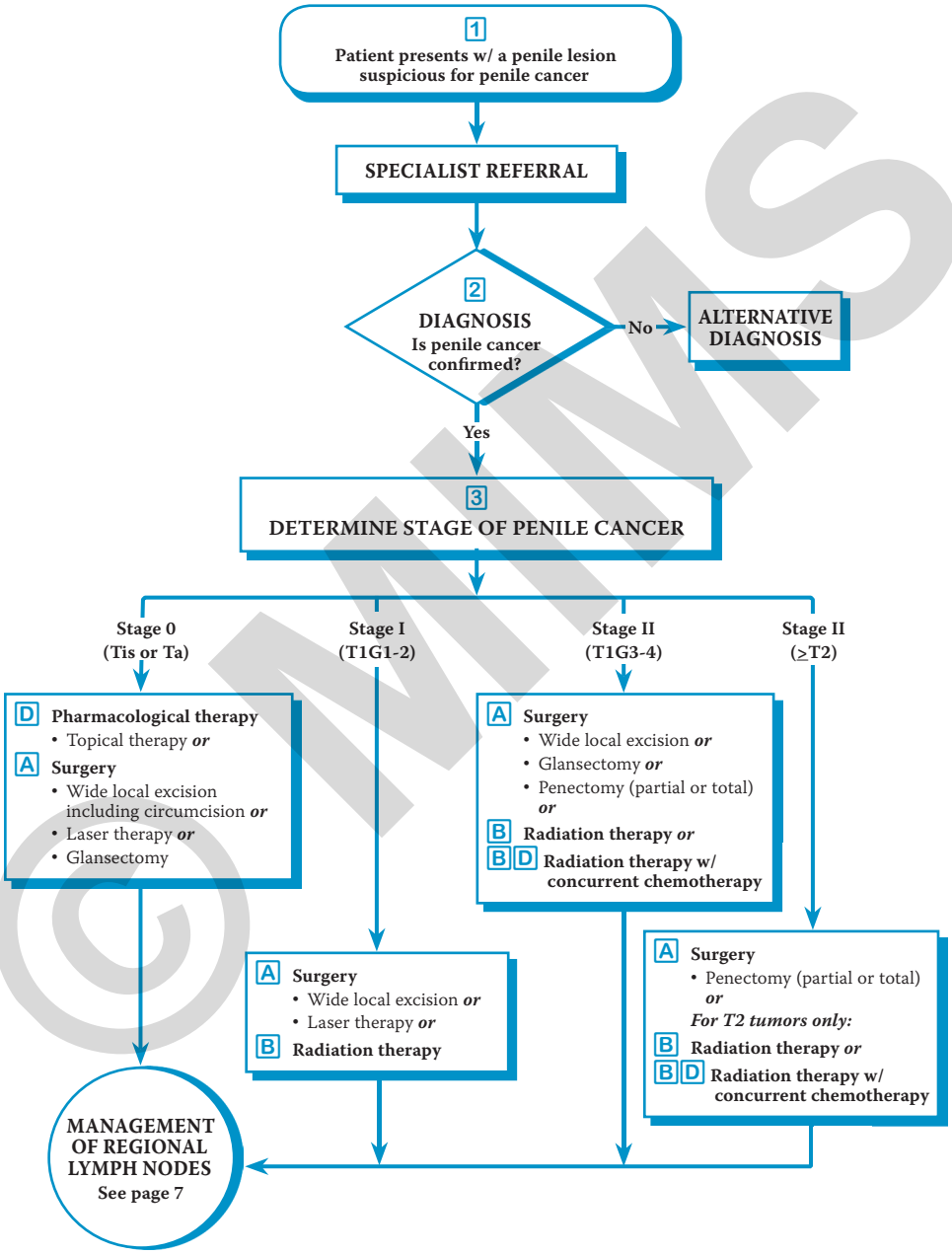
Penile Cancer (1 of 12)



1 PENILE CANCER

- Often presents as a palpable visible penile lesion w/ signs that may include pain, bleeding, discharge or a foul odor
  - The lesion may be fungating, nodular or ulcerative & may be concealed by phimosis
- An uncommon malignancy w/ a rate of <1 per 100,000 men in the United States & Europe but is more common in Asia, Africa & South America
  - Incidence varies according to ethnicity, geographical location & racial group
- Typically occurs in older men w/ rates steadily increasing w/ age, between 50 & 70 years, though it may occur in younger men
- >95% of penile cancer cases are of squamous cell origin & subtypes include verrucous carcinoma, warty carcinoma (verruciform), & basaloid carcinoma
  - Growth pattern may be through superficial spreading, nodular or vertical-phase, & verrucous
  - Warty carcinoma & basaloid carcinoma are less common but appear to be more associated w/ HPV, specifically HPV 16
  - High-risk squamous cell carcinoma variants w/ early metastases & high mortality rate include adenosquamous, basaloid, sarcomatoid, & poorly differentiated types
- Carcinoma in situ of the penis occurring on the glans is referred to as erythroplasia of Queyrat & that occurring on the penile shaft is Bowen's disease or Bowenoid papulosis
  - Erythroplasia of Queyrat has the highest potential of developing squamous cell carcinoma

