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

JIN HO BAEK^{1*}, DONG WON BAEK^{1*}, BYUNG WOOG KANG¹, HYE JIN KIM²,
SU YEON PARK², JUN SEOK PARK², GYU SEOG CHOI² and JONG GWANG KIM¹

¹Department of Oncology/Hematology, Kyungpook National University Chilgok Hospital,
School of Medicine, Kyungpook National University,
Kyungpook National University Cancer Research Institute, Daegu, Republic of Korea;
²Department of Surgery, Kyungpook National University Chilgok Hospital,
School of Medicine, Kyungpook National University, Daegu, Republic of Korea

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: $(5ypN-3[cT-ypT]+12)^2 \div 9.61$. *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.

*These Authors contributed equally to this work.

Correspondence to: Jong Gwang Kim, MD, Ph.D., Department of Oncology/Hematology, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, Kyungpook National University Cancer Research Institute, 807 Hogukno, Buk-gu, Daegu 41404, Republic of Korea. Tel: +82 532002623, Fax: +82 532002029, e-mail: jkk21c@knu.ac.kr

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 groups (easy to find); Grade 3 (TRG 3), very few tumor cells in fibrotic tissue with or without mucous substances (difficult to find 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: $(5 \text{ ypN} - 3[\text{cT} - \text{ypT}] + 12)^2 \div 9.61$ (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)

Table I. Patient and tumor characteristics.

Characteristics	Total (n=284)	NAR score		p-Value
		Low (n=105, 36.9%)	High (n=179, 63.1%)	
Age				
Median (range)	59 (25-88)	58 (35-85)	59 (25-88)	0.998
Gender, n (%)				
Male	198 (69.7%)	73 (69.5%)	125 (69.8%)	0.884
Female	86 (30.3%)	32 (30.5%)	54 (30.2%)	
Clinical T stage, n (%)				
cT2	15 (5.3%)	4 (3.8%)	11 (6.1%)	0.033
cT3	228 (80.3%)	78 (74.3%)	150 (83.8%)	
cT4	41 (14.4%)	23 (21.9%)	18 (10.1%)	
Clinical N stage, n (%)				
cN0	44 (15.5%)	25 (23.8%)	19 (10.6%)	<0.001
cN1	95 (33.5%)	38 (36.2%)	57 (31.8%)	
cN2	145 (51.1%)	42 (40.0%)	103 (57.5%)	
Clinical stage, n (%)				
Stage II	44 (15.5%)	25 (23.8%)	19 (10.6%)	0.016
Stage III	240 (84.5%)	80 (76.2%)	160 (89.4%)	
Pathologic T stage, n (%)				
ypT0	40 (14.1%)	40 (38.1%)	0	<0.001
ypT1	8 (2.8%)	8 (7.6%)	0	
ypT2	51 (18.0%)	40 (38.1%)	11 (6.1%)	
ypT3	172 (60.6%)	17 (16.2%)	155 (86.6%)	
ypT4	13 (4.6%)	0	13 (7.3%)	
Pathologic N stage, n (%)				
ypN0	195 (68.7%)	102 (97.1%)	93 (52.0%)	<0.001
ypN1	62 (21.8%)	3 (2.9%)	59 (33.0%)	
ypN2	27 (9.5%)	0	27 (15.0%)	
Pathologic M stage, n (%)				
ypM0	277 (97.5%)	103 (98.1%)	174 (97.2%)	0.538
ypM1	7 (2.5%)	2 (1.9%)	5 (2.8%)	
Pathologic Stage, n (%)				
ypStage 0 (pCR)	39 (13.7%)	39 (37.1%)	0	<0.001
ypStage I	51 (18.0%)	47 (44.8%)	4 (2.2%)	
ypStage II	102 (35.9%)	16 (15.2%)	86 (48.0%)	
ypStage III	85 (29.9%)	2 (1.9%)	83 (46.4%)	
ypStage IV	7 (2.5%)	1 (1.0%)	6 (3.4%)	
TRG, n (%)				
n=147		n=72	n=75	
TRG 4	40 (27.2%)	40 (55.6%)	0	<0.001
TRG 3	49 (33.3%)	15 (20.8%)	34 (45.3%)	
TRG 2	29 (19.7%)	9 (12.5%)	20 (26.7%)	
TRG 1	24 (16.3%)	7 (9.7%)	17 (22.7%)	
TRG 0	5 (3.4%)	1 (1.4%)	4 (5.3%)	
Recurrence, n (%)				
No	189 (66.5%)	86 (81.9%)	103 (57.5%)	0.021
Yes	95 (33.5%)	19 (18.1%)	76 (42.5%)	
Death, n (%)				
No	195 (68.7%)	86 (81.9%)	109 (60.9%)	0.039
Yes	89 (31.3%)	19 (18.1%)	70 (39.1%)	

TRG: Tumor regression grade; NAR score: neoadjuvant rectal score; pCR: pathologic complete response.

