Support Care Cancer (2011) 19:187–192
DOI 10.1007/s00520-009-0798-9

ORIGINAL ARTICLE

# Standardized phase angle from bioelectrical impedance analysis as prognostic factor for survival in patients with cancer

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Received: 27 July 2009 / Accepted: 8 December 2009 / Published online: 29 December 2009


**Abstract**
*Purpose* Phase angle (PA), determined by bioelectrical impedance analysis (BIA), has been considered as a prognostic factor in several clinical conditions. The purpose of this study is to investigate PA, after adjusting for sex and age (standardized phase angle; SPA) as a prognostic factor for survival in cancer patients.
*Methods* A prospective study was conducted in 195 patients before the first chemotherapy course. BIA was performed in all patients and SPA was calculated. The Kaplan-Meier method was used to calculate survival. The Cox regression method was used to evaluate the independent prognostic effect of PA after adjustment for other variables.
*Results* Patients with SPA<−1.65 had a smaller survival rate than those with SPA≥−1.65 ($p<0.001$). Using Cox regression, the mortality rate was higher in patients with SPA< −1.65 (RR 3.12 CI: 2.03–4.79; $p<0.001$). After multivariate analysis, patients with PA<−1.65 still presented a higher mortality rate (RR 2.35 CI: 1.41–3.90; $p=0.001$).
*Conclusions* The present study demonstrates that PA, used as SPA, is an independent prognostic indicator in this group of cancer patients receiving chemotherapy treatment even after adjustment for other prognostic variables.

**Keywords** Cancer · Bioelectrical impedance analysis · Phase angle · Survival · Prognostic marker · Standardized phase angle

## Introduction

Weight loss is a frequent complication in patients with cancer, and it is present in almost 85% of patients with specific kinds of tumor [1]. Not only the disease, but also side effects due to the methods used in cancer treatment can be causes of such underfeeding. The results of several studies showed that at least 20% of the people with cancer die more due to the associated cachexia during weight loss and not due to the tumor itself [2].

Historically, nutritional status has been assessed through various objectives parameters, including anthropometric and biochemical measurements, both influenced by non-nutritional factors [3]. The malnutrition can be detected earlier by the alterations on the cellular membrane and the fluids imbalance that precede the anthropometric measurement and changes in biochemical markers, which can be analyzed through the bioelectrical impedance analysis (BIA) [4].

BIA is a method for body composition assessment and it has been validated in several pathologies, including patients with cancer [5–9]. It is a quick, easy and non-invasive

This work was partially funded by CAPES, Ministry of Education, Brazil.

This study was presented as a poster in the 8th International Symposium on In vivo Body Composition Studies, New York, July 2008.

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method, which can be conducted at bedside [10]. However, this method depends on specific predictive equations for each population and its use limited in some clinic situations [11].

Phase angle (PA), one of the parameters obtained from BIA, is estimated by the direct ratio between resistance (R) and reactance (Xc). PA can be understood as a marker of the fluid distribution between the intra and extra-cellular medium and can be considered a reliable signal of malnutrition [12]. In relation to the other nutritional indicators, PA has the advantage of being useful even in those patients with fluid alterations or those who are unable to have their body weight measured. Moreover, it does not depend on regression equations to be obtained, differently from the other BIA parameters such as lean body mass.

A low PA may suggest a decrease in the cellularity, but also could stand for impairment in the function of the cell´s membrane (e.g., cellular death or poor integrity). However, a high PA suggests a huge quantity of intact cellular membrane [13]. In the last decade, several researches have shown the role of PA as a prognostic marker in several clinic situations [3, 6, 8, 12–20].

The studies in cancer patients using PA as a prognostic marker were conducted in a retrospective way and did not check patients' survival. Furthermore, until 2005 there were no published reference values for phase angle published. Barbosa-Silva et al. in 2005 and 2008 and Bosy-Westphal et al. in 2006 presented these values for American, Brazilian, and German population, respectively. The three studies showed PA variations according to age and sex [21–23]. From these reference values, it is possible to obtain standard phase angle (SPA), making the comparison among samples with different sex and age possible.

