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ORIGINAL ARTICLE

Neoadjuvant CAPOX and bevacizumab alone for locally advanced rectal cancer: long-term results from the N-SOG 03 trial

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Abstract

Background Neoadjuvant chemotherapy (NAC) alone for locally advanced rectal cancer (LARC) remains an experimental treatment, and the efficacy in terms of long-term outcome has not been fully elucidated. The N-SOG 03 trial examined the safety and efficacy of neoadjuvant CAPOX and bevacizumab (Bev) without radiotherapy in patients with poor-risk LARC.

Methods Thirty-two patients with MRI-defined LARC received neoadjuvant CAPOX and Bev followed by curative resection between 2010 and 2011. The overall survival (OS), progression-free survival (PFS), and local-relapse rate (LRR) were calculated using the Kaplan–Meier method, and the risk factors were evaluated by multivariate analysis using the Cox proportional hazard models. This trial is registered with UMIN, number 000003507.

Results In the entire cohort, the 5-year OS was 81.3%. Because of disease progression during chemotherapy, 3 patients ultimately did not undergo curative surgery. As a result, 29 patients underwent R0/1 resection. Among these 29 patients, the 5-year OS, PFS, and LRR were 89.7%, 72.4% and 13.9%, respectively. In multivariate analysis, cT4b tumor was an independent poor prognostic factor for OS and LRR, and ypT4b tumor and absence of N down-staging were independent poor prognostic factors for PFS.

Conclusions Patients with cT4b tumor were not suitable for NAC alone. However, the long-term outcomes of the other patients were satisfactory, and NAC alone might be an option for treatment of LARC. N down-staging was likely to bring favorable PFS, even in patients with cStage III.

Keywords Rectal cancer · Neoadjuvant chemotherapy · Phase II trial · Outcome

Introduction

Although preoperative fluorouracil (FU)-based chemoradiotherapy (CRT) remains the state of the art in the treatment of locally advanced rectal cancer (LARC) with favorable local control, it has no impact on survival [1–5]. To improve survival, systemic chemotherapy has been adopted in a supporting or a leading role in preoperative treatment, combined with FU-based CRT [6–10]. Recently, to control both local and systemic disease, a concept of "total neoadjuvant

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therapy" has been proposed [11]. This new concept emphasizes local control leading to non-surgical treatment and improved survival. However, when we aim for non-surgical treatment and fail to omit subsequent surgical resection, there might be overtreatment for some patients. It is an important but difficult problem to choose the best approach for individual patients.

Neoadjuvant chemotherapy (NAC) alone is an experimental approach for LARC. It can avoid both early and late adverse effect of radiotherapy (RT), and can shorten the treatment period and save costs. Although two small trials demonstrated the safety and efficacy of NAC alone for low-risk and intermediate-risk LARC [12, 13], preoperative CRT is generally considered mandatory, and its omission presents the risk of increasing local relapse [14]. Currently, in Japan, the standard treatment for LARC remains initial primary resection followed by adjuvant chemotherapy. The Japanese guidelines do not recommend preoperative CRT, even for poor-risk disease, although neither survival nor local control is satisfactory [15]. Therefore, NAC for LARC has been gradually accepted as an option in Japan, because it is an easy method with small changes only to shift a part of adjuvant chemotherapy to the preoperative period. Several single-arm phase II trials including patients with poor-risk disease demonstrated safety and short-term efficacy [16–20].

The N-SOG 03 trial was a multi-center phase II trial that started in 2010 and examined the safety and efficacy of neoadjuvant capecitabine (Cap) and oxaliplatin (Ox) (CAPOX) and bevacizumab (Bev) without RT in patients with poor-risk LARC. The short-term results including the safety, treatment compliance, and adverse events were reported in 2013 [16]. Briefly, although the short-term results with the completion rate of 84.4% were met to the endpoint, it caused a high rate of anastomotic leakage and experienced a case with perforation during chemotherapy, both of which were bevacizumab-related toxicity. Here we reported the long-term outcomes and a planned analysis of risk factors for poor outcomes.

Patients and methods

This multi-center, single-arm, prospective phase II trial was designed by the Nagoya Surgical Oncology (N-SOG) Group (UMIN 000003507). The protocol was approved by the institutional review boards of all participating hospitals. Written informed consent was obtained from each patient before enrollment. Seven participating hospitals enrolled patients between February 2010 and December 2011.

