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ORIGINAL RESEARCH ARTICLE

Differentiated vulvar intraepithelial neoplasia long-term follow up and prognostic factors: An analysis of a large historical cohort

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Abstract

Introduction: Differentiated vulvar intraepithelial neoplasia (dVIN) is a high-risk preinvasive vulvar lesion and precursor of human papillomavirus-independent vulvar squamous cell carcinoma (VSCC). Due to its rarity, literature data on its malignant potential are scant. The aim of the study is to assess the risk of developing VSCC in patients surgically treated for dVIN not associated with VSCC (solitary dVIN) and the risk of VSCC recurrence in patients treated for dVIN associated with VSCC (dVIN-VSCC) at first diagnosis.

Material and methods: A historical cohort study was performed in a northern Italy referral center for vulvar neoplasms. All consecutive women surgically treated for histologically confirmed dVIN from 1994 to 2021 were collected. Primary outcome was cancer risk or recurrent cancer risk, secondary outcomes were risk factors associated with VSCC development or recurrence. Kaplan–Meier method and log-rank test were used to estimate cancer risk or recurrent cancer risk differences and uni- and multivariate Cox regression analyses to identify risk factors associated with VSCC development in solitary dVIN and recurrence of dVIN-VSCC.

Results: Seventy-six patients with dVIN at preoperative biopsy were included: at excisional specimens 44 were solitary dVIN and 32 were dVIN-VSCC. The absolute risk of VSCC development after solitary dVIN treatment was 43.2% with median time to to VSCC diagnosis of 25.4 months (range 3.5–128.0 months). VSCC recurrence absolute risk in treated dVIN-VSCC patients was 31.3% with median time to VSCC recurrence of 52.9 months (range 6.5–94.8 months). At uni- and multivariate regression analyses, only compliant topical ultrapotent corticosteroid treatment after solitary

Abbreviations: dVIN, differentiated vulvar intraepithelial neoplasia; HPV, human papillomavirus; IQR, interquartile range; ISSVD, International Society for the Study of Vulvovaginal Disease; LS, lichen sclerosus; TCS, topical corticosteroid; VHSIL, vulvar high-grade squamous intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; VSCC, vulvar squamous cell carcinoma; WHO, World Health Organization.

dVIN excision showed an ability to prevent VSCC development. No protective effect by corticosteroid treatment was shown for VSCC recurrence in dVIN-VSCC patients. Smoking was associated with higher cancer recurrence risk in dVIN-VSCC patients on both uni- and multivariate regression analyses.

Conclusions: Patients with dVIN have a high risk of developing both primary and recurring VSCC. Early recognition, long-term follow up, and compliant ultrapotent topical corticosteroid treatment are recommended.

KEYWORDS
differentiated vulvar intraepithelial neoplasia, oncology, topical corticosteroid therapy, vulvar cancer, vulvar intraepithelial neoplasia

1 | INTRODUCTION

Vulvar squamous cell carcinoma (VSCC) is an uncommon gynecological malignancy developing through two pathways: human papillomavirus (HPV)-associated and HPV-independent.[1] The former, with increasing incidence in recent decades,[2] has vulvar high-grade squamous intraepithelial neoplasia (VHSIL) as precursor lesion and is mainly driven by HPV type 16 infection.[3–6] However, more than half of VSCCs are HPV-independent,[7] and they originate from chronic inflammation and vulvar dermatoses such as lichen sclerosus (LS)[8,9] and lichen planus,[10] with differentiated vulvar intraepithelial neoplasia (dVIN) as the preinvasive lesion.[11,12]

HPV-independent vulvar intraepithelial neoplasia was first distinguished from HPV-associated lesions by Abell and Gosling[13] as "intraepithelial carcinoma of simplex type". Hart and Millman added the term "differentiated" in 1977 to highlight the diffusely differentiated morphology.[14] The term vulvar intraepithelial neoplasia (VIN) was adopted by the International Society for the Study of Vulvovaginal Disease (ISSVD) in 1986[15] and by WHO in 2003. Currently, both organizations recognize dVIN and VHSIL as separate entities.[5,12]

