Perioperative variations in indices derived from noninvasive assessments to detect postmastectomy lymphedema

Kotaro Suehiro, MD,[a] Shigeru Yamamoto, MD,[b] Saiko Honda, MD,[c] Noriyasu Morikage, MD,[a] Eijiro Harada, MD,[a] Yoshihiro Takemoto, MD,[a] Hiroaki Nagano, MD,[b] *and* Kimikazu Hamano, MD,[a]
Ube, Yamaguchi, Japan

ABSTRACT

Objective: This study aimed to clarify the variations in indices derived from noninvasive assessments for the early detection of postmastectomy lymphedema (LE) from 1 month preoperatively until 2 years postoperatively.

Methods: In total, 120 patients who underwent surgery for breast cancer in our institution were prospectively followed up with a questionnaire for arm swelling as well as with tape measurements, bioimpedance analysis (BIA), and skin and subcutaneous tissue ultrasound at 1 month before and 3, 6, 12, 18, and 24 months after surgery.

Results: Ninety-seven patients completed the study. Among 93 patients who did not present with LE, 9% complained of arm swelling even before surgery, and the incidence peaked at 17% at 6 months after surgery. There were no differences in the circumferences of the upper arm, forearm, and hand between sides throughout the study period. However, the postoperative circumference values of the upper arm only on the operation side were slightly increased compared with the preoperative values. The mean excess fluid in the arm on the operation side compared with the contralateral side, as assessed by BIA, was nearly zero throughout the study period. There were no differences in subcutaneous echogenicity or skin and subcutaneous thicknesses between the sides throughout the study period. However, time-dependent increases in subcutaneous thicknesses were noticed on both sides. Four patients (4.1%) developed LE. In three of these patients, abnormality in the BIA was recorded 6 to 12 months before presentation. Immediately after presentation, the common findings included BIA abnormality and increased subcutaneous echogenicity and skin thickness in the medial forearm.

Conclusions: In this study, a complaint of arm swelling was not sensitive enough for detection of the early onset of LE because a certain number of patients constantly complained of this symptom. Measurements of circumference might help in the diagnosis of LE onset, but this method is not specific enough because these measurements are also affected by various factors. However, BIA and skin and subcutaneous ultrasound were identified as potential tools for the early detection of LE. (J Vasc Surg: Venous and Lym Dis 2019;7:562-9.)

Keywords: Breast cancer; Lymphedema; Bioelectrical impedance analysis; Ultrasound

Arm lymphedema (LE) develops in approximately 20% of patients after breast cancer surgery.[1] Because earlier intervention for LE may result in better treatment outcome and may save treatment costs,[2] early detection of LE is important. Until recently, noninvasive methods have been used for the detection of LE; although patients' complaints are subjective, they may represent subtle symptoms. Moreover, a moderate correlation between the sensation of arm swelling and objective measures (eg, bioimpedance analysis [BIA], perometry) has been reported.[3] Tape measures have a long history for the evaluation of LE. A difference in circumference of 2 cm in any part of the arm strongly suggests the presence of LE.[4] BIA has been gaining popularity for the diagnosis of LE as it can detect very mild edema, which is believed to be the first symptom of early-stage LE.[1,5] Ultrasound (US) around 10 MHz is also popular as it is convenient and economical. Although skin and subcutaneous tissue US is not used widely, we have observed edema and inflammatory changes caused by LE even in earlier stages by US.[6]

These assessments can also be affected by other factors, such as inflammation caused by surgery and side effects of adjuvant therapy; therefore, the clarification of postoperative variations in these assessments, especially in patients who do not develop LE, is important for the accurate diagnosis of LE. In this study, we aimed to clarify the variations in indices derived from noninvasive assessments for the early detection of postmastectomy LE from 1 month preoperatively until 2 years postoperatively.

From the Department of Surgery and Clinical Science,[a] and Department of Gastroenterological, Breast, and Endocrine Surgery,[b] Yamaguchi University Graduate School of Medicine; and the Department of Nursing, Yamaguchi University Hospital.[c]

Author conflict of interest: none.

Correspondence: Kotaro Suehiro, MD, Department of Surgery and Clinical Science, Yamaguchi University Graduate School of Medicine, 1-1-1 Minamikogushi, Ube, Yamaguchi 755-8505, Japan (e-mail: ksuehiro-circ@umin.ac.jp).

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METHODS

This prospective study was approved by the Institutional Review Board of Yamaguchi University Hospital (Ube, Yamaguchi, Japan). All participants provided informed consent before enrollment. The participants included in this study were 120 patients who underwent surgery for breast cancer at Yamaguchi University Hospital between April 2015 and August 2016. Among 120 participants, 23 declined or had improper assessments. Accordingly, 97 patients were included in the analysis. The characteristics of the patients are summarized in the Table. During the study period, no significant changes in patients' body mass index were recorded, and patients' performance status, which was assessed by the Eastern Cooperative Oncology Group scale (0-4), was 0 to 1. Among 93 patients who did not present with LE, more operations were performed on the right side, whereas the ratio of dominant to nondominant side was similar. The most common procedure was total mastectomy with sentinel lymph node biopsy (43 patients [46%]), followed by partial mastectomy with sentinel lymph node biopsy (26 patients [28%]) and total mastectomy with axillary lymph node dissection (23 patients [25%]). Among cases of total mastectomy with axillary lymph node dissection, a median of 10 lymph nodes were dissected (range, 2-24), of which the status of lymph node metastases was pN0 of 5, pN1 of 14, pN2 of 3, and pN3 of 1. All four patients who presented with LE were in an advanced stage and underwent total mastectomy with axillary lymph node dissection. In these patients, a median of 15 lymph nodes were dissected (range, 11-24), of which the status of lymph node metastases was pN0 of 0, pN1 of 3, pN2 of 0, and pN3 of 1.

