Detecting subclinical secondary lymphoedema using bioimpedance: A preliminary study

Maho Takeuchi, Toyoko Yoshizawa, Yuko Kusaka, Yoshihito Furusawa, Yasuka Nakamura, Fumi Atogami, Hitoshi Niikura

Key words

Bioimpedance analysis, early assessment, secondary lymphoedema

Maho Takeuchi, PhD student, Department of Palliative Nursing; Toyoko Yoshizawa, Professor, Women's Health Nursing; Yuko Kusaka, Master's student, Women's Health Nursing; Yoshihito Furusawa, Attending Staff, Department of Physical Medicine and Rehabilitation; Yasuka Nakamura, Assistant Professor, Women's Health Nursing; Fumi Atogami, Associate Professor, Women's Health Nursing; Hitoshi Niikura, Professor, Department of Gynecology; all at Tohoku University Graduate School of Medicine, Sendai, Japan

Declaration of interest: None.

Abstract

Background: Early intervention is an important facet of the prevention of secondary lymphoedema. However, it is difficult to predict symptoms before swelling becomes clinically significant. **Aims:** To detect the potential occurrence of secondary lymphoedema due to lymph node dissection (LND) by examining variance in body water composition from pre- to early post-operative phases. **Methods:** This prospective observational study was carried out on two groups of patients who had undergone gynaecologic surgery, with or without LND (LND and control [CONT] groups, respectively). Weight, lower-limb circumference, and the ratio of extracellular fluid to total body fluid (E/T) were measured preoperatively and on postoperative day 7 (POD 7). **Results:** Eighteen patients completed the study (LND group, 12; CONT group, 6). Two patients in the LND group had genital swelling on POD7. In the LND group, a significant increase in E/T in the right leg and body trunk was observed. **Conclusion:** Early changes in LND group E/T were observed. Further studies are required to develop a reliable index for predicting the occurrence of lymphoedema.

Secondary lymphoedema reduces both a patient's physical and psychological quality of life (QOL; Franks et al, 2006; Chase and Wenzel, 2011; Fu et al, 2013) and is frequently seen in cancer patients after treatment that includes lymph node dissection (LND) or radiation therapy (Moffatt et al, 2003). The major symptoms of lymphoedema include discomfort, heaviness, problems with physical mobility, and pain. The condition can be debilitating and require intensive, costly treatment (Ryan et al, 2003; Tiwari, 2003). As the condition is irreversible, patients with, or at risk of developing, lymphoedema require care throughout their life.

Prevention and early intervention are two of the main issues in lymphoedema care (Paskett et al, 2012). Precise assessment of the condition is important for timely intervention and to prevent worsening of the patient's condition. In many cases, lymph transport impairment is only suspected after the reporting of discomfort, by which time a severe condition has often developed (Weissleder and Schuchhardt, 2008).

Preventing lymphoedema following cancer treatment is an important issue with long-term health costs. Preventive education for postoperative patients with gynaecological, prostate, or breast cancer with LND in Japan is provided twice by national health insurance; perioperatively on admission for surgery, and within one month of discharge.

A reliable predictive index for the onset of lymphoedema that enables early intervention and preventative care is required.

Multiple frequency bioimpedance analysis (MF-BIA) is a noninvasive method used in various clinical settings to estimate body fluid (Bellizzi et al, 2006; Mager et al, 2008). In recent years, MF-BIA has been applied to the quantification of lymphoedema (Hayes et al, 2009; Loudon et al, 2012). The technique is based on different conductive and resistive properties when a small electric current is applied to tissues *in vivo* (Ackland et al, 2004).

At low frequencies, most of the current will flow preferentially through the extracellular fluid (ECF). In contrast, reactance of the cell membranes decreases at higher frequencies, and the current passes through both the ECF and intracellular fluid (ICF; Dittmar and Reber, 2002). The ratio of the body water component ECF/ICF or ECF/total body fluid (TBF) is widely used to assess fluid changes in oedematous patients, including those with lymphoedema.

