Anal squamous intraepithelial lesions

Dr. Mohamed Abunada

Head of colorectal surgery unit-HMC

No conflict of interest

Outline

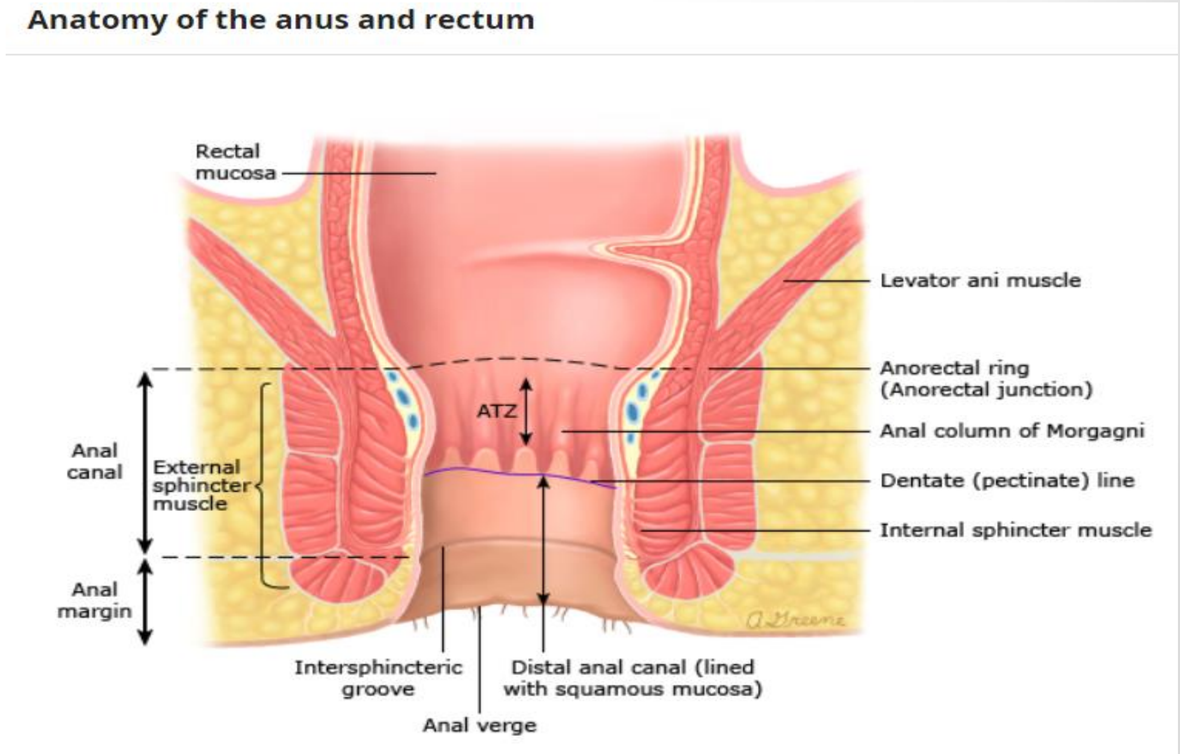
- Introduction
- Epidemiology and risk factors
- Natural history
- Clinical manifestations, and evaluation
- Prevention
- Treatment
- Post-treatment surveillance

Introduction

- Anal canal and cervix share embryologic, histologic, and pathologic characteristics.

- HPV is the most common sexual transmitted disease (STD) in US. It's linked with malignancies, especially those involving the anogenital (cervical, vaginal, vulvar, penile, anal) tract.

