RESEARCH ARTICLE

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Pathologic Features of Rectal Adenocarcinoma after Preoperative Neoadjuvant Chemoradiation Therapy and the Prognostic Factors for Local Recurrence: A Retrospective Study at Maharaj Nakorn Chiang Mai Hospital

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Abstract

Background: Colorectal cancer is a significant global health concern, with Thailand reporting notable incidence rates. Locally advanced rectal cancer demands effective treatment strategies to reduce the risk of local recurrence post-surgery; however, the predictive factors for local recurrence are uncertain.. **Objective:** This study investigated patients with rectal adenocarcinoma undergoing preoperative concurrent chemoradiation (CCRT). The pathological findings and predictors of local recurrence in rectal adenocarcinoma were examined following preoperative CCRT. **Methods:** A retrospective cohort study was conducted in patients with rectal adenocarcinoma who underwent preoperative CCRT and surgery at the Maharaj Nakorn Chiang Mai Hospital from January 2018 to December 2022. Data were collected from patients to investigate the associations between pathological prognostic factors and local recurrence of rectal adenocarcinoma. For the analysis of continuous variables, the Student's t-test was employed to assess univariate associations. In the case of categorical variables, comparisons were made using the chi-square test and the Kruskal-Wallis test. Furthermore, the Kaplan-Meier method, supplemented by the log-rank test, was utilized to examine the relationships between baseline prognostic variables and disease-free survival endpoints. **Results:** Of the 70 patients who received preoperative CCRT, 14 (20%) experienced recurrence. Univariate log-rank analysis identified five pathologic predictors of the disease-free survival of preoperative CCRT patients: ypT stage ($p = 0.0030$), lymphatic space invasion ($p = 0.0033$), venous invasion ($p = 0.0345$), circumferential resection margin (CRM) ($p = 0.0003$), and TNM staging ($p = 0.0109$). In multivariate Cox regression analysis, ypTNM stage and CRM status were independent predictors for disease progression of preoperative CCRT patients. **Conclusion:** ypTNM staging and CRM status emerged as independent predictors of local recurrence. The study also identified age and gender variations in rectal cancer incidence, highlighting the importance of tailored screening approaches.

Keywords: Rectum- adenocarcinoma- neoadjuvant therapy- local recurrence

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Introduction

Colorectal cancer (CRC), known as colorectal adenocarcinoma, is the third. most lethal and fourth most prevalent malignancy worldwide [1]. According to an article on Current Colorectal Cancer in Thailand, the National Cancer Institute reported in 2018 that the age-standardized CRC rates in the country per 100,000 population were 16.2 for men and 11.2 for women [2]. The highest incidence of CRC (approximately 50% of all CRC cases) was observed in patients aged 60–75 years [2]. CRC can be divided into three categories according to their location: (1) right side or proximal colon cancers, which include cecum, ascending, and transverse colon adenocarcinoma; (2) left side or distal colon cancers, which mean adenocarcinomas arising anywhere between the sphenic flexure and the sigmoid colon; and (3) rectal cancers, which is rectum-originating adenocarcinoma [3]. Rectal cancers account for approximately 30% of cancer cases and are associated with poorer clinical outcomes [4]. The European Society for Medical Oncology suggests the use of neoadjuvant therapy in patients with locally advanced rectal cancer, lymph node involvement on imaging, and uncertainty regarding the adequacy of total mesorectal excision (TME) surgery [4].

Setthalikhit et al. [4] conducted a retrospective cohort

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study of patients with locally advanced rectal cancer who received preoperative concurrent chemoradiation (CCRT) following surgery between January 2011 and December 2017 at a single center. In this study, 145 patients were classified as having either a pathologic complete response (pCR) or a non-pathologic complete response (non-pCR). Of the 145 patients, 83% did not achieve a pCR, while 17% did. A pretreatment computed tomographic scan length of less than 5 cm and a postoperative lymph node count of less than 12 were associated with a pCR. Another study by Al-Qudah et al. [5] investigated the pathological prognostic indicators influencing the treatment of patients with rectal cancer following radiotherapy and neoadjuvant chemotherapy, revealing that radiotherapy and neoadjuvant chemotherapy have an impact on the macroscopic pathological and histopathological characteristics of rectal lesions, which in turn affect patient outcomes. Furthermore, they emphasized the importance of tissue sampling for pathological analysis as appropriate lesion selection is crucial for ensuring an accurate diagnosis and determining the prognosis.

