

A Subcentimeter Distal Rectal Margin and its Impact on Local Recurrence in Rectal Cancer Patients Undergoing Curative Surgery after Preoperative Chemoradiotherapy

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ABSTRACT

Background and objectives: A 1 cm Distal Resection Margin (DRM) was recommended. Controversy still exists if we can obtain DRM less than 1 cm who had preoperative Chemoradiotherapy (CRT). Our study aimed to determine the clinical outcomes who had subcentimeter DRM.

Methods: 740 patients with rectal cancer were assessed. 145 patients with rectal cancer underwent curative resection after preoperative CRT were included. The median follow-up time was 28 months.

Results: 36 (24.8%) patients had DRM <1 cm. Local recurrence occurred in 27 patients (18.6%). Overall recurrence was significantly higher in patients with DRM ≤ 0.4 cm than DRM >0.4 cm (50% vs. 16.1%; p=0.015). Moreover, patients who had DRM ≤ 0.4 cm were significantly associated with higher local recur-

rence than systemic recurrence (p=0.037). Disease Free Survival (DFS) of patients with DRM >0.4 cm was significantly higher than that of patients with DRM ≤ 0.4 cm (p=0.002). In patients with DRM <0.5 cm and >0.5 cm, there were no statistically significant differences in recurrence (p=0.068) and DFS (p=0.107).

Conclusion: The results suggest that cutoff point at 0.5 cm was a minimally acceptable DRM. Minimizing DRM to <1 cm to increase chance of sphincter-saving. Intense adjuvant therapy should be used in these patients to reduce recurrence.

Keywords: Rectal cancer, distal resection margin, surgery, preoperative chemoradiotherapy

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INTRODUCTION

According to the Global Cancer Observatory (GLOBOCAN) 2018 (Bray F, *et al.*, 2018), Rectal cancer is the 8th most incidence. The mortality rate is 3.2%. Overall, it is apparent that the oncologic resection of rectal cancer depend on Circumferential Resection Margin (CRM) and Distal Resection Margin (DRM). A negative CRM is defined as tumor more than 1 millimeter from the margin (Benson AB, *et al.*, 2021). Total Mesorectal Excision (TME) in rectal cancer surgery reduces local recurrence rate from 14%-40% down to 6.5% (Ahuja V, 2010). The distal rectal margin is defined as the distance from the lowest mesorectal cancer spread from TME and intramural spread to the distal dissection line. Therefore, DRM is important factor for the decision of function outcome if sphincter preserving procedure is feasible.

From the literature reviews (Krishnamurthy MD and Wise PE, 2016) of the cut point of DRM in rectal cancer patient treated without neoadjuvant therapy, DRM of 1 cm-2 cm was found to be oncologic all sufficient. Therefore, the current guidelines (Benson AB, *et al.*, 2021; Hashiguchi Y, *et al.*, 2020) supported with previous evidence show that 2 cm distal mural margin combined with TME in middle and lower rectal cancer is acceptable (Figure 1).

In case of rectal cancer patient treated with neoadjuvant therapy, preoperative CCRT induces regression in most rectal cancers (Manegold P, *et al.*, 2019). However rectal cancer regression in response to CCRT follows a scattered approach. Hayden DM, *et al.*, 2012 reported 49.1% of patients with tumor scatter had tumor cells scatter distally from the inferior edge of the visible ulcer. The distance of distal scatter found 0.1 cm to 3 cm. The reason why the optimal distal rectal margin after preoperative CCRT from the literature reviews (Krishnamurthy MD and Wise PE, 2016; Mane-

gold P, *et al.*, 2019) of the cut point of DRM in rectal cancer patient treated with neoadjuvant therapy, adequate DRM is still controversial. A 1 cm DRM was recommended as the shortest clearance margin in clinical guidelines. Controversy still exists if we can obtain DRM less than 1 cm in order to achieve goal of sphincter-saving, especially in patients who had preoperative CRT. So, this study aimed to determine the clinical outcomes of rectal cancer patients who had subcentimeter DRM and the cutoff point that may affect the oncological outcomes.

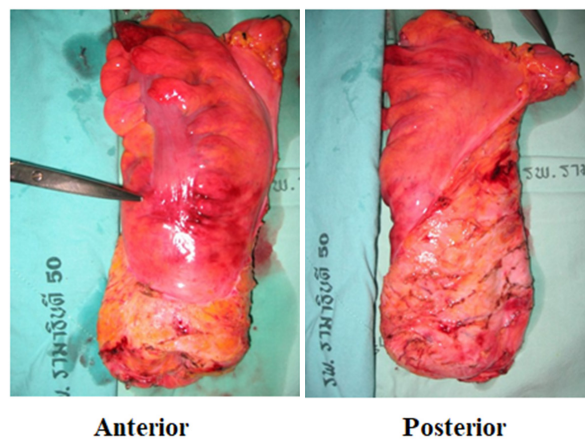


Figure 1: These pictures illustrate the specimens of middle and lower rectal cancer after TME

MATERIAL AND METHODS

This retrospective study was approved by the human research Ethics Committee, Faculty of Medicine Ramathibodi Hospital,

Mahidol University (COA. MURA2021/427). We reviewed the data of locally advanced rectal cancer underwent curative resection after preoperative CCRT from a prospective cancer database institution between 2015 and 2019 in Ramathibodi hospital.

