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Evaluation of the association between perineural invasion and clinical and histopathological features of cervical cancer

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Abstract. Perineural invasion (PNI) has been investigated as a new prognostic factor in a number of carcinomas. However, studies on PNI in cervical cancer are limited, and inconsistent conclusions have been reported by different groups. The aim of the present study was to analyze the relationship between perineural invasion (PNI) and clinical and histopathological features of cervical cancer, and to evaluate the clinical significance of PNI of cervical cancer. Retrospective review identified 206 patients with cervical cancer who underwent radical hysterectomy plus pelvic lymphadenectomy between December 2012 and August 2014. The association between PNI and clinical and histopathological features of cervical cancer and post-operative radiotherapy was evaluated based on univariate and multivariate analyses. PNI of cervical cancer was identified in 33 of 206 (16%) cervical cancer patients. Univariate analysis demonstrated that PNI was associated with clinical stage, tumor grade, tumor size, depth of invasion, lymphovascular space invasion (LVSI), and lymph node metastasis ($P<0.05$), but not associated with age and histopathological types ($P>0.05$). Multivariate analysis suggests that LVSI and lymph node metastasis were associated with PNI of cervical cancer ($P<0.05$). In addition, post-operative radiotherapy was significantly more recommended for patients with PNI than those without PNI ($P<0.001$). In conclusion, PNI of cervical cancer is associated with LVSI and lymph node metastasis and can be used as an index for the determination of post-operative radiotherapy for cervical cancer patients.

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Introduction

Perineural invasion (PNI) refers to the presence of tumor cells within any of the epineurium, perineurium, or endoneurium of a nerve. In some cases, PNI is considered to be a tumor in close proximity to nerve and involving at least one-third of its circumference (1). It was first reported in European literature during the mid-1800s by scientists who described head and neck cancer that exhibited a predilection for growth along nerves as they made their way toward the intracranial fossa (1). PNI has since emerged as a prognostic factor in numerous malignancies, including head and neck, pancreatic cancer, prostate and gastrointestinal cancer types (2-5). PNI has been generally accepted as a poor prognostic factor in head and neck squamous cell carcinoma (HNSCC) (6). Therefore, the 2014 National Comprehensive Cancer Network guidelines cite PNI as an established indication for adjuvant radiotherapy for HNSCC (7). In a previous study on gastric cancer, PNI emerged as an independent prognostic factor for survival. Additionally, the proportion of PNI positivity increased with progression and clinical stage of disease; therefore, it was suggested to incorporate this into tumor, node, metastasis staging (8). In another previous study on pancreatic cancer, PNI was considered as an independent predictor of prognosis and was associated with neuropathic pain (9). At present, studies on the PNI in cervical cancer are limited and inconsistent conclusions have been reported by different groups. In the current study, we conducted a retrospective study to evaluate the PNI in 206 cases of cervical cancer. The association between PNI in cervical cancer and a number of clinicopathological features and postoperative radiotherapy may allow improved prediction of the prognosis for cervical cancer and lead to better therapeutic strategies.

Materials and methods

Patients. A total of 206 cervical cancer patients who received surgical therapy in The Affiliated Tumor Hospital of Guangxi Medical University between December 2012 and August 2014 were included in the present retrospective study. The age of the 206 cervical cancer patients ranged from 28-73 years and their mean age was 48.2±8.9 years. According to the FIGO 2009 staging classification criteria (10), these tumors were identified as cervical cancer of IB1-IIB stages. Four major inclusion criteria were used in the patient selection: (i) Pre-operative adjuvant chemotherapy and/or radiotherapy were not conducted, (ii) The cancers are squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma based on histopathological examination, (iii) all patients received radical hysterectomy plus pelvic lymphadenectomy with or without para-aortic lymph node dissection, and (iv) abnormal function of vital organs was not observed. Post-operative adjuvant radiotherapy was conducted for patients who had ≥1 of the high risk factors for recurrence, including lymph node metastasis, parametrial invasion, and positive margins, or ≥2 of the medium risk factors for recurrence, including tumors >4 cm, depth of stromal invasion (>1/2), and lymphovascular space invasion (11-14).

The present study was approved by the Ethics Committee of The Affiliated Tumor Hospital of Guangxi Medical University (Guangxi, China) and all experiments adhered to the Declaration of Helsinki. Written informed consent was obtained from all patients.

