



The role of bioimpedance spectroscopy method in severity and stages of breast cancer-related lymphedema

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ABSTRACT

Objective: The correlation between lymphedema severity and stages determined by standard diagnostic methods and Bioimpedance Spectroscopy (BIS) technique was examined in breast cancer-related lymphedema (BCRL) patients.

Material and Methods: The bioimpedance analyzer device was connected to the 1.0 cm disc electrodes which were connected to the affected and unaffected (healthy) arm of the patients. We evaluated the performance of the impedance (Z) at multiple frequencies (5-50-100-200 kHz) and phase angle (PA), resistance (R), and reactance (XC) at 50 kHz on the lymphedema severity and stages. Bioimpedance measurements were applied to all volunteers in cooperation with the Physical Therapy and Rehabilitation Department. In this study, the correlation between BCRL severity and stages and bioimpedance values was examined.

Results: A total of 31 female patients were recruited to compare the BIS technique with standard diagnostic techniques. The severity of lymphedema was found among the patients as follows; mild 14 (45.2%), moderate 10 (32.3%), and severe 7 (22.6%). The stage distribution of volunteers was; 15 (48.4%) patients in Stage 0, 10 (32.3%) patients in Stage 1, 5 (16.1%) patients in Stage 2, and 1 (3.2%) patient in Stage 3. The ratio of affected and unaffected arm bioimpedance mean values were calculated. Although, this ratio at 50-100-200 kHz Z and 50kHz R were significantly correlated with the lymphedema stages ($p < 0.05$), there was no correlation and significant difference between the ratio of the bioimpedance values and lymphedema severity ($p > 0.05$).

Conclusion: The BIS technique is timesaving and can determine lymphedema stages. We found a significant correlation between BCRL stages and BIS, and it appears that BIS is an appropriate, inexpensive, simple, and noninvasive technique for detecting the stages of BCRL.

Keywords: Bioimpedance spectroscopy, breast cancer, lymphedema, stages, severity

INTRODUCTION

Breast cancer (BC) is the most common cancer among women with an estimated 2.3 million new cases in 2020, accounting for 11.7% of all cancers. This disease is also the leading cause of cancer deaths in more than 100 countries. Its incidence and mortality rates are gradually increasing in developing countries, including Turkey (1).

Breast cancer-related lymphedema (BCRL) is one of the most frightening and disturbing complications of BC treatment caused by obstruction of lymphatic ducts and lymph nodes and infiltration with tumor cells (lymphangitis carcinomatosa) (2).

Traditionally, BCRL has been associated with multidisciplinary treatments (breast-conserving surgery versus mastectomy; axillary lymph node dissection (ALND) and sentinel lymph node biopsy (SLNB); radiation therapy including regional nodal irradiation, regional nodal-free irradiation) and systemic treatments (3).

Early diagnosis and monitoring of the disease, even in subclinical BCRL, allows for reduced limb volume. Conventional methods used to obtain limb measurements include perometer, arm circumference, and water displacement. Besides, the early stage of BCRL can be identified via some techniques that include dual energy X-ray absorptiometry (DXA), bioimpedance spectroscopy (BIS), computed tomography (CT), magnetic resonance imaging (MRI), lymphoscintigraphy, color doppler imaging, and lymphography (4).

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Impedance (Z) is an electrical term that represents the capacity of a material to resist alternating current flow. When an electrical potential is applied to the tissue, the current flows through the intra and extra-cellular spaces at high frequencies, and the current passes extracellular spaces at low frequencies. The cell membrane acts as an insulator at low frequencies while acts as a conductor at high frequencies. Resistance (R) and reactance (X_C) are the components of Z and X_C is related to the capacitance that generates the phase shift that is determined by the phase angle [$PA = \tan^{-1}(X_C/R)$].

Bioimpedance analysis is a potential tool with proven benefits in the diagnosis and follow-up of even subclinical BCRL (5). In recent years, early diagnosis of BCRL has focused on non-invasive and less costly interventions (6,7).

Bioimpedance values were simultaneously measured with electrodes and these values were compared with the conventional circumference tape measurement (TM) technique. The aim of our study was to investigate the electrical differentiation of BCRL patients' healthy and affected arms. We hypothesized that the BIS could be used as a non-invasive, quick diagnostic tool especially in BCRL patients with early stage.

