Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Neoadjuvant rectal cancer score as a prognostic factor in locally advanced rectal cancer

Gonca Altinisik Inan[a,*], Gulhan Guler Avci[b], Feyza Yasar Dasgin[a], Suheyla Aytac Arslan[a], Yilmaz Tezcan[a]

[a] *Ankara City Hospital, Department of Radiation Oncology, Ankara, Türkiye*
[b] *Tokat Gaziosmanpaşa University, Faculty of Medicine, Department of Radiation Oncology, Tokat, Türkiye*

ARTICLE INFO

Keywords:
Neoadjuvant rectal cancer score
Rectal cancer
Chemoradiotherapy

Received: Oct 25, 2021
Accepted: Feb 14, 2022
Available Online: 25.07.2022

DOI:
10.5455/annalsmedres.2021.10.596

Abstract

Aim: Magnetic Resonance Imaging (MRI) is used to evaluate response in neoadjuvant treatment of rectal cancer, and the predictive value of MRI results is important for clinical decisions. The neoadjuvant rectal cancer (NAR) score is the most commonly used score developed for this purpose. This study aimed to evaluate the power of the NAR score in predicting prognosis in patients with locally advanced rectal cancer who received neoadjuvant chemoradiotherapy treatment in two different centers.

Materials and Methods: The data of 85 patients diagnosed with locally advanced rectal cancer who received neoadjuvant chemoradiotherapy and whose treatment-follow-up information can be accessed were evaluated retrospectively, and NAR scores were calculated. Patients were divided into two groups according to NAR score (score $\leq$16 and patients with $>$ 16), and overall survival (OS) and disease-free survival (DFS) results were compared.

Results: The median follow-up was 25 (1.3-56) months from the end of RT. The 13 patients died, 72 patients were alive, and relapse was observed in 25 patients. Patients' median OS was 28 months (range 4-59), median DFS was 24 (1-59) months. In patients with NAR $\leq$16, median OS was 27 (3-59) months; in patients with NAR $>$ 16, median OS was 24 (5-54) months (0.057). In patients with NAR $\leq$16, median DFS was 23 (1-59) months; In patients with NAR $>$ 16, median DFS was 21 (4-54) (p0.003, HR 3.2, 95% CI 1.4-7.3). A statistically significantly lower recurrence was observed in the patient group with NAR $\leq$16 ($p < 0.001$, HR 2.03, CI 95% 1.2-3.2). A statistically significant lower exitus was seen in the patient group with NAR $\leq$16 (p0.040, HR 1.7, CI 95% 0.89-3.5).

Conclusion: Consistent with the literature in our study, significantly higher DFS and lower recurrence and death rates were observed in low NAR scores.

Introduction

Colorectal cancers are the most common gastrointestinal tract tumors and the third most common type of cancer worldwide. Rectal cancers constitute one-third of these cancers [1]. In recent years, advances in surgical techniques and neoadjuvant/adjuvant treatment modalities have resulted in improvements in the treatment of locally advanced rectal cancer (LARC) [2]. However, a prolonged survival expectancy makes it necessary to develop more successful and less morbid treatment modalities in rectal cancer management.

In rectal cancer treatment studies, disease-free survival (DFS) and overall survival (OS) were used as endpoints to assess the success of the treatment modality. Because of the long time to reach these endpoints and the delay in evaluating studies, researchers have focused on developing different endpoints and predictive formulas that could give information in a short time after neoadjuvant therapy. [3, 4, 5, 6]. On the other hand, response assessment obtained in the pathology specimen has also been used as a popular endpoint to predict the disease's prognosis and survival [7, 8]. The neoadjuvant Rectal Cancer Score (NAR score) is the most widely used and frequently validated formula among the predictive formulas developed [9].

