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Perineural Invasion in Cervical Cancer: Clinical Correlates and Prognostic Implications from a Retrospective Cohort Study

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Abstract

Background: Cervical cancer remains a major global health concern, particularly in developing countries. Perineural invasion (PNI) is a well-established adverse prognostic indicator in several cancers; however, its prognostic significance in cervical cancer has been reported inconsistently.

Objectives: This study aimed to determine the prevalence of PNI in cervical cancer, investigate its associations with clinicopathological characteristics, and evaluate its impact on patient survival. We hypothesized that PNI is associated with more aggressive tumor characteristics and poorer survival outcomes.

Methods: This retrospective cohort study included a consecutive series of 33 patients with cervical cancer who underwent abdominal radical hysterectomy at Shahid Sadoughi Hospital, Yazd, between 2012 and 2023. Patients were included if they underwent primary surgical treatment and had complete medical records. Adjuvant chemotherapy was administered postoperatively in selected cases according to clinical indications. Patients who had received neoadjuvant therapy or had incomplete data were excluded. When pathology slides or paraffin blocks were unavailable, PNI status could not be evaluated; however, the remaining variables were analyzed in these cases. Clinical and pathological data, including age, tumor stage and size, depth of stromal invasion, lymph node involvement, lymphovascular space invasion (LVSI), parametrial involvement, margin status, tumor histological type, treatment method, and PNI status, were reviewed. Survival data were obtained through follow-up. Statistical analyses included descriptive statistics, chi-square tests, t tests, and Kaplan-Meier survival curves.

Results: Perineural invasion was detected in 32% of evaluable cases (8/25) and was significantly associated with deep stromal invasion (P = 0.04) and positive surgical margins (P = 0.03). No significant correlations were observed with tumor size, lymph node status, LVSI, parametrial involvement, treatment type, or other clinicopathologic variables. Most patients presented with early-stage disease (66.7% stage IB1), and nonkeratinized squamous cell carcinoma (SCC) was the predominant subtype (48.5%). Survival analysis was limited by low mortality (2 deaths) and showed no significant difference by PNI status (P = 0.51).

Conclusions: Perineural invasion is present in a substantial proportion of cervical cancer cases and is associated with aggressive tumor characteristics. Although survival data are limited, PNI is indicative of a poorer prognosis. Routine assessment of PNI is recommended to improve risk stratification and guide therapy. Larger studies are needed to clarify its prognostic and therapeutic significance.

Keywords: Perineural Invasion, Cervical Cancer, Prognostic Factor

1. Background

Cervical cancer remains a major global health burden among women. It is the third most common cancer in women worldwide, although its incidence varies considerably by region (1). In high-income countries, widespread screening and vaccination programs have reduced its prevalence, making it the

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tenth most common cancer (1, 2). However, in many low- and middle-income countries, it remains the second most frequent cancer and a leading cause of cancer-related mortality among women (1). Despite advances in prevention, diagnosis, and treatment, cervical cancer continues to pose serious challenges, particularly in its advanced stages (1, 3).

Perineural invasion (PNI) is a well-established feature of several solid tumors, including pancreatic, prostate, and head and neck cancers (1). It is considered a marker of aggressive behavior and is associated with increased local recurrence, poor treatment response, and reduced survival. In some cases, PNI may be the only identifiable route of tumor spread, even in the absence of vascular or lymphatic invasion (2).

In cervical cancer, established intermediate- and high-risk factors are used to assess prognosis and guide decisions regarding adjuvant treatment. Intermediate prognostic risk factors, also known as the Sedlis criteria, include tumor size greater than 4 cm, deep stromal invasion, and lymphovascular space invasion (LVSI). High-risk factors include positive lymph nodes, positive surgical margins, and parametrial invasion (3).

Some studies have reported that PNI is associated with advanced disease, larger tumors, lymph node metastasis, and poorer outcomes. However, other studies have not demonstrated a clear correlation, resulting in inconsistent recommendations in clinical practice. Nonetheless, PNI may represent a prognostic risk factor in cervical cancer (4).

