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Association between Multi-Frequency Phase Angle and Survival in Patients with Advanced Cancer

David Hui, MD, MSc[1], **Rony Dev, MD**[1], **Lindsay Pimental, BSN**[1], **Minjeong Park, PhD**[2], **Maria Agustina Cerana, MD**[1], **Diane Liu, MS**[2], and **Eduardo Bruera**[1]

[1]Department of Palliative Care and Rehabilitation Medicine, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, USA, 77030

[2]Department of Biostatistics, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, USA, 77030

Abstract

Context—The ability to predict survival accurately has implications in clinical decision making.

Objective—We determined the association of phase angle obtained from multi-frequency bioelectric impedance analysis (MF-BIA) with overall survival in patients with advanced cancer.

Methods—We included consecutive patients with advanced cancer who had an outpatient palliative care consultation. MF-BIA assessed phase angle at three different frequencies (5 kHz/50 kHz/250 kHz) on each hemibody (right/left). Survival analysis was conducted using the Kaplan Meier method, log rank test and multivariate Cox regression analysis.

Results—Among 366 patients, the median overall survival was 250 days (95% confidence interval 191–303 days). The mean phase angle for 5 kHz, 50 kHz and 250 kHz were 2.2°, 4.4°, 4.2° on the right, and 2.0°, 4.2° and 4.1° on the left, respectively. For all 6 phase angles, a lower value was significantly associated with a poorer overall survival ($P<0.001$). After adjusting for cancer type, performance status, weight loss and inflammatory markers, phase angle remained independently associated with overall survival (hazard ratio 0.85 per degree increase, 95% confidence interval 0.72–0.99; $P=0.048$).

Conclusion—Phase angle represents a novel objective prognostic factor in outpatient palliative cancer care setting, regardless of frequency and body sides.

Keywords

Electric impedance; forecasting; neoplasms; palliative care; prognosis; survival

Corresponding author: David Hui, MD, MSc, Department of Palliative Care, Rehabilitation and Integrative Medicine, University of Texas MD Anderson Cancer Center, Unit 1414 - 1515 Holcombe Boulevard, Houston, TX, USA 77030, Phone: 713-606-3376, Fax: 713-792-6092, dhui@mdanderson.org.

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Introduction

In the advanced cancer setting, a patient's prognosis is an important determinant in clinical decision making. Recommendations regarding cancer treatments, palliative procedures, total parenteral nutrition and hospice admissions are dependent on a patient's expected survival (1–3). Furthermore, an accurate understanding of prognosis allows patients and families to have a sense of control, prioritize their goals in life, and prepare for the end-of-life. Although many prognostic factors and prognostic models are available, they have not used routinely in the clinical setting because of some key limitations, such as subjectivity, low accuracy and difficulty in interpretation (4, 5).

Previous studies by our group and others have demonstrated that phase angle is a novel prognostic factor in patients with advanced cancer (6–8). Phase angle is a function of cellular membrane integrity and hydration level (9). It is typically assessed using single frequency bioelectric impedance analysis (SF-BIA) at 50 Hz over the right side of the body. The development of multi-frequency bioelectric impedance analysis (MF-BIA) allows assessment of body composition at different frequencies that range from 1 kHz to 1000 kHz typically. MF-BIAs have been found in several studies to have higher accuracy and greater precision compared to SF-BIAs in assessing body composition (10–14). MF-BIA devices can also assess phase angle at different frequencies over the right and left hemibody. However, the utility of phase angle at different frequencies has not been examined in the palliative care population. A better understanding of the prognostic utility of phase angle at different frequencies may assist clinicians to estimate survival more accurately. In this study, we determined the association of 6 different phase angles (3 frequencies and 2 sides of the body) with overall survival in patients with advanced cancer.

Methods

Study Setting and Criteria

This is a retrospective study of consecutive patients who had multi-frequency BIA completed between January 1, 2012 and March 31, 2014. Inclusion criteria included diagnosis of advanced cancer, defined as locally advanced, recurrent or metastatic disease for solid tumors or progressive/refractory/incurable disease for hematologic tumors, age 18 or greater, and seen at the Supportive Care outpatient clinic. The Institutional Review Board at The University of Texas MD Anderson Cancer Center approved this study, and waived the requirement for informed consent.

