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FULL PAPER

Nomogram for radiation-induced hypothyroidism prediction in nasopharyngeal carcinoma after treatment

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Objective: The aim of this study was to develop a nomogram for radiation-induced hypothyroidism (RHT) prediction.

Methods: We collected data from 164 patients with nasopharyngeal carcinoma (NPC) in our previous prospective study. Biochemical hypothyroidism was defined as a serum thyroid-stimulating hormone level greater than the normal value. We collected both clinical and dose-volume factors. A univariate Cox regression analysis was performed to identify RHT risk factors. Optimal predictors were selected according to the least absolute shrinkage and selection operator (LASSO). We then selected the Cox regression models that best balanced the prediction performance and practicability to build a nomogram for RHT prediction.

Results: There were 38 (23.2%) patients who developed RHT, and the median follow-up was 24 months. The univariate Cox regression analysis indicated that gender, minimum dose, mean dose (D_{mean}) and V_{25-60} [V_x (%),

the percentage of thyroid volume receiving $>x$ Gy] of the thyroid were significantly associated with RHT. The variables of gender, receiving chemotherapy or not (chemo), D_{mean} and V_{50} were selected using the LASSO analysis. A nomogram based on a three-variable (gender, chemo and V_{50}) Cox regression model was constructed, and its concordance index was 0.72. Good accordance between prediction and observation was showed by calibration curves in the probability of RHT at 18, 24 and 30 months.

Conclusion: This study built a nomogram for RHT in NPC survivors by analyzing both clinical and dose-volume parameters using LASSO. Thus, the individual dose constraint could be achieved in a visual format.

Advances in knowledge: This study used LASSO to more accurately address the multicollinear problem between variables. The resulting nomogram will help physicians predict RHT.

INTRODUCTION

Radiation-induced hypothyroidism (RHT) is a common late complication after irradiation to the neck area. The majority of early RHT cases are silent because subclinical hypothyroidism (HT) can be detected only by thyroid hormone tests [elevated serum thyroid-stimulating hormone (TSH) and normal serum free thyroxine (fT4) and/or serum free triiodothyronine (fT3)]. However, other cases show overt disease [overt hypothyroidism (overt HT)] that presents with elevated TSH and decreased fT4 and/or fT3. The incidence of subclinical HT is 24–50%, and overt HT develops in 6–20% of patients with head and neck cancer who receive radiotherapy (RT).¹ HT has been demonstrated to be correlated with the development of cardiovascular and pulmonary disorders in addition to diabetes mellitus,^{2–7} which increases the adverse effects of RHT on patient quality of life.

Previous studies found that gender,^{8,9} age,¹⁰ neck surgery¹¹ and thyroid volume^{12–14} were risk factors for RHT. In addition, a high radiation dose and large thyroid volume in the treatment field are related to RHT.^{10,15} Three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) enable the analysis of dose-volume factors. The minimum dose (D_{min}) and mean dose (D_{mean}), the percentage of thyroid volume receiving >30 , 45 or 50 Gy, the absolute thyroid volume spared from 45 Gy or less and volume spared from 60 Gy or less^{13,14,16–24} were found to be dosimetric predictors for RHT. However, predictors and dose constraints varied according to the study.^{13,14,16–25}

Nasopharyngeal carcinoma (NPC) is a prevalent cancer in southern China. Irradiation to the bilateral neck is a regular practice because of a high incidence²⁶ of neck node

involvement. This treatment causes unavoidable irradiation to regions of the thyroid, which may increase the risk of RHT in patients with NPC, especially in long-term survivors, owing to the improvement of radiation techniques and concurrent chemoradiotherapy.²⁷ Thus, radiation therapists should consider RHT in patients with NPC.

A normal tissue complication probability (NTCP) model is the principal method for RHT prediction.^{13,14,18,28} However, NTCP model is not convenient in clinical practice. A nomogram is widely used for cancer prognosis and reduces statistical predictive models into a graphical format. The least absolute shrinkage and selection operator (LASSO) is a statistical technique of variable shrinkage and selection. This technique is performed with regularization to improve the accuracy and interpretability of regression models.²⁹ LASSO has recently been utilized to select optimal predictors from data that are multicollinear for other radiation-induced complications.^{30,31} However, no studies have investigated RHT with this sophisticated statistical method. In this study, we used LASSO to identify predictors of Cox regression and present a nomogram for the prediction of RHT in patients with NPC.

