PREMALIGNANT AND MALIGNANT PENILE LESIONS
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Objectives

• Recognize benign and malignant lesions of the penis
• Recognize pre malignant lesions and the risk of future cancer they pose
• Understand management of localized and metastatic penile cancer
  • How to manage lymph nodes

No scientifically sound recommendations can be given. Institutional experience and available techniques play an important role in decision making
Contents

- Case study
- **Penile lesions**
  - Benign
  - Pre malignant
  - Malignant
    - Non invasive management
    - Invasive management
- Staging
- Lymph node management
- Prevention

Case study

- 67 year old male presents with irritation on the right base of the penis which extended onto the scrotum
- Multiple topical creams applied with no change
- Never pruritic
- PHx –
  - Hypertension
  - No prior skin history, nil psoriasis
  - No GI history
  - Mild LUTs, but no hematuria
- Medications
  - Ramipril and prostate ‘herbs’ for LUTs
  - Nil other medications
  - Nil allergy
  - Never smoked
- FHx – father died stomach cancer
- SHx – lives with wife and children. Speaks Korean
Case study

- Examination
  - 4cm erythematous lesion at the penoscrotal junction. ?SCC/CIS penis
- Biopsy Jun 21 2013 – for ?Bowen disease
  - Pathology – CIS SCC
- Excisional biopsy September 9 2013
  - 4.5 x 3cm wide local incision
  - Extramammary Paget’s disease
  - All margins negative
  - Good post operative recovery with no functional impairment

- Normal cystoscopy and colonscopy
Extramammary paget disease

- Uncommon intraepithelial adenocarcinoma of sites bearing apocrine glands.
- Mostly found on the perineum, vulva, axilla, scrotum and penis
- More common in females
- Rare on penis
- Often pruritic
- 10 - 30% have underlying malignancy. Association with urethral, bladder, rectal and apocrine malignancies have been described and therefore need to do a systematic review for underlying cancer
- Up to 42% of patients have associated underlying secondary or non-cutaneous malignancy, but seems to be lower when the origin is penoscrotal
  - The location of the internal malignancy appears to relate to the location of the primary
- Treatment – surgical excision
- Recurrence rates up to 60%

BENIGN LESIONS
Benign

- **Non cutaneous**
  - Cystic
    - Inclusion cysts (acquired from trauma/circumcision)
    - Syringomas (sweat duct tumors)
    - Neurilemomas (nerve tumors)
  - Solid
    - Angiomas, fibromas, neuromas, lipomas, myomas
- **Cutaneous**

Benign - Cutaneous

![Image of Angiokeratoma of Fordyce]
Benign - Cutaneous

Pearly penile papules

Condyloma accuminatum (warts)
Benign - Cutaneous

• **Angiokeratoma of Fordyce**
  - Vascular ectasias of dermal blood vessels. 1 - 2mm purple papules

• **Papilloma** (pearly penile papules, hirsuite papilloma, coronal papillae)
  - 1 – 2mm white/yellow papules on corona glans
  - Histology - acral angiofibromas (similar to TS)
  - Do not contain HPV
  - No treatment required
  - 15% of post pubertal men, more common in uncircumcised
  - Treatment – only for cosmesis. CO₂ laser or cryotherapy
Benign - Cutaneous

• **Condyloma accuminatum (warts)**
  - Non-tender, wart like, papillary or frondular
  - STI, caused by HPV
  - 90% are caused by type 6 and 11 which have extremely low malignant potential
  - HPV rarely leads to cervical cancer, penile cancer and anal cancer

Benign - Cutaneous

• **Zoon’s (plasma cell) balanitis**
  - Usually involves the glans, but can involve prepuce
  - Unknown aetiology (local infections, poor hygiene, heat, friction, and constant rubbing)
  - Circumcision seems to be protective
  - Usually over age 30
  - Dense plasma cell infiltrate
  - Ex – asymptomatic, well circumscribed, red, flat lesion that contains pinpoint redder spots (‘cayenne pepper spots’)
    - Looks similar to CIS
  - Treatment - circumcision. If declines circumcision - topical steroids, laser ablation
# Pre Malignant Lesions

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Location and appearance</th>
<th>Progression rate to invasive cancer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythroplasia of Queyrat (non-keratinising CIS)</strong></td>
<td>Velvety plaques on glans and inner prepuce</td>
<td>30</td>
</tr>
<tr>
<td><strong>Bowen disease (keratinising CIS)</strong></td>
<td>Pigmented lesions affecting follicle bearing areas of penile shaft and scrotum</td>
<td>5</td>
</tr>
<tr>
<td><strong>Buschke-Lowenstein tumour</strong> (giant condyloma)</td>
<td>Confluent <a href="#">HPV</a> oxophytic cauliflower-like growths</td>
<td>30</td>
</tr>
<tr>
<td><strong>Bowenoid papulosis</strong></td>
<td>Velvety, maculopapular areas, may form larger plaques</td>
<td>1 - 3</td>
</tr>
<tr>
<td><strong>Lichen sclerosis et atrophicus</strong></td>
<td>White sclerotic patches prepuce, glans, meatus</td>
<td>?</td>
</tr>
<tr>
<td><strong>Leukoplakia</strong></td>
<td>White verrucose plaques on mucosal surfaces</td>
<td>?</td>
</tr>
<tr>
<td><strong>Cutaneous penile horn</strong></td>
<td>Conical and exophytic lesion associated with areas of chronic inflammation</td>
<td>30 (usually low grade)</td>
</tr>
<tr>
<td><strong>Pseudoepitheliomatous, keratotic and micaceous balanitis</strong></td>
<td>Single lesions, well demarcated, elevated. Hyperkeratotic and inelastic</td>
<td>?(high rate)</td>
</tr>
</tbody>
</table>
Pre malignant lesion

