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ORIGINAL RESEARCH

Association of Pretreatment Neutrophil-to-Eosinophil Ratio with Clinical Outcomes in Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma Treated with Nivolumab

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Background: There is a need to develop biomarkers for a more efficient use of immune checkpoint inhibitors (ICIs). Recently, it has been reported that peripheral blood components, including eosinophils, may be effective ICI biomarkers. This study was designed to evaluate the prognostic value of eosinophils for measuring the effects of nivolumab on recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC).

Materials and Methods: The study included 47 patients with R/M HNSCC treated with nivolumab. Eosinophil-related biomarkers, such as absolute eosinophil count (AEC), relative eosinophil count (REC), and neutrophil-to-eosinophil ratio (NER), were measured from the peripheral blood of the patients before nivolumab treatment. For each biomarker, the patients were divided into a high- and a low-value group according to their cutoff values, and these groups were compared.

Results: Regarding AEC and REC, no significant improvement in the objective response rate (ORR) was observed between patients with AEC $>0.9 \times 10^3/\mu L$ and those with AEC $<0.9 \times 10^3/\mu L$ ($p = 0.147$) and between patients with REC >2.2% and those with REC <2.2% ($p = 0.110$). However, patients with NER <32 had improved ORR compared with those with NER >32 ($P = 0.0361$). Additionally, although patients with AEC $>0.9 \times 10^3/\mu L$, REC >2.2%, and NER <32 had longer overall survival (OS) than those with AEC $<0.9 \times 10^3/\mu L$, REC <2.2%, and NER >32, only patients with NER <32 showed prolonged progression-free survival (PFS) compared with those with NER >32 according to the Log rank test ($p = 0.046$, 0.027, and 0.035, respectively). Furthermore, the multivariate analysis revealed that baseline NER >32 ($p = 0.027$) was an independent prognostic factor for worse OS.

Conclusion: A pretreatment feature of low NER (NER <32) may predict better clinical outcomes in patients with R/M HNSCC treated with nivolumab.

Keywords: head and neck cancer, nivolumab, eosinophil, neutrophil-to-eosinophil ratio, recurrent/metastatic head and neck squamous cell carcinoma

Introduction

Head and neck cancer was the seventh most common cancer worldwide in 2020 (932,000 new cases and 467,000 deaths)[1,2] Although many different histologies exist, the most common is squamous cell carcinoma. Locally advanced disease has a high risk of local recurrence (15–40%) and distant metastasis, and the prognosis for these recurrent and metastatic head and neck squamous cell carcinoma (R/M HNSCC) is poor (5-year overall survival < 50%).[3] Various treatments have been developed to improve the prognosis of R/M HNSCC.

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Recently, immune checkpoint inhibitors (ICIs) have dramatically changed the treatment of many malignancies, including head and neck cancers.[4,5]

Particularly in head and neck cancers, the prolonged effect of nivolumab, a PD-1 inhibitor, on platinum-resistant R/M HNSCC was confirmed,[4] and currently, it plays an important role in treating R/M HNSCC. Recently, the effectiveness based on real-world data has also been reported, and the effect of nivolumab for treating R/M HNSCC has been reaffirmed.[6,7]

However, the response rate is 13%–16%, which is inadequate, and only a limited number of cases have been reported wherein the effect lasted for a long time.[4,7]

Therefore, to use nivolumab more efficiently, there is a need to develop biomarkers that predict its therapeutic effects.

Various studies have examined the biomarkers for ICIs, including nivolumab.

The method using tumor tissues to evaluate tumor mutating burden,[8] tumor-infiltrating $CD8^+$ T-lymphocyte,[9] PD-L1 expression,[10] and other factors directly involved in tumor immune associations were evaluated.

