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ORIGINAL ARTICLE

Proposal of a clinical typing system and generation of a prognostic model in patients with nasopharyngeal carcinoma from Southern China

Peng Sun[1,2*], Cui Chen[3*], Xin-Lin Chen[4], Yi-Kan Cheng[1,5], Lei Zeng[1,5], Zhi-Jian Zeng[6], Li-Zhi Liu[1,7], Yong Su[1,5], Mo-Fa Gu[1,5]

[1]State Key Laboratory of Oncology in South China, Guangzhou, Guangdong Province; [2]Department of Medical Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, Guangdong Province; [3]Department of Oncology, the First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, Guangdong Province; [4]Department of Preventive Medicine and Biostatistics, Basic Medical College, Guangzhou University of Chinese Medicine, Guangzhou, Guangdong Province; [5]Department of Radiation Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, Guangdong Province; [6]Department of Oncology, the First People's Hospital of Zhaoqing City, Zhaoqing, Guangdong Province; [7]Imaging Diagnosis and Interventional Center, Sun Yat-Sen University Cancer Center, Guangzhou, Guangdong Province, P. R. China

** These authors contributed equally to this work.*

Summary

Purpose: *To propose a novel clinical typing classification focusing on the distinct progression patterns of nasopharyngeal carcinoma (NPC), to supplement our knowledge of the clinical-biological behavior, to provide useful knowledge for treatment planning, and to contribute to basic research in NPC.*

Methods: *632 consecutive patients were retrospectively reviewed and analyzed according to the novel typing system. We considered that NPC can be divided into 5 types as follows: limited (L), ascending (A), descending (D) ascending-descending (mixed) (AD), and distant metastasis types (M). The distribution of these clinical types, their association with Epstein-Barr virus (EBV) serology and prognostic value were explored.*

Results: *55 (8.70%), 59 (9.34%), 177 (28.01%), 321 (50.79%) and 20 (3.16%) patients were classified as Type L, A, D, AD and M, respectively. EBV (VCA)-IgA titers, EBV early antigen (EA)-IgA serum titers, and capsid antigen lg(EBV DNA) were positively associated with the clinical typing ($p<0.05$). The 3-year overall survival (OS) rates for Types L, A, D, AD and M were 100, 100, 95.10, 88.20 and 59.30%, respectively ($p<0.001$). A prognostic model was constructed based on pretreatment lg (EBV DNA) and clinical type, which were independent predictors of OS (multivariate Cox proportional model). The prognostic model stratified patients into 4 risk subgroups. The 3-year OS rates of the low, intermediate, high and extremely high risk groups were 99.5, 90.0, 85.5 and 53.2%, respectively ($p<0.001$). Compared with the low-risk group, the risk of death was 4.96, 8.75 and 35.9 in the intermediate, high and extremely high risk groups, respectively ($p<0.001$). The model also predicted OS independently of TNM classification.*

Conclusion: *This novel clinical typing system and prognostic model can supplement TNM classification, and may help design novel treatment strategies, evaluate risk stratification and investigate the varied biological characteristics of NPC.*

Key words: *clinical typing, Epstein-Barr virus, nasopharyngeal carcinoma, prognostic model*

Introduction

NPC is a unique head and neck malignancy with a distinct geographic distribution [1-3]. An accurate clinical classification system which can effectively predict prognosis and help to plan treatment protocols is crucial for NPC.

The tumor-node-metastasis (TNM) staging system, published by the American Joint Committee for Cancer (AJCC) and International Union

Correspondence to: Peng Sun, MD. 651st Dongfeng Road East, Department of Medical Oncology, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangzhou 510060, P. R. China. Tel/Fax: +86 020 87343765, E-mail: sunp@sysucc.org.cn, mofagu@126.com
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Against Cancer (UICC), is the most widely used prognostic system in NPC [4]. Prior to development of the TNM staging system, a number of other clinical typing systems had been proposed by colleagues working in areas where NPC is endemic; these staging systems focused on the natural characteristics of tumor extension and invasion in patients with NPC [5]. In the 1960s, Xie et al. [6] suggested a clinical typing system, called the Zhi-guang Xie typing system, to categorize patients with advanced stage NPC into 3 subtypes: the ascending type (A type), descending type (D type), and mixed type (AD type). Ho et al. [5] proposed another clinical typing model, dividing patients with NPC into a local invasive type, distant metastasis type, and mixed type. These clinical typing methods were based on a basic understanding of the characteristics of the natural pattern of progression in NPC, and demonstrated both clinical utility and prognostic ability [7].

