NCCN Penile Cancer Panel Members

Primary Evaluation, Pathologic Diagnosis, and Primary Treatment Tis, Ta (PN-1)

Primary Treatment T1, T2 or greater (PN-2)

Management of Non-Palpable Inguinal Lymph Nodes (PN-3)

Management of Palpable Inguinal Lymph Nodes (PN-4)

Management of Bulky/Unresectable Inguinal Lymph Nodes (PN-5)

Surveillance (PN-6)

Management of Recurrent Disease (PN-7)

Management of Metastatic Disease (PN-8)

See Principles of Surgery (PN-A)

See Principles of Radiotherapy (PN-B)

See Principles of Chemotherapy (PN-C)

Clinical Trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified. See NCCN Categories of Evidence and Consensus.

Staging (ST-1)
**NCCN Guidelines Version 1.2012**

**Penile Cancer**

### PRIMARY EVALUATION

**H&P**
- Risk factors
  - balanitis, chronic inflammation, penile trauma, lack of neonatal circumcision, tobacco use, lichen sclerosus, poor hygiene, sexually transmitted disease
- Lesion characteristics
  - diameter
  - location
  - number of lesions
  - morphology (papillary, nodular, ulcerous, or flat)
  - relationship to other structures (submucosal, corpora spongiosa and/or cavernosa, urethra)

**Cytology or histological diagnosis**
- Punch, excisional, or incisional biopsy
- MRI or ultrasound

### PATHOLOGIC DIAGNOSIS

**Tis or Ta**

**T1**
- Grade 1-2

**T2 or greater**
- Grade 3-4

### PRIMARY TREATMENT

**Tis or Ta**
- Topical therapy
  - or
  - Wide local excision including circumcision
  - or
  - Laser therapy (category 2B)
  - or
  - Complete glansectomy (category 2B)

**T1**
- See Primary Treatment (PN-2)

**T2 or greater**
- If recurrent disease, see PN-7 or if metastatic disease, see PN-8

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*a*MRI or ultrasound are optional studies based on clinical suspicion and to further define concerning physical exam findings.

*b*Topical therapy may include topical imiquimod (5%) or 5-fluorouracil (5-FU) cream.

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PATHOLOGIC DIAGNOSIS

Grade 1-2

T1

Grade 3-4

T2 or greater

Primary Treatment

Wide local excision; possible STSG or FTSG\(^d\)

or Laser therapy (category 2B)

or Radiotherapy\(^e\) (category 2B)

Wide local excision\(^d, f\)

or Glansectomy\(^g\)

or Partial penectomy\(^f, h\)

or Total penectomy\(^f, h\)

or Radiotherapy\(^e\) ± concurrent chemotherapy

(category 2B)

Partial penectomy\(^f, h\)

or Total penectomy\(^f, h\)

or Radiotherapy\(^e\) ± concurrent chemotherapy

(category 2B)

See Management of Non-Palpable Inguinal Lymph Nodes (PN-3) or Palpable Inguinal Lymph Nodes (PN-4)

\(^c\) See Principles of Surgery (PN-A).

\(^d\) Complete excision of skin with a wide negative margin with skin grafting needed. STSG = split-thickness skin grafts; FTSG = full-thickness skin grafts.

\(^e\) See Principles of Radiotherapy (PN-B).

\(^f\) If positive or close margins and/or lymphovascular invasion (LVI), consider radiotherapy (category 2B).

\(^g\) Appropriate with proven negative margins. For tumors involving the glans only: glansectomy or radiotherapy (interstitial brachytherapy at experienced centers) with prior circumcision.

When it is necessary to dissect into the corpora cavernosum to achieve a negative margin, a partial penectomy is performed. Total penectomy is required for lesions extending into the corpora cavernosum.

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**MANAGEMENT OF NON-PALPABLE INGUINAL LYMPH NODES**

**NODAL STATUS**

**RISK STRATIFICATION BASED ON PRIMARY LESION**

- **Low risk** (Tis, TaG1-2, T1G1)
  - Surveillance (See PN-6) or Dynamic sentinel node biopsy (DSNB)\(^1\) (category 2B)

- **Intermediate risk** (T1G2)
  - Lymphovascular invasion
    - **Absent**
      - Surveillance (See PN-6)
    - **Present**
      - Inguinal lymph node dissection (ILND) or DSNB\(^1\) (category 2B)

- **High risk** (Any T2 or G3)

\(^1\)DSNB is recommended provided the treating physician has experience with this modality. If positive lymph nodes are found on DSNB, ILND is recommended.
MANAGEMENT OF PALPABLE INGUINAL LYMPH NODES

NODAL STATUS RISK STRATIFICATION BASED ON PRIMARY LESION TREATMENT

Palpable inguinal lymph nodes

≥4 cm lymph node (fixed or mobile)\(^{\text{j}}\)

\(\text{≥4 cm lymph node} \rightarrow \text{Fine needle aspiration (FNA)}^{\text{k}}\)

Unilateral lymph node <4 cm

Note: All recommendations are category 2A unless otherwise indicated.

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\(^{\text{j}}\)Imaging to assess regional nodes and distant metastases.

