The published version is available via https://doi.org/10.1016/j.nut.2022.111798.

Association of phase angle with muscle function and prognosis in patients with head and neck cancer undergoing chemoradiotherapy

Running title: Association of phase angle with muscle function and prognosis

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Word count: 6068

Number of figure: 1

Number of tables: 4

Acknowledgements

The authors acknowledge the medical staff of the Department of Otolaryngology and the dietitians at the Department of Nutrition in Tokushima University Hospital for their cooperation.

Conflict of Interest Statement and Funding Sources

The authors declare no conflict of interest.

Funding

This work was partially supported by JSPS KAKENHI (Grant Numbers 26750042 and 20K11530).

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Abstract

Objective: We aimed to investigate the correlation of phase angle (PhA) with other parameters (e.g., muscle mass/quality/strength and physical function), assess the prognostic relevance of pre-chemoradiotherapy (CRT) PhA, and suggest a reference value of PhA in Asian patients with head and neck cancer (HNC).

Research Methods & Procedures: Ninety-six patients with HNC who underwent CRT were divided into two groups, maintained-PhA group and low-PhA group, according to the PhA 25th percentile values by sex. Pretreatment PhA was measured using direct segmental multi-frequency bioelectrical impedance analysis, and muscle quality was assessed using echo intensity in ultrasound images. Correlation of PhA with other parameters was investigated, and between-group differences with respect to adverse events, treatment interruption, and 3-year survival were assessed.

Results: PhA showed a positive correlation with isometric knee extension force ($R = 0.710$), handgrip strength ($R = 0.649$), skeletal muscle mass index ($R = 0.620$), and maximum gait speed ($R = 0.543$) ($P < 0.001$). PhA showed a negative correlation with echo intensity ($R = -0.439$) and five times sit-to-stand test ($R = -0.505$) ($P < 0.01$). The low-PhA group had a higher incidence of severe anemia (52% in low-PhA vs. 17% in maintained-PhA), aspiration (17% vs. 1%), radiotherapy interruption (17% vs. 3%), and poor 3-year survival (47% vs. 81%) than the maintained-PhA group ($P < 0.05$).

Conclusion: PhA was correlated with muscle mass/quality/strength, and physical function. Low PhA was associated with severe adverse events, treatment interruption, and shorter survival. These findings suggested that 4.6° for men and 4.0° for women may be useful as prognostic reference values in Asian patients with HNC.

Keywords: Phase angle, Muscle strength, Muscle quality, Physical function, Prognosis, Head and neck cancer

Abbreviations

AC, arm circumference; AMA, mid-upper arm muscle area; ASM, appendicular skeletal muscle mass; BFM, body fat mass; BMI, body mass index; BW, body weight; CI, confidence intervals; CRT, chemoradiotherapy; DSM-BIA, direct segmental multi-frequency bioelectrical impedance analysis; EI, echo intensity; FT, fat thickness; HGS, handgrip strength; HNC, head and neck cancer; HR, hazard ratio; IKEF, isometric knee extension force; MT, muscle thickness; PhA, phase angle; R, resistance; RF, rectus femoris; ROC, receiver operating characteristic; SMI, skeletal muscle mass index; SMM, skeletal muscle mass; SPPB, short physical performance battery; 5-STS, five times sit-to-stand; TSF, triceps skinfold thickness; VI, vastus intermedius; Xc, reactance.

Introduction

An estimated 25%–50% of patients with head and neck cancer (HNC) are affected by malnutrition at the time of initiation of treatment [1]. Some studies have demonstrated that patients with HNC who are malnourished are at a higher risk of treatment-related severe adverse events, treatment interruption, and shorter survival [2,3]. Therefore, detection of malnutrition prior to initiation of treatment in these patients is a key imperative.

