

# A nomogram for predicting survival of nasopharyngeal carcinoma patients with metachronous metastasis

Zixun Zeng (MD)<sup>a</sup>, Lujun Shen (MD)<sup>b,c</sup>, Yue Wang (MD)<sup>b,c</sup>, Feng Shi (MD)<sup>b,c</sup>, Chen Chen (MD)<sup>c,d</sup>, Ming Wu (MD)<sup>a</sup>, Yutong Bai (MD)<sup>a</sup>, Changchuan Pan (MD)<sup>e</sup>, Yunfei Xia (MD)<sup>c,d</sup>, Peihong Wu (MD)<sup>b,c</sup>, Wang Li (MD)<sup>b,c,\*</sup>

## Abstract

Patients with metachronous metastatic nasopharyngeal carcinoma (NPC) differ significantly in survival outcomes. The aim of this study is to build a clinically practical nomogram incorporating known tumor prognostic factors to predict survival for metastatic NPC patients in epidemic areas.

A total of 860 patients with metachronous metastatic nasopharyngeal carcinoma were analyzed retrospectively. Variables assessed were age, gender, body mass index, Karnofsky Performance Status (KPS), Union for International Cancer Control (UICC) T and N stages, World Health Organization (WHO) histology type, serum lactate dehydrogenase (sLDH) level, serum Epstein–Barr virus (EBV) level, treatment modality, specific metastatic location (lung/liver/bone), number of metastatic location(s) (isolated vs multiple), and number of metastatic lesion(s) in metastatic location(s) (single vs multiple). The independent prognostic factors for overall survival (OS) by Cox-regression model were utilized to build the nomogram.

Independent prognostic factors for OS of metastatic NPC patients included age, UICC N stage, KPS, sLDH, number of metastatic locations, number of metastatic lesions, involvement of liver metastasis, and involvement of bone metastasis. Calibration of the final model suggested a c-index of 0.68 (95% confidence interval [CI], 0.65–0.69). Based on the total point (TP) by nomogram, we further subdivided the study cohort into 4 groups. Group 1 (TP < 320, 208 patients) had the lowest risk of dying. Discrimination was visualized by the differences in survival between these 4 groups (group 2/group 1: hazard ratio [HR] = 1.61, 95%CI: 1.24–2.09; group 3/group 1: HR = 2.20, 95%CI: 1.69–2.86; and group 4/group 1: HR = 3.66, 95%CI: 2.82–4.75).

The developed nomogram can help guide the prognostication of patients with metachronous metastatic NPC in epidemic areas.

**Abbreviations:** CT = chemotherapy, EBV = serum Epstein–Barr virus, KPS = Karnofsky Performance Status, LDH = lactate dehydrogenase, OS = overall survival, TP = total point, UICC = Union for International Cancer Control, WHO = World Health Organization.

**Keywords:** metastasis, nasopharyngeal carcinoma, nomogram, prognosis

Editor: Jianfeng Li.

ZZ and LS contributed equally to this work.

Conception/Design: ZZ, LS, and PW; Provision of study materials or patients: PW, Y-FX, and WL; Collection and/or assembly of data: ZZ, LS, JD, CP, SL, and YW; Data analysis and interpretation: ZZ, LS, JD, WS, MW, and YB; Manuscript writing: LS, ZZ, JD, SL, YW, AD, WS, MW, CP, Y-FX, and PW; and Final approval of manuscript: LS, ZZ, JD, SL, YW, AD, WS, MW, CP, Y-FX, PW, and WL.

The authors have no funding and conflicts of interest to disclose.

<sup>a</sup>Zhong Shan Medical School, Sun Yat-sen University, <sup>b</sup>Department of Medical Imaging and Interventional Radiology, Sun Yat-sen University Cancer Center, <sup>c</sup>Collaborative Innovation Center of Cancer Medicine, Sun Yat-sen University, <sup>d</sup>Department of Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou, <sup>e</sup>Department of Medical Oncology, Sichuan Cancer Hospital and Institute, Chengdu, People's Republic of China.

\*Correspondence: Wang Li, Department of Medical Imaging and Interventional Radiology, Sun Yat-sen University Cancer Center, Guangzhou 510060, , Guangdong, People's Republic of China (e-mail: liwang@susucc.org.cn).

Copyright © 2016 the Author(s). Published by Wolters Kluwer Health, Inc. All rights reserved.

