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Development and Validation of a Prognostic Nomogram Based on Residual Tumor in Patients With Nondisseminated Nasopharyngeal Carcinoma

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Abstract

Objectives: To investigate the prognostic value of residual tumor based on Magnetic resonance imaging(MRI) and establish an effective prognostic nomogram model referring to clinical,pathological and other related factors for predicting prognosis in nasopharyngeal carcinoma. **Methods:** Overall, 538 patients with non-metastatic, histologically-confirmed nasopharyngeal carcinoma were retrospectively examined. Data from 397 patients were used for the construction and validation of a nomogram based on the presence of residual tumor. A concordance index (C-index) was employed to assess the predictive accuracy and discriminative ability of the nomogram. **Results:** The 3-year survival rates in the non-residual and residual tumor cohorts were as follows: progression-free survival, 73.4% vs. 61.0%, P = 0.009; locoregional recurrence-free survival, 81.9% vs. 72.0%, P = 0.02; and distant metastasis-free survival, 80.7% vs. 73.5%, P = 0.11. Nine significant factors were included in the nomogram model. The calibration curve for the probability of progression-free survival showed that the nomogram-based predictive values had good concordance with the actual observations. **Conclusion:** The results showed that the patients in the residual tumor cohorts had a worse prognosis.The proposed nomogram may predict the prognosis and guide clinical decision-making concerning local residual tumors in nasopharyngeal carcinoma patients. Patients with a high risk of progression require more timely and aggressive treatment.

Keywords

progression-free survival, nomogram, residual tumor, magnetic resonance imaging

Abbreviations

CI, confidence interval; DMFS, distant metastasis-free survival; EBV, Epstein-Barr virus; FLAIR, fluid attenuated inversion recover; IMRT, intensity-modulated RT; LRFS, locoregional recurrence-free survival; MRI, magnetic resonance imaging; c-index, concordance index; NPC, nasopharyngeal carcinoma; PFS, progression-free survival; RT, radiotherapy.

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Introduction

Nasopharyngeal carcinoma (NPC) is a highly prevalent neoplasm in southern China and southeast Asia, especially in the Guangdong and Guangxi Provinces, with a high incidence rate of 50 cases per 100,000 population.[1] Radiotherapy (RT) is the mainstay of NPC treatment. Tumor residual often occur after RT; which, according to some scholars, is related to RT sensitivity. Several studies have reported mechanisms on RT sensitivity or resistance.[2-5] At the same time, several studies have

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shown that tumor residual is related to primary tumor volume, N stage,Epstein-Barr virus DNA and so on.[6-9]

However, the effect of residual tumor presence after RT on NPC is controversial.

Moreover, treatment strategy and outcome vary greatly in patients with residual tumors. According to some investigators, boost irradiation has a clinical benefit in patients with persistent tumors after RT.[10] The study showed that nasopharyngeal biopsies were performed several times after radiotherapy for nasopharyngeal carcinoma, and some patients were still positive for pathological biopsies until 3 months later.[11] Tumor stem cells have the characteristics of epithelial-mesenchymal transformation and can proliferate rapidly, thus increasing the possibility of tumor recurrence and metastasis.[12] Others agree that as long as the target dose is sufficient, blind administration of additional RT to the residual tumor is unwise.[13] Various changes will occur in nasopharynx after radiotherapy, such as inflammation, edema, fibrosis, residue, scar and so on. Under the premise of sufficient dose in the target area, it may cause excessive treatment and bring more side effects.Therefore, the current study aimed to investigate the prognostic value of residual tumors and establish a model that can help clinicians to predict prognosis and in decision-making regarding residual tumor.

However, no consensus statement exists about the proper time and modality for evaluating RT response in NPC patients. He et al.[14] reported an association between MRI-detected residual tumors at the end of intensity-modulated RT (IMRT) with poor prognosis in advanced NPC patients. Kwong et al.[11] showed a significantly poorer local control rate in NPC patients with persistent residual tumors 12 weeks after RT. Furthermore, Lin et al.[15] demonstrated that recurrence was strongly related to residual tumor 3-6 months after RT. Based on these findings, we chose 0-6 months after RT as the time-point for the evaluation of response . Additionally, although pathological biopsy is well-regarded as the gold standard in diagnosing residual tumors, some residual tumors may not be located in the nasopharynx. In 72 patients with recurrence who underwent MRI, a nasopharyngeal mass was only observed in 50 patients (69.4%).[16] A previous study demonstrated that the overall accuracy of MRI in the detection of residual and/or recurrent NPC at the primary site was 92.1%.[17] Therefore, MRI was used as a post-radiation evaluation tool in this study.

Nomograms are graphical depiction scans that employ multiple predictors to jointly diagnose or predict disease onset or progression. They have been developed for various types of cancers.[18-20] Nomograms have a stronger predictive prognostic ability than traditional staging, and are often used as a means of guiding treatment strategies.[19,21]

Material and Methods

Patients

This retrospective study was initiated on a primary cohort of NPC patients between January 2008 and October 2017 at our center. Patients enrolled in this study are required to meet the following criteria: (1) histologically confirmed, non-metastatic NPC patients (World Health Organization type II-III) without previous malignant disease . (2)receiving radical radiotherapy.(3)MRI examination of nasopharynx and neck in our hospital before treatment and within 6 months after radiotherapy.(4)This treatment must be the first course of treatment, and there is no previous history of radiotherapy and chemotherapy for head and neck tumors.(5)Regular follow-up after treatment.At the same time, the following situations also need to be excluded:(1)failure to complete radiotherapy course due to serious side effects or personal reasons (2)there are serious underlying diseases, including severe infection, severe liver and kidney dysfunction,myocardial infarctio, etc.

A total of 538 patients were eligible for this analysis. All patients were restaged according to the 7th edition of the International Union for Cancer Control/American Joint Committee on Cancer staging system. Concomitantly, due to a lack of data in some patients, 379 patients were finally enrolled for the development and validation of a nomogram model for progression-free survival (PFS) prediction. The data-splitting method was used to randomly assign 60% of the patients to the training set (n = 230) for nomogram establishment and 40% to the internal validation set (n = 149) for nomogram validation with the aid of the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA). Medical Ethics Committee in Southern Hospital of Southern Medical University approved the study,and the ethical approval number is NFEC-2020-020. All patients provided written informed consent prior to enrollment in the study.

Epstein-Barr Virus DNA

The level of plasma Epstein-Barr virus (EBV) DNA was measured using quantitative polymerase chain reaction.[22,23] EBV DNA lower than 500 copies/mL could not be detected in our hospital.

