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Vulvar and Vaginal Dysplasia: Management and Updates

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Disclosures

- Conflict of Interest
  - No financial relationships or conflict of interest to disclose

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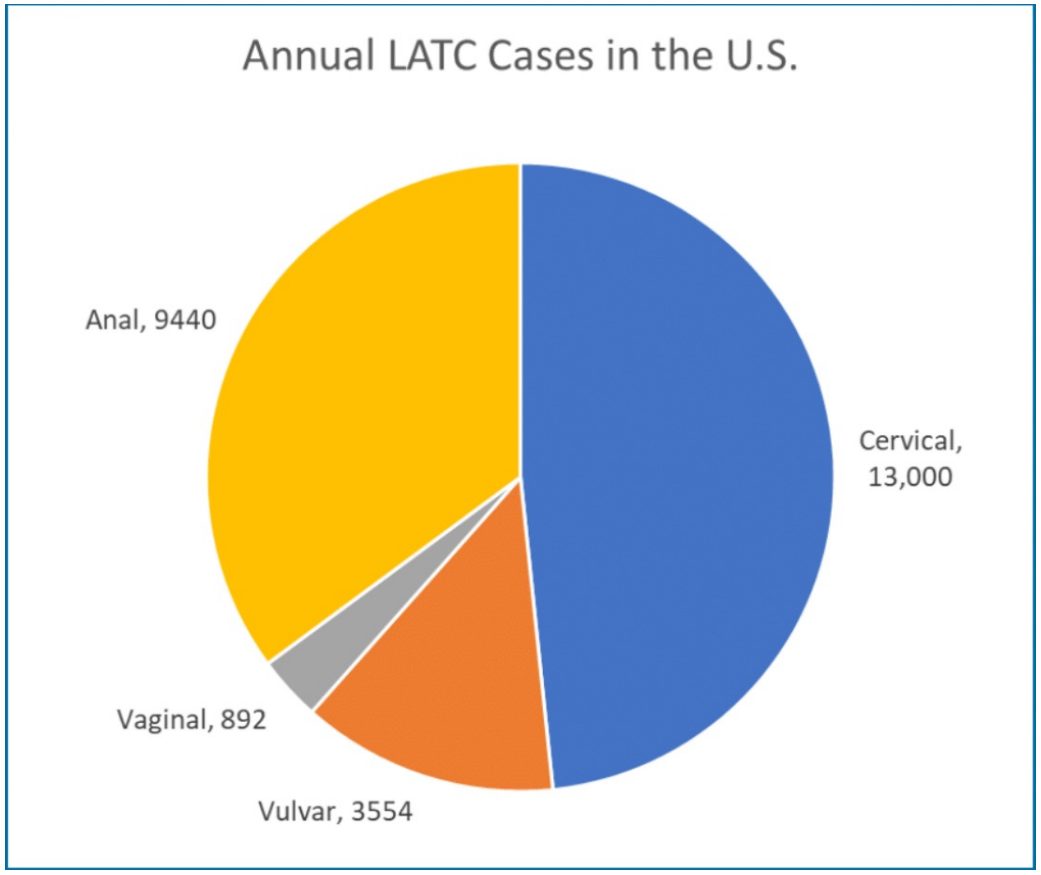
Objectives

1. Review epidemiology and pathogenesis of vulvar and vaginal dysplasia

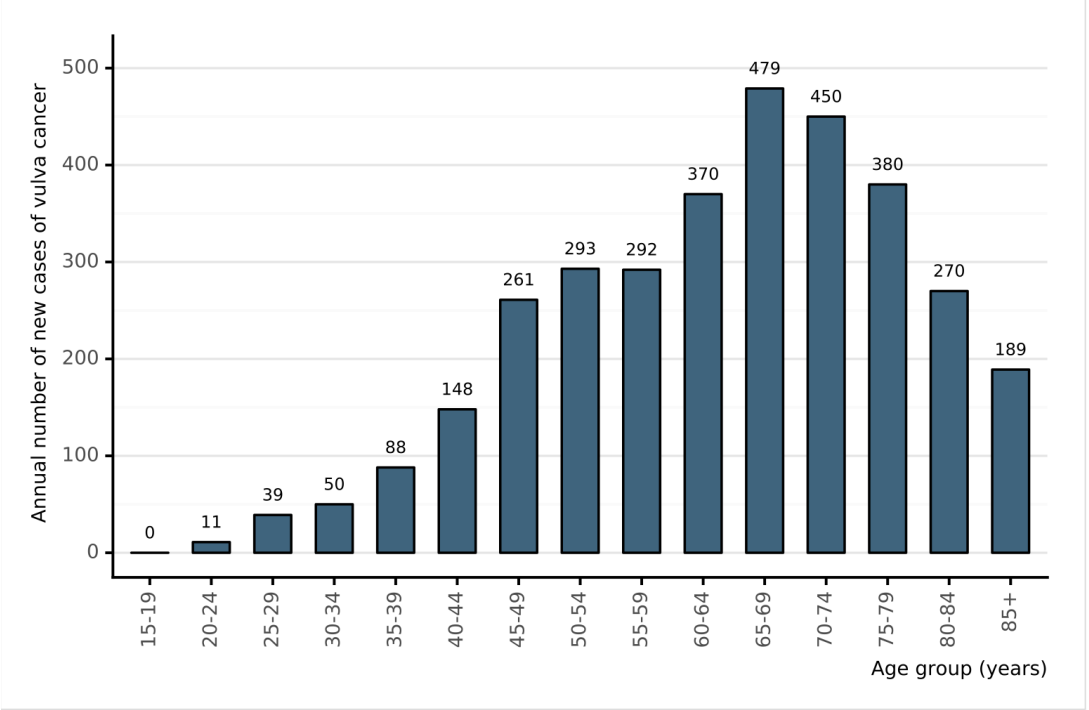
2. Discuss current strategies and updates in the management of vulvar and vaginal dysplasia

