

# A bioimpedance analysis of head-and-neck cancer patients undergoing radiotherapy

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## ABSTRACT

Malnutrition is a frequent manifestation in patients with head-and-neck cancer undergoing radiation therapy and a major contributor to morbidity and mortality. Thus, body composition is an important component of an overall evaluation of nutrition in cancer patients. Malnutrition is characterized by weight loss, loss of muscle mass, changes in cell membrane integrity, and alterations in fluid balance. Bioelectrical impedance analysis is a method to analyze body composition and includes parameters such as intracellular water content, extracellular water content, and cell membrane integrity in the form of a phase angle ( $\Phi$ ). Bioelectrical impedance analysis has consistently been shown to have prognostic value with respect to mortality and morbidity in patients undergoing chemotherapy. The goal of the present study was to evaluate the relationship between  $\Phi$ , time, intracellular water content, and weight for head-and-neck cancer patients undergoing radiotherapy. The results demonstrate that  $\Phi$  decreases with time and increases with intracellular water content and weight.

**Key Words** Head-and-neck cancer, radiation therapy, bioimpedance analysis, phase angle, intracellular water, extracellular water, malnutrition

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## INTRODUCTION

Head-and-neck squamous cell cancer (HNSCC) includes cancer of the oral cavity, oropharynx, hypopharynx, and larynx<sup>1</sup>. It constitutes the 7th most common malignancy in the world, and it is typically treated with external-beam radiation. Common treatment-related complications in HNSCC patients include dysphagia, mucositis, and generalized nausea<sup>1,2</sup>. Because of those side effects, daily food intake is often diminished, leading to unintentional weight loss and malnutrition. Malnutrition is a frequent manifestation in patients with advanced cancer and a major contributor to morbidity and mortality<sup>3</sup>. It is reported that, before the start of radiotherapy (RT) or chemoradiotherapy, 3%–52% of patients are malnourished<sup>1,4</sup>. During RT and chemoradiotherapy, the percentage of malnourished patients rises to 44%–88%<sup>1,5</sup>. Malnutrition in HNSCC is not only affected by radiation, it can also be further exaggerated by mechanical difficulties (swallowing or chewing, for example) resulting from mass effect or prior surgery, by poor nutrition related to heavy smoking and excessive alcohol consumption, and by the toxicities of multimodal cancer treatment such as chemoradiotherapy<sup>6</sup>.

Malnutrition is characterized by weight loss, loss of muscle mass, changes in cell membrane integrity, and alterations in fluid balance<sup>7</sup>. Body composition is an important component of overall nutrition evaluation in cancer patients<sup>7–10</sup>. However, there is no standard clinical mechanism of assessing nutrition status other than measuring current weight and attempting to quantify weight loss—a technique that is fraught with difficulty because it relies on patient memory and does not take into account nutrition status at the patient's own “baseline.” Of various available techniques, bioelectrical impedance analysis (BIA) is a method for body composition analysis. It uses parameters such as body fat mass, extracellular water content (ECW), intracellular water content (ICW), and phase angle ( $\Phi$ ). It is able to overcome the challenges of commonly used methods in nutrition evaluation such as anthropometry (weight change, arm muscle circumference, triceps-fold thickness, and so on) and laboratory measurements (serum albumin, transferrin assay, and nitrogen-balance studies). In addition, BIA is noninvasive and easily reproducible, and it can be performed quickly at bedside<sup>11,12</sup>.

Bioelectrical impedance analysis measures body component resistance and capacitance by recording a voltage

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drop in applied current<sup>8</sup>. Capacitance causes the voltage to lag behind the current, and the measurement of that lag is the  $\Phi$  shift. The shift is quantified geometrically as the angular transformation of the ratio of capacitance to resistance. The  $\Phi$  reflects the relative contributions of fluid (resistance) and cellular membranes (capacitance) of the human body, and by definition, it is positively associated with capacitance and negatively associated with resistance. That analysis suggests that a lower  $\Phi$  implies cell death or decreased cell integrity and that a higher  $\Phi$  suggests larger numbers of intact cell membranes. The  $\Phi$  for a healthy individual varies between 4 and 10 degrees<sup>9</sup>.

