Hindawi Publishing Corporation
Disease Markers
Volume 35 (2013), Issue 6, Pages 925–932
http://dx.doi.org/10.1155/2013/251209

Research Article

Nuclear p27 Expression Confers a Favorable Outcome for Nasopharyngeal Carcinoma Patients

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Received 25 June 2013; Revised 23 September 2013; Accepted 23 September 2013

Academic Editor: Stamatios Theocharis

Objective. The purpose of the present study is to explore the correlation between nuclear expression of cyclin-dependent kinase inhibitor 1B (p27) and clinicopathologic features in nasopharyngeal carcinoma (NPC), including patient survival. *Methods*. Immunohistochemistry was used to examine the expression of p27 in 130 primary NPC tissues. The relationship between the levels of p27 expression and clinicopathologic characteristics was analyzed. Survival curves were plotted using the Kaplan-Meier method and compared using the log-rank test. The significance of various survival variables was analyzed using multivariate Cox proportional hazards model. *Results*. p27 was expressed in both nuclear and cytoplasmic compartments. Nuclear expression of p27 was inversely correlated with T classification and clinical stage. Patients with nuclear p27 expression had better overall survival rates than those without nuclear expression of p27. Further, we observed that nuclear expression of p27 was positively associated with survival time of NPC patients not only in N0-1 and M0 classifications but also in radiotherapy and chemotherapy treatment groups. Finally, we found that nuclear expression of p27 was not an independent prognostic factor for patients with NPC. *Conclusions*. Our findings hint that nuclear expression of p27 is a potentially favorable factor in the progression and prognosis of NPC.

1. Introduction

Nasopharyngeal carcinoma (NPC) is the most common primary malignant neoplasm of the nasopharynx with nearly 100% of cases associated with Epstein-Barr virus (EBV) infection [1]. It is rare in most populations but is frequent in both genders in areas such as Southeast Asia, Southern China, and North Africa. Due to its anatomical location and ambiguous symptoms, patients with this malignancy most often present with a cervical mass from metastatic spread to a lymph node or adjacent structures, thus leading to a poor prognosis.

Genetic susceptibility, environmental factors, Epstein-Barr virus infection, and epigenetic changes are key factors in nasopharynx carcinogenesis deregulating a number of significant genes and miRNAs, such as EZH2, HDGF, NESG1, CTGF, and miR-26a [2–8]. In a previous investigation, we used cDNA microarray to compare differentially expressed genes among NPC and noncancerous nasopharyngeal tissues. p27, a gene encoding cyclin-dependent kinase inhibitor 1B, was shown to be markedly decreased in NPC tissues, suggesting its potentially suppressive role in NPC pathogenesis [9].

p27 is an enzyme inhibitor encoded by the CDKN1B gene in humans that belongs to the Cip/Kip family of cyclin-dependent kinase (Cdk) proteins. The encoded protein binds to and prevents the activation of cyclin E-CDK2 or cyclin D-CDK4 complexes, and thus controlling cell cycle progression

at G1. Downregulation of P27 has been implicated in the progression of several malignancies, including lung cancer [10], hepatocellular carcinoma [11], salivary cancer [12], oral squamous cell carcinomas [13, 14], and gastric cancer [15]. Further, p27 was also observed to play a significant role in suppressing tumor pathogenesis [16, 17] yet its function in NPC has not been determined.

Our objective in this study is to investigate the expression of p27 in NPC tissues by immunohistochemistry and explore the correlation of p27 nuclear expression with clinicopathologic features and patient survival prognosis. Our results suggest that positive nuclear expression of p27 is a favorable factor for delaying disease progression and elevating overall survival time of NPC patients.

2. Patients and Methods

2.1. Sample Collection. One hundred and thirty (130) undifferentiated NPC paraffin-embedded specimens with clinical and prognosis information were obtained from patients ranging from 21 to 80 years old (median, 49.6 years) at the People's Hospital of Zhongshan City. These samples were totally absent of keratinization and lymphoepitheliomatous morphology with different degrees of infiltrating lymphocytic presence ranging from 5% to 55% in the carcinoma cells and stroma. Among these patients, there were 19 patients treated by radiotherapy alone, 4 by chemotherapy, and 97 by combination radiotherapy and chemotherapy. Eleven patients did not accept any treatment. For the use of these clinical materials for research purposes, prior consent from the patients and approval from the Ethics Committees of these two hospitals were obtained. All specimens had confirmed pathological diagnosis and were staged according to the 1997 NPC staging system of the UICC [18].

