Int J Clin Exp Med 2016;9(10):19634-19643
www.ijcem.com /ISSN:1940-5901/IJCEM0025099

Original Article

The significance of perineural invasion as a prognostic factor in cervical cancer patients of different ethnicities

Nan Tian, Gulina Kuerban

Gynecological Radiotherapy Unit 1, Tumor Hospital of Xinjiang Medical University, Urumqi, Suzhou Road 789, Xinjiang, China

Received July 10, 2015; Accepted July 4, 2016; Epub October 15, 2016; Published October 30, 2016

Abstract: Objective: The prognostic significance of perineural invasion (PNI) in cervical cancer has been previously investigated with no consistent conclusion. This study aimed at determining the prognostic value of PNI in cervical cancer patients who underwent radical hysterectomy. Method: Clinical data of 413 patients with cervical cancer (stages IB-IIB) who underwent radical hysterectomy between 2009 and 2014 were investigated retrospectively. Results: 8.0% of all patients (33/413) represented with PNI. Large tumor size (≥ 4 cm), lymph node metastasis, parametrial invasion and lymphovascular space invasion were closely associated with the presence of PNI. The 5-year recurrence-free-survival (RFS) rate was significantly decreased in all the patients with PNI (P = 0.048) or within Uyghur ethnic group (P = 0.034). The 5-year-overall-survival-rate (OS) for PNI-positive and PNI-negative patients were 70.5% and 79.9%, respectively with no significant difference (P = 0.383). Cox multivariate analysis indicated that PNI is not an independent prognostic factor for RFS or OS. Conclusion: Patients represented with PNI exhibited significantly decreased RFS in the whole cohort of patient samples as well as within Uyghur ethnic group. PNI cannot serve as an independent prognostic factor for cervical cancer patients, but is significantly associated with prognostic factors. Therefore, PNI may be a new risk factor candidate for cervical cancer.

Keywords: Cervical cancer, perineural invasion, ethnicity, prognosis

Introduction

Cervical cancer is the second most common cause of female specific cancer deaths in women over 65 years old worldwide [1]. In 2014, there was an estimated 12,900 new cases of invasive cervical cancer expected to be diagnosed, and about 4,100 women were expected to die of cervical cancer [20]. It is well-known that lymph node (LN) metastasis, resection margin involvement and tumor size are prognostic factors in cervical cancer [2-4]. However, the prognostic value of other factors, such as depth of stromal invasion and lymphovascular space invasion remains controversial [5, 6]. Therefore, the identification of new prognostic factor that can aid in determining the postoperative therapy is urgently needed.

Recent studies reported that perineural invasion (PNI) may have prognostic value in cervical cancer [19]. PNI is defined as cancer cell infiltration into the perineurium or neural fascicles around a tumor, and is considered to be another route for tumor dissemination in addition to blood vessel and lymphovascular invasion [13]. Prognostic significance of PNI has been evaluated in many malignancies, including pancreatic, gastrointestinal, prostate and biliary tract cancers [7-9]. Since its first description in mid-1800s, PNI has been identified in approximately 90% of surgical specimens in head and neck cancer, prostate cancer, and pancreatic cancer and in up to 33% of colorectal cancer specimens. PNI has been reported to be significantly associated with high recurrence rates and poor survival in these cancer types [1]. In cervical cancer, there are few studies regarding the prognostic value of PNI and the results have not reached a consensus.

In this study, we aimed to investigate the incidence of PNI and the prognostic significance of PNI in cervical cancer patients as a whole or within ethnicity based subgroups as well. In addition, we examined the association between

Table 1. Clinicopathological characteristics of patients with cervical cancer

Characteristics	PNI (+)	PNI (-)	P
Age (yr) ±	49.18±9.272	50.07±9.739	0.809
Ethnicity			0.129
Han	13 (6.0%)	202 (94%)	
Uyghur	20 (10.1%)	178 (89.9%)	
Histologic subtype			0.650
Squamous carcinoma	28 (84.8%)	334 (87.9%)	
Adenocarcinoma	3 (9.2%)	31 (8.1%)	
Adenosquamous carcinoma	1 (3.0%)	12 (3.2%)	
Small cell carcinoma	1 (3.0%)	3 (0.8%)	
Lymph node metastasis			0.010
Positive	11 (33.3%)	60 (15.8%)	
Negative	22 (66.7%)	320 (84.2%)	
Size			0.030
≥ 4 cm	9 (27.3%)	51 (13.4%)	
< 4 cm	24 (72.7%)	329 (86.6%)	
Depth of stromal invasion			0.248
≥ 1/2	24 (72.7%)	238 (62.6%)	
< 1/2	9 (27.3%)	142 (37.4%)	
Parametrial invasion			0.003
Positive	7 (78.8%)	25 (6.6%)	
Negative	26 (21.2%)	355 (93.4%)	
Lymphovascular space invasion			< 0.001
Positive	22 (63.6%)	53 (14.2%)	
Negative	11 (36.4%)	327 (85.5%)	
Resection margin involvement			0.111
Positive	2 (6.1%)	7 (1.8%)	
Negative	31 (93.9%)	373 (98.2%)	
Tumor stage			0.062
IB	5 (15.2%)	105 (27.6%)	
IIA1	16 (48.5%)	122 (32.1%)	
IIA2	8 (24.2%)	61 (16.1%)	
IIB	4 (12.1%)	92 (24.2%)	
Tumor grade			0.960
Well differentiated	1 (3.0%)	13 (3.4%)	
Moderately differentiated	28 (84.8%)	315 (82.9%)	
Low differentiated	4 (12.2%)	52 (13.7%)	

Clinicopathological characteristics of Han patients with cervical cancer.

