Original Article

The Impact of a 5 mm-Distal Resection Margin on Oncological Outcome for Patients with Low Rectal Cancer Undergoing Preoperative Concurrent Chemoradiation Therapy

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Purpose. The optimal distal resection margin (DRM) for patients with low rectal cancer remains a subject of debate; accordingly, we herein investigate the impact of a 5 mm-DRM in low rectal cancer.
Methods. We retrospectively surveyed patients with low rectal cancers undergoing neoadjuvant concurrent chemoradiation therapy (CCRT) and radical proctectomy surgery at the Kaohsiung Medical University Hospital from January 2018 to December 2020. Patient characteristics, clinicopathological parameters, and outcomes, including locoregional relapse, distant metastasis and overall survival were analyzed.
Results. Forty-two patients were included, with mean duration post-radical surgery being 41.6 months. There was no significant difference of 3-year disease-free survival (DFS) rate between the two groups but patients with ≤ 5 mm DRM had non-significantly worse DFS with significantly better overall survival being noted in patients with > 5 mm DRM.
Conclusions. A DRM of ≤ 5 mm of patients with low rectal cancers undergoing CCRT and radical proctectomy surgery was associated with unfavorable oncological outcomes. Securing a clear distal margin during surgical procedures for low rectal cancer remains crucial, nevertheless, long-term oncological outcomes warrant further exploration through studies with extended follow-up durations and substantial sample sizes.

[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2024;35:290-301*]

Key Words
Distal resection margin;
Oncological outcome;
Low rectal cancer;
Preoperative concurrent chemoradiation therapy

Received: May 28, 2024. Accepted: July 21, 2024.
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Colorectal cancer (CRC) stands as the third most frequently diagnosed type of cancer and ranks second among the leading contributors to cancer-related fatalities globally.[1] A 2020 estimate indicated more than 1.9 million newly diagnosed cases of CRC, resulting in approximately 930,000 deaths linked to the disease.[2] In Taiwan, CRC stands as the third most prevalent cancer type and has consistently ranked as the third leading cause of cancer-related death. The incidence of CRC was 65.94 per 100,000 population in 2011 (with 15,315 new diagnoses) and 69.47 per 100,000 population in 2021 (with 16,238 new diagnoses). Notably, the mortality rates for 2012 and 2022 were 23.1 per 100,000 population and 29.4 per 100,000 population respectively.[3]

Over recent decades, the management of rectal cancer has undergone significant revolution, driven by advancements such as total mesorectal excision (TME) and neoadjuvant concurrent chemoradiation therapy (CCRT), leading to notable enhancements in both locoregional relapse rates and survival outcomes.[4] Critical parameters like circumferential resection margin (CRM) and distal resection margin (DRM) strongly correlate with locoregional relapse and distant metastases, while positive distal margins are associated with worse oncological results and CCRT cannot compensate accordingly.[5-8]

In the early 1950s, a distal resection margin (DRM) of 5 cm for rectal cancer was recommended, but with the adoption of TME and CCRT, this paradigm has shifted.[9,10] Studies dating back to the 1980s indicate that a 2-cm DRM was sufficient from an oncological standpoint, while recent research has shown that a DRM of less than 1 cm yields comparable oncological outcomes in patients undergoing neoadjuvant CCRT for low rectal cancer.[11-13] Additionally, several studies have demonstrated that a distal margin of ≤ 5 mm does not compromise oncologic safety, although few studies have examined the prognostic significance of a microscopic margin of ≤ 1 mm in rectal cancer, revealing worse oncological outcomes.[4,14-17] With the advent of TME, increased tolerance for shorter DRM, the availability of circular stapling devices, and the rising utilization of neoadjuvant CCRT for locally advanced rectal cancers (LARC), sphincter-saving surgeries have become more prevalent, aiming to enhance patient quality of life.[18]

Consequently, the optimal DRM remains a subject of debate, especially in cases of low rectal cancer, necessitating further exploration to inform clinical practice and enhance outcomes. In this study, we conducted a retrospective study to investigate the impact of a 5 mm-DRM following neoadjuvant CCRT and radical proctectomy surgery for low rectal cancers.

Materials and Methods

We retrospectively compiled data from Kaohsiung Medical University Hospital in Taiwan spanning from January 2018 to December 2020. Initially, 381 consecutive cases undergoing elective radical proctectomy with histologically confirmed rectal cancer were enrolled. Assessment of the pathological staging adhered to the 8th edition of the American Joint Committee on Cancer (AJCC) criteria.[19] The inclusion criteria comprised histologically proven rectal adenocarcinoma with the tumor located within 5 cm from the anal verge, neoadjuvant CCRT, and radical proctectomy surgery. Exclusion criteria encompassed distant metastasis, positive CRM or DRM, or unknown margin status. Subsequently, 42 cases meeting the inclusion criteria were included in the final analysis (Fig. 1). The study protocol was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-E(I)-20230267).

To assess preoperative staging, all patients underwent colonoscopy and abdominal and pelvic computed tomography (CT) scans, then were stratified into Group A (≤ 5 mm) and Group B (> 5 mm) based on the distal resection margin. Those with clinical stages II-III adenocarcinoma of the low rectum underwent neoadjuvant CCRT, either with a Folinic acid, fluorouracil and oxaliplatin (FOLFOX) regimen administered every 2 weeks or daily capecitabine and long course chemoradiation (LCRT) totaling 5000 cGy in 25 fractions, followed by radical surgery, as previously outlined.[20] Patients with cT2 rectal cancer located within 5 cm from the anal verge also underwent the same preoperative CCRT.