Identification of PNI. Immunohistochemistry was conducted for S-100 protein staining of cervical and uterine tissue slides. The immunohistochemistry results were independently examined by two pathologists. PNI was defined as tumor cells within any of the three layers of the nerve sheath or tumor in close proximity to nerve and involving at least one-third of its circumference (1). In addition, the histologic subtype, tumor grade, tumor size, depth of stromal invasion, lymphovascular space invasion, and lymph node metastasis were also documented for association analyses.

Statistical analysis. Statistical analyses were conducted using the SPSS 16.0 software package. Measurement data were presented as the mean ± SD, and analyzed using the *t*-test. Count data were analyzed using the χ^2 test. Multivariate analyses were conducted using the Logistic regression method. $P<0.05$ was considered to indicate a statistically significant difference.

Results

PNI was detected in 16.0% (33 of 206 cases) of patients. Among the 33 PNI-positive cases, PNI in the cervix was identified in 28 patients and PNI in both the cervix and parametrium was identified in five patients. LVSI and lymph node metastasis were identified in four and three of the five patients, respectively, of those who had PNI in both the cervix and parametrium.

Based on univariate analysis, patients with positive PNI exhibited lower tumor differentiation and a higher incidence of large tumor size (>4 cm), depth of stromal invasion, LVSI, and lymph node metastasis compared with patients of negative PNI ($P<0.05$) (Table I). However, no significant difference in histopathological type and age were identified between the patients of positive and negative PNI ($P>0.05$; Table I).

Multivariate analysis was conducted to identify risk factors of PNI. In the multivariate logistic regression analysis, positive PNI was used as the dependent variable and significantly different variables identified in univariate analysis were used as arguments. Clinical stages were divided into two categorical variables (stages I and II) in the multivariate analysis. Our multivariate analysis results showed that LVSI and lymph node metastasis were risk factors of PNI ($P<0.05$) (Table II).

Post-operative adjuvant radiotherapy was recommended for 27 (81.8%) of 33 patients of positive PNI and 66 (38.2%) of 173 patients of negative PNI. Post-operative adjuvant radiotherapy had a significantly higher level of recommendations for patients with positive PNI than for patients with no PNI (χ^2=21.340, $P<0.001$).

Discussion

In the present study, PNI was identified in 33 of 206 cervical cancer patients between Ib1 and IIb stages. The PNI incidence of 16% in cervical cancer patients is consistent with that reported in previous studies (11,15). Additionally, it has been reported that the incidence of PNI in pancreatic, head and neck, prostate, gastric cancers is 98, 80, 75, and 60%, respectively (1). The incidence of PNI in cervical cancer is relatively lower than that in the aforementioned cancer types, which may be explained by extensive nerves around these tumor tissues and the strong interaction between these tumors and surrounding nerves (16).

Previous studies have explored the molecular mechanisms underlying PNI associated with tumors. First, potential gaps between the perineurium and fascicles of the nerve serves as a conduit for tumor cells migration (17,18). In addition, the mutual coexistence between tumors and surrounding nerves facilitates PNI. Specifically, nerve cells secret a number of cytokines that promote the growth and invasion of tumor cells (19,20). Moreover, tumor cells improve the growth of nerve cells by secreting a number of cytokines, such as neurotrophic factors, chemokines, and nerve adhesion factors (1,17,21,22). It has been reported previously that some tumor-derived cytokines are involved in the development and invasion of pancreatic and head and neck cancers (4,5,23,24), however, the role of tumor-derived cytokines in the invasion of cervical cancer is not well understood. Furthermore, it has been demonstrated that the expression of brain-derived neurotrophic factor and its receptor TrkB may be involved in the development and invasion of cervical cancer (25).

Inconsistent clinical significance of PNI of cervical cancer has been reported by different studies. However, most studies agree that PNI of cervical cancer is strongly associated with a number of risk factors and associated with poor prognosis of cervical cancer (26). Horn *et al* (27) reported that PNI was associated with post-operative tumor stage, cervical stromal invasion, and pelvic lymph node metastasis in early cervical cancer patients. The authors also identified that the 5-year survival rate of cervical cancer patients with PNI was significantly lower than that of patients with negative PNI. Multivariate regression analysis suggested that PNI and pelvic lymph node metastasis were independent prognostic factors for evaluating the survival of cervical cancer patients. Zhang *et al* (28) reported that PNI of cervical cancer was associated with tumor size, depth of stromal invasion, LVSI, parametrial invasion, and lymph node metastasis. While univariate analysis identified the association between PNI and disease-free survival (DFS) and overall survival (OS) in cervical cancer patients, multivariate analysis showed that PNI

Table I. The association between PNI and clinical and histopathological features of 206 cervical cancer patients.

