JOURNAL OF PALLIATIVE MEDICINE
Volume 12, Number 11, 2009

DOI: 10.1089/jpm.2009.0093

Original Articles

Estimating Survival in Patients with Cancer Receiving Palliative Care: Is Analysis of Body Composition Using Bioimpedance Helpful?

Gregory Brian Crawford, M.B.B.S., M.D.,[1] Julie Ann Robinson, Ph.D.,[2]
Roger Wayne Hunt, B.M.B.S., M.D.,[1] Neil Brenton Piller, Ph.D.,[3] and Adrian Esterman, Ph.D.[4]

Abstract

Background: This research investigated whether bioimpedance spectroscopy (BIS) has the potential to improve prognostication in an outpatient clinic for patients with cancer receiving palliative care.
Methods: Survival time, and BIS measures of basal metabolic rate and 11 body composition parameters (extracellular fluid [ECF], intracellular fluid [ICF], ratio of ECF to ICF, fluid in trunk and each arm and leg, protein mass, mineral mass, and percent body fat) were recorded for 84 oncology patients.
Results: None of the BIS measures showed a linear association with survival time. However, threshold values associated with short survival were identified for basal metabolic rate and 6 of the body composition measures related to fluid (ECF, ratio of ECF to ICF, fluid in right and left arms, and right and left legs). In addition, almost all patients who died within 6 weeks of assessment reached the threshold values for ECF and/or ECF:ICF ratio.
Conclusion: Results confirm that elevated metabolic rate and accumulation of body fluid are indicators of a poor prognosis in patients with cancer receiving palliative care. Because BIS is simple for clinicians to use, is noninvasive, and allows early detection of these parameters, it has the potential to improve prognostication.

Introduction

An accurate estimate of survival time for patients with a life-limiting illness is desirable for optimal treatment and counseling of patients and their families.[1] For example, more accurate assessment of the individual's prognosis can improve decision making about active versus palliative treatments, and enables the timely preparation for an anticipated death. In addition, health expenditure escalates exponentially in the last months of life, and improved prognostication promotes more efficient use of limited health care resources.[2] Accurate prognosis is particularly important in countries such as Italy, the United States, and the United Kingdom, which use estimates of survival time to determine patients' access to hospice care and welfare benefits.[3] However, currently, clinicians' estimates of prognosis are often inaccurate.[3–7]

Ideally, there would be an inexpensive, quick, and noninvasive way to improve the accuracy of prognosis. Studies suggest that bioimpedance spectroscopy (BIS) might offer such a promise.[8–13] BIS examines the drop in voltage when a constant alternating current flows through the human body. The impedance of the current has two components: resistance, which is the opposition to the current flow in body fluids and reactance, which is the opposition to current flow due to cell membranes and the interfaces of tissues.

There have been three broad approaches to the use of bioimpedance in prognosis. Some researchers focus on phase angle, which refers to the lag of the current behind the voltage and is an index of cell integrity[14]; others focus on resistance and reactance.[15,16] These measures are dependent on the frequency of the current.[17] The third approach uses an arithmetic transformation to relate patterns of impedance in a range of different current frequencies to parameters of body composition (e.g., fat, extracellular fluid) with high accuracy and reproducibility.[15,18] Unlike other bioimpedance measures, body composition data are provided in units (liters, kilograms) that are easily understood by clinicians and patients and have obvious clinical relevance. Therefore, this study used BIS to measure body composition.

Many patient factors have a demonstrated relationship with survival time.[19] These include dyspnea and drowsiness,[20,21]

[1]Discipline of Medicine, The University of Adelaide, Adelaide, South Australia, Australia.
[2]School of Psychology, [3]School of Medicine, Flinders University, Bedford Park, South Australia, Australia.
[4]School of Nursing and Midwifery, University of South Australia, Adelaide, South Australia, Australia.
Accepted June 5, 2009.

site of primary tumor, weight loss,[22] edema,[23,24] changes in performance status,[25,26] serum albumin, and lactate dehydrogenase.[22] Nevertheless, available prognostic tools have limited sensitivity and specificity.[19,27–31]

No prior published studies have examined the usefulness of body composition measures obtained from BIS for prognosis in cancer patients receiving palliative care. However, BIS can detect differences in body composition between patients with and without cancer.[32] In addition, body composition assessed by bioimpedance[33–36] or other methods[37] predicts survival time for patients with several nonmalignant illnesses. BIS has two unique advantages when measuring body composition. First, it provides information that cannot be discovered from a physical examination. For example, a physical examination is of limited value in identifying whether weight loss reflects a loss of mineral, muscle, fat, fluids or a combination of these. However, BIS provides separate measures of each of these parameters. Second, changes in body composition that can be discovered by physical examination can be detected earlier using BIS. For example, BIS detects abnormal extracellular fluid accumulation up to 10 months before edema is apparent on clinical examination.[18]

