Update on the Management of LSIL and HSIL of the Vulva and Vagina

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No Disclosures
Vulvar Squamous Intraepithelial Lesions

Incidence is increasing, particularly in young women

The increase is more than fourfold in 30 years!

HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESIONS should be considered

A PREMALIGNANT VULVAR DESEASE

405 women with vulvar intraepithelial lesions

10 untreated cases progressed to invasion (with a mean duration of 3.9 years)

occult invasive cancer was reported in 3% of women undergoing surgery for vulvar intraepithelial lesions

Annual incidence of vulvar squamous intraepithelial lesions

1.2/100,000

Peak of women age

45-49 years (Watson)

HPV prevalence in vulvar squamous intraepithelial lesions

80.4%

Most common HPV subtype

HPV 16 (71.2%)
HPV 33 (Smith)
Recently

The ISSVD terminology for Vulval Squamous Intraepithelial Lesions has been modified to include the Lower Anogenital Squamous Terminology (LAST)

LAST includes only HPV related lesions and was adopted in 2012 by the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology

However, not all Vulvar intraepithelial lesions are caused by HPV

For this reason the WHO presented a terminology that combined the two terminologies, and the ISSVD terminology committee has proposed to accept it
This 2015 ISSVD terminology for Vulvar Squamous Intraepithelial Lesions will be presented and voted upon at the ISSVD World Congress:

Low grade Squamous Intraepithelial Lesions (LSIL)

High grade Squamous Intraepithelial Lesions (HSIL)
OBJECTIVE OF THIS PROPOSAL

To reach a consensus for:

- Classification
- Terminology
- Appropriate management

For vulvar and vaginal squamous intra-epithelial lesions

according to:

- evidence based medicine
- recent terminology and classification
- expert experience
OBJECTIVE OF THIS PROPOSAL

Management is strictly related to a correct diagnosis

Please, pay particular attention to low grade lesions!

Flat lesions associated with basal atypia and koilocytic changes (VIN 1 or VAIN1)

Should be managed as condyloma.
OBJECTIVE OF THIS PROPOSAL

-Preferred treatment cascade for each clinical situation

  Management of low grade lesions
  Management of high grade lesions

-Treatment of recurrences

-Follow-up recommendations

-Cancer risk over time for the various lesions

-Treatment in uncertain cases (for example disease at the vaginal apex)
METHODOLOGY

Different treatment modalities

according to the published literature

Medical therapy

Surgical therapy

Radiation therapy

Therapeutic vaccines
VAGINAL LSIL (VAIN 1, condylomata)

**Histological pattern**

- Nuclear pleomorphism and hyperchromasiasia (low third of the epithelium)
- Increased mitotic activity in the lower third
- Koilocytic changes
VAGINAL INTRA-EPITHELIAL LESIONS

VAGINAL LSIL (VAIN 1, condylomata)

Diagnosis and clinical correlates

Located in the upper third of the vagina

Colposcopic finding: acetowhite epithelium

Diagnosis: Biopsy necessary!
VAGINAL INTRA-EPITHELIAL LESIONS

VAGINAL LSIL (VAIN 1, condylomata)

Treatment Options

Wait! close follow up in the asymptomatic patient

Medical therapy (indicated only for extensive visible disease in asymptomatic patient)

  Intravaginal self-administered Imiquimod cream
  (proposed regimen: 250 mg of 5% imiquimod daily or twice a week for a minimum of 12 doses)

Surgical therapy (indicated only for extensive visible disease in asymptomatic patient)

Radiation therapy: not indicated for LSIL lesion

Vaccine: immunization could potentially prevent 70% of VAIN!
VAGINAL INTRA-EPITHELIAL LESIONS

VAGINAL LSIL (VAIN 1, condylomata)

Follow up

Examination every 6 months with cytology until 2 normal results have been obtained
VAGINAL HSIL (VAIN 2-3)

Histological pattern

- Nuclear pleomorphism and hyperchromasia (low 2/3 of the thickness of the epithelium (VAIN 2) or the entire thickness of the epithelium (VAIN 3))
- Binucleate or multinucleate cells are present
- Atypical mitotic figures are identifiable
- Koilocytic changes may be seen within or adjacent to the lesion
VAGINAL INTRA-EPITHELIAL LESIONS

VAGINAL HSIL (VAIN 2-3)

Diagnosis and clinical correlates

**Colposcopic finding:** acetowhite epithelium with mosaic and punctuation, non-staining areas with application of Lugol’s solution. A spiky surface may be present.