The primary endpoint was treatment compliance, evaluated according to the rate of completion of scheduled treatments. Secondary endpoints were overall survival (OS), progression-free survival (PFS), local relapse rate (LRR), objective response rate, R0 resection rate, pathological response rate and adverse events.

Eligibility

Inclusion criteria were as follows: (1) histologically proven rectal adenocarcinoma; (2) lower edge of the tumor located under the lower edge of the second sacrum; and (3) magnetic resonance imaging (MRI)-defined poor-risk rectal cancer. MRI-defined poor-risk rectal cancer had to fulfill at least one of the following criteria: tumor extending to within 1 mm of or beyond the mesorectal fascia [i.e., circumferential resection margin (CRM) involved or threatened], tumor extending 5 mm into peripheral fat, tumor invading surrounding structures or peritoneum (cT4) or any TN2 tumors. Patients with metastatic disease were excluded.

Neoadjuvant chemotherapy

Bev 7.5 mg/kg was administered on day 1 and was followed on the same day by Ox 130 mg/m2. Cap was administered orally at a dose of 2000 mg/m^2/day, divided into two split daily doses for 14 days followed by 7 days of rest. This regimen was repeated every 3 weeks. Treatment was administered for 4 cycles, but the fourth cycle of therapy did not include Bev.

Surgery and adjuvant chemotherapy

Surgery was performed between 3 and 8 weeks after the completion of chemotherapy. Total mesorectal excision (TME) was performed but combined resection of the surrounding organs was performed at the surgeons' discretion. No adjuvant chemotherapy was allowed after R0 resection. For patients with consequent R1/2 resection or non-resection, subsequent therapy was not stipulated and was determined by each clinician.

Histopathology

Resected specimens were subjected to conventional processing. Grades of histopathological regression were assessed according to colorectal carcinoma classification [21]. Patients were divided into two groups: responder (pathological complete response (pCR) or necrosis of more than two-thirds of the lesion) and non-responder (necrosis of less than two-thirds of the lesion).

Follow-up

Carcinoembryonic antigen and carbohydrate antigen 19–9 were measured at registration and every 3 months during the first 5 years after surgery. Recurrence was diagnosed

based on the chest and abdominopelvic computed tomography, performed at 6-month intervals during the first 5 years after surgery.

Statistical analysis

The planned sample size was 30 patients, calculated by the Southwest Oncology Group's two-stage attained design based on a target rate of treatment completion of 90% and a minimum completion rate of 70%, with an *a* error of 0.05 and a *b* error of 0.15 [22].

PFS was measured from date of registration to date of disease relapse or death from any cause, and OS was calculated from date of registration to date of death from any cause or censorship at last follow-up. Actuarial curves were calculated by the Kaplan–Meier method and were compared by the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model to investigate the predictive factors for poor OS, PFS and LRR. All tests were two-sided. A value of $p < 0.05$ was considered statistically significant. Statistical analyses were done using SPSS software version 23.0 (SPSS Inc., Chicago, IL, USA).

Results

Thirty-two patients (28 males and 4 females; median age 62 years) with MRI-defined poor-risk LARC started neoadjuvant CapeOX and Bev. Figure 1 shows a flowchart of the enrolled 32 patients. Twenty-nine patients completed the scheduled chemotherapy and 27 of these underwent R0/1 resection within the predetermined period. An additional 2 patients underwent R0/1 resection with deviation from the protocol treatment and 29 patients finally underwent R0/1 resection.

The clinical characteristics of the 32 patients are summarized in Table 1. Ten patients (31.3%) had cT4b disease, and 12 patients (37.5%) had cN2 disease. In 29 patients who underwent R0/1 resection, pCR was observed in 4 (13.8%), and 11 (37.9%) were judged as pathological responders. The T and N down-staging rates were 62.1% and 75.9%, respectively. Four of 7 (57.1%) patients with cT4b were finally diagnosed as having ypT4b (Table 2).