The main objective of this research is to evaluate, in a prospective way, the prognosis role of PA, used as SPA, in the survival of chemotherapy patients.

## Methodology

Patients who started a chemotherapy application for the first time at the University Hospital/FAU—Federal University of Pelotas were evaluated in a prospective way. This investigation was included in a larger study, where other outcomes were studied. The project was approved by the Ethics Committee in Research of UFPel.

Patients were invited to take part of the study if they were aged 18 or older, receiving chemotherapy for the first time and if they could lie in bed in an adequate position for BIA examination. All clinical situations that prevented the patients to be submitted to chemotherapy and the presence of edema were considered as exclusion criteria.

All the data were collected before the first chemotherapy course. Demographic data such as sex, age, and race were collected. Data related to the illness were taken from the hospital's electronic data system. Body weight was checked with a digital Filizola scale PL 150, weighing up to 150 Kg and with an accuracy of 100 g. The height was measured by a standardized technique using a metal tape measure of 200 cm and accuracy of 1 mm attached to the scale.

The social-economic level was evaluated according to the criteria of the Brazilian Economic Classification adopted by the Associação Brasileira de Empresas de Pesquisa. This criterion is based on the possession of domestic consumption assets, the presence of maids in their homes, and education level of the family's head, classifying them in five groups, from the richest (A) to the poorest (E).

BIA was performed before the chemotherapy course, using a BIA Quantum 101 (RJL Systems®) instrument, according to a standardized technique [11]. R and Xc were measured directly in Ohms (Ω) at a single frequency of 50 kHz and 800 μA. Three measurements of R and Xc were obtained. PA was calculated using the following equation: $\mathrm{PA} = \arctan(\mathrm{Xc}/R) \times (180/3.14)$ [8]. The SPA was estimated from the reference values for the Brazilian population, according to the equation: subtracting the reference PA value according to sex and age from the observed PA and then, dividing the result by the respective age and sex reference standard deviation $\mathrm{SPA} = \mathrm{PA} - \mathrm{PA}_{\mathrm{ref}}/\mathrm{s}.d._{ref}$ [22, 24]. A SPA cutoff value of −1.65 was chosen to classify the patients in two groups: low PA or not. This should be understood in the same way as $Z$ score (as used for weight and height in children). The SPA cutoff values of −1.65 stands for the fifth percentile of normal population, therefore, it can be considered as the lower limit accepted in a healthier population [25]. Comparisons among groups with different mean ages and sex distribution can be done using the same SPA cutoff (−1.65), as SPA was obtained from an already adjusted age and sex reference values.

Patients' survival was defined as the time interval between the first examination and the patient's death date, caused by any cause, or the date of the last contact or news obtained while the patient was still alive. The patients were followed up from March 2004 to May 2007.

The sample size was calculated to detect a difference of at least 5% in body weight and phase angle, evaluated in the beginning and at the end of the research, based in weight and PA averages from a previous study on surgical patients from which patients with digestive system cancer were selected [14]. The estimated sample size was 200 patients, providing an 80% power and a confidence level of 95% to the study.

Data were collected by a previously trained dietitian and were validated after double typing, using the EpiInfo 6®.

Statistical analysis was made by the Stata 9.2 (StataCorp. Texas, USA). The Kaplan-Meier method was used to analyze the survival and the log rank test to evaluate the difference between the curves. Cox regression was used to determine SPA effects on the mortality rate. In the multivariate analysis, the correlation between SPA and mortality was determined after controlling for other possible confounding factors, such as age, gender, social class, type of chemotherapy, location of the tumor, and stage. In all the tests, a value of $p<0.05$ was considered significant.

## Results

One hundred and ninety five patients were studied with an average age of 58±12.9 years old. Most of them were females (62%) and the mean phase angle was 5.12°±0.89°. Breast or gynecologic cancers (46.6%) were the most frequent types of cancer found in the study and 64.6% was receiving neo-adjuvant/adjuvant chemotherapy. Most patients were on stage I and II (41.8%). A significant difference was found in phase angle values among age, social class, chemotherapy course, and tumor stage, but not in sex, race, or site of primary tumor categories. As expected, patients with SPA<1.65 showed phase angle absolute values significantly smaller than the other group (Table 1). Most of the patients (56.9%) had body mass index (BMI) over 25 kg/m$^2$ and the mean BMI was 26.5± 5.1 kg/m$^2$. Eighty five patients (43.2%) died during the study period.