- Anal squamous intraepithelail lesions (ASIL) happen most commonly at anal transitional zone (ATZ)

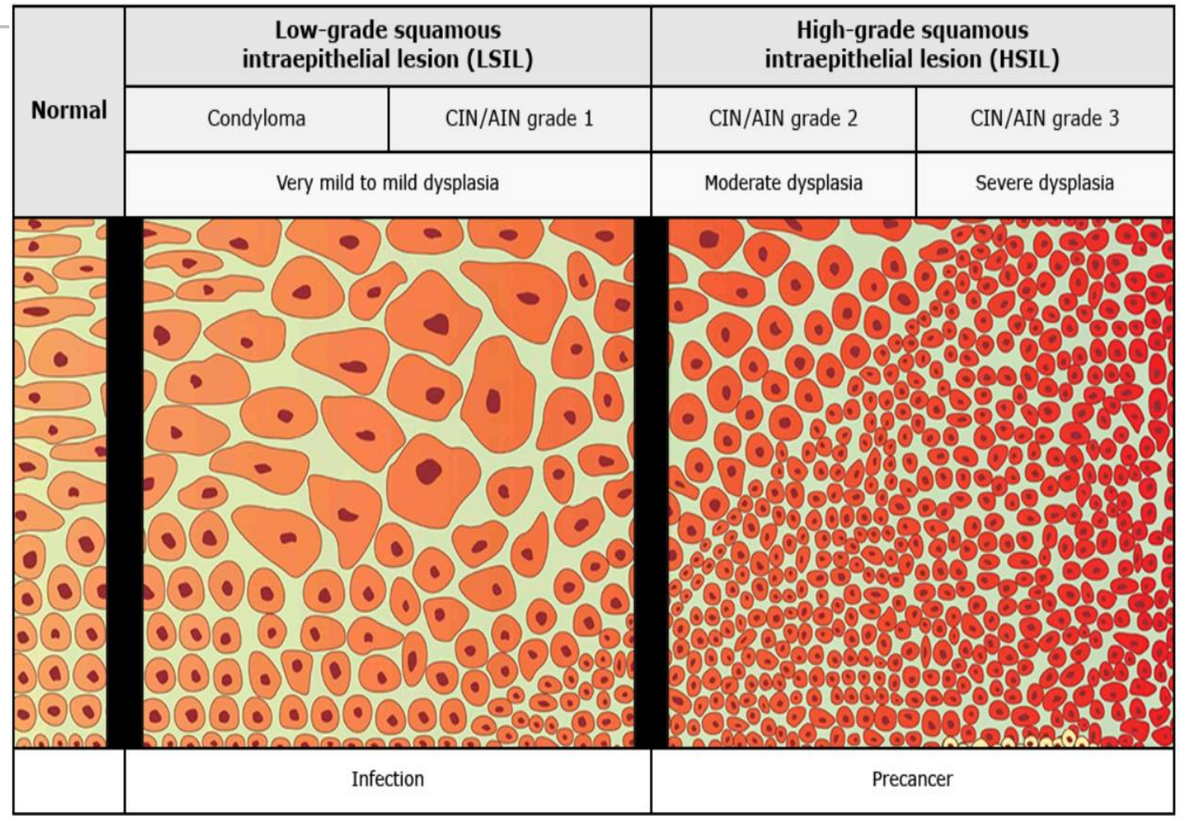


Cytology-Bethesda classification

Epithelial cell abnormalities

- **Squamous cell**
  - Atypical squamous cells
    - Of undetermined significance (ASC-US)
    - Cannot exclude HSIL (ASC-H)
- Low-grade squamous intraepithelial lesion (LSIL)
  (encompassing: HPV/mild dysplasia/CIN-1)
- High-grade squamous intraepithelial lesion (HSIL)
  (encompassing: moderate and severe dysplasia, CIS; CIN-2 and CIN-3)
  - With features suspicious for invasion (*if invasion is suspected*)
- Squamous cell carcinoma

Schematic representation of squamous intraepithelial lesions (SIL)



Epidemiology and risk factors

- Prevalence varies according to the population
- ASIL in female adolescents without HIV: USA 5.7 % in Brazil (1.4-2.6%).
- ASIL among males with men sex with men (MSM) without HIV: 20%

Risk factors:

1. Human papillomavirus (HPV) infection:

✓ Highest risk for ASIL are HPV16 and HPV18

✓ Low-risk HPV types are mainly associated with low-grade SIL (LSIL), including genital warts or condyloma acuminata (90% are HPV6 and 11)

✓ Among females, there is significant concordance between cervical and anal HPV infection, (in a study, females with cervical HPV, had 25% risk of anal HPV HSIL)

2. Sexual behavior :

- MSM
- Females. With history of anal receptive intercourse, number of partners, HPV infection and a history of SIL at other genital sites (cervical, vaginal, vulvar)

Risk factors

3.HIV

❑ People living with HIV (PLWH): Risk of ASIL is almost double

4. Solid organ transplant with immunosuppression.

Other risk factors: history of rectal discharge, a history of anogenital warts, intravenous drug abuse, current cigarette smoking

Progression of anal squamous intraepithelial lesions (ASIL)

- LSIL is considered to represent a marker for risk of HSIL rather than a direct precursor.