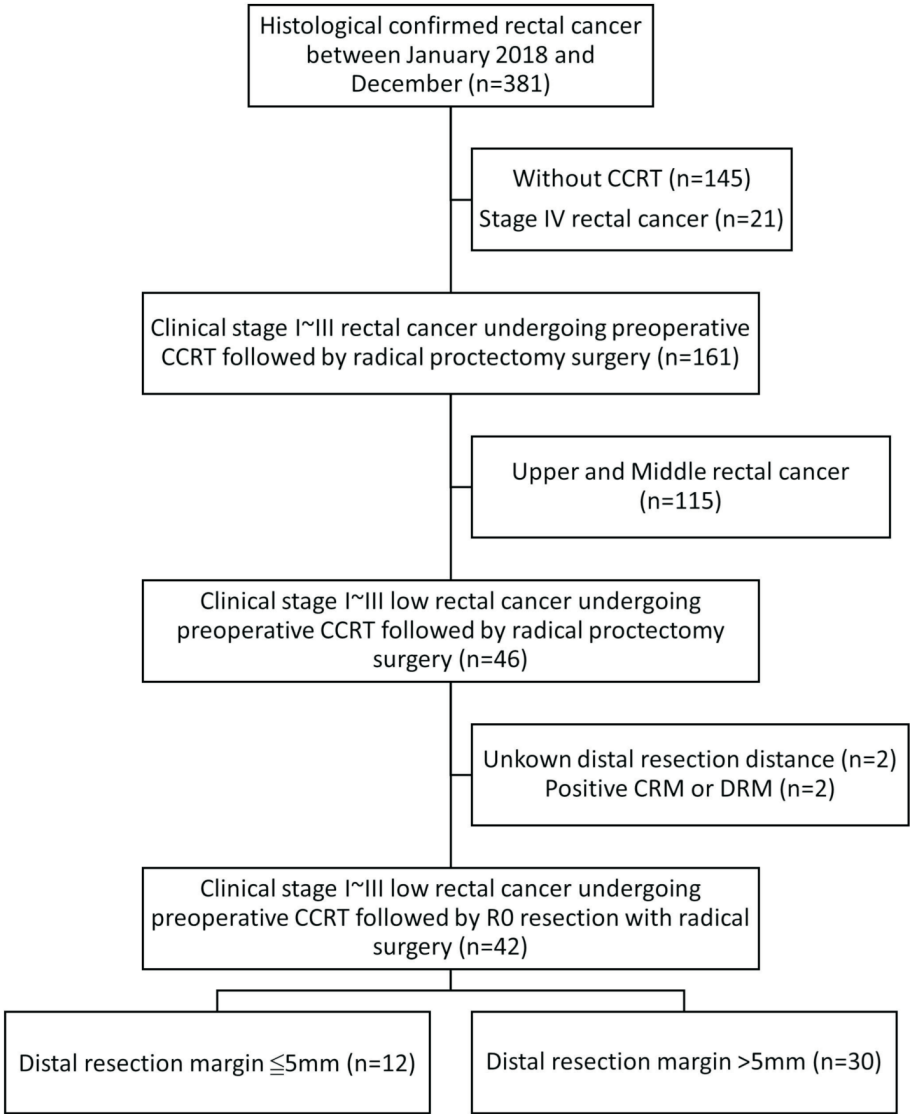

Fig. 1. CONSORT diagram showing the inclusion and exclusion criteria in the present study.

Various clinicopathological parameters were scrutinized, including age, gender, pre-CCRT and post-CCRT serum carcinoembryonic antigen (CEA) levels, albumin level, body mass index (BMI), tumor location (distance from the anal verge), neoadjuvant chemotherapy regimen, interval between preoperative radiotherapy and operation, and tumor, node, and metastasis (TNM) classification, along with perineural and vascular invasion. TNM classification adhered to the criteria of the AJCC, while tumor regression grade (TRG) was determined following AJCC and College of American Pathologists standards.[21]

Perioperative outcomes encompassed the procedure of operation, presence of protective diverting enterostomy, and operation time. The DRM was gauged post microscopic examination of the formalin-fixed specimen, delineating the closest distance from the lowest lesion border (or scar tissue post-CCRT) to the distal mucosal resection margin. Locoregional relapse, comprising anastomotic and pelvic lymph node recurrence, was defined as any clinically or histopathologically confirmed carcinoma recurrence post primary operation. Distant metastasis entailed the spread of cancer cells to distant organs (e.g., lung, liver, bone, and so on) or lymph nodes (e.g., para-aortic or supraclavicular lymph nodes, and so on).

Statistical analysis

Categorical variables were delineated by frequencies and percentages, while continuous variables were expressed as mean ± standard deviation (SD) or median for skewed or kurtotic distributions. Differences between categorical variables were determined using Pearson's chi-squared test, whereas continuous variables were analyzed via Student's *t*-test and survival analysis was conducted using the Kaplan-Meier method with the log-rank test. Statistical significance was set at a *p*-value of < 0.05. Statistical analyses were performed utilizing SPSS version 27.0 (SPSS Inc., Chicago, IL, USA).

All patients were regularly followed up until their demise or last follow-up, whichever transpired first. Disease-free survival (DFS) was defined as the interval from radical surgery to the diagnosis of recurrent or metastatic disease or last follow-up. Similarly, overall survival (OS) was the interval between radical surgery and death from any cause or last follow-up. DFS and OS were assessed using the Kaplan-Meier method, with the log-rank test utilized to compare time-to-event distributions.

Results

Patient characteristics and perioperative outcomes

From January 2018 to December 2020, 381 patients with a pathohistological diagnosis of rectal adenocarcinoma underwent radical surgery. Among these patients, 42 patients meeting the inclusion criteria were enrolled in this study. Twelve patients had a ≤ 5 mm DRM, while thirty patients had a > 5 mm DRM (Fig. 1). Summary data regarding baseline characteristics and perioperative outcomes are detailed in Table 1A and 1B.

