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# Bioelectrical Impedance as a Diagnostic Factor in the Clinical Practice and Prognostic Factor for Survival in Cancer Patients: Prediction, Accuracy and Reliability

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#### Abstract

Bioimpedance analysis could provide a clear figure about changes in cells and tissues based on frequencydependent changes, due to their electrical resistances for the applied electrical current. This review explains the physical principle of bioimpedance. And to monitor the progression of radiation induced tissue injury, particularly in radiotherapies. The interaction of radiation with the biological tissues and a prediction for their earlier and later alterations due to exposure are discussed. As well as, an overview for tissue identification by bioelectrical impedance analysis (BIA) is proposed. Bioimpedance analysis "applications and its limitations" in the health care, clinical practice and prognosis of overall survival in cancer patients are discussed.

**Keywords:** Phase Angle (PhA); Body Mass Index (BMI); Fat-Free Mass (FFM); Extracellular Fluid (ECF); Intracellular Fluid (ICF); Estimated Blood Loss (EBL)

# Introduction

Bioelectrical impedance analysis (BIA) is a simple, inexpensive, quick and non-invasive technique for measuring body composition. "Impedance" is a physical variable describing the resistance characteristics of an electrical circuit in the presence of an alternating current between electrodes located in a circumference surrounding the studied object. Thus, it reflects global opposition to the passage of current [1]. Using bioelectrical impedance analysis as a diagnostic tool to examine the electrical characteristics of tissues provides information on a noninvasive and continuous basis, at the patient bedside without need for radiological investigations. Mathematically, the bioelectrical impedance is represented as a complex number comprising a real component (resistance) and an imaginary dimension (reactance) [1]. The electrical impedance (Z) consists of two components, resistance (R) and reactance (Xc). Resistance is a measure of total body water and reactance a measure of BCM. From the determined impedance a number of BIA parameters can be estimated [2]. Body Cell Mass (BCM), consists of all cells that have an effect on metabolism % BCM in FFM, extra cellular mass (ECM), extracellular water (ECW), fat-free mass (FFM), fat mass (FM), total body water (TBW) [3-6]. The impedance unit is the ohm  $(\Omega)$ , when this variable is applied to biological tissue we speak of "bioimpedance" [1]. In this context, it is very important to note that the biological tissues have complex electrical impedance. And that is dependent on the frequency of the electrical applied field and tissue cellular structure. Therefore, the electrical impedance of tissue is a function of its structure and it can be used to differentiate normal and cancerous tissues in a variety of organs. Bioimpedance analysis could apply easly and rountely in the arm, trunk, and leg and from wrist to ankle (Figure 1). One of the most important applications of the BIA is its use as a prognostic tool for overall survival, particularly for patients with severe cancers. In this concern, the phase angle (PhA), is one of the most important indicators for predecting life qualty and overall survival, particularly for cancer patients. Since, the phase angle provides an image about the case of cell membrane function, and R<sub>o</sub> and R<sub>m</sub> have been used to predict clinical outcome.

Physically, using of BIA method for characterizing different tissues is to fit data by the Cole equation models, which describe the



behavior of permittivity and conductivity as a function of frequency. The commonly used circuit represents biological tissues activities, in which, the R of extracellular fluid is arranged in parallel to the second arm of the circuit "which consists of capacitance" and R of intracellular fluid in series. Resistive part (R) and capacitance can all be measured over a range of frequencies (most single frequency BIA analyzers operate at 50-kHz). At zero (or low) frequency, the current does not penetrate the cell membrane, which acts as an "insulator", and therefore the current passes through the extracellular fluid, which is responsible for the measured R of the body  $R_0$ . At infinite frequency (or

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very high frequency) the capacitor behaves as a perfect (or near perfect) capacitor, and therefore the total body R ( $R_{\infty}$ ) reflects the combined of both intracellular and extracellular fluid (Figure 2). The impedance version is shown Cole equation, the corresponding Cole plot in the impedance plane is shown in Figure 2.

$$Z(\omega) = R_{\infty} + \frac{R_0 - R_{\infty}}{1 + (j\omega\tau)^{\alpha}}$$

Where, Z ( $\omega$ ) is the complex impedance in ohm ( $\Omega$ ), R<sub>0</sub> is the resistive part at zero frequency ( $\Omega$ ), R<sub>0</sub> is the resistive part at infinite frequencies ( $\Omega$ ), t is a time constant, e.g., the mean relaxation time in a distribution of time constants, and  $\alpha$  (p/2) is the constant phase angle, w is the frequency (in rad s<sup>-1</sup>), the constant 1- $\alpha$  may also be viewed as describing the width of the distribution of time constants.

