Title

Prognostic nomogram for refining the prognostication of the proposed 8th edition of the AJCC/UICC staging system for nasopharyngeal cancer in the era of intensity-modulated radiotherapy

Journal

Cancer, 122(21)

ISSN

0008-543X

Authors

Pan, Jian Ji
Ng, Wai Tong
Zong, Jing Feng
et al.

Publication Date

2016-11-01

DOI

10.1002/cncr.30198

Peer reviewed

HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2017 November 15.

Published in final edited form as:

Cancer. 2016 November 15; 122(21): 3307–3315. doi:10.1002/cncr.30198.

Prognostic nomogram for refining prognostication of the proposed AJCC/UICC 8th edition for nasopharyngeal cancer in the era of intensity-modulated radiotherapy

Jian Ji Pan, MD[1], **Wai Tong Ng, MD**[2], **Jing Feng Zong, MD**[1], **Sarah W.M. Lee, FRCR**[2], **Horace C.W. Choi, PhD**[3], **Lucy L.K. Chan, BSc**[2], **Shao Jun Lin, MD**[1], **Qiao Juan Guo, MD**[1], **Henry C.K. Sze, FRCR**[2], **Yun Bin Chen, MD**[4], **You Ping Xiao, MD**[4], **Wai Kuen Kan, FRCR**[5], **Brian O'Sullivan, MD**[6], **Wei Xu, PhD**[7], **Quynh Thu Le, MD**[8], **Christine M. Glastonbury, MBBS**[9], **A**

[*]Corresponding author: Anne Lee, MD, Department of Clinical Oncology, the University of Hong Kong, 1/F, Professorial Block, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong. awmlee@hku.hk; Office telephone: 852-22555050.

CONFLICT OF INTEREST DISCLOSURES

None of the authors have any potential conflict of interest.

AUTHOR CONTRIBUTIONS

- Conceptualization — Formulation of overarching research goals and aims. : **Jian Ji Pan, Wai Tong Ng, Anne W.M. Lee**
- Methodology — Development or design of methodology; creation of models. : **Jian Ji Pan, Wai Tong Ng, Horace C.W. Choi, Anne W.M. Lee**
- Software — Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code components. : **Horace C.W. Choi, Lucy L.K. Chan**
- Validation — Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs. : **Wei Xu**
- Formal analysis — Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data. : **Horace C.W. Choi**
- Investigation — Research and investigation process, specifically performing the experiments, or data/evidence collection. : **Lucy L.K. Chan, Shao Jun Lin, Qiao Juan Guo**
- Resources — Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools. : **Jing Feng Zong, Jian Ji Pan, Wai Tong Ng, Anne W.M. Lee**
- Data curation — Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later re-use. : **Jing Feng Zong, Yun Bin Chen, You Ping Xiao, Lucy L.K. Chan**
- Writing – original draft — Preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation). : **Wai Tong Ng, Sarah W.M. Lee**
- Writing – review and editing — Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre- or post-publication stages. : **Jian Ji Pan, Wai Tong Ng, Jing Feng Zong, Sarah W.M. Lee, Horace C.W. Choi, Lucy L.K. Chan, Shao Jun Lin, Qiao Juan Guo, Henry C.K. Sze, Yun Bin Chen, You Ping Xiao, Wai Kuen Kan, Brian O'Sullivan, Wei Xu, Quynh Thu Le, Christine M. Glastonbury, A. Dimitrios Colevas, Randal S. Weber, William Lydiatt, Jatin P. Shah, Anne W.M. Lee**
- Visualization — Preparation, creation and/or presentation of the published work, specifically visualization/data presentation. : **Lucy L.K. Chan**
- Supervision — Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team. : **Anne W.M. Lee**
- Project administration — Management and coordination responsibility for the research activity planning and execution.: **Anne W.M. Lee**

Dimitrios Colevas, MD[10], **Randal S. Weber, MD**[11], **William Lydiatt, MD**[12], **Jatin P. Shah, MD**[13], and **Anne W.M. Lee, MD**[14,*]

[1]Department of Radiation Oncology, Fujian Provincial Cancer Hospital, Provincial Clinical College of Fujian Medical University and Fujian Provincial Key Laboratory of Translational Cancer Medicine, Fujian, China

[2]Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, Hong Kong, China

[3]Department of Systems Engineering and Engineering Management, City University of Hong Kong

[4]Department of Radiology, Fujian Provincial Cancer Hospital, Provincial Clinical College of Fujian Medical University

[5]Department of Diagnostic Radiology, Pamela Youde Nethersole Eastern Hospital, Hong Kong, China

[6]Department of Radiation Oncology, Princess Margaret Cancer Centre, University of Toronto, Canada

[7]Department of Biostatistics, Princess Margaret Cancer Centre, Canada

[8]Department of Radiation Oncology, Stanford University, USA

[9]Department of Clinical Radiology, University of California, San Francisco, USA

[10]Department of Medicine (Oncology), Stanford Cancer Institute, Stanford University, USA

[11]Department of Head and Neck Surgery, University of Texas MD Anderson Cancer Center, USA

[12]Department of Otolaryngology, University of Nebraska Medical Center, Omaha, NE, USA

[13]Department of Head and Neck Surgery, Memorial Sloan Kettering Cancer Center, USA

[14]Department of Clinical Oncology, the University of Hong Kong and the University of Hong Kong-Shenzhen Hospital, Hong Kong, China

Abstract

Objective—To develop a nomogram for refining prognostication for patients with non-disseminated nasopharyngeal cancer (NPC) staged with the proposed AJCC/UICC 8th edition.

Material and methods—Consecutive patients investigated by magnetic resonance imaging, staged by the proposed AJCC/UICC 8th edition, and irradiated by intensity- modulated radiotherapy (IMRT) from June 2005 to December 2010 were analyzed. The cohort of 1197 patients treated at Fujian Provincial Cancer Hospital was used as the training set and the results were validated by 412 patients from Pamela Youde Nethersole Eastern Hospital. Cox regression analyses were performed to identify significant prognostic factors for developing a nomogram to predict overall survival (OS). The discriminative ability was assessed with concordance index (C-index). Patients were categorized into three risk groups by performing recursive partitioning algorithm (RPA) on the survival scores of the combined set.

