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Yield of cytology surveillance after high-grade vulvar intraepithelial neoplasia or cancer

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Abstract

Objectives—To estimate the risk of high-grade cervical and vaginal intraepithelial neoplasia (CIN/VAIN 2+) and cancer among women treated surgically for high-grade vulvar intraepithelial neoplasia (HGVIN) and vulvar cancer.

Methods—We performed a retrospective cohort study of women who underwent surgery for HGVIN/vulvar cancer between 2006 and 2010. Univariate and multivariate analyses using stepwise selection were used to identify correlates of abnormal cytology after treatment for VIN and vulvar cancer.

Results—Among 191 women under surveillance for a median of 3.7 years who underwent treatment for HGVIN/vulvar cancer, primary vulvar lesions included VIN2 (10, 5%), VIN3 (102, 53%), and carcinoma (79, 41%). During follow-up, 71 (37%) had abnormal cytology, including 47 (25%) low-grade, 23 (12%) high-grade, and 1 (0.5%) carcinoma. Subsequent risk for VAIN2+ was 11% (6/57) after prior hysterectomy and 8% for CIN2+ (10/124) with intact cervix. Overall risk for CIN3+ was 5%. Correlates of high-grade cytology following treatment for HGVIN/vulvar cancer included non-white race [odds ratio (OR) 3.3, 95% confidence interval (CI) 1.50–7.36], immunodeficiency (OR 4.2, 95% CI 1.76–9.94), and prior abnormal cytology (OR 2.7, 95% CI 1.29–5.78). Stepwise multivariate analysis revealed immunosuppression as the only significant correlate of high-grade cytology after vulvar treatment (adjusted OR 3.7, 95% CI 1.26–10.83).

Conclusions—Women with HGVIN/cancer should have cervical/vaginal cytology prior to vulvar surgery. Those with a negative cervical or vaginal cytology result should undergo cytology testing at 1–3 year intervals, based on the threshold for CIN3+ set forth by the American Society for Colposcopy and Cervical Pathology.

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Keywords

abnormal cervical cytology; vulvar intraepithelial neoplasia; Pap; and vulvar cancer

Introduction

Cancers of the lower genital tract, including cervical, vaginal, and most vulvar cancers, are caused by infection with human papillomavirus (HPV). HPV prevalence among vulvar intraepithelial neoplasia (VIN) 1, VIN2/3, and vulvar carcinoma is approximately 68%, 85%, and 40% respectively [1]. Because patients infected with HPV can have multifocal disease, regular examination of the lower genital tract is recommended for women treated for VIN and vulvar cancer [2, 3].

Current guidelines set forth by the American College of Obstetricians and Gynecologists and the American Society for Colposcopy and Cervical Pathology (ASCCP) state that women with VIN who have had a complete response to initial treatment and no new lesions at their 6 and 12 month follow-up visits should be monitored by visual inspection of the vulva annually thereafter [4]. Recurrence rates after treatment for VIN range from 9 to 50%, and are associated with cigarette smoking, larger lesions, and positive excision margins [2, 3, 5–7]. As an adjunct to vulvar surveillance examination, cervical/vaginal cytologic screening is recommended on the basis of expert opinion only. According to the National Comprehensive Cancer Network 2017 guidelines [8], cervical/vaginal cytology screening can be considered for detection of lower genital tract dysplasia, although its value in detection of recurrent genital tract cancer is considered limited.

Subsequent risks of cervical or vaginal intraepithelial neoplasia (CIN or VAIN) and cancer after treatment for HGVIN/vulvar cancer are not well defined. This is especially true for women who have previously undergone hysterectomy since risk for VAIN is low. Prior work is dated, includes low-grade cervical disease now understood to represent non-neoplastic HPV infection, and may involve case selection that biases risk estimates. Nonetheless, extant studies show substantial variation in risk, between 8 and 85%, of coexisting cervical disease at time of diagnosis of vulvar HSIL or cancer [9–11]. We were unable to identify studies quantifying the subsequent risks of cervical or vaginal disease after vulvar disease treatment. Therefore, our study objectives were to estimate the risk of cervical or vaginal intraepithelial neoplasia or cancer after surgical treatment for HGVIN/vulvar cancer with the goal of providing evidence-based recommendations for cytologic screening of these women. We hypothesized that among women treated surgically for HGVIN/vulvar cancer, with and without prior hysterectomy, the subsequent risk for CIN/VAIN2+ and cervical/vaginal cancer is less than 1% and 3% respectively. We also hypothesized that 75% of abnormal cytology obtained after vulvar surgery for HGVIN/vulvar cancer do not lead to high-grade CIN/VAIN or cervical/vaginal cancer.