2.2. Immunohistochemistry. Immunohistochemistry was carried out according to our previous description [3, 4]. P27 antibody was used at a concentration of 1 : 100 (Santa Cruz Biotechnology, USA).

2.3. Evaluation of Staining. The immunohistochemically stained tissue sections were reviewed and scored separately by two pathologists blinded to the clinical parameters and evaluated for the presence of nuclear staining. Nuclear staining of 10% or more tumor cells was considered as positive for nuclear expression. On the contrary, less than 10% staining was regarded as negative nuclear expression.

2.4. Statistical Analyses. All statistical analyses were performed using SPSS 13.0. The χ^2 test was used to analyze the relationship between the levels of p27 expression and clinicopathologic characteristics. Survival curves were plotted using the Kaplan-Meier method and compared using the log-rank test. The significance of various survival variables was analyzed using multivariate Cox proportional hazards model. A P value of less than 0.05 was considered statistically significant.

Table 1: Correlation between the clinicopathologic characteristics and nuclear expression of p27 protein in NPC.

Characteristics	n	Nuclear expression of P27 (%)		P
		No	Yes	
Gender				
Male	93	42	51	
Female	37	22	15	0.175
Age (y)				
≥50	68	34	34	
<50	62	30	32	0.863
Smoking				
Yes	32	12	20	
No	98	52	46	0.156
Family tumor history				
Yes	4	2	2	
No	126	62	64	1.000
T classification				
T_1-T_2	90	36	54	
T_3-T_4	40	28	12	0.002
N classification				
N_0-N_1	73	32	41	
N_2-N_3	57	32	25	0.216
Distant metastasis				
Yes	10	5	5	
No	120	59	61	1.000
TNM clinical stage				
I~II	49	17	32	
III~IV	81	47	34	0.012

3. Results

3.1. Immunohistochemical Analysis of p27 Protein Expression in NPC Tissues. We measured the expression levels and cellular localization of p27 protein in 130 archived paraffin-embedded NPC samples using immunohistochemical staining (Figure 1). Specific p27 protein staining was detected in the nuclei and cytoplasm of malignant epithelial cells. Furthermore, we observed that 50.8% (66/130) of cases showed clear expression of p27 (Table 1).

3.2. Relationship between Clinicopathological Characteristics and p27 Nuclear Expression in NPC Patients. The relationship between clinicopathological characteristics and p27 nuclear expression in individuals with NPC is summarized in Table 1. We did not find a significant association between p27 nuclear expression with patient's age, sex, smoking, N classification, or distant metastasis (M classification) in 130 NPC cases. However, we observed that p27 nuclear expression was inversely correlated with T classification ($P = 0.002$) (T_1-T_2 versus T_3-T_4) ($P = 0.012$) and clinical stage (I-II versus III-IV) ($P = 0.012$) in NPC patients (Table 1).

