Penile and Urethral Cancer

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BEST HOSPITALS U.S.NEWS

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Penile Cancer

Step 1 (easy): Treat and stage the primary

Step 2 (hard): Stage and treat the inguinal LNs

Understanding staging is critical

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Penile Cancer Staging

AJCC TNM 8th ed

A 68 year old male has a partial penectomy for a 4cm SCC with LVI and involvement of his subepithelial connective tissue.

Physical exam reveals a fixed 1.5cm, right inguinal mass.

CT of the abd/pelvis are normal

His TNM stage is:

a. pTa cN1
b. pT1a cN1
c. pT1b cN2
d. pT1b cN3
e. pT2 cN3

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Penile Cancer Staging

AJCC TNM 8th ed

Primary tumor (T)

•Tis: Carcinoma *in situ (Penile Intraepithelial Neoplasia)*

•Ta: Noninvasive localized squamous cell carcinoma (verrucous carcinoma)

•T1 = invades subepithelial connective tissue

- Glans = tumor invades lamina propria
- Foreskin = tumor invades dermis, lamina propria or dartos
- Shaft = tumor invades tissue between epidermis and corpora regardless of location

- T1a: NO LVI, NO PERINEURAL INVASION AND IS NOT HIGH GRADE (i.e. grade 3 or sarcomatoid)
- T1b: EXHIBITS LVI and/or PERINEURAL INVASION OR IS HIGH GRADE

•T2: Tumor invades corpus spongiosum (glans or ventral shaft) with or without urethral invasion

•T3: Tumor invades corpus cavernosum (including tunica albuginea) with or without urethral invasion

•T4: Tumor invades adjacent structures (i.e. scrotum, prostate, pubis)

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Penile Cancer Staging

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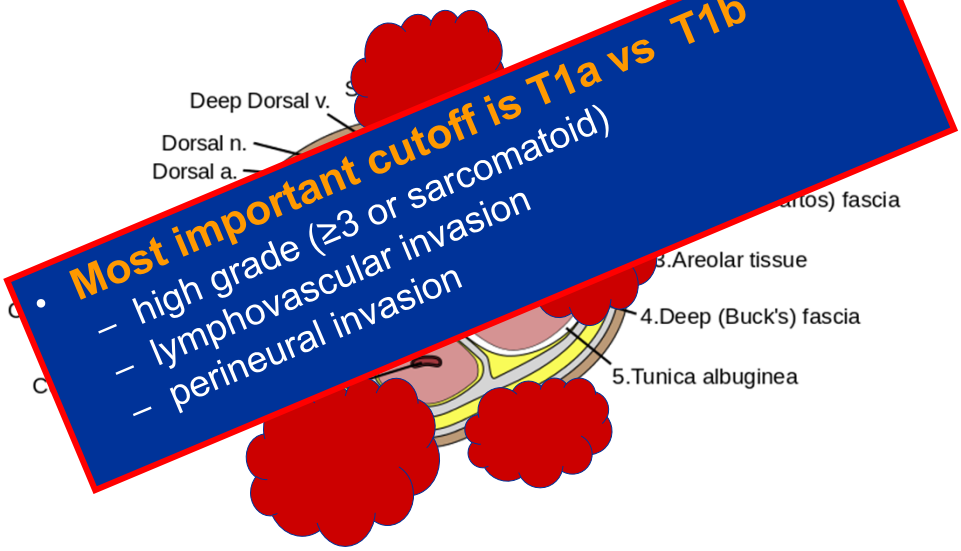

- **Most important cutoff is T1a vs T1b**
  - high grade (≥3 or sarcomatoid)
  - lymphovascular invasion
  - perineural invasion

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Penile Cancer Staging

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Regional lymph nodes (N)

- cN0: No palpable or visibly enlarged inguinal lymph nodes
- cN1: Palpable mobile unilateral inguinal lymph node
- cN2: Palpable mobile ≥2 unilateral or bilateral inguinal lymph nodes
- cN3: Palpable fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral

- pN1: ≤2 unilateral inguinal lymph node, no ENE
- pN2: ≥3 unilateral or bilateral inguinal lymph nodes
- pN3: ENE of LN metastases or pelvic LN metastases

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Penile Cancer Staging

AJCC TNM 8th ed

Managing Inguinal LNs with penile cancer:

Depends on stage of primary and palpability of nodes

1. **Non-palpable** inguinal LNs (cN0)
   - *observation for low risk primary*
   - *surgery or DSNB for high risk primary*

2. **Palpable (non bulky = <4cm)** inguinal LNs (cN1/cN2)
   - *low risk primary = is it cancer? antibiotics/perc biopsy/DSNB…if negative consider surveillance vs superficial LND (formal superficial and deep ILND if +)*
   - *high risk primary or + = ILND*

3. **Palpable (bulky = >4cm)** inguinal LNs (cN2/cN3)
   - *FNA and Neoadjuvant chemotherapy if +*
   - *FNA negative or FNA + and massively symptomatic = surgery*

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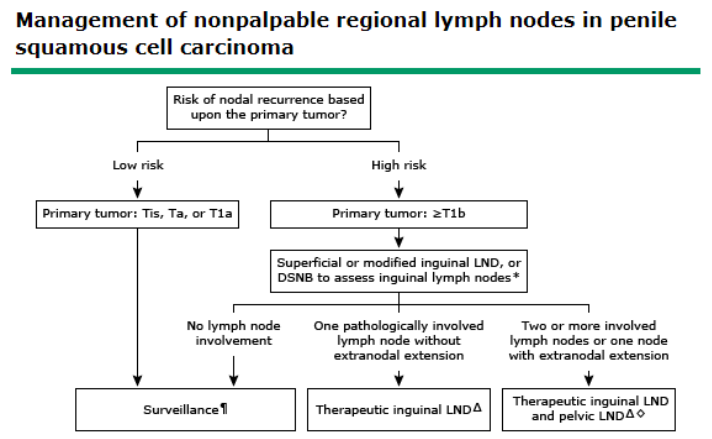
Take Home Message:

Managing inguinal LN with Penile Ca

3 conditions of the inguinal LN = **(1) Non-Palpable = cN0**



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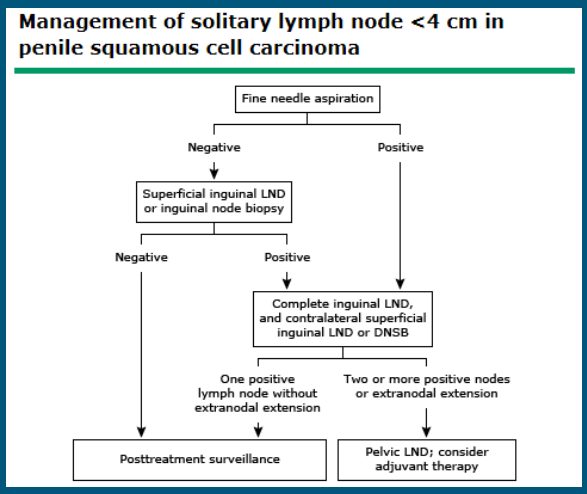
Take Home Message:
Managing inguinal LN with Penile Ca

3 conditions of the inguinal LN = **(2) Palpable but non-bulky (cN1/cN2) = image and then**



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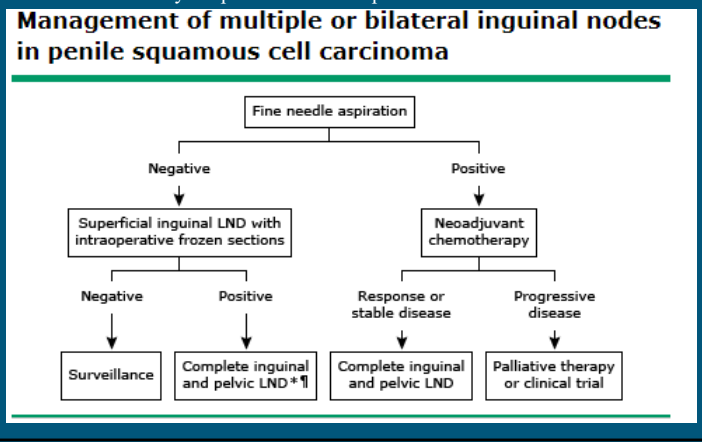
Take Home Message:
Managing inguinal LN with Penile Ca

3 conditions of the inguinal LN = **(3) Palpable and bulky or fixed = cN2/cN3**

- Up front ILND if very symptomatic or unilateral and mobile
- XRT only for palliation if unresponsive and unresectable



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Overview

- Squamous Cell Carcinoma
  - Presentation
  - Prognosis
  - Surgical management
    - Managing the primary tumor
    - Managing LNs
  - Systemic Rx
- Non squamous Penile Malignant Tumors
- Urethral Cancers

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AUA Core Curriculum: Penile Cancer

https://auau.auanet.org/core

SCC

- **Usual**
- **Warty (condylomatous)**
- **Verrucous**
- **Papillary**
- **Basaloid**
- **Sarcomatoid**
- **Adenosquamous**
- **Pseudoglandular**
- **Cuniculatum**
- **Pseudohyperplastic**
- **mixed**

Malignant Epithelial tumors

- Clear cell carcinoma
- Extramammary Paget's Disease
- Melanoma

Other

- sarcoma (Kaposi's, leiomyosarcoma)
- Malignant lymphoma
- metastases

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Etiology and Incidence of SCC

- Incidence low (1500-2000 cases/yr in US with about 400 deaths)
  - Most common in 50-70 year old range
  - <1% of all male cancers in US
  - 10-20% of male cancers in Africa/Asia
- Risk factors
  - No circumcision (22x), chronic inflammation/poor hygiene
    - Neonatal circ *nearly eliminates risk* of invasive SCC but not CIS
    - **Adult circumcision does not decrease risk**
  - 60%+ of all SCC associated with HPV (16>18)
    - HPV vaccination may/should decrease risk
      - Current vaccine is a quadrivalent (6, 11, 16, 18)
      - New vaccine is a against 9-valent - 6, 11, 16, 18, 31, 33, 45, 52 and 58
  - Tobacco exposure (all forms)

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Benefits of Circumcision

Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial

Robert C Bailey, Stephen Moses, Corette B Parker, Kawango Agot, Ian Maclean, John N Krieger, Carolyn F M Williams, Richard T Campbell, Jeckoniah O Ndinya-Achola

RCT n=2784 men aged 18-24 randomized to circ vs control

The 2-year HIV incidence:
- **2.1% in circumcision group vs 4.2% in control group (p=0.0065)**

The relative risk of HIV infection in circumcised men was 0.47 (0.28–0.78)
- **reduction in the risk of acquiring HIV decreased by 53%**

AEs related to the circumcision was 1.5% (n=21) and resolved quickly

No behavioral risk compensation after circumcision was observed

www.thelancet.com Vol 369 February 24, 2007

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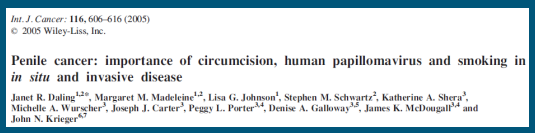
Benefits of Circumcision



Int. J. Cancer: 116, 606–616 (2005)
© 2005 Wiley-Liss, Inc.

