Original Article

Development and validation of a normal tissue complication probability model for acquired nasal cavity stenosis and atresia after radical radiotherapy for nasopharyngeal carcinoma

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Purpose: Curative radiotherapy for nasopharyngeal carcinoma (NPC) can lead to acquired nasal cavity stenosis and atresia (ANCSA). As the first study to investigate risk factors of ANCSA in a large cohort of NPC patients, this article aims to develop and validate a multivariate normal tissue complication probability (NTCP) model to predict the development of ANCSA and to establish a nomogram for clinical use.

Methods and materials: The retrospective cohort was comprised of 548 NPC patients treated with radical radiotherapy. The cohort was randomly divided into training and validation groups. Least absolute shrinkage and selection operator regression was performed for variable selection from the clinical and dosimetric characteristics in the training group. A multivariate NTCP model and a nomogram were established for the prediction of ANCSA development. Discrimination and calibration were tested using receiver operating characteristic (ROC) curves and calibration tests, respectively, for both groups.

Results: ANCSA was observed in 132 (24.1%) of 548 patients with NPC who underwent radical radiotherapy. The median time to ANCSA detection after treatment was 2.8 months (range, 0.0–57.7 months). Five potential predictors, including choanal invasion, low white blood cell count, high C-reactive protein level, high serum amyloid A level, and high V70Gy of the nasal cavity, were selected to develop the NTCP model based on 365 patients in the training group. The model had a fairly good discriminative power according to the ROC analysis in both the training (area under ROC curve = 0.79, 95%CI: 0.73–0.84) and validation (0.73, 0.64–0.82) groups. The calibration power was tested using the calibration test in the training (E-max = 0.069, E-avg = 0.015, p = 0.977) and validation (E-max = 0.057, E-avg = 0.032, p = 0.747) groups.

Conclusions: We developed and successfully validated an NTCP model for early prediction of ANCSA in patients with NPC after radical radiotherapy. This could help clinicians assess the risk of ANCSA before the initiation of follow-ups and ensure appropriate and timely management of this complication.

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Nasopharyngeal carcinoma (NPC) is an endemic malignancy in East and South-East Asia. With the widespread application of intensity-modulated radiotherapy (IMRT) and optimization of chemotherapy regimens, the mortality rate of patients with NPC has been reduced substantially. According to previous studies, the 5-year overall survival rates for patients with stage I-IV NPC were 100%, 91%, 72%, and 44% respectively, meaning NPC has become a highly curable disease [1–4]. However, the quality of life in survivors is often highly impaired because of toxicity associated with comprehensive radical treatment [5,6].

Acquired nasal cavity stenosis and atresia (ANCSA) is a common toxicity observed in patients with NPC after radiotherapy. Postirradiation ANCSA, defined as irreversible nasal obstruction or transnasal respiratory malfunction after radiation to the nasal cavity, can be diagnosed by the use of nasal airway obstruction score,
nasal obstruction symptom evaluation, peak nasal inspiratory flow test, 4-phase rhinomanometry test, or diagnostic imaging [7]. Transnasal endoscopy (TNE), magnetic resonance imaging (MRI), and computed tomography (CT) of the nasopharynx are the most commonly used imaging techniques in clinical practice. Acquired nasal cavity stenosis is diagnosed using TNE when nasal obstruction, adhesion, or changes in mucosal morphology that cannot be restored using a vasoconstrictor occur. Furthermore, acquired nasal cavity atresia is diagnosed if a blind end is detected using endoscopy [8].