MATERIAL and METHODS

Study Design

A total of 31 patients diagnosed with BCRL who applied to Sanko University Faculty of Medicine Physical Medicine and Rehabilitation between January 2020 and August 2020 for the first time or control purposes were included in this cross-sectional descriptive research. Age, body mass index (BMI), disease severity and stages, disease durations, history of radiotherapy (RT), chemotherapy (CT), hormone replacement therapy (HRT), and neoadjuvant therapy (NT), types of surgery, and the number of positive dissected lymph nodes were recorded. The inclusion criteria were defined as: (1) an affected arm circumference of 2 cm greater than that of the healthy; (2) the presence of BCRL for at least a month or longer; (3) being aged 18 years over. All volunteers who met these criteria were recruited in our study. The exclusion criteria were defined as: (1) Patients with metastatic or advanced cancer; (2) those with bilateral BC; (3) those with a previous history of neurologic and/or orthopedic disease in the affected arm. This clinical research was conducted at Physical Medicine and Rehabilitation department with the approval of the Sanko University Ethics Committee (2020/01-01). Written informed consent was acquired from all BCRL patients.

Circumferential measurements (cm) of the arms taken at the same place were made using a TM.

Lymphedema severity was defined according to the difference between the extremities (affected and unaffected) that was adopted by the American Physiotherapy Association (8). Lymph-

edema staging was evaluated with a degree between 0 and 3 according to the International Society of Lymphology. In this regard, BCRL patients were classified as:

Stage 0: subclinical lymphedema;

Stage 1: spontaneous reversible;

Stage 2: spontaneous irreversible;

Stage 3: severe lymphedema (9).

Bioimpedance Measurements

Bioimpedance Analyzer (Quadscan 4000, Bodystat Inc.) device was used for bioimpedance measurement, and it was connected to the 1.0 cm disposable Ag/AgCl disc electrodes (3M, Brazil). The electrode placement protocol was set to maximize the current pathway in the arm and minimize the variable's influence. For this reason, the volunteers were seated, and two-disc electrodes were placed on the 10 cm above and below the elbow of affected and unaffected arms. We used electrodes to send an electrical signal to the arms and get its response (10). Current at multiple frequencies was given to the affected and unaffected arm of the patients and the Z at multiple frequencies (5-50-100-200 kHz), PA , R , and X_C values at 50 kHz were recorded according to this current information. These bioimpedance measurements were applied to all volunteers in cooperation with the Physical Therapy and Rehabilitation Department. Acquired bioimpedance values were recorded to examine the correlation between the BIS values and severity and stages of lymphedema. Numerous bioimpedance analyzers use 50 kHz as a frequency where the capacitor's X_C becomes relatively small so that the current is represented mostly by the R . The 50 kHz is one of the most basic and optimal frequencies. Also, most literature has been carried out using bioimpedance devices with a frequency of 50 kHz to discriminate the biological structures (11). For this reason, we found it appropriate to give your R , PA , and X_C values only at 50 kHz. Three bioimpedance measurements were taken from each volunteer within 1-2 minutes, and the ratio of affected to unaffected arm bioimpedance mean values were used for analysis. Because Z , R , X_C , and PA decrease with increased fluid, the ratio was expressed as affected/unaffected to provide a lymphedema index less than 1.

Statistical Analysis

IBM SPSS Statistics 23 was utilized for statistical analyses (12). As descriptive statistics: mean \pm standard deviation and median (min-max values) values for continuous variables, frequency, and percentages for qualitative variables were given. We performed a Kendall Tau-B coefficient to investigate the correlation between mean values ratio of Z at multiple frequencies (5-50-100-200 kHz), PA , R , and X_C values at 50 kHz, and severity, and stages of lymphedema. P-values less than 0.05 were considered statistically significant.

