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Penile Cancer

Clinical Practice Guidelines in Oncology

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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.[1] In 2012, the estimated number of new penile cancer cases in the United States was 1570, with 310 cancer-specific deaths predicted.[2] The 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 50 and 70 years.[3] Early diagnosis is of utmost importance, because this disease can result in devastating disfigurement and has a 5-year survival rate of approximately 50% (>85% for patients with negative lymph nodes and 29%–40% for patients with positive nodes, with the lowest survival rates

Abstract

Squamous cell carcinoma of the penis represents approximately 0.5% of all cancers among men in the United States and other developed countries. Although rare, it is associated with significant disfigurement, and only half of the patients survive beyond 5 years. Proper evaluation of both the primary lesion and lymph nodes is critical, because nodal involvement is the most important factor of survival. The NCCN Clinical Practice Guidelines in Oncology for Penile Cancer provide recommendations on the diagnosis and management of this devastating disease based on evidence and expert consensus. (*JNCCN* 2013;11:594–615)

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.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Penile Cancer Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Penile Cancer Panel members can be found on page 615. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

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at 0% for patients with pelvic lymph node (PLN) involvement).[4] As the rarity of this disease makes it difficult to perform prospective, randomized trials, the NCCN Penile Cancer Panel relied on the experience of penile cancer experts to minimize the controversies associated with treating penile SCC and collectively lay a foundation to help standardize the management of the malignancy.

