Cancer Management and Research

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ORIGINAL RESEARCH

Clinical Impact of Cachexia in Head and Neck Cancer Patients Who Received Chemoradiotherapy

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Purpose: There have been few reports on the evaluation of cancer cachexia based on skeletal muscle mass index (SMI) in patients with head and neck cancer.

Patients and Methods: One hundred and ninety-two head and neck cancer patients were enrolled. In definitive and adjuvant chemoradiotherapy settings, clinical outcomes were compared between cachexia and non-cachexia patients.

Results: Forty patients were diagnosed with cachexia (20.8%). In the definitive setting, overall survival (OS) was significantly shorter in the cachexia group (3-year OS: 50.0% vs 88.5%; $p < 0.01$), and multivariate analysis identified UICC stage IV, baseline albumin of <4 and cachexia as poor prognostic factors. However, cachexia was not significant in the adjuvant setting.

Conclusion: Cancer cachexia was negatively associated with prognosis in patients with HNC who received definitive chemoradiotherapy. Nutritional intervention during chemoradiotherapy may improve survival in these patients.

Keywords: head and neck cancer, squamous cell carcinoma of head and neck, sarcopenia, cachexia, muscle, skeletal, chemoradiotherapy, prognosis

Introduction

Head and neck cancer (HNC) was the seventh most common cancer worldwide in 2018, accounting for 3% of all cancer types.[1] Although risk factors for HNC are not completely understood, several factors such as smoking, alcohol, diet, and chronic viral infection, including human papillomavirus-associated oropharyngeal carcinoma, have been reported to increase its risk.[2–4] Conversely, several factors, such as improvement in lifestyle, reduce the risk of cancer.

Sarcopenia, characterized as an age-related decline in muscle mass and strength, has been recognized to be an important prognostic factor in various types of cancers.[5–7] It has also been associated with severe toxicity in cancer patients with chemotherapy.[8] Many studies about sarcopenia have been performed using computed tomography (CT) imaging. Sarcopenia based on CT imaging has been previously reported as an indicator of poor prognosis of HNC.[9–11]

Patients with cancer also have a risk of decline of muscle mass via cachexia. Cachexia is a multifactorial disease in which weight loss including skeletal muscle declines due to systemic inflammation from cancer.[12] It is caused by the activation of cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interferon-γ (IF- γ),[13] leading to a decline in protein synthesis and increase in proteolysis and lipolysis, frequently occurring in solid tumors, particularly gastric,

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Received: 19 July 2021
Accepted: 26 October 2021
Published: 8 November 2021

pancreatic, lung cancer, and HNC.[14] There have been many reports of associations between cachexia and prognosis on cancer patients; however, few studies strictly evaluated using CT imaging, opposed to sarcopenia. Actually, the studies about cachexia in HNC patients have been performed only based on nutritional status.[15]

Cachexia is often present in patients with head and neck squamous cell carcinoma (HNSCC)[9] and progresses during concurrent chemoradiotherapy (CCRT), which is administered for a few months. There are two settings of CCRT, definitive and adjuvant. Definitive CCRT is performed with locally advanced HNSCC to achieve cure by CCRT alone; Patients sometimes select definitive CCRT for laryngeal preservation and avoiding change in appearance or other quality of life degradation even if their lesions are resectable. Adjuvant CCRT is performed with post-operative high-risk HNSCC to reduce recurrence risk. Although it is important to assess their condition, little is known about clinical impact of cachexia in HNSCC patients who received CCRT. In this study, we evaluated the association between cachexia (including CT imaging evaluation) and prognosis in patients with HNSCC who received CCRT.

