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Prognostic Significance Of Body Composition Analysis Measurements In Patients With Locally Advanced Or Metastatic Cancers

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Abstract

Objectives: There are many parameters in the body composition analyses and Bio-impedance analysis (BIA) measurements such as total weight, body fat (BF%), fat-free mass (FFM), muscle mass, metabolic age, basal metabolic rate, resistance and phase angle. But we do not well known which of the parameter is the most important or which one of them are associated with overall survival (OS).

Material and Method: In total, 173 patients have included in the study.

Results: The mean age 54 years in man and 51 years in woman. Patients with cancer had lower hemoglobin and albumin levels compared to the healthy controls. The median OS was 17 (3-45) months of the cancer group and women were alive longer than men (22 vs 13 months, p<0.001). Multivariate analysis revealed that, BF% (HR, 0.8, 95% CI, 0.75-0.87, r=35.8, P<0.001), total body water (TBW%) (HR, 0.89, 95% CI, 0.82-0.97, r=7.8, P=0.035), BMI (HR, 0.83, 95% CI, 0.74-0.93, r=13.9, P=0.003) were found to be statically significantly associated with OS.

Conclusion: Present study showed that, increased BMI, fat mass and total body water at the time of diagnosis of cancer, are good prognostic factors in patients with metastatic disease. Gender did not have any impact on relation of BIA parameters with survival.

Keywords: Bio-impedance analysis, metastasis, cancer, survival

Özet

Amaç: Biyoimpedans analizinde (BIA) ölçülen bir çok parametre mevcuttur;total vücut ağırlığı (TVA),vücut yağı (%VY), Yağsız vücut kütlesi (%YVK), Kas kütlesi, metabolizma yaşı, bazal metabolzma hızı, rezistans ve faz açısı gibi. Ama bu parametrelerden hangisinin daha önemli olduğu ve yaşam süresi ile ilişkili olduğu tam olarak bilinmemektedir.

Gereç ve Yöntem: Toplamda 173 hasta çalışmaya dahil edildi.

Bulgular: Ortanca yaş erkeklerde 54, kadınlarda 51' di. Kanser hastalarında kontrol grubuna göre daha düşük hemoglobulin ve albumin düzeyleri mevcuttu. Ortanca sağ kalım süresi kanser grubunda 17 (3-45) aydı ve kadınların yaşam süresi erkeklere göre anlamlı olarak daha uzun bulundu (22 aya karşın 13 ay, P<0.001). Multivaryant analize göre %VY (HR, 0.8, 95% CI, 0.75-0.87, r=35.8, P<0.001), total vücut suyu (%TVS) (HR, 0.89, 95% CI, 0.82-0.97, r=7.8, P=0.035) ve vücut kütle indeksi (VKI) (HR, 0.83, 95% CI, 0.74-0.93, r=13.9, P=0.003) genel sağkalımla anlamlı olarak ilişkili saptandı.

Sonuç: Güncel çalışma gösterdiki artmış VKI, yağ kütlesi ve total vücut suyu kanser tanısı konulduğu anda metastatik hastalar için iyi prognostik bir bulgudur. Cinsiyetin BIA parametreleri ve sağkalıma ek bir katkısının olmadığı gösterildi.

Anahtar Kelimeler: Biyoo-impedans analizi, metastaz, kanser, survival

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Introduction:

Anorexia with cachexia is associated with fatigue and may be the most common symptoms encountered in patients with advanced cancer. This boring situation is more presented by some cancers especially, upper gastrointestinal cancers, lung cancer and pancreatic cancer [1]. Loss of more than 5% of premorbid weight before the receiving chemotherapy predicts a significantly shorter survival [2]. Body mass index (BMI) of the patients at the time of the diagnosis of cancer is suggestive for baseline nourishment but not enough for extensively evaluate the nutritional status. Many methods have been used to evaluate nutritional status including BMI, serum biomarkers such as serum albumin, C reactive protein, other inflammatory markers and anthropometric measurements [3]. Subjective global assessment (SGA) is a validated method of nutritional assessment [4]. Also, it has been accepted as a reliable method of assessing nutritional status and predicting complications in different patient groups, including patients with cancer [5]. Body mass index and SGA can change by the cancer stage and types [6]. However, these methods could be misleading in some cases, so a combination of these classical methods with body composition analyses such as the dual-energy radiographic absorptiometry (DEXA) and bioelectrical impedance analysis (BIA) could be useful [7]. Bioelectrical impedance analysis is a practical and noninvasive method for assessment of body composition that provides more consistent and reproducible results than standard anthropometry alone [8]. However, BIA has affected by biological factors such as blood flow and total amount of body water, so it has some limitations in healthy and non-healthy populations [9]. Kyle et al. reported that single frequency-bioelectrical impedance (SF-BIA) analysis is not accurate enough in subjects with a BMI > 34 kg/m [10]. There are many parameters in BIA such as total weight, body fat (BF%), fat-free mass (FFM), muscle mass, metabolic age, basal metabolic rate, resistance and phase angle. To date we do not well known which of the parameter is the most important? Or which one of them are associated with overall survival (OS) in locally advanced or metastatic cancers. So we investigated the relationship of BIA parameters with OS in patients with locally advanced or metastatic cancer.

