common co-morbidity was hypertension (33.9%) followed by diabetes mellitus (17.3%), cardiovascular disease (12.6%), dyslipidemia (10.4%), neurovascular disease (8%), respiratory disease (6.5%), and renal disease (3.4%), respectively. The median preoperative CEA was 4.4 ng/mL [IQR; 2.5-12.1]. Forty-one patients (6.5%) presented with acute obstruction. Of these, 15 patients were treated with colonic stent; 10 patients with Hartmann's procedure; 12 patients with one-stage colonic resection and anastomosis; and 4 patients with subtotal colectomy and ileorectal anastomosis. Nine percent of the rectal cancer patients received preoperative neoadjuvant concurrent chemoradiation.

Tumor locations and operations

Regarding colon cancer, 99 patients (30.5%) had right-sided colon cancer, including 27 cecum, 26 ascending colons, 21 hepatic flexure, and 25 transverse colons. Meanwhile, 226 patients (69.5%) had left-sided tumors, including 10 splenic flexure colons, 43 descending colons, 123 sigmoid colons, and 50 rectosigmoid colons. For the rectal cancers, 74 lesions were located above the peritoneal reflection, 62 at the peritoneal reflection, and 165 below the peritoneal reflection. Considering the surgery technique, most patients in this study (94.7%) were operated with open surgery. Only 5.3% of patients were operated with minimally invasive surgical techniques, including both laparoscopic-assisted and hand-assisted surgery. The most common type of operation in colon cancer was sigmoidectomy or anterior resection (59.7%). Overall, 212 (70.4%) of the rectal cancer patients could have had a sphincter preserving operation. Of these, 33 patients (15.6%) had a protective diverting stoma. Meanwhile, 89 patients (29.6%) underwent abdominoperineal resection.

Pathology and staging

This cohort consisted of 56 (8.9%) well differentiated carcinomas, 536 (85.6%) moderately differentiated carcinomas, 24 (3.8%) poorly differentiated carcinomas, 4 (0.6%) signet ring cell carcinomas, and 3 (0.5%) mucinous carcinomas. Regarding pT staging, the tumors were 27 (4.3%) T1, 133 (21.2%) T2, 399 (63.7%) T3, 42 (6.7%) T4a, and 25 (4%) T4b. More than one-quarter of patients (27.8%) had lymphovascular invasion and 20.6% of patients had a perineural invasion. The median number of total harvested lymph nodes was 19 [IQR: 14-27]. The positive all resection margin rate in the specimens was

9.3%; comprising 8.1% positive circumferential margin (CRM) and 1.3% positive distal resection margin. As per our anticipation, there were more positive CRM cases in rectal cancer than in colon cancer (10.6% versus 5.8%), as well as more positive distal resection margin cases in rectal cancer than in colon cancer (1.9% versus 0.6%). Most patients had pathological stage II and III diseases, both for colon and rectal cancer (Fig 1).

Short-term outcomes
The overall complication rate in this study was 20.8%; 7.2% medical-related complications, and 17.1% surgical-related complications. Respiratory complication was the most common medical-related complication (3.2%) followed by 2.2% urinary tract infection, 1.6% cardiac complication, and 0.5% thromboembolism complications. Meanwhile, superficial surgical site infection was the most common surgical-related complication (10.1%), followed by 7.8% stoma complication, 2.7% urinary retention, 1.9% intraabdominal collection, 0.8% wound dehiscence, and 0.5% deep surgical site infection. The overall anastomotic leakage rate was 3%; 1.7% in colon cancer operations and 5.2% in rectal cancer operations. One percent of patients had to be re-admitted within 30 days after surgery. Approximately, 12.8% of patients required postoperative ICU stay and the postoperative mortality rate was 1%.

Long-term outcomes
The 5-yr OS of all the patients in this cohort (stage I–III, including both colon and rectal cancer) was 70.9%;

89.1% in stage I, 78.6% in stage II, and 57.9% in stage III; while the 5-yr DFS of all the patients in this cohort was 70.4%; 85.9% in stage I, 79% in stage II, and 57.8% in stage III. Comparing stage by stage, rectal cancer had a poorer prognosis than colon cancer, as demonstrated by the 5-yr OS and 5-yr DFS (Table 1, Fig 2, and Fig 3). Compared to the colon cancer patients, the rectal cancer patients had a higher 5-year local recurrence rate: 3.1% in colon cancer and 8.3% in rectal cancer, respectively. The overall distant recurrence rate of both the colon and rectal cancer patients in this study was approximately 24%; 20% in colon cancer patients and 28.6% in rectal cancer patients. The liver was the most common distant recurrence site in colon cancer, while the lung was the most common distant recurrence site in rectal cancer (Table 2).