Assessments were performed 1 month preoperatively and 3, 6, 12, 18, and 24 months postoperatively as described later. All assessments except symptom assessment were performed by qualified technicians between 11 AM and 3 PM with the patient in a supine position in a room conditioned at 25°C.

Subjective symptoms. Arm symptoms were evaluated using the Functional Assessment of Cancer Therapy—Breast tool (version 4, Japanese version).[7] In this questionnaire, the patient is asked to respond to each question as follows: 0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; or 4, very much. From this questionnaire, subscale B3, "One or both of my arms are swollen or tender," was assessed as one of the main outcomes.

Tape measurement. The circumferences of the arms were measured at 10 cm above and 15 cm below the cubital fossa and the hand.

BIA. A bioimpedance spectrometer (U400; Impedimed Ltd, Brisbane, Australia) was used for BIA. The electrodes were attached to the dorsal wrists and the anterior surface of the ankle. Because the magnitude of the electrical impedance is inversely proportional to the volume of fluid in the tissue, the impedances in the arms were obtained. Using measured impedances, the L-Dex (Impedimed Ltd) score (LDS) was calculated automatically. The LDS is a normalized scale of the ratio of the extracellular fluid (ECF) in the affected arm to that in the contralateral arm.[8-10] A greater LDS indicates a larger difference in the ECF between arms.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center prospective cohort study
- **Key Findings:** Among 93 postmastectomy patients without lymphedema (LE), there were no differences in the arm circumferences, bioimpedance analysis (BIA), and ultrasound (US) measurements between sides until 2 years postoperatively. In four patients with LE, the common findings included abnormal BIA and US measurements in the medial forearm.
- **Take Home Message:** BIA and US findings, particularly in the medial forearm, could be valuable for the diagnosis of LE onset.

Skin and subcutaneous US. A Logiq S6 system (GE Healthcare, Little Chalfont, Buckinghamshire, UK) with a 7- to 12-MHz linear transducer was used for US assessments. Each arm was scanned at five points (medial and lateral, upper arm and forearm, and dorsum of hand). The probe was placed longitudinally on the arm. The size and gain were adjusted as necessary to optimize the image quality and boundary definition. The thickness of the skin was defined as the distance between the posterior echogenic border of the epidermal entrance echo and the posterior echogenic border of the dermis. The thickness of the subcutaneous tissue was defined as the distance between the posterior echogenic border of the dermis and the anterior echogenic border of the deep muscular fascia.

The subcutaneous echogenicity (SEG) increases in limbs with LE[11]; therefore, we assessed the SEG on the basis of two findings: diffuse increases in echogenicity in the subcutaneous layer; and echogenic lines representing the superficial fasciae that were unclear, chopped, or unidentifiable.[12] The presence of subcutaneous echo-free space (SEFS) was also assessed as its detection directly indicates the presence of edema.

In this study, we diagnosed LE as both the presence of typical skin manifestation on physical examination and abnormality in the objective examination including LDS, any part of the circumference, and US findings in the arm. The abnormal findings were defined as follows:

- Functional Assessment of Cancer Therapy—Breast tool subscale B3 >0, namely, any complaints were included

Table. Patients' characteristics

	Patients who did not present with LE (n = 93)	Patients who presented with LE (n = 4)
Age at inclusion, years	61 (34-87)	63 (51-75)
Preoperative BMI, kg/m^2	22 (16-37)	24 (23-25)
Side of surgery	Right: 50 (right-handed, 47; left-handed, 3) Left: 43 (right-handed, 39; left-handed, 4)	Right: 1 (right-handed, 1; left-handed, 0) Left: 3 (right-handed, 3; left-handed, 0)
Types of surgery	Total mastectomy with axillary lymph node dissection: 23 (level 1, 5; level 2, 18; level 3, 0) Partial mastectomy with axillary lymph node dissection: 1 (level 1) Total mastectomy with sentinel lymph node biopsy (or sampling): 43 Partial mastectomy with sentinel lymph node biopsy: 26	Total mastectomy with axillary lymph node dissection: 4 (level 1, 1; level 2, 1; level 3, 2)
No. of dissected nodes (patients with axillary lymph node dissection only)	10 (2-24)	15 (11-24)
Postoperative complications	Bleeding: 2 Skin flap necrosis: 5 Wound infection: 4 Seroma/lymphorrhea: 11	Bleeding: 1 Skin flap necrosis: 0 Wound infection: 0 Seroma/lymphorrhea: 1
Length of hospital stay, days	12 (4-34)	13 (12-14)
Clinical stage	I, 51; IIA, 25; IIB, 7; IIIA, 2; IIIC, 1; IV, 3 Others (carcinoma in situ, 2; adenomyoepithelial adenosis, 1)	I, 0; IIA, 1; IIB, 2; IIIA, 0; IIIC, 1; IV, 0
Pathologic process	Invasive ductal carcinoma: 81 Mucinous carcinoma: 4 Invasive lobular carcinoma: 3 Others: 5	Invasive ductal carcinoma: 4
Adjuvant therapy	Radiotherapy: 29 Chemotherapy: 19 (F) EC: 17 DTX or PTX: 18 Trastuzumab: 10	Radiotherapy: 1 Chemotherapy: 3 (F) EC: 2 DTX or PTX: 2

