Lymphology 52 (2019) 134-142

BIOIMPEDANCE SPECTROSCOPY IS NOT ASSOCIATED WITH A CLINICAL DIAGNOSIS OF BREAST CANCER-RELATED LYMPHEDEMA

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ABSTRACT

The objective of this study was to evaluate the accuracy of bioimpedance spectroscopy measurements (L-Dex) in the diagnosis of breast cancer-related lymphedema. A retrospective review of a prospectively maintained database was performed of all patients that underwent surgical treatment for breast cancer at a tertiary medical center. Patients who had preoperative and postoperative evaluation for possible lymphedema by limb circumference measurements and bioimpedance were eligible for inclusion in the study. No significant demographic differences were found between the group of patients clinically diagnosed with lymphedema (N=134) and those without a clinical diagnosis of lymphedema (N=261). The ability of bioimpedance to diagnose lymphedema based on the manufacturer's criteria demonstrated low sensitivity, which was 7.5% when lymphedema was defined as an absolute L-Dex value greater than 10, and 24.6% when defined as a relative change of >10 between preoperative and postoperative measurements. This corresponded with a positive predictive value of 61-71% and a negative predictive value of 67-70%. We are unable to recommend the use of bioimpedance as a screening tool or for measurement of breast cancer-related lymphedema.

Keywords: lymphedema, breast cancer-related lymphedema, bioimpedance spectroscopy, L-Dex, tape measurements, predictive value

Lymphedema is a serious complication that, in the Western world, is mostly iatrogenic, associated with the treatment of cancer and manifests itself as swelling (volume excess), tightness, heaviness, pain, fibrosis and in some with recurrent episodes of cellulitis in the affected area of the body (1). Current treatments aimed at curing cancer often include multiple modalities, such as surgical resection, chemotherapy, and radiation therapy, all of which increase the patient's risk for the development of lymphedema to the region distal to the treated cluster of lymph nodes (2,3). Unfortunately, there is no standardized method for measuring lymphedema (4,5).

Clinical definitions and measurements of lymphedema are inconsistent in the literature (5,6). This presents a significant dilemma for clinicians monitoring treatment. Numerous methods exist to evaluate lymphedema in clinical settings but these methods rely on quantifying changes in volume or circumference of the affected extremity or head and neck region, which fails to capture changes in tissue composition associated with disease progression (6). Methods currently utilized include water displacement, tape circumference, tonometry, and perometry (1,4,7,8). None of these methods address the underlying etiology

of the volume change specific to lymphedema, namely the excess proteinaceous fluid accumulation due to inefficient clearance (9).

A newer technology, bioimpedance spectroscopy (bioimpedance), evaluates tissue fluid fluctuations. Bioimpedance relies on detecting the change of tissue impedance to a small amount of introduced electrical current or applied potential over a set distance of measurement electrodes (10-13). As tissues retain increasing amounts of fluid, bioimpedance decreases over time. The bioimpedance device most widely used in clinical practice measures lymphedema through a proprietary Lymphedema Index (L-Dex) score, which utilizes frequency dependent current flow to quantify changes in extracellular fluid in the patient's limb (L-Dex - Trademark of ImpediMed, Carlsbad, CA, USA). L- Dex scores that lie outside of the normal range (-10 to +10 L-Dex units) for this scale or those scores that represent a 10-point increase from prior measurements in the same patient are said to be indicators of lymphedema (14).

Here we sought to evaluate our experience with bioimpedance measurements and the relationship of L-Dex Scores to clinically evident secondary lymphedema in breast cancer patients.

METHODS

All patients who underwent surgical treatment of breast cancer at Ohio State University Wexner Medical Center from January 2013 - January 2015 were reviewed retrospectively after approval by the Institutional Review Board. Patient data were collected from the electronic health record using physical therapy visits, operative reports, and plastic surgery notes. Patient L-Dex scores, circumferential arm tape measurements, age, gender, comorbidities, surgical history, treatment history, and clinical diagnosis of lymphedema were examined. Individuals with metal implants and/or pacemakers were excluded, based upon recommendations of the impedance device manufacturer. Pregnant women, patients with bilateral disease, and patients with renal failure or heart failure were excluded because of patterns of fluid fluctuation associated with these medical conditions. Patients with incomplete or missing data were excluded from this study.

