ORIGINAL ARTICLE

Survival Outcomes and Prognostic Factors in Patients with Colorectal Adenocarcinoma after Curative Surgery: A Single-Surgeon Experience at Rayong Hospital, Thailand

Supoj Laiwattanapaisal, MD[1]

[1] Department of General Surgery, Rayong Hospital, Rayong, Thailand

Objective: To evaluate overall survival (OS) and disease-free survival (DFS) in patients with colorectal adenocarcinoma (COAD) undergoing curative surgery and to identify independent prognostic factors.

Materials and Methods: The present study was a retrospective cohort study that included 221 patients with COAD who underwent curative resection by the same surgeon at Rayong Hospital, Thailand, between January 2012 and December 2021. Their demographic, clinical, and pathological characteristics were analyzed. Survival was examined using Kaplan-Meier analysis, and independent prognostic factors were identified using multivariate Cox regression.

Results: Among the patients studied, the mean follow-up duration was 66.6 months. The 5-year OS rate was 81.2%, and the 5-year DFS rate was 76.6%. By stage, the 5-year OS rate was 97.4% for patients in stage I, 91.4% for those in stage II, 65.9% for those in stage III, and 76.2% for those in stage IV. Multivariable analysis identified female (hazard ratio [HR] 2.39, 95% confidence interval [CI] 1.27 to 4.50, p=0.007), body mass index (BMI) of 25 kg/m^2 or more (HR 2.42, 95% CI 1.31 to 4.47, p=0.005), preoperative carcinoembryonic antigen (CEA) level of 5 ng/mL or more (HR 1.82, 95% CI 1.00 to 3.32, p=0.050), lymph node involvement (N1: HR 3.65, 95% CI 1.74 to 7.66, p=0.001; N2: HR 4.87, 95% CI 2.16 to 10.94, p<0.001), and having four high-risk pathological features (HR 79.7, 95% CI 7.62 to 833.57, p<0.001) as significantly associated with worse DFS.

Conclusion: Female, high BMI, nodal involvement, elevated preoperative CEA level, and multiple high-risk pathological features independently predict worse survival outcomes in patients with COAD. Therefore, these factors should be used to guide individualized follow-up and adjuvant therapy decisions.

Keywords: Colorectal cancer; Overall survival; Disease-free survival; Prognostic factors; Curative surgery

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Colorectal cancer (CRC) is one of the most commonly diagnosed malignancies worldwide. Globally, its age-standardized incidence rate (ASIR) is approximately 19.5 per 100,000 population, and its age-standardized mortality rate (ASMR) is 9 per 100,000 population[1]. The ASIR and ASMR for CRC exhibit regional variations. For example, the ASIR is 17.6 per 100,000 population and the ASMR is 8.6 per 100,000 population in Asia, while the ASIR is 14.8 per 100,000 population and the ASMR is 7.9 per 100,000 population in Southeast Asia[1,2]. In Thailand, the ASIR is 16.9 per 100,000 population and the ASMR is 8.4 per 100,000 population[1].

Studies in Thailand have reported stage-specific survival outcomes for CRC. One study noted a 5-year overall survival (OS) rate of 44.1% across all stages, but OS rates of 80%, 68%, 45%, and 11% for stages I to IV, respectively[3]. Another study reported a higher OS rate of 52.7%[4], and a third study reported an OS rate of 38.6%[5]. More favorable survival outcomes have been observed in studies focusing on stages I-III, with reported 5-year OS rates ranging from 65% to 83%[6-9]. These studies highlight variability in survival among patients with CRC, emphasizing the need to identify prognostic factors influencing outcomes in different populations.

Known prognostic factors for worse survival in CRC include male, older age (65 years or older), advanced tumor stage at T3/T4, N1/N2, poor histological differentiation, and higher American Society of Anesthesiologists (ASA)

Correspondence to:

Laiwattanapaisal S.
Department of General Surgery, Rayong Hospital, Rayong 21000, Thailand.
Phone: +66-95-5467033
Email: Supoj_Laiwattana@yahoo.co.th

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classification[3-9]. Recognizing these factors is crucial for tailoring treatment and follow-up strategies. Therefore, the present study aimed to evaluate survival outcomes and identify prognostic factors in patients with stage I to IV colorectal adenocarcinoma (COAD), the most common type of CRC, undergoing curative resection. To minimize variability in surgical techniques, all operations were performed by the same experienced surgeon at a single hospital.

Materials and Methods

The present study was a retrospective cohort study conducted at Rayong Hospital in Thailand. It received approval from the Human Research Ethics Committee at Rayong Hospital (approval number: E003/2567). Eligible patients were identified by reviewing the medical records of patients diagnosed with CRC between January 1, 2012, and December 31, 2021. Of the 494 identified patients, 221 with COAD who underwent R0 resection by the same colorectal surgeon were included in the study. The inclusion criteria were patients who underwent intended curative surgery with simultaneous metastasis resection. The exclusion criteria were patients 1) with synchronous or a history of other primary cancers or who developed other primary cancers during the study period, 2) with a histology other than COAD, 3) with stage IV COAD with more metastases at more than one site, 4) with hereditary CRC syndrome, such as Lynch syndrome and familial adenomatous polyposis, or 5) who received neoadjuvant chemoradiotherapy.

