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Periclavicular Lymph Node Activation Maintains the Lymphatic Circulation of Upper Extremity Following Breast Cancer Surgery with Axillary Lymph Node Dissection

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Abstract

Backgrounds: Axillary lymph node dissection (ALND) can cause breast cancer-related lymphedema (BCRL). However, ALND does not always produce lymphedema to the breast cancer survivors. Therefore, we aimed to investigate the correlation between the finding of lymphoscintigraphy and lymphedema in patients undergoing breast cancer surgery with ALND.

Methods and Results: Patients with BCRL ($n = 73$, mean age: 53.92 ± 11.13 years) after full ALND (levels I, II, and III) were retrospectively included in this study. All patients underwent lymphoscintigraphy and according to the findings of the imaging, patients were divided into three groups: negative group, periclavicular lymph nodes (P-LN) activation, and axillary lymph nodes (A-LN) activation. According to the extent of radiation therapy, groups were classified as the following: no radiation group (None), breast radiation group (BI), and breast irradiation in addition to P-LN (BI+PC). The percentage difference in the upper extremities was used as the marker of severity of lymphedema. The subjects in the negative group, P-LN, and A-LN were 34 (46.6%), 33 (45.2%), and 6 (8.2%) patients, respectively. The findings of lymphangiography showed statistically significant relationship with the severity of lymphedema. The extent of radiation therapy did not have statistically significant relationship. Despite ALND, 53.4% patients had active L/N capable of removing the upper limb lymphatic fluids and 45.2% patients showed activation of collateral formation of lymphatic circulation after ALND.

Conclusion: The collateral lymphatic formation was provoked after breast cancer operation with ALND, which decreased the severity of lymphedema in breast cancer survivors.

Keywords: breast cancer survivors, axillary lymph node, axillary lymph node dissection

Introduction

Axillary lymph node dissection (ALND) and no axillary dissection in patients with breast cancer with sentinel-node micrometastases showed similar survival rate.[1] However, ALND still has been frequently conducted as one of the essential surgical managements to increase the overall survival of a patient, as well as to diagnose the staging of breast cancer.[2] ALND produces several complications in breast cancer survivors.[3] Breast cancer-related lymphedema (BCRL) is not only one of the common complications of ALND, but also one of the crucial issues related to a patients' quality of life.[4] As BCRL requires long-term self-care management and medical treatment after breast cancer surgery, BCRL decreases the individual's activity level and increases mental burden.[5] Therefore, evaluation of the prognosis of BCRL is an important factor in establishing an effective treatment strategy.

ALND increases the incidence of BCRL.[6] Full ALND (levels I–III) has a higher incidence of BCRL than does partial ALND (levels I and II).[7] However, some of the patients undergoing breast cancer operation with full ALND did not show lymphedema or relatively light symptom. It is still unclear why there is a difference in the severity of lymphedema within patients with full range of ALND. Surgical oncologists aim to maximize the local control for node-

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positive patients. Therefore, not only the incidence but also the severity of BCRL, according to the range of ALND, is essential information for cancer survivors and caregivers.

Over the past few decades, lymphoscintigraphy has proven reliable and reproducible in the diagnosis of different types of lymphedema[8] and is now commonly used. The lymphatic system has complex connections between the deep and superficial collecting systems. ALND causes changes in the patterns of the connecting system among the lymphatic circulation.[9,10] Based on this notion, lymphoscintigraphy in patients with BCRL shows these changes in images, for example, dermal backflow and changes in the activity on the axillary lymph nodes (A-LNs). However, there is currently no research concerning the activity of collateral lymphatic formation on lymphangiography after full range of ALND.

Therefore, we aimed to determine the changes in lymphoscintigraphy after ALND, and whether the changes after ALND are associated with the severity of BCRL.

Methods

Subjects

This study was conducted retrospectively, and data collected were based on an electronic medical record database. Ethic approval was obtained from the institutional review board of the Yeungnam University Hospital (YUMC 2020-03-043). We recruited breast cancer survivors who satisfied our inclusion and exclusion criteria. All the subjects were transferred to the rehabilitation department for subjective and objective symptoms of lymphedema after surgery between March 2014 and January 2020. The inclusion criteria were as follows: (1) had a unilateral breast cancer diagnosis and underwent surgery, (2) had a complete ALND (levels I, II, and II), (3) underwent lymphoscintigraphy, and (4) received complete decongestive therapy treatment. The exclusion criteria were as follows: (1) had a history of bilateral breast cancer surgery, (2) had a history of cervical lymph nodes dissection, and (3) underwent upper extremity (UE) amputation.

Information regarding radiotherapy was collected. The patients were classified based on their radiation status as follows: nonradiation group (None); patients without a history of radiotherapy; breast radiation group (BI), patients who received whole breast irradiation excluding the periclavicular area; and periclavicular irradiation group (BI+PC), patients who received additional breast irradiation on the supraclavicular lymph nodes.

