

# HPV-Related Penile Neoplasms

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# Overview

- Human Papilloma Virus
  - DNA containing virus spread directly through skin to skin contact
- In male patients HPV infection is associated with benign and malignant genital manifestations
  - Anogenital condyloma acuminata
  - Penile and anal carcinoma
- Most infections are asymptomatic and subclinical
  - HPV infected patients usually clear the infection spontaneously
- Penile cancers are rare in occurrence
  - 1570 new cases in 2013
- Neoplasms typically develop on the epidermal or mucosal surfaces mucosal surfaces of the glans penis or inner prepuce

# Etiology

- Four genotypes prevalent in male genital HPV
  - 6, 11 – benign diseases (condyloma and dysplasia)
  - 16, 18, 31, 33 – premalignant and malignant disease
- Transmission rates
  - Over 6-month estimated to be 3.7 cases per 100 person-months
- Clearance rates
  - Overall 70% in a 12 month period
  - By genotype
    - 6, 11 - 6.1 months each
    - 16, 18 - 7.7 and 6.2 months

# Epidemiology – Benign Lesions

- Most common viral sexually transmitted infection in men and women in the United States
  - Approximately 6.2 million new cases diagnosed each year
  - Most sexually active adults will be infected at some point during their lives
- Ages 18-30 sexually active men are at greatest risk
  - Incidence rate of genital warts is 3.43 cases / 1000 person-years in the US
- Prevalence
  - By country:
    - Europe 28.5%, US 51.7%, Mexico 56.1%, Brazil 59.4%
  - By genital site/origin:
    - Penile shaft 52%, Scrotum 40%, Glans/Corona 32%, Urine 10%, and Semen 6%
  - By presence of prepuce
    - 50% circumcised men, 60% uncircumcised men
- Risk factors for HPV
  - presence of foreskin, increasing numbers of sexual partners, lack of condom use, and smoking

# Epidemiology – Malignant Lesions

- Penile cancers typically present after the fifth decade
  - Greatest incidence between ages 50-70 years
  - Historic studies show incidence of up to 22% of patients less than 40 years
- Incidence varies based on economic development
  - Industrialized countries (US, Canada, Europe)
    - 1/100,000 man-year / population
    - 0.4 – 0.6% of cancers in the US
  - Non-Industrialized countries (South America, Asia, Africa)
    - 5-10/100,000 man-year / population
    - Up to 10% of malignant neoplasms in these countries
  - No difference in incidence based on race
    - white men, 0.8/100,000; for black men, 0.7/100,000 in the US

# Risk Factors – Malignant Lesions

- Risk factors for development of penile cancer - Similar to risk factors for HPV infection
  - Circumcision practice/phimosis
  - HPV infection
  - Poor genital hygienic standard
  - Number of sexual partners
  - Low socioeconomic status
  - Chronic inflammation
  - Exposure to tobacco products
- Protective effect of circumcision
  - Risk of penile cancer in circumcised US males is 1/100,00
  - Risk of penile cancer in uncircumcised US males is 1/400
  - 22% risk reduction in circumcised males
    - Translates to sexually transmitted infections as well – HPV
  - Protective effect of circumcision is greatest if performed in newborn period but benefit is lost after puberty

# Risk Factors – Malignant Lesions

- HPV association
  - 60% of penile cancers are associated with HPV infection
    - Most basaloid and warty subtypes have associated HPV infection
  - HPV infection is 5-10 more likely to occur in uncircumcised men
  - Risk of HPV association is directly correlated with lifetime number of sexual partners
    - Both HPV infection status and number of sexual partners are independent risk factors for penile carcinoma
- Chronic Inflammation
  - Typically multifactorial influence
    - Driven by phimosis, smegma, and balanitis
    - Lichen sclerosis (balanitis xerotica obliterans) present in 50% of penile cancers

# Pathology/Pathogenesis

- HPV
  - Types 6, 11
  - No malignant transformation
  - Common locations
    - Prepuce
    - Glans
    - Penile Shaft
  - 5% of men have involvement of the urethral meatus