Surgeons require a range of information on pathological reports, including the post-treatment pathological stage (ypTNM), microscopic status of the circumferential resection margin (CRM), local fibroinflammatory response, and stage-independent prognostic factors such as histologic grade, lymphovascular invasion, perineural invasion, and tumor deposit [6]. These findings should be communicated to surgeons at each stage to guide subsequent treatment decisions. Moreover, preoperative CCRT can influence various pathological findings, including tumor size, lymph node status, CRM involvement, and lymphovascular invasion.

This study aims to report the pathological findings of patients with rectal cancer undergoing preoperative CCRT and discuss the significant pathological factors that can increase the risk of local recurrence.

Materials and Methods

Study population

All rectal cancer patients who diagnosed with rectal adenocarcinoma and underwent preoperative CCRT followed by tumor resection with pathological examination at the Maharaj Nakorn Chaing Mai Hospital between 2018 and 2022 were enrolled in this study. Patients who did not undergo preoperative CCRT or lacked a complete pathological report were excluded from the study. The diagnosis of rectal adenocarcinoma in this study was based on histopathological examination, which is the gold standard for diagnosis [7]. Pathologic diagnostic slides from patients were blindly re-evaluated by two independent, experienced pathologists. The pathologic reports of all cases adhered to the guidelines provided by the College of American Pathologists. In the event of any discrepancy, the slides were re-evaluated by both pathologists until a consensus was reached. The surgical pathological diagnosis was made based on the criteria outlined in the 5th edition of the World Health Organization classification of gastrointestinal and hepatobiliary tumors. Patient data were collected on age, sex, lesion site, tumor histological type, tumor differentiation grade, tumor response grade (according to the Modified Ryan scheme), tumor stage (ypT), lymphatic space invasion, venous invasion, perineural invasion, lymph node involvement, CRM status, ypTNM, and time of local recurrence-free survival.

Statistical analysis

All statistical analyses were performed using STATA version 16 (STATA Corp., Texas, USA). The univariate associations with pathological prognostic factors and local recurrence of rectal cancer were compared using the Student's t-test for continuous data. Furthermore, the chi-square test and Kruskal–Wallis test were used to compare the categorical data. The Kaplan–Meier method and log-rank test were used to explore the association between baseline prognostic variables and disease-free survival endpoints. Variables with a p-value of less than 0.05 based on the univariable analysis were included in the multivariable analysis using a Cox proportional hazards model to estimate the effect of pathological prognostic factors on survival outcome. A p-value of less than 0.05 was considered significant.

Results

Among the 70 patients included in the study who underwent preoperative CCRT, 64.29% (45 out of 70) were men, and 35.71% (25 out of 70) were women. The mean age of patients was 60.83 years. The youngest patient was aged 31 years, and the oldest was 82 years. In addition, women exhibited significantly younger mean ages than men [53.90 years (ranging from 31–77) vs. 64.6 years (ranging from 42-82); Student's t-test; p = 0.0002]. According to the Modified Ryan scheme, the tumor response grades among patients were as follows: 12 patients (17.14%) were classified as Grade 0 or complete response, 11 patients (15.71%) as Grade 1 or near complete response, 33 patients (47.14%) as Grade 2 or partial response, and 14 patients (20.00%) as Grade 3 or poor response. The patient characteristics and pathological prognostic factors are listed in Table 1.