Risk Factors

In the United States, the median age of penile cancer diagnosis is 68 years, with an increased risk in men older than 50 years.[5] Early detection is assisted by the ability to perform a good physical examination. Phimosis may hinder the ability to properly in-
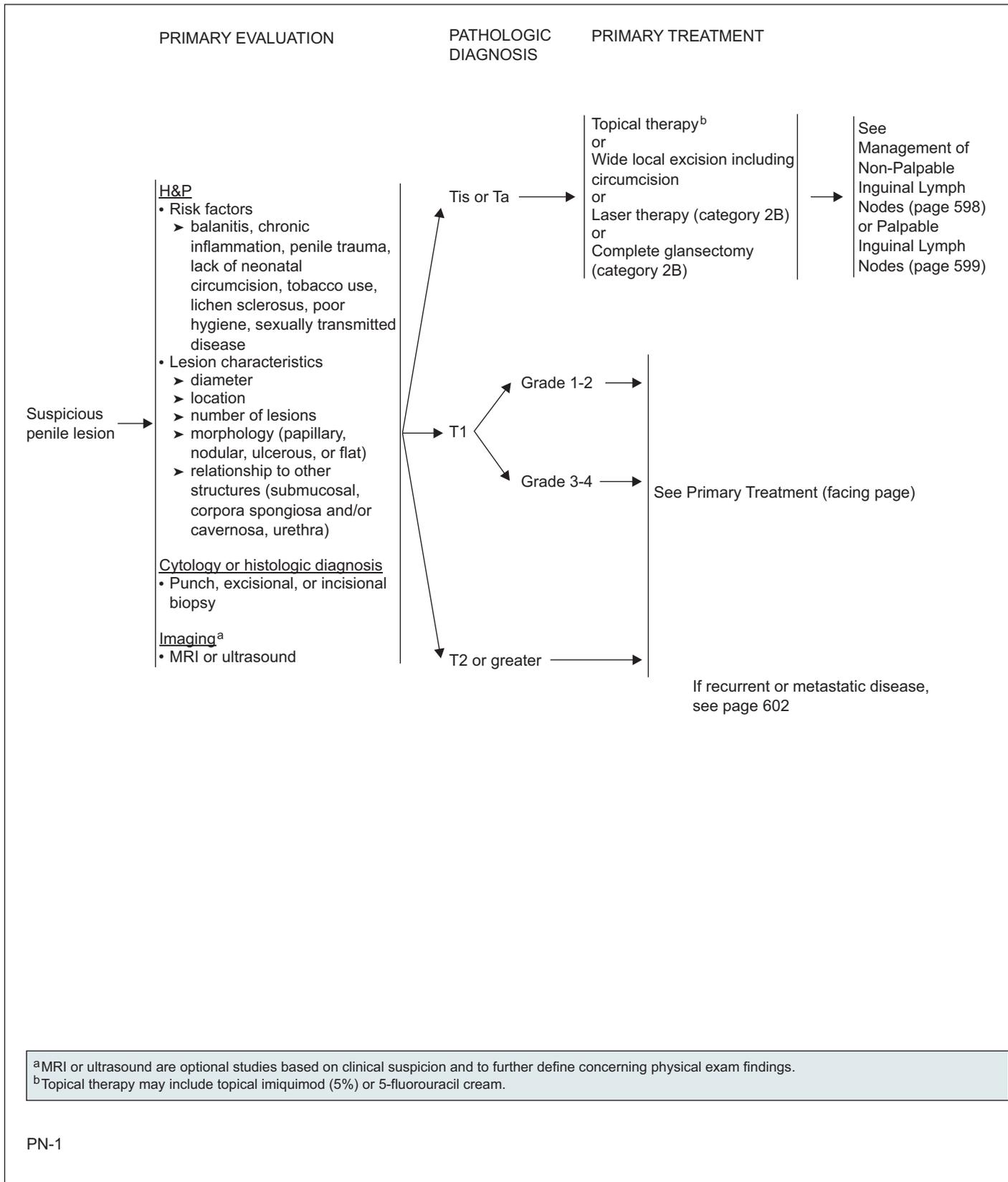
spect the areas of highest incidence: the glans, inner preputial layer, coronal sulcus, and shaft. Men with phimosis carry an increased risk of 25% to 60%.[3,6,7] A more recent review of penile SCC in the United States showed that 34.5% of patients had the primary lesion on the glans, 13.2% on the prepuce, and 5.3% in the shaft, with 4.5% overlapping and 42.5% unspecified.[5] Other risk factors include balanitis, chronic inflammation, penile trauma, tobacco use, lichen sclerosus, poor hygiene, and a history of sexually transmitted diseases, especially HIV and human papillomavirus (HPV).[3] Overall, 45% to 80% of penile cancers are related to HPV, with a strong correlation with types 16 and 18.[3,6,8,9] Patients with HIV have an 8-fold increased risk, which may correspond to a higher incidence of HPV among men
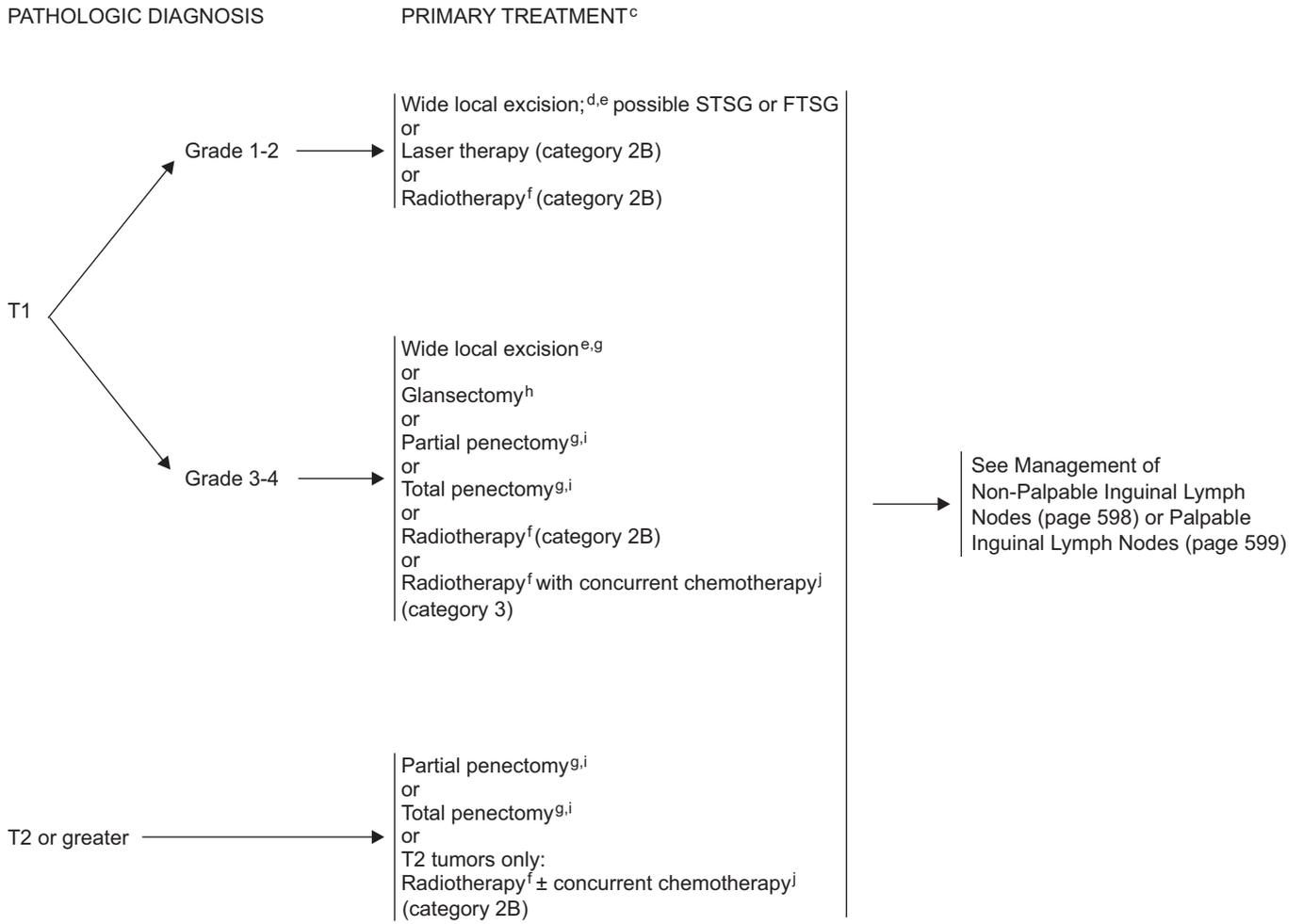
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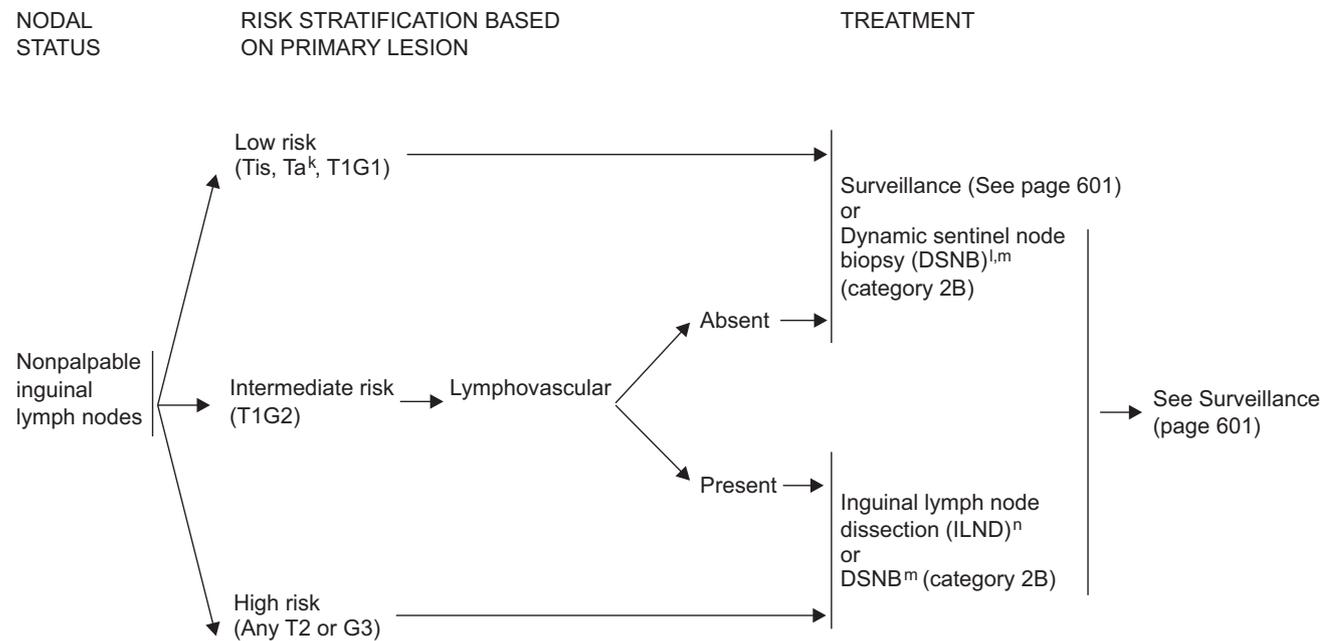National
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PRIMARY EVALUATION