This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Medicine (2016) 95:27(e4026)

Received: 9 September 2015 / Received in final form: 16 May 2016 / Accepted: 20 May 2016

<http://dx.doi.org/10.1097/MD.0000000000004026>

## 1. Introduction

Nasopharyngeal carcinoma (NPC) accounts for 80,000 new cases and 50,000 deaths annually, ranking 11th among all malignancies in China.<sup>[1]</sup> Past reports showed that metastasis to distant sites account for 50% of treatment failure for NPC,<sup>[2,3]</sup> while an increasing interest in the use of local therapy for metastases and a series of reports published showed that even long-term survival could be achieved for selective NPC patients with oligometastasis by combined systemic and local therapies.<sup>[4–7]</sup> As cancer metastasis covers a wide spectrum of different conditions,<sup>[8,9]</sup> it is attracting to explore the theoretical margin of the susceptible target patients worth aggressive management.

Patients presenting distant metastasis at the time of diagnosis of NPC are termed synchronous metastatic NPC patients, indicating stage IV. Other patients suffering distant metastasis over 6 months after radical therapy are termed metachronous metastatic NPC patients. To the best of our knowledge, there had been limited published reports on prognostic model of metachronous metastatic NPC patients. Due to the rarity of synchronous metastatic NPC patients, most published studies included both patients with metastases at diagnosis and subsequent after 6 months. However, compared with synchronous metastasis,

patients with metachronous metastasis were 1.7 times more prevalent,<sup>[10]</sup> underwent different treatment regimens, and had different survival rates, warranting a differentiated analysis.

Therefore, in this study, we aim to build a prognostic model for metachronous metastatic NPC patients predictive of overall survival (OS) after metastasis, and we further visualize it as nomogram for more friendly clinical practice.

## 2. Patients and method

### 2.1. Study population

We retrospectively reviewed 1648 NPC patients with distant metastasis treated at Sun Yat-sen University Cancer Center between January 1995 and December 2010. The inclusion criteria were as following: histologically confirmed primary NPC; distant metastases confirmed by histological evaluation, ultrasound, or chemotherapy (CT) of the abdomen during subsequent follow-up; and presence of complete pretreatment evaluation, including complete history, physical examination, hematology and biochemistry profiles, CT or magnetic resonance imaging scans of the head and neck regions, radiographs/CT scans of the chest, sonography/CT scans of the abdomen, and whole-body bone scan. The exclusion criteria were any of the following: presence of metastasis at diagnosis or presence of other malignancies, and refusal of treatment. The Hospital Ethics Committee in Sun Yat-sen University Cancer Center approved this study.

### 2.2. Treatment

All patients received multimodality treatment. A total of 439 (51.0%) patients received palliative chemotherapy as a systemic treatment after admission. The 1st-line regimen was nearly exclusively platinum-based, with cisplatin in combination with 1 or 2 of the following drugs: 5-fluorouracil, paclitaxel, gemcitabine, and bleomycin for 4 to 6 cycles. Treatment was discontinued by request of the patients or for intolerable drug toxicity; the median number of cycles was 4 (range 1–27). Other chemotherapy regimens included newer agents, such as gemcitabine and paclitaxel. Local therapies for distant metastasis consist of minimal invasive therapy, including trans-arterial chemoembolization, radiofrequency ablation, or both, radiotherapy, and surgery.

### 2.3. Study protocol

We retrospectively collected patients' demographic, clinical, and therapeutic characteristics, collecting data of metastasis (number of lesions in metastatic locations, number of metastatic locations, liver/lung/bone involvement, etc.) We assessed the effect of age, gender,<sup>[11]</sup> body mass index, and the Union of International Cancer Control (UICC) stage classification for T and N on metastatic survival. Metastatic OS was defined as the interval between the diagnosis of distant metastasis to the time of death or to the end of the study. Data from patients alive at the end of study (December 31st, 2010) were defined as censored. We verified survival status on August 31st, 2010 by direct telecommunication with the patient or family and checking the clinic attendance records.

### 2.4. Statistical methods

Statistical analyses were performed on IBM SPSS Statistics 20.0 (IBM Corp.) and R version 2.15.3 (R Foundation for Statistical

Computing, Vienna, Austria. ISBN 3–900051–07–0, 187 URL <http://www.R-project.org/>)

Survival was estimated with the Kaplan–Meier method and was compared by using the log-rank test. Multiple regression analysis was undertaken by using Cox proportional hazard models. Alpha was set at 0.05, and all tests were 2 tailed. Backward stepdown selection process was utilized for the selection of covariates for the final model. To maximize the predictive ability of the model, all variables in the multivariable model were used to develop a prognostic nomogram using the linear predictor method (by the package of rms in R). The performance of nomogram was measured by concordance index (c-index) by using rcorrp.cens package in Hmisc in R and calibration through comparing nomogram-predicted survival with observed Kaplan–Meier estimated survival probability.<sup>[12]</sup>

## 3. Results

### 3.1. Patient characteristics

A total of 1648 patients were sort out as metastasis population. A total of 252 patients were excluded due to lack of appropriate full data, 536 patients were excluded due to synchronous metastasis. The remaining 860 patients met all criteria were enrolled for our study.