Data Collection

We collected baseline patient demographics on the day of multi-frequency BIA, including age, sex, race, cancer diagnosis (most active/serious cancer if multiple diagnoses), stage and Eastern Cooperative Oncology Group (ECOG) performance status.

We assessed phase angle using the InBody720 device (Inbody, Cerritos, CA). The test procedure was conducted according to the manufacturer's instructions. Ambulatory patients stepped on the multi-frequency BIA device with bare feet and held onto the hand rails bilaterally, and remained on the device for 2 minutes. This analyzer uses an alternate current of 250mA and assesses phase angle at 5 kHz, 50 kHz, and 250 kHz. The MF-BIA device measures segmental impedances at the right arm (RA), left arm (LA), right leg (RL), left leg (LL) and trunk (TR) for all 3 frequencies. The phase angle for the each half of body at each frequency is then calculated using the following formula:

$$PA^{right} = \text{Atan}[Xc(RA+TR+RL)/R(RA+TR+RL)]$$

$$PA^{left} = \text{Atan}[Xc(LA+TR+LL)/R(LA+TR+LL)]$$

where Xc is reactance and R is resistance.

Symptom burden was assessed using the Edmonton Symptom Assessment Scale (ESAS), a validated 10-item symptom battery examining average intensity of pain, fatigue, nausea, depression, anxiety, drowsiness, and shortness of breath, appetite, feeling of well being and sleep over the past 24 hours using numeric rating scales ranging from 0 (none) to 10 (worst) (15, 16).

We also retrieved several objective laboratory-based prognostic variables that were collected within 2 weeks of phase angle, including leukocyte count, lymphocyte count, hemoglobin, serum albumin, calcium, and lactate dehydrogenase (8, 17–22).

Survival from time of multi-frequency BIA assessment was collected from institutional databases and electronic health records.

Statistical Analysis

We summarized the baseline demographics using descriptive statistics, including mean, standard deviation (SD), median, interquartile range (IQR), frequency and percentage. We examined the association between pairwise phase angle by frequency and body side using the Spearman rank correlation test.

We estimated overall survival using the Kaplan Meier method and compared among degrees of phase angle using the log rank test. We used the Contal and O'Quigley method to identify the optimal cutoff of a phase angle for overall survival.(23) We then applied this survival analysis to other laboratory variables based on pre-defined, established cutoffs from the literature, including leukocytosis (serum leukocyte >11,000/mm^3), lymphopenia (lymphocyte <1%), anemia (hemoglobin <8.0 g/dL), and neutrophil-lymphocyte ratio >3, hypoalbuminemia (serum albumin <4.0 g/dL), hypercalcemia (corrected calcium >10.2 mg/dL), and elevated lactate dehydrogenase (>618 IU/L) (18, 22).

The Cox Proportional Hazard model was used to assess the effect of phase angle on overall survival, adjusting for patient characteristics and the objective laboratory-based prognostic factors. Stepwise selection was used to build the final multivariate model that included all covariates with P-value <0.05 in univariate analysis.

All computations were carried out in SAS 9.3 (SAS Institute, Cary, North Carolina), Splus 8.2 (TIBCO software Inc, Palo Alto, CA) and R 3.1.3 (University of Twente, Enschede, the Netherlands). A P-value of <0.05 is considered to be statistically significant.

Results

Patient characteristics

Table 1 shows the baseline characteristics of 366 patients at time of multi-frequency BIA assessment. The median age was 58 (range 21–90), 168 (46%) were female, and 242 (66%) were White. The most common cancer diagnoses were gastrointestinal (N=111, 30%), breast cancer (N=50, 14%) and head and neck cancer (N=48, 13%). The median overall survival this cohort was 250 days (95% confidence interval 191–303 days). Among the patients alive, the median followup was 924 days.

Phase angle values

Table 2 illustrates the average phase angle values by frequency and body side. The values for 50 kHz and 250 kHz were comparable, although the values for 5 kHz were significantly lower.