Methods

This was a retrospective cohort study evaluating all patients surgically treated for VIN and vulvar cancer by the Division of Gynecologic Oncology at Washington University School of

Medicine from January 1, 2006 to December 31, 2010. Before initiation of our study, all procedures were reviewed and approved by Washington University's Human Research Protection Office (institutional review board, IRB Project 201503040). Abstracted data from patient medical records were deidentified, and because of the retrospective nature of this project informed consent was waived.

Eligible women were older than 18 years of age with a histologically confirmed diagnosis of HGVIN or vulvar cancer. Patients were included if they had at least one liquid-based cytology after vulvar surgery. Decisions on cervical/vaginal cancer screening, and management after abnormal cytology, including colposcopy, were at the discretion of the treating gynecologic oncologist. All specimens underwent centralized review by subspecialized gynecologic pathologists in the Ackerman Laboratory of Surgical Pathology, Barnes-Jewish Hospital/Washington University School of Medicine. Women were excluded if they had no follow-up after their vulvar surgery or never underwent surveillance cervical/vaginal cytology. Women were also ineligible if they underwent a vulvar excision procedure for low-grade squamous intraepithelial lesion of the vulva or were treated with laser ablation. All cases of vulvar melanoma in situ, invasive melanoma, or Paget's disease were excluded.

Cytology results were read according to the Bethesda system for cervicovaginal cytologic diagnosis as normal, atypical squamous cells of uncertain significance (ASC-US), atypical squamous cells of uncertain significance with high-risk HPV positivity (ASC-US +HPV), atypical squamous cells favor high-grade (ASC-H), low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL), and atypical glandular cells (AGC) favor neoplasia [12].

Demographic and clinical characteristics were summarized by descriptive statistics, i.e., mean and standard deviation (SD) for continuous variables; and count and percentage for categorical variables. The group difference between normal and abnormal cytology cases after vulvar therapy was examined by independent t-test for continuous variables and Fisher Exact or chi-square tests for categorical variables, depending on the distribution of each individual variable. All the tests were two-sided and the significance level was set at 0.05. The uncertainty of estimates was assessed by confidence intervals. To test our hypotheses, the one-sample binomial proportion test was used to assess whether a sample proportion was significantly different from our hypothesized value. We used a composite outcome for a high-grade cervical/vaginal disease based the worst cytology or biopsy results including ASC-H, HSIL, AGC, AGC, CIN/VAIN2, CIN/VAIN3 or cervical/vaginal cancer. Univariate and multivariate logistic regression models were used to examine the association between abnormal cytology results after vulvar therapy and clinical risk factors including age, race, current cigarette smoking, immunosuppression (patients with a diagnosis of human immunodeficiency virus (HIV) or transplant patients who were taking immunosuppressant medications), prior abnormal cervical/vaginal cytology, and prior hysterectomy. Stepwise selection was used in the multivariate logistic regression, where a significance level of 0.3 was required to allow a risk factor into the model, and a significance level of 0.15 was required for a risk factor to stay in the model. The final model included risk factors with a

significance level of 0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

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Results

We reviewed 234 charts of women undergoing vulvar surgery between 2006 and 2010, of which 43 were excluded due to no cervical/vaginal surveillance cytology after vulvar surgery. Our final analysis included 191 women who contributed 816 cytology results. The median number of surveillance cytology results after vulvar surgery per patient was two (range 1–18). Most women were white (84%) with a mean age of 52.6 years at the time of diagnosis. Primary vulvar lesions included VIN2 (n=10, 5%), VIN3 (n=102, 53%), and carcinoma (n=79, 41%). Risk factors for abnormal cytology after vulvar surgical management included white race (p=0.002), HIV (p=0.021), other immunosuppression (p=0.007), and prior abnormal cervical/vaginal cytology (p=0.008) (Table 1).

