EUROPEAN JOURNAL OF CANCER 48 (2012) 882–888

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

To build a prognostic score model containing indispensible tumour markers for metastatic nasopharyngeal carcinoma in an epidemic area

Y. Jin, X.Y. Cai, Y.C. Cai, Y. Cao, Q. Xia, Y.T. Tan, W.Q. Jiang, Y.X. Shi *

State Key Laboratory of Oncology in South China & Department of Medical Oncology, Sun Yat-Sen University Cancer Center, 651 Dongfeng East Road, Guangzhou 510060, China

ARTICLE INFO

Article history:
Available online 24 October 2011

Keywords:
Circulating tumour markers
Metastatic nasopharyngeal carcinoma
Prognostic factors
Prognostic score model

ABSTRACT

Background and objective: The survival outcomes of patients with metastatic nasopharyngeal carcinoma (NPC) differ significantly between individuals. The aim of this study is to build a prognostic score model (PSM) incorporating circulating tumour markers for metastatic NPC in an epidemic area.

Methods: Seven hundred and ninety-nine patients with disseminated NPC were analysed retrospectively. Univariate and multivariable analyses were conducted using the Cox proportion hazards model. Factors analysed included patients' characteristics (gender, age group, performance status), circulating tumour-marker characteristics (Epstein–Barr virus (EBV) DNA level, EBV VCA-IgA level, lactate dehydrogenase (LDH) level, alkaline phosphatase (ALP) level), basic laboratory characteristics (leucocyte count, haemoglobin level, albumin level), and disease characteristics (presence of metastasis at presentation, disease-free interval, number of metastatic sites, specific metastatic sites). The PSM was built according to numerical score derived from the regression coefficients of each independent prognostic variable. The prognostic score of each patient was calculated by totalling up the scores of each independent variable.

Results: Independent prognostic factors included performance status, age, haemoglobin level, LDH level, ALP level and EBV DNA level. Three prognostic groups based on PSM were obtained: low risk (total score = 0–4); intermediate risk (5–8); high risk (9–12). Median survivals of the three groups were 25.5, 15.1 and 7 months, respectively, ($P < 0.001$).

Conclusion: Clinical and laboratory characteristics can help guide the prognostication of patients with metastatic NPC in epidemic areas.

1. Introduction

Nasopharyngeal carcinoma (NPC) is a disease with a distinct racial and geographical distribution. Although the incidence of NPC is very low (less than 1 per 100,000 person-years) in most parts of the world, it is a leading cancer in a few well-defined populations, including natives of Southern China, Southeast Asia, the Arctic, the Middle East and North Africa.[1–3] Most NPCs in epidemic areas are of the World Health Organization (WHO) types II (non-keratinising carcinoma) and III (undifferentiated carcinoma).[4,5] In endemic areas, the association of Epstein–Barr virus (EBV) with NPC has been well established and the prognostic value of circulating EBV DNA load on survival outcome has also been explored in various reports.[6–8]

* *Corresponding author:* Tel./fax: +86 20 87343352.
E-mail address: shi_yx@sina.cn (Y.X. Shi).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.09.004

Among the head and neck cancer, NPC has the highest propensity to metastasize to distant sites. Different reports have shown that about 17–54% of patients with NPC had failed treatment due to distant metastases [9,10] and systemic disease remains the major cause of death among patients with NPC.[11–13] Once metastasis is diagnosed, the overall survival (OS) of patients is typically under 15 months with palliative chemotherapy.[14,15] However, these patients do not always behave uniformly. Several reports have shown that for selected patients' the overall survival had exceeded 10 years.[16,17] Therefore, it is necessary to create a risk-stratification system which will be able to predict survival outcome.

