Management of Pre-invasive Vulvar and Vaginal Lesions

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Overview

• Review management of vulvar intraepithelial neoplasia
• Review patient-administered treatments for genital warts
• Review management of vaginal intraepithelial neoplasia

Committee Opinion

Management of Vulvar Intraepithelial Neoplasia

Included in the 2017 ABOG MOC articles

I have no financial conflicts of interest
**SCOPE OF THE PROBLEM**

- Vulvar disease is an increasingly common problem
- From SEER, the rate of in situ vulvar disease has increased 4-fold since 1973
- But it remains relatively rare: 3/100,000 women/year (10 fold lower than CIN)

**TERMINOLOGY FOR VIN**

- The old terminology for vulvar disease matched that for cervical disease:
  - Vulvar intraepithelial neoplasia (VIN)
    - VIN 1 (corresponding to mild dysplasia)
    - VIN 2 (corresponding to moderate dysplasia)
    - VIN 3 (corresponding to severe dysplasia/carcinoma in situ)

**TERMINOLOGY**

- In 2004 ISSVD* changed the VIN terminology to be used only for high grade disease
- subdivided VIN into 2 categories:
  - **Usual type VIN** (associated with HPV, immunocompromise, smoking). There are 3 categories of usual type VIN: warty, basaloid or mixed
  - **Differentiated type VIN** (associated with vulvar dermatoses such as lichen sclerosus, and more likely to be associated with squamous cell cancer)

*ISSVD= International Society for the Study of Vulvovaginal Disease

**TERMINOLOGY**

- LSIL: Low grade squamous intraepithelial neoplasia
- HSIL: High grade squamous intraepithelial neoplasia
TERMINOLOGY

• In 2015 the ISSVD changed terminology to unify nomenclature with WHO, ACOG and ASCCP:
  – **Vulvar LSIL** (external genital warts, condyloma, HPV effect, VIN 1)
  – **Vulvar HSIL** (precancer, usual type VIN)
  – **Differentiated VIN** (remains the same)

NATURAL HISTORY

• Vulvar HSIL is considered a true cancer precursor
• 16% of women with untreated vulvar disease progressed to cancer
• Occult invasive cancer was present in 3% of excisions performed for VIN
• Women with a history of vulvar HSIL remain at increased risk of recurrent disease and vulvar cancer throughout their lifetime

RISK FACTORS

<table>
<thead>
<tr>
<th>Vulvar cancer</th>
<th>Vulvar HSIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection with high risk genital HPV types</td>
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<tr>
<td>Age &gt; 50</td>
<td>Age &lt; 50</td>
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<tr>
<td>Smoking</td>
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<td>HIV infection</td>
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<tr>
<td>Immune suppression</td>
<td>Immune suppression</td>
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DIAGNOSIS

• There is no screening strategy for prevention of vulvar cancer
• Detection of vulvar LSIL and HSIL is based on visual inspection with biopsy as needed
Vulvar biopsy: technique

- Topical anesthesia (optional)
  - Lidocaine gel (2-5%) to skin before biopsy
  - Hurricane spray
  - Ice
- Application of antiseptic solution (acetic acid, Lugol’s solution, betadine)

Vulvar biopsy: technique

- 1-2% lidocaine
  - Consider buffering by adding bicarbonate solution 1 part bicarbonate (7-10%) to 9 parts of lidocaine
  - Inject superficially
  - Smallest needle available: 27-30 gauge

Vulvar biopsy: technique

- Instrument options
  - Keyes dermatologic punch: typical options are 3-5 mm diameter
  - Don’t go too deep
  - Use scissors or scalpel to excise base
  - Suture not usually necessary

Vulvar biopsy: technique

- Instrument options
  - Cervical punch forceps (e.g. Baby Tischler)
  - Center over the area of interest
Vulvar biopsy: technique

• Instrument options
  – Forceps and scissors
  – Scalpel

Vulvar biopsy: technique

• Hemostasis
  – Pressure and time
  – Silver nitrate or Monsel’s
  – Suture (3.0 or 4.0)

