Radiotherapy and Oncology 131 (2019) 35–44

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

The value of detailed MR imaging report of primary tumor and lymph nodes on prognostic nomograms for nasopharyngeal carcinoma after intensity-modulated radiotherapy

Yanzi Wan [a,1], Li Tian [b,c,1], Guoyi Zhang [d], Hongyu Xin [a], Haojiang Li [b,c], Annan Dong [b,c], Yiqin Liang [a], Bingzhong Jing [b,c], Jian Zhou [b,c], Chunyan Cui [b,c], Mingyuan Chen [b,c], Ying Sun [b,c], Chuanbo Xie [b,c], Lizhi Liu [b,c,e,*], Yuanzhi Shao [a,*]

[a] School of Physics, Sun Yat-sen University, Guangzhou; [b] Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China; [c] Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou; [d] Department of Radiation Oncology, Cancer Center, First People's Hospital of Foshan; and [e] Department of Radiology, The Third People's Hospital of Shenzhen

ARTICLE INFO

Article history:
Received 12 May 2018
Received in revised form 23 October 2018
Accepted 6 November 2018
Available online 20 December 2018

Keywords:
Nasopharyngeal neoplasms
Magnetic resonance imaging
Nomograms
Survival analysis

ABSTRACT

Purpose: To establish effective prognostic nomograms using clinical features and detailed magnetic resonance imaging (MRI) findings for primary tumor and regional lymph nodes after intensity-modulated radiotherapy (IMRT) in patients with nasopharyngeal carcinoma.

Method: The nomogram for overall survival (OS) was based on a retrospective study of 595 patients who underwent IMRT at Sun Yat-sen University Cancer Center from 2010 to 2012. The predictive accuracy and discriminative ability of our nomogram models were determined by concordance index and calibration curve, and were compared with the nomogram models combining clinical features with tumor-node-metastasis (TNM) classification. The results were validated using bootstrap resampling and a cohort study of 241 patients. The same data cohort was used to predict the progress-free survival (PFS) of nasopharyngeal carcinoma with 3:1 training cohort ($N = 558$) and validation cohort ($N = 278$).

Results: The following factors were assembled into our prognostic survival nomogram models: Age, Epstein–Barr virus DNA copy number before treatment (EBV_DNA_CN), tensor veli palatini (TVP) involvement, musculus pterygoideus lateralis (MPL) involvement, prestyloid space (PS) involvement, prevertebral space (PVS) involvement, base of sphenoid bone (BOSB) involvement, paranasal sinus (PNS) involvement, the laterality of Ⅱ (Ⅱ_laterality), the laterality of retropharyngeal lymph node (RPLN_laterality), nodal grouping (NG), extranodal neoplastic spread (ENS), contrast-enhancing rim (CER) and Nodal_number. The calibration curves showed good agreement between nomogram-predicted and actual survival. Our nomogram models for OS and PFS, provided better results than the nomogram models combining clinical features with TNM classification. Results were further confirmed in the validation set.

Conclusion: Detailed MRI findings of primary tumor and regional lymph nodes can improve the performance of prognostic nomograms for patients with nasopharyngeal carcinoma.

Abbreviations: NPC, nasopharyngeal carcinoma; MRI, magnetic resonance imaging; CT, computed tomography; IMRT, intensity-modulated radiotherapy; TNM, tumor-node-metastasis; AJCC, American Joint Committee on Cancer; UICC, Union for Cancer Control; OS, overall survival; PFS, progress-free survival; LASSO, least absolute shrinkage and selection operator; C-index, concordance index; SPSS, statistical package for the social sciences; EBV, Epstein–Barr virus; EBV_DNA_CN, Epstein–Barr virus DNA copy number before treatment; EA-IgA, early antigen-immunoglobulin A; VCA-IgA, viral capsid antigen-immunoglobulin A; WBC, white blood cell count; LYMPH, lymphocyte count; PLT, platelet count; HbsAg, hepatitis B virus surface antigen; LDH, lactate dehydrogenase; KPS, Karnofsky's performance scale; WHOHT, World Health Organization histologic type; TM, therapeutic model; TVP, tensor veli palatini; MPL, musculus pterygoideus lateralis; PS, prestyloid space; PVS, prevertebral space; BOSB, base of sphenoid bone; PNS, paranasal sinus; RPLN, retropharyngeal lymph node; PLN, parotid lymph nodes; ENS, extranodal neoplastic spread; NG, nodal grouping; CER, contrast-enhancing rim; CN, central necrosis; RDD, research data deposit; DFS, disease-free survival; DMFS, distant metastasis-free survival; CI, confidence interval; BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; NLR, neutrophil–lymphocyte ratio; GTV-P, primary gross tumor volume.

* Corresponding authors at: No. 651 Dongfeng East Road, Yuexiu District, Guangzhou City, Guangdong Province, PR China, (Lizhi Liu). No. 135 Xingang West Road, Haizhu District, Guangzhou City, Guangdong Province, PR China (Yuanzhi shao).

E-mail addresses: Liulizhidoc@163.com (L. Liu), stssyz@mail.sysu.edu.cn (Y. Shao).

[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.radonc.2018.11.001
0167-8140/

Nasopharyngeal carcinoma (NPC) is one of the head and neck cancers with high incidence in Southeast Asia, and is connected with Epstein–Barr virus (EBV) infection [1]. Intensity-modulated radiotherapy (IMRT) alone or in combination with chemotherapy, targeted therapy, and immunotherapy is the main treatment for non-metastatic NPC, achieving good disease-free survival and overall survival (OS) [2,3]. But NPC tends to relapse and/or metastase after definitive treatment [4,5]. Therefore, NPC patients, who develop local recurrence or distant metastases after treatment, require more intensive follow-up and effective treatment strategies.

Although the tumor-node-metastasis (TNM) system is the most widely used staging system, NPC patients at the same TNM stages still have different survival rates [6,7]. Hence, the American Joint Committee on Cancer (AJCC) has increasingly recognized the growing need for more accurate, probabilistic, and individualized outcome prediction models, incorporating additional anatomic and non-anatomic prognostic factors alongside the TNM system, with the aim of developing a more precise medical approach.

Nomograms have been widely used as practical prediction tools, which incorporate various significant factors to quantify individual risk and predict prognoses for cancer patients [8,9]. In many types of cancers, nomograms have been proved to provide more precise prediction than the traditional TNM classification [10,11]. However, nomograms for predicting OS and progress-free survival (PFS) after IMRT for non-metastatic NPC patients are relatively few, while most providing a prognostic model by incorporating TNM stage and other clinical factors to predict the survival of NPC patients [12–22].