2. Objectives

This retrospective cohort study investigated the presence of PNI in patients with cervical cancer who were diagnosed and treated at Shahid Sadoughi Hospital in Yazd, Iran, between 2012 and 2023. Specifically, we evaluated associations between PNI and clinical and pathological features, including tumor stage, tumor size, lymph node involvement, and histological subtype. We also assessed the prognostic value of PNI in relation to treatment outcomes and overall survival. The findings contribute to the growing body of evidence on PNI and its clinical significance in cervical cancer management.

3. Methods

3.1. Study Design

This study was conducted as a descriptive retrospective cohort study. The target population included all patients diagnosed with cervical cancer who underwent primary abdominal radical hysterectomy without neoadjuvant chemotherapy at any stage and were referred to the Pathology Department of Shahid Sadoughi Hospital in Yazd between 2012 and 2023. Adjuvant chemotherapy was administered postoperatively in selected cases according to clinical indications. Sampling was census-based; all eligible cases referred during this period were included.

After ethical approval was obtained, patients' medical records were retrieved and reviewed. Data were collected on several clinical and pathological variables, including age, tumor stage, tumor size, depth of stromal invasion, lymph node involvement, LVSI, parametrial involvement, lower uterine segment involvement, margin status, tumor type, PNI, and presence of metastasis. Clinical symptoms and treatment modalities were also recorded. Survival status was determined through follow-up using phone numbers available in the hospital records. Patients with missing data, those who received nonsurgical treatment with chemoradiation only, and those who underwent neoadjuvant therapy before surgery were excluded. Cases in which both slides and paraffin blocks were unavailable for PNI assessment were excluded from the PNI analysis but were included in the evaluation of other variables.

3.2. Pathological Review

All previously reported specimens were independently reviewed by 2 experienced pathologists, and discrepancies were resolved by consensus to minimize interobserver variability. When PNI was not documented in the initial pathology report, the histopathological slides were reexamined. If the original slides were unavailable, new sections were cut from the corresponding paraffin blocks and stained with hematoxylin and eosin for assessment. Unfortunately, in 8 patients, neither pathology slides nor paraffin blocks were available; therefore, PNI status could not be determined in these cases. Perineural invasion was defined as tumor in close proximity to a nerve, involving at least 33% of its circumference, or as the presence of tumor cells within any of the 3 layers of the nerve sheath. Perineural invasion was initially

identified throughout the tumor section area at ×40 or ×100 magnification and then confirmed at ×200 or ×400 magnification.

3.3. Ethical Considerations

This project was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran (Ethics Code: IR.SSU.MEDICINE.REC.1403.089). Informed consent was obtained from all participants before inclusion in the study.

3.4. Statistical Analysis

All collected data were entered into SPSS software, version 26, and analyzed using appropriate statistical tests. Baseline characteristics were summarized using descriptive statistics. The Kaplan-Meier method was applied to assess overall survival, and t tests and chi-square tests were used to compare continuous and categorical variables, respectively. Ethical considerations were carefully addressed throughout the study.

4. Results

In this study, 33 patients diagnosed with cervical cancer who underwent abdominal radical hysterectomy were analyzed. PNI status was available for only 25 of the 33 patients because slides and paraffin blocks were missing, making PNI assessment infeasible in 8 cases; however, other variables were evaluated in these cases. Among the 33 patients, the mean age was 44.3 ± 9.5 years (range, 19 - 65 years). Overall, 51.5% of patients were younger than 44 years, and 48.5% were 44 years or older. The most common presenting symptom was abnormal vaginal bleeding (54.6%). Other symptoms included postcoital bleeding and treatment-resistant discharge (15.1% each), abdominal pain (9.1%), and asymptomatic cases diagnosed by Pap smear (6.1%). Histopathological analysis showed that nonkeratinized SCC was the most common tumor type (48.5%), followed by keratinized SCC and endocervical adenocarcinoma (15.2% each). Rare tumor types, including basaloid SCC, mucinous carcinoma, clear cell adenocarcinoma, neuroendocrine carcinoma, and villoglandular carcinoma, were each observed in 1 case (3.0%), except for serous papillary carcinoma, which was observed in 2 cases (6.1%) (Table 1).