Patient characteristics are described in Table 1. The median age was 44 (ranging from 11 to 80 years), 689 male patients (80.1%) compared with 171 female patients (19.9%). Histologically, most patients were World Health Organization (WHO) III type NPC (803, 93.4%); the others were WHO II (38, 4.4%) and WHO I (12, 1.4%). The most frequent involved locations for metastases were bone (492, 57.2%), lung (433, 50.3%), and liver (346, 40.2%); isolated organ metastases were bone (446, 51.9%), lung (398, 46.3%), and liver (289, 33.6%). Multiple lesions (768, 89.3%) were detected more than single lesion (92, 10.6%). Single organ involvement accounted for over half (439, 51.0%) patients.

### 3.2. Metastatic characteristics and survival

Overall, 510 patients (59.3%) died before last follow-up. The median follow-up time after the diagnosis of distant metastasis was 38 month. Median metastatic OS was 19 months (interquartile range [8–31] months), the 3- and 5-year OS rate of the study cohort were 20.7% and 6.3%, respectively.

On univariate analysis, age, body mass index, Karnofsky Performance Status (KPS), UICC N stage, serum lactate dehydrogenase (LDH) level, and metastasis characteristics (number of metastatic lesions, number of metastatic locations, liver metastasis, and bone metastasis) were identified as independent prognosticators for metastatic OS (Table 2).

On multivariable analysis using backward method, age, KPS, UICC N stage, serum LDH level, and metastasis characteristics (number of metastatic lesions, number of metastatic sites, primary liver metastasis, and primary bone metastasis) remain significant (Table 2).

### 3.3. Prognostic nomogram for OS

We built a Cox regression model incorporating all independent prognostic factors for metastatic OS based on multivariable analysis, and further visualized it into a nomogram as shown in Fig. 1. The C-index for metastatic OS prediction was 0.68 (95% confidence interval [CI], 0.65–0.69). The calibration plot for the

**Table 1**

**Basic characteristics: demographic clinicopathologic characteristics of patients with metachronous metastatic nasopharyngeal carcinoma in epidemic area.**

Demographic or characteristic		No.	%
Gender	Male	689	80.12
	Female	171	19.88
Age	Median	44	
	Range	69	
BMI	<18.5	206	23.95
	18.5–23	468	54.42
	>23	184	21.40
WHO histology	I	803	93.37
	II	38	4.42
	III	12	1.40
AJCC T	T1	49	5.70
	T2	276	32.09
	T3	324	37.67
	T4	197	22.91
AJCC N	N0	139	16.16
	N1	341	39.65
	N2	283	32.91
	N3	97	11.28
KPS	<80	73	8.49
	≥80	787	91.51
CT		439	51.05
EBV DNA (copies/mL)	<1000	58	6.74
	≥1000	199	23.14
sLDH (U/mL)	<245	360	41.86
	≥245	234	27.21
Primary involvement of metastasis	Lung	398	46.28
	Liver	289	33.60
	Bone	446	51.86
Relapse with metastasis		172	20.00
Locations of metastasis	1	439	51.05
	2	280	32.56
	3	112	13.02
	4	22	2.56
	5	7	0.81
Sites of metastasis	Single	92	10.70
	Multiple	768	89.30
Lung metastasis		433	50.35
Liver metastasis		346	40.23
Bony metastasis		492	57.21
OS (month)	Median	18.8	
	Range	219.5	
	<12	284	33.02
	[12,36]	399	46.40
	[36,60]	123	14.30
Death	[60,120]	54	6.28
		510	59.30

BMI=body mass index, CT=chemotherapy, EBV=serum Epstein-Barr virus, KPS=Karnofsky Performance Status, OS=overall survival, sLDH=serum lactate dehydrogenase, WHO=World Health Organization.

probability of survival at 3 or 5 year after surgery showed an optimal agreement between the prediction by nomogram and actual observation in Fig. 2.