To the best of our knowledge, there has only been one report that designed a prognostic index score system containing both clinical characteristics and laboratory results for patients with disseminated NPC.[18] However, this was a small study containing a cohort of 220 patients from a non-epidemic region of NPC. In addition, an essential circulating tumour marker, EBV DNA copies, was not contained in that model. Since EBV is closely associated with NPC in epidemic areas, it is important to incorporate it into the prognostic system. There has been limited or no research performed to develop a prognostic evaluation model incorporating circulating tumour markers of patients with metastatic NPC in the literature currently. This study aims to investigate the utility of clinical and laboratory characteristics in prognostication and to build a prognostic score model to predict survival outcome for disseminated NPC in an epidemic area.

2. Patients and methods

2.1. Inclusion criteria and enrolment

Between January 1999 and December 2005, 1885 patients with metastatic NPC were referred to Sun Yat-Sen University Cancer Center. The entry criteria in this study consisted of the following: (i) patients with pathologically confirmed WHO type II or WHO type III NPC; (ii) patients with radiologically confirmed distant metastatic lesion(s); (iii) patients with baseline clinical information and laboratory data; (iv) patients with normal renal, cardiac and liver function; (v) patients who had received at least one cycle of palliative chemotherapy and (vi) patients with complete follow-up data. Exclusion criteria were as followed: (i) patients with brain metastases; (ii) patients with other types of malignancy Data for 799 patients were retrieved. Of those, 81 patients were excluded from the total score analysis because of missing laboratory data, leaving 718 patients eligible for risk stratification.

2.2. Definition

Patients, Karnofsky Performance Scores were determined at the time of diagnosis of metastatic disease. The clinical and laboratory assessment was performed at the time of diagnosis of distant metastases. Metastasis at presentation was defined as patients who presented with distant metastasis while first diagnosed with NPC. It was analysed as a separate category from patients who presented with localised disease, but developed metastases at a later date in the multivariate analysis. Disease-free interval (DFI) was defined as the time from the onset of primary radiotherapy to the time of relapse or metastases in patients who achieved complete response. For patients who had metastasis at presentation the DFI was recorded as zero. Overall survival was defined as the time from the first diagnosis of metastasis to the time of death. Patients whose deaths were not caused by cancer progression were excluded from the study.

Titres of IgA antibodies against EBV capsid antigen (EBV VCA-IgA) were dichotomised into binary variables (positive or negative). A titre of more than 1:20 was considered to be positive for the IgA antibodies as adopted in previous study on the marker.[19] The level of plasma EBV DNA concentrations was also dichotomised into binary variables (detectable or undetectable). The cutoff level was 1×10^3 copies/ml which was described as previous research.[20]

2.3. Follow up

Patients were followed up by direct telecommunication mean until death. Till the 31st May 2011, OS data of all the 799 patients were obtained.

2.4. Statistical analysis

Statistical analysis was performed using SPSS17.0 package. OS was analysed using the Kaplan–Meier method and was compared using the log-rank test. Univariate and multivariable analyses were performed using the Cox proportion hazards model. Factors that were considered for analyses included patient' characteristics (gender, age group, performance status), circulating tumour-marker characteristics (EBV-DNA level, VCA-IgA level, lactate dehydrogenase (LDH) level, alkaline phosphatase (ALP) level), basic laboratory characteristics (leucocyte count, haemoglobin level, albumin level), and disease characteristics (metastasis at presentation, DFI, number of metastatic sites, specific metastatic sites). A P value of <0.05 was considered significant. The regression coefficient (the n in the Cox regression equation $HR = e^n$) of each independent prognostic factor is then changed into an integral number to build a PSM.

3. Results

3.1. Patient characteristics

Patient characteristics are described in Tables 1 and 2. All patients were of Chinese ethnicity with a male predominance (83.1%). The mean age of diagnosis of metastatic NPC was 45.4 years (ranging from 11 to 80 years). The mean DFI was 15.4 months (ranging from 0 to 279.8 months). One third of the patients had distant metastasis at presentation. About half of the patients had more than one metastatic site with bone being the most common site (60.7%). More than two thirds of the patients had detectable plasma EBV-DNA level ($>1 \times 10^3$ copies/ml) and more than half of the patients had positive serum VCA-IgA level (>1:20).

Table 1 – Laboratory characteristics.

