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Vulvar Paget disease: A national retrospective cohort study

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Background: Vulvar Paget disease (VPD) is a rare skin disorder that is considered premalignant.

Objective: To assess the clinical course, treatment schedules, and effect of invasion and treatment on recurrence and survival in patients with VPD.

Methods: Data on women with VPD were retrieved from the medical files and pathology reports in all Dutch tertiary university medical centers. Disease-free survival and 5-year disease-specific survival were estimated by using Kaplan-Meier curves.

Results: Data on 113 patients whose VPD was diagnosed between 1991 and 2016 were analyzed; 77% had noninvasive VPD. Most of the women (65%) underwent a surgical procedure. Recurrences were reported in 40%. Of the women with noninvasive VPD, 8% developed invasion. There were no disease-specific deaths reported in the women with noninvasive VPD. The 5-year disease-specific survival rate was greater than 98% in noninvasive and microinvasive VPD, but significantly worse in invasive VPD (50% [$P < .0005$]).

Limitations: The main limitations of this study are its retrospective character and the fact that original pathology samples were not available for reassessment.

Conclusions: VPD is extremely rare, and the recurrence rates are high. Most patients have noninvasive VPD, which does not affect survival and should be considered a chronic disorder with limited invasive potential. In cases of invasive disease, survival decreases significantly. (J Am Acad Dermatol 2019;81:956-62.)

Key words: extramammary; Paget disease; recurrence; survival; vulva; vulvar neoplasms.

Vulvar Paget disease (VPD) is an extremely rare skin disorder. Most women with VPD are postmenopausal and experience vulvar or perineal irritation, burning sensations, itching, and pain. Clinical examination may reveal

Abbreviations used:

DFS: disease-free survival
DSS: disease-specific survival
VPD: vulvar Paget disease

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an eczematous, papillomatous, scaling, or ulcerating erythematous plaque.[1] At the first clinical presentation, VPD is often not recognized and is misdiagnosed as eczema or fungal. Early histologic assessment with a biopsy is crucial to make the correct diagnosis.

In the literature, about 25% of VPD cases are associated with invasion or an underlying vulvar adenocarcinoma.[2-4] Noninvasive VPD is considered an adenocarcinoma in situ, and debate on the malignant potential of noninvasive VPD is ongoing. Treatment of women with invasive VPD is comparable to that of women with vulvar squamous cell carcinoma, with surgery as the cornerstone of treatment.

Historically, surgical excision was considered the treatment of choice for both invasive and noninvasive VPD. Recurrence rates range from 15% to 70%: the influence of positive surgical margins on the recurrence rate is still debated. Wide local excision often leads to permanent mutilation and functional impairment.[3,5-8] Recently, there has been more attention paid to other treatment options such as topical treatment with 5% imiquimod cream, but large studies on this topic are lacking.

The influence of VPD on survival is unclear. Retrospective analysis of limited literature (with the largest study in 76 women) shows that death from disease in cases of noninvasive and microinvasive VPD is rare and more common in cases of invasive disease.[1,8]

For 2 decades, treatment of vulvar malignancies has been centralized in 8 gynecologic oncology centers in the Netherlands.[9,10] Gynecologic oncologists are involved in multidisciplinary teams of vulvar clinics because of their experience and surgical skills.

To understand the course of this rare disease, and to optimize the current protocols, it is important to gain more insight on VPD. Clinical data on a high number of women may help in recognizing possible areas for improvement in clinical care and the effect of different treatment options and disease-specific outcomes. The objective of this national study was to assess the clinical course of VPD, analyze current treatment schedules, and study the effect of invasion and treatment on recurrence and survival rates.

CAPSULE SUMMARY

- Vulvar Paget disease is a rare skin disorder with unknown malignant potential.
- Recurrence rates are about 40%. The risk of development of invasive disease after a diagnosis of noninvasive vulvar Paget disease is 8%. The 5-year disease-specific survival of invasive disease is significantly worse than in noninvasive or microinvasive vulvar Paget disease (50% versus 98%).

MATERIAL AND METHODS

This retrospective cohort study took place in all 8 gynecologic oncology units in the Netherlands: Amsterdam Medical Centre, Antoni van Leeuwenhoek Hospital Amsterdam, Erasmus Medical Center in Rotterdam, Leiden University Medical Centre, Maastricht University Medical Centre, Radboud University Medical Centre in Nijmegen, University Medical Centre Groningen, and the University Medical Centre Utrecht.

