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Can neoadjuvant chemoradiotherapy affect exfoliated cancer cells in colorectal cancer?

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Abstract

Background To prevent local recurrence caused by exfoliated cancer cells caught in the suture line, intraoperative rectal washout during surgery can be performed to eliminate exfoliated cancer cells. However, the impact of neoadjuvant chemoradiotherapy on exfoliated cancer cells is not well known. This study aimed to identify positive rate of malignant cells in rectal washout fluids of neoadjuvant chemoradiotherapy patients and to determine if neoadjuvant chemoradiotherapy could affect exfoliated cancer cells.

Methods A total of 105 patients who underwent rectal washout intraoperatively for distal sigmoid colon and rectal cancer from April 2020 to September 2021 were analyzed. The primary outcome was positive rate of malignant cells in rectal washout fluids of patients who had received neoadjuvant chemoradiotherapy.

Results The positive rate of malignant cells in washout fluids of patients who had received neoadjuvant chemoradiotherapy was 0.0% and those who had not was 32.1%. The overall positive rate was 23.8%. In the positive group, tumor sizes were bigger (4.64 ± 1.68 cm vs. 3.64 ± 2.00 cm, $p = 0.026$) and more patients had a fungating tumor shown in preoperative colonoscopy (96.0% vs. 71.3%, $p = 0.012$). Although these factors did not show statistical significance in multivariable logistic regression analysis, fungating tumor showed a trend towards significance (OR: 7.28, 95% CI: 0.90-58.77, $p = 0.063$).

Conclusions Our study suggests that neoadjuvant chemoradiotherapy could reduce exfoliated cancer cells, and rectal washout for the purpose of eliminating exfoliated cancer cells might be unnecessary in patients who have received neoadjuvant chemoradiotherapy.

Keywords Colorectal cancer, Neoadjuvant chemoradiotherapy, Rectal washout, Exfoliated cancer cells, Fungating tumor

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Background

Local recurrence of rectal cancer can occur due to several reasons such as inadequate resection margin, positive circumferential margin, and implantation of exfoliated cancer cells in the double-stapled line [1–9]. Rectal washout (RW) during surgery has been proposed as a preventive measure to avoid local recurrence caused by exfoliated cancer cells caught in the suture line [8–10]. The procedure aims to eliminate any remaining exfoliated cancer cells in the bowel lumen by washing them out mechanically. However, since the effectiveness of RW in reducing local recurrence after colorectal surgery is still controversial [3, 5, 7], not all colorectal surgeons at our center perform RW routinely. Nonetheless, some surgeons choose to perform RW because it is a relatively easy and quick procedure during surgery [11].

With the introduction of neoadjuvant chemoradiotherapy (nCRT) and total mesorectal excision for advanced rectal cancer, 5-year local recurrence has decreased [12–15]. However, the impact of nCRT on exfoliated cancer cells is not well known, and there are few studies on the effect of RW for patients who have undergone nCRT. Therefore, before confirming the efficacy of RW in nCRT, we conducted a study through cytological evaluation under the hypothesis that nCRT could decrease exfoliated cancer cells. The purpose of this study was to identify positive rate of malignant cells in RW fluids and to determine whether nCRT could affect exfoliated cancer cells.

Methods

Patients and data collection

From April 2020 to September 2021, patients who underwent surgeries for distal sigmoid colon and rectal cancer in Samsung Medical Center were retrospectively reviewed. Patients who did not undergo a rectal washout procedure, those who had undergone endoscopic mucosal resection or submucosal dissection for the primary cancer lesion before surgery, those with sigmoid colon cancer lesions too high for the rectal tube to reach the anastomosis level, and those who underwent intersphincteric resection with hand-sewn colo-anal anastomosis were excluded. Finally, a total of 105 patients were analyzed for this study.