As radiation technology has recently undergone dramatic development, it may be of great value to re-explore typing systems based on the characteristics of natural disease progression in patients with NPC at the present time. Therefore, we re-introduced the concept of the Zhi-guang Xie typing system, and established a novel clinical typing system which focuses on the pattern of local and nodal involvement. We suggest that NPC can be divided into 5 types, as follows: (1) limited type (L type), which is confined to the nasopharynx or extends to the oropharynx and/or nasal cavity without parapharyngeal extension, or tumors with parapharyngeal extension but without nodal involvement; (2) ascending type (A type): tumor spreading beyond the space defined by L type without nodal involvement; (3) descending type (D type): tumor located within the space defined by L type with nodal involvement; (4) ascending-descending mixed type (AD type): tumor spreading beyond the space defined by L type with nodal involvement; and (5) distant metastasis type (M type), which includes all patients with distant metastasis.

In this study, we determined the proportional distribution of these 5 types in a consecutive cohort of patients with NPC who were treated at Sun Yat-Sen University Cancer. As EBV serology plays an important role in the development of NPC [8], we also investigated whether the clinical typing system correlated with EBV sero-status. In addition, we investigated whether the clinical typing system had prognostic value. The objectives of this study were to supplement our knowledge of the clinical-biological behavior of NPC, to provide useful knowledge for treatment planning, and to contribute to basic research in NPC.

Methods

Patients

Six hundred and thirty-two patients attending the Sun Yat-Sen University Cancer Center who were newly diagnosed with NPC were recruited for this study from January, 2008 to December 2009. All of the patients had undergone a complete pretreatment evaluation. The patient medical records and imaging results were retrospectively analyzed. Two radiologists independently re-defined the patient TNM stages and defined the clinical types. The TNM classification for each patient was determined according to the 7th edition of the AJCC/UICC staging system for NPC. The blood samples used for EBV biomarker testing were collected within the week before treatment began.

Serologic testing of EBV antibodies and measurement of plasma EBV DNA load

The serum antibody titers of VCA-IgA and EBV early EA-IgA were determined using enzyme-linked immunoadsorbent assay methods. Measurement of plasma EBV DNA load was performed at baseline by quantitative real-time PCR assay [9].

Statistics

Statistical analysis was performed using the SPSS13.0 package. The chi-square and Fisher's exact tests were used to analyze the differences in the proportions of EBV biomarker-positive cases in patients with different clinical types; the logarithm10 (EBV DNA) values were calculated in this study to overcome bias due to the gaps in the EBV DNA concentrations of the patients. The serum titers for VCA-IgA and EA-IgA were recorded as the geometric mean titer (GMT) and interquartile range (IQ range). The correlation between EBV-related biomarkers (VCA-IgA, EA-IgA and EBV DNA), and clinical typing classification was analyzed using the Kruskal-Wallis rank-sum test. Receiver operating characteristic (ROC) curve analysis was performed to select pretreatment logarithm10 (EBV DNA) cutoff values with respect to OS. OS was calculated as the time from diagnosis to last follow up or death. Survival differences were determined by Kaplan-Meier analysis and the log-rank test. Cox proportional hazards model was performed to identify independent prognostic factors by multivariate analysis. All statistical tests were two-sided, and a p value less than 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 632 patients with NPC were includ-

ed in this study, with a significant predominance of males (459/632; 72.63%). The median age at initial diagnosis was 44 years (range 9-89), with no significant difference in age at initial diagnosis for the different clinical types. The majority of cases were WHO pathological type III (577/632; 91.30%). According to the clinical typing classification, the proportion of patients with L, A, D, AD and M types was 8.70% (55/632), 9.34% (59/632), 28.01% (177/632), 50.79% (321/632) and 3.16% (20/632), respectively. No significant imbalances were found in the patient distribution of any clinical type in terms of gender, age or histological grade (Table 1).

Relationship between EBV-related biomarkers and clinical type

VCA-IgA was detected in the serum of 598 patients (94.6%), and serum EA-IgA and plasma EBV DNA were detected in 75.8% and 67.2% of the patients, respectively. The GMTs for serum VCA-IgA and serum EA-IgA in the entire cohort were 1:221.90 and 1:33.95, respectively. The plasma EBV DNA load ranged from 0 to 1.36×10^9 copies/ml in the cohort of 632 NPC patients, with a median of 1530 copies/ml.

