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ORIGINAL ARTICLE

Walking one hour per day and the derived neutrophil-to-lymphocyte ratio are associated with outcome in palliative second-line immunotherapy for patients with recurrent and/or metastatic squamous cell carcinoma of head and neck

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HIGHLIGHTS

- Immune system status influences the effectiveness of immunotherapy.
- Exercising improves the immune system.
- The neutrophil-lymphocyte derived ratio is a measure of the immune system.
- Walking one hour a day improves survival in patients treated with immunotherapy.
- High neutrophil-lymphocyte derived ratio improves survival in these patients.

KEYWORDS
Head and neck cancer;

Abstract
Objectives: To determine whether routinary walking activity and the derived neutrophil-to-lymphocyte ratio are associated with outcomes in patients with recurrent and/or metastatic squamous cell carcinoma of head and neck.

Abbreviations: SCCHN, Squamous Cell Carcinoma of the head and neck; R/M, Regional or Metastatic; PD-L1, Programmed Death-Ligand-1; PD-1, Programmed Death-1; HR, Hazard Ratio; CI, Confidence Intervals; NLR, Neutrophil/Lymphoid Ratio; dNLR, Derived Neutrophil/Lymphoid Ratio; ECOG, Eastern Cooperative Oncology Group; WA, Walker; NW, Non-Walker; TPS, Tumor Positive Score; CPS, Combined Positive Score; OS, Overall Survival; PFS, Progression-Free Survival.

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Physical activity;
Immunotherapy;
Derived neutrophil-to-lymphocyte ratio;
Prognosis

Methods: This multicenter retrospective cohort study included 64 patients diagnosed with recurrent and/or metastatic squamous cell carcinoma of head and neck and treated with immunotherapy (Programmed Death-1 and Programmed Death-ligand-1 proteins inhibitors) at two tertiary centers. We compared a group that performed uninterrupted physical activity for 1 h per day and controls who performed no activity. The derived neutrophil-to-lymphocyte ratio was calculated as follows: [neutrophils / (leukocytes − neutrophils)]. Progression-free survival and overall survival were evaluated.

Results: We included 28 (44%) and 36 (56%) patients in the activity and non-activity groups, respectively. Patient characteristics, treatment details, and tumor Programmed Death-ligand-1 expression were not associated with either progression-free survival or overall survival. Physical activity was an independent beneficial factor for progression-free survival ($p < 0.001$) and overall survival ($p < 0.001$). By contrast, a derived neutrophil-to-lymphocyte ratio <3.5 was an independent beneficial factor for overall survival ($p = 0.013$), but not for progression-free survival ($p = 0.328$).

Conclusions: Walking one hour per day and having a high proportion of lymphocytes to neutrophiles (expressed as a low derived neutrophil-to-lymphocyte ratio) independently predict a better prognosis in patients with recurrent and/or metastatic squamous cell carcinoma of head and neck treated with immunotherapy.

Level of evidence: III.

Introduction

Primary tumors located in the oral cavity, hypopharynx, and larynx have an annual incidence of more than 700,000 cases worldwide and a mortality rate of about 50%.[1] Squamous Cell Carcinoma of the Head and Neck (SCCHN) accounts for most cases, with surgery and/or chemoradiotherapy as the main treatment strategies. The curative rate for early-stage disease is high. On the contrary, despite advances in these treatments, approximately 40% of locally advanced SCCHN will not respond or recur after treatment. In addition, up to 50% will develop loco-regional recurrence and up to 20% will develop distant metastasis.[2]