Sakuda et al (2010) showed the characteristics of body fluid by ICF/ECF in breast cancer patients after surgery (Sakuda et al, 2010). Some studies have shown the success of using MF-BIA as a tool to predict the early onset of lymphoedema (Cornish et al, 2001; Halaska et al, 2010). However, there is currently no reliable index to predict the occurrence of lymphoedema.

The aim of the present prospective study was to detect the potential occurrence of secondary lymphoedema due to LND by examining variance in the body water composition of patients' lower limbs before, and during the early stages after, LND.

Methods

A prospective, single-centre, observational, preliminary study of two groups of patients who had undergone gynaecological surgery, with are without LND, was conducted between February and September 2011.

Settings

This study was conducted in the outpatient department of the gynaecology unit and the outpatient department of the lymphoedema care ward at a university hospital in the Tohoku region, Japan.

Table 1. Patient characteristics.

	Lymph node dissection (n=14)		Control (n=7)		Z-value	P-value
	Mean±SD	Median	Mean±SD	Median		
Age (years)	55.1±9.5	57.0	43.5±12.8	42.0	2.01	0.044
Height (cm)	158.0±7.3	158.0	156.1±7.1	155.7	0.10	0.920
Weight (kg)	58.5±9.3	57.6	67.7±23.4	57.0	0.50	0.615
BMI (kg/m²)	23.5±3.5	22.9	27.9±10.5	26.5	0.01	0.315
Cancer type	***N***	%	***N***	%		
Cervical	3	21.4	1	14.3	-	-
Uterine	10	71.4	2	28.6	-	-
Ovarian	1	7.1	1	14.3	-	-
Other / unknown	-	-	3	42.9	-	-
Surgery type (LND)	***N***	%	***N***	%		
Pelvic lymphadenectomy	1	7.1	-	-	-	-
Paraaortic lymphadenectomy	13	92.9	-	-	-	-

Sample

Patients scheduled to undergo gynaecological surgery were potential candidates for the study, except those who were diagnosed with primary lymphedema or had other oedema-related episodes (e.g. kidney, liver, or circulation disorders). Patients were divided into two groups according to whether or not they had undergone LND: a LND group, and a control (CONT) group, respectively.

Procedure

Patients were recruited on the date of admission. The first examination (pre-OPE) was conducted after informed consent was obtained, and the second examination was conducted on the seventh day postoperatively (POD7), after the patient's general condition was stable and after all drainage, intravenous drips, and staples had been removed. Due to the circadian variation in body water, measurements were conducted between 2pm and 4pm local time.

Assessment of lower-limb conditions

The circumference of each lower limb was measured at the following seven locations with a plastic measuring tape: acrotarsium (mid-foot); immediately above the ankle joint; 10 cm distal to the patella; directly above the patella; 12 cm and 20 cm proximal to the patella; and at the uppermost part of the lower limb (*Figure 1*).

MF-BIA

For taking body water measurements a bioimpedance spectrometer was used. Before the examination, patients urinated and removed jewellery. Patients wore hospital gowns or clothes without any metallic accessories. The measurement took place with the patient in the supine position after a minimum of 5 minutes rest. Both upper limbs were positioned away from the body trunk, and the thighs were opened to about 30°. The ratio of ECF to TBF (E/T) was then calculated. The "eight electrodes method" (Bosy-Westphal et al, 2013) was employed to measure the fluid content of the whole body and also specific body parts (i.e. right/left upper limb, body trunk, and right/left lower limb).

For healthy individuals, E/T values of 0.36 to 0.40 are expected; higher E/T values indicate an increase in TBF (Van Loan and Mayclin, 1992; Kyle et al, 2004).

Statistical analysis

Demographic characteristics were summarised. Wilcoxon's test was used to evaluate the statistical significance of differences between the two groups, and between pre-OPE and POD7 measurements.

