VULVAR CANCER

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Statistics

Number of New Cases and Deaths per 100,000: The number of new cases of vulvar cancer was 2.4 per 100,000 women per year. The number of deaths was 0.5 per 100,000 women per year. These rates are age-adjusted and based on 2009-2013 cases and deaths.

Lifetime Risk of Developing Cancer: Approximately 0.3 percent of women will be diagnosed with vulvar cancer at some point during their lifetime, based on 2011-2013 data.
Statistics

Compared to other cancers, vulvar cancer is rare.

<table>
<thead>
<tr>
<th>Common Types of Cancer</th>
<th>Estimated New Cases 2016</th>
<th>Estimated Deaths 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Breast Cancer (Female)</td>
<td>246,660</td>
<td>40,450</td>
</tr>
<tr>
<td>2. Lung and Bronchus Cancer</td>
<td>224,390</td>
<td>158,080</td>
</tr>
<tr>
<td>3. Prostate Cancer</td>
<td>180,890</td>
<td>26,120</td>
</tr>
<tr>
<td>4. Colon and Rectum Cancer</td>
<td>134,490</td>
<td>49,190</td>
</tr>
<tr>
<td>5. Bladder Cancer</td>
<td>76,960</td>
<td>16,390</td>
</tr>
<tr>
<td>6. Melanoma of the Skin</td>
<td>76,380</td>
<td>10,130</td>
</tr>
<tr>
<td>7. Non-Hodgkin Lymphoma</td>
<td>72,580</td>
<td>20,150</td>
</tr>
<tr>
<td>8. Thyroid Cancer</td>
<td>64,300</td>
<td>1,980</td>
</tr>
<tr>
<td>10. Leukemia</td>
<td>60,140</td>
<td>24,400</td>
</tr>
<tr>
<td>28. Vulvar Cancer</td>
<td>5,950</td>
<td>1,110</td>
</tr>
</tbody>
</table>

Vulvar cancer represents 0.4% of all new cancer cases in the U.S.

In 2016, it is estimated that there will be 5,950 new cases of vulvar cancer and an estimated 1,110 people will die of this disease.
Changes over the time
Survival by stage

Cancer stage at diagnosis, which refers to extent of a cancer in the body, determines treatment options and has a strong influence on the length of survival. In general, if the cancer is found only in the part of the body where it started it is localized (sometimes referred to as stage 1). If it has spread to a different part of the body, the stage is regional or distant. The earlier vulvar cancer is caught, the better chance a person has of surviving five years after being diagnosed. For vulvar cancer, 59.5% are diagnosed at the local stage. The 5-year survival for localized vulvar cancer is 86.1%.

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Vulvar Cancer

- Localized (59%)
  - Confined to Primary Site
- Regional (31%)
  - Spread to Regional Lymph Nodes
- Distant (5%)
  - Cancer Has Metastasized
- Unknown (5%)
  - Unstaged

5-Year Relative Survival:
- Localized: 86.1%
- Regional: 57.1%
- Distant: 17.4%
- Unstaged: 51.9%

SEER 18 2006–2012, All Races, Females by SEER Summary Stage 2000
Age at diagnosis

Percent of New Cases by Age Group: Vulvar Cancer

Vulvar cancer is most frequently diagnosed among women aged 75–84.

Median Age At Diagnosis

68
# Diagnosis by race

## Number of New Cases per 100,000 Persons by Race/Ethnicity: Vulvar Cancer

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Races</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>White</td>
<td>2.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Black</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Asian / Pacific Islander</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>American Indian / Alaska Native</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>2.6</td>
<td>2.6</td>
</tr>
</tbody>
</table>

*SEER 18 2009–2013, Age-Adjusted*
Deaths

Percent of Deaths by Age Group: Vulvar Cancer

The percent of vulvar cancer deaths is highest among women aged 85+.

Median Age At Death

78

U.S. 2009–2013, All Races, Females

Number of Deaths per 100,000 Persons by Race/Ethnicity: Vulvar Cancer

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex-Specific Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Races</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>White</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Black</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Asian / Pacific Islander</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>American Indian / Alaska Native</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

U.S. 2009–2013, Age-Adjusted
Histology type

- 90% planocellular carcinoma
- 2-10% Malignant melanoma
- 5% Adenocarcinoma (Bartolini gland)
- 2% Paget’s disease
  - In situ adenocarcinoma
Pathogenesis

HPV → Intraepithelial Neoplasia → Carcinoma

Lichen sclerosus
Human Papilloma Virus (HPV)

• HPV is the most commonly diagnosed sexually transmitted infection
  • Asymptomatic infection
  • Genital warts
  • Squamous intraepithelial lesions and malignancy

• ASSOCIATION WITH MALIGNANCY
  • “high-risk”: 16, 18, 31, 33, 35, 39, 45, 52, 53, 56, 58, 59, 66, 67, 68
  • “low-risk”: 6, 11, 44, 55, 74

• HPV 16, 18 are the most commonly isolated types in cancer
HPV- Risk factors

• Age at initiation of sexual activity

• Number of sexual partners (and their previous partners)

• Higher persistent infection among smokers!

