Gynecologic Oncology 152 (2019) 101–105

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Perineural invasion (PNI) in vulvar carcinoma: A review of 421 cases☆

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HIGHLIGHTS

- Perineural invasion should be considered a poor prognostic factor in vulvar carcinoma.
- Perineural invasion was associated with higher stage disease.
- Perineural invasion was associated with poorer overall survival.

ARTICLE INFO

Article history:
Received 31 August 2018
Received in revised form 18 October 2018
Accepted 23 October 2018
Available online 3 November 2018

Keywords:
Vulvar cancer
Invasive vulvar carcinoma
Perineural invasion
Prognostic factors

ABSTRACT

Objectives. To evaluate the prevalence and associated prognostic indicators in patients with vulvar carcinoma with and without evidence of perineural invasion (PNI).

Methods. A retrospective review identified 421 patients with invasive vulvar carcinoma evaluated at a single institution between 1993 and 2011. Medical records were reviewed for demographic data, pathologic information and presence or absence of PNI, treatment type, and recurrence/outcome information. Variables were compared between patients with PNI to those without PNI.

Results. Of the 421 patients included in the study, 32 (7.6%) had tumors with PNI. There were no significant differences in age, race/ethnicity, smoking history, histologic subtype, or grade between the group of patients with PNI and the group without PNI. The group with PNI was more likely to have lichen sclerosus (25.0% vs. 15.4%, $p = 0.024$), stage III/IV disease (59.4% vs. 36.0%, $p = 0.007$), lymph node involvement (50.0% vs. 21.6%, $p = 0.002$), and lymphovascular space invasion (LVSI) (53.1% vs. 15.9%, $p < 0.001$). A higher proportion of patients in the PNI group underwent primary or adjuvant radiation therapy (68.8% vs. 45.0%, $p = 0.016$). The median follow-up was 67.1 months (range < 1.0 to 284.3). Patients with PNI had significantly shorter overall survival (OS), median 25.5 vs. 94.3 months ($p < 0.001$), and progression-free survival (PFS), median 17.5 vs. 29.0 months ($p = 0.004$). After adjusting for stage, patients with PNI had a greater risk for death and progression (OS: hazard ratio, 2.71; $p < 0.001$; PFS: hazard ratio, 1.64; p-value = 0.020).

Conclusion. PNI should be considered an independent poor prognostic factor for patients with vulvar carcinoma, and should be included as part of the pathologic analysis.

1. Introduction

Vulvar cancer is the fourth most common gynecologic cancer in the United States, comprising 5% of all gynecologic malignancies. The American Cancer Society projects about 6190 new cases of invasive vulvar cancer and about 1200 related deaths among women in the United States in 2018 [1]. Risk factors for vulvar cancer include advanced age, cigarette smoking, vulvar dystrophy such as lichen sclerosus, vulvar or

☆ This research was supported in part by the Raby/Dunaway Family Fund and the University of Texas MD Anderson Cancer Center Support Grant (NCI Grant P30 CA016672).

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https://doi.org/10.1016/j.ygyno.2018.10.035
0090-8258/

cervical intraepithelial neoplasia, high-risk human papillomavirus (HPV) infection, immunocompromised status, and a prior history of cervical cancer [2,3]. Most vulvar cancers are squamous cell carcinomas [4]; other histologies include melanoma, Bartholin gland adenocarcinoma, sarcoma, Paget's disease, verrucous carcinoma and basal cell carcinoma.

Perineural invasion (PNI) is defined as the detection of malignant cells in the perineural space of nerves, regardless of whether the nerve itself is infiltrated by tumor. PNI has been noted to be an important pathologic feature for several malignancies, particularly head and neck cancers where it is associated with poor prognosis and is now a required component of the pathologic analysis [5]. PNI has also been shown to be associated with poor prognosis in prostate, ampullary carcinoma and colorectal cancers [6–8]. The purpose of this study was to evaluate the prevalence and associated prognostic indicators in patients with vulvar carcinoma with and without evidence of perineural invasion (PNI). In addition, we sought to determine the prevalence of PNI in vulvar cancer.

2. Methods

A retrospective cohort study of patients diagnosed with invasive vulvar carcinoma between 1993 and 2011 at The University of Texas MD Anderson Cancer Center was performed after Institutional Review Board approval. Patients were identified through the electronic medical records from the Departments of Gynecologic Oncology and Pathology. Patient demographics, clinical characteristics, pathologic information including histologic subtype and presence or absence of perineural invasion (defined as presence of tumor cells in the perineural space of nerves), treatment type, oncologic outcomes, disease status and survival status were collected. Variables were compared between patients with and without PNI. Patients without histologically confirmed vulvar carcinoma or with histology other than squamous cell carcinoma or adenocarcinoma were excluded. The follow-up period was defined as the time between initial vulvar cancer diagnosis and the date of last contact or death. All pathology slides were read by a MD Anderson Cancer Center gynecologic pathologist with expertise in vulvar cancer.

