Patterns of recurrence in patients with curative resected rectal cancer according to different chemoradiotherapy strategies: Does preoperative chemoradiotherapy lower the risk of peritoneal recurrence?

HYUNGWOO CHO[1*], JEONG EUN KIM[1*], SUN YOUNG KIM[1], KYU-PYO KIM[1], TAE WON KIM[1], JIN-HONG PARK[2], JONG HOON KIM[2], SEOK-BYUNG LIM[3], CHANG SIK YU[3], JIN CHEON KIM[3] and YONG SANG HONG[1]

Departments of [1]Oncology, [2]Radiation Oncology and [3]Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul 05505, Republic of Korea

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Abstract. The present study aimed to compare the pattern of distant recurrence between patients with non-metastatic rectal cancer treated with pre-operative (OP) and those treated with post-operative (post-OP) chemoradiotherapy (CRT). A total of 631 patients with newly diagnosed non-metastatic rectal cancer who had received pre-OP or post-OP CRT with curative intent surgery between August 2008 and April 2015 were identified. Inverse probability of treatment weighting (IPTW) was performed to account for baseline differences between the two arms. Overall, 449 and 182 patients were treated with pre-OP and post-OP CRT, respectively. Sex, tumor location, clinical tumor stage, CRT regimen and adjuvant chemotherapy regimen were significantly different between the two arms. The median follow-up duration was 55.4 months (range, 53.7-57.1). The 5-year distant recurrence-free survival (RFS) rates and 5-year overall survival (OS) rates were not significantly different between the pre-OP and post-OP CRT arms (RFS, 67.5 vs. 71.6%, P=0.595 and OS, 81.9 vs. 77.0%, P=0.449), and no difference was observed in the distant recurrence patterns. Following IPTW, there was still no difference in distant RFS (pre-OP vs. post-OP CRT; hazard ratio (HR)=0.62; P=0.911), but pre-OP CRT was significantly associated with lower peritoneal recurrence (pre-OP vs. post-OP CRT; HR, 0.13; P=0.032). In addition, there was no significant difference in OS between the two arms (pre-OP vs. post-OP CRT; HR, 0.85; P=0.665). In conclusion, although distant RFS was not significantly different between the two arms, pre-OP CRT was significantly associated with a lower risk of peritoneal recurrence than post-OP CRT in patients non-metastatic rectal cancer.

Correspondence to: Dr Yong Sang Hong, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea
E-mail: yshong@amc.seoul.kr

[*]Contributed equally

Abbreviations: CI, confidence interval; CRT, chemoradiotherapy; CT, computed tomography; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; IPTW, inverse probability of treatment weighting; OS, overall survival; post-OP, post-operative; pre-OP, pre-operative; PS, propensity score; RFS, recurrence-free survival; TME, total mesorectal excision

Key words: rectal neoplasms, pre-operative chemoradiotherapy, post-operative chemoradiotherapy, recurrence pattern, peritoneal recurrence

Introduction

Colorectal cancer is the third most common type of cancer and was the second leading cause of cancer-associated mortality worldwide in 2015, with rectal cancer accounting for ~40% of these mortalities (the number of deaths from colon cancer was 551,269 and the number of deaths from rectal cancer was 310,394) (1). While the treatment approaches for metastatic colon and rectal cancer are similar, treatment approaches for resectable cancer vary according to the affected organ.

The adoption of multimodal therapy that combines chemoradiotherapy (CRT) and total mesorectal excision (TME) has led to more efficient local disease control and improved survival for patients with non-metastatic rectal cancer (2-5). Previous studies have suggested that pre-operative (pre-OP) CRT has advantages over post-operative (post-OP) CRT in terms of treatment compliance, safety, and local control (6,7). Accordingly, the current standard course of treatment involves pre-OP CRT followed by TME, particularly in cases of locally advanced disease. However, pre-OP CRT has not led to improvements in rates of distant recurrence and overall survival (7,8). Furthermore, patients with early-stage tumors that do not require radiotherapy may be overtreated with pre-OP CRT (8). In addition, potential disadvantages of pre-OP CRT include the development of distant metastasis during the pre-OP CRT period and the resting period until surgery, thereby missing the opportunity for curative resection (9). For these reasons, a subpopulation of rectal cancer patients continues to receive upfront surgery followed by post-OP CRT (10).

