Bioelectrical impedance phase angle in clinical practice: implications for prognosis in advanced colorectal cancer1–3

Digant Gupta, Carolyn A Lammersfeld, Jessica L Burrows, Sadie L Dahlk, Pankaj G Vashi, James F Grutsch, Sara Hoffman, and Christopher G Lis

ABSTRACT

Background: Phase angle, determined by bioelectrical impedance analysis (BIA), detects changes in tissue electrical properties and 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 receiving dialysis.

Objective: This study was conducted to investigate the prognostic role of phase angle in advanced colorectal cancer.

Design: We evaluated a case series of 52 patients with histologically confirmed stage IV colorectal cancer. BIA was conducted on all patients and phase angle was calculated. 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.

Results: Patients with a phase angle ≤5.57 had a median survival of 8.6 mo (95% CI: 4.8, 12.4; n = 26), whereas those with a phase angle >5.57 had a median survival of 40.4 mo (95% CI: 21.9, 58.8; n = 26; P = 0.0001).

Conclusion: Phase angle is a prognostic indicator in patients with advanced colorectal cancer. Similar studies of other cancer types with larger sample sizes are needed to further validate the prognostic significance of phase angle in cancer treatment settings. Am J Clin Nutr 2004;80:1634–8.

KEY WORDS Advanced colorectal cancer, bioelectrical impedance analysis, phase angle, nutritional assessment, prognostic significance, survival

INTRODUCTION

Malnutrition is a frequent manifestation of advanced cancer and is a major contributor to morbidity and mortality (1). Malnutrition is characterized by changes in cellular membrane integrity and alterations in fluid balance (2). As a result, measurement of body composition is an important component of overall nutritional evaluation in cancer patients (3–5).

Historically, nutritional status has been evaluated by various objective measures, including anthropometric (eg, weight change, arm muscle circumference, and triceps skinfold thickness) and laboratory (serum albumin, transferrin assays, and nitrogen balance studies) measurements. In the clinical setting, anthropometric methods are not ideal because they are time consuming and require well-trained staff. Some of the objective measures, such as serum albumin, have long half-lives; thus, assessing changes in nutritional status over a short period of time is challenging. A less used tool for assessing nutritional status called bioelectrical impedance analysis (BIA) can overcome some of these challenges. BIA is an easy-to-use, noninvasive, and reproducible technique for evaluating changes in body composition.

BIA has been validated for the assessment of body composition and nutritional status in various patient populations, including cancer patients (1, 4, 10–20). BIA measures body component resistance (R) and capacitance (Xc) by recording a voltage drop in applied current (21). Capacitance causes the current to lag behind the voltage, which creates a phase shift. This shift is quantified geometrically as the angular transformation of the ratio of capacitance to resistance, or the phase angle (22).

Phase angle reflects the relative contributions of fluid (resistance) and cellular membranes (capacitance) of the human body. By definition, phase angle is positively associated with capacitance and negatively associated with resistance (22). Lower phase angles suggest cell death or decreased cell integrity, whereas higher phase angles suggest large quantities of intact cell membranes (23). Phase angle has been found to be a prognostic marker in several clinical conditions, such as HIV infection, liver cirrhosis, chronic obstructive pulmonary disease, hemodialysis, sepsis, and lung cancer (23–29). The primary objective of the present study was to evaluate the association of BIA-derived phase angle with survival in patients with advanced (stage IV) colorectal cancer.

