PREDICTIVE MODEL FOR DISTANT METASTATIC FREE SURVIVAL IN NASOPHARYNGEAL CARCINOMA

BY

THITIPORN JARUTHIEN

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CLINICAL EPIDEMIOLOGY
FACULTY OF MEDICINE
THAMMASAT UNIVERSITY

ACADEMIC YEAR 2024

PREDICTIVE MODEL FOR DISTANT METASTATIC FREE SURVIVAL IN NASOPHARYNGEAL CARCINOMA

BY

THITIPORN JARUTHIEN

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CLINICAL EPIDEMIOLOGY

FACULTY OF MEDICINE

THAMMASAT UNIVERSITY

ACADEMIC YEAR 2024

THAMMASAT UNIVERSITY
FACULTY OF MEDICINE

DISSERTATION

BY

THITIPORN JARUTHIEN

ENTITLED

PREDICTIVE MODEL FOR DISTANT METASTATIC FREE SURVIVAL
IN NASOPHARYNGEAL CARCINOMA

was approved as partial fulfillment of the requirements for
the degree of Doctor of Philosophy (Clinical Epidemiology)

on September 30,2024

Chairman _______________________
(Professor Chawalit Lertbutsayanukul, M.D.)

Member and Advisor Prapasri Kulalert
(Associate Professor Prapasri Kulalert, M.D., Ph.D.)

Member _______________________
(Associate Professor Thammanard Charernboon, M.D., Ph.D.)

Member _______________________
(Assistant Professor Pichaya Tantiyavarong, M.D., Ph.D.)

Member _______________________
(Associate Professor Anussara Prayongrat, M.D., Ph.D.)

Dean _______________________
(Associate Professor Auchara Tangsathapornpong, M.D.)

Dissertation Title	PREDICTIVE MODEL FOR DISTANT METASTATIC FREE SURVIVAL IN NASOPHARYNGEAL CARCINOMA
Author	Thitiporn Jaruthien
Degree	Doctor of Philosophy
Major Field/Faculty/University	Clinical Epidemiology Faculty of Medicine Thammasat University
Dissertation Advisor	Associate Professor Prapasri Kulalert, Ph.D., M.D.
Academic Year	2024

ABSTRACT

Background: The improvement in diagnosis and treatment for nasopharyngeal carcinoma (NPC) has shifted the pattern of failure toward distant metastasis. This study aimed to develop a simplified prognostic scoring model to predict distant metastatic free survival (DMFS) for NPC patients.

Methods: Patients with non-metastatic NPC were identified from a retrospective cohort diagnosed between 2010 and 2018. Flexible parametric survival analysis was used to identify potential predictors for DMFS and establish a scoring model. The prognostic accuracy between the 8^{th} AJCC system and the scoring model was compared using Harrell's C-index.

Results: Of total 393 patients, median follow-up time was 85 months. The 3-year DMFS rate was 83.3%. Gender, T-stage, pre-EBV (cut-off 2300 copies/ml), and a number of metastatic lymph node regions (LNR) were identified as independent risk factors for distant metastasis and were included in the final scoring model.

Our established model achieved a high C-index in predicting DMFS (0.79) and was well-calibrated. The score divided patients into two categories: low-risk (score 0-4) and high-risk (score 5-7), corresponding with the predicted 3-year DMFS of 96% and 64.5%, respectively.

Conclusions: A feasible and applicative prognostic score was established and validated to discriminate NPC patients into low- and high-risk groups.

Keywords: Nasopharyngeal carcinoma, Distant metastatic free survival, Prognosis, Score, Model

ACKNOWLEDGEMENTS

First, I would like to extend my heartfelt gratitude to each member of my thesis committee: Chairman Professor Chawalit Lertbutsayanukul, my advisor Associate Professor Prapasri Kulalert, Assistant Professor Pichaya Tantiyavarong, Associate Professor Thammanard Charernboon, and Associate Professor Anussara Prayongrat for their insightful comments on this dissertation. I deeply appreciate their contributions, especially Associate Professor Prapasri Kulalert and Professor Chawalit Lertbutsayanukul for their unwavering support throughout my Ph.D. studies and research, and Assistant Professor Pichaya Tantiyavarong for performing data analysis to confirm my findings.

Secondly, I would also like to express my gratitude to the neuroradiology team at King Chulalongkorn Memorial Hospital: Associate Professors Nutchawan Jittapiromsak and Aniwat Sriyook, M.D., for assisting in reporting the radiologic findings for this research. Additionally, I am thankful to my co-authors from the Radiation Oncology department at King Chulalongkorn Memorial Hospital for providing valuable comments on the manuscript.

Lastly, I would like to thank my family—my parents and husband—for their constant love and support. Their encouragement has been instrumental in helping me successfully complete my Ph.D. studies.

Thitiporn Jaruthien

TABLE OF CONTENTS

Page

Page

APPENDICES

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Symbols/Abbreviations	Terms
AJCC	American joint committee on cancer
AIC	Akaike information criterion
BIC	Bayesian information criterion
CCRT	Concurrent chemoradiotherapy
CNN	Cervical node necrosis
CRP	C-reactive protein
CT	Computed tomography
DM	Distant metastasis
DMFS	Distant metastatic free survival
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
GTV	Gross tumor volume
GTVp	Gross tumor volume of primary tumor
Hb	Hemoglobin
HR	Hazard ratio
IMRT	Intensity-modulated radiation therapy
IQR	Interquartile range
LDH	Lactate dehydrogenase
LNR	Metastatic lymph node region
LN	Lymph node
MRI	Magnetic resonance imaging
NPC	Nasopharyngeal carcinoma
NLR	Neutrophil/lymphocyte ratio
OS	Overall survival
PTV	Planning target volumes
PTV HR	Planning target volumes high-risk
PTV LR	Planning target volumes low-risk

rENE	Radiologic extra-nodal extension
RT	Radiotherapy
SD	Standard deviation
SIB	Simultaneous integrated boost
TNM	Tumor-node-metastasis
VMAT	Volumetric modulated arc therapy

CHAPTER 1
INTRODUCTION

1.1 Background

Nasopharyngeal carcinoma (NPC) is one of the most common head and neck cancers, with an estimated 130,000 new cases worldwide in 2020. It has a distinct epidemiological feature, as more than 80% of the cases occur in Asia, particularly in southern China and Southeast Asia (1). Chemoradiotherapy is a mainstay treatment in NPC for stages II-IV, while in stage I, radiotherapy (RT) alone is the standard of care with good efficacy. Improvements in imaging at diagnosis and radiation techniques have shifted the pattern of recurrence from locoregional recurrence toward distant metastasis (DM). After distant progression occurs, the prognosis for this patient group remains poor, with a 5-year survival rate of less than 30% (2, 3). Therefore, precise risk estimation for DM is essential for optimizing treatment.

The anatomical tumor–node–metastasis (TNM) staging system is currently the most common prognostic factor for risk stratification and treatment decisions (4). However, a recent study found that using only TNM staging had limitations in portraying the risk of DM consistently within each stage (5). Patients within the same TNM stage receiving similar treatments exhibited varying outcomes. Therefore, recognizing additional prognostic factors and developing more precise tools to predict the risk of DM are essential.

Recently, an increasing number of predictive models have been developed to assist physicians in tailoring personalized treatment based on individual risk factors. Most of these models were primarily evaluated to predict overall survival. Previous models for predicting distant metastatic-free survival (DMFS) were based on sophisticated approaches, such as gene expression, radiomic features, or positron emission tomography–computed tomography (6-9). However, practical models to assess the risk of DM have been limited.

