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PHYSICS CONTRIBUTION

Development and Validation of a Normal Tissue Complication Probability Model for Lymphedema After Radiation Therapy in Breast Cancer

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Purpose: To develop and test a multivariable normal tissue complication probability (NTCP) model predicting lymphedema in patients with breast cancer receiving radiation therapy.

Methods and Materials: We retrospectively reviewed 1345 patients with breast cancer who received radiation therapy from 2 independent institutions. The patients were divided into a training cohort (institution A, n = 368, all treated with 3-dimensional conformal external beam radiation therapy [RT] with 2 Gy/fraction) and an external validation cohort (institution B, n = 977, treated either with 3-dimensional conformal external beam RT or with volumetric modulated RT and either with 1.8-2.0 Gy/fraction or with 2.67 Gy/fraction). Axillary−lateral thoracic vessel juncture (ALTJ) was delineated. The multivariable model was generated using dosimetric and clinical parameters. The performance of the model was comprehensively validated internally and externally.

Results: During a median follow-up of 78.7 months for the entire cohort, 97 patients (7.2%) developed lymphedema. The multivariable model that took into account the number of lymph nodes dissected, as well as the volume of the ALTJ receiving a dose ≥35 Gy equivalent doses in 2-Gy fractions (ALTJ V35), showed good agreement between predicted and observed results for both internal and external validation (Hosmer−Lemeshow P value > .05). The area under the receiver operating characteristic curve (AUC) and negative log-likelihood values for the multivariable NTCP model were 0.89 and 0.19 in internal validation and 0.83 and 0.19 in external validation. In addition, the multivariable model performance was acceptable for hypofractionated regimens (AUC 0.70) and volumetric modulated arc therapy (AUC 0.69). The number of lymph nodes dissected and ALTJ V35 were found to be the most important factors influencing lymphedema after radiation therapy.

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Conclusions: We first developed and validated the multivariable NTCP model for the lymphedema incidence in patients with breast cancer after radiation therapy. The multivariable NTCP model showed excellent performance and robustness in predicting lymphedema in both internal and completely independent external validations. The multivariable model for lymphedema prediction was robust and reliable for different treatment modalities and fractionation regimens.

Introduction

Breast cancer is the most frequently diagnosed cancer in women, and given the favorable clinical outcome as the current standard of care, there is an increasing emphasis on reducing late toxicities.[1] Lymphedema of the arms is one of the common toxicities in patients receiving radiation therapy (RT) for breast cancer.[2] This can negatively affect the patient's quality of life and, in severe cases, lead to treatment discontinuation.[3]

Previous studies have been confirmed that risk factors including regional nodal irradiation (RNI) and the number of axillary lymph node dissections are associated with the development of lymphedema.[4-7] In particular, dosimetric parameters are controlled variables for toxicity mitigation in radiation therapy. By identifying and avoiding the anatomic region associated with lymphedema, radiation-induced toxicity can potentially be minimized. Gross et al[8] suggested the axillary−lateral thoracic vessel junction (ALTJ) as an organ at risk associated with an increased risk of lymphedema with RT. ALTJ minimum dose (<38.6 Gy) was the most significant dosimetric parameter associated with lymphedema risk. Our recent study successfully validated that increased dose to ALTJ was associated with greater rates of lymphedema for patients with breast cancer.[9]

Although the anatomic region and dosimetric predictor related to lymphedema development have been identified, it is difficult to effectively guide dose constraints for lymphedema only by finding the risk factors. A normal tissue complication probability (NTCP) model using dose-volume histogram (DVH) parameters and the clinical risk factors is needed to predict a lymphedema level for patients who undergo RT. NTCP prediction can guide reasonable ALTJ dose constraint in an attempt to prevent the development of, as well as to evaluate the likelihood of developing, lymphedema. However, to the best of our knowledge, no NTCP model for lymphedema in patients with breast cancer has yet been reported. Therefore, our goal was to characterize the prediction of lymphedema as a function of the dose-volume of ALTJ.