Results—Multivariable analysis showed that age, gross primary tumor volume (GTV-P) and lactate dehydrogenase (LDH) were independent prognostic factors for OS in addition to stage-

group. The OS nomogram based on all these factors had a statistically higher bias-corrected C-index than prognostication based on stage-group alone (0.712 vs 0.622, $p<0.01$). These results were consistent for both the training and the validation cohorts. Patients with <135 points were categorized as low-risk, ≥135–<160 points as intermediate-risk and ≥160 points as high-risk, respectively. Their 5-year OS rates were 92%, 84% and 58%, respectively.

Conclusions—The proposed nomogram could improve prognostication when compared with TNM stage-group. This could aid in risk stratification for individual NPC patients.

Keywords

Nasopharyngeal carcinoma; Nomogram; TNM staging; Prognostication; Intensity modulated radiotherapy

Introduction

Nasopharyngeal carcinoma (NPC) is a peculiar cancer that is endemic in Southeast Asia. The natural behavior and therapeutic considerations for NPC are different from other head and neck cancers. Radiotherapy (RT) is the primary treatment modality; chemotherapy is added to radiation in patients with locoregionally advanced disease. For this highly infiltrative cancer anatomically surrounded by critical structures, conformal RT techniques are needed for optimal coverage of tumor extent with better protection of normal tissues. The technology of RT has evolved substantially during the past decades; intensity-modulated technique (IMRT) is the current standard of care if resources are available.

Accurate prediction of failure pattern and survival outcome is crucial for patient management. TNM stage is presently the most important known prognostic factor. Besides meeting the demand for accurate prognostication, the ideal staging system must also be globally applicable. The American Joint Committee for Cancer Staging (AJCC) and the International Union against Cancer (UICC) have been taking concerted efforts to continually improve the TNM Staging system in line with evolving investigation and treatment methods. The AJCC/UICC 8th edition will soon be introduced [1]; multidisciplinary international experts are involved in the preparatory process. The proposed system is based not only on extensive literature review, but also on validation of recommendations by a contemporary series of 1609 patients who were staged with MRI and irradiated with IMRT from 2 hospitals (one in Hong Kong and the other in Fujian in Mainland China).

It is well recognized that the TNM system does have limitations because it is entirely based on anatomical disease extension [2]. Variability in outcome among patients within the same stage receiving similar treatments is commonly observed; this could be attributed to heterogeneity in patient factors and other tumor factors. Literature review suggests the following potential alternative or additional prognostic factors may be useful: age [3, 4], gender [3], performance status [5], gross primary tumor volume (GTV-P) [6–9], lactate dehydrogenase (LDH) level [10–12], deoxyribonucleic acid (DNA) copies of Epstein-Barr Virus (EBV) [13–15], hemoglobin level [16]. Among these factors, EBV-DNA is a promising parameter, but not routinely available for all patients in most centers; the test methodology is difficult and requires further harmonization for global application [17]. The

aim of the current study is to identify commonly available factors with independent statistical significance and to explore development of a prognostic nomogram by combining TNM parameters with these factors for further refinement of prognostication for individual NPC patients.

Methods

Patients Characteristics

Consecutive patients with non-disseminated NPC treated with curative intent from Fujian Provincial Cancer Hospital (mainland China) and Pamela Youde Nethersole Eastern Hospital (Hong Kong, China) from June 2005 to December 2010 were analyzed (Table 1). All patients had histological confirmation. They were staged with MRI and irradiated with IMRT. None had history of previous treatment or prior malignancy. The series of 1197 patients from Fujian Provincial Cancer Hospital was used as the training cohort. Their median age was 46, with a male to female ratio of 3:1. The majority of patients had advanced locoregional diseases: 70% were categorized as stage III-IVA by the proposed AJCC/UICC 8th edition [1]. The corresponding series of 412 patients from Pamela Youde Nethersole Eastern Hospital was used as the validation cohort. Table 1 shows the characteristics of the two cohorts of patients.

Clinical Staging and Treatment

All patients had complete physical examination, fiberoptic nasopharyngoscopy and MRI of the nasopharyngeal and cervical regions. Additional metastatic evaluation was performed in accordance with institutional polices. All of the patients were re-staged using the criteria of the proposed AJCC/UICC 8th edition [1]. All patients were irradiated with IMRT technique. The GTV-P was first contoured by a diagnostic radiologist on contrast enhanced MRI. After rigid fusion with contrast enhanced planning computer tomography, the GTV-P was modified and delineated by a radiation oncologist according to the fused images. The median total dose was 69.8Gy (range, 61.6–86.7). Details of IMRT planning and dose prescription have been described previously [18, 19]. Additional treatment with cisplatin-based chemotherapy (various schedules) was administered to 85% of the training cohort and 83% of the validation cohort (Table 1).

Statistical analysis

All events were measured from the date of histological diagnosis. The primary end-point in the current study was overall survival (OS) which was defined as the interval from histological diagnosis to date of death due to any cause. Survival rates were calculated by the Kaplan-Meier method and were compared using log-rank test. Two-sided tests were used and those with p value <0.05 were considered statistically significant. Potential factors routinely evaluated in the current cohorts (including age, gender, performance status, GTV-P, LDH level, hemoglobin level) were analyzed by the Cox's proportional hazards model. The hazard ratio (HR) with 95% confidence level (CI) was assessed. Variables were tested in both univariate and multivariate analyses. The final model was obtained by a backward selection; and this was used to generate the nomogram for predicting 5-year and 8-year survival rates [20]. The discrimination ability was evaluated by the concordance index (C-

index) with bias-correction. Internal validation was performed by bootstrap algorithm and 1000 bootstrapping replications were generated to provide the bias-corrected C-index and corresponding 95% credible intervals. The calibration plot comparing the nomogram predicted versus observed Kaplan-Meier estimates of the survival probability was used to assess the accuracy. To test for generalizability, the proposed nomogram developed from the training cohort was tested with the validation cohort.