All patients who met inclusion criteria were examined by an experienced lymphedema physical therapist at our Breast Center both before and within one year after surgical treatment of breast cancer. During each examination, any pitting edema and subcutaneous fibrosis, Stemmer's sign, range of motion of the upper limb joints, patient report of symptoms, and sensory and motor functions were evaluated. Circumference measurements were performed at two points: 10 cm proximal to the styloid process in the forearm, and 10 cm proximal to the medial epicondyle in the upper arm. A single set of measurements was performed and used to calculate inter-arm difference. Hand dominance was not taken into account. Bioimpedance measurements were also taken at the same visit as detailed below. A clinical diagnosis of lymphedema was made by the lymphedema physical therapist, based on physical examination and circumference measurements, and served as our clinical standard against which bioimpedance measurements were compared.

The bioimpedance measurement was performed using a multi-frequency bioimpedance analysis device developed for extracellular fluid measurement (L-Dex U400®, ImpediMed, Carlsbad, CA). During the procedure, an alternative current with a frequency between 3 KHz and 1000 KHz was applied through the electrodes placed at the wrists and the resistance of the extracellular fluid against this current was measured.

Before the measurement, the patent's age, dominant limb, and the side of surgery were entered into the device. For the measurement, the patient was brought to the supine position, and after both wrists and right ankle of the patient were cleaned with a skin antiseptic, special electrodes were attached. The colored wires of the device were connected to the

electrodes in line with the instruction manual and measurements were conducted first on the right arm, followed by the left arm. The difference of the extracellular fluid between both arms was recorded as the unit of lymphedema. According to the manufacturer, an absolute L-Dex value greater than 10, or a relative change of +10 L-Dex units from the patient's baseline value is indicative of a diagnosis of lymphedema (14). In addition, further analysis was performed utilizing additional criteria that have been proposed, specifically where lymphedema is defined as an absolute L-Dex value greater than 6.5, or a relative change of +6.5 L-Dex units from the patient's baseline value (15).

Statistical Analysis

Sensitivity, specificity, positive predictive value, and negative predictive value were used to evaluate the ability of L-Dex scores to measure lymphedema. Frequency data were compared using the Fisher test or chi-square test, as appropriate. Continuous data were compared using the Mann-Whitney test. All tests were two tailed. The p-values < 0.05 were considered significant. All analyses were performed using SPSS version 25 (IBM Corp, Armonk, NY).

TABLE 1
Patient Characteristics

		Lymphedema present (n=134)		Lymphedema absent (n=261)		P
		Avg or n	SD or %	Avg or n	SD or %	
Age		56.28	11.85	60.55	12.62	0.36
Sex	Female	134	100.0%	260	99.6%	0.55
	Male	0	0.0%	2	0.8%	
BMI		31.55	6.80	29.32	7.06	0.88
Radiotherapy	Yes	99	73.9%	144	55.2%	*0.0003*
	No	35	26.1%	117	44.8%	
Chemotherapy	Yes	111	82.8%	146	55.9%	*0.0001*
	No	23	17.2%	115	44.1%	
Surgical therapy (breast)	Lumpectomy	40	29.9%	123	47.1%	*0.0012*
	Mastectomy	94	70.1%	138	52.9%	
Surgical therapy (axilla)	SLNB	29	21.6%	175	67.0%	*0.0001*
	ALND	105	78.4%	86	33.0%	
Last L-Dex	Actual	8.2	9.8	3.2	4.0	
	Absolute	8.7	9.3	4.1	3.1	
Initial L-Dex	Actual	2.2	8.9	0.5	25.4	
	Absolute	5.6	7.2	5.7	24.7	
		Diff > 10	Diff < 10			
Lymphedema	33	101	134		Sp	92.0%
No lymphedema	21	241	262		Sn	24.6%
	54	342			PPV	61.1%
	54	342			NPV	70.5%