Survival

As of March 2017, 63 months had passed since the last patient was registered in this trial. No patients missed the follow-up survey. The median follow-up time was 65.3 (2.3–85.7) months. During the follow-up period, 8 patients died of the primary disease, including 3 patients with R2 resection or without resection. In the entire cohort, the 5-year OS was 81.3%. Among the 29 patients with R0/1 resection, recurrence developed in 8 patients (27.6%). The most common relapse site was the lung ($n = 4$), followed by local recurrence ($n = 3$), and liver ($n = 2$). Among these 29 patients, the 5-year OS, PFS, and LRR were 89.7%, 72.4%, and 13.9%, respectively. All 3 patients with R2 resection or

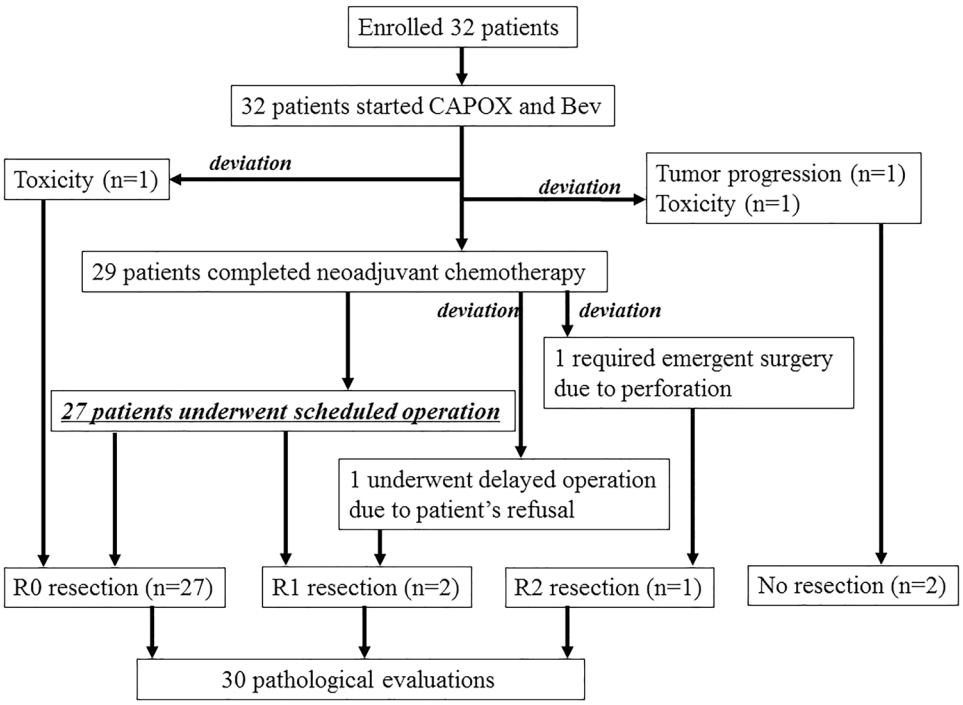

Fig. 1 Flowchart of enrolled 32 patients

Table 1 Characteristics of patients and disease ($n=32$)

	No.	%
Distance from the AV to tumor (cm)		
<5	16	50.0
5≤, <9	11	34.4
≥9	5	15.6
cT stage		
T3	13	40.6
T4a	9	28.1
T4b	10	31.3
cN stage		
N0	6	18.7
N1	14	43.8
N2	12	37.5
Poor risk factor on MRI (overlapped)		
CRM < 1 mm	16	50.0
cT4b	10	31.3
cN2	12	37.5
Mesorectal invasion ≥5 mm	21	65.6
Operative procedures ($n=30$)		
Low anterior resection	11	36.7
Intersphincteric resection	7	23.3
Hartmann	2	6.7
Abdominoperineal resection	7	23.3
Total pelvic exenteration	3	10.0
Residual tumor classification ($n=30$)		
R0	27	90.0
R1	2	6.7
R2	1	3.3
Tumor regression grading (JSCCR) ($n=30$)		
Responder	11	36.6
Non-responder	19	63.4
ypT stage ($n=30$)		
pCR	4	13.3
Tis	1	3.3
T1	2	6.7
T2	3	10.0
T3	15	50.0
T4b	5	16.7
ypN-stage ($n=30$)		
N0	26	86.7
N1	4	3.3

AV anal verge, *MRI* magnetic resonance imaging, *CRM* circumferential resection margin, *JSCCR* Japanese Society for Cancer of the Colon and Rectum, *pCR* pathological complete response

without resection had cT4b disease, and their median OS was 7.5 months (2.3–11.3 months).