The bioelectrical  $\Phi$  has consistently been shown in several studies to have great prognostic relevance with respect to morbidity and mortality in various disease processes, including HIV, sepsis, breast cancer, lung cancer, and colon cancer<sup>10–16</sup>. In addition,  $\Phi$  has been found to be an indicator for cell membrane integrity, distribution of water between the intracellular and extracellular spaces, and prediction of body cell mass in various other disease conditions<sup>17–19</sup>.

Although extensive studies have been conducted on the properties of  $\Phi$  in cancer patients, no studies have looked at the changes in phase angle that occur in patients who are undergoing RT treatment for head-and-neck cancer. In the present work, we characterized changes in  $\Phi$  with time elapsed ( $t$ ) since the onset of RT treatment, with percentage ICW content ( $w$ ), and with percentage weight ( $m$ ) for head-and-neck cancer patients. The goal was to correlate those variables in terms of the overall population rather than the individuals. We extracted population statistics by performing repeated measures of  $t$ ,  $w$ ,  $m$ , and  $\Phi$  for each patient. The slopes and intercepts from univariate and multivariate linear models of those variables are normally distributed, and the means and standard deviations of the distributions are characteristic of the population.

Considering the strong association between poor nutrition and side effects of RT, BIA can be a powerful prognostic tool. The focus is to understand the changes in  $\Phi$  that occur for patients who are undergoing RT.

## METHODS

### Patients

After approval was obtained through the Research Ethics Board of BC Cancer, 20 patients were recruited for the study. All participants signed informed consent forms agreeing to participate. All patients were being treated with radical curative-intent RT, with or without concurrent chemotherapy, for head-and-neck cancer. Patients were accrued from August 2012 until July 2015. Those receiving postsurgical RT or palliative RT, those with recurrent or metastatic disease, and those with a history of irregular heart rhythm or seizure disorder were excluded. In addition, patients with an implanted electrical device (for example, a pacemaker) were excluded because of the possibility that the current induced by the impedance measurements would interfere with the device.

### BIA Measurements

The BIA measurements were performed using the BIA 450 Bioimpedance Analyzer from Biodynamics Corporation

(Seattle, WA, U.S.A.). For safety during the BIA measurements, the frequency of the alternating current is typically 50 kHz, because a small current of this frequency passing through a body is unlikely to stimulate electrically excitable tissues such as nerve cells and cardiac muscles. In practice, the magnitude of the current, about 800  $\mu$ A, is chosen to be low enough so as not to be perceived by the participant, but high enough to produce voltages that are above interfering “noise.” Thus, for the present study, we applied alternating electrical currents of 800  $\mu$ A at 50 kHz.

Measurements were made according to the standardized protocol found in the operating manual for the analyzer. In brief, participants were measured in the supine position with arms and legs abducted from the body. Four adhesive electrocardiographic electrodes were placed on the dorsum of both the wrist and the ankle on the dominant side of the body.

Three separate measurements of electrical impedance were taken, all by a member of the health care team. The first measurement was taken just before treatment on the first treatment day; the second was taken at the halfway point of the treatment course (depending on the treatment duration for each patient, this measurement was taken approximately 2–3 weeks after the start of RT); and the third was taken immediately after RT on the last treatment day. The resistance, reactance,  $\Phi$ , ICW, and ECW values were recorded for each patient at each of those time points. Data for 2 patients (patients 8 and 15) were incorrectly recorded and not analyzable, and therefore had to be omitted from further analysis and discussion. Demographic characteristics such as weight, height, age, and sex were also recorded for all subjects.

The  $\Phi$  (in degrees) was calculated using the equation

$$\Phi = \arctan (X_C / R) \times (180 \text{ degrees} / \pi),$$

where  $X_C$  is the measured reactance, and  $R$  is the measured resistance. The analyzer uses an equation developed by multiple linear regression analysis to provide an estimate of water compartments.

## RESULTS

### Patient Demographics

Table 1 presents descriptive statistics for the 20 male patients diagnosed with HNSCC who participated in the study.