Patients who were alive at the present study end but lost to follow-up were censored. The collected data included demographics such as age, gender, and body mass index (BMI), clinical parameters such as ASA classification and preoperative carcinoembryonic antigen (CEA) levels, pathological features such as tumor histology, TNM staging, and the high-risk features as stage T4, perforation, obstruction, positive margin, poorly differentiated adenocarcinoma, lymphovascular invasion, perineural invasion, and less than 12 lymph nodes harvested, treatment modalities such as surgery, chemotherapy, and radiation, and outcomes such as recurrence date, recurrence site, and survival status. The primary objectives were to determine the OS and disease-free survival (DFS) rates, the prognostic impact of high-risk features, and the influence of treatment modalities on survival outcomes.

Statistical analysis

All analyses were conducted using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). All statistical tests were two-sided, and a p-value less than 0.05 was considered statistically significant. Continuous variables are summarized as the mean ± standard deviation (SD) or median (range), as appropriate, and were compared between groups using the independent samples t-test or Mann-Whitney U test, as appropriate. Categorical variables were summarized as the frequency (percentage) and were compared between groups using the chi-square test. Survival analyses were performed using the Kaplan-Meier method to estimate OS and DFS, with subgroup comparisons performed using the log-rank test. Univariate analyses were conducted using Cox proportional hazards regression or the log-rank test to evaluate potential prognostic factors. Variables with p-value of less than 0.05 in the univariate analyses were included in the multivariable Cox regression model using forward stepwise selection.

Results

Patients' clinical characteristics

Four hundred ninety-four patients were diagnosed with CRC in the Department of Colorectal Surgery at Rayong Hospital between January 1, 2012, and December 31, 2021. Of these, 221 were diagnosed with COAD and underwent curative resection (R0) by the same surgeon, with a mean follow-up of 66.63 months. Of the 221 patients, 100 had colon tumors and 121 had rectal tumors (Figure 1). The demographic and clinical characteristics of 221 patients are shown by tumor location in Table 1. Demographically, the cohort comprised 119 males (53.8%) and 102 females (46.2%) with a mean age of 59.55 years, a mean weight of 58.54 kg, and a mean BMI of 22.89 kg/m². Most patients had a BMI under 25 kg/m² with an overall at 71.0%, colon at 78.4%, and rectal at 67.2%. Clinically, most patients were classified as ASA II, with an overall at 45.2%, colon at 48.0%, and rectal at 43.3%, or ASA III with an overall at 44.3%, colon at 38.0%, and rectal at 50.0%. The mean CEA levels were 19.62±52.40 ng/mL among those with colon tumors and 22.32±71.41 ng/mL among those with rectal tumors. The mean length of hospital stay was 14.78 days. Overall, 19 patients (19.0%) with colon tumors and 21 patients (17.7%) with rectal tumors were lost to follow-up. The demographic and clinical characteristics did not differ significantly between patients with colon and

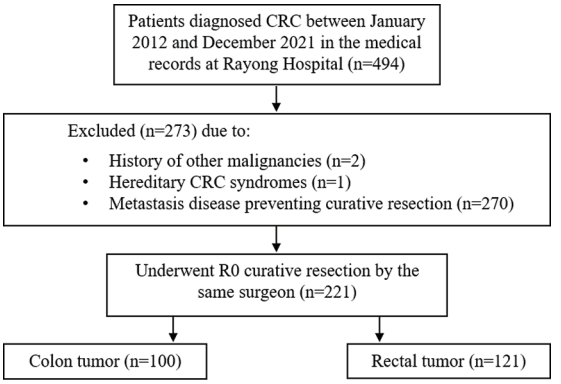

Figure 1. Flow diagram of patient selection.

Table 1. Patients' demographic and clinical characteristics by tumor location

Variable	Colon (n=100)	Rectal (n=121)	p-value
Sex; n (%)			0.189
Male	49 (49.0)	70 (57.9)	
Female	51 (51.0)	51 (42.1)	
Age (years); mean±SD	57.86±13.21	60.95±11.88	0.069
Age group; n (%)			0.348
≤60 years	60 (60.0)	65 (53.7)	
>60 years	40 (40.0)	56 (46.3)	
Weight (kg); mean±SD	56.60±10.41	60.14±12.00	0.045
BMI (kg/m^2); n (%)	(n=98)	(n=119)	0.063
≤25	77 (78.6)	80 (67.2)	
>25	21 (21.4)	39 (32.8)	
ASA classification; n (%)	(n=100)	(n=120)	0.174
I	9 (9.0)	5 (4.2)	
II	48 (48.0)	52 (43.3)	
III	38 (38.0)	60 (50.0)	
IV	5 (5.0)	3 (2.5)	
Preoperative CEA (ng/mL); mean±SD	(n=79) 22.32±71.41	(n=99) 19.62±52.40	0.674
≤5 ng/mL; n (%)	27 (34.2)	43 (43.4)	0.209
>5 ng/mL; n (%)	52 (65.8)	56 (56.6)	
Length of hospital stay (days); mean±SD	(n=95) 14.15±4.86	(n=117) 15.29±7.74	0.212
Loss of follow-up; n (%)	19 (19.0)	21 (17.7)	0.723

ASA=American Society of Anesthesiologists; BMI=body mass index; CEA=carcinoembryonic antigen; SD=standard deviation

* Significance, p<0.05

rectal tumors (Table 1).

