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Review

Is Perineural Invasion a Novel Prognostic Factor Useful to Tailor Adjuvant Treatment in Patients Treated With Primary Surgery for Cervical and Vulvar Carcinoma?

ANGIOLO GADDUCCI[1], SABINA PISTOLESI[2], STEFANIA COSIO[1] and ANTONIO GIUSEPPE NACCARATO[2]

[1]*Department of Experimental and Clinical Medicine, Division of Gynecology and Obstetrics, University of Pisa, Pisa, Italy;*
[2]*Department of New Technologies and Translational Research, Division of Pathology, University of Pisa, Pisa, Italy*

Abstract. *Perineural invasion (PNI) is detected in 7.0-35.1% of cervical carcinomas. This histological finding correlates with cervical invasion, lymph-vascular space invasion (LVSI), tumor size, positive resection margins, parametrial invasion, node metastases and advanced stage. Some authors have reported that PNI has no prognostic relevance, others have found that PNI is related to disease-free survival or overall survival (OS) at univariate analysis, and others have observed that it is an independent poor prognostic factor for OS. The evaluation of PNI status should be included in the decision-making process for planning adjuvant treatment. PNI has been found in 7.6-52.4% of vulvar carcinomas. This feature, which is strongly associated with depth of invasion, LVSI, tumor size, advanced stage and nodal involvement, is an independent prognostic variable for the risk of recurrence and death in most series. PNI should be evaluated routinely in histopathology reports of vulvar carcinoma and could help clinicians to tailor adjuvant treatment.*

Perineural invasion (PNI) is usually defined as the presence of tumor cells within any of the three layers of the nerve sheath (endoneurium, perineurium and epineurium) or as the presence of tumor in close proximity to a nerve and involving at least one-third of the nerve's circumference (1). An immuno-histochemical staining using the S100 antibody for nerve tissue or a double immunostaining using this antibody and an antibody against cytokeratin AE1/3 for epithelial cells can be useful for the pathologist (2-7).

From a histopathological point of view, the definition of PNI can be referred to the presence of tumor cells "in, around and through the nerve" (8). In the histopathological reports two types of PNI are generally described: the invasion of perineurium (Figures 1 and 2) and the invasion of endoneurium (Figures 3). The latter is less frequent because the epineurium is resistant to invasion. However, both of types can be observed together (Figure 4).

PNI which expresses the potential of the tumor to infilter nervous structures and to spread along nerve sheaths, is detectable in several malignancies, such as cutaneous squamous cell carcinoma (9), prostate cancer (10), pancreatic cancer (11), ampullary cancer (12), gastric cancer (13), colon cancer (12, 14) and head and neck cancer (2, 15, 16). This feature correlates with a high risk of loco-regional relapse and unfavorable clinical outcome.

The present paper reviews the literature data on the prognostic relevance of PNI in cervical and vulvar carcinoma.

Carcinoma of the Uterine Cervix

PNI has been detected in 7.0-35.1% of patients with cervical cancer who underwent radical hysterectomy and pelvic lymphadenectomy (5, 17-23) (Table I). This histological finding significantly correlates with deep cervical invasion (5, 17, 18, 23-26), lymph-vascular space invasion (LVSI) (5, 19, 20, 23, 26), large tumor size (5, 19, 23, 25, 26), tumor extension to the uterus (19, 24), positive resection margins (26), parametrial invasion (19, 20, 22, 23, 26), lymph node metastases (5, 17, 23, 26), and more advanced stage (5, 17-19, 25, 26). Meinel *et al.* (18) found that PNI was also

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Correspondence to: Angiolo Gadducci, MD, Department of Clinical and Experimental Medicine, Division of Gynecology and Obstetrics, University of Pisa, Via Roma 56, Pisa, 56127, Italy. E-mail: a.gadducci@med.unipi.it