The present work was designed to provide a rational explanation for the physical principle of bioimpedance and its clinical applications/ limitations. Due to the worldwide spreading for the applications of radiotherapy and radiology, we set this work to provide an imagination for the earlier and later alteration in cellular tissues as a result of radiation exposed.

# Radiation: Global Exposure and Safety Standards: An Overview

The physical properties of the ionizing particles and their interactions with the biological subjects are too comprehensive to be presented here, and readers are referred to an excellent review of Iijima [7]. However, to summarize briefly, energy deposition of the alpha particle is concentrated in a correspondingly small volume near the decay site. Therefore, the radiation dose from alpha emitting radionuclides distributed in the body (for therapeutic purposes or as a result of internal contamination) is highly localized. For instance, cells near the site of radionuclide concentration receive very high doses, whereas more distant cells receive no dose. In contrast, the beta particle is spontaneously decelerated near the nucleus of the target atom, and thus, photons are emitted from the interaction site "braking radiation". A worth note is that the energy of this photons are equal to the difference in the energy of the beta particles before and after the event. In this concern, it is also important to note that low mass, high energy charged particles traveling in high atomic number media may lose energy in a form of photons. And the rate of such loss is termed "the radiative" stopping power. This effect is not often seen for alpha particles and is of limited importance for beta particles and electrons in biologic materials at nuclear medicine energies.



Figure 2: Cole plot in the impedance plane, derivation of the phase angle, resistance (R), reactance (Xc), impedance (Z) and the frequency of the applied current.

On the other hand, the global radiation exposure and allowed effective dose are varied depending on the local geology. Radon and thorium are the largest natural sources of exposure, far ahead of cosmic and internal radiation. Data collected over the last 12 years [8] show a medical effective dose per caput of three ranges: higher exposure in Luxemburg, Belgium and Germany (1.8–2.0mSv/year). Low exposure in the UK, the Netherlands and Sweden (0.4–0.75 mSv/ year), intermediate exposure in Norway and Switzerland (1.1 mSv/y). While western countries showing rather low values of 2.7 mSv/year (UK) or 4 mSv/year (Germany). It is assumed that roughly 5% of a population exposed to 1Sv of effective dose will develop cancer during their lifetime. While such risk is reduced to 2–3% in the population of western European patients with a peak age of 60-70years, because of the age related lower biological impact of ionizing radiation.

# Radiation effects and interactions with the biological system and medical utilization

In a long-term follow-up study of atomic bomb survivors, data collected for over the last 60 years show that radiation significantly increases the risks of death (22%), cancer incidence (47%), death due to leukemia (310%) at 1Gy, as well as the incidence of several non-cancer diseases (e.g. thyroid nodules, chronic liver disease and cirrhosis, uterine myoma, and hypertension). Significant effects on maturity (e.g. growth reduction and early menopause) were also observed. Women are much higher section in any population, which expose for the ionizing radiation, due to the worldwide spread for radiologic diagnostic modalities. The exposure to ionizing radiation increases levels of estradiol and other sex hormones, which are acknowledged breast cancer risk factors. A study carried out on cancer-free female A-bomb survivors examined whether ionizing radiation exposure is associated with levels of serum hormones and other markers that may mediate radiation-associated breast cancer risk [9]. This study postulated that at 1Gy of radiation dose, a significant increase in the levels of total estradiol (17%), bioavailable estradiol (21%) and testosterone (30.0%) in postmenopausal women, has been recorded. In contrast, in premenopausal women, the total estradiol, bioavailable estradiol and testosterone were significantly decreased (-11% and -12%, -10%, respectively) at 1Gy.

It is very apt notion that tissues sensitivities for radiation "are varied" depending on their cellular structure. For instance, "slowly dividing" cellular tissues such as the liver, kidney, muscle, bone, lung and connective tissue are radioresistant. Whereas, the "rapidly dividing" cellular tissues such as bone marrow, testis "germinal cells", skin "epithelial cells", gastrointestinal mucosa are radiosensitive [10-14]. The extent of the damage in a tissue is also closely related to radiation type, dose, and location. These factors will determine the violence and interval of the cellular depletion. In this sense, the damage effect of radiation may be delayed for months due to "delayed acute reactions". The most important factor for determining the extent of injury in a tissue is its ability to repopulate after radiation damage [15-18]. The dividing stem cells and nondividing functionally mature cells are involved in the process of tissue repopulation. The former will begin to die when they attempt their first or second post-irradiation divisions. While the nondividing differentiated cells, which are relatively unaffected by radiation, will continue to function and to die at their normal rate. However, they will not be so efficiently replaced because of the damage to the stem cell compartment [19]. Tissue injury will not become notable until the number of functional cells falls below a critical level.