Palliative treatments for patients with R/M SCCHN usually include radiotherapy, which is limited by normal tissue dose tolerance, and systemic therapy with platinum-based drugs, antifolates, taxanes, and cetuximab.[3] Fortunately, the more recent study of cancer immunology has led to the development of new treatments that modulate the immune system and improve survival.[4] Among these, immune checkpoint inhibitors block certain proteins, called ''checkpoints'', created by T-cells and some cancer cells. These checkpoints help prevent immune responses from becoming too strong and can sometimes prevent T-cells from killing cancer cells. Examples include Programmed Death-Ligand-1 (PD-L1) on tumor cells and Programmed Death-1 (PD-1) on T cells. The development of immune checkpoint inhibitors (e.g., avelumab, nivolumab, tremelimumab, or pembrolizumab) that block PD-L1 binding to PD-1 enable T-cells to eliminate tumor cells, showing durable responses and survival improvements in patients with R/M SCCHN treated using platinum-based drugs.[5–7] Some authors have also studied the effectiveness of immune checkpoint inhibitors in patients with R/M SCCHN who have low or negative PD-L1 expression.[7]

Many authors have demonstrated the importance of immune cell distribution in patients with cancer. Chronic inflammation in these patients results in an increased neutrophil count and a decreased lymphocyte count in the peripheral blood that are associated with poor clinical response.[8] Kuss et al. demonstrated that patients with head and neck cancer have lower lymphocyte counts compared with healthy controls.[9] Since lymphocytes are responsible for the immune response against cancer, their counts inversely correlate with cancer severity.[10] Given these associations, several markers of cancer-related inflammation have been proposed, with the Neutrophil/Lymphoid Ratio (NLR)[7,11,12] and the derived NLR (dNLR; Neutrophil/Leukocyte minus Lymphocyte ratio) becoming strong predictors of outcome.[13] Higher NLR or dNLR values indicate lower lymphocyte counts and worse prognosis.[10] Despite the low cost and ease of collection of these biomarkers in routine clinical practice, few articles have studied their value for head and neck cancer.[14,15]

Finally, it has been suggested that regular physical activity after a cancer diagnosis may improve treatment outcomes.[16] Some authors have even argued that regular physical activity could modify the distribution of immune cells in the tumor microenvironment and improve the antitumor response.[17]

This study aimed to evaluate the effect of routine physical activity (defined as walking for $\geq$1 h/day), the immune biomarker dNLR, and tumor cell PD-L1 expression on the outcomes of patients with R/M SCCHN treated with PD-1/PD-L1 inhibitors.

Methods

Patients

The design of this study was a multicenter cohort study of consecutive patients with R/M SCCHN undergoing treatment with PD-1/PD-L1 inhibitors (nivolumab, durvalumab, and avelumab) in two tertiary referral hospitals. Clinical data were collected prospectively, and histopathological evaluation of tumors were analyzed retrospectively. The inclusion criteria were as follows: biopsy-proven R/M SCCHN in the oral, pharyngeal, laryngeal, or rhinosinus region before treatment; not amenable to curative treatment; having received PD-1 or PD-L1 inhibitor therapy either in routine practice or within a clinical trial; having an Eastern Cooperative Oncology Group (ECOG) performance-status score $\leq$2; and having no physical or mental limitations to perform the minimum physical activity requirement.

Treatment protocol

All included patients were presented at a multidisciplinary board with participation of head and neck surgeons or dermatologists, radiation oncologists, and medical oncologists where treatment plan was discussed and decided together.

PD-L1 or PD1 inhibitors were used to the point of disease progression or unacceptable toxicity. Patients received either nivolumab (240 mg), durvalumab (10 mg/kg), or avelumab (10 mg/kg) every 2 weeks. This treatment, as a second-line palliative treatment for recurrent and metastatic disease, did not require PD-L1 assessment for initation and was conducted for research purposes.

All enrolled patients were advised to walk every day for 1 h from one week before to the end of treatment. Patients were divided into Walker (WA) and Non-Walker (NW) groups by whether they completed the activity.

This study was approved by the Institutional Review Board (HCB/2022/1152). All patients signed the informed consent form.

