ACTA ONCOLOGICA
2019, VOL. 58, NO. 3, 377–392

Taylor & Francis
Taylor & Francis Group

LETTER TO THE EDITOR

Neutrophil lymphocyte ratio is significantly associated with complete response to chemoradiation in locally advanced cervical cancer

Aparna Gangopadhyay[a,b]

[a]Department of Radiotherapy, Medical College Hospitals Kolkata, Kolkata, India; [b]Department of Radiotherapy, Chittaranjan National Cancer Institute, Kolkata, India

Introduction

Definitive chemoradiation remains the gold standard in the management of locally advanced cervical cancer [1,2]. Radio curability is achievable in these tumors owing to anatomical advantages and favorable tolerance of organs at risk that allow delivery of high doses to the tumor while respecting normal tissue dose constraints. Radiosensitivity is a key factor in cell kill and is significantly enhanced by concomitant chemotherapy. Numerous patient and tumor-related factors influence radiosensitivity and clinical response in cervical cancer; large tumor volumes and tissue hypoxia are known to be particular challenges to radiation response in locally advanced stages [3–5]. However, the association of radiation response with immune balance in these cancers is unclear.

Neutrophil lymphocyte ratio (NLR) is a marker of systemic inflammation, easily obtained from the results of a routine hemogram. As an indicator of cell mediated immune balance, it has prognostic value in various medical conditions. Its impact on survival and outcomes has been demonstrated in many cancers [6–10]. NLR has also been found to be related to tumor microenvironment immune balance. Studies have demonstrated alterations in tumor radiosensitivity with concomitant activation of the patient immune system during radiation therapy, and clinical benefits of immunomodulatory agents on radiotherapy outcomes are becoming increasingly evident [11–15]. Data on the association of immune balance and radiation response in cervical cancer is scarce. This study investigated whether NLR, an easily available, clinically relevant marker of systemic inflammation and immune response could predict clinical response to radiation in cervical cancer.

Material and methods

The present study evaluated 583 women from two cancer centers, presenting with histologically proven locally advanced cervical cancer (stages IIB–IVA) between February 2007 and January 2014. Every patient underwent routine investigations during assessment at baseline, and NLR was obtained from the complete hemogram. In view of the established relationship between nutrition and immune balance, the prognostic nutritional index (PNI) was calculated at baseline for every subject. Histology, baseline hemoglobin, tumor stage, and presence of pelvic inflammatory disease at presentation were also individually recorded. These women received pelvic chemoradiation to a dose of 50 Gy in 25 fractions over 5 weeks with weekly concomitant Cisplatin at a dose of 40 mg/m^2. Treatment was completed after conclusion of subsequent brachytherapy. Tumor response was assessed clinically by gynecological examination immediately prior to the first brachytherapy fraction, which ranged from 7 to 12 d after completion of pelvic chemoradiation. Complete clinical response was considered if no evidence of tumor was found visibly on speculum inspection and on bimanual examination.

Statistical analysis was performed using MedCalc Statistical Software version 18.6 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018).

Logistic regression was performed to find association between the two variables, namely NLR and complete response. Receiver operating characteristics were analyzed to find the optimal cut off NLR value that had the highest specificity and sensitivity in predicting complete response.

Pearson's correlation test was performed to investigate any association between baseline NLR and PNI in this cohort.

Results

In this cohort, a majority had FIGO stage IIIB disease (83.7%). Median age at presentation was 34 years (range 26–63 years). Five hundred twenty-four (89.9%) women had squamous cell histology. Among the 583 women evaluated, clinical complete response was noted in 505 (86.6%).

In the group achieving clinical complete response, 22.9% had baseline hemoglobin levels below 12 g/dl as opposed to 19.2% in the partial responders. Of the women achieving complete response, 18.4% had symptomatic pelvic inflammatory disease at presentation that required antibiotics. Drainage of pyometra was also necessary in 27 women in this group. In contrast, pelvic inflammatory disease at baseline was recorded in 24.3% women who failed to achieve complete response. The majority (79.2%) of the complete responses was noted at NLR levels below 3.1 (Table 1).

CONTACT Aparna Gangopadhyay mails7778@gmail.com; aparna.radt@gmail.com Medical College Hospitals Kolkata, 88, College Street, Kolkata 700073, India.

https://doi.org/10.1080/0284186X.2018.1556803

Table 1. Patient characteristics ($n = 583$).

