

Original Research Article

Identification of Patients with Locally Advanced Rectal Cancer in Whom Preoperative Radiotherapy Can Be Omitted: A Multicenter Retrospective Study at Yokohama Clinical Oncology Group (YCOG1307)

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Abstract

Objectives: The present study aimed to identify patients with locally advanced rectal cancer in whom preoperative radiotherapy (RT) can be omitted.

Methods: This study was a retrospective multi-institutional study for patients with pathological stage II and III rectal cancer who underwent surgery without preoperative therapy between January 2008 and December 2012. Clinicopathological factors were examined by univariate and multivariate analyses to clarify independent risk factors of local recurrence (LR).

Results: The 5-year cumulative local recurrence rate (LRR) of 815 patients was 11.2%. Independent predictive factors of LR were determined by a multivariate analysis to be a tumor location of <10 cm from the anal verge, a tumor diameter of ≥ 50 mm, undifferentiated histological type, and advanced T-N substage (T3 N+ or T4Nany). In lower rectal cancer located <10 cm from the anal verge (n = 510), the 5-year cumulative LRR of patients without any remaining three factors was 4.4%, with one factor was 13.0%, with two factors was 22.2%, and with all three factors was 41.6%.

Conclusions: Preoperative RT may be omitted in patients with lower rectal cancer with no risk factors. However, in addition to the present risk factors, we need to further examine the extramural vascular invasion (EMVI) status and circumferential resection margin (CRM) using magnetic resonance imaging (MRI) findings.

The trial was registered with UMIN Clinical Trails Registry, number 000006039.

Keywords

rectal cancer, total mesorectal excision, local recurrence, preoperative radiotherapy, preoperative chemoradiotherapy

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Introduction

Controlling local recurrence (LR) after rectal cancer surgery is important. Although preoperative radiotherapy (RT) plus total mesorectal excision (TME) is a standard treatment

in Western countries[1-4], TME plus lateral lymph node dissection (LLND) has been the standard procedure for advanced lower rectal cancer for a long time in Japan[5,6]. While RT improves local control for rectal cancer, some patients suffer from late complications associated with RT,

such as urinary disorder, defecation dysfunction, sexual dysfunction, and secondary carcinogenesis[7-9]. Therefore, identifying those patients with advanced rectal cancer in whom preoperative RT/CRT can be omitted is important.

This retrospective study aimed at identifying patients with locally advanced rectal cancer in whom preoperative RT can be omitted.

Methods

Patients

This retrospective multi-institutional study was conducted to evaluate the occurrence and risk factors of LR after radical surgery for rectal cancer. From January 2008 to December 2012, 815 patients with pathological stage II and III rectal cancer who underwent curative-intent surgery without preoperative therapy (no chemotherapy, RT, or chemoradiotherapy [CRT]) were enrolled at 14 institutions in the Yokohama Clinical Oncology Group (YCOG) in Japan. The inclusion criteria were patients with rectal cancer within 12 cm from anal verge as per previous clinical trials[4,10,11]. The study protocol was approved by the Ethical Advisory Committee of Yokohama City University Graduate School of Medicine and the institutional review board of each participating hospital before the study was initiated (registry number: 22193). The study was registered with the Japanese Clinical Trials Registry (UMIN-CTR) as UMIN000006039 (<http://www.umin.ac.jp/ctr/index.htm>). Individual consent was not required because of the retrospective nature of the study.

Clinicopathological investigations

All data were retrospectively collected. Patient-related variables, including age, gender, body mass index, American Society of Anesthesiologists score, ECOG-performance status, preoperative hemoglobin, prognostic nutritional index, comorbid diabetes mellitus, preoperative bowel preparation, tumor location, maximum tumor diameter, histological type, preoperative serum tumor markers (carcinoembryonic antigen and carbohydrate antigen 19-9), surgical approach, surgical procedure, and Union International Centre le Cancer tumor-node-metastasis stage (eighth edition), were analyzed. This study used pathological TNM grading. The tumor location was determined by pelvic computed tomography (CT), magnetic resonance imaging (MRI), colonoscopy, and barium enema preoperatively as well as during surgery. The tumor location was divided into two groups based on whether the lower edge was located <10 or \geq 10 cm from the anal verge (lower or upper rectal cancer, respectively).

