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# Relationship of the number and size of superficial groin lymph nodes with the stage of secondary lymphatic edema

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# Relationship of the number and size of superficial groin lymph nodes with the stage of secondary lymphatic edema

Short title/running head: Superficial groin lymph nodes

Satoshi Onoda[1] PhD, Yoshihiro Kimata[1] PhD, Kiyoshi Yamada[1] MD, Noriko Seki[2] PhD, Yuji Hiramatsu[2] PhD

[1]Department of Plastic and Reconstructive Surgery, Graduate School of Medicine, Dentistry and Pharmaceutical Science, University of Okayama, Okayama 700-8558, Japan: E-mail: satoshiprs18@gmail.com

[2]Department of Obstetrics and Gynecology, Graduate School of Medicine, Dentistry and Pharmaceutical Science, University of Okayama, Okayama 700-8558, Japan

Correspondence to: Satoshi Onoda

Department of Plastic and Reconstructive Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Science

2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan

Tel: +81-086-223-7151; Fax: +81-086-235-7210

Email: satoshiprs18@gmail.com

Key words: superficial groin lymph nodes, lower limb lymphedema, secondary lymphedema, gynecologic cancer, risk factor

Synopsis: We reviewed the relationship between the size, number, and laterality of superficial groin lymph nodes and the staging and laterality of lower limb lymphedema and reported that the size and number of superficial groin lymph nodes was a factor associated with the development of lymphedema.

ABSTRACT

**Purpose**: This study evaluated the relationships of the size and number of superficial groin lymph nodes with the lower limb lymphedema stage and thus examined the role of superficial lymphatic lymph nodes in secondary lymphedema development.

**Methods**: We determined the number and size of superficial groin lymph nodes using horizontal plane computed tomography (CT) and the lymphedema stage in the lower limbs of 25 patients with gynecologic cancer.

**Results**: The patients had an average of 2.92 (range, 1–7) superficial groin lymph nodes; the mean size of the 146 evaluated lymph nodes was 7.55 mm (range, 5–15 mm). In 19 of 25 patients (76%), the side with major edema contained fewer superficial groin lymph nodes. In total, 22 patients (88%) had fewer superficial groin lymph nodes or a smaller total lymph node size on the edematous dominant side.

**Conclusions**: In this evaluation of the link between superficial groin lymph node laterality and secondary lymphedema staging, we found that patients with large lymph node numbers and sizes tended to present with a relatively earlier stage of lymphedema. Our results therefore suggest that the size and number of superficial groin lymph nodes affect the lymphedema stage.

Lymphedema can be classified roughly as primary lymphedema, which occurs without a particular cause, and secondary lymphedema, which is consequent to lymphadenectomy during malignant tumor resection, infection, or trauma.[1-3] Lymphedema can occur in various regions of the body, including the upper limbs,[4-8] lower limbs,[9-10] external genitalia,[11] lower abdomen, and head and neck region.[12] However, most cases of secondary upper limb lymphedema are attributed to axillary lymphadenectomy during breast cancer resection[13-15], whereas most cases of lower limb lymphedema are attributed to pelvic lymphadenectomy during gynecologic or urologic cancer resection[16-18].

Lymphatic flow can also be classified as superficial lymphatic flow, which occurs in the skin and subcutaneous fat tissue, and deep lymphatic flow, which occurs in the muscle and deep anatomic structures[19-21]; notably, previous studies have used lymphatic scintigraphy and indocyanine green fluorescence lymphography to demonstrate the former.[22-24] Generally, lymphatic drainage network reconstruction is assumed to occur via lymphatic neogenesis at the site of injury and at sites of other lymphatic outflow tracts that have been impeded by lymphadenectomy, infection, or injury. According to Kutuna, who conducted detailed examinations of lymphatic systems in a Japanese population, lymph flow in the lower limbs is refluxed through both superficial groin lymph nodes and the pelvic lymph nodes.[25] Scaglioni et al. further reported connections between the superficial and deep lymphatic system in the inguinal region. These findings suggest that superficial lymphatic flow in the groin plays an important role in the reconstruction of lymphatic circulation after malignant tumor resection with pelvic lymphadenectomy, as this procedure does not injure the superficial lymphatic flow.[26-27]

To date, few reports have described the relationship between superficial lymphatic flow and secondary lymphedema. Accordingly, this study aimed to examine the role of superficial lymphatic circulation in the development of secondary lymphedema. Therefore, we reviewed the relationship between superficial groin lymph node laterality (i.e., non-equal number/size of lymph nodes in each limb) and lower limb lymphedema staging in patients with secondary lymphedema.

## MATERIALS AND METHODS

This study was performed under a protocol approved by the Okayama University Hospital ethics committee. Informed patient consent was deemed unnecessary for this study and was therefore not obtained. From January 2009 to June 2014, 373 patients with concerns regarding secondary lower limb lymphedema underwent follow-up evaluation at Okayama University Hospital. We retrospectively reviewed data of

patients who met the following selection criteria: history of gynecologic malignant tumor resection with pelvic lymph node dissection performed at our hospital, absence of superficial groin lymph node metastasis (determined using positron emission tomography), and a difference in lymphedema stage between the lower limbs. Regarding the latter factor, because the severity of cellulitis, prophylactic antibiotic use, radiotherapy dosage, chemotherapy, additional operative procedures for lymphedema (e.g., lymphaticovenular anastomosis) are considered factors affecting lymphedema staging, we decided to compare stage laterality within individual cases rather than differences in stage between individuals. A total of 25 patients were selected. For these patients, we evaluated the primary disease associated with lymphedema, cancer stage, bilateral lymphedema stage, history of chemotherapy and radiation therapy, and interval from the initial resection to lymphedema development (Table 1).