Patients and Methods

Patients

We retrospectively analyzed prospectively collected data from consecutive patients with HNSCC who were initiated with concurrent chemoradiotherapy (CCRT) with cisplatin at the Cancer Institute Hospital of Japanese Foundation for Cancer Research (JFCR) between January 2015 and December 2018. Patients' data included the following characteristics: age, sex, height, weight, smoking status, Eastern Cooperative Oncology Group performance status (PS, ECOG PS), location of the primary tumor, histological diagnosis (including p16 protein expression), clinical stage (based on UICC TNM classification), baseline albumin, total dose of cisplatin, radiation details, and pretreatment CT findings. These factors were categorized for analysis as follows: age: <65 years or ≥65 years; sex: male or female; ECOG PS: 0 or ≥1; smoking: current/former or never; primary tumor site: nasopharynx, oropharynx, or other; clinical stage: 1–3 or 4; and baseline albumin: <4 or ≥4. Cachexia was defined when 1) weight loss of >5% in 6 months (in the absence of simple starvation), 2) body mass index (BMI) of <20 kg/m^2 and weight loss of >2%, or 3) sarcopenia and weight loss of >2%.[12,16] We analyzed CT images, including the CT component of whole-body PET-CT scans, at the level of the third lumbar vertebra (L3). Skeletal muscle mass area was calculated using the Volume Analyzer SYNAPSE VINCENT image analysis system (Fujifilm Medical, Tokyo, Japan).[17] Abdominal skeletal muscle includes the psoas major, paraspinals (erector spinae and quadratus lumborum), and muscles of the abdominal wall (transversus abdominus, external and internal obliques, and rectus abdominus). The skeletal muscle mass index (SMI) which normalizes skeletal muscle area adjusted by height was used as an indicator of sarcopenia.[8] The cross-sectional area of skeletal muscle at L3 was measured using the SYNAPSE VINCENT with Hounsfield unit thresholds of −30 to +150. After segmentation, minor manual measurements were performed as required. Sarcopenia was diagnosed with reference to Martin's cut-off value: SMI of <43 cm^2/m^2 for men with BMI <25 kg/m^2 or <53 cm^2/m^2 for men with BMI ≥25 kg/m^2 and <41 cm^2/m^2 for women.[18]

Cisplatin was administered at a dose of 80 mg/m^2 (from 2012 to August 2015) or 100 mg/m^2 (from August 2015 to 2018) every 3 weeks for a total of three cycles. Elderly patients and those with reduced organ function received a reduced cisplatin dose according to the discretion of their physician. When patients complicated with intolerable adverse events from cisplatin, skip, delay, or dose reduction of the second and/or third cisplatin cycle were permitted. Radiotherapy was performed as 3-dimensional conformal radiotherapy (3D-CRT) or intensity-modified radiotherapy (IMRT) with the conventional fraction, 2–2.12 Gy per fraction, once per day, five times per week. Prophylactic percutaneous endoscopic gastrostomy was performed unless particular reasons forbid it (such as refusal by the patient or past history of gastrectomy). Follow-up examinations using enhanced CT and measurements of blood biochemistry and serum tumor markers were performed approximately every 3 months after CCRT.

Statistical Analysis

Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method and Log rank test. Data were censored on January 31, 2021. Patients who were lost to follow-up were censored at the date of last contact or follow-up. PFS was calculated from the date of radiation initiation to the date of disease relapse, disease progression or death from any cause. OS was calculated from the date of radiation initiation to the date of death from any cause. Patients who were alive on January 31, 2021, were censored for OS analysis. We estimated survival

curves by definitive or adjuvant CCRT using the Kaplan–Meier method and Log rank test. We performed univariate and multivariate analyses to estimate factors potentially prognostic for PFS and OS by calculating hazard ratios (HRs) using the Cox proportional hazards model. The level of significance was set at p value of <0.05 for univariate and multivariate analysis, which was two-sided. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a modified interface for R software (www.r-project.org).[19]

Results

Patients' Characteristics

Three hundred and forty-four patients were included. Of all the patients, 152 were excluded because presence or absence of cachexia could not be evaluated based on criteria. Overall, 192-patient cohort comprised 40 (20.8%) with cachexia patients and 152 (79.2%) without cachexia patients with a median age of 61 years (range, 20–78 years). The median observation time was 38.6 months (range, 4.6–68.9 months) after the initiation of CCRT. Among these, 39 patients could not complete CCRT because of toxicity. The median radiation dose was 66 Gy and the median cisplatin dose was 280 mg, which differed between 2015 and 2016–2018 (240 mg and 300 mg, respectively) owing to alteration of the standard dose. At the time of censoring, 43 patients (22.4%) had died from the primary disease. The-192 patients were divided into definitive CCRT (n = 148) and adjuvant CCRT (n = 44) groups. For data analysis, the two groups were categorized into the following four: 1) definitive CCRT with cachexia, 2) definitive CCRT without cachexia, 3) adjuvant CCRT with cachexia, and 4) adjuvant CCRT without cachexia (Figure 1). The characteristics of the 192 patients classified into four groups are shown in Table 1. Sixty-six patients were oropharyngeal cancer patients. Of 66 patients, 42 patients (73.6%) in definitive CCRT and 2 patients (40%) in adjuvant CCRT were P16 positive. The median interval between CT imaging and initial chemotherapy was 28 days (range: 1–60). In the definitive CCRT setting, the groups with cachexia and without cachexia significantly differed in PS and baseline albumin. In the adjuvant CCRT setting, the two groups showed no difference.