DIAGNOSIS

• Biopsy is indicated for visible lesions in which:
  – A definitive diagnosis cannot be made clinically
  – Appearance suggests possible malignancy
  – There are atypical vascular patterns
  – The lesion was previously stable but changes rapidly in color, border or size

ACOG 2016

DIAGNOSIS

• Expert opinion is varied as to the need for biopsy of women with warty lesions, but is indicated if
  – suspected condyloma do not respond to topical therapy
  – in postmenopausal women with apparent genital warts

ACOG 2016

DIAGNOSIS

• Colposcopy of the vulva can be useful
  – in women with no visible lesion but with focal symptoms (pain, itching)
  – in women who remain symptomatic after appropriate treatment for vulvovaginitis
  – To delineate the extent of disease

ACOG 2016
### DIAGNOSIS
- Colposcopy of the vulva requires longer application of acetic acid (3-5%)
- Usual colposcopic features seen on the cervix (punctuation, mosaicism) are not usually present on vulva

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### TREATMENT of VULVAR HSIL
- Vulvar HSIL is considered a true cancer precursor
- 16% of women with untreated vulvar disease progressed to cancer
- Therefore treatment is recommended for vulvar HSIL
- Treatment can be with excision, laser ablation or topical imiquimod (off-label use)

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### TREATMENT: Excision
- Wide local excision is indicated in cases in which invasion is suspected from the clinical or pathological impression, even if a biopsy only shows vulvar HSIL
- Margins of 0.5-1.0 cm are recommended, although this may need to be modified to avoid injury to structures such as the urethra, clitoris, anus etc.

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### TREATMENT: Laser
- Laser is acceptable if cancer is not suspected
- Use of appropriate power density and micromanipulator or hand piece allow precise ablation without deep coagulation injury
- Ablation of vulvar LSIL can be more superficial confined to the lesions, whereas ablation of vulvar HSIL should extend through the full thickness of the epithelium and extend into hair follicles in hair-bearing areas

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TREATMENT: 5% imiquimod

- Off-label use with well-documented efficacy in randomized trials
- Applied to lesions 3x weekly for 12-20 weeks
- Assessment at 4-6 week intervals
- Side effects can be severe erythema and pain, at which point therapy should be terminated
- Mechanism of action is to activate local immune response, therefore may have reduced efficacy in immunosuppressed women

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TREATMENT: Other medical therapies

- 5% 5-fluorouracil (effudex) cream- used frequently in the 1970s and 80s, has fallen out of fashion and there are no recent studies about efficacy
- Topical cidofovir cream is under investigation. At this point it needs to be formulated into a cream base by the pharmacy and is expensive.

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RECURRENCE AFTER TREATMENT

- Cure rates range from 50-90%
- Women with a history of vulvar HSIL remain at increased risk of recurrent disease and vulvar cancer throughout their lifetime
- Recurrence is higher in women with
  - Multifocal disease
  - Positive margins on surgical samples
  - Medical rather than surgical disease
  - Immune suppression
  - Smoking

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SURVEILLANCE AFTER TREATMENT

- ACOG recommends follow-up visits at 6 and 12 months after treatment
- Annual visual inspection is recommended thereafter in women with no evidence of recurrence

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PREVENTION

- Vaccination with the quadrivalent or 9-valent HPV vaccine has been shown to reduce the incidence of vulvar LSIL and HSIL
- CDC recommends vaccination of girls ages 11-12, with catch-up to the age of 26

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PREVENTION

- Smoking cessation
- Treatment of vulvar dermatologic disorders (lichen sclerosus) that are associated with differentiated VIN and with squamous cancer

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Treatment?

Quiz

Which of the following vulvar conditions is an associated risk for differentiated vulvar intraepithelial neoplasia?

A. 1. lichen sclerosus
B. 2. recurrent candidiasis
C. 3. capillary hemangioma
D. 4. herpes simplex virus infection

Quiz

Which of the following increases recurrence rates following treatment of vulvar high-grade squamous intraepithelial lesions?