PATHOLOGIC
DIAGNOSIS

PRIMARY TREATMENT

Suspicious penile lesion

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 histologic diagnosis
• Punch, excisional, or incisional biopsy

Imaging[a]
• MRI or ultrasound

Tis or Ta →

Topical therapy[b]
or
Wide local excision including circumcision
or
Laser therapy (category 2B)
or
Complete glansectomy (category 2B)

→ See Management of Non-Palpable Inguinal Lymph Nodes (page 598) or Palpable Inguinal Lymph Nodes (page 599)

T1
- Grade 1-2 →
- Grade 3-4 →

T2 or greater →

See Primary Treatment (facing page)

If recurrent or metastatic disease, see page 602

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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 cream.

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PATHOLOGIC DIAGNOSIS

PRIMARY TREATMENT[c]

T1

Grade 1-2 →

Wide local excision;[d,e] possible STSG or FTSG
or
Laser therapy (category 2B)
or
Radiotherapy[f] (category 2B)

Grade 3-4 →

Wide local excision[e,g]
or
Glansectomy[h]
or
Partial penectomy[g,i]
or
Total penectomy[g,i]
or
Radiotherapy[f] (category 2B)
or
Radiotherapy[f] with concurrent chemotherapy[j]
(category 3)

→ See Management of Non-Palpable Inguinal Lymph Nodes (page 598) or Palpable Inguinal Lymph Nodes (page 599)

T2 or greater →

Partial penectomy[g,i]
or
Total penectomy[g,i]
or
T2 tumors only:
Radiotherapy[f] ± concurrent chemotherapy[j]
(category 2B)

[c]See Principles of Surgery (page 603).
[d]Moh's surgery is an option.
[e]Complete excision of the skin with a wide negative margin with skin grafting is needed. STSG, split-thickness skin graft; FTSG, full-thickness skin graft.
[f]See Principles of Radiotherapy (page 603).
[g]Recommend intraoperative frozen sections to achieve negative margins.
[h]Appropriate with proven negative margins for tumors involving the glans only.
[i]When it is necessary to dissect into the corpora cavernosum to achieve a negative margin, a partial or total penectomy is performed.
[j]See Principles of Chemotherapy (pages 604 and 605).