- LSIL may spontaneously regress (50% in some studies).

- HSIL is considered a true cancer precursor with potential to progress to anal squamous cell carcinoma. Spontaneous regression is less likely than anal LSIL (23-30%)

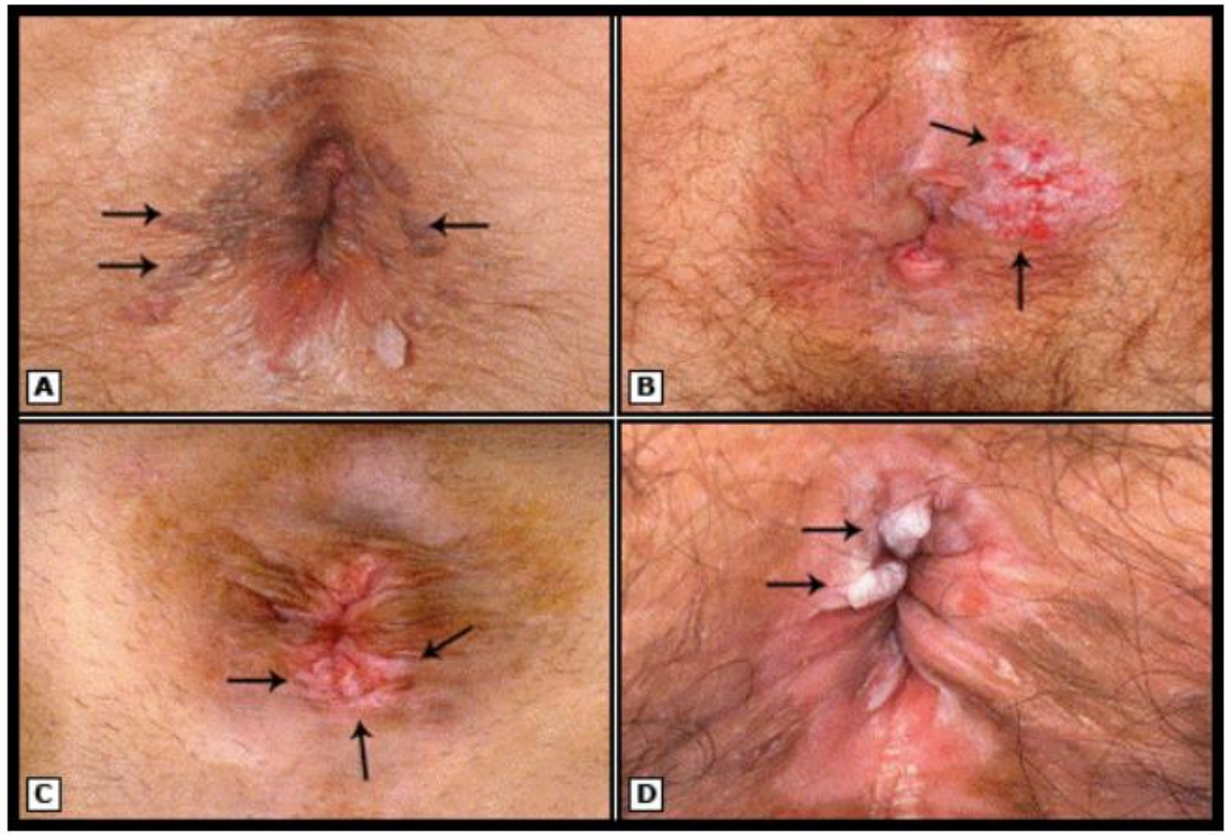
- People living with HIV (**PLWH**), females with a history of **cervical or vulvar** HSIL or cancer, and **recipients of a solid organ transplant** are at risk for progression

Clinical manifestations

- Typically asymptomatic

- Sometimes local symptoms: pruritus, bleeding, discharge, irritation, and tenesmus

- May present as frond-like or plaque-like condyloma



(A) Bowenoid anal squamous intraepithelial lesion.