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.

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).

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. ≥ 14.98) and ypTNM stage

Table II. Univariate and multivariate analyses of disease-free survival.

Variables	Disease-free survival					
	Univariate analysis			Multivariate analysis		
	HR	95%CI	p-Value	HR	95%CI	p-Value
Age <59 vs. ≥59	1.212	0.835-1.760	0.311	0.481	0.220-1.050	0.066
Male vs. Female	1.017	0.680-1.520	0.936	0.816	0.543-1.226	0.328
ypStage 0-I vs. ypStage II-IV	3.200	1.908-5.367	<0.001	5.223	1.332-20.474	0.018
TRG 4-3 vs. TRG 2-0	2.008	1.132-3.564	0.017	1.265	0.596-2.684	0.540
NAR score <14.98 vs. ≥14.98	2.514	1.600-3.951	<0.001	0.639	0.192-2.131	0.466
Initial CEA <5 ng/ml vs. ≥5 ng/ml	1.137	0.767-1.687	0.522	0.840	0.386-1.828	0.661

CEA: Carcinoembryonic antigen; CI: confidence interval; HR: hazard ratio; NAR score: neoadjuvant rectal score; TRG: tumor regression grade; ypStage: post-neoadjuvant treatment stage.

Table III. Univariate and multivariate analyses of overall survival.

Variables	Overall survival					
	Univariate analysis			Multivariate analysis		
	HR	95%CI	p-Value	HR	95%CI	p-Value
Age <59 vs. ≥59	1.442	0.941-2.209	0.093	2.065	0.957-4.453	0.064
Male vs. Female	0.969	0.614-1.531	0.894	0.701	0.312-1.572	0.388
ypStage 0-I vs. ypStage II-IV	2.859	1.613-5.067	<0.001	3.591	1.536-8.394	0.003
TRG 4-3 vs. TRG 2-0	1.689	0.834-3.420	0.145	1.223	0.586-2.552	0.592
NAR score <14.98 vs. ≥14.98	2.292	1.378-3.814	0.001	0.656	0.198-2.174	0.490
Initial CEA <5 ng/ml vs. ≥5 ng/ml	1.393	0.903-2.147	0.134	0.840	0.386-1.828	0.661

CEA: Carcinoembryonic antigen; CI: confidence interval; HR: hazard ratio; NAR score: neoadjuvant rectal score; TRG: tumor regression grade; ypStage: post-neoadjuvant treatment 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, $p=0.017$) (Table II and Table III). 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)

References

- 1 Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R and German Rectal Cancer Study Group: Preoperative *versus* postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 351: 1731-1740, 2004. PMID: 15496622. DOI: 10.1056/NEJMoa040694
- 2 De Caluwe L, Van Nieuwenhove Y and Ceelen WP: Preoperative chemoradiation *versus* radiation alone for stage II and III resectable rectal cancer. *Cochrane Database Syst Rev* (2): CD006041, 2013. PMID: 23450565. DOI: 10.1002/14651858.CD006041.pub3
- 3 Bujko K, Glimelius B, Valentini V, Michalski W and Spalek M: Postoperative chemotherapy in patients with rectal cancer receiving preoperative radio(chemo)therapy: A meta-analysis of randomized trials comparing surgery+/-a fluoropyrimidine and surgery+a fluoropyrimidine+/-oxaliplatin. *Eur J Surg Oncol* 41: 713-723, 2015. PMID: 25911110. DOI: 10.1016/j.ejso.2015.03.233
- 4 Kahn KL, Adams JL, Weeks JC, Chrischilles EA, Schrag D, Ayanian JZ, Kiefe CI, Ganz PA, Bhoopalam N, Potosky AL, Harrington DP and Fletcher RH: Adjuvant chemotherapy use and