BMI, Body mass index; *C,* cyclophosphamide; *DTX,* docetaxel; *E,* epirubicin; *F,* fluorouracil; *LE,* lymphedema; *PTX,* paclitaxel.
Continuous variables are presented as median (range).

- Difference in circumferences greater than the tentative normal range, which was defined as mean ± 2 standard deviations calculated from the data obtained from the patients who did not present with LE, in any sites
- LDS >10 according to the manufacturer's validated definition
- Unilateral increase in SEG or the presence of SEFS in any sites
- Difference in skin or subcutaneous thicknesses greater than the tentative normal range calculated in any sites

Statistical analysis. The results are expressed as mean ± standard deviation or counts unless otherwise indicated. Analysis of variance was used to evaluate the changes in measurements in the same limb. Post hoc tests were used for multiple comparisons. Unpaired *t*-test was used to test the differences in measurements between limbs. Finally, χ^2 test was used to test differences in incidence. Statistical analyses were performed using JMP 11.0 (SAS Institute, Cary, NC). *P* values $< .05$ were considered statistically significant.

RESULTS

Patients who did not present with LE. The changes in the incidence and intensity of the complaint of arm swelling are shown in Fig 1. During the study period, 28 patients (30%) complained of arm swelling with or without tenderness at least once. Before surgery, eight patients (9%) complained of arm swelling, but the intensity was mild (range, 1-2 in subscale B3). The incidence of the complaint increased gradually after surgery, peaking at 6 months, when 16 patients (17%) complained, and then gradually decreased (Fig 1, *A*). The intensity of the complaint also peaked at 6 months in patients complaining of arm swelling only and at 3 months in patients complaining of both arm swelling and tenderness. In addition, the intensity of this symptom was more severe in these patients (based on subscale B3) compared with that in patients complaining of arm swelling only (Fig 1, *B*). No significant correlations were found between subscale B3 and objective parameters obtained in this study.

The changes in circumferences are shown in Fig 2. No time-dependent changes or differences between sides

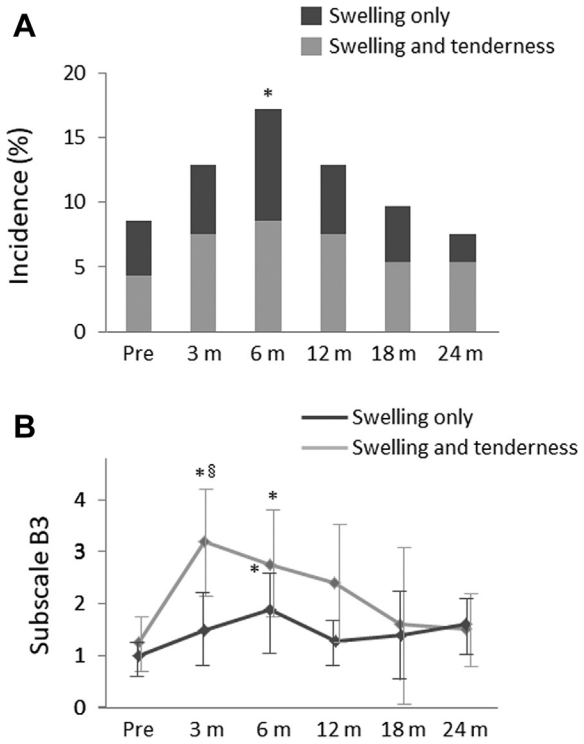

Fig 1. Changes in the complaint of arm swelling with or without tenderness in patients who did not present with lymphedema (LE). **A,** Incidence. **B,** Intensity as expressed by subscale B3. *$P < .05$ vs preoperative value. §$P < .05$ vs swelling only.

were observed in the forearm and hand. In the upper arm, however, a significant postoperative increase in circumference limited to the operation side was observed. This increase persisted through the end of the study period, and a time-dependent increase was

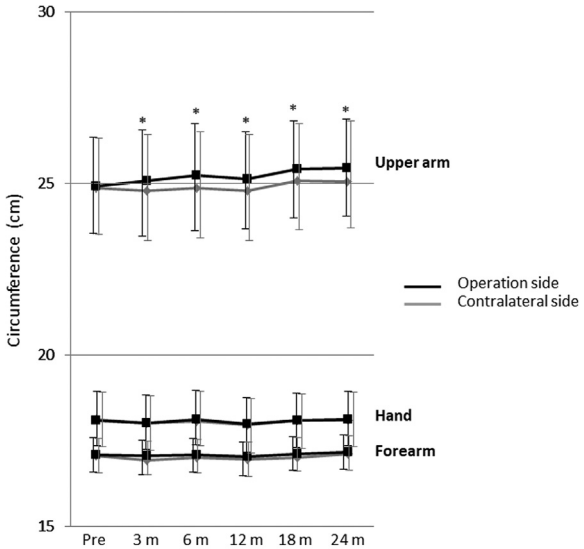

Fig 2. Changes in arm circumferences in patients who did not present with lymphedema (LE). *$P < .05$ vs preoperative value.

not observed. The difference between the sides did not reach statistical significance at any time point.

