Penile cancer

Introduction

- **Incidence**: squamous or epidermal cell carcinoma accounts for 95% of tumors of the penis. Others are very rare and include: melanoma, basal cell carcinoma, Kaposi’s sarcoma, angiosarcoma. In Europe and the US the incidence is <1/100,000 men, but in developing countries it accounts for up to 20% of male cancers.
- **Location**: glans 48%, foreskin 21%, glans & foreskin 9%, coronal sulcus 6%, penile shaft 2%.
- **Risk factors**:
  - ↑ *risk*: phimosis, poor hygiene, chronic inflammation (e.g. *balanitis xerotica obliterans*), smoking, *sporalene* treatment or photochemotherapy with UVA, sexual promiscuity (infection with human papilloma virus serotypes 11, 16, and 18 is responsible for 50% of cases). Cervical cancer in sexual partners is not a risk factor for men. The HPV vaccine is currently recommended in ♀ between 11-12 years, but not in ♂.
  - ↓ *risk*: early circumcision (adult circumcision does not reduce the risk).
- **Prognostic factors**: the presence and degree of lymph node involvement and the number of nodes involved are the best predictors, followed by the location, type and degree of infiltration of the primary tumor and the presence of vascular or lymphatic invasion.
- **5-year survival rates**: 66% in node-negative and 27% in node-positive cases.

Natural history

- **Primary lesion**: exophytic papillary or ulcerated flat lesion (earliest lymphadenopathies).
- **Regional spread**: bilateral, more common than hematogenous spread. It affects first the inguinal and then the iliac and para-aortic lymph nodes; if there is invasion of the CC or urethra, these are affected earlier. Complications of lymph nodes: chronic infection, bleeding.
- **Distant metastasis**: via vascular spread. Rare.

Pathology

- **Types of squamous cell carcinoma of the penis**:
  - *Classic*: 57% risk of lymphadenopathy.
  - *Basaloid*: very aggressive.
  - *Verrucous and variants*:
    - Condylomatous carcinoma: 18% risk of lymphadenopathy
    - Verrucous carcinoma: slow growing, non-metastasizing
    - Papillary carcinoma
    - Hybrid verrucous carcinoma
    - Mixed carcinoma (basaloid condylomatous, adenobasaloide, and others).
  - *Sarcomatoid*: very aggressive and metastasizing. 89% risk of lymphadenopathy.
  - *Adenosquamous*.
- **Growth patterns**:
  - Superficial spread.
  - Nodular or vertical infiltration.
  - Verrucous.
- **Histopathological grading**: the classic *Broders* classification system (1921) coexists with the more recent *Maiche* system (1991), which assesses keratinization, mitosis, cellular atypia, and inflammation.
  - **Gx**: degree cannot be assessed.
  - **G1**: Well-differentiated (5-year survival rate of 83%).
  - **G2**: Moderately differentiated.
  - **G3**: Poorly differentiated.
  - **G4**: Undifferentiated (5-year survival rate of 30%).
Staging (Fig 1)

