

# Comparison of bilateral lymphedema and unilateral lymphedema in lower extremities after gynecologic cancer surgery

S.H. Ryu<sup>1</sup>, B.S. Jang<sup>1</sup>, J.H. Lee<sup>1</sup>, H.J. Jeong<sup>1</sup>, G.C. Kim<sup>1</sup>, Y.J. Sim<sup>1,\*</sup>

<sup>1</sup>Department of Physical Medicine and Rehabilitation, Kosin University Gospel Hospital, Kosin University College of Medicine (Republic of Korea)

## Summary

**Purpose of investigation:** To identify factors associated with bilateral lymphedema in lower extremities that occur after gynecological cancer surgery. **Materials and methods:** Retrospective chart review was performed on 110 patients who were hospitalized for lymphedema after gynecological cancer surgery from 2006 to 2018. Statistical significance was verified using Pearson's Chi-square test, Fisher's exact test, and exact logistic regression analysis. **Results:** The types of cancer, cancer stage, genital swelling, and extensive lymph node dissection were significantly different between the two groups. Exact logistic regression analysis showed that cancer stage and genital swelling were associated with bilateral lymphedema. Significant differences were observed for radiation therapy and lymphangitis. Exact logistic regression analysis revealed that radiation therapy and lymphangitis were factors associated with unilateral to bilateral progression. **Conclusion:** Cancer stage, genital swelling, and extensive lymph node dissection were identified as factors related to bilateral lower limb lymphedema. Radiation therapy and infection history were identified as factors related to lymphedema progressing from unilateral to bilateral. **Content:** The associated factors for bilateral lymphedema in lower extremities after gynecological cancer surgery

**Key words:** Lymphedema; Gynecological cancer; Associated factor.

## Introduction

Lymphedema is a disease in which fluids and proteins accumulate in local tissues due to damage to the lymphatic system. It may be asymptomatic or accompanied by symptoms such as heaviness and pain [1, 2]. Lymphedema in the lower extremities has various causes. The most common is damage to the lymphatic system after gynecological cancer surgery [3]. The incidence of gynecological cancers is increasing in Korea and survival rates are also increasing. Therefore, management of cancer survivors is emerging as an important problem [4, 5]. Lymphedema of the lower extremities is a representative complication after gynecologic cancer treatment. The incidence is reported to be from 10% to 70%, with unilateral lymphedema accounting for 80% and bilateral lymphedema accounting for 20% [3, 6-8]. Patients with lymphedema can undergo conservative or surgical treatments, but lymphedema is not yet curable. Lymphedema of the lower extremities leads to a decrease in patient quality of life [9]. Patients with bilateral lymphedema of the lower extremities complain of more discomfort than patients with unilateral lymphedema and can have gait disturbances [10]. Lymphedema of the upper limbs that occurs after breast cancer surgery is unilateral, but lymphedema after gynecological cancer surgery may be unilateral or bilateral. Therefore, predicting if lymphedema will occur uni-

laterally or bilaterally in patients who had gynecological cancer surgery is necessary but the factors causing bilateral lymphedema are unknown. In this study, we compared groups of patients with bilateral and unilateral lower limb lymphedema to determine which factors influence the development of bilateral lymphedema.

## Materials and Methods

### Participants

This study was conducted with patients admitted to the Department of Rehabilitation Medicine of Kosin University Gospel Hospital from 2006 to 2018 for lymphedema in the lower extremities. Lymphedema specialists diagnosed lymphedema by interview, leg circumference measurement, and physical examination. When a patient with suspected lymphedema visits our outpatient clinic, we measure the circumference of the lower limb at 3 cm intervals using a tape measure and compare the two sides. After this size measurement and physical examination, lymphoscintigraphy is taken as a routine. Lymphoscintigraphy was used to identify patients with lymphatic flow reduction, decreased lymph node uptake, and dermal back flow. Lymphoscintigraphy confirmed unilateral and bilateral lymphedema. If a patient diagnosed with unilateral complains that edema has occurred on the opposite side while following up through

Table 1. — Patient characteristics.

