

Original Research Article

Feasibility and Efficacy of Neoadjuvant Chemotherapy without Radiotherapy for Locally Advanced Rectal Cancer

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Abstract

Objectives: This retrospective study explored the feasibility of neoadjuvant chemotherapy (NAC) without radiotherapy in patients with locally advanced rectal cancer (LARC).

Methods: Patients with clinical stage of T3-T4 and/or N-positive LARC patients were included. We retrospectively analyzed patients' NAC-related and perioperative outcomes.

Results: The study enrolled 30 patients. mFOLFOX6 or SOX plus cetuximab was administered to 12 patients with the wild-type RAS gene and FOLFOXIRI or SOXIRI to 18 patients with mutant-type RAS. The NAC completion rate was 90.0%. All patients underwent total mesorectal excision, and 29 patients underwent combined bilateral lateral lymph node dissection. The R0 operation rate was 90.0%. Although the postoperative complication rate was 40%, no complications were associated with NAC. The response rate of NAC and the proportion of histological anti-tumor effect grade ≥ 2 were 56.7% and 46.7%, respectively.

Conclusions: NAC was considered to be a safe, feasible treatment option for LARC.

Keywords

neoadjuvant chemotherapy, rectal cancer, mFOLFOX6, cetuximab, FOLFOXIRI

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Introduction

Locally advanced rectal cancer (LARC) often recurs locally in the pelvis, and the treatment strategies differ among countries. In Western countries, neoadjuvant chemoradiotherapy (NACRT) and rectal surgery, with total mesorectal excision (TME), are recommended for LARC therapy for preoperatively local control and to downstage LARC[1-3]. According to previous studies, NACRT for rectal cancer is recommended for LARC in the second version of the 2015 National Comprehensive Cancer Network guidelines[4]. On the other hand, the standard treatments for LARC in Japan are TME and pelvic lateral lymph node dissection (LLND) from the outcomes of the randomized controlled trial examining the non-inferiority of TME alone to TME plus LLND[5].

The phase III trial of neoadjuvant chemotherapy (NAC) without radiotherapy in LARC patients was conducted, and NAC (mFOLFOX6) was as effective in downstaging of LARC as NACRT with less toxicity and fewer postoperative complications[6]. Several phase II clinical trials also reported that NAC was safe and effective for LARC patients[7-11]. In addition, a randomized trial comparing standard NACRT versus FOLFOX, as NAC with selective use of chemoradiation for LARC patients (PROSPECT), has been conducted in North America[12].

In our institute, we previously administered NACRT for LARC in accordance with the data from Western countries. However, although NACRT exerted local control effects, it did not contribute to improved long-term prognosis in LARC[13]. Therefore, we changed our treatment strategy for

LARC from NACRT to NAC, beginning in April 2014, to improve long-term outcomes, such as overall survival and relapse-free survival. Simultaneously, we reintroduced LLND with TME to reduce local recurrence in the pelvis.

In the present study, we examined the usefulness of NAC for LARC to evaluate the effects, such as histological anti-tumor effect (HATE), relative response, and perioperative short-term outcomes.

Methods

We began administering NAC as a multimodal therapy instead of NACRT for LARC, beginning in April 2014. We judged that NAC could be safely introduced to eight LARC patients in the pilot study of NAC, and we planned and conducted a phase II study to evaluate the efficacy and safety of first-line chemotherapy for LARC, which began in September 2016 (The efficacy and safety of perioperative chemotherapy for locally advanced colorectal cancer-The phase II study-UMIN ID: 000024323, Japanese Registry of Clinical Trials (JRCTs) ID: 051180167). This study was conducted in accordance with the World Medical Association Declaration of Helsinki and all its amendments and was approved by the ethics committee of Kansai Medical University Medical Center (Approval code: 2016410). In the present study, we investigated the feasibility and efficacy of NAC for LARC to evaluate the chemotherapy-related outcomes and perioperative short-term outcomes in patients enrolled in the pilot study who were treated from April 2014 to October 2020.

We began administering NAC as a multimodal therapy instead of NACRT for LARC in April 2014. In the present study, we investigated the feasibility and efficacy of NAC for LARC to evaluate the chemotherapy-related outcomes and perioperative short-term outcomes in patients treated from April 2014 to October 2020. The primary end-point of this study was the R0 operation rate, and the secondary end-points were the response rate on NAC and incidence rate of adverse events. This study was conducted in accordance with the Declaration of Helsinki and all its amendments.

