

Prognostic Significance of Neoadjuvant Rectal Score and Indication for Postoperative Adjuvant Therapy in Rectal Cancer Patients After Neoadjuvant Chemoradiotherapy

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Abstract. *Background/Aim:* Neoadjuvant chemoradiotherapy (CRT) is a standard treatment for patients with clinical Stage II/III rectal cancer. However, the benefit of postoperative adjuvant chemotherapy for patients after neoadjuvant CRT is uncertain. Recently, neoadjuvant rectal (NAR) score was suggested as an independent prognostic factor for patients with rectal cancer after neoadjuvant CRT. The aim of this study was to examine the prognostic significance of NAR score in rectal cancer patients who underwent neoadjuvant CRT followed by surgery, and to investigate which patients may benefit from postoperative adjuvant therapy. *Patients and Methods:* A total of 72 patients who underwent neoadjuvant CRT followed by R0 resection for clinical stage II /III rectal cancer were evaluated. The correlation between NAR score, various clinicopathological factors and disease recurrence were evaluated. *Results:* Disease recurrence was significantly more often observed in patients with incomplete neoadjuvant CRT, tumor regression grade (TRG) 3-4, and high NAR score. *Multivariate analysis revealed that NAR score was an independent predictor of disease recurrence. Conclusion:* NAR score may be one of the predictive markers for disease recurrence in patients who underwent neoadjuvant CRT followed by surgery for rectal cancer. Patients with a low NAR score may benefit from postoperative adjuvant chemotherapy.

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A number of studies have demonstrated that neoadjuvant chemoradiotherapy (CRT) significantly reduces the risk of local recurrence in locally advanced rectal cancer (LARC) (1-5). The National Comprehensive Cancer Network (NCCN) guidelines (6) recommended neoadjuvant CRT followed by surgery for clinical (c) Stage II or III rectal cancer. The NCCN guidelines also recommend postoperative combined administration of fluoropyrimidine (FL) and oxaliplatin (OX), such as FOLFOX and CapeOX, as adjuvant chemotherapies for patients with cStage II or III disease regardless of the surgical pathology results. However, unfortunately, the role of postoperative adjuvant chemotherapies remains controversial in patients who underwent neoadjuvant CRT followed by R0 resection for rectal cancer (7-14). Bujko *et al.* (7) conducted a meta-analysis on 4 trials involving 2398 patients who underwent neoadjuvant CRT followed by surgery, and reported that the use of postoperative adjuvant chemotherapy is not based on scientific evidence. Whereas, Petrelli *et al.* (8) analyzed data from 5 randomized trials and 10 retrospective studies, and reported that adjuvant chemotherapy improved both 5-year overall survival and 5-year disease-free survival.

FOLFOX or CapeOX administration may cause grade III or more severe adverse events (AE) in 30-40% of the patients who receive these treatments (15). Oxaliplatin-induced neuropathy is one of the most frequently observed AE and may reduce the quality of life. Under rare circumstances, AE may be life threatening and may require hospitalization. Owing to these observations, some experts have questioned whether adjuvant chemotherapy should be administered to all patients who undergo neoadjuvant CRT followed by R0 resection.

Therefore, patients with higher risk of disease recurrence and poor survival, who may be candidates for postoperative adjuvant chemotherapy, were selected.

According to the prognosis of the patients with neoadjuvant therapy, the degree of tumor downstaging is thought to be more important than the absolute ypStage. The neoadjuvant

rectal (NAR) score was proposed by the National Surgical Adjuvant Breast and Bowel Project (NSABP) as a surrogate end point to assess preoperative treatment efficacy in clinical trials of rectal cancer (16). It is calculated based on data only using the clinical T stage and pathological T and N stages and standardizes the degree of tumor downstaging.

The aim of this study was to examine the prognostic significance of NAR score in patients with LARC who underwent neoadjuvant CRT followed by R0 resection, and to investigate which patients may benefit from postoperative adjuvant therapy.

Patients and Methods

This study was approved by the institutional review board at Osaka City University Hospital and Osaka City General Hospital. Each patient gave his/her written informed consent prior to any study procedure.

