Prognostic Impact of the Neoadjuvant Rectal Score as Compared With the Tumor Regression Grade and Yield Pathologic TNM Stage in Patients With Locally Advanced Rectal Cancer After Neoadjuvant Chemoradiotherapy

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Abstract. Background/Aim: The present study compared the prognostic value of the yield pathologic (yp) stage, tumor regression grade (TRG), and neoadjuvant rectal (NAR) score in patients with locally advanced rectal cancer (LARC) who received neoadjuvant chemoradiotherapy (nCRT). Patients and Methods: For the assessment of tumor regression, the Dworak grading system was used. The NAR score was calculated using the following equation: (5ypN−3[cT−ypT]+12)2÷9.61. Results: In univariate analysis, the NAR score and ypTNM stage were significantly associated with DFS [hazard ratio (HR)=2.514, p<0.001 and HR=3.200, p<0.001] and OS (HR=2.292, p=0.001 and HR=2.859, p<0.001), whereas the TRG was significantly associated with only DFS (HR=2.008, p=0.017). In multivariate analysis, the ypTNM stage was the only independent prognostic factor for DFS (HR=3.796, p<0.001) and OS (HR=3.591, p=0.0034). Conclusion: Only the ypTNM stage was significantly associated with survival outcomes in multivariate analysis, suggesting that it is the most powerful prognostic factor of nCRT in patients with LARC.

Neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME) has become the standard treatment for patients with locally advanced rectal cancer (LARC) (1). Nevertheless, LARC patients exhibit heterogeneity in responses to nCRT, and only about 15%-20% of patients might achieve a pathologic complete response (pCR) (2). To improve clinical outcomes, adjuvant chemotherapy is generally recommended for patients with pathologic stage II/III rectal cancer following nCRT and resection (3). However, it is important to identify patients at high risk of disease progression prior to postoperative therapy, as adjuvant chemotherapy involving fluoropyrimidine and oxaliplatin can cause severe adverse events in 30%-40% of patients (4).

Previous studies have suggested that pathologically determined responses to neoadjuvant treatment correlated with long-term outcomes, and thus, yield pathologic (yp) stage and tumor regression grade (TRG) have been evaluated widely to predict the prognosis of patients with LARC (5-7). Recently, neoadjuvant rectal (NAR) score was presented as an independent prognostic factor for patients who received nCRT. The NAR score is calculated according to data supported by the Valentini nomogram for overall survival (OS), using the clinical T (cT) stage and pathologic T (pT) and N (pN) stages (8, 9). Importantly, this score is designed to be sensitive to the changes in factors that are affected by neoadjuvant therapy, and has been validated in international clinical trials to provide evidence of clinical utility (9). In the NSABP R-04 clinical trial, which involved 1479 patients with stage II/III rectal cancer who underwent nCRT, the

This article is freely accessible online.

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Key Words: Rectal neoplasms, neoadjuvant therapy, neoplasm staging, prognosis.
continuous NAR score was significantly associated with OS. In particular, patients with a low NAR score were reported to show a better 5-year OS (10). Moreover, the NAR score outperformed pCR in predicting OS in a retrospective study with 1,172 LARC patients. However, few studies have compared the prognostic power of the NAR score with ypStage and TRG (11).

Accordingly, the present study assessed the prognostic value of the NAR score in patients with LARC who received nCRT followed by curative surgical resection by performing comparisons with the ypStage and TRG. In addition, we attempted to identify the predictive factors that could potentially influence the response to neoadjuvant therapy.

**Patients and Methods**

Patients and treatment. This study retrospectively reviewed the data of 284 patients diagnosed with LARC who underwent neoadjuvant CRT followed by surgical excision at Kyungpook National University Chilgok Hospital (KNUCH) between January 2006 and October 2015. The patients were enrolled according to the following criteria: pathological diagnosis of primary rectal cancer; clinical stage II or III rectal cancer classified by the American Joint Committee on Cancer Staging (7th edition) (12); and treatment with nCRT followed by surgical excision.

The nCRT consisted of 45-50.4 Gy delivered in 25 daily fractions over 5 weeks with concurrent infusion of 5-fluorouracil (400 mg/m²) and leucovorin (20 mg/m²) on days 1-4 and 29-32 or oral capecitabine (825 mg/m²) twice daily, 5 days per week for 5 weeks. The TME was performed 6-8 weeks after the completion of nCRT.

Assessment of the TRG and NAR score. All surgically resected specimens were examined by pathologists at KNUCH. The pathologic reports included details on ypT stage, ypN stage, lymphovascular invasion, and perineural invasion. For assessment of the TRG, the following Dworak grading system was used: Dworak regression Grade 0 (TRG 0), no regression; Grade 1 (TRG 1), dominant tumor mass with obvious fibrosis and/or vasculopathy; Grade 2 (TRG 2), dominant fibrotic changes with few tumor cells or microscopically); and Grade 4 (TRG 4), no tumor cells (only fibrotic mass) (13). The NAR score was developed according to Valentini’s nomograms for OS, incorporating a weighted combination of the pre-CRT cT stage, post-CRT ypT stage, and ypN stage, and calculated using the following equation: \((5 \times \text{ypN} - 3 \times (\text{cT} - \text{ypT}) + 12)^2 / 9.61\) (14). The NAR score was classified as low (NAR <14.98) and high (NAR≥14.98) according to the median value (14.98).