Table 1A. Baseline characteristics of 42 patients with low rectal cancer undergoing preoperative CCRT followed by radical surgery

Characteristic	All patients (N = 42)	Distal resection margin		*p* value
		Group A (≤ 5 mm) (N = 12)	Group B (> 5 mm) (N = 30)	
Age (years)				0.223
Mean ± SD (range)	62.64 ± 11.34 (32-84)	67.25 ± 7.39 (54-76)	60.80 ± 12.19 (32-84)	
Median	63	67	61.5	
Gender				0.443
Male	22 (52.4%)	7 (58.3%)	15 (50.0%)	
Female	20 (47.6%)	5 (41.7%)	15 (50.0%)	
Pre-CCRT serum CEA level				0.037*
< 5 ng/ml	28 (66.7%)	5 (41.7%)	23 (76.7%)	
≥ 5 ng/ml	14 (33.3%)	7 (58.3%)	7 (23.3%)	
Post-CCRT serum CEA level				0.216
< 5 ng/ml	36 (85.7%)	9 (75.0%)	27 (90.0%)	
≥ 5 ng/ml	6 (14.3%)	3 (25.0%)	3 (10.0%)	
Albumin level (g/dL)				0.212
Mean ± SD (range)	4.33 ± 0.35 (3.25-5.01)	4.14 ± 0.43 (3.25-4.81)	4.41 ± 0.28 (3.81-5.01)	
Median	4.40	4.21	4.46	
BMI kg/m^2				0.275
Mean ± SD (range)	23.84 ± 3.99 (12.9-34.4)	23.70 ± 5.33 (12.9-34.4)	23.90 ± 3.43 (17.4-29.6)	
Median	23.53	23.58	23.5	
Tumor distance from anal verge (cm)				0.557
Mean ± SD (range)	3.69 ± 1.33 (1-5)	3.33 ± 1.37 (2-5)	3.83 ± 1.31 (1-5)	
Median	4	3	4	
Regimen of neoadjuvant chemotherapy				0.688
Capecitabine	7 (16.7%)	2 (16.7%)	5 (16.7%)	
mFOLFOX	35 (83.3%)	10 (83.3%)	25 (83.3%)	
Interval between Pre-op RT and OP (week)				0.434
10-12 weeks	27 (64.3%)	7 (58.3%)	20 (66.7%)	
≥ 12 weeks	15 (35.7%)	5 (41.7%)	10 (33.3%)	

SD, standard deviation; CCRT, concurrent chemoradiotherapy; CEA, carcinoembryonic antigen; BMI, body mass index; Pre-op RT, preoperative radiotherapy; OP, operation. * *p* value < 0.05.

Table 1B. Perioperative outcomes of 42 patients with low rectal cancer undergoing preoperative CCRT followed by radical surgery

Perioperative outcomes	All patients (N = 42)	Distal resection margin		*p* value
		Group A (≤ 5 mm) (N = 12)	Group B (> 5 mm) (N = 30)	
Procedure				0.485
LAR	16 (38.1%)	4 (33.3%)	12 (40.0%)	
ISR	26 (61.9%)	8 (66.7%)	18 (60.0%)	
Protective diverting enterostomy in operation				0.320
Yes	38 (90.5%)	10 (83.3%)	28 (93.3%)	
No	4 (9.5%)	2 (16.7%)	2 (6.7%)	
Operation time (minutes)				0.069
Mean ± SD (range)	371.6 ± 58.7 (270.0-565.0)	404.8 ± 74.6 (285.0-565.0)	358.37 ± 46.0 (270.0-465.0)	
Median	362.5	396.5	355	

LAR, low anterior resection; ISR, intersphincteric resection; SD, standard deviation.

The mean tumor distance from anal verge was 3.33 ± 1.37 cm and 3.83 ± 1.31 cm in the two groups, respectively ($p = 0.357$). Significantly more patients had ≥ 5 ng/ml pre-CCRT serum CEA levels in group A than those in group B (58.3% vs. 23.3%, $p = 0.037$); however, there were no significant differences in various parameters including age, gender, post-CCRT serum CEA levels, albumin level, BMI, tumor location, neoadjuvant chemotherapy regimen, interval between preoperative radiotherapy and operation, surgical procedure, presence of protective diverting enterostomy, and operation time (all $p > 0.05$).

Pathological and oncological outcomes

The preoperative clinical staging characteristics, postoperative pathological characteristics and oncological outcomes of the patients are summarized in Table 2. There were no significant differences in clinical T, N, and AJCC stages between the two groups (all $p > 0.05$), although preoperative clinical staging revealed a non-significant higher proportion of cT4 and cN2 in group A than group B (16.7% vs. 3.3% and 33.3% vs. 23.3% respectively). Furthermore, no significant differences were observed regarding pathological T, N, and AJCC stages, tumor regression,

Table 2A. Preoperative clinical staging characteristics of 42 patients with low rectal cancer undergoing preoperative CCRT followed by radical surgery

Preoperative clinical staging	All patients (N = 42)	Distal resection margin		*p* value
		Group A (≤ 5 mm) (N = 12)	Group B (> 5 mm) (N = 30)	
Tumor depth				0.429
T2	1 (2.4%)	0 (0%)	1 (3.3%)	
T3	38 (90.5%)	10 (83.3%)	28 (93.3%)	
T4	3 (7.1%)	2 (16.7%)	1 (3.3%)	
Lymph node metastasis				0.908
N0	14 (33.3%)	4 (33.3%)	10 (33.3%)	
N1	17 (40.5%)	4 (33.3%)	13 (43.3%)	
N2	11 (26.2%)	4 (33.3%)	7 (23.3%)	
AJCC stage				1.000
I	1 (2.4%)	0 (0%)	1 (3.3%)	
II	13 (31.0%)	4 (33.3%)	9 (30.0%)	
III	28 (66.7%)	9 (66.7%)	20 (66.7%)	

AJCC, American Joint Commission on Cancer.

lymph node yield, vascular invasion, perineural invasion, specimen length, proximal resection margin distance or adjuvant chemotherapy (all $p > 0.05$) (Table 2B).