Table 1. Clinicopathological and Demographic Characteristics of Patients with Cervical Cancer [a]

Characteristics	Values
Demographics	
Age, y (mean ± SD)	19 - 65 (44.3 ± 9.5)
< 44	17 (51.5)
≥ 44	16 (48.5)
Tumor type	
Nonkeratinized SCC	16 (48.5)
Keratinized SCC	5 (15.2)
Adenocarcinoma, usual type	5 (15.2)
Serous papillary carcinoma	2 (6.1)
Basaloid carcinoma	1 (3.0)
Villoglandular carcinoma	1 (3.0)
Mucinous carcinoma	1 (3.0)
Clear cell adenocarcinoma	1 (3.0)
Neuroendocrine carcinoma	1 (3.0)
Tumor characteristics	
Tumor size > 2 cm	19 (57.6)
Tumor size ≤ 2 cm	7 (21.2)
Tumor size unknown	7 (21.2)
Lymph node involvement	
Positive	14 (42.4)
Negative	19 (57.6)
Stage	
IA1	1 (3.0)
IA2	4 (12.1)
IB1	22 (66.7)
IB2	1 (3.0)
IIA2	1 (3.0)
IIB	1 (3.0)
IIIB	3 (9.1)
Pathological findings	
Presence of PNI, %	32 (8/25 evaluable cases)
Invasion of middle/deep third of stroma	12 (36.4)
Surgical margin positive	4 (12.1)
Lower uterine segment involvement	8 (24.2)
Metastasis	5 (15.2)
LVSI	7 (21.2)
Parametrial involvement	5 (15.2)
Clinical symptoms	
Abnormal vaginal bleeding	18 (54.5)
Postcoital bleeding	5 (15.2)
Persistent vaginal discharge	5 (15.2)
Abdominal pain	3 (9.1)
Asymptomatic (diagnosed by Pap smear)	2 (6.1)

[a] Values are expressed as No. (%) unless otherwise indicated. Abbreviations: LVSI, lymphovascular space invasion; PNI, perineural invasion; SCC, squamous cell carcinoma.

Tumor size exceeded 2 cm in 57.6% of cases. Lymph node involvement was present in 42.4% of patients. Most

Table 2. Clinicopathological Characteristics of Patients with Cervical Cancer with Positive and Negative Perineural Invasion [a]

Tumor Feature/Variables	PNI Positive	PNI Negative	P-Value
Age (y)			0.40
< 44	6 (40)	9 (60)	
≥ 44	2 (20)	8 (80)	
Tumor type			0.15
SCC, keratinized	1 (25)	3 (75)	
SCC, nonkeratinized	4 (30.8)	9 (69.2)	
Basaloid carcinoma	1 (100)	0 (0)	
Adenocarcinoma [b]	0 (0)	4 (100)	
Serous papillary carcinoma	1 (100)	0 (0)	
Villoglandular carcinoma	0 (0)	1 (100)	
Mucinous carcinoma	1 (100)	0 (0)	
Tumor characteristics			
Tumor size ≤ 2 cm	2 (28.6)	5 (71.4)	0.71
Tumor size > 2 cm	6 (37.5)	10 (62.5)	0.71
Lymph node involvement	4 (25)	12 (75)	0.39
Stage			0.34
IA1	0 (0)	1 (100)	
IA2	1 (25)	3 (75)	
IB1	4 (25)	12 (75)	
IB2	1 (100)	0 (0)	
IIA2	1 (100)	0 (0)	
IIIB	1 (50)	1 (50)	
Pathological findings			
Stromal invasion, middle/deep third	6 (60)	4 (40)	0.04
Surgical margin involvement	2 (100)	6 (26.1)	0.03
Lower uterine segment involvement	2 (33.3)	6 (33.3)	0.78
Metastasis	2 (50)	2 (50)	0.40
LVSI	1 (50)	5 (72.2)	0.74
Parametrial involvement	3 (75)	4 (21.1)	0.08
Treatment			0.65
Surgery + adjuvant therapy	6 (33.3)	12 (66.6)	
Surgery only	2 (28.6)	5 (71.4)	
Mortality, overall	2 (25)	0 (0)	0.51