METHODS AND MATERIALS

Patient eligibility

The patient population in this study was that from our previous prospective study,^{16,32} which is an ongoing study of radiation-induced changes in the thyroid gland. No stratification or matching methods were performed in this study. All patients were previously untreated, non-metastatic and pathologically diagnosed as having NPC in the Cancer Hospital of Shantou University Medical College from December 2007 to March 2014. A baseline thyroid function test included TSH, fT3 and fT4 and was performed before any treatment. The study exclusion criteria included the following: (1) a history of thyroid dysfunction; (2) abnormal baseline thyroid hormone levels before RT; and (3) surgery or irradiation to the neck area. There were 173 patients who met the inclusion criteria. However, nine patients were excluded because of electron boost to residual lymph nodes after RT ($n = 3$) and missing dose-volume histogram (DVH) data ($n = 6$). The remaining 164 patients were analyzed. The patients were restaged using the 7th edition of the American Joint Committee on Cancer staging system. This study was approved by our centre institutional review board, and all patients signed written informed consent before therapy initiation.

Chemotherapy

Concurrent chemotherapy (PF) consisted of cisplatin (P) 75 mg m^{-2} on Day 1 and 96 h of continuous infusion fluorouracil (F) $750 \text{ mg m}^{-2}/\text{day}$ every 3 weeks for two cycles. The neoadjuvant chemotherapy regimens were one cycle of docetaxel (T) 75 mg m^{-2} on Day 1 and cisplatin (P) 75 mg m^{-2} on Days 1 and one cycle of P on Day 22. Adjuvant chemotherapy (PF) was administered every 3 weeks for two cycles post-RT.

Radiation therapy and dosimetric analysis

The details of our institution radiation therapy protocol were described in our previous publications.^{16,32}

All patients were immobilized in the supine position with a tailor-made thermoplastic cast from head to shoulders. CT scans (3-mm slice thickness) were performed from the head to 2 cm below the sternoclavicular joint (Philips Brilliance CT Big Bore Oncology Configuration, Cleveland, OH) with i.v. contrast. The CT images were subsequently transferred to the Pinnacle 7.6c treatment planning system (Pinnacle3; Philips, Eindhoven, Netherlands) for target and organ at risk delineation and treatment planning.

NPC RT planning for gross tumour volume (GTV) included the primary disease (GTV of the nasopharynx) and lymph nodes (GTV of the lymph nodes). The clinical target volume (CTV) of the nasopharynx included the following structures: the parapharyngeal space, uvula, pterygomaxillary fissure, outer table of the clivus, basisphenoid, petrous tip, foremen ovale, foremen rotundum, inferior half of the sphenoid sinus, anterior vertebral body of C1 and prevertebral muscle/fascia, and posterior 1–2 cm of maxillary antrum and nasal septum. CTV of the lymph nodes included lymph nodes at Levels II–V. The planning target volume (PTV) was established by adding 3–5 mm to the CTV.

We prescribed 70 Gy and 66 Gy to the PTV of the nasopharynx and PTV of the lymph nodes, respectively. We also prescribed 60 Gy to the PTV of high-risk CTV and 54 Gy to the PTV of low-risk CTV. The high-risk CTV indicated soft tissues adjacent to GTV and involved lymphatic drainage regions. In addition, II, III and Va of the ipsilateral negative of node, as well as IV and Vb of the ipsilateral positive II and/or III level was defined as low-risk CTV. The fractionation doses delivered to the PTV of high-risk CTV and/or the PTV of low-risk CTV were 2 Gy for 3D-CRT and 1.8–2 Gy per fraction for IMRT. The dose constraints of critical organs were the following: the maximum dose (D_{max}) of the brainstem, optic nerves and optic chiasm $<54 \text{ Gy}$; the D_{max} for the spinal cord and lens $<45 \text{ Gy}$ and $<5 \text{ Gy}$; and the D_{mean} of the parotid gland and larynx $<35 \text{ Gy}$ and $<38 \text{ Gy}$, respectively. There were no specific dose constraints in IMRT planning for the constrictors, pituitary or thyroid glands.

There were no patients who underwent re-CT and replanning during the radiation treatment. The thyroid glands were contoured manually on the CT images of the treatment planning system with i.v. contrast with a window width of 181 and window level of -50 . The dosimetric data of the D_{min} , D_{max} and D_{mean} to the thyroid, the percentage of thyroid volume receiving $>x \text{ Gy}$ [V_x (%), $x = 10, 15, 20, 25, 30, 35, 40, 45, 50, 55$ and 60] and absolute thyroid volume were calculated and collected.