Clinical and histopathological features	Negative PNI (n=173)	Positive PNI (n=33)	χ^2	P-value
Age, years	48.2±9.1	48.0±7.8	-	0.878
Cervical cancer stage, no. (%)[a]			9.618	0.047
IB1	71 (41)	7 (21.2)		
IB2	35 (20.2)	5 (15.2)		
IIA1	30 (17.3)	6 (18.2)		
IIA2	22 (12.7)	9 (27.3)		
IIB	15 (8.7)	6 (18.2)		
Tumor grade			6.082	0.048
G1	15 (8.7)	0 (0.0)		
G2	78 (45.1)	11 (33.3)		
G3	80 (46.2)	22 (66.7)		
Histopathological type, no. (%)			0.003	0.958
Squamous cell carcinoma	137 (79.2)	26 (78.8)		
Adeno/adenosquamous carcinoma	36 (20.8)	7 (21.2)		
Tumor size, no. (%)			4.151	0.042
≤4 cm	116 (67.1)	16 (48.5)		
>4 cm	57 (32.9)	17 (51.5)		
Depth of stromal invasion, no. (%)			5.909	0.015
≤1/2	70 (40.5)	6 (18.2)		
>1/2	103 (59.5)	27 (81.8)		
Lymphovascular space invasion, no. (%)			6.035	0.014
Yes	70 (40.5)	21 (63.6)		
No	103 (59.5)	12 (36.4)		
Lymph node metastasis, no. (%)			11.878	0.001
Yes	35 (20.2)	16 (48.5)		
No	138 (79.8)	17 (51.5)		

[a]Cervical cancer staged using criteria from FIGO 2009. PNI, perineural invasion.

Table II. The association between PNI and clinical and histopathological features of cervical cancer based on multivariate analyses.

Variable	Regression coefficients	s	Wald-χ^2	P-value	OR	95%CI
Clinical stage	0.862	0.405	4.039	0.052	2.361	1.084-5.267
Tumor grade	0.777	0.416	3.485	0.062	2.175	0.692-4.919
Tumor size	-0.091	0.419	40.047	0.828	0.913	0.402-2.074
Depth of stromal invasion	0.816	0.519	2.476	0.116	2.262	0.818-6.265
Lymphovascular space invasion	0.391	0.435	4.807	0.047	1.478	0.630-3.469
Lymph node metastasis	0.952	0.432	4.853	0.028	2.592	1.111-6.047
Constant	-3.164	0.533	35.301	0.000		

PNI, perineural invasion; OR, odds ratio; CI, confidence interval.

was not an independent factors of the evaluation of DFS or OS. The study conducted by Cho *et al* (11) suggests that PNI of cervical cancer was associated with both high risk factors including lymph node metastasis, positive margins, and parametrial invasion and medium risk factors such as LVSI and depth of stromal invasion. The lymph node metastasis rate in cervical cancer patients with PNI was four times higher than that in cervical cancer patients with negative PNI. While no statistically significant difference in the 5-year survival rate between cervical cancer patients with and without PNI, the

5-year survival rate of cervical cancer patients with PNI was lower than that of cervical cancer patients with negative PNI. In the present study, our univariate analysis showed that PNI of cervical cancer was associated with clinical stage, tumor grade, tumor size, depth of invasion, lymph vascular space invasion (LVSI), and lymph node metastasis (P<0.05), regardless of age and pathological type (P>0.05). In addition, our multivariate analysis revealed PNI of cervical cancer was associated with LVSI and lymph node metastasis, suggesting PNI is a poor prognostic factor for cervical cancer patients.