- High index of suspicion
- Follow up
- Usually these respond to steroids or emollients
- When diagnosis is in doubt and not responding to conservative management – all pre malignant/benign lesions are best treated with local excision and histologic examination to rule out malignancy
- Erythematous lesions, consider:
  - Eczema
  - Psoriasis
  - STIs

Pre malignant - CIS

- CIS
  - Full thickness intraepidermal carcinoma, Mucosa replaced by atypical hyperplastic cells with disorientation, vacuolation, multiple hyperchromatic nuclei and mitotic figures. Epithelial rete ridges extend into submucosa and appear elongated, broadened and bulbous. Submucosa shows capillary proliferation and ectasia
  - Originally described by Queyrat in 1911
  - Histologically Queyrat and Bowen are similar
  - Erythroplasia of Queyrat – velvety bright red patches on mucosal surfaces of penis.
  - Bowen disease - solitary well defined red plaques on penile shaft, often with crusting ulceration
CIS

Pre malignant – CIS risk factors

- HPV has been detected in CIS, especially 16, 18, 31, 33
- Immunosuppression
- Hygiene
- Phimosis
- Number sexual partners
- Tobacco products
Giant condyloma (Buscke-Lowenstein tumor)

- Locally aggressive, exophytic, low grade variant of SCC that has little metastatic potential
- Warty appearance
- Slow growing and **locally destructive**
- Usually – uncircumcised on **glans or prepuce** (can be on urethra, vulva, vagina, cervix, anus, oral/nasal cavities, plantar surfaces of feet)
- Associated with HPV 6, 11 (NOT 16, 18)
- Treatment – local excision

Giant condyloma

Exophytic and wart-like appearance, histologically look benign
Bowenoid papulosis

- Histologically resembles Bowen disease, except that the abnormal keratinocytes are spread **discontinuously** throughout the epidermis
- Red-brown papules on glans or shaft (can occur in females as well)
- Multiple red velvety maculopapular areas. Similar to warts
- Age 20 – 30 (sexually active/promiscuous). Usually uncircumcised male
- Clear association with **HPV 16**
- Sexually transmitted. Female partners have increased risk of cervical neoplasia and should have close follow up.
- Spontaneous regression may occur
- Transition between genital wart and Bowen disease
- Management – conservative surveillance, 5-FU or ablation (laser, cryotherapy, electric ablation)
  - Often runs benign course unless immunosuppressed

**May be mistaken for Bowen disease**
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bowenoid papulosis</th>
<th>CIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Dx</td>
<td>20 – 30</td>
<td>50 – 60</td>
</tr>
<tr>
<td>Foreskin</td>
<td>Circumcised</td>
<td>Uncircumcised</td>
</tr>
<tr>
<td>HPV has been detected</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Risk of SCC</td>
<td>Rare</td>
<td>10%</td>
</tr>
</tbody>
</table>

Balanitis xerotica obliterans (Lichen sclerosus atrophicus)

- Arises from chronic infection, trauma, inflammation
- Most common pre malignant condition
- Unknown aetiology
- Presentation
  - Flat, white patches on glans or prepuce
  - Pathologic phimosis. May involve meatus or fossa navicularis
  - Fibrotic
  - Male and female (usually uncircumcised)
  - Usually asymptomatic. May have pruritus, burning, painful erections, dyspareunia in females
  - Associated with meatus and urethral strictures
- Histology
  - Hyperkeratosis, thinning of rete pegs, chronic inflammatory infiltrate (lymphocytes, plasma cells)
Balani/s xerotica obliterate (Lichen sclerosus atrophicus)

• Treatment
  – Asymptomatic – no therapy
  – Symptomatic – topical steroids to relieve itching and burning (betamethasone BD or 0.1% triamcinolone BD)
  – Avoid excision as recurrence high. Can do circumcision
  – Biopsy if poor response to therapy
  – Assess for urethral stricture if history suggests
• 2.3% of those diagnosed with BXO have SCC
• Synchronous BXO is found in 28-50% of those treated for penile cancer
  • 10 - 33% progress to invasive SCC
  • Annual F/U because of malignancy risk (controversial)
• SCC latency time 15-17 years

Leukoplakia

- Rare
- White, verrucous plaques on mucosal surfaces
- Usually glans or prepuce
- Clinically resemble BXO
- More common in patients with diabetes
- Probably related to recurrent or chronic infection