(B) Erythroplakic anal squamous intraepithelial lesion.

(C) Leukoplakic anal squamous intraepithelial lesion.

(D) Verrucous anal squamous intraepithelial lesion.

Evaluation

- History related to STD's

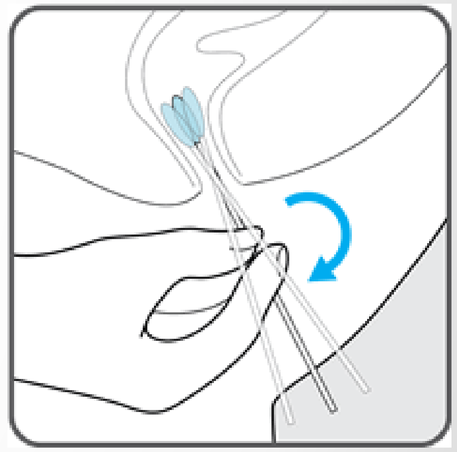
- Visual inspection of the perianal skin sometimes is enough

- Digital examination and high-resolution anoscope (HRA) of the anal canal.
- If anal cytology is planned, it should be performed before the DRE and in the absence of lubricant.

- Assessment of palpable lymphadenopathy.

Screening

People living with HIV
Men who have sex with men
Iatrogenic immunosuppression (eg, solid organ transplant recipients, long-term oral corticosteroids)
Women with a history of cervical, vulvar, or vaginal SIL (also termed intraepithelial neoplasia) or cancer
Women with a history of cervical HPV 16 infection
Individuals with a history of anogenital warts



- Age to start and frequency are not well defined
- CDC for risk individuals ≥ 35 years

- Society of Transplantation Infectious Diseases Community of Practices, recommend yearly anal cytology in solid organ transplant recipients, particularly those with a history of receptive anal intercourse and/or CIN

Screening

- Anal HSIL screening relies on cytology. Individuals with abnormal cytology are subsequently referred for HRA to biopsy suspicious areas.

- High risk HPV (HrHPV) testing as screening: less evidence

- HRA follows abnormal results

High resolution anoscope (HRA) technique

- Left lateral or lithotomy position

- We use 5% acetic acid and Lugol iodine solutions to identify anal lesions

- Prior to examination, a 4 x 4 gauze is wrapped around a Q-tip and soaked in 5% acetic acid. By inserting this Q-tip into the anal canal, the acetic acid is applied evenly prior to visualization.

- Colposcope is then used for lighting and magnification

Abnormal findings on high resolution anoscope

- Acetic acid produces a white appearance in areas of abnormal epithelium

What to consider for biopsy?