Characteristic	N (%)
White cell ($\times 10^9$/l)[a]	
<4	78 (10.1)
4–11	599 (77.3)
>11	98 (12.6)
Haemoglobin (g/l)[a]	
<12	184 (24.2)
⩾2	576 (75.8)
Albumin (g/l)[a]	
⩾35	641 (86.0)
<35	104 (14.0)
Lactate dehydrogenase (LDH) (IU/l)[a]	
⩽245	409 (54.2)
>245	345 (45.8)
Alkaline phosphatase (ALP) (IU/l)[a]	
⩽110	572 (74.7)
>110	194 (25.3)
Epstein–Barr virus (EBV) DNA (copies/ml)[a]	
Undetectable	237 (30.2)
Detectable	547 (69.8)
VCA-IgA	
Negative	380 (47.6)
Positive	419 (52.4)

[a] Some data are missing.

Table 2 – Clinical characteristics.

Characteristics	N (%)
Gender	
Male	664 (83.1)
Female	135 (16.9)
Age (years)	
<45	390 (48.8)
⩾45	409 (51.2)
Karnosky performance score (KPS)	
⩾80	720 (90.1)
<80	79 (9.9)
Metastasis at presentation	
Present	247 (30.9)
Absent	552 (69.1)
Disease-free interval (DFI) (months)	
⩽6	354 (44.3)
>6	445 (55.7)
Lung metastasis	
Present	332 (41.6)
Absent	467(58.4)
Liver metastasis	
Present	329 (41.2)
Absent	470 (58.8)
Bone metastasis	
Present	485 (60.7)
Absent	314 (39.3)
Distant nodal metastasis	
Present	129 (16.1)
Absent	670 (83.9)
Number of metastatic sites	
Single	446 (55.8)
Multiple	353 (44.2)

3.2. Treatment

An overwhelming majority (95%) of the patients were treated with cisplatinum-based doublets. The regimens included cisplatin (25–30 mg/m^2 intravenously on days 1–3 every 21 days) plus 5-fluorouracil (500 mg/m^2 intravenously on days 1–5 every 21 days), and paclitaxel (175 mg/m^2 intravenously over 3 h on day 1 every 21 days) plus cisplatin (25–30 mg/m^2 intravenously on days 1–3 every 21 cycles). Five percent of the patients had a poor Karnosky performance score (KPS < 70). These patients received mono-therapy with capecitabine (1000 mg/m2 twice a day by month on days 1–14 every 21 days). The mean number of cycles of chemotherapy was four (ranging from 1–12).

3.3. Overall survival

All 799 patients had died by 31st May 2011. The mean OS was 24.7 months (ranging from 1 to 144 months). The 1-year, 2-year and 3-year survival rate were 76%, 38% and 20%, respectively. (Fig. 1). The OS differences among the different treatment regimen were not statistically significant ($P = 0.161$). (Fig. 2).

3.4. Univariate analysis

Factors that were analysed are listed in Table 3. Statistically significant negative prognostic factors included age ⩾ 45 - years (HR = 1.276, $P = 0.003$), KPS < 80 (HR = 2.107, $P < 0.001$), haemoglobin < 12 g/l (HR = 1.322, $P = 0.005$), LDH > 245 IU/l