Characteristics	PNI (+)	PNI (-)	P
Age (yr) ±	46.23±10.042	49.07±9.901	> 0.050
Histologic subtype			0.770
Squamous carcinoma	11 (84.3%)	173 (85.6%)	
Adenocarcinoma	2 (15.3%)	19 (9.4%)	
Adenosquamous carcinoma	0	9 (4.5%)	
Small cell carcinoma	0	1 (0.5%)	
Lymph node metastasis			0.002
Positive	6 (46.1%)	28 (13.9%)	
Negative	7 (53.9%)	174 (86.1%)	

PNI and clinicopathological factors in patients with cervical cancer.

Materials and methods

Patients

Clinical data of 413 cervical cancer patients admitted into Affiliated Cancer Hospital of Xinjiang Medical University who underwent radical hysterectomy between 2009 and 2014 were analyzed retrospectively. 198 of the patients are from Uyghur ethnicity group and the rest patients are from Han ethnicity group. All patients care classified as stages IB-IIB according to the criteria of the International Federation of Gynecology and Obstetrics. The ages of these patients range from 23-77, with the average age of 50. Histologic subtypes of these patients included squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, squamous adenocarcinoma and small cell carcinoma. Complete clinical data including surgical, pathologic, staging, operative records and survival data were reviewed. The recurrence of disease was identified by radiologic findings such as computed tomography, magnetic resonance imaging, chest radiograph and PET-CT.

Histopathologic analysis

The pathologic features were diagnosed and recorded by a gynecologic pathologist by reviewing histopathology slides with hematoxylin and eosin staining. PNI was identified positive when the presence of cancer cells outside of nerves involves at least one thirds of the nerves and/or within the epineurial, peri-

Size			0.130
≥ 4 cm	4 (30.8%)	30 (14.9%)	
< 4 cm	9 (69.2%)	172 (85.1%)	
Depth of stromal invasion			0.770
≥ 1/2	9 (69.2%)	124 (61.4%)	
< 1/2	4 (30.8%)	78 (38.6%)	
Parametrial invasion			0.061
Positive	3 (23.1%)	13 (6.4%)	
Negative	10 (76.9%)	189 (93.6%)	
Lymphovascular space invasion			< 0.001
Positive	11 (84.6%)	26 (12.9%)	
Negative	2 (15.4%)	176 (87.1%)	
Resection margin involvement			0.222
Positive	1 (7.7%)	3 (1.5%)	
Negative	12 (92.3%)	199 (98.5%)	
Tumor stage			0.011
IB	2 (15.4%)	66 (32.6%)	
IIA1	9 (69.2%)	53 (26.2%)	
IIA2	1 (7.7%)	31 (15.3%)	
IIB	1 (7.7%)	52 (25.7%)	
Tumor grade			0.424
Well differentiated	0	9 (44.6%)	
Moderately differentiated	12 (92.3%)	156 (77.2%)	
Low differentiated	1 (7.7%)	37 (18.3%)	

Clinicopathological characteristics of uyghur patients with cervical cancer.

Characteristics	PNI (+)	PNI (-)	P
Age (yr) ±	51.10±8.441	51.20±9.454	> 0.050
Histologic subtype			0.203
Squamous carcinoma	17 (85%)	161 (91%)	
Adenocarcinoma	1 (5%)	12 (6.8%)	
Adenosquamous carcinoma	1 (5%)	3 (1.7%)	
Small cell carcinoma	1 (5%)	1 (0.5%)	
Lymph node metastasis			0.445
Positive	5 (25%)	32 (18%)	
Negative	15 (75%)	146 (82%)	
Size			0.097
≥ 4 cm	5 (25%)	21 (11.8%)	
< 4 cm	15 (75%)	157 (88.2%)	
Depth of stromal invasion			0.330
≥ 1/2	15 (75%)	114 (64%)	
< 1/2	5 (25%)	64 (36%)	
Parametrial invasion			0.062
Positive	4 (20%)	12 (6.7%)	
Negative	16 (80%)	166 (93.3%)	
Lymphovascular space invasion			< 0.001
Positive	11 (55%)	27 (15.2%)	
Negative	9 (45%)	151 (84.8%)	
Resection margin involvement			0.416
Positive	1 (5%)	4 (2.2%)	
Negative	19 (95%)	174 (97.8%)	

neurial and endoneurial spaces of the neuronal sheath [10-12]. Other pathologic characteristics including histologic subtype, tumor stage, tumor size, parametrial invasion, resection margin involvement, LN metastasis, depth of cervical stromal invasion, and LVSI were recorded.

Statistical analysis

Statistical analyses were performed using SPSS Version 17.0 (SPSS Inc., Chicago, IL). The association between PNI and various clinicopathological factors was examined using χ^2 analysis or Fisher exact test. Survival curves were esti-mated by the Kaplan-Meier method, and statisti-cal significance was determined by a log-rank test. Recurrence-free-survival (RFS) was calculated from the end of surgery to the time of recurrence as identified by radiologic findings. Overall survival (OS) was calculated from the end of surgery to death. Cox proportional hazard regression analysis was carried out to determine clinicopathological variables as prognostic factors. $P < 0.05$ was considered statistical significant.

Results

Association between PNI positivity and clinicopathological characteristics

Of 413 cervical cancer patients, 198 are from Uyghur ethnicity group and 10.1% of them (20/198) are PNI positive. The rest of the patients are from Han ethnicity group and 6% of them (13/215) are PNI positive. The average age of patients with PNI is 49.18± 9.27 yr compared with 50.07± 9.74 yr for patients without PNI ($P = 0.809$).

