Clinical and Translational Radiation Oncology 41 (2023) 100629

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Incorporating axillary-lateral thoracic vessel juncture dosimetric variables improves model for predicting lymphedema in patients with breast cancer: A validation analysis

Jee Suk Chang [a,1,*], Heejoo Ko [b,1], Sang Hee Im [c], Jin Sung Kim [a], Hwa Kyung Byun [a], Yong Bae Kim [a], Wonguen Jung [d], Goeun Park [e], Hye Sun Lee [e], Wonmo Sung [f], Robert Olson [g], Chae-Seon Hong [a], Kyubo Kim [d,*]

[a] Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Republic of Korea
[b] College of Medicine, The Catholic University of Korea, Republic of Korea
[c] Department and Research Institute of Rehabilitation Medicine, Severance Hospital, Yonsei University College of Medicine, Republic of Korea
[d] Department of Radiation Oncology, Ewha Womans University College of Medicine, Republic of Korea
[e] Biostatistics Collaboration Unit, Yonsei University College of Medicine, Republic of Korea
[f] Department of Biomedical Engineering and of Biomedicine & Health Sciences, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[g] British Columbia Cancer Agency - Centre for the North, Prince George, BC, Canada

ARTICLE INFO

Keywords:
Breast cancer
Lymphedema
Dose-volume histogram
ALTJ

ABSTRACT

Background: A relationship between the axillary-lateral thoracic vessel juncture (ALTJ) dose and lymphedema rate has been reported in patients with breast cancer. The purpose of this study was to validate this relationship and explore whether incorporation of the ALTJ dose-distribution parameters improves the prediction model's accuracy.

Methods: A total of 1,449 women with breast cancer who were treated with multimodal therapies from two institutions were analyzed. We categorized regional nodal irradiation (RNI) as limited RNI, which excluded level I/II, vs extensive RNI, which included level I/II. The ALTJ was delineated retrospectively, and dosimetric and clinical parameters were analyzed to determine the accuracy of predicting the development of lymphedema. Decision tree and random forest algorithms were used to construct the prediction models of the obtained dataset. We used Harrell's C-index to assess discrimination.

Results: The median follow-up time was 77.3 months, and the 5-year lymphedema rate was 6.8 %. According to the decision tree analysis, the lowest lymphedema rate (5-year, 1.2 %) was observed in patients with $\leq$ six removed lymph nodes and $\leq$ 66 % ALTJ V_{35Gy}. The highest lymphedema rate was observed in patients with $>$ 15 removed lymph nodes and an ALTJ maximum dose (D_{max}) of $>$ 53 Gy (5-year, 71.4 %). Patients with $>$ 15 removed lymph nodes and an ALTJ $D_{max} \leq$ 53 Gy had the second highest rate (5-year, 21.5 %). All other patients had relatively minor differences, with a rate of 9.5 % at 5 years. Random forest analysis revealed that the model's C-index increased from 0.84 to 0.90 if dosimetric parameters were included instead of RNI (P <.001).

Conclusion: The prognostic value of ALTJ for lymphedema was externally validated. The estimation of lymphedema risk based on individual dose-distribution parameters of the ALTJ seemed more reliable than that based on the conventional RNI field design.

Abbreviations: ALTJ, axillary-lateral thoracic vessel juncture; BMI, Body mass index; CI, Confidence interval; CTV, Clinical target volume; DVH, Dose volume histogram; ESTRO, European Society for Radiotherapy and Oncology; EQD2, Equivalent 2-Gy dose; HR, Hazard ratio; OAR, organs-at risk; RNI, Regional nodal irradiation; RT, Radiation therapy; RTOG, Radiation Therapy Oncology Group; 3D, Three-dimensional.

* Corresponding authors.
E-mail addresses: changjeesuk@yuhs.ac (J. Suk Chang), kyubokim.ro@gmail.com (K. Kim).

[1] J.S. Chang and H. Ko contributed equally and share first authorship.

https://doi.org/10.1016/j.ctro.2023.100629
Received 25 January 2023; Received in revised form 13 April 2023; Accepted 17 April 2023
Available online 20 April 2023

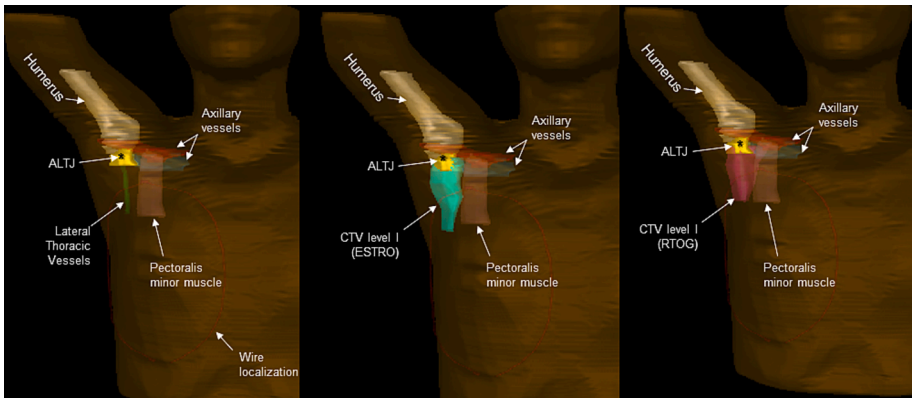


Fig. 1. Three-dimensional contour surface areas of the axillary-lateral thoracic vessel juncture (ALTJ)[10] in relation to surroundings and CTV of the axillary lymph node level I according to ESTRO and RTOG guidelines in a patient with right-sided breast cancer. The ALTJ is the anatomical junction where the lateral thoracic vein and the subscapular vein join the axillary vein. To contour the ALTJ, we first identified the axillary vein on the planning CT image, which typically begins at the lower border of the Teres major, crosses the axilla, and becomes the subclavian vein at the outer border of the first rib. We then identified the lateral thoracic vein, which runs diagonally along the bony thorax from the anterior to the lateral wall and is directed upwards into the axillary vein. The ALTJ is located superior to the axillary level I node basin and typically encompasses the junction of these veins, usually 1–3 cm in length. However, in some cases, the ALTJ may be overlapped with the CTV of the axillary lymph node level I.

Table 1
ALTJ dosimetric parameters converted into equivalent 2-Gy doses considering an α/β ratio of 3 Gy.

