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RESEARCH

CT-assessed sarcopenia and prognostic nutritional index are associated with poor prognosis in oral squamous cell carcinoma

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Abstract

Purpose Recently, it has been reported that sarcopenia and nutritional evaluation are associated with the prognosis of patients with cancer; however, there are only a few detailed reports on oral cancer. This single-center retrospective study aimed to analyze the relationship between computed tomography (CT)-assessed sarcopenia (CT-SP), immunocompetence, nutritional status, and the prognosis of patients with oral squamous cell carcinoma (OSCC).

Methods This retrospective study included patients who underwent radical therapy with surgery for OSCC between January 2014 and January 2021. Skeletal muscle in the third cervical vertebra (C3) was measured using preoperative cervical CT, and the skeletal muscle index (SMI) was calculated. Nutritional status were investigated using blood tests. The correlation between each parameter and prognosis was analyzed. The primary predictor variables were SMI, ECOG performance status, BMI, and nutritional status. The primary outcome variable was the 5-year overall survival rate (OS) and the secondary outcome variable was 5-year disease-specific survival rate (DSS).

Results One hundred sixty-three patients were registered retrospectively. The number of patients with CT-SP was 76 (52%). In the univariate analysis, CT-SP, prognostic nutritional index (PNI), and lymphocyte-monocyte ratio (LMR) were associated with poor prognosis, with statistically significant differences in OS and DSS. In the multivariate analysis, only CT-SP was identified as an independent prognostic factor for DSS. CT-SP was significantly correlated with the PNI.

Conclusion CT-SP was associated with a significant decrease in survival rate in patients with OSCC. Furthermore, CT-SP was correlated with the PNI.

Keywords Oral squamous cell carcinoma · Sarcopenia · Nutritional status · Prognostic nutritional index

Introduction

The annual incidence of oral cancer worldwide is 377,713 cases with 177, 757 deaths [1]. Oral cancer can be treated curatively due to advances in reconstruction methods; however, despite the development of various drug therapies for advanced and recurrent cases, the prognosis is poor. Many patients with oral cancer present with advanced disease and malnutrition or dysfunction before surgery.

Sarcopenia is a condition characterized by the loss of skeletal muscle mass and function and is strongly correlated with physical disability, poor quality of life, and death [2]. In recent years, there have been reports that sarcopenia is a poor prognostic factor for head and neck cancer; therefore, preoperative evaluation of sarcopenia is very important. However, there are only a few reports specifically on oral cancer. Sarcopenia is often diagnosed by measuring the skeletal muscle in the third lumber vertebra (L3) region. Computed tomography (CT), including for the lumbar spine, is not usually performed on patients with oral cancer. Recently, sarcopenia has been diagnosed in patients with oral cancer by measuring the skeletal muscle mass in the third cervical vertebra (C3) region [3].

The prognostic nutritional index (PNI), which incorporates the serum albumin level and peripheral blood lymphocyte

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count, serves as an indicator of immunocompetence and nutritional status. The PNI is often used as a biomarker for various carcinomas, including esophageal, gastric, and lung cancers [4]. Similarly, the PNI is a marker of poor prognosis in patients with oral and head and neck cancers [4, 5]. Moreover, the association of prognosis with nutritional status, modified Glasgow Prognostic Score (mGPS), C-reactive protein-albumin ratio (CAR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), and neutrophil–lymphocyte ratio (NLR) as indicators of immunocompetence has been reported in cancer patients [4, 6–9]. It has been suggested that skeletal muscle destruction may occur due to malnutrition and inflammatory reactions and is associated with sarcopenia [10]. However, there have been no reports on the association of immunocompetence and nutritional status with sarcopenia from the perspective of preoperative nutritional evaluation in patients with oral cancer. In this study, we investigated the correlation between the prognosis of CT-assessed sarcopenia (CT-SP) in the C3 region and that of various immuno-nutritional indicators in patients who underwent radical therapy with surgery for oral squamous cell carcinoma (OSCC) at a single institution.

