ปัจจัยทำนาย Circumferential Resection Margin (CRM) ของการผ่าตัดมะเร็งลำไส้ตรงในโรงพยาบาลพระนั่งเกล้า

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Factor Determining Circumferential Resection Margin of Rectal Cancer: Operation in Pranangklao Hospital

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Abstract

Background: The incidence of colorectal cancer in Thailand ranks as the first most common cancer in males and the second most common cancer in females. The incidence increases in individuals over 50 years of age. Regional lymph node metastasis is observed in 27% of cases. Treatment outcomes for rectal cancer are generally less favorable than those for colon cancer. Total mesorectal excision (TME) remains the standard treatment. **Objective:** This study aimed to analyze the factors associated with positive circumferential resection margin (CRM) (≤ 1 mm) in patients with rectal cancer after surgery. **Methods:** This study retrospectively analyzed data from medical records of patients with rectal cancer (ICD 10th: C19, C20) who underwent definitive surgery (ICD 9th: 48.50, 48.51, 48.51, 48.62, 48.63) between 2019 and 2024 (5 years) at Pranangklao Hospital (n = 85). Univariate, univariable, and multivariable statistical analyses were performed to assess risk factors. **Results:** The main statistically significant risk factors ($p < .05$) identified were anterior tumor location, T4 lesion, and stage III disease (lymph node metastasis). The overall positive CRM rate was 31.8% of all patients. **Conclusion:** This study demonstrated that anterior tumor location, T4 lesion, and stage III disease are statistically significant factors associated with positive CRM in patients with rectal cancer. Identifying these factors will enable surgeons to plan treatment through interdisciplinary care and reduce the risk of positive CRM, which will ultimately improve overall survival and long-term quality of life for patients.

Keywords: Circumferential resection margin, Rectal cancer, Total mesorectal excision

บทคัดย่อ

ภูมิหลัง: อุบัติการณ์ของ colorectal cancer ในประเทศไทยต่ำกว่าประเทศอื่น ๆ พบมากขึ้นในอายุมากกว่า 50 ปีขึ้นไปเป็น common cancer พบการแพร่กระจายไปที่ regional lymph node 27% โดยผลการรักษาของ rectal cancer จะต่ำกว่าการรักษา colon cancer **วัตถุประสงค์:** เพื่อวิเคราะห์ปัจจัยที่ส่งผลต่อการเกิด positive CRM (≤ 1 มม.) ในผู้ป่วยมะเร็งลำไส้ตรงหลังการผ่าตัด **วิธีการ:** ศึกษาข้อมูลย้อนหลังจากเวชระเบียนผู้ป่วยมะเร็งลำไส้ตรง (ICD 10^{th}: C19, C20) ที่ได้รับการผ่าตัด definitive surgery (ICD 9^{th}: 48.50, 48.51, 48.51, 48.62, 48.63) ระหว่างปี 2562–2567 (5 ปี) ที่โรงพยาบาลพระนั่งเกล้า (85 ราย) วิเคราะห์ทางสถิติแบบ univariate, univariable และ multivariable analysis เพื่อประเมินปัจจัยเสี่ยง **ผล:** ปัจจัยเสี่ยงหลักที่มีนัยสำคัญทางสถิติ ($p < .05$) ได้แก่ ตำแหน่งมะเร็งด้านหน้า (anterior tumor), เนื้องอกระยะ T4 (T4 lesion), มะเร็งระยะที่ III (แพร่กระจายสู่ต่อมน้ำเหลือง) พบอัตราการเกิด positive CRM: 31.8% ของผู้ป่วยทั้งหมด **สรุป:** anterior tumor,

T4 lesion และ stage III เป็นปัจจัยที่มีนัยสำคัญทางสถิติที่สัมพันธ์กับการเกิด positive CRM ในผู้ป่วย rectal cancer การระบุปัจจัยเหล่านี้จะช่วยให้ศัลยแพทย์สามารถวางแผนการรักษาโดยการดูแลแบบสหวิชาชีพและลดความเสี่ยงของการเกิด positive CRM ซึ่งจะส่งผลดีต่อ overall survival และคุณภาพชีวิตของผู้ป่วยในระยะยาว

คำสำคัญ: ขอบเขตโดยรอบของการผ่าตัด, มะเร็งลำไส้ตรง, การตัดเยื่อหุ้มและเนื้อเยื่อข้างเคียงออกอย่างสมบูรณ์

