in vivo *35*: 1051-1056 (2021)
doi:10.21873/invivo.12349

Perineural Invasion Correlates With Common Pathological Variables and Clinical Outcomes of Patients With Squamous Cell Carcinoma of the Vulva Treated With Primary Radical Surgery and Inguinal-femoral Lymphadenectomy

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Abstract. *Background/Aim: The aims of the study were: i) to assess the incidence of perineural invasion (PNI) in squamous cell carcinoma of the vulva and ii) to correlate PNI with common pathological prognostic variables and clinical outcome of patients. Patients and Methods: The hospital records of 64 patients with vulvar squamous cell carcinoma who underwent primary radical surgery were reviewed. Results: PNI was significantly related to stage (p=0.038), size (p=0.038), lymph-vascular space involvement (p=0.013) and nodal status (p=0.038), but not to patient age, tumor grade and stromal invasion. Five-year disease-free survival was 30.0% in patients with PNI and 53.1% in those without PNI (p=0.018), and the corresponding 5-year overall survival was 50.0% and 77.1% (p=0.031), respectively. Conclusion: PNI was associated with common pathological prognostic variables and with a poorer clinical outcome in patients with vulvar squamous cell carcinoma.*

The GLOBOCAN 2018 database, which has estimated the worldwide incidence and mortality for 36 cancers in 185 countries, reported 44.235 new cases of vulvar carcinoma and 15.222 deaths due to malignancy in 2018 (1). Squamous cell carcinoma is the most common histological type, with an age-related incidence ranging from 0.4:100,000 among women in their thirties to 20:100,000 among women older than 70 years old (2). Surgery is the cornerstone of treatment for most tumors, and includes deep partial or total vulvectomy with bilateral inguinal-femoral lymphadenectomy or sentinel node biopsy in selected cases (3-8). Lymph nodal status is the strongest prognostic variable, with 5-year overall survival (OS) rates ranging from 70% to 98% for patients with negative nodes to 12% to 41% for those with positive nodes. Also, the number, the size, and growth pattern of nodal metastases as well as tumor stage, tumor grade, stromal invasion and lymph vascular space involvement (LVSI) impact on the clinical outcome (2, 9, 10). Patients with locally advanced disease can be treated with ultra-radical surgery, radiotherapy, definitive concurrent chemo-radiation or concurrent chemo-radiation followed by individualized surgery, but there are no well-defined guidelines for this clinical setting (11-13). Postoperative adjuvant inguinal and pelvic radiotherapy is warranted after radical surgery and inguinal-femoral lymphadenectomy in patients with more than one intranodal metastasis or with extra-nodal tumor growth (5-7).

Perineural invasion (PNI) has been found to correlate with a high loco-regional recurrence rate and an unfavorable clinical outcome in several malignancies (14-19). On the other hand, a few data are currently available on the biological and clinical relevance of PNI in surgically-treated patients with squamous cell carcinoma of the vulva (20-24).

The aims of the present retrospective investigation were: i) to assess the incidence of PNI in surgical samples of patients with vulvar squamous cell carcinoma who underwent primary radical surgery and inguinal-femoral lymphadenectomy and ii) to correlate PNI with common pathological prognostic factors, disease-free survival (DFS) and OS.

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Key Words: Perineural invasion, vulvar squamous cell carcinoma, radical vulvectomy, inguinal-femoral-lymphadenectomy, recurrence.

Table I. *Correlation between perineural infiltration and common prognostic variables*.

Variable	N	Perineural infiltration	*p*-Value
Age			
≤72	32	6 (18.7%)	0.38
>72	32	10 (31.3%)	
Tumor stage			
III	25	10 (40.0%)	0.038
I-II	39	6 (15.4%)	
Tumor grade			
G3	30	10 (33.3%)	0.161
G1-2	34	6 (17.6%)	
Tumor size			
>2 cm	42	14 (33.3%)	0.038
≤2 cm	22	2 (9.1%)	
Stromal invasion			
>5 mm	32	10 (31.2%)	0.38
≤5 mm	32	6 (18.7%)	
LSVI			
Yes	22	10 (45.4%)	0.013
Not	42	6 (14.3%)	
Nodal status			
Positive	25	10 (40%)	0.038
Negative	39	6 (15.4%)	

G3: Poorly differentiated; G1: well differentiated; G2: moderately differentiated; LVSI: lymph vascular space involvement.

Table II. *Recurrence rate by prognostic variables*.