Patients were categorized into three risk groups (low, moderate and high risk) by performing recursive partitioning algorithm (RPA) [21] on the survival probability scores of the whole series. Statistical analyses were performed using software R version 3.13, with packages rms and rpart for constructing the nomogram and performing the RPA, respectively.

Results

Among the training cohort, 219 (18%) patients had died, the 5-year OS rate was 82 %. Univariate analysis on OS showed that age, gender, performance status, stage-group, GTV-P and pre-treatment LDH level were all associated with survival outcome (p<0.05). Hemoglobin level was not statistically significant. Multivariate analyses showed that in addition to stage-group, three more factors also showed independent significance: age, GTV-P and LDH level (Table 2).

Development of nomogram

A nomogram predicting the 5-year and 8-year OS rates was generated using these four prognostic factors with their relative contributions (Figure 1). Different weighted points were assigned to the different factors as continuous variables. Weighted total point was calculated by summing up the point of each variable, which was then vertically aligned to the 5-year and 8-year OS rates. Internal validation of the proposed nomogram using bootstrapping resampling revealed a bias-corrected C-index of 0.712 [median, 95% credible interval (CrI): 0.674–0.747]. This was statistically higher than that of prognostication based on stage-group alone (0.622, 95% CrI: 0.590–0.653, p <0.01), indicating superior discrimination ability. The calibration plot of the proposed nomogram also showed a perfect agreement between the predicted versus observed Kaplan-Meier estimates of the OS probability (Figure 2A, intercept=−0.05, p=0.60; slope=1.06, p=0.59).

Repeating the analyses using the validation cohort showed consistent improvement with the proposed nomogram: the bias-corrected C-index was 0.760 (95% CrI: 0.723–0.796); the superiority in discriminating ability as compared with stage-group alone [bias-corrected C-index 0.654 (95% CrI: 0.622–0.686)] was confirmed (p<0.01). There was good agreement between the predicted and observed OS estimates (Figure 2B, intercept=0.15, p=0.25; slope=0.89, p=0.47).

Risk-Groups Categorization

Basing on the scores estimated from the developed nomogram on OS, the whole series of patients could be categorized into three risk groups by RPA (Figure 3). Rounding the classified cutoff scores, 45% patients with <135 points were categorized as low-risk, 27% patients with ≥135–<160 points as intermediate-risk, and 29% patients with ≥160 points as

high-risk. Their 5-year OS rates were 92%, 84% and 58%, respectively. The c-index was 0.705 (95% CrI: 0.676–0.730).

Basing on the proposed 8th edition of the AJCC/UICC staging system [1], the distribution pattern was: 4% stage I, 20% stage II, 35% stage III, 41% stage IVA. Their 5-year OS rates were 98%, 92%, 83% and 71%, respectively. The c-index was 0.628 (95% CrI: 0.602–0.653). Comparison of the proposed nomogram versus the 8th edition AJCC/UICC staging system regarding distribution pattern, OS at 5-year and the c-index of risk-groups were summarized in Table 3, and the respective Kaplan-Meier estimates on OS were shown on Figure 4. The comparison of c-index suggested that the risk groups based on nomogram (taking into account all significant prognostic factors) had significantly better differentiating ability than stage-group alone ($p<0.01$).

Discussion

Nomograms are pictorial representations of complex mathematical relationships. They enable incorporation of both patient and disease characteristics into the calculation of a simple numerical estimate of the event probability. In addition to the anatomical disease extent, nomograms incorporate other key prognostic factors into the estimation of survival outcomes. These can tremendously facilitate individualized risk stratification and decision making [22–24]. The utilization of nomograms has been well recognized in other cancers and has been shown to yield more accurate survival predictions over the traditional TNM staging system [25–30]. These findings underlined the inadequacy of the current staging system and the unmet need of a more robust prognostic tool for risk categorization of individual patients.

Six studies on development of nomograms for NPC have been reported in recent years [5, 31–35]. They demonstrated feasibility of using nomogram to predict survival in NPC and consistently achieved superiority to the conventional TNM staging system. However, despite the stronger predictive power of these nomograms, they suffered from important limitations including obsolete RT techniques [33–35] and lack of external validation [31, 33] that hampered their generalizability and validity in modern era. Furthermore, all were based on the 6–7th editions of AJCC/UICC staging system [5, 31–35]. With the imminent introduction of the 8th edition, applicability of these nomograms will become outdated.

Five of these nomograms were developed using patient data from the same cancer institute in China [31–35]. The nomogram by Tang et al. [33] was based on a large cohort of 4630 patients, but only 34% of patients were treated with IMRT. In addition to common prognostic factors (age, gender, T-category, N-category, LDH level and hemoglobin), factors not observed in other centers [body mass index (BMI), C-reactive protein (CRP)], and factors not routinely available in majority of centers (plasma EBV-DNA) were incorporated into the proposed nomogram. Furthermore, all the continuous variables were transformed into categorical data in the statistical analyses. Although all these prognostic factors were statistically significant in multivariate analyses, the uncertainties of the best cut-off value and the issue of over-fitting in the model should be carefully considered.

The nomogram proposed in the current paper is the first based on the 8th edition of the AJCC/UICC TNM staging system [1] that soon will be implemented. The whole series of 1609 patients were all staged and treated with current standard of care (using MRI and IMRT). The prognostic factors included are well recognized and routinely captured by contemporary centers (independent factors identified being age, GTV_P and LDH level). Moreover, two data cohorts during the same study period were analyzed so that the nomogram based on the primary institute was validated by data from another institute to ensure its robustness and generalizability.

Among the host factors, age was a powerful prognostic factor for OS [36–38]. Elderly patients had poorer survival partly due to comorbidities and partly due to poorer performance status leading to a lower compliance to intensive treatment [4]. The current study did not show substantial significance attributed to gender or performance status.

