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Vulvar Intraepithelial Neoplasia (VIN2/3): comparing clinical outcomes and evaluating risk factors for recurrence

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Abstract

Objective—To determine risk factors for the development of vulvar intraepithelial neoplasia (VIN 2/3), and factors associated with recurrence.

Methods—A retrospective chart review of 303 patients with VIN 2/3 evaluated at a single institution between 1993 and 2011 was performed. Medical records were reviewed for demographic information, risk factors, treatment type, pathologic diagnosis, and recurrence/outcome information. Recurrent disease was defined as a diagnosis of VIN 2/3 and/or invasive vulvar cancer after initial treatment of VIN 2/3. Patients with VIN 1 and patients with invasive disease, including microinvasion, were excluded.

Results—The median age at diagnosis was 47 years (range 14–87). 33% of patients were symptomatic, with pruritus being the most common presenting symptom. Smoking history was available for 299 patients, with 40% reporting current tobacco use and 26% reporting previous use. Primary treatment included excision (n=176, 59%), laser ablation (n=40, 13%), imiquimod (n=22, 7.4%), excision with laser (n=24, 8.1%), or excision with imiquimod (n=10, 3.4%). Margin status was available for 147 patients. 92 patients (62.6%) were noted to have positive margins, which were associated with larger tumor size (p=0.004). 87 patients (28.7%) developed recurrent disease and it was associated with smoking (p<0.001), larger lesion size (p=0.016), and positive margins (p=0.005). Furthermore, higher rates of recurrence were associated with laser (41.9%) compared with excision (26.4%) or imiquimod (13.6%) (p=0.003). 7 patients (2.3%) recurred with invasive disease a median of 109 months (range 12–327) from initial VIN 2/3 diagnosis.

Conclusions—This large cohort of women with VIN2/3 further delineates the demographic and clinical factors associated with VIN2/3. High rates of recurrence were noted and found to be associated with smoking, large lesion size, positive margins, and treatment with laser ablation.

Background

The incidence of vulvar intraepithelial neoplasia (VIN) is increasing, with 60–75% occurring in young women (1, 2, 3). The risk of progression from VIN to invasive cancer is

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3 to 9 percent (3, 4). Treatment options for VIN include surgical excision, laser ablation, and topical treatment with imiquimod. In many women, a combination of these modalities is used. Retrospective data have shown that approximately 30% of patients treated for VIN develop recurrent disease, irrespective of treatment modality used. Reported risk factors for recurrence include multifocal disease and positive margins; however, smoking, a well-known risk factor for VIN incidence, has not been shown to be associated with VIN recurrence (3, 4, 5, 6). The purpose of this study was to utilize data from a large series of patients treated for VIN to assess for differences in outcome with regard to treatment modality used. We also set out to further investigate risk factors for recurrence and progression to invasive cancer.

Methods

Following approval from the University of Texas MD Anderson Cancer Center Institutional Review Board, a retrospective chart review of 303 patients with VIN 2/3 evaluated between 1993 and 2011 was performed. Medical records were reviewed for demographic information, risk factors, treatment type, pathologic diagnosis, and recurrence/outcome information. Recurrent disease was defined as a diagnosis of VIN 2/3 and/or invasive vulvar cancer after initial treatment of VIN 2/3. Patients with VIN1 were excluded, as were patients with invasive disease, including microinvasion, without a prior history of VIN 2/3.

Group comparisons of patient characteristics were conducted. The Wilcoxon test and Fischer's exact test were used to compare patients with a positive margin and those with a negative margin with respect to treatment and tumor size. In a similar fashion, patients with and without recurrence were compared with respect to several demographic and clinical factors. All p-values were 2-sided and considered statistically significant if $p < 0.05$. Data were analyzed using SAS 9.1 software (Cary, NC).