\(^{\text{k}}\)For a high-risk primary lesion, it is recommended to proceed directly to ILND and not FNA.
Note: All recommendations are category 2A unless otherwise indicated.
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See Principles of Radiotherapy (PN-B).
On CT or MRI, not pathologic stage.
See Principles of Chemotherapy (PN-C).
Consider adjuvant chemotherapy (category 2B).
Consider postoperative radiotherapy (category 2B).
Consolidation surgery consists of bilateral superficial and deep ILND and possible bilateral PLND.

Additional systemic chemotherapy or Consider radiation therapy for local control or Clinical trial

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PN-5
**NCCN Guidelines Version 1.2012**  
Penile Cancer

### ANATOMIC SITE  

#### Primary lesion
- Topical therapy  
- Laser therapy  
- Radiation therapy  
- Wide local excision including circumcision  
- Partial penectomy  
- Total penectomy  

### INITIAL TREATMENT  

#### N0, N1

### SURVEILLANCE  

Clinical exam:
- Year 1-2, every 3 mo then year 3-5, every 6 mo then year 5-10, every 12 mo

#### N2, N3

Clinical exam:
- Year 1-2, every 3-6 mo then year 3-5, every 12 mo

**For patients with recurrence at either local or distant sites,**  
see Management of Recurrent Disease (PN-7).

- Patients on active surveillance of clinically negative nodes and at low risk for inguinal metastases.
- Clinical exam includes examination of the penis and inguinal region.
- If an abnormal clinical exam, obese patient, or prior inguinal surgery, ultrasound, CT, or MRI of the inguinal region can be considered.

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MANAGEMENT OF RECURRENT DISEASE

Recurrence of penile lesion after initial treatment → Invasion of corpora cavernosa

Absent → Partial penectomy or Total penectomy or Repeat penile-sparing treatment (category 2B)

Present → Partial penectomy or Total penectomy

Local recurrence in inguinal region → Consider systemic chemotherapy and/or Consider external beam radiation therapy (EBRT) and/or Consider surgical resection

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
MANAGEMENT OF METASTATIC DISEASE

Metastatic penile cancer

Systemic chemotherapy\(^t\) or Radiotherapy\(^e\) or Radiotherapy with concurrent chemotherapy

Complete/partial response or stable

Consolidative surgery\(^p\)

See Surveillance (PN-6)

No response/Disease progression

Consider salvage systemic chemotherapy\(^m\) or Consider radiotherapy for local control\(^e\) and/or Best supportive care/clinical trial, See NCCN Palliative Care Guidelines

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\(^t\) See Principles of Chemotherapy (PN-C).

\(^e\) See Principles of Radiotherapy (PN-B).

\(^m\) See Principles of Chemotherapy (PN-C).

\(^p\) Consolidation surgery consists of bilateral superficial and deep ILND and possible bilateral PLND.

\(^t\) Such as (a) paclitaxel, ifosfamide, and cisplatin, (b) 5-fluorouracil and cisplatin See Principles of Chemotherapy (PN-C).

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF SURGERY

- Tis, Ta penile cancer lesions may be amenable to conservative penile organ-sparing approaches, including: topical therapy, laser, circumcision, local excision, or glansectomy.

- Partial penectomy should be considered the standard for high-grade primary penile tumors, provided a functional penile stump can be preserved and negative margins are obtained.

- Standard or modified ILND is indicated in patients with penile cancer in the absence of palpable inguinal adenopathy if high-risk features for nodal metastasis are seen in the primary tumor:
  - Lymphovascular invasion
  - pT1G3 or greater primary penile tumor
  - Greater than 50% poorly differentiated primary penile tumor

- PLND should be considered at the time of ILND in patients with ≥2 inguinal nodes (on frozen section) on the ipsilateral ILND site.

- Neoadjuvant chemotherapy should be considered the standard (prior to ILND) in patients with ≥4 cm or fixed inguinal lymph nodes, if FNA is positive for metastatic penile cancer.

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PRINCIPLES OF RADIOTHERAPY

Primary Radiation Therapy (category 2B) (Penile Preservation)

**T1-2, N0**
- If tumor <4 cm
  - Circumcision followed by either:
    - Brachytherapy alone (should be performed with interstitial implant);
      or
    - EBRT with or without chemotherapy: Total dose 65-70 Gy to primary penile lesion with 2 cm margins.
      Consider prophylactic inguinal lymph node irradiation.

- If tumor ≥4 cm
  - Circumcision followed by either:
    - EBRT with chemotherapy: 45-50.4 Gy to a portion of or whole penile shaft depending upon bulk and extent of lesion plus pelvis/inguinal nodes, then boost primary lesion with 2 cm margins EBRT (total dose 60-70 Gy);
      or
    - Brachytherapy (in select cases and with careful post-treatment surveillance)

**T3-4 or N+**
- Circumcision followed by:
  - EBRT with chemotherapy: 45-50.4 Gy to whole penile shaft, pelvic lymph nodes, and bilateral inguinal lymph nodes, then boost primary lesion with 2 cm margins and gross lymph nodes (total dose 60-70 Gy).

Postoperative Adjuvant Radiotherapy (category 2B)

- Inguinal Lymph Node Positive
  - Inguinal and pelvic lymph node EBRT to 45-50.4 Gy (strongly consider concomitant chemotherapy).
  - Boost gross nodes and areas of extracapsular extension to a total dose of 60-70 Gy.
  - Treat primary site of disease if positive margin. (consider primary site irradiation if lymphovascular space invasion or close margin).

- Primary Site Margin Positive
  - Treat primary site of disease and surgical scar to 60-70 Gy (for close margin consider radiation treatment versus observation).
  - Brachytherapy (in select cases)
  - Treat bilateral inguinal lymph nodes and pelvic lymph nodes if no or inadequate lymph node dissection.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF CHEMOTHERAPY

- Neoadjuvant, cisplatin-based chemotherapy should be considered the standard (prior to ILND) in patients with \( \geq 4 \) cm or fixed inguinal lymph nodes.\(^1\)
  - Patients with initially unresectable (T4) primary tumors may be downstaged by response to chemotherapy.

- Patients with a Tx, N2-3, M0 penile cancer can receive 4 courses of preoperative paclitaxel, ifosfamide, and cisplatin.\(^2\) Stable or responding patients should then undergo surgical resection with curative intent.
  - The phase II response rate was 50% in the neoadjuvant setting.
  - The estimated rate of long-term progression-free survival for intent to treat was 36.7%.
  - Improved progression-free and overall survival times were associated with objective response to chemotherapy.

- There are no sufficient data to form conclusions about the use of adjuvant chemotherapy. By extrapolation from the neoadjuvant data, it is reasonable to give 4 courses of paclitaxel, ifosfamide, and cisplatin in the adjuvant setting if it was not given preoperatively and the pathology shows high-risk features. (See Management of Bulky/Unresectable Inguinal Lymph Nodes, PN-5) For high-risk patients, for whom adjuvant EBRT or chemoradiotherapy can also be considered, include those with any of the following:
  - Pelvic lymph node metastases
  - Extranodal extension
  - Bilateral inguinal lymph nodes involved
  - 4 cm tumor in lymph nodes

- Paclitaxel, ifosfamide, and cisplatin is a reasonable first-line treatment for patients with metastatic penile cancer, including palliative treatment of patients with distant metastases.\(^2\)
  - 5-fluorouracil (5-FU) + cisplatin has been used historically for metastatic penile cancer and can be considered as an alternative to paclitaxel, ifosfamide, and cisplatin.\(^3\) It appears to be effective for some patients, although the toxicities may be limiting and require dose reductions.\(^4\)
  - Bleomycin-containing regimens were associated with unacceptable toxicity and are no longer recommended.\(^5\)
  - There are no randomized clinical trials due to the rarity of penile cancer in industrialized countries.

- No standard second-line systemic therapy exists. Depending on first-line therapies, palliative options include single-agent therapy such as capecitabine, carboplatin, docetaxel, 5-FU, irinotecan, methotrexate, paclitaxel, and panitumumab.\(^4,6-10\) Continued on PN-C 2 of 2
**Preferred combination chemotherapy regimens**

**TIP**
- Paclitaxel 175 mg/m\(^2\) IV over 3 hours on Day 1
- Ifosfamide 1200 mg/m\(^2\) IV over 2 hours on Days 1-3
- Cisplatin 25 mg/m\(^2\) IV over 2 hours on Days 1-3
- Repeat every 21 days

**5-FU + Cisplatin**
- (category 2B)
  - Continuous infusion 5-FU 1000 mg/m\(^3\)/d IV on Days 1-5
  - Cisplatin 100 mg/m\(^2\) IV on Day 1
  - Repeat every 3 to 4 weeks

**Preferred radiosensitizing agents and combinations**
- (For concurrent treatment with radiotherapy) (category 2B)
  - Cisplatin alone, or in combination with 5-FU
  - Mitomycin C in combination with 5-FU
  - Capecitabine

**References**

**Note:** All recommendations are category 2A unless otherwise indicated.

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**Table 1**

**American Joint Committee on Cancer (AJCC)**

**TNM Staging System for Penile Cancer (7th ed., 2010)**

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>ANATOMIC STAGE/PROGNOSTIC GROUPS</th>
</tr>
</thead>
</table>
| TX               | Stage 0  
| Primary tumor cannot be assessed | Tis  N0  M0 |
| T0               | Ta  N0  M0 |
| No evidence of primary tumor |
| Ta               | T1a  N0  M0 |
| Noninvasive verrucous carcinoma* |
| Tis              | Stage I  
| Carcinoma in situ |
| T1a              | T1b  N0  M0 |
| Tumor invades subepithelial connective tissue without lymph vascular invasion and is not poorly differentiated (i.e., grade 3-4) |
| T1b              | T2  N0  M0 |
| Tumor invades subepithelial connective tissue with lymph vascular invasion or is poorly differentiated |
| T2               | T3  N0  M0 |
| Tumor invades corpus spongiosum or cavernosum |
| T3               | Stage IIIa  
| Tumor invades urethra |
| T4               | T1-3  N1  M0 |
| Tumor invades other adjacent structures |

*Note:* Broad pushing penetration (invasion) is permitted; destructive invasion is against the diagnosis

<table>
<thead>
<tr>
<th>Regional Lymph Nodes (N)</th>
<th>ANATOMIC STAGE/PROGNOSTIC GROUPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Stage Definition*</td>
<td></td>
</tr>
</tbody>
</table>
| cNX                     | Stage IV  
| Regional lymph nodes cannot be assessed |
| cN0                     | T4  Any N  M0 |
| No lymph node metastasis |
| cN1                     | Any T  N3  M0 |
| Palpable mobile unilateral inguinal lymph node |
| cN2                     | Any T  Any N  M1 |
| Palpable mobile multiple or bilateral inguinal lymph nodes |
| cN3                     | Palpable fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral |

Pathologic Stage Definition*  

| pNX                    | Regional lymph nodes cannot be assessed |
| pN0                    | No regional lymph node metastasis |
| pN1                    | Metastasis in a single inguinal node |
| pN2                    | Metastasis in multiple or bilateral inguinal lymph nodes |
| pN3                    | Extranodal extension of lymph node metastasis or pelvic lymph node(s) unilateral or bilateral |

*Note:* Pathologic stage definition based on biopsy or surgical excision.

<table>
<thead>
<tr>
<th>Distant Metastasis (M)</th>
<th>ANATOMIC STAGE/PROGNOSTIC GROUPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC (SBM). (For complete information and data supporting the staging tables, visit [www.springer.com](http://www.springer.com).) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.
Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Squamous cell carcinoma (SCC) of the penis is a rare disease, representing 0.4% to 0.6% of all malignant neoplasms among men in the United States and Europe. In 2012, the estimated number of new cases of penile cancer in the United States is 1,570, with 310 predicted cancer-specific deaths. Incidence is higher (up to 10%) among men in the developing countries of Asia, Africa, and South America. The most common age of presentation is between ages 50 and 70. Early diagnosis is of utmost importance, as this is a disease that can result in devastating disfigurement and has a 5-year survival rate of approximately 50% (over 85% for patients with negative lymph nodes and 29% to 40% for patients with positive nodes, with the lowest survival rates at 0% for patients with pelvic lymph node involvement). As the rarity of this disease makes it difficult to perform prospective, randomized trials, the NCCN panel relied on the experience of penile cancer experts to minimize the controversies associated with treating penile SCC and collectively lay down a foundation to help standardize the management of the malignancy.

Risk Factors

In the United States the median age of diagnosis is 68 years, with an increase in risk for males older than 50 years. Early detection is assisted by the ability to do a good physical exam. Phimosis may hinder the capability to properly inspect the areas of highest incidence—the glans, inner preputial layer, coronal sulcus, and shaft. Men with phimosis carry an increased risk of 25% to 60%. A more recent review of penile SCC in the United States showed that 34.5% of patients had the primary lesion on the glans, 13.2% on the prepuce, and 5.3% in the shaft, with 4.5% overlapping and 42.5% unspecified. Other risk factors include balanitis, chronic inflammation, penile trauma, tobacco use, lichen sclerosus, poor hygiene, and a history of sexually transmitted disease(s), especially human immunodeficiency virus (HIV) and human papillomavirus (HPV). Overall, about 45% to 80% of penile cancers are related to HPV, with a strong correlation with types 16 and 18. There is an 8-fold increased risk for patients with HIV, which may correspond to a higher incidence in HPV among males with HIV. Cigarette smokers are noted to be 3 to 4.5 times more likely to develop penile cancer. Patients with lichen sclerosus are noted to have a 2% to 9% risk of developing penile carcinoma. Psoriasis patients undergoing psoralen plus ultraviolet A (PUVA) treatment have an increased incidence of 286 times compared to the general population. Therefore, they should be shielded during treatment and any penile lesion should be closely monitored.
Clinical Presentation

Most often penile SCC presents as a palpable, visible lesion on the penis, which may be associated with penile pain, discharge, bleeding, or a foul odor if the patient delays in seeking medical treatment. The lesion may be characterized as nodular, ulcerative, or fungating, and may be obscured by phimosis. The patient may exhibit signs of more advanced disease, including palpable nodes and/or constitutional symptoms (eg, fatigue, weight loss).

Characterization and Clinical Staging

SCC is the most common variant of penile cancer. Penile intraepithelial neoplasia (PIN) is a premalignant condition at high risk of developing into SCC of the penis. The American Joint Committee on Cancer (AJCC) recognizes four subtypes of SCC: verrucous, papillary squamous, warty, and basaloid. The verrucous subtype is felt to be of low malignant potential, while other variants reported—adenosquamous and sarcomatoid variants—carry a worse prognosis. The primary lesion is further characterized by its growth pattern with superficial spread, nodular or vertical-phase growth, and verrucous pattern. In addition to the penile lesion, evaluation of lymph nodes is also critical, as involvement of the inguinal lymph nodes (ILNs), the number and site of positive nodes, and extracapsular nodal involvement provide the strongest prognostic factors of survival.

The AJCC Tumor, Nodes, and Metastasis (TNM) system for penile carcinoma has been used for staging, with the most recent update published in 2010. It was initially introduced in 1968 and was subsequently revised in 1978, 1987, and 2002. In the 2010 update, the AJCC has made the distinction between clinical and pathologic staging while eliminating the difference between superficial and deep inguinal metastatic nodes. Other changes to the 2010 TNM system include: T1 subdivided into T1a and T1b determined by the presence or absence of lymphovascular invasion or poorly differentiated cancers; the T3 category is now limited to urethral invasion and T4 is limited to prostatic invasion; and stage II grouping includes T1b N0M0 as well as T2-3 N0M0 (see staging tables in the algorithm). A grading system for SCC of the penis based on degree of cell anaplasia is defined as: grade 1, well differentiated (no evidence of anaplasia); grade 2, moderately differentiated (<50% anaplasia); and grade 3, poorly differentiated (>50% anaplastic cells). According to the AJCC, if no grading system is specified, a general system should be followed: GX, grade cannot be assessed; G1-3 as previously mentioned above; and G4, undifferentiated. The overall degree of cellular differentiation with high-risk, poorly differentiated tumors is an important predictor factor for metastatic nodal involvement. The AJCC also recommends collection of site-specific factors, including: the distinction between corpus spongiosum and corpus cavernosum involvement, the percentage of tumor that is poorly differentiated, the depth of invasion in verrucous carcinoma, the size of the largest lymph node metastasis, and HPV status.