Long-Term Outcomes

Figure 2 shows PFS and OS stratified by cachexia and CCRT setting. There were significant differences for definitive CCRT between cachexia and non-cachexia groups: PFS (15.4 months vs NA; HR, 4.01; 95% CI, 2.15–7.47; $p < 0.01$) and OS (42.8 months vs NA; HR, 5.81; 95% CI, 2.72–12.41; $p < 0.01$). Three-year survival rate and local recurrence rate were significantly different in the cachexia group (50.0% vs 88.5%; $p < 0.01$ and 26.9% vs 6.6%, $p < 0.01$). In the adjuvant CCRT setting, there were no significant differences between the two groups for PFS (NA vs 19.0 months; HR, 0.48; 95% CI, 0.18–1.31; $p = 0.15$) or OS (NA vs NA; HR, 0.64; 95% CI, 0.20–2.01; $p = 0.45$). Three-year survival rate and local

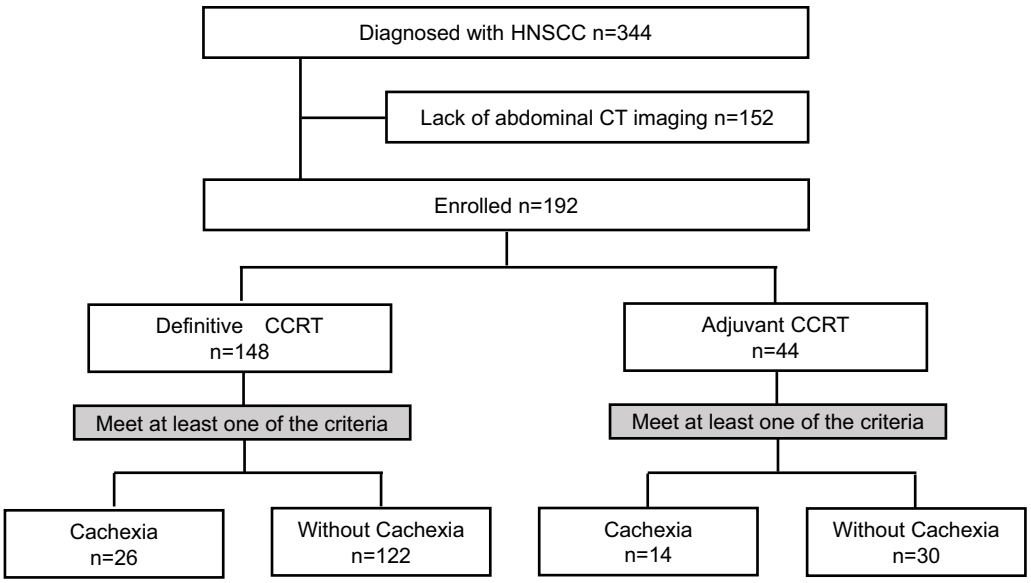

Figure 1 CONSORT diagram of this study.

