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Hemoglobin Level as a Prognostic Factor of Neoadjuvant Chemoradiotherapy in Patients with Rectal Cancer

Berrin Yalçın, Begüm Ökten, Ebru Tuncay, Özlem Mermut

University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Radiation Oncology, İstanbul, Turkey

ABSTRACT

Introduction: This retrospective study aimed to determine the effect of pre-treatment hemoglobin (Hgb) value on the prognosis of patients with advanced rectal carcinoma undergoing neoadjuvant chemoradiotherapy (nCRT) in terms of pathologic complete response (pCR).

Methods: A total of 192 individuals with rectal cancer who underwent nCRT were included in the study between 2011 and 2019. The patients were separated into anemic and non-anemic categories based on pretreatment Hgb values (Hgb <11 gr/dL).

Results: The Hgb threshold for defining anemia was assessed using receiver operating characteristic curve analysis. Of the 48 (25%) patients, 144 (75%) were in the non-anemic group. The median overall survival (OS) time was 27 months in the anemic group and 69 months in the non-anemic group patients (p=0.028). No statistically significant difference was observed in disease-free survival between the groups. When comparing the two groups "patients" pCR and partial response ratio was elevated in the non-anemic group (p<0.001). In anemic groups patients, female, median age, >60 years, and CA19-9 value was high (p=0.021, p=0.042, p=0.014 and p=0.030). In logistic regression analysis for pCR, tumor regression grade (0-1 vs. 2-3) and pathologic T-stage (0 vs. 1-2) was statistically significant (p<0.001 and p=0.03), anemia (Hgb <11 gr/dL vs. >11 gr/dL) was not statistically significant (p=0.219).

Conclusion: In the group with lower pretreatment Hgb values (<11 gr/dL), the pCR, partial response, and OS time were lower. However, Hgb levels with a cut-off of 11 gr/dL were not statistically proven to be prognostic factors for rectal carcinoma treated with nCRT.

Keywords: Rectal cancer, anemia, concurrent chemoradiotherapy, complete response

Introduction

Neoadjuvant chemoradiotherapy (nCRT) plays a significant role in locally advanced rectum cancer. It is currently the preferred treatment modality to resect tumors and preserve the rectal sphincter (1,2). While most patients receiving nCRT will experience tumor shrinkage, approximately 10-30% are expected to exhibit a pathological complete response (pCR), indicating the lack of living tumor cells in the excised specimen (3). Some patients achieve pCR, whereas others show significantly different results. It is unclear which patients will respond well to neoadjuvant therapy and whether responders will benefit from systemic adjuvant therapy. The reason for the difference in treatment responses is that their predispose to radiosensitivity is different. The ability to identify more radiosensitive patients using genetic, clinical, and histopathological biological markers may permit personalized intervention, better treatment, and lower local recurrence.

The prognostic factors currently known for rectal cancer receiving nCRT include age, carcinoembryonic antigen (CEA), tumor grade, total mesorectal resection, surgical margin, postoperative lymph node status, and pCR (4-6). Complete pCR after neoadjuvant therapy has been considered one of the most important prognostic response indicators. The ability to anticipate the pCR outcome among individuals receiving nCRT may allow for the provision of more individualized treatments. Individuals anticipated to exhibit good sensitivity to nCRT could be considered for the organ-preserving "watchful waiting" strategy, whereas those anticipated to exhibit poor sensitivity could be considered for the "total neoadjuvant therapy" strategy (7-9).

Tumor hypoxia is an indicator of resistance to radiotherapy (RT) and chemotherapy in various tumors, including colorectal cancer. As a result of hypoxia, neo-angiogenesis is caused in the tumor with the help of increased free radicals in the blood, which turns the tumor into an aggressive tumor resistant to apoptosis (10,11). Reduced hemoglobin (Hgb) concentration is considered an indirect sign of tumor hypoxia. Several studies have revealed that low pre-treatment Hgb values can be prognostic factors for chemoradiotherapy responses, tumor control, and survival outcomes in individuals diagnosed with rectal carcinoma (12,13). This investigation aimed to assess patients who reached pCR after

Address for Correspondence: Berrin Yalçın MD, University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Radiation Oncology, İstanbul, Turkey
E-mail: byalcin77@hotmail.com **ORCID ID:** orcid.org/0000-0002-6354-4609

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nCRT in treatment and to illustrate the effect of low pre-treatment Hgb levels on pCR.