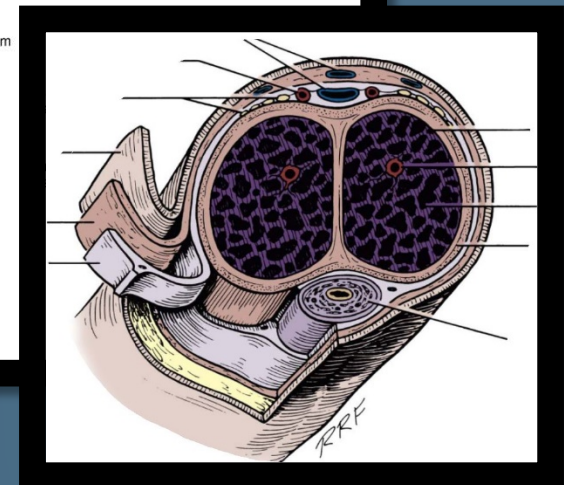
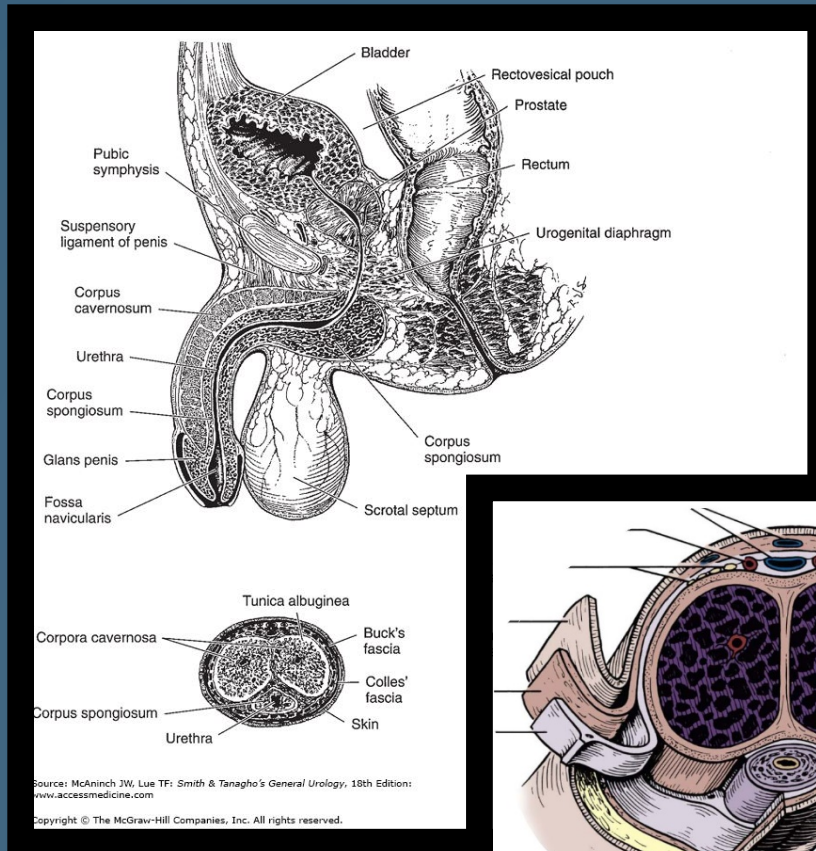


# Pathology/Pathogenesis

- HPV – Malignant Transformation
  - Most common subtypes
    - 16 – 4.5 per 1000 person/years
    - 18 – 2.5 per 1000 person/years
    - 31, 33 0-1 per 1000 person/years
  - Same infection sites as Types 6, 11
  - Tumor transforming proteins in subtypes result in malignant transformation
    - E6 - complexes with the tumor suppressor protein TP53
    - E7 – binds to the retinoblastoma (RB) protein
    - Both act by affecting cell cycle regulation