Risk Factors:

- A correlation is suggested by some studies between human papillomavirus (HPV) infection & penile cancer
  - Types 16 & 18 are the most common HPV subtypes in penile cancer & cancer risk is increased w/ condyloma acuminata
  - Mediation by HPV increases the incidence of penile cancer in HIV-infected individuals
- Circumcision is associated w/ a lower risk of penile cancer & observational studies demonstrated that circumcised men have a lower prevalence of penile HPV
- Other risk factors for penile cancer include the following:
  - Poor personal hygiene
  - First intercourse at early age
  - Multiple sexual partners
  - Tobacco smoking
  - Psoralen & ultraviolet A (PUVA) photochemotherapy
  - Phimosis
  - Penile trauma or tear
  - Urethral stricture
  - Lichen sclerosus
  - Chronic inflammation, balanitis

2 DIAGNOSIS

Physical Examination (PE)

- Examine for physical signs of advanced disease (eg palpable nodes, hepatomegaly) aside from constitutional symptoms in the history (eg fatigue, weight loss, cachexia, confusion, pain)
- Description of the primary tumor of a suspected penile cancer must include the following:
  - Color, number, diameter, location, boundary, morphology (eg flat, nodular, papillary or ulcerous) of the lesion
  - Relationship of the lesion to other structures (eg corpus cavernosum, corpus spongiosum, submucosa, tunica albuginea, & urethra); PE can determine tumor infiltration into the corpora cavernosa
  - Penile length
- Assess extent of local invasion by palpating penis

2 DIAGNOSIS (CONT'D)

Physical Examination (PE) (Cont'd)

- As penile cancer primarily drains to the inguinal nodes, palpate both groins if the lymph nodes are palpable or not
  - If palpable, note the characteristics of the nodes: Diameter, unilateral or bilateral localization, number of nodes on each side, relationship to other structures, ie mobility or fixation to adjacent structures or involvement of overlying skin
  - Palpable lymph nodes are highly suspicious for metastases to lymph nodes while nonpalpable nodes have a 25% possibility of micrometastatic disease; thus, perform an invasive pathologic lymph node staging in high-risk patients w/ nonpalpable lymph nodes

Penile Biopsy

- A cytological &/or histological diagnosis should be made of the penile lesion via excisional, incisional or punch biopsy
  - A punch biopsy may be adequate for superficial lesions; however, an excisional biopsy is preferred because it can properly determine the depth of invasion & stage
- Result will show grade of the tumor, will aid in patient's risk stratification for involvement of regional lymph nodes, & will determine treatment approach based on a pathologic diagnosis

Imaging Studies

- Ultrasound can show infiltration of the corpora or enlargement of inguinal nodes
- MRI w/ intracavernosal injection of prostaglandin E1 can help detect invasion into the corpora cavernosa & assess if limited surgery is possible
- MRI & CT scan can detect inguinal & pelvic node enlargement
  - Above imaging studies are especially performed in patients w/ a large BMI or who have undergone a previous inguinal procedure due to the limitation of PE in these circumstances
- Routine diagnostic imaging for assessment of metastases should only be done w/bulky regional nodal metastases, ie CT of chest, abdomen & pelvis, as reliable detection of micrometastases cannot be performed w/ conventional CT or MRI scans
- For regional (inguinal & pelvic nodes) & more distant metastases, a PET/CT scan can be performed in patients w/ positive inguinal nodes
  - 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET/CT) scan can accurately detect pelvic lymph node metastases & more distant metastases in palpable inguinal node-positive penile cancer
- A bone or brain scan may be indicated in symptomatic patients for detection of distant metastases

Laboratory Tests

- A serum calcium should be included in the routine lab tests to check for tumor-induced hypercalcemia
- Penile cancer has no established tumor marker
  - Squamous cell carcinoma antigen is not a sensitive marker of tumor burden & is currently not useful in clinical practice

Alternative Diagnosis

- There are several differential diagnoses that need to be ruled out & these include infectious, inflammatory, premalignant & malignant etiologies:
  - Infectious: Genital herpes, primary syphilis
  - Inflammatory: Angiokeratomas, genital psoriasis, lichen planus
  - Premalignant: Condyloma acuminata, cutaneous horn, leukoplakia, lichen sclerosis or balanitis xerotica obliterans, pseudoepitheliomatous keratotic & micaceous balanitis (PKMB)
  - Malignant: Basal cell carcinoma, Kaposi sarcoma, malignant melanoma, urethral carcinoma, metastasis from another primary tumor site
- Refer patient for further investigation & appropriate treatment