In addition, we subdivided the study cohort into 4 groups based on the linear predictor of nomogram and we plotted Kaplan-Meier curves (Fig. 3). Group 1 (total points [TPs] <320, 208 patients) had the highest probability of survival as 38.3% for 3 years and 12.9% for 5 years, respectively, followed by group 2 (320 ≤ TP < 360, 226 patients; group 2/group 1, hazard ratio [HR]=1.61, 95%CI: 1.24–2.09,  $P < 0.01$ ) as 24.2% and 8.1%

**Table 2**

**Univariable and multivariable analysis.**

Variable	HR	P
Univariate analysis		
Gender	Female/male	0.41 0.52
Age	≥44 years/<44 years	3.05 0.08
KPS	≥80/<80	32.77 <0.01
BMI	≥18.5/<18.5	4.38 0.04
AJCC T category	T3–4/T1–2	4.00 0.05
AJCC N category	N2–3/N0–1	6.92 0.01
Locations of metastasis	Multiple/isolated	60.87 <0.01
Sites of metastasis	Multiple/single	41.84 <0.01
Primary lung metastasis		0.08 0.78
Primary liver metastasis		22.23 <0.01
Primary bony metastasis		20.21 <0.01
WHO histology	I	Ref
	II	0.02 0.89
	III	19.91 <0.01
sLDH (U/mL)	≥245/<245	47.38 <0.01
EBV DNA (copies/mL)	<1000/≥1000	1.33 0.25
Local-regional disease status	Uncontrolled/controlled	0.86 0.35
Relapse with metastasis	1.46	0.23
CT		0.53 0.47
Multivariable analysis		
Age	≥44 years/<44 years	4.21 0.04
KPS	≥80/<80	6.88 <0.01
BMI	≥18.5/<18.5	1.07 0.30
AJCC N category	N2–3/N0–1	2.95 0.09
Primary liver metastasis		2.63 0.11
Primary bony metastasis		2.77 0.10
sLDH (U/mL)	≥245/<245	20.62 <0.01
Locations of metastasis	Multiple/isolated	5.01 0.03
Sites of metastasis	Multiple/single	13.88 <0.01

BMI=body mass index, CT=chemotherapy, EBV=serum Epstein-Barr virus, HR=hazard ratio, KPS=Karnofsky Performance Status, Ref=reference, sLDH=serum lactate dehydrogenase, WHO=World Health Organization.

for 3 and 5 years, respectively, group 3 (360 ≤ TP < 410, 202 patients; group 3/group 1, HR=2.20, 95%CI: 1.69–2.86,  $P < 0.01$ ) as 16.1% and 3.7% for 3 and 5 years, respectively, and group 4 (TP ≥ 410, 224 patients; group 4/group 1, HR=3.66, 95%CI: 2.82–4.75,  $P < 0.01$ ) as 5.1% and 4.7% for 3 and 5 years, respectively. The discrimination was showed by the differences in survival between these 4 groups (Table 3).

#### 4. Discussion

We developed a prognostic model predictive of 3-year and 5-year OS after subsequent metastases of patients with primary NPC. Our model was built on a metachronous metastatic cohort of 860 eligible NPC patients. In accordance with previous literatures, we found 8 independent predictors associated with metastatic OS of study cohort. Furthermore, the Cox regression models were visualized in nomogram, which might facilitate individualized prediction for future consultation.

A few prognostic models were designed for metastatic NPC patients in previous studies. Ong et al<sup>[13]</sup> in 2003 built a prognostic index score (PIS) for metastatic NPC based on 6 independent negative factors: liver metastasis, lung metastasis, anaemia, poor PS, distant metastasis at initial diagnosis, and a disease-free interval (DFI) of <6 months. Khanfir et al<sup>[14]</sup> in 2007 found out that poor performance status (PS), multiple metastatic sites, and prior chemotherapy were independently significant

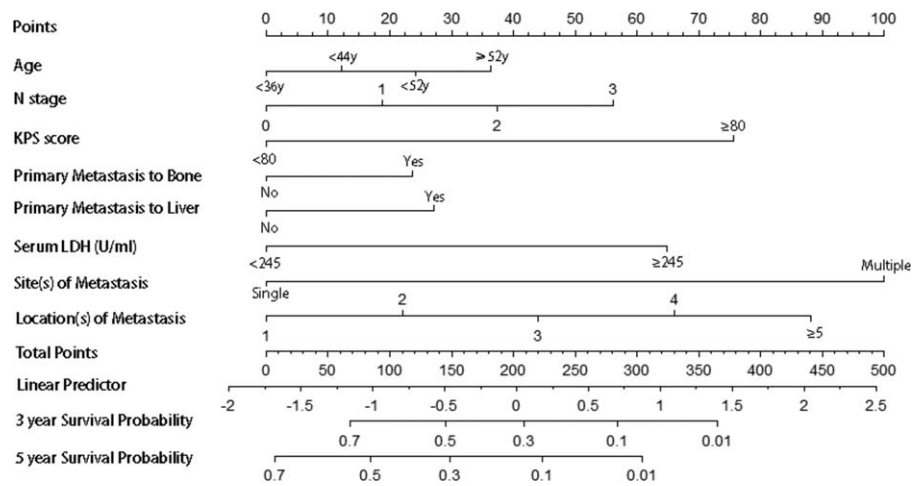


Figure 1. Metastatic OS nomogram for metachronous metastatic NPC patients. NCP= nasopharyngeal carcinoma, OS= overall survival.