	Complete response ($n = 505$)	Partial response ($n = 78$)
Stage		
IIB	76	6
IIIA	2	7
IIIB	421	67
IVA	6	4
Histology		
Squamous cell carcinoma	452	72
Adenocarcinoma	52	6
Small cell carcinoma	1	0
Hemoglobin		
Above 12 g/dl at baseline	389	63
Below 12 g/dl at baseline	116	15
Symptomatic pelvic inflammatory disease at baseline requiring treatment		
Present	93	19
Absent	412	59
NLR values range		
1.0–2.0	74	5
2.1–3.0	326	2
3.1–4.0	27	14
4.1–5.0	69	43
5.1–6.0	9	13
6.1–7.0	0	1

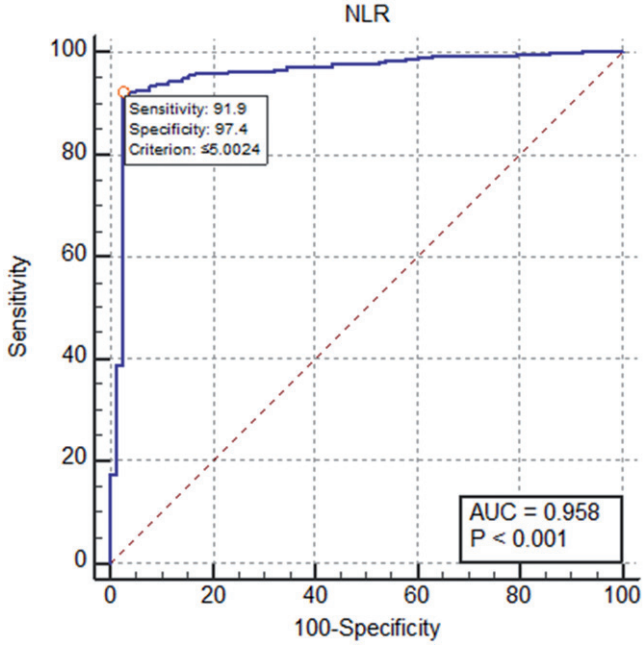

Figure 1. ROC curve for NLR and complete response.

Logistic regression demonstrated significant association of NLR with complete response following chemo radiation ($p < .0001$). Overall model fit was good (Nagelkerke R^2 0.6549, Hosmer & Lemeshow test Chi-squared value 42.71). ROC curve analysis of NLR demonstrated an optimal cut off value of 5.002 ($p < .0001$, sensitivity 91.9, specificity 97.4). Area under the ROC curve, 0.958 (Youden's index J, 0.8932) (Figure 1).

Pearson's correlation coefficient r showed a significant negative linear relationship between NLR and PNI in this group ($r = -0.69$, $p < .0001$).

Discussion

As ongoing studies continue to evaluate impact of immunity on radiotherapy response and patient outcomes, relationships between patient immune balance and tumor radiosensitivity become increasingly relevant.

Locally advanced cervical cancer presents many challenges to the radiation oncologist. A large irregular tumor volume with hypoxic zones, hemorrhage-induced anemia, and pelvic inflammatory disease commonly found at presentation are some of the factors that hinder cell kill [3–5]. Each individual factor is independently predictive of lower radiosensitivity in these tumors. Various interventions have been employed in an attempt to achieve meaningful responses in the clinic. Enhanced tumor cell kill has been demonstrated by reducing tumor hypoxia [14]. Despite these improvements, the use of concomitant chemotherapy has been by far the most successful in addressing radiosensitivity in locally advanced cervical cancer clinical practice. Further improvement of the present day clinical response rates may be possible with better understanding of modifiable factors that may alter radiation response.

Results from this study show a significant association of NLR, a marker of patient's immune and inflammatory response, with clinical radiation response. Higher NLR values at baseline were found to be associated with poorer complete response to chemoradiation in this cohort. In the clinical context, these findings indicate that lower baseline NLR values in patients with locally advanced cervix cancers are more favorable and likely to lead to clinical complete response after chemoradiation.

Interestingly, incidence of anemia in this cohort, as defined by hemoglobin levels below 12 g/dl in accordance with WHO criteria, was higher in women who achieved complete response than partial responders 22.9% versus 19.2%, respectively. However, the difference was not statistically significant (Fisher's two-tailed p value = .56). The proportion of women with symptomatic pelvic inflammatory disease at presentation was lower in complete responders compared to partial responders, at 18.4% versus 24.3%, respectively, but the difference was not statistically significant (Fisher's two-tailed p value = .22).

Over three quarters of those who achieved complete response in this cohort had NLR values below 3.1 at baseline. These findings suggest that systemic inflammatory response

plays a significant role in radiation induced cell kill and NLR could be a useful biomarker.

