Positive Relation between Standardized Phase Angle and Clinical Neoplasm Staging in Individuals with Cancer

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Relação Positiva entre o Ângulo de Fase Padronizado e o Estadiamento Clínico em Indivíduos com Câncer

Relación Positiva entre Ángulo de Fase y Estadificación Clínica de Neoplasias Individuos con Cáncer

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ABSTRACT

Introduction: Cancer is characterized by the abnormal growth of cells in a tissue, with the potential to invade another organs and tissues. The knowledge of the anatomical extent of cancer and its infiltration capacity are important to guide therapies and prognosis, and the evolution of this disease has severe negative impact on the patient's nutritional status. Phase angle (PA) is an excellent prognostic tool for this group. **Objective:** To associate the standardized phase angle (SPA) with clinical staging in cancer patients. **Method:** Observational and cross-sectional study with adults and older adults with cancer non-hospitalized. Clinical information and clinical staging (TNM) of cancer were obtained from electronic charts. Patient-Generated Subjective Global Assessment (PG-SGA) was performed, and the PA was calculated using values collected by bioimpedance and then the standardized PA (SPA). **Results:** 25 volunteers participated, with mean age of 58.3 years (±13.7), 54.8% females and 54.8% older adults. The most frequent tumor site was in the stomach (36%), 44% of the participants were in clinical stages II and 56%, III or IV. According to the PG-SGA, 74% of the volunteers had some degree of nutritional impairment (score B or C), and a positive association was detected between SPA and tumor staging (p>0.0414). **Conclusion:** SPA was positively related to clinical staging in individuals with cancer.

Key words: Neoplasms; Neoplasm Staging; Electric Impedance; Nutritional Status.

RESUMO

Introdução: O câncer é caracterizado pela multiplicação desordenada de células de um dado tecido, com potencial para invadir outros órgãos e tecidos. O conhecimento da extensão anatômica do câncer e sua capacidade de infiltração são importantes para nortear terapias e prognóstico, e a evolução dessa doença tem forte impacto negativo no estado nutricional do paciente. O ângulo de fase (AF) se apresenta como ótima ferramenta prognóstica para esse grupo. **Objetivo:** Associar o ângulo de fase padronizado (AFP) com o estadiamento clínico em indivíduos com câncer. **Método:** Estudo observacional e transversal, realizado com adultos e idosos com câncer não hospitalizados. As informações clínicas e o estadiamento clínico (TNM) do câncer foram obtidos por meio de prontuário eletrônico. Foi realizada a Avaliação Subjetiva Global Produzia pelo Próprio Paciente (ASG-PPP), e calculados o AF, mediante os valores obtidos pela bioimpedância e, em seguida, o AFP. **Resultados:** Participaram da pesquisa 25 voluntários com média de idade de 58,3 anos (±13,7), sendo 54,8% do sexo feminino e 54,8% idosos. O tipo de câncer mais frequente foi o de estômago (36%); 44% dos participantes tinham estádios clínicos II e 56%, III ou IV. Segundo a ASG-PPP, 74% dos voluntários apresentavam algum grau de comprometimento nutricional (escores B ou C), e foi detectada associação positiva entre o AFP e o estadiamento tumoral (p>0,0414). **Conclusão:** O AFP se relacionou positivamente com o estadiamento clínico em indivíduos com câncer.

Palavras-chave: Neoplasias; Estadiamento de Neoplasias; Impedância Elétrica; Estado Nutricional.