In this context, the permanent and temporal changes-related genes would be very important for understanding the underlying mechanisms of cellular response to radiation [20]. Radiation therapy has been universally approved and widely used as an effective treatment for various cancer types. Amongst cell structures, DNA is much rather sensitive, particularly at high-dose exposure [2,21,22]. Radiation causes DNA double strand breaks, base damage and DNA-protein crosslink to increase genomic instability in the target cancer tissues. Subsequently, it leads to cell cycle arrest, cell death and microvascular destruction. However, radiation effect also may extent to the other healthy cell normal tissue. This effect promotes multiple cytotoxic events, DNA damage and inactivation in the DNA repair system. Upon DNA is damage by ionizing radiation, ultimate signaling activates in the cell take place [23], e.g., cell cycle arrest, DNA damage and mitochondrial disruptions (Figure 3 and 4) [24,25]. In fact, the ability of ionizing radiation to cause the mitotic death of cell and the radio sensitivity of a tissue is directly related to its mitotic activity and inversely proportional to the degree of differentiation of its cells.

Lastly, there has been a universal trend for increasing nuclear medicine utilization for radiologic diagnostic modalities and radio therapeutics. For instance, in Germany, nuclear medicine currently is accounting for around 7% of the total medical exposure [8]. In some countries the medical contribution to the population dose is in the range of 50%, similar to the USA. Radiation effects whither "stochastic" increasing the probability of cancer induction, and or "deterministic", induces surface damages e.g., skin burns [8]. In fact, there are stringent rules making the vast majority of diagnostic examinations never reach the threshold for this deterministic effect. However, the major problem is that such radiological applications are often require long periods and numerous numbers of spot exposures. The skin is the first and largest outside barrier that protects the internal organs from different



Figure 3: Radiation is interact directly or indirectly with the target, direct effect of radiation on the mitochondria through its interaction directly with DNA leading to deleterious mutations, which in turn, could mediate cancer progression. However, radian could indirectly interact with mitochondrial macromolecules and generate ROS (superoxide anion, hydrogen peroxide, and hydroxyl radicals), which have the ability to damage the mitochondrial DNA, or causing deleterious mutations. This consequently leads to impair in the mitochondrial function or the manifestations of apoptosis, aging, endothelial damage and tissue toxicity without causing a further increase in ROS.



**Figure 4:** This diagram gives the impression that alpha particle breaks the DNA, the beta particle breaks hydrogen bonds, and X- $\gamma$  rays damage bases when in fact all three types of radiation can cause direct damage. However, heavy charged particles such as a particle have a greater probability of causing direct damage compared to low charged particles such as X-rays which may cause the most of its damage by indirect effects. Radiation mediates DNA mutations by insertions or deletions of DNA sequences, resulting in apoptosis, cancer, and tissue toxicity.

environmental cosmic insults. Energy deposition from particle tracks, when ionizing radiation penetrate skin arises stochastically throughout the exposed mass [26,27]. Thus, the local dose may reach the threshold of roughly 3Gy for erythema and more severe skin damage [8]. Furthermore, repeated examinations will add up and proportionally increase the risk.