Multifrequency BIS can also be used to estimate basal metabolic rate. No previous studies have examined whether there is an association between such estimates and survival time in patients with advanced cancer. However, when metabolic rates are assessed by other means, elevated rates are associated with shorter survival time in patients with cancer[38] and some nonmalignant diseases.[39]

This research investigated whether BIS has the potential to improve prognostication in an outpatient clinic for patients with cancer receiving palliative care by examining the relationship between patients' survival time and BIS measures of basal metabolic rate and a range of body composition parameters. Because previous research has shown that other BIS measures taken at a single time point[11] and changes over time in some BIS measures[40] are predictors of survival time, it was predicted that between-patient differences in BIS measures of body composition would be associated with differences in the survival time. The original plan was to take repeated measures of body composition to also assess the relationship between survival time and within-patient changes in body composition. It was hypothesized that changes in body composition within an individual patient would be more informative than a single assessment. However, due to rapid decline and death of patients, it was possible to obtain repeated BIS measures for only half the sample. These patients were often assessed long before their death, when abnormal values for body composition parameters would not be expected. In particular, this study tested the prediction that patients with high amounts of body fluid and low protein mass would have a shorter survival time than other patients.

Method

Participants

All participants had advanced cancer and had been referred to a specialist palliative care service. The health system in which the study took place allows such referrals not only for patients requiring end-of-life care, but also for those with life-limiting illnesses who do not have a short estimated survival time if management of complex symptoms or multidisciplinary co-ordination for complex circumstances is required.

Inclusion criteria were fluency in English, age over 18 years, and a judgement by their primary medical specialist that they were in the palliative phase of their illness, showed no severe cognitive impairments and were sufficiently robust to tolerate a 40-minute research interview. (The lengthy time commitment was not due to the bioimpedance measures but because this study was part of a larger project looking at a range of possible prognostic indicators in patients with advanced cancer.)

One hundred and fifteen patients attending outpatient oncology and palliative care clinics at two teaching hospitals in Adelaide, Australia, were identified as being eligible. A research nurse who was not associated with patient care approached 103 of these patients. Four patients declined to participate (3.9%), 15 were recruited to the study but did not participate due to physical decline (14.6%), and 84 participated in the study (81.6%). The analyses are based on the 78 participants who have since died. More than 90% of the patients were Caucasian. None of the participants were receiving artificial hydration.

The study was approved by the relevant university and health service ethics committees and all participating patients provided informed consent.

Measures

Data were collected immediately after the patients' scheduled clinic visits by the research nurse.

Bioimpedance measures were obtained using an InBody 720 (Biospace Ltd., Seoul, Korea). This is a multifrequency (5–500 kHz) analyzer that provides measures for the whole body, and separate measures for the four limbs and trunk. The electrodes were applied to eight contact sites (two points on each hand and each foot). Equations are based on segmental bioimpedance analysis first developed and validated by Cha et al.,[41] which assumes the body can be divided into five cylindrical conductors. Many studies have demonstrated the reliability and validity of BIS in measuring body fluid in healthy adults and medical patients.[11,13,42,43] The current study assessed basal metabolic rate and 11 body composition parameters: extracellular fluid (ECF), intracellular fluid (ICF), ratio of extracellular fluid to intracellular fluid (ECF:ICF), fluid in trunk and each arm and leg, protein mass, mineral mass, and percent body fat. All measures except percent body fat, ECF:ICF ratio and basal metabolic rate were adjusted for patient height.

Statistical analysis

We explored two lines of inquiry. The first examined whether there were linear relationships between BIS measures and survival time. Since all patients had died by the end of follow-up, survival time was not censored. Spearman correlation was used to assess the relationship between survival time and BIS measures, while the exact Kruskal-Wallis H procedure was used to examine differences in survival by groups of patients with high, low, and intermediate BIS scores. Logistic regression was used to determine predictors of survival time, after this dependent variable had been dichotomized. The second, exploratory line of inquiry used visual inspection to identify possible nonlinear relationships

between BIS measures and survival, such that thresholds or tipping points could be identified. These relationships were then tested using Fisher's exact test.

With respect to the power of statistical analyses, a sample of 47 patients would allow detection of correlations between survival time and BIS parameters that were of a magnitude likely to have clinical significance ($r > 0.40$) with 80% power and $\alpha = 0.05$. However, it was anticipated that the distribution of data for BIS variables would often be skewed. Because this was likely to inflate the type I error rate and require the use of less powerful nonparametric statistics, a larger sample size was sought.

Analyses were undertaken using the SPSS 15.0 statistical package (SPSS Inc., Chicago, IL).

