Acta Med. Nagasaki 66: 13－19

Neoadjuvant chemotherapy in locally advanced colorectal cancer: a Japanese multicenter study

Keisuke Noda[1,4], Tetsuro Tominaga[1], Takashi Nonaka[1], Masato Araki[2], Yorihisa Sumida[2], Hiroaki Takeshita[3], Hidetoshi Fukuoka[4], Kazuo To[5], Kenji Tanaka[6], Terumitsu Sawai[1], Takeshi Nagayasu[1]

[1] Department of Surgical Oncology, Nagasaki University Graduate School of Biomedical Science, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan
[2] Department of Surgery, Sasebo City General Hospital, 9-3 Hirasemachi, Nagasaki 857-8511, Japan
[3] Department of Surgery, National Hospital Organization Nagasaki Medical Center, 1-1001-1, Omura, Nagasaki 856-8562, Japan
[4] Department of Surgery, Isahaya General Hospital, 24-1, Isahaya, Nagasaki 854-8501, Japan
[5] Department of Surgery, Ureshino Medical Center, 4279-3, Ureshino, Saga 843-0393, Japan
[6] Department of Surgery, Saiseikai Nagasaki Hospital, 2-5-1 Katafuchi, Nagasaki 850-0003, Japan

Purpose: The impact of neoadjuvant chemotherapy for locally advanced colorectal cancer has not yet been investigated; thus, this study aimed to examine the safety, feasibility, and oncological effects of neoadjuvant chemotherapy for locally advanced colorectal cancer.
Methods: In this multicenter study, we retrospectively reviewed the data of 83 locally advanced colorectal cancer patients (cT3/4 or N1/2) who received neoadjuvant chemotherapy followed by radical resection between April 2016 and September 2020. The NAC regimens were FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin), XELOX (capecitabine and oxaliplatin), or SOX (S-1 and oxaliplatin). We evaluated the pathological responses as well as the short- and long-term outcomes.
Results: A pathological complete response was achieved in 4 patients (4.8%). Tumor down-staging and nodal down-staging were achieved in 57 (68.7%) and 49 (59.0%) patients, respectively. One patient (1.2%) experienced progressive disease. Postoperative complications occurred in 21 patients (25.3%). Multivariate analysis revealed that the pathological N positive status (p = 0.015; odds ratio, 4.458; 95% confidence interval, 1.331 to 7.9300) was an independent predictive factor for relapse-free survival.
Conclusion: Neoadjuvant chemotherapy for colorectal cancer could achieve good tumor control and down-staging without increasing the rate of complications. Appropriate preoperative treatment that can reduce the rate of the pathological node-positive disease may improve oncological outcomes.

ACTA MEDICA NAGASAKIENSIA 66: 13－19, 2022

Key words: neoadjuvant chemotherapy, colorectal cancer, pathological node-positive

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer death[1]. Complete tumor resection with margin negative resection (R0) is the standard curative modality for localized colon cancer[2]. However, locally advanced colon cancer (LACC) and locally advanced rectum cancer (LARC) often involve bulky tumors that directly invade adjacent organs, and there is often extensive nodal involvement, which could result in margin positive resection or micro-metastases[3,4]. Several studies have examined the effectiveness of neoadjuvant treatment for shrinking tumors to increase the likelihood of achieving a complete resection and decrease tumor cell shedding during surgery[5-7].

Address correspondence: Tetsuro Tominaga
Department of Surgical Oncology, Nagasaki University Graduate School of Biological Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan
Phone: +81-95-819-7304; Fax: +81-95-819-7306; E-mail: tetsuro.tominaga@nagasaki-u.ac.jp

Received December 21, 2021; Accepted February 5, 2022

Chemoradiotherapy (CRT) followed by surgery is the current standard treatment for LARC, and several randomized studies have shown that CRT reduces the local recurrence rate[5,6]. However, these studies failed to prove the oncological benefit of CRT. In addition, CRT may lead to radiation-induced disorders that end up decreasing the quality of life of the patient. Neoadjuvant chemotherapy (NAC) alone is being explored as an alternative treatment for LARC to avoid the early and late side effects of radiotherapy[8,9]. However, reports on NAC for LARC are limited[8-11].

Regarding LACC, the National Comprehensive Cancer Network (NCCN) guidelines weakly recommend NAC using FOLFOX/CapeOX only for primary colon cancers that have invaded adjacent organs[12]. A recent FOxTROT study demonstrated that patients who underwent NAC had significantly fewer postoperative complications and a significantly better R0 resection rate[7]. The long-term oncological benefits of NAC for LACC have not yet been proven, and there is no strong evidence to support its use. Longer follow-up periods and further trials are required to confirm its long-term benefits, refine its use, and optimize case selection.