Binding of PD-L1 on a tumor cell to its receptor PD-1 on activated T cells inhibits antitumor immunity by counteracting T cell-activating signals, resulted in evade-tumor immunity.[11] Therefore, the relationship between PD-L1 expression in tumor tissue and prognosis has also been studied in head and neck cancer, even before PD-L1 was studied as a biomarker for ICI. However, in these studies that focus solely on PD-L1 expression, the relationship between PD-L1 expression and prognosis was inconsistent depending on the site of cancer and the method of analysis.[12–15]

In contrast, PD-L1 is widely known to be useful for many cancers when it was evaluated as a biomarker for the treatment targeting PD-1/PD-L1 axis. Binding of PD-L1 on a tumor cell to its receptor PD-1 on activated T cells Checkmate-141 is an analysis comparing OS between nivolumab group and an investigator's choice of treatment group according to PD-L1 expression status in R/M HNSCC. The results showed that nivolumab provided an OS benefit in patients with PD-L1 of ≥1%.[4] Additionally, an analysis of pembrolizumab, a PD-1 inhibitor like nivolumab (KEYNOTE048), PD-L1 expression in tumor tissue from patients with R/M HNSCC was assessed by a combined positive score (CPS). Then, according to this CPS, a comparative analysis of OS between pembrolizumab alone, pembrolizumab/chemotherapy, and cetuximab/chemotherapy was performed. The results indicate that pembrolizumab monotherapy is the appropriate treatment for PD-L1–positive patients (CPS ≥1).[5]

Therefore, the method using tumor tissue is expected to enable more accurate ICI biomarker retrieval. However, if collecting tissues, such as a distant metastatic lesion, is difficult, or if the preserved tissue is in poor condition, searching biomarkers using the tissue may be impossible. Therefore, tissue-based validation methods are often restricted in their clinical use.[16,17]

In contrast, peripheral blood has also been investigated as a material for searching ICI biomarkers.

Peripheral blood has been investigated in various malignant tumors in the search for ICI biomarkers. It has been suggested that factors derived from peripheral blood, such as absolute neutrophil count (ANC), absolute lymphocyte count, and neutrophil-to-lymphocyte ratio (NLR), are promising biomarkers for ICIs;[18,19] however, no definitive biomarkers have been determined to date.

Recently, eosinophils in the peripheral blood have been reported to be related to the therapeutic efficacy of ICIs in many cancers.[20,21]

In addition to directly damaging tumor cells,[22] eosinophils induce $CD8^+$ lymphocytes into the cancer microenvironment via cytokines, such as C–C motif chemokine ligand 5, C–X–C motif chemokine ligand (CXCL) 9, and CXCL10, to damage tumor cells.[23] Therefore, an increase in eosinophils in the peripheral blood reflects the antitumor capacity of the patient, and therefore, eosinophils are considered a potent biomarker for ICIs. Specific factors derived from eosinophils in peripheral blood include absolute eosinophil count (AEC),[17,21] relative eosinophil count (REC),[24] and neutrophil-to-eosinophil ratio (NER),[25] which have been suggested to be excellent biomarkers for ICIs in several cancers.

However, the relationship between eosinophils and ICIs in head and neck cancers has not yet been fully studied.

Based on these results, we hypothesized that eosinophils would be associated with the clinical outcome in patients with R/M HNSCC treated with nivolumab.

To identify promising prognostic markers related to eosinophils, we performed a retrospective evaluation of eosinophil-related factors, such as AEC, REC, and NER, in the pretreatment peripheral blood of patients with R/M HNSCC treated with nivolumab. The relationship between these eosinophil-related factors and the response to nivolumab was examined, and their usefulness as biomarkers was investigated.

Materials and Methods

Patients and Data Collection

We retrospectively reviewed clinical and radiological data from the medical records of patients with R/M HNSCC treated with nivolumab after the failure of platinum-based chemotherapy between October 2017 and December 2021 at Akita University Hospital. The patients were followed up until death or the cutoff date (June 1, 2022).

This study was approved by the Institutional Review Board of Akita University Hospital (#2873) and was conducted according to the principles of the Declaration of Helsinki. The requirement for obtaining informed consent was waived as the study was a retrospective analysis of existing administrative and clinical data.

Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors, version 1.1. The objective response rate (ORR) was defined as the proportion of patients who exhibited complete response (CR) or partial response (PR) as the best response. The disease control rate (DCR) was defined as the proportion of patients who exhibited CR, PR, or stationary disease (SD) as the best response. The clinical response to treatment was evaluated using computed tomography every 8–12 weeks.

Progression-free survival (PFS) was defined as the time from the initiation of nivolumab until disease progression, death due to any cause, or the cutoff date when no progression was observed. Overall survival (OS) was defined as the time from the initiation of nivolumab until death due to any cause or the cutoff date.

Measurement of Peripheral Blood Biomarkers

We analyzed three peripheral blood biomarkers related to eosinophils: AEC, REC, and NER.

AEC was defined as the number of eosinophil cells $\times 10^3/\mu L$.

REC was defined as the rate of eosinophil count divided by the leukocyte count (%).

NER was calculated by the ANC (number of cells $\times 10^3/\mu L$) divided by the AEC (number of cells $\times 10^3/\mu L$). To allow the NER to be calculated for patients with an AEC of zero (ie, to avoid zero in the denominator), the AEC for these patients was adjusted to $0.1 \times 10^3/\mu L$ (the lowest cell count that can be detected in the laboratory).

These parameters were simultaneously measured as complete blood count measurements before the initial initiation of nivolumab.

Statistical Analysis

Receiver operating characteristic (ROC) curve analysis was performed to determine the best cutoff value of the continuous variables.

Logistic regression analysis was used to estimate the odds ratio (OR) for having the ORR and disease DCR.

Survival analysis was estimated using the Kaplan–Meier method, and differences in OS and PFS were evaluated using the Log rank test.

A Cox proportional hazard regression model was developed and applied to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs).

The significance of associations between the clinical parameters and OS was assessed using the Cox proportional hazards regression model.

Statistical analyses were performed using EZR, version 4.0.0 (Saitama Medical Center, Jichi Medical University, Saitama, Japan). P-values of <0.05 were used to denote statistical significance.

Results

Patient Characteristics

During the study period, 57 patients were treated with nivolumab. One patient whose treatment response was not evaluated and nine patients who lacked complete blood count were excluded from the study. Finally, 47 patients (39 men and 8 women) were included in the analysis.

The patient characteristics are shown in Table 1.

Table 1 Patients' Characteristics

Characteristics (n = 47)		
Age (years), median (range)	67 (29–84)	
Sex	n	%
Male	39	83
Female	8	17
ECOG PS score	n	%
0	9	19.1
1	27	57.4
2	7	14.9
3	4	8.5
Primary tumor site	n	%
Oral cavity	11	23.4
Nasopharynx	1	2.1
Oropharynx	11	23.4
Hypopharynx	9	19.1
Larynx	2	4.3
Others	13	27.7
Evaluation lesion site	n	%
Locoregional	37	78.7
Distant metastasis	10	21.3
Pretreatment peripheral blood biomarkers		
AEC, median (range)	1.0 (0.1–5.0)	
REC, median (range)	1.9 (0.1–10.4)	
NER, median (range)	32 (5.5–672)	