Several studies have demonstrated that certain baseline characteristics, such as male sex and advanced age, increase the risk of DM (10, 11). Currently, it is widely accepted that the Epstein-Barr virus (EBV) plays a pivotal role in initiating, developing, and progressing of disease. Numerous studies have indicated that the circulating plasma EBV DNA concentration can predict patient prognosis in the early stage of NPC management (12-14). Moreover, certain distinct characteristics of lymph nodes from magnetic resonance imaging (MRI), such as the size, volume, extracapsular extension, nodal necrosis, and the number of metastatic lymph node regions (LNR) were found to be independent predictors for DM (15-18). All these variables are easily obtained from blood examinations and imaging modalities, routinely used in the diagnosis and treatment of NPC patients. To the best of our knowledge, limited models have incorporated clinical variables, hematological biomarkers, and imaging features to predict the risk of distant metastasis.

1.2 Objective

Our aim of this study is to develop a simplified predictive model using easily obtainable prognostic variables at the time before starting the treatment, including patient characteristics, hematologic biomarkers, and lymph node characteristics to help predict DMFS, which could potentially be used in routine clinical settings to assist physicians in promptly selecting the individualized treatment.

1.3 Expected benefits

- Develop a predictive model as a simple tool to identify patients with different risks of distant metastasis using inexpensive and available parameters.
- Can be used in routine clinical settings to aid individualized treatment strategies and surveillance, especially intensification of treatment in high-risk groups.
- May further implement the model as a web application or mobile phone application.
- Conduct further studies: Conduct stratified medicine research by selecting treatments according to risk characteristics shared by subgroups of patients.
- Target users: Radiation oncologists, medical oncologists, and otolaryngologists

CHAPTER 2
REVIEW OF LITERATURE

2.1 Factors that are associated with DMFS.

In recent years, there have been an increasing number of multiple prognostic variables that could help predict the risk of distant metastasis in nasopharyngeal carcinoma. Selected variables that can be conveniently obtained prior to treatment are reviewed.

2.1.1 Patient factors

Several studies have demonstrated that some patient's baseline characteristics such as male sex and advanced age increased the risk of DM (**Table 1**).

Table 1 Patient factors that are associated with DMFS.

Factors		**N**	
Sex	Xiao G. 2013 (10) Retrospective	299	Male patients had a poorer 5-year DMFS (77.2% vs 89.7%, P = 0.036)
Age	Zhang LN. 2016 (11) Retrospective	1252	The 4-years DMFS decreased with age group (86.7% [20-49 years], 86.7% [50-59 years], 77.1% [≥60 years], P=0.014)

Abbreviation: DMFS = distant metastasis-free survival

2.1.2 Hematological biomarkers

Currently, it is widely accepted that the Epstein-Barr virus (EBV) plays a pivotal role in initiating, developing, and progressing of disease. Numerous studies have indicated that the circulating plasma EBV DNA concentration including pre- and post-treatment level can predict patient prognosis.

Table 2 Studies of pre-treatment EBV DNA level associated with DMFS.

Studies	**Outcomes**
Zhang J. et al 2016(12) Meta-analysis 23 studies N= 10,732	High pre-treatment plasma EBV DNA level predicts worse DMFS. Pooled HR for DMFS 3.26, 95% CI 2.67-3.98
Alami IE. et al.2022(13) Meta-analysis 26 studies N= 9966	High pre-treatment plasma EBV DNA level predicts worse DMFS. Pooled HR for DMFS 2.53, 95% CI 2.18-2.92
Lertbutsayanukul et al. 2018(14) N=208	Pre-treatment EBV DNA<2,300 copies/ml predicts better DMFS. HR 0.29, 95% CI 0.13-0.63

Abbreviations: DMFS = distant metastasis-free survival; EBV = Epstein-Barr virus; HR = hazard ratio; NPC = nasopharyngeal carcinoma

Pre-treatment EBV DNA cut-off values vary among studies. The most commonly used values were 4,000 copies/ml and 1500 copies/ml (13). Most studies were from the Chinese population. Studies from Thailand reported a cut-off value of 2,300 copies/ml and suggested that this cut-off level was optimal for predicting DMFS(14, 19).

2.1.3 Lymph node characteristics

Certain distinct characteristics of lymph nodes from magnetic resonance imaging (MRI), such as the size, volume, extracapsular extension, nodal necrosis, and the number of metastatic lymph node regions were found to be independent predictors for DM (**Table 3**).

Table 3 Lymph node (LN) characteristics that are associated with DMFS.

LN characteristics	Studies	Outcomes
Volume of LN	Chen F. 2017(15) Retrospective N = 1,230	Large nodal tumor volume was correlate with worse DMFS.
Size of LN	Zhou X. 2018(16) Retrospective N = 354	Maximal LN diameter > 6 cm is strongly predictive for worsening DMFS.
Number of metastatic lymph node region (LNR)	Zhou X. 2018(16) Retrospective N = 354	Increasing of LNR (0-1 vs 2-6 vs >7) is strongly predictive for worsening DMFS.
Cervical node necrosis (CNN)	Lan M 2015(17) Retrospective N = 1,800	The DM rate was 18.7% for CNN group vs 4.6% for non-CNN group. 5-year DMFS 78.4% vs 91.6%, p<0.001
Radiologic extra-nodal extension (rENE)	Lu T. 2019(18) Retrospective N= 1,390	rENE+ group had a significantly inferior 5-years DMFS (73.8% vs 88.4%, p <0.001) The higher the grade of rENE, the lower the 5-year DMFS

Abbreviations: DMFS = distant metastasis-free survival; HR = hazard ratio; NPC = nasopharyngeal carcinoma

2.2 Previous predictive models for DMFS

Developed practical models to assess the risk of distant metastatic free survival (DMFS) were limited. Most of the previous models for predicting DMFS were based on variables that are not generally used in Thailand such as gene expression, radiomic features or positron emission tomography–computed tomography. Few models that have incorporated clinical variables, hematological biomarkers, or lymph node characteristics to help predict risk of distant metastasis are shown in **Table 4.** These models showed better discrimination performance compared to TNM staging alone.

Table 4 Models that have incorporated clinical variables, hematological biomarkers, or lymph node characteristics to help predict DMFS.

	Xie C 2020 (20)	Li Q 2020 (21)	Zeng L 2015 (22)
N	733	5,903	338
Prognostic factors	- Age (>45 years) - T stage (AJCC 8^{th}) - EBV level (>4000 copies/ml) - Central nodal necrosis - Nodal number	- Sex - Age - T category (AJCC 8^{th}) - N category (AJCC 8^{th}) - Hb - CRP - LDH - Induction chemotherapy - Concurrent chemotherapy	- LDH - N2 (AJCC 7^{th}) - N3 (AJCC 7^{th}) - GTVp
C-index: Developmental model	0.737	0.705	0.76
C-index: Internal Validation	0.718	0.701	0.73
TNM system	-	0.673 (AJCC 8^{th})	0.67 (AJCC 7^{th})

Abbreviations: AJCC = American Joint Committee on Cancer; CRP = C-reactive protein; EBV = Epstein-Barr virus; Hb = hemoglobin; LDH = lactate dehydrogenase; GTVp = Gross Tumor Volume of primary tumor

CHAPTER 3
RESEARCH METHODOLOGY

3.1 Research Design

Theoretical design: Prognostic prediction research

Time point for prediction: pre-treatment

Data collection design: Retrospective cohort study

Occurrence relation: y = *ƒ* (x1+x2+x3+…)

Distant metastatic free survival = *ƒ* (Clinical variables + hematological Biomarkers + lymph node characteristics)

3.2 Target population

Non-metastatic nasopharyngeal carcinoma

3.3 Study population:

Non-metastatic nasopharyngeal carcinoma treated at King Chulalongkorn Memorial Hospital between 2010 and 2018.