Cutaneous horn

- Rare. Usually develops over a preexisting lesion (wart, nevus, trauma, malignant neoplasm)
- Characterized by overgrowth and cornification of the epithelium
- Microscopy – extreme hyperkeratosis, dyskeratosis and acanthosis (abnormal thickening of the prickle-cell layer of the skin)
- High risk of malignant transformation
- Associated with HPV 16
- Treatment – surgical excision with a margin
- Careful histologic assessment of base and close follow up of excision site
PEKMB

- Pseudoepitheliomatous, keratotic and micaceous (white, scaly) balanitis
- Rare. Develops thick, hyperkeratotic, laminated plaque on glans of penis
- Usually elderly, uncircumcised
- Can have concurrent verrucous carcinoma
- Controversial if pre malignant
- Histology – hyperplastic epidermia with ridges extending deep into dermis
- Treat by surgical excision or ablation with close follow up
Treatment of pre malignant lesions

- **Surgical excision**
  - All premalignant lesions are suitable
  - Good if compliance an issue
  - May require total glans resurfacing with split thickness skin graft
    - Good histopathology required. Up to 40% (10 of 25) have been diagnosed with invasive disease when pre operatively had been diagnosed with CIS only on biopsy
    - Allows penile length, form preservation, adequate cosmesis
  - Circumcision may be all that is required (5mm margin)
- **Mohs’ micrographic surgery**
  - Layer-by-layer excision of lesion in multiple sessions with microscopic review
  - Time consuming, expensive, need trained pathologist
  - High recurrence rate (up to 32%)

Treatment of pre malignant lesions

- **5% 5-fluorouracil** most common first line treatment
  - Antimetabolite (pyrimidine inhibitor)
  - Usually applied topically alternate days for 4 – 6 weeks
  - Wear gloves and wash hands after application
  - Treated area often becomes encrusted and inflamed
  - Can use topical steroids to decrease inflammation
  - Response rate up to 100% at 5 years
  - Largest study – 42 cases (retrospective) 50% achieved complete response, 31% partial response
  - Suitable for CIS, Bowenoid papulosis, PKMB
  - NOT suitable for BXO, cutaneous horn or Giant condyloma accuminatum

- Non or partial responders
  - Immunotherapy (5% imiquimod)
  - Apply 5 days per week for 4 – 6 weeks
  - 70% complete response, 30% partial response

Treatment of pre malignant lesions

- **CO\(_2\) or neodymium:YAG laser**
  - CO\(_2\) 1mm depth
    - 3 - 4 weeks to heal
  - Nd:YAG 6mm depth
    - 2 - 3 months to heal
  - Treatment
    - CIS, Bowenoid papulosis.
    - NOT suitable BXO, giant condylomata accuminatum, cutaneous horn
  - Higher rate of progression
    - Depending on study – approximately 20% recurrence
Treatment of pre malignant lesions

- **Cryotherapy**
  - Liquid nitrogen
  - Higher risk of recurrence
  - Hansen et al, compared to 5-FU and excision:
    - Recurrence of CIS
      - Cryotherapy 13.4%
      - 5-FU 9%
      - Surgical excision 5.5%


Follow up

- Tailored to individual patient depending on lesion and risk factors
- Up to 30% malignant transformation
- Up to 30% recurrence rate
- 3 monthly for 2 years, then 6 monthly until 5 years
- ?lifelong
Kaposi sarcoma

- Endothelial origin
- ?neoplastic or hyperplastic
- HIV has increased incidence 700 fold (usually with advanced immune impairment)
- Clear association with HPV 8 and Kaposi
- Slow growing, blue-red-pigmented macules on lower extremities. In AIDS presentation is diverse from single lesion to disseminated cutaneous and visceral lesion
- Edema (blocks lymphatics)
- Urethral obstruction
- Treatment - excise, laser, cryotherapy, radiotherapy and individual based
Kaposi sarcoma

Other lesions

• Melanoma
  – Risk factors – family history, fair skin, ultraviolet radiation exposure
  – 100 cases in the literature. Can occur of the urethra
• Cutaneous T cell lymphoma
  – Involves neoplasms from T cells in the skin. Increased in HIV
  – Extra genital disease is usually present
  – Chronic condition that may progress over years
  – Presents as pruritis. May then develop hematologic involvement, cutaneous plaques, erosions, ulcers or frank skin tumous
PENILE CANCER
SCC penis

Exophytic erosive lesion on the glans with evident keratinization.

Epidemiology – Invasive SCC

- Mean age diagnosis 60
- 0.3 – 1 per 100 000 in Europe and USA
- Developing countries
  - 3 per 100 000 India
  - 8.3 per 100 000 Brazil
  - Higher still in Uganda where it is the most commonly diagnosed cancer in men (10 – 20% of all tumors) and 1% by age 75
- Incidence and prevalence of premalignant lesions is not known
  - Denmark 0.9 per 100 000 in 2006-08 (retrospective)

Presentation

- Embarrassment is a big issue (fear, guilt, ignorance, neglect)
- Embarrassment, anxiety and fear often results in delayed presentation
  - 5.8 months is average delay

- Lump 47%
- Ulcer 35%
- Erythematous lesion 17%
- Bleeding/discharge from lesion concealed by prepuce
- Usually sharply demarcated lesion


Risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative increased risk of penile cancer</th>
</tr>
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<tbody>
<tr>
<td>Not circumcised</td>
<td>3.2x</td>
</tr>
<tr>
<td>Phimosis</td>
<td>11x</td>
</tr>
<tr>
<td>HPV (types 16, 18 most common)</td>
<td>-</td>
</tr>
<tr>
<td>Genital warts</td>
<td>5.9x</td>
</tr>
<tr>
<td>Multiple sexual partners and early age of first intercourse (correlates with HPV infection)</td>
<td>3-5x</td>
</tr>
<tr>
<td>HIV</td>
<td>8x</td>
</tr>
<tr>
<td>Smoking (cigarettes, chewing tobacco, snuff)</td>
<td>2.8x</td>
</tr>
<tr>
<td>Psoralen plus ultraviolet light A (PUVA) for psoriasis</td>
<td>58.8x</td>
</tr>
<tr>
<td>Penile injury (small tears and abrasions)</td>
<td>3.9x</td>
</tr>
<tr>
<td>Lichen sclerosus et atrophicus</td>
<td>-</td>
</tr>
</tbody>
</table>
Risk factors

- Foreskin
  - 3.2 x greater risk SCC in men NOT circumcised
  - 3.0 x greater risk in men circumcised after neonatal period compared to those circumcised in neonatal period
  - Adult circumcision – nil effect
  - Early circumcision protects against phimosis, poor hygiene, retention of smegma (desquamated epidermal cells and urinary products). These predispose to chronic inflammation of glans/prepuce – thought to promote penile cancer

- Phimosis is found in 25 - 75% of patients with SCC

Risk factors - HPV

- Systematic review. 50% (range 15 – 81%) of cancers associated with HPV, main subtype HPV-16 (60% cases), HPV 18 (13% cases)
- Its presence is not invariable in invasive SCC
- Well established link to cervical cancer with a latency period of 8 - 10 years
- Vaccination may alter the role in penile cancer
Presentation

- Location
  - Glans 48%
  - Prepuce 21%
  - Glans and prepuce 9%
  - Coronal sulcus 6%
  - Shaft <2%
- Rare – nodal metastases, hemorrhage, urinary retention, urethral fistula

Penile cancer

- Examination
  - Size, location, number, fixation, involvement of corporal bodies
  - Morphology – papillary, nodular, ulcerous, flat
  - Inspect base of penis, scrotum to rule out extension
  - Inspect corpus spongiosum/cavernosum
  - Inguinal lymphadenopathy
  - Penile length
- Laboratory
  - Hypercalcemia is seen in approximately 20% (paraneoplastic)
  - LFTs - metastases
Palpable lymph nodes

- Describe
  - Node consistency
  - Location
  - Diameter
  - Unilateral/bilateral
  - Number of nodes in each area
  - Mobile/fixed
  - Relationship to other strictures (e.g., skin)
  - Edema of leg/scrotum
- Up to 50% palpable LNs at diagnosis are reactive
- If persistent nearly 100% are malignant

PRIMARY LESION
Penile cancer

- Flat, ulcerative tumour tends to earlier nodal metastasis and poorer 5 year survival
- Should be managed in high volume centers
- Incisional/excisional biopsy to confirm diagnosis, depth, vascular invasion, grade. This will help with primary as well as assess the risk of nodal metastases
- Survival is related to stage and therefore staging should be as accurate as possible


Histology

<table>
<thead>
<tr>
<th>Histological subtype</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC variants</td>
<td>95</td>
</tr>
<tr>
<td>Usual type</td>
<td>60-70</td>
</tr>
<tr>
<td>Papillary</td>
<td>7</td>
</tr>
<tr>
<td>Condylomatous (HPV related)</td>
<td>7</td>
</tr>
<tr>
<td>Basaloid (aggressive)</td>
<td>4-10</td>
</tr>
<tr>
<td>Verrucous (less aggressive)</td>
<td>7</td>
</tr>
<tr>
<td>Sarcomatoid (aggressive)</td>
<td>1-4</td>
</tr>
<tr>
<td>Others</td>
<td>5</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>2</td>
</tr>
<tr>
<td>BCC</td>
<td>2</td>
</tr>
<tr>
<td>Extramammary Paget's disease</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>
Histology SCC

- Most demonstrate keratinisation, epithelial pearl formation with various degrees of mitotic activity
- Normal rete pegs are disrupted
- Broders classification (grade 1 – 4)
  - Based on level of differentiation, keratinization, nuclear pleomorphism, number of mitoses
  - Low grades (1,2) 70 – 80% cases. Well differentiated
  - Shaft – more likely to be high grade
  - Grade and stage often linked


Histology and metastatic risk

- Subtype and risk of metastatic lymph nodes
  - Condylomatous 18.2%
  - SCC 56.7%
  - Sarcomatoid 89%
- Adverse prognostic features:
  - Higher grade = more likely nodal metastases
    - Metastases present in 58% of those with any grade 3 compared to 14% without any grade 3
  - Vascular invasion = more likely nodal metastases
  - Perineural invasion = more likely nodal metastases
Primary lesion staging

- Physical examination of primary lesion was correct in 74% cases. 10% under staged, 16% over staged
- Can use ultrasound or MRI for primary lesion
  - Artificial erections and MRI. Retrospective study – 55 patients. MRI over staged 6 cases of T1 as T2
  - Ultrasound – unreliable

- Overall imaging studies add little benefit in addition to examination. If concerned regarding corpus cavernosum invasion, consider it.


