Observational Study

Medicine®

OPEN

Identifying pretreatment baseline factors predictive of distant metastasis in patients with nasopharyngeal carcinoma after radiotherapy

Yu Wang, MD*, Guojian Chen, MD

Abstract

This retrospective study was performed to identify pretreatment baseline factors that could predict the development of distant metastasis (DM) in patients with nasopharyngeal carcinoma (NPC).

A cohort of 119 NPC patients undergoing radiotherapy (RT) or chemoradiotherapy (CRT) were recruited into the study. Among them, 51 developed DM (DM group) within 3 years after treatment and 68 did not (DM-free group). Various clinicopathological factors were measured before the treatment and analyzed by univariate as well as multivariate analyses for the potential correlation with DM development.

Univariate analysis revealed that increased peripheral lactate dehydrogenase (LDH) level, lower lymphocyte–monocyte ratio (LMR), higher neutrophil–lymphocyte ratio (NLR), advanced American Joint Committee on Cancer (AJCC) stage, advanced T stage, and advanced N stage were significantly correlated with the presence of DM. Multivariate analysis identified advanced AJCC stage and high LDH level were independent predictive factors for DM.

Routinely measured pretreatment clinical factors, including AJCC state and serum LDH level, could independently predict DM. These factors will benefit the selection of appropriate treatment options and improve the overall survival of NPC patients.

Abbreviations: DM = distant metastasis, LDH = lactate dehydrogenase, LMR = lymphocyte–monocyte ratio, NPC = nasopharyngeal carcinoma, RT = radiotherapy.

Keywords: distant metastasis, nasopharyngeal carcinoma, predictive factor, survival

1. Introduction

Nasopharyngeal carcinoma (NPC) is a major health concern in Southeast Asia, particularly in southern China. In 2010, 41,503 patients were diagnosed with NPC and 20,058 died from the disease in China, corresponding to an incidence and a mortality of 3.16 of 100,000 and 1.53 of 100,000, and accounting for 1.34% of all new cancer cases and 1.03% of all cancer-related deaths, respectively.[1] At the initial diagnosis, most NPC patients presented no clinical evidence of metastases and are frequently treated with radiotherapy (RT) alone or chemoradiotherapy (CRT).[2] When 2-dimensional RT (2D-RT) was the predominant option for NPC, locoregional recurrence and distant metastasis (DM) represented 2 equally important causes of treatment failures.[3–6] The later development and application of intensity-modulated radiotherapy (IMRT) has significantly reduced the locoregional recurrence, leaving DM responsible for 68.4% to 73.6% of all treatment failures among NPC patients.[7–11] Therefore, it is essential to identify novel factors predictive of DM among NPC patients to enable early interference with more aggressive treatment options and to improve the overall patient survival.

Several molecular markers have shown values in predicting the survival and DM among NPC patients, yet technical challenges and high costs associated with detecting these markers generally preclude their use in clinic.[10,12,13] Although other risk factors also influence survival,[3,4,9,14,15] few studies have assessed the pretreatment baseline parameters to DM. These factors could play a significant role in the choice of treatment NPC patients upon initial diagnosis. To address this issue, we retrospectively analyzed the correlations between various pretreatment baseline factors and the development of DM among NPC patients. Specifically, we focused on DM within the first 3 years after initial RT or CRT treatment, since 77.0% to 82.4% of metastases develop within this timeframe.[3,4,16]

2. Materials and methods

2.1. Patients

This retrospective study was approved by the Institutional Review Board of the Jiangmen Central Hospital (Jiangmen, China). A cohort of 119 NPC patients between 18 and 79 years of age and admitted into the Jiangmen Central Hospital from January 2009 to August 2011 were recruited into this study. The inclusion criteria included: histologically confirmed NPC without

Editor: Eric Bush.

The authors have no conflicts of interest to disclose.

Department of Oncology, Jiangmen Central Hospital, Jiangmen, China.

* Correspondence: Yu Wang, Department of Oncology, Jiangmen Central Hospital, Jiangmen 529000, China (e-mail: 25406115@qq.com).

Medicine (2017) 96:17(e6692)

Received: 24 October 2016 / Received in final form: 28 March 2017 / Accepted: 3 April 2017

http://dx.doi.org/10.1097/MD.0000000000006692

evidence of DM before treatment; an Eastern Cooperative Oncology Group performance status of ≤2; adequate renal, cardiac, and liver function; and achievement of complete remission following either RT or CRT. Patients with missing data, clinical signs of sepsis or other inflammatory diseases, serious concurrent medical issues, and a history of other malignancies were excluded from this study.