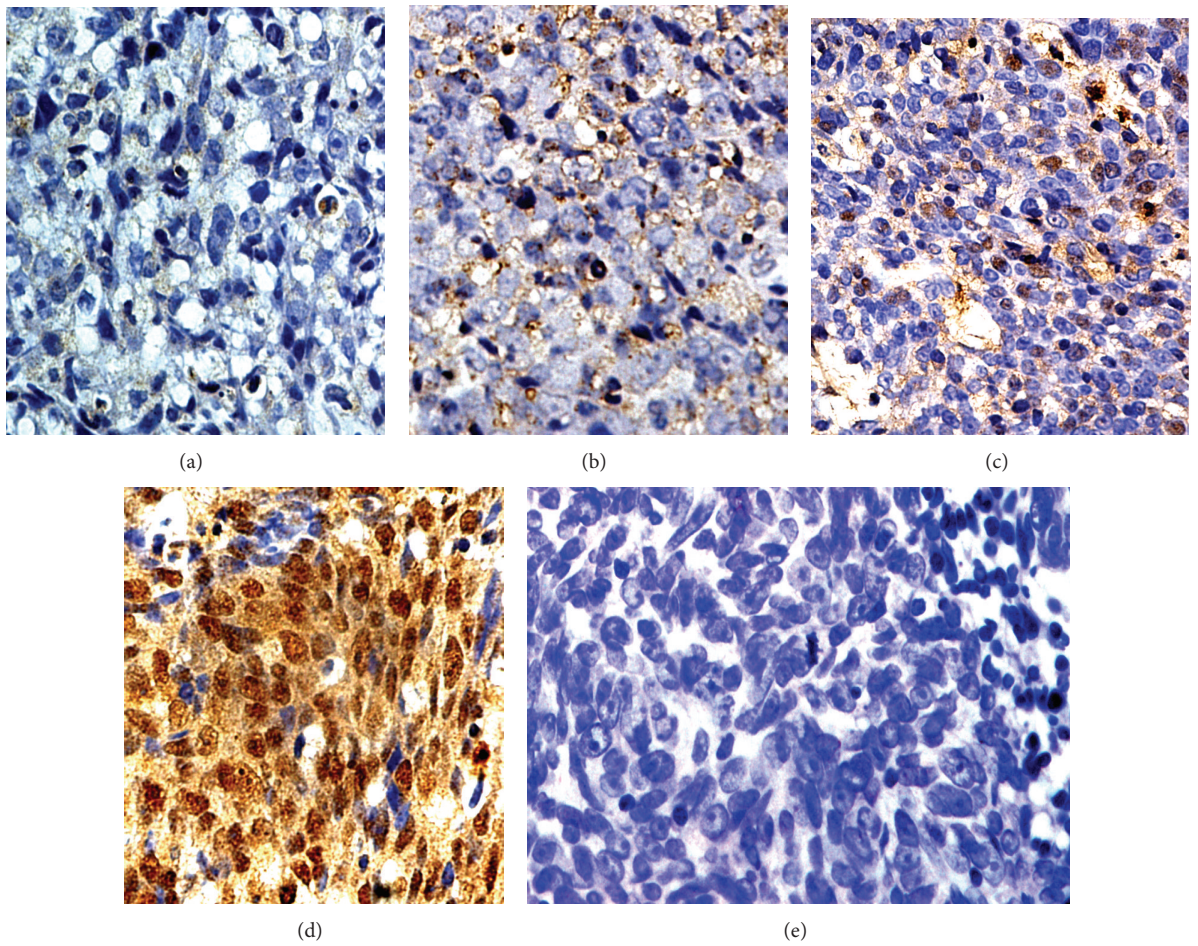

Figure 1: p27 protein is expressed in the cytoplasm and nuclei of malignant epithelial cells in NPC samples (original magnification: ×400). (a) and (b) p27 protein expression in cytoplasm of NPC tissues (negative nuclear expression); (c)-(d) p27 protein expression in the nucleus of NPC tissues (positive nuclear expression). (e) Negative control.

3.3. p27 Nuclear Expression Is Associated with Overall Survival Time of NPC. To investigate the prognostic value of p27 protein expression in NPC, we assessed the association between the levels of p27 nuclear expression and patients' survival using Kaplan-Meier analysis with the log-rank test. In 130 NPC cases with prognosis information, we observed that nuclear expression of p27 was significantly correlated with the overall survival of NPC patients. Patients with nuclear expression had better prognoses than those with negative nuclear expression of p27 (Figure 2) ($P = 0.007$).

3.4. p27 Nuclear Expression Is Correlated with Survival Time of NPC Patients with N_0-N_1 Classification and M_0 Classification. We further analyzed the correlation of p27 nuclear expression with prognosis for NPC patients by stratification analysis against T classification, N classification, M_0 classification, and clinical stage. Positive p27 protein nuclear expression was significantly associated with survival time for NPC patients in N_0-N_1 classification and M_0 classification but did not correlate with T_1-T_2, T_3-T_4, or N_2-N_3 classifications nor clinical stages I-II or III-IV. Patients with nuclear expression had better prognosis than those with negative nuclear expression of p27 in N_0-N_1 classification ($P = 0.002$) and M_0 classification ($P = 0.003$) (Figure 3).