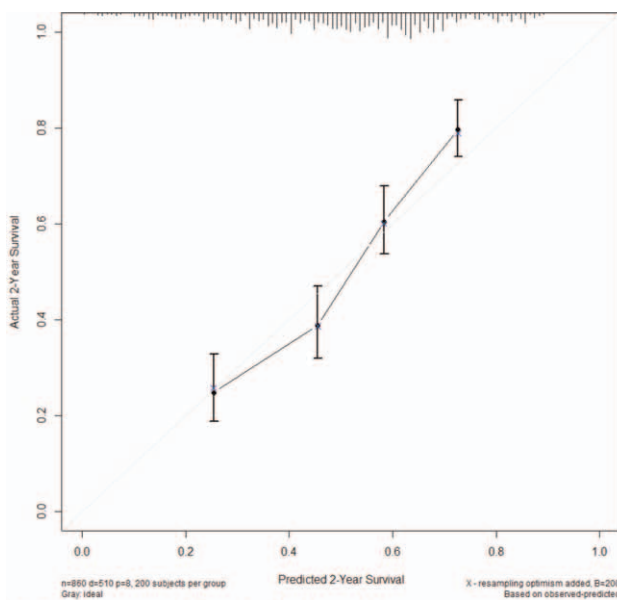
negative prognostic factors in multivariable analysis for metastatic NPC. Furthermore, Jin et al<sup>[15]</sup> in 2012 developed a prognostic score model (PSM) incorporating some biomarkers, based on PS, age, hemoglobin level, LDH level, ALP level, and serum Epstein–Barr virus (EBV) DNA level for metastatic NPC in epidemic area. Kumar et al<sup>[16]</sup> in 2014 evaluated scoring system and prognostic factors in patients with spinal metastases from NPC, finding out that general condition ( $P < 0.01$ ), visceral metastases ( $P < 0.01$ ), and vertebral metastases ( $P < 0.01$ ) showed significant association with survival.

NPC patients with methchronous metastatic differ from that of synchronous in the heterogeneity of survival. Our previous study on patients with synchronous metastatic<sup>[7]</sup> NPC revealed that the number of metastatic lesions and liver involvement are the most important prognostic factors. Screening out a subgroup of NPC patients with synchronous single metastases in nonhepatic

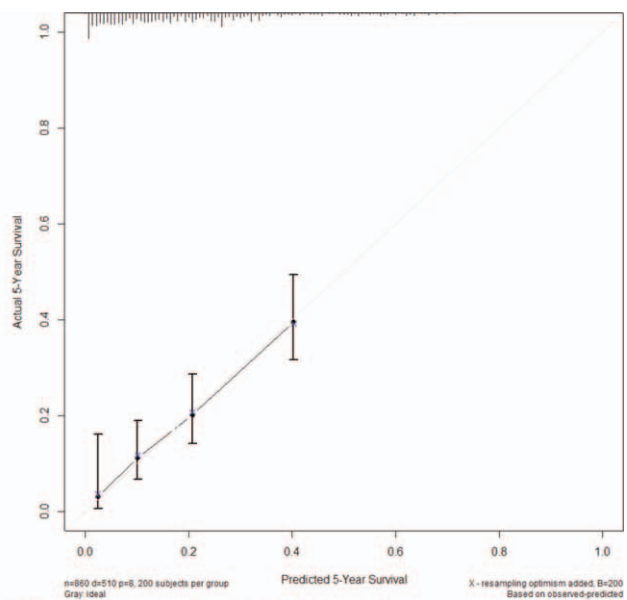
location might benefit more from aggressive treatment. However, situations differ for patients with metachronous metastasis, for most of whom the aggressive treatment might benefit and more treatment options might be available without concerning of primary lesion, and as a result survival seemed more heterogeneous. We felt it valuable to discuss the heterogeneity of survival for the metachrous metastatic NPC patients.

Our model incorporated 8 independent predictors based on a metachronous cohort, covering general and geographic conditions of patient (age, KPS), anatomical characteristics from TNM staging (N), literature-reported biochemical markers (sLDH),<sup>[17,18]</sup> and metastatic characteristics (primary metastasis to bone, primary metastasis to liver, multiple lesions, and number of locations).