Strictly correlated with previous cervical dysplasia or cervical cancer

Incidence of VAIN after hysterectomy for CIN: up to 7.4% of the cases
VAGINAL INTRA-EPITHELIAL LESIONS

VAGINAL HSIL (VAIN 2-3)

Treatment Options

Medical therapy

- Intravaginal self-administered Imiquimod cream
  (proposed regimen: 250 mg of 5% imiquimod daily or twice a week for a minimum of 12 doses)
  (22-29% recurrence rate)
- 5-FU 5% cream
  (proposed regimen: 1-2 mL (1.5g) of 5% cream weekly for 10 weeks or 5g nightly for 5 nights)
  (75-92% of efficacy)

Tricholoroacetic acid: poor effect on HSIL VAIN (53% of efficacy)
VAGINAL INTRA-EPITHELIAL LESIONS

VAGINAL HSIL (VAIN 2-3)

Treatment Options

Surgical therapy - Excision

-Wide Local Excision (WLE): removal of the entire visible lesion with 5 mm margin of normal tissue (66-83% of efficacy)

-LEEP procedure: avoid for the risk of injury to adjacent structures!

-Vaginectomy (partial or total upper vaginectomy): only in selected cases (multifocal disease or disease located in posthysterectomy suture recesses)

-Laser excision: removal of the entire visible lesion with 5 mm margin of normal tissue
VAGINAL HSIL (VAIN 2-3)

Treatment Options

Surgical therapy - Ablation

- **Laser:** Epithelial destruction to a depth of 1.5 mm, including the zone of thermal necrosis: only in selected cases

- **Cryotherapy:** not applicable to vagina

- **Cavitational ultrasonic surgical aspiration** (CUSA): only in trained centers (similar efficacy to other surgical procedures
VAGINAL INTRA-EPITHELIAL LESIONS

VAGINAL HSIL (VAIN 2-3)

Treatment Options

- Radiation therapy: not recommended as first line treatment
- Vaccine: immunization could potentially prevent 70% of VAIN!
- Chemosurgical: 5-FU pre surgical: no increased efficacy in respect to surgery alone
VAGINAL INTRA-EPITHELIAL LESIONS

VAGINAL HSIL (VAIN 2-3)

Follow up

- Examination every 6 months with citology
- Re-treatment in any case of recurrence
### Vaginal Intra-Epithelial Lesions

Summarizing..

<table>
<thead>
<tr>
<th>Method of treatment</th>
<th>No. studies</th>
<th>Total no. patients in identified studies</th>
<th>Cure rates within the follow-up period, %</th>
<th>Duration of follow-up, mo</th>
<th>Authors with references in brackets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excision (surgical)</td>
<td>3</td>
<td>129</td>
<td>69–85</td>
<td>44–61</td>
<td>Cheng et al. [12], Rome et al. [13], and Curtis et al. [14]</td>
</tr>
<tr>
<td>Laser ablation</td>
<td>5</td>
<td>152</td>
<td>68–87.5</td>
<td>12–60</td>
<td>Dodge et al. [2], Rome et al. [13], Sopracofove [16], Diakomanolis et al. [17], and Yalcin et al. [49]</td>
</tr>
<tr>
<td>CUSA</td>
<td>2</td>
<td>138</td>
<td>74</td>
<td>21–53</td>
<td>Matsuo et al. [21] and Robinson et al. [22]</td>
</tr>
<tr>
<td>Vaginectomy</td>
<td>3</td>
<td>55</td>
<td>80–100</td>
<td>23</td>
<td>Dodge et al. [2], Diakomanolis et al. [17], and Fanning et al. [26]</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>4</td>
<td>68</td>
<td>86–100</td>
<td>6–90</td>
<td>Graham et al. [28], Woodman et al. [29], Ogino et al. [30], and Blanchard et al. [31]</td>
</tr>
<tr>
<td>5-FU</td>
<td>4</td>
<td>89</td>
<td>45–100</td>
<td>3–60</td>
<td>Dodge et al. [2], Rome et al. [13], Gonzalez Sanchez et al. [34], and Caglar et al. [35]</td>
</tr>
</tbody>
</table>
VAGINAL INTRA-EPITHELIAL LESIONS