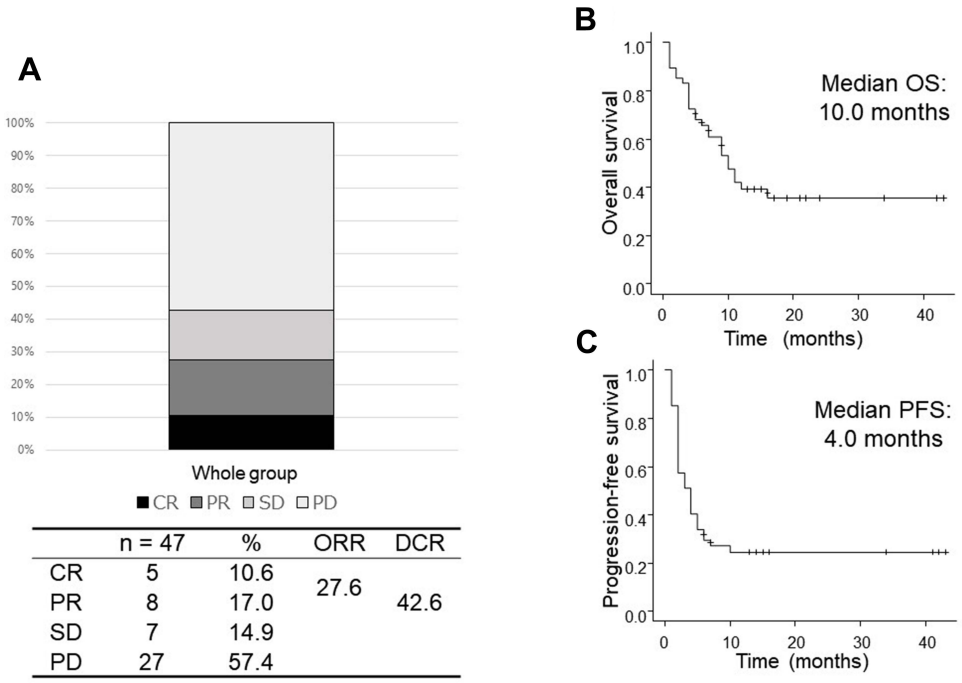
The median age was 67 years (range, 29–84 years). Most patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; however, seven and four patients had an ECOG PS of 2 and 3, respectively. The oral cavity and oropharynx were the most common primary sites in 11 cases, followed by the hypopharynx in nine cases and the larynx in two cases. The lesion sites evaluated were locoregional in 37 cases and distant metastases in 10 cases.

The median AEC, REC, and NER during the pretreatment with nivolumab were $1.0 \times 10^3/\mu L$ (range, $0.1–5.0 \times 10^3/\mu L$), 1.9% (range, 0.1–10.4%), and 32 (range, 5.5–672), respectively.

Clinical Outcomes According to Pretreatment AEC, REC, and NER Values in Patients Treated with Nivolumab

In the whole group analysis, CR = 5 (10.6%), PR = 8 (17.0%), SD = 7 (14.9%), and PD = 27 (57.4%). The ORR and DCR were 27.6% (13 of 47 patients) and 42.6% (20 of 47 patients), respectively (Figure 1A). The median OS and PFS were 10.0 months (95% CI, 7–NA months) and 4.0 months (95% CI, 2.0–5.0 months), respectively (Figure 1B).

The most appropriate cutoff values for patients with controlled disease and those with progressive disease were as follows: $0.9 \times 10^3/\mu L$ for AEC, 2.2% for REC, and 32 for NER, according to the ROC curve analysis (area under the ROC curve = 0.560, 0.621, and 0.625, respectively).



	n = 47	%	ORR	DCR
CR	5	10.6	27.6	42.6
PR	8	17.0		
SD	7	14.9		
PD	27	57.4		

Figure 1 Clinical outcomes of the whole group analysis (n = 47). BOR (**A**), OS (**B**), and PFS (**C**).
Abbreviations: BOR, best overall response; CR, complete response; PR, partial response; SD, stationary disease; PD, progressive disease; OS, overall survival; PFS, progression-free survival.

When the patients were divided according to AEC and REC, no significant improvement in the ORR was observed between patients with AEC ≥0.9 × 10^3/μL and those with AEC <0.9 × 10^3/μL (34.4% vs 13.3%; OR, 0.294; p = 0.147) and between patients with REC ≥2.2% and those with REC <2.2% (40.0% vs 18.5%; OR, 0.341; p = 0.110).

However, patients with NER <32 had improved ORR compared with those with NER ≥32 (41.7% vs 13.0%; OR, 4.76; p = 0.0361).