Circumference measurements

The circumference of the UEs was measured at the midpoint of the upper arm between the lateral epicondyle of the humerus and the acromion of the shoulder. The midpoint of the forearm circumference was measured at the point between the ulnar styloid process and the lateral epicondyle of the humerus.[11,12] We calculated the percentage difference in the forearm and arm in the UEs as the lymphedema severity: percentage difference in UEs = ([affected UE − unaffected UE]/[(affected UE + unaffected UE)/2]) × 100.

Lymphoscintigraphy

A total 4 mCi of millipore-filtered Tc-Phytate was suspended in 0.40 mL of saline and divided into four syringes. Each of these was injected into the interdigital web spaces between the first and second digits on both of the patient's UEs, creating a wheal. Both hands were massaged for 2 minutes, immediately after the injections. A high-resolution collimator was used for the early image and the camera speed was set at 8 cm/min, with images of at least 300,000 counts being acquired. After taking the early image, the patient waited for 1-hour and 2-hour delay shots.

We classified lymphoscintigraphy findings into three groups on the 2-hour delay shot (Fig. 1). One nuclear medicine physician, who was blinded to the clinical information, interpreted the uptake patterns of the lymphoscintigraphy images. Periclavicular lymph nodes (P-LNs) group had a radioactivity above the axillar lesion and around the periclavicular area. A-LN groups had a radioactivity within axillary area only. The negative group did not show any radioactivity in the lymphoscintigraphy scan around the shoulder and neck.

Statistical analysis

Data input and statistical analyses were performed using SPSS ver. 23.0 (SPSS, Inc., Chicago, IL). The severity of lymphedema, according to the radiotherapy and findings of lymphoscintigraphy, was analyzed by Kruskal–Wallis test and Mann–Whitney *U*-test. The relationships between radiation therapy and finding of lymphoscintigraphy were analyzed by chi-squared test. A p-value of <0.05 was considered to be statistically significant.

Results

A total of 73 patients (mean age: 53.92 ± 11.13) were included in this study (Table 1). Thirty-nine (53.54%) patients showed positive activity of lymphoscintigraphy despite ALND. The radioactivity on lymphoscintigraphy significantly affected the severity of lymphedema in the forearm and arm (Table 2). The positive activity of lymph nodes on lymphoscintigraphy showed an overall better outcome than negative activity. The type of radiotherapy did not show statistically significant influence on severity of lymphedema of the affected forearm and arm. However, BI+PC groups showed statistically significant severe lymphedema than BI and None groups. Therefore, radiation on the periclavicular area, not radiation therapy itself, had an effect on the severity of lymphedema after ALND. The pattern of lymphoscintigraphy and radiation therapy did not have a statistically significant relationship in frequency.

Discussion

A-LNs recruit lymph from the UEs. Patients who undergo full ALND have a higher extent of ALND than those who undergo partial ALND surgery.[7,13] A dissection of more lymph nodes is thought to have a negative impact on lymphedema.[14] However, the results of this study showed that activation of collateral lymphatic formation compensated the function of removed A-LNs. The activity of P-LNs on lymphangiography showed a statistically significant correlation with the severity of lymphedema. Therefore, after dissecting the A-LNs, plasticity of lymphatic system provoked the activation of collateral lymphatic formation.

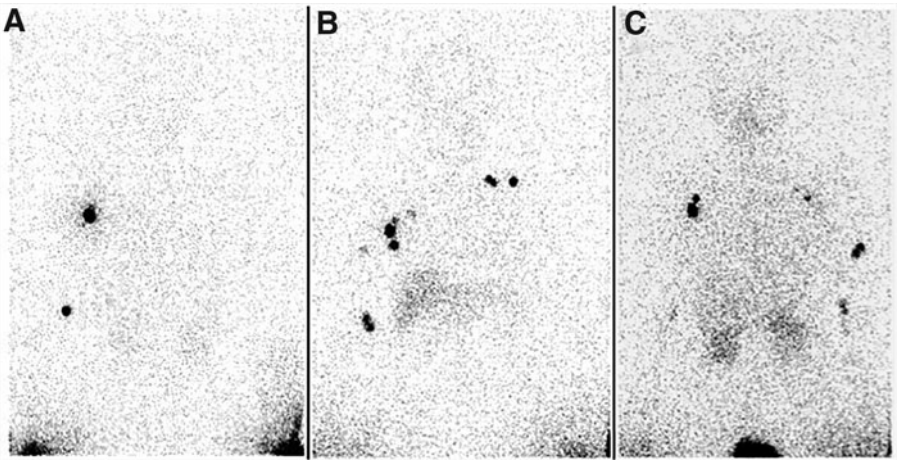

FIG. 1. The findings of lymphoscintigraphy imaging. No radioactivity can be observed around the A-LNs on lymphoscintigraphy. **(A)** On *left side*, lymphoscintigraphy shows positive periclavicular lymph nodes radioactivity **(B)** above the axillary lesion and A-LNs radioactivity **(C)**. The patients underwent surgery on the *left side* for breast cancer with full range ALND. A-LNs, axillary lymph nodes; ALND: axillary lymph nodes dissection.