Methods

In total, 173 patients have included in the study. The Ethics committee of Bülent Ecevit University School of Medicine approved the study. Inclusion criteria were as follows: patients with a diagnosis of histopathologically confirmed stage III or IV cancer according to the TNM staging; Eastern Cooperative Oncology Group (ECOG) score of 0-2; aged 18–80 years, and eligibility to receive chemotherapy. Exclusion criteria were, patients who refused to include in the study, who had score 3-4 of ECOG, and patients with signs of infection, acute inflammatory processes, or liver disorders. Also all clinical findings prevented the patients to be submitted to chemotherapy, presence of edema, body mass index lower the 18 or higher than the 30 were considered as exclusion criteria. Body mass index was calculated as body weight/height squared. In the study 140 patients had locally advanced or metastatic cancer and all these patients were selected as randomly for the study inclusion. All patients were treated as their cancer types and overall survivals were recorded. The most common cancer types were colorectal cancer (CRC), gastric cancer (GC), breast cancer (BC) and lung cancers. The control group was defined as had no any known chronic disease, cancer, history of surgery as well as any dieting for weight loss. The control group was mostly selected from the relatives of patients

The nutritional status was assessed through the use of the Subjective global assessment (SGA), according to Detsky (4). A numeric score of nutritional risk is obtained, which suggests different levels of intervention. A higher score suggests a higher nutritional risk. SGA nutritional status classification such as: A, well fed; B, moderately (or suspicion of cahcexia) malnourished; and C, severely malnourished. All the data were collected before the first chemotherapy cycle.

All parameters were measured by two models of commercially available foot-to-foot impedance devices (Tanita Inc., Tokyo, Japan, Models TBF 300A). The measurements were performed in the morning fasting. Measured parameters by BIA were, total weight, body fat % (BF%), fat mass (FM) and fat-free mass (FFM), muscle mass, metabolic age, basal metabolic rate (Kilo Cal). Overall survival was defined as the time interval between the first assessment in the clinic and the patient's death date or the time of the last contact or news obtained while the patient was still alive. The patients were followed up from September 2011 to August 2013.

Statistical analyses

Descriptive and continuous variables were summarized as arithmetic means with standard deviation (SD) and medians with range, and categorical variables were summarized as relative frequency proportions and 95% confidence intervals (95% CI). Overall survival (OS) defined as interval from the patient's date of diagnosis until date of death and was calculated by the Kaplan-Meier method and Cox proportional hazards models were used to evaluate the multivariate prognostic effect. Hazard ratios (HR) were calculated along with their corresponding 95% CI as a measurement of association. A P value of 0.05 or lower was considered significant in all cases. Analyses were done by SPSS v. 17 software package (SPSS, Inc., Chicago, IL).

Results

173 patients were studied, with a mean age 54 years in man and 51 years in woman, in addition study population had more man compared to women. There were 33 healthy controls and 140 patients with diagnosed cancer. Characteristics of the two groups were summarized and compared in the table-1. Patients with cancer had lower hemoglobin and albumin levels compared to the healthy controls (11.5 gr/dL vs 13 gr/dL, P=0,04 and 3.75 gr/dL vs 4.2 gr/dL, P<0.001, respectively). Percentage of body fat was significantly lower in control group compared to the cancer group and the other parameters of BIA (TBW, TBM, BMR/Weight ratio, Activity calorie, BMR kilo cal.) were significantly higher compared to the cancer group.

We excluded the patients with BMI lower than 18 and higher than 30, because BIA not standardized method for extreme situations such as cachexia and obese patients. Despite this exclusion, some of the patients SGA status were severely malnourished. Twenty two percent of man and 10% of women had SGA-C status although they have normal BMI.

Colorectal and gastric cancers were the most prevalent tumors (68%), followed by breast in women and lung cancer in both gender. Demographic characteristics of the study population according to the gender were summarized in table-2. All patients were stage in metastatic stage whom were diagnosed with colorectal, gastric, breast and other GI cancers but 80% of patients with lung cancer had metastatic cancer and remaining of 20% of lung cancer were in locally advanced stage. All patients received at least 4-6 cycles of chemotherapy according to the cancer types. Because of the study design we did not included the patients with BMI fewer than 20 and over the 30 such as underweight, overweight and obese patients.