The inclusion criteria were 1) LARC patients (the tumor present rectum below the peritoneal reflection (Rb)) with clinical (c) stage of T3-T4/any cN or any cT/cN-positive disease assessed *via* colonoscopy, enhanced computed tomography (CT), and enhanced pelvic magnetic resonance imaging (MRI); 2) Eastern Cooperative Oncology Group Performance Status ≤ 2 ; 3) age > 20 years and < 85 years; and 4) written informed consent obtained from the LARC patients to undergo NAC. In this study, cN-positive was defined as having a lymph node with a short diameter ≥ 6 mm in the mesorectal region. In the lateral lymph node region, cN-positive was defined as having lymph nodes detectable *via* enhanced MRI or CT.

The interventions in this phase II study are as follows: 1) LARC patients with wild-type RAS: six courses of mFOL-FOX6 (oxaliplatin 85 mg/m² intravenously and leucovorin 400 mg/m² intravenously, followed by fluorouracil 400 mg/m² intravenously on day 1 of each chemotherapy cycle and fluorouracil 2.4 g/m² by 48-h continuous intravenous infusion) plus cetuximab (Cmab: initial dose of 400 mg/kg (week 1) and each subsequent dose at 250 mg/kg once a week)[14] or four courses of SOX (oxaliplatin 130 mg/m² intravenously on day 1 and tegafur, gimeracil, and oteracil potassium (S1) 80-120 mg/day on day 1-14 of each chemotherapy cycle) plus Cmab (initial dose of 400 mg/kg (week 1) and each subsequent dose at 250 mg/kg once a week)[15], followed by curative operation and adjuvant chemotherapy (AC) with the same regimen and courses. 2) LARC patients with mutant-type RAS: six courses of FOL-FOXIRI (oxaliplatin 85 mg/m², irinotecan 150 mg/m², and leucovorin 400 mg/m² intravenously on day 1 of each chemotherapy cycle and fluorouracil 2.4 g/m² by 48-h continuous intravenous infusion)[16,17] or four courses of SOXIRI (oxaliplatin 130 mg/m² and irinotecan 85 mg/m² intravenously on day 1 + S1 at 80-120 mg/day on day 1-14 of each chemotherapy cycle)[18,19], followed by radical operation and AC with the same regimen and courses. Radical operation was performed 4 weeks after the last administration of cytotoxic agents.

The staging and HATE for NAC were performed in accordance with the *Japanese Society for Cancer of the Colon and Rectum* (9th edition) guidelines[20]. The histological tumor response to NAC was determined using grades 0, 1a, 1b, 2, and 3 as follows: HATE G0, no response to treatment; HATE G1a, tumor size reduction $< 1/3$; HATE G1b, tumor size reduction of $1/3$ - $2/3$; HATE G2, tumor size reduction $> 2/3$; and HATE G3, complete tumor ablation equal to a pathological complete response (pCR). The longitudinal axis diameter of the tumor was measured on the sagittal plane of enhanced MR images, and the type of surgery was determined at a preoperative conference according to each patient's oncological condition.

Results

We enrolled 30 patients who underwent NAC at our surgery department between July 2014 and October 2020. The patients' demographics and pretreatment variables are summarized in Table 1 and constituted each patient's age, tumor location, histological tumor type, clinical (c) stage, cN stage, longitudinal axis diameter of the tumor before NAC, and carcinoembryonic antigen and carbohydrate antigen 19-9 (CA19-9) levels in each patient's pretreatment peripheral blood. We did not measure the longitudinal axis tumor diameter in two patients because they did not undergo MRI due to the presence of implanted metallic medical devices.

Table 1. Patients' Demographics and Pretreatment Variables.