The development of new imaging technologies and the rapidly increasing knowledge of cancer biology provide prognostic information that can complement TNM classification and in some cases, be more relevant to patients survival compared to TNM classification [6,7]. Attempts have been made in incorporating such information in cancer prognostic models. Chen et al. subclassified T4 patients into T4a or T4b according to the site of invasion and discovered that such classification has prognostic value in NPC [23]. Mao et al. had evaluated nodal size, level, laterality, extranodal neoplastic spread (ENS), and necrosis for their prognostic value in patients with NPC, and found that level, cervical lymph node laterality, and ENS are independent prognostic factors [24]. Therefore in this study, we tried to establish prognostic nomograms combining clinical features with detailed magnetic resonance imaging (MRI) findings of the primary tumor and regional lymph nodes, to perform a more accurate prediction for NPC patients. Therein, the MRI findings replace T and N stages, respectively. The optimal and individualized follow-up strategies for NPC patients after IMRT are determined by identifying patients into different risk groups for death, locoregional failure and distant metastases.

Materials and methods

The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (www.researchdata.org.cn), with the approval RDD number as RDDA2018000484.

Training cohort

The training cohort ($N = 595$) that develops nomogram for OS was obtained from Sun Yat-sen University Cancer Center between January 2010 and December 2012. The following items are the inclusion criteria for this research: (i) diagnosed as NPC pathologically; (ii) access to complete clinical data and detailed MRI findings; (iii) received intensity-modulated radiation therapy (IMRT) with or without chemotherapy, and (iv) effective and accurate follow-up. Ethical approvals were obtained from institutional review boards of Sun Yat-sen University Cancer Center. Informed consent was waived because of the retrospective property of this study. The research protocol was consistent with the guidelines outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Sun Yat-sen University Cancer Center.

We used a standardized data collection form to search all related information including sociodemographic data (age; gender), baseline clinical information (Epstein–Barr virus DNA copy number before treatment, EBV_DNA_CN; early antigen-immunoglobulin A, EA-IgA; viral capsid antigen-immunoglobulin A, VCA-IgA; white blood cell count, WBC; lymphocyte count, LYMPH; platelet count, PLT; hepatitis B virus surface antigen, HbsAg; lactate dehydrogenase, LDH; Karnofsky's performance scale score, KPS score; World Health Organization histologic type, WHOHT; and blood type), detailed MRI findings of primary tumor and regional lymph nodes (nodal size; nodal number; level; laterality; extranodal neoplastic spread, ENS; nodal grouping, NG, presence of three or more contiguous and confluent lymph nodes at the same level for the same side, each of which should have a minimal axial diameter of 8–10 mm; contrast-enhancing rim, CER; central necrosis, CN; and so on), and therapeutic data (radiation fractions and dosage; therapy method; et al.). Two radiologists with more than ten-year experience in head and neck cancers evaluated all MRI scans separately. Disagreement was resolved by consensus.

MRI examinations were performed in the head and neck regions (i.e., from the saddle pool to the lower edge of the sternal collarbone) using 1.5T or 3.0T MR imaging systems with head-neck combined coils. Unenhanced and enhanced T1 and T2-weighted imaging (T1W1, T2WI) scans were implemented in the axial, coronal and the sagittal planes, respectively. Gd-DTPA was injected by venous blood by means of automatic high pressure injector with a dosage of 0.1 mmol per kg body weight. The scanning parameters for T1WI scan were as follows: FSE (fast spin echo), for T1WI scan, TR (repetition time) = 540 ms and TE (echo time) = 11.8 ms, for T2WI scan, TR = 4000 ms and TE = 99 ms. The scanning section thickness is 5 mm and the section gaps are 1 mm.

The clinical features and detailed MRI findings are shown in Table S1 in Supplementary information.

Validation cohort

For validation, we used a separate cohort of 241 NPC patients who also received IMRT to assess the generalizability of the model for OS. The 241 NPC patients were from the Sun Yat-sen University Cancer Center and the First Hospital of Foshan between January 2010 and December 2013. Specifically, thirty-nine cases came from the First Hospital of Foshan, and 202 cases came from the Sun Yat-sen University Cancer Center. The inclusion criterion for these patients was having enough data to score all the features in the established nomogram. In the same way, the research protocol was consistent with the guidelines outlined in the Declaration of Helsinki and was approved by the Ethics Committee of the Sun Yat-sen University Cancer Center and the First Hospital of Foshan. Specific acquisition parameters of MRI imaging for validation cohort are the same as the parameters for training cohort.

On the other hand, we randomly assigned all the 836 NPC patients from Sun Yat-sen University Cancer Center and the First Hospital of Foshan at a ratio of 3:1, so that we got the training cohort ($N = 558$) and validation cohort ($N = 278$) for predicting the PFS of NPC.

The entire procedure of this research for OS is shown in Fig. 1. The overall research idea of PFS is similar to that of OS, except that there are some differences in the distribution of data sets.

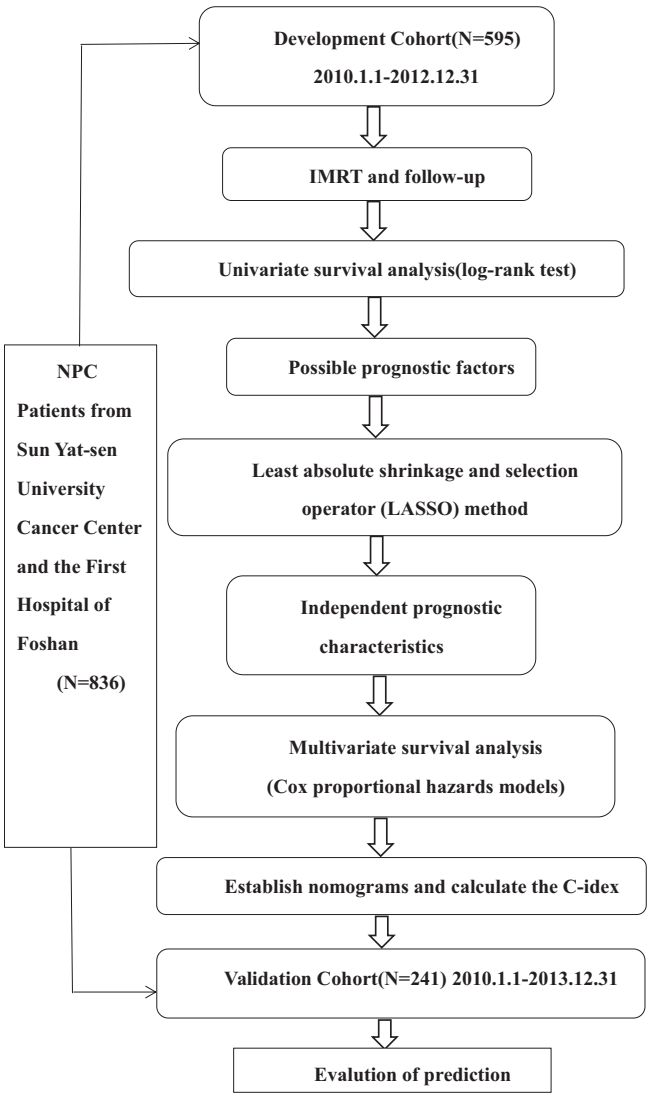

Fig. 1. The entire procedure of this analysis for OS.

Follow up

Distant metastasis and locoregional failure were assessed by physical examination, nasopharyngoscope, head and neck MRI, chest x-ray and/or computed tomography (CT) scan, abdominal ultrasound, and bone scan. The frequency of the above examinations was biannual during the first three years after treatments and annual thereafter until the patient dies. The follow-up was implemented through phone contact or clinic attendance records.

OS was defined as the time from radiotherapy or chemotherapy to the date of death from any cause, or censor at the date of last follow-up. PFS was defined as the time from radiotherapy or chemotherapy to the date of death from any cause, recurrence and metastasis or censor at the date of last follow-up.

Statistical analysis

All features were classified into several categories based on clinical practice. Detailed classification is shown in Table S1. Firstly, Kaplan–Meier's estimates were used to plot survival curves and then log-rank test was applied to do comparison between different survival curves for every feature. We can look for gaps in these curves in a horizontal or vertical direction. A vertical gap means that at a specific time point, one group had a greater fraction of subjects surviving. A horizontal gap means that it took longer for one group to experience a certain fraction of deaths or disease progression. Every feature with significant level of $P < 0.05$ was selected, it means that when features were in different categories, there was a statistically significant difference between their survival curves, which indicated that this factor might be a potential factor affecting survival.

Secondly, we used least absolute shrinkage and selection operator (LASSO) method to reselect features that were most significant. The LASSO is a data analysis method that may be applied for biomarker selection in high dimensional data [25,26]. It was originally proposed for linear regression models to minimize the residual sum of squares, subject to the sum of the absolute value of the coefficients being less than a tuning parameter (λ) [25,26]. The LASSO method was cross-validated to determine an optimal tuning parameter lambda. We established model with the cv.glmnet function in the glmnet package, and the cv-glmnet function makes use of cross test to observe model error with different lambda values. We chose the tuning parameters which minimize the model error as the optimal tuning parameter. All features with non-zero coefficients (at the optimal lambda) were selected. The LASSO method was performed on R 3.3.1 (http://www.r-project.org). Finally, we built a Cox proportional hazards model using the selected variables.

Statistical Package for the Social Sciences version 20.0 (SPSS, Chicago, IL) was used to do statistical analyses. Nomograms were applied to visualize the results of multivariate analysis through R 3.3.1. To avoid over-optimism, we also performed 1000 bootstrap resamples to correct the concordance index (C-index), which assess the performance of nomogram models. Comparisons among different nomogram models were carried out with the rcorrp.cens in Hmisc in R. For calibrating the predictive performance of nomograms, we compared the predicted 1-, 3-, and 5-year OS and PFS with actual survival respectively. In the validation cohort, we calculated total points for every patients based on established nomograms and used it as a predictor to do survival analysis.

Results

Patient characteristics and survival rate

We did survival analyses on 595 patients from training cohort and 241 patients from validation cohorts. Average follow-up for OS and PFS in the training cohort were 77.9 months and 71.2 months, while in the validation dataset the values were 68.7 months and 69.9 months respectively. Besides, the five-year event rates for OS and PFS in the training cohort were 89.0% and 79.0%, and were 85.9% and 79.3% respectively in the validation cohort.

Univariate analysis to select significant features

For OS and PFS, we used Kaplan–Meier's estimates and log-rank test to do univariate analyses, and selected 29 features for OS and 42 features for PFS in the training set, which had P values less than 0.05. These are marked with an asterisk in Table S1.

LASSO method to reduce feature dimension

For OS, the residual sum of squares was minimum when lambda equaled 0.009732984. This yielded 11 independent and highly significant features including (1) clinical features: Age, EBV_DNA_CN; (2) imaging features of primary tumor: MPL (musculus pterygoideus lateralis) involvement, PS (prestyloid space) involvement, PVS (prevertebral space) involvement, BOSB (base of sphenoid bone) involvement, PNS (paranasal sinuses) involvement; and (3)

imaging features of regional lymph nodes: II_laterality, RPLN (retropharyngeal lymph node)_laterality, NG and ENS.

For PFS, the residual sum of squares turned out to be minimum when lambda equaled 0.02463867, yielding 12 independent and highly significant features including (1) imaging features about primary tumor lesions: LCM (longus capitis muscle) involvement, TVP (tensor veli palatini) involvement, PS involvement, PVS involvement, V3_ES (V3 extracranial segment) involvement, PNS involvement; and (2) imaging features of lymph nodes: II_laterality, III, RPLN_laterality, ENS, CER and Nodal_number.

Detailed description of the LASSO method is presented in Supplementary information (Fig S1 and S2).

Multivariate analysis

We did multivariate analyses with the Cox proportional hazards model to determine the coefficient and hazard ratio for each feature. The results of multivariate analysis are shown in Table 1. Besides, we provided a detailed atlas on the respective anatomical spaces that were eventually incorporated into model for OS or PFS in the Supplementary information.

Prognostic nomogram and calibration curves

The results of Cox proportional hazards models for OS and PFS were visually represented by nomograms (Fig. 2A and B). Each subtype within the features was assigned a score. By adding up the scores from all features in the nomograms and locating it on the total point scale, we could predict the probabilities of different outcomes by drawing a vertical line to the total score. PNS involvement and RPLN_laterality were the important common contributing factors for the prediction of OS and PFS.

In the training cohort, the nomogram for OS had a bootstrap-corrected C-index of 0.786 (95% confidence interval (CI), 0.782–0.790), which was significantly better than that of the nomogram model combining clinical features with TNM classification

Table 1
Multivariate analysis to build the nomogram model for OS and PFS.

Characteristics	OS			PFS		
	P	95%CI	Hazard ratio	P	95%CI	Hazard ratio
Age	0.002	1.365–4.260	2.411			
<45						
>=45						
EBV_DNA_CN	0.442	0.673–2.479	1.292			
<103						
≥103						
TVP				0.002	1.273–3.097	1.986
No violation						
Violation						
MPL	0.650	0.535–2.725	1.208			
No violation						
Violation						
PS	0.622	0.635–2.137	1.165			
No violation						
Violation						
PVS	0.412	0.709–2.316	1.281			
No violation						
Violation						
BOSB	0.495	0.644–2.487	1.265			
No violation						
Violation						
PNS	0.006	1.292–4.750	2.477	0.001	1.386–3.323	2.146
No violation						
Violation						
II_laterality						
No violation	0.408					
Unilateral	0.231	0.751–3.271	1.567			
Bilateral	0.203	0.750–3.885	1.707			
RPLN_laterality						
No violation	0.010			0.027		
Unilateral	0.640	0.403–1.747	0.839	0.642	0.495–1.542	0.874
Bilateral	0.036	1.049–4.154	2.088	0.090	0.927–2.876	1.633
NG	0.014	1.172–4.045	2.178			
No						
Yes						
ENS	0.571	0.589–2.611	1.240			
No						
Yes						
CER				0.044	1.018–3.644	1.926
No						
Yes						
Nodal_number						
0				0.006		
1				0.410	0.682–2.555	1.320
2				0.190	0.254–1.312	0.578
≥3				0.065	0.968–3.004	1.705

Abbreviations: OS, overall survival; PFS, progress-free survival; EBV_DNA_CN, Epstein–Barr's virus DNA copy number before treatment; TVP, tensor veli palatini; MPL, musculus pterygoideus lateralis; PS, prestyloid space; PVS, prevertebral space; BOSB, base of sphenoid bone; PNS, paranasal sinus; RPLN, retropharyngeal lymph node; NG, nodal grouping; ENS, extranodal neoplastic spread; CER, contrast-enhancing rim.

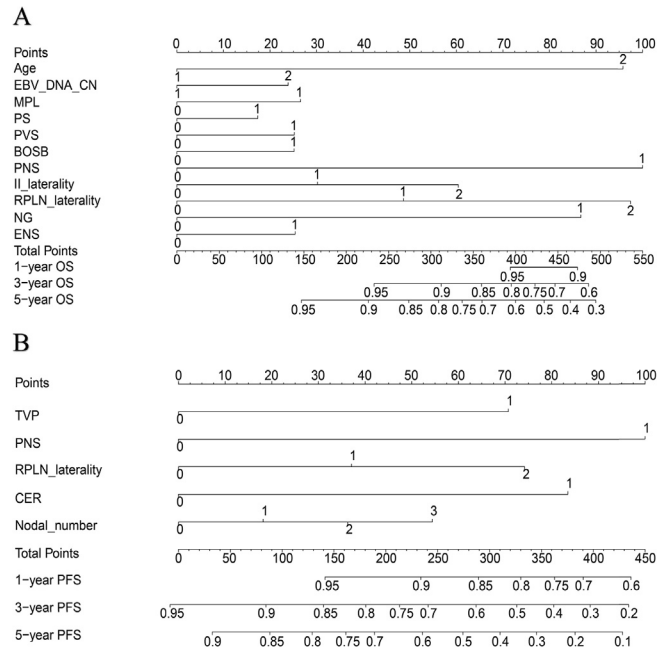

Fig. 2. Nomograms of non-metastatic NPC patients prior to receiving IMRT for OS (A) and PFS (B). NPC, nasopharyngeal carcinoma; IMRT, intensity-modulated radiotherapy; EBV-DNA-CN, Epstein–Barr virus DNA copy number before treatment; MPL, musculus pterygoideus lateralis; PS, prestyloid space; PVS, prevertebral space; BOSB, base of sphenoid bone; PNS, paranasal sinuses; RPLN, retropharyngeal lymph node; NG, nodal grouping; ENS, extranodal neoplastic spread; TVP, tensor veli palatini; CER, contrast-enhancing rim; OS, overall survival; PFS, progress-free survival.

(0.743; 95% CI, 0.739–0.747), with a P value less than 0.001. Likewise, the C-index of our nomogram model for PFS (0.679; 95% CI, 0.675–0.683) also performed significantly better than the nomogram model combining clinical features with TNM classification (0.665; 95% CI, 0.661–0.669), with a P value less than 0.001.

In the validation cohort, the C-index of our models were also better than the other models. Furthermore, the difference in C-index between different models is statistically significant both for OS ($P < 0.05$) and PFS ($P < 0.001$). The detailed results are shown in Table 2. Baseline clinical model is the model established to take into account all the clinical features in Table 1. For example, with regard to OS, the baseline clinical model is a prognostic model that contains only two characteristics, namely age and EBV_DNA_CN.

Calibration curves presented excellent agreement between our nomogram prediction and actual observation for OS in the validation cohorts (Fig. 3B). What's more, our nomogram models for PFS showed better prediction performance than the model combining clinical features with TNM classification in the validation cohort (Fig. 3D). The excellent performance of our model in the validation cohort can prove that our model has a certain generalizability. But whether it's our model or the other model based on TNM classification, the C-index presented comparatively low agreement between the nomogram prediction and actual observation, which means that more research is needed to uncover the underlying causes of progress in NPC patients.

Classifying patient risk using the nomograms

Based on the established models and the total scores from nomograms, we can evenly classify the patients in the training cohort into three risk groups (Table S2), which enables us to effectively discriminate the survival outcomes for different risk groups by Kaplan–Meier's estimates both in the training and validation cohort (Fig. 4). For patients at the same TNM stage, we can also do detailed risk stratification for OS (Fig S3) and PFS (Fig S4) with a statistical significance except for a few cases.

Discussion

To the best of our knowledge, this is the first study to combine clinical features with MRI findings of primary tumor lesions and regional lymph nodes to develop visualized and reliable prognostic models for OS and PFS in NPC patients after IMRT within a large database.

There have been a series of studies to develop a nomogram for NPC in recent years [12–22]. These proposed nomograms are based on the AJCC/International Union for Cancer Control (UICC) TNM staging system, which has some shortcomings in predicting the prognosis of NPC patients. The tumor extent described in the TNM staging system is less accurate than our nomogram model, which is based on detailed MRI findings of primary tumor and regional lymph nodes and includes a combination of different anatomic parameters. Besides, when the considering endpoint is different, the prediction accuracy of TNM staging system is different accordingly. With the TNM staging system, the prognosis of NPC performed relatively good for predicting OS, but not so good for PFS predictions. Furthermore, the different versions of TNM staging system are not universal in defining some anatomic features, which has led to varied prediction performances of established nomograms combining TNM classification and other nonanatomic parameters. Since the performance of our nomogram is based on anatomic parameters from detailed MR imaging report, it is more consistent and accurate.

Excellent soft tissue contrast resolution and multiplanar imaging capability make MRI imaging modality, a diagnostic tool of choice in the evaluation of tumor invasion. It is also an important tool for pretreatment staging and treatment program design. With nasopharyngeal and cervical MRI scans being easily available and having become a routine part of the assessment in NPC, prognostic models depending on MRI information can be conveniently used in an outpatient clinic. Further research on predictive models based on MRI findings of NPC is necessary.

Since NPC patients are largely treated nonsurgically, the T and N staging is mainly determined based on CT/MRI findings. In the 8th

Table 2
Compared with nomogram models based on clinical features and TNM classification, the C-index of OS and PFS for our multivariate model turn out to be superior both in the training set and the validation set.

Model for survival prediction	Training			Validation		
	C-index	95% CI	*P*	C-index	95% CI	*P*
Clinical + Imaging(OS)	0.786	0.782–0.790	<0.001	0.730	0.717–0.743	<0.05
Clinical + TNM classification(OS)	0.743	0.739–0.747		0.709	0.697–0.721	
Clinical + Imaging(PFS)	0.679	0.675–0.683	<0.001	0.627	0.618–0.636	<0.001
Clinical + TNM classification (PFS)	0.665	0.661–0.669		0.601	0.592–0.610	

Abbreviations: OS, overall survival; PFS, progress-free survival; CI, confidence interval.

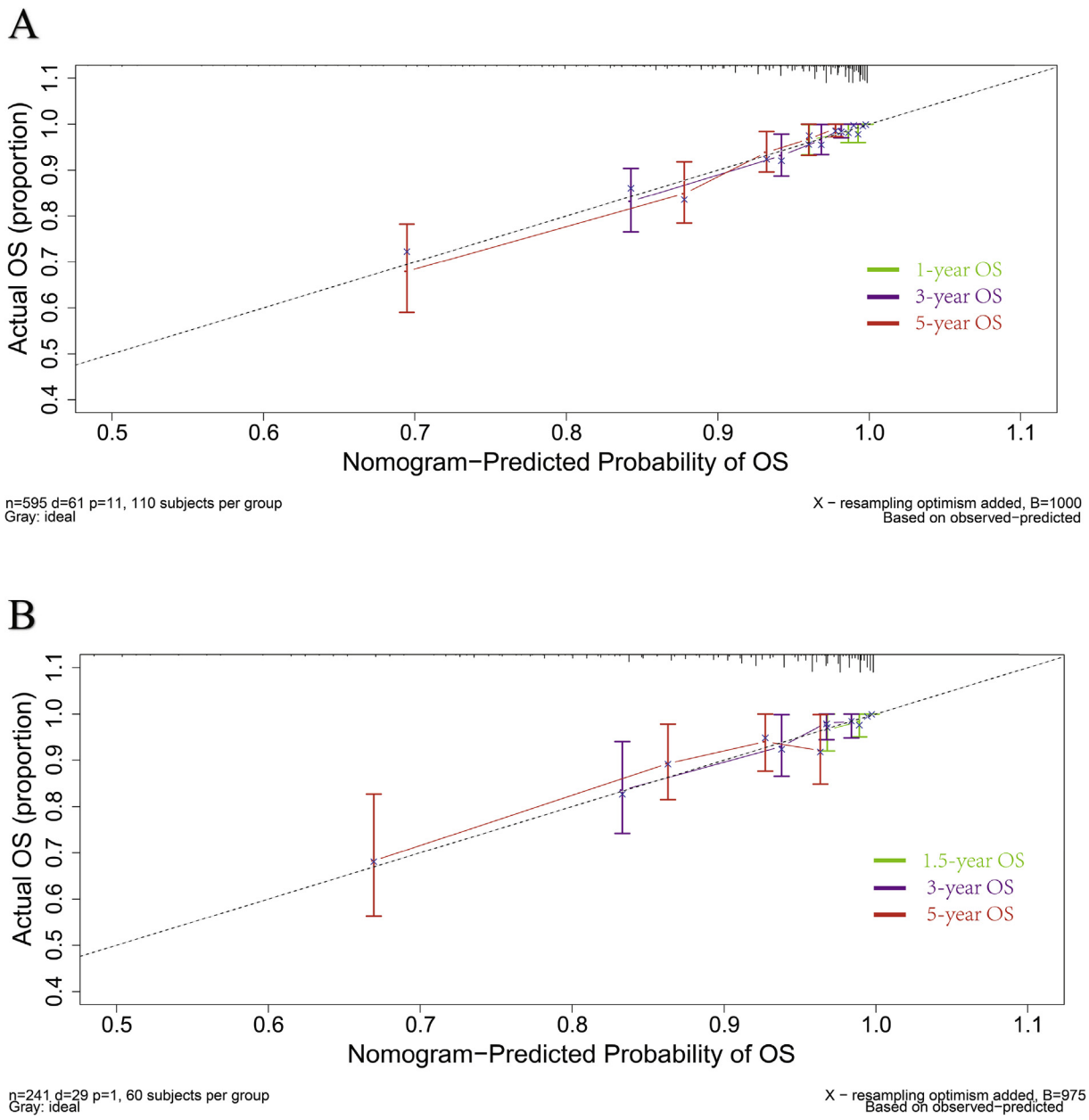

Fig. 3. . Calibration plots for OS in 1, 3 and 5 years in training cohort (A) and calibration plots for OS in 1.5, 3 and 5 years in validation (C) cohort; Calibration plots for PFS in 1, 3, 5 years in training (B) and validation (D) cohort. Nomogram-predicted OS and PFS are plotted on the x-axis; actual OS and PFS are plotted on the y-axis. Dashed lines along the 45-degree line passing through the point of origin represent perfect calibration models in which predicted probabilities are identical to actual probabilities. OS, overall survival; PFS, progress-free survival.

edition of the UICC/AJCC TNM staging system for NPC, there are 17 specific anatomic locations used to describe the invasion extent of original tumor and 4 parameters to describe the invasion extent of regional lymph nodes [27]. In our study, 29 MRI parameters for primary tumor lesions and 18 MRI parameters for regional lymph nodes including nodal size, nodal number, level, laterality, ENS, NG, CER and CN were used to determine the local and regional extension of NPC. Twenty-two nonanatomic parameters were also included in our study. Compared with UICC/AJCC staging system, the clinical and MRI features in our study may provide more precise information on cancer extent and biology.

There are two clinical factors, namely Age and plasma EBV DNA levels, that were assembled into the prognostic nomograms. Older NPC patients have a lower OS due to increased risk of comorbidities, lower tolerance to intensive therapies, and an impaired immune system [28,29]. This calls for a multidisciplinary approach alongside oncology care to further improve the outcome in elderly patients. EBV infection is associated with an increased risk for NPC in endemic areas. Several studies have reported that circulating EBV DNA originates from EBV-infected primary tumor cells, and can reflect the overall tumor load and tumor metabolic activity [30].

The independent imaging variables of primary tumor was MPL, PS, PVS, BOSB and PNS, which were assembled in our nomogram for OS, while TVP and PNS were assembled in our nomogram for PFS. The 8th edition TNM staging system also eliminated the ambiguity of "masticator space", the medial and lateral pterygoid muscle involvement was stage as T2, infratemporal fossa involvement (beyond the lateral surface of the lateral pterygoid muscle) was classified as T4, and staging criterion of soft-tissue involvement

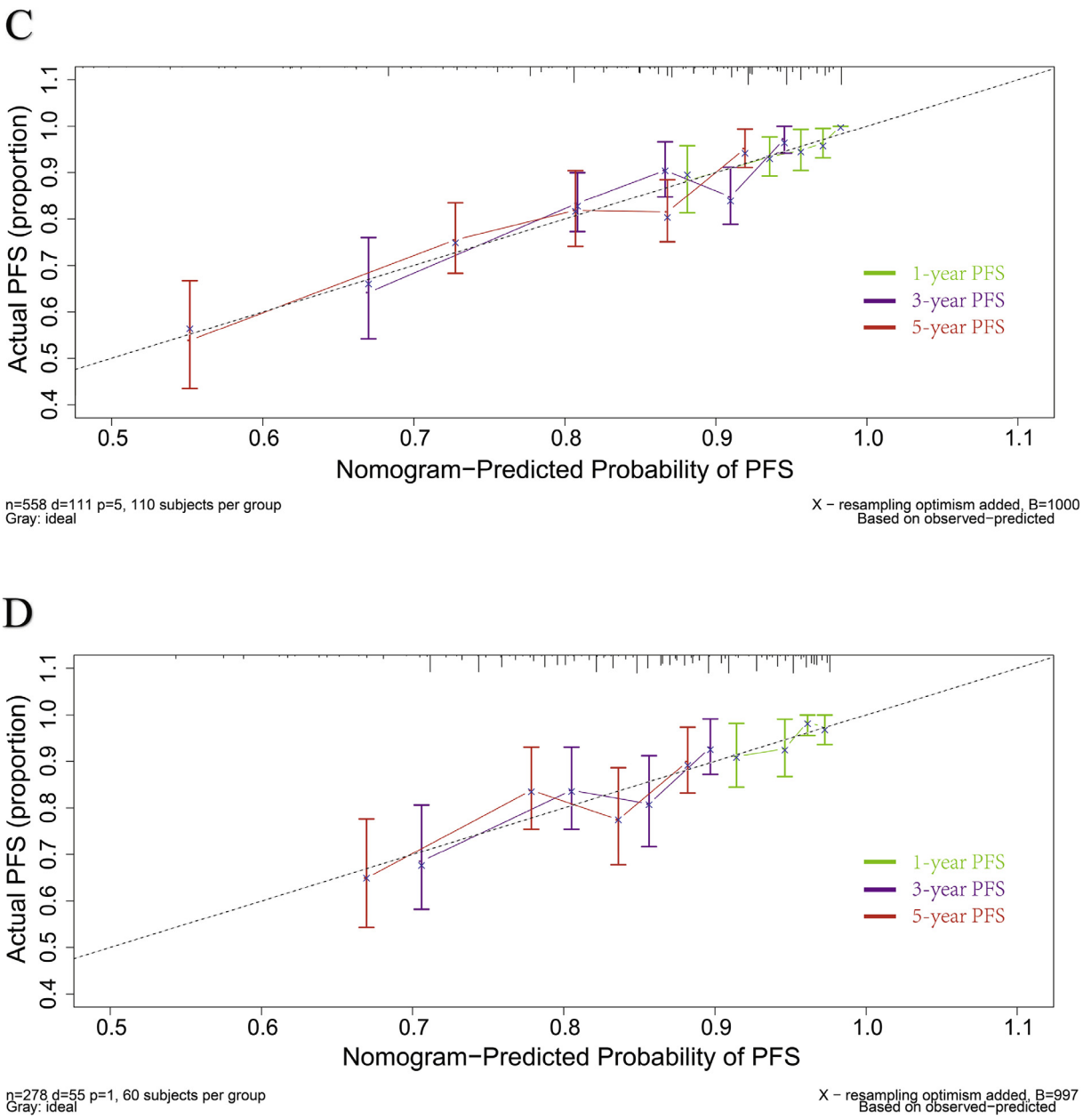

Fig. 3 (*continued*)

lacked. A further research on the prognostic value of musculus pterygoideus lateralis involvement and its classification is necessary. It happen to be that our results found musculus pterygoideus lateralis involvement is poor prognostic factor for OS. Lee C C et al. had revealed that NPC patients with prevertebral space involvement have more recurrence and poorer survival rates and should be the group to benefit from concurrent chemoradiotherapy followed by adjuvant chemotherapy [31]. Our results conformably revealed that prevertebral space involvement is independent factor for OS. Besides, we found that prestyloid space involvement tend to associate with poor OS. Bony structures of skull base and paranasal sinuses involvement are considered T3. Our research revealed that base of sphenoid bone involvement is the only bone marker assembled into the nomogram for OS. Our results also revealed that paranasal sinus invasion is likely to lower OS and PFS. Tian et al. had found that paranasal sinus invasion was an independent negative prognostic factor for NPC, and confirmed that it was scientific and reasonable for the AJCC staging system for nasopharyngeal carcinoma to define paranasal sinus invasion as stage T3 disease [32]. With regard to TVP, paralysis of the tensor veli palatini muscle is an significant factor that leads to eustachian tube dysfunction in NPC extension with upper prestyloid parapharyngeal infiltration [33], therefore TVP involvement is closely related to inferior PFS.

Our results of multivariate analysis showed different endpoint related with different lymph nodes variable. Ⅱ_laterality, RPLN_laterality, NG and ENS of lymph nodes were concerned with OS. For PFS, RPLN_laterality as well as CER and Nodal_number of lymph nodes were independent prognostic factors. We found RPLN_laterality is the common prognostic factors about lymph nodes for OS and PFS. Tang et al. had also revealed that RPLN metastasis remains an independent prognostic factor for disease-free survival (DFS) and distant metastasis-free survival (DMFS) in NPC [34,35]. On the other hand, Mao et al. [24] had found that nodal variables including level, cervical lymph node laterality, and ENS

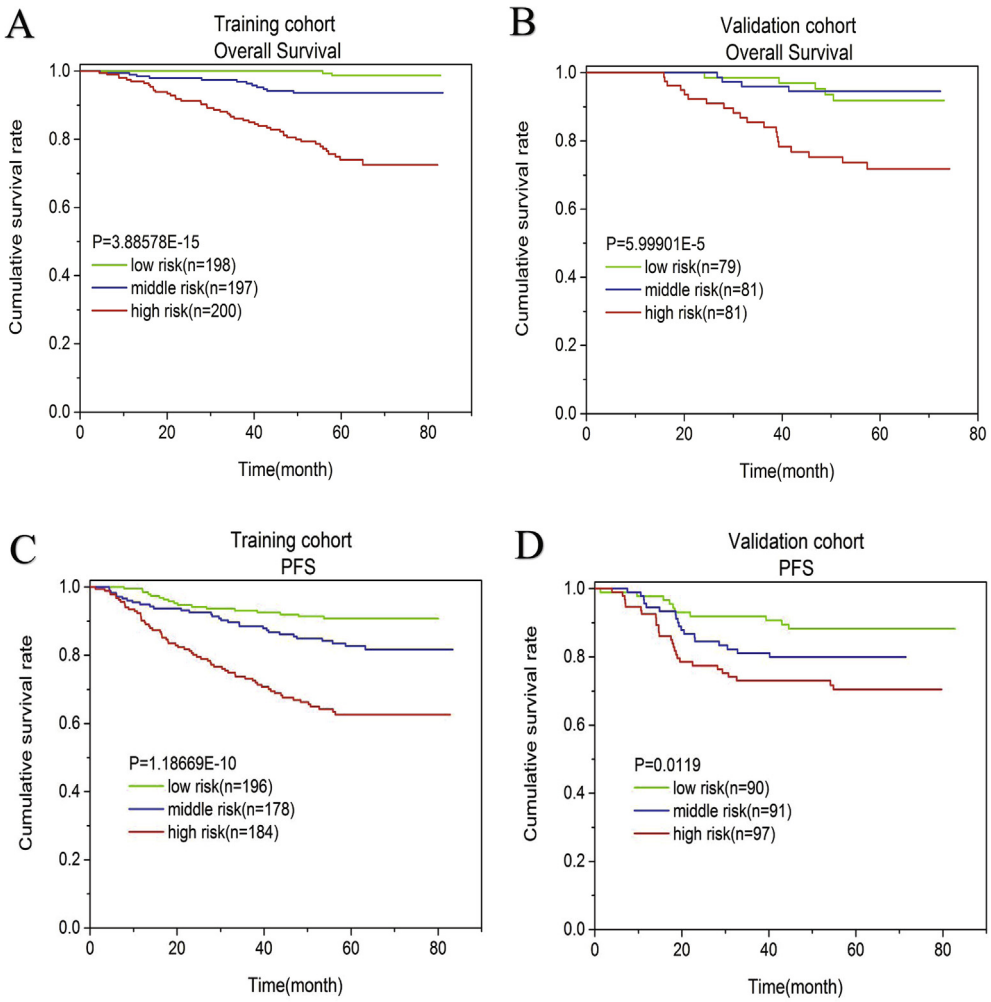

Fig. 4. Kaplan–Meier's curves for risk group stratification of OS (A, B) and PFS (C, D). Nomogram risk group stratifications for the 75 and 25 percentiles are shown for the training cohort (left) and for the validation cohort (right). PFS, progress-free survival.

are independent prognostic factors for NPC. Their definition of N staging criteria based on MRI avoids the ambiguity in determining level, thereby leading to a more consistent assessment. What's more, we found that NG was a vital MRI-detected prognostic factor about regional lymph nodes to predict OS. Especially, our results uncover that CER is a independent predictor of poor PFS. Mao et al. [24] also revealed that MRI-determined nodal variables including multiplicity (1, single; 2, multiple) were significant for distant failure and disease failure. Consistently, our results show that Nodal_number is critical to predicting PFS.

The results of C-index and calibration curves showed that our nomogram models had a better discrimination ability over the nomogram models combining clinical features with TNM classification. Furthermore, for OS and PFS in the training and validation cohort, the difference between the C-index of our nomogram models and the nomogram models combining clinical features with TNM classification were statistically significant, which means that our nomogram models based on clinical and imaging performed excellently than the others. Further, detailed MR imaging report of primary tumor and lymph nodes really have value in improving the performance of prognostic nomograms for nasopharyngeal carcinoma. Based on our nomogram models, we successfully classified NPC patients into three distinct risk groups by Kaplan–Meier's estimates for OS and PFS.

Of course, our study also had several limitations. We did not consider additional relevant prognostic factors, such as body mass index (BMI) [17,20,22], high-sensitivity C-reactive protein (hs-CRP) [12,20], neutrophil–lymphocyte ratio (NLR) [14,16,17], and primary gross tumor volume (GTV-P) [13,16,19,21]. These factors will be considered and potentially combined with anatomic factors in future revisions. The second shortcoming of our model was that our data set was relatively small, which contributed to inferior prediction performance for PFS in our validation set. Chen et al. have established pretreatment nomograms for local and regional recurrence for primary NPC after radical radiation therapy, which offer accurate prognostic prediction for local recurrence and regional recurrence cases with a high concordance [36]. The good performance of their nomograms is not merely because of their big database, but also because of them taking into consideration specific imaging locations, which further supports our theory that detailed MRI findings of primary tumor and regional lymph nodes can improve the performance of prognostic nomograms. Furthermore, some features such as ENS and CER were subjective diagnoses, which might differ among different radiologists or be time dependent. Therefore, it is imperative to use a quantitative radiomics approach to extract features describing specific anatomic features such as ENS and CER for a better prediction.

A future approach might be to consider pathological, radiomics, and genomics features to establish a multi-modal prediction model to achieve a better predictive performance. On the other hand, deep learning will play a critical role in screening variables and establishing models that describe the growth and metastatic behavior of the tumor through an unsupervised approach.

At last, we came to the following conclusion. The results of this research showed that the nomogram models based on MR imaging report and clinical features performed better than the nomogram models combining clinical features with TNM classification in predicting OS and PFS for NPC patients, supporting the fact that detailed MRI findings can improve the performance of prognostic nomograms for NPC patients. Based on our nomogram prognostic models and risk categorization, post-treatment follow-up and/or adjuvant therapy can be tailored, paving the way toward personalized and precision medicine. Finally, we recommend an imaging reporting staging system for nasopharyngeal carcinoma, which may play an important role in improving the treatment effect and quality of life of nasopharyngeal cancer patients.

Funding source

This study has received funding by the Foundation of the Sci-Tech Office of Guangdong Province, China (No. 2012A030400038 and No. 2013B021800073), the National Natural Science Foundation of China (No. 81572652), the Natural Science Foundation of Guangdong Province, China (No. 2014A030313137 and No. 2016A030310464), the Medical Research Fund of Guangdong Province, China (No. 2016A2016320 and No. 2016C2016072) and the Health & Medical Collaborative Innovation Project of Guangzhou City, China (No. 201604020003).

Ethical considerations

Institutional Review Board approval was obtained.

Conflict of interest.

All authors declare no conflict of interest.

Acknowledgements

We acknowledge financial support from the Foundation of the Sci-Tech Office of Guangdong Province, the National Natural Science Foundation of China, and the Natural Science Foundation of Guangdong Province, and the Medical Research Fund of Guangdong Province, China.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.11.001.

References

[1] Cao SM, Simons MJ, Qian CN. The prevalence and prevention of nasopharyngeal carcinoma in China. Chin J Cancer 2011;30:114–9.
[2] Lai SZ, Li WF, Chen L, Luo W, Chen YY, Liu LZ, et al. How does intensity-modulated radiotherapy versus conventional two-dimensional radiotherapy influence the treatment results in nasopharyngeal carcinoma patients? Int J Radiat Oncol Biol Phys 2011;80:661–8.
[3] Peng G, Wang T, Yang KY, Zhang S, Zhang T, Li Q, et al. A prospective, randomized study comparing outcomes and toxicities of intensity-modulated radiotherapy vs. conventional two-dimensional radiotherapy for the treatment of nasopharyngeal carcinoma. Radiother Oncol 2012;104:286–93.
[4] Lin JC, Jan JS, Hsu CY, Liang WM, Jiang RS, Wang WY. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. J Clin Oncol 2003;21:631.
[5] Lee AW, Foo W, Mang O, Sze WM, Chappell R, Lau WH, et al. Changing epidemiology of nasopharyngeal carcinoma in Hong Kong over a 20-year period (1980–99): an encouraging reduction in both incidence and mortality. Int J Cancer 2003;103:680–5.
[6] Tang LL, Chen YP, Mao YP, Wang ZX, Guo R, Chen L, et al. Validation of the 8th Edition of the UICC/AJCC staging system for nasopharyngeal carcinoma from endemic areas in the intensity-modulated radiotherapy era. J Natl Compr Cancer Network JNCCN 2017;15:913.
[7] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–4.
[8] Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. Lancet Oncol 2015;16:e173–80.
[9] Kattan MW, Scardino PT. Evidence for the usefulness of nomograms. Nat Clin Pract Urol 2007;4:638–9.
[10] Kim Y, Spolverato G, Ejaz A, Squires MH, Poultsides G, Fields RC, et al. A nomogram to predict overall survival and disease-free survival after curative resection of gastric adenocarcinoma. Ann Surg Oncol 2015;22:1828–35.
[11] Wang Y, Li J, Xia Y, Gong R, Wang K, Yan Z, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. J Clin Oncol 2013;31:1188–95.
[12] Yang L, Hong S, Wang Y, Chen H, Liang S, Peng P, et al. Development and external validation of nomograms for predicting survival in nasopharyngeal carcinoma patients after definitive radiotherapy. Sci Rep 2015;5:15638.
[13] Wu S, Xia B, Han F, Xie R, Song T, Lu L, et al. Prognostic nomogram for patients with nasopharyngeal carcinoma after intensity-modulated radiotherapy. PLoS One 2015;10:e0134491.
[14] Li XH, Chang H, Xu BQ, Tao YL, Gao J, Chen C, et al. An inflammatory biomarker-based nomogram to predict prognosis of patients with nasopharyngeal carcinoma: an analysis of a prospective study. Cancer Med 2017;6:310–9.
[15] Cho JK, Lee GJ, Yi KI, Cho KS, Choi N, Kim JS, et al. Development and external validation of nomograms predictive of response to radiation therapy and overall survival in nasopharyngeal cancer patients. Eur J Cancer 2015;51:1303–11.
[16] Li AC, Xiao WW, Wang L, Shen GZ, Xu AA, Cao YQ, et al. Risk factors and prediction-score model for distant metastasis in nasopharyngeal carcinoma treated with intensity-modulated radiotherapy. Tumor Biol 2015;36:8349.
[17] Liang W, Shen G, Zhang Y, Chen G, Wu X, Li Y, et al. Development and validation of a nomogram for predicting the survival of patients with non-metastatic nasopharyngeal carcinoma after curative treatment. Chin J Cancer 2016;35:98.
[18] Zeng Z, Shen L, Wang Y, Shi F, Chen C, Wu M, et al. A nomogram for predicting survival of nasopharyngeal carcinoma patients with metachronous metastasis. Medicine (Baltimore) 2016;95:e4026.
[19] Pan JJ, Ng WT, Zong JF, Lee SW, Choi HC, Chan LL, et al. Prognostic nomogram for refining the prognostication of the proposed 8th edition of the AJCC/UICC staging system for nasopharyngeal cancer in the era of intensity-modulated radiotherapy. Cancer 2016;122:3307–15.
[20] Tang LQ, Li CF, Li J, Chen WH, Chen QY, Yuan LX, et al. Establishment and validation of prognostic nomograms for endemic nasopharyngeal carcinoma. J Natl Cancer Inst 2016. 108.pii:djv291.
[21] Zeng L, Guo P, Li JG, Han F, Li Q, Lu Y, et al. Prognostic score models for survival of nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy and chemotherapy. Oncotarget 2015;6:39373–83.
[22] Zeng Q, Hong MH, Shen LJ, Meng XQ, Guo X, Qian CN, et al. Nomograms for predicting long-term survival in patients with non-metastatic nasopharyngeal carcinoma in an endemic area. Oncotarget 2016;7:29708–19.
[23] Chen L, Liu LZ, Chen M, Li WF, Yin WJ, Lin AH, et al. Prognostic value of subclassification using MRI in the t4 classification nasopharyngeal carcinoma intensity-modulated radiotherapy treatment. Int J Radiat Oncol Biol Phys 2012;84:196–202.
[24] Mao YP, Liang SB, Liu LZ, Chen Y, Sun Y, Tang LL, et al. The N staging system in nasopharyngeal carcinoma with radiation therapy oncology group guidelines for lymph node levels based on magnetic resonance imaging. Clin Cancer Res 2008;14:7497–503.
[25] Vasquez MM, Hu C, Roe DJ, Chen Z, Halonen M, Guerra S. Least absolute shrinkage and selection operator type methods for the identification of serum biomarkers of overweight and obesity: simulation and application. BMC Med Res Methodol 2016;16:154.
[26] Zhang B, Tian J, Dong D, Gu D, Dong Y, Zhang L, et al. Radiomics features of multiparametric MRI as novel prognostic factors in advanced nasopharyngeal carcinoma. Clin Cancer Res 2017;23:4259–69.
[27] Tang LL, Chen YP, Mao YP, Wang ZX, Guo R, Chen L, et al. Validation of the 8th edition of the UICC/AJCC staging system for nasopharyngeal carcinoma from endemic areas in the intensity-modulated radiotherapy era. J Natl Compr Canc Netw 2017;15:913–9.
[28] Sham J. Prognostic factors in nasopharyngeal carcinoma investigated by computer tomography–an analysis of 659 patients by Teo, et al.. Radiother Oncol 1992;25:216–7.
[29] Sham JS, Choy D. Prognostic factors of nasopharyngeal carcinoma: a review of 759 patients. Br J Radiol 1990;63:51–8.
[30] Ma BB, King A, Lo YM, Yau YY, Zee B, Hui EP, et al. Relationship between pretreatment level of plasma Epstein–Barr virus DNA, tumor burden, and

metabolic activity in advanced nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2006;66:714–20.
[31] Lee CC, Chu ST, Chou P, Lee CC, Chen LF. The prognostic influence of prevertebral space involvement in nasopharyngeal carcinoma. Clin Otolaryngol 2008;33:442–9.
[32] Tian L, Li YZ, Mo YX, Liu LZ, Xie CM, Liang XX, et al. Nasopharyngeal carcinoma with paranasal sinus invasion: the prognostic significance and the evidence-based study basis of its T-staging category according to the AJCC staging system. BMC Cancer 2014;14:832.
[33] Su CY, Hsu SP, Lui CC. Computed tomography, magnetic resonance imaging, and electromyographic studies of tensor veli palatini muscles in patients with nasopharyngeal carcinoma. Laryngoscope 1993;103:673–8.
[34] Tang LL, Guo R, Zhou GQ, Sun Y, Liu LZ, Lin AH, et al. Prognostic value and staging classification of retropharyngeal lymph node metastasis in nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy. PLoS One 2014;9:e108375.
[35] Tang L, Li L, Mao Y, Liu L, Liang S, Chen Y, et al. Retropharyngeal lymph node metastasis in nasopharyngeal carcinoma detected by magnetic resonance imaging : prognostic value and staging categories. Cancer 2008;113:347.
[36] Chen FP, Lin L, Qi ZY, Zhou GQ, Guo R, Hu J, et al. Pretreatment nomograms for local and regional recurrence after radical radiation therapy for primary nasopharyngeal carcinoma. J Cancer 2017;8:2595–603.