A total of 740 patients with rectal cancer were enrolled. Then, 595 patients were excluded by less than 6 months of follow up (n=96), no radiotherapy (n=190), post-operative RT (n=129), no surgery (n=68), stage 4 (n=69), synchronous lesion (n=15), colon cancer (n=21), benign disease (n=1), watch and wait management after preoperative CCRT (n=1), R2 resection (n=2) and local excision (n=3). Finally, there were 145 patients with locally advanced rectal cancer underwent curative resection after preoperative CCRT for data collection and analysis.

All patients had preoperative clinical assessment and staging, including medical history, digital rectal examination, colonoscopy, sigmoidoscopy, Computerized Tomography (CT) and magnetic resonance imaging.

All patients underwent preoperative CCRT. Data of preoperative CCRT were collected including chemosensitization regimen, waiting time to surgery, post CCRT Carcinoembryonic Antigen (CEA) and clinical response. All patients had radical resection of rectal cancer after neoadjuvant treatment. Operation included low anterior resection, ultra-low anterior resection, intersphincteric resection and coloanal anastomosis, abdominoperineal resection, low anterior resection and end colostomy surgery.

Final pathology with DRM, CRM, number of examined Lymph Nodes (LNs), number of positive lymph node, Perineural Invasion (PNI), Lymphovascular Invasion (LVI), tumor deposit, postoperative CEA, postoperative complication, adjuvant chemotherapy, postoperative CEA were collected. The following clinical outcomes were analyzed for recurrence and disease free survival.

Primary outcomes were clinical outcomes of subcentimeter DRM and the cutoff point of DRM. Secondary outcome were other prognosis factors related recurrence.

Definition of variables

Measurement of distal rectal margin by the pathologist from lowest edge of tumor or ulcer to distal rectal margin after tissue fixation was carried out. Complete response to CCRT, the lowest edge from scar tissue to the distal resection was measured.

Circumferential Resection Margin (CRM): A clear CRM was defined as the absence of tumor involvement of the margin on microscopic examination of the pathologic specimen.

Preoperative chemoradiotherapy: In general, T3/T4 or nodal metastasis are indications for preoperative chemoradiotherapy at our institution. Preoperative CCRT consisted of a radiation dose of 50.4 to 55.8 Gy in 28 to 33 fractions, administered five times a week. Concurrent chemotherapy consisted of 5-fluorouracil, 1,000 mg/m²/day continuous drip for 5 days per cycle for the first and last weeks of RT, or capecitabine, 850 mg/m²/day for 5 days per week for 5 weeks.

Technique of total mesorectal excision: In case of low and middle rectal cancer, surgical dissection (*Figure 2*) along embryonic plane comprising avascular areolar tissue between the mesorectal fascia and the fascia of pelvic sidewall while upper rectal cancer, the mesorectum was divided at 5 cm distal to the mucosal edge of tumor. All the surgeons were experienced in colorectal surgery. Intravenous antibiotics were administered 30 minutes before operation and continued for 24-48 hours after surgery. Anastomosis was performed by circular stapling devices or handsewn. According to tumor location and the intraoperative situation, a temporary ileostomy was performed at the surgeon's preference.

Adjuvant therapy: Indications for adjuvant therapy included positive lymph nodes, unfavorable prognostic factors, pT3 or T4, pathological stage 3. Moreover, for patient with a microscopically positive DRM (0 mm < DRM ≤ 1 mm), the decision for adjuvant chemotherapy was made by multidisciplinary team.



Figure 2: Specimen of middle rectal cancer after preoperative CCRT

Follow up

Patients were followed with history, DRE and CEA 3 month interval within the first 2 years and 6 months interval thereafter. Patients were recommended to CT abdomen and pelvis at 6-month interval and colonoscopy every 1-2 years. If recurrence was suspected, MRI ± PET/CT were performed.

Recurrence

Local recurrence was defined as recurrence in the intrapelvic area, including the anastomotic area and/or regional lymphatics. Systemic recurrence was defined as recurrence beyond the local recurrence, such as in the liver, lung, and/or non-regional lymphatics and other extra pelvic sites. DFS and OS were defined as the interval to the date of the first recurrence and to the date of death from any cause, respectively.

Statistical analysis

Patients with a distal margin of ≤ 0.4 cm (group A) were compared with those with a distal margin >0.4 cm (group B). Categorical variables were summarized as counts and percentages and compared with the use of Chi-square test. Continuous variables compared with the use of two-sample independent T-test. Univariate and multivariate analysis compared with the use of Cox proportional hazards model. Survival and recurrence were calculated by the Kaplan-Meier method. STATA version 14 was used for statistical analysis. The level of significance was set at p<0.05.

RESULTS

Study population

One hundred, 45 patients were included in the study. 93 (64.13%) were male with a mean age at surgery 61.4 years. Preoperative clinical staging included T2 (n=6), T3 (n=120), T4 (n=19) and N stage included N0 (n=47), N1 (n=78), N2 (n=19), and N3 (n=1). The median distance of the tumor from the anal verge on preoperative assessment was 6.7 cm. The median tumor length was 4 cm. Histology confirmed rectal cancer including 30 (20.7%) well differentiated adenocarcinoma, 108 (74.5%) moderately differentiated adenocarcinoma, 5 (3.5%) poorly differentiated adenocarcinoma, 2 (1.4%) dysplasia cell (Table 1).