### Cell membrane and bioelectrical impedance (functions)

It is very apt notion that, cells are naturally acquired electrical charges that is due to the process of ions exchanges between the extra and intracellular space. Therefore, one can say that the bioelectric potentials are have critical roles in the body and involved in different regulatory and metabolic processes. Further reinforcing for the biologically importance of bioimpedance, some cells make specialized use of bioelectric potentials and currents for distinctive physiological functions. For instance, in nerve and muscle cells, contraction or relaxation process initiates by which called "electric pulses" due to the action potentials passing along nerve fibres. In fact, cell membrane is consists of an extra-and-intra-cellular membrane, each membrane consists of a lypopylic layer (has an affinity for lipids) and hydrophilic layer (has an affinity for water). Of note, fat is a much poorer conductor of electricity relative to water, thus the changes in body fat and water balance will reflect on tissue impedance. At the low-frequency, the outer lipid membrane could charge completely within the time. At the low-frequency, the outer lipid membrane could charge completely within the time. The accumulation of charges in lipid membrane prevents the current to flow through the extracellular space. With frequency increasing of the applied field, a point is reached at which the time required to charge the intra-and extracellular membranes. These events allowing current to flow through intracellular space, since, the action potential initiation has a threshold behavior. Such application is producing transmembrane voltages above a threshold value initiate action potentials, while those below do not. The degree of injury due to radiation will be depending on the type of the organism and absorbed doses. These injuries will change the physical properties of the exposed tissues

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Author	Subject group	n	Refer- ence	BIA parameter	Method/equation used	Instrument	Comments/appreciation
Vilaça et al. [56]	Elderly	41	DXA-L	FFM	SF-BIA	RJL	Mean values for FM and FFM did not differ significantly in the subject group. The correlation was less strong among the two subject groups one, suggesting caution when BIA is to be applied in studies including undernourished older subjects. Since, variability was high between individuals.
Lubans et al. [57]	Year 9 sec- ondary school students	68	%BF	FMM	Cole el al. [58]	SFB7	Although the BIA machine produced reliable estimates of percent body fat, the tests of muscular fitness resulted in high systematic error. N.P. These measures may require an extensive familiarization phase before the results can be considered reliable.
Jean et al. [59]	ALS	47	DXA	FMM	BIA	RJL	BIA is valid for use in ALS patients, both for a single exam measure and for longitudinal monitoring
Kim et al. [60]	Healthy	174	DXA	FFM	BIA	Eight-electrode BIA model DPX-L	Eight-electrode BIA model had small, but systemic, errors in %fat and FFM in terms of the predictive accuracy for individual estimation. The total errors led to an overes- timation of %fat in lean individuals among men and an underestimation of %fat among obese women. N.P. This study recommend equations or the correction of these total errors when the present eightelectrode BIA model.
Hoyle et al. [61]	Elderly-h.	22	<sup>2</sup> H <sub>2</sub> O	TBW	Bussolotto et al. [62]	RJL	Total body water estimation by bioelectrical impedance analysis correlates well with estimation by measurement of dilution of <sup>2</sup> H <sub>2</sub> O. N.P. BIA providing a potentially useful tool to improve the management of the elderly hypona- traemic patient.
Nagai et al. [63]	Healthy	133	СТ	VFA	МВІ	VFA (IPVFA)	The excess accumulation of visceral fat area (VFA), which is associated with metabolic syndrome can easily screen by MBI N.P. The method may be a useful tool for primary preven- tion of metabolic syndrome.
Medoua et al [64]	HIV	24	²H₂O	TBW	Paton et al.[65], Sluys et al.[66], Kushner and Schoeller. [67]. Sun et al. [68], Schoeller and, Luke. [69], Kotler et al. [70]	Xitron	The valid published or developed predictive equations should be cross-validated in large independent samples of HIV-infected patients.
Anita et al. [71]	COPD	41	DXA	FFM, RMR	Harris and Benedict. [72]	DXA BIA-101	BIA accurately screened FFM, which is the dominating factor influencing resting metabolic rate (RMR)
Jimenez et al. [73]	morbidly obese	159	DXA	FFM	Data input	RJL	BIA parameters provide accurate estimates of body com- position in MO subjects
Zhao et al. [74]	Pulmonary ventilation distribution	50	DXA	GI index	LEE	EIT	The global inhomogeneity index quantifies the gas distri- bution in the lung with a single number and reveals good interpatient comparability.
Reilly et al. [53]	11-12-year- olds, 84 boys, 92 girls	176	DXA	2H2O	Manufacturer	RJL	N.P. Errors in estimation of fat mass using BIA and DXA can be very large, and the direction of error can differ between the sexes.
Haroun et al. [52]	obese and adolescents	77	DXA	See reference	Wells et al. [75]	BIA, 3C model	In boys, regression analysis indicated significant differ- ences in slope ( $p$ <0.001) for DXA, and both slope ( $p$ <0.001) and intercept ( $p$ <0.001) for BIA. In girls, mean fat mass from TBW was 12.1 kg (SD 7.7); bias for DXA was +1.2 kg (limits of agreement -1.9 to +5.1) and bias for BIA was -0.2 kg (limits of agreement -5.4 to +5.1).
LaForgia et al. [54]	obese	18	DXA	TBW, FFM, %BF	Manufacturer	SBIA 4C model	The BIA estimates of TBW were significantly different from the criterion measures and intraindividual differences displayed a large range (-0.6 to 3.6 kg). Significant un- derestimations of TBW via BIA are concerning given that this is the parameter initially established by this method. Furthermore, the BIA data resulted in a FFM hydration value of 68.5% which was significantly (p<0.001) lower than the four compartment value of 72.0%. N.P. The BIA device tested displayed poor individual ac- curacy for the estimation of body composition compared with a four compartment criterion method