Table 1 Patients' Characteristics

		Definitive CCRT					Adjuvant CCRT				
		Cachexia n=26		Without Cachexia n=122		P value	Cachexia n=14		Without Cachexia n=30		P value
		n	(%)	n	(%)		n	(%)	n	(%)	
Age	Median (range)	58.5 (37–73)		61.0 (36–78)		0.29	61.0 (43–72)		60.0 (20–76)		0.63
Sex	Male	21	(80.8)	98	(80.3)	1.00	11	(78.6)	29	(96.7)	0.08
	Female	5	(19.2)	24	(19.7)		3	(21.4)	1	(3.3)	
PS	0	18	(69.2)	112	(91.8)	<0.01	10	(71.4)	24	(80.0)	0.70
	≥1	8	(30.8)	10	(8.2)		4	(28.6)	6	(20.0)	
Smoking	Yes	21	(80.8)	98	(80.3)	1.00	10	(71.4)	24	(80.0)	0.70
	No	5	(19.2)	24	(19.7)		4	(28.6)	6	(20.0)	
Primary site	Naso/oropharynx	10	(38.5)	62	(50.8)	0.28	2	(14.3)	4	(13.3)	1.00
	Other	16	(61.5)	60	(49.2)		12	(85.7)	26	(86.7)	
P16	Positive	6	(23.1)	44	(36.1)	0.45	1	(7.1)	5	(16.7)	0.63
	Negative	14	(53.8)	61	(50.0)		9	(64.3)	15	(50.0)	
	Unknown	6	(23.1)	17	(13.0)		4	(28.6)	6	(20.0)	
Stage	I–III	12	(46.2)	89	(73.0)	0.01	4	(28.6)	10	(33.3)	1.00
	IV	14	(53.8)	33	(27.0)		10	(71.4)	20	(66.6)	
Sarcopenia	Yes	12	(46.2)	33	(27.0)	<0.01	2	(14.3)	6	(20.0)	0.56
	No	7	(26.9)	87	(71.3)		3	(21.4)	24	(80.0)	
	Unknown	7	(26.9)	2	(1.6)		9	(64.3)	0	(0.0)	
Baseline albumin	Median (range)	4.1(2.5–4.3)		4.2 (3.3–4.9)		<0.01	4.0 (3.5–4.6)		4.1 (2.1–4.5)		0.89
CCRT dose	Median	240		300		0.22	240		260		0.42
RT dose	Median (range)	66 (60–66)		66 (60–70)		0.52	66 (60–70)		66 (46–70)		0.16

Abbreviations: PS, performance status; CCRT, concurrent chemoradiotherapy; RT, radiation therapy.

recurrence rate were not significantly different between the two groups (71.4% vs 60.0%, p = 0.52 and 14.3% vs 30.0%, p = 0.45).

Risk Factor of Prognosis

In the definitive CCRT setting, multivariate Cox proportional hazard analysis indicated that the stage (HR, 2.74; 95% CI, 1.46–5.12; p < 0.01), baseline albumin (HR, 2.83; 95% CI, 1.53–5.23; p < 0.01), and cachexia (HR, 3.51; 95% CI, 1.65–6.01; p < 0.01) were independent risk factors for PFS. Independent risk factors for poor OS were stage (HR, 2.64; 95% CI, 1.15–6.07; p = 0.02), baseline albumin (HR, 3.91; 95% CI, 1.78–8.59; p < 0.01), and cachexia (HR, 4.31; 95% CI, 1.93–9.61; p < 0.01). Analysis by adjuvant CCRT setting revealed no independent predictive factors (Tables 2 and 3).

Adverse Events

The frequency of grade 3–4 adverse events is presented in Table 4. In definitive CCRT, all adverse events were strongly associated with cachexia. Among the grade 3–4 adverse events, the frequency of anemia, leukopenia and neutropenia had significant difference between the two groups (23.8% and 0.8%, p < 0.01, 53.8% and 32.7%, p < 0.01, 23.1% and 19.7%, p = 0.03, respectively). In the adjuvant CCRT setting, there were no significant differences in the frequency of severe adverse events.

Discussion

We investigated the association between cancer cachexia and prognosis in patients with HNSCC who received chemoradiotherapy. The results demonstrated that cachexia was an independent predictor of poor prognosis, particularly in the

