

Bioelectrical impedance phase angle as a prognostic indicator in advanced pancreatic cancer

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Bioelectrical impedance analysis (BIA) is an easy-to-use, non-invasive and reproducible technique to evaluate changes in body composition and nutritional status. Phase angle, determined by BIA, has been found to be a prognostic indicator in several chronic conditions, such as HIV, liver cirrhosis, chronic obstructive pulmonary disease and lung cancer, and in patients undergoing dialysis. The present study investigated the prognostic role of phase angle in advanced pancreatic cancer. We evaluated a case series of fifty-eight stage IV pancreatic cancer patients treated at Cancer Treatment Centers of America® at Midwestern Regional Medical Center (Zion, IL, USA) between January 2000 and July 2003. BIA was conducted on all patients using a bioelectrical impedance analyser that operated at 50 kHz. The phase angle was calculated as capacitance (X_c)/resistance (R) and expressed in degrees. The Kaplan–Meier method was used to calculate survival. Cox proportional hazard models were constructed to evaluate the prognostic effect of phase angle independent of other clinical and nutritional variables. The correlations between phase angle and traditional nutritional measures were evaluated using Pearson and Spearman coefficients. Patients with phase angle $<5.0^\circ$ had a median survival time of 6.3 (95% CI 3.5, 9.2) months (n 29), while those with phase angle $>5.0^\circ$ had a median survival time of 10.2 (95% CI 9.6, 10.8) months (n 29); this difference was statistically significant ($P=0.02$). The present study demonstrates that phase angle is a strong prognostic indicator in advanced pancreatic cancer. Similar studies in other cancer settings with larger sample sizes are needed to further validate the prognostic significance of the phase angle.

Pancreatic cancer: Bioelectrical impedance analysis: Phase angle: Survival time

Pancreatic cancer is the fourth leading cause of cancer deaths in the USA (Rocha Lima & Centeno, 2002). Despite considerable progress in the areas of epidemiology, molecular genetics, diagnostics, operative techniques and overall patient management, the overall 5-year survival rate for pancreatic cancer is 4.4%, whereas distant stage pancreatic cancer is merely 1.6% (Rocha Lima & Centeno, 2002; Bohmig & Rosewicz, 2004).

Progressive weight loss and nutritional deterioration are commonly found in patients with pancreatic cancer (Ottyer, 1996) and a majority of patients are already in a state of malnutrition on admission (Higashiguchi *et al.* 1988). According to the National Cancer Institute's *Nutrition in Cancer Care* guidelines, timely identification and treatment of nutrition problems may improve a cancer patient's prognosis by helping the patient to gain or maintain weight, improving the patient's response to therapy and reducing the complications of treatment. As a result, identifying and treating malnutrition early in the course of the pancreatic cancer is critical to achieving favourable patient outcomes. However, this has been a significant challenge for oncologists because

of the lack of a valid and reliable tool to measure nutritional status.

Historically, nutritional status has been evaluated by various objective measures, including anthropometric (e.g. weight change, mid-arm muscle circumference, triceps skin-fold thickness) and laboratory (serum albumin, transferrin assays and N balance studies) measurements. In the clinical setting, anthropometric methods are not ideal, because they are time-consuming and difficult to perform, especially in bed-ridden patients. Some of the objective measures such as serum albumin are likely to be influenced by many non-nutritional factors (Bauer *et al.* 2002; Carney & Meguid, 2002; Waitzberg & Correia, 2003). The interpretation of these objective measures is often difficult because non-nutritional factors, such as hydration state and disease process, can obscure the effects of actual nutrient deprivation (Detsky *et al.* 1984). Furthermore, some objective indicators such as serum albumin have long half-lives, making it difficult to assess changes in the nutritional status over a short period of time. A less-used tool to assess nutritional status – bioelectrical impedance analysis (BIA) – exists, and may overcome some of these challenges.

Abbreviation: BIA, bioelectrical impedance analysis.