Results

Demographic characteristics are shown in Table 1. The median age at diagnosis was 47 years (range 14–87). Thirty-three percent of patients were symptomatic, with pruritus being the most common presenting symptom. Smoking history was available for 299 patients, with 40% reporting current tobacco use and 26% reporting previous use. Twenty-seven patients (8.9%) were immunosuppressed due to autoimmune disease (3.0%), HIV (3.0%), or exposure to immunosuppressive medications such as chronic steroid use (2.3%) or chemotherapy (1.0%). Five percent of patients had a diagnosis of lichen sclerosis or other inflammatory vulvar condition. Fifty-six percent of patients had a history of cervical dysplasia. Of those, 6 (4.9%) had invasive cervical cancer.

The median lesion size was 1.5 cm (range 0.2–7). Primary treatment included excision (n=176, 59%), laser ablation (n=40, 13%), imiquimod (n=22, 7.4%), excision with laser ablation (n=24, 8.1%), and excision with imiquimod (n=10, 3.4%) (Table 2). Margin status was available for 147 of 210 patients who underwent excision. Ninety-two (62.6%) were noted to have positive margins, which was associated with larger tumor size ($p=0.004$). Eighty-seven patients (28.7%) developed recurrent disease a median of 25 months (range 1.6–326) from primary diagnosis. Fourteen patients (4.6%) had 2 recurrences, 8 patients (2.6%) had 3 recurrences, and 6 patients (2.0%) had 4 or more recurrences. Seven patients (2.3%) recurred with invasive vulvar cancer. Recurrence was associated with smoking ($p<0.001$), larger lesion size ($p=0.016$), and positive margins ($p=0.005$) (Table 3). Regarding treatment modality, higher rates of recurrence were associated with laser ablation (41.9%) compared with excision (26.4%) or imiquimod (13.6%) ($p=0.003$) (Table 4). Median follow-up for all patients in this study was 21 months (range 0–340).

Seven patients (2.3%) developed invasive vulvar cancer a median of 109 months (range 12–327) from initial VIN2/3 diagnosis. Among these patients, initial VIN 2/3 treatment included excision (n=4), laser ablation (n=2), and excision with laser ablation (n=1). Margin status was only available for 1 of the 7 patients and was positive. Three patients had microinvasive disease. Lesion size was not available for any of the patients with invasive disease. Treatment for these lesions included excision only (n=3), excision with radiation (n=1), and chemoradiation (n=1); treatment was unknown in one of these patients. Site of invasive recurrence was the same in 2 patients, different in 2 patients, and unknown in 3 patients. 3 of the patients have died; 2 not of the disease and 1 of unknown causes. All patients who eventually developed invasive disease were currently smoking at the time their VIN 2/3 was initially treated.

Discussion

The principal findings from our study include that recurrence after initial treatment of VIN 2/3 occurred in 28.7% of patients and was associated with smoking, larger lesion size, and positive margins. Furthermore, patients treated with laser ablation had significantly higher rates of recurrence compared to excision or imiquimod.

Similar to previous studies (3, 4, 7), we noted a higher rate of recurrent disease in those whom had positive surgical margins on excision of VIN 2/3. Of those with positive margins, 31.5% recurred, whereas 10.9% of those with negative margins recurred. Jones et al. (3) noted a recurrence rate of 50% among those with positive surgical margins vs. 15% in those whose margins were negative. In addition, van Seters et al. (4) reported recurrence in 47% of those with involved margins, compared to 17% of patients with free surgical margins. Furthermore, Modesitt et al. (7) found recurrence in 46% with positive margins, while 17% with negative margins had recurrent disease. Our study had a 62.6% rate of positive margins, which was similar to the 66% rate reported by Modesitt et al. Those authors theorized that, given such a high positive margin rate, microscopic disease likely exists beyond areas with acetowhite changes. In addition to a significant association with recurrent disease, Modesitt et al. found that median time to recurrence was significantly shortened in those with positive margins (15 months) compared to those with negative margins (41 months). While the goal of VIN 2/3 treatment is prevention of invasive disease, and negative surgical margins should be attempted, it remains to be established whether obtaining negative margins actually reduces the risk of progression to invasive cancer (4). In our study, it was unclear if the 7 patients with invasive disease developed the lesions due to treatment failure with invasion occurring at the primary site of prior VIN 2/3 treatment, or due to a new “field” lesion occurring at separate site. Further study is warranted in this area.