Among the disease factors, there are increasing data suggesting that tumor volume and LDH have independent significance that could supplement prognostication by the current TNM staging system that only takes into account the anatomical extent of gross disease. A larger tumor burden often signifies an increase in the number of clonogenic tumor cells and radio-resistance associated with tumor hypoxia. Sze et al. [6] estimated that the local failure would increase by 1% for every 1 ml increase in tumor volume. Wu et al. [7] reported 48 ml and 25 ml were the GTV-P cut-off points for local control and distant metastasis respectively. Willner et al. [8] found that tumors larger than 64 ml had poorer control rate. Among all these studies, the series by Guo et al. [9] was the largest (n=694) and their results suggested that incorporation of tumor volume could improve the prognostic ability of T-category. Our finding concurred with these publications. In the past, there are concerns that measurement of GTV-P was not easy or routinely available. However, with the contouring of gross tumor volume for all patients irradiated with modern RT technique, this factor is now captured by computerized planning system for all patients (except those treated with 2D technique). Hence, refining prognostication by incorporating GTV-P into the nomogram has become widely achievable.

The current study concurred with other reports that high pre-treatment LDH level was an adverse prognostic factor, associated with increased distant metastasis [10–12, 31, 33–35]. A retrospective study done by Wan et al. (32) showed that patients with high pre-treatment LDH > 177.0 U/L had significantly inferior 5-year distant metastasis free survival as compared with those with ≤ 177.0 U/L (65% vs 77%, p =0.016). As LDH is easily measurable in all centers, this should be incorporated for refining prognostication.

The currently proposed nomogram based on incorporation of age, GTV_P and LDH in addition to stage group by the new TNM 8th edition [1], showed significantly better discrimination ability as compared with stage group alone (p <0.01): the median bias-corrected C-index was 0.712 (95% CrI: 0.674–0.747) by nomogram versus 0.622 (95% CrI: 0.590–0.653) by stage.

Besides risk estimation for individual patient by nomogram, we further explore the feasibility of using the proposed nomogram to categorize patients into more accurate risk

groups. By performing RPA based on the scores estimated from the proposed nomogram on OS, 45% patients with <135 points were categorized as low-risk, 27% patients with ≥135–<160 points as intermediate-risk, and 29% patients with ≥160 points as high-risk. Their corresponding 5-year OS rates were 92%, 84% and 58%, respectively. The c-index was 0.705 (95% CrI: 0.676–0.730). Not only does this risk-group categorization exhibit superior differentiating ability than the TNM stage-group alone, but it also achieves a more even pattern of patient distribution, as compared with stage-group distribution of 4% stage I, 20% stage II, 35% stage III, 41% stage IVA.

A more precise risk stratification system is always desirable in patient counseling and treatment decision. Furthermore, this is valuable for future clinical trial design. Further studies based on this risk categorization to evaluate the possibility of treatment de-escalation for the low-risk group and treatment intensification for the high-risk group will be valuable. This refined prognostic tool is fundamental for working towards personalized treatment strategies according to individual risk.

Nevertheless, our study did have several limitations. Firstly, it is a retrospective study, predominantly on patients with non-keratinizing subtype of NPC. Prospective validation in non-endemic centers will be desirable. Secondly, the measurement of GTV-P depends heavily on the quality of diagnostic imaging and the current contouring could be operator dependent. Further enhancement of accuracy in delineating GTV-P by standardized imaging protocols and computerized program are be desirable.

Another potentially valuable prognostic factor to be considered is plasma EBV DNA. There are increasing data suggesting that it is an important marker with strong correlation with tumor burden, TNM stage, response to treatment and survival [13–15]. However, this is not yet routinely available in most centers worldwide. The measurement of EBV DNA is not easy; harmonization of the methodology for quantitative plasma EBV DNA assay is currently being explored by international collaboration [17] It is also an expensive test and the optimal cut-off value has yet to be defined.

In conclusion, the currently proposed nomogram for NPC patients provides a valuable tool for refining prognostication and working towards personalized medicine. This is the first proposed system for improving the differentiating ability and distribution pattern of stage group by the AJCC/UICC TNM 8th edition [1] that will soon be introduced. This is applicable to patients staged and treated with modern standard of care; the incorporated factors are consistently recognized as significant factors and globally available (except in centers without 3D/IMRT facilities for measuring GTV-P). Further confirmation through larger scale prospective multi-institutional collaborative studies is warranted. Continuous efforts for further improvement by incorporation of novel markers will be valuable. Lastly, development of an easily operated smartphone app can be considered to enhance the usage of the prognostic model.

Condensed abstract: A nomogram incorporating TNM stage-group, age, GTV-P volume and LDH significantly improves the prognostic power when compared with TNM stage-group

alone. More personalized treatment decisions can be achieved with this refinement of risk stratification for individual NPC patients.

Acknowledgments

Grant: P30 CA008748

FUNDING

None.