Management of Primary Lesions

Diagnosis

Evaluation of the primary lesion, regional lymph nodes, and distant metastasis will dictate the appropriate and adequate management of SCC of the penis, beginning with the first evaluation at presentation and then throughout follow-up. Vital to the initial management is a good physical exam of the penile lesion(s) that remarks on the diameter of the lesion(s) or suspicious areas; location(s) on the penis; number of lesions; morphology of the lesion(s); whether the lesion(s) are papillary, nodular, ulcerous or flat; and relationship with other structures including submucosal, urethra, corpora spongiosa, and/or corpora cavernosa.
complete the initial evaluation, histologic diagnosis with a punch, excisional, or incisional biopsy is paramount in determining the treatment algorithm based on a pathologic diagnosis.\textsuperscript{17,27} This will provide information on the grade of the tumor, and will assist in the risk stratification of the patient for regional lymph node involvement.\textsuperscript{27} Magnetic resonance imaging (MRI) or ultrasound can be used to evaluate the depth of tumor invasion.\textsuperscript{28} For the evaluation of lymph nodes, see Management of Regional Lymph Nodes.

**NCCN Recommendations**

**Tis or Ta**

For patients with penile carcinoma in situ or noninvasive verrucous carcinoma, penis-preserving techniques may be utilized, including topical imiquimod (5\%) or 5-fluorouracil (5-FU) cream, circumcision and wide local excision such as Mohs surgery, laser therapy (category 2B) using carbon dioxide or neodymium:yttrium-aluminum-garnet, and complete glansectomy (category 2B). Among these, topical therapy\textsuperscript{29-31} and excisional organ-sparing surgery\textsuperscript{32} are the most widely used. Retrospective studies of laser therapy reported local recurrence rates of around 18\% comparable to that of surgery, with good cosmetic and functional results.\textsuperscript{33,34} Glansectomy, removal of the glans penis, has also been studied with no recurrence observed in some cases.\textsuperscript{35-38}

**T1G1-2**

Careful consideration should be given to penile-preserving techniques if the patient is reliable with regards to compliance with close follow-up. These techniques include wide local excision plus reconstructive surgery,\textsuperscript{39} laser therapy (category 2B),\textsuperscript{40} and radiotherapy delivered as external beam radiation therapy (EBRT) or brachytherapy with interstitial implant (category 2B).\textsuperscript{41-44} Emphasis is placed again on patient selection and close follow-up, as the 2-year recurrence rate may reach up to 50\%.\textsuperscript{45} Recent studies have shown that surgical margins of 5-10 mm are as safe as 2 cm surgical margins, and 10-20 mm margins provide adequate tumor control.\textsuperscript{46} Circumcision should always precede radiation therapy (RT) to prevent radiation-related complications.

**T1G3-4, T≥2**

These lesions typically require more extensive surgical intervention with partial or total penectomy depending on the characteristics of the tumor and depth of invasion.\textsuperscript{27} If the tumor encompasses less than half the glans and the patient agrees to very close observation, then a more conservative approach such as wide local excision or glansectomy may be considered. The patient should understand that there is an increased risk for recurrence and potential for a repeat wide local excision should a local recurrence be noted, provided there is no invasion of the corpora cavernosa.\textsuperscript{34,36} A clear and frank discussion should be had with the patient that a partial or total penectomy will likely be required should a larger or more invasive lesion be present.

The tumor size is an important factor when choosing RT as treatment (category 2B). As the average length of the glans is about 4 cm, this serves as a cutpoint to reduce the risk of under-treating cavernosal lesions. In a study of 144 patients with penile cancer restricted to the glans treated by brachytherapy, larger tumors, especially those over 4 cm, are associated with higher risk of recurrence.\textsuperscript{47} A high 10-year cancer-specific survival rate of 92\% was achieved in this series. For tumors smaller than 4 cm, brachytherapy with interstitial implant or EBRT with or without chemotherapy are viable options. Consider prophylactic ILN irradiation if selecting EBRT. For tumors 4 cm or larger, EBRT combined with chemotherapy may be used. Brachytherapy may still be appropriate in select cases, but careful monitoring is necessary as the risks of complications and failures increase. RT should be given after circumcision has been performed.
Post-surgical RT to the primary tumor site may be considered for positive or close margins and/or upon detection of lymphovascular space invasion (category 2B).

**Management of Regional Lymph Nodes**

**Evaluation and Risk Stratification**

The presence and extent of regional ILN metastases has been determined to be the single most important prognostic indicator in determining long-term survival in men with invasive penile SCC. Evaluation of the groin and pelvis is an essential component of the metastatic work-up of a patient. The involvement of the ILN can be clinically evident, ie palpable versus non-palpable, adding to the difficulty in management. Clinical exam for ILN involvement should attempt to evaluate and assess for palpability, number of inguinal masses, unilateral or bilateral, dimensions, mobility or fixation of nodes or masses, relationship to other structures (eg, skin, Cooper’s ligaments), and edema of the penis, scrotum, and/or legs.