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MANAGEMENT OF NONPALPABLE INGUINAL LYMPH NODES

NODAL
STATUS

RISK STRATIFICATION BASED
ON PRIMARY LESION

TREATMENT

Nonpalpable
inguinal
lymph nodes

Low risk
(Tis, Ta[k], T1G1) ⟶ Surveillance (See page 601)
or
Dynamic sentinel node
biopsy (DSNB)[l,m]
(category 2B)

Intermediate risk
(T1G2) ⟶ Lymphovascular

Absent ⟶

Present ⟶ Inguinal lymph node
dissection (ILND)[n]
or
DSNB[m] (category 2B)

High risk
(Any T2 or G3) ⟶

⟶ See Surveillance
(page 601)

[k] Ta verrucous carcinoma is by definition a well-differentiated tumor and would require surveillance alone of inguinal lymph nodes.
[l] DSNB is recommended provided the treating physician has experience with this modality.
[m] If positive lymph nodes are found on DSNB, ILND is recommended.
[n] A modified/superficial inguinal dissection with intraoperative frozen section is an acceptable alternative to stage the inguinal lymph nodes.
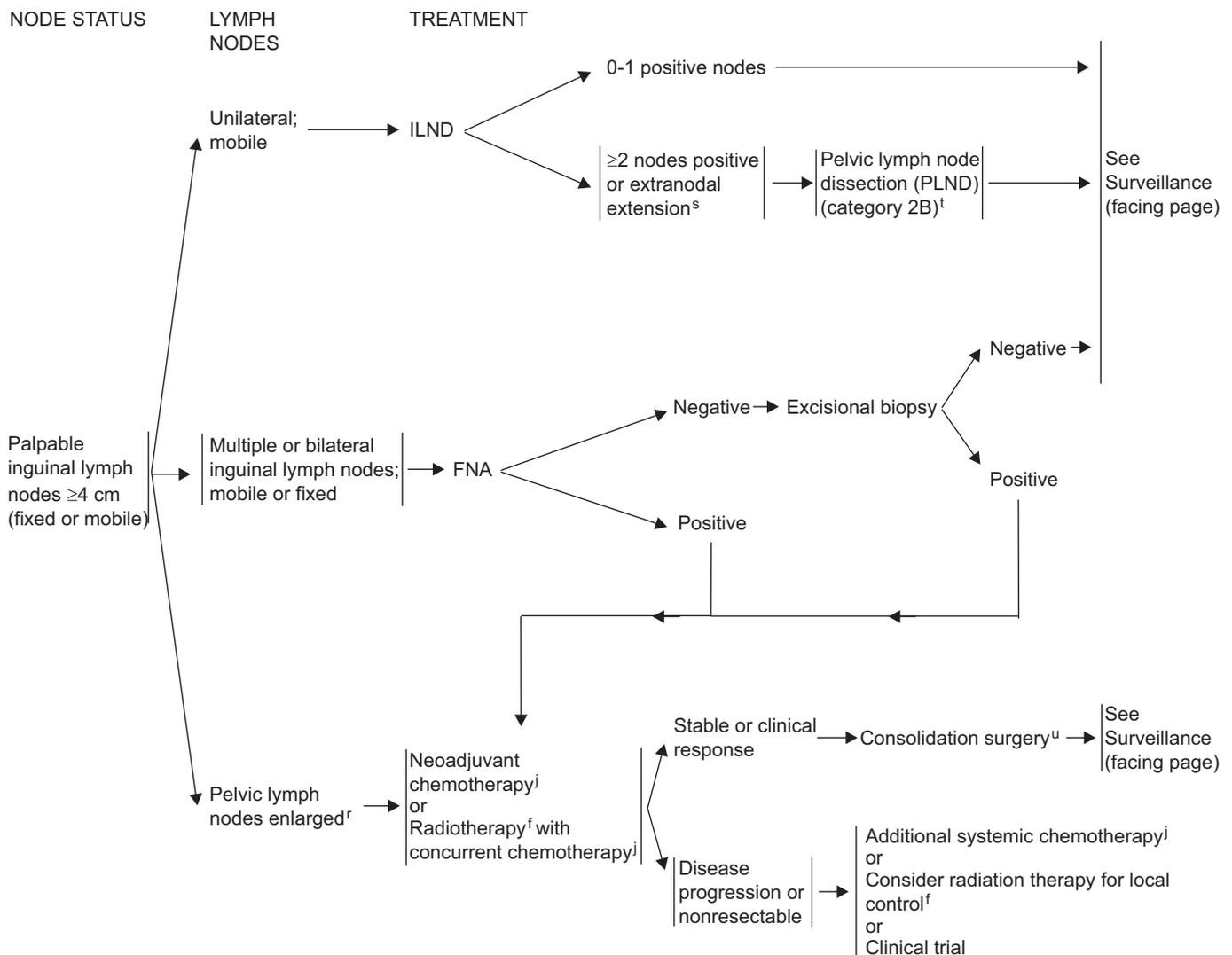
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Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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MANAGEMENT OF PALPABLE INGUINAL LYMPH NODES

NODAL STATUS	RISK STRATIFICATION BASED ON PHYSICAL EXAMINATION FINDINGS		TREATMENT

Palpable inguinal lymph nodes

→ Unilateral lymph node <4 cm → Fine-needle aspiration (FNA)[p]

- Negative → Excisional biopsy[q]
  - Negative → See Surveillance (page 601)
  - Positive → ILND → See Surveillance (page 601)
- Positive → ILND → See Surveillance (page 601)

→ ≥4 cm lymph node (fixed or mobile)[o] → Management of Bulky/Unresectable Inguinal Lymph Nodes (page 600)

[o] Imaging to assess regional nodes and distant metastases.
[p] For a high-risk primary lesion, it is recommended to proceed directly to ILND and not FNA.
[q] Surveillance can be considered in patients with a negative FNA provided they are carefully surveyed. See Surveillance (page 601).

