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Original Article

Characterizing early postoperative changes in body composition in patients with secondary lymphedema after breast cancer surgery: potential screening indicators for preventive intervention

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Abstract. [Purpose] To characterize changes in the body composition of individuals with secondary lymphedema that developed in the early postoperative period after breast cancer surgery, before the manifestation of volume increase in the affected limb, and to test its potential as a screening indicator for preventive intervention. [Participants and Methods] A total of 219 patients with breast cancer who underwent axillary lymph node dissection and sentinel lymph node biopsy were included in this study. Body composition (extracellular water content, extracellular water content ratio, low-frequency impedance value, and phase angle) was evaluated using bioelectrical impedance analysis before surgery and three and six months after surgery. Changes in the body composition of the affected limb over time were compared between the lymphedema- and non-lymphedema-affected groups. [Results] Sixteen patients who developed lymphedema six months after breast cancer treatment showed significant changes in all body composition parameters at three months postoperatively, compared to those who did not develop lymphedema. [Conclusion] In patients with upper extremity lymphedema that develops within six months after breast cancer surgery, increases in extracellular water content, extracellular water content ratio, low-frequency impedance, and phase angle may precede apparent volume increases. Our findings suggest the usefulness of these parameters as screening indicators for early treatment triaging.
Key words: Breast cancer, Upper-extremity lymphedema, Body composition

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INTRODUCTION

Lymphedema is a condition where fluid containing high concentrations of albumin and other proteins accumulates in the interstitium, instead of being collected by lymphatic vessels[1)]. In Japan, secondary lymphedema, which arises after cancer treatment and due to other causes, accounts for 90% of all cases[1)]. Furthermore, the number of Japanese women diagnosed with breast cancer exceeds 90,000 individuals per year and continues to rise annually[2)]. A large Japanese survey reported an incidence of upper extremity lymphedema of 50.9% following breast cancer surgery[3)], and the number of patients with breast cancer-related lymphedema is expected to increase in the future.

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In addition to cosmetic problems, such as deformities associated with increased volume of the affected limb, lymphedema causes discomfort, impairs the function and movement of the affected limb, and reduces the quality of life of breast cancer survivors[4]. Moreover, lymphedema is difficult to cure completely. In severe cases, it causes irreversible changes such as lipogenesis of the affected limb, elephantiasis, and subcutaneous tissue fibrosis. These conditions require lifelong specialized and costly treatment. Therefore, the prevention and early detection of lymphedema are of great importance from both patient and societal perspectives.

Early detection of lymphedema is challenging because of the difficulty in identifying initial symptoms[5]. Traditionally, the clinical criteria for diagnosing lymphedema, as defined by the Western world, include a 2-cm increase in circumference or a 200 mL or ≥10% increase in volume, compared to healthy limbs[6]. However, there is a concern that volume increases may be underestimated in the Japanese because the lymphedema-related increase in volume is relatively small, considering the smaller build of Japanese individuals compared with Westerners[7]. Additionally, volume-dependent assessments cannot distinguish between bone, fat, muscle, and other soft tissues or between extracellular and lymphatic fluids. For example, if lymphedema occurred simultaneously with muscle and fat atrophy after breast cancer surgery, the volume would cancel out and the development of lymphedema would be missed. In such cases, it is necessary to identify potential indicators that can be evaluated before an apparent increase in volume is observed because lymphedema may have already progressed by the time the apparent increase in volume is observed.

Direct segmental multifrequency impedance analysis (DSM-BIA) has been used to evaluate indicators related to pre-volume gain. It can noninvasively measure body composition, including extracellular water (ECW)/total body water (TBW) ratio, low-frequency impedance, and phase angle (PhA) measurements for the left and right upper and lower limbs and trunk. A previous study utilizing DSM-BIA indicated that increased ratios of ECW/TBW and decreased PhA are correlated with enhanced severity of lymphedema in postoperative breast cancer patients who have manifested this condition, in contrast to those who have not developed lymphedema[8]. While these studies provide cross-sectional validations, lymphedema after breast cancer surgery often develops in the early postoperative period, with 77% of cases reported to occur within 36 months[9] and within 12 months[10] after surgery, with a peak between 12 and 30 months[11]. Therefore, it is necessary to examine the association between changes in body composition over time and lymphedema development in the early postoperative period. This study aimed to characterize changes in the body composition of lymphedema-affected limbs in the early postoperative period after breast cancer surgery, before the apparent increase in the volume of the affected limb, and to provide a screening index for identifying patients who require early treatment. We hypothesized that in patients who developed upper extremity lymphedema 6 months after breast cancer surgery, changes in the body composition would be observed before the apparent increase in the affected limb volume.

