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Matched case-control analysis comparing oncologic outcomes between preoperative and postoperative chemoradiotherapy for rectal cancer

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Purpose: To investigate patterns of recurrence and oncologic outcomes after recurrence between preoperative and postoperative chemoradiotherapy (CRT).
Methods: Records of patients with stage II or III locally advanced rectal cancer seen between January 2000 and December 2010 were analyzed. The outcomes for patients undergoing preoperative CRT followed by radical resection (n = 466) were compared with outcomes of patients matched for sex, age, and stage who had surgery and then postoperative CRT (n = 466). Recurrence rates and sites, treatment of recurrence, and oncologic outcomes after recurrence were investigated. The rate of sphincter preservation and permanent stoma formation were also evaluated.
Results: Recurrence occurred in 124 and 140 patients in the pre- and postoperative CRT groups, respectively. The local and systemic recurrence rates were 3.6% and 20.8%, respectively, in the preoperative CRT group and 3.0% and 25.3%, respectively, in the postoperative CRT group (P = 0.245). Time to recurrence was longer in the postoperative CRT group (19 months *vs*. 24.2 months, P = 0.029). The overall rates of sphincter preservation (sphincter preservation operation and postoperative permanent stoma formation) did not significantly different between the two groups (P = 0.381). The 5-year overall survival rate after recurrence did not differ between the two groups (25.6% *vs*. 18.6%, P = 0.051).
Conclusion: Preoperative and postoperative CRT are both safe and suitable treatment methods for rectal cancer, so the choice can be tailored to the patient's situation.
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Key Words: Chemoradiotherapy, Colorectal surgery, Rectal neoplasms, Recurrence, Treatment outcome

INTRODUCTION

Studies show that 20%–50% of patients who undergo curative resection for colorectal cancer with adjuvant therapy experience recurrence during follow-up [1-3]. Pre- or postoperative chemoradiotherapy (CRT) is important in preventing recurrence in locally advanced rectal cancer (LARC). Improved surgical techniques, such as total mesorectal excision (TME), have also lowered the local recurrence rate; TME with CRT has reduced local recurrence rates of LARC to 5%–10% [4].

For patients with LARC, preoperative CRT reportedly improves local control and causes less treatment-related toxicity than postoperative CRT, as well as improves sphincter preservation [4]. These findings led to a change from postoperative to preoperative CRT, with preoperative CRT followed by radical resection, including TME, and adjuvant chemotherapy becoming the standard treatment for patients with clinical stage II/III rectal cancer. Although the data do not show a clear

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oncologic benefit, preoperative CRT tends to be preferred over postoperative CRT. However, the latter is more often used when clinical staging is underestimated or bowel obstruction requires upfront surgery.

Some studies have investigated recurrence patterns after LARC [5-7], but few compared treatment and oncologic outcomes after recurrence in patients initially treated with pre- or postoperative CRT. This study is a retrospective analysis of patients with LARC who underwent pre- or postoperative CRT to investigate patterns of recurrence and the treatment and oncologic outcomes after recurrence in terms of overall survival (OS) and recurrence-free survival (RFS).

METHODS

Patient identification

Between January 2000 and December 2010, 2007 consecutive patients with primary rectal adenocarcinoma underwent pre- or postoperative CRT at Asan Medical Center, Seoul, Korea. All patients had low (defined as within 5 cm of the anal verge [AV]) to mid (defined as between 5 cm and 10 cm of the AV) rectal tumors, locally advanced disease (T3/4 or node-positive by clinical staging in the preoperative CRT group and by pathology in the postoperative CRT group), and no evidence of distant metastasis. We identified 1,157 patients who underwent preoperative CRT and 850 who underwent postoperative CRT. We selected 466 patients from each group using case-matching of sex, age, and clinical (preoperative CRT group) or pathologic stage (postoperative CRT group). This study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2016-0988).