Local pathology databases were searched for all women for whom a first diagnosis of VPD or a recurrence between January 1,1991, and January 1, 2016, was reported. The lesion had to be located on the vulva, perineum, and/or perianal skin. We retrieved the medical files of all the women. Data on each woman's characteristics, diagnostic methods used, and treatment schedule for the first episode and for recurrences, including follow-up data, were collected. All data were entered into a blinded digital database (CastorEDC, the Netherlands) according to the Good Clinical Practice guidelines.[11]

Data on the women' characteristics, processes used to diagnose their VPD, and treatment schedules were analyzed in a descriptive manner. We estimated disease-free survival (DFS), defined as the time from the date of diagnosis to the date of the first recurrence, or in the case of no recurrence, until the last date of follow-up (or death), by using a Kaplan-Meier curve. The 5-year disease-specific survival (DSS), defined as the time from the date of diagnosis to the date of death from vulvar carcinoma, or in case of no death or death from some other cause, the date of last follow-up/date of death, was estimated by using a Kaplan-Meier curve. Recurrences were defined as histologically confirmed diagnoses after a complete response or in cases in which a complete response was not obtained and the residual lesion necessitated treatment. We performed subgroup analyses for 3 different initial diagnoses: noninvasive VPD, microinvasive VPD, and invasive VPD. We also analyzed the main treatment methods: surgery, topical treatment, and no treatment (watchful waiting), along with surgical margin status in the women who underwent a surgical procedure. Differences in DFS and DSS rates between groups

were analyzed by using log-rank tests. A *P* value less than .05 was considered statistically significant. All analyses were performed with SPSS for Windows software (version 20, IBM Inc, Armonk, NY).

As assessed by the institutional review board of the Radboud University Medical Center, this study was not subject to the Dutch Medical Research Involving Human Subjects Act (ie, it was exempt from approval).

RESULTS

Study population

Searches of the local pathology databases in the 8 participating centers identified 151 cases of VPD diagnosed before January 1, 2016. After exclusion of cases because data were not available (n = 27) or because the cases were diagnosed as other diseases (n = 11), data on a total of 113 women were available for the study.

Woman characteristics

Overall, the initial diagnosis in the cases of 87 women (77.0%) was noninvasive VPD, in 10 (8.8%) it was microinvasive VPD, in 7 (6.2%) it was invasive VPD, in 6 (5.3%) it was VPD with an underlying vulvar adenocarcinoma, and in 3 (2.7%) the VPD had metastasized. The median age of the 113 included women was 73 years (range, 41-97 years) at time of diagnosis, and there was no statistically significant difference between the different diagnoses ($P > .3$) (Table I).

Table I. Clinical characteristics of patients with VPD

Characteristic	ni-VPD (n = 87)	mi-VPD (n = 10)	i-VPD (n = 16)
Median age, y (range)	72 (41-97)	73.5 (54-86)	74 (49-89)
Hospital of diagnosis, n (%)			
Referring hospital	56 (64.4%)	6 (60%)	10 (62.5%)
University medical center	30 (34.5%)	4 (40%)	6 (37.5%)
Unknown	1 (1.1%)	0	0
Initial treatment, n (%)			
Surgery	51 (58.6%)	10 (100%)	13 (81.3%)
Topical, imiquimod	18 (20.7%)	0	0
Topical, other	3 (3.6%)	0	0
Chemotherapy	1 (1.1%)	0	0
Radiotherapy	1 (1.1%)	0	2 (12.5%)
None	12 (13.8%)	0	1 (6.2%)
Unknown	1 (1.1%)	0	0

i-VPD, Invasive vulvar Paget disease; *mi-VPD*, microinvasive vulvar Paget disease; *ni-VPD*, noninvasive vulvar Paget disease; *SD*, standard deviation.

Noninvasive VPD

At the first consultation with the medical specialist, the duration of symptoms was often reported as symptoms for "several months," "about a year," or even "a few years." In all, 49 women (56.3%) had their disease diagnosed within 4 weeks after the first consultation; 29 women (34.5%) had a history of VPD or had already had the disease diagnosed elsewhere when they first presented at the hospitals included in our study. Reports of mammography performed as screening after VPD diagnosis were available for 33 women after the diagnosis of VPD and in 1 case (1.1%) a malignancy was found. Additional diagnostics and screening did not reveal any abnormalities. Vulvar mapping, with several biopsy samples taken from all suspected areas, was performed in 37 women (42.5%): 1 woman was suspected of having invasive disease and was treated with a skinning vulvectomy, but invasion was not found in the surgical specimen.