Methods

Patients' Characteristics

In this retrospective analysis, we assessed 192 individuals recently confirmed to have locally advanced rectal carcinoma following biopsy. The patients underwent nCRT between February 2011 and December 2019. The acceptability requirements included that the individuals must be over 18 years of age, Karnofsky performance ≥70 and diagnosed with histologically confirmed rectal cancer who had no prior rectal RT, who had not received palliative RT, had no distant metastasis and had not a blood disease that would cause anemia. Moreover, patients who underwent wait-and-see treatment were not included in the study.

Approval for the investigation was granted by the Institutional Review Board of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 17, date: 14.01.2022), aligning in accordance with the guidelines outlined in the Declaration of Helsinki. Informed consent was secured from all participants following a comprehensive description of the research. Relevant pathology and laboratory findings were extracted from the medical facility records, while information regarding post-treatment monitoring was sourced from the medical records.

Data on Chemoradiotherapy

Before undergoing nCRT, all individuals underwent diagnosis through biopsy. Each patient received external beam RT administered in daily fractions of 1.8-2.0 Gy, utilizing 6/18 megavolt photon radiation beams, five days per week, spanning a 6-week duration, facilitated by linear accelerators. RT was delivered through either the four-field box three-dimensional conformal technique or the field-in-field intensity modulated radiotherapy. The clinical target volume comprised both the tumor mass volume and the lymph nodes in the pelvic region, including their immediate extensions. The treatment planning volume was determined by adding a 1 cm clearance around the rectum and a 0.7 cm clearance around the pelvic lymph nodes to the clinical target volume. Each patient underwent a phase 2 tumor boost, with the rectum and pelvic lymph nodes receiving doses of 40-45 Gy, while the tumor(s) were irradiated with an administered dose of 50.4 Gy.

Concurrent chemotherapy was administered continuously during RT. The chemotherapy protocol included continuous infusion of 5-fluorouracil (5-FU) intravenously (180 mg/m^2/day) for a duration of 7 days or orally administered 5-FU-derived capecitabine (825 mg/m^2 twice a day) for a period of 5 days concurrent with RT. Postoperatively, individuals were directed to the medical oncology facility for adjuvant chemotherapy.

Evaluation of Therapeutic Outcome and Posttreatment Monitoring

Treatment toxicity was assessed according to the Common Terminology Criteria for Adverse Events version 3.0. Throughout RT, patients underwent weekly evaluations, including clinical examinations, along with blood count and biochemistry parameter analysis. Pelvic magnetic resonance imaging (MRI) and colonoscopy were used to assess treatment response after 8-12 weeks of nCRT. After surgery, the treatment response was assessed by a gastrointestinal pathologist. The tumor regression grade (TRG) was measured using the modified Ryan classification. In the context of the modified Ryan classification, TRG0 corresponds to a pCR, TRG1 indicates the presence of several clusters of tumor cells, TRG2 indicates residual tumor, and TRG3 denotes no response (14).

Follow-up assessments included physical examinations and radiological scans every 3 months. The follow-up schedule comprised evaluations every 3 months for the initial 2 years and subsequently shifted to every six months for 3-5 years. Throughout the follow-up period, patients exhibiting suspected local or regional recurrence underwent MRI examinations for further evaluation.