Lower Ano-Genital Tract Cancers (LATC)

- Squamous cell carcinoma accounts for 80-90%
- High rates of HPV-positivity
- Risk of LATC increases with age



Vulvar Cancer in USA



- Annual number of new cases: 6900
- Cumulative risk (%) at age 75: 0.03%
- Annual number of deaths: 1630

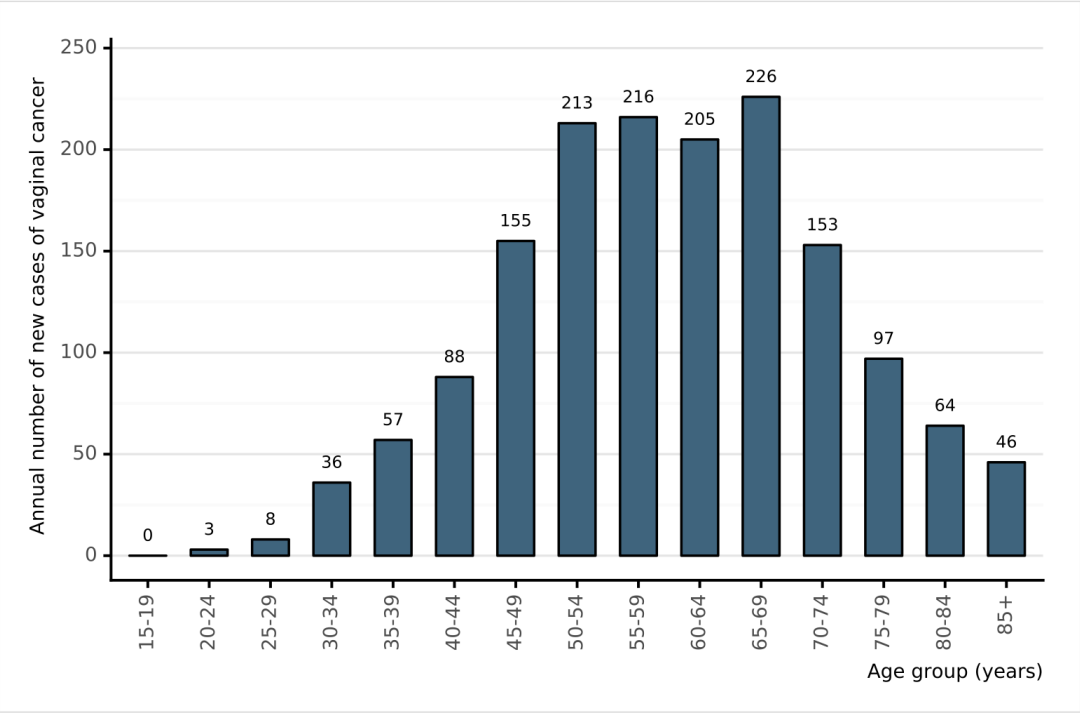
Vulvar Cancer

- HPV-associated vulvar cancers:
  - Have warty and basaloid patterns
  - Are typically undifferentiated
  - Found in younger women with similar risk factors for cervical cancer
  - Have higher overall survival rates and lower risk of recurrence than non-HPV associated vulvar cancers
- HPV independent vulvar cancers:
  - Primarily driven by inflammatory precoursors
  - Usually multifocal
- Melanoma
  - Have the worst prognosis

Risk Factors: Vulva

Family Health History	Prior Health History
• Rare genetic conditions (WHIM), Fanconi anemia • Primary immune deficiencies	• HPV infections (especially 16/18) • Genital condyloma • Anogenital tract dysplasia or cancer • Solid organ transplant recipient • Lichen sclerosus, Paget's disease, lichen planus • ESR

Vaginal Cancer in USA



- Annual number of new cancer cases: 8650
- Cumulative risk at 75 years old: 0.02%
- Annual number of deaths: 1870

Vaginal cancer

- Primary vaginal cancer: 1-2% of all gynecologic cancers
- 90% squamous cell in origin
  - Most commonly HPV-related
  - Other types: clear cell adenocarcinomas and melanoma
- Incidence rates have been stable over time

- Risk of vaginal cancer increases for patients with history of:
  - CIN 3/AIS (SIR 18.5)
  - Cervical cancer (SIR 8)
  - DES Exposure (SIR 40.7)
- Risk remains increased even after hysterectomy

Risk Factors: Vagina

Hormonal	Family Health History	Prior Health History
• DES exposure in utero (OR 1.9)	• Rare genetic conditions (WHIM), Fanconi anemia • Primary immune deficiencies	• HPV infection • Genital condyloma • Anogenital tract dysplasia or cancer • Solid organ transplant recipient

Lessons from the cervix

- High Grade Squamous Intraepithelial Lesions (HSIL) is the vulvar/vaginal precursor lesion
- Natural history of HPV, HSIL, and vulvar cancer is similar to cervical HPV, HSIL, and cervical cancer

- Hypothesize that:
  - Identification of HSIL -> treatment of HSIL -> prevent progression to lower genital tract cancer

Different from the cervix: Screening

- There are no studies of screening for vaginal or vulvar cancers in average risk patients
- No guidelines for screening for vulvar cancer in any patient population
- ASCCP recommends against screening for vaginal cancer after hysterectomy for benign disease

