Distinguished expert series

Diagnostic and therapeutic dilemmas in vulvar cancer

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Summary

Invasive vulvar cancer is rare. The etiology of vulvar cancer is incompletely understood. Human papilloma virus is known to be the major causal factor. The keystep in the diagnosis is punch biopsy with attention to unifocal or multifocal lesions and involvement of adjacent regions. The therapeutic procedure is based mostly on histomorphologic parameters e.g. unifocal/multifocal lesion, localisation, tumor typing/grading, depth of invasion; the goal of these morphologic and morphometric parameters is to reduce radicality in order to avoid postoperative morbidity without jeopardising the chances of cure. This individualization considers treatment options in both the vulvar and the groin.

Key words: Precancerous lesions; Preventable delay in diagnostics and therapy; Reduced surgical morbidity; Sentinel node concepts without worsening the prognosis.

The vulva is a morphologic and functional unit with ectodermal, neuroectodermal and mesenchymal components [1].

Invasive vulvar cancer is rare with incidence rates around two per 100,000 women in different parts of the world. Variations between countries in the incidence of invasive vulvar cancer are generally unremarkable with the possible perception that elevated rates have been reported from Portugal and parts of Brazil [2]. The temporal sequence of the incidence of intraepithelial and invasive carcinomas suggests a biphasic course in the development of carcinoma [3]. The risk for patients with chronic vulvar dystrophy to develop carcinoma is 1-5 %. Patients with cellular atypia are at particular risk.

The etiology of vulvar cancer is incompletely understood. Constitutional factors, menstrual disorders and parity do not seem to play a role: diabetes mellitus, hypertension and obesity are found in about 25 % of women with vulvar cancer, but there are no convincing correlations with the development of malignant tumor (Table 1). These concurrent conditions are typical of the age group, since 75% of patients with vulvar cancer are older than 60 years of age [4]. For these patients unifocal tumor growth is characteristic.

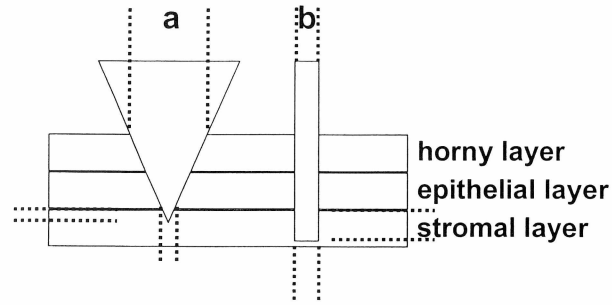
In the last decades the age of patients with vulvar cancer has been declining. Human papilloma virus is known to be the major causal factor involved in the development of vulvar cancer [5]. This especially applies to primary multicentric lesions in young women in contrast to unicentric tumors seen in older patients.

The leading symptom in cancer and precancer of the vulva is pruritus. This symptom however is very common in almost all malignant or non malignant diseases of the vulva. Noteworthy is that 20% of the patients have no symptoms at all. Typical for these patients is the long interval between symptoms and diagnosis. Reasons for this preventable delay include reluctance of the patients to present to their physician, failure of the physician to examine the patients adequately, the rarity of the condition, the heterogeneous appearance of vulvar skin conditions and the reluctance to biopsy suspicious lesions (Table 2).

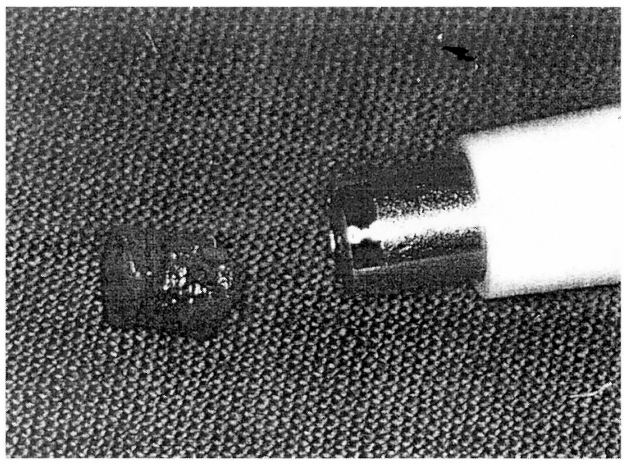
There is confusion about the malignant potential of precurser lesions. The established description and definition of intraepithelial neoplastic disorders is based on the determinations of the International Society for the Study of Vulvar Disease (ISSVD) [6] (Table 3). For clinical examination the colposcope and dye-test are useful, not for distinguishing between malignant and non malignant, but to outline the extent of a lesion (toluidin-blue-test, Table 5).

