

Development and external validation of a nomogram for predicting the overall survival of patients with stage II nasopharyngeal carcinoma after curative treatment

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Objective: To facilitate decision-making support for individual patients, development and external validation of a nomogram was undertaken to reveal prognostic factors and predict the value of concurrent chemoradiotherapy (CCRT) compared with radiotherapy (RT) for stage-II nasopharyngeal carcinoma (NPC) patients.

Methods: Clinical data of 419 and 309 patients with American Joint Committee on Cancer (2017) stage-II NPC in two institutions in China were collected retrospectively. Overall survival (OS) and progression-free survival were compared using Kaplan–Meier estimates. Cox regression analysis was used to identify the prognostic factors for building the nomogram. Predictive accuracy and discriminative ability were measured using the Concordance Index.

Results: Finally, there were 24 and 20 deaths in the development and validation group, respectively. Patients with stage T2N1, N1 stage, involvement of retropharyngeal and unilateral cervical lymph nodes, and who had RT alone had worse OS ($P=0.019, 0.035, 0.003$ and 0.010 , respectively; log-rank test) than patients with stage T1N1 and T2N0, N0 stage, involvement of retropharyngeal or unilateral cervical lymph nodes, and CCRT, respectively. After multivariate analysis of the training set, age, neutrophil-to-lymphocyte ratio, therapy type, and pretreatment plasma concentration of Epstein–Barr virus DNA were independent prognostic factors of OS. A nomogram was established externally by involving all the factors stated above. The Concordance Index for the established nomogram to predict the OS of the training set was 0.793 (95% CI 0.689–0.897), and 0.803 (95% CI 0.696–0.910) in the validation set.

Conclusion: These data suggest that the nomogram was validated externally, could predict long-term outcome accurately, and enable accurate stratification of risk groups for stage-II NPC. Our model facilitated individualized care of NPC patients.

Keywords: chemotherapy, nasopharyngeal carcinoma, nomogram, prognosis, radiotherapy

Introduction

Nasopharyngeal carcinoma (NPC) has unique epidemiologic features (regional, racial, and familial) in southern China,¹ where the highest incidence of NPC was found to be 1.9–2.8 per 100,000 person-years.² Increasing attention has focused on advanced NPC, which causes the highest incidence of death-related recurrence and distant metastasis. The prognosis of patients with stage I–II NPC is, in general, favorable upon radiotherapy (RT) initiation. Overall survival (OS) is 84–90% for early stage NPC with RT alone.³

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While, treatment of stage-II NPC is controversial. A retrospective study⁴ revealed that addition of concurrent chemoradiotherapy (CCRT) did not improve survival significantly but increased the prevalence of acute-toxicity reactions in patients with stage-II NPC. A meta-analysis⁵ of 2138 patients with stage-II NPC concluded that intensity-modulated radiotherapy (IMRT) alone was superior to CCRT with equivalent survival outcomes and fewer grade-3–4 acute-toxicity reactions. Either survival or complications, there were many studies in favor of RT alone. Chemotherapy for stage-II NPC is sometimes not recommended because an advantage of CCRT compared with RT alone has not been shown.

Patients with early stage NPC and positive lymph nodes are likely to develop distant metastasis and have poor OS.⁶ The role of adjunctive chemotherapy for stage-II NPC has been defined in a phase-III randomized trial.⁷ Results showed that chemotherapy improved 5-year OS ($P=0.007$), progression-free survival (PFS) ($P=0.017$), and distant metastasis-free survival (DMFS) ($P=0.007$) significantly; the CCRT group experienced more acute toxic effects ($P=0.001$) and the prevalence of late toxic effects did not increase significantly. A meta-analysis⁶ comprising 16 studies (3038 patients) compared conventional RT alone with CCRT. It demonstrated that CCRT could improve the prognosis significantly in terms of OS, PFS, and LRFS for stage-II NPC, but not DMFS whereas, with IMRT, patients with stage-II NPC did not benefit from the addition of chemotherapy. Nevertheless, a subgroup of patients with T2N1 disease carried a higher risk of regional recurrence and distant metastasis. In addition, the National Comprehensive Cancer Network has recommended CCRT for stage-II NPC, but the evidence for its efficacy is weak, which may attribute to the subgroups of various stages and other prognostic factors.

In recent years, a “nomogram” has been shown to be a reliable model for prognosis prediction for people suffering from cancer.^{8,9} Some nomograms have validated the prognostic factors in advanced NPC.^{10,11} However, a nomogram has not been developed for early stage NPC.