Data including age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) score, preoperative carcinoembryonic antigen (CEA), and carbohydrate antigen 19−9 (CA 19−9) level were collected, as well as information on cancer obstruction, perforation, stenting, and stoma formation prior to surgery. The clinical stage data for patients who underwent nCRT reflects the tumor's stage approximately 6 weeks after the completion of chemoradiotherapy. Cancer obstruction was defined as symptoms of obstruction, passage disturbance during colonoscopy, proximal dilation on imaging studies or operation field. All patients underwent preoperative colonoscopy, esophagogastroduodenoscopy, and imaging studies, such as abdomen and pelvis CT, chest CT for all patients, and rectum MRI for rectal cancer patients. Tumor morphology was assessed using colonoscopic images, and clinical stages were determined according to imaging studies and classified by the AJCC 8th guidelines [16]. Figure 1 illustrates the flowchart of treatment protocols for mid to lower rectal cancer at our center. Patients with mid to low rectal cancer stages 2 and 3 were treated with neoadjuvant chemotherapy and long-course radiotherapy (RT), following the National Comprehensive Cancer Network guideline and our hospital's policy. The total radiation dose and chemotherapy regimen were determined based on the decisions of radiologists and oncologists. For stage 4 patients who were able to undergo surgery after chemotherapy, neoadjuvant short-course RT was performed only for those who were considered to need it according to the multidisciplinary team's discussion and decision. All other patients underwent surgery as the first step. Additionally, all patients expected to undergo surgery completed mechanical bowel preparation the day before the procedure with same medication.

After colectomy or proctectomy, all tissues were taken and evaluated by several pathologists. Information of tumor size, cell type, tumor-nodal status, lymphovascular and perineural invasion, tumor budding, and distance from cancer to free distal resection margin was obtained. For patients who had undergone nCRT, we collected additional information on the duration of nCRT, the time from the completion of RT to surgery, radiation dose, chemotherapy drugs, and the tumor regression grade confirmed in the postoperative pathology examination. Tumor regression grade was classified by the Dworak tumor response grading system [17].

Procedure of rectal washout and cytology

After dissecting the tissue around the rectum and sufficiently clearing the area to transect the rectum, the operator clamped the proximal portion above the rectal transection site using a Fehland intestinal clamp for laparotomy and a nylon tape for laparoscopic surgery (Fig. 2). Once rectal irrigation was prepared, a rectal tube was inserted up to the clamped site, and the rectal lumen was irrigated with 500 ml of normal saline. All washout fluids were collected for cytological evaluation to check for malignant cells. After RW was completed, the bowel was transected below the clamped level. Figure 3 shows laparoscopic bowel transection after RW using a laparoscopic linear stapler.

All collected samples were centrifuged, and Papanicolaou staining was applied. Cytotechnologists evaluated