Ethical approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Statistical analysis. Descriptive statistics are reported as incidences and proportions. Associations between categorical variables were evaluated using the chi-squared test. Disease-free survival (DFS)
was calculated from the date of surgery to the date of tumor recurrence or death from any cause. OS was calculated from the date of diagnosis to death from any cause. In event-free subjects, data were censored at the last follow-up. Survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. Multivariate analysis of prognostic factors was carried out using a Cox proportional hazard regression model. The hazard ratio (HR) and 95% confidence interval (CI) were estimated for each factor. A \( p \)-value <0.05 was considered statistically significant. The statistical analyses were performed using SPSS for Windows (version 20.0; SPSS Inc., Chicago, IL, USA).

Results

Patient and tumor characteristics. The median patient age was 59 (range=25-88) years at the time of diagnosis, and the male-to-female ratio was 2.3:1. The clinical TNM stages before nCRT were II and III in 44 (15.5%) and 240 (84.5%) patients, respectively. The predominant histology was moderately differentiated adenocarcinoma. The pathologic stages after nCRT were as follows: ypStage 0, \( n=39 \) (13.7%); ypStage I, \( n=51 \) (18.0%); ypStage II, \( n=102 \) (35.9%); ypStage III, \( n=85 \) (29.9%); and ypStage IV, \( n=7 \) (2.5%). The Dworak grading system was applied to the 147 patients to evaluate the TRG after nCRT, and the results were as follows: TRG 4, \( n=40 \) (27.2%); TRG 3, \( n=49 \) (33.3%); TRG 2, \( n=29 \) (19.7%); TRG 1, \( n=24 \) (16.3%); and TRG 0, \( n=5 \) (3.4%) (Table I).

![Figure 1. Kaplan-Meier curves for long-term survival outcomes. Patients with a low neoadjuvant rectal (NAR) score showed superior (A) disease-free survival (DFS) and (B) overall survival (OS) as compared to those with a high NAR score.](image)

The relevance of the NAR score with regard to clinicopathologic factors. According to the median NAR score, 179 (63.1%) patients were classified in the high NAR score group and 105 (36.9%) were classified in the low NAR score group. A high NAR score was significantly associated with a more advanced cN stage (\( p<0.001 \)), clinical stage (\( p=0.016 \)), pT stage (\( p<0.001 \)), pN stage (\( p<0.001 \)), ypStage (\( p<0.001 \)), and TRG (\( p<0.001 \)). In particular, 39 (37.1%) patients achieved pCR in the low NAR score group. However, patients with a high NAR score failed to achieve pCR and showed higher probability of more advanced pathologic stages. Patients with a high NAR score tended to experience more often disease recurrence and death as compared to patients with a low NAR score (Table I).

Clinical outcomes and the prognostic role of the NAR score. With a median follow-up duration of 60.3 months (range=5.0-151.0 months), local or distant recurrence occurred in 95 patients (33.5%), and 89 patients (31.3%) died during the follow-up period. The 5-year DFS and OS rates were 61.3% and 74.7%, respectively. In the subgroup analyses, patients with a low NAR score showed superior long-term survival outcomes in terms of DFS and OS (Figure 1). The 5-year DFS and OS rates were 81.4% and 85.8%, respectively, in patients with a low NAR score and 56.4% and 67.4%, respectively, in patients with a high NAR score.

Independent prognostic factors affecting long-term outcomes and prognostic value comparison of the NAR score, TRG, and ypStage. In the univariate survival analysis, the NAR score (NAR score <14.98 vs. \( \geq 14.98 \)) and ypTNM stage
ypStage 0-I vs. ypStage II-IV) were significantly associated with DFS (HR=2.514, 95% CI=1.600-3.951, \( p < 0.001 \) and HR=3.200, 95%CI=1.908-5.367, \( p < 0.001 \), respectively) and OS (HR=2.292, 95%CI=1.378-3.814, \( p = 0.001 \) and HR=2.859, 95%CI=1.613-5.067, \( p < 0.001 \), respectively), whereas the TRG category (TRG 4-3 vs. TRG 2-0) was significantly associated with DFS only (HR=2.008, 95%CI=1.132-3.564, \( p = 0.001 \) and HR=2.859, 95%CI=1.613-5.067, \( p < 0.001 \), respectively), whereas the TRG category (TRG 4-3 vs. TRG 2-0) was significantly associated with DFS only (HR=2.008, 95%CI=1.132-3.564, \( p = 0.001 \) and HR=2.859, 95%CI=1.613-5.067, \( p < 0.001 \), respectively). The HR of the ypTNM stage was higher than that of the NAR score and TRG in the univariate analysis for DFS and OS. In the multivariate survival analysis, the ypTNM stage was the only independent prognostic factor for DFS (HR=2.859, 95%CI=1.613-5.067, \( p < 0.001 \)) and OS (HR=2.292, 95%CI=1.378-3.814, \( p = 0.001 \)).

