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Research Article

The Ratio of Hemoglobin to Red Cell Distribution Width Predicts Pathological Complete Response with Rectal Cancer Treated by Neoadjuvant Chemoradiotherapy

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Abstract

Objectives: Concurrent neoadjuvant chemoradiotherapy followed by total mesorectal excision is the standard treatment for locally advanced rectal cancer (LARC). Approximately 20% of patients achieved pathological complete response (pCR) after neoadjuvant treatment. This study aimed to evaluate the relationship between the ratio of hemoglobin to red cell distribution (HRR) width and response to neoadjuvant chemoradiotherapy for rectal cancer.

Methods: We retrospectively analyzed patients with locally advanced rectal cancer who underwent neoadjuvant chemoradiotherapy followed by surgery between July 2014 and March 2020. The effects of hematological parameters on the response to neoadjuvant chemoradiotherapy were analyzed.

Results: A total of 49 patients were eligible for analysis. Red blood cell distribution width (p=0.04), lower systemic immune-inflammation index (p=0.03), and a higher pre-chemoradiotherapy ratio of hemoglobin to red cell distribution width (p=0.03) were associated with a pathological complete response. The multivariate analysis showed that pretreatment ratio of hemoglobin to red cell distribution width >0.88 significantly predicted a complete pathological response, and it was an independent predictor of complete histological response (p=0.009, OR:8, %95 CI: (1,69–37,6).

Conclusion: The ratio of hemoglobin to red cell distribution width can be used to predict complete pathological response in rectal cancer patients receiving neoadjuvant treatment.

Keywords: Complete Response, Rectal Cancer, Ratio of Hemoglobin to Red Cell Distribution Width

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Concurrent neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME) is a standard of care treatment for locally advanced rectal cancer (LARC).[1, 2] The use of nCRT in LARC is associated with improved rates of local control and tumor regression as well as an improved toxicity profile.[3]

About 20% of patients achieve pathological complete response (pCR) after nCRT.[4, 5] Patients who respond to nCRT have demonstrated improved outcomes, including disease-free survival (DFS) and overall survival (OS).[6-8] Identification of pCR after nCRT remains a major challenge.[9] Predicting the complete response in patients undergoing neoadjuvant treatment for rectal cancer may allow clinicians to develop risk-adapted treatment strategies. Unfortunately, there are no effective biomarkers for predicting response to nCRT.

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Systematic inflammatory response is associated with cancer development.[10, 11] Furthermore, some studies have demonstrated that the systemic inflammatory response is associated with tumor regression after radiation, which may influence the response to nCRT.[10, 12] A complete blood count (CBC) is a routine test performed in patients with cancer and reflects the systemic inflammatory response. Therefore, routine blood tests may be useful for evaluating treatment response in cancer patients.

In recent years, hematologic parameters and hematological inflammation-based indices included in CBC, such as the systemic immune-inflammation index (SII), prognostic nutritional index (PNI), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), hemoglobin (HB), and red blood cell distribution width (RDW), have been extensively studied in different types of cancer.

Among these hematologic parameters, both HB and RDW levels are valuable factors in predicting the pathological response and prognosis in malignancies receiving neoadjuvant therapies, especially in rectal cancer.[13, 14] Although HB levels and RDW are successful parameters separately, it may be even more beneficial to combine them. The ratio of hemoglobin to red cell distribution width (HRR) reflects these two parameters simultaneously.

HRR is obtained by dividing HB by the RDW. Its importance has been demonstrated in esophageal, head and neck, lung, and gastric cancers.[15-18] However, HRR and its clinical significance in patients with rectal cancer are unclear. Thus, we designed a study to assess the ability of hematologic parameters, such as HRR, to predict the response to nCRT in patients with LARC.

Methods

A retrospective database of all patients with LARC who underwent neoadjuvant CRT followed by TME at our hospital from July 2014 to March 2020 was analyzed.