In addition, we confirmed that pelvic lymph nodes were surgically resected and determined the metastatic positive rate and the sizes and number of superficial groin lymph nodes for each patient (Table 2). The number of pelvic lymph nodes resected during primary surgery was determined according to the postoperative pathological diagnosis. The number and sizes of superficial groin lymph nodes were determined using preoperative horizontal plane computed tomography (CT) images (Figures 1 and 2). We defined superficial groin lymph nodes as those present in adipose tissue on the anterior surface of the fascia lata in the inguinal lower groin area (Figure 3) In addition, these nodes were larger than 5 mm, as preoperative CT was unable to identify smaller nodes (Figures 4 and 5).

For lymphedema staging, we used the International Society of Lymphology classification. Stage was determined by examining clinical records and photographs obtained at the initial diagnosis (Table 3), and decisions were confirmed in consensus by three physicians. Regarding edema laterality, we defined the side with the higher stage as the dominant edema side, and the side with the lower stage as the inferior edema side.

*Data analysis*

A two-sided Student's t test was used to evaluate differences of in the pelvic lymph nodes resected from the dominant and inferior edema sides. Chi-square analyses (with Fisher's transformation if necessary) were performed to evaluate the correlation of the presence or absence of lymph node metastases of the malignant tumor and the dominant edema side. A P value $<0.05$ was considered to indicate statistical significance. Furthermore, we calculated the correlation coefficient between the total size of the superficial groin lymph nodes and lower limb lymphedema staging to identify a

potential statistical relationship between these factors.

## RESULTS

Patients in our study had the following primary disease diagnoses: cervical cancer, 15 patients; endometrial cancer, 9 patients; and endometrial and ovarian cancer, 1 patient. All patients underwent pelvic lymphadenectomy during primary tumor resection, and a mean of 2.92 (range, 1–7) superficial groin lymph nodes were removed from each of the 50 lower limbs of the patients. The mean size of the 146 resected lymph nodes was 7.23 mm (range, 5–12 mm). Regarding laterality, 16 patients exhibited right leg-dominant edema, whereas 9 patients exhibited left leg-dominant edema (Table 1). The mean numbers of pelvic lymph nodes resected from the dominant and inferior edema sides were 19.4 (range, 7–40) and 15.5 (range, 6–26), respectively. Sixteen and 18 metastatic lymph nodes were observed at the dominant and inferior edema sides, respectively, and the corresponding mean numbers of pelvic metastatic lymph nodes were 0.64 (range, 0–6) and 0.72 (range, 0–7), respectively. Notably, the sides did not differ significantly with respect to the resected pelvic lymph nodes (P = 0.5510) or pelvic lymph node metastasis (P = 0.2890); however, dominant edema side was found to contain fewer superficial groin lymph nodes in 19 of 25 patients (76%). Three (12%) of the remaining 6 patients had equal numbers of lymph nodes in both legs, although the sum total size of the superficial lymph nodes was smaller on the dominant edematous side. In total, 22 patients (88%) had either fewer superficial groin lymph nodes or a smaller total lymph node size on the dominant edema side. Using scatter plots, we determined a correlation coefficient between the sum total size of the superficial groin lymph nodes and the lymphedema stage of -0.2866 (Figure 6). The mean interval from initial resection to lymphedema development was 17 months.

*Representative case*

Seven years prior to our study, a 68-year-old woman had undergone radical hysterectomy with pelvic lymphadenectomy and postoperative radiotherapy for stage 2B cervical cancer; at this time, 2 superficial groin lymph nodes (7 and 8 mm) in the right groin and 5 nodes (7, 8, 8, 9, and 10 mm) in the left groin were detected via preoperative CT, and the case was designated left superficial groin lymph node dominant. She developed right lower limb lymphedema at approximately 4 months postoperatively and experienced cellulitis of the right lower limb twice per year.

Seven years after the initial surgery, during which the patient experienced no recurrence of cervical cancer, she underwent a checkup at our department. At that time, her right

limb exhibited stage 3 lymphedema whereas the left limb was not edematous. Conservative treatment for lymphedema was initiated after diagnosis.

## DISCUSSION

According to previous reports, the incidence of lower limb lymphedema after gynecologic cancer resection ranges from 30% to 40%.[28] In addition, individual cases vary in terms of lymphedema development, elapsed time prior to edema onset, and edematous stage, even among patients who have undergone the same surgical procedure for the same type of cancer. Furthermore, although bilateral pelvic lymphadenectomy is primarily performed for patients undergoing surgical resection for gynecologic cancers, secondary lymphedema tends to develop differently in terms of both incidence and staging. These phenomena, which remain poorly understood, are thought to reflect inherent individual differences in lymphatic system function and even bilateral differences within an individual. We note that for almost all cases in our series, primary tumor resection and lymph node dissection were performed via a lower midline incision. This might have led to the formation of horizontal scars that could interrupt the flow of superficial lymph, thus accounting for some of the observed differences.