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MANAGEMENT OF BULKY/UNRESECTABLE INGUINAL LYMPH NODES

NODE STATUS   LYMPH NODES   TREATMENT

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

Unilateral; mobile → ILND
- 0-1 positive nodes → See Surveillance (facing page)
- ≥2 nodes positive or extranodal extension[s] → Pelvic lymph node dissection (PLND) (category 2B)[t] → See Surveillance (facing page)

Multiple or bilateral inguinal lymph nodes; mobile or fixed → FNA
- Negative → Excisional biopsy → Negative → See Surveillance (facing page) / Positive
- Positive

Pelvic lymph nodes enlarged[r] → Neoadjuvant chemotherapy[j] or Radiotherapy[f] with concurrent chemotherapy[j]
- Stable or clinical response → Consolidation surgery[u] → See Surveillance (facing page)
- Disease progression or nonresectable → Additional systemic chemotherapy[j] or Consider radiation therapy for local control[f] or Clinical trial

[f] See Principles of Radiotherapy (page 603).
[j] See Principles of Chemotherapy (pages 604 and 605).
[r] On CT or MRI, not pathologic stage.
[s] Consider adjuvant chemotherapy (category 2B).
[t] Consider postoperative radiotherapy (category 2B).
[u] Consolidation surgery consists of bilateral superficial and deep ILND and possible bilateral PLND.

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

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ANATOMIC SITE	INITIAL TREATMENT	SURVEILLANCE

Primary lesion

- Topical therapy
- Laser therapy
- Radiation therapy
- Wide local excision including circumcision

Clinical exam:[w,x]
year 1-2, every 3 mo then
year 3-5, every 6 mo then
year 5-10, every 12 mo

- Partial penectomy
- Total penectomy

Clinical exam:[w,x]
year 1-2, every 6 mo then
year 3-5, every 12 mo

Lymph nodes

Nx[v]

Clinical exam:[w,x]
year 1-2, every 3 mo then
year 3-5, every 6 mo

N0, N1

Clinical exam:[w,x]
year 1-2, every 6 mo then
year 3-5, every 12 mo

N2, N3

Clinical exam:[w]
year 1-2, every 3-6 mo then
year 3-5, every 6-12 mo

Imaging:
- Chest (CT or x-ray)
  ➤ year 1-2, every 6 mo
- Abdominopelvic (CT or MRI)
  ➤ year 1, every 3 mo then
  ➤ year 2, every 6 mo

For patients with recurrence at either local or distant sites, see Management of Recurrent Disease (page 602).

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[v] Patients on active surveillance of clinically negative nodes and at low risk for inguinal metastases.
[w] Clinical exam includes examination of the penis and inguinal region.
[x] If an abnormal clinical exam, obese patient, or prior inguinal surgery, then 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

MANAGEMENT OF METASTATIC DISEASE

Metastatic penile cancer →
Systemic chemotherapy[j]
or
Radiotherapy[f]
or
Radiotherapy[f] with concurrent chemotherapy[j]

Complete/ partial response or stable → Consolidative surgery[u] → See Surveillance (page 601)

No response/ Disease progression →
Consider salvage systemic chemotherapy[j]
or
Consider radiotherapy for local control[f]
and/or
Best supportive care/clinical trial
(See NCCN Clinical Practice Guidelines in Oncology for Palliative Care; to view the most recent version of these guidelines, visit NCCN.org)

[f]See Principles of Radiotherapy (page 603).
[j]See Principles of Chemotherapy (pages 604 and 605).
[u]Consolidation surgery consists of bilateral superficial and deep ILND and possible bilateral PLND.

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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 or DSNB (category 2B) 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 penile tumor:
  - Lymphovascular invasion
  - pT1G3 or ≥T2, any grade
  - >50% poorly differentiated

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

PRINCIPLES OF RADIOTHERAPY

<u>Primary Radiation Therapy</u> (category 2B) (Penile Preservation)
<u>T1-2, N0</u>
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 posttreatment surveillance)

<u>T3-4 or N+</u>
- 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).

<u>Postoperative Adjuvant Radiotherapy</u>
- Inguinal Lymph Node Positive (category 2B)
  - 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.

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

PN-A
PN-B

PRINCIPLES OF CHEMOTHERAPY

Neoadjuvant
- Neoadjuvant, cisplatin-based chemotherapy should be considered the standard (prior to ILND) in patients with ≥4 cm inguinal lymph nodes (fixed or mobile), if FNA is positive for metastatic penile cancer.[1]
  ➤ Patients with initially unresectable (T4) primary tumors may be downstaged by response to chemotherapy.

- A Tx, N2-3, M0 penile cancer can receive 4 courses of neoadjuvant paclitaxel, ifosfamide, and cisplatin (TIP).[2] Stable or responding patients should then undergo consolidative surgery 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.

Adjuvant
- 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 TIP 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, page 600) 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

Metastatic
- TIP is a reasonable first-line treatment for patients with metastatic penile cancer, including palliative treatment of patients with distant metastases.[2]
- 5-fluorouracil + cisplatin has been used historically for metastatic penile cancer and can be considered as an alternative to TIP.[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.
- There are no randomized clinical trials because of the rarity of penile cancer in industrialized countries.