Clinical/pathologic staging and CRT

Clinical staging was done preoperatively by MRI using a high-spatial-resolution phased-array magnetic resonance technique and by transrectal ultrasound (TUS) using a 7–10 MHz probe. MRI diagnosis of a T3 lesion was based on the presence of tumor signal intensity extending through the muscle layers into the perirectal fat with a broad-based bulging configuration and in continuity with the intramural portion of the tumor. Positive lymph node (LN) status was ascertained by signal intensity, border characteristics, irregular contour, and/or heterogeneous texture. Morphology was not considered a predictor of LN positivity. Circular hypoechoic structures ≥3 mm in diameter were classified as malignant LNs. Nodes <3 mm in diameter and those with central hyperechogenicity were considered benign. Pathologists specializing in gastrointestinal cancers staged resected specimens histopathologically according to the guidelines of the College of American Pathology and the 7th edition of the American Joint Committee on Cancer.

The radiotherapy regimen consisted of a 45-Gy dose of pelvic external beam radiation delivered in 25 fractions over 5 weeks, followed by a 5.4-Gy boost to the tumor in 5 fractions delivered as second daily fractions during the last week of treatment, for a cumulative dose of 50.4 Gy. Concurrent chemotherapy consisted of intravenous 5-fluorouracil or capecitabine monotherapy. Within 6–8 weeks of completing CRT, the preoperative CRT group underwent radical resection including TME. For the postoperative CRT group, adjuvant chemotherapy started within 4 weeks of curative resection, with most patients receiving intravenous 5-fluorouracil or capecitabine monotherapy. Radiotherapy started at the third cycle of chemotherapy for five cycles, and the total radiation dose was 50.4–54 Gy. Surgery was performed by experts with more than 5 years' experience and they followed the rule of TME surgery.

Follow-up and evaluation

Patients underwent standardized postoperative follow-up consisting of physical examination, including digital rectal examination, complete blood count, liver function tests, and serum CEA concentration. Computed tomography of the abdomen and pelvis was performed every 6 months and of the chest, every year. Colonoscopy was performed within 1 year postoperatively and then every 2 years. Recurrence was diagnosed upon radiological findings showing a newly developed lesion over time. Local recurrence was defined as recurrence in the pelvic area, and distant metastasis was defined as any recurrence outside the pelvic cavity. The primary endpoints were recurrence, RFS, and OS after recurrence. OS after recurrence was defined as the time between recurrence after surgery and death or last follow-up. RFS after recurrence was defined as the time between recurrence after surgery and rerecurrence.

Statistical analysis

Categorical variables were summarized as percentages, and differences were compared using a chi-square test, Fisher exact test, and Student t-test. The Kaplan-Meier method was used to calculate OS, RFS, 5-year recurrence rates, and OS after recurrence and was followed by log rank test comparisons. Interaction between factors and treatment effects were summarized as hazard ratios and 95% confidence intervals using Cox proportional hazards regression analysis. A P-value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA).

RESULTS

Patient characteristics

There were no significant differences between pre- and postoperative CRT groups in sex, age, T and N category, tumor site,

or circumferential resection margin status (Table 1). Perineural and lymphovascular invasion rates were significantly higher in the post- than in the preoperative CRT group. Of the total 932 patients, 708 (78.0%) underwent sphincter-preserving resection, with no significant difference between the 2 groups. However, the sphincter-preservation rate among patients with low rectal cancer (AV ≤ 5 cm) was significantly higher in the pre- than in the postoperative CRT group (P = 0.002). Patients who had permanent stoma formation after surgery was 24 (5.2%) and 12 (2.6%), respectively, with a significant difference between the 2 groups (P = 0.041). Permanent stoma formation was resulted from radiotherapy induced complications which were anastomosis leakage (14), stricture (4), proctitis (3), fistula (3) in the preoperative CRT group and stricture (7), anastomosis leakage (3), fistula (1), proctitis (1) in the postoperative CRT group. The overall rates of sphincter preservation and permanent stoma did not significantly different between the 2 groups (P = 0.381). Since postoperative CRT was mainly used in the early 2000s and preoperative CRT mainly in the late 2000s, the follow-up period of the postoperative CRT group was longer than that of the preoperative CRT group.