Treatment

- Principles
  - Many different methods for treatment
  - Mostly based on case series
  - No good scientific comparison made between different treatment modalities (surgery, radiotherapy, laser)
  - Good pathology assessment and negative margins a must
  - Positive margins will inevitably lead to recurrence
  - Balance between conservative approach, penile preservation and functional control versus oncological control
  - More aggressive intervention generally have a decreased recurrence
  - Multiple lesions – less conservative approach
Treatment – Non invasive (CIS, Ta, T1a)

• Same treatment options as CIS

• **Surgical excision** –
  - Wide local excision with closure may be possible if small
  - Partial or total glans excision may be required if large. Can reconstruct with split skin graft
  - Most patients with recurrences if detected and treated early, survival not significantly adversely affected

• Moh’s micrographic surgery

• Circumcision is maybe all that it requires (excisional biopsy). This aids surveillance also


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Treatment – Non invasive (CIS, Ta, T1a)

• **Lasers** (carbon dioxide, Nd: YAG, KTP – potassium titanyl phosphate), Modest papers reported only.
  - CO₂ depth too shallow, with recurrences up to 50%
  - Nd:YAG depth 6mm and therefore less recurrence
  - CIS recurrence rate 14.2% with laser

• **5-fluorouracil** or 5% imiquimod (immunotherapy). Only supported by uncontrolled cohort studies and case reports. High recurrence rate
Treatment T1b

- Wide local excision with reconstruction or total glans resurfacing with or without skin graft
- Neoadjuvant chemotherapy (vinblastine, bleomycin, methotrexate) followed by CO₂ laser with spontaneous glands re-epithelialisation
- Radiotherapy
- Glansectomy

- In general a **3mm** margin is considered safe

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Treatment T2 (limited to glans)

- Total glansectomy
- Radiotherapy
- Partial amputation in those unfit for conservative reconstructive options
Treatment – T2 (into corpus cavernosum)

- Partial amputation with a negative margin
- Recommend **5 - 10mm** margin
- Conventional 2cm is not required to achieve long term oncological control and disease specific survival
- 4cm long penis should allow standing voiding and penetrative intercourse


Treatment – T3/4

- Rare cases
- Represent approximately 5% of penile cancers
- Radical surgery – partial/total penectomy with perineal urethrostomy
- Neoadjuvant chemotherapy in advanced T4 lesions followed by surgery in responding patients
- OR adjuvant chemotherapy or consolidating radiotherapy
- Limited response to chemotherapy
  - Very limited data
  - Can be used as palliation in advanced/metastatic disease
Local disease recurrence after conservative surgery

- A second conservative approach can be used if there is no corpus cavernosum invasion
- Partial or total amputation if there is a large or deep recurrence
- Then phallic reconstruction can be considered

Margins

Minhas S et al. BJU Int. 2005 Nov;96(7):1040-3.

**What surgical resection margins are required to achieve oncological control in men with primary penile cancer?**

  - All staged with MRI pre operatively
  - Mean range follow up 26 months
  - Stage (Tis 3, T1 20, T2 26, T3 2)
  - Type – 8 basaloid, 4 verrucous, 26 not specified
- Margins
  - 48% within 10mm of tumor edge
  - 90% within <20mm resection margin
  - 6% had tumor at the margin (and had further surgery)
- **4% developed local tumour recurrence**
- Conclusion: 2cm margin NOT required
Margin

Radiotherapy

- Organ preserving for **T1-2** lesions of the glans < 4cm in size. Approximately 80% preserve the penis
- Often reserved for patients unfit for surgery, refuse surgery or palliative in metastatic disease
- EBRT and brachy uncommonly used
- Best results with brachytherapy with local control rates 70 – 90%
- If > 4cm brachytherapy NOT suitable
- EBRT – minimum 60Gy
- Higher local failure rates than partial penectomy (but salvage surgery can still be done)
- Complications
  - Urethral stenosis 20-35%
  - Glans necrosis 10-20%
  - Corpora cavernosa late fibrosis
Interstitial brachytherapy

Hypodermic needles are manually afterloaded with iridium wires

LYMPH NODES
Imaging for metastases

- Difficult to stage on physical examination alone and a more reliable technique is required

- CT (or MRI) staging
  - Inguinal, pelvic, distant metastases
  - Rely on size criteria
  - Useful if obese or if had previous inguinal surgery

- Staging options:
  - cN0 (impalpable) disease – CT/MRI sensitivity poor because based on size criteria
  - 18F PET FDG – pooled sensitivity 96.4% for cN+ disease, 56.5% cN0. Cannot reliably detect micro metastases <2mm in size
  - Other options:
    - U/S with FNAC of nodes
    - Bilateral dynamic sentinel LN biopsy

Staging - 2009

T0: No evidence of primary tumour
Tis: Carcinoma in situ
Ta: Non-invasive verrucous carcinoma, not associated with destructive invasion
T1: Tumour invades subepithelial connective tissue
T1a: Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated or undifferentiated (T1G1-2)
T1b: Tumour invades subepithelial connective tissue without with lymphovascular invasion or is poorly differentiated or undifferentiated (T1G3-4)

