

ORIGINAL ARTICLE

Risk Factors for Lymphedema in Breast Cancer Survivors Following Axillary Lymph Node Dissection

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Objective: The aim of the current study was to assess the risk factors for developing lymphedema following breast cancer treatment. **Methods:** The subjects of this study were 238 consecutive patients who underwent axillary lymph node dissection for breast cancer at Shikoku Cancer Center. The study variables were the occurrence of lymphedema, the body mass index, the follow-up period, the drain removal time, the level of lymph node dissection, the presence or absence of co-resident household members, radiation therapy, neoadjuvant chemotherapy, and adjuvant chemotherapy. **Results:** We observed lymphedema in 23.9% of patients after axillary lymph node dissection for breast cancer. Neoadjuvant chemotherapy and adjuvant chemotherapy using docetaxel and cyclophosphamide increased the risk of developing lymphedema ($P < 0.05$). **Conclusions:** Those patients treated with neoadjuvant chemotherapy and adjuvant chemotherapy using docetaxel and cyclophosphamide should be observed closely after axillary lymph node dissection, and appropriate intervention should be considered from an early stage.

Key Words: axillary lymph node dissection; breast cancer; chemotherapy; lymphedema; upper limb

INTRODUCTION

Lymphedema is one of the most burdensome complications of breast cancer treatment.¹⁾ It is caused by functional overload of the lymphatic system in which the lymph volume exceeds the transport capabilities.²⁾ Lymphedema causes pain, functional disability, deformity, and recurrent infections within the edematous limb.³⁻⁷⁾ Women with lymphedema also experience depression, anxiety, social isolation, and sexual problems.^{7,8)} Therefore, identifying the risk factors for developing lymphedema is important to enable measures to be taken to reduce its occurrence. The survival rate for early breast cancer patients continues to improve. As a result, the adverse effects of post-treatment complications, such as lymphedema, on the long-term quality of life (QOL)

have become increasingly serious problems.

Numerous studies have found that lymphedema is associated with radiation therapy,^{9,10)} obesity,¹¹⁻¹⁵⁾ and chemotherapy.^{13,16)} However, in Japan, the factors associated with lymphedema development after breast cancer surgery are not well established. The aim of the current study was to assess the risk factors for developing lymphedema following breast cancer treatment.

SUBJECTS AND METHODS

Subjects

The subjects of this study were 238 consecutive patients (238 women) who underwent axillary lymph node dissection for breast cancer at Shikoku Cancer Center between Novem-

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ber 2013 and November 2016. The average age \pm standard deviation (SD) at the time of the study was 56.4 ± 12.3 years, and the mean follow-up period was 31.2 ± 10.8 months.

Ethical Approval Statement

Shikoku Cancer Center Ethics Committee approved this study, and written informed consent was obtained from each participant (Approval No. 2018–45).

Outcome Measures

All patients gave their informed consent to participate in this study. The variables studied were the occurrence of lymphedema, the body mass index (BMI), the follow-up period, the drain removal time, the level of lymph node dissection, the presence or absence of co-resident household members, radiation therapy, neoadjuvant chemotherapy, and adjuvant chemotherapy.

Lymphedema in outpatients was diagnosed by a doctor following visual inspection, palpation, and confirmation of circumference differences. Inspections evaluated the visibility of veins or tendons in the hand. Palpation evaluated the presence of compression marks, Stemmer's sign, and skin hardness. Circumference differences were evaluated by comparing the surgical upper extremity and the contralateral upper extremity after surgery, and by comparing the ipsilateral upper extremity before and after surgery. The definition of lymphedema used in this study was that patients with stage one, two, or three lymphedema as defined by the International Society of Lymphology were categorized as the lymphedema group; those categorized as stage zero made up the non-lymphedema group. Occupational therapists and physical therapists checked for lymphedema once a month for the first 3 months after surgery, and any potential sign of lymphedema was reported to the doctor for further investigation. From 3 months after surgery, patients were examined for lymphedema by a doctor when they visited the hospital for adjuvant therapy. If the patients themselves suspected that they were developing lymphedema, they visited the outpatient clinic for confirmation of lymphedema. BMI was measured before surgery.

Radiation therapy was classified into three categories: irradiation of the subclavian lymph node and the anterior chest, irradiation of the anterior chest only, and no radiation therapy. Neoadjuvant chemotherapy was classified as yes or no. The basic policy for neoadjuvant chemotherapy was for it to be administered in patients who had lymph node metastasis at the time of diagnosis or whose tumor diameter was large (≥ 3 cm).