Based on a large cohort in our center, we aimed to establish a nomogram for survival prediction of individual patients with stage-II NPC. In addition, a cohort of patients were also included for external validation to test if this nomogram could be applied to predict their survival. Also, we stratified risk groups according to the factors which may help select individualized care of patients with stage-II NPC.

Methods

Inclusion criteria

The inclusion criteria for our study were (i) diagnosed with primary undifferentiated non-keratinized carcinoma according to pathology; (ii) stage-II NPC according to American Joint Committee on Cancer (AJCC) guidelines (8th edition); (iii) adequate clinical information in medical records; (iv) acquiring the standard and complete treatment: received radiotherapy with or without chemotherapy.

Patients

This study protocol was approved by the Research Ethics Committee of Sun Yat-sen University Cancer Center and The First People’s Hospital of Foshan, Guangzhou, China. Owing to the retrospective study design and analysis of clinical data, all data were anonymized; therefore, informed consent was formally waived by the Ethics Committee. All patient information is ensured to be confidential. All the procedures in this study are in accordance with the Helsinki Declaration.

Data from the training set were obtained from the medical records of 419 patients with NPC treated between 5 January 2010 and 14 October 2013 at Sun Yat-sen University Cancer Center. A total of 309 patients in the validation set were obtained from The First People’s Hospital of Foshan between January 2010 and August 2013. Demographic data (age, sex, smoking status, blood-test results [baseline laboratory data: plasma Epstein–Barr virus (EBV) DNA concentration, absolute neutrophil count, lymphocytes, and plasma fibrinogen], stage and treatment) were obtained from the electronic records of the hospital. All patients were restaged according to the 8th version of the AJCC staging system. Staging work-up comprised direct fiber-optic nasopharyngoscopy, magnetic resonance imaging of the nasopharynx and neck, abdominal ultrasound, chest radiography, whole-body scintigraphy, and/or positron emission tomography-computed tomography, and plasma EBV DNA concentration.

Treatment

The treatment strategies for all patients were based on National Comprehensive Cancer Network Guidelines. All patients received IMRT with or without chemotherapy. IMRT involved fractions of 2.12–2.24 Gy daily for 5 days per week, up to a total of 68–72 Gy to the primary tumor, 60–66 Gy to involved areas of the neck, and 54–56 Gy to uninvolved areas. CCRT consisted of

cisplatin or nedaplatin administered triweekly or weekly until the end of RT.

Quantification of plasma EBV DNA concentration

The pretreatment plasma EBV DNA concentration was measured using real-time quantitative polymerase chain reaction (qRT-PCR). This assay was developed for detection of the plasma EBV DNA concentration and targets the BamHI-W fragment region of the EBV genome. qRT-PCR was carried out using 2× TaqMan™ Reagent (Roche, Basel, Switzerland), the amplification primers W-44F (50-AGTCTCTGCCTCAGGGCA-30) and W-119R (50-ACAGAGGGCCTGTCCACCG-30) and the dual-labeled fluorescent probe W-67T (50-[FAM]-CACTGTCTGTAA AGTCCAGCCTCC-[TAMRA]-30). At both institutions, a plasma EBV DNA concentration of $<10^3$ copies/mL was defined as “undetectable”. The cutoff value for EBV DNA was defined by analysis of receiver operator characteristic curves.

Follow-up

The primary endpoint was OS, measured from the date of the first NPC diagnosis to the date of death or loss to follow-up. The secondary endpoint was PFS (to relapse, distant metastasis, patient censorship or death at final follow-up). All patients were followed up routinely after therapy: every 3 months during the first 2 years, every 6 months during years 3–5, and annually thereafter. The surveillance work-up comprised normal routine assessments, imaging evaluation as well as measurement of the plasma EBV DNA concentration.

Statistical analyses

Statistical analyses were done using IBM v22.0 (IBM, Armonk, NY, USA). Survival outcomes were estimated using the Kaplan–Meier method and compared with the log-rank test. All analyses were two-sided; the level of significance was set at $P<0.05$. Significant variables ($P<0.05$) were entered into a Cox proportional hazards multivariate model to identify independent prognostic factors *via* forward stepwise procedures ($P<0.05$). Based on multivariate analyses, nomograms were generated to provide visualized risk prediction using the “survival” and “rms” packages of R 2.14.1 (www.r-project.org). Nomograms were subjected to bootstrap resampling ($n=1000$) for internal and external validation

to correct the Concordance Index and explain variance with respect to over-optimism. During external validation, the nomogram point scores were calculated for individual patients, and then Cox regression analysis was undertaken using total point scores as predictors in the validation set.