T2: Tumour invades corpus spongiosum/corpora cavernosa
T3: Tumour invades urethra
T4: Tumour invades other adjacent structures

N: Regional lymph nodes
NX: Regional lymph nodes cannot be assessed
N0: No palpable or visibly enlarged inguinal lymph node
N1: Palpable mobile unilateral inguinal lymph node
N2: Palpable mobile multiple or bilateral inguinal lymph nodes
N3: Fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral

M: Distant metastases
M0: No distant metastasis
Pathological node staging

The pT categories correspond to the T categories. The pN categories are based upon biopsy, or surgical excision.

pN - Regional lymph nodes:
  pNX Regional lymph nodes cannot be assessed
  pN0 No regional lymph node metastasis
  pN1 Intracapsular metastasis in a single inguinal lymph node
  pN2 Metastasis in multiple or bilateral inguinal lymph nodes
  pN3 Metastasis in pelvic lymph node(s), unilateral or bilateral or extranodal extension of regional lymph node metastasis

pM - Distant metastases
  pM0 No distant metastasis
  pM1 Distant metastasis

G - Histopathological grading
  Gx Grade of differentiation cannot be assessed
  G1 Well differentiated
  G2 Moderately differentiated
  G3-4 poorly differentiated/undifferentiated
Penile cancer - lymphatics

- Earliest metastases are to the regional inguinal and iliac lymph nodes
- Lymphatics of prepuce joins those of shaft. These drain into superficial inguinal nodes (external to fascia lata), especially the **superomedial zone** bilaterally
- Lymphatics of glans drain to corporal bodies. Form a collar of channels at base of penis and to deep inguinal lymph nodes (below fascia lata)
- Then pelvic lymph nodes (external iliac, internal iliac, obturator). No direct drainage from penile tumour to pelvic lymph nodes
- Multiple cross connections. Therefore bilateral

Anatomy

- The inguinal nodes distal to inguinal ligament can be divided:
  - **Superficial**
    - Deep to scarpas, but superficial to fascia lata (8-25 LNs)
    - Divided into superior/inferior by a horizontal line through junction greater saphenous and femoral veins. Superior has medial and lateral groups
  - **Deep**
    - Deep to fascia lata, medial to femoral vein (3-5LNs). Most consistent is the node of Cloquet situated in the femoral canal
Anatomy – Zonal anatomy

Penile cancer - lymphatics

- Further spread is then to distant sites (lung, bone, liver). In 1 - 10% cases
- Inguinal lymph nodes is the most important prognostic indicator
- Local node invasion can lead to skin necrosis, infection, sepsis, hemorrhage (erode femoral vessels)
- Metastatic to pelvic lymph nodes: 5 year survival 0 - 21%

Management of the lymph nodes in Penile Cancer

Suzanne Richter, MD, MSc, FRCPC; J. Dean Rueler, MD; Lot Wood, MD, MSc; Christina Canil, MD, FRCPC; Patrice Moreto, MD; Peter Verran, MD; Joel Gingerich, MD, FRCPC; Urban Emmenegger, MD; Andrea Eilen, MD, FRCPC; Paweł Zalewski, MD, FRCPC; Anthony Joshua, MBBS, PhD, FRACP; Som Dev Muthupillai, MD, MSc, FRCPC; Daniel Heng, MD; Piotr Czakowski, MD, MSc, FRCPC; Doris Souleles, MD; Norman Bains, MD, MSc; Ricardo Rendon, MD, FRCSC; Neil Fleshner, MD, FRCSC, MPH; Juanita M. Cook, MD, FRCPC; and Shikha S. Sidhu, MD, MSc, FRCPC

Dynamic SIB with lymphoscintigraphy and blue dye localization can be performed if the technology and expertise are available (G2; C).

Limited LND can be performed instead of complete LND to reduce the complications rate, although the false-negative rate might be similar to that of selective SIB (G2; C).

Intravenous indocyanine green can be used during SIB or limited LND. If the results are positive, complete LND can be performed immediately (G2; C).

In patients with unilaterally or bilaterally proven inguinal metastases, complete LND should be performed preferentially (G2; B).

In patients with histologically confirmed inguinal metastases involving 2 nodes on one side, contralateral limited LND with frozen section analysis can be performed, with complete LND if the frozen section analysis is positive (G2; B).


Inguinal nodes

- 20% initially present with palpable LNs
- 50% lymphadenopathy caused by metastatic disease at presentation
- 25% bilateral
- Physical examination NOT reliable. False negative rate of 11 - 62%
- 20% patients with no clinically palpable nodes will harbor occult metastases
- Lymphadenectomy has shown metastases in:
  - 6.3% pT1 G1
  - 12.2% pT1 G2
  - 44.6% pT1 G3
Inguinal nodes according to grade

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients (n)</th>
<th>G1 (%)</th>
<th>G2 (%)</th>
<th>G3 (%)</th>
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<tr>
<td>Fraley et al. 1989</td>
<td>58</td>
<td>30</td>
<td>70</td>
<td>60</td>
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<td>Schon et al. 1992</td>
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<td>65</td>
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<td>64.1</td>
<td>66.7</td>
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<td>79</td>
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<td>Villari et al. 1997</td>
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<td>0</td>
<td>38.5</td>
<td>80</td>
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<td>Schon et al. 2001</td>
<td>37</td>
<td>10</td>
<td>69</td>
<td>75</td>
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<td>Slaton et al. 2001</td>
<td>48</td>
<td>20</td>
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<td>Lopes et al. 2002</td>
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<td>Facca et al. 2005</td>
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<td>Guzman et al. 2005</td>
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<td>Campo et al. 2006</td>
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<tr>
<td>Dai et al. 2006</td>
<td>44</td>
<td>20.8</td>
<td>32.3</td>
<td>47.1</td>
</tr>
</tbody>
</table>

Risk of node metastases

Penile Carcinoma Prognostic Factors for Inguinal Lymph Node Metastasis

- **Risk Group**
  - **Low**
    - Tis Ta
    - T1 G2*, T2 G1-2, No Vascular Invasion
  - **Intermediate**
    - Moderate
    - Incidence Metastasis
    - <10% ICUD(1)
    - <16% EAU(2-3)
    - ≥17% EAU(2-3)
  - **High**
    - Incidence Metastasis
    - >50% ICUD(1)
    - 68-73% EAU(2-3)

* (1) ICUD—intermediate risk in some series (e.g., 65, 108, 109)
(2) EAU—European Association of Urology
(3) Grade III vascular invasion

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2014-04-03
Nomogram

Radical lymphadectomy

- Can be curative
- Treat as early as possible
- Margins of resection
  - Superior: line from superior margin of external ring to ASIS
  - Lateral: vertical line from ASIS to 20cm inferiorly
  - Medial: vertical line from pubic tubercle 15cm down medial thigh

- Skeletonize femoral vessels
- Transpose sartorius after detaching it proximally from ASIS and suture to inguinal ligament
Modified inguinal lymph node dissection

- First described by Catalona in 1988
- Shorter skin incision
- Preservation of subcutaneous tissue superficial to Scarpas’ fascia
- No dissection lateral to femoral artery or caudal fossa ovalis
- Preservation saphenous vein
- Elimination of sartorius muscle transposition

- All superficial nodes are removed and deep ones medial to femoral vein up to inguinal ligament
- Can combine with frozen section at the time and if positive change to radical ILND
Regional lymph nodes

- Lymphadenectomy should be performed by experience surgeons
- Requires
  - Careful skin flap management
  - Meticulous lymph node dissection
  - Prophylactic antibiotics
  - Compression stockings
  - Early mobilisation
  - Advanced cases may require reconstruction techniques
- Complications (30 - 70%)
  - Lymph leakage
  - Leg/scrotal oedema
  - Skin flap necrosis
  - Wound infection
  - Lymphocele

Timing of inguinal lymph node dissection

- 2 reasons to delay – Historical now
  - Allow time for metastatic cells to embolize from the primary tumour to the nodes (avoid metastases in the tract between the tumor and nodes)
  - To give Abx and allow inflammatory nodes to regress and decrease risk of infection after ILND
  - Allows histopathological review of tumor and indicate risk of metastases
- Reasons to not delay
  - Potentially miss chance to cure
  - May become inoperable
Regional lymph nodes – Non palpable

- Surveillance – CIS, Ta, T1G1
- Intermediate group (T1G2) is the difficult group. A potentially significant portion will develop node metastases
  - Can use nomogram to help decide risk
    - Surveillance recommended:
      - If risk <10%
    - Balance over treatment with risk of missing metastatic disease
- Ultrasound with fine needle aspiration is an option
- Consider prophylactic ILND if obese, previous radiotherapy, previous inguinal surgery

Sentinel node biopsy (SNB)

- For non palpable nodes
- 5cm incision parallel to inguinal ligament 2 finger breaths lateral and inferior to pubic tubercle
- Insert finger under upper flap toward tubercle – SN is found and excised. BUT high false negative (up to 25%):
  - Incorrect identification
  - Inadequate sectioning
DSNB (dynamic sentinel lymph node biopsy)

- **Non-palpable** nodes only
- Tc99m is injected intradermally around the primary tumour one day prior to surgery
- Patent blue is injected and gamma ray detection probe is used intraoperatively
- Serial sectioning of lymph nodes
- Complete LAD is performed if tumor positive
- Prospective studies – specificity of 100%, sensitivity of 95%. False negative rate of 20 – 30%
- Reproducible and short learning curve and much reduced complications

- Drawbacks
  - Inguinal skin contamination
  - Intracavernous administration
  - Delayed lymph node filling
  - High false negative rate
  - Expertise – some say should do 20 per year
  - High cost and time taken to perform

Pre operative lymphoscintigraphy

Preoperative lymphoscintigrams obtained after injection of 99m-Technetium-labeled nanocolloid around the primary tumor, showing radio-activity in the penile lesion and sentinel lymph nodes
Pre- and intra-operative use of a gamma probe to localize radio-labeled sentinel lymph nodes.