A. Multifocal disease
B. Positive surgical margins
C. Medical rather than surgical treatment
D. All of the above

Quiz

Which of the following was a suggested prevention for vulvar high-grade intraepithelial lesion?

A. Vulvar colposcopy every 3 years in postmenopausal women
B. Human papillomavirus vaccination for girls 11-12 years
C. Chronic acyclovir suppression in women with known vulvar herpes simplex virus infection
D. All of the above
Quiz

Which of the following vulvar lesion characteristics is an indication for biopsy?

A. Rapid growth  
B. Atypical vascular pattern  
C. Postmenopausal genital warts  
D. All of the above

TREATMENT of VULVAR LSIL

- The goal of treatment is to destroy genital warts, when desired
- Another option is to forego treatment and await spontaneous resolution
- Preserve integrity of normal adjacent tissue
- Reduce potential for transmission (?)
- Prevent high grade disease
- Minimize chance of disease recurrence
- Address psychological concerns
- Provide patient education

TREATMENT of VULVAR LSIL: CDC 2015

- **Patient-Applied:**
  - Imiquimod 5% cream
  - Podofilox 0.5% solution or gel
  - Siloxychlor 15% ointment
- **Provider-Applied:**
  - Cryotherapy with liquid nitrogen or cryoprobe
  - Surgical removal either by tangential incision excision, tangential shave excision, curetage, laser, or electrosurgery
- **TCA** or **BICCA** solution

*Many persons with external anal warts also have intra-anal warts. Thus, persons with external anal warts might benefit from an inspection of the anal canal by digital examination, anoscopy, or high resolution anoscopy.

**Might weaken condoms and vaginal diaphragm.**
Genital warts: patient administered

- Eliminates need for multiple clinic visits, usually painless, convenient
- Requires that patient be able to reach the affected area, is comfortable with self examination and self treatment
- Follow-up visit to determine efficacy of therapy

TREATMENT of VULVAR LSIL

- Podophylox 0.5% solution or gel
  - Anti-mitotic: cause necrosis of warts
  - Apply BID for 3 consecutive days, 4 days off
  - Repeat for a total of 4 weeks
  - Mild to moderate erythema can result
  - Contra-indicated in pregnancy

TREATMENT of VULVAR LSIL

- Imiquimod
  - Enhances local immunity, results in production of interferons and other cytokines
  - 5% cream is applied 3x weekly at bedtime
  - 3.5% cream is applied nightly
  - Both should be washed off after 6-10 hours
  - Both are used for up to 16 weeks
  - Local inflammatory reactions might occur (redness, irritation, induration, ulceration/erosions, vesicles)
  - Limited data about safety in pregnancy

TREATMENT of VULVAR LSIL

- 15% sinecatechins (Veregan)
  - Green tea extract
  - 0.5 cm strand of ointment is applied to each wart
  - Apply TID for up to 4 months
  - Side effects are erythema, pruritis/burning, pain, ulceration, edema, induration, and vesicular rash
  - Safety in pregnancy is unknown
Case

• 34 year old G2P2 with history of normal Paps has an annual exam and Pap shows high grade SIL (moderate dysplasia)
• Colposcopy is unsatisfactory, biopsy of faint AWE at 3:00 shows squamous metaplasia, ECC benign

Case

• Loop excision of the transformation zone was performed without complication; pathology showed normal cervical ectocervix and endocervix, no dysplasia
• Repeat Pap smear 6 months later again showed high grade SIL
### VAGINAL COLPOSCOPY

| 5% Acetic acid |

### Vaginal Intraepithelial Neoplasia (VAIN)

- **Prevalence**: 0.2-0.3/women/year
- **Risk factors**:
  - HPV infection
  - HPV-related disease elsewhere in the genital tract (e.g., CIN or VIN)
  - Smoking
  - DES exposure
  - Immune suppression