		Total (n = 30)	RAS status	
			Wild-type (n = 12)	Mutant-type (n = 18)
Gender	Male	23	11	12
	Female	7	1	6
Age, years (range)		69.5 (53–78)	69.5 (54–78)	69 (53–78)
ECOG* performance status	0	27	11	16
	1	2	1	1
	2	1	0	1
Tumor location	Rs-Rb	3	2	1
	Ra-Rb	7	3	4
	Rb	18	6	12
	Rb-P	2	1	1
Histological type	tub1*	8	2	6
	tub2*	17	8	9
	muc*	3	1	2
	por*	2	1	1
Clinical (c) T stage**	T3	18	7	11
	T4a	4	1	3
	T4b	8	4	4
cN stage**	0	6	2	4
	1	9	0	9
	2	6	4	2
	3	9	6	3
Longitudinal axis diameter of the tumor before NAC, mm (range)		44.9	52.6 (31.6–132.0)	43.4 (29.6–61.0)
CEA, ng/mL (range)		4.7	3.8 (2.5–16.8)	6.4 (1.9–217.8)
CA19-9: U/mL (range)		14.7	11.6 (1.0–28.8)	15.9 (2.0–157.9)

*ECOG, Eastern Cooperative Oncology Group

*tub1, well-differentiated tubular adenocarcinoma

*tub2, moderately differentiated tubular adenocarcinoma

*muc, mucinous adenocarcinoma

*por, poorly differentiated adenocarcinoma

***Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma*, 9th edition

NAC, neoadjuvant chemotherapy; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; T, tumor stage; N, node stage

The NAC regimen, effect of NAC, and relative dose intensity of each agent are summarized in Table 2. Doublet chemotherapy (dCT) plus Cmab was administered to all patients with wild-type RAS and triplet chemotherapy (tCT) to all patients with mutant-type RAS. Three patients did not continue tCT: two because of their wish to discontinue and one because of complicated colonic ileus secondary to LARC. The longitudinal axis diameters of the tumor after the administration of dCT plus Cmab and tCT were 25.9 and 21.9 mm, respectively. The tumor sizes after the administration of dCT plus Cmab and tCT were 67.1% and 70.6%, respectively, and the response rates of dCT plus Cmab vs. tCT were 66.7% vs. 50.0%, respectively. The proportions of patients with HATE \geq grade 2 after the administration of dCT plus Cmab and tCT were 50% and 44.4%, respectively.

The adverse events according to the Common Terminol-

ogy Criteria for Adverse Events, version 4 (CTCAE v.4.0), are summarized in Table 3. In the tCT group, although the incidence of neutropenia (CTCAE v.4.0 grade \leq 2) was 72.2%, no affected patients discontinued CT. Three patients in the tCT group could not continue NAC; these patients underwent immediate curative surgery (TME with bilateral LLND).

The surgical procedures and postoperative short-term outcomes are summarized in Table 4. Laparoscopic LLND plus TME was performed in 29 patients (96.7%) without conversion to open laparotomy. The R0 operation rate (primary endpoint) was 90% (27 patients), and the R1 operation rate was 10% (3 patients). The operation for seven patients who were diagnosed with ycT4b were as follows: three for total pelvic exenteration, two for ultra-low anterior resection (one is R1 operation), one for posterior pelvic exenteration, and

Table 2. NAC Regimen, NAC Effect, and Relative Dose Intensity of Each NAC Agent in the NAC and Adjuvant Chemotherapy Regimens.

		Total	Doublet chemotherapy (Oxaliplatin+5FU agent) plus Cmab*	Triplet chemotherapy (Oxaliplatin+Irinotecan +5FU agent)
RAS status	wild	12	12	0
	mutant	18	0	18
Relative dose intensity of NAC, % (range)	Cmab		100 (88.8–100)	
	Oxaliplatin		100	88.4 (25–100)
	Irinotecan		-	83.2 (13.3–100)
	5FU; mFOLFOX6, FOLFOXIRI		100	100 (63.3–100)
	S1*; SOX, SOXIRI		95.3 (75–100)	90.0 (25–100)
Number of patients discontinuing NAC		3	0	3
Longitudinal axis diameter of the tumor after NAC (mm)		24.6	25.9 (15.0–88.6)	21.9 (12.0–47.2)
Tumor size after NAC, % (range)		67.1	67.1 (13.1–124.3)	70.6 (23.1–104.4)
Response	PR	17	8	9
	SD	10	3	7
	PD	1	1	0
	unknown	2	0	2
Histological anti-tumor effect	1a	14	5	9
	1b	2	1	1
	2	12	4	8
	3	2	2	0
Number of patients undergoing AC*		22	11	11
Relative AC* dose intensity, % (range)	Cmab		87.5 (0–100)	-
	Oxaliplatin		56.5 (33–100)	33.3 (0–100)
	Irinotecan		-	58.3 (0–100)
	5FU; mFOLFOX6, FOLFOXIRI		91.5 (80–100)	58.3 (0–100)
	S1*; SOX, SOXIRI		97.9 (0–100)	25 (0–100)