In this study, we developed the first reliable NTCP model using a cohort of the previous study[9] to predict the lymphedema risk in patients with breast cancer who received RT. A novel logistic regression NTCP model was developed that optimizes risk prediction by combining clinical and dosimetric parameters. Internal validation and independent external validation were then carried out to evaluate the performance of the developed model.

Methods and Materials

Patient and treatment characteristics

This study was approved by the institutional review board of each participating center, and informed consent was waived, given the retrospective study design. A total of 1362 consecutive patients who received a diagnosis of nonmetastatic breast cancer who underwent treatment of the axilla with surgery and RT between 2012 and 2016 were enrolled from 2 independent centers. Patients with a previous history of malignancy, including contralateral breast cancer, or follow-up of <1 year were excluded. A few patients who developed lymphedema before initiating RT (n = 8) or <3 months after surgery (n = 11) were excluded from the analysis.[10] Finally, 1345 eligible patients were included in this analysis. We divided patients into a training cohort (n = 368 in institution A) and an external validation cohort (n = 977, from group 1 and group 2 in institution B).

Treatment plans for all patients were generated using a 3-dimensional (3D) treatment planning system. All patients from institution A were selected for a training cohort because they were homogeneously treated with 3D conformal radiation therapy (3DCRT) in conventional dose-fraction (a total dose of 50 Gy in 25 fractions, followed by a tumor bed dose of 10 Gy in 5 fractions). Patients in the external validation cohort, institution B, were treated with 3DCRT or volumetric modulated arc therapy (VMAT) via either conventional fractionated (CF) (1.8-2.0 Gy per fraction) or hypofractionated (HF) regimen. Hypofractionated RT used 2-dose prescription levels: 40.05 Gy in 15 fractions (2.67 Gy per fraction) and 42.56 Gy in 16 fractions (2.67 Gy per fraction). All patients were treated in the supine position with the ipsilateral arm elevated above the head on an inclined breast board or customized immobilization device. Patient and treatment characteristics are detailed in Table 1.

Lymphedema

The primary endpoint was the development of lymphedema after RT. The diagnosis of lymphedema followed the Clinical Guideline for the Diagnosis and Treatment of Lymphedema after Cancer Therapy from the Korean Society of Lymphedema.[11] Consequently, lymphedema development was diagnosed by rehabilitation expert clinicians considering both objective (circumference measurement, bioimpedance measurement, and/or lymphoscintigraphy) and

Table 1 Patient and treatment characteristics for all patients in this cohort

	Institution A (n = 368)	Institution B		
		Group 1	Group 2	
		CF-3DCRT (n = 280)	HF-3DCRT (n = 428)	HF-VMAT (n = 269)
BMI (kg/m^2)	23.4 (21.5-25.4)	23.0 (21.0-25.0)	22.7 (20.9-25.1)	23.1 (20.9-25.4)
Surgery				
Partial mastectomy	347 (94.3%)	237 (84.6%)	388 (90.7%)	181 (67.3%)
Total mastectomy	21 (5.7%)	43 (15.4%)	40 (9.3%)	88 (32.7%)
LNDno	6 (3-13)	4 (3-10)	4 (2-8)	7 (4-16)
Chemotherapy				
No	271 (73.6%)	191 (68.2%)	312 (72.9%)	146 (54.3%)
Yes	97 (26.4%)	89 (31.8%)	116 (27.1%)	123 (45.7%)
RT field				
B/CW only	260 (70.7%)	184 (65.7%)	312 (72.9%)	118 (43.9%)
B/CW + axillary level II-III	108 (29.3%)	47 (16.8%)	107 (25.0%)	133 (49.4%)
B/CW + axillary level I-III		49 (17.5%)	9 (2.1%)	18 (6.7%)
Follow-up time (month)	79.2 (72.6- 85.9)	84.2 (71.5- 90.5)	78.3 (71.0- 85.4)	75.4 (69.0- 81.5)
Lymphedema event	28 (7.6%)	20 (7.1%)	27 (6.3%)	22 (8.2%)