Introduction

Colorectal cancer (CRC) is a major global health burden. In Thailand, it's the most common male cancer (20.7%) and second most common in females (12.2%), predominantly affecting those >50 years. Metastasis occurs in 27% (regional) and 42.1% (distant); 30.9% present as stage III, 41.8% as stage IV.[1] Rectal cancer outcomes are poorer than colon cancer, potentially due to anatomy, tumor biology, or surgical complexity.[2] Total Mesorectal Excision (TME) is the standard for mid/low rectal cancers, improving oncology outcomes.[3-5] Negative CRM (>1mm clearance)[6-7] reduces locoregional recurrence (LRR). The surgeon should perform more than 12 operations per year to have a better LRR rate (4% vs. 10%).[8] TME with negative CRM reduces LRR and increases overall survival (OS) and disease free survival (DFS).[3,5,6,9-12] Negative CRM has a local recurrence rate (LRR) rate of 10% and 5-year disease free survival (DFS) rate of 66% compared with positive CRM have LRR rate of 78% and 5-year DFS rate of 15%.[10,12] The study of Krishnamurty et al.[13] found that tumor size > 5.9 cm, low location distance of ≤ 2.6 cm from the dentate line were at risk of positive CRM, i.e. incomplete TME, number of positive nodes, microvascular and perineural invasion, together with the study of Kang et al that found anterior tumors[14] were associated with positive CRM, the study of Sugimoto et al that found larger primary tumors, open surgery, abdominoperineal resection (APR) and T4 tumor were associated with positive CRM.[15]

This study aimed to evaluate the factors affecting CRM involvement of rectal cancer after definitive surgery (anterior resection (AR), low anterior resection (LAR), APR).

Materials and methods

Setting: Pranangklao Hospital, Nonthaburi Province

Study design: This is a retrospective study of hospitalized patients who sustained CA rectum.

Study population: This retrospective study included 85 patients with rectal cancer (ICD 10th: C19, C20) patients who had definitive operation from October 1, 2019 to September 30, 2024 (5 years) at Pranangklao Hospital was conducted.

Inclusion criteria

1. Age 15 years and above
2. Underwent definitive surgery (ICD 9th: 48.50, 48.51, 48.51, 48.62, 48.63)

Exclusion criteria

1. Secondary carcinoma or recurrence carcinoma of rectum
2. Non-adenocarcinoma of rectum such as carcinoid, lymphoma, sarcoma, gastrointestinal stromal tumor (GIST), neuroendocrine tumor (NET), teratoma, melanoma, etc.

This study collected demographic data, pathological feature, TNM staging,[16] tumor location, tumor size, level of tumor location, type of operation, preoperative radiation, and CRM.

Sample size: We will fit a Poisson regression model with robust variance for the binary outcome of positive CRM (≤1 mm), including six prespecified predictors (anterior tumor, size > 6 cm, T4, stage III, low tumor, and APR). To ensure stable coefficient estimates, we apply the events-per-variable (EPV) rule of 10[17-18]. For our primary analysis focusing on three main predictors, this requires at least 30 events to satisfy EPV ≥ 10. Based on the expected event rate of 30-40%, this corresponds to approximately

30 events in a total of 85 participants, which is considered sufficient for the planned analysis.

Statistical analysis: Data are presented as mean±SD Prevalence ratios (PR) were calculated via Poisson distribution. Multivariable model 1 included variables with p < .1 from univariable analysis. model 2 incorporated clinically relevant factors associated with CRM, with significance at $p < .05$.

Ethical considerations: Ethical approval was sought from the Ethics Committee of Pranangklao Hospital, Nonthaburi.

Results

Table 1 Demographic data (N=85)

Characteristics	Number (%)
Sex male:female	48(56.5):37(43.5)
Age (years) (mean±SD) (range)	64.6±9.07 (43-84)
Preoperative Chemoradiation	51 (60)
Pathological features	
- Mucin producing or poor differentiation or signet ring cell	8 (9.4)
- Neural invasion	30 (35.3)
- Lymphovascular invasion	42 (49.4)
T category	
- T0	7 (8.2)
- T1	0 (0)
- T2	10 (11.8)
- T3	53 (62.4)
- T4a	13 (15.3)
- T4b	2 (2.4)
Tumor size (cm) (mean±SD) (range)	4.5±2.55 (0-12)
N category	
- N0	54 (63.5)
- N1a	10 (11.8)
- N1b	6 (7.0)
- N2a	10 (11.8)
- N2b	5 (5.9)
M category	
- M0	85 (100)
- M1	0 (0)