The inclusion criteria were as follows: (i) pathologically confirmed LARC (clinically T3/T4 or node-positive), (ii) medically fit (Eastern Cooperative Oncology Group Performance Status (ECOGPS) of 0 or 1), (iii) nCRT followed by TME, (iv) pretreatment, and (v) no clinical evidence of acute or chronic systemic inflammatory disease or other malignancies. Patients who received short-term radiotherapy and had distant metastases at the time of diagnosis were excluded from the study. A total of 49 eligible patients met the inclusion criteria.

For all patients, clinical work-up was based on digital rectal examination, laboratory tests including pretreatment CBC, colonoscopy with biopsy, computed tomography (CT) of the thorax and abdomen, and magnetic resonance imaging (MRI) of the pelvis. All 49 patients underwent neoadjuvant chemoradiotherapy (CRT). Standard CRT consisted of 45 Gy of radiation delivered in 25 daily fractions over 5 weeks with concurrent capecitabine (825 mg/m^2) twice daily throughout the radiation period. Surgery was performed 4-12 weeks after the completion of CRT. A standard patient follow-up protocol was applied according to The National Comprehensive Cancer Network (NCCN).

Pathological responses were evaluated by the pathologists. A modified system was used to grade tumor response as recommended by the American Joint Committee on Cancer (AJCC) Staging Manual, 8th Edition, and the College of American Pathologists (CAP) guidelines.[19] (0) Complete response, no viable remaining cancer cells (1) Moderate response, only small cluster or single cells remaining (2) Minimal response, residual cancer remaining but with predominant fibrosis, (3) Poor response, minimal or no tumor kill

Laboratory tests were performed within one week prior to CRT. Hemoglobin (Hb) values below 13 g/dL in males and 12 g/dL in females were considered to indicate anemia. The normal reference range of RDW-CV in blood cells is 11.5-15.4%. The NLR, PLR, and MLR were calculated according to the following formula: The SII was calculated using the platelet × neutrophil/lymphocyte formula. The PNI was calculated as follows: 10x serum albumin (g/dL) + 0.005 × total lymphocyte count (per mm^3). The HRR was calculated by dividing HB (g/dL) by RDW (%). The cutoff values for the parameters were calculated using receiver operating characteristic (ROC) analyses. The optimal cutoff levels for RDW-CV, PLR, NLR, PNI, and SII were 15%, 148.7, 2.79, 39, and 649, respectively.

Informed consent was obtained from all patients. The study protocol was approved by the local ethics committee (approval number: 2020-140).

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences 17. The relationships between clinicopathological variables were studied in the x^2 test and Fisher's exact test. Differences were considered significant at $p<0.005$.

Results

A total of 49 patients with rectal cancer were eligible for our analysis, including 36 (63,2%) and 13 (22,8%). The median age of the cohort was 64 years (range 37-85 years). In total, 12 patients (24,5%) achieved pCR and 4 patients (8,2%) were classified as having a moderate response, while 11 patients (22,4%) and 22 patients (44,9%) were included in the minimal and poor response groups, respectively.

The clinicopathological characteristics of the patients are shown in Table 1.

Table 1. Baseline clinicopathological characteristics in patients with rectal cancer

Characteristics	Values
Gender	
Male	36 (63.2%)
Female	13 (22.8%)
Age	
<60	23 (40.4%)
>60	26 (45.6%)
Tumor Localization	
Upper Rectum	9 (18.4%)
Middle Rectum	17 (34.7%)
Distal Rectum	23 (46.9%)
Distance from anal verge	7 cm (2-14)
Lymph Node Harvested	8.25 (0-33)
Type of surgery	
LAR	34 (69.4%)
APR	15 (30.6%)
ypT stage	
0	13 (26.5%)
1	6 (12.3%)
2	10 (20.4%)
3	13 (26.5%)
4	7 (14.3%)
ypN stage	
0	31(63.2%)
1	8 (16.4%)
2	5 (10.4%)
Response to neoadjuvant treatment	
Complete response	12 (24.5%)
Moderate response	4 (8.2%)
Minimal response	11 (22.4%)
Poor response	22 (44.9%)

ECOG, Eastern Cooperative Oncology Group; LAR, Low anterior resection; APR, Abdominoperineal resection.