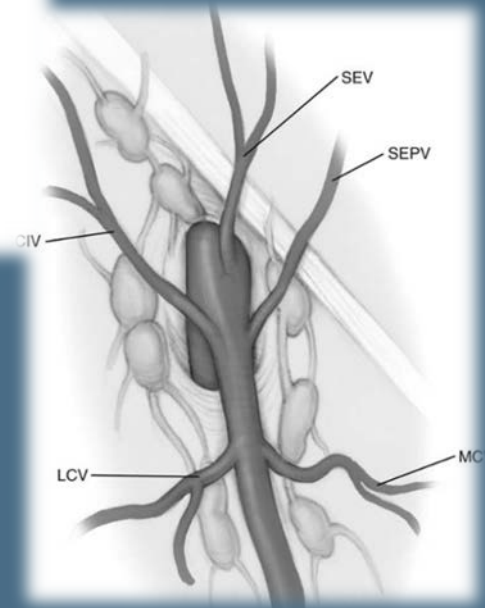
# Anatomy

- Deep penile structure
  - 3 cylindrical chambers: corpora cavernosa, urethra
  - Enveloping fascial layer
- Superficial penile structures
  - Squamous epithelium of skin surface
  - Superficial fascial layer – Dartos
  - Deep fascial layer – Buck's
  - Exception is the Glans
    - Epithelial layer of skin
    - Superficial layer of tunica albuginea



# Anatomy

- Ilioinguinal lymph nodes
  - Located in each groin
  - No predictable laterality of drainage
  - 60-85% cross-over
- Superficial and deep nodes
  - Located either above (superficial) or below (deep) the fascia lata
  - Coalesce at the saphenofemoral junction
  - Junction point with the deep lymph nodes
- Travel along the femoral vein proximally
- Cross under the inguinal ligament to become pelvic lymph nodes



# Natural History

- Genital warts associated with HPV subtypes 6,11 rarely progress to advanced disease
- Invasive disease begins as a small lesions that progresses to involve the entire glans, prepuce, and penile shaft
  - Lesion may be papillary and exophytic or flat and ulcerative
  - Ulcerative lesions progress faster to lymph node metastasis
- Buck's fascia of the penis is an initial anatomic barrier to invasion of penile carcinoma
- Penile cancer that penetrates Buck's fascia and the tunica albuginea invade into the corpora cavernosa with vascular extension
- Early metastatic disease is via the inguinal lymph nodes
  - Regional femoral and iliac nodes
  - Predictable course of metastasis: superficial inguinal → deep inguinal → pelvic lymph nodes
  - Advanced lymph node metastatic disease
    - skin necrosis, chronic infection, sepsis, or hemorrhage secondary to erosion into the femoral vessels
- Advanced penile carcinoma is characterized by a progressive course, with death occurring in the majority of untreated patients within 2 years

# Presentation – Non-Invasive

- Non-invasive lesions
  - Erythroplasia of Queyrat
    - Red, velvety, well-margined
    - First described in 1911
    - Localized to the glans or inner prepuce
  - Bowen's disease
    - Well defined plaques of scaly erythema
    - Crusted or ulcerated variants can occur
    - Localized to the penile shaft
  - Now re-termed **Penile Intraepithelial Neoplasia (PeIN)**
    - With disease on the glans disease progression to invasive carcinoma – 10-33%
    - With disease on the penile shaft disease progression to invasive carcinoma - 5%
    - Metastatic disease is rare but reported



Erythroplasia of Queyrat



Bowen's Disease

# Presentation – Invasive Lesions

- Invasive lesions
  - Subtypes of invasive cancers are based on the microscopic evaluation
    - Superficial spreading
    - Vertical growth
    - Verruciform
    - Multicentric
    - Mixed
  - All subtypes of patterns are based on variations of squamous cell carcinomas
  - Lesions also present on similar locations of the penile shaft
    - Glans – 60%
    - Prepuce – 23%
    - Penile shaft – 9%