<table>
<thead>
<tr>
<th>TNM Clinical and pathological classification (UICC, 2009)</th>
<th>cN corresponds with clinical stage, pN corresponds to pathological stage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Tumor</strong></td>
<td></td>
</tr>
<tr>
<td>T&lt;sub&gt;x&lt;/sub&gt;</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T&lt;sub&gt;0&lt;/sub&gt;</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T&lt;sub&gt;is&lt;/sub&gt;</td>
<td>Carcinoma in situ.</td>
</tr>
<tr>
<td>T&lt;sub&gt;a&lt;/sub&gt;</td>
<td>Non-invasive verrucous carcinoma, not associated with destructive invasion.</td>
</tr>
<tr>
<td>T&lt;sub&gt;1a&lt;/sub&gt;</td>
<td>Tumor invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated (G3) or undifferentiated (G4).</td>
</tr>
<tr>
<td>T&lt;sub&gt;1b&lt;/sub&gt;</td>
<td>Tumor invades subepithelial connective tissue with lymphovascular invasion or is poorly differentiated (G3) or undifferentiated (G4).</td>
</tr>
<tr>
<td>T&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Tumor invades corpus spongiosum (CS)/corpora cavernosa (CC). For some authors CS invasion has better prognosis than CC invasion.</td>
</tr>
<tr>
<td>T&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Tumor invades urethra.</td>
</tr>
<tr>
<td>T&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Tumor invades other adjacent structures.</td>
</tr>
<tr>
<td>(m)</td>
<td>“m” between brackets indicates multiple tumor, e.g. T&lt;sub&gt;a&lt;/sub&gt; (m) N&lt;sub&gt;0&lt;/sub&gt;M&lt;sub&gt;0&lt;/sub&gt;.</td>
</tr>
<tr>
<td><strong>Regional lymph nodes</strong></td>
<td></td>
</tr>
<tr>
<td>cN&lt;sub&gt;x&lt;/sub&gt;</td>
<td>Regional lymph nodes cannot be assessed.</td>
</tr>
<tr>
<td>cN&lt;sub&gt;0&lt;/sub&gt;</td>
<td>No palpable or visibly enlarged inguinal lymph node.</td>
</tr>
<tr>
<td>cN&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Palpable mobile unilateral inguinal lymph node.</td>
</tr>
<tr>
<td>cN&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Palpable mobile multiple or bilateral inguinal lymph nodes.</td>
</tr>
<tr>
<td>cN&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral.</td>
</tr>
<tr>
<td>pN&lt;sub&gt;x&lt;/sub&gt;</td>
<td>Regional lymph nodes cannot be assessed.</td>
</tr>
<tr>
<td>pN&lt;sub&gt;0&lt;/sub&gt;</td>
<td>No regional lymph node metastasis.</td>
</tr>
<tr>
<td>pN&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Intranodal metastasis in a single inguinal lymph node.</td>
</tr>
<tr>
<td>pN&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Metastasis in multiple or bilateral inguinal lymph nodes.</td>
</tr>
<tr>
<td>pN&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Metastasis in pelvic lymph node(s); unilateral, bilateral, or extranodal extension of regional lymph node metastasis.</td>
</tr>
<tr>
<td><strong>Distant Metastasis</strong></td>
<td></td>
</tr>
<tr>
<td>M&lt;sub&gt;0&lt;/sub&gt;</td>
<td>No distant metastasis.</td>
</tr>
<tr>
<td>M&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Distant metastasis (bone, visceral, or extrapelvic lymph nodes).</td>
</tr>
</tbody>
</table>

**Staging**

- **Stage 0**: T<sub>x</sub>N<sub>0</sub>M<sub>0</sub>, T<sub>a</sub>N<sub>0</sub>M<sub>0</sub>
- **Stage I**: T<sub>1a</sub>N<sub>0</sub>M<sub>0</sub>
- **Stage II**: T<sub>1b</sub>N<sub>0</sub>M<sub>0</sub>, T<sub>2</sub>N<sub>0</sub>M<sub>0</sub>, T<sub>3</sub>N<sub>0</sub>M<sub>0</sub>
- **Stage IIIa**: T<sub>1</sub>‐T<sub>3</sub>N<sub>1</sub>M<sub>0</sub>
- **Stage IIIb**: T<sub>1</sub>‐T<sub>3</sub>N<sub>2</sub>M<sub>0</sub>
- **Stage IV**: T<sub>4</sub>N<sub>0</sub>‐N<sub>3</sub>M<sub>0</sub>, T<sub>1</sub>‐T<sub>4</sub>N<sub>3</sub>M<sub>0</sub>, T<sub>1</sub>‐T<sub>4</sub>N<sub>0</sub>‐N<sub>3</sub>M<sub>1</sub>

**Primary lesion:**
- **Physical examination**: number, size, location, morphology, and color of the lesion; palpation of the CC and CS to detect invasion; length of penis.
- **Incisional, scraping, ABC, or excision biopsy (preferred)**: essential.
- **Imaging studies**: ultrasound or MRI after injection of PGE1 to detect invasion of the CC.