3.5. p27 Nuclear Expression Is Favorable for Prognosis of NPC Patients with Radiotherapy and Chemotherapy. We also explored the association of p27 nuclear expression with NPC patient survival in groups treated by chemotherapy and radiotherapy. We found a significant correlation between p27 nuclear expression and NPC prognosis in the chemotherapy and radiotherapy treated groups, but not in untreated patients. Patients with nuclear expression had better prognosis than those with negative nuclear expression of p27 after the respective treatment of chemotherapy ($P = 0.009$) and radiotherapy ($P = 0.023$) (Figure 4).

3.6. Nuclear Expression of p27 Is Not an Independent Prognosis Factor for NPC Patients. Univariate analyses showed that radiotherapy, T, N, and M classifications, clinical stages, and p27 nuclear expression were all significantly correlated with

Table 2: Summary of univariate and multivariate Cox regression analysis of overall survival duration.

Parameter	Univariate analysis			Multivariate analysis		
	P	HR	95% CI	*P*	HR	95% CI
Gender						
Male versus female	0.485	0.488	0.665–2.361			
Age						
≥50 versus <50 years	0.787	0.073	0.620–1.881			
Family tumor history						
Yes versus no	0.349	0.877	0.000–28.401			
Smoking						
Yes versus no	0.387	0748	0.368–1.474			
Chemotherapy						
Yes versus no	0.700	1.153	0.560–2.372			
Radiotherapy						
Yes versus no	0.005	0.369	0.184–0.742	0.990	0.994	0.419–2.358
T classification						
T_1-T_2 versus T_3-T_4	0.000	28.042	2.674–8.496	0.014	2.725	1.222–6.075
N classification						
N_0-N_1 versus N_2-N_3	0.000	2.950	1.662 –5.237	0.240	1.633	0.720–3.702
M classification						
M_0 versus M_1	0.000	35.042	5.031–24.906	0.005	4.461	1576–12.633
TNM clinical stage						
I-II versus III-IV	0.000	19.386	3.592–27.943	0.051	3.758	0.992–14.239
p27 nuclear expression						
Positive expression versus negative expression	0.009	0.460	0.257–0.822	0.690	0.878	0.464–1.661

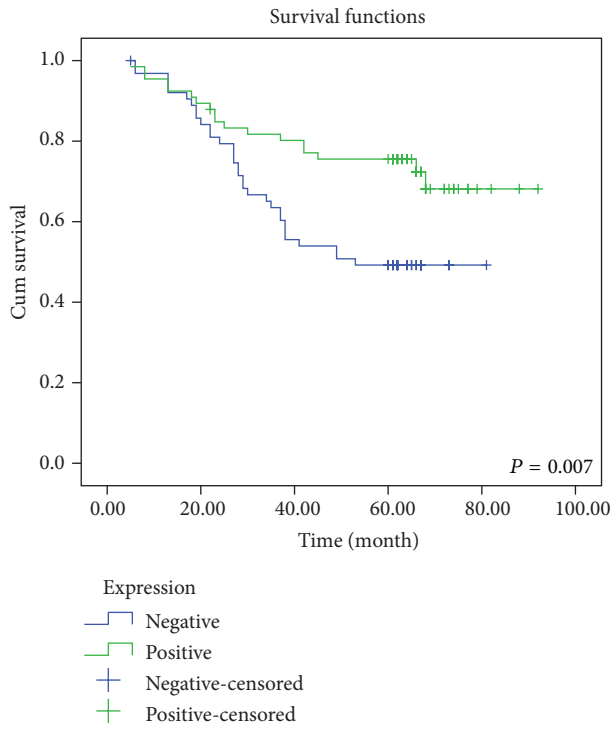

Figure 2: Nuclear expression or nuclear expression level of p27 protein predicts NPC patients' overall survival time. Patients with nuclear positive expression of p27 had better survival than those with negative nuclear expression of p27.

patients' survival ($P = 0.005$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, and $P = 0.009$, resp.). To determine whether p27 is an independent prognostic factor for NPC, we performed multivariate analysis of p27 protein expression levels adjusted for radiotherapy, T classification, N classification, M classification, and clinical stages of NPC patients. These results showed that the level of p27 expression was not an independent prognostic factor for NPC ($P = 0.690$) (Table 2).