In contrast, no significant improvement in the DCR was observed between patients with AEC ≥0.9 × 10^3/μL and those with AEC <0.9 × 10^3/μL (46.9% vs 33.3%; OR, 0.567; p = 0.384); however, a significant improvement was observed in patients with REC ≥2.2% and those with REC <2.2% (60.0% vs 29.6%; OR, 0.281; p = 0.0409) and those with NER <32 compared with those with NER ≥32 (58.3% vs 26.1%; OR, 3.97; p = 0.0287) (Figure 2).

When considering survival, patients with AEC ≥0.9 × 10^3/μL, REC ≥2.2%, and NER <32 had longer OS (12 months, unreached, and unreached, respectively) than those with AEC <0.9 × 10^3/μL, REC <2.2%, and NER ≥32 (9.0, 9.0, and 6.0 months, respectively) according to the Log rank test (p = 0.046, 0.027, and 0.035, respectively) (Figure 3).

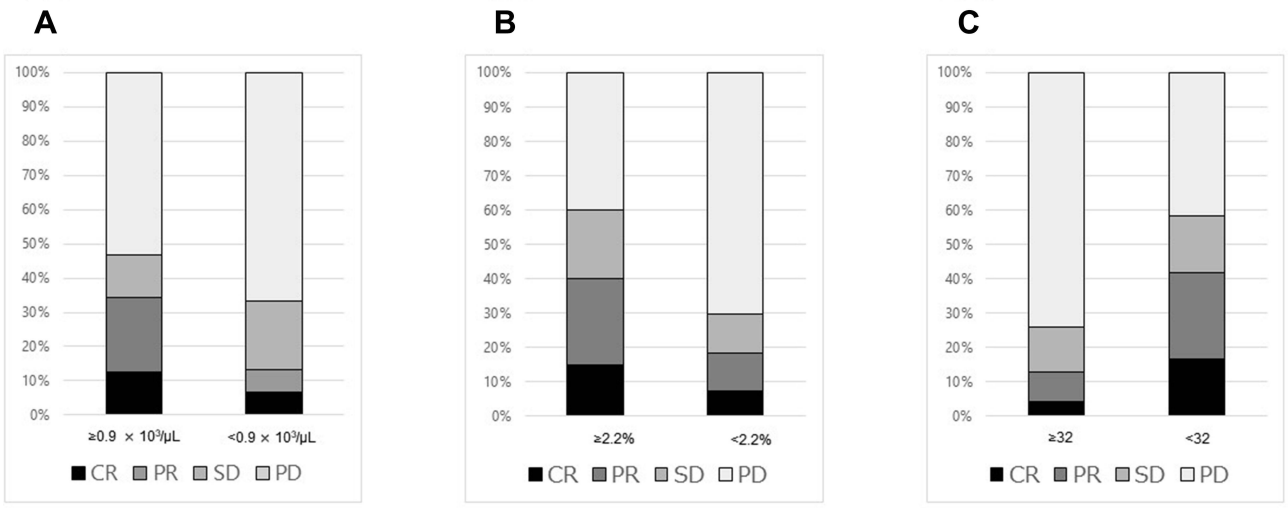
However, only patients with NER <32 had prolonged PFS compared with those with NER ≥32 (p = 0.013), whereas those with AEC ≥0.9 × 10^3/μL and REC ≥2.2% did not have prolonged PFS compared with those with AEC <0.9 × 10^3/μL and REC <2.2% (p = 0.206 and 0.052, respectively) (Figure 4).

Univariate and Multivariate Analyses of the Factors Associated with OS in Patients Treated with Nivolumab

To identify the prognostic factors associated with OS in patients treated with nivolumab, univariate and multivariate analyses using the Cox proportional hazards model were performed (Table 2).

The univariate analysis showed that PS and NER were prognostic variables. However, AEC and REC were not prognostic variables.