This scoring system was developed for patients who underwent surgery 6-8 weeks after neoadjuvant chemoradiotherapy (CRT). It has also been validated in rectal cancer cases where other treatment approaches were applied [7-9]. The parameters evaluated in the NAR score are clinical T stage, pathological T, and N stages. In this respect, it

*Corresponding author:
Email address: goncaaltinisikinan@gmail.com (Gonca Altinisik Inan)

provides ease of use. The NAR score gives a value between 0 and 100, and the complete response is equal to 0, while 100 points indicate disease progression. Consequently, a lower NAR score is associated with a better prognosis. Although the underlying cause of stratification was not clearly stated, < 8 points are defined as a low-risk group, 8-16 points as a medium risk group, and > 16 points as a high-risk group disease [3].

MRI response to chemoradiotherapy is crucial in the neoadjuvant treatment of rectal cancer. The clinical decisions are made for the patient based on the MRI results. However, to what extent the MRI response parallels the pathological response; this information is the key question. This study is aimed to retrospectively examine the treatment results of patients with locally advanced rectal cancer receiving treatment in our clinic, to evaluate the importance of NAR score in determining the prognosis of patients, and accordingly, to decide the use of this score in patients with locally advanced rectal cancer.

Materials and Methods

Patients who were operated within 6-8 weeks after neoadjuvant chemoradiotherapy for locally advanced rectal cancer in two radiotherapy clinics between August 2010 and January 2019 were retrospectively evaluated. The data of 85 patients whose treatment and follow-up data could be accessed were analyzed. Patient interview information, files, treatment plans, and electronic data systems were used to collect data. The patients' demographic information, tumor localization, clinical and pathological stage of the disease, applied treatment, treatment response, and final disease and patient status were noted. Ethics committee approval for the study was obtained from the "Ankara City Hospital Clinical Research Ethics Committee No. 1" with the decision numbered E1-21-1915.

Patient selection

Patients with a diagnosis of pathologically proven adenocarcinoma, aged 18 years and over, who were operated on 6-8 weeks after receiving long-term CRT treatment for locally advanced rectal cancer, according to AJCC 7 tumor staging, whose treatment and follow-up information can be obtained, were included in the study. The definition of rectum cancer includes tumors located 15 cm from the anal verge. Patients with secondary malignancies, known diseases such as familial adenomatous polyposis coli syndrome, Lynch syndrome, operated under emergency conditions due to obstruction, and operated after short-term RT were not included in analysis.

Patient assessment and imaging

In the patients' initial evaluation, digital rectal examination, thoracic-abdominal and pelvic computed tomography (CT), colonoscopy, and pelvic magnetic resonance imaging (MRI) were obtained as standard and endorectal USG and PET CT were requested some patients if deemed necessary by the clinician. Although MRI was not required for clinical staging in NAR score, pelvic MRI imaging of all patients included in the analysis was obtained, and clinical staging was done accordingly.

After CRT, the follow-up of the patients was done immediately before the surgery, in obtaining the pathology report, and in the following 3-month periods. The follow-up period of patients who completed two years without recurrence was increased to six months.

The primary endpoint

The study's primary endpoint was to examine the predictive value of MRI in the follow-up of patients with rectal cancer. For this purpose, the relationship between NAR score and oncological outcomes was examined. Oncological outcomes were OS, PFS, local recurrence, and disease-related exitus. The date of diagnosis was accepted as the starting date for OS and PFS. The endpoint for OS was the last control date for surviving patients, ex-date for patients who died. The endpoint for DFS was the date of progression for patients who progressed, the date of last control for patients who survived, and the date of exitus for patients who died.

Treatment

Simulations of the patients were performed with 2.5 mm slice thickness CT images. It is aimed to have an empty rectum of the patient before simulation. Due to the intensity-modulated radiotherapy (IMRT) applied to most patients, each patient's amount of water consumed and the waiting time are specially recorded in determining the bladder fullness. The same conditions are tried to be provided during the treatment process. RT was administered at 1.8-2 Gy / fraction daily for 45-50.4 Gy. Chemotherapy regimens applied concurrently with radiotherapy; continuous infusional 5-FU from 225mg / m2 / week or oral capecitabine 825 mg/m2 twice a day in equally divided doses. Patients who completed the CRT were operated on within 6-8 weeks after the MR evaluation.