Tumor stage			0.251
IB	3 (15%)	39 (21.9%)	
IIA1	7 (35%)	69 (38.8%)	
IIA2	7 (35%)	30 (16.9%)	
IIB	3 (15%)	40 (22.5%)	
Tumor grade			0.456
Well differentiated	1 (5%)	4 (2.2%)	
Moderately differentiated	16 (80%)	159 (89.3%)	
Low differentiated	3 (15%)	15 (8.4%)	

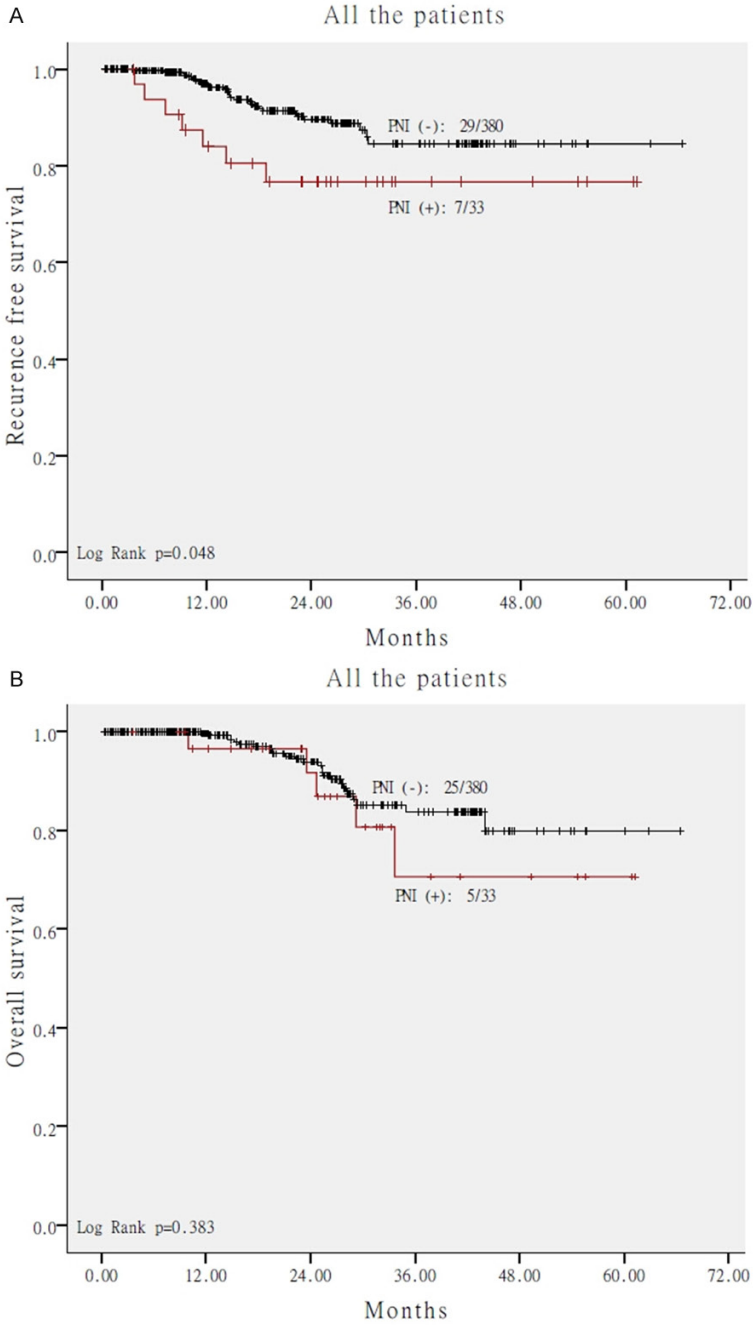

Figure 1. Kaplan-Meier curves for recurrence-free survival in all the patients with and without perineural invasion (A) and overall survival in all patients with and without perineural invasion (B). *P* value was determined by a log-rank test. PNI (+): PNI positive, PNI (-): PNI negative.

Among all the clinicopathological factors, there is significant association between PNI and lymph node metastasis (P = 0.01), tumor size greater than 4 cm (P = 0.039), parametrial invasion (P = 0.007) and most notably lymphovascular space invasion (LVSI) (P < 0.001). As shown in **Table 1**, 63.6% of PNI positive patients (21/33) are affected with LVSI whereas only 14.2% of PNI negative patients (54/380) are affected with LVSI. There is no significant correlation between PNI and resection margin involvement (P = 0.332), depth of stromal invasion ≥ 1/2 (P = 0.266), histological subtypes (P = 0.761), tumor stages (P = 0.062) and tumor grade (P = 0.96). Within Han ethnicity group, lymph node metastasis (P = 0.002), LVSI (P < 0.001), and tumor stage (P = 0.11) are significantly associated with PNI. However, within Uyghur ethnicity group, only LVSI (P < 0.001) is associated with PNI. Taken together, these results showed that PNI is closely associated with high-risk factors for cervical cancer and the associated factors are different within different ethnicity groups.

Impact of PNI on RFS and OS for cervical cancer patients

Kaplan-Meier curves showed that RFS is significantly lower in PNI-positive patients

Table 2. 5-year recurrence free survival (RFS) and 5-year overall survival rate (OS) in cervical cancer patients with or without perineural invasion (PNI) within Uyghur and Han ethnicity subgroups

	5-year OS	*p*	5-year RFS	*p*
All the patients				
PNI (+)	70.6%		76.7%	
PNI (-)	79.9%	P = 0.383	84.6%	P = 0.048
Han ethnicity group				
PNI (+)	85.7%		81.5%	
PNI (-)	85.1%	P = 0.614	84.0%	P = 0.481
Uyghur ethnicity group				
PNI (+)	68.1%		73.6%	
PNI (-)	70.6%	P = 0.738	86.3%	P = 0.034

The two *p* values are for OS and RFS, respectively. This data is analyzed using Kaplan-Mier survival analysis method and tested using long-rank test.