This multicenter study aimed to examine the safety and feasibility of NAC for locally advanced CRC, and also to investigate the prognostic factors in CRC patients receiving NAC.

Methods

This multicenter retrospective study was designed by the Nagasaki Colorectal Oncology Group. We reviewed the collected data of 2496 consecutive patients who underwent colorectal surgery in six participating hospitals between April 2016 and September 2020. Patients who received NAC followed by radical resection with curative intent were included. The following patients were excluded: those who had undergone radiation therapy, emergency surgery, or a procedure for unresectable cancer (bypass or stoma), and those who had distant metastasis of synchronous colon cancer or incomplete laboratory data. Finally, a total of 83 patients were included in the analysis. Informed consent was obtained from each of these patients for the use of their data in this study. The study was reviewed and approved by the Clinical Research Review Boards of all participating hospitals. The study was performed by the ethical standards laid down in the 1964 Declaration of Helsinki.

The following patient data were collected: sex, age, body mass index (BMI), American Society of Anesthesiologists (ASA) performance status (PS), comorbidities, tumor location (right side colon, left side colon, or rectum), clinical T/N status, and NAC regimen. The NAC regimens were FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin), XELOX (capecitabine and oxaliplatin), or SOX (S-1 and oxaliplatin). NAC was administered using the standard dose and schedule used in daily clinical practice. The specific toxicity profile of each regimen and the differences in the incidences of some side effects were explained to the patients. We performed NAC for patients with clinical T4 and/or N2. However, the final decision on the indication or regimen was based on the preferences of the patients and physicians. Patients received to 6 cycles before surgical assessment according to the treating physician's criteria. Surgical and pathological data that were collected included the operation time, blood loss, postoperative complications, hospital stay, pathological T/N status, number of retrieved lymph nodes, the presence or absence of lymphovascular invasion, tumor differentiation, attainment of a pathological complete response (pCR), tumor regression grade, and the presence or absence of T/N down-staging. The presence of postoperative complications was defined as the presence of Clavien-Dindo (CD) complications grade 2 or higher occurring within 30 days of the operation. We usually perform 5-fluorouracil-based adjuvant chemotherapy (AC) within 8 weeks of the initial surgery for patients with the pathological node-positive disease or patients with the node-negative disease with high-risk factors for recurrence, such as lymphovascular invasion, T4 cancer, and poorly differentiated adenocarcinoma.

The data are presented as the median values with ranges. Survival curves were constructed by the Kaplan–Meier method with the log-rank test. Multivariate analysis using a Cox proportional hazards model was performed to identify the independent risk factors for relapse-free survival (RFS) and overall survival (OS). Variables with a p-value less than 0.05 in the univariate analysis were examined by multivariate analysis. All p-values less than 0.05 were statistically significant. Statistical analysis was performed using Bell Curve for Excel software version 2.02 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

Results

Table 1 lists the clinical and surgical characteristics of the 83 patients. The population included 58 males and 23 females with a median age of 67 years (range, 40 to 83 years). The median BMI was 22.0 kg/m^2 (range, 15 to 33 kg/m^2). Poor PS (PS $\geq$ 2) was observed in 62 patients (74.7%), and 47 patients (56.6%) had comorbidities. Most patients had rectum

Table 1. Patient characteristics

	All patients (n = 83)
Sex	
Male	58 (69.9%)
Female	23 (30.1%)
Age, years (range)	67 (40 – 83)
Body mass index, kg/m^2	22 (15 – 33)
ASA performance status	
1	21 (25.3%)
2	60 (72.3%)
3	2 (2.4%)
Comorbidity, present	47
Tumor location	
Right side colon	8 (9.6%)
Left side colon	17 (20.5%)
Rectum	58 (69.9%)
Clinical T factor	
3	33 (39.8%)
4a	28 (33.7%)
4b	22 (26.5%)
Clinical N factor	
0	8 (9.6%)
1	36 (43.4%)
2	39 (47.0%)
Preoperative chemotherapy	
FOLFOX	28 (33.7%)
XELOX	22 (26.5%)
SOX	33 (39.8%)
Operation time, min (range)	411 (61 – 791)
Blood loss, mL (range)	115 (0 – 3935)
Postoperative complications, CD ≥ 2	21 (25.3%)
Hospital stay, days (range)	16 (8 – 60)

