

ORIGINAL RESEARCH

Prognostic value of neutrophils for patients with nasopharyngeal carcinoma

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Abstract

Objective: To investigate the relationship between absolute neutrophils count (ANC) in different periods of treatment and the outcomes of patients and assess effect of longitudinal neutrophils variation during radiotherapy (RT) on prognosis in patients with nasopharyngeal carcinoma (NPC).

Methods: A total of 1753 patients with newly diagnosed NPC were retrospectively analyzed. Complete blood counts of patients were obtained before treatment, before, during, and end of RT. The survival rate was calculated by Kaplan-Meier method and the result was compared by the log-rank test. The univariate and multivariate COX regression analyses were performed to investigate the association between the variation of ANC and survival for patients in different periods.

Results: Higher ANC pretreatment ($>4 \times 10^9/L$) and pre-RT ($>7 \times 10^9/L$) were correlated with poor OS (89.7% vs 85.6%, $P = .009$; 88.3% vs 77.3%, $P = .002$, respectively). An increase $>5 \times 10^9/L$ of ANC during RT was associated with adverse OS (87.9% vs 73.6%, $P = .042$). The multivariate Cox regression analysis showed that high ANC of pre-RT ($>7 \times 10^9/L$) and a high increase ($>5 \times 10^9/L$) of ANC during RT were independent prognostic factors of patients with NPC ($P = .002$, .044, respectively).

Conclusion: Our results demonstrated that ANC was an independent prognostic factor for survival in patients with NPC who received RT. Neutrophils may promote tumor resistance to radiotherapy in NPC.

Level of Evidence: 2a.

KEYWORDS

nasopharyngeal carcinoma, neutrophil, prognosis value, radiotherapy, radiotherapy resistance

1 | INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignant tumor with a significant geographic distribution and particularly prevalent in east and

Lisha Chen and Mengying Li have contributed equally to this work and share first authorship.

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southeast Asia.^{1,2} With the development of intensity-modulated radiation therapy (IMRT), one of the most crucial therapeutic modalities of NPC, the 5-year overall survival (OS) is more than 80%.³ Recurrence and distant metastasis, nevertheless remain the main causes of treatment failure in NPC.⁴ Therefore, to identify patients with poor prognosis is crucial for optimizing treatments.

The TNM staging system of the American Joint Committee on Cancer (AJCC) is generally accepted as the most widely used tool for cancer staging and plays a key role in guiding treatment and determining the prognosis of NPC in clinical practice.⁵ However, many authors proposed that TNM stage, based on anatomical structures, is insufficient to predict the prognosis.⁶⁻⁸ At present, the Epstein-Barr virus (EBV) DNA is the only proven tumor biomarker in NPC.⁹⁻¹¹ However, EBV is negative in some patients, which means that prognosis of patients cannot be predicted through dynamic change of EBV DNA. Thus, there is an essential need for additional reliable and feasible prognostic biomarkers for NPC to assist in obtaining additional prognostic information.

Previous studies have indicated that inflammatory cells (such as neutrophils, monocytes, lymphocytes and platelets) and proteins (such as albumin, c-reactive protein and high-density lipoprotein cholesterol) were effective to predict survival in cancer, including NPC.¹² A recent study had emphasized that increasing neutrophil-to-lymphocyte ratio (NLR) pretreatment might be a practicable biomarker for reduced OS and PFS in a wide variety of tumor, such as colorectal cancer, lung cancer and renal cell carcinoma.¹³ Some of studies only focus on the prognostic value of pretreatment neutrophils for patients with tumors.^{14,15} There was limited research on the relationship between the dynamic variation of circulating neutrophils and the prognosis of patients throughout the course of treatment. Hence, this study was conducted to assess the prognostic value of ANC and its variation in peripheral blood during treatment of NPC patients.