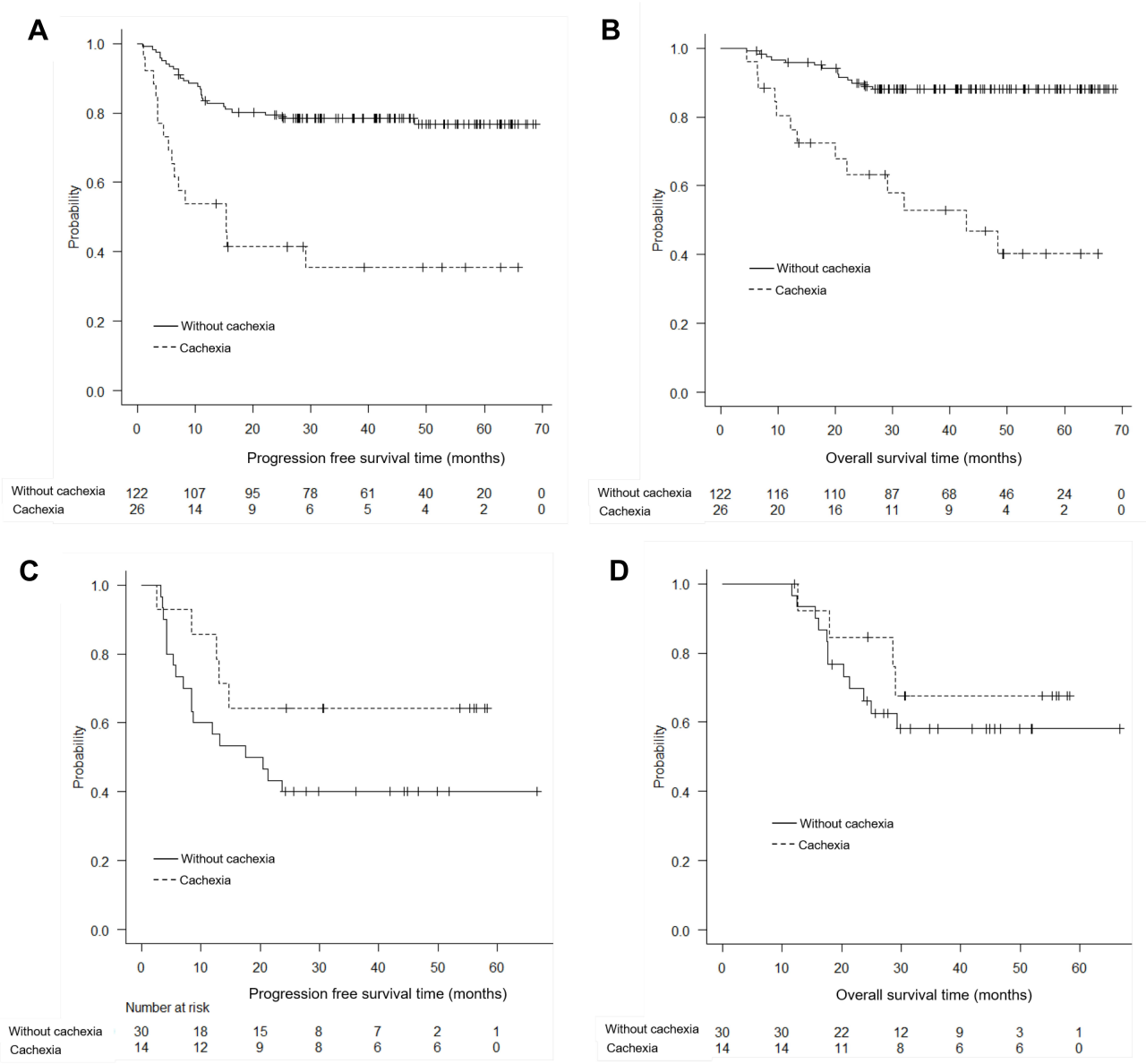

Figure 2 Kaplan–Meier curves for progression-free survival and overall survival according to treatment setting. Definitive CCRT-progression-free survival (PFS) (**A**), definitive CCRT-overall survival (OS) (**B**), adjuvant CCRT-progression-PFS (**C**) and adjuvant CCRT-OS (**D**) comparing patients with cachexia vs those without cachexia.

definitive setting. Grade 3–4 adverse events occurred more frequently in patients with cachexia.

To the best of our knowledge, this is the first study with a large sample size to evaluate the influence of cachexia in patients with HNSCC who received CCRT, including CT imaging at the level of L3. Our findings showed that cachexia is an important prognostic factor regardless of stage. A previous retrospective study could not show a significant difference between sarcopenia and non-sarcopenia in prognosis among HNSCC patients receiving CCRT.[9] In the present study, of the patients who received definitive CCRT, 139 patients evaluated both cachexia and sarcopenia were also analyzed. The hazard ratio of OS was 2.24 in sarcopenia (p=0.053) and 4.9 in cachexia (p<0.01) (Supplemental Figure 1). These results suggested that evaluation of cachexia could be a better predictor for prognosis than that of sarcopenia in HNSCC patients before CCRT. It is biologically plausible that background systemic inflammation or weight loss from causes other than skeletal muscle in cachexia would have led to this result.