References

1. Pan JJ, Ng WT, Zong JF, Chan LL, O'Sullivan B, Lin SJ, Sze HC, Chen YB, Choi HC, Guo QJ, et al. Proposal for the 8th edition of the AJCC/UICC staging system for nasopharyngeal cancer in the era of intensity-modulated radiotherapy. Cancer. 2016; 122(4):546–558. [PubMed: 26588425]
2. Ng WT, Yuen KT, Au KH, Chan OS, Lee AW. Staging of nasopharyngeal carcinoma–the past, the present and the future. Oral oncology. 2014; 50(6):549–554. [PubMed: 23838426]
3. 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. [PubMed: 23642234]
4. Sze HC, Ng WT, Chan OS, Shum TC, Chan LL, Lee AW. Radical radiotherapy for nasopharyngeal carcinoma in elderly patients: the importance of co-morbidity assessment. Oral oncology. 2012; 48(2):162–167. [PubMed: 21925925]
5. Cho JK, Lee GJ, Yi KI, Cho KS, Choi N, Kim JS, Kim H, Oh D, Choi SK, Jung SH, et al. Development and external validation of nomograms predictive of response to radiation therapy and overall survival in nasopharyngeal cancer patients. European journal of cancer. 2015; 51(10):1303–1311. [PubMed: 25934438]
6. Sze WM, Lee AW, Yau TK, Yeung RM, Lau KY, Leung SK, Hung AW, Lee MC, Chappell R, Chan K. Primary tumor volume of nasopharyngeal carcinoma: prognostic significance for local control. International journal of radiation oncology, biology, physics. 2004; 59(1):21–27.
7. Wu Z, Zeng RF, Su Y, Gu MF, Huang SM. Prognostic significance of tumor volume in patients with nasopharyngeal carcinoma undergoing intensity-modulated radiation therapy. Head & neck. 2013; 35(5):689–694. [PubMed: 22715047]
8. Willner J, Baier K, Pfreundner L, Flentje M. Tumor volume and local control in primary radiotherapy of nasopharyngeal carcinoma. Acta oncologica (Stockholm, Sweden). 1999; 38(8): 1025–1030.
9. Guo R, Sun Y, Yu XL, Yin WJ, Li WF, Chen YY, Mao YP, Liu LZ, Li L, Lin AH, et al. Is primary tumor volume still a prognostic factor in intensity modulated radiation therapy for nasopharyngeal carcinoma? Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2012; 104(3):294–299. [PubMed: 22998947]
10. Zhou GQ, Tang LL, Mao YP, Chen L, Li WF, Sun Y, Liu LZ, Li L, Lin AH, Ma J. Baseline serum lactate dehydrogenase levels for patients treated with intensity-modulated radiotherapy for nasopharyngeal carcinoma: a predictor of poor prognosis and subsequent liver metastasis. International journal of radiation oncology, biology, physics. 2012; 82(3):e359–365.
11. Wan XB, Wei L, Li H, Dong M, Lin Q, Ma XK, Huang PY, Wen JY, Li X, Chen J, et al. High pretreatment serum lactate dehydrogenase level correlates with disease relapse and predicts an inferior outcome in locally advanced nasopharyngeal carcinoma. European journal of cancer. 2013; 49(10):2356–2364. [PubMed: 23541571]
12. Turen S, Ozyar E, Altundag K, Gullu I, Atahan IL. Serum lactate dehydrogenase level is a prognostic factor in patients with locoregionally advanced nasopharyngeal carcinoma treated with chemoradiotherapy. Cancer investigation. 2007; 25(5):315–321. [PubMed: 17661206]
13. Leung SF, Zee B, Ma BB, Hui EP, Mo F, Lai M, Chan KC, Chan LY, Kwan WH, Lo YM, et al. Plasma Epstein-Barr viral deoxyribonucleic acid quantitation complements tumor-node-metastasis staging prognostication in nasopharyngeal carcinoma. Journal of clinical oncology : official

journal of the American Society of Clinical Oncology. 2006; 24(34):5414–5418. [PubMed: 17135642]

14. Chai SJ, Pua KC, Saleh A, Yap YY, Lim PV, Subramaniam SK, Lum CL, Krishnan G, Mahiyuddin WR, Teo SH, et al. Clinical significance of plasma Epstein-Barr Virus DNA loads in a large cohort of Malaysian patients with nasopharyngeal carcinoma. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2012; 55(1):34–39. [PubMed: 22739102]
15. Lin JC, Wang WY, Chen KY, Wei YH, Liang WM, Jan JS, Jiang RS. Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. The New England journal of medicine. 2004; 350(24):2461–2470. [PubMed: 15190138]
16. Chang H, Gao J, Xu BQ, Guo SP, Lu RB, Li G, Huang SM, Han F, Liu ZG, Tao YL, et al. Haemoglobin, neutrophil to lymphocyte ratio and platelet count improve prognosis prediction of the TNM staging system in nasopharyngeal carcinoma: development and validation in 3,237 patients from a single institution. Clinical oncology (Royal College of Radiologists (Great Britain)). 2013; 25(11):639–646. [PubMed: 23910226]
17. Le QT, Zhang Q, Cao H, Cheng AJ, Pinsky BA, Hong RL, Chang JT, Wang CW, Tsao KC, Lo YD, et al. An international collaboration to harmonize the quantitative plasma Epstein-Barr virus DNA assay for future biomarker-guided trials in nasopharyngeal carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research. 2013; 19(8):2208–2215. [PubMed: 23459720]
18. Ng WT, Lee MC, Hung WM, Choi CW, Lee KC, Chan OS, Lee AW. Clinical outcomes and patterns of failure after intensity-modulated radiotherapy for nasopharyngeal carcinoma. International journal of radiation oncology, biology, physics. 2011; 79(2):420–428.
19. Lin S, Pan J, Han L, Zhang X, Liao X, Lu JJ. Nasopharyngeal carcinoma treated with reduced-volume intensity-modulated radiation therapy: report on the 3-year outcome of a prospective series. International journal of radiation oncology, biology, physics. 2009; 75(4):1071–1078.
20. Harrell, FE, Jr. Regression modeling strategies. 2. Springer; 2015.
21. Zhang, H., Singer, BH. Recursive Partitioning and Applications. 2. Springer; 2010.
22. Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008; 26(8):1364–1370. [PubMed: 18323559]
23. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. The Lancet Oncology. 2015; 16(4):e173–180. [PubMed: 25846097]
24. Greiner M, Pfeiffer D, Smith RD. Principles and practical application of the receiver-operating characteristic analysis for diagnostic tests. Preventive veterinary medicine. 2000; 45(1–2):23–41. [PubMed: 10802332]
25. Gross ND, Patel SG, Carvalho AL, Chu PY, Kowalski LP, Boyle JO, Shah JP, Kattan MW. Nomogram for deciding adjuvant treatment after surgery for oral cavity squamous cell carcinoma. Head & neck. 2008; 30(10):1352–1360. [PubMed: 18720518]
26. Polterauer S, Grimm C, Hofstetter G, Concin N, Natter C, Sturdza A, Potter R, Marth C, Reinthaller A, Heinze G. Nomogram prediction for overall survival of patients diagnosed with cervical cancer. British journal of cancer. 2012; 107(6):918–924. [PubMed: 22871885]
27. Liang W, Zhang L, Jiang G, Wang Q, Liu L, Liu D, Wang Z, Zhu Z, Deng Q, Xiong X, et al. Development and validation of a nomogram for predicting survival in patients with resected non-small-cell lung cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015; 33(8):861–869. [PubMed: 25624438]
28. Wang Y, Li J, Xia Y, Gong R, Wang K, Yan Z, Wan X, Liu G, Wu D, Shi L, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013; 31(9):1188–1195. [PubMed: 23358969]
29. Han DS, Suh YS, Kong SH, Lee HJ, Choi Y, Aikou S, Sano T, Park BJ, Kim WH, Yang HK. Nomogram predicting long-term survival after d2 gastrectomy for gastric cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012; 30(31):3834–3840. [PubMed: 23008291]