Variable	N	Recurrence 26	*p*-Value
Age (years)			
≤72	31	11 (35.5%)	0.29
>72	29	15 (51.7%)	
Tumor stage			
III	23	14 (60.9%)	0.036
I-II	37	12 (32.4%)	
Tumor grade			
G3	28	14 (50.0%)	0.434
G1-2	32	12 (37.5%)	
0.434			
Tumor size			
>2 cm	39	20 (51.3%)	0.108
≤2 cm	21	6 (28.6%)	
Stromal invasion			
>5 mm	29	14 (48.3%)	0.602
≤5 mm	31	12 (38.7%)	
LSVI			
Yes	19	12 (63.2%)	0.050
Not	41	14 (34.1%)	
PNI			
Yes	15	11 (73.3%)	0.014
No	45	15 (33.3%)	
Nodal status			
Positive	23	14 (60.9%)	0.036
Negative	37	12 (32.4%)	

G3: Poorly differentiated; G1: well differentiated; G2: moderately differentiated; LVSI: lymph vascular space involvement; PNI, perineural invasion.

Patients and Methods

This retrospective study was conducted on 64 patients with squamous cell carcinoma of the vulva who underwent primary deep partial or total vulvectomy and inguinal-femoral lymphadenectomy at the Department of Gynecology and Obstetrics of the University of Pisa between January 2006 and July 2019. Patients who underwent surgery without lymphadenectomy because of stage Ia_1 disease or poor performance status as well as those who received primary chemo-radiation followed by individualized surgery for locally advanced disease were not included in the present analysis.

The surgical treatment of the vulva was classified according to the glossary of terminology proposed by Micheletti *et al*. (4). The surgical excision encompassed the lesion with a free margin of at least 1 cm of clinically normal skin, and removed a portion of the vulva in all its thickness from the surface to the urogenital diaphragm. Deep partial vulvectomy indicated that the vulvar excision was limited to a portion of the vulva, whereas deep total vulvectomy denoted the removal of the whole vulva.

Deep partial vulvectomy was usually performed in patients with T_1 disease when the lesion was unifocal and the remainder of the vulva was normal. Deep total vulvectomy was the standard treatment for patients with T_1 tumor and with multifocal disease or widespread intraepithelial vulvar neoplasia or lichen sclerosus as well as for those with more advanced tumor.

The tumor stage of each case was retrospectively determined according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO) 2009 (25).

The histological samples were reviewed by two pathologists (S.P. e G.N.). PNI was defined as the presence of tumor cells within any of the three layers of the nerve sheath or as the presence of tumor in close proximity to a nerve and involving at least one-third of the nerve's circumference (26). An immuno-histochemical staining with the S100 antibody was often used to detect nerve tissues (21-23, 27-29).

Postoperative management was individually established by a multidisciplinary team on the basis of histological findings on surgical specimens, patient age and general conditions, after an exhaustive discussion with the patient herself. Adjuvant external beam irradiation was usually administered to patients with more than one intra-nodal metastasis or with extra-nodal tumor growth. Irradiation field usually encompassed groin, obturator, external and internal iliac areas and primary tumor bed, and patients received a total dose of 45-50 Gy in 5-6.5 weeks. Concomitant weekly cisplatin 40 mg/m^2 was added to radiotherapy in some cases. Follow-up data were available for 60 patients. The median follow-up of survivors was 33 months (range=9-133 months).

Statistical methods. The SAS statistical package (release 8.2, SAS Institute, Cary, NC, USA) was used for the computations. PNI was compared to the common pathological variables using Fisher's exact test. Recurrence rates were compared to the prognostic variables using Fisher's exact test. The time from surgery to first recurrence

Table III. *Variables predictive of disease--free survival.*

Variables	Patient number	2-year	5-year	7-year	*p*-Value
Age					
≤72	31	86,5%	54,8%	48.7%	0.006
>72	29	56.0%	39.2%	31.4%	
Tumor stage					
III	23	61.5%	22.0%	14.7%	0.005
I-II	37	78.8%	62.6%	56.9%	
Tumor grade					
G3	28	61.4%	46.0%	38.4%	0.179
G1-2	32	80.8%	50.0%	43.8%	
Tumor size					
>2 cm	39	68.2%	39.3%	30.4%	0.268
≤2 cm	21	78.9%	62.7%	62.7%	
Stromal invasion					
>5 mm	29	71.9%	43.7%	31.9%	0.455
≤5 mm	31	71.5%	49.8%	49.8%	
LSVI					
Yes	19	49.4%	16.5%	8.2%	0.001
Not	41	82.4%	60.6%	55.6%	
PNI					
Yes	15	60.0%	30.0%	15.0%	0.018
No	45	76.1%	53.1%	53.1%	
Nodal status					
Positive	23	59.8%	20.5%	13.7%	0.002
Negative	37	79.4%	63.6%	57.8%	

G3: Poorly differentiated; G2: moderately differentiated; G1: well differentiated; LSVI: lymph vascular space involvement; PNI: perineural invasion.

