research article

MRI-identified multidimensional nodal features predict survival and concurrent chemotherapy benefit for stage II nasopharyngeal carcinoma

Yang Liu[1], Jianghu Zhang[1], Jingbo Wang[1], Runye Wu[1], Xiaodong Huang[1], Kai Wang[1], Yuan Qu[1], Xuesong Chen[1], Yexiong Li[1], Ye Zhang[1], Junlin Yi[1,2]

[1] Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, China

[2] Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Hebei Cancer Hospital, Chinese Academy of Medical Sciences (CAMS), China

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Correspondence to: Junlin Yi, M.D., Ph.D., 17 Panjiayuan Nanli, Chaoyang District, Beijing, 100021, P.R. China and Tongxi Road, Guangyang District, Langfang, Hebei Province, 065001, P.R. China. E-mail: yijunlin1969@163.com and Ye Zhang, MD, PhD, 17 Panjiayuan Nanli, Chaoyang District, Beijing, 100021, P.R. China. E-mail: dr_zye1983@163.com

Dr. Yang Liu and Dr. Jianghu Zhang contributed equal to the work.

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Background. Reliable predictors are urgently needed to identify stage II nasopharyngeal carcinoma (NPC) patients who could benefit from concurrent chemoradiotherapy (CCRT). We aimed to develop a nomogram integrating MRI-identified multidimensional features of lymph nodes to predict survival and assist the decision-making of CCRT for stage II NPC.

Patients and methods. This retrospective study enrolled 242 stage II NPC patients treated from January 2007 to December 2017. Overall survival (OS) was the primary endpoint. Performance of nomogram was evaluated using calibration curves, Harrell Concordance Index (C-index), area under the curve (AUC) and decision curves analysis (DCA) and was compared with TNM staging. According to the individualized nomogram score, patients were classified into two risk cohorts and therapeutic efficacy of CCRT were evaluated in each cohort.

Results. Three independent prognostic factors for OS: age, number and location of positive lymph nodes were included into the final nomogram. T stage was also incorporated due to its importance in clinical decision-making. Calibration plots demonstrated a good match between the predicted and our observed OS rates. C-index for nomogram was 0.726 compared with 0.537 for TNM staging ($p < 0.001$). DCAs confirmed the superior clinical utility of nomograms compared with TNM staging. CCRT compared to intensity-modulated radiotherapy (IMRT) delivered OS benefit to patients in the high-risk group (5-year: 89.9% *vs.* 72.1%; 10-year: 72.5% *vs.* 34.2%, $p = 0.011$), but not in the low-risk group.

Conclusions. This lymph node features-based nomogram demonstrated excellent discrimination and predictive accuracy for stage II patients and could identify patients who can benefit from CCRT.

Key words: nasopharyngeal carcinoma; stage II; concurrent chemotherapy; nomogram; nodal features

Introduction

Nasopharyngeal carcinoma (NPC) is a disease in head and neck that is especially prevalent in Southeast Asia, with an age-standardized incidence rate of five per 100,000 population.[1] Given its complex anatomical location and high radiosensitivity, radiotherapy (RT) has been the mainstay of treatment. The predominant failure pattern of distant metastases highlights the importance of chemotherapy to improve survival outcomes in NPC patients.[2,3] Currently, the National Comprehensive

Cancer Network (NCCN) guidelines recommend that concurrent chemoradiotherapy (CCRT) be the primary treatment for T1–2N1M0 patients and T2N0M0 patients with high-risk features.[4] This is based on a prospective phase III study that showed that CCRT provided survival benefits over two-dimensional (2D) conventional RT alone for stage II NPC.[5]

With rapid technological advances, intensity-modulated radiotherapy (IMRT) has yielded excellent treatment outcomes for patients with stage II NPC, with 5-year overall survival (OS) and local control rates exceeding 90%.[6] A recent phase II randomized clinical trial demonstrated that CCRT might be unnecessary for stage II patients treated with IMRT, as it failed to improve treatment efficacy while increasing the incidence of toxicity.[7] A similar recommendation can be found in the latest European Society for Medical Oncology (ESMO) guidelines.[8] Nonetheless, the survival outcomes remain poor for certain populations screened using adverse prognostic determinants (*e.g.*, high plasma Epstein–Barr virus [EBV] DNA levels).[9,10] The latest American Society of Clinical Oncology/Chinese Society of Clinical Oncology (ASCO/CSCO) guideline also highlights that CCRT can be offered when a bulky tumor burden is present.[11] Therefore, the application of CCRT should consider risk assessment, and more effective prognostic factors are urgently needed to identify stage II NPC patients who may benefit from CCRT.