Data collection and assessments

We collected demographic and clinical data. This included the complete blood cell count at baseline, within 30 days before the first immunotherapy treatment to calculate the dNLR. The dNLR was then calculated as previously defined: [absolute neutrophil count/(white blood cells − absolute neutrophil count)].[13]

Biopsies of the primary tumor were analyzed to determine PD-L1 expression by immunohistochemistry on formalin-fixed, paraffin-embedded tissue sections using PD-L1 22C3 pharmDx antibody on a Dako Autostainer Link 48. A sample was considered valid when a minimum number of 100 viable tumor cells were present. The PD-L1 expression level was then expressed as the Tumor Positive Score (TPS) and the Combined Positive Score (CPS). TPS evaluates the percentage of viable tumor cells showing partial or complete membrane staining at any intensity and is reported as a percentage. CPS evaluates the number of PD-L1 stained cells (e.g., tumor cells, lymphocytes, and macrophages) relative to all viable tumor cells on a scale from 0 to 100.

Clinical response was classified according to the immune-related modified Response Evaluation Criteria in Solid Tumors (iRecist) criteria based on radiological assessments at baseline and every 12 weeks thereafter, according to established guidelines.[18] The Overall Survival (OS) was defined as the length of time that patients survived from the start of treatment. Progression-Free Survival (PFS) was defined as the length of time that patients survived with the disease, without progression or death, during and after treatment.

Statistical analysis

To achieve an 80% statistical power with a bilateral alpha error of 5%, the sample size was calculated. After analysis of type I and II error, at least 62 patients would be necessary, 31 patients in each arm, using Fleiss formula and assuming a 25% of survival after 1 year of follow-up in patients with less than 1 h of exercise and anticipating a 60% of survival after 12 months of follow-up in patients with more than 1 h of exercise. The study was designed to detect this difference if it occurred.

Patient characteristics were compared using the chi-squared or Fisher exact test, or for continuous variables, using analysis of variance. Receiver-Operating Characteristic (ROC) curve was used to determine cut-off point of dNLR that best differentiate survivance after 1 year of follow-up. Survival analyses were performed using the Kaplan-Meier method and the log-rank test. Multivariate Cox regression was performed to determine the factors independently associated with OS and PFS, with outcomes expressed as Hazard Ratios (HRs) with 95% Confidence Intervals (CIs). Statistical analyses were performed using IBM SPSS, Version 25.0 (IBM Corp., Armonk, NY, USA), and all p-values < 0.05 were considered statistically significant.

Results

Patients and treatment

This study included 64 consecutive patients treated with the PD-1/PD-L1 inhibitors nivolumab (n = 54), durvalumab (n = 9), and avelumab (n = 1). Their characteristics are shown in Table 1. Gender, age, ECOG status, primary tumor, HPV p16+ status (in oro/hypo-pharyngeal tumors), and previous treatments were not associated with either the OS or the PFS (Table 1).

Physical activity

In total, 28 patients (44%) completed $\geq$1 -h/day of uninterrupted physical activity during the treatment period and were included in the WA group. The remaining 36 patients (56%) comprised the NW group. The main argument for not walking was discomfort in social contact due to either a tracheotomy or aesthetic alterations from previous surgeries.

At the first evaluation, 12 weeks after the start of treatment, 15 patients (23%) had obtained clinical benefit

Table 1 Baseline patient characteristics and survival data.

