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Lymphedema after regional nodal irradiation for breast cancer: a retrospective cohort study

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Purpose: We aimed to analyze the occurrence of lymphedema as a side effect in patients who underwent regional nodal irradiation (RNI) following surgery for breast cancer.
Methods: This retrospective study was conducted on patients with breast cancer who underwent surgery from July 2014 to October 2020 at Inje University Busan Paik Hospital. The analysis included 113 cT1-3N1-3M0 breast cancer patients who underwent RNI as part of radiotherapy (RT). Mostly, surgeries were performed using breast-conserving surgery (n = 99, 87.6%), except for 14 patients with modified radical mastectomy. The total RT dose for RNI was 45–60 Gy, and the fraction size was 1.8–2.0 Gy. Most patients underwent chemotherapy (n = 98, 86.7%), including taxanes (n = 92, 81.4%).
Results: The median follow-up was 61.1 months (range, 5.0–110.5 months). Lymphedema occurred in 54 patients (47.8%) after surgery. Twenty of them (17.7%) developed a new onset of lymphedema after RT, while 34 (30.1%) detected lymphedema before the completion of RT. Over the follow-up, 16 patients (14.2%) experienced recurrence. High radiation dose (>50.4 Gy) for RNI (P = 0.003) and taxane use (P = 0.038) were related to lymphedema occurrence after RT. Moreover, lymphedema occurrence after RT was also related to recurrence after surgical resection (P = 0.026). Breast-conserving surgery was related to early-onset lymphedema before the completion of RT (P = 0.047). Furthermore, the degree of lymph node dissection (≤4) was related to the overall occurrence of lymphedema (P = 0.045).
Conclusion: Considering a reduction in RNI dose may be beneficial in mitigating the incidence of lymphedema after RT in patients with breast cancer.
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Key Words: Breast neoplasms, Lymphedema, Radiotherapy, Regional nodal irradiation

INTRODUCTION

Administration of regional nodal irradiation (RNI) to breast cancer patients is known to increase the risk of lymphedema development compared to chest wall irradiation alone [1]. When there is metastasis to regional lymph nodes (LNs) in breast cancer, RNI including the axillary LN and supraclavicular LN is generally performed in addition to standard breast radiotherapy (RT) in the majority of breast cancer cases. A notable side effect is the occurrence of early-onset lymphedema immediately after breast surgery with axillary LN dissection (LND) before RT [2]. However, late-onset lymphedema after RT also occurs, affecting up to 40% of cases following breast cancer surgery [2,3].

The risk of developing lymphedema may be related to factors such as the method of lymphadenectomy (the large number of dissected axillary LNs), a shorter interval between

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surgery and RT (<1 month), high irradiation dose, older age at surgery, and a high body mass index. Recently, there has been growing interest in the relationship between taxane use in chemotherapy and the occurrence of lymphedema [4].

From a treatment perspective, in addition to prescribed pneumatic compression, compression garments (stocking), or physical therapy from the department of rehabilitation, there has been widespread use of oral drug medications such as the *Vitis vinifera* extract tablet, Entelon (150 mg twice a day, Hanlim Pharm Co., Ltd.) in Korea [5]. Entelon is known to be an effective drug for improving symptoms related to venous lymphatic dysfunction. Consequently, there is a need to analyze the current patterns in lymphedema treatment.

In this study, we aimed to analyze the occurrence and treatment of lymphedema in breast cancer by examining breast cancer patients who received RNI.

METHODS

Patient

This retrospective study was conducted on breast cancer patients who underwent surgery and regional LND for cT1-3N1-3M0 breast cancer from July 2014 to October 2020 at Inje University Busan Paik Hospital. All 113 patients underwent RNI during postoperative RT. Those with bilateral breast cancer and male subjects were excluded from the study. Additionally, patients with a prior diagnosis of other cancers were excluded from the analysis. Approval for this study protocol was obtained from the Institutional Review Board of Inje University Busan Paik Hospital (No. 2023-04-041). Electronic medical records (EMR) were reviewed to evaluate the occurrence of lymphedema and its related factors.

Treatment

All patients underwent computed tomography simulation with an immobilization device (Wing board) for RT planning. Following simulation, RT was delivered using a linear accelerator and a 3-dimensional conformal planning technique. The RNI field encompassed the axillary and supraclavicular LN areas. The total RT dose for RNI ranged from 45 to 60 Gy with a fraction size of 1.8–2.0 Gy. The whole breast irradiation dose equaled the RNI dose, and the majority of patients (n = 93, 81.4%) received an additional tumor bed boost (6–16 Gy with 1.8–2.0 Gy per fraction size), typically using an electron beam. Clinical factors related to lymphedema occurrence were retrospectively evaluated, and RT was conducted under free breathing conditions.