The mean LDSs were nearly 0 throughout the study period (preoperative value, 0.0 ± 6.3; 3 months, −0.3 ± 6.0; 6 months, 0.6 ± 6.8; 12 months, 0.2 ± 6.6; 18 months, −0.1 ± 5.9; 24 months, −0.2 ± 6.4). Although abnormal LDSs (ie, LDS >10) were recorded (range, 10.1-22.4) in 14 patients (15%) during the study period for unclear reasons, all cases were transient. Although we did not treat these patients particularly, LDS returned to normal spontaneously.

The incidence of increased SEG is shown in Fig 3, *A*. There were no time-dependent changes or differences between sides. Increased SEG occurred more frequently in the lateral upper arm than in the other sites. Increased SEG was observed in 64 patients (69%) throughout the study period, 44 of whom had a bilateral increase. SEFS was not observed in patients without LE.

The changes in skin and subcutaneous thickness are shown in Fig 3, *B* and *C*, respectively. The dorsum of the hand was not long enough to fit the probe properly; therefore, measurement at this site was omitted. Regarding skin thickness, no time-dependent changes or differences between sides were observed. Regarding subcutaneous thickness, significant increases were observed in the upper arm after 12 months and in the forearm at 24 months compared with the preoperative values. There were no significant differences between the sides at any time point in any sites.

For diagnosis of LE, the tentative normal range (ie, mean ± two standard deviations) was calculated for each measurable parameter obtained from the patients who did not present with LE. Slight deviations of the tentative normal ranges were observed, depending on the time of assessment. The maximum values of the upper limits were as follows:

- Difference in circumferences: upper arm, 2.3 cm (at 18 months); forearm, 1.8 cm (at 3 months); hand, 1.1 cm (at 6 months)
- Difference in skin thickness: medial upper arm, 0.4 mm (at 3 and 12 months); lateral upper arm, 0.5 mm (at 3 and 12 months); medial forearm, 0.5 mm (at 18 months); lateral forearm, 0.4 mm (at 3 and 12 months)
- Difference in subcutaneous thickness: medial upper arm, 4.6 mm (at 24 months); lateral upper arm, 3.9 mm (at 3 and 24 months); medial forearm, 2.3 mm (at 12 months); lateral forearm, 2.2 mm (at 24 months)

Patients who presented with LE. In this study, 4 of 97 patients (4.1%) presented with LE. This was 16.7% of patients who underwent axillary node dissection. No patient who had only sentinel node biopsy presented with LE. None of the patients remembered the particular trigger for the LE presentation. The timings of the appearances of the abnormal findings for each case are shown in Fig 4, *A-D*, respectively.