	Total	Walkers	Non-walkers	PFS (median, 95% IC)	OS (median, 95% IC)
n (%)	64 (100%)	28 (44%)	36 (56%)		
Gender				$p = 0.748$	$p = 0.748$
Male	47 (72%)	22 (79%)	25 (69%)	3 (1.7–4.3)	8 (4.2–11.8)
Female	17 (28%)	6 (21%)	11 (31%)	2 (0.9–3.1)	10 (3.8–16.1)
AGE (median)	63 (49–85)	61 (49–78)	64 (54–85)		
Age coded				$p = 0.936$	$p = 0.862$
<65 years	41 (64%)	20 (56%)	21 (75%)	2 (1.2–2.8)	10 (6.2–13.8)
>65 years	23 (36%)	16 (44%)	7 (25%)	3 (2.1–3.9)	6 (3.2–8.8)
ECOG				$p = 0.546$	$p = 0.533$
1	55 (86%)	25 (39%)	30 (47%)	3 (2.0–4.0)	9 (5.4–12.6)
2	9 (14%)	3 (5%)	6 (9%)	2 (0.2–3.9)	3 (0.8–5.9)
Primary tumor				$p = 0.875$	$p = 0.366$
Rhinosinusal	4 (6%)	2 (7%)	2 (6%)	3 (0.9–5.1)	9 (3.2–14.8)
Oral Cavity/Oropharynx	31 (48%)	11 (39%)	20 (59%)	3 (0.7–5.3)	10 (6.6–13.3)
Hypopharynx	15 (23%)	10 (36%)	5 (29%)	2 (0.7–3.3)	3 (0.0–6.3)
Larynx	14 (22%)	5 (18%)	9 (6%)	2 (2.1–3.9)	9 (5.1–13.1)
HPVp16 (oropharyngeal)				$p = 0.125$	$p = 0.076$
Positive	6 (9%)	4 (15%)	2 (5%)	5 (0.2–9.8)	6 (2.3–9.7)
Negative	31 (49%)	11 (39%)	20 (56%)	2 (1.0–3.0)	11 (6.6–15.4)
Non evaluated	27 (42%)	13 (46%)	14 (39%)	3 (1.4–4.6)	11 (2.2–19.8)
Previous treatment				$p = 0.476$	$p = 0.102$
Chemoradiotherapy	33 (52%)	15 (24%)	18 (28%)	3 (1.7–4.3)	7 (2.9–11.1)
(Extreme)	31 (48%)	13 (20%)	18 (28%)	2 (0.5–3.9)	14 (4.9–23.1)
PD-L1 expression					
TPS > 50	3 (5%)	1 (2%)	2 (3%)	$p = 0.987$	$p = 0.766$
CPS > 1	14 (22%)	5 (8%)	9 (14%)	$p = 0.985$	$p = 0.830$

CPS, Combined Positive Score; TPS, Total Positive Score; PFS, Progression Free Survival; OS, Overall Survival.

(Objective response or Stable disease) according to the iRecist criteria. The number of patients with clinical benefit was higher in the AW group (10 patients; 36%) than in the NW group (5 patients; 14%). The percentage of patients with a survival longer than 12 months only showed a trend, not statistically significant ($p = 0.08$), to be higher in the WA group (9 patients, 47%) than the NW group (5 patients, 16%).

The entire group had a mean follow-up of 8.6 months (range, 1–45) and a mean PFS of 5.3 months (range, 1–39). The median PFS was significantly longer in the WA group (9-months) than in the NW group (2-months; $p < 0.001$; Fig. 1). The median OS was also better in the WA group (25-months) than in the NW group (4-months; $p < 0.001$; Fig. 2).

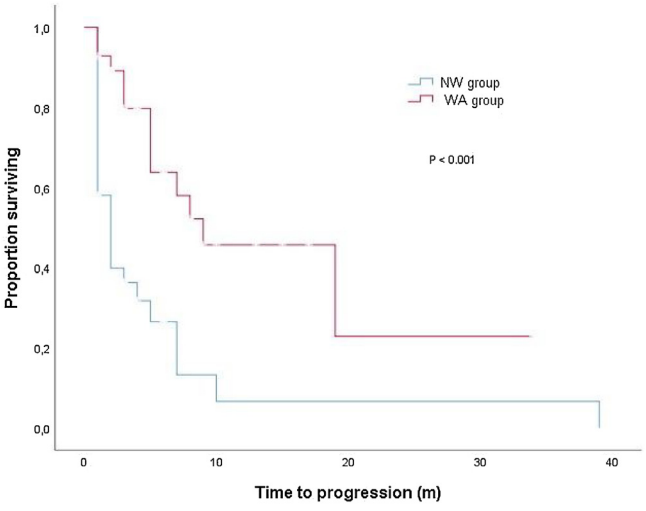

Fig. 1 Progression-free survival by whether patients completed a walking activity. We compared walking (≥1 h/ day; WA = 28) and non-walking (NW = 36) groups.