ANCSA is rarely studied as a complication of curative radiotherapy in large cohorts of NPC patients. The prevalence of ANCSA ranges from 10.7% to 43.5% in patients with NPC, and it has only been investigated in a few studies involving small sample sizes [9,10]. ANCSA can lead to various symptoms, including hypoxemia, headache, anosmia, sinusitis, aggravation of xerostomia, and increased difficulty of early detection of recurrence or nasopharyngeal necrosis [8,11,12]. Development of early-stage nasal cavity adhesion can be prevented using a simple TNE examination, which indicates that early detection is essential for preventing aggravation of such complications. Liu et al [8] reported that the management of early-stage ANCSA using TNE substantially reduced symptoms of xerostomia, obstruction, and anosmia. Compared to surgery for severe nasal cavity stenosis and atresia, disease management using TNE at an early stage was shown to be easier, safer, and more efficient [16]. However, most studies have focused on various management strategies for advanced stages of ANCSA, including transnasal endoscopic resection, temperature-controlled radio frequency repair, and the application of septonal bidirectional mucoperiosteal flap [8–11,13–16]. Risk factors associated with ANCSA after radical radiotherapy for NPC must be urgently identified to distinguish patients at high risk, thus enabling early detection and management. As the first study to investigate risk factors of ANCSA after radical radiotherapy in a large cohort of NPC patients, we aimed to develop and validate a multivariate normal tissue complication probability (NTCP) model for predicting this side effect and to establish a nomogram for clinical use.

Methods and materials

Patients and characteristics

This study included 1399 consecutive patients with pathologically confirmed NPC who underwent curative radiotherapy with or without chemotherapy in the authors’ institution between January 2010 and October 2016. Using the following inclusion criteria, 548 patients were screened for inclusion from among 1399 patients: a) age ≥ 18 years; b) no diagnosis of metastatic disease; c) radiotherapy conducted with IMRT and dosimetric data available; d) endoscopy follow-up data available; e) no diagnosis of congenital or acquired nasal cavity stenosis or atresia before treatment; f) no prior history of radiotherapy to the head and neck region. The resulting cohort was randomly divided into a training group and a validation group with a ratio of 2:1. This retrospective study was approved by the Clinical Research Ethics Committee of the authors’ institution (IRB number B2021-050-01), and all participants provided written informed consent before treatment.

Patients accepted different radical radiotherapy regimens, including concurrent chemoradiotherapy and radiotherapy alone. IMRT was administered to all patients. The radiotherapy regimen included, 2.12–2.33 Gy per fraction per day, five times per week. The following were the total doses administered to the target areas: Planning Target Volume of nasopharynx (PTVnasopharynx): 68–70 Gy; PTV<inf>lymph node</inf>: 64–70 Gy; PTV<inf>1</inf>: 60–64 Gy; and PTV<inf>2</inf>: 50–54 Gy. Dose calculation for radiotherapy plans was done in Eclipse using an anisotropic analytical algorithm (AAA). Dose calculation grid size was 2.5 mm. For most patients, concurrent cisplatin (80–100 mg/m², Q3W) was administered during radiotherapy. A few regimens, including the TP/docetaxel, cisplatin and fluorouracil, PF/cisplatin and fluorouracil, and TP/docetaxel, cisplatin regimens, combined two to three cycles of neoadjuvant chemotherapy with concurrent chemoradiotherapy.

Baseline clinicopathological data were drawn from the institutional database. Notably, tumor invasion of the choanae was diagnosed using MRI examination before treatment. Blood tests for the detection of inflammatory indicators were conducted within 1 week of the end of radiotherapy. Budesonide nasal spray (64 μg/spray, 120 sprays/bottle), claritine (10 mg/tablet, 6 tablets/box), ambroxol hydrochloride (30 mg/tablet, 20 tablets/box), and eucalyptol-based medicine (300 mg/capsule, 10 capsules/box) were prescribed to patients after treatment based on their complaints.

Nasal cavity dosimetry

Structures of the nasal cavity were retrospectively contoured on contrasted simulation CT images based on the anatomic atlas proposed by Neil et al. [Supplement Fig. 1] [17]. The ANCSA status of the patients was blinded from the investigators during contouring. The details of the structure that made up the superior border of contour included two nasal bones, the lower part of the frontal bone, the cribiform plate of the ethmoid bone, and the sphenoid bone. The lower parts of the nasal bones, the cartilage attached to them, and the posterior border of the nasal vestibule formed the anterior border. The upper-back and sides were bordered with a number of cranial bones including the maxilla, ethmoid bone, palatine bone, sphenoid bone, and the back of the nasal septum. The hard palate made up its floor. Dosimetric parameters, including volume of the nasal cavity, D<inf>mean</inf>, D2%, D98%, and the relative volumes receiving 5–75 Gy, in 5 Gy dose bins (V5Gy–V75Gy) were determined from dose-volume histograms, which were generated from the original radiotherapy plans and the retrospectively contoured volumes.

Endpoints

The detection and diagnosis of ANCSA was based on TNE (Fig. 1). TNE examinations were conducted as routine follow-ups at 0, 1st, 3rd, 6th, and 12th month after treatment completion, followed by every half year within the first three years, and once a year thereafter. A Hopkin’s rigid endoscope (Karl Storz, Tuttlingen, Germany), with an insertion tube of 4 mm diameter, 0° viewing angle, and a charge-coupled device camera (Karl Storz, Germany), was used for the examination. ANCSA free (ANCSAF) was defined as the length of time from the end of radiotherapy that patients did not have ANCSA.

Statistical analysis

Clinicopathological characteristics and dosimetric parameters in both the training and validation groups were assessed using the Mann-Whitney U test and the chi-squared test. To develop a prediction model for the endpoint analysis, univariate logistic regression analyses were first performed to show the effect of each factor on the end point in the training group. [18]. Variables with p-value less than 0.2 in univariate analysis were included [19] in the least absolute shrinkage and selection operator (LASSO) regression for the training group. Before LASSO regression analysis, the continuous clinicopathological variables with an area under the curve (AUC) > 0.5 and p < 0.05 were converted into nominal variables based on the Youden index (YI). Z-
score was applied to standardize variables with different dimensionality based on training group for LASSO regression. LASSO regression is a logistic regression analysis method with a penalty for the magnitude of the regression coefficients. By adjusting the penalty value ($\lambda$), LASSO regression shrinks the regression coefficients down to zero for insignificant ANCSA predictors and therefore selected significant predictors. Using LASSO regression prevents overfitting and solves collinearity of the candidate variables. The optimal penalty value ($\lambda$) was determined by the one standard error of the minimum criteria (1-SE criteria) selected by cross-validation [20–23]. The software RStudio (v1.2.1335, Boston, MA, USA) was used for statistical analysis above.

Forward stepwise multivariate logistic regression was used to develop the prediction model with variables selected from the training group. The final NTCP model was selected using the likelihood ratio test with the Akaike information criterion as the stopping rule. In addition, odds ratios (ORs) and 95% confidence intervals (CIs) of the final predictive variables were calculated. The ANCSA risk score was calculated as:

\[ \text{NTCP} = 1/(1 + e^{-S}) \]

with $S$ being a linear combination of selected variables, weighted by their corresponding regression coefficients. The software Stata/SE (v13.1, StataCorp, College Station, TX, USA) was used for the statistical analysis above.

Model performance was evaluated using the receiver operating characteristic curve (ROC) and calibration tests. Discrimination performance was quantified using the ROC curve. Calibration tests were conducted to verify the calibration of the model [24,25]. The nomogram for clinical use were created based on the multivariate NTCP model. The Kaplan–Meier method and the log-rank test were used to verify the difference in ANCSA free rate between the high-risk and low-risk groups and the overall survival rate of the whole cohort. The software RStudio (v1.2.1335, Boston, MA, USA) was used for the statistical analysis above.

**Results**

The whole cohort included 548 NPC patients without metastasis who underwent radical radiotherapy with or without chemotherapy. There were 365 patients and 183 patients included in the training group and validation group, respectively. There were no significant differences among the clinicopathological and dosimetric variables between the training group and validation group (Supplement Table 1).

The mean and median TNE follow-up duration after patients finished treatment were 32 and 31 months, respectively. ANCSA occurred in 132 (24.1%) patients with an incidence of 24.4% and 23.5% ($p = 0.819$) in the training and validation groups, respectively. Among the patients with ANCSA, 21 (15.9%) patients had severe ANCSA, which was defined as atresia of both choanal openings, and 56 (42.4%) had bilateral ANCSA. The median time until ANCSA detection after treatment was 2.76 months (range, 0.00–5 7.69 months). The median follow-up duration of the survivals in the whole cohort was 65.08 months with a 1-year overall survival rate of 99.3%. Four out of 548 patients died within 1 year. The most common location of detection was the inferior nasal meatus (40.9% left nasal cavity and 33.3% right nasal cavity). Dose volume histogram (DVH) ± 2 standard error of mean (SEM) of the nasal cavity showed that ANCSA positive patients tended to have higher relative volume to all doses compared to ANCSA negative patients (Supplement Fig. 2).

Clinicopathological characteristics and dosimetric parameters (41 independent variables and 1 dependent variable) in the training and validation groups are listed in Table 1. Using univariate analysis of the training group, 32 out of 41 variables ($p < 0.2$) were selected for multivariate analysis (Table 1). In the univariate logistic analysis of ANCSA in the whole cohort of 548 patients (Supplement Table 2), gender (OR: 1.75, 95% CI: 1.14–2.68, $p = 0.010$), smoking history (OR: 0.65, 95% CI: 0.44–0.97, $p = 0.034$), stage T (OR: 1.46, 95% CI: 1.11–1.91, $p = 0.007$), chemotherapy (OR: 3.69, 95% CI: 1.30–10.47, $p = 0.014$), lymphocytes count (OR: 0.47, 95% CI: 0.17–0.98, $p = 0.044$), and the use of Myrtol standardized medicine (OR: 0.96, 95% CI: 0.94–0.99, $p = 0.003$) were identified as related to ANCSA after radical radiotherapy in NPC patients.

Five out of nine clinicopathological continuous variables were converted into nominal variables for the training group, including white blood cells (WBCs) (cut-off value = 3.29 E09/L, YI = 0.218), lymphocytes (0.405 E09/L, YI = 0.174), eosinophils (0.045 E09/L, YI = 0.164), C-reactive protein (CRP) level (3.145 mg/L, YI = 0.187), and serum Amyloid A (SAA) (56.2 mg/L, YI = 0.187).

Using the LASSO regression in the training group, the optimal penalty value ($\lambda$) of 0.0139 resulted in five non-zero coefficients out of 32 variables (Fig. 2). Stepwise multivariate logistic regression verified that all five factors were independent predictors of...
## NTCP model for ANCSA in patients with NPC

<table>
<thead>
<tr>
<th>Characteristic No.</th>
<th>Training Cohort</th>
<th>Validation Cohort</th>
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<td>Chemotherapy(*)</td>
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### Table 1: Comparison of Clinical-pathological and Dosimetric Characteristics between ANCSA(+) and ANCSA(-) patients in the Training cohort and Validation cohort.

- **Characteristics No.**:
  - Gender, Male
  - Age, years
  - BMI, kg/m²
  - Allergy History(*)
  - Smoking History(*)
  - HBV Infection(*)
  - Stage T
  - Stage N
  - Choanal Invasion(*)
  - Chemotherapy(*)
  - WBC ≤ 3.29E9/L
  - Neutrophils, E9/L
  - Monocytes, E9/L
  - Lymphocytes ≤ 0.405E9/L
  - Eosinophils ≤ 0.04SE9/L

- **Training Cohort**
  - ANCSA(-) / ANCSA(+)

- **Validation Cohort**
  - ANCSA(-) / ANCSA(+)

### Notes:
- P-values are provided for statistical significance.
- NTCP model for ANCSA in patients with NPC.
ANCSA after radical radiotherapy for NPC patients in the training group, including choanal invasion (OR: 2.03, 95%CI: 1.10–3.72, \(p = 0.022\)), WBC count (OR: 2.28, 95%CI: 1.33–3.91, \(p = 0.003\)), SAA level (OR: 2.60, 95%CI: 1.27–5.29, \(p = 0.009\)), CRP level (OR: 2.45, 95%CI: 1.35–4.43, \(p = 0.003\)), and V70Gy of the nasal cavity (OR: 1.68, 95%CI: 1.23–2.28, \(p = 0.001\)).

The respective coefficients of variants formula \(S\) are shown below:

\[
S = -2.533852 + 0.706174 \times (\text{Choanal Invasion}) \\
+ 0.8244032 \times (\text{WBC}) + 0.9541486 \times (\text{SAA}) + 0.8953562 \times (\text{CRP}) + 0.5177874 \times (V70Gy)
\]

NTCP risk was shown to increase as V70Gy increased in both choanal invasion patients and non-choanal invasion patients with different risk factors (Fig. 3). A nomogram (Supplement Fig. 3) was constructed with the above independent predictors for clinical use. The status of each risk factor corresponded to a specific score from 0 to 100 on the point scale, and for each individual, a total score could be calculated with all the factors considered. The NTCP of ANCSA can be easily estimated by locating the total score on the scale. For individual cases, a probability higher than 21.7% in the NTCP model (\(Y1 = 0.479\)) were considered a high-risk group for ANCSA, and a probability lower than 21.7% were considered a low-risk group. The ANCSAF rates after radiotherapy were significantly different between high-risk patients and low-risk patients (\(p < 0.001\), Fig. 4). The NTCP model was demonstrated to have fairly good discrimination power\(^{26}\) based on the area under the ROC curves of the training group (AUC = 0.79, 95%CI: 0.73–0.84, \(p < 0.001\)) and the validation group (AUC = 0.73, 95%CI: 0.64–0.82, \(p < 0.001\)) (Fig. 5A). The calibration power was tested using the calibration test in the training group (\(E_{\text{max}} = 0.069, E_{\text{avg}} = 0.015, p = 0.977\), Fig. 5B) and validation group (\(E_{\text{max}} = 0.057, E_{\text{avg}} = 0.032, p = 0.747\), Fig. 5C), which showed satisfactory agreement between predicted and observed values.

**Discussion**

The main objective of this study was to develop a predictive model for ANCSA. We randomly divided our cohort into a training group and a validation group. There was no significant difference among the demographic variables between the training and validation groups except for gender, which was not selected as a predictive factor in the model. The analysis resulted in a model with five
highly predictive factors, including choanal invasion, WBC count, SAA level, CRP level, and V70Gy of the nasal cavity. The model showed fairly good discrimination [26] and was well-calibrated in both the training and validation groups, and this model may provide valuable guidance in clinical decision making. To our knowledge, this is the first large cohort study of NPC patients to investigate the association between the probability of ANCSA after radical radiotherapy and dosimetric parameters or clinicopathological characteristics. Furthermore, this is the first study to establish and validate an NTCP model for ANCSA after primary radiotherapy with curative intent in patients with NPC.

NPC is an endemic malignancy that rarely occurs outside East and South-East Asia. Moreover, TNE is not routinely performed in most institutions until recurrence is observed through other examinations, or until severe symptoms are caused by an obstruction in the nasal cavity. Thus, previous studies have tended to underreport ANCSA as a rare complication with severe adhesion [9,14–16,29,31], due to their mostly small sample sizes and their focus on the management of patients with severe ANCSA [9,14–16,29,31].

However, there is a high incidence of ANCSA in NPC patients after treatment. According to a few studies from the prevalent area, the incidence of ANCSA among NPC patients was reported as 10.7%, 28.5%, and 43.3% [9,10]. In our results, the incidence of ANCSA was 24.1% (132/458), which is in line with previous reports. Among 132 patients with ANCSA, 21 (15.9%) had severe ANCSA (Fig. 1), which indicates atresia of both sides of the nasal cavity, and 56 (42.4%) had bilateral stenosis or atresia.

Early detection of ANCSA may be more effective than surgery in preventing development of severe ANCSA [8]. Kamel et al. reported that early hyperemia, edema, macerated mucosa, and discharge in the nasal cavity after radiation could be replaced by delayed adhesions, choanal stenosis, and/or atresia [33]. Although the difference was not significant, the present study found that the mean detection time of severe ANCSA (6.45 months) was one month later than that of mild and moderate ANCSA (5.44 months). In our clinical practice, except for patients diagnosed with severe ANCSA in their first TNE after treatment, most patients with early-stage adhesion in the nasal cavity could be managed effectively with endoscopic examinations using gun-shaped forceps, suctions, ephedrine, and gel foam. The management of early-stage ANCSA through TNE could substantially reduce the symptoms of xerostomia, obstruction, and anosmia.

