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A Prospective Validation Study of Bioimpedance with Volume Displacement in Early-Stage Breast Cancer Patients at Risk for Lymphedema

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Abstract

BACKGROUND—Although volume displacement (VD) is considered the gold standard for diagnosing breast cancer (BC)-related lymphedema, it is inconvenient. We compared bioimpedance (L-Dex) and VD measurements in a prospective cohort of BC patients at risk for lymphedema.

METHODS—Between 2010–2014, 223 BC patients were enrolled. Following exclusions (n=37), 186 received baseline VD and L-Dex; follow-up measurements were performed at 3–6 month intervals for 3 years. At each visit, patients fit into one of three categories: normal (normal VD and L-Dex); abnormal L-Dex (L-Dex>10 or increase in 10 from baseline and normal VD); or lymphedema (relative arm volume difference of >10% by VD +/- abnormal L-Dex). Change in L-Dex was plotted against change in VD; correlation was assessed using Pearson correlation.

RESULTS—At a median follow-up of 18.2mos, 152 patients were normal; 25 had an abnormal L-Dex; and 9 developed lymphedema without a prior L-Dex abnormality. Of 25 abnormal L-Dex patients, 4 progressed to lymphedema for a total of 13 patients with lymphedema. Evaluating all time points, 186 patients had 829 follow-up measurements. Sensitivity and specificity of L-Dex compared to VD were 75% and 93%, respectively. There was no correlation between change in VD and change in L-Dex at 3mos (R=0.31) or 6mos (R=0.21).

CONCLUSIONS—VD and bioimpedance demonstrated poor correlation with inconsistent overlap of measurements considered abnormal. Of patients with an abnormal L-Dex, few progressed to lymphedema; most with lymphedema did not have a prior L-Dex abnormality. Further studies are needed to understand the clinical significance of bioimpedance.

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Keywords

lymphedema; bioimpedance; volume displacement

INTRODUCTION

Breast cancer-related lymphedema (BCRL) is one of the most feared complications following axillary surgery for breast cancer. The diagnosis of lymphedema is usually based on clinical findings of non-pitting edema of the limb following sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND). A variety of methods for limb volume evaluation are reported in the literature¹; currently, no standardized method exists.

Volume displacement (VD) is considered the “gold standard” for lymphedema diagnosis. Measurements obtained by VD have been shown to be reproducible, with an error rate of <1%.^{2,3} However, VD can be cumbersome and time consuming, limiting its clinical utility.

Bioimpedance has emerged as a non-invasive method to measure limb volume. Bioimpedance involves passing a low-frequency electrical current through the extremity and measuring the opposition to flow of this current, also known as impedance. A cited advantage of bioimpedance is its ability to measure changes in extracellular fluid volume, which may more accurately reflect changes in lymphatic volume.^{4,5} A study of 102 breast cancer patients evaluating the use of bioimpedance for the early detection of lymphedema documented a sensitivity of 100% and a specificity of 98% when compared to circumferential arm measurements.⁶

Bioimpedance has been primarily studied as a diagnostic tool for lymphedema; however, most investigators have compared bioimpedance with circumferential arm measurements,^{4,6,7} which has limited reproducibility among raters. Furthermore, longitudinal prospective studies evaluating bioimpedance as a predictor of lymphedema are lacking. Here we compare bioimpedance against the “gold standard” VD in a prospective cohort of breast cancer patients at risk for lymphedema utilizing serial measurements. We also sought to determine if the development of early abnormalities in bioimpedance could predict subsequent development of lymphedema.

METHODS

Patient Eligibility

From 7/2010–7/2014, 223 newly diagnosed breast cancer patients were enrolled in this institutional review board-approved prospective study. Informed consent was obtained on all patients. Although study recruitment ended 7/2014, follow-up volumetric measurements and data collection continued until 12/2014. Patient eligibility included: female patients >age 18 years; newly diagnosed invasive or in situ breast carcinoma; and planned unilateral axillary surgery with either SLNB or ALND. 37 patients total were excluded due to ineligibility (n=28) or withdrawal (n=9), resulting in 186 evaluable patients.