Derived neutrophil/lymphoid ratio

The cut-off of dNLR to analyze survival was greater than 3.25 according to the results of the ROC curve (AUC = 72%, 95% IC 57%–86%; Sensitivity = 0.64; 1-Specificity 0.28; $p = 0.014$). The 28 patients with a baseline dNLR < 3.25 showed a significantly better OS than the 36 patients with a dNLR ≥ 3.25 (17 vs. 10-months; $p = 0.012$; Fig. 3). The PFS was not different according to baseline dNLR (9 vs. 5-months, $p = 0.160$). The dNLR expression after the first immunotherapy dose (dNLR-post) was only determined in 61 patients because 3 did not receive the second treatment cycle. The OS and PFS were not significantly different between patients in the low and high dNLRpost groups (14 vs. 13-months, $p = 0.954$; and 7 vs. 6-months, $p = 0.604$, respectively).

Treatment with immunotherapy did not result in a significant change in dNLR scores when looking at all patients. The categories of the variables Age coded, Gender, Perfomance status (ECOG), Primary tumour and Physical activity were

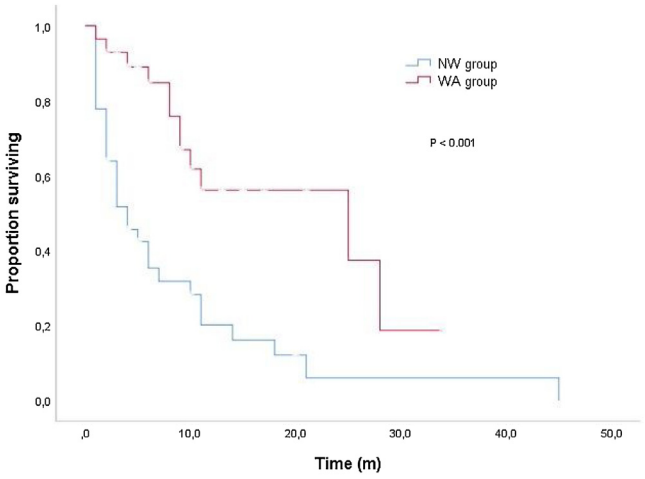

Fig. 2 Overall survival by whether patients completed a walking activity. We compared walking (≥1 h/day; WA = 28) and non-walking (NW = 36) groups.

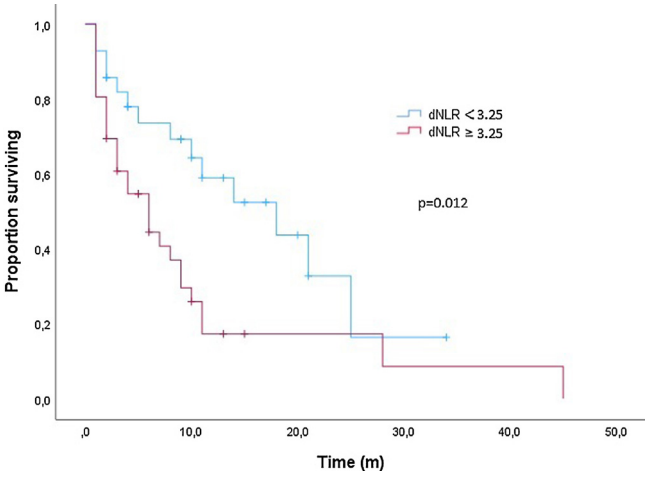

Fig. 3 Overall survival according to the baseline dNLR. The dNLR was calculated as [absolute neutrophil count / (white blood cells − absolute neutrophil count)], with a cut-off point of <3.5 for a low ratio (high, ≥3.5). dNLR, Derived Neutrophil-to-Lymphocyte Ratio.

independently assessed and a significant decrease in dNLR after treatment was observed in Females, patients with Oral tumors and in patients in the NW group (Table 2).