4. Discussion

P27 is a key cell cycle protein kinase inhibitor which forms a nuclear complex with CCND1 and CDK4. This prevents CDK4 from adding phosphate residues to its principal substrate, retinoblastoma (pRb) protein blocking cell cycle G1/S transition. P27 expression levels are inversely related with CCND1 and CDK4 in NPC [9, 19]. Furthermore, p27 is able to bind other Cdk proteins when complexed to cyclin subunits such as cyclin E/Cdk2 and cyclin A/Cdk2 and suppress cell cycle transition. Decreased expression of p27 has been described in many tumors, including bladder cancer [20], melanoma [21], and ovarian cancer [22], and is associated with unfavorable clinical parameters and poor outcomes in these tumor types. Del Pizzo et al. found decreased expression of p27Kip1 in poorly differentiated bladder tumors (grades III) compared to well and moderately differentiated (grades I and II) tumors and it was an unfavorable prognostic

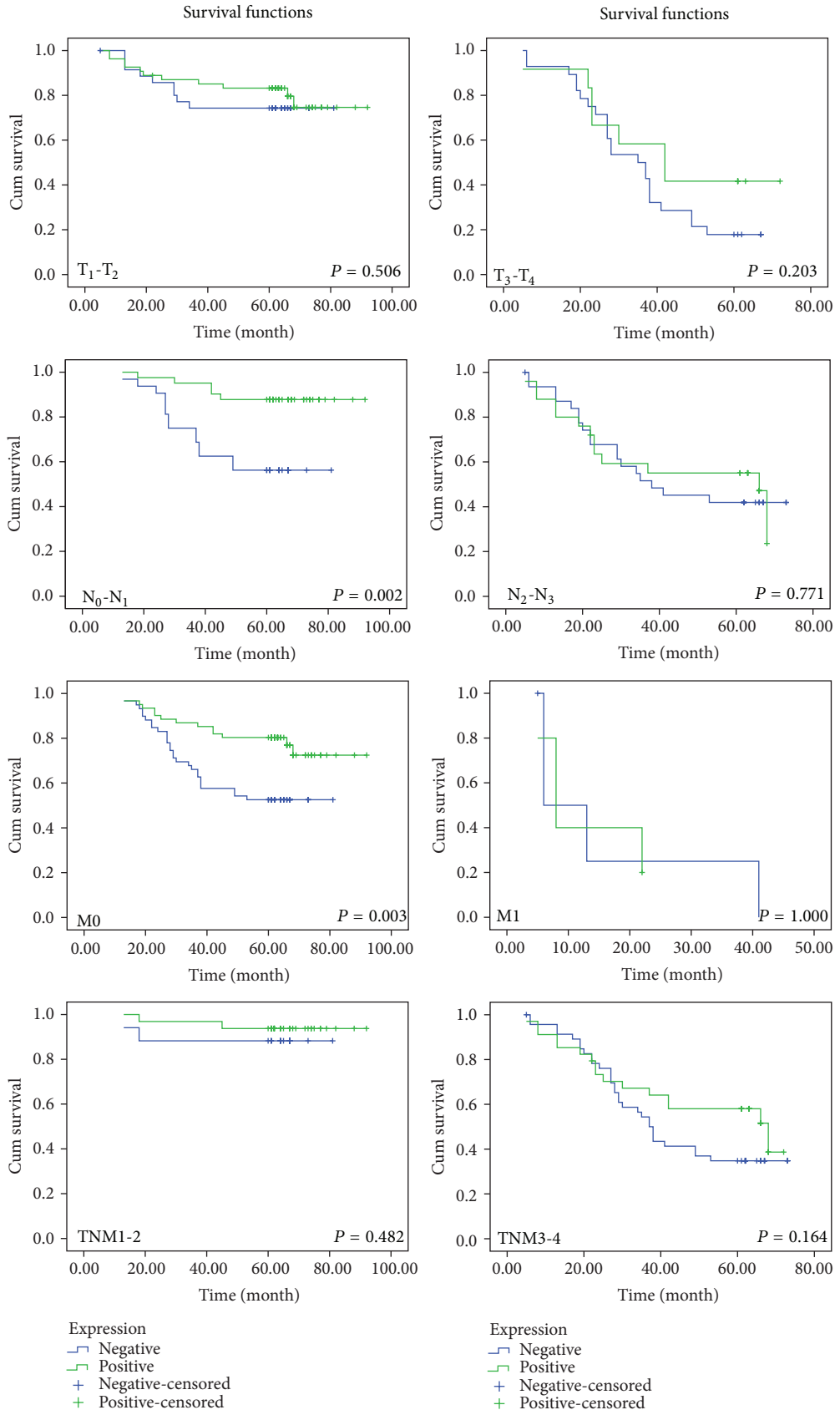

FIGURE 3: The correlation of p27 expression with NPC patients' survival time in strata analysis in TNM stage, T classification, N classification, and M classification P27 protein expression was significantly associated with the survival time for NPC patients with N_0-N_1 or M_0 classifications. NPC patients with nuclear expression of p27 protein had longer survival times.