Adjuvant chemotherapy was classified as docetaxel and cyclophosphamide (TC); TC + trastuzumab; doxorubicin and cyclophosphamide (AC) + paclitaxel; trastuzumab + paclitaxel; paclitaxel; and other. The basic method for determining the adjuvant chemotherapy regimen was as follows: node-negative patients were treated with TC, whereas node-positive patients were treated with AC or epirubicin + cyclophosphamide followed by taxane (docetaxel or paclitaxel). Furthermore, patients with hormone receptor-positive and only one to three lymph node metastases were treated with TC.

Rehabilitation Program

During hospitalization before surgery, upper limb exercise instruction was given. The patients were instructed not to mobilize the shoulder beyond 90° of abduction and flexion until postoperative day four (or until the day of drain removal). Once the drains were removed, no restriction of movement was imposed except that resulting from pain. After discharge, patients were encouraged to perform exercises home and were provided with a DVD demonstrating upper limb exercises. At the time of discharge, occupational therapists and physical therapists instructed patients to visit the hospital if postoperative adverse events, including lymphedema, occurred.

Statistical Analysis

The differences between the lymphedema group and the non-lymphedema group were compared using the independent *t*-test, the χ^2 test, and the Mann-Whitney U test. Variables with $P < 0.20$ by these tests were selected for multivariate analysis. Logistic regression was utilized to assess the relationship between risk factors and lymphedema. The variables with $P < 0.05$ were retained in the final multivariate analysis. SPSS software version 22.0 (IBM, Tokyo, Japan) was used to analyze the collected data.

RESULTS

We observed lymphedema in 23.9% (57/238) of patients after axillary lymph node dissection for breast cancer. The time of diagnose of lymphedema was on average 10.5 ± 8.3 months after surgery.

The results of the univariate analysis are shown in **Table 1**. The drain removal time, the level of lymph node dissection, neoadjuvant chemotherapy, adjuvant chemotherapy using TC, and adjuvant chemotherapy using AC + paclitaxel were significantly different between the lymphedema group and

Table 1. Comparison of variables between the lymphedema and the non-lymphedema groups

Variable	Lymphedema group (n=57)	Non-lymphedema group (n=181)	P value
Age (years) ^a	55.3 ± 10.9 (53)	56.4 ± 12.8 (58)	0.568
Body mass index (kg/m ²) ^a	23.6 ± 4.3 (23)	22.9 ± 3.8 (22.4)	0.295
Follow-up period (months) ^a	32.3±11.5	30.9±10.6	0.308
Drain removal time (days) ^a	5.2 ± 1.7 (5)	4.8 ± 1.5 (5)	0.126
Level of lymph node dissection (level 1/2/3) ^b	40/12/5	144/23/14	0.167
Presence or absence of co-resident household members (yes/no) ^b	51/6	158/23	0.818
Radiation therapy (subclavian lymph node and the anterior chest/anterior chest/no) ^b	7/15/35	25/36/120	0.303
Neoadjuvant chemotherapy (yes/no) ^b	22/35	47/134	0.093
Adjuvant chemotherapy (n) ^b			
Docetaxel and cyclophosphamide	17	25	0.009
Docetaxel and cyclophosphamide + trastuzumab	1	9	0.459
Doxorubicin and cyclophosphamide + paclitaxel	1	13	0.197
Trastuzumab and paclitaxel	1	0	0.239
Paclitaxel	1	1	0.422
Other	9	34	0.696

^aMean ± standard deviation (median). ^bProportion.

Table 2. Results of logistic regression analysis

Variable	Odds ratio (95% CI)	P value
Drain removal time	1.119 (0.933–1.341)	0.227
Level of lymph node dissection	1.386 (0.819–2.345)	0.225
Neoadjuvant chemotherapy	2.310 (1.067–5.000)	0.034
Adjuvant docetaxel and cyclophosphamide	4.020 (1.776–9.098)	0.001
Adjuvant doxorubicin and cyclophosphamide + paclitaxel	0.358 (0.042–3.029)	0.346

CI: confidence interval.

the non-lymphedema group (P <0.2).

The results of the logistic regression analysis are shown in **Table 2**. Neoadjuvant chemotherapy and adjuvant chemotherapy using TC resulted in an increased risk of developing lymphedema (P <0.05). The drain removal time, the level of lymph node dissection, and adjuvant chemotherapy using AC + paclitaxel did not affect lymphedema development.