3.4 Eligibility criteria

3.4.1 Inclusion criteria

3.4.1.1. Diagnosed biopsy-proven squamous cell carcinoma of nasopharynx

3.4.1.2. Stage II-IVa

3.4.1.3. Age > 18 years old

3.4.1.4. No distant metastasis before treatment (complete work up with Chest X-Ray, ultrasonography of liver, and Tc99m-methylene diphosphonate bone scan)

3.4.1.5. Underwent MRI of head and neck

3.4.1.6. Treated with curative intent by concurrent chemoradiation

3.4.1.7. Radiotherapy treatment using intensity-modulated radiation therapy (IMRT) or Volumetric modulated arc therapy (VMAT)

3.4.2 Exclusion criteria

3.4.2.1. Follow up less than 2 years.

3.4.2.2. Incomplete treatment.

3.4.2.3. Induction chemotherapy

3.5 Sample size calculation

From our institutional data, phase III prospective randomized study compare sequential versus simultaneous integrated boost intensity-modulated radiation therapy in nasopharyngeal carcinoma. Rate of distant metastasis was reported 20 percent at 3 years (23).

For 5 predictors, we need 50 events (rule of thumb: 10 events per predictor) with prevalence of event 20 %, so the calculated sample size was 250 patients.

3.6 Treatment of nasopharyngeal carcinoma

Nasopharyngeal carcinoma stage II-IVA: concurrent chemoradiation with or without adjuvant chemotherapy

3.6.1 Radiation treatment

All patients were immobilized in the supine position with a tailored head-shoulder thermoplastic mask then a CT simulation was performed.

MR simulation was performed on every patient and co-registration with the CT images.

Two planning target volumes (PTVs) were designated as follows:

3.6.1.1 PTV-high risk (PTV-HR) is defined as gross tumor and pathologic lymph node plus 0.8 cm margin.

3.6.1.2 PTV-low risk (PTV-LR) encompassed PTV-HR and entire nasopharynx, retropharyngeal lymph node, skull base, clivus, pterygoid fossa, parapharyngeal space, pterygopalatine fossa, sphenoid sinus, and posterior 1/3 of nasal cavity/maxillary sinuses, as well as elective lymph node level Ib-V plus 0.5 cm margin.

2 techniques of radiotherapy

1. Sequential technique: 50Gy in 25 fractions to the PTV-LR followed by 20 Gy in 10 fractions boost to PTV-HR.
2. Simultaneous integrated boost (SIB) technique: 70Gy for PTV-HR at 2.12 Gy/fraction and 56 Gy for PTV-LR at 1.7 Gy/fraction, delivered in 33 fractions.

Volumetric modulated arc therapy (VMAT) or Intensity-modulated radiation therapy (IMRT) was applied to both techniques.

3.6.2 Chemotherapy

Concurrent chemotherapy regimen: platinum-based chemotherapy given weekly or tri-weekly.

Adjuvant chemotherapy regimen: cisplatin/5-fluorouracil or carboplatin/5-fluorouracil at 4-week intervals for 3 cycles

3.7 Follow-up

Patients were follow-up weekly during chemoradiation, before each cycle of adjuvant chemotherapy and 1 month after complete treatment. Fiberoptic nasopharyngeal examination, and CT or MRI of the nasopharynx was done 3 months after the completion of chemoradiation to determine tumor response. The patients were evaluated every 3-6 months during the first 3 years, every 6 months from the fourth to the fifth year, and annually thereafter. At each follow-up visit, a physical examination, endoscopic examination, and blood test were performed. When patients had clinical suspicion of locoregional recurrence or distant metastasis, additional imaging and/or tissue biopsy was performed to confirm disease progression.

3.8 Outcome

DMFS was measured from the date of the start of treatment until the date of proven metastasis. Overall survival (OS) was measured from the date of the start of treatment until the date of death (any cause). Patients without any endpoints were censored on July 25, 2022.

Distant metastasis definition:

- A new lesion in a remote region such as distant LN (below the clavicle), lung, bone, liver, or others
- No evidence of a second primary tumor
- Biopsy proven when indicated

3.9 Data collection

Demographic, tumor characteristics and baseline laboratory data were obtained from electronic medical records. Plasma EBV DNA levels were collected before treatment (pre-EBV). Pretreatment MRI was reviewed by experienced head and neck radiologists to determine the TNM classification according to the eighth edition of the AJCC/UICC staging system and the lymph node characteristics including number of metastatic lymph node regions (LNR), necrotic features, and extracapsular extension (ECE). The nodal level classification was mapped following the eighth edition of the AJCC/UICC staging system (4). Assessed regions included bilateral IA, IB, IIA, IIB, III, IV, VA, VB, VI, and VII. For retropharyngeal LN (RP), bilateral RP was considered as one unit when counting the number of LNR. LNs located on the border of neighboring levels were recorded as involving both regions. More details on diagnostic criteria for metastatic lymph nodes such as central necrosis, ECE, and a summary of the imaging-based nodal level classification can be found in the appendix.

3.10 Data Analysis and Statistics

Analysis was carried out using Stata/SE 18.0 (StataCorp, Texas, USA). Continuous variables were reported as mean with standard deviation (SD). Categorical variables were presented as counts and percentages.

A flexible parametric survival model, developed by Royston and Parmar in 2002, was used to derive the prognostic model via the stpm2 package. The advantage of this model over the Cox regression model is its ability to estimate the baseline cumulation hazard function which allows more accurate prediction. Sensitivity analysis was employed to determine the optimal degrees of freedom or knots for the baseline spline function. In our model, we opted for a cumulative hazard scale featuring two degrees of freedom after considering the criteria of the lowest Akaike information criterion (AIC) and Bayesian information criterion (BIC) values. The proportional hazard assumption was tested using Schoenfeld residuals before deriving the model. Eight potential predictors were included in the multivariable flexible parametric model. Backward elimination was conducted using a significance threshold of P-value less than 0.05. Model discriminative performance was measured using Harrell's c-index. We assessed the calibration of the derived model by using calibration plots. We performed internal validation using a bootstrapping procedure with 100 bootstrap samples. This procedure quantified the optimism of the developed model. The model optimism of Harrell's C-statistics was calculated and the shrinkage factor for external validation studies was also reported.

To generate the clinical prediction score, the coefficients of all predictors were weighted by dividing the lowest coefficient, and any result equal to or greater than 0.5 was rounded up to the nearest integer. For clinical implications, we categorized the prediction score into two risk groups: low-risk and high-risk groups using the 80% cut-off of 3-year DMFS.

3.11 Missing data management

The analyses were done using the complete-case method without data imputation. Missing data of all variables was less than 5%.

3.12 Ethical Consideration

Due to the retrospective analysis of the results, a waiver of informed consent was obtained. The study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (IRB no. 768/63) and by the institutional review board and ethical committee of the Faculty of Medicine, Thammasat University (MTU-EC-ES-4-211/60).

CHAPTER 4
RESULTS

4.1 Patients demographics

Between January 2010 and December 2018, 547 patients met our eligibility criteria. After excluding 147 patients according to the exclusion criteria and excluding 7 patients for missing pre-treatment plasma EBV levels, 393 patients were included for model development (**Figure 1**). Mean age was 50 years, with males predominating. Patient characteristics are outlined in **Table 5**. The median follow-up time was 85 months. A total of 71 cases developed distant metastasis (18%). A total of 110 cases died (28%). The 3- and 5-year DMFS rates were 83.3% and 81.2%, respectively. The overall survival rates at 3 and 5 years were 84.5% and 77.2%, respectively.