Pattern and treatment of recurrence

There were 264 recurrences, 124 (26.6%) in the preoperative and 140 (30.0%) in the postoperative CRT group. The overall systemic, local, and systemic and local recurrence rates were 20.8%, 3.6%, and 2.1%, respectively, in the preoperative and 25.3%, 3.0%, and 1.7%, respectively, in the postoperative CRT

Table 1. Characteristics of patients with rectal cancer

Characteristic	Preoperative CRT (n = 466)	Postoperative CRT (n = 466)	P-value
Sex			>0.999
Male	312 (67.0)	312 (67.0)	
Female	154 (33.0)	154 (33.0)	
Age (yr)	56.9 ± 9.2	56.9 ± 9.2	0.932
T category			0.074
T1/2	26 (5.6)	40 (8.6)	
T3/4	440 (94.4)	426 (91.4)	
N category			0.249
N0	362 (77.7)	347 (74.5)	
N1/2	104 (22.3)	119 (25.5)	
Tumor site (AV ≤ 5)	241 (51.7)	222 (47.6)	0.213
Lymphovascular invasion	55 (11.8)	148 (31.8)	<0.001
Perineural invasion	40 (8.6)	59 (12.7)	0.043
Circumferential resection margin involved	6 (1.3)	10 (2.1)	0.313
Sphincter preservation	366 (78.5)	342 (73.4)	0.066
In low rectum (AV ≤ 5)	146/241 (60.6)	103/222 (46.4)	0.002
Permanent stoma formation	24 (5.2)	12 (2.6)	0.041
Overall sphincter preservation	342 (73.4)	330 (70.8)	0.381
Follow-up period (mo)	68.9 ± 35.6	77.8 ± 45.4	0.001

Values are presented as number (%) or mean ± standard deviation.
CRT, chemoradiotherapy; AV, anal verge.

Table 2. Recurrence of rectal cancer after curative treatment

Variable	Preoperative CRT (n = 466)	Postoperative CRT (n = 466)	P-value
Type of recurrence	124 (26.6)	140 (30.0)	0.245
Systemic recurrence	97 (20.8)	118 (25.3)	0.102
Local recurrence	17 (3.6)	14 (3.0)	0.584
Systemic and local recurrence	10 (2.1)	8 (1.7)	0.634
Time to recurrence (mo)	19.0 ± 15.6	24.2 ± 21.3	0.029
Systemic recurrence	19.1 ± 16.3	22.4 ± 18.8	0.173
Local recurrence	20.7 ± 14.8	34.1 ± 26.1	0.085
Systemic and local recurrence	15.5 ± 9.4	32.5 ± 39.4	0.203

Values are presented as number (%) or mean ± standard deviation.
CRT, chemoradiotherapy.

group, all nonsignificant differences between the 2 groups. Time to recurrence was longer in the postoperative than in the preoperative CRT group (P = 0.029), particularly for local recurrence (Table 2).

The major systemic recurrence site was the lung, followed by the liver and distant LNs. The major local recurrence site was the pelvic cavity, followed by pelvic LNs and the anastomosis site. For treatment of systemic recurrence, chemotherapy and/or radiotherapy (46.4% *vs.* 57.6% in preoperative *vs.* postoperative CRT group) was performed, followed by curative treatment including surgery, radiofrequency ablation (RFA), or stereotactic body radiotherapy (SBRT), with or without combined chemotherapy (37.1% *vs.* 27.1%). The major treatment for local recurrence was chemotherapy and/or radiotherapy (76.5% *vs.* 64.3%), followed by surgery combined with chemotherapy (23.5% *vs.* 21.4%) (Fig. 1).

In the preoperative CRT group, systemic recurrence occurred in 97 patients, including the lung in 49, the liver in 26, and multiple sites in 22. In the postoperative CRT group, systemic recurrence occurred in 118, including the lung in 55, the liver in 40, and multiple sites in 23. Patients with recurrences in the lung and liver were more likely to undergo curative treatment for the recurrence than those with systemic recurrences in other sites. In the preoperative CRT group, curative treatment was given to 19 patients (38.8%) with lung recurrence and 16 (61.5%) with liver recurrence. In the postoperative CRT group, curative treatment was administered to 14 patients (25.5%) with lung recurrence and 18 patients (45%) with liver recurrence (Fig. 1).