PD-L1 tumor expression

PD-L1 expression was only evaluated in 52 patients due to either a lack of material or poor material preservation (12 cases). The TPS was ≥ 50% in 3 patients (WA group, 1; NW group, 2; $p = 0.645$) and the CPS was ≥ 1 in 34 patients (WA group, 13; NW group, 21; $p = 0.443$). A CPS ≥ 20 was observed in 4 patients from the WA group and 6 from the NW group ($p = 0.613$). No significant differences were observed in the PFS or OS by PD-L1 status.

Multivariate analysis

Patient characteristics, treatments, physical activity, baseline dNLR, and post-treatment (12-weeks) dNLR were introduced to a Cox proportional hazards regression model. Physical activity was independently associated with PFS, the WA group having a better PFS (HR = 2.451; 95% CI 1.234–4.868; $p = 0.010$). Both physical activity and baseline dNLR were independently associated with OS, the WA group having a better OS ($p = 0.002$) and the group with a low baseline dNLR having a better OS ($p = 0.042$) (Table 3).

Table 2 Values of dNLR.

	Basal dNLR media (SD)	dNLR after treatment media (SD)	*p*
All cases	5.4 (5.1)	3.5 (3.2)	0.250
Gender			
Male	4.5 (4.4)	3.7 (3.6)	0.146
Female	7.8 (6.0)	3.1 (1.7)	0.008
Age coded			
<65 years	5.5 (4.8)	3.6 (3.7)	0.275
>65 years	5.3 (5.5)	3.4 (2.1)	0.082
ECOG			
1	5.8 (5.3)	3.6 (3.3)	0.08
2	2.9 (1.5)	3.3 (2.3)	0.334
Primary tumor			
Rhinosinusal	2.3 (1.3)	2.2 (2.1)	0.444
Oral	6.7 (6.2)	3.3 (4.0)	0.008
Cavity/Oropharynx			
Hypopharynx	5.3 (4.6)	4.0 (1.9)	0.138
Larynx	5.6 (4.8)	3.6 (2.2)	0.100
Physical activity			
Walking group	3.7 (2.1)	3.8 (1.6)	0.394
No walking group	6.7 (6.2)	3.3 (4.0)	0.008

Table 3 Cox proportional hazards regression analysis results of overall survival.

Risk factor	Hazard ratio (HR) (95% CI for HR)	*p*-value
Walking group	3.433 (1.568–7.517)	0.002
Low baseline dNLR	2.190 (1.029–4.660)	0.0042

Discussion

A healthy immune system has an important effect on the prognosis of cancer, especially in patients treated with immunotherapy. Many conditions can modify the immune system, including physical activity. Our study found that both routine physical activity (walking one hour per day) and the proportion of lymphocytes to neutrophils in the blood (i.e., dNLR) independently affect survival in patients with R/M SCCHN who receive PD-1/PD-L1 inhibitors.

