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Predictive value of leukocyte- and platelet-derived ratios in rectal adenocarcinoma

William H. Ward, MD, MS,[a,*] *Neha Goel, MD,*[a] *Karen J. Ruth, MS,*[b] *Andrew C. Esposito, BS,*[c] *Fernando Lambreton, MD,*[a] *Elin R. Sigurdson, MD, PhD,*[a] *Joshua E. Meyer, MD,*[d] *and Jeffrey M. Farma, MD*[a]

[a] *Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania*
[b] *Biostatistics and Bioinformatics Facility, Fox Chase Cancer Center, Philadelphia, Pennsylvania*
[c] *Lewis Katz School of Medicine, Temple University, Philadelphia, Pennsylvania*
[d] *Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania*

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ABSTRACT

Background: Advances in treatment of rectal cancer have improved survival, but there is variability in response to therapy. Recent data suggest the utility of the lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) in predicting survival. Our aim was to examine these ratios in rectal cancer patients and determine whether any association exists with overall survival (OS).

Methods: Using prospectively maintained institutional data, a query was completed for clinical stage II-III rectal adenocarcinoma patients treated from 2002 to 2016. We included patients who had a complete blood count collected before neoadjuvant chemoradiation (pre-CRT) and again before surgery (post-CRT). The LMR, NLR, and PLR were calculated for the pre-CRT and post-CRT time points. Potential cutpoints associated with OS differences were determined using maximally selected rank statistics. Survival curves were compared using log-rank tests and were adjusted for age and stage using Cox regression.

Results: A total of 146 patients were included. Cutpoints were significantly associated with OS for pre-CRT ratios but not for post-CRT ratios. Within the pretreatment group, a "low" (<2.86) LMR was associated with decreased OS (log-rank $P = 0.004$). In the same group, a "high" (>4.47) NLR and "high" PLR (>203.6) were associated with decreased OS (log-rank $P < 0.001$). With covariate adjustment for age, and separately for final pathologic stage, the associations between OS and LMR, NLR, and PLR each retained statistical significance.

Conclusions: If obtained before the start of neoadjuvant chemoradiation, LMR, NLR, and PLR values are accurate predictors of 5-y OS in patients with locally advanced rectal adenocarcinoma.

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* *Corresponding author*. Address: Department of Surgical Oncology, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA 19111. Tel.: +1 215 728 6900; fax: +1 215 728 2773.
E-mail address: william.ward@fccc.edu (W.H. Ward).

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Introduction

As the fourth most common cancer diagnosed annually in the United States, colorectal adenocarcinoma is estimated to have resulted in over 50,000 deaths in 2017.[1] Although overall incidence has decreased,[2] existing data confirm that prognosis among patients with advanced-stage disease remains poor.[3] Within the subset of locally advanced rectal adenocarcinoma, a multidisciplinary approach has been championed as the standard of care and overall survival (OS) has improved.[1,4] Current evidence-based treatment for patients with locally advanced disease includes neoadjuvant chemoradiation, subsequent total mesorectal excision, and postoperative chemotherapy.[2]

Despite a standardized approach in the treatment of rectal cancer, there is significant variability in response to therapy.[5] Of patients who receive neoadjuvant treatment followed by surgical excision, only 15% to 30% achieve a complete pathologic response, whereas others achieve only a partial or no discernible response within the surgical specimen.[6] The possibility of complete pathologic response has led to the growth of a "watch-and-wait" approach, through which a limited number of institutions have demonstrated successful patient outcomes following nonoperative treatment.[7] If tumor response to preoperative therapy was able to be reliably predicted, rectal preservation and the elimination of a proctectomy could be considered. Likewise, if inherent tumor resistance to routine systemic therapy was elucidated in the pretreatment setting, avoidance of unnecessary radiation and chemotherapy-associated toxicity could be achieved, and such patients could proceed directly to extirpation.

Although individual tumor biology has long been assumed to be a primary contributor to variability in treatment response,[8] recent investigations have examined the role that host factors may play in resistance to therapy.[9-11] The relationship between inflammation and malignant growth has been well established, but renewed interest in the specific interaction of tumor cells and their host's stromal microenvironment has revealed that the degree of systemic inflammatory cellular activity in the pretreatment setting may facilitate risk stratification for recurrence and survival.[9,10] It has been shown that the number of circulating lymphocytes, as markers of immunologic response, may be lower in patients with disseminated colorectal cancer.[3,12] Conversely, increased platelets have been implicated in facilitating local tumor growth via mechanisms promoting angiogenesis, access to the extracellular environment, enhanced adhesive capability, and ultimately metastatic spread.[9] Neutrophil involvement appears to play a similar role, as the ability of signaling and associated recruitment by tumor cells has been recently demonstrated.[13] Monocytes have also been identified as important mediators of oncologic growth, with higher numbers in circulation indicative of increased tumor burden and decreased immunosurveillance.[3,10] In this context, previous studies have established the lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) as possible indicators of ongoing systemic inflammation and, in turn, worse outcomes in several malignancies.[3,9,10,14-17]

The relatively universal availability of the serum complete blood count (CBC) makes the LMR, NLR, and PLR attractive as potential prognostic biomarkers because of the ease and convenience of computation. Although recent data have demonstrated their use in colorectal adenocarcinoma, a limited number of investigations have examined the predictive value of these tools in locally advanced rectal cancer treated with standard neoadjuvant chemoradiation and total mesorectal excision.[16,18-22] Only two previous studies have examined the use of all three ratios in this population.[23,24] The aim of our study was to examine our institutional experience and determine whether any association exists between LMR, NLR, and PLR values and OS. As previously suggested in other cancers,[3,9,25] we hypothesized that patients with an increased LMR would have greater OS, whereas those with an increased NLR and PLR would have lower OS.

Materials and Methods

Following approval by our center's institutional review board, the prospectively maintained Fox Chase Cancer Center tumor registry was queried for all patients with locally advanced rectal adenocarcinoma who underwent treatment at our institution from 2002 to 2016. Waiver of individual informed consent was granted for this retrospective investigation. Only those patients with AJCC stage II or III disease who underwent neoadjuvant chemoradiation and subsequent surgical resection at Fox Chase were included. In addition, only patients with a CBC within 60 d of chemoradiation initiation (i.e., before neoadjuvant chemoradiation [pre-CRT]) were included, as were those with a CBC result within 60 d of definitive surgery (post-CRT) (Fig. 1). In cases where multiple CBCs were drawn before initiation of neoadjuvant treatment, we used the most recent value (i.e., the CBC closest to the start of therapy). In cases where multiple CBCs were drawn in the time between treatment conclusion and surgery, we used the most recent value (i.e., the CBC closest to the day of surgery). We did not use values drawn on the day of treatment initiation or on the day of surgery to avoid therapy-related confounding. Standard practice at Fox Chase involved definitive surgical extirpation 8-10 wk after the completion of external beam radiation. Throughout the study period, all patients underwent an open, laparoscopic, or robotic total mesorectal excision. Demographic, pretreatment, posttreatment, and final pathologic TNM staging data were collected as well as treatment intervals in days, recurrence status, and vital status. The LMR, NLR, and PLR were calculated for the pre-CRT and post-CRT time points using standard platelet counts and absolute lymphocyte, monocyte, and neutrophil counts within the most recent CBC. Patients with incomplete laboratory data, staging information, survival, or recurrence status were excluded. The primary outcome of interest was OS, and the secondary outcome of interest was disease-free survival (DFS).

Statistical analysis

We hypothesized that the LMR, NLR, and PLR variables could be split into low and high groups associated with OS. We