Thyroid function evaluation

We collected 3 ml of venous blood from patients in a commercially available tube (3 ml, serum separator tube) at each follow-up visit. After the blood coagulated, we isolated the plasma and serum by centrifugation at 3500 rpm for 5 min. The separated serum was stored at $15\text{--}30^\circ\text{C}$ and used within 8 h or stored at $2\text{--}8^\circ\text{C}$. The separated samples were frozen at -15 to -20°C if the assays were not completed within 48 h. Each sample was defrosted only once. The thyroid function was evaluated by testing TSH, fT3 and fT4 using the electrochemiluminescence method with the Elecsys 2010 analyzer (Hitachi High Technology

Corporation, Tokyo, Japan). The reference range was $0.27\text{--}4.20\ \mu\text{IU ml}^{-1}$, $3.1\text{--}6.8\ \text{pmol l}^{-1}$ and $12.0\text{--}22.0\ \text{pmol l}^{-1}$, respectively. After RT was completed, the thyroid hormone tests were conducted every 3 months during the first year and then every 6 months in the second to the fifth year. The testing was performed annually thereafter at the follow-up visit. The end point in this study was biochemical HT (TSH value $>4.2\ \mu\text{IU ml}^{-1}$) including both subclinical HT and overt HT. Central HT was defined as low fT3 and fT4 levels with a low or normal TSH level.

Statistical analysis

The dose–volume parameters of the thyroid gland were calculated using DVH. The cumulative incidence of RHT was estimated using the Kaplan–Meier method. We performed univariate analysis using Cox regression for both the clinical and dosimetric factors. LASSO was performed to select predictors and develop a multivariable Cox prediction model. The discrimination of Cox regression models with different combinations of variables (selected by LASSO) was evaluated using the concordance index (C-index) proposed by Harrell et al³³. The final model was chosen to build the nomogram after balancing prediction performance and practicability. LASSO with 10-fold

cross-validation was performed using the glmnet^{34,35} package in R (v. 3.3.1, available from: <https://www.r-project.org/>).

The nomogram based on the multivariate Cox regression model for RHT prediction was formulated through the package of rms³⁶ in R v. 3.3.1 (available from: <https://www.r-project.org/>). The prediction performance of the nomogram was measured using the C-index and calibration curves. We used bootstrap resampling (1000) for nomogram calibration. A *p*-value of <0.05 was considered statistically significant.

SPSS® v. 21.0 software (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) was used for all other analyses.

RESULTS

In this study, we analyzed the data from 164 patients (119 males and 45 females) with a median age of 49 years (range 16–69 years). A total of 32 (19.5%) patients were treated with the 3D-CRT technique; the other 132 (80.5%) patients were treated using IMRT. A total of 145 (88.4%) patients were treated with chemotherapy (additional details are given in Table 1).

Table 1. Patient characteristics and the correlation between clinical factors and radiation-induced hypothyroidism

Variables	<i>n</i> (%)	Univariate	Multivariate		
		<i>p</i> -value	<i>p</i> -value	HR	95% CI
Numbers	164				
Gender		0.012	0.005	2.415	2.218–2.612
Female	45 (27.4)				
Male	119 (72.6)				
Age (years)		0.979			
Median	49				
Range	16–69				
T stage		0.330			
1–2	64 (39.0)				
3–4	100 (61.0)				
N stage		0.155			
0	15 (9.1)				
1–3	149 (90.9)				
Stage		0.256			
I–II	18 (11.0)				
III–IV	146 (89.0)				
Technique		0.474			
3D-CRT	32 (19.5)				
IMRT	132 (80.5)				
Chemotherapy		0.101	0.051	6.822	0.920–50.589
Yes	145 (88.4)				
No	19 (11.6)				

3D-CRT, three-dimensional conformal radiotherapy; CI, confidence interval; HR, hazard ratio; IMRT, intensity-modulated radiotherapy.

After a median follow-up of 24 months (range 3–66 months), 38 (23.2%) patients developed biochemical HT. No patients were diagnosed with central HT. The estimated incidence of RHT was 6.8%, 14.3%, 22.2%, 24.6% and 26.6% at 6, 12, 18, 24 and 30 months, respectively. The median latency of HT was 10.5 months (range 3–48 months) after RT, and 34 (89.5%) patients developed HT within 18 months. The Kaplan–Meier curve for the cumulative incidence of RHT is shown in Figure 1.