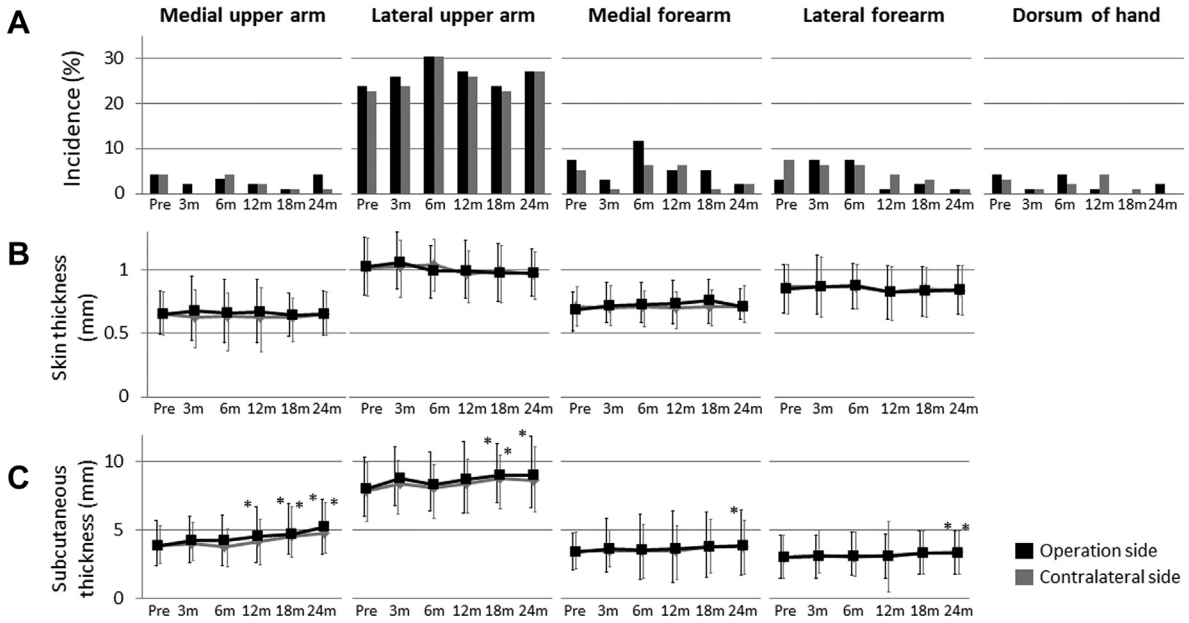

Fig 3. Changes in ultrasound (US) findings in patients who did not present with lymphedema (LE). **A,** Incidence of increased subcutaneous echogenicity (SEG). **B,** Skin thickness. **C,** Subcutaneous thickness. *$P < .05$ vs preoperative value.

Immediately after presentation, two of the four patients did not complain of arm swelling (cases 3 and 4). An increased circumference was observed in the upper arms of three patients (cases 1, 3, and 4) and in the forearm of two patients (cases 1 and 2). An increase in circumferences of >2 cm was observed in the upper arms of three patients (cases 1, 3, and 4) but in only one forearm (case 1). The LDSs were all abnormal (case 1, 83.6; case 2, 20.4; case 3, 18.4; case 4, 23.5). Notably, an increased LDS had been observed 6 to 12 months before LE presentation in three patients (cases 1, 2, and 3) and had persisted until presentation. An increase in SEG was confirmed in all patients, although the extent was not uniform. SEFS was noted in two patients (cases 1 and 4). Increased skin thickness was observed in parts of the affected arm in all patients, but increased subcutaneous thickness was found only in two patients (cases 1 and 4). The common findings in all four cases immediately after LE presentation were increased LDS and increased SEG and skin thickness in the medial forearm.

DISCUSSION

In this study, 30% of patients without LE complained of arm swelling during the study period, whereas two of the four patients with LE did not complain of it immediately after presentation. Szuba et al[13] reported that approximately 20% of patients without LE complained of arm edema, whereas only 50% to 62% of patients who developed LE were aware of their LE presentation. Moreover, the patients without LE complained of pain more frequently, similar to our current results. Although patients' complaints cannot be ignored, their usefulness for the diagnosis of LE onset was limited.

Because ratios of the dominant and nondominant sides were similar between the groups that had cancer on the right and left sides and because the side on which the cancer occurred does not affect the limb volume differences,[14] we did not separate these conditions for our analysis. A 2-cm increase in circumference is one of the most common criteria for LE.[15] However, as a matter of course, the significance of a 2-cm difference varies according to physique (ie, lean, fatty, or muscular) and site (ie, upper arm, forearm, or hand). The tentative normal ranges for the differences in circumferences between the sides revealed that the upper limit of the normal range was up to 2.3 cm for the upper arm, 1.8 cm for the forearm, and 1.1 cm for the hand in the cases without LE. Thus, whereas the "2-cm rule" seems to be somewhat true, more accurate standards may be necessary. Because arm circumferences may be affected by other factors, such as body mass index,[16,17] the differences between sides may be more useful than comparisons with preoperative values.

In this study, the average difference in ECF status between the limbs (ie, the mean LDS) was nearly 0 in cases without LE throughout the study period. Although an LDS of >10 was recorded in 15% of patients without LE, these observations were transient. In contrast, increased LDS was observed 6 to 12 months before LE presentation in three of the four patients who developed LE, and this increase persisted until presentation. This phenomenon was previously reported by Cornish et al[18] using a different device. An increase in ECF might simply