RESULTS

A total of 395 patients met inclusion criteria, of which there were 134 (33.9%) patients with lymphedema and 261 (66.1%) patients without lymphedema based on physical examination and limb circumference measurements. As expected, the difference in limb circumference measurements between the unaffected limb and affected limb was greater in patients with lymphedema compared to patients without lymphedema ($p = 0.017$ at forearm, $p = 0.02$ at upper arm). A summary of the characteristics of the study population is presented in *Table 1.* There were no significant differences identified between patients with and without lymphedema with respect to age ($p=0.76$), sex ($p=1.00$), or BMI ($p=0.88$). Patients with a clinical diagnosis of lymphedema were more likely to have undergone mastectomy ($p=0.0012$), axillary lymph node dissection ($p=0.0001$), chemotherapy ($p=0.0001$), and radiation therapy ($p=0.0003$). The mean follow up period was 10.2 months (7.1-12.0 months).

The average postoperative L-Dex score was 2.1 ± 6.4 for all patients. The average absolute L-Dex score was 2.2 ± 8.9 and 2.1 ± 4.6 for patients with and without lymphedema, respectively ($p = 0.77$). Of the patients with lymphedema, 10 (7.5%) patients demonstrated an absolute bioimpedance >10, 124 (92.5%) patients demonstrated an absolute bioimpedance <10, 33 (24.6%) patients demonstrated a relative change in bioimpedance >10, and 101 (75.4%) patients demonstrated a relative change in bioimpedance <10. Of the patients without a clinical diagnosis of lymphedema, 4 (1.5%) demonstrated an absolute bioimpedance >10, 258 (98.5%) patients demonstrated an absolute bioimpedance <10, 21 (8.0%) demonstrated a relative change in bioimpedance >10, and 241 (92.0%) demonstrated a relative change in bioimpedance <10. When utilizing the criteria of an absolute bioimpedance measurement of greater than 10 L-Dex units for diagnosis of lymphedema compared to patients with a clinical diagnosis of lymphedema based on physical exam and tape measurements, L-Dex exhibited a sensitivity of 7.5% and a specificity of 98.5%, with a positive predictive value of 71.4% and a negative predictive value of 67.5%. When utilizing the criteria of a relative change in bioimpedance between two separate measurements of +10 L-Dex units, L-Dex exhibited a sensitivity of 24.6% and a specificity of 92.0%, with a positive predictive value of 61.1% and a negative predictive value of 70.5% when compared to patients with a clinical diagnosis of lymphedema based on physical exam and tape measurements.

Further analysis was performed utilizing alternative criteria that have been proposed for the use of bioimpedance in lymphedema patients. When utilizing the criteria of an absolute bioimpedance measurement of greater than 6.5 L-Dex units for diagnosis of lymphedema compared to patients with a clinical diagnosis of lymphedema based on physical exam and tape measurements, L-Dex exhibited a sensitivity of 22.4% and a specificity of 90.8%, with a positive predictive value of 55.6% and a negative predictive value of 69.6%. When utilizing the criteria of a relative change in bioimpedance between two separate measurements of +6.5 L-Dex units, L-Dex exhibited a sensitivity of 41.0% and a specificity of 86.6%, with a positive predictive value of 56.1% and a negative predictive value of 73.5% when compared to patients with a clinical diagnosis of lymphedema based on physical exam and tape measurements.

DISCUSSION

Breast cancer related lymphedema represents a great physical and psychological burden for patients with increased rates of anxiety and depression, perceived social and sexual dysfunction, and lower quality of life (3,16). It is associated with heaviness, pain, decreased mobility, disfigurement, difficulty fitting clothing, and a constant reminder of the prior cancer (17). Other complications include

increased risk of infection and higher overall medical costs (an increase of nearly $10,000 per year over those individuals without lymphedema) placing a greater burden on cancer survivors and society (17). It is imperative that we find a reproducible, efficient, hygienic, cost- effective way to measure lymphedema in order to provide appropriate diagnosis and evaluate treatment (18).

Bioimpedance measurements are an attractive method of evaluating BCRL due to the relatively quick measurement with a dichotomous result and the device is simple to operate, which makes it easy to incorporate into clinical practice (1,19,20). Therefore, we set out to determine if bioimpedance measurements were a reliable indicator of BCRL in our patient population of breast cancer survivors who had undergone prior treatment.