Risk factor analysis

Table 2 shows the univariate and multivariate analysis of OS using the Cox proportional hazards regression model in 29 patients with R0/1 resection. Univariate analysis revealed that cT4b disease ($p=0.002$), ypT4b disease ($p=0.006$), and absence of T down-staging ($p=0.038$) were the possible prognostic indicators of poor OS. In multivariate analysis using these possible factors with p value of less than 0.1, cT4b disease remained an independent poor prognostic factor for OS (Fig. 2a).

Table 3 demonstrates the univariate and multivariate analysis of PFS and LRR in 29 patients with R0/1 resection. Regarding PFS, univariate analysis indicated that patients with cT4b disease ($p=0.014$), ypT4b disease ($p=0.002$), and without T down-staging ($p=0.008$) or N down-staging ($p=0.042$) had poor outcome. In multivariate analysis, ypT4b disease and absence of N-down-staging remained independent poor prognostic factors for PFS (Fig. 2b, c). The results for LRR were similar to those for OS. Univariate analysis indicated that cT4b disease ($p=0.006$), ypT4b disease ($p=0.012$), and absence of T down-staging ($p=0.010$) were potential poor indicators. In multivariate analysis, only cT4b disease remained an independent poor indicator of LRR (Fig. 2d).

Discussion

Hoping to achieve both local control and reduction of distant relapse, we introduced Ox-based NAC without RT in treatment of poor-risk LARC. Two small phase II trials were conducted in our regional study groups, and we previously reported the short-term results [16, 18]. In this long-term analysis, we found that patients with cT4b tumor had significantly poor OS and LLR. On the other hand, we confirmed that N down-staging provided favorable PFS even in clinical stage III patients.

Poor-risk LARC is a heterogeneous group including patients with large T factor, widespread N factor, or both. Naturally, this study included patients with various conditions including cT4, involved or threatened circumferential resection margins, tumors extending 5 mm into peripheral fat, and cN2. In the era of advanced chemotherapy and radiotherapy, the best preoperative treatment for whole LARC might not be standardized, and we have to establish the best treatment for individual patients with each risk factor. We hope that this small phase II trial may provide value regarding preoperative use of chemotherapy for poor-risk LARC.

Needless to say, the efficacy of preoperative CRT in local control remains unquestionable. The FOWARC trial, which investigated differences of efficacy in preoperative treatment in China, clearly demonstrated the superior effect with

Table 2 Univariate and multivariate analysis of OS using the Cox proportional hazards regression model in 29 patients with R0/1 resection

	n	5y-OS	*p*	HR	95% CI	*p*
Gender			0.525			
Male	25	92.0				
Female	4	75.0				
BMI			0.094			0.351
≥23	10	100				
<23	19	84.2				
Distance from AV			0.091			0.107
≥60 mm	11	100				
<60 mm	18	83.3				
cT stage			0.002	0.071	(0.008–0.641)	0.019
T4b	7	57.1				
T4a or less	22	100				
cN stage			0.870			
cN0/1	18	88.9				
cN2	11	90.9				
cCRM			0.779			
Negative	16	93.8				
Positive	13	84.6				
Mesorectal invasion			0.503			
<5 mm	10	90.0				
≥5 mm	19	89.5				
Response to chemotherapy			0.100			0.235
Responder	11	100				
Non-responder	18	83.3				
ypT stage			0.006			0.736
T4b	4	96.0				
T4a or less	25	50.0				
ypN stage			0.399			
N0	25	88.0				
N1/2	4	100				
T down-staging			0.038			0.298
Yes	18	94.4				
No	11	81.8				
N down-staging			0.758			
Yes	22	90.9				
No	7	85.7				

OS overall survival, *BMI* body mass index, *AV* anal verge, *CRM* circumferential resection margin

respect to local control in the CRT groups compared to those in the chemotherapy alone group [23]. In the FOLFOX alone group, the pCR and down-staging rate were 6.6% and 35.5%, respectively, whereas in the FU-based CRT group, these values were 14.0% and 37.1%, respectively, and in the FOLFOX-RT group, they were 27.5% and 56.4%, respectively. Nevertheless, several large trials that contributed a framework for the prominent guidelines avoided cT4b disease. In the Dutch trial, patients with fixed tumors were excluded, and no patients underwent extended surgery combined with adjacent organs [1]. In the German trial, only 33 of 799 eligible patients (4.1%) had cT4 tumors [4]. In the EORTC 22921 trial, eligibility criteria included cT3 or resectable cT4M0 and 101 of 1011 eligible patients (10.0%) had cT4 tumors [24]. It is difficult to say that treatment strategy for cT4b tumor has been established.