MRI

MRI was performed using a 1.5-T unit-GE Optima MR360 (GE Medical Systems, Milwaukee, WI, USA). The protocol used included axial and sagittal T1-weighted fluid attenuated inversion recovery (FLAIR) images without fat saturation, axial and coronal T2-weighted images, and postcontrast axial, coronal, and sagittal T1-weighted images with fat saturation. The upper extent covered a 2 cm area above the sella turcica and the lower extent reached 2 cm below the lower edge of the clavicle. An intravenous bolus injection of 0.1 mmol/kg of body weight gadopentetate dimeglumine (Kangchen, Guangzhou, China) was administered at a rate of 2.5 mL/sec for the contrast-enhanced series.

Estimation of Residual Tumor

The presence of radiographic residual tumors was confirmed by the consensus agreement of 2 experienced imaging

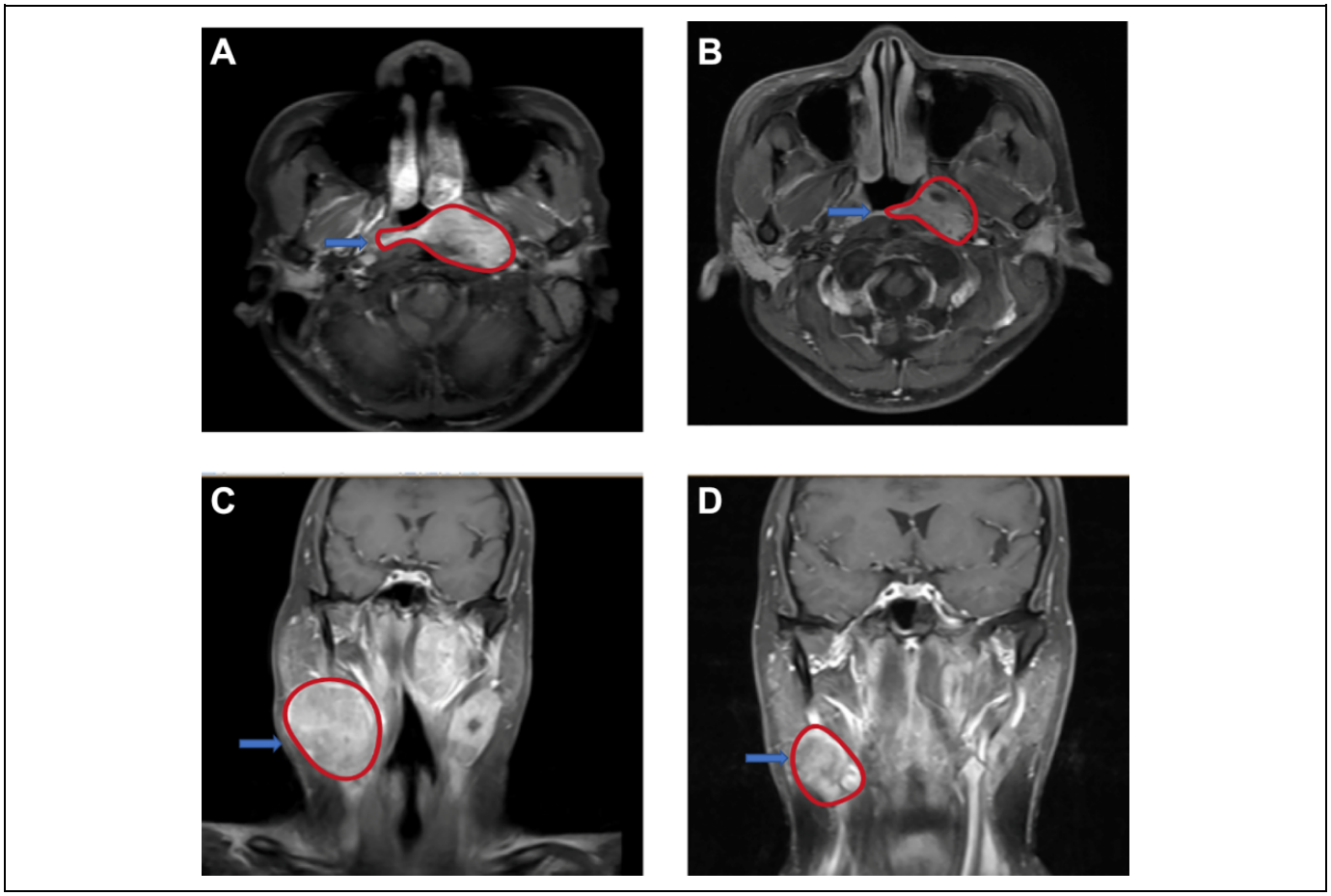

Figure 1. Pre-and post-treatment MRI in patients with residual NPC; red lines represent tumor lesions. (A) MRI showing a local tumor in an NPC patient before radiotherapy; (B) MRI showing local residual tumor within 6 months after RT completion in the same patient in (A) above; (C) MRI showing the lymph node of another NPC patient before RT; (D) MRI showing the lymph node residual tumor within 6 months after RT completion in the same patient as in (C) above. NPC, nasopharyngeal carcinoma; MRI, magnetic resonance imaging; RT, radiotherapy.

specialists and 2 senior radiation oncologists. The diagnostic criteria for residual tumors on MRI were based on the recommendation of Lv et al.[24] and included (1) residual tumors located in the nasopharynx or other soft tissues presenting as hypointense signals on T1-weighted imaging and hyperintense signals on T2-weighted imaging, and which showed enhancement following the administration of gadolinium-diethylenetriamine pentaacetic acid; (2) cervical lymph nodes with a short-axis diameter >10 mm and/or retropharyngeal nodes with a corresponding value >5 mm; and (3) residual tumors present at the skull base on MRI, as described previously.[25,26] Residual tumors were categorized as local or lymph node residual tumors Figure 1 shows.

Follow-Up

The median follow-up duration of 32.4 (range: 1.9-115) months was calculated from the first day of RT completion to the date of last follow-up or the patient's death. PFS was defined as the date from RT completion to the date of progression, including distant metastasis and recurrence, or death from any cause, whichever occurred first. Locoregional recurrence-free survival (LRFS) was defined as the date from RT completion to the date of first locoregional recurrence or death from any cause, whichever occurred first. Distant metastasis-free survival (DMFS) was defined as the date from RT completion to the date of the first distant metastasis or death from any cause, whichever occurred first.