The median age at presentation of dVIN is close to that for VSCC,[1] and it is considered a high-risk preinvasive lesion that can have more rapid and frequent progression to invasive VSCC than VHSIL.[1] However, solitary dVIN (dVIN without invasion at first diagnosis) is often underrecognized because of difficulties in clinical suspicion and histopathological diagnosis,[16] and its frequent association with invasive foci at diagnosis (dVIN-VSCC). Current dVIN management involves its complete surgical resection and treatment of associated LS or lichen planus with ultrapotent topical corticosteroids (TCS) during follow up to reduce the risk of subsequent VSCC development or recurrence.[17,18] Surgical excision is mandatory for a complete histopathological examination because invasive foci are frequent at presentation and because of the low specificity of vulvoscopy.[19]

Literature on the risk of developing VSCC in patients with dVIN is scarce and based on small case series with confounding factors. This study aims to assess the risk of VSCC in patients with solitary dVIN and the risk of recurrence in patients with dVIN associated with VSCC (dVIN-VSCC) in a large series from a referral center for vulvar neoplasms.

Key message

Differentiated vulvar intraepithelial neoplasia bears a high cancer risk and topical corticosteroid therapy after surgical excision reduces the risk of development of invasive vulvar squamous carcinoma.

2 | MATERIAL AND METHODS

Data for all women diagnosed with histologically confirmed dVIN at incisional biopsy and subsequently surgically treated at the Department of Surgical Sciences, St. Anna Hospital, University of Turin, from 1994 to 2021, were retrospectively retrieved from a dedicated institutional database. Patients with previous VSCC and recurrent dVIN were excluded from this study.

As criteria for dVIN diagnosis have been recently detailed, all hematoxylin and eosin-stained pathological slides were reviewed by expert pathologists to confirm diagnosis according to ISSVD criteria[16] and 2020 WHO VIN terminology.[5] Immunohistochemistry for p16 and p53 was not systematically performed to integrate morphological patterns features.[16] Clinical data were collected: age at diagnosis, presence of symptoms (vulvar itching or burning), clinical features at diagnosis, localization of the lesion, focality of the lesion, association with lichen planus or LS, and subsequent TCS therapy. LS was either diagnosed clinically or histologically.

All patients diagnosed with dVIN at incisional biopsy were treated with wide local excision.

Free margin was considered as the absence of atypical cells at the dVIN resection margins. In case of involved margins at local excision, further excision was performed to obtain free margins.

In case of unexpected invasive foci (dVIN-VSCC) ≤1 mm[20] at original histopathological analysis, a subsequent local radical surgical excision was performed only if margins were positive. Patients

with an original depth of invasion >1 mm underwent additional groin lymph node evaluation (sentinel lymph node or inguinofemoral lymphadenectomy). VSCC were staged according to the TNM classification.[21]

After solitary dVIN or dVIN-VSCC surgical treatment, ultrapotent TCS was recommended three times a week to control local symptoms and to treat associated dermatoses, as the regular clinic protocol for dVIN patients.

All patients underwent a regular follow up at 3- to 4-month intervals during the first 3 years, then every 6 months indefinitely, according to the patients' characteristics. Patients' compliance with TCS was assessed at every visit and they were considered compliant when reporting "all of the time" or "most of the time" compliance to treatment in terms of frequency of application of TCS over time.

Follow-up visits included vulvoscopy and groin clinical examination, along with biopsy in case of any suspicious lesions. Survival time in months was measured from the date of diagnosis until the last follow-up visit or presence of recurrence/progression. Solitary dVIN cancer progression was considered as any histologically confirmed invasive VSCC at least 3 months from dVIN treatment, while VSCC recurrence of dVIN-VSCC, was considered to be any histologically confirmed VSCC at least 3 months after dVIN-VSCC treatment.

Descriptive statistics were reported as median and interquartile range (IQR) for continuous variables and as absolute frequency and percentage for categorical variables.

To test the difference between the two groups (dVIN and dVIN-VSCC), Wilcoxon–Mann–Whitney test and Fisher exact test were applied to continuous and categorical variables, respectively.