Factors related to distant recurrences
On multivariate analysis, the independent predictors of distant recurrence in rectal cancer patients were preoperative CEA > 5 ng/mL, (HR=1.701; 95% CI, 1.069-2.706; P = 0.025), N2 stage (HR=2.837; 95% CI, 1.779-4.524; P < 0.001), presence of tumor deposit (HR=3.567; 95% CI, 1.539-8.271; P = 0.003), positive circumferential margin (HR=2.117; 95% CI, 1.226-3.657; P= 0.007), and tumor located below peritoneal reflection (HR=2.279; 95% CI, 1.239-4.192; P=0.008). Howerever, preoperative CEA > 5 ng/mL, (HR=2.363; 95% CI, 1.399-3.989; P = 0.001) and pathological N2 staging (HR = 4.254 ; 95% CI, 2.228-8.123; p < 0.001) were related to distant recurrence in colon cancer patients.
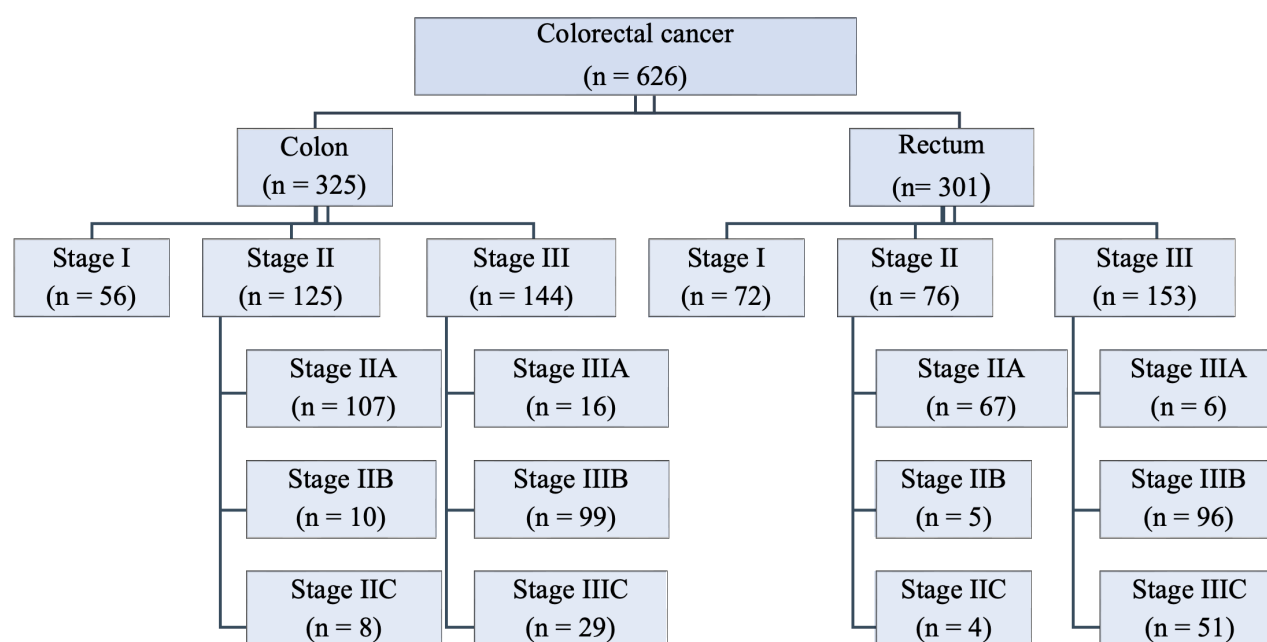

Fig 1. Pathological staging of the study cohort.

TABLE 1. Kaplan–Meier estimated 5-year overall survival and 5-year disease-free survival in stage I–III colon and rectal cancer patients.

