Neutrophil-to-lymphocyte ratio trend: A novel prognostic predictor in patients with nasopharyngeal carcinoma receiving radiotherapy

Pei Yang1,2, Yu Zhao2,4, Hao Liang3, Guanzhi Zhou5,2, Bassem Youssif6, Hesham Elhalawani7, Meizhen Li8, Fengbo Tan1, Yi Jin2, Hekun Jin2, Hong Zhu1, Abdallah Sherif Radwan Mohamed9, Nantavithya Chonnipa10, Danita Kannarunimit10, Yingrui Shi2, Hui Wang2 and Clifton David Fuller9

Abstract

Background: Peripheral neutrophil-lymphocyte ratio (NLR), reflecting immune-inflammation status, shows great potential for tumor progression and outcome. Pre-treatment NLR does not fully reflect the immune-inflammatory response to treatment. This study aimed to introduce the NLR trend as a new indicator and to investigate its prognostic value in patients with nasopharyngeal carcinoma receiving radiotherapy.

Methods: This retrospective study evaluated patients with nasopharyngeal carcinoma treated with radiotherapy. The NLR trend value was calculated from the fitted line gradient via the NLRs before, during (at least once), and after each patient’s first radiotherapy. The Kaplan–Meier curve and log-rank test were used to calculate and compare survival outcomes of different pretreatment NLRs and NLR trends for progression-free survival, locoregional recurrence-free survival (LRFS), and overall survival at 3 and 5 years. Multivariate Cox regression analyses were performed to assess the association between the NLR trend plus 3- and 5-year overall survival.

Results: The study included 528 patients. A lower NLR trend predicted worse progression-free survival, LRFS, plus 3- and 5-year overall survival. Multivariate Cox regression analysis showed that the NLR trend independently predicted 3- and 5-year overall survival. Sub-group analysis showed that the prognosis of patients with a low pretreatment NLR and a high NLR trend were superior to those of other groups.

1Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China
2Key Laboratory of Translational Radiation Oncology, Hunan Cancer Hospital, Affiliated Hospital of Xiangya Medical School, Central South University, Changsha, Hunan, People's Republic of China
3Institute of TCM Diagnostics, Hunan University of Chinese Medicine, Changsha, Hunan, People's Republic of China
4The Miriam Hospital, Providence, RI, USA
5University of South China, Hengyang, Hunan, People's Republic of China
6Department of Radiation Oncology, American University of Beirut, Beirut, Lebanon, Lebanon
7Department of Radiation Oncology, Cleveland Clinic, Cleveland, OH, USA
8Research Institute of Drug Metabolism and Pharmacokinetics, Xiangya School of Pharmaceutical Sciences, Central South University, Changsha, Hunan, People's Republic of China
9Department of Radiation Oncology, MD Anderson Cancer Center, Houston, TX, USA
10Department of Medicine, Chulalongkorn University/King Chulalongkorn Memorial Hospital, Bangkok, Thailand

Corresponding authors: Pei Yang, Hunan Cancer Hospital, the Affiliate Hospital of Xiangya Medical School, Key Laboratory of Translational Radiation Oncology, Central South University, 283 Tongzipo Rd, Yuelu Region, Changsha, Hunan, 410013, People’s Republic of China. Email: yangpei@hncarc.org.cn

Hao Liang, Institute of TCM Diagnostics, Hunan University of Chinese Medicine, 300 Xueshi Rd, Science-Education Industrial Park, Yuelu Region, Changsha 410208, Hunan, People’s Republic of China. Email: lianghao@hnucm.edu.cn

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (https://us.sagepub.com/en-us/nam/open-access-at-sage).
Conclusion: The NLR trend independently predicted the prognosis of patients with nasopharyngeal carcinoma receiving radiotherapy. The NLR trend and the pretreatment NLR combination is more precise than pretreatment NLR in predicting prognosis. A high NLR trend may be evidence of a positive immune response to radiotherapy in patients with nasopharyngeal carcinoma.