### TERMINOLOGY FOR VAIN

- The old terminology for vaginal disease matched that for cervical disease:
- Vaginal intraepithelial neoplasia (VAIN) was graded as 1, 2, 3 (corresponding to mild, moderate and severe dysplasia/carcinoma in situ respectively)
TERMINOLOGY FOR VAIN
• In 2012 the Lower Anogenital Squamous Terminology (LAST) standardization project was sponsored by the American College of Pathologists and the American Society for Colposcopy and Cervical Pathology (ASCCP)
• Recommended a 2-tiered nomenclature for all squamous lesions: LSIL and HSIL
• Vaginal LSIL corresponds to VAIN 1
• Vaginal HSIL corresponds to VAIN 2 and 3

NATURAL HISTORY OF VAIN
• No large prospective studies
• 0-10% of women with vaginal HSIL developed vaginal cancer (retrospective studies and small prospective studies)
• The current standard of care is that vaginal HSIL is considered a true cancer precursor

DIAGNOSIS
• Vaginal HSIL is usually asymptomatic, but may be associated with abnormal bleeding, post-coital bleeding, vaginal discharge or pain
• Consider the presence of vaginal HSIL in a woman with HSIL cytology and no obvious source on cervical colposcopy

DIAGNOSIS
• There is some evidence that women s/p hysterectomy with a history of cervical HSIL remain at increased risk of development of vaginal HSIL with a mean interval of 10 years
• ACOG (2016) recommends cytology every 3 years for 20 years in women s/p hysterectomy with a history of CIN 2+
**DIAGNOSIS**

- Digital exam to assess for areas of uneven texture or masses
- Colposcopic exam to assess for acetowhitening, vascular abnormalities, and Lugol’s iodine or Schiller’s non-staining
- Biopsy of abnormal areas for histological diagnosis

**TREATMENT**

- If the lesion is worrisome for cancer, excision is indicated (wide local excision, partial vaginectomy, vaginectomy)
- Disease in the hysterectomy cuff can be challenging to visualize and is optimally treated with excision
- CO2 laser ablation is appropriate for lesions in which no invasion is suspected colposcopically and on biopsy
- Multifocal disease can be best treated with laser ablation

**SURVEILLANCE AFTER TREATMENT**

- Recurrence rates are approximately 20-30%
- Vaginal cytology is appropriate for surveillance, with colposcopic exam if the cytology is abnormal

**TREATMENT**

- Treatments can lead to vaginal shortening and stenosis, more common with excisional treatments
- Topical therapies eg 5% 5-fluorouracil are of unproven efficacy
- Imiquimod is not intended for internal use
PREVENTION

• Vaccination with the quadrivalent or 9-valent HPV vaccine is recommended by CDC in girls ages 11-12, with catch-up to the age of 26
• Smoking cessation

Quiz

Vaginal HSIL can be treated with:
A. Laser ablation
B. 5% imiquimod
C. HPV vaccination
D. all of the above
Genital warts: Provider-administered: podophyllin

- Podophyllin resin 25% compounded in a tincture of benzoin. Works by anti-mitotic activity
  
  - A small amount should be applied to each wart and allowed to air dry. The treatment can be repeated weekly if necessary.

- To avoid the possibility of complications associated with systemic absorption and toxicity, some specialists recommend that application be limited to <0.5 mL of podophyllin or an area of <10 cm² of warts per session. Do not use on mucosal surfaces (vagina, anus)

- podophyllin should be thoroughly washed off 1-4 hours after application to reduce local irritation.

- not recommended during pregnancy

- If warts are unchanged after 3 treatments, try another therapy

Genital warts: Provider-administered: BCA or TCA

- 80-90% solution of bichloroacetic acid or trichloroacetic acid: works by chemical denaturation of proteins
  
  - Apply to wart as a thin coat (difficult because the TCA is a non-viscous liquid). It will dry as a white frosting on the wart. Apply several coats to achieve a snowy white cover on the wart. Allow each coat to dry before applying the next one

  - Consider protecting the surrounding normal skin with petrolatum

- Reapply every 1-2 weeks up to 6 times

- If warts are unchanged after 3 treatments, try another therapy

- Do not apply TCA/BCA if the area is still raw/ulcerated from the previous treatment. Wait one more week until skin is healed.
Genital warts: Provider-administered: cryotherapy