### *Limitations of this study*

We further note that various factors might ultimately affect lymphedema. Therefore, we examined the relationship between lymphedema laterality and staging within the same patient, rather than comparing individual cases. Despite this precaution, some problems in this study can be attributed to the retrospective design. For example, different postoperative observation periods were implemented, and we did not perform lymphoscintigraphic evaluations of lymph flow. In addition, we did not evaluate symptoms of edema by measuring changes in the limb circumference/CT volume. Finally, the time to lymphedema onset varied considerably among individuals. In future, a prospective study of patients with gynecologic cancer who have undergone pelvic lymph node dissection, including a multivariable analysis of the above-mentioned risk factors, would be of interest.

The interpretation of our study is also limited by the variability in reported CT findings. In addition, the retrospective nature precluded the detection of small lymph nodes (<5 mm) or 2-dimensional measurements of lymph node size. Although we had wanted to evaluate lymphatic network function,[29] this parameter cannot be measured using a static imaging technique such as CT; accordingly, we instead selected a lymph node analysis. However, CT quantification of superficial groin lymph nodes might also be inaccurate,

especially with regard to the actual function and flow of the nodes. Generally, deep pelvic lymph nodes such as the obturator, internal and external iliac, and para-aortic lymph nodes are resected along with primary gynecologic cancers (e.g., cervical, endometrial, and ovarian cancer). However, it is not possible to define the number of lymph nodes after surgery using the postoperative statuses of the remaining deep lymph nodes/vessels. Accordingly, in this study we indirectly examined the relationship between secondary lymphedema and superficial groin lymph nodes via horizontal plane CT evaluations. Moreover, the extent of pelvic lymphadenectomy in individual cases is affected by both the primary disease and the tumor stage, as well as differences in surgeons' skills. In the present study, we were not able to review the potential influences of these elements because of the limited number of included patients.

*Relationship between superficial groin lymph nodes and secondary lymphedema*

The restoration of lymphatic flow can be classified roughly as a return to either a superficial lymph course, which includes the superficial groin lymph nodes, or a deep lymph course, which includes pelvic lymph nodes. We note that these courses intercommunicate in the process of lymphatic fluid drainage into the thoracic duct.[25] Therefore, as deep lymph course lymphatics are resected during pelvic lymphadenectomy, the remaining superficial groin lymph nodes are expected to play an important role in the postoperative reconstitution of lymph flow. Based on this theory, conservative treatment, including manual lymphatic drainage, is often performed for patients with secondary lymphedema in an attempt to encourage the return of superficial lymphatic flow. Similarly, most surgical procedures intended to improve lymphatic flow, such as lymphaticovenular anastomosis and lymph node transfer, are performed in the skin and subcutaneous fat tissue.[30-31]

Regarding the relationship between the number of lymph nodes and lymphatic function, a larger number of lymph nodes is generally thought to permit better lymphatic flow and function.[32-35] In addition, larger lymph nodes are thought to provide better lymphatic flow and function. However, evaluations of lymph node size should also consider the effect of lymph node metastasis. In the present series, no superficial groin lymph nodes were affected in metastatic cases. In addition, the rate of pelvic lymph node metastasis was very low and was not thought to affect unilateral edema dominance. Although this study focused on the function of superficial groin lymph nodes after pelvic lymphadenectomy, it is clear that lymphedema development involves various complex, interconnected elements. Additional factors that may be related to lymphedema development after gynecologic tumor resection and should therefore be

considered include the type of primary disease, tumor stage, presence of lymph node metastases, and lymphadenectomy. Moreover, previous studies have suggested other risk factors that might affect the development of secondary lymphedema, including age, obesity, and a history of radiation therapy. Furthermore, the present study indicates that a lack of development of superficial groin lymph nodes affects the severity of lymphedema.

In the present study, patients with a large total lymph node number and/or size tended to have present with relatively earlier-stage lymphedema; in other words, superficial lymph nodes are thought to affect the onset of secondary lymphedema. Accordingly, a weak negative correlation was confirmed between the sum total superficial lymph node size and lymphedema stage. However, the lymph node number and size varied considerably among our study subjects because the groin lymph nodes were counted pre-operatively and were thus not influenced by the number of resected pelvic nodes. As a result, an inter-case of the numbers of resected pelvic lymph nodes and superficial groin lymph nodes would lack relevance.

## CONCLUSIONS

In this study, we reviewed the relationship between superficial groin lymph node laterality and secondary lymphedema staging after primary gynecologic tumor resection with pelvic lymphadenectomy. Our results suggest that the presence of superficial groin lymph nodes affects the severity of lymphedema. However, future large-scale prospective studies are needed to determine the risk factors of patients who undergo gynecologic cancer resection and more clearly identify patients at high risk for lymphedema development.

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**Figure legends**

Figure 1.
Lymph node measurement using horizontal plane contrast-enhanced computed tomography, femoral bone neck level.
Bilateral superficial groin lymph nodes are elliptical (yellow circle).
Blood vessels (red arrow) are visible medial to each lymph node.

Figure 2.
Lymph node measurement using horizontal plane contrast-enhanced computed tomography, femoral bone metaphyseal level.
The left superficial groin lymph node has a rounded shape and is 8 mm in size (yellow circle).
Blood vessels (red arrow) are visible medial to each lymph node.