- ** ASCCP **does recommend** screening with vaginal cytology after hysterectomy for cervical dysplasia or cancer

Prevention and Risk Reduction

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HPV vaccination

The single most powerful prevention against lower anogenital tract cancers

HPV Vaccination: Vulva/Vagina

- 100% effective against VAIN 2+/VIN 2+ without prior HPV exposure
- 79% effective against VAIN2+/VIN 2+ with prior HPV exposure

- Epi studies from Denmark demonstrate a decrease in vulvar/vaginal cancers post-introduction of HPV vaccine

Garland SM, 2007; Rasmussen, 2020; Bertoli 2020

Treatment of Cancer Precursors: Average-Risk People

- Little data regarding treatment of VaIN, VIN
- Extrapolated from cervical studies
- Systematic review of 3,322 cases
  - 9% HSIL VIN progressed to cancer if untreated
  - 3% HSIL VIN progressed to cancer if treated

Treatment is recommended for all vulvar and vaginal HSIL lesions

American College of Obstetrics and Gynecology (ACOG)	European College for the Study of Vulval Disease (ECSVD)
ASCCP	European Federation for Colposcopy (EFC)
European Society of Gynaecological Oncology (ESGO)	International Society for the Study of Vulvovaginal Disease (ISSVD)
Society of Gynecology Oncology (SGO)	


Treatment of Vulvar and Vaginal HSIL
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HSIL of the Vulva

Acceptable treatment modalities:

- Surgical excision
- Ablation (CO_2 laser, argon beam, cavitational ultrasonic surgical aspiration)
- Electrosurgical excision
- Medical Therapy: imiquimod
  - ? Utility: 5-FU, Cidofovir, Photodynamic therapy (eg aminolevulinic acid)

Factors influencing treatment decisions

- Management plans must be individualized by patient
- Important variables to consider in making management plan:
  - Histologic features on biopsy
  - Distribution of disease
    - Size
    - Location
  - Patient's risk of progression
    - Age
    - Immunosuppression

Consider importance of preservation of normal anatomy, symptom relief, maintenance of quality of life and sexual function

Vulvar HSIL may be associated with invasive cancer

Risk of occult cancer from wide local excision of vulvar HSIL surgical specimen is 11-22%

Pretl, J Gyn Onc, 2017; Thuis, Int J Gyn Onc, 2000; Husseinzadeh, Gyn Onc, 1999; Modesitt, Ob Gyn, 1998

Surgical excision Vulvar HSIL

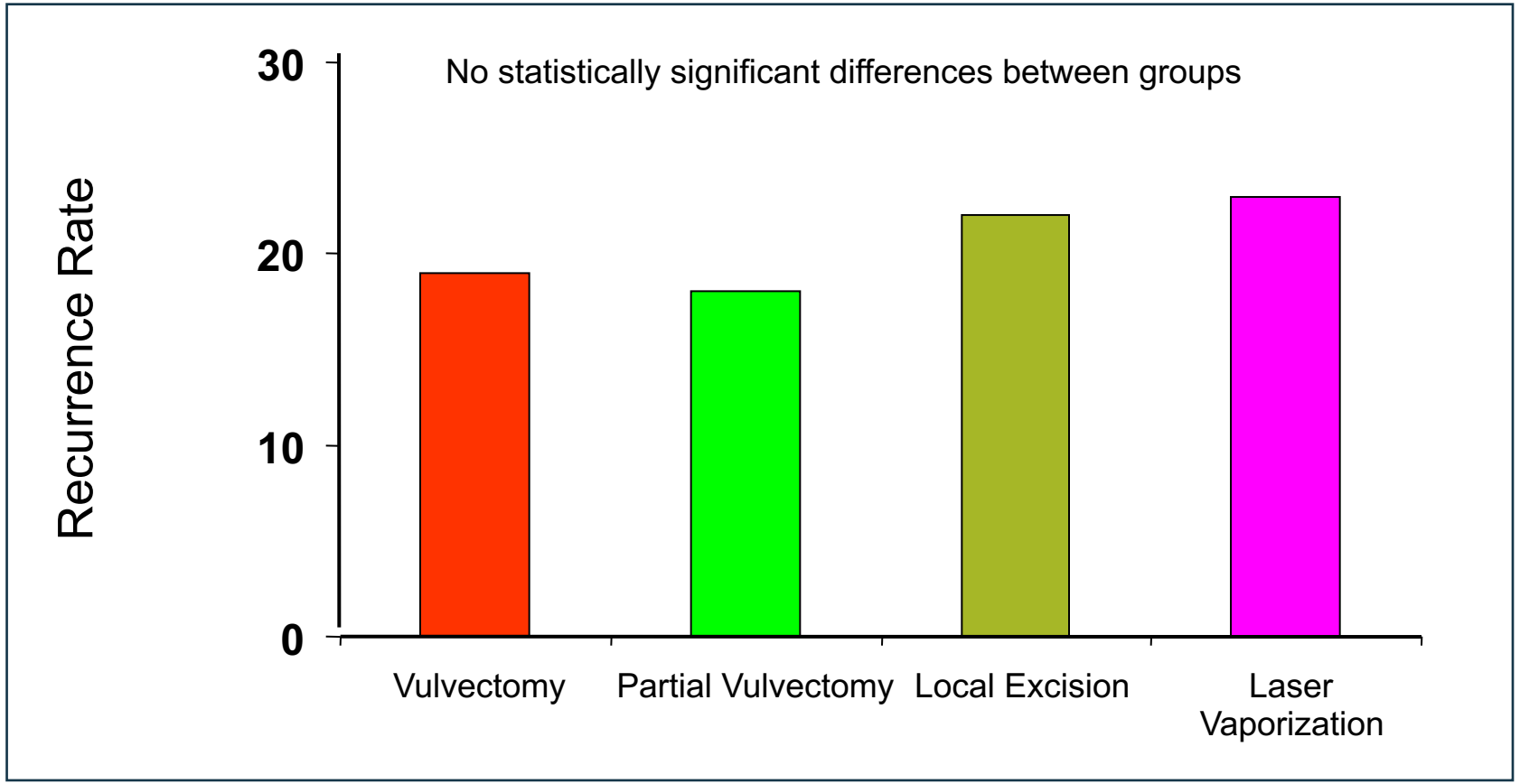
- Margins– 1cm if able
- Depth
  - Hair bearing areas to 2.7 mm
  - Non-hair bearing = 0.1 to 1.9 mm (average = 0.5 +/- 0.2 mm)