Chemotherapy was performed in a number of patients, with anthracycline and/or taxane chemotherapy commonly used for systemic treatment. Those with locally advanced-stage breast cancer received neoadjuvant chemotherapy to reduce the degree of breast resection. Notably, the use of taxanes was specifically examined to assess its effect on lymphedema.

Lymphedema development

Lymphedema was defined based on the physician's diagnosis, by primarily assessing ipsilateral arm swelling, with a specific criterion of limb circumference differences of 2 cm indicating its presence. The timing of lymphedema occurrence was defined from the operation date to its occurrence, distinguishing between pre-RT lymphedema (occurring before the end of RT) and post-RT lymphedema (occurring after the completion of RT).

Statistical methods

For statistical evaluation, IBM SPSS Statistics ver. 25 (IBM Corp.) and MedCalc software (MedCalc Software Ltd.) were used. The chi-square test was used for assessing factors related to lymphedema occurrence using univariate analysis. A P-value of <0.05 in a 2-tailed test was considered statistically significant. The Kaplan-Meier test was used to describe the timing of lymphedema occurrence, and the log-rank test was used to compare the effect of RNI dose on lymphedema occurrence. For the multivariate analysis, multiple regression was used for evaluation.

Table 1. Patient characteristics

Characteristic	Data
No. of patients	113
Age (yr)	55 (35–78)
≤60	77 (68.1)
>60	36 (31.9)
Disease side	
Right	39 (34.5)
Left	74 (65.5)
Body mass index (kg/m^2)	
≤25	75 (66.4)
>25	38 (33.6)
Diabetes mellitus	
Yes	18 (15.9)
No	95 (84.1)
Hypertension	
Yes	21 (18.6)
No	92 (81.4)
Type of surgery	
BCS	99 (87.6)
MRM	14 (12.4)
No. of LND	
≤4	28 (24.8)
>4	85 (75.2)
Neoadjuvant chemotherapy	
Yes	44 (38.9)
No	69 (61.1)

Table 1. Continued

Characteristic	Data
Adjuvant chemotherapy	
Yes	67 (59.3)
No	46 (40.7)
Taxane use	
Yes	92 (81.4)
No	21 (18.6)
RNI dose (Gy)	
≤50.4	97 (85.8)
>50.4	16 (14.2)
pT stage	
T0–Tis	17 (15.0)
T1	59 (52.2)
T2	34 (30.1)
T3	3 (2.7)
pN stage	
N0	25 (22.1)
N1	75 (66.4)
N2	10 (8.8)
N3	3 (2.7)
Tumor grade	
low	10 (8.8)
Intermediate	46 (40.7)
high	57 (50.4)
Perineural invasion	
Yes	11 (9.7)
No	102 (90.3)
Lymphedema	
Yes	54 (47.8)
Pre-RT	34
Post-RT	20
No	59 (52.2)

Values are presented as number only, median (range), or number (%).
BCS, breast-conserving surgery; MRM, modified radical resection; LND, lymph node dissection; RNI, regional nodal irradiation; RT, radiation therapy.

RESULTS

Patients and treatment

Table 1 presents the patients' characteristics. The median age of the patients was 55 years (range, 35–78 years). The majority of patients had breast cancer in the left breast (n = 74, 65.5%). Approximately 1 in 3 of the patients were classified as obese (body mass index >25 kg/m^2; n = 38, 33.6%). Regarding metabolic syndrome, 18 patients (15.9%) were diagnosed with diabetes mellitus, and 21 patients (18.6%) were diagnosed with hypertension before treatment. Mostly, surgeries were performed using breast-conserving surgery (BCS; n= 99, 87.6%). The remaining 14 patients (12.4%) underwent modified radical resection (MRM. Approximately a quarter of the patients underwent 1–4 axillary LND (n = 28, 24.8%), while the remaining 85 patients underwent 5–34 axillary LND (75.2%). Forty-four patients (38.9%) underwent neoadjuvant chemotherapy before surgery, and adjuvant chemotherapy was performed in 67 patients (59.3%); 12 patients underwent both neoadjuvant chemotherapy and adjuvant chemotherapy.

Table 2. Pattern of failure and lymphedema occurrence after RT

Variable	Post-RT lymphedema		P-value
	No	Yes	
Locoregional recurrence			
Yes	2	2	0.086
No	91	18	
Distant metastasis			
Yes	8	4	0.135
No	85	16	
Total	93	20	

RT, radiotherapy.