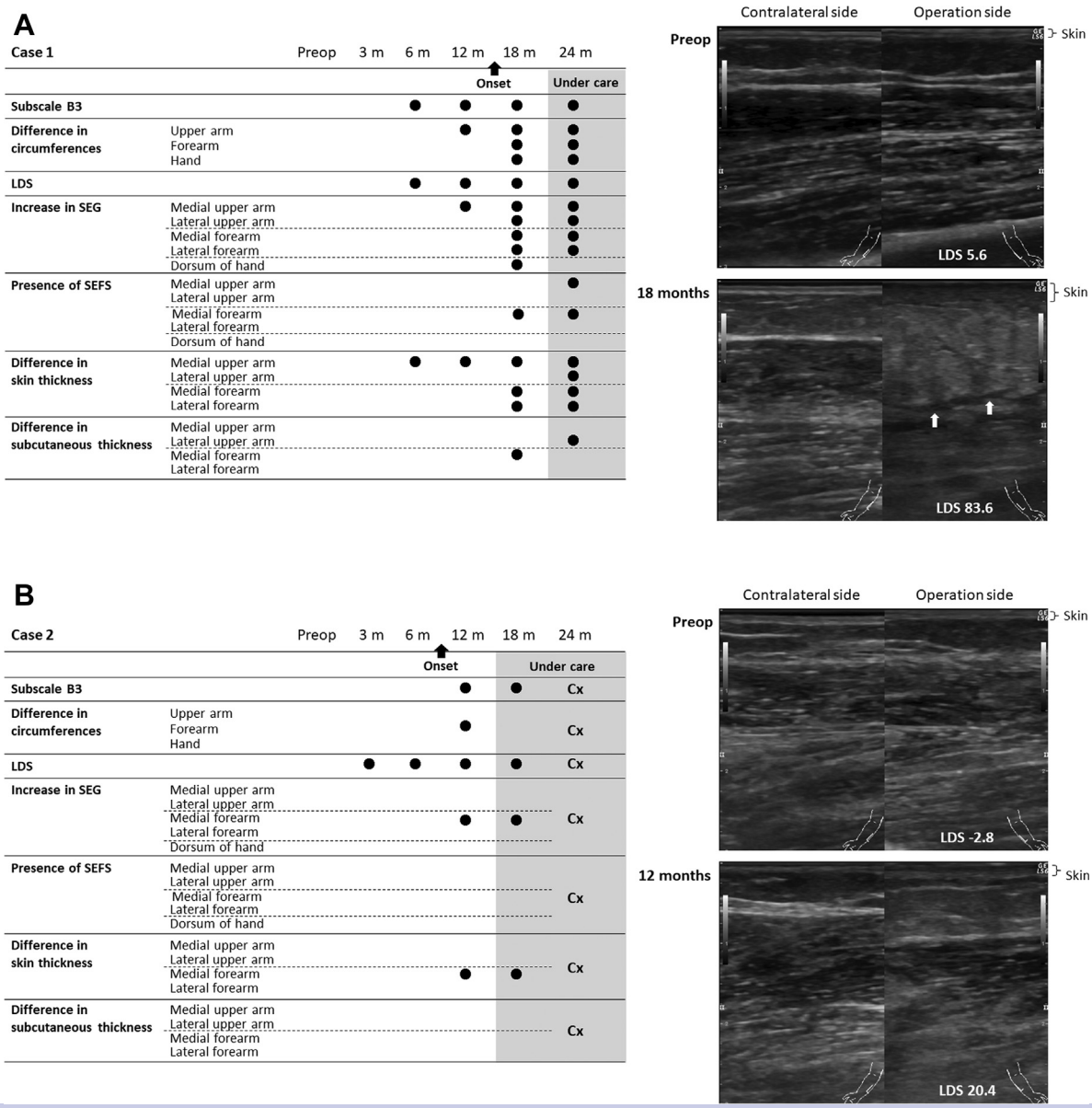

Fig 4. The perioperative courses and ultrasound (US) images of patients who presented with lymphedema (LE). **A,** Case 1. **B,** Case 2. **C,** Case 3. **D,** Case 4. In each noninvasive assessment, abnormal values or findings are shown as *black circles*; *arrow,* subcutaneous echo-free space (*SEFS*). *Cx,* Cyclophosphamide; *DTX,* docetaxel; *LDS,* L-Dex score; *SEG,* subcutaneous echogenicity.

be due to lymph congestion but might also be due to inflammatory edema caused by locally increased monocyte chemoattractant protein 1, for example.[19,20] The reasons for this increase require clarification in future studies, but this finding could be a key for the early detection of LE onset.

Increased SEG is a nonspecific finding that is considered to result from increased cell density and increased collagen content in the tissue, which indicates the presence of subcutaneous inflammation.[21-23] This finding is not typically used for staging of LE because similar findings can be found in the affected and unaffected tissues. However, detecting the presence of inflammation only on the operation side may be valuable for the diagnosis of LE onset. In the patients without LE, increased SEG was observed more frequently in the lateral upper arm compared with the incidence in the other sites. The reason for this finding is unclear, but it might be because subcutaneous fat tissue is thicker in the locations in which increased SEG is often observed.[24] Because Mellor et al[25] reported a circumferential increase in skin and subcutaneous thickness in the arm with LE, these measurements are important. We previously reported that abnormal US findings were most evident in the