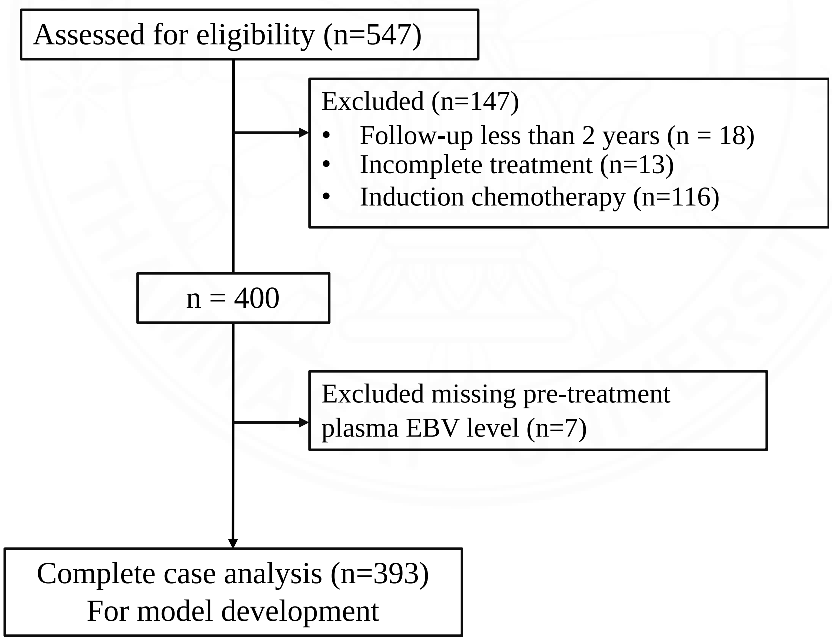


Figure 1. Study flow diagram.

Table 5. Baseline characteristics of patients (**Con.**)

Characteristics	Total N=393
	N (%)
Age (mean +/-SD)	50 (38-62)
<60	304 (77.4)
≥60	89 (22.6)
Sex	
Female	108 (27.5)
Male	285 (72.5)
Histologic type	
Nonkeratinizing SCCA	72 (18.3)
Undifferentiated SCCA	320 (81.4)
Basaloid SCCA	1 (0.3)
T stage (AJCC 8th)	
T1	105 (26.7)
T2	80 (20.4)
T3	133 (33.8)
T4	75 (19.1)
N stage (AJCC 8th)	
N0	20 (5.1)
N1	214 (54.5)
N2	98 (24.9)
N3	61 (15.5)
Stage grouping (AJCC 8th)	
II	118 (30)
III	150 (38.2)
IVA	125 (31.8)
Initial plasma EBV DNA (copies/mL)	
<2300 or undetectable	215 (54.7)
≥ 2300	178 (45.3)

Table 5. Baseline characteristics of patients (Con.)

Number of LN region (LNR)	
0-1	113 (28.8)
2-6	225 (57.2)
≥ 7	55 (14)
Necrotic LN	
No	223 (56.7)
Yes	170 (43.3)
Extracapsular extension (ECE)	
No	360 (91.6)
Yes	33 (8.4)
Concurrent chemotherapy	
Weekly cisplatin	257 (65.4)
Cisplatin tri-weekly	79 (20.1)
Weekly carboplatin	35 (8.9)
Carboplatin tri-weekly	12 (3.1)
Weekly carboplatin/paclitaxel	2 (0.5)
Missing	8 (2)
Cumulative cisplatin dose	
>200 mg/m2	331 (84.2)
<200 mg/m2	44 (11.2)
Missing	18 (4.6)
Adjuvant chemotherapy	
None	64 (16.3)
1 cycle	26 (6.6)
2 cycles	28 (7.1)
3 cycles	257 (65.4)
Unknown	9 (2.3)
Missing	9 (2.3)

Abbreviations: SD; standard deviation, AJCC; American Joint Committee on Cancer, EBV; Epstein-Barr virus

4.2 Model development

4.2.1 Potential predictors

From the univariable flexible parametric survival analysis, eight predictors were identified as candidate predictors of DMFS: aged > 60 years, male gender, T stage, N stage, pre-treatment EBV level ≥ 2,300 copies/mL, number of LNR, the presence of necrotic LN and the presence of ECE. All candidate predictors listed in **Table 6** were included in the full multivariable flexible parametric survival analysis. No statistical evidence of a violation of the proportional hazard assumption was found in the Schoenfeld residuals test (P= 0.43). The reduced model was generated through backward elimination based on a P value < 0.05. The four final predictors include male gender, T stage, pre-treatment EBV level, and number of LNR. The estimated beta coefficients and their 95% confidence intervals are shown in **Table 7**.

Table 6. Estimated hazard ratios in the univariable and multivariable flexible parametric regression models.

Predictors	**Univariable model**			**Multivariable model**		
	HR	***95% CI***	***P*- value**	**HR**	**95% CI**	***P*- value**
Age <60	1					
Age ≥ 60	1.61	0.96-2.67	0.069			
Female	1			1		
Male	2.84	1.41-5.72	0.003	2.51	1.24-5.07	0.01
T1	1			1		
T2	2.16	0.93-4.98	0.072	2.02	0.87-4.69	0.103
T3	2.88	1.36-6.11	0.006	2.67	1.25-5.69	0.011
T4	3.85	1.75-8.47	0.001	2.91	1.32-6.42	0.008
N 0-1	1					
N2	2.46	1.41-4.28	0.001			
N3	4.02	2.25 -7.18	<0.001			

Table 6. Estimated hazard ratios in the univariable and multivariable flexible parametric regression models. (Con.)

Pre-treatment EBV						
<2,300	1			1		
≥2,300	3.2	1.93- 5.29	<0.001	1.90	1.12-3.24	0.018
No of LNR						
0-1	1			1		
2-6	4.48	1.77- 11.35	0.002	3.99	1.55-10.25	0.004
7-13	14.71	5.65-38.34	<0.001	9.36	3.46-25.30	<0.001
Presence of LN Necrosis						
No	1					
Yes	2.40	1.49- 3.88	<0.001			
Presence of ECE						
No	1					
Yes	2.63	1.41-4.88	0.002			

Abbreviations: EBV; Epstein-Barr virus, LN; lymph node, LNR; number of lymph node region, ECE; radiologic gross extracapsular extension