RESULTS

A total of 31 female patients were included in our study to compare BIS with standard diagnostic techniques. Demographic and clinical-pathological data of the patients were given in Table 1. Mean age of the volunteers was 52.58 ± 8.72 . Their average BMI was 28.30 ± 4.49 kg/m². Median number of positive dissected lymph nodes was 9 (0-55). Median disease duration was 12 (1-108) months, and the onset of BCRL was 8 (1-84) months for patients. The stage distribution was as follows; 15 (48.4%) patients in Stage 0, 10 (32.3%) patients in Stage 1, 5 (16.1%) patients in Stage 2, and 1 (3.2%) patient in Stage 3. Cancer types among patients were invasive ductal carcinoma (87.1%); invasive lobular carcinoma (9.7%); and sarcoma (3.2%). The pathological stages of the patients in the study were mostly staged 2A (32.3%). Most of the patients who developed lymphedema after surgery had received CT (71%) and RT (51.6%). The severity of lymphedema among the patients was as follows: mild 14 (45.2%), moderate 10 (32.3%), and severe 7 (22.6%). Affected and unaffected arm bioimpedance mean values and their ratios were given in table 2. Although, the ratio of 50-100-200 kHz Z (Figure 1) and 50 kHz R (Figure 2) values were significantly correlated with the lymphedema stages ($p < 0.05$) (Table 3), there was no correlation and significant difference between the ratio of the bioimpedance values and lymphedema severity ($p > 0.05$) (Table 4).

DISCUSSION

The primary object of this study was to investigate whether bioimpedance measurements could help in predicting the severity and staging of lymphedema in BCRL patients. The ratio of 50-100-200 kHz Z and 50 kHz R values were significantly correlated with the lymphedema stages ($p < 0.05$) and this result agrees with results from previous studies (13-15).

There was no correlation and significant difference between the ratio of the bioimpedance values and lymphedema severity ($p > 0.05$).

BCRL may develop months or even years after diagnosis and treatment start (16,17) where the critical point is not to miss the latent stage in follow-up, even if patients do not have clinical edema despite the presence of lymphatic dysfunction. The average time for lymphedema development was 8 (1-84) months in our study.

BCRL is known as a significant clinical problem for BC survivors in that causes a negative impact on the quality of life (18). While there is no definitive way to predict patients likely to develop BCRL, a consensus has been reached on some risk factors such as ALND (19), BMI (20), ALN radiotherapy (19), and the number of positively dissected lymph nodes (21). The risk of BCRL is significantly higher in patients who underwent a total mastectomy and modified radical mastectomy compared to patients

Table 1. Demographics of the patients

Characteristics	
Age ^a	52.58 ± 8.72
BMI ^a	28.30 ± 4.49
Cancer type ^b	
IDC	27 (87.1%)
ILC	3 (9.7%)
SAR	1 (3.2%)
Disease stage ^b (Pathology report)	
1	2 (6.5%)
2A	10 (32.3%)
2B	8 (25.8%)
3A	8 (25.8%)
3C	3 (9.7%)
Affected extremity ^b	
Right	14 (45.2%)
Left	17 (54.8%)
Dominant extremity ^b	
Right	27 (87.1%)
Left	4 (12.9%)
Type of surgery ^b	
Modified Radical Mastectomy	21 (67.7%)
Total Mastectomy	10 (32.3%)
RT ^b	
Yes	16 (51.6%)
No	15 (48.4%)
CT ^b	
Yes	22 (71%)
No	9 (29%)
HRT ^b	
Yes	10 (32.3%)
No	21 (67.7%)
NT ^b	
Yes	4 (12.9%)
No	27 (87.1%)
Severity of lymphedema ^b	
Mild	14 (45.2%)
Moderate	10 (32.3%)
Severe	7 (22.6%)
Lymphedema stage ^b	
Stage 0	15 (48.4%)
Stage 1	10 (32.3%)
Stage 2	5 (16.1%)
Stage 3	1 (3.2%)
Disease duration (months) ^c	12 (1-108)
Number of dissected positive lymph node ^c	9 (0-55)
The onset of BCRL (months) ^c	8 (1-84)
BMI: Body mass index, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma sarcoma, SAR: Sarcoma, CT: Chemotherapy, RT: Radiotherapy, NT: Neoadjuvant therapy, HRT: Hormone replacement therapy, BCRL: Breast cancer-related lymphedema, ^a (Mean ± SD), ^b n (%), ^c [Median (min-max)].	