A P-value of <0.05 was considered significant. All tests were two tailed. The authors acknowledge that the comparisons in this analysis may inflate the type 2 error rate in this pilot study. Data were managed in Microsoft Excel and analysed in SPSS predictive analytics software, while the study was assessed and approved by the Ethics Committee of Tohoku University Graduate School of Medicine.

Results

Twenty-one patients (LND n=14; CONT n=7) participated in the study. The key demographic, diagnostic, and treatment characteristics are detailed in *Table 1*. They were: cancer of the cervix (LND, n=3; CONT, n=1), cancer of the uterus (LND, n=10; CONT, n=2), cancer of the ovary (LND, n=1; CONT, n=1), and three other diseases (myoma, ovarian tumour, and choriocarcinoma) in the CONT group.

The extension of LND in the LND group comprised one case of pelvic lymphadenectomy and 13 cases of paraaortic lymphadenectomy. In the CONT group, all patients underwent abdominal total hysterectomy (ATH, n=1) or ATH *and* bilateral salpingo-oophorectomy (BSO, n=6). Two patients in the LND group were unable to participate in the study on POD7 due to their still receiving an intravenous drip, and one patient in the CONT group was discharged early and therefore missed

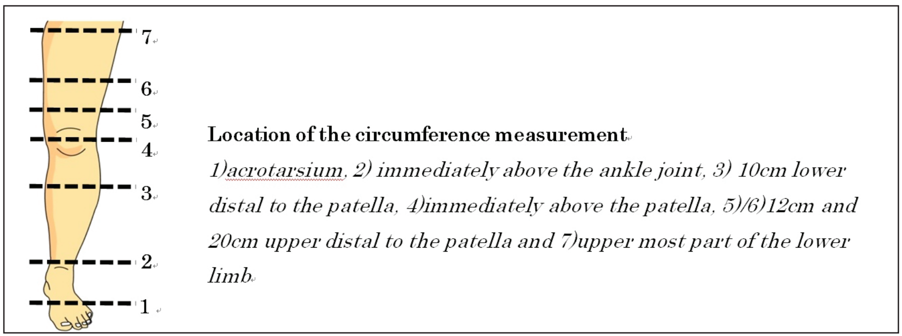

Figure 1. Location of the circumference measurement.

Table 2. Circumference measurement of the lower limb preoperatively (pre-OPE) and seventh day postoperatively (POD7) in the lymph node dissection group (n=12).

	Pre-OPE (cm) Mean±SD	Median	POD7 (cm) Mean±SD	Median	Z-value	*P*-value
Weight (kg)	59.3±9.8	57.6	58.4±9.3	57.0	0.84	0.401
Right leg						
1. Acrotarsium	21.1±1.1	21	21.0±1.1	20.7	0.41	0.681
2. Ankle	20.3±1.7	20	19.9±1.5	19.5	1.20	0.229
3. 10cm lower patella	34.2±2.5	34.4	33.4±2.1	33.5	1.65	0.100
4. Patella	33.5±2.9	32.8	33.0±2.9	32.6	0.40	0.688
5. 12cm upper patella	41.5±3.7	40.4	40.4±3.4	39.7	2.49	0.013
6. 20cm upper patella	47.9±4.2	48.2	47.2±4.2	47.6	1.91	0.056
7. Upper most	51.9±5.2	52.45	51.9±5.3	51.7	1.07	0.283
Left leg						
1. Acrotarsium	21.01±1.1	20.8	20.8±1.1	20.4	1.43	0.514
2. Ankle	20.2±1.8	19.8	20.6±2.3	19.5	1.23	0.218
3. 10cm lower patella	33.8±2.4	34.4	35.7±5.2	32.5	1.79	0.074
4. Patella	33.4±2.9	32.9	32.7±2.7	32.7	1.21	0.228
5. 12cm upper patella	41.3±3.6	41.7	40.1±3.7	40.4	2.49	0.013
6. 20cm upper patella	47.5±4.4	47.8	46.5±4.0	47.6	2.27	0.023
7. Upper most	51.9±5.3	52.3	51.6±4.7	52.3	2.81	0.412

the POD7 measurement. Twelve patients in the LND group and six patients in the CONT group completed the study, and their data were subsequently analysed.