Primary penile lesion with intradermally injected patent blue dye, and inguinal lymph node stained with blue dye.
CT/MRI

- Recommended in presence of palpable nodes to further characterise size, extent, location, blood vessels
- Help to detect deep, pelvic nodes and distant metastases
- No help if non-palpable as based on size criteria
Regional lymph nodes - Palpable

- Ultrasound FNAC
- Positive cytology is conclusive, but negative does not guarantee absence or metastases
- Increases diagnostic yield of ultrasound
- Still high false negative rate

- If negative:
  - Antibiotics
  - FNAC repeated
  - Suspicious nodes removed surgically
  - Perform inguinal lymphadenectomy

- DSNB is not reliable in palpable suspected nodes

Pelvic nodes

- 5 year survival rates with positive pelvic nodes = 0%
- If pelvic nodes visible on CT it is already too late and curative surgery unlikely
- In a study of 73 patients who underwent ILND and were positive, 48.5% had positive pelvic nodes. A tumor positive Cloquet’s node indicated 88.9% risk of positive pelvic nodes
- Incidence of positive pelvic nodes was:
  - 87.5% in patients with 3 or more inguinal nodes
  - 11.8% in those with 1 – 2 positive inguinal nodes
- Pelvic lymphadenectomy if node of Cloquet involved, extranodal disease or 2 more more inguinal LNs involved

Neoadjuvant chemotherapy

- Consider for inguinal nodes > 4cm or fixed
- Some early prospective data coming
- Should contain cisplatin. Bleomycin should not be used
- Regimen could include (no RCTs have evaluated the regimens)
  - Paclitaxel
  - Ifosfamide
  - Cisplatin
- Potentially offer surgery to those who respond

Adjuvant chemotherapy

- Few heterogenous series only
- Previously used Vinblastine, bleomycin, methotrexate
- pN1 – observe only
- Recommended for:
  - pN2 - 3
  - Node > 4cm
  - Extra nodal extension
  - Cisplatin based regimen
Fixed inguinal lymph nodes

- Surgery not recommended
  - Cure unlikely
  - Short survival
  - High complication rate
- Neoadjuvant chemotherapy followed by surgery an option in experienced institutions
- Cisplatin based regimen

Radiotherapy to lymph nodes

- N0 – not recommended as:
  - Does not prevent metastatic lymph nodes
  - Associated complications
  - Difficult follow up secondary to fibrotic changes
- Can use for locoregional control with extensive metastases
Prognosis

- 5 yr survival of SCC penis:
  - > 85% no inguinal metastases
  - 75 – 88% 1 – 2 inguinal metastases
  - 25% > 2 inguinal metastases
  - 5 – 10% extranodal extension, nodes > 4cm or pelvic metastases

- Without treatment, most die within 2 years secondary to complications of uncontrollable locoregional growth or distant metastases
Follow up

• Most local/regional recurrences potentially curable
• Physical examination every 3 months for 2 years and then every 6 months for 5 years
• PET/CT – becoming more useful
• 92.2% recurrences occur within first 5 years (with most in first 2 years)
• Local recurrence in up to 30% with penis preserving surgery
  – No impact on survival
  – Self examination important part of education

Follow up

• Regional recurrence
• For those on wait and see protocol
  – Every 3/12 review and examination for 2 years
• Post lymphadenectomy:
  – pN0
    • 6/12 review and examination for 2 years then annually
    • Consider groin ultrasound
  – pN+
    • 3/12 review and examination for 2 years and then 6 monthly
    • Consider groin ultrasound
Prevention

- Education on risks of smoking, poor genital hygiene and STIs
- Circumcision?
- Circumcision decreases HIV by 53-60% (and oncological high risk HPV by 32-35%)
- HPV vaccination
- Cessation of smoking
- Shielding of genital area when using PUVA
- Condom use

HPV vaccine

- Gardasil – HP 6, 11, 16, 18
- Male vaccine – seroconversion similar to females at 99.1 – 100%
- No long term data but in theory should reduce rate of penile cancer
- Should be given prior to first sexual contact
- Alternatively you could target high risk populations:
  - Men with multiple partners
  - Countries with high prevalence
  - High rates of HPV 16,18
  - High rates of genital warts
Prevention - circumcision

American Academy of pediatrics

• After a comprehensive review of the scientific evidence, the American Academy of Pediatrics found the health benefits of newborn male circumcision outweigh the risks, but the benefits are not great enough to recommend universal newborn circumcision. The final decision should still be left to parents to make in the context of their religious, ethical and cultural beliefs.

Conclusion

• Penile lesions
  • High index of suspicion
  • Follow up
  • When diagnosis is in doubt and not responding to conservative management — all pre malignant/benign lesions are best treated with local excision and histologic examination to rule out malignancy

• Encourage prevention strategies
Conclusion – penile cancer

- Primary tumour
  - Tis, Ta, T1a (G1,2) – conservative
    - Surgical excision, Laser, WLE, glans resurfacing, Moh’s
  - T1b (G3) and T2 (glans)
    - Glansectomy
  - T2 (into corpora)
    - Partial amputation
  - T3
    - Total amputation
  - T4
    - Neoadjuvant chemotherapy followed by surgery or radiation

- No antibiotics for lymphadenopathy
- Consider use of groin U/S +/- FNAC
Thank you

Rete ridges