SUBJECTS AND METHODS

A retrospective chart review was performed on a consecutive case series of 52 patients with stage IV colorectal cancer who were treated at Cancer Treatment Centers of America at Midwestern Regional Medical Center (MRMC) between January 2000 and March 2003. The patients were identified from the...
Vital status [%]
Expired 24 (46.2)
Censored 28 (53.8)

Prior treatment history [%]
Progressive disease 27 (51.9)
Newly diagnosed 25 (48.1)

Tumor grade [%]
Well differentiated 3 (5.8)
Moderately differentiated 38 (73.1)
Poorly differentiated 10 (19.2)
Unknown 1 (1.9)

Age at diagnosis (y) 55.8 ± 10.8 (29–79)
Time between diagnosis and first hospital visit (mo) 9.2 ± 10.5 (0–40.8)
Height (m) 1.7 ± 0.1 (1.5–1.9)
Weight (kg) 75.1 ± 18.3 (45.3–126.8)
Lean body mass (kg) 54.1 ± 13.7 (33.6–87.1)
Fat mass (kg) 20.9 ± 11.2 (1.3–65.8)
Body cell mass (kg) 25.3 ± 7.3 (14.1–38.6)
Albumin (g/dL) 3.5 ± 1.7 (2.2–4.5)
Transferrin (mg/dL) 235.3 ± 56.4 (76–367)
Prealbumin (mg/dL) 5.6 ± 1.5 (3.2–10.7)

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MRMC tumor registry. Only patients with a histologically confirmed diagnosis of stage IV colorectal cancer were included in this study. All tumors were adenocarcinomas. The baseline characteristics of the patient cohort are shown in Table 1.

All patients underwent a baseline nutritional assessment, which included laboratory measurements of serum albumin, prealbumin, and transferrin; subjective global assessment; and BIA. BIA was performed by a registered dietitian using a model BIA-101Q analyzer (RJL Systems, Clinton Township, MI). BIA was conducted while the patients were lying supine on a bed or exam table, with their legs apart and their arms not touching the torso. All evaluations were conducted on the patients' right side by using the 4 surface standard electrode (tetra polar) technique on the hand and foot (17). R and Xc were measured directly in Ω at 50 kHz, 800 μA. One assessment of R and Xc was made. Phase angle was calculated by using the following equation:

\[
\text{Phase angle} = \frac{(R/Xc) \times (180/\pi)}{1}
\]

All data were analyzed by using SPSS 11.5 (SPSS Inc, Chicago). Patient survival was defined as the time between the date of the 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. 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 the P value was ≤0.05. Survival was also evaluated by using univariate and multivariate Cox regression analysis. Variables evaluated included phase angle, tumor grade, age at diagnosis, weight, prior treatment history, serum prealbumin, serum transferrin, serum albumin, and subjective global assessment. 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 ≥ 0.10 for removal of variables. For the purpose of this analysis, phase angle measurements were categorized by using SPSS into 2 mutually exclusive groups with a median of 5.57 as the cutoff.

RESULTS

At the time of this analysis, 24 patients had died and 28 had reached the end of the follow-period, as shown in Table 1. The univariate survival analysis of different prognostic factors is shown in Table 2. The variables are rank-ordered based on their statistical strength of association with survival. Phase angle was most significantly associated with survival, followed by patient’s age at diagnosis. Tumor grade, serum albumin, serum transferrin, serum prealbumin, weight, lean body mass, and subjective global assessment were not significantly associated with survival.

FIGURE 1. Survival stratified by phase angle categories of ≤5.57 (dashed line) or >5.57 (solid line). Each drop in a probability curve indicates one or more events in that group. Vertical lines indicate censored patients, ie, those who reached the end of their follow-up without dying.
The survival curves for the 2 categories of phase angle are shown in Figure 1. Patients with a phase angle ≤ 5.57 had a median survival of 8.6 mo (95% CI: 4.8, 12.4; n = 26), and those with a phase angle > 5.57 had a median survival of 40.4 mo (95% CI: 21.9, 58.8; n = 26); this difference was significant (P = 0.0001).

The results of the univariate and multivariate Cox regression analyses are summarized in Tables 3 and 4, respectively. In the univariate Cox regression analysis with survival as the endpoint, phase angle ≤ 5.57 was associated with a relative risk increase of 7.0 (95% CI: 2.3, 21.0). Multivariate Cox modeling, after adjustment for multiple physical and clinical variables, found phase angle ≤ 5.57 to be associated with a relative risk increase of 10.75 (95% CI: 1.92, 62.4).