To compare patients with PNI and without PNI, a Fisher's exact test was used with respect to categorical variables and the Wilcoxon rank sum test was used for continuous variables. Overall survival (OS) was measured from the date of diagnosis until the date of last contact or death. Progression-free survival (PFS) was measured from the date of diagnosis to the date of first recurrence or death; patients without recurrence or death were censored at their last visit date. The product limit estimator of Kaplan and Meier [9] was used to estimate OS and PFS stratified by PNI, and the log-rank test was used to compare these two groups for each of these outcomes. Exploratory multivariable Cox proportional-hazards models for OS and PFS were used to compare PNI versus no PNI adjusting for stage. Lymph node status and LVSI were strongly correlated with stage and therefore not included in the multivariate analysis. To determine the statistical significance, we used the corresponding Wald chi-square tests for each variable included in the model. Time to recurrence was calculated from the date of treatment completion to the date of last visit or first recurrence. For the competing risks analysis, we used the methods of Gooley et al. to estimate the cumulative incidence of recurrence stratified by PNI while considering death without recurrence as a competing event [10]. Then, we used the methods of Fine and Gray to compare the two groups with respect to cumulative incidence of recurrence [11].

3. Results

A total of 421 patients were diagnosed with invasive vulvar carcinoma and met inclusion criteria for the study. The median age at diagnosis was 63 years (range: 30 to 98). There were 32 patients with perineural invasion for a prevalence rate of 7.6% (95% CI 5.1%–10.1%). Demographic and clinical characteristics are shown in Table 1. There were no significant differences in age, race/ethnicity, body mass index (BMI), or smoking history. A higher percentage of patients with PNI had lichen sclerosus than those without PNI (25.0% vs. 15.4%, p = 0.024).

Table 1
Demographic and clinical characteristics.

	Overall (N = 421)	Perineural invasion		p-Value
		No (N = 389)	Yes (N = 32)	
Age				0.783
Mean (SD)	62.1 (15.1)	62.2 (15.2)	61.5 (14.7)	
Median (Range)	63 (30–98)	63 (30–98)	63 (37–90)	
BMI (kg/m2)				0.296
Mean (SD)	29.5 (6.8)	29.4 (6.7)	31.4 (8.3)	
Median (Range)	28.5 (16.1–52.5)	28.6 (16.1–50.2)	28.3 (20.1–52.5)	
	N (%)	N (%)	N (%)	
Race				0.204
Caucasian	328 (77.9%)	299 (76.9%)	29 (90.6%)	
African American	47 (11.2%)	46 (11.8%)	1 (3.1%)	
Asian	5 (1.2%)	4 (1.0%)	1 (3.1%)	
Hispanic	39 (9.3%)	38 (9.8%)	1 (3.1%)	
Other	1 (0.2%)	1 (0.3%)	0 (0.0%)	
Unknonwn	1 (0.2%)	1 (0.3%)	0 (0.0%)	
Smoking				0.237
Never	190 (45.1%)	173 (44.5%)	17 (53.1%)	
Past	106 (25.2%)	96 (24.7%)	10 (31.3%)	
Current	118 (28.0%)	113 (29.0%)	5 (15.6%)	
Unknown	7 (1.7%)	7 (1.8%)	0 (0.0%)	
Dystrophy				0.024
None	344 (81.7%)	322 (82.8%)	22 (68.8%)	
Lichen sclerosus	68 (16.2%)	60 (15.4%)	8 (25.0%)	
Unknown	9 (2.1%)	7 (1.8%)	2 (6.3%)	

Surgical and pathologic findings are shown in Table 2. There were no significant differences with regard to histologic type: 90.6% of patients with PNI had squamous cell histology and 9.4% had adenocarcinoma, compared with the group without PNI where 96.4% had squamous cell histology and 3.6% had adenocarcinoma (p = 0.131). There were no significant differences in tumor grade between the two groups. However, the group with PNI was more likely to have stage III/IV disease (59.4% vs. 36.0%, p = 0.007), lymph node involvement (50.0% vs. 21.6%, p = 0.002), and lymphovascular space invasion (LVSI) (53.1% vs. 15.9%, p < 0.001).