Keywords
Neutrophil-to-lymphocyte ratio trend, immune-inflammation response, prognosis, nasopharyngeal carcinoma, radiotherapy

Date received: 1 February 2022; revised: 27 May 2022; accepted 13 June 2022

Introduction
Nasopharyngeal carcinoma (NPC) is an endemic disease in China.1,2 Salted fish consumption, cigarette smoking, alcohol intake, and nitrate exposure are associated with an increased NPC risk.3,4 It is challenging to treat NPC with surgery because of its anatomic location and local aggression characteristics;5 thus, radiotherapy (RT) with or without chemotherapy is the first-line treatment.6 NPC’s current survival prognostic and therapeutic evidence relies on the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) tumor node metastasis (TNM) stage.7

NPC prognosis has improved dramatically due to standard treatment strategies for patients based on the staging system.8 However, locally advanced NPC prognosis is clinically heterogeneous and characterized by increased local recurrence and distant metastasis.9,10 This is because NPC cells have different biological behaviors, immune system levels, and chemoradiotherapy sensitivity. The clinical use of quantitative assessment of circulating Epstein–Barr virus DNA as an NPC surrogate biomarker increases population screening, prognosis, and disease surveillance.1 However, it is expensive and has great inter-laboratory variability. Thus, identifying novel biomarkers for NPC prognosis and precise treatment stratification is still important.11

Increasing evidence suggests that cancer-associated immune inflammation is a key determinant of outcomes. Rearrangements of hematological components, including neutrophils, lymphocytes, and monocytes, often manifest in the host immune system’s tumor-related response. An abnormal white blood cell count is often the first motivation for cancer screening. The neutrophil-to-lymphocyte ratio (NLR) is generally believed to be a biomarker of the immune-inflammatory response to cancer.12,14 Elevated NLR has been associated with poor prognosis in many malignancies.15 A correlation between an elevated NLR and a worse prognosis has also been found in NPC.16,17 NLR may be clinically useful for risk stratification, depending on its combination with other information in particular clinical scenarios.18 However, pretreatment NLR alone cannot reflect the immune-inflammation status during therapy. In these cases, radiation oncologists cannot provide individual strategies based on the different responses to treatment in patients with NPC.

Therefore, we report a novel index of cancer-associated immune inflammation, called the NLR trend, from dynamically monitored NLR during therapy. This study aimed to investigate the prognostic value of the NLR trend in patients with NPC treated with conventional segmented RT alone and to compare NLR trend accuracy with pretreatment NLR and other common factors for NPC survival prediction.

Materials and methods
Patients
The study retrospectively investigated all newly diagnosed patients with NPC who underwent two-dimensional conventional radiotherapy (2DCRT) without chemotherapy between January 1992 and December 2005 at the Head and Neck Department of RT at the Hunan Cancer Hospital. The inclusion criteria were: (a) histologically confirmed NPC; (b) no malignancy history; (c) not on chronic steroid or immunomodulators; (d) stage I–IV disease (restaged according to the Chinese 2008 staging system19); (e) patients without hematological disease, infection, inflammatory conditions, or hyperpyrexia, previous treatment (such as chemotherapy or RT) for NPC; (f) patients with complete blood count (CBC) tests obtained before, during (at least once), and after (BDA) first RT; and (g) patients with complete follow-up data. Eligible patients’ clinical features, including sex, age, Karnofsky Performance Scale,20 AJCC/UICC 1997 stage,21 and World Health Organization (WHO) histologic type, were acquired from medical records. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Hunan Cancer Hospital Ethics Board and hospital review committee. Informed consent was obtained from all the participants. This article is presented in accordance with the REMARK Reporting Guidelines (Supplemental Table 1).22

