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# Local recurrence after curative resection for rectal carcinoma

## The role of surgical resection

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**Abstract**

Local recurrence of rectal cancer is difficult to treat, may cause severe and disabling symptoms, and usually has a fatal outcome. The aim of this study was to document the clinical nature of locally recurrent rectal cancer and to determine the effect of surgical resection on long-term survival.

A retrospective review was conducted of the prospectively collected medical records of 2485 patients with primary rectal adenocarcinoma who underwent radical resection between September 1994 and December 2008.

In total, 147 (5.9%) patients exhibited local recurrence. The most common type of local recurrence was lateral recurrence, whereas anastomotic recurrence was the most common type in patients without preoperative concurrent chemoradiotherapy (CCRT). Tumor location with respect to the anal verge significantly affected the local recurrence rate ($P < 0.001$), whereas preoperative CCRT did not affect the local recurrence rate ($P = 0.433$). Predictive factors for surgical resection of recurrent rectal cancer included less advanced tumor stage ($P = 0.017$, RR = 3.840, 95% CI = 1.271–11.597), axial recurrence ($P < 0.001$, RR = 5.772, 95% CI = 2.281–14.609), and isolated local recurrence ($P = 0.006$, RR = 8.679, 95% CI = 1.846–40.815). Overall survival after diagnosis of local recurrence was negatively influenced by advanced pathologic tumor stage ($P = 0.040$, RR = 1.867, 95% CI = 1.028–3.389), positive CRM ($P = 0.001$, RR = 12.939, 95% CI = 2.906–57.604), combined distant metastases ($P = 0.001$, RR = 2.086, 95% CI = 1.352–3.218), and nonsurgical resection of recurrent tumor ($P < 0.001$, RR = 4.865, 95% CI = 2.586–9.153).

In conclusion, the clinical outcomes of local recurrence after curative resection of rectal cancer are diverse. Surgical resection of locally recurrent rectal cancer should be considered as an initial treatment, especially in patients with less advanced tumors and axial recurrence.

**Abbreviations:** CCRT = concurrent chemoradiotherapy, CEA = carcinoembryonic antigen, CRM = circumferential resection margin, CT = computed tomography, MRI = magnetic resonance imaging, PET = positron emission tomography, TME = total mesorectal excision.

**Keywords:** clinical course, local recurrence, prognosis, rectal cancer, surgical resection

### 1. Introduction

In patients with curatively resected rectal cancer, local recurrence is often difficult to treat, may cause severely disabling symptoms, and usually has a fatal outcome. Thus, previous studies have focused on identifying risk factors for local recurrence or on preventing local recurrence. In particular, considerable effort has been invested in treating patients with rectal cancer through advanced surgical techniques, adjuvant therapy, and neoadjuvant treatment. Heald et al[1] Heald and Ryall[2] standardized a novel total mesorectal excision (TME) approach for treating rectal cancer, whereas other groups have developed neoadjuvant treatment modalities that have further improved local control. After these types of treatment, the local recurrence rate has been reported to be 2.4% to 5.6% in various clinical trials.[3–5] Other studies on the clinical course, optimal treatment and prognosis of patients with local recurrence have also been

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performed. Treatment failure patterns after management of recurrent rectal cancer have been reviewed elsewhere.[6]

Some authors have reported survival benefit and long-term preservation of quality of life after curative reresection of local recurrence[7]; however, such reresection is possible only in approximately one-third of all recurrent tumors.[8] Moreover, achievement of an optimal resection margin is technically challenging, even though advanced combined adjuvant and neoadjuvant chemoradiation modalities have been developed.[9] Another challenge for patients who undergo radical surgery for recurrent rectal cancer is the risk of synchronous distant metastasis. The combination of local and distant recurrences reduces not only the opportunity for curative resection, but also the potential radiotherapies that are available for local control. Therefore, obtaining information regarding recurrence patterns, natural course, associated risk factors, and treatment outcomes is extremely important. This knowledge will help improve oncologic outcomes and identify optimal care strategies for patients with recurrent rectal cancer.

The purpose of this study was therefore to document the clinical course and prognosis of local recurrence after curative resection for rectal adenocarcinoma and to identify the effect of surgical resection on long-term survival. This study also aimed to identify factors that affect patient prognosis after local recurrence.

## 2. Patients and methods

### 2.1. Patient selection and follow-up

From September 1994 to December 2008, 2485 patients underwent TME for primary rectal adenocarcinoma (tumor location: <15 cm from anal verge by rigid sigmoidoscopy or digital rectal examination),[10] either with or without preoperative concurrent chemoradiotherapy (CCRT). The exclusion criteria were as follows: (1) hereditary colorectal cancer, (2) combined synchronous colorectal cancer, (3) combined other primary malignancy, (4) distant metastasis at the time of diagnosis. Among these 2485 patients, 435 were diagnosed with an isolated distant metastasis without local recurrence during the follow-up period; thus, 2050 patients were ultimately included in the analysis.