Survival curves for the two SPA groups (low PA or not) are shown in Fig. 1. Survival time between the two curves is significantly different ($p<0.001$). The average survival of low PA patients (SPA<−1.65) was 12 months, while in the group with SPA≥−1.65, the survival was at least for 3 years. At the end of the study, only 35.4% of the low PA group was still alive comparing to 66.9% of the other group. When a subgroup analysis between patients in tumor stage I/II and III/IV was performed, a significant difference in the survival was found only in patients with SPA<−1.65 in the most advanced disease group. At the end of the study, more than 75% of the patients in tumor stage I/II were alive, independently if their SPA were lower or higher than 1.65 (data not showed).

All the variables were tested in a univariate analysis, and only those with $p$ value was <0.05 were considered significant after the multivariate Cox regression, although all variables with a $p$ value <0.2 were kept in the final model (Table 2). In the univariate analysis, low SPA patients presented an especially higher mortality rate when compared to those with SPA<−1.65 (RR=3.12, CI: 2.03; 4.79). After multivariate analysis, low PA continued to be a significant determining factor of a higher mortality in this group of patients. Patients with low PA showed a relative risk 2.35 times higher for mortality ($p=0.001$) when compared to those with SPA≥−1.65.

## Discussion

The development of new screening and nutritional assessment tool is very important because they can make an earlier nutritional intervention possible. This can assure better results in the treatment, as malnutrition associated with cancer negatively affects the patients' response to the therapy and increases the incidence of side effects related to the treatment. All these facts can determine a reduction in the patients' survival. PA has been referred sometimes as a very sensible nutritional marker because it evaluates the fluid distribution between the intra and extra-cellular medium, as well as the amount of intact and healthy cellular membranes [12, 13, 24]. Maybe this fact could explain the lack of significance in the survival found in patients in the tumor stage I/II when a subgroup analyses was performed. These patients had a very much longer survival than the subgroup III/IV, and at the end of the study, more than 75% were still alive. This fact could mean that they died a long time after PA measurement; in this case, the SPA predictive effect was not so strong.

Several studies showed that PA can be considered a prognostic marker to predict survival on patients with cancer. Gupta et al. studied the association between PA and survival in patients with colorectal and pancreatic cancer at an advanced stage. Patients with colorectal cancer having PA values≤5.57° presented an average survival of 8.6 months, while those with PA>5.57° had an average survival of 40.0 months. In a sample of patients with pancreatic cancer, this survival time was 6.3 months for patients with PA<5.0° and 10.2 months to those with PA> 5.0° [3, 16].

Similar results were found on a study where patients with lung cancer were evaluated. Patients with PA<4.5° presented a survival significantly lower ($p<0.001$) than those with values higher than 4.5°, while weight loss did not have any association with survival [20].

Another study conducted on patients with HIV classified the patients according to their PA quartiles. It showed that PA could be considered as an independent prognosis marker for survival and clinical improvement [12]. In a sample of 48 patients in peritoneal dialysis was also found a higher survival with PA>6.0° than those with values lower than 6.0° ($p=0.008$) [18].

All these studies created PA risk categories using different cutoff values based on sample quartiles, with a low external validity. Once PA changes according to gender