Kaplan–Meier method and log-rank test were used to evaluate the difference in cancer risk within the two different population groups (dVIN and dVIN-VSCC); cumulative VSCC incidence was also estimated.

Univariate and multivariate Cox proportional hazard models were performed to evaluate the association of cancer risk with selected clinical parameters. The statistical significance threshold was considered to be $p < 0.05$. All the statistical analyses were performed with R software version 4.2.2 (R Core Team [2022]).

3 | RESULTS

During the investigational period, 86 cases were retrieved from the institutional database, as dVIN at incisional preoperative biopsy. At histopathological revision we confirmed 76 dVIN cases (88%), giving a dVIN prevalence of 0.82% at our institution (76 of 9268 first referral vulvological visits). Original histopathology of wide local excision, performed after incisional biopsy, revealed 44 cases of solitary dVIN (57.9%) and 32 of dVIN-VSCC (42.1%).

Among dVIN-VSCC, median depth of invasion was 1.1 ± 0.9 mm (range 0.2–3.0 mm). Sixteen cases were superficially invasive squamous cell carcinoma (pT1a), and 16 cases were pT1b VSCC without inguinofemoral lymph node involvement, according to TNM staging.[21]

Most of the dVIN cases (49/76) were diagnosed in the last decade of the investigational period, with no significant difference in median age within solitary dVIN and dVIN-VSCC across the whole study period.

In Table 1, baseline characteristics of the study population are reported.

Median follow-up time of patients with solitary dVIN was 55.9 months (IQR 32.9–95.3 months). During follow up, 19/44 (43.2%) patients were diagnosed with an incident VSCC. Median time to VSCC diagnosis was 25.4 months (range 3.5–128.0 months). Eight cases were classified as pT1a VSCC, and 11 as pT1bN0.

Immunohistochemistry for p16 was performed in 11.4% (5/44) of solitary dVIN cases and showed negative staining in 80.0% (4/5) and non-block patchy positivity in 20.0% (1/5). Immunohistochemistry for p53 was performed in 20.5% (9/44), and showed a staining compatible with a mutant pattern in 55.6% (5/9), 60.0% (3/5) with basal overexpression and 40.0% (2/5) with null staining. In the remaining 44.4% (4/9) scattered positive cells were observed, consistent with p53 wild-type status.

In dVIN-VSCC patients, the median follow up was 37.7 months (IQR 17.5–98.1 months) and 31.3% (10/32) developed a VSCC recurrence. Median time to VSCC recurrence was 52.9 months (range 6.5–94.8 months).

The cumulative incidence of VSCC in solitary dVIN and dVIN-VSCC patients is reported in Figure 1. Ten-year cumulative incidence of VSCC in solitary dVIN was 59.3% (95% confidence interval [CI] 30.8%–76.0%), rising steadily in the first 4 year-period and with a second rapid increase at around 9 years from diagnosis. Ten-year cumulative incidence of recurrent VSCC in dVIN-VSCC patients was 71.4% (95% CI 27.4%–88.7%) and the risk increased steadily over time.

In univariate Cox regression analysis, only compliant TCS treatment after solitary dVIN surgery was associated with a significantly lower risk of VSCC development (hazard ratio 0.27, $p = 0.007$; Table 2).

Corrected for all variables in the multivariate Cox regression, compliant TCS treatment after solitary dVIN diagnosis remained statistically significant (hazard ratio 0.29, $p = 0.014$; Table 2).

Only smoking was identified to be associated with VSCC recurrence for dVIN-VSCC both in univariate and in multivariate analysis. (Table 3).

4 | DISCUSSION

Our study showed that invasive foci at original histopathological examination after dVIN incisional biopsy diagnosis are frequent findings (42.1% in our series), thus reinforcing the essential role of complete surgical excision in dVIN management.[17] It is likely that in some patients, dVIN was diagnosed in the original biopsy while clinically suspicious for VSCC (then revealed during excision), because biopsies may sometimes be insufficient to make a confident diagnosis of VSCC.

TABLE 1 Baseline characteristics of the study population.