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BIA is an easy-to-use, non-invasive and reproducible technique to evaluate changes in body composition. BIA has been validated for the assessment of body composition and nutritional status in a variety of patient populations including cancer patients (Lukaski *et al.* 1985; Fredrix *et al.* 1990; Adami *et al.* 1993; Azcue *et al.* 1993; Marken Lichtenbelt *et al.* 1994; Chertow *et al.* 1995; Simons *et al.* 1995; Pencharz & Azcue, 1996; Chertow *et al.* 1997; Pupim *et al.* 1999; Nagano *et al.* 2000; Fein *et al.* 2002; Desport *et al.* 2003; Sarhill *et al.* 2003). BIA is based on the principle that a fixed, low-voltage, high-frequency alternating current introduced into the human body is conducted almost completely through the fluid compartment of the fat-free mass (Simons *et al.* 1995). BIA measures body component resistance (R) and capacitance (Xc) by recording a voltage drop in applied current (Zarowitz & Pilla, 1989). Bioelectric resistance is the pure opposition of a biological conductor to the flow of an alternating electric current, whereas capacitance is the resistive effect due to capacitance produced by tissue interfaces and cell membranes. Capacitance causes the current to lag behind the voltage, creating a phase shift. This shift is quantified geometrically as the angular transformation of the capacitance:resistance ratio, or phase angle (Baumgartner *et al.* 1988).

The phase angle reflects the relative contributions of fluid (resistance) and cellular membranes (capacitance) of the human body. By definition, the phase angle is positively associated with capacitance and negatively associated with resistance (Baumgartner *et al.* 1988). The phase angle can also be interpreted as an indicator of water distribution between the extra- and intra-cellular spaces, one of the most sensitive indicators of malnutrition (Talluri *et al.* 1999; Schwenk *et al.* 2000). The phase angle has been found to be a prognostic marker in several clinical conditions where cell membrane integrity is compromised and alterations in fluid balance are noted, such as HIV infection, liver cirrhosis, chronic obstructive pulmonary disease, haemodialysis and sepsis (Ott *et al.* 1995; Maggiore *et al.* 1996; Schwenk *et al.* 1998; Faisy *et al.* 2000; Schwenk *et al.* 2000; Selberg & Selberg, 2002). In the current study, we investigated whether the phase angle could provide any prognostic information in patients with advanced pancreatic cancer. The primary objective of the present study was to evaluate the association of the BIA-derived phase angle with overall survival in patients with stage IV pancreatic cancer. The secondary objective was to investigate the relationship between the phase angle and traditional indicators of nutritional status.

Materials and methods

Subjects

A retrospective chart review was performed on a consecutive case series of fifty-eight stage IV pancreatic cancer patients treated at Cancer Treatment Centers of America® at the Midwestern Regional Medical Center (Zion, IL, USA) between January 2000 and July 2003. The patients were identified from the Midwestern Regional Medical Center tumour registry. All tumours were adenocarcinomas.

Nutritional assessment

All patients underwent a baseline nutritional assessment by a registered dietitian, including laboratory measurements of serum albumin, prealbumin and transferrin, subjective global assessment and BIA. BIA was performed using a bioelectrical impedance analyser (model BIA-101Q; RJL Systems Inc., Clinton Township, MI, USA). BIA was conducted while patients were lying supine on a bed or examination table, with legs apart and arms not touching the torso. All evaluations were conducted on the patients' right side using the four surface standard electrode (tetrapolar) technique on the hand and foot (Lukaski *et al.* 1985). One electrode was placed on an imaginary line from the protruding bone on the little finger side of the wrist to bisect the ulnar head on the right hand. Another electrode was placed below the knuckle of the middle finger on the right hand. A third electrode was placed on an imaginary line from the protruding bone on the big toe side on the ankle, to bisect the medial malleolus of the right foot. The fourth and final electrode was placed just below the middle toe of the right foot. Resistance (R) and capacitance (Xc) were directly measured in ohms (Ω) at 50 kHz, 800 μ A using the BIA (RJL Systems Inc.). One assessment of resistance (R) and capacitance (Xc) was made. The phase angle was calculated using the following equation:

$$\text{phase angle} = (\text{resistance/capacitance}) \times (180/\pi).$$

Statistical analysis

All data were analysed using SPSS 11.5 (SPSS Inc., Chicago, IL, USA). Overall patient survival was defined as the time interval between the date of first patient visit to the hospital and the date of death from any cause or the date of last contact or last known to be alive. The Kaplan–Meier or product-limit method was used to calculate survival time. The log rank test statistic was used to evaluate the equality of survival distributions across different strata. A difference was considered to be statistically significant if $P \leq 0.05$. Survival time was also evaluated using univariate and multivariate Cox regression analysis. Variables evaluated included the phase angle, age at diagnosis, previous treatment history, serum albumin, serum prealbumin and serum transferrin. Variables in the multivariate models were selected with the backward elimination likelihood ratio method and with thresholds of $\alpha < 0.05$ for entry and $\alpha \geq 0.10$ for removal of variables. The correlations between the phase angle and traditional measures of malnutrition such as serum albumin, prealbumin, transferrin and subjective global assessment were studied using Pearson (r) and Spearman's rho (ρ) coefficients for normally and non-normally distributed variables respectively. For the purpose of Kaplan–Meier survival analysis, phase angle measurements were arbitrarily categorized using SPSS (SPSS Inc.) into two equal and mutually exclusive groups with a median phase angle score of 5.0° as the cut-off. For Cox regression analysis, the phase angle was used as a continuous variable.

Results

At the time of this analysis, forty-two patients had expired and sixteen were censored (reached the end of their follow-up without experiencing death). Tables 1 and 2 show the baseline characteristics of the patient cohort in greater detail. Table 3 shows the results of correlation analyses between phase angle and traditional indicators of malnutrition. There was a modest, but statistically significant, positive correlation between phase angle and albumin ($P < 0.04$), and between phase angle and prealbumin

Table 1. Baseline characteristics of fifty-eight pancreatic cancer patients

Characteristic	Categories	n	%
Gender	Male	35	60.3
	Female	23	39.7
Vital status	Expired	42	72.4
	Censored*	16	27.6
Previous treatment history	Progressive disease	32	55.2
	Newly diagnosed	26	44.8
Subjective global assessment	Well-nourished	18	31
	Moderately malnourished	20	34.5
	Severely malnourished	13	22.4
	Unknown	7	12.1
Albumin	Well-nourished (≥ 32 g/l)	34	58.6
	Malnourished (< 32 g/l)	19	32.8
	Unknown	5	8.6
Prealbumin	Well-nourished (≥ 150 mg/l)	24	41.4
	Malnourished (< 150 mg/l)	20	34.5
	Unknown	14	24.1
Transferrin	Well-nourished (≥ 2000 mg/l)	24	41.4
	Malnourished (< 2000 mg/l)	20	34.5
	Unknown	14	24.1

* Those who reached the end of their follow-up without experiencing death.

Table 2. Baseline characteristics of fifty-eight pancreatic cancer patients

(Mean values, standard deviations and ranges)

Characteristic	Mean	SD	Range	Normal range
Age at diagnosis (years)	56.2	10.7	32–82	–
Phase angle ($^{\circ}$)	5.3	1.5	2.5–10.1	–
Albumin (g/l)	34	5.3	23–43	39–50
Prealbumin (mg/l)	165	66	70–340	180–357
Transferrin (mg/l)	1963	525	200–3130	2020–3640

Table 3. Correlations between phase angle and traditional indicators of malnutrition in advanced pancreatic cancer*

(Correlation coefficients)

Variables...	Albumin (n 53)	Prealbumin (n 44)	Transferrin (n 44)	SGA (n 51)
Phase angle	0.32	0.32	0.19	-0.26
Statistical significance: P	0.04	0.04	0.25	0.10

SGA, subjective global assessment.

* For details of subjects and procedures, see Tables 1 and 2 and p. 958.