We found 33.9% of our treated breast cancer patients had a clinical diagnosis of lymphedema by limb circumference measurements, which is comparable to other rates in the literature (0-56%) (2,21-23). The two groups of patients (those diagnosed with and without lymphedema postoperatively) were similar with respect to age, sex, and BMI. While a higher BMI predisposes to lymphedema (24,25), we did not find a statistically significant difference of obese patients in the group diagnosed with lymphedema post breast cancer treatment in our patient population. This may have been the result of our study population size and composition, and the multifactorial nature of lymphedema pathogenesis. Similar to other findings in the literature, the patients who were clinically diagnosed with lymphedema postoperatively were more likely to have undergone mastectomy (p=0.0012), axillary lymph node dissection (p=0.0001), chemotherapy (p=0.0001), and radiation therapy (p=0.0003) (1,2,5,7,20,24,26).

While there is no gold standard in lymphedema measurement, a commonly accepted definition is a 2 cm increase in limb circumference or a 2 cm inter-limb difference (or 200 ml of difference in limb volume if water displacement is used) (5,15,27). In patients diagnosed with lymphedema by the criteria listed above, tape measurements at both the affected forearm and upper arm were significantly greater than the contralateral unaffected arm at both data points.

The main aim of this study was to evaluate how the L-Dex score compares to clinical diagnosis of lymphedema based on tape measurements, clinical exam, and patient symptoms. We did not find that the L-Dex scores were accurate in diagnosing lymphedema when compared to our clinical diagnoses. The average postoperative L-Dex score was 2.1 ± 6.4 for all patients. The average absolute L-Dex score was 2.2 ± 8.9 and 2.1 ± 4.6 for patients with and without lymphedema, respectively (p = 0.77). If there was good correlation between patients with clinical lymphedema and L-Dex scores, we would expect patients with clinical lymphedema to have an average L-Dex score >10 or 10 points above their baseline. This was not the case.

In this study, we chose to apply the manufacturer's criteria for the diagnosis of lymphedema using bioimpedance spectroscopy. Other investigators have proposed alternative criteria, such as utilizing a 2 SD (L-Dex score >6.5, or a change of >6.5 compared to baseline) rather than a 3 SD (L-Dex score >10, or a change of >10 compared to baseline) cutoff (19,28). The choice of which criteria to apply might certainly have implications with regard to the interpretation of our results. Thus, we additionally analyzed this alternative criteria of 2 SD, and observed marginal improvements in sensitivity compared to the 3 SD criteria, as might be expected. However, sensitivity remained relatively low, and came at the expense of a decrease in specificity.

Bioimpedance testing is currently in practice to screen patients for lymphedema (8,19,20,24,29,30). In general, screening tests should have a high sensitivity so that few patients have a false negative result, and a high specificity so that few patients will require further testing or treatment if they receive a false positive result (31). When utilizing the criteria of an absolute bioimpedance mea-

surement of greater than 10 L-Dex units for diagnosis of lymphedema, L-Dex exhibited a sensitivity of 7.5% and a specificity of 98.5%, with a positive predictive value of 71.4% and a negative predictive value of 67.5%. Therefore, with such a low sensitivity, it is not able to identify a large proportion of patients that were diagnosed with clinical lymphedema in our patient population.

When utilizing the criteria of a relative change in bioimpedance between two separate measurements of +10 L-Dex units, L-Dex exhibited a sensitivity of 24.6% and a specificity of 92.0%, with a positive predictive value of 61.1% and a negative predictive value of 70.5%. While the sensitivity of this diagnostic criterion was improved from the absolute value of 10 units, we do not believe that a sensitivity of 24.6% is adequate for medical decision making and further treatment planning.