Operative procedures

TME or tumor-specific mesorectal excision (TSME) was

performed as the standard procedure, mobilizing the rectum while keeping the plane around the mesorectum and resecting the attached mesorectum with at least 3- and 2-cm clear-ance margins distal to the tumor for upper and lower rectal cancer, respectively. The following types of rectal resection were selected according to the tumor and patient condition: anterior resection (AR), intersphincteric resection (ISR), Hartmann's procedure, abdominoperineal resection (APR), abdominosacral resection (ASAR), and total pelvic exenteration (TPE). Patients with clinical T3 or more or clinical N1 or more lower rectal cancer underwent LLND with TME to prevent LR after surgery.

Follow-up protocol after surgery

After surgery, postoperative surveillance of patients was performed at each of the 14 institutions in the YCOG in Japan. Patient history and physical examination findings were obtained every three months for three years and then every six months for at least five years. Chest, abdominal, and pelvic CT were performed every 6-12 months for at least 5 years. Colonoscopy was performed every 1-2 years.

Outcomes

The primary end point was the cumulative local recurrence rate (LRR), defined as the time from surgery to LR or to the latest date at which a LR-free status was verified.

Definition of LR

LR was defined as the occurrence of a new lesion in any of three regions on CT, MRI, or colonoscopy: central pelvis, lateral pelvis, and anastomosis.

Statistical analyses

Continuous variables were divided into two groups by the median values or cutoff values of receiver operating characteristics curves. For the multivariate analysis, the clinicopathological variables found to be significant were entered into the Cox proportional hazards model to clarify the risk factors of LR. Results are shown as the percentage of patients or as the median (interquartile range [IQR]). To visualize the cumulative incidence of LR, the cumulative incidence curves according to the number of risk factors were analyzed using the log-rank test. The JMP Pro (SAS Institute, Cary, NC, USA) software program was used for the statistical analyses, and differences with two-tailed P-values of <0.05 were considered significant.

Results

Patient characteristics and surgical findings of the 815 patients are summarized in Table 1. A total of 305 patients (37.4%) had upper rectal cancer, and the remaining 510 (62.4%) had lower rectal cancer. The surgical procedure was

Table 1. Patient Characteristics and Surgical Findings.

| | |
|-------------------------------------|---|
| Age (year) | 67 (60–75) |
| Gender | |
| Male/female | 541 (66.4)/274 (33.6) |
| ASA-PS | |
| I/II/III/unknown | 249 (31.0)/506 (62.9)/49 (6.1)/11 |
| ECOG-PS | |
| 0/1/2/3/unknown | 703 (88.9)/76 (9.6)/12 (1.5)/0 (0)/24 |
| BMI (kg/m ²) | 22.1 (20.1–24.2) |
| PNI | 49.1 (44.0–53.2) |
| Tumor location | |
| Upper/lower | 305 (37.4)/510 (62.6) |
| CEA (ng/ml) | 4.3 (2.4–9.6) |
| CA19-9 (U/ml) | 11 (5.9–23) |
| Approach | |
| Open/Lap | 672 (82.5)/143 (17.5) |
| Procedure | |
| AR/ISR/Hartmann/APR/ASAR/TPE | 583 (71.5)/22 (2.7)/49 (6.0)/109 (13.4)/42 (5.2)/10 (1.2) |
| Lateral lymph node dissection | |
| Presence/absence | 160 (19.6)/655 (80.4) |
| Operation time (min) | 231 (180–301) |
| Intraoperative bleeding (ml) | 291 (100–550) |
| Intraoperative blood transfusion | |
| Presence/absence | 101 (12.4)/714 (87.6) |
| Anastomotic height (mm) | 50 (30–60) |
| ≤30/>30/unknown | 98 (26.8)/268 (73.2)/449 |
| Degree of autonomic nerve sparing | |
| AN0/1/2/3/4/unknown | 7 (0.9)/6 (0.8)/20 (2.6)/20 (2.6)/730 (93.1)/32 |
| Postoperative hospitalization (day) | 17 (12–26) |
| Postoperative complication | |
| Overall (≥Gr.2) presence/absence | 311 (38.2)/504 (61.8) |
| Leak (≥Gr.2) presence/absence | 108 (13.3)/707 (86.7) |