DXA: Dual energy X-ray Absortiometry; DXA-L: Dual energy X-ray Absortiometry-Lunar; RJL Systems, Inc, Clinton Twp, MI, USA; Xitron Technologies, San Diego, CA, USA; Analycor3, Spengler, France; SF-BIA, Single Frequency BIA; BIS: Bioelectrical Impedance Spectroscopy; BIA: Bioelectrical Impedance Analysis; 3C Model: three-Component Model; 4C Model: four Compartment Criterion Method; CT: Computed Tomography; MBI: Multifrequeny BI; ALS: Amyotrophic Lateral Sclerosis; Elderly-h: Elderly hyponatraemic patients; COPD: Chronic Obstructive Pulmonary Disease; LEE: Lung area Estimation Method; <sup>2</sup>H<sub>2</sub>O: Deuterium Oxide; RMR: Resting Metabolic Rate; BMI: Body Mass Index; FFM: Fat-Free Mass; BF: Body Fat; BCM: Body Cell Mass; ECF: Extracellular Fluid; ICF; Intracellular Fluid; EBL: Estimated Blood Loss; TBW: Total Body Water.

Table 1: BIA studies evaluating FFM, BF and BCM in specific groups of subjects.

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Author	Subject group	n	Method/BIA pa- rameter	Instrument	Comments/ appreciation
Kim et al.	Breast cancer-Rel	73	ECF	InBody®720	Estimation of ECF and SFBIA before treatment are useful screening tools for predicting the treatment outcome of patients with lymphedema.
Vicini et al. [76]	Upper limb Lym- phoma	64	ECF	L-Dex	L-Dex readings paralleled the extent of surgical interventions and suggest that they can be used to monitor patients for the early onset of edema.
Fu et al. [77]	symptomatic seroma	130	arm swelling	BIS	Patients who developed symptomatic seroma had 7.78 and 10.64 times the odds of developing arm swelling and chest/breast swelling versus those who did not, respectively ( $p < 0.001$ ).
Badalato et al. [46]	Prostate tumor	63	FFM, ECW, ICW, TBW	ImpediMed SFB7	The correction of metric analysis indicated that BMI correlated with FFM (p = 0.002), FM (p = 0.01), and %TBW (p = 0.02). %FFM (p = 0.03), %FM (p = 0.03) and %TBW (p = 0.04) correlated with % tumor volume. ICW (p = 0.01) and TBW (p = 0.009) correlated with EBL. BMI (p = 0.04), %ECW (p = 0.04), FM (p = 0.05), and %ICW (p = 0.03) correlated with pathologic tumor stag.
Badalato et al. [46]	Breast cancer	14	BF	BIA	In this study a comparison between ADP, SKF and BIA screening was carried out. Although ADP and SKF produce similar estimates of BF percentage in all partici- pants, BIA overestimated BF percentage relative to the other measures.
Ward et al. [35]	Healthy	172		BIS	The presence of lymphedema is indicated when the impedance ratio exceeded 1.106 when the nondominant limb is at risk, and 1.134 when the dominant limb is at risk compared with the currently used values of 1.066 and 1.139, respectively. The impedance ratio thresholds for early detection of lymphedema remain suitable for clinical use with present day bioimpedance spectroscopy analyzers.
Ward et al. [35]	Healthy	18,700	BMI, FFM	BIA	This study found some evidence for a possible relationship between higher levels of physical activity, body size and increased ovarian cancer risk. Ovarian cancer in relation to BMI was 1.22 (95% CI: 1.00, 1.48; p-trend, 0.06) per 5 kg/m(2) increment, and for fat mass, 1.23 (95% CI: 1.01, 1.49; p-trend, 0.04) per 10 kg increment.
Burden et al. [78]	Colorectal cancer	132	BMI, %weight loss	BIA	BIA screening would be beneficial at an early stage in the care pathway when they initially enter the secondary care system.
Liu et al. [79]	Breast cancer.	200	%BF	BIA	BMI and BF% were highly correlated (r=0.91; p<0.001). However, BMI exhibited poor sensitivity for identifying obesity (47%). The sensitivity of BMI to detect obesity was better in women over age 60. The best BMI cutoff for obesity was 22.3 kg/m2 with a sensitivity and specificity of 89% (95% CI=83-94%) and 87% (95% CI=77-93%) respectively, and the total accuracy rate improved from 65% to 89%.