Characteristics	N
Age (yr)	52.65 ± 11.83
Onset duration	35.43 ± 29.19
Location of lymphedema	
Group A	71 (64.5)
Group B	27 (24.5)
Group C	12 (10.9)
Type of cancer, N (%)	
Cervical cancer	72 (65.5)
Ovarian cancer	24 (21.8)
Endometrial cancer	14 (12.7)
Cancer stage	
Stage I	60 (54.5)
Stage II	24 (21.8)
Stage III	15 (13.6)
Stage IV	11 (10.0)
BMI (kg/m <sup>2</sup> )	24.11 ± 3.62
≥ 23	70 (63.6)
< 23	40 (36.4)
Radiation therapy, N	
Yes	49 (44.5)
No	61 (55.5)
Chemotherapy, N	
Yes	82 (74.5)
No	28 (25.5)
Lymphangitis, N	
Yes	59 (53.6)
No	51 (46.4)
Genital swelling, N	
Yes	48 (43.6)
No	62 (56.4)

Values are mean ± standard deviation or number. BMI: Body mass index.

the outpatient field, a new lymphoscintigraphy is taken. Doppler ultrasonography and CT venogram were also taken to rule out edema caused by vascular abnormalities. A total of 174 patients were diagnosed with lymphedema. Among them, patients with primary lymphedema and those who underwent surgery for cancer other than gynecological cancer were excluded. Lymphedema developing after vulvar cancer was excluded because only one patient had this condition. Patients with insufficient medical records, such as lacking cancer stage, chemotherapy and radiation therapy, were excluded. A total of 110 patients were included in the study. We performed a retrospective study based on patient medical records. Among 110 patients, for 82 we confirmed the extent of lymph node dissection using medical records. In addition, we performed a separate analysis to determine if the extent of lymph node dissection affected unilateral or bilateral lymphedema.

## Method

We divided patients into three groups. Patients with unilateral lymphedema were defined as group A and those with bilateral lymphedema after surgery were defined as group B. Patients with initially unilateral lymphedema that progressed to both sides were defined as group C. By comparing groups A and B, factors related to bilateral lymphedema were identified, and factors affecting bilateral progression were determined by comparing groups A and C. Age, onset duration, cancer type, cancer stage, BMI, chemotherapy, radiation therapy, genital swelling, and infection history of the lower extremities were compared among the groups. Age was categorized based on age 55, which was found to be significant factor for lymphedema in previous study [11]. We classified cancer types into cervical, ovarian, and endometrial, and stages were divided into 1, 2, 3, and 4. We divided the cancer stage according to the FIGO staging system. BMI groups were divided based on a BMI of 23, which is classified as overweight in Korea [12]. Radiation therapy and chemotherapy were divided according to whether treatment was performed, regardless of the number of treatments. Genital swelling and infection history were confirmed by medical records. The extent of lymph node dissection was confirmed by surgical and histological records of a Pathology Department. We classified patients into 3 groups according to the extent of lymph node dissection. Each group was patients without dissection, patients with dissection of pelvic lymph node, and patients with dissection of pelvic lymph node and paraaortic lymph node. We compared the patients with confirmed lymph node dissection in groups A and B, and A and C.

## Statistics

Age, cancer type, stage, BMI, chemotherapy, radiation therapy, genitalia swelling, lymphangitis, and lymph node dissection were compared using Pearson's Chi-square test. If number of patients were 5 or less, Fisher's exact test was used. A *p*-value of < 0.05 was considered significant. The statistically significant factors were selected from Pearson's Chi-square test and Fisher's exact test to perform logistic regression analysis. Exact logistic regression analysis was performed to identify factors related to the development and progression of bilateral lymphedema. Development or progression of bilateral lymphedema, the dependent variable (outcome variable), had a binary value (0 and 1). Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated for exact logistic regression. Pearson's Chi-square test and Fisher's exact test were performed with SPSS version 25 (SPSS Inc., Chicago, IL, USA). Exact logistic regression analysis was performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

## Results

Group A had 71 patients with a mean age of 52.24 ± 11.47 years, group B had 27 patients with a mean age of 53.07 ± 12.39, and group C had 12 patients, with a mean

Table 2. — Univariate analysis of groups A and B.