3 STAGING OF PENILE CANCER

- The staging system together w/ tumor grade is the most simple & accurate way of predicting cancer-specific mortality for penile cancer after excision of primary tumor
  - Surgical staging of the groin (eg FNA, DSNB, or ILND) would depend on the features of the primary tumor & the presence or absence of palpable inguinal lymph nodes
- Risk factors for lymph node metastasis include anatomical site, growth pattern, invasion of perineural spaces, irregular front of invasion, lymphovascular invasion, pathological subtypes, positive margins of resection, size of the primary tumor, tumor depth or thickness (tumor grade), & urethral invasion
  - Strongest predictors of penile cancer metastasis & a poor prognosis are a high histological grade & perineural & lymphovascular invasion
- The most important prognostic factor for overall survival is the presence & extent of metastases to the inguinal nodes which include inguinal lymph node involvement, number & site of positive nodes, & involvement of extracapsular nodes
  - Patients w/ nonpalpable inguinal lymphadenopathy can be grouped prognostically based on the likelihood of having an occult node-positive disease w/ risk stratified based on primary tumor: Low risk (Tis, TaG1-2 or T1G1), intermediate risk (T1G2), & high risk (≥T2 or any G3 or G4)
  - Recent data suggest that high-risk HPV DNA expression in tumors is associated with a survival benefit as it does not appear to be related w/ lymph node metastasis

TNM Classification for Penile Cancer According to the American Joint Committee on Cancer (AJCC) (2010, 7th ed)

T	**Primary tumor**
TX	Primary tumor cannot be assessed
T0	Primary tumor not evident
Ta	Non-invasive verrucous carcinoma not associated w/ destructive invasion
Tis	Carcinoma in situ
T1a	Tumor invades subepithelial connective tissue without lymphovascular invasion & is well or moderately differentiated (T1G1-2)
T1b	Tumor invades subepithelial connective tissue w/ lymphovascular invasion or is poorly differentiated or undifferentiated (T1G3-4)
T2	Tumor invades corpus cavernosum or spongiosum
T3	Tumor invades urethra
T4	Tumor invades adjacent structures
	Regional lymph nodes
N	**Clinical**
NX	Regional lymph nodes cannot be assessed
N0	No palpable or visibly enlarged lymph node
N1	Inguinal lymph node is palpable, mobile, unilateral
N2	Inguinal lymph nodes are palpable, mobile, multiple, or bilateral
N3	Palpable fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral
pN	**Pathologic[1]**
pNX	Regional lymph nodes cannot be assessed
pN0	No metastasis to regional lymph node
pN1	Metastasis in a single inguinal node
pN2	Metastases in multiple or bilateral inguinal lymph nodes
pN3	Extranodal extension of lymph node metastasis or pelvic lymph node(s) unilateral or bilateral
M	**Distant metastasis**
M0	No distant metastasis
M1	Distant metastasis
G	**Histopathological grading**
GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3-4	Poorly differentiated/undifferentiated

[1]The pN categories are based upon biopsy or surgical excision

3 STAGING OF PENILE CANCER (CONT'D)

Anatomic Stage/Prognostic Group for Penile Cancer

Stage 0	Tis	N0	M0
	Ta	N0	M0
Stage I	T1a	N0	M0
Stage II	T1b	N0	M0
	T2	N0	M0
	T3	N0	M0
Stage III A	T1-3	N1	M0
Stage III B	T1-3	N2	M0
Stage IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

A SURGERY

- Goal is to remove penile cancer completely w/ negative surgical margins preserving as much of the penis as possible
  - Intra-operative frozen sections may confirm negativity of surgical margins

Penile-preserving Techniques

- For tumors which are superficial or confined to the glans, a penile-preserving procedure is recommended, though recurrence rates are higher than radical surgical procedures
  - Local recurrence depends on tumor grade & presence of lymphovascular invasion
- As primary treatment approach for localized lesions, penile-preserving techniques appear to have superior cosmetic & functional results
  - Whenever possible, treatment for organ preservation should be offered for better quality of life & sexual function
- Surgical excision can lead to scarring, deformity & function impairment

Circumcision

- Performed prior to considering conservative non-surgical treatments
- Radical circumcision alone may be curative for lesions limited to the prepuce provided that negative surgical margins are confirmed histologically

Wide Local Excision

- Wide local excision w/ circumcision may be done in patients w/ Tis, Ta, T1 grade 1-4, or stage I penile cancer limited to the foreskin
  - For stage I infiltrating tumors of the glans w/ or without adjacent skin involvement, treatment depends on size of tumor, extent of infiltration, & degree of tumor destruction of normal tissue & options may include penectomy or microscopically controlled surgery
- A limited excision can be performed on distal, smaller T2 to T3 tumors as long as a tumor-free margin can be obtained