Crossover drainage from left to right and vice versa does occur and is reproducible with lymphoscintigraphy. The physical exam should describe the diameter of node(s) or mass(es), unilateral or bilateral localization, number of nodes identified in each inguinal, and the relationship to other structures, (eg, skin, Cooper’s ligament) with respect to infiltration, perforation, etc. Imaging for palpable disease by computed tomography (CT) or MRI may be used to assess the size, extent, location, and structures that are in close proximity to the ILN, as well as the presence of pelvic and retroperitoneal lymph nodes and distant metastasis. CT and MRI are limited in patients with non-palpable disease.

While studies have looked at the use of nanoparticle-enhanced MRI, positron emission tomography-CT (PET/CT), and 18F-fluorodeoxyglucose (FDG) PET/CT, their small sample size requires validation in larger prospective studies. When considering one imaging modality to evaluate the stage of the primary lesion and lymph node status, MRI appears to be the best choice to not only enhance, but potentially replace the physical exam in patients where the inguinal region is difficult to assess (eg, morbidity, previous chemo/radiotherapy).

Consideration needs to be given to whether or not the primary lesion demonstrated any adverse prognostic factors. If one or more of these high-risk features is present, then pathological ILN staging must be performed. Up to 25% of patients with non-palpable lymph nodes harbor micrometastases. Therefore, several predictive factors have been evaluated to help predict the presence of occult lymph node metastasis. Slaton et al. concluded that patients with pathologic stage T2 or greater were at significant risk (42% - 80%) of nodal metastases if they exhibited greater than 50% poorly differentiated cancer and/or vascular invasion, and therefore should be recommended to undergo an inguinal lymph node dissection (ILND). These factors can then further define patients into low-, intermediate-, and high-risk groups for lymph node metastasis. The European Association of Urology determined risk stratification groups for patients with non-palpable ILNs, and validated this in both uni- and multivariate analyses of prognostic factors. Patients can be stratified based on stage and/or grade into risk groups based on the likelihood of harboring occult node-positive disease, with the low-risk group defined as those patients with Tis, TaG1-2 or T1G1, the intermediate group as those with T1G2, and the high-risk group as those with T2 or G3.

**Dynamic Sentinel Node Biopsy**

The work by Cabanas used lymphangiograms and anatomic dissections to evaluate the sentinel lymph node drainage for penile cancer with non-palpable ILNs. This technique has been shown to have false-negative rates as high as 25%; therefore, it is no longer
Advancements have been made with the dynamic sentinel node biopsy (DSNB) technique developed for penile cancer by the Netherlands Cancer Institute using lymphoscintigraphy and performed with technetium-99m-labeled nanocolloid and patent blue dye isosulfan blue. Initially, this technique was associated with a low sensitivity and high false-negative rate (16% - 43%). Refinement of the technique to improve the false-negative rate includes serial sectioning and immunohistochemical staining of pathological specimens, preoperative ultrasonography with and without fine needle aspiration cytology, and exploration of groins in which no sentinel node is visualized on intraoperative assessment, achieving a decrease in false-negative rate from 19% to only 5%. Using fine needle aspiration with ultrasound can increase the diagnostic yield in metastasis > 2 mm in diameter. Crashaw et al. used ultrasound with DSNB and noted improved accuracy in identifying patients with occult lymph node metastases. With modification of the National Cancer Institute (NCI) protocol, Hadway et al. were able to achieve a similar false-negative rate (5%) with an 11-month follow-up. Secondary to the technical challenges associated with DSNB, it is recommended that DSNB be performed at tertiary care referral centers where at least 20 procedures are done per year. It should be noted that DSNB is not recommended in patients with palpable ILNs.

**Inguinal Lymph Node Dissection**

The most frequent site of metastasis is the ILN typically presenting as palpable inguinal lymphadenopathy. The management of the ILN by ILND has been fraught with great fears of surgical morbidity. Early treatment of lymph node involvement has been shown to have a positive impact on survival, except if the patient has bulky nodal spread or other sites of metastases. Palpable lymphadenopathy at the time of diagnosis does not warrant an immediate ILND. Of the patients with palpable disease, 30% to 50% will be secondary to inflammatory lymph node swelling instead of metastatic disease. Although the distinction between reactive lymph nodes and metastatic disease may be done after a 6-week course of antibiotics, fine needle aspiration is becoming the most favored approach among many penile cancer experts. In this setting, antibiotics are useful if the patient has a suspected underlying cellulitis at the site of palpable inguinal lymphadenopathy and future site of ILND.

In attempts to decrease the morbidity associated with standard ILND, Catalona pioneered a modified lymphadenectomy surgical approach in 1988. This technique uses a shorter skin incision, limiting the field of inguinal dissection by excluding the area lateral to the femoral artery and caudal to the fossa ovalis, with preservation of the saphenous vein and elimination of the need to transpose the sartorius muscle while providing an adequate therapeutic effect. This technique is commonly reserved for patients with a primary tumor that places them at increased risk for inguinal metastasis and clinically negative groins on examination. The modified technique has shown a decrease in complications by preserving the saphenous vein and leaving the sartorius muscle in place. Contemporary modified ILND should include the central and superior zones of the inguinal region, as these sections were not included in the dissection leading to a false-positive rate of 15%. It is important to note that if nodal involvement is detected on frozen section, the surgical procedure should be converted to a standard extended lymphadenectomy.