[a] Values are expressed as No. (%) unless otherwise indicated. Abbreviations: LVSI, lymphovascular space invasion; PNI, perineural invasion; SCC, squamous cell carcinoma.
[b] Endocervical adenocarcinoma, usual type.

cases (66.7%) were classified as stage IB1, with lower frequencies in stages IA1, IA2, IB2, IIA2, IIB, and IIIB. Stromal invasion into the middle or deep third of the cervix was present in 36.4% of cases, whereas surgical margin involvement was identified in 12.1%. Lower uterine segment involvement, metastasis, LVSI, and parametrial involvement were reported in 24.2%, 15.2%, 21.2%, and 15.2% of cases, respectively. Most patients (69.7%) underwent surgery followed by adjuvant therapy, whereas 30.3% received surgery alone (Table 1).

Perineural invasion was observed in 32% of patients (8 of 25 evaluable cases). No statistically significant associations were found between PNI and tumor type (P = 0.15), tumor size (P = 0.71), lymph node involvement (P = 0.39), stage (P = 0.34), or treatment type (P = 0.65); however, significant correlations were identified with middle or deep third stromal invasion (P = 0.04) and positive surgical margins (P = 0.03). Specifically, 60% of patients with middle or deep third stromal invasion exhibited PNI, compared with only 14.3% of those without such invasion. In addition, all patients with

positive surgical margins demonstrated PNI, whereas only 26.1% of patients with negative margins exhibited PNI (Table 2).

No significant relationships were found between PNI and lower uterine segment involvement, metastasis, LVSI, or parametrial involvement (all $P > 0.05$). Perineural invasion was observed more frequently in advanced stages: 100% of patients in stages IB2 and IIA2 exhibited PNI, and 50% of patients in stage IIIB exhibited PNI. Conversely, no PNI was reported in stage IA1, and PNI was reported in only 25% of patients in stages IA2 and IB1; however, these differences were not statistically significant ($P > 0.05$) (Table 2).

Regarding survival outcomes, 2 patients (6.1%) died during follow-up. Both were older than 44 years and had advanced disease: 1 patient had stage IIB disease at diagnosis, which progressed to stage IVA at death, and the other had stage IIA2 disease at diagnosis, which progressed to stage IVB at death. One patient had a 5-cm keratinized SCC, and the other had a 6-cm nonkeratinized SCC. Among patients with PNI, 25% died, whereas none of the patients without PNI died ($P = 0.51$). Survival analysis according to age showed no significant association ($P = 0.13$), despite both deaths occurring in the older age group (Table 2).

5. Discussion

In this study of 33 patients with cervical cancer, PNI was identified in 8 of 25 evaluable cases (32%), which aligns with the internationally reported range of 7% to 35% and is consistent with the findings of Wan et al., who reported a prevalence of 27% (5). Similarly, Chen et al., in their multicenter study, reported comparable rates, reinforcing the global consistency of PNI occurrence among patients with cervical cancer (6). According to the Iranian National Population-Based Cancer Registry, Iran is considered a low-risk area for cervical cancer (7, 8). This study found significant associations between PNI and middle or deep third stromal invasion ($P = 0.04$), as well as positive surgical margins ($P = 0.03$), mirroring observations by Zhu et al. (4). Vural et al. and a European meta-analysis also reported strong associations between PNI and advanced cervical cancer (1, 9).

Regarding survival outcomes, despite the limited number of deaths (only 2 patients) and insufficient survival analysis, external evidence strongly supports the prognostic importance of PNI. National data from the Iranian Cancer Registry show a 5-year survival rate of approximately 58% for patients with cervical cancer, with considerable geographic variation across the country (8). Although PNI showed no statistically significant association with overall survival in our cohort ($P = 0.51$), all mortality events occurred exclusively in the PNI-positive group. This clinical trend, despite limited statistical power because of the small number of deaths, suggests a potential prognostic implication of PNI that warrants further investigation in larger studies. Chen et al. reported that PNI increased the mortality risk by 2.21 times in patients with cervical cancer (10). Both Chen et al. and Cui et al. documented significantly reduced overall survival in patients with PNI-positive tumors (10, 11). However, consistent with Elsahwi et al., who found that PNI was not an independent risk factor for recurrence or death after multivariate adjustment, our study did not identify a statistically significant survival impact of PNI, which may be attributable to the limited sample size and low mortality rate (12).