	Mean	SD	Median	IQR
ALTJ D_{max} (Gy)	24	19.2	24.5	2.6–43.8
ALTJ D_{mean} (Gy)	12.5	13.3	6.5	1.6–21.8
ALTJ D_{min} (Gy)	3.2	4.9	1.7	0.8–3.3
ALTJ V_{5Gy} (%)	43.7 %	42.2 %	33 %	0–93 %
ALTJ V_{10Gy} (%)	37.1 %	39.7 %	18 %	0–81 %
ALTJ V_{15Gy} (%)	32.1 %	37.4 %	10 %	0–70 %
ALTJ V_{20Gy} (%)	26.4 %	34.4 %	3 %	0–56 %
ALTJ V_{25Gy} (%)	20.7 %	31.3 %	0 %	0–37 %
ALTJ V_{30Gy} (%)	17.1 %	28.9 %	0 %	0–23.5 %
ALTJ V_{35Gy} (%)	14.2 %	26.5 %	0 %	0–14 %
ALTJ V_{40Gy} (%)	10.8 %	22.7 %	0 %	0–4.7 %
ALTJ V_{45Gy} (%)	4.9 %	14.6 %	0 %	0–0.1 %
ALTJ V_{50Gy} (%)	0.8 %	0.5 %	0 %	0–0 %

Abbreviations: ALTJ, axillary-lateral thoracic vessel juncture; SD, standard deviation; IQR: interquartile range; RNI, regional nodal irradiation; RT, radiation therapy.

1. Introduction

Regional nodal irradiation (RNI) was established to improve locoregional control and decrease the risk of subsequent distant metastasis and breast cancer mortality in patients with high-risk node-negative or node-positive breast cancer [1,2]. However, RNI is reportedly-one of the most important risk factors for lymphedema development [3], which causes pain and increased risk of cellulitis and can detrimentally affect a woman's career [4].

Meanwhile, the extent of the RNI field can predict lymphedema risk [5]. Namely, a more limited field that includes the coracoid process while excluding the humeral head laterally has been associated with a lower lymphedema risk compared with that for an extended field that includes the surgical neck of humerus. However, target volume contouring based on anatomical definitions is becoming standard beyond conventional field-based radiation therapy (RT) techniques [6] to individualize RT planning and optimize radiation dose distribution while minimizing doses to organs-at risk (OARs) [6]. Many recent studies have reported wide intra-institutional and inter-institutional variations in target volume contouring and RT planning in modern RT for breast cancer [7]. In real-world practice, a severe heterogeneity issue was reported in terms of RNI administration [7,8]. In patients who undergo breast RT using intensity-modulated radiotherapy, lymphedema risk estimation based on the lateral border of the RNI field is no longer in effect. These factors may partly explain the inconsistent findings regarding the extent of RT fields in a previous multi-institutional retrospective study [9].

In this context, Gross et al. demonstrated the axillary-lateral thoracic vessel juncture (ALTJ) as a potential OAR for lymphedema among eight distinct subaxillary regions [10], suggesting a possible dose–effect relationship with lymphedema. In the present study, we aimed to validate the previous results of a larger cohort study and determine whether the incorporation of the individual three-dimensional (3D) dose-distribution parameters of ALTJ improves the accuracy of multiparametric models.

2. Material and methods

2.1. Patient cohort

This study was approved by the institutional review boards of Severance Hospital and Ewha Womans University Mokdong Hospital, and the requirement for informed consent was waived. We identified patients diagnosed with non-metastatic breast cancer who underwent definitive treatment of the axilla with surgery and/or RT between 2012 and 2016. Patients with follow-up periods of <1 year, a history of other previous or concurrent malignancies, including contralateral breast cancer, or a history of lymphedema prior to the initiation of RT were excluded.

2.2. Radiation therapy

In Hospital A, RNI was generally indicated in patients with mastectomy with N2–3 disease, high-risk N1 disease, and/or T3–4 disease, and in patients with receiving breast-conservation who had N1–3 or high-risk N0 disease (e.g., medial tumors and/or multiple adverse features). The regions to which RNI was administered included the internal mammary, axillary, and supraclavicular lymph nodes. Prescribed doses to the regional nodes consisted of 50.4 Gy in 28 fractions, 40.05 Gy in 15 fractions, and 42.56 Gy in 16 fractions. Two tangential photons and an anterior photon beam with a single isocenter technique (3D-conformal radiation therapy) or volumetric modulated arc therapy with two partial arcs were used [11].

In Hospital B, RNI was generally indicated in patients with N2–3 disease regardless of surgery type during the study period. The regions that were subjected to RNI included the axillary and supraclavicular lymph nodes. The prescribed dose to the regional nodal area was 50.4 Gy in 28 fractions. The field arrangement generally consisted of two tangential photons for the whole breast/chest wall RT and/or anterior-posterior opposing photons for RNI.