2 | MATERIALS AND METHODS

2.1 | Patient selection

We retrospectively analyzed 1753 NPC patients who were diagnosed and completed treatment at our cancer center between January 2013 and December 2016. The inclusion criteria were as follows: (a) pathologically confirmed primary NPC; (b) completed treatment including RT plus or without chemotherapy in our center; (c) no evidence of other synchronous malignancy; (d) follow up data were complete. The exclusion criteria were as follows: (a) diagnosed with a previous malignancy or other concomitant malignant disease; (b) pregnancy or lactation; (c) acute infection; (d) hematologic disorder; (e) patients >70 years old. We collected ANC at four stages in these patients: pretreatment, pre-RT, the lowest value during RT and end of RT. This study was approved by the Ethics Committee of Fujian Cancer Hospital (No. YKT2019-022-01), in accordance with the Declaration of Helsinki and our editorial ethics policy. The written forms of informed consent for individual patients were not required since the study was retrospective, and the data was anonymized or maintained with confidentiality.

2.2 | Neutrophils counts

The medical records of patients were reviewed retrospectively, and clinical and laboratory information was collected for analysis. Data regarding neutrophils counts were collected from the complete blood count test performed pretreatment, weekly during RT and at end of RT. All the results were collected the ANC values without raising neutrophils therapy.

2.3 | Treatment protocol

All patients enrolled received simultaneous intensity modulated radiation therapy (IMRT) with or without chemotherapy. The total dose of standard fractionated radiotherapy to the gross tumor of nasopharynx and cervical metastatic lymph nodes (GTV) of up to 69.7 Gy-70Gy divided into in 31-35 fractions. The staging of patients relied on the seventh TNM system designed jointly by the AJCC. RT was applied to patients of stage I only, patients of stage II received concurrent chemoradiotherapy (CCRT). Besides, CCRT with or without neoadjuvant chemotherapy (NACT) were applied in patients of stage III and IV. CCRT regimen was consisted of platinum (80 mg/m²) once every 3 weeks per cycle until RT completed. NACT were performed with gemcitabine (1000 mg/m²) or paclitaxel (135 mg/m²) with platinum per 21 days. There is no unified criterion for adjuvant chemotherapy.

2.4 | Data statistics

All statistical analyses were performed using a social science statistical software package, version 25.0 (SPSS Inc., Armonk, New York: IBM Corp). Any statistical results were all two-sided, and the significant effect was set at *P*-value <0.05. Compare the 3-year incidence of death of patients in different ANC value in different stages of treatment. The demarcation points were the values of ANCs with the most significant change in 3-year incidence of death and patients were grouped accordingly. To investigate the relationship between dynamic variation of ANC and prognosis of patients with NPC during RT, the difference of ANC between the end of RT and pre-RT was analyzed. The threshold was the value of difference with the greatest variation in 3-year incidence of death. The survival rate was calculated by Kaplan-Meier method. The log-rank test was used to evaluate differences between survival curves. The independent prognostic factors that were determined in univariate analysis as important predictors of OS were then incorporated in the multivariate analysis conducted by the Cox regression model.

2.5 | Follow-up

Patients were followed up by these rules: every 3 months in the first 2 years, every 6 months in the three to 5 years, and then annually after 5 years until death. To exclude recurrence and metastasis, EBV-DNA, fiber nasopharyngoscope, nasopharynx and neck MRI, CT scans

of lung, color ultrasound of liver were reexamined in follow-up. OS, the duration from the date of diagnosis of NPC to the date of death or the date of last follow-up, was the primary endpoint.

3 | RESULTS

3.1 | Patient characteristics

A total of 1753 consecutive patients with NPC were enrolled in this study. Other specific clinical features of the patients are shown in Table 1. The median follow-up time was 42 months (range, 3-64 months). We recorded a total of 32 patients were lost to follow-up, 114 patients developed local or regional recurrence, 174 patients developed distant metastasis and 214 patients died. 3-years distant metastasis-free survival (DMFS), 3-years OS, 3-years progression free survival (PFS) and 3-years loco-regional recurrence-free survival (LRFS) for the cohort were 90.0%, 89.4%, 79.9%, and 96.2%, respectively. Patient characteristics are shown in Table 1.

