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Prognostic nomogram to predict the distant metastasis after intensity-modulated radiation therapy for patients with nasopharyngeal carcinoma

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Abstract

Distant metastasis-free survival (DMFS) significantly differs among individuals with nasopharyngeal carcinoma (NPC). This analysis was carried out to find prognostic risk factors of DMFS and create a nomogram to predict DMFS for NPC patients who received Intensity-Modulated Radiation Therapy (IMRT).

During March 2008 to January 2010, 437 patients with confirmed NPC from First Affiliated Hospital of Guangxi Medical University were recruited into this study. We developed a nomogram for predicting DMFS according to Cox regression analysis. Nomogram performance was assessed by concordance index (C-index), bootstrap validation method, and operating characteristics curves (ROC), respectively.

Four independent prognostic factors for distant metastasis were identified, including age, chemotherapy, N-stage and residual tumor. C-index of the nomogram for prediction of DMFS was 0.807 (95% confidence interval, 0.726 to 0.738), which was confirmed using bootstrap validation, indicating satisfactory predictive accuracy. The calibration curves also showed adequate agreement in predicting the 3 and 5-year DMFS. The 3 and 5-year area under the curve (AUC) of ROC for nomogram and TMN stage were 0.828 and 0.612, 0.809, and 0.571, respectively. Classifying risk subgroups based on optimal cut-off value contributes to the effective discrimination of distant metastasis.

The nomogram developed for this study is useful for oncologists to accurately predict DMFS and facilitates individualized treatment for patients with NPC.

Abbreviations: AUC = area under the curve, C-index = concordance index, DMFS = distant metastasis-free survival, IMRT = intensity-modulated radiation therapy, NPC = nasopharyngeal carcinoma, ROC = operating characteristics curves, TNM = tumor-node-metastasis.

Keywords: distant metastasis, intensity-modulated radiation therapy, nasopharyngeal carcinoma, nomogram

1. Introduction

Nasopharyngeal carcinoma (NPC) is a malignant disease with a specific geographic distribution.[1] Worldwide, approximately 13,000 individuals were diagnosed with NPC in 2018. However, the highest incidence occurred in the eastern hemisphere and southeast Asia.[2] Non-keratinizing differentiated subtype is more common in endemic areas and is predominantly attributed to the Epstein-Barr virus (EBV) infection.[3] About 70% of NPC patients are initially diagnosed with locally advanced disease. Standard-of-care treatment is radiotherapy and chemotherapy, due to its special anatomical location.[4] With recent advances in radiotherapy, the locoregional control rates of NPC have reached to >80%.[5] However, distance metastasis remains a major cause of treatment failure for NPC patients.[6] Despite the use of intensity-modulated radiotherapy (IMRT) in conjunction using neoadjuvant chemotherapy or concurrent or adjuvant chemotherapy, distant metastasis occurs in up to 20% of patients with NPC.[7] Moreover, the survival time of patients diagnosed with metastasis is usually less than 15 months, even while receiving palliative chemotherapy.[8,9] Therefore, identifying individuals that are at a higher risk for distant metastasis is required for personalized therapy and follow-up. Staging using the tumor-node-metastasis (TNM) method is most crucial model for prognostication and risk classification for therapeutic

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strategies.[10] NPC patients with similar TNM stage are given similar therapeutic regimens. Nevertheless, the distant metastasis-free survival (DMFS) is heterogeneous, revealing that additional characteristics may play a role in determining prognosis.[11] Over the past decade, several additional factors affecting survival outcomes of NPC have been identified, such as levels of early antigen immunoglobulin A (EA-IgA) and C-reactive protein (CRP).[12,13] However, the risk factors of distant metastasis in NPC have not yet been fully clarified.

Nomograms have been proven to be a useful model for predicting prognosis for people suffering from cancer, such as breast cancer, hepatocellular carcinoma and gastric cancer.[14–16] Unfortunately, few nomograms have been developed for predicting the possibility of distant metastasis after radiotherapy for patients with NPC. The goal of this present analysis is to assess the prognostic characteristics for distant metastasis and predict DMFS by constructing a nomogram. Furthermore, we classified risk groups based on the risk factors, which can help choose individualized therapy for individuals with NPC.