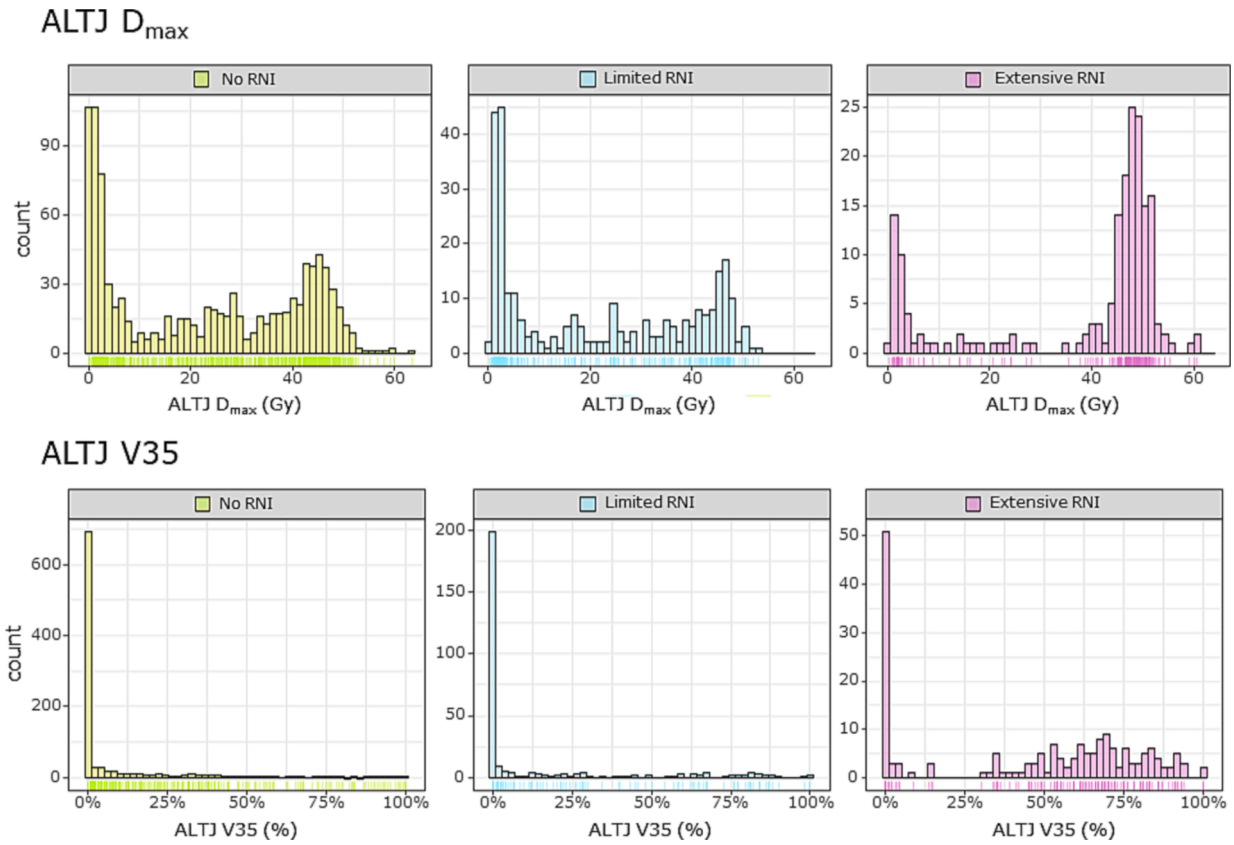


Fig. 2. Distribution of ALTJ D_{max} and ALTJ V35 stratified by RNI (no RNI vs limited RNI vs extensive RNI). Abbreviations: ALTJ, axillary-lateral thoracic vessel juncture; 3DCRT, 3-dimensional conformal radiation therapy; RT, radiation therapy; VMAT, volumetric modulated arc therapy; EQD2, equivalent 2-Gy dose considering an α/β ratio of 3 Gy; RNI, regional nodal irradiation.

2.3. ALTJ contouring

The ALTJ was delineated retrospectively by one experienced radiation oncologist from each participating hospital using the contouring suggestions published by Gross et al. in 2019 (Fig. 1) [10]. The ALTJ is defined as the region superior to the axillary level I lymph node basin and the cranial border below the lowest contour of the humeral head. In some patients whose arms were not fully abducted and externally rotated at the shoulder due to pain and sequelae from breast cancer surgery, we anatomically focused on the surrounding vessels rather than the location of the lowest contour of the humeral head. To minimize interobserver variability, cross-checks were periodically performed for randomly selected cases to ensure that the ALTJ was delineated in compliance with the consensus-based guideline.

According to the European Society for Radiotherapy and Oncology (ESTRO) atlas [12], the clinical target volume (CTV) axillary level 1 (CTVn_L1) should include the axillary vein with a 5-mm cranial margin, which leads to a larger target volume than that obtained with the Radiation Therapy Oncology Group (RTOG) CTV in the cranial direction. Hence, the ALTJ can be overlapped with the upper part of the ESTRO-based CTVn_L1 and the surrounding region can be located superior to the RTOG-based CTV axilla-level 1 simultaneously [6].

2.4. Lymphedema

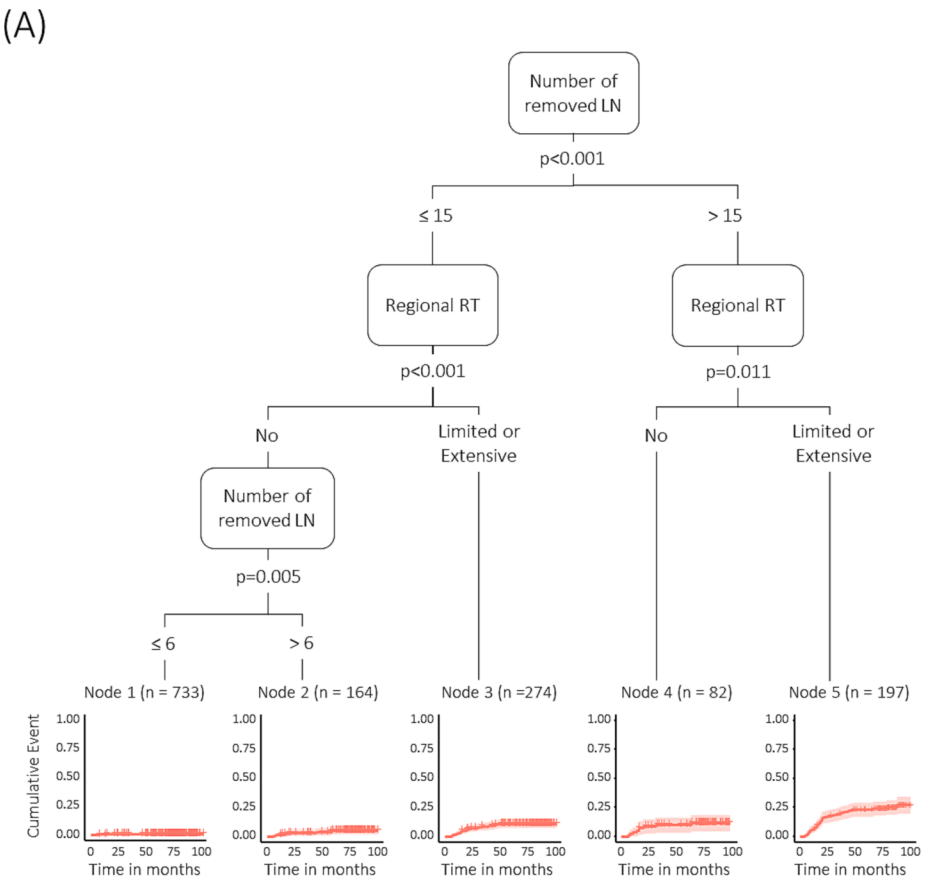
The primary endpoint was the cumulative incidence of symptomatic lymphedema, which was calculated from the date of initial breast cancer diagnosis to the date of lymphedema diagnosis using the Kaplan–Meier method. In general, lymphedema diagnoses were in accordance with the Clinical Guideline for the Diagnosis and Treatment of Lymphedema after Cancer Therapy from the Korean Society of Lymphedema [13]. Briefly, the diagnosis of lymphedema was made in consideration of both objective (circumference measurement, bioimpedance measurement, and/or lymphoscintigraphy) and subjective (symptoms and signs) assessments by rehabilitation expert clinicians.