Treatment
All patients who received 2DCRT without chemotherapy were immobilized in the supine position using a
thermoplastic mask. Two lateral-opposing faciocervical portals were used to cover the nasopharynx and upper neck in one volume, followed by a shrinking-field technique to limit spinal cord exposure. The neck was treated with an anterior cervical field using a laryngeal block. Total radiation with doses 66–74 Gy, (2 Gy per fraction) was delivered to the primary tumor, 60–64 Gy to the other areas involved in the neck, and 50 Gy to the uninvolved areas. RT was administered 5 days per week in daily fractions of 2 Gy. A boost portal was performed, if necessary, during the last one-third of the treatment course. A booster dose (8–12 Gy per 4–6 fractions) was delivered to the skull base of patients with NPC involving the skull base and intracranial extension. The radiation energies used megavoltage photons (6 or 8 MV) and electrons.

Hematological tests

Blood samples (2 mL) from the patients for neutrophil and lymphocyte counts were obtained before breakfast CBCs were detected using a SysmexXE-5000 automated hematology analyzer (Sysmex, Kobe, Japan). The tests were performed at least once before RT (usually 1 day before RT), once a week during RT, and once after RT (usually 1 week after RT).

NLR trend calculation

The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. Each patient’s NLR trend value equaled the gradient (slope) value calculated from a linear model on the NLRs’ BDA scatter plot.

Outcome and follow-up

Overall survival (OS) was selected as the primary endpoint, while progression-free survival (PFS) and locoregional recurrence-free survival (LRFS) were secondary endpoints. All terms were defined according to the NCI Dictionary of Cancer Terms (https://www.cancer.gov/publications/dictionaries/cancer-terms). The patients were followed-up every 3 months for the first 2 years, every 6 months for 3–5 years, and annually after 5 years. Follow-up time was calculated as the first day of therapy to either the day of the last follow-up or death.

Table 1. Pre-treatment NLR cut-off values and prediction of survival analysis.

| Event       | Cutoff value | AUC   | P-value | HR (95% CI)   | χ²     | P-value |
|-------------|--------------|-------|---------|---------------|--------|---------|
| PFS         | Low ≤5.00    | 0.520 | 0.589   | 1.431 (0.792–2.587) 0.699 (0.387–1.263) 1.407 | 0.236  |
| LRFS        | Low ≤2.53    | 0.533 | 0.433   | 0.394 (0.202–0.766) 2.540 (1.305–4.942) 7.533 | 0.006* |
| 3-year OS   | Low ≤3.39    | 0.563 | 0.038*  | 0.638 (0.437–0.932) 1.567 (1.073–2.289) 5.397 | 0.020* |
| 5-year OS   | Low ≤3.50    | 0.544 | 0.091   | 0.658 (0.488–0.885) 1.521 (1.130–2.047) 7.652 | 0.005* |

*P < 0.05.

AUC: area under the ROC curve; CI: confidence interval; HR: hazard ratio; LRFS: locoregional recurrence-free survival; OS: overall survival; PFS: progression-free survival; ROC: receiver operating characteristic.

Statistical analysis

The numerical variables were calculated as median and range, while categorical variables were presented as numbers and percentages. The pretreatment NLR and NLR trend cut-off values for survival prediction were determined using the receiver operating characteristic (ROC) curve (Youden index).

The Kaplan–Meier estimate and log-rank test were used to calculate and compare survival outcomes among the different groups of pretreatment NLR or the NLR trend via PFS, LRFS, and 3- and 5-year OS. Multivariate Cox regression was used to determine the independent association of the NLR trend with 3- and 5-year OS after adjusting for other confounding prognostic factors.

The survival prediction accuracy of the pretreatment NLR and the NLR trend was compared using the area under the curve (AUC) of the ROC curve. According to the cut-off values of pretreatment NLR and the NLR trend for OS prediction, the patients were divided into four subgroups: (a) low pretreatment NLR and low NLR trend; (b) low pretreatment NLR and high NLR trend; (c) high pretreatment NLR and low NLR trend; and (d) high pretreatment NLR and high NLR trend. Kaplan–Meier curves of 3- and 5-year OS and Cox regression analysis stratified according to pretreatment NLR and the NLR trend subgroups were illustrated. They were calculated to compare the subgroups’ prognoses and confirm whether pretreatment NLR and NLR trend combinations could accurately predict OS. All data were analyzed using MedCalc statistical software (version 19.0; MedCalc Software, Mariakerke, Belgium) and R Project for Statistical Computing (4.0, https://cran.r-project.org). All tests were two-sided, and statistical significance was set at P < 0.05.