(76.7%) compared with PNI-negative patients (84.6%) (P = 0.048). However, the 5-yr OS was not significantly different on the basis of the presence of PNI (70.6% vs 79.9%, P = 0.383) (**Figure 1**).

Comparison of PNI's impact on RFS and OS between Uyghur and Han ethnicity groups

We separated patients into subgroups based on their ethnicity and investigated the impact of PNI on RFS and OS. 25% of Uyghur patients with PNI experienced recurrence (5/20) and 20% die (4/20). In comparison, 15.4% and 7.7% of PNI-positive patients from Han ethnicity group experience recurrence (2/13) and death (1/13), respectively. Further analysis of the PNI's impact on RFS and OS among the subgroups showed that within the Uyghur ethnicity group, 5-year RFS is significantly lower in PNI-positive patients (73.6%) than PNI-negative patients (86.3%) (P = 0.034). However, there is no significant difference in RFS on the basis of PNI positivity within the Han ethnicity group (P = 0.481). Analysis of 5-year OS showed that there is no significant differences between PNI-positive or -negative patients in both ethnicity groups (P = 0.614, P = 0.732). (**Table 2**; **Figure 2**) These results suggest that the risk of recurrence is higher in Uyghur PNI-positive than Han PNI-positive cervical cancer patients.

Prognostic significance of PNI and other clinicopathological factors

Univariate and multivariate analyses were carried out to determine a predictive association of the clinicopathological variables with recurrence and overall survival of cervical cancer in all patients or in either Han or Uyghur ethnicity group (**Tables 3**-**8**). Univariate analyses indicated that adjuvant therapy, lymph node metastasis, parametrial invasion and LVSI were independent prognostic factors for RFS and/or OS of all cervical cancer patients (**Table 3**). These parameters were also independent prognostic factors for RFS in Han group whereas tumor stage, lymph node metastasis, resection margin involvement and parametrial invasion were prognostic factors for OS in Han group patients (**Table 4**). In Uyghur patients, adjuvant therapy, lymph node metastasis, PNI status and LVSI were prognostic factors for RFS whereas tumor stage, adjuvant therapy, histologic subtype, lymph node metastasis, parametrial invasion and LVSI were prognostic factors (**Table 5**). When Cox proportional hazard regression model was applied, adjuvant therapy (P = 0.028), lymph node metastasis (P = 0.02), and parametrial invasion (P = 0.034) were independent prognostic factors for RFS whereas tumor stage (P = 0.011), lymph node metastasis (P = 0.008) and LVSI (P = 0.008) were independent prognostic factors for OS in all patients (**Table 6**). In Han group, parametrial invasion (P = 0.019) was an independent prognostic factor for RFS (**Table 7**). In Uyghur group, lymph node metastasis (P = 0.028) and LVSI (P = 0.011) was an independent prognostic factor for RFS and OS, respectively. However, PNI was not an independent prognostic factor for RFS or OS in these multivariate analysis.

Discussion

Leibig et al. defined perineural invasion (PNI) as the presence of cancer cells outside of nerves involving at least one thirds of the nerves and/or within the epineurial, perineurial and endoneurial spaces of the neuronal sheath [10, 13]. PNI is now recognized as another route through which dissemination occurs in additional to blood vessel and lymphovascular invasion. It is also considered to be a distinct pathological feature independent of LVSI because it has

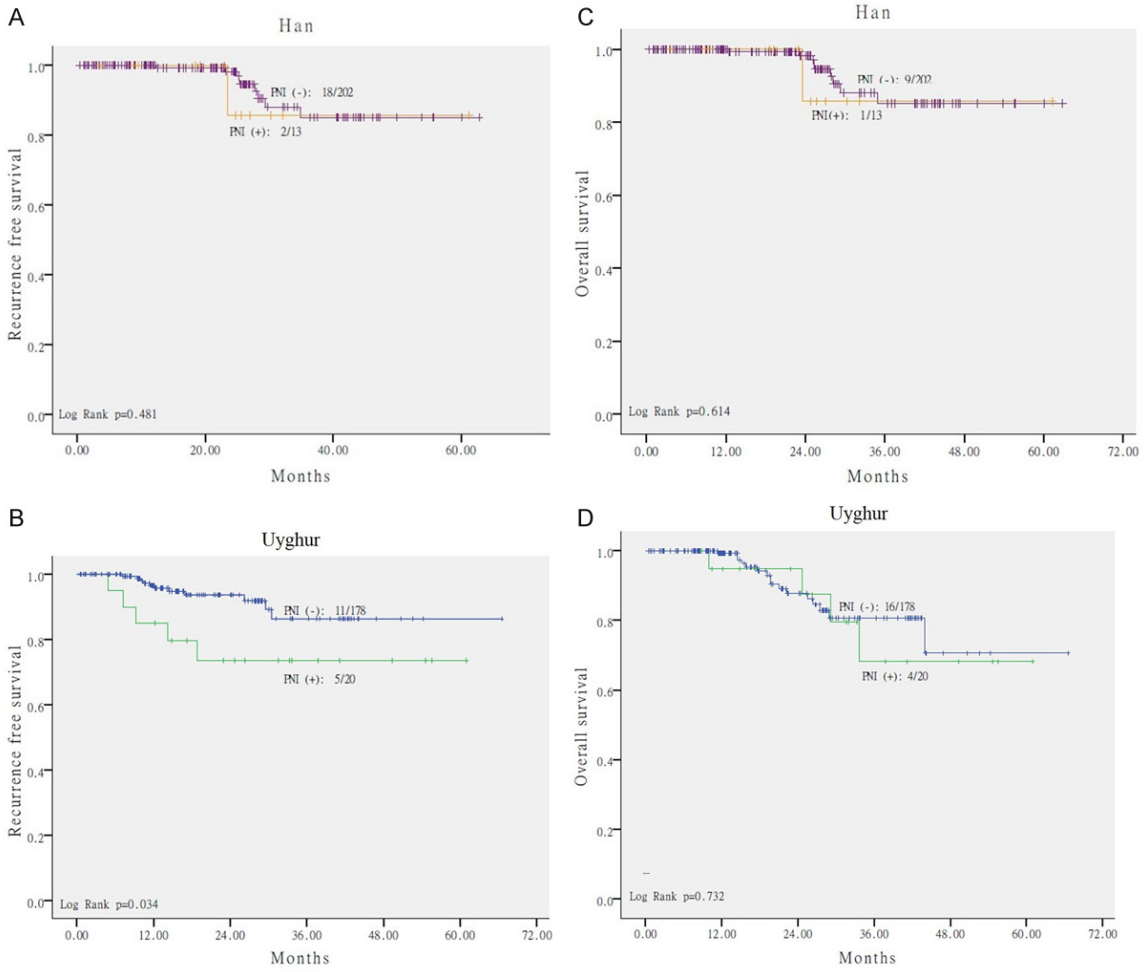

Figure 2. Kaplan-Meier curves for recurrence-free survival in patients with and without perineural invasion in Han (A) versus Uyghur ethnicity subgroups (B) and overall survival in patients with and without perineural invasion in Han (C) versus Uyghur ethnicity subgroups (D). *P* value was determined by a log-rank test. PNI (+): PNI positive, PNI (-): PNI negative.

recently been shown that lymphatic channels do not penetrate the epineurium [11, 12]. The pathological mechanism for PNI of cancer cells has not been fully understood. Recent studies have demonstrated that axonal migration may be a key component of PNI. Axonal growth requires neurotrophic growth factors and axonal guidance molecules such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin (NT). It has been shown that there is an up-regulation in neurotrophin expression in both tumor cells and intratumoral nerves in pancreatic cancer, supporting its potential role in PNI [13]. In addition, recent research in pancreatic cancer patients showed that some cytokines are also associated with PNI, including hematopoietic CSFs and chemokine CX3CL1 [14, 15]. Most, if not all of these results were observed in pancreatic cancer, the pathological mechanism of PNI in cervical cancer is largely unknown. Further investigations are urgently needed.

PNI has been established as an important clinicopathological feature in stomach, pancreatic, colorectum, biliary tract and prostate cancers. It has also been shown to be a poor prognostic factor in pancreatic and stomach cancer patients [7-9]. However, whether PNI can serve as an independent prognostic factor in cervical cancer remains controversial. In a study led by Memarzadeh S. et al. in 2003 [16], it was shown that the presence of PNI in the parametria more than doubles the risk of recurrence in the patients with large (greater than 4 cm) tumors. Similar results were observed in anoth-

Table 3. Univariate analysis of the prognostic factors in all patients with cervical cancer

	RFS			OS		
	OR (95% CI)	*P*	β	OR (95% CI)	*P*	β
Age	1.01 (0.98~1.05)	0.539	-0.004	1.01 (0.96~1.05)	0.794	0.10
Tumor stage	1.15 (0.82~1.60)	0.425	0.339	1.75 (1.14~2.69)	0.011	0.548
Adjuvant therapy	3.81 (1.16~12.55)	0.028	2.016	1.27 (0.38~4.24)	0.694	1.361
Histologic subtype	1.27 (0.87~1.83)	0.214	0.246	1.13 (0.77~1.67)	0.537	0.282
Tumor grade	1.57 (0.71~3.46)	0.268	0.615	0.33 (0.10~1.07)	0.066	-0.346
Size	0.90 (0.37~2.21)	0.823	0.391	2.44 (0.87~6.82)	0.090	0.701
lymph node metastasis	2.56 (1.16~5.62)	0.020	1.71	3.56 (1.40~9.03)	0.008	1.804
Depth of stromal invasion	1.66 (0.64~4.31)	0.302	0.924	0.60 (0.26~1.35)	0.215	-0.184
Resection margin involvement	1.74 (0.36~8.44)	0.492	1.767	3.33 (0.59~18.78)	0.172	1.909
Parametrial invasion	2.66 (1.08~6.57)	0.034	1.516	2.19 (0.74~6.45)	0.156	1.437
PNI	0.817 (0.29~2.31)	0.703	0.814	0.57 (0.17~1.90)	0.363	0.426
Lymphovascular space invasion	1.81 (0.84~3.88)	0.129	1.245	3.40 (1.38~8.35)	0.008	1.157

Table 4. Univariate analysis of the prognostic factors in Han patients with cervical cancer