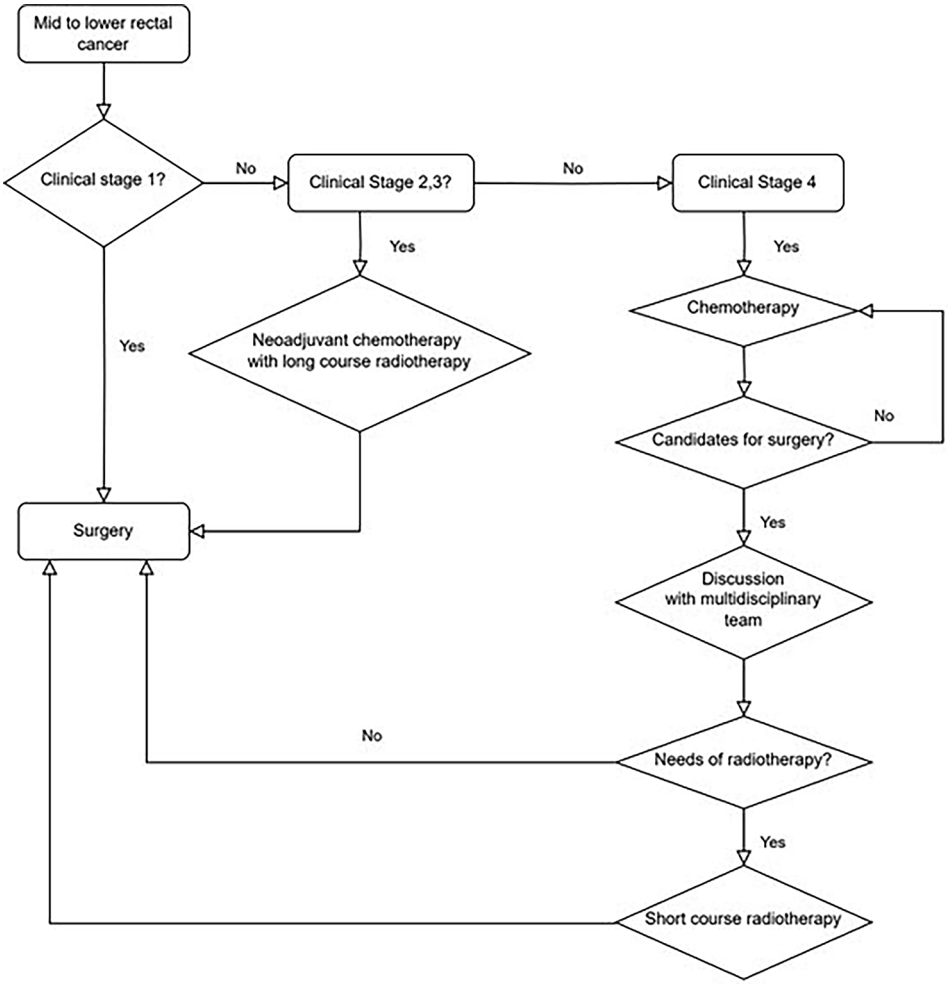

Fig. 1 Flowchart of treatment protocols for mid to lower rectal cancer at our center

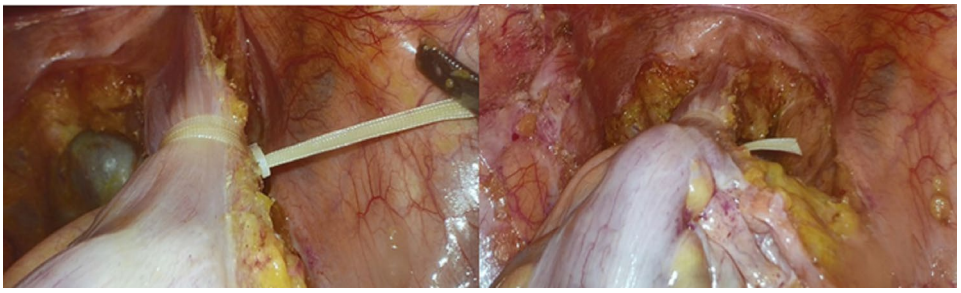

Fig. 2 Preparation of rectal washout using nylon tape during laparoscopic surgery

the presence of malignant cells in the stained samples, and pathologists double-checked the results before final reports were produced.

Outcomes and statistical analysis

We investigated positive rates of malignant cells in washing fluids of all analyzed patients. In addition, according to washing fluid cytology results, patients were divided into groups with positive and negative malignant cells and analyzed. Primary outcome was positive rate of malignant cells in washing fluids of patients who had received nCRT. Secondary outcomes were differences between positive and negative malignant cell groups and preoperative factors affecting positivity.

All statistical analyses were performed using SPSS version 27.0 (SPSS Inc., Chicago, IL, USA). A *p*-value of less than 0.05 was considered statistically significant. $\chi 2$ or Fisher's exact test was used to compare categorical

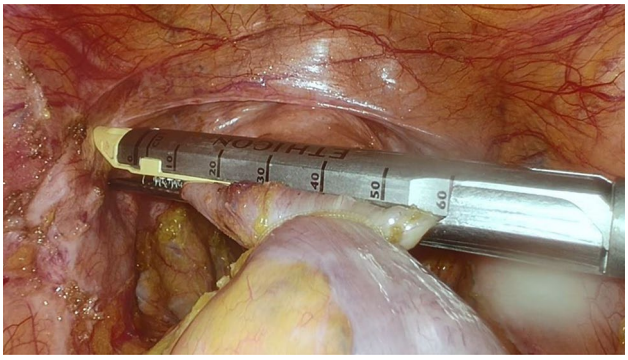

Fig. 3 Bowel transection after rectal washout in laparoscopic surgery

variables. Student's t-test and Mann-Whitney U test were used to compare continuous variables of baseline characteristics, perioperative characteristics, and pathologic outcomes. Logistic regression analysis was used for finding factors affecting positive cell cytology. After performing univariable logistic regression analysis, multivariable logistic regression analysis was performed with statistically significant factors identified in univariable analysis. This study was approved by the Institutional Review Board of Samsung Medical Center (Approval number: SMC 2021-12-024) and informed consent was waived because of the retrospective nature of the study.

