A Nomogram to Predict Survival and Determine Necessity of Induction Chemotherapy for Patients With Stage T3-4N1 Nasopharyngeal Carcinoma

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Abstract

Background

The value of induction chemotherapy (IC) is still controversial for stage T3-4N1 nasopharyngeal carcinoma (NPC) patients receiving concurrent chemoradiotherapy (CCRT). Therefore, we established a nomogram to predict clinical outcome and explore the therapeutic efficiency of IC.

Methods

Overall, 699 stage T3-4N1 NPC patients treated with CCRT with or without IC between January 2010 and December 2018 were examined. Overall survival (OS) was regarded the main endpoint. A nomogram was developed including prognostic variables selected by multivariate analysis. The Harrell Concordance Index (C-index), calibration curves, and time-dependent receiver operator characteristic (td-ROC) curves were performed to assess the predictive ability of the nomogram. All patients were divided into high- and low-risk groups based on the optimal cutoff of risk score to investigate the role of IC.

Results

The nomogram yielded C-index of C-index of 0.725 (95% CI: 0.672–0.778) in the training and 0.647 (95% CI: 0.580–0.742) in the validation cohort. Calibration curves for 3- and 5-year OS rate suggested a good association between the nomogram predicted and actual observed probabilities. Td-ROC analysis demonstrated good discriminatory ability. In the high-risk group, no statistically significant difference was observed between patients receiving IC + CCRT and those with CCRT alone. However, in the low-risk group, the applying of IC was associated with worse locoregional recurrence-free survival (LRRFS) and distant metastasis-free survival (DMFS).

Conclusions

We established and validated a nomogram for LA-NPC patients with N1 disease to predict OS and determine necessity of IC, which has satisfactory prognosis predicting ability and clinical practicability. The use of IC for stage T3-4N1 NPC patients should be considered carefully.

Background

Nasopharyngeal carcinoma (NPC) is a remarkable malignancy with high prevalence in southern China, northern Africa, and southeastern Asia (1). Due to its hidden anatomical location and non-specific symptoms, approximately 70% of patients are categorized as locally advanced stage at initial diagnosis (2). Concurrent chemoradiotherapy (CCRT) is now considered as the standard treatment plan for locally advanced nasopharyngeal carcinoma (LA-NPC) (3, 4). Recently, some prospective trials have explored the value of induction chemotherapy (IC) and reported the encouraging result that applying IC before CCRT significantly improved distant metastasis-free survival (DMFS) and overall survival (OS) in LA-NPC (except T3N0-1 and T3-4N0 subgroups) (5-7).

Nowadays, the treatment option is considered according to the National Comprehensive Cancer Network (NCCN) guideline and the AJCC/ UICC stage system, which recommended IC plus CCRT for patients with LA-NPC. Nevertheless, IC is considered for LA-NPC patients with positive lymph node metastasis, while CCRT alone is usually used for patients with N0 stage in clinical practice. Notably, patients with N1 disease have lower risk of disease progression compared to those with N2–3 disease (8). What more, the outcome among patients with T3-4N1 stage still presented discrepancy. Thus, the necessity of IC before for patients with T3-4N1 stage is still unclear. In the era of precision therapy, it is necessary to develop an accurate prognostic model for predicting survival prognosis and determining necessity of IC for LA-NPC patients with N1 stage. This can greatly improve clinical decision-making.

The prognosis differs among patients with the similar stage (9). Nowadays, nomogram has emerged as a new and reliable prognostic tool for prognosis predicting. Integrating additional relevant variables to TNM stage would enhance prognostication of survival outcomes for NPC patients. Previous research reported a great deal of clinicopathological information and serum markers were regarded as prognostic factors for NPC patients, containing gender, pathologic types, age, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to lymphocyte ratio (LMR), albumin (ALB), hemoglobin (HGB)), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), Epstein-Barr virus DNA (EBV DNA) levels and so on (10-16). These factors are regularly tested and conveniently gained in common clinical practice.

Given this premise, we aimed at developing a comprehensive prognostic nomogram and further identifying the value of IC for T3-4N1 NPC patients treated with CCRT.

Methods

Patients

The current study reviewed 699 NPC patients treated at Guangxi Medical University Cancer Hospital from January 2010 to December 2018 who met the following inclusion criteria: (1) biopsy-proven NPC; (2) newly diagnosed stage T3-4N1 disease, by the eighth edition AJCC/UICC staging system; (3) completion of CCRT with or without IC; (4) without other malignancies; (5) complete data on follow-up. This study was approved by the Medical Ethics Committee of our center and was waived of informed consent.