Tumor characteristics

Histopathologic grading indicated that most tumors were moderately differentiated among the patients with colon at 74.5% and rectal at 72.7% tumors, with well-differentiated tumors accounting for 25.5% of the patients with colon and 25.6%rectal tumors. High-risk tumor features were present in about half of patients with colon tumors (45.6%) and rectal tumors (54.4%), while no-risk features were present in about one-third of patients (33.5%). Tumor obstruction was more common among patients with colon tumors at 41.0%, than with rectal tumors at 14.9%, whereas lymphovascular invasion was more common in patients with rectal tumors at 54.5%, than with colon tumors at 40.0%. Regarding high-risk features, almost half of patients with colon tumors (51.0%) and rectal tumors (52.1%) had fewer than two, not differing significantly by site (p=0.831). Regarding cancer staging, most patients were classified as TNM stages I, IIa, and IIIb had colon tumors at 22.0%, 33.0%, and 29.0% and rectal tumors at 14.9%, 27.3%, and 28.1%, respectively. Tumors were classified as T3 in 71.0% for colon tumors and 66.1% for rectal tumors. Regarding lymph node involvement, over half of the patients were stage N0, with 59.0% in the case of colon tumors and 54.5% in the case of rectal tumors. Additionally, nearly half of the patients had inadequate lymph nodes for colon at 44.9% and rectal at 55.1%. Regarding metastasis, the liver and ovaries were the most commonly affected organs, with a potential for R0 resection.

Surgical outcomes and recurrence patterns

The most common surgeries were right hemicolectomy, at 39.0%, and sigmoidectomy, at 29.0%, among the patients with colon tumors, and low anterior resection, at 47.9%, among the patients with rectal tumors. A permanent colostomy was required in almost half of the patients with rectal tumors at 51.9% and using Hartmann's procedure in 24.7% and the abdominoperineal resection in 27.2%. Intraoperative blood loss was significantly greater among the patients with rectal tumors, with a mean of 380 cc, than among those with colon tumors, with a mean of 231.91 cc (p<0.001). Postoperative complications included anastomotic leakage for the colon patients at 7.7% and for the rectal patients at 26.7%, wound infections for the colon patients at 46.2% and for the rectal patients at 40.0%, wound dehiscence for the colon patients at 7.7% and for the rectal patients at 20.0%, duodenal perforation for the colon patients at 7.7%, and spleen injury for the colon patients at 7.7%. The primary cause of death was CRC at 14% for the colon patients and 17.4% for the rectum patients. Recurrence occurred in 55 patients (24.9%), with recurrence more common among those with rectal tumors at 61.8% than colon

Table 2. Treatment of COAD by pathological stage and tumor location

Treatment type	Stage I; n (%)		Stage II; n (%)		Stage III; n (%)		Stage IV; n (%)		Total (n=207) n (%)	p-value
	Colon tumor (n=19)	Rectal tumor (n=14)	Colon tumor (n=33)	Rectal tumor (n=41)	Colon tumor (n=33)	Rectal tumor (n=56)	Colon tumor (n=5)	Rectal tumor (n=6)		
Chemotherapy										0.878
Rejected	1 (5.3)	1 (7.1)	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.4)	
UFUR	1 (5.3)	1 (7.1)	3 (9.1)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.9)	
Capecitabine	0 (0.0)	2 (14.3)	3 (9.1)	1 (2.4)	0 (0.0)	1 (1.8)	0 (0.0)	1 (16.7)	8 (3.9)	
5-FU/LV	2 (10.5)	4 (28.6)	5 (15.2)	8 (19.5)	6 (18.2)	7 (12.5)	0 (0.0)	0 (0.0)	32 (15.5)	
Xelox	0 (0.0)	0 (0.0)	2 (6.1)	2 (4.9)	3 (9.1)	3 (5.4)	0 (0.0)	0 (0.0)	10 (4.8)	
FOLFOX4	14 (73.7)	6 (42.9)	20 (60.6)	29 (70.7)	23 (69.7)	42 (75)	3 (60)	4 (66.7)	141 (68.1)	
mFOLFOX6	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.4)	2 (40.0)	1 (16.7)	7 (3.4)	
Radiation										
Yes	1 (4.5)	1 (5.6)	0 (0.0)	7 (17.1)	0 (0.0)	15 (26.8)	0 (0.0)	2 (33.3)	26 (11.8)	
No	21 (95.5)	17 (94.4)	37 (100)	34 (82.9)	36 (100)	41 (73.2)	5 (100)	4 (66.7)	195 (88.2)	

UFUR=tegafur + uracil; 5-FU=5-fluorouracil; LV=leucovorin; FOLFOX4=5-FU + LV infusion + oxaliplatin; XELOX=capecitabine + oxaliplatin; mFOLFOX6=modified 5-FU + LV infusion + oxaliplatin

* Significance, $p<0.05$

tumors at 38.2%. By stage, recurrence occurred in 1.8% patients in stage I, 25.5% of patients in stage II, 67.3% of patients in stage III, and 5.5% of patients in stage IV. The most common recurrence sites were the liver and lung among patients with colon tumors, at 28.6%, and the lung among patients with rectal tumors, at 23.5%. In summary, liver metastasis was more common in patients with colon tumors, while lung metastasis was most common in patients with rectal tumors.

Adjuvant treatment

The treatments administered to the 221 patients are shown by tumor stage and location in Table 2. Of the 221 patients, 204 (92.3%) received chemotherapy, while three (1.4%) declined treatment, and treatment data were missing for 14 (6.3%). The most common regimen was FOLFOX4 (5-fluorouracil [5-FU], leucovorin [LV], and oxaliplatin) in 69.1%, followed by 5-FU/LV in 15.7%. Chemotherapy was administered to patients in stages I, thus, 14.9%, II, and III with high-risk features. Regimen choice did not differ significantly between patients with colon and rectal tumors (p=0.878). Radiation therapy was administered to 11.8% of patients with rectal tumors and 4.5% of patients with colon tumors. Importantly, no treatment-related mortality was observed. In cases with recurrence, the most used regimens were capecitabine in 30.8%, and Xelox (capecitabine/oxaliplatin) in 25.6%, with no significant differences between patients with colon and rectal tumors (p=0.428).