**Regional nodes:**
- **If there are no palpable lymph nodes**: ultrasound with a 7.5 mHz transducer is recommended and if lymphadenopathy is detected, a guided ABC. In patients with poor prognostic factors in a primary tumor, a dynamic sentinel node biopsy with Isosulfan blue and Tc<sup>99m</sup> colloid is useful. Pelvic lymph nodes never occur without inguinal metastasis.
- **Palpable lymph nodes** are present in 58% of cases at diagnosis, but only ½ of those are due to metastasis; the rest are due to infection. A biopsy is required (ultrasound-guided ABC or open biopsy) if they persist after 6 weeks of antibiotic treatment. If the biopsy is negative, monitoring and rebiopsy are recommended.

**Distant metastasis**: search for this only if there are confirmed positive nodes. CT or PET, chest X-ray, and bone scan (in cases of bone pain) are recommended.
Fig 1. Staging of penile tumors (UICC 2009)
Treatment of the primary lesions

- **T\textsubscript{1a}, T\textsubscript{3}, and T\textsubscript{1b} (G1-2) lesions:** *conservative surgery of the penis.*
  - \textit{CO\textsubscript{2} or Nd:YAG laser}: gives the best results. Treatment of choice in lesions of the glans. Small recurrences can also be treated with lasers.
  - \textit{Wide excision with 3 mm margins with/without circumcision}: in foreskin lesions. Biopsy of the surgical margins is mandatory.
  - \textit{Mohs’ micrographic surgery}: for T\textsubscript{3} lesions and verrucous carcinoma.
  - \textit{Topical 5-fluorouracil or Imiquimod} (5%) for T\textsubscript{1b}: high rate of recurrence.
  - \textit{Photodynamic therapy}: high rate of recurrence.

- **T\textsubscript{1b} and G3-4 lesions of the glans:** *conservative surgery of the penis* when close monitoring can be performed. If close monitoring is unfeasible, a glansectomy or partial penectomy is preferable.
  - \textit{Local resection with CO\textsubscript{2} or Nd:YAG laser with 3 mm margins}: biopsy of margins is crucial. In multifocal cases, the entire surface of the glans should be treated and a circumcision performed. Spontaneous epithelialization can be expected or reconstructive surgery can be performed (large defects can be covered with grafts).
  - \textit{Neoadjuvant chemotherapy + local laser excision}.
  - \textit{External radiotherapy or interstitial brachytherapy}.
  - \textit{Glansectomy}: has the lowest recurrence rates.

- **T\textsubscript{2} lesions of the glans:** almost always call for **total glansectomy**. In selected patients with involvement of $<\frac{1}{2}$ the glans, a partial glansectomy can be performed. If close monitoring cannot be guaranteed, it is better to perform a partial penectomy.

- **T\textsubscript{2} lesions of the penile shaft:** call for **partial penectomy**. Classic techniques used 2 cm margins, but 5-10 mm margins are safe when margin biopsies are negative. Reconstructive surgery can be performed in selected patients.

- **T\textsubscript{3} lesions:** the standard treatment entails **total penectomy + perineal urethrostomy**. Reconstructive surgery can be performed in selected patients.

- **T\textsubscript{4} lesions:** normally associated with spread of cancer and a poor prognosis; thus, **palliative radiotherapy** is the most appropriate. In some cases an attempt can be made to reduce local extension with neoadjuvant chemotherapy followed by a total penectomy or, as an alternative, surgery followed by radiation therapy.

**Recurrences:**

- \textit{After conservative surgery}: there is a recurrence rate of 12-17%. A second conservative surgery can be performed if there is no CC invasion or broad infiltration. In the latter case, a total or partial penectomy is preferred.