Second-line
- No standard second-line systemic therapy exists.
- Depending on first-line therapies, palliative options include single-agent therapy, such as capecitabine, carboplatin, docetaxel, 5-fluorouracil, irinotecan, methotrexate, paclitaxel, and panitumumab.[4,6-10]

Preferred combination chemotherapy regimens
TIP[2]
   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-Fluorouracil + cisplatin[4] (category 2B)
   Continuous-infusion 5-fluorouracil, 1000 mg/m^2/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[11] (for radiotherapy with concurrent chemotherapy)
- Cisplatin alone or in combination with 5-fluorouracil
- Mitomycin C in combination with 5-fluorouracil
- Capecitabine

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PRINCIPLES OF CHEMOTHERAPY

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Penile Cancer

with HIV.[10] Cigarette smokers are noted to be 3.0 to 4.5 times more likely to develop penile cancer.[8,11] Patients with lichen sclerosus are noted to have a 2% to 9% risk of developing penile carcinoma.[12–14] The incidence among patients with psoriasis undergoing psoralen plus ultraviolet A is 286 times that of the general population. Therefore, these patients should be shielded during treatment, and any penile lesion should be closely monitored.[15]

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 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 is a premalignant condition at high risk of developing into penile SCC.[16] The AJCC recognizes 4 subtypes of SCC: verrucous, papillary squamous, warty, and basaloid.[17] The verrucous subtype is believed to be of low malignant potential, whereas other variants reported, such as adenosquamous and sarcomatoid, have a worse prognosis.[18,19] The primary lesion is further characterized by its growth pattern with superficial spread, nodular or vertical-phase growth, and a verrucous pattern. In addition to the penile lesion, evaluation of lymph nodes is also critical, because 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.[4,20]

The AJCC 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.[17,21–24] 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.[17] 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,N0,M0 and T2–3,N0,M0 (see Staging Table in these guidelines, available online, at NCCN.org [ST-1]). 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).[25] According to the AJCC, if no grading system is specified, a general system should be followed: GX, grade cannot be assessed; G1–3 as mentioned previously; and G4, undifferentiated.[17] The overall degree of cellular differentiation with high-risk, poorly differentiated tumors is an important predictor factor for metastatic nodal involvement.[26] 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.[17]

Management of Primary Lesions

Diagnosis

Evaluation of the primary lesion, regional lymph nodes, and distant metastasis will dictate the appropriate and adequate management of penile SCC, beginning with the first evaluation at presentation and then throughout follow-up. Vital to the initial management is a good physical examination of the penile lesions that remarks on the diameter of the lesions or suspicious areas; locations on the penis; number of lesions; morphology of the lesions; whether the lesions are papillary, nodular, ulcerous or flat; and relationship with other structures, including submucosal, urethra, corpora spongiosa, and/or corpora cavernosa. To 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.[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.[27] MRI or ul-

trasound can be used to evaluate the depth of tumor invasion.[28] For the evaluation of lymph nodes, see "Management of Regional Lymph Nodes," this page.

NCCN Recommendations

Tis or Ta: For patients with penile carcinoma in situ or noninvasive verrucous carcinoma, penile-preserving techniques may be used, including topical imiquimod (5%) or 5-FU cream; circumcision and wide local excision such as Mohs surgery; laser therapy (category 2B) using carbon dioxide or neodynium:yttrium-aluminum-garnet; and complete glansectomy (category 2B). Among these, topical therapy[29–31] and excisional organ-sparing surgery[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.[33,34] Glansectomy, removal of the glans penis, has also been studied, with no recurrence observed in some cases.[35–38]

T1,G1–2: Careful consideration should be given to penile-preserving techniques if the patient is reliable regarding compliance with close follow-up. These techniques include wide local excision and Mohs surgery as an option plus reconstructive surgery[39]; laser therapy (category 2B)[40]; or radiotherapy (RT) delivered as external-beam RT (EBRT) or brachytherapy with interstitial implant (category 2B).[41–45] Emphasis is placed again on patient selection and close follow-up, because the 2-year recurrence rate may reach up to 50%.[46] Recent studies have shown that surgical margins of 5 to 10 mm are as safe as 2-cm surgical margins, and 10- to 20-mm margins provide adequate tumor control.[47] Circumcision should always precede RT to prevent radiation-related complications.

T1,G3–4, 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.[27] Intraoperative frozen sectioning is recommended to achieve negative surgical margins. 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 they have an increased risk for recurrence and that the potential exists that a repeat wide local excision may be needed should a local recurrence be noted, provided there is no invasion of the corpora cavernosa.[34,38] A

clear and frank discussion should be conducted with the patient regarding the likelihood that a partial or total penectomy will be required should a larger or more invasive lesion be present.

Tumor size is an important factor when choosing RT as treatment. Because the average length of the glans is approximately 4 cm, this serves as a cutpoint to reduce the risk of undertreating cavernosal lesions. In a study of 144 patients with penile cancer restricted to the glans treated with brachytherapy, larger tumors, especially those greater than 4 cm, are associated with higher risk of recurrence.[48] A high 10-year cancer-specific survival rate of 92% was achieved in this series.

The NCCN panel reached nonuniform consensus on the use of RT as primary therapy. For T1,G3–4 tumors, RT is a category 2B recommendation, whereas RT with concurrent chemotherapy is a category 3 recommendation. For T2 tumors, RT with or without chemotherapy is a category 2B option. RT should be given after circumcision has been performed.