Survival outcomes

At the present study's conclusion, 178 of the 221 patients were alive (80.5%), 43 had died (19.5%), and 40 were lost to follow-up (18.1%). The 5-year OS rate was 81.2% across all stages, stages I to IV, 97.4% for stage I, 91.4% for stage II, 65.9% for stage III, and 76.2% for stage IV. The corresponding 5-year DFS rate was 76.6% across all stages, stages I to IV, 96.7% for stage I, 84.6% for stage II, 62.4% for stage III, and 59.7% for stage IV. Interestingly, patients in stage IV who underwent R0 resection had better 5-year OS and DFS than those in stage III (Figure 2-5). Regarding tumor location, the 5-year OS was 82.8% for patients with colon tumors and 79.9% for patients with rectal tumors (p=0.645, log-rank). Similarly, the 5-year DFS was 79.2% for patients with colon tumors and 77.1% for patients with rectal tumors (p=0.469, log-rank). The median follow-up time was 72 months (95% confidence interval [CI] 64.2 to 79.7). Median survival time was not reached, as fewer than 50% of the patients had died by the study's end.

Univariate analyses

As shown in Table 3, the DFS rates were 88.9% at 3 years, 76.6% at 5 years, 70.1% at 7 years, and 68.0% at 10 years, and the OS rates were 90.6% at 3 years, 81.2% at 5 years, 79.4% at 7 years, and 72.4% at 10 years. Univariate analyses revealed that OS was significantly associated with preoperative CEA level (p=0.044), number of high-risk features (p=0.032), T stage (p=0.014), N stage (p<0.001), and TNM stage (p<0.001). Similarly, univariate analyses

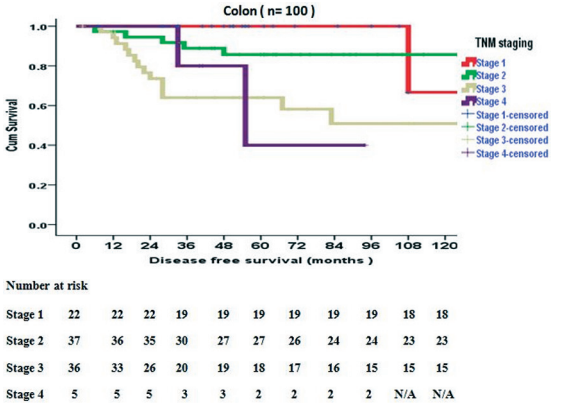

Figure 2. DFS of patients with stage I-IV colon tumors.

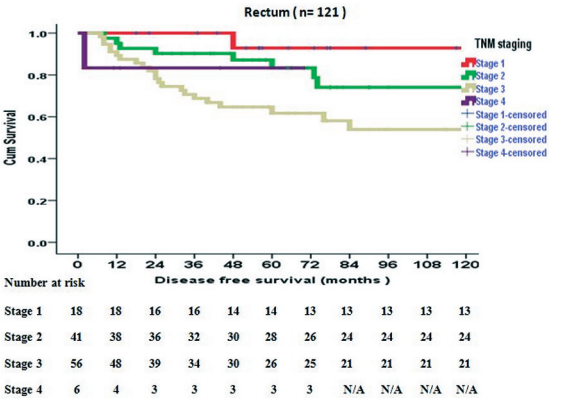

Figure 3. DFS of patients with stage I-IV rectal tumors.

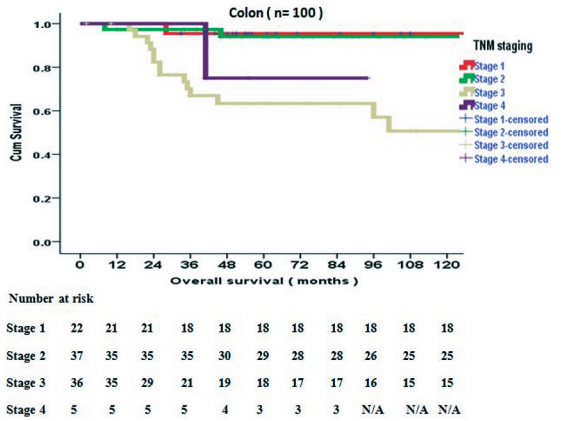

Figure 4. OS of patients with stage I-IV colon tumors.

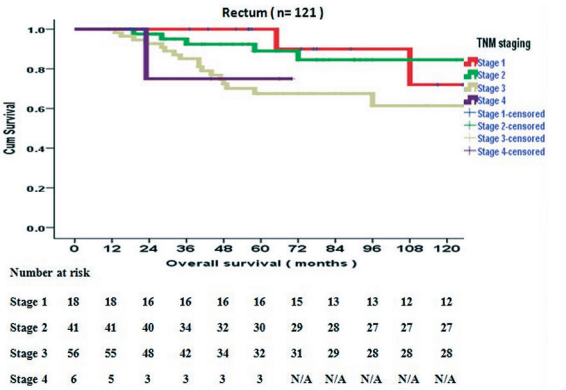

Figure 5. OS of patients with stage I-IV rectal tumors.

revealed that DFS was significantly associated with preoperative CEA level (p=0.009), number of high-risk features (p<0.001), T stage (p=0.002), N stage (p<0.001), and TNM stage (p<0.001).