Statistical Analysis

Patient and treatment characteristics were compared between the low Hgb and high (Hgb) Hgb groups using Pearson's chi-square test. The Mann-Whitney U test was used to evaluate non-parametric variables. Osteosarcoma (OS) and disease-free survival (DFS) were analyzed in both groups using Kaplan-Meier survival curves. The time between the onset of nCRT and either the last visit or the time of death was defined as OS. DFS was characterized by the time span between the inception of nCRT and disease progression. The factors associated with pCR were identified using binary logistic regression. The analysis was conducted with a significance level of 5% and a confidence interval of 95% using SPSS version 17.0 for windows (Chicago, IL, USA)

Results

The study included 192 individuals diagnosed with locally advanced rectal cancer. Patients were categorized into anemic (n=48 , 25%) and non-anemic (n=144, 75%) groups according to Hgb levels. During the analysis of the receiver operating characteristic (ROC) curve, the cut-off Hgb was identified at 11.1 g/dL [area under the curve (AUC): 602 sensitivity 83.8% and specificity 85.1%], which showed significant correlations with median OS (p=0.13). Table 1 presents the baseline parameters of patients and treatment characteristics. Comparative analyses showed that female patients (n=23, 35.9%) were found in the anemic group more than male patients (n=25, 19.5%), and this was statistically significant (p=0.021). The mean age was 65.5 (27-84) years in the anemic group and 59 (24-83) years in the non-anemic group, and there was a significant difference (p=0.042). The proportion of patients with mean age ≥60 (n=24, 35.8%) years and pre-treatment CA19.9 (33.5 ng/dL) level was elevated in the anemic group compared with the non-anemic group (p=0.014 and p=0.030). After nCRT, the pCR and partial response rates were higher in patients in the non-anemic group (n=25, 83.3% and n=95, 93.1%, respectively).

The Kaplan-Meier curves DFS and OS time are shown (Figure 1A, B). No statistical difference was found when the DFS value was evaluated in both groups. The median OS time was longer in the non-anemic group (69 versus 27 months). The 3-year OS was 71 in the non-anemic group and 58 in the anemic group patients (p=0.028). The 3-year DFS was 69 and 68% in the non-anemic group and 68% in anemic group (p=0.358).

Table 1. Comparison of anemic and non-anemic groups of patient's characteristics and treatment results

	Anemic, (n %)	Non-anemic, (n %)	Total, (n)	p-value
Gender				
Female	23 (35.9%)	41 (64.1%)	64	0.021
Male	25 (19.5%)	103 (80.5%)	128	
Median age	65.5 (27-86)	59 (24-83)	192	0.042
Age group				
≤60	24 (19.2%)	101 (80.8%)	125	0.014
>60	24 (35.8%)	43 (60.2%)	67	
CEA, ng/dL	30	17	20.5	0.222
CA19-9, ng/dL	33.5	13.5	47	0.030
cT-stage				
2-3	37 (24.3%)	115 (75.7%)	152	0.685
4	11 (27.5%)	29 (72.5%)	40	
cN-stage				
N0	1 (12.5%)	7 (87.5%)	8	0.682
N1-2	47 (25.5%)	137 (74.5%)	184	
pT-stage				
T0	6 (19.4%)	25 (80.6%)	31	0.602
T1-2	17 (28.8%)	42 (71.2%)	59	
T3-4	25 (24.5%)	77 (75.5%)	102	
pN-stage				
N0	29 (22.8%)	98 (77.2%)	127	0.380
N1-2	19 (29.2%)	46 (70.8%)	65	
Tumor regression grade				
0-1	15 (22.7%)	51 (77.3%)	66	0.726
2-3	33 (26.2%)	93 (73.8%)	126	
Chemoradiotherapy response				
Complete response	5 (16.7%)	25 (83.3%)	30	<0.001
Partial response	42 (8.9%)	95 (93.1%)	102	
Stabil response	36 (60.0%)	24 (40%)	60	

CEA: Carcinoembryonic antigen, CA19-9: Carbohydrate antigen 19-9

When all patients were included in the pCR analysis, the outcomes of the binary logistic regression analysis are presented in Table 2. Before nCRT, Hgb was found to be insignificant for pCR (anemic vs. non-anemic, p=0.219). TRG and after treatment pathologic T-stage were found to be significant (0-1 vs. 2-3, p<0.001 and 0 vs. 1-2, p=0.03).