Penile cancer: importance of circumcision, human papillomavirus and smoking in *in situ* and invasive disease

Janet R. Daling[1,2]*, Margaret M. Madeleine[1,2], Lisa G. Johnson[1], Stephen M. Schwartz[2], Katherine A. Shera[3], Michelle A. Wurscher[3], Joseph J. Carter[3], Peggy L. Porter[3,4], Denise A. Galloway[3,5], James K. McDougall[3,4] and John N. Krieger[6,7]

Population based case control study in Washington state

- **Men not circumcised at birth:**
  - **increased risk of invasive penile cancer (OR=2.3)**
  - ***not*** **at increased risk for in situ cancer**
  - **Phimosis strongly associated with penile cancer (OR=11.4)**
  - **No increased risk of penile cancer in absence of phimosis**
  - **Smoking increased risk (OR=4.5)**
  - **HPV detected in 79.8% of tumors (69.1% were HPV-16)**

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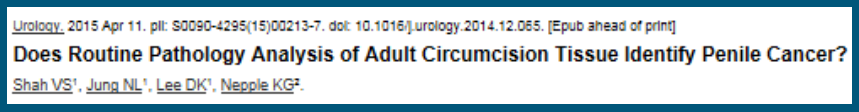
Foreskin Research



Urology. 2015 Apr 11. pii: S0090-4295(15)00213-7. doi: 10.1016/j.urology.2014.12.065. [Epub ahead of print]

Does Routine Pathology Analysis of Adult Circumcision Tissue Identify Penile Cancer?

Shah VS[1], Jung NL[1], Lee DK[1], Nepple KG[2].

Should you send foreskin for pathology in uncomplicated cases?

n=147 (excluded any cases with clinically suspicious lesions)

- **58% noted "inflammation"**
- **42% noted "normal skin"**
- **<1% (1 case) noted unsuspected pTis SCC in a pt with HIV**
- **Cost per case = $311**
- **Total cost >$30,000**

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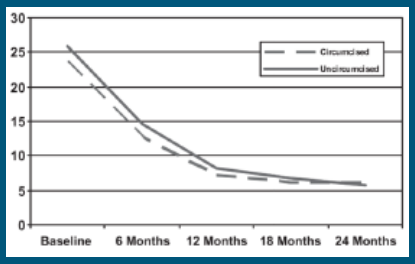
Sexual Risks of Circumcision

Adult Male Circumcision: Effects on Sexual Function and Sexual Satisfaction in Kisumu, Kenya

John N. Krieger, MD*, Supriya D. Mehta, PhD, MHS†, Robert C. Bailey, PhD, MPH†, Kawango Agot, PhD, MPH‡, Jeckoniah O. Ndinya-Achola, MD§, Corette Parker, PhD¶, and Stephen Moses, MD**

- **Evaluated inability to ejaculate, premature ejaculation, pain with intercourse, pleasurability, difficulty achieving or maintaining erections and overall risk of any sexual dysfunction**
- **Noted higher than expected baseline rates in young men**
- **Noted no difference with circumcision in *any* parameter measured**



J Sex Med. 2008 November ; 5(11): 2610–2622.

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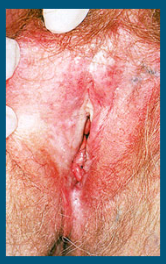
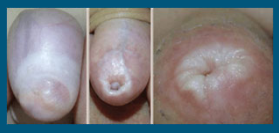
Lichens Sclerosus
(a benign condition)



- Pathology/Etiology (unknown)
  - Benign progressive inflammatory condition
  - 85-95% in the anogenital region
- In women mostly vulvar
  - Two peaks = prepubertal and perimenopausal
  - pruritis/dyspareunia/dysuria
  - Dx is clinical +/- biopsy
  - Have increased risk of developing vulvar SCC
  - Treat all women with this dx – even if asymptomatic (mostly topical steroids)
    - clobetasol propionate 0.05% for 6-12 weeks



- In men this is called BXO (balanitis xerotica obliterans)
  - Can develop thick, phimotic foreskin or strictures
  - Rx = topical steroids until remission then weekly
  - If resistant – use systemic retinoids (acitretin)

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Precancerous Lesions
(80% are HPV related)

- Penile Intraepithelial Neoplasia (PeIN)
  - Carcinoma In Situ
    - On the Glans or prepuce = Erythroplasia of Queyrat
    - On the Penile Shaft = Bowen's disease
  - Subdivided morphologically/ microscopically
    - Differentiated – flat, pearly white/red, irregular borders
    - Basaloid - small cells with scant basophilic cytoplasm
    - Warty and warty-basaloid subtypes - epithelium composed of papillary fronds of atypical squamous cells.
  - strongly correspond with the appearance of their invasive counterparts

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Precancerous Lesions

- Bowenoid Papulosis vs CIS:
  - Can occur in males or females
- Penile CIS vs Bowenoid papulosis
  - both have HPV 16
  - Bowenoid = pigmented papules on the skin or glans, dx by bx, younger patients, histologically similar to CIS, clinical course is benign. *Rx is observation* as many will regress spontaneously vs excision
- CIS = Rx requires excision and or topical therapy

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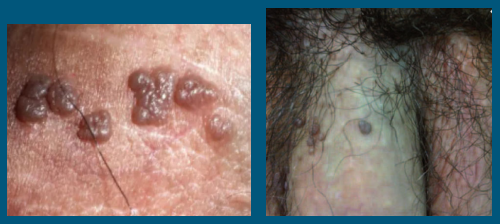
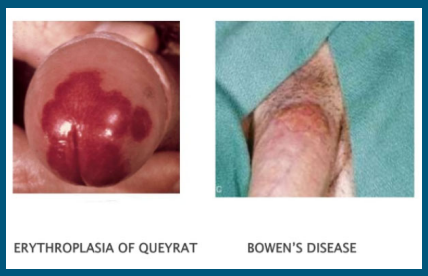
Precancerous Lesions

Both are intraepithelial neoplasias but they differ in age, growth patterns, risk of progression to Ca, Rx

Papulosis (observe) **CIS (treat)**





ERYTHROPLASIA OF QUEYRAT BOWEN'S DISEASE

https://www.slideshare.net/VikasKumar59/carcinoma-penis

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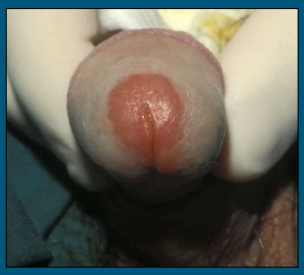
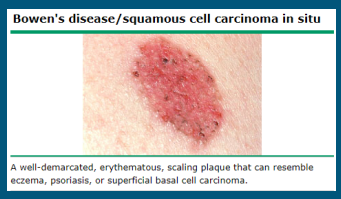
SCC in situ (Tis)

- Erythroplasia of Queyrat
  - Glans or prepuce
- Bowen's disease
  - Penile shaft
- 10% may progress to invasive carcinoma
  - Not associated with visceral malignancies
- Treatment – bx for dx
  - 5-FU
    - 5% cream applied QOD x 4-6 weeks
  - 5% imiquimod cream
    - 5% cream applied 5 of 7 days x 4-6 weeks
  - Laser + circ
  - Excision +/- STSG + circ
  - Glansectomy or resurfacing





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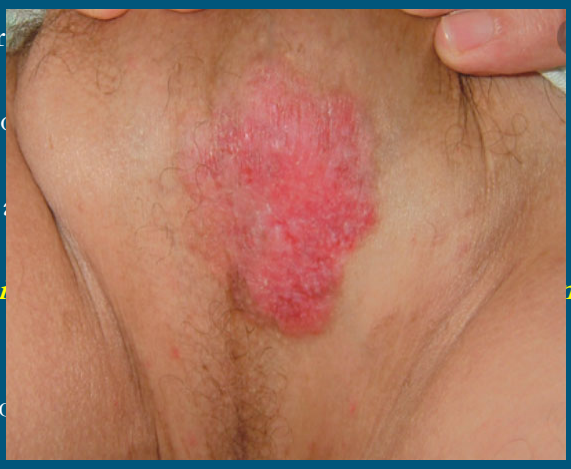
Extramammary Pagets