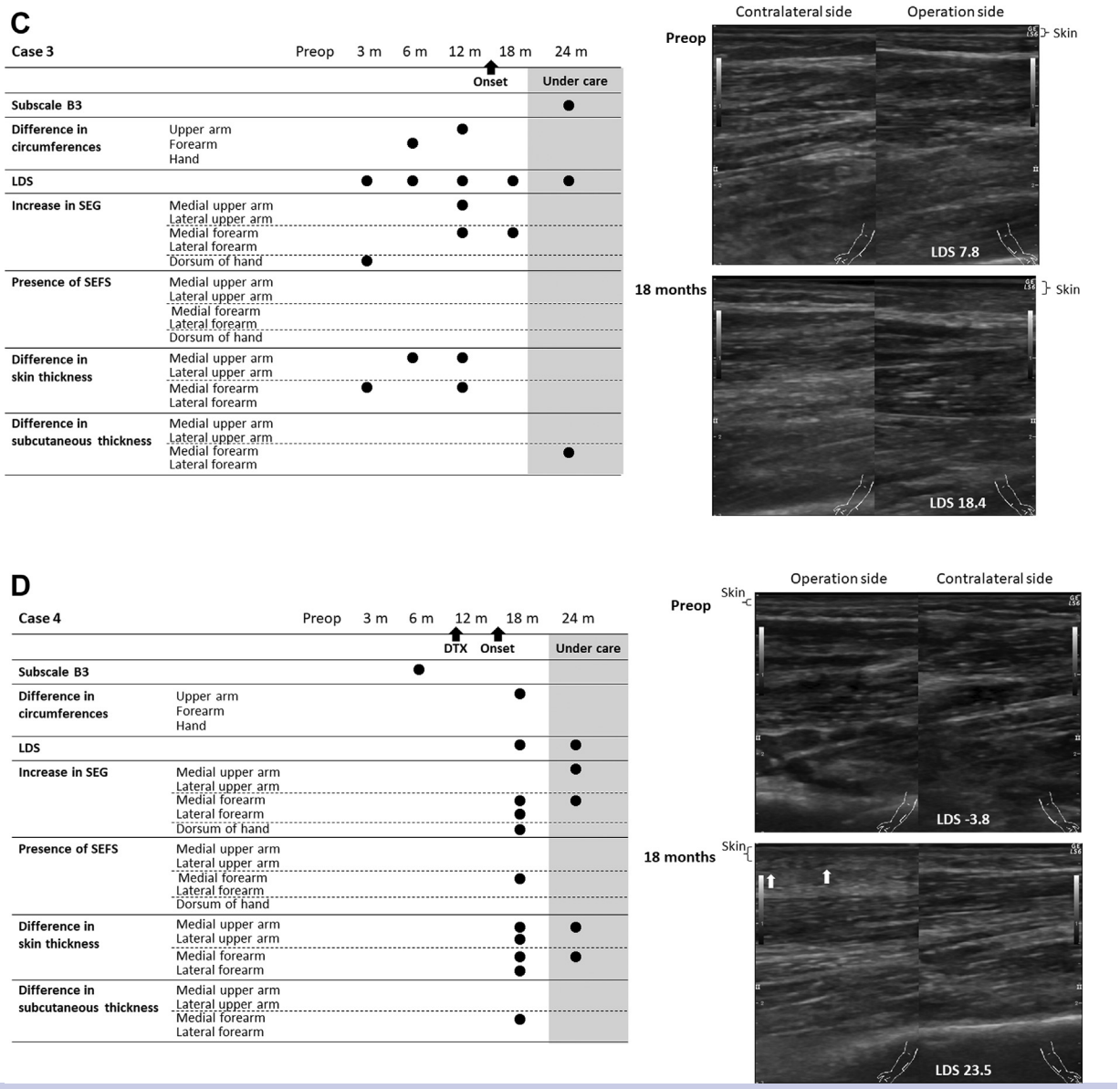

Fig 4. Continued.

medial forearm in postmastectomy stage II patients with LE.[26] Among these findings, an increase in skin thickness and SEG might indicate the earliest change. In this study, cases 3 and 4 had circumference increases only in the upper arm; however, these US findings were still present in the forearm.

Limitations. First, this single-center study involved a limited number of patients, and only four patients presented with LE. Therefore, drawing definite conclusions may be difficult.

Second, qualitative US assessment is still developing. In particular, the significance of an increased SEG has not been well clarified and is simply defined on the basis of empirical facts. In addition, the interobserver and intraobserver differences in determining the presence of SEG and SEFS have not been validated. Regarding quantitative US assessments, the currently employed 12-MHz linear transducer might not be sufficient to clearly delineate skin structures, which might cause a certain range of error.

CONCLUSIONS

In this study, a complaint of arm swelling was not sensitive enough for detection of the early onset of LE because a certain number of patients constantly complained of this symptom. Measurements of circumferences might help in the diagnosis of LE onset, but this method is not specific enough because these measurements are also affected by various factors. However, BIA and skin and subcutaneous US were identified as potential tools for the early detection of LE.

AUTHOR CONTRIBUTIONS

Conception and design: KS, SY, SH
Analysis and interpretation: KS, SY, SH, NM, EH, YT, HN, KH
Data collection: KS, SY, SH, NM, EH, YT
Writing the article: KS
Critical revision of the article: SY, SH, NM, EH, YT, HN, KH
Final approval of the article: KS, SY, SH, NM, EH, YT, HN, KH
Statistical analysis: KS, SY, YT
Obtained funding: SY, NM, EH, HN, KH
Overall responsibility: KS