2.2. Collection of pretreatment baseline parameters

The following clinicopathological information was collected from each patient before the initiation of any treatment: sex, age, pathological type, NPC stage as defined by the 7th edition of the American Joint Committee on Cancer (AJCC) staging system, blood test results, and treatment strategies including RT dose and type of chemotherapy. Pretreatment albumin (ALB) and lactate dehydrogenase (LDH) level were measured using a Hitachi-7080 automated chemistry analyzer (Hitachi, Japan), and white blood cell differential counts using an AC.T 5diff AL hematology analyzer (Beckman Coulter, USA). The peripheral neutrophil–lymphocyte ratio (NLR) was calculated as the ratio of absolute counts between the peripheral neutrophil and lymphocyte measurements. Finally, the peripheral lymphocyte–monocyte ratio (LMR) was calculated as the lymphocyte count divided by the monocyte count.

2.3. Treatment

ALL patients received RT, including 79 treated with conventional 2D-RT and 40 with 3-dimensional conformal RT (3D-CRT). The total doses delivered were 68 to 70 Gy to the gross tumor, 60 to 62 Gy to the involved areas of the neck, and 50 Gy to uninvolved areas. Boost irradiation not exceeding 6 Gy to the skull base and primary nodal sites was administered to patients presenting severe enlargement of the primary lymph nodes or showing no dissipation of lymph nodes after initial RT.

Chemotherapy was administered to 76 patients as a concurrent (n = 31), neoadjuvant (n = 13), adjuvant (n = 7), or a combination of 2 or all 3 options (n = 25), in addition to RT. The regimens for concurrent chemoradiotherapy (CCRT) were cisplatin alone, consisting of 30 to 40 mg/m^2 cisplatin every week for 3 to 6 cycles during RT. For neoadjuvant or adjuvant chemotherapy, cisplatin or carboplatin plus one of the following 3 agents were used: 5-fluorouracil (5-FU), docetaxel (DOC), or gemcitabine. The doses were as follows: 20 to 25 mg/m^2/day on days 1 to 4 for cisplatin; 300 to 400 mg/m^2 on day 1 for carboplatin; 500 to 1000 mg/m^2/day on days 1 to 5 for 5-FU; 75 mg/m^2/day once every 3 to 4 weeks for 1 to 3 cycles for DOC; and 1 g/m^2/day on day 1 and day 14 for gemcitabine. The exact doses were selected based on the patients' conditions, and if severe side effects were experienced, the dose was reduced accordingly.

2.4. Follow-up

All patients were assessed every 3 to 6 months from the last date of RT, up to 3 years or the time when DM was detected, whichever occurred first. DM was diagnosed based on clinical symptoms, physical examination and imaging, including chest radiography, bone scan, computed tomography, and abdominal ultrasonography.

2.5. Statistical analysis

Statistical analysis was performed using SPSS software (version 19.0). Qualitative variables were presented as frequencies and percentages, while quantitative variables as mean ± standard error (SE). Kaplan–Meier analysis was performed to assess the incidence of DM over time after the treatment. Univariate analysis was performed using Log-rank test. Parameters showing significance from the univariate analysis were used in multivariate analysis using a Cox proportional hazards regression model. A P-value of $<.05$ was considered statistically significant.

3. Results

In this study, we retrospectively analyzed 119 NPC patients with a mean age of 48 years, including 86 males and 33 females. Of them, 99.2% were diagnosed with nonkeratinizing NPC and 0.8% with adenocarcinoma. The general clinicopathological information of all patients are summarized in Table 1. Upon the diagnosis of NPC, 43 patients received RT alone and 76 went through CRT, including 31 (40.8%) receiving CCRT, 13 (17.1%) receiving neoadjuvant CRT only, 7 (9.2%) receiving adjuvant CRT only, and 25 (32.9%) receiving a combination of therapies (neoadjuvant plus adjuvant CRT, neoadjuvant plus CCRT, CCRT plus adjuvant CRT or neoadjuvant plus CCRT plus adjuvant CRT). Kaplan–Meier analysis showed that the incidence of DM increased over time following the treatment: from 16.81 ± 3.43% within the first 12 months, to 35.29 ± 4.38% within the first 2 years and 42.86 ± 4.54% within the first

Table 1

Baseline clinicopathological characteristics of all patients.