30. Karakiewicz PI, Briganti A, Chun FK, Trinh QD, Perrotte P, Ficarra V, Cindolo L, De la Taille A, Tostain J, Mulders PF, et al. Multi-institutional validation of a new renal cancer-specific survival nomogram. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007; 25(11):1316–1322. [PubMed: 17416852]

31. Zeng L, Guo P, Li JG, Han F, Li Q, Lu Y, Deng XW, Zhang QY, Lu TX. Prognostic score models for survival of nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy and chemotherapy. Oncotarget. 2015; 6(36):39373–39383. [PubMed: 26415223]

32. Wu S, Xia B, Han F, Xie R, Song T, Lu L, Yu W, Deng X, He Q, Zhao C, et al. Prognostic Nomogram for Patients with Nasopharyngeal Carcinoma after Intensity-Modulated Radiotherapy. PloS one. 2015; 10(8):e0134491. [PubMed: 26248338]

33. Tang LQ, Li CF, Li J, Chen WH, Chen QY, Yuan LX, Lai XP, He Y, Xu YX, Hu DP, et al. Establishment and Validation of Prognostic Nomograms for Endemic Nasopharyngeal Carcinoma. Journal of the National Cancer Institute. 2016; 108(1)

34. Yang L, Hong S, Wang Y, Chen H, Liang S, Peng P, Chen Y. Development and External Validation of Nomograms for Predicting Survival in Nasopharyngeal Carcinoma Patients after Definitive Radiotherapy. Scientific reports. 2015; 5:15638. [PubMed: 26497224]

35. Zeng Q, Hong MH, Shen LJ, Meng XQ, Guo X, Qian CN, Wu PH, Huang PY. Nomograms for predicting long-term survival in patients with non-metastatic nasopharyngeal carcinoma in an endemic area. Oncotarget. 2016

36. Chang TS, Chu ST, Hou YY, Chang KP, Chi CC, Lee CC. Validation of bidimensional measurement in nasopharyngeal carcinoma. Radiation oncology (London, England). 2010; 5:72.

37. Lee AW, Sze WM, Au JS, Leung SF, Leung TW, Chua DT, Zee BC, Law SC, Teo PM, Tung SY, et al. Treatment results for nasopharyngeal carcinoma in the modern era: the Hong Kong experience. International journal of radiation oncology, biology, physics. 2005; 61(4):1107–1116.

38. Yi JL, Gao L, Huang XD, Li SY, Luo JW, Cai WM, Xiao JP, Xu GZ. Nasopharyngeal carcinoma treated by radical radiotherapy alone: Ten-year experience of a single institution. International journal of radiation oncology, biology, physics. 2006; 65(1):161–168.

Condensed abstract

A nomogram incorporating TNM stage-group, age, GTV-P volume and LDH significantly improves the prognostic power when compared with TNM stage-group alone. More personalized treatment decisions can be achieved with this refinement of risk stratification for individual NPC patients.

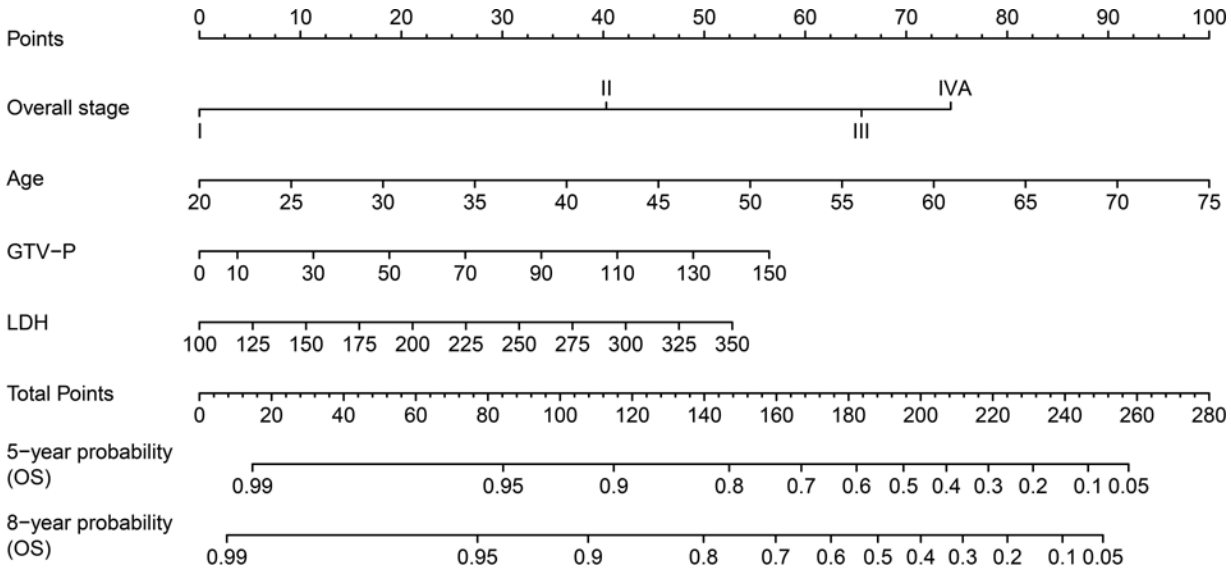

Figure 1.
Nomogram for 5-year and 8-year overall survival (OS) based on the training cohort