Table 1: Characteristics of patients

Characteristics	n=145
Distal margin (cm), median (IQR)	2 (1.1 to 3.9)
Age; mean ± SD	61.4 ± 10.9
Gender, n (%)	
Male	93 (64.1)
Female	52 (35.9)
Location (cm from AV), median (IQR)	6.7 (4.8 to 9.0)
Preoperative biopsy, n (%)	
Well differentiation	30 (20.7)
Moderate differentiation	108 (74.5)
Poor differentiation	5 (3.5)
Fragment of dysplastic cell	2 (1.4)
Tumor length (cm), median (IQR)	4 (3 to 5.2)
Clinical T stage, n (%)	
T2	6 (4.1)
T3	120 (82.8)
T4	19 (13.10)

Clinical N stage, n (%)	
N0	47 (32.4)
N1	78 (53.8)
N2	19 (13.1)
N3	1 (0.7)
Concurrent chemotherapy regimen, n (%)	
5 FU/LV	67 (46.2)
Xeloda	76 (52.4)
FOLFOX	2 (1.4)
Waiting time from last RT (days), median (IQR)	69 (60 to 88)
Pre CRT CEA, median (IQR)	5.6 (2.9 to 13.9)
Post CRT CEA, median (IQR)	3.2 (2.2 to 5.2)
Postoperative CEA, median (IQR)	2.6 (1.7 to 3.9)
Clinical response, n (%)	
No	3 (2.1)
Partial (by scope)	119 (82.1)
complete Clinical Response (cCR)	14 (9.7)
Not assessed	9 (6.2)
Operation, n (%)	
LAR	68 (46.9)
Ultra LAR	5 (3.5)
APR	22 (15.2)
LAR with end colostomy	18 (12.4)
Diversion then LAR	7 (4.8)
Diversion then APR	3 (2.1)
Laparoscopic LAR	16 (11.0)
ISR with CCA	2 (1.4)
Laparoscopic APR	4 (2.8)
Complication, n (%)	
Surgical site infection (SSI)	4 (2.8)
Perineal SSI	3 (2.1)
Presacral collection	8 (5.5)
Urine retention	1 (0.7)
Ureteric injury	1 (0.7)
Specimen, n (%)	
No residual tumor	20 (13.8)
Well differentiation	13 (8.9)
Moderate differentiation	102 (70.3)
Poorly differentiation	3 (2.1)
Residual tumor (could not classify)	7 (4.8)
T down staging, n (%)	76 (52.4)
ypT staging, n (%)	
0	23 (15.9)
1	4 (2.8)
2	39 (26.9)

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3	74 (51.0)
4	5 (3.5)
N down staging; n (%)	91 (62.8)
Positive(number) LN, median (IQR)	0 (0 to 1)
LN all (number), median (IQR)	13 (8 to 19)
LN ratio group, n (%)	
0	97 (67.8)
0.1-0.2	30 (20.9)
0.2	16 (11.2)
ALI, n (%)	33 (23.2)
PNI, n (%)	27 (19.4)
CRM, median (IQR)	1 (0.5 to 2)
Tumor deposit, n (%)	7 (46.7)
Timing adjuvant CMT (days), median (IQR)	43 (32 to 56)
Adjuvant chemotherapy regimen, n (%)	
FOLFOX	20 (19.4)
XELOX	31 (30.1)
5FU/LV	25 (24.3)
Xeloda	27 (26.2)
Cycle, median (IQR)	6 (6 to 8)
Follow-up time (months); median (IQR)	28 (19 to 44)

Preoperative chemoradiotherapy

Preoperative CRT consisted of a median radiation dose of 50.4 Gy and concurrent intravenous fluorouracil in 67 (46.2%) patients or oral capecitabine in 76 (52.4%) patients. 2 (1.38%) patients received a combination of fluoropyrimidine based chemotherapy and oxaliplatin. Median of CEA level before and after CRT were 5.6 and 3.2, respectively.

Surgery

Surgery was performed 69 weeks (range 60 to 88 weeks) after completion of CRT. Operative procedure performed included 68 (46.9%) Low Anterior Resection (LAR), 5 (3.5%) ultraLAR, 22 (15.2%) abdominoperineal resection, 18 (12.4%) LAR with end colostomy, 7 (4.8%) diversion colostomy in case obstruction follow by LAR, 3 (2.1%) diversion colostomy in case obstruction follow by APR, 16 (11.0%) laparoscopic LAR, 4 (2.8%) laparoscopic APR, and 2 (1.4%) intersphincteric resection with coloanal anastomosis. Median of CEA level after operation was 2.6.

Postoperative morbidity

Post-operative complication occurred in 17 (11.72%) out of 145 patients. Surgical Site Infection (SSI), perineal SSI, persacral collection, anastomosis stricture, urinary retention and ureteric injury developed in 4 (2.8%), 3 (2.1%), 8 (5.5%), 1 (0.7%), 1 (0.7%) patients, respectively.

Tumor characteristics

Distal margin of resection ranged from 0 to 11.3 cm, with a median of 2 cm. Thirty-six (24.8%) patients had DRM <1 cm. Circumferential rectal margin range 0.5-2, with median of 1 cm. Complete and partial clinical response were resulted in 14 (9.7%), 119 (82.1%) patients, respectively. No clinical response was found in 3 (2.1%) patients. Final pathology reported 20 (13.8%) no residual tumor or complete pathological response, 13 (8.9%) well differentiated adenocarcinoma, 102 (70.3%) moderately differentiated adenocarcinoma, 3 (2.1%) poorly differentiated adenocarcinoma, 7 (4.8%) unclassified residual tumor. There were 33 (23.2%) Angiolymphatic In-

vasion (ALI), 27 (19.4%) Perineural Invasion (PNI) and 7 (46.7%) tumor deposit. Pathological staging included T0 (n=23), T1 (n=4), T2 (n=39), T3 (n=74) and T4 (n=3.5). Pathological T and N down staging were found in 76 (52.4%) and 91 (62.8%). Median of total lymph nodes were 13, ranged 8 to 19.