Table 2. Bioimpedance values

Factors	Frequency	Affected arm	Unaffected arm	Ratio of affected to unaffected arm
Impedance (Z)	5 kHz	1419.11 ± 747.43	1496.89 ± 793.33	0.96 ± 0.19
	50 kHz	500.41 ± 119.31	525.35 ± 162.89	0.97 ± 0.14
	100 kHz	437.86 ± 85.49	448.40 ± 96.46	0.98 ± 0.13
	200 kHz	405.50 ± 73.95	411.73 ± 74.03	0.99 ± 0.13
Resistance (R)	50 kHz	452.23 ± 82.26	461.32 ± 84.77	0.98 ± 0.12
Reactance (X _c)	50 kHz	196.98 ± 121.11	225.54 ± 178.85	0.94 ± 0.21
Phase angle (PA)	50 kHz	22.20 ± 8.62	23.76 ± 10.37	0.96 ± 0.15

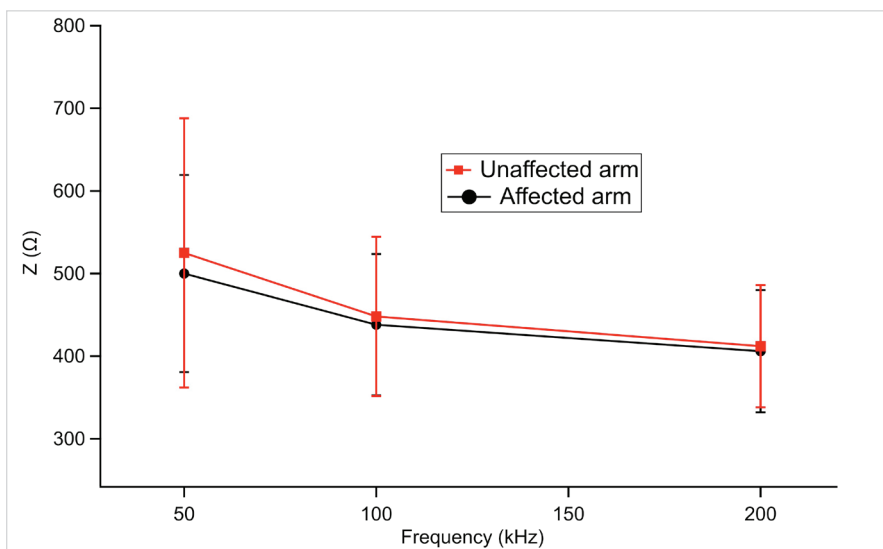


Figure 1. Affected and unaffected arm Z values at 50-100-200 kHz.

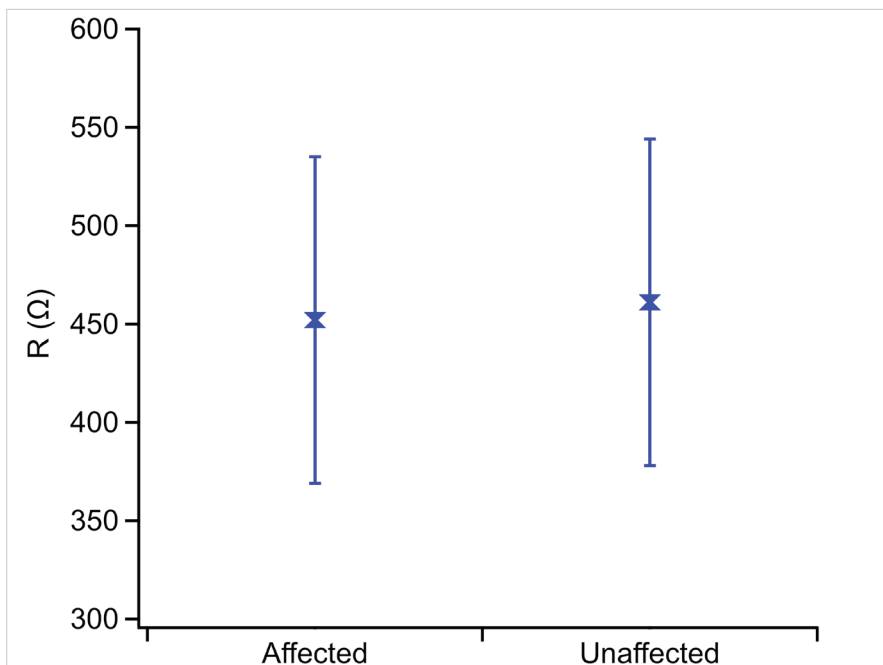


Figure 2. Affected and unaffected arm R values at 50 kHz.

