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Biological parameters and the histological response in rectal cancer treated by neoadjuvant chemoradiotherapy: A Moroccan Cohort

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RESEARCH ARTICLE

Biological Parameters and the Histological Response in Rectal Cancer Treated by Neoadjuvant Chemoradiotherapy: A Moroccan Cohort

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Abstract

Introduction: Multimodal management of rectal cancer, combining neoadjuvant Radio chemotherapy followed by total Mesorectal therapy (TME), has been shown to improve locoregional control. However, the histological response is variable independently of the initial tumor stage. Some recent data suggest the usefulness of the lymphocyte-monocyte ratio (LMR), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) in predicting the histological response to neoadjuvant therapy. This study aimed to investigate the correlation between the complete histological response (pCR) after neoadjuvant radio chemotherapy and biological parameters (LMR, NLR and PLR) in rectal cancer patients.

Patients and methods: This retrospective study was conducted in three Moroccan Oncology centers, between June 1, 2015 and June 30, 2019. The authors included 64 cases of rectal adenocarcinoma treated initially by neoadjuvant radio chemotherapy followed by radical surgery (TME). We report sociodemographic, biological and histological parameters. All data were extracted from the hospital medical records by two trained physicians.

Results: The complete histological remission ypT0N0 was reached on nine cases (14%), with either a normal appearance of the rectal mucosa or necrotic tissue in the tumor bed without perennial residue, while the rest of patients still had tumor mass with minimal to moderate size regression or as a high-grade dysplasia-like tumor residue.

The lymphocyte-to-monocyte ratio was high in 33,3% of pCR versus 52,7% in the cases of no remission ($p = 0,28$), neutrophil-lymphocyte ratio was high in 55,6% of pCR versus 49,1% ($p = 0,71$). The platelet-lymphocyte ratio was high in 55,6% of pCR versus 85,5% ($p\text{-value} = 0,03$).

Conclusion: In this study, we did not detect any significant correlation between LMR, NLR and the histological response in rectal cancer patients. However, the high level of PLR was statistically associated with a poor response.

Keywords: Neutrophil lymphocyte ratio, Platelet-lymphocyte ratio, Rectal neoplasms, Radiotherapy, Biomarkers

1. Introduction

Colorectal cancer is the fourth most common cancer worldwide and rectal cancer represents

approximately 30% of all colorectal cancers [1]. Neoadjuvant chemo/radiotherapy followed by Total Mesorectal Excision (TME) remains the standard treatment for rectal cancer with less than 5% of 5-year

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local recurrence and a disease-free survival rate at almost 90% [2,3].

Indeed, it has been demonstrated that the response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer is correlated to the disease-free survival (DFS) and 10-year cumulative incidence of distant metastasis [4]. In fact, Wan et al. recently published a meta-analysis of 21 studies involving 6780 cases of digestive cancers treated with neoadjuvant chemoradiotherapy which showed that pCR correlated significantly with good prognosis either of overall survival or disease-free survival [5]. This gain was maintained in the subgroup analyses of rectal cancer and was confirmed by numerous previous studies [6,7].

However, such surgery is associated with non-negligible mortality (0.9–1.5%) and significant morbidity rates (38–54%) [8–10]. Furthermore, due to definitive colostomy, worse quality of life is reported in cases of low rectal cancer. For this reason, many very attractive alternative approaches, such as trans anal local excision or “wait and see” had been suggested for good responder patients. Thereby, predicting the complete pathological response following neoadjuvant chemo radiotherapy could help to select cases where radical surgery may be avoided. However, it is still difficult to previously distinguish the good or bad responders [11]. Thereby, predicting the complete pathological response following neoadjuvant chemoradiotherapy could help select cases where radical surgery will be avoided.

Some recent data suggest the usefulness of the lymphocyte-monocyte ratio (LMR), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) in predicting the histological response to neoadjuvant therapy.

The aim of the present study is to identify the association between biological parameters and the histological response in rectal cancer treated by neoadjuvant chemoradiotherapy in our country.

2. Materials and methods

2.1. Study design and setting

This is a retrospective study conducted in three Moroccan Oncology centers, Cheikh Khalifa University Hospital of Casablanca, Mohamed VI Oncology Center of Casablanca and University Hospital of Agadir. All data were extracted retrospectively from the hospital medical records after informed consent obtained from the study participants. Data included in our study were collected from patients treated between June 1, 2015 and June 30, 2019.