2. Material and methods

2.1. Patients

We retrospectively enrolled people with NPC from March 2008 and January 2010 from the First Affiliated Hospital of Guangxi Medical University. The inclusion criterion for this analysis included having a new diagnosis, histologically proven NPC, no previous chemotherapy, radiotherapy or surgery, no metastasis (M0) before treatment, Eastern Cooperative Oncology Group performance status (ECOG-PS) <3, and complete clinicopathologic and treatment data. Tumor staging was based on AJCC/UICC 8th edition. Written informed consent were obtained from all patients. The protocol was performed according to the Good Clinical Practice Guideline and this investigation was granted approval through the Research Ethics Committee of the university.

2.2. Treatment strategies

All enrolled patients underwent IMRT. A dose of 68 to 74 Gy was administrated to gross tumor volume of the nasopharynx, 66 to 70 Gy to gross tumor volume of the positive cervical lymph node, 60 to 66 Gy to higher risk clinical target volumes (CTV1) and 50 to 56 Gy to lower risk clinical target volumes (CTV2). Irradiation was administered 5 days (Monday to Friday) per week over a period of 6 to 7 weeks. The chemotherapy consisted of a platinum-based combination regimen. A total of 88.3% (386/437) of patients received induction chemotherapy, concurrent or adjuvant chemotherapy.

2.3. Imaging estimation

Residual tumors were classified as tumors that appeared in the nasopharynx or additional soft tissues after the completion of radiotherapy. Residual tumors usually present as a signal of hypo-intensity on T1-weighted imaging and hyper-intensity on T2-weighted imaging. Regional lymph nodes were thought to have residual tumors if their MRI showed short-axis diameter was >10 mm for cervical lymph nodes and >5 mm for retropharyngeal nodes after radiotherapy ended. Skull base lesions were diagnosed as residual tumor depending on whether skull base bone was invaded by soft tissues and the level, or capacity of bone strengthening had not increased or decreased in comparison to pre-treatment imaging. Tumor residues were evaluated through consensus between 2 head and neck radiology specialists and 2 radiation oncology specialists.

2.4. Follow up and evaluation

Overall survival (OS) was measured as the period from registration to day of death due to any reason. DMFS was measured as time from registration to day of metastasis detection. After the treatment had ended, participants were monitored once every 3 months through the first 3 years, then every 6 months for the subsequent 4 to 5 years, and every year after. Physical examination, mirror examination, MRI or intensive CT scanning of the residual tumor were performed. Chest, liver CT or bone scans were recorded if clinically indicated.

2.5. Statistics

Thirteen candidate factors including age, gender, WHO classification, T stage, N stage, lymph node with enhancing rim, lymph node necrosis, matted lymph nodes, treatment mode, chemotherapy, dose to gross tumor volume of the positive cervical lymph node, dose to gross tumor volume of the positive cervical lymph node and residual tumor were analyzed. Univariable and multivariable analysis were performed using the Cox regression model. The independent risk factors correlated to metastasis were identified, and hazard ratios (HR) and 95% confidence interval (95% CI) were measured. Nomogram was utilized to virtualize the prediction model. Concordance index (C-index) was used, in addition to operating characteristics curves (ROC), to evaluate the predictive discrimination of nomogram. Bootstrapping validation, with 1000 resamples, was utilized to correct the C-index. Calibration curves was conducted to evaluate the predictive accuracy for DMFS of nomogram. Furthermore, based on the total scores of nomogram, patients were separated into either low or high-risk subgroups for metastasis using the X-tile software (version 3.6.1).[17] Survival plot was depicted using Kaplan–Meier analysis and compared utilizing log-rank assessment. The HR and 95% CI, and log rank P value were recorded. All statistical assessments were conducted utilizing SPSS 22.0 and R software (version 3.5.2). A two-sided $P < .05$ represented statistical significance.pt