Results

Patient characteristics

A total of 528 patients with a median age of 46 years (range 18–77 years) who met the inclusion criteria were included in this study. The characteristics of patients with NPC are shown in Supplemental Table 2; 393 (74.4%) patients were males, and 135 (25.6%) were females, with a sex ratio of 2.9:1. Most patients had stage III or IV NPC.
(76.3%) and 210 (39.8%) received additional boost therapy. Within a median follow-up time of 76.4 months (range, 1–219 months), 316 (59.8%) patients died. The remaining 212 patients (40.2%) were either alive or lost to follow-up. The 3- and 5-year OS rates were 78.4% and 63.6%, respectively.

**Pre-treatment NLR for survival analysis**

The median pretreatment NLR was 2.81 (0.08–1458.33). The pretreatment NLR cut-off values for predicting PFS, LRFS, 3-year OS, and 5-year OS were 5.00, 2.53, 3.39, and 3.50, respectively. Patients were divided according to the cut-off values into low and high NLR groups. No significant difference was observed in PFS between the two groups. The LRFS, 3- and 5-year OS rates were significantly higher in patients with low NLR than in those with high NLR (Table 1).

**NLR trend for survival analysis**

The median NLR trend value was 0.81 (range 0.59–155.73). The NLR trend cutoff values to predict PFS and LRFS were 0.37 and 0.35, respectively (Supplemental Figure 1). The patients were divided into low- and high-trend groups according to the cut-off values. The PFS (hazard ratio (HR) 2.42; 95% confidence interval (CI) [1.45 to 4.04]; \( P = 0.000 \); Supplemental Figure 2(a)) and LRFS (HR 3.15; 95%CI [1.55 to 6.40]; \( P = 0.001 \); Supplemental Figure 2(b)) rates were significantly higher in the high NLR trend group than in the low NLR trend group.

The NLR trend cut-off values to predict 3-year OS and 5-year OS were 0.63 (HR = 0.32, Supplemental Figure 3(a)) and 0.68 (Supplemental Figure 4(a)), respectively. The patients in the low-trend group had a lower 3-year OS than the patients in the high-trend group (HR = 1.68; 95%CI [1.16 to 2.44]; \( P = 0.006 \); Supplemental Figure 3(b)), and a similar result was also observed in the 5-year OS of the two groups (HR = 1.41; 95%CI [1.06 to 1.87]; \( P = 0.019 \); Supplemental Figure 4(b)).

**Multivariate Cox regression analysis**

Multivariate analysis showed that pretreatment NLR, NLR trend, age, T-stage, N-stage, and M-stage were significant predictors of survival. The results of the multivariate analysis are shown in Table 1. The Forrest plot of multivariate analysis for 3-year overall survival of pretreatment NLR and NLR-trend determined by cut-off values for patients.

**Figure 1.** Forrest plot of multivariate analysis for 3-year overall survival of pretreatment NLR and NLR-trend determined by cut-off values for patients.

NLR: neutrophil-lymphocyte ratio.

![Table](attachment://table.png)

| Variable         | Reference | Hazard ratio | \( P \)   |
|------------------|-----------|--------------|-----------|
| Sex F          |           |              | 0.322     |
| Age             |           |              | <0.001    |
| T-stage T1     |           |              |           |
| T-stage T2     |           |              |           |
| T-stage T3     |           |              |           |
| N-stage N0     |           |              |           |
| N-stage N1     |           |              |           |
| N-stage N2     |           |              |           |
| N-stage N3     |           |              |           |
| M-stage M0     |           |              |           |
| AJCC Stage     |           |              |           |
| WHO Type       |           |              |           |
| Pre-treatment NLR | reference |              |           |
| NLR-trend Low  |           |              |           |
| NLR-trend High |           |              |           |

# Events: 114  Global \( P \)-value (Log-Rank): 0.0358  C-index: 0.7
independent risk factors for both 3- and 5-year OS, while AJCC/UICC stage and WHO type were not associated with 3- or 5-year OS (Figures 1 and 2).

Comparison of ROC curves for survival prediction

The AUC from ROC curves of the NLR trend and NLR for predicting PFS, LRFS, 3-year OS, and 5-year OS were 0.56 (95%CI 0.52–0.60) versus 0.52 (95%CI 0.48–0.56), 0.60 (95%CI 0.56–0.64) versus 0.53 (95%CI 0.49–0.58), 0.57 (95%CI 0.52–0.61) versus 0.56 (95%CI 0.52–0.60) and 0.55 (95%CI 0.50–0.59) versus 0.54 (95%CI 0.50–0.59), respectively (Supplemental Figure 5). There was no statistically significant difference between the NLR trend and NLR for all predictions ($P > 0.05$).

Sub-group analysis

The patients with 3- and 5-year OS in the four subgroups differed significantly, and the prognosis of those with low pretreatment NLR and high NLR trend were superior to that in the other three groups (Figures 3(a) and (d)). In patients with low pretreatment NLR, a low NLR trend was associated with a lower 3-year OS ($P = 0.008$, Figure 3(b)), while no significant difference was found between the high and low NLR trends in high pretreatment NLR patients (Figure 3(c)). A low NLR trend predicted a lower 5-year OS in patients with a low pretreatment NLR, although the difference was not statistically significant ($P = 0.051$, Figure 3(e)). The Cox regression analysis of 3-year and 5-year OS also showed that the prognosis of patients with low pretreatment NLR and a high NLR trend improved significantly (Figure 4).

Discussion

This study targeted patients who only received radiotherapy to exclude the effect of chemotherapy on NLR, and the NLR trend was calculated from dynamically monitored NLRs during RT. A low NLR trend was found to be a poor predictor of PFS, LRFS, 3-year OS, and 5-year OS in patients with NPC who underwent RT. Multivariate
analysis revealed that the NLR trend was an independent prognostic factor. Similarly, Li et al. found that the delta-NLR obtained from pre- and posttreatment NLRs was an independent prognostic factor for OS in early-stage colon cancer; patients with increased delta-NLR had a favorable clinical outcome. Peng et al. concluded that an increased NLR helped predict worse OS and recurrence-free survival in patients with small hepatocellular carcinoma who underwent curative resection. NLR change prognostic values are dissimilar in different cancers, and exploration of the reasons behind this are interesting.

In recent years, evidence has shown that cancer-associated inflammation is a key determinant of various tumors’ prognosis and therapeutic decisions. The correlation between an elevated NLR and poor prognosis is based on immune-inflammatory theories. Inflammation represents the host immune response to malignancy with respect to neutrophil and lymphocyte activities on tumor cell invasion into the peripheral blood. Neutrophils and related cytokines are the main mediators of angiogenesis and growth in circulating tumors. A decrease in lymphocyte count usually indicates lymphocyte-mediated anti-tumor immunity inhibition and poor clinical outcomes. However, pretreatment NLR prognostic ability has not been conclusively determined for NPC. Recently, a pooled study of two randomized controlled trials revealed the negative result that a high pretreatment NLR was not associated with OS, PFS, and DMFS. Similar results were found in our study, which showed that pretreatment NLR was not significantly correlated with PFS. This negative result can be attributed to several reasons. First, the NLR cut-off value for prediction was confirmed using different methods, such as the median value or ROC curve. Second, the evidence was mostly from retrospective series with sample and design biases. Third, collecting NLR data only once before treatment can be affected by many factors, including age, environment, and immune