### Univariate Analysis

We started with univariate linear models to describe  $\Phi$  as a function of  $t$ ,  $w$ , and  $m$ . The ICW and ECW are inversely related when they are expressed as a percentage of total body water because the ECW equals 100% –  $w$ . We therefore restricted our focus to ICW alone.

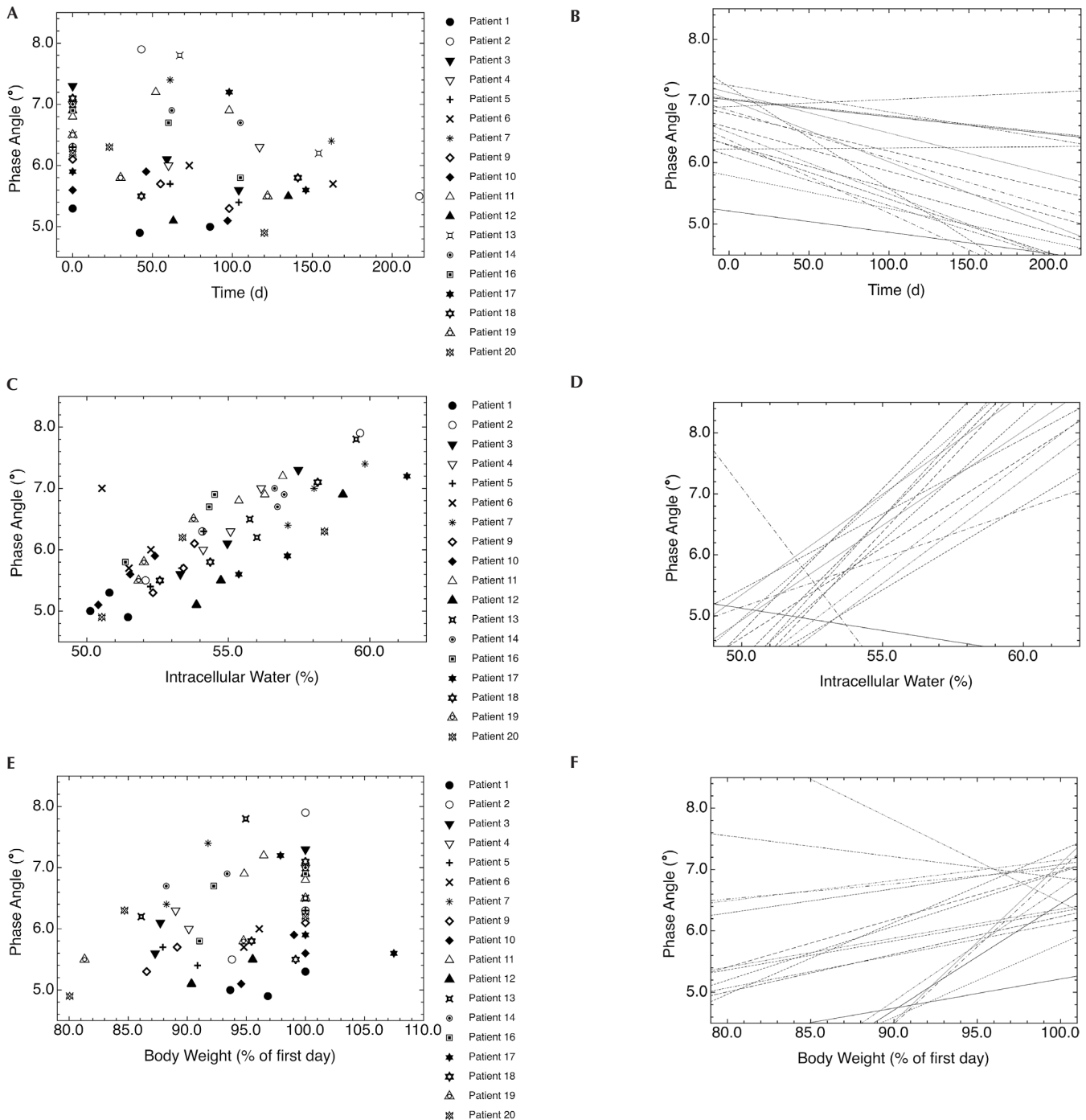
TABLE 1 Patient characteristics

Characteristic	Range	Median	Mode
Age (years)	27–77	62	56
Height (cm)	165–188	176	178
Weight (kg)	52.1–116	84.8	82

The goal of the univariate model was to determine population properties. A linear fit was determined for each patient's data, and in Figure 1, plots of the fitted lines are shown separately from the data points for clarity.