Phase angle values between the right and left side of the body were also highly similar (Table 2). The Spearman correlation coefficient (ρ) between left and right side were 0.85, 0.91 and 0.87 for 5 kHz, 50 kHz and 250 kHz, respectively (Table 3). The lowest level of correlation was between the left 250 kHz measurement and right sided 5 kHz measurement (ρ=0.56, P<0.001). We found that phase angle was significantly associated with age, sex, body mass index at all frequencies and both sides, with the only exception at 250 kHz for sex (data not shown).

Survival analysis

Univariate analysis was conducted with cutoff based on log rank test when phase angle was analyzed by degree (Table 4). A lower phase angle was associated with worse survival in all 6 measures (Figure 1). In multivariate analysis adjusting for patient characteristics and many known objective laboratory variables, phase angle remained significantly associated with overall survival (hazard ratio 0.85 per degree increase in phase angle, 95% CI 0.72 – 0.99; P=0.048; Table 4).

DISCUSSION

To our knowledge, this is the first study to examine phase angle at different frequencies measured using MF-BIA in the palliative care setting. We found that phase angle was strongly associated with survival in patients with advanced cancer. Survival prediction was highly similar among the different frequencies and between the two sides of the body. Upon further validation, this objective, non-invasive and relatively inexpensive prognostic tool may be useful to support clinical decision making.

Multiple studies have reported that low phase angle is associated with poorer survival in cancer and non-cancer patients (8, 24–27). However, only a handful of studies have specifically focused on the advanced cancer population, in which the survival was relatively homogeneous (6, 28, 29). In a recent study by our group, we enrolled 222 hospitalized patients with advanced cancer who were seen by palliative care team for consultation. The median survival was 106 days, and lower phase angle (assessed with SF-BIA) was associated with worse survival independent of other known prognostic variables such as the Palliative Prognostic Score, Palliative Prognostic Index, lean body mass and hypoalbumenia (8). Because survival can differ substantially between patients seen by inpatient and outpatient palliative care, our current study contributes to the literature by documenting phase angle values in ambulatory palliative care setting. With median survival of 250 days, the mean phase angle was 4.4 (SD 1.0).

In contrast to single frequency BIA which is most often conducted at 50 kHz, MF-BIAs assess impedance at different frequencies ranging between 1 and 1000 kHz. Lower frequency currents (<50 kHz) generally flows through the extracellular compartment, while higher frequency currents (>200 kHz) can penetrate cell membranes and pass through lean tissues.(30) This differential tissue penetration at various frequencies allows fat free mass, total body water, intracellular water and extracellular water to be delineated and measured accurately (31, 32). Several studies reported that MF-BIA was either comparable or more accurate than SF-BIA for assessment of body composition in healthy subjects (10, 11) and patients on hemodialysis (13, 14). A meta-analysis of 16 studies also reported the MF-BIA was more accurate than SF-BIA in estimating total body water in patients with CKD (12). More studies are needed to assess the utility of MF-BIA compared to SF-BIA in assessing body composition in the oncology setting.

To date, only a handful of studies have reported the use of MF-BIA in survival prediction. O'Lone included 529 patients on peritoneal dialysis, and reported that the overhydration to extracellular water ratio was an independent predictor of mortality when the BMI and lean tissue index were included in multivariate model (33). Caravaca et al. reported that phase angle at 50 kHz was associate with mortality (hazard ratio=0.49; P=0.026) in 175 patients with chronic kidney disease (34).

To date, only a few groups have studied phase angle at other frequencies. Malecka-Massalska et al. examined phase angle at 5 kHz, 50 kHz, 100 kHz and 200 kHz in 31 patients with head and neck cancer, and reported that phase angle was also significantly lower than normal control at all frequencies (35). Moreover, phase angle significantly decreased at followup after surgery at all frequencies except 200 kHz (36). Sarode et al. examined phase angle at 20 Hz, 50 kHz, 1.3 MHz, 2.5 MHz, 3.7 MHz and 5 MHz in 100 individuals, and reported that phase angle decreased with increasing frequency (37). Given the differential tissue penetration, phase angle assessed at 5 kHz, 50 kHz and 250 kHz could potentially provide different prognostic information. We found that the phase angle values at 50 kHz and 250 kHz were comparable to each other, while the phase angle values at 5 KHz was significantly lower. There was also a high level of correlation between the left and right side of the body, which was not surprising. Importantly, a lower phase angle value was consistently associated with shorter survival, and the phase angle at the 3 frequencies provided similar level of discrimination. The implications of our findings are as follows: (1) phase angle at 50 kHz alone is a reasonable measure because it is most frequently used and reference data are available (38); (2) phase angle at other frequencies may also be informative and strongly correlate with 50 kHz, and (3) further research is needed to examine if phase angle at other frequencies outside of our range (i.e. <5 kHz or >250 kHz) remain accurate for prognostication of survival.