3. Result

3.1. Patient characteristics and univariate analysis

The median follow-up for the cohort was 57.3 months (range, 4–81 months). A total of 437 people were recruited for this analysis. Overall, 11.6% (51/437) of patients had TNM stage II NPC, 66.3% (290/437) patients had TNM stage III NPC, whereas 19.2% (84/437) had TNM stage IVa NPC, 7.3% (32/437) patients had keratinising squamous subtype, 28.8% (126/437) patients had non-keratinising differentiated subtype, 63.8% (279/437) patients had non-keratinising undifferentiated subtype. In total, 22.8% (100/437) patients were diagnosed with residual tumor after receiving IMRT. There were 56 (12.8%) patients that developed metastasis by last follow-up. Clinical characteristics of each participant is summarized in Table 1. The 3 and 5-year OS was 89.0% and 81.8%, respectively, while the 3 and 5-year DMFS was 90% and 87.2%, respectively. Univariate analysis indicated that age, chemotherapy, N-stage and presence of residual tumor were significant prognostic factors for distant

Table 1

Characteristics and treatment mode of 437 patients and association with distant metasitasis in univariate analysis.

Characteristics	Case numbers (%) (n = 437)	Univariate analysis		
		HR	95% CI	*P* value
Age (yr)				
≥50	290 (66.4%)	–	–	Reference
<50	147 (33.6%)	2.182	1.291–3.685	.004
Gender				
Female	109 (24.9%)	–	–	Reference
Male	328 (75.1%)	1.154	0.62–2.145	.652
Histology				
Keratinising squamous	32 (7.3%)	–	–	Reference
Non keratinising differentiated	126 (28.8%)	1.309	0.379–4.524	.67
Non keratinisingundifferentiated	279 (63.8%)	1.549	0.478–5.021	.466
T stage				
T1	31 (7.1%)	–	–	Reference
T2	77 (17.6%)	1.193	0.323–4.406	.791
T3	281 (64.3%)	1.435	0.443–4.649	.547
T4	48 (11%)	1.418	0.354–5.67	.622
N stage				
N0	69 (15.8%)	–	–	Reference
N1	152 (34.8%)	1.728	0.573–5.206	.331
N2	177 (40.5%)	2.713	0.947–7.775	.063
N3	39 (8.9%)	6.285	2–19.756	.002
Lymph node with enhancing rim				
no	384 (87.9%)	–	–	Reference
yes	53 (12.1%)	1.098	0.497–2.425	.816
Lymph node necrosis				
no	328 (75.1%)	–	–	Reference
yes	109 (24.9%)	1.432	0.81–2.531	.217
Matted lymph nodes				
no	276 (63.2%)	–	–	Reference
yes	161 (36.8%)	1.594	0.943–2.696	.082
Treatment mode				
RT alone	52 (11.9%)	–	–	Reference
IC	7 (1.6%)	1.276	0.283–5.757	.751
CCRT	195 (44.6%)	0.465	0.224–0.964	.039
IC+CCRT	129 (29.5%)	0.581	0.272–1.24	.160
CCRT+AC	34 (7.8%)	0.41	0.114–1.471	.171
IC+CCRT+AC	20 (4.6%)	0.435	0.096–1.961	.278
Chemotherapy				
no	51 (11.7%)	–	–	Reference
yes	386 (88.3%)	0.498	0.258–0.964	.038
Dose to GTVnx				
<71.3 Gy	211 (48.3%)	–	–	Reference
>71.3 Gy	226 (51.7%)	0.599	0.35–1.024	.061
Dose to GTVnd				
<68.3 Gy	215 (49.2%)	–	–	Reference
>68.3.3 Gy	222 (50.8%)	1.168	0.691–1.975	.563
Residual tumor				
no	337 (77.1%)	–	–	Reference
yes	100 (22.9%)	7.53	4.37–12.974	.000

AC = adjuvant chemotherapy, CI = confidence interval, CCRT = concurrent chemoradiotherapyv, GTVnx = gross tumor volume of the nasopharynx, GTVnd = gross tumor volume of the positive cervical lymph node, HR = hazard ratio, IC = induction chemotherapy, RT = radiotherapy, WHO = World Health Organization.

metastasis of NPC, in addition, chemotherapy modes weren't significant prognostic factors for distant metastasis of NPC, as is shown in Table 2.