Patients. We retrospectively collected and reviewed data on patient characteristics and perioperative data after obtaining approval from the review boards of Osaka City General Hospital and Osaka City University Hospital. Between January 2010 and December 2014, a total of 72 consecutive patients who underwent neoadjuvant CRT followed by R0 resection, for previously untreated cStage II /III rectal cancer at our departments, were evaluated. Clinical stage was confirmed by colonoscopy, magnetic resonance imaging (MRI), and computed tomography of the chest, abdomen, and pelvis. When distant metastasis was suspected, positron emission tomography (PET) was also performed. Clinical and pathological staging were determined according to the American Joint Committee (AJCC) TNM staging system. The location of each tumor was within 10 cm from the anal verge.

In all cases, the disease was considered to be resectable at the time of entry, with no evidence of distant metastases.

Chemoradiotherapy. Radiotherapy was administered using a 4-field conformal coplanar technique (anteroposterior, posteroanterior, right lateral and left lateral fields) and 6-10 MV photon beams. A total dose of 50.4 Gy was administered as 1.8 Gy fractions, five fractions per week, for 5 weeks and 3 days. Preoperative chemotherapy with concurrent radiotherapy included capecitabine 900 mg/m² or S-1 40 mg/m² twice a day during the entire period of radiotherapy.

Surgery. Within 6-10 weeks after completing chemoradiotherapy, surgery with total mesorectal excision was performed. Postoperative complications were recorded not only during hospital admission, but also during the first 30 days after discharge. The severity of surgical complications was scored using the Clavien-Dindo classification of surgical complications (17).

The physician determined whether postoperative adjuvant chemotherapy was administered or not, and which chemotherapy regimen was chosen.

Pathological evaluation. A postoperative, pathological evaluation of the surgical specimen was performed. A pathological complete response (pCR) was defined as the complete disappearance of all tumor cells. The pathological tumor regression grade (TRG) was

Table I. Characteristics of 72 patients who underwent neoadjuvant chemoradiotherapy followed by surgery for rectal cancer.

Gender	
Male	56
Female	16
Age	
≥70 years	33
<70 years	39
cStage (Pretreatment)	
II	35
IIIB	19
IIIC	18
ypStage	
0	11
I	20
II	30
III	11
Completion of chemoradiotherapy	
Complete	64
Incomplete	8
Postoperative complications (Clavien-Dindo IIIa or more)	
Present	14
Absent	58
Postoperative adjuvant chemotherapy	
None	37
FL	21
FL+OX	14
Pathological tumor regression grade	
1, 2	42
3, 4	30
NAR score	
>16	11
≤16	61

FL: Fluoropyrimidine; OX: oxaliplatin; NAR score: neoadjuvant rectal score.

evaluated using histological regression. TRG-1, pCR, absence of viable cancer cells in the resected specimen, TRG-2, presence of residual cancer cells; TRG-3, fibrosis outgrowing residual cancer cells, TRG-4, residual cancer cells outgrowing fibrosis, TRG-5, absence of response (18).

Variables. The following 8 parameters were evaluated as potential risk factors for disease recurrence: age at the time of surgery (≥70 or <70 years), gender, pretreatment cStage, ypStage, TRG, NAR score, completion of neoadjuvant CRT, and the presence of postoperative adjuvant chemotherapy.

The NAR score was developed on the basis of Valentini's nomograms for overall survival incorporating a weighted combination of the pre-CRT clinical T (cT) stage, post CRT pathologic T (ypT) stage and pathological nodal (ypN) stage, and were calculated using the equation $[5 \text{ ypN}-3(\text{cT}-\text{ypT})+12]^2 \div 9.61$ (17). The NAR score was classified as low (NAR≤16) and high (NAR>16) according to Valentini *et al.* (17).

Statistical analysis. Statistical analyses were performed using the JMP 10 software program (SAS Institute Japan, Tokyo, Japan). The Chi-square test was used to compare the data. Survival curves were

Table II. Results of the univariate and multivariate analyses of the prognostic factors in 72 patients who underwent neoadjuvant chemoradiotherapy followed by surgery for rectal cancer.