Among these 2050 patients, 356 (17.4%) underwent preoperative CCRT. The indication for preoperative CCRT in our institution was T3 or T4 rectal cancer or suspected perirectal lymph node metastases based on radiologic imaging studies. All patients underwent preoperative therapy performed according to the same protocol. Radiation therapy was administered using a 3-field technique; doses of 40.4 to 50.4 Gy were delivered. Chemotherapy was delivered concurrently using 2 chemotherapeutic regimens: (1) 5-fluorouracil (500 mg/m$^2$ per day) for 3 days during the first and last weeks of radiotherapy; and (2) oral capecitabine (825 mg/m$^2$) twice daily during radiotherapy without weekend breaks. In principle, surgery was performed 6 to 8 weeks after the completion of preoperative therapy.

The Institutional Review Board at Samsung Medical Center approved this study. Clinicopathologic information was obtained through comprehensive chart review, and follow-up data were obtained from patient medical records and the National Bureau of Statistics. A circumferential resection margin (CRM) ≤1 mm was scored as a negative resection margin based on results from a recent study at our institution.[11] The primary outcome measured in this analysis was local recurrence, and all patients were clinically evaluated for both local and distant recurrence during the follow-up period. Surveillance for recurrence was comprised of a physical examination, measurement of the serum carcinoembryonic antigen (CEA) level, colonoscopy, chest computed tomography (CT), and an abdomen-pelvis CT scan. These procedures were performed every 6 months for 3 years and annually thereafter. Other examinations, such as magnetic

**Table 1**

**Patient demographics (n = 2050).**

| | No recurrence (n = 1903) | Local recurrence (n = 147) | *P* |
|---|---|---|---|
| Sex, n (%) | | | 0.440 |
| Female | 754 (39.6) | 63 (42.9) | |
| Male | 1149 (60.4) | 84 (57.1) | |
| Age, y | | | |
| Median, range | 59 (22–89) | 58 (22–87) | 0.346 |
| ≥60 | 906 (47.6) | 66 (44.9) | 0.526 |
| ASA | | | 0.511 |
| 1–2 | 1831 (96.2) | 143 (97.3) | |
| 3–4 | 72 (3.8) | 4 (2.7) | |
| Distance from the anal verge, cm | | | <0.001 |
| Median, range | 7.0 (1.0–15.0) | 5.0 (1.0–14.0) | |
| DRM, cm | | | 0.760 |
| Median, range | 2.0 (0.1–9.0) | 2.0 (0.1–7.0) | |
| CRM | | | 0.323 |
| Negative | 1207 (63.4) | 90 (61.2) | |
| Positive | 16 (0.8) | 3 (2.0) | |
| Not checked | 680 (35.7) | 54 (36.7) | |
| Pathologic T stage | | | <0.001 |
| T0–2 | 729 (38.3) | 27 (18.4) | |
| T3–4 | 1174 (61.7) | 120 (81.6) | |
| Pathologic N stage | | | <0.001 |
| N0 | 1243 (65.3) | 62 (42.2) | |
| N1–2 | 660 (34.7) | 85 (57.8) | |
| Number of harvested lymph node | | | 0.334 |
| Median, range | 15 (1–62) | 14 (1–45) | |
| Surgical procedure | | | <0.001 |
| Sphincter-preserving resection | 1615 (84.9) | 108 (73.5) | |
| Non-sphincter-preserving resection | 288 (15.1) | 39 (26.5) | |
| Initial CEA, ng/mL | | | <0.001 |
| ≤5 | 1282 (67.4) | 74 (50.3) | |
| >5 | 365 (19.2) | 41 (27.9) | |
| Not available | 256 (13.5) | 32 (21.8) | |
| Cell type | | | 0.001 |
| WD+MD | 1781 (93.6) | 127 (86.4) | |
| PD+MUC+SRC | 122 (6.4) | 20 (13.6) | |
| LVI | | | <0.001 |
| No | 875 (46.0) | 38 (25.9) | |
| Yes | 317 (16.7) | 48 (32.7) | |
| Not checked | 711 (37.4) | 61 (41.5) | |
| PNI | | | <0.001 |
| No | 806 (42.4) | 45 (30.6) | |
| Yes | 76 (4.0) | 20 (13.6) | |
| Not checked | 1021 (53.7) | 82 (55.8) | |
| Neoadjuvant CCRT | | | 0.433 |
| No | 1576 (82.8) | 118 (80.3) | |
| Yes | 327 (17.2) | 29 (19.7) | |
| Adjuvant chemotherapy/CCRT | | | 0.012 |
| No | 673 (35.4) | 37 (25.2) | |
| Yes | 1230 (64.6) | 110 (74.8) | |

ASA = American Society of Anesthesiologists, CCRT = concurrent chemoradiotherapy, CEA = carcinoembryonic antigen, CRM = circumferential resection margin, DRM = distal resection margin, LVI = lymphovascular invasion, MD = moderately differentiated, MUC = mucinous, N = node, PD = poorly differentiated, PNI = perineural invasion, SRC = signet ring cell, T = tumor, WD = well differentiated.