3.2. Multivariate analysis and construction of nomogram

In multivariate analysis, age, chemotherapy, N-stage and presence of residual tumor were independent prognostic risk factors for metastasis of NPC. Results of multivariate analyses are summarized in Table 3. Furthermore, all these independent predictors were incorporated by the nomogram, which is shown in Figure 1. Within the nomogram, each value of the model covariates is assigned a score ranging from 0 to 100, by totaling up the overall score of all characteristics projected in the total point scale, we can predict the 3 and 5-year DMFS for NPC patients.

3.3. Validation of the predictive nomogram

The nomogram's C-index for metastasis was 0.807 (95% CI 0.754–0.859), which was verified by 1000-replication

Table 2

Univariate analysis of the association between individual chemotherapy regimens and distant metastasis.

Characteristics	Univariate analysis		
	HR	95% CI	*P* value
Treatment mode			
CCRT	–	–	Reference
IC+CCRT	1.249	0.659–2.367	.496
CCRT+AC	0.888	0.265–2.978	.848
IC+CCRT+AC	0.936	0.219–3.991	.929

AC = adjuvant chemotherapy, CI = confidence interval, CCRT = concurrent chemoradiotherapy, HR = hazard ratio, IC = induction chemotherapy.

bootstrapping analysis. The calibration curves for predicting 3 and 5-year DMFS in NPC patients showed promising agreement between nomogram prediction and real-life observation (Fig. 2). The ROC curve was used to verify the predictive nomogram, and the results revealed that the model (3-year DMFS: area under the curve [AUC], 0.828, 95% CI 0.768–0.889; 5-year DMFS: AUC, 0.809, 95%CI 0.753–0.865) had a higher predictive ability compared to the TMN-stage (3-year DMFS: AUC, 0.612, 95% CI 0.527–0.699; 5-year DMFS: AUC, 0.571, 95% CI 0.490–0.652), indicating that the nomogram represents a feasible model for predicting metastasis (Fig. 3).

3.4. Identification of high- and low-risk groups for NPC patients

As per the optimal cut-off values calculated by X-tile software, all the participants were separated into either a low-risk (score <120) or high-risk group (score ≥120). Overall, 74.8% (327/437) patients were incorporated in the lower risk group, while 25.2% (110/437) patients were encompassed in higher risk group. Moreover, Kaplan–Meier survival curves indicated that DMFS of the high-risk group was substantially reduced versus the low-risk group ($P < .001$), as is showed in Figure 4.

4. Discussion

The broad application of IMRT and optimization of chemotherapy regimen have facilitated an improvement in survival and reduced toxicities. However, distant metastasis of NPC remains an essential treatment obstacle to improve patients' overall survival.[18,19] Therefore, early diagnosis and treatment for metastatic NPC is necessary.

In this study, we constructed a nomogram to evaluate DMFS among NPC patients. Results indicated that age, chemotherapy, N stage and residual tumor are independent prognosticators of distant metastasis. The ROC curve showed that the nomogram significantly outperformed the TMN stage for predicting risk of distant metastasis. The excellent accuracy and reliability of this nomogram was further confirmed by bootstrap resampling, C-index and calibration curves. Furthermore, NPC patients were successfully separated into either high or low-risk group by applying risk scores of the mode.

In our study, young age likely has an adverse effect on DMFS among patients with NPC. The prognostic influence of age has been proven in NPC and other cancer. For example, Xiao et al showed that age is a independent prognostic risk factor for NPC, young NPC patients were more tend to have distant metastases,[20] Zhou et al found that risk of metastasis in young patients

Table 3

Multivariate analysis of the association between independent prognostic factors and distant metastasis.