Continuous variables are demonstrated by median (interquartile range, IQR). ASA-PS, American Society of Anesthesiologists-physical status; ECOG-PS, Eastern Cooperative Oncology Group-performance status; BMI, body mass index; PNI, prognostic nutrition index calculated by $10 \times \text{albumin (g/dL)} + 0.005 \times \text{total lymphocyte count (mm}^3\text{)}$; tumor height, distance between tumor and anal verge; anastomotic height, distance from anastomosis and anal verge

583 AR (71.5%), 22 ISR (2.7%), 49 Hartmann's procedure (6.0%), 109 APR (13.4%), 42 ASAR (5.2%), and 10 TPE (1.2%). LLND was performed in 160 cases (19.6%). Preoperative treatment (chemotherapy or RT or CRT) was not performed in any cases. Pathological findings and patient outcomes are shown in Table 2. UICC pathological stages II and III were found in 333 cases (40.8%) and 482 cases (59.2%), respectively. Postoperative adjuvant chemotherapy was performed in 403 patients (50.6%). Of the 403 patients, 81 (20.0%) have received oxaliplatin-based adjuvant chemotherapy. Patients were observed for a median of 56.5 months (IQR, 35.9–71.2). LR occurred in 70 patients (8.6%): 13 patients (4.3%) with upper rectal cancer and 57 patients (11.2%) with lower rectal cancer. Of the 13 patients with upper rectal cancer, the details of LR site were central pelvis in 2 cases, lateral pelvis in 2 cases, anastomosis in 1 case,

and unknown in 8 cases. Of the 57 patients with lower rectal cancer, the details of LR site were central pelvis in 11 cases, lateral pelvis in 14 cases, anastomosis in 3 cases, and unknown in 30 cases (one duplication). Among the 482 patients with pathological stage III rectal cancer, 94 (19.5%) have performed LLND. Of these, lateral pelvis recurrence occurred in three patients (3.2%). Of the 388 patients who have not performed LLND, lateral pelvis recurrence occurred in 11 patients (2.8%). Although about half of the LR patterns were unknown, there was no deference among lateral pelvis recurrence between those with and without LLND.

The overall cumulative LRR at 3 and 5 years was 9.3% and 11.2%, respectively. ESMO guidelines recommends[12] that patients with T3N0 should undergo “surgery alone.” Therefore, all 815 patients were stratified into five groups

Table 2. Pathological Findings and Patient Outcomes.

| | |
|--|---|
| Tumor size (mm) | 50 (40–65) |
| Histological type | |
| tub1/tub2/por/sig/muc | 228 (28.0)/537 (65.9)/29 (3.5)/0 (0)/21 (2.6) |
| UICC T category | |
| T1/2/3/4a/4b | 23 (2.8)/63 (7.7)/596 (73.1)/97 (11.9)/37 (4.5) |
| UICC N category | |
| N0/1/2 | 334 (41.0)/305 (37.4)/176 (21.6) |
| UICC TMN stage (8th) | |
| II/III | 333 (40.5)/482 (59.5) |
| UICC T-N substage | |
| T1-T2N+/T3N0/T3N+/T4N0/T4N+ | 85 (10.4)/278 (34.1)/318 (39.0)/55 (6.8)/79 (9.7) |
| Number of harvested lymph node | 21 (14–31) |
| Lateral lymph node metastasis | |
| Presence/absence | 32 (20.0)/128 (80.0) |
| Vascular invasion | |
| Presence/absence/unknown | 610 (75.7)/196 (24.3)/9 |
| Lymphatic invasion | |
| Presence/absence/unknown | 440 (55.3)/356 (44.7)/19 |
| Distal margin (mm) | 22 (15–35) |
| Positive/negative | 8 (1.0)/807 (99.0) |
| Radial margin (mm) | 3 (1.5–5.5) |
| Positive/negative/unknown | 27 (3.4)/769 (96.6)/19 |
| Adjuvant chemotherapy | |
| Presence/absence/unknown | 403 (50.6)/393 (49.4)/19 |
| Follow-up period after operation (day) | 1724 (1098–2176) |
| Recurrence | |
| Presence/absence | 248 (30.4)/567 (69.6) |
| Local recurrence | |
| Presence/absence | 70 (8.6)/745 (91.4) |
| Distant metastases | |
| Presence/absence | 210 (25.8)/605 (74.2) |
| Lung/liver/lymph node/peritoneum/bone/brain/others | 116 (51.8)/79 (35.3)/34 (15.2)/10 (4.5)/6 (2.7)/4 (1.8)/5 |