Characteristics	Group A	Group B	p value
Age, N(%)			0.806
≥ 55 years	27 (38.0)	11 (40.7)	
< 55 years	44 (62.0)	16 (59.3)	
Type of cancer, N (%)			0.010*
Cervical cancer	49 (69.0)	13 (48.1)	
Ovarian cancer	11 (15.5)	12 (44.4)	
Endometrial cancer	11 (15.5)	2 (7.4)	
Cancer stage, N(%)			0.000**
Stage I	47 (66.2)	6 (22.2)	
Stage II	15 (21.1)	6 (22.2)	
Stage III	6 (8.5)	8 (29.6)	
Stage IV	3 (4.2)	7 (25.9)	
BMI (kg/m <sup>2</sup> ), N(%)			0.707
≥ 23	45 (63.4)	16 (59.3)	
< 23	26 (36.6)	11 (40.7)	
Radiation therapy, N(%)			0.906
Yes	28 (39.4)	11 (40.7)	
No	43 (60.6)	16 (59.3)	
Chemotherapy, N(%)			0.058
Yes	50 (70.4)	24 (88.9)	
No	21 (29.6)	3 (11.1)	
Lymphangitis, N(%)			0.580
Yes	36 (50.7)	12 (44.4)	
No	35 (49.3)	15 (55.6)	
Genital swelling, N(%)			0.002**
Yes	23 (32.4)	18 (66.7)	
No	48 (67.6)	9 (33.3)	
Lymph node dissection, N(%)			0.002**
None	2 (3.9)	0 (0)	
Pelvic lymph node	35 (67.3)	8 (34.8)	
Pelvic lymph node & paraaortic lymph node	15 (28.8)	15 (65.2)	

BMI: Body mass index. \* $p < 0.05$ , \*\* $p < 0.01$ .

Table 3. — Multivariate analysis of groups A and B.

Characteristics	Adjusted OR	95% CI	p value
Type of cancer	0.604	0.198-1.473	0.351
Cancer stage	2.909	1.653-5.641	0.000**
Genital swelling	3.471	1.103-11.551	0.004**

OR: odds ratio, CI: confidence interval. \* $p < 0.05$ , \*\* $p < 0.01$ .

age of  $54.08 \pm 13.53$ . The duration of lymphedema development was  $35.43 \pm 29.19$  days on average, and there was no statistically significant difference when comparing the mean through Independent Sample *t* Test. Group A had 49 patients with cervical cancer and 11 each with ovarian and endometrial cancer. Group B had 14 with cervical, 12 with ovarian, and 2 with endometrial, and C had 10, 1 and 1, respectively. Mean BMI was  $24.11 \pm 3.62$  with 70 patients with a BMI of 23 or more. In addition, 49 patients received radiation therapy, and 82 patients received chemotherapy.

Lymphangitis developed in 59 patients and genital swelling in 48 (Table 1). Age, BMI, radiation therapy, chemotherapy, and lymphangitis were not significantly different between groups A and B. However, the types of cancer, cancer stage, and genital swelling were significantly different between the two groups (Table 2). Exact logistic regression analysis showed that cancer stage and genital swelling were associated with bilateral lymphedema (Table 3). No significant difference was seen in age, type of cancer, cancer stage, BMI, chemotherapy or genital swelling between groups A and C. Significant differences were observed for radiation therapy and lymphangitis (Table 4). Exact logistic regression analysis revealed that radiation therapy and lymphangitis were factors associated with unilateral to bilateral progression (Table 5). A total of 82 patients were identified by extent of lymph node dissection with 52 in group A, 23 in B, and 7 in C groups. In comparisons between groups A and B, the extent of lymph node dissection was significantly different (Table 2). However, comparisons between groups A and C showed no significant differences.