We recently reported that objective prognostic factors have higher accuracy than clinician prediction of survival alone, supporting the use of objective measures for prognostication (39). Here, we found that phase angle was a predictor of survival independent of many established objective laboratory markers, such as hypoalbuminemia, leukocytosis, neutrophil to leukocyte ratio, and elevated lactate dehydrogenase. This may be because phase angle assesses a different physiologic aspect than these other variables. Further studies are needed to compare the accuracy of these measures, and to derive a prognostic score based solely on objective variables that can have high accuracy.

This study has several limitations. First, the retrospective nature of data gathering means that we were not able to include several key prognostic variables such as the Palliative Prognostic Score and C-reactive protein. Second, patients need to be able to stand on the scale for a few minutes to use the Inbody 720 device. Thus, a few individuals seen at the outpatient clinic were excluded due to muscle weakness. Thus, the Inbody 720 device may not be feasible in the inpatient setting, although other MF-BIAs are available that can be conducted with patient in a supine position.

In summary, phase angle represents a novel objective prognostic factor in outpatient palliative cancer care setting, regardless of frequency and body sides. Future studies should examine how phase angle values can be used to inform both patients with advanced cancer and clinicians in decision making on the many complex issues in the last months of life, such as palliative procedures, chemotherapy and nutrition.

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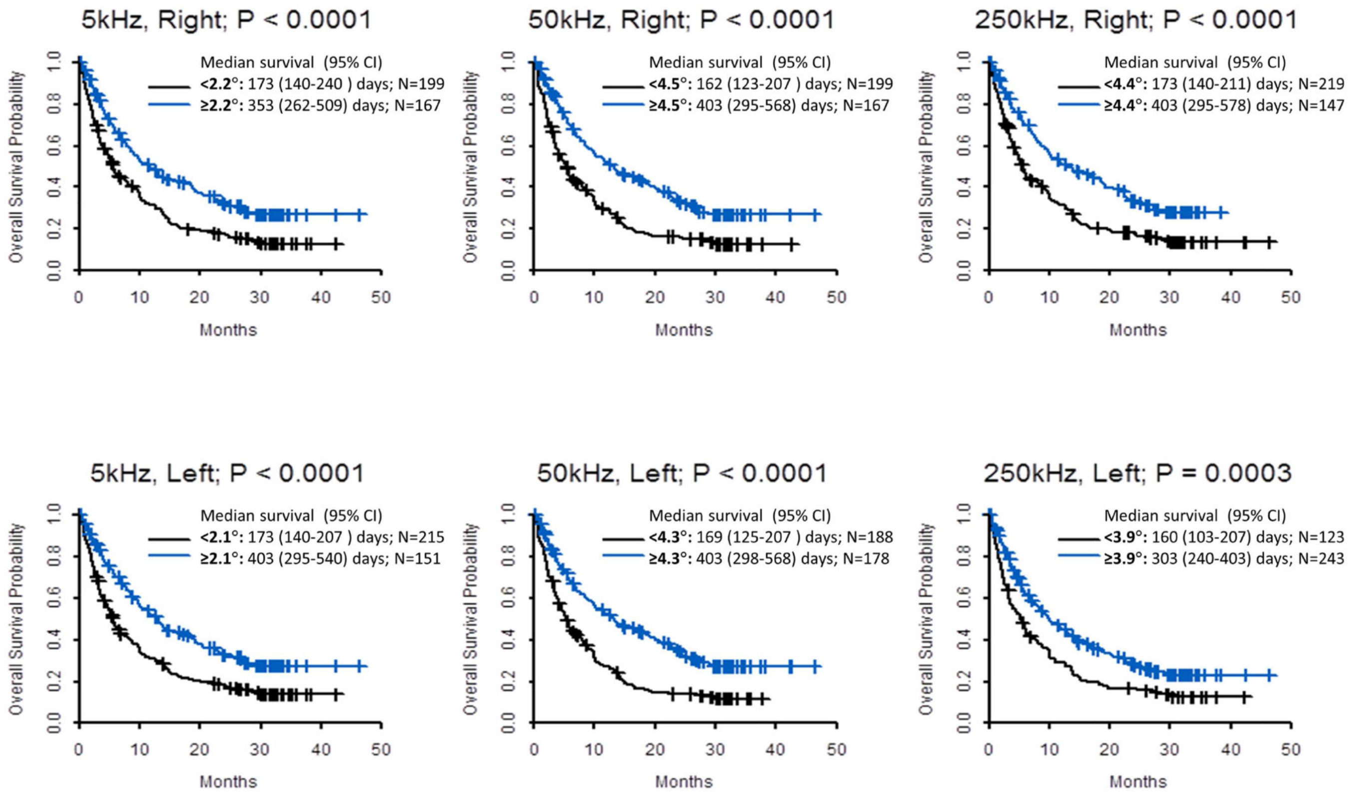