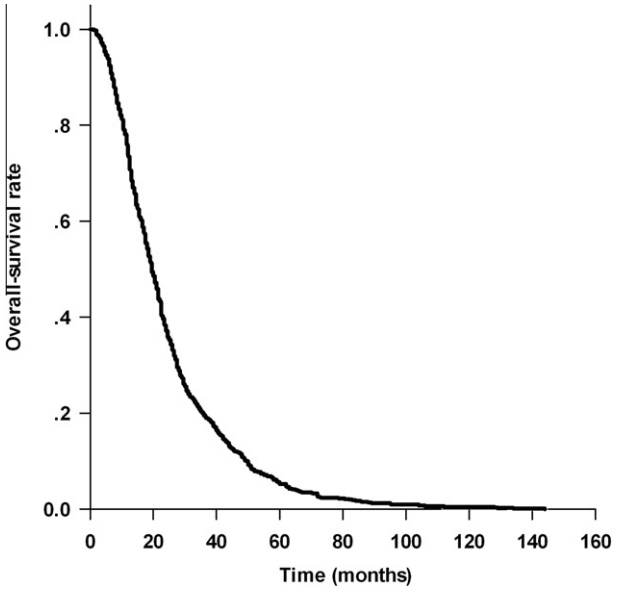

Fig. 1 – Kaplan–Meier overall survival (OS) curves of 799 patients with metastatic nasopharyngeal carcinoma (NPC). Mean OS ± standard error (SE) was 24.7 ± 0.7 months (ranging from 1 to 144 months). The 1-year, 2-year and 3-year OS rate was 76%, 38% and 20%, respectively.

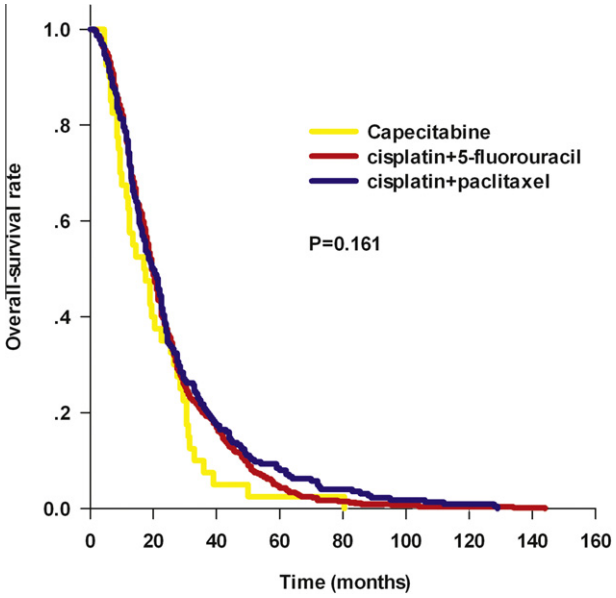

Fig. 2 – Kaplan–Meier overall survival (OS) curves of 799 patients with metastatic nasopharyngeal carcinoma (NPC) treated with three different regimens. Mean OS ± standard error (SE) (95% confidence interval (CI)) was 17.0 ± 3.5 (10.2–23.8) months in the capecitabine group, 19.5 ± 0.6 (18.2–20.8) months in the cisplatin + 5-fluorouracil group and 20.0 ± 1.4 (17.1–22.8) months in the cisplatin + paclitaxel group, $P = 0.161$.

(HR = 1.734, $P < 0.001$), ALP > 110 IU/l (HR = 1.366, $P = 0.001$) and EBV DNA $\geqslant 1 \times 10^3$ copies/ml (HR = 1.763, $P < 0.001$).

3.5. *Multivariate analysis*

The Cox multivariate analysis identified the following independent negative prognostic factors for overall survival: age $\geqslant$ 45 years (HR = 1.234), KPS < 80 (HR = 2.102), haemoglobin < 12 g/l (HR = 1.310), LDH > 245 IU/l (HR = 1.842), ALP > 110 IU/l (HR = 1.388) and EBV DNA $\geqslant 1 \times 10^3$ copies/ml (HR = 1.775) (Table 4). The 2-year OS rate for patients younger than 45 years was 41%, with a rate of 36% for those older than 45 years. Patients with good performance status had a 2-year OS rate of 40%, as compared with that of 20% for those with poor performance status. Patients with undetectable EBV-DNA level had the 2-year OS rate of 56%, as compared with that of 31% for those with detectable EBV-DNA level. Patients with normal haemoglobin level had a2-year OS rate of 43%, as compared with that of 26% for those with anaemia. Patients with normal LDH levels had a 2-year OS rate of 51%, as compared with that of 23% for those with high LDH level. Patients with normal ALP level had a2-year OS rate of 44%, as compared with that of 21% for those with normal ALP level.

3.6. *Prognostic score model*

Since there were no statistically significant differences of OS among the three treatment regimens, the effect of chemotherapy on OS outcome was ignored when the PSM was built. As we mentioned above, to build a systemic PSM, an integral score was derived from the regression coefficients of each independent prognostic factor. If the factor was absent, a score of zero was recorded. If the factor was present, a score of 1 or 3 was recorded according to the n value (Table 5). The maximum score is 12. The PSM for each patient was calculated by totalling up the scores of each independent factor. The total scores were calculated for 718 patients who had complete data. Three risk stratification groups were obtained based on the PSM: (i) the low risk group (total score = 0–4) which included 379 patients; (ii) the intermediate risk group (total score = 5–8) which included 279 patients; and (iii) the high risk group (total score = 9–12) which included 60 patients. The median survivals of these groups were 25.5, 15.1 and 7 months, respectively ($P < 0.001$). The OS curves of these groups were distinctly separated from each other (Fig. 3).

4. Discussion

This is the first time a PSM utilising circulating tumour markers has been built for patients with disseminated NPC in an epidemic area, A relatively large cohort of people were included in this study. Previous studies have not included tumour markers such as plasma EBV DNA load, serum VCA-IgA tiers, LDH and ALP into the univariate analysis.

Part of our results was consistent with those reported by Ong et al.[18] We also found that anaemia and poor performance status were independent negative prognostic factors for survival outcome and there were no significant differences in OS between single site and multiple sites of metastasis. However, some of our results were different with those in that study. Our model had observed several additional independent factors such as age, circulating EBV-DNA level, LDH level and ALP level. Notably, when these tumour markers were considered into analysis, liver metastases and lung metastases were no longer the independent factors described as Ong et al.[18] and Teo et al.[21] One reasonable explanation is that these tumour markers can reflect tumour burden more sensitively and precisely than simply the site of metastases. Even in the specific groups with liver metastases or lung metastases, there still exist patients with relatively good prognosis as Hui et al.[17] reported. Additionally, the different sizes and quantity of the lesions may have different prognostic implications. Numerous large lesions may represent more extensive spread than fewer and smaller lesions. Therefore, we think it is rational that the tumour markers mentioned above but not liver or lung metastases stood out to be independent prognostic factors in this paper.

With respect to these tumour markers, each of them has been shown to have vital significance in malignancies in previous researches. EBV infection has been reported to be associated with risk for NPC[22] and plasma EBV DNA level has been shown to be a useful marker in prognostication both in non-disseminated and disseminated NPC.[23,24] Our present study also revealed that circulating EBV DNA load was an independent prognostication in disseminated NPC. Turen et al.[25] has reported that high serum LDH level is an independent unfavourable risk factor for OS in patients with locoregionally advanced NPC. Our present study for the first time revealed that high serum LDH level is also an independent negative

Table 3 – Univariate analysis of clinical and laboratory variables.

Characteristics	HR(95% confidence interval (CI))	P value
Gender		
Male	Baseline	
Female	1.083(0.880–1.334)	0.451
Age (years)		
<45	Baseline	
⩾45	1.276(1.088–1.496)	0.003
Karnosky performance score (KPS)		
⩾80	Baseline	
<80	2.107(1.585–2.802)	<0.001
White cell ($\times 10^9$/l)		
<4	Baseline	
4–11	1.325(1.045–1.681)	
>11	1.398(1.037–1.866)	Overall 0.520
Haemoglobin (g/dl)		
⩾12	Baseline	
<12	1.322(1.090–1.604)	0.005
Albumin (g/l)		
⩾35	Baseline	
<35	1.084(0.845–1.391)	0.526
Lactate dehydrogenase (IU/l)		
⩽245	Baseline	
>245	1.734(1.464–2.054)	<0.001
Alkaline phosphatase (IU/l)		
⩽110	Baseline	
>110	1.366(1.130–1.652)	0.001
Epstein–Barr virus DNA (copies/ml)		
Undetectable	Baseline	
Detectable	1.763(1.481–2.099)	<0.001
VCA-IgA		
Negative	Baseline	
Positive	1.048(0.895–1.228)	0.558
Disease-free interval (DFI)		
⩽6 months	Baseline	
>6 months	0.894(0.707–1.130)	0.347
Number of metastatic sites		
Single	Baseline	
Multiple	1.103(0.807–1.509)	0.538
Metastasis at presentation	0.910(0.695–1.190)	0.490
Lung metastasis	1.108(0.862–1.424)	0.424
Liver metastasis	1.041(0.814–1.331)	0.750
Bone metastasis	1.025(0.779–1.315)	0.846
Distant nodal metastasis	1.037(0.794–1.354)	0.790