Of the 51 surgically treated women, 33 (64.7%) underwent a wide local excision, 5 (9.8%) had a hemivulvectomy, and 12 (23.5%) had a (skinning) vulvectomy. Data on the type of surgery were missing for 1 woman. Margin status was available for 47 (92%) of the surgically treated women: surgical margins were clear in only 5 women.

A total of 18 women were treated with topical 5% imiquimod cream; the treatment schedules varied from 1 to 5 times per week, and the women were treated for 3 weeks to an entire year. Of all the women initially treated with topical 5% imiquimod cream, 4 (22.2%) had a complete response, 7 (38.8%) had a partial response, and 4 (22.2%) had no response or stable disease. Data on the treatment response were unavailable for 3 women. Of the 13 women without a complete response, 4 (30.7%) underwent an additional surgical procedure.

Microinvasive VPD

Of 10 women with microinvasive VPD, 5 (50%) had their VPD diagnosed at their first hospital visit; 3 women (30%) had already had their disease diagnosed at time of referral. Screening for additional malignancies did not reveal other tumors. Vulvar mapping was performed in 6 cases (60%).

All the women with microinvasive VPD were treated with surgery. None of the women with microinvasive disease underwent groin surgery. Margin status was available for 9 patients: all the margins were positive for Paget cells but clear of microinvasion.

Invasive VPD

All the women with invasive VPD had their disease diagnosed within 4 weeks of their first

Table II. Groin metastases in patients with invasive vulvar Paget disease

Patient No.	Groin treatment	Groin metastases	Status at last FU	FU, mo
1	None		DVC	6
2	None		DVC	2
3	None		AWD	42
4	None		NED	118
5	None		AWD	5
6	None		NED	138
7	None		DVC	1
8	None		AWD	21
9	SLN procedure, bilateral	Negative for metastasis	DAC	7
10	IFL, unilateral	Negative for metastasis	DVC	131
11	SLN procedure, unilateral	Positive for metastasis	DVC	18
12	IFL, unilateral	Positive for metastasis	DVC	6
13	IFL, unilateral	Positive for metastasis	DAC	17
14	IFL, bilateral	Positive for metastasis	DVC	19
15	Radiotherapy	Positive for metastasis	DVC	2
16	Radiotherapy	Positive for metastasis	AWD	6

Overview of treatment of the groin in all patients with an initial diagnosis of invasive VPD, conclusion of the pathology report, and status of the patient.
AWD, Alive with disease; *DAC*, death from another cause; *DVC*, death from vulvar carcinoma; *FU*, follow-up; *IFL*, inguinofemoral lymphadenectomy; *NED*, no evidence of disease; *SLN*, sentinel lymph node.

hospital visit; 5 of them (31.3%) had a history of VPD or had received the diagnosis at time of referral. Screening for additional malignancies via mammography, colonoscopy, or cystoscopy was performed in 5 women and did not reveal other tumors. Vulvar mapping was performed; the results were positive for invasion in 9 cases (56.3%). In 5 women an ultrasound of the groin was performed; in 4 of them, a suspected groin lesion was detected.

Most of the women with invasive VPD (n = 13 [81.3%]) were initially treated with surgery: 6 (37.5%) had a (skinning) vulvectomy, 2 (12.5%) had a hemivulvectomy, and 5 (31.3%) had a wide local excision. The type of surgery was unknown for 1 woman. Groin surgery (a unilateral or bilateral sentinel lymph node procedure or inguinofemoral lymphadenectomy) was performed in 7 women (29.2%). In all, 6 women had lymph node metastases (see Table II for details on lymph node status for all patients with invasive disease). Margin status was available for 11 women; the margins were clear of Paget cells in only 1 patient.

Of the women with invasive VPD, 2 were initially treated with radiotherapy, of whom 1 received chemotherapy in advance. Limited data on the details of treatment were available.

Recurrence rates

Overall, 46 women (37.4%) had 87 recurrences (range, 1-9 recurrences per woman).

