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NEUTROPHIL-LYMPHOCYTE RATIO (NLR) AND LYMPHOPENIA AS PROGNOSTIC FACTORS OF OVERALL SURVIVAL IN LOCAL ADVANCED RECTAL CANCER

Oncology

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ABSTRACT

Purpose: Inflammation is a marker associated with carcinogenesis in solid tumours. In locally advanced rectal cancer (LARC), neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME) is the standard treatment with high rates of local control, although we lack prognostic factors that involve the patient's immune status. Specific immunity measured in a blood count can be helpful in determining the neutrophil-lymphocyte ratio (NLR) and lymphopenia. **Method:** Retrospective study in 137 patients diagnosed with LARC, who underwent nCRT and TME. Blood analysis was obtained prior to initiation of nCRT to obtain lymphocytes and NLR with a cut-off value of 3, the cut-off value of lymphopenia was determined for toxicity scale of Common Terminology Criteria for Adverse Events (CTCAE v5.0), and the sample were divided in two groups: 0-3 and 4-5 toxicity scale. Both prognostic factors were compared with tumour regression grade (TRG) and overall survival (OS). **Results:** Pre-operative NLR showed 75,2% of patients with a value under 3 a 24,8% with a value up 3, with a significantly pathologic regression (p=0,004) and with OS (p=0,001) in favor to low NLR. Lymphopenia was significantly higher in the second group (p=0,034) and associated with poor OS. The follow-up were 34,35 months. **Conclusion:** Elevated pre-operative NLR and lymphopenia are prognostic factors for poor outcome and OS in rectal cancer patients. Therefore, these factors may be considered as potential biomarkers that need to be further validated by prospective studies.

KEYWORDS

Cancer, rectum, radiotherapy, biomarkers

INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy and the second cause of cancer-related death world-wide [1]. Approximately 50% of rectal cancers (RC) are diagnosed at the locally advanced stage [2].

Neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME) is the gold standard treatment for these patients [3], with down sizing, lower rate of postoperative local recurrence, higher rate of preservation of sphincter and longer survival [4]. However recently studies (RAPIDO Trial) [5], may be change the peri-operative strategy, but it also depends of prognostic factors identified in previous studies as carcinoembryonic antigen (CEA), vascular invasion, tumour size, perineural invasion and recently budding tumoral [3,6].

In 1863, Rudolf Virchow described a possible association between malignant tumours and inflammation [7], years later and with multiple studies about immunotherapy, carcinogenesis, and systemic inflammatory response (SIR), the results are controversial in solid tumours [7], but several studies have shown that (SIR) can affect tumour progression [8].

Many inflammatory response indicators have been studied as the level of lymphocytes (lymphopenia), neutrophils, monocytes, platelets, C-reactive protein, erythrocyte sedimentation rate, interleukin-6 and their combinations, high neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and lymphocyte-monocyte ratio (LMR) [9].

Therefore, we propose of this study was to evaluate the predictive and prognostic role of neutrophil-lymphocyte ratio (NLR) and lymphopenia in patients with local advanced rectal cancer (LARC).

METHODS

Patients

One-hundred and thirty-seven patients with LARC (8th edition of the American Joint Committee on Cancer: AJCC) who underwent nCRT followed by TME between January 2016 and March 2020 at our center were evaluated. Patients aged rate were 68.15 years. Medical records, clinical and pathological staging, blood test analysis (BTA), radiological reports, histologically confirmed rectal adenocarcinoma, Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, were retrospectively reviewed. The exclusion criteria were patients who had short course neoadjuvant radiotherapy, did not complete treatment and received adjuvant radiotherapy or palliative treatment. This study was approved by ethics committee of our institution (Nº PI-4819) June 10th, 2021.

Clinical Staging

Clinical staging was performed by physical examination, colonoscopy, BTA with tumoral blood markers (CEA and Ca 19-9), computerised tomography (CT-scan) and pelvic magnetic resonance imaging (MRI) previous and after nCRT. All patients were evaluated by a multidisciplinary team (MDT).