Laser Therapy

- A penile-preserving technique, laser ablation is correlated w/ a high continuity rate of sexual activity & sexual satisfaction
- May be considered in patients w/ Tis, Ta, & T1 grade 1-2 penile cancer
- Nd:YAG or CO_2 laser results in excellent cosmetic & functional results in patients w/ stage 0 penile cancer
- Nd:YAG laser therapy may be done in patients w/ stage I penile cancer resulting in excellent control w/ cosmetic appearance & sexual function preservation
- Stage II patients w/ small lesions may be treated w/ Nd:YAG laser therapy for penis preservation

Glansectomy

- Complete removal of the glans & prepuce results in the lowest recurrence rate of the treatments for small penile lesions
- Total glansectomy w/ or without corporeal head resurfacing may be recommended for T2 lesions
- Total glansectomy may be considered for patients w/ Tis or Ta penile cancer

Mohs Micrographic Surgery

- Successive horizontal layers of tissue are excised followed by microscopic examination of each layer in frozen section
- Used in patients w/ in situ, T1 grade 1-2, & invasive penile cancer

A SURGERY (CONT'D)

Partial/Total Glans Resurfacing

- A surgical procedure primarily used for Tis lesions that removes the epithelial & subepithelial layers of the glans to the corpus spongiosum which is followed by skin graft placement
- Offered as a primary treatment for carcinoma in situ or as a secondary treatment when treatment w/ topical chemotherapy or laser therapy fails
- Determination of long-term disease control requires further follow-up

Cryosurgery

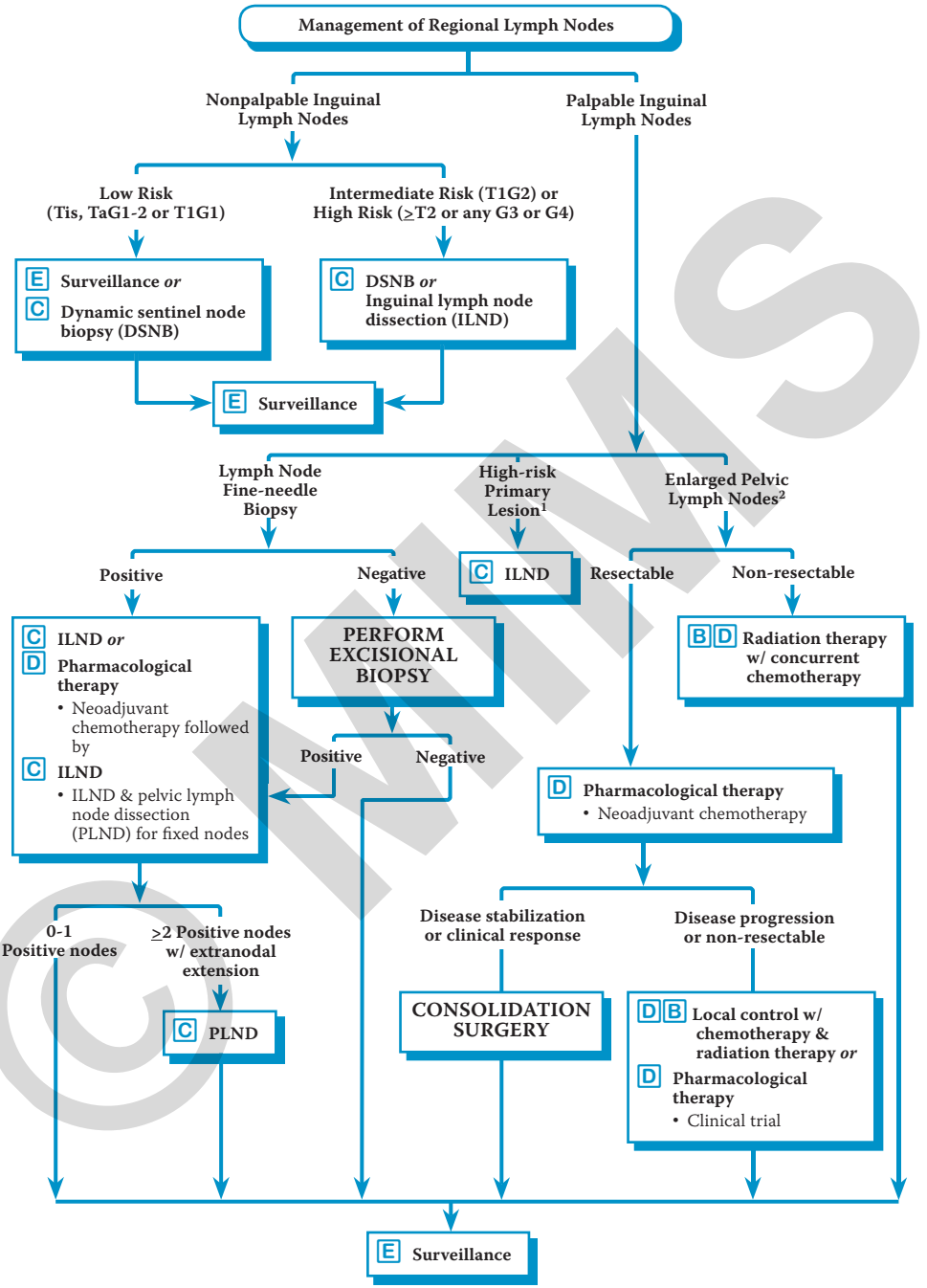
- Used in patients w/ erythroplasia of Queyrat & verrucous penile carcinoma w/ good cosmetic results