Results

From April 2020 to September 2021, a total of 105 patients had undergone RW and their washout fluids were cytologically confirmed (nCRT, $n=27$; no nCRT, $n=78$). Table 1 compares the baseline and perioperative characteristics between patients who received nCRT and those who did not. The nCRT group had a higher incidence of mid to lower rectal cancer and lower anastomosis levels (both $p<0.001$). Conversely, the no nCRT group had a significantly higher percentage of fungating tumor morphology (93.6% vs. 29.6%, $p<0.001$). The positive rate of malignant cells in RW fluids of patients who had received nCRT was 0.0% and those who had not was 32.1%. The overall positive rate was 23.8%. Table 2 shows characteristics of twenty-seven patients who had undergone nCRT. Most (92.6%) patients had received long-course RT. The median value of the total radiation dose was 50.4 Gy (range, 25.0–60.0 Gy). Among patients who underwent long-course RT, all but one patient were concurrently treated with capecitabine (88.9%). The one patient received 5-Fluorouracil and Leucovorin (FL) combination chemotherapy. The remaining two patients who received short-course RT had metastasis before surgery and they were treated with Avastin+FOLFOX or FOLFIRI. Distributions of tumor regression grades shown in postoperative pathological examinations were: grade 1 (minimal regression), 3.7%; Grade 2 (moderate regression), 59.3%; Grade 3 (near-total regression), 22.2%; and Grade 4 (total regression), 14.8% (Table 2).

Table 1 Baseline and perioperative characteristics of patients who received neoadjuvant chemoradiotherapy and who did not

	nCRT (*n* = 27)	*No-nCRT* (*n* = 78)	*P-value*
Age, mean ± SD, years	61.78 ± 10.00	60.72 ± 11.35	0.15
Sex			0.41
Male	20 (74.1%)	51 (65.4%)	
Female	7 (25.9%)	27 (34.6%)	
BMI, mean ± SD, kg/m2	22.85 ± 2.92	24.23 ± 2.84	> 0.99
ASA score			0.91
1	8(29.6%)	21(26.9%)	
2	15(55.6%)	47(60.3%)	
>=3	4(14.8%)	10(12.8%)	
Preoperative CEA, median (range), ng/ml	2.77 (0.61-33.00)	2.82 (0.47–672.00)	0.40
Preoperative CA19-9, median (range), ng/ml	9.18 (2.00-2823.00)	8.69 (2.00-90.70)	0.72
Obstruction	1 (3.7%)	8 (10.3%)	0.44
Perforation	1 (3.7%)	2 (2.6%)	> 0.99
Preoperative colonic stent insertion	2 (8.0%)	1 (1.3%)	0.14
Clinical T stage[a]			0.11
T1 +T2	9 (33.3%)	17 (21.8%)	
T3	12 (44.4%)	26 (33.3%)	
T4	6 (22.2%)	35 (44.9%)	
Tumor location			< 0.001
Sigmoid colon	0 (0.0%)	31 (39.7%)	
Upper rectum	3 (11.1%)	41 (52.6%)	
Mid to lower rectum	24 (88.9%)	6 (7.7%)	
Fungating morphology in colonoscopy	8 (29.6%)	73 (93.6%)	< 0.001
Surgical technique			0.11
Open	3(11.1%)	2(2.6%)	
MIS[b]	24(88.9%)	76(97.4%)	
Anastomosis level			< 0.001
Above peritoneal reflection	0(0.0%)	36(46.2%)	
Below peritoneal reflection	27(100.0%)	42(53.8%)	

nCRT, neoadjuvant chemoradiotherapy; SD, standard deviation; BMI, body mass index; ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen; CA 19−9, Carbohydrate antigen 19−9; MIS, minimally invasive surgery

[a] The clinical T stage in the nCRT group refers to the tumor's stage approximately 6 weeks after completing chemoradiotherapy

[b] This includes laparoscopy, and robotic surgery

Table 3 shows baseline and perioperative characteristics of patients according to positivity in cytology (positive malignant cell, $n=25$; negative malignant cell, $n=80$). In 68.0% of patients with positive results, tumors were located in the upper rectum, but in the negative group, the distribution was similar at all locations ($p=0.005$). There were more patients who had a fungating tumor shown in preoperative colonoscopy in the positive group (96.0% vs. 71.3%, $p=0.01$, Table 3). In pathologic results,

Table 2 Clinicopathologic characteristics of patients who had received neoadjuvant chemoradiotherapy (n = 27).