Multivariate Cox proportional hazard regression analysis

The variables identified as significantly associated with worse DFS in patients with COAD were shown in Table 4. Worse DFS was significantly associated with female (adjusted hazard ratio [HR] 2.39, 95% CI 1.27 to 4.50, p=0.007), BMI greater than 25 kg/m² (adjusted HR 2.42, 95% CI 1.31 to 4.47, p=0.005), lymph node involvement (N1: adjusted HR 3.65, 95% CI 1.74 to 7.66, p=0.001; N2: adjusted HR 4.87, 95% CI 2.16 to 10.94, p<0.001), and having four high-risk features (adjusted HR 79.69, 95% CI 7.62 to 833.57, p<0.001), while worse DFS was marginally associated with a CEA level of 5 ng/mL or greater (adjusted HR 1.82, 95% CI 0.999 to 3.32, p=0.050).

To evaluate the potential impact of loss to follow-up on the survival estimates, the author conducted sensitivity analyses assuming best-case and worst-case scenarios. The results were consistent with the main findings. Additional sensitivity analysis was conducted by regrouping patients by their number of high-risk features into three categories, 0 to 1, 2 to 3, and 4. The number of high-risk features exhibited a strong overall association with DFS (p=0.003), where patients with four high-risk features had a significantly increased risk of death compared to those with no high-risk features (HR 28.73, 95% CI 3.58 to 230.56, p=0.002), but no those with 2 to 3 high-risk features (p=0.129). When patients with stage IV COAD were excluded, preoperative CEA level and nodal stage were no longer independent predictors of DFS in the multivariate analysis.

The variables identified as significantly associated with worse OS in patients with COAD are shown in Table 5. Worse OS was significantly associated with BMI of 25 kg/m² or greater (adjusted HR 2.51, 95% CI 1.22 to 5.15, p=0.012), lymph node

Table 3. The 3-, 5-, 7-, and 10-year survival rates by patients' demographic and clinical characteristics and their prognostic significance according to the Kaplan-Meier method

Variable	3-year survival rate (%)	5-year survival rate (%)	7-year survival rate (%)	10-year survival rate (%)	p-value (log-rank)
Sex					0.426
Male	86.2	82.5	81.0	74.5	
Female	83.3	79.5	77.6	70.1	
Age (years)					0.344
≤60	88.0	83.8	82.3	76.1	
>60	87.1	78.0	76.0	67.8	
BMI (kg/m^2)					0.068
<25	91.8	86.1	84.9	75.1	
≥25	81.4	73.1	70.3	70.3	
ASA classification					0.521
I	92.3	83.1	83.1	60.9	
II	90.6	82.3	80.6	77.5	
III	84.9	78.8	76.5	71.0	
IV	100	100	100	N/A	
Preoperative CEA (ng/mL)					0.044
<5	89.3	83.8	80.8	80.8	
≥5	81.9	72.1	72.1	57.2	
Histopathologic grade					0.778
Well differentiated	92.6	84.9	80.3	74.4	
Moderately differentiated	87.0	80.1	80.1	70.8	
Poorly differentiated	N/A	N/A	N/A	N/A	
High-risk features					0.139
Present	86.9	80.0	78.8	73.5	
Absent	90.4	83.3	80.8	75.5	
Number of high-risk features					0.032
0	94.2	87.9	87.9	87.9	
1	89.6	81.3	81.3	72.1	
2	86.5	79.1	74.1	69.2	
3	81.9	81.9	81.9	61.4	
4	0	0	0	0	
T stage					0.014
T1	100	100	100	N/A	
T2	97.7	97.7	92.2	80.7	
T3	86.7	77.5	77.5	72.7	
T4	76.1	71.0	62.1	41.4	
N stage					0.001
N0	94.9	92.4	89.3	85.5	
N1 (1 to 3 nodes)	79.0	64.8	64.8	47.1	
N2 (≥4 nodes)	75.0	67.8	67.8	67.8	
TNM staging					0.001
Stage 1	97.4	97.4	91.6	80.2	
Stage 2	94.7	91.4	88.9	88.9	
Stage 3	78.1	65.9	65.9	56.3	
Stage 4	88.9	76.2	76.2	N/A	
DFS rate	88.9	76.6	70.1	68.0	
OS rate	90.6	81.2	79.4	72.4	

ASA=American Society of Anesthesiologists; BMI=body mass index; CEA=carcinoembryonic antigen; DFS=disease-free survival; OS=overall survival; N/A=not applicable

* Significance, $p<0.05$

Table 4. Multivariate Cox's proportional hazard model for the most important independent predictors of DFS in patients with COAD

Variable	Adjusted HR	95% CI	p-value
Sex			
Male	Reference		
Female	2.393	1.274 to 4.495	0.007
BMI (kg/m^2)			
<25	Reference		
≥25	2.417	1.308 to 4.469	0.005
CEA level (ng/mL)			
<5	Reference		
≥5	1.820	0.999 to 3.317	0.050
N stage			
N0	Reference		
N1 (1 to 3 nodes)	3.646	1.736 to 7.659	0.001
N2 (≥4 nodes)	4.865	2.163 to 10.939	<0.001
Number of high-risk features			
0	Reference		
1	1.206	0.427 to 3.412	0.724
2	1.174	0.409 to 3.368	0.765
3	1.187	0.330 to 4.272	0.793
4	79.691	7.619 to 833.572	<0.001

BMI=body mass index; CEA=carcinoembryonic antigen; CI=confidence interval; HR=hazard ratio
Significance, p<0.05

Table 5. Multivariate Cox's proportional hazard model for the most important independent predictors of OS in patients with COAD

Variable	Adjusted HR	95% CI	p-value
N stage			
N0	Reference		
N1 (1 to 3 nodes)	4.98	2.04 to 12.20	0.001
N2 (≥4 nodes)	5.37	1.98 to 14.52	0.001
Number of high-risk features			
0	Reference		
1	0.73	0.22 to 2.40	0.608
2	0.85	0.26 to 2.76	0.792
3	0.78	0.17 to 3.67	0.753
4	26.69	2.75 to 259.07	0.005
BMI (kg/m^2)			
≤25	Reference		
>25	2.51	1.22 to 5.15	0.012

BMI=body mass index; CI=confidence interval; HR=hazard ratio
* Significance, p<0.05

involvement (N1: adjusted HR 4.98, 95% CI 2.04 to 12.20, p<0.001; N2: adjusted HR 5.37, 95% CI 1.98 to 14.50, p=0.001), and having four high-risk pathological features (adjusted HR 26.69, 95% CI 2.75 to 259.07, p=0.005).