Stage	Colon and rectal cancer		Colon cancer		Rectal cancer	
	5-yr OS	5-yr DFS	5-yr OS	5-yr DFS	5-yr OS	5-yr DFS
Stages I–III	70.9%	70.4%	76.3%	76.5%	65.1%	63.8%
Stage I	89.1%	85.9%	94.6%	91.4%	84.7%	81.5%
Stage II	78.6%	79.0%	80.8%	81.3%	75.0%	75.1%
Stage IIA	81.6%	78.6%	83.2%	80.6%	79.1%	75.7%
Stage IIB	66.7%	84.4%	70.0%	88.9%	60.0%	80.0%
Stage IIC	50.0%	80.0%	62.5%	83.3%	25.0%	75.0%
Stage III	57.9%	57.8%	65.3%	66.4%	51.0%	50.1%
Stage IIIA	72.7%	79.8%	81.3%	86.7%	50.0%	55.6%
Stage IIIB	65.1%	63.1%	71.7%	71.4%	58.3%	55.1%
Stage IIIC	36.3%	37.7%	34.5%	33.4%	37.3%	39.6%

Abbreviations: *5-yr OS = 5-year overall survival; 5-yr DFS = 5-year disease free survival.*
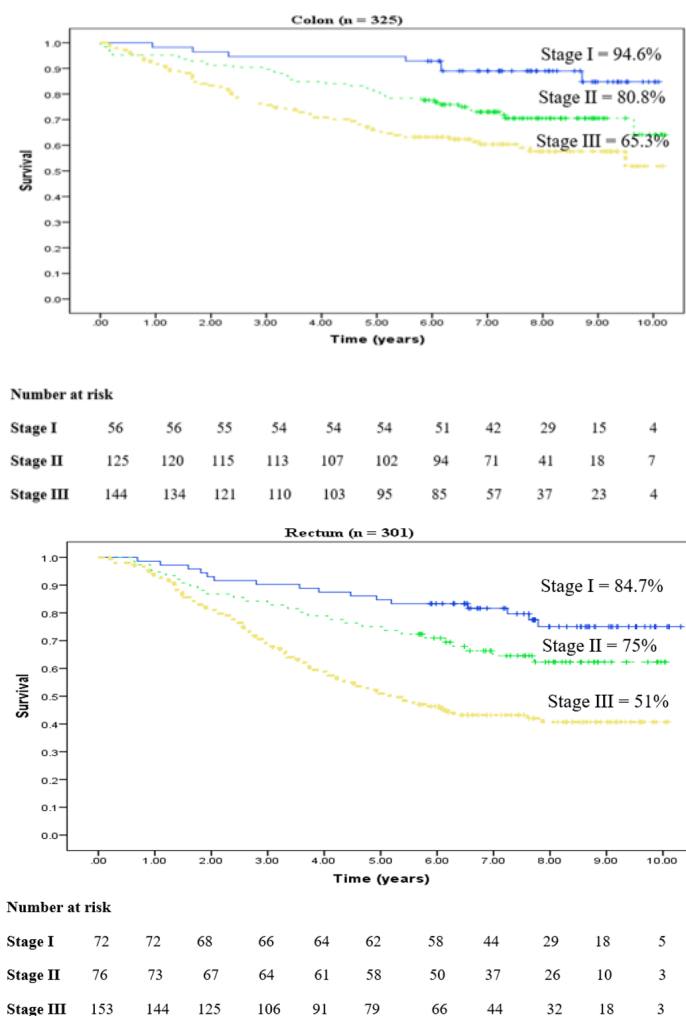
Fig 2. Five-year overall survival in stage I-III colon and rectal cancer patients.
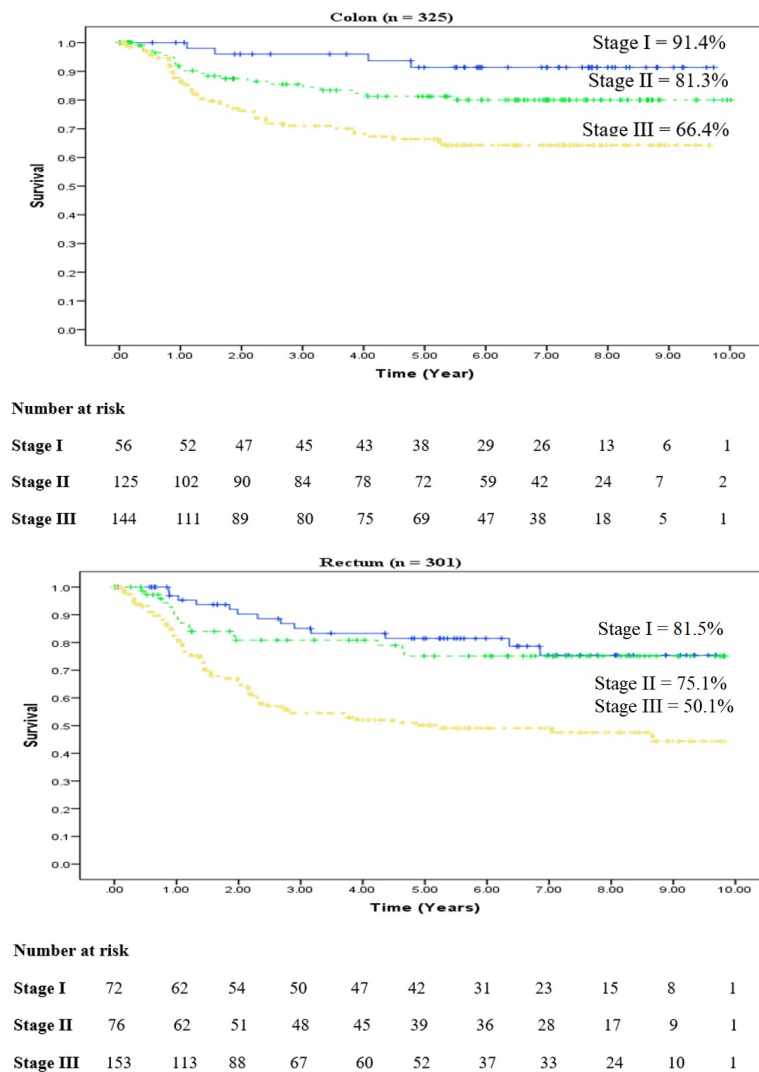
Fig 3. Five-year disease-free survival in stage I-III colon and rectal cancer patients