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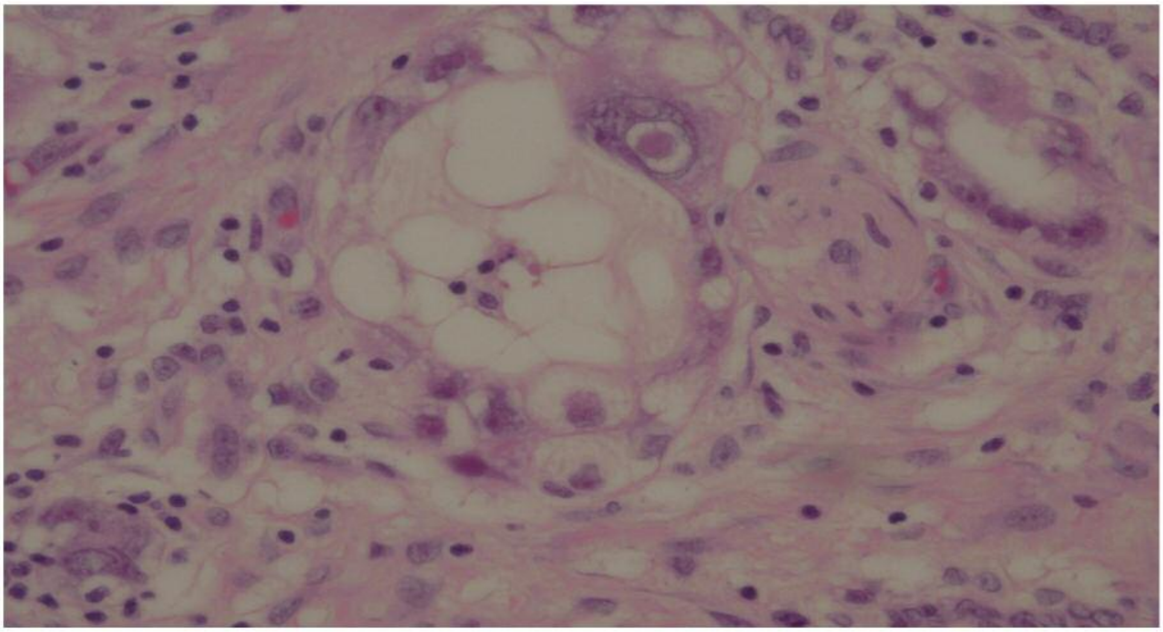

Figure 1. *Cervical clear cell carcinoma: invasion of perineurium (HE, 20×).*

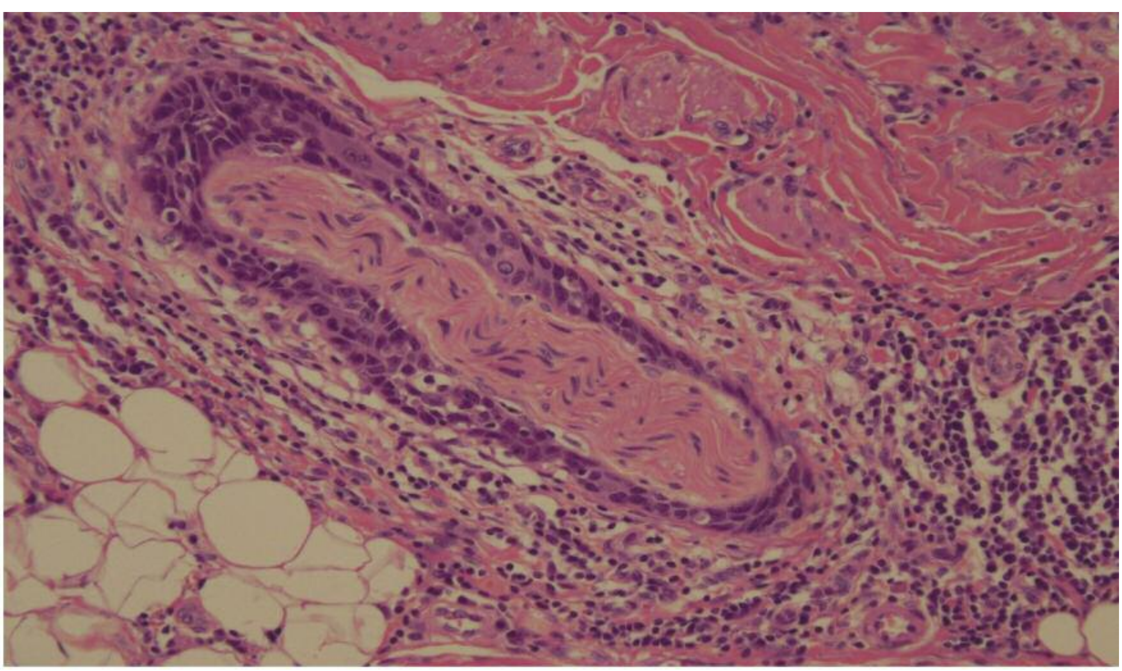

Figure 2. *Vulvar squamous cell carcinoma: circumferential invasion of the perineurium; neoplastic cells occupy the space located between the nerve axons and the epineural fibrous sheath (HE, 10×).*

associated with high grade of tumor cell dissociation (*i.e.*, spray-like rather than finger-like or pushing pattern of invasion), strong peritumoral desmoplastic stromal reaction, and reduced peritumoral inflammation. A study on surgical samples of 312 patients with FIGO stage I-IIB cervical adenocarcinoma treated with radical surgery noted that PNI was significantly related to the risk of ovarian metastases at univariate but not at multivariate analysis (21). Patients with