Previous reports showed, in sarcopenia, owing to reduced age-related changes in body composition, polar drugs that are mainly water-soluble tend to have smaller volumes of distribution, resulting in higher serum levels in

Table 2 Univariate and Multivariate Analysis for PFS

	Definitive CCRT						Adjuvant CCRT		
	Univariate			Multivariate			Univariate		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age, ≥65	0.95	0.50–1.80	0.88	1.01	0.52–1.95	0.96	0.46	0.18–1.18	0.10
Sex, Male	1.36	0.60–3.07	0.44	1.54	0.67–3.51	0.30	1.08	0.25–4.60	0.91
PS, ≥1	1.94	0.89–4.19	0.09				1.66	0.68–4.07	0.26
Smoking, Current/former	0.91	0.44–1.91	0.83				0.66	0.26–1.68	0.38
Primarysite, Naso/oropharynx	0.55	0.29–1.03	0.06				0.96	0.28–3.24	0.95
Stage, IV	3.40	1.86–6.22	<0.01	2.74	1.46–5.12	<0.01	2.83	0.96–8.35	0.05
Baseline albumin, <4	2.97	1.62–5.44	<0.01	2.83	1.53–5.23	<0.01	0.70	0.30–1.60	0.40
Cachexia	4.01	2.15–7.47	<0.01	3.51	1.65–6.01	<0.01	0.48	0.18–1.31	0.15

Abbreviations: PS, performance status; CCRT, concurrent chemoradiotherapy.

Table 3 Univariate and Multivariate Analyses for OS

	Definitive CCRT						Adjuvant CCRT		
	Univariate			Multivariate			Univariate		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age, ≥65	0.85	0.37–1.94	0.69	0.89	0.38–2.11	0.80	0.26	0.07–0.95	0.04
Sex, Male	1.56	0.54–4.52	0.41	2.10	0.68–6.41	0.19	1.45	0.19–11.0	0.71
PS, ≥1	2.56	1.04–6.40	0.04	1.23	0.47–3.20	0.66	0.68	0.19–2.39	0.54
Smoking, Current/former	0.67	0.28–1.60	0.37				1.03	0.29–3.62	0.96
Primarysite, Naso/oropharynx	0.58	0.26–01.28	0.18				0.82	0.18–3.01	0.79
Stage, IV	3.99	1.83–8.73	<0.01	2.64	1.15–6.07	0.02	3.77	0.85–16.6	0.07
Baseline albumin, <4	4.01	1.88–8.56	<0.01	3.91	1.78–8.59	<0.01	0.62	0.22–1.72	0.36
Cachexia	5.81	2.72–12.41	<0.01	4.31	1.93–9.61	<0.01	0.64	0.20–2.01	0.45

Abbreviations: PS, performance status; CCRT, concurrent chemoradiotherapy.

Table 4 Frequency of Adverse Events of More Than Grade 3

	Definitive CCRT					Adjuvant CCRT				
	Cachexia n=26		Without Cachexia n=122		P value	Cachexia n=14		Without Cachexia n=30		P value
	n	(%)	n	(%)		n	(%)	n	(%)	
Anemia	6	(23.1)	1	(0.8)	<0.01	0	(0.0)	4	(13.3)	0.20
Leukopenia	14	(53.8)	40	(32.7)	<0.01	8	(57.1)	14	(46.7)	0.89
Neutropenia	6	(23.1)	24	(19.7)	0.03	6	(42.9)	13	(43.3)	0.95
Thrombocytopenia	2	(7.7)	1	(0.8)	0.09	0	(0.0)	1	(3.3)	0.17
Liver failure	0	(0.0)	1	(0.8)	0.38	1	(7.1)	0	(0.0)	0.17
Renal failure	0	(0.0)	0	(0.0)	1.00	0	(0.0)	0	(0.0)	1.00

Abbreviation: CCRT, concurrent chemoradiotherapy.

sarcopenia;[20] and poor prognosis in elderly patients with cachexia may result from dose reduction owing to anticancer drug therapy.[21] In the same study, the frequency of grade 3–4 adverse events was high in cachexia. In our study, frequency of grade 3–4 some hepatotoxicity was observed highly in cachexia, especially in definitive CCRT. The frequency of other adverse events was low, to begin with, so it was considered that there was no

difference. It has been reported that cisplatin may improve prognosis at a total dose of ≥200 mg.[22,23] Owing to dose reduction or poor PS, the median cisplatin total dose was 240 mg in cachexia without renal failure. The change in standard dose for cisplatin made in 2015 did not affect the distribution of cachexia. Cachexia was a significantly poor prognostic factor, regardless of cisplatin dose.