	Number (%) or median (range)
Tumor location from AV	
≤ 5cm	5 (18.5%)
5-10cm	18 (66.7%)
> 10cm	4 (14.8%)
RT duration (month)	1.30 (0.20–3.23)
Long course RT	25 (92.6%)
Short course RT	2 (7.4%)
Time from the completion of RT to surgery (month)	1.85 (0.75–2.30)
Total radiation dose (Gy)	50.4 (25.0–60.0)
Chemotherapy agents	
Capecitabine	24 (88.9%)
Etc.[a]	3 (11.1%)
Tumor size (cm)	2 (0-6.50)
Tumor regression grade	
Grade 1 (Minimal)	1 (3.7%)
Grade 2 (Moderate)	16 (59.3%)
Grade 3 (Near total)	6 (22.2%)
Grade 4 (Total)	4 (14.8%)

AV, anal verge; RT, radiotherapy

[a]This includes 5-Fluorouracil, Leucovorin (FL) combination chemotherapy and AVASTIN with FOLFOX or FOLFIRI combination therapy

Table 3 Baseline and perioperative characteristics of positive and negative cytology results

	Positive (n = 25)	*Negative (n = 80)*	*P-value*
Age, mean ± SD, years	63.08 ± 13.33	60.34 ± 10.14	0.28
Sex			
Male	19 (76.0%)	52 (65.0%)	0.31
Female	6 (24.0%)	28 (35.0%)	
BMI, mean ± SD, kg/m2	23.61 ± 2.46	23.96 ± 3.05	0.60
ASA score			0.95
1	7(28.0%)	22(27.5%)	
2	14(56.0%)	48(60.0%)	
>=3	4(16.0%)	10(12.5%)	
Preoperative CEA, median (range), ng/ml	3.14 (1.27–672)	2.75 (0.47–64.40)	0.051
Preoperative CA19-9, median (range), ng/ml	7.34 (2.00-90.70)	9.55 (2.00-2823.00)	0.51
nCRT	0 (0.0%)	27 (33.8%)	0.001
Preoperative chemotherapy	0 (0.0%)	5 (6.3%)	0.34
Obstruction	1 (4.0%)	8 (10.0%)	0.68
Perforation	1 (4.0%)	2 (2.5%)	0.56
Preoperative colonic stent insertion	2 (8.0%)	1 (1.3%)	0.14
Clinical T stage			0.27
T1 + T2	4 (16.0%)	22 (27.5%)	
T3	8 (32.0%)	30 (37.5%)	
T4	13 (52.0%)	28 (35.0%)	
Tumor location			0.005
Sigmoid colon	6 (24.0%)	25 (31.3%)	
Upper rectum	17 (68.0%)	27 (33.8%)	
Mid to lower rectum	2 (8.0%)	28 (35.0%)	
Fungating morphology in colonoscopy	24 (96.0%)	57 (71.3%)	0.01
Surgical technique			> 0.99
Open	1(4.0%)	4(5.0%)	
MIS[a]	24(96.0%)	76(95.0%)	
Anastomosis level			0.48
Above peritoneal reflection	7(28.0%)	29(36.3%)	
Below peritoneal reflection	18(72.0%)	51(63.7%)	

SD, standard deviation; BMI, body mass index; ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen; CA 19−9, Carbohydrate antigen 19−9; nCRT, neoadjuvant chemoradiotherapy; MIS = minimally invasive surgery

[a]This includes laparoscopy, and robotic surgery

patients with positive results showed bigger tumor size (4.64±1.68 cm vs. 3.64±2.00 cm, p=0.03). In addition, the negative group included more patients with well- and moderately differentiated cancer than the positive group (well-differentiated: 0.0% vs. 22.5%, p=0.003). However, other characteristics did not show statistically significant differences between the two groups (Table 4).

To identify factors influencing positive cell cytology, univariable and multivariable logistic regression analyses were performed. In univariable analysis, tumor size increase was a significant factor affecting positive cell cytology (OR: 1.31, 95% CI: 1.03–1.68, p=0.03) and fungating tumor significantly increased the risk of positive results than non-fungating tumor (OR: 9.68, 95% CI: 1.24–75.84, p=0.03). Although these two factors did not show statistical significance (p>0.05) in multivariable analysis, the presence of a fungating tumor showed a trend towards significance (OR: 7.28, 95% CI: 0.90-58.77, p=0.06) (Table 5).