Fu et al had similar results to our study when evaluating L-Dex values and tape measurements in women with BCRL (19). Their study evaluated the reliability and reproducibility of 3 consecutive L-Dex measurements in healthy women volunteers, women with breast cancer without lymphedema, and women with BCRL and found strong intra-class correlation coefficients (ICC= 0.99) among healthy women and women at risk for BCRL, however only fair agreement (ICC= 0.69) among women diagnosed with BCRL (19). The unreliable measurements in women with BCRL are likely due to the fact that human tissues are highly heterogeneous material systems with anisotropic properties. Women with lymphedema have an impaired ability to maintain tissue fluid homeostasis, which directly affects the L-Dex measurement and may cause variable readings (32). Moreover, the reduced reliability for L-Dex values in the known lymphedema group may be due to tissue changes, adipose infiltration or more general adiposity (19). Furthermore, structural changes in tissues such as fibrosis, level of tissue hydration and fluid content, and amount of muscle and fat content easily induce variability in measurements from patient to patient (12,33). Therefore L-Dex score comparisons are only meaningful within the same patient over time and may not serve as a reliable staging method of lymphedema.

Other studies in the past have evaluated the role of bioimpedance in patients with lymphedema, but these studies are severely limited in sample size, do not analyze women with breast cancer associated lymphedema, compare bioimpedance to other methods of lymphedema measurements (such as perometry or water displacement), or use a different bioimpedance device (4,8,20,24,29,30,34). Due to the heterogeneity and limited data quality in the literature, we are unable to directly compare our results to these other studies.

Soran et al used bioimpedance to diagnose subclinical lymphedema in women following breast cancer treatment and then instituted compression therapy to women that were diagnosed with subclinical lymphedema and found that there was a low rate of progression to clinical lymphedema versus a control group of similar women at risk for BCRL that did not undergo routine bioimpedance testing due to insurance restrictions (26). While this study demonstrates the importance of early diagnosis and treatment for patients with BCRL, it does not validate the accuracy or reliability of L-Dex values. All the women in this study that were diagnosed as subclinical lymphedema (stage 0) were by definition asymptomatic. It is unclear if the L-Dex value was instrumental in dictating who would benefit from compression wrapping or if all women following breast cancer treatment undergoing prophylactic wrapping would have the same outcome. The reliability of L-Dex values in diagnosing BCRL was not the main objective in this study.

Dylke et al compared the diagnostic accuracy of commonly used methods such as L-Dex and perometer against lymphoscintigraphy as the standard for the diagnosis of lymphedema in women with breast cancer associated lymphedema. Normatively determined thresholds were set at 2SD and 3SD above the mean for all tools utilized. Interestingly, they found that when women with

dermal backflow score of 3 on lymphoscintigraphy were excluded from the analysis, fewer diagnostic thresholds were able to discriminate between patients with lymphedema compared to L-Dex. Similar to our results, Dylke et al found a higher positive likelihood ratio using the arm circumference ratio compared to BIS. They believe this was due to the whole arm being surveyed in the BIS measurement and circumference measurements can pick up isolated areas of lymphedema and have improved detection of localized changes (15). While Dylke et al found a very strong correlation of L-Dex values to circumference measurements and perometer readings at 2 and 3 SD thresholds, these data include 38 women out of 68 in the known breast cancer associated lymphedema group that have well- established lymphedema with an assigned dermal backflow score of 3. Our patient population was evaluated at an average of 10.2 months postoperatively following their surgical breast cancer treatment, and it would be too early to have well established lymphedema at the time point that they were being measured. Therefore, our results are consistent with those of Dylke et al when participants with well established lymphedema were excluded from the analysis.

Limitations inherent to bioimpedance measurements include the need to compare the affected extremity to a non-affected contralateral limb. Some patients with lymphedema have bilateral affected extremities and would not be able to undergo bioimpedance measurements. Additionally, the L-Dex value is based on a ratio of the affected to non-affected limb which has an underlying assumption that the two limbs are symmetric at baseline. Armer et al found that this assumption does not hold true, and that there may be a limb volume difference of 160 ml in healthy women (18). Furthermore, bioimpedance measurements can change significantly with variations in lead placement (12).

The limitations of our study include the small sample size, one set of pre and postoperative tape measurements and L-Dex scores per patient, not controlling for arm dominance, the lack of a gold standard for diagnosing lymphedema and use of a 2 cm inter-arm circumference difference as a surrogate for statistical purposes, and limited long term follow up. The retrospective nature of our study limited our ability to have standard time points postoperatively for clinical lymphedema evaluation and bioimpedance analysis. In the future, we suggest that each patient be measured at consistent postoperative time points that would address potential confounders such as postoperative edema at varying time out from surgery. The study design also limited the way patients with discordance between physical exam and symptoms were classified. The lymphedema physical therapist used her most educated clinical judgment on any individual case where discordance occurred. This should be addressed with a specific protocol in future prospective studies to mitigate the issue. Additionally, we recommend the use of taxanes be recorded for each patient, as they can impact the amount of extremity swelling with use (35).