	Disease recurrence		Univariate analysis	Multivariate analysis		
	Present	Absent	<i>p</i> -Value	<i>p</i> -Value	OR	95%CI
Gender						
Male	14	42	0.504			
Female	6	10				
Age						
≥71 years	13	20	0.078			
<71 years	7	32				
cStage (Pretreatment)						
II	11	24	0.682			
III	9	28				
ypStage						
0, I	31	5	0.098			
II, III	15	26				
Completion of chemoradiotherapy						
Complete	15	49	0.033	0.07	1.76	0.87-10.83
Incomplete	5	3				
Postoperative complications (Clavien-Dindo IIIa or more)						
Present	16	42	0.796			
Absent	4	10				
Postoperative adjuvant chemotherapy						
None	12	25	0.519			
Present	8	27				
Pathological tumor regression grade						
1, 2	7	35	0.026	0.03	2.93	1.08-8.55
3, 4	13	17				
NAR score						
>16	7	4	0.011	0.02	3.72	1.22-13.7
≤16	13	48				

NAR score: Neoadjuvant rectal score.

created by the Kaplan-Meier method and analyzed using the log-rank test. The Cox proportional hazard model was used for the multivariate analysis to identify the independent prognostic factors.

All variables with a *p*-value of <0.05 in the univariate analyses were included in a multivariate logistic regression analysis. A *p*-value of <0.05 was considered to be statistically significant.

Results

Patient characteristics. The clinical characteristics of all 72 patients are summarized in Table I. The median age at surgery was 73 years (range= 41-80 years). All patients were diagnosed as cStage II or III by pretreatment diagnostic imaging. All patients underwent R0 resection 6 to 10 weeks after CRT. According to the postoperative pathological classification defined by ypStage using resected specimens, 11 patients (15.3%) were diagnosed as ypStage 0 (pCR), 20 as ypStage I, 30 as ypStage II, and 11 as ypStage III.

Sixty-four (88.9%) patients completed all the process of CRT without severe adverse events. However, 8 patients

required interruption or reduction of CRT. Clavien-Dindo IIIa or more postoperative complications were observed in 14 (19.4%) patients. Among them, pelvic sepsis was the most frequently observed (5 patients) complication and ileus was the second most observed complication (4 patients). With regard to the administration of postoperative chemotherapy, 35 patients underwent chemotherapy. Among these 35 patients, 21 patients were administered a single FL-based chemotherapy, such as infusional 5-fluorouracil or an oral pro-drug. The other 14 patients were treated with a combination of FL and OX. Eleven patients were diagnosed to be in the high NAR group and the others in the low NAR group.

Correlation between clinicopathological factors and disease-recurrence. The overall incidence of disease recurrence was 27.8% (20/72). The correlations between various clinicopathological factors and disease recurrence are shown in Table II. In the univariate analysis, no significant correlations existed among gender, age, pretreatment clinical