- Ablative technique used to destroy discrete warts
- Goal is to bring tissue temperature to -20 degrees Celsius
- Highly effective (60-100%) for individual warts, but recurrences are common (20-80%)

Genital warts: Provider-administered: cryotherapy

- Use either liquid nitrogen on a cotton applicator, or a cryogun, or a cryoprobe
- Most effective if used in a freeze-thaw-freeze pattern. Blistering of the skin after treatment is common
- Local pain is common, consider use of topical analgesia prior to freezing
- It is difficult to control the depth of freezing, therefore be cautious to avoid scarring

Genital warts: Provider-administered: other options

- Fulguration with electrocautery
- Excision with scissors or scalpel or electrosurgery
- Laser ablation
- Interferon

Laser therapy

- Uses high density laser beam to ablate warts
- Requires anesthesia- usually general, although sometimes local is adequate (small discrete lesions)
- Usually reserved for widespread disease recalcitrant to other modalities
- Requires training and certification to perform
Laser therapy

- Laser beam allows careful ablation to the base of the epithelium and not deeper
- Key to healing is careful postoperative care with Sitz baths 4 times daily, Silvadene cream, and topical analgesia (2% or 5% lidocaine gel)

Genital warts: patient administered: Condylox

- Podofilox 0.5% solution or gel. This is the purified active ingredient from podophyllin
- If possible, the health-care provider should apply the initial treatment to demonstrate the proper application technique and identify which warts should be treated.
- The safety of podofilox during pregnancy has not been established.

Condylox: patient instructions

- Apply condylox with a cotton swab, or podofilox gel with a finger, to visible genital warts twice a day for 3 days, followed by 4 days of no therapy.
- For example, apply on Monday morning and evening, Tuesday morning and evening, Wednesday morning and evening, then no treatment on Thursday, Friday, Saturday, Sunday
- This cycle may be repeated, as necessary, for up to four cycles.

Condylox: patient instructions

- The safety of podophyllin in pregnancy is not established, so use contraception while using this drug
- If there is no change in the warts after 4 weeks, or if the warts enlarge at any time during the therapy, return to your provider
- If the treated area burns or becomes raw, stop the treatment for that week and allow the area to heal before resuming treatment
Before condylox

After 4 weeks of condylox

After 4 weeks of condylox

Patient-applied therapies for Genital Warts: Immune Response Modifiers

- Imiquimod (Aldara)
- Resiquimod
- Good reviews:
  - S. Garland, Current Opinions in Infectious Dis 2003:16, 85-89
Imiquimod

• Results in immunostimulation of innate arm of the mucosal immune response with subsequent release of proinflammatory cytokines and chemokines (e.g.: interferon alpha, tumor necrosis factor alpha, interleukins 12, 1, 6, 8, 10).
• Cytokines result in activation of the acquired arm of the mucosal immune response (Th1 cells, activation of cytotoxic T lymphocytes).

Imiquimod: clinical trials

• Data from 3 prospective randomized double blind vehicle-controlled trials are available.
• Results showed that imiquimod is safe and well tolerated at the 1% and 5% dose.
• Clearance rate with 5% cream was 37-52%, with higher responses in women than men.

Imiquimod: clinical trials

• Large open-label multicenter phase IIIB trial, overall clearance rate was 53.3%.
• Median time to clearance was 8.8 weeks.
• Retreatment after recurrence was as effective as first-time treatment.
• Female clearance > male clearance.
• Overall complete clearance rate for females was 75.5%.
  – Int J STD AIDS 2001;12,722-9
  – Int J Gyn Obs 2001;77,231-8

Imiquimod

• Less effective in HIV-positive group, but better than vehicle.
• Effective in smokers, patients with outbreaks >6 months, patients previously treated for warts, with overall efficacy approx 50% in all groups (Sauder et al, STD 2003;30,124-8).
• More frequent application (>3 times weekly) does not improve outcomes (Trofatter et al, Int J Gyn Obs 2002;76,191-3).
**Imiquimod: patient instructions**