Parakeratosis, papule formation and pigment incontinence (3P) are the characteristics of at-risk lesions of the vulva (Table 6) [7].

The key step in the diagnostic procedure with almost any vulvar lesion is punch biopsy. The diameter of these disposable biopsy punches ranges from 2-12 mm. We usually use a 4 mm punch [8]. This punch works



a) Biopsy with forceps



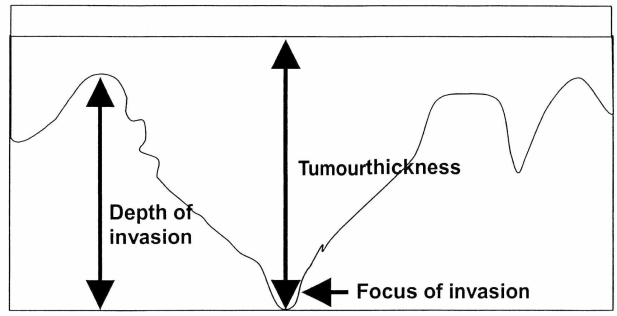
b) Punch biopsy

Figure 1. — Vulvar biopsies.

very much like a tork screw and removes the circumscribed pack of skin from the surface to the stromal layer. This procedure allows the pathologist to give an accurate diagnosis on the nature of the lesion and in cases with early carcinoma the measurement of depth of invasion. In cases with circumscribed lesions the excision of the whole lesion is indicated to prevent omitting the maximum atypia of the lesion.

The measurement of depth of invasion is according to Wilkinson [9] (Figure 2).

Tumor thickness is defined as the measurement from the granular layer or surface if non keratinized to the deepest point of invasion. Depth of invasion is defined as the measurement from the epithelial stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion. Today there is no generally excepted definition of the term "microinvasive" carcinoma of the vulva. Definitions include various cut-offs of the depth of invasion. The first proposal was made by Rutledge *et al.* in 1970 [10] with a stromal invasion depth of



From the epithelial dermal junction of the adjacent dermal papilla to the deepest point of invasion.

Figure 2. — Measurement of the depth of invasion.

Table 1. — *Possible risk factors for vulvar cancer.*

Chronic medical illnesses
– Diabetes mellitus
– Hypertension
– Obesity
– Immunosuppression
Sexually transmitted disease/infections
– Granulomatous disease
– Syphilis
– Herpes simplex virus infection
– Human papillomavirus infection
Chronic inflammatory diseases
– Lichen sclerosus
– Hypertrophic dystrophy
Personal/lifestyle factors
– Cigarette smoking
– Multiple sexual partners
– Prior genital-tract neoplasia

Table 2. — *Reasons for preventable delay.*

Include:
– reluctance by the patients to go all their physician
– failure of the physician to examine the patients adequately
– the rarity of the condition
– the heterogeneous appearance of vulvar skin conditions
– reluctance to biopsy suspicious lesions
– confusion over the malignant potential of precursor lesions

Table 3. — *Intraepithelial neoplastic disorders of vulvar skin and mucosa.*

A. Squamous (may include HPV change)
1. Vulvar intraepithelial neoplasia (VIN I) - Mild dysplasia
2. VIN II - Moderate dysplasia
3. VIN III - Severe dysplasia, carcinoma *in situ*
B. Other
1. Paget's disease (intraepithelial)
2. Melanoma *in situ* (level 1)
Lesions in the past which had been classified under "hyperplastic dystrophy with atypia" are now included within the VIN category

Table 4. — *Carcinoma of the vulva diagnostic methods.*

Inspection
Colposcopy
Cytology
Toluidin blue
Palpation
Punch biopsy

Table 5. — *Toluidine blue test.*

– Clean vulva
– Paint vulva with 1% aqueous solution of toluidine blue
– After 3 minutes, rinse vulva with 1% acetic acid

Table 6. — *"3 P" characteristics of risk-lesions of the vulva.*

Parakeratosis
Papule formation
Pigment incontinence

Table 7. — *"Early" cancer of the vulva* different definitions.