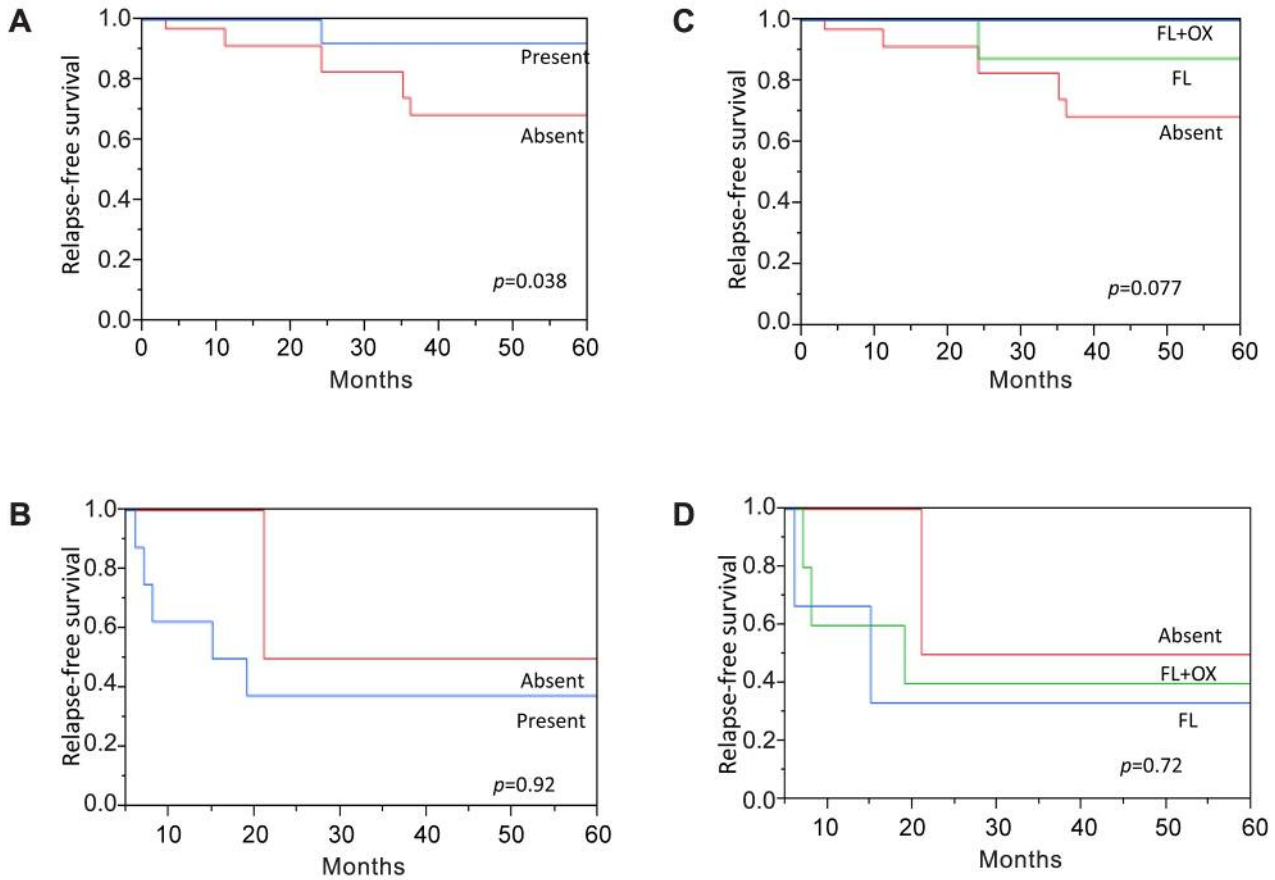


Figure 1. The relapse-free survival subdivided by a combination of NAR score and postoperative adjuvant chemotherapy. The prognosis was significantly ($p=0.038$) better in the patients who received postoperative adjuvant therapy in the low NAR group (Figure 1A). Whereas, no difference existed between postoperative adjuvant therapy and survival in the high NAR group (Figure 1B). No correlation was observed between regimen and survival, based on the types of adjuvant chemotherapy regimen (Figure 1C, D).

stage, ypStage, postoperative complications, postoperative adjuvant chemotherapy and disease recurrence. However, disease recurrence was significantly more often observed in the patients with incompleteness of neoadjuvant CRT, TRG 3-4, and high NAR score. Moreover, multivariate analysis revealed that NAR score was an independent predictor of disease recurrence along with TRG.

We examined relapse-free survival subdivided by a combination of NAR score and postoperative adjuvant chemotherapy. As a result, the Kaplan-Meier analysis and log-rank test demonstrated that the prognosis was significantly ($p=0.038$) better in the patients who received postoperative adjuvant therapy in the low NAR group (Figure 1A). Whereas, no difference existed between postoperative adjuvant therapy and survival in the high NAR group (Figure 1B). No correlation was observed between regimen and survival, regarding the types of adjuvant chemotherapy regimen used (Figure 1C, D).