The rates of positivity for VCA-IgA and EA-IgA varied significantly between the different clinical types, with AD type being the highest (x^2, $p<0.05$). The proportion of EBV DNA-positive cases increased gradually with the clinical type ($p<0.001$), with L type having the lowest and M type having the highest proportion of EBV DNA-positive cases (Table 2).

The GMTs for serum VCA-IgA and EA-IgA increased significantly from L type to AD type (VCA-IgA/EA-IgA:1:130.71/1:22.45 in L type, 1:261.19/1:40.38 in AD type; both $p<0.05$; Figure 1A). Additionally, the median lg (EBV DNA) increased significantly from L type [0 lg (copies/ml)] to M type [4.19 lg (copies/ml); $p<0.001$; Figure 1B and Table 2].

The proportion of EBV triple-positive cases, and the mean number of positive EBV-related biomarkers varied significantly in patients with different clinical types, with both increasing gradually from L type to M type ($p<0.001$ for both ; Table 2).

Survival analyses by clinical type and pretreatment EBV DNA

After a median follow up time of 40 months, the 3-year OS rate for the entire cohort was 91.0%. The 3-year OS rates for L, A, D, AD and M types were 100, 100, 95.10, 88.20 and 59.30%, respectively (log-rank, $p<0.001$; Figure 2A).

We constructed ROC curves for death events and censors to identify the impact of the pretreatment lg (EBV DNA) load on the survival of patients with NPC, and selected 3.56 lg (copies/ml) as the cutoff point for subsequent analysis (Figure 3). There were 364 patients in the low EBV group and 268 patients in the high EBV group. The 3-year OS rates for the low EBV group and

Table 1. Clinicopathological characteristics of the 632 patients with nasopharyngeal carcinoma by clinical type

Characteristics	*L type (N=55) N (%)*	*A type (N=59) N (%)*	*D type (N=177) N (%)*	*AD type (N=321) N (%)*	*M type (N=20) N (%)*	*p-value*
Age (years)						0.172
Median	43	50	44	45	44	
Range	26-68	21-76	12-80	9-89	22-73	
Gender						0.097
Male (N=459)	40 (72.7)	50 (84.7)	133 (75.1)	221 (68.8)	15 (75)	
Female (N=173)	15 (27.3)	9 (15.3)	44 (24.9)	100 (31.2)	5 (25)	
WHO pathological type						0.072
I (N=1)	0	0	0	1(0.3)	0	
II (N=54)	9 (16.4)	7 (11.9)	13 (7.3)	23 (7.2)	2 (10)	
III (N=577)	46 (83.6)	52 (88.1)	164 (92.7)	297 (92.5)	18 (90)	
AJCC/UICC stage						<0.001
I (N=30)	30 (54.5)	0	0	0	0	
II (N=121)	25 (45.5)	0	96 (54.2)	0	0	
III (N=341)	0	51 (86.4)	62 (35.0)	228 (71.0)	0	
IV (N=140)	0	8 (13.6)	19 (10.8)	93 (29.0)	20 (100)	

L:limited type, A:ascending type, D:descending type, AD:ascending-descending type, M:distant metastasis type

Table 2. Serum EBV EA-IgA and VCA-IgA status and plasma EBV DNA load in 632 patients with nasopharyngeal carcinoma by clinical type

EBV biomarker	*Clinical subtype*					*p-value*
	L *N (%)*	*A* *N (%)*	*D* *N (%)*	*AD* *N (%)*	*M* *N (%)*	
VCA-IgA						0.001
Positive	48 (87.3)	51 (86.4)	169 (95.5)	312 (97.2)	18 (90.0)	
Negative	7 (12.7)	8 (13.6)	8 (4.5)	9 (2.8)	2 (10)	
GMT	130.71	178.38	206.82	261.19	193.97	<0.001
IQ range (lg)	40-160	40-320	80-320	160-640	80-320	
EA-IgA						
Positive	30 (54.5)	36 (61.0)	133 (75.1)	265 (82.6)	15 (75.0)	<0.001
Negative	25 (45.0)	23 (39.0)	44 (24.9)	56 (17.4)	5 (25.0)	
GMT	22.45	25.20	30.03	40.38	21.94	<0.001
IQ range	0-20	0-40	5-40	10-80	2.5-35	
EBV DNA						
Positive	16 (29.1)	26 (44.1)	113 (63.8)	250 (77.9)	20 (100)	<0.001
Negative	39 (70.9)	33 (55.9)	64 (26.1)	71 (22.1)	0	
Median (lg)	0	0	2.95	3.59	4.09	<0.001
IQ range (lg)	0-1.95	0-3.71	0-4.23	2.20-4.49	3.41-5.53	
No. of positive EBV biomarkers						
0	3 (5.5)	4 (6.8)	4 (2.3)	4 (1.2)	0	
1	18 (32.7)	15 (25.4)	23 (13.0)	26 (8.1)	2 (10)	<0.001
2	26 (47.3)	22 (37.3)	58 (32.8)	72 (22.4)	3 (15)	
3	8 (14.5)	18 (30.5)	92 (51.9)	219 (68.3)	15 (75)	
Mean	1.71	1.92	2.34	2.58	2.65	<0.001