The correlations between the thyroid dose–volume parameters and the incidence of RHT are shown in Table 2. The univariate Cox regression analysis indicated that gender, $D_{\min}$, D_{mean} and V_{25} – V_{60} of thyroid were significantly associated with RHT ($p = 0.012, 0.013, 0.000, 0.039, 0.022, 0.008, 0.001, 0.000, 0.000, 0.000$ and 0.018 , respectively). The LASSO analysis showed that the optimal predictors were gender, receiving chemotherapy or not (chemo), D_{mean} and V_{50} . A comparison of Cox regression models based on different variable combinations is shown in Table 3. The C-indexes for the three-variable (gender + chemo + V_{50}) and four-variable (gender + chemo + D_{mean} + V_{50}) Cox regression models were equal (0.72). A nomogram (Figure 2) based on the three-variable (gender + chemo + V_{50}) Cox regression model was constructed. Good accordance between prediction and observation was showed by calibration curves (Figure 3) in the probability of RHT at 18, 24 and 30 months.

DISCUSSION

HT is a common complication caused by RT in head and neck cancers. Previous studies reported a high incidence of RHT (>40%).^{15,37} The use of chemotherapy and the development of RT techniques such as IMRT have improved NPC treatment in the past decade.²⁷ Prolonged patient survival raises the issue of quality of life after treatment; thyroid function represents one primary concern.

In this study, the estimated incidence of RHT for patients with NPC was 6.8% at 6 months, 14.3% at 12 months, 22.2% at 18 months, 24.6% at 24 months and 26.6% at 30 months. These

results are similar to those in patients with NPC from other reports.^{16,24,32,38} The median latency of HT was 10.5 months after RT, and 89.5% of patients developed HT within 18 months. This finding is consistent with previous studies reporting that RHT primarily occurred in the first 2–3 years after RT.^{24,37} The latency of RHT is shorter when the thyroid gland receives higher doses.⁴¹ Therefore, regular follow-up for thyroid function in the first two years post-RT is particularly important for NPC survivors.

Diaz et al¹² reported that doses to the thyroid were higher in IMRT than that in 3D-CRT if the constraints were not set for thyroid during plan optimization. Doses to the thyroid may be reduced without compromising target coverage. The study by Cella et al¹⁷ showed that 42% of the 53 patients with Hodgkin's lymphoma treated by 3D-CRT experienced biochemical HT. The authors suggested V_{30} of 62.5% as the threshold value for the thyroid gland. However, it is difficult to reach that level during NPC RT planning owing to the high dose delivered to the neck area especially for patients with advanced nodal stage. Kim et al²¹ (114 patients, 29 patients with NPC), Sachdev et al²³ (75 patients, 5 patients with NPC) and Fujiwara et al²⁵ (116 patients, 8 with NPC) suggested 50% of V_{45} , 60% of V_{50} and D_{mean} of 30 Gy as possible thresholds for the thyroid gland in head and neck cancers, respectively. Lee et al²⁴ (149 patients with NPC) suggested that volume spared from 60 Gy or less $\geq 10 \text{ cm}^3$ and volume spared from 45 Gy or less $\geq 5 \text{ cm}^3$ should be the constraints to prevent HT.

Boomsma et al¹³ built an NTCP model based on the D_{mean} and volume of the thyroid for RHT prediction. In their study, when the Pearson's product moment correlation coefficients were not < 0.80 between the two variables, one of the variables was excluded from the multivariate analysis to avoid the problem of multicollinearity. The bootstrapping technique was applied for logistic regression variable selection.⁴² A similar methodology was applied in the study by Cella et al.¹⁸ The authors reported a three-variable NTCP model for Hodgkin's lymphoma. Bakhshandeh et al²⁸ (65 patients, 11 patients with NPC) compared 6 RHT NTCP models, and the mean dose model was identified as the best model according to Akaike's information criterion value. The study by Ronjom et al¹⁴ used a mixture NTCP model considering latency time and found that the independent risk predictors for RHT were the volume and D_{mean} of the thyroid. The constraints from the NTCP model derivation for a 25% risk of HT were 26, 38, 48 and 61 Gy of D_{mean} for thyroid volumes of 10, 15, 20 and 25 cm^3 , respectively.

We selected gender, chemotherapy, D_{mean} and V_{50} using LASSO in our study. We found that female gender and D_{mean} were risk factors, as was found in previous studies.^{8,9,13,14,25} The role of chemotherapy as a risk factor of RHT is unclear;^{10,43,44} however, in our nomogram, chemo plays a significant role in RHT prediction (Figure 2, >70 points) because there was only 1 patient diagnosed with RHT who did not receive chemotherapy [(11.6%) 19 patients]. The study by Sachdev et al²³ identified V_{50} as the only risk factor using a receiver-operating characteristic curve to obtain the cut-off point of V_{50} for patients with RHT. Our study identified four risk factors suitable for the nomogram analysis.