Over a median surveillance interval of 3.7 years, 71 (37%) women treated for HGVIN/vulvar cancer had abnormal cervical/vaginal cytology, including 47 (25%) low-grade (ASCUS and LSIL), 23 (12%) high-grade (ASC-H, HSIL, AGC), and 1 (0.5%) carcinoma (Table 2). This led to 44 (62%, 44/71) cervico-vaginal colposcopic evaluations with biopsies resulting in 30 (42%, 30/71) histologic diagnoses of normal or CIN1/VIN1, which was less than our hypothesized rate of 75% (p=1). Among the 44 women with cervico-vaginal colposcopic evaluation, five were diagnosed with CIN/VAIN2 and nine CIN/VAIN3, but overall this represented 7% of our total sample population of 191 women. Subgroup analysis by prior hysterectomy status also resulted in higher than expected risk for CIN2+/VAIN 2+. Among women treated for HGVIN/vulvar cancer without prior hysterectomy (n=124), the subsequent risk for high-grade cervical/vaginal disease or cancer (n=10, 8%) was greater than our hypothesized rate of 3% (p<0.001). Furthermore, among women who had a hysterectomy (n=57) prior to vulvar surgery, the subsequent risk for high-grade VAIN/vaginal cancer (n=6, 11%) was also greater than our hypothesized rate of 1% (p<0.0001). Overall, there was no significant difference in high-grade cervical/vaginal disease after vulvar surgery between women with and without a hysterectomy (11%, CIN2+ vs. 8%, VAIN2+, p=0.59).

The one patient with malignant cytology was an 82 year old with Stage III squamous cell carcinoma of the vulva who had undergone a radical vulvectomy with advancement flaps and bilateral inguinal lymph node dissection followed by adjuvant pelvic radiation. She underwent a total of seven surveillance cervical cytologies at six month intervals, six that were negative and one LSIL (19 months after surgery). She was lost to follow-up for 40 months, but then presented to an emergency room with heavy postmenopausal bleeding nearly eight years after her vulvar surgery. Her work-up included cervical cytology and dilation and curettage which both confirmed a grade 1 endometrioid adenocarcinoma.

Univariate analysis demonstrated that non-white race [odds ratio (OR) 3.3, 95% confidence interval (CI) 1.50–7.36], immunosuppression (OR 4.19, 95% CI 1.76–9.94) and prior abnormal cytology (OR 2.7, 95% CI 1.29–5.78) were associated with abnormal high-grade cytology (Table 3). In our multivariate logistic regression model, after adjusting for age, race, smoking status, prior abnormal cytology, and prior hysterectomy, immunosuppression remained significantly associated with the development of abnormal cytology after vulvar surgery for HGVIN/vulvar cancer (adjusted OR 3.69, 95% CI 1.26–10.83).

Discussion

Women with HGVIN/vulvar cancer are at risk for co-existing cervical or vaginal disease and should be screened with cervical/vaginal cytology prior to treatment for HGVIN/vulvar cancer. Those treated surgically for HGVIN/vulvar cancer have an 8–11% risk of high-grade cervical/vaginal cytology depending on prior hysterectomy status, and an overall 5% risk of CIN3+. Immunosuppression, defined as HIV seropositive or a transplant patient on immunosuppressive medications, remained a statistically significant risk factor for high-grade cytology even after adjusting for potential confounders. To put our study results in clinical context, we apply the concept of “similar management for similar risk” per the 2012 ASCCP guidelines [13]. According to their criteria, a 6 to 12-month return for a 5-year CIN3+ risk of 2–5%, and a 3-year return for risk of 0.1–2% are recommended. Extrapolating these standards to women surgically treated for HGVIN/vulvar cancer, especially in the initial years after treatment, they should be followed with at least annual cytology testing. Expeditious follow-up of abnormal results should be in accordance with ASCCP guidelines. Even our most conservative calculation of CIN3+ risk that includes all 234 patients, assuming those with no surveillance cytology (n=43) would have had a negative result, equals 3.8%. Furthermore, if we then excluded all immunocompromised patients (n=30), including the three who had CIN3, the risk decreases from 3.8% (9/234) to 2.9% (6/204), which is still within the threshold set forth by the ASCCP to recommend a short interval surveillance. Therefore, taking into consideration our small sample size and a conservative estimate, we recommend all women with HGVIN/cancer should have cervical/vaginal cytology prior to therapy. Women with a negative result should be followed with cytology testing at one to three year intervals and those with an abnormal result should have colposcopy and managed according to ASCCP guidelines.

