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# Prognostic Impact of Sarcopenia on Clinical Outcomes in Patients With Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma Treated With Immune Checkpoint Inhibitors

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## Abstract

*Background/Aim:* Poor nutritional status is one of the key contributing factors to sarcopenia, which negatively influences postoperative complications and clinical outcomes in patients with head and neck squamous cell carcinoma (HNSCC). This study aimed to investigate the potential association between sarcopenia and clinical outcomes in patients with recurrent and/or metastatic HNSCC treated with immune checkpoint inhibitors (ICIs).

*Patients and Methods:* A retrospective review was conducted on the medical records of 119 patients with recurrent and/or metastatic HNSCC who received ICI therapy.

*Results:* The objective response rates (ORRs) were 30.7% in the non-sarcopenia group and 15.8% in the sarcopenia group, showing a statistically significant difference between the two groups ($p$=0.048). Patients with good performance status (PS), absence of sarcopenia, and distant metastasis exhibited significantly longer overall survival (OS) compared to those with poor PS, sarcopenia, and locoregional recurrence, respectively ($p$=0.014, $p$=0.003, $p$=0.026). Multivariate analysis identified sarcopenia and locoregional recurrence as independent prognostic factors for OS. The incidence of immune-related adverse events (irAEs) did not significantly differ between patients with and without sarcopenia.

*Conclusion:* These findings underscore the detrimental impact of sarcopenia on the efficacy of immune checkpoint inhibitor therapy in patients with recurrent and/or metastatic HNSCC. Careful consideration of sarcopenia is warranted in the clinical management of these patients.

**Keywords:** Head and neck squamous cell carcinoma, immune checkpoint inhibitors, sarcopenia, chemotherapy.

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## Introduction

The global incidence of newly diagnosed head and neck cancers is estimated to range from 400,000 to 600,000 cases annually, with a corresponding mortality of approximately 223,000 to 300,000 deaths per year (1, 2). Among these, head and neck squamous cell carcinoma (HNSCC) accounts for approximately 90% of all cases (3).

Treatment selection for HNSCC is primarily guided by tumor staging, the patient's overall performance status, and the presence of functional or systemic comorbidities. However, considering that locally advanced HNSCCs comprise more than 60% of all localized HNSCCs, approximately half of these cases experience recurrence, with the majority of recurrences occurring within the first two years following treatment (4-7). In recent years, immune checkpoint inhibitors (ICIs) such as nivolumab and pembrolizumab have significantly improved survival outcomes in patients with recurrent and/or metastatic HNSCC (8, 9). Moreover, the trend toward an increasing age at cancer diagnosis has become more pronounced, and the clinical application of ICIs has gradually extended to older patients. Conversely, there is a growing body of reports indicating an increasing prevalence of sarcopenia among elderly patients diagnosed with head and neck squamous cell carcinoma (HNSCC), a pathological condition characterized by the loss of skeletal muscle mass due to aging or disease. Poor nutrition is one cause of sarcopenia. Undernutrition causes weight loss and leads to decreased muscle strength through loss of muscle mass (10, 11).

In the case of cancer patients with sarcopenia, there are many reports indicating that sarcopenia has an adverse effect on postoperative complications and prognoses in HNSCC (11, 12). Moreover, an increasing number of studies have focused on the impact of sarcopenia on the efficacy of immune checkpoint inhibitor (ICI) therapy (13). However, the influence of sarcopenia on ICI response in HNSCC patients is still a topic of controversy.

Given these statistics, there is a need to evaluate the efficacy and safety of cancer treatments in those patients. This study aimed to examine the possible relationship between sarcopenia and clinical outcomes in patients with recurrent and/or metastatic HNSCC who received ICI treatment.

## Patients and Methods

This retrospective study included patients with recurrent and/or metastatic HNSCC treated with nivolumab or pembrolizumab at Kindai University Hospital, Japan, from April 2017 to October 2024. Patients were included if they had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, had adequate organ function, and had received at least one cycle of nivolumab or pembrolizumab therapy. Nivolumab was administered to patients at 3 mg/kg or 240 mg/body every 2 weeks and pembrolizumab (200 mg/body) was administered once every 3 weeks based on individual patient conditions. The treatment continued until either disease progression or unacceptable toxicity occurred, with patients monitored until death or the cutoff date (December 31, 2024).