Characteristics	Multivariate analysis		
	HR	95% CI	*P* value
Age (yr)			
≥50	–	–	Reference
<50	2.04	1.192–3.489	.009
Chemotherapy			
no	–	–	Reference
yes	0.426	0.219–0.83	.012
N stage			
N0	–	–	Reference
N1	1.662	0.551–5.014	.367
N2	1.91	0.658–5.544	.234
N3	5.717	1.786–18.298	.003
Residual tumor			
no	–	–	Reference
yes	6.902	3.935–12.106	.000

CI = confidence interval, HR = hazard ratio.

with lung cancer is significantly higher than in elderly patients.[21] These studies imply that age is a vital prognostic indicator for clinical outcome. There are some possible reasons for the contrary relationship between age and metastasis. First, a study revealed that co-opting the immune system, such as CD4+ T cells, has a vital function in the development of metastasis.[22] Therefore, increasing age is associated with deterioration of the immune system and thus, affects the process of metastasis.[23] In addition, in a previous study, extracellular matrix (ECM) protein was proven to be linked to tumorigenesis and metastasis in NPC.[24] Age-related changes of ECM as a result of non-enzymatic glycosylation (NEG) may protect against the development of metastasis. Experiments have shown that microvessel density of tumors in elderly mice was significantly reduced compared to younger mice.[25] Further clinical analysis is needed to explore this relationship between aging and metastasis in NPC. Another prognostic factor that was identified for distant metastasis is the N-stage. A study also indicted that N2–3 stage was an independent risk factors for distant metastasis of patients with NPC (HR, 2.423, 95%CI 1.55–3.77 $P < .001$).[26] It is well recognized that lymph nodes are initial sites in the process of cancer metastasis, including for NPC.[27] Microenvironment of lymph nodes might contribute to the proliferation and aggressiveness of tumor cells in this organ, which correlates with poor prognosis.[28] Similar to previous studies, result of our study support the fact that higher N-stage correlates with unfavorable survival outcomes.

Even though NPC is very sensitive to radiotherapy, in about 7% to 13% of patients, residual disease persists after treatment.[29] Result of multivariate analysis demonstrated that residual tumor is a robust independent prognostic factor for DFMS. The occurrence of residual tumor is associated with less favorable prognosis for these patients. Wang et al. revealed that residual tumor status was substantially correlated with poor overall survival in NPC.[30] Moreover, a report showed that residual tumor was an independent unfavorable factor for progression-free survival (PFS) and Locoregional failure-free survival (LRFS) in NPC patients,[31] He et al revealed that the appearance of residual tumor post-IMRT was a substantial negative independent prognostic risk factor for DMFS (HR, 1.91, 95% CI 1.23–2.98, $P = .004$).[32] Many factors can lead to the