	RFS			OS		
	OR (95% CI)	*P*	β	OR (95% CI)	*P*	β
Age	0.993 (0.94~1.03)	0.76	-0.007	1.02 (0.96~1.09)	0.442	0.027
Tumor stage	1.39 (0.995~2.020)	0.085	0.329	2.65 (1.18~5.97)	0.018	0.978
Adjuvant therapy	8.493 (1.96~36.62)	0.004	2.139	3.12 (0.663~14.76)	0.150	1.141
Histologic subtype	1.47 (0.91~2.374)	0.116	0.385	0.13 (0.001~29.67)	0.467	-2.00
Tumor grade	1.54 (0.58~4.031)	0.379	0.432	0.542 (0.142~2.072)	0.371	-0.612
Size	2.491 (0.98~6.331)	0.055	0.913	2.37 (0.58~9.569)	0.226	0.862
lymph node metastasis	4.02 (1.64~9.85)	0.002	1.392	9.12 (2.56~32.51)	0.001	2.221
Depth of stromal invasion	2.89 (0.84~9.89)	0.089	1.064	0.716 (0.202~2.54)	0.605	-0.334
Resection margin involvement	6.40 (0.852~48.11)	0.071	1.857	14.15 (1.68~119.0)	0.015	2.65
Parametrial invasion	5.89 (2.13~16.31)	0.001	1.774	4.91 (1.019~23.7)	0.047	1.593
PNI	1.68 (0.39~7.24)	0.486	0.52	1.692 (0.214~13.40)	0.618	0.526
Lymphovascular space invasion	2.94 (1.20~7.21)	0.018	1.08	1.628 (0.419~6.32)	0.482	0.487

Table 5. Univariate analysis of the prognostic factors in Uyghur patients with cervical cancer

	RFS			OS		
	OR (95% CI)	*P*	β	OR (95% CI)	*P*	β
Age	1.005 (0.953~1.05)	0.865	0.005	0.996 (0.95~1.043)	0.85	-0.004
Tumor stage	1.42 (0.90~2.24)	0.132	0.351	1.54 (1.025~2.32)	0.038	0.433
Adjuvant therapy	6.68 (1.518~29.47)	0.012	1.901	4.40 (1.28~15.084)	0.018	1.483
Histologic subtype	1.17 (0.682~2.008)	0.569	0.157	1.474 (1.034~2.102)	0.032	0.388
Tumor grade	2.49 (0.78~7.994)	0.123	0.916	0.953 (0.275~3.305)	0.94	-0.048
Size	0.396 (0.052~3.007)	0.371	-0.925	2.00 (0.724~5.527)	0.181	0.693
lymph node metastasis	8.75 (3.16~24.17)	0.000	2.169	4.692 (1.941~11.34)	0.001	1.546
Depth of stromal invasion	2.197 (0.625~7.721)	0.219	0.787	0.895 (0.357~2.247)	0.813	-0.111
Resection margin involvement	4.77 (0.613~37.22)	0.135	1.564	3.74 (0.497~28.178)	0.200	1.319
Parametrial invasion	3.34 (0.95~11.75)	0.06	1.206	3.69 (1.221~11.159)	0.021	1.306
PNI	2.99 (1.03~8.706)	0.044	1.098	1.212 (0.401~3.662)	0.733	0.192
Lymphovascular space invasion	4.26 (1.594~11.42)	0.004	1.451	4.397 (1.819~10.627)	0.001	1.481

Table 6. Cox proportional hazards model analysis of the prognostic factors in all patients with cervical cancer

	RFS			OS		
	OR (95% CI)	*P*	β	OR (95% CI)	*P*	β
Age	1.01 (0.98~1.05)	0.539	0.012	1.01 (0.96~1.05)	0.794	0.006
Tumor stage	1.15 (0.82~1.60)	0.425	0.136	1.75 (1.14~2.69)	0.011	0.559
Adjuvant therapy	3.81 (1.16~12.55)	0.028	1.337	1.27 (0.38~4.24)	0.694	0.242
Histologic subtype	1.27 (0.87~1.83)	0.214	0.235	1.13 (0.77~1.67)	0.537	0.123
Tumor grade	1.57 (0.71~3.46)	0.268	0.449	0.33 (0.10~1.07)	0.066	-1.096
Size	0.90 (0.37~2.21)	0.823	-0.102	2.44 (0.87~6.82)	0.090	0.891
lymph node metastasis	2.56 (1.16~5.62)	0.020	0.938	3.56 (1.40~9.03)	0.008	1.269
Depth of stromal invasion	1.66 (0.64~4.31)	0.302	0.504	0.60 (0.26~1.35)	0.215	-0.517
Resection margin involvement	1.74 (0.36~8.44)	0.492	0.553	3.33 (0.59~18.78)	0.172	1.204
Parametrial invasion	2.66 (1.08~6.57)	0.034	0.978	2.19 (0.74~6.45)	0.156	0.783
PNI	0.817 (0.29~2.31)	0.703	-0.202	0.57 (0.17~1.90)	0.363	-0.555
Lymphovascular space invasion	1.81 (0.84~3.88)	0.129	0.592	3.40 (1.38~8.35)	0.008	1.223

Table 7. Cox proportional hazards model analysis of the prognostic factors in Han patients with cervical cancer

	RFS			OS		
	OR (95% CI)	*P*	β	OR (95% CI)	*P*	β
Age	1.01 (0.95~1.07)	0.789	0.008	0.99 (0.90~1.10)	0.902	-0.006
Tumor stage	0.99 (0.57~1.07)	0.962	-0.013	4.47 (0.74~27.03)	0.103	1.497
Adjuvant therapy	4.05 (0.65~25.4)	0.135	1.40	0.36 (0.018~7.42)	0.509	-1.019
Histologic subtype	1.67 (0.97~2.83)	0.062	0.51	0.00 (0.00~)	0.976	-12.69
Tumor grade	1.77 (0.603~5.18)	0.299	0.57	0.19 (0.015~2.219)	0.183	-1.693
Size	1.18 (0.36~3.95)	0.782	0.17	1.85 (0.208~16.41)	0.582	0.614
lymph node metastasis	2.36 (0.75~7.47)	0.143	0.86	11.10 (0.88~139.6)	0.062	2.407
Depth of stromal invasion	1.25 (0.327~4.80)	0.741	0.227	0.423 (0.072~2.48)	0.341	-0.86
Resection margin involvement	6.10 (0.59~63.11)	0.129	1.809	23.05 (0.77~693.9)	0.071	3.138
Parametrial invasion	4.29 (1.27~14.54)	0.019	1.457	3.29 (0.145~74.69)	0.454	1.192
PNI	0.483 (0.075~3.096)	0.443	-0.727	20.38 (0.48~861.3)	0.115	3.015
Lymphovascular space invasion	1.98 (0.67~5.93)	0.218	0.687	1.27 (0.085~19.07)	0.861	0.242