A total of 119 patients were identified for analysis. There were 93 men and 26 women with a median age of 69 years (range=34-88 years). Performance status (PS) was 0-1 in 104 patients, and 2 in 15 patients. Body composition was assessed prior to the initiation of ICI therapy using bioelectrical impedance analysis (BIA) with the InBody 370 device (InBody Japan Co., Ltd., Tokyo, Japan). The diagnosis of sarcopenia was based on the AWGS2019 criteria proposed by the Asian Working Group for Sarcopenia in 2019 (14).

The primary tumor site was the nasopharynx in six patients, the oropharynx in 24 patients, the hypopharynx in 31 patients, the oral cavity in 27 patients, the larynx in 13 patients, the paranasal sinus in eight patients, and others in 10 patients. Regarding the site of progression at ICI start, sixty-three patients experienced local or regional recurrence, while fifty-six developed distant metastases. A total of 82 patients received nivolumab and 37 patients received pembrolizumab. Patients were divided into sarcopenia and non-sarcopenia groups (Table I).

Clinical response to treatment was assessed every eight to 12 weeks using computed tomography (CT), and

Table I. *Patient and tumor characteristics.*

| Characteristics | | Total | (%) | Non-sarcopenia | (%) | Sarcopenia | (%) | *p*-Value |
|---|---|---|---|---|---|---|---|---|
| | | 119 | 100 | 81 | 68.1 | 38 | 31.9 | |
| Age | | 34-88 | | 34-85 (65) | | 47-88 (74) | | 0.000137 |
| Sex | | | | | | | | |
| | Male | 93 | 78.2 | 63 | 77.8 | 30 | 78.9 | |
| | Female | 26 | 21.8 | 18 | 22.2 | 8 | 21.1 | 1 |
| ECOG PS at ICI start | | | | | | | | |
| | 0,1 | 104 | 87.4 | 78 | 96.3 | 26 | 68.4 | |
| | 2 | 15 | 12.6 | 3 | 3.7 | 12 | 31.6 | 0.0000602 |
| Tumor site | | | | | | | | |
| | Nasopharynx | 6 | 5 | 5 | 6.2 | 1 | 2.6 | |
| | Oropharynx | 24 | 20.2 | 14 | 17.3 | 10 | 26.3 | |
| | Hypopharynx | 31 | 26.1 | 26 | 32.1 | 5 | 13.2 | |
| | Oral cavity | 27 | 22.7 | 17 | 21.0 | 10 | 26.3 | |
| | Larynx | 13 | 10.9 | 6 | 7.4 | 7 | 18.4 | |
| | Paranasal sinus | 8 | 6.7 | 5 | 6.2 | 3 | 7.9 | |
| | Other | 10 | 8.4 | 8 | 9.9 | 2 | 5.3 | 0.153 |
| Site of progression at ICI start, | | | | | | | | |
| | Loco-regional with or without distant metastasis | 63 | 52.9 | 41 | 50.6 | 22 | 57.9 | |
| | Distant metastasis | 56 | 47.1 | 40 | 49.4 | 16 | 42.1 | 0.555 |
| Type of ICI | | | | | | | | |
| | Nivolumab | 82 | 68.9 | 63 | 77.8 | 19 | 50 | |
| | Pembrolizumab | 37 | 31.1 | 18 | 22.2 | 19 | 50 | 0.00309 |

PS: Performance status; ICI: Immune checkpoint inhibitor.

tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The best overall response (BOR) for each patient was categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Overall survival (OS) was defined as the time from the start of treatment to the date of death or cutoff date, regardless of cause. Progression-free survival (PFS) was defined as disease progression, death from any cause, or cutoff date, whichever occurred first.

The overall response rate (ORR), PFS, and OS were examined for all subjects. Immune-related adverse events (irAEs) were investigated as part of the safety evaluation. The onset of irAEs was evaluated considering the Grade by using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. TNM classification was performed in accordance with the 8th edition of the guidelines provided by the Union for International Cancer Control.

The study received approval from the Institutional Review Board of Kindai University Hospital (receipt number R04-063) and was conducted in compliance with the principles of the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of this analysis, which used existing administrative and clinical data.