Direct segmental multi-frequency bioelectrical impedance analysis (DSM-BIA) technology utilizes different electrical frequencies (1 to 1,000 kHz) to estimate extracellular water, intracellular water, and total body water and is widely used for the assessment of body composition. Phase angle (PhA) obtained by BIA provides information on hydration status and body cell mass and cell integrity without algorithm-inherent errors or requiring assumptions such as constant tissue hydration [4]. In our previous study of patients with gastrointestinal and hepatobiliary-pancreatic cancer, PhA showed a positive correlation with height, body weight (BW), body mass index (BMI), skeletal muscle mass (SMM), and handgrip strength (HGS), and negative correlation with age and C-reactive protein level [5]. In addition, recent reports showed a correlation of PhA with echo intensity (EI) obtained by ultrasound images, which reflects muscle quality in healthy population [6,7], and also correlated with physical function [8–12]. However, to the best of our knowledge, no studies have assessed the correlation of PhA with muscle quality in patients with cancer and only a few reports have described correlation of PhA with physical function indices.

In our previous study, low PhA was also associated with increased postoperative severe complications, extended length of stay in postoperative high-care units or intensive care units, and poor 5-year survival rate [5]. In other studies, PhA in healthy people differed by race (Asians had lower PhA than other races) and sex (men had higher PhA than women) [13], and was associated with cancer stage in patients with HNC [14]. In patients with various cancers, low PhA has been shown to be associated with adverse outcomes such as malnutrition, decreased quality of life, increased complications, prolonged hospitalization, and shorter survival [15–30]. In patients with HNC, low PhA was associated with prolonged hospitalization and shorter survival time [23–27]. However, there are no reports about association of PhA with adverse events or treatment interruption during chemoradiotherapy (CRT). In addition, the reference values of PhA to predict poor survival in patients with HNC have been reported in Europeans [24–27], but not in Asians.

The primary aim of this study was to examine the correlation of PhA with other parameters, especially EI or physical function indices. The secondary aim was to investigate the association of pre-CRT PhA with adverse events, treatment interruption, and 3-year survival rate, and to suggest the reference value of PhA in Asian patients with HNC.

Patients and methods

Patients and study design

In this prospective observational study, patients with HNC who were hospitalized for receiving radical CRT as first-line treatment without surgery at the Department of Otolaryngology in Tokushima University Hospital between January 2015 and August 2021 were eligible for inclusion. Patients with pacemaker or amputated limbs were excluded because DSM-BIA measurement cannot be performed in these patients. Patients were asked to participate in this prospective study, and 100 patients who were willing to participate underwent pretreatment assessment. Four patients in whom the cancer stage was not known were excluded from the analysis. Finally, data of 96 patients were included in the analysis. Regimens of chemotherapy were considered individually and total planned dose of radiotherapy was 70 Gy for all patients. This study was conducted in accordance with the principles enshrined in the Declaration of Helsinki, and the study protocol was approved by the ethical committee of the Tokushima University Hospital (No. 2161–2). Written informed consent for participation was obtained from all patients prior to their enrolment.

Data collection

Data pertaining to age, sex, height, cancer site, cancer stage, and treatment information were collected from the electronic medical records.

Direct segmental multi-frequency bioelectrical impedance analysis

BW was measured with a scale (TANITA, Tokyo, Japan), with subjects wearing light clothing and not wearing shoes, to the nearest 0.1 kg. The body composition was assessed via DSM-BIA using InBodyS10® (InBody, Tokyo, Japan). Measurement was performed after admission until the start of the treatment. Patients were required to fast for at least 4 h prior to measurement and the measurement was performed in the supine position. InBodyS10® measures impedance with six frequencies (1, 5, 50, 250, 500, and 1,000 kHz) and reactance (Xc) with three frequencies (5, 50, and 250 kHz) at each of the five segments (right arm, left arm, trunk, right leg, and left leg) using an eight-point tactile electrode. Body composition parameters, such as SMM, are calculated using formulas in the inner software based on the height and 30 impedances measured using six frequencies. This tool is not based on the statistical data of any specific population, and its clinical formulas are not publicly available. InBodyS10® automatically displays SMM, appendicular skeletal muscle mass (ASM), and body fat mass (BFM). BMI was calculated as BW/height^2 (kg/m^2). Skeletal muscle mass index (SMI) was calculated as ASM/height^2 (kg/m^2). Resistance (R) was calculated mathematically from the impedance and Xc values using trigonometric functions. R and Xc at 50 kHz were standardized by the heights of patients (i.e., R/H and Xc/H) and expressed in ohms per meter. PhA values at 50 kHz were calculated as follows: PhA (degrees) = arctan (Xc/R) × (180/π).