Blood test analysis

The initial peripheral BTA were performed within 1 week before the start nCRT and 1 week after finishing the nCRT and included: neutrophil, lymphocyte, CEA and Ca 19-9. The NLR was obtained by dividing the absolute neutrophil count by the absolute lymphocyte count.

Treatment

All patients received whole pelvic radiotherapy (RT) and primary tumour boost using three-dimensional conformal radiotherapy (3D-C) with 6 MV photons from a linear accelerator (Elekta Synergy). A total dose of 50.4 Gy was delivered in 28 fractions on 5 days per week and few patients received 53.20 Gy whole pelvic radiotherapy (RT) with primary tumour boost using intensity-modulated radiotherapy (IMRT) with volumetric arc therapy (VMAT) and image guide radiotherapy (IGRT) with cone-beam CT image (CBCT) daily. All patients received oral capecitabine (825 mg/m2 each 12 hours) during days of radiotherapy as radiosensitizer. TME was performed 8 to 10 weeks after the end of nCRT by experienced colorectal surgeons who decide the indication of surgery according to location: low anterior resection (LAR), ultralow anterior resection (UAR) and abdominoperineal resection (APR).

Assessment of Tumour Response

All respected specimens were evaluated by the same an experienced pathologist as form part of MDT. Tumour regression grading (TRG) was performed according Dworak regression scoring system [10]. This system is defined as follows: 0, no regression; 1, dominant tumour mass with obvious fibrosis and/or vasculopathy; 2, dominant fibrotic changes with few tumour cells or groups (easy to find); 3, very few (difficult to find microscopically) tumour cells in fibrotic tissue with or

without mucous substance; and 4, no tumour cells and only a fibrotic mass (total regression or response).

Follow-up

Follow up was performed every 3 months for the first 2 years after treatment and every 6 months thereafter. Evaluations included BTA, physical examination with digital rectal examination (DRE), CT-scan of the abdomen and pelvis and colonoscopy.

Statistical Analysis

All statistical operations were performed using SPSS version 22.0 for Windows (IBM Corp., Armonk, NY). All statistical significance levels were with $p<0.05$. The primary endpoint was overall survival (OS), defined as the time from the day of disease diagnosis until the date of death. The cut-off value of NLR were 3 and lymphopenia grades according to Common Terminology Criteria for Adverse Events (CTCAE v5.0) establish: grade 1: less of normal value and 800/mm3, grade 2: <800-500 mm3, grade 3: <500-200mm3 and grade 4: <200mm3 The OS were described using the Kaplan-Meier method, and differences were compared using log-rank statistics. Univariate, multivariate Cox regression and logistic regression models were used to evaluate the effect of NLR and lymphopenia OS.

RESULTS

Patient characteristics

In our study, 137 patients were retrospectively evaluated. Included patients had a mean age of 68,15 (range 40-88) the median follow-up period for all patients was 34,35 months (SD ± 15,92 months). There was a male predominance with 71 (51.8%) and 66 (48.2%) females.

The clinicopathological characteristics of the patients are presented in Table 1. Thirty patients (22.4%) experienced pathological complete response (pCR), one-hundred and one (75.4%) patient experienced partial pathological response (pPR) and six patients (2.2%) no experienced response.

TABLE 1. Patient characteristics

Characteristic	Value
Age (years)	68.15 ± 11.01
Gender	
Male	71 (51.8%)
Female	66 (48.2%)
ECOG*	
0	104 (75.9%)
1	33 (24.1%)
Tumour location	
Low	40 (29.2%)
Medium	77 (56.2%)
High	20 (14.6%)
Surgery	
URA**	47 (34.3%)
LAR***	47 (34.3%)
AP+	43 (31.4%)
cPR++	30 (22.4%)
pPR+++	101 (75.4%)
No response	6 (2.2%)
NLR	
> 3	34 (24.8%)
≤ 3	103 (75.2%)
Lymphopenia	
0-3 grades	95 (69.4%)
4-5 grades	42 (30.6%)
CEA	4.73 ± 8.73
Ca 19.9	16.02 ± 19.42
Radiotherapy technique	
VMAT¨	34 (24.8%)
3D-C¨	103 (75.2%)