GMT: geometric mean titer, IQ: interquartile range, lg: immunoglobulin, VCA-IgA: virus capsid antigen, EA: early antigen, EBV: Epstein-Barr virus. For other abbreviations see footnote of Table 1.

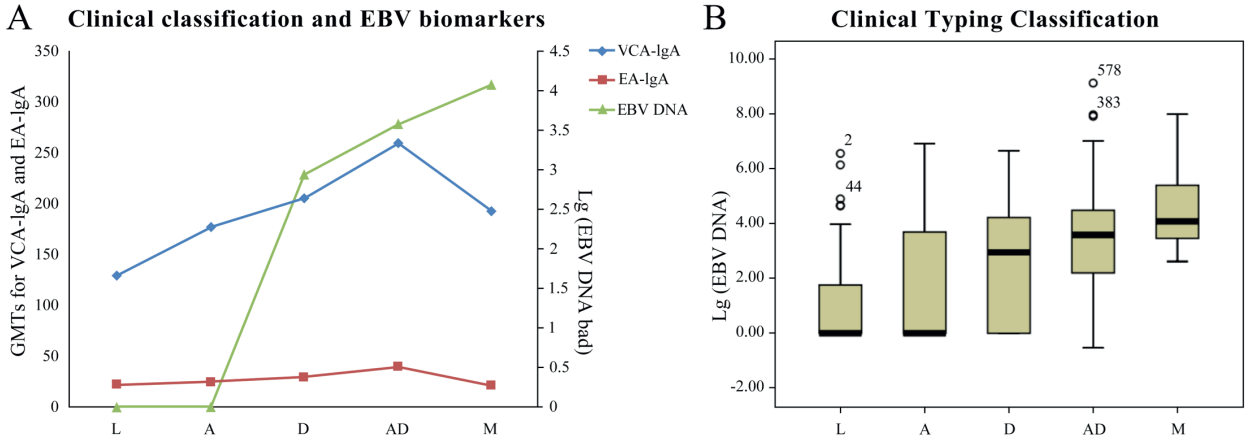

Figure 1. A: EBV-related biomarkers and clinical type; **B:** Pretreatment lg (EBV DNA) value and clinical type (p<0.05 for all). For abbreviations see text

high EBV group were 95.3 and 85.2%, respectively (p<0.001; Figure 2B).

Cox proportional hazards model analyses

A Cox proportional hazards model was constructed for univariate analyses to determine if age, gender, tumor grade, clinical type, disease stage (according to the 7th edition of the AJCC/UICC staging system), VCA-IgA titer (using the GMT as a cutoff point), EA-IgA titer (using the GMT as a cutoff point) or the lg (EBV DNA) load were prognostic factors for OS. The results showed that clinical type, disease stage and lg (EBV DNA)

Table 3. Univariate and multivariate analyses of prognostic factors for overall survival in 632 patients with nasopharyngeal carcinoma

Variables	*3-year OS (%)*	*Univariate analysis*		*Multivariate analysis*			
		p value	*HR*	*p value*	*HR*	*95% CI for HR*	
						Lower	*Upper*
Age (years)							
≤ 44	91.9	0.245	1.354	0.348	1.279	0.765	2.140
> 44	90.2						
Gender							
Male	91.3	0.949	1.018	0.998	0.999	0.566	1.765
Female	91.0						
WHO pathological type							
I-II	87.8	0.740	0.867	0.385	0.686	0.293	1.604
III	91.3						
Clinical type							
L, A and D	96.3	<0.001	3.263	0.022	2.554	1.146	5.690
AD and M	86.6						
AJCC/UICC stage							
I - II	97.4	0.007	3.028	0.870	1.097	0.365	3.292
III - IV	89.1						
VCA-IgA							
≤1:160	90.6	0.530	0.848				
>1:160	91.7						
EA-IgA							
≤1:20	90.7	0.572	1.159				
>1:20	90.0						
Lg (EBV-DNA)							
≤3.56	95.3	<0.001	3.158	0.001	2.593	1.481	4.540
>3.56	85.2						