- May pr
- Often
- A rare
- *Assoc*
  - Get
- Wide l



of the skin

ncy in 45%

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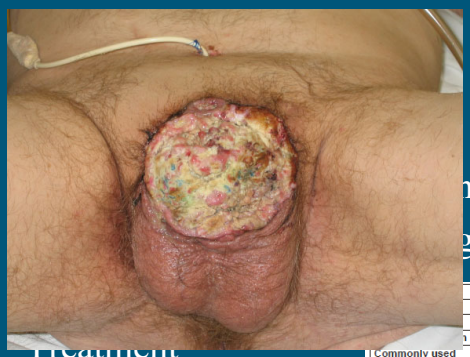
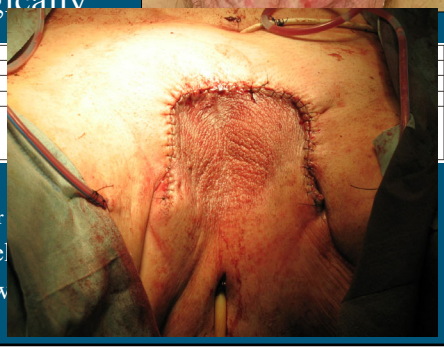
Verrucous Carcinoma (Ta)

By definition = well differentiated





- nt tissues
- gically
- Treatment
  - Topical
    - 5-FU 5% BID for 2-6 weeks
    - 5% imiquimod cream at night 3x/week for
  - Laser (3-5% acetic acid perioperativel
  - Excision (i.e. glansectomy or Mohs) w

Commonly used settings

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AUA Core Curriculum: Invasive Penile Cancer

https://auau.auanet.org/core

Invasive SCC of the Penis	Risk of Progression/Death
Usual (2/3 of all cases)	30-40%
Warty (condylomatous)	20%
Verrucous	<1%
Papillary	20%
Basaloid	50-100%
Sarcomatoid	50-100%
Adenosquamous	50% (but high CSS)
Pseudoglandular	
Cuniculatum	<1%
Pseudohyperplastic	<1%
mixed	

** tumor grade, depth of invasion, and the presence of perineural invasion remain most important prognostic factors

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Invasive SCC

- 0.4-0.6% of cancers in US and Europe
- Preputial cavity of uncircumcised older men
- Neonatal circumcision eliminates risk
- HPV-16 (also HPV-18, -31, -33)
  - New vaccine is a against 9-valent - 6, 11, 16, 18, 31, 33, 45, 52 and 58
- Risk factors
  - Poor hygiene
  - Smoking
  - Phimosis
  - # Sexual partners
  - Lichen sclerosis
- If untreated, most die within 2 years
- Wives and partners of men with penile cancer have a 3x risk of cervical cancer
  - PAP smear and pelvic exam is prudent

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Invasive SCC

- Presentation
  - Non-healing ulcer
  - Papule
  - Indurated mass
  - Exophytic growth
- Most common location is glans (46%), then prepuce (21%)
- Bleeding or purulent discharge
- Can rarely present as an inguinal mass or abscess related to metastatic disease

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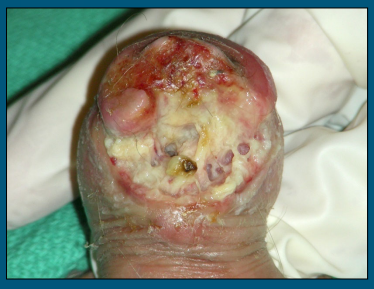
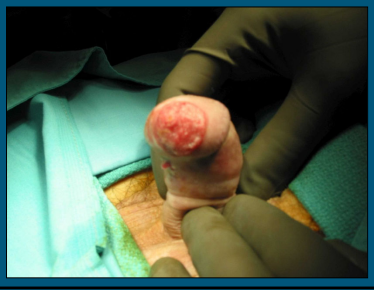
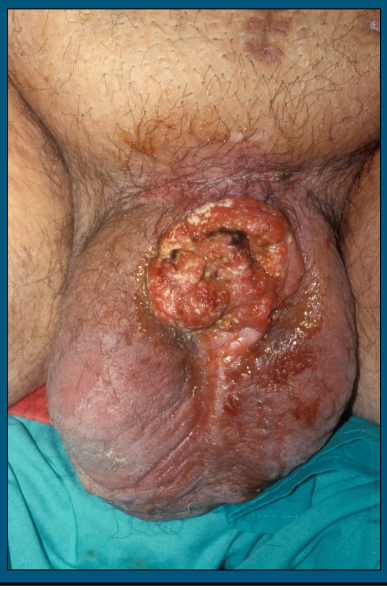
Invasive SCC







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Diagnosis and Staging

- Delay in diagnosis is common
  - Requires physician awareness and examination
- Need biopsy to confirm diagnosis
- Careful palpation primary and inguinal regions
- CT
  - Evaluate inguinal nodes if obese or previous surgery
  - Evaluate pelvic nodes if inguinal nodes (+)
- MRI
  - Best study for assessment of extent of primary tumor (if needed)

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Penile Cancer Staging

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Primary tumor (T)

•Tis: Carcinoma *in situ (Penile Intraepithelial Neoplasia)*

•Ta: Noninvasive localized squamous cell carcinoma (verrucous carcinoma)

•T1 = invades subepithelial connective tissue

- Glans = tumor invades lamina propria
- Foreskin = tumor invades dermis, lamina propria or dartos
- Shaft = tumor invades tissue between epidermis and corpora regardless of location

- T1a: NO LVI, NO PERINEURAL INVASION AND IS NOT HIGH GRADE (i.e. grade 3 or sarcomatoid)
- T1b: EXHIBITS LVI and/or PERINEURAL INVASION OR IS HIGH GRADE

•T2: Tumor invades corpus spongiosum (glans or ventral shaft) with or without urethral invasion

•T3: Tumor invades corpus cavernosum (including tunica albuginea) with or without urethral invasion

•T4: Tumor invades adjacent structures (i.e. scrotum, prostate, pubis)

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Penile Cancer Staging

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Managing Inguinal LNs with penile cancer:

Depends on stage of primary and palpability of nodes

1. **Non-palpable** inguinal LNs (cN0)
   - *observation for low risk primary*
   - *surgery or DSNB for high risk primary*

2. **Palpable (non bulky = <4cm)** inguinal LNs (cN1/cN2)
   - *low risk primary = is it cancer? antibiotics/perc biopsy/DSNB…if negative consider surveillance vs superficial LND (formal superficial and deep ILND if +)*
   - *high risk primary or + = ILND*

3. **Palpable (bulky = >4cm)** inguinal LNs (cN2/cN3)
   - *FNA and Neoadjuvant chemotherapy if +*
   - *FNA negative or FNA + and massively symptomatic = surgery*

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Penile Cancer - Step 1

- First step = Treat the primary (eliminate it) and stage
- Options
  - Laser
  - Mohs
  - Local excision
    - circumcision/partial/total glans resection +/- skin graft
  - Partial or total penectomy

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Laser

- Preserves surrounding tissues and penile function
  - Tis, small Ta and T1 tumors
  - Apply 5% acetic acid prior to Rx to identify pre-malignancy areas
  - Manageable T2 tumors in patients who refuse more aggressive treatment
- CO_2 or ND-Yag – best suited for Tis
- 3-5 mm surgical margin
- Local recurrence: ~ 20%

	CO2	Nd:YAG	KTP
Type	Gas	Solid state	Solid state
Wavelength	10,600 nm	1,064 nm	532 nm
Tissue penetration	0.1 mm	3–4 mm	1–2 mm
Commonly used settings	Spot size: 3 mm Power: 5–10 W Pulse: continuous or superpulse 100–200 Hz	Spot size: 5 mm Power: 40 W Pulse duration: 1 ms Pulse frequency: 10–40 Hz	Fiber size: 400 or 600 um Power: 5–10 W Pulse duration: 10–20 ms Repetition Rate: 2 Hz

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Mohs Microsurgery

- **Tissue excision in thin layers with immediate microscopic exam and tumor mapping**
- **Elimination of tumor with maximal local tissue preservation**
- **Requires significant technical support and surgeon experience**
- **Tis or small superficially invasive tumors**
- **Local recurrence: 6%**

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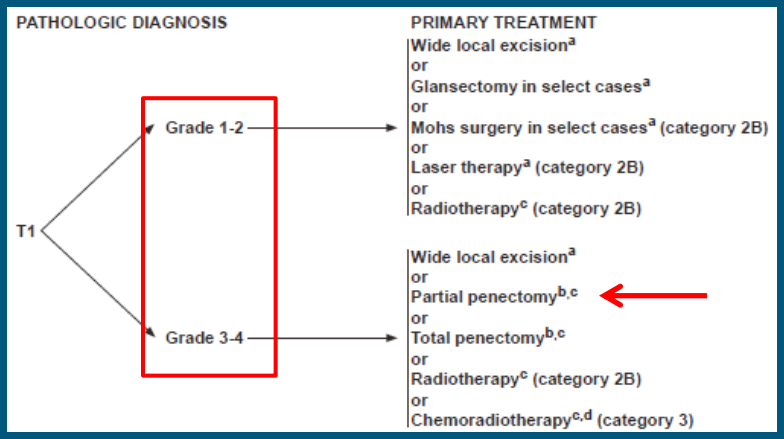
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Penile Cancer



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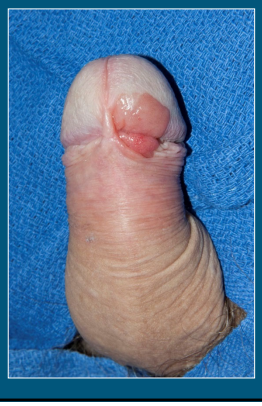
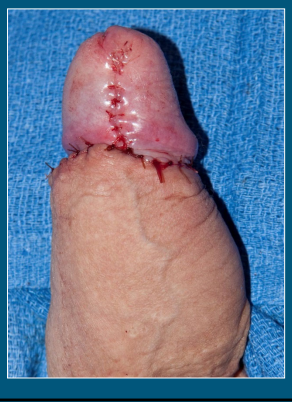
Conservative Surgical Excision

- Recent studies have indicated that a 2 cm margin may not always be required for effective local tumor control
- Simplest form
  - Excisional biopsy
  - Circumcision