Discussion

In this study, 192 patients with rectal carcinoma who received nCRT indicated that pretreatment Hgb levels were related to markedly poorer overall survival times. Furthermore, we demonstrated that high pretreatment Hgb levels were strongly associated with pCR in patients undergoing nCRT for rectal cancer.

Radiobiology has shown that hypoxia is responsible for the development of chemoresistance and radioresistance in numerous tumors (15,16). This has been studied under the name of re-oxygenation, which is called the 5-R of RT. In the presence of sufficient O_2 in the environment, therapeutic radiation has a greater effect. Enhancing the oxygen-carrying capacity of blood can improve tumor oxygenation and, consequently, tumor radiosensitivity. It is known that 40-60% of patients with malignancy experience anemia at the initiation of RT, and those with anemia generally exhibit a less favorable prognosis than individuals with normal Hgb values (17,18). Consequently, many studies have investigated the impact of anemia on outcomes in the treatment of rectal carcinoma (19,20).

The World Health Organization threshold for anemia is 12 g/dL for women and 13 g/dL for men (21). Many studies have used ROC analysis to determine the Hgb cut-off value (such as, 12 g/dL, 11 gr/dL) for the definition of anemia before treatment (22,23). We determined our cut-off value for the definition of anemia by ROC analysis. As a result of ROC analysis according to OS and DFS, we determined our cut-off value as 11 gr/dL (AUC: 602 sensitivity 83.8% and specificity 85.1%, p=0.013). We attributed the reason why the cut-off value was lower than the cut-off values in other studies, the bleeding before diagnosis in advanced rectal patients.

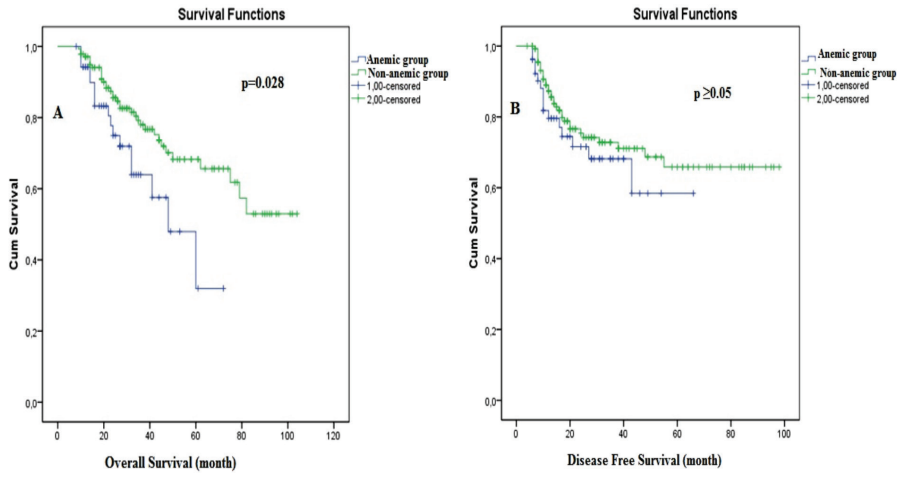

Figure 1. A) Kaplan-meier curve for OS, B) Kaplan-meier curve for DFS
OS: Osteosarcoma, DFS: Disease-free survival

Table 2. Binary logistic regression analysis of pCR

	HR	95%	p-value
Gender (female vs. male)	0.547	0.250-1,196	0.131
Age group (<60 vs. ≥60 years)	0.601	0.253-1,430	0.250
Clinic T-stage (2-3 vs. 4)	0.309	0.103-1,248	0.107
Clinic N-stage (0-1 vs. 2)	0.733	0.880-6,180	0.775
Pathologic T-stage (0 vs. 1-2)	0.107	0.025-0.465	0.003
(0 vs. 3-4)	0.522	0.325-1,311	0.145
Pathologic N-stage (0 vs. 1-2)	0.854	0.952-1,786	0.320
Tumor regression grade (0-1 vs. 2-3)	0.033	0.010-0.115	<0.001
Pretreatment hemoglobin (anemic vs. non-anemic)	0.528	0.191-1,462	0.219