The connections between the lymph nodes in the axillary and periclavicular area are complex. A-LNs are deep collectors of lymph from the breast, chest wall, and UEs.[8] The efferent lymph vessels of the central A-LNs are connected to the apical lymph nodes (level III A-LNs). Then, the apical lymph nodes transfer lymphatics to the circulating vessel system. Therefore, dissecting level III A-LNs can cause dysfunction of the deep lymphatic collectors, which leads to lymphedema.

However, 55.9% patients who underwent full ALND showed positive radioactivity around shoulder on lymphoscintigraphy. Moreover, 33 patients (45.2%) showed P-LNs activation on lymphoscintigraphy. We speculate this result comes from the formation of a new lymphatic connection between the deep and superficial lymph vessels or activation of the latent lymphatic system. Patients without lymphedema after breast cancer surgery showed communication between the superficial and deep lymphatic system on the UE.[15] Moreover, occasionally, patients may show collateral lymphatic formation connecting the efferent lymph vessels to the supraclavicular lymph nodes.[16] The supraclavicular lymph nodes are subcutaneous lymph collectors receiving lymphatic from the dorsolateral upper arm and deltoid territories. In the presence of a collateral lymphatic formation or activated latent collateral lymphatic connection, lymph can skip the A-LNs to prevent lymphedema after full ALND.

Inflammation provoked the change of junction type in lymphatics. Vascular endothelial growth factor can provoke the proliferation of lymphatic vessels.[17] Therefore, lymphatic vessels are not static but dynamic in structure. We speculate that provoked lymphatic vessel after operation activates the collateral lymphatic formation.

Table 1. Demographic Data

	Total
Age	53.92 ± 11.13
Lesion side (right left)	34:39
Lymphoscintigraphy negative:	34 (46.6%):
P-LN: A-LN	33 (45.2%):6 (8.2%)
Radiation therapy None:	9 (12.3%):
BI: BI+PC	11 (15.1%):53 (72.6%)

Negative: no radioactivity on the lymphoscintigraphy, P-LN: the group showed radioactivity above the axillary lesion and around the periclavicular area, A-LN: the group showed radioactivity within the axillary area only, None: no history of radiotherapy, BI: breast irradiation group, BI+PC: breast irradiation with additional P-LNs area.

A-LN, axillary lymph nodes; P-LN, periclavicular lymph nodes.

Table 2. The Severity of Lymphedema According to the Radiotherapy and Findings of Lymphoscintigraphy

	Percentage difference	
	Upper arm	*Forearm*
Lymphoscintigraphy		
Negative ($n=34$)	9.18 ± 1.10	11.00 ± 1.36
P-LN ($n=33$)	5.19 ± 0.93	6.68 ± 1.05
A-LN ($n=6$)	2.33 ± 0.83	1.28 ± 0.47
p	0.00*	0.00*
Radiation therapy among three patterns		
None	3.63 ± 1.44	5.62 ± 1.98
BI	4.70 ± 1.18	4.21 ± 0.74
BI+PC	7.79 ± 0.90	9.53 ± 1.08
p	0.06	0.06
Radiation therapy between two groups		
BI+PC	7.79 ± 0.90	9.53 ± 1.08
BI and None	4.22 ± 0.90	4.85 ± 0.96
p	0.02*	0.03*

*$p < 0.05$.

Negative: no radioactivity on the lymphoscintigraphy, P-LN: The group showed radioactivity above the axillary lesion and around the periclavicular area, A-LN: the group showed radioactivity within the axillary area only, None: no history of radiotherapy, BI: breast irradiation group, BI+PC: breast irradiation with additional P-LNs area.

Radiation causes fibrosis of the lymphatic vasculature, which decreases the function of the lymphatic system.[18] Therefore, it is already understood that radiation therapy is a risk factor for lymphedema.[19] Moreover, radiation therapy itself also increases the severity of lymphedema.[20] The extent of radiation therapy has been shown to increase the incidence of lymphedema.[21] In this study, the extent of radiation therapy did not have a relationship with the severity of BCRL. However, specifically, breast with clavicular lymph node irradiation therapy increased the severity of BCRL. The BI+PC group showed more severe lymphedema than the None and BI groups. Based on activated collateral lymphatic formation maintaining the lymphatic drainage of the UE after ALND, P-LN irradiation therapy could affect the exacerbation of lymphedema.

This study has some limitations. First is the absence of quantitative data for the radioactivity seen on lymphoscintigraphy. The quantitative activity of the lymph nodes could affect the severity of lymphedema. Another limitation is that patient compliance with rehabilitation therapy was not taken into consideration. Depending on the individual situation and personality, treatment compliance can vary, which may affect the outcome of lymphedema treatment. Moreover, lymphoscintigraphy could detect the radioactivity of lymph nodes for up to 2 hours. Thus, if lymphoscintigraphy was performed after >2 hours, functional lymph nodes may still be present. However, delayed radioactivity of >2 hours means that the delayed-activated lymph nodes did not functionally and effectively accomplish lymph drainage in the UE.

Conclusion

Collateral lymphatic formation can be activated after ALND in breast cancer survivors, this promotes lymphatic drainage in the UE. The presence of collateral lymphatic formation is a major factor that influences the severity of lymphedema after breast cancer surgery with ALND.

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Author Disclosure Statement

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