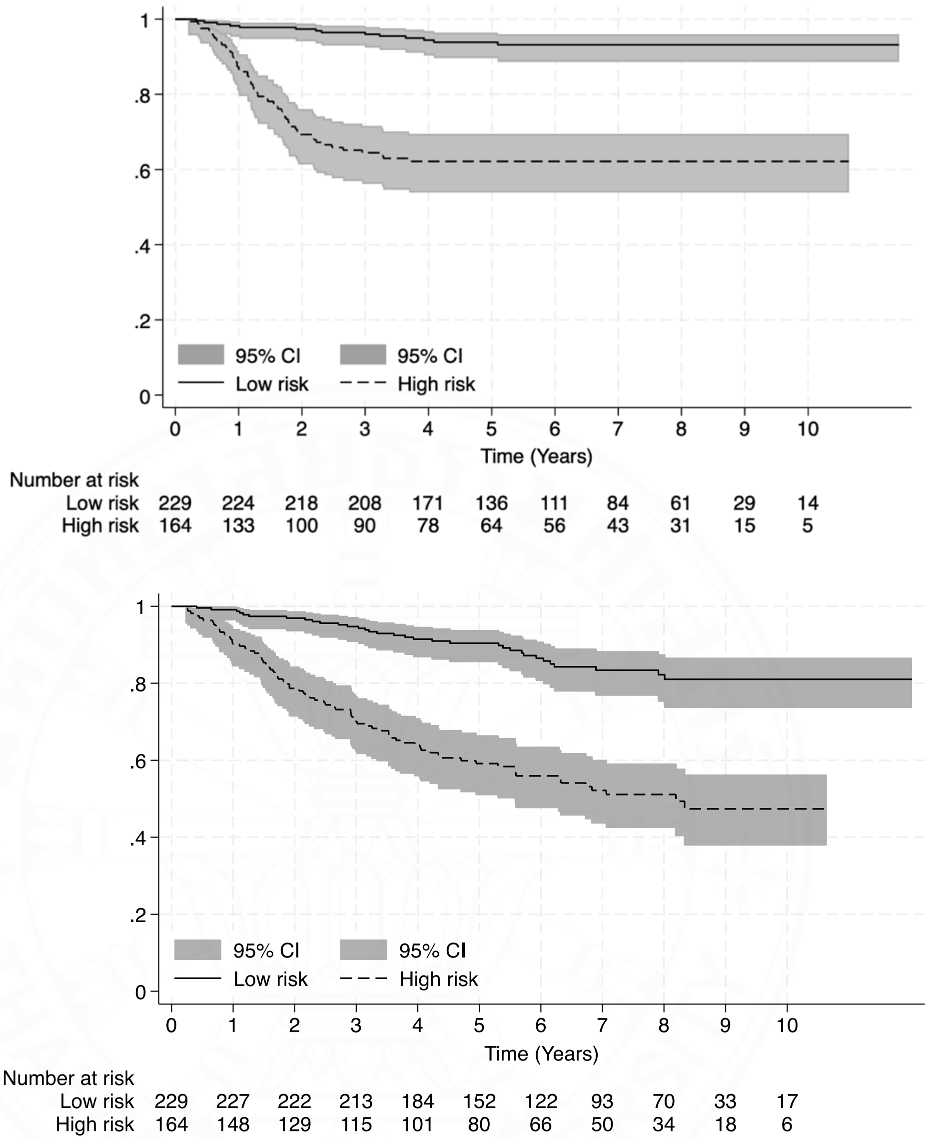
4.3 Clinical prediction score

We used the lowest beta-coefficient, 0.642, as a dominator, and assigned weighted scores: 1 for male gender, T2 stage, and pre-treatment Epstein-Barr virus (EBV) level ≥2,300 copies/mL; 2 for T3 or T4 stage, and a number of lymph node regions (LNR) in the range of 2-6 regions; and 3 for a number of LNR in the range of 7-13 regions (**Table 7**). The total score ranged from 0 to 7. The cut-off value for the risk score, distinguishing between low-risk and high-risk patients, was set at 5 using the 80% cut-off of 3-year DMFS (**Appendix C**). The scores were divided into two categories: low-risk for DMFS (score 0-4) and high-risk for DMFS (score 5-7). The predicted 3-year DMFS for low-risk and high-risk groups were 96% and 64.5%, respectively. The predicted 3-year OS for low-risk and high-risk groups were 94.8% and 70.1%, respectively. The Kaplan-Meier curves with 95% CIs of 2 risk groups of DMFS and OS are shown in **Figure 2**. The log-rank test of both graphs yielded a P-value of < 0.001.

Table 7. Best multivariable clinical predictors, hazard ratio (HR), 95% confidential interval (CI), regression beta coefficient (β), and assigned item score.

Predictors	**Multivariable model**				
	HR	**95% CI**	***P*- value**	**β *coeff***	***Score***
Female	1				0
Male	2.51	1.24-5.07	0.01	0.920	1
T1	1				0
T2	2.02	0.87-4.69	0.103	0.701	1
T3	2.67	1.25-5.69	0.011	0.980	2
T4	2.91	1.32-6.42	0.008	1.068	2
EBV pre-treatment					
<2,300	1				0
≥2,300	1.90	1.12-3.24	0.018	0.642	1
No of LNR					
0-1	1				0
2-6	3.99	1.55-10.25	0.004	1.384	2
7-13	9.36	3.46-25.30	<0.001	2.236	3

Abbreviations: EBV; Epstein-Barr virus, LNR; number of lymph node region



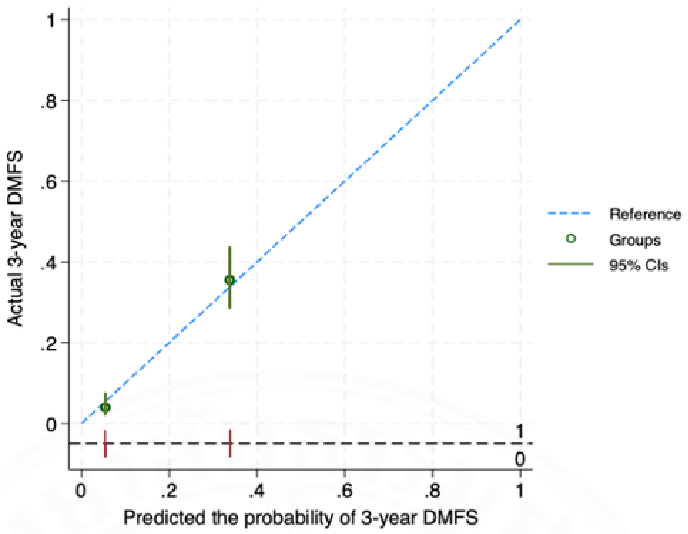
(A)

(B)

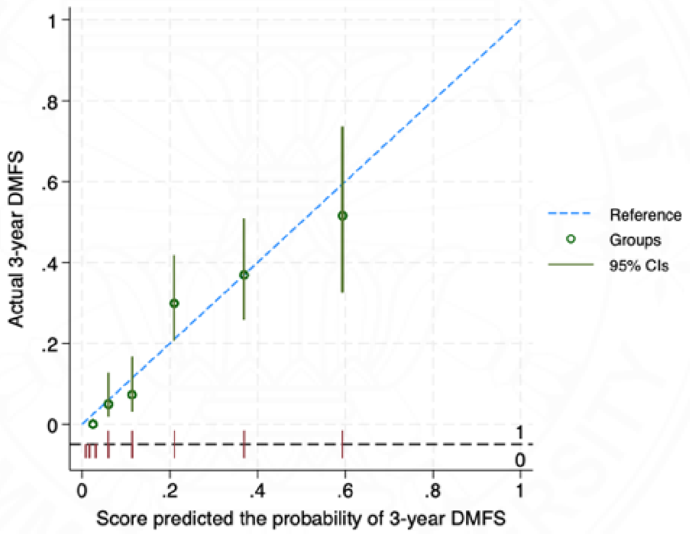
Figure 2. The Kaplan-Meier curve with 95% CIs of 2 risk-groups of DMFS (A) and OS (B).

4.4 Model discrimination and calibration

For the measure of discrimination performance, the Harrell C-statistic for the final model was 0.79. The calibration of the final model was visualized with a calibration plot (**Figure 3**), demonstrating that the prognostic model was well-calibrated.



(A)



(B)

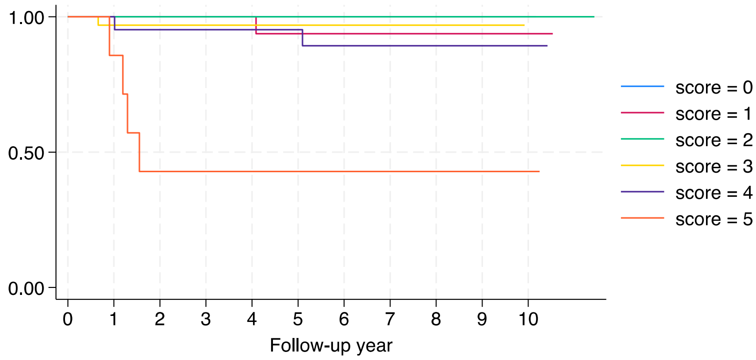
Figure 3. Calibration plots compare the model-predicted probability of 3-year DMFS and the observed outcomes against one another within each of the risk groups (A) and score (B).

4.5 Internal validation

Internal validation of the derived prognostic model was performed via a bootstrap resampling method with 100 replicates. The apparent C-statistics and the test C-statistics were 0.79 and 0.77 respectively. The shrinkage factor was 0.886, and subsequent validation studies should multiply the regression coefficients by this factor for a more reliable estimation. When comparing the predictive accuracy for DMFS between the derived model and the 8^{th} AJCC staging systems, the derived model demonstrated superior accuracy. The c-index of the model was higher than that of the 8th edition of the AJCC staging system (0.79 vs. 0.70).