Study Design

Following enrollment and prior to surgery, patients received baseline volumetric measurements with VD and bioimpedance. All patients then underwent planned breast and axillary surgery. Follow-up volumetric measurements were performed at 3, 6, 12, 18, 24, 30, and 36 months post-surgery. In the initial protocol, measurements were also taken at 9 months; this visit was later removed from the trial design, but the data included in the analysis.

VD

Arm volume measurements with water displacement were performed using a graduated plastic cylinder for both the ipsilateral and contralateral arms. A distance 10cm proximal to the olecranon process in a straight line was measured and marked with a marker. The arm was then inserted into the cylinder and the cylinder was filled with water up to the mark on the arm. The water level on the graduated cylinder with the arm immersed was recorded. The water level was subsequently recorded after the arm was carefully removed from the cylinder. The difference between the two volumes represented the arm volume. The process was then repeated for the contralateral arm. Interlimb volume difference (ILD) at each time point was calculated using the following formula:

$$ILD = (Volume\ ipsilateral\ arm - volume\ contralateral\ arm) / volume\ contralateral\ arm$$

where the contralateral arm served as the control. To account for changes in arm volume from baseline, relative arm volume difference (RAVD) was calculated using the following formula:

$$RAVD = ILD_{f/u} - ILD_b$$

where *f/u* indicates follow-up and *b* indicates baseline. Using Armer and Stewart's criteria, RAVD of >10% was diagnostic of lymphedema.⁸

Bioimpedance

Bioimpedance measurements were conducted using L-Dex[®] U400 (ImpediMed, Brisbane, Australia) according to manufacture guidelines. Following removal of shoes, socks, and jewelry, patients were positioned supine with feet shoulder-width apart for 3 minutes. After prepping the skin with alcohol, electrodes were placed on the dorsum of each wrist and over the dorsum of the right foot at the ankle joint. Hand dominance and affected limb information were entered prior to measurement acquisition. An impedance, or L-Dex, ratio—a measure of the impedance in the unaffected limb divided by that of the affected limb—was then calculated. As extracellular fluid in the affected limb increases, the impedance decreases, resulting in an increase in the L-Dex ratio.⁴ The “normal” L-Dex ratio ranges from −10 to +10; an L-Dex ratio of >10 or a 10-unit increase from baseline was considered abnormal. For patients with a baseline L-Dex measurement of >10 (n=2), only a 10-unit increase from baseline was considered abnormal.

Outcome Measures

At each scheduled visit, patients fit into one of three categories: normal (normal VD and L-Dex); abnormal L-Dex (L-Dex ratio of >10 or 10-unit increase from baseline and a normal VD); or lymphedema (RAVD of $>10\%$ by VD with or without an abnormal L-Dex). Patients diagnosed with lymphedema by VD (RAVD $>10\%$) were referred to a certified lymphedema specialist for decongestive therapy and compression garments.

Statistical Analysis

Patient characteristics were summarized using median and range for continuous covariates, and frequency and percentage for categorical covariates. Concordance between VD and L-Dex measurements were assessed using scatterplots, Pearson correlations and 2x2 tables (normal/abnormal). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using lymphedema by VD as the standard method. The performance of L-Dex as a predictor of lymphedema was based on whether patients had an abnormal L-Dex measurement *prior* to lymphedema by VD; simultaneous abnormal L-Dex and VD without prior abnormal L-Dex was considered a false negative. In addition, the performance of L-Dex as a predictor of lymphedema was only assessed in patients with at least 6 months of follow-up after their first abnormal L-Dex measurement.

Time to abnormal L-Dex was estimated using Kaplan-Meier methodology, with follow-up censored at time of lymphedema or last visit if no abnormal L-Dex was measured.

All statistical analysis was performed in SAS (SAS institute, Cary, NC) and R (R Foundation, Vienna, Austria); p-values <0.05 were considered significant.