Adjuvant chemotherapy

Patients were received adjuvant chemotherapy on median 43 days after surgery with 20 (19.4%) FOLFOX, 31 (30.1%) XELOX, 25 (24.3%) 5FU/LV and 27 (26.2%) capecitabine. A median cycles of adjuvant chemotherapy were 6 (range 6 to 8). There were 8 patients in group A and 137 patients in group B. Comparison of patient characteristics between the 2 groups is shown in Table 2.

Table 2: Characteristics of patients in different subgroups

Variables	≤ 0.4 cm (n=8)	>0.4 cm (n=137)	p-value
Distal margin (cm), median (IQR)	0.2 (0.0-0.3)	2.2 (1.5-4.0)	<0.001
Age, mean ± SD	55 (43-58.5)	62 (54-69)	0.006
Gender, n (%)			
Male	5 (62.5)	88 (64.2)	0.921
Female	3 (37.5)	49 (35.8)	
Location (cm from AV), median (IQR)	3.7 (2.3-4.1)	7.0 (5.0-9.0)	0.0005
Preoperative biopsy, n (%)			
Well differentiation	3 (37.5)	27 (19.7)	0.631
Moderate differentiation	5 (62.5)	103 (75.2)	
Poorly differentiation	0 (0)	5 (3.7)	
Fragment of dysplastic cell	0 (0)	2 (1.5)	
Tumor length (cm), median (IQR)	4.1 (3.1-5.4)	4.0 (3.0-5.2)	0.758
Clinical T stage, n (%)			
T2	0 (0)	6 (4.4)	0.934
T3	7 (87.5)	113 (82.5)	
T4	1 (12.5)	18 (13.13)	
Clinical N stage, n (%)			
N0	0 (0)	47 (34.3)	0.219
N1	6 (75)	72 (52.6)	
N2	2 (25)	17 (12.4)	
Concurrent chemotherapy regimen, n (%)			
5 FU/LV	2 (25)	65 (47.5)	0.014
Xeloda	5 (62.5)	71 (51.8)	
FOLFOX	1 (12.5)	1 (0.7)	
Waiting time from RT (days), median (IQR)	70.5 (61.5-78.5)	69.0 (60.0-89.0)	0.883
Pre CRT CEA, median (IQR)	2.5 (1.7-4.6)	5.8 (3.1-14.1)	0.071

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Post CRT CEA, median (IQR)	2.0 (1.5-5.9)	3.2 (2.2-5.2)	0.272	
Post-operative CEA, median (IQR)	2.0 (1.5-3.5)	2.6 (1.7-3.9)	0.547	
Clinical response, n (%)				
No	1 (12.5)	2 (1.5)	0.059	
Partial (by scope)	5 (62.5)	114 (83.2)		
cCR (complete Clinical Response)	2 (25.0)	12 (8.8)		
Not assessed	0 (0)	9 (6.6)		
Operation, n (%)				
LAR	3 (37.5)	65 (47.45)	0.192	
Ultra LAR	1 (12.5)	4 (2.9)		
APR	1 (12.5)	21 (15.3)		
LAR with end colostomy	0 (0)	18 (13.1)		
Diversion then LAR	0 (0)	7 (5.1)		
Diversion then APR	1 (12.5)	2 (1.5)		
Laparoscopic LAR	1 (12.5)	15 (10.9)		
ISR with CCA	0 (0)	2 (1.5)		
Laparoscopic APR	1 (12.5)	3 (2.2)		
Complication, n (%)				
Surgical site infection (SSI)	0 (0)	4 (2.9)		0.624
Perineal SSI	0 (0)	3 (2.2)		0.672
Presacral collection	0 (0)	8 (5.8)		0.482
Urine retention	0 (0)	1 (0.7)	0.808	
Ureteric injury	0 (0)	1 (0.7)	0.808	
Specimen, n (%)				
no residual tumor	2 (25)	18 (13.1)	0.71	
Well differentiation	0 (0)	13 (9.5)		
Moderate differentiation	6 (75)	96 (70.1)		
Poorly differentiation	0 (0)	3 (2.2)		
Residual tumor (could not classify)	0 (0)	7 (5.1)		
T down staging, n (%)	5 (62.5)	71 (51.8)	0.557	
ypT staging, n (%)				
0	2 (25)	21 (15.3)	0.384	
1	0 (0)	4 (2.9)		
2	3 (37.5)	36 (26.3)		
3	2 (25)	72 (52.6)		
4	1 (12.5)	4 (2.9)		
N down staging, n (%)	5 (62.5)	86 (62.8)	0.988	

Pos LN, median (IQR)	0 (0, 2)	0 (0, 1)	0.885
LN all (number), median (IQR)	18.5 (15, 27)	13 (8, 18.5)	0.022
LN ratio group, n (%)			
0	6 (75)	91 (67.4)	0.193
0.1-0.2	0 (0)	30 (22.2)	
0.2	2 (25)	14 (10.4)	
ALI, n (%)	1 (12.5)	32 (23.9)	0.459
PNI, n (%)	3 (37.5)	24 (18.3)	0.183
CRM, median (IQR)	1.3 (0.5, 2)	1 (0.5, 2)	0.962
Adjuvant chemotherapy regimen, n (%)			
FOLFOX	1 (16.7)	19 (19.6)	0.586
XELOX	1 (16.7)	30 (30.9)	
5FU/LV	1 (16.7)	24 (24.7)	
Xeloda	3 (50)	24 (24.7)	
Cycles, median (IQR)	7 (6, 8)	6 (6, 8)	0.261
Tumor deposit, n (%)	1 (20)	6 (60)	0.143