Discussion

RW is a procedure commonly performed to remove exfoliated cancer cells from the bowel lumen. It aims to reduce the chance of recurrence due to implantation of cancer cells at the anastomosis site. While several studies have reported that RW can reduce local recurrence [1, 2, 4, 6, 8, 9, 18], randomized controlled studies have not been reported, and the question of whether RW can reduce anastomosis site recurrence remains controversial [3, 5, 7]. The 2020 American society of colon and rectal surgeons clinical practice guidelines suggest that RW may be considered, but weakly recommend it due to the low quality of evidence [19]. However, RW is commonly performed because it does not take much time and is relatively easy to perform without additional postoperative complications, particularly when performed by a skilled colorectal surgeon [20].

Table 4 Pathologic outcomes of positive and negative cytology results

	Positive (n = 25)	*Negative (n = 80)*	*P-value*
Tumor size, mean ± SD, cm	4.64 ± 1.68	3.64 ± 2.00	0.03
Cell differentiation			0.003
WD	0(0.0%)	18(22.5%)	
MD	22(88.0%)	57(71.3%)	
PD	1(4.0%)	0(0.0%)	
Mucinous	2(8.0%)	1(1.3%)	
TNM stage			0.12
Stage 0	0 (0.0%)	4 (5.0%)	
Stage I	2 (8.0%)	23 (28.7%)	
Stage II	8 (32.0%)	18 (22.5%)	
Stage III	14 (56.0%)	30 (37.5%)	
Stage IV	1 (4.0%)	5 (6.3%)	
T classification			0.07
T0 + Tis + T1	1 (4.0%)	16 (20.0%)	
T2	2 (8.0%)	15 (18.8%)	
T3	20 (80.0%)	41 (51.2%)	
T4	2 (8.0%)	8 (10.0%)	
N classification			0.22
N0	10 (40.0%)	47 (58.8%)	
N1	10 (40.0%)	23 (28.7%)	
N2	5 (20.0%)	10 (12.5%)	
Distal margin, mean ± SD, cm	3.44 ± 2.87	3.21 ± 2.71	0.72
Lymphatic invasion	9 (36.0%)	21 (22.9%)	0.48
Perineural invasion	8 (32.0%)	29 (36.3%)	0.60
Vascular invasion	4 (16.0%)	8 (10.0%)	0.52
Positive tumor budding	10 (28.6%)	25(31.3%)	0.59

SD, standard deviation; WD, well-differentiated; MD, moderately differentiated; PD, poorly differentiated; TNM, tumor-node-metastasis

Several studies investigating exfoliated cancer cells in the bowel lumen have reported varying percentages of positive results, ranging from 40.0 to 96.7% [21–26]. In our study, the positive rate was 23.8% in all analyzed patients, 0.0% in those who had received nCRT, and 32.1% in those who had not. The overall positive rate was significantly lower than that of previous studies, which might be explained by the absence of exfoliated cancer cells in patients who had undergone nCRT. Dafnis et al. have analyzed 60 patients (of them, 72% and 20% had received neoadjuvant short-course and long-course radiotherapy, respectively) and found that the overall positive rate is 55.0% [25]. Okada et al. [21]. have reported that the positive cytology rate of 86 patients who have received a long-course nCRT with a total dose of 45 Gy is 24.4%. They noted that the reason for the lower positive rate than that of Dafnis et al. was that most patients in Dafnis et al. received short-course RT, but in their study, all patients received long-course RT. They have suggested that such results indicate that nCRT can reduce the number of exfoliated cancer cells [21]. In our study, except for two patients who received short-course RT, all others underwent long-course RT. The median total radiation dose was 50.4 Gy. Only one patient received 45 Gy, which is the same dose used in the study of Okada et al. [21], all patients who underwent long-course RT received a total dose of 50.4 Gy or more. The reason that the positive rate of patients who received nCRT was 0% regardless of the degree of tumor regression might be explained by the fact that the radiation dose in our study was higher than that used in the study of Okada et al. We hypothesize that this added radiation dose may have had a greater impact on exfoliated cancer cells, thereby reducing their numbers. Based on the above results, our study can suggest

Table 5 Univariable and multivariable logistic regression analysis of positive exfoliated cancer cell