Table 2
Surgical and pathologic findings.

		Perineural Invasion		
	Overall (N = 421)	No (N = 389)	Yes (N = 32)	p-Value
	N (%)	N (%)	N (%)	
Histology				0.131
Squamous cell	404 (96.0%)	375 (96.4%)	29 (90.6%)	
Adenocarcinoma	17 (4.0%)	14 (3.6%)	3 (9.4%)	
Grade				0.123
I	50 (11.9%)	48 (12.3%)	2 (6.3%)	
II	221 (52.5%)	204 (52.4%)	17 (53.1%)	
III	97 (23.0%)	84 (21.6%)	13 (40.6%)	
Unknown	53 (12.6%)	53 (13.6%)	0 (0%)	
Stage				0.007
I/II	244 (58.0%)	233 (59.9%)	11 (34.4%)	
III/IV	159 (37.8%)	140 (36.0%)	19 (59.4%)	
Unknown	18 (4.3%)	16 (4.1%)	2 (6.2%)	
Lymph node status				0.002
Negative	152 (36.1%)	142 (36.5%)	10 (31.3%)	
Positive	100 (23.8%)	84 (21.6%)	16 (50.0%)	
Unknown	169 (40.1%)	16 (41.9%)	6 (18.8%)	
LVSI				<0.001
Yes	79 (18.8%)	62 (15.9%)	17 (53.1%)	
No	146 (34.7%)	138 (35.5%)	8 (25.0%)	
Unknown	196 (46.6%)	189 (48.6%)	7 (21.9%)	

There were significant differences in the proportion of patients who underwent surgery with resection of the vulvar tumor: 90.6% (n = 29) in the group with PNI compared with 79.2% (n = 308) in the group without PNI (p = 0.017). A significantly higher proportion of patients with PNI (n = 27, 84.4%) underwent lymphadenectomy compared with patients without PNI (n = 226, 58.1%), p = 0.011. In addition, a higher proportion of patients in the PNI group underwent primary or adjuvant radiation therapy (68.8% vs. 45.0%, p = 0.016). There was no difference between the two groups with regard to chemotherapy administration (Table 3). The median follow-up for all patients was 67.1 months (range < 1 to 284.3).

A significantly higher proportion of patients with PNI had a recurrence compared to those without PNI (20/32 (62.5%) vs. 143/389 (37.5%), p = 0.008). Patients with PNI had significantly shorter OS (median 25.5 vs. 94.3 months, p < 0.001) (Fig. 1). After adjusting for stage, the risk of death was nearly three times higher for patients with PNI (hazard ratio, 2.71; p < 0.001) (Table 4). Patients with PNI also had significantly shorter PFS (median 17.5 vs. 29.0 months, p = 0.004) (Fig. 2). After adjusting for stage, the risk of progression was higher for patients with PNI (hazard ratio, 1.64; p-value = 0.020). Median time to recurrence (TTR) was significantly shorter in the PNI group (median 28.5 months) compared with the group without PNI (median 180.0 months), p = 0.004.

4. Discussion

Our study showed that patients with vulvar cancer with PNI had a significantly shorter PFS and OS compared with the group without PNI, suggesting a poorer prognosis associated with PNI. These findings are similar to previous studies that have evaluated the prevalence and prognostic value of PNI in vulvar cancer as well as other disease sites. [6,8,12–14]. An early study by Rowley and colleagues reported PNI in two of 22 patients (9.1%) with early vulvar cancer (≤2 cm in diameter, <5 mm of invasion); with lymph node metastases present in both these patients [15]. A subsequent study by Lerma and colleagues detected PNI in 21.4% of 71 cases of invasive squamous cell carcinoma of the vulva. All slides and paraffin blocks were re-reviewed specifically for the study. The majority of the patients had stage II (48.8%) or III (27.9%) disease [12]. A more recent study by Holthoff et al. identified PNI in 54 of 103 (52%) patients with vulvar cancer, and noted PNI to be associated with an increased risk of recurrence [16]. In the current study, the prevalence of PNI was 7.7%, and was associated with lymph node metastasis, stage III/IV disease and LVSI.

Several studies have evaluated PNI in other cancer sites including prostate, head and neck, colorectal and cervical cancer [5,6,8,13,14,17–20]. In a systematic review of 21 studies of patients with prostate cancer, PNI was associated with recurrence following radical prostatectomy or radiotherapy and was considered to be a poor prognostic factor [6]. PNI has also been associated with poorer prognosis in head and neck cancers and the National Comprehensive Cancer Network (NCCN) guidelines for head and neck cancers state that PNI is an established indication for post-operative radiotherapy [21]. A study by Gil and colleagues retrospectively evaluated 208 patients with paranasal sinus cancer and found PNI to be associated with a high rate of positive margins and adjuvant radiotherapy [5]. Similarly, in our study a higher proportion of patients with PNI underwent adjuvant radiotherapy compared with the patients without PNI.