Table 6. Comparison of the 5-year OS and DFS rates in patients with CRC after curative surgery by stage between the present study and previous studies

Stage	5-year OS (%)		5-year DFS (%)	
	Previous studies[3,4,6,9,13-21]	Present study	Previous studies[7-9,19-21]	Present study
I	80 to 94	97.4	85 to 90	96.7
II	68 to 90	91.4	75 to 85	84.6
III	43 to 72	65.9	57 to 58	62.4
IV	41 to 65.5	76.2	25 to 37.9	59.7
I-IV		81.2		76.6

DFS=disease-free survival; OS=overall survival

Additional sensitivity analysis was conducted by regrouping patients by their number of high-risk features into three categories: 0 to 1, 2 to 3, and 4 features. The number of high-risk features exhibited a significant overall association with OS (p=0.040), where patients with four high-risk features classified had a significantly increased risk of death compared to those with no high-risk features (HR 8.13, 95% CI 1.07 to 61.77, p=0.043). When patients with stage IV COAD were excluded, the findings emphasized the prognostic importance of obesity, the extent of lymph node involvement, and the cumulative burden of adverse pathological factors in early-stage COAD.

Discussion

This retrospective cohort study investigated the survival outcomes and prognostic factors in patients with COAD who underwent curative resection by the same surgeon over 10 years at Rayong Hospital, Thailand. As shown in Table 6, the present study findings revealed favorable 5-year OS and DFS rates of 81.2% and 76.6%, respectively, higher than those reported in national and regional studies. The present study included patients with stage IV COAD who underwent curative surgery. Fifty to sixty percent of patients diagnosed with CRC develop metastases, of whom 80% to 90% develop unresectable hepatic and extra-hepatic metastases[10-12].

The excellent survival outcomes in patients with stage I and II COAD in the present study, with 5-year OS rates of 97.4% and 91.4%, respectively, and DFS rates of 96.7% and 84.6%, respectively, are likely attributable to early detection, complete surgical resection with negative margins, and adherence to standardized oncologic principles. For patients with stage III CRC, the 5-year OS of 65.9% and DFS of 62.4% found in the present study were within the range of those reported in previous studies[3,4,6-9,13-21], suggesting effective implementation of adjuvant

chemotherapy and postoperative surveillance protocols in this cohort. Notably, for patients with stage IV CRC, the 5-year OS and DFS rates were higher in the present study at 76.2% and 59.7%, respectively, than those reported in most previous studies at 41% to 65.5% and 25% to 37.9%, respectively. Studies in Thailand and internationally have reported 5-year OS rates in patients with stage I-IV CRC of 38.6% to 63.5%[3-5,13,22,23].

Overall, the present study findings indicated that the survival outcomes of patients with COAD following curative resection at Rayong Hospital are comparable to international standards. The present study highlights the importance of surgical expertise, perioperative management, and appropriate adjuvant treatment in improving long-term outcomes for patients with CRC in regional healthcare settings. Notably, the patients with stage IV COAD demonstrated a surprisingly high 5-year OS rate, which may be attributed to careful patient selection and the fact that R0 resection, including metastasectomy, was achieved in all included patients with stage IV COAD. This finding aligns with studies suggesting that complete resection of metastatic disease can significantly prolong survival in selected patients[10-12,18-20].

Prognostic significance of pathological factors

However, improving survival rates depends on several prognostic factors. Firstly, tumor stage and grade, with high T- and N-stages strongly associated with poor 5-year OS rate in studies with T4 at 15% to 72.7% and N2 at 19% to 53.1%[5,6,9,15,16,24,25]. The present study showed that the 5-year OS rate for patients with T4 and N2 COAD tumors was 71.0% and 67.8%, respectively. Secondly, tumor differentiation plays a critical role, as poorly differentiated tumors were associated with significantly worse survival in many previous studies[5-7,15,16,24,25] and in the present study, although the number of patients included with poorly differentiated tumors was small, so the present results could not be interpreted. Thirdly, tumors with a higher number of high-risk features are associated with worse OS and DFS[26]. In the sensitivity analyses, the present study reclassified the number of high-risk features into three categories (0 to 1, 2 to 3, and 4) to explore a potential dose-response relationship. While the HRs for both DFS and OS increased progressively with the number of high-risk features, the associations were not statistically significant, suggesting a potential trend toward worse outcomes with accumulating pathological risk factors. However, the lack of statistical significance may be due to limited sample size, patients lost to follow-up, low event rate, or wide CIs. Therefore, the prognostic role of the number of high-risk factors should be interpreted cautiously and validated in larger, prospective studies with more complete data.