Figure 3.
Schema of the superficial groin lymph nodes.
All lymph nodes within the dotted line are counted.

Figure 4.
Measurement of the sizes of round lymph nodes.
Lymph node sizing was based on square dimensions, as shown.

Figure 5.
Measurement of the sizes of elliptical lymph nodes.
Lymph node sizes were determined using the mean major and mean minor dimensions, as shown.

Figure 6.
Scatter plot analysis of the relationship between the sum total size of the superficial groin lymph nodes and the stage of lymphedema.

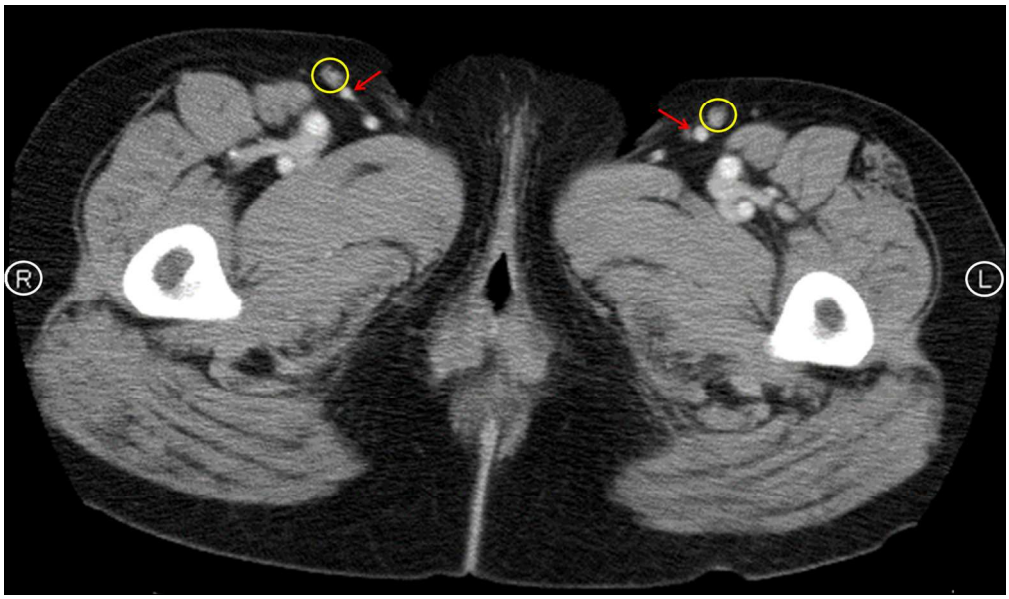


Figure 1.
Lymph node measurement using horizontal plane contrast-enhanced computed tomography, femoral bone neck level.
Bilateral superficial groin lymph nodes are elliptical (yellow circle).
Blood vessels (red arrow) are visible medial to each lymph node.

165x97mm (300 x 300 DPI)

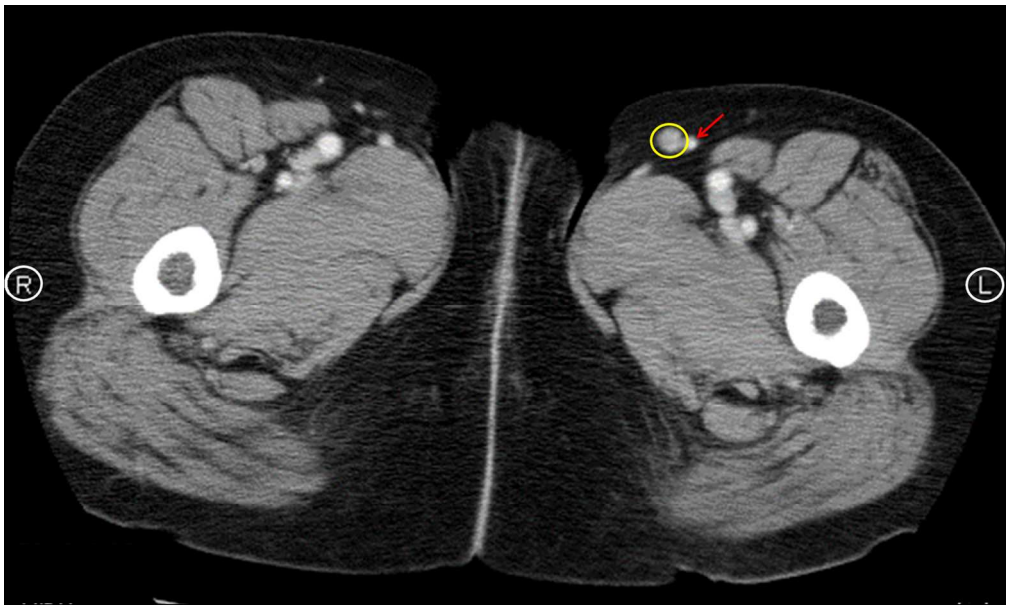


Figure 2.
Lymph node measurement using horizontal plane contrast-enhanced computed tomography, femoral bone metaphyseal level.
The left superficial groin lymph node has a rounded shape and is 8 mm in size (yellow circle).
Blood vessels (red arrow) are visible medial to each lymph node.