A standard extended lymphadenectomy may be considered if the patient has resectable metastatic adenopathy, although recent studies would favor a neoadjuvant chemotherapy approach followed by surgical consolidation. Generally, the procedure follows the primary tumor...
treatment by 4 to 6 weeks. Again during this time, antibiotics may be administered if an overlying cellulitis is suspected at the future surgical site. The extent of the standard ILND includes the superficial and the deep ILNs. The boundaries of the dissection are defined by the superior margin of the external ring to the anterior superior iliac spine, laterally from the anterior superior iliac spine extending 20 cm inferiorly and medially to a line drawn from the pubic tubercle 15 cm downward. Typically it is recommended to keep the patient on bed rest for 48 to 72 hours, especially after myocutaneous flaps or the repair of large skin defects. The drains are removed when drainage is less than 30 to 50 mL/day, usually 3 to 17 days post-operatively. Consideration should be given to keeping the patient on a suppressive dose of an oral cephalosporin (or other gram positive covering broad spectrum) for several weeks post-operatively in an attempt to decrease the risk of wound-related issues and minimize the risk for overall complications.

**Pelvic Lymph Node Dissection**

Pelvic lymph node dissection (PLND) includes the lymph nodes along the external iliac vessels and in the obturator fossa (up to 12 to 20 nodes). Crossover from one pelvic side to the other has not been observed, unlike crossover at the inguinal level. The limits of the PLND include the iliac bifurcation for proximal, ilioinguinal nerve for lateral, and obturator nerve for medial boundary. Consideration should be given to performing a PLND only among patients with 2 or more positive ILNs, extracapsular nodal extension, or poorly differentiated metastases, as highlighted in a retrospective study by Lont et al.

**Advances in Surgical Approach: Video/Endoscopy**

Minimally invasive surgical techniques including video endoscopicinguinal lymphadenectomy (VEIL) or robotic-assisted laparoscopy offer the potential for fewer cutaneous complications while attempting to maintain comparable oncologic outcomes. The endoscopic approach was initially described by Bishoff et al. in 2003, with a subcutaneous modified inguinal lymphadenectomy in two cadaveric models. The patient selection for VEIL includes those patients who warrant an open procedure, including: (1) patients with palpable lymphadenopathy; and (2) patients with non-palpable nodes and primary tumor ≥T2, in the presence of high-grade features and/or vascular invasion. The lymph node template is as described by Catalona et al. for the modified inguinal lymphadenectomy. A difference is that this technique does not always preserve the saphenous vein. The boundaries of the dissection include the Sartorius muscle laterally, the adductor longus muscle medially, and the inguinal ligament and spermatic cord superiorly. Tobias-Machado et al. modified the technique from Bishoff’s series and selected patients with non-palpable ILNs for their first successful report. In another series, they reported that with VEIL they obtained good results, meaning that they were able to dissect and excise the same number of nodes in patients who had an open procedure on one groin and a VEIL procedure on the other groin. From the patients’ perspective, they reported increased pain with the open procedure compared to the laparoscopic approach. This series of 10 patients recorded no recurrences or cases of disease progression with a mean follow-up of 18.7 months. Subsequently, Tobias-Machado et al. presented a comparative study of 20 groins that underwent VEIL and 10 that underwent an open procedure. This series had complication rates of 70% for the open procedure and 20% for the VEIL procedure, with no recurrences at median follow-up of 33 months. Another group, Sotelo et al., also used the endoscopic approach in 8 patients (14 lymphadenectomies) and noted no peri-operative or wound-related complications, with three groins (23%) developing a lymphocele. Minimally invasive techniques show promise with reduced complication.
rates while preserving the principles of oncologic surgery. Nevertheless, at this time the open surgical approach should be considered the standard, and laparoscopic approaches will require validation in larger surgical series and longer follow-up before they can be recommended.

Chemotherapy
A patient who presents with resectable bulky disease will rarely be cured with a single treatment modality. Consideration should be given to neoadjuvant chemotherapy if ILNs are >4 cm or are fixed to surrounding tissues. One of the most commonly utilized neoadjuvant systemic chemotherapy regimens is a combination of bleomycin, methotrexate, and cisplatin (BMP). Patients who may benefit from surgical consolidation would be those who had stable, partial, or complete response following systemic chemotherapy, and thus increasing their potential for disease-free survival. Recently, Pagliaro et al. performed a phase II clinical trial in 30 patients, with stage N2 or N3 (stage III or stage IV) penile cancer without distant metastases, receiving neoadjuvant chemotherapy with paclitaxel, ifosfamide, and cisplatin. In their series, 50% of patients were noted to have a clinically meaningful response and 22 (73.3%) subsequently underwent surgery. There was an improved time to progression and overall survival associated with chemotherapy responsiveness \((P < .001\) and \(P = .001\), respectively), absence of bilateral residual tumor \((P = .002\) and \(P = .017\), respectively), and absence of extranodal extension \((P = .001\) and \(P = .004\), respectively) or skin involvement \((P = .009\) and \(P = .012\), respectively).