Data are presented as the number of patients (%) or the median (range)
ASA, American Society of Anesthesiologists; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; XELOX, capecitabine and oxaliplatin; SOX, S-1 and oxaliplatin; CD, Clavien–Dindo classification

Table 2. Pathological results and tumor responses to neoadjuvant treatment

	All patients (n = 83)(%)
ypT status	
0	4 (4.8%)
1	4 (4.8%)
2	21 (25.3%)
3	43 (51.8%)
4a	4 (4.8%)
4b	7 (8.4%)
ypN status	
0	56 (67.5%)
1	13 (15.7%)
2	14 (16.9%)
Retrieved lymph nodes, median (range)	20 (0 – 62)
Lympho-vascular invasion	
No	40 (48.2%)
Yes	43 (51.8%)
Tumor differentiation	
Well	67 (80.7%)
Moderate	10 (12.0%)
Poor	6 (7.2%)
Pathological complete response	
No	79 (95.2%)
Yes	4 (4.8%)
Tumor regression grade	
1	4 (4.8%)
2	20 (24.1%)
3	22 (26.5%)
4	30 (36.1%)
5	7 (8.4%)
Pathological T stage	
Down-staged	57 (68.7%)
Stable	25 (30.1%)
Progressive	1 (1.2%)
Pathological N stage	
Down-staged	49 (59.0%)
Stable	33 (39.8%)
Progressive	1 (1.2%)

Data are presented as the number of patients (%) or the median (range)

cancer (n = 58; 69.9%). Twenty-eight patients (33.7%) received FOLFOX, 22 patients (26.5%) received XELOX, and 33 patients (39.8%) received SOX. The median operation time was 411 min (range, 61 to 791 min), and the median blood loss was 115 mL (range, 0 to 3935 mL). Postoperative complications (CD ≥ 2) occurred in 21 patients (25.3%).

Table 2 shows the pathological results and tumor responses to NAC. Four patients (4.8%) achieved ypT0 (pCR), and 56 patients (67.5%) achieved ypN0. The median number of lymph nodes retrieved was 20 (range, 0 to 62). Major regression (TRG 1) and moderate regression (TRG 2) were achieved in 4 patients (4.8%) and 20 patients (24.1%), respectively. Comparisons between the changes in the clinical and pathological stages revealed that primary tumor down-staging and nodal down-staging were achieved in 57 patients (68.7%) and 49 patients (59.0%), respectively.

Table 3 shows the ability of the clinical factors to predict the RFS and OS. Univariate analysis revealed that the pathological N positive status was significantly associated with the RFS, and that rectum cancer, pathological T4 status, and pathological

Table 3. Univariate and multivariate analyses of clinical factors that predict the long-term outcome

	Relapse-free survival				Overall survival			
	Univariate analysis	Multivariate analysis			Univariate analysis	Multivariate analysis		
	P value	Odds ratio	95%CI	P value	P value	Odds ratio	95%CI	P value
Sex	0.808				0.615			
Female								
Male								
Age, years	0.862				0.782			
<70								
≥ 70								
ASA performance status	0.770				0.735			
1 – 2								
3								
Location	0.137				0.023			0.205
Colon						1		
Rectum						0.256	0.031 – 2.110	
Pathological T status	0.089			0.375	0.013			0.581
1 – 3		1				1		
4		1.821	0.438 – 6.868			1.768	0.232 – 13.454	
Pathological N status	0.003			0.015	0.042			0.098
No		1				1		
Yes		4.458	1.331 – 7.930			6.405	0.701 – 10.499	
Adjuvant chemotherapy	0.208				0.860			
No								
Yes								

HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologists
A Cox proportional hazards model was used to identify independent risk factors for the long-term outcome

N positive status were significantly associated with the OS. Multivariate analysis revealed that the pathological N positive status (p = 0.015; odds ratio, 4.458; 95% confidence interval, 1.331 to 7.9300) was an independent predictive factor for the RFS.

Figure 1 shows the survival outcomes in CRC patients with NAC. The median duration of follow-up was 36 months. Overall, patients with pathological node-positive disease showed a poor RFS rate (51.9% vs. 87.8% at 3 years; p = 0.003) and OS rate (73.9% vs. 97.3% at 3 years; p = 0.006) when compared to patients with pathological node-negative disease (Fig. 1a, 1b). When cohorts were subdivided by the presence or absence of AC, patients who received AC showed a poor 3-year RFS rate (85.1% vs. 90.0% in node-negative cases; 55.6% vs. 100% in node-positive cases; p = 0.024) and a poor 3-year OS rate (96.1% vs. 100% in node-negative cases; 76.5% vs. 100% in node-positive cases; p = 0.148; Fig. 1c, 1d). Among the pathological N-positive patients who underwent AC, 3-year RFS and OS were similar between patients with N1 and N2 (Fig. 1e, 1f).

