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Araştırma

The correlation between neutrophil - lymphocyte ratio and neoadjuvant chemoradiotherapy response prediction in locally advanced rectal cancer

Lokal ileri evre rektum kanserinde nötrofil lenfosit oranı ile neoadjuvan kemoradyoterapiye yanıtın ilişkisi

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ABSTRACT

Objective: The determination of predictive factors for neoadjuvant chemoradiotherapy response in locally advanced rectum cancer is critical concerning treatment management. We aim to analyze the predictive value of clinicopathologic findings of locally advanced rectal cancer patients before neoadjuvant chemoradiotherapy.
Methods: Fifty patients who were diagnosed with locally advanced rectum cancer without distant metastasis and underwent surgery after the neoadjuvant CRT treatment in the department of general surgery, between January 2008-2015 were analyzed.
Results: Twenty three (46%) cases did not yield pathologic response, while 27 (54%) responded to neoadjuvant chemoradiotherapy. There was no statistically significant difference between the responding, and the non-responding groups in terms of mean ages and gender distribution (p=0.360, p=0.665), the distribution of tumor distance from anal verge (p=0.777), pathologic types (p=0.451), pre-op T stage and N stage (p=0.322 and p=0.321), type of surgical procedures (p=0.061, p=0.200), levels of CEA (p=0.195), and PLR (p=0.704). The possiblity of not responding in cases with NLR> 4 was statistically significantly different from those with NLR <4 (95% Confidence Interval: 2.043-62.915) compared to NLR <4 cases (p=0.005).
Conclusion: NLR can be used as a predictive factor in locally advanced rectal cancer before initiating neoadjuvant chemoradiotherapy.

Keywords: Neutrophil lymphocyte ratio, neoadjuvant chemoradiotherapy, rectal cancer

ÖZ

Amaç: Lokal ileri evre rektal kanserde neoadjuvan kemoradyoterapi yanıtı için öngörülen faktörlerin belirlenmesi tedavi yönetimi açısından çok önemlidir. Neoadjuvan kemoradyoterapi öncesi lokal ileri evre rektal kanser hastalarının klinikopatolojik bulgularının öngörülen değerini araştırmayı amaçladık.
Yöntem: Ocak 2008-2015 tarihleri arasında neoadjuvan KRT tedavisinden sonra opere edilen, uzak metastazı olmayan, lokal ileri evre rektum kanseri tanısı konan hastalar geriye dönük olarak incelendi.
Bulgular: Olguların 23'ü (%46) patolojik yanıt vermezken, 27'si (%54) neoadjuvan kemoradyoterapiye yanıt vermiştir. Yanıt veren grup ile yanıtsız grup arasında yaş ortalamaları ve cinsiyet dağılımı (p=0,360, p=0,665), tümörün anal çizgiden mesafesinin dağılımı (p=0,777), patolojik tiplerin dağılımı (p=0,451), pre-op T evre ve N evre (p=0,322 ve p=0,321), cerrahi prosedür tipi (p=0,061, p=0,200), CEA düzeyi (p=0,195), PLO düzeyi (p=0,704) açısından istatistiksel olarak anlamlı fark saptanmadı. NLO> 4 saptanan olgularda yanıt vermeme olasılığı NLO <4 olanlara göre istatistiksel olarak anlamlı derecede farklıydı (%95 güven aralığı: 2,043-62,915) (p=0,005).
Sonuç: Neoadjuvan kemoradyoterapi öncesi NLO lokal ileri evre rektal kanserde öngörülen bir faktör olarak kullanılabilir.

Anahtar kelimeler: Nötrofil lenfosit oranı, neoadjuvan kemoradyoterapi, rektal kanser

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INTRODUCTION

Preoperative staging of rectal cancer is important hence tumor staging is the most important factor for deciding the most appropriate treatment option for the patient. At the present time, total mesorectal excision followed by neoadjuvant chemoradiotherapy (CRT) is the accepted treatment approach in locallly advanced rectal cancer (LARC) treatment [1,2]. It has been reported that local control and sphincter protective surgery rates increased due to the applied CRT regimen [1].

Treatment response to neoadjuvant CRT is determined by the pathologic evaluation, but the prognosis varies hence the response to CRT is diverse among patients [3-5]. The predictive factors that determine the patient who will respond to treatment have not been fully clarified.

This study aims to analyze retrospectively the predictive efficacy of the clinic and pathologic findings of the patients with diagnosis of LARC who were given neoadjuvant treatment. Gender, age, level of carcinoembryonic antigen (CEA) at initial diagnosis, distance of the tumor from the anal verge, pathologic differentiation grade, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) were examined as the predictive factors for the outcome of treatment.