Of the 87 women with noninvasive VPD, 32 (36.8%) had at least 1 recurrence. In all, 19 (59.4%) had only 1 recurrence. In 1 case the recurrence was invasive, in 1 case the disease metastasized, and in all the other women the recurrences were noninvasive (see Fig 1 for an overview of all recurrences in women with noninvasive VPD). One woman had a clinical recurrence and was also found to have a metastasized cervical adenocarcinoma that was the cause of her death; invasion of the VPD was not reported.

In all, 87 women with an initial diagnosis of noninvasive VPD, 7 (8.0%) eventually progressed (Fig 1). Progression into invasion occurred after a median of 62 months following the initial diagnosis (range, 31-165 months).

Of the 10 women with microinvasive VPD, 6 (60%) had at least 1 recurrence, 2 had microinvasive recurrences, and 4 had noninvasive recurrences (Fig 1).

Of the women with invasive disease, 5 (31.3%) had at least 1 recurrence. In 2 cases the VPD was metastatic. Three women (18.7%) had noninvasive recurrences (see Fig 1 for an overview of all recurrences in women with invasive VPD).

Survival

The estimated median DFS time was 69.3 months for noninvasive disease, 39.3 months for microinvasive disease, and 26.5 months for invasive disease (P = 301). There was no difference in the DFS between the women with clear margins

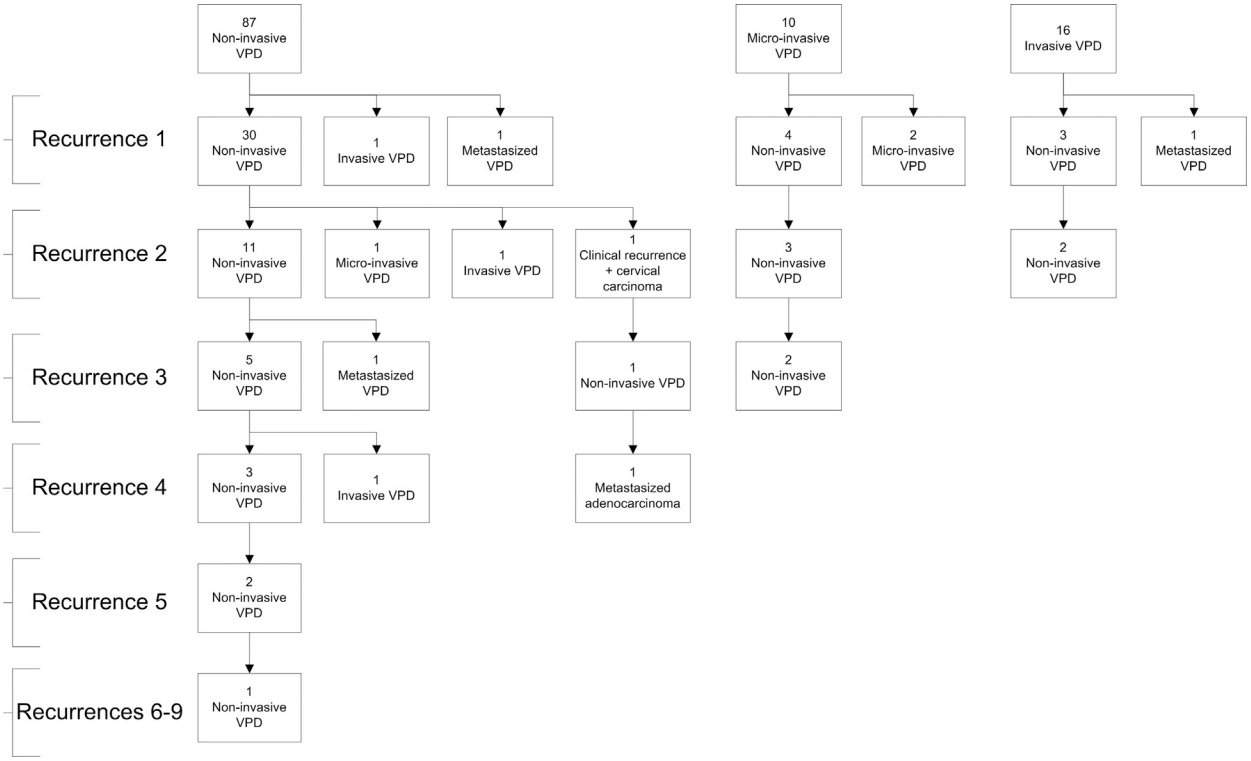

Fig 1. Recurrences. *VPD*, Vulvar Paget disease.

and those with margins positive for Paget cells after initial surgical treatment (P = .491).