Figure 1. The Kaplan–Meier curve for the cumulative incidence of radiation-induced hypothyroidism (RHT).

Table 2. Univariate and multivariate analysis of dosimetric variables

Variables	Mean $\pm$ SD	Univariate	Multivariate		
		<i>p</i> -value	<i>p</i> -value	HR	95% CI
Volume (cc)	17.327 $\pm$ 8.139	0.642			
$D_{\min}$ (cGy)	2003.622 $\pm$ 1290.328	0.013			
D_{mean} (cGy)	4285.144 $\pm$ 1024.424	0.000			
$D_{\max}$ (cGy)	6575.549 $\pm$ 548.037	0.611			
V_x (%)					
V_{10}	91.095 $\pm$ 16.496	0.085			
V_{15}	88.908 $\pm$ 19.097	0.078			
V_{20}	86.815 $\pm$ 21.095	0.053			
V_{25}	84.502 $\pm$ 22.945	0.039			
V_{30}	81.241 $\pm$ 25.159	0.022			
V_{35}	75.430 $\pm$ 24.911	0.008			
V_{40}	63.834 $\pm$ 22.970	0.001			
V_{45}	52.031 $\pm$ 21.481	0.000			
V_{50}	40.239 $\pm$ 19.919	0.000	0.000	1.027	1.012–1.042
V_{55}	25.531 $\pm$ 16.794	0.000			
V_{60}	12.667 $\pm$ 13.297	0.018			

CI, confidence interval; $D_{\max}$, maximum dose; D_{mean} , mean dose; $D_{\min}$, minimum dose; HR, hazard ratio; SD, standard deviation; V_x (%), percentage of thyroid volume receiving $>x$ Gy.

As noted above, various clinical and dosimetric predictors were previously considered as risk factors for RHT. However, no studies have presented these risk factors in a visual format such as the nomogram. The advantage of the nomogram compared with conventional multivariate regression models is that all the crucial predictors for RHT can be graphically displayed instead of presenting a complex NTCP model. The optimal predictors

were selected using the LASSO method, which handles the multicollinearity problem between variables and prevents data overfitting in the Cox regression model. The nomogram was built to predict the probability of RHT and to access the individual dose constraint according to clinical (gender and chemo) and dosimetric (V_{50}) parameters using a more practical method.

Table 3. Comparison of Cox models based on different variable combinations

Variable combination	C-index	95% CI
V_{50}	0.67	0.65–0.68
D_{mean}	0.66	0.64–0.67
Chemo + D_{mean}	0.67	0.66–0.69
Gender + D_{mean}	0.70	0.68–0.71
Chemo + V_{50}	0.69	0.67–0.70
Gender + V_{50}	0.69	0.68–0.71
Gender + chemo + V_{50}	0.72	0.70–0.73
Gender + chemo + D_{mean}	0.71	0.70–0.72
Gender + D_{mean} + V_{50}	0.70	0.68–0.71
Chemo + D_{mean} + V_{50}	0.68	0.67–0.70
Gender + chemo + D_{mean} + V_{50}	0.72	0.70–0.73

Chemo, chemotherapy or not; CI, confidence interval; C-index, concordance index; D_{mean} , mean dose; V_{50} , percentage of thyroid volume receiving >50 Gy.

We used data from a prospective study and excluded the patients with surgery before or after RT to create a relatively

Figure 2. Nomogram for radiation-induced hypothyroidism (RHT) prediction.

Figure 3. Calibration curves for the probability of radiation-induced hypothyroidism (RHT) at 18 (a), 24 (b) and 30 (c) months.

homogeneous patient population (NPC). This patient selection improves the reliability of the dose–response analysis. However, there are limitations to our study. The median follow-up (24 months) of our study was relatively short. In addition, this was a retrospective study and the sample size was relatively small. Thus, a prospective study with a longer follow-up period is necessary to validate our results. The thyroid DVH data were not converted to an equivalent dose in 2 Gy/fraction because

different parts of the thyroid glands received different fractionation doses (1.8 or 2.0 Gy) in several cases.

CONCLUSION

This study built a nomogram for RHT in NPC survivors by analyzing both clinical and dose–volume parameters with LASSO. An individual dose constraint based on different clinical and dosimetric predictors can be achieved using this nomogram.

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