Table 4. — *Univariate analysis of groups A and C.*

Characteristics	Group A	Group C	<i>p</i> value
Age, N (%)			0.811
≥ 55 years	27 (38.0)	5 (41.7)	
< 55 years	44 (62.0)	7 (58.3)	
Type of cancer, N (%)			0.599
Cervical cancer	49 (69.0)	10 (83.3)	
Ovarian cancer	11 (15.5)	1 (8.3)	
Endometrial cancer	11 (15.5)	1 (8.3)	
Cancer stage, N (%)			0.913
Stage I	47 (61.2)	7 (58.3)	
Stage II	15 (21.1)	3 (25.0)	
Stage III	6 (8.5)	1 (8.3)	
Stage IV	3 (4.2)	1 (8.3)	
BMI (kg/m <sup>2</sup> ), N (%)			0.435
≥ 23	45 (63.4)	9 (75.0)	
< 23	26 (36.6)	3 (25.0)	
Radiation therapy, N (%)			0.005**
Yes	28 (39.4)	10 (83.3)	
No	43 (60.6)	2 (16.7)	
Chemotherapy, N (%)			0.793
Yes	50 (70.4)	8 (66.7)	
No	21 (29.6)	4 (33.3)	
Lymphangitis, N (%)			0.008**
Yes	36 (50.7)	11 (91.7)	
No	35 (49.3)	1 (8.3)	
Genital swelling, N (%)			0.084
Yes	23 (32.4)	7 (58.3)	
No	48 (67.6)	5 (41.7)	

BMI: Body mass index. \**p* < 0.05, \*\**p* < 0.01.

## Discussion

In comparisons of groups A and B, cancer type, cancer stage, and genital swelling were significantly different. Patients with bilateral lymphedema had a higher cancer stage than those with unilateral lymphedema. Ovarian cancer was seen in a higher proportion of patients in group B than group A. However, in exact logistic regression, the cancer type was not significant. Ovarian cancer patients with higher stage cancer undergo cytoreduction surgery to reduce cancer volume [13]. Cytoreductive surgery is often performed with extensive lymph node dissection. Although exact logistic regression analysis was not performed due to the small number of patients with confirmed records for lymph node dissection, a significant difference was seen for lymph node dissection in groups A and B. This result meant that extensive lymph node dissection increased the likelihood of bilateral lymphedema in the lower extremities. The wider the lymph node dissection in high stage cancer, the greater the likelihood of bilateral lymphedema. Therefore, it is believed that bilateral lymphedema in high stage ovarian cancer is not a characteristic of ovarian cancer, but an influence of extensive lymph node dissection. Genital swelling was significantly higher in group B than group A,

indicating that it was associated with bilateral lower limb lymphedema. Genital lymphedema is an abnormality in the proximal lymphatic system, which is more likely to drain on both sides because the lymph nodes are closer to each other than in distal regions [14, 15]. Patients with bilateral lymphedema are more likely to have damage to the proximal region because both lymphatic systems are injured. For this reason, patients with bilateral lymphedema are more likely to have genital swelling than patients with unilateral lymphedema.

Table 5. — *Multivariate analysis of groups A and C.*

Characteristics	Adjusted OR	95% CI	<i>p</i> value
Radiation therapy	7.601	1.379-79.830	*0.014
Lymphangitis	10.551	1.317-494.259	*0.018

OR: odds ratio, CI: confidence interval. \**p* < 0.05, \*\**p* < 0.01.