Patients were divided into two groups according to the PhA 25th percentile values by sex. The maintained-PhA group was PhA >25th percentile (Q2–Q4) and the low-PhA group was PhA ≤25th percentile (Q1).

Anthropometry

Well-trained dietitians measured arm circumference (AC) and triceps skinfold thickness (TSF) at the midpoint of the triceps of the nondominant arm using adipometer calipers (Abbot Laboratories, Tokyo, Japan). Mid-upper arm muscle area (AMA) was calculated using the following equation: AMA (cm^2) = [AC (cm) − {π × TSF (cm)}]^2/4π [31].

Measurement of muscle strength

HGS of both hands was measured while standing using a dynamometer (Takei Scientific Instruments, Niigata, Japan). Each patient repeated the tests twice with each hand and the maximum value was recorded. Isometric knee extension force (IKEF) of the right leg was measured using hand-held dynamometer (μTas F-1, Anima, Tokyo, Japan). Patients repeated the test twice and the maximum value was used for analysis. The IKEF value was expressed relative to BW (%BW) [32].

Ultrasound measurement and physical functional assessments

Among 96 patients, 46 patients agreed to undergo ultrasound measurement and physical functional assessments prior to the initiation of therapy. Images were obtained using a B-mode ultrasound imaging device (EUB-8500, Hitachi, Tokyo, Japan) equipped with a linear-array probe. Ultrasound images were obtained at the midpoint of the right anterior thigh in a relaxed supine position. A water-soluble permeable gel was applied to the skin surface of the thigh and ultrasonic measurements were taken in a manner not to deform the shape of the muscles without pressing the skin surface. All ultrasound assessments were performed by the same well-trained physical therapist. EI value was determined by performing an 8-bit gray-scale analysis, and the mean EI of the regions of interest of rectus femoris (RF) muscle and vastus intermedius (VI) muscle was expressed as a value from 0 (black) to 255 (white). Muscle thickness (MT) of the quadriceps femoris muscle was defined as the sum of the muscle thickness of RF muscle and VI muscle. Fat thickness (FT) of the front of thigh was measured as the distance between the fascia of RF muscle and dermis. For physical functional assessment, we evaluated the walking speed, the five times sit-to-stand (5-STS), and the short physical performance battery (SPPB). Gait speed was assessed by measuring 10 m usual and maximum gait speed. For 5-STS, patients were instructed to fold their arms in front of their chest and perform five sitting to standing operations as quickly as possible. The SPPB consisted of the standing balance test, the usual gait speed, and the 5-STS, and each test was assigned a categorical score ranging from 0 (inability to complete the test) to 4 (best performance possible). In the standing balance test, the patient had to maintain three stances (legs side by side, semitandem, tandem) for 10 seconds. Finally, we calculated summary score as SPPB total score ranging from 0 (worst performance) to 12 (best performance) [33]. All tests were performed by the same well-trained physical therapist.

Outcomes

Adverse events were classified according to Common Terminology Criteria for Adverse Events ver.5 and Grade 3 or higher was regarded as severe adverse events. Treatment interruption was defined as failure to complete the planned treatment. Survival time was calculated as the time between the date of the start of the treatment and the date of death or the date of last contact or last known to be alive. The patients were followed up till November 30, 2021.