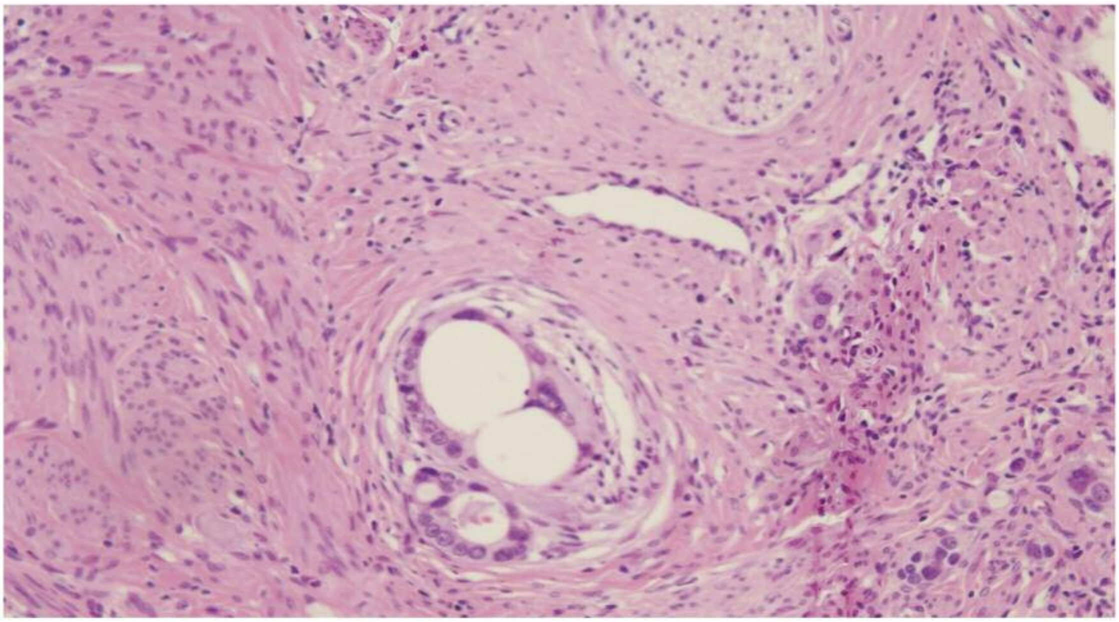

Figure 3. *Cervical clear cell carcinoma: invasion of endoneurium; the axon blundles are almost completely replaced by neoplastic glands (HE, 10×).*