Finally, the predictive accuracy for OS was validated by calculating the Concordance Index of the nomogram in the validation set. The value of the Concordance Index ranged from 0.5 to 1.0, which denotes a random chance to a perfect ability to correctly discriminate between the outcome and model, respectively. The 3-, 5-, and 6-year OS was calibrated by comparing predicted and observed survival.

Results

Clinicopathologic characteristics of patients in the primary cohort

A total of 409 patients with stage-II NPC who had undergone RT or CCRT in the primary set were eligible for the final analysis. There were 24 deaths at a median follow-up of 65 (range, 7.567–99.233) months. The predominant histology type was World Health Organization type III. All patients received IMRT with or without platin-based chemotherapy. An independent external validation set of 309 patients was recruited, with 20 events at a median follow up of 65.433 (range, 13.7–99.0) months. The clinicopathologic features of patients in the training set and external validation set are summarized in Table 1.

Survival outcomes according to the 8th edition of the AJCC staging system in the training set

Five-year OS and PFS for the training set was 95.3% and 95.2%, respectively. We restaged patients according to the AJCC staging system (8th version), and compared survival outcomes for T stage, N stage, lymph-node site and category of plasma EBV DNA concentration. Stage T2N1 vs T1N1 vs T2N0 showed worse OS ($P=0.019$, Figure 1A). Stage N1 expressed worse OS than N0 ($P=0.035$, Figure 1B). Involvement of retropharyngeal or unilateral cervical lymph nodes resulted in better OS than both sites ($P=0.003$, Figure 1C). Patients with a higher EBV DNA concentration (≥ 3000 copies/mL) had worse OS ($P=0.010$; Figure 1D).

Table 1 Clinical features of patients with nasopharyngeal carcinoma in the training set and validation set

Characteristic	Training set	Validation set
	n (%)	n (%)
Total	419 (100)	309 (100)
Sex		
Male	393 (93.8)	292 (94.5)
Female	26 (6.2)	17 (5.5)
Age (years)		
<45	216 (51.6)	165 (53.4)
≥45	203 (48.4)	144 (46.6)
Smoking		
Yes	113 (27.0)	82 (26.5)
No	306 (73.0)	227 (73.5)
Stage (8th edition)		
T2N0	77 (18.3)	54 (17.5)
T1N1	198 (47.3)	151 (48.9)
T2N1	144 (34.4)	104 (33.6)
Lymph node site		
Site1	94 (22.4)	72 (23.3)
Site2	163 (38.9)	117 (37.9)
Site3	162 (38.7)	120 (38.8)
N category		
N0	77 (18.3)	54 (17.5)
N1	342 (81.7)	255 (82.5)
Treatment		
RT	109 (26.0)	80 (25.9)
CCRT	310 (74.0)	229 (74.1)
CT regimen		
Triweekly	257 (61.3)	159 (51.5)
Weekly	53 (12.7)	70 (22.6)
NLR group		
<2.8	263 (62.8)	188 (60.8)
≥2.8	156 (37.2)	121 (39.2)
Fibrinogen (mg/mL)		
<3.3	274 (65.4)	203 (65.7)
≥3.3	145 (34.6)	106 (34.3)
EBV DNA (copies/mL)		
<3000	237 (56.6)	175 (56.6)
≥3000	182 (43.4)	134 (43.4)
Outcomes		
Death	24	20
Distant metastasis	20	14
Local/regional relapse	6	5

Abbreviations: RT, radiotherapy; CCRT, concurrent chemoradiotherapy; CT, chemotherapy; NLR, neutrophil-lymphocyte ratio; EBV DNA, EBV (Epstein-Barr virus) DNA concentrations.

Survival outcomes according to therapeutic regimen

Compared with RT alone, patients who received CCRT had longer OS ($P=0.002$; Figure 2A) and PFS ($P=0.032$; Figure 2B).