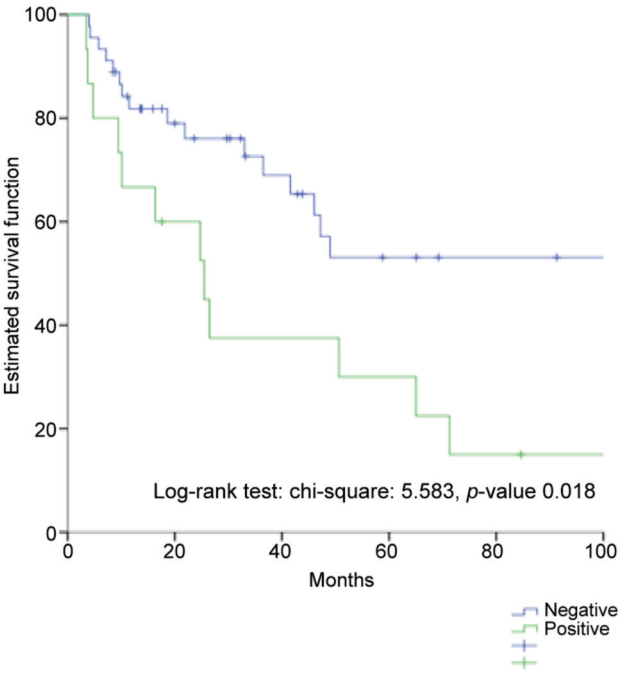

Figure 1. *Disease-free survival by perineural invasion.*

or death for any cause without recurrence was defined as DFS, and the time from surgery to death or last observation was defined as OS. The cumulative probability of DFS and OS was estimated by the product-limit method. The log-rank test was used to compare the homogeneity of DFS and OS functions across strata defined by categories of prognostic variables.

Results

The surgical treatment consisted of deep total vulvectomy in 49 (76.6%) and partial deep vulvectomy in 15 (23.4%) patients. Inguinal-femoral lymphadenectomy was bilateral in 52 (81.25%) and unilateral in 12 (18.75%) patients. The median age of women was 72 years (range=35-88 years).

FIGO stage was I in 38 (59.4%), II in 1 (1.6%), IIIa in 5 (7.8%), IIIb in 6 (9.4%) and IIIc in 14 (21.9%) patients, respectively. Tumor grade was well differentiated in 12 (18.7%), moderately differentiated in 22 (34.4%) and poorly differentiated in 30 (46.9%) patients. Tumor size was ≤2 cm in 22 (34.4%) and >2 cm in 42 (65.6%), deep stromal invasion was ≤5 mm in 32 (50.0%) and >5 mm in 32 (50.0%), and LVSI was present in 22 (34.4%) and absent in 42 (65.6%) cases, respectively. PNI was detected in 16 (25.0%) patients. Histologically assessed groin nodes were positive in 25 (39.1%) and negative in 39 (60.9%) patients, respectively. Among the 25 patients with metastatic groin nodes, 9 (36.0%) had one positive node and 16 (64.0%) had two or more positive nodes.

PNI was significantly related to tumor stage (p=0.038), tumor size (p=0.038), LVSI (p=0.013) and nodal status (p=0.038), but not to patient age, tumor grade and stromal invasion (Table I).

Follow-up data were available for 60 patients. Nine and five patients underwent adjuvant radiotherapy and adjuvant cisplatin–based concurrent chemo-radiation, respectively. One patient received adjuvant chemotherapy with cisplatin 50 mg/m^2+paclitaxel 175 mg/m^2 every 3 weeks for 5 cycles for the presence of 9 histologically proven positive groin nodes and extensive LVSI on the surgical samples.

Twenty-six (43.3%) patients relapsed after a median time of 16 months (range=3-122 months). The failure was local only in 13 patients (50.0%), inguinal in 9 (34.6%) (associated with local recurrence in 5 cases) and distant in 4 (15.4%) (associated with groin recurrence in 2 cases). The recurrence rate significantly correlated with tumor stage (p=0.036), LVSI (p=0.050), nodal status (p=0.036) and PNI (p=0.014) (Table II). It is worth noting that inguinal and/ or distant failure developed in 8 of the 15 (53.3%) patients with PNI *versus* 5 of the 45 (11.1%) patients without PNI (p=0.001).

Table IV. *Variables predictive of overall survival.*

Variables	Patient number	2-year	5-year	7-year	*p*-Value
Age					
≤72	31	93.4%	93.4%	69.9%	0.001
>72	29	66.9%	66.9%	32.1%	
Tumor stage					
III	23	62.5%	54.7%	27.3%	0.002
I-II	37	93.9%	80.7%	73.4%	
Tumor grade					
G3	28	77.9%	55.8%	37.2%	0.161
G1-2	32	83.8%	79.4%	64.9%	
Tumor size					
>2 cm	39	76.5%	68.5%	49.8%	0.548
≤2 cm	21	90.5%	72.0%	60.0%	
Stromal invasion					
>5 mm	29	71.9%	71.9%	44.5%	0.104
≤5 mm	31	89.4%	72.8%	63.7%	
LSVI					
Yes	19	57.9%	41.4%	20.7%	<0.0001
Not	41	92.2%	84.0%	74.1%	
PNI					
Yes	15	66.7%	50.0%	30.0%	0.031
No	45	88.5%	77.1%	64.3%	
Nodal status					
Positive	23	60.9%	53.3%	26.6%	0.001
Negative	37	94.1%	81.5%	74.1%	

G3: Poorly differentiated; G2: moderately differentiated; G1: well differentiated; LSVI: lymph vascular space involvement; PNI: perineural invasion.

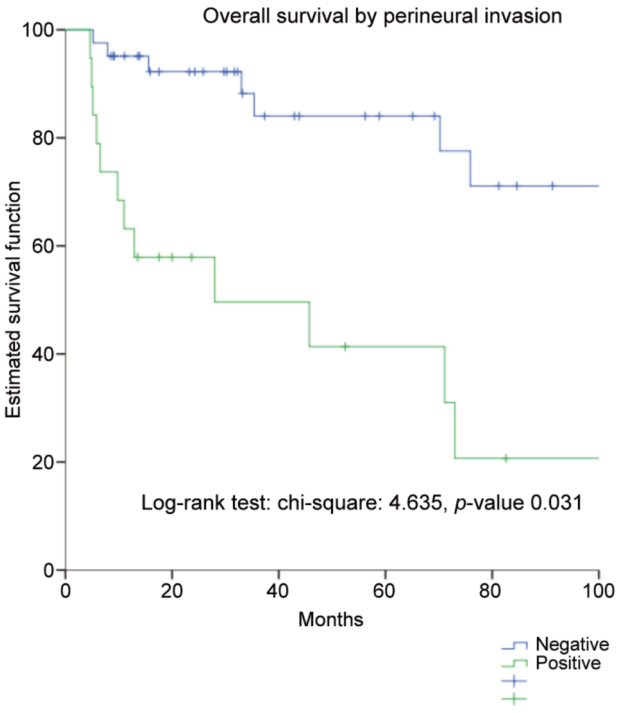

Figure 2. *Overall survival by perineural invasion.*

DFS was significantly related to patient age (p=0.006), tumor stage (p=0.005), LVSI (p=0.001), nodal status (p=0.002) and PNI (p=0.018) (Table III) (Figure 1).

At present, 29 (48.3%) patients are alive with no evidence of tumor, 8 (13.3%) are alive with tumor, 18 (30.0%) died of tumor, and 5 (8.3%) died of intercurrent disease with no evidence of tumor.

OS was significantly related to patient age (p=0.001), tumor stage (p=0.002), LVSI (p<0.0001), nodal status (p=0.001) and PNI (p=0.031) (Table IV, Figure 2).

Discussion

PNI has been detected in 7.6-52.4% of patients with squamous cell carcinoma of the vulva (20-24, 29). In the present study PNI was found in 25.0% of 64 surgical specimens of primary deep partial or total vulvectomy and inguinal-femoral lymphadenectomy. In agreement with the literature, this variable was significantly associated with large tumor size (22), advanced tumor stage (24), LVSI (22, 24) and nodal involvement (22, 24, 30).

In the study of Long *et al.* (22) including 105 patients, PNI correlated with a higher risk of recurrence and death at univariate analysis [hazard ratio (HR)=2.93, 95% confidence interval (CI)=1.20-7.34, and HR=3.04, 95%CI=1.19-7.72, respectively] but not at multivariate analysis. Similar conclusions have been reported by a Spanish study on 43 patients (20). An investigation of Holthoff *et al.* (21) has found that PNI was present in 67.7% of the 31 tumors that relapsed *versus* 42.8% of the 63 tumors that did not (p=0.0290). PNI was associated with 1.64-fold higher risk and 2.74-fold-higher risk of recurrence and 2.71-fold higher risk and 4.93-fold higher risk of death, respectively, in the series of Salcedo *et al.* (24) including 421 patients and in the series of Ferrari at al. (23) including 74 patients. In the present investigation, PNI was significantly related to overall recurrence rate (p=0.014), inguinal and/or distant recurrence rate (p=0.001), DFS (p=0.018) and OS (p=0.031) at univariate analysis.

Our study confirms that PNI correlates with the common pathological prognostic variables and with the clinical outcome of patients with squamous cell carcinoma of the vulva who underwent primary radical surgery. This finding should be assessed routinely in the surgical specimens and could be taken into consideration when planning adjuvant treatment (21-24, 29).

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, Writing - original draft: AG; Data curation, Formal analysis, Methodology, Writing-review & editing: AG, SB, SC, CC, AF, AGN.

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Received October 23, 2020
Revised November 24, 2020
Accepted November 26, 2020