However, it has been suggested by Jones et al. that, among who had been treated for VIN, invasive disease arises in one of two patterns—(a) after “treatment failure” specified by invasion occurring at a site of prior VIN treatment and/or in a patient who had positive margins at the time of VIN excision, or (b) a new “field” carcinoma occurring many years after VIN treatment, at a location distinct from the previously treated site (3).

In contrast to other studies, we found a history of current or former smoking to be associated with recurrence after treatment for VIN 2/3. Cigarette smoking is an established risk factor for VIN 2/3 incidence (3). However, in studies that specifically addressed recurrence with regard to smoking status, no such association has been reported (6, 7, 8). Kuppers et al. (6) performed a prospective study of 102 patients treated for VIN; after a mean follow-up of 3.5 years, no association was found between recurrence and smoking. In addition, Modesitt et al (7) found no significant correlation between VIN 3 recurrence and tobacco use in a retrospective review of 73 patients treated for VIN 3. von Gruenigen et al. (8) also found no

association between recurrence and smoking in a prospective trial of laser vs. ultrasonic surgical aspiration for vulvar and vaginal dysplasia. It is possible that these studies may have been under-powered to detect such an association. In contrast, while Jones and colleagues (3) did not specifically analyze for an association between smoking and VIN recurrence, 15 (88%) of the 17 patients who progressed to invasive vulvar, perianal, or urethral carcinoma were cigarette smokers. This is consistent with our study's finding that all 7 patients who progressed to invasive vulvar cancer were current cigarette smokers cigarettes at the time their initial VIN 2/3 lesions were treated.

To date, there are limited data regarding the effectiveness of various treatments for VIN 2/3 and associated recurrence rates. We noted lower rates of recurrence in patients treated with surgical excision or imiquimod compared to those treated with laser ablation. Similar to our findings, Herod et al. (9) found, in a review of 114 women with VIN treated with surgical methods, a significantly higher rate of recurrence among those treated with laser ablation (75%) vs. local excision (40%). These findings are in contrast to most prior reports, including a Cochrane Review, which have not shown a difference in recurrence rates among the most commonly employed treatment modalities, surgical excision and laser ablation (4, 6, 8, 10). There have been, however, differences with respect to recurrence among less commonly used techniques. A meta-analysis of 3322 total patients (4) found increased recurrence rates for patients treated with cryosurgery (N = 16, recurrence in 56%), but did not find a significant difference in recurrence rates among patients treated with vulvectomy (19%), partial vulvectomy (18%), local excision (22%), or laser ablation (23%). However, a smaller retrospective review of 93 patients by Hillemans et al. (11) showed no significant difference in recurrence between wide local excision (41.7%) and laser ablation (40.4%), but no recurrences were found among 7 patients treated with vulvectomy. Finally, imiquimod has been shown to be effective vs. placebo, but there is a lack of research comparing this treatment to other common interventions for VIN 2/3 (12). Our data suggest imiquimod may be superior to laser ablation in preventing recurrence, but prospective evaluation is needed.