2.5. Covariates

Five clinical parameters identified in our previous work [14] were collected as follows: body mass index (BMI; ≥ 25 vs < 25 kg/m^2), receipt of RNI (no vs limited vs extensive RNI), type of surgery (partial vs total mastectomy), number of lymph nodes removed (continuous variable), and receipt of chemotherapy (yes vs no). RNI volume was categorized as limited RNI, which excluded axillary level I/II, and extensive RNI, which included axillary level I-II. Thirteen dosimetric parameters of the ALTJ were collected using a dose volume histogram (DVH) that was converted into an equivalent 2-Gy dose (EQD2) to generalize the biological effectiveness related to each dose per fraction considering an α/β ratio of 3 Gy. The minimum, maximum, and mean doses in the ALTJ and the ratio of the volume of the ALTJ receiving more than X Gy (V_{XGy}) were considered candidate predictors for lymphedema (X = 5, 10, 15, 20, 25, 30, 35, 40, 45, and 50).

2.6. Analysis

Classification models using decision trees and random forests were constructed either by including five or four clinical parameters (excluding RNI) plus 13 dosimetric parameters. We used decision tree analysis to divide patients into subgroups based on the statistically significant cutoff values of variables within five maximum nodes. Decision trees were implemented to find an optimal prognostic model that accounted for interactions among other treatments and patient factors.



Node number	Total	Lymphedema (%)	5-year (%)	HR (95% CI)	p-value	Harrell's C-index	p-value of Log-rank test					
							Overall	1	2	3	4	5
1	733	7 (0.95)	1.0%	Ref		0.79	<.001	Ref				
2	163	8 (4.91)	5.1%	5.33 (1.93-14.70)	<.001			<.001	Ref			
3	274	29 (10.58)	10.7%	11.58 (5.08-26.44)	<.001			<.001	0.045	Ref		
4	82	9 (10.98)	11.3%	12.48 (4.65-33.50)	<.001			<.001	0.07	0.85	Ref	
5	197	49 (24.87)	27.2%	29.36 (13.30-64.81)	<.001			<.001	<.001	<.001	0.015	Ref

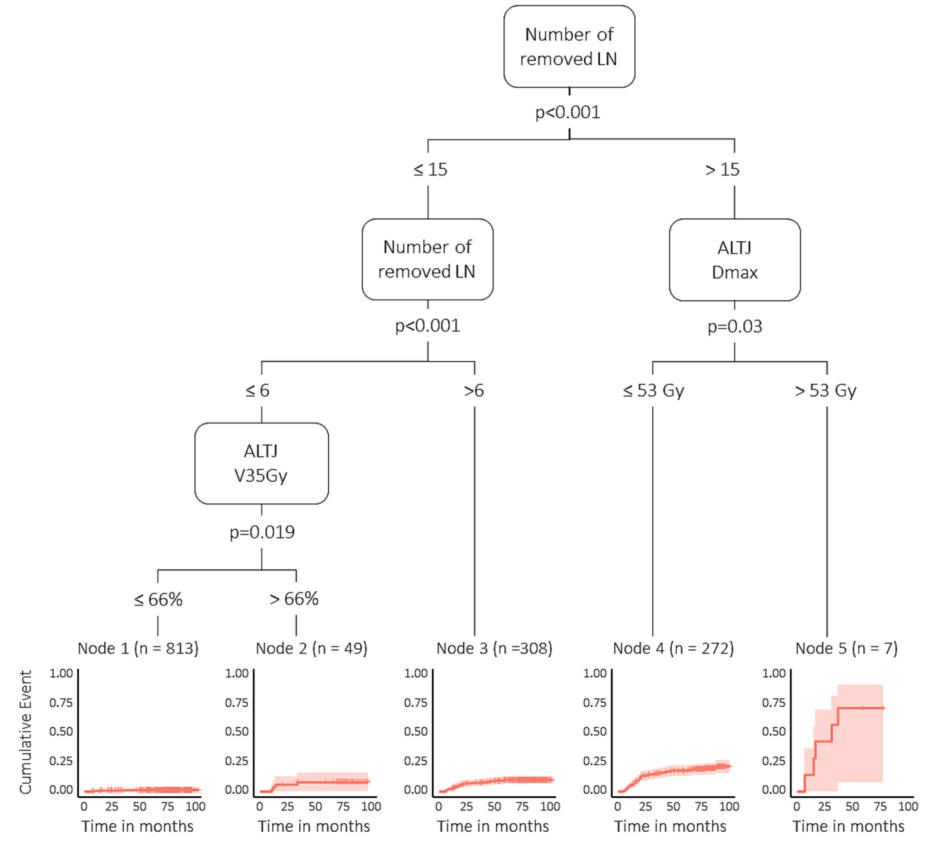
Fig. 3. Prediction models constructed using hierarchical classification and a regression tree for predicting 5-year lymphedema risk. (A) Model 1 included five clinical parameters as inputs: BMI ($\geq$25 vs $<$ 25 kg/m^2), RNI (no vs limited vs extensive RNI), type of surgery (partial vs total mastectomy), number of removed lymph nodes (continuous variable), and receipt of chemotherapy (yes vs no). (B) Model 2 included four clinical parameters (excluding RNI) and 13 ALTJ dosimetric parameters as inputs. Lymphedema risk was stratified into four risk categories computed from the five nodes from (A) Model 1 or (B) Model 2. (C) (D) Abbreviations: LN, lymph node; BMI, body mass index; ALTJ, axillary-lateral thoracic vessel juncture; HR, hazard ratio; CI, confidence interval; Ref, reference; RT, radiation therapy; RNI, regional nodal irradiation.

A random forest model consisting of 500 survival trees was generated to assess the importance of each variable for survival without lymphedema. Harrell's C-index was calculated with the bootstrapping method in the decision tree and random forest models. Next, we attempted to determine whether incorporating dose-volume metrics into the classification model could significantly increase the descriptive power. In addition, the cumulative risk of lymphedema for the different groups was estimated individually from the one minus Kaplan–Meier curves. Statistical analyses were conducted using R (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) and SAS (version 9.4, SAS Institute, Cary, NC, USA). *P* values $<$ 0.05 were considered statistically significant.