PARTICIPANTS AND METHODS

This study was a retrospective observational study. The participants were adult women who were diagnosed with breast cancer and underwent surgery, including axillary manipulation, at the International University of Health and Welfare, Narita Hospital, between April 1, 2022, and March 31, 2023. Patients with contraindications to the BIA method, bilateral breast cancer, a history of edema-causing diseases other than lymphedema, a history of infectious or inflammatory diseases, or those who had already developed lymphedema before surgery were excluded. This study was approved by the Ethical Review Committee of the International University of Health and Welfare (Approval No. 22-Ig-280).

The bilateral upper extremity volume and body composition were measured preoperatively and at 3 and 6 months postoperatively. The upper extremity volume was calculated using formula 1 according to previous reports[12, 13] for the circumferential diameter measured using a tape imager.

Circumferential diameters were measured at 5 and 10 cm proximal and at 5, 10, and 15 cm distal to the fossa line of the elbow. The area distal to the wrist joint was excluded from the volume calculation. Body composition was measured using an Inbody770® scanner (Inbody Japan Inc., Tokyo, Japan), and included ECW/TBW, 1 kHz and 5 kHz impedance, and the PhA of both upper extremities for evaluation items, and the technique was verified through medical records.

The criteria for lymphedema onset were defined as a 10% or greater increase in the interlimb volume ratio, based on previous reports[7, 8]. At each time point, the participants were divided into lymphedema-onset and lymphedema non-onset groups based on the defined onset criteria. Body composition before onset was compared between the two groups. A two-way analysis of variance with repeated measures was performed to compare the differences in the measured items between the onset and non-onset groups at the pre-onset measurement time points, followed by a post-hoc test (Bonferroni). Unpaired t-tests were used to compare the participant attributes and the presence or absence of disease onset based on background factors. The significance level was set at 5%. SPSS (Version 23.0, IBM, Armonk, NY, USA) was used for statistical analysis.

Sampling was performed using the statistical software G*Power to calculate the number of cases needed, with an effect size f=0.25 (moderate effect) based on previous studies[14], a significance level α=0.05, and power of the test set at 0.80. As a result, it was calculated that theoretically 28 cases in each group would be required.

RESULTS

A total of 219 cases of data were available for collection during the observation period, of which 16 exceeded the incidence criteria. This was due to a lower than expected incidence rate as a result of following the short postoperative period identified in this study, within 6 months of surgery.

Body composition was compared between the onset and non-onset groups preoperatively and at 1 and 3 months postoperatively, using the onset of lymphedema at 6 months as the baseline. Participant attributes and background factors (Table 1) indicated that the mean age and BMI did not differ significantly between the two groups. The overall incidence of lymphedema was 13.4%, 34.8%, and 2.3% in the three axillary lymph node biopsy groups, respectively. A comparison of the body composition preoperatively and at 3 and 6 months postoperatively between the onset and non-onset groups is shown in Table 2. Notably, no significant preoperative differences were observed in any of the endpoints between the two groups.

In the onset group, ECW/TBW and ECW were significantly higher at 3 months postoperatively than preoperatively and higher at 6 months after onset than at 3 months. In the between-group comparison, ECW/TBW and ECW were significantly higher at 3 and 6 months in the onset group than in the non-onset group. In the symptomatic group, the 1 kHz and 5 kHz impedance and PhA were significantly lower at 3 months postoperatively than preoperatively, and even lower at 6 months than at 3 months. In the between-group comparison, the values were significantly lower at 3 and 6 months than those in the non-onset group. In the asymptomatic group, only PhA was substantially lower than preoperative values at 3 and 6 months, with no change at 3 and 6 months. In the asymptomatic group, the other endpoints did not change appreciably at any time point.

