VULVAR CANCER

FLAME LECTURE 224B:

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LEARNING OBJECTIVES

- List the risk factors for vulvar neoplasms
- Understand the three classifications of VIN, including presentation and treatment
- Describe the symptoms and physical examination findings of a patient with vulvar cancer
- Understand the staging of vulvar cancer
- Describe the treatment and prognosis of vulvar cancer

EPIDEMIOLOGY

- Accounts for 4% of gynecologic malignancies in U.S.
- In 2021, an estimated 6120 women will be diagnosed with vulvar cancer and 1550 (25%) are expected to die from the disease.
  - Squamous cell carcinoma (SCC) is most common type (90%)
  - Highly associated with HPV infection (30 to 69%)
  - Average age at VIN diagnosis is 45-50 years
  - Average age at Vulvar SCC in 65-70 years
  - Five-year survival rate after diagnosis is 86% for localized disease (stages I/II), 53% for regional or locally advanced disease (stages III/IVA), and 19% for stage IVB disease

RISK FACTORS FOR VULVAR CANCER

- Age over 70
- Vulvar or cervical intraepithelial neoplasia
- History of cervical cancer
- Cigarette smoking
- Vulvar lichen sclerosis and other inflammatory conditions of the vulva
- Immunodeficiency syndromes
- Northern European ancestry

Other types include:

- Melanoma of the vulva, extramammary Paget's disease, Bartholin gland adenocarcinoma, verrucous carcinoma, basal cell carcinoma of the vulva, and sarcoma

VULVAR INTRAEPITHELIAL NEOPLASIA (VIN)

A premalignant condition of the vulva

- Higher prevalence in premenopausal women
  - Associated with **HPV**, immunosuppression, cigarette smoking
  - Postmenopausal women have non-HPV-associated VIN
- Three classifications:
  - Low grade squamous intraepithelial lesion (LSIL)
  - High grade squamous intraepithelial lesion (HSIL)
  - Differentiated VIN (dVIN)

VULVAR INTRAEPITHELIAL NEOPLASIA (VIN)

- Vulvar LSIL
  - Low risk types of HPV infection, anogenital warts
  - Should NOT be considered neoplastic, limited risk of progression
- Vulvar HSIL
  - Associated with 20% of vulvar cancers
  - Typically occurs in premenopausal women
  - 76% are HPV+, high risk types (precursor of HPV+ vulvar cancer)
  - Multifocal lesions - Mixtures of warty and condylomatous subtype
- Differentiated VIN
  - Associated with 80% of vulvar cancers
  - Typically occurs in postmenopausal women
  - Precursor for HPV negative vulvar cancer
  - Unifocal and unicentric lesions
  - Associated with lichen sclerosus and chronic inflammation

VIN: PRESENTATION AND DIAGNOSIS

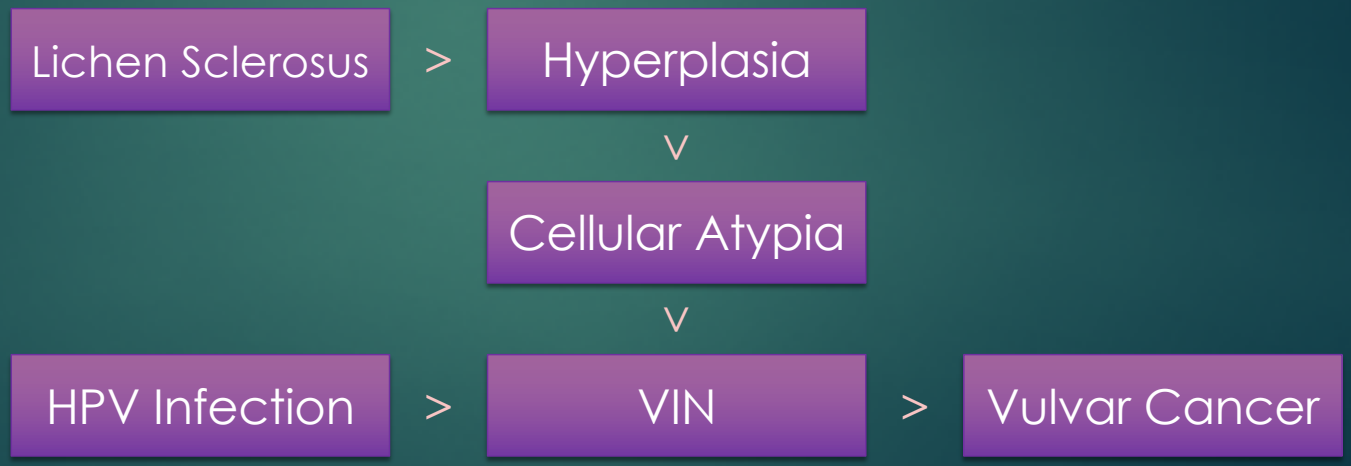
- Lesion is verrucous and white, but can be red, grey, pink, or brown
- Presentation is similar to vulvar cancer
  - Vulvar pruritus/discomfort and vulvar lesion
  - However: many women are asymptomatic
  - Definitive diagnosis by biopsy