RESUMEN

Introducción: El cáncer se caracteriza por la multiplicación desordenada de células en un tejido, con potencial para invadir otros órganos y tejidos. El conocimiento de la extensión anatómica del cáncer y su capacidad de infiltración son importantes para orientar las terapias y el pronóstico, y la evolución de esta enfermedad tiene un fuerte impacto negativo en el estado nutricional del paciente. Y el ángulo de fase (AF) es una excelente herramienta de pronóstico para este grupo. **Objetivo:** Asociar el ángulo de fase estandarizado con la estadificación en individuos con cáncer. **Método:** Estudio observacional y transversal, realizado con adultos y ancianos con cáncer no hospitalizados. La información clínica y la estadificación clínica (TNM) del cáncer se obtuvieron a través de registros médicos electrónicos, y se realizó la Valoración Global Subjetiva Generada por el Paciente (VG-SGP) y se calculó el AF y AF estandarizado utilizando los valores obtenidos por bioimpedancia y luego el AF estandarizada. **Resultados:** Participaron 25 voluntarios, con una edad promedio de 58,3 años (±13,7), 54,8% mujeres y 54,8% eran ancianos. El tipo de cáncer más frecuente fue el de estómago (36%), y el 44% de los participantes tenía estadios clínicos II y 56% III o IV. Según la VG-SGP 74% de los voluntarios presentaban algún grado de deterioro nutricional (puntuaciones B o C) y se detectó una asociación positiva entre el AF estandarizado y estadificación tumoral (p>0,0414). **Conclusión:** El AF estandarizada se relacionó positivamente con la estadificación en personas con cáncer.

Palabras clave: Neoplasias; Estadificación de Neoplasias; Impedancia Eléctrica; Estado Nutricional.

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INTRODUCTION

Cancer is a multifactorial, chronic non-communicable disease (NCD) encompassing a set of more than 100 diseases characterized by the abnormal growth of cells of a certain tissue potentially spreading to other organs and tissues[1]. For each year of the triennium 2020-2022, the National Cancer Institute José Alencar Gomes da Silva (INCA) estimates more than 625 thousand new cases in the country. In the State of Rio Grande do Norte, 11,140 new cases were detected in 2020, being prostate and female breast the most prevalent[1].

Because it is a heterogeneous group of diseases affecting various tissues and with specific forms, it was necessary to establish classification methods. Among them, the TNM System of clinical staging stands out, it is based in the amount and spread of cancer with three subclassifications: T – the characteristics of the primary tumor (T); N – spread to lymph nodes and lymphatic infiltration of the organ; M – presence of not of metastasis[2].

Its extension spread capacity and location directly determine the treatment of choice and the patient's nutritional profile. Cancer itself and different modalities of treatment as antineoplastic drugs and radiotherapy bring significant physiologic and metabolic alterations with adverse events as vomits, mucositis, diarrhea, and fatigue, in addition to surgeries removing tumor tissues and changing the functioning of organs and systems[3].

It is recommended triage and nutritional evaluation to assess the nutritional impact of cancer. Bioelectrical impedance analysis, BIA stands out among the available methods of evaluation for being low invasive, versatile, and quickly applicable. From BIA, resistance (R) and reactance (Xc) values are obtained to estimate body composition, distribution of body fluids, calculation of lean mass, fat mass and phase angle (PA)[4].

The evaluation of the body composition has gained space while reflecting accurately the metabolic profile of the patient, in special, the values related to skeletal muscle which is a reference for the clinical prognosis of several types of cancer[5]. In that line, the value of PA is related with cellular integrity because indicates alterations in the body composition at cellular level, in the functions of the membrane and, consequently, in the health condition; it is being utilized as a tool with strong prognostic association, assessing the severity and/or extent of chronic diseases as cancer, being clinically viable to guide conducts and detect individuals requiring early and specialized intervention[6-9].

However, there are controversies about the cutoff of PA as prognostic indicator, mainly related with the discrepancies in the cutoff utilized which are associated with sex, age, ethnicity, and body mass index (BMI). Reference values validated for the calculation of standardized phase angle (SPA) have been established to control these variables[10,11].

Literature has been demonstrating that PA is positively relating with body composition and clinical and nutritional status of individuals with several diseases, among them, cancer[12-16]. Possibly there is a direct relation between SPA and cancer staging because the extent of a cancer impacts these factors. The extension of the tumor determines the metabolic and nutritional impact for the patient and its knowledge allows better accuracy of nutritional planning. This study has the objective of relating SPA with clinical staging in individuals with cancer.