REFERENCES

1. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol 2013;14:500-15.
2. Executive Committee. The Diagnosis and Treatment of Peripheral Lymphedema: 2016 Consensus Document of the International Society of Lymphology. Lymphology 2016;49:170-84.
3. Czerniec SA, Ward LC, Refshauge KM, Beith J, Lee MJ, York S, et al. Assessment of breast cancer-related arm lymphedema—comparison of physical measurement methods and self-report. Cancer Invest 2010;28:54-62.
4. Langbecker D, Hayes SC, Newman B, Janda M. Treatment for upper-limb and lower-limb lymphedema by professionals specializing in lymphedema care. Eur J Cancer Care (Engl) 2008;17:557-64.
5. Ward LC. Bioelectrical impedance analysis: proven utility in lymphedema risk assessment and therapeutic monitoring. Lymphat Res Biol 2006;4:51-6.
6. Suehiro K, Morikage N, Murakami M, Yamashita O, Samura M, Hamano K. Significance of ultrasound examination of skin and subcutaneous tissue in secondary lower extremity lymphedema. Ann Vasc Dis 2013;6:180-8.
7. Brady MJ, Cella DF, Mo F, Bonomi AE, Tulsky DS, Lloyd SR, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. J Clin Oncol 1997;15:974-86.
8. Ward LC, Dylke E, Czerniec S, Isenring E, Kilbreath SL. Confirmation of the reference impedance ratios used for assessment of breast cancer-related lymphedema by bioelectrical impedance spectroscopy. Lymphat Res Biol 2011;9:47-51.
9. Ward LC, Dylke E, Czerniec S, Isenring E, Kilbreath SL. Reference ranges for assessment of unilateral lymphedema in legs by bioelectrical impedance spectroscopy. Lymphat Res Biol 2011;9:43-6.
10. Ward L, Winall A, Isenring E, Hills A, Czerniec S, Dylke E, et al. Assessment of bilateral limb lymphedema by bioelectrical impedance spectroscopy. Int J Gynecol Cancer 2011;21:409-18.
11. Balzarini A, Milella M, Civelli E, Sigari C, De Conno F. Ultrasonography of arm edema after axillary dissection for breast cancer: a preliminary study. Lymphology 2001;34:152-5.
12. Suehiro K, Morikage N, Murakami M, Yamashita O, Harada T, Ueda K, et al. A study of increase in leg volume during complex physical therapy for leg lymphedema using subcutaneous tissue ultrasonography. J Vasc Surg Venous Lymphat Disord 2015;3:295-302.
13. Szuba A, Chacaj A, Koba-Wszedybyl M, Hawro R, Jasinski R, Tarkowski R, et al. Upper extremity lymphedema after axillary lymph node dissection: prospective lymphoscintigraphic evaluation. Lymphology 2016;49:44-56.
14. Smoot B, Paul SM, Aouizerat BE, Elboim C, Levine JD, Abrams G, et al. Side of cancer does not influence limb volumes in women prior to breast cancer surgery. Lymphat Res Biol 2014;12:189-93.
15. Armer JM, Stewart BR. Post-breast cancer lymphedema: incidence increases from 12 to 30 to 60 months. Lymphology 2010;43:118-27.
16. Benitez Brito N, Suarez Llanos JP, Fuentes Ferrer M, Oliva Garcia JG, Delgado Brito I, Pereyra-Garcia Castro F, et al. Relationship between mid-upper arm circumference and body mass index in inpatients. PLoS One 2016;11:e0160480.
17. Bering T, Mauricio SF, Silva JB, Correia MI. Nutritional and metabolic status of breast cancer women. Nutr Hosp 2014;31:751-8.
18. Cornish BH, Chapman M, Hirst C, Mirolo B, Bunce IH, Ward LC, et al. Early diagnosis of lymphedema using multiple frequency bioimpedance. Lymphology 2001;34:2-11.
19. Jensen MR, Simonsen L, Karlsmark T, Bulow J. Microvascular filtration is increased in the forearms of patients with breast cancer-related lymphedema. J Appl Physiol (1985) 2013;114:19-27.
20. Jensen MR, Simonsen L, Karlsmark T, Lanng C, Bulow J. Higher vascular endothelial growth factor-C concentration in plasma is associated with increased forearm capillary filtration capacity in breast cancer-related lymphedema. Physiol Rep 2015;3:e12403.
21. Liu T, Zhou J, Yoshida EJ, Woodhouse SA, Schiff PB, Wang TJ, et al. Quantitative ultrasonic evaluation of radiation-induced late tissue toxicity: pilot study of breast cancer radiotherapy. Int J Radiat Oncol Biol Phys 2010;78:811-20.
22. Adriaenssens N, Belsack D, Buyl R, Ruggiero L, Breucq C, De Mey J, et al. Ultrasound elastography as an objective diagnostic measurement tool for lymphoedema of the treated breast in breast cancer patients following breast conserving surgery and radiotherapy. Radiol Oncol 2012;46:284-95.
23. Padhani AR, Yarnold J, Regan J, Husband JE. Dynamic MRI of breast hardness following radiation treatment. J Magn Reson Imaging 2003;17:427-34.
24. Suehiro K, Morikage N, Yamashita O, Samura M, Tanaka Y, Takeuchi Y, et al. Differentiation of functional venous insufficiency and leg lymphedema complicated by functional venous insufficiency using subcutaneous tissue ultrasonography. J Vasc Surg Venous Lymphat Disord 2017;5:96-104.
25. Mellor RH, Bush NL, Stanton AW, Bamber JC, Levick JR, Mortimer PS. Dual-frequency ultrasound examination of skin and subcutis thickness in breast cancer-related lymphedema. Breast J 2004;10:496-503.
26. Suehiro K, Morikage N, Yamashita O, Harada T, Samura M, Takeuchi Y, et al. Skin and subcutaneous tissue ultrasonography features in breast cancer-related lymphedema. Ann Vasc Dis 2016;9:312-6.

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