American Joint Committee on Cancer (AJCC) N staging is consistently recognized as one of the most important determinants for prognosis prediction and treatment decision-making in stage II NPC. However, N1 disease represents a heterogeneous setting in which the size of the lymph node ranges from 1 to a 6-cm mass. Furthermore, the unresolved issue is the accuracy and consistency of N staging, which merely considers nodal size, laterality and location. With advances in imaging modalities, MRI imaging-based analyses have extracted diverse nodal features containing essential information closely related to NPC staging, treatment, and prognosis.[12-16] As morphological lymph node features, high-level extranodal extension and central nodal necrosis have consistently been proven to be predictors of distant metastases.[17-19] Furthermore, the burden-related lymph node features, such as volume and number of positive lymph nodes (PLNs), and number of positive lymph node regions, are proved prognostic factors for NPC progression.[20-23] However, to the best of our knowledge, no comprehensive lymph node feature-based prognosis stratification and concurrent chemotherapy decision-making protocol has been reported for patients with stage II NPC.

In this study, we explored the prognostic value of multidimensional lymph node features in stage II NPC patients and established a lymph node feature-based nomogram. Furthermore, we examined the clinical validity of this model in guiding CCRT utility for patients with stage II NPC.

Patients and methods

This study was approved by the Ethics Committee of our institute, and the requirement for informed consent was waived due to its observational nature. The present study was conducted in accordance with the guidelines from the Declaration of Helsinki.

Patients

Between January 2007 and December 2017, 242 stage II NPC patients were consecutively included (restaged according to the 8th AJCC staging system,). The eligibility criteria were as follows (Supplementary Figure 1): (1) histologically confirmed World Health Organization (WHO) type II–III NPC; (2) no evidence of distant metastases; (3) complete pretreatment evaluation and having complete baseline MRI scans of the nasopharynx and neck; and (4) treatment with IMRT or CCRT (cisplatin, cumulative dose ≥ 200 mg/m^2).

MRI image acquisition

Head and neck T1- and T2-weighted MRI images (T1WI, T2WI) were obtained with a 1.5 or 3T scanner (GE Healthcare, Discovery MR, United States) axially, coronally, and sagittally. The axial slice thickness was 3 mm from the suprasellar cistern to the inferior margin of the sternal end of the clavicle.

Nodal characteristics identified on MRI images

The gross volumes of the primary tumor and nodes were identified as GTVnx and GTVnd, respectively. The diagnostic criteria of positive lymph nodes included: (1) any cervical lymph node with the shortest diameter > 10 mm, any retropharyngeal lymph node (RPLN) in the lateral group with the minimum diameter > 5 mm, and any visible RPLN in the me-

dian group; (2) central nodal necrosis or a contrast-enhanced rim; (3) extranodal extension; and (4) ≥ 3 contiguous converging lymph nodes, each with an minimum diameter > 8 mm.[24] When more than two lymph nodes could not be distinguished from each other, they were counted as one. The maximal axial diameter of lymph nodes was measured on the largest plane of cross-sectional images. Extranodal extension was assessed on T1-weighted fat-suppressed contrast images and classified as follows (Figure 1): Grade 0, without extranodal extension; Grade 1, infiltrating the surrounding fat; Grade 2, matted nodes; and Grade 3, infiltrating the adjacent muscle, parotid gland, vessels and skin.[13] Central nodal necrosis was identified as a focal area of high signal intensity on T2WI.[19]

Treatment

All 242 patients completed whole-course simultaneous-integrated boost (SIB) IMRT. Doses of 69.96 Gray (Gy)/33 fractions were prescribed for GTVnx and GTVnd. High- and low-risk regions of the clinical target volume (CTV) received a prophylactic dose of 60.06 Gy/33 fractions and 50.96 Gy/28 fractions, respectively. The concurrent chemotherapy plan included a weekly (40 mg/m²) or three-weekly (80–100 mg/m²) cisplatin regimen.

Clinical outcomes and follow-up

The primary endpoint was OS (date of treatment start, to date of documented death from any cause or last follow-up). The secondary endpoints were disease-specific survival (DSS, date of treatment start to date of documented death from NPC-related cause or last follow-up), regional recurrence-free survival (RRFS, date of treatment start to date of the first observation of regional recurrence) and distant metastasis-free survival (DMFS, date of treatment start to date of the first observation of distant metastases).