er study from Horn L.C. group [17], establishing PNI as an independent poor prognostic factor. However, in 2011, Elsahwi K.S et al. [18] analyzed 192 cases of cervical cancer patients and discovered that there is no significant difference in 5-year RFS between PNI-positive or -negative cervical cancer patients. In addition, analyses of 185 cervical cancer patients who underwent radical hysterectomy and pelvic lymphadenectomy by Hyun Chul Cho et al. in 2013 [19] showed no difference in disease-free survival (P = 0.292) or overall survival (P = 0.346) according to the presence of PNI. These two studies argue against the prognostic value of PNI in cervical cancer. In our study, we analyzed a larger cohort of cervical cancer patients who underwent radical hysterectomy and found that there is significant difference in 5-year RFS on the basis of PNI positivity (P = 0.048) but no difference in 5-year OS (P = 0.371). Moreover, PNI cannot serve as an independent poor prognostic factor in cervical cancer. In addition, we compare the impact of PNI on RFS and OS between Uyghur and Han ethnicity groups and found that the 5-year RFS of PNI-positive patients is significantly lower than PNI-negative patients only in Uyghur group (P = 0.034), suggesting that there is higher risk of recurrence in Uyghur PNI-positive patients compared with Han PNI-positive patients .

Table 8. Cox proportional hazards model analysis of the prognostic factors in Uyghur patients with cervical cancer

	RFS			OS		
	OR (95% CI)	*P*	β	OR (95% CI)	*P*	β
Age	1.00 (0.95~1.07)	0.886	0.004	1.01 (0.96~1.06)	0.743	0.009
Tumor stage	1.43 (0.86~2.37)	0.173	0.355	1.45 (0.87~2.42)	0.157	0.37
Adjuvant therapy	2.93 (0.50~17.4)	0.236	1.076	2.33 (0.516~10.52)	0.271	0.846
Histologic subtype	0.876 (0.47~1.632)	0.676	-0.133	1.26 (0.83~1.97)	0.271	0.234
Tumor grade	2.18 (0.51~9.23)	0.29	0.779	0.43 (0.074~2.55)	0.356	-0.833
Size	0.25 (0.028~2.26)	0.218	-1.374	1.97 (0.521~7.48)	0.317	0.68
lymph node metastasis	4.02 (1.16~13.9)	0.028	1.39	2.45 (0.804~7.500)	0.115	0.898
Depth of stromal invasion	2.0 (0.49~7.93)	0.342	0.676	0.757 (0.257~2.23)	0.614	-0.279
Resection margin involvement	0.476 (0.04~5.72)	0.559	-0.742	1.308 (0.09~18.92)	0.844	0.268
Parametrial invasion	0.914 (0.17~5.06)	0.918	-0.09	4.101 (0.99~16.87)	0.05	1.411
PNI	1.57 (0.38~6.53)	0.532	0.454	0.341 (0.087~1.33)	0.122	-1.075
Lymphovascular space invasion	2.84 (0.83~9.78)	0.098	1.044	4.33 (1.40~13.40)	0.011	1.466

Previous studies indicated that PNI is closely associated with clinicopathological factors such as tumor size, tumor stage, parametrial invasion, stromal invasion depth, lymph node metastasis, etc [16, 18]. Specifically, PNI-positive cervical cancer patients have more lymph node metastasis, larger tumor size, deeper stromal invasion, and higher risk of LVSI [19]. Our study indicated that in all the patient population, PNI is significantly associated with lymph node metastasis, larger tumor size (≥ 4 cm), parametrial invasion and LVSI ($P < 0.05$), but not associated with resection margin involvement, depth of stromal invasion ≥ 1/2, histological subtypes, tumor stage and differentiation ($P > 0.05$). However, only LVSI is significantly associated with PNI in either Han or Uyghur ethnicity. These results suggest that PNI is closely correlated with prognostic risk factors, further demonstrating the potential prognostic value of PNI for cervical cancer. However, multivariate analysis indicated that PNI can not serve as independent prognosis marker for RFS or OS either in all patient population or within specific ethnicity group. The potential reasons may be due to the lack of precise definition of PNI which has been identified as a barrier to proper analysis and conclusion [18]. In addition, the diagnosis of PNI has been challenging, as in hematoxylin and eosin stained slides, small PNI foci may be difficult to observe or may be obscured by inflammatory cells or large mucinous pools. Moreover, PNI has been found to associated adjuvant therapy [19], in this study, all patients received surgery before the introduction of chemotherapy, thus may affect the results. Additional reasons accounting for the discrepancies between our study and some previous studies may be due to different sample size, patient population, and patient disease stages etc.

In summary, PNI is another route for tumor spreading independent of blood vessel and lymphovascular invasion. It has prognostic value in a variety of malignancies, but the pathological mechanism remains unclear. Differences exist in terms of the impact of PNI on RFS or OS within different ethnicity subtypes. The presence of PNI is correlated with prognostic risk factors in cervical cancer but its value as an independent prognostic factor is limited. Further investigations are needed to gain more insight into its clinical impact and how it may assist in determining postoperative adjuvant therapy.