HR: hazard ratio, CI: confidence interval. For other abbreviations see footnote of Table 1

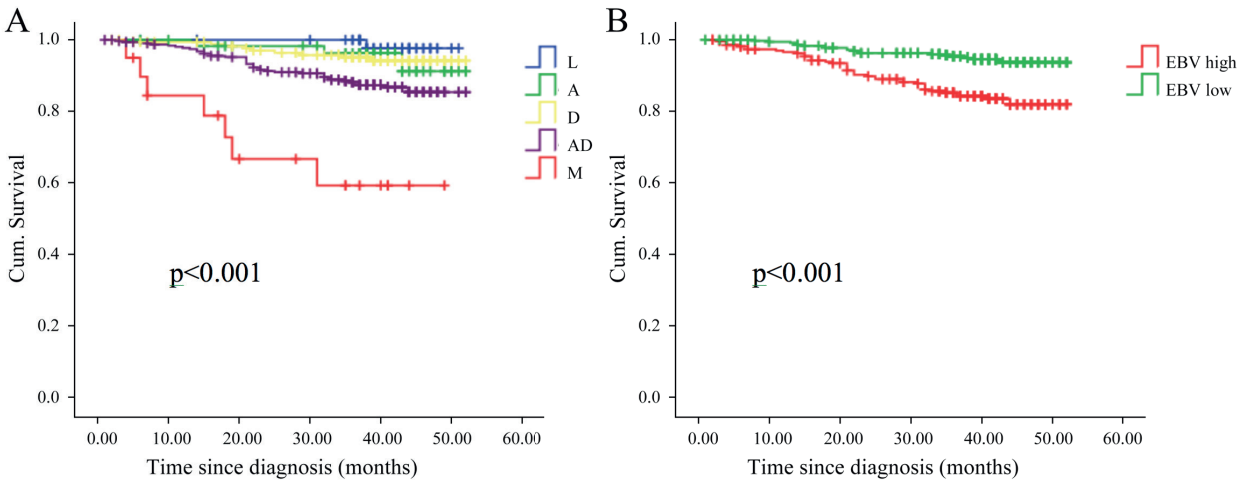

Figure 2. Overall survival curves for 632 patients with nasopharyngeal carcinoma stratified by clinical type (**A**) and pretreatment lg (EBV DNA) load (**B**). For abbreviations see text

Table 4. Prognostic model combining clinical type and pretreatment EBV DNA load for overall survival in nasopharyngeal carcinoma

Risk factor	*Score*
Clinical subtype	
L, A and D	1
AD	2
M	3
Lg (EBV DNA)	
≤3.56	1
>3.56	2

For abbreviations see footnote of Tables 1,2 and 3

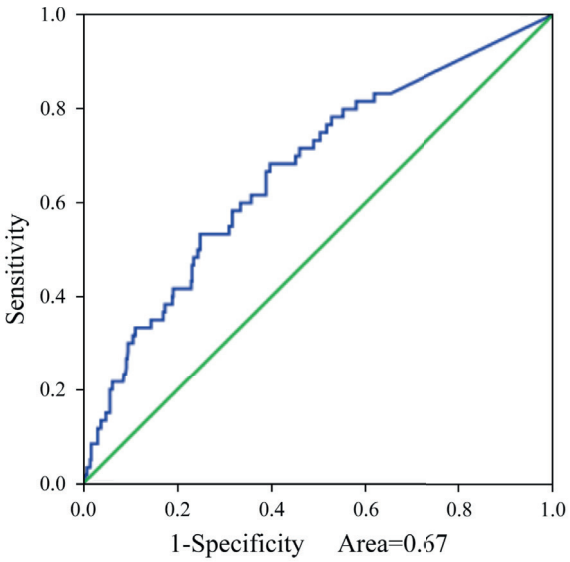

Figure 3. Receiver operating characteristics (ROC) curve for pretreatment lg (EBV DNA) and overall survival in 632 patients with nasopharyngeal carcinoma.