MATERIALS and METHODS

In this study, 50 patients who had locally advanced rectum cancer (T3, T4 or stage 2-3 with lymph node involvement) without distant metastasis between January 2008 and January 2015, were evaluated retrospectively. All the patients underwent surgery after the neoadjuvant CRT treatment in the department of general surgery. All the patients were treated with standard radiotherapy (RT) dose which was 4500-5040 cGy. For the chemotherapy regimen, 5-fluorouracil at a dose of 425 mg/m^2, was given on the first four and the last three days of RT or 1700 mg/m^2 capecitabine was given every day simultaneously with RT.

The CEA levels of these patients were evaluated before the neoadjuvant therapy. The distance of the tumors from the anal verge was determined by colonoscopy at the time of the diagnosis. Tumors located on the 6th centimeter or further from the anal verge were classified as distal rectum tumors, tumors located 7 and 12 cm away as middle rectum tumors. At the time of the initial diagnosis T and N stages were evaluated according to the MRI images by the radiologists. All the patients diagnosed with LARC were operated 6-8 weeks after the end of the neoadjuvant CRT treatment and total mesorectal excision was performed. Patients were divided into two groups according to the type of the surgical procedures performed as low anterior resection and abdominoperineal resection groups (Miles Procedure).

Pathology reports of the postoperative specimens were examined. At the end of the pathologic examination patients were classified according to the pathologic type and grade of differentiation. Colorectal tumor classification proposed by WHO in 2010 was used for the classification of pathologic type. The neutrophil/lymphocyte ratio was determined by examination of the hemograms of the patients at the time of the initial diagnosis. Patients were divided into two groups as NLR <4 and NLR> 4. The platelet/lymphocyte ratio (PLR) was also examined in two groups as PLR <150.000 and PLR >150.000. Pathologically, T and N stages were identified according to the AJCC 2010 TNM staging system. The patients were divided into two groups as responders and nonresponders to neoadjuvant CRT, and T and N stages before and after the neoadjuvant CRT were compared . Tumor regression grade system of AJCC [6] was used to determine the level of response to CRT.

Data were analyzed with SPSS for Windows 11.5 package program. The Shapiro-Wilk test was used to examine the normally distributed continuous and interrupted numerical variables. Descriptive statistics were presented as mean±standard deviation or median (minimum-maximum) for continuous and intermittent numerical variables; and categorical variables were

presented as the number of cases and percentage (%).

Student's t-test was used for the significance of differences between the groups regarding averages. Mann- Whitney U test was used to estimate the significance of the difference in median values. Categorical variables were evaluated by Pearson's Chi-Square, Fisher's exact or Likelihood Ratio tests. The statistically significant difference between the responding and non-responding groups concerning T and N stages in the pre-and post-operative periods was studied by the Wilcoxon Sign Test. To differentiate the respondent group from the non-respondent group, the area under the ROC curve and 95% confidence interval examined aiming to decide whether the distance to anal verge and CEA levels were statistically significant or not. As a result of the univariate statistical analyzes, combined effects of all the possible risk factors that are thought to be useful in the differentiation of responding and non- responding groups, were studied by the multivariate logistic regression analysis. As a result of the univariate statistical analyzes, all the variables with a p-value of $p<0.25$ were included in the multivariate model as candidate factors. The odds ratio, 95% confidence interval and Wald statistics for each variable were calculated. The results were considered statistically significant for $p<0.05$.

The approval was obtained from the ethical committee of our hospital with the report dated (05.12.2015 and decision # 20). Informed consents for the study and the publication were obtained from all patients.

RESULTS

The clinical characteristics of the included patients were evaluated. Thirty-one patients (62%) were male, 19 (38%) were female. The ages of the patients ranged between 35-90 years. Twenty-six patients (52%) were under 65, and 24 patients (48%) over 65 years old. As to the distance of the tumor from the anal verge, middle and lower rectum tumors were equal in number [25-25] (50-50%). As for the histologic distribution of the patients' tumors, the patients had adenocarcinoma (n=42: 84%), 7 mucinous type carcinoma, and signet-ring cell carcinoma (n=1: 16%). As the patients were evaluated in terms of the grade of differentiation, the patients had poorly (n=14: 28%), moderately (n=30: 60%) and well-differentiated tumors (n=6: 12%). Before the neoadjuvant CRT, 28 the patients had Stage 2 (n=28: 56%:2A: n=1: 2%; 2B, n=1: 2%; 2C, n=2:4%), 3 (n=22: 44%: 3B, n=20: 40%; 3C n=2) disease. According to the types of the operations performed; 37 (74%) patients underwent low anterior resection, and 13 (26%) patients underwent Miles Procedure.