Patients were followed up at least every three months for the first two years, every six months for the third to fifth years, and then yearly. Evaluations included complete physical examination, fiberoptic nasopharyngoscopy, MRI of the nasopharynx and neck, chest X-ray/CT, and abdomen sonography/CT with or without bone scans. Other additional investigations (*e.g.*, FDG PET/CT) would also be scheduled if clinically necessary. Late toxicities were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

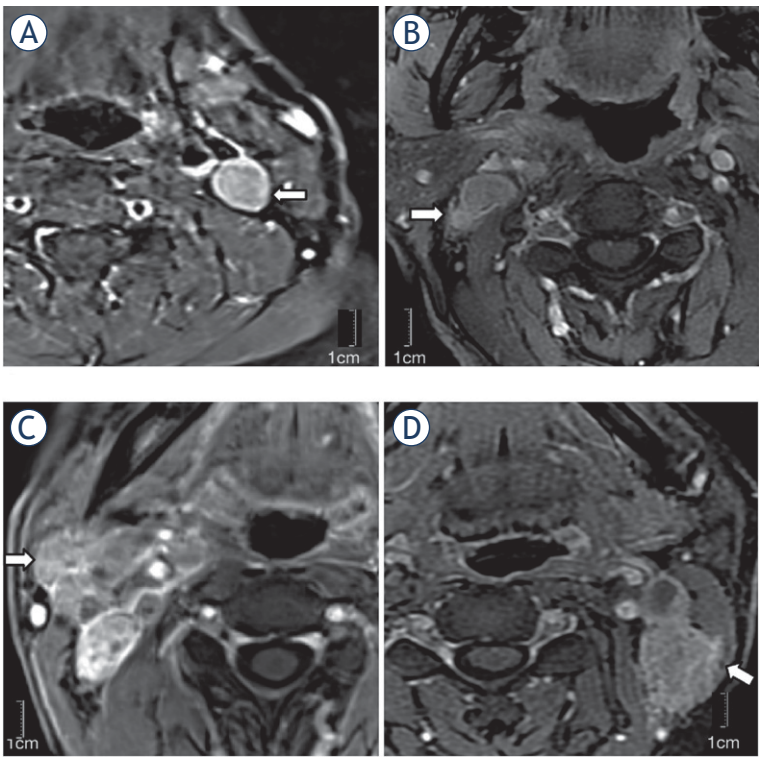

FIGURE 1. Axial T1-weighted fat-suppressed contrast MRI images of grade 0–2 extranodal extension (ENE) in four stage II nasopharyngeal carcinoma patients. **(A)** Grade 0: without ENE; **(B)** Grade 1: lymph node (LN) infiltrating surrounding fat; **(C)** Grade 2: matted LNs; and **(D)** Grade 3: LN infiltrating sternocleidomastoid muscle (wight arrows).

Statistical analysis

The Kaplan–Meier method was performed to estimate survival rates, and log-rank test was used to examine the significance of differences. Youden indexes derived from the time-dependent receiver operating characteristic (ROC) analysis were utilized to dichotomize continuous variables into categorical variables and determine the optimal cutoffs. Cox proportional hazards regression with backward selection was performed in multivariable analysis (MVA) and to calculate hazard ratios (HRs). To assess the effect of the continuous variables on OS, an additive Cox model was used to generate pointwise estimates of HR curves by using the "smoothHR" package.[25] Based on the risk factors identified by MVA, a nomogram was developed. The calibration curves, Harrell concordance index (C-index), area under the curve (AUC) and decision curve analysis (DCA) were used to evaluate the performance of nomogram. Each patient was stratified into low- or high-risk groups based on the final sum of the nomogram scores. R (ver-

TABLE 1. Characteristics of 242 patients with stage II nasopharyngeal carcinoma

Characteristics	No. (%)
Age, median (range)	50 (18–76)
< 50	120 (49.6)
≥ 50	122 (50.4)
Sex	
Male	173 (71.5)
Female	69 (28.5)
AJCC 8th T stage	
T1	104 (43.0)
T2	138 (57.0)
AJCC 8th N stage	
N0	30 (12.4)
N1	212 (87.6)
AJCC 8th subgroup	
T1N1M0	104 (43.0)
T2N0M0	31 (12.8)
T2N1M0	107 (44.2)
GTVnx volume (cm^3), median (range)	19.1 (2.1–74.0)
< 13.7	70 (28.9)
≥ 13.7	172 (71.1)
GTVnd volume (cm^3), median (range)	8.7 (0–71.0)
< 29.1	212 (87.6)
≥ 29.1	30 (12.4)
Lateral of RPLNs	
None	90 (37.2)
Unilateral	113 (46.7)
Bilateral	39 (16.1)
LN located in level III	
Yes	195 (80.6)
No	47 (19.4)
LN size (cm)	1.7 (0–6.0)
MAD < 2.2	152 (62.8)
MAD ≥ 2.2	90 (37.2)
Number of positive LN	2 (0–9)
0	30 (12.4)
1	69 (28.5)
2	60 (24.8)
3	51 (21.1)
4	19 (7.9)
≥ 5	13 (5.4)
†ENE grade	
Grade 0	153 (63.2)
Grade 1,2	52 (21.5)
Grade 3	37 (15.3)
CNN	
No	179 (74.0)
Yes	63 (26.0)
Treatment	
IMRT	158 (65.3)
CCRT	84 (34.7)