TREATMENT OF VIN

- HSIL
  - Concern for malignancy: surgical excision
  - Malignancy excluded:
    - Excision for single lesions
    - Ablative therapy for young women, multifocal disease, or if excision may have adverse effects
    - If recurrent without invasion: Ablative or topical therapy with Imiquimod (16-week course)
- dVIN
  - Surgical excision given high risk of developing invasive carcinoma
- LSIL
  - No treatment unless symptomatic
  - Reminder: not a precancerous lesion

CAUSES OF SQUAMOUS CELL VULVAR CANCER

- HPV-positive and HPV-negative (lichen sclerosus) pathways



CLINICAL PRESENTATION OF VULVAR SCC

- Vulvar lesion
  - plaque, ulcer, or mass) on labia majora
  - Labia minora, perineum, clitoris, and mons are also possible locations
- Vulvar pruritus
  - Less reported symptoms: vulvar bleeding/pain, dysuria, and discharge

- Examination should include vulvar and perianal surfaces, cervix, and vagina

INDICATIONS FOR BIOPSY

- Risk factors and/or symptoms associated with cancer
- Pelvic exam of vulva and groin is suspicious for malignancy
  - Vulvar lesion with asymmetry, border irregularity, color variation, rapid change, bleeding, or non-healing ulcers
- Colposcopy identifies lesions

STAGING

AJCC STAGE	STAGE GROUPING	FIGO STAGE	STAGE DESCRIPTION
IA	T1a N0 M0	IA	➢ The cancer is in the vulva or the perineum (the space between the rectum and the vagina) or both and has grown no more than 1 mm into underlying tissue (stroma) and is 2 cm or smaller (about 0.8 inches) (T1a). ➢ It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IB	T1b N0 M0	IB	➢ The cancer is in the vulva or the perineum or both and is either more than 2 cm (0.8 inches) or it has grown more than 1 mm (0.04 inches) into underlying tissue (stroma) (T1b). ➢ It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
II	T2 N0 M0	II	➢ The cancer can be any size and is growing into the anus or the lower third of the vagina or urethra (the tube that drains urine from the bladder) (T2). ➢ It has not spread to nearby lymph nodes (N0) or to distant sites (M0).

STAGING

AJCC STAGE	STAGE GROUPING	FIGO STAGE	STAGE DESCRIPTION
IIIA	T1 or T2 N1 M0	IIIA	➢ Cancer is in the vulva or perineum or both (T1) and may be growing into the anus, lower vagina, or lower urethra (T2). ➢ It has either spread to a single nearby lymph node with the area of cancer spread 5 mm or more OR it has spread to 1 or 2 nearby lymph nodes with both areas of cancer spread less than 5 mm (N1). ➢ It has not spread to distant sites (M0).
IIIB	T1 or T2 N2a or N2b M0	IIIB	➢ Cancer is in the vulva or perineum or both (T1) and may be growing into the anus, lower vagina, or lower urethra (T2). ➢ The cancer has spread either to 3 or more nearby lymph nodes, with all areas of cancer spread less than 5 mm (N2a); OR the cancer has spread to 2 or more lymph nodes with each area of spread 5 mm or greater (N2b). ➢ It has not spread to distant sites (M0).
IIIC	T1 or T2 N2c M0	IIIC	➢ Cancer is in the vulva or perineum or both (T1) and may be growing into the anus, lower vagina, or lower urethra (T2). ➢ The cancer has spread to nearby lymph nodes and has started growing through the outer covering of at least one of the lymph nodes (called extracapsular spread; N2c). ➢ It has not spread to distant sites (M0).