Variables	Mean (range)	No. of patients (%)
Age, y	48 (20–74)	
Gender		
Male		86 (72.3)
Female		33 (27.7)
DM		
Yes		51 (42.9)
No		68 (57.1%)
LDH, IU/L	172 (103–571)	
ALB, g/L	44.8 (34.0–68.10)	
LMR	3.49 (0.74–17.93)	
NLR	2.31 (0.62–18.24)	
Hb, g/L		
Anemia		29 (24.4)
Normal		90 (75.6)
PLT count, $\times 10^9$/L		
Thrombocytosis		11 (9.2)
Normal		103 (86.5)
Thrombocytopenia		5 (4.2)
AJCC stage		
I		2 (1.7)
II		21 (17.7)
III		66 (55.5)
$IV_{A–B}$		30 (25.2)
T stage		
T1–2		67 (56.3)
T3–4		52 (43.7)
N stage		
N0		13 (10.9)
N1–3		106 (89.1)
Chemotherapy		
No		41 (34.5)
Yes		78 (65.5)

AJCC = American Joint Committee on Cancer, ALB = albumen, DM = distal metastasis, Hb = hemoglobin, LDH = lactate dehydrogenase, LMR = lymphocyte–monocyte ratio, NLR = neutrophil–lymphocyte ratio, PLT = platelet.

Table 2

Univariate analysis using Log-rank test to identify potential risk factors for distant metastasis development (n = 119).

	n	DM, n (%)	DM onset (days after treatment)	χ^2	P
Gender					
Male	86	41 (47.67)	25.86 ± 1.29	2.805	.094
Female	33	10 (30.3)	29.85 ± 1.81		
Age, y					
≤49	65	23 (35.38)	28.85 ± 1.38	3.584	.058
>49	54	28 (51.85)	24.70 ± 1.64		
LDH					
≤240 IU/L	90	34 (37.78)	28.54 ± 1.15	15.911	<.001
>240 IU/L	12	10 (83.33)	16.50 ± 3.06		
ALB					
≤44.5 g/L	56	29 (51.79)	24.43 ± 1.66	3.619	.057
>44.5 g/L	59	21 (35.59)	28.95 ± 1.40		
LMR					
≤3.49	60	32 (53.33)	24.70 ± 1.52	5.166	.023
>3.49	59	19 (32.2)	29.27 ± 1.47		
NLR					
<2.60	73	26 (35.62)	28.55 ± 1.32	4.126	.042
≥2.60	46	25 (54.35)	24.46 ± 1.77		
Hb					
Anemia	24	7 (29.17)	30.21 ± 2.01	2.252	.133
Normal	95	44 (46.32)	26.15 ± 1.23		
PLT					
Normal or less	108	47 (43.52)	26.98 ± 1.12	0.077	.781
Thrombocytosis	11	4 (36.36)	26.82 ± 3.75		
Chemotherapy					
Yes	76	34 (44.74)	26.82 ± 1.33	0.166	.684
No	43	17 (39.53)	27.23 ± 1.82		
AJCC stage					
I–II	23	3 (13.04)	33.35 ± 1.59	8.776	.003
III–IV	96	48 (50)	25.44 ± 1.22		
T stage					
T1–2	67	22 (32.84)	28.99 ± 1.32	6.165	.013
T3–4	52	29 (55.77)	24.37 ± 1.71		
N stage					
N0	13	1 (7.69)	34.77 ± 1.18	6.116	.013
N1–3	106	50 (47.17)	26.01 ± 1.16		

AJCC = American Joint Committee on Cancer, ALB = albumen, DM = distant metastasis, Hb = hemoglobin, LDH = lactate dehydrogenase, LMR = lymphocyte–monocyte ratio, NLR = neutrophil–lymphocyte ratio, PLT = platelet.

3 years. On average, DM occurred at 26.97 ± 1.07 months after the initial RT or CRT treatment.

Univariate analysis (Table 2) revealed that increased LDH level (LDH >240 IU/L, $\chi^2 = 15.911$, $P < .001$), lower LMR value (LMR ≤ 3.49, $\chi^2 = 5.166$, $P = .023$), higher NLR value (NLR ≥ 2.60, $\chi^2 = 4.126$, $P = .042$), advanced AJCC stage (III/IV stage, $\chi^2 = 8.776$, $P = .003$), advanced tumor (T) stage (T3–4 stage, $\chi^2 = 6.165$, $P = .013$) and advanced lymph node (N) stage (N1–3 stage, $\chi^2 = 6.116$, $P = .013$) were significantly correlated with the presence of DM. In contrast, no significant correlations were noted between DM and gender ($\chi^2 = 2.805$, $P = .094$), age ($\chi^2 = 3.584$, $P = .058$) or ALB level ($\chi^2 = 3.619$, $P = .057$). The presence of anemia ($\chi^2 = 2.252$, $P = .133$) and thrombocytosis ($\chi^2 = 0.077$, $P = .781$) did not increase the risk of DM. Moreover, treatment with RT or CRT did not significantly affect the incidence of DM ($\chi^2 = 0.166$, $P = .684$).