In this trial, the outcome of patients with cT4b was disastrous. All 3 patients with R2 resection or without resection had cT4b disease, and their median OS was only 7.5 (2.3–11.3) months. Additionally, only a risk factor for poor OS among the other patients was still cT4b. The long-term survival of cT4b patients after pelvic exenteration was reported from a leading Japanese hospital [25]. Initial surgery was performed in 81.2%, and the 5-year OS and

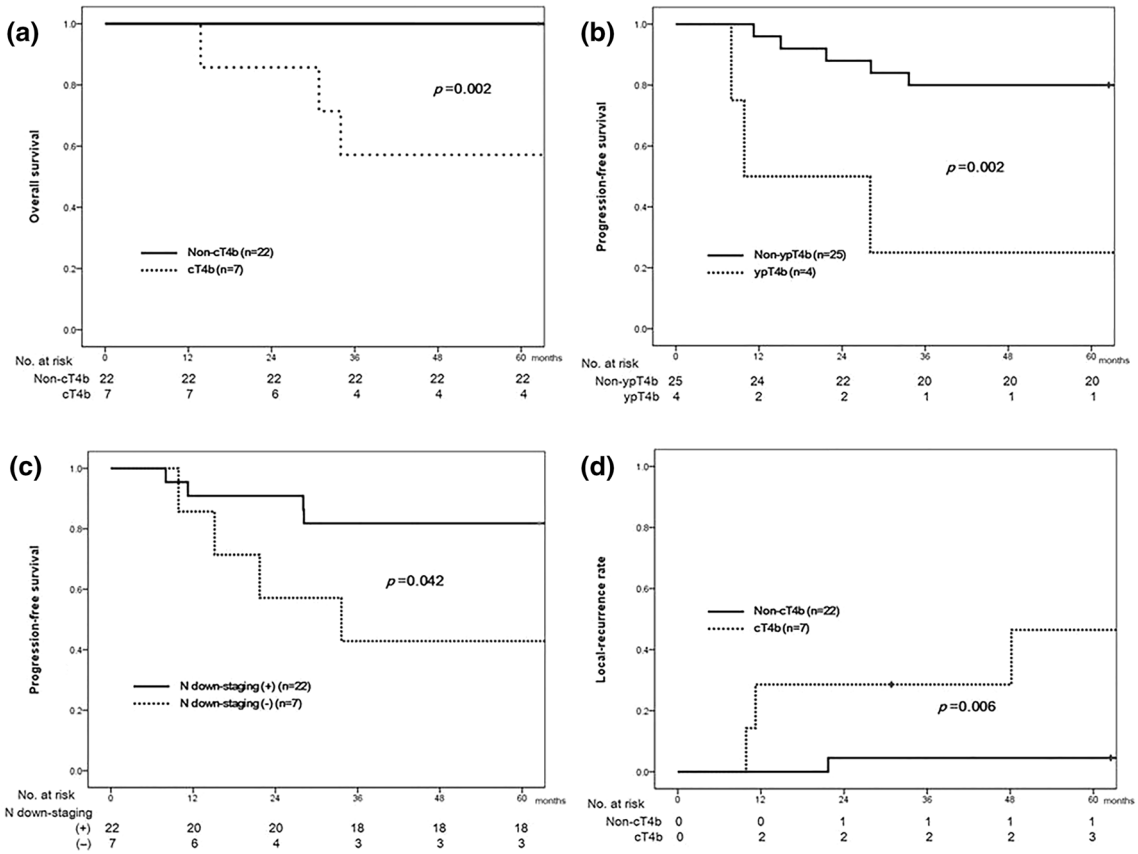

Fig. 2 **a** Patients with cT4b disease had significantly poorer OS than those with non-cT4b ($p=0.002$). **b, c** ypT4b and absence of N down-staging were significant prognostic factors for poor PFS ($p=0.002$ and 0.042, respectively). **d** Local relapse occurred significantly more often in patients with cT4b tumor ($p=0.006$)

PFS were 52% and 46%, respectively, similar to our data. NAC is unlikely to improve the outcome and preoperative CRT should not be omitted cavalierly for patients with cT4b tumor. If the initial chemotherapy is introduced, a more powerful regimen, including FOLFOXIRI with or without Bev, should be considered and subsequent CRT should be undertaken especially for non-responders to NAC. Conversely, the 5-year OS of 100% and LLR of 4.4% in the remaining patients were favorable. The omission of CRT might be an option for LARC excluding cT4b tumors.

