"Influence of Nutritional State and the Phase Angle in the Health Related Quality of Life and Clinical Outcome in Head and Neck Cancer"

IMSS — UNIDAD MÉDICA DE ALTA ESPECIALIDAD HOSPITAL DE ESPECIALIDADES CENTRO MÉDICO NACIONAL DE OCCIDENTE

Daniel Sat-Muñoz (daniel.sat@cademicos.udg.mx), Brenda-Eugenia Martínez-Herrera, Javier-Andrés González-Rodríguez, Leonardo-Xicotencatl Gutiérrez-Rodríguez, Benjamín Trujillo-Hernández, Luis-Aarón Quiroga-Morales, Aldo-Antonio Alcaráz-Wong, Carlos Dávalos-Cobián, Alejandro Solórzano-Meléndez, Juan-Daniel Flores-Carlos, Benjamín Rubio-Jurado, Mario Salazar-Páramo, Gabriela-Guadalupe Carrillo-Nuñez, Eduardo Gomez-Sánchez , Arnulfo-Hernán Nava-Zavala and Luz-Ma Adriana Balderas-Peña (luz.balderas@académicos.udg.mx).

Introduction

- In patients with head and neck cancer (H&NC), malnutrition is a frequent condition even before treatment, regardless of the anatomical site of the primary tumor. Most of them are treated by chemo-radiotherapy and surgery; these are usually associated with adverse events such as dysphagia, mucositis, nausea, and other aerodigestive symptom.

- Bioelectrical impedance analysis (BIA) is a crucial tool used in the clinical setting to assess body composition in different types of patients and allows analysis of not only weight loss but also changes in muscle mass and, through phase angle (PA), the integrity of membranes in cells. These are related to functionality, quality of life, and even the risk of complications and mortality.

- PA could be a cornerstone for predicting outcome, functionality, response to treatment, and mortality in this specific group of patients. This report aimed to determine the role of phase angle in the outcomes of head and neck cancer patients in a population with a high prevalence of overweight and obesity.

Materials & Methods

- It is a prospective *cohort analysis* of naïve patients with head and neck cancer followed all of them for at least two years.

- **Body composition analysis:**

  - Phenotype of the patients: Sarcopenia, sarcopenic obesity, obesity, or typical body composition. The Seca 213 height scale measured the height. The BIA multisegmental and multifrequency device mBCA Seca 514 was used to obtain the patients' weight, phase angle, total skeletal muscle mass, and total body fat percentage

  - The BMI was calculated as described by the WHO. The SMI was calculated by dividing the total skeletal muscle mass (kg) by the height squared (m2)

  - The handgrip strength was measured using a Jamar Plus+ Digital Hand Dynamometer according to the American Association of Hand Therapist.

- **Quality of Life:**

  - The EORTC QLQ-C30 v.3 and the EORTC QLQ-H&N35 complementary module for H&NC (validated for Mexican population) was used to evaluate the QoL. The analysis of both EORTC questionnaires items required the linear transformation of each item or multi-item scale to get a range of scores from 0 to 100.

- **Methods**:

  - Means ± standard deviation (SD) for variables with normal distributions. Non-parametric variables were described as medians (interquartile intervals (IQIs))

  - Categorical variables were expressed as numbers and percentages of the total.

  - Pearson's chi-square tests were performed to assess differences between the two groups (Fishers' tests if the estimated values were <5), and one-way ANOVA and Kruskal–Wallis tests with Bonferroni correction were used to assess differences between the three groups. To determine the relationship,

  - Pearson's correlation or Spearman's Rho was calculated depending on the type of variable. Survival analysis was carried out using the Kaplan–Meier method and hazard risk was estimated by Cox regression. Analyses were two-sided, and a p-value < 0.05 was considered significant. Cronbach's alpha value was used for reliability in the multi-item scales of the EORTC questionnaires.

Results & Discussion

- In total, 139 patients with H&NC with a mean age of 63.5 (±13) years, 32 (23%) women and 107 (77%) men, were studied. The selected subjects were divided into normal- and low-phase-angle (PA) group.