The pretreatment factors showing a $P < .05$ from univariate analysis were used in the multivariate analysis, which showed that only AJCC stage and LDH were independent risk factors of DM. An AJCC stage III–IV or high LDH level (>240 IU/L) significantly increased the risk of DM, with OR values of 5.043 (95% CI: 1.218–20.882; $P = .026$), and 3.420 (95% CI: 1.655–7.067; $P = .001$), respectively (Table 3).

4. Discussion

Survival in NPC is severely compromised by the development of DM, whether in the early 2D-RT period or following treatment with IMRT,[3–9,11] indicating that DM is a formidable task for the treatment of NPC.[17,18] Patients without obvious clinical evidence of DM at the time of initial diagnosis may already have subclinical micrometastases not detected by routine examinations.[19,20] This may explain why the majority of DM develops within 3 years of treatment. Thus, the key strategy to improve the survival of NPC patients is to be able to predict the risk of DM and to select the treatment options accordingly. In this study, we

Table 3

Multivariate analysis using a Cox proportional hazards regression model.

Variables	OR	95% CI	P
Gender (male)	0.602	0.286–1.268	.182
Age (≤49)	1.534	0.845–2.787	.160
AJCC Stage (I–II)	5.043	1.218–20.882	.026
LDH (≤240 IU/L)	3.420	1.655–7.067	.001

CI = confidence interval, LDH = lactate dehydrogenase, OR = odds ratio.

retrospectively analyzed the correlations between various pretreatment baseline factors and DM to identify those predictive of DM and thus high-risk patients who may benefit from early aggressive therapy.

We first used the Log-rank test for univariate analysis to identify pretreatment clinical factors significantly correlated with DM after RT. Given that many clinical factors are interrelated, it is challenging to separate factors or to identify relationships between factors. Therefore, we included factors showing a $P < .05$ from the univariate analysis in the multivariate analysis, and established an optimal formula to accurately predict DM.

We found that an advanced clinical stage (AJCC III/IV) at the time of diagnosis had a strong impact on predicting DM, consistent with previous reports.[3,4,9,21]The AJCC N stage and AJCC T stage, although significant factors for DM by univariate analysis, were not significant by multivariate analysis. The value of AJCC T stage for predicting DM varied between studies.[4,9,21]

We found that the pretreatment baseline LDH level significantly correlated with DM development. Patients with higher LDH were more likely to develop DM, as reported previously.[2,3,22] In spite of extensive efforts, the underlying mechanisms linking LDH to DM remain largely unknown,[23–25] although it was noted that elevated serum LDH levels were associated with advanced clinical stage.[22]

In addition, the pretreatment LMR value and pretreatment NLR were sometimes used to study the prognosis of NPC. A meta-analysis revealed that enhanced LMR was significantly associated with favorable overall survival in patients with digestive system cancers (HR = 0.63, 95% CI: 0.49–0.81), urinary tract tumors (HR = 0.66, 95% CI: 0.52–0.84), lung cancer (HR = 0.62, 95% CI: 0.54–0.72), and NPC (HR = 0.50, 95% CI: 0.43–0.57).[26] This is likely because inflammation has been confirmed as a key component of cancer progression, and lymphocytes and monocytes are important inflammatory components. Pretreatment LMR reflects the balance of lymphocytes and monocytes.[27,28] We also found a few studies have examined the relationship between NLR and DM in cancer patients.[22,29,30] One found that NLR > 5 predicts shorter overall survival in patients with head and neck squamous cell carcinoma.[29] Another study demonstrated that NLR > 2.81 was a significant adverse independent predictive factor for DM.[30] However, in our study, the pretreatment LMR value and pretreatment NLR were not statistically significant by multivariate analysis, although its *P*-value was <.05 by univariate analysis. The relationship between these 2 factors and metastasis of NPC remains to be further explored.