Subjects and methods

Study design

In this retrospective study, patients with OSCC who underwent radical therapy with surgery for stage I–IV at Shizuoka city Shizuoka Hospital between January 2014 and January 2021 were included. Patients whose blood samples were not collected due to outpatient surgery or who did not undergo contrast-enhanced CT or magnetic resonance imaging (MRI) were excluded. Skeletal muscle in the third cervical vertebra (C3) was measured using preoperative cervical CT, and the skeletal muscle index (SMI) was calculated. Nutritional status were investigated using blood tests. The correlation between each parameter and prognosis was analyzed. The primary predictor variables were SMI, Eastern Cooperative Oncology Group performance status (PS), body mass index (BMI), and nutritional status. The primary outcome variable was the 5-year overall survival rate (OS) and the secondary outcome variable was 5-year disease-specific survival rate (DSS).

Treatment

Patients with advanced-stage oral cancer received preoperative chemoradiotherapy (2 Gy per day and low-dose pepleomycin [2.5 mg/day] subcutaneously as a 100-h continuous injection daily for approximately 3 weeks) [11]. Other patients received a combination of TS1 or cetuximab and radiation therapy or a combination of radiation therapy and super selective intra-arterial infusion chemotherapy. Postoperative treatment included concurrent chemoradiation therapy (cisplatin or carboplatin) or radiotherapy (RT) alone.

Evaluation of CT-SP and immunocompetence and nutritional status

For skeletal muscle evaluation, preoperative cervical contrast-enhanced CT was used to select the slice in which the transverse and spinous processes of the third cervical spine were most widely secured. All images were analyzed by a single researcher using the open-source software ImageJ (Fig. 1). The sternocleidomastoid and paravertebral muscles were measured as described by Lee et al. [12]. (Fig. 1) The internal jugular and common carotid arteries were excluded. When a simple CT scan was obtained, the measurement was performed using the blood vessel information of the same MRI slice. The total cross-sectional area (CSA) (cm^2) of the sternocleidomastoid and paravertebral muscles was calculated, and the CSA of L3 was estimated using the formula proposed by Lee et al. [12] [Eq. (1)]. The skeletal muscle index (SMI) was calculated by adjusting the patient's height [Eq. (2)].

$$\begin{aligned}\text{CSA at L3}(cm^2) = {} & 27.304 + 1.363 \times \text{CSA at C3 } (cm^2) \\ & - 0.671 \times \text{age} + 0.640 \times \text{weight (kg)} \\ & + 26.442 \times \text{sex (sex} = 1 \text{ for female, } 2 \text{ for male)}\end{aligned} \quad (1)$$

$$\text{SMI } (cm^2/m^2) = \text{CSA at L3 } (cm^2)/\text{Height}^2(m^2) \quad (2)$$

The blood samples of the patients were examined at the first visit or near the time of the first visit. The following parameters were evaluated: platelet count, C-reactive protein (CRP) level, albumin (Alb) level, and white blood cell count, including neutrophil, lymphocyte, and monocyte counts. The mGPS is a modified version of the GPS reported by McMillan et al. [13]: CRP ≤ 0.5 mg/dL and Alb ≥ 3.5 g/dL indicate an mGPS score of 0, CRP > 0.5 mg/dL or Alb < 3.5 g/dL indicates an mGPS score of 1, and CRP > 0.5 mg/dL and Alb < 3.5 g/dL indicates an mGPS score of 2. The prognostic nutritional index (PNI), neutrophil–lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and C-reactive protein-albumin ratio (CAR) were examined as the indicators of immunocompetence and nutritional status [4, 6–9]. The PNI was calculated as (10 × the serum Alb level) + (0.05 × the lymphocyte count). The NLR was calculated by dividing the neutrophil count by the lymphocyte count. The PLR was calculated by dividing the platelet count by the lymphocyte count. The LMR was calculated by dividing the lymphocyte count by the monocyte count. The CAR was calculated by dividing serum CRP by serum Alb level.