HR: Heart rate, pCR: Pathologic complete response

In the investigation by Box et al. (19) 100 individuals diagnosed with rectal cancer and treated with nCRT were included. Among 25 individuals who were experiencing anemia (< mean Hgb value 12.4 g/dL), 75 patients were found to be non-anemic (>mean Hgb value 12.4 g/dL). Overall survival at 2 years was significantly higher in the non-anemic patients (p=0.021). In contrast, Khan et al. (20) study, who evaluated 463 patients with rectal cancer patient. They found that the Hgb cut-off value was 12 g/dL, and they could not show an association between Hgb level and overall survival or distant metastasis. In our study, we found that Hgb cut-off value 11 gr/dL and overall survival were higher in the non-anemic group (p=0.028).

Another vital finding of our study was Hgb <11.0 g/dL was effective for achieving a pCR. We found a statistically significant pCR in non-anemic and anemic individuals (p<0.01). While pCR was obtained in 5 (16.7%) patients in the anemic group, pCR was assessed in 25 patients (83.3%) in the non-anemic group. In addition, partial response was assessed in 42 patients (8.9%) in the anemic patient group, while it was assessed in 95 patients (93.1%) in the non-anemic group. Similarly, in the study of Box et al. (19), pCR was obtained in 7 (28%) of 25 anemic patients, whereas pCR was obtained in 41 (54%) of 75 non-anemic patients (p=0.028).

In a study by McGrane at al. (12), 273 individuals with rectal cancer who underwent nCRT were analyzed. Among these patients, 63 (23%) exhibited Hgb levels <120 g/L at diagnosis. Grades of Rectal Cancer Regression was worse (less regression, χ^2=10.14; p=0.006), and mortality rates were higher in anemic individuals than in non-anemic individuals. Our findings also showed that pCR, partial response, and survival were elevated in non-anemic individuals.

Wallin et al. (24) assessed the influence of various factors, including patient characteristics, tumor stage and size, circumferential extent, tumor location, and CEA pretreatment levels, on the occurrence of pCR following CRT. Their findings revealed a significant association between a smaller mean tumor size (4.7 vs. 4.2 cm; p=0.02) and a lower pretreatment CEA (9.6 vs. 3.4 ng/mL; p=0.008) and the occurrence of pCR. In our study, pretreatment CA19-9 levels were higher in anemic patients (33.5 gr/dL vs. 13.5 gr/dL, p=0.030). Logistic regression analysis showed that TRG (0-1 vs. 3-4) and pathologic T-stage (0 vs. 1-2) was statistically significant (p<0.001 and p=0.03). Low pretreatment Hgb level (<11 gr/dL) was not significantly associated with pCR, but low Hgb level was associated with OS.

Study Limitations

Some limitations inherent to our study comprise; First, it is not clear whether low Hgb values before treatment occur *de novo* (e.g., family history of anemia) or are due to bleeding. Moreover, this study did not examine whether blood transfusion or an erythropoiesis-stimulating agent is used due to anemia was not examined in this study. The second significant limitation is toxicity due to nCRT treatment, and discontinuation of treatment is one of the factors affecting the pCR response. The relationship between treatment side effects and anemia was not investigated in our study.

Conclusion

Based on the outcomes of the investigation, patients with pretreatment anemia had poorer survival than those with non-anemia who underwent nCRT for rectal cancer. Although pCR and partial response were higher in

patients without anemia, anemia could not be identified as a prognostic factor affecting pCR.

Ethics Committee Approval: The present study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 17, date: 14.01.2022).

Informed Consent: Informed consent was secured from all participants following a comprehensive description of the research.

Authorship Contributions: Concept - B.Y., B.Ö., E.T., Ö.M.; Design - B.Y., E.T., Ö.M.; Data Collection or Processing - B.Y., E.T., Ö.M.; Analysis or Interpretation - B.Y., B.Ö., Ö.M.; Literature Search - B.Y., B.Ö., E.T., Ö.M.; Writing - B.Y., B.Ö., E.T., Ö.M.

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