The multivariate analysis revealed that ECOG PS ≥2 (HR, 8.724; 95% CI, 3.356–22.68; p < 0.001) and pretreatment NER ≥32 (HR, 2.474; 95% CI, 1.109–5.518; p = 0.027) were independent prognostic factors for a worse OS.



AEC	≥0.9 × 10^3/μL		<0.9 × 10^3/μL	
	n	%	n	%
CR	4	12.5	1	6.7
PR	7	21.9	1	6.7
SD	4	12.5	3	20.0
PD	17	53.1	10	66.7
Total	32		15	

REC	≥2.2%		<2.2%	
	n	%	n	%
CR	3	15.0	2	7.4
PR	5	25.0	3	11.1
SD	4	20.0	3	11.1
PD	8	40.0	19	70.4
Total	20		27	

NER	≥32		<32	
	n	%	n	%
CR	1	4.3	4	16.7
PR	2	8.7	6	25.0
SD	3	13.0	4	16.7
PD	17	73.9	10	41.7
Total	23		24	

Figure 2 Best overall response of the patients divided by AEC (**A**), REC (**B**), and NER (**C**). (**A**) AEC ≥0.9 × 10^3/μL: CR 12.5%, PR 21.9%, SD 12.5%, and PD 53.1%. AEC <0.9 × 10^3/μL: CR 6.7%, PR 6.7%, SD 20.0%, and PD 66.7%. Odds ratio for ORR and DCR was 0.294 (p = 0.147) and 0.567 (p = 0.384), respectively. (**B**) REC ≥2.2%: CR 15.0%, PR 25.0%, SD 20.0%, and PD 40.0%. REC <2.2%: CR 7.4%, PR 11.1%, SD 11.1%, and PD 70.4%. Odds ratio for ORR and DCR was 0.341 (p = 0.110) and 0.281 (p = 0.041), respectively. (**C**) NER ≥32: CR 4.3%, PR 8.7%, SD 13.0%, and PD 73.9%. NER <32: CR 16.7%, PR 25.0%, SD 16.7%, and PD 41.7%. Odds ratio for ORR and DCR was 4.76 (p = 0.361) and 3.97 (p = 0.0287), respectively.

Abbreviations: CR, complete response; PR, partial response; SD, stationary disease; PD, progressive disease.

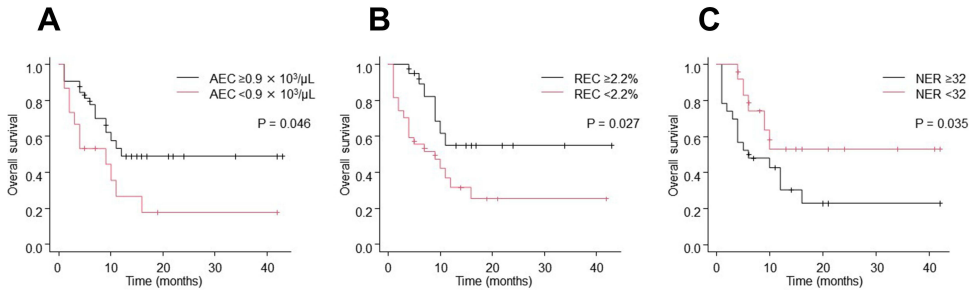


Figure 3 The overall survival (OS) of the patients divided by AEC (**A**), REC (**B**), and NER (**C**). (**A**) The median OS was 9.0 months in patients with AEC <0.9 × 10^3/μL vs 12.0 months in those with AEC ≥0.9 × 10^3/μL (p = 0.046). (**B**) The median OS was 9.0 months in patients with REC <2.2% vs unreached in those with REC ≥2.2% (p = 0.027). (**C**) The median OS was unreached in patients with NER <32 vs 6.0 months in those with NER ≥32 (p = 0.035).