In univariate Cox proportional regression analyses for OS, 3 variables were associated with poorer OS: advanced T stage ($P < .0001$), N stage ($P < .0001$) and pretreatment EBV-DNA level ($P < .001$) (Table 2).

3.2 | Distinct ANC defines distinct prognosis

Firstly, we grouped ANC by comparing the 3-year incidence of death of patients with different values of neutrophils over four periods of

treatment (Figure 1). We observed that incidence of death of patients varied significantly as the value of ANC increased to a certain level in every period of treatment. Then the values of ANCs with the great change in 3-year incidence of death were determined as points of demarcation. Next, based on these points, we defined distinct groups of ANCs in four stages (Table 2).

Based on Kaplan-Meier analysis, pre-RT ANC $\geq 7 \times 10^9/L$ was negatively related to 3-year OS (88.3% vs 77.3%, $P = .001$) (Figure 2A), and patients with higher pretreatment ANC ($>4 \times 10^9/L$) was a significant risk factor for 3-year OS (89.7% vs 85.6%, $P = .009$) (Figure 2B). In the univariate analysis, higher ANC pretreatment ($>4 \times 10^9/L$) and pre-RT ($>7 \times 10^9/L$) were correlated with poor OS ($P = .009, .001$). However, univariate Cox regression revealed that the ANC $> 7 \times 10^9/L$ at end of RT ($P = .083$) and the lowest ANC

TABLE 1 Clinical features of the patients

Variables		NO.
Age (years)	Median (range)	47(10-86)
Gender	Male	1252
	Female	501
TNM-stage	T1/T2/T3/T4	331/348/575/499
	N0/N1/N2/N3	185/679/530/359
	I/II/III/IV	46/295/626/786
Pathologic types	WHO I	41
	WHO II	129
	WHO III	1577
	Other	6
Therapeutic regimens		
Neoadjuvant chemotherapy	Yes	1548
	No	205
Concurrent chemotherapy	Yes	384
	No	1369
Adjuvant chemotherapy	Yes	514
	No	1239
Boost irradiation	Yes	278
	No	1475

Abbreviation: WHO, World Health Organization.

TABLE 2 Univariate analysis for overall survival in primary cohort

Variables	OS%	Univariate analysis		
		HR	95%CI	P-values
<i>Age</i>				
<50	88.4	1.11	0.845-1.458	.454
≥ 50	87.3			
<i>Gender</i>				
Female	87.8	1.005	0.747-1.352	.974
Male	87.7			
<i>T-staging</i>				
T1/T2/T3/T4	92.4/88.8/88.1/83.1	1.294	1.133-1.478	<.0001
<i>N-staging</i>				
N0/N1/N2/N3	95.1/92.7/84.7/79.1	1.72	1.48-2.00	<.0001
<i>Pretreatment EBV-DNA (copy/ml)</i>				
0	94.2	2.207	1.387-3.287	<.001
>0	83.6			
<i>Pretreatment ANC ($\times 10^9/L$)</i>				
≤ 4	89.7	1.428	1.090-1.872	.009
>4	85.6			
<i>Pre-RT ANC ($\times 10^9/L$)</i>				
≤ 7	88.3	2.170	1.354-3.476	.001
>7	77.3			
<i>Lowest ANC during RT ($\times 10^9/L$)</i>				
≤ 1	83.2			
1-4	88.5	0.675	0.462-0.984	.083
≥ 4	81.6	1.049	0.50-2.20	
<i>RT end ($\times 10^9/L$)</i>				
≤ 6	88.1			
6-7	82.3	1.468	1.053-2.047	.078
>7	76.6			
<i>ANC increased during RT ($\times 10^9/L$)</i>				
≤ 5	87.9	2.256	0.927-5.490	.042
>5	73.6			

Abbreviations: CI, confidence interval; HR, hazard ratio.