- \textit{After total amputation}: recurrences have a very poor prognosis. May be treated with chemo- or radiotherapy.

**External/interstitial radiotherapy:**

- \textit{Indication}: as a conservative alternative in T\textsubscript{1-2} lesions $<4$ cm that do not invade the CC, or as a palliative treatment in locally advanced lesions or metastatic patients, or when surgery is rejected or ruled out. In carefully selected patients with the possibility of close monitoring, good results are obtained.

- \textit{Advantage}: complete conservation of the penis in 80% of cases.

- \textit{Disadvantage}: local recurrence rate between 5-60%, although these patients can undergo salvage surgery without compromising their oncological situation.

- \textit{Complications} described include meatal stenosis, glans necrosis, or late fibrosis with severe ED.
Treatment of regional lymph nodes

- If lymphadenopathy is confirmed through open or ABC biopsy:
  - **Bilateral radical inguinal lymphadenectomy**: the inguinal, adductor, and sartorius ligaments must be dissected, taking the femoral artery and vein as the limit of the dissection. Required in cases of:
    - Adenopathy confirmed by biopsy.
    - If *de novo* lymphadenopthies appear during follow-up.
  - **Modified inguinal lymphadenectomy**: decreases morbidity by preserving the saphenous vein and reducing the lateral and lower dissection margins 1-2 cm. Can be considered for the contralateral side and should be extended to a radical lymphadenectomy if lymph node involvement is detected in the intraoperative biopsy.
  - **Unilateral radical inguinal lymphadenectomy**: can be performed if lymphadenopathy appears unilaterally after a long follow-up period.
  - **Pelvic lymphadenectomy** *(external iliac and iliobdurator)*: should be carried out on the side of the inguinal lymph nodes. Can be performed in the same surgery as the inguinal lymphadenectomy or be deferred. Indicated in the following cases:
    - If 2 or more inguinal lymph nodes are affected.
    - 1 affected lymph node in aggressive variants of carcinoma, e.g. basaloid carcinoma.
    - Extracapsular extension.
    - If the Cloquet node is affected.
  - **Adjuvant chemotherapy**: indicated after bilateral ilio-inguinal lymphadenectomy when a pN2-3 nodal stage is confirmed (≥2 affected lymph nodes or extranodal spread).
  - **Neoadjuvant chemotherapy** is recommended in:
    - Cases of fixed lymphadenopathy.
    - Nodal recurrences.
    - Chemotherapy followed by surgery can achieve longer survival in almost 50% of these patients.
  - **Radiotherapy**: for regional treatment the results are much worse than with surgery. Neoadjuvant treatment complicates surgery. It is an alternative only as an adjuvant therapy.

Complications of lymphadenectomy: prolonged lymphedema, necrosis of cutaneous flaps, wound infection, severe bleeding. Careful handling of skin flaps, prophylactic antibiotics, compression stockings, and early ambulation are recommended.

- If there are no palpable or radiologically visible lymph nodes: prophylactic lymphadenectomy improves prognosis, but in 50% of cases the nodes are negative. To avoid overtreatment with surgery that has 50% morbidity and 1% mortality, patients must be carefully selected:
  - **Low risk** *(pT1a, pT2 G1-2, or pT1 G1)*: 16.5% risk of micrometastasis. Monitoring is recommended; prophylactic modified inguinal lymphadenectomy is not recommended.
  - **Intermediate risk** *(T1 G2) and high risk** *(>T2 or G3)*: 68-73% risk of micrometastasis in the high risk group. Modified (or radical, if the nodes are positive) inguinal lymphadenectomy is indicated when:
    - **Dynamic sentinel node biopsy** with *Isosulfan blue* and *Tc-99 colloid* is positive: currently reproducible technique with short learning curve. If unavailable, risk factors must be taken into account.
    - **High risk factors are present**: stage and degree, lymphatic or vascular invasion, infiltrative growth pattern, etc. Nomograms that include these factors can help with treatment decisions.
Follow-up