**Discussion**

We investigated the clinical impact of the NAR score and compared the prognostic value with the ypStage and TRG in a relatively large cohort of patients with LARC. The present study showed the potential of the NAR score to be a prognostic indicator after nCRT. However, the NAR score was not the most reliable prognostic factor when compared with the ypStage and TRG.

George et al. demonstrated that the pT stage and pN stage are potentially influenced by nCRT, and tumor downstaging is more important than the absolute pathologic stage (9). Thus, the NAR score was proposed as a clinical trial surrogate endpoint using only the cT stage, pT stage, and pN stage according to the Valentini nomogram for OS (8, 9). Although, it has already been adopted in clinical trials, such as those involving total neoadjuvant therapy and novel interventions for rectal cancer, validation and standardization for clinical use are still needed. In the NSABP R-04 trial, the NAR score was categorized as low (NAR<8), intermediate (NAR=8-16), and high (NAR>16), and these categories were significantly associated with OS, with 5-year OS rates of 92%, 89%, and 68%, respectively (14). In the present study, patients were classified according to a mean NAR score of 14.98. Similar to previous studies, the proportions of
advanced cT stage, pT stage, and pN stage were higher in patients with high NAR scores, which were correlated with recurrence rate and death.

Recent data showed that the NAR score had greater predictive value than pCR, and it could help in predicting DFS in LARC patients after nCRT (15). Nevertheless, the NAR score alone may not be the most suitable prognostic factor for LARC. Previous studies have reported that the Dworak TRG system and pathologic TNM staging are independent prognostic factors for recurrence and survival in patients with LARC treated with nCRT followed by surgery (16-19). Song et al. demonstrated that the prognostic value of the TRG remained significant, even after adjusting for other well-established prognostic factors, such as the ypN stage, in multivariate analysis (20). In addition, patients with pCR and those with good tumor regression, even in the absence of pCR, have been reported to have good outcomes (18, 19, 21, 22). Meanwhile, Quah et al. reported that the ypStage was more strongly associated with DFS than the TRG in 342 patients with rectal cancer who received nCRT (23). In accordance with previous studies, our data showed that the ypStage, TRG, and NAR score were associated with DFS and the ypStage and NAR score were associated with OS in univariate survival analysis. However, the HR of the ypStage was higher than the values of the TRG and NAR score. Furthermore, in the multivariate survival analysis, including these 3 prognostic factors, only the ypStage was significantly associated with DFS and OS, suggesting that the ypStage is the most influential prognostic factor in patients with LARC after nCRT.

Some previous studies have evaluated the effect of adjuvant chemotherapy following nCRT and surgery in patients with LARC. Although a meta-analysis of four randomized trials demonstrated that adjuvant fluorouracil-based chemotherapy did not improve DFS and OS (15), more recent studies showed that adjuvant chemotherapy improved long-term survival outcomes and that adding oxaliplatin to fluorouracil-based regimens significantly improved DFS in patients with LARC (24, 25). However, its role is not well-defined yet, and there is no consensus on the precise indication of adjuvant chemotherapy. In a study of 245 LARC patients, the 5-year DFS and OS rates were 96% and 100%, respectively, in patients who achieved pCR and were only followed up without additional adjuvant chemotherapy (26). In addition, according to results from the NCCN colorectal cancer database, achieving pCR was associated with not receiving adjuvant chemotherapy (27). Our results showed that patients with a high NAR score tended to have a more advanced pathologic stage and that the proportions of recurrence and death were higher in these patients than in those with a low NAR score. Therefore, poor prognosis is predicted in LARC patients with a high NAR score, which might lead these patients to be classified as a high-risk group, which might be helpful in the decision regarding whether or not to recommend adjuvant chemotherapy in an individual patient. However, since the ypTNM was the most important prognostic factor in the multivariate analysis, oxaliplatin plus fluorouracil-based adjuvant chemotherapy could be recommended after nCRT and surgery according to the ypStage.

In conclusion, only the ypTNM stage was significantly associated with survival outcomes in the multivariate analysis, suggesting that it is the most powerful prognostic factor of nCRT in patients with LARC. Well-designed multicenter studies are still needed to validate the prognostic significance of the NAR score in order to make better strategies after nCRT and improve long-term clinical outcomes in patients with LARC.

Conflicts of Interest
The Authors declare that they have no conflicts of interest regarding this study.

Authors’ Contributions
J.G.K designed the study; J.H.B, D.W.B, B.W.K, H.J.K, S.Y.P, J.S.P and G.S.C collected the data; J.H.B, D.W.B and J.G.K analyzed and interpreted the data; J.H.B and D.W.B wrote the paper; J.G.K contributed to the review and revision of the manuscript.

Acknowledgements
This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (2014R1A5A2009242)

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Received April 6, 2020
Revised April 13, 2020
Accepted April 14, 2020