Independent prognostic factors in the training set

Data from the training set were used to identify prognostic factors and build the model. The results of the univariate analysis are listed in Table 2. A poor prognosis was associated with: age >45 years; stage T2N1; N1 stage; involvement of retropharyngeal and unilateral cervical lymph nodes; increased neutrophil-to-lymphocyte ratio (NLR) (≥ 2.8); increased plasma fibrinogen level (≥ 3.30 mg/dL); higher plasma EBV DNA concentration (≥ 3000 copies/mL); RT alone. Variables considered to be significant in the univariate analysis were entered into the Cox multivariate analysis. Age, NLR, plasma EBV DNA concentration and therapy were shown to be independent in the multivariate Cox regression model and were incorporated in the nomogram according to the algorithm.

Prognostic nomogram for OS prediction

Using the data of patients in the training set, a nomogram was constructed for OS prediction (Figure 3). Longer lines indicate a greater prognostic impact of specific variables, and larger points in the nomogram indicate a shorter OS. Therapy had the greatest impact on OS, followed by the NLR, plasma EBV DNA concentration, and age. Each subtype within the variables stated above was assigned a score on the point scale. By addition of the total score and locating it on the total point scale, we could draw a straight line down to determine the estimated probability of survival. It could predict the 3-, 5-, and 6-year OS of NPC patients.

Validation of the nomogram

Data from the external validation set were used to validate the model. The calibration plot based on the data from the external validation set for the probability of OS at 3, 5, and 6 years demonstrated excellent agreement between the prediction according to the nomogram and actual observation in training and validation sets (Figure 4). The Concordance Index for the established nomogram to predict the OS of the training set was 0.793 (95% confidence interval, 0.689–0.897) and 0.803 (0.696–0.910) in the validation set (Table 3).

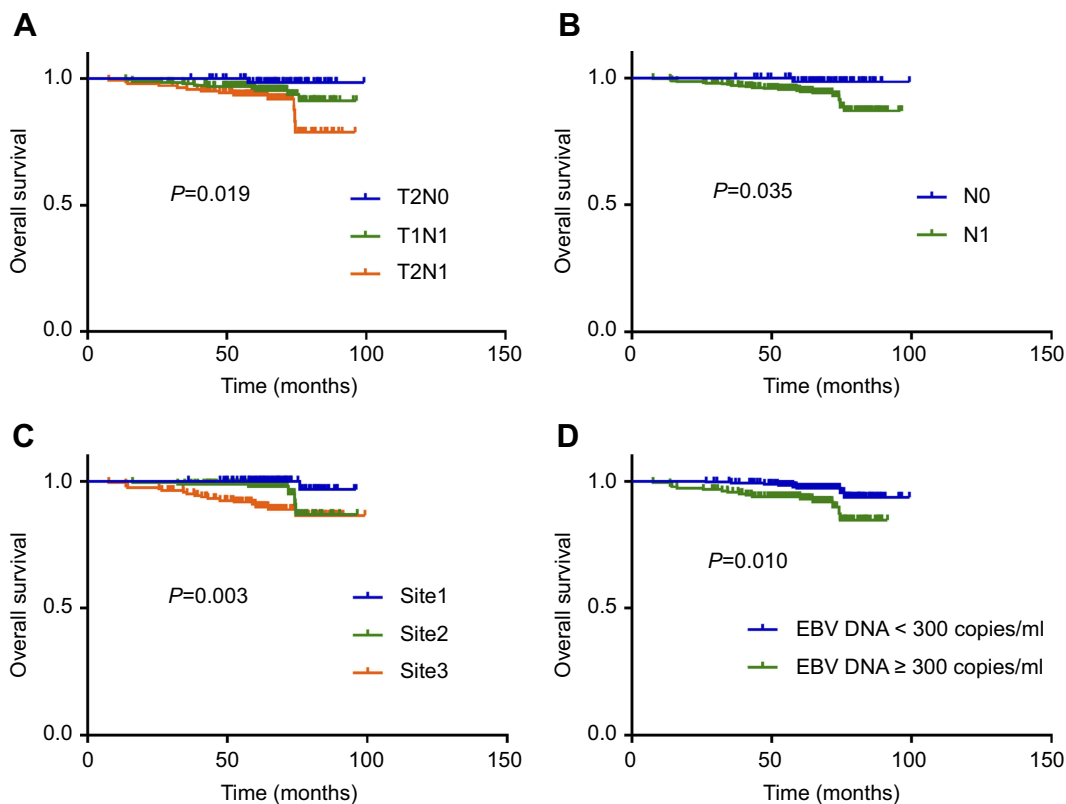


Figure 1 Kaplan–Meier overall survival curves for all 419 patients with NPC in training set stratified by stage (A), N category (B), lymph node site (C), and EBV DNA concentration (D).