Several preclinical studies have suggested that radiotherapy may induce changes in the tumor microenvironment, including dysfunction of the endothelial cells of the tumor vasculature and epithelial-to-mesenchymal transition in tumor cells, which may promote tumor invasion and spread (11,12). Furthermore, it is well-known that histological subtype influences metastatic patterns; therefore, radiation-induced biological changes within the primary tumor prior to resection may also affect the distribution of metastatic spread (13). Although the incidence of distant recurrence is not different between pre-OP and post-OP CRT, the pattern of distant relapse may be affected by the timing of CRT. A recent study suggested that pre-OP CRT in patients with rectal cancer may affect the pattern of recurrence (14). However, to date, to the best of our knowledge no studies have compared the pattern of distant relapse between patients treated with pre-OP and those treated with post-OP CRT. Understanding the patterns of distant recurrence following initial treatment may aid clinicians in improving the monitoring of patients with resectable rectal cancer.

Therefore, the present study analyzed and compared patterns of distant recurrence in patients with non-metastatic rectal cancer according to treatment with pre-OP or post-OP CRT.

Materials and methods

Patients. The present study identified and retrospectively reviewed the medical records of patients with histologically-confirmed non-metastatic rectal cancer who received pre-OP or post-OP CRT with curative intent surgery at Asan Medical Center (Seoul, South Korea) between August 2008 and April 2015. Patients were excluded if they had metastatic disease prior to or at the time of surgery. The following patient data were extracted from the medical records for analysis: Age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS) (15), tumor pathology (16), clinical stage (17), tumor location relative to the anal verge, neoadjuvant CRT regimen (18), adjuvant chemotherapy regimen (19), and initial site(s) of recurrence. The protocols of the present study were approved by the Institutional Review Board at Asan Medical Center (AMC IRB 2008-0256), which waived the requirement for informed consent.

Treatment and response assessment. Pre-OP or post-OP CRT was selected for patients following consultation by a multidisciplinary team that included a medical oncologist, surgeon, and radiation oncologist. For patients who received pre-OP CRT, surgery was performed within 4-6 weeks after completion of CRT. With the exception of laparoscopic trans-anal excision surgery in a subpopulation of patients, all surgeries were performed using TME (4). Adjuvant chemotherapy was initiated between 3 and 8 weeks after surgery or immediately after completion of post-OP CRT. Following the completion of adjuvant chemotherapy, chest radiography and carcinoembryonic antigen measurements were performed every 3 months for the first 2 years and every 6 months thereafter. Computed tomography (CT) scans were performed every 6 months for the abdominopelvic region and annually for the chest region. Colonoscopic assessments were performed at 1, 3 and 5 years after surgery.

Statistical analyses. All time-to-event endpoints were calculated from the start date of CRT for patients who underwent pre-OP CRT and from the date of surgery for patients who underwent post-OP CRT. Local recurrence was defined as clinically-confirmed relapse within the perineum or pelvis. Distant recurrence was defined as relapse in sites other than the perineum or pelvis. Disease-free survival (DFS) was calculated from the start date of CRT (pre-OP CRT arm) or surgery (post-OP CRT arm) until tumor relapse. Local and distant recurrence-free survival (RFS) rates were calculated from the start date of CRT (pre-OP CRT arm) or surgery (post-OP CRT arm) until local or distant recurrence, respectively. Overall survival (OS) was calculated as the time from the start date of CRT (pre-OP CRT arm) or surgery (post-OP CRT arm) until mortality from any cause. The Kaplan-Meier method was used to calculate DFS, local/distant RFS, and OS, and comparisons were analyzed using the log-rank test.

Baseline characteristics and recurrence patterns were compared between the arms using the Student's t-test for continuous variables and the Fisher's exact test or Pearson's Chi-square test for categorical variables, as appropriate. To reduce the impact of treatment selection bias and potential confounding, adjustment for significant differences in baseline characteristics of patients was performed using weighted Cox proportional hazards regression models using inverse probability of treatment weighting (IPTW) and robust standard errors (20,21). The propensity score (PS) to receive pre-OP vs. post-OP CRT was estimated using a multivariable logistic regression model based on age, ECOG PS, sex, clinical stage, tumor location from the anal verge, tumor histology, CRT regimen, and adjuvant chemotherapy regimen. The PS was estimated without accounting for outcomes. Tumor histology, CRT regimen, and adjuvant chemotherapy regimen were included in the IPTW analysis since it has been reported that variables associated with outcomes of interest should be included even if they are unrelated to treatment selection to further reduce bias in the PS model (20,22). IPTW for patients treated with pre-OP CRT were the inverse of PS, and IPTW for patients treated with post-OP CRT were the inverse of 1-PS. The treatment effect of pre-OP vs. post-OP CRT was estimated using weighted Cox proportional hazards regression models with IPTW and robust standard errors.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 631 patients with newly diagnosed non-metastatic rectal cancer who received pre-OP CRT (n=449) or post-OP CRT (n=182) with curative intent surgery were identified between August 2008 and April 2015. The median total irradiation dose was 50 Gy (range, 6-55 Gy).