**Table 2**

**Clinicopathologic features of patients according to preoperative CCRT (n = 2050).**

| | Preoperative CCRT (–) (n = 1694) | | | Preoperative CCRT (+) (n = 356) | | |
|---|---|---|---|---|---|---|
| | No recurrence (n = 1576) | Local recurrence (n = 118) | *P* | No recurrence (n = 327) | Local recurrence (n = 29) | *P* |
| Sex, n (%) | | | 0.576 | | | 0.434 |
| Female | 653 (41.4) | 52 (44.1) | | 101 (30.9) | 11 (37.9) | |
| Male | 923 (58.6) | 66 (55.9) | | 226 (69.1) | 18 (62.1) | |
| Age, y | | | | | | |
| Median, range | 59 (24–89) | 58 (22–87) | 0.330 | 56 (22–79) | 54 (29–76) | 0.964 |
| ASA | | | 1.000 | | | 1.000 |
| 1–2 | 1514 (96.1) | 114 (96.6) | | 317 (96.9) | 29 (100.0) | |
| 3–4 | 62 (3.9) | 4 (3.4) | | 10 (3.1) | 0 (0.0) | |
| Distance from anal verge, cm | | | | | | |
| Median, range | 7.0 (0.0–15.0) | 5.0 (0.0–14.0) | <0.001 | 4.0 (0.0–12.0) | 4.0 (1.0–7.0) | 0.146 |
| DRM, cm | | | | | | |
| Median, range, | 2.0 (0.1–9.0) | 2.0 (0.1–7.0) | 0.904 | 1.5 (0.1–8.1) | 1.6 (0.2–5.5) | 0.626 |
| CRM | | | 0.623 | | | 0.283 |
| Negative | 970 (61.5) | 72 (61.0) | | 237 (72.5) | 18 (62.1) | |
| Positive | 13 (0.8) | 2 (1.7) | | 3 (0.9) | 1 (3.4) | |
| Not available | 593 (37.6) | 44 (37.3) | | 87 (26.6) | 10 (34.5) | |
| Pathologic T stage | | | <0.001 | | | 0.004 |
| (y)pT0–2 | 548 (34.8) | 19 (16.1) | | 181 (55.4) | 8 (27.6) | |
| (y)pT3–4 | 1028 (65.2) | 99 (83.9) | | 146 (44.6) | 21 (72.4) | |
| Pathologic N stage | | | <0.001 | | | 0.058 |
| (y)pN0 | 989 (62.8) | 44 (37.3) | | 254 (77.7) | 18 (62.1) | |
| (y)pN1–2 | 587 (37.2) | 74 (62.7) | | 73 (22.3) | 11 (37.9) | |
| Number of harvested lymph node | | | 0.300 | | | 0.551 |
| Median, range | 16 (1–62) | 15 (2–45) | | 9 (1–40) | 9 (1–26) | |
| Surgical procedure | | | 0.001 | | | 0.160 |
| Sphincter-preserving resection | 1344 (85.3) | 87 (73.7) | | 271 (82.9) | 21 (72.4) | |
| Nonsphincter-preserving resection | 232 (14.7) | 31 (26.3) | | 56 (17.1) | 8 (27.6) | |
| Initial CEA, ng/mL | | | <0.001 | | | 0.833 |
| ≤5 | 1085 (68.8) | 56 (47.5) | | 197 (60.2) | 18 (62.1) | |
| >5 | 294 (18.7) | 36 (30.5) | | 71 (21.7) | 5 (17.2) | |
| Not available | 197 (12.5) | 26 (22.0) | | 59 (18.0 | 6 (20.7) | |
| Cell type | | | 0.002 | | | 0.350 |
| WD+MD | 1489 (94.5) | 103 (87.3) | | 292 (89.3) | 24 (82.8) | |
| PD+MUC+SRC | 87 (5.5) | 15 (12.7) | | 35 (10.7) | 5 (17.2) | |
| LVI | | | <0.001 | | | 0.001 |
| No | 668 (42.4) | 27 (22.9) | | 207 (63.3) | 11 (37.9) | |
| Yes | 293 (18.6) | 40 (33.9) | | 24 (7.3) | 8 (27.6) | |
| Not available | 615 (39.0) | 51 (43.2) | | 96 (29.4) | 10 (34.5) | |
| PNI | | | <0.001 | | | 0.376 |
| No | 627 (39.8) | 31 (26.3) | | 179 (54.7) | 14 (48.3) | |
| Yes | 61 (3.9) | 17 (14.4) | | 15 (4.6) | 3 (10.3) | |
| Not available | 888 (56.3) | 70 (59.3) | | 133 (40.7) | 12 (41.4) | |
| Adjuvant chemotherapy | | | 0.011 | | | 0.748 |
| No | 642 (40.7) | 34 (28.8) | | 31 (9.5) | 3 (10.3) | |
| Yes | 934 (59.3) | 84 (71.2) | | 296 (90.5) | 26 (89.7) | |
| Adjuvant radiotherapy | | | 0.024 | – | – | – |
| No | 850 (53.9) | 51 (43.2) | | | | |
| Yes | 726 (46.1) | 67 (56.8) | | | | |
| Pattern of recurrence | – | | – | – | | 0.019* |
| Local only | | 80 (67.8) | | | 26 (89.7) | |
| Combined metastases | | 38 (32.2) | | | 3 (10.3) | |
| Site of local recurrence | – | | – | – | | 0.335* |
| Anterior | | 5 (4.2) | | | 2 (6.9) | |
| Posterior | | 21 (17.8) | | | 8 (27.6) | |
| Lateral | | 41 (34.7) | | | 11 (37.9) | |
| Anastomotic | | 43 (36.4) | | | 5 (17.2) | |
| Perineal | | 8 (6.8) | | | 3 (10.3) | |

* Calculated between CCRT(−) and CCRT(+) in patients with local recurrence.