Characteristics	Number (%)
TNM stage	
- 0	7 (8.2)
- I	9 (10.6)
- IIa	31 (36.5)
- IIb	5 (5.9)
- IIIa	0 (0)
- IIIb	26 (30.6)
- IIIc	5 (5.9)
- IV	0 (0)
CRM ≤ 1 mm.	27 (31.8)

Table 1 presents demographic and clinical characteristics of 85 patients treated between October 1, 2019, and September 30, 2024. The cohort was predominantly male (56.5%), with a mean age of 64.6±9.07 years; only 2.4% (n=2) were under 50 years. Pathologically, 9.4% exhibited mucinous production, poor differentiation, or signet ring cell features, while neural invasion and lymphovascular invasion were present in 35.3% and 49.4% of cases, respectively. Regarding staging, 42.4% were TNM stage II, 36.5% stage III, and 10.6% stage I. T-category distribution showed 62.4% T3, 17.7% T4, and 11.8% T2 tumors (no T1 cases). Most patients (63.5%) were node-negative (N0), with 18.9% N1 and 17.7% N2. Preoperative therapy was administered to 60% of patients. The overall positive CRM (≤1 mm) rate was 31.8%; when excluding T4 lesions, this decreased to 17.1% (12/70).

Table 2 Location, Treatment (N=85)

Location of tumor and treatment characteristics	Number (%)
Anterior tumor	24 (28.2)
Level of tumor	
- Upper rectum	41 (48.2)
- Middle rectum	28 (30.6)
- Lower rectum	18 (21.2)
Type of operation	
- Anterior resection (AR)	38 (44.7)
- Low anterior resection (LAR)	30 (35.3)
- Abdominoperineal resection (APR)	17 (20)
Elective operation	80 (94.1)
Laparoscopic surgery	8 (9.4)

The most common location of cancer was the upper rectum (48.2%) followed by middle and lower rectum at 30.6% and 21.2% respectively. The cancer location was found in the non-anterior

region at 71.8%. Anterior resection was the major operation performed (44.7%), followed by LAR (35.3%) and APR (20%) respectively. The majority (94.1%) was elective surgery and 90.6% was open surgery. as shown in Table 2.

Table 3 Poisson distribution for Univariable analysis

Factors	Unadjusted PR (95% CI)	p-value
Male gender	1.12 (0.59, 2.13)	.726
Elective surgery	0.78 (0.25, 2.41)	.668
Preoperative radiation	0.62 (0.33, 1.15)	.130
Anterior tumor	11.18 (4.76, 26.26)	< .001*
Open surgery	1.30 (0.37, 4.53)	.682
Low Tumor	1.40 (0.71, 2.77)	.333
APR	1.40 (0.71, 2.77)	.333
Large tumor > 6 cm	1.85 (1.01, 3.39)	.045*
T4 lesion	5.83 (3.47, 9.79)	< .001*
Stage III	2.96 (1.55, 5.66)	.001*

*p < .1

Table 3 has factors anterior tumor, T4 lesion, stage III, large tumor at $p < .01$, factors at $p < .05$ have anterior tumor, T4 lesion, stage III.

Table 4 Poisson distribution for multivariable analysis

Factors	Model 1 Adjusted PR (95%CI)	p-value	Model2 Adjusted PR (95% CI)	p-value
Anterior tumor	7.31 (2.80, 19.11)	< .001*	6.51 (2.51, 16.89)	< .001*
Large tumor > 6 cm	NA	-	1.36 (0.93, 1.98)	.113
T4 lesion	1.50 (1.09, 2.07)	.013*	1.75 (1.10, 2.79)	.018*
Stage III	1.72 (1.07, 2.76)	.026*	1.75 (1.08, 2.85)	.024*
Low tumor	NA	-	1.17 (0.75, 1.81)	.491
APR	NA	-	1.28 (0.84, 1.95)	.255

PR = Prevalence ratio, *significance p < .05

In multivariable model 1 (including factors with $p < .01$: anterior tumor, T4 lesion, stage III, large tumor), anterior tumor, T4 lesion, and stage III independently predicted CRM involvement ($p < .05$). These same three factors emerged as significant in model 2, which incorporated clinically relevant variables associated with positive CRM. (Table 4)

Discussion

This study evaluated factors influencing CRM positivity (≤1 mm) in rectal cancer patients undergoing surgery at Pranangklao Hospital. Demographic data revealed a mean patient age of 64.6 years, consistent with studies from China[19] and Europe[4, 13, 20]. TNM staging distributions aligned with prior studies[4, 6, 20], showing predominance of T3 tumors, N0 status, and stage II-III. Upper rectum was the most common tumor location. AR comprised 44.7% of surgeries, with 60% receiving preoperative chemoradiotherapy. This aligns with Marling[8] (49% chemoradiation) and Bernstein's[20] recommendation for preoperative radiotherapy. This study found a 13.7% pathologic complete response after preoperative chemoradiation (vs. 15-27% in Ferrari et al.[21].