CONCLUSION

Despite its popularity, L-Dex scores in this study correlated poorly with the presence of clinically evident lymphedema. Furthermore, a clinical improvement in lymphedema was not reflected in improved L-Dex scores. For the majority of our patients with a clinical diagnosis of lymphedema, L-Dex scores were within normal range (sensitivity of 7.5% and 24.6%; based on absolute value and 10 unit change from baseline respectively) making it a poor screening tool for diagnosis. Further studies evaluating tools to measure lymphedema in a reliable, reproducible, convenient, and inexpensive way are still warranted.

ACKNOWLEDGMENTS

The authors thank Dr. William Farrar and

Karen Hock, MS PT CLT-LANA for their help with data collection and outstanding patient care.

CONFLICT OF INTEREST AND DISCLOSURE

The authors declare no competing financial interests exist.

REFERENCES

1. Rockson, SG: Lymphedema after breast cancer treatment. N. Engl. J. Med. 379 (2018), 1937-1944.
2. Kim, M, SW Kim, SU Lee, et al: A model to estimate the risk of breast cancer-related lymphedema: Combinations of treatment-related factors of the number of dissected axillary nodes, adjuvant chemotherapy, and radiation therapy. Int. J. Rad. Oncol. Bio. Phys. 86 (2013), 498-503.
3. Fu, MR, SH Ridner, SH Hu, et al: Psychosocial impact of lymphedema: A systematic review of literature from 2004 to 2011. Psycho-oncology 22 (2013), 1466-1484.
4. Hayes, S, B Cornish, B Newman: Comparison of methods to diagnose lymphoedema among breast cancer survivors: 6-month follow-up. Br. Can. Res. Treat. 89 (2005), 221-226.
5. McLaughlin, SA, AC Staley, F Vicini, et al: Considerations for clinicians in the diagnosis, prevention, and treatment of breast cancer-related lymphedema: Recommendations from a multidisciplinary expert asbrs panel: Part 1: Definitions, assessments, education, and future directions. Ann. Surg. Oncol. 24 (2017), 2818-2826.
6. Johnson, KC, AG Kennedy, SM Henry: Clinical measurements of lymphedema. Lymph. Res. Bio. 12 (2014), 216-221.
7. Sharkey, AR, SW King, RY Kuo, et al: Measuring limb volume: Accuracy and reliability of tape measurement versus perometer measurement. Lymph. Res. Bio. 16 (2018), 182-186.
8. Ward, LC, S Czerniec, SL Kilbreath: Operational equivalence of bioimpedance indices and perometry for the assessment of unilateral arm lymphedema. Lymph. Res. Bio. 7 (2009), 81-85.
9. The Diagnosis and Treatment of Peripheral Lymphedema: 2016 Consensus Document of the International Society of Lymphology. Lymphology 49 (2016), 170-184.
10. Bard, AJ, LR Faulkner: Electrochemical methods: Fundamentals and Applications. Hoboken, NJ: Wiley; 1980.
11. Bayford, R, A Tizzard: Bioimpedance imaging: An overview of potential clinical applications. Analyst 137 (2012), 4635-4643.
12. Prakash, S, MP Karnes, EK Sequin, et al: Ex vivo electrical impedance measurements on excised hepatic tissue from human patients with metastatic colorectal cancer. Physio. Measure. 36 (2015), 315-328.
13. Vitarelli, MJ, Jr, S Prakash, DS Talaga: Determining nanocapillary geometry from electrochemical impedance spectroscopy using a variable topology network circuit model. Ana. Chem. 83 (2011), 533-541.
14. ImpediMed I. L-Dex U400 Datasheet Manufacturer. Carlsbad, CA. Mar 2016.
15. Dylke, ES, GP Schembri, DL Bailey, et al: Diagnosis of upper limb lymphedema: Development of an evidence-based approach. Acta Oncol. (Stockholm, Sweden). 55 (2016), 1477-1483.
16. Fallowfield, L, V Jenkins: Psychosocial/survivorship issues in breast cancer: Are we doing better? JNCI. 107 (2015), 335.
17. Shih, YC, Y Xu, JN Cormier, et al: Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: A 2-year follow-up study. J. Clin. Oncol. 27 (2009), 2007-2014.
18. Armer, JM: The problem of post-breast cancer lymphedema: impact and measurement issues. Can. Invest. 23 (2005), 76-83.
19. Fu, MR, CM Cleland, AA Guth, et al: L-dex ratio in detecting breast cancer-related lymphedema: Reliability, sensitivity, and specificity. Lymphology 46 (2013), 85-96.
20. Vicini, F, C Shah, M Lyden, et al: Bioelectrical impedance for detecting and monitoring patients for the development of upper limb lymphedema in the clinic. Clin. Breast Can. 12 (2012), 133-137.
21. Sakorafas, GH, G Peros, L Cataliotti, et al: Lymphedema following axillary lymph node dissection for breast cancer. Surg. Oncol. 15 (2006), 153-165.
22. Erickson, VS, ML Pearson, PA Ganz, et al: Arm edema in breast cancer patients. JNCI. 93 (2001), 96-111.
23. Deutsch, M, S Land, M Begovic, et al: The incidence of arm edema in women with breast cancer randomized on the National Surgical Adjuvant Breast and Bowel Project study B-04 to radical mastectomy versus total mastectomy and radiotherapy versus total mastectomy alone. Int. J. Rad. Oncol., Bio., Phys. 70 (2008), 1020-1024.