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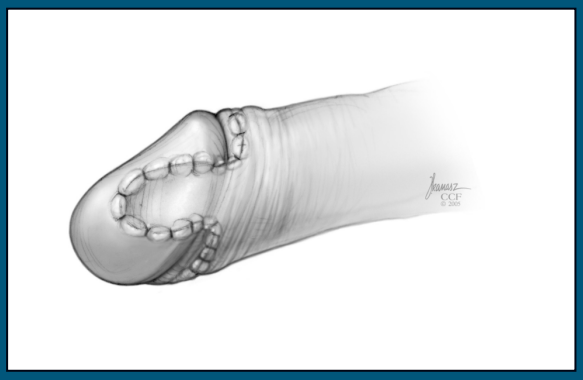
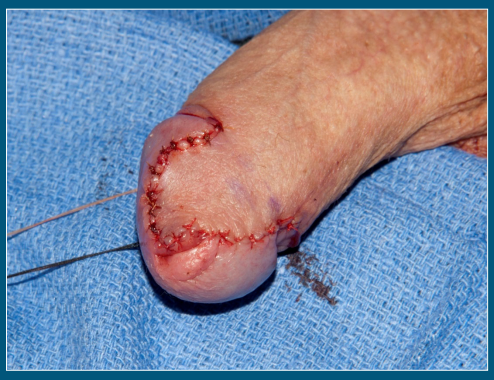
Conservative Surgical Excision

- Partial glans excision – preputial flap





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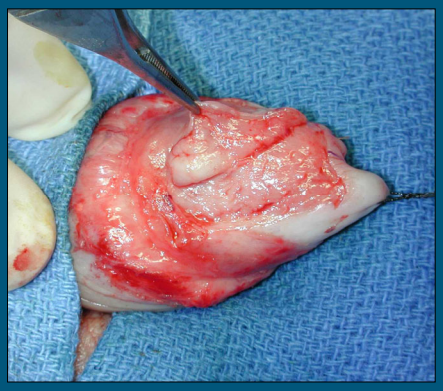
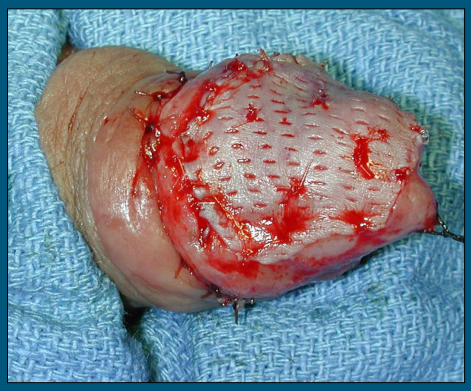
Conservative Surgical Excision
Glans Resurfacing

- Partial glans excision – STSG





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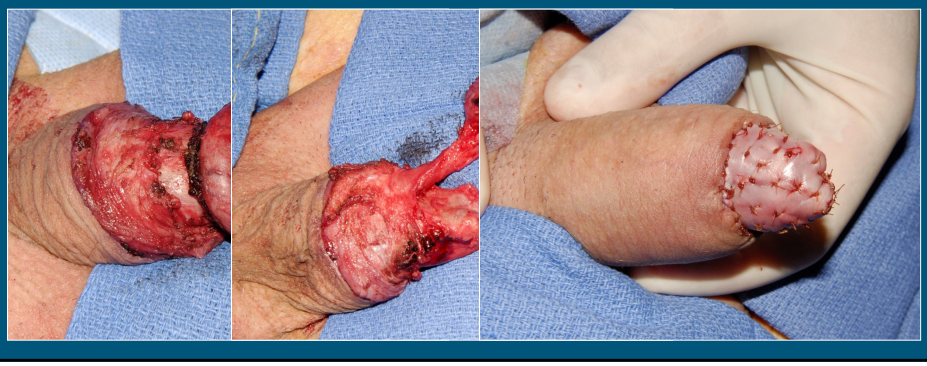
Conservative Surgical Excision
Glans Resurfacing

- Complete glansectomy sparing the corpora cavernosa, or with distal corporectomy
- Glans reconstruction using STSG to tips of corpora



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Conservative Surgical Excision

- Key points:
  - Negative margins important
    - Intraoperative frozen section
    - Local recurrence: 8-11%
  - Careful long-term follow-up mandatory for conservative Rxs
    - Pt self exam and physician re-exam

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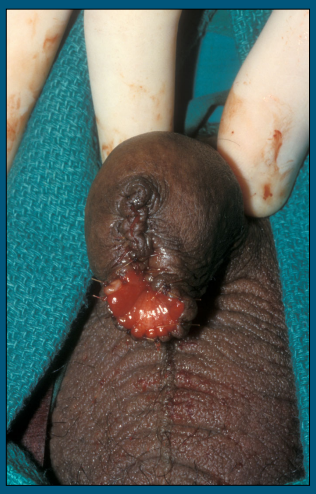
Partial Penectomy

- Most commonly performed procedure
- Amputation of penis
  - Prior margin was 2 cm proximal to tumor – now just a negative margin
- Goal is to allow standing to void
- Local recurrence: 0-8%
- Adequate sexual function: 20%



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Total Penectomy

- Performed when tumor size or location would not allow upright voiding when adequate margin is excised
- Amputation near the base of the penis
- Perineal urethrostomy
- Excellent rates of local control

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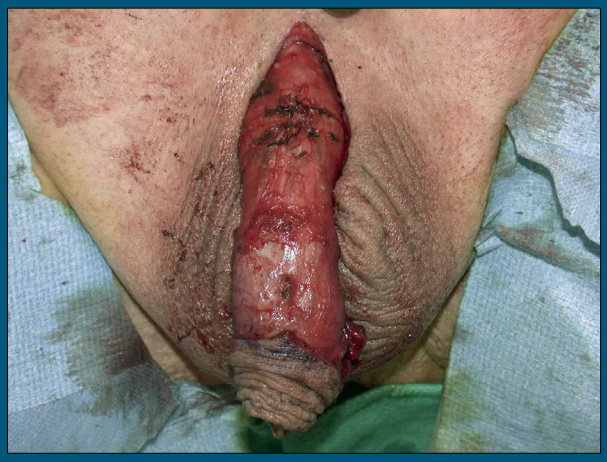

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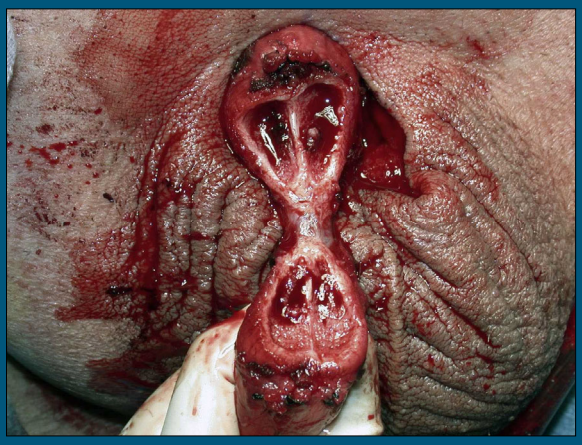

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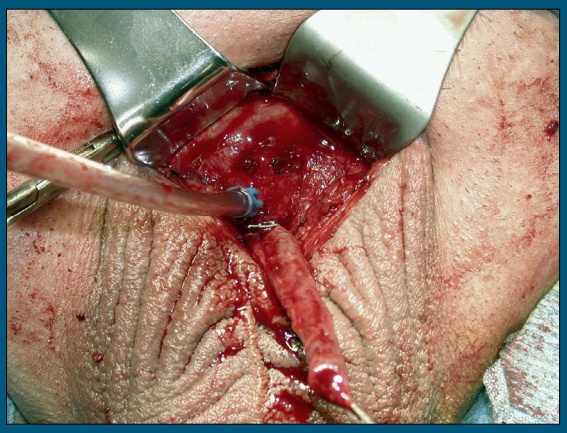

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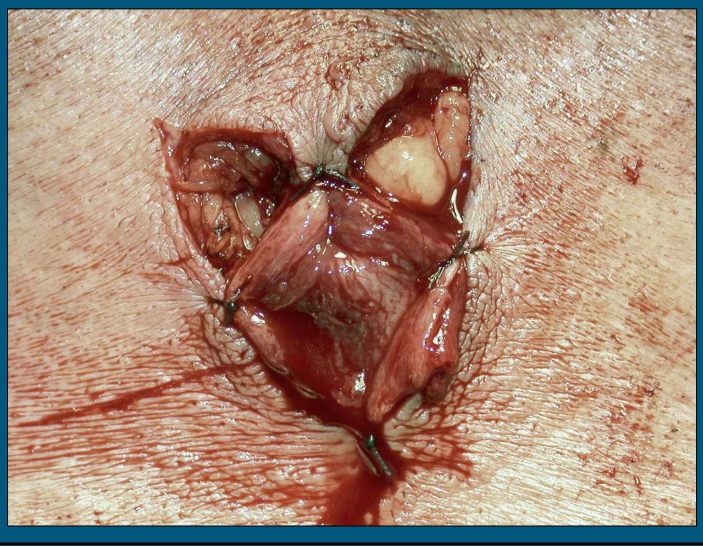

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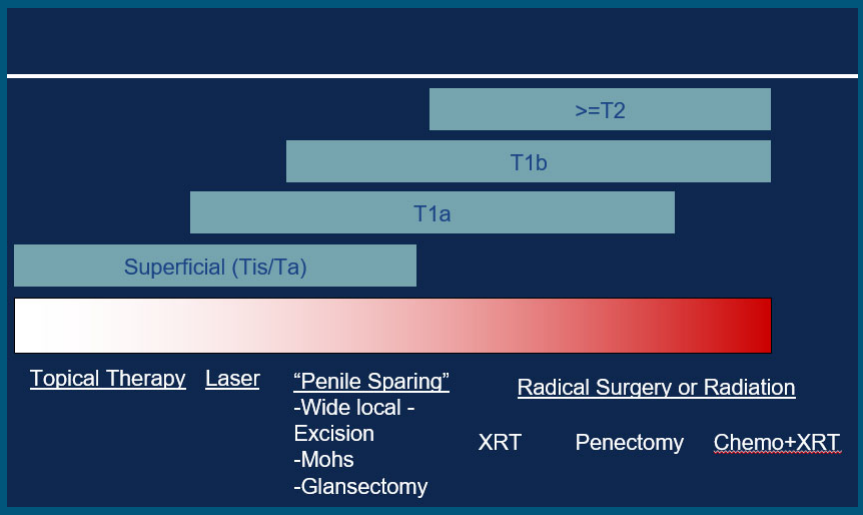
Overview penile cancer:

1. Manage the primary
2. Manage the nodes



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Summary of treatment of the Primary

- Use an organ sparing approach when possible
  - Patient selection key
  - Minimizes disfigurement
  - Minimizes functional disruption
- Risk Factors for local recurrence
  - 75% RFS all comers, all approaches (Baumgarten et al J Urol 2018)
  - a positive margin (data no longer mandate 2cm minimum)
  - > T2 stage
  - LVI
- Close postoperative surveillance
  - Node recurrences occur most often in year 1-2
  - Local recurrences can occur as far out as 5 years

Chakiryan et al J Urol 2021

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Penile Cancer - Step 2

- After eliminating the primary tumor, the next step is to manage the regional lymph nodes
- This step starts with staging/examination of the groin
  - Non-palpable inguinal LNs = cNo
    - ***observation for low risk – node dissection for high risk***
  - Palpable (non bulky = <4cm) inguinal LNs = cN1.cN2
    - ***node dissection***
  - Palpable (bulky = >4cm) inguinal LNs = cN2/cN3
    - ***neoadjuvant chemotherapy***

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Principles of Regional Lymph Nodes (LN's)

- Tumor spread is generally to regional nodes (superficial to deep to pelvic) prior to distant metastasis (Halsteadian)
- First echelon drainage is to superficial and deep inguinal LN's and may occur bilaterally (60-80% crossover)
- Second echelon drainage is from the inguinal LN's to the ipsilateral external iliac nodes
- Lymphadenectomy is both diagnostic and therapeutic in SCC of the penis
  - May cure 30-80% of patients
- In general you dissect one level beyond positivity

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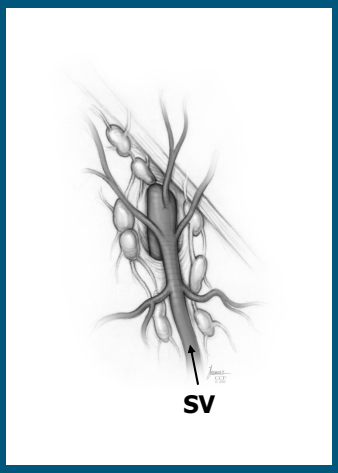
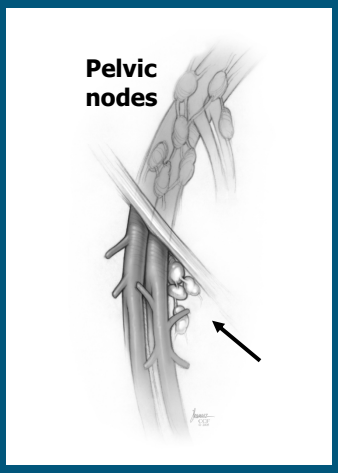
Inguinal Lymph Nodes

Superficial – above fascia lata



Deep - below fascia lata



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Clinically Negative Groins (non-palpable nodes)

- Low risk Disease (Tis, Ta, T1a (low grade))
  - Observation – frequent physical exam or periodic CT scan if obese or previous surgery (q3 mo)
- High risk disease (≥T1b)
  - Surgical assessment of inguinal nodes
    - *Bilateral superficial ILND – proceed to deep dissection if these are +*
  - Dynamic sentinel LN biopsy possible

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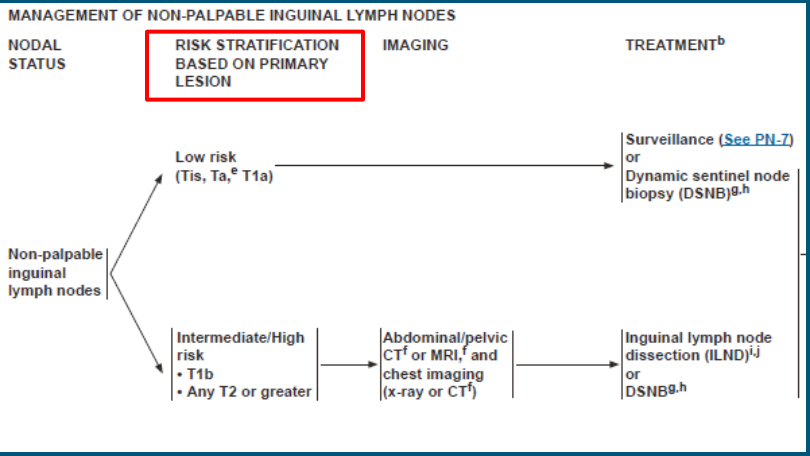
Management of Non-Palpable LNs

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Penile Cancer



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Surgical Assessment of cNo Inguinal nodes for high risk disease

- Superficial inguinal lymphadenectomy
  - Open/lap or robotic
    - similar nodal harvest, LOS, RFS, lymphocele – but more flap necrosis with open*
  - Create thick flaps
  - Exclude area lateral to the femoral artery, caudal to fossa ovalis
  - Preservation of saphenous vein
  - No sartorius transposition

- Modified (complete or therapeutic) inguinal LND
  - As above but include nodes within the fossa ovalis by dissecting down to the femoral vessels (i.e. deep inguinal nodes)

* Singh A et al J Urol 2017

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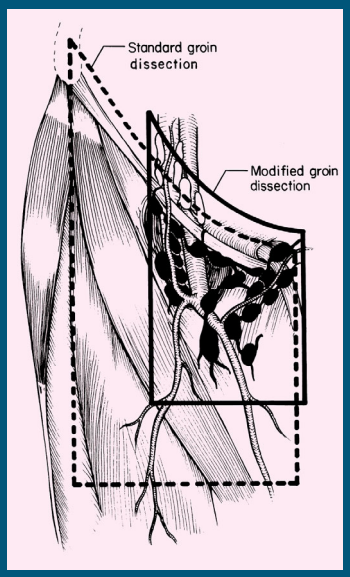
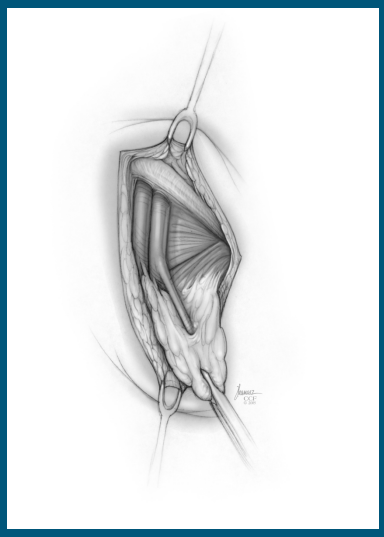
Modified Inguinal Lymphadenectomy





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Modified Inguinal Lymphadenectomy

- Complications – usually minor
  - Seroma (25%) or lymphorrhea (10%)
  - LE edema – usually mild (20%)
  - Infection (0-9%)
  - Open vs robotics = similar nodal harvest, LOS, RFS, lymphocele – but more flap necrosis with open
  - Can be done concomitant with primary – best if done within 3 mo (Huelster HL et al J Urol 2023)
- Caveats
  - If frozen section (+), convert to a standard lymphadenectomy
  - If inguinal metastatic disease develops on one side well after treatment of the primary tumor, contralateral surgical assessment of inguinal nodes not required

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Initial Management – Palpable Nodes

- Traditional teaching
  - Antibiotics for palpable nodes x 4-6 weeks as they may be inflammatory
  - Reasonable if nodes are small and there is a ***low risk*** of nodal metastases (e.g. low pT stage) with an infected primary
- However, if there is adenopathy and LN disease is strongly suspected, ***surgical treatment should not be unduly delayed***
- Lower threshold for FNA/biopsy to confirm diagnosis more quickly if needed

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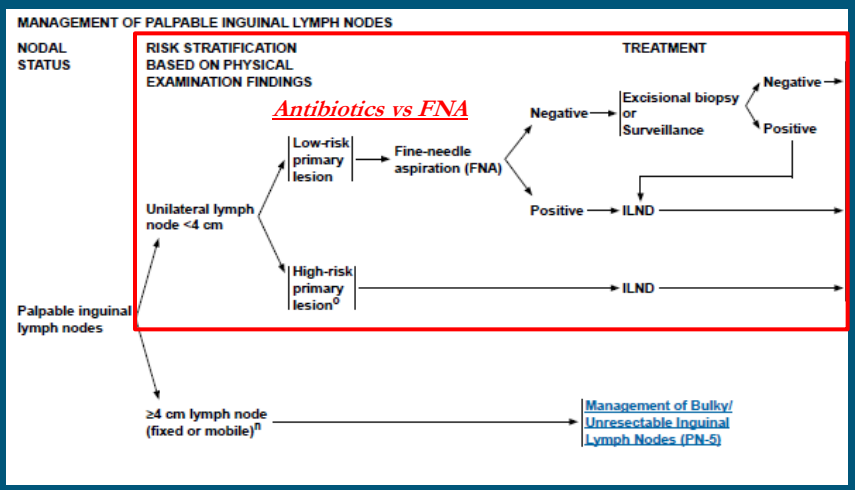
Management of Palpable (non-bulky) LNs cN1/cN2

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Penile Cancer



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ILND is diagnostic AND Therapeutic

Early lymph node dissection is associated with improved survival in patients with positive nodes as compared to delaying lymph node dissection until nodes become palpable.