Discussion

Preoperative chemoradiotherapy decreases the risk of local recurrence and remains a standard treatment for patients with LARC. However, the benefit of subsequent adjuvant chemotherapy for patients who have undergone neoadjuvant CRT is uncertain and a topic of intense debate (7-15). A number of studies, including several randomized studies and meta-analyses, have attempted to address this issue, however, they have collectively produced mixed and inconclusive results.

To avoid wasted medical expenses and adverse events caused by adjuvant chemotherapy, it is important to predict patients who will have disease recurrence after the administration of neoadjuvant CRT and who will benefit from adjuvant chemotherapy.

According to the predictive markers for survival, pathological TRG has been proposed to stratify tumor

response and is thought as one of the prognostic factors in rectal cancer patients after neoadjuvant CRT (19-22). In fact, it was discovered to be an independent predictor of disease recurrence in the present study. However, the role of TRG remains controversial in rectal cancer (23, 24). TRG in rectal cancer depends on several factors, such as the dose and schedule of radiotherapy, combination with chemotherapy, and time between medical treatment and surgery. Moreover, histopathological standardization is still lacking (25).

Whereas, George *et al.* (26) have reported that not only the absolute ypStage, but also the degree of tumor downstaging strongly associated with prognosis in rectal cancer patients after neoadjuvant CRT. The NAR score is calculated based on data supported by the Valentini nomogram for OS, using only the clinical T stage and pathological T and N stages, and is thought to be suitable for standardization of the degree of downstaging (16). Recently, Yothers *et al.* (27) showed that the NAR score had greater predictive ability than pCR for survival. Moreover, Sun *et al.* (28) have also reported that NAR score could help in predicting disease-free survival in rectal cancer patients after neoadjuvant CRT. The strength of the NAR score is the incorporation of both pre-and post-CRT variables to reflect the initial tumor extent and tumor response. Therefore, it is thought to reflect the treatment effect more accurately than absolute ypStage.

However, it remains controversial which patients will benefit from adjuvant chemotherapy after neoadjuvant CRT. Bregom *et al.* (28) and Sainato *et al.* (29) have reported that adjuvant chemotherapy improved neither overall survival nor disease-free survival in all rectal cancer patients after neoadjuvant CRT. However, Turner *et al.* (30) have reported that adjuvant chemotherapy may improve survival for rectal cancer with pCR. Collette *et al.* (31) have reported a survival benefit from adjuvant chemotherapy in patients with ypT0-2 tumors. In the present study, although no difference existed between postoperative adjuvant therapy and survival in the high NAR group, prognosis was significantly better in the patients who received postoperative adjuvant therapy in the low NAR group. From these results, it was suggested that adjuvant chemotherapy may improve survival of patients with a high therapeutic effect from neoadjuvant CRT.

In the present study, analysis of survival according to adjuvant chemotherapy revealed that no significant difference was observed in patients with single-FL based chemotherapy and patients with FL+OX combination chemotherapy. However, Hong *et al.* (32) reported that adjuvant FOLFOX may improve disease-free survival compared with single FL-based adjuvant chemotherapy. A further large-scale prospective randomized trial is needed to evaluate the true effects of adjuvant therapy.

The present study has several limitations. First, this was a retrospective study with a small sample size of 72 patients. Second, selection bias may have been introduced in the

decision to administer postoperative adjuvant therapy. A further large-scale prospective randomized trial is, therefore, needed to evaluate the true effects of adjuvant therapy.

In conclusion, NAR score may be one of the predictive markers for disease recurrence in patients who underwent neoadjuvant CRT followed by surgery for rectal cancer. The patients with low NAR score may benefit from postoperative adjuvant chemotherapy. This was a small retrospective study conducted at only two institutions and further larger multicenter studies are needed to clarify these findings.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Kiyoshi Maeda designed the study, analysed the data and wrote the draft of the manuscript. Masatsune Shibutani collected the clinical data and revised the manuscript critically; Akiko Tachimori, Takafumi Nishii, Naoki Aomatsu and Hisashi Nagahara helped collecting the updated clinical data of the patients. Tastunari Fukuoka performed the statistical analysis. Hiroshi Otani and Toru Inoue designed the study. Masaichi Ohira designed the study and critically reviewed the manuscript.

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