† ENE Grade 0 = none; Grade 1 = LN Infiltrating surrounding fat; Grade 2 = matted nodes; and Grade 3 = LN infiltrating adjacent muscle and (or) vessels and(or) skin

AJCC = American Joint Committee on Cancer staging system; CCRT = concurrent chemoradiotherapy; CNN = central nodal necrosis; ENE = extranodal extension; GTVnx/GTVnd = gross target volume of nasopharyngeal tumor/lymph nodes; IMRT = intensity-modulated radiotherapy; LN = lymph node; MAD = maximum diameter; RPLN = retropharyngeal lymph node

sion 4.1.0) and SPSS (version 26.0) were adopted for the statistical analysis. All the tests were two-sided, and significance was defined as $p < 0.05$.

Results

Patient characteristics

The general characteristics of the 242 stage II patients are summarized in Table 1 (median age 50-years old, range 18–76; 173 men, male-to-female ratio 2.5:1). Overall, 158 (65.3%) patients received IMRT, and 84 (34.7%) received CCRT.

Survival and toxicities after treatment

With a median follow-up of 10.3 years (range: 0.6–17.5 years), the 5-year and 10-year OS, DSS, RRFS and DMFS rates of the entire cohort were 91.9% and 79.1%, 93.6% and 86.7%, 96.5% and 93.6%, and 92.3% and 89.1%, respectively. At the last follow-up, 42 (17.4%) patients had died, and 45 (18.6%) experienced treatment failure. The patterns of treatment failure and causes of death are shown in Supplementary Table 1.

Compared with IMRT, patients receiving CCRT had significantly higher rates of Grade 1–2 gastrointestinal reactions, ear toxicities and severe (Grade 3–4) leukopenia. No significant differences were observed in terms of the incidence or severity of late toxicities between the two groups (Supplementary Table 2).

Risk score model and risk stratification

The ROC-determined optimal cutoffs for GTVnx volume, GTVnd volume and lymph node size to predict OS were 13.7 cm^3, 29.1 cm^3 and 2.2 cm, respectively. Smooth HR trend showed that the log HR of overall death increased linearly with an increasing number of PLNs from 1 to 4 and reached a plateau from 5 and above (Supplementary Figure 2). Therefore, the number of PLNs was categorized into 6 groups (*i.e.*, from 0 to 4 and ≥ 5).

Univariate analysis showed that age ≥ 50 years, GTVnd ≥ 29.1 cm^3, lymph nodes located in level III (Figure 2A), lymph node size ≥ 2.2 cm (Figure 2B), PLN number (Figure 2C), and positive central nodal necrosis (Figure 2D) were associated with poor OS. MVA demonstrated that age, location and number of PLNs were independent determinants for OS (Supplementary Table 3). T stage was also included in the nomogram for its importance in clinical decision-making (Figure 3A). The cali-

bration curves manifested excellent consistency in terms of the 5- and 10-year OS (Figure 3B–C).

The C-index of the nomogram in predicting OS was 0.726 (95% CI: 0.638–0.813) in comparison with 0.537 (95% CI: 0.498–0.608) for TNM stage ($p < 0.001$). Analysis of AUCs revealed that the total nomogram score for predicting OS was also significantly superior to TNM staging (Figure 4A). Likewise, DCAs indicated that the risk model had a higher net benefit for predicting 5- and 10-year OS than TNM staging for almost all threshold probabilities (Figure 4B–C).

The linear correlation between the nomogram score and the hazard of overall death is shown in Supplementary Figure 3. Based on cutoffs for the total score, patients were stratified into low-risk (score: 0–134) and high-risk groups (score: >134). There were no significant differences in any endpoint among the T1N1M0, T2N0M0, and T2N1M0 subgroups (Figure 5A–D). The high-risk group had significantly worse OS, DSS, RRFS or DMFS rates than low-risk group (Figure 5E–H).

Nomogram-based adaptive utilization of CCRT

Based on the stratified groups derived from the nomogram, we further analyzed the clinical efficacy of CCRT in two cohorts with different prognoses. Although a trend that CCRT improves OS was observed in the whole population, it did not reach a significant difference (Figure 6A). Nevertheless, high-risk patients could benefit from CCRT compared to IMRT (5-year OS 89.9% *vs.* 72.1% and 10-year OS: 72.5% *vs.* 34.2%, $p = 0.011$), while low-risk patients failed to benefit from CCRT (Figure 6B–C, Figure 7). CCRT did not improve the OS rates among the T1N1M0, T2N0M0, and T2N1 M0 subgroups (Figure 7).