ASA = American Society of Anesthesiologists, CCRT = concurrent chemoradiotherapy, CEA = carcinoembryonic antigen, CRM = circumferential resection margin, DRM = distal resection margin, LVI = lymphovascular invasion, MD = moderately differentiated, MUC = mucinous, N = node, PD = poorly differentiated, PNI = perineural invasion, SRC = signet ring cell, T = tumor, WD = well differentiated.

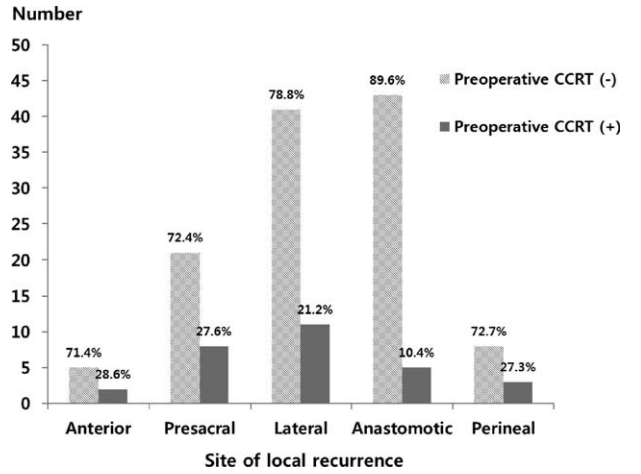


**Figure 1.** Site of local recurrence (n = 147).

resonance imaging (MRI) or positron emission tomography (PET), were performed every 6 to 12 months depending on patient status.

Recurrent rectal cancer may be isolated (local or metastatic) or combined (local and metastatic). Local recurrence was defined as any evidence of rectal cancer recurrence in the small pelvis.[12] Diagnosis of recurrent rectal cancer was established by meeting at least one of the following major criteria: (a) histological confirmation, (b) clear bone destruction, and (c) PET examination, and at least one of the following minor criteria: (a) progressive soft tissue mass on repeated CT or MRI examination, (b) invasion of adjacent organs, (c) subsequent rise in tumor markers, and (d) typical appearance on endoscopic ultrasound, CT, or MRI scan.[13,14] Recurrence location was classified into 1 of the following 5 subsites: presacral, anterior, anastomotic, lateral, and perineal.[15] Anastomotic and perineal recurrence were considered as axial and the rest were considered nonaxial recurrence in further analyses.

### 2.2. Statistical analysis

Data were analyzed using SPSS software, version 18.0 (SPSS Inc, Chicago, IL). The significance of differences between 2 groups was analyzed using Student's *t* test or Fisher's exact test. Continuous data were recorded as means and ranges (minimum to maximum). Variables with $P$ values $< 0.05$ according to univariate analysis were further analyzed using the Cox regression method for multivariate analysis. The disease-free and overall survival rates were determined using Kaplan–Meier analysis and a log-rank test. Statistical significance was defined as a $P$-value $< 0.05$. The date of local recurrence diagnosis was set to the starting point for survival analysis, as one of the aims of this study was to document the prognosis of locally recurrent rectal cancer. Also, 1:1 propensity score matching was performed by using bivariate logistic regression to correct selection bias for surgical resection of locally recurrent cancer.

## 3. Results

### 3.1. Basic demographics and clinical nature of local recurrences

The median follow-up period for the 2050 patients was 70 months (range 0.2–232.4 months). A total of 817 patients