Statistical Analysis

SPSS version 21.0 was used for the statistical analysis. Actuarial rates were calculated using the Kaplan–Meier method and differences were compared using the log-rank test. Multivariate analysis using the Cox proportional hazards model was used to test for independent significance factors by forward selection. GraphPad Prism 6.0 (GraphPad Software Inc., San Diego, CA, USA) was used for plotting of the survival curves.

The nomogram was developed based on the results of multivariable Cox regression analyses in the training set and based on existing literature. The predictive accuracy of the nomogram was evaluated by the concordance index (C-index) and

assessed by comparing the nomogram-predicted probabilities and the observed rates. A higher C-index indicated a greater degree of accurate prognostic stratification. The nomogram was formulated with the rms package in R version 3.4.3 (http://www.r-project.org/; The R Foundation, Vienna, Austria). All statistical tests were 2-sided, and the criterion for statistical significance was set at $\alpha = 0.05$.

Results

Clinical Characteristics of the Study Population

Collectively, 175 (32.5%) of the 538 patients had MRI-detected residual tumors within 6 months after RT, including 104, 28, and 43 with local, lymph node, and concomitant local and lymph node residual tumors, respectively. During the follow-up period, 50/538 patients (9.3%) died, 57/538 patients (10.6%) experienced recurrence, and 75/538 (13.9%) had distant metastasis.

Detailed data on the clinicopathological characteristics and treatment factors of the study population are presented in Table 1.

Table 1. Demographics and Clinical Characteristics in 538 Nasopharyngeal Carcinoma Patients.

	Residual cohort (n = 175)	Non-residual cohort (n = 363)	P value
Characteristic	No. (%)	No. (%)	
Age (years)			
<60	156 (89.1%)	327 (90.1%)	p = 0.74
≥60	19 (10.9%)	36 (9.9%)	
Gender			
Male	122 (69.7%)	267 (73.6%)	p = 0.35
Female	53 (30.3%)	96 (26.4%)	
Histology			
II	17 (9.7%)	15 (4.1%)	p = 0.01
III	158 (90.3%)	348 (95.9%)	
T-stage			
1	30 (17.1%)	102 (28.1%)	p = 0.03
2	43 (24.6%)	76 (20.9%)	
3	70 (40%)	139 (38.3%)	
4	32 (18.3%)	46 (12.7%)	
stage			
0	10 (5.7%)	47 (12.9%)	p = 0.003
1	31 (17.7%)	95 (26.2%)	
2	127 (72.6%)	209 (57.6%)	
3	7 (4%)	12 (3.3%)	
Clinical stage			
I	3 (1.7%)	25 (6.9%)	p = 0.02
II	14 (8%)	48 (13.2%)	
III	120 (68.6%)	233 (64.2%)	
IVa	31 (17.7%)	45 (12.4%)	
IVb	7 (4%)	12 (3.3%)	
RT technique			
IMRT	120 (68.6%)	245 (67.5%)	p = 0.80
3D-CRT	55 (31.4%)	118 (32.5%)	
Induction chemotherapy			
Yes	128 (73.1%)	262 (72.2%)	p = 0.81
No	47 (26.9%)	101 (27.8%)	
EBV DNA (copies/ml)			
≥500	86 (49.1%)	136 (37.5%)	p = 0.03
<500	54 (30.9%)	146 (40.2%)	
NA	35 (20%)	81 (22.3%)	
Time of MRI			
0-3 months after RT	103 (58.9%)	164 (45.2%)	p = 0.003
3-6 months after RT	72 (41.1%)	199 (54.8%)	

Abbreviation: IMRT,intensity-modulated radiation therapy;3D-CRT, 3-dimensional conformal radiation therapy; RT, radiation therapy.

Prognostic Value of Residual Tumor Presence After RT

For the entire cohort, the 3-year PFS, LRFS, and DMFS rates were 69.4%, 78.7%, and 78.4%, respectively. Based on the regression of the total tumor after RT, the 538 patients were divided into 2 groups: 175 patients with residual tumors and 363 without residual tumors. The 3-year rates in the residual tumor and non-residual tumor cohorts were as follows: PFS, 61.0% vs. 73.4%, P = 0.009; LRFS, 72.0% vs. 81.9%, P = 0.021; and DMFS, 73.5% vs. 80.7%, P = 0.11 as indicated in Figure 2A.

The 538 patients grouped into 147 and 391 patients with and without local residual tumors, respectively had 3-year rates as follows: PFS, 60.2% vs. 73.1%, P = 0.008; LRFS, 70.5% vs. 82.0%, P = 0.007; and DMFS, 73.5% vs. 80.3%, P = 0.14 as indicated in Figure 2B.

The 538 patients grouped into 71 with and 467 without lymph node residual tumors had 3-year rates as follows: PFS, 58.1% vs. 70.8%, P = 0.081; LRFS, 72.5% vs. 79.4%, P = 0.303; and DMFS, 65.9% vs. 80.0%, P = 0.032 as indicated in Figure 2C.

Predictive Nomogram for PFS Based on Residual Tumor Presence

The aforementioned results demonstrate that the presence of MRI-detected residual tumors was an adverse prognostic factor in NPC. To further predict survival outcomes and direct decision-making in the case of residual tumors, a nomogram model was constructed based on Cox proportional hazards regression models in the training set data and a review of the published literature. The results of the multivariate analyses for PFS are summarized in Table 2. T-stage, EBV DNA level before treatment, and presence of local residual tumor were found to be independent prognostic factors. Considering that residual tumor diameter has an effect on prognosis, the maximum diameter of the local residual tumor was included in the nomogram. The nine factors that were finally incorporated into the nomogram model for PFS were: EBV DNA level before treatment (<4000 vs. ≥4000 copies/mL), T stage, maximum diameter of local residual tumor, N stage, age (<60 vs. ≥60 y), RT technique, histologic classification, sex, and induction chemotherapy (Figure 3). The C-index of the nomogram for PFS was 0.71 (95% confidence interval [CI] 0.418 to 0.718) in the training set. The probability of 3-year PFS for the nomogram exhibited excellent agreement between the nomogram-