Research has shown that even moderate levels of regular physical activity can increase the effectiveness of the immune system.[19–21] This has been identified as an independent prognostic factor in both experimental animal models[22–24] and in patients with cancer,[19] including breast,[25] hematologic,[26] and colorectal cancers.[27] The exercise also improved the response in patients treated with immunotherapy, consistent with Gustafson et al.'s research.[28] Our study adds that walking for ≥1-h/day can also improve PFS and OS in patients with R/M SCCHN (rhinosinusal, oral, pharyngeal, and laryngeal tumors). However, our study could only show a trend in the percentage of patients who survived more than 12-months in the patients who did the physical activity; the lack of statistical significance in this variable could be due to the fact that survival in both groups was lower than expected and used for sample calculation, and we also had only 28 patients who did not the exercise. The biological mechanisms linking exercise to prognostic changes in cancer are poorly understood, with various hypotheses implicating changes in leukocyte populations, increased antioxidant defense mechanisms, alterations in inflammatory mediators, and changes in specific antitumor mechanisms.[19,25,29]

NLR and the dNLR have been popularized as biomarkers of systemic inflammatory response in patients with some types of cancer.[11–14,30–32] In particular, elevated dNLR values have been associated with poor prognosis, as in our study, for several types of cancer,[13] including melanoma,[33] breast cancer,[34] and more recently, laryngeal,[14,15,35] oral,[36,37] and nasopharyngeal[38] cancers, Researchers from our department have also demonstrated an association been high dNLR and a poor prognosis in patients with non-small cell lung cancer treated with PD-1/PD-L1 inhibitors,[39] similar to our results. However, this relationship was not observed in patients undergoing chemotherapy,[39] reflecting that our understanding of the relationship between dNLR and prognosis needs further clarification. Donnem et al. hypothesized that oncologic activity may be associated with decreased lymphocyte counts and increased neutrophil counts in patients with cancer.[40] We believe that immunotherapy requires a more efficient lymphocyte function for an anticancer response (specifically CD8+)[14] than chemotherapy.

Some authors have specifically studied the positive influence of physical activity on the NLR and, therefore, the dNLR.[41,42] Pedersen et al. explain this influence through an increase in part of the lymphocyte count, particularly the distribution of cytotoxic T lymphocytes, that improves the response to anti-PD-1/PD-L1 agents during treatment.[43] Our study revealed no association between physical activity and a low dNLR. Furthermore, PD-L1 expression in the tumor did not affect either PFS or OS. Both findings probably reflect the low number of patients involved. Ito et al. reported a strong correlation between a TPS ≥ 40% and a CPS ≥ 20 for head and neck cancer treated with nivolumab.[44] These investigators also noted that TPS may be used as a predictor of prognosis and efficacy, but they could not demonstrate the prognostic value of CPS, consistent with our results. However, the main limitation of this study was how we recorded physical activity. By failing to reflect personal differences in the practice of physical activity, we cannot draw definitive conclusions. A prospective controlled study will be necessary for such analysis, but it could have ethical implications. Despite the limitations, this study can inform future research in this area.

Conclusions

Walking for ≥1-h/day and having a high ratio of lymphocytes to neutrophiles (expressed as an elevated dNLR ratio) represent independent predictors of a better OS in patients with advanced SCCHN treated with immunotherapy. Despite the better results in patients who performed physical activity, studies with better control of variables and with larger numbers of patients are needed to establish a direct relationship between exercise and survival in cancer patients. The result on dNLR can serve as a potentially useful tool when selecting idoneal patients for immunotherapy treatment.

Authors' contributions

Design: JJG. Acquisition of data: AP, PC and AP. Analysis: OG. Writing and drafting: MC and PN. Critical Revision: AL.

Meetings at which the manuscript was presented

This investigation was presented in the 74th Congress of the Spanish Society for Otorhinolaryngology and Head and Neck Surgery (SEORL-CCC) and in the XIX Spanish-Portuguese Congress, October 5–8, 2023.

Justification of the number of authors

The number of investigators is justified because this study has been conducted by investigators from two independent institutions (4-authors each) and covers both clinical and basic research.

Ethics approval and consent to participate

Ethics approval and consent to participate this study was approved by the Ethics Committee of Hospital Clínic of Barcelona (HCB/2022/1152).

Consent for publication

Not applicable (the manuscript does not contain data from any individual person).

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The authors have no financial support or financial interests.

Conflicts of interest

The authors declare no conflicts of interest.

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