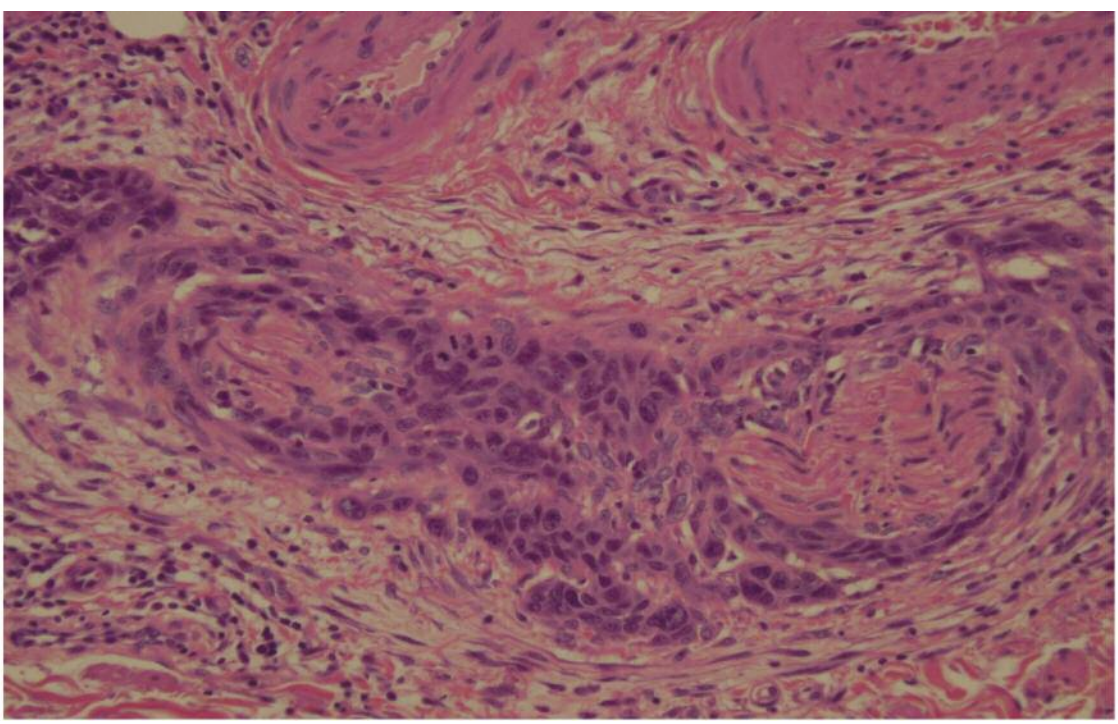

Figure 4. *Vulvar squamous cell carcinoma: invasion of perineurium and endoneurium (on the left) (HE, 10×).*

PNI had a higher chance to receive adjuvant radiotherapy or concurrent chemoradiation after surgery (5, 19, 20, 23, 27).

Nerve growth factor (NGF) may stimulate PNI through the interaction with the transmembrane tropomyosin-receptor kinase receptor (Trk-A) which triggers signaling pathways involving PI3-Akt-mTOR and Ras-MAP and activates neuronal growth and survival (28). Conversely, NGF binding to transmembrane p75 neurotrophin receptor (p75NRT)

Table I. *Incidence of perineural invasion in cervical carcinoma.*

Authors (ref.)	FIGO stage	Patients (n)	Perineural invasion
Wei *et al*. (5)	Ib1-IIb*	206	16.0%
Horn *et al*. (17)	Ib-IIb**	194	35.1%
Meinel *et al*. (18)	Ib1-IIb**	194	35.1%
Elsahwi *et al*. (19)	Ia-II*	192	12.5%
Cho *et al*. (20)	Ia_2-IIa_2*	185	7.0%
Zhou *et al*. (21)	Ia-IIb***	312	13.1%
Baiocchi *et al*. (22)	Ia_2-Ib_2*	345	17.9%
Zhu *et al*. (23)	Ia_2-IIa_2*	210	8.6%

*Squamous cell carcinoma, adeno/adenosquamous carcinoma; **squamous cell carcinoma; ***adenocarcinoma.

Table II. *Prognostic relevance of perineural invasion in cervical carcinoma.*

No prognostic relevance	Prognostic relevance at univariate analysis	Prognostic relevance at multivariate analysis
Elzawi *et al*. (19)	Vural *et al*. (26)	Horn *et al*. (17)
Cho *et al*. (20)	Zhu *et al*. (23)	Cui *et al*. (27)*
Skręt-Magierło *et al*. (25)	Known *et al*. (31)	
Tavares *et al*. (30)		

*Meta-analysis.

might enhance pro-apoptotic signaling through pathways involving nuclear factor-B and c-Jun N-terminal kinase (29). Long *et al*. (28) found that the expression of NGF and Trk-A, but not that of p75NRT, were strongly associated with PNI in 85 patients with FIGO stage Ib–IIb squamous cell carcinoma or adenocarcinoma of the uterine cervix treated with radical hysterectomy and pelvic lymphadenectomy. Moreover, a high expression of NGF and TrKA significantly correlated with worse disease-free survival (DFS) and worse overall survival (OS).

Although PNI is often associated with unfavorable prognosis, its real impact on the clinical outcome of surgically-treated patients with cervical carcinoma is still debated. Some authors reported that PNI has no prognostic relevance (19, 20, 25, 30), whereas others found that PNI is related to DFS or OS at univariate but not at multivariate analysis (23, 26, 31), and others observed that it is an independent poor prognostic factor for OS (17, 27) (Table II).

Cho *et al*. (20) failed to detect any significant difference in either DFS or OS according to the presence of PNI in 185 patients with stage Ia_2-IIa_2 disease, Elzawi *et al*. (19) reported no difference in either DFS or OS by PNI status in 192 patients with stage Ia-IIa disease, Skręt-Magierło *et al*. (25) found that PNI was not related to DFS in 50 patients with stage Ib1-IIb disease, and Tavares *et al*. (30) noted that PNI did not influence OS in a series of 301 patients.