Postirradiation ANCSA, defined as irreversible nasal obstruction or transnasal respiratory malfunction after radiation to the nasal cavity, can be diagnosed through endoscopy by the detection of nasal obstruction, adhesion, or changes in mucosal morphology, which cannot be restored by a vasoconstrictor. Furthermore, acquired nasal cavity atresia is diagnosed if a blind end is detected on endoscopy.

Although there is a lack of research investigating the pathology of ANCSA, we surmised that the changes in nasal mucosa after radiotherapy might be associated with mucosal non-infective inflammation and histomorphologic changes, including hypersecretion by goblet cells immediately after irradiation, stratified rearrangement of epithelial cells, gradual reduction of cytoplasmic volume, and higher percentages of neutrophil inflammation. Rhi-
norhea, nasal obstruction, and nasal mucosal hyperemia were observed in patients with NPC as gross pathologic changes during endoscopic examination after treatment [34–36]. Therefore, we suggested that susceptibility to ANCSA might be related with the degree of nasal mucositis. Moreover, clinical factors, including inflammatory markers and dosimetric parameters that were related to mucositis, were taken into consideration in the present study. In our clinical practice, ANCSA is commonly observed during the process of gradually repairing nasal mucosa after radiotherapy. Therefore, we suggested that utilizing blood tests after radiotherapy and along with the NTCP model constructed in this study to predict ANCSA risk soon after radiotherapy could be beneficial to patients under current radiotherapy technology.

For individual cases, scores higher than 46 in the nomogram (YI = 0.479) should be considered as high-risk for ANCSA, and the importance of regular endoscopic examination for early detection should be stressed. Patients with a score lower than 46 should be considered as low-risk. Fig. 4 showed that the ANCSAF rate for high-risk patients dropped rapidly after radiotherapy and was significantly lower than for low-risk patients. According to our NTCP model, high susceptibility to ANCSA in NPC patients is associated with choanal invasion, higher V70Gy, SAA level higher than 56.2 mg/L, CRP level higher than 3.145 mg/L, and WBC count lower than 3.29 E09/L.

Previous studies have reported that tumor location and high doses of radiotherapy are related to postirradiation stenosis in the vaginal canal and esophagus [37–40]. In line with these studies, the present research showed choanal invasion as a predictive factor that highly contributes to the development of ANCSA. Choanal invasion led to higher dose distribution in the nasal cavity and also resulted in more damage to the nasal cavity due to tumor recession after radiotherapy. Both of these factors accounted for severe mucositis [41], which might explain the higher ANCSA risk associated with choanal invasion. Multivariative regression analysis found that high radiation dose distribution in the nasal cavity (>70 Gy) was another predictor of ANCSA. Although we ought not to compromise the dose distribution of the gross tumor volume or the clinical target volume in order to lower V70Gy of the nasal cavity, with today’s photon radiotherapy, the importance of routine follow-ups in shorter intervals should be emphasized for patients with high V70Gy. With the development of intensity-modulated proton therapy (IMPT) and intensity-modulated carbon ion therapy (IMCT), photon radiotherapy might be replaced by these new methods in NPC treatment in the future. In theory, the dose distribution of NPC treatment plans will be more evidence-based, and the volume of nasal cavity V70Gy can be further reduced due to the characteristics of Bragg peak effect of proton/ion beams. However, further studies are needed to confirm whether IMPT/IMCT therapy could reduce the incidence of ANCSA due to the different biological effects of photon beams and proton/ion beams.