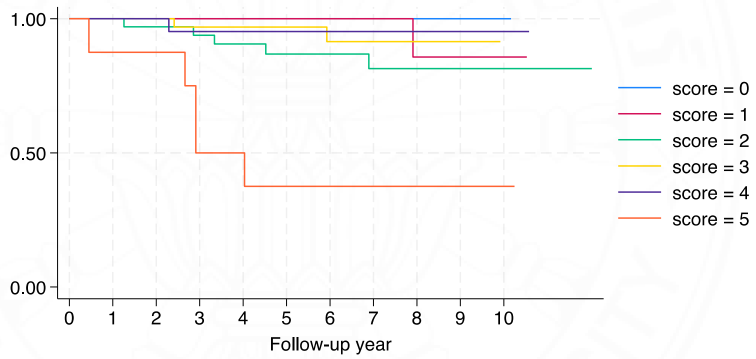
4.6 Subgroup analysis

According to the Chinese Society of Clinical Oncology (CSCO) and the American Society of Clinical Oncology (ASCO) guidelines (24), for patients with locoregionally advanced NPC stage III-IV (accepted T3N0), induction chemotherapy is recommended in addition to concurrent chemoradiotherapy (CCRT) or CCRT plus adjuvant chemotherapy due to distinctly poor survival outcomes. For stage II to early stage III (T3N0), which comprise heterogeneous groups of patients, there is a need to identify the low-risk cohort for de-intensified treatment and the high-risk cohort for treatment intensification. For example, for patients with T1-2N0-1 and T3N0 NPC, induction/adjuvant chemotherapy is not routinely recommended but may be offered if there are adverse features, such as bulky tumor volumes or high EBV DNA copy number. Therefore, we performed a subgroup analysis for patients with T1-2N0-1 and T3N0 NPC. There were 124 patients in this group composed of scores 0 to 5. The high-risk group with a score of 5 had significantly worse DMFS and OS compared to the low-risk group (**Figure 4**), suggesting intensified treatment for this group.



Number at risk											
score = 0	7	7	7	7	7	7	5	3	2	2	1
score = 1	23	23	23	21	17	10	9	8	5	2	1
score = 2	33	33	32	30	27	20	19	13	10	3	2
score = 3	32	31	31	31	25	22	13	11	5	1	0
score = 4	21	21	20	20	18	16	15	10	8	4	2
score = 5	8	6	3	3	3	3	3	3	3	3	1

(A)



Number at risk											
score = 0	7	7	7	7	7	7	5	3	2	2	1
score = 1	23	23	23	22	19	13	11	10	6	2	1
score = 2	33	33	32	30	27	20	19	14	12	5	4
score = 3	32	32	32	31	26	25	16	13	7	1	0
score = 4	21	21	21	20	19	17	16	12	10	5	3
score = 5	8	7	7	4	4	3	3	3	3	3	1

(B)

Figure 4. The Kaplan-Meier curve of DMFS (A) and OS (B) for patients with T1-2N0-1 and T3N0 NPC according to the prediction score.

CHAPTER 5
DISCUSSION AND CONCLUSION

In this study, we developed a prognostic score for predicting DMFS in patients with NPC, incorporating simple clinical characteristics, hematological biomarkers, and LN characteristics from imaging. Our score model demonstrated improved prognostic accuracy compared to the current staging system. In comparison with previous studies (20-22), our model had several advantages. Firstly, it is the first predictive model that uses flexible parametric survival analysis, which surpasses Cox regression in its ability to estimate the baseline cumulative hazard function, enabling more accurate survival predictions. Secondly, our model is the first to incorporate LNR into the model. Quantitative lymph node burden has been demonstrated to be a significant prognostic factor in various malignancies such as breast cancer, colorectal cancer, and squamous head and neck cancers. For instance, the number of metastatic LNs is a promising novel predictor of survival with demonstrated superiority to the 8th edition AJCC N classification in many squamous head and neck cancers (25, 26). For NPC, pathological quantification of LNs is unavailable. Therefore, the current N classification system is based on two-categorical nodal laterality, level, and size. The 8th AJCC N classification system does have limitations; for instance, patients with extensive metastatic LNs could be staged the same as those with single LN despite their much poorer prognosis. In the study by Zhou et al. (16), reported 5-year DMFS rates for LNR 0-1, 2-6, and ≥ 7 as 97%, 86.7%, and 69.7%, respectively. Their findings demonstrated an improved discrimination capability for DMFS compared with the 8th edition of AJCC N classification. Xie et al. (20) developed a nomogram incorporating nodal numbers which might be too laborious to apply in real-world settings. The difficulty arose from the challenge of counting nodal numbers accurately from imaging, particularly when two or more nodes coalesced. On the other hand, LNR was routinely reported by radiologists in the imaging report without requiring additional workload. Another advantage of our scoring model was its simplicity, user-friendliness, and utilization of readily available parameters. Unlike various previous models that incorporate variables not commonly used, such as gene expression, radiomic features, or positron emission tomography-computed tomography, our proposed score model was designed to be more applicable in routine clinical settings. It might assist in identifying low-risk and high-risk NPC candidates who could benefit from de-intensified or more intensified treatment. For example, in our subgroup analysis for patients with T1-2N0-1 and T3N0 NPC, who were a heterogeneous group of patients, our proposed score model could aid in selecting patients for the low-risk group for de-intensified treatment and suggest induction chemotherapy for the high-risk cohort.

Nevertheless, the present study had several limitations. Firstly, being conducted in a single intuition population with a relatively small sample size, external validation with a larger cohort should be warranted. Secondly, we used the pre-EBV cut-off of 2,300 copies/ml which was different from studies from the Chinese population (12, 13). However, since there is no standard pre-EBV cut-off value, our previous report suggested that this cut-off level was optimal for predicting DMFS (14). Thirdly, our study did not include patients who received induction chemotherapy, which might have a higher risk for distant metastasis and could introduce bias as a confounding by indication. However, induction chemotherapy was not a standard treatment during the period of the study, and we aimed to conduct a model for pre-treatment prediction with uniformly treated patients. Therefore, validation with this group of patients is warranted.

Conclusion

We established and validated a simplified score model to predict DMFS in NPC patients, incorporating gender, T-stage, pre-EBV, and number of LNR. This model can support physicians in decision-making for optimal management and exhibits higher predictive power compared to the traditional TNM staging system.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49.

2. Au KH, Ngan RKC, Ng AWY, Poon DMC, Ng WT, Yuen KT, et al. Treatment outcomes of nasopharyngeal carcinoma in modern era after intensity modulated radiotherapy (IMRT) in Hong Kong: A report of 3328 patients (HKNPCSG 1301 study). Oral Oncology. 2018;77:16-21.

3. Rusthoven CG, Lanning RM, Jones BL, Amini A, Koshy M, Sher DJ, et al. Metastatic nasopharyngeal carcinoma: Patterns of care and survival for patients receiving chemotherapy with and without local radiotherapy. Radiother Oncol. 2017;124(1):139-46.

4. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al. AJCC Cancer Staging Manual. 8th ed ed. New York: Springer International Publishing; 2017.

5. Guo Q, Lu T, Hui Huang S, O'Sullivan B, Zong J, Xiao Y, et al. Depicting distant metastatic risk by refined subgroups derived from the 8th edition nasopharyngeal carcinoma TNM. Oral Oncol. 2019;91:113-20.

6. Tang XR, Li YQ, Liang SB, Jiang W, Liu F, Ge WX, et al. Development and validation of a gene expression-based signature to predict distant metastasis in locoregionally advanced nasopharyngeal carcinoma: a retrospective, multicentre, cohort study. Lancet Oncol. 2018;19(3):382-93.

7. Zhang L, Dong D, Li H, Tian J, Ouyang F, Mo X, et al. Development and validation of a magnetic resonance imaging-based model for the prediction of distant metastasis before initial treatment of nasopharyngeal carcinoma: A retrospective cohort study. EBioMedicine. 2019;40:327-35.

8. Zhang Y, Li WF, Mao YP, Zhou GQ, Peng H, Sun Y, et al. Establishment of an integrated model incorporating standardised uptake value and N-classification for predicting metastasis in nasopharyngeal carcinoma. Oncotarget. 2016;7(12):13612-20.