Non-Palpable Nodes
Most low-risk patients and intermediate-risk patients without lymphovascular invasion are followed with a surveillance protocol, as the probability of occult micrometastases in ILNs is less than 17%. For patients in the high-risk group (T2 or G3) and intermediate-risk patients with lymphovascular invasion, a modified or radical inguinal lymphadenectomy is strongly recommended as occult metastatic disease ranges between 68% and 73%. If positive nodes are present on the frozen section, then a superficial and deep inguinal lymphadenectomy should be performed (with consideration of a PLND). As DSNB is currently not widely practiced in the United States, it is a category 2B option for examining non-palpable nodes to determine the need for a modified lymphadenectomy in place of predictive factors. This technique should be performed in tertiary care referral centers with substantial experience.

Unilateral Palpable Nodes < 4 cm
Fine needle aspiration of the lymph nodes is considered standard for these patients. However, the NCCN panel recommends omitting the procedure for patients with high-risk primary lesions to avoid delay of lymphadenectomy. A negative fine needle aspiration biopsy should be confirmed with an excisional biopsy. Positive findings from either procedure warrant an immediate ILND.

Palpable Nodes ≥ 4 cm (fixed or mobile)
Large, unilateral, mobile nodes are amenable to standard or modified ILND. No further treatment is necessary when only a single node or none is confirmed. Management is controversial otherwise. Category 2B is assigned to adjuvant chemotherapy when extranodal extension is found. PLND with or without postoperative radiation is also a category
2B recommendation where there are two or more positive inguinal nodes on the ipsilateral ILND site or extranodal involvement.

Patients with abnormal PLNs on imaging (CT or MRI) should receive neoadjuvant chemotherapy with consideration of a confirmatory percutaneous biopsy or PET/CT. Those who respond to therapy or become stable should undergo bilateral superficial and deep ILND and bilateral PLND if possible. For unresectable cases or on disease progression, patients may consider these options: additional systemic chemotherapy, local-field radiation, or participation in a clinical trial.

In the case of multiple or bilateral ILNs, patients should undergo a fine needle aspiration of the lymph nodes regardless of whether these are mobile or fixed. A negative result should be confirmed with excisional biopsy. If results are again negative, the patient should be closely followed. Patients with a positive aspiration or biopsy should be managed as those with enlarged PLNs.

**Surveillance**

Initial treatment of the primary tumor and lymph nodes dictates the follow-up schedule (see algorithm). A large retrospective review of 700 patients found that penile-sparing therapies carry a significantly higher risk of local recurrence (28%) than partial or total penectomy (5%) and thus require closer surveillance. Patients without nodal involvement had a regional recurrence rate of 2% compared to 19% for patients with N+ disease. Of all recurrences, 92% were detected within 5 years of primary treatment.

Follow-up for all patients includes a clinical exam of the penis and inguinal region. Imaging is not routinely indicated for early disease (except for obese patients or patients who have undergone inguinal surgery since physical exam may be challenging), but may be used upon abnormal findings. For patients with N2 or N3 disease, imaging of the chest, abdomen, and pelvic area is recommended.

**Recurrence**

Invasion of the corpora cavernosa is an adverse finding after initial organ-sparing treatment that warrants partial or total penectomy. For primary tumor recurrences without corpora cavernosa infiltration, salvage penile-sparing options can be considered (category 2B).

A recurrence in the inguinal region carries a poor prognosis (median survival < 6 months) and optimal management remains elusive. Possible salvage options include systemic chemotherapy, EBRT, surgery, or a combination thereof.

**Metastatic Disease**

Imaging of the abdomen and pelvis should be obtained when metastasis is suspected to evaluate for pelvic and/or retroperitoneal lymph nodes. PLN metastases is an ominous finding, with a 5-year survival rate of 0% - 66% for all cases and 17% - 54% for microscopic invasion only, with the mean 5-year survival being approximately 10%. In patients with ILN metastases, 20% to 30% will have PLN metastases. This can be further characterized such that if 2 to 3 ILNs are involved, there is a 23% probability of PLN involvement. With 3 or more ILNs this probability increases to 56%.

Pettaway et al. evaluated the treatment options for stage IV penile cancer - clinical stage N3 (deep inguinal nodes or pelvic nodes) or M1 disease (distant metastases) - including chemotherapy, radiotherapy, and inguinal lymphadenectomy. Cisplatin-based regimens are the most active first-line systemic chemotherapy regimens. Those patients with a proven objective response to systemic chemotherapy are amenable to consolidative ILND with curative potential or palliation. However,
surgical consolidation should not be performed on patients who progress during systemic chemotherapy except for local symptomatic control. Preoperative radiotherapy may also be given to patients who have lymph nodes ≥ 4 cm without skin fixation to improve surgical resectability and decrease local recurrence. For patients with unresectable inguinal or bone metastases, radiotherapy may provide a palliative benefit after chemotherapy. Salvage systemic chemotherapy may also be considered upon disease progression. Best supportive care remains an option for such advanced cases.

Summary
SCC of the penis is a disease that mandates prompt medical/surgical intervention and patient compliance to obtain the most favorable outcomes. A thorough history and physical is the initial step in this process, followed by a biopsy of the primary lesion to establish a pathologic diagnosis. Accurate clinical staging allows for a comprehensive treatment approach to be devised, thus optimizing therapeutic efficacy and minimizing treatment-related morbidity. Prognostic factors help predict if lymph node metastases are suspect in the absence of any palpable inguinal lymphadenopathy. When clinically indicated, an ILND has curative potential, particularly when performed early, with contemporary surgical series demonstrating its reduced morbidity.
References