	All patients $n=76$	Solitary dVIN $n=44$	dVIN-VSCC $n=32$	p value
Age, median (range, IQR)	70.5 (35–91, 61.9–78.0)	69.8 (46–91, 61.7–77.5)	73.3 (35–91, 62.8–78.0)	0.578[a]
Symptoms				
Yes	89.5% (68)	86.4% (38)	93.7% (28)	0.300[b]
No	10.5% (8)	13.6% (6)	6.3% (2)	
Type of lesion				
Plaque/nodule	43.4% (31)	45.5% (19)	40.6% (13)	0.823[b]
Papule	30.2% (21)	34.1% (15)	25% (8)	
Patches	26.3% (19)	20.4% (9)	34.4% (11)	
Localization				
Periclitoral area	23.7% (17)	20.5% (9)	28.1% (9)	0.727[b]
Perineum	9.2% (7)	9.1% (4)	9.4% (3)	
Labium minus	31.6% (22)	36.3% (12)	25.0% (8)	
Labium majus	35.5% (25)	34.1% (15)	37.5% (12)	
Lichen sclerosus				
Yes	80.3% (61)	79.5% (33)	81.2% (24)	1.000[b]
No	19.7% (15)	20.5% (9)	18.8% (6)	
Unifocality				
Yes	84.2% (64)	86.4% (38)	81.2% (24)	0.550[b]
No	15.8% (12)	13.6% (6)	18.8% (6)	
Diabetes				
Yes	11.8% (9)	20.5% (5)	12.5% (4)	0.576[b]
No	88.2% (67)	79.5% (39)	87.5% (26)	
Smoking				
Yes	5.3% (4)	6.8% (3)	3.1% (1)	0.634[b]
No	94.4% (72)	93.2% (41)	96.9% (29)	

Abbreviations: dVIN, differentiated vulvar intraepithelial neoplasia; VSCC, vulvar squamous cell carcinoma.

[a]Wilcoxon–Mann–Whitney test.

[b]Fisher exact test.

Furthermore, solitary dVIN is a high-risk preinvasive lesion, with an absolute cancer risk of 43.2% despite complete resection of the primary lesion and a median time to VSCC diagnosis of 25.4 months. The cancer risk rises in a time-dependent manner and persists after more than 10 years from dVIN diagnosis. Only compliant TCS after surgical excision significantly reduced the risk of developing VSCC in patients with solitary dVIN. We can therefore assume that patients affected by dVIN are in a high-risk carcinogenesis condition, and clinically normal tissues may already bear some of the molecular alterations.[22] Indeed, despite complete surgical resection of dVIN lesions, cancer risk persists.

Finally, the recurrence risk of dVIN-VSCC (10-year cumulative incidence of 71.4%), underlines the need for lifelong surveillance of this high-risk group of patients, where TCS seems to be ineffective to reduce the VSCC risk.

Few studies have assessed the risk of primary VSCC in dVIN and study populations are usually small with frequent limitations regarding potential confounders.[23]

The first study on dVIN progression risk was performed by Yang and Hart[24] where eight patients, surgically treated for solitary dVIN, had an absolute risk of 37.5% (median follow up 48.5 months, median time to recurrence as VSCC 9 months).

Two population-based studies included 67 and 12 solitary dVIN, respectively.[1,25] The largest one[25] considered dVIN and also "VIN, simplex type", "VIN not otherwise specified (NOS) with LS", "VIN NOS high-risk HPV-negative", while the other one[1] considered only dVIN. These different populations are reflected in reported cancer risk: 33% versus 58%, respectively.