Penectomy

- Penectomy is disfiguring & may have an impact on the patient's quality of life, self-esteem, sexual function, & overall mental health
  - Must consider the patient's preference in the choice of treatment w/ the risks & benefits carefully weighed
  - Counsel patients on the option of penile reconstruction
- Depending on extent & location of the neoplasm, penile amputation can be partial or total
  - Partial penectomy for glanular & distal penile tumors preserves more length w/ superior cosmetic & functional results; considered the standard approach for high-grade primary tumors of the penis provided a functional penile stump can be preserved & negative margins are achieved
  - Total penectomy is performed on very large tumors that extend down the penile shaft or tumors that cannot be controlled without leaving an adequate penile length for voiding
  - Considered in patients w/ T1 grade 3-4 & T2 or greater penile cancer
- Most frequent management for stage II penile cancer

B RADIATION THERAPY

- Eg External-beam radiation therapy (EBRT) or brachytherapy
  - EBRT course typically consists of 2 Gy daily fraction, 5 fractions per week for 6-7 weeks to total 60-70 Gy
    - External-beam radiation w/ chemotherapy may be given for tumors ≥4 cm
    - May be considered for patients w/ T1-2, N0 tumors <4 cm w/ or without chemotherapy w/ total dose of 65-70 Gy w/ conventional fractionation using appropriate bolus to lesion w/ 2-cm margins
    - May be given concurrently w/ chemotherapy after circumcision at 45-50.4 Gy to the whole penile shaft, penile lymph nodes, & bilateral inguinal lymph nodes, w/ additional EBRT to primary lesion w/ 2 cm margins & gross lymph nodes (total dose of 60-70 Gy)
  - Brachytherapy typical schedule consists of 55-60 Gy administered in 4-6 days, & w/ an interstitial implant is preferred for tumors <4 cm
    - Recommended by the ABS-GEC-ESTRO consensus statement for the primary treatment of invasive T1, T2 & selected T3 penile cancers due to its good tumor control rates, acceptable morbidity, & preservation of functional organ
    - May be considered for patients w/ T1-2, N0 tumors ≥4 cm
- Circumcision may be done before radiation therapy to ensure complete exposure of the penile cancer, avoid maceration & preputial edema, & allow healing of any superficial infection
- May be given to patients w/ stage I penile cancer
- Together w/ surgical salvage, it is an alternative option for stage II penile cancer
- An alternative to lymph node dissection in stage III patients who are not surgical candidates
  - May be given postoperatively to decrease incidence of inguinal recurrence
- May be palliative in the treatment of primary tumor, regional adenopathy & bone metastases in patients w/ stage IV penile cancer
- Local recurrences occurring after radiation therapy may be treated surgically if diagnosed early
- Adjuvant radiation therapy to the inguinal region may be beneficial in patients w/ pN2 to N3 penile cancer or as palliative treatment in patients w/ disease not amenable to surgery
  - If primary site margin is positive, bilateral inguinal & pelvic lymph nodes are treated if there had been no or inadequate lymph node dissection
  - Consider also adjuvant radiation therapy or chemoradiation therapy in patients w/ the following high-risk features: extranodal extension, metastases to pelvic lymph nodes, involvement of bilateral inguinal lymph nodes, or a 4-cm tumor in the lymph nodes
- Adverse effects of radiation therapy include edema, secondary infection, or urethral mucositis while late complications can also occur with fibrosis, skin atrophy & depigmentation, telangiectasia, urethral stenosis, necrosis & ulcerations



[1]Features include >50% poorly undifferentiated, T1, high grade, presence of lymphovascular invasion
[2]As seen on CT or MRI, not pathologic stage

C MANAGEMENT OF REGIONAL LYMPH NODES

Dynamic Sentinel Node Biopsy (DSNB)