Clinical and pathologic characteristics

Characteristics of each group are described in Table 2. The location of tumor and age were significantly higher in group B than group A (7 cm vs. 3.7 cm, $p=0.0005$, 62 years vs. 55 years, $p=0.006$, respectively). Other characteristics including gender, preoperative histology, tumor length and clinical stage were no significant difference between 2 groups. According to CCRT regimen, xeloda regimen was significantly higher than 5FU/LV regimen in group A ($p=0.014$). Most of patients in 2 groups had partial clinical response. Other characteristics including waiting time from last RT to surgery, CEA level before and after CCRT and postoperative CEA were no significant difference between 2 groups. The kind of procedure included non-diversion, diversion first and laparoscopic surgery. There was no significant difference between 2 groups ($p=0.192$). Pathological characteristics between 2 groups, overall LN was significantly higher in group A than group B (18.5 vs. 13, $p=0.022$). Other characteristics including final histology, pathological staging, angiolymphatic invasion, perineural invasion, tumor deposit, circumferential rectal margin were no significant difference between 2 groups. Post-operative complication, there was no significant difference between 2 groups. There was no significant difference for adjuvant chemotherapy regimen between 2 groups. Most patients received a combination of fluoropyrimidine based chemotherapy and oxaliplatin.

Local recurrence rate and disease free survival

After a median length of follow-up of 28 months (range 19-44), Local Recurrence (LR) occurred in 26 patients (17.9%). Local recurrence occurred in 27 patients (18.6%). Overall recurrence was significantly higher in group A than group B (50% vs. 16.1%; $p=0.015$). Moreover, group A were significantly associated with higher local recurrence than systemic recurrence ($p=0.037$). Disease Free Survival (DFS) of group B was significantly higher than that of patients with group A ($p=0.002$). In patients with DRM <0.5 cm and >0.5 cm, there were no statistically significant differences in recurrence ($p=0.068$) and DFS ($p=0.107$). No significant difference of survival between local and systemic recurrence group ($p=0.146$) (Figures 3-6 and Table 3).

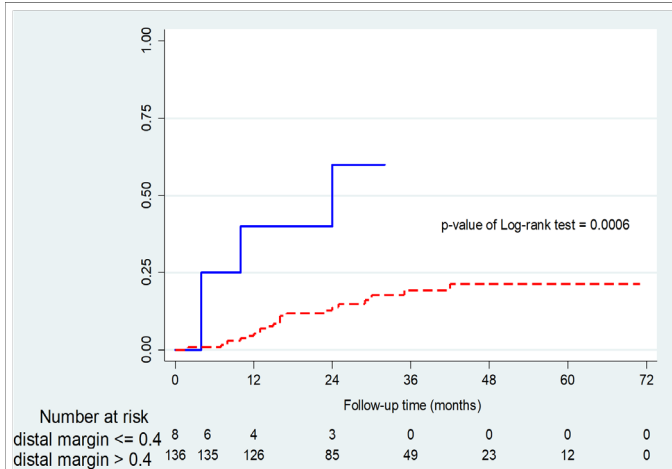


Figure 3: Kaplan-Meier curves evaluating recurrence for patients with distal margin of clearance ≤ 0.4 cm and >0.4 cm
 Note: (—): Distal margin ≤ 0.4 cm; (- - -): Distal margin >0.4 cm

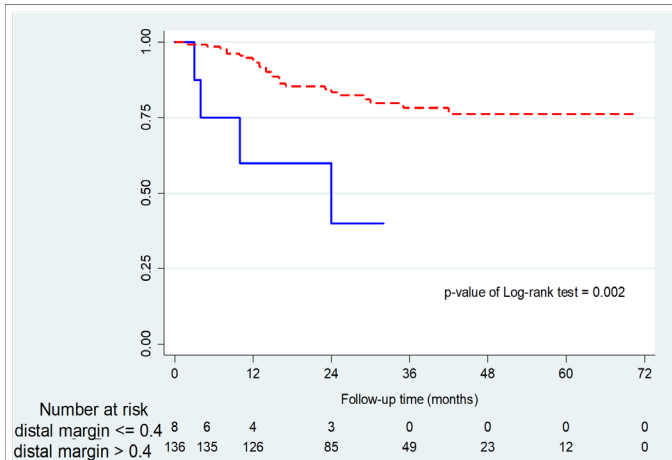


Figure 4: Kaplan-Meier curves evaluating disease-free survival for patients with distal margin of clearance ≤ 0.4 cm and >0.4 cm
 Note: (—): Distal margin ≤ 0.4 cm; (- - -): Distal margin >0.4 cm

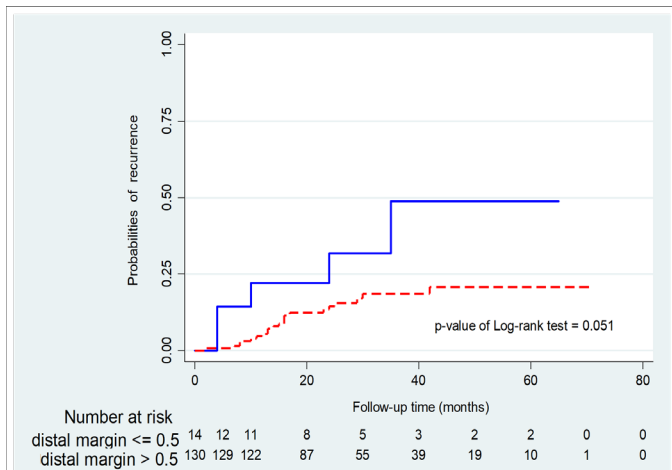


Figure 5: Kaplan-Meier curves evaluating recurrence for patients with distal margin of clearance ≤ 0.5 cm and >0.5 cm
 Note: (—): Distal margin ≤ 0.4 cm; (- - -): Distal margin >0.4 cm