167x100mm (300 x 300 DPI)

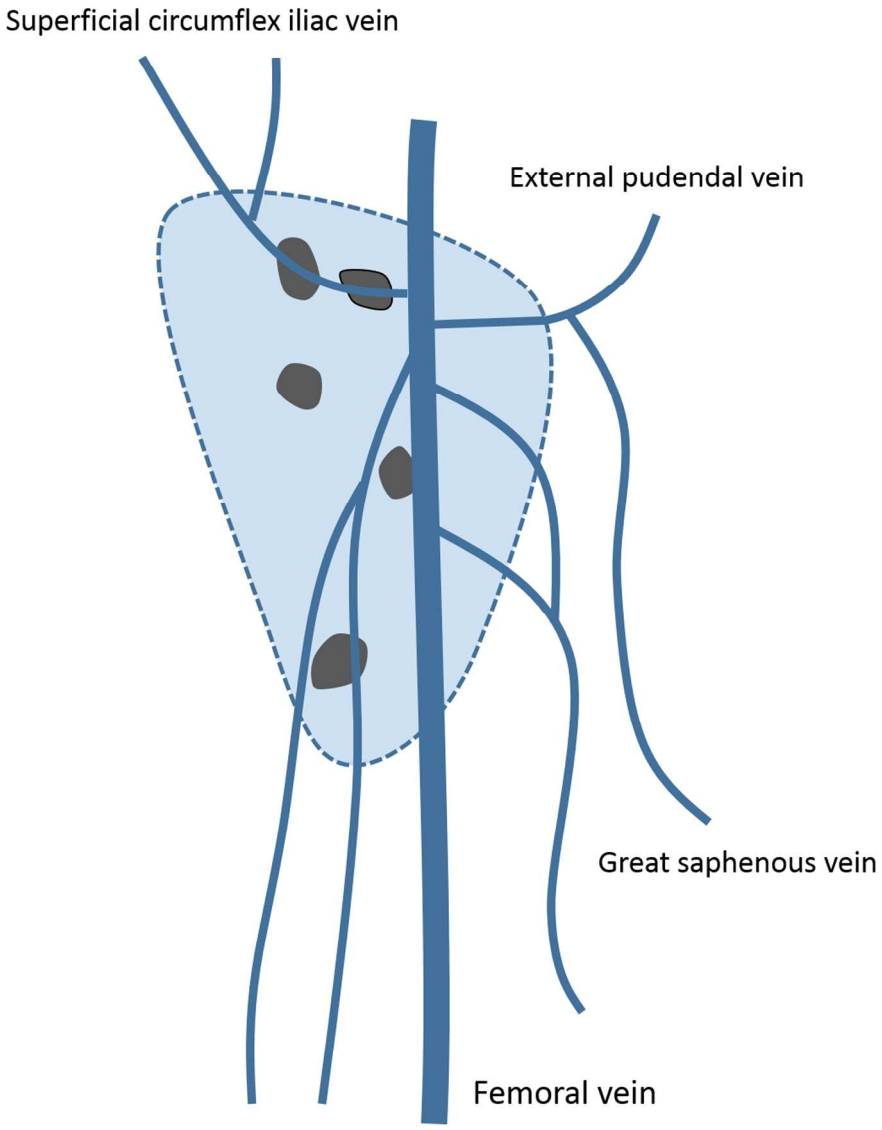


Figure 3.
Schema of the superficial groin lymph nodes.
All lymph nodes within the dotted line are counted.

304x376mm (300 x 300 DPI)