RESULTS

Table 1 shows clinical/pathologic characteristics of the 186 study participants. Median age was 60 years. The dominant limb was at risk in 99 (53%) patients. ALND was performed in 35 (19%) patients; the remainder ($n=151$) received SLNB. Median follow-up was 18.2 months (range, 2.4–41.3).

L-Dex as a Predictor of Lymphedema

At time of last follow-up, 152 patients were normal; 25 patients had an abnormal L-Dex; and 9 developed lymphedema without a prior L-Dex abnormality. Of 25 patients with an abnormal L-Dex, 4 progressed to lymphedema, for a total of 13 with lymphedema throughout the study period. Table 2 illustrates outcome measures by axillary surgery type.

The 12-month rate of an abnormal L-Dex was 11%, with ongoing cases identified out to 35 months (Fig. 1). At a median follow-up of 10.8 months from first abnormal L-Dex (range, 0–32.9 months), 4/25 abnormal L-Dex patients developed lymphedema while 21/25 continue to have a normal VD. Of 18 abnormal L-Dex patients with at least 6 months follow-up, 7 had a single L-Dex abnormality, while 11 had at least 2 L-Dex abnormalities.

Of 13 patients with lymphedema, only 4 had a prior L-Dex abnormality. As a predictor of lymphedema (including only patients with at least 6 months follow-up), L-Dex had a

sensitivity of 31% (4/13) and a specificity of 88% (129/147). NPV and PPV for L-Dex were 93% (129/138) and 18% (4/22), respectively.

L-Dex as a Diagnostic Tool for Lymphedema

The L-Dex ratio was abnormal in 12/13 lymphedema patients at the time of initial diagnosis, corresponding to a diagnostic sensitivity of 92%. The majority of lymphedema patients had an ALND (n=12); 1 had an SLNB (L-Dex was normal at diagnosis in this patient) (Table 2). Following lymphedema diagnosis, concordance between L-Dex and VD measurements in lymphedema patients was poor, with 12/32 (38%) post-lymphedema measurements demonstrating discordance.

Correlation of L-Dex and VD Measurements Taken Simultaneously

Evaluating all time points, 186 patients had 829 follow-up measurements. Of 28 abnormal VD measurements, 7 (25%) were normal by L-Dex, corresponding to a sensitivity of 75% and a false-negative rate of 25%. Of 801 normal VD measurements, 56 (7%) were abnormal by L-Dex, corresponding to a specificity of 93% and a false-positive rate of 7%. NPV and PPV were 99% and 27%, respectively (Fig. 2). Correlation between VD and bioimpedance is illustrated in Fig. 2, which demonstrates inconsistent overlap between abnormal L-Dex and abnormal VD measurements. There was no clear correlation between change in VD and change in L-Dex at 3 months ($R=0.31$) or 6 months ($R=0.21$) (Fig. 3).

Among the subset of SLNB patients, 151 patients had 681 follow-up measurements. Among 2 abnormal VD measurements (which occurred in 1 SLNB patient), L-Dex was normal in both, corresponding to a sensitivity of 0%. Specificity was 96% with a false-positive rate of 4% (28 false-positive measurements). NPV and PPV were 99.7% and 0%, respectively.

DISCUSSION

Due to limitations associated with traditional assessment of limb volume following axillary surgery, there has been renewed interest in identifying new, reliable measurement techniques that can identify lymphedema in the early stages. Bioimpedance has recently garnered attention due to its measurement simplicity and ability to measure changes in extracellular fluid volume. Advantages to identification of early lymphedema include the potential to prevent progression to clinical lymphedema⁹, resulting in improved quality of life and healthcare cost reduction.¹⁰ However, the optimal method to measure and diagnose early lymphedema is still unknown. Here we prospectively compared bioimpedance and VD measurements over time, and assessed the ability of bioimpedance to predict, and later diagnose, lymphedema in at-risk breast cancer patients, using VD as the standard for lymphedema diagnosis.