Calculation of neoadjuvant rectal cancer score

The patients included in the study were staged with the imaging and examination information obtained clinically, and their stages obtained from the pathological specimen were also recorded. In calculating the NAR score, the formula NAR = [5 pN - 3 (cT - pT) + 12] 2 / 9.61 was used [3].

Statistical analysis

This study aims to examine the predictive value of the NAR score in determining the prognosis of patients with rectal cancer. The relationship between the calculated NAR score of the patients and OS, DFS, development of local recurrence, and mortality due to the disease is evaluated. OS is defined as the time between pathologic diagnosis and death from any cause. DFS is defined as the time between pathologic diagnosis and the recurrence at any location (distant or local).

Descriptive statistics for continuous (quantitative) variables are expressed as mean, standard deviation, minimum-maximum, and median values, while categorical variables are expressed as number (n) and ratio (%). Chi-square and Fisher's exact test calculated categorical

Table 1. Patients demographics and treatment details

Gender			
	Female	33	38.8%
	Male	52	61.2%
Age			
	< 65 years	56	65.9%
	≥ 65 years	29	34.1%
cT Stage *			
	cT2	3	3.6%
	cT3	60	72.3%
	cT4	20	24.1%
pT Stage **			
	pT0	13	15.5%
	pT1	4	4.8%
	pT2	18	21.4%
	pT3	44	52.4%
	pT4	5	6%
cN Stage***			
	cN0	6	8%
	cN1	32	42.7%
	cN2	37	49.3%
pN Stage**			
	pN0	58	69%
	pN1	12	14.3%
	pN2	14	16.7%
cM			
	cM0	79	89.7%
	cM1a	6	10.3%
Recurrence			
	Local	3	12%
	Systemic	17	68%
	Local+ Systemic	5	20%
Last Status			
	Alive	72	84.5%
	Ex	13	15.5%

Abbr: T=Tumoral Stage, N=Nodal Stage, M= Metastasis, *Two data is missing, ** One data is missing, *** Ten data is missing

demographic characteristics of the patients. The odds ratio between variables was calculated by binary logistic regression analysis. Kaplan Meier test was used in univariate survey analyzes, and a comparison was made using the log-rank test. The Cox regression test was used in multivariate analysis. Hazard ratio (HR) and 95% confidence interval (CI) values of significant results were noted. If HR > 1, it is accepted that there is an increased relative risk compared to the reference category. Analyzes were made with IBM SPSS Package Program version 22.0 (IBM Corporation, Armonk, NY, USA), and the statistical significance level was accepted as p ≤0.05.

Results

Results of 85 rectal cancer patients who received neoadjuvant chemoradiotherapy for curative purposes were evaluated retrospectively. The median age of patients was 63 (range 32-86). 52 (61.2%) were male, and 33 (38.8%) were female. While 72.3% of patients had cT3, only 3.6% of patients had cT2 tumors. When evaluated in terms of the cN stage, 49.3% of patients had cN2 disease. It was found