9. Intarak S, Chongpison Y, Vimolnoch M, Oonsiri S, Kitpanit S, Prayongrat A, et al. Tumor Prognostic Prediction of Nasopharyngeal Carcinoma Using CT-Based Radiomics in Non-Chinese Patients. Front Oncol. 2022;12:775248.

10. 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.

11. Zhang L-N, Qiu X-S, OuYang P-Y, Xiao Y, Lan X-W, Deng W, et al. Age at diagnosis indicated poor prognosis in locoregionally advanced nasopharyngeal carcinoma. Oncotarget. 2016;0(0).

12. Zhang J, Shu C, Song Y, Li Q, Huang J, Ma X. Epstein-Barr virus DNA level as a novel prognostic factor in nasopharyngeal carcinoma: A meta-analysis. Medicine (Baltimore). 2016;95(40):e5130.

13. Alami IE, Gihbid A, Charoute H, Khaali W, Brahim SM, Tawfiq N, et al. Prognostic value of Epstein-Barr virus DNA load in nasopharyngeal carcinoma: a meta-analysis. Pan Afr Med J. 2022;41:6.

14. Lertbutsayanukul C, Kannarunimit D, Prayongrat A, Chakkabat C, Kitpanit S, Hansasuta P. Prognostic Value of Plasma EBV DNA for Nasopharyngeal Cancer Patients during Treatment with Intensity-modulated Radiation Therapy and Concurrent Chemotherapy. Radiol Oncol. 2018;52(2):195-203.

15. Chen FP, Zhou GQ, Qi ZY, Lin L, Hu J, Wang XJ, et al. Prognostic value of cervical nodal tumor volume in nasopharyngeal carcinoma: Analysis of 1230 patients with positive cervical nodal metastasis. PLoS One. 2017;12(5):e0176995.

16. Zhou X, Ou X, Yang Y, Xu T, Shen C, Ding J, et al. Quantitative Metastatic Lymph Node Regions on Magnetic Resonance Imaging Are Superior to AJCC N Classification for the Prognosis of Nasopharyngeal Carcinoma. J Oncol. 2018;2018:9172585.

17. Lan M, Huang Y, Chen CY, Han F, Wu SX, Tian L, et al. Prognostic Value of Cervical Nodal Necrosis in Nasopharyngeal Carcinoma: Analysis of 1800 Patients with Positive Cervical Nodal Metastasis at MR Imaging. Radiology. 2015;276(2):619.

18. Lu T, Hu Y, Xiao Y, Guo Q, Huang SH, O'Sullivan B, et al. Prognostic value of radiologic extranodal extension and its potential role in future N classification for nasopharyngeal carcinoma. Oral Oncol. 2019;99:104438.

19. Lertbutsayanukul C, Kannarunimit D, Netsawang B, Kitpanit S, Chakkabat C, Hansasuta P, et al. Optimal plasma pretreatment EBV DNA cut-off point for nasopharyngeal cancer patients treated with intensity modulated radiation therapy. Jpn J Clin Oncol. 2018;48(5):467-75.

20. Xie C, Li H, Yan Y, Liang S, Li Y, Liu L, et al. A Nomogram for Predicting Distant Metastasis Using Nodal-Related Features Among Patients With Nasopharyngeal Carcinoma. Front Oncol. 2020;10:616.

21. Li QJ, Mao YP, Guo R, Huang CL, Fang XL, Ma J, et al. A Nomogram Based on Serum Biomarkers and Clinical Characteristics to Predict Survival in Patients With Non-Metastatic Nasopharyngeal Carcinoma. Front Oncol. 2020;10:594363.

22. Zeng L, Guo P, Li JG, Han F, Li Q, Lu Y, et al. Prognostic score models for survival of nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy and chemotherapy. Oncotarget. 2015;6(36):39373-83.

23. Lertbutsayanukul C, Prayongrat A, Kannarunimit D, Chakkabat C, Netsawang B, Kitpanit S. A randomized phase III study between sequential versus simultaneous integrated boost intensity-modulated radiation therapy in nasopharyngeal carcinoma. Strahlenther Onkol. 2018;194(5):375-85.

24. Chen YP, Ismaila N, Chua MLK, Colevas AD, Haddad R, Huang SH, et al. Chemotherapy in Combination With Radiotherapy for Definitive-Intent Treatment of Stage II-IVA Nasopharyngeal Carcinoma: CSCO and ASCO Guideline. J Clin Oncol. 2021;39(7):840-59.

25. Ho AS, Kim S, Tighiouart M, Gudino C, Mita A, Scher KS, et al. Metastatic Lymph Node Burden and Survival in Oral Cavity Cancer. J Clin Oncol. 2017;35(31):3601-9.

26. Ho AS, Kim S, Tighiouart M, Gudino C, Mita A, Scher KS, et al. Association of Quantitative Metastatic Lymph Node Burden With Survival in Hypopharyngeal and Laryngeal Cancer. JAMA Oncol. 2018;4(7):985-9.

APPENDIX A

Certificate of Human Research Ethics Committee Approval

Certificate of Approval

The Human Research Ethics Committee of Thammasat University (Medicine)

99/209 Moo 18, Paholyothin Road, Ampher Klongluang, Pathumthani. Thailand 12120,

Tel 662-5644444 ext 7535 and Fax 662-9269704

Number of COA	**139/2021**
Project No.	MTU-EC-ES-0-149/64
Title of project	Predictive Model for Distant Metastatic Free Survival in Nasopharyngeal Carcinoma incorporating Hematological Biomarkers and Lymph Node Characteristics.
Investigator	Thitiporn Jaruthien, M.D. Asst.Prof.Prapasri Kulalert, M.D.
Study Center/site	Thammasat University Hospital
Responsible department	Faculty of Medicine at Chulalongkorn University Tel. 095-9945599

Document reviewed

1. Protocol Revised No. 1 : dated June 1, 2021
2. Case report form Version 1 : dated May 11, 2021

The Human Research Ethics Committee of Thammasat University (Medicine) is in full compliance with international guidelines such as Declaration of Helsinki, The Belmont Report, CIOMS Guidelines and the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP).

This document is a record of review and approval / acceptance of a clinical study protocol. The Human Research Ethics Committee of Thammasat University (Medicine) has approved the above study and the following documents for use in the study at the Expedited Review.

APPENDIX A (CONTINUED)

Certificate of Human Research Ethics Committee Approval

Approval period 1 year

Date of approval June 10, 2021

Date of expiry June 9, 2022

Progress report deadline June 9, 2022

Signed: ....

(Associate Professor Thana Khawcharoenporn, M.D.)

Secretary and Committee of The Human Research Ethics Committee of

Thammasat University (Medicine)

Signed: ....

(Associate Professor Waipoj Chanvimalueng, M.D.)

Chairman of The Human Research Ethics Committee of

Thammasat University (Medicine)

APPENDIX A (CONTINUED)

Certificate of Human Research Ethics Committee Approval

COA No. 1526/2020

IRB No. 768/63

INSTITUTIONAL REVIEW BOARD

Faculty of Medicine, Chulalongkorn University

1873 Rama 4 Road, Pathumwan, Bangkok 10330, Thailand, Tel 662-256-4493

Certificate of Approval

The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, has approved the following study which is to be carried out in compliance with the International guidelines for human research protection as Declaration of Helsinki, The Belmont Report, CIOMS Guideline and International Conference on Harmonization in Good Clinical Practice (ICH-GCP)

Study Title	: Predictive Model for Distant Metastasis Free Survival in Nasopharyngeal Carcinoma incorporating Hematological Biomarkers and Lymph Node Characteristics.
Study Code	: -
Principal Investigator	: Thitiporn Jaruthien, M.D.
Affiliation of PI	: Department of Radiology, Faculty of Medicine, Chulalongkorn University.
Review Method	: Expedited
Continuing Report	: At least once annually or submit the final report if finished.