Results

Table 1 shows the gender and primary diagnosis for participants. The mean age of participants at the first visit was 65.9 years (standard deviation [SD] = 10.8 years). Patients were recruited in a health care system that promotes the early referral to palliative care of patients with noncurable malignancy and unmet needs. Thus, while the median survival from the date of first assessment was less than 6 months (22.0 weeks), a large percentage of patients had lengthy survival times (range, 0.3–230 weeks).

Preliminary analyses indicated that there was no relationship between survival time and either gender or primary site of malignancy. Hence, data were pooled across these variables in all subsequent analyses.

There was no linear relationship between any BIS measure and survival time. Spearman correlations showed no relationships between the rank order of patients on any BIS measure and the rank order of their survival time (all ρ values <0.14). Kruskal-Wallis tests found no differences in survival time between four groups of approximately equal size formed on the basis of higher and lower scores for body composition measures (all $\chi^2 < 6.0$, all $p > 0.15$).

Nonlinear relationships between BIS measures and survival were examined in a planned exploratory analysis. Data were sorted in order of ascending survival time. Where possible, values in BIS data that appeared to differentiate patients with longer and shorter survival were identified using visual inspection (Table 2). Such potential threshold values were identified for 9 body composition measures (ECF, ICF, ECF:ICF ratio; fluid in legs, fluid in arms, fluid in trunk, percentage body fat) and basal metabolic rate (Table 3). Fisher exact tests confirmed that 7 of these thresholds predicted survival time of 6 weeks or less: ECF ($p = 0.024$), ECF:ICF ratio ($p = 0.024$), fluid in right ($p = 0.045$) and left arms ($p = 0.019$), right ($p = 0.026$) and left legs ($p = 0.011$), and basal metabolic rate ($p = 0.033$). There was a strong relationship between whether a patient met the thresholds for ECF and/or the ECF:ICF ratio and their survival time, χ^2 (3) = 14.7, $p = 0.002$ with Yates correction (Table 4).

However, it appears that measures of body water are overlapping. For example, all patients with scores over the threshold for ECF:ICF ratio ($n = 22$) also had scores for fluid in both legs and/or both arms over the relevant thresholds. When all measures of body water were included in a logistic regression predicting survival time of 6 weeks or less, only the ECF:ICF ratio was a significant predictor (Wald(1) = 4.22, $p = 0.04$).

Table 1. Patient Characteristics ($N = 84$)

Characteristics	%
Males	63
Primary malignancy	
Lung	25
Colorectal	20
Prostate	10
Pancreas	10
Unknown primary	8
Hematologic	6
Upper gastrointestinal tract	6
Melanoma	4
Other urologic	4
Breast	4
Liver and bile dust	4
Adrenal gland	1

Table 2. Demonstration of Method of Identifying Thresholds by Visual Inspection: ECF:ICF Ratios for First Thirty-Five Participants Ranked in Order of Ascending Survival Time

Survival time	*ECF:ICF ratio*
6 weeks or less	**0.65**
	0.83
	0.62
	0.49
	0.54
	0.61
	0.60
	0.52
	0.63
	0.68
7 to 12 weeks	0.59
	0.56
	0.51
	0.68
	0.56
	0.68
	0.61
	0.57
	0.65
	0.53
	0.64
	0.60
	0.53
	0.50
	0.68
	0.55
13 to 26 weeks	**0.65**
	0.57
	0.58
	0.55
	0.50
	0.59
	0.57
	0.57

Values under the threshold are marked in bold.
ECF, extracellular fluid; ICF, intracellular fluid.

TABLE 3. RELATIONSHIP BETWEEN BODY COMPOSITION MEASURES AND SURVIVAL TIME FROM BIOIMPEDANCE ASSESSMENT

	% patients meeting threshold			
Bioimpedance measure	*≤6 weeks* n = *10*	*7–12 weeks* n = *16*	*13–26 weeks* n = *19*	*27 weeks+* n = *33*
Total body water				
Extracellular fluid /height (L/cm) >0.09	60.0	37.5	21.1	18.2
Intracellular fluid /height (L/cm) <0.11	30.0	25.0	10.5	12.1
Extracellular: intracellular fluid >0.6	60.0	43.8	10.5	21.2
Segmental fluid distribution				
Right arm fluid/ height (L/cm) >0.15	50.0	31.6	31.6	24.2
Left arm fluid/ height (L/cm) >0.15	50.0	25.0	26.3	24.2
Right leg fluid/ height (L/cm) >0.40	60.0	37.5	21.1	24.2
Left leg fluid/ height (L/cm) >0.40	60.0	37.5	15.8	21.2
Trunk fluid/height (L/cm) >0.12	50.0	6.3	21.1	21.1
Body composition				
% body fat <17	30.0	25.0	10.5	12.1
Protein mass/height (kg/cm) >0.10	30.0	18.8	21.1	6.1
Mineral mass/height (kg/cm) >0.20	50.0	25.0	21.1	15.2
Basal metabolic rate (kcal) >1600	50.0	25.0	15.8	15.2