DISCUSSION

The identification of prognostic factors in advanced colorectal cancer is of considerable importance for clinical management of the disease. Tumor stage remains the single most important prognostic factor in advanced colorectal cancer. The current study was undertaken to investigate whether BIA-derived phase angle, a potential indicator of nutritional status, could predict survival in advanced colorectal cancer.

This study showed that phase angle is a strong predictor of survival in advanced colorectal cancer. A similar study conducted in patients with advanced lung cancer stratified the patient cohort by a mean phase angle score of 4.5. Interestingly, patients with phase angle scores ≤ 4.5 had a significantly shorter survival than did patients with phase angle scores > 4.5 (29). Another study conducted in HIV-infected patients stratified patients into 4 quartiles, with 5.3, 5.9, and 6.5 as the cutoffs. That study found phase angle to be an independent prognostic marker of clinical progression and survival (28). In another prospective study of patients with liver cirrhosis, phase angle ≤ 5.4 was associated with shorter survival than was phase angle > 5.4 (23). Similarly, a prospective study of peritoneal dialysis patients found that phase angle < 6 was an adverse predictor of survival (30).

The present study raises several important but complex questions. Can phase angle be considered a surrogate marker of an underlying nutritional 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? Given these results, what should be the next steps in phase angle research? Some earlier studies have tried to address these questions in a limited capacity. For instance, Schwenk et al (28) hypothesized that phase angle could be interpreted as a global marker of malnutrition in HIV-infected patients. In another study of HIV-infected patients, it was argued that phase angle reflects the integrity of vital cell membranes (26). In patients with liver cirrhosis, phase angle was speculated to be a marker of clinically relevant malnutrition characterized by both increased extracellular mass and decreased body cellular mass (23). In advanced lung cancer, phase angle was speculated to be an indicator of altered tissue electrical properties (29).

As a step toward further understanding of the clinical applications of phase angle assessment, we propose that future studies address the following issues. Can phase angle be used as a nutritional and prognostic indicator in patients with other cancer types, such as breast, stomach, and pancreatic? Does phase angle

### Table 3

Univariate Cox proportional hazard model

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Unit of increase</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase angle</td>
<td>&gt; 5.57 as referent</td>
<td>7.0 (2.3, 21.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>1 y</td>
<td>1.04 (1.001, 1.1)</td>
<td>0.045</td>
</tr>
<tr>
<td>Weight</td>
<td>1 kg</td>
<td>0.99 (0.98, 1.0)</td>
<td>0.238</td>
</tr>
<tr>
<td>Lean body mass</td>
<td>1 kg</td>
<td>0.99 (0.98, 1.0)</td>
<td>0.59</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>1 g/dL</td>
<td>0.47 (0.2, 1.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>Serum prealbumin</td>
<td>1 mg/dL</td>
<td>0.99 (0.92, 1.1)</td>
<td>0.71</td>
</tr>
<tr>
<td>Serum transferrin</td>
<td>1 mg/dL</td>
<td>0.99 (0.99, 1.0)</td>
<td>0.47</td>
</tr>
<tr>
<td>Subjective global assessment</td>
<td>Well nourished as referent</td>
<td>0.61 (0.24, 1.6)</td>
<td>0.32</td>
</tr>
<tr>
<td>Tumor grade</td>
<td>Well differentiated as referent</td>
<td>26.6 (0.06, 12 264.4)</td>
<td>0.29</td>
</tr>
<tr>
<td>Treatment history</td>
<td>Newly diagnosed as referent</td>
<td>1.33 (0.57, 3.1)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