# Clinical Diagnosis

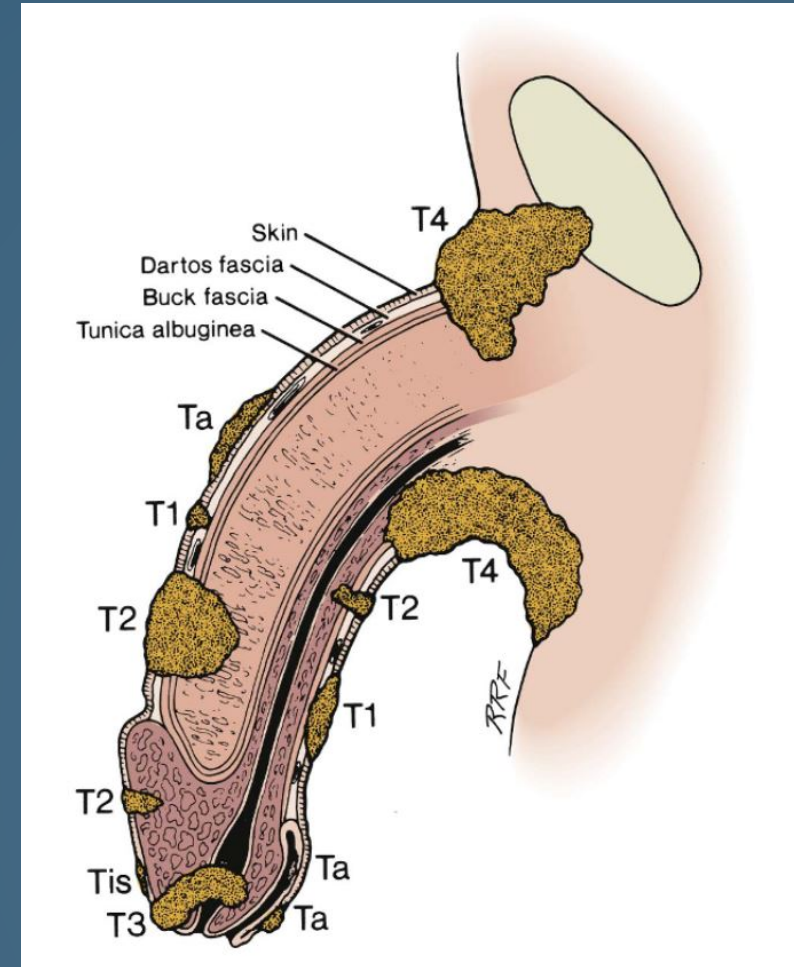
- General
  - Patients delay presentation more frequently than other disease processes
    - 15-50% of patients present with a lesion of one year duration or more
    - Multiple explanations including: embarrassment, guilt, fear, personal neglect and denial
    - Other causes of delay include prolonged treatment of lesions with antifungals or antibiotics
  - Pain is not a presenting symptom despite advanced disease
    - Patients present with weakness, weight loss, fatigue, and systemic malaise
- Focused historical questions directed toward penile cancer
  - Circumcision – what age?
  - History of balanitis or other chronic penile inflammation
  - Sexual history, including history of sexually transmitted infections (STIs)
  - History of tobacco use
- Physical exam focuses on phallus and bilateral inguinal lymph nodes
  - Characteristics of lesion: diameter, fixed or mobile, location on the phallus
  - Inguinal lymph nodes should be examined supine in the frog leg position
    - Characteristics of lymph nodes: shotty or gross, fixed or mobile, involvement of skin, and infection

# Staging

T—Primary tumor	
TX:	Cannot be assessed
T0:	No evidence of primary tumor
Tis:	Carcinoma in situ
Ta:	Noninvasive verrucous carcinoma
T1:	Invades subepithelial connective tissue
T2:	Invades corpus spongiosum or cavernosum
T3:	Invades urethra or prostate
T4:	Invades other adjacent structures
N—Regional lymph nodes	
NX:	Cannot be assessed
N0:	No regional lymph node metastasis
N1:	Metastasis in single superficial inguinal node
N2:	Metastasis in multiple or bilateral superficial inguinal nodes
N3:	Metastasis in deep inguinal or pelvic nodes
M—Distant metastasis	
MX:	Cannot be assessed
M0:	No distant metastasis
M1:	Distant metastasis present

Source: American Joint Committee on Cancer: *TNM Classification—Genitourinary Sites*, 2010.