The cutoff values for hematologic parameters and hematological inflammation-based indices were determined using ROC curves. As shown in Table 2, univariate analysis revealed that lower levels of pre-nCRT CEA and SII and lower levels of RDW were associated with a higher probability of pCR to neoadjuvant therapy (p=0.02, p=0.03, p=0.04, respectively). The lower NLR tended to be statistically significant (p=0.05). In contrast, a higher pre-nCRT HRR was associated with pCR (p=0.03). The multivariate analysis showed that prenCRT HRR >0,88 significantly predicted a favorable pathological response, and HRR was an independent predictor of complete histological response (p=0.009, OR:8, %95 CI: (1,69–37,6).

Univariate analysis also revealed that among hematological inflammatory markers, anemia, CRP, PNI, and PLR were not significantly associated with pathological response.

Discussion

Identification of pCR after neoadjuvant therapy to develop risk–adapted treatment strategies remain a major challenge in rectal cancer. Therefore, effective biomarkers should be identified to predict pCR. Therefore, in the present study, we investigated the use of hematological parameters as biological markers to predict treatment response in rectal cancer. We demonstrated RDW, SII, and HRR as predictive factors for pCR in the univariate analysis. We also found that only HRR was an independent predictive factor in multivariate analysis.

Inflammation plays a crucial role in every step of tumorigenesis and its progression.[10] Hematologic parameters and inflammation-based indices obtained from blood tests may reflect a systemic inflammatory response to cancer. NLR, PLR, PNI, and SII are well-known biomarkers that have previously been identified as predictors of response to nCRT in rectal cancer.[20-22] In this study, these parameters were used to evaluate this issue. ROC analysis was used to determine the optimal cutoff levels for PLR, NLR, PNI, and SII, which were 148.7, 2.79, 39, and 649, respectively. PLR and PNI were not significantly associated with pathological response, but a lower NLR tended to be significant (p=0.05). In the literature, a lower NLR is associated with a higher probability of tumor response and favorable survival.[23, 24] Lower levels of pre-nCRT SII were significantly associated with a good response (p=0.003), which is in accordance with previous studies.[25, 26]

Increase in cytokines due to inflammation, such as TNF, interleukin 1 (IL-1) leads to an increase in the number of immature red blood cells, which results in an elevated RDW level.[27, 28] Increased RDW levels are also associated with the inhibition of tumor progression via tumor cell glycolysis.[29] Previous studies have revealed that elevated RDW levels are an indicator of inflammation and may reflect systemic inflammatory responses in cancer.[27, 28] RDW has been shown to be an independent predictor of survival in patients with gastrointestinal cancers.[30-32] In a recent study, RDW was shown to be a reliable marker that could predict pathological response after neoadjuvant chemotherapy in rectal cancer patients with liver metastasis.[14] The normal reference range of RDW-CV in blood cells is 11.5-15.4%. In our study, the optimal RDW-CV level was determined using ROC analysis to be 15%. A lower level of pre-nCRT RDW-CV was also associated with tumor response to treatment (p=0.04).

Anemia is a common finding in various cancers. The definitions of anemia and HB levels vary in the literature (9–12 g/dL).[33, 34] Lower HB levels have been associated with poor response to treatment and poor prognosis in

Table 2. The relationship between pathologic complete response with clinical and hematological parameters