• Immune suppression
  • HIV
  • Medication
  • (Pregnancy)
HPV Vaccination

Effective primary prevention of HPV infection

• Silgard (in the USA Gardasil),
  • Quadrivalent
    • HPV 6, 11, 16, 18,
    • Al-hydroxid adjuvant

• Gardasil 9
  • Nonevalent
    • HPV 6, 11, 16, 18, 31, 33, 45, 52, 58

• Cervarix
  • Bivalent HPV 16, 18
  • AS04 adjuvat (more effective?, longer lasting?)
HPV

- Capsid
  - icosahedral symmetry with 72 capsomeres L1, L2
- DNA
  - Double-stranded circular ~8000 base pairs

- Genome - 3 major functional regions:
  - Early (E) region
    - codes for 6 nonstructural genes
  - Late (L) region
    - codes structural proteins, L1 and L2, that form the capsid
  - Long control region
    - a noncoding region that regulates replication and gene function
HPV replication

• HPV infects the basal keratinocyte of the epidermis
  • through disruptions of the skin or mucosal surface

• The virus remains latent in the cell as a circular episome in low copy numbers
HPV replication

- Two modes of replication:
  - Stable replication of the episomal genome in basal cells
  - Vegetative, replication in more differentiated cells

- The expression of viral genes is tightly linked to the state of cellular differentiation.

- Most viral genes are not activated until the infected keratinocyte leaves the basal layer
HPV replication

- As the epidermal cells differentiate and migrate to the surface
  - the virus is triggered to undergo replication and maturation
  - At the keratitic layer, the virus is present in high copy numbers
  - The process of virus replication alters the character of the epidermis → hyperkeratotic lesions - warts
  - Production of virus particles can occur only in highly differentiated keratinocytes

- HPV infections have not been shown to be cytolytic; rather, viral particles are released as a result of degeneration of desquamating cells
Genital warts

• Low risk HPV
  • 90% HPV 6, 11

• Forms
  • Condyloma accuminatum
  • Macular
  • Papular
  • Hyperkeratotic
Localization

- Vulva
- Introital region
- In the vagina
- Ectocervix
- Perianal
CO2 laser ablation

7 days after

7 days after
HPV malignant transformation

Potential to transform cells

• In benign or low-risk HPV lesions (HPV types 6 and 11)
  • HPV genome exists as a circular episomal DNA separate from the host cell nucleus

• In malignant lesions, the genomes of high-risk HPV types 16 and 18
  • HPV genome is integrated into the host cell DNA
  • → hallmark of malignant transformation
  • The time of integration E2 function is damaged (controls E6, E7)

• HPV proteins E6 and E7 of high-risk serotypes
  • inactivate the host’s tumor suppressor proteins p53 and Rb
  • unregulated host cell proliferation and malignant transformation
Intraepithelial neoplasia

<table>
<thead>
<tr>
<th>Condition</th>
<th>AIN grade 1</th>
<th>AIN grade 2</th>
<th>AIN grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade squamous intraepithelial lesion (LSIL)</td>
<td>Very mild to mild dysplasia</td>
<td>Moderate dysplasia</td>
<td>Severe dysplasia/Si in situ carcinoma</td>
</tr>
<tr>
<td>High-grade squamous intraepithelial lesion (HSIL)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1. Schematic Representation of SIL**

As shown in this illustration, with increasing severity of SIL of the anus, the proportion of the epithelium replaced by immature cells with large nuclear-cytoplasmic ratios increases. Invasive cancer probably arises from one or more foci of high-grade SIL (HSIL), as depicted in the drawing by epithelial cells crossing the basement membrane below the region of HSIL.
Roden and Wu Nature Reviews Cancer 6, 753–763 (October 2006) | doi:10.1038/nrc1973
Vulvar Intraepithelial Neoplasia VIN

- Hyperkeratotic
- Pigmented
- Thickening
Lichen sclerosus

- Pale discolouration
- Hyperkeratosis
- Vulvar atrophy
- Atrophic, fragile skin
- Itching
- Autoimmun background
- Before puberty
- After menopausa
- Potentially premalignant!
Lichen Sclerosus- Therapy