The plot of the fitted lines shows a distribution of lines with differing slopes and intercepts that is representative of our patient group. We can describe this behaviour with a hierarchical model in which the slopes are normally

distributed around a mean value  $\mu_{IG}$ , and the intercepts are normally distributed around a mean value  $\mu_{OG}$ . The mean and variance of those normal distributions are characteristic of the population. Bayesian statistical analysis is particularly useful for estimating means and variances in a hierarchical model, and we adapted code from Kruschke 2011<sup>20</sup>, which we ran using the software applications RStudio (version 1.0.136: RStudio, Boston, MA, U.S.A.),



**FIGURE 1** Univariate analysis of phase angle by time (days), intracellular water content (% of total water content), and weight (% of initial weight). (A,C,E) Data plots. (B,D,F) Plots of the fitted lines for individual patients. The purpose of the fitted line plots is to show a distribution of slopes and intercepts that are characteristic of the population and to suggest that a hierarchical model is appropriate.

R (version 3.3.3: The R Foundation, Vienna, Austria), rjags (version 4.3.0, <http://mcmc-jags.sourceforge.net>), and JMP (version 10.0.2: SAS Institute, Cary, NC, U.S.A.).

The outputs from the Bayesian models are posterior distributions for the believability of the mean values. However, those values are not independent and are negatively correlated, in that larger positive slopes tend to have larger negative intercepts. Care is therefore required to avoid choosing group slope and intercept values independently of one other. Table II sets out the mean values and the 95% highest-density intervals.

The slopes are of particular interest when they have a non-zero value, which implies a relationship between the  $\Phi$  and the predictor. In Table II, zero is excluded from the 95% highest-density intervals in all three relationships, and we can conclude that  $\Phi$  depends significantly on  $t$ ,  $w$ , and  $m$ . There is a possibility that the predictors are confounded, which could lead to misinterpretation about the relationship between  $\Phi$  and a predictor. For example, if a patient loses weight over time and the  $\Phi$  is very sensitive to  $m$ , then a significant relation will be seen between  $\Phi$  and  $t$  in addition to  $\Phi$  and  $m$ .

We formulated hierarchical models between  $w$  and  $t$ ,  $m$  and  $t$ , and  $w$  and  $m$  to determine whether any significant relationships existed. We speculated that if both  $w$  and  $m$  are related to nutrition status, then they might be correlated. The results presented in Figure 2 and Table III show that  $w$  and  $t$ , and  $m$  and  $t$ , are significantly correlated, but that  $w$  and  $m$  are not.

When looking at the behaviour of  $\Phi$ , adjustments have to be made for the interrelationships between  $t$ ,  $w$ , and  $m$ . Multivariate linear models can look at the behaviour of  $\Phi$  for any of those parameters while adjusting for the influence of the others.

The intercepts are not particularly meaningful at this point, except perhaps for predictive modelling or data simulation. Moreover, the intercepts are meaningless in some circumstances. For example, the intercept value when  $m$  is 0 has no physical meaning. That observation suggests the need to consider a shifted set of variables. The intercepts will become more important in future work when patients are compared with a control group.

### Multivariate Analysis

The multivariate approach considers fitting  $\Phi$  as a function of the other 3 parameters taken together:

$$\Phi = \beta_0 + \beta_t t + \beta_w w + \beta_m m$$

In principle, a hierarchical approach could also be used, except that, in our experiment, with 3 data points per patient and 4 parameters to fit, we are over-fitted. Patient data were pooled, and combinatorial methods were used for the analysis. Table IV shows the results.