2.2. Participants and eligibility criteria

The inclusion criteria were: a) newly-diagnosed, histologically-confirmed invasive adenocarcinoma rectal cancers, b) had tumor location in lower or middle rectum, c) had not received any treatment before a hematological assessment, d) treated with neoadjuvant chemoradiotherapy followed by total Mesorectal Excision (TME), and e) had anatomopathological report of the final surgical procedure.

2.3. Data collection

All data were extracted from the hospital medical records by two trained physicians, using standardized data collection forms.

Data collected included sociodemographic and clinical parameters (age, sex, clinical stage), biological parameters (lymphocytes, monocyte, neutrophil, platelets' counts) and histology (Tumor Regression Grade (TRG)).

Three ratios were assessed:

- Lymphocyte-to-monocyte ratio, LMR
- Neutrophil-to-lymphocyte ratio, NLR
- Platelet-to-lymphocyte ratio, PLR

2.4. Statistical analyses

Monocytes, lymphocytes and neutrophils counts were reported in all patients. Three ratios were calculated, namely LMR, NLR and PLR and compared between two groups depending on the histological response to chemoradiotherapy. We subdivided the three ratios depending on their status: High or low according to the most frequently reported threshold in the literature.

The threshold retained for the LMR, NLR and PLR was respectively 3, 4 and 130 based on the largest published series and/or meta-analyses [12–14].

The data extraction was carried out via Excel data sheet, coded and analyzed using the SPSS 21 software using the Test Khi-2, and by GraphPad prime 6.

2.5. Ethical considerations

The present study was approved by the ethical comity of Mohamed VI University of Health Sciences (Ethic's Code: CERB/UM6SS/12/21) and conducted in accordance with the ethical aspects respecting all the conditions of confidentiality, anonymity and self-determination of participants.

3. Results

3.1. Description of epidemiological characteristics

The study included 64 patients, of whom the sex ratio was 1 and the median age was 58 years (range 24–98 years). All patients included in our study were locally advanced stage (Table 1).

3.2. Histopathological response to chemoradiotherapy

No one of our patients received neoadjuvant chemotherapy. All the patients (n = 64) received concomitant chemotherapy radiotherapy by combining bidaily capecitabine and the same delivery scheme of radiotherapy. The histopathological response to neoadjuvant chemoradiotherapy treatment was in nine cases (14%), a complete pathological response classified as ypT0N0M0. While 7.8% of patients had significant regression with ypT1N0M0 (n = 1) or ypT2N0M0 (n = 4), we observed a poor or no regression from the initial stage in 78.2% of cases.

3.3. Description of hematological data

The lymphocyte-to-monocyte ratio was high in 33,3% of Histological Complete Remission (pCR) versus 52,7% in the cases of no remission (p = 0,28); the neutrophil-lymphocyte ratio was high in 55,6% of pCR versus 49,1% (p = 0,71). The platelet-lymphocyte ratio was high in 55,6% of pCR versus 85,5% (p-value = 0.03) (Table 2). The correlation between the complete

remission and PLR was negative based on Spearman Correlation test (r = -0,26, p = 0,03) (Fig. 1).

4. Discussion

This study aimed to investigate the correlation between the complete histological response (pCR) after neoadjuvant radio chemotherapy and biological parameters (LMR, NLR and PLR) in rectal cancer patients. According to the published meta-analysis of 8984 patients, the cut-off of the LMR has been established as 3 [12].

Low lymphocyte to monocyte ratio has been associated with a poor prognostic factor for hematologic malignancies and solid tumors. Indeed, several studies have shown that a low LMR is associated with poor survival and a high ratio is associated with better overall survival in patients with colorectal cancer [12–17]. In the present study, LMR was not statistically significantly correlated with histological response.

The neutrophil-to-lymphocyte ratio (NLR) is an easily measurable inflammatory biomarker in gastric, breast and colorectal cancer and it is used as an indicator of mortality risk in patients [18–21]. It has been reported that NLR is correlated with tumor response. The high level of preoperative NLR was associated with poor histological response in rectal cancer. In fact, Kim et al. have reported that patients with locally advanced rectal cancer treated with preoperative radio chemotherapy have a poor tumor response when their LR is greater than 4 [13].

Similarly, Lee et al. showed that initially high NLR was significantly associated with poor tumor response

Table 1. Summary of patients' epidemio-clinical characteristic of Moroccan cohort.