No significant differences in age, height, weight, or body mass index were identified between the LND and CONT groups by Wilcoxon's test. Two patients from the LND group reported an oedematous condition around their vulva on POD7, which was confirmed by their physician. No other swelling was reported by these two patients or by any other patients in the study.

Weight and circumferential changes

No significant differences were observed between the LND and CONT groups at either examination. An unexpected, but significant, decrease in circumference 12 cm distal to the patella on both legs (P=0.013) in the LND group was seen between pre-OPE and POD7 (*Table* 2). No significant differences in circumferential measurements were observed in the CONT group.

Bioimpedance analysis

The LND group showed a significantly higher E/T than the CONT group in the body trunk on POD7 (P=0.04). No significant differences in other regions of the body were observed.

Table 3 provides a summary of the E/T of the body fluid in each region at each examination. In the LND group, POD7 E/T was significantly higher than that of pre-OPE in the body trunk (P=0.003) and right lower limb (P=0.005).

No significant differences between the two groups were seen throughout the measurement term (pre-OPE to POD7). Measurements in the upper limb indicated significant changes in E/T.

Discussion

This study revealed changes in the lower limb during the early phase after gynaecological surgery with LND. Patients who had LND showed a change in E/T in the right lower limb and trunk, although subjective symptoms were reported in only few cases (*Table* 3). This finding indicates that body fluid changes could be detected before the symptomatic awareness. Cornish et al (2001) have previously made this point by using the MF-BIA technique in breast cancer patients, however, there are limited studies relevant to gynaecologic cancer-related lymphoedema.

After gynaecological cancer surgery with LND, swelling is often clinically observed in the genital and inguinal region and can extend to other regions, such as the upper and lower limbs. Our results are compatible with these observations. The changes were only observed in the right lower limb. This might be due to the short follow-up period (7 days) and small sample size, which are limitations of this study. The short-term and unexpected trend in decreasing circumference 12 cm and 20 cm proximal to the patella in the LND group (*Table* 3) could also be due to the limitations of the study.

A previous retrospective study showed that 75% of postsurgical lymphoedema cases occur within one year (Beesley et al, 2007). In another retrospective study, Tada et al (2009) reported that secondary lymphoedema of the lower limbs can be observed at a mean of 4.2 months after the surgery but can occur as early as 0.1 month. Prospectively, monitoring parameters related to lymphoedema presurgery would allow detection of subtle changes before patients are aware of their symptoms, allowing early intervention.

The MF-BIA was used to monitor one of these parameters in the present study. Halaska et al (2006) also used this method to prospectively assess patients for lymphoedema 3 months before and 6 months after surgery for uterine cervical cancer. They reported a 47.6% prevalence of lymphoedema 6 months after surgery. Since lymphoedema has been reported in some studies as early as 0.1 month after surgery, it is reasonable to assume that some changes would have occurred 3 months after surgery. This would be consistent with the subtle changes the authors observed in the lower limbs after only a week (POD7).

This short-term study does not include any of the effects of adjuvant therapy, such as radiotherapy, which is reported to increase the risk of lymphoedema (Tada et al, 2009). Therefore, the authors propose follow-up of parameters related to lymphoedema (particularly changes in body fluid) before and as early as possible after surgery to avoid missing the opportunity for timely treatment.