Figure 3. Kaplan–Meier 3-year overall survival curve stratified according to pretreatment NLR and NLR-trend for: (a) comparison between low pretreatment NLR and low NLR-trend, low pretreatment NLR and high NLR-trend, high pretreatment NLR and low NLR-trend and high pretreatment NLR and high NLR-trend; (b) the comparison between high NLR-trend and low NLR-trend of low pretreatment NLR patients; (c) the comparison between high NLR-trend and low NLR-trend of high pretreatment NLR patients. Kaplan–Meier 5-year overall survival curve stratified according to pretreatment NLR and NLR-trend for: (d) comparison between low pretreatment NLR and low NLR-trend, low pretreatment NLR and high NLR-trend, high pretreatment NLR and low NLR-trend and high pretreatment NLR and high NLR-trend; (e) the comparison between high NLR-trend and low NLR-trend of low pretreatment NLR patients; (f) the comparison between high NLR-trend and low NLR-trend of high pretreatment NLR patients.

NLR: neutrophil-lymphocyte ratio.
condition, resulting in heterogeneous results. The NLR trend in our study was a neutrophil-lymphocyte change type that reflects the immune-inflammatory response to treatment. Although there was no statistical significance between the NLR trend and NLR predictions, the NLR trend is slightly better. Subgroup analysis in the present study revealed that the NLR trend and NLR combination were more precise in predicting survival. Even though a low pretreatment NLR means favorable outcomes, the prognosis of patients with a low pretreatment NLR and a low NLR trend was still poor in the current study (\(P < 0.05\)). Thus, radiation oncologists could optimize the NLR trend strategies during treatment.

With diagnostic imaging and RT technology development, especially intensity-modulated RT (IMRT), the

---

**Figure 4.** Forrest plot of sub-group Cox regression analysis for 3-year overall survival (a) and 5-year overall survival (b) stratified according to pretreatment NLR and NLR-trend. NLR: neutrophil-lymphocyte ratio.

| Hazard ratio | P       |
|--------------|---------|
| 3-year OS    |         |
| H_NLR-H_trend (N=109) | reference |         |
| H_NLR-L_trend (N=102) | 1.38 (0.76 - 2.41) | 0.315 |
| L_NLR-H_trend (N=58) | 0.53 (0.37 - 0.80) | 0.005 * |
| L_NLR-L_trend (N=33) | 0.99 (0.63 - 1.57) | 0.838 |

| Hazard ratio | P       |
|--------------|---------|
| 5-year OS    |         |
| H_NLR-H_trend (N=109) | reference |         |
| H_NLR-L_trend (N=102) | 1.34 (0.81 - 2.19) | 0.229 |
| L_NLR-H_trend (N=58) | 0.64 (0.42 - 0.96) | 0.032 * |
| L_NLR-L_trend (N=32) | 0.92 (0.61 - 1.40) | 0.599 |

---

**Figure 5.** The illustrated summary of NLR-trend for nasopharyngeal carcinoma. NLR: neutrophil-lymphocyte ratio.
The NLR trend is a new independent prognostic factor for patients with NPC treated with RT. The combination of the NLR trend and pretreatment NLR is more accurate in predicting NPC prognosis than pretreatment NLR alone. A high NLR trend may be evidence of a positive immune response to RT in NPC, and it can be a promising index for individualized radioimmunotherapy.

Acknowledgments

The authors gratefully acknowledge the help of the support from the information department of Hunan Cancer Hospital for providing previous release files of the database.
conducted between 1979 and 2011. Am J Epidemiol 2013; 178: 325–338.

5. Huang WB, Wong STS and Chan JYW. Role of surgery in the treatment of osteoradionecrosis and its complications after radiotherapy for nasopharyngeal carcinoma. Head Neck 2018; 40: 369–376.

6. Lee A, Ma B, Ng WT, et al. Management of nasopharyngeal carcinoma: current practice and future perspective. J Clin Oncol 2015; 33: 3356–3364.