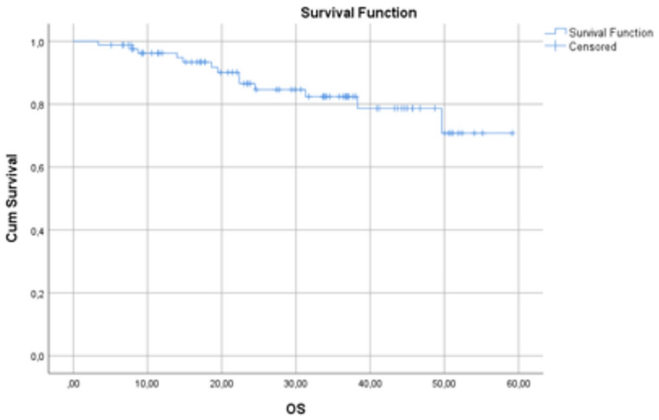

Figure 1. Kaplan meier results for OS analysis

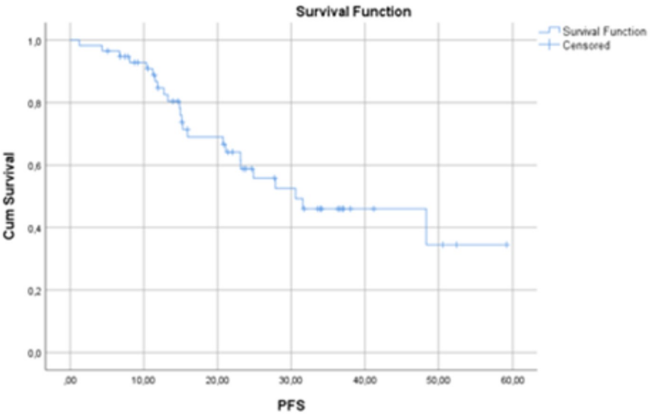

Figure 2. Kaplan meier results for DFS analysis

that oral capecitabine treatment (86.2%) was frequently preferred as concurrent chemotherapy. Patient characteristics and treatment details are summarized in Table 1. The median NAR value was 14.9 (range 0- 65), 57 (69.5%) of the patients had a NAR score of 16 or below; it was over 16 in 25 (30.5%) patients.

The median follow-up period was 25 (1.3-56) months from the end of RT. During the follow-up period, 13 patients died, and 72 patients were alive. Besides, relapse was observed in 25 patients. Patients' median OS was 28 months (range 4-59), 1-year OS 96.2%; 2-year OS is 84.6% . Median DFS 24 (1-59); 1-year DFS 82.6%; The 2-year DFS is 73.7% (Figure 1 and 2).

The median NAR value is 14.9 (range 0-65). Due to the small number of patients and the relatively low number of cases with NAR score below 8, the evaluation was made between the two groups as cases with a score of 16 or less and cases with a score above 16. NAR score of 16 or less in 57 (69.5%) of the patients; It is over 16 in 25 (30.5%) patients. In patients with NAR ≤16, the median OS was 27 (3-59) months; in patients with NAR > 16, the median OS was 24 (5-54) months. In the median 2-year follow-up period, a 3-month overall survival advantage was observed in the patient group with a low NAR-group, but the difference was not statistically significant even though it was close to the limit (0.057). This difference may become significant if the follow-up period is prolonged or the number

Table 2. Results of NAR and OS/DFS analysis

	NAR ≤16	NAR > 16	Univariate analysis		Multivariate analysis	
	Median (Range) mo	Median(Range) mo	p	p	HR	95% CI
OS	27 (3-59)	24 (5-54)	0.057	0.069	2.9	0.9-9.1
DFS	23 (1-59)	21 (4-54)	0.003	0.005	3.2	1.4-7.3

Abbr: NAR=Neoadjuvant Rectal Score, OS=Overall Survey, DFS= Disease Free Survey, HR= Hazard Ratio, CI= Confidence Interval, Mo= months

Table 3. The results of NAR and recurrence analysis

			NAR Score		Total			
			NAR ≤16	NAR > 16		χ^2	p	HR (95%CI)
Recurrence	Negative	N	46	9	55	6300	< 0.001	2.03 (1.2-3.2)
	Positive	Row percentage	%83.6	%16.4	%100,0			
		Column percentage	%80.7	%36	%67.1			
		N	11	16	27			
		Row percentage	%40.7	%59.3	%100,0			
		Column percentage	%19.3	%64	%32.9			
Total		N	57	25				
		Row percentage	%69.5	%30.5	%100.0			
		Column percentage	%100,0	%100,0	%100.0			

Abbr: NAR=Neoadjuvant Rectal Score, OR= Odds Ratio, CI= Confidence Interval
* Chi-Square Test (Fisher's Exact Test)

Table 4. The results of NAR and exitus analysis

			NAR Score		Total			
			NAR ≤16	NAR > 16		χ^2	p	HR (95%CI)
Last Status	Alive	N	51	18	69	4981	0.040	1.7 (0.89-3.5)
	Exitus	Row percentage	%73.9	%26.1	%100.0			
		Column percentage	%91.1	%72	%85.2			
		N	5	7	12			
		Row percentage	%41.7	%58.3	%100.0			
		Column percentage	%8.9	%28	%14.8			
Total		N	56	25				
		Row percentage	%69.1	%30.9	%100.0			
		Column percentage	%100,0	%100,0	%100.0			

Abbr: NAR=Neoadjuvant Rectal Score, OR= Odds Ratio, CI= Confidence Interval,
* Chi-Square Test (Fisher's Exact Test)

of patients increases. In patients with NAR ≤16, the median DFS was 23 (1-59) months; in patients with NAR > 16, the median DFS was 21 (4-54) (p0.003, HR 3.2, 95% CI 1.4-7.3) (Table 2).