DISCUSSION

This study compared the preoperative and 3-month postoperative body composition in lymphedema-onset and non-onset groups by observing the volume and body composition of the affected limb of patients with breast cancer preoperatively and up to 6 months postoperatively. The onset group had significantly increased ECW and ECW/TBW and decreased impedance at 1 and 5 kHz 3 months postoperatively. In addition, the PhA was significantly lower at 3 and 6 months postoperatively than

Table 1. Characteristics and background factors of participants

		Onset group (n=16)	Non-onset group (n=219)
Age (years)		62.9 ± 14.8	58.9 ± 12.0
Weight (kg)		53.1 ± 8.5	52.9 ± 6.6
Height (cm)		155.9 ± 6.6	156.3 ± 5.8
Body mass index (kg/m^2)		23.4 ± 4.0	23.8 ± 3.6
Surgery side (Right)		7 (43.75)	1.15 (52.51)
Surgical procedure	Axillary lymph node dissection	15 (93.75)	56 (25.58)*
	Sentinel lymph node biopsy	1 (0.68)	147 (67.12)*

Mean ± standard deviation. *p<0.05.

Table 2. Comparison of body composition between groups with and without onset at each evaluation time

Evaluation Item	Onset or Non-onset	Pre-surgery	3 months	6 months
ECW/TBW	Onset group	0.383 ± 0.012	0.389 ± 0.028*†	0.394 ± 0.035*†#
	Non-Onset group	0.380 ± 0.010	0.381 ± 0.013	0.380 ± 0.013
ECW	Onset group	0.553 ± 0.150	0.586 ± 0.142*†	0.676 ± 0.133*†#
	Non-Onset group	0.555 ± 0.116	0.554 ± 0.117	0.557 ± 0.115
1 kHz Impedance (Ω)	Onset group	380.490 ± 36.715	355.240 ± 29.084*†	321.460 ± 52.426*†#
	Non-Onset group	400.400 ± 52.000	390.900 ± 52.300	405.600 ± 59.900
5 kHz Impedance (Ω)	Onset group	374.070 ± 37.913	345.800 ± 36.321*†	307.860 ± 42.130*†#
	Non-Onset group	391.770 ± 49.945	399.880 ± 52.045	397.240 ± 47.970
PhA (°)	Onset group	4.210 ± 0.389	3.657 ± 0.516*†	3.460 ± 0.660*†#
	Non-Onset group	4.630 ± 0.577	4.266 ± 0.519†	4.310 ± 0.440†

Mean ± standard deviation. *p<0.05 vs. Non-Onset Group, †p<0.05 vs. Pre-surgery, #p<0.05 vs. 3 months.
ECW: extracellular water; TBW: total body water; PhA: phase angle.

preoperatively in the onset group. Proving our hypothesis correct, these results indicated that changes in the body composition preceded any apparent increase in volume in the lymphedema-onset group at 6 months postoperatively.

Kim et al.[8] reported that the PhA correlated with the volume and ECW/TBW of the affected limb, after measuring the body composition using BIA in patients with lymphedema secondary to breast cancer surgery divided into mild, moderate, or severe cases. In addition, Roh et al.[15] used PhA to determine the efficacy of lymphangioarteriovenous anastomosis in treating secondary lymphedema after breast cancer surgery. They found that the PhA of the upper extremities decreased with increasing severity of lymphedema and increased 6 months after lymphangioarteriovenous anastomosis. These reports indicate that in patients with lymphedema, ECW/TBW increases and PhA decreases in proportion to the disease severity. In contrast, in the present study, an increase in ECW/TBW and a decrease in PhA were observed prior to an overt increase in volume, indicating that these metrics are critical indicators of impending volume increase.