7. Pan JJ, Ng WT, Zong JF, et al. Proposal for the 8th edition of the AJCC/UICC staging system for nasopharyngeal cancer in the era of intensity-modulated radiotherapy. Cancer 2016; 122: 546–558.

8. Blanchard P, Lee A, Marguet S, et al. Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis. Lancet Oncol 2015; 16: 645–655.

9. Yang Z, Shi Q, Zhang Y, et al. Pretreatment 18 F-FDG uptake heterogeneity can predict survival in patients with locally advanced nasopharyngeal carcinoma—a retrospective study. Radiat Oncol 2015; 10: 4.

10. Chang H, Gao J, Xu BQ, et al. Haemoglobin, neutrophil to lymphocyte ratio and platelet count improve prognosis prediction of the TNM staging system in nasopharyngeal carcinoma: development and validation in 3237 patients from a single institution. Clin Oncol 2013; 25: 639–646.

11. Petersson F. Nasopharyngeal carcinoma: a review. Semin Diagn Pathol 2015; 32: 54–73.

12. Guthrie GJ, Charles KA, Roxburgh CS, et al. The systemic inflammation-based neutrophil–lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol 2013; 88: 218–230.

13. Sierzega M, Lenart M, Rutkowska M, et al. Preoperative neutrophil-lymphocyte and lymphocyte-monocyte ratios reflect immune cell population rearrangement in resectable pancreatic cancer. Ann Surg Oncol 2017; 24: 808–815.

14. Ock C-Y, Nam A-R, Lee J, et al. Prognostic implication of antitumor immunity measured by the neutrophil–lymphocyte ratio and serum cytokines and angiogenic factors in gastric cancer. Gastric Cancer 2017; 20: 254–262.

15. Chen QZ, Yu XS, Mao LJ, et al. Prognostic value of neutrophil–lymphocyte ratio in critically ill patients with cancer: a propensity score matching study. Clin Transl Oncol 2021; 23: 139–147.

16. Takenaka Y, Kitamura T, Oya R, et al. Prognostic role of neutrophil–lymphocyte ratio in nasopharyngeal carcinoma: a meta-analysis. PLoS One 2017; 12: e0181478.

17. Sun W, Zhang L, Luo M, et al. Pretreatment hematologic markers as prognostic factors in patients with nasopharyngeal carcinoma: neutrophil-lymphocyte ratio and platelet-lymphocyte ratio. Head Neck 2016; 38: E1332–E1340.

18. Song M, Graubard BI, Rabkin CS, et al. Neutrophil-to-lymphocyte ratio and mortality in the United States general population. Sci Rep 2021; 11: 64.

19. Pan J, Xu Y, Qiu S, et al. A comparison between the Chinese 2008 and the 7th edition AJCC staging systems for nasopharyngeal carcinoma. Am J Clin Oncol 2015; 38: 189–196.

20. de Kock I, Mirhosseini M, Lau F, et al. Conversion of Karnofsky Performance Status (KPS) and Eastern Cooperative Oncology Group performance Status (ECOG) to Palliative Performance Scale (PPS), and the interchangeability of PPS and KPS in prognostic tools. J Palliat Care 2013; 29: 163–169.

21. Au J, Law C, Foo W, et al. In-depth evaluation of the AJCC/UICC 1997 staging system of nasopharyngeal carcinoma: prognostic homogeneity and proposed refinements. Int J Radiat Oncol Biol Phys 2003; 56: 413–426.

22. Ahnman DG, McShane LM, Sauerbrei W, et al. Reporting recommendations for tumor marker prognostic studies (REMARK): explanation and elaboration. BMC Med 2012; 10: 51.

23. Li Z, Zhao R, Cui Y, et al. The dynamic change of neutrophil to lymphocyte ratio can predict clinical outcome in stage I-II colon cancer. Sci Rep 2018; 8: 9453.

24. Peng W, Li C, Wen T-F, et al. Neutrophil to lymphocyte ratio changes predict short hepatocellular carcinoma survival. J Surg Res 2014; 192: 402–408.