HR: hazard ratio; 95%: 95% CI.

Table 4 – Independent prognostic factors from the multivariate analysis.

Factors	HR(95% confidence interval (CI))	P value
Haemoglobin < 12 g/l	1.310(1.096–1.565)	0.003
Lactate dehydrogenase (LDH) > 245 IU/L	1.842(1.575–2.155)	<0.001
Alkaline phosphatase (ALP) > 110 IU/L	1.388(1.161–1.660)	<0.001
Epstein–Barr virus (EBV) DNA ⩾ 1×10^3 copies/ml	1.775(1.504–2.096)	<0.001
Karnosky performance score (KPS) < 80	2.102(1.644–2.688)	<0.001
Age ⩾ 45 years	1.234(1.064–1.430)	0.005

HR: hazard ratio; 95%: 95% CI.

Table 5 – Prognostic score model.

Factor	Score	$n(HR = e^n)$
Haemoglobin < 12 g/l	1	0.27
Lactate dehydrogenase > 245 IU/L	3	0.61
Alkaline phosphatase > 110 IU/L	1	0.33
Epstein–Barr virus DNA $\geqslant 1 \times 10^3$ copies/ml	3	0.57
Karnosky performance score (KPS) < 80	3	0.74
Age $\geqslant$ 45 years	1	0.21
Maximum score	12	

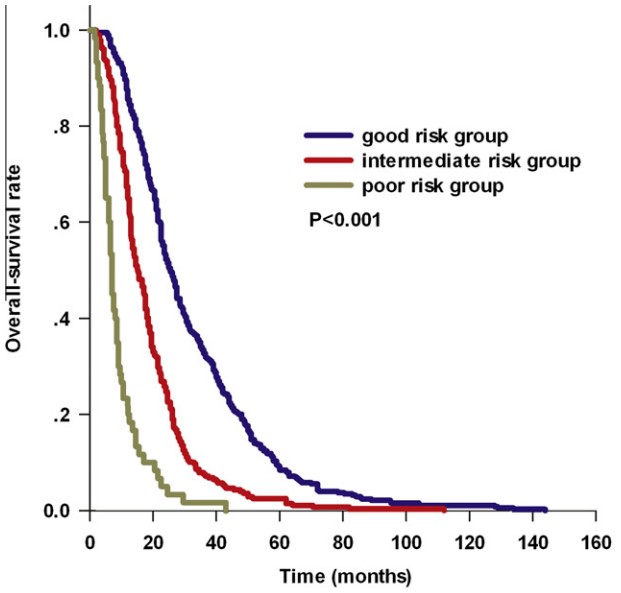

Fig. 3 – Kaplan–Meier overall survival (OS) curves of 718 patients with metastatic nasopharyngeal carcinoma (NPC) in three risk stratification groups. Mean OS ± standard error (SE) (95% confidence interval (CI)) was 25.5 ± 1.0 (23.5–27.5) months in the good risk group, 15.1 ± 1.0 (13.1–17.1) months in the intermediate risk group, and 7.0 ± 0.4 (6.2–7.8) months in the poor risk group, $P < 0.001$.

prognostic factor in patients with metastatic NPC. Serum ALP concentration is used to detect bone metastasis in malignancy.[26,27] Sonpavde et al.[28] has reported that increased serum ALP level could predict survival in men with bone metastasis from prostate cancer. In this study, we have shown that serum ALP level can also predict survival outcome as an independent factor in metastatic NPC. These results will need to be verified in future prospective studies.