VINs and vulvar cancers are commonly caused by carcinogenic types of HPV, which also can cause similar vaginal and cervical lesions [14]. Cervical disease risk is increasing among women with genital warts and those infected with HIV, however, the subsequent risk of

cervical and vaginal intraepithelial neoplasia (CIN, VAIN) and cancer is not well defined. Prior work is dated and the estimated risk of coexisting cervical/vaginal disease at the time of HGVIN/vulvar cancer, although quite substantial, varies between 8% and 85% due to biases of case selection and inclusion of low-grade cervical disease [9–11]. Mitchell and associates found cervical lesions in 17 (10%) of 169 women with VIN or vulvar cancer [11]. Spitzer et al found cervical disease of various grades in 164 (85%) of 194 women with vulvar lesions, though many were condylomas [15]. Lastly, Basta and associates found CIN or cervical/vaginal cancer in 14 (8%) of 68 women with coexisting VIN or vulvar cancer [9].

A study by Hording and colleagues provided HPV genotype data to support the concept that VIN3 and some vulvar carcinomas are highly associated with other genital primary tumor(s) due to a “field effect” of an underlying HPV infection involving the entire lower genital tract [10]. They examined cervical and vulvar tissues from 143 women with multifocal genital neoplasia for HPV types 6, 11, 16, 18, and 33. Over a 5-year median follow-up, they found CIN3 or cervical cancer in 39 (27%) women with vulvar cancer or VIN3. HPV deoxyribonucleic acid testing revealed that 81% of patients with double primary tumors had the same HPV type in both lesions. However, one of the major limitations of their study is lack of data from seropositive HIV women or those receiving immunosuppressive therapy. Though our retrospective study did not include routine HPV testing, our results corroborate with their increased rates of CIN/VAIN2+ in women with HGVIN/vulvar carcinoma. Our study further strengthens generalizability of results, given that we also included immunocompromised patients, although we acknowledge the small percentage of HIV seropositive women.

Given our small sample size of immunocompromised women, we cannot reliably predict the prevalence of abnormal cytology after surgical treatment for HGVIN/vulvar cancer. However, immunocompromised women are at substantial risk for CIN3+ regardless of vulvar disease history. Specifically, HIV seropositive women are at greater risk for abnormal cytology results than seronegative women and their results are more often high-grade [16, 17]. The Women’s Interagency HIV Study (WIHS) recently published on the long term cumulative incidence of CIN3+ after abnormal cytology and showed that less than 40% of HIV seropositive women with ASCUS and LSIL developed CIN2+ over 10 years, and less than 20% developed CIN3+. Although our study had a shorter follow-up period, our results corroborate with their findings that HIV infection is a risk factor for CIN2+. Interestingly, they also showed that it was not a significant risk factor for CIN3+, suggesting HIV infection may disproportionately increase CIN2. Findings from our multivariate analysis highlight the correlation between immunosuppression and abnormal cytology; lending further support that HIV seropositive women with abnormal cytology merit scrupulous surveillance [4, 18].

Some limitations of our study are inherent to our retrospective study design, such as lack of randomization, limited sample size, and incomplete follow-up. However, socio-demographic and clinical characteristics displayed in Table 1 show that our two treatment groups were overall well-balanced. We also addressed the possibility of selection bias by comparing baseline characteristics between women who were excluded and included based on availability of follow-up data, and no statistically significant differences were detected.