Continuous variables are demonstrated by median (interquartile range, IQR). ≥G2, Clavien–Dindo classification G2 or more; I.V., intravenous; P.O., per os

Table 3. Cumulative Local Recurrence Rate by T-N Substage.

| UICC T-N substage | No. of patients | No. of LR | 3-year LRR (%) | 5-year LRR (%) | Univariate analysis | |
|-------------------|-----------------|-----------|----------------|----------------|---------------------|---------|
| | | | | | HR (95% CI) | P-value |
| T3N0 | 278 | 14 | 5.0 | 5.7 | Reference | |
| T1-2N+ | 85 | 4 | 5.2 | 5.2 | 0.878 (0.249–2.447) | 0.816 |
| T3N+ | 318 | 36 | 13.2 | 16.7 | 2.708 (1.494–5.195) | <0.001* |
| T4N0 | 55 | 6 | 10.4 | 13.1 | 2.233 (0.791–5.566) | 0.122 |
| T4N+ | 79 | 10 | 16.5 | 19.4 | 3.187 (1.373–7.132) | 0.008* |

The 3- and 5-year cumulative local recurrence rates were evaluated using the Cox regression hazard model. *P-values of <0.05 were considered significant and shown in boldface. HR, hazard ratio; CI, confidence interval; LR, local recurrence; LRR, local recurrence rate

according to the T-N substage (T3N0 [reference], T1N+ or T2N+, T3N+, T4N0, and T4N+), and the LLR of each was examined (Table 3). T3N0, T1N+, and T2N+ were taken to indicate the low-risk group, while T3N+, T4N0, and T4N+ were taken to indicate the high-risk group. Subsequent

analyses were performed using the substage instead of UICC T-N classification alone.

The LR prognostic factors determined by the univariate analysis were age <70 years old (P = 0.039), lower rectal cancer (P < 0.001), tumor size of >50 mm (P < 0.001), un-

differentiated histological type ($P < 0.001$), non-anus-preserving procedure ($P = 0.003$), advanced T-N substage; T3N+ or T4N_{any} ($P < 0.001$), and lateral lymph node metastasis ($P = 0.002$). The multivariate analysis showed that lower rectal cancer (hazard ratio [HR], 2.416; 95% confidence interval [CI], 1.308-4.753), tumor size of >50 mm (HR, 1.732; 95% CI, 1.002-3.137), undifferentiated histological type (HR, 2.590; 95% CI, 1.174-5.091), and advanced T-N features (HR, 2.310; 95% CI, 1.344-4.136) were independent risk factors of LR (Table 4).

Among the aforementioned four independent factors, the tumor location (upper or lower rectum) was independently analyzed. This was because lower rectal cancer located within <10 cm from the anal verge has a lateral lymphatic flow and is distinguished from upper rectal cancer in terms of the surgical procedure applied (LLND) in Japan. The LRR was therefore stratified by the remaining three factors (tumor size, undifferentiated histological type, and advanced T-N substage). In upper rectal cancer cases, the 5-year cumulative LRR of the groups with 0, 1, 2, and 3 risk factors was 0% (reference), 3.6% (HR, not applicable [NA]; $P = 0.064$), 9.5% (HR, NA; $P = 0.002$), and 40.0% (HR, NA; $P < 0.001$), respectively. In lower rectal cancer cases, the 5-year cumulative LRR of the groups with 0, 1, 2, and 3 risk factors were 4.4% (reference), 13.0% (HR, 3.112; 95% CI, 1.191-10.641), 22.2% (HR, 4.933; 95% CI, 1.921-16.721), and 41.6% (HR, 12.532; 95% CI, 3.305-50.781), respectively. The cumulative LRR for upper and lower rectal cancer is shown in Figure 1a and 1b.

During the follow-up period, distant metastases occurred in 209 patients (25.6%). The overall cumulative distant metastasis rate at 3 and 5 years was 25.2% and 28.2%, respectively. In upper rectal cancer cases, the 5-year cumulative distant metastasis rates of the groups with 0, 1, 2, and 3 risk factors were 11.3%, 29.3%, 28.1%, and 50.0%, respectively. In lower rectal cancer cases, the 5-year cumulative distant metastasis rates of the groups with 0, 1, 2, and 3 risk factors were 17.1%, 29.1%, 39.9%, and 34.5%, respectively.