**Table 1** Baseline characteristics and phase angle of the cancer patients ($n=195$)

| Characteristics | Percentage | Phase angle mean (SD) | $p$[a] |
|---|---|---|---|
| Sex | | | |
| Male | 38.0 | 5.04 (0.99) | 0.3 |
| Female | 62.0 | 5.18 (0.82) | |
| Age (years) | | | |
| 20-39 | 8.2 | 6.05 (0.80) | <0.001[b] |
| 40-59 | 42.6 | 5.42 (0.66) | |
| >60 | 49.2 | 4.71 (0.86) | |
| Social class[c] | | | |
| E | 5.8 | 4.91 (0.96) | 0.03[b] |
| D | 42.1 | 5.02 (0.84) | |
| C | 36.8 | 5.10 (0.95) | |
| A/B | 15.3 | 5.45 (0.62) | |
| Race | | | |
| White | 88.7 | 5.15 (0.89) | 0.2 |
| Non-white | 11.3 | 4.90 (0.86) | |
| Site of primary tumor | | | |
| Breast/gynecology | 46.6 | 5.24 (0.81) | 0.2 |
| Head neck/gastrointestinal | 26.7 | 5.12 (0.90) | |
| Lung | 13.9 | 4.92 (0.87) | |
| Others sites | 12.8 | 4.91 (1.09) | |
| Chemotherapy course | | | |
| Curative | 8.2 | 5.42 (0.72) | 0.003[b] |
| Neo-adjuvant/adjuvant | 64.6 | 5.21 (0.83) | |
| Palliative | 27.2 | 4.83 (0.99) | |
| Tumor stage | | | |
| I/II | 41.8 | 5.30 (0.75) | 0.001[b] |
| III | 38.1 | 5.12 (0.88) | |
| IV | 20.1 | 4.73 (1.05) | |
| Total | $N=195$ | 5.12 (0.89) | |

[a] $p$ value from ANOVA test for heterogeneity

[b] $p$ value from ANOVA test for trend

[c] *A/B* richest, *E* poorest

and age, and also through different populations, the use of these cutoff values makes it impossible the comparison between samples when gender and age distribution is different from the one studied [15, 21–23]. The use of standardized PA from reference values allows the use of a single cutoff value of −1.65 (corresponding to values under fifth percentile of normality) even to compare studies from different populations, with different gender and age distribution. The use of SPA obtained from reference values of each original population could be considered a way to use PA as a global prognostic marker, making them comparable in several clinical situations. This study could be considered a validation study for SPA using the reference values from the Brazilian population. The analyses were performed using SPA from the American population (data not showed) and then from the Brazilian population. The use of Brazilian reference values showed a stronger association than the American values, showing that the use of suitable reference values can improve the results.

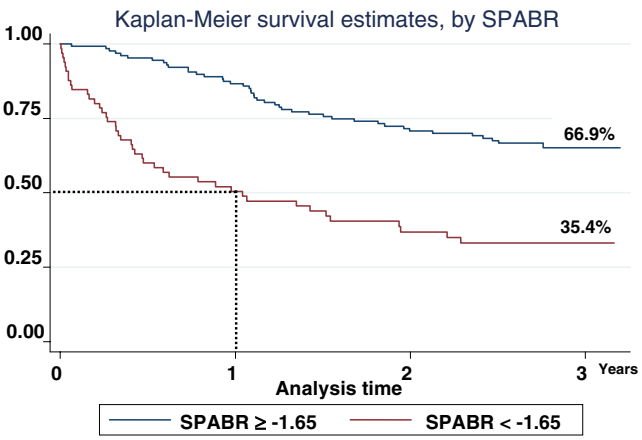


**Fig. 1** Survival curves for the two SPA groups

Some studies evaluated PA prognostic value comparing it to other commonly used nutritional parameters. In the first one, where PA was compared to other nutritional parameters as prognostic factors of post-operative complications, only PA remained associated, even after the adjusted analysis [14]. Selberg also found, after adjusted analysis, that PA was the only variable associated to