- **Clinical Aspects and Anthropometrical and Biochemical Indicators**

  - Patients with PA < 4.42∘ had significant differences in age, anthropometric and biochemical indicators of malnutrition, and inflammatory status compared to patients with PA > 4.42

Clinical Characteristic	Phase Angle < 4.42° n (% Inside Specific Group)	Phase Angle ≥ 4.42° n (% Inside Specific Group)	Total n (% Total Patients)	p Value *
Gender				
Female	22 (68.8%)	10 (31.3%)	32 (100%)	
Male	52 (48.6%)	55 (51.4%)	107 (100%)	
Total	74 (53.2%)	65 (46.8%)	139 (100%)	0.035
Phenotype by Body Composition				
No Sarcopenia	17 (34.7%)	32 (65.3%)	49 (100%)	
Sarcopenia	35 (67.3%)	17 (32.7%)	52 (100%)	
Sarcopenic obesity	22 (57.9%)	16 (42.1%)	38 (100%)	
Total	74 (53.2%)	65 (46.8%)	139 (100%)	0.004

* Significant p value < 0.05. Chi squared test.

Anthropometrical and Biochemical Indicators	Phase Angle < 4.42° n = 74 Mean (SD Standard Deviation)	Phase Angle ≥ 4.42° n = 65 Mean (SD Standard Deviation)	p Value *
Age and Anthropometrical Indicators			
Age	67.2 (12.32)	59.3 (12.57)	0.001
Handgrip strength	22.6 (8.0)	31.1 (8.0)	<0.001
Gait speed	0.75 (0.2)	0.92 (0.2)	<0.001
Phase angle	3.6 (0.6)	5.1 (0.5)	0.001
Body Mass Index (BMI)	24.9 (6.0)	26.7 (4.2)	0.042
Total Fat percentage	33.5 (11.2)	30.7 (8.9)	<0.057
Skeletal Muscle Mass Index (SMMI)	7.3 (3.4)	10.1 (5.1)	<0.001
Biochemical Indicators			
Hemoglobin	12.6 (1.9)	13.9 (1.7)	<0.001
Absolute lymphocyte count	1587 (946)	1920 (1016)	0.024
Albumin **	4.1 (3.6–4.3)	4.4 (4.15–4.5)	<0.001
C-Reactive Protein **	23.15 (5.8–28.25)	10.4 (2.9–21.3)	<0.001
Total cholesterol	184.2 (50.0)	183.5 (32.3)	0.465

* Significant p value < 0.05. Student's T test. ** Significant p value < 0.05. U de Mann–Whitney test. Nonparametric distribution values. Median (interquartile interval).
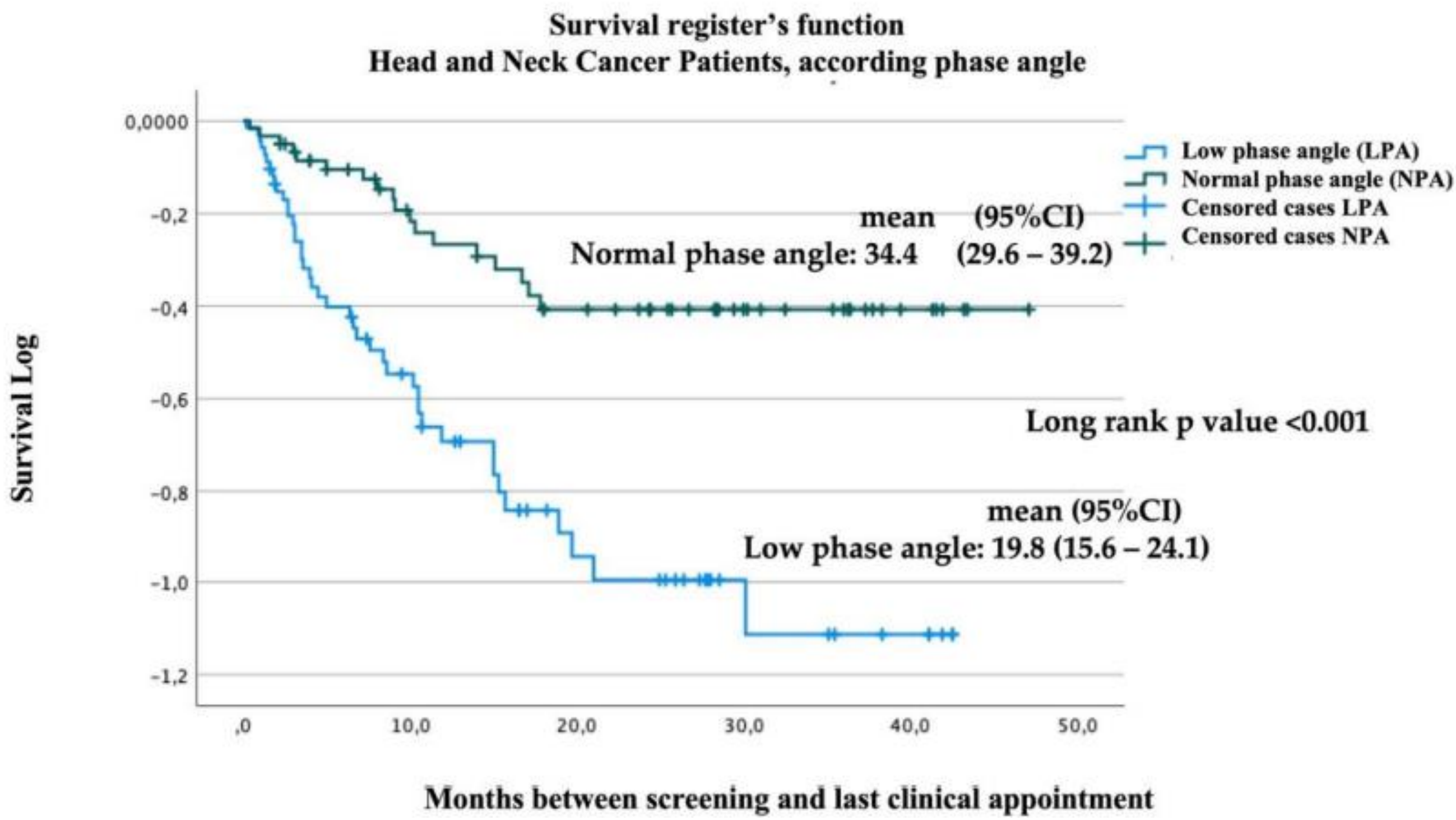
- **Characteristics of the Health-Related Quality of Life in the Head and Neck Cancer Patient**:

  - EORTC QLQ-C30 showed differences in the following scores: global health status/quality of life, physic functioning, role functioning, fatigue, pain, insomnia, and loss of appetite, with lower scores on the functional scales and higher scores on symptoms in patients with a low phase angle.

Scores for the QLQ Scales	Phase Angle < 4.42° n = 74 Mean (SD Standard Deviation)	Phase Angle ≥ 4.42° n = 65 Mean (SD Standard Deviation)	p Value *
EORTC QLQ-C30 (SCORE 0–100)			
Global Health Status/Quality of Life	62.2 (25.7)	76.4 (21.7)	<0.001
Physic Functioning **	70 (40–93)	93.3 (80–100)	<0.001
Role Functioning	83.3 (33.3–100)	100 (75–100)	0.003
Emotional Functioning	67.7 (27.9)	72.4 (27.3)	0.314
Cognitive Functioning	79.9 (21.0)	83.9 (20.6)	0.264
Social Functioning	71.4 (30.5)	79.5 (33.0)	0.135
Fatigue	47.7 (29.0)	21.4 (25.47)	<0.001
Nausea and vomiting	8.3 (17.3)	10.8 (25.6)	0.508
Pain **	16.7 (0–50)	0.0 (0–33.3)	0.009
Dyspnea **	0.0 (0–33.3)	0.0 (0–33.3)	0.121
Insomnia	45.5 (39.2)	31.8 (37.9)	0.039
Loss of appetite **	16.7 (0.0–66.7)	0 (0.0–0.0)	<0.001
Constipation **	32 (36.4)	26.7 (35.5)	0.386
Diarrhea	6.3 (14.2)	6.1 (19.4)	0.958
Financial Difficulties	40.1 (35.7)	31.8 (35.1)	0.171

- EORTC QLQ-H&N35 showed significantly higher scores in patients with a low phase angle for the following items: pain, swallowing, senses problems, trouble with social eating, teeth, opening mouth, dry mouth, sticky saliva, felt ill, pain killers, and nutritional supplements.