Factors	Number of patients(N)	Univariate analysis (N)	P	Multivariate analysis
Age				
<60	23 (40.4%)	6	0.8	
≥60	26 (45.6%)	6		
Gender				
Female	13 (22.8%)	4	0.7	
Male	36 (63.2%)	8		
ECOG Performance Status				
0	30 (61.2%)	8	0.74	
1	19 (38.8%)	4		
Clinical lymph node involvement				
Negative	40 (81.6%)	12	0.09	
Positive	9 (18.4%)	0		
Time interval to surgery				
≥5	42 (85.7%)	8	0.05	NS
<5	7 (14.3%)	4		
Tumor localization				
≤5cm	22 (44.9%)	8	0.08	NS
>5cm	27 (55.1%)	4		
LDH				
<245	39 (79.6%)	11	0.41	
≥245	10 (20.4%)	1		
CRP				
≥5	32 (65.3%)	9	0.5	
<5	17 (34.7%)	3		
Albumin				
≥3.5	35 (71.4%)	10	0.46	
<3.5	14 (28.6%)	2		
PNİ				
≥39	26 (53.1%)	9	0.08	NS
<39	23 (46.9%)	3		
Anemia				
Absent	28 (57.1%)	8	0.44	
Present	21 (42.9%)	4		
RDW				
<15	15 (30.6%)	8	0.04	NS
≥15	34 (69.4%)	4		
NLR				
<2.79	28 (57.1%)	8	0.05	NS
≥2.79	21 (42.9%)	4		
PLR				
<148,7	29 (59.2%)	7	0.18	
≥148.7	20 (40.8%)	5		
HRR				
≥0.88	19 (38.8%)	8	0.03	P=0.009, OR:8,
<0.88	30 (61.2%)	4		%95 CI: (1.69–37.6)
SII				
<649	19 (38.8%)	8	0.03	NS
≥649	30 (61.2%)	4		
CEA				
<5	37 (75.5%)	12	0.02	NS
≥5	12 (24.5%)	0		

CRP, C reactive protein; CEA, Carcinoembryonic antigen.

gastrointestinal tract cancers.[35, 36] The relationship between lower HB levels and poor outcomes, such as a poor response to neoadjuvant treatment and poor prognosis, can be caused by several factors. The antitumor activity of radiation therapy is mainly based on oxygen-producing free radicals. Under hypoxic conditions, the effect of radiotherapy is decreased due to the reduction of free radicals, and hypoxia contributes to neoplastic instability and progression.[37, 38] Hypoxia may accelerate tumor angiogenesis and cause resistance to chemotherapy.[39] Despite these findings, in our study, the tumor response after n-CRT in anemic patients did not differ from that in non-anemic patients (p=0.44). We think that this is due to the fact that anemia patients were given blood transfusion at the time of diagnosis before n-CRT in our institution. Thus, it was not possible to evaluate the exact effect of anemia on the response to n-CRT.

Considering the effects of RDW and anemia separately on treatment response and prognosis in patients with cancer, we believe that the combined evaluation of these two parameters would be more useful. HRR is a new hematological parameter that combines HB levels and RDW. The HRR value was obtained using the HB/RDW ratio. HRR has been shown to be a good predictor of survival in esophageal, lung, and gastric cancer.[15, 16, 18] Although HRR's predictive importance of HRR for survival has been revealed by a limited number of studies, its importance in the evaluation of chemotherapy response has not yet been fully demonstrated. Therefore, we mainly focused on this topic. We found that a prenCRT HRR >0,88. significantly predicted a complete pathological response after neoadjuvant treatment. To the best of our knowledge, for the first time in the literature, HRR has been shown to be an independent predictor of histological complete response after CRT in patients with rectal cancer. We believe that HRR can be used as an indicative marker to determine treatment algorithms for rectal cancer.

Present study has some important limitations. This was a retrospective, single-center study. The number of patients in our study was limited because of the rigid inclusion criteria used to obtain a more uniform patient population and the lack of follow-up of some patients. Therefore, we believe that further well-designed multicenter prospective studies with a larger cohort are required to confirm the above-mentioned findings.

Conclusion

HRR is a reliable marker that can be used to predict a complete pathological response in rectal cancer patients receiving nCRT, which is helpful for treatment decision-making.

Disclosures

Ethics Committee Approval: Informed consent was obtained from all patients. The study protocol was approved by the local ethics committee (approval number: 2020-140).

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Conflict of Interest: None declared.

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