L-Dex performed poorly as a predictor of lymphedema. Among the 25 patients with an abnormal L-Dex (and normal VD), only 4 subsequently developed lymphedema at a median follow-up of 10.8 months from first abnormal L-Dex. In addition, few patients with lymphedema had a prior L-Dex abnormality (4/13; sensitivity for prediction 31%). Our findings differ from Cornish et al, who reported subsequent development of lymphedema in 20/22 patients with an abnormal bioimpedance. 8/22 were diagnosed with lymphedema

immediately after their abnormal measurement, which does not legitimately reflect a “lag time” between early bioimpedance abnormalities and subsequent lymphedema. Moreover, all breast cancer patients in their study (n=102) underwent ALND (+/- radiation) compared to only 35/186 patients (19%) in our study, thereby representing a patient cohort at higher risk for lymphedema development. Finally, Cornish et al compared bioimpedance to circumferential arm measurements, while we utilized VD as the standard to define lymphedema. Prior studies have demonstrated different diagnostic methods may result in varying incidence of lymphedema, which may account for the discrepancy in the reported sensitivity of bioimpedance between the two studies.¹¹

Even if the abnormal values by bioimpedance were reflective of early volume change, the inability to quantify the percentage change in volume difference between arms limits our understanding of the clinical impact of these changes. Specht et al demonstrated that patients with arm volume changes (by perometry) between 3–5% occurring >3 months after surgery were not at increased risk for development of lymphedema in their cohort of 1173 breast cancer patients.¹² If the value of bioimpedance is to detect early or subclinical volume changes, correlation between diagnostic cutoff points with percent volume change may allow for better prognostication for future lymphedema risk and avoid potential overtreatment of these patients.

As a diagnostic tool, bioimpedance identified 92% of lymphedema cases (12/13) at the time of initial diagnosis, which more closely resembles the 100% sensitivity of bioimpedance reported by Cornish et al.⁶ However, following lymphedema diagnosis, considerable discordance was noted in our study between bioimpedance and VD measurements (12/32, 38%). Fu et al evaluated the reproducibility of bioimpedance among 250 women, including healthy females, breast cancer survivors at risk for lymphedema, and those with lymphedema; bioimpedance was highly reliable in healthy women and at risk survivors using a test/re-test method, with an intra-class correlation coefficient (ICC) of 0.99 (p<0.001). In women with lymphedema, bioimpedance showed fair agreement with an ICC of 0.69 (p<0.001)⁴, suggesting that bioimpedance may not be a reliable method to monitor limb volume in lymphedema patients after diagnosis.

Among our study's 829 follow-up bioimpedance and VD measurements, we found poor correlation between measurements considered abnormal, with a correlation coefficient of 0.31 at 3 months and 0.21 at 6 months. Blaney et al compared circumferential arm measurements and bioimpedance in a prospective cohort of 115 breast cancer patients in the first year post-surgery and similarly found poor correlation between the two diagnostic measurement methods. In their study, lymphedema was identified in 29% of patients by arm circumference and in 11% patients by bioimpedance; agreement between the two measurements for lymphedema diagnosis occurred in 25.5% of cases.⁷ In contrast, Fu et al did find that bioimpedance and arm circumference were correlated in their cross-sectional study; however, their patient population differed from the aforementioned studies and notably, baseline measurements were not obtained on the study participants⁴—a limitation of their findings. Although one “best” method for lymphedema diagnosis has not reached consensus, our study results raise concerns for bioimpedance as a single tool to diagnose BCRL.

Among patients undergoing SLN biopsy (n=151), the predictive and diagnostic value of bioimpedance is questionable. Although our follow-up is short, <1% of our sentinel node study population developed lymphedema, which was not predicted or diagnosed by bioimpedance (sensitivity=0%). Our study population, comprised largely of patients undergoing SLN biopsy (81%), is representative of most patients undergoing treatment for early-stage breast cancer, as patients with pathologically positive sentinel nodes are increasingly being treated with SLN biopsy alone, according to ACOSOG Z0011 criteria.^{13,14} Given the lack of benefit of bioimpedance screening in this low-risk population, future studies about the predictive and diagnostic role of bioimpedance should focus on high-risk patients treated with ALND or axillary radiation.