The median follow-up duration post radical surgery was 41.6 (range: 11.87-60.00) and 49.75 (range: 6.13-65.40) months in groups A and B respectively. The postoperative relapse was similar between the two groups, including locoregional relapse and distant metastases, so postoperative relapse rates were comparable in both groups (33.3% vs. 26.7%, $p = 0.469$), encompassing locoregional relapse (8.3% vs. 13.3%, $p = 0.554$) and distant metastases (33.3% vs. 23.3%, $p = 0.382$) (Table 2C). There was no significant difference of the estimated 1-year and 3-year DFS rate between both groups (83.3% vs. 86.7%, 66.7% vs. 80.0%, respectively, $p = 0.579$) (Fig. 2A). However, during the follow-up period, 4 (33.3%) patients in group A and 3 (10.0%) patients in group B succumbed ($p = 0.088$), so the postoperative mortality rate was non-significantly higher in group A than in group B (33.3% vs. 10.0% respectively, $p = 0.088$). Resultantly, the overall survival (OS) rate was 66.7% in group A and 90.0% in group B ($p = 0.088$) (Table 2C); moreover, significantly better 3-year overall survival rate was noted in group B than in group A (96.7% vs. 75.0%, $p = 0.018$) (Fig. 2B).

Discussions

In this retrospective study, we compared the preoperative clinical staging features, postoperative pathological characteristics, and oncological outcomes of preoperative CCRT followed by radical surgery in patients with low rectal cancer, stratified by a ≤ 5 mm DRM versus > 5 mm DRM. There were no notable differences between the groups in preoperative clinical staging features or postoperative pathological characteristics. Meanwhile, we demonstrated that a significantly better OS in the group with a DRM > 5 mm. The DFS did not show significant differences between the groups; nonetheless, a trend toward better DFS was noted in the group with a DRM > 5 mm.

The surgical management of low rectal cancer, locating within 5 cm from the anal verge, poses challenges regarding sphincter preservation while maintaining oncological safety.[22] Standardization of TME, adoption of neoadjuvant CCRT, utilization of abdominal CT scans, endorectal ultrasonography, magnetic resonance imaging (MRI), and advancements in surgical technique and staplers have elevated the frequency of sphincter-preserving surgeries.[23] In contrast to upper and middle rectal cancers, low rectal cancer exhibits higher rates of local and systemic recurrence, decreased survival, inferior functional outcomes, and reduced quality of life in patients experiencing local relapse.[24] Nevertheless, laparoscopic or robotic surgery, offering high-resolution images, affords superior anatomical visualization, facilitating the adoption of function-preserving surgical approaches and techniques.[25] In this study, all patients received sphincter-preserving surgeries, as low anterior resections with stapled coloanal anastomosis or inter-sphincteric resection; moreover, a markedly greater proportion of patients underwent laparoscopic and robotic surgery (38 out of 42; 90%).

An enduring but unresolved challenge in surgical oncology concerns the adequacy of the DRM in rectal cancer. The majority of studies assessing the significance of DRM within 10 mm have encompassed middle rectal tumors, within 8-12 cm from the anal verge.[26] The median DRM reported in these studies typically ranges from 10-20 mm.[26,27] The optimal length of DRM has not been determined during sphincter-preserving surgery for patients with low rectal cancer due to the dearth of robust evidence. Andreola et al. enrolled patients with low rectal cancers within 5 cm from the anal verge, undergoing total rectal resection with TME and coloanal anastomosis. All patients were devoid of lymph node metastasis and had undergone neoadjuvant CCRT. The median DRM was 5 mm. The results demonstrated that a DRM of less than 10 mm might be adequate for radical surgery, followed by chemoradiotherapy.[28] Leo et al. analyzed 203 patients with low rectal cancer undergoing total rectal resection, possibly followed by chemoradiotherapy and there was a significant association between positive DRM and unfavorable oncological outcomes, although there was no significant difference in postoperative

Table 2B. Postoperative pathologic characteristics of 42 patients with low rectal cancer undergoing preoperative CCRT followed by radical surgery