3. Results

This analysis included a total of 1,449 patients with histologically proven breast cancer who received multimodal therapies at two hospitals (977 and 472), as shown in Supplementary Table S1. The mean age of the patients was 51.9 $\pm$ 10.7 years, and the mean BMI was 23.3 $\pm$ 3.4 kg/m^2. Of the included patients, 23.9 % had node-positive disease, and axillary surgery involved the removal of six or fewer lymph nodes in 59.5 % of cases. RNI was used in 32.5 % of patients. The median follow-up time was 77.3 months (interquartile range, 70–85 months), and the cumulative incidence of lymphedema development was 6.8 % at 5 years. The median interval to lymphedema development was 17.5 months (interquartile range, 10.6–31.5 months). No significant difference was

(B)



Node number	Total	Lymphedema (%)	5-year (%)	HR (95% CI)	p-value	Harrell's C-index	p-value of Log-rank test Overall	1	2	3	4	5
1	813	10 (1.23)	1.2%	Ref		0.78	<.001	Ref				
2	49	4 (8.16)	8.2%	6.98 (2.19-22.26)	<.001			<.001	Ref			
3	308	30 (9.74)	10.0%	8.33 (4.07-17.04)	<.001			<.001	0.73	Ref		
4	272	53 (19.49)	21.5%	17.54 (8.92-34.47)	<.001			<.001	0.067	<.001	Ref	
5	7	5 (71.43)	71.4%	92.48 (31.52-271.36)	<.001			<.001	<.001	<.001	<.001	Ref

Fig. 3. (*continued*).

observed in 5-year lymphedema rates between the two hospitals (6.9 % [A] vs 6.5 % [B], P =.955). Cox proportional hazard analysis was conducted to determine the prognostic values of five clinical covariates, which were selected from our previous work. Number of removed lymph nodes (hazard ratio [HR] 1.05, 95 % confidence interval [CI] 1.03–1.07); RNI (limited vs no RNI: HR 3.27, 95 % CI 1.90–5.63 and extensive vs no RNI: HR 3.27, 95 % CI 1.83–5.86), and prior chemotherapy (HR 3.12, 95 % CI 1.29–7.53) were independent predictors for lymphedema development.

The mean ALTJ volume was 17.3 ± 6.1 cc. Various dosimetric parameters such as the mean, maximum, and minimum ALTJ doses and V_{5Gy}, V_{10Gy}, V_{15Gy}, V_{20Gy}, V_{25Gy}, V_{30Gy}, V_{35Gy}, V_{40Gy}, V_{45Gy}, and V_{50Gy} of ALTJ analyzed from the DVH are reported in Table 1. All metrics showed positive correlations, and the correlation coefficients decreased with increasing dose differences (e.g., V_{5Gy} and V_{50Gy}, Supplementary Figure S1). Significant differences were observed in dosimetric values according to the extent of RNI and RT techniques (Supplementary Table S2). Significant individual differences were also observed, as shown in Fig. 2.

3.1. Decision tree

Decision tree analysis was implemented to develop two models for the prediction of lymphedema development. Model 1, which included five clinical variables, comprised two variables (number of removed lymph nodes and RNI) with five nodes (Fig. 3A). Model 2, which included four clinical variables (excluding RNI) and 13 ALTJ dosimetric parameters, was constructed using three variables (number of removed lymph nodes, ALTJ V_{35Gy}, and maximum dose to ALTJ) with five nodes (Fig. 3B). According to the decision tree analysis, the lowest lymphedema rate (5-year, 1.2 %) was observed in patients with ≤ six removed lymph nodes with an ALTJ V_{35Gy} of ≤ 66 %. The highest lymphedema rate was seen in patients with > 15 lymph nodes removed, with an ALTJ maximum dose of > 53 Gy (5-year, 71.4 %). Patients with > 15 removed lymph nodes and an ALTJ maximum dose of ≤ 53 Gy had the second highest rate (5-year, 21.5 %). Relatively minor differences in lymphedema rates were observed in all the other patients, with a rate of 9.5 % at 5 years. Our dataset was split into four patient groups according to lymphedema risk, with significantly different survival curves in both models (Fig. 3C, D). No significant difference in discriminative power was observed between the two models (Harrell's C-index model 1: 0.79,