Discussion

In the present multicenter study, we investigated the safety and feasibility of NAC for locally advanced CRC, and we also examined the prognostic factors in CRC patients receiving NAC. The tumors were well controlled by NAC (the disease control rate was 98.8%) without any increase in the rate of perioperative complications. Multivariate analysis revealed that pathological node-positive disease was an independent prognostic factor.

One of the advantages of NAC is down-staging. Down-staging enables easier surgical resection, increasing the likelihood of complete resection, and decreasing tumor cell shedding at the time of surgery[13]. In addition, reducing the number and viability of tumor cells that can invade lymph nodes and blood vessels or spread locally within the bowel and adjacent peritoneum is likely to lower the micrometastatic rate[14].

Regarding LACC, Jan-Marie de Gooyer et al. reported that in a study of 149 patients who underwent NAC for LACC, 13 (8.7%) clinical T4 tumors were down-staged to pT0-2,

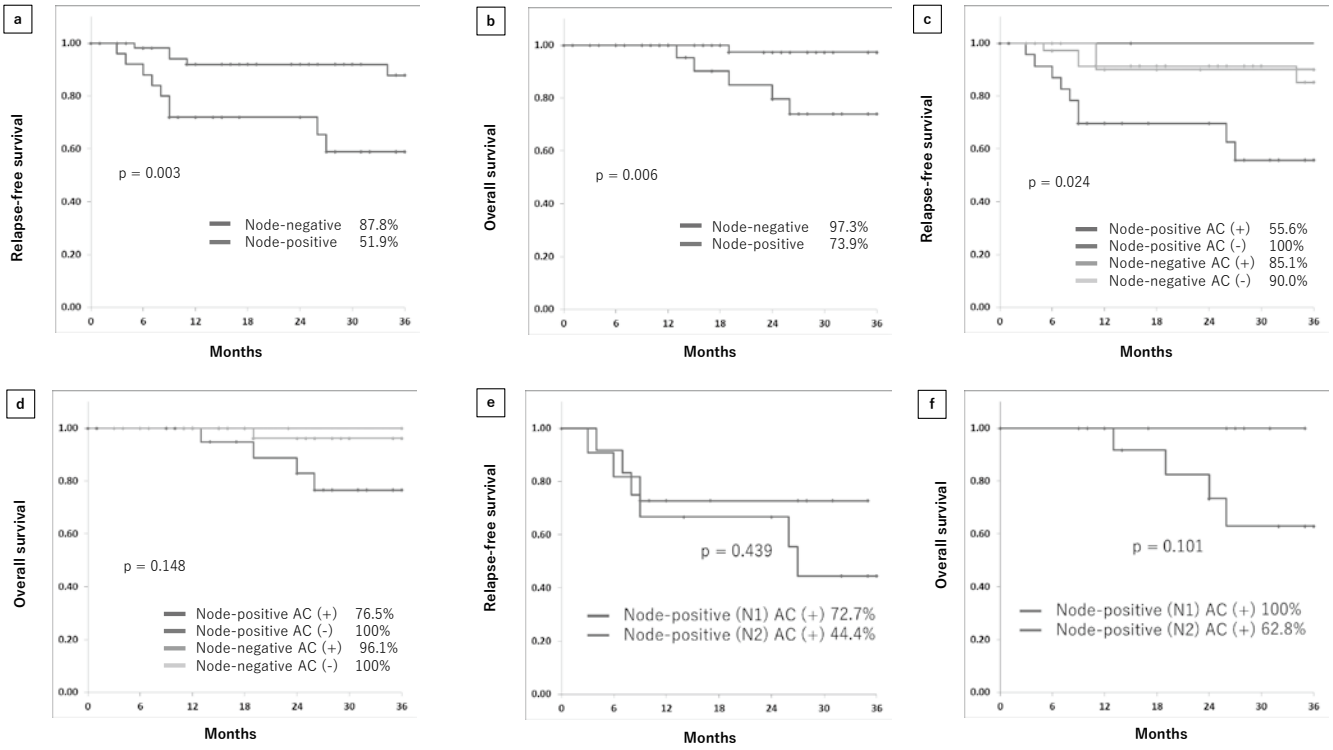

Figure 1. Comparison between pathological node-positive and negative for relapse-free survival (1a) and overall survival (1b). The cohorts were subdivided by the presence or absence of AC for relapse-free survival (1c) and overall survival (1d). AC, Adjuvant chemotherapy; N, node

and 5 tumors were suggested to be pT0. In addition, nodal down-staging was suggested in 34 of 65 patients (52%) who were clinically node-positive[15]. According to a FOxTROT study that examined the efficacy of NAC for LACC, 31% of tumors in the NAC group showed moderate to complete regression as compared to 2% in the control series. There were reductions in the tumor diameter, tumor thickness, and depth of spread beyond the muscularis propria in the preoperatively treated group when compared to the controls[7].