✓ Acetowhite change on flat/slightly raised lesion

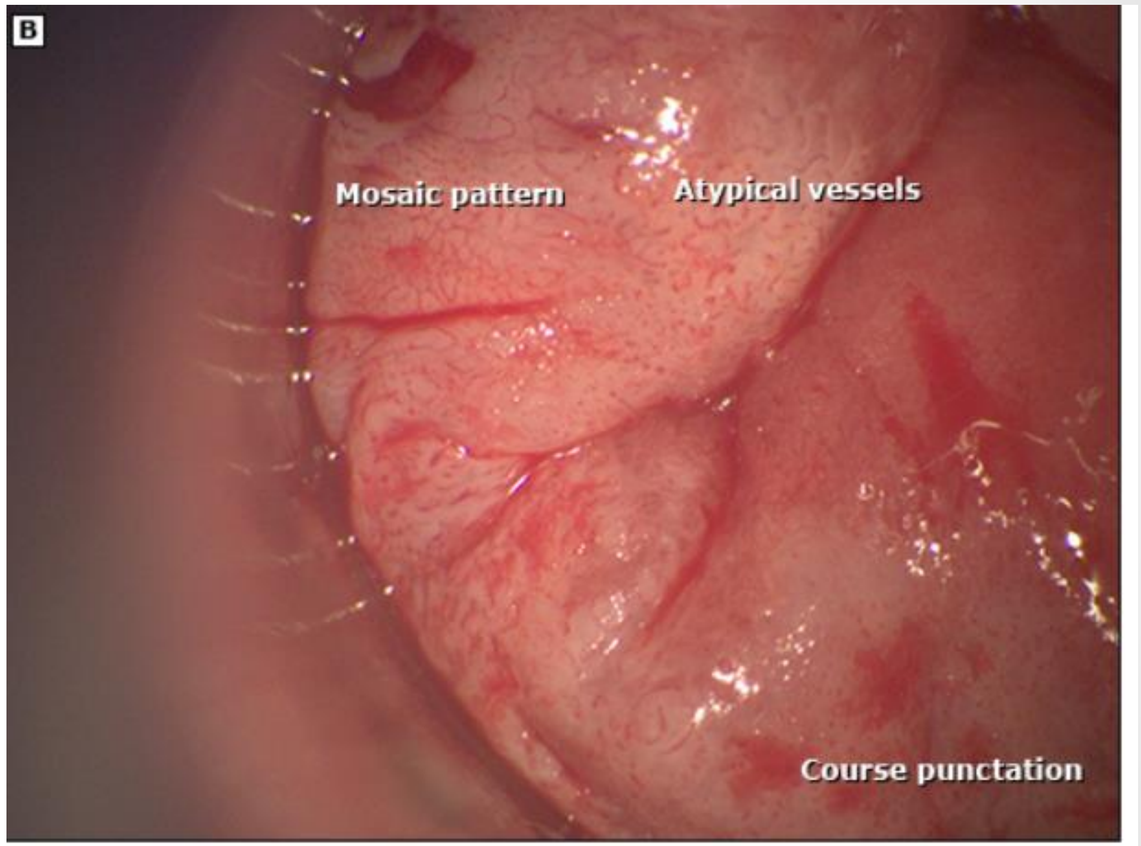
✓ Thickened abnormal blood vessels (mosaic pattern/punctuation)

✓ Tissues that do not take up Lugol stain

Abnormal features with acetic acid should be considered highly suspicious for HSIL if stained negatively with Lugol iodine.

High resolution anoscope (HRA)

A. Slightly raised, flat lesion with acetowhitening and coarse punctation after application of 5% acetic acid



B. Acetowhite, thickened lesion with vascular changes including coarse punctation, mosaic pattern and atypical vessels. consistent with HSIL and can also be seen with early invasion

Vaccination

- Routine vaccination, should ideally occur prior to the onset of sexual activity
- Advisory Committee on Immunization Practices (ACIP), recommend immunization with (HPV) vaccine of all males and females at age 11 to 12 years old, with vaccination starting as early as age 9 and continuing through age 26

- Conditional for adults ages 27 through 45 years old.

- Bivalent (HPV 16,18), quadrivalent (HPV 6,11,16,18) , 9-valent vaccine (HPV types 6, 11, 16, and 18 as well as types 31, 33, 45, 52, and 58)

- Still recommended even with evidence of prior HPV infection, as it can provide protection against HPV types not already acquired.
- Vaccination has no therapeutic effect on pre-existing HPV infection (including HSIL).

Treatment

- Intra-anal HSIL:

Small lesions (ie, <1 cm^2 at the base) or <50% of the circumference of (ATZ):
80% trichloroacetic acid (TCA) or targeted ablation in the office using infrared coagulation (IRC), radiofrequency ablation (RFA), or electrocautery/hyfrecation.

If there is concern for stenosis, these procedures may be undertaken in a stepwise manner.

topical therapies like the immune modulator imiquimod or 5% fluorouracil (FU) may be used in the anal canal

- Perianal HSIL:

Electrodessication and curettage, or excisional surgery

- LSIL including conylomata: Controversial, optional treatment (not precancerous,spontaneous resolution) vs mandatory treatment (may progress locally)

Clinical Trial > N Engl J Med. 2022 Jun 16;386(24):2273-2282. doi: 10.1056/NEJMoa2201048.