TABLE 2. Sites of distant recurrence in stage I–III colon and rectal cancer patients.

	Colon cancer (n = 325)	Rectal cancer (n = 301)
Local	10 (3.1%)	25 (8.3%)
Distant	65 (20%)	86 (28.6%)
Liver	39 (12%)	32 (10.6%)
Lung	24 (7.4%)	47 (15.6%)
Peritoneal	8 (2.5%)	12 (3.9%)
Bone	8 (2.5%)	16 (5.3%)
Brain	4 (1.2%)	3 (1%)
Supraclavicular lymph node	3 (0.9%)	0 (0%)
Para-aortic lymph node	6 (1.8%)	3 (1%)

DISCUSSION

In our study, the age incidence of colorectal cancer was between the fifth and seventh decades of life. The incidence was higher in males than females. These patient characteristics were comparable to the previous studies reported in Western countries.[2-7] Regarding the locations of the tumors, approximately half of the patients were diagnosed with rectal cancer, which was a relatively high proportion. For the colon cancers, most were in the left-sided colon and located distal to the splenic flexure. We also noticed that most tumors were locally advanced stage. The incidence of acute obstruction was 6.5%, which was similar to previous reports. The postulated reasons to explain these results were: 1) most rectal cancer patients who needed multimodalities treatment were referred to our hospital, which is a tertiary university hospital, and 2) most patients presented with symptoms and signs of colorectal cancer rather than asymptomatic ones. This might reflect the low participation rate in colorectal

cancer screening programs and poor patient education on colorectal cancer in our country.

Concerning the treatment modalities, surgery was the primary treatment for both colon and rectal cancer. Most patients were operated with the open technique, because the long-term oncologic outcomes of minimally invasive surgery in colon cancer were just reported as an acceptable treatment and comparable to the open surgical technique during the study period. Meanwhile, minimally invasive surgery for rectal cancer was still debatable during that time. The abdominoperineal resection rate in rectal cancer in this study was 29.5%, which is acceptable for a standard colorectal cancer surgery center.[8-12] In colon cancer, postoperative adjuvant chemotherapy was given if the stage of disease was pathological stage III or high-risk pathological stage II, i.e., obstruction, perforation, poorly differentiated histology, positive lymphovascular or perineural invasion, and if the total lymph nodes harvested was less than 12 nodes. Postoperative adjuvant concurrent chemoradiation was given in most pathological stage II and stage III rectal cancer patients, while less than 10 % of rectal cancer patients in this study received preoperative neoadjuvant concurrent chemoradiation. This could be explained by the long waiting list for radiation therapy in our hospital. However, the setting up of a multidisciplinary team in our hospital among surgeons, radiation oncologists, and medical oncologists in colorectal cancer management has now resolved this problem. Previous reports have emphasized the significance of a multidisciplinary team in colorectal cancer.[13-15]