Discussing.. on VAGINAL LSIL

- **EXPECTANT MANAGEMENT** with close follow up for 1 year

- **MEDICAL THERAPY WITH IMIQUIMOD SELF ADMINISTERED CREAM**
  as first line treatment in those patients requiring treatment

- **SURGICAL WLE**
  as second line treatment in those patients requiring treatment

- **EXAMINATION** every 6 months with cytology until 2 normal results have been obtained
Discussing.. on VAGINAL HSIL

- **SURGICAL WLE**
  
as first line treatment in those patients requiring treatment

- **MEDICAL THERAPY WITH IMIQUIMOD SELF ADMINISTERED CREAM**
  
as adjuvant treatment

- **EXAMINATION** every 6 months with cytology until 2 normal results have been obtained
Discussing on VAGINAL HSIL in vaginal apex after hysterectomy

- **MEDICAL THERAPY WITH IMIQUIMOD SELF ADMINISTERED CREAM** as first line treatment

- **UPPER VAGINECTOMY** as second line treatment
VULVAR SQUAMOUS INTRA-EPITHELIAL LESIONS

VULVAR LSIL (VIN 1, condylomata)

Histological pattern

- Nuclear pleomorphism and hyperchromasia (low third of the epithelium)
- Increased mitotic activity in the lower third
- Koilocytic changes
VULVAR SQUAMOUS INTRA-EPITHELIAL LESIONS

VULVAR LSIL (VIN 1, condylomata)

*Diagnosis and clinical correlates*

- Direct visual inspection “naked eye” or bright lighting
- Use of the colposcope and acetic acid: UNUSEFULL
- Diagnosis: Biopsy necessary if uncertain or HSIL is suspected!
- In case of warts: test for other sexually transmitted infections
VULVAR SQUAMOUS INTRA-EPITHELIAL LESIONS

VULVAR LSIL (VIN 1, condylomata)

Treatment VS no Treatment?

The choice is based on:
- Patient and/or provider preference
- Size/location of warts
- Cost of treatment
- Convenience
- Side effects

High incidence of recurrence (13-65%) with condylomata
VULVAR SQUAMOUS INTRA-EPITHELIAL LESIONS

VULVAR LSIL (VIN 1, condylomata)

Treatment Options

Medical therapy

- Bi and trichloroacetic acid: BCA/TCA (80-90% solution)
  (Applied by provider, and washed off after 6 hours. Treatment occurs at 1-2 week intervals until resolution of condyloma.)
  (Response rate 56-81%. Recurrence rate 36%)

- Podophyllin (0.15% cream or 0.5% solution)
  (proposed regimen: Applied twice a day for 3 days; then 4 days off. Cycle may be repeated up to 4 times.)
  (Recurrence rate: 6-100%)

- Imiquimod 5% cream
  (Applied by patient once daily (bedtime) 3 days a week. Washed off in morning after 8 hours. Maximum length of treatment 16 wks.
  (Recurrence rate: 6-26%)

- Botanical: Sincechatechin 15% ointment
  (Applied by patient 3 times a day with maximum duration of 16 weeks)
  (Response rate 47-59%. Recurrence rate: 7-11%)
## Treatment comparison