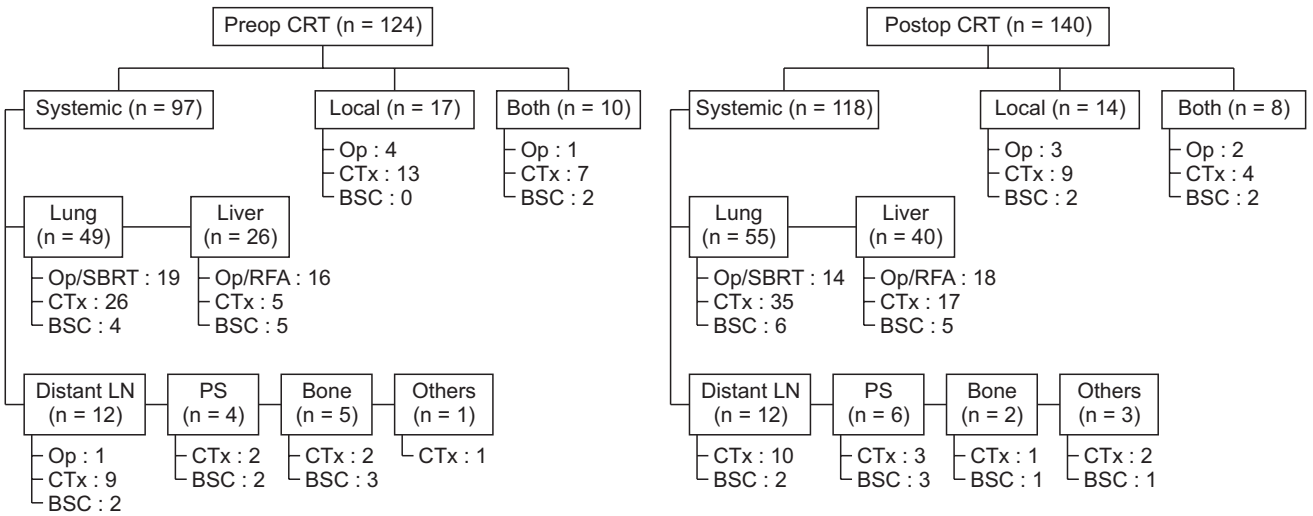

Fig. 1. Pattern and treatment of recurrences of rectal cancer. CRT, chemoradiotherapy; Op, operation; SBRT, stereotactic body radiotherapy; RFA, radiofrequency ablation; CTx, chemotherapy; BSC, best supportive care; LN, lymph node; PS, peritoneal seeding.