Risk of Recurrence

- Ranges from 6 to 50% post treatment
- 50% recurrence reported within 16.9 months post-surgery
- Influential factors:
  - Margin status
  - Duration of follow-up
  - VIN type
  - Patient factors
    - Multifocal disease
    - Immunosuppression
    - Smoking

Recurrence After Treatment

(mean follow-up 39 months)



Gynecologic Oncology. 2005; 97: 645-651

Margin Status

	Recurrence	No Recurrence	P-value
Number	22	37	
Average age (yr)	42	47	0.23
Positive margins	18 (82%)	21 (57%)	0.05
Negative margins	3 (14%)	15 (41%)	0.03

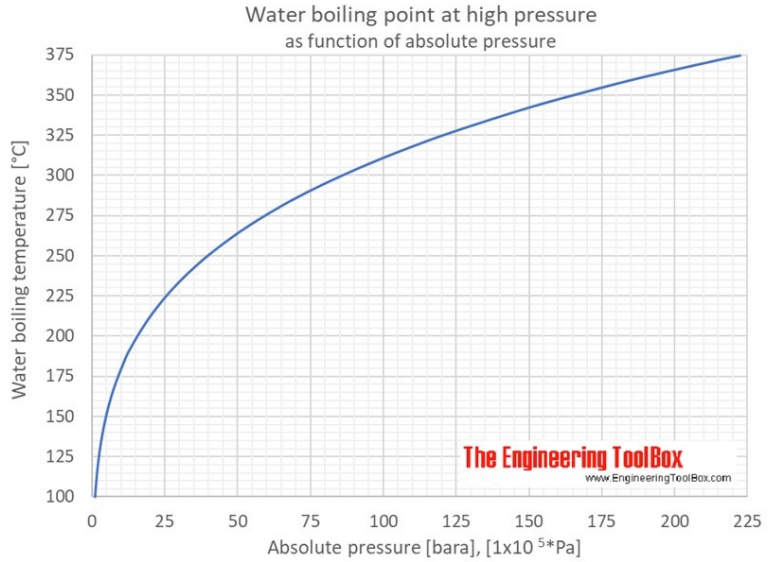
Median Time to recurrence:
Positive margins 22 months
Negative margins 44 months

Vulvar Ablative Techniques: CUSA

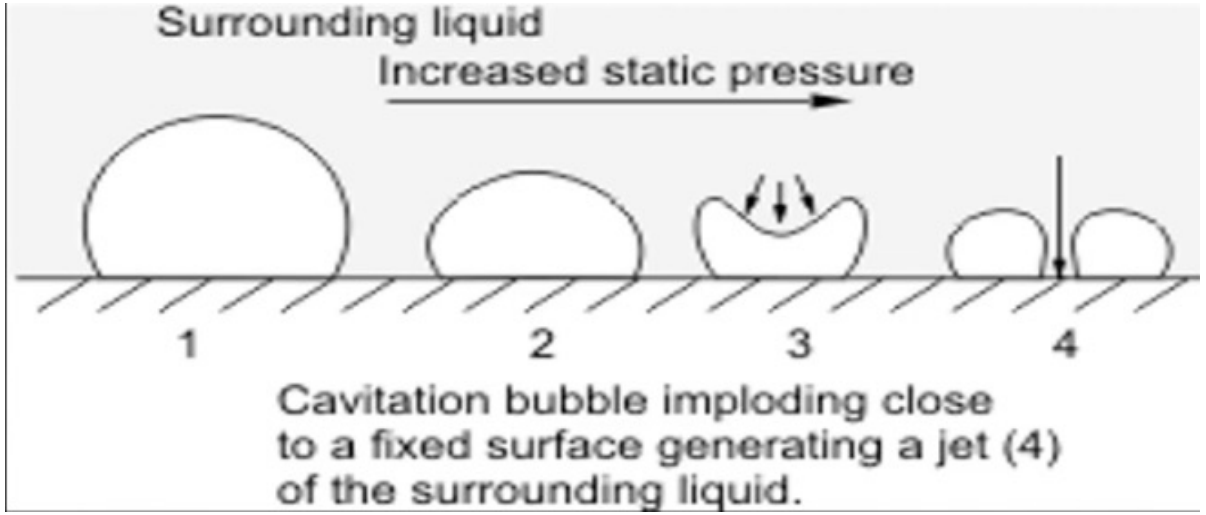
- Cavitational ultrasonic surgical aspiration
- Generates ultrasonic waves in the range of 23 kHz to produce tissue cavitations
- Tissue fragmentation is accomplished by a hollow titanium tip that vibrates up to 23,000 times per second
- An irrigating fluid is delivered through the handpiece to create an emulsion while suction is provided through another portal to aspirate tissue and provide a clean operative site

CUSA Principle

- High speed mechanical waves can be used in non-elastic media, such as water, to create a cavitation effect
- Cavitation is the process of boiling a liquid (vapour formation) as a result of pressure reduction rather than heat addition
- Tissues with weak intracellular bonds and high water content, such as tumors and lipomas, are easy to fragment, whereas tissues with strong intracellular bonds, such as nerves and vessel walls, resist fragmentation.