Czerniec et al. [28]	Lymphedema	33 18	self-report, Perom- eter, the truncated cone method	BIS	The physical measurement tools were highly reliable (ICC( $(2,1)$ ): 0.94 to 1.00) with high concordance (r(c): 0.89 to 0.99). While, Self-report correlated moderately with physical measurements (r = 0.65 to 0.71) and was moderately reliable (ICC( $(2,1)$ ): 0.70).
Wang et al. [80]	Breast cancer	583	Techniques sensitivities	EIS, ultrasound	Of the 583 cases, 143 were diagnosed with breast cancer. The sensitivities of EIS, ultrasound and the combination method were 86.7% (124/143), 72% (103/143), and 93.7% (134/143); the specificities were 72.9% (321/440), 82.5% (363/440), and 64.1% (282/440), and the relative possibilities of breast cancer for the positive young women detected by EIS, ultrasound, and the combination method were 8.67, 5.77, and 14.84, respectively. N.P. The combination of EIS and ultrasound is an applicable method for early detection of breast cancer in young women.
Halpern-Silveira et al. [82]	cancer	174	FFM, BW	BIA	A significant BW change was found during the treatment in patients submitted to previous/adjuvant and palliative chemotherapy (weight gain of 4.15% and 2.23%, respectively, $p = 0.05$ ) and a significant FFM loss (7.61%, $p < 0.01$ ) in patients with severe malnutrition at admission.
Wallstrom et al. [83]	Prostate cancer risk	10,564	ВМІ	BIA	General adiposity, expressed as BMI or body fat percentage, and prevalent diabetes were not associated with PCa risk.
Isenring et al. [84]	Oncology	37	TBW	BIS	A cross-sectional, observational study was conducted in 37 outpatients receiving radiotherapy (27 males/10 females, aged 68.3 ± 10.2 years). In this study, TBW estimated by BIS cannot be directly compared with oncology-specific BIA equations. N.P. BIS cannot be used at the group level in outpatients receiving radiotherapy.
Wu et al. [85]	Cancer Healthy	936 840	ICF, ECF, FM, FFM	BIA	BIA confirmed that cancer patients exhibited lower FM and FFM

DXA: Dual energy X-ray Absortiometry; DXA-L: Dual energy X-ray Absortiometry-Lunar; ImpediMed SFB7 Device (San Diego, CA, USA); InBody®720, (Biospace, Korea). BIS: Bioelectrical Impedance Spectroscopy; BIA: Bioelectrical Impedance Analysis; BMI: Body Mass Index; FFM: Fat-Free Mass; BF: Body Fat; BCM: Body Cell Mass; ECF: Extracellular Fluid; ICF; Intracellular Fluid; EBL: Estimated Blood Loss; TBW: Total Body Water; ADP: Air Displacement Plethysmography; SKF: Skinfold Thickness; RARP: Robotic Assisted Radical Prostatectomy; Breast Cancer-Rel: Breast Cancer Related Lymphedema; UL.Lymphedema: Upper Limb Lymphedema.

Table 2: BIA studies evaluating body composition in subjects with cancers.

# **Tissue Identification and Monitoring**

Any changes in tissue physiology should produce changes in the tissue electrical properties [28]. Based on this phenomenon, BIA analysis has been widely used to identify or monitor the presence of various illnesses or conditions such as body fluid shift, blood flow, cardiac output, and muscular dystrophy [29-32]. Different tissues exhibit different electrical properties, in addition, tissue electrical properties change with respect to tissue status evolution. Thus it is easy to conceive that bioimpedance method can be applied to identify and monitor tissues. The bioimpedance method can be adopted for characterizing different tissues. [30,31]. For instance, the lung tissues