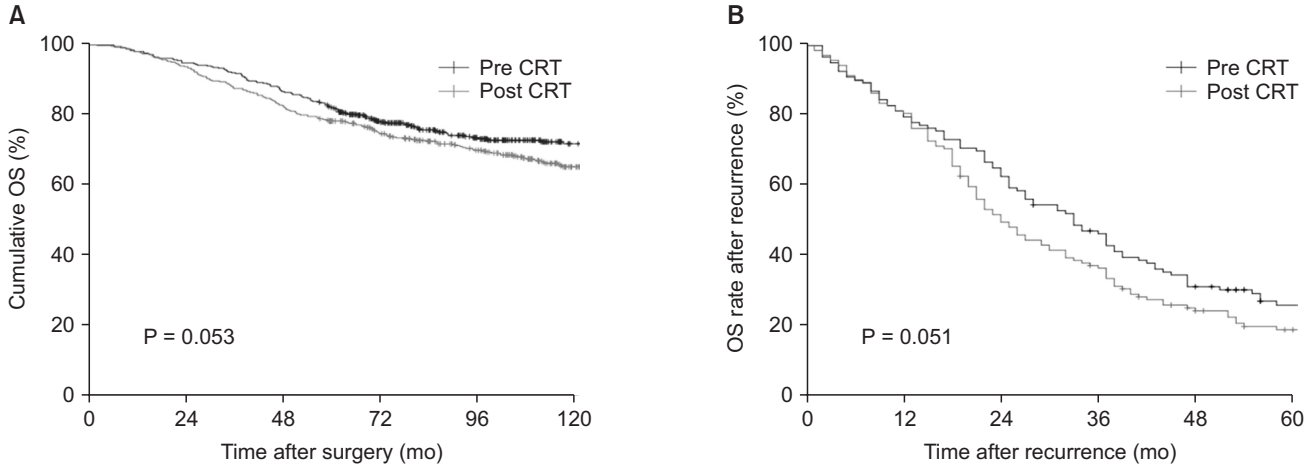

Fig. 2. (A) Overall survival (OS) in pre- and postoperative chemoradiotherapy (CRT) groups. (B) Overall survival after recurrence in the pre- and postoperative CRT groups.

Oncologic outcomes after recurrence

The 10-year OS did not differ statistically between pre- and postoperative CRT groups (71.8% *vs.* 65.3%, P = 0.053) nor did the 5-year OS after recurrence (25.6% *vs.* 18.6%, P = 0.051). (Fig. 2). Multivariate analysis including sex, site, stage, timing of CRT, and pathologic features showed that CEA ≤ 6, and curative treatment of recurrence were associated with a better OS (Table 3). Similarly, preoperative CRT, CEA ≤ 6, and curative treatment of recurrence were associated with a better RFS (Table 4).

In the preoperative (35 patients) and postoperative (32 patients) CRT groups of patients with liver or lung metastases, the 5-year OS after recurrence were 29.4% *vs.* 22.3% (P = 0.159) and the 5-year OS after recurrence were 58.0% *vs.* 44.0% (P = 0.290) in patients who received curative treatment for the recurrence. Of 35 and 32 patients, 18 patients (51.4%) and 13 patients (40.6%) did not have another recurrence after curative treatment, respectively (P = 0.208).

DISCUSSION

In the National Surgical Adjuvant Breast and Bowel Project R-03 trial, preoperative CRT resulted in a significantly higher 5-year RFS and a better 5-year OS than postoperative CRT [8]. A representative study by the German Rectal Cancer Group showed that preoperative CRT provided better local control, toxicity profile, and sphincter preservation than postoperative CRT [4]. Since those reports, preoperative CRT followed by TME surgery has been extensively used and provides better local

Table 3. Multivariate analysis of factors associated with 5-year overall survival after treatment for a first recurrence of rectal cancer

Variable	HR	95% CI	P-value
Sex			0.498
Male	1		
Female	0.903	0.673–1.212	
Timing of CRT			0.397
Preoperative CRT	1		
Postoperative CRT	1.138	0.844–1.534	
Distance from AV (cm)			0.283
AV ≤ 5	1		
5 < AV ≤ 10	0.853	0.638–1.140	
CEA (ng/mL)			0.034
≤6	1		
>6	1.402	1.026–1.915	
T category			0.763
T1/2	1		
T3/4	1.126	0.519–2.445	
N category			0.245
N0	1		
N1/2	1.215	0.875–1.686	
Lymphovascular invasion			0.322
Negative	1		
Positive	1.185	0.847–1.656	
Perineural invasion			0.145
Negative	1		
Positive	0.738	0.491–1.110	
Circumferential resection margin			0.838
Negative	1		
Positive	0.931	0.468–1.853	
Treatment for recurrence			<0.001
Operation/RFA/SBRT	1		
CTx and/or RTx	3.022	2.097–4.355	
BSC	5.693	3.613–8.970	

HR, hazard ratio; CI, confidence interval; CRT, chemoradiotherapy; AV, anal verge; SBRT, stereotactic body radiotherapy; RFA, radiofrequency ablation; CTx, chemotherapy; RTx, radiotherapy; BSC, best supportive care.