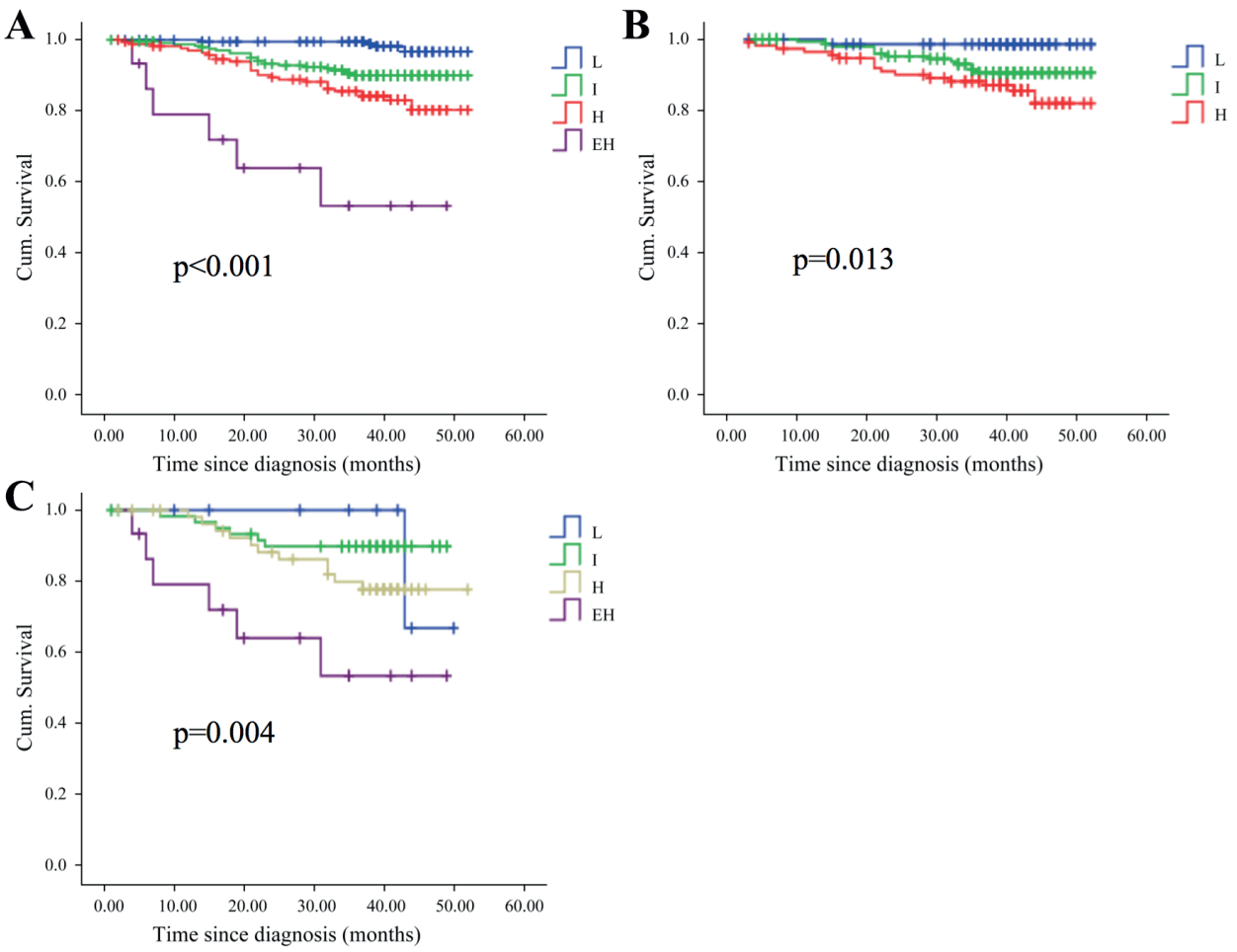

Figure 4. Overall survival curves for 632 patients with nasopharyngeal carcinoma in different risk groups according to the C-E model (**A**), for 341 stage III nasopharyngeal carcinoma patients in different risk groups according to the C-E model (**B**), and for 140 stage IV nasopharyngeal carcinoma patients in different risk groups according to the C-E model (**C**). For abbrevations see text

load were significantly associated with OS (Table 3).

Furthermore, the results of multivariate analyses showed that both clinical type and pretreatment lg (EBV DNA) load were also independent predictors for OS, even after adjustment for age, gender and histological grade.