Impact of patient-related factors

Patient-related factors such as male[7], BMI greater than 25 kg/m^2[27,28], age 40 to 65 years[3-5,24,25,29], ASA classification of 3 or more[5], CEA level greater than 5 ng/mL[9,24,25], and healthcare coverage[4,30] are consistent predictors of recurrence and worse survival. The present study found that higher BMI of 25 kg/m^2 or greater ($p=0.005$) and female ($p=0.007$) were also independently associated with worse DFS. An elevated preoperative CEA level of 5 ng/mL or greater, a well-established biomarker, was also associated with worse survival outcomes in both the univariate ($p<0.044$) and multivariable ($p<0.05$) analyses, confirming its utility in risk stratification. Although older age (60 years or older) and higher ASA classification (stage III or greater) were associated with slightly worse survival outcomes in the univariate analyses, they did not remain significant in the multivariable analysis, suggesting that biological tumor behavior and pathological staging may outweigh comorbid status in predicting survival when curative resection is achieved.

Surgical and adjuvant treatment considerations

In the present study, the author performed curative resection (R0) by removing both the primary tumor and metastases simultaneously, as previous studies have found that incomplete resection (R1) leads to markedly lower cure rates[11,31]. Surgery was performed using an open technique due to a shortage of nursing teams specializing in minimally invasive surgery. However, studies in Thailand and internationally have found that DFS and OS rates did not differ significantly between laparoscopic and open surgery[32-34]. The rate of abdominoperineal resection for rectal tumors in the present study was 27.7%, which is considered acceptable for a standard CRC surgery center[9]. The postoperative complications did not result in death or affect survival ($p=0.499$).

While the present study focused on survival, functional complications are also important considerations when assessing postoperative functional and quality-of-life outcomes. During outpatient follow-up, patients reported bowel dysfunction after low anterior resection, increased

bowel frequency, which can recover in six months, while others experienced sexual dysfunction after abdominoperineal resection, including ejaculation, impotence, and stoma-related problems such as skin irritation, prolapse colostomy, and parastomal hernia. These complications were not systematically recorded and thus not analyzed, which is one limitation of the present study. Prior studies have reported frequent bowel complications after sphincter-preserving surgery at 80%[35], frequent sexual dysfunction after pelvic dissection, including ejaculation for 43% and impotence for 32% problems[36] and the stoma-related problems, including skin irritation for 3.6%, prolapse colostomy for 4.1%, and parastomal hernia for 59.3%[37]. Future studies should include standardized patient-reported outcomes to provide a more complete picture of treatment impact.

In present study, almost all patients (98.6%) received adjuvant chemotherapy at all stages of COAD. According to the National Comprehensive Cancer Network's guidelines for CRC (version 4.2023), all patients with high-risk stage II and stage III CRC should receive adjuvant chemotherapy, while patients with stage I CRC and stage II CRC with high microsatellite instability (MSI-H) do not require adjuvant therapy, as well as patients with low-risk stage II CRC with low MSI or proficient MMR[38]. However, in the present study, 28 patients (14.9%) with stage I CRC received adjuvant chemotherapy, accounting for 70% of patients with inadequate, less than 12 lymph node, harvesting, a high-risk feature known to be associated with lower OS and DFS[26], and thus may not be true stage I CRC, which requires a thorough pathological assessment. In this present study, 30% of the patients had two or more high-risk features, and a prior study showed that administering adjuvant chemotherapy to patients with stage I CRC and two or more high-risk features improved OS[39]. In the present study, 11.8% of the patients with COAD received postoperative radiotherapy, similar to the 10% reported in a study conducted at the Faculty of Medicine in Siriraj Hospital[9], due to the difficulty in requesting a referral for radiotherapy and the inconvenience of traveling. At the time of the present study, the author's hospital did not conduct molecular or genetic profiling such as MSI/deficient mismatch repair (dMMR), KRAS, BRAF was not routinely performed, limiting the depth of analysis regarding tumor biology and treatment response. Under Thailand's universal coverage (UC) scheme, most patients in the 30-Baht healthcare program had limited access to molecular testing because of reimbursement restrictions and no medical oncologist at that time. As a result, adjuvant chemotherapy was frequently administered without molecular guidance, leading to non-fully standardized regimen and potential variation in survival outcomes. Moreover, adjuvant therapy protocols were not fully standardized across patients, which may have contributed to treatment heterogeneity and affected the precision of survival analysis. In recent years, biomarkers such as MSI/dMMR, KRAS, BRAF, NRAS, PIK3CA alterations, and circulating tumor DNA (ctDNA) have been shown to significantly influence prognosis, recurrence risk, and treatment response in CRC[40-42]. For instance, recent meta-analyses indicate that KRAS and BRAF mutations are associated with poorer OS, particularly in microsatellite-stable (MSS) tumors following curative resection[41]. Meanwhile, postoperative detection of ctDNA has emerged as a promising marker of minimal residual disease and relapse risk[42]. Because this present study registry lacked these molecular data, the author was unable to adjust for biological heterogeneity among patients with similar clinicopathologic characteristics. Consequently, the survival differences observed in this present study may reflect unmeasured genetic or molecular influences. Future studies incorporating molecular profiling are recommended to enhance prognostic precision and provide a more comprehensive understanding of tumor biology in this population.

Implications for clinical practice

The present study findings have implications for clinical practice. Regarding enhanced screening and early detection, improving early-stage detection through population-wide fecal immunochemical testing and colonoscopy could significantly improve survival outcomes. Effective screening has been shown to reduce the incidence of CRC by approximately 20% and CRC-related mortality by 33%, highlighting the value of both primary and secondary prevention strategies[40]. However, patients with CRC in Thailand are still diagnosed at advanced stages due to barriers such as limited public awareness, restricted access to testing kits, prolonged waiting times for results, and social discomfort with stool sample collection[41]. Most general surgeons in Thailand begin screening for CRC at age 50 years and continue until age 80 years, although increasing evidence, including data from the Surveillance, Epidemiology, and End Results registry showing a 1.3% annual increase in CRC incidence among

individuals aged under 50 years, suggests the need to initiate screening at a younger age[38].