Postoperative pathological outcomes	All patients (N = 42)	Distal resection margin		*p* value
		Group A (≤ 5 mm) (N = 12)	Group B (> 5 mm) (N = 30)	
Tumor size				0.505
< 5 cm	40 (95.2%)	12 (100%)	28 (93.3%)	
≥ 5 cm	2 (4.8%)	0 (0%)	2 (6.7%)	
Tumor size (cm)				0.815
Mean ± SD (range)	1.66 ± 1.36 (0.0-5.5)	1.64 ± 1.36 (0.0-4.5)	1.67 ± 1.38 (0.0-5.5)	
Median	1.5	1.6	1.5	
Tumor depth				0.701
T0	17 (40.5%)	4 (30.8%)	13 (43.3%)	
Tis	1 (2.4%)	0 (0%)	1 (3.3%)	
T1	5 (11.9%)	1 (7.7%)	4 (13.3%)	
T2	8 (19.0%)	4 (38.5%)	4 (13.3%)	
T3	11 (26.2%)	3 (23.1%)	8 (26.7%)	
Lymph node metastasis				0.570
N0	34 (81.0%)	9 (75.0%)	25 (83.3%)	
N1	7 (16.7%)	3 (25.0%)	4 (13.3%)	
N2	1 (2.4%)	0 (0%)	1 (3.3%)	
AJCC stage				0.523
0	14 (32.6%)	2 (16.7%)	12 (40.0%)	
I	11 (25.6%)	4 (33.3%)	7 (23.3%)	
II	6 (16.3%)	2 (16.7%)	4 (13.3%)	
III	11 (25.6%)	4 (33.3%)	7 (23.3%)	
Down stage of T stage				0.618
Down stage	31 (73.8%)	9 (75.0%)	22 (73.3%)	
Unchanged	11 (26.2%)	3 (25.0%)	8 (26.7%)	
Down stage of N stage				1.000
Down stage	24 (57.1%)	7 (58.3%)	17 (56.7%)	
Unchanged	17 (40.5%)	5 (41.7%)	12 (40.0%)	
Up stage	1 (2.4%)	0 (0%)	1 (3.3%)	
Down stage of AJCC stage				0.799
Down stage	27 (64.3%)	7 (58.3%)	20 (66.7%)	
Unchanged	14 (33.3%)	5 (41.7%)	9 (30.0%)	
Up stage	1 (2.4%)	0 (0%)	1 (3.3%)	
Tumor regression				0.521
Good (0 + 1)	25 (59.5%)	8 (66.7%)	17 (56.7%)	
Poor (2 + 3)	15 (35.7%)	3 (25.0%)	12 (40.0%)	
Not available	2 (4.8%)	1 (8.3%)	1 (3.3%)	
Harvested lymph node				0.139
Mean ± SD (range)	11.86 ± 6.00 (2-33)	10.25 ± 3.70 (3-15)	12.5 ± 6.60 (2-33)	
Median	11.5	10.5	12.0	
Vascular invasion				1.000
No	34 (81.0%)	10 (83.3%)	24 (80.0%)	
Yes	1 (2.4%)	0 (0%)	1 (3.3%)	
Not available	7 (16.7%)	2 (16.7%)	5 (16.7%)	
Perineural invasion				1.000
No	32 (76.2%)	9 (75.0%)	23 (76.7%)	
Yes	3 (7.1%)	1 (8.3%)	2 (6.7%)	
Not available	7 (16.7%)	2 (16.7%)	5 (16.7%)	
Specimen length (cm)				0.186
Mean ± SD (range)	9.42 ± 2.90 (4.5-19.5)	9.91 ± 3.87 (6.0-19.5)	9.23 ± 2.47 (4.5-17.5)	
Median	8.5	8.75	8.5	
Distance of proximal resection margin (cm)				0.498
Mean ± SD (range)	5.95 ± 2.29 (2.0-14.2)	6.28 ± 2.91 (3.5-14.2)	5.82 ± 2.04 (2.0-10.0)	
Median	5.5	5.65	5.4	
Adjuvant chemotherapy				0.495
No	2 (4.8%)	1 (8.3%)	1 (3.3%)	
Yes	40 (95.2%)	11 (91.7%)	29 (96.7%)	

SD, standard deviation; AJCC, American Joint Commission on Cancer.

Table 2C. Oncological outcomes of 42 patients with low rectal cancer undergoing preoperative CCRT followed by radical surgery

Oncological outcomes	All patients (N = 42)	Distal resection margin		*p* value
		Group A (≤ 5 mm) (N = 12)	Group B (> 5 mm) (N = 30)	
Postoperative relapse				0.469
No	30 (71.4%)	8 (66.7%)	22 (73.3%)	
Yes	12 (28.6%)	4 (33.3%)	8 (26.7%)	
Postoperative locoregional relapse				0.554
No	37 (88.1%)	11 (91.7%)	26 (86.7%)	
Yes	5 (11.9%)	1 (8.3%)	4 (13.3%)	
Postoperative distant relapse				0.382
No	31 (73.8%)	8 (66.7%)	23 (76.7%)	
Yes	11 (26.2%)	4 (33.3%)	7 (23.3%)	
Postoperative mortality				0.088
No	35 (83.3%)	8 (66.7%)	27 (90.0%)	
Yes	7 (16.7%)	4 (33.3%)	3 (10.0%)	

A

Disease-free Survival (DFS)	Patients N	Events N (%)	1-year DFS Rate (%)	3-year DFS Rate (%)
Total	42	12	7 (83.3)	10 (76.2)
≤5 mm	12	4	2 (83.3)	4 (66.7)
>5mm	30	8	4 (86.7)	6 (80.0)

B

Overall Survival (OS)	Patients N	Events N (%)	1-year Rate (%)	3-year Rate (%)
Total	42	7	1 (97.6)	4 (90.5)
≤5 mm	12	4	0 (100.0)	3 (75.0)
>5mm	30	3	1 (96.7)	1 (96.7)

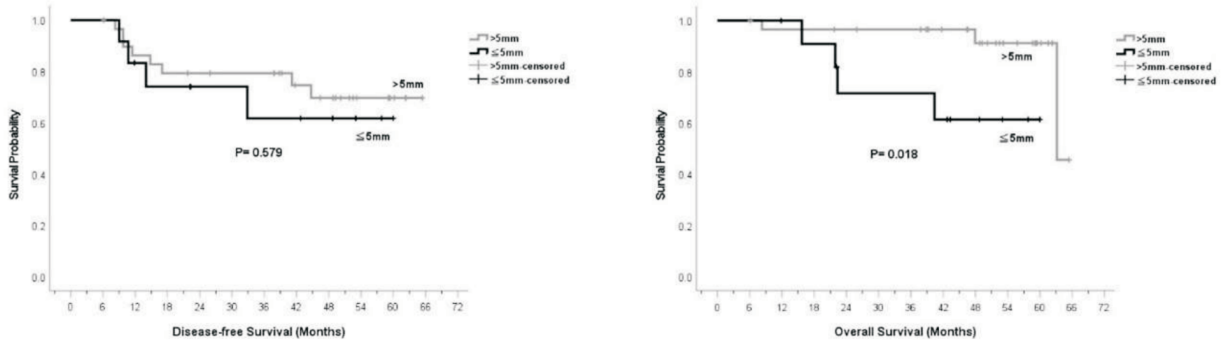

Fig. 2. Kaplan-Meier survival curves for patients with low rectal cancer undergoing preoperative CCRT. (A) Disease-free survival. (B) Overall survival.

mortality, local recurrence and distant metastasis between groups with DRM < 1 cm and ≥ 1 cm.[29] In the present study, we exclusively enrolled patients with low rectal cancer undergoing neoadjuvant chemoradiotherapy and radical surgery, yielding a median DRM of 10 mm, and there were no significant differences in local recurrence, distant metastasis or post-operative mortality rate between groups with DRM ≤ 5 mm and > 5 mm; nevertheless, we demonstrated that there was significant correlation between a ≤ 5 mm DRM and poor 3-year DFS, poor 3-year OS and inferior OS.