Table 1. Comparison of the bio-impedance analyses parameters with control and patients with cancer

Characteristics	Control group n=33	Cancer group n=140	P
Age, years	50 (38-64)	52 (38-75)	0.7
Glucose, mg/dL	84 (68-105)	99(62-142)	0.8
Hemoglobin, gr/dl	13 (11-16)	11.5 (8-16)	0.04
Creatinine, mg/dl	0.85 (0.65-1)	1.1 (0.9-1.2)	0.1
Albumin, gr/dL	4.2 (3.2-5)	3.75 (2.7-4.9)	<0.001
Body Mass Index	25.2 (25-33)	24.6 (18-30)	0.3
BF, %	20,3 (13-40)	26.5 (13-51)	<0.001
TBW, %	58,3 (43-66)	53,6 (35-63)	<0.001
TBM, %	15,4 (11-17)	14.3(10-17.8)	0.1
BMR/Weight ratio	22,3(20-23)	20,46(16-26)	<0.001
Activity calorie	195(156-214)	180(146-246)	<0.001
BMR kilo cal.	1606(1270-1890)	1422(1000-1854)	0.001

BF: Body fat, TBW: Total body water, TBM: Total body mass (protein), BMR: Basal metabolism rate,

The median OS was 17 (3-45) months of the cancer group and women were alive longer than men (22 vs 13 months, p<0.001). According to the cancer types, median OS was highest in mBC (23 months), following the mBC, mOS was 19 months in mCRC and 16 months in mGC. Shortest mOS were in lung cancer (14 months). Multivariate analysis revealed that, BF% (HR, 0.8, 95% CI, 0.75-0.87, r=35.8, P<0.001), TBW% (HR, 0.89, 95% CI, 0.82-0.97, r=7.8, P=0.035), BMI (HR, 0.83, 95% CI, 0.74-0.93, r=13.9, P=0.003) were found to be statically significantly associated with OS. Also cancer group was significantly associated with OS (summarized in the table 3). Patients with lung cancer have 5.5 times as likely, mGC have 3.9 times as likely have mortality risk compared to the mBC patients. Body mass index was most prominent in mGC patients and Roc curve analysis showed that BMI hig-

her than 22.1 had 93% sensitivity and 75% specificity with AUC=0.71.

Table 2. Demographic characteristics of the study population according to the gender.

Characteristics	Male, (n=74) Median/ Mean	Range	Female, (n=66) Median/ Mean	Range
Age, years	54	2-75	51	38-72
Overall survival, months	13	3-32	22	5-45
Status, Exitus %	65	-	47	-
Alive %	35	-	53	-
Body Mass Index	24.7	18-29	25.2	18-30
Glucose, mg/dL	98	62-142	102	62-140
Hemoglobin, gr/dl	11.1	8-15.4	12	8.9-16
Creatinine, mg/dl	1.1	0.9-1.20	1.2	0.9-1.23
White Blood Cell, mm3	7200	5800-11500	7700	6200-12000
Albumin, gr/dL	3.7	2.7-4.8	3.8	2.8-4.9
BF, %	20	13.8-38	33	14-51.4
TBW, %	58	44-64	48	35-63
TBM, %	16.3	12.5-17.8	13.5	10-17.7
BMR kilo cal.	1412	1088-1854	1373	1002-1712
BMR/Weight ratio	21	19-26	20	16-23
Activity calorie	185	156-246	164	146-204-
mCRC, %	39	-	36	-
mGC, %	38	-	23	-
mBC,%	0	-	35	-
Lung Cancer, %	23	-	6	-
SGA,%				
A	45	-	56	-
B	33	-	34	-
C	22	-	10	-

BF: Body fat, TBW: Total body water, TBM: Total body mass (protein), BMR: Basal metabolism rate, mCRC: metastatic colorectal cancer, mGC: metastatic gastric cancer, mBC: metastatic breast cancer, Lung Cancer: included locally advanced and metastatic cancer, SGA: Subjective global assessment, SGA-A:Well fed, SGA-B: Moderate malnourished, SGA-C: severely malnourished

Discussion

In the present study we showed that patients with metastatic cancer had lower hemoglobin and serum albumin levels compared to the healthy controls. Percentage of BF% was significantly lower in control group compared to the metastatic cancer group and the other parameters of BIA (TBW, TBM, BMR/Weight ratio, Activity calorie, BMR kilo cal.) were significantly higher compared to the cancer group. Despite all these findings, only BF% and TBW are the significantly correlated with OS. In addition BMI and cancer type were significantly correlated with OS. So we may defend that, BF%, TBW and BMI are more clinically valuable parameters for BIA.