For tumors smaller than 4 cm, brachytherapy with interstitial implant or EBRT with or without chemotherapy are viable options. Prophylactic ILN irradiation should be considered 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.[49] Crook et al[45] reported a 10-year cause-specific survival of 84% in 67 patients with T1–2 (select cases of T3) penile lesions treated with primary brachytherapy.

Postsurgical RT to the primary tumor site may be considered for positive margins.

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.[20] Evaluation of the groin and pelvis is an essential component of the metastatic workup of a patient. The involvement of the ILN can be clinically evident (ie, palpable vs nonpalpable), adding to the difficulty in management. Clinical examination for ILN in-

volvement 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 ligaments), and edema of the penis, scrotum, and/or legs.[50,51] Crossover drainage from left to right and vice versa does occur and is reproducible with lymphoscintigraphy.[4,52] The physical examination should describe the diameter of nodes or masses, unilateral or bilateral localization, number of nodes identified in each inguinal, and the relationship to other structures (eg, skin, Cooper ligament), with respect to infiltration and perforation. CT or MRI for palpable disease may be used to assess the size, extent, location, and structures that are in proximity to the ILN, and the presence of pelvic and retroperitoneal lymph nodes and distant metastasis. CT and MRI are limited in patients with nonpalpable disease.[50,53] Although studies have examined the use of nanoparticle-enhanced MRI, PET/CT, and 18F-fluorodeoxyglucose (FDG) PET/CT, their small sample size requires validation in larger prospective studies.[54–57] When considering one imaging modality to evaluate the stage of the primary lesion and lymph node status, MRI seems to be the best choice to not only enhance but also potentially replace the physical examination in patients in whom the inguinal region is difficult to assess (eg, morbidity, previous chemo/RT).[54,58]

Consideration must be given to whether the primary lesion showed any adverse prognostic factors. If one or more of these high-risk features is present, then pathologic ILN staging must be performed. Up to 25% of patients with nonpalpable lymph nodes harbor micrometastases.[25] Therefore, several predictive factors have been evaluated to help predict the presence of occult lymph node metastasis.[46,59] Slaton et al[25] 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 an inguinal lymph node dissection (ILND) should be recommended.[4,25] These factors can then further define patients into low-, intermediate-, and high-risk groups for lymph node metastasis.[18,60,61] The European Association of Urology determined risk stratification groups for patients with nonpalpable ILNs, and validated this in both univariate and multivariate analyses of prognostic

factors. Patients can be stratified according to stage and/or grade into risk groups based on the likelihood of harboring occult node-positive disease, with the low-risk group defined as patients with Tis, Ta,G1–2 or T1,G1; the intermediate-risk group as those with T1,G2; and the high-risk group as those with T2 or G3.[51,60]

Dynamic Sentinel Node Biopsy: The work by Cabanas[62] used lymphangiograms and anatomic dissections to evaluate the sentinel lymph node drainage for penile cancer with nonpalpable ILNs. This technique has been shown to have false-negative rates as high as 25%; therefore, it is no longer recommended.[51,63] 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.[64,65] Initially, this technique was associated with a low sensitivity and high false-negative rate (16%–43%).[66–69] Refinement of the technique to improve the false-negative rate includes serial sectioning and immunohistochemical staining of pathologic 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%.[64,70] Using fine-needle aspiration with ultrasound can increase the diagnostic yield in metastasis greater than 2 mm in diameter.[53,71] Crawshaw et al[72] used ultrasound with DSNB and noted improved accuracy in identifying patients with occult lymph node metastases. With modification of the NCI protocol, Hadway et al[73] were able to achieve a similar false-negative rate (5%) with an 11-month follow-up. Secondary to the technical challenges associated with DSNB, to be accurately and reliably performed, it is recommended that DSNB be performed at tertiary care referral centers where at least 20 procedures are performed per year.[64,74] It should be noted that DSNB is not recommended in patients with palpable ILNs.[50]

Inguinal Lymph Node Dissection

The most frequent site of metastasis is the ILN, typically presenting as palpable inguinal lymphadenopathy. Management of the ILN with ILND has been fraught with great fears of surgical morbidity.[51,75] 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.[76,77] Palpable lymphadenopathy at diagnosis does not warrant an immediate ILND. Of the patients with palpable disease, 30% to 50% of these cases will be secondary to inflammatory lymph node swelling instead of metastatic disease.[59] Although the distinction between reactive lymph nodes and metastatic disease may be made after a 6-week course of antibiotics, fine-needle aspiration is becoming the most favored approach among many penile cancer experts.[4,50] 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.[4,50,78]

In attempts to decrease the morbidity associated with standard ILND, Catalona[79] pioneered a modified lymphadenectomy surgical approach in 1988. This technique uses a shorter skin incision, limiting the field of inguinal dissection through 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.[78] 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 because these sections were not included in the dissection, leading to a false-positive rate of 15%.[80,81] 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.[82,83] 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 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.[78] 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/d, usually 3 to 17 days postoperatively.[78,84] Consideration should be given to keeping the patient on a suppressive dose of an oral cephalosporin (or other gram-positive–covering broad-spectrum antibiotic) for several weeks postoperatively in an attempt to decrease the risk of wound-related issues and minimize the risk for overall complications.[78]