Positive circumferential margin is a strong unfavorable survival indicator for colorectal cancer patients, with an increased risk of local relapse and poorer survival.[30,31] Kiran et al. and Kang et al. excluded patients with positive CRM, DRM and those at stage IV, and demonstrated that a DRM of 5 mm was deemed acceptable.[32,33] Additionally, neoadjuvant CCRT was also advocated for patients with clinical stages II and III rectal cancer as it enhances pathologi-

cal response and improves local control.[34-36] Moore et al. investigated groups of individuals diagnosed with rectal cancer who underwent neoadjuvant CCRT, and found that a DRM measuring less than 10 mm did not adversely impact oncological outcomes; Kim et al. observed no notable discrepancy in DFS following neoadjuvant CCRT between ≤ 3 mm and > 3 mm DRM except in cases involving non-responders or individuals with ypT3-4 tumors; while Manegold et al. analyzed 88 patients with clinical stage II or III rectal cancer within 12 cm from the anal verge who received neoadjuvant CCRT and low anterior rectal resection, and found that local recurrences of DRM < 1 cm and DRM ≥ 1 cm were similar (6.1% vs. 5.5%), and there were no significant differences in overall or local recurrence-free survival between the groups.[12,37-38]

Limitations

This study possesses certain limitations that should be considered. Firstly, this is a single-institution retrospective study including only 42 patients, raising the possibility of sampling bias. Secondly, despite all specimens in this study being pinned by formalin, data regarding the DRM distance were derived from the pathology report rather than being directly assessed by a consistent pathologist, so various measurement techniques might influence the length of the DRM. Thirdly, we did not evaluate histology of anastomotic doughnuts in patients receiving low anterior resection with use of circular stapler, and although some studies suggest routine histological examination of anastomotic doughnuts, evidence indicates its low yield and minimal clinical relevance in patient management or prognosis.[39-41] In 2021, a systematic review by Jordan et al. advocated reconsideration of routine evaluation, except in cases with positive margins, as neoplastic findings are exceedingly rare (< 1%).[42] Finally, the follow-up period was relatively brief, with a median duration of 48.3 months, thereby allowing for the reporting of solely short-term (3-year) survival rates and oncological outcomes. According to a multicenter Japanese investigation, the aggregation of recurrences in stages II and III colorectal cancers manifest most rapidly within the first 3 years after curative resection, and although an extended period of observation would be preferable, the median survival of 48.3 months, as evidenced in our study, offers a reasonable indication of oncological outcomes.[43] Despite these limitations, our investigation demonstrated the association of a 5-mm DRM with unfavorable prognostic implications.

Conclusions

In conclusion, this consecutive retrospective study from a single institution demonstrated that a DRM of ≤ 5 mm is associated with unfavorable oncological outcomes. Our results emphasize the importance of securing a clear distal margin during surgical procedures for low rectal cancer. A shorter DRM identifies individuals with poor overall survival and might increase the risk of overall cancer recurrence. For patients with low rectal cancer undergoing neoadjuvant CCRT and radical surgery, a DRM of ≤ 5 mm could present unfavorable oncological outcomes; nevertheless, long-term oncological outcomes warrant further exploration through studies with extended follow-up durations and substantial sample sizes.

Sources of Financial Support

None.

References

1. World Health Organization. Home/Newsroom/Fact sheets/Detail/Colorectal cancer. Available at: https://www.who.int/news-room/fact-sheets/detail/colorectal-cancer
2. Morgan E, Arnold M, Gini A, Lorenzoni V, Cabasag CJ, Laversanne M, Vignat J, Ferlay J, Murphy N, Bray F. Global burden of colorectal cancer in 2020 and 2040: incidence and mortality estimates from GLOBOCAN. *Gut* 2023;72(2):338-44.
3. Ministry of Health and Welfare, the Executive Yuan, Republic of China. Health and Vital Statistics. Available at: https://www.hpa.gov.tw/Pages/List.aspx?nodeid=119. Assessed Nov 10, 2023.
4. Zeng WG, Liu MJ, Zhou ZX, Wang ZJ. A distal resection margin of ≤ 1 mm and rectal cancer recurrence after sph-