Table 3. Multivariate analysis of cancer group and survival

Group	HR	95%CI	P value
mBC*			<0.001
Lung cancer	5.5	2.2-13.5	<0.001
mGC	3.9	1.7-8	0.001
mCRC	2.1	0.9-4.6	0.066

mCRC: metastatic colorectal cancer, mGC: metastatic gastric cancer, mBC: metastatic breast cancer.
*All groups compared to mBC group and HR values were analyzed according to this comparison.

Bioelectrical impedance analysis is a practical method for the assessment of body composition and it has been validated in several pathologies, including patients with cancer [11,12]. It is an easy, non-invasive method and informative, which can feasible at bedside [13]. However, this method depends on specific predictive equations for each population and it's use limited in some clinic situations [12,14]. Mourtzakis et al. studied Dual-energy X-ray absorptiometry (DXA)-based analysis of fat and fat-free mass in 50 cancer patients and compared with bioelectrical impedance analysis (BIA) and with regional computed tomography (CT) images. They found that BIA overestimated or underestimated fat-free mass substantially compared with DXA as the method of reference (up to 9.3 kg difference) and also they emphasized the CT had a great practical significance compared to the whole-body composition [7]. Actually we could not compare the BIA parameters with DXA and CT parameters, but our main aim was to investigate the relationship between the BIA parameters with oncologic outcomes such as overall survival. While DEXA is a valid method to assess body composition, its utility clinically is limited as it is not widely available in cancer centers. Severe obesity have not only increases in fat mass but also have some changes in the composition of FFM, TBW, and its extracellular compartment, which can cause difficulties in measuring fat [15]. Because of

these limitations we excluded the obese and cachectic patients in the study but our study population had approximately 15% of SGA-C patients without cachexia.

Malnutrition is prevalent in cancer patients with an increase by its stage and is associated to a decrease in tolerance and response to the treatment, poor survival, decreased quality of life, and increased mortality [16]. Chemotherapy may affect the nutritional status and can make some alterations such as nausea, vomiting, diarrhea, anorexia, and loss of body weight (BW) [6, 16]. Halpern-Silveira et al. found a prevalence of malnutrition of 23% at the beginning of chemotherapy in 174 patients with cancer. They found a significant change in FFM levels following the chemotherapy, and this change was most prominent in patients with severely malnourished (loss of 8.2% of FFM) [6]. In the same study there was no significantly change in body weight following the chemotherapy. This controversy explained by heterogeneity of study population by the authors. In our study we found a significant correlation with fat mass and body water with OS. Base line fat mass and body water are a good prognostic factor for patients with metastatic cancer. We included the metastatic cancer, not stage 1-2 cancer, because of metastatic cancer patients have an increased catabolism compared to the early stage of cancer. So our study population have more homogeny to other study despite the including 4 types of cancer.

Cachexia caused decrease in survival in patient with cancer [2], and cancer stage also imply the survival and cachexia, patients whose stage was III, a malnutrition prevalence of 21.9% was found, although, in those whose stage was IV, it was 62.1%[17]. We excluded the cahcectic and obese patients before the analysis, and all patients were in stage 4, except 20% of lung cancer in stage 3 but they were surgically inoperable. We may speculate that, BMI (who were higher than 20) is good prognostic factor even patients had in stage 4, but patients with metastatic gastric cancer may higher than 22.1 of BMI according to our study analysis.

In multivariate analysis we selected the breast cancer as base group because of patients with mBC have overweight compared to lung cancer, mCRC and mGC, also these 3 cancer types were usually more aggressive and have increased catabolism compared to the mBC. Our study revealed that patients with lung cancer have nearly 5 times, patients with mGC have nearly 4 times, patients with mCRC have 2 times mortality risk more than mBC.

Phase angle (PA), determined by bioelectrical impedance analysis, has been considered as a prognostic factor in several clinical conditions and it has shown that it was an independent indicator of survival for patients with cancer receiving chemotherapy [12]. This was the major limitation of our study, we could not investigate the correlation of our study parameters with PA, because PA can evaluate by more technological devices unfortunately TANITA TBF300A did not have this analysis. Also we have major limitations such as change by BIA parameters by chemotherapy. But this is not primary endpoint because we firstly aimed which of the BIA parameters were more correlated with survival in patients with metastatic cancer.

In conclusion present study showed that, increased BMI, fat mass and total body water at the time of diagnosis, are good prognostic factors in patients with metastatic cancer. Gender did not have any impact on relation of BIA parameters with survival.

Cemil Bilir, Huseyin Engin, Selcuk Ergen, Yasemin Bakkal Temi declare that they have no conflict of interest.

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Kaynaklar

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