*Cmab, cetuximab

*S1, tegafur/gimeracil/oteracil

*AC, adjuvant chemotherapy

NAC, neoadjuvant chemotherapy; 5FU, 5-fluorouracil; PR, partial response; SD, stable disease; PD, progression of disease

one for abdominoperineal resection, respectively. The median operation time and operative blood loss volumes were 534 min and 59 mL, respectively. As postoperative complications, neurogenic bladder occurred in six patients (all Clavien-Dindo (CD) grade II); abdominal bleeding in three patients (two cases of CD grade II and one case of CD grade IIIb); and chronic subdural hematoma (CD grade IIIa), enteritis (CD grade II), and perineal wound infection (all CD grade I) in one case each. No postoperative complications were associated with NAC.

Twenty-two patients received AC with the same regimen of NAC. AC was not administered to eight patients due to the following reasons: four due to their wish not to undergo AC, three due to postoperative complications, and one due to the radiation therapy performed after the R1 operation.

The c, yc, and yp stages are summarized in Table 5. Downstaging of the T and N factors in LARC was achieved

in 46.2% and 73.1% of the patients after NAC, respectively (data not shown). Recurrence after surgery was reported in four cases. The recurrence sites were the liver in two patients, lung in one, and pelvic floor in one (median follow-up time: 40 months).

Discussion

In Western countries, the standard treatment for LARC is NACRT and TME[1-3,21]. So far, in our institution, we have introduced NACRT. However, the long-term outcomes, such as the 5-year relapse-free survival (RFS) and 5-year overall survival (OS), were not improved by NACRT[13]. We considered that NAC for LARC might be effective in improving the RFS and OS by controlling distant micrometastases. Subsequently, we changed the neoadjuvant therapy for LARC from NACRT to NAC without radiotherapy. At

Table 3. Adverse Events According to CTCAE v.4.0*.

		Doublet CT* plus Cmam* n = 12 (%)	Triplet CT n = 18 (%)
Hematological toxicity (CTCAE v.4.0 ≥ grade 2)	Neutropenia	2 (16.7)	13 (72.2)
	Thrombocytopenia	2 (16.7)	1 (5.6)
Non-hematological toxicity (CTCAE v.4.0 ≥ grade 2)	Appetite loss	0	2 (11.1)
	Acneiform eruption	3 (25)	0
	Inflamed oral mucosa	1 (8.3)	0
	Fatigue	0	2 (11.1)
	Xerosis cutis	0	1 (5.6)
	Paronychia	1 (8.3)	0
	Colonic perforation	0	1 (5.6)
	Liver dysfunction	1 (8.3)	0
	Peripheral neuropathy	1 (8.3)	0

*CTCAE v.4.0, Common Terminology Criteria for Adverse Events, version 4

*Cmam, cetuximab

*CT, chemotherapy

Table 4. Operative Procedure and Intraoperative and Postoperative Short-Term Outcomes.

		Total	RAS status	
			Wild-type	Mutant-type
Operative procedure	Lap* sLAR*+bil.* LLND*	20	7	13
	Lap APR*+bil. LLND	2	1	1
	Lap Hartmann+bil. LLND	1	1	0
	Lap ISR*+bil. LLND	2	0	2
	Lap TPE*+bil. LLND	3	2	1
	Lap PPE*+bil. LLND	1	1	0
	Lap sLAR	1	0	1
R0 operation, % (range)		27 (90.0)	11 (91.7)	16 (88.9)
Harvested lateral pelvic nodes, number (range)		15 (4–30)	12 (4–27)	16 (11–30)
Operation time, minutes (range)		534 (208–682)	532 (423–589)	534 (208–682)
Operative blood loss volume, mL (range)		59.0 (5–760)	120 (10–490)	40.0 (5–760)
Postoperative hospital stay, days (range)		15.0 (6–46)	19 (6–46)	13.5 (9–36)
Postoperative complication (CD* score ≥ 3)	Overall	12 (1)	6	6
	Neurogenic bladder	6	4	2
	Abdominal bleeding	3 (1)	1	2 (1)
	Chronic subdural hematoma	1 (1)	-	1 (1)
	Enteritis	1	1	0
	Perineal wound infection	1	-	1

*Lap, laparoscopic-assisted surgery

*APR, abdominoperineal resection

*sLAR, super-low anterior resection

*ISR, intersphincteric resection

*TPE, total pelvic floor exenteration

*PPE, posterior TPE

*bil, bilateral

*LLND, lateral lymph node dissection

*CD, Clavien–Dindo classification

the same time, we reintroduced TME with LLND as radical surgery.