*Statistical analysis.* For the statistical significance test, continuous variables were assessed using the Mann–Whitney *U*-test, and categorical variables were assessed using Fisher's exact test. OS was calculated using the Kaplan–Meier method and was compared using the log-rank test. Univariate and multivariate Cox proportional hazards regression models were used to assess the associations between potential confounding variables and OS. Differences with a $p$-value <0.05 were considered significant. Risk was expressed as the hazard ratio (HR), and the 95% confidence interval (CI) was determined

Table II. *Best overall response.*

| Efficacy | Total | (%) | Non-sarcopenia | (%) | Sarcopenia | (%) | *p*-Value |
|---|---|---|---|---|---|---|---|
| BOR | | | | | | | |
| CR, PR | 36 | 30.2 | 30 | 37.0 | 6 | 15.8 | |
| SD | 28 | 23.5 | 17 | 21.0 | 11 | 28.9 | |
| PD | 55 | 46.2 | 34 | 42.0 | 21 | 55.3 | |
| ORR | 36 | 30.2 | 30 | 37.0 | 6 | 15.8 | 0.048 |
| DCR | 64 | 53.7 | 47 | 58.0 | 17 | 44.7 | 0.15 |

BOR: Best overall response; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: overall response rate; DCR: disease control rate.

using the reference groups. All statistical analyses were performed with the statistical software 'EZR' (Easy R) (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (15).

## Results

Table I summarizes the demographic and clinical characteristics of patients in the sarcopenia and non-sarcopenia groups. No significant differences were observed between the two groups with respect to sex, initial tumor location, or site of progression at the ICI therapy. In contrast, significant differences were found in the mean age and the type of ICI administered. Additionally, the ECOG PS was significantly poorer in the sarcopenia group ($p$=0.00006). The best overall response (BOR) among all patients was CR or PR in 36 cases (30.2%), SD in 28 cases (23.5%), and PD in 55 cases (46.2%). The ORR was 30.2%, and the disease control rate (DCR) was 53.7%. Among the 81 patients in the non-sarcopenia group, 30 achieved CR or PR, 17 had SD, and 34 experienced PD. In the sarcopenia group, CR or PR was observed in six patients, SD in 11 patients, and PD in 21 patients. The ORRs were 30.7% in the non-sarcopenia group and 15.8% in the sarcopenia group, with a statistically significant difference between the two groups ($p$=0.048). In contrast, no significant difference in DCR was observed between the groups (Table II).

As illustrated in Figure 1A and B, the 2-year OS rate was 39.3%, while the 2-year PFS rate was 21.7%. No statistically significant difference in OS was observed between elderly patients (aged ≥75 years) and non-elderly patients (aged <75 years) ($p$=0.68), nor between patients treated with nivolumab and those treated with pembrolizumab ($p$=0.79) (Figure 2A and B).

Conversely, patients with good PS, absence of sarcopenia, and distant metastasis demonstrated significantly better OS compared to those with poor PS, sarcopenia, and locoregional recurrence, respectively ($p$=0.014, $p$=0.003, $p$=0.026) (Figure 3A–C). The results of the univariate and multivariate analyses of factors associated with OS are presented in Table III. Sarcopenia and locoregional recurrence were identified as independent prognostic factors for OS. irAEs were observed in 32 patients (26.9%), with cutaneous reactions and endocrine dysfunction being the most frequently reported. The majority of irAEs were classified as grade 1 or 2, while grade ≥3 toxicities were observed in only six patients. Notably, the development of irAEs was associated with a significantly improved prognosis; however, there was no statistically significant difference in the incidence of irAEs between patients with and without sarcopenia (Figure 4, Table IV).

## Discussion

In this study, the median OS was 18.2 months and the median PFS was 14.3 months, which were favorable compared to the outcomes reported in the CheckMate 141 and KEYNOTE-048 studies (8, 9). These favorable outcomes were consistent with previously reported real-world clinical data (16, 17).

In recent years, with the advent of an aging society, the number of patients with sarcopenia has been increasing, raising significant concerns in the management of various diseases. The age-related decline in muscle mass and strength is known as sarcopenia, and it is observed across various chronic diseases, including cancer, regardless of chronological age (10). Sarcopenia is a skeletal muscle disorder characterized by the progressive loss of muscle mass and strength. In patients with cancer, sarcopenia has been reported to adversely affect both OS and postoperative