**Table 3**

**Clinicopathologic characteristics of patients with local recurrence according to recurrence site (n = 147).**

| | Axial (n = 59) | Nonaxial (n = 88) | *P* |
|---|---|---|---|
| Sex, n (%) | | | 0.437 |
| Female | 23 (39.0) | 40 (45.5) | |
| Male | 36 (61.0) | 48 (54.5) | |
| Age, y | | | 0.112 |
| Median, range | 61 (38–87) | 56 (22–81) | |
| ASA | | | 1.000 |
| 1–2 | 57 (96.6) | 86 (97.7) | |
| 3–4 | 2 (3.4) | 2 (2.3) | |
| Distance from anal verge, cm | | | 0.004 |
| Median, range | 6.0 (1.0–14.0) | 4.5 (1.0–14.0) | |
| Initial stage | | | 0.195 |
| I | 4 (6.8) | 11 (12.5) | |
| II | 13 (22.0) | 27 (30.7) | |
| III | 42 (71.2) | 50 (56.8) | |
| Pathologic T stage | | | 0.830 |
| T0 | 0 (0.0) | 2 (2.3) | |
| T1 | 1 (1.7) | 2 (2.3) | |
| T2 | 9 (15.3) | 13 (14.8) | |
| T3 | 45 (76.3) | 66 (75.0) | |
| T4 | 4 (6.8) | 5 (5.7) | |
| Pathologic N stage | | | 0.630 |
| N0 | 27 (45.8) | 35 (39.8) | |
| N1 | 18 (30.5) | 26 (29.5) | |
| N2 | 14 (23.7) | 27 (30.7) | |
| Number of harvested lymph node | | | 0.391 |
| <12 | 20 (33.9) | 36 (40.9) | |
| DRM | | | 0.174 |
| <1cm | 7 (11.9) | 18 (20.5) | |
| ≥1cm | 52 (88.1) | 70 (79.5) | |
| CRM | | | 0.177 |
| Negative | 31 (52.5) | 59 (67.0) | |
| Positive | 1 (1.7) | 2 (2.3) | |
| Not available | 27 (45.8) | 27 (30.7) | |
| Surgical procedure | | | 0.164 |
| Sphincter-preserving resection | 47 (79.7) | 61 (69.3) | |
| Non-sphincter-preserving resection | 12 (20.3) | 27 (30.7) | |
| Initial CEA, ng/mL | | | 0.260 |
| ≤5 | 25 (42.4) | 49 (55.7) | |
| >5 | 20 (33.9) | 21 (23.9) | |
| Not available | 14 (23.7) | 18 (20.5) | |
| Cell type | | | 0.320 |
| WD+MD | 53 (89.8) | 74 (84.1) | |
| PD+MUC+SRC | 6 (10.2) | 14 (15.9) | |
| LVI | | | 0.482 |
| No | 14 (23.7) | 24 (27.3) | |
| Yes | 17 (28.8) | 31 (35.2) | |
| Not available | 28 (47.5) | 33 (37.5) | |
| PNI | | | 0.380 |
| No | 15 (25.4) | 30 (34.1) | |
| Yes | 7 (11.9) | 13 (14.8) | |
| Not available | 37 (62.7) | 45 (51.1) | |
| Neoadjuvant CCRT | | | 0.124 |
| No | 51 (86.4) | 67 (76.1) | |
| Yes | 8 (13.6) | 21 (23.9) | |
| Adjuvant chemotherapy | | | 0.222 |
| No | 18 (30.5) | 19 (21.6) | |
| Yes | 41 (69.5) | 69 (78.4) | |
| Pattern of metastasis | | | 0.562 |
| Local only | 41 (69.5) | 65 (73.9) | |
| Combined metastases | 18 (30.5) | 23 (26.1) | |

ASA = American Society of Anesthesiologists, CCRT = concurrent chemoradiotherapy, CEA = carcinoembryonic antigen, CRM = circumferential resection margin, DRM = distal resection margin, LVI = lymphovascular invasion, MD = moderately differentiated, MUC = mucinous, N = node, PD = poorly differentiated, PNI = perineural invasion, SRC = signet ring cell, T = tumor, WD = well differentiated.

**Table 4**

**Treatment for locally recurrent rectal cancer according to local recurrence site.**

| | Local recurrence only (n = 106) | | | Combined recurrence (n = 41) | | |
|---|---|---|---|---|---|---|
| | Axial (n = 41) | Nonaxial (n = 65) | *P* | Axial (n = 18) | Nonaxial (n = 23) | *P* |
| Surgical resection | 21 (51.2) | 10 (15.4) | 0.001 | 1 (5.6) | 1 (4.3) | 0.620 |
| CCRT | 3 (7.3) | 16 (24.6) | | 0 (0.0) | 2 (8.7) | |
| Radiotherapy only | 2 (4.9) | 2 (3.1) | | 0 (0.0) | 0 (0.0) | |
| Chemotherapy only | 6 (14.6) | 27 (41.5) | | 11 (61.1) | 14 (60.9) | |
| None or conservative management | 9 (22.0) | 10 (15.4) | | 6 (33.3) | 6 (26.1) | |

CCRT = concurrent chemoradiotherapy.

(39.9%) were female; the median patient age was 59 years (range 22–89 years). Among the 2050 patients, 356 (17.4%) underwent preoperative CCRT and 147 were diagnosed with local recurrence during the follow-up period (7.2%, 106 isolated and 41 combined with distant recurrence). The local recurrence rate was higher for patients with preoperative CCRT compared with patients without preoperative CCRT; however, this difference was not significant (7.0% vs 8.1%, $P = 0.433$). The subsite of local recurrence was not affected by preoperative CCRT either ($P = 0.335$). However, preoperative CCRT significantly lowered the combined distant and local recurrence rate (32.2% vs 10.3%, $P = 0.019$).

The mean tumor distance from the anal verge was significantly lower ($P < 0.001$) and the pathologic tumor and nodal status were more advanced (both, $P < 0.001$) in patients with locally recurrent rectal cancer who did not receive preoperative CCRT. Also, the initial CEA level, rate of lymphovascular invasion, and rate of perineural invasion were significantly higher in patients with local recurrence who did not receive preoperative CCRT (all, $P < 0.001$). Histologic differentiation was also significantly different between the groups ($P = 0.002$). However, only pathologic tumor stage and rate of lymphovascular invasion were significantly different in patients who received preoperative CCRT ($P = 0.004$ and $P = 0.001$, respectively) (Tables 1 and 2). The most common type of local recurrence out of the 147 patients was lateral recurrence (n = 52,35.4%); however, anastomotic recurrence was the most common type of local recurrence in patients who did not receive preoperative CCRT (36.4%) (Fig. 1). Tumor locations within 5 cm from the anal verge were observed more frequently in patients with nonaxialrecurrence. No other significant clinicopathologic differences were observed between patients with axial andnonaxial recurrence including the rate of combined recurrence (30.5% vs 26.1%, respectively; $P = 0.562$) (Table 3).

