Review Article
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# The main differences between vulvar intraepithelial neoplasia and vulvar intraepithelial lesion

## Abstract

Vulvar cancer is a recurrent subject in gynecological cancer. Vulvar Intraepithelial Neoplasia is known for being a precursor lesion of vulvar cancer and can be divided in three different subtypes: Low-grade Vulvar Intraepithelial Lesion (vulvar LSI), High-grade Vulvar Intraepithelial Lesion (vulvar HSIL) and Differentiated Vulvar Intraepithelial Neoplasia (dVIN). These subtypes differ in several aspects, and this article aims to present those differences in order to facilitate its treatment and the final diagnosis. The HSIL is the most associated with cronic Human Papilloma Virus (HPV) infection and can be related to other environment factors. As for dVIN, it's more frequent in post-menopausal women with sclerosis lichen and it has a higher rate of progression to vulvar squamous carcinoma. The difference must be made in order to choose what is the best treatment, once there are various modalities, such as simple excision, $CO_2$ ablation and topical application of imiquimod or fluoracil. This differences is also important for the development of measures that seek specific prevention, such as HPV vaccine for the HSIL and the proper treatment of vulvar conditions for the dVIN.

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## Introduction

Vulvar cancer accounts for about 3 to 5% of all cases of gynecological cancer.[1] The incidence of carcinoma *in situ* or intraepithelial vulvar neoplasia, the precursor lesion of invasive tumor, has doubled in recent years. In 90% of the cases, it is squamous cell carcinoma or squamous cell carcinoma.[2]

The International Society for the Study of Vulvovaginal Disease (ISSVD) has led the process in recent years to change the terminology of vulvar intraepithelial neoplasia to a more appropriate one. The most current was accepted in 2015:[3,4]

a) Low-grade vulvar intraepithelial lesion (vulvar LSIL, flat condyloma, HPV effect).

b) High-grade vulvar intraepithelial lesion (vulvar HSIL, usual NIV).

c) Differentiated vulvar intraepithelial neoplasia (dVIN).

While high-grade vulvar intraepithelial lesion (HSIL) is associated with chronic Human Papilloma Virus (HPV) infection, it is suggested that differentiated vulvar intraepithelial neoplasia is independent of HPV infection and is often associated with chronic inflammatory dermatoses, such as vulvar lichen sclerosus.[5]

HPV infection has a strong association with vulvar intraepithelial neoplasia, with most studies showing HPV positivity greater than 80% in this type of lesion. HPV 16 is the most commonly found (77.2%), followed by HPV 33 (10.2%) and HPV 18 (2.6%).[6–9]

Vulvar HSIL mainly affects women between the third and fifth decades.[10] Other risk factors include smoking, a greater number of sexual partners and immunosuppression.[10,11,12] Concomitant infection with the Human Immunodeficiency Virus (HIV) can be present in up to 30% of cases.[10]

Unlike HSIL, dVIN typically occurs after menopause, between the sixth and eighth decades.[10] Although dVIN represents only 5% of the diagnoses of vulvar neoplasia, it has a higher rate of progression to vulvar squamous carcinoma and higher recurrence rates than HSIL, thus considered as the real precursor lesion of vulvar squamous carcinoma.[13]

Regarding symptoms, most patients with HSIL report pruritus or dysuria. Asymptomatic patients represent only 20% of all cases.[10] The clinical presentation consists of macules or papules that can be hypochromic or erythematous, sometimes hyperchromic, with brownish or grayish tones, and may or may not coalesce into verrucous plaques. They show acetowhitening patterns and up to 2/3 are multifocal. In general, they affect areas of greater friction in sexual activity, such as introitus, perineum and interlabial grooves.[14,15] Between 18 and 53% of patients have synchronous squamous neoplasia in other parts of the anogenital tract, especially in the cervix.[10] The lesion can regress spontaneously in 1% of cases, with most regressions occurring in young pregnant women.[13] Meanwhile, the most common clinical presentation of dVIN is hyperkeratotic plaque, resistant to clinical treatment, associated with some inflammatory dermatosis, with vulvar lichen sclerosus being the most frequent. However, the NIVd lesion can be indistinguishable from these dermatoses.[13,16] Other morphological characteristics include atrophic papules or raised nodules, further complicating the diagnosis. Unlike HSIL lesions, they are usually unicentric and affect mainly the vulvar skin area.[10]