Treatment of Anal High-Grade Squamous Intraepithelial Lesions to Prevent Anal Cancer

Joel M Palefsky [1], Jeannette Y Lee [1], Naomi Jay [1], Stephen E Goldstone [1], Teresa M Darragh [1], Hillary A Dunlevy [1], Isabella Rosa-Cunha [1], Abigail Arons [1], Julia C Pugliese [1], Don Vena [1], Joseph A Sparano [1], Timothy J Wilkin [1], Gary Bucher [1], Elizabeth A Stier [1], Maribel Tirado Gomez [1], Lisa Flowers [1], Luis F Barroso [1], Ronald T Mitsuyasu [1], Shelly Y Lensing [1], Jeffrey Logan [1], David M Aboulafia [1], Jeffrey T Schouten [1], Juan de la Ossa [1], Rebecca Levine [1], Jessica D Korman [1], Michael Hagensee [1], Thomas M Atkinson [1], Mark H Einstein [1], Bernadette M Cracchiolo [1], Dorothy Wiley [1], Grant B Ellsworth [1], Cristina Brickman [1], J Michael Berry-Lawhorn [1]; ANCHOR Investigators Group

Methods: We conducted a phase 3 trial at 25 U.S. sites. Persons living with HIV who were 35 years of age or older and who had biopsy-proven anal HSIL were randomly assigned, in a 1:1 ratio, to receive either HSIL treatment or active monitoring without treatment. Treatment included office-based ablative procedures, ablation or excision under anesthesia, or the administration of topical fluorouracil or imiquimod. The primary outcome was progression to anal cancer in a time-to-event analysis. Participants in the treatment group were treated until HSIL was completely resolved. All the participants underwent high-resolution anoscopy at least every 6 months; biopsy was also performed for suspected ongoing HSIL in the treatment group, annually in the active-monitoring group, or any time there was concern for cancer.

Results: Of 4459 participants who underwent randomization, 4446 (99.7%) were included in the analysis of the time to progression to cancer. With a median follow-up of 25.8 months, 9 cases were diagnosed in the treatment group (173 per 100,000 person-years; 95% confidence interval [CI], 90 to 332) and 21 cases in the active-monitoring group (402 per 100,000 person-years; 95% CI, 262 to 616). The rate of progression to anal cancer was lower in the treatment group than in the active-monitoring group by 57% (95% CI, 6 to 80; P = 0.03 by log-rank test).

Conclusions: Among participants with biopsy-proven anal HSIL, the risk of anal cancer was significantly lower with treatment for anal HSIL than with active monitoring. (Funded by the National Cancer Institute; ClinicalTrials.gov number, NCT02135419.).

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ANCHOR trial

In the trial population (Persons living with HIV who were >35 years old)

-HSIL treatment reduced the risk of progression by **57%** (95% CI 6-80, p = 0.03).

-Progression to cancer at 48 months was **0.9%** for treatment Vs **1.8%** for active monitoring group.

Available modalities

- **<u>Topical therapies:</u>**

✓ **TCA** – More effective for small lesions.

✓ **Fluorouracil (FU)** – Can be applied by the patient

✓ **Imiquimod** – An immune modulator, can be self-applied

- **<u>Ablative therapies:</u>**

❖ **Infrared coagulation** – IRC. Ddirect application of a 1.5-second pulse of irradiation in the infrared range to the anal epithelium, which results in tissue destruction to a depth of approximately 1.5 mm.

❖ **Electrocautery ablation**: commonly used to treat anal HSIL. Some clinicians prefer it over IRC because it may be faster, particularly for large and keratotic lesions. It is also easier to use than IRC for perianal disease. Its efficacy profile appears to be similar to IRC.

❖ Argon plasma coagulation (**APC) and** radiofrequency ablation **(RFA)** – are less commonly used ablative modalities.