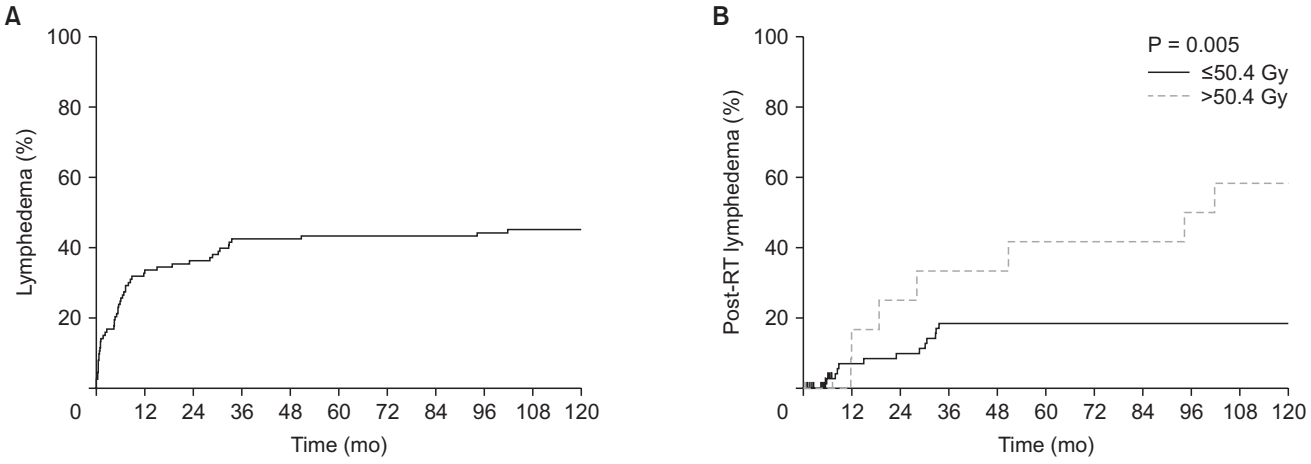

Fig. 1. (A) Overall lymphedema occurrence after breast cancer surgery. (B) Comparison of lymphedema occurrence according to regional nodal irradiation dose after radiotherapy (RT).

A significant number of patients (n = 92, 81.4%) received chemotherapy agents including taxane.

Concerning adjuvant RT, 16 patients (14.2%) received doses exceeding 50.4 Gy during RNI. At the time of cancer pathologic staging, the majority of patients were within T0–2 stage (97.3%), and there were 25 N0 patients (22.1%). This study included 57 high tumor grade patients (50.4%). Eleven patients with perineural invasion (9.7%) were included. Postoperative lymphedema was reported in 54 patients (47.8%), approximately half of the total evaluated patients. Among these, 34 patients were confirmed to have lymphedema before the end of RT (pre-RT lymphedema, 30.1%), while lymphedema was identified in 20 patients after the completion of RT (post-RT lymphedema, 17.7%).

Recurrence

The median follow-up was 61.1 months (range, 5.0–110.5 months). Over the follow-up periods, 16 patients (14.2%) experienced recurrence. Specifically, 4 patients (3.5%) exhibited locoregional recurrence (ipsilateral breast and/or regional LNs relapse), and 12 patients (10.6%) presented with distant

Table 3. Lymphedema occurrence and related factors

Factor	Lymphedema, total		P-value	Pre-RT lymphedema		P-value	Post-RT lymphedema		P-value
	No	Yes		No	Yes		No	Yes	
Surgery			0.336			0.047*			0.257
MRM	9	5		13	1		10	4	
BCS	50	49		66	33		83	16	
No. of LND			0.045*			0.091			0.553
≤4	10	18		16	12		22	6	
>4	49	26		63	22		71	14	
Diabetes mellitus			0.758			0.817			0.901
Yes	10	8		13	5		15	8	
No	49	46		66	29		78	17	
Hypertension			0.327			0.489			0.651
Yes	13	8		16	5		18	3	
No	46	46		63	29		75	17	
Body mass index (kg/m^2)			0.646			0.851			0.706
≤25	38	37		52	23		61	14	
>25	21	17		27	11		32	6	
Pathologic N stage			0.405			0.420			0.618
N0	11	12		16	7		19	4	
N+	48	42		66	23		74	16	
Perineural invasion			0.437			0.608			0.303
Yes	5	6		8	3		8	3	
No	54	48		74	27		85	17	
RNI dose (Gy)			0.071			0.634			0.003*
≤50.4	54	43		67	30		84	13	
>50.4	5	11		12	4		9	7	
Neoadjuvant chemotherapy			0.127			0.115			0.915
Yes	19	25		27	17		36	8	
No	40	29		52	17		57	12	
Adjuvant chemotherapy			0.056			0.084			0.668
Yes	40	27		51	16		56	11	
No	19	27		28	18		37	9	
Taxane use			0.153			0.867			0.038*
Yes	51	41		64	28		79	13	
No	8	13		15	6		14	7	
Recurrence			0.071			0.913			0.026*
Yes	5	11		11	5		10	6	
No	54	43		68	29		83	14	
Total		54			34			20	

RT, radiotherapy; MRM, modified radical resection; BCS, breast-conserving surgery; LND, lymph node dissection; RNI, regional nodal irradiation.
*P < 0.05.

metastases. Table 2 shows the relationship between post-RT lymphedema and pattern of failure. Locoregional recurrence showed a tendency to be related to the occurrence of post-RT lymphedema (P = 0.086, Table 2). Only 4 patients (3.5%) were reported deceased during the follow-up periods.

Lymphedema occurrence and its related factors

Fig. 1A illustrates the occurrence of lymphedema by the period after surgery. Most cases of lymphedema occurred within 3 years after surgical resection. Late-onset lymphedema, which developed after RT, occurred at a median of 20.2 months after the conclusion of RT. In Table 3, lymphedema occurrence-related factors are presented, categorized by the onset time of lymphedema. The overall incidence of lymphedema was associated with the extent of LND. Lymphedema occurred more frequently in patients who underwent 1–4 LND compared to patients who underwent 5–34 LND through the follow-up periods (P = 0.044). Differences in surgical methods were linked to the occurrence of lymphedema in patients who developed early-onset lymphedema before the end of RT (pre-RT lymphedema, P = 0.047). Specifically, in patients who underwent BCS, more patients developed pre-RT lymphedema than those who underwent MRM (P = 0.047).

The occurrence of lymphedema after completion of RT (post-RT lymphedema), closely linked to the side of RT, was significantly influenced by the RNI dose (P = 0.003), whether taxane was used during chemotherapy (P = 0.038), and recurrence (P = 0.026). In the univariate analysis, RNI over 50.4 Gy (P = 0.003) significantly increased the risk of post-RT lymphedema. According to further multivariate analysis, high RNI dose (P= 0.007) and recurrence (P = 0.029) were independent prognostic factors for post-RT lymphedema.

Fig. 1B shows the correlation between the time-dependent incidence of lymphedema occurring after RT (post-RT lymphedema) and the total radiation dose during RNI. The utilization of a dose exceeding 50.4 Gy during RNI resulted in a higher subsequent incidence of lymphedema compared to using a dose equal to or less than 50.4 Gy (P = 0.005).

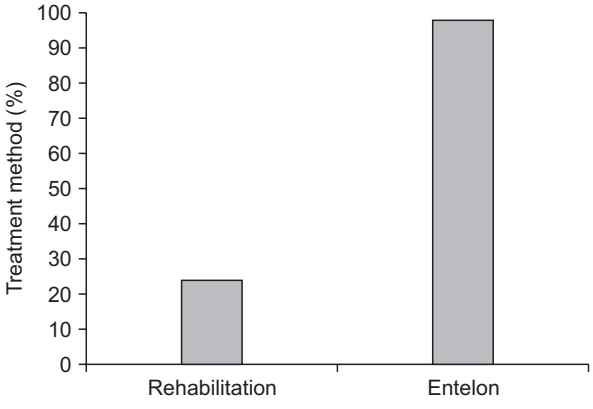

Fig. 2. Lymphedema treatment methods. Entelon, Hanlim Pharm Co., Ltd.

Treatment of lymphedema

Fig. 2 shows the methods used to treat lymphedema (n = 54). All patients received treatment after lymphedema diagnosis. The majority of patients received Entelon (n = 53, 98.1%) prescription. Only 13 patients (24.1%) received rehabilitation consultations and related interventions such as physical therapy, ultrasound therapy, or compression garment (stocking) prescriptions. Most patients visited the rehabilitation medicine department several times (9 of 13, 69.2%) No patients underwent surgical procedures for the treatment of lymphedema.