In the histological evaluation, HSIL presents as basophilic cells with several mitoses, apoptotic cells and deforestation, involving more than 1/3 of the total epithelial thickness.[13] The

immunohistochemical study shows positivity for the p16 protein, an important marker of chronic infection indicative of high-risk HPV.[15] The histological characteristics of dVIN are subtle and the diagnosis is usually facilitated by comparing the lesion with the normal adjacent skin.[13] In practice, most dVIN have one or more of the following types of changes: prominent basal atypia associated with lichen sclerosus, proliferation and expansion of the basal layer, defects in cell maturation, spongiosis or acantholysis in the basal third of the epithelium.[17] Immunohistochemistry shows positivity for p53 protein in more than 80% of cases, unlike HSIL lesions, which are negative for this biomarker.[8,10,18]

The main differences between differentiated vulvar intraepithelial neoplasia and HSIL are listed in Table 1.

**Table 1** Comparative description between dVIN and HSIL

| | dVIN | HSIL |
|---|---|---|
| Age | 6th to 8th decades | 3rd to 5th decades |
| Percentage of all vulvar premalignant lesions | 5% | 95% |
| Multifocality | Unusual | >50% |
| Smoking | Not associated | Association in 60% of smokers |
| Most common association | Lichen Sclerosis | >80% HPV+<br>HPV 16: 77%<br>HPV 33: 10%<br>HPV 18: 2,5% |
| Progression to cancer | 35% | 5% |
| Recurrence | Common | Less common, but between 15-50% |
| Immunohistochemistry | p53+ | p16+ |
| Extension for skin attachments | Rare | Common |
| Most common histological type in case of invasion | Keratinizing vulvar squamous carcinoma | Verrucous vulvar squamous cell carcinoma |

Source: ALLBRITTON, 2017[13]

## Development

No screening strategy has been developed to prevent vulvar squamous cell carcinoma through the early detection of vulva intraepithelial neoplasia. Vulvar cytology is hampered by the keratinization of the vulva skin, making performance and interpretation of test results problematic. The diagnosis is limited to visual assessment. There are disagreements among experts regarding the need for biopsy of all verrucous lesions, but it is recommended that the biopsy be performed in all postmenopausal women with apparent genital warts and in women in whom topical therapies have failed.[19]

The Brazilian Federation of Gynecology and Obsterics Associations (FEBRASGO) mentions that although the colposcope can be useful in viewing details of the lesions, the final diagnosis is histopathological. However, the clinician must always pay attention to details in order to rule out stromal invasion. It is noteworthy that the most common clinical and vulvoscopic characteristics of invasive disease consist of white hyperkeratotic plaques, erythematous macules and brown or black papular areas.[20]

The differential diagnosis of vulvar intraepithelial neoplasms includes the following benign lesions: lichen simple, lichen sclerosus, lichen planus, condyloma acuminata; it can also include infectious lesions like candidiasis, herpes and molluscum contagiosum. Vulvar intraepithelial neoplasms can be confused with lesions known to be malignant, such as basal cell carcinoma, squamous cell carcinoma, Paget's disease or melanoma.[21]

Among the various treatment modalities, simple excision with a 5mm margin is more common in HSIL lesions, especially in potentially malignant ones, such as ulcerated lesions, with raised relief and irregular borders, and in patients with risk factors for invasion, such as immunosuppression and smoking. In hair-bearing areas, it is recommended to excise at a depth of 4 mm, while in areas without hair, a depth of 1mm is sufficient.[13]