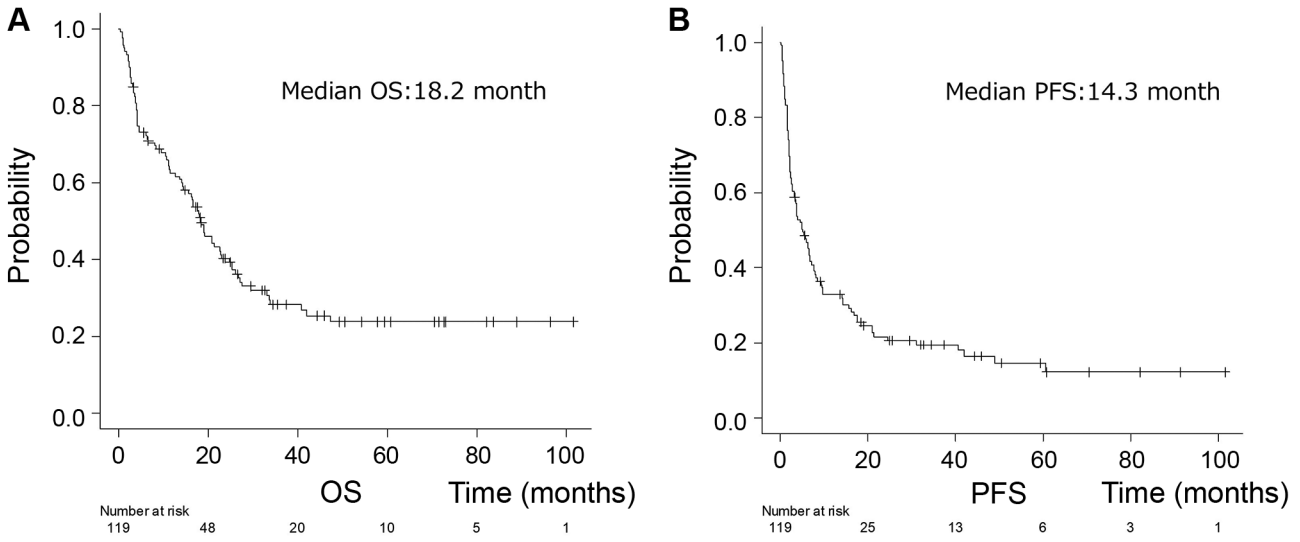


Figure 1. *Kaplan–Meier curves of the (A) overall survival and (B) progression-free survival.*

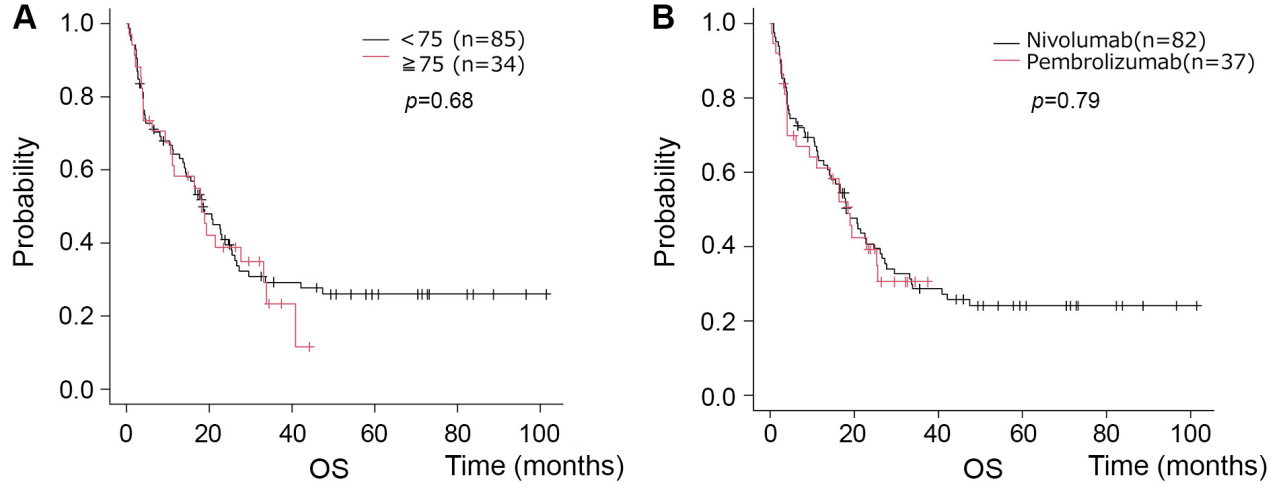


Figure 2. *Overall survival (OS) curves according to (A) age and (B) type of immune check point inhibitor (ICI).*

complications (13, 18). Similar trends have been observed specifically in patients with head and neck cancer (11). Recently, an increasing number of studies have focused on the impact of sarcopenia on the efficacy of ICI cancer therapy (19).