Figure 1. Kaplan Meier Survival Curves by Phase Angle

Overall survival was calculated from time of study assessment to last follow-up date or death. Cutoffs based on the Contal and O'Quigley method.

Table 1

Baseline characteristics (N=366)

Characteristics	**N (%)**[*]
Age, average (range)	58 (21–90)
Female sex	168 (46)
Race	
White	242 (66)
Black	59 (16)
Hispanic	39 (11)
Other	26 (7)
Cancer type	
Breast	50 (14)
Gastrointestinal	111 (30)
Genitourinary	20 (6)
Gynecological	34 (9)
Head and neck	48 (13)
Hematologic	8 (2)
Respiratory	40 (11)
Other	55 (15)
Edmonton Symptom Assessment Scale, mean (SD)	
Pain	4.2 (3.0)
Fatigue	5.2 (2.9)
Nausea	2.0 (2.7)
Depression	2.7 (2.9)
Anxiety	3.1 (3.1)
Drowsiness	3.5 (3.1)
Dyspnea	3.1 (3.2)
Appetite	4.7 (3.1)
Well being	4.5 (2.9)
Sleep	4.7 (2.9)
ECOG Performance status	
0–1	81 (22.6)
2	147 (41.1)
3	130 (36.3)
4	0
Percentage weight loss over past 6 months, mean (SD)	7.8 (14.6)
Serum albumin in g/dL, mean (SD)	3.8 (0.7)
Hypercalcemia (corrected calcium >10.2 mg/dL)	11 (4.1)
Lactate dehydrogenase in unit, mean (SD)	778.5 (1226.2)

Characteristics	N (%)*
Leukocytosis (serum leukocyte >11,000/mm^3)	40 (12.0)
Lymphopenia (lymphocyte <1%)	140 (42.2)
Anemia (hemoglobin <8.0 g/dL)	13 (3.9)
Neutrophil-lymphocyte ratio, mean (SD)	5.9 (7.0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group

*Unless otherwise specified

Table 2

Distribution of Phase Angle

Frequency/ hemibody	<=2° N (%)	>2–3° N (%)	>3–4° N (%)	>4–5° N (%)	>5–6° N (%)	>6° N (%)	Mean (SD)
5kHz right	161 (44)	167 (46)	27 (7)	7 (2)	2 (0.6)	2 (0.6)	2.2 (0.8)
50 kHz right	4 (1)	24 (7)	105 (29)	133 (36)	83 (23)	17 (5)	4.4 (1.0)
250 kHz right	1 (0.3)	7 (2)	122 (33)	211 (58)	23 (6)	2 (0.6)	4.2 (0.6)
5kHz left	184 (50)	163 (45)	17 (5)	2 (0.6)	0 (0)	0 (0)	2.0 (0.6)
50 kHz left	5 (1)	25 (7)	125 (34)	132 (36)	68 (19)	11 (3)	4.2 (1.0)
250 kHz left	0 (0)	9 (3)	137 (37)	201 (55)	18 (5)	1 (0.3)	4.1 (0.6)