Despite the recommendation for excision with margins, its need is still uncertain. One study found a recurrence rate of 46% in 22 months of injuries with positive margins, but also found a rate of 27% in 44 months even in injuries with negative margins.[22] Furthermore, the progression of HSIL to vulvar squamous carcinoma does not appear to be influenced by its excision.[23]

Another treatment modality is $CO_2$ laser ablation, however, it is not possible to assess the possibility of invasion, due to the absence of the specimen for histopathological study.[13,4] Therefore, it should not be considered when there is a clinical suspicion of malignancy. As with excision, the margin of healthy skin must also be treated. CO2 laser ablation requires destruction of cells across the entire thickness of the epithelium. In areas with hair, the ablation must extend deeply for 3mm or more. Consequently, large lesions in regions with hair must be treated by another modality. Ablation in hairless areas of skin, on the other hand, must reach up to 2mm in depth.[19]

Topical application of Imiquimod at 5% is also an option for the treatment of HSIL, despite being off-label in neoplasia. In fact, it is equally effective in treating all types of HPV infection, acting through toll-like receptors to shift the immune response to T cell-mediated type 1 immunity.[23] Imiquimod can be applied two to four times a week for 12 to 20 weeks, the scheme of three weekly applications being the most common. However, as it works in conjunction with

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local immunomodulators, its effectiveness in immunocompromised patients is reduced and should be avoided.[19,13] A 2011 study[24] showed that 88% of patients whose lesions initially responded to treatment were free of the disease in seven years of follow-up. The main adverse effects of the application are: erosion and irritation of the affected area and pain. The main advantage of topical Imiquimode is the preservation of vulvar architecture and sexual function, since its use in large lesions will reduce the radicality of excision.[13] The main objections to its use include uncertainty about the depth of penetration into the epithelium and its effectiveness in lesions with extension to the epithelial attachments.[25]

The application of fluoracil is another treatment option, since it causes chemical desquamation of the lesion, but it is also considered to be off-label for vulvar neoplasia. Success rates of up to 75% have already been reported. However, it has limited use as primary therapy, since it can cause significant adverse effects, such as burning, pain, inflammation, edema or painful local ulcerations.[26]

In the face of dVIN, the goal is to prevent the development of squamous carcinoma of the vulva and relieve symptoms, preserving the vulvar anatomy and function.[2,18] Conservative excision of the lesion is recommended as an initial treatment, since there is a need to assess occult invasion.[13,18]

Strict clinical monitoring is recommended regardless of the therapeutic modality for HSIL lesions. Control is suggested every three months for up to three years and thereafter every six months.[22] The American College of Obstetricians and Gynecologists (ACOG) suggests follow-up at six and twelve months after the initial treatment. If there is a complete response and absence of new injuries, follow-up can be annual.[19]

In the first two years, patients with dVIN should be evaluated every three months and, thereafter, every six months.[22] The most recent 2016 European guideline on the management of vulvar injuries recommends monitoring at least every six months.[4]

Patients with vulvar lichen sclerosus and lichen planus are at increased risk for dVIN and squamous carcinoma and should receive adequate clinical monitoring.[16] Lifelong clinical follow-up is recommended for all patients with lichen sclerosus, since the risk of progression to squamous cell carcinoma increases over time, reaching 37% after 25years of disease.[27] A 2015 study showed that the only risk factor for the progression of lichen sclerosus to vulvar squamous carcinoma was the refusal to treat lichen, due to resistance to treatment with corticotherapy.[28]

## Conclusion

Despite the similarities between vulvar HSIL and dVIN, it is paramount to make the correct diagnosis so that the proper treatment can be performed. Knowing its predisposing and clinical factors allows for specific prevention. For HSIL, as there is an important relationship with the HPV virus, immunization with the HPV vaccine is effective between 97% and 100% of all cases, while for dVIN, the main way to reduce the risk of cancer is the appropriate treatment of vulvar conditions such as lichen sclerosus and the managment of risk factors, such as postponing the first sexual intercourse until the end of adolescence, avoiding sexual intercourse with multiple partners, practicing safe sex and quitting smoking.

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## Conflicts of interest

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