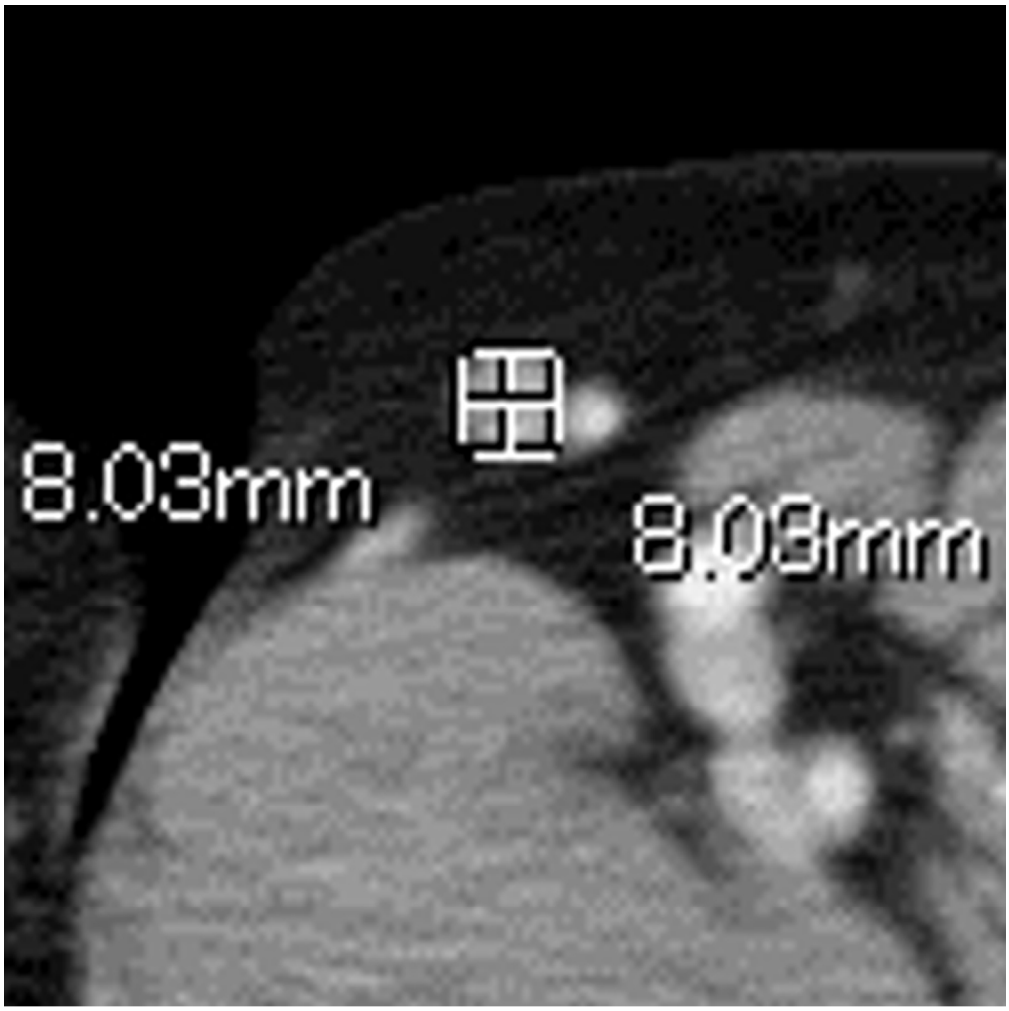


Figure 4.
Measurement of the sizes of round lymph nodes.
Lymph node sizing was based on square dimensions, as shown.

135x135mm (300 x 300 DPI)

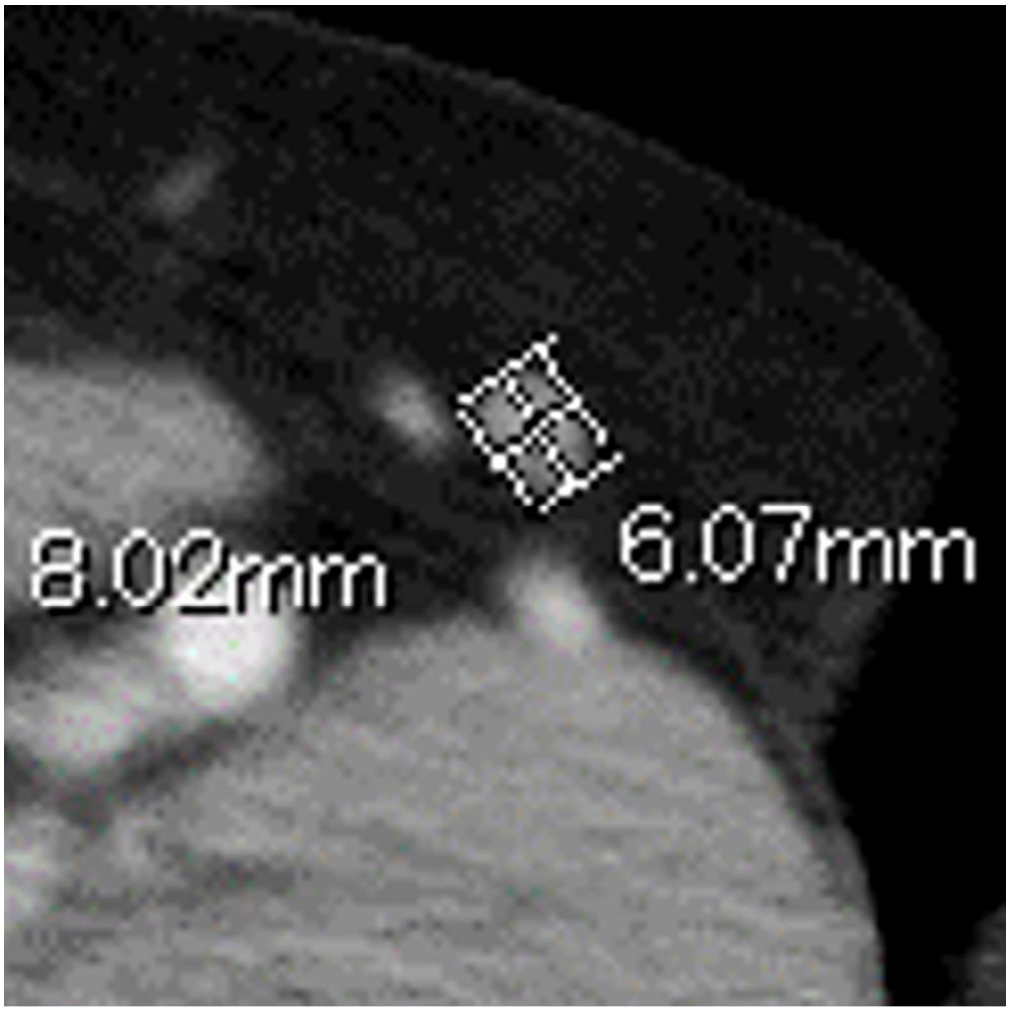


Figure 5.
Measurement of the sizes of elliptical lymph nodes.
Lymph node sizes were determined using the mean major and mean minor dimensions, as shown.