To identify the pathologic predictive factors for local recurrence in patients, the pathologic predictive factors were compared between the no local recurrence group and the local recurrence group. Of the 70 patients, 20.0% (14 out of 70) presented with local recurrence, whereas 80.0% (56 out of 70) were in the no local recurrence group. A comparative analysis of the pathological predictive factors between the two groups is shown in Table 2.

The median disease-free survival time in this study was 22.75 months (ranging from 1.05 to 60.65 months). From the univariate log-rank analysis, five pathologic predictive factors were identified as potential predictors of disease-free survival for preoperative CCRT patients: ypT stage (p = 0.0093), lymphatic space invasion (p = 0.0033), venous invasion (p = 0.0345), CRM status (p = 0.0003), and ypTNM staging (p = 0.0109). The survival probabilities at 12, 36, and 60 months for each pathological predictive factor were estimated using Kaplan–Meier curves.

Table 3 reports the results of a multivariate Cox

Table 1. Clinical Characteristics and Pathological Prognostic Factors of the Patients in This Study

Factor	Category	No. of patients (%)
Sex	Female	25 (35.71)
	Male	45 (64.29)
Location	Upper rectum	15 (21.43)
	Middle rectum	15 (21.43)
	Lower rectum	39 (55.71)
	Anal canal	1 (1.43)
Histologic type	No viable tumor	12 (17.14)
	Adenocarcinoma	58 (82.86)
Differentiation	Well differentiated	45 (64.29)
	Moderately differentiated	22 (31.43)
	Poorly differentiated	3 (4.29)
Tumor response grade: modified Ryan scheme	Grade 0	12 (17.14)
	Grade 1	11 (15.71)
	Grade 2	33 (47.14)
	Grade 3	14 (20.00)
Tumor (ypT) stage	No residual tumor	12 (17.14)
	T1	4 (5.71)
	T2	18 (25.71)
	T3	34 (48.57)
	T4	2 (2.86)
Lymphatic space invasion	Negative	43 (61.43)
	Positive	27 (38.57)
Venous invasion	Negative	51 (72.86)
	Positive	19 (27.14)
Perineural invasion	Negative	51 (72.86)
	Positive	19 (27.14)
Lymph node (N) stage	0	47 (67.14)
	1	18 (25.71)
	2	5 (7.14)
Circumferential margin	Negative	65 (92.86)
	Positive	5 (7.14)
Distal margin	Negative	69 (98.57)
	Positive	1 (1.43)
Proximal margin	Negative	69 (98.57)
	Positive	1 (1.43)
ypTNM staging	No residual tumor	6 (8.57)
	1	13 (18.57)
	2	15 (21.43)
	3	7 (10.00)
	4	29 (41.43)

regression analysis aimed at identifying independent predictors of local recurrence in patients with rectal cancer. The primary outcome variable was the occurrence of local recurrence following treatment, defined as the return of cancer to the rectal area. The model included two key pathologic features: CRM status, indicating the presence of cancer cells at the edges of the surgical specimen, and ypTNM staging, which reflects the extent of the tumor and lymph node involvement following neoadjuvant therapy.

The analysis revealed that a positive CRM significantly increased the risk of local recurrence, with a hazard ratio (HR) of 9.257 (95% CI: 1.880–45.600; P = 0.0060), suggesting that these patients were approximately nine times more likely to experience recurrence. Similarly, the ypTNM staging was associated with an increased risk, yielding an HR of 7.496 (95% CI: 1.496–37.556; P = 0.0140), indicating that patients who had high ypTNM staging (stage 3–4) were approximately 7.5 times more likely to experience recurrence.

Discussion

According to Lotfollahzadeh et al. [8], approximately 135,439 patients are newly diagnosed with colorectal cancer in the United States annually. The global ratio of male-to-female colorectal cancer incidence rates in 2012 was 1.38, with the highest incidence observed in patients aged >70 years [9]. In 2018, 17,534 CRC cases were reported in Thailand, accounting for 10.3% of all new cancer cases [2]. Depending on age, the incidence rate ratio between men and women for rectal cancer varies, with 1.10 in those aged 0–49 years, 1.19 in those aged 50–64 years, 1.27 in those aged 50–79 years, and 1.29 in those aged 80 years and older [10]. In contrast, the investigation conducted in this study revealed that the incidence rate ratio in 70 male and female patients was 1.80. The female group had a significantly younger mean age (53.90 years, ranging from 31–77 years) than the male group (64.61 years, ranging from 42–82 years, p = 0.0002). Therefore, women should begin screening for rectal cancer at a younger age than men.