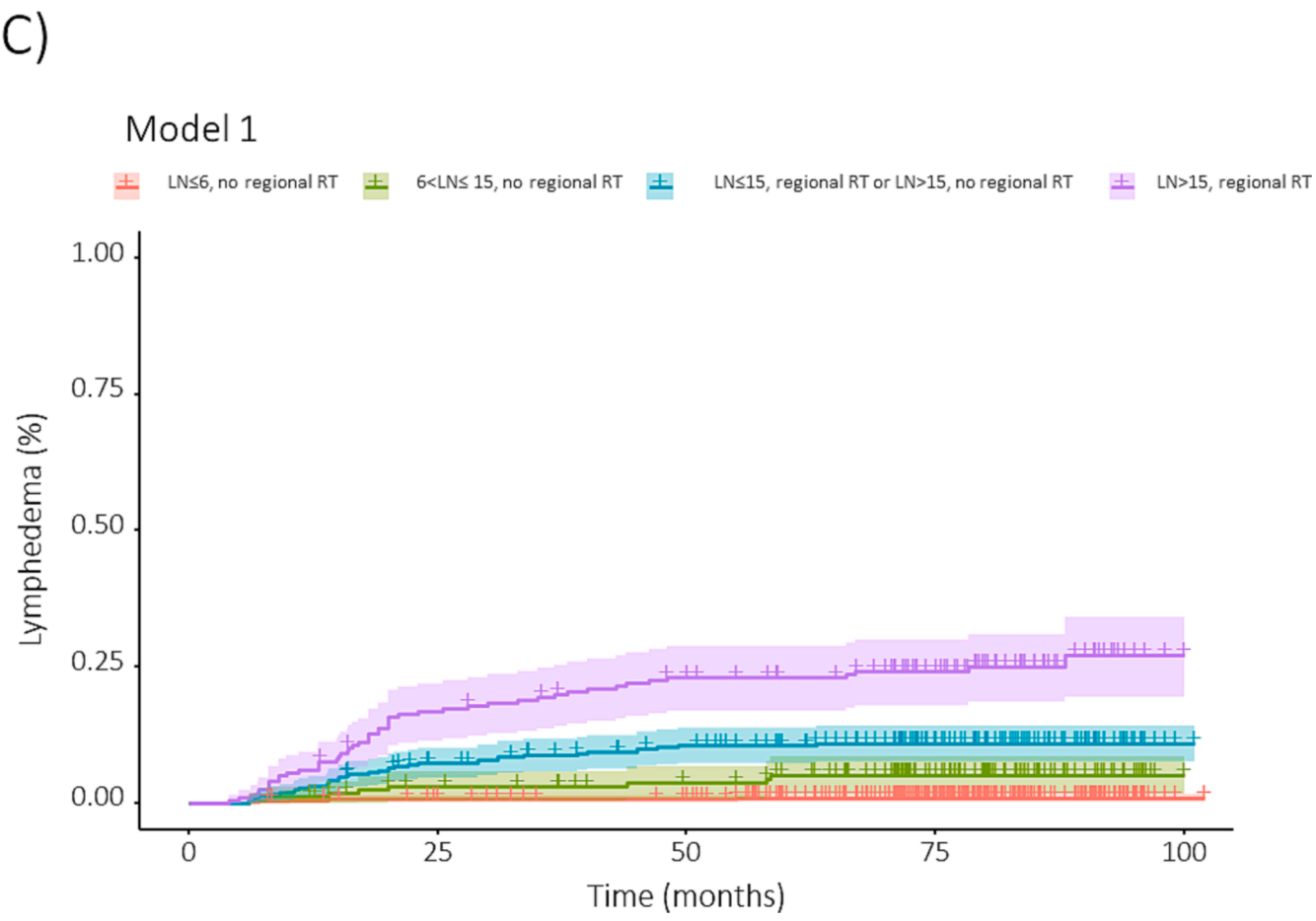


Fig. 3. (*continued*).

95 % CI [0.76–0.83] vs model 2: 0.78, 95 % CI [0.74–0.82], P =.288).

3.2. Random forest

Random survival forest analysis was implemented to develop two models for the prediction of lymphedema development. Model 2, which included four clinical parameters (excluding RNI) and 13 ALTJ dosimetric parameters, provided significantly higher C-index scores compared with model 1 (0.90, 95 % CI [0.87–0.92] vs 0.84, 95 % CI [0.81–0.87], P <.001). Fig. 4 illustrates the order of importance for all variables in the model. The number of removed lymph nodes was the most important predictor, while multiple parameters had similar levels of importance although less than one-third the importance of the extent of axillary surgery.

4. Discussion

In the present study, we successfully validated the previous finding first proposed by Gross et al. in 2019 in a large, multicenter, external dataset that the ALTJ is an OAR for lymphedema [10]. Although both multiparametric prediction models incorporating either RNI or dosimetric parameters as covariates showed similarly excellent accuracy, we showed that integrating the ALTJ dose-volume information into the model significantly increased the model's performance for predicting individual lymphedema risk. According to the decision tree model, an ALTJ V_{35Gy} of > 66 % was significantly associated with increased risk of lymphedema in patients with ≤ six removed lymph nodes, which could represent the population of patients who underwent sentinel lymph node biopsy. Our findings are clinically relevant as the findings of several recent trials have led to a shift in treatment from axillary node dissection to sentinel lymph node biopsy to prevent morbidity and improve quality of life while maintaining regional control and treatment outcomes in patients with only a few positive lymph nodes [1,15].

One of the key findings of the present study is that the multiparametric predictive model using ALTJ dosimetric parameters outperformed the model incorporating the conventional RNI field design (no vs limited vs extensive RNI). This implies that the volume of irradiated axillary tissue is more accurately reflected by individual 3D dose-volume information in the axilla compared with that for either the lateral border of the RNI field or intention to treat. In our study, a significant range of ALTJ dose-volume distributions were observed, although a correlation was observed between the RNI extent and ALTJ dose parameters. Interestingly, some patients had non-negligible rates of ALTJ dose-volume histograms, including patients who were not treated with RNI. This can be partly explained by variations in cranial borders of the tangential fields, whole breast target volumes, anatomy, and the angle of the patients' arm in the simulation set-up. In addition, the RT technique that used an additional posterior beam to cover the axillary area was associated with an increased ALTJ dose (Supplementary Table S2).

In the present study, decision tree and random forest analyses indicated that the number of removed lymph nodes is the most important factor in determining the overall lymphedema risk. This result corroborates the findings reported by Naoum et al., in which 1,815 patients