In contrast to some studies, our findings showed no significant associations between PNI and LVSI, tumor size, or clinical stage, whereas prior research has repeatedly reported meaningful correlations in these domains (13, 14). Wei's study of 174 patients in China identified PNI positivity as significantly associated with poorer overall survival and highlighted lymph node metastasis as an independent risk factor; however, this latter association was not observed in our cohort (13). Tang et al., in a larger cohort of 406 patients, reported significant correlations between PNI and lymph node metastasis, deep stromal invasion, margin involvement, and vascular invasion, establishing PNI as an independent predictor of overall survival. These findings support the associations observed in our study between PNI and surgical margin involvement and stromal infiltration (14).

Clinically, the presence of PNI has important implications. Chen et al. reported that PNI positivity is correlated with higher rates of paravaginal recurrence, highlighting the potential role of PNI in guiding surgical and adjuvant treatment decisions (6). According to the National Comprehensive Cancer Network treatment guidelines, patients with PNI-positive cervical cancer typically require more aggressive adjuvant therapies, including radiotherapy. This recommendation aligns with findings from a

European multicenter cohort study showing an increased need for adjuvant chemoradiotherapy in PNI-positive patients (1). Our study observed a trend toward greater use of adjuvant therapy in the PNI-positive group; however, this did not reach statistical significance, possibly because of the limited sample size.

Moreover, 75% of patients with parametrial involvement in our study exhibited PNI, compared with only 21.1% of those without parametrial involvement, suggesting that PNI may be associated with more aggressive tumor behavior and extension beyond the cervix. This finding aligns with the conclusions of Cai et al.'s 2025 review, which emphasized the role of PNI as an indicator of advanced FIGO stage and parametrial involvement, and Zhu et al.'s 2019 review, which highlighted that PNI-positive patients are more likely to require treatment beyond surgery (1, 15).

From a histopathological perspective, PNI reflects the ability of tumor cells to invade surrounding tissues and bypass natural anatomical barriers, facilitating spread into parametrial tissues rich in nerves and vessels. These observations suggest that PNI is not only a marker of aggressive disease but may also represent a potential pathway for tumor dissemination. The results of this study demonstrate that PNI in cervical cancer is significantly associated with markers of aggressive tumor behavior, such as deep stromal invasion and margin involvement. Given the accumulating evidence, PNI should be considered a valuable prognostic marker and be routinely assessed in pathology reports to guide treatment decisions.

5.1. Conclusions

This study demonstrated that PNI is present in a substantial proportion of cervical cancer cases (32%) and is significantly associated with adverse pathological characteristics, including deep stromal invasion and positive surgical margins. These findings, which are consistent with international reports, support the routine inclusion of PNI assessment in histopathological evaluations. Routine PNI assessment may improve risk stratification and inform decisions regarding adjuvant therapy for early-stage cervical cancer. Despite limitations related to the small sample size and retrospective design, this study highlights the prognostic relevance of PNI. Future large-scale, multicenter studies incorporating molecular markers are warranted to further elucidate its prognostic role and underlying biological mechanisms.

5.2. Limitations

This study has several limitations. Most patients had early-stage disease (66.7% stage IB1), which restricts the generalizability of the findings to more advanced stages. The retrospective, single-center design introduces potential selection bias and unmeasured confounding. The small sample size (n = 33), the limited number of patients with evaluable PNI status (n = 25), and the very low number of deaths (n = 2) resulted in imprecision in the survival analysis. The lack of statistical significance in survival outcomes (P = 0.51) is likely due to insufficient statistical power. In addition, the absence of detailed demographic and molecular data limits the depth of analysis and further limits generalizability. Future prospective, multicenter studies with larger cohorts and longer follow-up periods are needed to more accurately assess the prognostic impact of PNI.

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Footnotes

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Ethical Approval: This study was approved by the Ethics Committee of Shahid Sadoughi University of

Medical Sciences (Ethics Code: IR.SSU.MEDICINE.REC.1403.089). All procedures were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.

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