Regauer et al. reported 16 cases of solitary dVIN: 9 of them progressed, with an absolute risk of 56.3%.[26]

McAlpine et al. described a single-center experience with a cohort of seven patients and the highest absolute risk in the literature: 85.7% with a median follow up of 22.8 months.[27]

A recent paper by Thuijs et al. with the largest group of HPV-independent VIN demonstrated the utility of integration of p16 and p53 immunohistochemistry with morphological features in

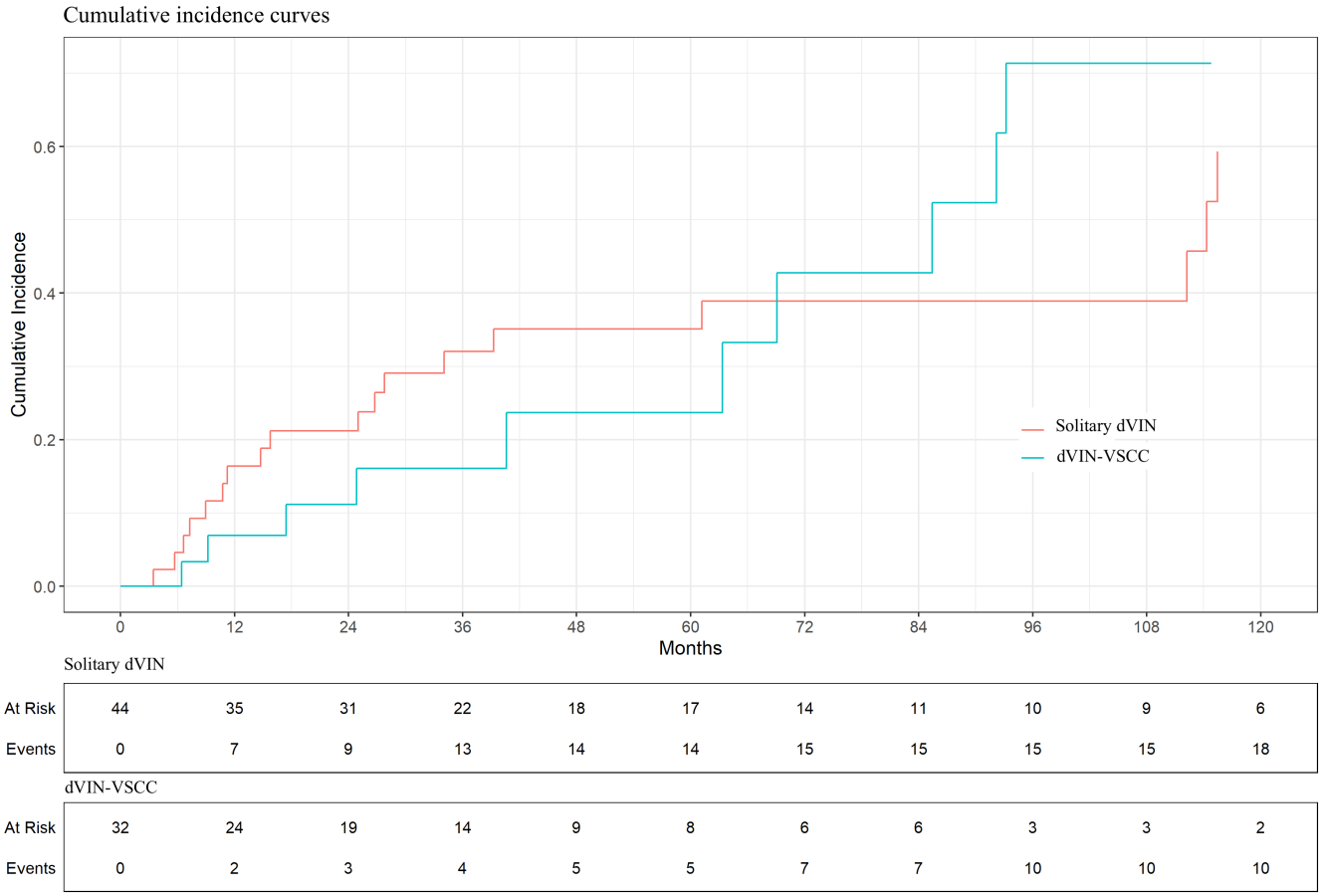

FIGURE 1 Cumulative incidence of vulvar squamous cell carcinoma (VSCC) in solitary differentiated vulvar intraepithelial neoplasia (dVIN; red line) and in dVIN-VSCC (blue line).