### 3.2. Treatment for local recurrence of rectal cancer

The rate of surgical resection was lower in cases of combined distant and local recurrence compared with cases of only local recurrence (4.9% vs 29.2%, $P = 0.001$). Axial recurrence was treated with surgical resection more frequently than nonaxial recurrence (37.3% vs 12.5%, $P < 0.001$). Chemotherapy was the preferred treatment option for all patients with local recurrence, regardless of the presence of synchronous distant metastasis (Table 4). Univariate analysis revealed that predictive factors for surgical resection in patients with local recurrence were: less advanced T stage of the previously resected primary tumor ($P = 0.002$), lymph node-negative primary tumor ($P = 0.042$), axial recurrence ($P < 0.001$), and limited local recurrence ($P = 0.001$). Multivariate analysis revealed that a less advanced tumor stage (below T3), axial recurrence, and isolated local recurrence were significant predictors for surgical resection ($P = 0.017$, RR = 3.840, 95% CI = 1.271–11.597; $P < 0.001$, RR = 5.772, 95% CI = 2.281–14.609; and $P = 0.006$, RR = 8.679, 95% CI = 1.846–40.815, respectively) (Table 5). Among the 33 patients with surgical resection of locally recurrent rectal cancer, R0 resection was achieved in 26 patients (78.8%). Thirteen patients (39.4%) including 1 patient with combined distant lymph node metastasis underwent excision of recurrent tumor, 17 patients (42.4%) underwent abdominoperineal resection and Hartmann's operation, and 3 patients (9.1%) underwent low anterior resection.

### 3.3. Survival analysis after local recurrence

The 1-, 3-, and 5-year overall survival rates of patients after diagnosis of local recurrence were 75.4%, 36.7%, and 19.1%, respectively. Univariate analysis revealed that advanced pathologic tumor stage ($P = 0.001$); positive nodal status ($P = 0.011$); ≥ 1 cm distal resection margin ($P = 0.048$); poorly differentiated, mucinous, or signet ring cell histologic cell type ($P = 0.010$); positive CRM ($P = 0.025$); combined distant metastases ($P < 0.001$); and nonsurgical treatment of locally recurrent rectal cancer ($P < 0.001$) significantly affected overall survival after local recurrence. However, the site of local recurrence was not associated with prognosis ($P = 0.146$). Multivariate analysis revealed that advanced pathologic tumor stage ($P = 0.040$, HR = 1.867, 95% CI = 1.028–3.389), positive CRM ($P = 0.001$, HR = 12.939, 95% CI = 2.906–57.604), combined distant metastases ($P = 0.001$, HR = 2.086, 95% CI = 1.352–3.218), and nonsurgical resection of the recurrent tumor ($P < 0.001$, HR = 4.865, 95% CI = 2.586–9.153) were significant predictors of worse overall survival after local recurrence (Table 6, Fig. 2A). After propensity score matching to correct selection bias for surgical resection of locally recurrent cancer, surgical treatment was associated with significantly better survival (Supplementary Table 1 and Figure 1, http://links.lww.com/MD/B108). However, R0 resection did not

**Table 5**

**Multivariate analysis of predictive factors for surgical treatment in patients with local recurrences.**

| Parameter | *P* | Ratio of risk | 95% CI |
|---|---|---|---|
| Synchronous distant metastasis (no vs yes) | 0.006 | 8.679 | 1.846–40.815 |
| Pathologic T stage* (T0–2 vs T3–4) | 0.017 | 3.840 | 1.271–11.597 |
| Pathologic N stage* (N0 vs N+) | 0.737 | 1.177 | 0.454–3.048 |
| Site of local recurrence (axial vs nonaxial) | <0.001 | 5.772 | 2.281–14.609 |

CI = confidence interval, N = node, T = tumor.
* Pathologic results of previously resected primary tumors.

**Table 6**

**Univariate and multivariate analyses of prognostic factors affecting overall survival after local recurrence in patients with locally recurrent rectal cancer (n = 147).**