Statistical analysis

Non-normally distributed continuous variables were expressed as median and interquartile range and between-group differences assessed using the Wilcoxon rank sum test. The Chi-squared test was used to compare the categorical variables between the two groups. The correlation of PhA with other parameters was assessed using Spearman's correlation coefficient. Kaplan–Meier analysis was applied to calculate survival time and between-group differences were assessed using the log-rank test. Univariate and multivariate Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) and to assess the prognostic effect of PhA. A univariate analysis was conducted with possible confounding factors (age, sex, cancer site, and cancer stage). Variables associated with P values < 0.1 in the univariate analysis were included in the multivariate analysis. All statistical analyses except Kaplan–Meier analysis were performed using JMP version 13.0 (SAS Institute, Cary, NC, USA). The Kaplan–Meier analysis was performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). P values < 0.05 were considered indicative of statistical significance. We used standard methods to estimate the appropriate sample size for multivariate Cox proportional hazards regression models, with at least 10 outcomes required for each included independent variable. The sample size was calculated using data from our preliminary study. With an expected mortality rate of 35%, we required 86 (3 × 10 / 0.35) patients (30 incidents) to appropriately perform multivariate Cox proportional hazard regression analysis with three variables. We enrolled a total of at least 96 patients, accounting an expected attrition rate of 10%.

Results

Patient characteristics

The clinical characteristics of the study population (n = 96) are shown in Table 1. The median (IQR) PhA value for men and women was 5.2° (4.6°–5.9°) and 4.5° (4.0°–5.2°), respectively. Patients were stratified into following two groups: low-PhA group (PhA ≤ 25th percentile [4.6° in men and 4.0° in women]) and maintained-PhA group (PhA > 25th percentile of PhA). Age, BW, and BMI were significantly different between the two groups.

Table 1. Characteristics of the study population

	All n = 96	Low-PhA group n = 23	Maintained-PhA group n = 73	P-value
Age (y)	67 (60–74)	71 (68–80)	67 (59–72)	**0.002**
Sex, n (%)				0.848
Men	78 (81)	19 (83)	59 (81)	
Women	18 (19)	4 (17)	14 (19)	
Cancer site, n (%)				0.099
Oral cavity	12 (13)	4 (17)	8 (11)	
Maxillary sinus	8 (8)	4 (17)	4 (5)	
Nasopharynx	14 (15)	1 (4)	13 (18)	
Oropharynx	20 (21)	4 (17)	16 (22)	
Hypopharynx	23 (24)	8 (35)	15 (21)	
Larynx	19 (20)	2 (9)	17 (23)	
Cancer stage, n (%)				0.349
I	2 (2)	0 (0)	2 (3)	

II	24 (25)	3 (13)	21 (29)	
III	23 (24)	6 (26)	17 (23)	
IV	47 (49)	14 (61)	33 (45)	
Regimens of Chemotherapy, n (%)				0.378
Triweekly CDDP	41 (43)	8 (35)	33 (45)	
Others	55 (57)	15 (65)	40 (55)	
Height (cm)	165 (159–170)	162 (158–170)	166 (160–169)	0.345
BW (kg)	58.0 (49.0–67.4)	50.6 (45.5–61.5)	60.0 (52.1–69.1)	**0.006**
BMI (kg/m^2)	21.2 (18.9–24.3)	19.8 (18.1–22.9)	21.9 (19.8–24.8)	**0.016**
R (Ω) at 50 kHz	600.7 (540.5–670.7)	638.8 (583.6–697.5)	589.6 (530.5–644.4)	**0.016**
R/H (Ω/m) at 50 kHz	369.1 (322.8–422.5)	402.0 (341.3–431.5)	362.7 (313.2–404.0)	**0.014**
Xc (Ω) at 50 kHz	53.3 (47.3–60.6)	43.0 (41.0–53.0)	56.1 (50.0–61.4)	**< 0.001**
Xc/H (Ω/m) at 50 kHz	32.1 (28.9–36.4)	28.0 (26.1–32.2)	33.2 (30.7–38.1)	**< 0.001**
PhA (°) at 50 kHz	5.1 (4.5–5.7)	4.1 (3.6–4.5)	5.4 (4.9–5.9)	**< 0.001**

BMI, body mass index; BW, body weight; CDDP, cisplatin; H, height; PhA, phase angle; R, resistance; Xc, reactance.