STAGING

AJCC STAGE	STAGE GROUPING	FIGO STAGE	STAGE DESCRIPTION
IVA	T1 or T2 N3 M0	IVA	➢ Cancer is in the vulva or perineum or both (T1) and may be growing into the anus, lower vagina, or lower urethra (T2). ➢ The cancer has spread to nearby lymph nodes and has become stuck (fixed) to the underlying tissue or has caused an ulcer(s) to form on the lymph node(s)(ulceration) (N3). ➢ It has not spread to distant sites (M0).
			OR
	T3 Any N M0	IVA	➢ The cancer has spread beyond nearby tissues to the bladder, rectum, pelvic bone, or upper part of the urethra or vagina (T3). ➢ It might or might not have spread to nearby lymph nodes (any N). It has not spread to distant sites (M0).
IVB	Any T Any N M1	IVB	➢ The cancer has spread to distant lymph nodes (pelvic) or organs such as lung or bone (M1). The cancer can be any size and might or might not have spread to nearby organs (Any T). ➢ It might or might not have spread to nearby lymph nodes (Any N).

STAGING AND TREATMENT

- Staged according to melanoma staging system
- T1 lesions (confined to vulva)
  - Less than 1 mm depth of invasion: wide local excision
  - Greater than 1 mm depth of invasion: radical local excision or modified radical vulvectomy with groin SLND
- T2 lesions (extension to adjacent structures)
  - Modified radical vulvectomy w/ or w/o neoadjuvant chemoradiation
- T3 lesions (extension to upper/proximal 2/3 urethra or vagina, bladder or rectal mucosa, fixed to pelvic bone)
  - Chemoradiation followed by selective surgery

STAGING AND TREATMENT

- Mode of spread: direct extension to local structures then lymphatic spread
- Superficial inguinal lymph nodes → femoral LN → pelvic LN

ADJUVANT TREATMENT OF VULVAR SCC

- Node negative tumors > 4 cm or positive/close margins
  - Adjuvant radiation (EBXRT)
- Node positive
  - RT alone for one nodal micrometastasis
  - Chemoradiation for macroscopic or 2+ micrometastatic nodes
- Unresectable, locally advanced disease
  - Chemoradiation with weekly cisplatin
- Distant metastases
  - Chemotherapy with carboplatin/paclitaxel and/or EBRT

PROGNOSIS

- Prognostic factors
  - Inguinal/femoral node involvement most significant for survival
  - Stage, capillary lymphatic space invasion, older age
- Two-year survival
  - With positive groin LN: 68%
  - With positive pelvic LN: 23%
- Surveillance strategy
  - Serial ROS and physical/pelvic exam
  - Stage I and II: every 6 months for 2 years, then annually
  - Stage III and IVa: every 3 months for 2 years, every 6 months for 3 years, then annually
  - Cervical or vaginal cytology annually

REFERENCES AND RESOURCES

- UpToDate:
  - Colposcopy
  - Vulvar cancer: Epidemiology, diagnosis, histopathology, and treatment
  - Squamous cell carcinoma of the vulva: Medical therapy and prognosis
  - Squamous cell carcinoma of the vulva: Staging and surgical treatment
  - Vulvar cancer: Epidemiology, diagnosis, histopathology, and treatment of rare histology
  - Vulvar intraepithelial neoplasia
  - Vulvar lesions: Diagnostic evaluation
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- Vulvar Cancer. NCCN Clinical Practice Guidelines in Oncology. Version 3.2021. April 26, 2021.