• Potent steroid
  • Dermovate, Closanasol (clobetasol)

• Non-steroid
  • Protopic 0,1-0,03% (tacrolimus)

• Emollients
  • Ung. Boraxatum
Vulvar cancer
VULVAR CANCER
RECOMMENDATIONS

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Vulvar Cancer
(Squamous Cell Carcinoma)

NCCN.org

- Complete report -
Staging

Table 1. Staging systems of squamous cell vulvar cancer

<table>
<thead>
<tr>
<th>PRIMARY TUMOR (T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>REGIONAL LYMPH NODES (N)</td>
</tr>
<tr>
<td>DISTANT METASTASIS (M)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TNM categories</th>
<th>FIGO stages</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td></td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>IVB</td>
<td>Distant metastasis (including pelvic lymph node metastasis)</td>
</tr>
</tbody>
</table>

* FIGO no longer includes stage 0 (Tis). ** the depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion, *** FIGO uses the classification T2/T3. This is defined as T2 in TNM, **** FIGO uses the classification T4. This is defined as T3 in TNM.
Vulvar malignant melanoma staging
Vulvar cancer - Symptoms

• **VIN**
  • Itching
  • Thickening of the skin
  • Pain

• **Carcinoma**
  • Pain
  • Nodule / ulcer
  • Discharge / bleeding
  • Nodules in the groin
Vulvar cancer- Diagnosis

- Inspection

- Punch biopsy or incisional biopsy
  - From the border of normal-abnormal
  - Represents the depth of invasion

- In toto excision is NOT PREFERABLE!

- Vulvar mapping

- Referring to Cancer Centre
Vulvar cc. – Preoperative evaluation

- Documentation / Photo documentation
  - Diameter
  - Distance from the midline
  - Relation to the - Clitoris, Anus, Vagina, Urethra
  - Palpation of inguinal lymph nodes

- Evaluation of inguinal lymph nodes
  - US
  - CT, PET-CT, MR,
  - FNAB

- Searching for distant metastasis
  - Positive lymph node
  - Locally advanced tumor
  - CT chest- abdominal- pelvic region
  - PET-CT
Vulvar cc. – Preoperative evaluation

- **Cervix**
  - **Citology**
    - **HR-HPV**

- **Pathology report of biopsy**
  - **Histologic type**
  - **Depth of invasion <1mm**
  - **LVSI (Lymphovascular Space Involvement)**
    - **Negative**
      - 20% chance for Metastatic Lymph node
    - **Positive**
      - 90% chance for Metastatic Lymph node
Vulvar cancer- Surgical therapy

1. Surgical excision of primary tumor

2. Surgical evaluation of the lymph nodes
   1. Invasion >1mm
   2. Clinically positive nodes
Vulvar cancer- Surgical therapy

Radical vulvectomy and inguinal lymphadenectomy

- Traditional „butterfly shape” „en bloc” excision of the primary tumor with bilateral groins
  - High risk of complication
  - Bad cosmetic result
  - Distorted anatomy
• Aim ➞ New method = therapeutic effect < complication > cosmetic result > quality of life
Vulvar cancer

Radical vulvectomy and inguinal lymphadenectomy

Triple incision technique

• Less wound dehiscence
• Equal oncologic outcome
• Better quality of life
Vulva cc. – Surgical treatment

• Radical vulvectomy

  • What does radicality means?
    • The whole vulva is removed
      • Clitoris
      • Major and minor labia
      • Perineal area
    • Horizontal: min. 1 cm free margin
    • Vertical: until the fascia
Vulva cancer – Surgical treatment

• New tendency - Tumor
  • Radical vulvectomy
    • Multifocal malignancy
    • Premalignant disease on large areas
  • Modified radical vulvectomy
    • Partial vulvectomy

• Radical excision
  • Free margin: minimal 1cm

• Skinning vulvectomy
  • Premalignant disease
Vulvar field resection: Novel approach to the surgical treatment of vulvar cancer based on ontogenetic anatomy by: Michael Hökel
• Vulvar compartment /Green/

1. Inner compartment - vestibulum

2. Middle compartment - glans / labial

3. Interlabial compartment
Vulva cc. – Surgical treatment

• Reconstruction surgery
  • Better cosmetic result
  • Better functional outcome
  • Better quality of life

• Innervated Island Flaps in Morphofunctional Vulvar Reconstruction
  • Moschella and Cordova
Limberg flap
Labial flap
Pubolabial V-Y flap
Pudendal thigh flap
Rekonstruktive surgical skills

• Early + Advanced stages

• Flaps
  • Cutan
    • V-Y
    • Rhomboid
    • Lotus petal

• Fasciocutan
  • Singapure

• Myocutan
  • Gracilis
  • Tensor fasciae latae
Lymphatic drainage of the vulva
Vulvar cc.- Lymph node metastasis

• Invasion > 1mm + Clinically negative groins
  • 30% positive lymph node

• Clitoris region
  • Bilateral
  • Rarely primary pelvic met.