P values < 0.05 are represented in bold.

Correlation of PhA with other parameters

Correlation of PhA with other parameters is shown in Table 2. PhA showed a strong positive correlation with IKEF, and moderate positive correlation with HGS, SMM, SMI, quadriceps-MT, 10 m maximum gait speed, AMA, and AC, and weak positive correlation with BW, SPPB, BMI, and height (P < 0.05). On the other hand, PhA showed moderate negative correlation with 5-STS, quadriceps-EI, and age, and weak negative correlation with cancer stage (P < 0.05). TSF, BFM, front of thigh-FT, and 10 m usual gait speed showed no correlation with PhA.

Table 2. Correlation of pretreatment PhA with other parameters

	Spearman's correlation coefficient	P-value
Basic characteristics		
Age (y)	−0.422	**< 0.001**
Cancer stage	−0.210	**0.040**
Height (cm)	0.228	**0.026**
BW (kg)	0.399	**< 0.001**
BMI (kg/m^2)	0.309	**0.002**
Anthropometry		
AC (cm)	0.487	**< 0.001**
TSF (mm)	0.199	0.054
AMA (cm^2)	0.502	**< 0.001**
DSM-BIA		
SMM (kg)	0.576	**< 0.001**
SMI (kg/m^2)	0.620	**< 0.001**
BFM (kg)	0.033	0.753
Ultrasonography		
Quadriceps-EI (pixel)	−0.439	**0.002**
Quadriceps-MT (cm)	0.579	**< 0.001**
Front of thigh-FT (cm)	−0.023	0.880

Muscle strength		
HGS (kg)	0.649	**< 0.001**
IKEF (%BW)	0.710	**< 0.001**
Physical functions		
10 m usual gait speed (m/s)	0.273	0.070
10 m maximum gait speed (m/s)	0.543	**< 0.001**
5-STS (s)	−0.505	**< 0.001**
SPPB, total score	0.336	**0.029**

AC, arm circumference; AMA, mid-upper arm muscle area; BFM body fat mass; BMI, body mass index; BW, body weight; DSM-BIA, direct segmental multi-frequency bioelectrical impedance analysis; EI, echo intensity; FT, fat thickness; HGS, handgrip strength; IKEF, isometric knee extension force; MT, muscle thickness; PhA, phase angle; SMI, skeletal muscle mass index; SMM, skeletal muscle mass; SPPB, short physical performance battery; 5-STS, five times sit-to-stand; TSF, triceps skinfold thickness.

P values < 0.05 are represented in bold.

Adverse events and treatment interruption

Incidence rates of adverse events and treatment interruption in the two groups are compared in Table 3. The incidence rates of severe anemia, aspiration, and radiotherapy interruption in the low-PhA group were significantly higher than those in the maintained-PhA group. All patients with severe aspiration developed aspiration pneumonia.

Table 3. Differences in adverse events and treatment interruption between the low-PhA and maintained-PhA groups

	Low-PhA group	Maintained-PhA group	P-value

	n = 23	n = 73	
Severe adverse events, n (%)			
Thrombocytopenia	2 (9)	5 (7)	0.780
Anemia	12 (52)	12 (17)	< **0.001**
Leucopenia	9 (39)	31 (43)	0.740
Lymphocytopenia	21 (91)	62 (86)	0.514
Neutropenia	6 (26)	21 (30)	0.748
Febrile neutropenia	4 (17)	9 (13)	0.552
Hypoalbuminemia	1 (5)	2 (3)	0.680
Aspiration	4 (17)	1 (1)	**0.003**
Sepsis	0 (0)	0 (0)	1.000
Treatment interruption, n (%)			
Chemotherapy interruption	2 (9)	6 (8)	0.943
Radiotherapy interruption	4 (17)	2 (3)	**0.011**

PhA, phase angle.