($P < 0.04$). No statistically significant correlations were found between phase angle and transferrin, and between phase angle and subjective global assessment. Table 4 shows the univariate survival analysis of different prognostic factors. The variables are rank-ordered based on their statistical strength of association with survival. The corresponding log rank scores and P values are also included. Previous treatment history had the strongest statistical strength of association with survival ($P < 0.02$). Among the nutritional indicators, phase angle was most strongly associated with survival ($P < 0.03$), followed by serum prealbumin ($P < 0.04$). Other nutritional indicators such as serum albumin, serum transferrin and subjective global assessment were not found to be statistically significantly associated with survival time.

Fig. 1 shows the survival curves stratified by treatment history. Patients with previous treatment history had a median survival time of 4.9 (95% CI 2.3, 7.7) months ($n = 26$), while newly diagnosed patients had a median survival time of 10.2 (95% CI 8.8, 11.6) months ($n = 32$). The difference was statistically significant ($P = 0.02$). Fig. 2 shows the survival curves for the two categories of phase angle. Patients with phase angle $< 5.0^{\circ}$ had a median survival time of 6.3 (95% CI 3.5, 9.2) months ($n = 29$), while those with phase angle $> 5.0^{\circ}$ had a median survival time

Table 4. Univariate Kaplan–Meier survival analysis*

Variable	Log rank score	Statistical significance: P
Previous treatment history	5.24	0.02
Phase angle	4.92	0.03
Prealbumin	4.34	0.04
Subjective global assessment	1.64	0.2
Age	1.22	0.27
Transferrin	0.55	0.46
Albumin	0.29	0.59

* For details of subjects and procedures, see Tables 1 and 2 and p. 958.

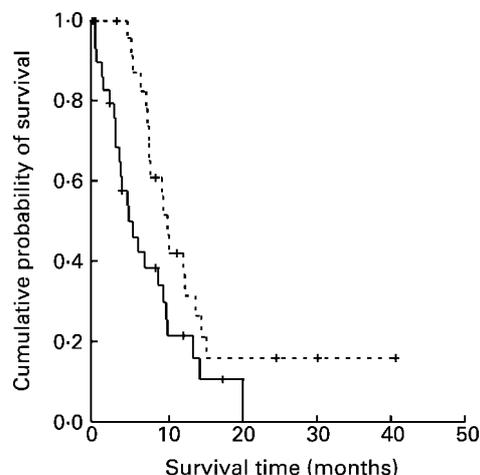


Fig. 1. Survival time stratified by previous treatment history. Each drop in a probability curve indicates one or more events in that group. - - - -, No previous treatment; —+—, previous treatment. Vertical lines indicate censored patients (those who reached the end of their follow-up without experiencing death). For details of subjects and procedures, see Tables 1 and 2 and p. 958.

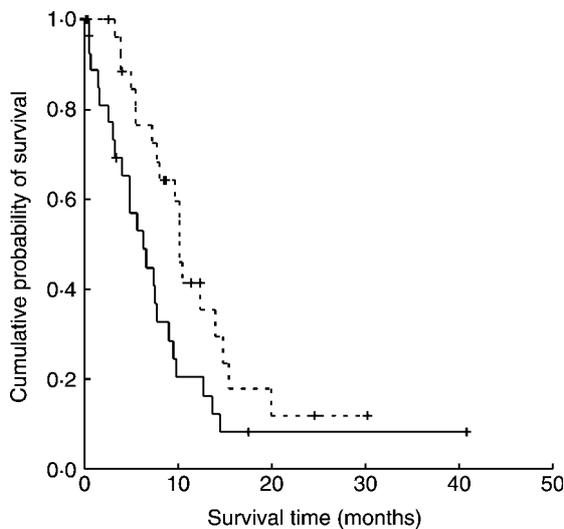


Fig. 2. Survival time stratified by phase angle categories with cut-off of 5.0°. Each drop in a probability curve indicates one or more events in that group. - - + - -, High phase angle; — + —, low phase angle. Vertical lines indicate censored patients (those who reached the end of their follow-up without experiencing death). For details of subjects and procedures, see Tables 1 and 2 and p. 958.

of 10.2 (95 % CI 9.6, 10.8) months (*n* 29). The difference was statistically significant (*P*=0.02).