Table 4. Multivariate analysis of factors associated with 5-year recurrence-free survival after treatment for a first recurrence of rectal cancer

Variable	HR	95% CI	P-value
Sex			0.329
Male	1		
Female	0.868	0.653–1.153	
Timing of CRT			0.019
Preoperative CRT	1		
Postoperative CRT	1.374	0.053–1.792	
Distance from AV (cm)			0.927
AV ≤ 5	1		
5 < AV ≤ 10	0.987	0.749–1.302	
CEA (ng/mL)			0.030
≤6	1		
>6	1.414	1.035–1.933	
T category			0.596
T1/2	1		
T3/4	0.810	0.373–1.762	
N category			0.164
N0	1		
N1/2	1.259	0.911–1.740	
Lymphovascular invasion			0.843
Negative	1		
Positive	0.967	0.695–1.346	
Perineural invasion			0.341
Negative	1		
Positive	0.823	0.552–1.228	
Circumferential resection margin			0.371
Negative	1		
Positive	0.730	0.366–1.455	
Treatment for recurrence			<0.001
Operation/RFA/SBRT	1		
CTx and/or RTx	2.942	2.072–4.177	
BSC	10.035	6.349–15.861	

HR, hazard ratio; CI, confidence interval; CRT, chemoradiotherapy; AV, anal verge; CEA, carcinoembryonic antigen; SBRT, stereotactic body radiotherapy; RFA, radiofrequency ablation; CTx, chemotherapy; RTx, radiotherapy; BSC, best supportive care.

control but no significant survival benefit [4,8,9]. Contrary to other reports, neither 5-year OS nor 5-year RFS in our study differed between the pre- and postoperative CRT groups. The 5-year OS was 82.1% *vs.* 79% and the 5-year RFS 73% *vs.* 70.7% in the pre- and postoperative CRT groups, respectively, which did not differ significantly. Our study is important in that we investigated time to recurrence, recurrence pattern, and oncologic survival after recurrence.

We found no significant difference in systemic and local recurrence between pre- and postoperative CRT. Improvement in surgical techniques, such as TME, and radiotherapy have reduced local recurrence rates in LARC. Several studies suggested that preoperative CRT had a major advantage over postoperative CRT in providing local control [4,10], but that was not found in the present study. In both groups, the local recurrence rate was less than 5%. This may be explained by the fact that TME was performed well by experienced, skilled surgeons. Based on the circumferential resection margin, the success rate of TME is expected to be 98.7% and 97.9% in the pre- and postoperative CRT groups, respectively. Because surgery results in increased fibrosis and decreased vascularity, CRT is assumed to provide greater benefit against local recurrence if given preoperatively. However, in the present study, local recurrence did not differ between the 2 groups.

We found that time to both systemic and local recurrence tended to be longer in the postoperative than in the preoperative CRT group, and time to overall recurrence of the postoperative CRT group was also significantly longer. This might be due to the timing of chemotherapy. Sadahiro et al. [11] indicated that chemotherapy significantly prolonged the time to recurrence in patients with colon or rectal cancer. Our result might also have been affected by the longer follow-up period (mean, 90 months) of the postoperative CRT group; six patients had a late recurrence: 5–10 years after surgery. In the preoperative CRT group, four patients had a recurrence that late, with a mean follow-up of 73 months. In terms of organ-specific recurrence, the time to lung metastasis (23.04 months) was significantly longer than time to liver metastasis (15.39 months, P = 0.003). This is consistent with the hypothesis by Weiss et al. [12] that the hepatic capillary network may represent an effective filter into the systemic circulation.

The liver is the most common recurrence site in colon cancer [9,13,14], while the lung is the most common site in rectal cancer [7,15]. Yeo et al. [7] showed that recurrence site differed depending on the tumor site within the rectum, with lung metastasis more frequent in patients with low- to midrectal cancer than upper rectal cancer. The present study found that mid- to low-rectal cancers most frequently metastasized to the lung, followed by liver and distant LNs, regardless of the timing of CRT. The difference in these recurrence patterns is due to blood flow and lymphatic drainage [12,16]. Colon cancer cells travel via the portal blood flow. Lymphatic vessels in the lower half of the rectum, however, travel via the midrectal vessels to the internal iliac nodes, so rectal cancer cells can travel via both systemic and portal blood flow. Weiss et al. [12] explained that the hepatic capillary network acts as an effective filter, trapping tumor emboli in the portal system and preventing their entry into the systemic circulation. These reasons explain why LARC metastasizes most frequently to the lung.