incter-preserving surgery: the role of a positive distal margin in rectal cancer surgery. *Dis Colon Rectum* 2017;60(11): 1175-83.
5. Gosens MJ, Klaassen RA, Tan-Go I, Rutten HJ, Martijn H, van den Brule AJ, Nieuwenhuijzen GA, van Krieken JH, Nagtegaal ID. Circumferential margin involvement is the crucial prognostic factor after multimodality treatment in patients with locally advanced rectal carcinoma. *Clin Cancer Res* 2007;13(22 Pt 1):6617-23.
6. Trakarnsanga A, Gonen M, Shia J, Goodman KA, Nash GM, Temple LK, Guillem JG, Paty PB, Garcia-Aguilar J, Weiser MR. What is the significance of the circumferential margin in locally advanced rectal cancer after neoadjuvant chemoradiotherapy? *Ann Surg Oncol* 2013;20(4):1179-84.
7. Nash GM, Weiss A, Dasgupta R, Gonen M, Guillem JG, Wong WD. Close distal margin and rectal cancer recurrence after sphincter-preserving rectal resection. *Dis Colon Rectum* 2010; 53(10):1365-73.
8. Marijnen CA, Nagtegaal ID, Kapiteijn E, Kranenbarg EK, Noordijk EM, van Krieken JH, van de Velde CJ, Leer JW; Cooperative investigators of the Dutch Colerectal Cancer Group. Radiotherapy does not compensate for positive resection margins in rectal cancer patients: report of a multicenter randomized trial. *Int J Radiat Oncol Biol Phys* 2003;55(5):1311-20.
9. Baker JW, Margetts LH, Schutt RP. The distal and proximal margin of resection in carcinoma of the pelvic colon and rectum. *Ann Surg* 1955;141(5):693-706.
10. Goligher JC, Dukes CE, Bussey HJ. Local recurrences after sphincter saving excisions for carcinoma of the rectum and rectosigmoid. *Br J Surg* 1951;39(155):199-211.
11. Hojo K. Anastomotic recurrence after sphincter-saving resection for rectal cancer. Length of distal clearance of the bowel. *Dis Colon Rectum* 1986;29(1):11-4.
12. Moore HG, Riedel E, Minsky BD, Saltz L, Paty P, Wong D, Cohen AM, Guillem JG. Adequacy of 1-cm distal margin after restorative rectal cancer resection with sharp mesorectal excision and preoperative combined-modality therapy. *Ann Surg Oncol* 2003;10(1):80-5.
13. Rutkowski A, Bujko K, Nowacki MP, Chmielik E, Nasierowska-Guttmejer A, Wojnar A; Polish Colorectal Study Group. Distal bowel surgical margin shorter than 1 cm after preoperative radiation for rectal cancer: is it safe? *Ann Surg Oncol* 2008;15(11):3124-31.
14. Kiran RP, Lian L, Lavery IC. Does a subcentimeter distal resection margin adversely influence oncologic outcomes in patients with rectal cancer undergoing restorative proctectomy? *Dis Colon Rectum* 2011;54(2):157-63.
15. Rutkowski A, Nowacki MP, Chwalinski M, Oledzki J, Bednarczyk M, Liszka-Dalecki P, Gornicki A, Bujko K. Acceptance of a 5-mm distal bowel resection margin for rectal cancer: is it safe? *Colorectal Dis* 2012;14(1):71-8.
16. Kwak JY, Kim CW, Lim SB, Yu CS, Kim TW, Kim JH, Jang SJ, Kim JC. Oncologically safe distal resection margins in rectal cancer patients treated with chemoradiotherapy. *J Gastrointest Surg* 2012;16(10):1947-54.
17. Sorrentino L, Sileo A, Daveri E, Battaglia L, Guaglio M, Centonze G, Sabella G, Patti F, Villa S, Milione M, Belli F, Cosimelli M. Impact of microscopically positive (≤ 1 mm) distal margins on disease recurrence in rectal cancer treated by neoadjuvant chemoradiotherapy. *Cancers (Basel)* 2023; 15(6):1828.
18. Wu XJ, Wang JP, Wang L, He XS, Zou YF, Lian L, Zhang LJ, Lan P. Increased rate change over time of a sphincter-saving procedure for lower rectal cancer. *Chin Med J (Engl)* 2008; 121(7):636-9.
19. Weiser MR. AJCC 8th edition: colorectal cancer. *Ann Surg Oncol* 2018;25(6):1454-5.
20. Huang CW, Yeh YS, Su WC, Tsai HL, Choy TK, Huang MY, Huang CM, Wu IC, Hu HM, Hsu WH, Su YC, Wang JY. Robotic surgery with high dissection and low ligation technique for consecutive patients with rectal cancer following preoperative concurrent chemoradiotherapy. *Int J Colorectal Dis* 2016;31(6):1169-77.
21. Mace AG, Pai RK, Stocchi L, Kalady MF. American Joint Committee on Cancer and College of American Pathologists regression grade: a new prognostic factor in rectal cancer. *Dis Colon Rectum* 2015;58:32-44.
22. Piozzi GN, Baek SJ, Kwak JM, Kim J, Kim SH. Anus-preserving surgery in advanced low-lying rectal cancer: a perspective on oncological safety of intersphincteric resection. *Cancers (Basel)*. 2021;13(19):4793.
23. Do L, Syed N, Puthawala A, Azawi S, Shbeeb I, Gong IY. Low-lying rectal cancer with anal canal involvement: abdominoperineal or low anterior resection after neoadjuvant chemoradiotherapy. *Gastrointest Cancer Res* 2011;4(3):90-5.
24. Chen ZH, Song XM, Chen SC, Li MZ, Li XX, Zhan WH, He YL. Risk factors for adverse outcome in low rectal cancer. *World J Gastroenterol* 2012;18(1):64-9.
25. Varela C, Kim NK. Surgical treatment of low-lying rectal cancer: updates. *Ann Coloproctol* 2021;37(6):395-424.
26. Bhamre R, Mitra A, Tamankar A, Desouza A, Saklani A. Impact of length of distal margin on outcomes following sphincter preserving surgery for middle and lower third rectal cancers. *Indian J Surg Oncol* 2019;10(2):335-41.
27. Metwally IH, Zuhdy M, Hamdy O, Fareed AM, Elbalka SS. The impact of narrow and infiltrated distal margin after proctectomy for rectal cancer on patients' outcomes: a systematic review and meta-analysis. *Indian J Surg Oncol* 2022;13(4): 750-60.
28. Andreola S, Leo E, Belli F, Bonfanti G, Sirizzotti G, Greco P, Valvo F, Tomasic G, Gallino GF. Adenocarcinoma of the lower third of the rectum surgically treated with a < 10-mm distal clearance: preliminary results in 35 N0 patients. *Ann Surg Oncol* 2001;8(7):611-5.
29. Leo E, Belli F, Miceli R, Mariani L, Gallino G, Battaglia L, Vannelli A, Andreola S. Distal clearance margin of 1 cm or less: a safe distance in lower rectum cancer surgery. *Int J*