135x135mm (300 x 300 DPI)

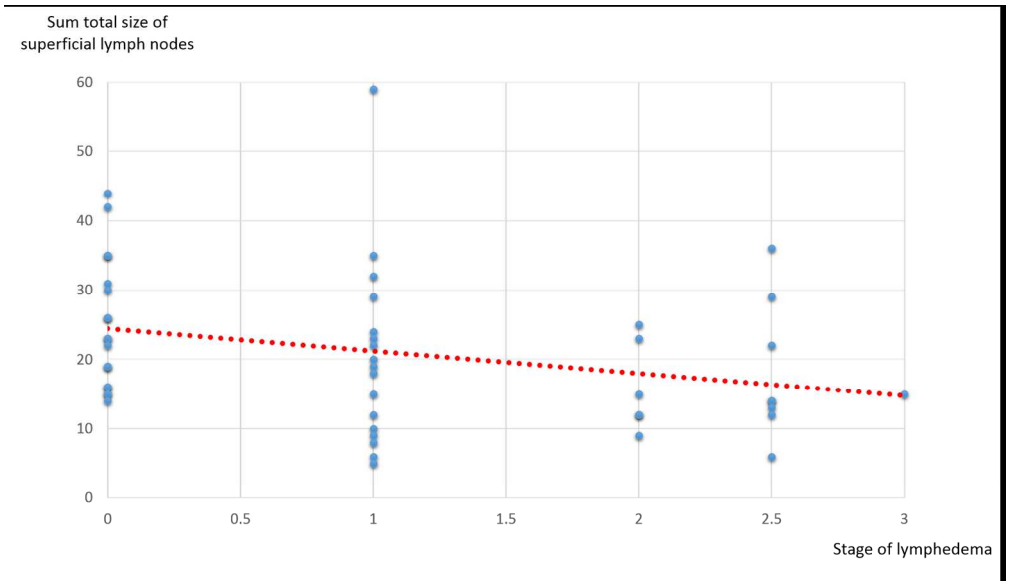


Figure 6.
Scatter plot analysis of the relationship between the sum total size of the superficial groin lymph nodes and the stage of lymphedema.

489x280mm (300 x 300 DPI)

Table.1 Patient Treatment History

| No. | Age | Primary Disease | Ca. Stage | LE Stage | | CT | RT | Follow up time |
|---|---|---|---|---|---|---|---|---|
| | | | | Right | Left | | | |
| 1 | 68 | Cervical ca. | 2B | 3 | 0 | − | + | 5M |
| 2 | 31 | Cervical ca. | 2B | 2L | 1 | + | + | 1Y |
| 3 | 33 | Cervical ca. | 1B | 2L | 1 | − | − | 5Y |
| 4 | 59 | Cervical ca. | 2B | 2L | 1 | + | + | 7M |
| 5 | 65 | Cervical ca. | 1B | 2L | 0 | + | + | 6M |
| 6 | 51 | Endometrial ca. ＋Ovarian ca | 1C ＋1B | 2L | 0 | + | − | 2M |
| 7 | 67 | Endometrial ca. | 1B | 2 | 1 | + | + | 1Y 6M |
| 8 | 63 | Endometrial ca. | 1B | 2 | 0 | + | − | 6M |
| 9 | 69 | Endometrial ca. | 2B | 2 | 0 | + | + | 3M |
| 10 | 60 | Endometrial ca. | 1B | 1 | 0 | + | − | 7Y 8M |
| 11 | 74 | Endometrial ca. | 1C | 1 | 0 | + | − | 6Y 6M |
| 12 | 71 | Endometrial ca. | 1C | 1 | 0 | − | − | 3M |
| 13 | 50 | Cervical ca. | 1B | 1 | 0 | + | + | 1M |
| 14 | 40 | Cervical ca. | 2B | 1 | 0 | − | + | 1M |
| 15 | 32 | Endometrial ca. | 3C | 1 | 0 | − | − | 1M |
| 16 | 42 | Cervical ca. | 1B | 1 | 0 | + | + | 3M |
| 17 | 49 | Cervical ca. | 1B | 0 | 1 | − | + | 5Y |
| 18 | 76 | Endometrial ca. | 1C | 0 | 1 | + | − | 1M |
| 19 | 39 | Cervical ca. | 2B | 0 | 1 | + | + | 1M |
| 20 | 65 | Endometrial ca. | 1B | 0 | 2 | + | + | 6M |
| 21 | 45 | Cervical ca. | 1B | 0 | 2 | + | − | 1M |
| 22 | 61 | Cervical ca. | 1B | 1 | 2 | + | + | 6M |
| 23 | 67 | Cervical ca. | 1B | 0 | 2L | + | − | 1M |
| 24 | 57 | Cervical ca. | 1B | 1 | 2L | − | + | 1M |
| 25 | 37 | Cervical ca. | 1B | 1 | 2L | − | + | 8M |

ca.: carcinoma, LE: lymphedema, 2L: late stage 2, CT: chemotherapy, RT: radiation therapy, Follow up time: follow-up time from initial resection to lymphedema development, Y: year, M: month