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Author	Subject group	n	BIA- parameter	Instrument	Comments/ appreciation	Limitations
Sanchez-Lara et al. [86]	Advanced Non-Small- Cell Lung Cancer	119	PhA	RJL	Patient with Phase angle ≤5.8° has significant (p<0.01) poor survival.	Controlled clini- cal trial
Malecka-Massals- ka et al. [87]	Head and neck cancer Healthy volunteers	28 28	PhA	ImpediMed BIA	Mean vectors of H and NC group vs. the control group were characterized by an increased normalized resistance component with a reduced reactance component (separate 95% confidence limits, P<0.05), indicating a decreased ionic conduction (dehydration) with loss of dielectric mass (cell membranes and tissue interfaces) of soft tissue.	Controlled clini- cal trial
Norman et al. [88]	Cancer	399	PhA	BIA	Patients with a phase angle $\leq 5^{\circ}$ had significantly lower nutri- tional and functional status, impaired quality of life (P lt 0.0001), and increased mortality (P lt 0.001).	Controlled clini- cal trial
Paiva et al. [89]	Cancer	195	PhA	BIA	The present study demonstrates that PA, used as SPA, is an independent prognostic indicator. Patients with PA <-1.65° still presented a higher mortality rate (RR 2.35 Cl: 1.41-3.90; p = 0.001).	Prospective cohort
Santarpia et al. [90]	Advanced cancer	13	PhA	BIA	Phase angle =0.384, P=0.024) was found to be strictly related to survival time and can be therefore considered a prognostic tool in patients with advanced cancer.	prospective study: small sample size
Davis et al. [91]	Advanced cancer	50	PhA	underwent BIA	Weight loss was associated with shorter survival. A higher phase angle (PA) on day 1 predicted longer survival. Increased PA during hydration predicted shorter survival: increased weight during hydration predicted longer survival. An increase in phase angle during hydration predicted poorer survival and preexisting intracellular dehydration, cachexia, or poor mem- brane function.	Controlled clini- cal trial
Gupta et al. [92]	ta et al. [92] advanced NSCLC 165 PhA BIA BIA Patients with phase angle ≤ months (95% CI: 4.7 to 9.5; had 12.4 months (95% CI: 1 Every one degree increase a relative risk of 0.79 (95% N.P. Nutritional interventions could potentially lead to an advanced non-small cell lun		Patients with phase angle $\leq 5.3^{\circ}$ had a median survival of 7.6 months (95% CI: 4.7 to 9.5; n = 81), while those with $> 5.3^{\circ}$ had 12.4 months (95% CI: 10.5 to 18.7; n = 84); (p = 0.02). Every one degree increase in phase angle was associated with a relative risk of 0.79 (95% CI: 0.64 to 0.97, P = 0.02). N.P. Nutritional interventions targeted at improving phase angle could potentially lead to an improved survival in patients with advanced non-small cell lung cancer (advanced NSCLC).	Prospective clinical trial		

Table 3: BIA studies showing an association between Phase Angle (PhA) and survival in cancer patients.

show a 5-fold greater electrical current resistance than the rest of the intrathoracic soft tissues [1]. During the cyclic breathing process, the impedance of the pulmonary tissues changes 5% in the context of calm breathing, and up to 300% when inhaling from residual volume to total lung capacity [33]. One of the most attractive applications of bioimpedance characterization is cancer detection [34-39]. Hence, there are vast majority physiological differences in tumor tissues, thus BIA is efficiently applicable method for monitoring and distinguish normal healthy and tumor tissues. For instance tumors have much higher water content in their cells rather normal cells because of cellular necrosis and fenestrated vascularization and that will reflects on the tissue conductivity [19]. The cancerous tissues exhibit sharply different bioelectrical properties as compared with the normal tissues. The higher conductivity of tumors could lead to their selective targeting by radio frequency hyperthermia treatment [40]. In early stages of tumor a disturbance in the cellular water/electrolyte content, cell membrane permeability, and orientation/packing density of cells will occur. These changes and abnormalities will reflect on tissue impedance, which could be detected by using bioimpedance.