A retrospective Indian study on 111 patients reported a lower 5-year OS for the patients with PNI compared with those without PNI (80.9% *versus* 95.3%, p=0.022), but this variable was not an independent prognostic factor (26). Five-year DFS was not significantly different according to PNI. A subsequent assessment performed by grouping patients on the basis of stage (early stage, ≤IIa, *versus* advanced stage, ≥IIb) and nodal status, showed that the 5-year OS was 42.6% for advanced stage patients with PNI compared to 58.0% for those in advanced stage without PNI (p=0.047), and that the 5-year OS was 35.5% for patients with node metastases and PNI compared to 60.1% for those with node metastases without PNI (p=0.039). Although PNI was not an independent prognostic factor, this variable seemed to have a relevant impact on OS of patients with advanced stage and/or positive nodes.

In a series of 210 patients with FIGO stage Ia_2-IIa cervical carcinoma, PNI was significantly related to DFS [hazard ratio (HR)=3.56, 95% confidence Interval (CI)=1.53-8.29, p=0.009] and OS (HR=2.98, 95%CI=0.84-10.86, p=0.049) at univariate but not at multivariate analysis (23).

A retrospective investigation on 50 high-risk, FIGO stage Ia_2-IIb cervical carcinoma patients who underwent radical surgery followed by adjuvant radiation or concurrent chemoradiation reported a 5-year DFS of 38.1% for the patients with PNI *versus* 82.2% for those without PNI (p=0.012) (31). Again, this variable was not an independent prognostic factor. Moreover, the 5-year OS was not significantly different in the two groups (83.3% *versus* 87.0%, p=0.801).

Conversely, Horn *et al*. (17), who reassessed 194 surgically-treated patients with cervical carcinoma, noted that the 5-year OS was 51.1% for the patients with PNI *versus* 75.6% for those without PNI (p=0.001) and that this difference retained statistical significance at multivariate analysis.

A meta-analysis of retrospective observational studies with survival analysis for PNI after radical hysterectomy and lymphadenectomy demonstrated that patients with PNI had a trend to a worse DFS (HR=1.35, 95%CI=0.78-2.31, p=0.28) and a significant worse OS (HR=2.21, 95%CI=1.36-3.59, p=0.001) (27).

Two large retrospective studies, which assessed patients treated with pelvic exenteration for gynecological cancers, mostly consisting of cervical cancers, showed that PNI was a significant poor predictive factor for the risk of recurrence, for the risk of death and for the risk of death from cancer at univariate but not at multivariate analysis (32, 33).

Table III. *Incidence of perineural invasion in squamous cell vulvar carcinoma.*

Authors (ref.)	FIGO stage	Patients (n)	Perineural invasion
Lerma et al. (34)	I-IV	71	21.4%
Holthoff et al. (4)	I-IV	103[a]	52.4%
Salcedo et al. (35)	I-IV	421	7.6%
Long et al. (6)	I-IV	105	28.6%
Ferrari et al. (7)	I-IV	74	31.1%

[a]Nine patients had recurrent tumor.

Table IV. *Prognostic relevance of perineural invasion in squamous cell vulvar carcinoma.*

Prognostic relevance at univariate analysis	Prognostic relevance at multivariate analysis
Long *et al*. (6)	Holthoff *et al*. (4)
Lerma *et al*. (34)	Salcedo *et al*. (35)
	Ferrari *et al*. (7)

Carcinoma of the Vulva

PNI has been found in 7.6-52.4% of patients with squamous cell carcinoma of the vulva (4, 6, 7, 34, 35) (Table III). Most papers reported that this feature significantly correlates with depth of invasion (4, 6), LVSI (6, 35), large tumor size (6), more advanced stage (35) and nodal involvement (6, 35, 36).

In a retrospective review of 421 patients treated at the Memorial Anderson Cancer Center between 1993 and 2011, the patients with PNI were more likely to have LVSI (53.1% *versus* 15.9%, $p<0.001$), stage III-IV disease (59.4% *versus* 36.0%, $p=0.007$), positive lymph nodes (50.0% *versus* 21.6% $p=0.002$) than those without PNI (35). PNI was also associated with a higher incidence of lichen sclerosus (25.0% *versus* 15.4%, $p=0.024$), whereas no significant differences in age, race/ethnicity, smoking history, histologic subtype, or grade were detected according to PNI status.