Continuous variables are shown as the median and interquartile range (IQR), and categorical variables are shown in the number and percentage.
Abbreviations: 3DCRT = 3-dimensional conformal radiation therapy; B/CW = breast/chest wall; BMI = body mass index; CF = conventional fractionated; HF = hypofractionated; LNDno = number of lymph node dissected; VMAT = volumetric modulated arc therapy.

subjective (patient's symptoms and signs) assessments. Furthermore, the predefined endpoints were periodically reviewed and cross-checked to ensure consistent and high-quality endpoint evaluation.

Clinical and dosimetric parameters

A total of 5 clinical and 13 dosimetric parameters were considered initially in the current study. The following clinical parameters were considered as prognostic factors for lymphedema: body mass index (BMI), use of RNI, type of surgery, use of chemotherapy, and the number of lymph nodes dissected (LNDno).

The dosimetric parameters of the ALTJ along with the clinical parameters were included in the analysis. The ALTJs were manually delineated retrospectively in all patients at the institution by one experienced radiation oncologist from each participating institution according to the consensus-based guideline. ALTJ delineation was based on previously published suggestions by Gross et al.[8] Consensus-based guidelines were finally generated after the consistency and differences of ALTJ delineations between institutions were fully discussed. In addition, 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. DVHs of the ALTJ were extracted from the treatment planning system for data analysis. Because the external validation cohort included patients treated with the HF regimen, DVHs were converted into equivalent doses in 2-Gy fractions (EQD2) considering an α/β ratio of 3 Gy[12,13] to correct for different fractionation regimens. The EQD2-corrected dosimetric parameters for ALTJ used included the maximum dose (Dmax), minimum dose (Dmin), mean dose (Dmean), and V5 (percentage of the ALTJ volume receiving at least 5 Gy), V10, V15, V20, V25, V30, V35, V40, V45, and V50.

Parameter selection and multivariable NTCP model

The logistic regression model was applied to generate a multivariable risk model combining clinical and dosimetric predictors. Clinical predictors with nonbinary values, BMI and LNDno, were simplified into 2 groups each according to a cut-off value estimated from univariate logistic regression. All risk predictor variables with a P value <.05 in the univariate analysis were considered candidate variables to be used in developing the multivariable logistic regression model. To select the optimal combination of input variables for the multivariable logistic model, we used stepwise forward feature selection with the Akaike information criterion (AIC). Subsets of variables were generated by adding one variable at a time in each step of forward selection. Input variables that were highly correlated with other variables were excluded during stepwise feature selection to reduce redundancy. In each step of forward selection, the AIC score was

calculated for every subset of variables with Spearman correlation coefficient <0.9 to select the optimal subset for predicting lymphedema. The subset of variables with the lowest AIC score was selected for developing the multivariable NTCP model.[14] Eligible patients in the training cohort (institution A) were randomly divided into a subtraining cohort (80%) and an internal validation cohort (20%), with no significant difference between the 2 cohorts (Mann−Whitney *U* test, $P > .05$).

Statistical analysis and performance evaluation

To evaluate the performance of multivariable NTCP, we calculated area under the receiver operating characteristic curve (AUC) from receiver operating characteristic and normalized negative log-likelihood (NLL), $NLL = \frac{1}{N}\sum_{i=1}^{N}(y_i \log(p_i) + (1-y_i)\log(1-p_i))$, where y is observed outcome, P is predicted risk, and N is number of patients. Model with high prediction performance gain high AUC closer to 1, and low NLL.