On MVA – ILND was associated with improved CSS = Joshi et al JAMA Oncology 2018

Unfortunately, as many as 60%+ of those eligible do not get a ILND
Zhu et al Annals of Surg Onc 2019

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Management of Palpable (bulky) LNs (cN2/cN3)

- For patients with bulky (>4cm) or fixed nodes
  - Establish dx by FNA or bx
  - ***Multimodal approach***
    - neoadjuvant systemic chemotherapy (+ XRT if unresectable)
    - Consolidative surgery (superficial/deep ILND) in pts with tumor regression or stability
  - Upfront ILND if highly symptomatic pts (pain, skin infection/breakdown, bleeding) provided fully resectable
  - *Ipsilateral pelvic LND in patients with 2 or more +LNs on the superficial/deep ILND or extranodal extension*
  - Adjuvant systemic chemotherapy in selected high risk pts

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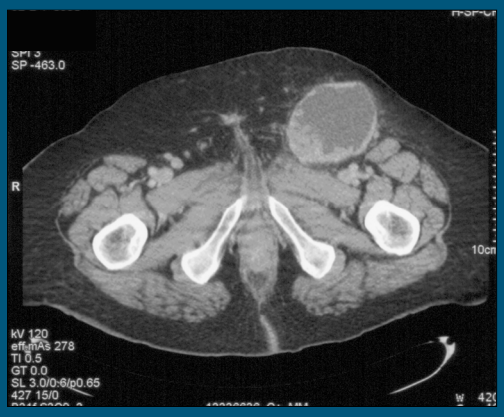
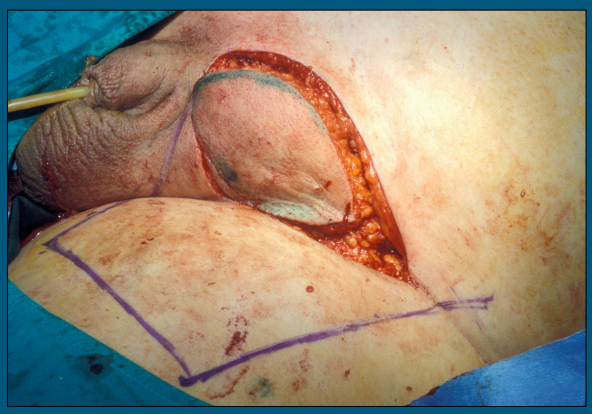
Management of Palpable (bulky) LNs





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Management of Palpable (bulky) LNs (cN2/cN3)

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Penile Cancer

MANAGEMENT OF BULKY/UNRESECTABLE INGUINAL LYMPH NODES

NODE STATUS | LYMPH NODES | TREATMENT

Palpable inguinal lymph nodes ≥4 cm (fixed or mobile)

- Unilateral; mobile → FNA
  - Positive → ILND[b] or Consider neoadjuvant chemotherapy[l] followed by ILND
    - 0-1 positive nodes with viable disease[q] → See Surveillance (PN-6)
    - ≥2 nodes positive or extranodal extension[r] → Pelvic lymph node dissection (PLND)[b] (category 2B)[s] → See Surveillance (PN-6)
  - Negative → Excisional biopsy
    - Negative → See Surveillance (PN-6)
    - Positive → Neoadjuvant chemotherapy[l] → ILND[b] and PLND[b] → See Surveillance (PN-6)
- Multiple or bilateral inguinal lymph nodes; mobile or fixed → FNA
  - Negative → Excisional biopsy
  - Positive → Neoadjuvant chemotherapy[l]
- Pelvic lymph nodes enlarged[p]
  - Potentially resectable → Neoadjuvant chemotherapy[l]
    - Stable or clinical response → Consolidation surgery[t] → See Surveillance (PN-6)
    - Disease progression or non-resectable → Additional systemic chemotherapy[l] with consideration of radiation therapy for local control[e] or Clinical trial
  - Non-surgical candidate → Radiotherapy[e] with concurrent chemotherapy[l] → See Surveillance (PN-6)

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Management of Clinically Positive Nodes

- Radical (Standard) Ilioinguinal Lymphadenectomy
  - Resectable metastatic disease
- Boundaries
  - Superior: Line from external ring to ASIS
  - Lateral: Line from ASIS inferiorly for 20 cm
  - Inferior: Inferior boundary of femoral triangle
  - Medial: Line from pubic tubercle inferiorly 15 cm
- May be curative in 30-60% of cases

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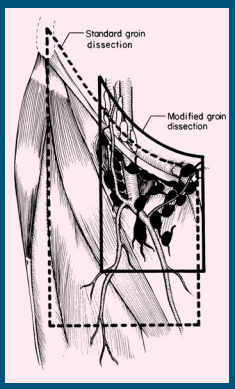
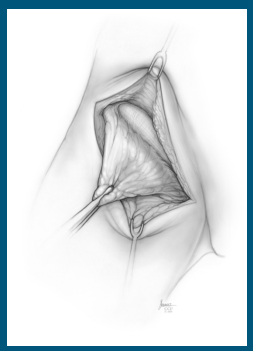
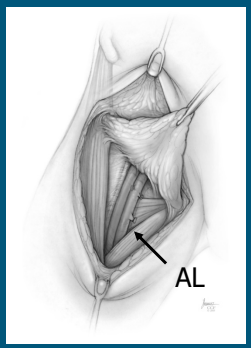
Radical (Standard) Ilioinguinal Lymphadenectomy







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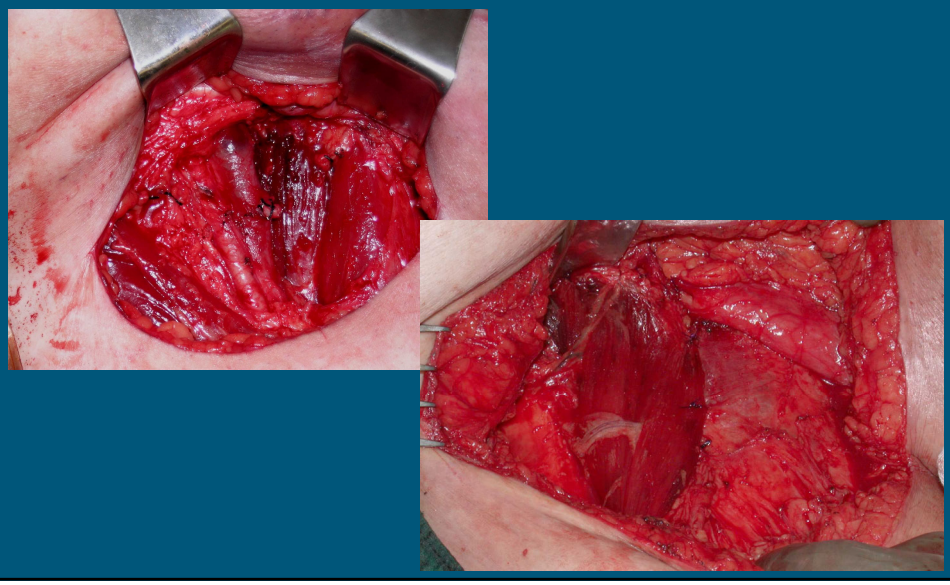
Radical (Standard) Ilioinguinal Lymphadenectomy



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Radical (Standard) Ilioinguinal Lymphadenectomy

- Saphenous vein may be preserved in some patients with low volume metastatic disease
- Ipsilateral pelvic nodes almost never involved if inguinal nodes are negative
- Pelvic lymphadenectomy indicated in setting of ≥2 positive ipsilateral inguinal nodes or extranodal extension
  - External iliac
  - Obturator
  - Distal common iliac
- Palliative ilioinguinal lymphadenectomy may be indicated in selected patients to prevent complications of infection, drainage or femoral hemorrhage

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Radical (Standard) Ilioinguinal Lymphadenectomy

- Minor Complications: 40-50%
- Major Complications: 5-21%
  - Marked lymphedema
  - Flap necrosis
  - Symptomatic lymphocele
- Associated with cure following LN surgery
  - Unilateral inguinal nodal involvement
  - ≤ 2 positive nodes
  - No extranodal tumor extension
  - No pelvic metastases

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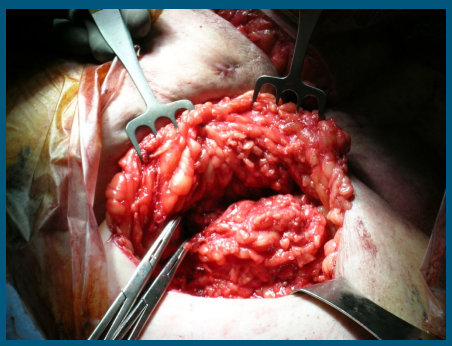
Prognosis

- The most important factor determining survival is the extent of lymph node metastases
- Poor prognosis
  - Bilateral inguinal nodes (N2+)
  - > 2 inguinal nodes (N2+)
  - Extracapsular tumor
  - Pelvic nodes (N3)
  - HPV negative tumors (as with Head and Neck tumors)
    - May respond better to chemo and radiation therapy



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Patient Management

- A positive groin exam
  - With low risk primary – consider antibx vs FNA
  - With high risk primary - bilateral superficial ± deep dissection (standard dissection)
  - If bulky – multimodal therapy - chemo +/- dissection

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Recurrent Disease

- 74.1% of recurrences within first 2 years
  - Regional (Nodal): All < 5 years
  - Local: May occur later and represent a second tumor site
- Follow for 5 years, and emphasize patient self-exam thereafter

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Radiation Therapy

- Limited role in SCC penis
- EBRT and brachytherapy have been used
- May be considered:
  - Small, superficial lesions on the glans penis
  - Patients who refuse surgery
- Local control rates inferior to surgery
- Complications
  - Urethral fistula or stricture
  - Necrosis
  - Pain and edema

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Chemotherapy

- Indicated for unresectable locoregional tumor or distant metastatic disease
- Sites of distant metastases
  - Lung
  - Bone
  - Liver
- Most commonly used
  - TIP
    - Paclitaxel, ifosfomide, cisplatin
  - 5FU + cisplatin

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Chemotherapy for Penile Cancer

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Penile Cancer

PRINCIPLES OF CHEMOTHERAPY

Preferred combination chemotherapy regimens

TIP[2]

Paclitaxel 175 mg/m² IV over 3 hours on Day 1
Ifosfamide 1200 mg/m² IV over 2 hours on Days 1-3
Cisplatin 25 mg/m² IV over 2 hours on Days 1-3
Repeat every 21 days