Regarding N factors, 37.5% of 32 patients had cN2 disease and 81.3% had clinically positive LNs in this study. Nevertheless, in 29 patients with R0/1 resection, the 5-year OS and PFS of 89.7% and 72.4%, respectively, were satisfactory. The high N down-staging rate of 75.9% was a possible reason and only 4 patients (13.3%) had pathological LN metastasis. NAC might introduce favorable N down-staging and improve survival. Initial treatment with systemic chemotherapy is a promising option for LARC with clinically positive LNs. Conversely, when N down-staging cannot be achieved and pathological LN metastasis remains, the outcome is likely to be poor. This result is similar to that of patients with metastatic LNs after preoperative CRT [26]. Stage III patients without N down-staging in the preoperative re-evaluation after NAC should be treated with additional CRT. On the other hand, the ADORE trial conducted in Korea showed that Ox-based adjuvant chemotherapy significantly improved disease-free survival in patients with ypStage III after CRT [27]. Although no patients received adjuvant chemotherapy in this study based on the protocol, it is imperative for patients with ypStage III after NAC.

The limitations of the present study include its small sample size and single-arm nature. Moreover, the significance of adjuvant chemotherapy could not be discussed, because of the protocol stipulations. However, we could clearly show the efficacy of NAC for LN metastasis and its lack of efficacy for cT4b tumor. Establishment of treatment strategies for cT4b tumor is urgently desired.

Conclusions

Patients with cT4b tumor were not suitable for NAC alone. However, the long-term outcomes of the other patients were satisfactory, and NAC alone might be an option of

Table 3 Univariate and multivariate analysis of PFS and LRR using the Cox proportional hazards regression model in 29 patients with R0/1 resection

	n	PFS					LRR				
		5y-PFS	*p*	HR	95% CI	*p*	5y-LRR	*p*	HR	95% CI	*p*
Gender			0.984					0.418			
Male	25	72.0					12.2				
Female	4	75.0					25.0				
BMI			0.919					0.652			
≥ 23	10	70.0					10.0				
< 23	19	73.7					16.1				
Distance from AV			0.319					0.528			
≥ 60 mm	11	81.8					9.1				
< 60 mm	18	66.7					16.7				
cT stage			0.014			0.769		0.006	0.082	(0.008–0.792)	0.031
T4b	7	42.9					46.4				
T4a or less	22	81.8					4.5				
cN stage			0.421					0.553			
cN0/1	18	66.7					16.7				
cN2	11	81.8					10.0				
cCRM			0.746					0.778			
Negative	16	68.8					12.5				
Positive	13	76.9					15.4				
Mesorectal invasion			0.559					0.469			
< 5mm	10	80.0					20.0				
≥ 5mm	19	68.4					10.8				
Response to chemotherapy			0.097			0.437		0.099			0.221
Responder	11	90.9					0				
Non-responder	18	61.1					22.6				
ypT stage			0.002	0.086	(0.016–0.452)	0.004		0.012			0.667
T4b	4	25.0					8.0				
T4a or less	25	80.0					62.5				
ypN stage			0.220					0.406			
N0	25	68.0					16.2				
N1/2	4	100					0				
T down-staging			0.008			0.167		0.100			0.277
Yes	18	88.9					5.6				
No	11	45.5					28.4				
N down-staging			0.042	6.013	(1.269–28.490)	0.024		0.175			
Yes	22	81.8					9.3				
No	7	42.9					28.6				

PFS progression-free survival, *LRR* local recurrence rate, *BMI* Body Mass Index, *AV* anal verge, *CRM* circumferential resection margin

the treatment for LARC. N down-staging was likely to give favorable PFS even in patients with cStageIII.

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Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the insti-

tutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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