Several studies have evaluated PNI in cervical cancer. Vural and colleagues detected PNI in 34 out of 111 (30.6%) patients with squamous cell carcinoma, adenosquamous carcinoma, and adenocarcinoma of the cervix treated with surgery. PNI was not considered an independent prognostic factor, but the overall survival rate was reduced in patients with PNI with advanced stage disease and/or positive lymph nodes [19]. A retrospective study by Wei et al. identified 206 patients with cervical cancer and 33 of them with PNI (16%). The authors found PNI to be associated with LVSI and positive lymph nodes. The authors suggested PNI to be an index to determine post-operative radiotherapy [18]. A subsequent study by Zhu and colleagues described 210 patients diagnosed with early-stage cervical cancer who underwent radical hysterectomy and pelvic lymphadenectomy, and found PNI to be associated with poor outcome but PNI was not identified as an independent risk factor for

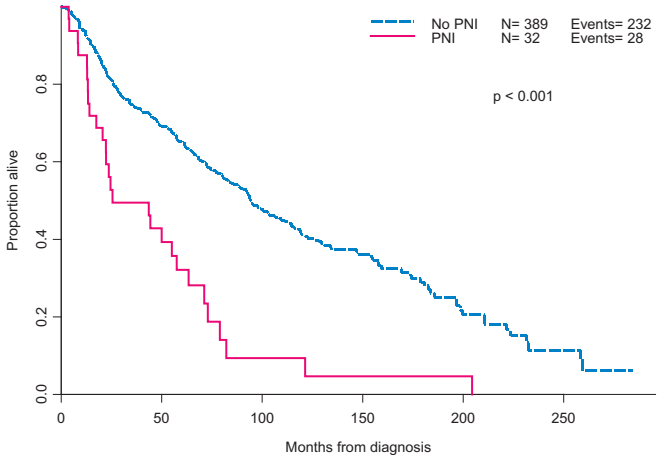

Fig. 1. Kaplan-Meier curve for overall survival (OS).

Table 3
Treatment modalities.

		Perineural Invasion		
	Overall (N = 421)	No (N = 389)	Yes (N = 32)	p-Value
	N (%)	N (%)	N (%)	
Surgical excision				0.017
Yes	337 (80.0%)	308 (79.2%)	29 (90.6%)	
No	74 (17.6%)	73 (18.8%)	1 (3.1%)	
Unknown	10 (2.4%)	8 (2.1%)	2 (6.3%)	
Lymphadenectomy				0.011
Yes	253 (60.1%)	226 (58.1%)	27 (84.4%)	
No	165 (39.2%)	160 (41.1%)	5 (15.6%)	
Unknown	3 (0.7%)	3 (0.8%)	0 (0%)	
Chemotherapy				0.113
Yes	87 (20.7%)	77 (19.8%)	10 (31.3%)	
No	327 (77.7%)	306 (78.7%)	21 (65.6%)	
Unknown	7 (1.6%)	6 (1.5%)	1 (3.1%)	
Radiation therapy				0.016
Yes	197 (46.8%)	175 (45.0%)	22 (68.8%)	
No	218 (51.8%)	208 (53.5%)	10 (31.3%)	
Unknown	6 (1.4%)	6 (1.5%)	0 (0%)	

Table 4
Cox proportional hazards models.

Overall survival			
Univariate model			
Variable	Description	HR (95% CI)	p-Value
PNI	PNI vs. No PNI	2.73 (1.83–4.07)	<0.001
Multivariable model			
Variable	Description	HR (95% CI)	p-Value
PNI	PNI vs. No PNI	2.71 (1.78–4.13)	<0.001
Stage	III/IV vs. I/II	1.70 (1.32–2.20)	<0.001
Recurrence free survival			
Univariate model			
Variable	Description	HR (95% CI)	p-Value
PNI	PNI vs. No PNI	1.65 (1.11–2.44)	0.004
Multivariable model			
Variable	Description	HR (95% CI)	p-Value
PNI	PNI vs. No PNI	1.64 (1.08–2.48)	0.020
Stage	III/IV vs. I/II	1.58 (0.24–2.02)	<0.001