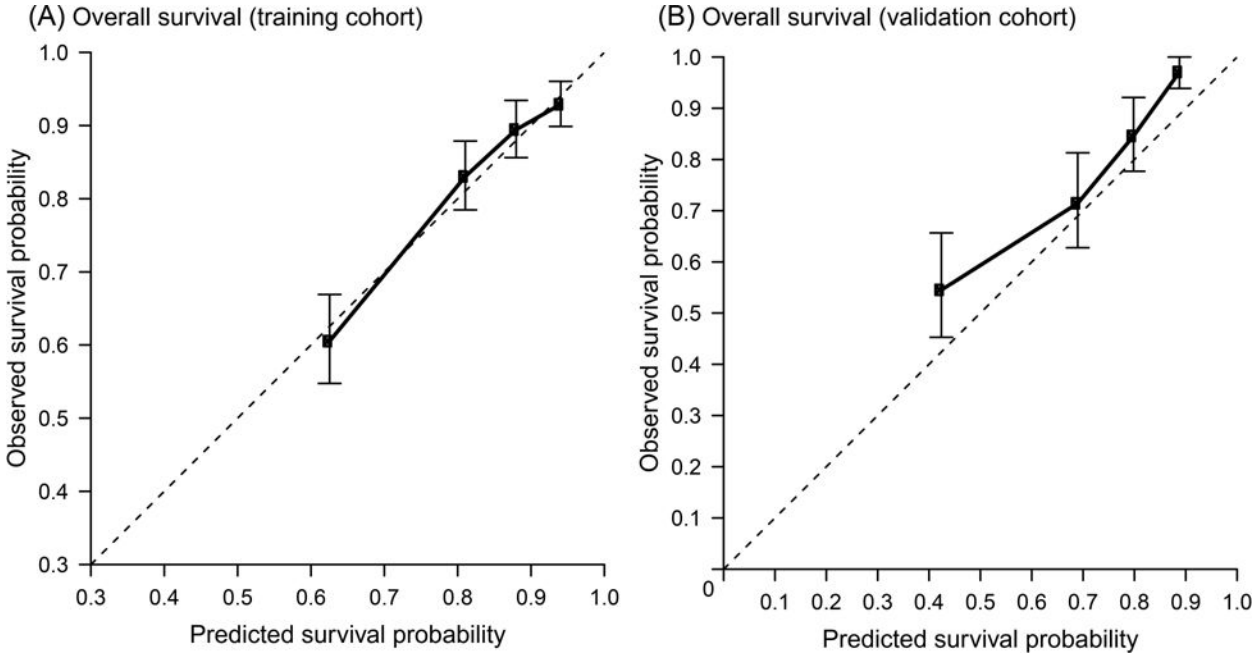

Figure 2.

Calibration plot for overall survival on (A) training cohort (intercept=−0.05, p=0.60; slope=1.06, p=0.59) and (B) validation cohort (intercept=0.15, p=0.25; slope=0.89, p=0.47)

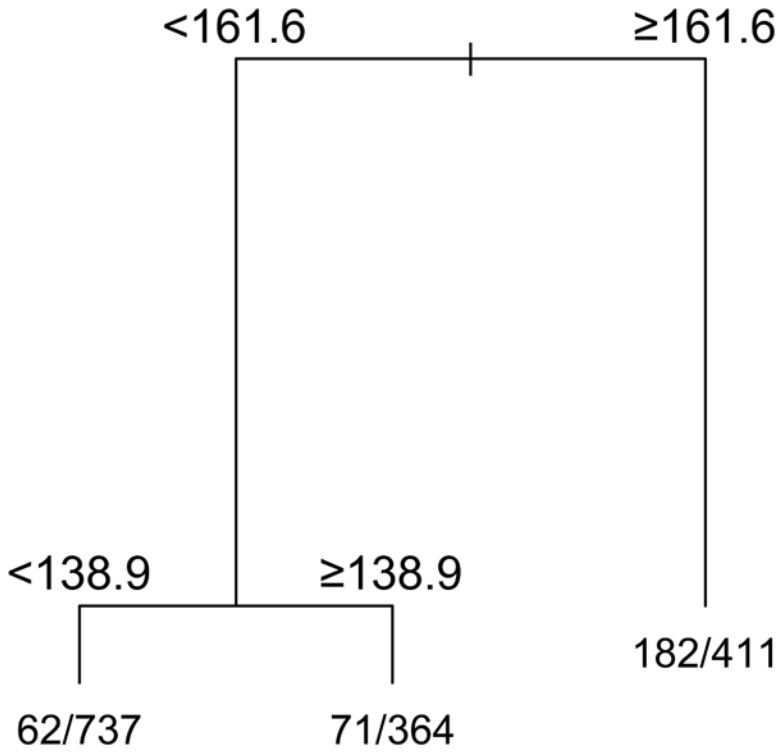

Figure 3.
Recursive partitioning algorithm for overall survival of the whole series based on the score derived from the nomogram