5-FU + cisplatin[4] (category 2B)

Continuous infusion 5-FU 1000 mg/m²/d IV on Days 1-5
Cisplatin 100 mg/m² IV on Day 1
Repeat every 3 to 4 weeks

Radiosensitizing agents and combinations[11] (For radiotherapy with concurrent chemotherapy)

- Preferred
  - Cisplatin alone, or in combination with 5-FU
- Alternate options
  - Mitomycin C in combination with 5-FU
  - Capecitabine

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In-PACT Trial

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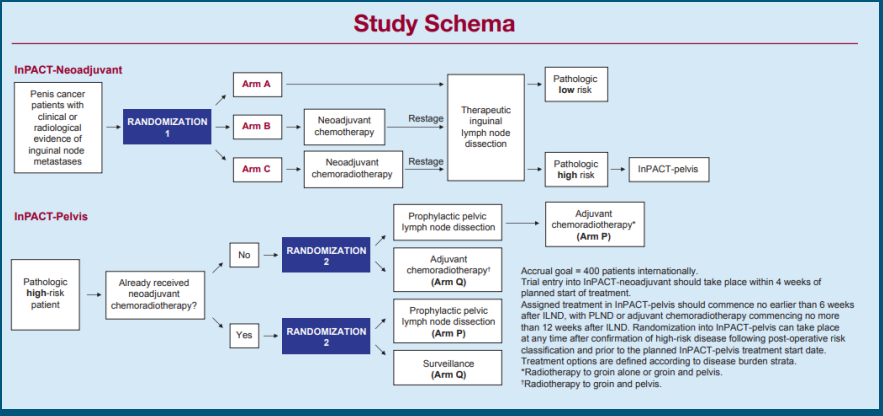
(international penile advanced cancer trial)



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Uncommon Penile Cancers

- Basal cell – local excision is curative
- Melanoma – most often on glans
  - Local or radical excision +/- systemic Rx
- Sarcomas – local aggressive surgical Rx
- Metastatic disease
  - Virulent, painful, advanced – Rx locally
  - Prognosis <1y

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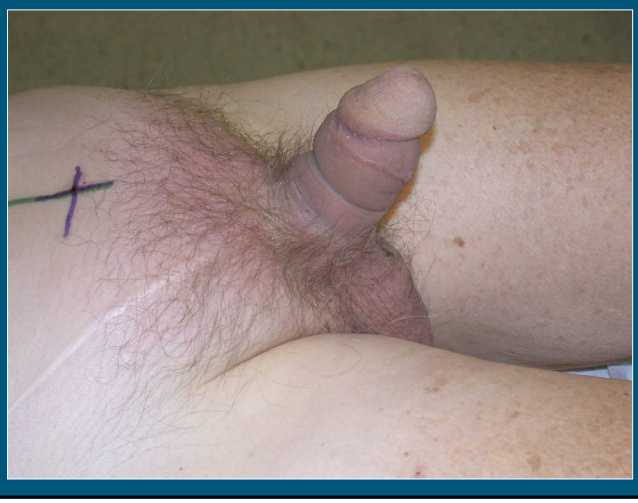
Uncommon Penile Cancers



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Male Urethral Cancer

- Rare
- Etiologic factors
  - Chronic inflammation
    - Urethral stricture
    - Urethritis
    - STD
  - Probably HPV-16
- Onset is usually insidious
- Symptoms
  - Urethral bleeding
  - Palpable mass
  - Obstructive voiding symptoms

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AUA Core Curriculum: Urethral Cancer

https://auau.auanet.org/core

- Location
  - Bulbomembranous (posterior): 60%
  - Penile (anterior): 30%
  - Prostatic: 10%
- Pathology
  - Bulbomembranous: SCC 80%
  - Penile: SCC 90%
  - Prostatic: UCC 90%

Table 1. Urethral Cancer Histology and Location
Male Urethra
Histology: 80% Squamous; 15% Urothelial; 5% Adenocarcinoma and others
Sites: Bulbomembranous = 60%; Penile = 30%; Prostatic Urethra = 10%

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Tumor Staging

Male penile urethra and female urethra	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades any of the following: Corpus spongiosum, periurethral muscle
T3	Tumor invades any of the following: Corpus cavernosum, anterior vagina
T4	Tumor invades other adjacent organs (eg, invasion of the bladder wall)

- Direct extension to adjacent structures
  - Corpus spongiosum, Periurethral tissues, Corpora cavernosa
- Lymphatic drainage
  - Anterior: Superficial and deep inguinal nodes
  - Posterior: Pelvic nodes
  - Palpable inguinal nodes occur in 20% and nearly always represent metastatic disease

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Evaluation and Staging

- Cystoscopy with biopsy
- Bimanual exam under anesthesia
- Urine cytology
  - Not very reliable for dx of primary urethral ca
  - Sensitivity is greatest for UCC
- CT scan to evaluate for metastatic disease
- MRI to evaluate local tumor extent
- TNM staging

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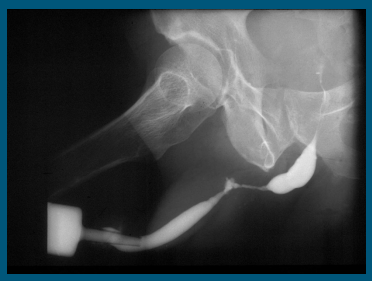
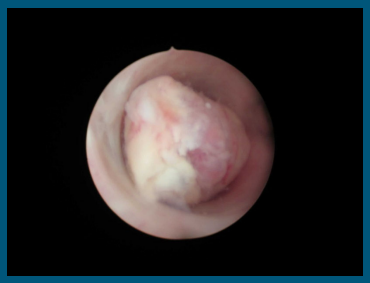
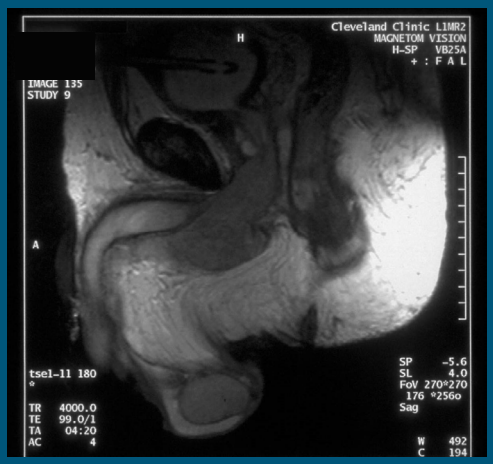
Evaluation and Staging







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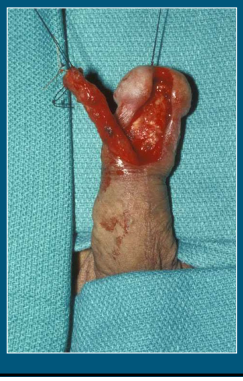
Surgical Treatment

Penile Urethra

- Anterior urethral cancer is more amenable to surgical control and has a better prognosis than posterior cancer
  - Overall survival: 69%
- Superficial, low grade tumors
  - Transurethral resection
  - Local excision
  - Distal urethrectomy



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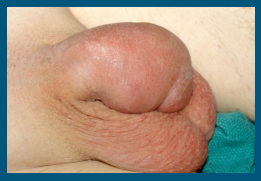
Surgical Treatment: *Penile Urethral Ca*

- Infiltrating tumors may require partial/radical penectomy
- cN+ nodes are usually pN+. Ilioinguinal lymphadenectomy indicated in the presence of palpable inguinal adenopathy with *no pelvic or distant disease*
- For clinically negative groins, prophylactic inguinal lymphadenectomy has not been shown to be of benefit (but some will perform if ≥T1G3)

The role of inguinal lymph node dissection in men with urethral squamous cell carcinoma

Ryan P. Werntz, M.D.*, Christopher B. Riedinger, Richard J. Fantus, Zachary L. Smith, Vignesh T. Packiam, Melanie A. Adamsky, Norm Smith, Gary D. Steinberg

- NCDB study of n=725 men with urethral SCC ≥T1
  - 26% underwent ILND
  - 9% of men with cNo had + LNs
  - 76% of men with cN1/N2 had + LNs (ILND improved OS)
  - Argues against routine ILND for cN0 disease



Urol Onc: 36 (12), 2018

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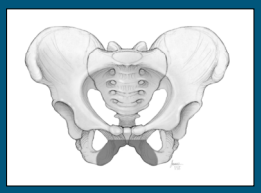
Surgical Treatment
Bulbomembranous Urethra

- Early, small lesions may be treated with transurethral resection or segmental excision, but appropriate tumors are rare
- Standard treatment for invasive tumors
  - Total penectomy
  - Cystoprostatectomy
  - Inferior pubectomy



- Large pelvic floor defects may require rectus abdominus or myocutaneous flap closure

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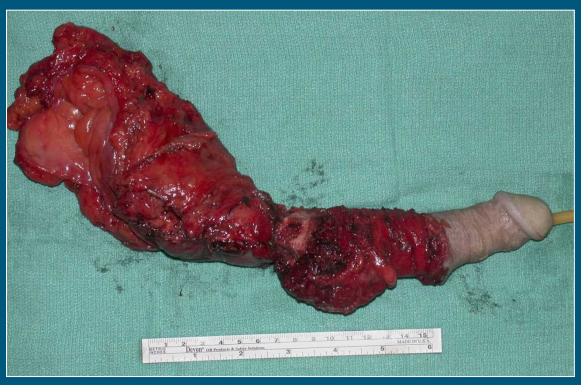
Surgical Treatment
Bulbomembranous Urethra



- Overall survival: 26%

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Radiation and Chemotherapy

- Radiotherapy alone
  - Early stage anterior urethral tumors in patients who refuse surgery
- Combination chemotherapy has shown some success in a small number of patients with localized or metastatic urethral cancer
- Patients with advanced stage or metastatic disease are most commonly treated with a multimodal approach

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Urethral Tumor Recurrence Following Cystoprostatectomy