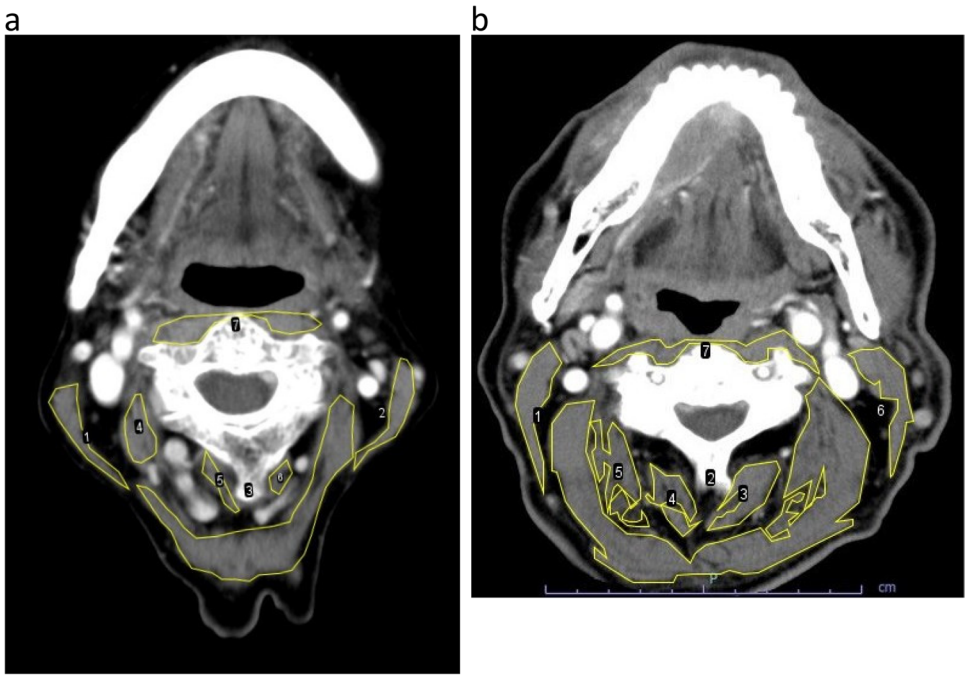

Fig. 1 Measurements of computed tomography (CT)-assessed sarcopenia. The total cross-sectional areas (CSA) of the sternocleidomastoid and paravertebral muscles were calculated by preoperative cervical CT using the open-source software ImageJ. CT slices of the CT-SP-positive patient (**a**) and CT-SP-negative patient (**b**). The area surrounded by the yellow line is the muscle to be measured. Numbers indicate muscle blocks

The optimal cutoff values for immunocompetence and nutritional status were determined using receiver operating characteristic (ROC) curve analysis based on Youden's index. The cut-off values are presented in Table S1. Based on these cut-off values, the patients were classified into two groups: Those with a BMI (mass (kg)/height^2 (m)) < 18.5 were classified as underweight, and those with a BMI ≥ 25 were classified as overweight [14].

Prognostic factors

PS, CT-SP, BMI (underweight vs. normal weight and overweight vs. normal weight), immunocompetence, and nutritional status (mGPS, NLR, PNI, PLR, LMR, and CAR) were examined as the prognostic factors for the constitution and condition of the patients (Table 3). Age, sex, clinical stage, pathological lymph node metastasis (pN), neoadjuvant therapy, Yamamoto–Kohama criteria (YK), World Health Organization (WHO) differentiation classification, vascular invasion, lymphatic invasion, and perineural invasion were examined as the prognostic factors for cancer. The YK classification was used to determine the grade of invasion [15]. Grade 1 denotes a tumor with a well-defined border, Grade 2 denotes a tumor with a less-marked border, Grade 3 denotes a group of cells and no distinct border, and Grade 4 denotes diffuse invasion. Grade 4 was sub-classified into Grades 4C and 4D. Grade 4C refers to diffuse invasion with cord-like pattern. Tumors of this type invade deeply in the form of a cord-shaped microtumor nest. Grade 4D refers to diffuse invasion. Tumor cells of this type invade the deeper portion diffusely as a single or a few cells [15]. As per the WHO differentiation classification, there are three degrees of differentiation: well-differentiated (G1), moderately differentiated (G2), and poorly differentiated (G3).