- Has a high sentinel node detection rate & sensitivity for lymph node metastases diagnosis in nonpalpable nodes
  - The entire lymph node basin should be tumor free if the sentinel nodes are uninvolved
- Indicated treatment in intermediate- or high-risk disease & an alternative to surveillance in low-risk disease when inguinal lymph nodes are nonpalpable at PE
- DSNB reduces morbidity associated w/ prophylactic lymph node dissection in patients w/ stage T2 & T3 clinically node-negative penile cancer
- Due to the technical challenges related to DSNB, it is recommended that it should be performed in experienced centers
- If DSNB is unavailable, visualized nodes may be diagnosed w/ ultrasound-guided fine-needle aspiration cytology (FNAC) biopsy or an inguinal lymph node dissection

Lymph Node Dissection

Inguinal Lymph Node Dissection (ILND)

- Detects microscopic metastases without a pelvic dissection in patients w/ nonpalpable inguinal nodes
  - Provides more information than a biopsy; however, the procedure has a higher complication rate than DSNB
- Indicated in high-risk disease & is an alternative procedure to DSNB in intermediate-risk patients for treatment & staging of the inguinal region
  - ILND is also done if positive nodes are found on DSNB
- ILND is the standard treatment of metastases to inguinal lymph nodes & like DSNB is warranted in patients w/ nonpalpable inguinal lymph nodes if the following high-risk features for nodal metastasis are noted in the primary penile tumor: >50% poorly differentiated, ≥T1G3 or ≥T2 any grade, or presence of lymphovascular invasion
- Bilateral lymph node dissection is performed in patients w/ high-risk features but w/ nonpalpable lymph nodes as laterality of inguinal nodal metastasis cannot be predicted based on the location of the tumor on the penis
  - It is also performed in immediate ILND for high-risk primary tumors or because of palpable nodes as 30% of patients w/ unilateral palpable node will have contralateral positive nodes that are unpalpable
- A percutaneous biopsy is currently favored over the traditional 6-week antibiotic course in differentiating reactive lymph nodes from metastatic disease in patients w/ palpable nodes; however, a bilateral ILND should be done if ≥3 weeks after completing antibiotic therapy & removing infected primary lesion, enlarged lymph nodes are palpated as it is likely to be a metastatic lymph node disease
- Modified inguinal lymph node dissection involves removal of the nodes within the fossa ovalis by skeletonizing the femoral vessels
  - Has demonstrated a reduction in complications & is performed in patients w/ nonpalpable inguinal nodes on PE but w/ a primary tumor that increases their risk for inguinal metastasis

Pelvic Lymph Node Dissection (PLND)

- Approximately 20-30% of positive inguinal lymph nodes will also have cancer in the pelvic lymph nodes & its presence is associated w/ <10% 5-year survival rate
- Recommended in patients with ≥2 positive inguinal nodes & in the clinical context of high-grade cancer in the inguinal lymph node pathologic specimen

Nonpalpable Inguinal Lymph Nodes

Low-risk Disease (Tis, TaG1-2 or T1G1)

- Patients may undergo surveillance if they are compliant w/ follow-up recommendations as occult micrometastases in inguinal lymph node is <17%
- Inguinal node staging by DSNB should be offered to patients unable to continue w/ surveillance

Intermediate- (T1G2) or High-risk Disease (≥T2 or any G3 or G4)

- Patients in this group should undergo DSNB or a superficial or modified ILND for treatment
- After DSNB or ILND, further therapy may include the following:
  - Posttreatment surveillance for patients w/ negative inguinal nodes
  - Complete inguinal dissection for patients w/ 1 involved inguinal node
  - Inguinal & pelvic node dissection for patients w/ >2 involved inguinal nodes

C MANAGEMENT OF REGIONAL LYMPH NODES (CONT'D)

Palpable Inguinal Lymph Nodes

- A percutaneous fine-needle aspiration (FNA) biopsy can diagnose lymph node metastases in palpable nodes
  - Procedure is omitted for high-risk tumors to prevent delay of initiating ILND
- A repeat biopsy or node excision may be done if FNA is negative but nodes are clinically suspicious
  - If results are negative on excisional biopsy, offer surveillance
  - If positive, patient should undergo ILND
- Positive FNA findings in unilateral, mobile inguinal node indicate immediate ILND
  - Patients should also undergo a staging ILND on the opposite side as it is common to have bilateral inguinal drainage from the primary tumor
  - A 0-1 positive node finding without extranodal cancer extension on ILND warrants surveillance
  - ≥2 positive nodes or presence of extranodal extension requires pelvic lymph node dissection
- Positive FNA findings in multiple or bilateral inguinal lymph nodes (mobile or fixed) require neoadjuvant chemotherapy followed by ILND & PLND as patient possibly has stage N2 metastatic disease & is at risk of failing treatment w/ surgery alone