Variables	Total population (%)
Sample size	64 (100%)
Age (years)	
< 56	29 (45,31%)
≥56	35 (54,69%)
Gender	
Male	32 (50%)
Female	32 (50%)
Depth of tumor	
T1	3 (4,84%)
T2	10 (16,13%)
T3	46 (74,19%)
T4	3 (4,84%)
Lymph node metastasis	
N0	27 (43,55%)
N1	29 (46,77%)
N2	5 (8,06%)
N3	1 (1,61%)
Stage	
I	5 (7,81%)
II	22 (34,37%)
III	36 (56,25%)
IV	1 (1,56%)

Table 2. Table summarizing Haematological parameters (LMR = Lymphocyte-Monocyte-Ratio, NLR= Neutrophils-Lymphocyte-Ratio, PLR= Plaquettes-Lymphocytes Ratio) of Moroccan rectal patients.

Biological Parameters		Histological Complete Remission		P value
		No (n = 55) (%)	Yes (n = 9) (%)	
LMR Status	Low <3	n = 26 (47,3)	n = 6 (66,7)	0,28
	High >3	n = 29 (52,7)	n = 3 (33,3)	
NLR Status	Low <4	n = 28 (50,9)	n = 4 (44,4)	0,71
	High >4	n = 27 (49,1)	n = 5 (55,6)	
PLR Status	Low <130	n = 8 (14,5)	n = 4 (44,4)	0,03
	High >130	n = 47 (85,5)	n = 5 (55,6)	

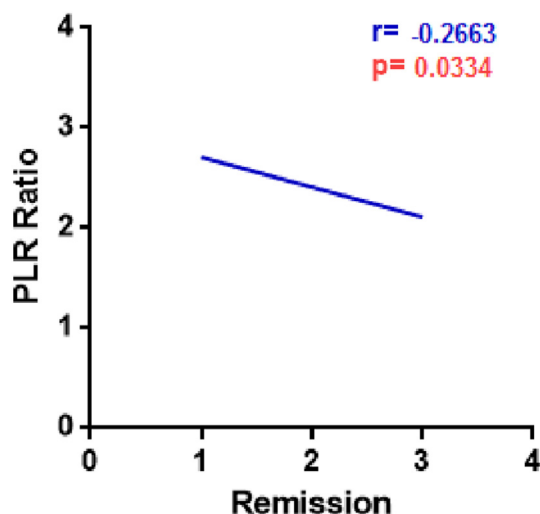


Fig. 1. Graph illustrating the correlation between the ration PLR and remission in our study.

after preoperative chemoradiotherapy [15]. The 959-patient meta-analysis conducted by Dong et al. confirmed that the high NLR was associated with worse pathological and clinical outcome [22].

However, in the present study, the NLR had no significant impact on the prognosis response whether based on our own cut off or the other ratios already published.

To date, the optimal cut-off value of PLR for predicting prognosis in colorectal cancer remains unknown. Based on the results of a large study investigating 1845 patients, the cut off could be defined in 130. It has been demonstrated in many studies that high PLR is a predictor of a poor prognosis [14]. In fact, platelets can prevent tumor cell death by natural killer cells and secretion of angiogenic and tumor growth factor; promote tumor growth and spread. Lymphocytes are the main components of the host's immune system and can kill cancer cells and prevent tumor progression. Some studies have shown that low lymphocyte count is a factor of poor prognosis in patients with CRC [23–25]. In the present study, high PLR level was associated with poor prognosis with 85,5% of patients not reaching complete histological response and this difference was statistically significant, with negative correlation.

The authors are aware of the limited number of patients included in this retrospective study as well as parameters variety (chemo-radiotherapy regimens, the interval between radiotherapy and surgery); therefore, conducting a large prospective national study is warranted.

5. Conclusion

It is a real challenge to identify resistant from responder patients prior to treatment. Hence, the definition of biological predictive factors of therapeutic response could modify the therapeutic management of rectal cancer. The hematological biomarkers, such as the lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) are routine and accessible exams that will guide for personalized treatment of rectal cancer.

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Ethics approval and consent to participate

Studies including human participants were examined and agreed upon by the Ethics Council of the University Mohamed VI University of Health Sciences (CERB/UM6SS/12/21).

Conflict of Interest

The authors declare no conflicts of interest.

Author contributions

A. Naim conceived and designed, did the literature search, writing of the manuscript.

N. Bouanani participate to the literature search, interpreted data writing of the manuscript.

F. Safini collected data.

S. Mouunaim collected data.

S. Rafii Analyzed, and interpreted data writing of the manuscript and made the figures.

M. Khaliss revised the manuscript.

L. Lachker collected data.

F. Guessous reviewed and edited the manuscript.

N. Tawfiq revised the manuscript.

A. Baddou Supervised, reviewed and edited the manuscript.

All authors contributed to the article and approved the submitted version.

Compliance with ethical standards

All authors declare no competing interests.

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