Nomogram visualizes Cox regression model and facilitates individualized risk prediction in a variety of cancers.<sup>[19–21]</sup> A



A Calibration curve at 2 years in the primary cohort.



B Calibration curve at 5 years in the primary cohort.

Figure 2. The calibration curves for predicting patient survival at 2, 3, and 5 years in the primary cohort.

**Table 3****Cox regression analysis for groups based on the model.**

Group	OS Median	3-years (%)	5-years (%)	Sig.	HR	95%CI for HR	
						Lower	Upper
1	45.57	38.3	12.9		–	–	–
2	26.23	24.2	8.1	<0.01	1.61	1.24	2.09
3	22.40	16.1	3.7	<0.01	2.20	1.69	2.86
4	16.97	5.1	4.7	<0.01	3.66	2.82	4.75

Groups were divided by cutoff values of TPs cumulated from nomogram we designed. (TP ≤ 320, 320 < TP ≤ 360, 360 < TP ≤ 410, TP > 410) (group 1, 2, 3, and 4 with 208, 226, 202, and 224 patients, respectively.) Group 1 had the lowest risk of dying. CI=confidence interval, HR=hazard ratio, OS=overall survival, TP=total point.

rapid computation, precise assessment, and pellucid prognosis might facilitate better interpretation of disease and clinical decision-making.

However, there were limited studies on nomogram designed for metachronous metastatic NPC patients. Liang W et al<sup>[22]</sup> in 2014 developed a nomogram to predict OS in 1520 nonmetastatic NPC patients. And Cho et al<sup>[23]</sup> in 2015 developed and external validated nomogram for OS (age, performance status, smoking status, and N classification) in both synchronous and metachronous metastatic patients. Whereas on metastatic OS, we observed that metastasis related predictors – number of metastatic locations and number of lesions of locations – impact more, compared with age, UICC N stage, and KPS. Smoking status<sup>[24–26]</sup> was proved of prognostic impact on OS for NPC patients, especially for male patients. Whereas, smoking was observed of weaker impact on OS, compared with other predictors such as serum LDH, age, N stage, etc. and was finally ruled out in multivariable analysis.<sup>[27–29]</sup>

Although based on prospective studies, nomogram might present perspective value in proposing treatment protocol. For patients with higher TP computed from nomogram intergrating all known vital factors for prognosis, aggressive treatment might worth commencing. However, for low TP patients, palliative treatment might benefit more. Thus, we believe that the utilizing

of powerful predictors confirmed in previous studies and also observed in our study might help approach a little bit further for precise prediction.

Recent studies reported similar findings that EBV DNA level was a powerful prognosticator for OS, while in our study EBV DNA was ruled out based on the results of multivariate analysis.<sup>[30–32]</sup> As the PCR-based techniques in EBV DNA assay vary in sensitivities, even using the same primer and sets of experimental conditions, great discrepancies in the median concentration among different studies. The cut-off varies widely in different study groups and different studies from the same study group as well.<sup>[33,34]</sup> According to the time span of our study design, we failed to collect full comparable data of EBV DNA copies in our study cohort. The ongoing international effort to harmonize the assay may facilitate future exploration.

Another concern of our model could be that the amount of residual tumor after (CT) is not an independent prognostic factor, while in previous studies it is believed related to tumor biology and survival of patients.<sup>[35]</sup> Nevertheless, there might be confounding factors. Aside from amount of residual tumor after CT, the location, extend, biological behavior of the residual tumor, as well as the general condition of the patients, the preferences and experiences of doctors and the feasibility of treatment might affect the final protocol and OS.<sup>[36,37]</sup> Functioning as a “gray box,” for a prediction model this issue does not matter because our goal is to accurately predict survival rather than prove a causal relationship between survival and residual tumor. Predicting survival is perfectly possible when residual tumor functions as a surrogate predictor instead of an independent predictor.

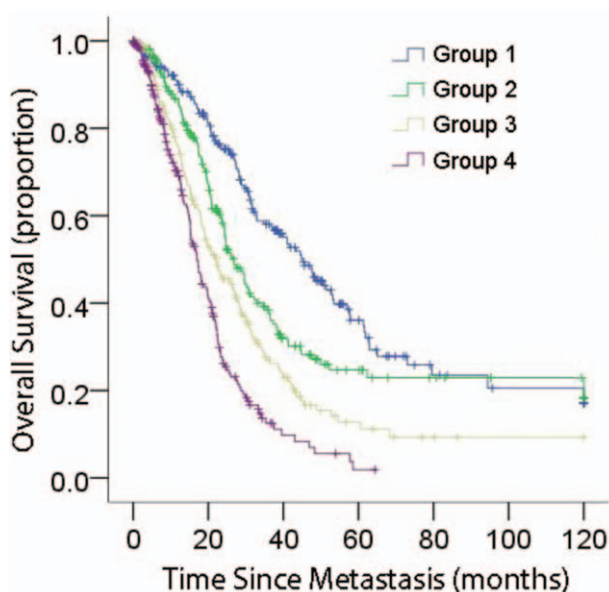
There are several limitations of this study. First the nomogram was developed based on a retrospective cohort in a regionally based population in a single institute. Second, the heterogeneity in treatment protocol for metachronous metastasis patients might bring confounding effects. Finally, most patients with metastasis were diagnosed by imaging modalities, while limited patients had pathologically proofs, which could be potential source of bias. Therefore, prospective studies and external validation in multi-institute are needed in the future.