Enlarged Pelvic Lymph Nodes

- A CT, CT/PET, or MRI may be done if w/ positive FNA to detect adverse nodal features, eg ≥3 positive nodes, extranodal extension or pelvic metastases
  - A bulky (≥4 cm nodal size) but resectable pelvic lymphadenopathy should be given neoadjuvant chemotherapy followed by consolidation surgery if disease responds or is stable; chemotherapy w/ radiation therapy for local control or participation in a clinical trial if disease progresses or is unresectable
  - If patient is not a candidate for surgery, radiation therapy w/ concurrent chemotherapy followed by surveillance can be given for enlarged pelvic lymphadenopathy

D PHARMACOLOGICAL THERAPY

- Penile cancer is highly curable when diagnosed in its early stages, eg stages 0, I, & II; however, because of its rarity, specific clinical trials are infrequent & literature on the role of chemotherapy is limited
  - Stages III & IV can be included in phase I & II clinical trials that test biologicals, new drugs, or surgical procedures that will improve local control & distant metastases
- There is no standard second-line systemic therapy as evidence to support its palliative use is limited
- Choice of treatment depends on the invasiveness, location, size, & stage of the tumor
  - Includes an accurate histological diagnosis & staging of the primary tumor & regional nodes

Topical Chemotherapy

- An effective 1st-line penile-preserving technique for carcinoma in situ, topical chemotherapy w/ 5-Fluorouracil (5-FU) or Imiquimod has low adverse effects & toxicity but w/ limited efficacy
  - Topical therapy should not be repeated if it fails
- 5-FU cream has been reportedly effective in the treatment of erythroplasia of Queyrat & Bowen disease
- Imiquimod cream, a topical immune response modifier, is also effective w/ good cosmetic & functional outcomes

D PHARMACOLOGICAL THERAPY (CONT'D)

Neoadjuvant Chemotherapy

- Cytoreductive neoadjuvant chemotherapy induces a treatment response that facilitates local control through surgery or radiation therapy & should be considered if inguinal lymph nodes are >4 cm
  - Consolidation surgery after neoadjuvant chemotherapy results in remission in a number of patients
  - Radical surgery after neoadjuvant chemotherapy may be done in patients w/ unresectable or recurrent lymph node metastases
- Patients unresponsive to neoadjuvant chemotherapy should be offered palliative treatment
- Cisplatin is the cornerstone of combination therapies for ≥4 cm mobile or fixed inguinal lymph nodes positive for metastatic disease on FNA
  - Four courses of Paclitaxel, Cisplatin & Ifosfamide (TIP) (preferred) chemotherapy were effective & well tolerated in patients w/ bulky regional disease (any T, N2 or N3) but without distant metastases
  - Other alternative regimens include Paclitaxel/Docetaxel, Cisplatin & 5-FU; Bleomycin, Methotrexate, & Cisplatin (BMP); Cisplatin & Irinotecan
  - Regimens that can be used in both neoadjuvant & adjuvant setting are Cisplatin & 5-FU (PF) (preferred); Bleomycin, Vincristine, & Methotrexate (BVM); Cisplatin, 5-FU, & Docetaxel (TPF)

Adjuvant Chemotherapy

- Adjuvant chemotherapy is given in pN2-3 penile cancer patients or patients w/ high-risk features not previously treated w/ neoadjuvant chemotherapy w/ any of the following: >3 positive nodes, bilateral inguinal node involvement, extranodal extension, metastases to pelvic lymph nodes
  - Adjuvant chemotherapy in pN1 disease is recommended only in clinical trials

Clinical Trials

- Whenever possible & if available, participation in clinical trials is encouraged
- Clinical trials making use of radiosensitizers or cytotoxic drugs are suitable for stage III penile cancer
  - Radiosensitizing agents are used for radiation therapy w/ concurrent chemotherapy
    - Cisplatin alone or in combination w/ continuous-infusion 5-FU is preferred
    - Other alternate agents include Mitomycin C & 5-FU; Capecitabine for palliation; Bleomycin, Methotrexate & Vincristine combination therapy
- Patients w/ stage IV penile cancer are given palliative therapy as there is no existing curative standard treatment; thus, clinical trials joining chemotherapy w/ palliative surgery or radiation therapy are suitable for stage IV penile cancer
  - Chemotherapeutic agents w/ demonstrable activity include Bleomycin, Cisplatin, Methotrexate & Vincristine