Furthermore, the calibration performance of the developed model was assessed using the Hosmer−Lemeshow (HL) goodness-of-fit test[15] and calibration plot. From the HL test, P value > .05 indicates the model was reasonably calibrated, with no statistical deviants between observed incidence and predicted outcome. The calibration plot displayed model predictions versus observed lymphedema in patient subsets. Kaplan−Meier method was used to analyze the cumulative incidence of lymphedema between patient groups categorized by risk predictors selected from the logistic model. The cumulative incidence of lymphedema was calculated from the date of surgery to the date of lymphedema diagnosis.

Both internal and external validations were performed to evaluate the performance of the developed model. The internal validation of the model was assessed from the validation cohort at institution A. External validation of the model was performed in an independent cohort at institution B. The external validation cohort included 3 different RT regimens: CF-3DCRT, HF-3DCRT, and HF-VMAT.

Results

Patients

A total of 1345 patients with breast cancer who received RT at 2 different institutions were included in this study. In total, 368 patients treated with CF-3DCRT at institution A were applied to model development. They were assigned randomly into a training set of 293 patients (80%) and a validation set of 75 patients (20%). In the external validation cohort (institution B) of 977 patients, 280 and 428 patients were treated with CF-3DCRT and HF-3DCRT, respectively. In addition, there were 269 patients treated with HF-VMAT. The median follow-up months were 79.2 (72.6-85.9) in institution A and 78.4 (70.9-86.2) in institution B. Incidence of lymphedema was 7.6% in institution A (28/368 patients), and 7.1% in institution B (69/977 patients). Patient characteristics are shown in Table 1.

Parameter selection and development of the NTCP model

The univariate analysis for clinical parameters demonstrated that the development of lymphedema was associated with LNDno, chemotherapy, and RNI. The LNDno was classified into 2 groups based on an optimum cut-off value of 10. All DVH parameters except Dmin were significantly associated with the development of lymphedema (Tables E1 and E2, and Fig. E1). A total of 15 risk predictors (3 clinical and 12 dosimetric parameters) were used as initial parameters in forward stepwise variable selection. Two risk predictors, LNDno and V35, were selected as the optimal subset with the minimum AIC value for developing the multivariable logistic model (Fig. E2).

Figure 1 shows the multivariable NTCP model ($NTCP_{logit}$) for lymphedema based on logistic regression. The final NTCP model using 2 highly predictive variables, LNDno and V35, was generated as follows:

$$NTCP_{logit} = \frac{1}{1 + e^{-S}}$$

$$S = 1.25 \times V35 + 1.85 \times LND_{no} - 3.97$$

where V35 is the relative percentage of ALTJ volume receiving 35 Gy (range, 0-1), and LNDno is a binary variable

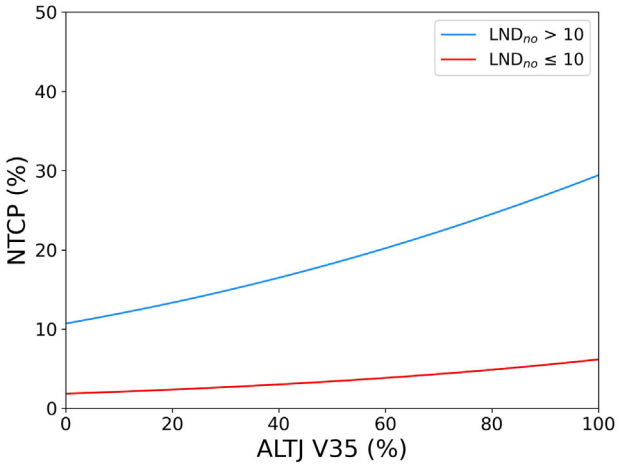

Fig. 1. The multivariable NTCP model for lymphedema. NTCP curves are plotted against ALTJ V35. Patients were categorized as patients with LNDno >10 (blue line) and LNDno ≤10 (red line). *Abbreviations:* ALTJ = axillary thoracic vessel juncture; ALTJ V35 = the volume of the ALTJ receiving a dose ≥35 Gy EQD2; EQD2 = equivalent doses in 2-Gy fractions; LNDno = number of lymph nodes dissected; NTCP = normal tissue complication probability.

Table 2 Overview of the performance evaluation metrics for the multivariable NTCP model

	Multivariable NTCP		
Validation	**AUC**	**NLL**	**HL *P* value**
Internal			
CF-3DCRT (n = 75)	0.89	0.19	.52
External			
CF-3DCRT (n = 281)	0.83	0.19	.24
HF-3DCRT (n = 430)	0.70	0.23	.11
HF-VMAT (n = 270)	0.69	0.20	.09

Abbreviations: 3DCRT = 3-dimensional conformal radiation therapy; AUC = area under the receiver operating characteristic curve; CF = conventional fractionated; HF = hypofractionated; HL = Hosmer−Lemeshow; NLL = normalized negative log-likelihood; NTCP = normal tissue complication probability; VMAT = volumetric modulated arc therapy.

expressed as over or under the cutoff (1 is taken as over, 0 is taken as under).

Performance evaluation

The predictive performance of the multivariable NTCP model was evaluated using a validation set and summarized in Table 2. The AUC and NLL values for the multivariable NTCP model were 0.89 and 0.19 in internal validation and 0.83 and 0.19 in external validation. The HL test between model outcome and detected lymphedema shows acceptable goodness-of-fit in both internal and external validation (*P* values .52 and .24, respectively). The model's receiver operating characteristic curves for CF-3DCRT patients are described in Fig. E3.

Calibration plots of the NTCP model are shown in Fig 2. In the calibration plots of the multivariable model, the predicted and observed ratio was located near the y = x line, which revealed a good calibration. The robustness of the model for different treatment modalities and fractionation regimens was validated in the external validation cohort. The multivariable NTCP model showed no significant deviation between the predicted and observed risk in patients who underwent 3DCRT or VMAT with the hypofractionated regimen (see Fig. 2).

Patients were classified as 3 risk categories in the entire cohort at institution A for simplified patient stratification: high-risk (LNDno >10 and ALTJ V35 >39.9%), moderate risk (LNDno >10 and ALTJ V35 ≤39.9% or LNDno ≤10 and ALTJ V35 >39.9%), and low risk (LNDno ≤10 and ALTJ V35 ≤39.9%). The 3-year cumulative incidence of lymphedema for the high-, moderate-, and low-risk groups was 18.7% (95% confidence interval [CI], 12.7%-30.5%), 5.9% (95% CI, 2.3%-15.1%), and 0.5% (95% CI, 0.0%-3.2%), respectively. The 5-year cumulative incidence was 25.0% (95% CI, 16.9%-36.1%), 5.9% (95% CI, 2.3%-15.0%), and 0.9% (95% CI, 0.2%-3.7%) in the high, moderate, and low-risk groups, respectively (Fig. 3). The lymphedema risk was significantly greater in high-risk patients with both LNDno and V35 exceeding cutoff values ($P < .001$).

Discussion

Breast cancer−related lymphedema can deeply affect a patient's long-term quality of life. Therefore, guidance strategies are required to identify and prevent high-risk patients from the treatment planning process. In this study, we developed the first NTCP model to predict the incidence of lymphedema in patients with breast cancer who received RT. We analyzed a cohort of 1345 patients retrospectively to establish a multivariable NTCP model, and the model performance was validated on internal and independent external validation cohorts. Consequently, the multivariable NTCP model considering both the dosimetric and clinical parameters had good performance in both the training and validation cohorts. The number of lymph nodes dissected and the volume of the ALTJ receiving a dose ≥35 Gy EQD2 were identified as strong predictors of lymphedema in the multivariable model. This predictive model provides guidance for determining appropriate dose constraints for ALTJ in clinical practice and for treatment plan evaluation.