P values < 0.05 are represented in bold.

Survival outcome

The survival curves of the two groups are shown in Figure 1. The overall 3-year survival rate in the low-PhA group was significantly lower than that in maintained-PhA group (47% vs. 81%, P = 0.002).

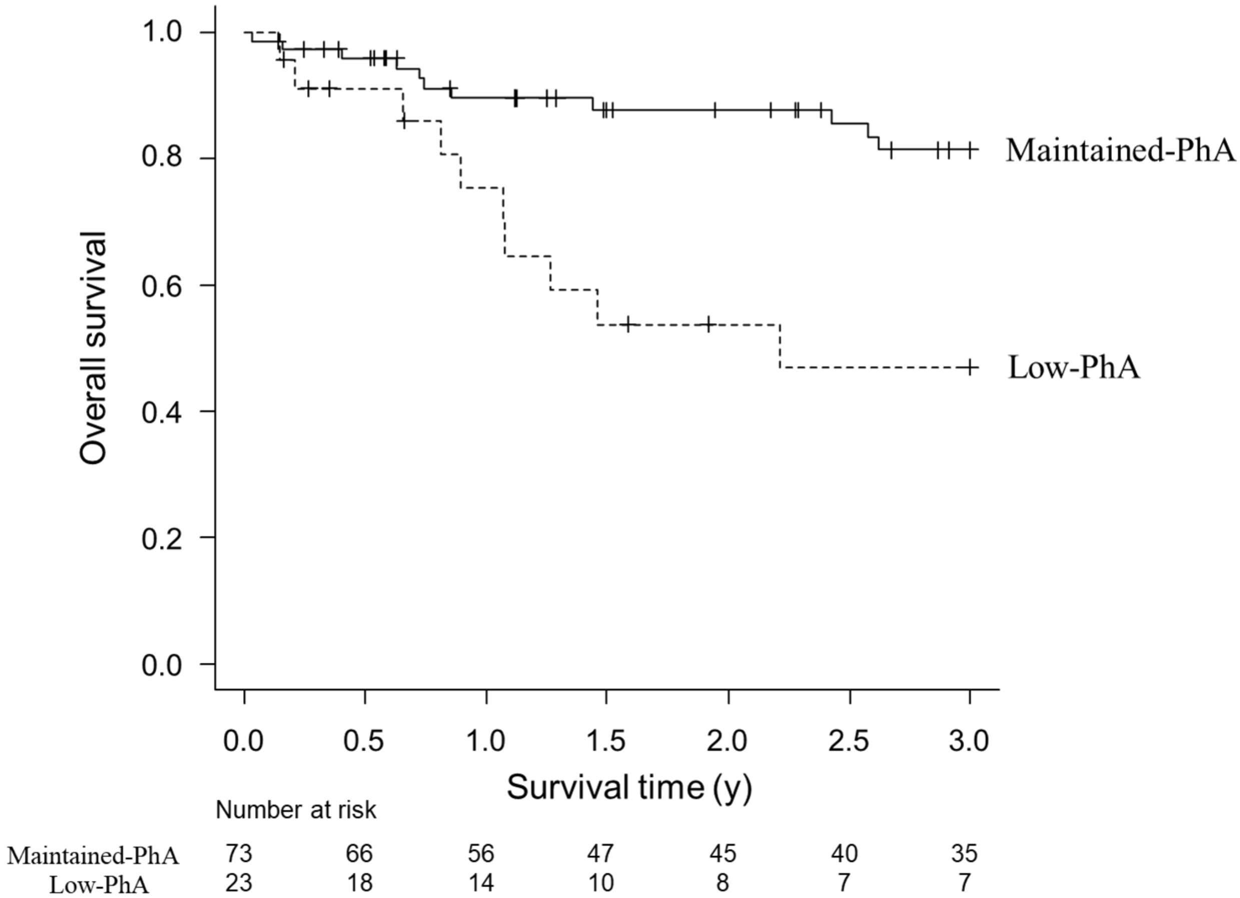

Fig. 1. Kaplan–Meier survival curves by PhA. The solid line represents the maintained-PhA group and the dotted line represents the low-PhA group. Vertical lines indicate censored patients, ie, those who reached the end of their follow-up without dying.