25. Hanahan D and Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144: 646–674.

26. Diakos CI, Charles KA, McMillan DC, et al. Cancer-related inflammation and treatment effectiveness. Lancet Oncol 2014; 15: e493–e503.

27. Galdiero MR, Varricchi G, Loffredo S, et al. Roles of neutrophils in cancer growth and progression. J Leukoc Biol 2018; 103: 457–464.

28. Valero C, Pardo L, López M, et al. Pretreatment count of peripheral neutrophils, monocytes, and lymphocytes as independent prognostic factor in patients with head and neck cancer. Head Neck 2017; 39: 219–226.

29. Grossman SA, Ellsworth S, Campian J, et al. Survival in patients with severe lymphopenia following treatment with radiation and chemotherapy for newly diagnosed solid tumors. J Natl Compr Canc Netw 2015; 13: 1225–1231.

30. Chu MLK, Tan SH, Kusumawidjaja G, et al. Neutrophil-to-lymphocyte ratio as a prognostic marker in locally advanced nasopharyngeal carcinoma: a pooled analysis of two randomised controlled trials. Eur J Cancer 2016; 67: 119–129.

31. Yin J, Qin Y, Luo Y-K, et al. Prognostic value of neutrophil-to-lymphocyte ratio for nasopharyngeal carcinoma: a meta-analysis. Medicine (Baltimore) 2017; 96: e7577.

32. Lai S-Z, Li W-F, Chen L, et al. How does intensity-modulated radiotherapy versus conventional two-dimensional radiotherapy influence the treatment results in nasopharyngeal carcinoma patients? Int J Radiat Oncol Biol Phys 2011; 80: 661–668.

33. Qiu W-Z, Peng X-S, Xia H-Q, et al. A retrospective study comparing the outcomes and toxicities of intensity-modulated radiotherapy versus two-dimensional conventional radiotherapy for the treatment of children and adolescent nasopharyngeal carcinoma. J Cancer Res Clin Oncol 2017; 143: 1563–1572.

34. Arnold KM, Flynn NJ, Raben A, et al. The impact of radiation on the tumor microenvironment: effect of dose and fractionation schedules. Canc Growth Metastasis 2018; 11: 1–17.

35. Boustanji J, Grapin M, Laurent P-A, et al. The 6th R of radiobiology: reactivation of anti-tumor immune response. Cancers (Basel) 2019; 11: 860.

36. Demaria S, Ng B, Devitt ML, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. Int J Radiat Oncol Biol Phys 2004; 58: 862–870.
37. Abuodeh Y, Venkat P and Kim S. Systematic review of case reports on the abscopal effect. *Curr Probl Cancer* 2016; 40: 25–37.

38. Walle T, Martinez Monge R, Cerwenka A, et al. Radiation effects on antitumor immune responses: current perspectives and challenges. *Ther Adv Med Oncol* 2018; 10: 1–27.

39. Hsu C, Lee S-H, Ejadi S, et al. Safety and antitumor activity of pembrolizumab in patients with programmed death-ligand 1–positive nasopharyngeal carcinoma: results of the KEYNOTE-028 study. *J Clin Oncol* 2017; 35: 4050–4056.

40. Ma BB, Lim W-T, Goh B-C, et al. Antitumor activity of nivolumab in recurrent and metastatic nasopharyngeal carcinoma: an international, multicenter study of the mayo clinic phase 2 consortium (NCI-9742). *J Clin Oncol* 2018; 36: 1412.

41. Wang H-Y, Sun B-Y, Zhu Z-H, et al. Eight-signature classifier for prediction of nasopharyngeal carcinoma survival. *J Clin Oncol* 2011; 29: 4516–4525.

42. Ribassin-Majed L, Marguet S, Lee AW, et al. What is the best treatment of locally advanced nasopharyngeal carcinoma? An individual patient data network meta-analysis. *J Clin Oncol* 2017; 35: 498.