Table 3. Correlation of bioimpedance ratio values and lymphedema stages

Factors	Frequency	p
Impedance (Z)	5 kHz	0.052
	50 kHz	0.012*
	100 kHz	0.015*
	200 kHz	0.021*
Resistance (R)	50 kHz	0.015*
Reactance (X_C)	50 kHz	0.115
Phase angle (PA)	50 kHz	0.781

* Correlation is significant $p < 0.05$.

Table 4. Correlation of bioimpedance ratio values and lymphedema severity

Factors	Frequency	p
Impedance (Z)	5 kHz	0.659
	50 kHz	0.825
	100 kHz	0.713
	200 kHz	0.769
Resistance (R)	50 kHz	0.825
Reactance (X_C)	50 kHz	0.769
Phase angle (PA)	50 kHz	0.912

who did not undergo axillary intervention. Similar to the previous literature, axillary surgery 67.7% (n= 21), RT 51% (n= 16), number of dissected lymph nodes [9 (0-55)], and BMI (28.30 \pm 4.49) values were found compatible with lymphedema development in our study.

Mean age of the patients was 52.58 \pm 8.72 in our study. The presence of CT history was 71% (n= 22) among patients, and the number of patients receiving NT was very low 12.9% (n= 4). It is still controversial whether age (22-24) and CT (24,25) are risk factors for BCRL.

Among the extremity circumferential measurements used in the diagnosis and follow-up of BCRL, there are many non-invasive volumetric measurement methods such as water displacement, perometer, and 3D laser scanning (26). However, assessment of volume alone is insufficient as results depend on subjective estimates. Circumferential measurements do not provide an accurate assessment of volume. The displacement of water is not a hygienic method, and it does not provide information about the swelling localization. Although the perometer method detects localized lymphedema, the results are highly variable and not very reliable as arm tissue composition is not evaluated. 3D laser scanner can detect extremely small variations of arm volume, but it is a costly assessment method with difficulties in identifying arm reference points. Lymphoscintigraphy is currently considered the gold standard imaging

technique for the diagnosis of limb lymphedema. However, it has disadvantages such as exposure to radiation, low resolution, and high cost (27).

Compared to traditional methods, BIS seems to be more objective and more specific, and sensitive in studies (80-99%) (28).

We evaluated the performance of BIS based on severity and clinical stage. According to extremity circumference measurements, 14 (45.2%) of our patients were in the mild stage. Clinical symptoms vary in each patient according to the severity of BCRL. However, in our study, there was no correlation and no significant difference between the ratio of bioimpedance values and the severity of lymphedema.

The International Lymphedema Society (ISL) defines lymphedema stages as 0 to 3. Among the volunteers, 15 stages 0 patients had subjective complaints such as heaviness, tightness, and numbness in the arms or hands but did not have any apparent swelling. Patients with Stage 0 lymphedema can live for months or years without showing any symptoms (9). Stage 0-1 lymphedema is considered reversible with treatment. This stage, which is defined as the latent phase, may not always be easily detected by physical examination. BIS technique is a potential for the detection of this reversible subclinical phase, which can last for months or years and even result in progressive and fibrotic lymphedema. Aside from being a safe, painless, and rapid method, BIS provides objective data for the early diagnosis of lymphedema and is reproducible. Traditional diagnostic tools used for early detection and therefore early intervention have limited ability to confirm and detect BCRL. Ward et al. have recommended that bioimpedance is a sensitive and accurate early detection system for identifying patients at risk of developing lymphedema (29).

It is known that BIS can detect lymphedema in as early as four months compared to volume-based evaluation methods (5), thus reducing lymphedema-related morbidity. Soran et al. have detected subclinical lymphedema with BIS- follow-up managed to reduce the incidence of clinical lymphedema from 36.4% to 4.4% with early treatment (30). Because of extreme accumulation of lymph fluid, lymphedema usually results in an overall increase in the total amount of extracellular water in the affected limb. As the volume of extracellular water increases, the Z to the current decreases (31-34). We found Z, R, X_C , and PA values decrease with increased fluid. In our study, it was determined that the device we used did not correlate with the stages of lymphedema at a frequency lower than 50 kHz and the severity of lymphedema at multiple frequencies.

