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# The impact of preoperative chemoradiotherapy on anastomotic leakage in mid and low rectal cancer surgery using a propensity score matching analysis

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# The impact of preoperative chemoradiotherapy on anastomotic leakage in mid and low rectal cancer surgery using a propensity score matching analysis

Directed by Professor Seung Hyuk Baik

The Master's Thesis
submitted to the Department of Medicine
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

Sejin Lee

June 2020

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This certifies that the Master's Dissertation of Sejin Lee is approved.

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ABSTRACT

# The impact of preoperative chemoradiotherapy on anastomotic leakage in mid and low rectal cancer surgery using a propensity score matching analysis

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(Directed by Professor Seung Hyuk Baik)

**Background:** Preoperative chemoradiotherapy (PCRT) is the standard treatment for locally advanced rectal cancer because it can down-stage tumors and preserve the anal sphincter. However, the effect of PCRT on anastomotic leakage is controversial. We used propensity score matching to determine if preoperative CRT affects anastomotic leakage after mid- and low-rectal cancer surgery.

**Methods:** We retrospectively evaluated 1617 patients who underwent low anterior resection or ultra-low anterior resection for mid- and low-rectal cancer between June 2004 and May 2012 at two Yonsei University Health System hospitals. A propensity score based on age, sex, tumor location, initial T-stage, operative procedure, operative method, and stoma creation was calculated for 343 patients in each group. Anastomotic leakage was analyzed by leakage subtype, grade, and development time. Postoperative outcomes and risk factors

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for anastomotic leakage were assessed.

**Results:** The overall incidence of anastomotic leakage was 8.5%. The rate of anastomotic leakage was higher in the PCRT(+) group (11.1%) than in the PCRT(−) group (6.1% (P = 0.021). The incidences of free leakage were similar between the two groups, but contained leakage was more frequent in the PCRT(+) group (6.7% vs. 2.6%, P = 0.011). Previous abdominal operation, American Society of Anesthesiologists score, tumor location, and PCRT were significant risk factors for increased anastomotic leakage in univariate and multivariate analyses.

**Conclusions:** PCRT increased the risk of anastomotic leakage after mid- and low-rectal cancer surgery. Especially, leakage subtype analysis showed that PCRT did not affect free leakage but increased the risk of contained leakage.

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Key words: preoperative chemoradiotherapy, rectal cancer, anastomotic leakage

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(Directed by Professor Seung Hyuk Baik)

## I. INTRODUCTION

Anastomotic leakage is one of the most serious complications after rectal cancer surgery. The incidence of anastomotic leakage reportedly ranges from 1% to 19%.1,2 Anastomotic leakage has been associated with local recurrence3,4 as well as gastrointestinal function, and quality of life.5,6 Known risk factors of anastomotic leakage after rectal cancer surgery are male sex, smoking, alcohol abuse, malnutrition, lower tumor level, blood transfusion, and absence of protective stoma.7-10 It is not yet clear if preoperative chemoradiotherapy (PCRT) is a risk factor for anastomotic leakage after surgery for rectal cancer.

PCRT has become the standard treatment for locally advanced rectal cancer. As an aspect of oncological outcomes, the rate of local recurrence has been shown to be significantly reduced by PCRT in previous large-scale randomized controlled trials,11-13 although there was no benefit in long-term overall survival.14,15 PCRT also has improved functional outcomes by increasing the rate of sphincter preservation.16,17 Several studies have found that PCRT was a risk factor for anastomotic leakage.18-20 Pelvic radiation induces a local

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inflammatory response and fibrosis in the pelvic cavity, which could affect anastomotic leakage.21 However, a prospective study failed to demonstrate that preoperative radiotherapy increased the rate of anastomotic leakage.22

The conflicting findings on the effect of PCRT on anastomotic leakage are probably because of the arbitrary definition of anastomotic leakage and the difficulty in establishing an appropriate control group, even in the previous prospective randomized control study. Recently, our institution reported precise definitions of anastomotic leakage subtypes.23 The study aim was to evaluate the effect of PCRT on anastomotic leakage, as defined according to our criteria, by using propensity score matching analysis to eliminate selection bias for comparison with a well-matched control group.