– 5 mm depth of invasion	Rutledge *et al.*, 1970
– Microinvasive carcinoma	Wharton *et al.*, 1974
– Early invasive cancer	Parker *et al.*, 1975
– Superficially invasive carcinoma	Barnes *et al.*, 1980
– Microinvasive carcinoma Exact definition for measuring the depth of invasion	Wilkinson *et al.*, 1982 (ISSVD)

Table 8. — *Nodal status in T1 vulvar cancer in relation to depth of invasion.*

Depth of invasion (mm)	Total number	Number of positive nodes	Percentage positive nodes
< 1	163	0	0
1.1-2	145	11	7.6
2.1-3	131	11	8.3
3.1-5	101	27	26.7
> 5	38	13	34.2
Total	578	62	10.7

5 mm or less defining a subgroup in which no lymph node involvement was found (Table 7). However since then lymph node metastases have been reported even in cases with microinvasion defined in this way. Wilkinson reviewed the literature on the issue and showed that no metastases are found in lesions with a depth of invasion of 1 mm or less. The frequency of lymph node metastasis increases to 12.1% in lesions with an invasion depth of up to 3 mm and increases further to 15.2% with an invasion depth up to 5 mm [9]. These basic findings correspond to greater study on nodal status T1-vulvar cancer in relation to depth of invasion [11] (Table 8).

The clinical examination also has to pay attention to the following points: Size and surface of the tumor, site of the tumor, unifocal or multifocal growth and involvement of adjacent regions such as the urethra, vagina and anus.

The clinical T-classification is necessary to establish an individualized plan of management whereas the clinical groin nodal status has no significance for therapeutic decisions due to its notorious unreliability (Table 9). A clear correlation can be shown between nodal involvement and special morphologic and morphometric parameters of tumors, for example, tumor grading is correlated with the incidence of lymph node metastasis (Table 10).

There is also a clear correlation between depth of invasion and lymph node metastasis. Only in lesions with a defined depth of 1 mm or less is there no incidence of inguinal lymph node metastasis. Therefore the ISSVD proposed the term "Stage I a carcinoma of the vulva for solitary lesions confined to a maximum of 2 cm in diameter and with a depth of invasion of 1 mm or less". The incidence of lymph node metastasis with more depth of invasion is increasing. Lymphatic spread starts from inguinal metastasis to the nodes of the pelvic wall and then

Table 9. — *The FIGO staging of vulvar cancer 1995. (The TNM classification is included for comparison).*

Stage	Description	TNM
I	Lesions ≤ 2 cm confined to the vulva or perineum. No lymph nodes metastases	T1N0M0
Ia	Lesions ≤ 2 cm confined to the vulva or perineum with stromal invasion ≤ 1 mm.* No lymph nodes metastases	
Ib	Lesions ≤ 2 cm confined to the vulva or perineum with stromal invasion > 1 mm.* No lymph nodes metastases	
II	Tumour confined to the vulva and/or perineum of > 2 cm in the greatest dimension with no nodal metastases	T2N0M0
III	Tumor of any size arising on the vulva and/or perineum with (1) adjacent spread to the lower urethra and/or the vagina or anus and/or (2) unilateral regional lymph node metastases	T3N0M0 T3N1M0 T1N1M0 T2N1M0
IVa	Tumour invading any of the following: upper urethra, bladder mucosa, rectal mucosa, pelvic bone and/or bilateral regional nodal metastases	T1N2M0 T2N2M0 T3N2M0
IVb	Any distant metastases including pelvic lymph nodes	AnyTanyNM1

*The depth of invasion is defined as measurement of the tumour from the epithelial stromal junction of the adjacent most superficial dermal papilla, to the deepest point of invasion.

the propagation may continue to the paraaortic nodes. There is no evidence of spread to the pelvic nodes without first involving the inguinal lymphnodes. Of interest is the incidence of positive contralateral nodes in patients with strong lateral T1-squamous cell cancer of the vulva. The incidence of positive contralateral nodes is 0.4% [11] (Table 11). Haematogenious spread is rare.

Five-year survival rates correlate with FIGO stage. The five-year survival rate in Stage 1 was 86.5%, while in Stage 4 the rate dropped to 21.7% [4] (Table 12).

Although the role of surgery in the treatment of squamous cell cancer of the vulva has changed over the last 20 years, surgery still provides the basis for management [3, 8, 12-14].

For a long time the standard procedure was en bloc radical vulvectomy with inguinal lymphadenectomy. Now the management of patients with T1-vulvar cancer is a major field of treatment individualization. The goal is to reduce the radicality to the most conservative local and inguinal procedures in order to avoid the typical postoperative morbidity common with the radical en bloc procedure, and to decrease the psychosexual sequelae especially in younger women without jeopardizing the chances of cure. Individualization must consider treatment options in both the vulva and the groin.

In patients with vulvar cancer with an invasion depth of less than 1 mm there is the recommendation to omit inguinal lymphadenectomy. In patients with strong lateral lesions there is the recommendation to omit bilateral groin dissection, and to restrict the operative treatment to unilateral dissection if the primary lesion is a strong lateral lesion. For centrally localized lesions bilateral lymphadenectomy is mandatory (Table 13).

Table 10. — *Carcinoma of the vulva. Tumorgrading versus inguinal lymph node metastases.*

Grading	n	Metastases (%)
G1	227	26.9
G2	260	35.8
G3	71	55.0

Table 11. — *Incidence of positive contralateral nodes in patients with strong lateral T1-squamous cell carcinoma of the vulva, who all had a bilateral inguinal node dissection with negative ipsilateral nodes.*

Reference	Year	Unilateral lesions	Contralateral nodes positive (%)
Wharton	1974	25	0 (0)
Parker	1975	41	0 (0)
Magrina	1979	77	2 (2.6)
Iversen	1981	112	0 (0)
Hoffman	1983	70	0 (0)
Hacker	1984	60	0 (0)
Struijk	1992	53	0 (0)
Buscema	1981	38	0 (0)
Total		476	2 (0.4)

Table 12. — *Carcinoma of the vulva survival by FIGO stage.*

Stage	Pat.	5-years
I	193	86.5%
II	247	67.7%
III	201	40.3%
IV	74	21.7%

Table 13. — *Operative treatment of vulvar cancer.*

Depth of invasion	Therapy
< 1 mm	wide excision
1-3 mm	wide excision, ipsilateral ing. lymphnode dissection
3-5 mm	vulvectomy based on localisation bilateral ing. lymphnode dissection

Sentinel lymph node identification and excision could prove to be a rational alternative to extensive inguino-femoral lymphadenectomy in selected patients with vulvar carcinoma. If consistent predictability is shown patients with SLN-metastasis could forego lymphadenectomy resulting in deminishing morbidity [15-17] (Table 14).

Wound disruption and infection are the main complications of en bloc radical vulvectomy with bilateral groin dissection and occur in about 40%. To reduce this frequency the triple-incision technique was introduced i.e., bilateral inguino-femoral lymphadenectomy through separate incisions (Figure 3). Skin-bridge recurrencies are reported in 1-2% of the patients treated by separate groin incisions. It is important to note that these bridge recurrencies are found in patients with positive nodes [11].

In T2/T3 lesions radical vulvectomy with inguinal lymphadenectomy is the appropriate surgical procedure (Figure 4).

In T3-cancers the surgical procedure is extended according to the involvement of the urethra, vagina or anus. In patients with very large tumors recon-

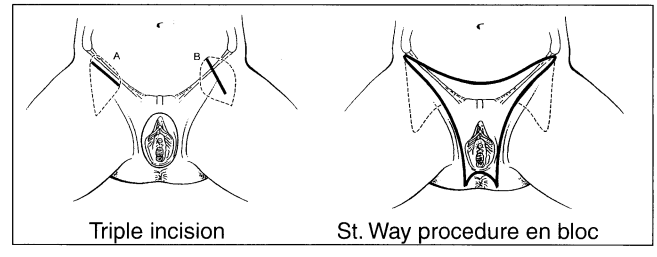


Figure 3. — Triple incision and St. Way procedure en bloc.

Table 14. — *Sentinel node in vulvar cancer literature review.*

Reference	Year	Number of cases	Technique	Tumor staging	Identification of SN (%)	Positive SN (%)	Negative PV (%)
Ansik	1999	51	VD	–	56	17	96
Levenback	2000	52	VD	T1-T3	88	19*	100
De Hullu	2000	59	RT+VD	T1-T3	100	32*	100
Sideri	2000	44	RT	T1-T2	100	29	100
Sliutz	2002	26	RT+VD	T1-T2	100	35*	100

SN, sentinel node; PV, predictive value; VD, vital dye; RT, radioactive tracer (^{99m}Tc nanocolloid). *Serial sectioning + immunohistochemistry in H&E negative SN.

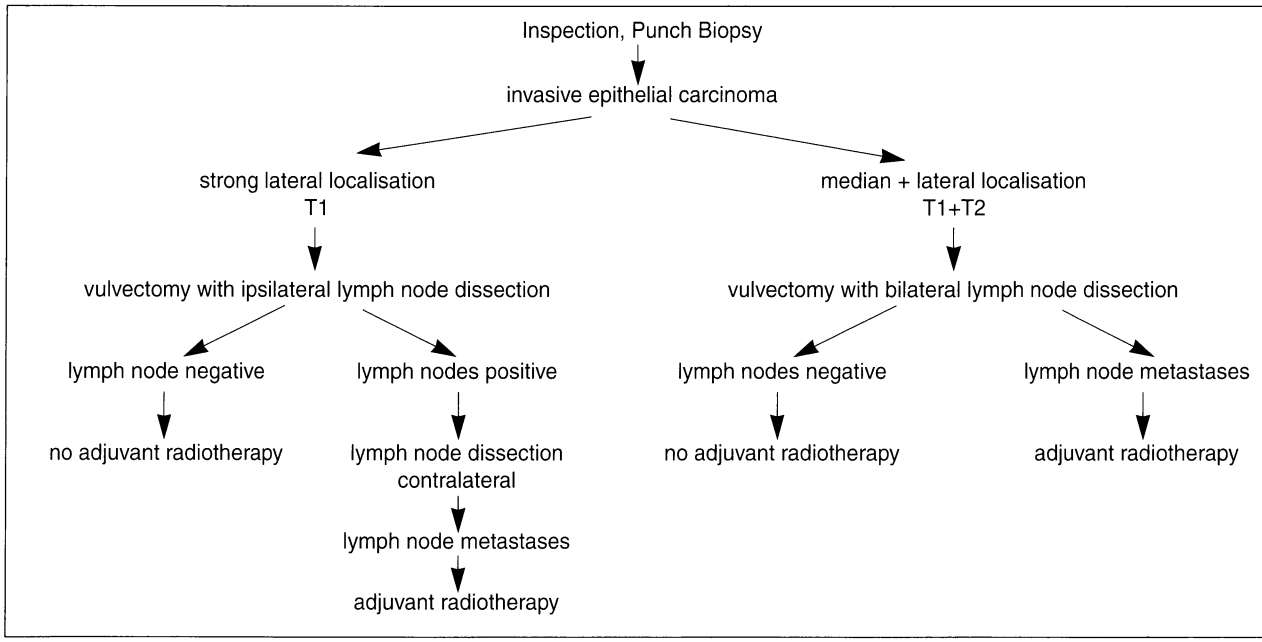


Figure 4. — Diagnostic and therapeutic procedure in patients with vulvar cancer (T1-T2).

structive procedures may be necessary to close the defects (gluteus maximus graft, tensor fascia latae muscle graft, rectus abdominis muscle graft). Most important for the survival of patients is the complete excision of the tumor.

Adjuvant radiotherapy can be considered in patients postoperatively to the vulvar region if the surgical margins are not free of disease, to the regional lymph nodes after limited surgery or to the regional lymph nodes after radical surgery and histologic evidence of extensive lymph node involvement [18-22].

Chemotherapy has only a limited role in squamous cell carcinoma of the vulva. Bleomycin, adriamycin and cisplatin alone or in combination have been recommendet as a neo adjuvant or adjuvant therapy [23-25].

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