Statistical analysis

The primary outcome variable was the 5-year overall survival rate (OS) and the secondary outcome variable was 5-year disease-specific survival rate (DSS). The statistical software EZR 2.7–1' (Easy R) was used for the statistical analysis [16]. Survival rates were calculated using the Kaplan–Meier method. Log-rank and chi-square tests were used to compare survival rates between groups, and multivariate analysis was performed using the Cox proportional hazards model. Multivariate analysis was performed using prognostic factors that met a cut-off p value of < 0.05 on univariate analysis. Statistical significance was set at $p < 0.05$. The association between CT-SP and nutritional index was analyzed using logistic regression analysis.

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee Shizuoka City Shizuoka Hospital (Registry No.20–40) and was performed in accordance with the latest version of the Declaration of Helsinki.

Results

This retrospective study included 163 patients with oral squamous cell carcinoma (OSCC) who underwent radical primary surgery for stage I–IV between January 2014

and January 2021. Patients were excluded if 1) their blood samples were not collected due to outpatient surgery (10 patients) or if 2) they did not undergo contrast-enhanced CT or MRI (seven patients). Therefore, a total of 146 patients (67 males and 79 females) were subjected to CT assessment and prognostic analyses. The age of the patients ranged from 20 to 94 years (average: 69.9 years). Patient characteristics are shown in Table 1. The CT-SP measurements based on the CSAs of the slice in the C3 area of the positive (Fig. 1a) and negative cases (Fig. 1b) are shown in Fig. 1. The CT-SP-positive patient was an 84-year-old woman with stage I lower gingival carcinoma (SMI: 18.63 cm^2/m^2). The CT-SP-negative patient was an 81-year-old man with stage III oral floor carcinoma (SMI: 64.8 cm^2/m^2). The treatment and outcomes are shown in Table 2. The 5-year OS and DSS were 74.9% and 82.2%, respectively. The prognostic factors are listed in Table S2. Univariate analysis showed that pN, YK, vascular invasion, lymphatic invasion, and perineural invasion were significantly correlated with prognosis (Table S2). The prognostic factors for the constitution and condition of the patients are listed in Table 3. Univariate analysis of PS, CT-SP, nutritional index, BMI (underweight vs. normal weight), and BMI (overweight vs. normal weight) revealed that CT-SP, PNI, and LMR are correlated with DSS and OS (Table 3). Figure 2 shows the Kaplan–Meier curves for OS and DSS with and without CT-SP. DSS as well as OS of patients without CT-SP was significantly better than those of patients with CT-SP. In the multivariate analysis of the prognosis factors for nutritional status and PS, only CT-SP was identified as an independent prognostic factor for DSS (Table 4). Logistic analysis was performed to analyze the relationship among CT-SP, PNI, and LMR, as they were found to be correlated with both OS and DSS in the univariate analysis. It was found that the PNI was independently and significantly correlated with CT-SP (Table 5).