## II. MATERIALS AND METHODS

### 1. Study population

We retrospectively reviewed patients diagnosed as having rectal cancer between June 2004 and May 2012 at two hospitals (Severance Hospital and Gangnam Severance Hospital) of the Yonsei University Health System, Seoul, South Korea. Of these, patients who underwent low anterior resection (LAR) and ultra-LAR for mid- and low-rectal cancer with or without PCRT were included. Patients who underwent abdominoperineal resection, Hartmann's operation, or trans-anal excision were excluded. Patients with stage IV disease, R1 or R2 resection, or missing data were also excluded.

### 2. Treatment

PCRT was performed for patients with mid- or low-rectal cancer that was clinical stage T3/T4 or had suspected nodal metastasis after a review of

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preoperative imaging studies. The patients received a total of 50.4 Gy of radiation therapy, including 45.0 Gy to the whole pelvis and 5.4 Gy to the gross tumor. For the chemotherapy of PCRT, 307 patients received 5-fluorouracil and leucovorin, 81 patients received oral S-1 and irrinotecan, 44 patients received oral capecitabine, 21 patients received oral doxifluridine, and five patients received FOLFOX chemotherapy.

Surgery was performed approximately 6 to 8 weeks after completion of PCRT. Nine surgeons, including four with >10 years of experience, performed all laparotomy, laparoscopic, or robotic operative procedures. Total mesorectal excision was performed before formation of the anastomosis, and the double-stapling method for anastomosis in LAR or hand-sewn colo-anal technique in ultra-LAR was applied. A protective loop stoma was formed at the surgeon's discretion during the operation if there were risk factors of anastomotic leakage.

### 3. Definition of Anastomotic leakage

According to the proposal of the International Study Group of Rectal Cancer, the definition of anastomotic leakage is a defect of the anastomotic site, which leads to a communication between the intraluminal and extra-luminal spaces.24 Recently, we reported classification of anastomotic leakages as free leakages and contained leakages. Free leakage is defined as a major defect of the anastomotic site that results in free perforation of the rectal wall with generalized peritonitis due to diffuse contamination of the abdomen by the bowel contents. Contained leakage is defined as a minor defect of the anastomotic site leading to limited contamination of the pelvic cavity with localized peritonitis, including rectovaginal fistula, rectovesical fistula, and perirectal abscess.23 We retrospectively reviewed all electronic medical charts, including imaging findings, and classified subtypes of anastomotic leakage.

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### 4. Definition of analyzed parameters

"Hospital days" was defined as the period from the day of surgery to discharge. Pathological stage was evaluated according to the 7th edition of the American Joint Committee on Cancer staging system.

The grades of anastomotic leakage severity were as follows: Grade A, anastomotic leakage without active treatment; Grade B, anastomotic leakage with active treatment but requiring no re-operation; and Grade C, anastomotic leakage requiring re-operation.24 All anastomotic leakage grades were included in this study.

We classified early and late anastomotic leakage according to whether it occurred 30 days before or after the operation. The development time of anastomotic leakage was defined as the duration from the day of surgery to the day of anastomotic leakage. We did not limit the development time of anastomotic leakage.

### 5. Propensity score matching

Propensity score matching analysis was used to remove confounding factors for the presence of anastomotic leakage. The propensity score for an individual was calculated on the basis of age, sex, tumor location, preoperative T-stage, operative procedure and method, and protective ileostomy. Patients in the PCRT (+) and PCRT (−) groups were matched 1:1 by using the nearest propensity score on the logit scale. After propensity score matching, patient demographics, surgical data, pathological data, and follow-up status were re-evaluated.

### 6. Statistical analyses

All categorical variables were analyzed by using the chi-squared test and

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Fisher's exact test, and continuous variables were analyzed by using Student's t-test. Univariate and multivariate analysis using multinomial or binomial logistic regression models were performed to identify anastomotic leakage risk factors. Multivariate analysis was evaluated for risk factors with a P value of <0.05 in the univariate analysis. The odds ratio and 95% confidence intervals of multivariate analysis were schematized by a forest plot. Statistical analyses were performed by using the SPSS program (IBM SPSS Statistics for Windows, Version 20.0.; IBM Corp., Armonk, NY). A value of $P < 0.05$ was considered to be indicative of statistical significance.

.

## III. RESULTS

A total of 1617 consecutive patients were included in this study. Of these patients, 468 were treated with PCRT and 1149 patients were treated only with rectal cancer surgery. A propensity score was calculated for each patient with identified variables (age, sex, tumor location, initial T-stage, operative procedure and method, and protective ileostomy) that were known risk factors for anastomotic leakage after rectal surgery and not equally distributed between PCRT(+) (n = 343) and PCRT(−) (n = 343) groups.

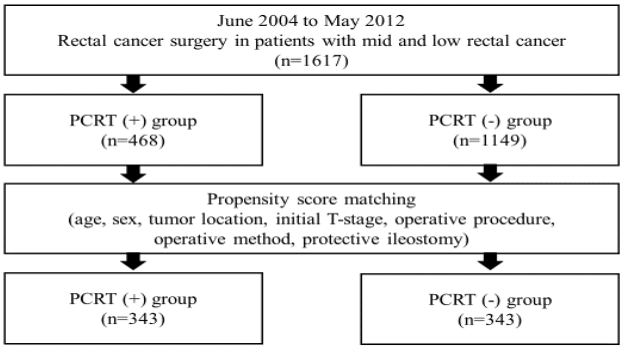


**Figure 1.** Flow chart of patient selection.

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### 1. Clinicopathological characteristics (Table 1)

The clinicopathological characteristics of the patients are shown in Table 1. Of the factors included in the propensity score matching analysis, age, sex, tumor location, preoperative T-stage, operative procedure, protective ileostomy, operation time, estimated blood loss, TNM stage, tumor size, and retrieved lymph nodes significantly differed between the PCRT(+) and PCRT(−) groups. After adjustment of background factors by propensity score matching, most clinicopathological factors were no longer significantly different between the two groups. However, body mass index, operation time, and tumor size remained significantly different between both groups.

### 2. Characteristics of anastomotic leakage (Table 2)

From the entire cohort, the overall incidence of anastomotic leakage was 8.5%. The rate of anastomotic leakage was higher in the PCRT(+) group than in the PCRT(−) group: 11.1% vs. 7.4% (before matching, $P = 0.015$) and 11.1% vs. 6.1% (after matching, $P = 0.021$), respectively. The incidences of free leakage were similar between the two groups ($P = 0.556$). However, contained leakage developed more frequently in the PCRT(+) group than in the PCRT(−) group: 7.7% vs. 3.6% (before matching, $P < 0.001$) and 6.7% vs. 2.6% (after matching, $P = 0.011$), respectively. There was no significant difference in leakage grade between the two groups. Before matching, the incidence of late anastomotic leakage was higher in the PCRT(+) group than in the PCRT(−) group (23.1% vs. 10.6%, respectively; $P = 0.049$), however there was no statistical difference after matching (23.7% vs. 4.8%, respectively; $P = 0.080$). The mean development time of anastomotic leakage was significantly longer in the PCRT(+) group than in the PCRT(−) group: 13.0 vs. 30.7 days (before matching, $P < 0.001$) and 9.4 vs. 33.5 days (after matching, $P = 0.015$), respectively.

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### 3. Risk factors of anastomotic leakage (Table 3)

Table 3 shows the results of the univariate and multivariate analyses of the risk factors for anastomotic leakage in the propensity score matching population. On univariate and multivariate analysis, previous abdominal operation (OR = 2.64, P = 0.006), American Society of Anesthesiologists score (OR = 0.53, P = 0.030), tumor location (OR = 2.15, P = 0.015), and PCRT (OR = 1.95, P = 0.020) were significantly associated with the incidence of anastomotic leakage.

### 4. Effect of chemotherapy regimen and time of surgery from radiotherapy on anastomotic leakage (Table 4)

We analyzed the effect of chemotherapy regimen on anastomotic leakage. Of the total 468 patients who underwent PCRT, 10 patients without information on chemotherapy regimen and five patients who received FOLFOX chemotherapy were excluded. Chemotherapy regimen was not statistically different between the patients with anastomotic leakage and those without it. (P=0.369). Moreover, We analyzed the effect of time of surgery from radiotherapy on anastomotic leakage in PCRT(+) patients, except five patients who had no record for time of radiotherapy. There was no effect for time of surgery from radiotherapy on anastomotic leakage. (P=0.738)

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**Table 1. Clinicopathological characteristics**

| | Before matching | | | After matching | | |
|---|---|---|---|---|---|---|
| | **PCRT(-) n=1149** | **PCRT(+) n=468** | **p-value** | **PCRT(-) n=343** | **PCRT(+) n=343** | **p-value** |
| **Age** | | | <0.001 | | | 1.000 |
| <60 year | 482(41.9) | 255(54.5) | | 164(47.8) | 164(47.8) | |
| ≥60 year | 667(58.1) | 213(45.5) | | 179(52.2) | 179(52.2) | |
| **Sex** | | | 0.015 | | | 1.000 |
| Male | 702(61.1) | 316(67.5) | | 239(69.7) | 239(69.7) | |
| Female | 447(38.9) | 152(32.5) | | 108(30.3) | 108(30.3) | |
| **BMI** | | | 0.162 | | | 0.041 |
| <25 kg/$m^2$ | 825(71.8) | 352(75.2) | | 235(68.5) | 259(75.5) | |
| ≥25 kg/$m^2$ | 324(28.2) | 116(24.8) | | 108(31.5) | 84(24.5) | |
| **Previous abdominal operation** | | | 0.789 | | | 0.906 |
| No | 996(86.7) | 408(87.2) | | 302(88.0) | 303(88.3) | |
| Yes | 153(13.3) | 60(12.8) | | 41(12.0) | 40(11.7) | |
| **ASA score** | | | 0.256 | | | 0.654 |
| 1 | 510(44.4) | 226(48.3) | | 152(44.3) | 162(47.2) | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| 2 | 606(52.7) | 226(48.3) | | 178(51.9) | 171(49.9) | |
| 3 | 33(2.9) | 16(3.4) | | 13(3.8) | 10(2.9) | |
| **Preoperative albumin** | | | 0.819 | | | 0.524 |
| <3.3 g/dL | 19(1.7) | 7(1.5) | | 4(1.2) | 6(1.7) | |
| ≥3.3 g/dL | 1130(98.3) | 461(98.5) | | 339(98.8) | 337(98.3) | |
| **Tumor location** | | | <0.001 | | | 1.000 |
| Mid† | 912(79.4) | 231(49.4) | | 206(60.1) | 206(60.1) | |
| Low†† | 237(20.6) | 237(50.6) | | 137(39.9) | 137(39.9) | |
| **Preoperative T-stage** | | | 0.045 | | | 1.000 |
| Tis-T2 | 536(46.6) | 244(52.1) | | 176(51.3) | 176(51.3) | |
| T3-T4 | 613(53.4) | 224(47.9) | | 167(48.7) | 167(48.7) | |
| **Operative procedure** | | | <0.001 | | | 1.000 |
| LAR | 997(86.8) | 280(59.8) | | 240(70.0) | 240(70.0) | |
| Ultra-LAR | 152(13.2) | 188(40.2) | | 103(30.0) | 103(30.0) | |
| **Operative method** | | | 0.466 | | | 1.000 |
| Open | 511(44.5) | 194(41.5) | | 131(38.2) | 131(38.2) | |
| Laparoscopy | 336(29.2) | 139(29.7) | | 117(34.1) | 117(34.1) | |
| Robot | 302(26.3) | 135(28.8) | | 95(27.7) | 95(27.7) | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| **Protective ileostomy** | | | <0.001 | | | 1.000 |
| No | 868(75.5) | 227(48.5) | | 184(53.6) | 184(53.6) | |
| Yes | 281(24.5) | 241(51.5) | | 159(46.4) | 159(46.4) | |
| **Operation time (min)*** | 251.7(90.8) | 313.4(101.0) | <0.001 | 272.1(92.9) | 305.5(95.6) | <0.001 |
| **EBL (ml)*** | 201.4(341.8) | 320.3(397.4) | <0.001 | 299.1(648.3) | 2516(246.0) | 0.174 |
| **Conversion** | | | 0.178 | | | 0.485 |
| No | 1131(98.4) | 456(97.4) | | 335(97.7) | 332(96.8) | |
| Yes | 18(1.6) | 12(2.6) | | 8(2.3) | 11(3.2) | |
| **Hospital days (day)*** | 13.6(8.8) | 13.7(11.3) | 0.135 | 23.5(14.8) | 16.2(11.3) | 0.055 |
| **TNM stage** | | | 0.001 | | | 0.177 |
| Stage I | 438(38.1) | 214(45.7) | | 146(42.6) | 152(44.3) | |
| Stage II | 290(25.2) | 126(26.9) | | 78(22.7) | 93(27.1) | |
| Stage III | 421(36.6) | 128(27.4) | | 119(34.7) | 98(28.6) | |
| **Tumor size (cm)*** | 4.0(2.0) | 2.2(1.6) | <0.001 | 4.0(2.6) | 2.4(1.5) | 0.034 |
| **Retrieved lymph nodes*** | 18.2(9.9) | 14.3(8.5) | <0.001 | 19.9(11.1) | 16.6(8.3) | 0.157 |

Values in parentheses are percentages; *Values are mean (SD); †Mid: Anal verge 5.1-10cm; ††Low: Anal verge<5cm

Abbreviation: BMI, body mass index; ASA, American Society of Anesthesiologists; LAR, low anterior resection; EBL, estimated blood loss

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**Table 2. Characteristics of anastomotic leakage**

| . | Before matching | | | After matching | | |
|---|---|---|---|---|---|---|
| | **PCRT(-) n=1149** | **PCRT(+) n=468** | **p-value** | **PCRT(-) n=343** | **PCRT(+) n=343** | **p-value** |
| **Anastomotic leakage** | | | 0.015 | | | 0.021 |
| No | 1064(92.6) | 416(88.9) | | 322(93.9) | 305(88.9) | |
| Yes | 85(7.4) | 52(11.1) | | 21(6.1) | 38(11.1) | |
| Free leakage | 44(3.8) | 16(3.4) | 0.692 | 12(3.5) | 15(4.4) | 0.556 |
| Contained leakage | 41(3.6) | 36(7.7) | <0.001 | 9(2.6) | 23(6.7) | 0.011 |
| **Leakage grade** | | | 0.086 | | | 0.893 |
| Grade A | 10(11.8) | 4(7.7) | | 1(4.8) | 4(10.5) | |
| Grade B | 4(4.7) | 8(15.4) | | 3(14.3) | 5(13.2) | |
| Grade C | 71(83.5) | 40(76.9) | | 17(81.0) | 29(76.3) | |
| **Leakage duration** | | | 0.049 | | | 0.080 |
| Early(≤30days) | 76(89.4) | 40(76.9) | | 20(95.2) | 29(76.3) | |
| Late(>30days) | 9(10.6) | 12(23.1) | | 1(4.8) | 9(23.7) | |
| **Developing time of anastomotic leakage (days)*** | 13.0(15.3) | 30.7(60.8) | <0.001 | 9.4(8.4) | 33.5(69.7) | 0.015 |

Values in parentheses are percentages; *Values are mean (SD)

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**Table 3. Univariate and multivariate analysis for the risk factors of anastomotic leakage in the propensity score matching population**

| | No leakage (n=627) | Leakage (n=59) | Univariate analysis OR ratio (95% CI) | Univariate analysis p-value | Multivariate analysis OR ratio (95% CI) | Multivariate analysis p-value |
|---|---|---|---|---|---|---|
| **Age** | | | | | | |
| <60 year | 293(46.7) | 35(59.3) | 0.60 (0.35-1.04) | 0.066 | | |
| ≥60 year | 334(53.3) | 24(40.7)) | | | | |
| **Sex** | | | | | | |
| Male | 435(69.4) | 43(72.9) | 1.19 (0.65-2.16) | 0.576 | | |
| Female | 192(30.6) | 16(27.1) | | | | |
| **BMI** | | | | | | |
| <25 kg/m$^2$ | 447(71.3) | 47(79.7) | 0.63 (0.33-1.22) | 0.174 | | |
| ≥25 kg/m$^2$ | 180(28.7) | 12(20.3) | | | | |
| **Previous abdominal operation** | | | | | | |
| No | 559(89.2) | 46(78.0) | 2.32 (1.20-4.52) | 0.013 | 2.64 (1.33-5.25) | 0.006 |
| Yes | 68(10.8) | 13(22.0) | | | | |
| **ASA score** | | | | | | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| 1 | 280(44.7) | 34(57.6) | 0.58 (0.33-1.01) | 0.050 | 0.53 (0.30-0.94) | 0.030 |
| 2 | 326(52.0) | 23(39.0) | | | | |
| 3 | 21(3.3) | 2(3.4) | 0.78 (0.18-3.49) | 0.75 | 1.03 (0.23-4.69) | 0.969 |
| **Preoperative albumin** | | | | | | |
| <3.3 g/dL | 8(1.3) | 2(3.4) | 2.72 (0.56-13.1) | 0.213 | | |
| ≥3.3 g/dL | 619(98.7) | 57(96.6) | | | | |
| **Tumor location** | | | | | | |
| Mid† | 368(58.7) | 44(74.6) | 2.06 (1.13-3.79) | 0.020 | 2.15 (1.16-3.99) | 0.015 |
| Low†† | 259(41.3) | 15(25.4) | | | | |
| **Preoperative T-stage** | | | | | | |
| Tis-T2 | 321(51.2) | 31(52.5) | 0.95 (0.56-1.62) | 0.843 | | |
| T3-T4 | 306(48.8) | 28(47.5) | | | | |
| **Operative procedure** | | | | | | |
| LAR | 434(69.2) | 46(78.0) | 1.57 (0.83-2.98) | 0.164 | | |
| Ultra-LAR | 193(30.8) | 13(22.0) | | | | |
| **Operative method** | | | | | | |
| Open | 248(39.6) | 14(23.7) | 2.21 (1.13-4.35) | 0.210 | | |
| Laparoscopy | 208(33.2) | 26(44.1) | 1.97 | 0.640 | | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| Robot | 171(27.3) | 19(32.2) | (0.96-4.03) | | | |
| **Protective ileostomy** | | | | | | |
| No | 331(52.8) | 37(62.7) | 0.67 (0.38-1.15) | 0.146 | | |
| Yes | 296(47.2) | 22(37.3) | | | | |
| **PCRT** | | | | | | |
| No | 322(51.4) | 21(35.6) | 1.91 (1.10-3.33) | 0.022 | 1.95 (1.11-3.43) | 0.020 |
| Yes | 305(48.6) | 38(64.4) | | | | |
| **TNM stage** | | | | | | |
| Stage I | 274(43.7) | 24(40.7) | 0.82 (0.44-1.51) | 0.520 | | |
| Stage II | 157(25.0) | 14(23.7) | | | | |
| Stage III | 196(31.3) | 21(35.6) | 0.83 (0.41-1.69) | 0.611 | | |

Values in parentheses are percentages; †Mid: Anal verge 5.1-10cm; ††Low: Anal verge<5cm

Abbreviation: BMI, body mass index; ASA, American Society of Anesthesiologists; LAR, low anterior resection

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**Table 4. Effect of chemotherapy regimen and time of surgery from radiotherapy on anastomotic leakage**

| | Anastomotic leakage (-) | Anastomotic leakage (+) | p-value |
|---|---|---|---|
| **Chemotherapy regimen** | | | 0.369 |
| 5FU+LV (n=307) | 268 (66.7) | 39 (76.5) | |
| Xeloda (n=44) | 42 (10.4) | 2 (3.9) | |
| TS-1+Irrinotecan (n=81) | 72 (17.9) | 9 (17.6) | |
| Doxifluridine (n=21) | 20 (5.0) | 1 (2.0) | |
| **Time of surgery from radiotherapy** | | | 0.738 |
| ≤8weeks (n=345) | 305 (74.2) | 40 (76.9) | |
| >8weeks (n=118) | 106 (25.8) | 12 (23.1) | |

Values in parentheses are percentages

Abbreviation: FU, fluorouracil; LV, leucovorin; TS, Titanium silicate

## IV. DISCUSSION

Our results showed that PCRT increased anastomotic leakage, especially contained leakage, after rectal surgery in patients with mid- and low-rectal cancer when we analyzed not only the entire study cohort but also the propensity score-matched cohort. The development time of anastomotic leakage was longer in the PCRT(+) group than in the PCRT(−) group. Both the univariate and multivariate analyses of the propensity score matching population identified PCRT as one of the risk factors for anastomotic leakage.

A prospective phase III randomized controlled trial from the Dutch Colorectal Cancer Group showed that preoperative radiotherapy did not increase the rate of anastomotic leakage after LAR, including total mesorectal excision [RT(+): 11% vs. RT(−): 12%].22 A German prospective phase III trial also showed that there was no significant difference between the preoperative and postoperative treatment groups (preoperative: 11% vs. postoperative: 12%; P = 0.77).13

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Although these were randomized controlled trials, their designs still made it difficult to compare only the effect of preoperative CRT on anastomotic leakage. In the Dutch trial, the researchers recommended a diversion in case there was any doubt about the quality of anastomosis, and their RT(+) group more often received a protective stoma than did the RT(−) group [RT(+): 60% vs. RT(−): 53%; p = 0.05], which reduced anastomotic leakage.22 However, a protective stoma might mask the effect of PCRT on anastomotic leakage. In the present study, we applied propensity score matching analysis with identified variables (age, sex, tumor location, initial T-stage, operative procedure and method, and protective ileostomy) that were known risk factors for anastomotic leakage. We tried to demonstrate the independent effect of PCRT on anastomotic leakage.

Previously, Chang et al. reported a retrospective study that used a propensity score matching analysis to assess the effect of PCRT on anastomotic leakage after rectal cancer resection.25 There was no difference in the incidence of anastomotic leakage between patients with or without PCRT either before propensity score matching [PCRT(+) 7.5% vs. PCRT(−) 5.9%; p = 0.293] or after matching [PCRT(+) 7.5% vs. PCRT(−) 8.1%; p = 0.781]. They included upper rectal cancer (43%), which has a relatively low rate of anastomotic leakage (OR 2.2; 95% CI 1.29–3.76; p = 0.004) and grade C anastomotic leakage, which required a relaparotomy. The definition of anastomotic leakage and location of tumor could have potentially influenced the results. In our study, we included only patients with mid- and low-rectal cancer, which has a higher rate of anastomotic leakage than that of upper rectal cancer. In addition, we analyzed not only grade C anastomotic leakage but also grades A and B anastomotic leakage. Our results also showed that the rate of free leakage, which was treated with a relaparotomy, was not different between the two groups [PCRT(+) 4.4% vs. PCRT(−) 3.5%]. However, the rate of contained leakage, which included grades A, B, and C anastomotic leakage, was significantly higher in the PCRT(+) group (6.7%) than in the PCRT(−) group

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(2.6%). This finding implies that the possibility of contained leakage should be given greater attention in patients who receive PCRT than given in those who do not.