Discussion

The sites of LR after rectal cancer surgery are classified into three categories: central pelvis, lateral pelvis, and anastomotic recurrence. To prevent LR, securing good-quality TME, circumferential resection margin (CRM), and a distal margin is important[13-15]. TME/TSME plus LLND have been the standard procedure for advanced lower rectal cancer in Japan. Japanese multicenter collaborative research "JCOG 0212" on the significance of LLND in patients without apparent LLN metastases before surgery was reported in 2017. The LRR was significantly lower in TME plus LLND group (7.4%) than in TME alone group (12.6%); however, there was no significant difference in relapse-free survival

and overall survival[16]. In recent years, preoperative RT and CRT for locally advanced rectal cancer have been reported in Western countries. The LRR has been reported to be 4.4%-6.0%[3,4,17,18], and preoperative RT and CRT are regarded as very useful tools for reducing the risk of postoperative LR. Even in Japan, preoperative therapy (CRT) was included for the first time as a recommendation in the 2019 Japanese guidelines for CRC[19].

However, preoperative RT/CRT has an extended duration of treatment, increasing the associated costs; toxicity of anti-cancer drugs; and risks of urinary, defecation, and sexual dysfunction, as well as the risk of second primary malignancy[7-9]. Preoperative therapy for all cases of rectal cancer is clearly overtreatment.

Recently, in Europe, where preoperative diagnostic MRI is popular, the preoperative MRI findings (extramural vascular invasion [EMVI], CRM, subclassification of T3) have been added to conventional oncological factors to stratify the risk of postoperative LR[12,20,21]. While preoperative diagnostic MRI is a powerful tool to predict the LR after surgery, it is associated with some problems because accurately interpreting these findings is difficult, and no generally accepted protocol has been established in Japan. Therefore, in the present study, we explored the preoperative factors predictive for LR using conventional preoperative oncological factors and clarified in which patient preoperative RT/CRT could be omitted.

Our multivariate analysis showed that lower rectal cancer, a tumor diameter of ≥ 50 mm, undifferentiated adenocarcinoma, and advanced T-N substage (T3N+ or T4Nx) were independent factors of LR. We divided the patients into two groups of lower and upper rectal cancer (based on the height of the tumor), and the remaining three factors were then used to examine the relationship with LR. The 5-year cumulative LRR of upper rectal cancer patients with two risk factors was 9.5% and that of patients with all three risk factors was 40%. This suggests that preoperative RT/CRT is recommended for patients with upper rectal cancer with two or more risk factors. In contrast, the 5-year cumulative LLR of patients with lower rectal cancer with even one risk factor exceeded 10% across the board. Focusing on LLND, the LLR values of the 143 patients with LLND and the 367 without it were 14.3% and 10.7%, respectively (log-rank test, $P = 0.65$; data not shown). This suggests that merely adding LLND to TME is insufficient for preventing postoperative LR. Preoperative RT or CRT was thus considered to be recommended for patients with lower rectal cancer with even one risk factor. It should be noted that the LLR of patients without any risk factors was 4.4%, which was equivalent to the value included in a previous report of CRT + TME (4.4%-6.0%)[3,4,17,18]. We therefore concluded that preoperative treatment should be omitted in patients with lower rectal cancer without any risk factors.

Table 4. The Risk Factors for Local Recurrence.