Randomized Controlled Trial > Lancet Oncol. 2013 Apr;14(4):346-53.
doi: 10.1016/S1470-2045(13)70067-6. Epub 2013 Mar 15.

Comparison of imiquimod, topical fluorouracil, and electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive men who have sex with men: an open-label, randomised controlled trial

Olivier Richel [1], Henry J C de Vries, Carel J M van Noesel, Marcel G W Dijkgraaf, Jan M Prins

Affiliations + expand

PMID: 23499546 DOI: 10.1016/S1470-2045(13)70067-6

Findings: Between Aug 12, 2008, and Dec 1, 2010, we screened 388 HIV-positive MSM for AIN by high resolution anoscopy. Of the 246 (63%) patients who had AIN, 156 (63%) were randomly assigned to either receive imiquimod (54 patients), topical fluorouracil (48 patients), or electrocautery (46 patients) following withdrawing of consent by eight patients. Modified intention-to-treat analysis showed a complete response in 13 (24%, 95% CI 15-37) patients in the imiquimod group, eight (17%, 8-30) of patients in the fluorouracil group, and 18 (39%, 26-54) of patients in the electrocautery group (p=0·027). At week 24, 11 (22%) of 50 responders had recurrence; at week 48, 22 (46%) of 48 had recurred; and at week 72, 30 (67%) of 45 had recurred. Recurrence was observed at 72 weeks in 10 (71%) of 14 patients treated with imiquimod, seven (58%) of 12 patients treated with fluorouracil, and 13 (68%) of 19 patients treated with electrocautery. Grade 3-4 side-effects were noted in 23 (43%) of 53 patients in the imiquimod group, 13 (27%) of 48 patients in the fluorouracil group, and eight (18%) patients in the electrocautery group (p=0·019). The most common side-effects were pain, bleeding, and itching. Seven serious adverse events occurred, all not related to the study.

Interpretation: Electrocautery is better than imiquimod and fluorouracil in the treatment of AIN, but recurrence rates are substantial.

24% imiquimod, 17% in FU, and 39% electrocautery group.

Treatment

- lesions that are too large for office-based local ablation, a combination of initial HRA-guided surgical destruction in the OR with office-based ablation may be effective.
- In general, the HRA-guided surgical destruction is ablation unless there is concern for invasive malignancy, in which case, excision is attempted

Surveillance

- HSIL recurrence over time is high in high-risk patients and surveillance is recommended.

- Surveillance with HRA

- No optimal schedule has been established.

- Most institutions do follow up every 4-6 months.

- Anal cytology may also be useful as an adjunctive test.

- When HRA is not available, DRE should be offered to patients at risk.

Summery

Primary Prevention

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Gender neutral prophylactic HPV vaccination prior to sexual debût

Secondary Prevention

↓

Discussion of risk with all high-risk patients (Grade B)

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Aim: aHSIL diagnosis and management[1, 2]

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HRA-based assessment

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aHSIL not detected → **Surveillance**

aHSIL detected → **HSIL treatment[1]**

Tertiary Prevention

↓

Discussion of risk with all high-risk patients (Grade B)

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Aim: early cancer diagnosis and treatment

↓

DARE at regular intervals (Grade B)

[1] Grade A for PLWH ≥ 35 yo

[2] Typically includes screening tests such as anal cytology +/- HPV testing

Sources

- ASCRS 2018 guidelines

- CDC 2021 reviewed guidelines. Anal Cancer Screening and Prevention: Summary of Evidence Reviewed for the 2021 Centers for Disease Control and Prevention Sexually Transmitted Infection Guidelines

- ANCHOR Trial. Palefsky, Joel M et al. “Treatment of Anal High-Grade Squamous Intraepithelial Lesions to Prevent Anal Cancer.” *The New England journal of medicine* vol. 386,24 (2022): 2273-2282. doi:10.1056/NEJMoa2201048

- Richel, Olivier et al. “Comparison of imiquimod, topical fluorouracil, and electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive men who have sex with men: an open-label, randomised controlled trial.” *The Lancet. Oncology* vol. 14,4 (2013): 346-53. doi:10.1016/S1470-2045(13)70067-6

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Thank you