Regarding NAC for LARC, previous reports showed that T down-staging was achieved in 37% to 67% of cases, and N down-staging was achieved in 56% to 70% of cases[10, 11]. Furthermore, pCR was achieved in 8.2% to 41.9% of cases. In the present study, T down-staging was seen in 68.7% of cases, and N down-staging was seen in 59.0% of cases, which are similar to the previous reports. However, the pCR rate was lower (4.8%) when compared to the previous studies. One possible explanation is that the NAC regimens may have differed. In the studies that revealed favorable pCR rates, NAC was performed with bevacizumab (BEV), which was expected to provide a synergistic effect[10, 11, 12]. Arimoto et al. examined 47 LARC patients who received NAC with or without BEV; the T down-staging and N down-staging rates were 67.7% and 67.7%, respectively, in patients with BEV, and 37.5% and 56.3%, respectively, in patients without BEV[11]. A pCR was achieved in 41.9% of the patients with BEV, and in 12.5% of the patients without BEV. Although a synergistic antitumor effect was seen with BEV, there are serious drawbacks to using BEV for NAC, e.g., the use of BEV may increase the rate of severe postoperative complications, including anastomotic leakage due to wound healing delays, as a side effect[16, 17, 18]. Previous studies have reported that 32.0% to 43.3% of LARC patients who received BEV for NAC experienced severe postoperative complications, including anastomotic leakage, pelvic sepsis, and ileus[10, 19]. The relatively lower rate of postoperative complications (25.3%) in our study might be because we did not use BEV for NAC.

In the present study, the pathological N positive status was an independent predictor of the RFS. This result suggests that NAC alone is insufficient for improving the prognosis of patients with clinical 'advanced' node metastasis. Indeed, among the 27 patients with pathological node-positive disease, 14 patients (51.9%) had clinical 'advanced' node metastasis (N2). Recently, total neoadjuvant therapy (TNT) has been introduced for the treatment of advanced rectal cancer[20, 21]. TNT is an intensive preoperative treatment that combines preoperative chemotherapy and preoperative chemoradiation. The pCR rate is reported to be about 30% to 40%[22-24].

Currently, the NCCN guidelines state that TNT is an option for T3 tumors and is the first choice for tumors that are expected to be T4 or CRM-positive[12]. TNT is a treatment that may be considered for lowering the pathological N stage in the future.

For CRC, several guidelines recommend postoperative AC using a fluorouracil-based regimen plus oxaliplatin in patients with pathological lymph node metastasis to improve the oncological outcome[12, 25]. Patients who have received NAC or preoperative CRT are also recommended to receive AC for doublet treatment[26, 27]. However, in the present study, AC for patients with the pathological node-positive disease did not improve the oncological outcomes. One explanation for this is that our study had a small number of patients and selection bias. Although 63% of the pathological node-positive patients who received AC had clinical 'advanced' node-positive (cN2) disease, all pathological node-positive patients who did not receive AC had clinical 'limited' node-positive (cN1) disease. In addition, among the 27 patients with pathological node-positive disease, 3 patients (11%) did not receive AC, and 4 patients (14.8%) received AC with fluorouracil monotherapy without oxaliplatin due to postoperative complications or poor compliance. These results also support the notion that sufficient preoperative treatment is needed to improve the oncological outcomes in patients with clinical 'advanced' node-positive disease.

There were some limitations in this study. First, this was a retrospective study with a small number. Second, the chemotherapy regimen and duration depended on the surgeon's choice and the patient's wishes.

In conclusion, NAC for CRC could achieve good tumor control and down-staging without increasing the rate of postoperative complications. Based on the current findings, NAC may be a useful alternative for the management of CRC patients. To obtain better oncological outcomes, it is crucial to minimize pathological node-positive disease in patients with NAC. A further prospective study with a larger cohort is needed to validate these results.

Acknowledgments

We would like to thank FORTE Science Communications (www.forte-science.co.jp) for English language editing.

Conflict of Interest Statement

All of the authors have no conflicts of interest to declare.

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