Discussion

In this study, we comprehensively evaluated the prognostic value of multidimensional nodal features in patients with stage II NPC and further established a lymph node feature-based nomogram. The nomogram demonstrated superior predictive performance for OS and outperformed the current AJCC TNM staging. In addition, the nomogram-derived prognostic stratification contributes to identifying high-risk patients who are more likely to benefit from CCRT. To the best of our knowledge, this current study is the first to incorporate various nodal features into a nomogram to predict the prognosis of stage II NPC and to further guide the management of concurrent chemotherapy.

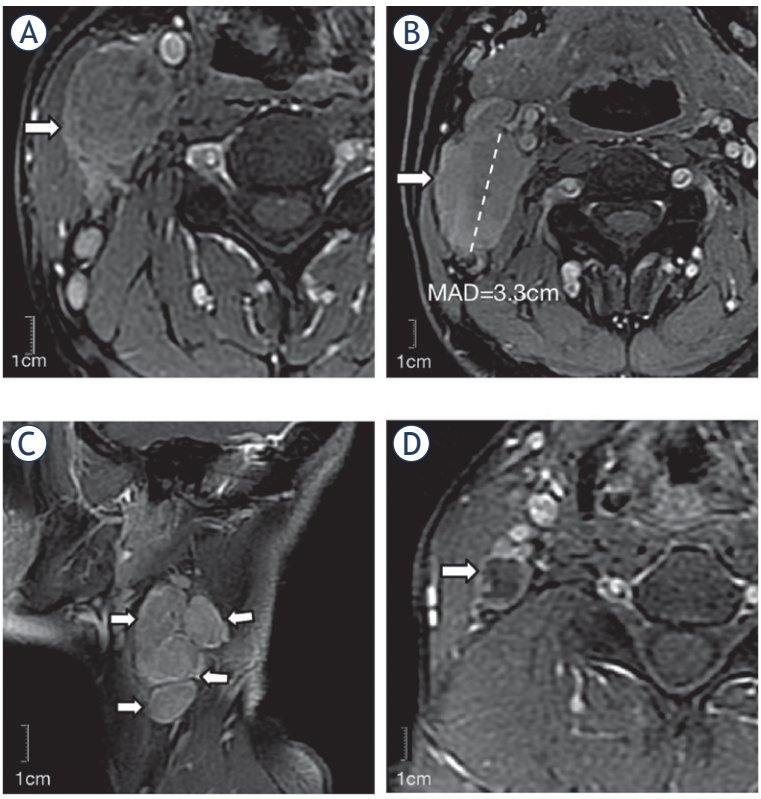

FIGURE 2. Multidimensional nodal features of stage II nasopharyngeal carcinoma significantly associated with survival outcomes in univariate or multivariate analysis. Axial T2-weighted fat-suppressed image of **(A)** a 24-year-old man with one lymph nodes (LN) in level III; **(B)** a 56-year-old man with maximum diameter of lymph node 3.3cm; **(C)** a 50-year-old woman with four metastatic LNs; and (D) Sagittal T1-weighted fat-suppressed contrast images of a 45-year-old woman showing central nodal necrosis (CNN) (wight arrows).

MAD = maximal axial diameter

The latest NCCN guidelines recommend CCRT for stage II NPC, which is based on a phase III study from the conventional 2D-RT era that showed significant improvements in 5-year OS and progression-free survival (PFS) with CCRT over RT alone.[4] The survival benefit of CCRT might be due to its radiosensitizing effect and the fact that it compensated for the dosimetric deficiencies of the conventional RT technique. In the IMRT era, the role of CCRT in stage II NPC has not been absolutely defined given the paucity of data from phase III trials. The majority of studies revealed that the addition of concurrent chemotherapy did not significantly improve survival but increased the prevalence of acute toxic reactions in patients with stage II NPC.[7,26] Nonetheless, Luo *et al.* reported that