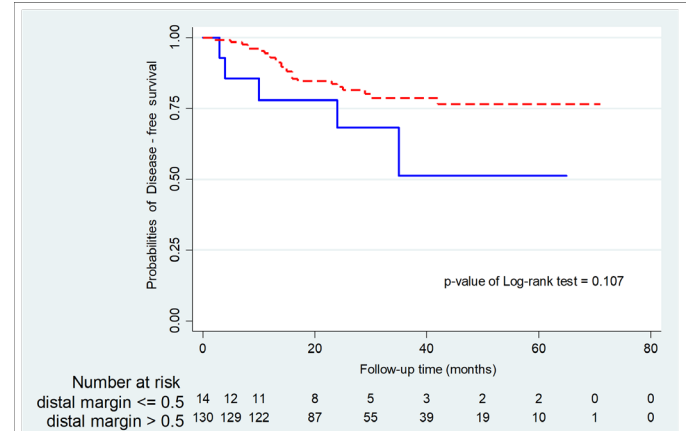


Figure 6: Kaplan-Meier curves evaluating disease-free survival for patients with distal margin of clearance ≤ 0.5 cm and >0.5 cm
 Note: (—): Distal margin ≤ 0.4 cm; (- - -): Distal margin >0.4 cm

Table 3: Recurrence and death between margin ≤ 0.4 cm and >0.4 cm

Variables	≤ 0.4 cm (n=8)	>0.4 cm (n=137)	p-value
Recurrence, n (%)	4 (50)	22 (16.1)	0.015
Type of recurrence, n (%)			
Local recurrence	3 (75)	5 (22.7)	0.037
Systemic recurrence	1 (25)	17 (77.3)	
Recurrence and death, n (%)	4 (50)	26 (19)	0.035
Death, n(%)	1 (12.5)	16 (11.7)	0.944

A univariable analysis (Table 4) of unfavorable factors associated with LR and DFS including N staging, waiting time from last RT to surgery, postoperative CEA, post-operative complication (surgical site infection, presacral collection), ypT staging, Lymph Node (LN) ratio (positive LN/total LN), perineural invasion. A multivariable analysis (Table 5) of unfavorable factors associated with LR and DFS including positive lymph node.

Table 4: Factors associated with recurrence and DFS after operations between distal margin ≤ 0.4 with >0.4 cm

Variables	Recurrence		DFS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Distal margin >0.4 cm	0.19 (0.06-0.55)	0.002	0.22 (0.08-0.64)	0.005
Age	1.00 (0.97-1.05)	0.804	0.99 (0.96-1.03)	0.61
Gender		0.631	0.814	
Male	Baseline	-	Baseline	-
Female	0.82 (0.35-1.88)		0.91 (0.43-1.95)	
Location (cm from AV)	0.97 (0.85-1.10)	0.63	0.97 (0.86-1.09)	0.638
Preoperative biopsy	0.57 (0.27-1.21)	0.144	0.65 (0.33-1.31)	0.229

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Tumor length (cm)	0.97 (0.80-1.17)	0.724	0.98 (0.83-1.16)	0.829
Clinical T stage	0.77 (0.30-1.98)	0.581	0.74 (0.31-1.80)	0.512
Clinical N stage	2.03 (1.14-3.60)	0.015	1.84 (1.08-3.13)	0.025
Concurrent chemotherapy regimen, n (%)				
5 FU/LV	Baseline	-	Baseline	-
Xeloda	0.76 (0.34-1.69)	0.504	0.78 (0.38-1.64)	0.517
XELOX	-	-	-	-
FOLFOX	3.27 (0.41-25.85)	0.261	3.34 (0.43-25.67)	0.247
Waiting time from last RT (days)	1.01 (0.99-1.01)	0.076	1.01 (1.00-1.01)	0.03
Pre CRT CEA	0.99 (0.99-1.01)	0.857	0.99 (0.99-1.00)	0.789
Post CRT CEA	1.02 (0.99-1.04)	0.197	1.02 (1.00-1.04)	0.043
Post-operative CEA	1.02 (1.01-1.02)	<0.001	1.02 (1.01-1.02)	<0.001
Clinical response				
No	Baseline	-	Baseline	-
Partial (by scope)	0.14 (0.03-0.67)	0.013	0.09 (0.03-0.33)	<0.001
cCR (complete Clinical Response)	0.04 (0.003-0.42)	0.008	0.02 (0.002-0.22)	0.001
Not assessed	0.08 (0.007-1.00)	0.05	0.10 (0.02-0.65)	0.016
Operation				
LAR	Baseline	-	Baseline	-
Ultra LAR	16.01 (4.18-61.35)	<0.001	14.30 (4.43-46.14)	<0.001
APR	2.78 (0.80-9.65)	0.106	2.42 (0.81-7.23)	0.112
LAR with end colostomy	1.46 (0.28-7.62)	0.654	1.04 (0.21-5.04)	0.965
Diversion then LAR	1.87 (0.22-16.16)	0.569	1.32 (0.16-10.82)	0.795
Diversion then APR	40.65 (9.06-182.42)	<0.001	30.04 (7.41-121.73)	<0.001
Laparoscopic LAR	3.96 (1.05-14.91)	0.042	2.77 (0.81-9.56)	0.106