Table 1 Clinical characteristics

	Number ($n = 146$)	%
Sex		
Male	67	45.9
Female	79	54.1
Site		
Tongue	59	40.4
Lower gingiva	45	30.8
Upper gingiva	17	11.6
Oral floor	12	8.2
Buccal mucosa	9	6.2
Palate	4	2.8
Tumor (T) stage		
T1	42	28.8
T2	48	32.9
T3	24	16.4
T4a	29	19.9
T4b	3	2.0
N stage		
N0	108	74.0
N1	17	11.6
N2	21	14.4
N3	0	0.0
Stage		
I	42	28.8
II	42	28.8
III	21	19.2
IVA	40	25.6
IVB	1	0.6

Table 2 Treatment and outcome

	Number ($n = 146$)	%
Primary treatment		
Surgery (S)	116	79.5
Chemotherapy (C) and S	1	0.6
Radiation, C and S	29	19.9
Neck dissection		
None	79	54.1
Ipsilateral	55	37.7
Bilateral	12	8.2
Pathologic nodal status		
Positive	50	34.2
Negative	96	65.8
Adjuvant therapy		
No	20	13.7
Yes	126	86.3

Discussion

Sarcopenia is a syndrome characterized by the progressive and generalized loss of skeletal muscle mass and strength, with a risk of adverse outcomes, such as physical disability, poor quality of life, and death [17]. To date, there is no consensus on the assessment of sarcopenia in routine clinical practice [18, 19]. The concept of using a single sentinel muscle for the diagnosis of sarcopenia was proposed by a group of experts; however, the assessment of a single muscle that best reflects systematic sarcopenia is controversial [20–22]. At the L3 vertebral body level, radiologically measured CSA is linearly related to the total body muscle mass, making it an excellent surrogate for detecting sarcopenia [23]. However, in the field of oral surgery, there are few opportunities to perform abdominal CT, and evaluation of sarcopenia in the L3 region is not considered useful. In recent years, there have been some reports on the diagnosis of sarcopenia by

Table 3 Univariable analyses of prognostic factors for constitutions and conditions of the patients

		Number ($n=146$)	5-y DSS, %	*p* value	5-y OS, %	*p* value
PS	0	130	82.4	0.544	75.2	0.409
	≧1	16	86.2		80.0	
CT-SP	No	76	93.2	< 0.01*	86.2	< 0.01*
	Yes	70	69.5		61.9	
BMI	≧18.5	126	80.5	0.323	73.3	0.347
Underweight	< 18.5	20	94.7		86.8	
BMI	< 25	124	79.5	0.068	72.9	0.247
Overweight	≧25	22	100		87.7	
mGPS	0	123	80.9	0.661	77.0	0.107
	1,2	23	90.9		65.0	
NLR	< 1.6	47	87.5	0.468	82.4	0.307
	≧1.6	99	78.9		70.7	
PNI	> 51.4	59	90.0	< 0.05*	86.4	< 0.01*
	≦51.4	87	76.5		66.4	
PLR	> 133	65	79.9	0.924	73.8	0.822
	≦133	81	83.0		74.8	
LMR	> 4.6	85	90.0	< 0.05*	84.2	< 0.05*
	≦4.6	61	70.4		61.4	
CAR	< 0.06	109	82.8	0.758	78.5	0.118
	≧0.06	37	80.1		63.8	

DSS disease-specific survival, *OS* overall survival, *PS* performance status, *CT-SP* CT-defined sarcopenia, *BMI* body mass index, *mGPS* modified Glasgow Prognostic Score, *NLR* neutrophil–lymphocyte ratio, *PNI* prognostic nutritional index, *PLR* platelet-lymphocyte ratio, *LMR* lymphocyte-monocyte ratio, *CAR* C-reactive protein-albumin ratio

measuring skeletal muscle mass in the C3 region using CT [23]. In addition, as it has been reported that L3 and C3 are correlated, and sarcopenia evaluation based on the C3 region is possible [24]. The C3 method is simple and useful for the diagnosis of sarcopenia because it can be determined by head and neck CT imaging of the C3 region.