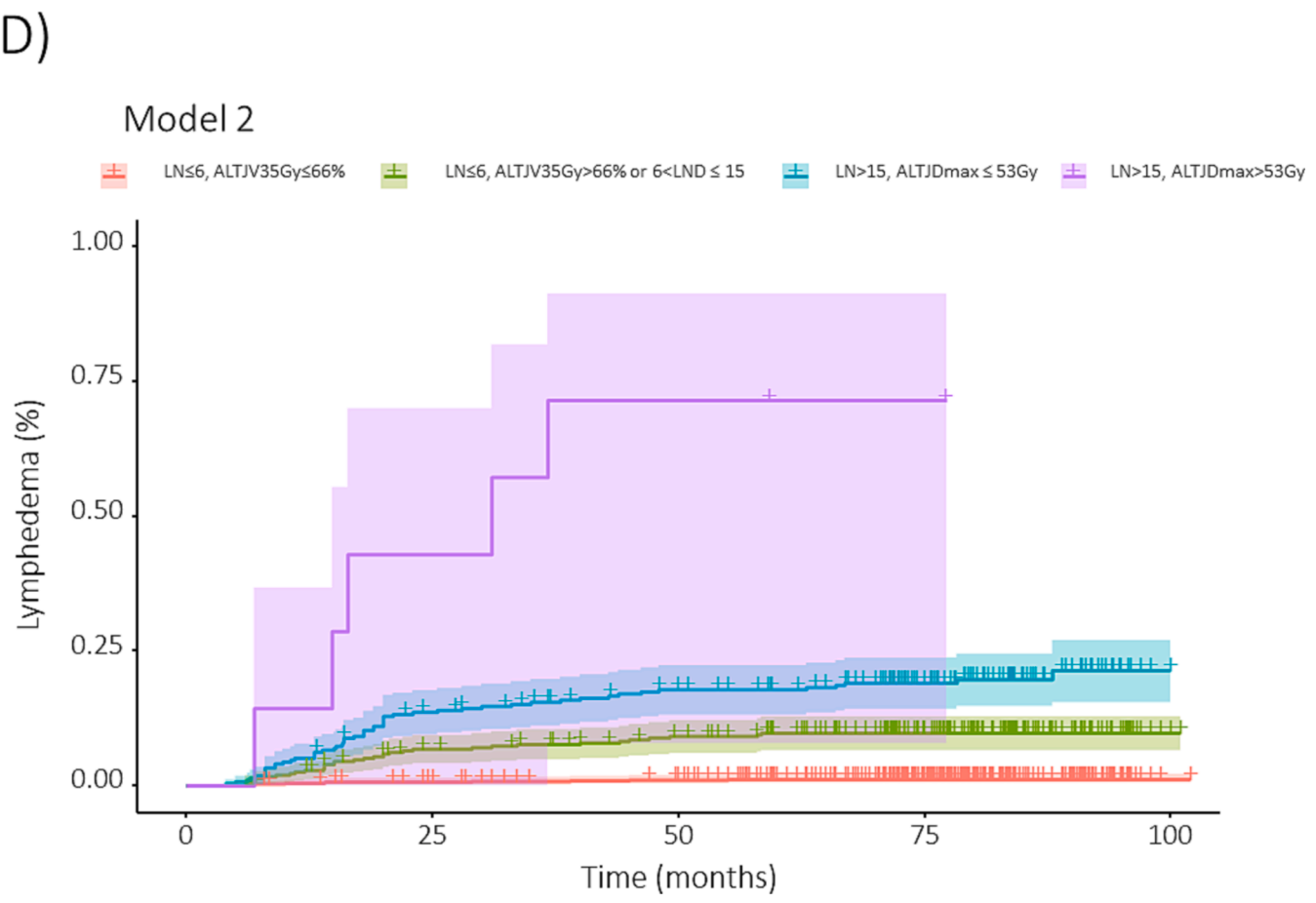
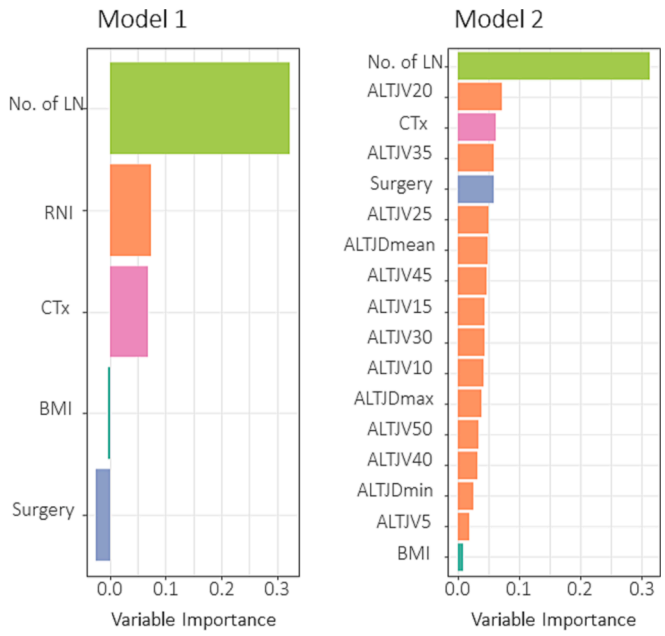


Fig. 3. (*continued*).

with breast cancer were prospectively and objectively assessed using a perometer in a longitudinal manner [16]. In our study, lymphedema risk was significantly lower when the ALTJ V_{35Gy} was $\leq$ 66 % and less than six lymph nodes were removed, whereas its risk was significantly higher when the ALTJ maximum dose was $>$ 53 Gy and$<$15 lymph nodes were removed. This implies that the interaction between ALTJ dose parameters and lymphedema risk appears to be influenced by the surgical extent. Our V35 value is somewhat similar to that previously reported by Gross et al. (D_{min} $<$ 36.8 Gy) [10]. However, the difference between these values may be due to the fact that only four patients in our cohort had an ALTJ $D_{min} \geq$ 36.8 Gy. This finding may suggest that the extent of RNI in our cohort is relatively less extensive than in Gross et al.'s study. Further validation studies with larger sample sizes from multiple centers are necessary to establish optimal cutoff values.

This study had several limitations. First, the alpha/beta ratio of lymphedema was assumed to be 3, despite the uncertainty associated with different fractionation schemes [17] that might be associated with the development of lymphedema. Regarding this issue, a phase 3 trial, HYPOG-01 (NCT03127995), is underway to compare a 3-week versus 5-week schedule for locoregional breast RT with the primary endpoint of arm lymphedema [18]. Second, owing to the definition of lymphedema [19] and the retrospective nature of this study, lymphedema rates can be underestimated in cases of asymptomatic lymphedema. Although the definition of lymphedema varies across studies, both subjective and objective findings in longitudinal prospective evaluations should be incorporated in the future [20]. Furthermore, while a recent large cohort study of 5900 mastectomy patients showed a protective effect of immediate breast reconstruction in the development of lymphedema [21], our study cohort, which included only 291 mastectomy patients (20 % of the total population), was limited in its ability to evaluate the impact of reconstruction. Similarly, our study was limited in its ability to analyze the influence of systemic treatment on lymphedema development. Thus, a separate study including only patients who underwent systemic treatment is ongoing. Finally, because this study was conducted with a dataset including only young Asians with a relatively low BMI, further validation might be needed in patients of another ethnicity. Lymphatic drainage in the arm may vary among patients; thus, individual imaging of the lymphatic system, including lymphatic vessel anatomy, might be an ideal approach [22]. Since none of the plans provided full-dose coverage to regional nodes in the MA.20, EORTC, AMAROS, or Z11 trials [23], we believe sparing the dose to the ALTJ could reduce the risk of lymphedema without increasing marginal recurrence, and can therefore be the focus of future research.

In conclusion, ALTJ dose-volume parameters were independently associated with lymphedema risk, although the number of lymph nodes dissected was the most important factor. Our findings suggest that estimation of lymphedema risk based on individual dose-distribution parameters of the ALTJ are more reliable than that using the conventional method. The model for predicting the probability of normal tissue-associated complications was developed and validated in a separate study [24].



	Harrell's C-index	p-value
Model 1	0.84 (0.81-0.88)	Ref
Model 2	0.90 (0.87-0.92)	<.001

Fig. 4. Selected predictors of development of lymphedema ranked by variable importance measure in each random forest model and comparison of prediction performance. Model 1 included five clinical parameters as inputs: BMI ($\geq$25 vs $<$ 25 kg/m^2), RNI (no vs limited vs extensive RNI), type of surgery (partial vs total mastectomy), number of removed lymph nodes (continuous variable), and receipt of chemotherapy (yes vs no). Model 2 included four clinical parameters (excluding RNI) and 13 ALTJ dosimetric parameters as inputs. Abbreviations: ALTJ, axillary-lateral thoracic vessel juncture; LN, lymph nodes removed; RT, radiation therapy; CTx, chemotherapy; BMI, body mass index; Ref, reference; RNI, regional nodal irradiation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

Presented at the 64th Annual Meeting of the American Society for Radiation Oncology, San Antonio, TX, October 23, 2022.