Early detection and management of lymphoedema have another benefit; reducing the potential risk of infection and hospitalisation in the longer term. Chronic oedema is a known risk factor for cellulitis, which can become recurrent after a single soft tissue infection (Swartz, 2004). Cox (2006) also found that there is a strong association between oedema and cellulitis, each of which is both a risk factor for, and

Table 3. Extracellular fluid to total body fluid of the lower limb preoperatively (pre-OPE) and seventh day postoperatively (POD7) in the lymph node dissection (LND; *n*=12) and control (*n*=6) groups.

	Pre-OPE		POD7		Z-value	*P*-value
	Mean±SD	Median	Mean±SD	Median		
LND group						
1. Right upper limb	0.3771±0.005	0.379	0.3771±0.045	0.376	0.717	0.474
2. Left upper limb	0.3799±0.003	0.381	0.3779±0.003	0.379	0.760	0.447
3. Body trunk	0.3937±0.005	0.384	0.3927±0.005	0.391	2.936	0.003
4. Right lower limb	0.3919±0.008	0.387	0.3919±0.008	0.391	2.807	0.005
5. Left lower limb	0.3904±0.007	0.387	0.3904±0.007	0.389	1.423	0.311
6. Total body	0.3905±0.005	0.385	0.3905±0.005	0.388	2.807	0.005
Control group						
1. Right upper limb	0.3773±0.003	0.379	0.3770±0.006	0.3775	0.365	0.715
2. Left upper limb	0.3785±0.003	0.379	0.3784±0.005	0.3790	0.406	0.684
3. Body trunk	0.3782±0.007	0.381	0.3830±0.009	0.3865	1.753	0.080
4. Right lower limb	0.3777±0.009	0.380	0.3798±0.016	0.3850	0.813	0.416
5. Left lower limb	0.3820±0.009	0.387	0.3870±0.100	0.3870	1.483	0.138
6. Total body	0.3788±0.007	0.382	0.3826±0.103	0.3855	1.355	0.176

consequence of, the other. Reducing oedema is effective in reducing cellulitic episodes, however, prevention of lymphoedema through early intervention may be the most effective prevention of cellulitis.

The authors are mindful that the swelling of limbs in the early phase following surgery is a temporary symptom (Moore, 1958; Wilmore, 2002) and secondary lymphoedema is often a late manifestation; a longer follow-up period is needed to predict the occurrence of lymphoedema. However, assessment and understanding of swelling or oedematous symptoms following surgery is important and may better inform our understanding of the clinical course of lymphoedema.

In the future, the authors intend to extend the observation period to prospectively monitor the spread of lymphoedema to other regions of the body and to elucidate the clinical course of lymphoedema in this patient population.

Conclusion

Body water changes were observed in the early postoperative phase in LND patients. MF-BIA is one of the tools for detecting potential early changes, even before the appearance of subjective symptoms. The methodological feasibility of this study has opened up the possibility of further studies on lymphoedema.

Acknowledgements

This work was supported by the Japan Society for the Promotion of Science KAKENHI (Grant Number 23390506). The authors would like to thank all participants for taking part in this study. We are also grateful to Rhian Davies, University of Glasgow, for her advice on the writing of this article.

References

Ackland GL, Singh-Ranger D, Fox S et al (2004) Assessment of preoperative fluid depletion using bioimpedance analysis. *Br J Anaesth* 92(1): 134–6

Beesley V, Janda M, Eakin E et al (2007) Lymphedema after gynecological cancer treatment : prevalence, correlates, and supportive care needs. *Cancer* 109(12): 2607–14

Bellizzi V, Scalfi L, Terracciano V et al (2006) Early changes in bioelectrical estimates of body composition in chronic kidney disease. *J Am Soc Nephrol* 17(5): 1481–7

Bosy-Westphal A, Schautz B, Later W et al (2013) What makes a BIA equation unique? Validity of eight-electrode multifrequency BIA to estimate body composition in a healthy adult population. *Eur J Clin Nutr* 67 (Suppl 1): S14–21

Chase DM, Wenzel L (2011) Health-related quality of life in ovarian cancer patients and its impact on clinical management. *Expert Rev Pharmacoecon Outcomes Res* 11(4): 421–31