Laparoscopic APR	10.86 (2.08-56.75)	0.005	7.74 (1.59-37.63)	0.011
Complication				
Surgical Site Infection (SSI)	4.06 (0.94-17.43)	0.06	3.30 (0.78-14.02)	0.105
Presacral collection	3.89 (1.14-13.24)	0.03	3.16 (0.94-10.57)	0.062
Specimen	1.08 (0.71-1.65)	0.706	1.02 (0.69-1.52)	0.903
T down staging	0.39 (0.16-0.93)	0.035	0.38 (0.17-0.85)	0.018
ypT stage	1.63 (1.02-2.60)	0.041	1.58 (1.03-2.44)	0.038
N down staging	0.61 (0.28-1.32)	0.211	0.53 (0.26-1.10)	0.088
Positive LN	1.44 (1.23-1.68)	<0.001	1.38 (1.18-1.60)	<0.001
LN all	1.00 (0.96-1.05)	0.857	1.01 (0.96-1.05)	0.794
LN ratio group				
0	Baseline	-	Baseline	-
0.1-0.2	3.29 (1.24-8.69)	0.016	2.42 (0.97-6.03)	0.057
>0.2	6.66 (2.47-17.95)	<0.001	5.66 (2.30-13.95)	<0.001
ALI	2.05 (0.88-4.74)	0.095	1.90 (0.86-4.17)	0.11
PNI	4.38 (2.00-9.58)	<0.001	4.48 (2.17-9.27)	<0.001
CRM				
<0.1	Baseline	-	Baseline	-
≥ 0.1	0.18 (0.04-0.82)	0.026	0.23 (0.05-0.99)	0.049
Waiting time adjuvant CMT (days)	1.00 (0.99-1.01)	0.778	1.00 (0.99-1.01)	0.631
Adjuvant chemotherapy regimen				
FOLFOX	Baseline	-	Baseline	-
XELOX	0.13 (0.03-0.58)	0.008	0.18 (0.05-0.66)	0.01
5FU/LV	0.26 (0.08-0.84)	0.024	0.25 (0.08-0.80)	0.02
Xeloda	0.04 (0.004-0.35)	0.004	0.03 (0.004-0.32)	0.003
Cycles	0.73 (0.53-0.99)	0.046	0.68 (0.51-0.91)	0.01

A Subcentimeter Distal Rectal Margin and its Impact on Local Recurrence in Rectal Cancer Patients Undergoing Curative Surgery after Preoperative Chemoradiotherapy

Tumor deposit	1.30 (0.17-10.12)	0.8	1.75 (0.28-11.04)	0.552
FOLFOX	Baseline	-	Baseline	-
XELOX	0.13 (0.03-0.58)	0.008	0.18 (0.05-0.66)	0.01
5FU/LV	0.26 (0.08-0.84)	0.024	0.25 (0.08-0.80)	0.02
Xeloda	0.04 (0.004-0.35)	0.004	0.03 (0.004-0.32)	0.003
Cycles	0.73 (0.53-0.99)	0.046	0.68 (0.51-0.91)	0.01
Tumor deposit	1.30 (0.17-10.12)	0.8	1.75 (0.28-11.04)	0.552

Table 5: Multivariable analysis of factors associated with recurrence and DFS after operation between distal margin ≤ 0.4 with >0.4 cm

Variables	Recurrence		DFS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Distal margin >0.4 cm	0.02 (0.001-0.63)	0.026	0.08 (0.003-2.36)	0.144
Operation				
LAR	Baseline	-	Baseline	-
Ultra LAR	143.98 (0.86-24206.39)	0.057	87.18 (0.93-8191.73)	0.054
APR	14.01 (0.85-231.43)	0.065	11.33 (0.87-148.28)	0.064
LAR with end colostomy	0.79 (0.008-77.73)	0.92	0.58 (0.007-49.15)	0.811
Diversion then LAR	3.97 (0.16-97.19)	0.398	2.08 (0.13-34.36)	0.608
Diversion then APR	2573.25 (9.54-694227.70)	0.006	679.08 (6.12-75310.44)	0.007
Laparoscopic LAR	2.93 (0.12-69.34)	0.505	0.52 (0.03-9.25)	0.658
Laparoscopic APR	49.08 (1.27-1896.19)	0.037	5.91 (0.34-103.73)	0.224
T down staging	-	-	1.47 (0.45-4.81)	0.526
ypT stage	-	-	1.47 (0.45-4.81)	0.526
Pos LN	6.63 (2.13-20.58)	0.001	3.97 (1.57-10.06)	0.004
LN ratio group				
0	Baseline	-	Baseline	-
0.1-0.2	0.14 (0.006-3.58)	0.237	0.28 (0.02-3.70)	0.334
>0.2	-	-	0.02 (0.00-2.32)	0.103
PNI	3.73 (0.30-45.77)	0.304	1.28 (0.16-10.45)	0.817

CRM				
<0.1	Baseline	-	Baseline	-
≥ 0.1	0.96 (0.02-60.44)	0.985	6.18 (0.20-191.17)	0.299
Adjuvant chemotherapy regimen				
FOLFOX	Baseline	-	Baseline	-
XELOX	0.02 (0.001-0.56)	0.021	0.09 (0.01-1.28)	0.076
5FU/LV	1.79 (0.06-49.13)	0.732	0.44 (0.03-7.03)	0.56
Xeloda	0.50 (0.004-59.65)	0.775	0.48 (0.01-18.29)	0.691
Cycles	-	-	0.38 (0.20-0.73)	0.004

A univariable analysis (Table 4) of favorable factors associated with LR and DFS including DRM >0.4 cm, clinical response (partial or complete clinical response), CRM ≥ 0.1 cm. A multivariable analysis (Table 5) of favorable factors associated with LR and DFS including DRM >0.4 cm, adjuvant XELOX regimen.