**Table 2** Univariate[a] and multivariate Cox regression analysis

| Variable | Univariate analyses | | Adjusted analyses[a] | |
|---|---|---|---|---|
| | RR[b] (CI95%) | $p$[b] | RR[c] (CI95%) | $p$[b] |
| Sex | | | | |
| Male | 1 | <0.001 | 1 | 0.5 |
| Female | 3.67 (2.38–5.66) | | 1.29 (0.64–2.60) | |
| Age (years) | | | | |
| 20–39 | 1 | 0.002[c] | 1 | 0.009[c] |
| 40–59 | 2.32 (0.71–7.59) | | 1.12 (0.31–4.00) | |
| >60 | 3.84 (1.20–12.31) | | 2.25 (0.65–7.84) | |
| Social Class | | | | |
| A/B | 1 | 0.03[c] | 1 | 0.16[c] |
| C | 1.85 (0.85–4.04) | | 2.08 (0.89–4.89) | |
| D | 2.07 (0.97–4.43) | | 1.73 (0.77–3.87) | |
| E | 3.33 (1.15–9.63) | | 3.81 (1.17–12.41) | |
| Race | | | | |
| White | 1 | 0.4 | 1 | 0.9 |
| No white | 1.30 (0.69–2.46) | | 1.06 (0.53–2.09) | |
| Site of primary tumor | | | | |
| Breast/gynecology | 1 | <0.001 | 1 | 0.001 |
| Head neck/gastrointestinal | 2.93 (1.69–5.10) | | 0.97 (0.45–1.89) | |
| Lung | 5.90 (3.25–10.72) | | 2.69 (1.38–5.23) | |
| Others sites | 2.80 (1.42–5.53) | | 2.80 (1.15–6.80) | |
| Type of chemotherapy | | | | |
| Curative | 1 | <0.001[c] | 1 | <0.001[c] |
| Neo-adjuvant/adjuvant | 1.09 (0.43–2.76) | | 2.33 (0.69–7.84) | |
| Palliative | 5.16 (2.02–13.15) | | 7.20 (2.24–23.12) | |
| Tumor stage | | | | |
| I/II | 1 | <0.001[c] | 1 | 0.08[c] |
| III | 3.18 (1.79–5.64) | | 2.27 (1.19–4.31) | |
| IV | 7.11 (3.88–13.01) | | 1.93 (0.83–4.48) | |
| Standardized phase angle | | | | |
| ≥−1.65 | 1 | <0.001 | 1 | 0.001 |
| <−1.65 | 3.12 (2.03–4.79) | | 2.35 (1.41–3.90) | |

[a] Adjusted for variables with $p$ value <0.20

[b] Test for heterogeneity

[c] Test for linear trend

survival on patients with cirrhosis, when compared to other nutritional parameters [13].

Most of the studies performed on cancer patients using PA as prognostic marker are retrospective; these studies focused some specific types of tumor and did not follow the patients since the diagnosis. Therefore, there is a need of prospective studies with a more diversified spectrum of samples. They should take into consideration the tumors location, as described here, and the patients should be evaluated since the beginning of the chemotherapy treatment. The study of these aspects may allow a better survival prediction.

One of the limitations of this research was the use of a single SPA measurement because it is a very sensitive prognostic tool, changing along time for several reasons. In the group where the patients died later (stage I/II), maybe another SPA measurement in the middle or in the last course of chemotherapy could show a better prognostic effect. Other limitation could be the use of a heterogeneous sample in which several types of tumor were analyzed together. This fact was controlled in the multivariate analyses, when SPA remained a significant prognostic factor even after controlling for the tumor's localization.

As our intention was not to compare SPA to other prognostic or nutritional factors, they were not included in the multivariate analysis. Other studies may show if SPA keeps its prognostic value after adjustment to other prognostic factors in cancer patients, as albumin and weight loss.

Although PA, here presented as SPA, has been showed to be an important marker for prognosis of survival in several clinical situations, new researches are necessary to demonstrate whether or not SPA can be modified by nutritional intervention and if this would imply in a better prognostic of the patient.

In conclusion, the present study has shown that PA, used as SPA, is a valid and independent indicator of survival for

patients with cancer receiving chemotherapy. The use of SPA shows a possibility to use an only one cutoff risk value among the studies. Further researches might demonstrate its usefulness in the initial evaluation of these patients and its modification after interventions.

**Acknowledgment** We would like to thank the Oncology Center of Hospital Escola da Universidade Federal de Pelotas (FAU), RS, Brazil.

We would also like to thank to the CAPES, Ministry of Education, Brazil, for the scholarship during this research.

**Conflict of interest** The authors have no conflict of interest to report.

**Statement of authorship** SIP conceived the study, participated in its design and coordination, performed the data analysis, and wrote the manuscript. LRB and DHS performed part of the data collection. MCG participated in the design of the study, performed the statistical analysis and data analyses, and wrote the manuscript. MCFA and AJB reviewed the manuscript. All authors read and approved the final manuscript.

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