Generation of a prognostic model

As both clinical type and pretreatment lg (EBV DNA) load were independent prognostic factors for OS, a C-E score model [clinical typing system-pretreatment lg (EBV DNA) load model] based on these factors was established. A score of 1 to 3 was assigned for the clinical type, and a score of 1 to 2 was assigned for the pretreatment lg (EBV DNA) load (Table 4). As the 3-year OS rates for patients with L, A and D types were not significantly different (100% for L and A types, 95.1% for D type, p=0.536), a score of 1 was assigned to patients with any of these 3 clinical types; AD and M types were scored 2 and 3, respectively. The pretreatment lg (EBV DNA) load was scored on the basis of the cutoff value of 3.56 lg (copies/ml). The total score for each patient was calculated by adding the two scores together (Table 4). Thus, the total scores ranged from 2 to 5 (mean=3, median=3). The patients were divided into 4 risk subgroups based on their total score: low risk (L, score 2; 202/632, 32.0%), intermediate risk (I, score 3; 246/632, 38.9%), high risk (H, score 4; 169/632, 26.7%) and extremely high risk (EH, score 5; 15/632, 2.4%). The 3-year OS rates for the L-, I-, H- and EH-risk groups were 99.5, 90.0, 85.5 and 53.2%, respectively (p<0.001). When compared with the L risk group, the risk (hazard ratios; HRs) of death in the I, H and EH risk groups were 4.96, 8.75 and 35.9, respectively (p<0.001; Figure 4A).

As patients with equivalent stages of NPC, as defined by the AJCC/UICC TNM staging system, can demonstrate heterogeneous outcomes, we further examined the prognostic value of the C-E model in patients with advanced TNM classification (stage III or stage IV). The 3-year OS rates of the L, I and H risk groups in patients with stage III disease were 98.6, 90.6 and 88.1%, respectively (p=0.013; Figure 4B). The 3-year OS rates of the L, I, H and EH risk groups in patients with stage IV disease were 100.0, 89.8, 77.6 and 53.2%, respectively (p=0.002; Figure 4C).

Discussion

NPC is a heterogeneous head and neck cancer, with a distinct geographic distribution [1,2]. Compared to other malignancies of the head and neck, NPC has a unique biological behavior and a relatively high risk of nodal involvement and distant metastasis [2,10].

In the 1960s, Chinese colleagues began to observe that patients confirmed to have the same pathological type of NPC demonstrated totally different patterns of disease progression [5]. Xie et al. [6] constructed a clinical typing method for intermediate/late stage NPC patients, and found that the major cause of failure in the ascending type was local recurrence, compared to distant metastasis for the descending type or mixed type.

The natural characteristics of local progression in NPC have also been observed and noted. Mo et al. [7] found that the treatment outcome and long term prognosis were closely correlated to the extension pattern of the primary tumor. In 2006, Li et al. [11] found that the tumors of patients with the descending type were more radiosensitive than those of the ascending type and mixed type by analyzing the outcome of 264 cases with locally advanced stage disease using the Zhi-guang Xie typing system. In addition, patients with the descending type and mixed type had a higher incidence of distant metastasis than patients with the ascending type. In 2012, Li et al. reported that the local tumor spread manifested in a stepwise manner from the proximal sites to distal sites [12].

The genetic and molecular variations between patients with different clinical extension types of NPC have also been studied. In 2008, Liang et al. [13] observed significantly different gene expression patterns between the ascending type and descending type of NPC, which might partly correspond to the different metastatic potential of each clinical type of NPC. Additionally, He et al. [14] detected different expression of proteins related to tumor metastasis, energy metabolism and the inhibition of metastasis among the different clinical types of NPC.

In the current study, we expanded the clinical typing method and applied it to patients with all stages of NPC. In total, 79.8% (498/632) of the patients were confirmed to have the descending or mixed type (D type and AD type), which reflects the relatively aggressive behavior of NPC. Clinicopathological features such as gender, age, and histological type did not show any association with clinical typing.

EBV can infect B lymphocytes and plays a critical role in the etiology of NPC [8,15]. The mechanisms of EBV infection, spread and pathogenesis have been researched for several decades, especially in nasopharyngeal cells [8]. Previously, the EBV infection status was correlated to the biological characteristics of disease in NPC, especially in patients with the undifferentiated subtype [15,16]. EBV biomarkers, including EBV antibodies and the plasma EBV DNA concentration, have long been employed for the screening and early detection of NPC [17-21]. The EBV serum VCA-IgA and EA-IgA titers have also been found to be significantly associated with TNM classification according to the AJCC/UICC staging system [9,22], and the baseline plasma EBV DNA load was proven to reflect the tumor burden and risk of metastasis in a series of previous studies [23,24].