DISCUSSION

Preoperative CRT may increase the rate of sphincter saving rectal cancer surgery due to shrinkage of the primary tumor. However, rectal cancer shows scattered regression after preoperative CRT (Smith FM, *et al.*, 2014; Kim TG, *et al.*, 2010). Hayden DM, *et al.*, 2012 demonstrated distal intramural spread of the primary cancer was not observed beyond 3 cm in 49.1% of patients. Several studies have evaluated oncologic outcomes after curative resection for patients who had preoperative CRT with a distal margin shorter than 1 cm. Kim TG, *et al.*, 2010 found 66.7% 5 year pelvic control rate in group of patients with distal margin less than 0.3 cm compared with 86.2% 5 year pelvic control rate in group of patients with distal margin more than 0.3 cm, (p=0.049). Rutkowski A, *et al.*, 2012 evaluated the cut off 5 mm DRM in 412 rectal cancer patients. In this study, 63% of patients received preoperative radiotherapy. The risk for local cancer recurrence was only slightly increased with a DRM of ≤ 5 mm (5.4%) compared to a DRM of >5 mm (4.1%). Nash GM, *et al.*, 2010 showed no significant difference of local recurrence at cut point 0.8 cm, (6% vs. 4%). Some studies 13-16 found no difference in LR for patients who underwent curative resection after preoperative CRT with a distal margin less or greater than 1 cm. However, these studies had small numbers of patients or other associated factors of recurrence. Kuvshinoff B, *et al.*, 2001 studied 28 patients with rectal cancer within 8 cm from the anal verge who received a sphincter preserving procedure after preoperative CRT, no significant difference at cut off 1 cm distal margin (Moore HG, *et al.*, 2003). Rutkowski A, *et al.*, 2008 included 94 rectal cancer patients post curative resection after preoperative CRT. Similarly, no significant difference at cut off 1 cm was seen (Leo E, *et al.*, 2009).

Whereas, Kiran RP, *et al.*, 2011 analyzed 784 patients with rectal cancer receiving preoperative CRT in 40% of patients. They found 5 year LR rate of 4.4% for patients with DRM ≤ 1 cm compared to 4.3% for a DRM >1 cm. A DRM ≤ 5 mm was associated with a 5-year LR of 6.4% compared to 4.1% for a DRM >5 mm. Thus a DRM of <1 cm might not compromise oncological outcome. Moreover, Zeng WG, *et al.*, 2017 analyzed 6,574 patients with rectal cancer 20% of patients received preoperative radiotherapy. This study found 24.1% LR in a group of patients with a distal margin less than 1 cm compared with 12% in patients with a distal margin >1 cm. In the current study suggest that a 1 cm distal margin is adequate in most patients who had preoperative CRT. Controversy still exists if we can obtain DRM

less than 1 cm in order to achieve goal of sphincter-saving, especially in patients who had preoperative Chemoradiotherapy (CRT).

In this study, there were 145 patients who were analyzed with median time follow up 28 months. DRM ranged from 0 cm-11.3 cm (median 2 cm). There were 36 patients (24.8%) who had DRM less than 1 cm. Recurrence was found in 27 (18.6%) patients. Local and systemic recurrence was found in 9 and 24 patients, respectively. In the local recurrence group, two patients had lymph node recurrence and other patients had anastomosis recurrence. There was statistically significant differences in recurrence and DFS at cut off 0.4 cm, $p=0.0006$ and 0.002 , respectively. Moreover, no statistically significant differences in recurrence and DFS were found at cut off 0.5 cm, $p=0.051$ and 0.107 , respectively. Similarly, no significant difference in recurrence and DFS at cut off 0.6 cm were seen, $p=0.061$ and 0.107 , respectively. On univariable and multivariable analysis of others factors, unfavorable recurrence and DFS were associated with N staging, waiting time from last RT to surgery, postoperative CEA, post-operative complication (surgical site infection, presacral collection), ypT staging, LN ratio (positive LN/total LN), perineural invasion and positive lymph node. In addition, favorable factors were associated with DRM >0.4 cm, clinical response (partial or complete clinical response), CRM ≥ 0.1 cm. and adjuvant XELOX regimen. It is important to consider these factors that who was good candidates for subcentimeter DRM.

Our study is a retrospective review conducted at a single institution; thus, it has some limitations. First, the study is statistically underpowered for a valid statistical analysis with small sample size in subcentimeter group. Second, measuring of DRM after tissue fixation may retract the specimen. Third, including R1 resection (DRM 3 patients, CRM 4 patients) might affect oncologic outcome. Finally, our study lacked pathological assessment other prognosis factors including extramural vascular invasion and tumor deposit in some patients. Therefore, we were not able to analyse these factors. Further study should be considered in rectal cancer patients who received total neoadjuvant therapy with benefit of higher pCR which improve prognosis.

CONCLUSION

In conclusion, the results suggest that cutoff point at 0.5 cm was a minimally acceptable DRM in rectal cancer after preoperative CCRT. Minimizing DRM to less than 1 cm to increase chance of sphincter-saving procedures should be balanced with individual patient and tumor characteristics including tumor staging, response to preoperative CRT and tumor differentiation. Intense adjuvant therapy should be used in these patients to reduce recurrence.

ETHICAL APPROVAL

The study was approved by Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University COA, MURA2021/427.

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AUTHOR CONTRIBUTION

Miss Yada Phengsalae Yada collected and analyzed the data.

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