Recently, in Japan, anamorelin—a high-affinity, selective agonist of the ghrelin receptor—was approved for the treatment of cachexia in patients with non–small-cell lung carcinoma, gastric cancer, pancreatic cancer, and colorectal cancer but not in those with HNC.[24] Thus, nutritional intervention may be one of the most effective approaches for the early stage of cachexia in HNSCC. However, several reports that evaluated the effects of nutritional intervention have failed to show any improvement for survival in HNSCC as a setting of both definitive and adjuvant chemotherapy.[25] Although nutritional status appears to improve with dietary counseling, megestrol acetate, and prophylactic enteral tube feeding, there is no evidence that nutritional intervention can improve the prognosis of patients with HNC.[26–28] However, these studies include few patients treated with chemotherapy; the results are limited; thus, further study in this area is warranted. Our data, at least, support the potential of a nutrition-based approach.

In this study, unlike several previous reports, we separately analyzed definitive and adjuvant CCRT settings. As the standard treatment for HNSCC is surgery plus adjuvant CCRT (in cases at high risk for recurrence) or definitive CCRT, several studies included both groups in their analysis. Our study showed that cachexia was an independent prognostic factor in patients who received definitive CCRT. This may be because definitive CCRT has a wide range of radiation, including cervical lymph nodes, causing patients to experience loss of oral intake. Evaluation of cachexia in the adjuvant CCRT setting was difficult because its presence or absence was determined using preoperative abdominal CT imaging findings. Postoperative imaging would have been more accurate; however, it provides no clinical benefit.

Several limitations of this study should be acknowledged. First, this was a single-institution retrospective study with potential selection bias and a short follow-up time. Second, data on adverse events associated with nutrition such as oral mucositis, appetite loss, or nausea were not included in our database because only objectively assessable adverse events such as hematotoxicity were collected. Third, there was a lack of data on sarcopenia because abdominal CT imaging is not routinely performed. Sarcopenia is normally diagnosed based on the skeletal mass index at L3 using one of the two cut-off value methods (Prado or Martin);[8,18] we used Martin's. These cut-off values derived from Western studies are unsuitable for Asian patients with BMI of <25 kg/m^2. An Asian sarcopenia working group proposed using dual-energy X-ray absorptiometry or bioimpedance measurements for the diagnosis of sarcopenia.[29] However, these are not performed routinely in real-world clinical practice and do not fit in retrospective analyses. Nutritional indexes, such as Glasgow Prognostic Scale, are considered as candidate surrogate markers for cachexia syndrome.[15] However, in actuality, no reports are verifying the association between nutritional index and cachexia. Therefore, we evaluated cachexia stick to the definition using CT imaging at the level of L3 for sarcopenia diagnosis in this study. In actuality, our data of criteria used for diagnosis cachexia in individual patients showed there was only one patient diagnosed cachexia by criteria of "sarcopenia and weight loss of >2%" (Supplemental Table 1). That could support the validity of our study although there were some missing data. And we are planning further research on whether the nutritional index can be an indicator of cachexia. This may make it possible to evaluate cachexia in any country where CT image analyses were not accessible in the public health system.

Conclusion

We have retrospectively evaluated the association between cancer cachexia and prognosis in patients with HNSCC who received CCRT. Cachexia was an independent poor prognostic factor in patients with HNSCC who received definitive CCRT. Ongoing nutritional intervention before CCRT can help improve survival. Further study is warranted.

Ethics Approval and Consent to Participate

The requirement for informed consent was waived because data were reported anonymously. The study was approved by the Institutional Review Board of The Cancer Institute Hospital of JFCR (2021-1037). All procedures were performed in accordance with the ethical standards of the responsible committees on human experimentation

(institutional and national) and with the Helsinki Declaration of 1964 and subsequent versions.

Acknowledgments

We thank to medical staff of the Department of Head and Neck Surgery, and Radiation Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research for their support during this study. We thank Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosure

NH reports personal fees from TAIHO Pharmaceutical Co., Ltd. YS reports personal fees from ONO Pharmaceutical Co., Ltd., Bristol-Myers Squibb Company, MSD K.K., and TAIHO Pharmaceutical Co., Ltd. NF reports personal fees from Eisai. JT reports personal fees from Eisai. ST reports grants and personal fees from ONO Pharmaceutical Co., Ltd., Bristol-Myers Squibb, MSD, AstraZeneca, Chugai, and BAYER. The authors report no other conflicts of interest in this work.

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