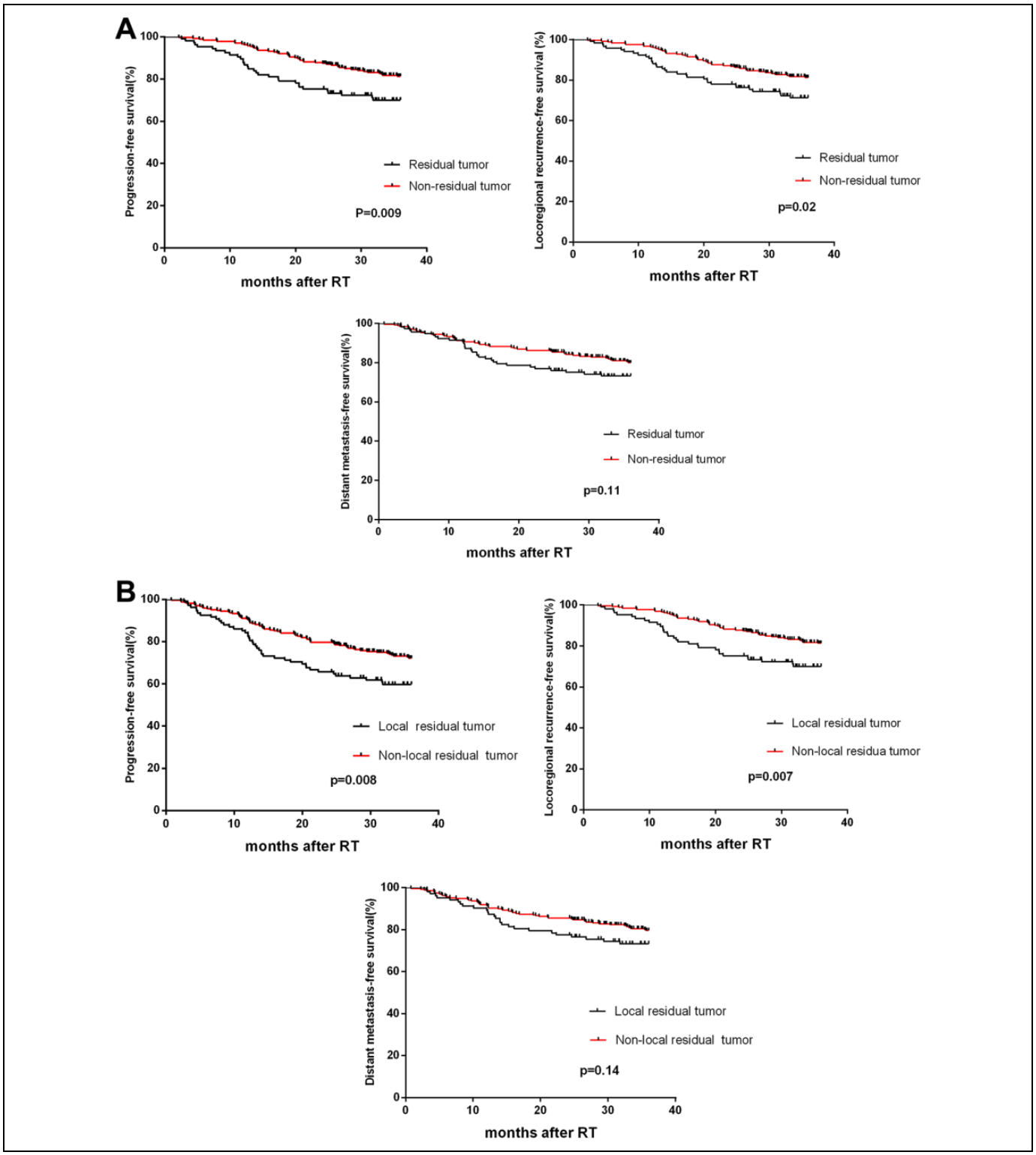

Figure 2. (A) Kaplan–Meier survival curves for the 538 patients with NPC stratified by residual tumor presence after RT. (A) Progression-free survival, (B) locoregional recurrence-free survival, and (C) distant metastasis-free survival. NPC, nasopharyngeal carcinoma; RT, radiotherapy. (B) Kaplan–Meier survival curves for the 538 patients with NPC stratified by local residual tumor presence after RT. (A) Progression-free survival, (B) locoregional recurrence-free survival, and (C) distant metastasis-free survival. NPC, nasopharyngeal carcinoma; RT, radiotherapy. (C) Kaplan–Meier survival curves for the 538 patients with NPC stratified by lymph node residual tumor presence after RT. (A) Progression-free survival, (B) locoregional recurrence-free survival, and (C) distant metastasis-free survival. NPC, nasopharyngeal carcinoma; RT, radiotherapy.