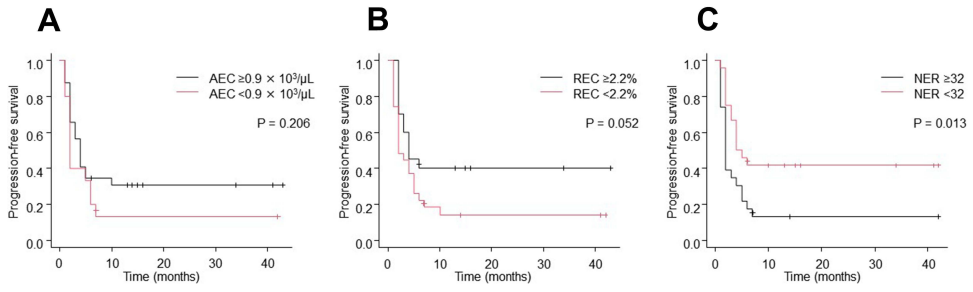


Figure 4 The progression-free survival (PFS) of the patients divided by AEC (**A**), REC (**B**), and NER (**C**). (**A**) The median PFS was 2.0 months in patients with AEC <0.9 × 10^3/μL vs 4.0 months in those with AEC ≥0.9 × 10^3/μL (p = 0.206). (**B**) The median PFS was 2.0 months in patients with REC <2.2% vs 4.0 months in those with REC ≥2.2% (p = 0.052). (**C**) The median PFS was 4.5 months in patients with NER <32 vs 2.0 months in those with REC ≥32 (p = 0.013).

Table 2 Univariate and Multivariate Analyses of the Factors Associated with the Overall Survival of Patients Treated with Nivolumab

Variable		Univariate		Multivariate	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (years)	<65 ≥65	1 0.958 (0.448–2.052)	0.914		
Sex	Male Female	1 0.697 (0.209–2.325)	0.557		
EOCG PS	0, 1 2, 3	1 7.606 (3.084–18.76)	<0.001	1 8.724 (3.356–22.68)	<0.001
Primary tumor site	Oral, pharynx, larynx Others	1 0.847 (0.358–2.006)	0.706		
Disease site	Locoregional Distant metastasis	1 0.543 (0.188–1.574)	0.261		
AEC	<0.9 ≥0.9	1 0.672 (0.337–1.338)	0.258		
REC	<2.2 ≥2.2	1 0.506 (0.227–1.129)	0.096		
NER	<32 ≥32	1 2.178 (1.008–4.709)	0.048	1 2.474 (1.109–5.518)	0.027

Discussion

To the best of our knowledge, this is the first study to compare the prognostic value of eosinophil-related factors, namely, AEC, REC, and NER, in patients with head and neck cancers treated with nivolumab and to show the importance of pretreatment NER.

In this study, the pretreatment values of each factor were used for the following reasons.

The timing of sample collection for searching a drug biomarker was roughly divided into before and after the administration of the drug. In addition to using the values at each time point as the material for consideration, other methods were used to compare the values before and after the administration of the drug and to predict prognosis based on the degree of change in those values. However, serious complications can occur immediately after the initiation of ICI treatment.[26] If the effect of an ICI can be predicted before its administration, patients who are not expected to respond to the treatment will not receive the drug, thus avoiding the development of meaningless complications. Therefore, we examined these values before the administration of nivolumab in this study.

In the Kaplan–Meier study in this study, the high AEC and REC groups and the low NER group had significantly prolonged OS compared with their respective comparator groups. These results are similar to those reported in previous studies on other malignant tumors,[21,27,28] suggesting that eosinophils are key to predicting prognosis in ICI.

However, particularly, this study focused on parameters related to tumor shrinkage and disease control, such as ORR, DCR, and PFS. In actual clinical practice, many patients with head and neck cancers exhibit tumor pain and bleeding due to disease progression. For this reason, some patients treated with nivolumab may have to be switched to conventional chemotherapy, which has a faster onset of therapeutic effect than ICIs,[29] even though nivolumab may have a promising therapeutic effect. Therefore, ORR, DCR, and PFS are critical in real-world clinical practice for nivolumab therapy.