Table 5 summarizes the results of univariate and multivariate Cox regression analyses. Upon univariate Cox regression analysis with survival as the endpoint, every 1° increase in phase angle was associated with a relative risk reduction of 0.75 (95 % CI 0.58, 0.96). Multivariate Cox modelling, after adjusting for prealbumin, demonstrated a relative risk reduction of 0.69 (95 % CI 0.49, 0.97) associated with every 1° increase in phase angle. Interestingly, phase angle continued to be statistically significant (*P*=0.02) after jointly controlling for serum albumin, prealbumin and previous treatment history. Cox regression modelling using the backward elimination

Table 5. Univariate and multivariate Cox proportional hazards model*

Independent variable(s)	RR	95% CI	Statistical significance: <i>P</i>
Univariate model			
Phase angle	0.75	0.58, 0.96	0.02
Multivariate models			
1. Phase angle	0.69	0.49, 0.97	0.03
Prealbumin	1.10	0.99, 1.12	0.09
2. Phase angle	0.78	0.60, 1.00	0.07
Albumin	0.59	0.30, 1.15	0.12
3. Phase angle	0.80	0.62, 1.02	0.07
Treatment history	1.80	0.93, 3.40	0.08
4. Phase angle	0.64	0.45, 0.92	0.02
Prealbumin	1.10	1.03, 1.20	0.01
Albumin	0.37	0.13, 1.10	0.07
Treatment history	1.62	0.72, 3.60	0.24
5. Phase angle	0.64	0.45, 0.91	0.01
Prealbumin	1.10	1.02, 1.20	0.01
Albumin	0.37	0.13, 1.04	0.06

RR, relative risk.

* For details of subjects and procedures, see Tables 1 and 2 and p. 958.

likelihood ratio method retained phase angle, prealbumin and albumin in the final model as predictors of patient survival.

Discussion

The identification of prognostic factors in advanced pancreatic cancer is of considerable importance for clinical management of the disease. While nutritional status has been hypothesized to have an association with survival, the published literature documenting its prognostic significance in advanced pancreatic cancer remains sparse. The current study was undertaken to investigate whether the BIA-derived phase angle, a potential indicator of nutritional status, could predict survival in advanced pancreatic cancer.

The present study demonstrated that phase angle is a more powerful predictor of survival than the traditional nutritional indices such as albumin, prealbumin and transferrin in patients with advanced pancreatic cancer. A similar study conducted in patients with advanced lung cancer stratified the patient cohort by mean phase angle 4.5°. Interestingly, patients with phase angle ≤4.5° had a significantly shorter survival than those with phase angle >4.5° (Toso *et al.* 2000). Another study conducted in HIV-infected patients stratified patients into four quartiles, with 5.3°, 5.9° and 6.5° as the cut-off points. The study found phase angle to be an independent prognostic marker of clinical progression and survival (Schwenk *et al.* 2000). In another prospective study of patients with liver cirrhosis, phase angle ≤5.4° was associated with shorter survival compared with phase angle >5.4° (Selberg & Selberg, 2002). Similarly, a prospective study conducted in forty-eight peritoneal dialysis patients found that phase angle <6° was an adverse predictor of survival time (Mushnick *et al.* 2003).

The present study raises several important but complex questions. Can phase angle be considered to be a surrogate marker of an underlying nutritional or metabolic disorder? Can phase angle be used as a nutritional assessment tool in advanced cancer? Can phase angle be altered by any direct or indirect medical or nutritional intervention with a subsequent improvement in prognosis? Some earlier studies have tried to address these questions in limited capacity. For instance, Schwenk *et al.* (2000) hypothesized that phase angle could be interpreted as a global marker of malnutrition in HIV-infected patients. In another study conducted on HIV-infected patients, it was argued that phase angle reflects the integrity of vital cell membranes (Ott *et al.* 1995). Selberg & Selberg (2002), who investigated whether phase angle could be adequate for nutritional assessment in patients with liver cirrhosis, speculated that phase angle could be a marker of clinically relevant malnutrition characterized by both increased extracellular mass and decreased body cellular mass. In advanced lung cancer, phase angle was speculated to be an indicator of altered tissue electrical properties (Toso *et al.* 2000).