Additionally, surveillance of cervical/vaginal cytology for women with HGVIN/vulvar cancer was at the discretion of the gynecologic oncology provider, as our practice has not yet adopted a standardized protocol for these particular patients. With regards to our sample size, we were limited by the prevalence of high-grade pre-invasive and invasive vulvar disease, but relied on our large, university-based clinical practice and included all patients who met eligibility criteria with follow-up of at least one cervical/vaginal cytology result. Furthermore, our retrospective chart review was limited by the original documentation of the pathology reports which did not include subclassification of VIN according to the International Society for the Study of Vulvovaginal Disease (ISSVD) as either usual-type or differentiated [19]. Nonetheless we acknowledge the differences in morphology and behavior of these two precursors and recommend that future studies report VIN in accordance to ISSVD classification to enhance diagnostic reproducibility, but also to further individualize the risk of a field effect of an underlying HPV infection involving the entire lower genital tract.

Currently, we are expanding our study methods to include retrospective data from three other academic centers across the country in order to more accurately estimate the incidence of CIN/VAIN2+, CIN/VAIN3+, and cervical/vaginal cancer among women treated surgically for HGVIN/vulvar cancer. In addition to validating our study results with this larger cohort, we aim to explore the risk among women with an initial negative cytology screening result after vulvar treatment and assess whether this negative cytology result portends a low enough subsequent risk of CIN/VAIN 2+ to allow for longer screening intervals. Other areas for future research include evaluation of CIN/VAIN2+ prevalence among women with HGVIN treated with laser or imiquimod compared to surgical management. A much broader question that remains to be addressed is the role for cotesting in a population that is likely to have a high prevalence of high-risk HPV.

Conclusion

Women treated surgically for HGVIN/vulvar cancer are at substantial risk for having an abnormal cytology. During surveillance screening, the prevalence of VAIN2+ was 11% in women with a prior hysterectomy and 8% for CIN2+ in women with an intact cervix. Extrapolating from guidelines set forth by the ASCCP, our findings suggest that women who undergo surgical treatment for HGVIN/vulvar cancer, especially those who are immunosuppressed, should be followed with at least annual cervical/vaginal cytology during the first several years after vulvar treatment. Those with an abnormal result should have colposcopy and should be followed according to ASCCP guidelines.

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List of abbreviations and Acronyms

CIN	cervical intraepithelial neoplasia
VAIN	vaginal intraepithelial neoplasia
HGVIN	high-grade vulvar intraepithelial neoplasia
OR	odds ratio
CI	confidence interval
VIN	vulvar intraepithelial neoplasia
HPV	human papillomavirus
ASCCP	American Society for Colposcopy and Cervical Pathology
IRB	institutional review board
ASC-US	atypical squamous cells of uncertain significance
ASC-H	atypical squamous cells favor high-grade
LSIL	low-grade squamous intraepithelial lesions
HSIL	high-grade squamous intraepithelial lesions
AGC	atypical glandular cells
SD	standard deviation
HIV	human immunodeficiency virus
WIHS	Women's Interagency HIV Study
ISSVD	International Society for the Study of Vulvovaginal Disease

References

1. De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. *Int J Cancer*. 2009; 124:1626–1636. [PubMed: 19115209]
2. Modesitt SC, Waters AB, Walton L, Fowler WC Jr, Van Le L. Vulvar intraepithelial neoplasia III: occult cancer and the impact of margin status on recurrence. *Obstet Gynecol*. 1998; 92:962–966. [PubMed: 9840558]
3. Wallbillich JJ, Rhodes HE, Milbourne AM, Munsell MF, Frumovitz M, Brown J, Trimble CL, Schmeler KM. Vulvar intraepithelial neoplasia (VIN 2/3): comparing clinical outcomes and evaluating risk factors for recurrence. *Gynecol Oncol*. 2012; 127:312–315. [PubMed: 22867736]
4. American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice and American Society for Colposcopy and Cervical Pathology. Committee Opinion No 675:

Management of Vulvar Intraepithelial Neoplasia. *Obstet Gynecol.* 2016; 128:e178–182. [PubMed: 27661656]