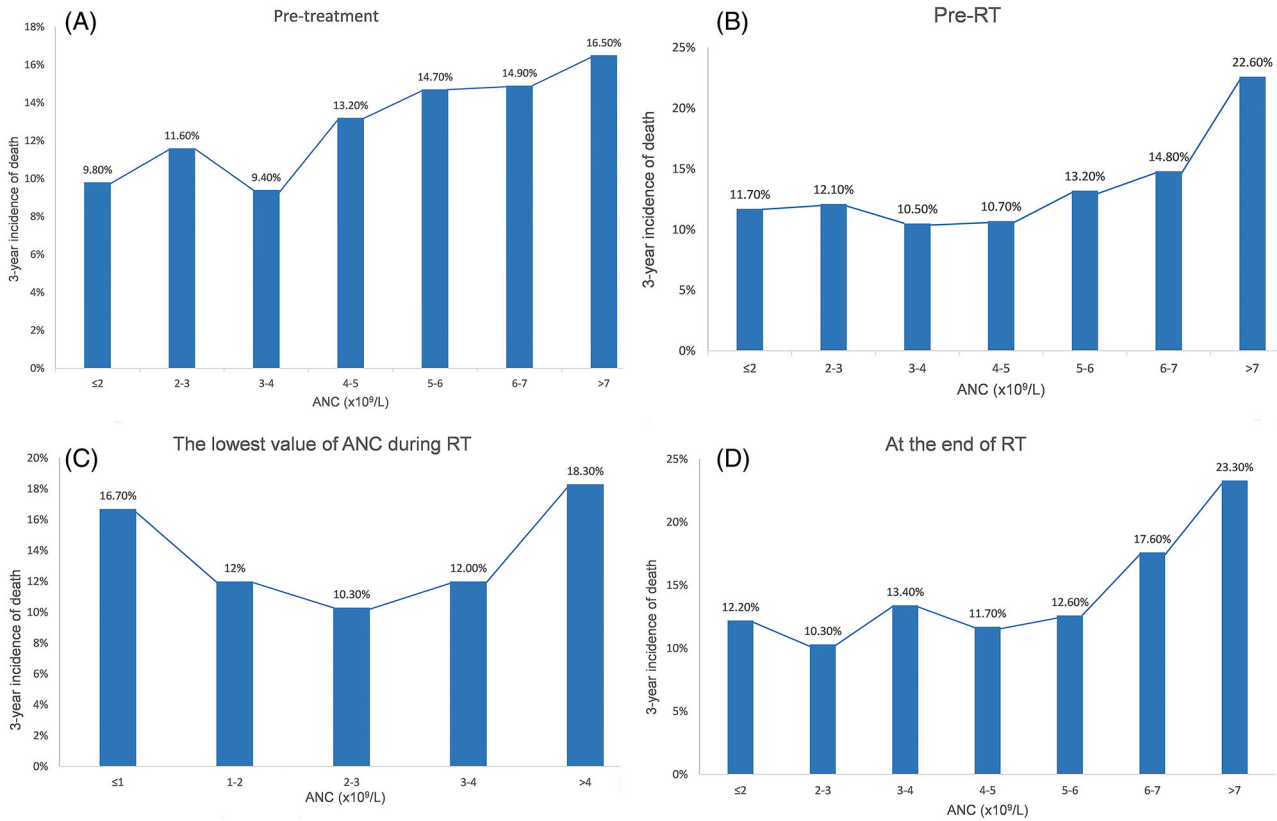


FIGURE 1 A-D, showed 3-year incidence of death variation tendency of different ANC value in four periods of treatment. A, Pretreatment: as ANC = $4 \times 10^9/L$, there was significant difference in 3-year incidence of death between the two ends; B, Pre-RT: When ANC = $7 \times 10^9/L$, the difference in 3-year incidence of death between the two ends is greatest; C, Lowest value of ANC during RT: $1 \times 10^9/L$ and $4 \times 10^9/L$ were the points that 3-year incidence of death had changed significantly; D, RT end: ANC value of $6 \times 10^9/L$ and $7 \times 10^9/L$ were selected as the points of demarcation