Our study is limited by its short (10.8 months) median follow-up from first abnormal L-Dex, which may not be long enough to capture all patients with an abnormal L-Dex who may eventually develop lymphedema. However, all of the Cornish study patients with an abnormal bioimpedance developed lymphedema within 10 months of the initial abnormal measurement⁶, suggesting that longer follow-up may not result in a substantial increase in lymphedema cases. Additionally, it is possible that patients with an abnormal L-Dex could develop lymphedema after completion of the 3-year study, which would not be captured in our dataset. The low incidence of lymphedema in our study also limits our results, as predictive and diagnostic sensitivity estimates are based on small denominators, resulting in a large variance. Furthermore, lack of correlation between bioimpedance and VD in select lymphedema patients could potentially be related to limb fibrosis (as seen in later-stage lymphedema), which may reportedly result in a “normal” bioimpedance even in the presence of limb swelling. Finally, information regarding patient symptoms was not collected at each measurement in a reproducible manner; knowledge of patient symptoms with respect to L-Dex changes could further enhance our understanding of future lymphedema risk.

Conclusions

VD and bioimpedance demonstrated poor correlation with inconsistent overlap of measurements considered abnormal. With short follow-up, few patients with an abnormal bioimpedance developed clinical lymphedema; most patients with lymphedema did not have a prior L-Dex abnormality. Abnormalities in bioimpedance are not well correlated with subsequent lymphedema development. Caution should be taken to avoid overdiagnosis and overtreatment in these patients. Until larger studies with longer follow-up are completed, there is no clear clinical role for routine lymphedema screening with bioimpedance, particularly in the subset of patients treated with SLN biopsy.

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Synopsis

We compared bioimpedance to volume displacement measurements over time in a prospective cohort of breast cancer patients at risk for lymphedema. We found that bioimpedance and volume displacement demonstrated poor correlation with inconsistent overlap of measurements considered abnormal.

Fig 1.

Cumulative incidence of abnormal L-Dex among 186 breast cancer patients at risk for lymphedema.

VOLUME DISPLACEMENT	L-DEX		Total
	Normal	Abnormal	
<10% change from baseline	745	56	801
>10% change from baseline	7	21	28
Total	752	77	

Fig 2.
Correlation between volume displacement (VD) and L-Dex measurements at all time points.

Fig 3.
Correlation between change in volume displacement and change in L-Dex at a) 3 months and b) 6 months.

Table 1

Clinical and pathologic characteristics of study participants

Participant characteristics		Total (n=186)	
		Median	Range
Age (years)		60	27–83
BMI (kg/m ²)		25.8	17–45
No. of nodes removed	SLNB	3	1–7
	ALND	20.5	2–53
		N	%
Dominant limb at risk		99	53%
Histology *	Invasive	176	95%
	DCIS	8	4%
Breast Surgery **	BCS	146	79%
	Mastectomy	38	20%
Axillary surgery	SLNB	151	81%
	ALND	35	19%
Pathologic nodal status	Negative	133	72%
	Positive	53	28%
Chemotherapy		77	41%
Radiotherapy		147	79%

* Includes invasive ductal, invasive lobular and other invasive; 1 unknown and 1 benign histology

** 1 unknown, 1 axillary surgery only

BMI, body mass index; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; DCIS, ductal carcinoma in situ; BCS, breast-conserving surgery

Table 2

Outcome measures among 186 breast cancer patients by type of axillary surgery

Status at last follow-up	Total (n = 186)	SLNB (n = 151)	ALND (n = 35)
Normal	152	136	16
Abnormal L-Dex/no lymphedema	21	14	7
Abnormal L-Dex/lymphedema	4	0	4
Lymphedema without prior L-Dex abnormality	9	1	8

SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection