Practical Radiation Oncology® (2026) 16, e90–e100

practical radiation oncology
pro
www.practicalradonc.org

Basic Original Report

Identifying the Axillary Substructure at Risk for Lymphedema in Operable Patients With Breast Cancer Receiving Regional Nodal Irradiation

Jia-Qi Huang, MD,[a,b,1] Si-Yue Zheng, MD,[a,b,1] Mao-Chen Zhang, MD,[a,b] Shu-Jun Zhang, MMed,[a,b] Jing-Jing Cao, BEng,[a,b] Kun-Wei Shen, MD, PhD,[c] Wei-Xiang Qi, MD, PhD,[a,b] Gang Cai, MD, PhD,[a,b] Lu Cao, MD, PhD,[a,b,*] and Jia-Yi Chen, MD, PhD[a,b,*]

[a]*Department of Radiation Oncology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China;* [b]*Shanghai Key Laboratory of Proton Therapy, Shanghai, China; and* [c]*Department of General Surgery, Comprehensive Breast Health Center, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China*

Received 28 May 2025; accepted 8 December 2025

Purpose: Axillary substructures may contribute to the development of breast cancer-related lymphedema (BCRL). This study aimed to compare dose-volume parameters of various substructures to identify high-risk regions associated with BCRL and to evaluate the clinical applicability of these findings.

Methods and Materials: Cohort-Initial included 336 patients with pT1-3N0-1M0 breast cancer who underwent mastectomy or lumpectomy with axillary lymph node dissection (ALND) and regional nodal irradiation (RNI) between August 2018 and February 2021. The Norman questionnaire was used to assess BCRL. Thirteen dose-volume parameters across 8 axillary substructures were assessed for association with BCRL. Cohort-Recurrence comprised 50 consecutive ALND-treated patients with regional nodal recurrence diagnosed using positron emission tomography/computed tomography, used to evaluate the recurrence risk in the candidate substructures. Cohort-Reoptimization involved 20 patients from the Cohort-Initial who received excessive radiation doses in the candidate substructure. Their treatment plans were reoptimized to assess the feasibility of dose reduction while maintaining target coverage and organ dose.

Results: The patient-reported cumulative incidence of BCRL was 33.9% during a median follow-up of 60 months. Significant baseline risk factors included body mass index $\geq$ 27.18 kg/m^2, tumor size $\geq$ 1.9 cm, premenopausal status, and $\geq$ 18 lymph nodes removed (all $P < .05$). The most significant dosimetric parameter was axillary-lateral thoracic vessel juncture (ALTJ)-V35$_{Gy}$ $\geq$ 79.2%. A predictive nomogram incorporating these clinicopathologic factors and the ALTJ parameter was developed with reasonable accuracy, as confirmed

Sources of support: This study was supported in part by Noncommunicable Chronic Diseases-National Science and Technology Major Project (grant number 2023ZD0502200, 2023ZD0502206, 2024ZD0519900, 2024ZD0519905), Shanghai Science and Technology Innovation Action Plan (grant number 23Y41900100), the National Key Research and Development Program of China (grant number 2022YFC2404602), Shanghai Hospital Development Center Foundation (grant number SHDC12023108), Scientific and Technological Innovation Action Plan of Shanghai Science and Technology Committee (grant number 22Y31900103), Clinical Research of Shanghai Municipal Health Commission (grant number 20224Y0025), Clinical Research Special Project of Shanghai Municipal Health Commission Health Industry (grant number 202340226), Shanghai Science and Technology Innovation Action Plan Medical Innovation Research Project (grant number: 23Y11904700), Beijing Science and Technology Innovation Medical Development Foundation (grant number KC2021-JX-0170-9), National Natural Science Foundation of China (grant number 82373514, 82373202).

Research data are stored in an institutional repository and will be available from the corresponding author on reasonable request.

*Corresponding authors: Lu Cao, MD, PhD; Email: cl11879@rjh.com.cn and *Jia-Yi Chen, MD, PhD; Email: cjy11756@rjh.com.cn

[1]J.-Q.H. and S.-Y.Z. contributed equally to this work.

https://doi.org/10.1016/j.prro.2025.12.003

by self-training (area under the curve value, 0.780) and internal validation (area under the curve value, 0.769). None of the 196 fluorodeoxyglucose-avid regional nodes in Cohort-Recurrence were located within the ALTJ. Reoptimization of ALTJ-$V35_{Gy}$ was feasible without compromising the radiation therapy plan quality.

Conclusions: ALTJ-$V35_{Gy}$ < 79.2% may serve as a recommended dose constraint for patients undergoing RNI after ALND. Avoiding excessive radiation to the ALTJ is clinically feasible and safe, potentially mitigating BCRL risk without compromising dose coverage to high-risk nodal regions.

Introduction

Breast cancer-related lymphedema (BCRL) remains a prevalent and challenging complication arising from the multidisciplinary treatment of breast cancer, especially following axillary lymph node dissection (ALND) and regional nodal irradiation (RNI). BCRL affects approximately 1 in 15 to 1 in 3 breast cancer survivors worldwide, with incidence rates varying depending on the therapeutic strategies.[1] Given its significant impact on quality of life, increasing attention has been paid to it in recent years.[2-4]

The extent of ALND and the application of RNI are 2 primary contributors to BCRL.[5] Prior studies have demonstrated that RNI may increase the absolute risk of BCRL by approximately 3% to 5%,[6-8] consistent with prior findings.[9,10] Although RNI poses a lower risk than ALND, it remains a clinically significant factor, particularly in patients with node-positive (pN+) or high-risk node-negative (pN0) disease, where RNI is the standard treatment.[11]

Several studies have found that specific axillary subregions may correlate with a heightened risk of BCRL when exposed to high radiation doses.[12-14] These areas can be delineated as organs at risk (OARs), allowing for targeted dose constraints without compromising therapeutic outcomes.[15,16] With increasing precision of treatment delivery, including knowledge-based treatment planning and better image guidance, the avoidance of specific axillary substructures becomes technically possible.

In this study, we aimed first to establish whether there are specific axillary substructures to which an increased radiation dose is associated with the risk of BCRL in operable patients with breast cancer receiving RNI. Another cohort of regional recurrent patients was prepared to validate whether the BCRL high-risk structures are located in the high-risk nodal recurrent area or not. A novel nomogram that integrates dosimetric parameters and clinicopathologic factors for predicting BCRL was then developed. Finally, we assessed the feasibility of replanning RNI cases based on the nomogram-recommended dose-volume constraints using a state-of-the-art intensity modulated radiation therapy (IMRT) technique.

Methods and Materials

Patients

Patients with pT1-3N0-1M0 breast cancer (according to the American Joint Committee on Cancer 8th staging system) who underwent definitive breast-conserving surgery or mastectomy with ALND, followed by postoperative radiation therapy (RT) (including RNI) between August 2018 and February 2021, were identified from the departmental database and included in this study as Cohort-Initial to investigate the substructure associated with BCRL. Patients who received neoadjuvant therapy, developed BCRL before RNI, had distant metastasis, or had incomplete clinical records were excluded.

Another cohort (Cohort-Recurrence) of consecutive patients with breast cancer with a prior ALND history, who underwent positron emission tomography (PET)/computed tomography (CT) scans between January 2018 and June 2021 and were diagnosed with regional nodal recurrence, was identified and analyzed for recurrence risk.

This study was approved by the institutional review board at Shanghai Ruijin Hospital.

Treatment

All patients in Cohort-Initial started the RT within 2 to 4 weeks after completing adjuvant chemotherapy or within 4 to 6 weeks after surgery in the absence of chemotherapy. All patients underwent CT scan simulation, and the clinical target volume, as well as OARs, was delineated according to the in-house guidelines.[17] The clinical target volumes include the ipsilateral whole breast or chest wall, supraclavicular nodes, and undissected axillary nodes, with or without the internal mammary chain. IMRT was used for all patients with either a conventional fractionation regimen (50 Gy in 25 fractions) or a hypofractionated regimen (40.05 Gy in 15 fractions). IMRT was delivered using multiple fixed fields, with 4 to 6 tangential beams covering the breast/chest wall and internal mammary region, and 2 to 3 beams for the supraclavicular area (gantry angles 300°-20°) using fixed posterior jaws.

RT plans were accepted if the D95 of the target volume exceeded 95% of the prescribed dose and the OAR constraints were met. The mean heart dose was limited to <5 Gy for patients with left-sided breast cancer and <2 Gy for patients with right-sided breast cancer. The mean dose was limited to <15 Gy for the ipsilateral lung, <2 Gy for the contralateral lung, and <3 Gy for the contralateral breast. Details of the RT plan are outlined in the protocol of the HARVEST trial (NCT03829553) conducted at our institution.[18]

Axillary substructures contouring

Following the description by Gross et al[15] and our institutional practice,[17] the axilla was divided into 8 substructures, as shown in Figs. E1 and E2 and detailed in Table E1. These substructures include (1) medial supraclavicular region; (2) lateral supraclavicular region; (3) axillary lymph node level III; (4) higher axillary lymph node level II (higher ALN-II); (5) axillary-lateral thoracic vessel junction (ALTJ); (6) lateral to ALTJ; (7) medial to ALTJ; and (8) lower axillary lymph node region, including ALN-II and ALN-I (lower ALN-II + ALN-I). The following dose-volume histogram (DVH) metrics were collected from the treatment planning system for data analyses: maximum dose (Dmax), minimum dose (Dmin), and mean dose (Dmean); $V50_{Gy}$, $V45_{Gy}$, $V40_{Gy}$, $V35_{Gy}$, $V30_{Gy}$, $V25_{Gy}$, $V20_{Gy}$, $V15_{Gy}$, $V10_{Gy}$, and $V5_{Gy}$. For patients treated with the hypofractionated regimen, DVH metrics were converted into equivalent doses in 2-Gy fractions (EQD2) using an α/β ratio of 3 Gy to correct for differences and facilitate analysis.[19,20]

Follow-up and assessment for lymphedema

All patients were assessed weekly during treatment, then every 3 months for the first 2 years, and subsequently every 6 months. Patients received health education on BCRL before initiating RT. The diagnosis, grading, and incidence of BCRL reported in this study were all based on patient self-reports using the Norman questionnaire.[21] All patients diagnosed with lymphedema were referred to the rehabilitation department during routine visits for further treatment to ensure effective management.

Statistical analysis

The Kaplan-Meier method was used to estimate the cumulative incidence of BCRL from the date of surgery to diagnosis. Univariate and multivariate Cox proportional hazards models were applied to assess the association of clinicopathologic factors, axillary substructures, and dose-volume parameters with the BCRL. *P*-values were adjusted for multiple testing using the Benjamini-Hochberg procedure, and a 2-sided $P < 0.05$ was considered statistically significant. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. Baseline characteristics between groups were compared using the chi-square test, Fisher's exact test, or Mann−Whitney U test, as appropriate. Optimal cut-off values for continuous variables were determined using the maximally selected rank statistics. The Akaike information criterion guided the selection of the optimal dose metric for the multivariable modeling and nomogram construction. The receiver operating characteristic curve was generated using a non-parametric empirical method and smoothed using a kernel-based density estimation for visualization; the area under the curve (AUC) values were calculated from the original unsmoothed curves. Associations between radiation dose and lymphedema severity were evaluated using Spearman's rank correlation analysis and ordinal logistic regression. Paired *t* tests were performed to compare DVH metrics between RT plans. All analyses were conducted using R version 4.2.2 and GraphPad Prism version 9.4.1.

Results

Patient characteristics

A total of 336 patients with breast cancer were enrolled in Cohort-Initial to identify the risk factors associated with BCRL, of whom 289 patients were previously reported in a prior publication and were followed up in this update.[9] The median age was 53 years (interquartile range [IQR], 44-64 years), and the median body mass index (BMI) was 23.0 kg/m^2 (IQR, 21.2-25.1 kg/m^2). Most patients underwent mastectomy (n = 282, 83.9%), and all patients received ALND, including 9 pN0 patients who failed sentinel biopsies and underwent RNI because of adverse pathologic features. The median number of lymph nodes removed was 19 (IQR, 14-22). Among the enrolled patients, 73.2% were treated with conventional fractionated RT. The detailed characteristics of Cohort-Initial are summarized in Table 1. The study scheme is illustrated in Fig. 1.

Clinicopathologic factors associated with lymphedema

During a median follow-up of 60 months (95% CI, 59-62 months), 114 patients in Cohort-Initial (33.9%) reported developing BCRL. The 2-year cumulative incidence of BCRL was 25.0%. Among the Cohort-Initial, mild, moderate, and severe lymphedema occurred in 25.0%, 6.0%, and 3.0% of patients, respectively. All factors with $P < .05$ in univariate Cox regression analysis were included in multivariate analysis (Table E2), and the

Table 1 Patient, tumor, and treatment characteristics of the cohort (n = 336)

Clinical features	Total (n = 336)	Training set (n = 236)	Test set (n = 100)
Age (median [IQR]), y	53 (44-64)		*P* = .9570
		51 (44-61)	53 (45-63)
BMI (median [IQR]), kg/m^2	23.0 (21.2-25.3)		*P* = .3664
		23.2 (21.2-25.3)	22.6 (21.1-24.8)
Menopausal status, n (%)			*P* = .1505
Premenopausal	138 (41.1)	91 (38.6)	47 (47.0)
Postmenopausal	198 (58.9)	145 (61.4)	53 (53.0)
Surgery type, n (%)			*P* = .7278
Mastectomy	282 (83.9)	197 (83.5)	85 (85.0)
Lumpectomy	54 (16.9)	39 (16.5)	15 (15.0)
Tumor laterality, n (%)			*P* = .8155
Left	178 (53.0)	126 (53.4)	52 (52.0)
Right	158 (47.0)	110 (46.6)	48 (48.0)
Tumor location, n (%)			*P* = .9976
Lateral	215 (64.0)	151 (64.0)	64 (64.0)
Median or central	121 (36.0)	85 (36.0)	36 (36.0)
Tumor size (median [IQR]), cm	3.0 (2.0-3.0)		*P* = .4106
		2.5 (2.0-3.0)	2.2 (2.0-3.0)
No. of LNs removed (median [IQR])	19 (14-22)		*P* = .3264
		17 (14-22)	17 (12-21)
No. of LNs positive, n (%)			*P* = .4889
0	9 (2.7)	7 (3.0)	2 (2.0)
1	157 (46.7)	110 (46.6)	47 (47.0)
2	106 (31.5)	79 (33.5)	27 (27.0)
3	64 (19.1)	40 (16.9)	24 (24.0)
Histologic type and grade, n (%)			*P* = .2061
IDC grade I	9 (2.7)	6 (2.5)	3 (3.0)
IDC grade II	175 (52.1)	131 (55.5)	44 (44.0)
IDC grade III	118 (35.1)	79 (33.5)	39 (39.0)
Others	34 (10.1)	20 (8.5)	14 (14.0)
Biological subtype, n (%)			*P* = .6497
Luminal A	55 (16.4)	41 (17.4)	14 (14.0)
Luminal B (HER2−)	152 (45.2)	110 (46.6)	42 (42.0)
Luminal B (HER2+)	45 (13.4)	28 (11.9)	17 (17.0)
HER2 enriched	48 (14.3)	33 (14.0)	15 (15.0)
Triple negative	36 (10.7)	24 (10.1)	12 (12.0)
Chemotherapy, n (%)			*P* = .3139
Yes	325 (96.7)	230 (97.5)	95 (95.0)
No	11 (3.3)	6 (2.5)	5 (5.0)

(*Continued*)

Table 1 (*Continued*)

Clinical features	Total (n = 336)	Training set (n = 236)	Test set (n = 100)
Taxane-based chemotherapy, n (%)			*P* = .3139
Yes	323 (96.1)	228 (96.6)	95 (95.0)
No	13 (3.9)	8 (3.4)	5 (5.0)
Hormone therapy, n (%)			*P* = .9344
Yes	253 (75.3)	178 (75.4)	75 (75.0)
No	83 (24.7)	58 (24.6)	25 (25.0)
Anit-HER2 therapy, n (%)			*P* = .2930
Yes	91 (27.1)	60 (25.4)	31 (31.0)
No	245 (72.9)	176 (74.6)	69 (69.0)
Fractionation			*P* = .9540
CFRT (50 Gy/25 Fx)	246 (73.2)	173 (73.3)	73 (73.0)
HFRT (40.05 Gy/15 Fx)	90 (26.8)	63 (26.7)	27 (27.0)

Abbreviations: BMI, body mass index; CFRT = conventional fractionation radiation therapy; Fx = fraction; HER2 = human epidermal growth factor receptor 2; HFRT = hypofractionated radiation therapy; IDC = invasive ductal carcinoma; IQR = interquartile range; LN = lymph node; No. = number.

following independent risk factors for developing BCRL were identified: BMI ≥ 27.18 kg/m^2 (HR, 2.02; 95% CI, 1.22-3.33; *P* = .006), tumor size ≥ 1.9 cm (HR, 1.75; 95% CI, 1.17-2.61; *P* = .006), and the number of lymph nodes removed ≥ 18 (HR, 1.52; 95% CI, 1.04-2.24; *P* = .031). Additionally, postmenopausal status was identified as a protective factor against BCRL development (HR, 0.59; 95% CI, 0.36-0.96; *P* = .035) (Fig. E3).

Substructure parameter determination and establishment of the nomogram

Following the analysis of clinicopathologic risk factors in the entire population of Cohort-Initial, this cohort was subsequently randomly divided into a training set (n = 236, 70%) and a test set (n = 100, 30%) (Table 1). Each DVH metric for the 8 axillary substructures was classified into 2 groups based on optimal cut-off values determined using maximally selected rank statistics. Except for axillary lymph node level III and higher ALN-II, all substructures had DVH metrics that were significantly associated with BCRL. A total of 39 DVH metrics, along with 4 clinicopathologic risk factors, were integrated into the multivariable Cox model developed in the training set (Table E3). Among these, ALTJ-V35$_{Gy}$ ≥ 79.2% was identified as the optimal parameter for predicting BCRL based on the minimum Akaike information criterion value. A nomogram for BCRL prediction was developed using Cox regression analysis (Fig. 2). The model achieved an AUC value of 0.780 in the training set and 0.769 in the test set, demonstrating good predictive accuracy (Fig. E4). Both ordinal logistic regression and Spearman rank correlation analysis in the training set

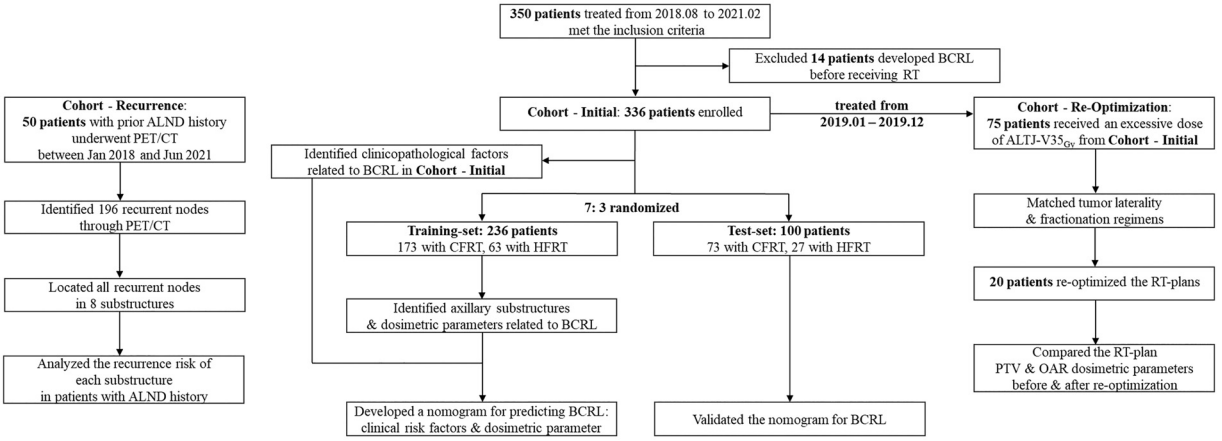

Figure 1 The study scheme. The scheme of this retrospective cohort study.

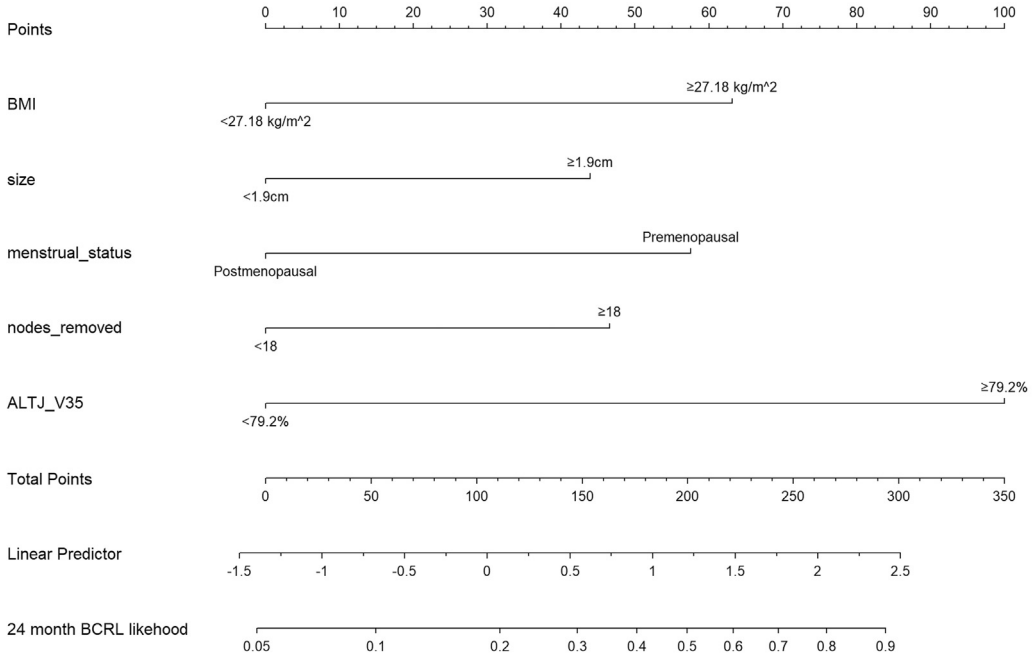

Figure 2 A nomogram for breast cancer-related lymphedema (BCRL) prediction. Combined nomogram predicting BCRL risk based on clinicopathologic factors and metric of the axillary substructure axillary-lateral thoracic vessel juncture (ALTJ).

demonstrated a significant positive association between ALTJ-V35$_{Gy}$ and lymphedema severity. ALTJ-V35$_{Gy}$ was associated with increased odds of higher lymphedema grades (odds ratio per 1% increase = 1.026; $P < .001$), and Spearman correlation supported a moderate monotonic trend ($\rho = 0.282$; $P < .001$), indicating a dose-response relationship. These findings were further corroborated in the test set, observing consistent results (odds ratio per 1% increase = 1.034, $P = .002$; $\rho = 0.310$, $P = .002$).

Regional nodal recurrence risk in substructures

Overall, 3 patients (0.89%) in Cohort-Initial experienced regional nodal recurrence during the 60-month follow-up. The location of recurrent regional lymph nodes (rLNs) is detailed as follows: patient 1, located in the medial and lateral supraclavicular region as well as higher ALN-II, with only the lateral supraclavicular region showing out-of-field recurrence; patient 2 had 1 in the medial upper cervical region as out-of-field recurrence and 1 in the lower ALN-I as marginal recurrence; patient 3 had 1 in the lateral supraclavicular region, which was out-of-field recurrence. All cases were confirmed using either core needle biopsy or fine-needle aspiration.

To address the challenge of assessing recurrent risk for each substructure because of the limited number of rLNs, we established an additional cohort, Cohort-Recurrence consisting of 50 consecutive patients who were initially diagnosed with stage II-III breast cancer and underwent ALND during their initial treatment and were subsequently diagnosed with regional nodal recurrence using PET/CT scans, of whom 46 had at least 1 nodal recurrence confirmed using cytology or histology. This group of patients had been described in a prior study, with 15 individuals (30%) having a prior history of RNI.[17] Patient characteristics are summarized in Table E4. The median time to regional nodal recurrence in the Cohort-Recurrence was 44 months (95% CI, 27-67 months). A total of 196 fluorodeoxyglucose-avid regional lymph nodes were identified. The majority were located in the supraclavicular region (n = 126, 64.3%) and the internal mammary chain region (n = 29, 14.8%). No positive nodes occurred directly on ALTJ, except for 2 (1.0%) medial to ALTJ and 1 (0.5%) lateral to ALTJ. A visual representation of the positive nodes and substructures was presented in Fig. 3. The distribution of rLNs across substructures is summarized in Table 2. For the 15 patients with a previous RNI history, Table E5 presents the initial RNI target volume and the recurrent type of the rLNs.

Clinical applicability of optimizing the ALTJ parameter

To evaluate the clinical applicability of optimizing the ALTJ-V35$_{Gy}$, 75 patients who received an excessive dose of ALTJ-V35$_{Gy}$ in the Cohort-Initial between January 2019 and December 2019 were retrospectively identified, a Cohort-Reoptimization was constructed. After balancing for tumor laterality and fractionation regimens, 20 patients were selected and stratified into 2 groups: 10 patients with 0-1 clinicopathologic risk factors (clinically low-risk) and 10 patients with ≥ 2 clinicopathologic risk

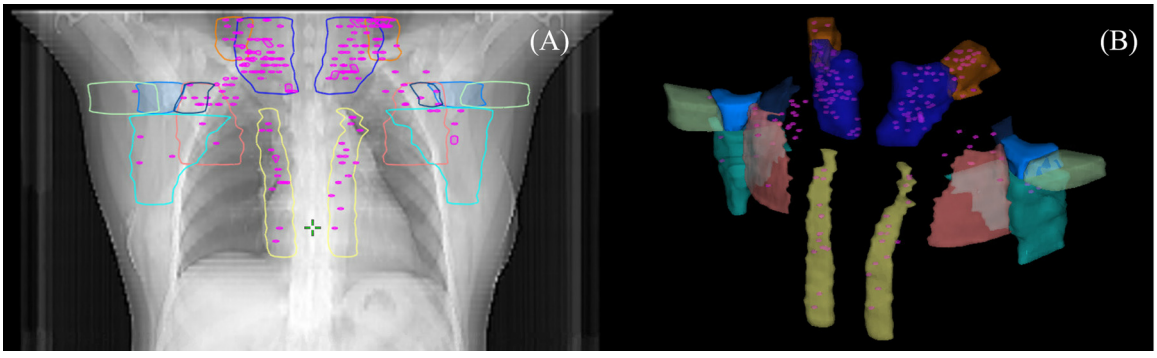

Figure 3 A visual representation of the positive nodes and substructures. A 2-dimensional (A) and 3-dimensional (B) overview of the ^{18}F-fluorodeoxyglucose-avid recurrent regional nodes based on the substructure delineation map of a modal case.

factors (clinically high-risk). Medical dosimetrists reoptimized the plans to reduce ALTJ-V35$_{Gy}$ to <79.2%, while ensuring adequate planning target volume (PTV) coverage and adherence to OARs' constraints. Figure 4 demonstrates a significant reduction in ALTJ dose after reoptimization in both groups, indicating the feasibility of reducing the risk of BCRL by optimizing ALTJ-V35$_{Gy}$ in the RT plan for all patients, irrespective of their number of clinicopathologic risk factors. Comparisons of DVH metrics for PTV and OARs before and after reoptimization are detailed in Tables E6 and E7. Although certain dosimetric parameters showed statistically significant differences, these changes consistently maintained or improved the overall RT plan quality.

Discussion

BCRL significantly impacts the quality of life, physical appearance, and mental health of breast cancer survivors.[22,23] For patients who undergo RNI after ALND, the risk of lymphedema is substantially elevated.[10,14] Therefore, developing practical tools for BCRL prediction is essential to assist oncologists in optimizing therapeutic strategies. In this study, apart from 3 classical factors, including higher BMI, larger tumor size, and increasing number of axillary nodes dissected, we identified a significant association between high radiation doses to the ALTJ—an axillary substructure located superior to ALN-I—and the development of BCRL. A nomogram for predicting BCRL incorporating ALTJ DVH metrics and clinicopathologic risk factors was developed, demonstrating strong predictive performance in both the training set (AUC value, 0.78) and test set (AUC value, 0.77). Regarding the recurrence pattern, we confirmed that the ALTJ is not a high-risk area for regional nodal recurrence in patients after ALND with rLNs detected using PET/CT scans, irrespective of prior RNI history. Finally, optimizing ALTJ-V35$_{Gy}$ did not compromise the quality of the RT plan.

Our study shares both similarities and differences in conclusions with 3 previous studies in this field (summarized in Table E8).[15,16,24] Regarding clinicopathologic

Table 2 Distribution of the recurrent lymph nodes in axillary substructures in Cohort-Recurrence

Substructures	Recurrent without RNI history (n = 35)	recurrent with RNI history (n = 15)
Lower axillary region	3 (rLNn = 6)	3 (rLNn = 5)
ALTJ	0	0
Lateral to ALTJ	1 (rLNn = 1)	0
Medial to ALTJ	0	2 (rLNn = 2)
Higher ALN-II	9 (rLNn = 14)	0
ALN-III	6 (rLNn = 7)	1 (rLNn = 1)
Rotter's nodes	3 (rLNn = 4)	1 (rLNn = 1)
Internal mammary chain region	14 (rLNn = 21)	5 (rLNn = 8)
Medial supraclavicular region	21 (rLNn = 72)	10 (rLNn = 22)
Lateral supraclavicular region	15 (rLNn = 23)	2 (rLNn = 9)

Abbreviations: RNI = regional nodal irradiation; rLNn = number of recurrent regional lymph nodes; ALTJ = the axillary-lateral thoracic vessel juncture; ALN-II = axillary lymph node level II; ALN-III = axillary lymph node level III.

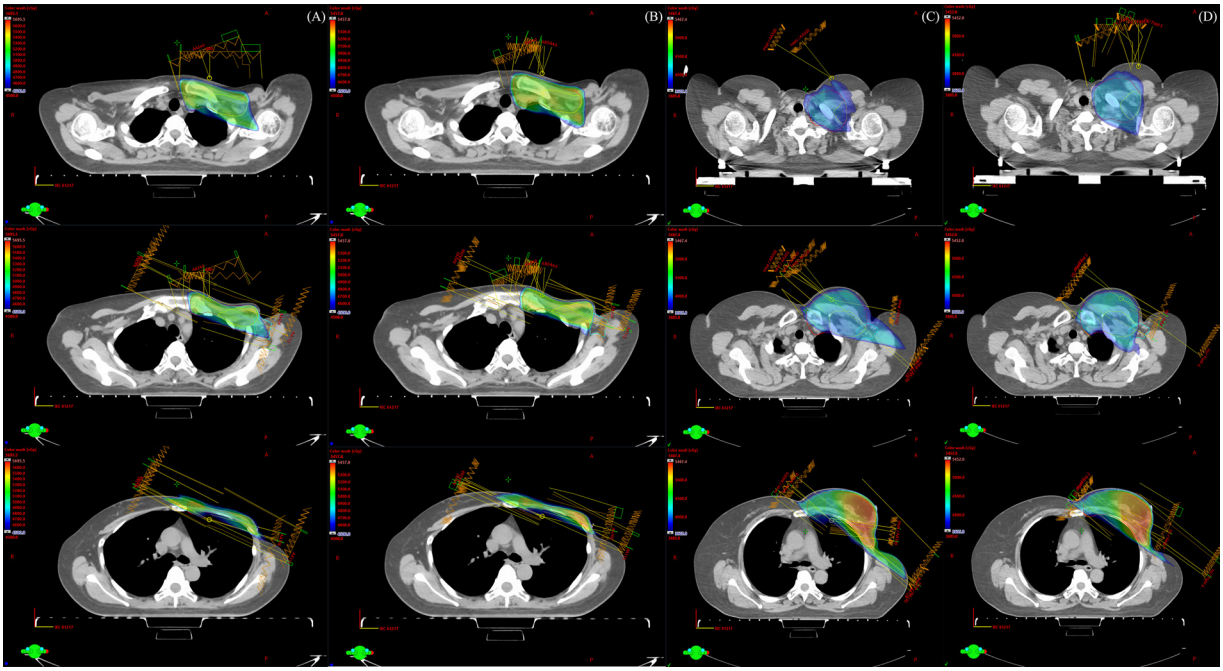

Figure 4 Dose comparison before and after plan reoptimization. Comparison of the radiation therapy (RT) plans before and after optimizing axillary-lateral thoracic vessel juncture (ALTJ)-$V35_{Gy}$ metric for patients who underwent different surgeries and different fractionated RT. Planning target volume (PTV) is delineated in red, and ALTJ in cyan. (A) and (B) present a comparison of the plans before and after optimization for a mastectomy patient receiving conventional fractionated RT (CFRT). The left-side dose line corresponds to 4500 cGy (90% of the prescribed dose). (C) and (D) present a comparison of the plans before and after optimization for a patient undergoing breast-conserving surgery and receiving hypofractionated RT (HFRT). The left-side dose line corresponds to 3605 cGy (90% of the prescribed dose).

factors, previous studies have consistently reported a positive correlation between the number of lymph nodes removed and the risk of lymphedema.[25,26] Two studies also identified higher BMI as a risk factor.[15,24] Our findings suggest that premenopausal patients might be at a higher risk of developing BCRL, which is not a traditional risk factor, probably explained by the fact that younger patients tend to be more physically active; however, it is also possibly biased by the questionnaire because they are more proactive in monitoring their health conditions. Using a more clinically relevant substructure-dividing approach, we found that ALTJ is the axillary substructure most strongly associated with BCRL, which aligns with the results of Gross et al[15] and Park et al[16]. By synthesizing our dosimetric findings with prior studies, we suggest that a dose range of 35 to 40 Gy may be critical for the risk of lymphedema. However, the study conducted by Healy et al[24] found that there did not exist a substructure in the axillary region associated with BCRL. It is worth noting that Healy et al[24] delineated the lymphatic drainage region according to the Radiation Therapy Oncology Group guidelines, delineating only the ALTJ region among the substructures. This may lead to a substantial overlap between the axillary PTV and ALTJ in most patients (91.3%). These discrepancies in retrospective studies likely arise from variations in substructure definitions and the incorporation of clinicopathologic factors.

The delineation of the ALTJ region as a high-risk area for lymphedema in RNI can be partially explained from an anatomic perspective. According to the axillary reverse mapping theory, the lymphatic drainage pathways of the upper extremity and the breast are distinct but may converge in certain instances.[27,28] Pavlista et al[29] demonstrated that some lymphatic collectors of the upper extremity are located cranially and medially to the axillary vein, while Han et al[30] and Ikeda et al[31] reported that 3% to 17% of patients have lymphatic drainage nodes primarily situated above the axillary vein. Although 63% to 97% of lymphatic drainage nodes are located between the axillary vein and the second intercostal nerve, most patients do not develop lymphedema after ALND.[32] This suggests that the lymphatic drainage system cranial to the axillary vein may play a protective role against lymphedema.[33] Therefore, for patients undergoing ALND, protecting the ALTJ region from high irradiation doses might be helpful in preserving the upper extremity lymphatic drainage and reducing the risk of lymphedema.

One of the challenges in identifying BCRL-related substructures during RNI is the uncertainty of oncological outcomes over long-term follow-up. Referring to large randomized controlled trials with similar populations, the 5-year regional nodal recurrence rate among patients undergoing ALND was 0.5% in the SENOMAC study, while the AMAROS study reported a 10-year cumulative

axillary recurrence rate of 0.93% in the ALND group.[34,35] Given the extremely low recurrence rate and the limited follow-up duration, evaluating regional control in the 336 patients enrolled in Cohort-Initial remains challenging. Therefore, another cohort of patients from our previous study[17] who underwent ALND and subsequently developed regional nodal recurrence diagnosed using PET/CT scan was analyzed. It is found that no recurrence was observed directly in the ALTJ region (0%) and only a distinctly low recurrence rate (1.5%) in its accessory regions. DeSelm et al[36] identified 243 rLNs in 153 patients. Most of the recurrence sites were in the axilla (42% of rLNs), internal mammary chain (32.5%), and supraclavicular region (25.5%).

Another challenge lies in the evolving landscape of auxiliary management. For patients with cN0 and 1 to 2 positive sentinel lymph nodes, ALND is no longer the standard of care.[11,37] We acknowledge this as the major limitation of our study. Nevertheless, our results demonstrated that the number of positive lymph nodes does not serve as a significant clinicopathologic risk factor, suggesting that our results can be extrapolated to higher-risk patients, such as those with pN2 or above, in whom ALND remains standard practice. Importantly, our study supports the use of dose constraints rather than complete dose exclusion of the ALTJ region, which provides clinical feasibility for balancing treatment outcomes and adverse toxicity. In the current era of axillary surgical de-escalation, the optimal approach to RNI for patients with 1 to 2 positive sentinel lymph nodes remains unsettled. Although the Z0011 trial specified whole-breast irradiation as the intended target, its RT quality assurance data revealed that a substantial proportion of patients received high-tangential fields or even RNI.[38] In the AMAROS trial, comprehensive RNI encompassing axillary levels I to III was used as an alternative to ALND.[35] The RT quality assurance analyses from the SENOMAC trial showed considerable heterogeneity in the indications for axillary level I irradiation across Sweden and Denmark; more than 80% of level I axillae received full-dose radiation regardless of whether it was the intended target.[39] Consequently, the dose to the ALTJ region may vary significantly depending on the defined RNI target volume. In response to this clinical uncertainty, the prospective trial NCT06583655 has been conducted to evaluate the incidence of lymphedema, as well as disease-free survival and overall survival among patients with cN0 disease undergoing different surgical and RT strategies; subsequent analyses from that study are expected to help define appropriate ALTJ dose constraints with various RNI target scenarios. From retrospective data, among patients receiving RNI—including 27.8% who underwent sentinel lymph node biopsy alone—omission of upper axillary level I (where the ALTJ is anatomically located) irradiation is oncologically safe.[40] Although current information does suggest that the ALTJ and its adjacent areas are not at high risk for axillary recurrence, it is possible that our results can be applied to patients with sentinel lymph node biopsy only, perhaps with less strict restrictions, as the general lymphatic drainage is preserved in this population. Finally, the technical transition has markedly improved our ability to sculpt the doses delivered to axillary substructures. Although all patients in our study were treated with IMRT, the beam configurations were relatively straightforward, making our findings translatable to centers still using 3-dimensional conformal RT techniques.

Besides the axillary surgical type, there are several limitations to our study. First, accurately defining and assessing BCRL remains a global challenge. In this study, we used a combined approach of patient self-report and physician assessment for diagnosis, and only the self-reporting results were included in the analysis. Research conducted by the American Society of Breast Surgeons highlights that patient self-reporting remains the most widely adopted screening method,[41] and self-reporting questionnaires can function as an educational tool, increasing patients' awareness of BCRL. Although the feasibility and stability of the Norman questionnaire in diagnosing BCRL have been validated, and several studies have found that self-reported symptoms may represent early indicators of BCRL,[42,43] patient self-report may overestimate BCRL incidence, potentially resulting in an overconservative dosimetric recommendation. Second, we assumed an α/β ratio of 3 Gy for lymphedema in this study, which was derived from breast cancer control but not lymphedema as the endpoint. Despite these limitations, our study benefits from a relatively large sample size and an extended follow-up. We would expect to reduce the incidence of BCRL by limiting the radiation dose to the ALTJ region to the given threshold without compromising the plan quality.

Conclusion

We identified the ALTJ region as a risk substructure in the axilla associated with BCRL in operable breast cancer patients undergoing ALND and RNI and found that ALTJ-$V35_{Gy}$ is an independent risk factor for BCRL. By integrating clinicopathologic risk factors, we developed a nomogram suggesting that ALTJ-$V35_{Gy}$ < 79.2% may serve as a dose constraint to reduce the risk of BCRL. The ALTJ region is not a high-risk area for regional nodal recurrence, and limiting ALTJ-$V35_{Gy}$ would not compromise PTV coverage or conventional OAR dose constraints. Prospective studies are warranted to confirm these findings.

Disclosures

None.

Acknowledgments

Jia-Qi Huang was responsible for statistical analysis.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.prro.2025.12.003.