Post-operative adjuvant radiotherapy is typically recommended for cervical cancer patients at early stage on the basis of a number of risk factors for tumor recurrence (13,14). Currently, lymph node metastasis, parametrial invasion, and positive margins are considered as high-risk factors for cervical cancer recurrence. Patients with one of these high-risk factors are asked to receive post-operative adjuvant radiotherapy. Multiple medium-risk factors such as LVSI, tumor size, and invasion depth are used to determine post-operative adjuvant radiotherapy when no high-risk factors are identified. PNI, which is considered as an independent risk factor for tumor recurrence in head and neck cancer and skin cancer, is frequently used as an index in the determination of post-operative adjuvant radiotherapy (5,17,29). In the present study, we found that post-operative adjuvant radiotherapy was recommended for 81.8% of cervical cancer patients with PNI. The post-operative adjuvant radiotherapy in cervical cancer patients with PNI was significantly higher than that in cervical cancer patients with negative PNI (P<0.05). In a previous study conducted by Elsahwi *et al* (15), post-operative adjuvant radiotherapy was recommended for 17 of 24 (70.8%) cervical cancer patients with PNI, which is significantly higher than that for cervical cancer patients with negative PNI (15). Cho *et al* (11) also reported that post-operative adjuvant radiotherapy was recommended for 92% of cervical cancer patients with PNI, which is significantly higher than that for patients with negative PNI. Taken together, cervical cancer patients with PNI have poor prognosis compared to those without PNI. PNI is associated with a number of high-risk factors of cervical cancer recurrence and it can be used as an important index for the determination of post-operative adjuvant radiotherapy for cervical cancer.

It has been widely recognized that parametrial invasion is a risk factor for cervical cancer recurrence. However, PNI identification is usually ignored in the pathological examination of parametrial invasion of cervical cancer. In the present study, we found that five of the 33 cervical cancer patients with PNI had parametrial PNI. Memarzadeh *et al* (30) identified parametrial PNI in seven of 93 (7.2%) cervical cancer patients and six of the seven cervical cancer patients with parametrial PNI were positive of parametrial LVSI. Univariate analysis suggested that parametrial PNI was one of the independent prognostic factors, and the risk of recurrence in cervical cancer patients with parametrial PNI was 2.5 times higher than that in cervical cancer patients with negative PNI. However, Skręt-Magierlo *et al* (16) reported that parametrial PNI was associated with clinical stage, depth of cervical stromal invasion, and tumor size, but not associated with parametrial invasion, lymph node metastasis, LVSI, and recurrence-free survival. The association between parametrial PNI and clinical stage, tumor invasion depth, tumor size, and lymph node metastasis was not conducted in the present study due to the small number of parametrial PNI. Given that most parametrial PNI derives from the growth tumor cells along nerves, parametrial PNI is of more clinical significance than regular PNI that exhibits as the growth and distribution of tumor cell around nerves.

Currently, nerve-sparing radical hysterectomy (NSRH) is widely used for the treatment of cervical cancer. NSRH is useful for restoring the function of bladder and rectum after the surgery (31). Studies on the safety of NSRN are predominantly focused on the post-operative function of bladder and rectum and sexual activities, however, these studies have a number of limitations such as poor comparison, small sampling size, or shorter follow-up period. Whether NSRH is safer than the traditional radical hysterectomy has not yet been determined (32-34). Given that PNI of cervical cancer is associated with poor prognosis of cervical cancer patients, NSRH should be carefully recommended for cervical cancer patients with PNI. Skręt-Magierlo *et al* (16) suggest that frozen section examination of uterine nerves should be conducted in the surgery for cervical cancer patients who exhibited high-risk factors such as tumor size ≥4 cm, cervical stromal invasion depth ≥1.5 cm, or pelvic or para-aortic lymph node metastasis (16). NSRH can be conducted if PNI was not identified based on frozen section examination. The traditional radical hysterectomy should be conducted if PNI of cervical cancer was identified. However, some researchers consider tumor size <2 cm, shallow myometrial invasion, and no LVSI as the indications of NSRH (32). In the present study, our multivariate analysis identified that PNI of cervical cancer was associated with LVSI and lymph node metastasis, suggesting that LVSI and lymph node metastasis are independent risk factors for PNI. Therefore, NSRH should not be conducted in patients with pre-operative identification of LVSI based on histopathological examination and lymph node metastasis based on imaging examination.

Gil *et al* (35) reported that transfection of NV1066, a herpes simplex virus-1 (HSV-1) oncolytic mutant, into pancreatic cancer, prostate carcinoma, and adenoid cystic carcinoma cell lines induced high expression of enhanced green fluorescent protein. Then, the authors established PNI models in nude mice by inoculating these tumor cells in sciatic nerve endings. After NV1066 was injected into the sciatic nerve endings, PNI of these tumor cells can be observed under stereo microscope or PET imaging. This approach can be used to identify PNI of tumor cells, which is of great significance for the selection of NSRH.

In conclusion, we identified that PNI of cervical cancer was associated with LVSI and lymph node metastasis. Postoperative radiotherapy is recommended for most cervical cancer patients with PNI. In addition, PNI is an additional risk factor for cervical cancer recurrence and should be fully considered by physicians when evaluating the prognosis of cervical cancer and selection of NSRH.

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