In this study, we demonstrated a significant correlation between EBV serology and the clinical typing classification. Patients with D or AD types had relatively higher rates of positivity and higher GMTs for both VCA-IgA and EA-IgA, compared to patients with other clinical types, indicating that EBV antibodies are a sensitive indicator of lymph node metastasis. Additionally, the pretreatment EBV DNA load was closely associated with nodal involvement and disseminated disease. Furthermore, the combined model indicated a strong, positive association between the subclassifications of the clinical typing system and the detection of all three EBV biomarkers.

These observations provide firm evidence that the infection status and replication of EBV vary between patients with different clinical types of NPC, indirectly supporting the hypothesis that molecular and cellular variations result in different biological behaviors of the primary tumor observed in patients with different clinical types of NPC. Thus, EBV serology testing was complimentary and necessary for clinical typing in our study.

The prognostic impact of the clinical typing system and the baseline plasma EBV DNA load were validated in the current study. Subsequently, we generated a simple and easily reproducible prognostic model (C-E model) to predict OS in patients with NPC. Using this model, we could stratify the patients into four distinct risk groups, and could easily separate the prognosis of the patients in each risk group. Compared to the low risk group, the intermediate-, high- and extremely high-risk groups had significantly higher risks of death (4.96, 8.75 and 35.9, respectively). More interestingly, when we used the C-E model to stratify the patients with the same advanced TNM classification (stage III or IV), the patients with a poorer prognosis could be effectively identified. On the other hand, when the TNM classification was included in the multivariate analysis along with clinical type and the pretreatment lg (EBV DNA) load, the TNM classification was not a significant prognostic factor for OS. These results suggest that the C-E model maybe a better indicator of prognosis and outcome than the TNM classification alone.

Several statistical prediction models have previously been proposed for NPC [25,26]. Some of these models focused on tumor characteristics, the clinicopathological features of the patients and/or biochemical markers used in the routine evaluation of NPC, and are relatively complicated to handle in clinical practice. In recent years, some novel serological markers were identified to be useful for the prediction of prognosis in NPC, and prognostic models combining these biomarkers with clinical classification were established. Zhang et al. [27] found that the C-X-C motif chemokine 5 (CXCL5) was an independent prognostic factor in NPC, and then constructed a scoring model based on this biomarker and the clinical disease classification. C-reactive protein was recently found to effectively predict distant metastasis in NPC, and a prognostic model was suggested based on the baseline C-reactive protein levels and nodal status [28]. Lactate dehydrogenase was also found to correlate with disease relapse in locally advanced NPC [29].

Compared to other prognostic models, our clinical typing system and prognostic model have a number of advantages. Firstly, we have introduced a distinctive clinical typing classification system, which emphasizes the natural characteristics of tumor progression in NPC, in contrast to the TNM classification system. Secondly, the prognostic value of the plasma EBV DNA concentration, in terms of treatment response, clinical outcome and long term prognosis, has received more research, is currently accepted worldwide [23,24,30-32], and clinical measurement of the plasma EBV DNA concentration is technically feasible and routinely performed . Compared to other serological markers such as C-reactive protein and lactate dehydrogenase [28,29], EBV DNA is not easily influenced by inflammation or other underlying diseases. Finally, the risk stratification in our model could predict prognosis independently of the TNM classification, and provides an additional, comprehensive method for evalu-

ating patients with NPC, which complements the TNM staging system.

Thus, our novel clinical typing system and prognostic model could provide new insights into NPC and help to evaluate and manage patients in a more individual manner. For patients with L or A types in the low risk group, enhancing the radiation dose provided by intensity modulated radiotherapy to the primary tumor may be extremely important to prevent local recurrence, while chemotherapy could be avoided. Patients with D or AD types in the intermediate/high risk group should be offered additional intensive therapy, such as adjuvant chemotherapy or targeted therapy to reduce the risk of distant metastasis. In addition, the current study provides a novel stratification method which can predict the heterogeneous outcomes of patients with the same TNM classification, which may help to design improved treatment strategies and assist with individual treatment planning.

Conclusion

We provided a simple, biological behavior-based clinical typing classification system which comprehensively categorizes patients with NPC into distinct clinical types. A significant correlation exists between EBV serology and clinical type, and both clinical type and pretreatment EBV DNA load were significant independent prognostic factors. The clinical typing classification system and the C-E model could potentially be used as supplementary method to the TNM classification system for NPC, and may help in the definition of novel treatment strategies, the evaluation of risk stratification, and future research into the varied biological characteristics of NPC. We look forward to prospective explorations of this clinical typing system in the future.

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