Other factors, including age, sex, pretreatment platelet count, serum ALB level, and anemia were not significantly correlated with DM in this study, which is consistent with other studies.[8,21,22,31–34]

It is noteworthy that no significant difference in DM was observed between patients receiving RT and those receiving CRT. The CRT options used in this study included concurrent, neoadjuvant, and adjuvant chemotherapy. However, it is controversial which treatment is more effective. Although it is commonly agreed that concurrent cisplatin-based CRT is the standard treatment plan for locally advanced NPC,[35,36] our study showed no advantage for any treatment option. However, the limited number of patients receiving each treatment in this study may obscure the potential significance of any regimen. In addition, analyzing patients from a single center may also generate selection bias. Therefore, future studies involving a greater number of patients from multiple centers and receiving different treatments are needed to the impacts of treatment options on DM and patient survival.

In summary, we identified that advanced AJCC stage and high LDH level were independent, significant risk factors for DM in NPC patients. As routinely measured factors before the initiation of treatment, they represent easily accessible, inexpensive, and robust predictors to be used in clinic. The findings from this study will pave the way for improved prediction of patient prognosis and thus a better selection of treatment options for NPC patients.

References

[1] Wei KR, Zheng RS, Zhang SW, et al. Nasopharyngeal carcinoma incidence and mortality in China in 2010. Chin J Cancer 2014;33:381–7.

[2] Paiar F, Di CV, Zei G, et al. Role of chemotherapy in nasopharyngeal carcinoma. Oncol Rev 2012;6:e1.

[3] 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.

[4] Lee AW, Poon YF, Foo W, et al. Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976–1985: overall survival and patterns of failure. Int J Radiat Oncol Biol Phys 1992;23:261–70.

[5] Yi JL, Gao L, Huang XD, et al. Nasopharyngeal carcinoma treated by radical radiotherapy alone: ten-year experience of a single institution. Int J Radiat Oncol Biol Phys 2006;65:161–8.

[6] Lee AW, Lau WH, Tung SY, et al. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. J Clin Oncol 2005;23:6966–75.

[7] Jiang F, Jin T, Feng XL, et al. Long-term outcomes and failure patterns of patients with nasopharyngeal carcinoma staged by magnetic resonance imaging in intensity-modulated radiotherapy era: the Zhejiang Cancer Hospital's experience. J Cancer Res Ther 2015;11(suppl 2):C179–84.

[8] Li AC, Xiao WW, Shen GZ, et al. Distant metastasis risk and patterns of nasopharyngeal carcinoma in the era of IMRT: long-term results and benefits of chemotherapy. Oncotarget 2015;6:24511–21.

[9] Wang W, Feng M, Fan Z, et al. Clinical outcomes and prognostic factors of 695 nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy. Biomed Res Int 2014;2014:814948.

[10] Zhao Y, Zhang J, Tian Y, et al. Met tyrosine kinase inhibitor, PF-2341066, suppresses growth and invasion of nasopharyngeal carcinoma. Drug Des Devel Ther 2015;9:4897–907.

[11] Zhao C, Lu L, Han F. Treatment outcomes of 122 nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy. Chinese J Radiat Oncol 2006;15:364–8.

[12] Shen T, Tang LQ, Gu WG, et al. Plasma Epstein-Barr viral deoxyribonucleic acid predicts worse outcomes in pediatric nonmetastatic nasopharyngeal carcinoma patients: an observational study of 89 cases in an endemic area. Medicine (Baltimore) 2015;94:e1945.

[13] Yang Q, Lin H, Wu S, et al. Prostate tumor overexpressed 1 (PTOV1) is a novel prognostic marker for nasopharyngeal carcinoma progression and poor survival outcomes. PLoS ONE 2015;10:e0136448.

[14] Peng H, Chen L, Tang LL, et al. Primary tumor inflammation in gross tumor volume as a prognostic factor for nasopharyngeal carcinoma patients. Oncotarget 2016;7:14963–72.

[15] Zeng Q, Shen LJ, Guo X, et al. Critical weight loss predicts poor prognosis in nasopharyngeal carcinoma. BMC Cancer 2016;16:169.

[16] Lee N, Harris J, Garden AS, et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. J Clin Oncol 2009;27:3684–90.

[17] Li Y, Pan K, Liu LZ, et al. Sequential cytokine-induced killer cell immunotherapy enhances the efficacy of the gemcitabine plus cisplatin chemotherapy regimen for metastatic nasopharyngeal carcinoma. PLoS ONE 2015;10:e0130620.