| Predictor | Univariate Ratio of risk (95% CI) | *P* | Multivariate Ratio of risk (95% CI) | *P* |
|---|---|---|---|---|
| Sex | | 0.684 | | |
| Female vs male | 1.081 (0.742–1.577) | | | |
| Age, y | | 0.058 | | |
| ≥60 vs <60 | 1.443 (0.988–2.108) | | | |
| ASA | | 0.073 | | |
| 3–4 vs 1–2 | 2.503 (0.917–6.834) | | | |
| Distance from anal verge, cm | | 0.856 | | |
| >5 vs ≤5 | 1.036 (0.709–1.514) | | | |
| pT stage | | 0.001 | | 0.040 |
| T3–4 vs T0–2 | 2.618 (1.486–4.612) | | 1.867 (1.028–3.389) | |
| pN stage | | 0.011 | | 0.942 |
| N+ vs N0 | 1.673 (1.125–2.488) | | 0.984 (0.637–1.519) | |
| Number of harvested lymph node | | 0.544 | | |
| ≥12 vs <12 | 1.131 (0.760–1.684) | | | |
| Distal resection margin, cm | | 0.048 | | 0.115 |
| ≥1 vs <1 | 1.795 (1.004–3.207) | | 1.621 (0.889–2.955) | |
| Sphincter-preserving | | 0.423 | | |
| No vs yes | 1.184 (0.783–1.791) | | | |
| Initial CEA level | | 0.104 | | |
| >5 vs ≤5 | 1.327 (0.851–2.069) | | | |
| Cell type | | 0.010 | | 0.375 |
| PD+MUC+SRC vs WD+MD | 1.988 (1.179–3.352) | | 1.282 (0.741–2.219) | |
| Positive LVI | 1.686 (0.977–2.909) | 0.061 | | |
| Positive PNI | 1.151 (0.594–2.232) | 0.678 | | |
| Positive CRM | 5.141 (1.224–21.584) | 0.025 | 12.939 (2.906–57.604) | 0.001 |
| Neoadjuvant CCRT | | 0.254 | | |
| No vs yes | 1.343 (0.809–2.227) | | | |
| Adjuvant chemotherapy/CCRT | | 0.420 | | |
| Yes vs no | 1.209 (0.762–1.920) | | | |
| Combined distant metastases | | <0.001 | | 0.001 |
| Yes vs no | 2.804 (1.845–4.263) | | 2.086 (1.352–3.218) | |
| Recurrence location | | 0.146 | | |
| Nonaxial vs axial | 1.343 (0.903–1.999) | | | |
| treatment for local recurrence | | | | <0.001 |
| Surgical resection (no vs yes) | 5.680 (3.077–10.485) | <0.001 | 4.865 (2.586–9.153) | |

ASA = American Society of Anesthesiologists, CCRT = concurrent chemoradiotherapy, CEA = carcinoembryonic antigen, CRM = circumferential resection margin, LVI = lymphovascular invasion, PNI = perineural invasion, MD = moderately differentiated, MUC = mucinous, N = node, PD = poorly differentiated, SRC = signet ring cell, T = tumor, WD = well differentiated.

significantly affect survival after surgery of locally recurrent rectal cancer ($P = 0.160$). Moreover, neither preoperative CCRT nor the location of the locally recurrent tumor significantly affected survival after diagnosis of local recurrence (Fig. 2B and C).

## 4. Discussion

The local recurrence rate of curatively resected rectal cancer in our large database was 5.9 %. Surgical resection of locally recurrent rectal cancer significantly increased overall survival after diagnosis of local recurrence, irrespective of R0 resection. Moreover, predictive factors for surgery included less advanced tumor stage (below T3), axial recurrence, and isolated local recurrence. The rates of local recurrence of curatively resected rectal cancer have been reported to vary from 3.7 to 13.0 % as the introduction of TME, regardless of whether or not preoperative chemoradiotherapy or radiotherapy are performed;[6,16–19] these rates are comparable with our results. We also found that the rate of local recurrence was significantly higher in patients who underwent nonsphincter-preserving surgery compared with sphincter-preserving surgery (11.9% vs 6.3%, $P < 0.001$), which is also consistent with other reports.[16,20] One possible explanation for this finding may be both the anatomical features of the pelvic floor and that tumor cells are pushed into the lateral lymph flow routes during surgery, leaking back into the surgical volume after resection of low rectal cancer.[21–23]

Preoperative CCRT did not lower the local recurrence rate, although it did significantly lower the combined distant and local recurrence rate. Interestingly, synchronous distant metastasis was revealed to significantly worsen overall survival after diagnosis of recurrence. However, preoperative CCRT did not prolong overall survival after either the first surgery or a diagnosis of local recurrence in this analysis. A number of studies in the last few years investigating preoperative CCRT treatment for locally advanced rectal cancer have demonstrated the efficacy of this treatment in complete pathologic response, tumor down-staging, and enhanced sphincter preservation, including local control.[24,25] However, the impact of preoperative CCRT on overall survival is highly controversial.[26–28] For example, 1 study found that local recurrence after previous radiotherapy was associated with a significantly shorter survival duration compared with patients with local recurrence who did not receive PRT for the primary tumor.[29] This finding could be due to selection bias for preoperative radiotherapy of patients with unfavorable primary