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Action</th>
<th>Pro</th>
<th>Side effects</th>
<th>Use in children/pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BCA/TCA</strong></td>
<td>chemical coagulation of proteins</td>
<td>Non-toxic</td>
<td>pain, burning and local irritation</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Podophyllin</strong></td>
<td>antimitotic agent: induces local tissue necrosis</td>
<td>Inexpensive, safe, easy to use</td>
<td>pain, local irritation</td>
<td>safety unknown</td>
</tr>
<tr>
<td><strong>Imiquimod</strong></td>
<td>Immune enhancer, stimulates local production of cytokines.</td>
<td></td>
<td>redness, irritation, vesicles, and hypopigmentation</td>
<td>safety unknown</td>
</tr>
<tr>
<td><strong>Sincechatechin</strong></td>
<td>not clear- thought to be antioxidant; immune enhancer</td>
<td></td>
<td>burning, pain, ulceration, vesicular rash</td>
<td>safety unknown</td>
</tr>
</tbody>
</table>
VULVAR SQUAMOUS INTRA-EPITHELIAL LESIONS

VULVAR LSIL (VIN 1, condylomata)

Treatment Options

Surgical therapy- Excision

(Success rate 89-100%. Recurrence rate 19-29%)

-Electrosurgery: high frequency electrical current to burn lesion. Requires local anesthetic. May cause scarring.
(Success rate 94-100%. Recurrence rate 14-22%)
VULVAR SQUAMOUS INTRA-EPITHELIAL LESIONS

VULVAR LSIL (VIN 1, condylomata)

Treatment Options

Surgical therapy - Ablation

-Cryotherapy: destroys warts via thermal-induced cytolysis using liquid nitrogen. -Applied directly to the wart -No anesthetic.

(Success rate 44-75%. Recurrence rate: 21-42%)

-CO2 laser: heats/vaporizes tissues. -Requires special equipment/training and is more expensive other treatments. -Must control depth and extent of vaporization to destroy the wart only -Often used for recurrent, widespread disease. -Associated with pain, bleeding, burning and potential scarring post procedure. -Requires anesthetic/ anesthesia.

(Success rates 60-100%. Recurrence rate up to 80%)
VULVAR SQUAMOUS INTRA-EPITHELIAL LESIONS

VULVAR HSIL (VIN 2-3)

Histological pattern

- Nuclear pleomorphism and hyperchromasia
  (low 2/3 of the thickness of the epithelium (VIN 2) or the entire thickness of the epithelium (VIN 3))

- Binucleate or multinucleate cells are present

- Atypical mitotic figures are identifiable

- Koilocytic changes may be seen within or adjacent to the lesion
VULVAR SQUAMOUS INTRA-EPITHELIAL LESIONS

VULVAR HSIL (VIN 2-3)

Diagnosis and clinical correlates

*No screening* strategies have been developed for the prevention of vulvar cancer.

Any lesion unknown to be benign *warrants a biopsy*.

HSIL is a *histologic* diagnosis.

Appropriate sites for biopsy is identified by *examination* including a lens or colposcope.
VULVAR SQUAMOUS INTRA-EPITHELIAL LESIONS

VULVAR HSIL (VIN 2-3)

Treatment Options

treatment always recommended!

Medical therapy

- Intravaginal self-administered **Imiquimod cream**
  *(proposed regimen: three times weekly for 12–20 weeks, with clinical re-evaluation at 4–6-week. Residual lesions require surgical treatment)*

Topical treatment with imiquimod is effective in stimulating cell-mediated immunity against different types of HPV including HPV related VIN.

*(22-29% recurrence rate)*

- **5-FU 5% cream**

  limited role in the treatment of vulvar intraepithelial lesions due to poor patient tolerance from the chemical desquamation despite reported *(Response rates of 75%)*
VULVAR SQUAMOUS INTRA-EPITHELIAL LESIONS

VULVAR HSIL (VIN 2-3)

Treatment Options

**Medical therapy**

- **Cidofovir 1% gel** compared with imiquimod in a randomized, phase 2 trial. Response were comparable in both groups (46% in each group). Adverse events were reported in 37% in the cidofovir group and 46% in the imiquimod group.