In previous studies on NAC, several regimens were selected as NAC for LARC[6-11]. Some institutes chose only

Table 5. c, yc, yp Stage, T Stage, and N Stage.

		c*	yc*	yp*
Stage*	0	0	0	2
	I	0	4	7
	IIa	4	12	7
	IIb	0	1	0
	IIc	2	2	2
	IIIb	11	4	8
	IIIc	13	7	4
T Stage*	T0	0	0	2
	T1a	0	0	1
	T1b	0	0	2
	T2	0	4	4
	T3	18	16	14
	T4a	4	3	2
	T4b	8	7	5
N Stage*	N0	6	18	18
	N1a	5	5	6
	N1b	4	1	4
	N2a	5	2	1
	N2b	1	0	0
	N3	9	4	1

*Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma, 9th edition

cytotoxic agent regimens, such as mFOLFOX6 and XELOX, whereas other institutes chose cytotoxic agent regimens plus molecular-targeted agents, such as bevacizumab (Bmab) and anti-epidermal growth factor receptor therapy. Recently, the long-term outcomes of a phase III study on NAC for LARC were published by Deng et al., who reported that mFOLFOX6, with or without radiation, did not significantly improve the 3-year DFS versus fluorouracil with radiation in patients with LARC. They also reported that there was no significant difference in the outcomes between mFOLFOX6 without radiotherapy and fluorouracil with radiotherapy[22]. Contrarily, Hasegawa et al. reported the usefulness of cytotoxic agents plus molecular-targeted agents as NAC[8]. The authors introduced mFOLFOX6 plus Cmab for wild-type KRAS and mFOLFOX6 plus bevacizumab (Bmab) for mutant-type KRAS and found no significant difference between the regimens in terms of response, postoperative complication, and pCR rates[8]. In addition, Glynne-Jones et al. reported that FOLFOXIRI and Bmab achieved promising pCR rates and that the regimen was well tolerated, despite the finding that the pCR rate, which was a primary endpoint, was not met in the BOCCHUS study[7]. These data suggested that mFOLFOX6 plus Cmab or Bmab and FOLFOXIRI plus Bmab were useful and safe NAC regimens for LARC. However, Uehara et al. reported that XELOX plus Bmab may have resulted in a high frequency of anastomotic

leakage (27.8%) because Bmab delayed wound healing[9]. Therefore, we considered it desirable to introduce a different regimen without Bmab for patients with mutant-type RAS; we also introduced tCT without molecular-targeted agents.

In accordance with previous outcomes, in the present study, we chose mFOLFOX6 or SOX plus Cmab for patients with wild-type RAS and FOLFOXIRI or SOXIRI as triplet regimens without molecular-targeted agents for patients with mutant-type RAS to improve long-term oncologic outcomes. To introduce NAC without a central venous port, we initially chose SOXIRI, as described in the phase II studies on metastatic colorectal cancer patients, as a regimen (irinotecan 150 mg/m², followed by oxaliplatin 85 mg/m² on day 1 and S-1 80 mg/m² per day from day 1 to 14 every 3 weeks) for seven LARC patients with mutant-type RAS[18,19]. However, regarding the relative dose intensity of oxaliplatin and irinotecan with this regimen, the SOXIRI regimen involved only a two-third dose compared with FOLFOXIRI. Therefore, we introduced FOLFOXIRI to seven recent patients with mutant-type RAS to achieve high-dose intensity of oxaliplatin and irinotecan, after constructing a central venous port. Recently, Kudo et al. reported that XELOXIRI without molecular-targeted drugs (irinotecan (150 mg/m²) and oxaliplatin (85 mg/m²) on day 1 and capecitabine (1000 mg/m² orally twice daily) on days 1-7 of a biweekly schedule) was a feasible and active regimen for patients with LARC[23]. The dose intensity of XELOXIRI was similar to that for FOLFOXIRI; therefore, XELOXIRI may be as effective as NAC for LARC.