Table I. Baseline characteristics of patients who received pre-OP CRT vs. post-OP CRT.

	Before IPTW			After IPTW		
Characteristic	Pre-OP CRT n (%) (n=449)	Post-OP CRT n (%) (n=182)	P-value[a]	Pre-OP CRT n (%) (n=634)	Post-OP CRT n (%) (n=520)	P-value[b]
Mean age, years ± SD	57.6±11.1	58.7±10.1	0.24	57.6±12.9	60.0±18.5	0.22
Sex			0.006			0.38
Female	143 (31.8)	79 (43.4)		228 (35.9)	223 (42.9)	
Male	306 (68.2)	103 (56.6)		406 (64.1)	297 (57.1)	
ECOG-PS			0.20			0.64
0-1	448 (99.8)	180 (98.9)		632 (99.6)	517 (99.4)	
2	1 (0.2)	2 (1.1)		2 (0.4)	3 (0.6)	
Location from AV			<0.001			0.75
0-4 cm	209 (46.5)	19 (10.4)		232 (36.5)	165 (31.8)	
>4 cm, ≤8 cm	207 (46.1)	109 (59.9)		310 (48.9)	263 (50.5)	
>8 cm	33 (7.3)	54 (29.7)		92 (14.6)	92 (17.8)	
Clinical tumor stage			<0.001			0.43
0-2	27 (6.0)	32 (17.6)		49 (7.7)	52 (10.1)	
3-4	422 (94.0)	150 (82.4)		585 (92.3)	468 (89.9)	
Clinical node stage			0.26			0.82
-	52 (11.6)	27 (14.8)		68 (10.8)	52 (10.1)	
+	397 (88.4)	155 (85.2)		566 (89.2)	468 (89.9)	
Clinical TNM stage			0.17			0.96
I-II	49 (10.9)	27 (14.8)		65 (10.3)	52 (10.1)	
III	400 (89.1)	155 (85.2)		569 (89.7)	468 (89.9)	
High grade histology			0.06			0.11
No[c]	414 (92.2)	177 (97.3)		594 (93.7)	502 (96.5)	
Yes[d]	30 (6.7)	5 (2.7)		34 (5.4)	18 (3.5)	
Undetermined	5 (1.1)	0 (0.0)		5 (0.9)	0 (0.0)	
CRT regimen			<0.001			0.86
5-FU/LV	307 (68.4)	162 (89.0)		468 (73.7)	390 (75.0)	
Capecitabine	117 (26.1)	16 (8.8)		133 (20.9)	109 (20.9)	
Other	19 (4.2)	3 (1.6)		26 (4.1)	19 (3.6)	
Unknown	6 (1.3)	1 (0.5)		8 (1.2)	3 (0.6)	
Adjuvant chemotherapy regimen			<0.001			0.003
5-FU/LV	285 (63.5)	143 (78.6)		431 (67.9)	372 (71.5)	
FOLFOX	87 (19.4)	3 (1.6)		91 (14.3)	22 (4.3)	
Capecitabine	15 (3.3)	15 (8.2)		33 (5.2)	29 (5.6)	
Other	25 (5.6)	3 (1.6)		28 (4.4)	7 (1.3)	
None	37 (8.2)	18 (9.9)		52 (8.2)	90 (17.2)	

Values are number of patients (%) or mean ± SD unless otherwise indicated. [a]P-value as determined by Pearson's chi-square test or Fisher's exact test for categorical variables and Student's t-test for continuous variables as appropriate. [b]P-value as determined by generalized estimating equation method. [c]Well-differentiated, moderately-differentiated. [d]Poorly-differentiated, signet ring cell, mucinous carcinoma. Pre-OP, preoperative; CRT, chemoradiotherapy; post-OP, postoperative; IPTW, inverse probability of treatment weighting; SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group Performance Status; AV, anal verge; 5-FU, fluorouracil; LV, leucovorin; FOLFOX, 5-FU/LV plus oxaliplatin; TNM, tumor-node-metastasis.