Table 3

Correlation among Phase Angle at Different Frequencies*

Frequency/ hemibody	5kHz right	50 kHz right	250 kHz right	5kHz left	50 kHz left	250 kHz left
5kHz right	-					
50 kHz right	0.79	-				
250 kHz right	0.63	0.85	-			
5kHz left	0.85	0.80	0.63	-		
50 kHz left	0.72	0.91	0.76	0.82	-	
250 kHz left	0.56	0.78	0.87	0.63	0.84	-

* All P-values <0.0001 from Spearman Rank Correlation test

Table 4

Univariate and Multivariate Cox Regression Analysis

	Univariate analysis		Multivariate analysis*	
	Hazard ratio (95% CI)	**P-value**	**Hazard ratio (95% CI)**	**P-value**
Age (per year increase)	1.004 (0.99 – 1.01)	0.45		
Male sex (vs. Female)	0.97 (0.76 – 1.24)	0.82		
Race				
Asian vs. White	1.16 (0.69 – 1.93)	0.21		
Black vs. White	1.19 (0.86 – 1.65)			
Hispanic vs. White	1.31 (0.88 – 1.96)			
Other vs. White	2.71 (1.001 – 7.36)			
Cancer type				
Breast vs. Respiratory	0.70 (0.43 – 1.15)	<0.0001		
Gastrointestinal vs. Respiratory	1.36 (0.90 – 2.07)			
Genitourinary vs. Respiratory	0.73 (0.39 – 1.38)			
Gynecological vs. Respiratory	1.64 (0.98 – 2.74)			
Head and neck vs. Respiratory	0.39 (0.23 – 0.68)			
Hematologic vs. Respiratory	1.35 (0.56 – 3.26)			
Other vs. Respiratory	0.69 (0.42 – 1.12)			
ECOG performance status	1.77 (1.49 – 2.11)	<.0001	1.53 (1.25 – 1.89)	<0.0001
Percentage weight loss over past 6 months	0.98 (0.97 – 0.99)	0.02		
Hypoalbuminemia (serum albumin <4.0 g/dL)	2.42 (1.82 – 3.21)	<0.0001	1.71 (1.24 – 2.36)	0.001
Hypercalcemia (corrected calcium >10.2 mg/dL)	1.82 (0.85 – 3.87)	0.12		
Elevated lactate dehydrogenase (>618 unit)	2.43 (1.81 – 3.26)	<0.0001	2.18 (1.59 – 2.98)	<0.0001
Leukocytosis (serum leukocyte >11,000/mm^3)	1.55 (1.06 – 2.26)	0.02		
Lymphopenia (lymphocyte % <1%)	1.63 (1.26 – 2.10)	0.0002		
Anemia (hemoglobin <8.0 g/dL)	1.42 (0.77 – 2.60)	0.26		
Neutrophil-lymphocyte ratio >3	2.02 (1.53 – 2.66)	<0.0001	1.65 (1.20 – 2.28)	0.002
Phase angle (per degree increase)				
5kHz right	0.76 (0.64 – 0.90)	0.002		
50 kHz right	0.72 (0.64 – 0.82)	<0.0001	0.85 (0.72 – 0.99)	0.048
250 kHz right	0.65 (0.54 – 0.79)	<0.0001		
5kHz left	0.60 (0.49 – 0.74)	<0.0001		
50 kHz left	0.71 (0.62 – 0.80)	<0.0001		
250 kHz left	0.69 (0.56 – 0.84)	<0.0001		

Abbreviations: ECOG, Eastern Cooperative Oncology Group

*Covariates with P-value <0.05 were included in the multivariate Cox Regression Model, and included cancer type, percentage weight loss, ECOG performance status, hypoalbuminemia, elevated lactate dehydrogenase, leukocytosis, lymphopenia, neutrophil-lymphocyte ratio and phase angle 50 kHz right. We only entered one of 6 phase angles in the model because they were all highly correlated with each other. We selected 50 kHz right because it is most often used in single frequency assessments. Stepwise selection was used to build the final multivariate model.