Neither the rate and pattern of recurrence nor the oncologic survival after recurrence did differ statistically between pre- and postoperative CRT groups. The 5-year OS rate after recurrence did not differ between the 2 groups, however, it showed marginal benefit for oncologic survival in the preoperative CRT group (P = 0.051). This difference may be due to poorer compliance with treatment protocol in the postoperative CRT group than the preoperative CRT group, in accordance with the result of German study [4]. It may also be due to overstaging in the preoperative CRT group. The accuracy of current imaging modalities, such as TUS and MRI, for clinical staging of rectal cancer is only 30%–40% when combined with cT and cN categories [17-19]. Multivariate analysis showed that normal CEA level and presence of curative treatment were associated with 5-year OS and RFS. Timing of CRT was also associated with 5-year RFS, which, may be due to higher proportion of curative treatment in the preoperative CRT group. Curative resection or RFA and SBRT are the most important predictive factors for survival in patients with systemic recurrence of rectal cancer. Curative treatment is often performed for patients with liver or lung metastases and in our study, the 5-year OS after recurrence were 29.4% *vs.* 22.3% (P = 0.159) in the pre- and postoperative CRT groups, respectively. However, it increased to 58.0% *vs.* 44.0% (P = 0.290) in patients who received curative treatment for the recurrence.

The choice of pre- or postoperative CRT is generally determined by the clinical stage based on imaging. However, due to the lack of accuracy of current imaging as noted above, this method for determining when CRT is administered may not be proper. In one study, more patients had a poor response (n = 357) to preoperative CRT and had worse oncologic outcomes than those who had a good response (n = 224) [20]. In another study, the stage after preoperative CRT for rectal cancer was closely correlated with recurrence free survival [21]. The controversy between pre- and postoperative CRT lies in the overstaging of patients given preoperative CRT but who have a poor response. A supposed benefit of preoperative CRT is an increased chance of sphincter preservation [4,22,23]. In our study, there was a significant advantage of sphincter preservation in low rectal cancer in the preoperative CRT group (P = 0.002). However, despite this benefit, radiotherapy induced complications which resulted in permanent stoma were more frequent in the preoperative CRT group (P = 0.041).

The overall rates of sphincter preservation and permanent stoma between the 2 groups were compared and there was no significant difference (P = 0.381). The complications were anastomosis leakage (14), stricture (4), proctitis (3), fistula (3) in the preoperative CRT group and stricture (7), anastomosis leakage (3), fistula (1), proctitis (1) in the postoperative CRT group. Therefore, overuse of preoperative CRT must be avoided.

This study was retrospective and thus has limitations. First, some cases in the preoperative CRT group might have been overstaged because of the inaccuracy of imaging modalities. Second, the follow-up period of the postoperative CRT group was slightly longer than that of the preoperative CRT group, since routine treatment for clinical stage T3 or node-positive mid- to low-rectal cancer was changed from postoperative to preoperative CRT between 2000 and 2010. However, the follow-up period after recurrence was similar between the 2 groups. Third, we evaluated the first site of recurrence, which might underestimate the true incidence of recurrence and affect the recurrence analysis, including oncologic outcomes.

In conclusion, preoperative CRT increased sphincter preservation in low rectal cancer patients, however, the rate of overall sphincter preservation did not differ between pre- and postoperative CRT groups. This is because there were more radiation induced complications which resulted in permanent stoma in preoperative CRT group. There was no significant difference in systemic and local recurrence rates, in recurrence patterns, and in 5-year OS after recurrence between preoperative and postoperative CRT. Preoperative and postoperative CRT are both safe and suitable treatment methods, so the choice can be tailored to the patient's situation.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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