In a Chinese study, PNI was associated with the risk of recurrence at univariate (HR=2.93, 95%CI=1.20-7.37, $p=0.018$) but not at multivariate analysis (HR=1.63, 95%CI=0.79-3.37, $p=0.187$) (6) (Table IV). In the study of Lerma et al (34) including 71 cases of invasive squamous cell carcinoma of the vulva, PNI was significantly related to OS at univariate analysis. In the retrospective investigation of the University of Arkansas, PNI was present in 21 of the 31 primary tumors that recurred (69%) *versus* 27 of the 63 (42%) that did not ($p=0.0290$), and this feature was found to be an independent predictor of failure (OR=2.613, 95%CI not available, $p=0.045$) (4).

In the series of the Memorial Anderson Cancer Center, the patients with PNI had worse PFS (median=17.5 months *versus* 29.0 months, $p=0.004$) and worse OS (median, 25.5 months *versus* 94.3 months ($p<0.001$) than those without PNI, and this finding retained statistical significance at multivariate analysis for both DFS (HR=1.64, $p=0.020$) and OS (HR=2.71, $p<0.001$) (35). An Italian study reported that the 5-year DFS and 5-year OS were significantly shorter for patients with PNI compared to those without PNI (18% *versus* 72%, $p=0.001$, and, respectively, 35% *versus* 75%, $p=0.001$) (7). PNI was an independent prognostic variable for both DFS (HR=2.74, 95%CI=1.10-7.13, $p=0.03$) and OS (HR=4.93, 95%CI=1.33-18.35, $p=0.01$) (7).

Conclusion

PNI correlates with a high risk of loco-regional relapse and unfavorable clinical outcome in several malignancies (2, 9-16, 37). For instance, in a series of 363 patients with Dukes' B or C stage rectal cancer who did not undergo chemoradiotherapy, patients with PNI-positive disease had a significantly higher recurrence rate compared to those with PNI-negative disease ($p<0.001$), which suggested that PNI status in primary rectal cancer specimens should be taken into consideration for therapy stratification (37).

As far as gynecological cancer is concerned, PNI status significantly correlates with several poor prognostic pathological variables of cervical carcinoma, but its relevance as independent predictor of either DFS or OS is still debated. The extensive use of adjuvant radiotherapy or concurrent chemoradiation after surgery in patients with PNI is probably due to the frequent coexistence of other unfavorable prognostic variables on surgical specimens, such as deep cervical invasion, LVSI, large tumor size, positive resection margins, parametrial invasion and lymph node involvement (18-20, 22-26). Nevertheless, the evaluation of PNI status should be included in the decision-making process for the planning of postoperative adjuvant treatment in patients with cervical carcinoma (27).

The few available data on vulvar carcinoma agree that the presence of PNI is suggestive of an aggressive biological behavior and show that this histologic finding is an independent prognostic variable for the risk of recurrence and death in most series (4, 7, 35).

According to both the European Society of Gynecological Oncology (ESGO) and the US NCCN clinical guidelines for the management of vulvar carcinoma, adjuvant inguinal and pelvic radiotherapy is warranted after radical vulvectomy and full inguino-femoral lymphadenectomy in patients with more than one intranodal metastasis or with extra-nodal tumor growth (38, 39). Personalized adjuvant irradiation is indicated also for patients with positive surgical margins not amenable of reexcision. Data from recent literature seem to suggest that PNI should be evaluated routinely and included in histopathology reports of carcinoma of the vulva, and that combining PNI with other prognostic risk factors could help the clinicians to tailor postoperative adjuvant treatment (4, 6, 7). A study conducted at Massachusetts General Hospital or Brigham and Women's Hospital in Boston on 114 primary cutaneous squamous cell carcinomas with PNI showed that tumors involving unnamed nerves of caliber <0.1 mm without other risk factors usually had a good prognosis (9). Conversely, large-caliber nerve invasion was associated with an elevated risk of lymph node metastasis and death, which might be due in part to the multiple other risk factors associated. The prognostic relevance of the diameter of the nerves involved by squamous cell carcinoma of the vulva should be accurately assessed in future clinical trials.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Conceptualization, Writing - original draft: Angiolo Gadducci; Data curation, Formal analysis, Methodology, Writing- review & editing: Angiolo Gadducci, Sabina Pistolesi, Stefania Cosio, Antonio Giuseppe Naccarato.

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