Discussion

This research investigated whether BIS had the potential to improve prognostication in an outpatient clinic for patients with cancer receiving palliative care. To do this, it assessed the relationship between a range of measures yielded by BIS and patients' survival time. It introduced a number of innovations. First, it used BIS to assess basal metabolic rate and body composition. Body composition measures are easy-to-understand for both patients and clinicians. In contrast, most previous research involving cancer patients has used BIS to measure overall body resistance and reactance to electrical current, or phase angle.[11–13,16,17,44] Second, the study explored both linear and nonlinear relationships between body composition measures and survival time. Third, the sample included patients with a very wide range of survival times. In particular, the sample included a natural comparison group in the large percentage (47%) of patients who survived for longer than 6 months.

In our study, one-off BIS measures of basal metabolic rate and several measures of body composition showed no linear relationship with survival time. This is consistent with previous research using other bioimpedance measures.[12,44] In contrast, this study identified nonlinear, threshold relationships or tipping points that may be important markers of the trajectory of illness. Similar threshold effects have been shown in the relationship between survival time and other patient factors[7,31] and other bioimpedance measures.[11–13,44] Basal metabolic rate and six measures of body composition, all of which relate to fluid (ECF, ratio of ECF to ICF, fluid in right and left arms and right and left legs), showed significant nonlinear relationships with survival time.

TABLE 4. RELATIONSHIP BETWEEN SURVIVAL TIME AND THRESHOLDS FOR EXTRACELLULAR FLUID AND THE RATIO OF EXTRACELLULAR FLUID TO TOTAL BODY FLUID

Survival time	*% Patients with ECF >0.09 or ECF:ICF ratio >0.6*	n
6 weeks or less	90.0	10
7–12 weeks	60.0	16
13–26 weeks	26.3	19
More than 26 weeks	30.3	33

ECF, Extracellular fluid, ICF, Intracellular fluid.

Thus, the prediction that patients with high amounts of body fluid have a shorter survival time than other patients was supported. Previous research has also found peripheral edema to be an important predictor of survival,[45] and the association between clinical edema and survival has led to its inclusion in both the Palliative Prognostic Index[24] and the Cancer Prognostic Score.[23] Although edema can be detected through a physical examination, BIS is able to detect fluid changes before these are clinically manifest.[43] In addition, previous findings show that higher basal metabolic rates were associated with shorter survival.[38,39] Through early identification of edema and estimation of basal metabolic rate, BIS has potential as a prognostic tool.

The prediction that patients with low protein mass had shorter survival time than other patients was not supported. One-off measures of protein, mineral and fat were not associated with survival. However, temporal changes in these parameters may be more informative than single-point measures and may warrant further investigation.

The present study had limitations. All statistically significant results were found in planned exploratory analyses. These analyses were based on a small sample size and need to be confirmed through hypothesis testing. In addition, BIS measures that were not included in the present study have also shown relationships with survival.[9,11–13,35,40,44] Unlike the machine used in this study, the most recent BIS machines can provide these other measures in addition to body composition and metabolic rate. We recommend that future studies use the full complement of BIS output variables now available: body composition, metabolic rate, resistance, reactance, F function, and phase angle and its shift. Another shortcoming of this research was that sufficient data for an-

alyses were available only for a single point in time. Changes in body composition and metabolic rate identified through repeated assessment, may offer better prognostic information. It would also be useful for future research to use multivariate modeling to determine whether these BIS parameters improve prediction over that obtained using usual prognostic factors (e.g., weight loss, serum albumin), which were not measured in this study.

In conclusion, BIS appears to have potential in predicting survival time in patients with advanced cancer. In this study, measures of body water and basal metabolic rate were associated with survival time. Because BIS can detect body composition changes before these are clinically manifest, and provides a simple way for clinicians to assess basal metabolic rate, it has the potential to improve prediction of survival time.

Acknowledgments

This research was funded by the National Health and Medical Research Council, Australia. This research would not have been possible without the contribution to recruitment and data collection of our dedicated research nurses, Ms. Libby Heinsohn-Deer and Ms. Beverley Heidenreich. We also thank A/Prof. Tim Price for his assistance in recruitment and data collection. Finally, we thank the patients and staff of Lyell McEwin and The Queen Elizabeth Hospitals, South Australia, for the generous contribution of their precious time and energy.

Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Gregory Brian Crawford, M.B.B.S., M.D.
Discipline of Medicine
The University of Adelaide
Calvary North Adelaide Hospital
89 Strangways Terrace
North Adelaide
South Australia 5006
Australia

E-mail: gregory.crawford@adelaide.edu.au