Scores for the QLQ Scales	Phase Angle < 4.42° n = 74 Mean (SD Standard Deviation)	Phase Angle ≥ 4.42° n = 65 Mean (SD Standard Deviation)	p Value *
EORTC QLQ-H&N35 (SCORE 0–100)			
Pain **	33.3 (14.6–58.3)	16.7 (0–29.2)	0.002
Swallowing	32.4 (27.0)	20.3 (26.7)	0.009
Senses problems **	23.3 (0.0–54.2)	0.0 (0.0–30)	0.003
Speech problems	42.5 (31.4)	33.1 (31)	0.080
Trouble with social eating	30.5 (31)	19.3 (27.3)	0.026
Trouble with social contact **	6.7 (0.0–26.7)	0.0 (0.0–10.3)	0.057
Less sexuality	43.5 (13.4)	41 (11.2)	0.206
Teeth **	20.7 (0.0–66.7)	0.0 (0.0–33.3)	0.023
Opening mouth **	33.3 (0.0–100)	0.0 (0.0–28.1)	<0.001
Dry mouth	46.8 (38.4)	30.6 (32.5)	0.008
Sticky saliva **	37.3 (0.0–100)	0.0 (0.0–41.3)	0.001
Coughing	33.5 (34.7)	25.0 (30.0)	0.128
Felt ill **	29.1 (0.0–66.7)	0.0 (0.0–33.3)	0.023
Pain killers	68.1 (45.5)	45.0 (47.4)	0.004
Nutritional supplements **	100 (0.0–100)	0.0 (0.0–60.4)	0.002
Feeding tube **	0.0 (0.00–0.00)	0.0 (0.00–0.00)	0.225
Weight loss	56.0 (48.1)	50.0 (48.0)	0.462
Weight gain **	0.0 (0.00–0.00)	0.0 (0.0–4.5)	0.072

* Significant p value < 0.05. Student's T test. ** Significant p value < 0.05. U de Mann–Whitney test. Nonparametric distribution values. Median (interquartile interval).

- **Survival Analysis of the Head and Neck Cancer Patient Cohort**

  - The relative risk of death was related to low PA (2.6; p < 0.001). The percentage of living patients (41.7%) is almost the same as the percentage of deceased subjects (43.1%; p = 0.002), with high death rates in patients with PA < 4.42∘. Phase angle was the most crucial predictor of survival and a risk factor for death in the studied cases.

Survival register's function
Head and Neck Cancer Patients, according phase angle
- Low phase angle (LPA)
- Normal phase angle (NPA)
- Censored cases LPA
- Censored cases NPA

mean (95%CI) Normal phase angle: 34.4 (29.6 – 39.2)

Long rank p value <0.001

mean (95%CI) Low phase angle: 19.8 (15.6 – 24.1)

Months between screening and last clinical appointment

Conclusion

- The phase angle in this cohort had a lower cut off than that reported by other groups, reflecting the prevalence of malnutrition in our population, which negatively impacts the HRQoL, outcome, and mortality percentage during the first two years of follow-up, and a significant increase in the HR for death. It is essential in areas with a high prevalence of obesity, where a multidisciplinary and transdisciplinary treatment team need to take actions directed toward the early detection of patients with a high malnourishment risk and perform intense nutritional management to avoid or limit sarcopenia, sarcopenic obesity, or tumor cachexia.

References:

1. Adkins, D.; Michel, L.; Wildes, T.; Ley, J.; Thorstad, W.; Nussenbaum, B. Cáncer de Cabeza y Cuello. In Manual Washington de Oncología; Wolters Kluwer: Barcelona, Spain, 2016; pp. 217–240.

2. Johnson, N.W.; Amarasinghe, H.K. Epidemiology and Aetiology of Head and Neck Cancers. In Head and Neck Cancer: Multimodality Management; Bernier, J., Ed.; Springer International Publishing: Cham, Switzerland, 2016; pp. 1–57. ISBN 978-3-319-27601-4.

3. Bennardo, L.; Bennardo, F.; Giudice, A.; Passante, M.; Dastoli, S.; Morrone, P.; Patruno, C.; Nisticò, S.P. Local Chemotherapy as an Adjuvant Treatment in Unresectable Squamous Cell Carcinoma: What Do We Know So Far? Curr. Oncol. 2021, 28, 2317–2325.

4. Fearon, K.; Strasser, F.; Anker, S.D.; Bosaeus, I.; Bruera, E.; Fainsinger, R.L.; Jatoi, A.; Loprinzi, C.; MacDonald, N.; Mantovani, G.; et al. Definition and classification of cancer cachexia: An international consensus. Lancet Oncol. 2011, 12, 489–495.