# Applications of Bia in Health Care, Medical Diagnosis and Quality of Life

Obesity is a common nutritional problem in both developed and developing countries. In a cross-sectional study, the prevalence of overweightness and obesity using both bioelectrical impedance analysis (BIA) and body mass index (BMI) has been investigated. Mean age of the studied subjects was  $21.1 \pm 1.7$  years. A close correlation (0.883 and 0.908 in males and females, respectively) for BMI and obesity has been confirmed [41]. Table 1 is a summary of BIA studies evaluating body composition including FFM, BF and BCM. On the other hand,

in a prospective study the usefulness of bioimpedance measurement have been investigated for predicting the treatment outcome in breast cancer related lymphedema (BCRL) patients [42]. In this study, the ratio of extracellular fluid (ECF) volume has been investigated by using bioelectrical impedance spectroscopy (BIS), and single frequency bioimpedance analysis (SFBIA) at a 5 kHz frequency before treatment. They also investigated whether there is correlation between ECF ratio and SFBIA ratio with the change of arm circumference. The study concluded that ECF volume measurements and SFBIA before treatment are useful tools for predicting the outcome of patients with lymphedema. Additionally, ECF volume measure can be used as a screening tool for predicting treatment outcome of BCRL patients. Table 2, summarized BIA studies evaluating body composition in subjects with cancers. There are lots of studies involved phase angle as a reliable predictive factor for quality of life and overall survival, particularly for cancer patients (Table 3).

# Physiological Parameters Affecting Bioelectrical Impedance Accuracy

Although the fact that an increased conductivity may be used to identify the presence of tumors [43,44], there are lots of limitations for BIA metric analysis due to the complication and variation in the biological system [45]. Their important review by author Damijan et al. [19] discussed efficiently lots of problems in the biological concern. Relative to water, fat is a much poorer conductor of electricity, thus the changes in body fat and water balance will reflect on tissue impedance. Cell and tissue death also cause many irreversible changes including viscosity of the extra/intracellular fluids [46]. And promote changes in the mobility and distribution of ions which have the ability to transport the current. In the lived physiological system, if the blood flow is

interrupted, metabolism could continue in an anaerobic manner. That in turn, leads to an increase in the level of the extracellular fluid due to the osmotic pressure. Therefore, BIA when applied in such conditions a false increase in the tissue impedance. Even, the brief decrease in the blood flow has an impact and could change tissue resistivity. The respective figures are not absolute and can vary according to the conditions of the environment or medium (e.g. temperature). A temperature increase is associated with a decrease in impedance [1], due to the prominent increase in ions mobility [47-49] that "transport the current", and decrease viscosity of the extracellular fluid. A general increase of about 2% occurs in the conductivity of tissue [50] in the frequency range below 1 GHz, up to a temperature of about 40°C. Above that point, the cell membrane begins to deteriorate and allows the cytosol to leak into the extracellular space. Nevertheless, the rapid increase of conductivity with temperature was suggested to be used to monitor the progress of hyperthermia treatment [51].

### Conclusion

BIA works well in healthy subjects and chronic diseases with a validated BIA equation that is appropriate with regard to age, sex and race. The metric measurements includes: body mass index, fat-free mass, body fat, body cell mass, extracellular fluid, intracellular fluid, blood loss, and total body water. Due to interindividual differences in growth velocity and puberty related changes in children making Bioimpedance metric analysis interpretation much difficult. For instance, errors in estimation of fat mass using Bioimpedance analysis and DXA can be very large, and the direction of error can differ between the sexes in children [52,53]. Furthermore, The Bioimpedance analysis device tested displayed poor individual accuracy for the estimation of body composition compared with a four compartment criterion method [54]. In this sense, it is very important to note that the use of segmental Bioimpedance analysis also requires further validation at increased temperature, edema and abnormal hydration. Thus, Bioimpedance analysis should be interpreted with caution until further validation has proven for Bioimpedance analysis algorithm to be accurate in such conditions. The potential sources of errors for Bioimpedance analysis in some specific subjects may be due to increased bone mass of limbs and changes in skin thickness and hydration, which might influence the extension of the tissues electrical characteristics. The eight-electrode BIA model had also small, but systemic, errors in %fat and fat-free mass. These errors led to an overestimation of %fat in lean individuals among men and an underestimation of %fat among obese women. Therefore, the general use of eight electrode BIA model should be interpreted with caution, until the valid or recommend equations or the correction of these total errors is resolved. Caution is recommended when using BIA as the body composition method for breast cancer survivors who have completed treatment but are still undergoing adjuvant hormonal therapy [46]. The use of more than one method should be used to derive more physiologically reliable information, which could be potentially useful for providing validation to avoid such errors. Lastly, the clinical benefit of BIA can be further enhanced by combining it with bioelectrical impedance vector analysis (BIVA) [55].

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