| | No. of patients | No. of LR (%) | Univariate analysis | | Multivariate analysis | |
|----------------------------------|-----------------|---------------|---------------------|---------|-----------------------|---------|
| | | | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Age (year) | | | | | | |
| ≥70 | 339 | 20 (5.9) | Reference | | | |
| <70 | 476 | 50 (10.5) | 1.697 (1.027–2.915) | 0.039* | 1.654 (0.985–2.891) | 0.057 |
| Gender | | | | | | |
| Female | 274 | 18 (6.57) | Reference | | | |
| Male | 541 | 52 (9.61) | 1.608 (0.960–2.823) | 0.072 | | |
| ASA-PS | | | | | | |
| I | 249 | 21 (8.43) | Reference | | | |
| II- | 555 | 49 (8.83) | 1.115 (0.678–1.897) | 0.675 | | |
| ECOG-PS | | | | | | |
| 0 | 703 | 63 (8.96) | Reference | | | |
| 1- | 88 | 5 (5.68) | 0.683 (0.239–1.537) | 0.387 | | |
| BMI (kg/m ²) | | | | | | |
| <25 | 660 | 52 (7.88) | Reference | | | |
| ≥25 | 150 | 18 (12.0) | 1.608 (0.916–2.694) | 0.096 | | |
| PNI | | | | | | |
| ≥45 | 516 | 42 (8.14) | Reference | | | |
| <45 | 197 | 16 (8.12) | 0.971 (0.557–1.778) | 0.920 | | |
| Tumor location | | | | | | |
| Upper | 305 | 13 (4.26) | Reference | | | |
| Lower | 510 | 57 (11.18) | 2.784 (1.576–5.312) | <0.001* | 2.416 (1.308–4.753) | 0.004* |
| Tumor size (mm) | | | | | | |
| <50 | 354 | 17 (4.80) | Reference | | | |
| ≥50 | 460 | 53 (11.52) | 2.475 (1.465–4.401) | <0.001* | 1.732 (1.002–3.137) | 0.049* |
| Histological type | | | | | | |
| Differentiated | 765 | 61 (7.97) | Reference | | | |
| Undifferentiated | 50 | 9 (18.0) | 3.308 (1.530–6.332) | <0.001* | 2.590 (1.174–5.091) | 0.021* |
| Approach | | | | | | |
| Open | 672 | 62 (9.23) | Reference | | | |
| Lap | 143 | 8 (5.59) | 0.571 (0.252–1.122) | 0.109 | | |
| Procedure | | | | | | |
| Anus preserving | 657 | 47 (7.15) | Reference | | | |
| Anus not preserving | 158 | 23 (14.56) | 2.231 (1.332–3.633) | 0.003* | 1.224 (0.706–2.144) | 0.442 |
| Intraoperative blood transfusion | | | | | | |
| Absent | 714 | 57 (7.98) | Reference | | | |
| Present | 101 | 13 (12.87) | 1.562 (0.819–2.760) | 0.167 | | |
| UICC T-N substage | | | | | | |
| T1-2N+ or T3N0 | 418 | 24 (5.74) | Reference | | | |
| T3N+ or T4Nany | 397 | 46 (11.59) | 2.477 (1.526–4.124) | <0.001* | 2.310 (1.344–4.136) | 0.002* |
| Lateral lymph node metastasis | | | | | | |
| Absent | 783 | 61 (7.79) | Reference | | | |
| Present | 32 | 9 (28.13) | 3.746 (1.734–7.161) | 0.002* | 1.514 (0.659–3.139) | 0.310 |

The risk factors for local recurrence were evaluated using the Cox regression hazard model. P-values of <0.05 were considered significant and shown in boldface. ASA-PS, American Society of Anesthesiologists-physical status; ECOG-PS, Eastern Cooperative Oncology Group-performance status; BMI, body mass index; PNI, prognostic nutrition index calculated by 10x albumin (g/dL) + 0.005x total lymphocyte count (mm³); undiff., undifferentiated; LR, local recurrence; HR, hazard ratio; C.I., confidence interval

As a basic principle to reduce the LR, performing good-quality TME is necessary. In addition, for cases in which LLN metastasis was suspected before CRT, it has been reported that the LLR decreased from 7.1% to 2.7% by add-

ing LLND to preoperative CRT + TME[22]. Recently, it was reported in the West that selective LLND with CRT + TME significantly decreased the LLR compared with CRT + TME alone (5.7% vs. 19.5%)[23]. Thus, LLND remains an impor-