In summary, recurrence after treatment for VIN 2/3 was associated with smoking, larger lesion size, and positive margins. Significantly fewer patients recurred after surgical excision or imiquimod compared to laser ablation. Our results confirmed existing data showing an association between positive margins and recurrence. However, in contrast to prior investigations, this study suggests that smoking is associated with recurrence and that patients treated with laser ablation may be more likely to recur than those treated with surgical excision or imiquimod. Our study is limited by retrospective data collection and a long study period, as well as smaller sample sizes of patients treated with laser ablation or imiquimod compared to those who underwent surgical excision. In addition, given the large number of providers in the Department of Gynecologic Oncology at the University of Texas MD Anderson Cancer Center, there could have been considerable variability across all providers' approaches to specific treatments in this study population. Despite these limitations, this study included a large number of subjects treated at a single institution. Given our findings in conjunction with the extensive data on the connection between smoking and the incidence of VIN, we suggest smoking also be considered a risk factor for recurrence after treatment of VIN 2/3. And while most other studies have not found an association between treatment method and recurrence, our data shows a higher rate of recurrence among those treated for VIN 2/3 with laser ablation. These findings suggest that the major treatment modalities for VIN 2/3 may not be equally effective. To improve clinical management of VIN 2/3, prospective clinical trials are needed. Our findings both encourage and provide hypothesis-generating material for such research.

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Table 1

Patient Demographics (n=303)

Characteristic	Value
Age at diagnosis (years)	
Mean	47.3
Median	47.1
Range	14.1–87.2
Body mass index (kg/m ²)	
Mean	28.7
Median	27.1
Range	15.8–56.9
Ethnicity	
Caucasian	232 (76.6%)
Hispanic	33 (10.9%)
African American	32 (10.6%)
Asian	2 (1.5%)
Unknown	4 (1.3%)
Smoking status	
Current	121 (39.9%)
Former	78 (25.7%)
Never	100 (33.0%)
Unknown	4 (1.3%)
Immunosuppression	
HIV	9 (3.0%)
Autoimmune disease	9 (3.0%)
History of chronic steroids	7 (2.3%)
History of chemotherapy	3 (1.0%)
History of other immunosuppressive medication	5 (1.7%)

Table 2

Primary treatment (n= 298) *

Treatment modality	
Excision	176 (59.1%)
Laser	40 (13.4%)
Imiquimod	22 (7.4%)
Excision + laser	24 (8.1%)
Excision + imiquimod	10 (3.4%)
Laser + imiquimod	3 (1.0%)
Other **	5 (1.7%)

* Primary treatment information not available for 5 patients

** Cavitron Ultrasonic Surgical Aspirator (n=2), interferon/accutane/cidofovir (n=1), radiation (n=1)

Table 3

Factors associated with recurrence

	Recurrence (N(%))	No Recurrence (N(%))	p-value
Smoking status (n=299)			<0.001
Yes	69 (34.7%)	130 (65.3%)	
No	16 (16.0%)	84 (84.0%)	
Immunosuppression (n=303)			Redo without DM
Yes			
No			
Age (years)			NS
Mean (standard deviation)	45.9 (11.9)	47.8 (15.1)	
Median (range)	46.1 (14.1–75.1)	47.6 (15.9–87.2)	
Body Mass Index (kg/m ²) (n=274)			NS
Mean (standard deviation)	28.2 (6.6)	28.8 (7.6)	
Median (range)	27.0 (15.8–45.5)	27.2 (16.1–56.9)	
Lesion size (cm) (n=97)			0.016
Mean (standard deviation)	3.1 (1.9)	1.8 (1.4)	
Median (range)	3.0 (1.0–7.0)	1.5 (0.2–7.0)	
Margin status (n=147)			0.005
Positive	29 (31.5%)	63 (68.5%)	
Negative	6 (10.9%)	49 (89.1%)	

Table 4Primary treatment modality and recurrence rates (n=298 ^{*})

	Recurrence rate (N (%))
Primary treatment modality (p=0.003)	
Excision	47 (26.4%)
Laser	18 (41.9%)
Imiquimod	3 (13.6%)
Excision + laser	12 (50.0%)
Excision + imiquimod	1 (10%)
Laser + imiquimod	0 (0%)
Other ^{**}	1 (20%)
None	1 (5.9%)

^{*} Primary treatment and/or recurrence information was not available for 5 patients.

^{**} Cavitron Ultrasonic Surgical Aspirator (n=2), interferon/accutane/cidofovir (n=1), radiation (n=1)