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 12–20 nodes). Crossover from one pelvic side to the other has not been observed, unlike crossover at the inguinal level.[4] The limits of the PLND include the iliac bifurcation for proximal, ilioinguinal nerve for lateral, and obturator nerve for medial boundary.[51,78] 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.[85]

Advances in Surgical Approach: Video/Endoscopy

Minimally invasive surgical techniques, including video endoscopic inguinal lymphadenectomy (VEIL) or robotic-assisted laparoscopy, offer the potential for fewer cutaneous complications while attempting to maintain comparable oncologic outcomes.[86–88] The endoscopic approach was initially described by Bishoff et al[89] in 2003, with a subcutaneous modified inguinal lymphadenectomy in 2 cadaveric models. The patient selection for VEIL includes those who warrant an open procedure, such as those 1) with palpable lymphadenopathy and 2) with nonpalpable nodes and a T2 or greater primary tumor in the presence of high-grade features and/or vascular invasion. The lymph node template is as described by Catalona[79] 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[86] modified

the technique from Bishoff's series and selected patients with nonpalpable ILNs for their first successful report. In another series,[87] they reported that they obtained good results with VEIL, 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. The patients reported increased pain with the open procedure compared with 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, these investigators[88] 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. Sotelo et al[90] also used the endoscopic approach in 8 patients (14 lymphadenectomies) and noted no perioperative or wound-related complications, with 3 groins (23%) developing a lymphocele. Minimally invasive techniques show promise, with reduced complication rates while preserving the principles of oncologic surgery. Nevertheless, the open surgical approach currently 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 greater. One of the most commonly used neoadjuvant systemic chemotherapy regimens is a combination of bleomycin, methotrexate, and cisplatin (BMP).[91] Patients who may benefit from surgical consolidation would be those who had a stable, partial, or complete response after systemic chemotherapy, thus increasing their potential for disease-free survival.[82,83] Recently, Pagliaro et al[92] performed a phase II clinical trial in 30 patients with stage N2 or N3 (stage III or 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. An improved time to progression and overall survival were associated with chemotherapy responsive-

ness ($P<.001$ 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).

NCCN Recommendations

Nonpalpable Nodes: Most low-risk patients and intermediate-risk patients without lymphovascular invasion are followed with a surveillance protocol, because the probability of occult micrometastases in ILNs is less than 17%.[60,93] 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, because occult metastatic disease ranges between 68% and 73%.[46,60,93] If positive nodes are present on the frozen section, then a superficial and deep inguinal lymphadenectomy should be performed (with consideration of a PLND).

Because DSNB is currently not widely practiced in the United States, it is a category 2B option for examining nonpalpable nodes to determine the need for a modified lymphadenectomy in place of predictive factors.[94,95] This technique should be performed in tertiary care referral centers with substantial experience. DSNB is not recommended for Ta tumors, because observation alone of the inguinal lymph nodes is sufficient for these well-differentiated lesions in the absence of palpable adenopathy.

Unilateral Palpable Nodes <4 cm: Fine-needle aspiration of the lymph nodes is considered standard for these patients. However, the 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. Alternatively, careful surveillance may be considered following a negative fine-needle aspiration. 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 in the presence of 2 or more positive inguinal nodes on the ipsilateral ILND site or extranodal involvement.

Patients with abnormal PLNs on imaging (CT or MRI) should receive either systemic chemotherapy or concurrent chemoradiation with consideration of a confirmatory percutaneous biopsy or PET/CT. Those whose disease responds to therapy or who become stable should undergo bilateral superficial and deep ILND and bilateral PLND if possible. For unresectable cases or on disease progression, patients may consider the following 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 the same as those with enlarged PLNs.

Surveillance

Initial treatment of the primary tumor and lymph nodes dictates the follow-up schedule (see algorithm, pages 596–605). 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.[96] Patients without nodal involvement had a regional recurrence rate of 2% compared with 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 examination of the penis and inguinal region. Imaging is not routinely indicated for early disease (except for patients who are obese or who have undergone inguinal surgery, because physical examination may be challenging), but may be used on 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.[97,98] 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.[50,99]

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% to 66% for all cases and 17% to 54% for microscopic invasion only, with the mean 5-year survival being approximately 10%.[4,100–104] In patients with ILN metastases, 20% to 30% will have PLN metastases.[4] 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%.[105]

Pettaway et al[106] 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, RT, and inguinal lymphadenectomy. Cisplatin-based regimens (paclitaxel, ifosfamide, and cisplatin or, alternatively, 5-FU plus cisplatin) are the most active first-line systemic chemotherapy regimens. The panel did not recommend regimens containing bleomycin because of high toxicity. 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 experience progression during systemic chemotherapy, except to provide local symptomatic control. Preoperative RT may also be given to patients who have lymph nodes 4 cm or greater without skin fixation to improve surgical resectability and decrease local recurrence. For patients with unresectable inguinal or bone metastases, RT may provide a palliative benefit after chemotherapy. Salvage systemic chemotherapy may also be considered on disease progression. Best supportive care remains an option for these advanced cases.

Summary

SCC of the penis is a disease that mandates prompt medical/surgical intervention and patient compli-

Penile Cancer

ance 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 whether 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 showing its reduced morbidity.

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Individual Disclosures for the NCCN Penile Cancer Panel					
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The NCCN guidelines staff have no conflicts to disclose.