PhA, phase angle.

Table 4 shows the HRs and 95% CIs. From the results of the univariate analysis, cancer site and cancer stage were adjusted for in the multivariate analysis. PhA (as both continuous and categorical variable) was a significant risk factor for mortality in the univariate analysis. The multivariate analysis revealed that high PhA (as a continuous variable) was associated with a significantly lower risk of mortality (HR, 0.49; 95% CI, 0.27–0.84; P = 0.009), and patients in the low-PhA group (as a categorical variable) had a significantly higher risk of mortality than those in the maintained-PhA group (HR, 3.23; 95% CI, 1.33–7.79; P = 0.011).

Table 4. Univariate and multivariate analyses of Cox proportional hazard ratio

	Univariate			Multivariate		
	HR	95%CI	P-value	HR	95%CI	P-value
PhA as a continuous variable, per degree increase	0.40	0.23–0.69	**<0.001**	0.49	0.27–0.84	**0.009**
PhA as a categorical variable						
Maintained-PhA	1.00	-	-	1.00	-	-
Low-PhA	3.66	1.52–8.71	**0.005**	3.23	1.33–7.79	**0.011**

CI, confidence interval; HR, hazard ratio; PhA, phase angle.

P values < 0.05 are represented in bold.

Discussion

This study investigated the correlation of PhA with other parameters and assessed the prognostic value of pre-CRT PhA in patients with HNC. The results showed that PhA correlated with muscle mass/quality/strength and physical function. Low PhA was associated with higher risk of severe anemia or aspiration, radiotherapy interruption, and poor survival. Our results suggested that PhA 4.6° in men and 4.0° in women were useful reference values for Asian patients with HNC.

BIA has been used widely because it is easy-to-use, noninvasive, inexpensive, portable, and reproducible. BIA measures the body composition based on the resistance of alternating current flowing through their body, such as R and Xc. R reflects the body's pure resistance to alternating current flow and Xc reflects the resistance effect produced by the bilayer of the cell membrane [34]. Variables such as muscle mass and body fat mass obtained by BIA are widely used, but these indices are estimated values calculated using a formula that assumes a certain body water equilibrium; therefore, due caution should be exercised while interpretating these values in the setting of abnormal body water balance, such as edema [5,13,35]. On the other hand, PhA obtained by BIA, the raw data calculated by R and Xc, has gained attention [4].

In this study, PhA showed negative correlation with quadriceps-EI. EI has been suggested as a surrogate measure of muscle quality [36]. Several previous studies which used magnetic resonance imaging showed the effectiveness of ultrasound-based intramuscular adipose tissue and muscle mass measurements [37,38]. According to the guideline by the European Working Group on Sarcopenia in Older People (2018), EI reflects muscle quality, since noncontractile tissue associated with myosteatosis shows hyper-echogenicity [33]. In addition, the same guideline stated that "muscle quality has been assessed by BIA-derived phase angle measurement" [33]. However, the correlation between PhA and EI has been reported only in healthy population [6,7], and this is the first report in patients with cancer. With respect to physical function indices, we observed that PhA had positive correlation with 10 m maximum gait speed and SPPB, and negative correlation with

5-STS. Similar results were reported in nononcological patients [8,9,12]; however, only a limited number of reports have reported the correlation between PhA and gait speed in cancer patients [10,11]. Regarding muscle strength, PhA showed the strongest positive correlation with IKEF and HGS among other parameters. Similar to this study, our previous report showed the strongest positive correlation of PhA with HGS ($R = 0.68$) among other parameters [5]. In addition, we observed a correlation of PhA with muscle mass, but not with fat mass, whether by anthropometry, ultrasound, or DSM-BIA measurements. To summarize our correlation results, in addition to the known fact that PhA correlates with muscle mass, our findings suggest that PhA is a potential marker of muscle quality and physical function. Similar to previous studies [6,12,39–44], our results suggest that PhA may be useful in diagnosing sarcopenia, which is usually diagnosed based on muscle mass, muscle strength, and physical function.