During the follow-up, 11 (19.3%) of the patients with NAR ≤16 had recurrence; In patients with NAR > 16, 16 (64%) recurrences were observed. In addition, 59.3% of all recurrences are in the patient group with NAR > 16. A statistically significantly lower recurrence was observed in the patient group with NAR ≤16 (p < 0.001, HR 2.03, CI 95% 1.2-3.2) (Table 3).

In patients with NAR ≤16, a total of 5 (8.9%) were ex, and in the group with NAR > 16, 7 (28%) were ex. In addition, 58.3% of all deaths were in the patient group with NAR > 16. A statistically significant lower exitus was seen in the patient group with NAR ≤16 (p0.040, HR 1.7, CI 95% 0.89-3.5) (Table 4).

Discussion

In our study, 85 patients who received neoadjuvant CRT were analyzed retrospectively, with a median follow-up of two years. Consistent with the literature, a low NAR value

was associated with better oncological results in the current study. The low NAR group had statistically significantly higher DFS and less recurrence and death. During the 2-year follow-up period, a 3-month survival advantage was observed in the patient group with a low NAR value (0.057). The insignificance of the difference may be due to the short follow-up period or the small number of patients.

In developing new methods and treatment schemes for the treatment of rectal cancer, producing short-term surrogate endpoints that would effectively evaluate the success of treatment in studies is essential to accelerate the developments in this area. For this purpose, a parameter used in randomized controlled studies is the presence of complete pathological response. Although many studies have previously reported that the prognosis is better in patients with a complete pathological response [7,8,10], its failure to evaluate the disease's regression information and the time taken for this regression reduce this parameter's predictive power in determining the prognosis [7-10].

Various pathological tumor regression grading systems have also been developed to evaluate complete pathological responses [11-14]. Although successful results are reported with these grading systems in predicting prognosis, they contain subjective parameters and lack of standardization between them, limiting their use, especially in multi-center studies. On the other hand, nomograms have also been developed to predict the prognosis of patients diagnosed with locally advanced rectal cancer. The most popular of them developed by Valentini et al. in 2011, the c-index of the nomogram was found to be high in determining local recurrence, distant metastasis development, and overall survival [6]. In predicting overall survival, clinical T stage, pathological nodal stage, pathological T stage, patient age, adjuvant chemotherapy administration, type of surgery, radiotherapy dose, and gender are the parameters involved in this calculation model.

The NAR score was developed using the cT, pT, and pN parameters, essential in Valentini's nomogram model. Since this newly developed nomogram would only be used in patients who will receive neoadjuvant therapy, other parameters are not included in the calculation. [3]. Thus, this prognostic scoring system that provides ease of clinical use has been achieved. On the other hand, the study was not clearly stated according to the scoring determined when creating the risk groups and how the coefficients were selected.

The first validation of the NAR score was made by the researchers who developed the formula with the NSABP R-04 study patient group results. 1479 stage 2-3 rectal cancer patients enrolled in this study were randomized into four arms using different radiosensitizer chemotherapy schemes. A strong relationship was found between the overall survival data of the study and the NAR risk groups of the patients ($p < 0.0001$), and the same study reported that the NAR score had a more substantial predictive power than the complete pathological response [3].

The importance of the NAR score in predicting disease-free survival was demonstrated in 2018 by validation with the CAO / ARO / AIO-04 randomized phase III trial [15]. In this study, a NAR score of 1191 patients could be obtained. NAR scores tend to be lower in the 5FU / OX CRT arm (5FU CRT vs 5FU / OX CRT $p = 0.034$). Also, a high NAR score was associated with increased patient age, clinical lymph node positivity, and the presence of poorly differentiated tumors. Correlation between NAR and DFS data in multivariate analysis was again shown.