References

1. Rockson SG. Lymphedema after Breast Cancer Treatment. *N Engl J Med*. 2018;379:1937-1944.
2. Pinto M, Gimigliano F, Tatangelo F, et al. Upper limb function and quality of life in breast cancer related lymphedema: a cross-sectional study. *Eur J Phys Rehabil Med*. 2013;49:665-673.
3. Chachaj A, Małyszczak K, Pyszel K, et al. Physical and psychological impairments of women with upper limb lymphedema following breast cancer treatment. *Psychooncology*. 2010;19:299-305.
4. Vassard D, Olsen MH, Zinckernagel L, Vibe-Petersen J, Dalton SO, Johansen C. Psychological consequences of lymphoedema associated with breast cancer: a prospective cohort study. *Eur J Cancer*. 2010;46:3211-3218.
5. McLaughlin SA, Brunelle CL, Taghian A. Breast cancer-related lymphedema: risk factors, screening, management, and the impact of locoregional treatment. *J Clin Oncol*. 2020;38:2341-2350.
6. Whelan TJ, Olivotto IA, Parulekar WR, et al. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med*. 2015;373:307-316.
7. Poortmans PM, Collette S, Kirkove C, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med*. 2015;373:317-327.
8. Naoum GE, Taghian AG. Regional lymph node radiation is not the main risk factor for breast cancer related lymphedema: Stop chasing radiation doses, fractionation or techniques—focus on axillary surgery de-escalation or prevention. *Int J Radiat Oncol Biol Phys*. 2023;117:461-464.
9. Zheng S-Y, Chen C-Y, Qi W-X, et al. The influence of axillary surgery and radiotherapeutic strategy on the risk of lymphedema and upper extremity dysfunction in early breast cancer patients. *Breast*. 2023;68:142-148.
10. Naoum George E, Roberts Sacha, Brunelle Cheryl L, et al. Quantifying the impact of axillary surgery and nodal irradiation on breast cancer-related lymphedema and local tumor control: Long-term results from a prospective screening trial. *J Clin Oncol*. 2020;38:3430-3438.
11. Gradishar WJ, Moran MS, Abraham J, et al. Breast Cancer, Version 3.2024, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2024;22:331-357.
12. Byun HK, Chang JS, Im SH, et al. Risk of lymphedema following contemporary treatment for breast cancer: An analysis of 7617 consecutive patients from a multidisciplinary perspective. *Ann Surg*. 2021;274:170-178.
13. Gross JP, Sachdev S, Helenowski IB, et al. Radiation therapy field design and lymphedema risk after regional nodal irradiation for breast cancer. *Int J Radiat Oncol Biol Phys*. 2018;102:71-78.
14. Gross JP, Whelan TJ, Parulekar WR, et al. Development and validation of a nomogram to predict lymphedema after axillary surgery and radiation therapy in women with breast cancer from the NCIC CTG MA.20 Randomized Trial. *Int J Radiat Oncol Biol Phys*. 2019;105:165-173.
15. Gross JP, Lynch CM, Flores AM, et al. Determining the organ at risk for lymphedema after regional nodal irradiation in breast cancer. *Int J Radiat Oncol Biol Phys*. 2019;105:649-658.
16. Park Y-I, Chang JS, Ko H, et al. Development and validation of a normal tissue complication probability model for lymphedema after radiotherapy in breast cancer. *Int J Radiat Oncol Biol Phys*. 2023;116:1218-1225.
17. Zhang M, Cao L, Chen J, et al. Mapping of PET/CT-based regional nodes distribution of recurrent/advanced breast cancer and comparison with current delineation atlas. *Br J Radiol*. 2022;95:20220382.
18. Xie J, Xu F, Zhao Y, et al. Hypofractionated versus conventional intensity-modulated radiation irradiation (HARVEST-adjuvant): study protocol for a randomised non-inferior multicentre phase III trial. *BMJ Open*. 2022;12:e062034.
19. Bentzen SM, Dische S. Morbidity related to axillary irradiation in the treatment of breast cancer. *Acta Oncol*. 2000;39:337-347.
20. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol*. 2013;14:1086-1094.
21. Norman SA, Miller LT, Erikson HB, Norman MF, McCorkle R. Development and validation of a telephone questionnaire to characterize lymphedema in women treated for breast cancer. *Phys Ther*. 2001;81:1192-1205.
22. Heller DR, Axelrod B, Sevilimedu V, Morrow M, Mehrara BJ, Barrio AV. Quality of life after axillary lymph node dissection among racial and ethnic minority women. *JAMA Surg*. 2024;159:668-676.
23. Yusof KM, Mohd Sidik S, Mahmud R, Abdullah M, Avery-Kiejda KA, Rosli R. Association of psychological distress with arm morbidity symptoms in breast cancer survivors: outcomes from the use of PHQ-9 and GAD-7 questionnaires. *Breast Cancer*. 2023;30:810-819.
24. Healy E, Beyer S, Jhawar S, White JR, Bazan JG. The axillary lateral vessel thoracic junction is not an organ at risk for breast cancer −related lymphedema. *Int J Radiat Oncol Biol Phys*. 2023;117:452-460.
25. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: A systematic review and meta-analysis. *Lancet Oncol*. 2013;14:500-515.
26. Warren LE, Miller CL, Horick N, et al. The impact of radiation therapy on the risk of lymphedema after treatment for breast cancer: a prospective cohort study. *Int J Radiat Oncol Biol Phys*. 2014;88:565-571.
27. Thompson M, Korourian S, Henry-Tillman R, et al. Axillary reverse mapping (ARM): a new concept to identify and enhance lymphatic preservation. *Ann Surg Oncol*. 2007;14:1890-1895.
28. Casabona F, Bogliolo S, Valenzano Menada M, Sala P, Villa G, Ferrero S. Feasibility of axillary reverse mapping during sentinel lymph node biopsy in breast cancer patients. *Ann Surg Oncol*. 2009;16:2459-2463.
29. Pavlista D, Eliska O. Relationship between the lymphatic drainage of the breast and the upper extremity: A postmortem study. *Ann Surg Oncol*. 2012;19:3410-3415.
30. Han JW, Seo YJ, Choi JE, Kang SH, Bae YK, Lee SJ. The efficacy of arm node preserving surgery using axillary reverse mapping for preventing lymphedema in patients with breast cancer. *J Breast Cancer*. 2012;15:91-97.
31. Ikeda K, Ogawa Y, Komatsu H, et al. Evaluation of the metastatic status of lymph nodes identified using axillary reverse mapping in breast cancer patients. *World J Surg Oncol*. 2012;10:233.
32. Shao X, Sun B, Shen Y. Axillary reverse mapping (ARM): Where to go. *Breast Cancer*. 2019;26.
33. Yuan Q, Hou J, Zhou R, et al. Development and validation of an intraoperative nomogram to predict breast cancer-related

lymphedema based on the arm lymphatics distribution. *Ann Surg Oncol*. 2021;28:7319-7328.
34. de Boniface J, Filtenborg Tvedskov T, Rydén L, et al. Omitting axillary dissection in breast cancer with sentinel-node metastases. *N Engl J Med*. 2024;390:1163-1175.
35. Bartels SAL, Donker M, Poncet C, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer: 10-year results of the randomized controlled EORTC 10981-22023 AMAROS Trial. *J Clin Oncol*. 2022JCO2201565.
36. DeSelm C, Yang TJ, Cahlon O, et al. A 3-Dimensional Mapping Analysis of Regional Nodal Recurrences in Breast Cancer. *Int J Radiat Oncol Biol Phys*. 2019;103:583-591.
37. Loibl S, André F, Bachelot T, et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2024;35:159-182.
38. Jagsi R, Chadha M, Moni J, et al. Radiation field design in the ACOSOG Z0011 (Alliance) Trial. *J Clin Oncol*. 2014;32:3600-3606.
39. Alkner S, Wieslander E, Lundstedt D, et al. Quality assessment of radiotherapy in the prospective randomized SENOMAC trial. *Radiother Oncol*. 2024;197:110372.
40. Byun HK, Park HS, Choi SH, et al. Excluding upper axillary level 1 in regional nodal irradiation does not increase axillary recurrence risk in patients with breast cancer. *Pract Radiat Oncol*. 2025;15:144-154.
41. DeSnyder SM, Yi M, Boccardo F, et al. American Society of Breast Surgeons' practice patterns for patients at risk and affected by breast cancer-related lymphedema. *Ann Surg Oncol*. 2021;28:5742-5751.
42. Kassamani YW, Brunelle CL, Gillespie TC, et al. Diagnostic criteria for breast cancer-related lymphedema of the upper extremity: The need for universal agreement. *Ann Surg Oncol*. 2022;29:989-1002.
43. Donahue PMC, MacKenzie A, Filipovic A, Koelmeyer L. Advances in the prevention and treatment of breast cancer-related lymphedema. *Breast Cancer Res Treat*. 2023;200:1-14.