Document Reviewed :

1. Research Proposal Version 1.0 Date 12 October 2020
2. Protocol Synopsis Version 1.0 Date 12 October 2020
3. Case record form Version 1.0, 12 October 2020
4. Curriculum Vitae and GCP Training

- Thitiporn Jaruthien, M.D.

Approval granted is subject to the following conditions: (see back of this Certificate)

APPENDIX A (CONTINUED)

Certificate of Human Research Ethics Committee Approval

- Assoc.Prof. Chawalit Lertbutsayanukul, M.D.

Signature	Signature ....
(Emeritus Professor Tada Sueblinvong MD)	(Associate Professor Supeecha Wittayalertpanya)
Chairperson	Member and Assistant Secretary, Acting Secretary
The Institutional Review Board	The Institutional Review Board

Date of Approval : December 17, 2020

Approval Expire Date : December 16, 2021

Approval granted is subject to the following conditions: (see back of this Certificate)

APPENDIX B

Criteria for diagnosis of nodal metastasis and lymph node characteristics in nasopharyngeal carcinoma (NPC) in Magnetic resonance imaging

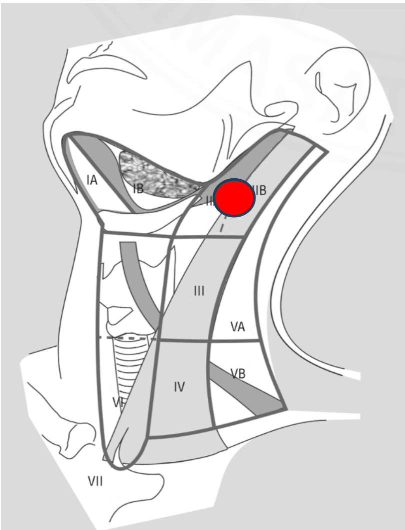
Criteria for diagnosis of nodal metastasis	Lateral retropharyngeal LN	MID ≥ 5 mm
	Medial retropharyngeal LN	Any size
	Jugulodigatric/diagastric LN	MID ≥ 11 mm
	Other cervical LN	MID ≥ 10 mm
	Other cervical LN	- Any size with central necrosis or ECE - ≥ 3 contiguous and confluent LN, each MID 8-10 mm
Characteristics	Central necrosis	Inhomogeneous signal intensity in LN and hypointense non-enhancing area on post contrast images
	Gross ECE	Infiltration into the adjacent fat or muscle

Abbreviations; LN = lymph node, MRI = Magnetic resonance imaging, MID = minimal axial diameter in the largest plane of an individual node/maximum short-axis diameter, ECE = extracapsular extension

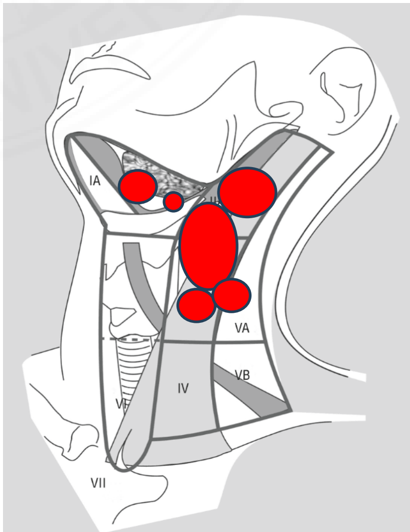
Criteria for lymph node regions

		Note
LN region definition[4]	7 levels IA, IB, IIA, IIB, III, IV, VA, VB, VI, VII Not include retropharyngeal (RP), suboccipital, parapharyngeal, Buccinator, preauricular, periparotid and intraparotid	1 level /1 side = 1 region Except retropharyngeal LN
Retropharyngeal LN	Bilateral RP was considered as one unit	
LN located in the border	LN located at border of 2 regions crossed different axial planes, the status of the node was recorded in both regions.	

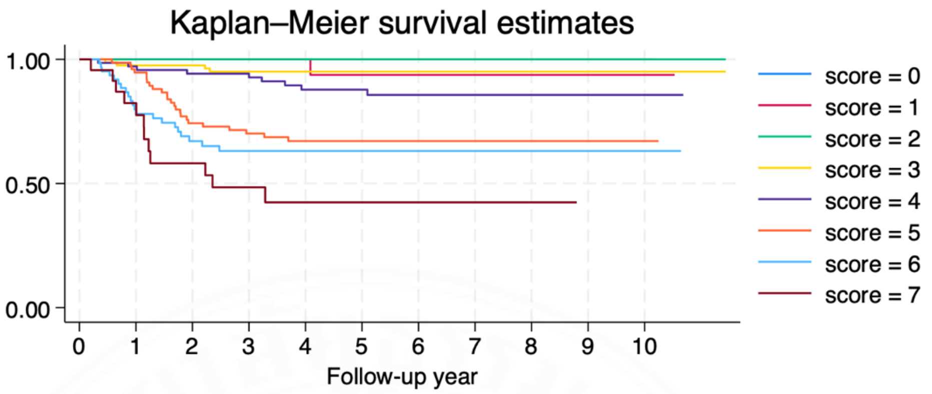
Number of LNR = 1



Number of LNR = 4



APPENDIX C



Number at risk

score = 0	7	7	7	7	7	7	5	3	2	2	1
score = 1	23	23	23	21	17	10	9	8	5	2	1
score = 2	46	46	45	43	36	26	23	16	13	6	3
score = 3	83	80	79	75	61	52	36	30	20	8	4
score = 4	70	68	64	62	50	41	38	27	21	11	5
score = 5	77	71	54	50	42	36	32	25	17	8	2
score = 6	64	45	34	32	29	22	20	16	13	7	3
score = 7	23	17	12	8	7	6	4	2	1	0	0

The Kaplan-Meier curve of DMFS according to the prediction score.

The total score ranged from 0 to 7. The cut-off value for the risk score, distinguishing between low-risk and high-risk patients, was set at 5 using the 80% cut-off of 3-year DMFS. The scores were divided into two categories: low-risk for DMFS (score 0-4) and high-risk for DMFS (score 5-7).

BIOGRAPHY

Name	Mrs. Thitiporn Jaruthien
Date of Birth	September 9th,1990
Educational Attainment	2013: Doctor of Medicine, Chulalongkorn University, Bangkok, Thailand (Second class Honors) 2019: Thai board of Radiation Oncology
Work Experiences	2019-2022 Staff Member of Division of Therapeutic Radiology and Oncology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Publications

1. **Jaruthien T**, Nantavithya C, Santisukwongchote S, Shuangshoti S, Techavichit P, Sosothikul D, Amornfa J, Shotelersuk K. Postoperative radiotherapy timing, molecular subgroups and treatment outcomes of Thai pediatric patients with medulloblastoma. PLoS One. 2023 Jan 17;18(1):e0271778. doi: 10.1371/journal.pone.0271778.

2. Saksornchai K, **Jaruthien T**, Nantavithya C, Shotelersuk K, Rojpornpradit P. Long-term results of hypofractionation with concomitant boost in patients with early breast cancer: A prospective study. PLoS One. 2021 Oct 7;16(10):e0258186. doi: 10.1371/journal.pone.0258186.

3. **Jaruthien T**, Kitpanit S, Kannarunimit D, Nantavithya C, Prayongrat A, Alisanant P, Saksornchai K, Amornwichet N, Raiyava T, Chakkabat C, Lertbutsayanukul C, Khorprasert C, Shotelersuk K. Flattening filter free stereotactic body radiation therapy for lung tumors: outcomes and predictive factors. Transl Cancer Res 2021;10(2):571-580. doi: 10.21037/tcr-20-3174

4. Khawcharoenporn T., Chuncharunee A., Maluangnon C., **Taweesakulvashra T**. and Tiamsak P. (2018). Active monotherapy and combination therapy for extensively drug-resistant Pseudomonas aeruginosa pneumonia. International Journal of Antimicrobial Agents, 52(6), pp.828-834.