- **Photodynamic therapy after Topical or systemic application of 5-Aminolevulinic acid (ALA)** light interacts with protoporphyrin IX resulting in generation of radicals capable of producing a local cytotoxic effect. *(Response rate 52%, Recurrence 48%)*
VULVAR SQUAMOUS INTRA-EPITHELIAL LESIONS

VULVAR HSIL (VIN 2-3)

Treatment Options

Surgical therapy

-Vulvectomy: no longer advisable for VIN

-Skinning Vulvectomy (removal of all vulvar skin): rarely indicated
  (useful in cases of confluent multifocal lesions)

-Surgical removal of visible lesions to:
  -relieve symptoms
  -prevent development of invasive disease
  -preserving normal anatomy and function of the vulva

  Performed using cold knife or CO2-laser vaporization
  (single techniques or in combination)

Excisional margin of 5-10 mm: desirable
Surgical therapy


- Population of women treated with surgical excision: 66% had positive margins
- Among them 46% recurrence
- Women with negative margins: 17% recurrence
- Occult squamous cancer found at the time of initial treatment: 22% of patients (missed without ablation performing)

FOCUS ON MARGIN NEGATIVITY:
- 3 time lower risk of recurrence
- Longer disease-free interval.
Recurrence after CO2 laser vaporization is more common

Requires regular, close, and extended monitoring

Surgical therapy

-50 women treated for vulvar HSIL

-Recurrence-free survival rates at 5 years:
  91.0% (Surgery)
  51.3% (Laser vaporization)

Surgical therapy over hair bearing areas

Hair follicles can contain diseases extending into the subcutaneous tissue for 3mm or more → Laser procedure must ablate them!

Vulvar HSIL over hair bearing areas → Other therapeutic modalities are preferred

Vulvar HSIL over non-hair bearing areas → Extend ablation through the dermis (to 2 mm)

TO: Adequately treat the disease
    Avoid skin retraction
    Avoid hypertrophic scarring
Therapeutic vaccine

Imiquimod treatment + Therapeutic HPV vaccination

combining effect of local immunomodulatory treatment and immunological platform for therapeutic HPV vaccination

GOAL: to achieve an ENHANCED AND DURABLE response
VULVAR SQUAMOUS INTRA-EPITHELIAL LESIONS

VULVAR HSIL (VIN 2-3)

**Therapeutic vaccine**  Daayana S et al- Phase II trial of imiquimod and HPV therapeutic vaccination in patients with vulvar intraepithelial neoplasia. Br J Cancer. 2010

Immunomodulation observed only in **Imiquimod** treatment lesion **responders**  (increasing of local CD8 and CD4 T cells)

Lack of immunomodulation in **non-responder** lesions: due to CD4 T cell secretion of IL10 in response to Imiquimod application

NO generation of CD4 and CD8 effector T cells able to migrate to the tumor site **to suppress** tumor cells.

**Liu** XS. Non-responders to topical Imiquimod followed by vaccination therapy in VIN patients may be due to the level of IL10. Br J Cancer. 2010

FOCUS ON THE ROLE OF IL 10 in order to improve efficacy of the combined medical and vaccination treatment!
VULVAR SQUAMOUS INTRA-EPITHELIAL LESIONS

VULVAR HSIL (VIN 2-3)

Follow up

- High incidence of recurrence (30-50% for all methods, higher if positive margins)
- Treatment failure for HSIL of the vulva.
- Adequate counselling of patients to monitoring progression to invasive vulvar cancer

This high rate of recurrence is likely due to the fact the underlying cause (persistent HPV infection) has not been cleared

Post-treatment recurrence rates may exceed 30-50% with all treatment regimens