CUSA Principle



- The ultrasonic aspirator has

two rupturing effects at the tissue interface:

- SUCTION EFFECT: couples tissue to the tip and forces impacted tissue to vibrate, accelerate, and decelerate with the tip, eventually fragmenting away from nonaffected tissues.
- CAVITATION: rapidly oscillating tip produces localized pressure waves, which cause vapor pockets around cells in tissues with high water contents; the collapse of these pockets causes the tissue cells to rupture.

Vulvar Ablative Techniques: CO2 Laser

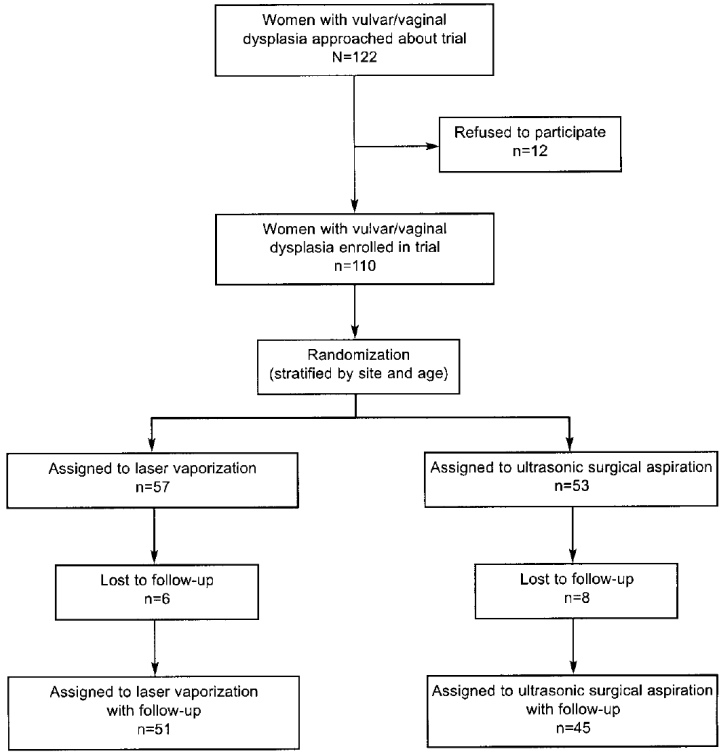
- 10,600 nanometer wavelength laser
- Heat injury
- Ablation of epidermis and dermis to the basement membrane
- Causes inflammatory healing response

- Challenges:
  - Special credentialling
  - Equipment
  - Fire risk

CUSA versus CO2 Laser

- Randomized control trial, single-site
  - 96 women completed 1 year of followup

	Laser (N=51)	CUSA (N=45)	Relative Risk (95% CI)
No evidence of dysplasia	38 (74.5%)	34 (75.6%)	0.96 (0.64-1.50)
Presence of dysplasia (bx)	13 (25.5%)	11 (24.4%)	



- Recurrence higher in VIN than VaIN patients

CUSA vs. CO2 Laser

- *Pain decreased in patients treated by ultrasonic surgical aspiration*
- *Presence of scarring significant reduced compared to CO2 laser treatment*

Table 2. Adverse effects and Visual Analog Scale Pain Scores by Treatment Group

	Laser (n=51)	USA (n=45)	P*
VAS pain scale (mm)	35.1±4.9	20.7±4.3	.032†
VAIN	46.5±5.8	36.7±6.6	
VIN	23.6±5.8	7.6±5.9	
Presence of scarring (VIN only)	6/22 (27)	0/20 (0)	.012
Infection (yeast, UTI, other)	8 (16)	5 (11)	.513
VAIN	5	3	
VIN	3	2	
Dysuria, burning	6 (12)	6 (13)	.817
VAIN	0	1	
VIN	6	5	
Adhesions	2 (4)	2 (4)	.898
VAIN	1	2	
VIN	1	0	
Abnormal discharge	6 (12)	2 (4)	.195
VAIN	3	1	
VIN	3	1	
Other	3 (5.9)	2 (4.4)	.75
Eschar	2	2	
Vaginal petechiae	1		

USA, ultrasonic surgical aspiration; VAS, visual analog scale; VAIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; UTI, urinary tract infection.
Data are n, n (%), or mean±standard error of the mean.
* Chi-square test for proportions.
† Independent samples *t* test.

Topical Therapy: Imiquimod treatment of vulvar HSIL

- Systematic review with 162 patients
  - Complete response rate → 51%
  - Partial response rate→ 25%
  - Recurrence rate →16%
  - Side effects mostly site inflammation
    - Mild to moderate erythema or erosions

Mahto M, et al. Int J STD AIDS 2010; 21:8.