Table 2

Relationship between lymphedema stages and each lymph nodes

| No. | Age | Primary Disease | LE Stage | | PLN and positive rate | | Number and Size (mm) of superficial groin lymph nodes | |
|---|---|---|---|---|---|---|---|---|
| | | | Right | Left | Right | Left | Right | Left |
| **Right Side Edema Dominant Cases** | | | | | | | | |
| 1 | 68 | Cervical ca. | 3 | 0 | 1/23 | 0/17 | **2**: 7, 8 | **5**: 7, 8, 8,9, 10 |
| 2 | 31 | Cervical ca. | 2L | 1 | 1/25 | 0/20 | **4**: 7, 9, 9, 11 | **7**: 6, 6, 7, 9, 9, 10, 12 |
| 3 | 33 | Cervical ca. | 2L | 1 | 0/17 | 0/14 | **1**: 6 | **1**: 8 |
| 4 | 59 | Cervical ca. | 2L | 1 | 0/23 | 0/11 | **3**: 6, 7, 9 | **4**: 8, 8, 9, 10 |
| 5 | 65 | Cervical ca. | 2L | 0 | 1/13 | 2/17 | **2**: 6, 7 | **2**: 7, 7 |
| 6 | 51 | Endometrial ca. ＋Ovarian ca | 2L | 0 | 0/46 | 0/21 | **2**: 6, 8 | **3**: 6, 8, 9 |
| 7 | 67 | Endometrial ca. | 2 | 1 | 0/14 | 0/10 | **1**: 12 | **3**: 9, 9, 11 |
| 8 | 63 | Endometrial ca. | 2 | 0 | 0/18 | 0/13 | **4**: 5, 5, 6, 9 | **5**: 6, 6, 6, 8, 9 |
| 9 | 69 | Endometrial ca. | 2 | 0 | 1/26 | 0/15 | **2**: 6, 9 | **2**: 6, 9 |
| 10 | 60 | Endometrial ca. | 1 | 0 | 0/11 | 0/31 | **2**: 8, 10 | **3**: 7, 9, 10 |
| 11 | 74 | Endometrial ca. | 1 | 0 | 0/29 | 0/15 | **1**: 9 | **3**: 6, 8, 9 |
| 12 | 71 | Endometrial ca. | 1 | 0 | 0/14 | 0/9 | **2**: 6, 6 | **5**: 6, 7, 7, 7, 8 |
| 13 | 50 | Cervical ca. | 1 | 0 | 0/23 | 0/24 | **1**: 6 | **2**: 7, 8 |
| 14 | 40 | Cervical ca. | 1 | 0 | 6/24 | 7/26 | **3**: 6, 8, 9 | **4**: 6, 8, 8, 9 |
| 15 | 32 | Endometrial ca. | 1 | 0 | 0/40 | 2/23 | **2**: 5, 5 | **2**: 7, 9 |
| 16 | 42 | Cervical ca. | 1 | 0 | 0/17 | 2/16 | **2**: 6, 9 | **4**: 5, 6, 6, 9 |
| **Left Side Edema Dominant Cases** | | | | | | | | |
| 17 | 49 | Cervical ca. | 0 | 1 | 0/9 | 0/23 | **3**: 6, 6, 7 | **3**: 6, 6, 7 |
| 18 | 76 | Endometrial ca. | 0 | 1 | 0/7 | 0/7 | **2**: 8, 11 | **1**: 5 |
| 19 | 39 | Cervical ca. | 0 | 1 | 4/15 | 2/21 | **3**: 5, 7, 9 | **4**: 7, 7, 8, 10 |
| 20 | 65 | Endometrial ca. | 0 | 2 | 0/11 | 0/14 | **2**: 7, 9 | **1**: 9 |
| 21 | 45 | Cervical ca. | 0 | 2 | 1/15 | 3/29 | **4**: 6, 7, 8, 9 | **3**: 7, 7, 9 |
| 22 | 61 | Cervical ca. | 1 | 2 | 0/6 | 1/7 | **2**: 10, 12 | **1**: 12 |
| 23 | 67 | Cervical ca. | 0 | 2L | 0/13 | 0/11 | **5**: 7, 8, 9, 10, 10 | **4**: 5, 6, 8, 10 |
| 24 | 57 | Cervical ca. | 1 | 2L | 0/14 | 0/14 | **2**: 9, 11 | **1**: 12 |
| 25 | 37 | Cervical ca. | 1 | 2L | 0/10 | 0/20 | **4**: 5, 5, 7, 7 | **2**: 5, 9 |

LE: lymphedema, PLN and positive rate : pelvic lymph nodes resected at surgery and

metastatic positive rate

Table.3 International Society of Lymphology (ISL) lymphedema staging

| | |
|---|---|
| **ISL stage 0** | A subclinical state where swelling is not evident despite impaired lymph transport. This stage may exist for months or years before edema becomes evident. |
| **ISL stage I** | This represents early onset of the condition where there is accumulation of tissue fluid that subsides with limb elevation. The edema may be pitting at this stage. |
| **ISL stage II** | Limb elevation alone rarely reduces swelling and pitting is manifest. |
| **ISL late stage II** | There may or may not be pitting as tissue fibrosis is more evident. |
| **ISL stage III** | The tissue is hard (fibrotic), and pitting is absent. Skin changes such as thickening, hyperpigmentation, increased skin folds, fat deposits, and warty overgrowths develop. |