We found a significant difference in radiation treatment and infection history between groups A and C. Patients who received radiation therapy were more likely to progress from unilateral to bilateral lymphedema, so continuous outpatient follow-up should examine for circumferential changes in the leg where no edema has occurred. If swelling occurs in the lower extremity that was normal in unilateral lymphedema patients, lymphoscintigraphy should be redone to check for changes in the patient's lymphatic system. Infection causes inflammation of the tissues, which can damage the lymphatic system. In breast cancer-related lymphedema, infection is a major risk factor for lymphedema aggravation [16]. In our study, infection was also a factor in the progression of unilateral into bilateral lymphedema. Radiation therapy was significantly different in comparisons of groups A and C, but not groups A and B. McDuff's study, which focused on the timing of lymphedema following breast cancer treatment, showed that regional lymph node radiation is associated with late onset lymphedema [17]. Both that and our study indicated that radiation therapy is the cause of delayed lymphedema. Therefore, further research should be conducted to identify why radiation therapy causes delayed lymphedema. Infection is one of the common complications in patients with lymphedema and is known to be mainly caused by wounds [18]. If patients pay attention to skin care, infection is a preventable factor. To prevent aggravation of bilateral lymphedema, patients with unilateral lower limb lymphedema should be educated about infection prevention. In addition, the possibility of bilateral progression should be described in patients with lymphangitis, and rapid control of the infection will help prevent progression.

In a comparison of groups A and C for lymph node dissection, the number of patients in group C was very small, at 7, making significance difficult to determine.

Previous studies showed that risk factors for lymphedema after gynecological cancer surgery are age, cancer stage, BMI, vulvar cancer, chemotherapy, and radiation therapy [7, 11, 19-21]. In this study, 63.6% of patients had BMI greater than 23, 44.5% had radiation therapy, 74.5% had chemotherapy, 53.6% had a history of lymphangitis, and 43.6% had genital swelling. In our previous studies on lower limb lymphedema associated with gynecological cancer, BMI, radiation therapy, chemotherapy and lymph node dissection were identified as risk factors [22]. Although BMI and chemotherapy are risk factors for lymphedema, they were not significant for any comparisons conducted in this study, indicating no association with bilateral lymphedema. Age was statistically insignificant even if the criteria were set to 60 and 65 years, and BMI was not significant even if the patients were classified by BMI 25. BMI was obtained by dividing body weight by the square of height and reflected the degree of body fat. Increasing the amount of adipose tissue causes lymphatic dysfunction, which can reduce proximal lymph flow, resulting in lymphedema [23]. However, because muscle mass and bone weight also contribute, BMI and adipose tissue are not directly proportional. Therefore, BMI does not reflect the exact amount of fat a person has. In our study, 5 patients with severe obesity (BMI above 30) were included in the A, B and C groups: 1 person (1.4%) was in group A, 3 (11.1%) in B, and 1 (8.3%) in C. Although findings were not statistically significant, the proportion of patients with severe obesity in groups B and C were considerably higher than the proportion in group A. Therefore, patients with severe obesity who had large amounts of adipose tissues that can cause lymphatic dysfunction can develop bilateral lymphedema. To confirm this finding statistically, a study with a sufficient number of patients with a BMI of 30 or more is needed. Vulvar cancer was not included in our analysis due to a small number of patients. Previous studies have studied risk factors of lymphedema, but we compared bilateral and unilateral lymphedema and identified the factors involved in bilateral lymphedema. We showed that the factors involved in lower limb lymphedema and the factors involved in bilateral lymphedema were only partially consistent.

## Conclusions

In this study, cancer stage, genital swelling, and extensive lymph node dissection were identified as factors related to bilateral lower limb lymphedema. Radiation therapy and infection history were identified as factors related to lymphedema progressing from unilateral to bilateral. Patients with unilateral lymphedema who had radiation therapy or had a history of infection were more likely to progress to bilateral lymphedema. These patients should be educated about the possibility of lymphedema progressing from unilateral to bilateral.

## Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Kosin University Gospel Hospital (approval number: KUGH 2020-03-006).

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## Conflict of Interest

The authors declare no competing interests.

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Corresponding Author:

YOUNGJOO SIM, M.D.

Department of Physical Medicine and Rehabilitation,  
Kosin University Gospel Hospital, Kosin University  
College of medicine (Republic of Korea)

e-mail: yooshs@naver.com