As a step to further understand the clinical applications of phase angle assessment, we propose that future studies should try to address the following issues. Can phase angle be used as a prognostic indicator in patients with

other cancer types, such as breast and colo-rectal? Does phase angle continue to be a predictor of survival after patients undergo definitive treatment for their advanced cancer? Can nutritional intervention have any effect on phase angle that could possibly improve patient survival? In addition, the use of phase angle as a nutritional assessment tool needs to be validated in a variety of cancer populations, because the underlying assumptions relevant to one type of cancer might not hold true for another. The present study provides a good starting point for future research in these directions.

Limitations of the present study relate to the BIA technique and retrospective study design. The present study, because of its retrospective nature, relies on data not primarily meant for research. One potential limitation of the BIA approach is the reliance on regression models, derived in restricted samples of human subjects, which restricts the usefulness of the derived model in other patients who differ from the original sample in which the model was developed (Elia, 1993; Lukaski, 1999). However, in our present study, we evaluated phase angle, which does not depend on regression equations to be calculated, thereby eliminating a large source of random error (Barbosa-Silva *et al.* 2003). It has also been suggested that the variability of direct bioimpedance measures (resistance, capacitance and phase angle) depends on age, gender and body mass characteristics of the study population; this may limit the validity of extrapolation of the model (Elia, 1993; Dittmar, 2003). In a review paper, Foster & Lukaski (1996) argued that although the correlation between whole-body impedance measurements and body composition is experimentally well established, the reason for the success of the impedance technique is much less clear.

Some other reported limitations of using BIA for assessment of body composition are hydration status and/or major disturbances of water distribution, body position during procedure, ambient air and skin temperatures, recent physical activity, conductance of the examining table and food consumption (Anon, 1996). Since the original intent of the BIA in the present study was to gather estimates of body composition as part of a baseline nutritional assessment in a clinical setting, not all of these factors could realistically be controlled. Patients were free of visible oedema or ascites, so there was control for obvious over-hydration. Body position was controlled because all patients were in the supine position in a bed or on an examination table. Air temperature was within a controlled range in our hospital setting. Physical activity was limited in these patients due to the advanced nature of their disease. Finally, food intake was not controlled in this clinical setting, which may have contributed to a small amount of variability.

The present study did not evaluate the prognostic significance of alternative nutritional indicators such as C-reactive protein and mid-arm muscle circumference because of the lack of data on these variables. These indicators have been shown to be more practical, better understood biologically, more strongly prognostic and better indicators of nutritional status than the phase angle. The cut-off point for the phase angle in the present study was generated so as to arbitrarily divide the patient population into two equal

and mutually exclusive groups. Although our cut-off point was in agreement with those reported by other researchers in the field (Chertow *et al.* 1997; Schwenk *et al.* 2000; Toso *et al.* 2000; Selberg & Selberg, 2002), there is a clear need to define threshold values for the phase angle as a nutritional assessment tool based on large prospective studies in advanced cancer. For example, a study conducted in a large sample of haemodialysis patients found a mean phase angle of 4.82° compared with a mean value of 5.3° in our present study (Chertow *et al.* 1997). We also think that restricting the analysis to newly diagnosed patients (patients with no previous treatment history) would have been more accurate, since it would have allowed for evaluation of true overall survival time, i.e. time from the date of diagnosis to the date of death. However, doing so would have caused a significant reduction in the sample size. In our present study, the survival time was calculated from the day of first patient visit at our hospital because the BIA measurements were not available at the time of diagnosis for previously treated patients. This limitation emphasizes the need for conducting prospective studies, which have nutritional information available since the date of diagnosis. No assessment of inter-rater reliability of the users of BIA was made in the present study. This bias, however, was minimized by restricting the use of BIA to well-trained dietitians with an expertise in the use of this clinical technique. All dietitians received a minimum of 2 weeks training in the BIA technique during their orientation to the department.

In summary, our present study has demonstrated the prognostic significance of the phase angle in advanced pancreatic cancer. To the best of our knowledge this is the first study to evaluate phase angle for its prognostic importance in advanced pancreatic cancer.

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