The overall positive CRM rate was 31.8% (all CRM+). This aligns with Tilney[22] (17.6% APR) and Bernstein[20] (15.5% positive CRM), though higher than Wibe[4] (9.4%) and European registries (5.4-7.8%)[23]. This study found only 9.4% laparoscopic surgeries (aligned with Patel's[9] suggestion that minimally invasive surgery (MIS) reduces CRM+ risk). Multivariable analysis confirmed model stability (no difference between model 1/2), a key strength. Results were consistent with univariable analysis, identifying three significant predictors of positive CRM: anterior tumor (PR=7.31; 95%CI: 2.80, 19.11), T4 lesion (PR=1.50; 95%CI: 1.09, 2.07), stage III (PR=1.72; 95%CI: 1.07, 2.76). These findings align with prior literature[8, 14, 19, 22] on positive CRM. Three factors demonstrated significant association with positive CRM (≤1 mm):

1) Anterior tumor location (PR=7.31; 95%CI: 2.80, 19.11), attributed to anatomical proximity to prostate/vaginal structures complicating mesorectal excision, aligning with Kang's[14] findings;

2) T4 lesions (PR=1.50; 95%CI: 1.09, 2.07), where deep invasion into adjacent tissues impedes margin clearance, consistent with Martling[8], Wang[19], and Tilney[22]; 3) Stage III disease (PR=1.72; 95%CI: 1.07, 2.76), as nodal involvement increases surgical difficulty, supported by Wang g[19] and Bernstein[20].

This study found no association between positive CRM and age, gender, preoperative chemoradiation, low tumor location, operative urgency, surgical approach (open vs. laparoscopic), or resection type (AR/LAR/APR), contradicting reports by Wang[19] and Kang[14] (low tumor), Krishnamurty[13] and Hiranyakas[24] (low/large tumor, nodal), Tilney[22] (APR), Patel et al.[9] (laparoscopic benefit), and Martling[6] (surgeon volume >12 cases/year). The incidence of positive CRM has decreased per year, however, this study did not examine this aspect. Nagtegaal et al.[3] reported that the presence of positive CRM after preoperative chemoradiation was a predictor of poor prognosis. Hall et al.[11] reported that positive CRM was associated with locally advanced disease rather than inadequate surgery. Park[7], Patel[9], and Birbeck[25] reported that positive CRM was associated with OS, DFS, and hospital-based quality of life. To enhance CRM outcomes in rectal cancer, implement standardized TME and APR surgical training per Heald[3-7], prioritize preoperative chemoradiation for T4/stage III patients (NCCN 2024)[16] with multidisciplinary support[10] to downstage tumors and achieve negative margins, incorporate high-risk factors (anterior location, T4, stage III) into treatment protocols, and address research limitations to align Thailand's care standards with international benchmarks.

Policy recommendations

1. Adjust the treatment plan in high-risk groups by considering preoperative chemoradiation to reduce the tumor size before surgery.
2. Develop surgical standards through surgical skills training according to the TME guidelines and promoting MIS.
3. Enhance multidisciplinary work to plan systematic treatment.

Limitation

1. Small sample size (n = 85) limiting analytical accuracy, particularly for Model 1/2 analyses and the laparoscopic subgroup (n = 8, 9.4%).

2. Short follow-up due to the retrospective, cross-sectional design, preventing long-term outcome assessment.

3. Unmeasured confounders affecting CRM: surgical technique (laparoscopic vs. open), surgeon annual caseload, and postoperative chemoradiation.

Recommendations for future research

Further larger, longer-term studies are needed to confirm results and investigate factors like surgical technique, surgeon experience, and pre-op chemoradiation effects on CRM.

Conclusion

This study showed that anterior tumor, T4 lesion and stage III were statistically significant factors associated with positive CRM in CA rectum patients. Identification of these factors would allow surgeons to plan treatment with multidisciplinary care and reduce the risk of positive CRM, which would benefit overall survival and long-term quality of life of patients.

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