In the recently published study of Lim et al., NAR score risk grouping validation was performed with long-term results [16]. The relationship between the data of 397 patients treated between 2004-2012 and the NAR score risk groups was evaluated. Lower OS and DFS were reported in high-risk group patients at a median follow-up of 76 months ($p = 0.011$ and $P = 0.008$). The results of this study are important in terms of validation with long-term results.

Although the NAR score is a formula developed to evaluate patients who underwent surgery 6-8 weeks after neoadjuvant CRT, average NAR scores were compared in patients in the newly published study of Imam et al. [9] who applied different neoadjuvant treatment schemes. The patients were divided into four arms according to the treatment schemes (1. Short-term RT-surgery at 3-8 weeks, 2. Short-term RT/surgery at 8-17 weeks, 3. CRT / surgery at 6-8 weeks, and 4. CRT / surgery at 8-17 weeks.). Although the relationship between NAR score and OS was demonstrated in all groups, the most substantial relationship was observed in the third CRT + surgery arm, which contains characteristics similar to the group in which the formulation was developed. The association was demonstrated more effectively in low and high-risk groups, while this was not valid in all groups for the intermediate-risk group. The studies in which the NAR score was validated are summarized in Table 3.

Contrary to all these studies, a study showing a lack of NAR scores to predictive value with extensive patient data was reported using the Dutch Cancer Registry [17]. Treatment results of 6596 patients who were treated with neoadjuvant CRT and surgery were evaluated with different predictive parameters. The compatibility of NAR score, only pT, and only pN parameters with overall survival was compared with various models. It was reported that the NAR score was not superior to other parameters. Although there is a contradiction between the publications regarding the NAR score's predictive power, most studies have found that the NAR score has a high predictive feature.

Although this study is a single-center retrospective study and the number of patients is relatively low are the weaknesses of the study, it is important to us that its predictive effect was shown in a small number of cases. On the other hand, oral capecitabine treatment was used as a radiosensitizing agent in most patients in the study; It is valuable in evaluating the use of the NAR score in these patients.

Conclusion

As supported by most of the literature publications, our study showed that the NAR score could be used to predict prognosis in rectal cancer patients who will receive neoadjuvant treatment. Since the score is easy to use and can get fast results, it is thought that it will be used to manage personalized treatments, evaluate new treatment schemes, and intensify treatment schemes according to prediction.