Our study showed that sarcopenia was significantly associated with worse OS, as well as lower ORR and DCR, in patients with recurrent and/or metastatic HNSCC treated with ICIs. Sarcopenia was also identified as an independent prognostic factor for reduced OS. Additionally, our results indicated that ICI monotherapy was more effective in patients with PS 0 or 1 compared to those with PS 2. Previous studies have also suggested that sarcopenia and/or poor PS predict worse OS and PFS in patients with melanoma (20) and non-small cell lung cancer treated with ICIs (21), consistent with our findings.

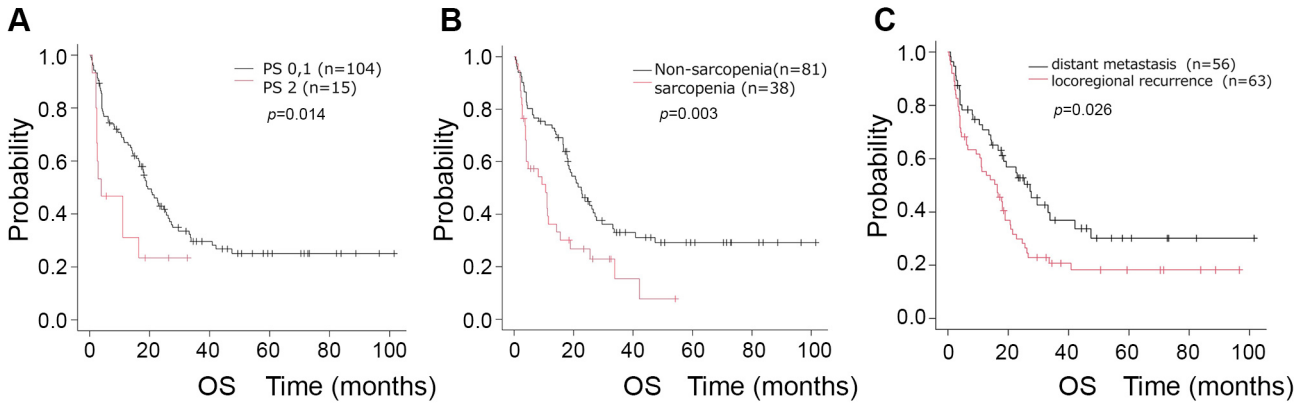


Figure 3. *Overall survival (OS) curves according to (A) PS, (B) sarcopenia status and (C) site of recurrence.*

Table III. *Univariate and multivariate Cox regression analyses of the association between clinical factors and overall survival (OS).*

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| Clinical factors | HR (95%CI) | *p*-Value | HR (95%CI) | *p*-Value |
| PS (2/0,1) | 2.199 (1.154-4.193) | 0.01666 | 1.4420 (0.6596-3.152) | 0.35910 |
| Sarcopenia/non-sarcopenia | 1.974 (1.245-3.128) | 0.003801 | 2.0150 (1.1650-3.488) | **0.01226** |
| Age (≥75/<75) | 1.107 (0.6859-1.786) | 0.6773 | 1.1060 (0.6513-1.876) | 0.71020 |
| Nivolumab/Pembrolizumab | 1.068 (0.6553-1.742) | 0.7907 | 0.7233 (0.3996-1.309) | 0.28470 |
| Locoregional recurrence/ distant metastasis | 1.646 (1.057-2.564) | 0.02733 | 1.6730 (1.0600-2.641) | **0.02710** |

PS: Performance status; HR: Hazard ratio. Significant values are shown in bold.

The incidence of irAEs is known as a favorable prognostic factor for ICI therapy. Our findings also demonstrated that patients who developed irAEs had significantly better prognosis compared to those who did not. However, no significant differences were observed in the incidence or severity of irAEs between the sarcopenia and non-sarcopenia groups.

The majority of patients with HNSCC are diagnosed at an advanced stage, and the disease predominantly affects older adults. Compared to their younger counterparts, older patients tend to exhibit lower response rates and reduced tolerability to conventional therapies, underscoring the importance of optimizing both the efficacy and safety of treatment strategies for this population. However, a subgroup analysis of the CheckMate-141 trial found no statistically significant difference in the efficacy of immune