The patients demonstrated / n=27: 54%) or did not (n=23: 46%) demonstrate pathological responses to neoadjuvant CRT Nine (18%) out of the 27 patients From pathological perspecttive, patients responded completely (9/27: 18%), moderately (n=12: 24%) or poorly (n=6: 12%) to CRT. When the T and N stages of the patients were examined separately, progression in the T and N stages was not determined in any of the patients. In T (22: 44%), and N (9: 18%). stages

Table 1. AJCC Tumor regression grade (TRG) system.

Complete regression	No viable cancer cells (TRG 0)
Near complete regression	Single or small groups of tumor cells (TRG1: Moderate response)
Moderate regression	Residual cancer outgrown by fibrosis (TRG 2: Minimal response)
Minimal regresion	Minimal or no tumor cells killed (TRG 3: Poor response)

Table 2. Distribution of age, gender,tumor placement and stage.

Gender	
Male	31 (%62)
Female	19 (%38)
Age	
>65	24 (%48)
<65	26 (%52)
Tumor placement	
Middle	25 (%50)
Distal	25 (%50)
Stage	
Stage 2	28 (%56)
Stage 2A	25 (%50)
Stage 2B	1 (%2)
Stage 2C	2 (%4)
Stage 3	22 (%44)
Stage 3B	20 (%40)
Stage 3C	2 (%4)

Table 3. Clinicopathologic characteristics of non-responding and responding groups.

Variables	Non-responding (n=23)	Responding (n=27)	p-value
Distance from anal verge			0,777
≤6 cm	11 (%47,8)	14 (%51,9)	
≥7 cm	12 (%52,2)	13 (%48,1)	
CEA level	4,3 (1,7-48,0)	2,8 (0,4-45,5)	0,195
Pathologic type of tumor			0,451
Adenocarcinom	19 (%82,6)	23 (%85,2)	
Mucinous carcinom	3 (%13,0)	4 (%14,8)	
Signet-ring cell carcinom	1 (%4,4)	-	
Pre-op T stage			0,322
T3	20 (%87,0)	26 (%96,3)	
T4	3 (%13,0)	1 (%3,7)	
Pre-op N stage			0,321
N0	11 (%47,8)	17 (%63,0)	
N1	10 (%43,5)	8 (%29,6)	
N2	2 (%8,7)	2 (%7,4)	
Tumor differentiation			0,061
Poorly	8 (%34,8)	6 (%22,2)	
Moderately	15 (%65,2)	15 (%55,6)	
Well	-	6 (%22,2)	
Type of surgical procedure			0,200
Low anterior	19 (%82,6)	18 (%66,7)	
Miles	4 (%17,4)	9 (%33,3)	
NLR			<0,001
<4	11 (%47,8)	25 (%92,6)	
>4	12 (%52,2)	2 (%7,4)	
TLR			0,704
<150000	9 (%39,1)	12 (%44,4)	
>150000	14 (%60,9)	15 (%55,6)	

respective number of patients demonstrated disease regression.

There was no statistically significant difference between the responding and the non-responding groups regarding distribution of mean ages and gender of the patients (p=0.360, p=0.665). There was no statistically significant difference in the distribution of tumor distance from anal verge between the two groups (p=0,777). The median CEA level was also statistically similar between the two groups (p=0.195). There was no statistically significant difference between the groups regarding the distribution of pathologic types of rectal tumors (p=0.451). There was also no statistically significant difference between the preoperative T and N stages (p=0.322 and p=0.321). The distribution of degrees of differentiation and type of surgical procedures was statistically similar between the two groups (p=0.061, p=0.200). There was no statistically significant difference between the groups concerning PLRs (p=0.704).

Statistically significantly higher number of patients with NLR> did not respond to CRT (p<0.001). Multivariate logistic regression analysis was used to examine the co-effects of all possible risk factors that were effective or likely to be effective in distinguishing the responding and nonresponding groups according to the results of univariate statistical analyzes. Multivariate logistic regression analysis revealed that NLR was a statistically significant predictor of the neoadjuvant CRT response independent of CEA, grade of differentiation, and type of the surgical procedure. After the corrections were performed for the other possible risk factors, the possibility of not responding to CRT in patients with NLR> 4 was statistically significantly increased as 11.337 times (95% Confidence Interval: 2.043-62.915) compared to patients with NLR <4 (p=0.005).