Recent developments in the procedure and management of rectal cancer have led to improved outcomes [11]. However, the absence of locoregional control leads to complications that often necessitate surgical intervention for effective treatment [12]. Total TME and neoadjuvant chemoradiation therapy (CRT) can significantly reduce the risk of local recurrence. Currently, the standard care for the treatment of locally advanced rectal cancer includes preoperative CRT, TME, and adjuvant chemotherapy (AT) [13]. In addition, preoperative CCRT plays an important role in the treatment of rectal cancer, particularly in locally advanced diseases [14]. It can reduce tumor size, increase the rate of tumor resection, and preserve the anus. Moreover, It may decrease the rate of local recurrence [14]. Preoperative CCRT can also significantly improve the pCR and local control rates. Moreover, compared with preoperative radiotherapy, pathological staging is reduced after preoperative CCRT. In addition, pathological stages can predict prognosis in preoperative CCRT patients. However, preoperative CCRT does not appear to enhance long-term survival or retention rates of rectal cancer patients [15].

In a previous study conducted by Bujiko et al. [16], preoperative CCRT resulted in a 15% pCR (p < 0.001) in 157 patients, whereas preoperative radiotherapy alone resulted in a 1% pCR in 155 patients. Another study conducted by Gérard et al. [17] reported a pCR rate of 11.4% (p = 0.001) in 375 patients treated with preoperative CCRT and a pCR rate of 3.5% in 367 patients treated with preoperative radiotherapy alone. Brandengen [18] also reported a pCR rate of 16% in 98

Table 2. Univariate analysis using log-rank test of potential pathological prognostic factors in preoperative CCRT patients

	No local recurrence, 56 n (%)	Local recurrence, 14 n (%)	12-month disease-free survival (%)	36-month disease-free survival (%)	60-month disease-free survival (%)	P-value
Age (year) mean, (± SD), (min, max)	60.75 (±11.88) (32, 80)	61.21 (±13.60) (31, 82)	-	-	-	0.8992*
Sex						
Female	23 (41.07)	2 (14.29)	-	-	-	0.061**
Male	33 (58.93)	12 (85.71)	-	-	-	
Location						0.8423
Upper rectum	12 (21.43)	3 (21.43)	100	71.43	NA	
Middle rectum	12 (21.43)	3 (21.43)	90.91	38.96	NA	
Lower rectum	31 (55.36)	8 (57.14)	85.93	72.54	72.54	
Anal canal	1 (1.78)	0 (0.00)	100	100	NA	
Histologic type						0.8234
No viable tumor	10 (17.86)	2 (14.29)	90.91	68.18	NA	
Adenocarcinoma	46 (82.14)	12 (85.71)	89.83	69.95	69.95	
Differentiation						0.7421
Well differentiated	36 (64.89)	9 (64.29)	88.01	72.12	72.12	
Moderately differentiated	17 (30.36)	5 (35.71)	92.31	58.74	NA	
Poorly differentiated	3 (5.36)	0 (0.00)	100	100	NA	
Tumor response grade: Modified Ryan Scheme						0.7306
Grade 0	10 (17.86)	2 (14.29)	90.91	68.18	NA	
Grade 1	10 (17.86)	1 (7.14)	88.89	88.89	NA	
Grade 2	26 (46.43)	7 (50.00)	92.35	71.26	71.26	
Grade 3	10 (17.86)	4 (28.57)	85.12	60.8	NA	
ypT stage						0.0093
T0–T2	31 (55.36)	3 (21.43)	96.55	87.77	87.77	
T3–T4	25 (44.46)	11 (78.57)	83.58	54.26	NA	
Lymphatic space invasion						0.0033
Negative	40 (71.43)	3 (21.43)	94.44	87.69	NA	
Positive	16 (28.57)	11 (78.57)	83.01	46.77	46.77	
Venous invasion						0.0345
Negative	45 (80.36)	6 (42.86)	93.25	80.4	80.4	
Positive	11 (19.64)	8 (57.14)	81.37	47.55	NA	
Perineural invasion						0.1368
Negative	43 (76.79)	8 (57.14)	90.23	77.53	77.53	
Positive	13 (23.21)	6 (42.86)	88.89	53.28	NA	
N stage						0.2075
0	40 (71.43)	7 (50.00)	95.45	73.48	73.48	
1	13 (23.21)	5 (35.71)	72.73	63.64	NA	
2	3 (5.36)	2 (14.29)	80	60	NA	
Circumferential margin						0.0003
Negative	55 (98.21)	10 (71.43)	90.91	79.01	79.01	
Positive	1 (1.79)	4 (28.57)	80	0	0	
Distal margin						0.5445
Negative	55 (98.21)	14 (100.00)	89.72	68.8	68.8	
Positive	1 (1.79)	0 (0.00)	100	100	NA	
Proximal margin						0.2709
Negative	56 (100.00)	13 (92.86)	89.72	73.39	73.39	
Positive	0 (0.00)	1 (7.14)	100	0	0	
ypTNM staging						0.0109
Stage 0-2	31 (55.36)	3 (21.43)	96.77	84.04	84.04	
Stage 3-4	25 (44.64)	11 (78.57)	82.69	54.77	NA	