TABLE 2 Univariate and multivariate analysis of factors associated with vulvar squamous cell carcinoma development for solitary differentiated vulvar intraepithelial neoplasia.

Age	Number at risk/events	Univariate HR (95% CI) 0.99 (0.95–1.03, $p=0.728$)	Multivariate HR (95% CI) 1.00 (0.95–1.05, $p=0.961$)
Localization			
Periclitoral area	9/4	Ref	Not calculable
Perineum	4/0	0.00 (0.00–Inf, $p=0.998$)	
Labium minus	16/9	0.97 (0.30–3.15, $p=0.954$)	
Labium majus	15/6	0.71 (0.20–2.51, $p=0.592$)	
Associated lichen sclerosus			
No	9/5	Ref	Ref
Yes	35/14	0.56 (0.20–1.56, $p=0.266$)	0.72 (0.25–2.07, $p=0.537$)
Compliant corticosteroid use after excision			
No	18/12	Ref	Ref
Yes	26/7	**0.27 (0.11–0.70, $p=0.007$)**	**0.315 (0.11–0.88, $p=0.027$)**
Unifocality			
Yes	38/17	Ref	Ref
No	6/2	0.53 (0.12–2.33, $p=0.40$)	0.66 (0.15–2.98, $p=0.58$)
Diabetes			
No	39/19	Ref	Not calculable
Yes	5/0	4.99 (0.16–153.39, $p=0.358$)	
Smoking			
No	41/17	Ref	Ref
Yes	3/2	4.75 (0.03–675.64, $p=0.538$)	1.18 (0.18–7.96, $p=0.864$)

Note: Statistically significant *p*-values are in bold.

Abbreviations: CI, confidence interval; HR, hazard ratio.

TABLE 3 Univariate and multivariate analysis of factors associated with VSCC recurrence for dVIN-VSCC.

		Univariate HR (95% CI)	Multivariate HR (95% CI)
Age	**Number at risk/events**	**1.02 (0.94–1.10, $p=0.695$)**	**1.01 (0.96–1.07, $p=0.611$)**
Localization			
Periclitoral area	9/4	Ref	Ref
Perineum	3/3	1.14 (0.23–5.59, $p=0.868$)	1.26 (0.24–6.56, $p=0.784$)
Labium minus	8/2	0.25 (0.04–1.74, $p=0.163$)	0.28 (0.03–2.31, $p=0.237$)
Labium majus	12/1	0.10 (0.01–1.02, $p=0.052$)	0.08 (0.01–1.18, $p=0.066$)
Associated lichen sclerosus			
No	6/2	Ref	Ref
Yes	26/8	0.88 (0.19–4.16, $p=0.869$)	0.48 (0.05–4.93, $p=0.540$)
Compliant corticosteroid use after excision			
No	16/4	Ref	Ref
Yes	16/6	1.49 (0.41–5.45, $p=0.544$)	0.87 (0.12–6.08, $p=0.886$)
Unifocality			
Yes	26/8	1.05 (0.207–5.36, $p=0.95$)	1.59 (0.14–17.67, $p=0.70$)
No	6/2	Ref	Ref
Diabetes			
No	28/9	Ref	Ref
Yes	4/1	1.87 (0.23–15.08, $p=0.555$)	8.239 (0.35–192.69, $p=0.19$)
Smoking			
No	31/9	Ref	Ref
Yes	1/1	**26.38 (1.65–423.09, $p=0.021$)**	**24.72 (1.02–600.74, $p=0.049$)**

Note: Statistically significant *p*-values are in bold.

Abbreviations: CI, confidence interval; dVIN, solitary differentiated vulvar intraepithelial neoplasia; dVIN-VSCC, dVIN associated with vulvar squamous cell carcinoma; HR, hazard ratio.

stratifying cancer risk.[28] As HPV-independent VIN may show a broad morphological spectrum and different cancer risk, a tailored diagnosis with characterization of p16 staining (negative or block positive) and p53 (wild-type or mutant patterns) is recommended for optimal classification. Indeed, the HPV-independent VIN/p53 mutant carries a 10-year cancer risk of 67.4%, whereas HPV-independent VIN/p53 wild-type has a risk of 27.8%, and HPV-independent VIN with nondifferentiated morphology ("HPV-associated-like") has a risk of 73.3%.