DISCUSSION

The progression of some malignancies has been reported to be connected to the systemic inflammatory response (SIR) [7]. SIR is responsible for many effects, mainly the inhibition of cell apoptosis. As a measure of SIR, CRP and albumin-based simple inflammation scoring (Glasgow scoring system) have been reported to be significant predictors of cancer progression, especially for colorectal cancers. Due to this fact they can be used independently of other factors in determining the course of the disease after surgery and chemotherapy [8-10].

Neutrophil and lymphocyte counts have also been studied as a marker of SIR, and NLR has been shown to be the measure of systemic inflammatory response [7,11]. In a study of 115 patients in whom the effects of neutrophil/lymphocyte ratio on the prediction of rectal cancer were examined, it was found that patients with NLR> 5 had a shorter overall and disease-free survival and shorter survival for local colorectal cancer [12]. There are other studies reporting that the neutrophil/lymphocyte ratio can be used as a prognostic factor for colorectal cancers [13,14].

Tada et al. studied the predictive effect of peripheral neuronal lymphocyte count, T lymphocyte count

and Th lymphocyte count in neoadjuvant CRT and reported that all three parametres increased in patients with a good response. Thus, it was reported that both Th lymphocyte and cytotoxic T lymphocyte count had been determined as predictive factors [15]. In a retrospective study of 89 patients, effects of PLR (another measure of CSF) and NLR on rectal cancer were studied, and it was reported that increased platelet levels, PLR and NLR had shortened overall survival [16]. On the other hand, there was no relationship between PLR and pathological response in our study.

Studies have also reported that peripheral lymphocyte counts are associated with survival independent factors, such as tumor spread, performance status, and weight loss [17,18]. Kitayama et al. reported that pathological complete response rate was higher in patients with high lymphocyte levels [19]. Demaria et al. studied the effects of T and B lymphocytes on tumor response separately and reported that the tumor response to radiotherapy was higher in patients with high T lymphocyte rates, but it was not associated with B-lymphocytes [20]. The conclusion of such studies suggests that the efficacy of neoadjuvant CRT in LARC patients may be directly related to lymphocyte-mediated immunological reactions.

In our study, the proportion of patients with NLR> 4 was found to be significantly higher in the non-responding group compared to the responding group. Furthermore, multivariate logistic regression analysis showed that NLR was a statistically significant predictor of the response independent from CEA, grade of differentiation, and type of surgical procedure. The probability of not responding to neoadjuvant CRT in the group of patients with NLR> 4 was found to be 11.3 times higher than the group with NLR <4. Similar to our study, the studies in the literature indicate that NLR values predict the pathological response. According to these data, we believe that NLR can be used as a reliable predictive marker in the evaluation of pathologic response to neoadjuvant CRT in LARC patients.

Several studies have reported that preoperative CEA level is a predictive factor for neoadjuvant CRT in rectal cancers [21-23]. In our study, there were no significant results in terms of the usability of pre-CRT blood CEA levels in the evaluation of the pathological response.

Huh et al. [24] reported that well-differentiated tumors had a complete pathologic response after neoadjuvant CRT, but it was not identified as a predictive factor by the multivariate analysis. In our study, there were no statistically significant differences between the tumor differentiation grade and tumor response based on the univariate and multivariate analyzes.

Das et al. [25] studied two groups of patients with tumors <5 cm, and > 5 cm away from the anal verge reported that tumors > 5 cm away from the anal verge had lower rates of pathologic response to neoadjuvant CRT, and they also reported that the distance of the tumor from the anal verge is a predictive factor for tumor downstaging. In a study by Armstrong et al. [26] the distance of the tumor from anal verge was reported as a predictive factor for the pathological response after the neoadjuvant treatment. In our study, patients divided into two groups as tumors < 6 cm, and > 6 cm away from the anal verge and no statistically significant difference was determined between the two groups regarding the pathologic response to neoadjuvant CRT.

This study suggests that the blood NLR level can be used as an inexpensive, easily achievable marker for predicting the pathological response to neoadjuvant CRT in LARC patients. The predictive factors identified in other studies such as CEA level, tumor distance from the anal verge and PLR did not reveal any statistical significance as predicting the pathological response to neoadjuvant CRT in LARC patients in our study. This situation can be due to the limitations of this study such as the retrospective structure of the study and the low number of patients.

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