## 5. Conclusions

We built a nomogram predictive of OS after metastasis based on the independent prognostic factors of OS from a metachronous metastatic cohort. Multiinstitutional external validation of the nomogram might be needed in the future.

## References

- [1] Cao SM, Simons MJ, Qian CN. The prevalence and prevention of nasopharyngeal carcinoma in China. *Chin J Cancer* 2011;30:114–9.



**Figure 3.** Kaplan–Meier curves for all four groups based on the linear predictor from nomogram.

- [2] Chiesa F, De Paoli F. Distant metastases from nasopharyngeal cancer. *ORL J Otorhinolaryngol Relat Spec* 2001;63:214–6.
- [3] Liu MT, Hsieh CY, Chang TH, et al. Prognostic factors affecting the outcome of nasopharyngeal carcinoma. *Jpn J Clin Oncol* 2003;33:501–8.
- [4] Pan C, Wu P, Yu J, et al. CT-guided radiofrequency ablation prolonged metastatic survival in patients with liver metastases from nasopharyngeal carcinoma. *Int J Hyperthermia* 2011;27:549–54.
- [5] Jin Y, Cai YC, Cao Y, et al. Radiofrequency ablation combined with systemic chemotherapy in nasopharyngeal carcinoma liver metastases improves response to treatment and survival outcomes. *J Surg Oncol* 2012;106:322–6.
- [6] Pan CC, Wu PH, Yu JR, et al. Comparative survival analysis in patients with pulmonary metastases from nasopharyngeal carcinoma treated with radiofrequency ablation. *Eur J Radiol* 2012;81:e473–7.
- [7] Shen L, Dong J, Li S, et al. M1 stage subdivision and treatment outcome of patients with bone-only metastasis of nasopharyngeal carcinoma. *Oncologist* 2015;20:291–8.
- [8] Hellman S. Karnofsky Memorial Lecture. Natural history of small breast cancers. *J Clin Oncol* 1994;12:2229–34.
- [9] Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol* 1995;13:8–10.
- [10] Chen MY, Jiang R, Guo L, et al. Locoregional radiotherapy in patients with distant metastases of nasopharyngeal carcinoma at diagnosis. *Chin J Cancer* 2013;32:604–13.
- [11] OuYang PY, Zhang LN, Lan XW, et al. The significant survival advantage of female sex in nasopharyngeal carcinoma: a propensity-matched analysis. *Br J Cancer* 2015;112:1554–61.
- [12] Iasonos A, Schrag D, Raj GV, et al. How to build and interpret a nomogram for cancer prognosis. *J Clin Oncol* 2008;26:1364–70.
- [13] Ong YK, Heng DM, Chung B, et al. Design of a prognostic index score for metastatic nasopharyngeal carcinoma. *Eur J Cancer* 2003;39:1535–41.
- [14] Khanfir A, Frikha M, Ghorbel A, et al. Prognostic factors in metastatic nasopharyngeal carcinoma. *Cancer Radiother* 2007;11:461–4.
- [15] Jin Y, Cai XY, Cai YC, et al. To build a prognostic score model containing indispensable tumour markers for metastatic nasopharyngeal carcinoma in an epidemic area. *Eur J Cancer* 2012;48:882–8.
- [16] Kumar N, Tan JJ, Zaw AS, et al. Evaluation of scoring systems and prognostic factors in patients with spinal metastases from nasopharyngeal carcinoma. *Spine J* 2014;14:2946–53.
- [17] Zhou GQ, Tang LL, Mao YP, et al. Baseline serum lactate dehydrogenase levels for patients treated with intensity-modulated radiotherapy for nasopharyngeal carcinoma: a predictor of poor prognosis and subsequent liver metastasis. *Int J Radiat Oncol Biol Phys* 2012;82:e359–65.
- [18] Wan XB, Wei L, Li H, et al. High pretreatment serum lactate dehydrogenase level correlates with disease relapse and predicts an inferior outcome in locally advanced nasopharyngeal carcinoma. *Eur J Cancer* 2013;49:2356–64.
- [19] Kim SH, Shin KH, Kim HY, et al. Postoperative nomogram to predict the probability of metastasis in Enneking stage IIB extremity osteosarcoma. *BMC Cancer* 2014;14:666.