Patient baseline characteristics are summarized in Table I. Age, ECOG PS, clinical stage, tumor histology, and CRT regimen were similar between the two arms. The pre-OP CRT arm had a higher proportion of male patients (68.2 vs. 56.6%, P=0.006), had a tumor location closer to the anal verge (distance from anal verge, ≤4 cm; 46.5 vs. 10.4%, P<0.001), and had higher clinical T stages (stage 3-4; 94.0 vs. 82.4%; P<0.001) than patients in the post-OP CRT arm. The two arms did not show

Table II. Initial distant recurrence pattern.

Recurrence pattern	Total n (%) (n=631)	Pre-OP CRT n (%) (n=449)	Post-OP CRT n (%) (n=182)	P-value
Distant metastasis				
Liver	54 (8.6)	38 (8.5)	16 (8.8)	0.89
Lung	113 (17.9)	83 (18.5)	30 (16.5)	0.55
Distant lymph node	47 (7.4)	38 (8.5)	9 (4.9)	0.13
Bone	8 (1.3)	6 (1.3)	2 (1.1)	1.00
Peritoneum	10 (1.6)	6 (1.3)	4 (2.2)	0.49
Other[a]	12 (1.9)	10 (2.2)	2 (1.1)	0.52
Sum of distant metastasis				0.93
1 organ	150 (23.8)	110 (24.5)	40 (22.0)	
≥2 organs	41 (6.5)	31 (6.9)	10 (5.5)	

[a]Brain, pleura, abdominal wall, bladder, or ovary. Pre-OP, preoperative; CRT, chemoradiotherapy; post-OP, postoperative.

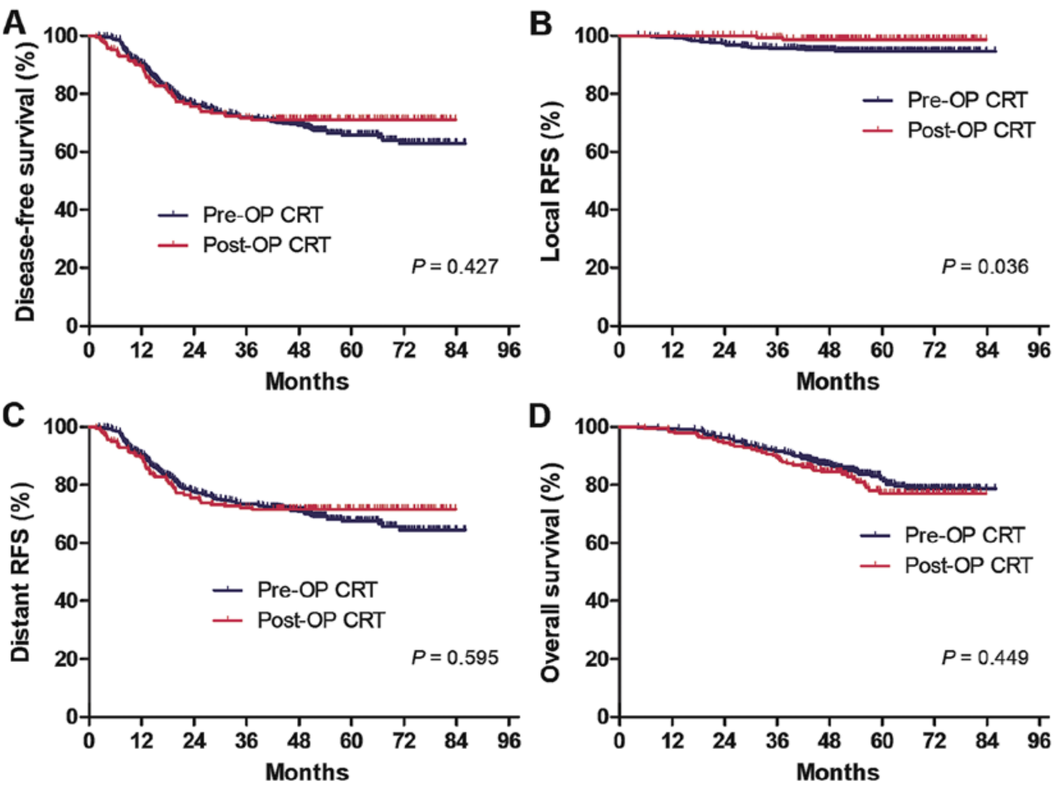

Figure 1. Survival outcomes in the unweighted cohort. (A) Disease-free survival, (B) local RFS, (C) distant RFS, and (D) overall survival rates. RFS, recurrence-free survival; Pre-OP, preoperative; Post-OP, postoperative; CRT, chemoradiotherapy.

significant differences in terms of CRT regimen or adjuvant chemotherapy regimens.