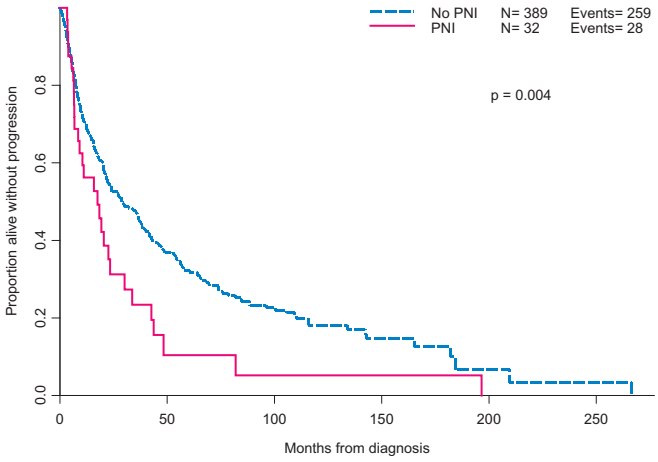

Fig. 2. Kaplan-Meier curve for progression free survival (PFS).

recurrence or death [20]. Cui et al. performed a systematic review of PNI and cervical cancer. Only three studies met criteria for inclusion and the authors reported that PNI was associated with a poor overall survival rate, and concluded that PNI is considered an adverse prognostic factor [17]. Our group previously performed a retrospective analysis of 160 patients who underwent pelvic exenteration for recurrent gynecologic malignancy, primarily cervical cancer. We found PNI to negatively impact PFS and OS [22]. Similar findings were noted by Baiocchi et al. who reported that PNI in gynecological malignancies after pelvic exenteration negatively impacted five-year progression free survival as well as cancer specific survival [23]. The current study findings are similar in that patients with PNI had a significantly shorter OS and PFS compared with the group without PNI.

PNI has also been associated with a poor prognosis in colorectal cancer patients [8,13,14]. Huh and colleagues [13] evaluated 341 stage II colorectal cancer patients and found PNI to be associated with more aggressive disease. They concluded that PNI should be included as a factor for consideration for postoperative chemotherapy [13]. A study by Shirouzu et al. [14] assessed 373 patients who have had curative surgery for rectal cancer, and reported that 9.9% (37/373) had tumors with PNI. In the patients with stage III disease with PNI, there was a higher recurrence rate as well as a lower 8-year survival rate [14].

Our study is limited by retrospective data collection, a long study period with variable treatment regimens and data from a single institution with possible referral bias. The FIGO staging for vulvar cancer also changed during the study period potentially impacting the results. The study also spanned a long period where adjuvant therapy regimens and modalities, as well as indications for postoperative treatment varied over time. In addition, a separate pathology re-review was not performed as part of the study, likely resulting in underreporting of PNI. Furthermore, we do not have HPV status for the majority of the tumors and patients included in the study. The strengths of our study include a large number of patients with vulvar cancer and a long-follow-up period. Our results suggest that PNI is associated with a poorer prognosis in patients with vulvar cancer. Including PNI information in pathology reports is warranted and further study is needed to see if patients with PNI should be managed differently in adjuvant therapy.

Disclosures

Dr. Sood reports grants (NIH) during the study. Dr. Frumovitz reports grants and personal fees from Stryker, grants from Navidea, personal fees from Ipsen Pharmaceuticals outside the submitted work. The remaining authors do not have any conflicts of interest to disclose.

Author contributions

- Mila Pontremoli Salcedo: conceived and designed the study and analysis; collected the data; contributed data or analysis tools; performed the analysis; wrote the paper; edited, reviewed and approved the final manuscript
- Anil K. Sood: conceived and designed the study and analysis; edited, reviewed and approved the final manuscript
- Ricardo dos Reis: collected the data; edited, reviewed and approved the final manuscript
- Preetha Ramalingam: provided pathology expertise and review; edited, reviewed and approved the final manuscript
- Chunling Chen: collected the data; edited, reviewed and approved the final manuscript
- Michael Frumovitz: conceived and designed the study and analysis; edited, reviewed and approved the final manuscript
- Anuja Jhingran: provided radiation oncology expertise and review; edited, reviewed and approved the final manuscript
- Brandelyn Pitcher: performed the statistical analysis; edited, reviewed and approved the final manuscript
- Pedro T. Ramirez: conceived and designed the study and analysis; edited, reviewed and approved the final manuscript
- Kathleen M. Schmeler: conceived and designed the study and analysis; collected the data; contributed data or analysis tools; performed the analysis; wrote the paper; edited, reviewed and approved the final manuscript; mentored the primary author

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