Ethical approval

Ethics committee approval for the study was obtained from the "Ankara City Hospital Clinical Research Ethics Committee No. 1" with the decision numbered E1-21-1915.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424
2. Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision-making. Ann Oncol 2012;23:2479–516
3. George TJ Jr, Allegra CJ, Yothers G. Neoadjuvant Rectal (NAR) Score: a New Surrogate Endpoint in Rectal Cancer Clinical Trials. Curr Colorectal Cancer Rep. 2015;11(5):275-280. doi: 10.1007/s11888-015-0285-2. PMID: 26321890; PMCID: PMC4550644.
4. Wei FZ, Mei SW, Chen JN, Wang ZJ, Shen HY, Li J, Zhao FQ, Liu Z, Liu Q. Nomograms and risk score models for predicting survival in rectal cancer patients with neoadjuvant therapy. World J Gastroenterol. 2020 Nov 14;26(42):6638-6657. doi: 10.3748/wjg.v26.i42.6638. PMID: 33268952; PMCID: PMC7673964.
5. Sun Y, Zhang Y, Wu X, Lin H, Lu X, Huang Y, Xu Z, Huang S, Wang X, Chi P. Prognostic significance of neoadjuvant rectal score in locally advanced rectal cancer after neoadjuvant chemoradiotherapy and construction of a prediction model. J Surg Oncol. 2018 Mar;117(4):737-744. doi: 10.1002/jso.24907. Epub 2017 Dec 11. PMID: 29228455.
6. Valentini V, van Stiphout RG, Lammering G, Gambacorta MA, Barba MC, Bebenek M, Bonnetain F, Bosset JF, Bujko K, Cionini L, Gerard JP, Rödel C, Sainato A, Sauer R, Minsky BD, Collette L, 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. 2011 Aug 10;29(23):3163-72. doi: 10.1200/JCO.2010.33.1595. Epub 2011 Jul 11. PMID: 21747092.
7. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic- Jelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med. 2006;355(11):1114–23.
8. Sauer R, Becker H, HohenbergerW, Rödel C,Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351(17):1731–40
9. Imam I, Hammarström K, Sjöblom T, Glimelius B. Neoadjuvant rectal (NAR) score: Value evaluating the efficacy of neoadjuvant therapy and prognostic significance after surgery? Radiother Oncol. 2021 Jan 14;157:70-77. doi: 10.1016/j.radonc.2021.01.002. Epub ahead of print. PMID: 33453311.
10. Roh MS, Colangelo LH, O'Connell MJ, Yothers G, Deutsch M, Allegra CJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol. 2009;27(31):5124–30.
11. Quah HM, Chou JF, Gonen M, Shia J, Schrag D, Saltz LB, et al. Pathologic stage is most prognostic of disease-free survival in locally advanced rectal cancer patients after preoperative chemoradiation. Cancer. 2008;113(1):57–64.
12. Mace AG, Pai RK, Stocchi L, Kalady MF. American Joint Committee on Cancer and College of American Pathologists regression grade: a new prognostic factor in rectal cancer. Dis Colon Rectum. 2015;58(1):32–44.
13. Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinico-Pathologic Correlations Cancer. 1994;73:2680–6
14. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Color Dis. 1997;12(1):19–23.
15. Fokas E, Fietkau R, Hartmann A, Hohenberger W, Grützmann R, Ghadimi M, Liersch T, Ströbel P, Grabenbauer GG, Graeven U, Hofheinz RD, Köhne CH, Wittekind C, Sauer R, Kaufmann M, Hothorn T, Rödel C; German Rectal Cancer Study Group. Neoadjuvant rectal score as individual-level surrogate for disease-free survival in rectal cancer in the CAO/ARO/AIO-04 randomized phase III trial. Ann Oncol. 2018 Jul 1;29(7):1521-1527. doi: 10.1093/annonc/mdy143. PMID: 29718095.
16. Lim YJ, Song C, Jeon SH, Kim K, Chie EK. Risk Stratification Using Neoadjuvant Rectal Score in the Era of Neoadjuvant Chemoradiotherapy: Validation With Long-term Outcome Data. Dis Colon Rectum. 2021 Jan;64(1):60-70. doi: 10.1097/DCR.0000000000001777. PMID: 33306532.
17. van der Valk MJM, Vuijk FA, Putter H, van de Velde CJH, Beets GL, Hilling DE. Disqualification of Neoadjuvant Rectal Score Based on Data of 6596 Patients From the Netherlands Cancer Registry. Clin Colorectal Cancer. 2019 Jun;18(2):e231-e236. Doi: 10.1016/j.clcc.2019.01.001 Epub 2019 Jan 19. PMID: 30772135.
18. Y. Nancy You, Thomas J. George, Yi-Ju Chiang, Cathy Eng, Prajnan Das, George J. Chang, A. Dasari, Amanda Cuddy, Yun Yang, and Greg Yothers. Validation of neoadjuvant rectal cancer (NAR) score as a surrogate endpoint for overall survival in real-life practice settings. Journal of Clinical Oncology 2018 36:15_suppl, 3517-3517
19. M Khalil, S Shehata, H Essa, R Mohamed. Neoadjuvant rectal cancer (NAR) score as a prognostic factor in locally advanced rectal cancer patients in Assiut University Hospital Clinical Oncology Department
20. Metzger A, Abel S, Kirichenko A, McCormick J, Monga D, Wegner R. Validation of the Neoadjuvant Rectal Cancer (NAR) Score for Prognostication Following Total Neoadjuvant Therapy (TNT) for Locally Advanced Rectal Cancer. VOLUME 108, ISSUE 2, SUPPLEMENT, E33, OCTOBER 01, 2020