Lymphedema is a condition in which excessive interstitial fluid accumulates subcutaneously due to impaired transport in the lymphatic system. In the BIA method, interstitial fluid is calculated as ECW, where ECW/TBW is the ratio of ECW to TBW. ECW/TBW tends to be higher in the edematous state because ECW increases relative to TBW[16]. In the present study, ECW and ECW/TBW exhibited comparable upward trends in the onset group, suggesting that ECW/TBW increased because of an increase in ECW. Furthermore, even when there was no apparent increase in the affected limb volume, ECW showed a slight gradual increase, and ECW/TBW increased accordingly. In the DSM-BIA, high-frequency currents pass through the intracellular membrane. However, low-frequency currents near the zero frequency cannot pass through the intracellular membrane, which acts as an insulator. Therefore, the resistance values obtained from low-frequency currents are less affected by intracellular water and more accurately reflect the ECW[17]. The fact that the 1 kHz and 5 kHz impedance values were significantly higher in the affected group than in the non-affected group at 3 months, similar to ECW, indicates that ECW content and its resistance value may change with the properties of the extracellular fluid, such as viscosity and protein concentration.

Phase angle is the angle calculated from the resistance (R) and reactance (Xc) of a current as it passes through body tissues, where R represents the direct resistance of the current due to water and electrolytes in the body and Xc represents the phase delay of the current caused by the cell membrane. The PhA is useful for predicting cellular health and nutritional status and is used as an indicator of nutritional status, particularly of muscle quality[18]. As mentioned above, in the lymphedema-affected limbs, ECW increases and low-frequency impedance decreases.

One possible mechanism of lymphedema is a decrease in the PhA, although lymphedema lesions are not only caused by lymphatic effusion but also by a combination of factors. For example, in the lymphedema-affected limb, the acquired immune system response, in which dendritic cells and other cells present antigens in the lymph nodes via lymphatic vessels, is disrupted, which results in a localized immunodeficiency state[19]. In lymphedema tissues, helper T cells and type 2 macrophages predominate, and a type 2 immune response prevails, which results in a chronic inflammatory state[20]. Persistence of this inflammatory state is believed to disrupt the electrolyte balance inside and outside the blood vessels, resulting in increased ECW, low-frequency impedance, and consequently increased lymphatic load. Tassenoy et al.[21] provided echographic evidence of subcutaneous tissue changes in postoperative lymphedema in patients with breast cancer. Tassenoy et al. also identified changes in the subcutaneous tissue in postoperative breast cancer lymphedema on echocardiography and suggested that these changes preceded the volume increase. Mihara et al.[22] reported that increased intralymphatic pressure in the collecting lymph vessels during lymph node dissection preceded the onset of lymphedema and led to histological changes in the collecting lymph vessels. Therefore, PhA may also reflect the inflammatory state of the affected limb, increased cell membrane permeability, degeneration of the subcutaneous tissue and lymphatic vessels, and other subtle structural changes related to compromised immunity owing to lymphatic system dysfunction. In future studies, we believe that the relationship between PhA and lymphedema can be further clarified through verification, including changes in blood parameters that serve as indicators of inflammation and nutritional status in patients with postoperative breast cancer.

Based on the above findings, we recommend that in the early postoperative period after breast cancer surgery, patients with a high ECW/TBW ratio in the affected limb, low-frequency impedance, and a low PhA be carefully monitored, even if there is no obvious volume increase of ≥10% suggestive of the onset of lymphedema. Using these values as screening indicators, preventive interventions can be introduced earlier in patients who are at a high risk of developing the disease. The significant difference in body composition between the onset group at 6 months and the non-onset group at 3 months suggests that this is a useful indicator for the early detection of lymphedema and monitoring its progression, which underscores the importance of lymphedema prevention and early intervention.

In patients who developed upper extremity lymphedema 6 months after breast cancer surgery, an increase in ECW/TBW and a decrease in low-frequency impedance and PhA preceded the apparent volume increase 3 months postoperatively. Altogether, our results suggest the importance of focusing on changes in these values as screening indicators for early interventions. Despite the modest cohort size of 16 cases in this study, the constrained observation period and the observed low incidence rate likely mirror the clinical realities encountered within this specific patient group. Consequently, the findings of this investigation might hold relevance in analogous clinical contexts, suggesting broader applicability of the outcomes under similar conditions.

Conflicts of interest

None.

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