Qiyuan et al. reported results of a randomized controlled trial that supported the risk of preoperative radiotherapy for anastomotic leakage.26 In this study, patients were assigned to preoperative radiotherapy and 5-fluorouracil infusion, preoperative radiotherapy and FOLOX, or preoperative FOLOX without radiation. The rate of anastomotic leakage was significantly higher in the patients with radiotherapy than in the patients without radiotherapy (20.2%, 23.6%, 8.5%, respectively, $p = 0.007$ all). The long-term effects of radiotherapy on the wound healing process include necrosis, atrophy, fibrosis, and vascular damage and can be prolonged >3 months after the end of treatment.27 In our results, the mean development time of anastomotic leakage was 33.5 days after surgery, which was 3 months after the end of radiotherapy. We assumed that the long-term effects of radiotherapy disturbed healing of the anastomosis and could cause minor defects at the anastomosis site.

Our study had some limitations that should be considered when interpreting the results, including the retrospective study design and the use of a protective ileostomy created when deemed necessary by the surgeon. These limitations may have introduced patient selection bias and results interpretation bias.

## V. CONCLUSION

PCRT can increase the frequency of anastomotic leakage, especially contained leakage, in patients with mid- and low-rectal cancer. The potential for anastomotic leakage in patients who receive PCRT should be given increased attention after discharge.

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**ABSTRACT(IN KOREAN)**

# 성향 점수 매칭법을 이용한 중·하부 직장암 수술에서의 문합부 누출에 대한 수술 전 항암 방사선 치료의 영향

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이세진

**연구의 배경**: 수술 전 화학 방사선 치료는 종양의 병기를 낮춰주고 수술 시 항문 괄약근을 보존의 가능성을 높여주며 수술 후 국소 재발을 줄여주기 때문에 국소 진행성 직장암의 표준 치료로 이용되고 있다. 하지만 아직까지 수술 전 화학 방사선 치료가 문합부 누출에 영향을 미치는 지에 대한 여부는 논란 중에 있다. 본 연구에서는 성향 점수 매칭법을 이용하여 수술 전 항암 방사선 치료가 직장암 수술 후 발생할 수 있는 중요한 합병증인 문합부 누출에 영향을 주는지 확인해 보고자 하였다.

**재료 및 방법**: 2004년 6월부터 2012년 5월까지 신촌 및 강남 세브란스 병원에서 저위 전방 절제술을 시행 받은 중·하부 직장암 환자 (1617

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명)을 후향적으로 평가 하였다. 문합부 누출의 위험 인자로 알려져 있는 연령, 성별, 종양의 위치, 초기 T-stage, 수술의 종류, 수술 방법 및 장루 형성 여부를 변수로 하여 성향 점수 매칭법으로 선정된 수술 전 화학 방사선 치료를 받은 343명의 환자와 받지 않았던 343명의 환자를 비교 분석 하였다. 각각의 군에서 발생한 문합부 누출을 종류, 등급, 발생 시간에 따라 분석하였으며 문합부 누출의 위험 인자에 대해서도 분석 하였다.

**결과**: 문합부 누출의 전체 발생률은 8.5% 였으며 수술 전 화학 방사선 치료를 받은 환자 (11.1%) 에서 받지 않은 환자에 비해 (6.1%) 문합부 누출이 더 많이 발생하였다. (P=0.021) 문합부 누출의 종류 중 free leakage의 발생은 비슷하였지만 contained leakage 가 수술 전 화학 방사선 치료를 받은 환자에게서 많이 발생하였다. (6.7 vs. 2.6%, P=0.011). 또한 다변량 로지스틱 회귀분석 결과 이전 복부 수술 과거력, ASA, 종양의 위치 및 수술 전 항암 방사선 치료 여부가 문합부 누출의 위험 인자로 평가 되었다.

**결론**: 본 연구 결과 수술 전 항암 방사선 치료가 문합부 누출, 특히 contained leakage 를 증가 시킬 수 있다고 여겨진다.

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핵심되는 말 : 수술 전 항암 방사선 치료, 직장암, 문합부 누출