Abbreviations: NPC, nasopharyngeal carcinoma

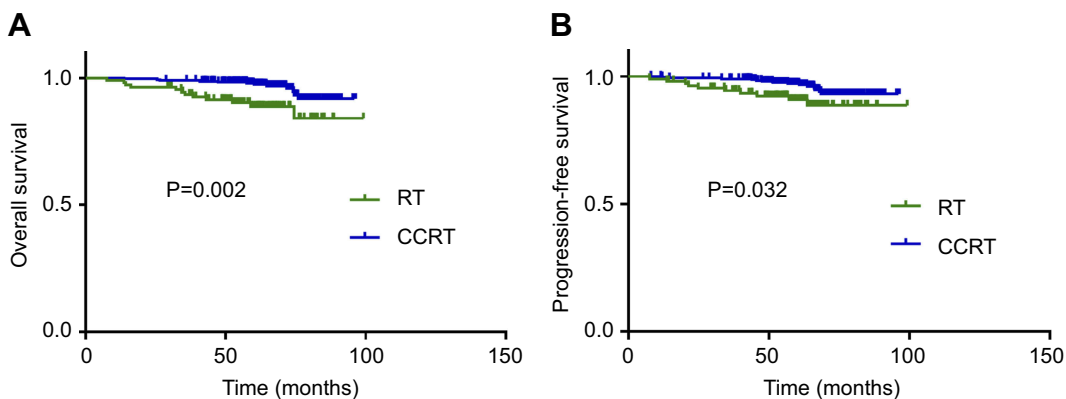


Figure 2 Effect of therapy regimen on survival outcomes. Kaplan–Meier overall survival (A) and progression-free survival (B) curves for all 419 patients with NPC in training set stratified as RT and CCRT group.

Abbreviations: RT, radiotherapy; CCRT, concurrent chemoradiotherapy;

Nomograms for risk stratification

We stratified patients in the training set and validation set into two risk groups according to scores generated by the nomogram. A “low risk” group was determined to be one with age <45 years, NLR <2.80 and plasma EBV DNA concentration <3000 copies/mL. A “high risk” group was determined to be with age \geq 45 years, NLR \geq 2.80 and plasma EBV DNA concentration \geq 3000

copies/mL. Higher OS was seen with CCRT compared with RT alone in the “high risk” group of the training set ($P=0.011$; Figure 5B), but a significant difference was not observed in the “low risk” group ($P=0.502$; Figure 5A). With regard to the validation set, CCRT also achieved higher OS in the “high risk” group ($P=0.021$; Figure 6B), but not in the “low risk” group ($P=0.514$; Figure 6A).

Table 2 Cox's proportional hazards regression model of overall survival for the 419 patients with nasopharyngeal carcinoma in training set

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age (years) ≥45 vs <45	2.656 (1.101–6.404)	0.030	2.454 (1.002–6.007)	0.049
Stage T2N0 T1N1 vs T2N0 T2N1 vs T2N0	I 4.865 (0.621–38.109) 9.650 (1.253–74.315)	0.043 0.132 0.030		
N category N1 vs N0	3.318 (1.940–5.677)	0.035		
Lymph node site Site I Site 2 vs Site I Site 3 vs Site I	I 4.455 (0.534–37.157) 11.586 (1.541–87.111)	0.013 0.167 0.017		
NLR group ≥2.80 vs <2.80	3.254 (1.421–7.451)	0.005	2.425 (1.024–5.739)	0.044
Fibrinogen (mg/mL) ≥3.30 vs <3.30	1.151 (1.008–1.314)	0.038		
EBV DNA (copies/mL) ≥3000 vs <3000	2.896 (1.238–6.774)	0.014	2.434 (1.009–5.871)	0.048
Therapy RT vs CCRT	3.315 (1.487–7.388)	0.003	2.716 (1.168–6.317)	0.020

Notes: Lymph node site: lymph node location. Site I= retropharyngeal lymph node, Site 2= unilateral cervical lymph node, Site 3= retropharyngeal and unilateral cervical lymph nodes.

Abbreviations: HR, hazard ratio; CI, confidence interval; NLR, Neutrophil/Lymphocyte Ratio; RT, Radiotherapy; CCRT, Concurrent chemoradiotherapy.