The patients in this cohort seemed to have multiple co-morbidities and a high rate of ICU admission because our hospital is a tertiary referral university hospital as previously mentioned. Nonetheless, the mortality rate and readmission rate were acceptable and quite low, as were other short-term outcomes, including medical-related complications, wound complications, and other surgical-related complications. Although approximately 15% of the rectal cancer patients who underwent low anterior resection had protective diversion of the stoma proximal to the anastomosis selectively performed, the anastomotic leakage rate was acceptable, as was the anastomotic leakage rate in colon cancer surgery. These promising short-term outcomes might result from the experience and colorectal surgery sub-specialty of the surgeons who mostly performed the operations in this study. Previous publications have underscored the association between the surgeon factor and the outcomes of colorectal cancer surgery.[16-21]

Focusing on the long-term oncologic outcomes,

the pathological stage of the disease has a major impact on the 5-year survival rate. Appropriate multimodalities curative treatment in non-metastasis cases results in a good prognosis. With a median follow-up time of 5.4 years in this study, the 5-yr OS and 5-yr DFS in stage I–III both in colon and rectal cancer were 70.9% and 70.4%, respectively, which were comparable to a previous report from Thailand by Techawathanawanna et al. They reported the 5-year OS in stage I–III colorectal cancers was 83% overall and the 5-yr DFS was 72% overall. The 5-year DFS in the specific stages I–III was 90%, 85%, and 58%; while the 5-year OS in the specific stages I–III was 93%, 93%, and 73%.[22] Meanwhile, a study from another Asian country, namely one in China by Yuan et al., reported 3-year and 5-year overall survival rates of 74% and 68% respectively.[23] When looking into the long-term oncologic outcomes stage by stage, either in colon or rectal cancer, the results from our study were comparable to the results reported from Western countries; for instance, the report by O'Connell et al. in 2004. They reported 5-year cancer-specific survival rates in 119,363 colon cancer patients in sub-stages as 93.2% for stage I, 84.7% for stage II A, 72.2% for stage II B, 83.4% for stage III A, 64.1% for stage III B, and 44.3% for stage III C.[24]

Comparing stage by stage, rectal cancer had a worse prognosis than colon cancer. Local recurrence of colon and rectal cancer in our study was also acceptable and comparable to in other recent publications. Authors from the Cleveland Clinic Foundation described 5-year overall local recurrence rates in colon cancer as 5.1%; 2.2%, 5.3%, and 7.7 for stages I, II, and III respectively.[25] As reported in other studies, distant recurrence in our study was still high, particularly in locally advanced stages.[26] These reflect the current clinical practice that stage III patients receive chemotherapy, whereas stage II patients do not. To improve long-term survival and decrease distant recurrence, we should reconsider the paradigm of management in locally advanced colorectal cancer. These strategies might include: 1) postoperative adjuvant chemotherapy in high-risk patients beyond current indications directed by tissue marker, 2) preoperative neoadjuvant chemotherapy as demonstrated by preliminary studies of the FOxTROT trial in locally advanced colon cancer[27], and 3) total neoadjuvant therapy in locally advanced rectal cancer, either with induction or consolidation chemotherapy, as demonstrated by the PROSPECT trial (induction chemotherapy before a long course of concurrent chemoradiation), the Time testing trial (consolidation therapy after a long course of concurrent chemoradiation)[28;29], and the RAPIDO

trial (short-course radiation followed by consolidation chemotherapy).[30]

From our multivariate analysis, we could identify the colorectal cancer patients with high risk of distant recurrence who might have benefit if the new paradigm of preoperative treatment is given. Therefore, preoperative neoadjuvant chemotherapy should be considered particularly in colon cancer patients with high preoperative CEA or clinically multiple enlarged lymph nodes (more than 3 lymph nodes). Meanwhile, rectal cancer patients with high preoperative CEA level, N2 stage, presence of tumor deposit, threaten circumferential margin, and tumor located below the peritoneal reflection might have benefit from receiving preoperative total neoadjuvant therapy.

Our study had some limitations to note. First, it was a retrospective study design. Another was that some patients' data were missing because they were referred to receive postoperative adjuvant therapy and surveillance at their primary care hospital. This suggests we require a national colorectal cancer registry database to answer more complicated questions and should set up a guideline for the management of Thai colorectal cancer patients.

CONCLUSION

The long-term oncologic outcomes after the curative treatments in this study were acceptable and comparable to previous publications. The prognosis of treatment depends on the disease stage. Comparing stage by stage, colon cancer has a better prognosis than rectal cancer. The new paradigm such as preoperative neoadjuvant chemotherapy in colon cancer patients or total neoadjuvant therapy in rectal cancer patients should be considered in patients with high risk of distant recurrence.

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