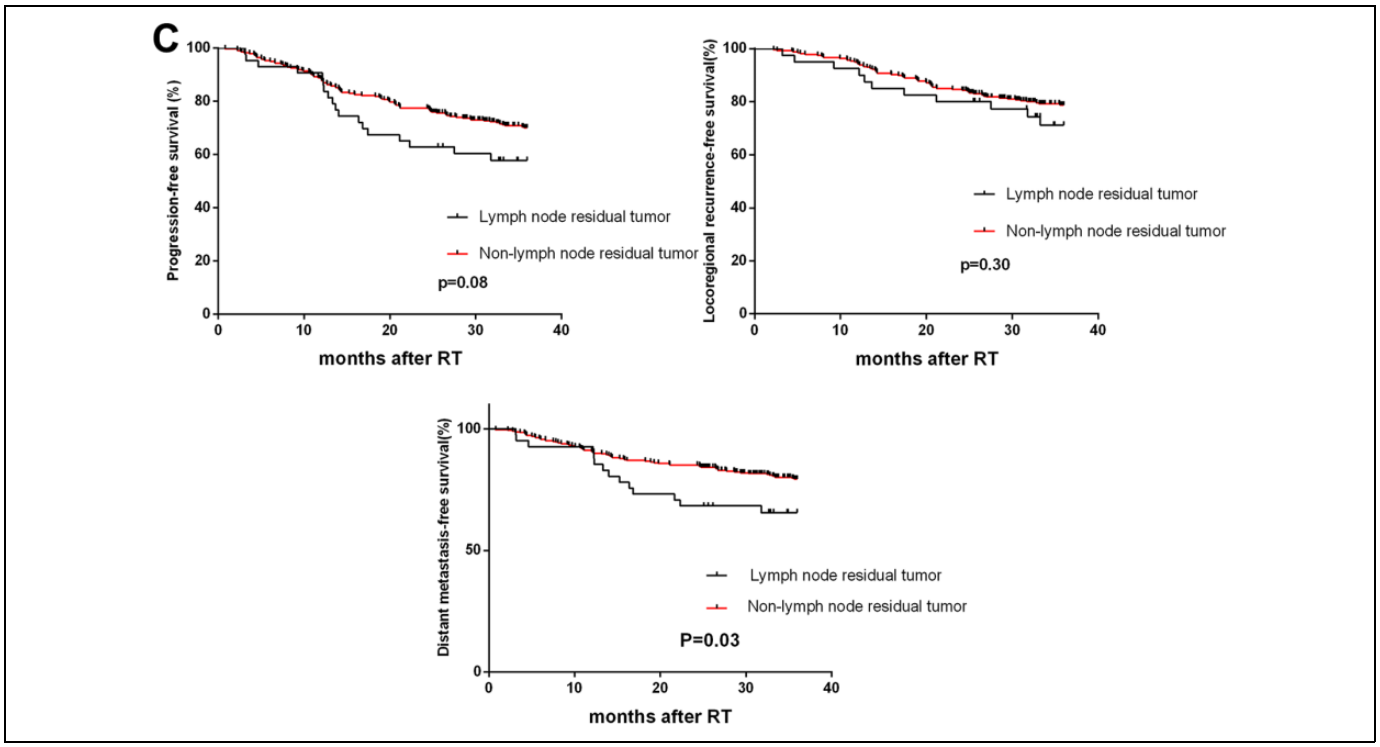

Figure 2. (continued)

Table 2. Multivariate Analysis of Factors Associated With Progression-Free Survival in Training Set.

Endpoint	Variable	HR	95% CI	P-value
PFS	Local residual	1.79	1.01-3.18	0.046
	T-stage	1.67	1.21-2.32	0.002
	EBV DNA(<4000 vs ≥4000 copies/ml)	1.97	1.10-3.52	0.022

Abbreviations: PFS = progression free survival; HR = hazard ratio; CI = confidence interval.

predicted outcomes and the actual observed outcomes, as indicated in Figure 4A.

Validation of the Nomogram

The data in the internal validation set were used for validating the nomogram model. The calibration plot, based on the internal validation set data for the probability of PFS at 3 years, illustrated excellent consistency between the actual observations and predictions according to the nomogram, as shown in Figure 4B. The C-index was 0.71 (95% CI 0.418 to 0.772) in the internal validation set.

Discussion

Many factors have been reported to be related to the prognosis of NPC.[27-29] In the present study, we found that the presence of residual tumors within 6 months after RT completion was an important prognostic factor in NPC. We also constructed a nomogram using the patients' clinicopathological information to predict the probability of PFS in NPC after RT completion based on residual tumor presence. The calibration curve for the nomogram model showed good agreement between the predictions and actual observations.

In this study, 32.5% of patients had residual tumors at 0-6 months after RT completion. He et al.[14] reported an MRI-detected NPC residual tumor rate of 40.1% at the end of IMRT. Lin et al.[15] showed that 50% (54/108) of patients with NPC had residual tumors on MRI, 1 month after RT completion. In addition, 20.3% of the patients had residual tumors at 3 months after IMRT completion, as presented by Lv et al.[24] The residual tumor rates observed in different studies vary, and multiple factors are responsible, including differences in clinical staging, residual tumor standard, radiation technology used, time of residual tumor presence evaluation, and therapeutic regimens. In addition, the 3-year prognostic outcomes were poorer in the present study than in the study by He et al[14]; this may be attributable to several factors. First, there were differences in the time-points at which the residual tumors were detected. In the study by He et al.,[8] MRI was performed at the end of IMRT, whereas in the present study, 72 (41.1%) patients were diagnosed as having residual tumors 3-6 months after RT completion. As previously reported,[11] the presence of persistent residual tumors until 12 weeks is associated with worse prognosis in NPC. Secondly, 173 (32.2%) of the patients received 3D-chemoradiotherapy in our study, whereas all the participants in the study by He et al. underwent IMRT. IMRT leads

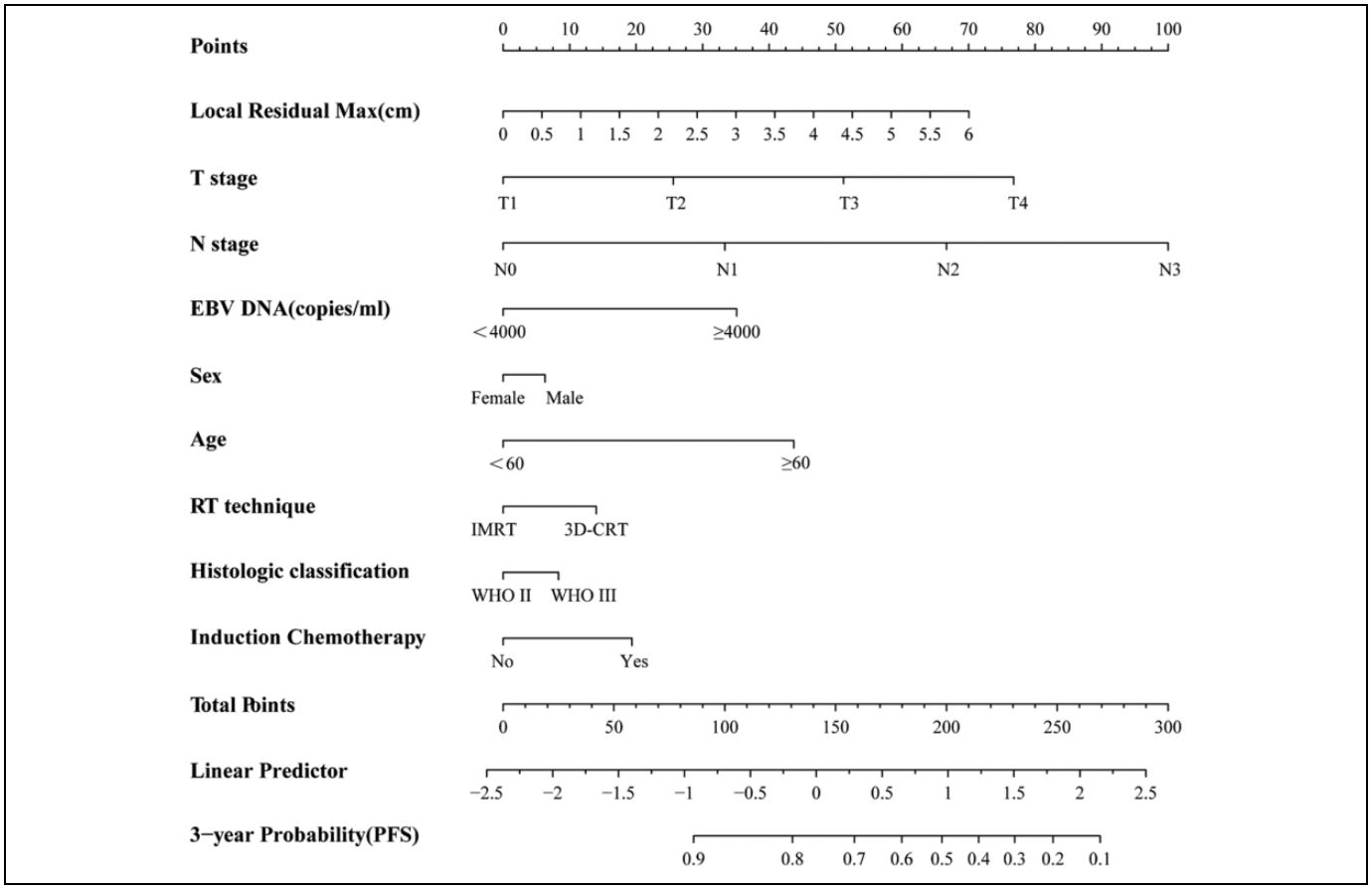

Figure 3. Prognostic nomogram for PFS in patients with non-metastatic NPC after radical radiotherapy. PFS, progression-free survival; EBV, Epstein-Barr virus; WHO II, The World Health Organization non-keratinizing differentiated carcinoma; WHO III, non-keratinizing undifferentiated carcinoma; NPC, nasopharyngeal carcinoma.

to better tumor control and lower occurrence of RT-related toxicities.[30,31]

In the present study, Kaplan-Meier survival analyses indicated that the presence of local residual tumors but not lymph node residual tumors had an adverse effect on PFS in patients with NPC. Moreover, multivariate analyses showed that local residual tumor presence was an independent prognostic factor in the training set. Local residual tumor diameter also influences prognosis.[32] Larger local residual tumors are associated with an increased number of clonogenic tumor cells and increased radioresistance due to tumor hypoxia, as well as possibly, changed levels of intercellular communication factors.[33] Therefore, we incorporated maximum local residual tumor diameter into the nomogram. Finally, the nomogram model was constructed based on the multivariate analyses and existing literature.[34-37]

In this nomogram model, notably, the maximum diameter of the local residual tumors had the third strongest influence on NPC-related prognosis, following N and T stage. This result suggests the importance of local residual tumor diameter. Generally, the greater the diameter of the local residual tumor, the greater the tumor burden. Additionally, age is often regarded as a prognostic factor in NPC.[38-40] Generally, younger age at diagnosis is associated with a more favorable prognosis. Increasing age is usually associated with a poorer performance status and increasing risk of comorbidities, reducing the rates of treatment tolerance. We set 60 years as the cut-off age based on a previous report.[41] EBV DNA copy number, which is gradually being recognized as having the potential to be the most influential biomarker in NPC, is associated with tumor burden,[42] short-term efficacy evaluation, and subsequent prognosis assessment.[7,43] Leung et al.[8] set 4000 copies/mL as the EBV DNA cutoff point and found that the pretherapy EBV DNA load improved risk discrimination in NPC patients. Similarly, plasma EBV DNA levels before treatment served as predictors of poor prognosis in NPC in our study. Induction chemotherapy was a risk factor for PFS in the nomogram, which may be explained by the fact that patients with advanced disease are likelier to receive induction chemotherapy. The poor prognosis of the disease itself offsets the benefits of induction chemotherapy.

The present study is the first to combine local residual tumors after RT based on MRI into a nomogram model for NPC . By obtaining some relevant clinicopathological factors, we can construct an easy-to-use nomogram model for the prediction of disease progression and may aid clinicians in decision-making for non-metastatic NPC. Further, the