Survival analysis in the unweighted cohort. With a median follow-up time of 55.4 months (range, 53.7-57.1), the 5-year DFS and OS rates of all the patients together were 65.1 and 80.4%, respectively. In decreasing order of frequency, distant recurrence occurred in the lung (17.9%), the liver (8.6%), and distant lymph nodes (7.4%; Table II). Single-organ distant recurrence was observed in 150 patients (23.8%) and multiple-organ distant recurrence in 41 patients (6.5%). The 5-year DFS rates for the pre-OP and post-OP CRT arms were 65.8 and 71.0%, respectively (P=0.43; Fig. 1A). The 5-year local RFS rates was significantly lower in the pre-OP CRT arm than in the post-OP CRT arm (94.5 vs. 98.8%; P=0.04; Fig. 1B), but no significant difference was observed in the 5-year distant RFS rates (pre-OP vs. post-OP CRT; 67.5 vs. 71.6%; P=0.60; Fig. 1C). The 5-year OS rate was 81.9% in the pre-OP CRT arm and

Table III. IPTW-adjusted estimated HR of preoperative CRT on DFS, local/distant RFS, OS, and sites of distant recurrence.

	IPTW analysis[a]	
Outcome variables	HR (95% CI)	P-value
DFS	1.07 (0.65-1.78)	0.79
OS	0.86 (0.42-1.73)	0.67
Local RFS	4.39 (0.86-22.37)	0.08
Distant RFS	1.03 (0.62-1.72)	0.91
Sites of distant recurrence		
Liver	0.60 (0.23-1.59)	0.31
Lung	1.50 (0.84-2.67)	0.17
Distant lymph node	1.21 (0.35-4.21)	0.76
Bone	0.26 (0.02-2.82)	0.27
Peritoneum	0.13 (0.02-0.84)	0.03
Other	3.68 (0.73-18.54)	0.11

[a]Using robust sandwich variance estimator. IPTW, inverse probability of treatment weighting; HR, hazard ratio; CRT, chemoradiotherapy; DFS, disease-free survival; RFS, recurrence-free survival, OS, overall survival; CI, confidence interval.

77.0% in the post-OP CRT arm (P=0.45; Fig. 1D). Distant recurrence patterns were not significantly different between the two arms (Table II).

IPTW analysis. Following IPTW-adjustment, the baseline characteristics of the two arms were well-balanced, with the exception of the adjuvant chemotherapy regimen (Table I), which was additionally adjusted for using regression for further analysis in the weighted cohort. Table III summarizes the IPTW-adjusted estimated hazard ratios (HRs) for DFS, OS, and recurrence of patients who received pre-OP CRT, compared with those who received post-OP CRT. There were no significant differences between the two arms in DFS [HR, 1.07; 95% confidence interval (CI), 0.65-1.78; P=0.79], local RFS (HR, 4.38; 95% CI, 0.86-22.37; P=0.08), or distant RFS (HR, 0.62; 95% CI, 0.62-1.72; P=0.91). The distant recurrence patterns were similar between the two arms, but pre-OP CRT was associated with a significantly lower risk of peritoneal recurrence (HR, 0.13; 95% CI, 0.02-0.84; P=0.03). The OS was not significantly different between the two arms (HR, 0.85; 95% CI, 0.42-1.73; P=0.67).

Discussion

Although it has been suggested that the cumulative incidence of distant recurrence in patients with resectable rectal cancer is not significantly different between patients who receive pre-OP or post-OP CRT (6,7), the patterns of distant recurrence following pre-OP or post-OP CRT have not been adequately compared. To the best of our knowledge, the present study was the first to evaluate and compare the distant recurrence patterns of patients with non-metastatic rectal cancer treated with either pre-OP or post-OP CRT. After performing IPTW-adjustment to balance the baseline characteristics, there was no significant difference in distant RFS, but peritoneal recurrence was significantly lower in patients treated with pre-OP CRT.