Treatment

For patients received IC, the IC regimens were TPF, TP, PF, and GP regimes. Concurrent chemotherapy regimen was mainly cisplatin regimen. The radiotherapy technique used was intensity modulated radiotherapy (IMRT). The detailed information on treatment is consistent in our previous study and available in **Supplementary Materials** (9).

Endpoints and follow-up

All patients received evaluation every three months in first two years after RT, and then every six months to a year thereafter until death or loss of follow-up. The main endpoints was overall survival (OS), other

endpoint included locoregional recurrence-free survival (LRRFS), distant metastasis-free survival (DMFS), and progression-free survival (PFS), which were calculated as the interval from pathological diagnosis to death for any cause; to locoregional recurrence; to distant metastasis; and to disease progression or death, respectively.

Nomogram development and validation

The nomogram incorporated all independent predictors for OS that were identified by univariable and multivariable analyses. The predictive performance of the nomogram was assessed for discrimination and calibration ability. Discrimination was measured via C-index (17) and tdROC curve analysis (18). Calibration ability was evaluated by the calibration curve to compare the observed OS with predicted survival.

Statistical analysis

We used SPSS (version 25.0) and R software (version 3.6.3) to perform statistical analyses. Categorical variables (gender, smoking status, pathological type, T stage, and treatment) were classified based on clinical knowledge, and numerical variables (age, HGB, ALB, NLR, PLR, LMR, LDH and ALP) were converted to categorical variables according to the cutoff values determined by ROC curve analyses. Categorical variables are presented as whole numbers and proportions. The Pearson χ^2 test or Fisher's exact test was used to compare the differences in patients' baseline characteristics between the training and validation cohorts. "Rms" package was for nomogram and calibration curves. "timeROC" package was used for time-dependent ROC curve (td-ROC). The calculation of C-index was performed by using "Hmisc" package. Kaplan–Meier curves were plotted by "survival" package and compared using the log-rank test.

Two-sided $P < 0.05$ was regarded as statistically significant.

Results

Patient characteristics

From January 2010 to December 2018, a total of 699 NPC patients with T3-4N1M0 stage were involved in the study. Additionally, 215 (30.8%) received IC plus CCRT and 484 (69.2%) received CCRT alone. We applied computer-generated random numbers with ratio of 7:3 to divide patients into a training cohort ($n = 490$) and a validation cohort ($n = 209$, **Table 1**). No significant difference was detected between the two groups except for gender ($p = 0.039$), NLR ($p = 0.047$), and LMR ($p = 0.028$).

For training and validation cohorts, the median follow-up duration were 57.7 months (range, 2-131.5 months) and 60.9 months (range, 3.1-113.6 months), respectively. Additionally, the 1-, 3-, and 5-year OS were 97.9%, 90.8%, 81.8%, and 98.5%, 92.0%, 82.0% for the training and validation sets, respectively.

Independent prognostic factors for OS

Univariate and multivariate analyses of the selection of independent predictors are showed in **Table 2**. According to the data of univariate analysis, older (> 50 years) patients experienced more unfavorable survival than younger (≤ 50 years) ($P < 0.001$). Advanced T stage also exhibited worse prognosis ($P < 0.001$). Moreover, higher HGB ($P = 0.040$) and ALB ($P < 0.001$), lower NLR ($P = 0.001$) and LDH ($P = 0.004$) were associated with better OS. Notably, the use of IC did not appear to improve outcome. We further conducted multivariable analysis and included potential prognostic variables identified by the univariable analysis. Finally, age (HR = 1.898; 95%CI = 1.331-2.075; $P < 0.001$), T stage (HR = 1.850; 95%CI = 1.301-2.631; $P = 0.001$), ALB (HR = 0.645; 95%CI = 0.442-0.942; $P = 0.023$), NLR (HR = 1.700; 95%CI = 1.155-2.502; $P = 0.007$), and LDH (HR = 1.602; 95%CI = 1.118-2.296; $P = 0.01$) remained regarded as independent predictors in the multivariate analysis.

Establishing and validating a nomogram

According to the above five independent predictors, a nomogram predicting the 3- and 5-year OS for stage T3-4N1 NPC was established (**Figure 1**). We can add up the score of each factor as the overall score and position it on the survival rate scale to predict 3- and 5- year OS.

The nomogram achieved satisfactory performance in predicting OS, with C-index of 0.725 (95% CI: 0.672–0.778) in the training cohort and 0.647 (95% CI: 0.580–0.742) in the validation cohort. The calibration curves of the nomogram showed good calibration in predicting 3- and 5-year OS (**Figure 2A–D**). Furthermore, td-ROC curves demonstrated good discriminatory ability (**Figure 3A-B**).