A multivariable model that considers the relationship between clinical and dosimetric factors can provide a robust prediction approach by quantifying various factors contributing to lymphedema risk. In this study, the optimal multivariable model combined with ALTJ V35 and LNDno showed good agreement between predicted risk and observed outcomes in both internal (AUC 0.89) and external (AUC 0.83) validation. In our multivariable model, the lymphedema risk gradually increased with increasing V35 both when LNDno was above and below the cutoff value of 10. In particular, the patient cohort with more than 10 LNDno showed relatively greater increments than those with less than 10 LNDno.

The lymphedema risk was significantly increased when both risk factors, ALTJ V35 and LNDno, exceeded the cutoff value. The 3- and 5-year lymphedema rates were 18.7% and 25.0% in patients with LNDno >10 and ALTJ V35 >39.9%, respectively. In contrast, the lymphedema rate was 5.9% in patients with only 1 of the 2 risk factors exceeding the cutoff, and 0.5% and 0.9%, respectively, in patients with none of the 2 risk factors exceeding the cutoff. This suggests that if any one of ALTJ V35 and LNDno is maintained at less than the cutoff value, the 3-year lymphedema risk can be reduced by approximately 3.2-fold (4.2-fold reduction at 5 years).

In recent years, the use of hypofractionated regimens and VMAT is increasing in RT for breast cancer.[16-18] NTCP models may differ for fractionated regimens and treatment techniques,[19] and this heterogeneity hampers the model's predictive accuracy. Therefore, the robustness of the model performance to heterogeneity in fractionated regimens and treatment techniques is a very important factor in deciding