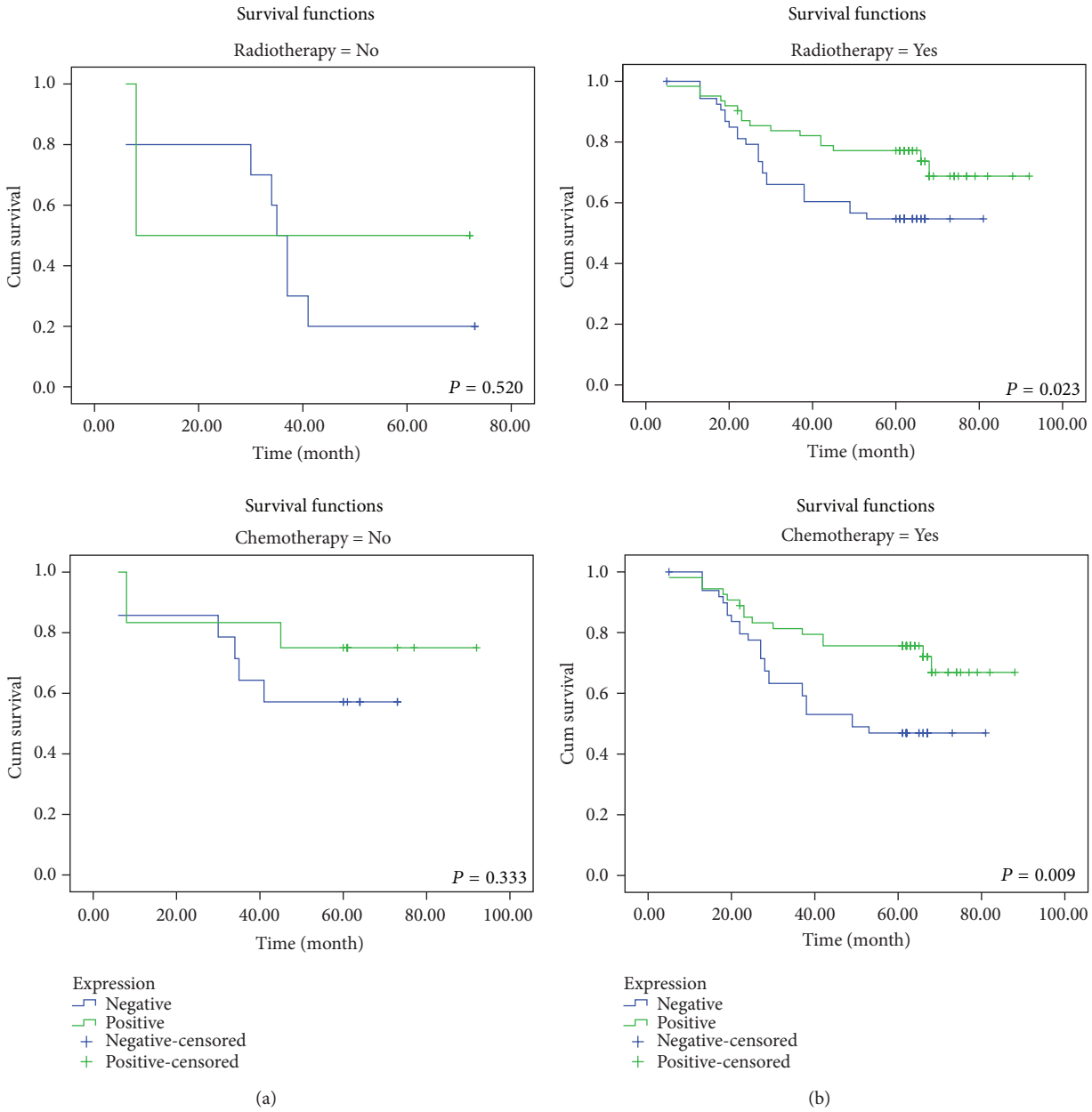

Figure 4: p27 nuclear expression was favorable for radiotherapy and chemotherapy treated NPC patients. p27 protein expression was significantly associated with the survival time for NPC patients treated by radiotherapy and chemotherapy but not for those untreated patients. (a) Patients with nuclear expression had better prognoses than those with negative nuclear expression of p27 after radiotherapy. (b) Patients with nuclear expression had better prognosis than those with negative nuclear expression of p27 after chemotherapy.