Nomogram for risk stratification

Given the nomogram showed good predictive ability, we used the nomogram to conduct risk stratification. Based on the optimal cutoff risk score of 11.5 by ROC curve, all patients were divided into low- (< 11.5) and high-risk groups (> 11.5). The log-rank test suggested that 5-year OS and PFS were statistically significantly different between the two groups (OS: 88.8% vs. 74.2%, $p < 0.001$; PFS: 83.8% vs. 71.4%, $p < 0.001$; **Supplementary Figure S1**).

Role of induction chemotherapy

We then conducted a subgroup analysis to evaluate the role of IC in low- and high-risk groups. In the low-risk group, IC + CCRT was inferior to CCRT alone in terms of LRFS (HR, 2.971; 95% CI: 1.095-8.060; $P = 0.025$) and DMFS (HR, 2.634; 95% CI: 1.246-5.569; $P = 0.008$) but not OS (HR, 0.824; 95% CI: 0.404-1.680; $P = 0.593$) and PFS (HR, 1.353; 95% CI: 0.809-2.263; $P = 0.247$; **Figures 4A-D**). In the high-risk group, no significant difference was observed between IC + CCRT and CCRT groups in terms of LRFS, DMFS, OS and PFS ($P = 0.165, 0.873, 0.620$ and 0.638 , respectively) (**Figures 5A-D**).

Discussion

We conducted this study to establish and validate a nomogram for stage T3-4N1 NPC patients. This prognostic model showed good prognosis predicting ability and aided in clinical decision-making. Based

on the risk score produced by the nomogram, we successfully stratified the patients into low- and high-risk groups with significantly different risk of treatment failure. In addition, we found that IC could not produce survival benefit for patients with high risk and even had an adverse effect on low-risk patients.

Recently, increasing evidence supported the application of IC before radical CCRT. Several multicenter, Phase 3, randomized controlled trials indicated the addition of IC to CCRT significantly improved clinical prognosis for patients with LA-NPC (5, 7, 19). Nevertheless, the role of IC in LA-NPC remains controversial in some other prospective studies. Fountzilias et al. compared the therapeutic efficiency of IC plus CCRT with CCRT alone for LA-NPC patients, suggesting the two treatment plans achieved similar data in 3-year OS and PFS rates (20). Another randomized study also revealed similar conclusion (21). Notably, unlike the other studies, these two studies covered all LA-NPC patients. The inclusion of stage T3-4N0-1 patients may decrease the power of the trials to detect a survival benefit, as these subgroups were considered to have low risk of treatment failure and not warranting additional IC (22-24). Although the latest NCCN guidelines recommended IC plus CCRT as one of the most appropriate treatments for LA-NPC, clinicians should notice inconsistent benefit of IC in various subgroups. We collected data of LA-NPC patients receiving CCRT with or without IC from 2010 to 2018. The data showed that only a small number of T3N0 and T4N0 patients (accounting for 4.1 and 3.6% respectively), and most of them accept CCRT alone (accounting for 93.5% and 74.1% respectively). The above data indicated that LA-NPC patients with N0 disease of are mainly treated with CCRT in clinical practice. A retrospective study with large population reported that a significant difference for DMFS could be observed in stage N1 and N2-3 NPC patient, which were the rates of 10-15% and 30–40%, respectively (8). For patients with large and/or extensive lymph node disease (N2-3), there is higher risk for distant metastasis and the therapeutic intensity of CCRT alone may not be sufficient (25, 26). Consequently, N2-3 patients are generally considered with high risk among LA-NPC and IC is always applied for them. However, patients with N1 disease had seems located in the intermediate risk zone among all LA-NPC patients, indicating the prognosis for these patients is not uniform and the survival prognosis and the necessary of IC need further investigation. Therefore, we paid attention to stage T3-4N1 NPC patients to establish an accurate prognostic model to better guide the clinical treatment.

The current study developed a nomogram for OS in stage T3-4N1 NPC patients integrating clinical characteristics and several serum biomarkers. The TNM staging system is now the most reliable tool to predict treatment outcomes. However, some prognostic factors verified in previous studies are ignored by this staging system. Therefore, it is necessary to carry out a more comprehensive assessment of patients' prognosis in combination with other predictors. Inflammation is associated with prognosis of cancer patients, as it can increase risk of tumor progression and metastasis by inhibiting apoptosis, promoting angiogenesis, and damaging DNA (27, 28). Some systemic inflammation variables, such as NLR, PLR and LMR are proved as independent prognostic factors for NPC patients (10, 11, 14, 16). Pretreatment serum LDH and ALP levels are also prognostic markers in patients with NPC, high level of which represents poor prognosis (12). Additionally, decreased levels of pretreatment serum ALB and HGB are important indicator of patients' nutritional status and have been successfully used to evaluate the prognosis of NPC patients (15). Thus, the levels of the above factors before treatment have been

analyzed in the current study, combined with gender, age, pathological type, T stage, smoking history, and treatment (CCRT with/ without IC). We selected the significant predictors for OS through univariate and multivariate Cox analyses, which included age, T stage, NLR, ALB, and LDH. The nomogram was thus developed based on the above factors.