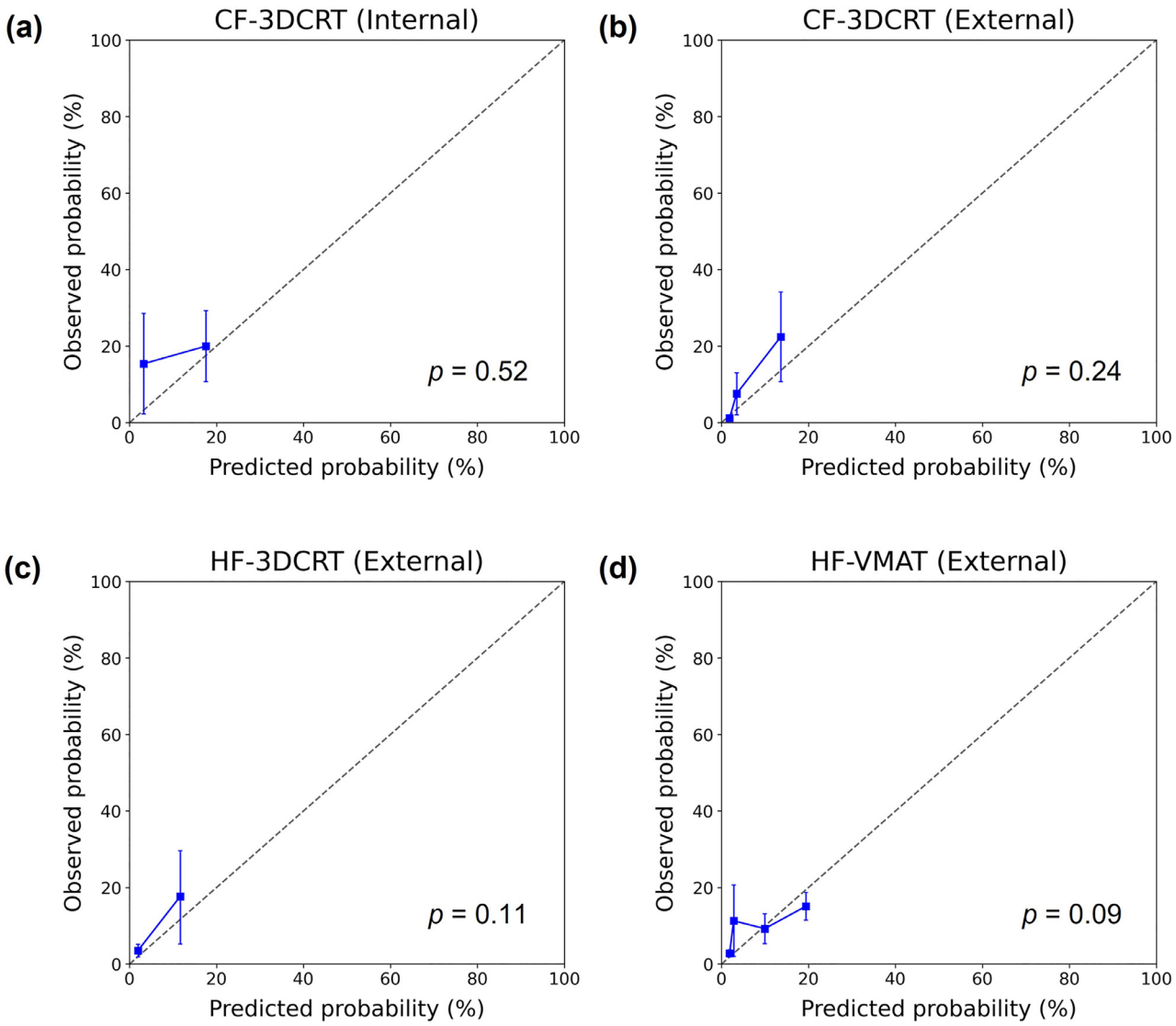

Fig. 2. Calibration plots of a NTCP model for internal (institution A) and external validation (institution B) cohorts. The prediction probability of the multivariable NTCP model was similar to the observed frequency in both internal and external validation (a-d). The dashed line represents the ideal calibration. *Abbreviations:* 3DCRT = 3-dimensional conformal radiation therapy; CF = conventional fractionated; HF = hypofractionated; NTCP = normal tissue complication probability; VMAT = volumetric modulated arc therapy.

its use in clinical practice. The NTCP model used here, constructed based on EQD2 using a 3DCRT patient cohort, was evaluated in a completely independent validation cohort comprising 3 different RT regimens (HF-3DCRT, CF-VMAT, and HF-VMAT). Consequently, the multivariable model developed in the 3DCRT cohort showed acceptable predictive performance not only in CF-3DCRT but also in HF-3DCRT and HF-VMAT. The multivariable model for lymphedema was robust and reliable when analyzing those treated with hypofractionated regimens and VMAT.

NTCP prediction can guide reasonable ALTJ dose constraints to prevent development as well as assess the likelihood of developing lymphedema. On the basis of these guidelines, a treatment plan that is safer and more tolerable for the patient can be established. However, to the best of our knowledge, an NTCP model for lymphedema in patients with breast cancer has not yet been reported, this is the first NTCP model for lymphedema. Although many studies have reported that the LNDno is an important predictor of lymphedema development,[5,7,20,21] the contribution of RT DVH parameters to lymphedema development is not fully known. Our multivariable NTCP model showed that the combination of ALTJ V35 and LNDno could be an appropriate guideline for minimizing lymphedema incidence after radiation therapy. Based on our model, to reduce the lymphedema incidence rate, ALTJ V35 should be minimized as much as possible, in particular, an RT plan maintaining ALTJ V35 (EQD2) $\leq$39.9% is required. A treatment