5. Jones RW, Rowan DM, Stewart AW. Vulvar intraepithelial neoplasia: aspects of the natural history and outcome in 405 women. *Obstet Gynecol.* 2005; 106:1319–1326. [PubMed: 16319258]
6. Bruchim I, Gotlieb WH, Mahmud S, Tunitsky E, Grzywacz K, Ferenczy A. HPV-related vulvar intraepithelial neoplasia: outcome of different management modalities. *Int J Gynaecol Obstet.* 2007; 99:23–27. [PubMed: 17462650]
7. Hillemanns P, Wang X, Staehle S, Michels W, Dannecker C. Evaluation of different treatment modalities for vulvar intraepithelial neoplasia (VIN): CO(2) laser vaporization, photodynamic therapy, excision and vulvectomy. *Gynecol Oncol.* 2006; 100:271–275. [PubMed: 16169064]
8. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology Version 1.2017. Oct 4. 2016 https://www.nccn.org/professionals/physician_gls/pdf/vulvar.pdf
9. Basta A, Adamek K, Pitynski K. Intraepithelial neoplasia and early stage vulvar cancer. Epidemiological, clinical and virological observations. *Eur J Gynaecol Oncol.* 1999; 20:111–114. [PubMed: 10376426]
10. Hording U, Daugaard S, Junge J, Lundvall F. Human papillomaviruses and multifocal genital neoplasia. *Int J Gynecol Pathol.* 1996; 15:230–234. [PubMed: 8811384]
11. Mitchell MF, Prasad CJ, Silva EG, Rutledge FN, McArthur MC, Crum CP. Second genital primary squamous neoplasms in vulvar carcinoma: viral and histopathologic correlates. *Obstet Gynecol.* 1993; 81:13–18. [PubMed: 8380102]
12. Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA.* 2002; 287:2114–2119. [PubMed: 11966386]
13. Massad LS, Einstein MH, Huh WK, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *Obstet Gynecol.* 2013; 121:829–846. [PubMed: 23635684]
14. Gargano JW, Wilkinson EJ, Unger ER, et al. Prevalence of human papillomavirus types in invasive vulvar cancers and vulvar intraepithelial neoplasia 3 in the United States before vaccine introduction. *J Low Genit Tract Dis.* 2012; 16:471–479. [PubMed: 22652576]
15. Spitzer M, Krumholz BA, Seltzer VL. The multicentric nature of disease related to human papillomavirus infection of the female lower genital tract. *Obstet Gynecol.* 1989; 73:303–307. [PubMed: 2536908]
16. Massad LS, Riestler KA, Anastos KM, et al. Prevalence and predictors of squamous cell abnormalities in Papanicolaou smears from women infected with HIV-1. Women's Interagency HIV Study Group. *J Acquir Immune Defic Syndr.* 1999; 21:33–41. [PubMed: 10235512]
17. Massad LS, Seaberg EC, Wright RL, et al. Squamous cervical lesions in women with human immunodeficiency virus: long-term follow-up. *Obstet Gynecol.* 2008; 111:1388–1393. [PubMed: 18515523]
18. Massad LS, Pierce CB, Minkoff H, et al. Long-term cumulative incidence of cervical intraepithelial neoplasia grade 3 or worse after abnormal cytology: impact of HIV infection. *Int J Cancer.* 2014; 134:1854–1861. [PubMed: 24170366]
19. Heller DS. Report of a new ISSVD classification of VIN. *J Low Genit Tract Dis.* 2007; 11:46–47. [PubMed: 17194951]

Table 1

Clinical risk factors for abnormal cytology after surgical treatment of VIN/vulvar cancer.

	Cytology results after vulvar therapy ^d		
	N=191	Normal (n=120)	Abnormal (n=71)
Age (years, mean $\pm$ SD)	52.6 $\pm$ 15.8	54.1 $\pm$ 15.8	50.2 $\pm$ 15.4
Primary vulvar lesion			
VIN2	10 (5)	6 (5)	4 (6)
VIN3	102 (53)	56 (47)	46 (65)
Cancer stage I-II	67 (35)	48 (40)	19 (27)
Cancer stage III-IV	12 (6)	10 (8)	2 (3)
Race ^{b**}			
White	158 (84)	107 (90)	51 (73)
Non-white	31 (16)	12 (10)	19 (27)
Current cigarette smoker ^c	82 (44)	51 (43)	31 (44)
Human immunodeficiency virus [*]	11 (6)	3 (3)	8 (11)
Other immunosuppression ^{**}	18 (9)	6 (5)	12 (17)
Prior hysterectomy	58 (30)	39 (33)	19 (27)
Prior abnormal cervical/vaginal cytology ^{d**}	94 (65)	48 (57)	46 (78)
Prior treatment for cervical disease ^e	54 (45)	30 (41)	24 (53)
Abnormal cervical/vaginal cytology prior to diagnosis of VIN/vulvar cancer ^{f***}			
Negative	92 (67)	70 (86)	22 (39)
ASCUS HPV positive	5 (4)	0 (0)	5 (9)
ASCUS HPV negative	4 (3)	2 (3)	2 (4)
ASCUS HPV unknown	2 (2)	2 (3)	0 (0)
ASC-H	2 (2)	1 (1)	1 (2)
LSIL	18 (13)	4 (5)	14 (25)
HSIL	13 (10)	2 (3)	11 (20)
Cancer	1 (1)	0 (0)	1 (2)