Followup after Treatment

- Patients should be seen on a regular basis for clinical assessment
  - Biopsy any suspicious areas
- Life long surveillance is likely recommended
- Follow up modulated according to risk of recurrence (type of lesion, patient's age, and immunological conditions)

HPV-associated HSIL: Risk of Progressive Disease

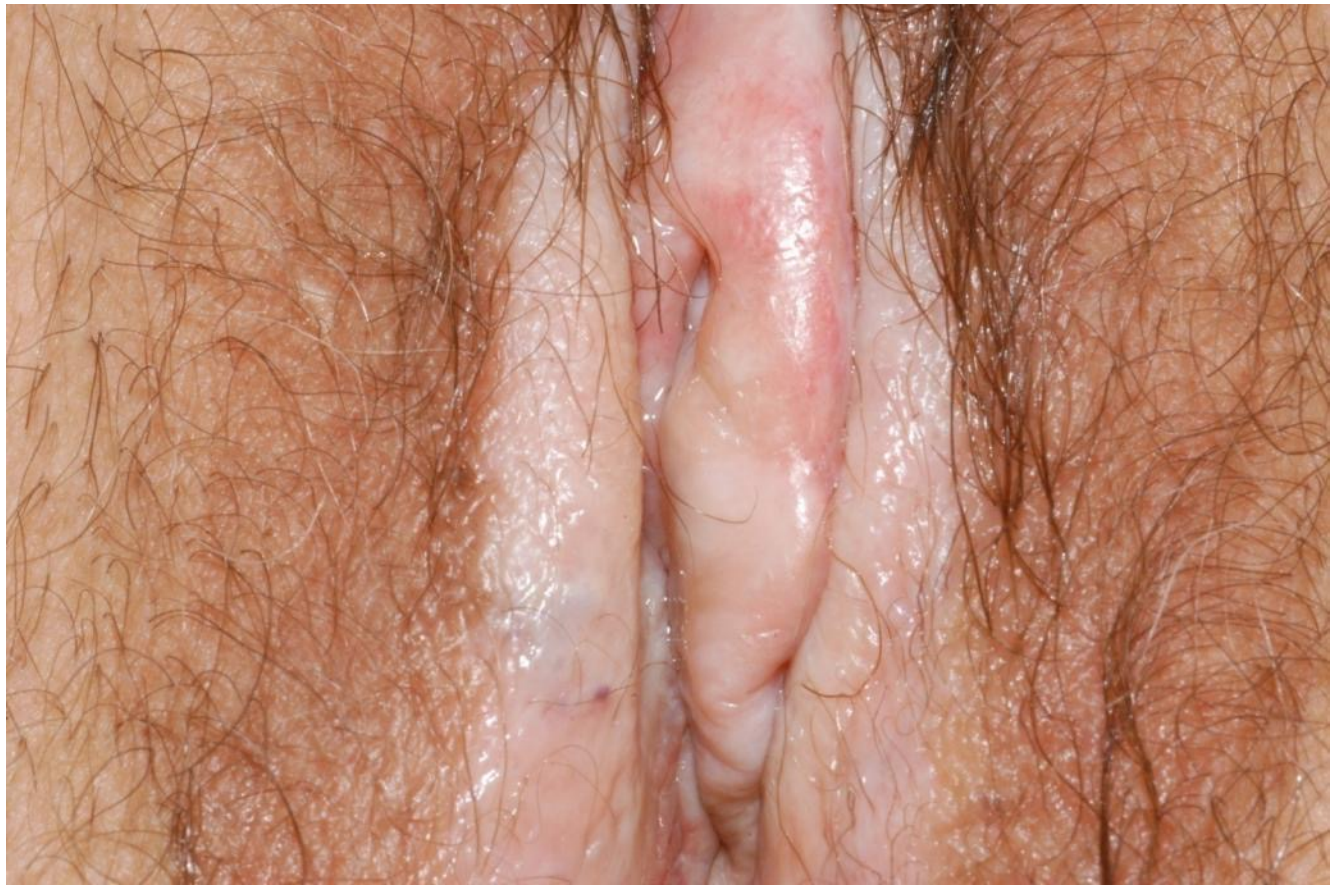
- Untreated HSIL → significant invasive potential
  - Particularly in women over 30[1]
- Untreated vulvar HSIL progression to invasive cancer ≥10% per year
  - Only about 2% for CIN 3[2]
- Lifetime risk of invasive vulvar cancer after treatment for HSIL = 3% to 6%
  - Only 0.3% to 0.4% for CIN 3[1]

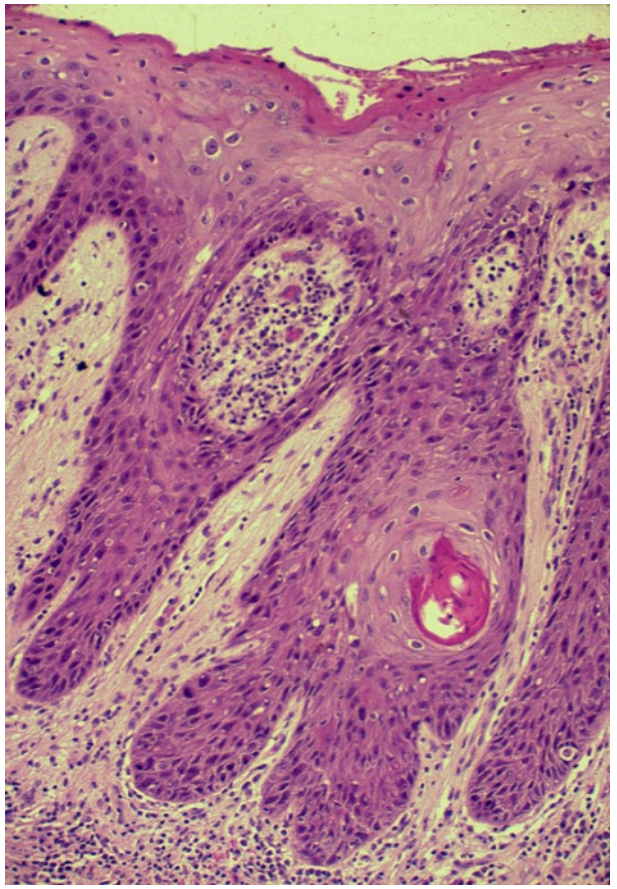
1. Jones RW et al. *Obstet Gynecol* 2005; 106: 1319–26
2. 2.Jones RW. *Eur J Gynaecol Oncol* 2001; 22: 393–402