The multilinear fit shows that  $t$ ,  $w$ , and  $m$  are all significant variables, in that none of the slopes include 0 in their respective 95% confidence intervals. The prediction for the  $\Phi$  is

$$\Phi = -6.579 - 0.002254t + 0.2072w + 0.01698m.$$

The coefficient of determination is  $R^2 = 0.698$ , and the model-fit  $p$  value is 0.0055.

## DISCUSSION

With the goal of understanding the behaviour of  $\Phi$  for a population of head-and-neck cancer patients, we used hierarchical and combinatorial linear models to study  $\Phi$  as a function of  $w$ ,  $t$ , and  $m$ . The resulting population parameters will be important for future work comparing this patient group with a control group. All 3 variables were statistically significant in predicting  $\Phi$  in both the univariate and multivariate models. Table V summarizes the univariate and multivariate slopes. The multivariate slopes are smaller in magnitude than the univariate slopes, which is not unexpected because of correlations between  $t$ ,  $w$ , and  $m$ . The  $w$  parameter shows the least relative change in slope from the univariate models to the multivariate models (Table V), reflecting the fact  $w$  has the highest correlation with  $\Phi$ . Ranking the predictor variables in terms of influence on prediction of  $\Phi$ ,  $w$  is highest, followed by  $t$  and then by  $m$ .

Our study demonstrates a change in  $\Phi$  for head-and-neck cancer patients undergoing a course of RT. The  $\Phi$  has multivariate relations with  $t$ ,  $w$ , and  $m$  such that it decreases with  $t$ , increases with  $w$ , and increases with  $m$ . As a consequence, future studies will require information about all the covariates and a minimum of 4 repeated BIA measurements and weighings per patient.

Our findings are consistent with the results of other studies that have shown the prognostic potential of  $\Phi^{21}$ . Because a great body of evidence indicates that malnutrition is a predictor of shortened survival in cancer, the association between  $\Phi$  and survival is not surprising. Malnutrition has a strong effect on the electrical properties of tissues and thus on the  $\Phi$ . That is, reduced reactance with