Given the nomogram showed good predictive ability for OS. Thus, we divided patients into two risk groups according to the nomogram, in which the high-risk group had a markedly poor OS and PFS. A subgroup analysis showed that IC would decrease LRRFS and DMFS rates in patients with low risk. The following reasons might explain the results of this study. Firstly, the use of IC would prolong the wait time from diagnosis to definitive radiotherapy, which might lead to miss the best occasion for treatment and give tumor more time to progress. Some studies have reported delay for radical radiotherapy would significantly increase risk of treatment failure in NPC patients (29, 30). Second, it was reported that IC plus CCRT were associated with higher incidences of hematological and nonhematologic acute toxicity (5, 7). The extra severe acute adverse events caused by IC may directly or indirectly impair the patient's immune system and reduce their tolerance to CCRT. Besides, about 20% of patients were insensitive to IC (31, 32), which makes the possible negative effects of IC more prominent. Therefore, it is worth considering avoiding overtreatment in low-risk patients within stage T3-4N1 NPC patients, who have a relatively good prognosis and may not benefit from intensive therapy. For the high-risk subgroup, the data in this study suggested that IC plus CCRT has similar treatment efficacy to CCRT alone. However, given the higher risk of treatment failure in the high-risk group, intensive treatment should be considered. According to the results of this study, the addition of IC may not be the most reasonable choice. The additional dose of radiotherapy and concurrent chemotherapy may improve systematic treatment efficacy and thus translate into survival benefit (33, 34). In conclusion, although IC is recommended to use in all LA-NPC patients based on the latest guideline, the benefit of IC in patients with stage T3-4N1 NPC may be limited.

This study also has some limitations. First, the retrospective nature of this study leads to inevitable selection bias. Secondly, although plasma EBV DNA load has been widely proved be an important biomarker for survival, pretreatment EBV DNA load was not included in the present study as some patients diagnosed with NPC at an early period when test of EBV DNA was not yet widespread. The large interlaboratory variability of EBV DNA testing also limits its routine clinical application. However, a further refinement of the nomogram including EBV DNA data would make the conclusion more convincing. Finally, external validations from other institutes are needed to enhance practical applicability of the model.

Conclusion

Our study developed a nomogram to predict OS for stage T3-4N1 NPC patients in an endemic area. According to this model, patients could be defined as low- and high-risk groups. The application of IC could not provide survival benefits for high- risk patients and even could decrease LRRFS and DMFS for patients with low risk. Our nomogram will help clinicians better predict clinical outcome and make more

reasonable treatment decisions. A validation cohort involving other centers is required to generalize the use of our model.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Guangxi Medical University Cancer Hospital. Informed consent was not necessary due to the retrospective nature of this study.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declared no conflicts of interest.

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Authors' contributions

Study conception and design: Xiao-Dong Zhu and Yu-Ting Jiang. Data acquisition and quality control: all authors; Statistical analysis: Yu-Ting Jiang and Kai-Hua Chen; Manuscript preparation: Yu-Ting Jiang; Manuscript review: all authors.

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Tables

Table 1 Baseline characteristics of the patients. (n = 699).

Abbreviations: WHO, World Health Organization; IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy; HGB, hemoglobin; ALB, albumin; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to lymphocyte ratio; LDH, lactate dehydrogenase; ALP, alkaline phosphatase.

Table 2 Identification of risk factors of OS by univariate and multivariate Cox models.