Regarding safety, NAC was administered safely for LARC, especially in the dCT plus Cmab group, and in this study, there were no postoperative complications associated with cytotoxic and molecular-targeted agents. The adverse events of NAC appeared to be well tolerated. However, three patients did not continue NAC in the SOXIRI group: two because of their wish to discontinue and the other because of complicated obstructive colonic ileus due to LARC. These patients underwent immediate curative surgery (TME and LLND). In the dCT plus Cmab group, the full course of NAC was administered to all patients. In the present study, NAC was considered acceptable in terms of short-term safety after surgery. However, the dose intensity of AC after surgery, especially with the SOXIRI regimen, was lower than that with NAC. It may be difficult to administer cytotoxic agents considering the patient's status after radical surgery. Therefore, when considering chemotherapy in an adjuvant setting, it may be efficient and safe to administer sufficient amounts of these agents before radical operation.

In the present study, the NAC response rate was 56.7%, and the rate of HATE ≥ 2 was 46.7%. Although the tumor control effect with NACRT is higher, NAC is considered to have a certain tumor control effect. Therefore, NAC may contribute to not only micro-distant metastasis control but

also local recurrence control. With regard to the regimens, we found no significant differences between dCT plus Cmap for wild-type RAS and tCT for mutant-type RAS in terms of the response and postoperative complication rates. However, two patients achieved pCR with dCT plus Cmap, and the reason may be associated with differences related to the RAS status of the tumor. Therefore, it is currently unclear which regimen to choose. To validate the usefulness, efficacy, and prognosis of NAC regimens, such as mFOLFOX6 plus Cmap and tCT in LARC patients, a multicenter, prospective, randomized controlled study is necessary.

In the present study, the R0 operation rate (primary endpoint) and R1 operation rate were 90% and 10%, respectively. The R1 operation rate was relatively higher than NACRT in our previous report[13]. This outcome may indicate that the local control power of NAC without radiotherapy may be insufficient. In fact, Zhong et al. reported that NACRT was more effective than NAC in terms of local recurrence[24]. However, the histopathological characteristics of the patients with R1 operation were poorly differentiated adenocarcinoma (por) in two of the three patients and mucinous adenocarcinoma (muc) in one of the three patients. The malignancy potential of por and muc is higher than that of tubular adenocarcinoma, and cancers with the por and muc histotypes are often treatment-resistant[25,26]. Accordingly, when treating LARC with the por or muc histotypes, total neoadjuvant therapy or early surgical treatment should be introduced instead of NAC.

We have reintroduced TME with LLND as radical surgery because NAC might be less effective than NACRT in terms of local control power for LARC. A randomized controlled trial (JCOG0212)[5], which was conducted to determine whether the effect of ME alone was comparable to that of ME with LLND for clinical stage II/III rectal cancer in the absence of LLN enlargement, did not confirm the non-inferiority of ME alone vs. ME plus LLND in terms of the 5-year RFS. In addition, the local recurrence rate of ME alone (12.6%) was significantly higher than that of ME + LLND (7.4%). According to these findings, LLND is recommended for Japanese LARC patients in the *Japanese Society for Cancer of the Colon and Rectum Guidelines 2019 for the Treatment of Colorectal Cancer*[27]. In the present study, we performed laparoscopic LLND for all patients, except in one patient with chronic heart failure[28]. In the present study, the median follow-up period was short (40 months), and there was only one patient who developed local recurrence in the pelvic floor. We will continue to perform TME plus LLND and NAC for LARC patients as a multimodal therapy until long-term outcomes are revealed.

According to the results of this study, NAC for LARC was considered safe and could effectively reduce local recurrence. However, this study has several limitations. First, it involved a small number of patients, and we analyzed retro-

spective data from a single institution. Second, the median follow-up period < 5 years was too short to draw firm conclusions. A multicenter, prospective, randomized controlled study is necessary to validate the usefulness, efficacy, and prognosis of NAC without radiation in LARC patients.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

KT made a substantial contribution to the conception of the study, conducted a literature search, and drafted the manuscript. KT and YM contributed to the acquisition of the data. KT, YM, and YU performed the operation. KT and KY reviewed the manuscript and gave final approval for the publication. All authors read and approved the final manuscript.

Approval by Institutional Review Board (IRB)

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