Numbers are reported as column percentage with the denominator excluding missing values.

SD = standard deviation, ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade intraepithelial lesion; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesions; HSIL, high-grade intraepithelial lesion.

^aFisher's exact test (if cell count less than 5) or Chi-square test for categorical variable; t-test for continuous variable.

^b Race was missing for 2 patients; 1 had normal and 1 had abnormal cytology after vulvar surgery.

^c Current cigarette smoking was missing for 4 patients; 2 had normal and 2 had abnormal cytology after vulvar surgery.

^d Prior abnormal cervical/vaginal Cytology was missing for 47 patients; 35 had normal and 12 had abnormal cytology after vulvar surgery.

^e Prior treatment for cervical disease was missing for 72 patients; 46 had normal and 26 had abnormal cytology after vulvar surgery.

^f Abnormal cervical/vaginal cytology prior to diagnosis of VIN/vulvar cancer was missing for 54 patients; 39 had normal and 15 had abnormal cytology after vulvar therapy.

* For $p < 0.05$,

** for $p < 0.01$, and

*** for $p < 0.001$

Table 2

Distribution of abnormal cytology test results after vulvar therapy and colposcopic examination.

	Abnormal cytology, n	Undergoing colposcopy n (%), 95%CI ^a	Worst colposcopy lesion, n (%) ^a			
			None/Benign n (%)	CIN/VIN 1 n (%)	CIN/VIN 2 n (%)	CIN/VIN 3 n (%)
ASCUS +/- HR HPV	17	3 (17.6, 0–35.8)	2 (10)	1 (10)	0 (0)	0 (0)
LSIL	30	21 (70, 53.6–86.4)	10 (50)	8 (80)	2 (40)	1 (11)
ASC-H	3	1 (33.3, 0–86.7)	1 (5)	0 (0)	0 (0)	0 (0)
HSIL	19	18 (94.7, 84.7–100)	6 (30)	1 (10)	3 (60)	8 (89)
AGC	1	1 (100)	1 (5)	0 (0)	0 (0)	0 (0)
Cancer	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

CIN, cervical intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; ASCUS, atypical squamous cells of undetermined significance; HR HPV, high-risk human papillomavirus; LSIL, low-grade intraepithelial lesion; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesions; HSIL, high-grade intraepithelial lesion; AGC, atypical glandular cells.

^aColumn percentage with the denominator excluding missing values.

Table 3

Univariate and multivariate analyses assessing correlates of high-grade cytology after surgical treatment of VIN/vulvar cancer.

Clinical Factors	Multivariate analysis ^a	
	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Age (years)	1.0 (0.97–1.00)	
Non-white race	3.3 (1.50–7.36) **	2.3 (0.86–6.19)
Cigarette smoking ^b	1.1 (0.59–1.95)	
Immunosuppression ^c	4.2 (1.76–9.94) ***	3.7 (1.26–10.83) *
Prior abnormal cytology ^d	2.7 (1.29–5.78) **	2.1 (0.95–4.59)
Prior hysterectomy	0.8 (0.40–1.45)	

^aSample size for multivariate logistic regression stepwise selection is 141 due to large missing in prior abnormal cytology.

^bCigarette smoking only included those patient who were current smokers.

^cImmunosuppression was defined as patients with human immunodeficiency virus or who were on immunosuppressive medications.

^dPrior abnormal cytology was missing for 47 patients.

* For p<0.05,

** for p<0.01, and

*** for p<0.001