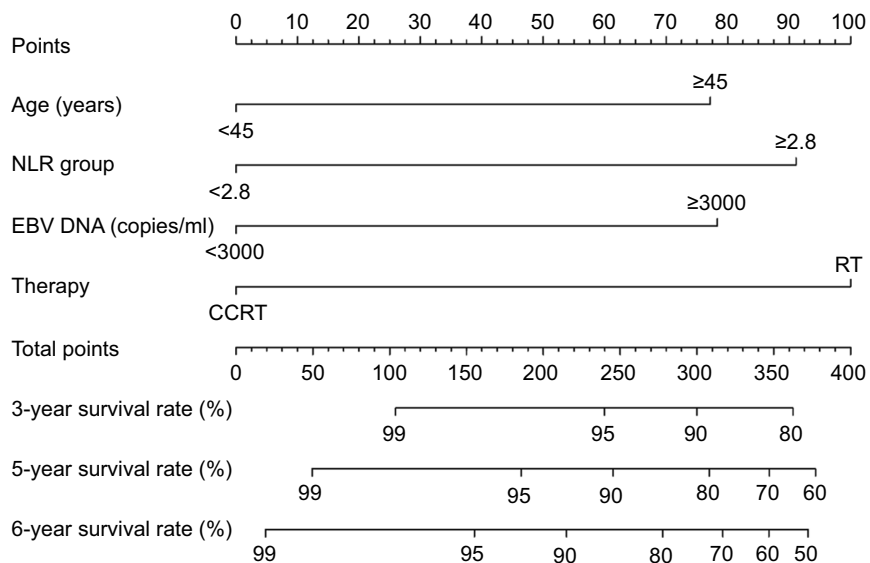


Figure 3 A nomogram predicts the overall survival (OS) of patients with NPC. This nomogram was based on age, the NLR (neutrophil–lymphocyte ratio), EBV (Epstein–Barr virus) DNA concentration and therapy regimen. The total score of each patient was the sum of the points identified at the top of the scale for each factor and was then identified on the total points scale to determine the probability of 3-year, 5-year, and 6-year OS.

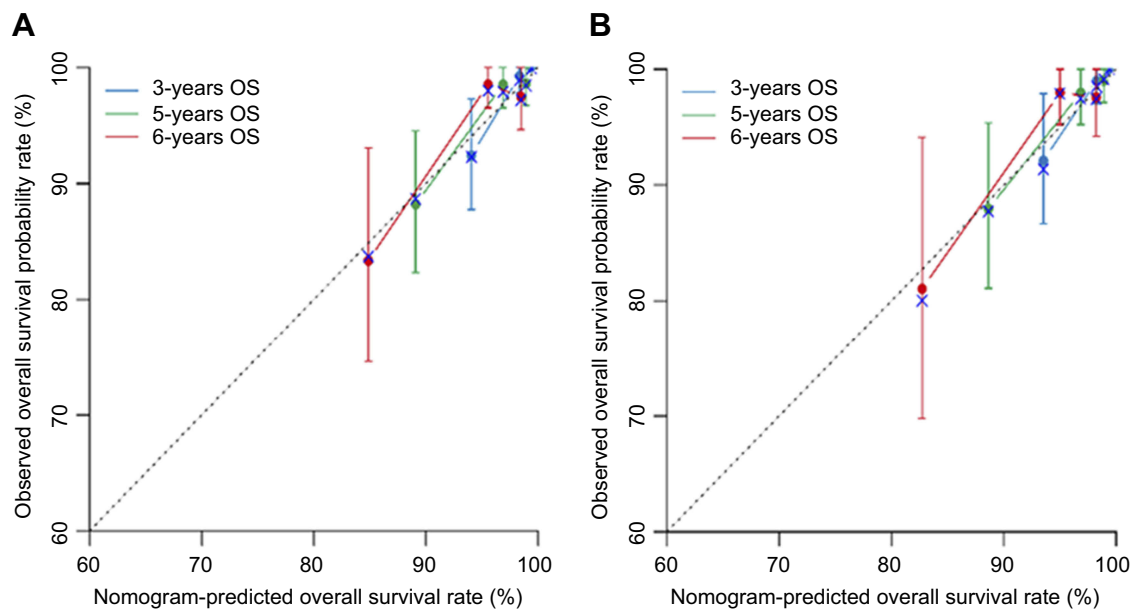


Figure 4 The calibration curve for predicting overall survival (OS) at 3-, 5-, and 6-year in the training set (A) and validation set (B). Nomogram-predicted OS is plotted on the x-axis; actual rates of OS are plotted on the y-axis. The dashed lines along the 45-degree line through the origin represent the perfect calibration models in which the predicted probabilities are identical to the actual probability.