METHOD

Observational, cross-sectional study, a roll-out of the clinical trial titled "Analysis of the nutritional care of oncologic patients" approved by the Institutional Review Board (IRB) of "*Hospital Universitário Onofre Lopes*" (HUOL) of "*Universidade Federal do Rio Grande do Norte*" (UFRN) (CAAE: 79715817.1.0000.5292). The volunteers were aware of the study and accepted to join by signing the Informed Consent Form (ICF).

From March 2018 to June 2019, data were collected from individuals with cancer consulted at the High Complexity Oncologic Care (UNACON) of HUOL with non-probabilistic sample.

Individuals of both genders, older than 20 years of age with confirmed diagnosis of cancer by biopsy and stage described in the chart were eligible to participate. Individuals with cancer carrying pacemakers or metal prosthetics who were in corticotherapy were excluded.

After signing the ICF a questionnaire elaborated by the team was applied in an interview to collect data about age, oncologic diagnosis, time of diagnosis, treatment, and comorbidities. Clinical staging was obtained from electronic charts based in medical exam and categorized in I/II and III/IV for the purpose of determining the form of analysis.

The Portuguese validated translation of the Patient-Generated Subjective Global Assessment (PG-SGA)/ Pt-Global Platform[17] was adopted.

During the outpatient consultation, a skilled analyst applied the PG-SGA to evaluate he nutritional status, asking all the questions to ensure the reliability of the data collected, considering the past history of the patient's weight and food intake, the metabolic demand of the disease and physical examination. Later, the final classification of the individual was reached: well-nourished (score A), suspected/moderately malnourished (score B) or severely mal-nourished (score C). The results of the

nutritional status were grouped to address the analyses of interest in two categories, well-nourished (classified as well nourished) and mal-nourished (classified as suspected/moderately mal-nourished or severely mal-nourished)[17].

PA was calculated from the values of R and Xc obtained by BIA with the analyzer of bioelectric impedance (RJL Systems®, Michigan, USA) according to the standard method[18]. The protocol of tetrapolar measurement techniques (with four adhesive electrodes placed in the upper and lower limbs) consisted in the fixation of the discharging electrodes distally to the dorsum surface of the hand and of the foot, in the third metacarpal and of the third metatarsal head plane, respectively. The receiving electrodes were placed proximal in the hand and foot, the first in the wrist, in an imaginary plan of union of two styloid apophysis and the second to the dorsum of the tibiotarsus articulation, in the imaginary line of the union of the most salient part of the two malleoli. By convention, the four electrodes were placed in the right hand and foot with the individual in supine to minimize the effects of the gravity in the tendency of stagnation of body water in the lower extremities when in biped position. The volunteers examined were lying down on their backs in a bed and remained motionless during the test. The upper limbs were placed to not touch the chest with hands turned downward and lower limbs separated to avoid touching one another[19,20]. The PA was obtained through the equation Xc/R x 180º/π[21]. The equation SPA = PA measured – mean PA (for age and gender)/standard deviation of the population for age and gender was used to calculate PA[22,23]. The mean/standard deviation PA was obtained through reference values for gender and age of healthy adults as proposed by Barbosa-Silva et al.[24]. Next, the values of SPA were categorized at risk when found below -1.65 (cutoff representing the percentile 5), the lower limit for the healthy population or without risk when values were above -1.65[20].

The information collected were entered in Excel® and imported to Graph Pad Prism 7.0® (Graph Pad Software, Inc., San Diego, CA, USA). The continuous variables were tested for normality of the distribution by the Shapiro-Wilk test.

Clinical and demographic data were expressed in absolute and relative frequency or mean with respective standard-deviations. For comparison, the test t of Student was used, and for associations, the exact test of Fisher. The level of significance adopted was $p<0.05$.

RESULTS

25 individuals with mean age of 56.4 years (±12.9), mostly females (56%) were enrolled. The modalities of treatment most utilized were chemotherapy (64.5%) and surgery (48.3%). According to PG-SGA, 76% of the individuals had nutritional compromise (scores B or C). Table 1 shows the characterization of the participants. The most frequent cancer was stomach (36%) (Figure 1).