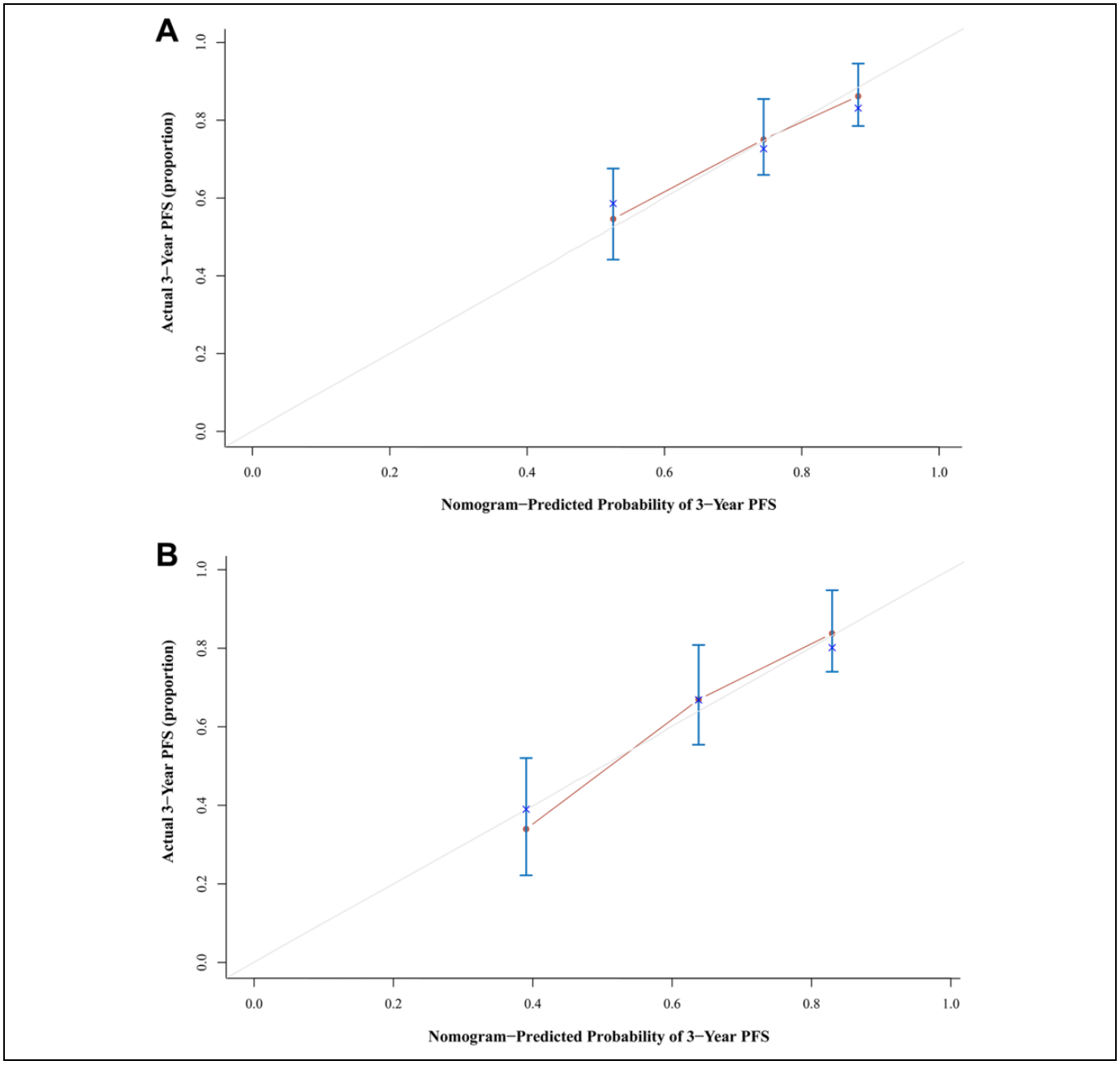

Figure 4. (A) Calibration curve for PFS prediction in patients with non-metastatic NPC in the training set. The nomogram-predicted probability of PFS is plotted on the x-axis; the actual PFS is plotted on the y-axis. PFS, progression-free survival; NPC, nasopharyngeal carcinoma. (B) Calibration curve for PFS prediction in patients with non-metastatic NPC in the internal validation set. The nomogram-predicted probability of PFS is plotted on the x-axis; the actual PFS is plotted on the y-axis. PFS, progression-free survival; NPC, nasopharyngeal carcinoma.

nomogram has the potential to aid physicians in dealing with local residual tumors. Patients with a maximum local residual diameter, advanced-stage disease, and a high EBV DNA level before treatment may need aggressive treatment, such as boost radiotherapy, adjuvant chemotherapy, targeted therapy, and immunotherapy,surgery and so on.

However, this study has some limitations. First, because of its retrospective design, heterogeneity was unavoidable in the clinical practices encompassing diagnosis, therapeutic regimens, and so on. Secondly, no external dataset was used to further validate the nomogram model. Additional research is required to validate the nomogram model externally to determine whether it can be applied extensively. Larger-scale randomized prospective clinical studies need to be conducted to further reduce the presence of various biases.

In conclusion, the presence of MRI-detected residual tumors after RT was negatively correlated with prognosis in patients with NPC. The proposed nomogram based on residual tumor

presence provides accurate prognosis stratification and can aid clinicians in decision-making for local residual tumors. Effective and timely treatment must be provided for patients with disease that is associated with a high risk of progression.

Authors' Note

The co-first author: Ping-Yan Liao, Zhong-Yi Dong, Chan-Tao Huang. The first author Ping-Yan Liao also hope to recieve all email regarding this manuscript until final author approval to receive timely feedback from the editors and better communication. Thank you very much.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

1. Wee JT, Ha TC, Loong SL, Qian CN. Is nasopharyngeal cancer really a "Cantonese cancer"? *Chin J Cancer*. 2010;29(5):517-526.
2. Wang WJ, Wu SP, Liu JB, et al. MYC regulation of CHK1 and CHK2 promotes radio resistance in a stem cell-like population of nasopharyngeal carcinoma cells. *Cancer Res*. 2013;73(3):1219-1231.
3. Zhang T, Sun Q, Liu T, et al. MiR-451 increases radio sensitivity of nasopharyngeal carcinoma cells by targeting Ras-related protein 14 (RAB14). *Tumour Biol*. 2014;35(12):12593-12599.
4. Sun Q, Liu T, Zhang T, et al. MiR-101 sensitizes human nasopharyngeal carcinoma cells to radiation by targeting stathmin 1. *Mole Med Rep*. 2015;11(5):3330-3336.
5. Liu T, Sun Q, Li Q, et al. Dual PI3K/mTOR inhibitors, GSK2126458 and PKI-587, suppress tumor progression and increase radio sensitivity in nasopharyngeal carcinoma. *Mole Cancer Therap*. 2015;14(2):429-439.
6. Guo R, Sun Y, Yu XL, et al. Is primary tumor volume still a prognostic factor in intensity modulated radiation therapy for nasopharyngeal carcinoma? *Radiother Oncol*. 2012;104(3):294-299.
7. Chan AT, Lo YM, Zee B, et al. Plasma Epstein-Barr virus DNA and residual disease after radiotherapy for undifferentiated nasopharyngeal carcinoma. *J Nat Cancer Inst*. 2002;94(21):1614-1619.
8. Leung SF, Zee B, Ma BB, et al. Plasma Epstein-Barr viral deoxyribonucleic acid quantitation complements tumor-node-metastasis staging prognostication in nasopharyngeal carcinoma. *J Clin Oncol*. 2006;24(34):5414-5418.
9. Li WF, Sun Y, Mao YP, et al. Proposed lymph node staging system using the international consensus guidelines for lymph node levels is predictive for nasopharyngeal carcinoma patients from endemic areas treated with intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys*. 2013;86(2):249-256.
10. Liang SB, Zhang N, Chen DM, et al. Prognostic value of gross tumor regression and plasma Epstein Barr Virus DNA levels at the end of intensity-modulated radiation therapy in patients with nasopharyngeal carcinoma. *Radiother Oncol*. 2019;132:223-229.
11. Kwong DL, Nicholls J, Wei WI, et al. The time course of histologic remission after treatment of patients with nasopharyngeal carcinoma. *Cancer*. 1999;85(7):1446-1453.
12. Shiman W, Yao Z. Epithelial-mesenchymal transition, cancer stem cells and radiotherapy resistance in nasopharyngeal carcinoma. *Ima Rese Med Appl*. 2018;2(23):1-3.
13. Han F, Xiao FF, Wang HY, et al. Influence of intensity-modulated radiotherapy on tumor regression in nasopharyngeal carcinoma. *Chin J Radiol Med Protect*. 2012;32(2):204-206.
14. He Y, Zhou Q, Shen L, et al. A retrospective study of the prognostic value of MRI-derived residual tumors at the end of intensity-modulated radiotherapy in 358 patients with locally-advanced nasopharyngeal carcinoma. *Radiat Oncol*. 2015;10:89.
15. Lin GW, Wang LX, Ji M, Qian HZ. The use of MR imaging to detect residual versus recurrent nasopharyngeal carcinoma following treatment with radiation therapy. *Euro J Radiol*. 2013;82(12):2240-2246.
16. Ng SH, Chang JT, Ko SF, Wan YL, Tang LM, Chen WC. MRI in recurrent nasopharyngeal carcinoma. *Neuroradiology*. 1999;41(11):855-862.
17. Comoretto M, Balestreri L, Borsatti E, Cimitan M, Franchin G, Lise M. Detection and restaging of residual and/or recurrent nasopharyngeal carcinoma after chemotherapy and radiation therapy: comparison of MR imaging and FDG PET/CT. *Radiology*. 2008;249(1):203-211.
18. Han DS, Suh YS, Kong SH, et al. Nomogram predicting long-term survival after d2 gastrectomy for gastric cancer. *J Clin Oncol*. 2012;30(31):3834-3840.
19. Karakiewicz PI, Briganti A, Chun FK, et al. Multi-institutional validation of a new renal cancer-specific survival nomogram. *J Clin Oncol*. 2007;25(11):1316-1322.
20. Wang Y, Li J, Xia Y, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. *J Clin Oncol*. 2013;31(9):1188-1195.
21. Mariani L, Miceli R, Kattan MW, et al. Validation and adaptation of a nomogram for predicting the survival of patients with extremity soft tissue sarcoma using a three-grade system. *Cancer*. 2005;103(2):402-408.
22. Lo YM, Chan LY, Lo KW, et al. Quantitative analysis of cell-free Epstein-Barr virus DNA in plasma of patients with nasopharyngeal carcinoma. *Cancer Res*. 1999;59(6):1188-1191.
23. Shao JY, Zhang Y, Li YH, et al. Comparison of Epstein-Barr virus DNA level in plasma, peripheral blood cell and tumor tissue in nasopharyngeal carcinoma. *Anticancer Res*. 2004;24(6):4059-4066.