In this study, focusing on these problems and examining AEC, REC, and NER, the following results were obtained. Comparing the high and low AEC groups, no significant differences in the ORR, DCR, and PFS were observed. Comparing between the high and low REC groups, only DCR showed a significant improvement in the high REC

group; however, no significant differences in the ORR and PFS were observed between the two groups. In contrast, the low NER group showed significant improvement in not only OS but also ORR, DCR, and PFS compared with the high NER group.

Furthermore, as a result of the multivariate analysis, low NER values were confirmed as an independent factor for OS.

From these results, it was shown that NER is a factor related not only to the survival but also to tumor shrinkage and disease control; therefore, it is one of the most effective biomarkers in clinical practice.

NER is calculated using the ratio of neutrophils to eosinophils in the peripheral blood. As mentioned earlier, eosinophils have direct or indirect antitumor effects,[22,23] whereas neutrophils induce tumor growth and infiltration.[30,31] Therefore, it can be said that NER reflects the balance between the tumor-promoting factor possessed by the patient and the antitumor factor particularly related to ICIs. This could be a reason why NER was a more accurate predictor of prognosis of patients treated with nivolumab.

In fact, the efficacy of NER as a biomarker in ICIs treatment has been demonstrated in various carcinomas, such as advanced renal cell carcinoma (RCC),[32] metastatic RCC,[25] and urothelial carcinoma.[33]

Alternatively, NLR values were similar to NER values. Lymphocytes are known as factors directly related to tumor immunity, and NLR is thought to reflect a patient's tumor immunity as well as NER.[34] Although have been reports on the association between NLR and ICI treatment efficacy in several carcinomas,[35,36] it is unclear whether NER is a better ICI biomarker than NLR. Few studies have been conducted on this issue in head and neck cancers. However, studies on metastatic renal cell carcinoma have shown that NER is superior to NLR in predicting the response to ICI treatment by comparing pretreatment NER and NLR in patients treated with ICI.[25] This suggests that NER is a better predictor of ICI treatment response than NLR. Further study on this issue in head and neck cancers is needed.

There were several limitations associated with the present study.

First, this study was a single-center retrospective study with a relatively small number of patients with a short-term follow-up period.

Second, PD-L1 in tumor tissue has only been measured in some patients. For this reason, although PD-L1 expression in tumors is an important factor in predicting the efficacy of nivolumab treatment, the impact on clinical outcome could not be examined. Also, the relationship between PD-L1 expression and eosinophil-related factors such as AEC, REC, and NER could not be compared.

Therefore, to optimize pharmacotherapy for R/M HNSCC, our findings should be validated in large prospective studies with long-term follow-up, and further individual studies on biomarkers in patients treated with nivolumab are needed.

Conclusion

This study highlights the role of eosinophils in R/M HNSCC treated with nivolumab and shows that low pretreatment NER (NER <32) in the peripheral blood is significantly associated with improved ORR, DCR, PFS, and OS.

Further large-scale and prospective studies are required to validate our conclusions.

Abbreviations

ICI, Immune checkpoint inhibitor; R/M HNSCC, recurrent/metastatic head and neck squamous cell carcinoma; ANC, absolute neutrophil count; NLR, neutrophil-to-lymphocyte ratio; CXCL, C–X–C motif chemokine ligand; AEC, absolute eosinophil count; REC, relative eosinophil count; NER, neutrophil-to-eosinophil ratio; ORR, objective response rate; CR, complete response; PR, partial response; SD, stationary disease; PR, progressive disease; ORR, overall response rate; DCR, disease control rate; OS, overall survival; PFS, progression-free survival; ROC, receiver operating characteristic; HR, hazard ratio; CI, confidence interval; EOCG, Eastern Cooperative Oncology Group; PS performance status.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; and all authors took part in drafting, revising, or critically reviewing the article, gave final approval of the version to be published, agreed on the journal to which the article has been submitted, and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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