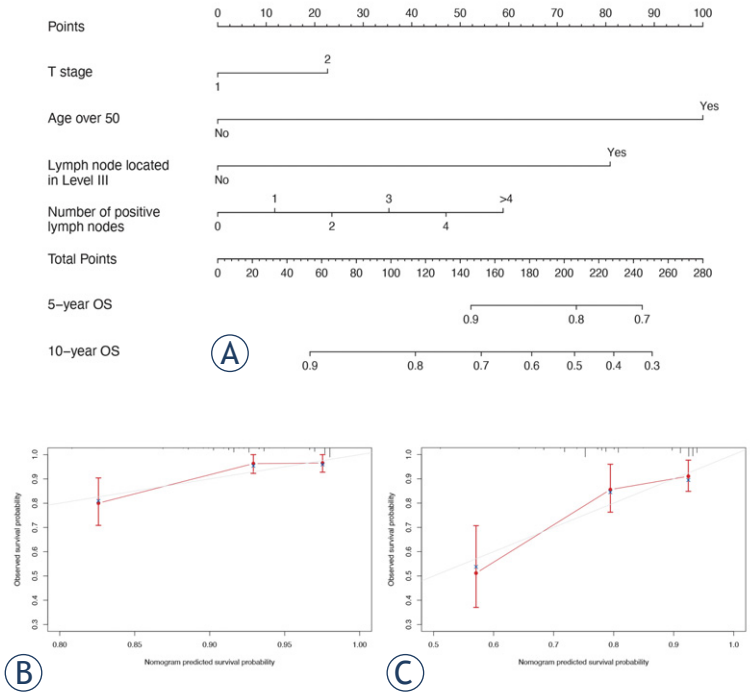

FIGURE 3. Nomogram and calibration plots of 5- and 10-year overall survival (OS). Number of positive lymph nodes was as continuous variable.

T2N1M0 patients receiving CCRT had better 3-year OS, LRFS, and DMFS than those receiving IMRT.[27] Similarly, Kang *et al.* found that CCRT contributed to improving the 5-year locoregional relapse-free survival and PFS for stage II patients.[28] It should be noted that the limitation of the above studies was that all patients were from nonendemic areas, and WHO I/II was the most common histological type. In our study, although a trend that CCRT could improve OS was observed in the whole population, it did not reach a significant difference. Collectively, this evidence supports the utilization of concurrent chemotherapy in a specific portion rather than the stage II disease population. Therefore, it is critical to identify high-risk patients with stage II NPC who are more likely to benefit from CCRT.

Lymph node status is one of the most important determinants associated with prognosis and treatment decisions.[15,16] The determination of AJCC N1 classification depends primarily on the location and size of the ipsilateral cervical lymph nodes. Nonetheless, in recent years, alternative nodal parameters, such as the number of PLNs, extranodal extension and central nodal necrosis status, have been increasingly reported to better assess the profile of nodal burden.[12-16] The number of MRI-positive lymph nodes has been reported to be a predominant independent prognostic factor for survival in NPC patients and is a better proxy for the cumulative effect of lymph nodes than AJCC N staging.[22] Additionally, quantitative metastatic lymph node regions were shown to be superior to N classification in terms of prognosis in NPC.[23] In addition, high-grade extranodal extension was reported as an evaluable predictor that could assist in the selection of stage II patients with a high risk of distant metastases.[13,17,18] Another critical lymph node feature was central nodal necrosis, which was proven to be an independent negative prognostic factor in patients with NPC.[12,16] In the current study, by applying an additive Cox model based on P-penalized, we observed the impact of consecutive PLN on survival: the hazard of overall death increased linearly with increasing PLNs from 1 to 4, eventually reaching a plateau at PLNs of 5 and above. Based on this tendency, PLN surpassed the traditional AJCC N stage and emerged as an independent variable in the MVA model. Likewise, lymph node located in level III was found to be an important prognostic factor that outperformed N stage, which could be explained by the fact that lymph node often metastasizes in an orderly fash-

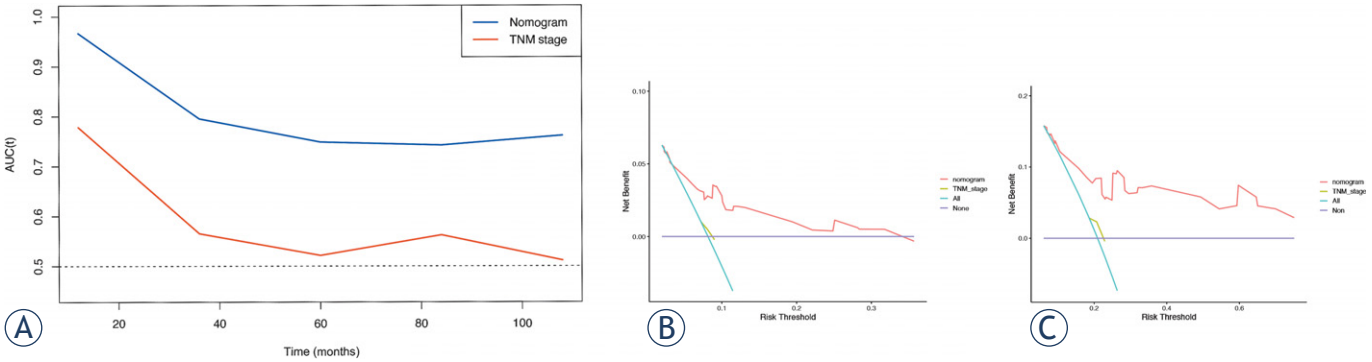

FIGURE 4. Comparison of **(A)** area under the curve (AUC) plots, decision curves of **(B)** 5-year overall survival (OS) and **(C)** 10-year OS between the nomogram and TNM stage.