24. Erdogan Iyigun, Z, D Selamoglu, G Alco, et al: Bioelectrical impedance for detecting and monitoring lymphedema in patients with breast cancer. Preliminary results of the Florence Nightingale breast study group. Lymph. Res, Bio. 13 (2015), 40-45.
25. Soran, A, E Menekse, M Girgis, et al: Breast cancer-related lymphedema after axillary lymph node dissection: Does early postoperative prediction model work? Suppor. Care in Can. 24 (2016), 1413-1419.
26. Soran, A, T Ozmen, KP McGuire, et al: The importance of detection of subclinical lymphedema for the prevention of breast cancer-related clinical lymphedema after axillary lymph node dissection: A prospective observational study. Lymph. Res. Bio. 12 (2014), 289-294.
27. Armer, JM, ME Radina, D Porock, et al: Predicting breast cancer-related lymphedema using self-reported symptoms. Nurs. Res. 52 (2003), 370-379.
28. Dylke, ES, J Yee, LC Ward, et al: Normative volume difference between the dominant and nondominant upper limbs in healthy older women. Lymph. Res. Bio. 10 (2012), 182-188.
29. Yasunaga, Y, D Yanagisawa, E Ohata, et al: Bioelectrical impedance analysis of water reduction in lower-limb lymphedema by lymphaticovenular anastomosis. J. Reconstr. Microsurg. 35 (2019), 306-314.
30. Warren, AG, BA Janz, SA Slavin, et al: The use of bioimpedance analysis to evaluate lymphedema. Ann. Plas. Surg. 58 (2007), 541-543.
31. Maxim, LD, R Niebo, MJ Utell: Screening tests: A review with examples. Inhal. Tox. 26 (2014), 811-828.
32. Rockson, SG: Update on the biology and treatment of lymphedema. Cur. Treat. Options in Cardiovas. Med. 14 (2012), 184-192.
33. Geddes, LA, LE Baker: The specific resistance of biological material–a compendium of data for the biomedical engineer and physiologist. Med. & Bio. Engineer. 5 (1967), 271-293.
34. Cornish, BH, M Chapman, C Hirst, et al: Early diagnosis of lymphedema using multiple frequency bioimpedance. Lymphology 34 (2001), 2-11.
35. Zhu, W, D Li, X Li, et al: Association between adjuvant docetaxel-based chemotherapy and breast cancer-related lymphedema. Anti-can. Drugs 28 (2017), 350-355.

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