• Well lateralised tumors >2cm from midline
  • Unilaterial
Inguinofemoral lymphadenectomy

- Femoral trigonum
  - Inguinal ligament
  - Sartorius muscle
  - Adductor longus muscle
- Superficial
  - Over the femoral fascia
- Deep
  - Below the fascia cribrosa
  - Medial to the femoral vein

- Lymphadenectomy improves oncological outcome
Inguinal lymphadenectomy

- 30-60% complication
  - Dehiscence
  - Wound infection
  - Skin necrosis
  - Lymphorrea
  - Lymphangitis
  - Lymphocyst
  - Late onset complication
    - Chronic lymphedema

- St IB and II the risk for lymph. node met. ~ 30%
Sentinel lymph node mapping

- Sentinel node represents the metastatic status of the regional lymph node area

- Advantage
  - Less surgical stress
  - Less complications
    - Wound related
    - Lymphocyst
    - Lymphedema
  - Less lymph node removal but more precise examination
  - Diagnosis of micro metastasis
Lympadenectomy - Sentinel technique in vulvar cc.

- Unifocal

- < 4 cm

- \( \geq T1b \) (>1mm invasion)

- Clinically negative lymph nodes
Lymphatic mapping

• Dual staining

  • Technetium 99m isotope labelled colloid
    • SPECT
    • Gamma probe

• Patent Blue

• Both injected
  • peritumoral
  • subcutaneously
Sentinel Lymph node

• Removal
• Pathological examination
  • **Intra-operative**
    • Frozen sectioning
  • Imprint cytology

• **Ultra staging**
  • Ultra sectioning
  • HE + Citokeratin

<table>
<thead>
<tr>
<th>Micro metastasis</th>
<th>0.2-2mm</th>
</tr>
</thead>
</table>
| Izolated tumor cell - ITC | 0-0.2mm | Lymphadenectomy

Lymphadenectomy
Sentinel lymph node technique

- Vulvar carciner
  - Sentinel lymph node detection rate 92%
  - Sensitivity 97.7%
  - Negative predictive value 99%
  - False negativity rate 2.3%
„Modern” indication of inguinal lymphadenectomy

• Bilateral, inguinofemoral
  • Tumor ≥ 4 cm, Multifocal

• Unilateral
  • Tumor location > 2 cm from the midline, < 4 cm

• Clinically evident metastatic lymph nodes
  • Total lymphadenectomy / Selective lymphadenectomy ????

• Pelvic lymphadenectomy
  • Bulky positive pelvic lymph node
Video Endoscopic inguinal lymphadenectomy (VEIL)

• **Aim**
  - Removal of the whole inguinal lympho-fatty tissue
  - Femoral trigonum

• **Doesn’t limit**
  - Size of primary tumor
  - Location
  - Clinically positive node

• **VEIL-L (L-leg)**
• **VEIL-H (H- hypogastric)**
Endoscopic inguinal lymphadenectomy
Video Endoscopic inguinal lymphadenectomy (VEIL)

- Review article from 2015
- 9 study, 138 patients, 249 VEIL operation
  - Early complication rate 13%
  - Need for conversation (1/249)
  - Operative time / lymph node area
  - Blood loss 5.5-22ml
  - Number of removed nodes (7.3-16)

- Not enough data on the oncological safety!!!
Vulvar cc. – Adjuvant radiation therapy

• Indication
  • Vulva
    • Positive resection margin
      • Re-excision/ irradiation
    • Close but negative margin
      • Distance is not defined

• Inguinal region
  • > 1 metastatic node
  • NOT intact capsule
Vulvar cc. – Adjuvant radiation therapy

• Start within six weeks

• Radio-chemotherapy might more effective
Locally advanced tumor

• Primary irresectable
• Resectable but with pelvic exenteration

• Neoadjuvant
  • Chemo / Chemoradiation / Radiation

• Palliative
Metastatic disease

• Distant nodal metastasis
  • Palliative chemotherapy
  • Extended field radiation therapy

• Parenchymal
  • Palliative chemotherapy
  • Best supportive care
    • Pain relief
    • Wound care
    • Urinary / Faecal deviation?
Thank you for your attention!