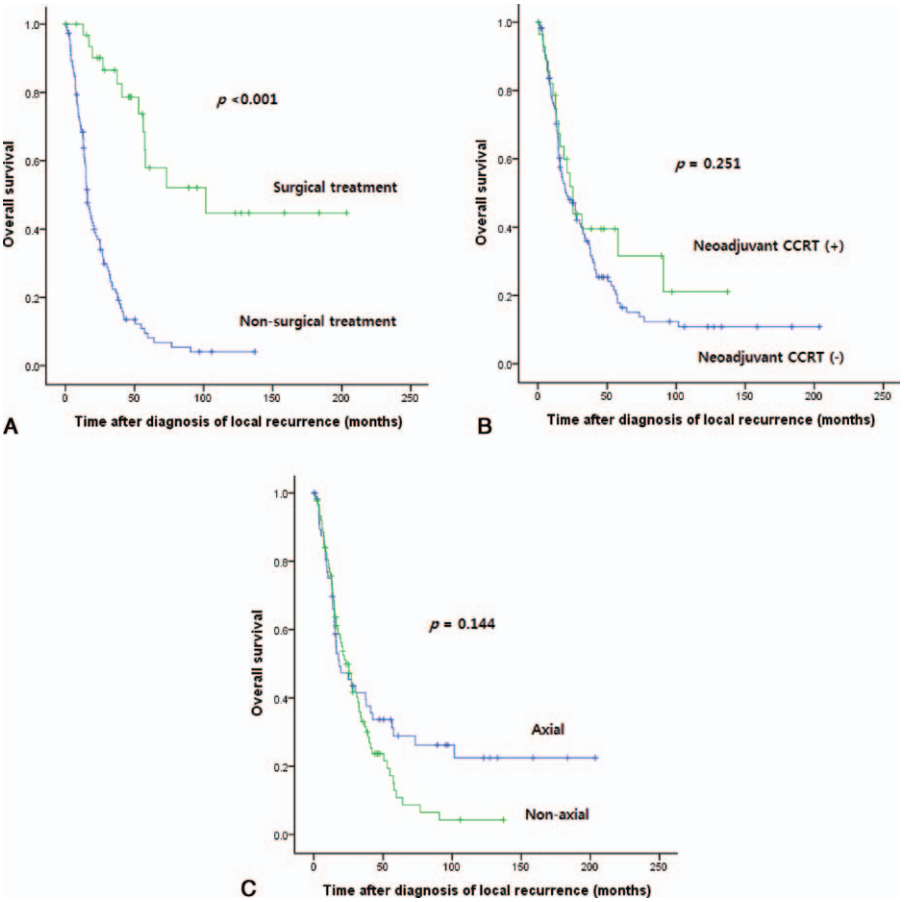


**Figure 2.** Overall survival rates after diagnosis of local recurrence: (A) according to surgical treatment; (B) according to neoadjuvant concurrent chemoradiotherapy; (C) according to the location of local recurrence.

tumor characteristics and other treatment options after recurrence.

The classification and subsites of local recurrences have been found to vary.[15,30–32] The most common site of local recurrence also remains controversial. Prior to the development of total mesorectal excision, the most common local types of recurrence tended to be central (perianastomotic and anterior). Lateral and posterior types (presacral), however, have become more common as combined treatments have come into use. A Dutch group analyzed local recurrence patterns using the same classification system as used in our analysis and found that presacral local recurrence was the most common subtype, especially in patients who underwent abdominoperineal resection.[15] They also found that preoperative radiotherapy reduced local recurrence, especially anastomotic recurrence. In our study, lateral recurrence was the most common, but less anastomotic recurrence was observed in patients with preoperative CCRT, which is consistent with previous findings. Furthermore, presacral recurrence was the second most common subtype (3.4%), following only lateral recurrence (4.6%) in patients who underwent nonsphincter-preserving surgery.

The survival benefit of surgical resection of locally recurrent rectal cancer has been clearly established by several studies.[33–36] Rahbari et al[9] reported that surgical resection of local recurrence can be carried out with acceptable morbidity and curative resection rates; moreover, R0 resection is a major prognostic factor that may enable long-term survival, even in patients with combined distant recurrence. In the present study, we found that surgery was also a prognostic factor for significantly improved overall survival in patients with rectal cancer, even after a diagnosis of local recurrence, regardless of R0 resection, possibly owing to the small number of patients.

In a recent study performed at our institution, a CRM $\leq$1 mm was an independent predictor of poor outcome in both the nonchemoradiotherapy and chemoradiotherapy groups.[11] In addition, a positive CRM was associated with a poor survival rate after treatment of local recurrence. Therefore, achieving a negative CRM appears to be very important in the initial primary rectal cancer surgery.

One of the limitations of this study is that R0 resection was not assessed in patients who underwent reoperation for locally recurrent rectal cancer. This study was also limited by its retrospective nature and its potential selection bias. Moreover, preoperative CCRT was performed according to preoperative clinical staging primarily based on radiologic imaging modalities, which may have resulted in over- or undertreatment. An additional limitation is that the effect of pelvic reirradiation could not be assessed, as only a small number of patients underwent radiotherapy for the treatment of locally recurrent rectal cancer. Recent studies have demonstrated the effects of combined treatment modalities with radical surgery. Bosman et al reported that reirradiation (with concomitant chemotherapy) had few side effects and also complemented radical resection of recurrent rectal cancer.[37] Despite these limitations, this study

also presents valuable data such as potential predictive factors for surgical reresection and prognosis evaluation after recurrence.

In conclusion, surgical resection of locally recurrent rectal cancer prolongs survival after diagnosis of recurrence, regardless of R0 resection. Thus, such resection should be considered as an initial treatment for locally recurrent rectal cancer. Predictive factors for surgery in patients with local recurrence were found to be less advanced tumor stage (below T3), axial recurrence, and isolated local recurrence. All patients with these factors can be candidates for active surgical management. Also, advanced pathologic tumor stage, positive CRM, and combined distant metastases were significant predictors of worse prognosis after diagnosis of recurrence. Thus, patients diagnosed with local recurrence during follow-up should be carefully examined for distant metastases before curative treatment options such as surgical reresection are considered.

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