Table 3 The concordance index values for performance of the multivariate model for prediction of OS in the training set and validation set

Model	Concordance Index	Concordance Index 95%CI	Z	P-value	n
Training set	0.793	0.689	0.897	<0.001	419
Validation set	0.803	0.696	0.910	<0.001	309

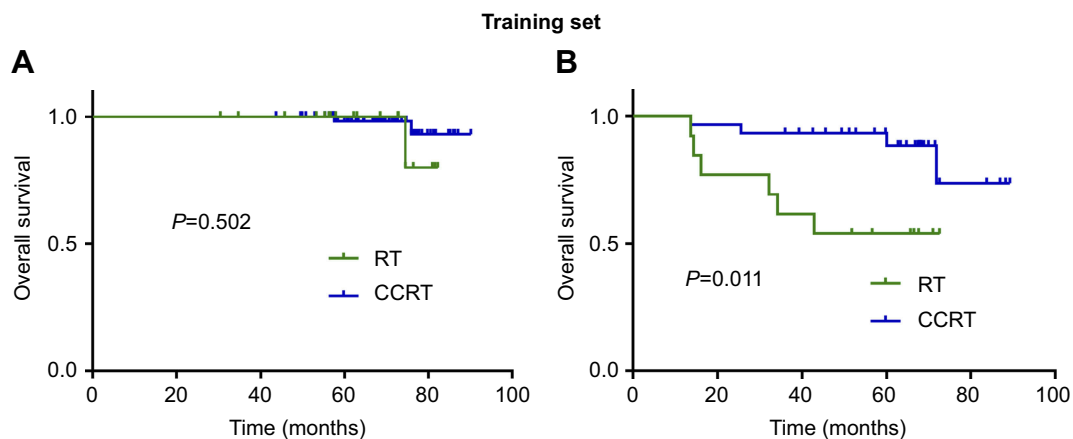


Figure 5 Kaplan-Meier overall survival curves for comparing CCRT vs RT in training set stratified by "low risk" (A) and "high risk" (B).

Discussion

RT remains the cornerstone of management of early stage and locoregionally advanced disease. However, systemic chemotherapy has been shown to improve survival in patients with advanced disease significantly.^{5,12,13} Whether patients with stage-II disease should also

receive chemotherapy is controversial. Lee and colleagues showed that the prevalence of local relapse, regional relapse, and distant metastasis was 17%, 3% and 28%, respectively, in stage-II NPC patients treated with RT alone.¹⁴ The primary pattern of failure was distant metastasis and local relapse, which was due mostly to the

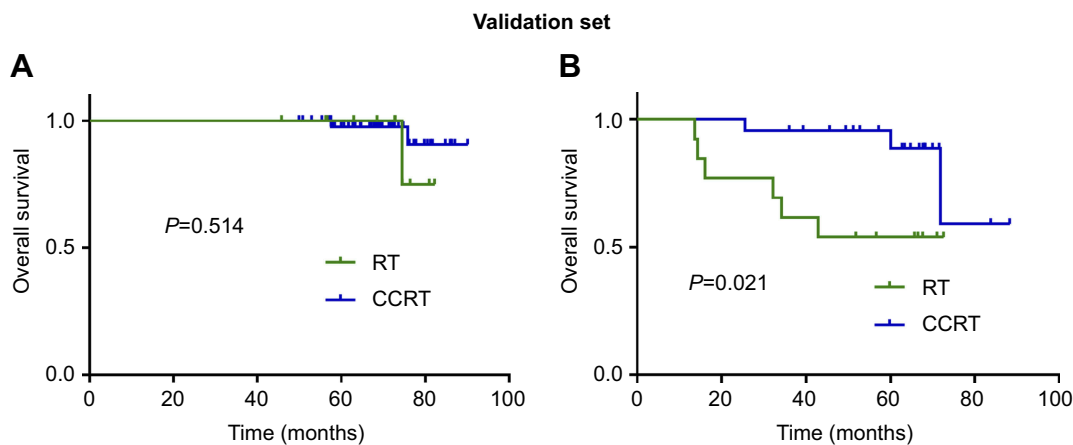


Figure 6 Kaplan-Meier overall survival curves for comparing CCRT vs RT in validation set stratified by “low risk” (A) and “high risk” (B).