The median follow-up after the diagnosis of VPD in all the women was 38 months (range, 0-451 months). Table III presents an overview of disease status at time of last follow-up. The 5-year DSS was significantly better in women with initially noninvasive and microinvasive VPD than in those with invasive VPD: 98.8% and 100.0% versus 50.0% ($P < .0005$) (Fig 2). One patient with noninvasive VPD died of metastasized VPD at time of first recurrence 30.6 months after initial diagnosis. The 5-year overall survival of noninvasive VPD women did not differ between women who were surgically treated, those who underwent topical treatment, and those who received no treatment (P = .713).

DISCUSSION

This is the largest cohort study of women with VPD so far. We analyzed clinical data on 113 women with VPD who were treated in 1 of the 8 gynecologic oncology university centers in The Netherlands.

We found that the women had had symptoms for several months to years before the diagnosis was finalized. Because of its rarity, VPD is not often recognized by clinicians at first evaluation. Most medical specialists performed a vulvar biopsy at the woman's first visit, confirming the diagnosis. The importance of early histologic assessment is stressed, especially in cases of vulvar lesions not responding to therapy. In the majority of cases the pathologist had no difficulty with recognizing the Paget cells in VPD.

VPD may be associated with invasion; we found that 23% of cases were invasive at initial diagnosis, and in 2.7% of cases, the disease had already metastasized. Progression of noninvasive VPD into invasive disease occurred in 7 cases (8%) after a median of 5 years. This long interval might suggest a de novo invasive lesion rather than progression of the noninvasive VPD.

The main issue in surgical excision of VPD is obtaining surgical margins free of Paget cells, as the histologic presence of disease does not overlap with the visibly affected skin on account of intradermal localization.[12] In our series, surgical margins were clear in only 9.4% of the women. A different surgical technique, such as Moh's micrographic surgery, seems to improve these figures.[13] With Moh's micrographic surgery, the lesion is excised through the epidermis and dermis, and 100% of the peripheral margins are examined immediately. Excision is repeated, enlarging the circumference each time, until the margins are clear. DFS seems longer and recurrence rate lower in women treated with Moh's micrographic surgery.[13-15] Our study did

Table III. Disease status at last follow-up

Disease status	Noninvasive VPD (n = 87)	Microinvasive VPD (n = 10)	Invasive VPD (n = 16)
Alive			
With disease	35 (40.2%)	3 (30.0%)	4 (25.0%)
With no evidence of disease	33 (37.9%)	5 (50.0%)	2 (12.5%)
With unknown disease status	3 (3.4%)	1 (10.0%)	—
Dead			
Due to vulvar carcinoma	1 (1.1%)	—	8 (50.0%)
Due to another cause	7 (8.0%)	1 (10.0%)	2 (12.5%)
Due to an unknown cause	8 (9.2%)	—	—

VPD, Vulvar Paget disease.