24. Lv JW, Zhou GQ, Li JX, et al. Magnetic resonance imaging-detected tumor residue after intensity-modulated radiation therapy and its association with post-radiation plasma Epstein-Barr virus deoxyribonucleic acid in nasopharyngeal carcinoma. *J Cancer*. 2017;8(5):861-869.
25. Ng SH, Chan SC, Yen TC, et al. Comprehensive imaging of residual/ recurrent nasopharyngeal carcinoma using whole-body MRI at 3 T compared with FDG-PET-CT. *Euro Radiol*. 2010; 20(9):2229-2240.
26. Liang FY, Sun W, Han P, Lu X, Lian YN, Huang XM. Detecting plasma Epstein-Barr virus DNA to diagnose post radiation nasopharyngeal skull base lesions in nasopharyngeal carcinoma patients: a prospective study. *Chine J Cancer*. 2012;31(3): 142-149.
27. Tian YM, Tian YH, Zeng L, et al. Prognostic model for survival of local recurrent nasopharyngeal carcinoma with intensity-modulated radiotherapy. *Brit J Can*. 2014;110(2):297-303.
28. Tian Y, Tian Y, Zhang W, et al. Junctional adhesion molecule-A, an epithelial-mesenchymal transition inducer, correlates with metastasis and poor prognosis in human nasopharyngeal cancer. *Carcinogenesis*. 2015;36(1):41-48.
29. Song Q, Zhang H, Wang M, et al. MTA1 promotes nasopharyngeal carcinoma growth in vitro and in vivo. *J Exp Clin Cancer Res*. 2013;32(1):54.
30. Zhang B, Mo Z, Du W, Wang Y, Liu L, Wei Y.Intensity-modulated radiation therapy versus 2D-RT or 3D-CRT for the treatment of nasopharyngeal carcinoma: a systematic review and meta-analysis. *Oral Oncol*. 2015;51(11):1041-1046.
31. Moon SH, Cho KH, Lee CG, et al. IMRT vs. 2D-radiotherapy or 3D-conformal radiotherapy of nasopharyngeal carcinoma: survival outcome in a Korean multi-institutional retrospective study (KROG 11-06). *Strahlentherapie Onkol*. 2016;192(6):377-385.
32. He BW, QZ Z, Zh FZ, et al. Relationship between the treatment result and residual lesion after radiotherapy for patients with nasopharyngeal carcinoma. *Chin J Radiat Oncol*. 2004;13(3):150-152.
33. Johnson CR, Thames HD, Huang DT, Schmidt-Ullrich RK. The tumor volume and clonogen number relationship: tumor control predictions based upon tumor volume estimates derived from computed tomography. *Int J Radiat Oncol Biol Phys*. 1995; 33(2):281-287.
34. Tang LQ, Li CF, Li J, et al. Establishment and validation of prognostic nomograms for endemic nasopharyngeal carcinoma. *J Natl Cancer Inst*. 2015;108(1):djv291.
35. Liang W, Shen G, Zhang Y, et al. Development and validation of a nomogram for predicting the survival of patients with non-metastatic nasopharyngeal carcinoma after curative treatment. *Chine J Cancer*. 2016;35(1):98.
36. Chen FP, Lin L, Qi ZY, et al. Pretreatment nomograms for local and regional recurrence after radical radiation therapy for primary nasopharyngeal carcinoma. *J Cancer*. 2017;8(13):2595-2603.
37. Zeng Q, Hong MH, Shen LJ, et al. Nomograms for predicting long-term survival in patients with non-metastatic nasopharyngeal carcinoma in an endemic area. *Oncotarget*. 2016;7(20): 29708-29719.
38. Xiao G, Cao Y, Qiu X, Wang W, Wang Y. Influence of gender and age on the survival of patients with nasopharyngeal carcinoma. *BMC Cancer*. 2013;13:226.
39. Lee AW, Sze WM, Au JS, et al. Treatment results for nasopharyngeal carcinoma in the modern era: the Hong Kong experience. *Int J Radiat Oncol Biol Phys*. 2005;61(4):1107-1116.
40. Yi JL, Gao L, Huang XD, et al. Nasopharyngeal carcinoma treated by radical radiotherapy alone: ten-year experience of a single institution. *Int J Radiat Oncol Biol Phys*. 2006;65(1): 161-168.
41. Qu Y, Chen Y, Yu H, et al. Survival and prognostic analysis of primary nasopharyngeal carcinoma in North China. *Clin Lab*. 2015;61(7):699-708.
42. Ma BB, King A, Lo YM, 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(3):714-720.
43. Lin JC, Wang WY, Chen KY, et al. Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. *N Engl J Med*. 2004;350(24):2461-2470.