Regarding multidisciplinary management, a multidisciplinary approach involving colorectal surgeons, medical oncologists, and radiation oncologists is essential for individualized, stage-specific care. Neoadjuvant chemotherapy should be considered for patients with stage III colon cancer, while total neoadjuvant therapy, with either induction or consolidation chemotherapy, is increasingly recommended for patients with locally advanced rectal cancer[9]. In patients with potentially resectable stage IV CRC, neoadjuvant chemotherapy may downstage tumors, facilitating R0 resection and improving long-term survival[10,19,42]. In the present study, neoadjuvant therapy was not administered prior to curative resection, instead, surgery was performed immediately if deemed feasible. In female patients, bilateral oophorectomy was routinely performed, despite the lack of guideline recommendations for prophylactic oophorectomy[34]. This decision was supported by the author's observation that ovarian metastases occurred in female patients who did not undergo the procedure with 9.5% for colon and 5.9% for rectal.

Regarding molecular profiling and biomarkers, the integration of molecular testing, including MMR deficiency or MSI-H status, is vital for guiding adjuvant or neoadjuvant treatment strategies and identifying candidates for immunotherapy[34,38]. Additionally, the use of ctDNA is an emerging tool for detecting minimal residual disease and identifying high-risk patients who may benefit from treatment intensification.

Regarding postoperative surveillance, post-operative ctDNA levels have shown promise as a predictor of recurrence in patients with stage II or III colon cancer[43]. Although not a replacement for imaging or CEA monitoring, ctDNA may serve as a complementary tool for earlier detection of recurrence in selected patients[44,45]. Incorporating ctDNA monitoring into postoperative surveillance protocols may help tailor follow-up intensity and improve outcomes.

Future directions

Firstly, to improve outcomes in patients with stage III and IV CRC, further research is warranted to optimize outcomes in advanced-stage CRC. In particular, the adoption and refinement of total neoadjuvant therapy in rectal cancer and the development of novel systemic treatment combinations may help close the survival gap in patients with stage III and IV CRC. These strategies should be validated through multicenter trials in Asian populations, where local practice patterns and patient characteristics may differ from those in Western populations.

Secondly, to address healthcare disparities, efforts to improve survival must also address disparities in healthcare access. In Thailand, significant survival differences exist between patients enrolled in the Civil Servant Medical Benefit Scheme (CSMBS) and those under the UC system. A recent study reported 5-year OS rates ranging from 59.9% to 84.3% for those enrolled in the CSMBS, compared to 52% to 74.6% for those enrolled in the UC system[4,30]. Moreover, being covered under the CSMBS scheme has been identified as an independent prognostic factor for survival. Policymakers and healthcare providers must work toward equitable access to advanced diagnostics, treatment modalities, and follow-up care across all insurance groups.

Generalizability (external validity)

This single-center, retrospective study examined curative surgeries conducted by the same experienced surgeon over ten years to ensure consistent surgical quality and potentially reduce variability, which enhances internal validity. However, the identified survival and predictive factor findings may not be directly generalizable to all healthcare settings, particularly tertiary centers or populations with different demographic and clinical characteristics. Although the use of widely recognized prognostic factors, such as preoperative CEA, BMI, lymph node status, and high-risk features, supports the clinical relevance of the results, these require external validation in multicenter cohort studies, national CRC registry databases, or prospective cohort studies to confirm the reproducibility across diverse settings.

Limitation

This retrospective study had a limited sample size, which reduced statistical power, and variables had missing data, which may introduce bias. Some patients were also lost to follow-up, potentially affecting the accuracy of survival estimates. Additionally, the wide CIs observed for prognostic factors suggest uncertainty in effect sizes, so this present study findings should be interpreted with caution. Moreover, the present study survival models and prognostic factors were not externally validated in an independent cohort. While the single-center

design with uniform surgical techniques improves internal consistency, it restricts the ability to confirm whether the identified prognostic factors, such as high BMI, lymph node status, preoperative CEA level, and multiple high-risk features, are reproducible across different populations and institutions. Therefore, they require external validation in larger, multicenter datasets to strengthen confidence in the applicability of the present study findings and ensure that the number of high-risk pathological features have robust predictive value in broader clinical practice.

Conclusion

Curative resection for CRC offers favorable long-term survival, especially with a consistent technique by experienced surgeons. Factors significantly associated with worse survival were female, high BMI, higher N stage, elevated preoperative CEA level, and having four high-risk pathological features. These factors highlight the need for thorough pathological assessment and individualized treatment. High-risk patients may benefit from tailored adjuvant therapy and closer postoperative surveillance.

What is already known about this topic?

- CRC is a leading cause of cancer-related death globally and in Thailand.
- Surgical resection is the standard curative treatment, but survival outcomes vary based on patient and tumor characteristics.
- Known adverse prognostic factors include TNM stage, lymphovascular invasion, poor differentiation, and elevated CEA level.

What does this study add?

- It provides updated survival data from a single-surgeon cohort at a provincial hospital in Thailand, with favorable 5-year OS and DFS rates.
- It identifies high BMI, female, lymph node involvement, and four high-risk pathological features as independent predictors of worse survival.
- It demonstrates the potential utility of the number of high-risk pathological features for guiding adjuvant treatment and follow-up strategies.

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Conflicts of interest

The authors declare no conflict of interest.

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