In addition to these findings, the significant negative linear relationship between baseline NLR and PNI in this study reinforce the importance of nutrition in supporting a healthy immune balance. This is of particular significance in low resource settings where locally advanced cervical cancer is mostly prevalent. Poor nutrition, reflected by a considerable burden of anemia and protein energy malnutrition, is a major health problem in these regions. Consequently, the interaction between nutrition and immune balance and the resulting impact on radiation response assumes particular importance in this scenario.

Despite the limited sample size, the findings of this study emphasize on the need for further investigations for determining the strength of the association between NLR and clinical tumor response following chemoradiation in locally advanced cervical cancer. In conclusion, NLR offers an inexpensive yet effective tool in the clinic for alerting the clinician of the possible treatment outcome. A baseline NLR value higher than 5 significantly lowers the clinical complete response, and close monitoring of these women during treatment could offer early and effective salvage in the event of treatment failure.

Ethical statement

This study was performed after informed consent and in accordance with the Code of Ethics of the World Medical Association.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Marth C, Landoni F, Mahner S, et al. ESMO Guidelines Committee. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28:iv72–iv83.

[2] Gupta S, Maheshwari A, Parab P, et al. Neoadjuvant chemotherapy followed by radical surgery versus concomitant chemotherapy and radiotherapy in patients with stage IB2, IIA, or IIB squamous cervical cancer: a randomized controlled trial. JCO. 2018;36:1548–1555.

[3] Harrison L, Blackwell K. Hypoxia and anemia: factors in decreased sensitivity to radiation therapy and chemotherapy? Oncologist. 2004;9:31–40.

[4] Suzuki Y, Nakano T, Ohno T, et al. Oxygenated and reoxygenated tumors show better local control in radiation therapy for cervical cancer. Int J Gynecol Cancer. 2006;16:306–311.

[5] Tsukahara Y, Sakai Y, Noguchi H, et al. A study on radiosensitivity and prognostic factors of cervical adenocarcinoma. Nihon Sanka Fujinka Gakkai Zasshi 1980; 32:1609–1614.

[6] Kim TG, Park W, Kim H, et al. Baseline neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in rectal cancer patients following neoadjuvant chemoradiotherapy. Tumori. 2018:300891618792476. DOI: 10.1177/0300891618792476.

[7] Thio QCBS, Goudriaan WA, Janssen SJ, et al. Prognostic role of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in patients with bone metastases. Br J Cancer. 2018. DOI: 10.1038/s41416-018-0231-6.

[8] Shu K, Zheng Y, Chen J, et al. Prognostic value of selected preoperative inflammation-based scores in patients with high-risk localized prostate cancer who underwent radical prostatectomy. OTT. 2018;11:4551–4558.

[9] Szkandera J, Absenger G, Liegl-Atzwanger B, et al. Elevated preoperative neutrophil/lymphocyte ratio is associated with poor prognosis in soft-tissue sarcoma patients. Br J Cancer. 2013;108:1677–1683.

[10] Cushman TR, Caetano MS, Welsh JW, et al. Overview of ongoing clinical trials investigating combined radiotherapy and immunotherapy. Immunotherapy. 2018;10:851–850.

[11] Cadena A, Cushman TR, Anderson C, et al. Radiation and anticancer vaccines: a winning combination. Vaccines (Basel). 2018;6:9.

[12] Aliru ML, Schoenhals JE, Venkatesulu BP, et al. Radiation therapy and immunotherapy: what is the optimal timing or sequencing? Immunotherapy 2018;10:299–316.

[13] Honeychurch J, Illidge TM. The influence of radiation in the context of developing combination immunotherapies in cancer. Ther Adv Vaccines Immunother. 2017;5:115–122.

[14] Tharmalingham H, Hoskin P. Clinical trials targeting hypoxia. BJR. 2018;20170966. DOI: 10.1259/bjr.20170966.

LETTER TO THE EDITOR

The efficacy of platinum-based chemotherapy for immune checkpoint inhibitor-resistant advanced melanoma

Takuya Maeda[a], Koji Yoshino[a], Kojiro Nagai[a], Satoe Oaku[a], Megumi Kato[a], Azusa Hiura[a] and Hiroo Hata[b]

[a]Department of Dermatologic Oncology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan; [b]Department of Dermatology, Faculty of Medicine and Graduate School of Medicine Hokkaido University, Sapporo, Japan

Background

Immune checkpoint inhibitors (ICIs) have been widely used as a first-line therapy for BRAF wild-type advanced melanoma, and they significantly improve the prognosis compared with chemotherapy [1–3]. However, an effective treatment for ICI-resistant melanoma has not been established. Furthermore, a

CONTACT Takuya Maeda mtakun.bsb.hkt@gmail.com Department of Dermatologic Oncology, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan

Supplemental data for this article can be accessed here.

https://doi.org/10.1080/0284186X.2018.1541252