Differentiated VIN

ISSVD 1986	ISSVD 2004	LAST 2012
VIN 1	Flat condyloma or HPV effect	LSIL
VIN 2	VIN, usual type a.VIN, warty type b.VIN, basaloid type c.VIN, mixed (warty/basaloid) type	HSIL
VIN 3		
Differentiated VIN	VIN, differentiated type	

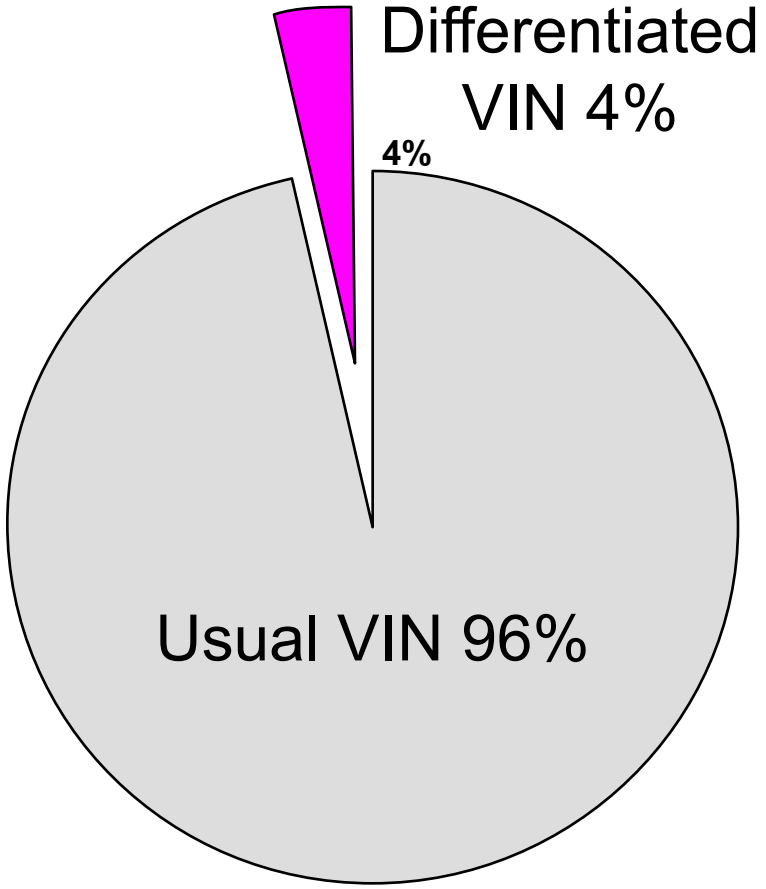
VIN differentiated





T Wright, MD collection

dVIN diagnosed infrequently compared to vulvar HSIL (Usual VIN)



European Journal of Cancer. 2009; 45: 851-856

dVIN prevention: Treatment of Lichen Sclerosus

- Prospective study of LS treated with high potency topical steroids (HPTS):
  - N = 507
  - Followup 4.7 years
  - Compliant group: 0 with VIN 2+
  - Partially compliant/non-compliant – 7 (4%) with VIN 2+ (3 cancers)
  - P < 0.001

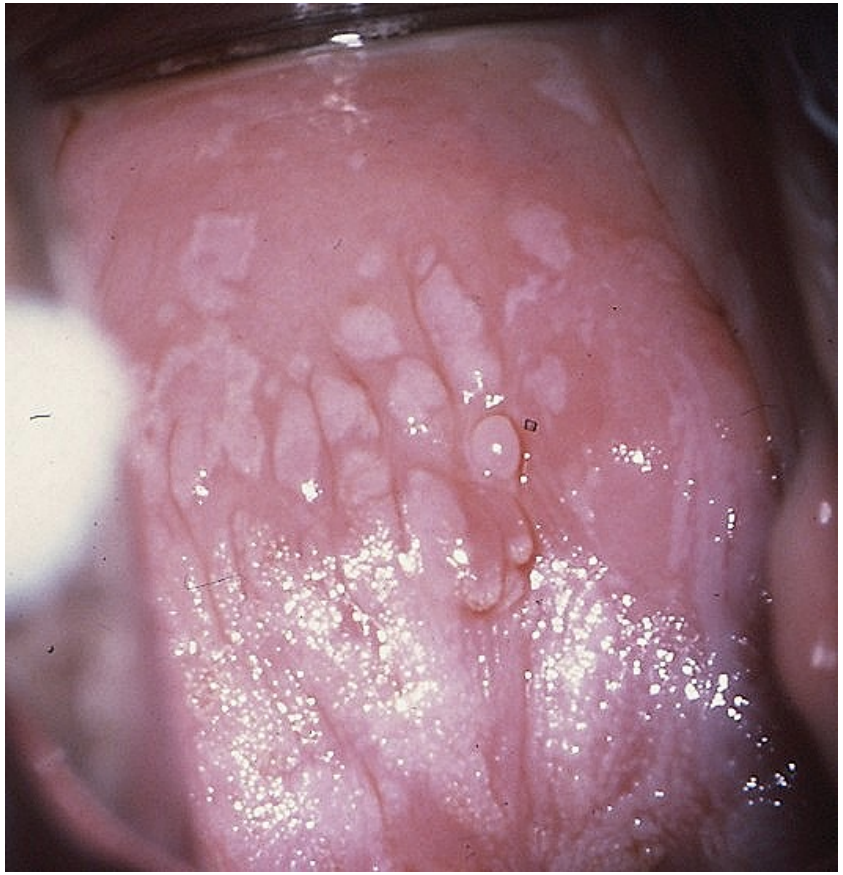
- ACOG endorses British Association of Dermatologist guidelines:
  - 3 months of medium to high potency steroids
  - Individualize use of of long term maintenance therapy

Vaginal Dysplasia

How is VaIN Diagnosed?

