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Original Research Article

Normal tissue complication probability models of hypothyroidism after radiotherapy for breast cancer

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ABSTRACT

Purpose: We aimed to develop Lyman–Kutcher–Burman (LKB) and multivariable normal tissue complication probability (NTCP) models to predict the risk of radiation-induced hypothyroidism (RIHT) in breast cancer patients.

Materials and methods: A total of 1,063 breast cancer patients who underwent whole breast irradiation between 2009 and 2016 were analyzed. Individual dose-volume histograms were used to generate LKB and multivariable logistic regression models. LKB model was fit using the thyroid radiation dose-volume parameters. A multivariable model was constructed to identify potential dosimetric and clinical parameters associated with RIHT. Internal validation was conducted using bootstrapping techniques, and model performance was evaluated using the area under the curve (AUC) and Hosmer–Lemeshow (HL) goodness-of-fit test.

Results: RIHT developed in 4 % of patients with a median follow-up of 77.7 months. LKB and multivariable NTCP models exhibited significant agreement between the predicted and observed results (HL P values > 0.05). The multivariable NTCP model outperformed the LKB model in predicting RIHT (AUC 0.62 vs. 0.54). In the multivariable model, systemic therapy, age, and percentage of thyroid volume receiving $\geq$ 10 Gy (V10) were significant prognostic factors for RIHT. The cumulative incidence of RIHT was significantly higher in patients who exceeded the cut-off values for all three risk predictors (systemic therapy, age $\geq$ 40 years, and thyroid V10 $\geq$ 26 %, $P < 0.005$).

Conclusions: Systemic therapy, age, and V10 of the thyroid were identified as strong risk factors for the development of RIHT. Our NTCP models provide valuable insights to clinicians for predicting and preventing hypothyroidism by identifying high-risk patients.

Introduction

The standard treatment regimen for breast cancer varies depending on the stage and clinical presentation but typically consists of surgery, radiation therapy (RT), and systemic therapy. Notably, comprehensive regional nodal irradiation (RNI) of the whole breast or chest wall RT has been established to improve the locoregional control and survival rate [1–5]. However, the growing application of RNI that includes the supraclavicular lymph nodes in breast cancer treatment may lead to increased exposure of the thyroid gland to irradiation, consequently raising concerns about the risk of radiation-induced hypothyroidism. Although hypothyroidism does not directly affect survival, it can cause symptoms, such as fatigue, weight gain, myalgia, and depression, and impair the quality of life, especially in long-term cancer survivors [6–9].

The risk of radiation-induced hypothyroidism varies and depends on factors related to the patient, the histological type and clinical stage of cancer, and the treatment administered. Previously, most studies have evaluated hypothyroidism in patients with head and neck cancers [10–12] or lymphoma [13,14]. More recently, a growing body of research has demonstrated that supraclavicular-directed RT is associated with a higher incidence of hypothyroidism in patients with breast cancer [15–24]. Although previous studies in patients with breast

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cancer had a small sample size or were retrospective in nature, attempts are constantly being made to determine the dose-volume parameters of irradiation to the thyroid gland, including the development of a radiobiological model based on normal tissue complication probability (NTCP) [23]. The thyroid gland must be considered an organ-at-risk (OAR), and dosimetric constraints must be applied using modern irradiation techniques. Owing to the thyroid gland being considered a parallel organ, various dose-volume parameters, such as the mean dose, have been explored. However, a single dose parameter exclusively responsible for causing hypothyroidism has yet to be determined. Rather, an integrated approach that additionally considers the susceptibility of the patient and the mutual influence of other oncological therapies on dose effect is required.

In this study, we aimed to develop an NTCP model to predict hypothyroidism in a large cohort of patients with breast cancer undergoing RT and to evaluate the parameters associated with an increased risk of developing hypothyroidism. Moreover, we developed an unbiased predictive model for hypothyroidism that is widely applicable for determining the RT field and irradiation dose to the thyroid gland by integrating whole breast and RNI patients. First, the classical Lyman–Kutcher–Burman (LKB) NTCP model was established, in which only dosimetric information was considered. The LKB model can be implemented in commercial treatment planning systems (TPS) for plan evaluation. Second, a multivariable NTCP model that optimizes risk prediction using dosimetric and clinical parameters was developed. Finally, we performed internal validation to assess the performance of the two developed models.

Materials and Methods

Patients

Women diagnosed with breast cancer who underwent adjuvant breast RT at our institution between 2009 and 2016 were included in this study. From our patient cohort consisting of 4,073 individuals, which was previously reported in our 2021 publication [17], patients who met the eligibility criteria for this study were selected. The eligibility criteria of historical cohort were as follows: (1) newly diagnosed with histopathologically proven breast cancer (invasive carcinoma, carcinoma in situ, or any other cancer histology); (2) breast surgery (breast-conserving surgery or mastectomy [± axillary node dissection]); (3) completed adjuvant RT to the ipsilateral breast or chest wall; (4) no primary thyroid disease or thyroid surgery prior to breast RT; (5) no evidence of distant metastasis; (6) no other cancer history. For this study, only patients with available thyroidal dose-volume histograms (DVHs) and adequate follow-up period (≥36 months to confirm event occurrence) after the first diagnosis were selected. A total of 1,063 patients were included in the analysis. This study was approved by the institutional review board of the Yonsei University Health System (9–2022-0181). The need for informed consent was waived owing to the retrospective nature of the study.

Radiation therapy

All patients received whole breast irradiation using three-dimensional conformal RT (3DCRT) or intensity-modulated RT (IMRT) after breast surgery. Both conventional fractionation (1.8–2.0 Gy per fraction, total dose 50–50.4 Gy) and hypofractionation (2.2–2.67 Gy per fraction, total dose 40.05–42.56 Gy) schemes were applied for whole breast irradiation. For tumor bed boost, sequential boost (1.8–2.0 Gy per fraction) or simultaneous integrated boost (3.2–3.4 Gy per fraction) was applied according to the RT technique. RNI has been used for select patients with positive lymph nodes and some with negative lymph nodes. RNI was performed in accordance with the target volume guidelines from the European Society for Radiotherapy and Oncology (ESTRO) or the Radiation Therapy Oncology Group (RTOG). Patients with a low nodal tumor burden received RNI to the lymph node regions, including level 4 nodes (RNI-Lv.4), as per the ESTRO guidelines, whereas the others received RNI to the supraclavicular lymph node (SCL) area as per the RTOG guidelines (RNI-SCL). The details of the institutional policy have been described previously [17,25,26]. We analyzed all patients ("WBI ± RNI group": whole breast/chest wall RT alone without RNI [WBI], WBI + RNI-Lv.4, and WBI + RNI-SCL), as well as separately analyzed a subset of patients who received RNI ("RNI group": WBI + RNI-Lv.4 or RNI-SCL) and who received WBI alone ("WBI alone group").

Thyroid function assessment and endpoint for the NTCP model

Thyroid function tests were performed at the discretion of the clinician, when considered necessary. Thyroid function was evaluated by measuring the serum fT4, fT3, and thyroid-stimulating hormone (TSH) concentrations before and/or after RT. The primary endpoint of this study was radiation-induced (clinical or subclinical) hypothyroidism, which was a newly diagnosed hypothyroidism event after RT, with or without radiologic evidence of thyroiditis. Clinical hypothyroidism was characterized by reduced serum fT4 concentrations (<0.8 ng/dL) with high serum TSH concentrations (>4.69 mIU/mL), along with the existence of clinical symptoms. Subclinical hypothyroidism was generally characterized by increased TSH concentrations without symptoms; the serum fT4 level could be low or within the normal limits.

Clinical and dosimetric variables

Four clinical and 13 dosimetric variables were considered initially in the current study. Clinical variables included systemic therapy (neoadjuvant/adjuvant chemotherapy or anti- human epidermal growth factor receptor 2 (HER2) target therapy), hormone therapy, age, and thyroid volume. Dosimetric variables were derived using the DVH of the thyroid gland from the planned dose. All dose values were converted into equivalent doses in 2-Gy fractions (EQD2) using an α/β ratio of 3 Gy [27]. The EQD2-corrected dosimetric variables for the thyroid gland analyzed included the maximum dose (D_{max}), mean dose (D_{mean}), minimum dose (D_{min}), V5 (percentage of the thyroid volume receiving ≥ 5 Gy), V10, V15, V20, V25, V30, V35, V40, V45, and V50.

LKB and multivariate NTCP models

The NTCP model for hypothyroidism was developed using WBI ± RNI group data to investigate whether hypothyroidism could be predicted regardless of the characteristics of the RT field design. LKB and multivariable logistic NTCP modeling approaches were used to predict the incidence of hypothyroidism. The LKB NTCP model incorporates only dosimetric information, and the formula is as follows:

$$LKBNTCP = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} e^{-\frac{x^2}{2}}dx$$

$$t = \frac{gEUD - TD_{50}}{m \times TD_{50}}, gEUD = \left(\sum_i v_i D_i^{\frac{1}{n}}\right)^n,$$

where the parameter n indicates the volume effect of the organ, m is the slope of the NTCP curve, and TD50 is the dose at an NTCP value of 50 %. The gEUD is the generalized equivalent uniform dose calculated from DVH of the thyroid gland, using the partial volume ratio (v_i) receiving EQD2 dose D_i with a dose step size of 0.5 Gy. The best fit of n, m, TD50 for predicting hypothyroidism was estimated by maximizing the log-likelihood using the formula:

$$LLH = \sum_{i=1}^{N} (y_i \log(NTCP) + (1 - y_i)\log(1 - NTCP))$$

where y is the observed outcome, with (1) or without hypothyroidism (0).

The multivariable NTCP model was developed by considering both clinical and dosimetric variables. A multivariable logistic regression with the bootstrapping technique was applied for NTCP modeling. To select the optimal combination of predictive variables for the multivariable NTCP model, stepwise forward selection using the Bayesian information criterion (BIC) was repeated 1,000 times with stratified bootstrapping. The optimal multivariable NTCP model was generated using the bootstrapping results, as a set of variables most frequently selected and included the number of variables with the lowest average BIC [28]. The threshold of Spearman's correlation coefficient of 0.8 was applied during bootstrapping and optimal model selection.

Model evaluation

The prediction performance of each model was evaluated using the area under the receiver operating characteristic curve (AUC). Estimation of model parameters and internal validation of each model were conducted using 500 bootstrapping to reduce the overfit bias. The calibration curve and Hosmer–Lemeshow (HL) goodness-of-fit test were used to assess model calibration. LKB and multivariable NTCP models were additionally generated for patients in the RNI group following the same modeling procedure as for the WBI ± RNI group. Patients were classified into subgroups according to the risk predictors in a multivariable NTCP model for the WBI ± RNI group, and the cumulative incidence of hypothyroidism was analyzed using the Kaplan–Meier method. Model development and statistical analysis were performed using Python 3.7 with open-source libraries (SciPy, Scikit-learn, Lifelines).

Results

Patient characteristics

We included 1,063 patients with breast RT in the analysis; patient characteristics are summarized in Table 1. Among them, 409 patients (38.5 %) received WBI alone, while 654 patients (61.5 %) received both WBI and RNI (RNI-Lv.4 irradiation [n = 192] and RNI-SCL [n = 462], respectively). Systemic therapy was administered to 757 patients (71.2 %), with 618 (94.5 %) in the RNI group and 139 (34.0 %) in the WBI alone group. The median follow-up duration was 77.7 months in all patients, and 74.2 months and 79.7 months in patients with WBI alone and with WBI + RNI, respectively. Hypothyroidism after RT developed in 43 patients (4.0 %), comprising 15 (34.9 %) clinical and 28 (65.1 %) subclinical events. The median time interval from RT to hypothyroidism detection was 14.2 months (range: 3.0–122.5). The incidence rate was 4.2 % in patients with WBI alone and 4.0 % in patients with WBI + RNI (1.6 % in RNI-Lv.4 [3/192] and 5.0 % in RNI-SCL [23/462]). The D_{mean} (interquartile range) for the thyroid gland was 0.34 Gy (0.20–0.55) in the patients with WBI alone, while it was 4.48 Gy (2.82–8.68) in those with WBI + RNI.

LKB NTCP

The fitted LKB model parameters estimated for predicting hypothyroidism were n = 0.62 (95 % confidence interval [CI] 0.31–1.00), m = 0.53 (95 % CI 0.50–0.56), and TD50 = 117.05 Gy EQD2 (95 % CI 66.77–248.02) in the WBI ± RNI group. The final LKB NTCP model is plotted in Fig. 1. Binned actual observed hypothyroidism rates are similar to the NTCP model. Table 2 presents parameter estimates for the LKB model in the WBI ± RNI and RNI groups. The doses for 5 % and 10 % probability of hypothyroidism were 14.1 Gy EQD2 and 36.8 Gy EQD2 in the WBI ± RNI group and 19.7 Gy EQD2 and 34.6 Gy EQD2 in the RNI group, respectively. The LKB model could not be established in the WBI alone group.

Table 1
Clinical and treatment characteristics of all patients.

Characteristic	All patients (n = 1063)
Age, mean (95 % CI), year	50.0 (32.0–72.0)
BMI, mean (95 % CI), kg/m^2	22.9 (18.0–30.7)
Smoking, n (%)	
Yes	35 (3.3)
No	1028 (96.7)
Thyroid volume, mean (95 % CI), cc	13.5 (5.0–27.0)
T stage, n (%)	
Tx	3 (0.3)
Tis	94 (8.9)
T1	500 (47.0)
T2	383 (26.0)
T3	58 (5.5)
T4	25 (2.4)
N stage, n (%)	
N0	525 (49.4)
N1	372 (35.0)
N2	97 (9.1)
N3	69 (6.5)
Pathology, n (%)	
IDC	841 (79.1)
DCIS	82 (7.7)
ILC	48 (4.5)
LCIS	2 (0.2)
Mucinous carcinoma	14 (1.3)
Others	66 (6.2)
Unknown	10 (0.9)
Type of surgery, n (%)	
PM	757 (71.2)
MRM	306 (28.8)
No. of sampled axillary lymph nodes, mean (95 % CI)	7.0 (0.0–30.0)
Adjuvant chemotherapy, n (%)	487 (45.8)
Neoadjuvant chemotherapy, n (%)	387 (36.4)
Neoadjuvant or adjuvant systemic therapy, n (%)	757 (71.2)
Taxane-based	542 (51.0)
Anthracycline-based	697 (65.6)
Anti-HER2	200 (18.8)
Hormone therapy, n (%)	699 (65.8)
RT field, n (%)	
WB/CW only	409 (38.5)
WB/CW + regional lymph nodes	654 (61.5)
Field of RNI, n (%)	
RNI–Lv.4	192 (18.1)
RNI–SCL	462 (43.5)
RT modality, n (%)	
3DCRT	793 (74.6)
IMRT	270 (25.4)
RT dose fractionation schedule, n (%)	
Conventional fractionation	458 (43.1)
Hypofractionation	605 (56.9)

Abbreviations: CI = confidence interval; BMI = body mass index; PM = partial mastectomy; MRM = modified radical mastectomy; HER2 = human epidermal growth factor receptor 2; RT = radiation therapy; RNI = regional nodal irradiation; WB/CW = whole breast and chest wall; SCL = supraclavicular lymph node; 3DCRT = three-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy.

Multivariable NTCP

In the WBI ± R NI group, the multivariable NTCP model was developed using three variables according to the bootstrap-based variable selection procedure. Systemic therapy (no = 0, yes = 1), age (years), and thyroid V10 (%) were selected as the risk variables in the multivariable NTCP model for the WBI ± RNI group. The multivariable NTCP model for the WBI ± RNI group was estimated as $S = -4.27 + 0.014 \times V10 + 0.396 \times \text{Systemic therapy} + 0.012 \times \text{Age}$, where $NTCP = (1 + e^{-S})^{-1}$. The predicted risk of hypothyroidism in the WBI ± RNI group increases in patients receiving systemic therapy and with increasing V10 and age. Age and thyroid V10 were selected as the optimal risk predictors for hypothyroidism in the RNI group. The multivariable NTCP model fitted for the RNI group to be $S = -4.82 + 0.021 \times V10 + 0.022 \times$ Age. NTCP values increased in both the WBI and RNI groups with

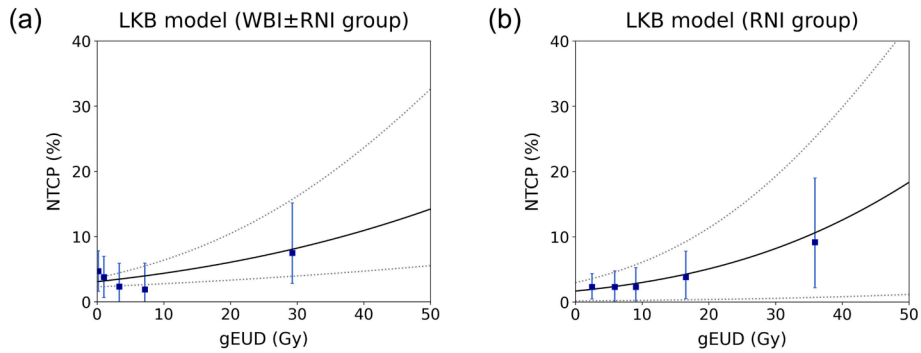


Fig. 1. Lyman–Kutcher–Burman (LKB) normal tissue complication probability (NTCP) model for predicting hypothyroidism. (a) LKB model for patients who received whole breast irradiation with/without regional nodal irradiation (WBI ± RNI group). (b) LKB model for patients who received RNI (RNI group). The dotted lines indicate the 95 % confidence interval. The range of generalized equivalent uniform dose (gEUD) was divided into five bins based on the quantile of the number of patients (box). A vertical bar in each bin is an interquartile range.

Table 2
Performance evaluation of normal tissue complication probability (NTCP) models.

	Model	Parameters	Coefficients (95 % CI)	AUC (95 % CI)
WBI ± RNI group (n = 1063)	LKB	n	0.62 (0.31, 1.00)	0.54 (0.44, 0.64)
		m	0.53 (0.50, 0.56)	
		TD50 (Gy)	117.05 (66.77, 248.02)	
	Multivariable	V10 (%)	0.014 (-0.001, 0.026)	0.62 (0.54, 0.70)
		Age (years)	0.012 (-2.17, 0.047)	
		Systemic therapy	0.396 (-3.05, 1.34)	
		Intercept	−4.27 (-6.27, −2.41)	
RNI group (n = 654)	LKB	n	0.42 (0.01, 1.00)	0.65 (0.49, 0.73)
		m	0.47 (0.34, 0.53)	
		TD50 (Gy)	86.86 (55.60, 219.94)	
	Multivariable	V10 (%)	0.022 (0.008, 0.035)	0.69 (0.59, 0.78)
		Age (years)	0.021 (-0.025, 0.068)	
		Intercept	−4.82 (-7.21, −2.58)	
WBI alone group (n = 409)	Multivariable	Systemic therapy	1.10 (0.07, 2.20)	0.63 (0.48,0.74)
		Intercept	−3.64 (-4.45, −3.16)	

Abbreviations: WBI ± RNI group = patients who received whole breast irradiation (WBI) with/without RNI; RNI group = patients who received RNI; WBI group = patients who received whole breast irradiation (WBI) without regional nodal irradiation (RNI); AUC = area under the receiver operating characteristic curve; CI = confidence interval; LKB = Lyman–Kutcher–Burman model; n = parameter for the volume effect of the organ; m = slope of the dose–response curve at TD50; TD50 = equivalent uniform dose to the organ with a 50 % probability for complications; V10 = percentage of thyroid volume receiving ≥ 10 Gy.

increasing age and thyroid V10 (Fig. 2). In the NTCP model for the WBI alone group, systemic therapy was selected as a significant risk variable to predict hypothyroidism (S = − 3.64 + 1.10 × systemic therapy). Cytotoxic chemotherapy or anti-HER2 therapy was not a significant variable in either the WBI group or the RNI group.

Performance evaluation

The predictive performance of the LKB and multivariable NTCP models was internally validated and is presented in Table 2. The AUC values for the LKB and multivariable NTCP models were 0.54 (95 % CI, 0.44–0.64) and 0.62 (95 % CI, 0.54–0.70) in the WBI ± RNI group, and 0.65 (95 % CI, 0.49–0.73) and 0.69 (95 % CI, 0.59–0.78) in the RNI group, respectively. The AUC of the NTCP model for the WBI alone group was 0.63 (95 % CI, 0.48–0.74). The AUC values for the multivariable NTCP model using cytotoxic chemotherapy or anti-HER2 therapy as variables are provided in Supplementary Table 1. Calibration curves for patient-wise prediction of the NTCP models are displayed in Fig. 3. The LKB and multivariable NTCP models revealed good agreement between the predicted and observed probability of hypothyroidism with acceptable goodness-of-fit ($P > 0.05$), and the calibration curves for the LKB and multivariable NTCP models demonstrated good agreement between the predicted and observed probability of hypothyroidism ($P > 0.05$).

Patients were classified into three risk groups based on the risk predictors (age ≥ 40 years and had received systemic therapy and thyroid V10 ≥ 26 %). Patients were categorized as high risk if they had all the risk factors (age ≥ 40 years and had received systemic therapy and thyroid V10 ≥ 26 %), moderate risk if the patients only had clinical risk factors (age ≥ 40 years and had received systemic therapy and thyroid V10 < 26 %), and low risk if the patients had no risk factors (age < 40 years and had not received systemic therapy and thyroid V10 < 26 %). The 3- and 5-year cumulative incidence rates of hypothyroidism were 6.4 % (95 % CI, 3.4–12 %) and 8.6 % (95 % CI, 5.0–14.7 %) for the high-risk group and 3.1 % (95 % CI, 1.9–5.0 %) and 3.3 % (95 % CI, 2.1–5.3 %) for the moderate-risk group, respectively ($P = 0.008$) (Fig. 4). A significant difference was observed in the high-risk versus moderate- and low-risk comparisons (log-rank $P < 0.05$).

In the WBI alone group, the 3- and 5-year cumulative incidence rates of hypothyroidism were 2.2 % (95 % CI, 1.0–4.9 %) and 2.6 % (95 % CI, 1.2–5.3 %) for patients with systemic therapy, and 5.8 % (95 % CI, 3.5–12.2 %) and 7.4 % (95 % CI, 4.0–13.3 %) for patients without systemic therapy, respectively ($P < 0.05$). The difference in the incidence of hypothyroidism according to the addition of systemic therapy in each patient group is shown in Supplementary Fig. 1.

Discussion

Previous studies mostly analyzed patients who received RT for head and neck tumors or RNI in a wider SCL field using 3DCRT [10,22,23]. The thyroid dose cut-off values and NTCP models presented thus far are considerably biased to be applied widely to patients who received adapted RT using modern RT technologies. Predictive models optimized

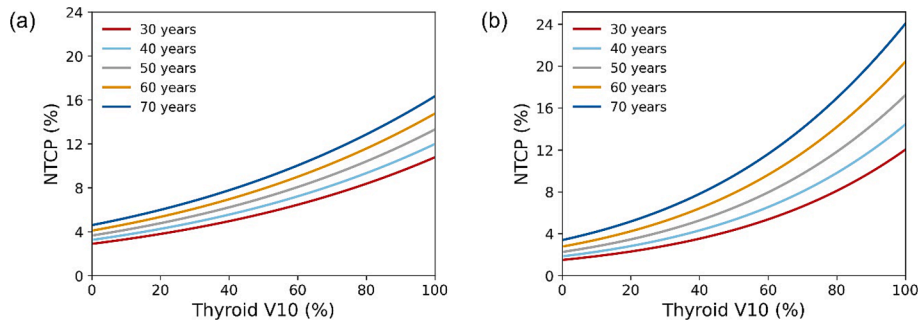


Fig. 2. The multivariable normal tissue complication probability (NTCP) model with the percentage of thyroid volume receiving ≥ 10 Gy (thyroid V10) calculated per age category in patients undergoing systemic therapy. (a) Patients who received whole breast irradiation with/without regional nodal irradiation (WBI ± RNI group), and (b) patients who received regional nodal irradiation (RNI group).

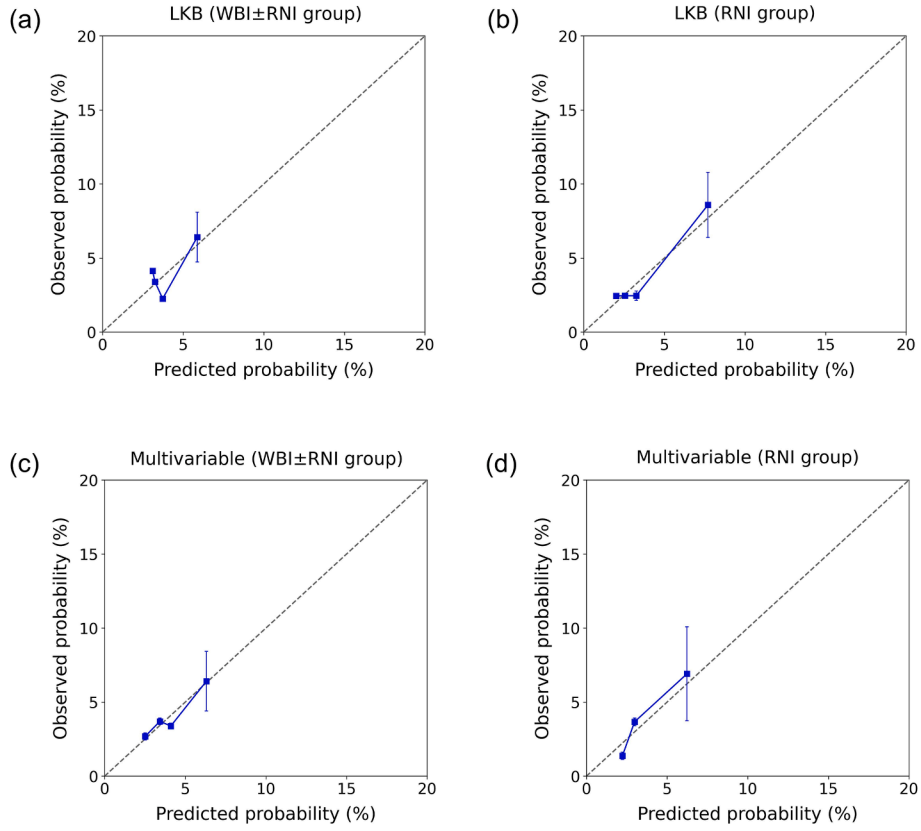
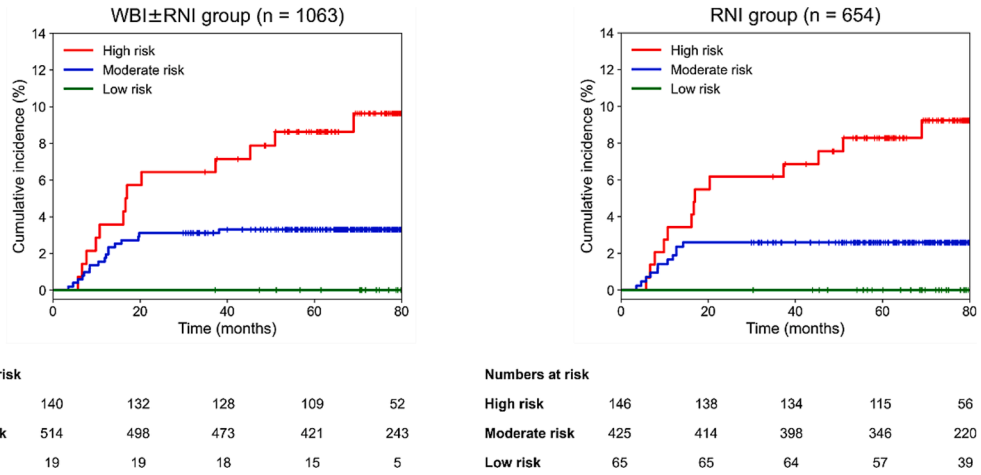


Fig. 3. Calibration curves for (a–b) Lyman–Kutcher–Burman (LKB) and (c–d) multivariable normal tissue complication probability (NTCP) models. The predicted probability of the two NTCP models was similar to the observed probability. The dashed line represents perfect prediction. *Abbreviations*: WBI ± RNI group = patients who received whole breast irradiation with/without regional nodal irradiation; RNI group = patients who received regional nodal irradiation.

for patients receiving only modest doses of radiation to the thyroid gland, such as those with breast cancer, are currently lacking. In this study, we constructed a novel NTCP model of hypothyroidism by incorporating dosimetric parameters and clinical factors of patients with breast cancer, which can provide an accurate basis for a more optimized thyroid dose restriction strategy. Our three-variable model demonstrated optimal performance in patients who received WBI only, as well as in patients who received RNI. Although more validation is required, our findings could serve as a crucial reference for protecting the thyroid gland during RT and determining the most optimal follow-up schedule for each patient.

As the thyroid gland is sensitive to RT, radiation-induced thyroid disorders have been reported in patients with cancer, mainly in those who received radiation in the cervical region. Studies have been conducted mainly in patients who received RT for head and neck tumors, and the incidence of hypothyroidism was approximately 40 % during a median follow-up period of 1.0–5.3 years [29–31]. Although the incidence of hypothyroidism in breast cancer is relatively low, the incidence was higher in breast cancer survivors than that in the general population based on several population-based studies [21,32,33]. The 8-year incidence in a Korean database study was as high as 9 % [20], which was significantly higher after RT (9.3 % vs. 8.6 %, hazard ratio = 1.081, P = 0.002). Most studies reported that hypothyroidism events occurred within 5 years, with a median clinical latency of 8–27 months; however, they can occur even after this period. Specifically, irradiation to the supraclavicular field was associated with an increased risk of hypothyroidism compared with radiation to the breast and chest wall only [17,19,21,34], with a pooled relative risk of 69 %, according to a recent *meta*-analysis [35]. Additionally, radiation-induced thyroid volume reduction [36–38] or a smaller thyroid volume was associated with a



Numbers at risk					
High risk	140	132	128	109	52
Moderate risk	514	498	473	421	243
Low risk	19	19	18	15	5

Numbers at risk					
High risk	146	138	134	115	56
Moderate risk	425	414	398	346	220
Low risk	65	65	64	57	39

Fig. 4. Cumulative incidence of hypothyroidism stratified by clinical (age and systemic therapy) and dosimetric risk factors. Patients were categorized as high risk if the patients had all risk factors (age ≥ 40 years and had received systemic therapy and thyroid V10 ≥ 26 %), moderate risk if the patients had only clinical risk factors (age > 40 years and had received systemic therapy and thyroid V10 < 26 %), and low risk if the patients had no risk factors (age < 40 years and had not received systemic therapy and thyroid V10 < 26 %). A significant difference was observed in the high-risk versus moderate- and low-risk comparisons (log-rank $P < 0.05$). *Abbreviations*: WBI ± RNI group = patients who received whole breast irradiation with/without regional nodal irradiation; RNI group = patients who received regional nodal irradiation.

higher incidence of radiation-induced hypothyroidism [23]. Female sex [39,40] or systemic therapy [17,40,41] may also contribute to an increased risk.

Minimizing inadvertent exposure of the thyroid gland to radiation is crucial to prevent the development of hypothyroidism. With the implementation of new RT techniques, especially computed tomography-based 3D planning or IMRT, dose-volume constraints have been refined for all OARs. However, there was no QUANTEC report focusing on thyroid disorders; furthermore, dose parameters and cut-off values vary significantly across studies. The dose–effect relationships between the thyroid radiation dose-volume parameters and hypothyroidism risk were investigated mainly for head and neck cancer. Several thyroid dose-volume parameters, including V25, V30, V35, V45, V50, VS45 (volume of thyroid gland spared from a dose of 45 Gy), VS60, D_{mean}, and D_{min}, were associated with radiation-induced hypothyroidism [31,42–45]. Four studies [27,46–48] presented the NTCP model, and three [40,49,50] developed clinico-dosimetric nomograms for radiation-induced hypothyroidism in patients with head and neck cancer. In the multivariable model and nomogram, dosimetric parameters, as well as sex, age, and chemotherapy, were highlighted as significant predictors, similar to the approach in our current study. In studies of patients with breast cancer, D_{mean}, V30, or CV20 (absolute volume of the thyroid gland receiving less than 20 Gy) were suggested as the significant predictors of hypothyroidism [17,18,23,24,51]. However, the number of studies on breast cancer is limited, and the NTCP model was developed in only one study [23].

Huang et al. [23] developed a multivariable NTCP model for hypothyroidism in 192 patients with breast cancer who underwent supraclavicular-directed RT. Owing to the low relative incidence of hypothyroidism in breast cancer, large data sets are required to establish a more reliable NTCP model; however, previous studies were based on a limited number of patients and treatment fields [23,39]. Conversely, we developed an NTCP model for predicting hypothyroidism in a large cohort of 1,063 patients with breast cancer treated with RT. Compared with the NTCP model of the previous study, our model included patients undergoing whole breast irradiation and RNI. The incidence of hypothyroidism correlates with RNI but may also increase in patients with breast cancer receiving RT without RNI. Therefore, there is a need for an NTCP model for hypothyroidism that can be widely applied to all patients with breast cancer undergoing RT without bias regarding the treatment field and irradiated dose of the thyroid gland.

In this study, we developed the first LKB NTCP model to predict the hypothyroidism risk in patients with breast cancer who received RT. The LKB model is the most well-known NTCP model and can be easily implemented in commercial TPS for plan evaluation. The LKB model was established by analyzing the DVH-derived dosimetric parameters to predict the risk of hypothyroidism. The LKB model exhibited a significant goodness-of-fit for predicting hypothyroidism in the WBI ± RNI and RNI groups (HL P value > 0.05). The developed LKB model demonstrated acceptable prediction performance in the RNI group (AUC 0.65) but exhibited inferior performance in the WBI ± RNI group (AUC 0.54) (Table 2). The poor predictive accuracy in the WBI ± RNI compared to the RNI group may be attributed to the heterogeneity of the patient cohort, which included many patients who had not received a radiation dose to the thyroid. The optimal n values for our fitted LKB model were 0.62 and 0.42 for the WBI ± RNI and RNI groups, respectively. The optimal n values indicate a relatively small volume effect compared to the previously reported n value of 0.92 in patients with head and neck cancer [27]. This difference in n values may be attributed to the different irradiated volumes of the thyroid gland during RT for breast and head-and-neck cancer.

Although the LKB model can intuitively interpret dose-volume histogram parameters and provide information regarding the dose tolerance level, dose–response sensitivity, and functional architecture of OARs, potentially important clinical parameters are not considered [28]. However, a multivariable model can provide a more robust approach by optimizing the clinical and dosimetric factors. Thyroid V10 and age were identified as strong predictors of hypothyroidism in our multivariable model. Systemic therapy was additionally included as a predictor in the WBI ± RNI group, possibly owing to the lower dose to the thyroid. Our multivariable model exhibited good agreement between the predicted probability and observed risk in the WBI ± RNI (AUC 0.62) and RNI (AUC 0.69) groups. The risk of hypothyroidism increased with age and thyroid V10. Compared with the WBI ± RNI group, the RNI group exhibited substantial differences in the incidence rates of hypothyroidism according to age and an increase in thyroid V10. The cumulative incidence of hypothyroidism significantly increased when the clinical risk factors and dosimetric risk factors exceeded the cutoff values. The 3- and 5-year hypothyroidism rates were 6.4 % and 8.6 %, respectively, in patients with age ≥ 40 years receiving systemic therapy and thyroid V10 ≥ 26 %. However, the hypothyroidism rates were 3.1 % and 3.3 %, respectively, in patients with only the clinical risk

factors exceeding the cutoff values and thyroid V10 $<$ 26 %. This suggests that even in patients with clinical risk factors, if the thyroid V10 is limited below 26 %, the risk of 3- and 5-year hypothyroidism can be reduced by approximately 2.1- and 2.6-fold, respectively. Our findings can provide guidelines for appropriate dose constraints for the thyroid gland to prevent hypothyroidism in patients with breast cancer undergoing RT.

We previously reported that [17] the risk of hypothyroidism increases after RNI-SCL but not after RNI-Lv 4. Furthermore, adjuvant systemic therapies and younger age were significant factors in the Cox multivariable model. Thus, risk-adapted RNI and thyroid dose constraints should be considered during breast cancer treatment. We demonstrated that the probability of hypothyroidism was 50 % with 26.27 Gy of thyroid D_{mean}, and the slope of the curve changed rapidly after approximately 15 Gy EQD2. However, we could not analyze the volume-based parameters of the thyroid gland other than the mean dose, and cut-off values that can be applied in clinical practice to patients stratified by risk group were not determined.

This study has several limitations. First, although this is the largest cohort study on an NTCP model of hypothyroidism, the number of hypothyroidism events was relatively small. Therefore, results from the NTCP model must be interpreted with caution. Second, we developed and internally validated the models using data from a single institution. External validation is required before widespread clinical use. Third, owing to the retrospective nature of this study, the rate of subclinical thyroid dysfunction may have been underestimated. Fourth, in our multivariable NTCP model, systemic therapy emerged as a significant variable; however, the specific significance based on the type of systemic therapy (anti-HER2 therapy or cytotoxic chemotherapy) could not be conclusively determined. This is attributed to the low frequency of patients experiencing hypothyroidism in each subgroup. Subsequent studies with larger cohorts are essential to provide more definitive insights into this issue. Finally, the NTCP model was based on a TPS-calculated dose and did not consider the actual delivered dose to the thyroid gland. The actual delivered dose to the thyroid gland may differ from the planned dose owing to uncertainties during treatment. Nonetheless, both NTCP and multivariable models developed in the study can be used to comprehensively assess clinical factors as well as individual dose parameters. Furthermore, at a time when the irradiated dose to the thyroid gland is being lowered owing to the increased application of ESTRO-recommended RNI field and IMRT, we could successfully construct a widely applicable NTCP model with a lower cut-off value (thyroid V10) than what has been previously suggested.

Conclusion

Our findings suggest that the thyroid gland must be protected during radiation to prevent its dysfunction, and patients with breast cancer who have received RT must be closely monitored. The thyroid gland must be considered as OAR during RT planning, and appropriate dosimetric constraints must be applied. Finally, our NTCP model could help predict the risk of RT-induced hypothyroidism in patients with breast cancer. Furthermore, these findings would provide valuable insights for clinicians to identify high-risk patients and implement preventive measures, such as limiting V10 EQD2 of the thyroid gland to 26 % in patients $\geq$ 40 years receiving systemic therapy.

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Role of the funding source

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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.

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Appendix A. Supplementary data

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