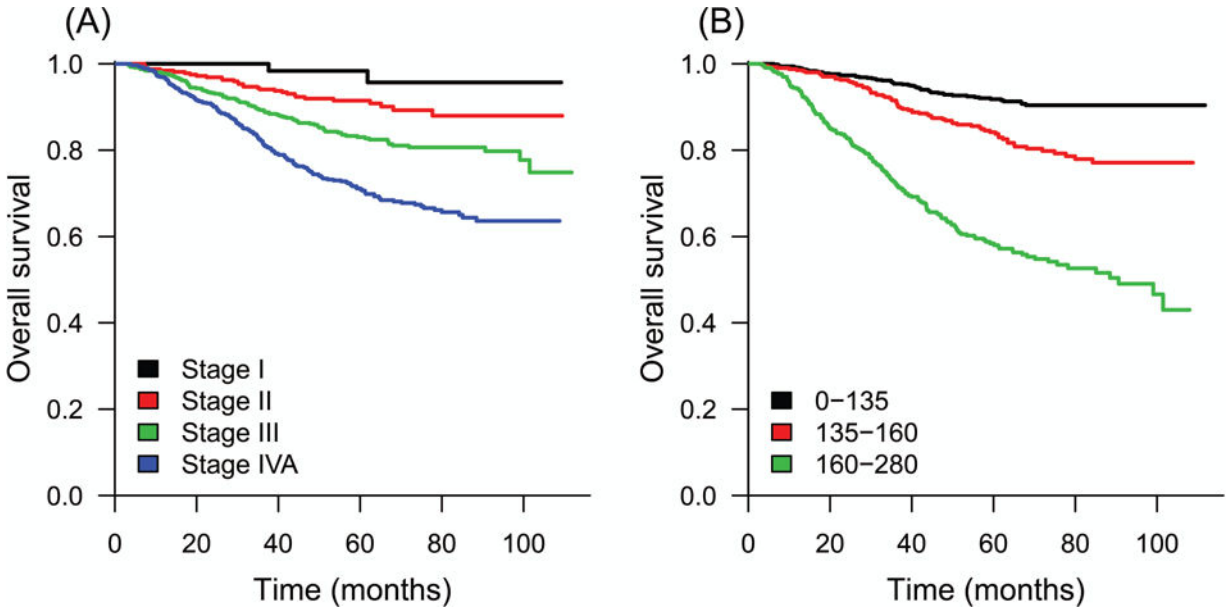

Figure 4.

Kaplan-Meier plots for overall survival of the whole series (A) Stage-group by AJCC/UICC Proposed 8th Edition, (B) risk-groups by nomogram

Table 1

Patient characteristics

Number (%)	Training Cohort (N=1197)	Validation Cohort (N=412)	P value
Age (years)			<0.001
Median (range)	46 (11–84)	50 (17–84)	
Mean	46.4	51.1	
Gender			0.706
Female	292 (24.4)	105 (25.5)	
Male	905 (75.6)	307 (74.5)	
Performance status			<0.001
0	1087 (90.8)	337 (81.8)	
1	107 (8.9)	65 (15.8)	
2–3	3 (0.3)	10 (2.4)	
T-category *			<0.001
1	285 (23.8)	57 (13.8)	
2	220 (18.4)	66 (16.0)	
3	294 (24.6)	191 (46.4)	
4	398 (33.2)	98 (23.8)	
N- category *			<0.001
0	174 (14.5)	20 (4.9)	
1	658 (55.0)	53 (12.9)	
2	270 (22.6)	209 (50.7)	
3	95 (7.9)	130 (31.6)	
Group stage *			<0.001
I	57 (4.8)	6 (1.5)	
II	297 (24.8)	26 (6.3)	
III	381 (31.8)	184 (44.7)	
IVA	462 (38.6)	196 (47.6)	
Histology			0.328
WHO Type 1	12 (1.0)	1 (0.2)	
WHO Type 2.1	51 (4.3)	17 (4.1%)	
WHO Type 2.2	1134 (94.7)	394 (95.6)	
GTV-P (cc)			0.053
Median (range)	32.8 (0.1–235.6)	31.1 (0.7–279.9)	
Mean	41.2	46.1	
LDH (IU/L)			<0.001
Median (range)	183 (106–751)	140 (71–859)	
Mean	193.4	148.1	
Hemoglobin (g/dL)			0.006
Median (range)	14.3 (8.0–17.1)	14.4 (7.1–17.9)	
Mean	14.3	14.0	

Number (%)	Training Cohort (N=1197)	Validation Cohort (N=412)	P value
Radiotherapy dose (Gy)			0.960
Median (range)	69.75 (61.60–86.65)	70 (66–70)	
Mean	69.98	69.98	
Addition of chemotherapy			
Overall (any sequence)	1016 (84.6)	343 (83.3)	0.479
Concurrent ± Non-concurrent	467 (39.0)	338 (82.0)	<0.001

Performance status: based on ECOG system;

* Proposed 8th Edition of AJCC/UICC Staging System; GTV-P = gross primary tumor volume; LDH – lactate dehydrogenase; WHO Type 1 = Keratinizing, WHO Type 2.1 = Non-Keratinizing (differentiated), WHO Type 2.2 = Non-Keratinizing (undifferentiated)

Table 2

Significant factors on overall survival by multivariate analysis of the training cohort (N = 1197)

Variables	HR (95% CI)	p
Stage-group		0.002
II vs I	2.58 (0.61, 10.83)	0.196
III vs I	4.67 (1.15, 18.98)	0.031
IVA vs I	5.86 (1.43, 24.06)	0.014
Age (per year increase)	1.04 (1.03, 1.06)	<0.001
GTV-P (per cc increase)	1.008 (1.004, 1.013)	<0.001
LDH (per IU/L increase)	1.005 (1.002, 1.008)	0.002

Gender and performance status were not statistically significant in the model.

Table 3

Comparison of risk-group based on nomogram versus stage-group per se for the whole series (N = 1609)

	Stage-group by AJCC/UICC system*		Risk-group by nomogram	
Distribution	I:	3.9%	Low:	44.6%
	II:	20.1%	Intermediate:	26.9%
	III:	35.1%	High:	28.5%
	IVA:	40.9%		
Overall survival (5-year)	I:	98.4%	Low:	91.8%
	II:	91.5%	Intermediate:	84.2%
	III:	83.0%	High:	58.4%
	IVA:	71.1%		
C-index, median (95% CrI)	0.628 (0.602–0.653)		0.704 (0.676–0.730)	

*(Proposed 8th edition);

Risk-groups based on nomogram: low-risk, 0–135; intermediate-risk, >135–<160; high-risk, ≥160 points.