- Imiquimod comes in a small package (sachet). Each sachet contains enough imiquimod to cover $20 \text{ cm}^2$, an area approximately half the size of a credit card. You can reuse the sachet over several days until it is empty.
- At bedtime, apply a thin film to affected areas, rub it into the skin until it disappears.
- Apply 3 times a week (eg MWF) for up to 16 weeks.
- Do not have sex after applying.
- Remove it in the morning with mild soap and water.
- Warts usually disappear within 8-10 weeks.
- Continue until the warts disappear or for up to 16 weeks. Do not continue beyond 16 weeks without consulting with your provider.

**Imiquimod: safety/side effects**

- Do not use in pregnancy, and avoid conception.
- Possible side-effects include local erythema, erosion, or ulceration. If these occur, advise patients stop using the drug.
- If patients experience ulceration, excoriation or extreme pain (rare), we advise frequent Sitz baths and prescribe silvadene and topical anesthetic such as 5% ElaMax or 2% lidocaine gel.
Imiquimod: patient instructions

- Rarely, local hyper- or hypo pigmentation can occur as a result of using this drug.

Imiquimod

Do not use in the vagina, cervix or anal canal (i.e. not for use on mucosal surfaces due to risk of ulceration and systemic absorption)

5% 5-FU (Effudex)

- Cream can be applied to discrete warts once a week
- Off-label use
- Also sometimes used intravaginally
- Risk of ulceration and scarring especially if used too liberally
- CDC no longer recommends effudex in management of genital warts
- Do not use in pregnancy

Polyphenon E (Veregen)

- Extract of green tea- contains polyphenols, esp catechins
- first botanical to be FDA approved
- 2 recent RCTs showed significant efficacy in clearing genital warts
- Apply to warts TID until warts resolve
Veregen (green tea extract)- recently FDA approved

From Meltzer and Monk AJOG 2008

<table>
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<tr>
<th>Patient-administered topical agents for treatment of external genital warts</th>
<th>Clearance</th>
<th>Time to clearance</th>
<th>Side effects*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polyphenols</strong>&lt;sup&gt;1,2&lt;/sup&gt; (Veregen)</td>
<td>50% (with donors), 60% (proven only)</td>
<td>Up to 16 wk</td>
<td>16% erythema, 17% pruritis or burning, 14% pain, 12% irritation, 11% edema, 10% induration, 5% vesicular rash</td>
</tr>
<tr>
<td><strong>5% imiquimod</strong> (Aldara)</td>
<td>30%</td>
<td>Up to 8 wk</td>
<td>30% itching, 26% burning, 18% pain, 2% pruritis, 1% swelling, &lt; 1% headache, flu-like symptoms, myalgia</td>
</tr>
<tr>
<td><strong>Polyflex</strong> (Combidex)</td>
<td>20-50%</td>
<td>Up to 12 wk</td>
<td>79% burning, 72% pain, 67% erosion, 65% inflammation, 65% itching</td>
</tr>
</tbody>
</table>

* As contained in FDA package insert.


VIN 3

**Basaloid type**

Clinical
- Younger women
- Associated with warty carcinomas
- HPV associated

Histology
- Acanthosis
- Parakeratosis / hyperkeratosis
- Spiky or undulating surface
- Cytoplasmic maturation

VIN 3

**Warty VIN 3**
Differentiated VIN 3

Clinical
- Older women
- Adjacent to usual vulvar carcinomas
- May not be HPV associated

Histology
- Abnormal cells confined to basal / parabasal areas
- Prominent eosinophilic cytoplasm
- Keratin pearls
- Nuclear chromatin changes

Differentiated VIN (LSA)
Differentiated VIN (Actinic-like)

www.bwhpathology.org

Differentiated VIN (Acantholytic)

www.bwhpathology.org

Squamous Cell Carcinoma of the Vulva

- Age: 60’s and older
- Most arise on the labia, followed by clitoris and fourchette
- Plaque, ulcer, nodule
- Prognosis depends on stage
  - Node negative 5 year survival = 80-90%