Table 1. Clinical and nutritional profile of the participants (n=25)

Variables	n	Frequency (%)
Sex		
Men	11	44
Women	14	56
Age (years)		
20 – 59	13	52
≥60	12	48
Modality of treatment		
Chemotherapy	20	64.5
Surgery	15	48.3
Radiotherapy	6	19.3
Treatment not initiated	4	12.9
Palliative Care	2	6.4
Staging		
I	0	0.0
II	11	44
III	11	44
IV	3	12
Nutritional status (PG-SGA)		
A	6	24
B	13	52
C	6	24
Phase angle		
Age-range*	Mean	Standard Deviation
20 – 59 years	5.3	1.4
>60 years	4.6	0.8

Caption: PG-SGA = Patient-Generated Subjective Global Assessment. (*)13 (20 – 59 years); 12 (older than 60 years).

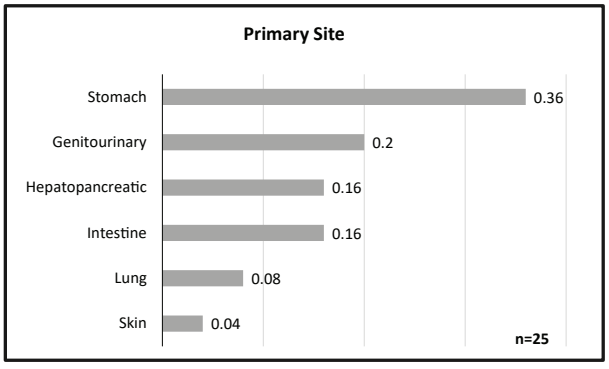

Figure 1. Frequency of the types of primary cancer

For individuals with cancer, values of PA lower than 5.0 indicate significant fragility; values between 4.0 and 2.0, severe condition with necessity of aggressive intervention and values under 2.0 mean imminent risk of death[25]. According to PA values and following the classification aforementioned, 62.5% were in good condition, 16.6% in significant fragility, 20.8% in severe condition and none was in apparent risk of death.

It was found association of SPA cutoff with tumor clinical staging (Table 2). However, no statistically significant difference (p=0.4086) was found among the values of SPA of the participants classified as nourished (A) in relation to malnourished (B and C) (Figure 2).

Table 2. Association between SPA and staging

		SPA < -1.65	SPA > -1.65	P value
		n (%)	n (%)	
Staging	I/II	5 (20%)	7 (28%)	0.0414*
	III/IV	11 (44%)	2 (8%)	

Caption: SPA = Standardized Phase Angle.
(*) Fisher exact test (p<0.05).

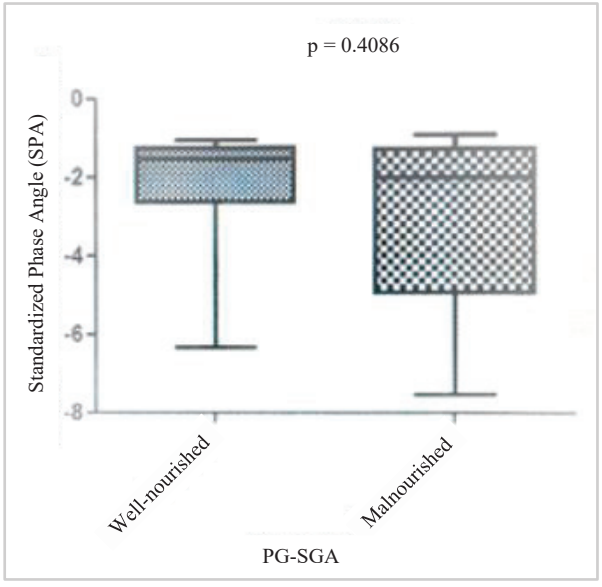

Figure 2. Comparison of the SPA values and nutritional participants status (n=25)

DISCUSSION

Association between SPA with clinical staging was found in individuals with cancer, meaning worse clinical and nutritional prognosis for those with more advanced tumor. However, according to PG-SGA classification, it was not encountered statistical difference between the values of SPA in nourished and malnourished individuals.