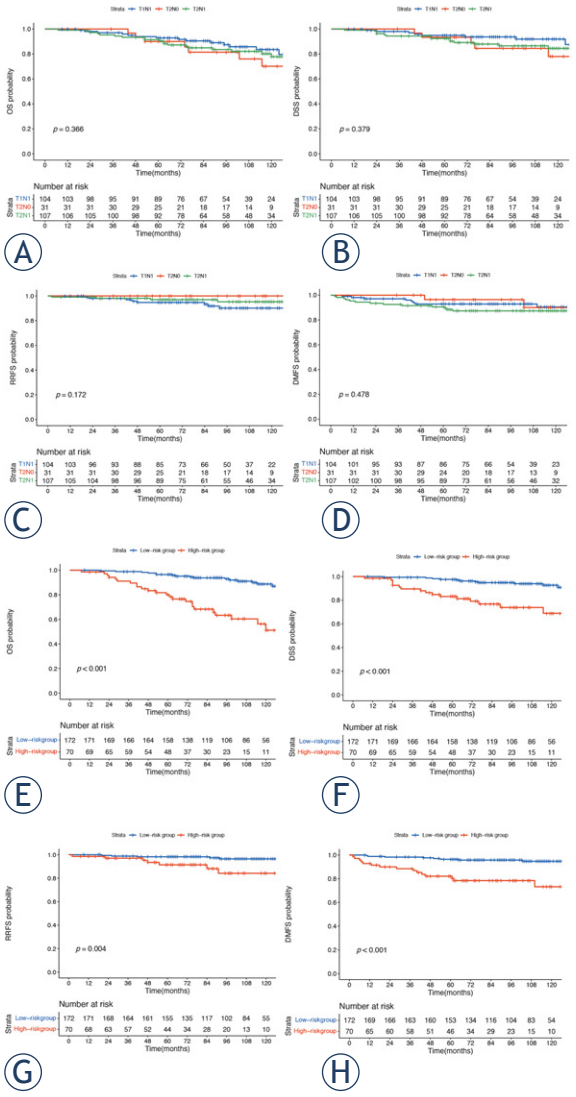

FIGURE 5. Survival curves of the **(A-D)** three subgroups in American Joint Committee on Cancer staging system (AJCC), TNM staging and **(E-H)** the low- and high-risk groups stratified by the nomogram-derived score.

ion from upper to lower level lymph nodes, and patients with level III lymph node involvement tend to have an increased number of positive lymph nodes. Lymph node size, GTVnd volume, extranodal extension and central nodal necrosis were no longer independent prognostic factors for OS, probably because they were surrogates for the number of PLNs or LNs located in level III and were included when all served as positive lymph node criteria in multivariable Cox analysis.

As per the results of the multivariate analysis, we finally included age, T stage, number of PLNs and location (lymph node located in level III) in

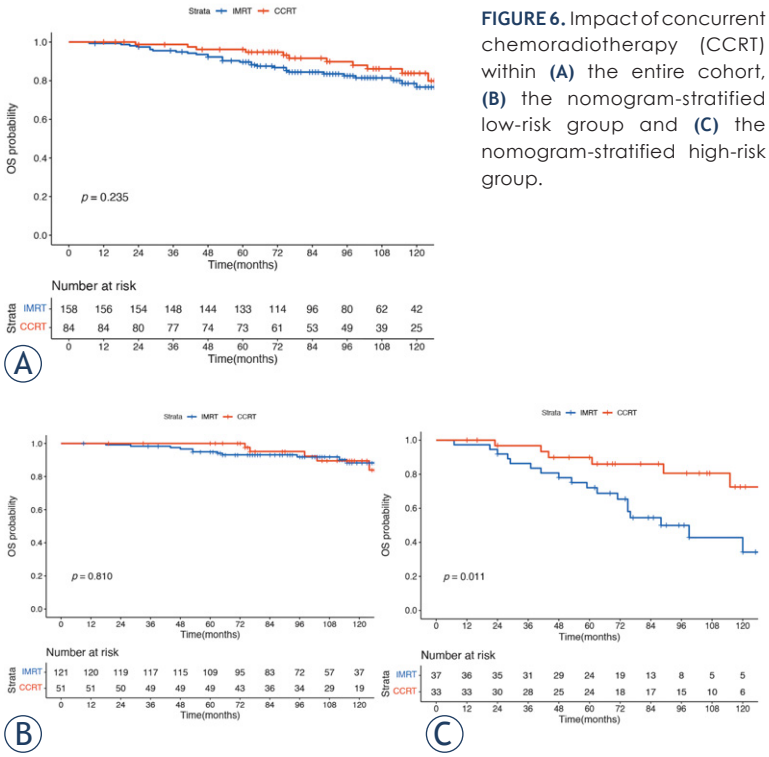

FIGURE 6. Impact of concurrent chemoradiotherapy (CCRT) within **(A)** the entire cohort, **(B)** the nomogram-stratified low-risk group and **(C)** the nomogram-stratified high-risk group.