- Median presentation: 18 months
- Cutaneous diversion
  - Incidence: 2.1-11.1%
  - Increased risk
    - Prostatic stromal invasion, CIS
    - Positive distal urethral margin
  - Symptoms: Urethral bleeding, discharge, mass
  - Monitoring: Urethral wash cytology
  - Pre-surgical assessment: CT/MRI

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Secondary Urethrectomy

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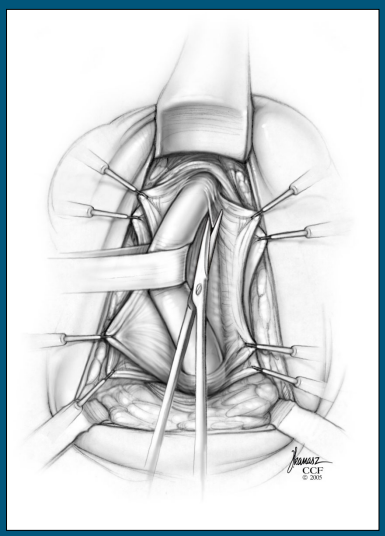

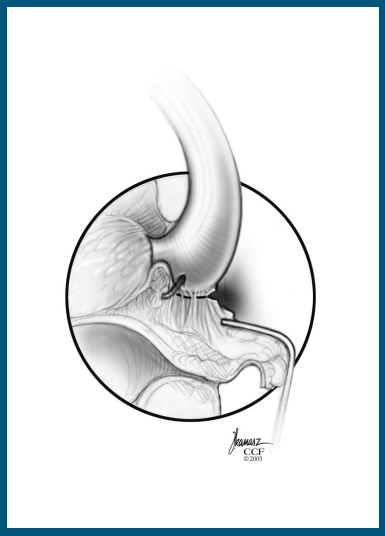

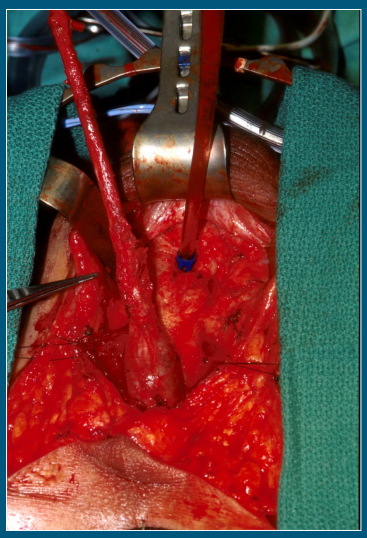

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Orthotopic Diversion

- Incidence of urethral recurrence: 0.5-4%
- Negative frozen section of distal prostatic urethral margin at the time of cystectomy results in low rate of recurrence
- Symptoms
  - Hematuria
  - Urethral discharge or mass
- Monitoring: Voided urine cytology
- Treatment
  - Urethrectomy with excision of a cuff of pouch
  - Cutaneous diversion using the neobladder

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Female Urethral Cancer

- Rare - 0.02% of all female cancers
- Incidence increases with age
- Etiology
  - Leukoplakia/Chronic irritation
  - Caruncles or polyps
  - HPV (16, 18)
- 5% arise within a diverticulum
- Symptoms
  - Obstructive voiding
  - Dysuria or urinary frequency
  - Urethral bleeding or mass
  - A FREQUENTLY MISSED DIAGNOSIS

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Anatomy and Pathology

- Divisions of the female urethra
  - Anterior – distal 1/3
  - Posterior – proximal 2/3
- Lymphatic drainage
  - Anterior – superficial and deep inguinal nodes
  - Posterior – iliac and obturator nodes
- Pathology
  - SCC 50-70%
  - Adenocarcinoma 25% (within diverticulum)
  - UCC 10%

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Evaluation

- Cystoscopy with biopsy (have an index of suspicion – i.e. pain) – ***cytologies often miss this diagnosis***
- Bimanual examination under anesthesia
- CT to evaluate for metastatic disease
- MRI to evaluate local urethral anatomy and tumor extent

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Treatment

- No difference in survival based on tumor histology
- Distal urethral cancers tend to be low stage and have better survival compared to proximal tumors
- Most significant prognostic factor for local control and survival is location and extent of the primary tumor
- Ilioinguinal lymphadenectomy only when palpable disease and no distant metastases
  - Some manage like with penile cancers and perform ILND if primary is T1 high grade or worse even if nodes are palpably normal, but as in men this has not been shown benefit

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Distal Tumors

- Circumferential distal urethrectomy
  - Distal third of the urethra may be excised without compromising continence
  - Cure rate: 70-90%
  - Complications: Meatal stenosis, incontinence
- Radiotherapy
  - EBRT, brachytherapy or combination
  - 5 year survival equivalent to surgery in some series
  - Complications: Incontinence, stricture, fistula

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Proximal Tumors

- More likely to be high stage and invade the bladder and vagina
- Surgery
  - Anterior exenteration with wide vaginal excision and pelvic lymphadenectomy
- Multimodality therapy
  - Suboptimal cure rates with surgery alone have led to recommendations for combination therapy in some cases
  - EBRT + Chemo:
    - 5FU/mitomycin C for SCC
    - MVAC for UCC
  - EBRT + Surgery

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ARS- Q1

Which of the following is true regarding the role of risk reduction in penile cancer:

a) Neonatal circumcision minimizes the risk of invasive disease and CIS

b) Post pubertal circumcision halves the risk of invasive disease and CIS

c) HPV vaccination prior to onset of sexual activity has been shown to decrease the risk

d) Lichen sclerosis is considered a risk factor

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ARS: Q2

A 56 yo male undergoes a partial penectomy for presumed SCC of the penis. The lesion is well differentiated and invades the subepithelial connective tissue but does not have lymphovascular invasion. Margins are negative. Which of the following is true:

a) The pathologic stage is T1b

b) A completion penectomy should be performed given the invasion

c) inguinal nodal involvement is common

d) tobacco exposure and HPV -16, 18, 31 and 33 are often causative

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ARS-Q3

A 60 year old uncircumcised male has a proximal clinical T2 penile cancer on the shaft and palpable bilateral inguinal nodes. The next step is:

a) Penectomy and antibiotics for 4-6 weeks with reexamination of the groin

b) an MRI of the penis and the groin nodes

c) Penectomy with early subsequent groin dissection

d) a punch biopsy of the penile lesion and FNA of the lymph nodes

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ARS Q4:

Which best describes the management of multiple, bulky or bilateral inguinal lymph nodes in pT2 penile cancer:

a) Antibiotics are initiated because the risk of underlying infection

b) If FNA is positive, the patient should be referred to medical oncology for neoadjuvant therapy

c) If FNA is negative a brief period of surveillance is warranted

d) Inguinal LN dissection is diagnostic but not therapeutic

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ARS: Q5

The most common histology of cancers arising in the bulbomembranous urethra is:

a) Urothelial carcinoma

b) Adenocarcinoma

c) Squamous cell carcinoma

d) prostate cancer

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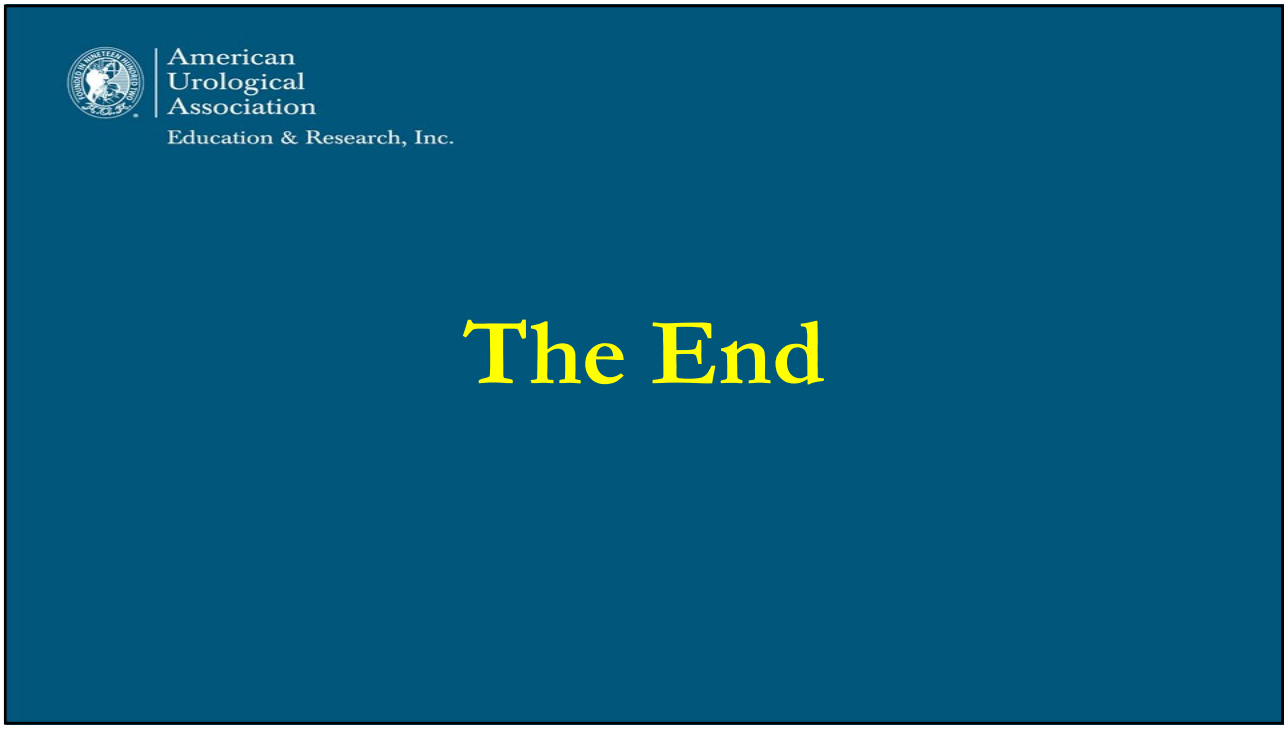

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