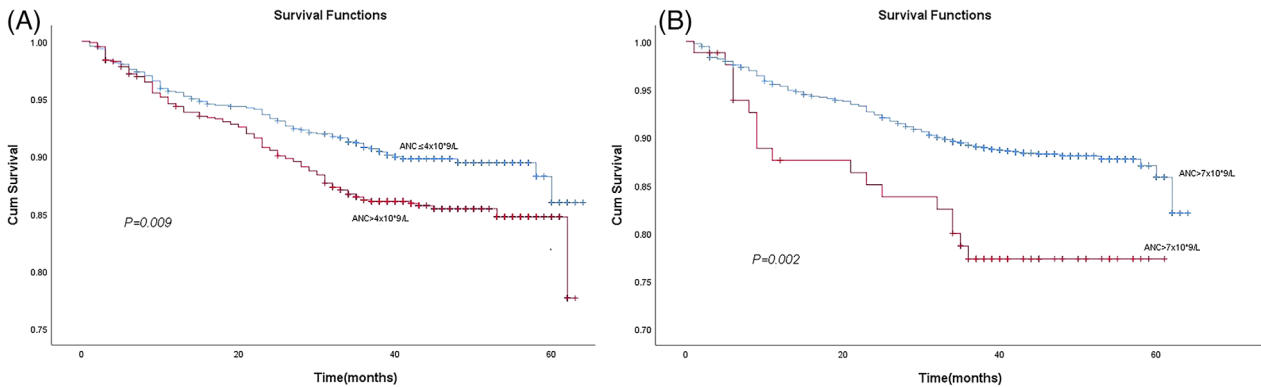


FIGURE 2 A, Kaplan-Meier survival curve of 3-year OS according to the value of pretreatment ANC, $P = .009$. B, Kaplan-Meier survival curve of 3-year OS on the basis of value of pre-RT ANC, $P = .002$

$\geq 4 \times 10^9/L$ during RT ($P = .078$) were not associated with poor OS (Table 2).

3.3 | Longitudinal ANC variation defines distinct prognosis

To evaluate the relationship between longitudinal variation of ANC during RT and patient prognosis, we calculated the difference

between ANC at the end of RT and pre-RT, which was the amplitude of increase in neutrophils during RT. Subsequently variations of the 3-year incidence of death in each difference interval were compared. We determined the difference of $5 \times 10^9/L$ with the most significant increase in incidence of death as point of demarcation, likewise (Figure 3A). And then the value was used as the point for categorizing the patients into two groups (Table 2). The difference $> 5 \times 10^9/L$ was associated with poor OS (87.9% vs 73.6%, $P = .042$) (Figure 3B). In the univariate analysis, a high