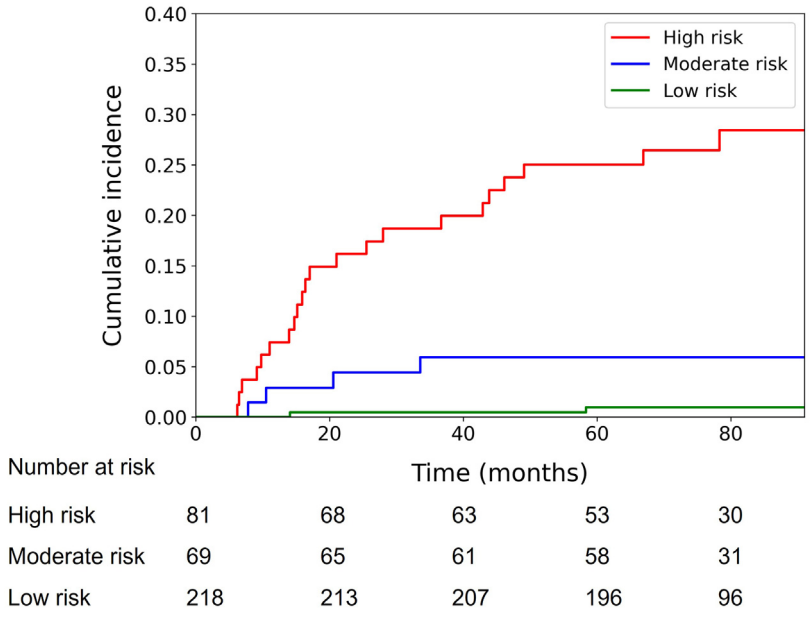

Fig. 3. Cumulative incidence of lymphedema stratified by clinical and dosimetric risk factors. Patients were classified into 3 risk categories for simplified patient stratification: high-risk (LNDno >10 and ALTJ V35 >39.9%), moderate risk (LNDno >10 and ALTJ V35 ≤39.9% or LNDno ≤10 and ALTJ V35 >39.9%), and low risk (LNDno ≤10 and ALTJ V35 ≤39.9%). A significant difference was observed in high-risk versus moderate-risk and high-risk versus low-risk comparisons (log-rank $P < .001$). *Abbreviations:* ALTJ = axillary thoracic vessel juncture; ALTJ V35 = the volume of the ALTJ receiving a dose ≥35 Gy EQD2; EQD2 = equivalent doses in 2-Gy fractions; LNDno = number of lymph nodes dissected.

plan maintaining ALTJ V35 ≤39.9% can lower the 3-year lymphedema incidence rate to less than 6%, regardless of LNDno. Our results will help create more specific treatment plans based on patient risk groups. In addition, the estimation of the concrete and quantified patient risk can be used to support physician decision-making and for patient counseling.

This study has some limitations. First, the lymphedema monitoring method used in this study was arm circumference measurement. Although both objective measurement and subjective symptoms have been used, they are insufficient to detect asymptomatic lymphedema or misclassification of BMI changes. This may potentially underestimate the lymphedema incidence rate. Second, the α/β ratio of lymphedema was assumed to be 3 Gy. Uncertainties in the α/β values used when converting fractionation schemes can affect the modeling results. In addition, variability in ALTJ region delineation may affect NTCP estimates. Third, in this study, the NTCP model was based on the planned dose data, and the true delivered dose to the ALTJs was not considered. The actual delivered dose to the ALTJs may differ from the planned dose due to geometric uncertainties such as patient setup errors and anatomic changes. Different uncertainties between 2 institutions can affect the final NTCP results for each institution and potentially lead to a difference in clinical effect. Finally, other variables not initially considered in the current study may be associated with lymphedema incidence, and their inclusion may potentially improve the multivariable NTCP model.

Conclusions

We first developed and validated the multivariable NTCP model for the incidence of lymphedema in patients with breast cancer after RT. The multivariable NTCP model based on dosimetric and clinical parameters showed excellent performance in predicting lymphedema in both internal and completely independent external validations for conventional-fractionated 3DCRT. In addition, the multivariable model achieved acceptable predictive performance and robustness in the hypofractionated regimen and VMAT. Our results show that ALTJ V35 and LNDno are key predictors of lymphedema development and that ALTJ V35 ≤39.9% may be an appropriate dose constraint to minimize lymphedema. NTCP of lymphedema can guide clinical guidelines for predicting lymphedema and preventing its onset.

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