Sarcopenia is correlated with the prognosis of cancer patients [17], and the postoperative survival rates with sarcopenia of those various carcinomas, such as gastric cancer [25], colorectal cancer, [26] lung cancer, [27] and head and neck cancer, are poor [23]. However, there are few reports on the association between sarcopenia and oral cancer. In our study, CT-SP was correlated with the prognosis of oral cancer. CT-SP served as a strong predictor of DSS in patients with oral cancer in the multivariate analysis. Yoshimura et al. reported that a low quantity of cervical muscle was statistically associated with short survival in the multivariate analysis [18]. Lee et al. reported that CT-SP was independently associated with poor outcomes in the multivariate analysis of OS.

mGPS, CAR, PNI, LMR, PLR, and NLR have been reported to function as nutritional indicators, inflammation-based prognostic scores, and indicators of systemic inflammatory response (SIR), and they can affect the outcome of cancer treatment [4, 6–9]. The mGPS and CAR both include C-reactive protein and serum albumin and are useful prognostic tools for malignant tumors [6, 7]. The mGPS correlates with clinical outcomes in patients with head and neck cancers [28]. High CAR predicts early recurrence and poor prognosis in patients with gastric cancer treated with curative intent [6]. NLR and PLR are correlated with head and neck cancer prognosis as systemic inflammation-based blood leukocyte indices [29]. Furthermore, preoperative NLR, PLR, and LMR are associated with poor prognosis in patients with oral cancer [5, 30]. The PNI derived from serum albumin level and absolute lymphocyte count was first established for preoperative nutritional status and postoperative complications in patients with gastrointestinal malignancies [31]. Fang et al. demonstrated that the PNI predicted the prognosis of patients with oral cancer [5]. In the present study, PNI and LMR, but not mGPS, NLR, or CAR, were associated with poor diagnosis of DDS and OS in the univariate analysis. In many of the studies, blood was collected 1 week before surgery, and in our study, blood was collected at a time close to the first visit, which could be the reason for the variation in the inflammation index and albumin level. These data suggest that skeletal muscle deteriorates in the presence of malnutrition and inflammatory reactions, and the SIR is associated with weight and muscle loss and poor outcomes in patients with cancer [32]. The combined effects

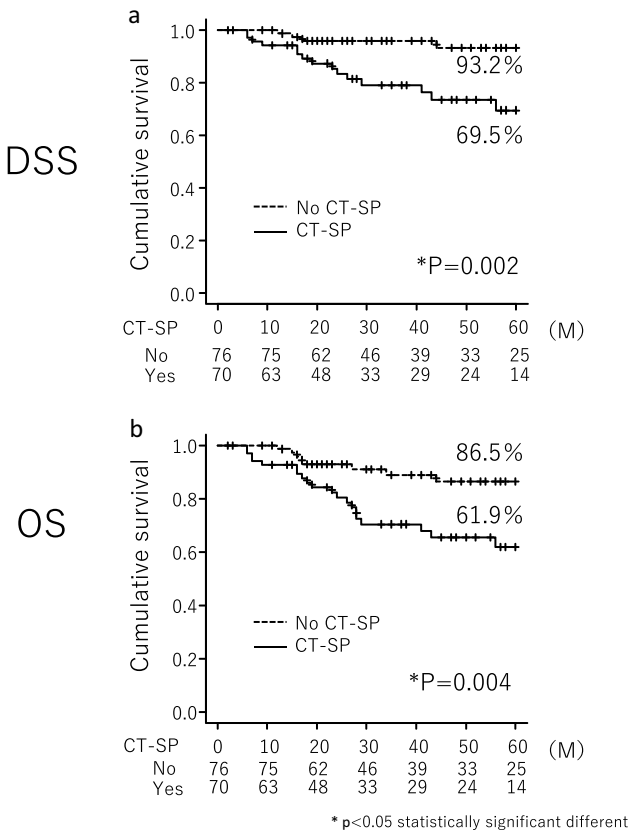

Fig. 2 Kaplan–Meier curve. Five-year survival rate (**a** the 5-year disease-specific survival rate (DSS); **b** the 5-year overall survival rate (OS)) of patients without CT-SP was significantly better than that of patients with CT-SP. CT-SP: computed tomography -assessed sarcopenia

of sarcopenia and SIR on the survival outcomes of patients with colorectal and esophageal cancers have been previously evaluated [32–35]. However, to the best of our knowledge, only mGPS has been reported to correlate with sarcopenia in oral cancer [3]. In the present study, we found that the PNI and CT-SP were correlated with prognosis and with each other. Therefore, it is important not only to consider PNI as a prognostic factor but also to consider it as a preoperative indicator of malnutrition and pro-inflammatory state and to correctly manage anti-inflammatory treatments and nutrition before surgery to improve the CT-SP and prognosis.