PA is a sensible predictor of mortality in older individuals with cancer regardless of age, gender, comorbidities, and BMI and helps to evaluate the time of hospitalization in critical patients[26,27]. The mean of PA in older adults was lower than in adults. From 18 years of age, PA tends to stabilize and after 48 years, drops progressively[28]. This condition can be explained by the fact that with ageing, the cellular integrity diminishes and occurs physiologic tissue loss, resulting in reduction of PA values. Thus, the association of advanced age with low values of PA also imply in situations that can interfere directly in the quality of life of the patient[29,30].

Individuals with advanced cancer, as concluded by Grundmann et al.[31], and consequently high clinical staging (III/IV) can present lower values of PA when compared with healthy population. This scenario can be related to metabolic stress that the oncologic patient suffers leading to malnourishment and cachexia with possible water imbalance and alterations in the cellular membranes[31].

A study evaluating the association between PA and survival of individuals with advanced lung cancer (IIIb and IV) showed that those with PA < 5.3 (cutoff adopted for the study) had survival five times lower when compared with PA >5.3 (p=0.02)[32]. Uccella et al. concluded that reduced values of PA encountered in women with advanced ovary cancer (III and IV), resulting from alterations of the body composition, made this indicator a reliable predictor and independent from morbidity and postoperative complications[33].

While evaluating the association of PA with general survival in individuals with colorectal cancer, Mohamed Sad et al.[34] found that higher values of PA were associated with more initial stages[34]. Yasui-Yamada et al.[7] investigated the effects of PA in the survival of individuals with gastrointestinal cancer, utilizing as cutoff the lower quartile of the population and concluded that lower PA values are independent risk factors of lower survival in the long-term and this indicator is a useful, short, and long-term marker for this population[7]. Similar to the study of Axelsson et al.[9], while investigating whether PA and SPA could be used to predict the survival in individuals with head and neck cancer, the authors concluded that low values of PA and SPA were significantly associated with shorter global survival and more advanced stages, indicating that the classification TNM and PA were significant prognostic factors for survival[9].

These findings were similar to the present study where low values of SPA were associated with more advanced clinical stage. It was possible to infer that low values of SPA in individuals at more advanced stages result from the own progress of the disease, which leads to higher

metabolic expenditure, higher toxicity associated with the treatment leading to low food intake, negatively impacting the muscle adipose reserves and compromise of the cellular integrity, harming the nutritional status and quality of life of the individual with cancer.

The present study did not find significant difference (p=0.4086) between SPA and PG-SGA classification of the nutritional status, similar to another study which compared an objective method as PA with a subjective method and encountered no satisfactory association, being impossible to compare both methods[35], because PA and PG-SGA address different aspects of the nutritional status and can complement one another for an accurate diagnosis. However, in hospitalized patients, PA is able to detect both the presence of malnourishment and classify it as moderate or severe[36]. In a study investigating the association between PA and PG-SGA in individuals with head and neck cancer, 40% of this population was classified as malnourished by PG-SGA against 80% by PA[37].

The small sample mainly because of the COVID-19 pandemic is a limitation of this study, nevertheless, it was possible to find relevant associations able to guide clinical and nutritional conducts. Its originality is a strong feature bringing innovative results that may be included in the clinical and nutritional evaluation, helping the decision making for the population with cancer.

CONCLUSION

SPA correlated positively with staging in individuals with cancer. It is suggested to make it a useful and practical option to help the evaluation, prognosis, clinical and nutritional monitoring of this population.

CONTRIBUTIONS

Thalles Marciano de Santana and Márcia Marília Gomes Dantas Lopes contributed substantially for the study conception/design, collection, analysis and/or interpretation of the data, drafting and/or critical review. Isabela Naves de Sousa, Ana Beatriz Dantas Mendes and Bruna Luísa Gomes de Miranda contributed for the collection, analysis and/or interpretation of the data. Ana Carolina Lúcio Pereira da Silva and Clélia Carla de Medeiros Carvalho Azevedo contributed substantially for the study conception and/or design, collection, analysis and/or interpretation of the data. All the authors approved the version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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