involvement of cervical lymph nodes. T1–2/N1 patients may need CCRT. To a certain extent, this therapeutic controversy may have been contributed by the stage migration of patients due to the discrepancies between various staging systems, as well as changes in N-staging classifications by the AJCC in their updates, especially with the recent changes in the 8th staging system (where there were large differences in the criteria for T and N stages). Thus, we restaged patients according to the newest AJCC staging system. The related prognostic factors (including therapeutic regimen) were analyzed and validated further externally by a nomogram. We explored the true role of CCRT for early stage NPC in the IMRT era.

We demonstrated that CCRT improved OS and PFS in patients with stage-II NPC. Our result is in contrast to a systematic review and meta-analysis¹⁵ that compared the outcomes for 1302 patients with stage-II NPC which showed that addition of CCRT to IMRT led to no survival benefit and more acute-toxicity reactions. Another meta-analysis⁶ showed that, compared with conventional RT alone, CCRT could improve the prognosis significantly in terms of OS, PFS, and LRFS for stage-II NPC, but not DMFS whereas, with IMRT, patients with stage-II NPC did not benefit from chemotherapy addition.

Recently, Xu et al⁵ conducted a systemic review and meta-analysis involving 2138 patients with stage-II NPC and concluded that CCRT was better than two-dimensional RT alone with a significant benefit in locoregional recurrence-free survival. IMRT alone was superior to CCRT with equivalent survival outcomes and fewer grade-3–4 acute-toxicity reactions.

In the IMRT era, Tham et al¹⁶ found no significant difference in treatment outcome in patients treated with or without chemotherapy of any schedule, and with acceptable toxicity. Those data may be due to advances in RT methods that offer a more satisfactory balance between target dose coverage and sparing of adjacent organs at risk. Such advances would lead to satisfactory therapeutic effects in patients with stage-II NPC treated with IMRT alone,^{4,16,17} and this may explain the non-significant difference in survival outcomes between CCRT and IMRT alone. Zhang et al¹⁸ conducted analyses of matching of propensity scores of cisplatin-based CCRT in low risk-NPC in the IMRT era and found no survival benefit.

OS for patients with early-stage NPC was approximately 80–90% with RT alone. The outcomes for this group after RT alone have been moderately satisfactory. Several studies have shown that addition of chemotherapy to IMRT can improve survival in these patients. The first randomized clinical trial to compare CCRT with RT alone in early-stage NPC was by Chen et al.⁷ They found that addition of cisplatin-based chemotherapy to RT resulted in a 10.9% increase in the prevalence of 5-year DMFS, which suggests that CCRT with cisplatin has systemic cytotoxicity in addition to radiosensitization. The large reduction in the prevalence of distant metastasis with CCRT using cisplatin could translate into substantial improvements in OS. The randomized controlled trial maybe the reason of the different survival results compared with systematic review and meta-analysis.

The retrospective studies, prospective studies, and meta-analysis detailed above suggest that uncertainty remains. Improved IMRT methods, increased toxicities of CCRT, and other related prognostic factors may be the reasons. Our observation that CCRT improved survival in patients with stage-II NPC is encouraging. Patients with

T2N1M0 NPC had worse OS than those with T1N1 or T2N0 disease. Patients with a higher NLR (which denotes inflammation status) and a higher plasma EBV DNA concentration also had worse OS. Thus, we can hypothesize that patients with those risks may benefit considerably from CCRT. The external validation in our study verified the unfavorable risk factors.

Furthermore, we selected patients with the highest scores as the high-risk group, and CCRT achieved better OS than RT alone in the high-risk group in the training and validation sets. While the limitation was the complications of the therapy has not been studied, this may be attributed to the retrospective records of uncertainty compared to the prospective trial. Thus, these models facilitated decision-making support in daily clinical practice and can be used for patient counseling and shared decision-making to select patients who would benefit most from CCRT.

Conclusions

In our study, we developed and validated a novel nomogram for patients with stage-II NPC. This nomogram provides an accurate and precise prediction for OS. Assessment of patients with stage-II NPC with precise population stratification may increase the benefits of CCRT considerably. This nomogram could help clinicians with decision-making, especially for guiding patients to have acquiring RT or CCRT.

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Disclosure

The authors report no conflicts of interest in this work.

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