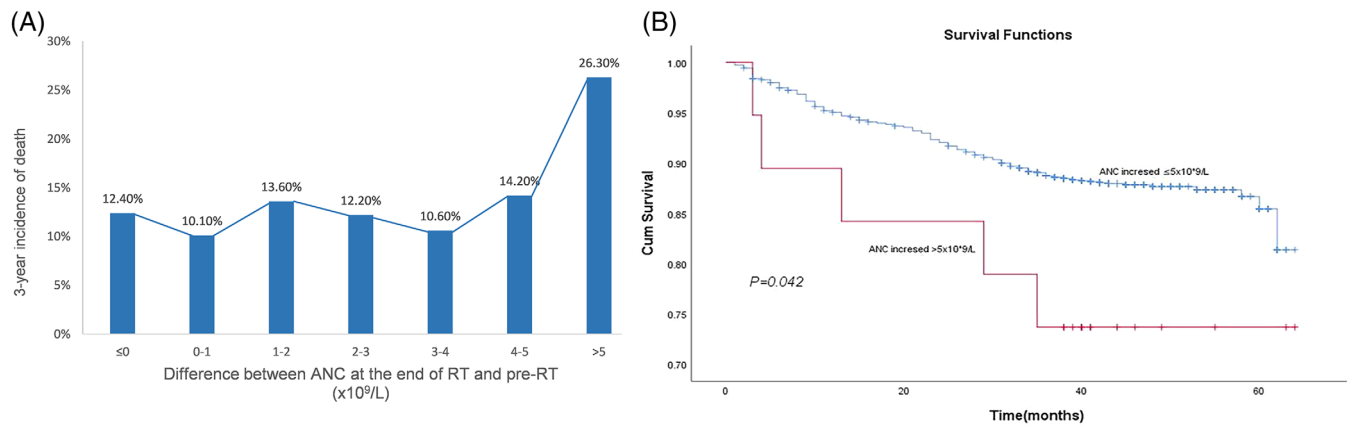


FIGURE 3 A, As ANC increased $> 5 \times 10^9/L$ during RT, there was a significant change in 3-year incidence of death; B, the Kaplan-Meier survival curve of OS according to the amplitude of ANC increased during RT

increase ($> 5 \times 10^9/L$) of ANC during RT was correlated with poor outcome ($P = .042$).

Subsequently, these six variables above were entered into the multivariate Cox regression analysis to correct for possible confounders. The result revealed that T-stage ($P < .0001$), N-stage ($P < .0001$), higher pre-RT ANC ($> 7 \times 10^9/L$) ($P = .002$) and ANC increased $> 5 \times 10^9/L$ ($P = .044$) during RT remained independent prognostic factors of patients with NPC (Table 3).

Based on these exploratory observations, we proposed that higher pre-RT ANC ($> 7 \times 10^9/L$) was a poor prognostic factor in NPC patients for OS. Our longitudinal surveillance of ANC revealed the prognosis of patients those who experienced significant increase ($> 5 \times 10^9/L$) during RT were adverse.

4 | DISCUSSION

NPC is a malignant tumor with high incidence in Southeast Asia and the Southern China,^{1,16} which occurrence and development are related to EBV infection, host genetics, and environmental factors.¹⁷ There is limitation in the TNM staging system, which did not take biological factors into consideration. Hence, predicting the possible survival before and during treatment is helpful for clinicians to determine the prognosis and provide individualized treatment. Currently, relevant studies have indicated that some factors such as EB-DNA, PTV have clinical significance to the evaluations of curative effect and prognosis among NPC patients.^{7,18,19} Furthermore, hematological markers, systemic inflammatory markers have attracted increasing attention for prediction of tumor prognosis.^{6,20} Recent studies have proposed that absolute inflammatory cell counts in peripheral blood (neutrophils, white blood cells, lymphocytes and monocytes) and ratios based on these cell counts may play a crucial role in predicting the overall survival of patients with tumors, including head and neck cancer,²¹ non-small cell lung cancer²² and esophageal cancer.²³ Liu and his colleagues have shown that treatment-related lymphopenia was a poor prognostic factor in NPC patients.²⁴ Chen and his team

TABLE 3 Multivariable analysis for overall survival in primary cohort

Variables	Multivariable analysis		
	HR	95%CI	P-values
T-staging	1.315	1.169-1.531	<.0001
N-staging	1.786	1.528-2.087	<.0001
<i>EBV-DNA pretreatment (copy/ml)</i>			
0	2.324	1.236-4.283	.72
> 0			
<i>Pretreatment ANC ($\times 10^9/L$)</i>			
≤ 4	1.315	1.148-1.506	.08
> 4			
<i>Pre-RT ANC ($\times 10^9/L$)</i>			
≤ 7	2.103	1.311-3.374	.002
> 7			
<i>ANC increased during RT ($\times 10^9/L$)</i>			
≤ 5	2.504	1.024-6.125	.044
> 5			

believed that pretreatment platelet count was a useful indicator for metastasis and survival in NPC patients.²⁵ However, there is limited research on circulating neutrophils throughout the NPC patient's treatment.