As previously reported, TME and CRT have significantly improved local control of rectal cancer, with patients with locally advanced rectal cancer showing a cumulative local recurrence rate of <10% (6,7,23). However, distant recurrence occurs in 20-50% of patients, with the lungs and the liver being the most frequent sites of metastasis (6,7,14,23). Similar results were observed in the present study with 5-year local DFS rates of 94.5 and 98.8% and 5-year distant RFS rates of 67.5 and 71.6% for the pre-OP and post-OP CRT arms, respectively. In addition, in the entire cohort of the present study, the lungs (17.9%) were the most common distant recurrence site, followed by the liver (8.6%).

In the unweighted cohort, the pre-OP and post-OP CRT arms did not have significantly different distant recurrence patterns. However, following IPTW adjustment, pre-OP CRT was associated with a significantly lower risk of peritoneal metastasis (vs. post-OP CRT; HR, 0.13; P=0.03). Although this result should be cautiously interpreted due to the low overall incidence of peritoneal recurrence in the present study, it is consistent with the findings observed in a recent study, where pre-OP radiotherapy was negatively associated with the risk of peritoneal carcinomatosis (24). It has been reported that radiotherapy causes an increase in the number of fibroblasts and a decrease in the number of immune cells within the tumor microenvironment (25). Furthermore, radiotherapy is also associated with an increase in the mucinous component within tumors (26). Although the mechanism driving the association between radiotherapy-induced changes in the tumor microenvironment and peritoneal metastasis is unclear, the characteristics of a tumor with a predilection for peritoneal metastasis in certain patients may be changed by radiotherapy, leading to a reduction in the likelihood of peritoneal metastasis.

In the unweighted cohort, the pre-OP CRT arm had a significantly lower 5-year local RFS rate than the post-OP CRT arm (94.5 vs. 98.8%; P=0.04). This finding contradicts the results of previous studies where pre-OP CRT had significantly improved local control than post-OP CRT (6,7). Discrepancies between the results of previous studies and those of the present study may be due to a higher proportion of patients with a tumor location closer to the anal verge (≤4 cm) in the pre-OP CRT arm (pre-op vs. post-OP CRT; 46.5 vs. 10.4%; P<0.001). It has been suggested in previous studies that distant rectal cancer has higher local recurrence rates (23,27). After performing IPTW-adjustment, a significant difference in the local RFS rates between the two arms was not observed (P=0.08). In line with the results of previous studies, the two arms did not show significant differences in terms of distant RFS and OS rates between the unweighted and weighted cohorts (6,7).

There are several limitations of the present study. As anticipated for any retrospective study, selection bias may exist. A considerable number of baseline characteristics were significantly different between the two arms. To minimize the impact of selection bias, weighted Cox proportional hazards regression modeling with IPTW was utilized. The IPTW approach is commonly used to control for confounding variables in observational studies of medical interventions, which uses the entire cohort and may address a large number of confounding variables. However, IPTW estimates may be highly unstable in the presence of large weights because the estimates may be driven by outcomes occurring in a small number of patients. In addition, differences in adjuvant chemotherapy regimens remained after IPTW, which is likely due to the small number of patients in the post-OP CRT arm, and therefore required additional adjustment. Furthermore, the effect of pre-OP CRT on the tumor microenvironment has not been evaluated, and a comparative analysis of pre-OP and post-OP CRT tumor specimens regarding histopathological or immunological changes and gene expression profiles is necessary to better understand the distant recurrence patterns. Furthermore, the median follow-up duration in the present study was relatively short. Despite these limitations, the present study is the first to directly evaluate and compare distant recurrence patterns in a large number of patients with non-metastatic rectal cancer treated with pre-OP or post-OP CRT.

The results of the present study demonstrated that, although there was no difference in distant RFS between patients who underwent pre-OP or post-OP CRT, after IPTW analysis, pre-OP CRT was associated with a lower risk of peritoneal recurrence in patients with non-metastatic rectal cancer, compared with post-OP CRT. Further study is required to evaluate the effect of CRT on the tumor micro-environment and the corresponding association with the recurrence pattern.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

HC and JEK contributed toward the acquisition, analysis, and interpretation of data; and drafted the manuscript. KPK, SYK, YSH and TWK contributed toward the conception and design of the study and interpretation of data, and critically revised the manuscript. JHP, JHK, SBL, CSY and JCK contributed toward the acquisition of data and critically revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The protocols of the present study were approved by the Institutional Review Board at Asan Medical Center (grant no. AMC IRB 2008-0256), which waived the requirement for informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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