An important finding of the present study is the selection of inflammation-related indicators as positive predictive factors for ANCSA. CRP and SAA proteins are the most prominent members of the acute phase response, which results in high serum levels after trauma, infection, and other stimuli, and they are widely used as inflammation markers [42]. CRP was further shown to facilitate complement binding and immune cell activation and was demonstrated to amplify inflammation and tissue damage in a broad range of clinical conditions [43]. Our results are in agreement with these findings because higher levels of CRP and SAA, serving as amplifiers of mucositis, were revealed as risk factors of ANCSA.

In contrast to the empirical observation that high WBC counts are usually related to inflammation, low WBC counts were another predictive factor in our model. Along with other neutrophilic inflammation after treatment, the infiltration of neutrophils as a cytological change was observed in the nasal cavity after radiotherapy (33), which may contribute to the high consumption of neutrophils. At the same time, myelosuppression caused by chemotherapy and radiotherapy accounts for insufficient supply of neutrophils. Unsurprisingly, when neutrophil consumption surpasses neutrophil supply, a decrease in WBC count in the peripheral blood would be observed [44]. Moreover, severe mucositis could lead to increased destruction of neutrophils and lower WBC counts. Therefore, the previously reported association between low WBC counts and severe treatment toxicities could potentially explain results found in this study.

The multivariate approach and nomogram made it possible to integrate different predictive variables in estimating the risk of developing ANCSA. The combination of clinical and dosimetric factors may also improve the prediction of endpoints [45]. Along with our study, prior research reported that dosimetric parameters are related to ANCSA after radiotherapy in NPC patients. In a self-controlled study by Chang et al [31] that involved 49 ANCSA patients, the susceptibility to ANCSA in NPC patients after radiotherapy was related with a higher mean dose, dose covering ≥ 33%
volume (D33), dose covering ≥ 66% volume (D66), and volume receiving ≥ 60 Gy (V60) with AUC values in the range of 0.67–0.69. However, Chang et al.’s study did not conduct multivariable regression or take clinical characteristics into consideration. In our study, the prediction model had a higher AUC value in both the training and validation groups, which indicated that combining dosimetric and clinical characteristics could improve the discrimination and accuracy of the prediction model. Therefore, the dose–effect relationships for the endpoint are described using multivariable NTCP curves instead of a univariate NTCP curve.

Additionally, it should be noted that, although they were excluded from the multivariate regression and the final model, gender, smoking history, stage T, lymphocytes count, monocytes count, chemotherapy, and the use of Myrtol standardized medicine were identified as related to ANCSA in the univariate logistic analysis. Myrtol standardized medicine, a secretomucolytic phytotherapy, is prescribed to patients with excessive nasal mucous discharge after radiotherapy in our clinical practice. It is commonly used in treating upper respiratory infection or inflammation by enhancing airway mucous clearance [46]. This might indicate that Myrtol standardized medicine could be used to reduce nasal mucous discharge and help prevent the occurrence of ANCSA. However, budesonide nasal spray, ambroxol hydrochloride, or claritryn, which were also prescribed for relieving nasal mucus discharge, were not found to be effective in preventing ANCSA. One possible explanation is that these three medicines were not commonly used and fewer samples were collected in the present study. Larger samples will be needed for further investigations.

This study has several limitations. First, the model was developed and validated based on two retrospective groups. Further validation in prospective cohorts is needed in future studies. Second, the model was established based on cases from a single center. Thus, caution is required during widespread application of this model, and further study needs to be conducted in different hospitals to validate our results. Third, our study could not verify the efficacy of medicines that prevent ANCSA, and a prospective trail is necessary to investigate their efficacy.

In conclusion, the generated NTCP model, along with the nomogram, is a simple and accurate tool for early prediction of ANCSA in patients with NPC after radiotherapy. With the application of this model, clinicians can easily assess the risk of ANCSA before initiating follow-ups and develop the most appropriate strategy for complication management. However, further validation of our result should be conducted in different centers using prospective cohorts, and the efficacy of medicines used to prevent ANCSA warrant further investigation.

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Ethics approval and consent to participate

This retrospective study was approved by the Clinical Research Committee of Sun Yat Sen University Cancer Center. IRB number is B2021-050-01.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.03.040.

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