the nomogram for OS. Although nomograms have been established in various manners in stage II NPC[20-23], the notable hallmark of our nomogram is that it is the first to incorporate lymph node status, while in the previous nomogram, the effect of lymph node burden was merely assessed by N staging and lacked more detailed categorization.[19] In terms of the discriminative performance of this nomogram, its C-index, AUC and DCA are

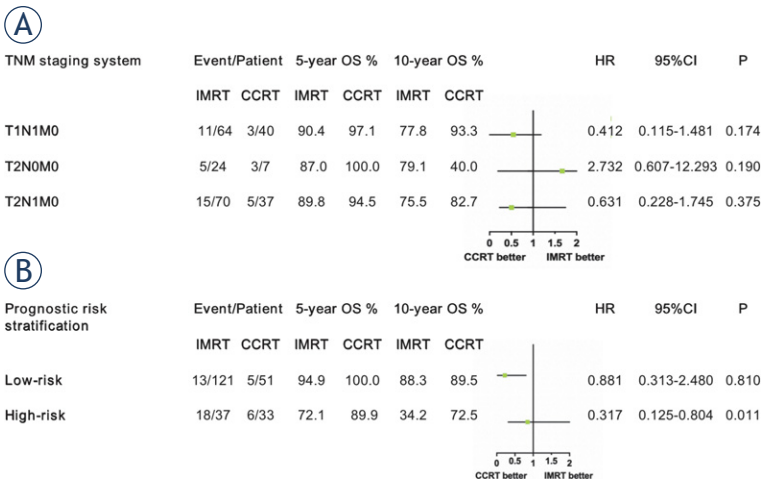

FIGURE 7. The 5-year and 10-year overall survival (OS) rates and hazard ratio (HR) between intensity-modulated radiotherapy (IMRT) group and concurrent chemoradiotherapy (CCRT) group according to **(A)** TNM staging system and **(B)** prognostic risk model.

significantly better than AJCC TNM staging and are comparable to previous nomograms for stage II NPC.[20-23]

Despite the growing evidence supporting the prognostic value of lymph node features in NPC, very little stratification based on lymph node features has been incorporated into treatment decisions from a clinical management perspective. To our knowledge, only one previously published study of nomograms in NPC analyzed the ability of the lymph node features-based nomogram model to guide personalized induction chemotherapy combined with CCRT management in stage II–IVA patients.[16] In the current study, we implemented the time-dependent ROC method to identify two subgroups according to the nomogram scores, which was more reasonable and discriminatory than arbitrary groupings based on medians or quartiles. We then found that CCRT was associated with improved survival outcomes in the high-risk group, with reductions in the overall death hazards of approximately 70%. These results underline that this nomogram may be valid enough to be used as a practical tool for clinicians to select stage II patients for concurrent chemotherapy.

This study has several limitations. First, the plasma EBV-DNA levels were not included in the survival analysis. Only five patients in this cohort had EBV-DNA over 500 copies/ml, which is consistent with previous studies reporting relatively low EBV-DNA copies in stage II patients[29,30], suggesting that their prognostic value may not be as critical as in stage III/IV patients. Another possible reason for the relatively low EBV-DNA in this cohort is the continued lack of standardized EBV-DNA testing[31,32]; therefore, we sought to re-examine the prognostic value of pretreatment EBV-DNA for stage II NPC after standardization of testing methods. Second, although the sample size of the present study was the largest reported for nodal feature prognostication in stage II NPC to date, our data were obtained from a single cancer center. A larger sample size cohort for external independent validation is warranted to further assess the prognostic and predictive value of this lymph node feature-based nomogram.

Conclusions

In summary, this study established a nodal features-based nomogram with excellent performance, which provided statistically significantly superior discrimination to TNM staging in predicting the OS in patients with stage II NPC. Furthermore, the nomogram-based stratification effectively identified patients who were more likely to gain survival benefit from CCRT. It offers a useful tool for providing patient counseling and clinical assessments. To generalize the clinical utility of this nomogram, external validation should be considered.

Acknowledgments

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