E SURVEILLANCE

- Goal is to detect early recurrence as majority of recurrences occur within the first 2-5 years of primary treatment
  - Local recurrence rate is higher in the first 2 years of follow-up after penile-preserving surgery than w/ penectomy
  - Regional recurrences happen within 2 years after DSNB or ILND
  - As life-threatening metastases are rare after 5 years, follow-up can be stopped after 5 years provided patient can reliably regularly perform self-examination & immediately report any changes
- Follow-up is also significant in the detection & management of complications arising from treatment
- Clinical evaluation includes examination of the penis & inguinal region
  - If clinical evaluation has abnormal results or patient is obese or had a prior inguinal surgery, consider imaging with an ultrasound, CT or MRI scan
- Additional imaging w/ a chest x-ray or CT or an abdominopelvic CT or MRI scan may be requested for surveillance in N2 or N3 lymph nodes
- Follow-up schedule for the primary tumor includes the following:
  - Clinical evaluation every 3 months in the first 2 years & every 6 months in the subsequent 3 years after penile-preserving treatment
  - Clinical evaluation every 6 months in the first 2 years & annually in the subsequent 3 years after penectomy
- Follow-up schedule for lymph node involvement includes a clinical evaluation every 3-6 months in the first 2 years & every 6-12 months in the subsequent 3 years

F RECURRENT DISEASE

- Up to 30% of all patients w/ penile cancer will later recur
  - A higher risk of recurrence can be seen in T2 to T4 tumors or grade 3 tumors of any T stage
- Local recurrent disease can be managed depending on the type of recurrence, ie penile or inguinal
  - Salvage penectomy (eg partial or total) is performed in most cases & may also be done if initial radiation therapy failed or if invasion of corpora cavernosa is present
  - Consider salvage penile-sparing options if without invasion of the corpora cavernosa
  - For a localized inguinal recurrence, multimodality treatment may be given using systemic chemotherapy, radiation therapy, &/or surgical resection
    - Phase I & II clinical trials using new chemotherapeutic drugs or biologicals may be offered to patients w/ nodal recurrence uncontrolled by above local treatment measures
- A nodal re-evaluation should be performed in patients undergoing recurrent penile tumor resection as a prophylactic inguinal staging procedure (ie DSNB or ILND) can be a treatment option if a prior node dissection has not been performed
- For patients w/ fixed inguinal nodes or high tumor burden not amenable to resection, radiation therapy to relieve pressure from tumor compression or further treatment w/ palliative chemotherapy may be advised

G METASTATIC DISEASE

- Presents a poor prognosis & palliative care should be considered early in the treatment
  - Overall survival is 0% at 5 years and <10% at 2 years
- Patients are treated w/ systemic chemotherapy, radiation therapy, or radiation therapy w/ concurrent chemotherapy
  - Complete or partial responders or those w/ stable disease are given consolidation ILND
  - Non-responders or those w/ disease progression may be treated w/ salvage systemic chemotherapy or consider radiation therapy for local control &/or best supportive care or clinical trial participation
- Though active combination regimens are available, there is no preferred regimen for metastatic penile cancer treatment & selection of therapy should consider potential toxicities
  - A literature review found that Cisplatin-containing regimens were most active for metastatic disease; Bleomycin, though possessing a similar activity, is associated w/ severe adverse effects but can be safely given w/ Cisplatin in patients who are young, not heavy smokers, & without compromised lung function
- For advanced disease, palliative chemotherapy w/ Cisplatin-based regimens had better results after adjustment for prognostic factors:
  - TIP may also be used as a reasonable 1st-line treatment in metastatic disease based on their activity w/ neoadjuvant usage
  - Cisplatin in combination w/ 5-FU or Irinotecan
    - Cisplatin & 5-FU can be considered an alternative option to TIP but toxicities may require dose reductions
  - Cisplatin & Gemcitabine had a sustained palliative response in patients w/ metastatic disease
  - Paclitaxel w/ Carboplatin is an alternative option for patients who cannot take Cisplatin
  - Paclitaxel as a single agent was effective in metastatic patients who previously were given Cisplatin combination regimens in the neoadjuvant or adjuvant setting
  - Other potentially active agents include Cetuximab, Panitumumab, Sorafenib, & Sunitinib

Dosage Guidelines

CYTOTOXIC CHEMOTHERAPY		
Drug	**Dosage[1]**	**Remarks**
Bleomycin	0.25-0.5 u/kg IV, IM or SC 1-2 times wkly	**Adverse Reactions** • Resp effects (pneumonitis, pulmonary fibrosis); Other effects (idiosyncratic & mucocutaneous reactions, fever, chills, vomiting, anorexia, wt loss) **Special Instructions** • Use w/ caution in patients w/ renal & hepatic impairment, compromised pulmonary function

All dosage recommendations are for non-elderly adults w/ normal renal & hepatic function unless otherwise stated.
Not all products are available or approved for above use in all countries.
Products listed above may not be mentioned in the disease management chart but have been placed here based on indications listed in regional manufacturers' product information.

Specific prescribing information may be found in the latest MIMS.

Please see the end of this section for the reference list.