*ECOG: Eastern Cooperative Oncology Group. ** URA: ultralow anterior resection. ***LAR: low anterior resection. +AP: abdominoperineal resection. cPR++: Complete pathological response. pPR+++: Partial pathological response. NLR : Neutrophil lymphocytes ratio. CEA¨: carcinoembryonic antigen. VMAT¨: volumetric arc therapy. 3D-C¨: three-dimensional conformal radiotherapy.

Correlations between NLR and tumour pathologic regression

To determinate the clinical significance of NLR and TRG, the association of NLR with clinicopathological features were analysed. The cut-off value was 3. 103 patients (75.2%) were a value under 3, and 34 patients (24.8%) have a value up 3. The results showed that NLR was significantly correlated with pathologic regression (p=0,004) and the multivariate analysis showed that low NLR was associate with positive OS (p=0.001).

Correlations between Lymphopenia and clinicopathological factors

The optimal cutoff value was determined for toxicity grade of CTCAE v5.0 and two groups were made (Grade 0-3 and 4-5). Into the first group (grade 0-3) were 95 patients (69.4%) and in the second group 42 patients (30.6%). The multivariate analysis showed superior OS in the first group (p=0.034).

Survival analysis with NLR and lymphopenia

The OS rates of the patients in different subgroups were subsequently calculated. As displayed figure 1 and table 2, patients with low NLR showed a much better OS rate than patients with high NLR. Patients with lymphopenia grade >3 showed much worse OS rate than patients with lymphopenia grade 0-2.

TABLE 2. Overall Survival

Characteristic	OS (months)
Lymphopenia	
0-3 grades	54.4 ± 1.6
4-5 grades	43.26 ± 8.1
NLR*	
>3	44.0 ± 1.5
≤ 3	55.9 ± 1.5

* NLR: Neutrophil lymphocytes ratio.

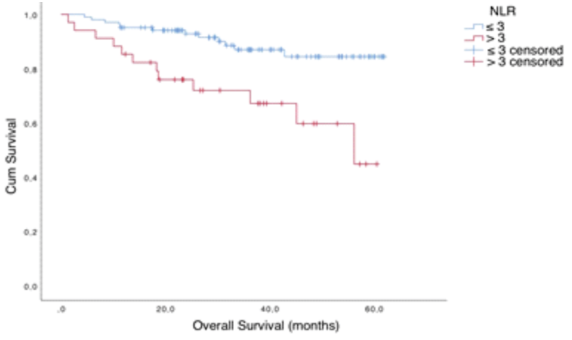

FIGURE 1. Neutrophil lymphocytes ratio (overall survival).

DISCUSSION

The evidence has indicated that approximately 25% of all human cancers in adults result from chronic inflammation [11]. Systemic inflammation plays a pivotal role in cancer proliferation by acting on the local tumour and microenvironment [8,12]. Inflammation contributes to tumour proliferation, angiogenesis, metastasis, and it defeats the adaptive immune responses [13].

During inflammation leukocytes (includes lymphocytes, monocytes, and macrophages) are movement from blood into inflamed tissue [11]. Macrophages have a pro-tumour effect and can secret cytokines and chemokines that can mediate cell recruitment and adaptive immune response suppression [8,9].

The occurrence of an immunologic anti-tumour reaction depends on lymphocytic infiltration (predominantly CD4+ or CD8+ T cells) into the tumour microenvironment, playing a positive role in achieving the complete eradication of tumour cells [9,11], therefore, lymphopenia could cause immune escape of malignant cells.

The evidence indicates that tumour growth is been influenced with myeloid cell, monocytes and macrophages can help the growth and

survival of tumour cells contribute to the suppression of host antitumor immunity [3,14]. On other hand maintaining the number of lymphocytes is beneficial, especially T cells [14].