DISCUSSION

In this study, 57 women (23.9%) had developed lymphedema by the end of the follow-up period. The predictors of breast cancer-related lymphedema were neoadjuvant chemotherapy and adjuvant chemotherapy using TC.

Upper-limb lymphedema is a chronic disabling sequel caused by lymphatic insufficiency; its prevalence varies from 6% to 49% among patients who have undergone lymphadenectomies.^{17–19} Lymphedema may present immediately or years after treatment, although the majority of cases occur during the first 18 months.^{20,21} In the current study, lymphedema occurred on average 10.5 months after surgery.

Neoadjuvant therapy reduced the size of the primary tumor, eventually allowing radical or more conservative surgical interventions. In the current study, neoadjuvant chemotherapy was a risk factor for lymphedema. Neoadjuvant chemotherapy is intended for patients with lymph node metastasis or large tumor diameters, and the associated wide-ranging surgical lymph node dissection may be

related to the occurrence of lymphedema. However, in the current study, the degree of lymph node dissection had little effect on the occurrence of lymphedema. For patients who underwent neoadjuvant chemotherapy, it was considered that fluid retention from chemotherapy may have overwhelmed the compromised lymphatic vessels after surgery.

Taxane-based chemotherapy is routinely used in the treatment of high-risk breast cancer. A side effect of taxane-based chemotherapy is skin hardening^{22,23}. Jung et al. reported that taxane-based chemotherapy was an independent risk factor for lymphedema on multivariate analysis in patients following axillary lymph node dissection.²⁴ A review comparing adjuvant chemotherapy with and without docetaxel in breast cancer patients showed that patients receiving docetaxel consistently had increased rates of edema compared with patients receiving docetaxel-free chemotherapy.²⁵ A common side effect of taxane-based chemotherapy, specifically docetaxel, is increased extracellular fluid, which often presents as fluid retention in the extremities.^{26–29} Furthermore, docetaxel exhibits relatively greater hematologic toxicity and is more commonly associated with edema than paclitaxel is.³⁰ In the current study, adjuvant chemotherapy using TC was one of the risk factors for lymphedema. TC includes docetaxel, and docetaxel may have influenced the development of lymphedema. Among our findings, adjuvant chemotherapy using TC + trastuzumab had little effect on the occurrence of lymphedema. However, the number of patients in the TC + trastuzumab group may have been too small to show a significant difference.

Ridner et al.³¹ found that breast cancer survivors whose BMI was ≥ 30 at the time of breast cancer treatment were approximately 3.6 times more likely to develop lymphedema than those with a BMI < 30 . Obesity is associated with fat necrosis, poor wound healing, and infection, all of which can lead to lymphedema. People with a larger BMI need a greater volume of blood circulation and an effective lymphatic system to facilitate fluid flow, maintain circulatory balance, and prevent any imbalance in lymphatic fluid. In contrast to previous studies, we found no association between the development of lymphedema and BMI. However, it should be taken into consideration that our patients had a lower median baseline BMI than those of Ridner et al.³¹ (22.4 vs. 28.8 kg/m²).

Many studies have suggested that radiotherapy is an independent risk factor of lymphedema.^{32–36} Radiotherapy can cause venous occlusion within the radiation field, lymphatic damage, and oppress venous and lymphatic circulation as a result of local muscle fibrosis.³⁷ In contrast to the findings of

previous studies, we found no association between lymphedema and radiation treatment. These differences may have resulted from the more refined radiation techniques being implemented in recent years. Moreover, lymphedema may not have occurred because the irradiation area of patients was limited to the subclavian lymph node and the anterior chest.

Study Limitations

The current study has some limitations. First, although the risk factors for lymphedema were clarified, currently, there is no known method for preventing lymphedema. Second, we did not examine whether lymphedema affects the activities of daily living and QOL. Third, from 3 months after surgery and during the follow-up period, confirmation of lymphedema depended on patients presenting with symptoms, and this may have affected the results. Further research is needed to examine these issues.

CONCLUSION

Our study showed that lymphedema occurred in 23.9% of patients after axillary lymph node dissection for breast cancer. The average time between surgery and the diagnosis of lymphedema was 10.5 months.

Neoadjuvant chemotherapy and adjuvant chemotherapy using TC presented an increased risk of developing lymphedema. Identification of these factors could help us to plan the prevention and control of lymphedema in patients after axillary lymph node dissection for breast cancer.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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