Perioperative rehabilitation is expected to improve physical fitness, promote early mobilization, and reduce postoperative pulmonary complications in patients with esophageal cancer [36]. Preoperative physical therapy improves pulmonary function and endurance in patients undergoing upper abdominal surgery [37]. Perioperative rehabilitation and nutrition management for sarcopenia patients with oral cancer is expected to improve not only malnutrition and loss of skeletal muscle mass, but also prognosis.

Our study has some limitations. First, it was a retrospective cohort study dating back up to 8 years; some treatments include preoperative chemoradiotherapy, which is not the current standard therapy. However, this study aimed to identify the prognostic value of the CT-SP. Therefore, the differences in treatment may not have significantly affected our results. No correlation was observed between the C3 and L3 levels. However, CT-SP based on C3 indicated the prognosis, and oral cancer patients may not undergo L3 imaging; therefore, the lack of a correlation between them is not considered a major issue. However, true sarcopenia could not be consistently evaluated. Since the cut-off value for sarcopenia has not been determined, it is not viable for clinical use in the future. Sarcopenia detection using C3 is excellent for preoperative evaluation; however, postoperative follow-up evaluation is difficult because the sternocleidomastoid muscle may be resected in patients who have undergone neck dissection as a first-line treatment. Therefore, evaluation of sarcopenia outside the scope of neck dissection is important for future investigations.

In this study, we found that CT-SP at the C3 correlated with oral cancer prognosis and the PNI. To contribute to

Table 4 Multivariable analyses of prognostic factors

	DSS			OS		
	HR	95% Cl	*p* value	HR	95%Cl	*p* value
PNI						
>51.4	1.615	0.4638–5.621	0.45	1.938	0.7005–5.36	0.20
≦51.4						
CT-SP						
Yes	3.517	1.088–11.36	0.04*	2.208	0.916–5.324	0.07
No						
LMR						
>4.6	1.796	0.653–4.936	0.26	1.645	0.726–3.730	0.23
≦4.6						

DSS disease-specific survival, *OS* overall survival, *HR* Hazard ratio, *PNI* prognostic nutritional index, *CT-SP* CT-defined sarcopenia, *LMR* lymphocyte-monocyte ratio

Table 5 Analysis of the correlation of CT-assessed sarcopenia with immunocompetence and nutritional status (PNI and LMR) by logistic regression analysis

	Odds Ratio	95% CI	*p* value
PNI			
>51.4	3.27	1.56–6.85	<0.005*
≦51.4			
LMR			
>4.6	1.73	0.841–3.57	0.136
≦4.6			

PNI prognostic nutritional index, *LMR* lymphocyte-monocyte ratio. * $p < 0.05$ statistically significant different

the improvement of treatment outcomes in patients with oral cancer, we intend to conduct further research in this area in the future.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10006-023-01191-1.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and data analysis were performed by Yoshio Ohyama, Yoshinori Inaba, Tomoki Kanemaru, and Mako Kubota. The first draft of the manuscript was written by Yoshio Ohyama and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval This study was approved by the Research Ethics Committee of Shizuoka City Shizuoka Hospital (Registry No.20–40) and was performed in accordance with the latest version of the Declaration of Helsinki.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent to publish Informed consent was obtained from all individual participants included in the study.

Competing interests The authors have no relevant financial or non-financial interests to disclose.

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