None of these studies assessed the impact of ultrapotent corticosteroid therapy on dVIN prognosis after treatment. A compliant TCS treatment of LS is reported to prevent progression towards VSCC;[18] however, our study is the first to report the impact of compliant TCS to significantly reduce the risk of VSCC development after solitary dVIN complete surgical resection. However, once an invasive VSCC is diagnosed and treated, a compliant TCS treatment does not reduce the risk of VSCC recurrence, implying that dVIN-VSCC is a different entity from solitary dVIN, and further genomic alterations may have occurred[22] and altered the TCS responsiveness. Even if a clinical LS is not diagnosed, or in the case of asymptomatic patients, TCS should be administered and application should be monitored. Indeed, post-surgical scarring or sequelae may hinder LS/dVIN classical clinical findings, thus underreporting a potential risk factor for progression. Long-term use of TCS was demonstrated to be safe and with no adverse effects, in particular no risk of vulvar atrophy, systemic effects or local infections.

Considering, on the other hand, the risk of recurrent VSCC in dVIN-VSCC, data in the literature vary from 32% to 94%,[23,27,29,30] with a median time to recurrence of 13–32 months. In our cohort, the risk is in line with the literature data, although time to recurrence is longer (52.5 months). As data about radicality of treatment in other series are lacking, it is difficult to compare the longer time to recurrence.

Smoking was identified as the only risk factor for VSCC recurrence in our cohort. In the literature, smoking has been linked to a higher risk of vulvar cancer, especially in the cohort of older patients.[31] Current smokers were found to be at significantly higher risk, whereas former smokers had no risk elevation,[32] reinforcing the importance of smoking cessation.

The series is, to our knowledge, one of the largest in the literature considering only dVIN with a long-term follow up. Further strengths of our study are data homogeneity and revision of histology slides, which avoided diagnostic pitfalls. The 88% of dVIN diagnosis confirmed after revision underlines the need for pathologists' attention in this difficult diagnosis.

Single-center experience and retrospective nature of the study could be considered limitations. Furthermore, lack of reliable and specific documentation regarding localization of recurrent disease made it impossible to distinguish progression or rather new foci evolving from adjacent LS or histologically normal tissue.

A question we can address is how much the histopathological diagnosis of the lesion, of free margins, and of adjacent normal tissue protects patients treated for dVIN from VSCC development? In the complex field of carcinogenesis such as HPV-independent vulvar carcinogenesis, the support of molecular genetics, which can definitely stratify the risk, seems now to be imperative.[33]

5 | CONCLUSION

A high-risk disease, dVIN requires careful management and surveillance after surgical treatment. Life-long follow up should be warranted, given the high dVIN malignancy risk that remains persistent many years after the first diagnosis. It is appropriate to recommend ultrapotent TCS to reduce the VSCC risk in solitary dVIN. The help of cancer-predicting biomarkers will certainly help in the identification of patients who are candidates for more conservative therapies and those patients who should be the subjects of more intensive follow ups and treatments.

AUTHOR CONTRIBUTIONS

Mario Preti conceived and co-ordinated the study. Sara Urru, Niccolò Gallio, Federica Bevilacqua, Federica Zamagni, and Mario Preti analyzed the data. Mario Preti, Fulvio Borella, and Niccolò Gallio wrote the first draft. Luca Bertero and Paola Cassoni carried out histopathological revision. Ronald W. Jones and Linn Woelber acted as external reviewers. All authors reviewed and approved the article.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

ETHICS STATEMENT

The study was approved by the Research Ethics Committee for Human Biospecimen Utilization (Department of Medical Sciences—ChBU) of the University of Turin (no 2/2022, date of approval February 22, 2022). All patients included in our historical cohort study were treated according to the ethical standards of our local committee on human experimentation and with the Declaration of Helsinki, and signed informed consent for the anonymous use of clinical and instrumental data for research purposes at the time of diagnosis.

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