Funding

This study was supported by a faculty research grant from Yonsei University College of Medicine (No. 6–2021-0233) and a National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2019R1C1C1009359).

Ethical Approval

This study was approved by the institutional review boards of Severance Hospital (4–2022-0089) and Ewha Womans University Mokdong Hospital (2021–01-038), and the requirement for informed consent was waived.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2023.100629.

References

[1] Poortmans PM, Weltens C, Fortpied C, Kirkove C, Peignaux-Casasnovas K, Budach V, et al. Internal mammary and medial supraclavicular lymph node chain irradiation in stage I-III breast cancer (EORTC 22922/10925): 15-year results of a randomised, phase 3 trial. Lancet Oncol 2020;21:1602–10.
[2] Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med 2015;373:307–16.
[3] McLaughlin SA, Brunelle CL, Taghian A. Breast Cancer-Related Lymphedema: Risk Factors, Screening, Management, and the Impact of Locoregional Treatment. J Clin Oncol 2020;38:2341–50.
[4] Vignes S, Fau-Prudhomot P, Simon L, Sanchez-Brechot ML, Arrault M, Locher F. Impact of breast cancer-related lymphedema on working women. Support Care Cancer 2020;28:79–85.
[5] Gross JP, Sachdev S, Helenowski IB, Lipps D, Hayes JP, Donnelly ED, et al. Radiation Therapy Field Design and Lymphedema Risk After Regional Nodal Irradiation for Breast Cancer. Int J Radiat Oncol Biol Phys 2018;102:71–8.
[6] Loganadane G, Truong PT, Taghian AG, Tesanovic D, Jiang M, Geara F, et al. Comparison of Nodal Target Volume Definition in Breast Cancer Radiation Therapy According to RTOG Versus ESTRO Atlases: A Practical Review From the TransAtlantic Radiation Oncology Network (TRONE). Int J Radiat Oncol Biol Phys 2020;107:437–48.
[7] Ciardo D, Argenone A, Boboc GI, Cucciarelli F, De Rose F, De Santis MC, et al. Variability in axillary lymph node delineation for breast cancer radiotherapy in presence of guidelines on a multi-institutional platform. Acta Oncol 2017;56:1081–8.
[8] Belkacemi Y, Kuten A. RE: Regional Nodal Irradiation After Breast-Conserving Surgery for Early HER2-Positive Breast Cancer: Results of a Subanalysis From the ALTTO Trial. J Natl Cancer Inst 2018;110:539–40.
[9] Byun HK, Kim JS, Chang JS, Cho Y, Ahn SJ, Yoon JH, et al. Validation of a nomogram for predicting the risk of lymphedema following contemporary treatment for breast cancer: a large multi-institutional study (KROG 20–05). Breast Cancer Res Treat 2022;192:553–61.
[10] Gross JP, Lynch CM, Flores AM, Jordan SW, Helenowski IB, Gopalakrishnan M, et al. Determining the Organ at Risk for Lymphedema After Regional Nodal Irradiation in Breast Cancer. Int J Radiat Oncol Biol Phys 2019;105:649–58.
[11] Kim N, Chang JS, Shah C, Shin H, Keum KC, Suh CO, et al. Hypofractionated volumetric-modulated arc therapy for breast cancer: A propensity-score-weighted comparison of radiation-related toxicity. Int J Cancer 2021;149:149–57.
[12] Offersen BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Biete Sola A, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. Radiother Oncol 2015;114:3–10.
[13] Korean Society of Lymphedema. Clinical Guideline for the Diagnosis and Treatment of Lymphedema after Cancer Therapy 2022.
[14] Byun HK, Chang JS, Im SH, Kirova YM, Arsene-Henry A, Choi 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;274:170–8.
[15] Giuliano AE, Ballman K, McCall L, Beitsch P, Whitworth PW, Blumencranz P, et al. Locoregional Recurrence After Sentinel Lymph Node Dissection With or Without Axillary Dissection in Patients With Sentinel Lymph Node Metastases: Long-term Follow-up From the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 Randomized Trial. Ann Surg 2016;264:413–20.
[16] Naoum GE, Roberts S, Brunelle CL, Shui AM, Salama L, Daniell K, 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;38:3430–8.
[17] McDuff SGR, Mina AI, Brunelle CL, Salama L, Warren LEG, Abouegylah M, et al. Timing of Lymphedema After Treatment for Breast Cancer: When Are Patients Most At Risk? Int J Radiat Oncol Biol Phys 2019;103:62–70.

[18] Rivera S, Brion T, Kirova Y, Racadot S, Benchalal M, Clavier JB, et al. 121MO Acute toxicity associated with a 3-week versus a standard 5-week regimen for locoregional breast radiotherapy delivered in the UNICANCER HypoG-01 phase III trial. Ann Oncol 2021;32:S409–10.
[19] Ancukiewicz M, Russell TA, Otoole J, Specht M, Singer M, Kelada A, et al. Standardized method for quantification of developing lymphedema in patients treated for breast cancer. Int J Radiat Oncol Biol Phys 2011;79:1436–43.
[20] Kassamani YW, Brunelle CL, Gillespie TC, Bernstein MC, Bucci LK, Nassif T, 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.
[21] Jeon HB, Jung JH, Im SH, Kim YB, Chang JS, Song SY, et al. Association between Immediate Breast Reconstruction and the Development of Breast Cancer-Related Lymphedema. Plast Reconstr Surg 2023;151:214e–e222.
[22] Boneti C, Korourian S, Bland K, Cox K, Adkins LL, Henry-Tillman RS, et al. Axillary reverse mapping: mapping and preserving arm lymphatics may be important in preventing lymphedema during sentinel lymph node biopsy. J Am Coll Surg 2008; 206:1038-42; discussion 42-4.
[23] Borm KJ, Oechsner M, Dusberg M, Buschner G, Weber W, Combs SE, et al. Irradiation of regional lymph node areas in breast cancer - Dose evaluation according to the Z0011, AMAROS, EORTC 10981–22023 and MA-20 field design. Radiother Oncol 2020;142:195–201.
[24] Park YI, Chang JS, Ko H, Im SH, Kim JS, Byun HK, et al. Development and Validation of a Normal Tissue Complication Probability Model for Lymphedema After Radiation Therapy in Breast Cancer. Int J Radiat Oncol Biol Phys 2023. https://doi.org/10.1016/j.ijrobp.2023.01.056.