			Univariable analysis			**Multivariable analysis**		
	Reference		**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Age			1.02	0.98–1.07	0.28			
Sex	Female	Male	1.71	0.61–4.76	0.31			
BMI			0.96	0.82–1.12	0.60			
Preoperative CEA			1.01	0.97–1.06	0.56			
Preoperative CA 19 – 9			0.99	0.98-1.00	0.69			
Obstruction	N	Y	0.38	0.04–3.15	0.37			
Perforation	N	Y	1.63	0.14–18.71	0.70			
Stent insertion	N	Y	6.87	0.60-79.21	0.12			
Clinical T stage	T1 + T2	T3	1.47	0.39–5.49	0.57			
		T4	2.55	0.73–8.93	0.14			
Tumor location	Sigmoid colon	UR	2.62	0.89–7.71	0.08			
		M-LR	0.30	0.06–1.61	0.16			
Tumor size			1.31	1.03–1.68	0.03	1.22	0.93–1.60	0.15
Fungating tumor	N	Y	9.68	1.24–75.84	0.03	7.28	0.90-58.77	0.06

BMI, body mass index; CEA, carcinoembryonic antigen; CA 19 – 9, carbohydrate antigen 19 – 9; UR, upper rectum; M-LR, mid to lower rectum

that RW may be unnecessary to remove exfoliated cancer cells for patients who have received nCRT with sufficient radiation dose.

The positive cytology group had more fungating and bigger-sized tumors than the negative group. There is the risk that cancer cells can flow into the bowel lumen during manipulation [10, 27, 28], and surgeons who excessively manipulate the primary tumor during surgery may cause more cancer cells to break away from the primary tumor. The proportion of fungating tumors with or without ulceration in the positive group was 96.0% (24/25). This might be because fungating tumors are more vulnerable to external mechanical factors such as bowel manipulation during surgery, thus increasing the shedding of cancer cells [25, 29, 30]. In addition, the mean tumor size of the positive group was larger than that of the negative group, which might be because the more extensive the tumor size, the more likely tumor cells will have a chance of exfoliation. Both tumor size and fungating tumor were identified as factors affecting positive cytological results in univariable logistic regression analysis, but they showed no significant correlation with positive results in multivariable analysis. However, since fungating tumor showed a trend towards significance in multivariable analysis, larger sample size may yield more significant results. Further studies are needed, but the recommendation of RW can be considered if a fungating tumor is confirmed by endoscopy.

One limitation of this study is its small sample size and its execution at a single center by a limited number of surgeons, which may limit the generalizability of the results. Future studies with larger sample sizes and multi-center studies could help to further validate the findings of this study and provide more robust evidence. Additionally, the patient groups were not matched, which may introduce selection bias. This could affect the validity of the results, as differences between the groups may have influenced the outcomes. Therefore, the findings should be interpreted cautiously, and future studies should ensure group matching to minimize bias. Furthermore, the inclusion of only a small subset of patients who underwent short-course radiation limits our ability to comprehensively compare the effects of different radiation therapies. A future, more detailed prospective study comparing radiation types is warranted to solidify our conclusions. Finally, our study did not investigate local recurrence, which is the main reason for performing RW. Therefore, further research is needed to determine whether there is a difference in local recurrence between patients who underwent RW and those who did not after receiving nCRT.

Conclusions

In conclusion, our study suggests that nCRT could reduce exfoliated cancer cells and that RW for the purpose of eliminating exfoliated cancer cells might be unnecessary in patients who have received nCRT. In particular, since rectal clamping for intraoperative RW might be difficult for novice surgeons lacking laparoscopic skills and patients whose tumor lesion is too low, the present study suggests that surgeons do not need to be burdened with performing RW in patients who have received nCRT. However, further studies of oncological outcomes with larger sample sizes are needed to confirm this result.

Abbreviations

RW	Rectal washout
nCRT	neoadjuvant chemoradiotherapy
BMI	Body mass index
ASA	American Society of Anesthesiologists
CEA	Carcinoembryonic antigen
CA 19 – 9	Carbohydrate antigen 19 – 9
RT	Radiotherapy

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Author contributions

JL and WL contributed to conception and design of the study. JL, WL, SY, HK, YC, JH, YP and JS organized the database. JL performed the statistical analysis and wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Data availability

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

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Samsung Medical Center (Approval number: SMC 2021-12-024) and informed consent was waived because of the retrospective nature of the study.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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