Characteristics	Number of NPC patients (%)		
	Training cohort (n = 490)	Validation cohort (n = 209)	p-value
Gender			0.039
Female	120 (24.5)	67 (32.1)	
Male	370 (75.5)	142 (67.9)	
Age (years)			0.208
≤ 50	329 (67.1)	130 (62.2)	
> 50	161 (32.9)	79 (37.8)	
Smoking			0.688
Yes	138 (28.8)	62 (29.7)	
No	352 (71.8)	147 (37.8)	
T stage			0.628
T3	291 (59.4)	120 (57.4)	
T4	199 (40.6)	89 (42.6)	
Pathological type			0.470
WHO I/II	41 (8.4)	21 (10.0)	
WHO III	449 (91.6)	188 (90.0)	
HGB (g/L)			0.344
≤ 140	267 (54.5)	122 (58.4)	
> 140	223 (45.5)	87 (41.6)	
ALB (g/L)			0.903
≤ 50	178 (36.3)	78 (37.3)	
> 50	312 (63.7)	131 (62.7)	
NLR			0.047
≤ 3.26	385 (78.6)	178 (85.2)	
> 3.6	105 (21.4)	31 (14.8)	
PLR			0.064
≤ 185.05	345 (70.4)	162 (77.5)	

> 185.05	145 (29.6)	47 (22.5)	
LMR			0.028
≤ 4.98	341 (69.6)	127 (60.8)	
> 4.98	149 (30.4)	82 (39.2)	
LDH (IU/L)			1.000
≤ 172	252 (51.4)	107 (51.2)	
> 172	238 (48.6)	102 (48.8)	
ALP			0.361
≤ 60	277 (56.5)	110 (52.6)	
> 60	213 (43.5)	99 (47.4)	
Treatment			1.000
IC + CCRT	151 (30.8)	64 (30.6)	
CCRT	339 (43.5)	145 (69.4)	
Clinical endpoints			0.791
None	372 (75.9)	160 (76.6)	
Recurrence	24 (4.9)	7 (3.3)	
Distant metastasis	43 (8.8)	18 (8.6)	
Death	95 (19.4)	36 (17.2)	

	Univariate cox regression		Multivariate cox regression	
Characteristic	HR (95% CI)	P	HR (95% CI)	P
Gender		0.386		
Female	Reference			
Male	1.198 (0.796-1.802)			
Age (years)		<0.001		<0.001
≤ 50	Reference		Reference	
> 50	2.230 (1.583-3.141)		1.898 (1.331-2.075)	
Smoking		0.661		
No	Reference			
Yes	0.918 (0.627-1.344)			
T stage		<0.001		0.001
T3	Reference		Reference	
T4	2.118 (1.498-2.995)		1.850 (1.301-2.631)	
Pathological type		0.939		
WHO I/II	Reference			
WHO III	0.979 (0.561-1.707)			
HGB (g/L)		0.040		0.219
≤ 140	Reference		Reference	
> 140	0.689 (0.482-0.983)		0.790 (0.543-1.150)	
ALB (g/L)		<0.001		0.023
≤ 50	Reference		Reference	
> 50	0.498 (0.351-0.706)		0.645 (0.442-0.942)	
NLR		0.001		0.007
≤ 3.26	Reference		Reference	
> 3.6	1.863 (1.277-2.718)		1.700 (1.155-2.502)	
PLR		0.060		
≤ 185.05	Reference			
> 185.05	1.415 (0.986-2.030)			

LMR		0.270	
≤ 4.98	Reference		
> 4.98	0.812 (0.560-1.176)		
LDH (IU/L)		0.004	0.01
≤ 172	Reference		Reference
> 172	1.677 (1.182-2.381)		1.602 (1.118-2.296)
ALP		0.859	
≤ 60	Reference		
> 60	1.032 (0.728-1.463)		
Treatment		0.546	
CCRT	Reference		
IC+CCRT	0.886 (0.597-1.313)		

Abbreviations: CI, confidence interval; HR, hazard ratio. WHO, World Health Organization; IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy; HGB, hemoglobin; ALB, albumin; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to lymphocyte ratio; LDH, lactate dehydrogenase; ALP, alkaline phosphatase.

Figures

Figure 1

Nomogram integrating all independent clinical factors (age, T stage, NLR, LDH, and ALB) for predicting 3- and 5-year OS.

Figure 2

The Calibration plots of the nomogram in predicting OS at 3 year and 5 year in the training (A-B) and validation cohorts (C-D).

Figure 3

The td-ROC curves of the nomogram in predicting OS at 3 year and 5 year in the training (A) and validation cohorts (B).

Figure 4

OS (A), LRRFS (B), DMFS (C) and PFS (D) Kaplan–Meier’s curves for patients receiving CCRT and IC + CCRT within the low-risk (A-D) group in the whole cohort.

Figure 5

OS (A), LRRFS (B), DMFS (C) and PFS (D) Kaplan–Meier’s curves for patients receiving CCRT and IC + CCRT within the high-risk (A-D) group in the whole cohort.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryFigureS1A.tiff](#)

- [SupplementaryFigureS1B.tiff](#)
- [SupplementaryFigureS1C.tiff](#)
- [SupplementaryFigureS1D.tiff](#)
- [Supplementarydata.docx](#)