After finding these independent prognostic factors, we further built the PSM described earlier in this article by analysing these factors in combination. Based on the PSM, we were able to separate the patients into three risk groups with different survival outcomes. Our result demonstrated that the PSM was able to discriminate patients with good prognosis from those with poor prognosis in metastatic NPC. Since there has been no randomised trial comparing the effect on long-term survival of different chemotherapy regimens and there were no significant differences of OS among the three treatment regimens in our study, we have ignored the therapeutic effect on prognosis when we built the PSM. Further research is needed to explore this issue.

This study had several limitations. First, our patients were restricted to one local hospital. A larger, multicentre design will be needed in further study. Second, the test set and validation set for the PSM were not created. We are planning to start a prospective study through collaborating with other centres to verify the PSM in the near future.

Generally speaking, there are two main points in this study. Firstly, we have found several circulating tumour markers as independent factors to predict survival for disseminated NPC in an epidemic area which has been never researched in combination before. Secondly, we have built a PSM for disseminated NPC by merging these important factors together which has been verified useful in a relatively large number of patients in the present study.

In addition, the factors included in the PSM are used routinely in clinical practice and are easily available, which makes the model practical and convenient. We anticipate more clinical trials will verify the results of this study and that the PSM will be used in clinical practice in the near future.

Conflict of interest statement

None declared.

Acknowledgements

This work was supported by the National-Eleventh Five Technology Major Project [2008ZX09312-002]; and the Research Award Fund for Outstanding Young Researchers in Sun Yat-Sen University Cancer Center.

We thank for the generous help in the linguistic review from Elgene Lim, M.D., Ph. D. and Seah, Davinia Shi Enn, M.D., MPH in the Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School.

The role of the funding source: W.Q. Jiang and Y.X. Shi supported the fee of data acquisition and statistical analysis of this study.

REFERENCES

1. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev* 2006;**15**(10):1765–77.
2. Shanmugaratnam K, Chan SH, de-The G, et al. Histopathology of nasopharyngeal carcinoma: correlations with epidemiology, survival rates and other biological characteristics. *Cancer* 1979;**44**(3):1029–44.
3. Yu MC, Yuan JM. Epidemiology of nasopharyngeal carcinoma. *Semin Cancer Biol* 2002;**12**(6):421–9.
4. Shanmugaratnam K. Nasopharyngeal carcinoma: epidemiology, histopathology and aetiology. *Ann Acad Med Singapore* 1980;**9**(3):289–95.
5. Zong YS, Zhang RF, Chen SH, Xiao ZD, Lao H. *Relationship between the histopathology of nasopharyngeal carcinoma (NPC) and*