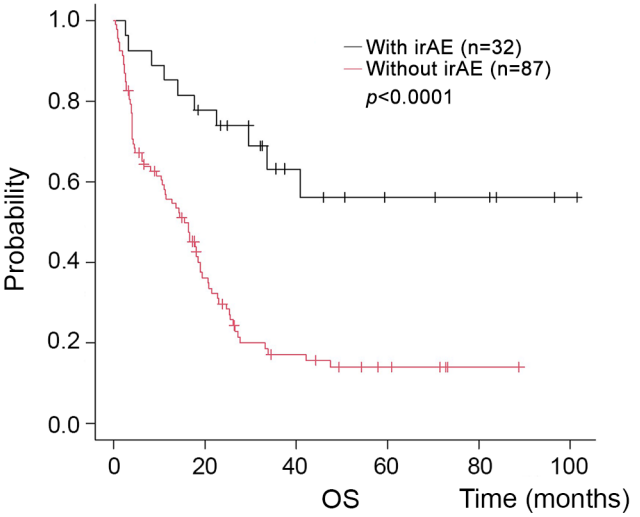


Figure 4. *Overall survival (OS) curves according to occurrence of immune-related adverse events (irAEs).*

Table IV. *Treatment-related adverse events.*

| Adverse event | Total | % | Non-sarcopenia | % | | Sarcopenia | % | | p-Value |
|---|---|---|---|---|---|---|---|---|---|
| | 119 | | 81 | | | 38 | | | |
| | | | Any grade | | Grade ≥3 | Any grade | | Grade ≥3 | |
| Any adverse event | 32 | 26.9 | 22 | 27.2 | 5 | 10 | 26.3 | 1 | 0.84 |
| General | 3 | | 3 | | 1 | 0 | | 0 | |
| Skin | 15 | | 9 | | 2 | 6 | | 0 | |
| Endocrine | 9 | | 6 | | 0 | 3 | | 1 | |
| Gastrointestinal | 1 | | 1 | | 0 | 0 | | 0 | |

checkpoint inhibitors (ICIs) between patients aged ≥65 and those younger than 65 years (22). However, elderly individuals are often underrepresented in clinical trials, leading to limited evidence on the efficacy and safety of ICIs in this population. In this context, pooled analyses of several clinical trials involving treatment-naïve patients with non-small cell lung cancer (NSCLC) have shown that ICI therapy significantly improves prognosis in older patients compared to chemotherapy alone, with outcomes comparable to those in younger patients (23). Furthermore, real-world evidence supports the notion that treatment efficacy does not substantially differ between younger and older patient populations (24, 25). In alignment with these findings, our study also demonstrated no significant difference in OS following ICI therapy between patients aged ≥75 years and those younger than 75. Taken together, these results suggest that chronological age alone should not be considered a limiting factor in the administration of ICIs.

Patients with locoregional recurrent HNSCC are at a significantly elevated risk of malnutrition, which has been recognized as an independent prognostic factor in patients with cancer (26). In HNSCC, nutritional status is often compromised at the time of diagnosis and tends to deteriorate further throughout the course of treatment. This decline is not only characterized by weight loss but also by the loss of skeletal muscle mass, both of which negatively impact prognosis and increase the risk of treatment-related complications (10, 27, 28). In our study, the pattern of recurrence was significantly associated with OS; patients with locoregional recurrence, whether accompanied by distant metastasis or not, had worse outcomes than those with distant metastasis alone. Pitakpaiboonkul *et al*. reported that most patients with locoregional recurrence underwent cisplatin monotherapy administered concurrently with radiotherapy, either on a weekly basis or every three weeks, with the cisplatin primarily serving as a radiosensitizer. Consequently, locoregional recurrence may reflect (chemo) radioresistant disease, which could respond differently to systemic therapies compared to cases of distant metastasis alone (26).

Although this study has limitations, including its single-center, retrospective design and a relatively small sample size, our findings suggest that sarcopenia is associated with worse OS, as well as lower ORR and DCR. These results highlight the importance of considering the negative impact of sarcopenia on the efficacy of ICI therapy in clinical practice. Further research is needed to determine whether interventions targeting sarcopenia can enhance ICI treatment outcomes and to clarify the biological mechanisms underlying the observed association between sarcopenia and reduced therapeutic efficacy.

## Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

## Authors' Contributions

Conceptualization: R.Y; Methodology, T.K and R.Y; Validation: D.A; Investigation: T.K, D.A, M.K, S.K, M.U, K.M, M.S, T.W and R.Y; Writing – Original Draft Preparation: T.K; Writing – Review & Editing: R.Y; Supervision: M.K and T.W; Project: R.Y; Administration: R.Y; Funding Acquisition: R.Y. All Authors have read and agreed to the published version of the manuscript.

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## Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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