- Most diagnosed on colposcopy for abnormal Pap (> 80%)
- Colposcopy of the vagina after diagnosis of other anogenital lesions
- Lesion found on pelvic exam
- > 90% asymptomatic but may report postcoital bleeding or unusual vaginal discharge

Treatment of Vaginal LSIL



C Conageski, MD collection

- No management guidelines for VaIN at ASCCP Consensus Conference
- Progression risk smaller than cervical LSIL - be conservative
- Treatment of all low grade disease almost impossible
- Studies support the observational approach to Vulvar - LSIL

Treatment of VaIN

- Excision: Vaginectomy or partial vaginectomy
  - Local excision
  - Electrosurgical loop excision
- Ablative techniques
  - Carbon dioxide (CO2) laser, CUSA
  - Photodynamic therapy
  - Electrocoagulation

VaIN Excisional Therapy

- Provide specimen for histopathological evaluation and diagnosis; may effectively rule out cancer

- Wide local excision associated with lowest risk recurrence
  - Limited by applicability due to high prevalence of multifocal disease
  - Success rates 66 to 80%
- Partial upper vaginectomy
  - Treatment of choice for high grade VaIN at the apical part or in the region of the vaginal cuff scar

- Total vaginectomy: NOT Recommended

VaIN Ablative Therapy

- Depth of destruction
  - General thickness less than 1 mm
  - Mean thickness of the total epithelium was 0.4 mm
  - Thickness did not differ between grades of VaIN

- Laser depth 1 – 1.5 mm
  - Larger spot sizes and the superpulse mode are used to avoid deep penetration and the conduction of excessive heat.

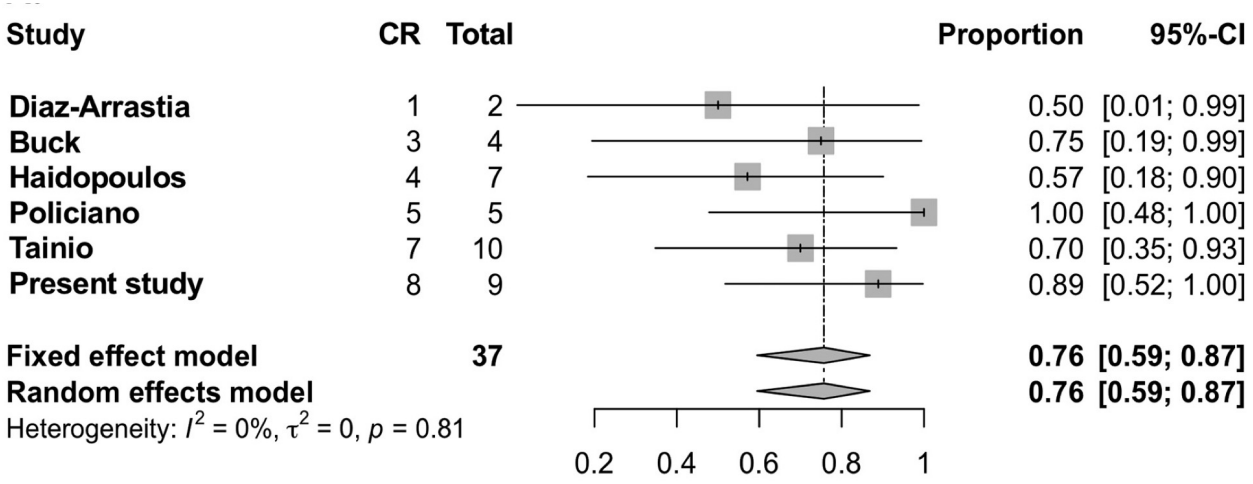
VaIN Ablative Therapy

- CUSA is a safe and effective option for treatment of VaIN
  - Allow exact removal of epidermal or mucosal lesions without thermal or mechanical damage to surrounding structures or underlying stroma.

- Prospective study
  - 92 patients underwent CUSA for VaIN
  - Median follow up 4.5 years
  - Cure rate 80.4%
  - No adverse events

VaIN Medical Therapy: Imiquiod

- Mechanism of Action:
  - Immune response modifier
  - Induces cytokines, simulates natural killer cells
  - Promote maturation and activity of Langerhans cells
  - Increases effectiveness of T-cell mediate response
- Metanalysis (5 articles, 29 women)
  - Complete response (histologically proven clearance of VaIN): 0.76
  - Response rates (rate of patients who showed CR or any response): 0.89



VaIN Treatment: 5-FU

- Cure rates from 62.5 – 86%
- Limited by side effects: vaginal discharge, burning, pain or ulcers and therefore reduced compliance
- Would NOT use this as first line

Choice of Therapy

- Individualized based on patient characteristics, extent of disease, number of lesions, location of lesions

- Recurrence rates
  - Topical treatment 20-62.5%
  - Laser ablation 26.4%
  - Excision 32.7%
  - Radiotherapy 0%

Kim MK 2018

Questions?

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THANK YOU