- adverse events among older patients with stage III colon cancer. *JAMA* 303: 1037-1045, 2010. PMID: 20233821. DOI: 10.1001/jama.2010.272
- 5 Omejc M and Potisek M: Prognostic significance of tumor regression in locally advanced rectal cancer after preoperative radiochemotherapy. *Radiol Oncol* 52: 30-35, 2018. PMID: 29520203. DOI: 10.1515/raon-2017-0059
- 6 Lee SY, Jo JS, Kim HJ, Kim CH, Kim YJ and Kim HR: Prognostic factors for low rectal cancer patients undergoing intersphincteric resection after neoadjuvant chemoradiation. *J Surg Oncol* 111: 1054-1058, 2015. PMID: 25977149. DOI: 10.1002/jso.23932
- 7 Chetty R, Gill P, Bateman AC, Driman DK, Govender D, Bateman AR, Chua YJ, Greywoode G, Hemmings C, Imat I, Jaynes E, Lee CS, Lockett M, Rowsell C, Rullier A, Serra S, Szentgyorgyi E, Vajpeyi R, Delaney D and Wang LM: Pathological grading of regression: an International Study Group perspective. *J Clin Pathol* 65: 865-866, 2012. PMID: 22859397. DOI: 10.1136/jclinpath-2012-201054
- 8 Valentini V, van Stiphout RG, Lammering G, Gambacorta MA, Barba MC, Bebenek M, Bonnetain F, Bosset JF, Bujko K, Cionini L, Gerard JP, Rodel C, Sainato A, Sauer R, Minsky BD, Collette L and Lambin P: Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. *J Clin Oncol* 29: 3163-3172, 2011. PMID: 21747092. DOI: 10.1200/JCO.2010.33.1595
- 9 George TJ, Jr., Allegra CJ and Yothers G: Neoadjuvant rectal (NAR) score: A new surrogate endpoint in rectal cancer clinical trials. *Curr Colorectal Cancer Rep* 11: 275-280, 2015. PMID: 26321890. DOI: 10.1007/s11888-015-0285-2
- 10 Roy A, Olsen JR, Myerson RJ, Markovina S, DeWees TA and Parikh PJ: Short-term endpoints for neoadjuvant rectal cancer therapy: Pathologic complete response or neoadjuvant rectal cancer score? *Int Radiat Oncol Biol Phys* 96(2S): abstr 2492, 2016. DOI: 10.1016/j.ijrobp.2016.06.1096
- 11 Raissouni S, Mercer J, Gresham G, Kumar A, Goodwin RA, Jiang M, Leung A, Heng D, Tang PA, Doll CM, MacLean A, Powell ED, Hiller JP, Monzon JG, Cheung WJ and Vickers MM: External validation of the neoadjuvant rectal (NAR) score and Valentini prediction nomogram (VPN): a multicenter study. *J Clin Oncol* 32(15_suppl): 3532, 2014. DOI: 10.1200/jco.2014.32.15_suppl.3532
- 12 Edge SB and Compton CC: The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 17: 1471-1474, 2010. PMID: 20180029. DOI: 10.1245/s10434-010-0985-4
- 13 Dworak O, Keilholz L and Hoffmann A: Pathological features of rectal cancer after preoperative radiochemotherapy. *Int J Colorectal Dis* 12: 19-23, 1997. PMID: 9112145. DOI: 10.1007/s003840050072
- 14 O'Connell MJ, Colangelo LH, Beart RW, Petrelli NJ, Allegra CJ, Sharif S, Pitot HC, Shields AF, Landry JC, Ryan DP, Parda DS, Mohiuddin M, Arora A, Evans LS, Bahary N, Soori GS, Eakle J, Robertson JM, Moore DF, Jr., Mullane MR, Marchello BT, Ward PJ, Wozniak TF, Roh MS, Yothers G and Wolmark N: Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. *J Clin Oncol* 32: 1927-1934, 2014. PMID: 24799484. DOI: 10.1200/JCO.2013.53.7753
- 15 Breugom AJ, Swets M, Bosset JF, Collette L, Sainato A, Cionini L, Glynne-Jones R, Counsell N, Bastiaannet E, van den Broek CB, Liefers GJ, Putter H and van de Velde CJ: Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. *Lancet Oncol* 16: 200-207, 2015. PMID: 25589192. DOI: 10.1016/S1470-2045(14)71199-4
- 16 Maas M, Nelemans PJ, Valentini V, Das P, Rodel C, Kuo LJ, Calvo FA, Garcia-Aguilar J, Glynne-Jones R, Haustermans K, Mohiuddin M, Pucciarelli S, Small W, Jr., Suarez J, Theodoropoulos G, Biondo S, Beets-Tan RG, Beets GL: Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol* 11: 835-844, 2010. PMID: 20692872. DOI: 10.1016/S1470-2045(10)70172-8
- 17 Guillem JG, Chessin DB, Cohen AM, Shia J, Mazumdar M, Enker W, Paty PB, Weiser MR, Klimstra D, Saltz L, Minsky BD and Wong WD: Long-term oncologic outcome following preoperative combined modality therapy and total mesorectal excision of locally advanced rectal cancer. *Ann Surg* 241: 829-836, 2005; discussion 836-828. PMID: 15849519. DOI: 10.1097/01.sla.0000161980.46459.96
- 18 Fokas E, Liersch T, Fietkau R, Hohenberger W, Beissbarth T, Hess C, Becker H, Ghadimi M, Mrak K, Merkel S, Raab HR, Sauer R, Wittekind C and Rodel C: Tumor regression grading after preoperative chemoradiotherapy for locally advanced rectal carcinoma revisited: updated results of the CAO/ARO/AIO-94 trial. *J Clin Oncol* 32: 1554-1562, 2014. PMID: 24752056. DOI: 10.1200/JCO.2013.54.3769
- 19 Kuo LJ, Liu MC, Jian JJ, Horng CF, Cheng TI, Chen CM, Fang WT and Chung YL: Is final TNM staging a predictor for survival in locally advanced rectal cancer after preoperative chemoradiation therapy? *Ann Surg Oncol* 14: 2766-2772, 2007. PMID: 17551794. DOI: 10.1245/s10434-007-9471-z
- 20 Song C, Chung JH, Kang SB, Kim DW, Oh HK, Lee HS, Kim JW, Lee KW, Kim JH and Kim JS: Impact of tumor regression grade as a major prognostic factor in locally advanced rectal cancer after neoadjuvant chemoradiotherapy: a proposal for a modified staging system. *Cancers (Basel)* 10: 319, 2018. PMID: 30205529. DOI: 10.3390/cancers10090319
- 21 Rodel C, Martus P, Papadopoulos T, Fuzesi L, Klimpfinger M, Fietkau R, Liersch T, Hohenberger W, Raab R, Sauer R and Wittekind C: Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. *J Clin Oncol* 23: 8688-8696, 2005. PMID: 16246976. DOI: 10.1200/JCO.2005.02.1329
- 22 Agarwal A, Chang GJ, Hu CY, Taggart M, Rashid A, Park IJ, You YN, Das P, Krishnan S, Crane CH, Rodriguez-Bigas M, Skibber J, Ellis L, Eng C, Kopetz S and Maru DM: Quantified pathologic response assessed as residual tumor burden is a predictor of recurrence-free survival in patients with rectal cancer who undergo resection after neoadjuvant chemoradiotherapy. *Cancer* 119: 4231-4241, 2013. PMID: 24089344. DOI: 10.1002/cncr.28331
- 23 Quah HM, Chou JF, Gonen M, Shia J, Schrag D, Saltz LB, Goodman KA, Minsky BD, Wong WD and Weiser MR: Pathologic stage is most prognostic of disease-free survival in locally advanced rectal cancer patients after preoperative chemoradiation. *Cancer* 113: 57-64, 2008. PMID: 18442099. DOI: 10.1002/cncr.23516