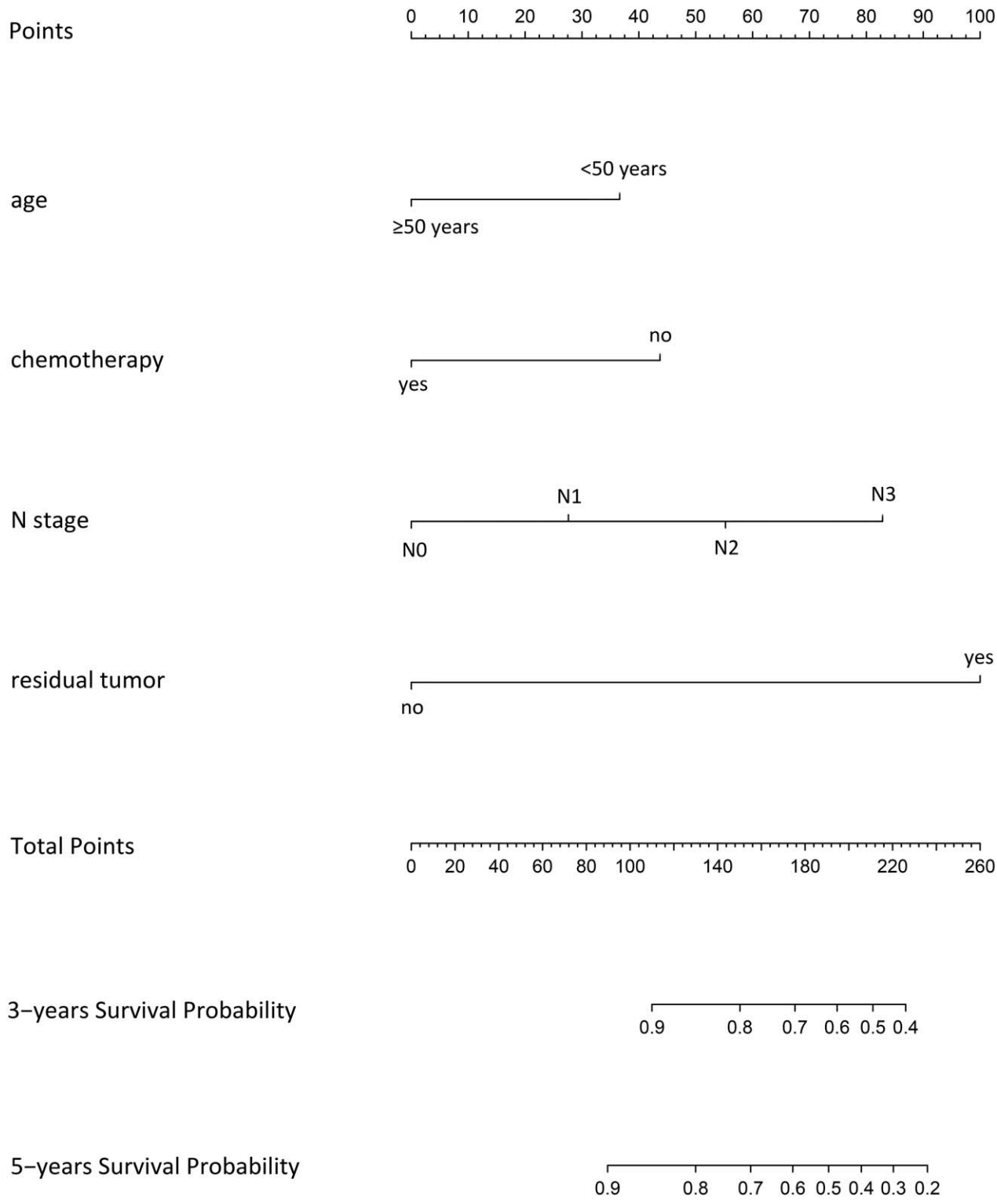

Figure 1. Nomogram for forecasting the 3 and 5-year DMFS for NPC patients. DMFS = distant metastasis-free survival.

development of residual tumor in patients with NPC after radiotherapy, including tumor angiogenesis, cancer stem cells, and immune response.[30] The optimal evaluation time-point is crucial for prognosis prediction, notably, we evaluated MRI-detected residual status at 3 months after treatment. In the study of Lv et al, they also selected 3 months after radiotherapy as the evaluation time-point to examine MRI-detected residual tumor in NPC.[31] Furthermore, Lin et al showed a solid correlation among recurrence and residual tumor at 3 to 6 months postradiotherapy.[33]

On the other hand, result from our study also found that chemotherapy was a candidate factor for distant metastasis in

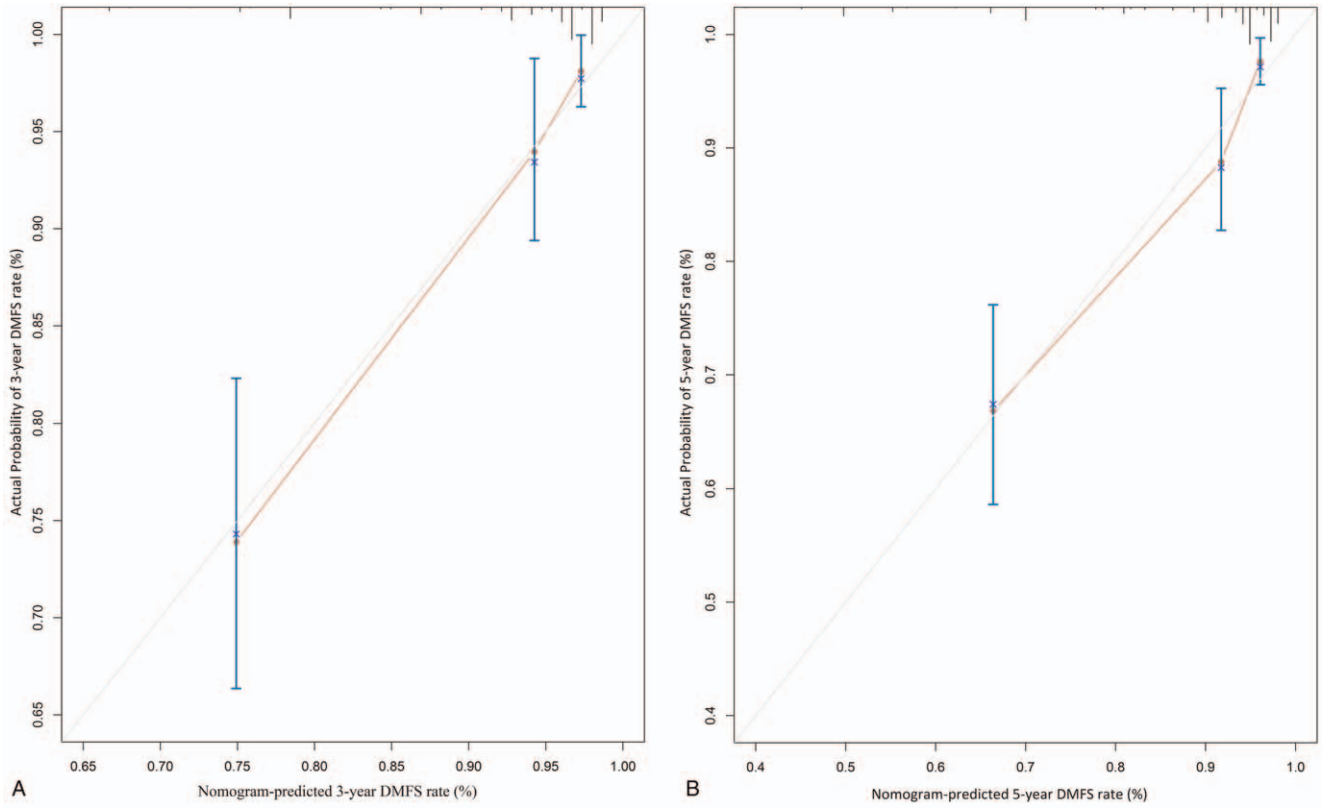

Figure 2. Calibration curves for prognosticating distant metastasis at 3 (A) and 5-years (B). X-axis is representative of Nomogram-predicted probability, while y-axis is representative of actual distant metastasis.

NPC. Although the excellent locoregional control was achieved by using IMRT, this improvement in locoregional control did not correspond to a longer DMFS. A probability of micrometastases in patients might contribute to this finding. Even through high-resolution imaging technologies, early spread of cancer cells is difficult to detect.[34] Therefore, a higher dose of irradiation may be unable to eradicate micrometastatic lesions. A meta-analysis found that adding chemotherapy to RT significantly lowered the risk of distant failure (HR, 0.72, 95% CI 0.59–0.87, $P = .001$).[35] Li et al also showed that the combination of chemotherapy and IMRT significantly decreased the metastasis risk compared to IMRT alone ($P = .025$).[36] These findings are consistent with our study. Thus, early examinations and possible intervention for high-risk patients are necessary for preventing the development of distant metastases.

Clinically, it is important for oncologists to assess the risk of distant metastasis. Our proposed nomogram may be a promising method to precisely predict the 3-year and 5-year DMFS.