Circulating cells in the blood reflected the immune response against the tumour and systemic inflammation in patients [8]. In this line, NLR is considered as a poor prognostic indicator, but with a controversial use.

Dong et al. [15], concluded that high NLR has been related with unfavourable OS. Şefika et al [8], found that high NLR were a significant prognostic factor of poor OS in concordance with the conclusion of Cha et al. with 131 patients [16].. Other study showed that preoperative NLR could predict tumour relapse in stage I-II [17] and other authors propose use NLR as predictor for tumour poor response (unfavourable factor) in LARC [3, 7, 18, 19, 20], Li et al evaluated in 140 patients determine that NLR were better predictor than other ratios like platelet-to-lymphocyte-ratio [21].

On other hand, 152 patients evaluated by Portale et al. [22], were not associated with survival after rectal cancer surgery in concordance with Wu et al., and their study [14].

Andras et al., establish that NLR is a simple and cost-effective predictor of nCRT response in LARC [23]. Same conclusion of Duque-Santana et al in their study where they included also platelet lymphocyte ratio with favourable results to be considered prognostic factors [24]

Cantero-Cid et al analysed the relationship of leukocyte ratios in blood and infiltrating peritumour cells (CD4+, CD8+, CD14) with strong results of worse OS in right and left colorectal cancer [25].

Our results using cutting-off value of 3 as many studies, are similar to describe in literature despite the controversial in this topic [26]. Therefore, pre-operative NLR was a predictor of poor response to nCRT. NLR result in higher pro-tumour activity which will affect the oncological outcomes of the patient [23].

Other important circulating cell related with anti-tumour activity are the lymphocytes, who are the most radiosensitive cells of the hematopoietic system.

Preclinical and clinical studies have shown that even low doses of radiation therapy (<1 Gy) can directly kill circulating lymphocytes with an important detrimental oncologic outcome [27].

Radiation therapy suppresses circulating immune responses by dysregulation PD-1/ligand signaling: decreased CD8+ T cells and elevated levels of circulating myeloid-derived suppressor cells (MDSC), however CD4+ T cells increased the expression of PD-1 (up regulating), therefore the blocking agents in combination with chemoradiotherapy (CRT) could be a new option in some specific tumours treatment like HPV-related oropharyngeal cancer (HPVOPC) [28].

Nowadays, several studies have demonstrated a significant detrimental prognostic association of treatment induced lymphopenia with pathologic progression free survival (PFS), and OS [29].

A recent systematic review suggests an important association between radio-induced lymphopenia (RIL) and reduced OS, with an increased risk of death (65%) with grade >3 compared with 0-2 lymphopenia and 50% for patients with grade 4 compared with grade 0-3 lymphopenia [27].

Many factors related to radiation therapy, such treatment volume, number of fractions could be related with lymphopenia and the hypothesis is the irradiation of large volume of the total blood pool (circulating lymphocytes) and bone marrow could produce more lymphopenia. Thus, Wild et al.[30] compared the grade of lymphopenia with ablative techniques and conventional CRT in locally advanced pancreatic cancer (LAPC); the investigators found that Stereotactic Body Radiotherapy (SBRT) is associated with significantly less severe RIL than CRT at 1 month in LAPC [30]. These results supporting the theory that radiation techniques (SBRT), decreasing fraction number, and shrinking target volumes may spare circulating lymphocytes and affects RIL and hence increase survival in patients.

Our results are in concordance with literature and demonstrate a significant and clinically relevant association of RIL with reduced OS in patients who undergo radiation therapy for rectal cancer, therefore, this prognostic factor could help to elucidate which patients are at high risk and explore strategies to decrease lymphopenia.

This study is limited by the low sample size, the fact that it was carried out in one center, the short follow-up time and the lack of homogeneous criteria in the literature to compare results.

CONCLUSIONS

Elevated pre-operative NLR and RIL are prognostic factors for poor outcome and OS in rectal cancer patients. Therefore, these factors may be considered as potential biomarkers that need to be further validated by prospective studies.

STATEMENTS AND DECLARATIONS

The authors declare that they have no conflict of interest.

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