Most important factors: Tumor grade, depth of invasion, presence of perineural invasion





# Treatment

- Non-invasive lesions
  - Identify and treat all lesions
    - 5% acetic acid solution to the penis and inspection with a magnifying glass
  - Topical therapy
    - Numerous topical treatments exist
      - None reduce transmission to sexual partners
      - None prevent progression to dysplasia or cancer
    - Most popular is imiquimod 5% cream
      - podophyllotoxin 0.5% solution or gel
      - trichloroacetic acid 35% to 85%
      - cryotherapy with liquid nitrogen
      - Electrofulguration
      - CO<sub>2</sub> laser therapy
  - Surgical excision
    - Ablate or excise the condyloma
    - Circumcision



# Treatment – Organ Sparing

- Invasive lesions
  - Surgical amputation is the gold oncologic standard for management of invasive penile cancer
  - Due to quality of life issues organ sparing techniques have been created
    - 55% of patients are  $\leq 60$  years of age
      - 35% of patients are  $\leq 50$  years of age
    - Favorable histologic features
      - stages Tis, Ta, T1
      - grades 1, 2 tumors
      - low risk for metastases
    - Techniques include
      - topical treatments (5-fluorouracil or imiquimod cream for Tis only)
      - radiation therapy
      - Mohs surgery
      - limited excision strategies
      - laser ablation

# Treatment – Organ Amputation

- Disease characteristics
  - Tumors  $\geq 4\text{cm}$  in size
  - Grade 3 on histologic analysis
  - Invasion into the urethra or corpora cavernosa
  - Necessary to obtain 2 cm margin of normal tissue
    - This paradigm is changing with contemporary series
  - Decision for partial or total penectomy depends on residual shaft to allow for upright voiding
- Outcomes
  - 0-8% local recurrence rate in contemporary series
- Management of inguinal lymph nodes remains controversial
  - Most patients with tumors requiring organ amputation should undergo lymph node dissection



# Prevention

- Circumcision
  - Controversial treatment concept
    - Only neoplasm with a know prevention to spare the organ at risk
  - Improved hygiene
    - Danish study showed decrease in incidence of penile cancer from 1.15/100,000 men to 0.82/100,000 men with 150% increase in homes with baths
  - Consider more frequent discussion with parents and in those socioeconomically depressed countries
- Modifiable Behaviors
  - Decreased tobacco usage
  - Condom usage
  - Decreased exposure to ultraviolet light
- HPV vaccination
  - Awaiting long term results for efficacy as men have a lower incidence of HPV related cancers
  - Advisory Council for Immunization Practices does recommend routine vaccination in certain age groups and populations

# Conclusions

- HPV is a prevalent disease in young, sexually active men
- Oncogenic HPV subtypes are the most common HPV subtypes men are infected with
- HPV are commonly transmitted between sexual partners
- Distinct correlation between HPV infection and development of penile cancers and pre-malignant conditions (PeIN)
- PeIN has a higher association with HPV than invasive cancers
- Penile cancer can be successfully treated with organ sparing and organ amputation strategies
- Multiple prevention strategies exist that can successfully prevent penile cancers

# Presentation Outline:

- 1. Definition
- 2. Epidemiology
- 3. Etiology
- 4. Pathology/Pathogenesis
- 5. Predisposing Factors
- 6. Clinical Presentation
- 7. Natural History of Disease
- 8. Differential Diagnosis
- 9. Therapy