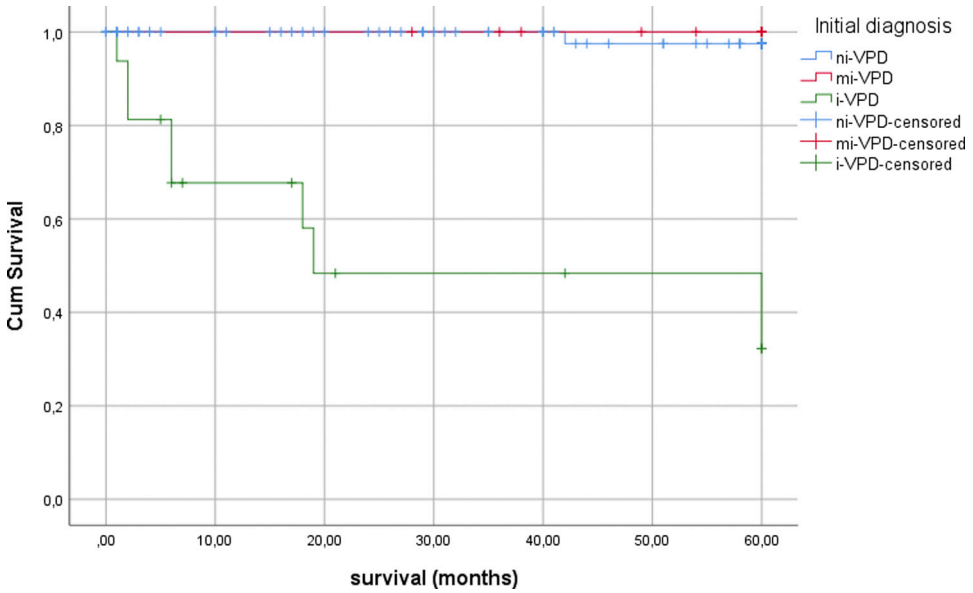

Fig 2. Disease-specific survival in noninvasive vulvar Paget disease (ni-VPD) versus microinvasive vulvar Paget disease (mi-VPD), and invasive vulvar Paget disease (i-VPD). Of the women at risk, 87 had ni-VPD, 10 had mi-VPD, and 16 had i-VPD.

not find that margin status influences DFS; moreover, enlarging the excision will raise the morbidity of treatment.

Topical 5% imiquimod cream is suggested as a new treatment option. It has been shown to be effective for high-grade vulvar squamous cell intraepithelial lesions.[16] Several case series and 2 small prospective studies have reported on use of imiquimod for VPD.[17,18] We found that 20% of the women initially treated with imiquimod had a complete response and 40% had a partial response, although data on histologic response were not available in most cases. Treatment schedules vary a lot with respect to frequency and overall duration. There is currently 1 ongoing study investigating the efficacy of topical 5% imiquimod cream in VPD in a standardized treatment schedule (ClinicalTrials.gov identifier NCT02385188). Results can be expected at the end of 2018.

Care for women with VPD should take place in specialized centers. Women should consult their physician frequently whenever new lesions and/or symptoms arise. In the case of noninvasive VPD, watchful waiting or symptomatic treatment with regular check-ups may be advised, as recurrence rates are high and the presence of residual noninvasive disease does not influence survival. Women with invasive VPD should be treated according to the guidelines for vulvar squamous cell carcinoma; however, sentinel lymph node procedures are not recommended in these women. Recurrences after invasive VPD are also not always invasive, a phenomenon that is also seen in squamous vulvar (pre)malignancies. Our study

identified 1 case of noninvasive VPD with an invasive recurrence that led to death of the patient. This patient was initially treated with topical imiquimod cream in a referring hospital; 31 months after the initial diagnosis, a vulvar adenocarcinoma was diagnosed and the patient was referred to a tertiary center. Groin and bone metastases of a vulvar adenocarcinoma were found and the patient received chemotherapy. Her disease progressed and she died 42 months after the initial diagnosis. The pathology reports on the first biopsy samples taken in the referring hospital were not available for pathologic review. The available reports have suggested a possible relation to her former breast carcinoma, which had been diagnosed 9 years prior.

The main limitation of this study is that we analyzed only clinical files and it was not possible to review pathology. The diagnosis of invasive VPD lacks a clear description: it can be hypothesized that the natural phenomenon of Paget cells in the skin adnexa are mistaken for invasive disease, whereas an inevitable vulvar adenocarcinoma may be a second diagnosis in cases in which the overlying (ie, intact) epithelium contains Paget cells. This may be regarded as noninvasive VPD with an underlying vulvar adenocarcinoma. The prognosis of the patient may then depend on the adenocarcinoma rather than on the VPD. We therefore advise, in view of the rarity of the disease, that all cases be reviewed by a specialist gynecologic and/or dermatologic pathologist.

In conclusion, this study has presented an overview of 113 patients with VPD from the Netherlands. In cases of a lesion suggestive of VPD, histology should confirm the diagnosis. Invasion occurs in about 14% of cases and is generally diagnosed with the first biopsy. Invasive disease has a worse prognosis than does noninvasive or microinvasive disease. A policy of symptomatic treatment or watchful waiting is acceptable in women with noninvasive VPD. The risk of recurrence is high, but the risk of progression is limited, generally occurring after several years. Care for women with VPD should take place in centers with specialized clinicians and pathologists who are experienced in treating this rare disease.

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