factor. Flørenes et al. observed a virtual complete loss of p27Kip1 protein expression in nodular melanoma which was a prognostic indicator of early relapse. In ovarian cancer, increased expression of p27 was associated with long-term survival of patients. These results strongly support that p27 functions as a tumor suppressor during carcinogenesis.

In previous investigation, Fan et al. reported that p27 expression was downregulated in EBV-infected nasopharyngeal carcinoma [23], a result similar to our findings in NPC [8]. Furthermore, suppression of p27 was also observed by LMP1 [24], a key EBV-expressing oncoprotein promoting the transformation of human nasopharyngeal epithelial cells [25]. These suggested that p27 is a significant gene downregulated during NPC progression, yet its correlation with clinical features and the prognostic value of NPC is not clear.

In this study, we evaluated the expression of p27 in NPC by immunohistochemistry and found that p27 protein was coexpressed in cytoplasm and nucleus of NPC tissues. This finding was consistent with previous reports from other tumors [10, 11, 15, 20–22]. Furthermore, we also observed that over half of NPC cases showed positive nuclear expression of p27. Because p27 drives cell cycle progression

when it translocates into the nucleus [26], we analyzed the correlation of p27 nuclear expression with clinical features of NPC patients and observed that p27 nuclear expression was inversely correlated with T classification and clinical stage. Furthermore, we found that nuclear expression of p27 protein in NPC was positively correlated with patient's overall survival time. Patients with nuclear expression of p27 protein had an overall longer survival time. Our results are similar to Del Pizzo, Flørenes, and Newcomb et al.'s reports from other tumors and together suggest that p27 nuclear expression inhibits the pathogenesis of NPC [20–22].

Further, survival prognosis was assessed by stratification analysis against T classification, N classification, M classification, and clinical stage. We observed that p27 nuclear expression was inversely associated with the survival time only for NPC patients with N_0-N_1 or M_0 classifications. Patients with nuclear expression had better prognosis than those of negative nuclear expression. These results hinted that p27 nuclear expression is a good biomarker for evaluating the prognosis of NPC patients with N_0-N_1 and M_0 classifications.

P27 functions as a cell cycle inhibitor blocking cell growth in many tumor types [27, 28]. We suspected that nuclear expression of p27 might be associated with the sensitivity to radiotherapy or chemotherapy, which would increase the overall survival time of NPC patients. Consistent with our hypothesis, we observed that patients with nuclear expression of p27 protein had an overall longer survival time in radiotherapy and chemotherapy groups, but no correlation in nontreated groups. This finding suggested that nuclear expression of p27 protein might decrease the resistance of radiotherapy and chemotherapy for NPC patients.

Finally, we evaluated the possibility of p27 nuclear expression as an independent prognostic factor for NPC. According to univariate analysis, patient's overall survival is inversely proportional to T/N/M classification and clinical stage but positively correlated with p27 nuclear expression and radiotherapy treatment. Multivariate analyses showed that nuclear expression of p27 protein was not an independent predictor of prognosis for NPC patients regardless of patient disease status.

In summary, our results provide evidence that lower nuclear expression of p27 may be involved in the clinical progression and poor prognosis of NPC patients. However, it could not serve as a potential independent prognostic factor for NPC.

Conflict of Interests

The authors declare that they have no conflict of interests.

Authors' Contribution

Zhen Liu, Yufei Long, Yajie Zhang, and Wei Huang contributed equally to this work.

Acknowledgments

This study was supported by National Nature Science Fund of China (no. 81071632), New Star Plan of Pearl River Science and Technology from Guangzhou City (no. 2011J2200009), and Yangchengz Scholar Research Projects from Universities of Guangzhou (no. 12A011D).

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