Acknowledgements

This study is funded by Xinjiang Science and Technology Department (#201591152).

Disclosure of conflict of interest

None.

Address correspondence to: Gulina Kuerban, Gynecological Radiotherapy Unit 1, Tumor Hospital of Xinjiang Medical University, Suzhou Road 789, Urumqi, Xinjiang, China. Tel: +86013579880657; E-mail: tiannan2178@126.com

References

[1] Tsubamoto H, Yamamoto S, Kanazawa R, Sakane R, Honda O, Kobayashi K, Shibahara H, Hirota S. Prognostic factors for locally advanced cervical cancer treated with neoadjuvant intravenous and transuterine arterial chemotherapy followed by radical hysterectomy. Int J Gynecol Cancer 2003; 23: 1470-5.

[2] Chiantera V, Rossi M, De Iaco P, Koehler C, Marnitz S, Ferrandina G, Legge F, Parazzini F, Scambia G, Schneider A, Vercellino GF. Survival after curative pelvic exenteration for primary or recurrent cervical cancer: a retrospective multicentric study of 167 patients. Int J Gynecol Cancer 2014; 24: 916-22.

[3] Moutardier V, Houvenaeghel G, Martino M, , Lelong B, Bardou VJ, Resbeut M, Delpero JR. Surgical resection of locally recurrent cervical cancer: a single institutional 70 patient series. Int J Gynecol Cancer 2004; 14: 846-851.

[4] Sardain H, Lavoue V, Laviolle B, Henno S, Foucher F, Levêque J. Prognostic factors for curative pelvic exenterations in patients with recurrent uterine cervical or vaginal cancer. Int J Gynecol Cancer 2014; 24: 1679-85

[5] Delgado G, Bundy B, Zaino R, Sevin BU, Creasman WT, Major F. Prospective surgicalpathologicalstudy of disease-free interval in patients with stageIB squamous cell carcinoma of the cervix: a GynecologicOncology Group study. Gynecol Oncol 1990; 38: 352-7.

[6] Ho CM, Chien TY, Huang SH, Wu CJ, Shih BY, Chang SC. Multivariate analysis of the prognostic factors and outcomes in early cervical cancer patients undergoing radical hysterectomy. Gynecol Oncol 2004; 93: 458-64.

[7] Law WL, Chu KW. Anterior resection for rectal cancer with mesorectal excision: a prospective evaluation of 622 patients. Ann Surg 2004; 240: 260-268.

[8] Beard CJ, Chen MH, Cote K, Loffredo M, Renshaw AA, Hurwitz M, D'Amico AV. Perineurm invasion is associated with increased relapse after external beam radiotherapy for men with low-risk prostate cancer and may be a marker for occult, high-gradecancer. Int J Radiat Oncol Biol Phys 2004; 58: 19-24.

[9] Duraker N, Sisman S, Can G. The significance of perineural invasion as a prognostic factor in patients with gastric carcinoma. Surg Today 2003; 33: 95-100.

[10] Marchesi F, Piemonti L, Mantovani A, Allavena P. Molecular mechanisms of perineural invasion, a forgotten pathway of dissemination and metastasis. Cytokine Growth Factor Rev 2010; 21: 77-82.

[11] Hassan MO, Maksem J. The prostatic perineural space and its relation to tumor spread: an uhrastrncturalstudy. Am J Surg Pathol 1980; 4: 143-148.

[12] Olsson Y. Microenvironment of the peripheral nervous system under normal and pathological conditions. Crit Rev Neurobiol 1990; 5: 265-311.

[13] Liebig C, Ayala G, Wilks JA, Berger DH, Albo D. Perineural invasion incancer: a review of the literature. Cancer 2009; 115: 3379-91.

[14] Schweizerhof M, Stosser S, Kurejova M, Njoo C, Gangadharan V, Agarwal N Schmelz M, Bali KK, Michalski CW, Brugger S, Dickenson A, Simone DA, Kuner R. Hematopoietic colony-stimulating factors mediate tumor-nerve interactions and bone cancer pain. Nat Med 2009; 802-7.

[15] Marchesi F, Piemonti L, Fedele G, Destro A, Roncalli M, Albarello L Doglioni C, Anselmo A, Doni A, Bianchi P, Laghi L, Malesci A, Cervo L, Malosio M, Reni M, Zerbi A, Di Carlo V, Mantovani A, Allavena P. The chemokine receptor CX3CR1 is involved in the neural tropism and malignant behavior of pancreatic ductal adenocarcinoma. Cancer Res 2008; 68: 9060-9.

[16] Memarzadeh S, Natarajan S, Dandade DP, Ostrzega N, Saber PA, Busuttil A, Lentz SE, Berek JS. Lymphovascular and perineural invasion in the parametria: a prognostic factor for early-stage cervical cancer. Obstet Gynecol 2003; 102: 612-9.

[17] Horn LC, Meinel A, Fischer U, Bilek K, Hentschel B. Perineural invasion in carcinoma of the cervix uteri-prognostic impact. J Cancer Res Clin Oncol 2010; 136: 1557-62.

[18] Elsahwi KS, Barber E, Illuzzi J, Buza N, Ratner E, Silasi DA, Santin AD, Azodi M, Schwartz PE, Rutherford TJ. The significance of perineural invasion in early-stage cervical cancer. Gynecol Oncol 2011; 123: 561-4.

[19] Cho HC, Kim H, Cho HY, Kim K, No JH, Kim YB. Prognostic Significance of Perineural Invasion in Cervical Cancer. Int J Gynecol Pathol 2013; 32: 228-233.

[20] American cancer Society. www.cancer.org.