DISCUSSION

In this study, the incidence rate of lymphedema and related factors were analyzed. Approximately half of the patients in the study experienced lymphedema. Notably, as lymphedema continues to increase in patients up to 3 years after RT, a prolonged follow-up period is necessary [6]. Particularly, considering the high incidence rate in patients using taxane or a high dose of RNI, long-term follow-up is crucial. Patients with advanced stage usually get more comprehensive surgery, high-dose radiation to regional lymphatics, and chemotherapy including taxane. Therefore, the correlation between recurrence and lymphedema may be inevitable. Given that taxane use was found to increase the risk of lymphedema, similar to a previous study [7], close monitoring of these patients using taxane is warranted during RT. Since a high RNI dose is related to the occurrence of lymphedema after RT, further research is necessary. Notably, this study revealed a connection between lymphedema occurrence and cancer recurrence. When lymphedema occurs in the arm, it may be difficult for the immune cells in the body to reach the site continuously. In this regard, the risk of cancer recurrence seems to increase in this swelled lesion. Conversely, locoregional recurrence after RT may interrupt lymphatic fluid flow, leading to lymphedema.

To prevent lymphedema, RNI dose reduction or omitting RNI for low recurrence risk patients may be necessary. De-escalation of treatment is attracting attention to improve the quality of life in breast cancer patients for whom treatment is mostly successful. Radiation may increase the interstitial fibrosis and decrease the lymphatic function and proliferation [8,9]. Therefore, reducing the use of RT may decrease the incidence of lymphedema [10]. As this study also included pathologic N0 patients after neoadjuvant chemotherapy, a more active consideration of omitting RNI for these low recurrence risk patients is warranted. Additionally, a more precise cutoff for RNI dose would be preferable rather than an arbitrarily set cutoff dose of 50.4 Gy.

This study focused on patients receiving conventional fraction RT. However, hypofractionation is frequently used in breast RT, including RNI. Abouegylah et al. [11] reported that hypofractionation reduced the occurrence of lymphedema compared to conventional fractionation. Therefore, data comparing these different fractionation approaches are needed in further studies.

This study showed that a large amount of resection at the tumor site or lymph site was associated with a lower incidence of lymphedema. This result runs counter to the general notion that lymphedema will occur more often when surgery is performed widely. If the degree of excision is big, excess fat removal also increases, which seems to have the effect of preventing the occurrence of lymphedema. LND has already been performed as minimally as possible at the time of surgery, so it may have less impact on the occurrence of lymphedema. In patients who have undergone RT and chemotherapy for breast cancer, the degree of the surgery may not have much of an effect on the occurrence of lymphedema, because the occurrence of lymphedema is influenced by multiple factors. On the one hand, the patients who underwent wide resection, who were well aware of the risks of lymphedema, may have reduced the incidence of lymphedema by improving their lifestyle, such as regular exercise.

Further analysis is necessary, not only in terms of lymphedema occurrence rate but also regarding quality of life. It is difficult to assess the impact on patients' quality of life based on simple incidence rates of lymphedema [12,13]. Patient-reported outcome studies may give more information about the quality of life of patients with lymphedema [14]. Early intervention for lymphedema could reduce the severity of disease [10]. Current studies [8,12,15] are focused on risk assessment, early intervention, and prevention of lymphedema, necessitating more active consultations with the rehabilitation department to improve the symptoms of lymphedema.

One limitation of this study is that it is a retrospective study in a single institution, which may introduce selection bias. Meanwhile, a large amount of resection at the tumor site or lymph site was associated with a lower incidence of lymphedema in this study, contrary to previous study results by Kim et al. [16]. It may be related that lymphedema occurring within a few months after breast cancer surgery complicates distinguishing transient arm swelling associated with surgery. In addition, the lymphedema degree was difficult to assess by reviewing EMR, and the degree was not addressed in this study. The utilization of lymphoscintigraphy [17] at the time of lymphedema diagnosis could facilitate the assessment and staging of lymphedema. Despite most patients taking Entelon, determining the possibility of other treatments or the efficacy of the patient's response to alternative treatment was difficult. Moreover, the relationship between discontinuation of this medication and problem-solving for lymphedema remains uncertain. No surgical approaches, such as lymphovenous anastomoses and vascularized LN transfers [18] were used to treat lymphedema in this study. Thus, it was not possible to estimate the treatment effectiveness. Therefore, further research is required to ascertain the actual impact of surgery on lymphedema. Additionally, treatment methods were restricted [19]. Given that lymphedema is often a chronic condition, continuous efforts to discover and explore new treatment options for lymphedema are still warranted [3,8]. For example, adding nighttime compression to daytime sleeve compression improves swelling according to a recent study by McNeely et al. [20].

In conclusion, given the significant number of patients who developed lymphedema after RNI in breast cancer, more caution is needed in clinical practice. Moreover, it is necessary to find strategies to minimize lymphedema occurrence. The consideration of omitting RNI or reducing the dose should be considered to mitigate lymphedema, particularly in selected patients with a low risk of recurrence.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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