*, Student t-test; **, Chi-square test

Table 3. Multiple Cox Regression Analysis of the Five Potential Pathological Prognostic Factors

Pathological prognostic factors	Hazard ratio (95% CI)	P-value
ypT stage: T3–T4	2.892 (0.446 – 18.746)	0.265
Lymphatic space invasion: positive	1.166 (0.229 – 5.948)	0.853
Venous invasion: positive	1.003 (0.253 – 3.982)	0.997
Circumferential resection margin: positive	9.257 (1.880 – 45.600)	0.006
ypTNM staging: stage 3-4	7.496 (1.496 – 37.556)	0.014

patients treated with preoperative CCRT (p = 0.04) and a pCR rate of 7% in 109 patients treated with preoperative radiotherapy alone. In the current study, all included patients underwent preoperative CCRT, with a pCR rate of 17.14%. The findings of our investigation indicated that the observed pCR rate was comparable to that reported in previous studies. Local rectal cancer recurrence rates have been reported to range from 3.7–13% with the introduction of TME, regardless of whether preoperative chemoradiotherapy or radiotherapy was administered [19]. Yu et al. [20] reported that their study revealed 408 patients in the postoperative CRT group and 245 patients in the neoadjuvant CRT group. The neoadjuvant CRT group exhibited a significantly lower local recurrence rate (4.1% vs. 10.3%, p = 0.004).

To determine the risk of local recurrence, histopathological factors associated with rectal cancer were evaluated. Dresen et al. [21] identified five significant pathological factors associated with local recurrence: lymphovascular invasion (p < 0.001), extramural venous invasion (p < 0.001), serosal invasion (p = 0.035), positive CRM (p = 0.032), and poor differentiation (p = 0.012). According to the findings of this study, lymphatic space invasion, extramural venous invasion, and positive CRM status were significantly correlated with local recurrence. Trakarnsanga et al. [22] studied the significance of the CRM. A CRM of ≤ 1 mm and high-grade tumors were independently correlated with local recurrence (p = 0.012 and p = 0.007, respectively). In addition, a CRM of <2 mm, pathological tumor staging, nodal staging, and overall tumor stage were independent risk factors for distant metastasis (p = 0.025, p = 0.010, and p = 0.001, respectively). Another study by Hwang et al. [23] involved an analysis of the data on 561 patients who underwent preoperative CRT and curative surgery for locally advanced rectal cancer. Local recurrence rates were lower in patients with a CRM of 0.1–1 cm (Group 3), 1.1–2.0 cm (Group 2), and >2 cm (Group 1) (p = 0.035, p = 0.002, and p < 0.0001, respectively) but high in a CRM of 0 mm (Group 4). In the presence of these characteristics, adjuvant therapy should be considered to reduce the risk of local recurrence. In the current study, tumor differentiation grade and depth of invasion (T stage) were not significant in terms of local recurrence (p = 0.653 and p = 0.158, respectively).