### Table 4

Multivariate Cox proportional hazard model

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Unit of increase</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase angle</td>
<td>&gt; 5.57 as referent</td>
<td>10.75 (1.9, 60.2)</td>
<td>0.007</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>1 y</td>
<td>1.0 (0.92, 1.1)</td>
<td>0.99</td>
</tr>
<tr>
<td>Weight</td>
<td>1 kg</td>
<td>0.97 (0.93, 1.0)</td>
<td>0.14</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>1 g/dL</td>
<td>4.0 (0.2, 78.6)</td>
<td>0.36</td>
</tr>
<tr>
<td>Serum prealbumin</td>
<td>1 mg/dL</td>
<td>1.03 (0.91, 1.18)</td>
<td>0.64</td>
</tr>
<tr>
<td>Serum transferrin</td>
<td>1 mg/dL</td>
<td>0.99 (0.96, 1.0)</td>
<td>0.28</td>
</tr>
<tr>
<td>Subjective global assessment</td>
<td>Well nourished as referent</td>
<td>1.42 (0.31, 6.4)</td>
<td>0.65</td>
</tr>
<tr>
<td>Treatment history</td>
<td>Newly diagnosed as referent</td>
<td>3.32 (0.68, 16.2)</td>
<td>0.14</td>
</tr>
<tr>
<td>Lean body mass</td>
<td>1 kg</td>
<td>1.02 (0.98, 1.1)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

\[ n = 52. \text{ RR, relative risk (Cox proportional hazard).} \]
continue to be a predictor of survival after patients undergo definitive treatment for advanced cancer? Can nutritional intervention have any effect on phase angle that could possibly improve patient survival? The present study provides a good starting point for future research in the above directions.

The limitations of this study relate to the BIA technique and the retrospective study design. Because of its retrospective nature, our study relied on data not primarily meant for research. One potential limitation of the BIA approach for estimating body composition is the reliance on regression models derived in restricted samples of human subjects, which thus limits the usefulness of the derived model in other patients who differ from the original sample (31, 32). However, in our study, we looked at phase angle, which does not depend on regression equations to be calculated, thereby eliminating a large source of random error (2). It has also been suggested that the variability of direct bioimpedance measures (resistance, capacitance, and phase angle) depends on age, sex, and body mass characteristics of the study population, which may limit the extrapolation of the model (31, 33). In a review article, Foster and Lukaski (34) 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 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 (35). Because the original intent of the BIA in this 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 edema or ascites, so there was control for obvious overhydration. Body position was controlled for, because all patients were in the supine position in a bed or on an exam table. Air temperature was within a controlled range in our hospital setting. Physical activity was limited in these patients because of the advanced nature of their disease. Finally, food intake was not controlled for in this clinical setting, which may have contributed to a small amount of variability.

The cutoff for phase angle in the present study was generated to divide the patient population into 2 equal and mutually exclusive groups. Although our cutoff agrees with those reported by other researchers in the field (23, 28, 29), there is a clear need to define thresholds for phase angle as a nutritional assessment tool by using receiver operating characteristic analysis based on large, prospective studies in advanced cancer. We also think that restricting the analysis to newly diagnosed patients (patients with no prior treatment history) would give more accurate results because this would allow for evaluation of true overall survival time, i.e., the 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 study, survival time was calculated from the day of the first visit at our hospital because BIA measurements were not available at the time of diagnosis for previously treated patients. This limitation emphasizes the need for conducting prospective studies, in which nutritional information is available from the date of diagnosis. No assessment of inter-rater reliability of the users of BIA was made in this study. This bias, however, was minimized by restricting the use of BIA to well-trained dietitians with expertise in this clinical technique.

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

DG was the main author of the manuscript and participated in conception, design, data collection, data analysis, and data interpretation. CAL, JLB, and SLD participated in conception, design, data collection, and writing. PGV participated in conception, design, and data interpretation. JFG assisted with the statistical analysis and data interpretation. SH participated in data collection and writing. CGL participated in conception, design, writing, and data interpretation.

DG is a Research Associate at CTCA. CAL is the Director of Nutrition at CTCA. JLB and SLD are Clinical Oncology Nutritionists at CTCA. PGV is the Medical Director of Nutrition and Metabolic Support at CTCA. JFG is a Scientific Consultant at CTCA. SH is a Cancer Research Fellow at CTCA. CGL is the Vice President of Research and Development at CTCA.

REFERENCES