Our study demonstrated that high pre-RT ANC ($> 7 \times 10^9/L$) may lead to poor OS ($P = .002$). Unlike any other studies, we divided the patients into two subgroups according to the increase of ANC during RT to analyze the relationship between longitudinal ANC variation and survival in patients with NPC who completed RT. In our study, the prognosis of patients who experienced significant increase ($> 5 \times 10^9/L$) were poor (3-year OS 87.9% vs 73.6%, $P = .042$). And our finding also revealed that at any stage of treatment, the prognosis of patients was poorer and the HR was increased as neutrophils increased. An exception to this result was that the group with the

lowest ANC value, less than $1 \times 10^9/L$, had a poorer prognosis than the group with the lowest ANC value between $1 \times 10^9/L$ and $4 \times 10^9/L$ during RT, which may be due to the increased mortality caused by severe bone marrow suppression.

What caused the difference of prognosis of different ANC? We proposed that neutrophils promote tumor resistance to radiation therapy in NPC. Neutrophils, the most common circulating leukocytes, are some of the earliest cells to respond to tissue injury and infection.²⁶ Neutrophil makes up a substantial proportion of the immune infiltrate in a wide variety of cancer types, including lung, breast and gastric cancers, melanoma, renal cell carcinoma (RCC) and others. A recent study indicated that neutrophil levels correlated with outcomes in cervical cancer patients treated with radiation therapy.²⁷ And a study of gastric cancer demonstrated that tumor-associated neutrophil fostered immune suppression and disease progression.²⁸ Moreover, it is demonstrated that neutrophils captured circulating tumor cells through neutrophil extracellular traps, and promoted tumor cells to migrate far away, thus promoting tumor cell proliferation in a research of colorectal cancer.²⁹ Recent studies have shown that neutrophils played an important role in tumor microenvironment through the formation of reticular structure, the release of reactive oxygen species (ROS), which can result in DNA base damages, as well as mutations, the secretion of pro-tumor cytokines and chemokines, and the promotion of immunosuppression.³⁰ Neutrophils are also activated and form neutrophil extracellular traps (NETs) in the tumor microenvironment. Based on previous studies, NET plays a pro-tumor role during tumor progression.³¹ These actions allow neutrophil to facilitate cancer progression and chemotherapy resistance. In addition, our result indicated that patients with high pre-RT ANC had a poor prognosis, which was a further evidence of neutrophil radiation resistance.

Simultaneously our findings suggested that rising neutrophil levels during radiotherapy may have the unintended consequence of increasing radiation resistance. Therefore, suppressing neutrophil levels moderately during RT may improve tumor response to RT and patients' prognosis. Certainly, oversuppress neutrophil levels can lead to granulocytopenia, which was not conducive to patient survival. Whereas, how to restrain neutrophil level reasonably is worthy of further study. In addition, ANC could be a tumor marker pre-RT or during RT for NPC patients.

But why did neutrophilia occur during RT? Long-term studies have shown that inflammation was related to the occurrence and development of tumors, and inflammatory microenvironment promoted tumor progression.³² RT further increased tumor inflammation. Neutrophilia is a response to the inflammatory process. In addition, leukocytosis particularly neutrophilia can be induced by upregulation of tumor-related hematologic growth factors, including granulocyte colony stimulating factor (G-CSF), interleukin-1, interleukin-6, and tumor necrosis factor.³³ It was demonstrated by Mabuchi et al, tumor-related leukocytosis was related to adverse OS and radiotherapy resistance, and the expression of G-CSF was significantly increased among patients with leukocytosis.³⁴ So we acknowledged

that tumor chronic inflammation, tumor microenvironment and cytokines of tumors lead to neutrophilia during RT.

Our data and results were based on observe method, which may be influenced by the number of patients enrolled. Besides, this study has some limitations. First, this was a single-center and retrospective study. Therefore, further study at multiple centers to confirm the reproducibility of the results are warranted. In addition, our study only verified the predictive value of ANC for patient survival, and we need further study to build a systematic mathematical prediction model for clinical decision.

5 | CONCLUSION

Our study demonstrates that ANC is a biomarker of prognosis for patients with NPC who receive radiotherapy. Neutrophils may promote tumor resistance to radiotherapy in NPC. Suppressing neutrophil level moderately during radiotherapy may improve tumor response to radiotherapy and patient prognosis, which is worthy of further study in future research.

CONFLICT OF INTEREST

The authors have declared that no competing interest exists.

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