Cornish BH, Chapman M, Hirst C et al (2001) Early diagnosis of lymphedema using multiple frequency bioimpedance. *Lymphology* 34(1): 2–11

Cox NH (2006) Oedema as a risk factor for multiple episodes of cellulitis/erysipelas of the lower leg: a series with community follow-up. *Br J Dermatol* 155(5): 947–50

Dittmar M, Reber H (2002) Evaluation of different methods for assessing intracellular fluid in healthy older people: a cross-validation study. *J Am Geriatr Soc* 50(1): 104–10

Franks PJ, Moffatt CJ, Doherty DC et al (2006) Assessment of health-related quality of life in patients with lymphedema of the lower limb. *Wound Repair Regen* 14(2): 110–8

Fu MR, Ridner SH, Hu SH et al (2013) Psychosocial impact of lymphedema: a systematic review of literature from 2004 to 2011. *Psychooncology* 22(7): 1466–84

Halaska MJ, Komarek V, Mala I et al (2006) A method for the detection of post-operative lymphoedema after operation for breast cancer: multifrequency bioelectrical impedance analysis. *J Appl Biomed* 4(4): 179–85

Halaska MJ, Novackova M, Mala I et al (2010) A prospective study of postoperative lymphedema after surgery for cervical cancer. *Int J Gynecol Cancer* 20(5): 900–4

Hayes SC, Reul-Hirche H, Turner J (2009) Exercise and secondary lymphedema: safety, potential benefits, and research issues. *Med Sci Sports Exerc* 41(3): 483–9

Kyle UG, Bosaeus I, De Lorenzo AD et al (2004) Bioelectrical impedance analysis--part I: review of principles and methods. *Clin Nutr* 23(5): 1226–43

Loudon A, Barnett T, Piller N et al (2012) The effect of yoga on women with secondary arm lymphoedema from breast cancer treatment. *BMC Complement Altern Med* 12: 66

Mager JR, Sibley SD, Beckman TR (2008) Multifrequency bioelectrical impedance analysis and bioimpedance spectroscopy for monitoring fluid and body cell mass changes after gastric bypass surgery. *Clin Nutr* 27(6): 832–41

Moffatt CJ, Franks PJ, Doherty DC et al (2003)Lymphoedema: an underestimated health problem. *QJM* 96(10): 731–8

Paskett ED, Dean JA, Oliveri JM, Harrop JP (2012) Cancer-related lymphedema risk factors, diagnosis, treatment, and impact: a review. *J Clin Oncol* 30(30): 3726–33

Ryan M, Stainton MC, Jaconelli C et al (2003) The experience of lower limb lymphedema for women after treatment for gynecologic cancer. *Oncol Nurs Forum* 30(3): 417–23

Sakuda H, Satoh M, Sakaguchi M et al (2010) Physiological characteristics of the body fluid in lymphedematous patients postbreast cancer surgery, focusing on the intracellular/extracellular fluid ratio of the upper limb. *Jpn J Nurs Sci* 7(1): 108–18

Swartz MN (2004) Clinical practice. Cellulitis. *N Engl J Med* 350(9): 904–12

Tada H, Teramukai S, Fukushima M, Sasaki H (2009)Risk factors for lower limb lymphedema after lymph node dissection in patients with ovarian and uterine carcinoma. *BMC Cancer* 9: 47

Tiwari A, Cheng KS, Button M et al (2003) Differential Diagnosis, Investigation, and Current Treatment of Lower Limb Lymphedema. *Arch Surg* 138(2): 152–61

Van Loan MD, Mayclin PL (1992) Use of multi-frequency bioelectrical impedance analysis for the estimation of extracellular fluid. *Eur J Clin Nutr* 46(2): 117–24

Weissleder H, Schuchhardt C (2008) *Lymphedema Diagnosis and Therapy* (4th edn). Viavital Verlag, Essen