Other factors, such as pathological T stage, N stage, and distal margin status, are also associated with local recurrence [19, 24]. However, these factors were not significant in the present study, which may have been due to the limited number of patients. Nonetheless, this study showed significance at the proximal margin rather than the distal margin. In this study, other factors such as age, sex, location, histologic type, differentiation, tumor response grade, and perineural invasion were not associated with local recurrence. As to the limitations of the small sample size and single institutional study, this issue could be addressed if future research were to be conducted involving the collection of more data.

Progression-free survival (PFS) is a measure of the time from the start of treatment to disease progression, relapse, or death from any cause [25]. This is an important endpoint in clinical trials and provides an indication of treatment efficacy. In rectal cancer, PFS is affected by multiple factors, including invasion depth and lymphovascular space invasion. However, tumor size, number of lymph nodes removed, number of positive lymph nodes, perineural invasion, and treatment methods do not significantly predict recurrence [26]. In this study, the ypTNM stage and CRM status were found to be predictors of local recurrence in patients undergoing preoperative CCRT.

In conclusion, preoperative CCRT has demonstrated clear benefits in the treatment of rectal cancer and its potential to contribute to a complete pathological response. However, despite these advancements, the risk of local recurrence still persists in certain patients. Our study highlights the importance of considering the ypTNM stage and CRM status as significant predictors of local recurrence. In order to expand our understanding and effectively address the issue of local recurrence in rectal cancer patients receiving neoadjuvant chemoradiotherapy, it is imperative to explore possible areas for further investigation. For instance, one potential area of focus could involve the identification of dependable biomarkers capable of accurately predicting the likelihood of local recurrence. Such biomarkers have the potential to refine treatment strategies. Additionally, conducting long-term follow-up studies on a larger cohort of patients who have undergone neoadjuvant chemoradiotherapy for rectal cancer may yield valuable insights. By directing attention toward these specific domains of further investigation, it is possible to enhance the efficacy of treatment approaches, enhance the overall prognosis of patients, and eventually mitigate the chance of local recurrence in individuals with rectal cancer who are undergoing neoadjuvant chemoradiotherapy.

Author Contribution Statement

Contributions of the authors are as follows: CB was responsible for conceptualization, methodology, validation, resources, data curation, writing of the

original draft, and review and editing. SK contributed to the investigation and writing, as well as visualization. ES participated in the investigation, resources, and data curation. WD and TW were involved in investigation, resources, data curation, writing of the original draft, and review and editing. KW handled conceptualization, methodology, validation, investigation, resources, data curation, writing of the original draft, writing review and editing, visualization, project administration, funding acquisition, and supervision. All authors have given their approval for the publication of this manuscript.

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Approval

The study received approval from the Institutional Ethics Committee of the Faculty of Medicine at Chiang Mai University, Chiang Mai, Thailand (study code: PAT-2566-09391).

Ethical Declaration

Ethical considerations were meticulously addressed as this research utilized a retrospective design and did not involve any patients' personal data. The research was conducted in accordance with Good Clinical Practice (ICH GCP) guidelines.

Data Availability

The datasets produced and examined during this study can be obtained from the corresponding author upon reasonable request.

Study Registration

Study registration is not applicable for this research.

Conflict of Interest

The authors declare that there are no identifiable conflicting financial interests or personal affiliations that may be perceived as influencing the research presented in this study.

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