TABLE II Group slope and intercept values

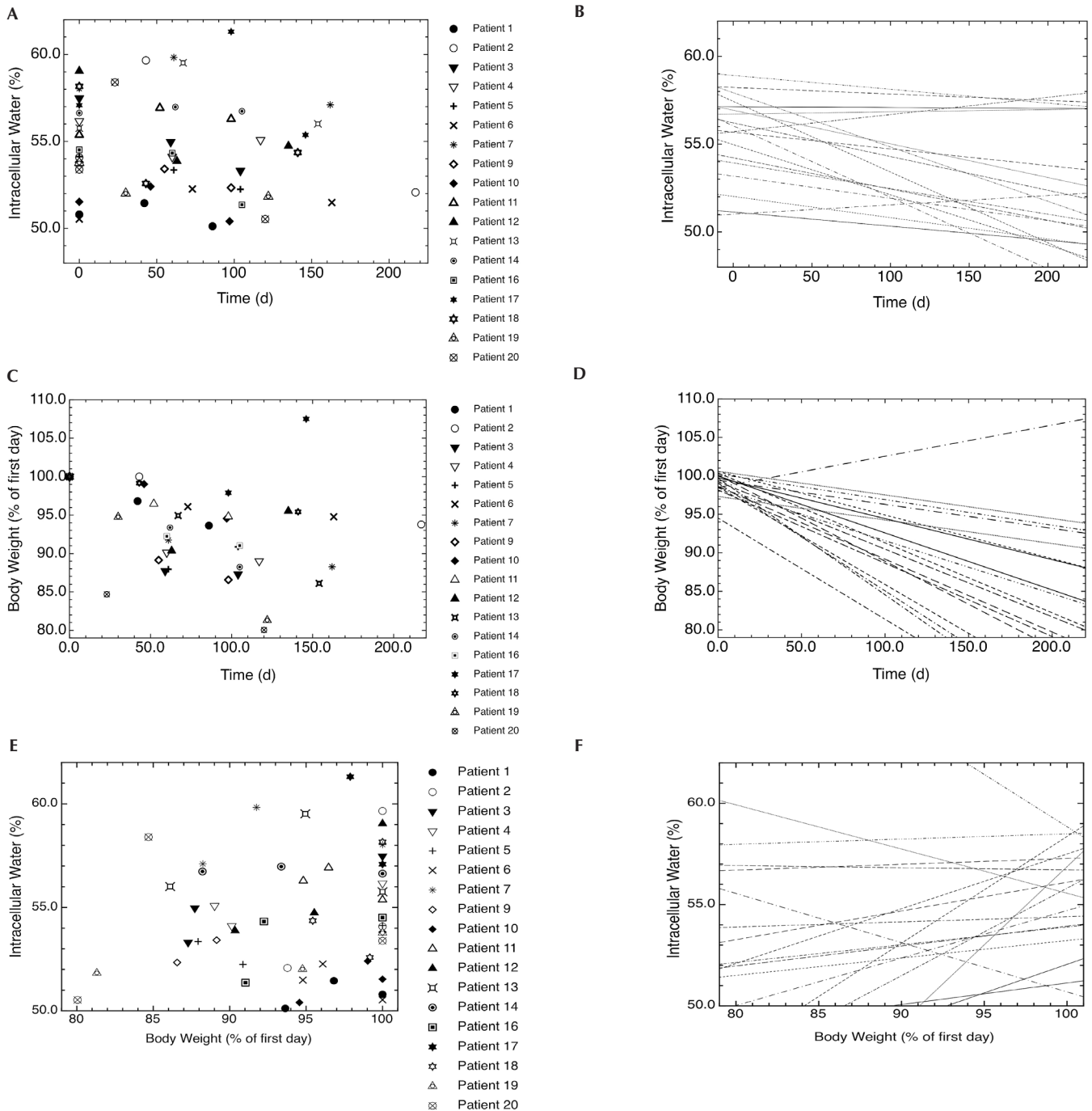
Relation	Slope		Intercept	
	Mean	95% HDI <sup>a</sup>	Mean	95% HDI <sup>a</sup>
Phase angle vs. time	-0.00634 per day	-0.00954 to -0.00319	6.572	6.232 to 6.919
Phase angle vs. ICW	0.299 per % ICW	0.236 to 0.366	-10.172	-13.644 to -6.551
Phase angle vs. weight	0.0588 per % weight	0.0202 to 0.0959	0.6367	-2.981 to 4.260

<sup>a</sup> If the 95% HDI for the slope does not contain 0, then the slope is believably nonzero and a significant relationship exists between the variables. HDI = highest-density interval; ICW = intracellular water content.

maintained resistance indicates comparable hydration, but loss of cell mass<sup>21</sup>.

Our study adds to the growing body of evidence about change in  $\Phi$  and the potential to use the BIA-derived  $\Phi$  in clinical applications such as prognostic indices, beyond body-composition equations. The biologic meaning of the  $\Phi$  is not well understood, but there is concrete evidence to prove its usefulness in reflecting a relation with cell-membrane

function and also with the ratio between  $\epsilon_{cw}$  and  $\epsilon_{cw}$ <sup>15</sup>. One study of  $\Phi$  with respect to  $\kappa T$ <sup>22</sup> recommend using a  $\Phi$  cut-off point of 5.2 as a criterion for identifying nutritional risk in pre-RT cancer patients. The diagnosis resulting from the 5.2 cut-off value was significantly associated with risk of death for patients in the sample group<sup>22</sup>. However, literature further evaluating that cut-off is limited. Despite the lack of standardized cut-off values in the literature, it is evident



**FIGURE 2** Univariate analysis of intracellular water content (% of total water content) by time (days), of weight (% of the initial weight) by time, and of intracellular water content by weight. (A,C,E) Data plots. (B,D,F) Plots of the fitted lines for the individual patients. The purpose of the fitted line plots is to show a distribution of slopes and intercepts that are characteristic of the population and to suggest that a hierarchical model is appropriate.