<table>
<thead>
<tr>
<th>Target</th>
<th>Treatment performed</th>
<th>1st-2nd year</th>
<th>3rd-5th year</th>
<th>Examinations/Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor</td>
<td>Conservative</td>
<td>3 months</td>
<td>6 months</td>
<td>PE / SE / QOL</td>
</tr>
<tr>
<td></td>
<td>Partial/total P</td>
<td>6 months</td>
<td>12 months</td>
<td>PE / SE / QOL</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Wait-and-see</td>
<td>3 months</td>
<td>6 months</td>
<td>PE / SE / QOL / US + ABC if necessary</td>
</tr>
<tr>
<td></td>
<td>IIL/PLND (pN0)</td>
<td>6 months</td>
<td>12 months</td>
<td>PE / SE / QOL / US + ABC if necessary</td>
</tr>
<tr>
<td></td>
<td>IIL/PLND (pN+)</td>
<td>3 months</td>
<td>6 months</td>
<td>PE / SE / QOL / US + ABC if necessary / CT / BS if symptoms</td>
</tr>
</tbody>
</table>


- **Overall recurrences**: 74% of all local, regional, and distant recurrences occur in the first 2 years and 92% in the first 5 years. After 5 years, follow-up can be discontinued if the patient is able to conduct a self-exam.
- **Local recurrences**: with partial or total penectomy the recurrence rate is 0-5%; with conservative treatment it is 30%. With early detection and treatment, local recurrence does not compromise survival.
- **Regional recurrences**: the risk is 9% if no lymphadenectomy was performed or if it was negative; the risk is 19% if affected lymph nodes were removed.
- **Distant recurrences**: 100% occur within the first 2 years.

Premalignant lesions

- **Lesions sporadically associated with squamous cell carcinoma of the penis**:
  - *Balanitis xerotica obliterans*. *(See chapter: Atlas of Urological Lesions)*
  - Cutaneous horn of the penis.
  - Bowenoid papulosis of the penis.
- **Lesions with malignant transformation risk in 1/3 of cases**:
  - *Erythroplasia of Queyrat*: velvety erythematous and pruritic lesion on the glans.
  - *Bowen’s disease*: ulcerated scales on the skin of the penile shaft.
  Both related to HPV serotypes 16 and 18.
Both are considered penile intraepithelial neoplasia (*carcinoma in situ*).
- **Treatment**:
  - Local excision.
  - Fulguration with CO₂ or Nd-YAG laser.
  - Cryotherapy.
  - Mohs’ micrographic surgery.

Verrucous carcinoma of the penis

- **Definition**: a variant of squamous cell carcinoma, but slow growing and non-metastasizing.
- **Diagnosis**: core biopsy to rule out invasion.
- **Treatment**: local conservative surgery; lymphadenectomy is not necessary. Radiotherapy is to be avoided as it can transform the carcinoma into a more aggressive, metastasizing tumor.
Penile cancer

- **T1a** - T1s
  - **T1a(G1,2)**
    - with easy follow-up
      - yes
      - cured
        - Invasion of corpus cavernosum
          - no
          - 2nd attempt:
            - Local excision
              - CO2 laser/ Nd:YAG
              - Mohs' surgery
              - Radiotherapy
          - yes
        - no
          - Palliative RT
          - Neoadjuvant chemotherapy
          - 2nd attempt:
            - Local excision
              - CO2 laser/ Nd:YAG
              - Mohs' surgery
              - Radiotherapy

- **T2** limited to the glans
  - with easy follow-up
    - yes
      - cured
    - no
      - yes
      - Total glansectomy
      - no

- **T2** in penile shaft
  - Possibility of 5-10 mm margins
    - yes
      - Partial Penectomy (or Radiotherapy)
    - no
      - Total Penectomy (or Radiotherapy)