Colorectal Dis 2009;24(3):317-22.
30. Rickles AS, Dietz DW, Chang GJ, Wexner SD, Berho ME, Remzi FH, Greene FL, Fleshman JW, Abbas MA, Peters W, Noyes K, Monson JR, Fleming FJ; Consortium for Optimizing the Treatment of Rectal Cancer (OSTRiCh). High rate of positive circumferential resection margins following rectal cancer surgery: a call to action. *Ann Surg* 2015;262(6):891-8.
31. Tang XY, Huang MX, Han SQ, Chang Y, Li ZP, Kao XM, Chen YY, Liu C, Huang YD, Chen YT, Lei ZJ, Chu XY. The circumferential resection margin is a prognostic predictor in colon cancer. *Front Oncol* 2020;10:927.
32. Kiran RP, Lian L, Lavery IC. Does a subcentimeter distal resection margin adversely influence oncologic outcomes in patients with rectal cancer undergoing restorative proctectomy? *Dis Colon Rectum* 2011;54(2):157-63.
33. Kang DW, Kwak HD, Sung NS, Yang IS, Baek SJ, Kwak JM, Kim J, Kim SH. Oncologic outcomes in rectal cancer patients with a ≤ 1-cm distal resection margin. *Int J Colorectal Dis* 2017;32(3):325-32.
34. Ceelen W, Fierens K, Van Nieuwenhove Y, Pattyn P. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer: a systematic review and meta-analysis. *Int J Cancer* 2009;124(12):2966-72.
35. Song JH, Jeong JU, Lee JH, Kim SH, Cho HM, Um JW, Jang HS; Korean Clinical Practice Guideline for Colon and Rectal Cancer Committee. Preoperative chemoradiotherapy versus postoperative chemoradiotherapy for stage II-III resectable rectal cancer: a meta-analysis of randomized controlled trials. *Radiat Oncol J* 2017;35(3):198-207.
36. Babaei M, Jansen L, Balavarca Y, Sjövall A, Bos A, van de Velde T, Moreau M, Liberale G, Gonçalves AF, Bento MJ, Ulrich CM, Schrotz-King P, Lemmens V, Glimelius B, Brenner H. Neoadjuvant therapy in rectal cancer patients with clinical stage II to III across European countries: variations and outcomes. *Clin Colorectal Cancer* 2018;17(1):e129-42.
37. Kim TG, Park W, Choi DH, Kim SH, Kim HC, Lee WY, Park JO, Park YS. The adequacy of the distal resection margin after preoperative chemoradiotherapy for rectal cancer. *Colorectal Dis* 2014;16(8):O257-63.
38. Manegold P, Taukert J, Neeff H, Fichtner-Feigl S, Thomusch O. The minimum distal resection margin in rectal cancer surgery and its impact on local recurrence - a retrospective cohort analysis. *Int J Surg* 2019;69:77-83.
39. Morgan A, Dawson PM, Smith JJ. Histological examination of circular stapled 'doughnuts': questionable routine practice? *Surgeon* 2006;4(2):75-7.
40. Dixon S, Barrow H, Hughes J. Doughnut bother! Histopathological examination of anastomotic doughnuts following colorectal anastomosis does not change patient management. *Surg Exp Pathol* 2020;3(1):2.
41. Ng CW, Lieske B, Tan KK. Routine histological sampling of doughnuts post oncologic anterior resection is not necessary. *Int J Colorectal Dis* 2014;29(7):843-5.
42. Wlodarczyk J, Gaur K, Mertz K, Wickham C, Mirza KL, Hsieh C, Cologne KG. Do or doughnut: a systematic review and pooled analysis on the utility of pathological evaluation of the anastomotic doughnut in oncological colorectal operations. *Colorectal Dis* 2022;24(1):8-15.
43. Kobayashi H, Mochizuki H, Sugihara K, Morita T, Kotake K, Teramoto T, Kameoka S, Saito Y, Takahashi K, Hase K, Oya M, Maeda K, Hirai T, Kameyama M, Shirouzu K, Muto T. Characteristics of recurrence and surveillance tools after curative resection for colorectal cancer: a multicenter study. *Surgery* 2007;141(1):67-75.

原　著

遠端切緣距離 5 毫米對術前輔助性同步化學放射治療和根治性直腸切除手術的低位直腸癌患者預後之影響

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目的　低位直腸癌患者的最佳的遠端切緣距離 (DRM) 仍具爭議，因此我們試圖探討遠端切緣距離 ≤ 5 毫米對低位直腸癌的影響。

方法　本研究以回溯方式蒐集自 2018 年 1 月至 2020 年 12 月在高雄醫學大學附設醫院接受術前輔助性同步化學放射治療 (CCRT) 和根治性直腸切除手術的低位直腸癌患者。本研究分析病人之臨床資訊、局部復發、遠端轉移及存活率。

結果　我們納入了 42 名患者。根治性手術後的平均追蹤時間為 41.6 個月。兩組間 3 年無疾病存活率無顯著差異，但遠端切緣距離 ≤ 5 毫米的患者無疾病存活期相對較短。而遠端切緣距離 > 5 毫米的患者有顯著性較好之整體存活率。

結論　接受術前輔助性同步化學放射治療和根治性直腸切除手術的低位直腸癌患者的遠端切緣距離 ≤ 5 毫米與不良的預後相關。手術中確保足夠的遠端切緣距離對低位直腸癌非常重要。然而，長期的腫瘤學結果值得透過延長追蹤時間和大量樣本量的研究進行進一步探索。

關鍵詞　遠端切緣距離、預後、低位直腸癌、術前輔助性同步化學放射治療。