the prognosis after radiotherapy [Author's Trans.]. Zhonghua Zhong Liu Za Zhi 1980;**2**(4):274–277.
6. Senba M, Zhong XY, Senba MI, Itakura H. EBV and nasopharyngeal carcinoma. *Lancet* 1994;**343**(8905):1104.
7. Wang WY, Twu CW, Chen HH, et al. Plasma EBV DNA clearance rate as a novel prognostic marker for metastatic/recurrent nasopharyngeal carcinoma. *Clin Cancer Res* 2010;**16**(3):1016–24.
8. Twu CW, Wang WY, Liang WM, et al. Comparison of the prognostic impact of serum anti-EBV antibody and plasma EBV DNA assays in nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2007;**67**(1):130–7.
9. Liu MT, Hsieh CY, Chang TH, et al. Prognostic factors affecting the outcome of nasopharyngeal carcinoma. *Jpn J Clin Oncol* 2003;**33**(10):501–8.
10. Chiesa F, De Paoli F. Distant metastases from nasopharyngeal cancer. *ORL J Otorhinolaryngol Relat Spec* 2001;**63**(4):214–6.
11. Leung SF, Teo PM, Shiu WW, Tsao SY, Leung TW. Clinical features and management of distant metastases of nasopharyngeal carcinoma. *J Otolaryngol* 1991;**20**(1):27–9.
12. Tao Y, Bidault F, Bosq J, Bourhis J. Distant metastasis of undifferentiated carcinoma of nasopharyngeal type. *Onkologie* 2008;**31**(11):574–5.
13. Gunn GB, Villa RD, Sedler RR, et al. Nasopharyngeal carcinoma metastasis to the pituitary gland: a case report and literature review. *J Neuro-Oncol* 2004;**68**(1):87–90.
14. Razak AR, Siu LL, Liu FF, et al. Nasopharyngeal carcinoma: the next challenges. *Eur J Cancer* 2010;**46**(11):1967–78.
15. Bensouda Y, Kaikani W, Ahbeddou N, et al. Treatment for metastatic nasopharyngeal carcinoma. *Eur Ann Otorhinolaryngol Head Neck Dis* 2011;**128**(2):79–85.
16. Fandi A, Bachouchi M, Azli N, et al. Long-term disease-free survivors in metastatic undifferentiated carcinoma of nasopharyngeal type. *J Clin Oncol* 2000;**18**(6):1324–30.
17. Hui EP, Leung SF, Au JS, et al. Lung metastasis alone in nasopharyngeal carcinoma: a relatively favorable prognostic group. A study by the Hong Kong nasopharyngeal carcinoma study group. *Cancer* 2004;**101**(2):300–6.
18. Ong YK, Heng DM, Chung B, et al. Design of a prognostic index score for metastatic nasopharyngeal carcinoma. *Eur J Cancer* 2003;**39**(11):1535–41.
19. Tsang RK, Vlantis AC, Ho RW, et al. Sensitivity and specificity of Epstein–Barr virus IGA titer in the diagnosis of nasopharyngeal carcinoma: a three-year institutional review. *Head Neck* 2004;**26**(7):598–602.
20. Yamamoto M, Kimura H, Hironaka T, et al. Detection and quantification of virus DNA in plasma of patients with Epstein–Barr virus-associated diseases. *J Clin Microbiol* 1995;**33**(7):1765–8.
21. Teo PM, Kwan WH, Lee WY, Leung SF, Johnson PJ. Prognosticators determining survival subsequent to distant metastasis from nasopharyngeal carcinoma. *Cancer* 1996;**77**(12):2423–31.
22. McDermott AL, Dutt SN, Watkinson JC. The aetiology of nasopharyngeal carcinoma. *Clin Otolaryngol Allied Sci* 2001;**26**(2):82–92.
23. Lo YM, Chan AT, Chan LY, et al. Molecular prognostication of nasopharyngeal carcinoma by quantitative analysis of circulating Epstein–Barr virus DNA. *Cancer Res* 2000;**60**(24):6878–81.
24. An X, Wang FH, Ding PR, et al. Plasma Epstein–Barr virus DNA level strongly predicts survival in metastatic/recurrent nasopharyngeal carcinoma treated with palliative chemotherapy. *Cancer* 2011.
25. Turen S, Ozyar E, Altundag K, Gullu I, Atahan IL. Serum lactate dehydrogenase level is a prognostic factor in patients with locoregionally advanced nasopharyngeal carcinoma treated with chemoradiotherapy. *Cancer Invest* 2007;**25**(5):315–21.
26. Min JW, Um SW, Yim JJ, et al. The role of whole-body FDG PET/CT, Tc 99m MDP bone scintigraphy, and serum alkaline phosphatase in detecting bone metastasis in patients with newly diagnosed lung cancer. *J Korean Med Sci* 2009;**24**(2):275–80.
27. Schindler F, Lajolo PP, Pinczowski H, et al. Bone and total alkaline phosphatase for screening skeletal metastasis in patients with solid tumours. *Eur J Cancer Care (Engl)* 2008;**17**(2):152–6.
28. Sonpavde G, Pond GR, Berry WR, et al. Serum alkaline phosphatase changes predict survival independent of PSA changes in men with castration-resistant prostate cancer and bone metastasis receiving chemotherapy. *Urol Oncol* 2010.