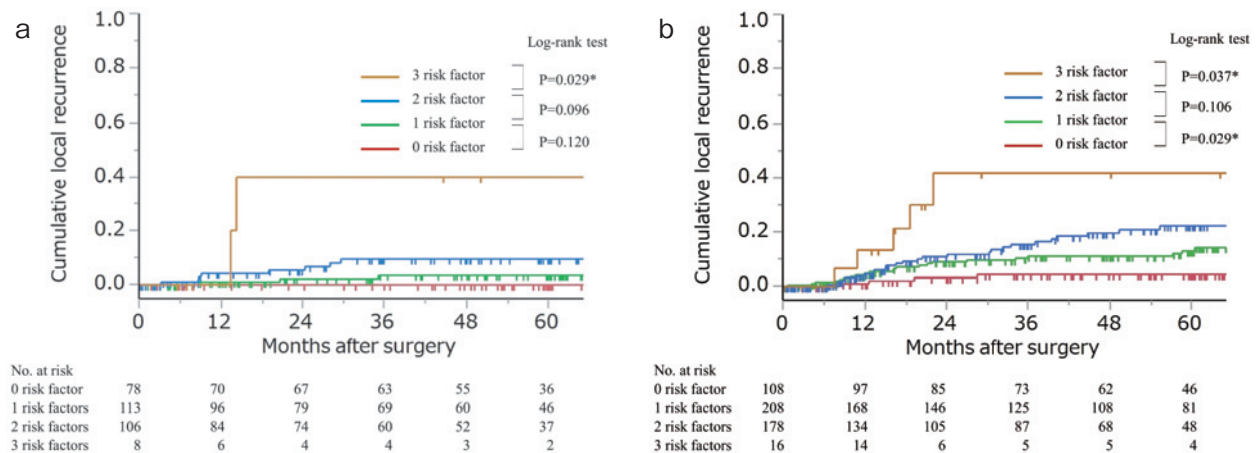


Figure 1. Cumulative local recurrence rate (LRR) for upper and lower rectal cancer.

In upper rectal cancer cases, the 5-year cumulative LRR of the groups with 0, 1, 2, and 3 risk factors were 0%, 3.6%, 9.5%, and 40.0%, respectively (a). In lower rectal cancer cases, the 5-year cumulative LRR of the groups with 0, 1, 2, and 3 risk factors were 4.4%, 13.0%, 22.2%, and 41.6%, respectively (b).

tant technique for reducing the LLR in Japan.

Several limitations associated with the present study warrant mention. First, the present study was retrospective. Second, the factor of T-N substage (T3N+, T4N0, and T4N+) proposed in the preset study was not a preoperative clinical diagnostic factor, but a pathologically confirmed factor. Although pathological TNM classification cannot be used to determine the therapeutic strategy, clinical TNM classification has one problem of diagnostic accuracy; therefore, improving the accuracy of the preoperative diagnosis will be a future task. Third, we have no data regarding the preoperative size of lateral lymph nodes. When we diagnosed as clinical stage I before surgery or when the attending surgeon judged that LLND was not indicated due to patient's age or comorbidities, we did not perform LLND. Therefore, LLND was not performed in all pathological stage II/III low rectal cancer. Fourth, we did not conduct an analysis according to LR sites (central or lateral or anastomosis). Finally, EMVI, CRM and subclassification of T3, which are well recognized as strong risk factors of LR, was not evaluated by preoperative MRI. Nowadays, we usually perform MRI as a preoperative examination to evaluate the CRM status, EMVI, and extent of invasion to adjacent organ in Japan. Based on these findings, we consider the indication of preoperative therapy. Therefore, we should need further examination about the EMVI status and CRM by MRI findings in addition to the present risk factors.

In conclusion, there were two new findings made in the present study. First, preoperative treatment is recommended for patients with two or more risk factors, even in cases of upper rectal cancer. Second, preoperative treatment may be omitted in patients without any risk factor in cases of lower rectal cancer. However, further examination about the EMVI status and CRM by MRI findings in addition to the present

risk factors is needed.

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Conflicts of Interest

There are no conflicts of interest.

Author Contributions

MK, JW, AI, and MO contributed to the study design. All of the authors contributed to the data collection, data analysis, and interpretation. KG and KN contributed to the statistical analyses. All of the authors contributed to the writing or review of the report and approved the final version.

Approval by Institutional Review Board (IRB)

The study protocol was approved by the Ethical Advisory Committee of Yokohama City University Graduate School of Medicine and the institutional review board of each participating hospital before the study was initiated (Registry as 22193).

Disclaimer

Mitsuyoshi Ota is one of the Associate Editors of Journal of the Anus, Rectum and Colon and on the journal's Editorial Board. He was not involved in the editorial evaluation or decision to accept this article for publication at all.

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