**TABLE III** Group slope and intercept values

Relation <sup>a</sup>	Slope		Intercept (%)	
	Mean	95% HDI	Mean	95% HDI
ICW vs. time	-0.0121 % per day	-0.0230 to -0.0012	55.25	53.92 to 56.60
Weight vs. time	-0.0707 % per day	-0.0961 to -0.0458	99.1	96.9 to 101.2
ICW vs. weight	0.0974% ICW per % weight	-0.0274 to 0.2204	45.3	33.6 to 57.3

<sup>a</sup> If the predictors ICW, weight, and time have significant relationships, then those relationships confound the interpretation of the behaviour of the phase angle with respect to those variables.

HDI = highest-density interval; ICW = intracellular water content.

**TABLE IV** Distributions of the slopes and intercepts for the multilinear fit of phase angle by time, intracellular water (ICW), and weight<sup>a</sup>

Variable	Mean	95% CI
Intercept (degrees)	-6.579	-8.016 to -5.161
Time slope (degrees/day)	-0.002254	-0.003137 to -0.001108
ICW slope (degrees/%)	0.2072	0.1899 to 0.2260
Weight slope (degrees/%)	0.01698	0.00742 to 0.02745

<sup>a</sup> Time, ICW, and weight all are significant because 0 is excluded from the 95% CI.

CI = confidence interval.

**TABLE V** Univariate and multivariate slopes for phase versus time, intracellular water (ICW), and weight

Relation	Slope		Multivariate-to-univariate ratio <sup>a</sup>
	Univariate	Multivariate	
Phase angle vs. time	-0.00634	-0.002254	0.36
Phase angle vs. ICW	0.299	0.2072	0.69
Phase angle vs. weight	0.0588	0.01698	0.29

<sup>a</sup> The ratio of the multivariate slope to the univariate slope provides a measure of the effect that the other variables have on the univariate behavior. The farther away from 1 the ratio is, the stronger the influence of the other variables.

that  $\Phi$  can play an important role as a marker of morbidity and mortality in a wide range of disease conditions, with a higher  $\Phi$  being a general indicator of wellness<sup>23</sup>.

In our patient population, we observed a downward trend in icw content of -0.0121% daily over time, with a corresponding upward trend in ecw. Changes in hydrostatic pressure, oncotic pressure, and vascular permeability can result in abnormal fluid shifts in the body, resulting in altered icw and ecw concentrations.

Being objective, noninvasive, low in cost, and simple to obtain, bioimpedance-measured parameters such as  $\Phi$ , icw, and ecw can easily be repeatedly measured during the daily clinical routine.

### Study Limitations

Our study has some limitations. First, the sample size was small, because this was a feasibility study. In future, a large number of patients should be recruited for a robust statistical analysis. Second, our analysis could benefit

from more data points per patient. We have seen evidence that a multivariate approach is necessary for analyzing the  $\Phi$  dependencies. With 4 parameters (1 intercept and 3 slopes), at least 4 measurements per patient will be required during the course of treatment. In the present work, we did not have 4 measurements per patient, and we addressed that issue by grouping the patient data and then using combinatorial techniques to analyze group behaviour. Third, the same analysis should be conducted in a control group of healthy participants with the intent to compare the  $\Phi$  between the groups. Fourth, the demographics of our patient population are narrow, although inadvertently so, with all recruited patients having been male.

Considering the importance of identifying safe ways to assess cell health and nutrition status in cancer patients undergoing treatment, parameters such as  $\Phi$ , icw, ecw, and weight should be studied periodically during the course of treatment such that, when those parameters cross a designated cut-off point, a clinical intervention can be implemented in a timely manner to potentially improve outcomes of treatment.

Further study to define clinical parameters for prognostication with BIA in RT patients is needed.

## CONCLUSIONS

In 20 HNSCC patients studied during their respective courses of RT (18 available for analysis), extensive univariate and multivariate analyses were used to determine changes in cell membrane integrity and cellular properties. Population-based parameters for  $\Phi$  can be described in a multilinear model in which the  $\Phi$  decreases with time (-0.00255 degrees daily) and increases with icw content (0.2072 degrees per percentage point) and weight (0.01698 degrees per percentage point). The multivariate relationship between  $\Phi$ ,  $t$ ,  $w$ , and  $m$  requires the acquisition of data for all those covariates in future studies of cancer patients and control groups.

### CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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