[18] Zheng W, Zong J, Huang C, et al. Multimodality treatment may improve the survival rate of patients with metastatic nasopharyngeal carcinoma with good performance status. PLoS ONE 2016;11:e0146771.

[19] Hong RL, Ting LL, Ko JY, et al. Induction chemotherapy with mitomycin, epirubicin, cisplatin, fluorouracil, and leucovorin followed

by radiotherapy in the treatment of locoregionally advanced nasopharyngeal carcinoma. J Clin Oncol 2001;19:4305–13.
[20] Lin JC, Chen KY, Wang WY, et al. Evaluation of cytokeratin-19 mRNA as a tumor marker in the peripheral blood of nasopharyngeal carcinoma patients receiving concurrent chemoradiotherapy. Int J Cancer 2002;97:548–53.
[21] Guo SS, Tang LQ, Chen QY, et al. Is hemoglobin level in patients with nasopharyngeal carcinoma still a significant prognostic factor in the era of intensity-modulated radiotherapy technology? PLoS ONE 2015;10: e0136033.
[22] Zeng Q, Hong MH, Shen LJ, et al. Nomograms for predicting long-term survival in patients with non-metastatic nasopharyngeal carcinoma in an endemic area. Oncotarget 2016;7:29708–19.
[23] Armstrong AJ, George DJ, Halabi S. Serum lactate dehydrogenase predicts for overall survival benefit in patients with metastatic renal cell carcinoma treated with inhibition of mammalian target of rapamycin. J Clin Oncol 2012;30:3402–7.
[24] Kim JW, Dang CV. Cancer's molecular sweet tooth and the Warburg effect. Cancer Res 2006;66:8927–30.
[25] Yu X, Zhen Y, Yang H, et al. Loss of connective tissue growth factor as an unfavorable prognosis factor activates miR-18b by PI3K/AKT/C-Jun and C-Myc and promotes cell growth in nasopharyngeal carcinoma. Cell Death Dis 2013;4:e634.
[26] Teng JJ, Zhang J, Zhang TY, et al. Prognostic value of peripheral blood lymphocyte-to-monocyte ratio in patients with solid tumors: a meta-analysis. Onco Targets Ther 2016;9:37–47.
[27] Li J, Jiang R, Liu WS, et al. A large cohort study reveals the association of elevated peripheral blood lymphocyte-to-monocyte ratio with favorable prognosis in nasopharyngeal carcinoma. PLoS ONE 2013;8:e83069.
[28] Lin GN, Peng JW, Liu DY, et al. Increased lymphocyte to monocyte ratio is associated with better prognosis in patients with newly diagnosed metastatic nasopharyngeal carcinoma receiving chemotherapy. Tumour Biol 2014;35:10849–54.
[29] Charles KA, Harris BD, Haddad CR, et al. Systemic inflammation is an independent predictive marker of clinical outcomes in mucosal squamous cell carcinoma of the head and neck in oropharyngeal and non-oropharyngeal patients. BMC Cancer 2016;16:124.
[30] Li AC, Xiao WW, Wang L, et al. Risk factors and prediction-score model for distant metastasis in nasopharyngeal carcinoma treated with intensity-modulated radiotherapy. Tumour Biol 2015;36:8349–57.
[31] Chen YP, Chen C, Mai ZY, et al. Pretreatment platelet count as a predictor for survival and distant metastasis in nasopharyngeal carcinoma patients. Oncol Lett 2015;9:1458–66.
[32] Du XJ, Tang LL, Mao YP, et al. Circulating EBV DNA, globulin and nodal size predict distant metastasis after intensity-modulated radiotherapy in stage II nasopharyngeal carcinoma. J Cancer 2016;7:664–70.
[33] Jin Y, Cai XY, Cai YC, et al. To build a prognostic score model containing indispensible tumour markers for metastatic nasopharyngeal carcinoma in an epidemic area. Eur J Cancer 2012;48:882–8.
[34] Li G, Gao J, Liu ZG, et al. Influence of pretreatment ideal body weight percentile and albumin on prognosis of nasopharyngeal carcinoma: long-term outcomes of 512 patients from a single institution. Head Neck 2014;36:660–6.
[35] Guigay J. Advances in nasopharyngeal carcinoma. Curr Opin Oncol 2008;20:264–9.
[36] Guigay J, Temam S, Bourhis J, et al. Nasopharyngeal carcinoma and therapeutic management: the place of chemotherapy. Ann Oncol 2006;17(suppl 10):x304–7.