- 24 Rodel C, Graeven U, Fietkau R, Hohenberger W, Hothorn T, Arnold D, Hofheinz RD, Ghadimi M, Wolff HA, Lang-Welzenbach M, Raab HR, Wittekind C, Strobel P, Staib L, Wilhelm M, Grabenbauer GG, Hoffmanns H, Lindemann F, Schlenska-Lange A, Folprecht G, Sauer R, Liersch T and German Rectal Cancer Study Group: Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 16: 979-989, 2015. PMID: 26189067. DOI: 10.1016/S1470-2045(15)00159-X
- 25 Hong YS, Nam BH, Kim KP, Kim JE, Park SJ, Park YS, Park JO, Kim SY, Kim TY, Kim JH, Ahn JB, Lim SB, Yu CS, Kim JC, Yun SH, Kim JH, Park JH, Park HC, Jung KH and Kim TW: Oxaliplatin, fluorouracil, and leucovorin *versus* fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. *Lancet Oncol* 15: 1245-1253, 2014. PMID: 25201358. DOI: 10.1016/S1470-2045(14)70377-8
- 26 Tranchart H, Lefevre JH, Svrcek M, Flejou JF, Tiet E and Parc Y: What is the incidence of metastatic lymph node involvement after significant pathologic response of primary tumor following neoadjuvant treatment for locally advanced rectal cancer? *Ann Surg Oncol* 20: 1551-1559, 2013. PMID: 23188545. DOI: 10.1245/s10434-012-2773-9
- 27 Khrizman P, Niland JC, ter Veer A, Milne D, Bullard Dunn K, Carson WE, 3rd, Engstrom PF, Shibata S, Skibber JM, Weiser MR, Schrag D and Benson AB: Postoperative adjuvant chemotherapy use in patients with stage II/III rectal cancer treated with neoadjuvant therapy: a national comprehensive cancer network analysis. *J Clin Oncol* 31: 30-38, 2013. PMID: 23169502. DOI: 10.1200/JCO.2011.40.3188

Received April 6, 2020

Revised April 13, 2020

Accepted April 14, 2020