- [20] Lee CK, Goldstein D, Gibbs E, et al. Development and validation of prognostic nomograms for metastatic gastrointestinal stromal tumour treated with imatinib. *Eur J Cancer* 2015;51:852–60.
- [21] Galsky MD, Moshier E, Krege S, et al. Nomogram for predicting survival in patients with unresectable and/or metastatic urothelial cancer who are treated with cisplatin-based chemotherapy. *Cancer* 2013;119:3012–9.
- [22] Liang W, Shen G, Wu X, et al. Development and validation of a nomogram for predicting overall survival of patients with non-metastatic nasopharyngeal carcinoma after curative therapy. *Ann Oncol* 2014;25:iv351.
- [23] Cho JK, Lee GJ, Yi KI, et al. Development and external validation of nomograms predictive of response to radiation therapy and overall survival in nasopharyngeal cancer patients. *Eur J Cancer* 2015;51:1303–11.
- [24] Ouyang PY, Su Z, Mao YP, et al. Prognostic impact of cigarette smoking on the survival of patients with established nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev* 2013;22:2285–94.
- [25] Shen GP, Xu FH, He F, et al. Pretreatment lifestyle behaviors as survival predictors for patients with nasopharyngeal carcinoma. *PLoS One* 2012;7:e36515.
- [26] Chen C, Shen LJ, Li BF, et al. Smoking is a poor prognostic factor for male nasopharyngeal carcinoma treated with radiotherapy. *Radiother Oncol* 2014;110:409–15.
- [27] Huang PY, Zeng Q, Cao KJ, et al. Ten-year outcomes of a randomised trial for locoregionally advanced nasopharyngeal carcinoma: A single-institution experience from an endemic area. *Eur J Cancer* 2015;51:1760–70.
- [28] Wang R, Tan Y, Wang X, et al. Prognoses and long-term outcomes of nasopharyngeal carcinoma in Han and Uyghur patients treated with intensity-modulated radiotherapy in the Xinjiang Autonomous Region of China. *PLoS One* 2014;9:e111145.
- [29] Tang LQ, Hu DP, Chen QY, et al. Elevated high-sensitivity C-reactive protein levels predict decreased survival for nasopharyngeal carcinoma patients in the intensity-modulated radiotherapy era. *PLoS One* 2015;10:e0122965.
- [30] Leung SF, Zee B, Ma BB, et al. Plasma Epstein-Barr viral deoxyribonucleic acid quantitation complements tumor-node-metastasis staging prognostication in nasopharyngeal carcinoma. *J Clin Oncol* 2006;24:5414–8.
- [31] Lin JC, Wang WY, Chen KY, et al. Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. *N Engl J Med* 2004;350:2461–70.
- [32] Chai SJ, Pua KC, Saleh A, et al. Clinical significance of plasma Epstein-Barr Virus DNA loads in a large cohort of Malaysian patients with nasopharyngeal carcinoma. *J Clin Virol* 2012;55:34–9.
- [33] Lin JC, Wang WY, Liang WM, et al. Long-term prognostic effects of plasma Epstein-Barr virus DNA by minor groove binder-probe real-time quantitative PCR on nasopharyngeal carcinoma patients receiving concurrent chemoradiotherapy. *Int J Radiat Oncol Biol Phys* 2007;68:1342–8.
- [34] Le QT, Zhang Q, Cao H, et al. An international collaboration to harmonize the quantitative plasma Epstein-Barr virus DNA assay for future biomarker-guided trials in nasopharyngeal carcinoma. *Clin Cancer Res* 2013;19:2208–15.
- [35] Yu KH, Leung SF, Tung SY, et al. Survival outcome of patients with nasopharyngeal carcinoma with first local failure: a study by the Hong Kong Nasopharyngeal Carcinoma Study Group. *Head Neck* 2005;27:397–405.
- [36] Wei WI, Kwong DL. Recurrent nasopharyngeal carcinoma: surgical salvage vs. additional chemoradiation. *Curr Opin Otolaryngol Head Neck Surg* 2011;19:82–6.
- [37] Stoker SD, van Diessen JN, de Boer JP, et al. Current treatment options for local residual nasopharyngeal carcinoma. *Curr Treat Options Oncol* 2013;14:475–91.