The limitations of our study include the fact that due to the low number of patients (n= 31) and secondly, due to the high number of patients with early-stage lymphedema, it was not possible to estimate how much BIS measurements reflect edema in chronic stage patients, and thirdly, the population in our study consisted of only female patients.

CONCLUSION

Our results show that 50-100-200 kHz Z and 50 kHz R values are correlating factors for the stages of patients with lymphedema. We concluded that these values can be used as a screening tool for predicting the stages of BCRL patients. The BIS technique was timesaving and noninvasive but was not able to determine the lymphedema severity in the present study. There was no significant correlation with arm circumferences changes, and it appears that BIS is not an appropriate technique for detecting the severity of lymphedema. We believe that the bioimpedance device applied in patients undergoing breast surgery will confirm the diagnosis of lymphedema in the subclinical stage and prevent the formation of chronic BCRL.

Ethics Committee Approval: This study was conducted in accordance with the amended Declaration of Helsinki. The institutional review board (Sanko University Ethics Committee (Decision No: 2020/01-01) approved the study, and all participants provided written informed consent.

Peer-review: Externally peer-reviewed.

Author Contributions: Author Contributions: Concept - T.T. T.D.; Design - T.T. T.D.; Supervision - T.T. T.D.; Materials - T.T., G.M.; Data Collection and/or Processing - T.T. T.D.; Analysis and/or Interpretation - T.T.; Literature Search - T.T. T.D.; Writing Manuscript - T.T. T.D.; Critical Reviews - All of authors.

Conflict of Interest: The authors have no conflicts of interest to declare.

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ORJİNAL ÇALIŞMA-ÖZET

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Meme kanserine bağlı lenfödem şiddeti ve evrelerinde biyoimpedans spektroskopisi yönteminin rolü

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ÖZET

Giriş ve Amaç: Meme kanserine bağlı lenfödem (BCRL) hastalarında lenfödem şiddeti ile standart tanı yöntemleri ve Biyoimpedans Spektroskopisi (BIS) tekniği ile belirlenen evreler arasındaki korelasyon incelendi.

Gereç ve Yöntem: Biyoimpedans analiz cihazı, hastaların etkilenen ve etkilenmeyen (sağlıklı) koluna bağlanan 1.0 cm'lik disk elektrotlara bağlandı. Çoklu frekanslarda (5-50-100-200 kHz) ve faz açısında (PA), dirençte (R) ve 50 kHz'de reaktansa (XC) empedansın (Z) performansını lenfödem şiddeti ve evreleri üzerinde değerlendirdik. Fizik Tedavi ve Rehabilitasyon Bölümü ile iş birliği içinde tüm gönüllülere biyoimpedans ölçümleri yapıldı. Bu çalışmada BCRL şiddeti ile evreleri ve biyoimpedans değerleri arasındaki ilişki incelenmiştir.

Bulgular: BIS tekniğini standart tanı teknikleri ile karşılaştırmak için toplam 31 kadın çalışmaya alındı. Hastalar arasında lenfödem şiddeti şu şekilde bulundu; hafif 14 (%45.2), orta 10 (%32.3) ve şiddetli 7 (%22,6). Gönüllülerin etap dağılımı ise; Evre 0'da 15 (%48,4) hasta, Evre 1'de 10 (%32,3), Evre 2'de 5 (%16,1) hasta ve Evre 3'te 1 (%3,2) hasta etkilenen ve etkilenmeyen kol biyoimpedans ortalaması oran değerleri hesaplandı. 50-100-200 kHz Z ve 50kHz R'de bu oran lenfödem evreleri ile anlamlı olarak korele olmasına rağmen (p< 0,05), biyoimpedans değerlerinin oranı ile lenfödem şiddeti arasında korelasyon ve anlamlı fark yoktu (p> 0,05).

Sonuç: BIS tekniği zamandan tasarruf sağlar ve lenfödem evrelerini belirleyebilir. BCRL evreleri ile BIS arasında anlamlı bir korelasyon bulduk ve BIS'nin BCRL evrelerini saptamak için uygun, ucuz, basit ve invaziv olmayan bir teknik olduğu görülüyor.

Anahtar Kelimeler: Biyoimpedans spektroskopisi, meme kanseri, lenfödem, evreler, şiddet

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