We found that patients with low PhA more often suffered from severe anemia, aspiration, and radiotherapy interruption. Patients with cancer are at a higher risk of developing anemia due to chemotherapy-induced myelosuppression. The risk of anemia increases with tumor growth and occurrence of distant metastases [45]. Another study found older age as a significant risk factor for severe anemia during induction chemotherapy [46]. In this study, PhA showed significant negative correlation with age and cancer stage, and patients in the low-PhA group were significantly older. Thus, patients in the low-PhA group are considered to show a higher incidence of more severe anemia than those in the maintained-PhA group. Regarding aspiration pneumonia during CRT, in previous studies, pretreatment hypoalbuminemia [47] and low SMI [48] were found to be independent risk factors for aspiration pneumonia. Our previous study showed a positive correlation of PhA with albumin level and SMI [5]. Although relevant data are not shown, we also observed significantly lower albumin level (3.2 [3.0–3.9] in low-PhA group vs. 3.9 [3.6–4.2] in maintained-PhA group) and lower SMI (5.8 [5.4–6.6] in low-PhA group vs. 6.8 [6.2–7.7] in maintained-PhA group) ($P < 0.001$) in patients in the low-PhA group than in those in the maintained-PhA group in our study. Thus, low PhA is considered a potential risk factor for aspiration pneumonia. In previous studies, malnourished patients more often experienced treatment interruption [2]. Thus, serious adverse events as described above and pretreatment malnutrition may have affected treatment interruption.

Patients with low PhA showed poor 3-year survival which is consistent with previous reports [24–27]. These reports suggested the reference prognostic values of PhA in patients with HNC, i.e., 5.95° in Sweden [24], 4.733° in Poland [25], and 5.0° [26] or 4.7° [27] in Germany. The reference values determined in our study (4.6° in men and 4.0° in women) were lower than those in the previous studies. This difference may have been influenced by racial difference (Asians have lower PhA than other races [13]) or different methods used for determining reference values. The need for PhA reference values specifically for Asians has been suggested. Since the PhA quartile of our results predicted a poor prognosis, we believe that 4.6° in men and 4.0° in women can be used as a clinical reference value for HNC in Asians.

The strengths of this study are as follows. First, we demonstrated significant correlation of PhA with other parameters, indicating that PhA is a marker of muscle mass/quality/strength and physical function. Second, this is the first study to demonstrate the association between low PhA and adverse events or treatment interruption during CRT in patients with cancer. Finally, this is the first study to propose the reference value of PhA to predict poor survival in Asian patients with HNC. However, some limitations of our study should be considered. First, the study population comprised of a small population of hospitalized patients with HNC in a single center. We could not adjust for other factors such as age and BMI in the multivariate analysis. Larger multicenter studies are required to confirm our results. Second, this study determined prognostic reference values by the lowest quartile value, but not based on outcome. In this cohort, patients who completed the 3-year follow-up (50 men and 10 women) were analyzed by receiver operating characteristic (ROC) curve analysis to calculate the optimal cutoff value of PhA predicting death within 3-year (data not shown). The significant cutoff value determined by the ROC curve was 4.5° in men, which was similar to our prognostic reference value determined by the lowest quartile value. However, in women, the significant cutoff value could not be obtained because of the small number of female patients with HNC. Further studies are required to determine the cutoff value based on outcome of HNC in Asians.

Conclusion

In this study, PhA showed a correlation with muscle mass, muscle quality, muscle strength, and physical function indices. Low PhA was a risk factor for severe adverse events, treatment interruption, and poor 3-year survival. Our results indicated that the lowest quartile value (4.6° for men and 4.0° for women) can be useful as prognostic reference value in Asian patients with HNC. Further studies are required to confirm our findings.

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