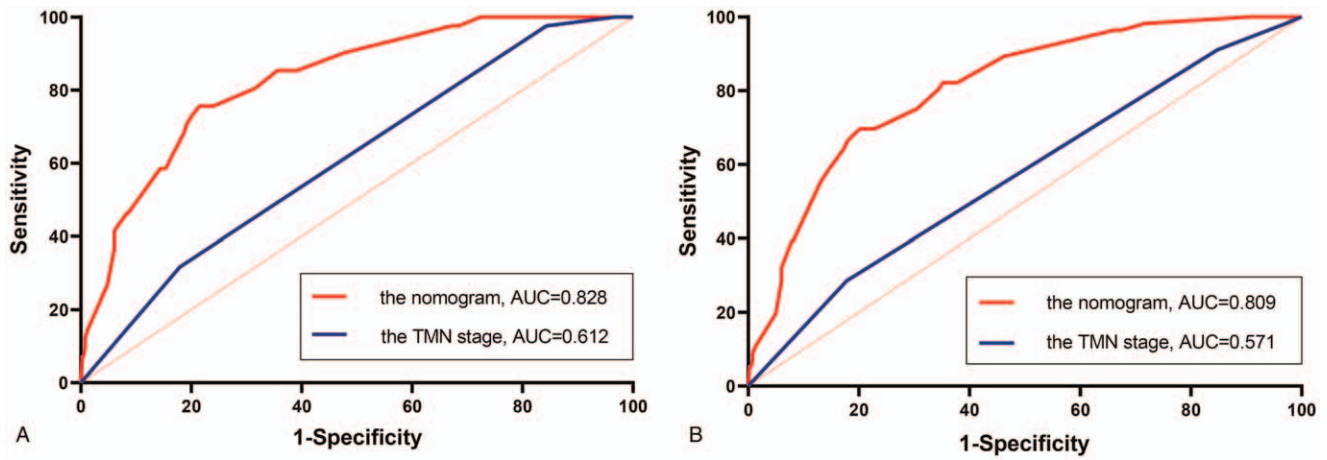

Figure 3. Time-dependent operating characteristics curves (ROC) for the nomogram and TMN stage. (A) 3-year DMFS. (B) 5-year DMFS. DMFS = distant metastasis-free survival.

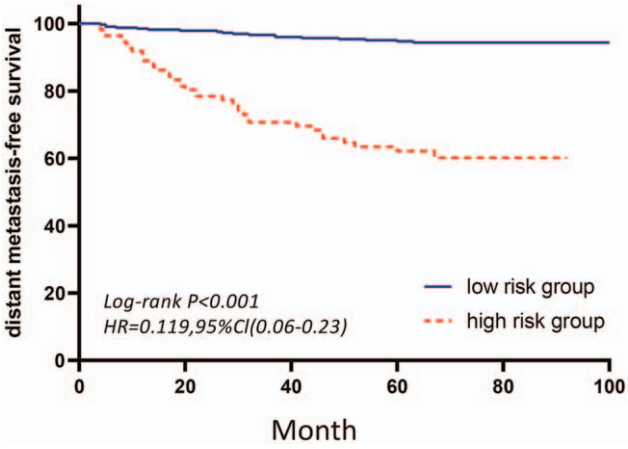

Figure 4. DMFS curves for the 437 NPC patients in high-risk and low-risk group. DMFS = distant metastasis-free survival.

However, our nomogram has some limitations. First, the model was constructed based on a retrospective cohort at a single institute. Furthermore, external validation are needed.

5. Conclusion

To summarize, this study identified the prognostic factors for DMFS and established a nomogram to forecast the 3 and 5-year DMFS in individuals with NPC. This nomogram has a relatively high accuracy and may help facilitate clinical decision of individualized therapy.

Author contributions

Conceptualization: Ren-Sheng Wang.
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Funding acquisition: Ren-Sheng Wang.
Project administration: Meng Xu.
Software: Jing-Lin Mi.
Supervision: Ren-Sheng Wang.
Validation: Meng Xu, Chang Liu.
Visualization: Chang Liu.
Writing – original draft: Jing-Lin Mi.
Writing – review & editing: Ren-Sheng Wang.

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